Functionalization of Propargyl Alcohol Derivatives and Terminal Alkynes Using Lewis/Brønsted Acids

DOCTOR OF PHILOSOPHY

by

Naganaboina Naveen

SCHOOL OF CHEMISTRY
UNIVERSITY OF HYDERABAD
HYDERABAD 500 046
INDIA

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A Thesis Submitted for the degree of

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to the

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Central University P.O.
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Statement

I hereby declare that the matter embodied in this thesis is the result of investigations carried out by me in the School of Chemistry, University of Hyderabad, Hyderabad, under the supervision of **Dr. Rengarajan Balamurugan**.

In keeping with the general practice of reporting scientific observations, due acknowledgement has been made wherever the work described is based on the findings of other investigators. Any omission, which might have occurred by oversight or error, is regretted.

University of Hyderabad
June, 2014

Naganaboina Naveen
08CHPH01

School of Chemistry
University of Hyderabad
Central University P.O.
Hyderabad 500 046
India

Certificate

Certified that the work embodied in this thesis entitled **"Functionalization of Propargyl Alcohol Derivatives and Terminal Alkynes Using Lewis/Brønsted Acids"** has been carried out by **Mr. Naganaboina Naveen** under my supervision and the same has not been submitted elsewhere for a degree.

Dr. R. BALAMURUGAN
(THESIS SUPERVISOR)

DEAN
SCHOOL OF CHEMISTRY

Dedicated to my Family & Lord Balaji

Acknowledgements

I wish to express my gratitude and profound respect to my mentor **Dr. Rengarajan Balamurugan for** his guidance, encouragement, and motivation throughout my tenure here. I will always be indebted to him for this.

I thank present and former deans of school of chemistry, Prof. M. Durga Prasad, Prof. M. V. Rajasekharan, Prof. D. Basavaiah, and Prof. M. Periasamy and all the faculty members of the school of chemistry for their timely help and cooperation.

I am very much thankful to my doctoral committee members Dr. K. Muralidharan and Dr. P. K. Panda for their support during doctoral tenure.

It is a great privilege to express my heartfelt honour to Johnson sir (my elementary school teacher) who gave me plenty of knowledge, motivation and his special care on me during my elementary schooling. Thanks to Scholars' High School, Warangal for high standard teaching.

I would specially thank Dr Ravinder Sir for his excellent coaching on chemistry and directing me to choose chemistry. I would like to thank my M.Sc teachers Prof Jayaprasada Rao, Prof Adinarayana, Prof Nageshwar Rao, Prof Jayaprakash Rao and Prof Surendar Rao (PGCS Saifabad).

I wish to extend my deep sense of gratitude to my cool seniors Mr Raveendra Babu, Mr. Srinivas Rao, Mr. Ganesh Kumar. They helped me a lot when I am in tough times. I also thank my labmates Dr. G. Vanajakshi, Mr. S. Manojveer, Mr. N. Ramana, Mr. S. Sakthivel and Mr. D. Tamilarasan for creating a pleasant working atmosphere.

My heartfelt thanks to my friends K. Satish, R. Madavachary, M Shivaprasad, Dr Swamy and Bharani Shashank for creating friendly atmoshphere throughout my tenure of Ph.D. The days spent with them were memorable.

I thank Mr. Krishna chary (devotional teachings), Dr G. Sekher Reddy, Dr Karunakar, Nandakishore, Gangadhar Rao, Yasin, P. Obaiah and Lings for their help.

I would thank Dr Ram Kumar, Dr Vijayendar Reddy, Dr M. Kishore, Srinivas Reddy, Murali, Ramu Yadav, Dr K. Mallesh, Dr Bhanuchander, K. Nagarjuna, Dr P. Venu, Dr Sheshadri, B. Ramakrishna, Madhu, Naren pati, B. Satish, Brijesh, Anoop, Vikrant, Nakka Srinivas, Ramavath Babu, Dr Nagaraju, Balavardhan Rao, Narendra, Praveen, Dr Vignesh,

Dr Ganesh, Dr Anish, Sunny, Srinivas, Malkappa, Sudhanshu, Raju, Narsimha Rao, PVVN. Kishore, Nagarjuna, Dr Viji, Dr Bharat, Dr. Kishore, Ramakrishna, N Chandrasekher, Ajay, YSLV Narayana, Ramudu, Venkanna, Obul Reddy, Suresh, Edukondalu, Uday, Satthy, Ramesh, Harish, Anand, Dr J. Raju, Chandrasekher Reddy, Santosh, Sayanna, Ragavaiah, Dr. Bhuvan Kumar, Dr Nagarjuna Reddy, Dr S Ramesh, Prasad, Sreenu, Sashi, Rajagopal Reddy, Ramakrishna, Kishore, Thirupathi, Pavan, Shiva Ramakrishna, Ashok, Chandu, Dr Rajesh Goud, Sudheer, Reddaiah (plant science), Venkatappa Naik (economics), my pgcs seniors P Srinivas, B Srikanth, Venkateshwarlu ….. many more for their help.

I would thank my friends Pavan, Dr Kishore Natte, Venu Chicha, Sola Sriram, Ashok Babai, Rajesh, Sunil, Kaka and all my well wishers.

All the instrument operators and non-teaching staff of the school for being helpful. . Mr. S. Satyanarayana, Mrs. Asia Parwez, Mr Venkata Ramana, Mr Turab, Mrs. Vijaya Lakshmi, Mr. V. Bhaskar Rao, Mr. Vijaya Bhaskar, Mr. Shetty, Mr. K. R. B. V. Prasad, Mr. Durgesh, Subbu, and Venkateshwar Rao are a few to mention.

I am blessed to be a member of my family to feel their love and affection. I am indebted to my brother Dr N. Vijay Kumar for his constant encouragement and support. He laid the road with his struggles and I just walked on it. Without him I am nowhere here. My warm wishes to my niece Sri Vaishnavi (new comer). I thank Swamy Vivekananda and Rama Krishna prabha for inspiring me. I thank Lord Balaji for his blessings.

I wish to extend my sincere thanks to Mother Nature at University Of Hyderabad, and the authorities for providing all the necessary facilities for this work. Finally I would like to thank the CSIR–INDIA for the financial support during my tenure.

Naganaboina Naveen

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List of acronyms used

[α]	Specific rotation [expressed without units; the actual units are deg $dm^{-1}cm^3$ g^{-1}]
Aq.	Aqueous
Ac	Acetyl
BA	Brønsted Acid
Bn	Benzyl
bs	Broad singlet (spectral)
Bu	Butyl
t-Bu	*tert*-Butyl
^oC	Degree Celsius
conc.	Concentrated
cm^{-1}	Wavenumber(s)
δ	Chemical shift in parts per million
DABCO	1,4-diazabicyclo[2.2.2]octane
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCE	Dichloroethane
DCM	Dichloromethane
dil.	Diluted
DMF	N,N-Dimethyl formamide
dr	Diastereomeric ratio
ee	Enantiomeric excess
ESI	Electron spin ionisation
equiv	Equivalent
g	Gram(s)
h	Hour(s)
HRMS	High resolution mass spectrometry
Hz	Hertz
i-Pr	Isopropyl
IR	Infrared

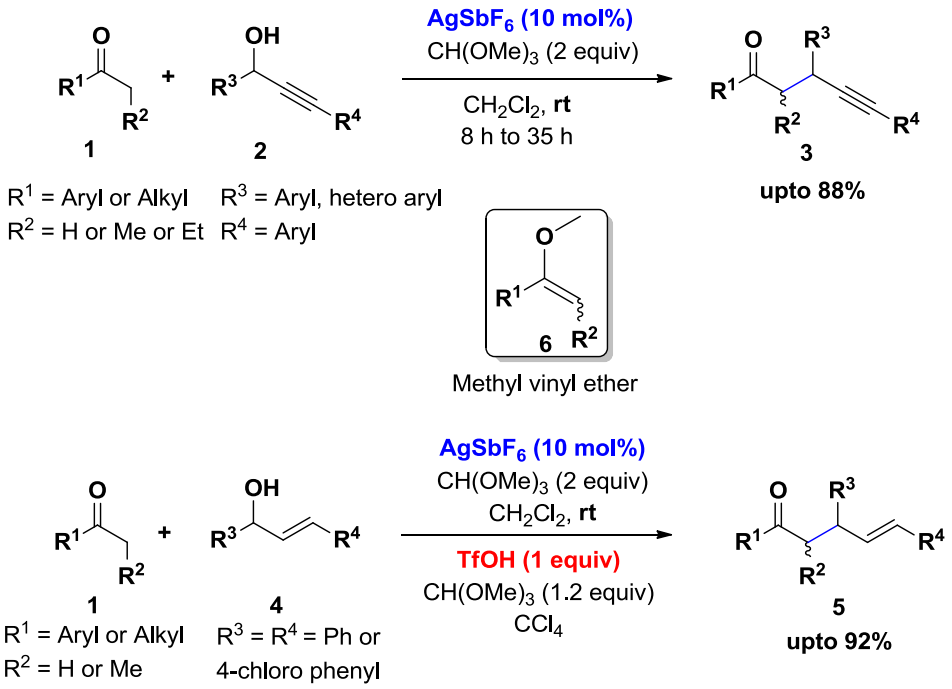
J	Coupling constant (in NMR Spectroscopy)
LA	Lewis acid
LDA	Lithium diisopropylamide
LHMDS	Lithium hexamethyl disilazide
LCMS	Liquid chromatography-mass spectrometry
m	Multiplet (spectral)
Me	Methyl
MeCN	Acetonitrile
MHz	Megahertz
min	Minute(s)
mmol	Millimoles
mp	Melting point
NIS	*N*-Iodosuccinimide
NMR	Nuclear magnetic resonance
Nu	Nucleophile
ORTEP	Oak ridge thermal ellipsoid plot
OTf	Trifluoromethanesulfonate
PMA	Phosphomolybdic acid
Ph	Phenyl
PTSA	*p*-Toluenesulfonic acid
q	Quartet (in spectroscopy)
rt	Room temperature
Selecfluor	1-Chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate)
TLC	Thin layer chromatography
TMEDA	*N*,*N*,*N*',*N*' Tetramethylethylenediamine
TMSCl	Trimethylsilyl chloride
TfOH	Triflic acid

Synopsis

The thesis entitled ***"Functionalization of Propargyl Alcohol Derivatives and Terminal Alkynes Using Lewis/Brønsted Acids"*** is presented in three chapters. In the first chapter functionalization at the propargylic and allylic positions of arylpropargyl and cinnamyl alcohols respectively is discussed. In the second chapter, study on functionalization of C≡C bond of tertiary propargyl alcohol is elaborated. Third chapter presents the work on Cu(II)-catalyzed homo- and heterocoupling of terminal alkynes. The title and brief summary of each chapter are given below.

Chapter 1: Silver-Catalyzed Direct α-Alkylation of Unactivated Ketones with Propargyl and Allyl Alcohols via In situ Generated Acetals

α-Alkylation of carbonyl compounds is a basic approach for the construction of C-C bonds. This approach can introduce diverse functional groups adjacent to carbonyl carbon. Traditional methods use carbonyls in the form of metal enolates, silyl enolates, enol acetates and enamines etc. and electrophiles attached to good leaving groups. These methods, often, generates huge amounts of byproducts such as metal salts. In an endeavor to develop direct α-alkylation of ketones, a method has been developed via in situ generated acetals using benzylic alcohols promoted by catalytic $AgSbF_6$ or stoichiometric amount of TfOH. In the presence of the promoter, the in situ formed acetal generates required nucleophile in the form of enol ether (**6**) and the alcohol generates electrophile. Triflic acid is excellent in promoting alkylation of ketones (**1**) with cinnamyl alcohols (**4**) and benzhydrols but less effective with propargyl alcohols (**2**). $AgSbF_6$ was found to be better for the alkylation of ketones with arylpropargyl alcohols (**2**). Here $AgSbF_6$ catalyst plays a dual role, by coordinating to arylpropargyl alcohol's hydroxyl and triple bond (both σ- and π-activation) to activate it. A variety of benzylic propargyl alcohols (**2**), cinnamyl alcohols (**4**) were used to get the desired products (**3** and **5**) in good yields. Unfortunately terminal or alkyl substituted secondary benzylic propargyl and allyl alcohols are ineffective in this reaction. Control experiments using optically active arylpropargyl alcohol suggest cationic intermediate. In addition, selected α-alkylated products formed from arylpropargyl alcohol were further cyclized into trisubstituted furans.



Scheme 1. Direct alkylation of ketones with arylpropargyl and cinnamyl alcohols

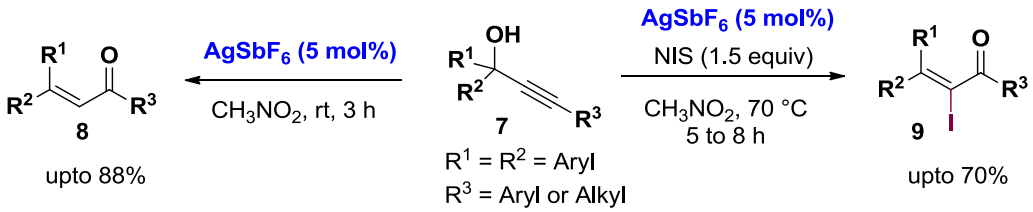
Chapter 2: Silver-Catalyzed Meyer-Schuster Rearrangement, Electrophilic Iodination and Fluorination of Tertiary Propargyl Alcohols

2.1 Meyer-Schuster Rearrangement and Electrophilic Iodination of Tertiary Propargyl Alcohols

While working on direct α-alkylation of ketones using $HC(OMe)_3$ and $AgSbF_6$ with tertiary propargyl alcohols, an unexpected α,β-unsaturated enone was obtained instead of α-alkylated product. This product was found to be the Meyer-Schuster rearrangement product. In Meyer-Schuster rearrangement allenol is the intermediate which on tautomerization gives the respective α,β-unsaturated ketone. This kind of rearrangement catalyzed by silver catalyst is not known. Hence silver-catalyzed Meyer-Schuster rearrangement was studied. Under the optimized condition, electron rich (if R^3 = −OMe), electron deficit (if R^3 = $-CO_2Et$) propargyl alcohols readily reacted to furnish very good yields of enones (**8**). This reaction is limited to tertiary propargyl alcohols only.

Deploying the Meyer-Schuster rearrangement, in the place of "H^+", the possibility of using "I^+" or "F^+" to incorporate, respectively, 'I' and 'F' was studied. The allenol

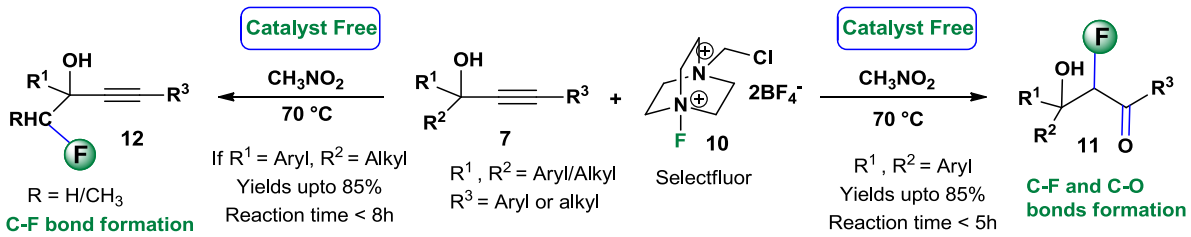
intermediate involved in the silver-catalyzed Meyer-Schuster rearrangement has been successfully trapped using NIS to synthesize α-iodoenones (**9**) in good yields. Thus formed highly substituted α-iodoenones (**9**) are valuable building blocks. The iodo function of α-iodoenones could, in principle, be substituted with diverse carbon substituents like alkyl, alkenyl, alkynyl, aryl *etc.* through transition metal catalysis.



Scheme 2. Silver-catalyzed Meyer-Schuster rearrangement and synthesis of α-iodoenones

2.2 Electrophilic Fluorination of Tertiary Propargyl Alcohols

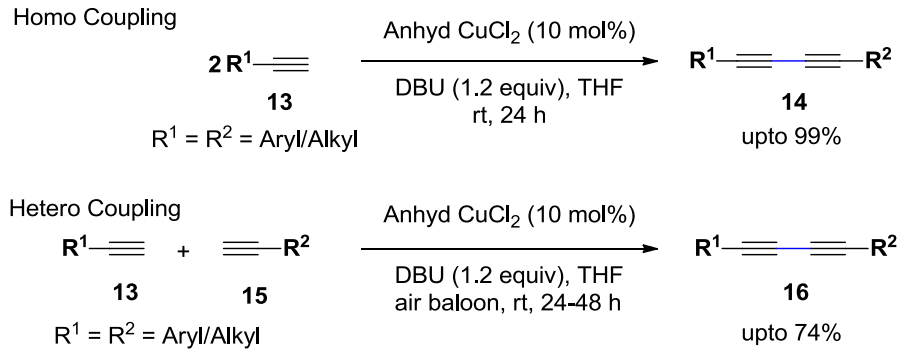
Fluorine incorporated organic compounds are few in nature but widely used in areas such as diagnostics, medicinal chemistry, pharmaceuticals and agrochemicals. α-Fluoro β-hydroxy ketones (**11**) are formed when tertiary propargyl alcohols (**7**) are reacted with selectfluor (**10**) without catalyst. Whereas, treatment of tertiary propargyl alcohol containing alkyl group (if R^2= methyl or ethyl) furnished the product **12**. Unsymmetrical (if $R^1 \neq R^2$) tertiary propargyl alcohols resulted in a mixture of diastereomers. Substituents like fluoro, bromo, chloro, methyl, aryl on R^1 of **7**, smoothly reacted to deliver the desired products in good yields. When 1-(phenylethynyl)-1,2,3,4-tetrahydronaphthalen-1-ol was subjected to reaction condition with 2.5 equivalents of selectfluor, difluorinated product was observed. Secondary arylpropargyl alcohols do not undergo similar transformation.



Scheme 3. Electrophilic fluorination of tertiary propargyl alcohols

Chapter 3: Copper(II)-Catalyzed Homo- and Heterocoupling of Terminal Alkynes

Among the methods available for C-C bond formation, coupling reactions are significant and show tremendous utility in building complex structures. Coupling of terminal alkynes brings special attraction in introducing C-C triple bonds to organic molecules. A simple protocol for making symmetrically (**14**) and unsymmetrically substituted 1,3-diynes (**16**) using catalytic $CuCl_2$, DBU at room temperature has been developed. The scope of the homo- and heterocoupling has been shown with a wide range of terminal alkynes. Homocoupling reactions were carried out at room temperature in open flask, which is in contrast to previously reported methods which need heating and oxygen bubbling. Even heterocoupling reactions were achieved at room temperature, but use of air balloon was necessary. The yields of the products are comparable and in some cases greater than those obtained in reported systems. This protocol has very good functional group tolerance such as $-NH_2$, −OH, −Br *etc*. Several unsymmetrical diynes synthesized by this method are new to literature.



Scheme 4. Copper(II)-catalyzed homo-and heterocoupling of terminal alkynes

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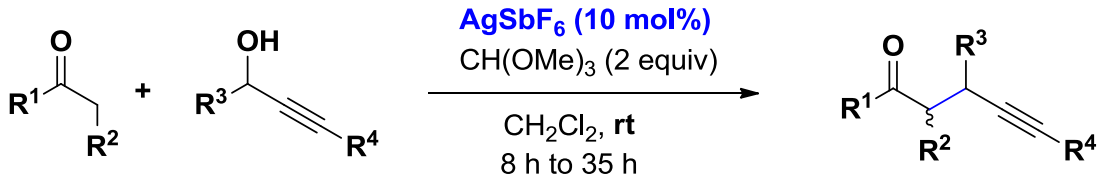
Note: Scheme numbers and compound numbers given in this synopsis are different from those given in chapters.

Chapter 1

Silver-Catalyzed Direct α-Alkylation of Unactivated Ketones with Propargyl and Allyl Alcohols via In situ Generated Acetals

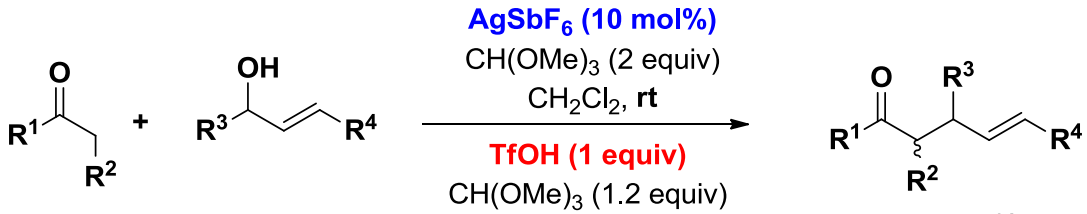
Direct Propargylation (benzylic) of Unactivated Ketones



R^1 = Aryl or Alkyl R^3 = Aryl, hetero aryl
R^2 = H or Me or Et R^4 = Aryl

upto 88%

Direct Allylation (cinnamyl) of unactivated Ketones

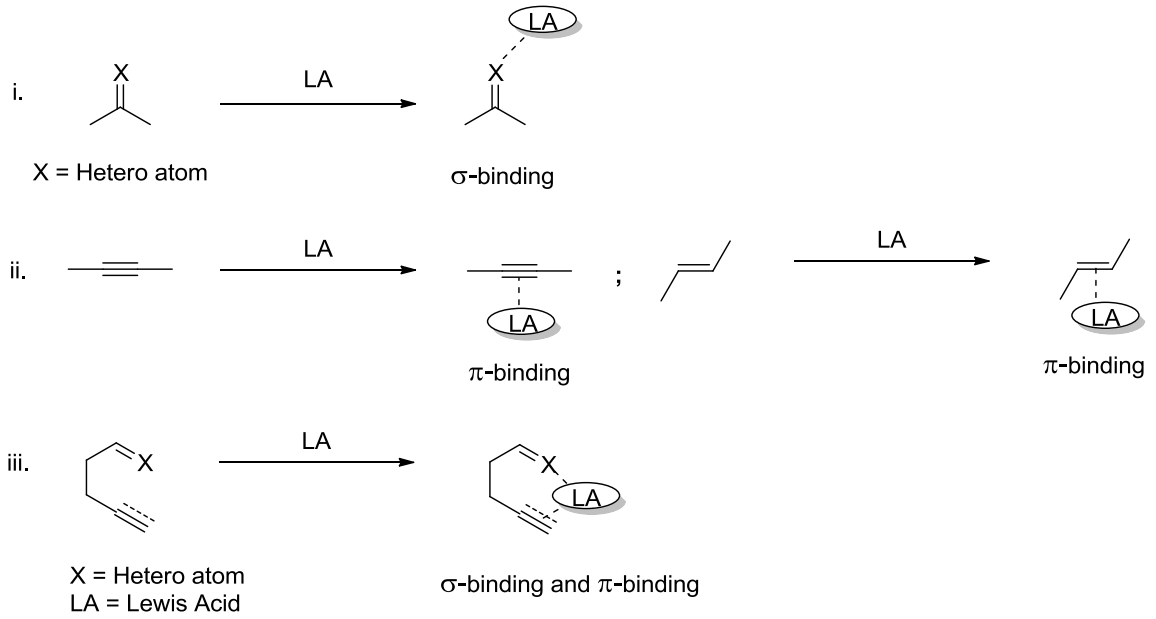


R^1 = Aryl or Alkyl R^3 = R^4 = Ph or
R^2 = H or Me 4-chloro phenyl

upto 92%

1.1 Introduction

Lewis acid catalysts can be classified into two types as (i) σ-electrophilic and (ii) π-electrophilic. Classical Lewis acids like BCl_3, $AlCl_3$, $SnCl_4$ etc., which makes strong σ-complexes with carbonyl, imine and heteroatoms come under σ-electrophilic Lewis acids. Lewis acids like $PtCl_2$, AuCl, CuCl etc., show affinity towards C-C multiple bonds and are considered as π-electrophilic or carbophilic. Some transition metal Lewis acids show dual behavior i.e., they can coordinate to hetero atom as well as C-C multiple bonds concomitantly. All these modes of activation are depicted in Scheme 1.



Scheme 1. Different modes of activation by Lewis acids

Coinage metals (Cu, Ag, Au) have emerged as powerful catalysts in carrying out interesting organic transformations.[1] Carbophilicity is one of the unique properties exhibited by these metals. Among them both Au and Ag show very good affinity towards carbon-carbon multiple bonds.[1f]

In the recent years under the shadow of Au, Ag is being used mainly for generating cationic gold species [$(L\text{-}Au)^+$] by sacrificing Ag as AgCl precipitate. Still, Ag salts are used considerably as catalysts and co-catalysts.[1b]

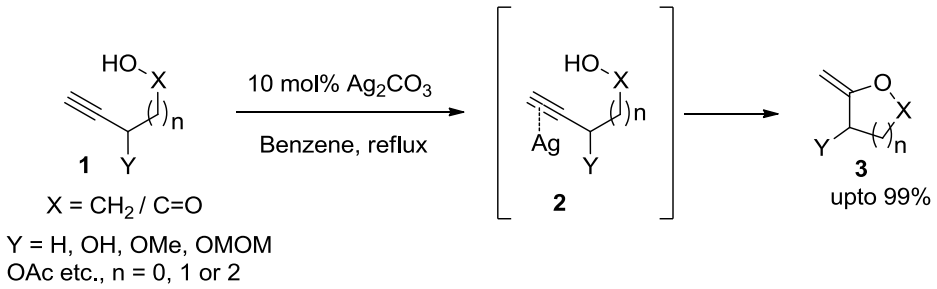
1.2 Silver-promoted/catalyzed homogeneous reactions

Homogeneous reactions facilitated by silver catalysts are known for a long time. But the intensity of activity in this field increased in the past two decades. Silver can act as carbophilic and oxophilic catalyst.[1e]

1.2.1 Carbophilic nature of silver-catalysts

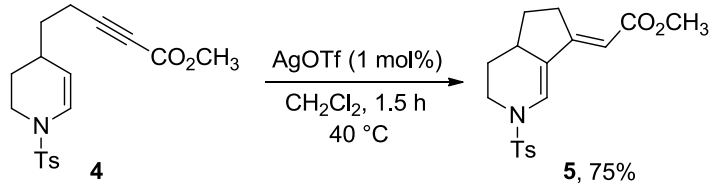
Activation of olefins, alkynes and allenes supports the carbophilic nature of silver. Although the carbophilicity of Ag is not good as that of gold, the silver-catalyzed nucleophilic cyclizations of allenes and alkynes are few examples for the utility of carbophilicity of silver. Representative examples are highlighted below.

Pale and co-workers demonstrated Ag_2CO_3-catalyzed regiospecific intramolecular cyclization (addition) of different alkynols (Scheme 2).[2] The reaction undergoes *via* initial coordination of silver to alkyne (**2**) followed by intramolecular nucleophilic attack.



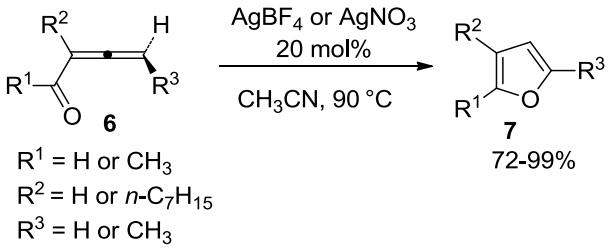
Scheme 2. Silver-catalyzed intramolecular heteroatomaddition to alkynes

Harrison *et al.* carried out an intramolecular addition of enamine to silver activated alkyne to get the cycloisomerized product (**5**) as shown in Scheme 3.[3]



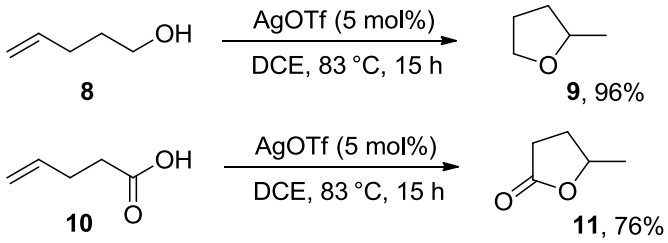
Scheme 3. Example for silver-catalyzed intramolecular addition of carbon nucleophile to alkyne

Marshall *et al.* found that substituted furans (**7**) are formed upon treatment of allenals, allenones (**6**) with $AgBF_4$ or $AgNO_3$ in acetonitrile in 72-99% yields.[4] In this reaction Ag^I initiates the reaction by coordinating to allenyl π-system (Scheme 4).



Scheme 4. Activation of allenones by silver to form furans

He and co-workers discovered AgOTf as an excellent catalyst for the intramolecular addition of hydroxyl to unactivated alkenes. Intramolecular hydroalkoxylation and hydroacyloxylation were demonstrated efficiently. Markovnikoff's products are obtained in these reactions (Scheme 5).[5]



Scheme 5. Silver-catalyzed intramolecular addition to alkenes

1.2.2 Oxophilic nature of Ag catalysts

In 1974, Crist *et al.* disclosed an excellent study on complexes formed between Ag^{I} cations and ketones. They found that cyclohexanones and acetophenones form complexes with $AgBF_4$. Here carbonyl group acts as an n-donor towards Ag^{I}. A series of NMR and IR experiments were conducted to confirm it.

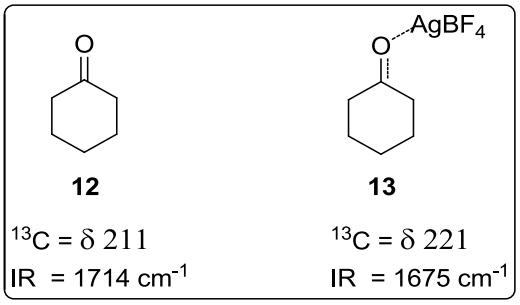


Figure 1. Effect of coordination of $AgBF_4$ to cyclohexanone

Table 1. ^{13}C chemical shifts of carbonyl of cyclohexanone in CH_2Cl_2 with different salts

Added Salt	Mole Ratio [Salt]/[Ketone][b]	δ (^{13}C)[a] C=O	Δδ
None	0.0	211.1	-
$AgBF_4$	0.45	221.7	10.6
$AgClO_4$[c]	0.26	216.4	5.3
Bu_4NBF_4	0.50	211.0	-0.1
$LiClO_4$[c]	0.30	216.3	5.2

[a]Downfield from internal TMS. [b]Solutions containing 0.920 g of ketone and the indicated amounts of salts in 5 g of CH_2Cl_2solution. [c] Saturated solutions. Δδ = Change in respect to standard.

Table 1 gives clear picture of shift in the δC=O of cyclohexanone in the ^{13}C-NMR spectrum after coordination to different metal salts. Cyclohexanone complexed to $AgBF_4$ showed δC=O at 221.7 (Table 1, entry 2) whereas free cyclohexanone carbonyl carbon appeared at 211.1 (Table 1, entry 1). The observed change can be taken as an evidence for carbonyl oxygen and Ag complexation (**13**). This is supported by the shift in the carbonyl stretching frequency in IR spectrum (1714 cm^{-1} to 1675 cm^{-1}).[6]

Oxophilic and azaphilic character of Ag^I is utilized in many asymmetric reactions like allylation of aldehydes, Aldol, cyclo-additions and group transfer reactions.[7-9]

1.2.3 Dual activation of silver catalyst

Some catalyst can coordinate to both heteroatoms and C-C multiple bonds at the same time, thereby increase the scope of the catalyst. Gold catalysts are excellent examples for such kind of activation. The dual role of gold has been used in several transformations previously.[10]

Sheppard and co-workers noticed the formation of allylated product (**16**) instead of α, β-unsaturated enones during their study on Mayer-Schuster rearrangement of propargyl alcohols using Au-catalyst. It was revealed that the formation of unexpected product is due to the presence of $AgNTf_2$ along with gold catalyst. With this finding they used $AgNTf_2$ alone for nucleophilic substitution reactions on propargyl alcohols. Propargyl alcohol (**14**) on reaction with allyltrimethylsilane (**15**) afforded the nucleophilic substitution product (**16**) as

shown in Scheme 6.[11] Coordination of silver to both alkyne and hydroxyl group is anticipated for the activation of propargyl alcohol for easy nucleophilic substitution.

Scheme 6. Silver-catalyzed nucleophilic substitution of propargyl alcohols

1.3 α-Alkylation of ketones

α-Alkylation of carbonyl compounds is a trivial reaction for the construction of C-C bonds. pK_a value of α-hydrogen of methyl ketone (**17**) is in the range of 18-20 in H_2O,[12] indicating its less acidity and less reactivity when compared to 1,3-dicarbonyls (**18**, pK_a = 9-11).

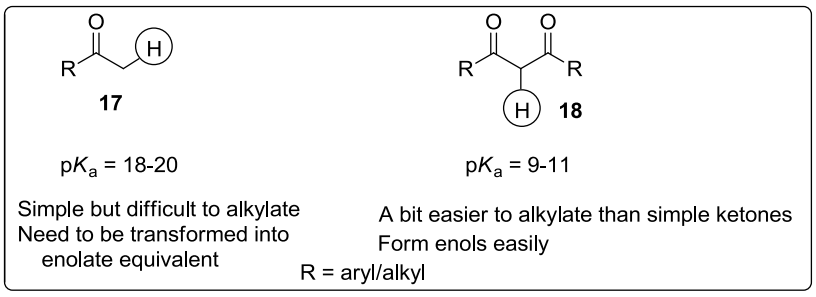
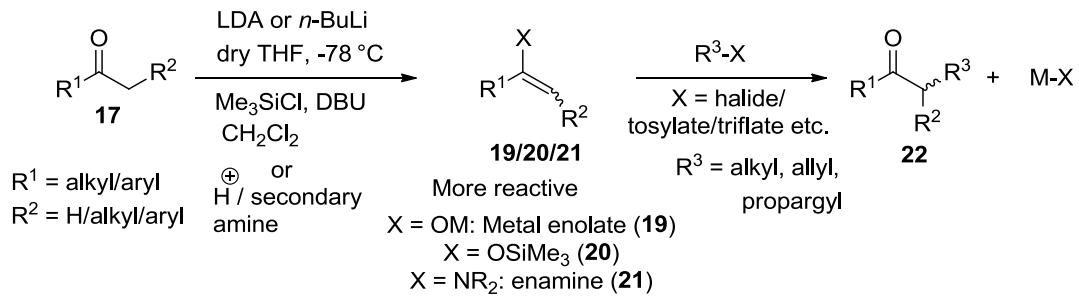


Figure 2. pK_a values of simple ketones and 1,3-dicarbonyls

Hence to functionalize the α-position of simple ketones classical methods require strong bases such as LDA, $NaNH_2$, *n*-BuLi to form reactive metal enolates (**19**). Other activated systems generally encountered for α-alkylation of ketones are enamines (**21**), silylenol ethers (**20**) and enol acetates.[13]



Scheme 7. Classical methods for α-alkylation of ketones

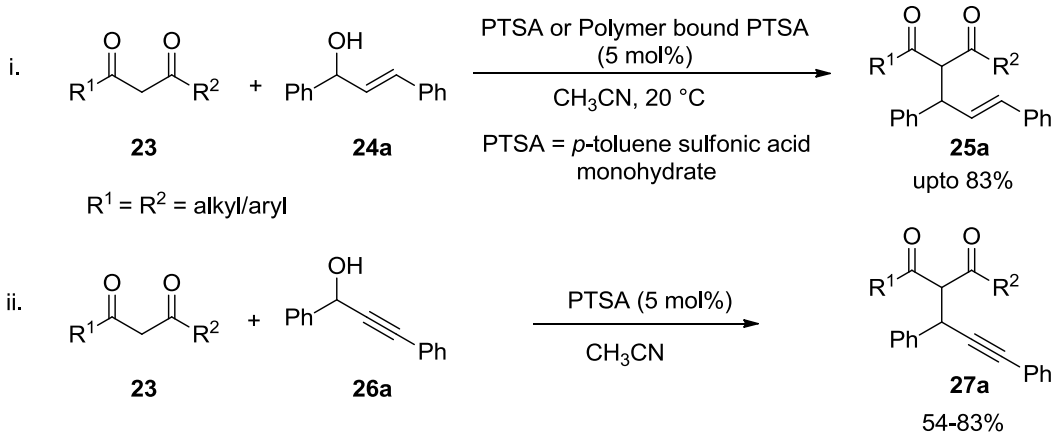
Although these methods solve the purpose and are used extensively, they have certain drawbacks such as use of stoichiometric reagents, uncontrolled polyalkylations at sometimes, self-condensation of ketones and generation of inorganic metal salts as by-products. Systems like silylenol ethers, enamines and enol acetates have to be prepared separately. The electrophiles need good leaving groups such as halo (preferably I/Br), tosyl, acyl, etc., which require one more additional step for making them. So, to overcome the drawbacks, direct alkylations are being explored using ketones and alcohols without any prior activation.

1.3.1 α-Propargylation and allylation of methyl ketones

Of the alkylation reactions of ketones, α-propargylation and α-allylation reactions are significant because of the introduction of multiple bonds at γ-position to ketone, which can be further functionalized to complex structures easily by simple transformations. They can be synthesized by Brønsted acid or Lewis acid-catalyzed alkylations using allyl and propargyl alcohols. Most of the studied systems are 1,3-dicarbonyls.

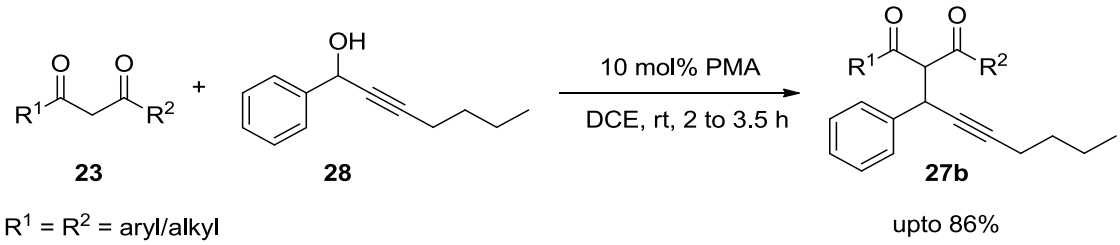
1.3.2 Brønsted acid-catalyzed α-alkylations of ketones

A simple PTSA-catalyzed alkylation of 1,3-dicarbonyls with allyl alcohols was reported by Rodríguez group (i, Scheme 8).[14a] Reaction conditions are mild and they used the reusable polymer bound PTSA catalyst as well, which gave equal or better yields than PTSA. Same group reported a direct propargylation of 1,3-diketones (ii, Scheme 8). Aliphatic propargyl alcohols such as 1-cyclohexyl-3-phenyl-2-propyn-1-ol failed to deliver the product. So a cation-stabilizing aryl type substitution at the propargyl position is necessary for the success of the reaction. They further functionalized the product into tetrasubstituted furan.[14b]



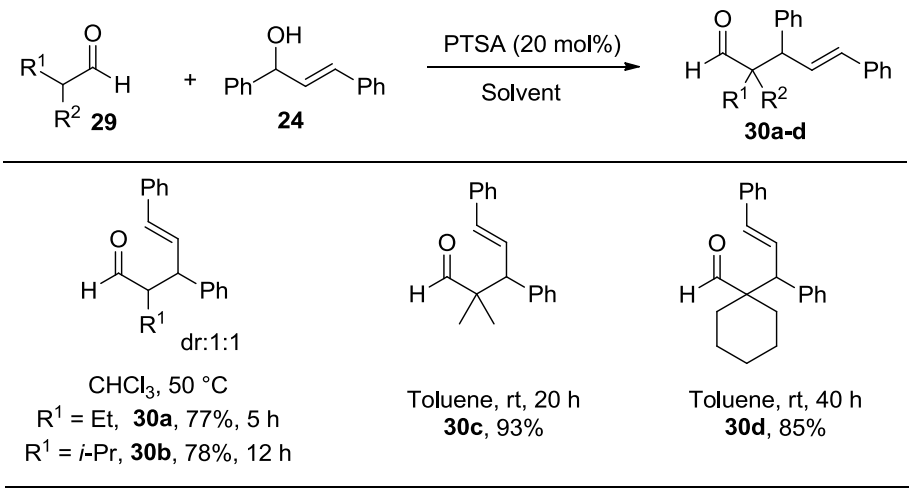
Scheme 8. Alkylation of 1,3-diketones using PTSA

Heteropolyacid-catalyzed highly efficient alkylation of 1,3-diketones was reported by Yadav *et al*. PMA (polymolybdic acid, $H_3PMo_{12}O_{40}$) a cost effective, recyclable, environment friendly catalyst on SiO_2 support was used for propargylation and benzylation of diketones (Scheme 9).[15]



Scheme 9. Alkylation of 1,3-diketones using PMA

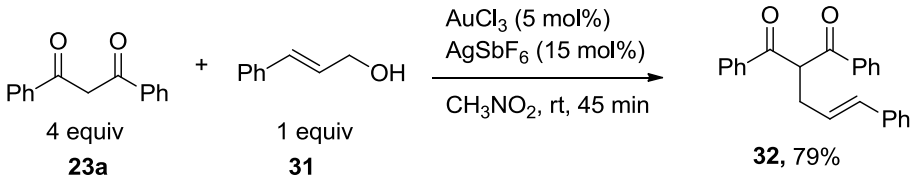
Chi and co-workers disclosed α-alkylation of aldehydes with benzhydrols and allyl alcohols using Brønsted acids as catalysts. They encountered the problem of ether formation which on self-redox gave undesired side products there by reduced the yield of α-alkylated products (**30**). Usage of tertiary butanol as additive suppressed the self-redox products. Drawback of the method is, due to difference in reactivity of the alcohols, reaction should be optimized in each case (Scheme 10).[16]



Scheme 10. Alkylation of aldehydes using PTSA

1.3.3 Lewis acid-catalyzed α-alkylations of ketones

Allylic alkylation of 1,3-dicarbonyl compounds with a broad range of allylic alcohols was reported by Chan and co-workers. $AuCl_3$ was used as catalyst and $AgSbF_6$ as co-catalyst. Use of less reactive primary allyl alcohols (**31**) under mild conditions is an important feature of the report, but usage of 4 equivalents of 1,3-dicarbonyl is necessary (Scheme 11).[17a]

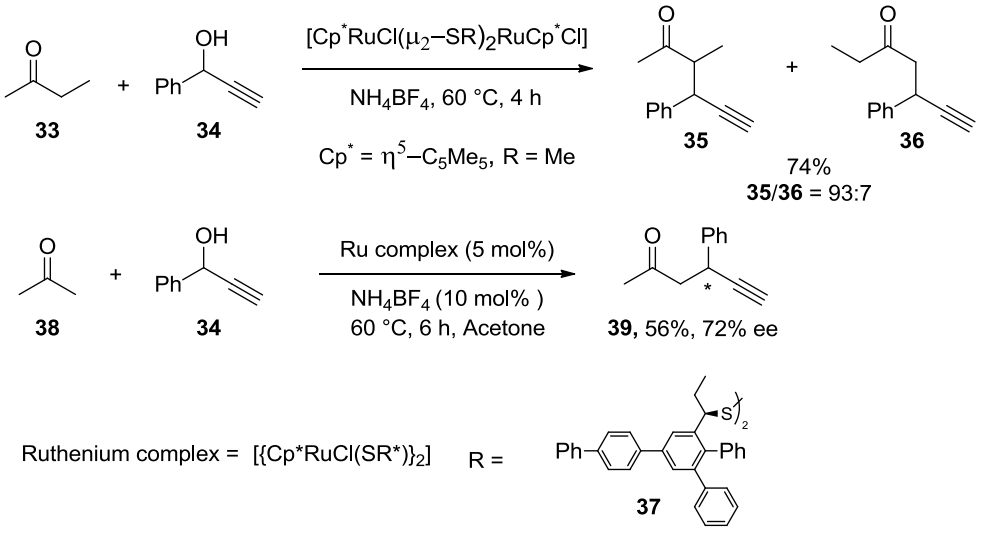


Scheme 11. Au/Ag-catalyzed allylation of 1,3-dicarbonyls

For similar allylation of 1,3-diketones catalysts like BF_3•OEt_2,[17b] $Pd(PPh_3)_4$,[17c] $Pd(OAc)_2$,[17d] Ru-complex,[17e] $Bi(OTf)_3$,[17f] and I_2[17g] have been used. For propargylation of 1,3-diketones, Rhenium complex,[18a] $FeCl_3$,[18b] Ir-Sn,[18c] $Yb(OTf)_3$,[19a] ionic liquids as solvent,[19b] $InBr_3$,[19c] and $SnCl_2$[19d] catalysts are used.

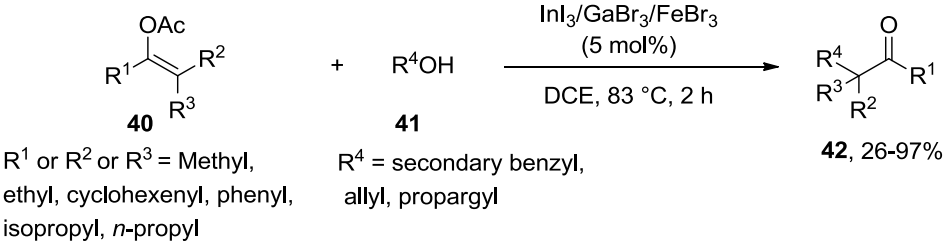
Uemura and co-workers discovered the propargylation of simple unactivated ketones and 1,3-diketones with propargyl alcohols using ruthenium catalyst. This reaction occurs *via* nucleophilic attack of enolate carbon on the electrophilic carbon in allenylidene intermediate. When unsymmetrical ketone (**33**) was used excellent regioselectivity was observed and the propargylation occurred at the more substituted α-carbon. But the main drawback of this method is use of excess of ketone (36 mL per 0.6 mmol of **34**).[20a] The first report on

asymmetric propargylic substitution with ketones was disclosed by the same group. Using a new type of ligand in which the phenyl ring makes π-π interactions with ruthenium allenylidene complex to achieve good asymmetric induction (Scheme 12).[20b]



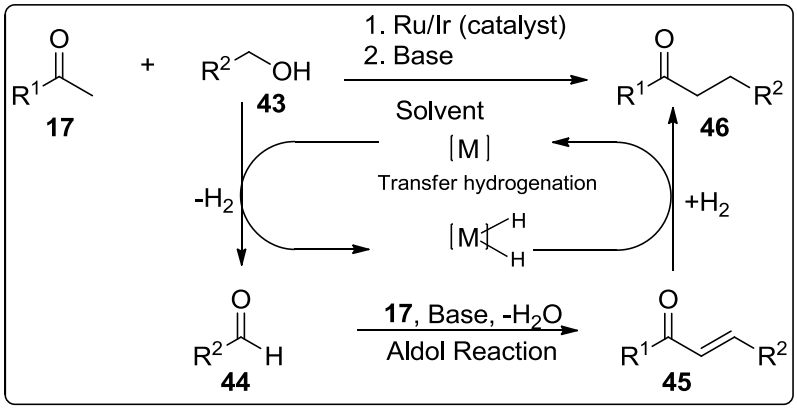
Scheme 12. Propargylation of ketones using ruthenium complex

A direct allylation of enol acetates (**40**) using alcohols (**41**) catalyzed by $InI_3/GaBr_3/FeBr_3$ was achieved by Baba and co-workers. α-Alkylation of enol acetates derived from ketones and aldehyde was carried out successfully by this method. Variety of alcohols like benzyl, allyl and propargyl alcohols could be used to get the respective alkylated products in good yield. They proposed that these Lewis acids are weakly coordinated to oxygen atoms of alcohol and also carbonyl moieties. Thus the alcohol turns into carbocation and subsequent attack of enol acetate affords the product. They found that all the Lewis acids used have almost similar reactivity (Scheme 13).[21] Although the authors claimed that it is direct method, the enol acetates have to be prepared separately prior to the reaction, this is an additional step.



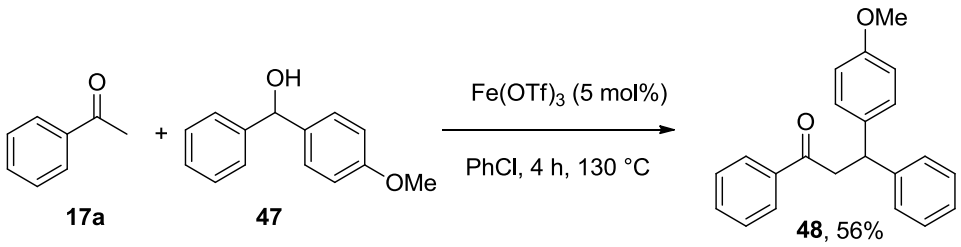
Scheme 13. Alkylation of enolacetates with In, Fe and Ga catalysts

In recent times, research activity in finding better strategy for direct α-alkylation of ketones is intense. One such finding is the transition metal catalyzed transfer hydrogenation reaction using primary alcohols.[22] These reactions involve metal-mediated abstraction of hydrogen from primary alcohol (**43**) to give the corresponding aldehyde (**44**) followed by aldol type reaction with ketone (**17**) in the presence of base to give enone (**45**). Finally hydrogenation of enone (transfer hydrogenation) influenced by the same metal catalyst gives the product of α-alkylation (**46**) (Scheme 14). But this method suffers from following drawbacks. i. This is limited to primary alcohols. ii. In some cases, products are further reduced to alcohols. iii. Stoichiometric amount of base is needed. iv. High temperatures are required.



Scheme 14. Mechanism of transfer hydrogenation

Recently decarboxylative and deaminative alkylation of amino acids with ketones under the influence of catalytic cationic ruthenium hydride complex in toluene under reflux was reported by Kalutharage *et al.*[23] Very recently, Gu and co-workers reported $Fe(OTf)_3$-catalyzed direct alkylation of aryl methyl ketones (**17**) with benzhydrols (**47**) in chlorobenzene at 130 ˚C (Scheme 15). However this reaction is limited to benzhydrols which contain methoxy group ('+M' group) on one of the phenyl ring of benzhydrol, because the carbocation generated is stabilized by the '+M' group present on phenyl ring of benzhydrol. Further, three to four equivalents of ketone is necessary for this transformation.[24]



Scheme 15. Alkylation of benzhydrols using $Fe(OTf)_3$

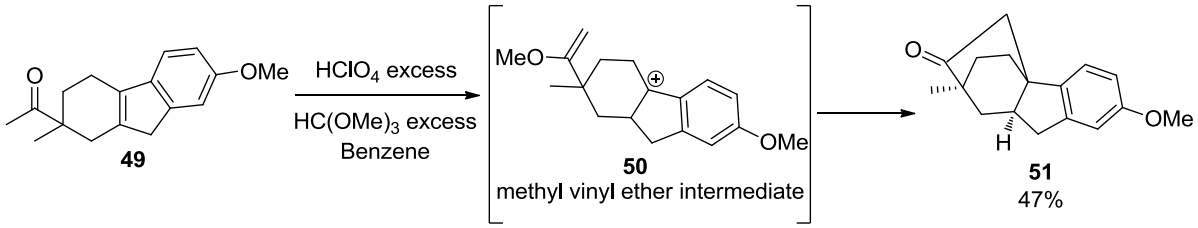
Very recent reports for α-alkylation of ketones are i. catalyst free dehydrogenative autocatalyzed alkylation of methyl ketone and alcohol with NaOH at 110 ˚C[25a] ii. Rhodium-catalyzed methylation of ketones using methanol which involves hydrogen barrowing mechanism.[25b]

1.4 Results and Discussion

Background

From the literature described in the above section, it is clear that the direct α-alkylation of ketones using alcohols is not a simple and straightforward task. Since the direct alkylation eliminates the generation of metal salt based by-products there is good scope for it to find application in industries. In this regard we envisaged that such alkylations using alcohols could be possible using in situ formed acetals under Lewis/Brønsted acid conditions. It is expected that the enol ether can form from acetal of ketones under the influence of Lewis/Brønsted acid. This enol ether is expected to undergo alkylation with the carbocationic center generated from alcohol under the reaction condition.

Ghatak and co-workers have reported an intramolecular cyclization of methyl ketones on a double bond. It was proposed that the reaction occurred by the C-alkylation of enol ether generated by heating methyl ketone containing substrate **49** with excess of $HC(OMe)_3$ and $HClO_4$ (Scheme 16). This reaction, however, occurred only when the double bond is attached to *p*-methoxyphenyl group. Hence the proposed alkylation using in situ formed acetal of ketone with alcohol is a viable process under Lewis/Brønsted acid conditions.[26]

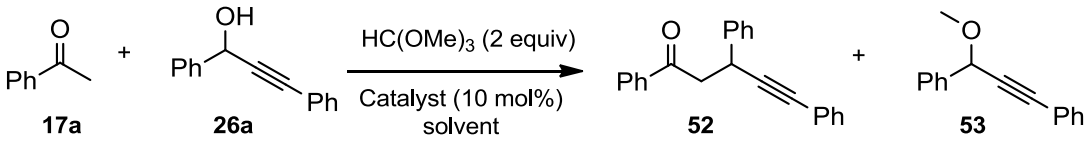


Scheme16. Intramolecular cyclization involving in situ formed acetal

In this regard, we developed a new TfOH/$HC(OMe)_3$ system for efficient α-alkylation of benzhydrols and cinnamyl alcohols in our laboratory.[27] When we applied this methodology for the α-propargylation of arylmethyl ketones, the reaction resulted in moderate yields only (Table 3, entries 1 and 2). This might be due to the instability of the product under the strong acidic conditions. So, to increase the yields and make our methodology (α-alkylation of ketones) catalytic, we considered using Lewis acids that can activate propargyl alcohol by its oxo and alkynophilicity at the same time.

Taking **17a**, **26a** as model substrates we screened different catalysts to find the most appropriate one. The reaction was first attempted with more oxophilic $AlCl_3$ to note no alkylation reaction (Table 2, entry 1). Similarly no product was obtained when the reaction was carried out with catalysts such as CuCl, $Cu(OTf)_2$, AgCl, $AgNO_3$ and $Au(PPh_3)Cl$. With $Yb(OTf)_3$, corresponding methyl ether of the propargyl alcohol (**53**) was formed as the product. It was obtained in 88% isolated yield. $InCl_3$ and $PtCl_4$ also showed similar result and the formed methyl ether, remained as such even after 24 h. Positive result was observed when $AuCl_3$ was used as catalyst and the desired product (**52**) was obtained in 44% yield. Reactions involving $Sn(OTf)_2$ and $FeCl_3$ catalysts resulted in 52% and 50% yields of **52** respectively. It was the silver catalysts with large counter anions gave good yields than other catalysts. Under the reaction conditions, $AgBF_4$ gave 59% yield. AgOTf and $AgSbF_6$ are equally effective and gave nearly the same yields. Among these two, $AgSbF_6$ was slightly better.

Table 2. Optimization studies:



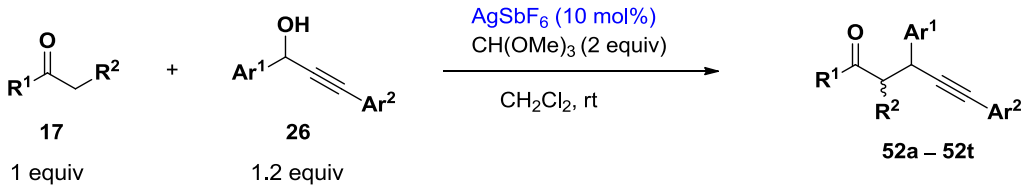
Entry	Catalyst	Solvent	% Yield[a] 52	53
1	Anhyd $AlCl_3$	CH_2Cl_2	nr	
2.	CuCl	CH_2Cl_2	nr	
3.	$Cu(OTf)_2$	CH_2Cl_2	nr	
4.	AgCl	CH_2Cl_2	nr	
5	$AgNO_3$	CH_2Cl_2	nr	
6	$Au(PPh_3)Cl$	CH_2Cl_2	nr	
7	$Yb(OTf)_3$	CH_2Cl_2		88
8	$InCl_3$	CH_2Cl_2		85[d]
9	$PtCl_4$	CH_2Cl_2		80[d]
10	$AuCl_3$	CH_2Cl_2	44	
11	$Sn(OTf)_2$	CH_2Cl_2	52	
12	$FeCl_3$	CH_2Cl_2	50	
13	$AgBF_4$	CH_2Cl_2	59	
14	AgOTf	CH_2Cl_2	68	
15	**$AgSbF_6$**	**CH_2Cl_2**	**70**	
16	AgOTf (2 mol%)[b]	CH_2Cl_2	27	
17	AgOTf (2 mol%)[c]	CH_2Cl_2	29	
18	AgOTf (5 mol%)[c]	CH_2Cl_2	37	
19	AgOTf (5 mol%)	CH_2Cl_2	58	
20	$AgSbF_6$	DCE	43	

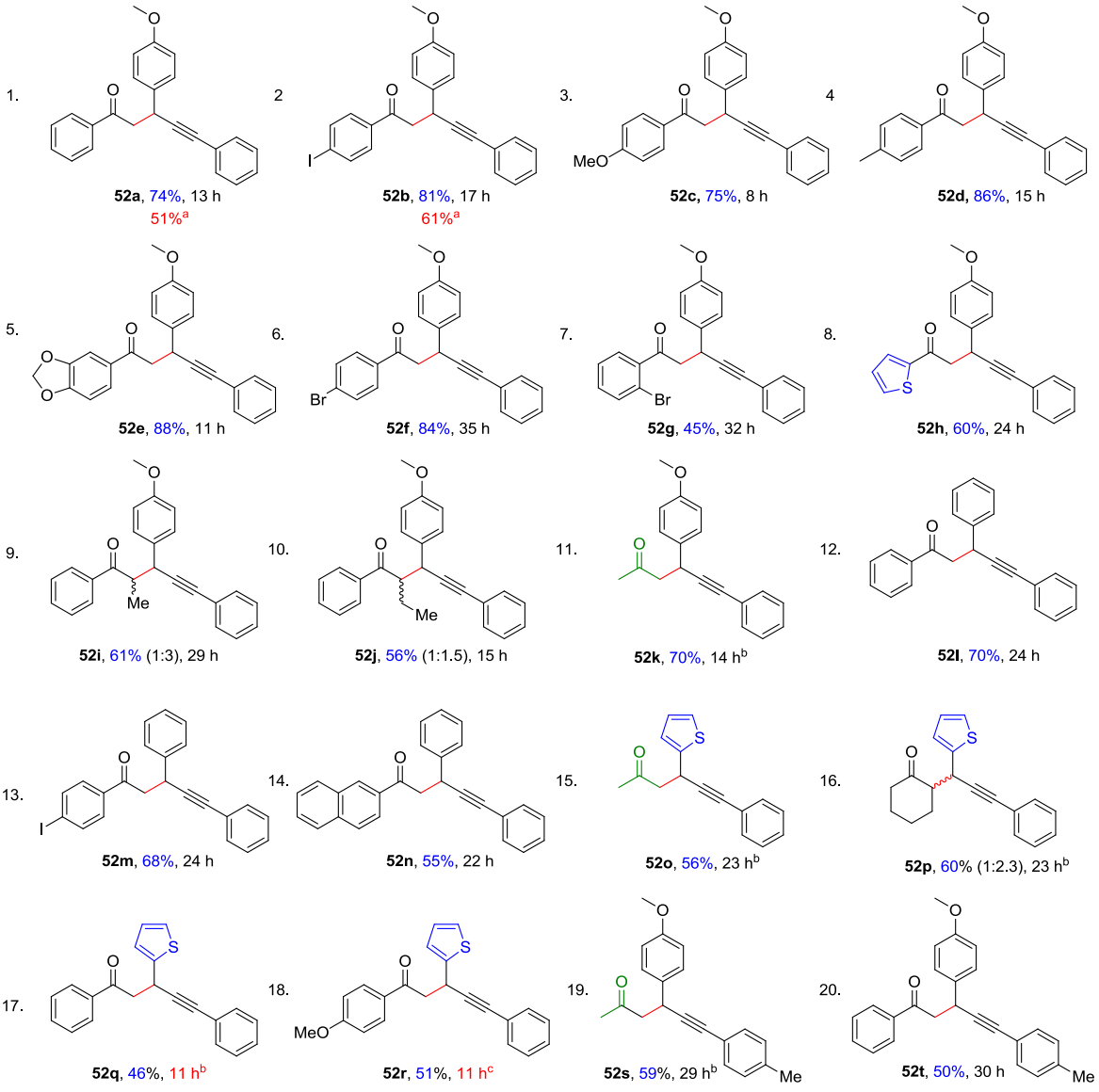
Entry	Catalyst	Solvent	% Yield[a]	
			52	**53**
21	$AgSbF_6$	$CHCl_3$	54	
22	$AgSbF_6$	DMF	nr	
23	$AgSbF_6$	THF	-	40[d]
24	$AgSbF_6$	Toluene	-	70[d]

In all experiments except 16-19, 1:1:2 equiv of **17a**, **26a** and $HC(OMe)_3$ were used, [a]isolated yields, [b]1:1:1 equiv ratio of **17a**, **26a** and $HC(OMe)_3$, [c]1:1:1.2 equiv of **17a**, **26a** and $HC(OMe)_3$, [d]NMR conversion with respect to **26a**. nr–no reaction.

When **17a**, **26a** and $HC(OMe)_3$ taken in 1:1:1 equivalents respectively, were treated with 2 mol% AgOTf only 27% of the product **52** was isolated (Table 2, entry 16). When the amount of $HC(OMe)_3$ was increased to 1.2 equivalents 29% yield of the product was observed (Table 2, entry 17). When the amount of AgOTf was increased to 5 mol% the yield increased to 37% (Table 2, entry 18). With two equivalents of $HC(OMe)_3$ it further increased to 58% (Table 2, entry 19). Finally 10 mol% of AgOTf was used and the reaction resulted in 68% yield of the product (Table 2, entry 14). Since $AgSbF_6$ was found to be better, further optimizations were done using it in different solvents. Out of solvents screened, chlorinated solvents were found to be better than other solvents. 54% and 43% yields were noticed in $CHCl_3$ and DCE respectively. DMF, THF and toluene solvents did not result the desired product. Hence the condition in entry 15 of Table 2 was used to study the substrate scope as the best yield was obtained using it. Under this condition different ketones were reacted with different diarylpropargyl alcohols and the results are presented in Table 3.

Table 3. Results of $AgSbF_6$-catalyzed α-alkylation of ketones using propargyl alcohols





[a]1 equiv of TfOH in CCl_4, rt, 24 h, [b]2 equiv of ketone was used, [c]refluxed, value in parenthesis indicates diastereomeric ratio based on ^{1}H NMR

The nature of substituents (electron donating and electron withdrawing) on the phenyl ring of acetophenone does not have much influence on the yields of the products. The highest yield

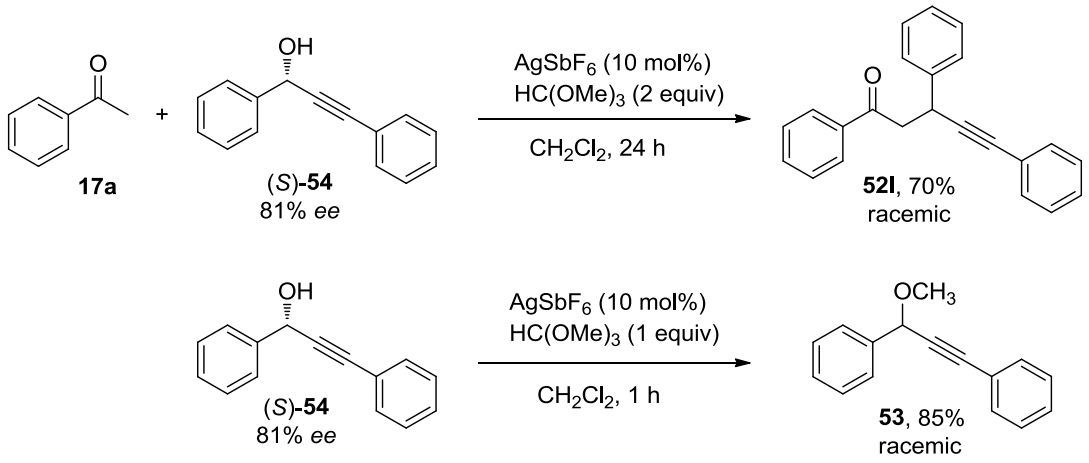
88% was achieved when methylenedioxyacetophenone was reacted with 1-(4-methoxyphenyl)-3-phenylprop-2-yn-1-ol. A drastic decrease in the yield of the product was observed in the reaction of *o*-bromoacetophenone compared that of its *p*-analogue (Table 3, entries 6 and 7). Interestingly, acetylthiophene reacted smoothly to furnish 60% yield (Table 3, entry 8). Propiophenone and butyrophenone resulted in diastereomeric mixtures (Table 3, entries 9 and 10) as expected. It is special to mention that aliphatic ketones such as acetone and cyclohexanone reacted nicely to result the mono alkylated products (Table 3, entries 11, 15, 16 and 19). In these cases we found that two equivalents of ketone were necessary for obtaining better yields. Simple diphenylpropargyl alcohol gave lower yields when compared to propargyl alcohol having electron donating methoxy substituent on one of the phenyl rings (Table 3, entries 1 and 12; 2 and 13).

Owing the importance of thiophene moiety in drugs we incorporated thiophene as one of the substituent in propargyl alcohols. To our delight the reaction worked without any problem (Table 3, entries 15-18). Substituents like CF_3/fluoro on one of the phenyl ring of propargyl alcohols failed to deliver the expected products. With these propargyl alcohols, the required benzylic carbocation may not form, because of the destabilizing effect of the electron withdrawing groups. In none of the reactions, possible allene product was not obtained. Terminal and aliphatic propargyl alcohols did not work under the reaction conditions to result the α-alkylated products.

In the $AgSbF_6$-catalyzed α-alkylation reactions using propargyl alcohols, corresponding methyl ether of the propargyl alcohol is formed first which was consumed during the course of the reaction in forming the α-alkylated products. This might be the reason for the better yields obtained with 2 equivalents of $HC(OMe)_3$ during the optimization studies.

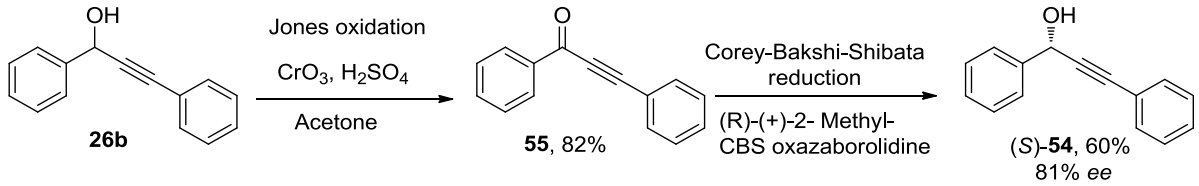
To evaluate the mechanism of the α-propargylation reaction (whether S_N1 or S_N2) we did an $AgSbF_6$-catalyzed α-alkylation reaction using enantioenriched propargyl alcohol (*S*)-**54** with acetophenone (Scheme 17). However this reaction resulted in racemic **52l**. Since the reaction takes place *via* methyl ether formation, the racemization can take place either during the methyl ether formation or in the alkylation step involving methyl ether. When (*S*)-**54** was treated with $HC(OMe)_3$ in the presence of $AgSbF_6$ catalyst, it resulted in the racemized

methyl ether **53**. Hence it is believed that methyl ether formation takes place *via* propargylic cation.



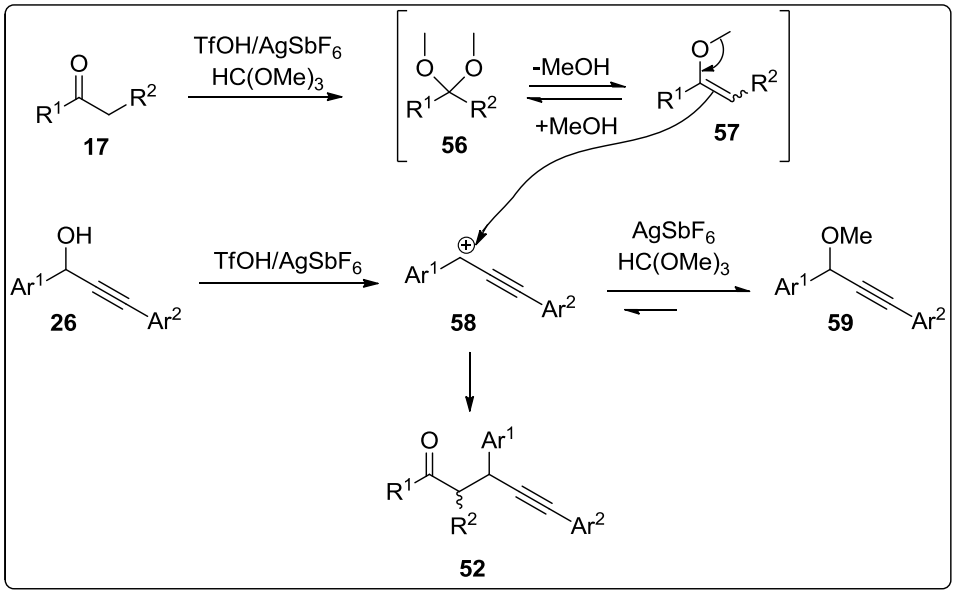
Scheme 17. Experiments using enantioenriched propargyl alcohols

The propargyl alcohol (*S*)-54 required for the above study was obtained from **55** by CBS (Corey-Bakshi-Shibata) reduction with 81% *ee* (Scheme 18).



Scheme 18. Synthesis of enantioenriched propargyl alcohols

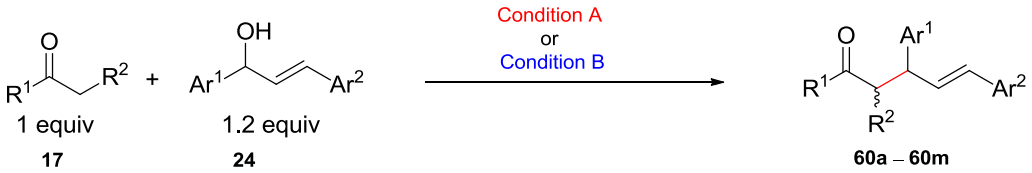
Based on the experiments using enantioenriched propargyl alcohol (Scheme 17), a plausible mechanism as shown in Scheme 19 can be visualized to explain the direct propargylation. The in situ formed acetal (**56**) of ketone eliminates a molecule of MeOH to generate methyl enol ether[28] (**57**) which will be in equilibrium with the acetal. Under the influence of TfOH/$AgSbF_6$ the benzylic propargyl alcohol generates a carbocation (**58**) which is quenched by $HC(OMe)_3$ to form the methyl ether (**59**) and sets up an equilibrium in the presence of $AgSbF_6$. Alkylation of the enol ether (**57**) with the carbocation will result the product (**52**).

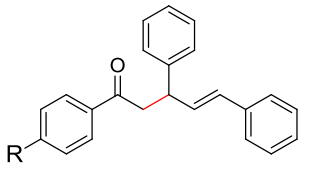


Scheme 19. Mechanism of direct α-propargylation of ketones

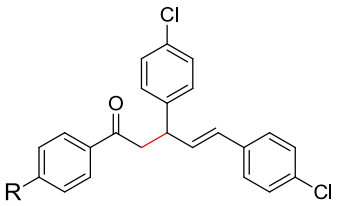
After demonstrating α-propargylation of ketones we shifted our focus on the allylation using cinnamyl alcohols[29] and we were pleased as the same optimized condition delivered the desired products in moderate yields as shown in Table 4. The α-allylation of ketones was carried out using stoichiometric amount of TfOH as well. The TfOH-promoted reactions took less time and resulted in excellent yields of the α-allylated products whereas $AgSbF_6$-catalyzed reactions resulted in moderate yields and required more time. Hence TfOH was found to be superior to $AgSbF_6$ in allylation of ketones which is in contrast to the propargylation of ketones. When strong electron withdrawing nitro group containing acetophenone was subjected to the reaction condition (Table 4, entry 4), 76% and 41% of yields were isolated with TFOH and $AgSbF_6$ respectively. The superiority of TfOH for allylation was realized in all the examples studied. It is worth mentioning that on reaction of acetone with cinnamyl alcohol (**24b**) resulted in 56% yield of α-allylated product with catalytic $AgSbF_6$ (Table 4, entry 13), whereas the same reaction using TfOH resulted in only trace amount of product. This reaction resembles Tsuji-Trost reaction (nucleophilic substitution of allyl alcohols).[30]

Table 4. Substrate scope for α-allylation of ketones

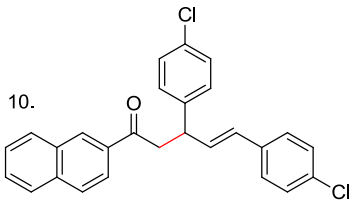




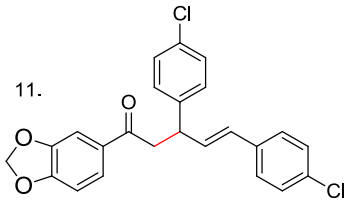
	TfOH	$AgSbF_6$
1. **60a**, R = H =	90%	52%
2. **60b**, R = Me =	92%	63%
3. **60c**, R = Cl =	83%	59%
4. **60d**, R = NO_2 =	76%	41%
5. **60e**, R = I =	88%	60%



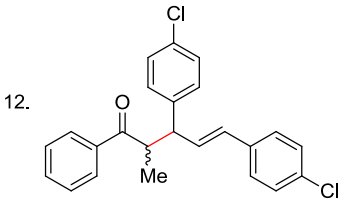
	TfOH	$AgSbF_6$
6. **60f**, R = H =	80%	56%
7. **60g**, R = I =	86%	61%
8. **60h**, R = Cl =	87%	54%
9. **60i**, R = Me =	82%	62%



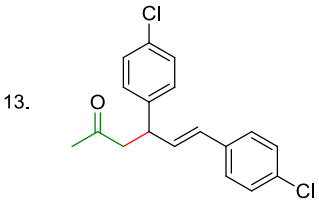
	TfOH	$AgSbF_6$
60j,	78%	42%



	TfOH	$AgSbF_6$
60k,	90%	46%



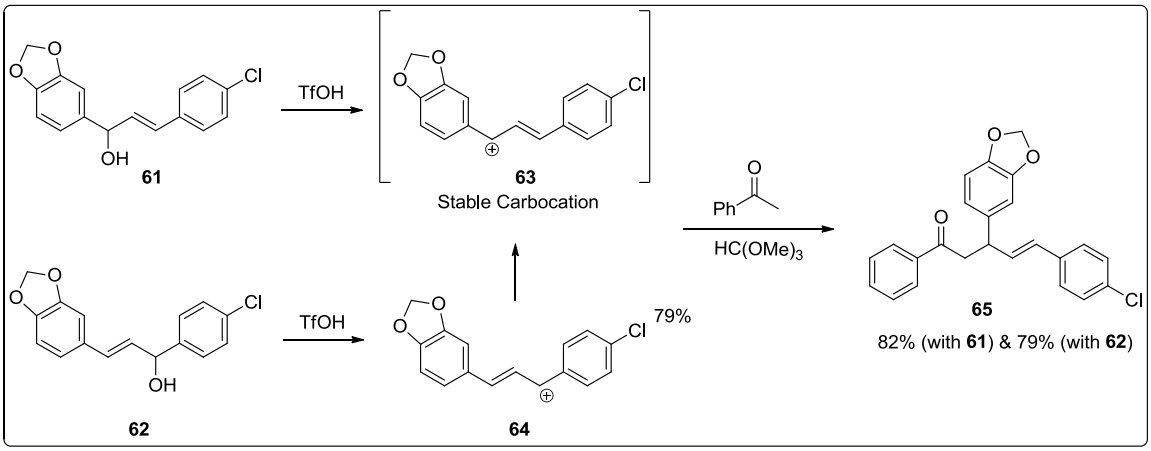
	TfOH	$AgSbF_6$
60l,	90%	63% (1:1.1)



	TfOH	$AgSbF_6$
60m,	trace	56%

Condition A: TfOH (1 equiv), $HC(OMe)_3$ (1 equiv), CCl_4, rt, 3 h. Condition B: $AgSbF_6$ (10 mol%), $HC(OMe)_3$ (2 equiv), CH_2Cl_2, rt, 24 h. value in parenthesis indicates diastereomeric ratio as determined from the ^1H NMR spectrum.

We then subjected unsymmetrical regioisomeric alcohols **61** and **62** to TfOH-promoted allylation separately to check the kind of intermediate involved. Surprisingly, both the substrates gave the same product **65** and the other regioisomer was not detected (Scheme 20). These experiments clearly indicate that the reaction takes place *via* a carbocation intermediate generated from cinnamyl alcohol derivative. The carbocation **64** generated from **62** first rearranges to the more stable carbocation **63** and then give the product **65**. Hence S_N1 mechanism operates in the α-allylation of ketones.

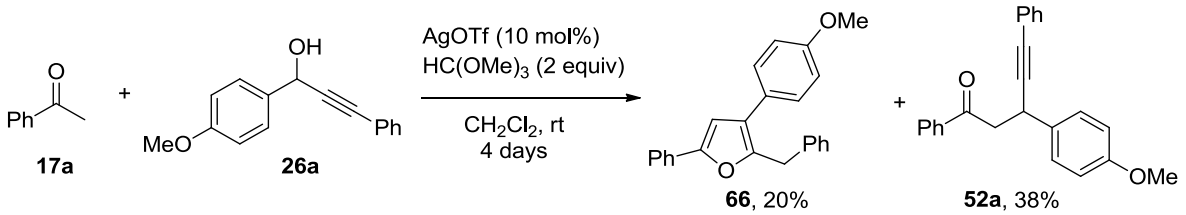


Scheme 20. Experimental proof for S_N1 type mechanism

1.5 Application of γ-alkynones:

γ–Alkynones are important starting materials for the synthesis of furan rings.[31] Furans rings are substructures of many natural products,[32] and found in drugs like ranitidine, furazolidinone, etc. Keeping the above application in mind we tried for a one pot furan formation starting from ketone and propargyl alcohol.

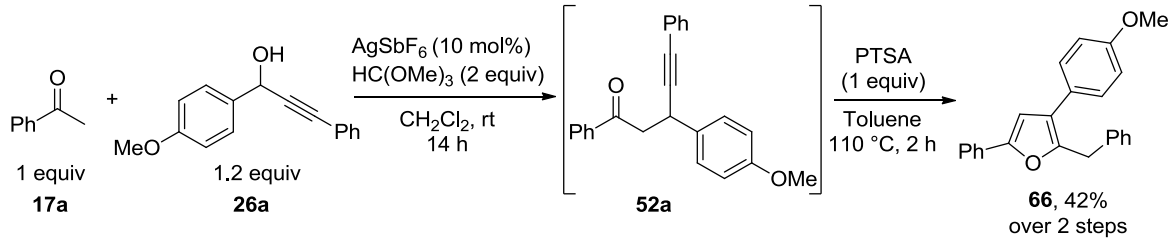
During our optimization of propargylation reaction we witnessed that the reaction using AgOTf under the optimized condition after stirring for 4 days resulted in 20% furan derivative (**66**) along with γ-alkynone product (**52a**) as shown in Scheme 21.



Scheme 21. Formation of substituted furan during α-propargylation of acetophenone

Based on this finding, several reactions were carried out to optimize the reaction condition. Keeping the substrates molar ratio constant, catalysts and solvents were changed. When we applied the reaction condition used in Scheme 21, in sealed tube at 60 ˚C for 18 h, disappointingly, the product was formed in 14% yield only. Under similar conditions in toluene at 120 ˚C it resulted in 21% yield. In another experiment with 10 mol% of AgOTf and 5 mol% of TfOH in toluene at 120 ˚C (sealed tube) 32% of furan product was obtained. We then used the optimized condition established by Zhan *et al.* for cyclization step after

alkylation.[33] After the formation of γ-alkynone (**52a**) under the condition presented in Table 3, the solvent was removed and toluene and PTSA (1 equiv) were added and the mixture was heated at 110 ˚C for 2 h to get the furan derivative (**66**). Although this reaction is better, it resulted in 42% yield of the product over two steps (Scheme 22).



Scheme 22. One pot synthesis of substituted furans

1.6 Conclusion:

We have developed a new catalytic method for the direct α-alkylation of ketones which do not need prefunctionization of ketones or alcohols involving additional steps. The role of trimethylorthoformate is crucial in the success of this methodology. The generality of the reaction is shown by employing alcohols like propargyl (benzylic) and allyl (cinnamyl) with a good range of ketones including aliphatic ones. The product of α-propargylation i.e., γ–alkynones are important as they can easily be transformed into substituted furans which have wide occurrence in natural products and drugs.

1.7 Experimental section

General information: All reagents were obtained commercially and used without further purification unless otherwise mentioned. TfOH and $AgSbF_6$ were purchased from Sigma-Aldrich chemical company and used without any further purification. Trimethyl orthoformate was distilled prior to use. HPLC grade CCl_4 procured from MERCK and dried CH_2Cl_2 (freshly distilled over CaH_2) was used as solvents for alkylation reactions. Thin-layer chromatography was performed by using Merck silica gel F_{254} coated aluminum plates and the visualization of spots were done using UV illumination and charring the TLC plates sprayed with Seebach solution. Column chromatography was performed on silica gel 100-200 mesh, using ethyl acetate and hexanes mixture as eluent. ^{1}H and ^{13}C NMR spectra of the synthesized compounds were recorded in Bruker Avance 400 NMR machine using their

solutions in $CDCl_3$. The ^1H NMR and ^{13}C NMR were referred respectively to TMS used as an internal standard and the central line of $CDCl_3$ peaks. IR spectra were recorded using JASCO FT/IR-5300 spectrometer. High resolution mass spectra (HRMS) were recorded using electro spray ionization in Bruker Maxis machine. Melting points were determined by using MR-VIS visual melting range apparatus and are uncorrected. The synthesis and data of alcohol electrophiles employed in this work are already reported in the literature.[34]

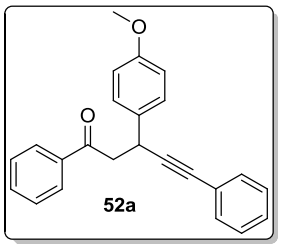
1.7.1 General procedure for $AgSbF_6$ catalyzed reactions:

Propargyl alcohol (**26**, 1.2 equiv) was weighed in a clean and dry round bottom flask, applied high vacuum and the vacuum was released in nitrogen atmosphere. Dichloromethane (3mL per 0.5 mmol of **17**), ketone (**17**, 1 equiv), trimethyl orthoformate (2 equiv) were added to it and stirred until it become a homogenous solution. Then $AgSbF_6$ (10 mol%) was added under nitrogen and the reaction mixture was stirred at room temperature under nitrogen atmosphere till the completion of the reaction. After completion of the reaction the solvent was evapourated and the crude product was directly loaded on silica gel column. Mixture of ethyl acetate and hexanes were used as eluents to get the pure products.

1.7.2 General procedure for TfOH promoted reactions:

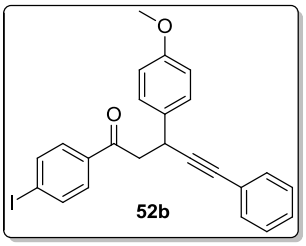
Cinnamyl alcohol (**24**, 1.2 equiv) was weighed in a clean and dry round bottom flask. CCl_4 (5ml per mmol of ketone), ketone (**17**, 1 equiv), trimethyl orthoformate (1 equiv) were added to it and stirred until all the substrates got dissolved. Then TfOH (1 equiv) was added and the reaction mixture was stirred at room temperature until completion of the reaction. After completion of the reaction the solvent was evapourated and the crude product was directly loaded on silica gel column. Mixture of ethyl acetate and hexanes were used as eluents to get the pure products.

3-(4-Methoxyphenyl)-1,5-diphenylpent-4-yn-1-one (52a):[34g]



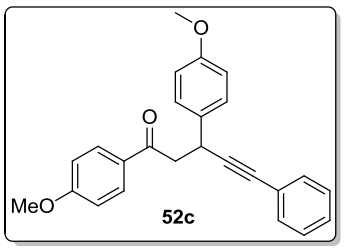
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.96-7.94 (m, 2H), 7.57-7.53 (m, 1H), 7.46-7.42 (m, 4H), 7.36-7.34 (m, 2H), 7.26-7.24 (m, 3H), 6.89-6.87 (m, 2H), 4.59 (t, *J* = 7.2 Hz, 1H), 3.78 (s, 3H), 3.63 (dd, *J* = 16.8 Hz, 7.2 Hz, 1H), 3.39 (dd, *J* = 16.8 Hz, 6.8 Hz, 1H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 197.4, 158.7, 136.9, 133.4, 133.3, 131.7, 128.7, 128.3, 128.2, 127.9, 123.5, 114.2, 91.2, 83.2, 55.4, 47.5, 33.0.

1-(4-Iodophenyl)-3-(4-methoxyphenyl)-5-phenylpent-4-yn-1-one (52b):



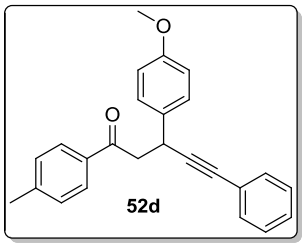
Yellow coloured solid, m.p. = 112-114 ˚C. **IR** (KBr, cm^{-1}): 2953, 1676, 1490, 1249, 1030, 761, 695. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.82-7.80 (m, 2H), 7.67-7.65 (m, 2H), 7.41 (d, *J* = 8.8 Hz, 2H), 7.35-7.33 (m, 2H), 7.27-7.26 (m, 3H), 6.88-6.86 (m, 2H), 4.57-4.54 (m, 1H), 3.79 (s, 3H), 3.55 (dd, *J* = 16.4 Hz, 7.6 Hz, 1H), 3.35 (dd, *J* = 16.4 Hz, 6.4 Hz, 1H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 196.8, 158.8, 138.1, 136.3, 133.2, 131.8, 129.8, 128.7, 128.3, 128.1, 123.5, 114.2, 101.4, 90.9, 83.5, 55.5, 47.4, 33.2. **HRMS** (ESI) Calculated for $C_{24}H_{19}IO_2$ $[M+H]^+$ 467.0508, found 467.0507.

1,3-Bis(4-methoxyphenyl)-5-phenylpent-4-yn-1-one (52c):



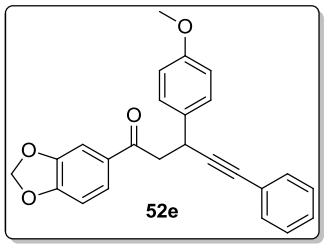
Light yellow coloured solid, m.p. = 102-104 ˚C. **IR** (KBr, cm^{-1}): 3061, 2957, 1676, 1510, 1253, 1032, 758, 692. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.95-7.93 (m, 2H), 7.42 (d, *J* = 8.4 Hz, 2H), 7.36-7.34 (m, 2H), 7.25-7.23 (m, 3H), 6.91-6.86 (m, 4H), 4.58 (t, *J* = 7.2 Hz, 1H), 3.83 (d, *J* = 0.8 Hz, 3H), 3.77 (d, *J* = 1.2 Hz, 3H), 3.57 (dd, *J* = 16.4 Hz, 7.6 Hz, 1H), 3.33 (dd, *J* = 16.4 Hz, 6.8 Hz, 1H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 195.8, 163.6, 158.6, 133.5, 131.7, 130.6, 130.1, 128.7, 128.2, 127.9, 123.5, 114.1, 113.8, 91.4, 83.1, 55.5, 55.4, 47.1, 33.1. **HRMS** (ESI) Calculated for $C_{25}H_{22}O_3$ $[M+H]^+$ 371.1647, found 371.1647.

3-(4-Methoxyphenyl)-5-phenyl-1-(p-tolyl)pent-4-yn-1-one (52d):



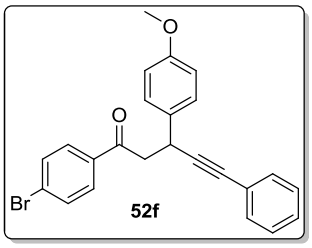
Thick colourless gummy liquid. **IR** (neat, cm^{-1}): 3059, 2957, 1682, 1510, 1249, 1035, 758, 692. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.85 (d, *J* = 8.4 Hz, 2H), 7.42 (dd, *J* = 6.8 Hz, 2.0 Hz, 2H), 7.36-7.34 (m, 2H), 7.25-7.21 (m, 5H), 6.87 (dd, *J* = 6.8 Hz, 2 Hz, 2H), 4.58 (t, *J* = 7.2 Hz, 1H), 3.76 (m, 3H), 3.59 (dd, *J* = 16.4 Hz, 7.6 Hz, 1H), 3.36 (dd, *J* = 16.4 Hz, 7.2 Hz, 1H), 2.37 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 196.9, 158.6, 144.1, 134.5, 133.5, 131.7, 129.4, 128.7, 128.4, 128.2, 127.9, 123.5, 114.1, 91.3, 83.1, 55.3, 47.3, 33.0, 21.7. **HRMS** (ESI) Calculated for $C_{25}H_{22}O_2$ $[M+H]^+$ 355.1698, found 355.1698.

1-(Benzo[d][1,3]dioxol-5-yl)-3-(4-methoxyphenyl)-5-phenylpent-4-yn-1-one (**52e**):



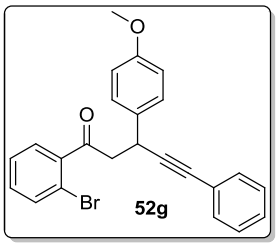
Light brown gel. **IR** (neat, cm^{-1}): 2966, 1678, 1510, 1251, 1037, 758, 692. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.53 (dd, *J* = 8.4 Hz, 2 Hz, 1H), 7.43-7.40 (m, 3H), 7.37-7.35 (m, 2H), 7.25-7.24 (m, 3H), 6.87 (dd, *J* = 6.8 Hz, 2 Hz, 2H), 6.80 (d, *J* = 8.4 Hz, 1H), 5.99 (s, 2H), 4.56 (t, *J* = 7.2 Hz, 1H), 3.77 (s, 3H), 3.53 (dd, *J* = 16.4 Hz, 7.6 Hz, 1H), 3.3 (dd, *J* = 16.4 Hz, 6.4 Hz, 1H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 195.4, 158.6, 151.9, 148.3, 133.4, 131.8, 131.7, 128.7, 128.2, 127.9, 124.6, 123.5, 114.1, 108.1, 107.9, 101.9, 91.3, 83.2, 55.4, 47.2, 33.2. **HRMS** (ESI) Calculated for $C_{25}H_{20}O_4$ $[M+H]^+$ 385.1440, found 385.1440.

1-(4-Bromophenyl)-3-(4-methoxyphenyl)-5-phenylpent-4-yn-1-one (52f):



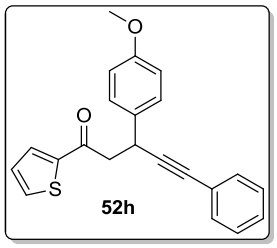
Yellow coloured solid, m.p. = 144-146 ˚C. **IR** (KBr, cm^{-1}): 3059, 2957, 1687, 1510, 1251, 1033, 758, 692. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.80 (d, *J* = 8.4 Hz, 2H), 7.57 (d, *J* = 8.4 Hz, 2H), 7.41 (d, *J* = 8.4 Hz, 2H), 7.35-7.33 (m, 2H), 7.26-7.24 (m, 3H), 6.87 (d, *J* = 8.8 Hz, 2H), 4.56 (t, *J* = 7.2 Hz, 1H), 3.78 (s, 3H), 3.57 (dd, *J* = 16.4 Hz, 8.0 Hz, 1H), 3.34 (dd, *J* = 16.8 Hz, 6.4 Hz, 1H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 196.4, 158.8, 135.7, 133.2, 132.0, 131.7, 129.8, 129.5, 128.7, 128.2, 128.0, 123.4, 114.2, 90.9, 83.4, 55.4, 47.4, 33.1. **HRMS** (ESI) Calculated for $C_{24}H_{19}BrO_2$ $[M+H]^+$ 419.0647, found 419.0647.

1-(2-Bromophenyl)-3-(4-methoxyphenyl)-5-phenylpent-4-yn-1-one (52g):



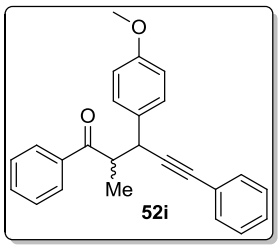
Light brown gummy liquid. **IR** (neat, cm^{-1}): 3055, 2984, 1699, 1512, 1265, 738, 704. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.58 (d, *J* = 7.6 Hz, 1H), 7.41-7.36 (m, 4H), 7.32 (d, *J* = 4.0 Hz, 2H), 7.28-7.25 (m, 4H), 6.88-6.86 (m, 2H), 4.52 (dd, *J* = 16.4Hz, 6.8Hz, 1H), 3.79 (s, 3H), 3.53 (dd, *J* = 16.4 Hz, 8.4 Hz, 1H), 3.39 (dd, *J* = 16.4 Hz, 6.4 Hz, 1H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 201.4, 158.7, 141.5, 133.6, 132.7, 131.7, 131.6, 128.9, 128.6, 128.2, 127.9, 127.4, 123.3, 118.7, 114.0, 90.5, 83.5, 55.3, 51.2, 33.4. **HRMS** (ESI) Calculated for $C_{24}H_{19}BrO_2$ $[M+H]^+$ 419.0647, found 419.0648.

3-(4-Methoxyphenyl)-5-phenyl-1-(thiophen-2-yl)pent-4-yn-1-one (52h):



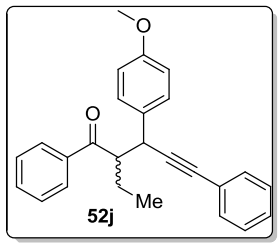
Brown coloured solid, m.p. = 99-101 ˚C. **IR** (KBr, cm^{-1}): 3078, 2957, 1662, 1512, 1249, 1033, 727, 692. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.69 (d, *J* = 3.6 Hz, 1H), 7.61 (d, *J* = 4.8 Hz, 1H), 7.42 (d, *J* = 8.4 Hz, 2H), 7.35-7.32 (m, 2H), 7.25-7.24 (m, 3H), 7.08 (t, *J* = 4.8 Hz, 1H), 6.87 (d, *J* = 8.4 Hz, 2H), 4.56 (t, *J* = 7.2 Hz, 1H), 3.77 (s, 3H), 3.51 (dd, *J* = 16 Hz, 8.0 Hz, 1H), 3.30 (dd, *J* = 16.0 Hz, 6.8 Hz, 1H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 190.2, 158.7, 144.4, 134.1, 133.1, 132.4, 131.7, 128.7, 128.2, 127.9, 123.4, 114.2, 90.8, 83.6, 55.4, 48.1, 33.4. **HRMS** (ESI) Calculated for $C_{22}H_{18}O_2S$ $[M+Na]^+$ 369.0925, found 369.0930.

3-(4-Methoxyphenyl)-2-methyl-1,5-diphenylpent-4-yn-1-one (52i):



Colourless gel. **IR** (neat, cm^{-1}): 3061, 2970, 1682, 1510, 1448, 1251, 1033, 758, 692. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.06 (d, *J* = 7.2 Hz, 0.7H), 7.79-7.77 (m, 2H), 7.57-7.50 (m, 0.4H), 7.50-7.43 (m, 4H), 7.39-7.33 (m, 5H), 7.29-7.28 (m, 3H), 7.18-7.12 (m, 1H), 7.09-7.07 (m, 0.7H), 6.91-6.88 (m, 0.7H), 6.79-6.75 (m, 2H), 4.35 (d, *J* = 8.8Hz, 1H), 4.11 (d, *J* = 9.6Hz, 0.3H), 3.94-3.85 (m, 1.45H), 3.80 (s, 1H), 3.71 (s, 3H), 1.45 (d, *J* = 6.8 Hz, 3H), 1.04 (d, *J* = 7.2 Hz, 1H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 203.3, 202.5, 158.9, 158.6, 137.4, 136.8, 133.2, 133.0, 132.6, 131.7, 131.6, 131.4, 129.7, 129.4, 129.3, 128.7, 128.6, 128.3, 128.2, 128.1, 128.0, 127.8, 123.6, 123.4, 114.1, 113.9, 91.0, 90.1, 84.7, 83.7, 55.4, 55.3, 48.2, 47.8, 40.8, 40.6, 16.6, 16.0. **HRMS** (ESI) Calculated for $C_{25}H_{22}O_2$ $[M+H]^+$ 355.1698, found 355.1698.

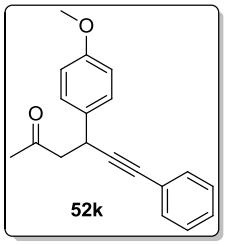
2-Ethylidene-3-(4-methoxyphenyl)-1,5-diphenylpent-4-yn-1-one (52j):



Colourless gel. **IR** (neat, cm^{-1}): 3059, 2964, 1678, 1510, 1251, 758, 692. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.08 (d, *J* = 7.2 Hz, 1H), 7.72 (d, *J* = 7.6 Hz, 2H), 7.59-7.56 (m, 0.67H), 7.51-7.48 (m, 1H), 7.47-7.43 (m, 3H), 7.36-7.28 (m, 8H), 7.17-7.10 (m, 1.8H), 6.98-6.97 (m, 1.2H), 6.90-6.88 (m, 1H), 6.74-6.72 (m, 2H), 4.29 (d, *J* = 9.6 Hz, 1H), 4.06 (d, *J* = 9.6 Hz, 0.6H), 3.87-3.84 (m, 1.7H), 3.80 (s, 2H), 3.69 (s, 3H), 2.10-2.08 (m, 2H), 1.74-1.67 (m, 0.6H), 1.46-1.40 (m, 0.7H), 0.88 (t, *J* = 7.2 Hz, 3H), 0.74 (t, *J* = 7.2 Hz,

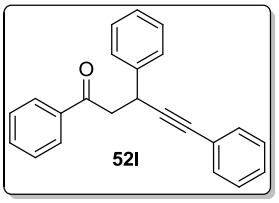
1.8H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 203.8, 202.8, 158.9, 158.5, 139.0, 138.3, 133.1, 132.9, 132.4, 131.7, 131.5, 129.6, 129.4, 128.7, 128.6, 128.5, 128.3, 128.1, 128.0, 127.8, 123.7, 123.4, 114.1, 113.9, 90.8, 90.5, 84.5, 83.9, 55.4, 55.3, 54.6, 54.5, 40.6, 39.9, 25.1, 24.3, 11.9, 11.5. **HRMS** (ESI) Calculated for $C_{26}H_{24}O_2$ $[M+H]^+$ 369.1855, found 369.1854.

4-(4-Methoxyphenyl)-6-phenylhex-5-yn-2-one (52k):



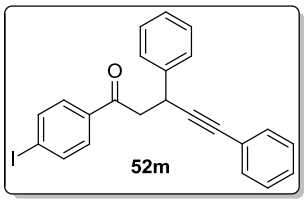
Colourless liquid. **IR** (neat, cm^{-1}): 3059, 2957, 1716, 1512, 1251, 1032, 758, 692. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.42-7.38 (m, 2H), 7.37-7.34 (m, 2H), 7.28-7.25 (m, 3H), 6.88-6.86 (m, 2H), 4.36 (t, *J* = 7.2 Hz, 1H), 3.79 (s, 3H), 3.04 (dd, *J* = 16.4 Hz, 8.0 Hz, 1H), 2.87 (dd, *J* = 16.4 Hz, 6.4 Hz, 1H), 2.16 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 206.2, 158.7, 133.1, 131.7, 128.6, 128.3, 128.1, 123.5, 114.2, 90.8, 83.2, 55.4, 52.1, 32.8, 30.8. **HRMS** (ESI) Calculated for $C_{19}H_{18}O_2$ $[M+H]^+$ 279.1385, found 279.1385.

1,3,5-Triphenylpent-4-yn-1-one (52l):[34f]



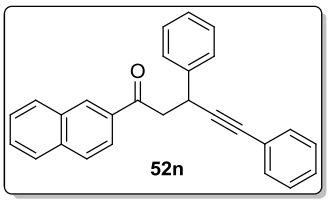
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.96 (d, *J* = 6.8 Hz, 2H), 7.56-7.53(m, 3H), 7.46-7.42 (m, 2H), 7.36-7.32 (m, 4H), 7.26-7.22 (m, 4H), 4.65 (dd, *J* = 7.6 Hz, 6.4Hz, 1H), 3.67 (dd, *J* = 16.4 Hz, 7.6 Hz, 1H), 3.41 (dd, *J* = 16.4 Hz, 6 Hz, 1H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 197.2, 141.3, 136.9, 133.3, 131.7, 128.8, 128.7, 128.3, 128.2, 127.9, 127.7, 127.2, 123.5, 90.8, 83.4, 47.4, 33.8.

1-(4-Iodophenyl)-3,5-diphenylpent-4-yn-1-one (52m):



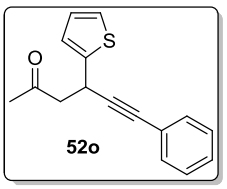
Light Brown coloured solid, m.p. = 106-108 ˚C. **IR** (KBr, cm^{-1}): 3059, 1670, 1512, 758, 692. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.81 (d, *J* = 8.4 Hz, 2H), 7.66 (d, *J* = 8.4 Hz, 2H), 7.50 (d, *J* = 7.2 Hz, 2H), 7.38-7.32 (m, 4H), 7.28-7.24 (m, 4H), 4.61 (dd, *J* = 7.6 Hz, 6.4Hz, 1H), 3.60 (dd, *J* = 16.4 Hz, 8.0 Hz, 1H), 3.35 (dd, *J* = 16.4 Hz, 6.4 Hz, 1H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 196.6, 141.1, 138.0, 136.2, 131.7, 129.7, 128.8, 128.3, 128.1, 127.7, 127.3, 123.3, 101.4, 90.6, 83.6, 47.2, 33.8. **HRMS** (ESI) Calculated for $C_{23}H_{17}IO$ $[M+H]^+$ 437.0402, found 437.0402.

1-(Naphthalen-2-yl)-3,5-diphenylpent-4-yn-1-one (52n):



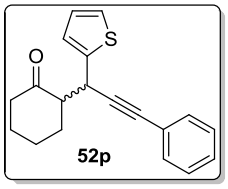
Light yellow coloured solid, m.p. = 110-112 ˚C. **IR** (KBr, cm^{-1}): 3057, 1671, 1594, 1030, 756, 695. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.44 (s, 1H), 8.02 (dd, *J* = 8.8 Hz, 1.2 Hz, 1H), 7.90 (d, *J* = 8.0 Hz, 1H), 7.86-7.82 (m, 2H), 7.58-7.55 (m, 3H), 7.51-7.49 (m, 1H), 7.37-7.34 (m, 4H), 7.27-7.25 (m, 1H), 7.24-7.20 (m, 3H), 4.73-4.69 (m, 1H), 3.79 (dd, *J* = 16.4 Hz, 8.0 Hz, 1H), 3.53 (dd, *J* = 16.4 Hz, 6.0Hz, 1H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 197.1, 141.4, 135.7, 134.2, 132.5, 131.7, 130.1, 129.6, 128.8, 128.6, 128.5, 128.2, 127.9, 127.8, 127.7, 127.2, 126.8, 123.9, 123.4, 90.9, 83.4, 47.4, 33.9. **HRMS** (ESI) Calculated for $C_{27}H_{20}O$ $[M+Na]^+$ 383.1412, found 383.1412.

6-Phenyl-4-(thiophen-2-yl)hex-5-yn-2-one (52o):



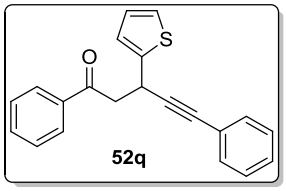
Brown cooured gummy liquid. **IR** (neat, cm^{-1}): 3062, 2920, 1714, 1495, 1358, 1067, 755, 689. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.44-7.42 (m, 2H), 7.30- 7.28 (m, 3H), 7.20-7.18 (m, 1H), 7.05-7.04 (m, 1H), 6.94 (dd, *J* = 5.2 Hz, 1.2 Hz, 1H), 4.71(t, *J* = 6.8 Hz, 1H), 3.13(dd, *J* = 16.8 Hz, 7.2 Hz, 1H), 3.01 (dd, *J* = 16.8 Hz, 6.8 Hz, 1H), 2.21 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 205.4, 144.4, 131.8, 128.4, 126.9, 124.9, 124.4, 123.1, 89.8, 83.1, 52.1, 30.7, 28.8. **HRMS** (ESI) Calculated for $C_{16}H_{14}OS$ $[M+Na]^+$ 277.0663, found 277.0661.

2-(3-Phenyl-1-(thiophen-2-yl)prop-2-yn-1-yl)cyclohexanone (52p):



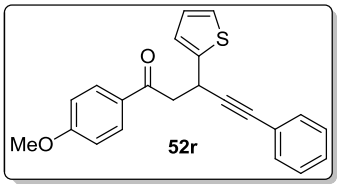
Colourless liquid, 30% single diastereomer, rest is mixture of diastereomers (1:2.3, 30%). **IR** (neat, cm^{-1}): 3057, 2936, 1709, 1484, 756, 695. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.47-7.45 (m, 2H), 7.31-7.29 (m, 3H), 7.19 (dd, *J* = 5.2 Hz, 0.8 Hz, 1H), 7.09-7.08 (m, 1H), 6.96 (dd, *J* = 5.2 Hz, 3.6 Hz, 1H), 4.91(d, *J* = 4.4 Hz, 1H), 2.73-2.71 (m, 1H), 2.53-2.49 (m, 1H), 2.36-2.29 (m, 2H), 2.08-2.07 (m, 1H), 1.97-1.94 (m, 1H), 1.89-1.87 (m, 1H), 1.74-1.63 (m, 2H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 209.7, 144.2, 131.8, 128.3, 128.1, 126.8, 125.5, 124.1, 123.4, 88.5, 84.6, 57.4, 42.2, 32.6, 29.8, 27.5, 25.0. **HRMS** (ESI) Calculated for $C_{19}H_{18}OS$ $[M+Na]^+$ 317.0976, found 317.0980.

1,5-Diphenyl-3-(thiophen-2-yl)pent-4-yn-1-one (52q):[34g]



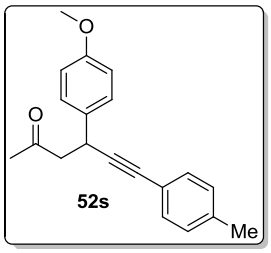
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.98-7.90 (m, 2H), 7.59-7.55 (m, 1H), 7.48-7.45 (m, 2H), 7.40-7.37 (m, 2H), 7.28-7.26 (m, 3H), 7.19 (dd, *J* = 4.8 Hz, 1.2 Hz, 1H), 7.12-7.09 (m, 1H), 6.94 (t, *J* = 4.4 Hz, 1H), 4.96 (t, *J* = 6.8 Hz, 1H), 3.70 (dd, *J* = 16.8 Hz, 7.2 Hz, 1H), 3.55 (dd, *J* = 16.8 Hz, 6.8 Hz, 1H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 196.7, 144.6, 136.7, 133.4, 131.7, 128.7, 128.3, 128.2, 128.1, 126.8, 124.9, 124.3, 123.1, 90.1, 82.9, 47.5, 28.9.

1-(4-Methoxyphenyl)-5-phenyl-3-(thiophen-2-yl)pent-4-yn-1-one (52r):



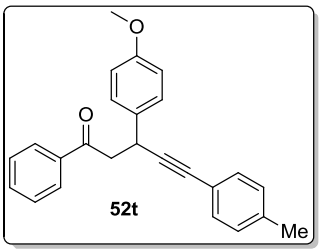
Light brown coloured liquid. **IR** (neat, cm^{-1}): 1676, 1490, 1265, 1057, 767, 706. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.96-7.94 (m, 2H), 7.39-7.37 (m, 2H), 7.26-7.24 (m, 3H), 7.16 (dd, *J* = 5.2 Hz, 1.2 Hz, 1H), 7.09-7.08 (m, 1H), 6.93-6.88 (m, 3H), 4.94 (t, *J* = 6.8 Hz, 1H), 3.82 (s, 3H), 3.63 (dd, *J* = 16.8 Hz, 6.8 Hz, 1H), 3.48 (dd, *J* = 16.8 Hz, 6.8 Hz, 1H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 195.2, 163.7, 144.8, 131.7, 130.6, 129.8, 128.2, 128.1, 126.8, 126, 124.9, 124.3, 123.2, 113.8, 90.4, 82.9, 55.5, 47.1. **HRMS** (ESI) Calculated for $C_{22}H_{18}O_2S$ $[M+Na]^+$ 369.0925, found 369.0945.

4-(4-Methoxyphenyl)-6-(p-tolyl)hex-5-yn-2-one (52s):



Colourless liquid. IR (neat, cm^{-1}): 2997, 1720, 1512, 1249, 756. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.36 (d, *J* = 8.8 Hz, 2H), 7.30 (d, *J* = 8.0 Hz, 2H), 7.09 (d, *J* = 8.0 Hz, 2H), 6.87 (d, *J* = 8.8 Hz, 2H), 4.34 (t, *J* = 7.2 Hz, 1H), 3.79 (s, 3H), 3.03 (dd, *J* = 16.4 Hz, 8 Hz, 1H), 2.86 (dd, *J* = 16.4 Hz, 6.8 Hz, 1H), 2.33 (s, 3H), 2.16 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 206.2, 158.7, 138.1, 133.2, 131.6, 129.1, 128.6, 120.4, 114.2, 90, 83.3, 55.4, 52.2, 32.9, 30.8, 21.6. **HRMS** (ESI) Calculated for $C_{20}H_{20}O_2$ $[M+Na]^+$ 315.1361, found 315.1362.

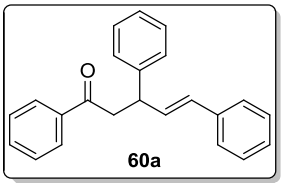
3-(4-Methoxyphenyl)-1-phenyl-5-(p-tolyl)pent-4-yn-1-one (52t):



Light yellow coloured solid, m.p. = 90-92 ˚C. **IR** (KBr, cm^{-1}): 2832, 1687, 1517, 1260, 761, 684. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.95 (d, *J* = 7.6 Hz, 2H), 7.55 (t, *J* = 7.2 Hz, 1H), 7.46-7.42 (m,

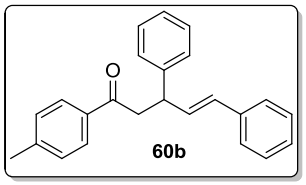
4H), 7.24 (d, *J* = 7.6 Hz, 2H), 7.05 (d, *J* = 8.0 Hz, 2H), 6.87 (d, *J* = 7.6 Hz, 2H), 4.58 (t, *J* = 7.2 Hz, 1H), 3.78 (s, 3H), 3.62 (dd, *J* = 16.4 Hz, 7.6 Hz, 1H), 3.38 (dd, *J* = 16.4 Hz, 6.4 Hz, 1H), 2.31 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 197.5, 158.7, 137.9, 137.1, 133.6, 133.3, 131.6, 129.0, 128.7, 128.7, 128.4, 120.5, 114.2, 90.4, 83.3, 55.4, 47.6, 33.1, 21.5. **HRMS** (ESI) Calculated for $C_{25}H_{22}O_2$ $[M+H]^+$ 355.1698 found 355.1698.

(*E*)-1,3,5-Triphenylpent-4-en-1-one (60a):[29a]



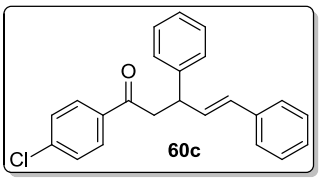
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.93 (d, *J* = 7.2 Hz, 2H), 7.53 (t, *J* = 7.6 Hz, 1H), 7.43 (t, *J* = 7.6 Hz, 2H), 7.32-7.18 (m, 10H), 6.40-6.39 (m, 2H), 4.33-4.28 (m, 1H), 3.54-3.47 (m, 2H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 198.3, 143.4, 137.3, 137.2, 133.2, 132.7, 130.2, 128.8, 128.7, 128.6, 128.2, 127.9, 127.4, 126.7, 126.4, 44.6, 44.1.

(*E*)-3,5-Diphenyl-1-(p-tolyl)pent-4-en-1-one (60b):



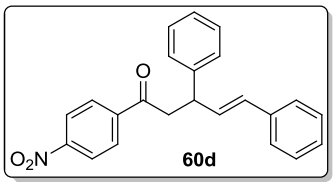
Yellow coloured gummy liquid. **IR** (neat, cm^{-1}): 3028, 1682, 1493, 1450, 1180, 966, 698. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.84 (d, *J* = 8.4 Hz, 2H), 7.30-7.26 (m, 6H), 7.24-7.17 (m, 5H), 7.16-7.14 (m, 1H), 6.44-6.35 (m, 2H), 4.32-4.27 (m, 1H), 3.51-3.40 (m, 2H), 2.38 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 197.8, 143.9, 143.5, 137.3, 134.7, 132.8, 130.1, 129.4, 128.8, 128.5, 128.3, 127.9, 127.3, 126.7, 126.3, 44.4, 44.1, 21.7. **HRMS** (ESI) Calculated for $C_{24}H_{22}O$ $[M+H]^+$ 327.1749, found 327.1749.

(*E*)-1-(4-Chlorophenyl)-3,5-diphenylpent-4-en-1-one (60c):



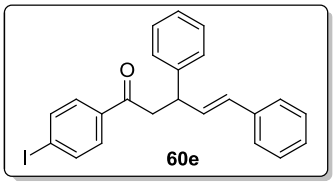
Yellow coloured gummy liquid. **IR** (neat, cm^{-1}): 3026, 1685, 1493, 1452, 1240, 1091, 696. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.88-7.86 (m, 2H), 7.42-7.40 (m, 2H), 7.32-7.29 (m, 6H), 7.26-7.24 (m, 3H), 7.23-7.18 (m, 1H), 6.39-6.38 (m, 2H), 4.30-4.25 (m, 1H), 3.51-3.40 (m, 2H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 197.1, 143.2, 139.6, 137.2, 135.5, 132.4, 130.3, 129.6, 129.1, 128.8, 128.6, 127.8, 127.4, 126.8, 126.4, 44.6, 44.1. **HRMS** (ESI) Calculated for $C_{23}H_{19}OCl$ $[M+Na]^+$ 369.1022, found 369.1022.

(*E*)-1-(4-Nitrophenyl)-3,5-diphenylpent-4-en-1-one (60d):



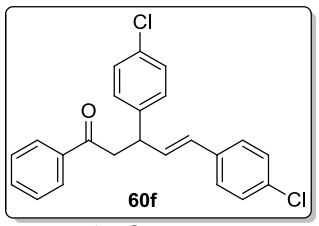
Yellow coloured solid, mp 97-100 ˚C. **IR** (KBr, cm^{-1}): 3024, 1680, 1493, 1448, 744, 694. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.25 (d, *J* = 8.8 Hz, 2H), 8.03 (d, *J* = 8.8 Hz, 2H), 7.36-7.29 (m, 6H), 7.25-7.19 (m, 3H), 7.18-7.16 (m, 1H), 6.40-6.35 (m, 2H), 4.30-4.25 (m, 1H), 3.53-3.52 (m, 2H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 196.9, 150.4, 142.8, 141.6, 137.0, 132.0, 130.5, 129.2, 128.9, 128.6, 127.8, 127.6, 127.0, 126.3, 123.9, 45.2, 44.1. **HRMS** (ESI) Calculated for $C_{23}H_{19}NO_3$ $[M+H]^+$ 358.1443, found 358.1445.

(*E*)-1-(4-Iodophenyl)-3,5-diphenylpent-4-en-1-one (60e):



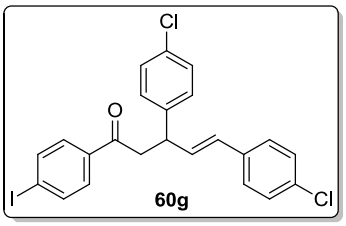
Pale yellow coloured solid, mp 101-104 ˚C. **IR** (KBr, cm^{-1}): 3026, 1687, 1493, 1450, 1392, 698. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.89-7.72 (m, 2H), 7.62-7.57 (m, 2H), 7.34-7.15 (m, 10H), 6.43-6.33 (m, 2H), 4.27-4.25 (m, 1H), 3.44-3.41 (m, 2H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 197.5, 143.2, 138.0, 137.2, 136.4, 132.4, 130.3, 129.6, 128.8, 128.6, 127.8, 127.4, 126.8, 126.3, 101.2, 44.5, 44.1. **HRMS** (ESI) Calculated for $C_{23}H_{19}IO$ $[M+H]^+$ 439.0559, found 439.0559.

(*E*)-3,5-Bis(4-chlorophenyl)-1-phenylpent-4-en-1-one (60f):



Light yellow coloured gummy liquid. **IR** (KBr, cm^{-1}): 3042, 1685, 1491, 1448, 1406, 1091, 690. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.94-7.92 (m, 2H), 7.57-7.55 (m, 1H), 7.46-7.44 (m, 2H), 7.29-7.28 (m, 2H), 7.25-7.25 (m, 2H), 7.23-7.22 (m, 4H), 6.37-6.30 (m, 2H), 4.30-4.26 (m, 1H), 3.52-3.42 (m, 2H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 197.8, 141.6, 137.1, 135.6, 133.4, 133.2, 132.9, 132.6, 129.4, 129.3, 128.9, 128.8, 128.7, 128.2, 127.6, 44.3, 43.3. **HRMS** (ESI) Calculated for $C_{23}H_{18}Cl_2O$ $[M+Na]^+$ 403.0632, found 403.0640.

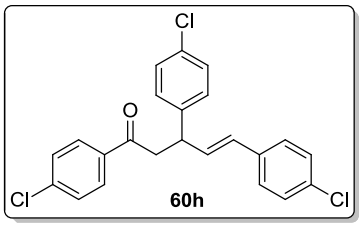
(*E*)-3,5-Bis(4-chlorophenyl)-1-(4-iodophenyl)pent-4-en-1-one (60g):



Yellow coloured solid, mp 117-119 ˚C. **IR** (KBr, cm^{-1}): 1678, 1489, 1392, 1089, 744, 694. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.77 (d, *J* = 8.0 Hz, 2H), 7.60 (d, *J* = 8.0 Hz, 2H), 7.27-7.18 (m, 8H), 6.31-6.30 (m, 2H), 4.25-4.21 (m, 1H), 3.41-3.38 (m, 2H).

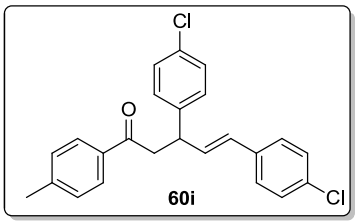
^{13}C NMR (100 MHz, $CDCl_3$): δ 196.9, 141.3, 138.0, 136.1, 135.4, 133.1, 132.6, 132.5, 129.5, 129.4, 129.2, 128.9, 128.7, 127.5, 101.4, 44.1, 43.2. **HRMS** (ESI) Calculated for $C_{23}H_{17}Cl_2IO$ $[M+H]^+$ 506.9774, found 506.9779.

(*E*)-1,3,5-Tris(4-chlorophenyl)pent-4-en-1-one (60h):



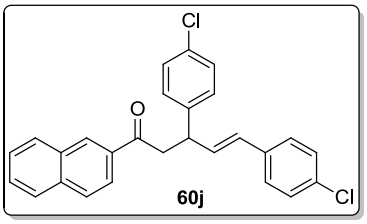
Yellow coloured gummy liquid. **IR** (neat, cm^{-1}): 3024, 1685, 1491, 1402, 1176, 1012, 825. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.88-7.86 (m, 2H), 7.44-7.42 (m, 2H), 7.31-7.30 (m, 2H), 7.25-7.24 (m, 6H), 6.35-6.34 (m, 2H), 4.28-4.25 (m, 1H), 3.46-3.44 (m, 2H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 196.5, 141.4, 139.8, 135.5, 135.3, 133.2, 132.7, 132.6, 129.6, 129.5, 129.2, 129.1, 129, 128.8, 127.6, 44.3, 43.3. **HRMS** (ESI) Calculated for $C_{23}H_{17}Cl_3O$ $[M+H]^+$ 415.0423, found 415.0423.

(*E*)-3,5-Bis(4-chlorophenyl)-1-(p-tolyl)pent-4-en-1-one (60i):



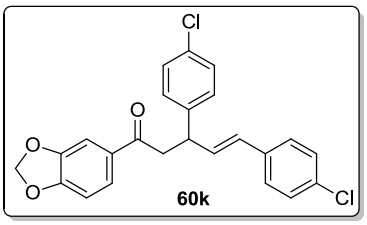
Yellow coloured solid, mp 93-95˚C. **IR** (neat, cm^{-1}): 3030, 1678, 1491, 1408, 1091, 736. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.82 (d, *J* = 8.0 Hz, 2H), 7.26-7.20 (m, 10H), 6.37-6.27 (m, 2H), 4.28-4.24 (m, 1H), 3.48-3.37 (m, 2H), 2.38 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 197.3, 144.2, 141.6, 135.5, 134.5, 133, 132.4, 129.4, 129.2, 128.8, 128.6, 128.2, 127.5, 44.1, 43.3, 21.7. **HRMS** (ESI) Calculated for $C_{24}H_{20}Cl_2O$ $[M+Na]^+$ 417.0789, found 417.0789.

(*E*)-3,5-Bis(4-chlorophenyl)-1-(naphthalen-2-yl)pent-4-en-1-one (60j):



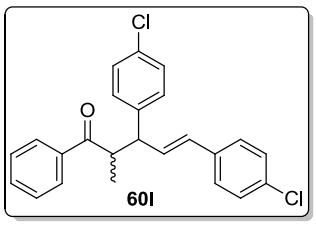
Orange coloured gummy liquid. **IR** (neat, cm^{-1}): 3055, 1680, 1491, 1412, 1091,746. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.43 (s, 1H), 7.99-7.96 (m, 1H), 7.93-7.91 (m, 1H), 7.86-7.83 (m, 2H), 7.59-7.51 (m, 2H), 7.28-7.25 (m, 4H), 7.23-7.21 (m, 4H), 6.40-6.30 (m, 2H), 4.35-4.30 (m, 1H), 3.59-3.57 (m, 2H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 197.6, 141.6, 135.7, 135.6, 134.3, 133.1, 132.9, 132.6, 129.9, 129.8, 129.6, 129.4, 129.3, 129.1, 128.9, 128.7, 128.5, 127.9, 127.6, 127, 123.8, 44.3, 43.4. **HRMS** (ESI) Calculated for $C_{27}H_{20}Cl_2O$ $[M+Na]^+$ 453.0789, found 453.0789.

(*E*)-1-(Benzo[d][1,3]dioxol-5-yl)-3,5-bis(4-chlorophenyl)pent-4-en-1-one (60k):



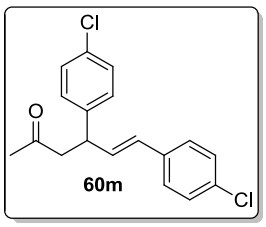
Gummy liquid. **IR** (neat, cm^{-1}): 1671, 1490, 1441, 1254, 1095, 816. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.54 (dd, *J* = 8.0 Hz, *J* = 1.6 Hz, 1H), 7.40-7.39 (m, 1H), 7.29-7.25 (m, 2H), 7.26-7.21 (m, 6H), 6.83-6.81 (d, *J* = 8.0 Hz, 1H), 6.36-6.26 (m, 2H), 6.01 (s, 2H), 4.27-4.22 (m, 1H), 3.43-3.32 (m, 2H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 195.6, 151.8, 148.2, 141.5, 135.4, 132.9, 132.8, 132.4, 131.7, 129.2, 129.1, 128.8, 128.7, 128.5, 127.4, 124.3, 107.8, 101.8, 43.8, 43.3. **HRMS** (ESI) Calculated for $C_{24}H_{18}Cl_2O_3$ $[M+Na]^+$ 447.0531, found 447.0531.

(*E*)-3,5-Bis(4-chlorophenyl)-2-methyl-1-phenylpent-4-en-1-one (60l):



Colourless liquid, mixture of diastereomers (1:1.1). **IR** (neat, cm^{-1}): 3059, 1682, 1595, 1491, 1448, 1408, 1012, 968, 653. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.97-7.94 (m, 1.77 H), 7.82-7.80 (m, 2H), 7.56-7.50 (m, 2H), 7.48-7.43 (m, 2H), 7.41-7.37 (m, 2H), 7.33-7.31 (m, 2H), 7.25-7.24 (m, 4H), 7.24-7.23 (m, 1.7H), 7.22-7.21 (m, 1H), 7.18-7.15 (m, 3H), 7.14-7.10 (m, 2H), 7.02-7.0 (m, 2H), 6.45-6.40 (m, 1H), 6.31-6.27 (m, 1H), 6.22-6.21 (m, 2H), 3.99-3.93 (m, 2H), 3.90-3.88 (m, 1.5H), 1.30-1.25 (m, 3H), 1.04-1.02 (m, 2.5H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 203.3, 202.9, 141.2, 140.1, 137.2, 136.7, 135.5, 133.2, 133.1, 132.8, 132.6, 132.2, 131.8, 131.1, 130.8, 130.1, 129.7, 129.1, 128.9, 128.8, 128.7, 128.6, 128.5, 128.2, 128.1, 127.5, 127.4, 51.7, 51.6, 45.5, 17.1, 16.9. **HRMS** (ESI) Calculated for $C_{24}H_{20}Cl_2O$ $[M+Na]^+$ 417.0789, found 417.0788.

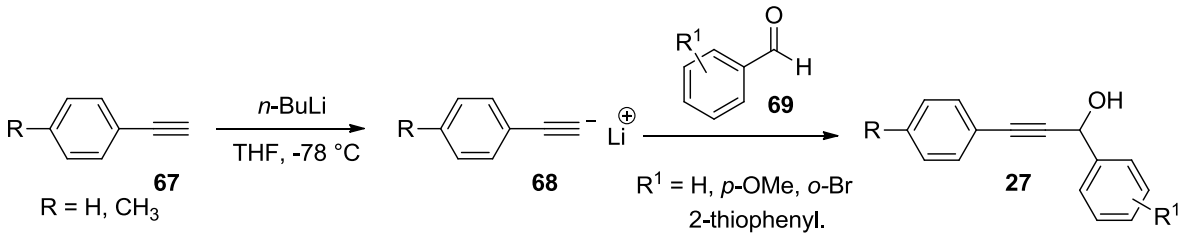
(*E*)-4,6-Bis(4-chlorophenyl)hex-5-en-2-one (60m):



Colourless liquid**. IR** (KBr, cm^{-1}): 2997, 1720, 1512, 1249, 756. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.30-7.27 (m, 2H), 7.24-7.20 (m, 4H), 7.19-7.17 (m, 2H), 6.32-6.21 (m, 2H), 4.08-4.03 (m, 1H), 2.97-2.86 (m, 2H), 2.10 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 206.4, 141.3, 135.5, 133.2, 132.7, 132.6, 129.3, 129.2, 128.9, 128.8, 127.6, 49.2, 43.2, 30.8. **HRMS** (ESI) Calculated for $C_{18}H_{16}Cl_2O$ $[M+Na]^+$ 341.0476, found 341.0478.

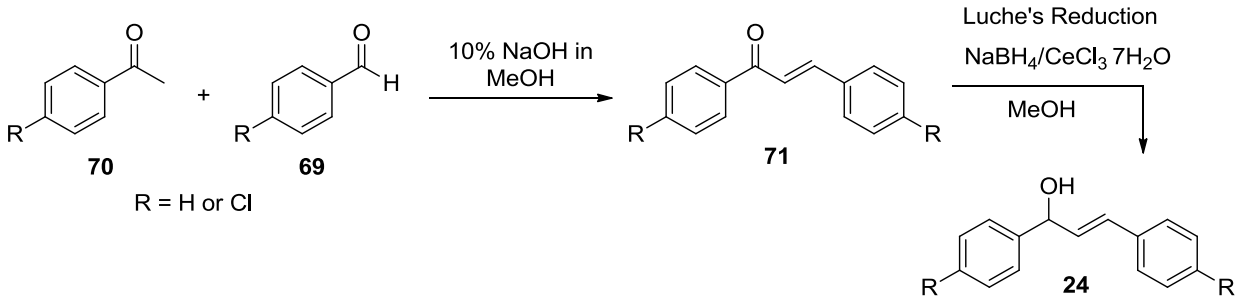
1.7.3 Preparation of starting materials

Preparation of diaryl substituted propargyl alcohols:



Using the literature procedure[16b], the substituted propargyl alcohols (**38**) are prepared as follows, phenyl acetylene (**67**, 1 equiv) was taken in a reaction vessel filled with nitrogen, dry THF(3mL for mmol) was added to it and cooled to -78 ˚C. After 20 minutes *n*-BuLi (1.6 M solution in hexanes, 1.1 equiv) was added drop wise under nitrogen for 15 to 20 minutes and stirred at -78 ˚C for 1 h. Then it was allowed to warm to room temperature and stirred for 1 h. Again the reaction mixture is cooled to -78 ˚C and respective aldehyde (**69**, 1 equiv) in dry THF (1mL for 5mmol) was added drop wise and allowed the reaction mixture to warm gradually to room temperature and stirred till completion. After completion of the reaction, saturated NH_4Cl was added, reaction mixture was extracted thrice with ethyl acetate. The resulting organic layer was washed with water, brine and dried over Na_2SO_4. The filtrate was concentrated using rotavapour and residue was purified by column chromatography on silica gel to get the pure products (**27**).

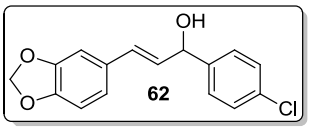
Preparation of substituted cinnamyl alcohols:



Using the literature procedure,[16] the substituted cinnamyl alcohols (**24**) are prepared as follows, ketone (**70**, 1 equiv) and aldehyde (**69**, 1 equiv) were taken in a reaction vessel and 10% NaOH in MeOH (4mL for 1mmol of **70**) was added to it and stirred at room temperature overnight. After completion of the reaction, it was neutralized using 10% HCl

and the resulting residue was extracted with CH_2Cl_2 thrice. The combined organic layer was washed with water several times, finally with brine and dried over Na_2SO_4. The organic layer was filtered using Buchner funnel and dried in a desiccator. The enone formed was used directly for luche's reduction without further purification to get the pure cinnamyl alcohols (**24**).

(*E*)-3-(benzo[d][1,3]dioxol-5-yl)-1-(4-chlorophenyl)prop-2-en-1-ol (62):



IR (KBr, cm^{-1}): 3358, 2892, 1648, 1593, 1489, 1445, 1248, 1034, 969, 870. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.29-7.28 (m, 4H), 6.85 (m, 1H), 6.77-6.70 (m, 2H), 6.49 (d, *J* = 16.0 Hz, 1H), 6.09 (dd, *J* = 16.0 Hz, 7.2 Hz, 1H), 5.90 (s, 2H), 5.25-5.23 (m, 1H), 2.73-2.71 (bs, 1H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 148.1, 147.5, 141.4, 133.4, 130.8, 130.7, 129.3, 128.7, 127.7, 121.5, 108.4, 105.8, 101.2, 74.5. **HRMS** (ESI) Calculated for $C_{16}H_{13}ClO_3$ $[M+Na]^+$ 311.0451, found 311.0453.

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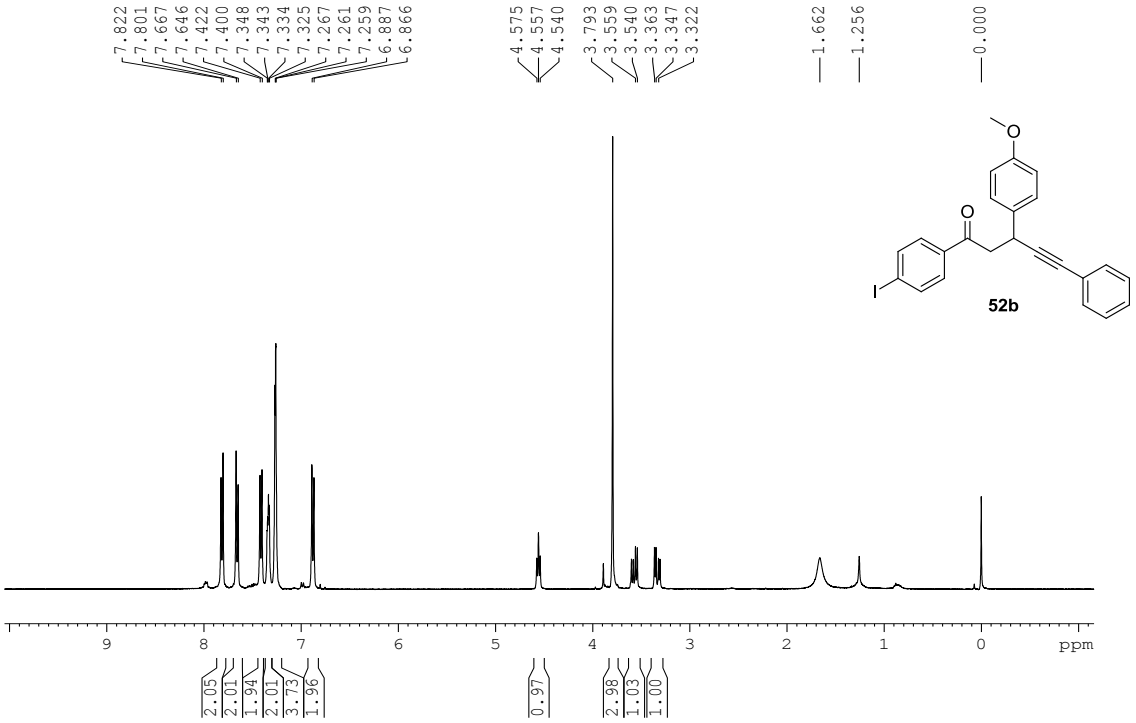

Figure 3. ^{1}H NMR spectrum of **52b**

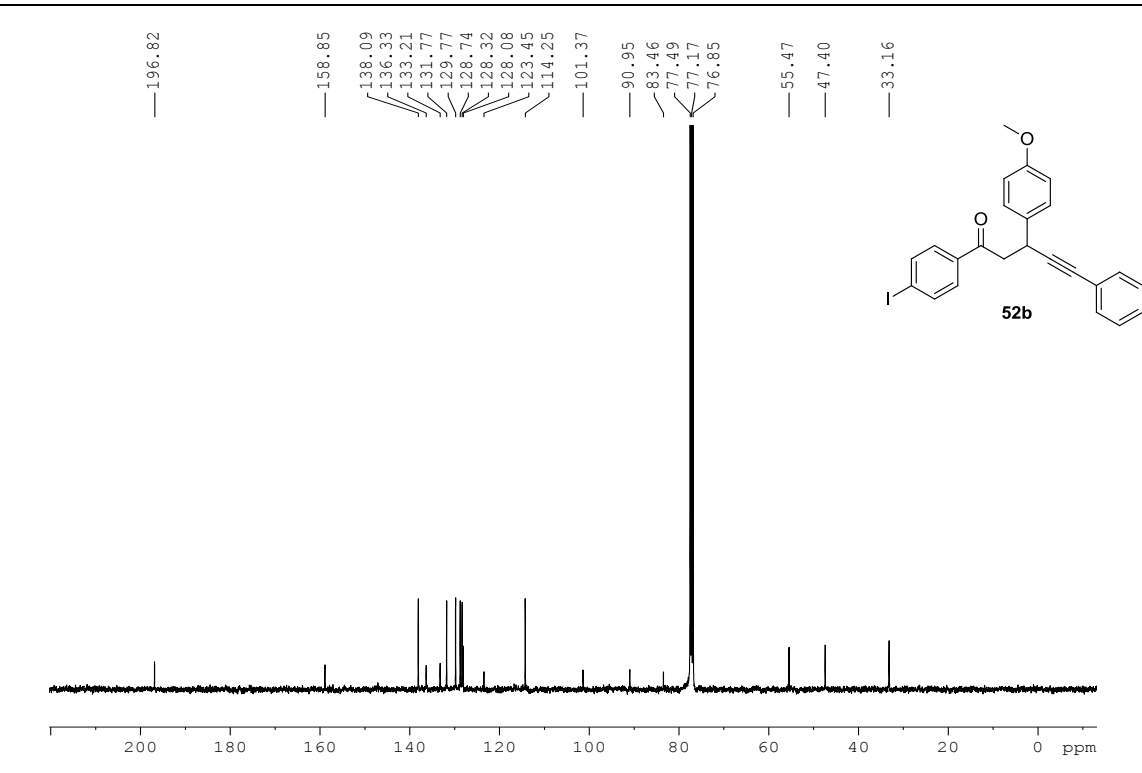

Figure 4. ^{13}C NMR spectrum of **52b**

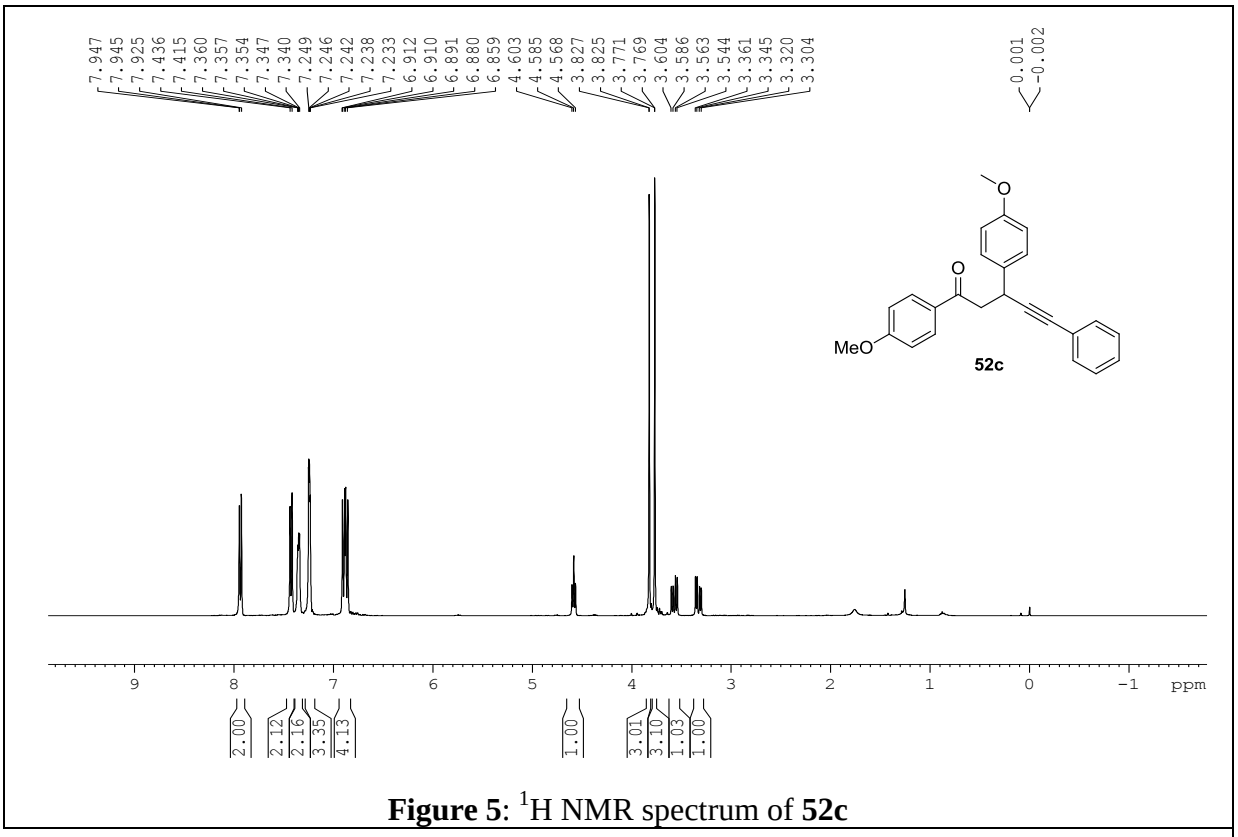

Figure 5: ^{1}H NMR spectrum of **52c**

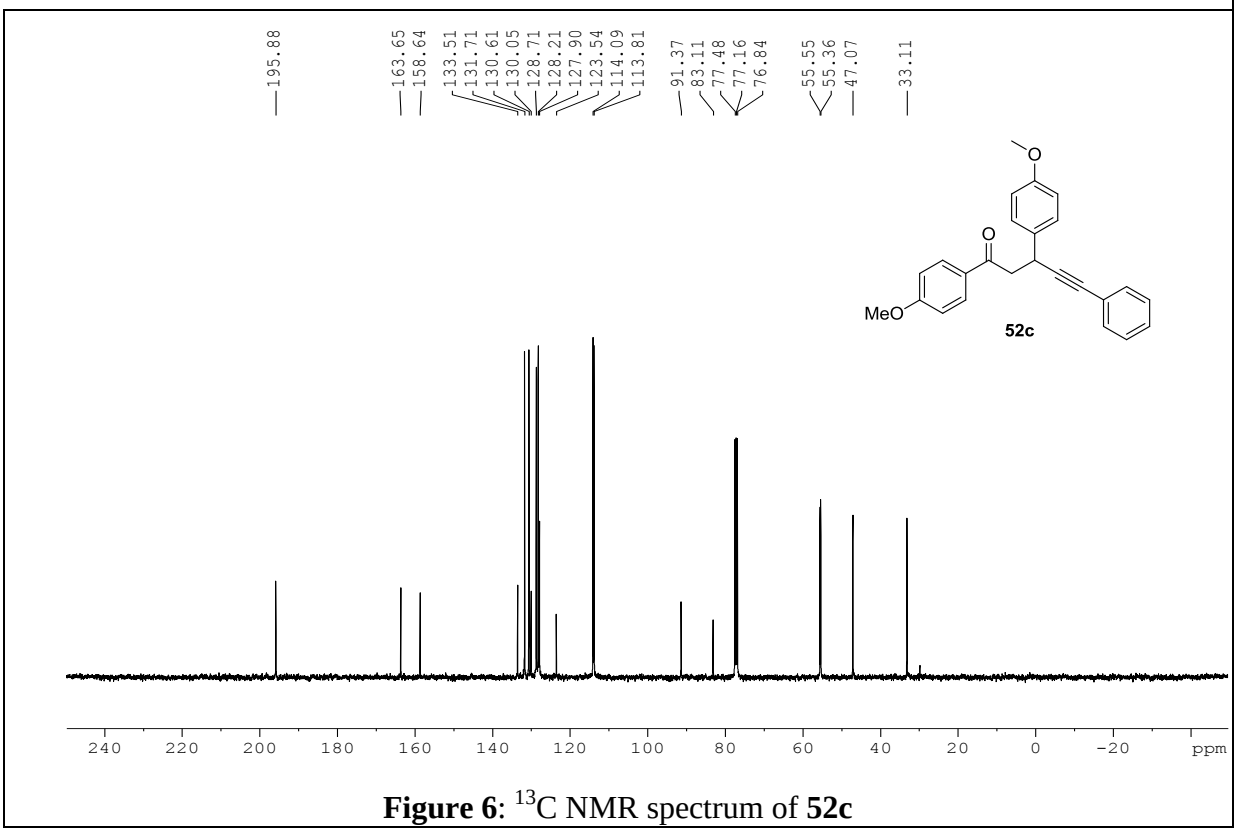

Figure 6: ^{13}C NMR spectrum of **52c**

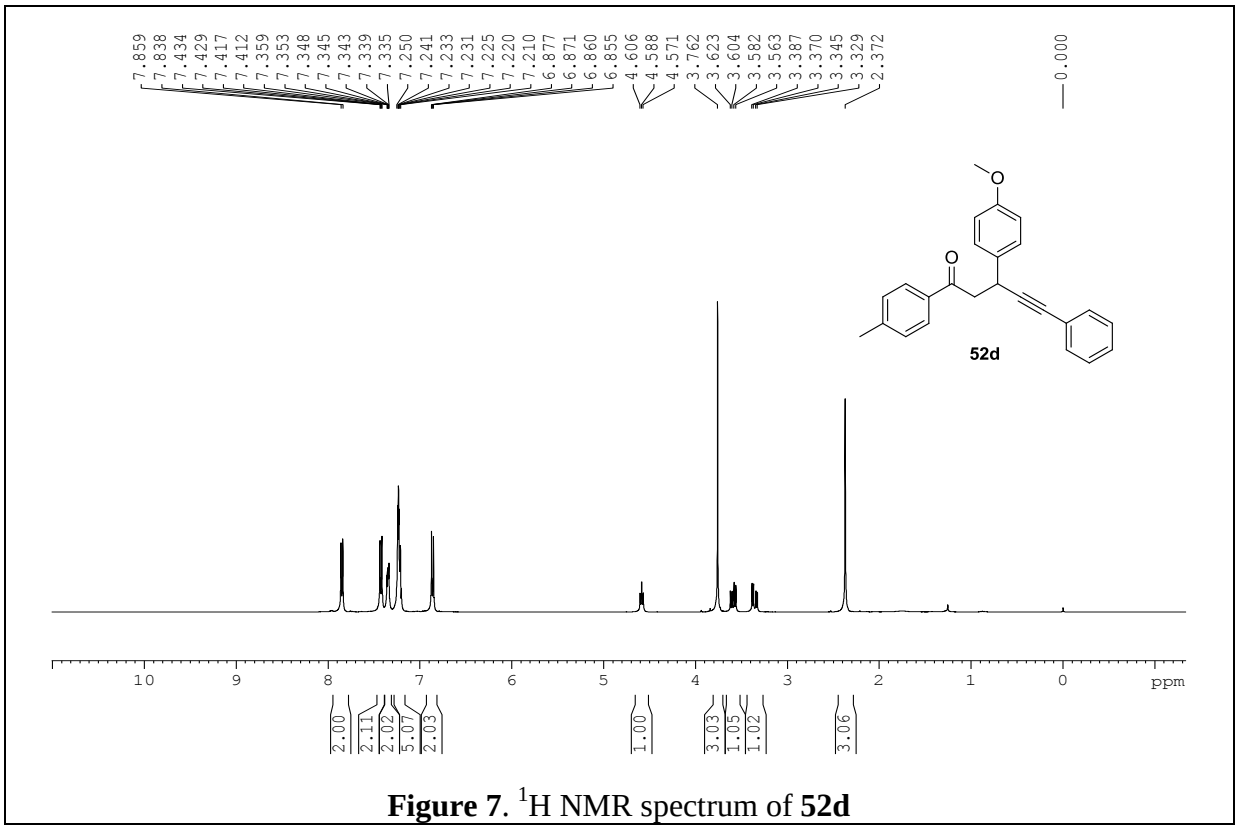

Figure 7. ^{1}H NMR spectrum of **52d**

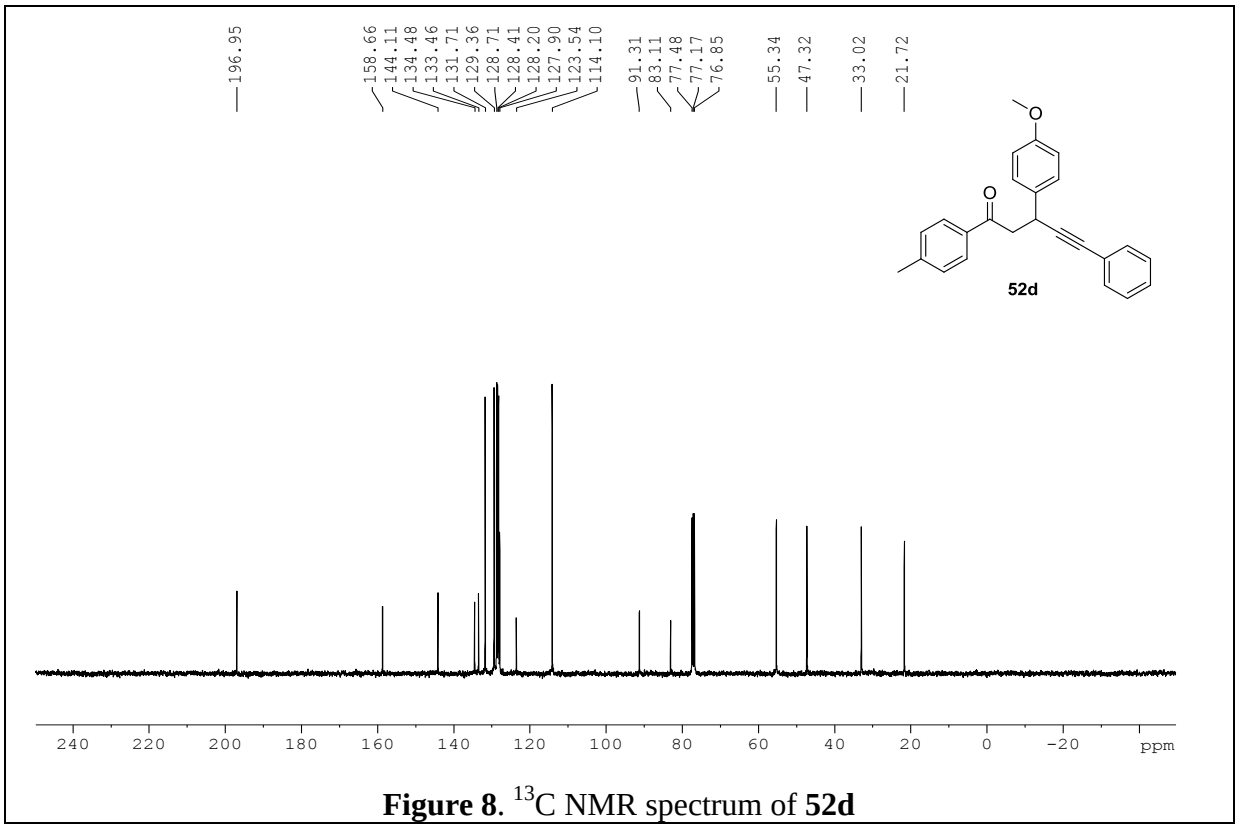

Figure 8. ^{13}C NMR spectrum of **52d**

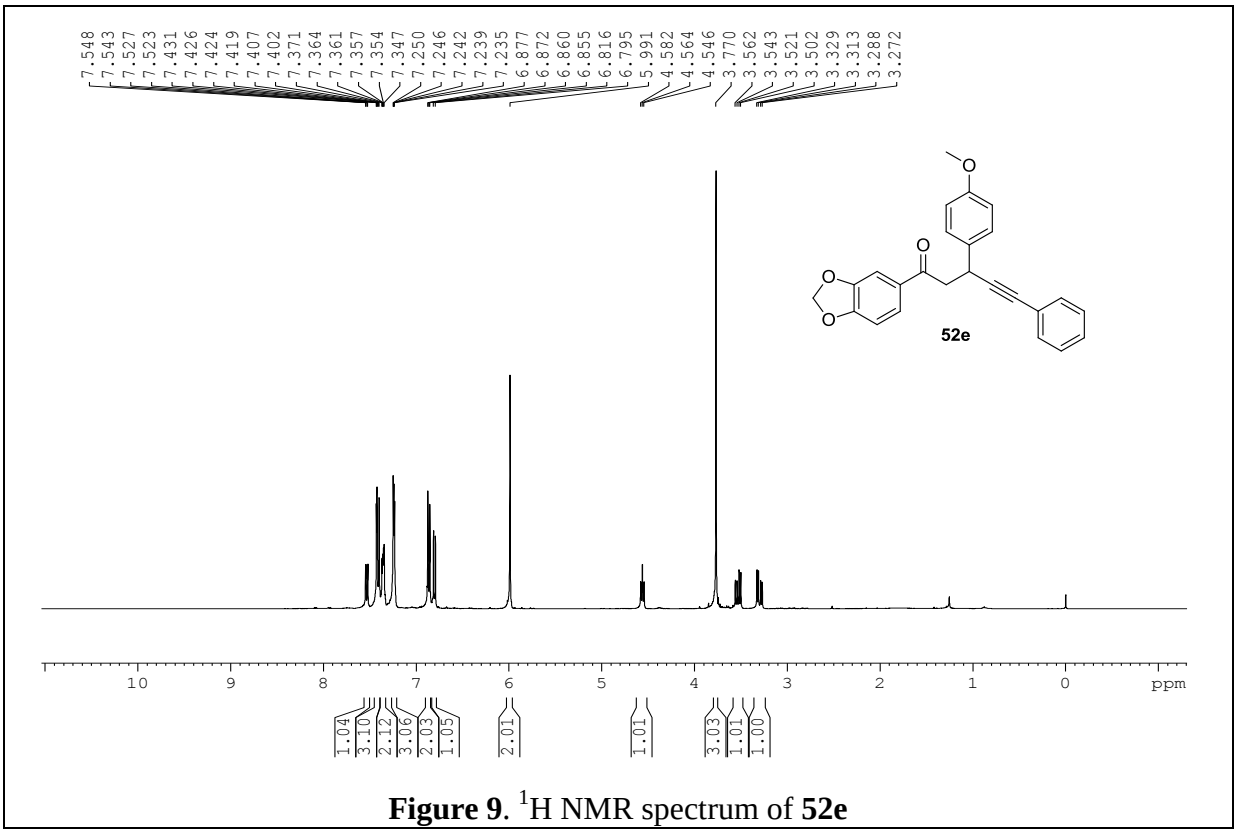

Figure 9. ^{1}H NMR spectrum of **52e**

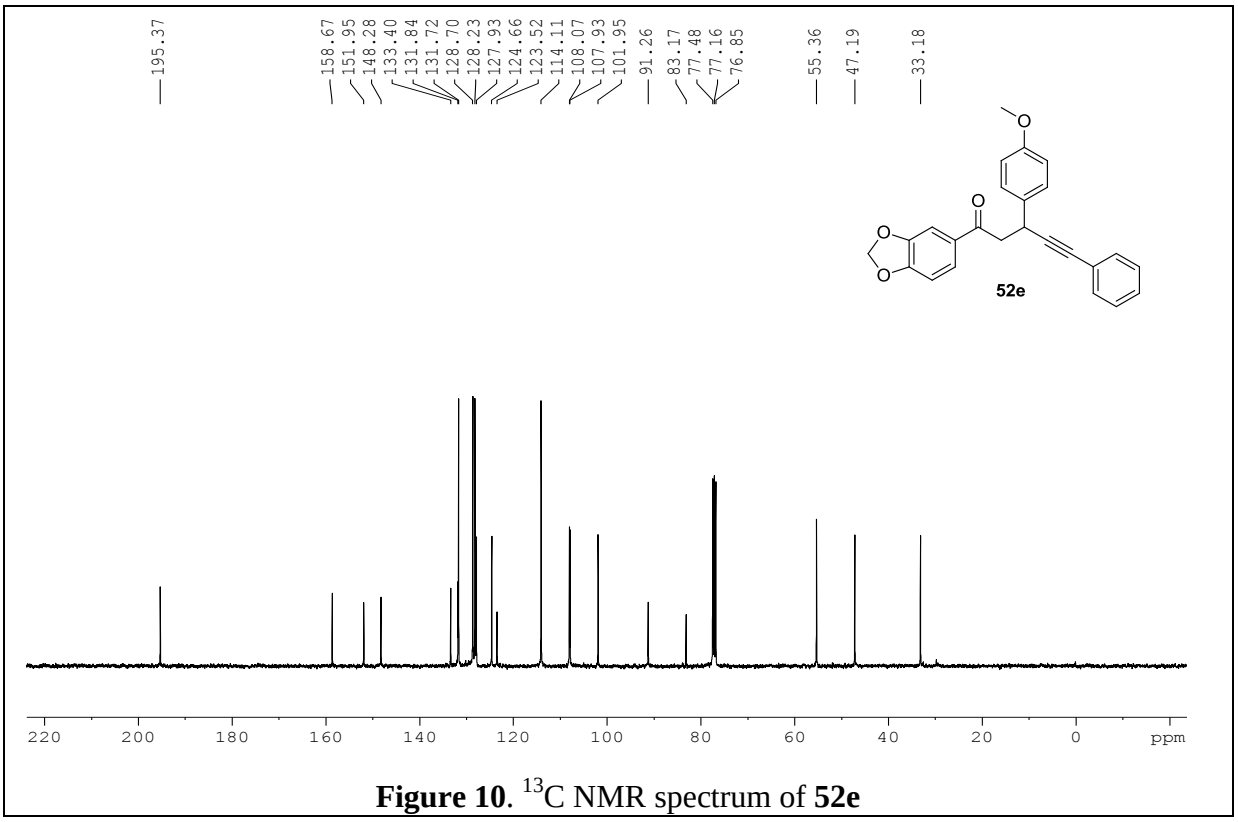

Figure 10. ^{13}C NMR spectrum of **52e**

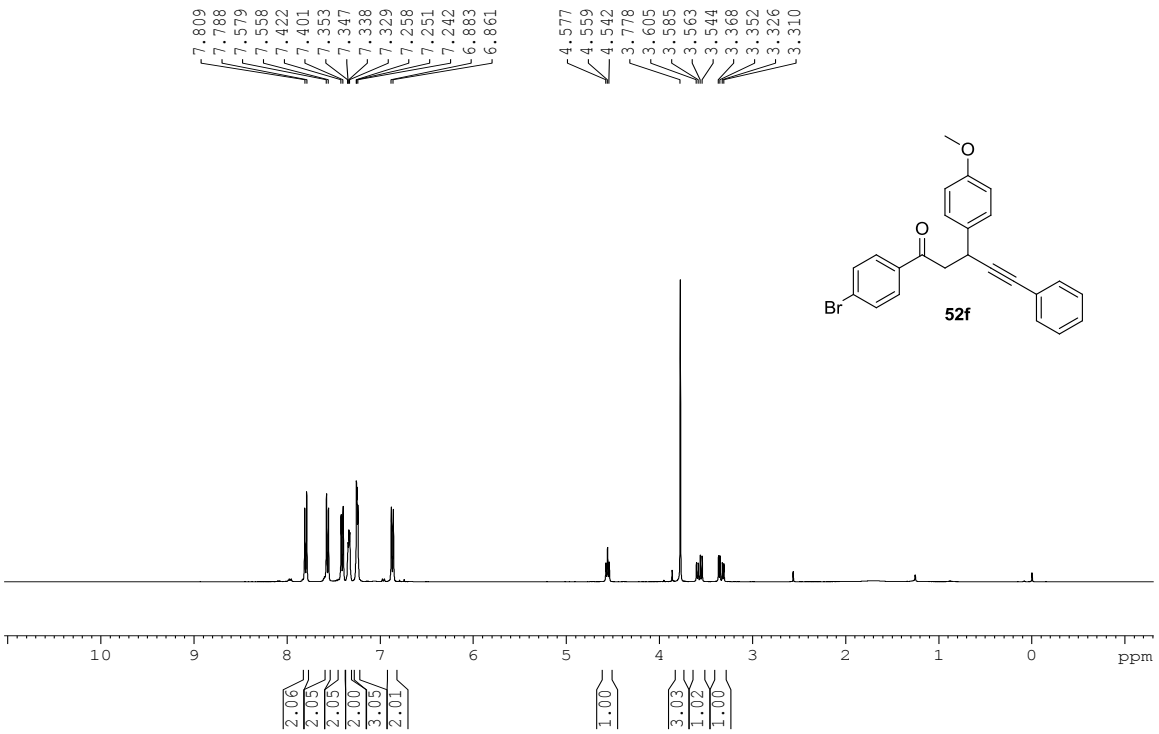

Figure 11. ^{1}H NMR spectrum of **52f**

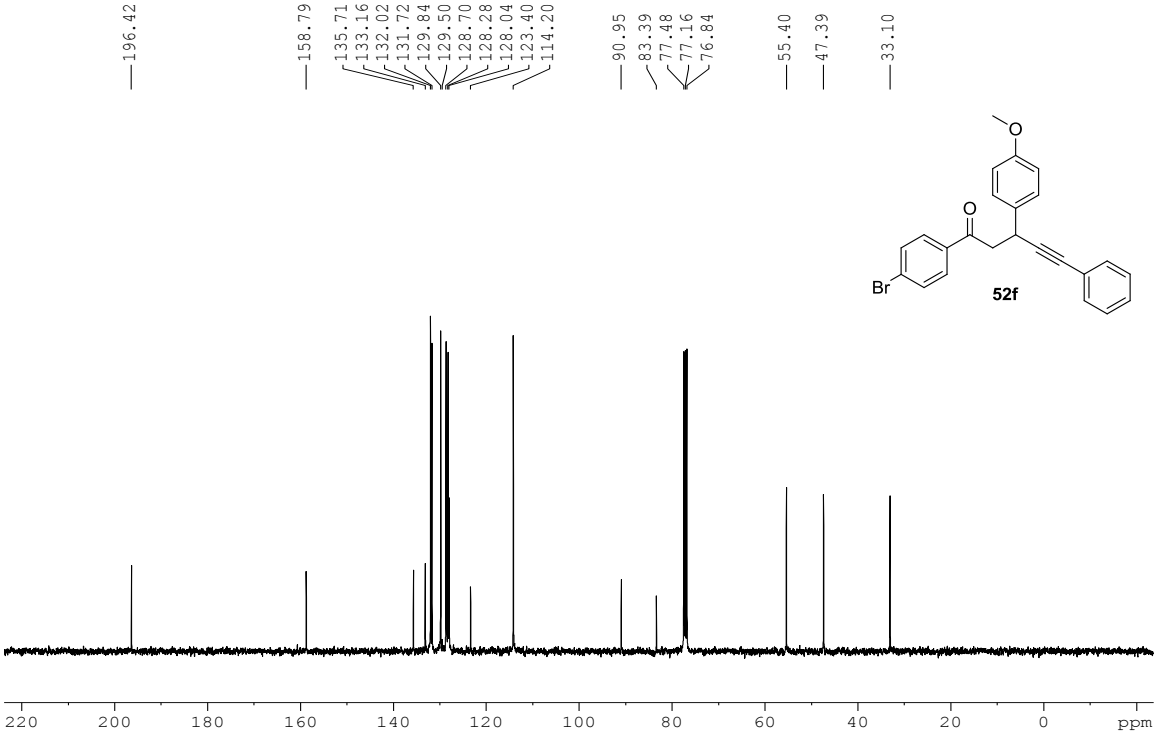

Figure 12. ^{13}C NMR spectrum of **52f**

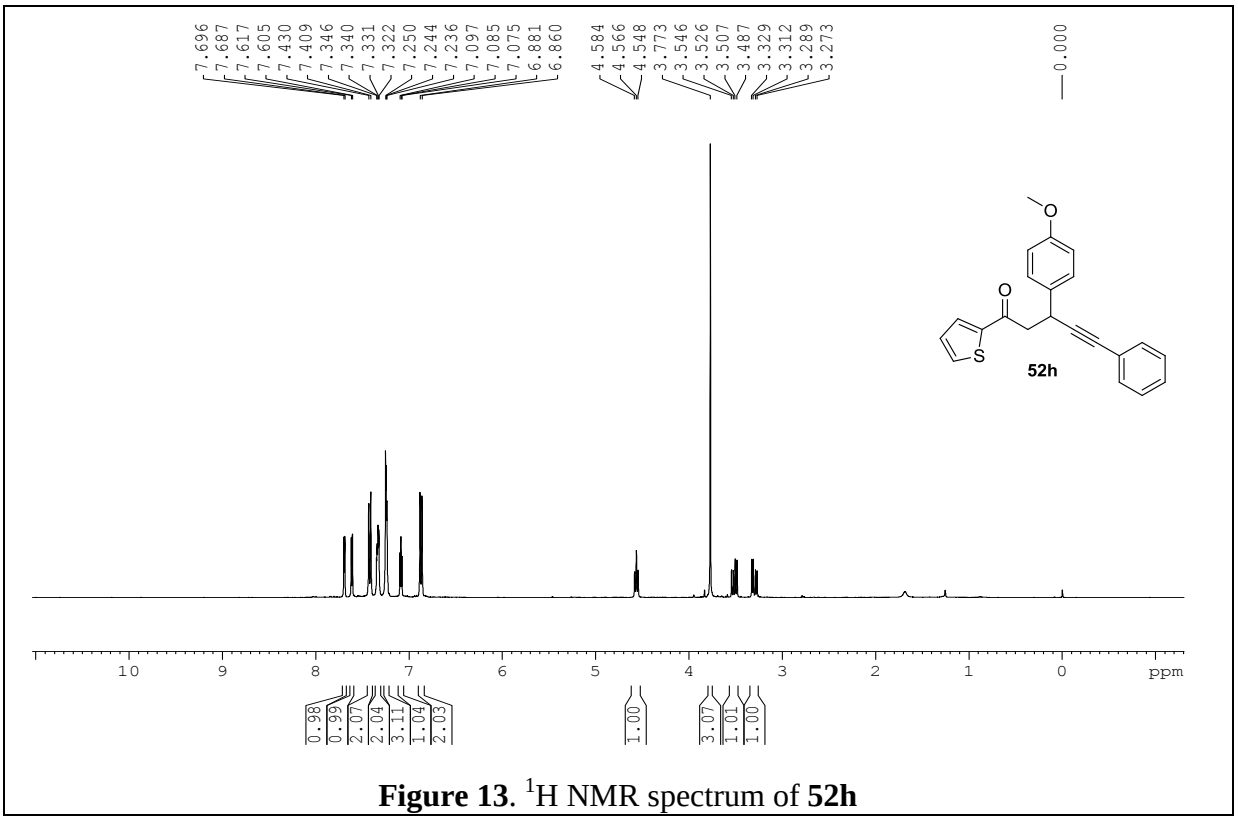

Figure 13. ^{1}H NMR spectrum of **52h**

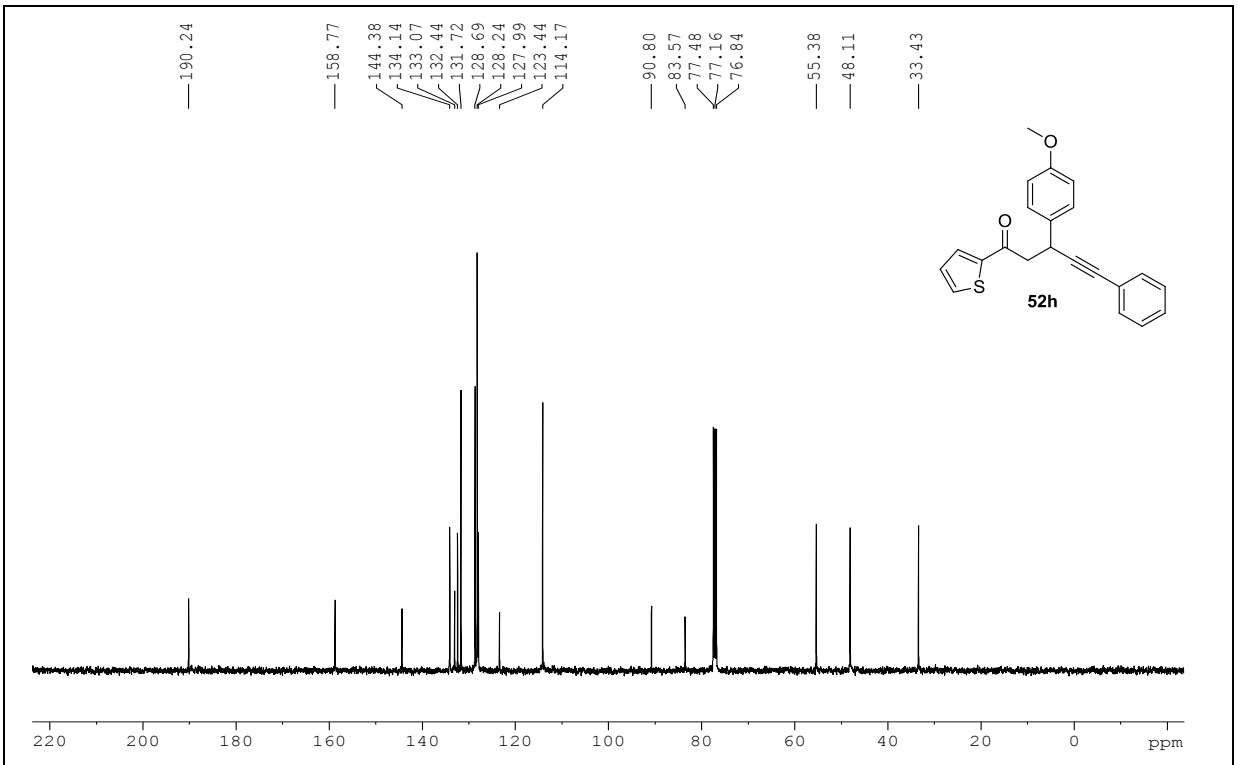

Figure 14. ^{13}C NMR spectrum of **52h**

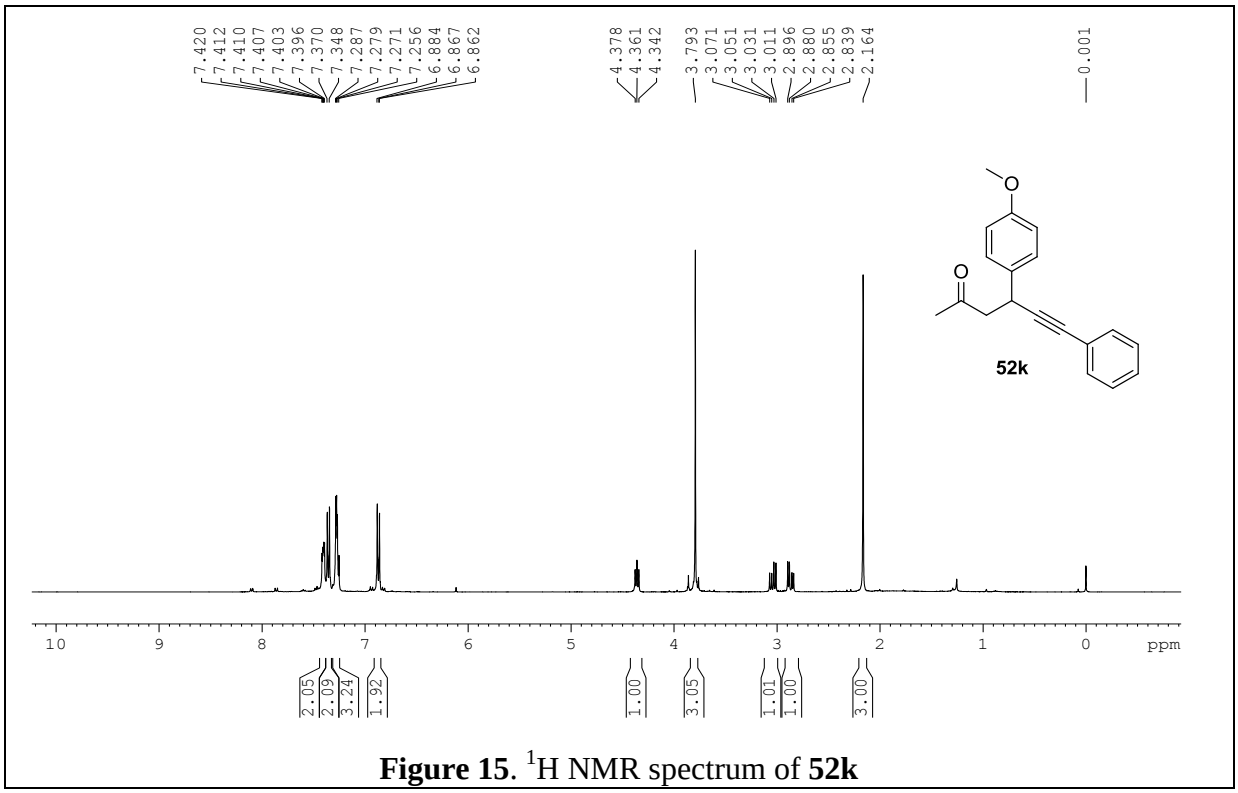

Figure 15. ^{1}H NMR spectrum of **52k**

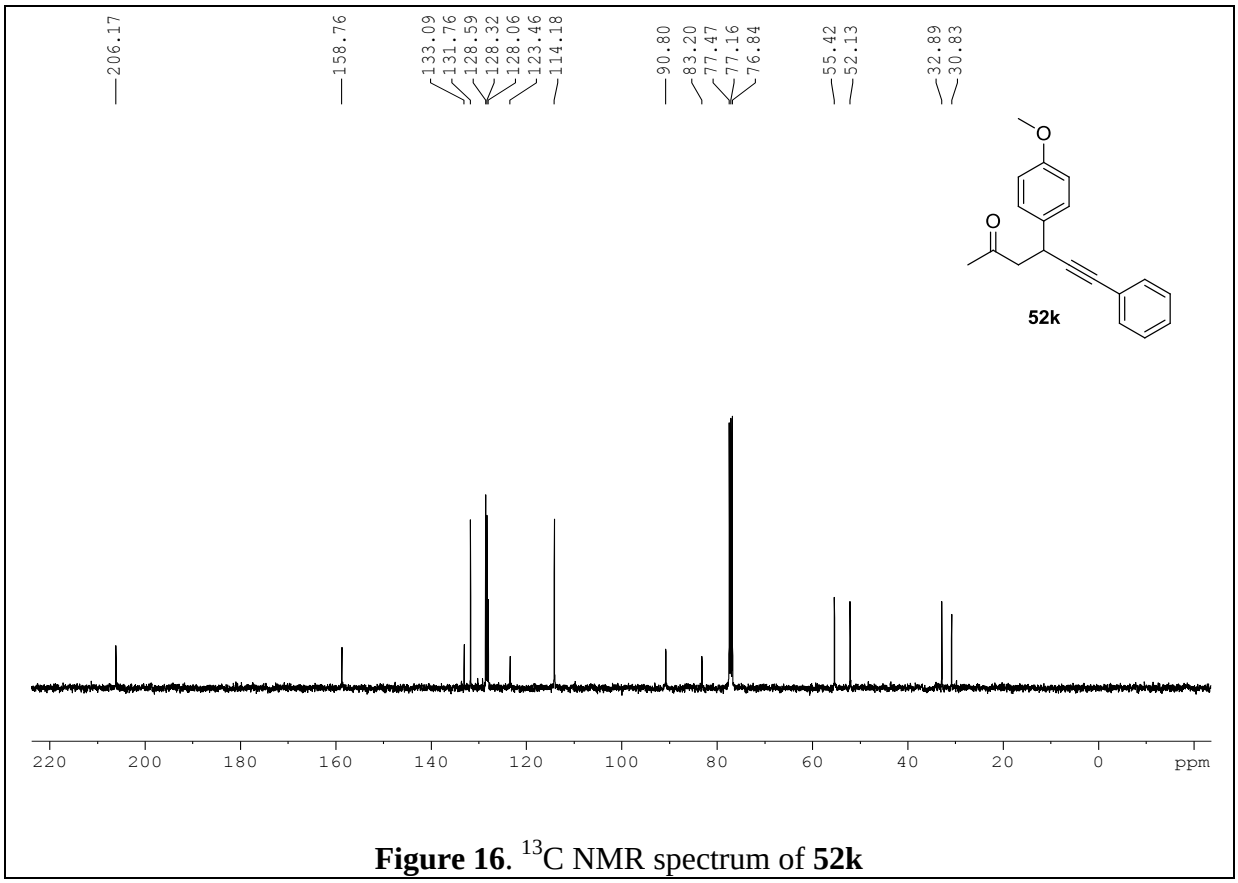

Figure 16. ^{13}C NMR spectrum of **52k**

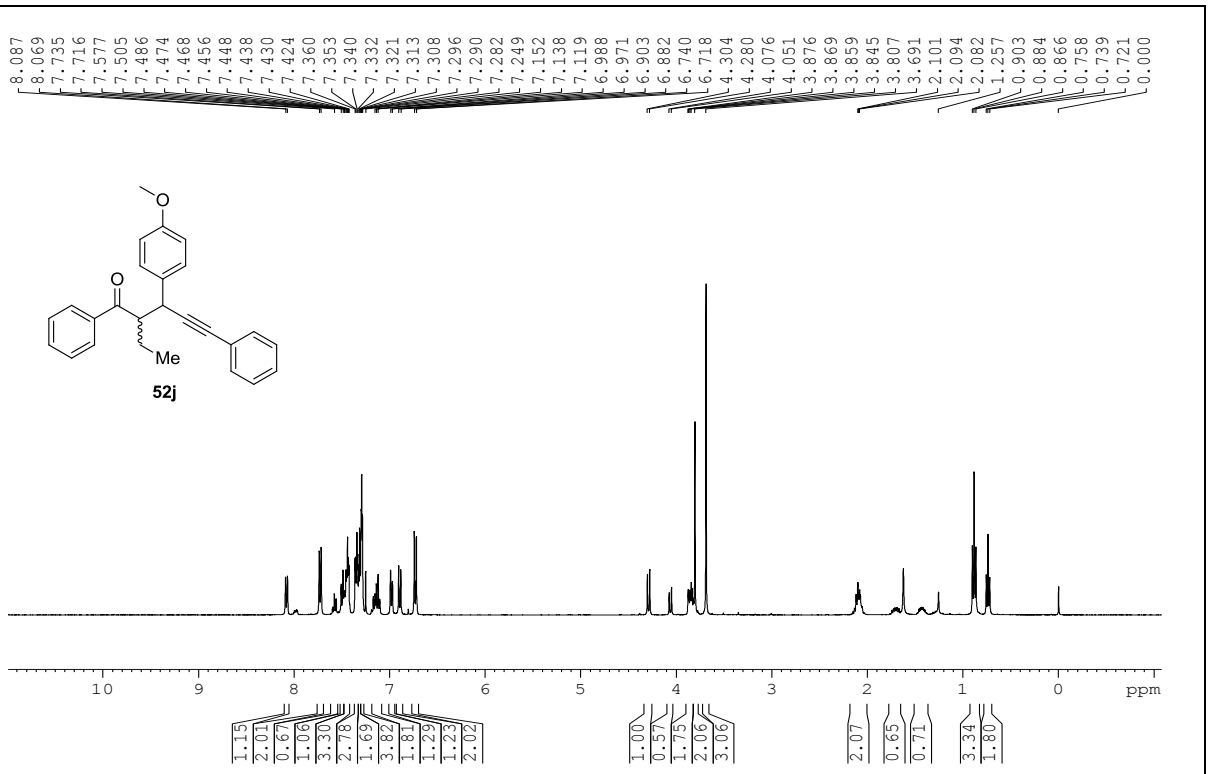

Figure 17. ^{1}H NMR spectrum of **52j**

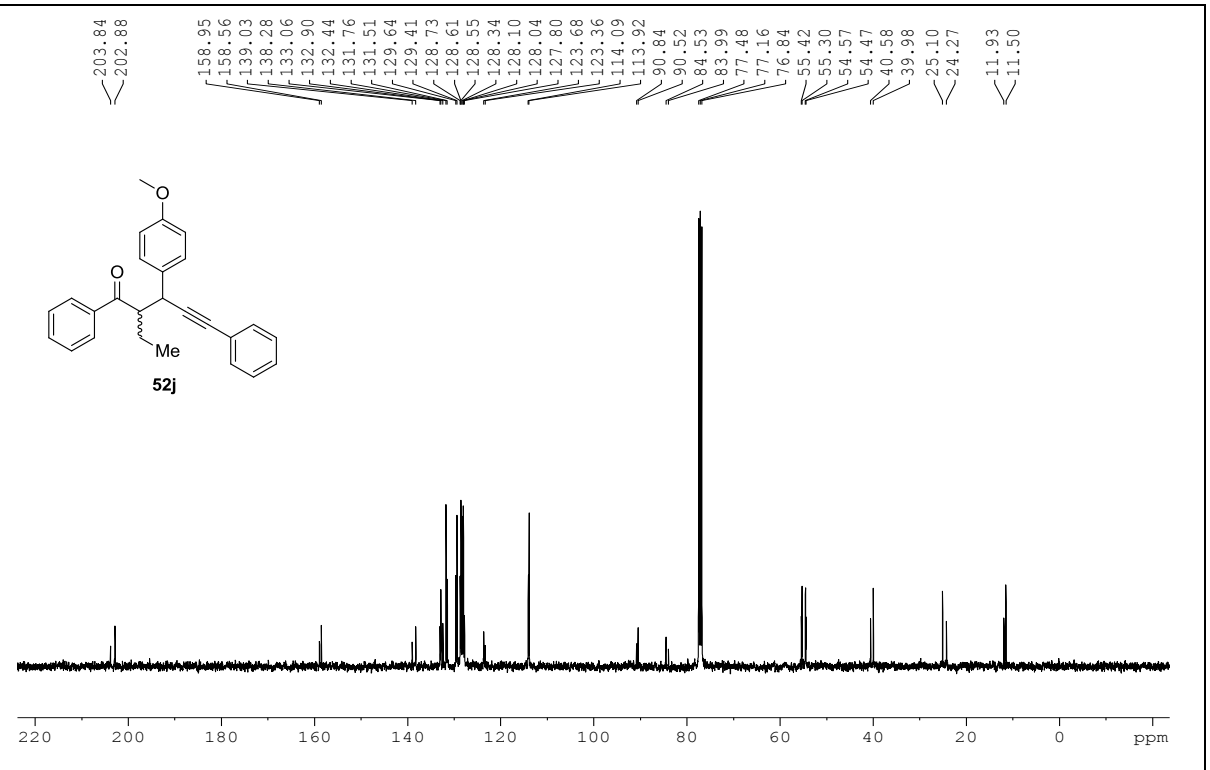

Figure 18. ^{13}C NMR spectrum of **52j**

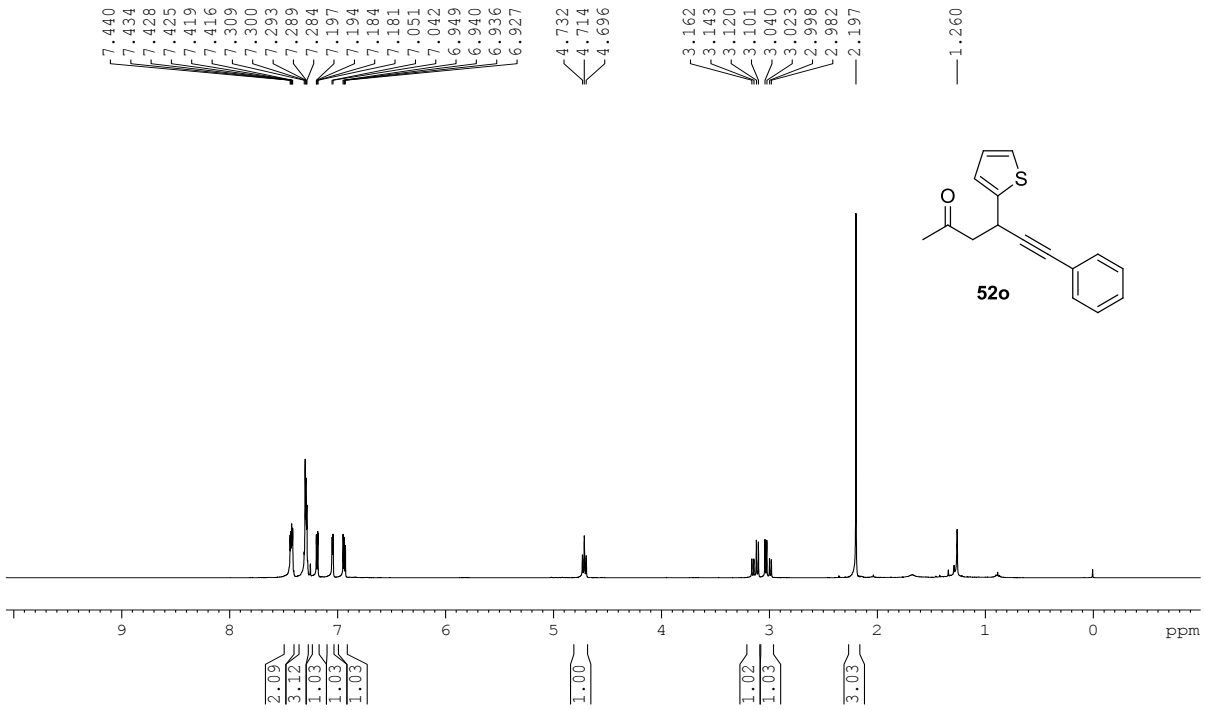

Figure 19. ^{1}H NMR spectrum of **52o**

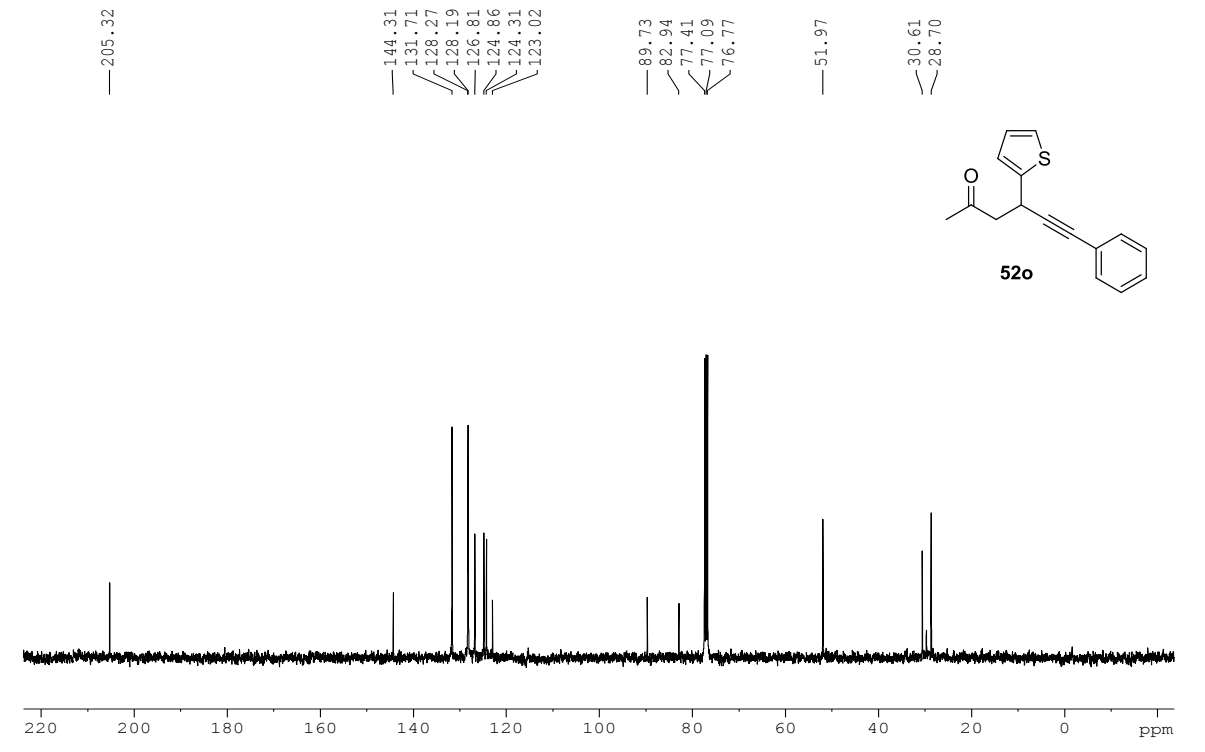

Figure 20. ^{13}C NMR spectrum of **52o**

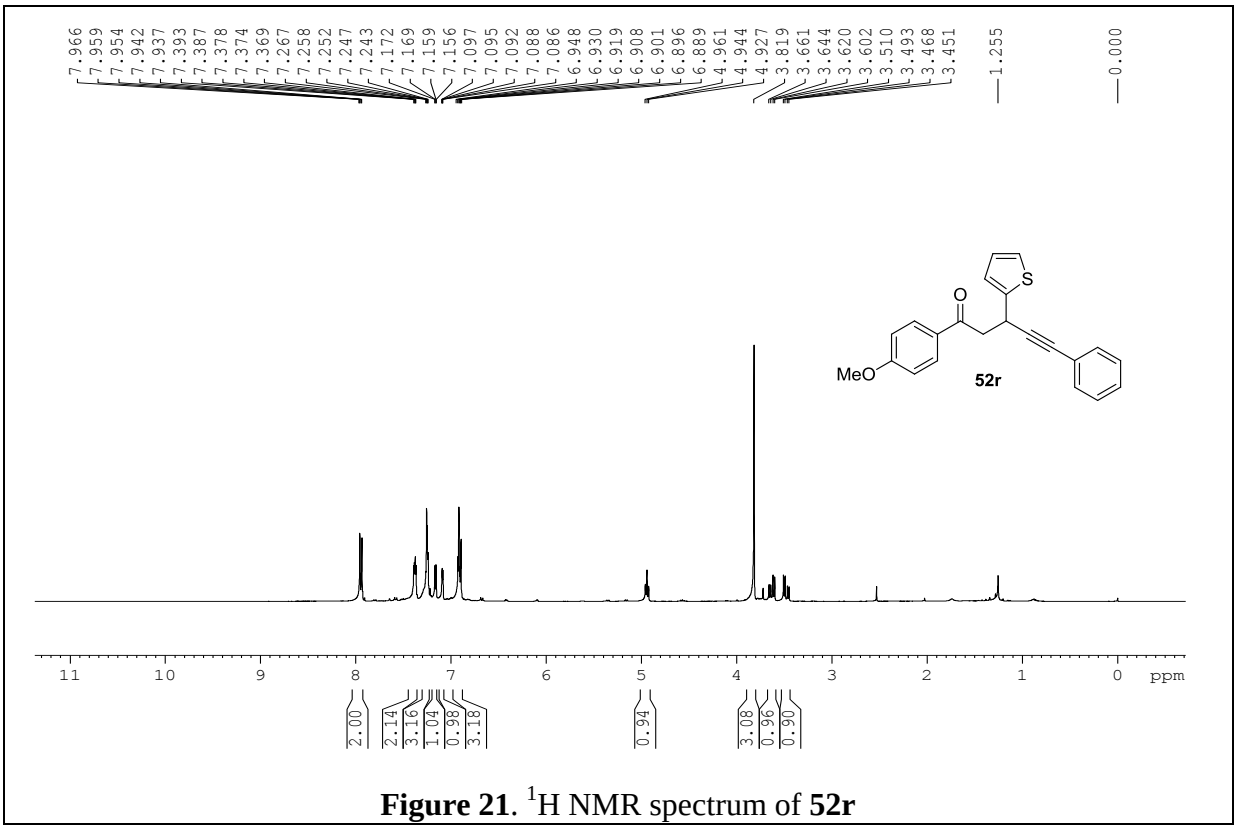

Figure 21. ^{1}H NMR spectrum of **52r**

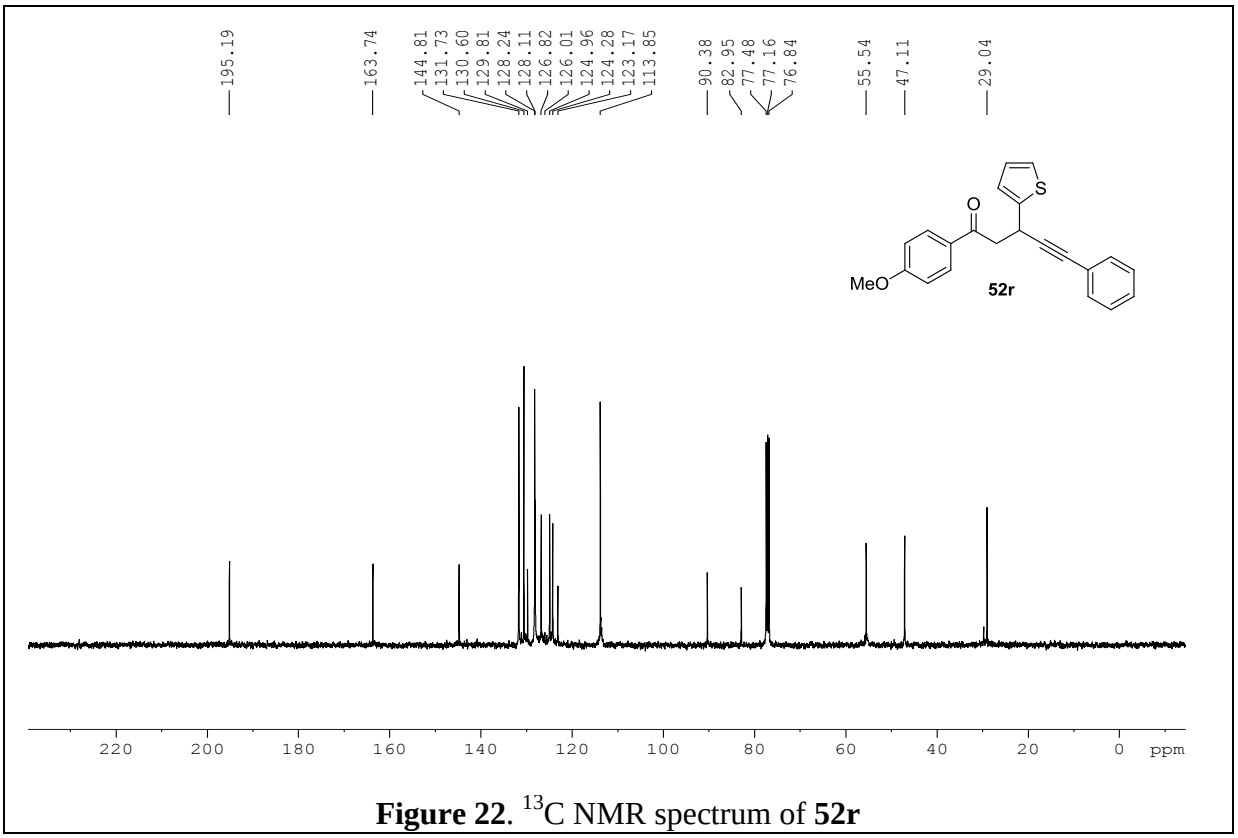

Figure 22. ^{13}C NMR spectrum of **52r**

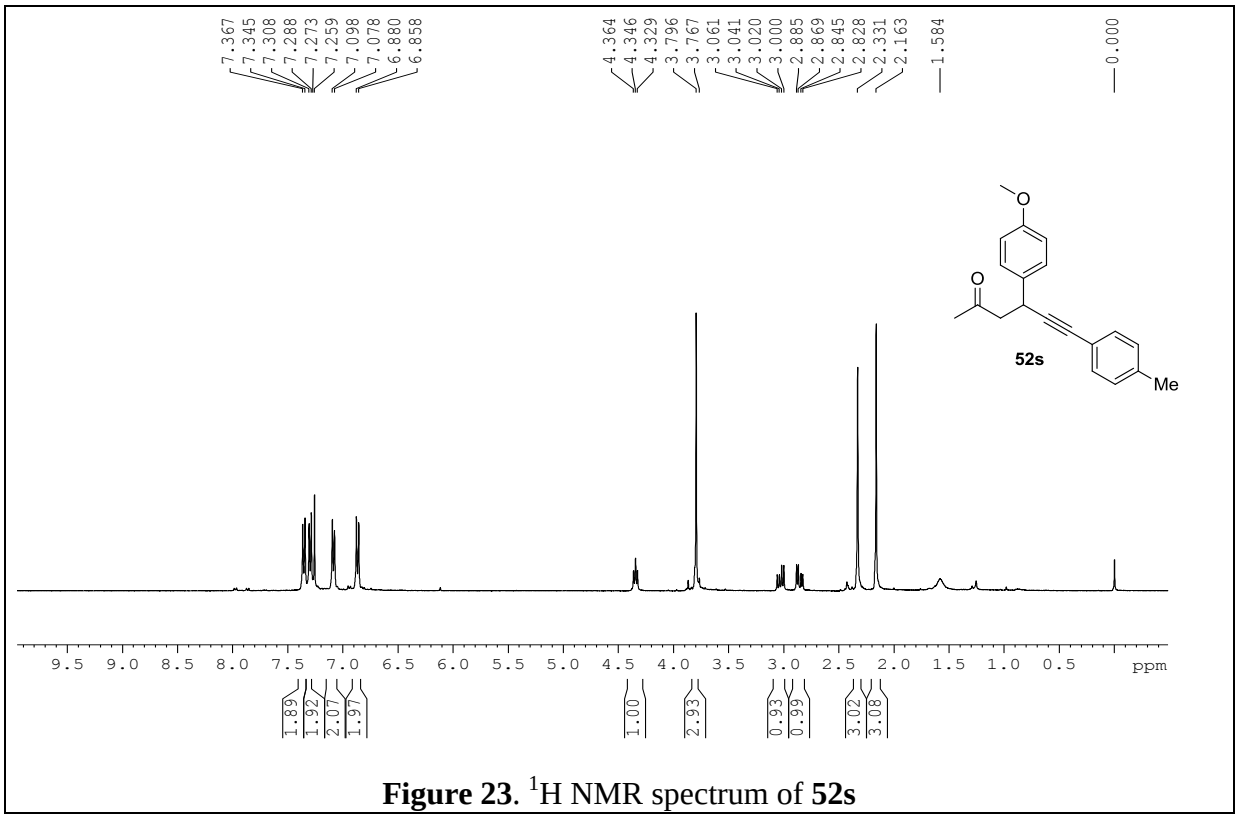

Figure 23. ^{1}H NMR spectrum of **52s**

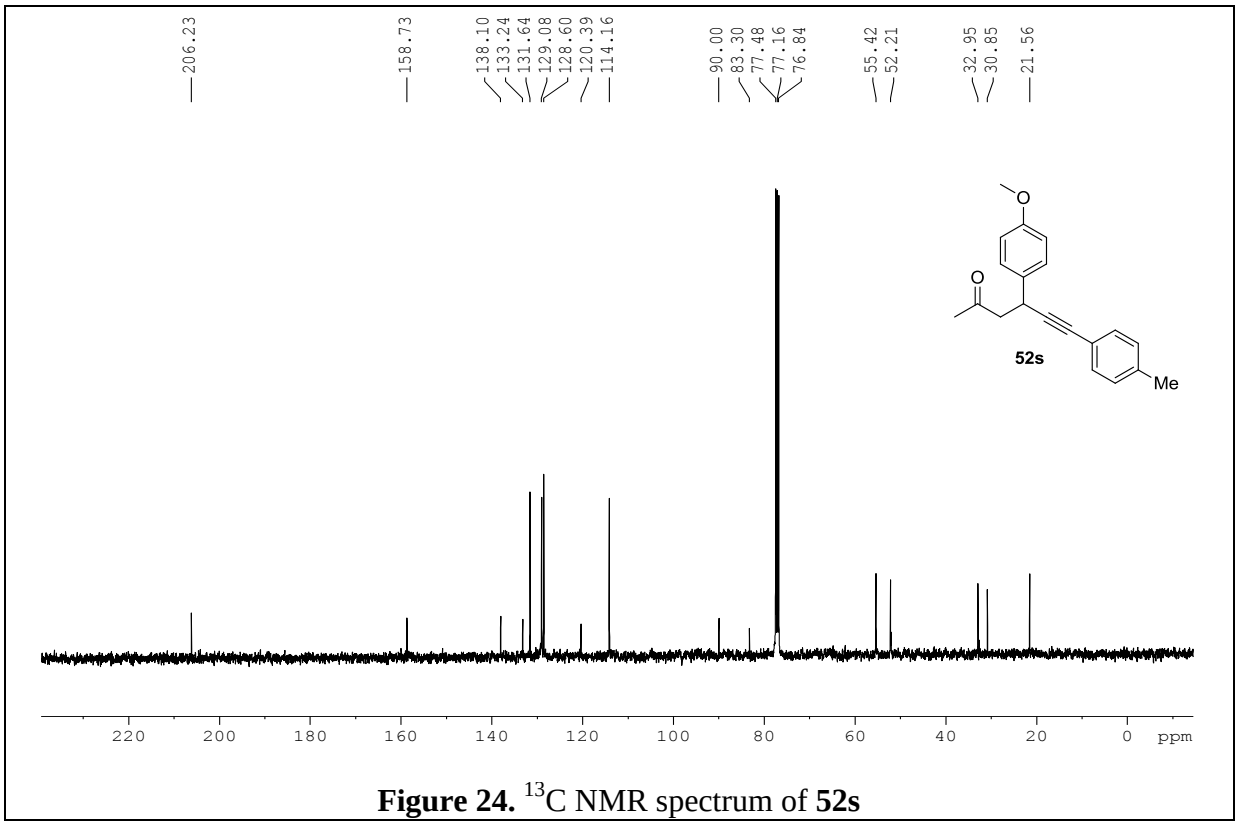

Figure 24. ^{13}C NMR spectrum of **52s**

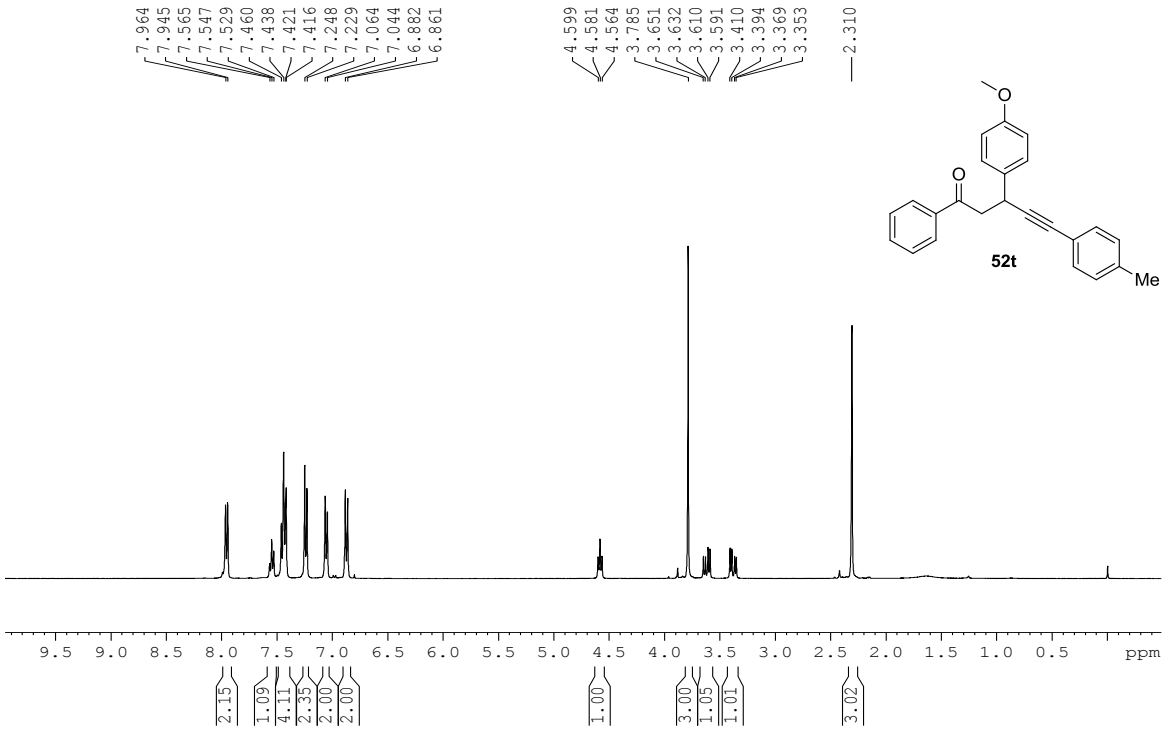

Figure 25. ^{1}H NMR spectrum of **52t**

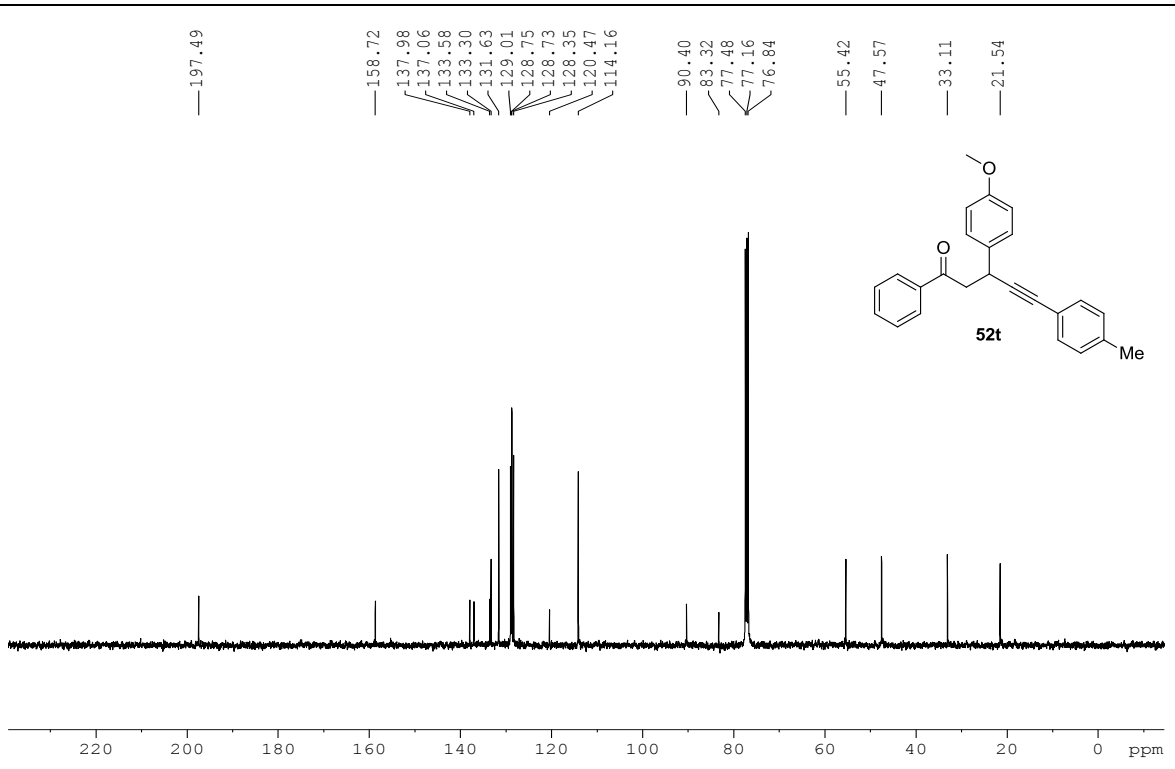

Figure 26. ^{13}C NMR spectrum of **52t**

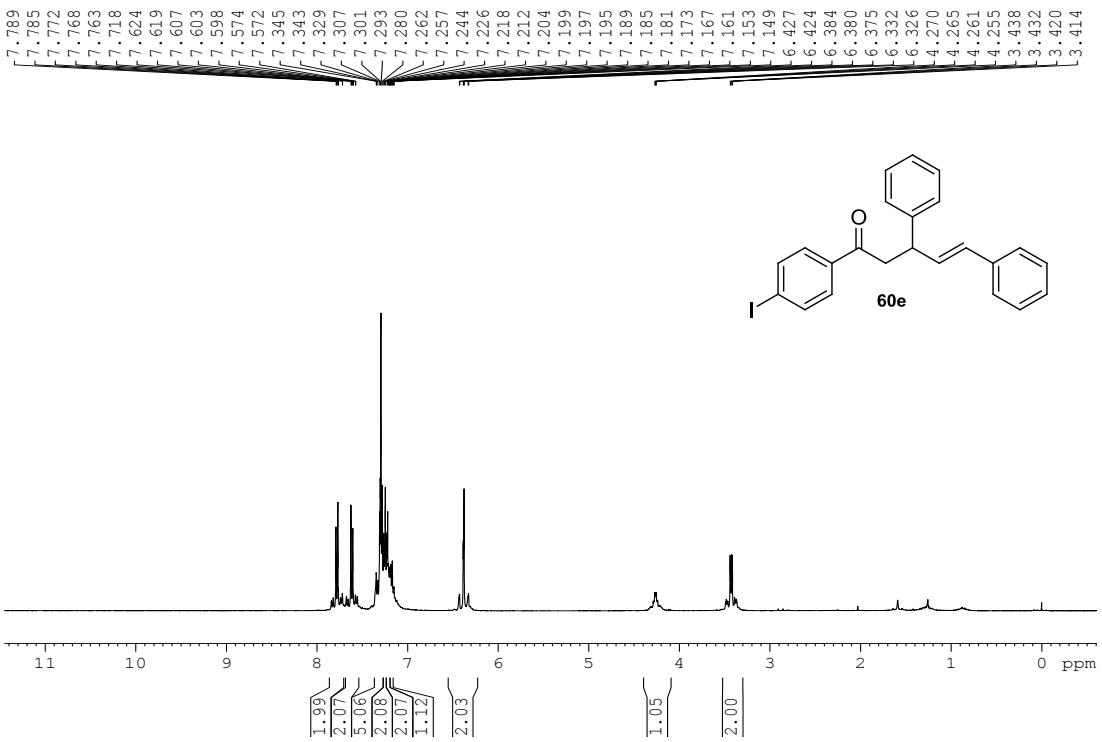

Figure 27. ^{1}H NMR spectrum of **60e**

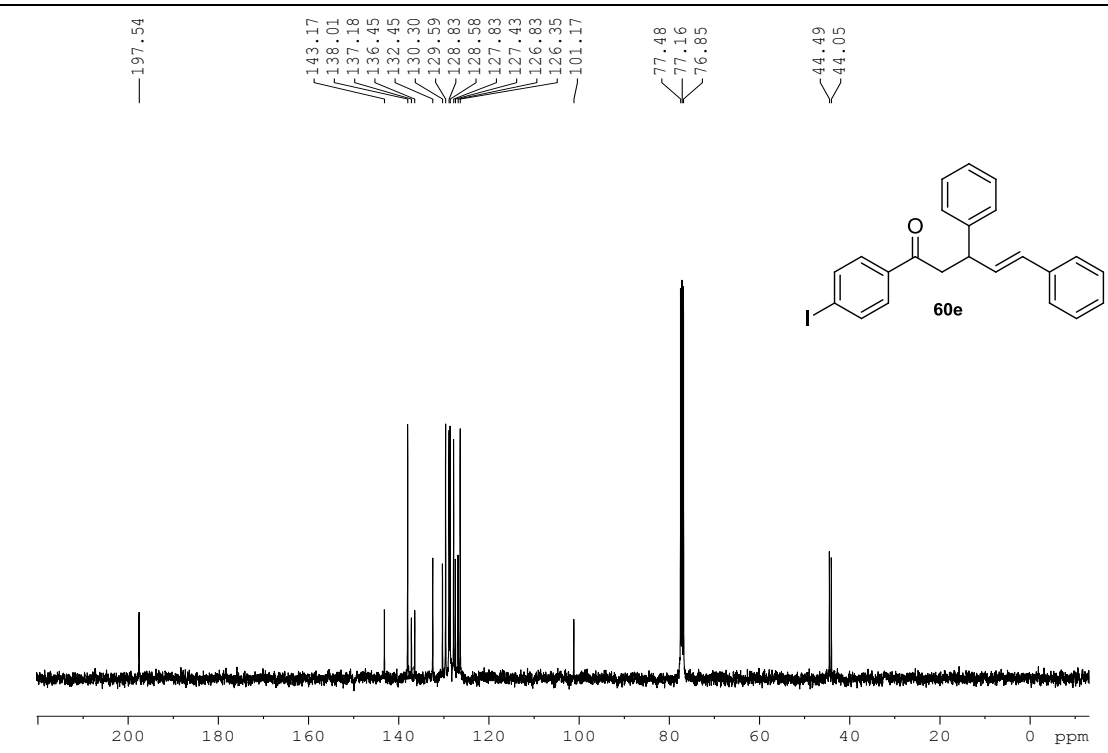

Figure 28. ^{13}C NMR spectrum of **60e**

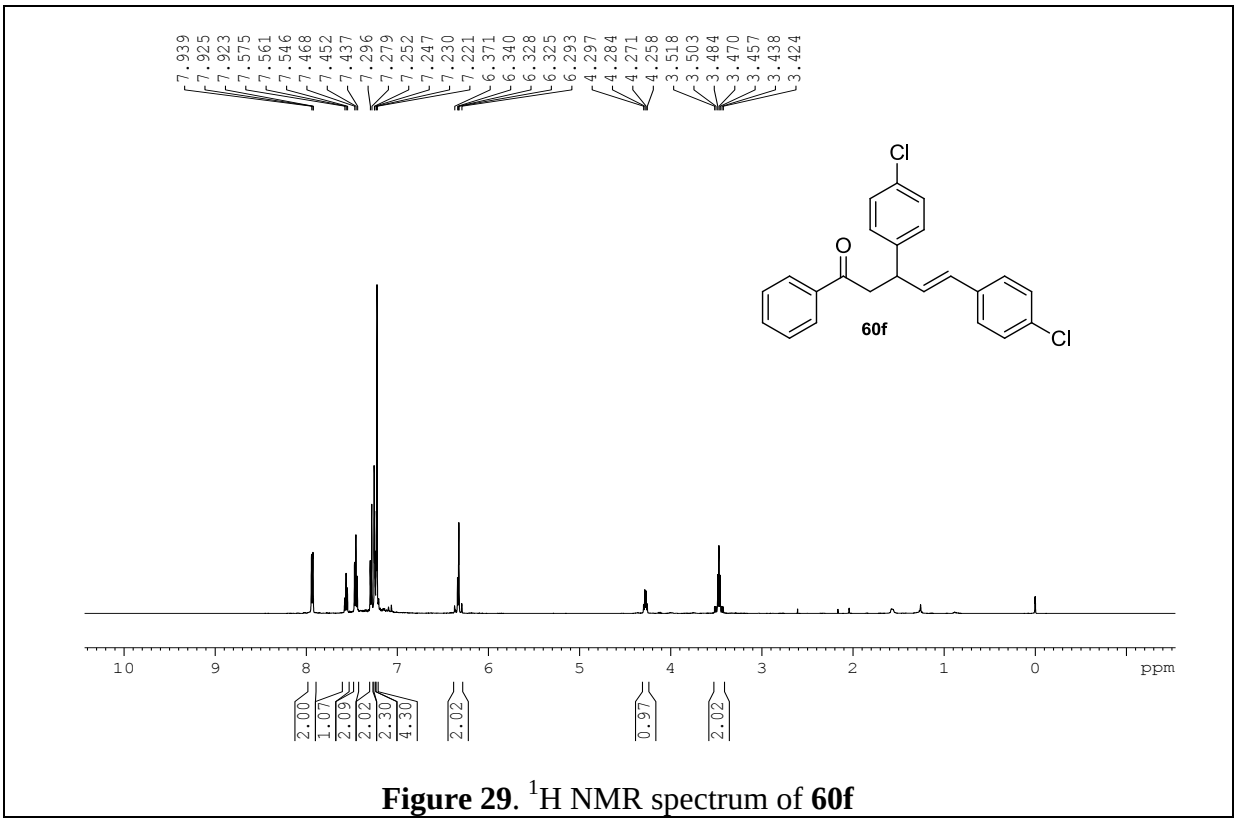

Figure 29. ^{1}H NMR spectrum of **60f**

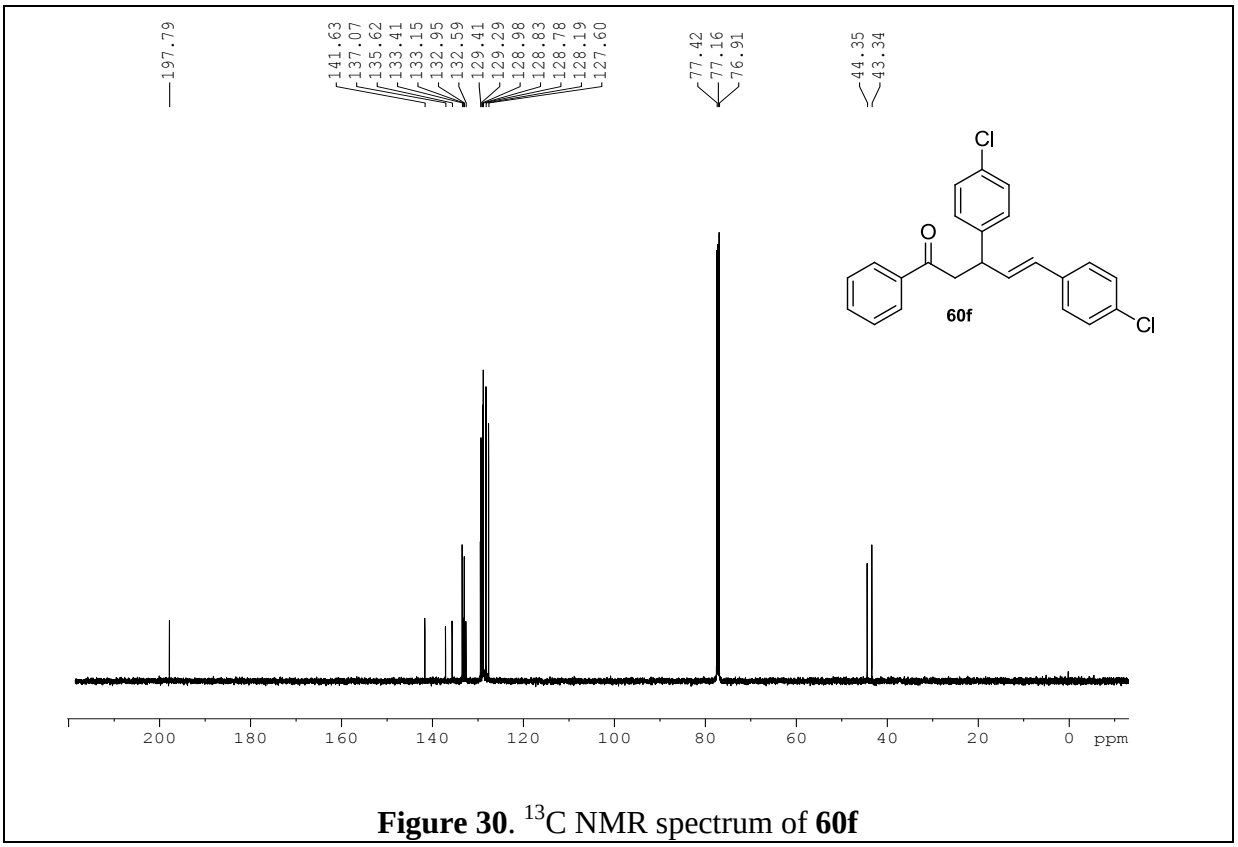

Figure 30. ^{13}C NMR spectrum of **60f**

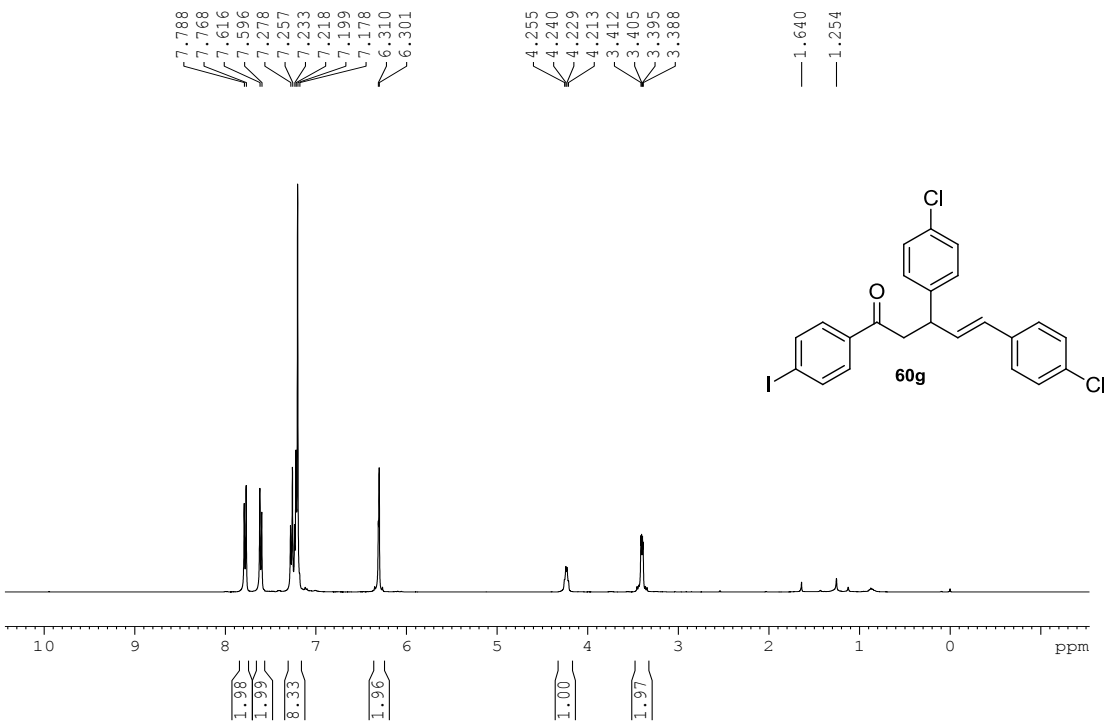

Figure 31. ^{1}H NMR spectrum of **60g**

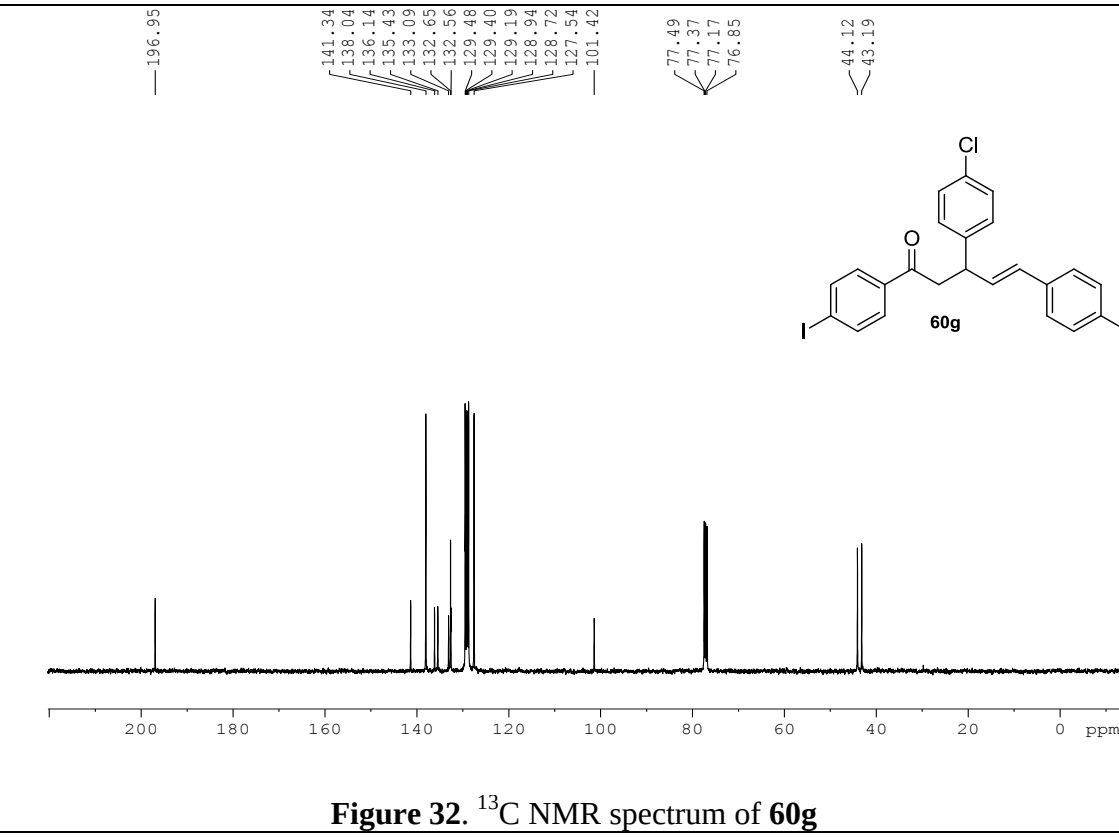

Figure 32. ^{13}C NMR spectrum of **60g**

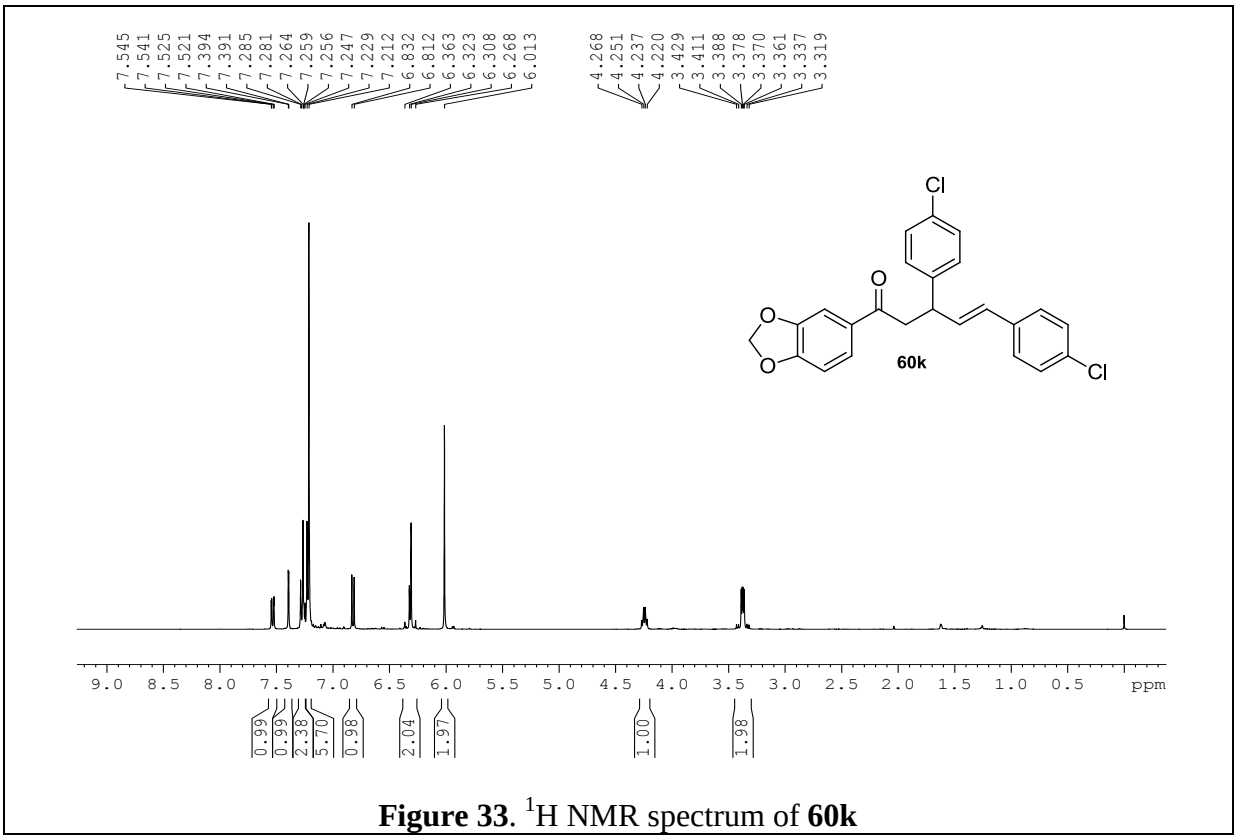

Figure 33. ^{1}H NMR spectrum of **60k**

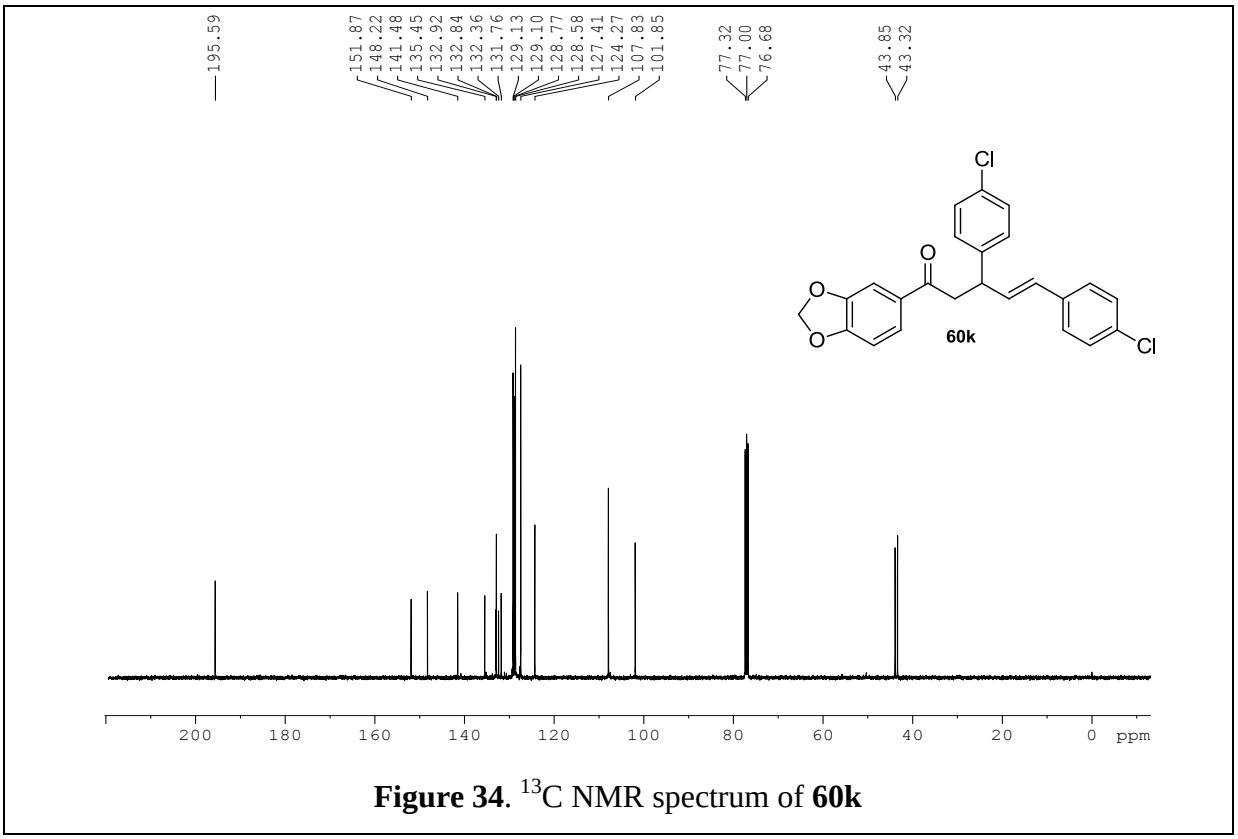

Figure 34. ^{13}C NMR spectrum of **60k**

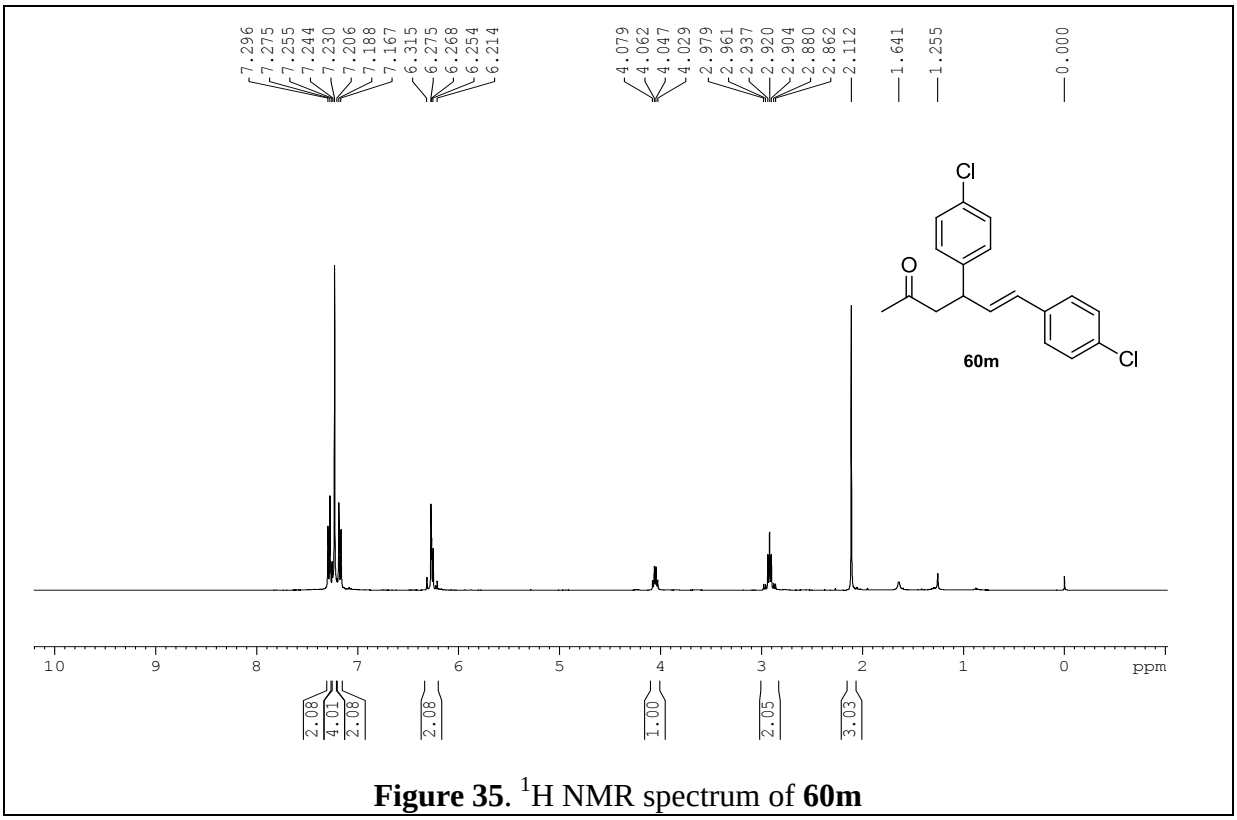

Figure 35. ^{1}H NMR spectrum of **60m**

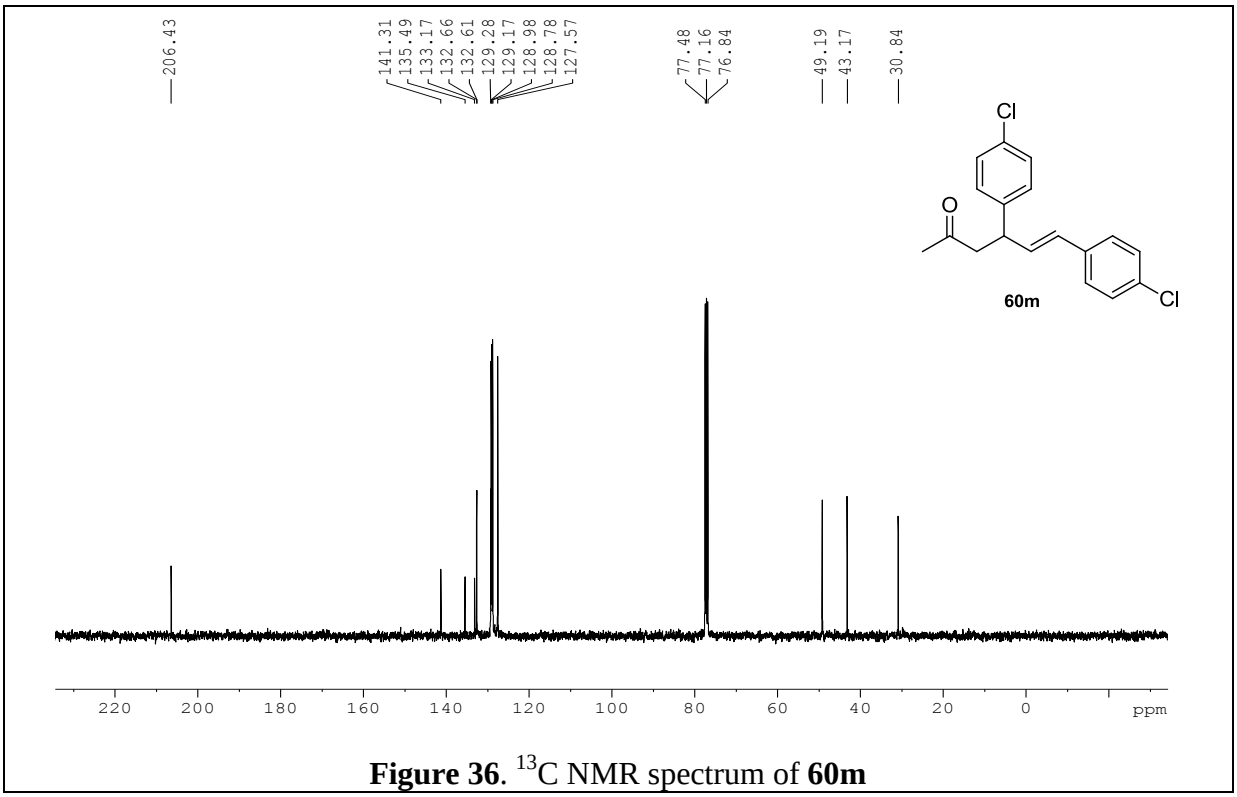

Figure 36. ^{13}C NMR spectrum of **60m**

10/5/2013 9:24 PM Chromatogram D:\DR.RBM LAB\NAVEEN\MMK1435REP-2.PRM Page 1 of 1

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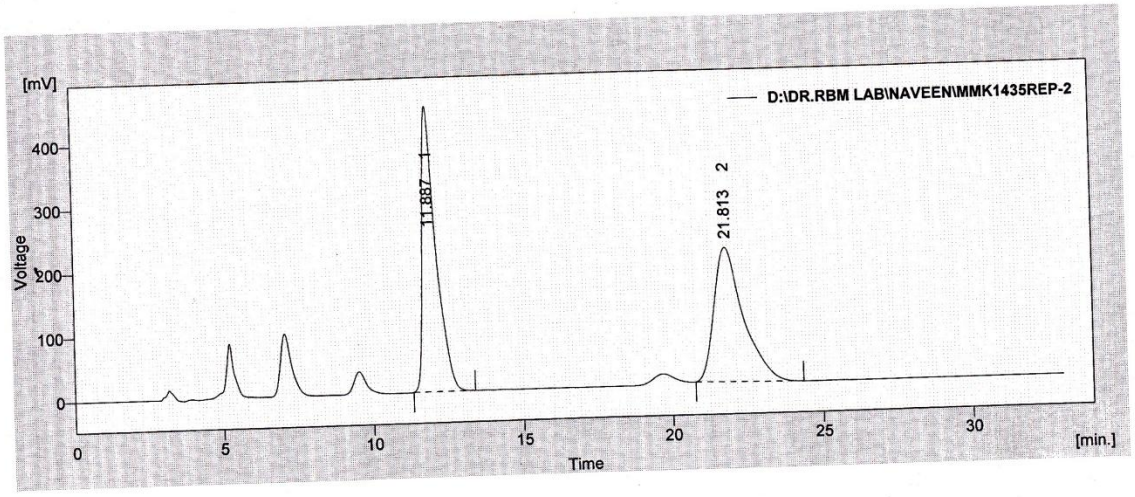

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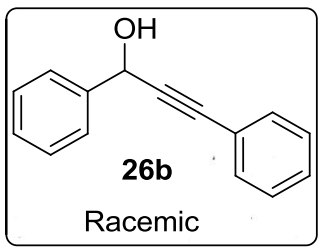

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ISTD Amount : 0
Dilution : 1

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Pressure : 38

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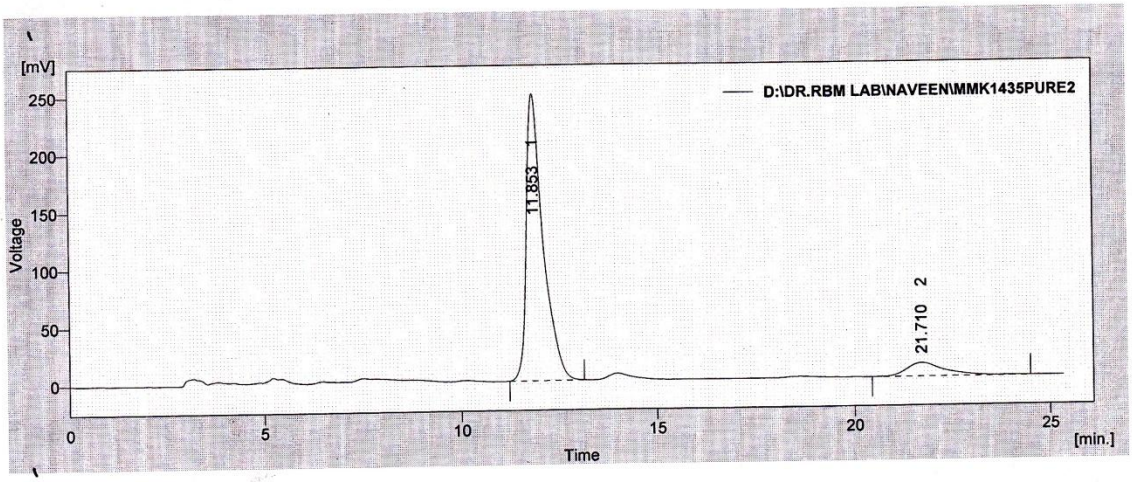

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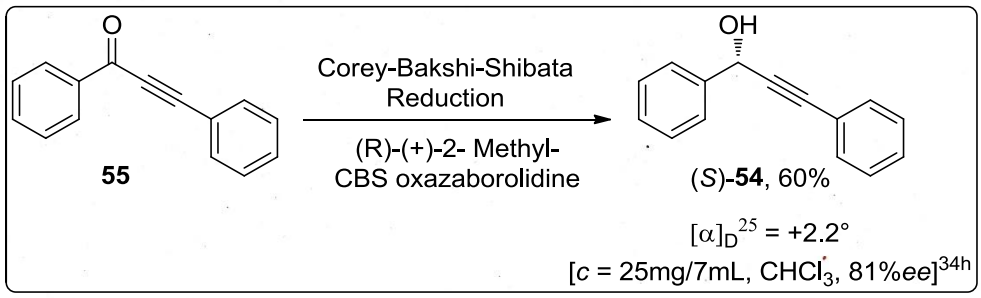

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SPINCHROM CFR
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ISTD Amount : 0
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Pressure : 41

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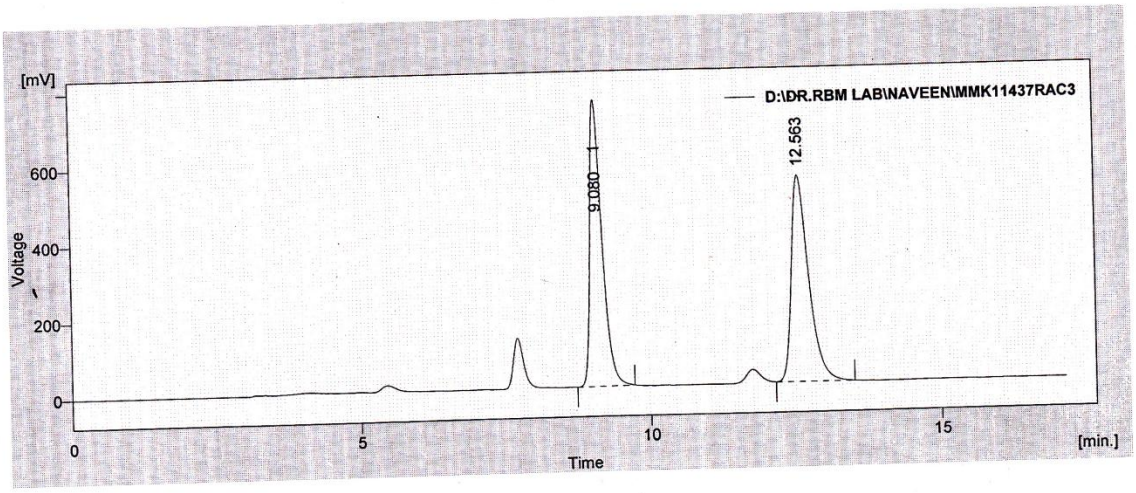

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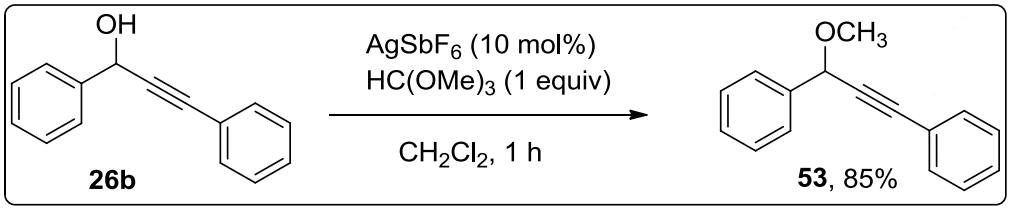

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SPINCHROM CFR
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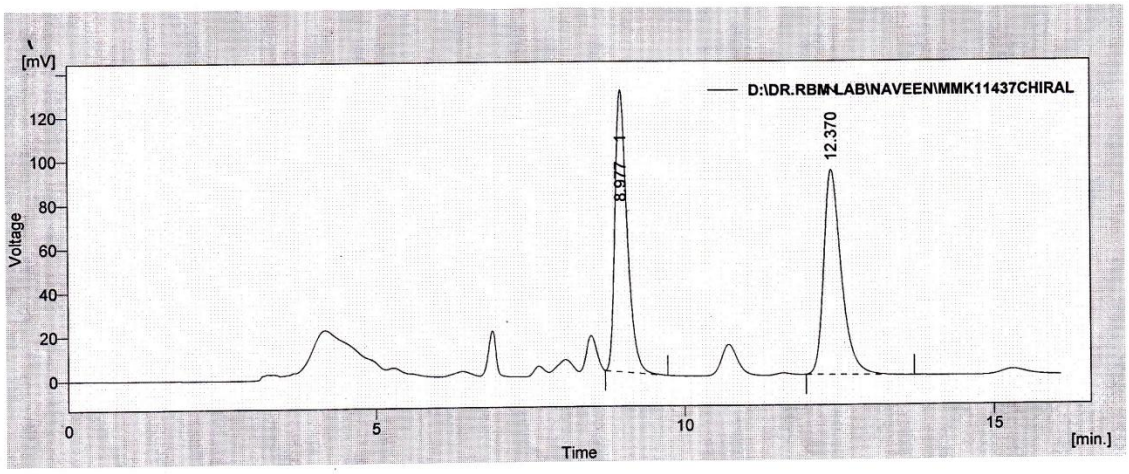
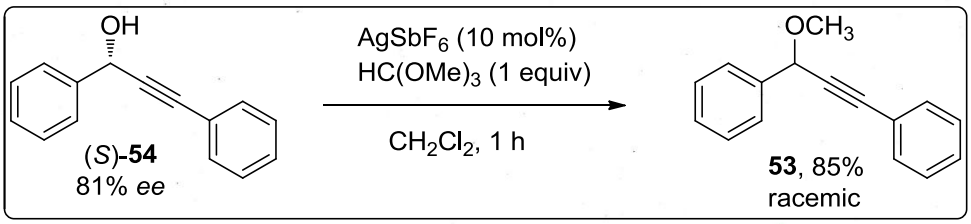
Detector 1	: Signal 1	Range 1	: Bipolar, 1250 mV, 10 Samp. per Sec.
Subtraction chromatogram	: (None)	Matching	: No Change



Result Table (Uncal - D:\DR.RBM LAB\NAVEEN\MMK11437CHIRAL)

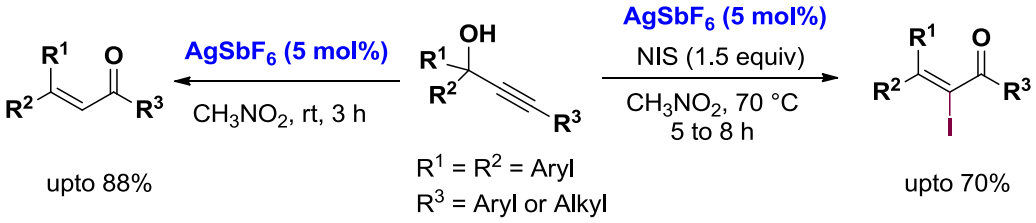
	Reten. Time [min]	Area [mV.s]	Height [mV]	Area [%]	Height [%]	W05 [min]
1	8.977	1762.269	128.897	48.8	57.9	0.21
2	12.370	1845.289	93.741	51.2	42.1	0.30
	Total	3607.558	222.638	100.0	100.0	



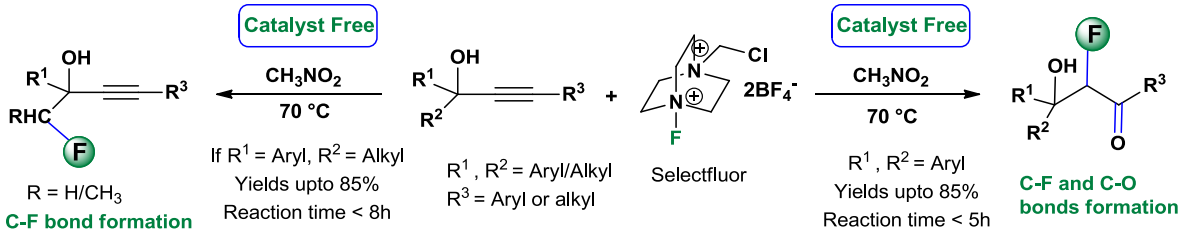
Chapter 2

Silver-Catalyzed Meyer-Schuster Rearrangement, Electrophilic Iodination and Fluorination of Tertiary Propargyl Alcohols

Silver-catalyzed Meyer-Schuster Rearrangement and Electrophilic Iodination



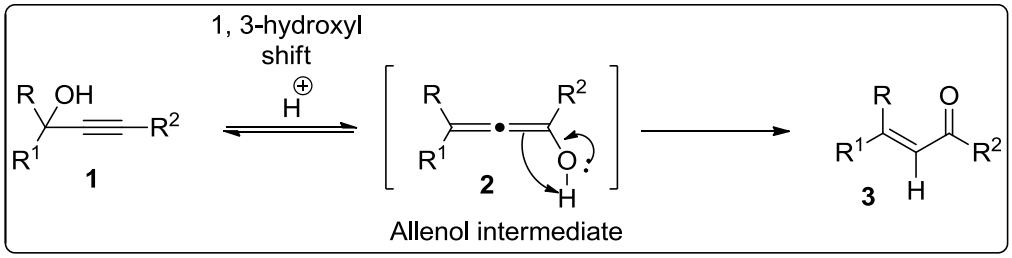
Electrophilic Fluorination Using Selectfluor



2.1 Introduction

2.1.1 Meyer-Schuster Rearrangement:

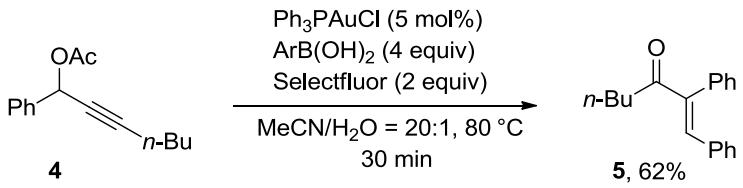
Transformation of propargylic alcohols to α,β-unsaturated carbonyl compounds *via* a simple 1,3-hydroxyl shift is Meyer-Schuster rearrangement (Scheme 1).[1a] This rearrangement enjoys significant interest in the view of atom economy, easily available starting materials, and possibility for the incorporation of electrophiles in the α-position of enone products.[1b]



Scheme 1. Meyer-Schuster rearrangement

Lewis acids like $AuCl_3$,[2] $AuCl(PPh_3)/AgOTf$,[3] $Au(PPh_3)NTf_2$,[4] $[(ItBu)AuCl]/AgSbF_6$[5], $Sc(OTf)_3$,[6] $InCl_3$,[6] and $Hg(OTf_2)$[7] catalyze this rearrangement. It is obvious from the mechanism that allenol (**2**) is the intermediate.

Homogenous gold-catalyzed oxidative coupling of propargyl acetates (**4**) with arylboronic acids has been reported by Zhang and co-workers. For the first time, Au^I/Au^{III} catalytic cycle was proposed for these coupling reactions that generate α-arylenones in one step. It involves a 3,3-propargyl rearrangement to afford allene intermediate similar to allenol. Hence it is identical to Mayer-Schuster rearrangement (Scheme 2).[8]

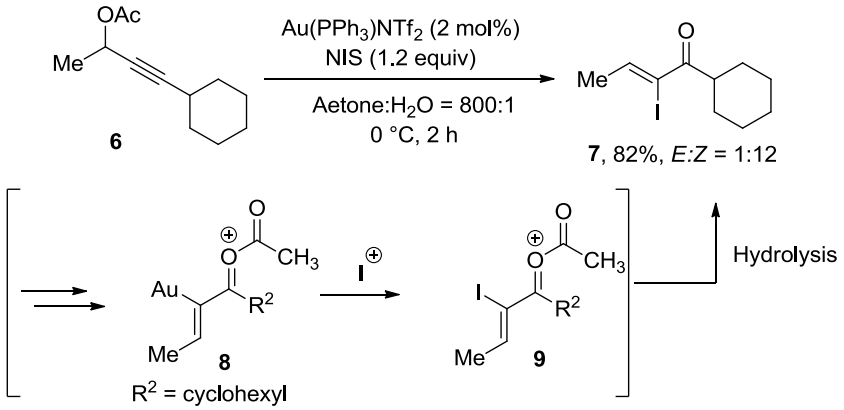


Scheme 2. Synthesis of arylenones using gold-catalysis

Keeping Meyer-Schuster rearrangement (Scheme 1) in mind we planned to capture allenol intermediate (**2**) with electrophiles like iodine and fluorine using tertiary propargyl alcohols. The outcome of these reactions is discussed in subsequent sections. A brief introduction for previous methods for electrophilic iodination is also described.

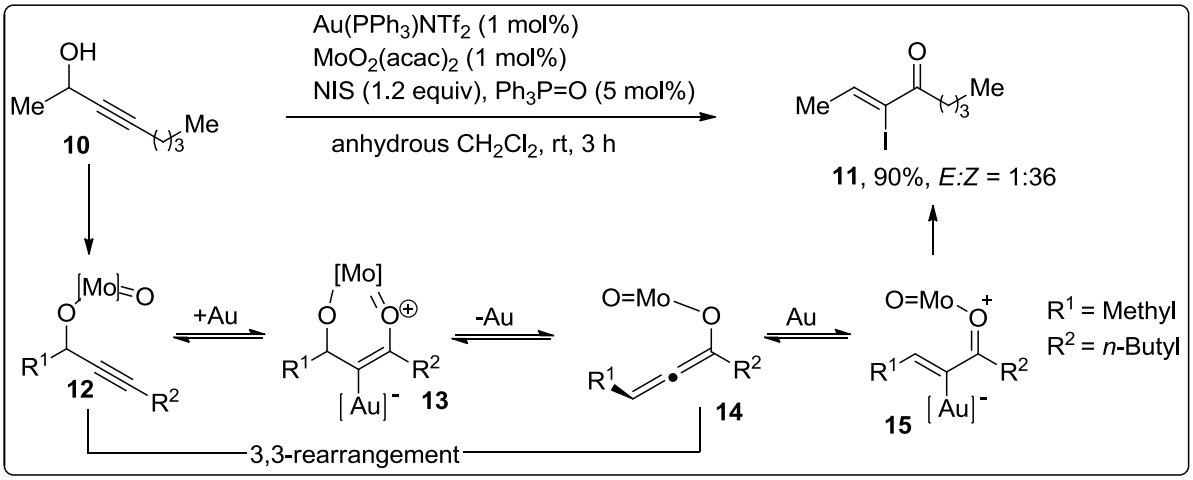
2.1.2 Lewis acids as catalysts in electrophilic iodination of propargyl alcohols

Transformation of propargylic acetates (**6**) into linear α-iodoenones (**7**) with *N*-iodosuccinimide (NIS) in the presence of gold-catalyst was reported by Zhang and co-workers. This reaction involves initial 3,3-rearrangement of propargylic esters to form carboxyallenes, followed by generation of highly reactive gold containing oxocarbenium ion (**8**) which in turn reacts with electrophilic iodine to give the product (Scheme 3).[9]



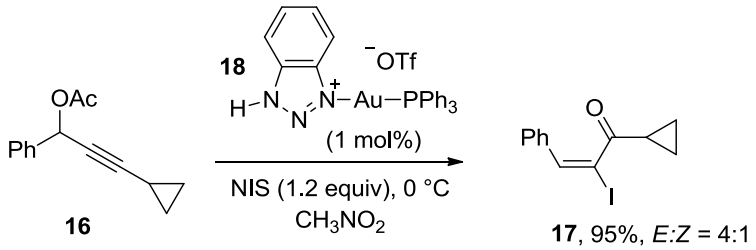
Scheme 3. Preparation of α-iodoenones using gold-catalysis

In 2009, same group used propargyl alcohol (**10**) as precursor instead of propargyl acetates for the same transformation and succeeded in preparing the desired α-haloenone products (**11**). The authors considered that replacing acetate with its equivalent surrogate (i,e which can easily be installed or cleaved) in situ could avoid prefunctionalization of propargyl alcohol. They found catalytic $MoO_2(acac)_2$ is excellent in serving this purpose (Scheme 3). They found that this methodology is superior than the previous reports in terms of broader substrate scope, reaction conditions and diastereoselectivity. The key step in the mechanism is 3,3-rearrangement (**14**) followed by formation of reactive gold and molybdenum containing oxocarbenium ion (**15**) (Scheme 4).[10]



Scheme 4. Preparation of α-iodoenones using gold-Mo catalysis

Shi and co-workers demonstrated an attractive chemoselective transformation of propargyl acetates (**16**) to α-haloenones (**17**) in the presence of triazole-gold catalysts (**18**). Unusually, kinetically favoured *E*-isomers were formed as major products in the reaction which is in contrast with the above mentioned reports (Schemes 3 and 4). The reaction proceeds through propargyl acetate rearrangement (3,3-rearrangement) and subsequent halogen addition to allene (Scheme 5).[11]



Scheme 5. Au-triazole catalyzed synthesis of α-iodoenones

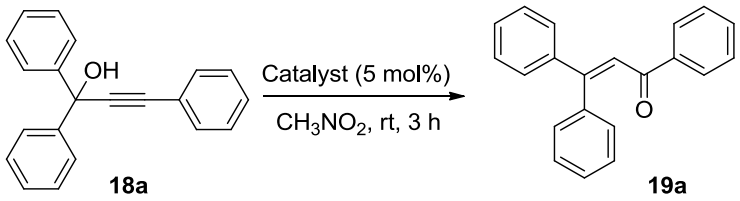
All the above illustrated methods used propargyl acetates/alcohols *via* initial propargyl rearrangement (3,3-shift/1,3-shift) to generate allene intermediates which resembles allenol intermediate (**2**) of Meyer-Schuster rearrangement.

2.1.3 Results and Discussion

While we were working on direct α-alkylation of ketones using $HC(OMe)_3$ and catalytic $AgSbF_6$ with tertiary propargyl alcohols an unexpected α,β-unsaturated enone (**3**) was obtained instead of α-alkylated product. This is due to the rearrangement of tertiary propargyl alcohol in the presence of $AgSbF_6$ famously known as Meyer-Schuster rearrangement (Scheme 1). Encouraged by this observation we started investigating this reaction in more detail using less expensive Ag catalyst as expensive gold catalysts have been employed to carry out this reaction.

Optimization of this rearrangement was carried out using **18a** as substrate and silver salts as catalysts. As described earlier, when **18a** and acetophenone, were reacted in the presence of $HC(OMe)_3$ and $AgSbF_6$ (10 mol%) it furnished 71% of **19a** at room temperature in 24 h. When we carried out the same reaction of **18a** in the absence of acetophenone with 5 mol% of $AgSbF_6$, we were pleased to get the same yield (Table 1, entry 10). After screening of different solvents, we found CH_3NO_2 as the best. We then tested different catalysts for Meyer-Schuster rearrangement of tertiary propargyl alcohols as shown in Table 1. Out of the screened catalysts $AgSbF_6$ delivered highest yield (Table 1, entry 7). Even anhydrous $FeCl_3$ and $Cu(OTf)_2$ are effective (Table 1, entry 8 and 9).

Table 1. Optimization Studies:



18a **19a**

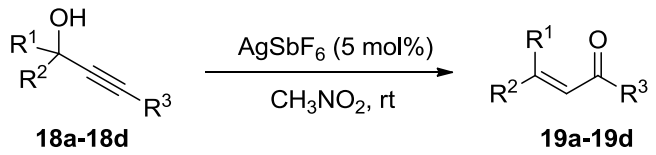
S. No	Catalyst [a]	Yield%[b]
1	$AgPF_6$	60
2	AgOTf	74
3	$AgBF_4$	66
4	$AgNTf_2$	65
5	$AgClO_4$	64

S. No	Catalyst [a]	Yield%[b]
6	$AgNO_3$	nr
7	**$AgSbF_6$**	**80**
8	$Cu(OTf)_2$	72
9	Anhyd $FeCl_3$	74
10	$AgSbF_6(CH_2Cl_2)$	71
11	$AgSbF_6$ (Toluene)	20
12	$AgSbF_6$ (DCE)	5
13	$AgSbF_6$ (MeOH)	nr
14	$AgSbF_6$ (CH_3CN)	nr

[a] 5 mol% of catalyst, [b] isolated yields, nr: no reaction

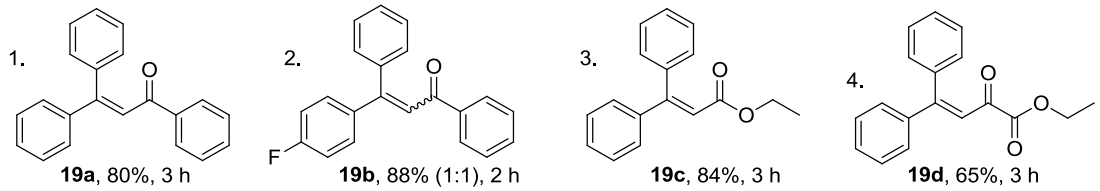
With the optimized condition in hand, we subjected few tertiary propargyl alcohols to the reaction conditions, to accomplish the corresponding rearranged products as shown in Table 2.

Table 2. Results of $AgSbF_6$-catalyzed Mayer-Schuster rearrangement of tertiary propargyl alcohols



18a-18d **19a-19d**

18a = $R^1 = R^2 = R^3$= Ph
18b = $R^1 = R^3$ = Ph, R^2 = *p*-fluorophenyl
18c = $R^1 = R^2$ = Ph, R^3= -OEt
18d = $R^1 = R^2$ = Ph, R^3= $-CO_2Et$



19a, 80%, 3 h **19b**, 88% (1:1), 2 h **19c**, 84%, 3 h **19d**, 65%, 3 h

Value in parenthesis indicates *E*/*Z* ratio based on ^{1}H NMR

Substrate with a of fluoro substituent at *p*-position at one of the phenyl of **18a** resulted in 88% of yield within two hours (Table 2, entry 2). Gratifyingly, electron rich

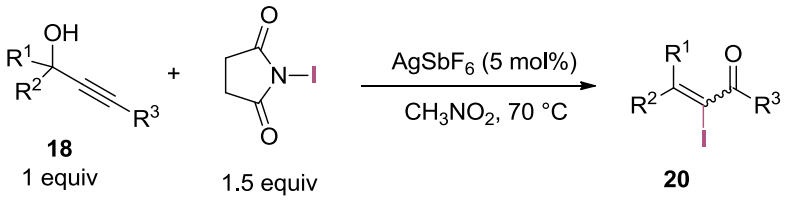
alkyne **18c** readily reacted under the reaction conditions to furnish 84% of **19c** (Table 2, entry 3). Similarly switching to electron defficient alkyne **18d** ended up in 19d in comparatively lesser yield 65% yield (Table 2, entry 4), this may be due to the electronwithdrawing nature of ester group (-CO_2Et), destabilizing the formation of allenol intermediate (**2**). Unfortunately, aliphatic or secondary benzylic propargyl alcohols didn't react under the reaction condition.

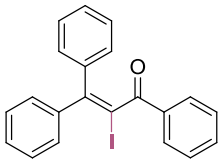
Since our interest were in introducing functionalities in the Mayer-Schuster rearrangement of tertiary propargyl alcohols using $AgSbF_6$, we were enthusiastic about carrying out the reaction in the presence of electrophiles like 'I^+' and 'F^+'. The summary of our results are described below.

Preliminary screening of our optimized reaction condition (i. e., 5 mol% of $AgSbF_6$ in CH_3NO_2) for electrophilic iodination was carried out in the presence of 1.5 equivalents of NIS at room temperature. It did not give the expected product. The same reaction was repeated by heating the reaction to 70 ˚C without changing any other parameters. It resulted in 70% of iodine incorporated product (**20)**. With this optimized condition we screened different tertiary propargyl alcohols to get the α-iodoenones as shown in Table 3.

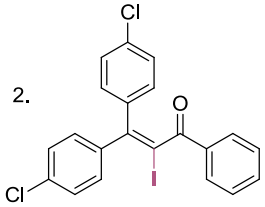
Tertiary propargyl alcohols having same aryl groups on the carbinol carbon resulted in single product (Table 3, entry 1 and 2), where as tertiary propargyl alcohols having different aryl groups on the carbinol carbon furnished, mixture of *E* and *Z* isomers (Table 3, entries 3 to 9). Substrates with substituents like chloro, methyl and bromo reacted smoothly to provide the corresponding products in moderate yield. Even alkyl substituted tertiary propargyl alcohols afforded good yields of the desired product (Table 3, entry 9). Thus formed highly substituted α-iodoenones are significant in constructing valuable building blocks.[12] The α-iodine can be substituted with diverse carbon substituents like alkyl, alkenyl, alkynyl, aryl *etc.* through transition metal catalyzed coupling reactions.[13]

Table 3: Results of $AgSbF_6$-catalyzed electrophilic iodination of tertiary propargyl alcohols with NIS

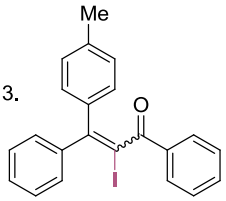


1. 

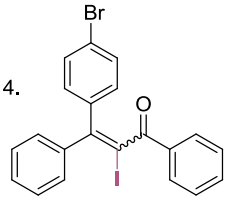
20a, 70%, 5 h

2. 

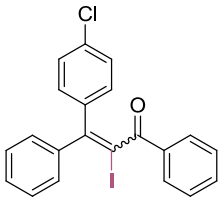
20b, 59%, 4 1/2 h

3. 

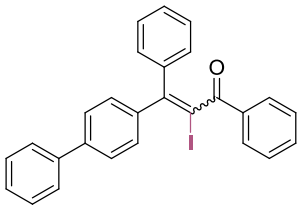
20c, 67% (1:2.5), 4 1/2 h

4. 

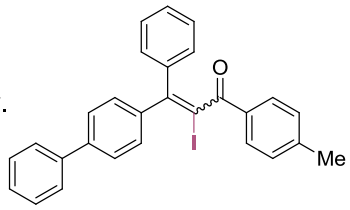
20d, 56% (1:1), 5 1/2 h

5. 

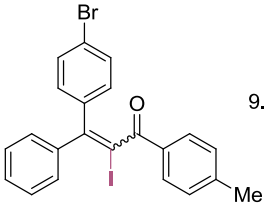
20e, 60% (1:1), 6 1/2 h

6. 

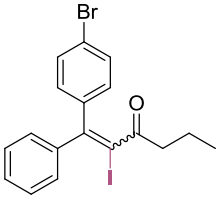
20f, 55% (1:1), 5 1/2 h

7. 

20g, 68% (1:1), 7 1/2 h

8. 

20h, 63% (1:1.3), 5 h

9. 

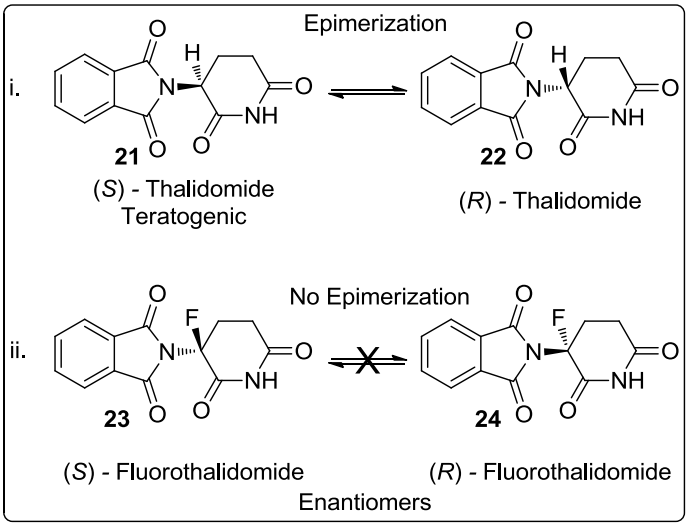
20i, 68% (1:1), 7 1/2 h

Value in parenthesis indicates *E*/*Z* isomeric ratio based on ^{1}H NMR

2.2 Electrophilic fluorination of tertiary propargyl alcohols

2.2.1 Importance of fluorine containing organic compounds:

Fluorine incorporated organic compounds are very important because they are few in nature[14] and widely used in areas such as diagnostics, medicinal chemistry, pharmaceuticals and agrochemicals.[15] This is because of the physicochemical[16a] and biological properties of fluorine and C-F bond. As C-F bond is a strong bond it is hard to dissociate thereby increases the selectivity and metabolic activity of drug. Further, it affects the pK_a value of neighbouring groups as well.[16b-f] So in this context 20% of pharmaceutical drugs contain C-F bond. Fluorine can, sometimes be used as an isostere for hydrogen or hydroxyl group in biologically active molecules, because van der Waal radius of fluorine is 1.47 Å, which lies between that of oxygen 1.57 Å and hydrogen 1.20 Å. Therefore fluorine substitution exerts only a minor steric perturbation when incorporated into a molecule. The pharmaceutical use of fluorine substitution is described with a familiar example of thalidomide.



Scheme 6. Fluorine incorporated thalidomide enantiomers

Racemic thalidomide was used as a sedative-hypnotic drug for the treatment of morning sickness in pregnant women. Later, it was found as teratogenic causing severe birth defects to babies born to mothers who administered it. It was realized that *(S)*-thalidomide (**21**) was the reason for teratogenic nature of racemic thalidomide. Thalidomide rapidly epimerizes *in vivo* due to the presence of acidic hydrogen atom on stereogenic centre (i, Scheme 6). So it is difficult to handle the enantiomers separately (**21** or **22**). By simple

replacement of acidic 'H' with 'F' allows synthesis of individual enantiomers and prevents epimerization (ii, Scheme 6).[15b]

Positron emission tomography (PET) is a powerful method to detect cancer cells in human body.[17] Radionuclides used for this process are ^{11}C, ^{13}N, ^{15}O and ^{18}F labeled atoms and the half lives of these atoms are 20 min, 10 min, 2 min and 110 min respectively. As the half life of ^{18}F is more, it is extensively used in this process.^{18}Fluorodeoxyglucose (**5**) is commonly used for this purpose (Figure 1).

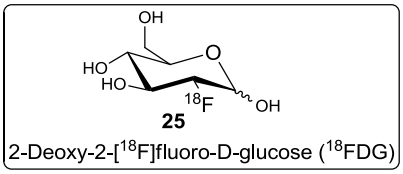
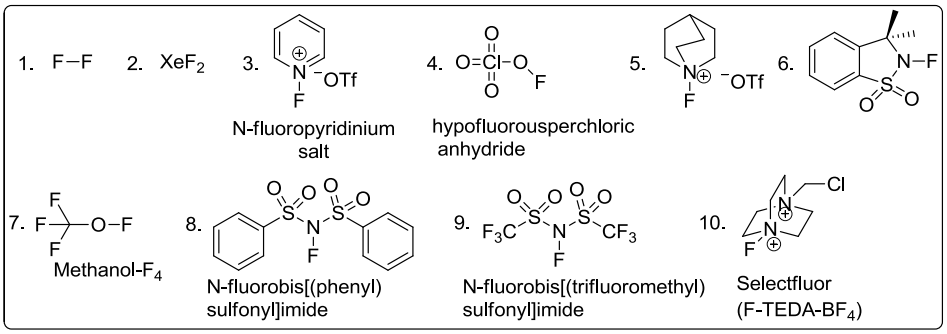


Figure 1. ^{18}Fluorine deoxyglucose used in PET imaging.

Introduction of F into organic molecules can be done by nucleophilic fluorinating reagents (F^-) or electrophilic fluorinating reagents (F^+) (Figure 2).[18]

(a) Electrophilic fluorinating reagents



(b) Nucleophilic fluorinating reagents

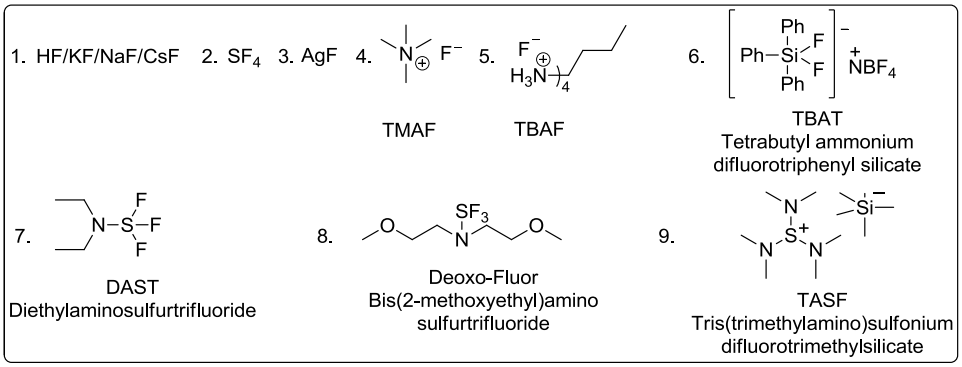


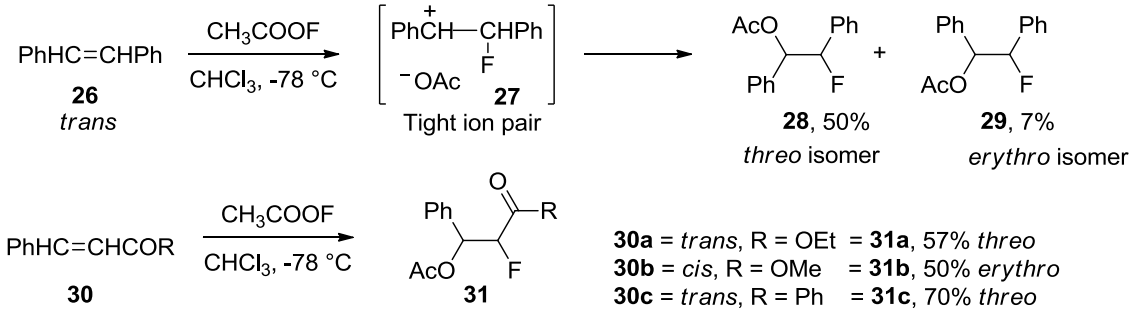
Figure 2. Electrophilic and nucleophilic fluorinating reagents[19]

2.2.2 Electrophilic fluorinations

Due to the high electronegativity of fluorine (F^-), nucleophilic fluorination involves high kinetic barriers in forming C-F bonds. The general tendency of fluorine (F^-) to form strong hydrogen bonds with hydrogen and hydrogen bond donors makes it difficult for nucleophilic fluorination. Whereas electrophilic fluorination involve a simple nucleophilic attack of nucleophile at fluorine *via* $\mathbf{S_N2}$ nucleophilic displacement. Functional group tolerant, stable electrophilic fluorinating reagents as shown in Figure 2 serve as excellent sources for "F^+"(electrophilic fluorine). Few reactions which involve electrophilic α-flourination with alkenes and alkynes compounds related to our work (α-fluoro hydroxy) are briefly described here.

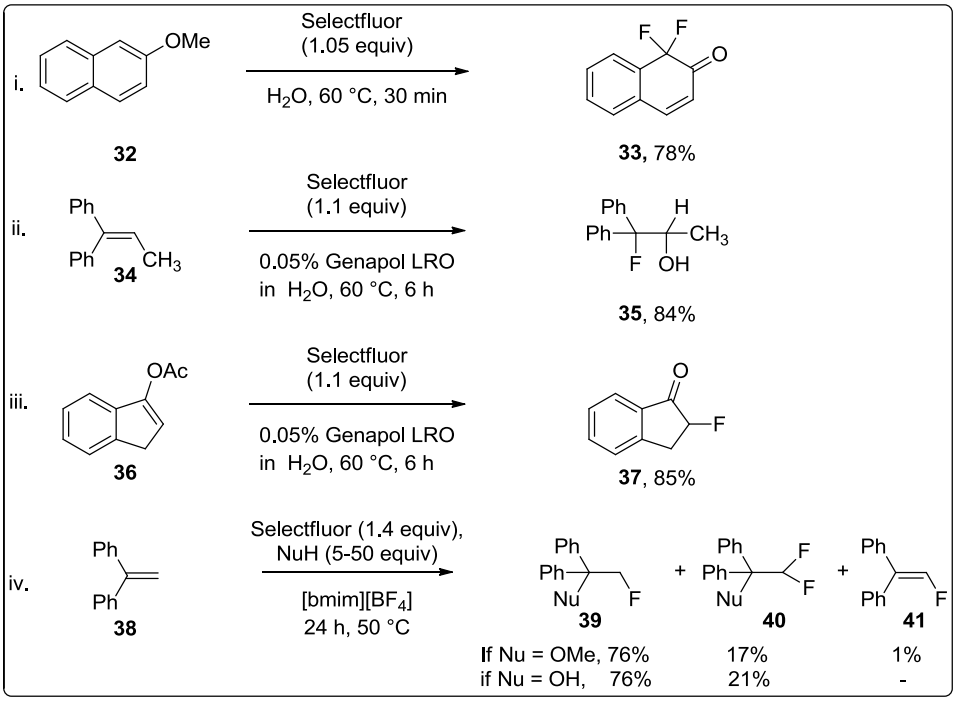
2.2.2.1 Electrophilic fluorination of alkenes

In 1981 Rozen group, for the first time, synthesized acetyl hypofluorite (CH_3COOF) from elemental fluorine. This new reagent 'AcOF' is a good source for electrophilic fluorine to react with unsaturated systems. It can incorporate '^{18}F' to specific sites in biologically interesting molecules which are difficult to make using other reagents. Generally, it reacts with olefins to produce fluorohydrins. The authors found that, this reagent is superior than their previous finding CF_3COOF[20a] as it is limited to the fluorination of stilbenes only. 'AcOF' adds across a variety of double bonds and predominantly in *syn* mode. For example, it reacts with *trans* stilbene (**26**) to produce *threo* isomer (**28**) as shown in the Scheme 7. It is proposed that reaction proceeds through a tight ion pair (**27**) which collapses rapidly to give *syn* addition products. Regioselectivity was observed when unsymmetrical alkenes were used. Even addition of fluorine to usually difficult deactivated α,β-unsaturated carbonyls can be achieved with CH_3COOF (Scheme 7).[20b]



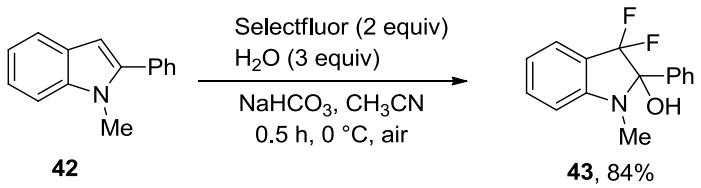
Scheme 7. Addition of CH_3COOF to alkenes to form fluorohydrins

In 2004, Stavber group reported fluorination of various types of organic compounds using selectfluor in green solvent water. Substrates like alkoxynapthalenes (**32**), alkenes (**34** and **38**) and acetoxyenols (**36**) underwent fluorinations smoothly (Scheme 8).[21a, 21b]



Scheme 8. Addition of electrophilic fluorine across double bonds

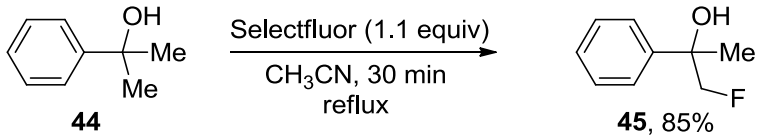
Difluorohydroxylation of substituted indoles (**42**) has been achieved with selectfluor by Lin *et al.* Two equivalents of selectfluor in acetonitrile solvent and 1 equivalent of base ($NaHCO_3$) were needed for this conversion (Scheme 9).[22]



Scheme 9. Electrophilic fluorination of indoles

In 1994, Stavber *et al.* reported a selective method for the conversion of alcohols (**44**) into vicinal fluorohydrins (**45**) using selectfluor. The preferred alcohols are benzylic tertiary alcohols. Using selectfluor the products were formed comfortably *via* electrophilic

fluorination (Scheme 10).[23] This method is advantageous over other known methods like ring-opening of epoxide by HF,[24] KHF_2-AlF_3,[25] and addition of HOF[26] to double bonds.



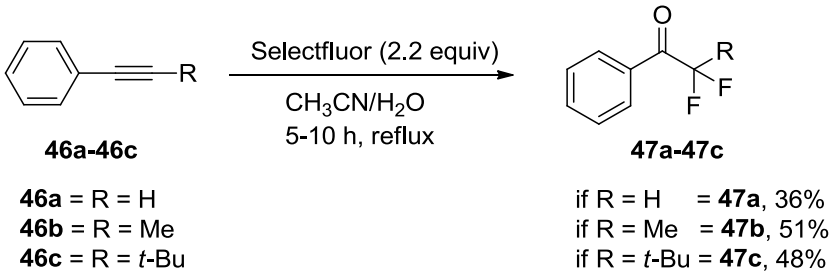
Scheme 10. Preparation of fluorohydrins with tertiary alcohols using selectfluor

Other methods for the introduction of 'F' in organic molecules includes, allylboration of ketones,[27] ring-opening of epoxides,[28] fluorination of allenes,[29] addition of fluorine to allyl silanes.[30a] Recently, synthesis of α,β-unsaturated monofluoro ketones was reported by Hammond and co-workers.[30b] Wolf and co-workers synthesized pentafluorinated β-hydroxy ketones from trifluoroketones.[30c]

2.2.2.2 Electrophilic fluorination of alkynes

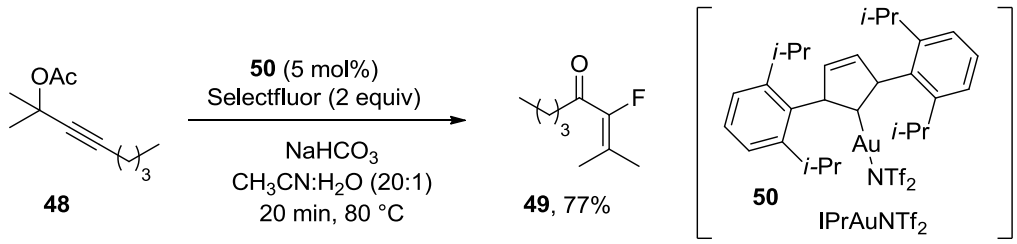
As discussed above in the section 2.2.2.1 there are a number of ways to incorporate fluorine to alkenes but only very few methods are known for electrophilic fluorination of alkynes. This is because of less reactivity of triple bond towards electrophilic reagents, which forms unstable vinyl cation. Fluorinating agents like F_3COF,[31] F_2/MeOH,[32] XeF_2,[33] and $CsSO_4F$,[34] add to alkynes and results in products of uncontrolled fluorinations (tri, tetra fluorinations) and oxidized products.

Stavber and co-workers reported a regioselective transformation of substituted phenyl acetylene to difluoro ketones. If acetylenic hydrogen of phenylacetylene (**46a**) is replaced by methyl group (**46b**), increase in reactivity is noticed. However a decrease in reactivity is observed when a methyl group is substituted by bulky tertiary butyl group as shown in Scheme 11.[35]



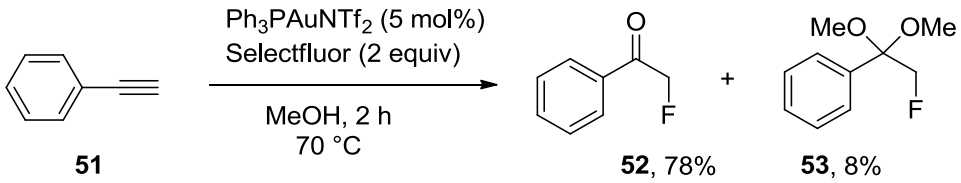
Scheme 11. Fluorination of alkynes using selectfluor

Nevado and co-workers reported an excellent method for the synthesis of α-fluoroenones (**49**) using Au-catalyst (**50**) in presence of selectfluor. 1,3-Acyloxy migration of acetoxy group of propargyl acetate (**48**) in presence of gold-catalyst is the key step in this method. They also found that, the ligand bound to gold plays an important role in the reaction outcome (Scheme 12).[36]



Scheme 12. Gold-catalyzed synthesis of α-fluoroenones

Gouverneur group achieved a similar transformation by using SIPrAuCl (2 mol%)/AgOTf (12.5 mol%) catalytic system.[37a] Nevado group reported the synthesis of α-fluoroketones and α-fluoroacetals from alkynes using gold catalyst and selectfluor (Scheme 13).[37b]

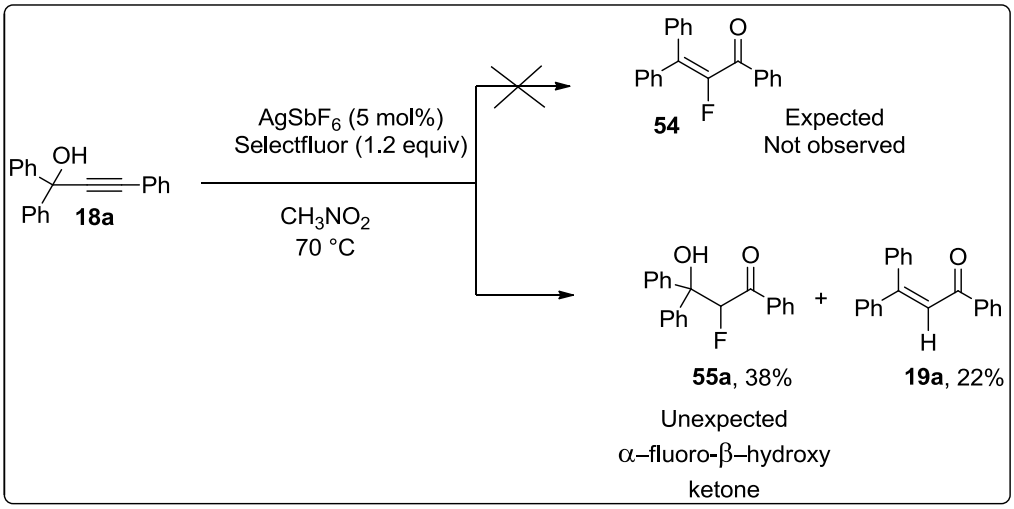


Scheme 13. Gold-catalyzed synthesis of α-fluoroketones and α-fluoroacetals

2.2.3 Results and Discussion

After successfully demonstrating electrophilic iodination of tertiary propargyl alcohols we shifted our focus on electrophilic fluorination. We chose selectfluor as electrophilic fluorine source because it is stable, non-hygroscopic, easy to handle and commercially available. Picking **18a** as substrate and selectfluor as fluorine source we applied our optimized condition of $AgSbF_6$-catalyzed Meyer-Schuster rearrangement to check the outcome of the reaction. Instead of expected α-fluoroenone product (**54**), surprisingly, α-fluoro-β-hydroxy ketone product (**55a**) was obtained along with α, β-unsaturated ketone (**19a**) as shown in Scheme 14. The obtained product has interesting

functionalities such as gem-diaryl methyl hydroxyl, fluoro and carbonyl groups. This forced us to investigate this reaction further.



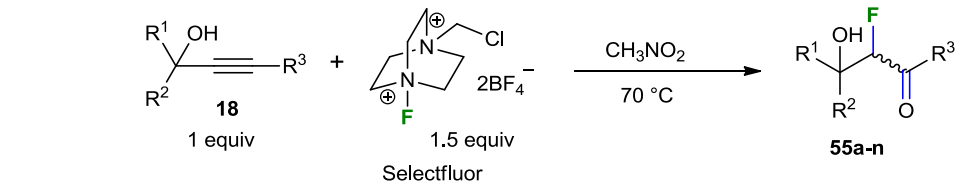
Scheme 14. Unexpected α-fluoro-β-hydroxy ketone formation

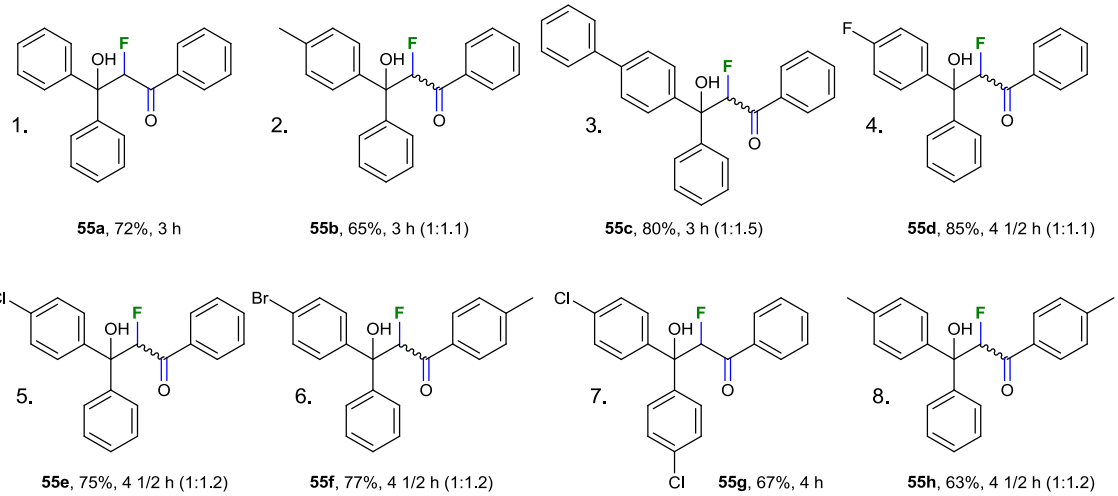
To examine the appropriate reaction condition we performed several reactions, but all the attempts to get the product were failed. This might be due to the competitive Meyer-Schuster reaction which gives the unwanted enone (**19a**). We believed that if the formation of enone product is suppressed the yield of desired product (**55a**) could be increased. During our study we realized that catalyst used is responsible for enone formation. Then we conducted a reaction without catalyst at room temperature. No reaction was observed and the starting material **18a** remained unreacted. We then performed the same reaction at 70 ˚C. To our delight the desired product (**55a**) was formed in 72% yield. Unfortunately when we applied the standard condition reported by Stavber group[35] i.e., CH_3CN as solvent and 10 equiv of water and 1.5 equiv of selectfluor the reaction resulted in only 45% of the desired product (**55a**) and in CH_3CN alone 48% yield was isolated. In CH_3NO_2, reaction of **18a** with selectfluor in the presence of 10 equiv of water at 70 °C resulted in 52% yield of **55a**. Hence the best way for the formation of **55a** is the reaction of 1.5 equivalents of selectfluor, 1 equiv of **18a** in CH_3NO_2 at 70 ˚C.

Different propargyl alcohols were subjected to the reaction conditions to get moderate to good yields of the desired products as shown in Table 4. Tertiary propargyl alcohols having same aryl groups as in **55a**, **55g** and **55n** (Table 4) resulted in racemic mixture, where as tertiary propargyl alcohols having different aryl groups on carbinol carbon gave a mixture

of diastereomers as expected. Substrates with substituents like F, Br, Cl, Ph on one of the phenyl rings of **18** reacted smoothly to furnish the products.

Table 4. Results of electrophilic fluorination of tertiary propargyl alcohols using $AgSbF_6$





55a, 72%, 3 h

55b, 65%, 3 h (1:1.1)

55c, 80%, 3 h (1:1.5)

55d, 85%, 4 1/2 h (1:1.1)

55e, 75%, 4 1/2 h (1:1.2)

55f, 77%, 4 1/2 h (1:1.2)

55g, 67%, 4 h

55h, 63%, 4 1/2 h (1:1.2)

55i, 64%, 4 1/2 h (1:1.3)

55j, 73%, 41 /2 h (1:1.1)

55k, 45%, 3 h (1:1)

55l, 47%, 2 h (1:1.3)

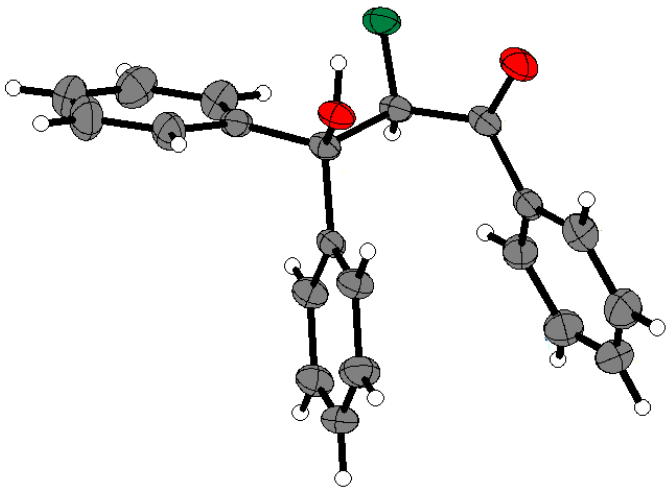
55m, 50%, 4 1/2 h

55n, 40%, 4 1/2 h

Reaction Conditions: 1 equiv of **18**, 1.5 equiv of selectfluor, ratio in parenthesis indicates diastereomeric ratio.

Even propargyl alcohols having aliphatic substituents on the alkyne reacted nicely to give moderate yields of the corresponding products (Table 4, **55k-55m**). We were pleased when electron rich propargyl alcohol (**18d**) resulted in 40% yield. Strong electron donating group 'OMe' containing propargyl alcohol, 1,1-bis(4-methoxyphenyl)-3-phenylprop-2-yn-1-ol didn't deliver the desired product. Aliphatic, terminal tertiary propargyl alcohols didn't react under the reaction conditions. Secondary propargyl alcohols didn't give the desired products under the reaction conditions. It is known that selectfluor is also a strong oxidant and if heteroatoms like oxygen is present with availability of hydrogen it tends to result in oxidized product rather than fluorinated product.[40] Structure of the product **55**a was further confirmed by X-ray crystallography. The ORTEP picture is shown in Figure 3

Figure 3. ORTEP picture of 55a

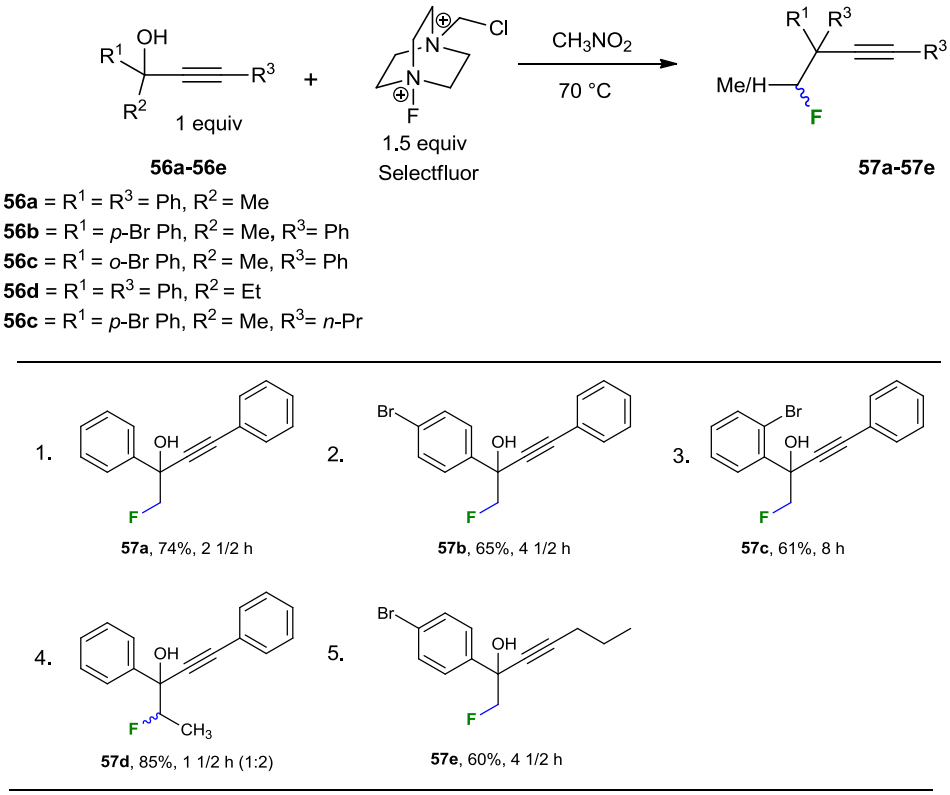


The reaction that we have developed produces product (**55**) have interesting structural features. Moreover, monofluorination, which is unusual, was observed in our case.[38a,b] On the other hand propargyl alcohols are employed for preparing propargyl fluorides.[39] which is in sharp contrast with our method. Checking their bioactivities is a meaningful work to carry out.

When we checked the scope of the reaction further with aliphatic substrates **56a**, under similar conditions, the reaction resulted in simple vicinal fluorohydrin **57a** without disturbing the alkyne moiety (Table 5). This result resembled the one which was reported by stavber group.[23] Few examples of β-alkyne fluorohydrins formation are shown in Table 5.

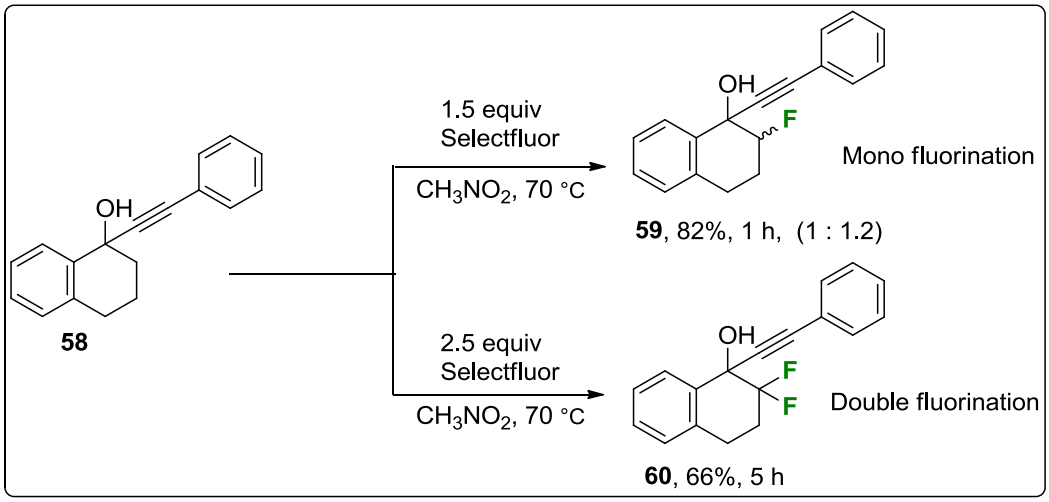
Substrate **56d** resulted in a diastereomeric mixture as expected. Aliphatic alkyne substituted propargyl alcohol reacted nicely to give 60% yield of **57e** (Table 5, entry 5). These fluorohydrins are important structural units in steroids. Unfortunately substrates like 4-phenyl-2-(thiophen-2-yl)but-3-yn-2-ol, 1-(hex-1-yn-1-yl)cyclopentanol, 2-methylbut-3-yn-2-ol did not worked under the reaction conditions.

Table 5. Results of $AgSbF_6$-catalyzed fluorination of alkyltertiary propargyl alcohols



Reaction conditions: 1 equiv of **56**, 1.5 equiv of selectfluor, ratio in parenthesis indicates diastereomeric ratio.

One more interesting feature of the reaction is, when tetralone derived propargyl alcohol (**58**) was subjected to the optimized reaction condition, it resulted in mono fluorinated product (**59**) in 82% yield. When 2.5 equiv of selectfluor was used, difluorinated product (**60**) was obtained in 66% yield (shown in Scheme 15). When **56d** was treated with 2.5 equiv of Selectfluor no difluorination product was observed and a decrease in yield of mono fluorination product i.e., **57d** (24%) was noticed.



Scheme 15. Mono-and difluorination of phenylethynyltetrahydronapthanol

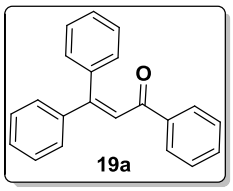
2.3 Conclusions:

In conclusion a simple electrophilic iodination, fluorination of tertiary propargyl alcohols with *N*-iodosuccinimide and selectfluor has been demonstrated. We have found that $AgSbF_6$ itself is enough to carry out Meyer-Schuster rearrangement of tertiary propargyl alcohols. While $AgSbF_6$-catalyzed reaction of tertiary propargyl alcohols give α-iodoenones with NIS, α-fluoro-β-hydroxy ketones are obtained in the reaction with selectfluor. In fact to get this α-fluoro-β-hydroxy ketones no catalyst is required. The products α-fluoro-β-hydroxy ketones, alkynyl vicinal fluorohydrins and α-iodoenones on further functionalizations may find application as bioactive molecules and pharmaceuticals[41a]. Diaryl carbinol moieties present in the product on further functionalization can be used as chemosensors for detection of nerve agents.[41b]

2.4 Experimental section:

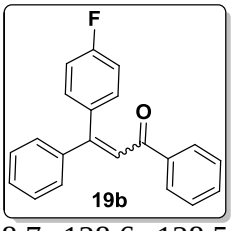
2.4.1 Data for products of Meyer-Schuster and α-Iodoenones:

1,3,3-Triphenylprop-2-en-1-one (19a):



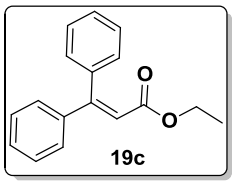
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.91-7.89 (m, 2H), 7.48-7.42 (m, 1H), 7.39-7.34 (m, 6H), 7.26-7.25 (m, 3H), 7.18-7.16 (m, 2H), 7.11 (s, 1H).
^{13}C NMR (100 MHz, $CDCl_3$): δ 192.7, 154.8, 141.4, 139.1, 138.3, 132.7, 129.8, 129.5, 128.8, 128.7, 128.5, 128.4, 128.1, 124.1.

3-(4-Fluorophenyl)-1,3-diphenylprop-2-en-1-one (19b):



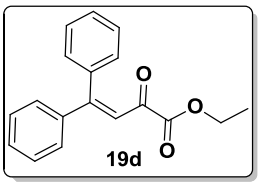
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.93-7.87 (m, 2H), 7.53-7.46 (m, 2H), 7.42-7.36 (m, 5H), 7.26-7.24 (m, 3H), 7.16-7.14 (m, 2 H), 7.11 (s, 1H).
^{13}C NMR (100 MHz, $CDCl_3$): δ 192.7, 192.2, 153.8, 153.4, 133.1, 132.9, 131.8, 131.5, 130.2, 129.8, 129.7, 128.8, 129.7, 128.9, 128.8, 128.7, 128.6, 128.5, 128.3, 124.5, 124.2, 123.8, 122.8.

Ethyl 3,3-diphenylacrylate (19c):



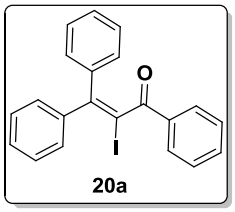
1H NMR (400 MHz, $CDCl_3$): δ 7.41-7.39 (m, 4H), 7.37-7.34 (m, 4H), 7.25-7.23 (m, 2H), 6.41-6.39 (m, 1H), 4.12-4.06 (m, 2 H), 1.17-1.12 (m, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 166.2, 156.5, 140.8, 139, 129.4, 129.2, 128.4, 128.3, 128.1, 127.9, 117.5, 60.1, 14.

Ethyl 2-oxo-4,4-diphenylbut-3-enoate (19d):



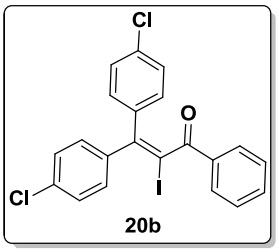
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46-7.36 (m, 8H), 7.24-7.22 (m, 2H), 6.91 (m, 1H), 3.87 (q, *J* = 7.2 Hz, 2H), 1.18 (t, *J* = 7.2 Hz, 3H).
^{13}C NMR (100 MHz, $CDCl_3$): δ 185.5, 163.1, 160.7, 140.2, 138, 130.6, 130.4, 129.6, 129.1, 128.6, 128.3, 121.5, 62.1, 13.8.

2-Iodo-1,3,3-triphenylprop-2-en-1-one (20a):



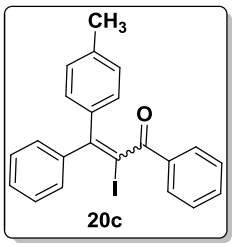
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.90 (d, *J* = 8 Hz, 2H), 7.49-7.36 (m, 6H), 7.36-7.31 (m, 2H), 7.11-7.05 (m, 5H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 193.8, 152.9, 143.7, 139.3, 134, 133.5, 129.9, 129.5, 129.2, 128.6, 128.5, 128.5, 128.2, 96.2.

3,3-Bis(4-chlorophenyl)-2-iodo-1-phenylprop-2-en-1-one (20b):



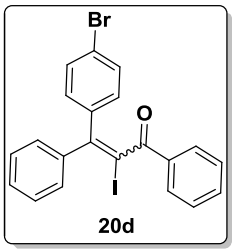
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.89 (d, *J* = 7.6 Hz, 2H), 7.51-7.47 (m, 1H), 7.42-7.32 (m, 6H), 7.06-7.01 (m, 4H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 193.3, 150.1, 141.5, 137.3, 134.8, 134.7, 133.9, 133.5, 131.2, 130.8, 130.7, 129.8, 128.8, 128.6, 97.2.

(*E*)-2-Iodo-1,3-diphenyl-3-(p-tolyl)prop-2-en-1-one (20c):



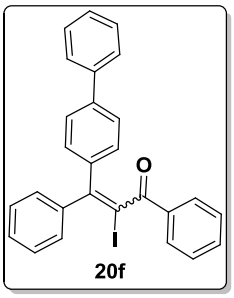
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.92 (d, *J* = 7.6 Hz, 3H), 7.85 (d, *J* = 7.6 Hz, 2H), 7.45-7.36 (m, 11H), 7.34-7.28 (m, 8H), 7.23-7.22 (m, 2.5H), 7.09-7.07 (m, 2.3H), 7.05-7.03 (m, 3H), 6.99-6.97 (m, 3H), 6.86-6.84 (m, 3H), 2.39 (s, 1.2H), 2.13 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 193.8, 193.8, 152.1, 152.8, 143.9, 140.8, 139.6, 138.6, 136.5, 134.1, 134, 133.4, 133.3, 129.9, 129.8, 129.6, 129.5, 129.3, 129.2, 129.1, 128.9, 128.6, 128.5, 128.4, 128.2, 95.6, 95.4, 21.5, 21.2.

(*E*)-3-(4-Bromophenyl)-2-iodo-1,3-diphenylprop-2-en-1-one (20d):



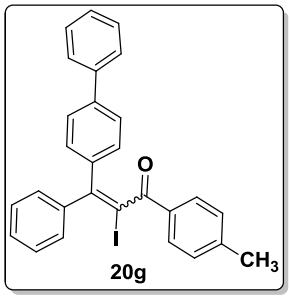
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.91-7.87 (m, 2H), 7.48-7.31 (m, 7H), 7.14-7.07 (m, 4H), 6.77-6.73 (m, 1H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 193.8, 193.7, 163.9, 163.8, 161.4, 161.3, 151.9, 151.7, 143.5, 139.6, 139.2, 135.4, 135.3, 133.9, 133.8, 133.7, 133.6, 131.5, 131.4, 131.3, 131.2, 129.8, 129.5, 129.2, 128.8, 128.7, 128.6, 128.5, 128.3, 115.6, 115.2, 96.4, 96.2.

(*E*)-3-([1,1'-Biphenyl]-4-yl)-2-iodo-1,3-diphenylprop-2-en-1-one (20f):



^{1}H NMR (400 MHz, $CDCl_3$): δ 7.95-7.91 (m, 2H), 7.67-7.63 (m, 2H), 7.45-7.40 (m, 6.5H), 7.35-7.28 (m, 5.5H), 7.17-7.12 (m, 2H), 7.08-7.07 (m, 1H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 193.9, 193.8, 152.6, 152.5, 143.7, 142.4, 141.3, 141.2, 140.4, 140.1, 139.4, 138.2, 137.9, 134, 133.5, 133.4, 130, 129.9, 129.8, 129.6, 129.3, 128.9, 128.8, 128.6, 128.6, 128.5, 128.3, 127.7, 127.6, 127.2, 127.1, 127, 126.8, 96.2, 96.

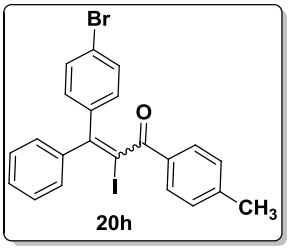
(*E*)-3-([1,1'-Biphenyl]-4-yl)-2-iodo-3-phenyl-1-(p-tolyl)prop-2-en-1-one (20g):



20g

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.87-7.83 (m, 2H), 7.67-7.64 (m, 2H), 7.49-7.40 (m, 5H), 7.39-7.36 (m, 1H), 7.35-7.29 (m, 2H), 7.24-7.19 (m, 1H), 7.17-7.08 (m, 5H), 2.34 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 193.4, 193.4, 151.9, 151.8, 144.6, 144.5, 143.9, 142.6, 141.3, 141.1, 140.5, 140.2, 139.4, 138.2, 131.3, 130.2, 130.2, 129.9, 129.8, 129.6, 129.5, 129.4, 129.3, 128.9, 128.8, 128.5, 128.3, 127.7, 127.6, 127.3, 127.1, 127, 126.8, 96.5, 96.3, 21.8.

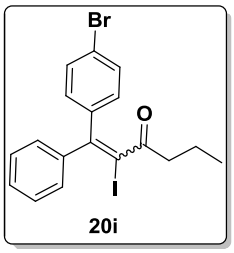
(*E*)-3-(4-Bromophenyl)-2-iodo-3-phenyl-1-(p-tolyl)prop-2-en-1-one) (20h):



20h

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.83 (d, *J* = 8 Hz, 2H), 7.80 (d, *J* = 8 Hz, 1.4H), 7.57-7.55 (m, 1.6H), 7.43-7.36 (m, 5H), 7.29-7.25 (m, 2H), 7.22-7.13 (m, 3H), 7.08 (m, 4H), 7-6.98 (m, 2H), 2.36 (s, 3H), 2.33 (s, 2.2H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 193.1, 151, 150.6, 144.9, 144.7, 143.4, 142.6, 138.8, 138.1, 131.7, 131.5, 131.1, 131, 130.2, 130.1, 129.6, 129.5, 129.2, 128.7, 128.6, 128.3, 122.8, 122.7, 96.9, 96.8, 21.9, 21.8.

(*E*)-1-(4-Bromophenyl)-2-iodo-1-phenylhex-1-en-3-one (20i):

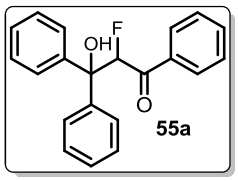


20i

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.53-7.51 (m, 2H), 7.43-7.36 (m, 5H), 7.33-7.23 (m, 6H), 7.10-7.11 (m, 4H), 7.03-7.01 (m, 2H), 2.35 (t, *J* = 7.2 Hz, 2H), 2.25 (t, *J* = 7.2 Hz, 2H), 1.55-1.44 (m, 4H), 0.78 (t, *J* = 7.2 Hz, 3H), 0.73 (t, *J* = 7.2 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 203.8, 203.7, 151.2, 150.6, 143.3, 142.5, 139.2, 138.4, 131.8, 131.7, 131.1, 130.9, 129.6, 129.3, 129.1, 128.8, 128.5, 123.4, 122.8, 100.6, 100.6, 43.1, 43, 18, 13.7.

2.4.2. Data for products of electrophilic fluorination of tertiary propargyl alcohols:

2-Fluoro-3-hydroxy-1,3,3-triphenylpropan-1-one (55a):



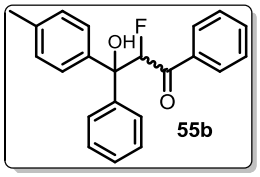
55a

Colourless solid 151-153 °C. **IR** (KBr, cm^{-1}): 3381, 3063, 1698, 1238, 953, 690. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.81-7.78 (m, 2H), 7.56-7.51 (m, 3H), 7.40-7.37(m, 4H), 7.33-7.28 (m, 3H), 7.26-7.18 (m, 3H), 6.04 (d, *J* = 46.4 Hz, 1H), 4.49 (s, 1H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 198.5 (d, *J* = 21 Hz), 143.1, 142.7, 135.8, 134.1, 129.3 (d, *J* = 5 Hz), 128.6, 128.3, 128.2, 127.9,

127.8, 127.1, 127.1, 94.1 (d, *J* = 196 Hz), 79.4 (d, *J* = 20 Hz). **^{19}F NMR** (376 MHz, $CDCl_3$): δ -182.9 (d, *J* = 48.8 Hz). **HRMS** (ESI) m/z calcd for $C_{21}H_{17}FO_2[M+Na]^+$= 343.1110, found = 343.1114.

2-Fluoro-3-hydroxy-1,3-diphenyl-3-(p-tolyl)propan-1-one (55b):

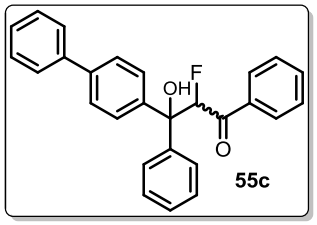
Colourless solid 113-115 °C. **IR** (KBr, cm^{-1}): 3380, 3063, 1698, 1238, 946, 695.



^{1}H NMR (400 MHz, $CDCl_3$): δ 7.79 (d, *J* = 8.0 Hz, 4H), 7.55-7.45 (m, 4H), 7.40-7.35 (m, 8.6H), 7.32-7.23 (m, 7H), 7.21-7.18 (m, 2H), 7.11 (d, *J* = 8 Hz, 2H), 7.04 (d, *J* = 8 Hz, 2H), 6.02 (d, *J* = 46.4 Hz, 2H), 4.46 (d, *J* = 0.8 Hz, 1H, major), 4.43 (d, *J* = 0.8 Hz, 0.92H), 2.31 (s, 3H), 2.25 (s, 3.3H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 198.5 (d, *J* = 21 Hz), 198.4 (d, *J* = 21 Hz), 143.2, 142.8, 140.1, 139.8, 137.6, 137.4, 135.8, 133.9, 129.3, 129.1, 128.9, 128.6, 128.3, 128.2, 127.8, 127.7, 126.9, 126.8, 94.1 (d, *J* = 195 Hz), 79.3 (d, *J* = 20 Hz), 21.2, 21.1. **^{19}F NMR** (376 MHz, $CDCl_3$): δ -182.8 (d, *J* = 48.8 Hz), -182.9 (d, *J* = 45.1 Hz). **HRMS** (ESI) m/z calcd for $C_{22}H_{19}FO_2[M+Na]^+$= 357.1267, found = 357.1269.

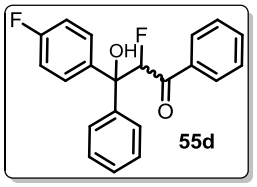
3-([1,1'-Biphenyl]-4-yl)-2-fluoro-3-hydroxy-1,3diphenylpropan-1-one (55c):

Colourless solid 171-173 °C. **IR** (KBr, cm^{-1}): 3375, 3057, 1687, 1484, 958, 695. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.82 (t, *J* = 8.0 Hz, 5.5H), 7.59-7.55 (m, 12H), 7.52-7.45 (m, 3.7H), 7.47-7.39 (m, 16.6H), 7.37-7.28 (m, 8.75H), 6.07 (d, *J* = 46.4 Hz, 2H), 4.53 (s, 1H,), 4.51 (s, 1.5H, major). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 198.6, 198.4, 143, 142.6, 142.1, 135.8, 134.1, 134, 129.4, 129.3, 128.9, 128.6, 128.4, 128.3, 127.9, 127.5, 127.2, 127.1, 127, 94.1 (d, *J* = 195 Hz), 79.4 (d, *J* = 19 Hz). **^{19}F NMR** (376 MHz, $CDCl_3$): δ -182.8, -182.9. **HRMS** (ESI) m/z calcd for $C_{27}H_{21}FO_2[M+Na]^+$= 419.1423, found = 419.1430.



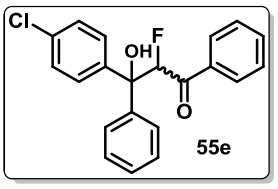
***p*-Fluoro 2-fluoro-3-(4-fluorophenyl)-3-hydroxy-1,3-diphenylpropan-1-one (55d):**

Colourless solid 121-123 °C. **IR** (KBr, cm^{-1}): 3369, 3057, 1698, 1452, 1243, 964, 690. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.81-7.78 (m, 4H), 7.57-7.54 (m, 2H), 7.49-7.46 (m, 4H), 7.41-7.31 (m, 9.7H), 7.29-7.21 (m, 4.4H), 6.98 (t, *J* = 8.8 Hz, 1.9H), 6.92 (t, *J* = 8.8 Hz, 2.3H), 6.0 (d, *J* = 46 Hz, 1H), 5.95 (d, *J* = 46.4 Hz, 1H, major), 4.54 (s, 1H), 4.51 (s, 1H, major).



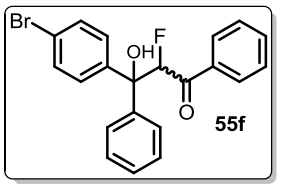
^{13}C NMR (100 MHz, $CDCl_3$): δ 198.6 (d, *J* = 21 Hz), 198.3, 162.3 (d, *J* = 242Hz), 162.2 (d, *J* = 238Hz), 142.9, 142.6, 138.8, 138.5, 135.8, 135.7, 134.2, 134.1, 129.3, 129.3, 129.3, 129, 128.9, 128.6, 128.4, 128.3, 128, 127.9, 126.9, 126.9, 115.2 (d, *J* = 21 Hz), 115 (d, *J* = 21 Hz), 94.5 (d, *J* = 197Hz), 93.9 (d, *J* = 196Hz), 79.2 (d, *J* = 20 Hz), 79.1 (d, *J* = 19 Hz). **^{19}F NMR** (376 MHz, $CDCl_3$): δ -114.7 (m), -182.2 (d, *J* = 45.1 Hz), -182.8 (d, *J* = 45 Hz). **HRMS** (ESI) m/z calcd for $C_{21}H_{16}F_2O_2[M+Na]^+$= 361.1016, found = 361.1018.

***p*-Chloro 3-(4-chlorophenyl)-2-fluoro-3-hydroxy-1,3-diphenylpropan-1-one (55e):**



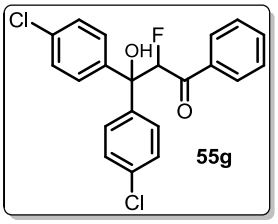
Colourless solid 118-120 °C. **IR** (KBr, cm^{-1}): 3369, 3057, 1693, 1495, 1238, 958, 695. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.82-7.79 (m, 4H), 7.58-7.55 (m, 2H), 7.48-7.38 (m, 8.4H), 7.36-7.34 (m, 2H), 7.33-7.26 (m, 8.2H), 7.25-7.20 (m, 4.1H), 6.01 (dd, *J* = 46 Hz, 0. 8 Hz, 1H), 5.93 (dd, *J* = 46 Hz, 0. 8 Hz, 1H, major), 4.56 (s, 0.8H), 4.53 (s, 1H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 198.5 (d, *J* = 22 Hz), 198.2,142.6, 142.4, 141.6, 141.3, 135.7, 135.6, 134.3, 134.2, 133.8, 133.7, 129.4, 129.3, 128.7, 128.6, 128.5, 128.4, 128.1, 128, 126.9, 126.9, 94.5 (d, *J* = 196 Hz), 93.9 (d, *J* = 195 Hz), 79.1 (d, *J* = 19 Hz), 79 (d, *J* = 20 Hz). ^{19}F NMR (376 MHz, $CDCl_3$): δ -182.2 (d, *J* = 45.1 Hz), -182.7 (d, *J* = 45.1 Hz). **HRMS** (ESI) m/z calcd for $C_{21}H_{16}ClFO_2[M+Na]^+$= 377.0721, found = 377.0723.

3-(4-Bromophenyl)-2-fluoro-3-hydroxy-1,3-diphenylpropan-1-one (55f):



Colourless solid 140-142 °C, **IR** (KBr, cm^{-1}): 3380, 3063, 1698, 1446, 1238, 964, 701. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.80 (m, 4H), 7.57 (t, *J* = 6.8 Hz, 2H), 7.48-7.45 (m, 2H), 7.43-7.34 (m, 12H), 7.31-7.24 (m, 8H), 5.98 (d, *J* = 46 Hz, 1H), 5.92 (dd, *J* = 46 Hz, 1H, major), 4.56 (s, 0.9H), 4.53 (s, 1H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 198.6, 198.3 (d, *J* = 21 Hz), 142.6, 142.3, 141.8, 135.7, 135.6, 134.3, 134.2, 131.4, 131.3, 129.4, 129.3, 128.8, 128.7, 128.5, 128.4, 128.1, 128.0, 126.9, 126.9, 122.1, 121.9, 94.4 (d, *J* = 196 Hz), 93.8 (d, *J* = 195 Hz), 79.2 (d, *J* = 20 Hz), 79.1 (d, *J* = 20 Hz). **^{19}F NMR** (376 MHz, $CDCl_3$): δ -182.3 (d, *J* = 45.1 Hz), -182.(d, *J* = 45.1 Hz). **HRMS** (ESI) m/z calcd for $C_{21}H_{16}BrFO_2[M+Na]^+$= 421.0215 found = 421.0214.

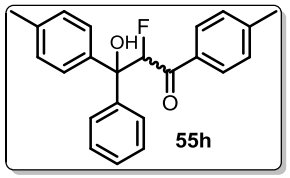
3,3-Bis(4-chlorophenyl)-2-fluoro-3-hydroxy-1-phenylpropan-1-one (55g):



55g

Light yellow solid 127-129 °C. **IR** (KBr, cm^{-1}): 3353, 3052, 1698, 1490, 1238, 958, 810. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.81 (d, *J* = 7.6 Hz, 2H), 7.59 (t, *J* = 7.6 Hz, 1H), 7.45-7.40 (m, 4H), 7.30-7.27 (m, 4H), 7.25-7.23 (m, 2H), 5.87 (d, *J* = 46 Hz, 1H), 4.61(s, 1H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 198.5(d, *J* = 22 Hz), 141.2, 140.9, 135.5, 134.5, 134.1, 133.9, 129.4, 129.4, 128.8, 128.6, 128.5, 94.3 (d, *J* = 196 Hz), 78.7 (d, *J* = 19 Hz). **^{19}F NMR** (376 MHz, $CDCl_3$): δ -181.8 (d, *J* = 45.1 Hz). **HRMS** (ESI) m/z calcd for $C_{21}H_{15}Cl_2FO_2[M+Na]^+$= 411.0331, found = 411.0335.

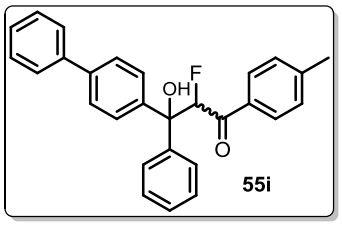
2-Fluoro-3-hydroxy-3-phenyl-1,3-di-*p*-tolylpropan-1-one (55h):



55h

Colourless solid 83-85 °C. **IR** (neat, cm^{-1}): 3462, 3062, 1670, 1445, 1045, 700. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.73 (d, *J* = 7.6 Hz, 4H), 7.49 (d, *J* = 7.2 Hz, 2H), 7.39-7.36 (m, 3.9H), 7.32-7.17 (m, 13H), 7.11 (d, *J* = 8 Hz, 2H), 7.05 (d, *J* = 8 Hz, 2.2H), 5.97 (d, *J* = 46.4 Hz, 2H), 4.58 (s, 1H), 4.56 (s, 0.8H), 2.38 (s, 6H), 2.31 (s, 2.6H), 2.26 (s, 3H, major) ; **^{13}C NMR** (100 MHz, $CDCl_3$): δ 198.0 (d, *J* = 21 Hz), 197.9 (d, *J* = 21 Hz), 145.3, 143.2, 143.1, 140.2, 140.1, 137.5, 137.3, 133.3, 129.6, 129.5, 129.4, 129, 128.9, 128.3, 128.2, 127.7, 127.6, 126.9, 126.8, 94.1 (d, *J* = 195 Hz), 79.3 (d, *J* = 20 Hz), 21.9, 21.2, 21.1; ^{19}F NMR (376 MHz, $CDCl_3$): δ -182.6 (d, *J* = 45 Hz), -182.7 (d, *J* = 48 Hz). **HRMS** (ESI) m/z calcd for $C_{23}H_{21}FO_2[M+Na]^+$= 371.1423, found = 371.1426

3-([1,1'-Biphenyl]-4-yl)-2-fluoro-3-hydroxy-3-phenyl-1-(*p*-tolyl)propan-1-one (55i):

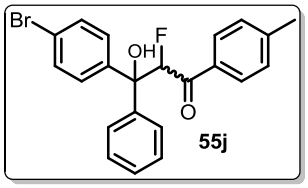


55i

Colourless solid 151-153 °C, **IR** (KBr, cm^{-1}): 3386, 1698, 1490, 1249, 969, 832. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.76-7.72 (m, 4H), 7.60-7.55 (m, 7.8H), 7.53-7.49 (m, 2.2H), 7.44-7.41 (m, 9H), 7.35-7.26 (m, 7.6H), 7.23- 7.17 (m, 6H), 6.04 (d, *J* = 46 Hz, 1H), 6.02 (d, *J* = 46.4 Hz, 1H, major), 4.68 (s, 1H), 4.63 (s, 0.8H, major), 2.38 (s, 3.4H), 2.36 (s, 2.4H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 198.1, 197.8, 145.4, 145.3, 143.1, 142.8, 142.1, 141.8, 140.7, 140.5, 133.3, 133.2, 129.5, 129.4, 128.8, 128.4, 128.3, 127.9, 127.8, 127.5, 127.2, 126.9, 93.9 (d, *J* = 195 Hz), 79.3 (d, *J* = 10 Hz),

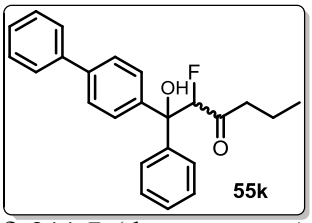
21.9, 21.8. **^{19}F NMR** (376 MHz, $CDCl_3$): Proton decoupled δ -186.8, -187.4. **HRMS** (ESI) m/z calcd for $C_{28}H_{23}FO_2[M+Na]^+$= 433.1580, found = 433.1584.

3-(4-Bromophenyl)-2-fluoro-3-hydroxy-3-phenyl-1-(*p*-tolyl)propan-1-one (55j):



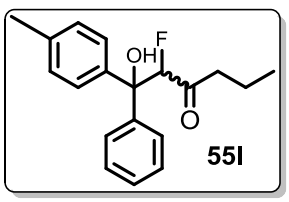
Colourless solid 113-115 °C, **IR** (KBr, cm^{-1}): 3364, 3063, 1693, 1490, 1294, 1084, 816. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.47-7.14 (m, 4H), 7.47-7.46 (m, 2.5H), 7.43-7.31 (m, 9.3H), 7.31-7.19 (m, 12.3H), 5.94 (d, *J* = 46 Hz, 1H), 5.88 (d, *J* = 46.4 Hz, 1H, major), 4.71 (s, 0.87H), 4.65 (s, 0.98H), 2.38 (s, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 197.9 (d, *J* = 22 Hz), 197.8 (d, *J* = 21 Hz), 145.6, 145.5, 142.6, 142.5, 142.3, 142, 133.1, 132.9, 131.5, 131.4, 131.3, 129.5 (d, *J* = 5 Hz), 129.4 (d, *J* = 3 Hz), 129.1, 128.8, 128.6, 128.4, 128.3, 128, 127.9, 127.1, 126.9, 126.8, 122.1, 121.8, 94.2 (d, *J* = 196 Hz), 92.6 (d, *J* = 195 Hz), 79.1 (d, *J* = 20 Hz), 79 (d, *J* = 20 Hz), 21.9. **^{19}F NMR** (376 MHz, $CDCl_3$): δ -182.1 (d, *J* = 48.8 Hz), -182.4 (d, *J* = 48.8 Hz). **HRMS** (ESI) m/z calcd for $C_{22}H_{18}BrFO_2[M+Na]^+$= 435.0372, found = 435.0374.

1-([1,1'-Biphenyl]-4-yl)-2-fluoro-1-hydroxy-1-phenylhexan-3-one (55k):



Colourless solid 121-123 °C. **IR** (KBr, cm^{-1}): 3364, 1720, 1446, 1068, 832, 695. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.60-7.53 (m, 6H), 7.46-7.41 (m, 4H), 7.39-7.28 (m, 4H), 5.32 (d, *J* = 47.6 Hz, 1H), 4.46 (dd, *J* = 13.6Hz, 1.6 Hz, 1H), 2.56-2.42 (m, 2H), 1.49-1.43 (m, 2H), 0.77 (t, *J* = 7.6 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 211.7 (d, *J* = 25 Hz), 211.5 (d, *J* = 25 Hz), 142.2, 141.9, 141.4, 141.1, 140.7, 140.6, 140.5, 128.8, 128.7, 128.4, 128.2, 127.9, 127.5, 127.4, 127.2, 127.2, 127.1, 126.9, 126.9, 126.7 (d, *J* = 3 Hz), 96.7 (d, *J* = 198 Hz), 78.8 (d, *J* = 20 Hz), 42.2, 42.2, 15.9, 13.5; **^{19}F NMR** (376 MHz, $CDCl_3$): δ -187.8 (d, *J* = 48.8 Hz), -187.9 (d, *J* = 48.8 Hz); **HRMS** (ESI) m/z calcd for $C_{24}H_{23}FO_2$ $[M+Na]^+$= 385.1580, found = 385.1576.

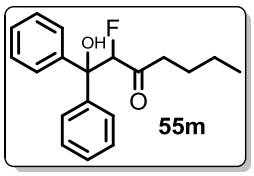
p-Methyl alkyl 2-fluoro-1-hydroxy-1-phenyl-1-(*p*-tolyl)hexan-3-one (55l):



Colourless solid 61-63 °C, IR (neat, cm^{-1}): 3407, 3051, 2964, 1692, 1489, 1067, 689. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.49 (d, *J* = 8.4 Hz, 2H), 7.38-7.36 (m, 4.3H), 7.34-7.30 (m, 4H), 7.29-7.28 (m, 1H),

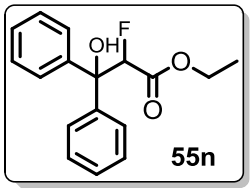
7.26-7.24 (m, 3H), 7.16-7.11 (m, 4H), 5.28 (d, *J* = 47.6 Hz, 1H), 5.27 (d, *J* = 47.6 Hz, 1H), 4.33 (d, *J* = 1.6 Hz, 1H, major), 4.32 (d, *J* = 2 Hz, 0.8H), 2.52-2.49 (m, 2H), 2.43-2.38 (m, 2H), 2.36 (s, 3H), 2.32 (s, 3H), 1.49-1.41 (m, 4H), 0.76 (m, 6H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 211.6 (d, *J* = 25 Hz), 211.4 (d, *J* = 26 Hz), 142.4, 142.2, 139.4, 139.1, 137.6, 137.6, 128.9, 128.8, 128.3, 128.1, 127.8, 127, 126.9 (d, *J* = 1 Hz), 126.8, 126.7, 126.7, 126.6, 96.8 (d, *J* = 198 Hz), 96.7 (d, *J* = 198 Hz), 78.8 (d, *J* = 19 Hz), 42.1, 42.0, 21.1, 15.8 (d, *J* = 2 Hz), 15.7 (d, *J* = 2 Hz), 13.4, 13.4. **^{19}F NMR** (376 MHz, $CDCl_3$): δ -187.9 (d, *J* = 48.8 Hz), -188 (d, *J* = 48.8 Hz). **HRMS** (ESI) m/z calcd for $C_{19}H_{21}FO_2[M+Na]^+$= 323.1423, found = 323.1424.

2-Fluoro-1-hydroxy-1,1-diphenylheptan-3-one (55m):



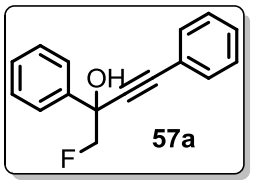
Colourless solid 91-93 °C, **IR** (KBr, cm^{-1}): 3397, 3063, 2958, 1720, 1446, 1063, 701; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.51-7.48 (m, 2H), 7.38-7.25 (m, 8H), 5.29 (d, *J* = 47.6 Hz, 1H), 4.40 (d, *J* = 1.2 Hz, 1H), 2.53-2.40 (m, 2H), 1.41-1.35 (m, 2H), 1.18-1.13 (m, 2H), 0.81 (t, *J* = 7.6 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 211.8 (d, *J* = 25 Hz), 142.4, 142.1, 128.4, 128.3, 128, 127.2, 126.8, 96.8 (d, *J* = 198 Hz), 79 (d, *J* = 19 Hz), 40, 24.5, 22.1, 13.8. **^{19}F NMR** (376 MHz, $CDCl_3$): δ -187.8 (d, *J* = 48.8 Hz); **HRMS** (ESI) m/z calcd for $C_{19}H_{21}FO_2[M+Na]^+$= 323.1423, found = 323.1426.

Ethyl 2-fluoro-3-hydroxy-3,3-diphenylpropanoate (55n):



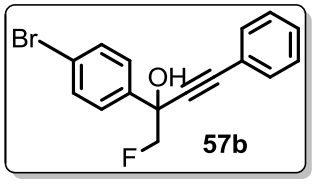
Colourless solid 109-111 °C, **IR** (KBr, cm^{-1}): 3408,1742, 1446, 1079, 750, 657. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.57-7.55 (m, 2H), 7.41-7.34 (m, 4H), 7.32-7.28 (m, 3H), 7.26-7.25 (m, 1H), 5.47 (d, *J* = 46.8 Hz, 1H), 4.13-4.03 (m, 3H), 1.03 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 168.7 (d, *J* = 24 Hz), 142.6, 141.6, 128.4, 128.2, 128.1, 127.9, 126.9, 126.6(d, *J* = 2 Hz), 91.9 (d, *J* = 199 Hz), 78.5 (d, *J* = 19 Hz), 62.1, 13.8. **^{19}F NMR** (376 MHz, $CDCl_3$): δ -189.1 (d, *J* = 48.8 Hz). **HRMS** (ESI) m/z calcd for $C_{17}H_{17}FO_3$ $[M+Na]^+$= 311.1059, found = 311.1062.

Methyl fluoro diphenyl. 1-fluoro-2,4-diphenylbut-3-yn-2-ol (57a):



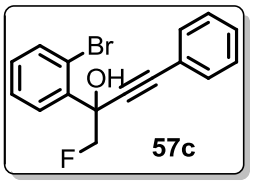
IR (neat, cm^{-1}): 3418, 3062, 2235, 1489, 1456, 1023, 936. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.75-7.72 (m, 2H), 7.52-7.49 (m, 2H), 7.43-7.36 (m, 3H), 7.36-7.33 (m, 3H), 4.57 (dd, *J* = 22 Hz, 8. 8 Hz, 1H), 4.45 (dd, *J* = 22.8 Hz, 8. 8 Hz, 1H), 3 (s, 1H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 139.2, 132.1, 129, 128.8, 128.6, 128.5, 126.3, 122.1, 89 (d, *J* = 185 Hz), 88, 87.1, 72.7 (d, *J* = 19 Hz). **^{19}F NMR** (376 MHz, $CDCl_3$): δ -127.5 (dd, *J* = 56.4, 37.6 Hz). **HRMS** (ESI) m/z calcd for $C_{16}H_{13}FO[M+Na]^+$= 263.0847, found = 263.0847.

2-(4-Bromophenyl)-1-fluoro-4-phenylbut-3-yn-2-ol (57b):



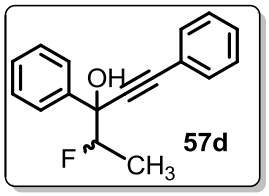
IR (neat, cm^{-1}): 3435, 2235, 1396, 1007, 821. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.59-7.57 (m, 1H), 7.54-7.47 (m, 2H), 7.45-7.41 (m, 2H), 7.36-7.28 (m, 4H), 4.50 (dd, *J* = 47.2 Hz, 9.2 Hz, 1H), 4.41 (dd, *J* = 47.6 Hz, 9.2 Hz, 1H), 3.06 (s, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 138.4, 132.1, 131.7, 129.2, 128.5, 128.1, 123, 121.7, 89.6, 88.7 (d, *J* = 185 Hz), 87.4, 72.2 (d, *J* = 20 Hz); **^{19}F NMR** (376 MHz, $CDCl_3$): δ 127.4 (dd, *J* = 56.4 Hz, 7.5 Hz); **HRMS** (ESI) m/z calcd for $C_{16}H_{12}BrFO[M+Na]^+$= 340.9953, found = 340.9956.

***o*-Bromo methyl 2-(2-bromophenyl)-1-fluoro-4-phenylbut-3-yn-2-ol (57c):**



IR (neat, cm^{-1}): 3451, 3062, 2224, 1467, 1018; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.94-7.92 (m, 1H), 7.64 (dd, *J* = 8 Hz, 1.2 Hz, 1H), 7.48 (dd, *J* = 7.6 Hz, 1.2 Hz, 2H), 7.42-7.37 (m, 1H), 7.32-7.29 (m, 3H), 7.24-7.19 (m, 1H), 5.04 (dd, *J* = 46.8 Hz, 9.2Hz, 1H), 4.74 (dd, *J* = 47.2 Hz, 9.2 Hz, 1H), 3.3 (s, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 137.4, 135.1, 131.9, 130.2, 128.9, 128.6, 128.4, 127.8, 122.2, 121.1, 87.6, 86.7 (d, *J* = 5 Hz), 86.3 (d, *J* = 190 Hz), 72.1 (d, *J* = 20 Hz); **^{19}F NMR** (376 MHz, $CDCl_3$): δ proton decoupled -129.9, -129.6. **HRMS** (ESI) m/z calcd for $C_{16}H_{12}BrFO[M+Na]^+$= 340.9953, found = 340.9953.

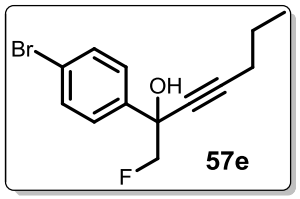
4-Fluoro-1,3-diphenylpent-1-yn-3-ol (57d):



IR (neat, cm^{-1}): 3440. 3068. 2224. 1489. 1034. 695; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.72-7.68 (m, 2.8H), 7.53-7.47 (m, 3H), 7.39-7.36 (m, 2.9H), 7.35-7.31 (m, 5.8H), 4.83 (ddd, *J* = 46.8 Hz, 12.4 Hz, 6.0

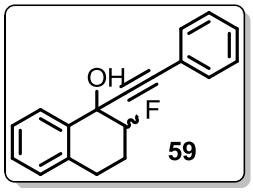
Hz, 0.45H), 4.75 (ddd, *J* = 48.4 Hz, 12.4 Hz, 6.4 Hz, 1H major), 3.25 (s, 1H), 2.88 (s, 0.5H), 1.38-1.26 (m, 4.5H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 140.4, 139.6, 132, 128.9, 128.8, 128.7, 128.4, 128.3, 126.7, 126.5, 122.2, 95.5 (d, *J* = 180 Hz), 94.4 (d, *J* = 180 Hz), 88.9, 88.1, 87.4, 86.9, 76.4 (d, *J* = 20 Hz), 74.9 (d, *J* = 22 Hz), 16.1 (d, *J* = 23 Hz), 15.5 (d, *J* = 22 Hz); **^{19}F NMR** (376 MHz, $CDCl_3$): δ -178.8 (m), -179.6 (m); **HRMS** (ESI) m/z calcd for $C_{17}H_{15}FO[M+Na]^+$= 277.1005, found = 277.1006.

2-(4-Bromophenyl)-1-fluorohept-3-yn-2-ol (57e)



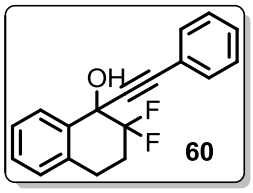
IR (neat, cm^{-1}): 3418, 2958, 2246, 1489, 1089, 832; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.54-7.49 (m, 4H), 4.38 (dd, *J* = 47.2 Hz, 8.8 Hz, 1H), 4.34 (dd, *J* = 48 Hz, 8.8 Hz, 1H), 2.85 (s, 1H), 2.27 (t, *J* = 7.2 Hz, 2H), 1.63-1.56 (m, 2H), 1 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 138.9, 131.6, 128.1, 122.7, 88.9 (d, *J* = 185 Hz), 88.5, 79, 77.8 (d, *J* = 20 Hz), 21.9, 20.8, 13.6; **^{19}F NMR** (376 MHz, $CDCl_3$): δ (proton decoupled) -127.6, -127.7; **HRMS** (ESI) m/z calcd for $C_{13}H_{14}BrFO[M+Na]^+$= 307.0110, found = 307.0108.

2-Fluoro-1-(phenylethynyl)-1,2,3,4-tetrahydronaphthalen-1-ol (59):



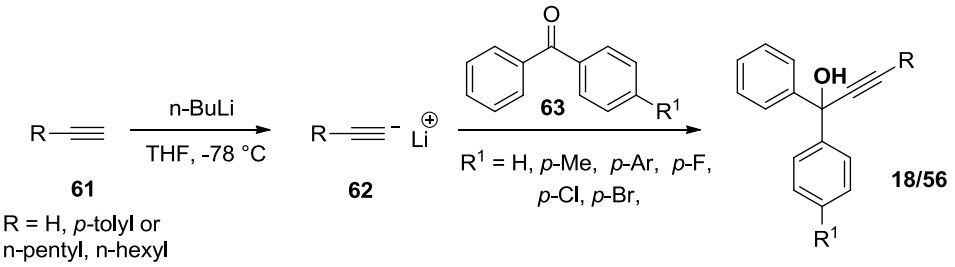
IR (neat, cm^{-1}): 3424, 3062, 2947, 2218, 1495, 1051, 700; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.90-7.87 (m, 1H major), 7.85-7.83 (m, 0.5H), 7.43-7.41 (m, 3H), 7.29-7.23 (m, 7.3H), 7.11-7.09 (m, 1.5H), 5.05 (ddd, *J* = 49.2 Hz, 8.4 Hz, 3.2 Hz, 1H major), 4.85 (ddd, *J* = 49.2 Hz, 7.6 Hz, 4.4 Hz, 0.5H), 3.13 (s, 0.5H), 3.04-3 (m, 2.5H), 2.91-2.81 (m, 1.5H), 2.41-2.24 (m, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 136.9, 136.9, 134.6, 134.4, 131.9, 131.8, 128.9, 128.7, 128.7, 128.6, 128.5, 128.5, 128.3, 128.3, 127.9, 127, 122.3, 122.2, 94 (d, *J* = 181 Hz), 93.8 (d, *J* = 181 Hz), 89.6, 89, 87.2, 86.3, 70.8 (d, *J* = 21 Hz), 69.5 (d, *J* = 21 Hz); 25.8 (d, *J* = 9 Hz), 25.6 (d, *J* = 10 Hz), 25. (d, *J* = 19 Hz), 24.4 (d, *J* = 19 Hz). **^{19}F NMR** (376 MHz, $CDCl_3$): δ -187.5 (m), -191.3 (dd, *J* = 48.8 Hz, 22.5 Hz); **HRMS** (ESI) m/z calcd for $C_{18}H_{15}FO[M]^+$= 266.1107, found = 266.1106.

2,2-Difluoro-1-(phenylethynyl)-1,2,3,4-tetrahydronaphthalen-1-ol (60):



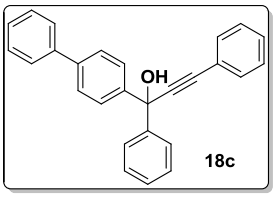
Colourless solid 74-76 °C, **IR** (KBr, cm^{-1}): 3567, 3063, 2230, 1495, 1216, 756. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.91-7.88 (m, 1H), 7.48-7.47 (m, 2H), 7.32-7.30 (m, 5H), 7.16-7.15 (m, 1H), 3.16-3.05 (m, 2H), 3.02 (s, 1H), 2.64-2.39 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 136.2, 133.5, 132.1, 129.2, 129.1, 128.9, 128.6, 128.4, 127.2, 121.9, 121.4 (t, *J* = 240 Hz), 87.5, 86.4, 71.2 (m), 26.9 (t, *J* = 23 Hz), 26.4 (m); **^{19}F NMR** (376 MHz, $CDCl_3$): δ -110.1 (ddd, *J* = 240.6Hz, 26.3 Hz, 7.5Hz), -112.9 (dd, *J* = 236.8 Hz, 15 Hz); **HRMS** (ESI) m/z calcd for $C_{18}H_{14}F_2O$ $[M+Na]^+$= 307.0910, found = 307.0910.

2.4.3 Preparation of tertiary propargyl alcohols:



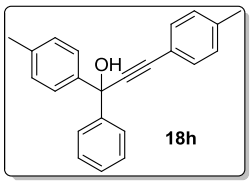
Using the literature procedure,[42] the substituted propargyl alcohols (**18/56**) are prepared as follows, aryl/alkyl acetylene (**61,** 1 equiv) was taken in a reaction vessel filled with nitrogen, dry THF(3mL for mmol) was added to it and cooled to -78 ˚C. After 20 minutes n-BuLi (1.6 M solution in hexanes, 1.1 equiv) was added drop wise under nitrogen for 15 to 20 minutes and stirred at -78 ˚C for 1hour. Then it is allowed to warm to room temperature and stirred for 1 hour. Again the reaction mixture is cooled to -78 ˚C and respective ketone (**63**, 1 equiv) in dry THF (1mL for 5mmol) was added drop wise and allowed the reaction mixture to warm gradually to room temperature and stirred till completion. After completion of the reaction, saturated NH_4Cl was added, reaction mixture was extracted thrice with ethyl acetate. The resulting organic layer was washed with water, brine and dried over Na_2SO_4. The filtrate was concentrated using rotavapour and residue was purified by column chromatography on silica gel to get the pure products (**18/56**).

1-([1,1'-biphenyl]-4-yl)-1,3-diphenylprop-2-yn-1-ol (18c):



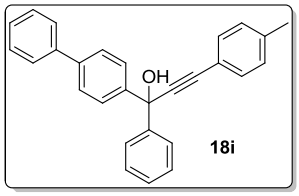
Colourless solid 95-97 °C, **IR** (KBr, cm^{-1}): 3539, 2219, 1490, 1052, 843, 767. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.75-7.72 (m, 4H), 7.61-7.58 (m, 4H), 7.54-7.58 (m, 2H), 7.44-7.39 (m, 3H), 7.37-7.29 (m, 6H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 145.1, 144.2, 140.7, 131.9, 128.8, 128.5, 127.9, 127.5, 127.2, 126.6, 126.2, 122.5, 91.8, 87.4, 74.8. **HRMS** (ESI) m/z calcd for $C_{27}H_{20}O[M+Na]^+$= 383.1412, found = 383.1410.

1-phenyl-1,3-di-*p*-tolylprop-2-yn-1-ol (18h):



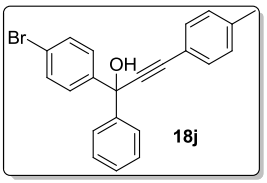
Colourless solid 72-74 °C, **IR** (KBr, cm^{-1}): 3544, 2218, 1440, 1045, 826, 722. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.68-7.65 (m, 2H), 7.57-7.54 (m, 2H), 7.41-7.38 (m, 2H), 7.35-7.32 (m, 2H), 7.27-7.26 (m, 1H), 7.15-7.12 (m, 4H), 2.87-2.84 (m, 1H), 2.34 (s, 6H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 145.4, 142.5, 138.9, 137.5, 131.8, 129.2, 129.1, 128.4, 127.7, 126.1, 119.5, 91.3, 87.3, 74.8, 21.6, 21.2. **HRMS** (ESI) m/z calcd for $C_{23}H_{20}O[M+H]^+$= 313.1592, found = 313.1591.

1-([1,1'-biphenyl]-4-yl)-1-phenyl-3-(*p*-tolyl)prop-2-yn-1-ol (18i):



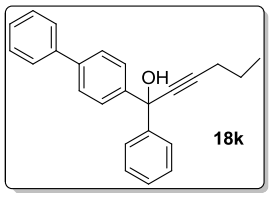
Colourless solid 121-123 °C, **IR** (KBr, cm^{-1}): 3550, 2213, 1484, 1045, 815, 760. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.75-7.71 (m, 4H), 7.57-7.56 (m, 4H), 7.43-7.27 (m, 8H), 7.14-7.13 (m, 2H), 2.98-2.92 (m, 1H), 2.35 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 145.2, 144.3, 140.8, 140.6, 139, 131.8, 129.2, 128.8, 128.5, 127.8, 127.5, 127.3, 127.2, 126.6, 126.2, 119.4, 91.1, 87.6, 74.8, 21.6. **HRMS** (ESI) m/z calcd for $C_{28}H_{22}O[M+Na]^+$= 397.1568, found = 397.1569.

1-(4-bromophenyl)-1-phenyl-3-(*p*-tolyl)prop-2-yn-1-ol (18j):



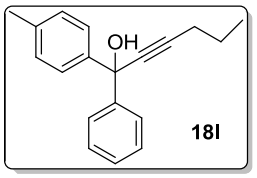
Pale yellow solid 61-63 °C, **IR** (KBr, cm^{-1}): 3364, 2218, 1478, 1051, 815, 700. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.62-7.59 (m, 2H), 7.49-7.47 (m, 2H), 7.38-7.34 (m, 4H), 7.28 (t, *J* = 7.6 Hz, 2H), 7.23-7.22 (m, 1H), 7.07 (d, *J* = 7.6 Hz, 2H), 3.15 (s, 1H), 2.29 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 144.7, 144.3, 139.1, 131.7, 131.3, 129.2, 128.4, 127.9, 127.6, 126, 121.7, 119.1, 90.5, 87.8, 74.5, 21.6. **HRMS** (ESI) m/z calcd for $C_{22}H_{17}BrO$ $[M+Na]^+$= 399.0362, found = 399.0362.

1-([1,1'-biphenyl]-4-yl)-1-phenylhex-2-yn-1-ol (18k):



Colourless solid 60-62 °C, **IR** (neat, cm^{-1}): 3435, 2958, 2235, 1490, 1008, 827, 761. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.69-7.64 (m, 4H), 7.58-7.53 (m, 4H), 7.44-7.39 (m, 2H), 7.36-7.32 (m, 3H), 7.28-7.24 (m, 1H), 2.76-2.75 (m, 1H), 2.36-2.32 (m, 2H), 1.67-1.60 (m, 2H), 1.06-1.02 (m, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 145.6, 144.7, 140.8, 140.5, 128.8, 128.3, 127.7, 127.4, 127.2, 127.1, 126.6, 126.1, 88.4, 83.3, 74.5, 22.2, 21.1, 13.8. **HRMS** (ESI) m/z calcd for $C_{24}H_{22}O[M+H]^+$= 327.1749, found = 327.1750.

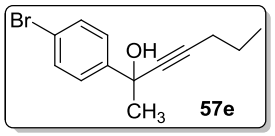
1-phenyl-1-(*p*-tolyl)hex-2-yn-1-ol (18l):



IR (neat , cm^{-1}): 3457, 2969, 2229, 1445, 1002, 815, 749.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.63-7.57 (m, 2H), 7.51-7.46 (m, 2H), 7.32-7.26 (m, 2H), 7.24-7.21 (m, 1H), 7.13-7.08 (m, 2H), 2.81-2.74 (m, 1H), 2.31-2.27 (m, 5H), 1.64-1.56 (m, 2H), 1.06-0.98 (m, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 145.8, 142.8, 137.2, 128.9, 128.2, 127.4, 126.1, 87.9, 83.5, 74.4, 22.2, 21.1, 20.9, 13.7. **HRMS** (ESI) m/z calcd for $C_{19}H_{20}O[M+Na]^+$= 287.1412, found = 287.1415.

2-(4-bromophenyl)hept-3-yn-2-ol (57e):



IR (neat, cm^{-1}): 3386, 2957, 2246, 1495, 1013, 827, 723.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.51 (d, *J* = 8.8 Hz, 2H), 7.45 (d, *J* = 8.8 Hz, 2H), 2.6 (s, 1H), 2.23 (t, *J* = 7.2 Hz, 2H), 1.69 (s, 3H), 1.58-1.53 (m, 2H), 0.99 (t, *J* = 7.2 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 145.4, 131.3, 126.9, 121.5, 85.9, 83.6, 69.7, 33.7, 22.1, 20.7, 13.6. **HRMS** (ESI) m/z calcd for $C_{13}H_{15}BrO[M+Na]^+$= 289.0204, found = 289.0200.

2.5 References

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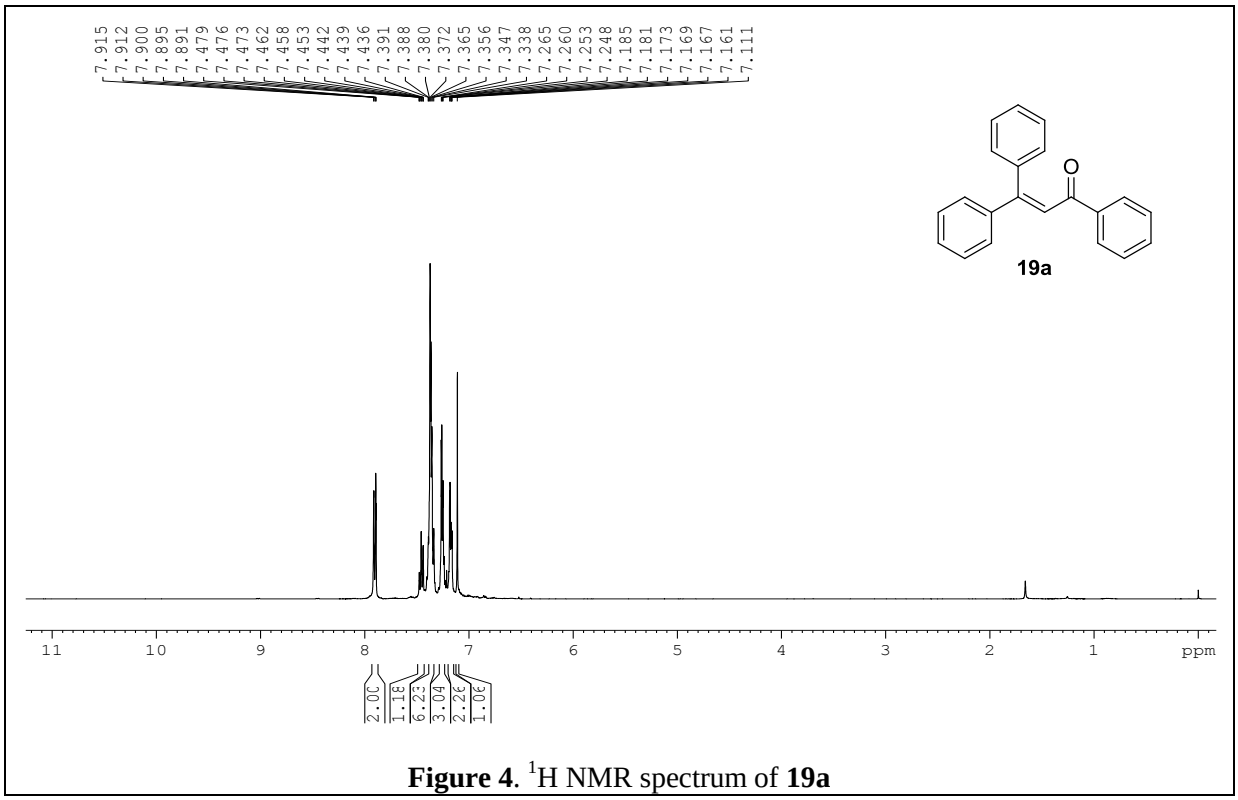


Figure 4. ^{1}H NMR spectrum of **19a**

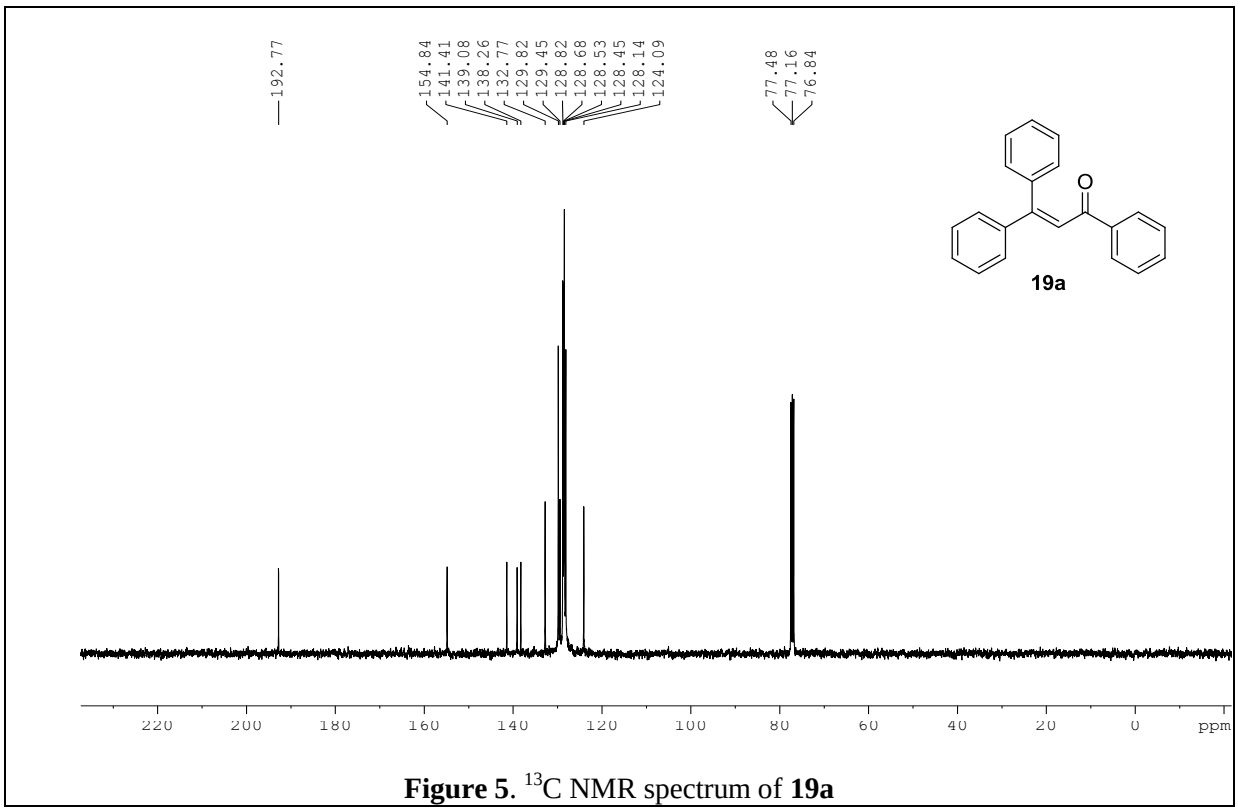


Figure 5. ^{13}C NMR spectrum of **19a**

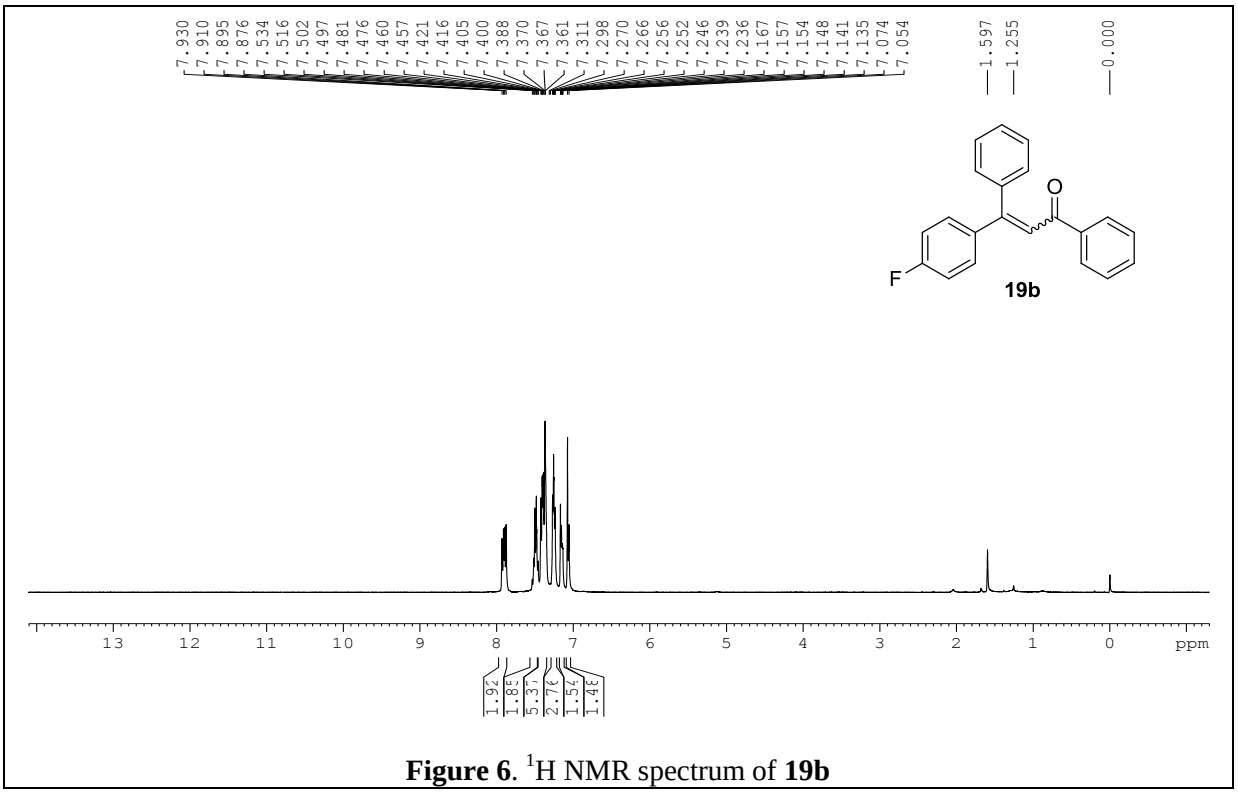


Figure 6. ^{1}H NMR spectrum of **19b**

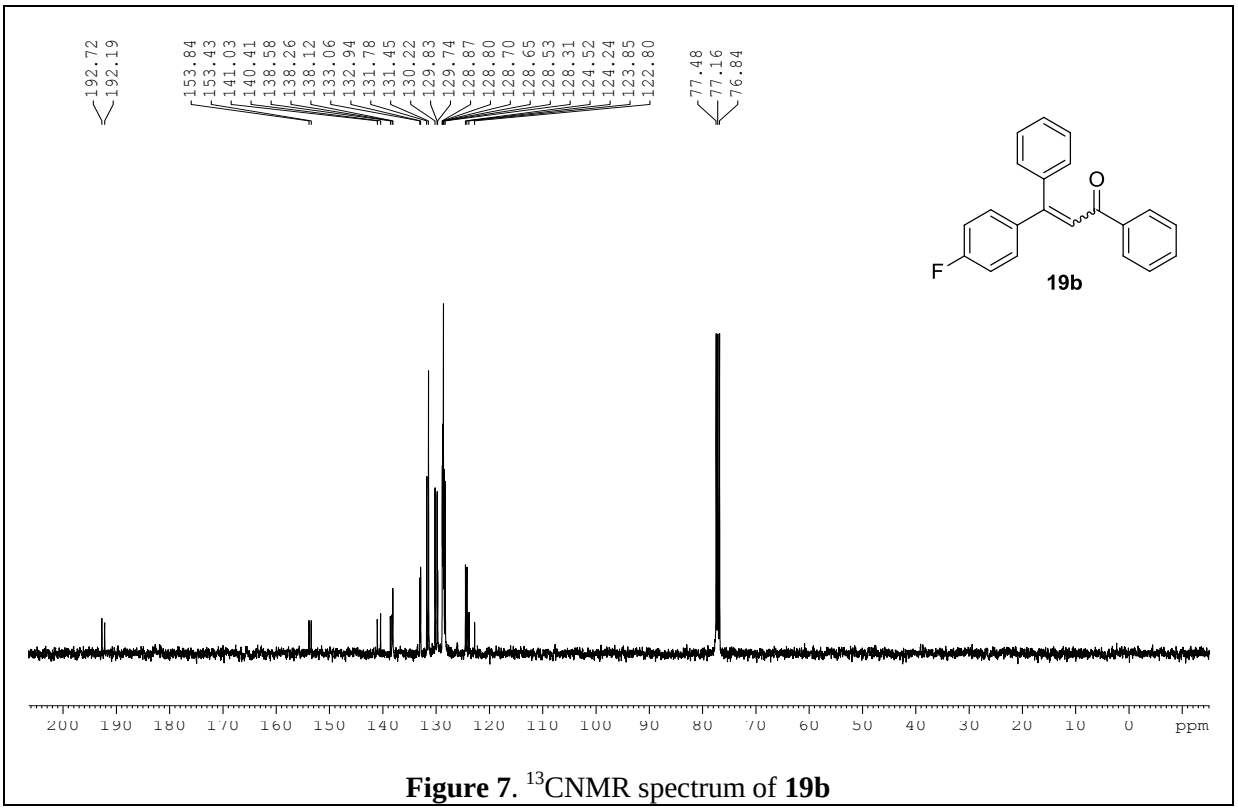


Figure 7. ^{13}CNMR spectrum of **19b**

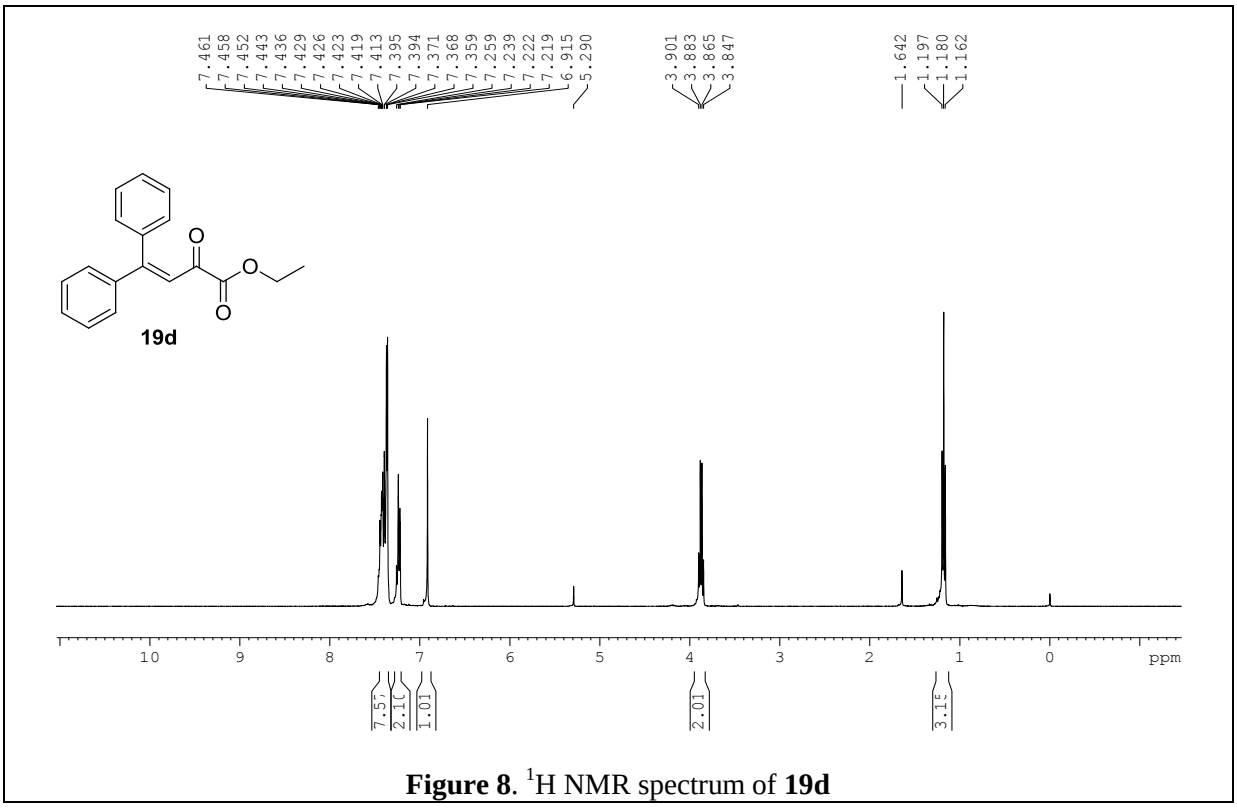


Figure 8. ^{1}H NMR spectrum of **19d**

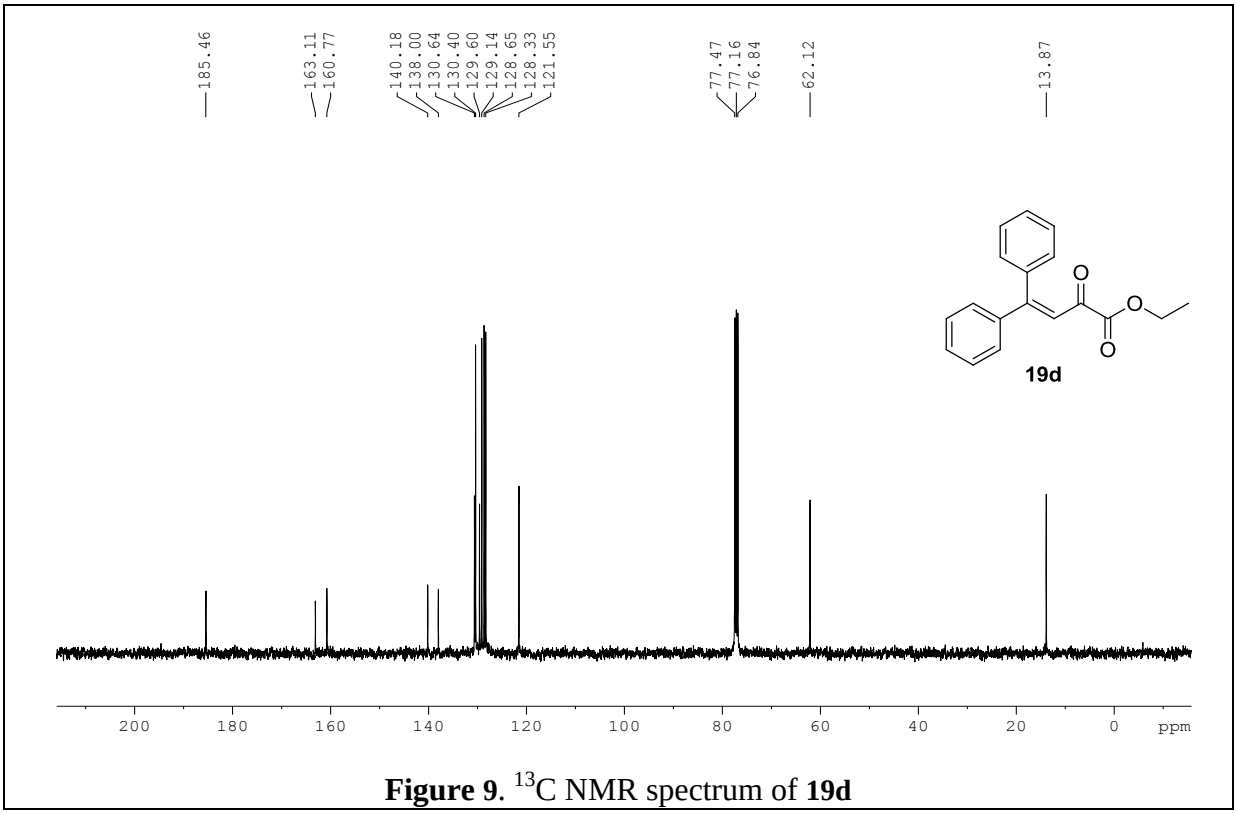


Figure 9. ^{13}C NMR spectrum of **19d**

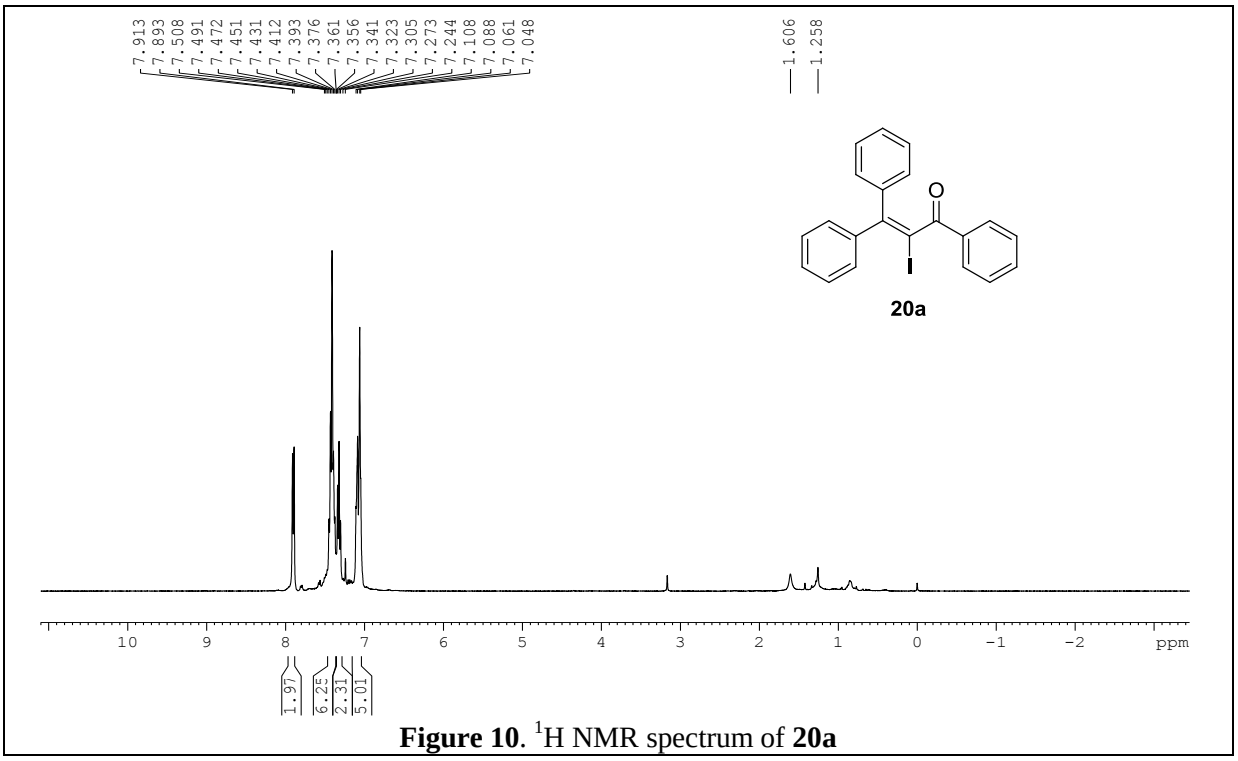


Figure 10. ^{1}H NMR spectrum of **20a**

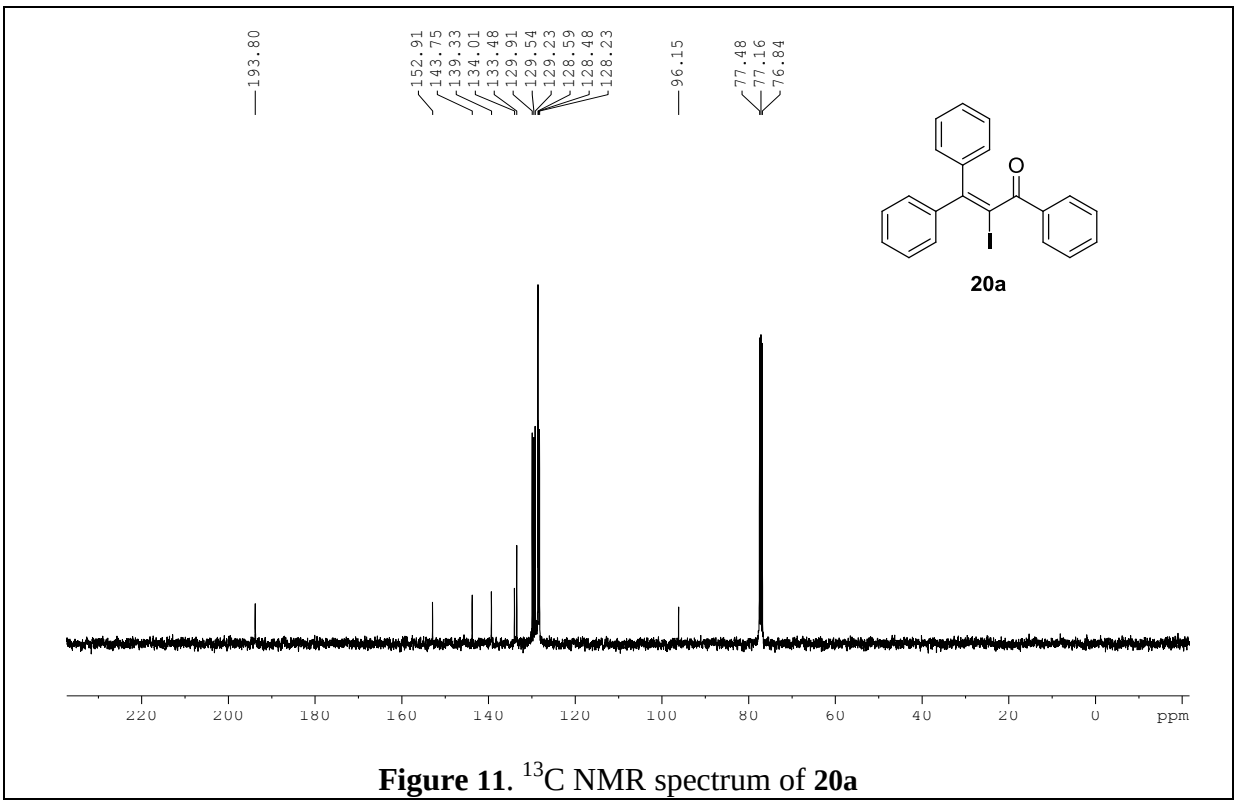


Figure 11. ^{13}C NMR spectrum of **20a**

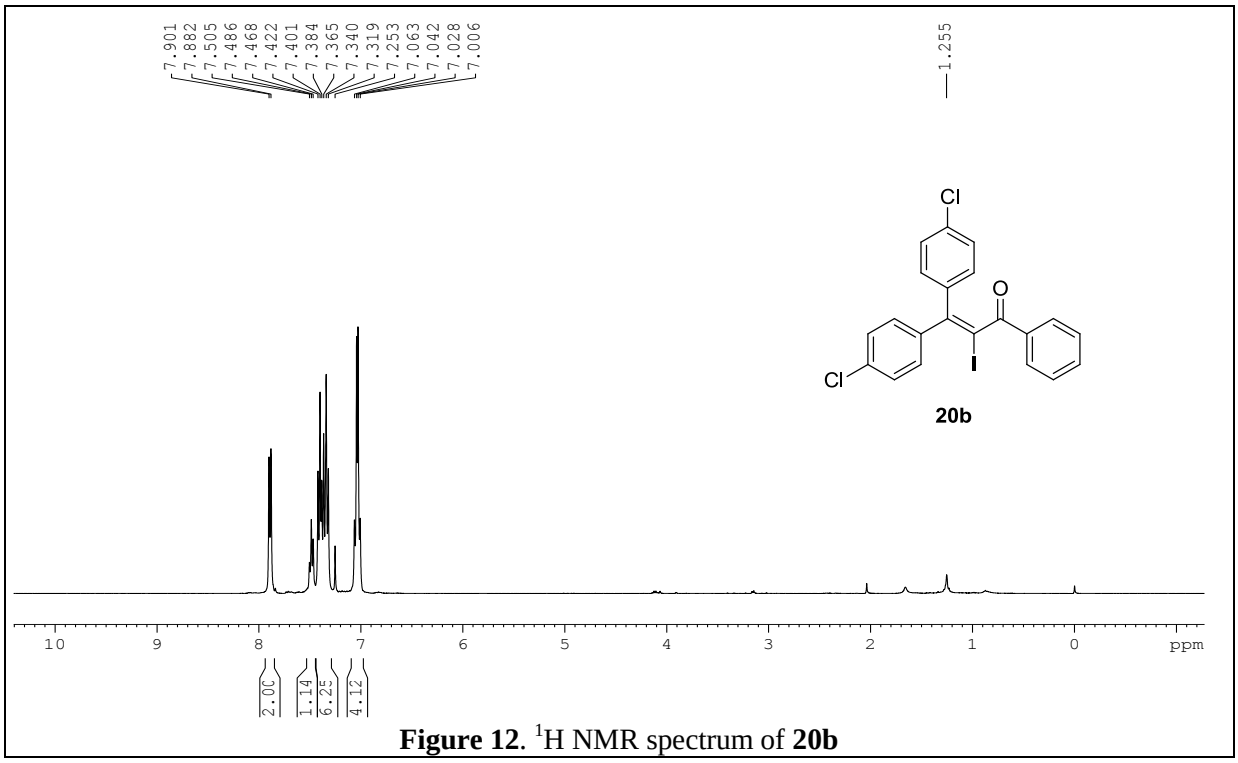


Figure 12. ^{1}H NMR spectrum of **20b**

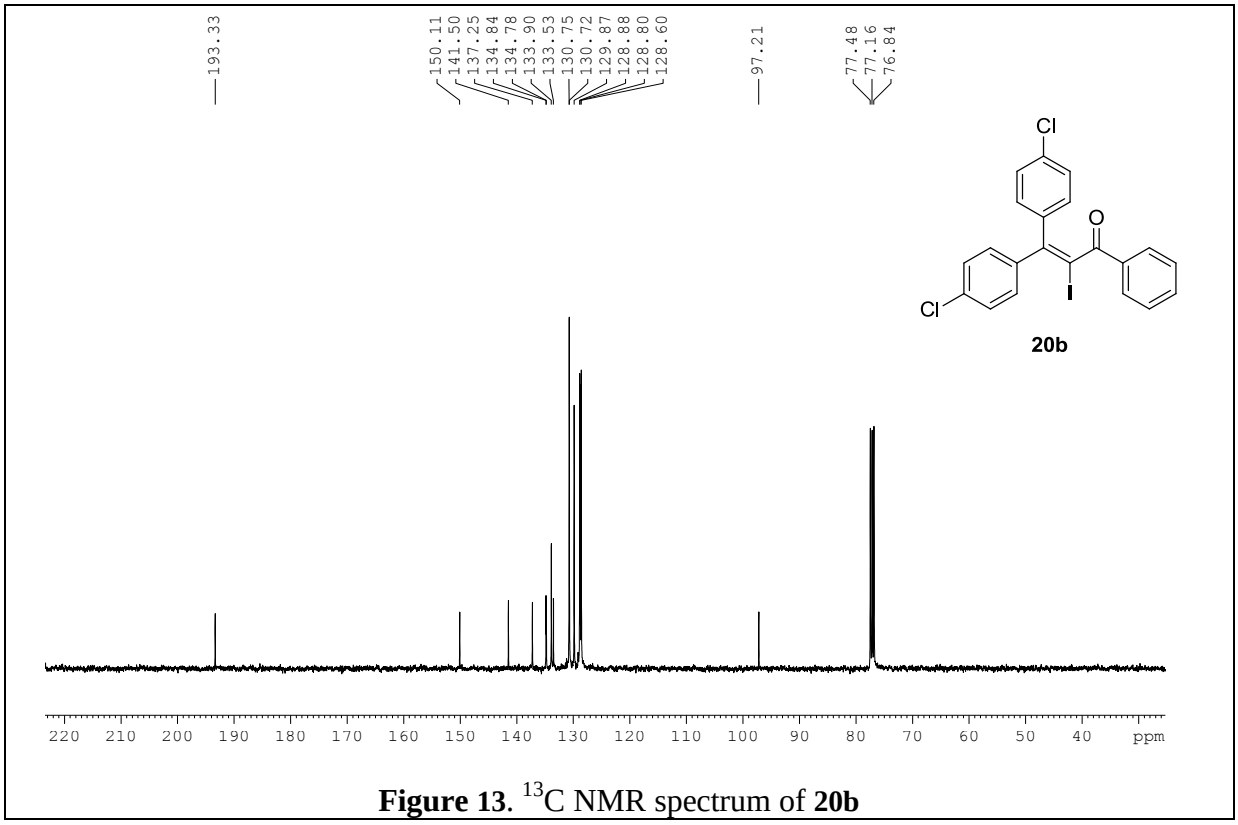


Figure 13. ^{13}C NMR spectrum of **20b**

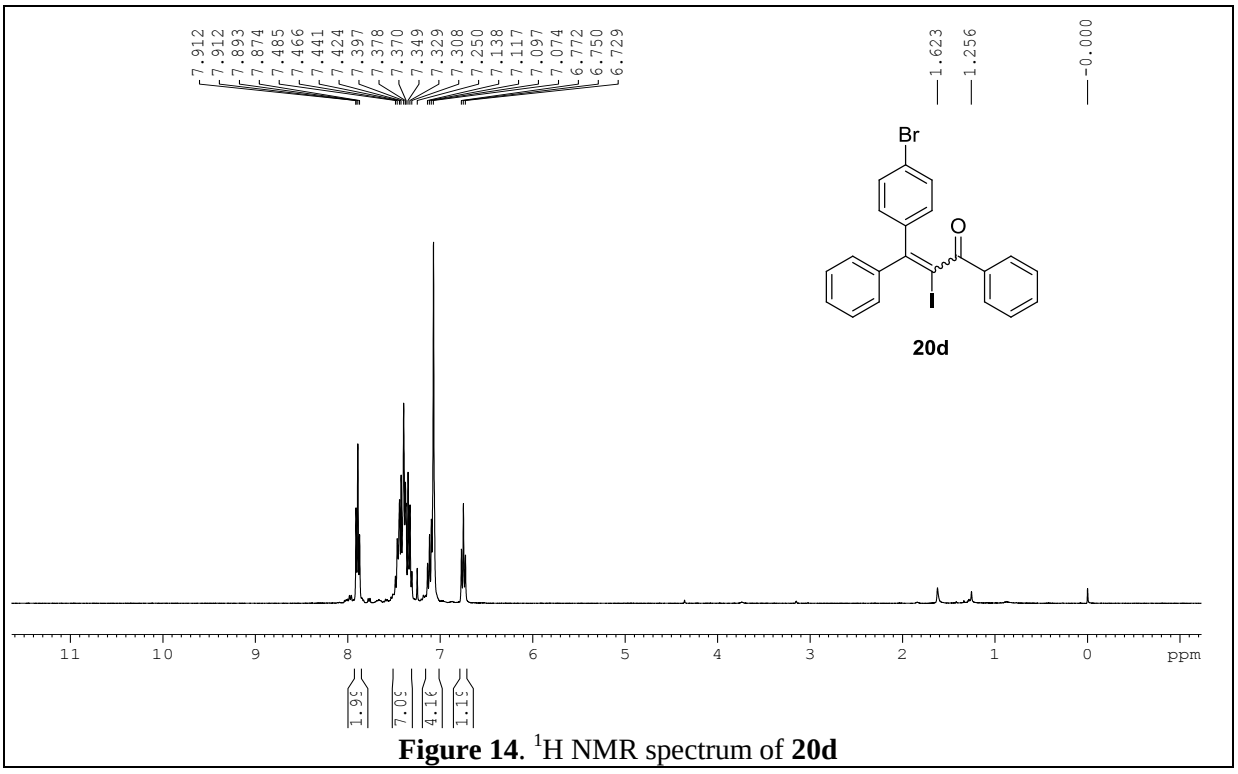


Figure 14. ^{1}H NMR spectrum of **20d**

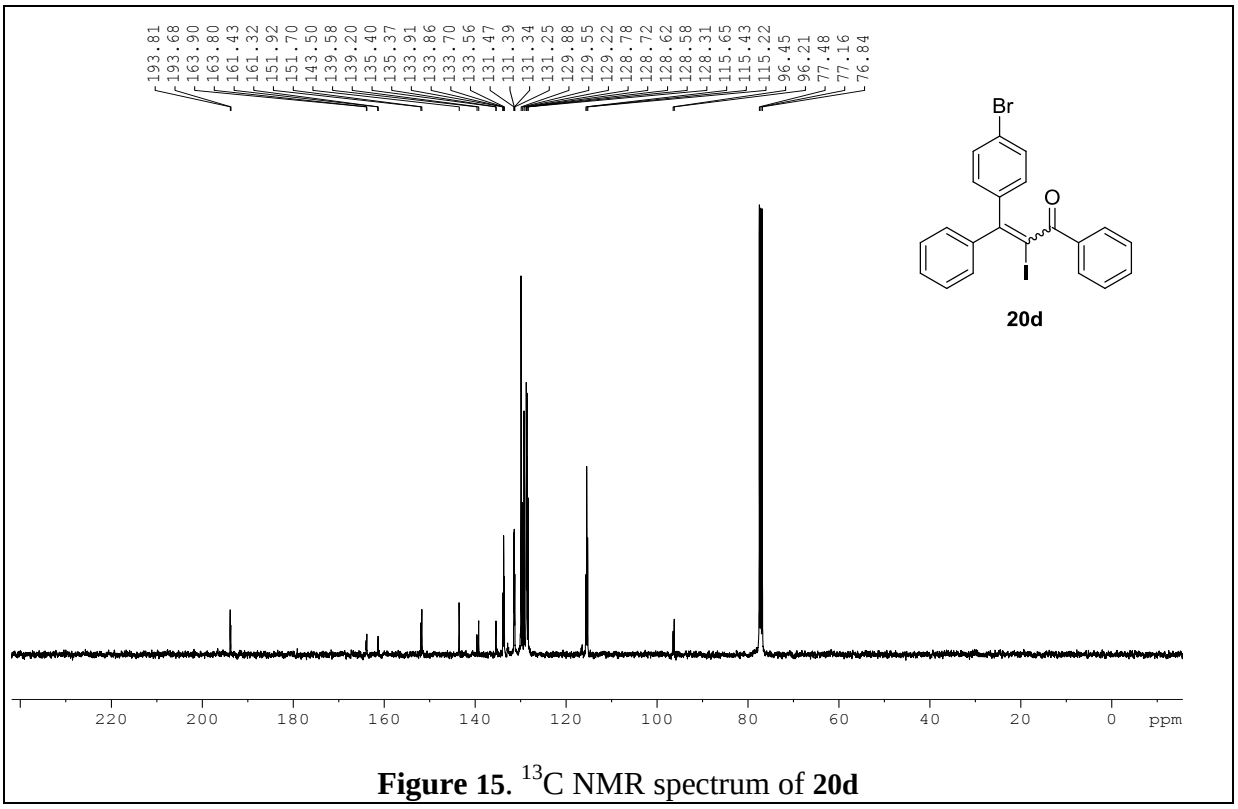


Figure 15. ^{13}C NMR spectrum of **20d**

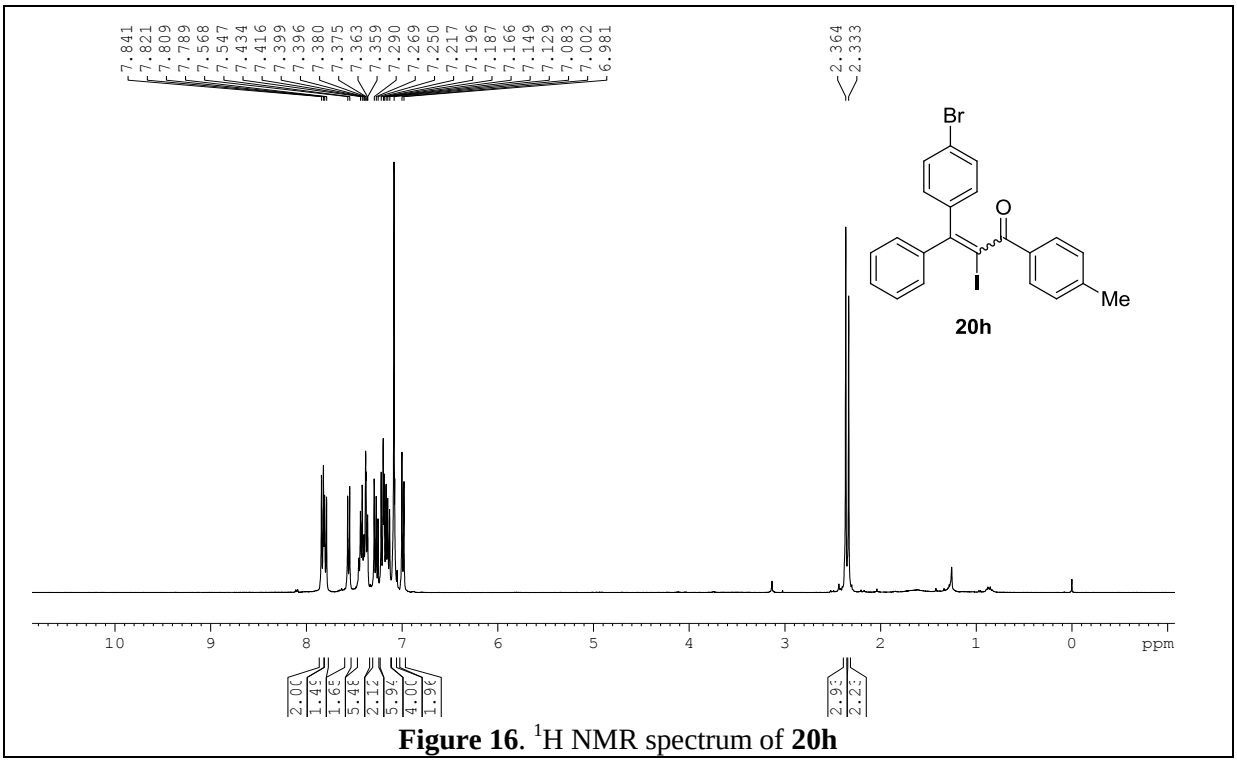


Figure 16. ^{1}H NMR spectrum of **20h**

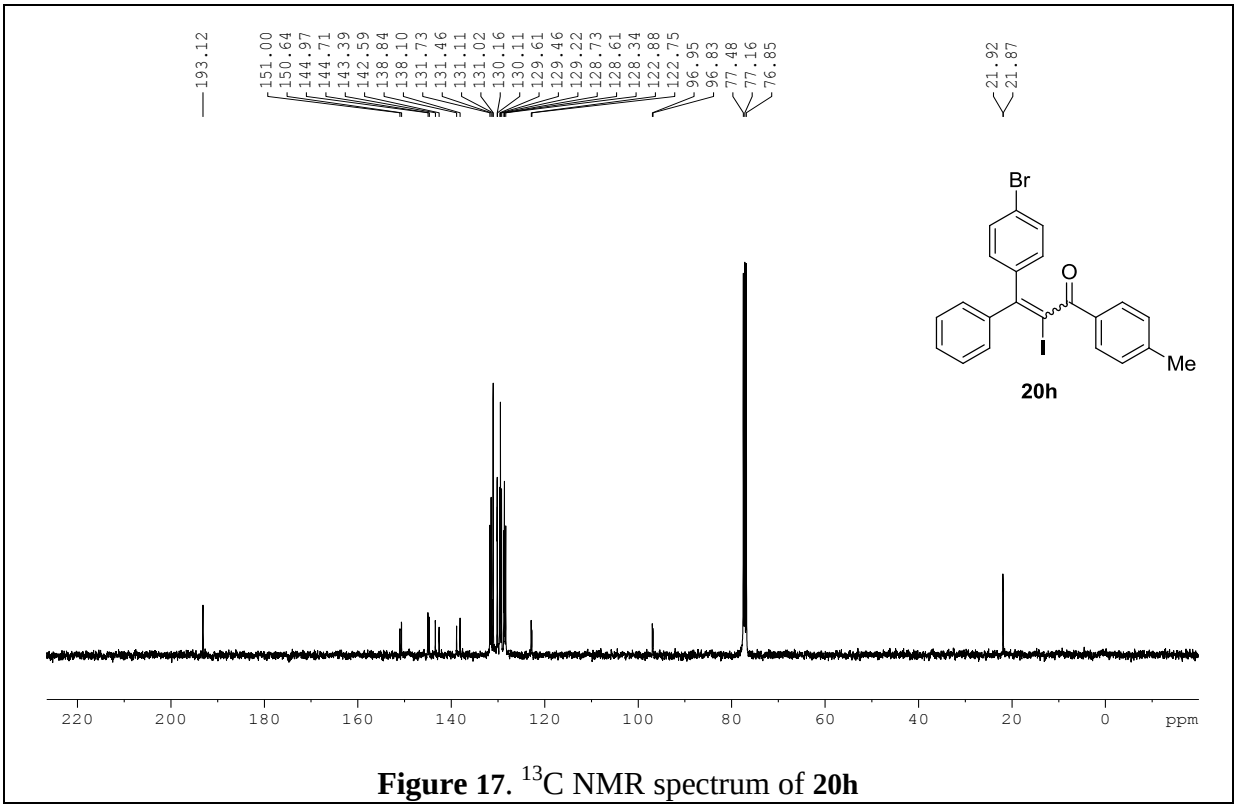


Figure 17. ^{13}C NMR spectrum of **20h**

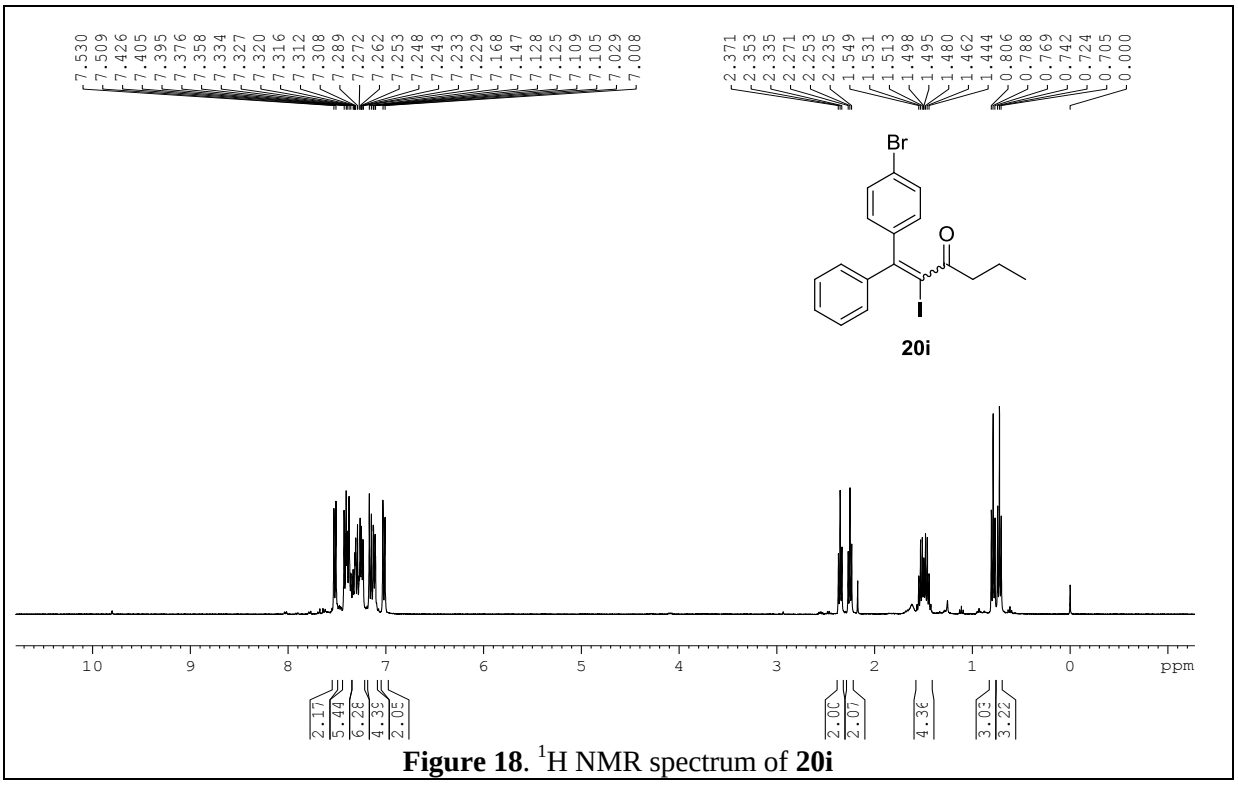


Figure 18. ^{1}H NMR spectrum of **20i**

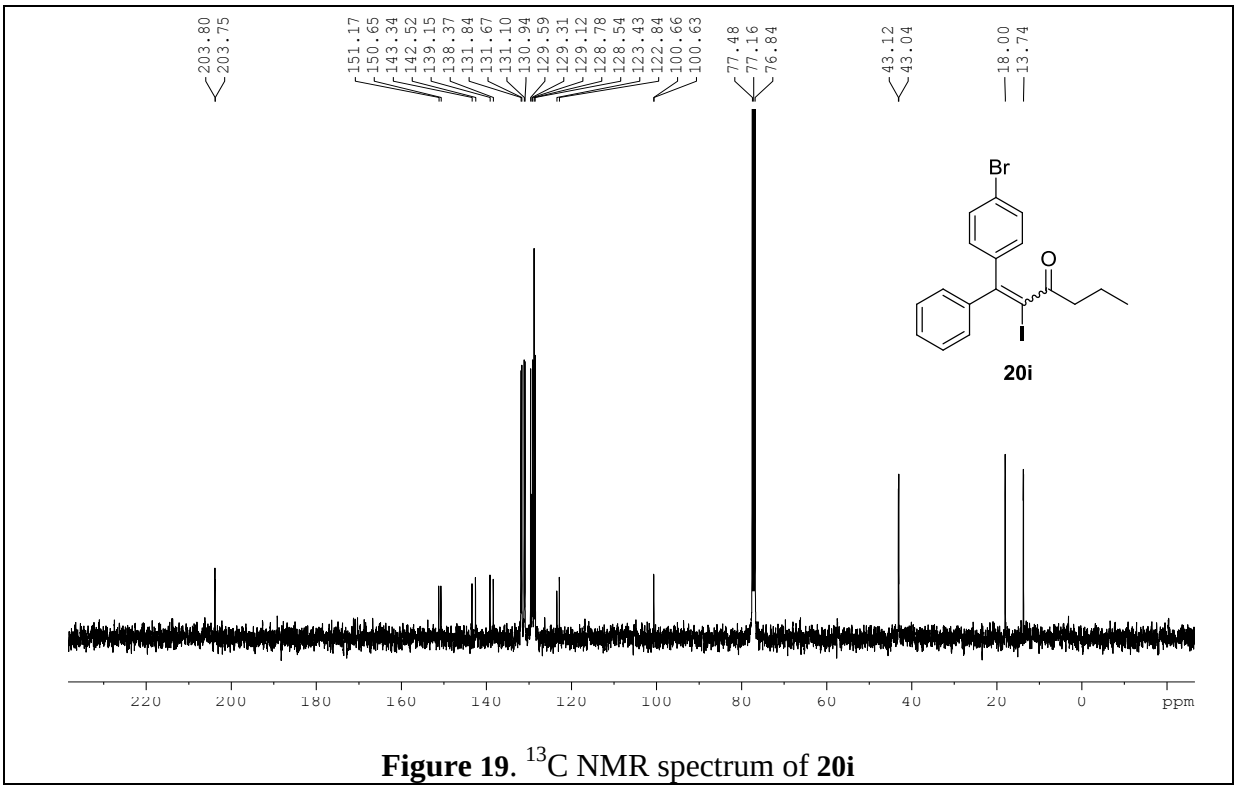


Figure 19. ^{13}C NMR spectrum of **20i**

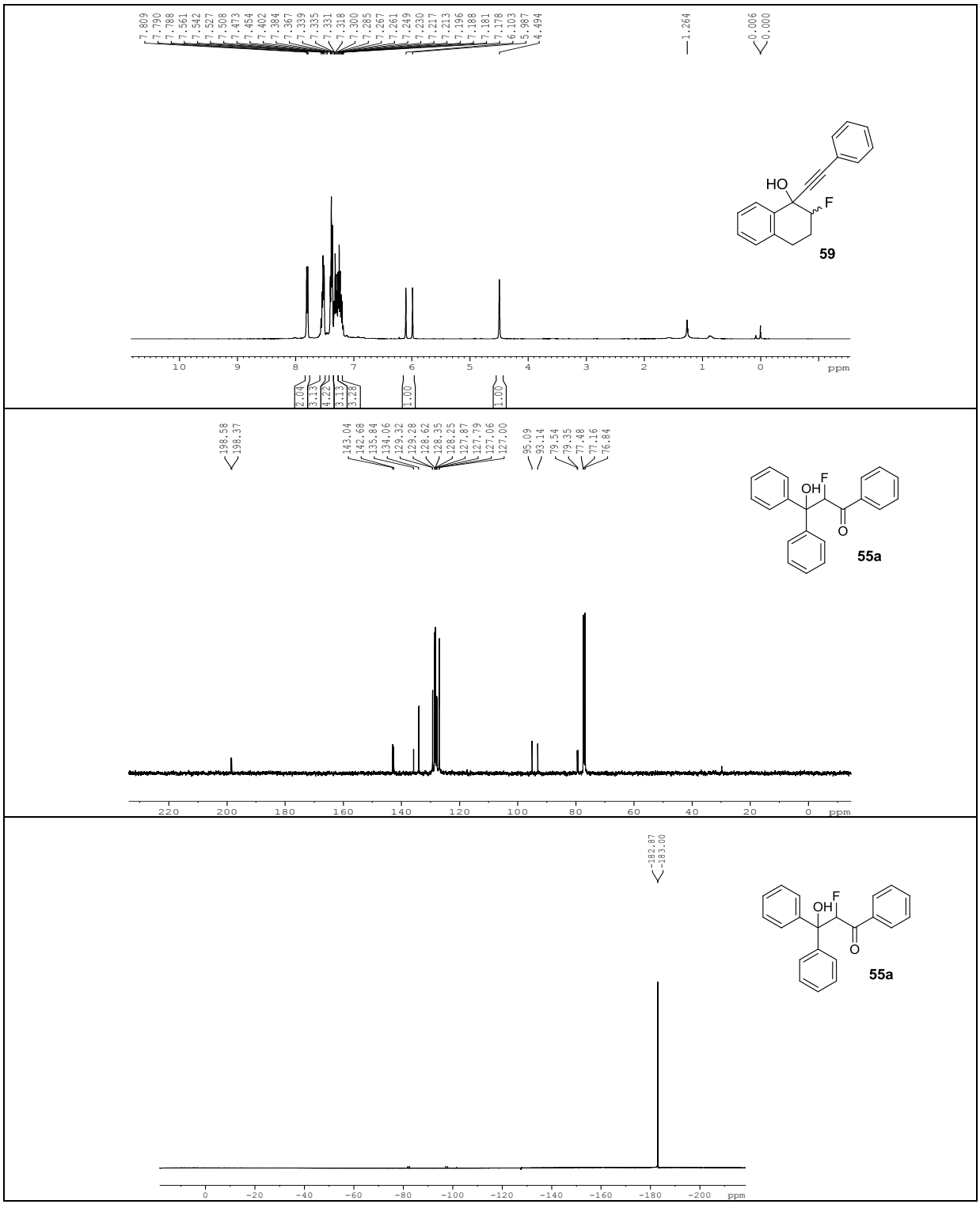


Figure 20. ^{1}H, ^{13}C and ^{19}F NMR spectra of **55a**

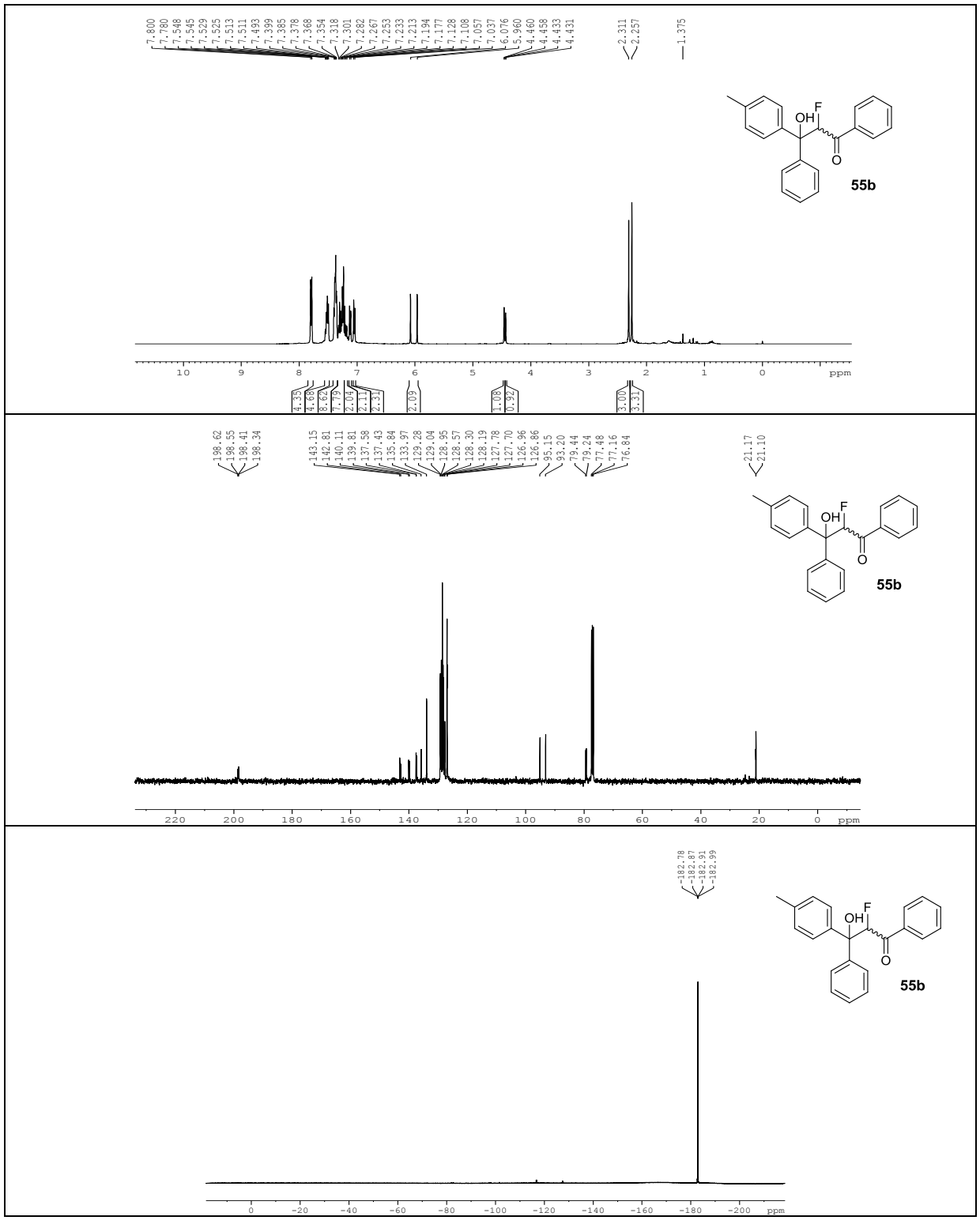


Figure 21. ^{1}H, ^{13}C and ^{19}F NMR spectra of **55b**

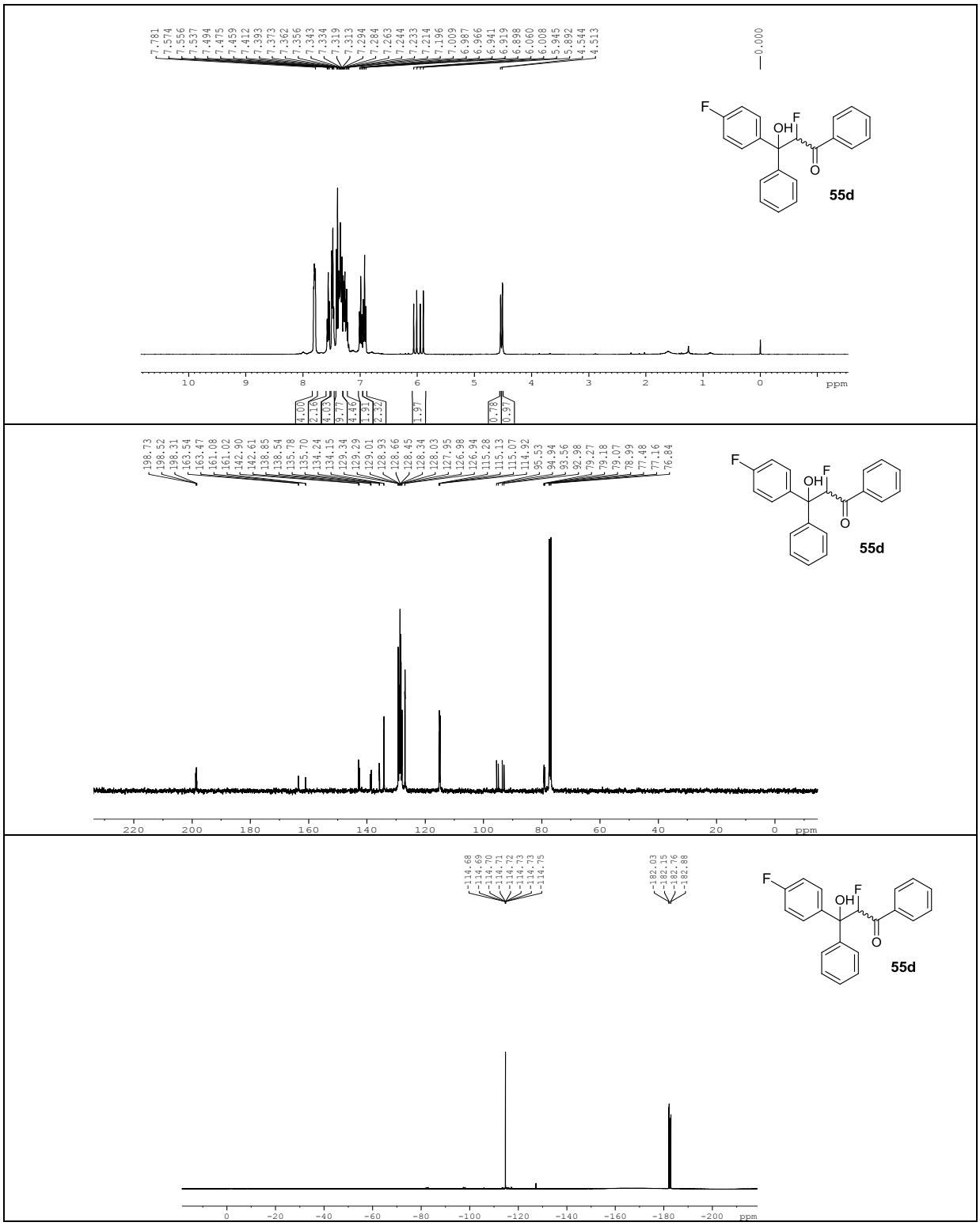


Figure 22. ^{1}H, ^{13}C and ^{19}F NMR spectra of **55d**

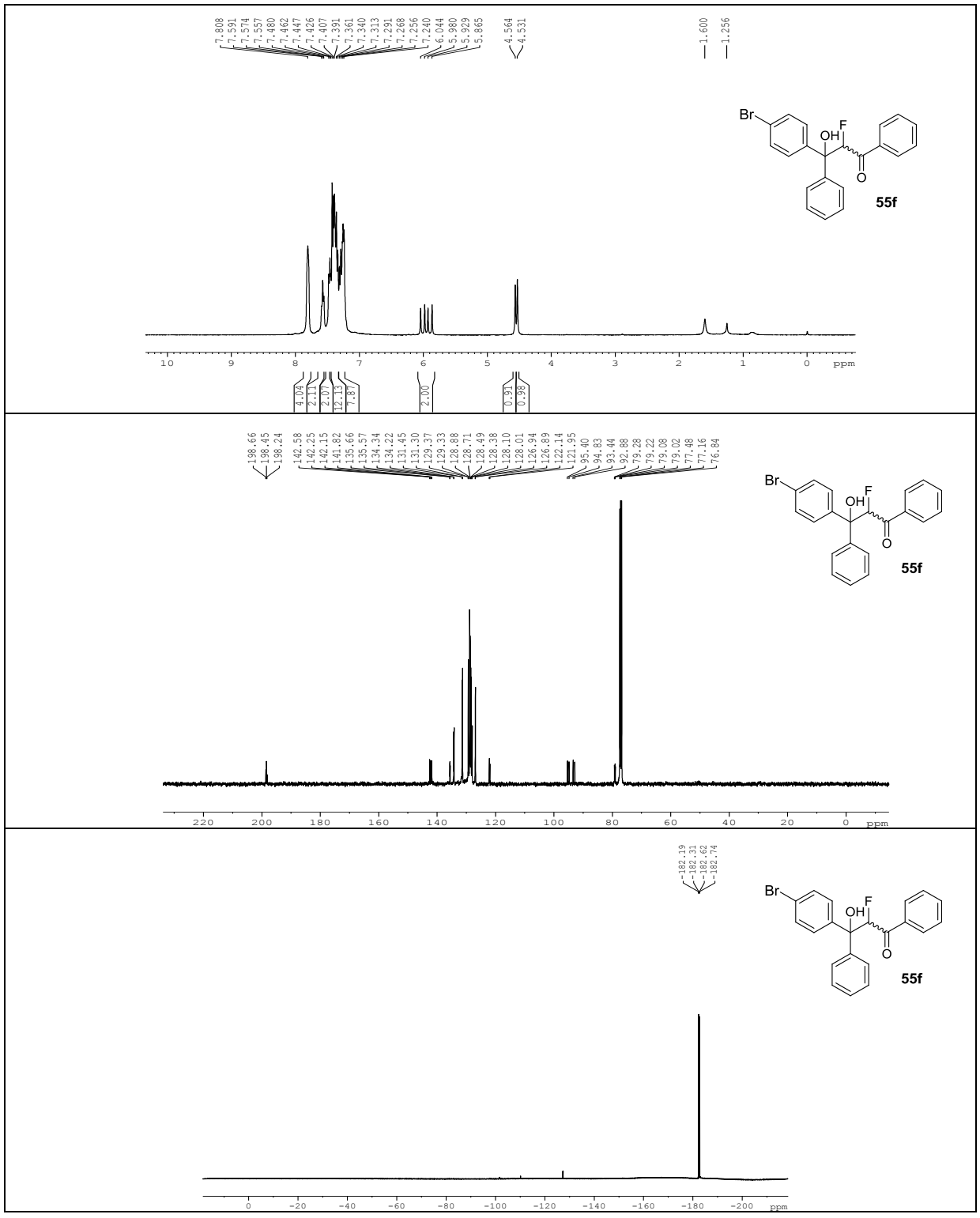


Figure 23. ^{1}H, ^{13}C and ^{19}F NMR spectra of **55f**

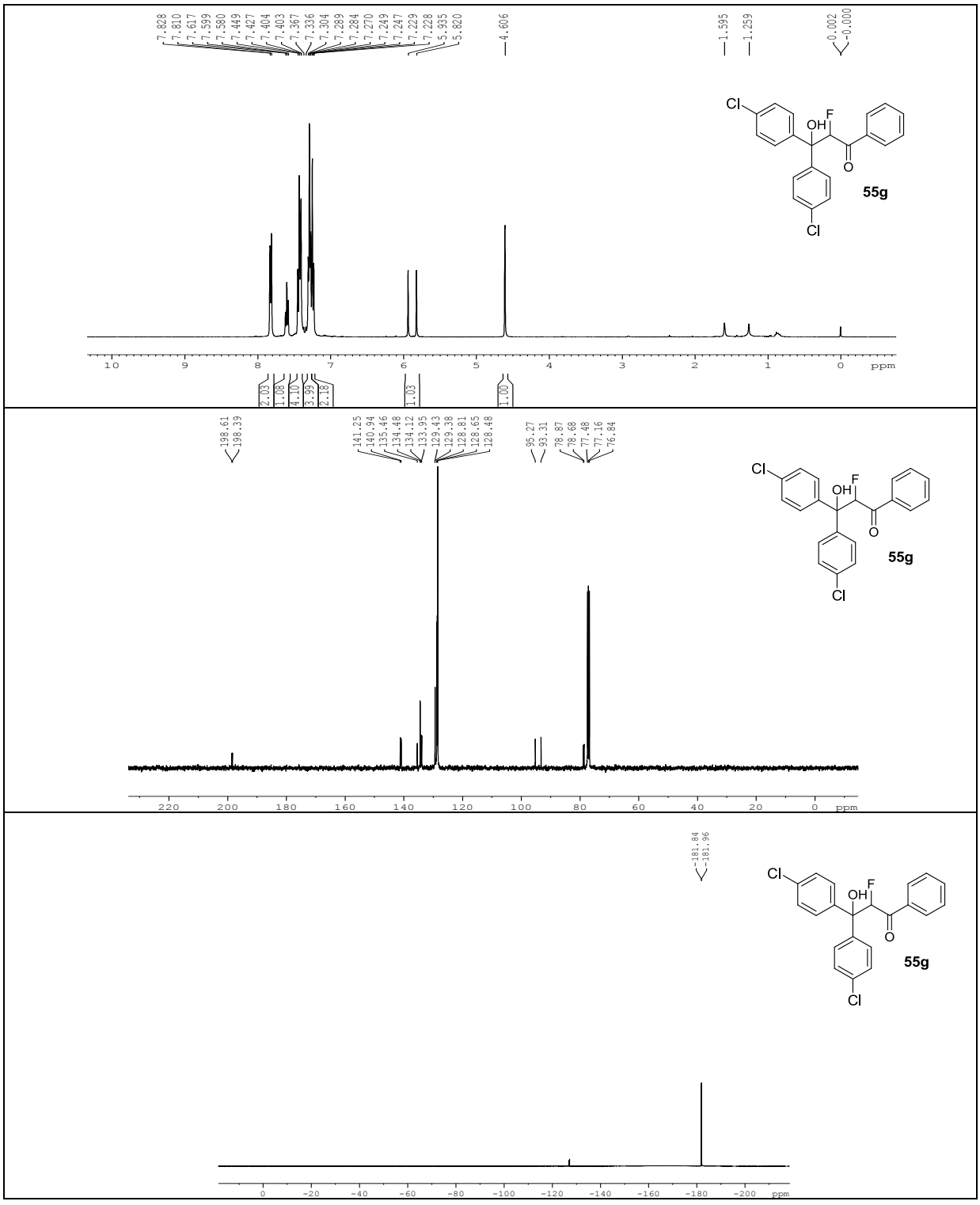


Figure 24. ^{1}H, ^{13}C and ^{19}F NMR spectra of **55g**

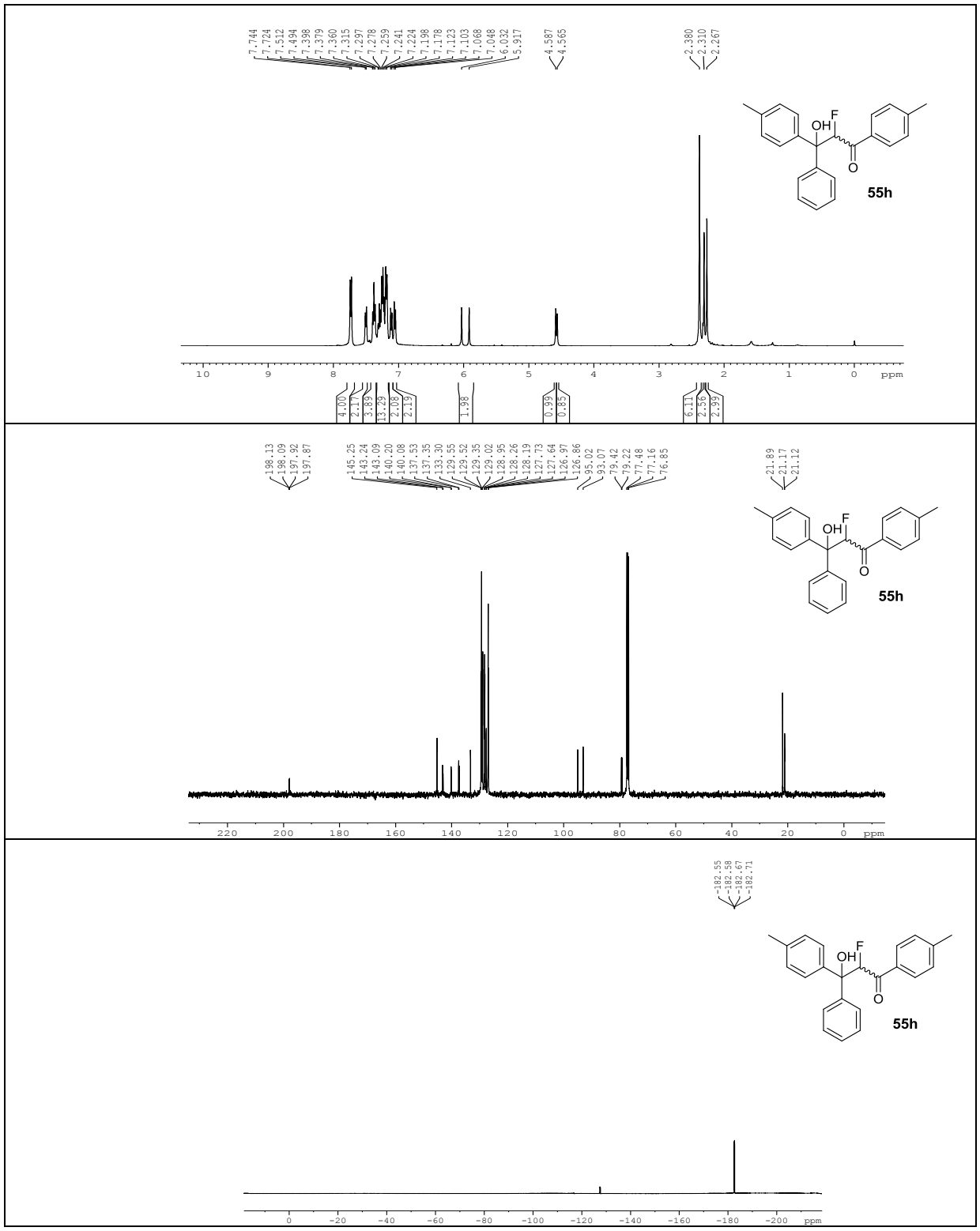


Figure 25. ^{1}H, ^{13}C and ^{19}F NMR spectra of **55h**

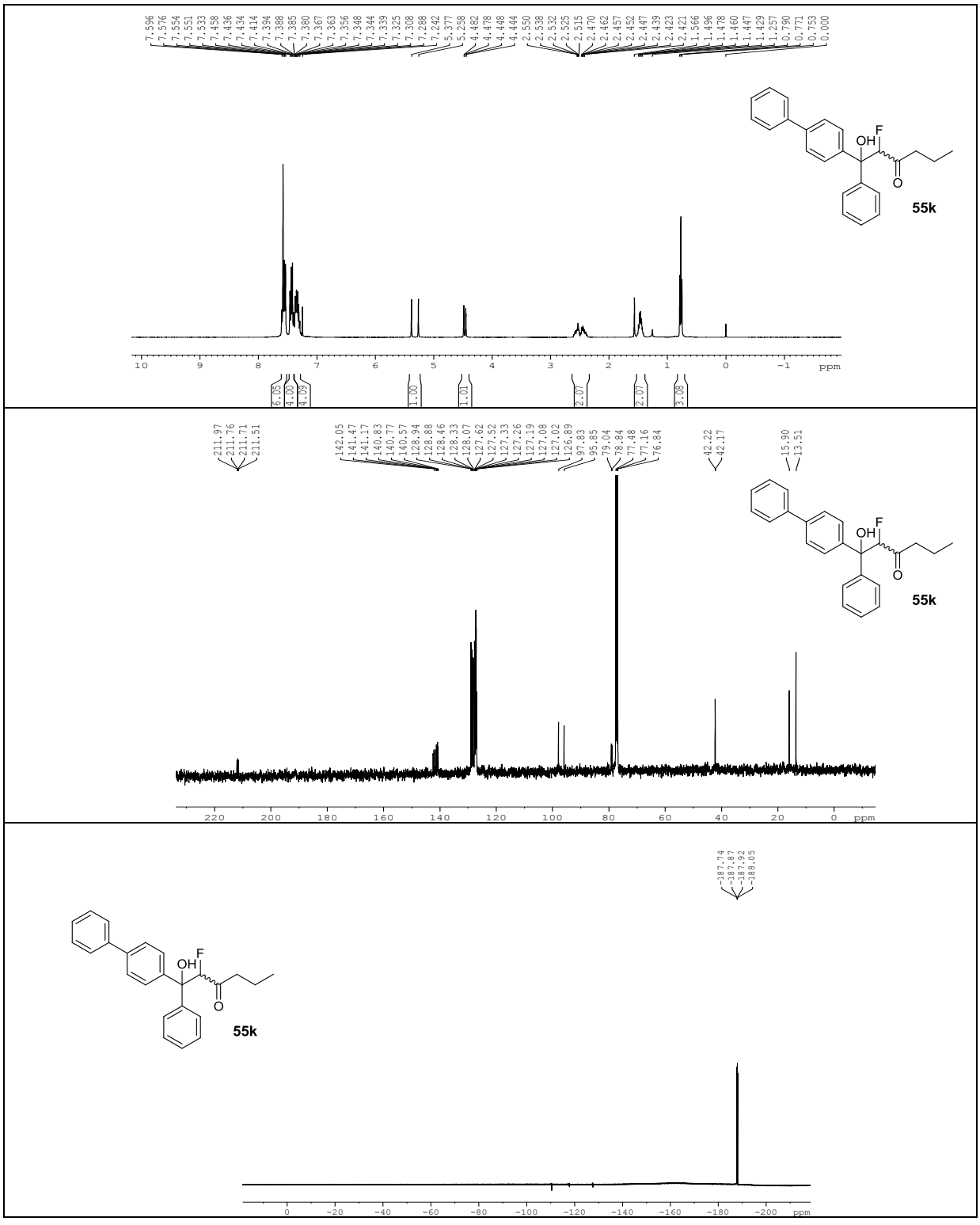


Figure 26. ^{1}H, ^{13}C and ^{19}F NMR spectra of **55k**

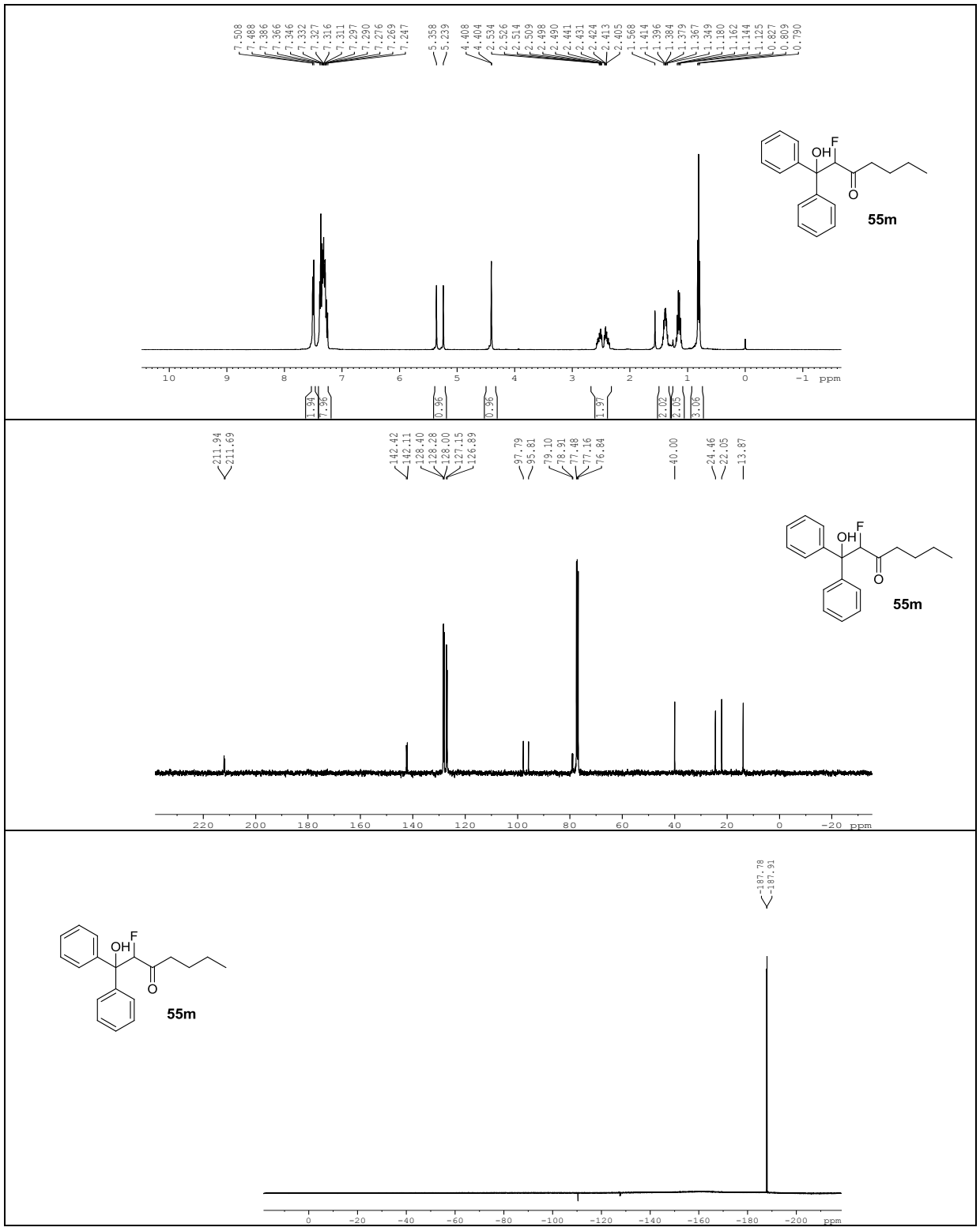


Figure 27. ^{1}H, ^{13}C and ^{19}F NMR spectra of **55m**

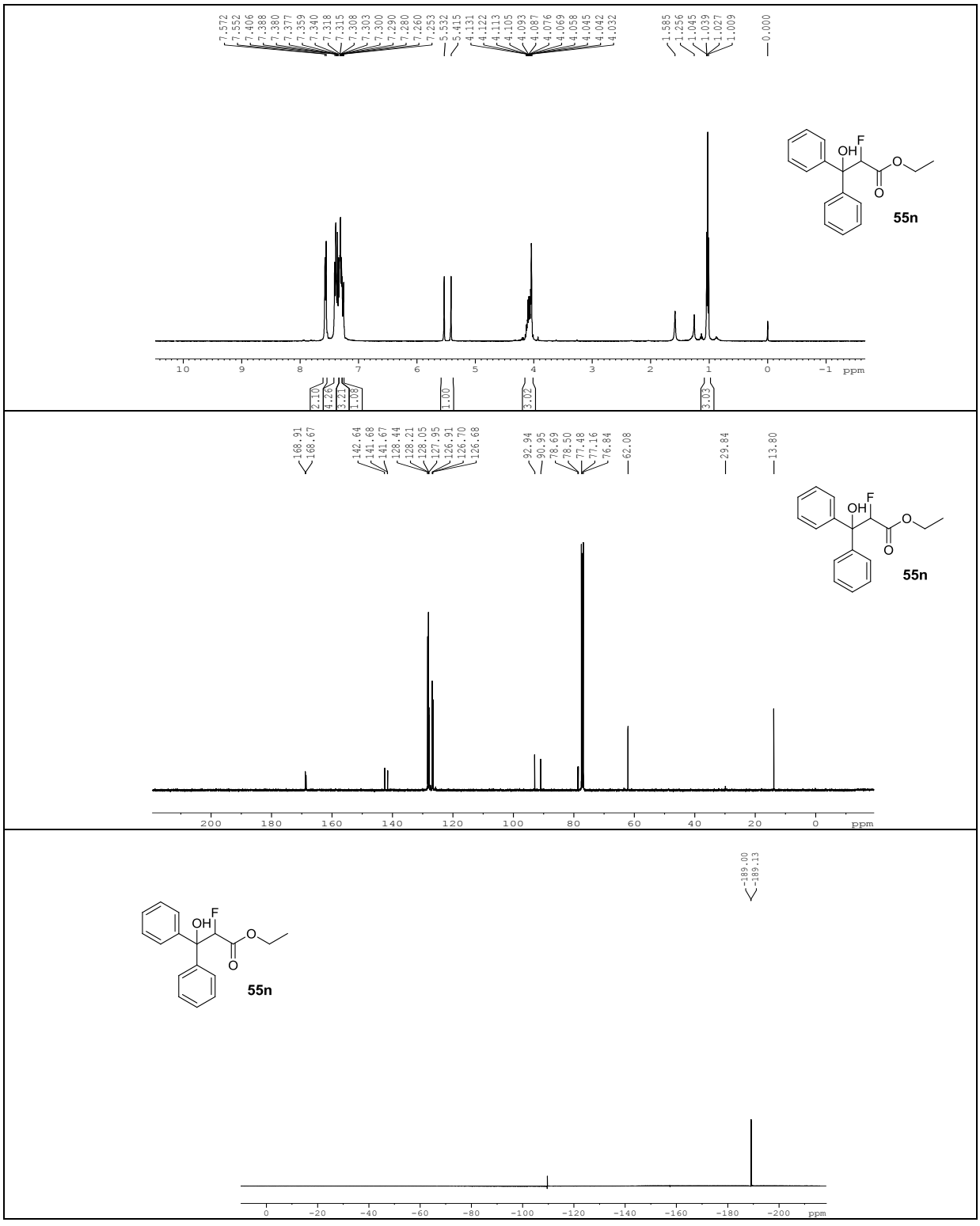


Figure 28. ^{1}H, ^{13}C and ^{19}F NMR spectra of **55n**

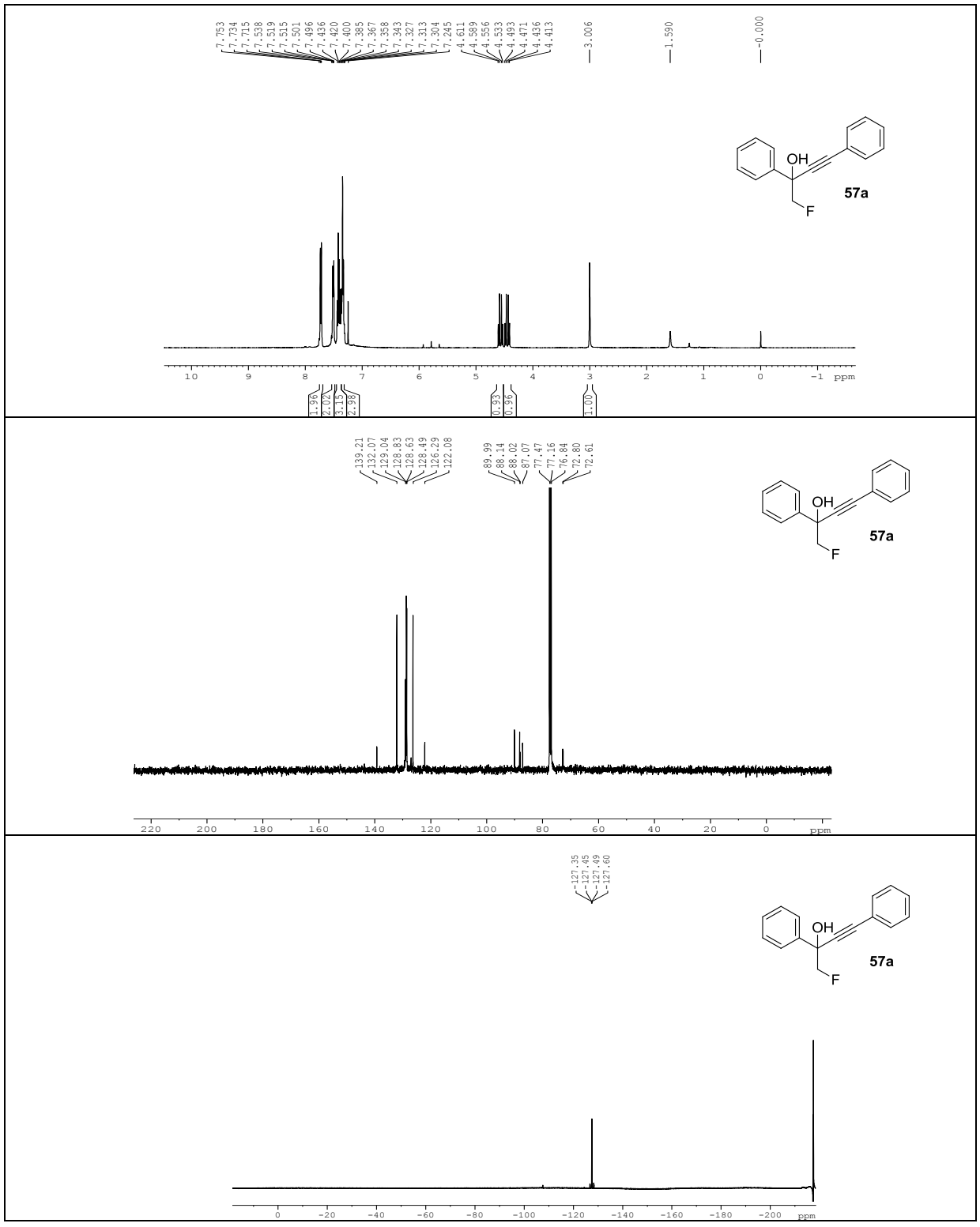


Figure 29. ^{1}H, ^{13}C and ^{19}F NMR spectra of **57a**

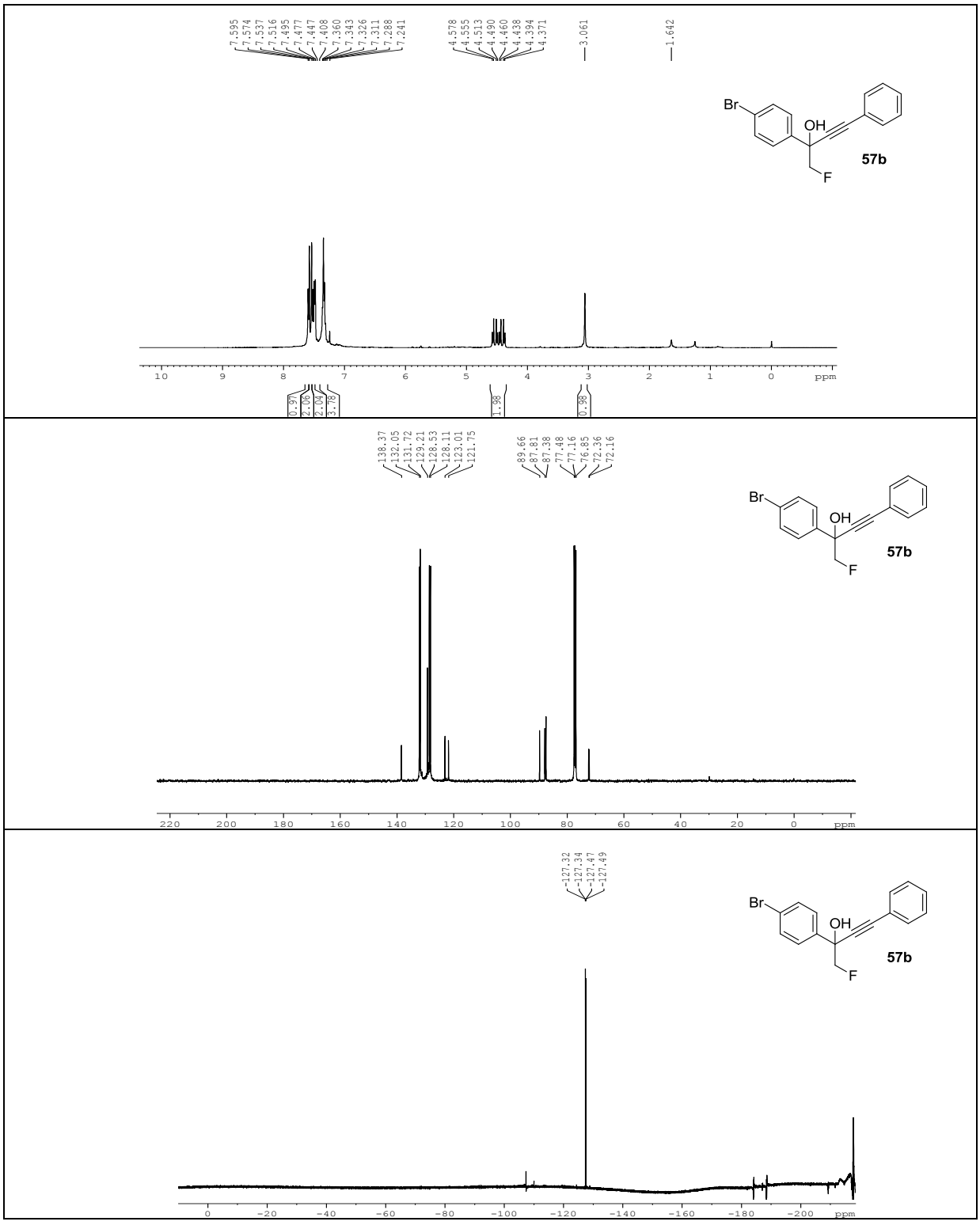


Figure 30. ^{1}H, ^{13}C and ^{19}F NMR spectra of **57b**

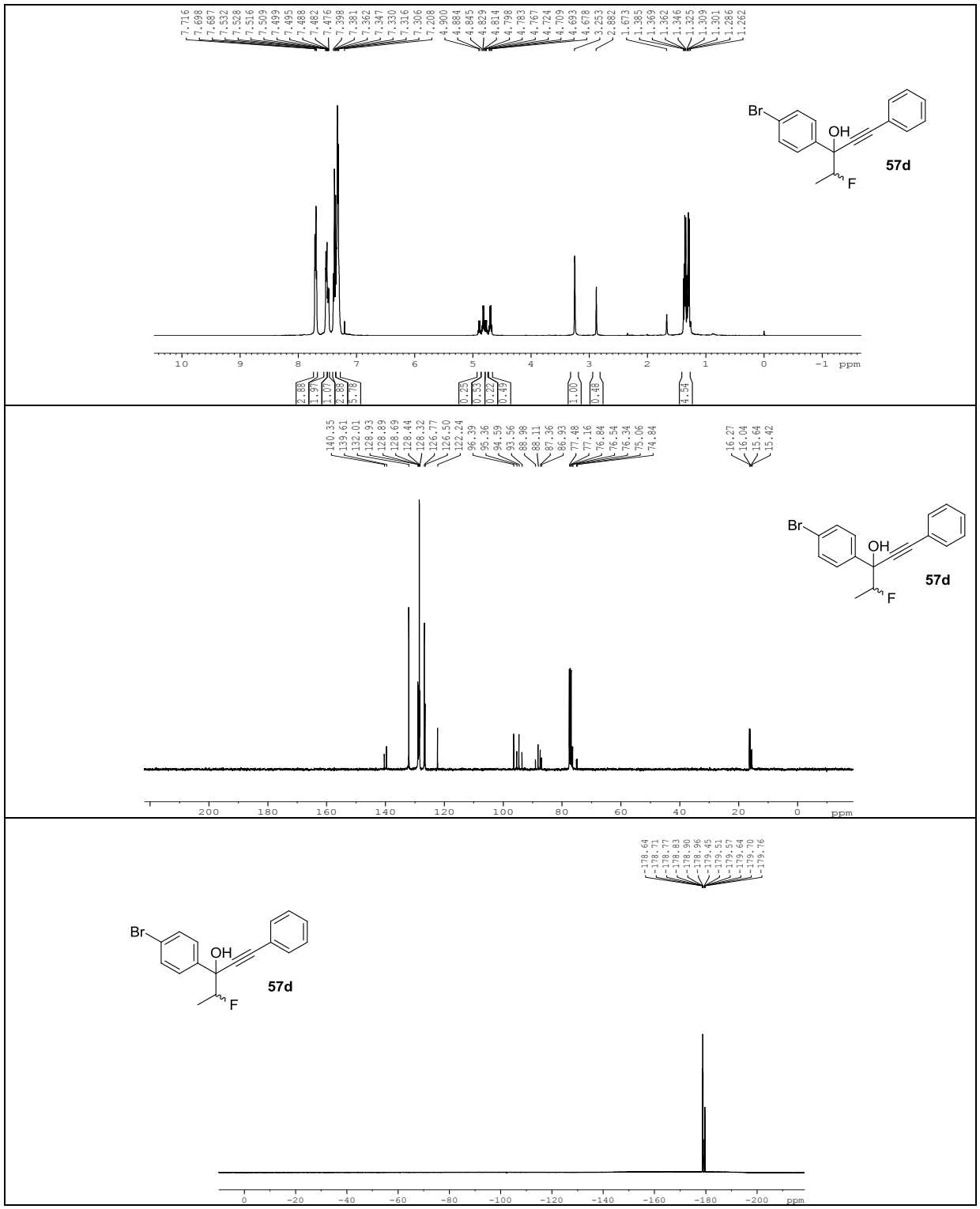


Figure 31. ^{1}H, ^{13}C and ^{19}F NMR spectra of **57d**

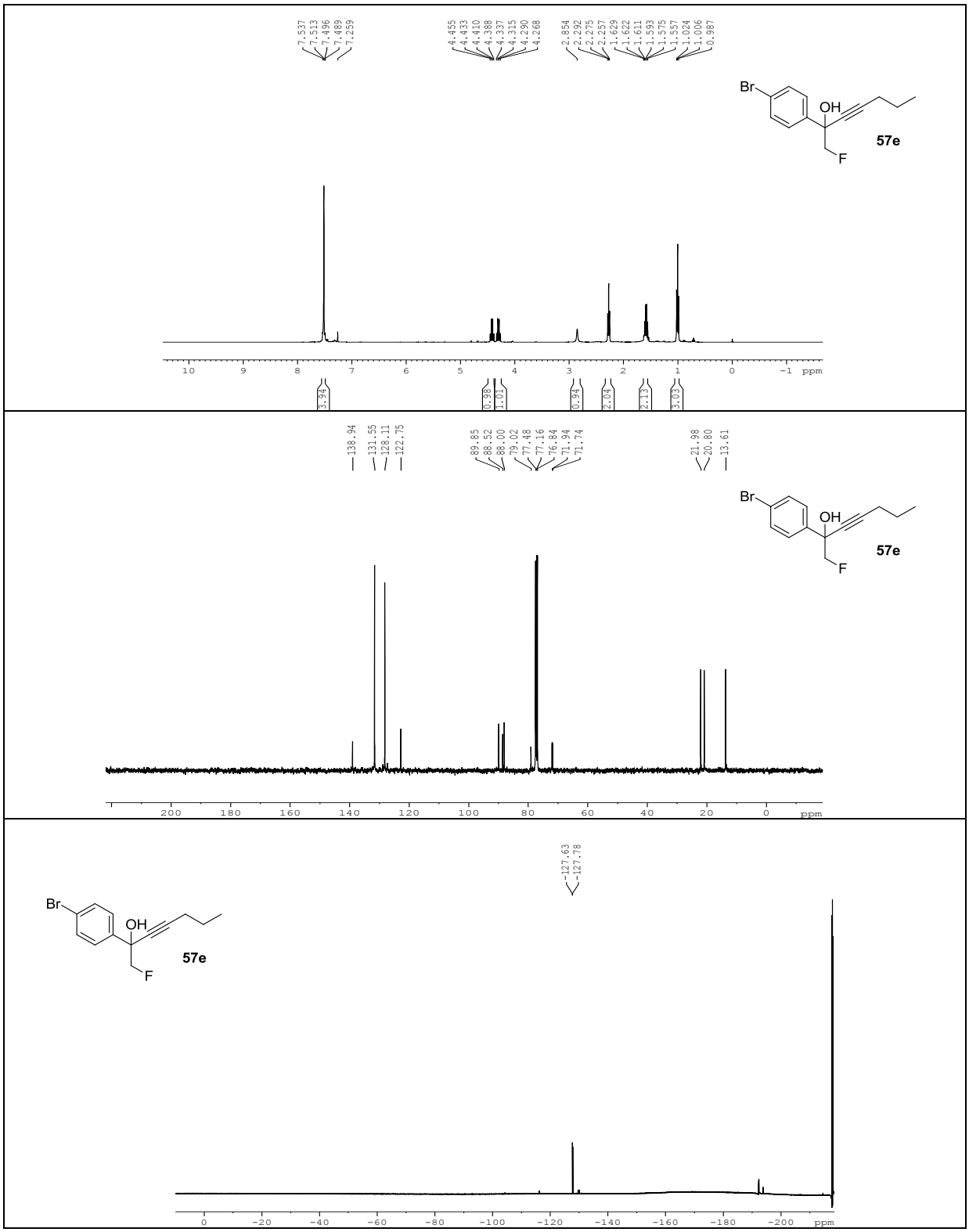


Figure 32. ^{1}H, ^{13}C and ^{19}F NMR spectra of **57e**

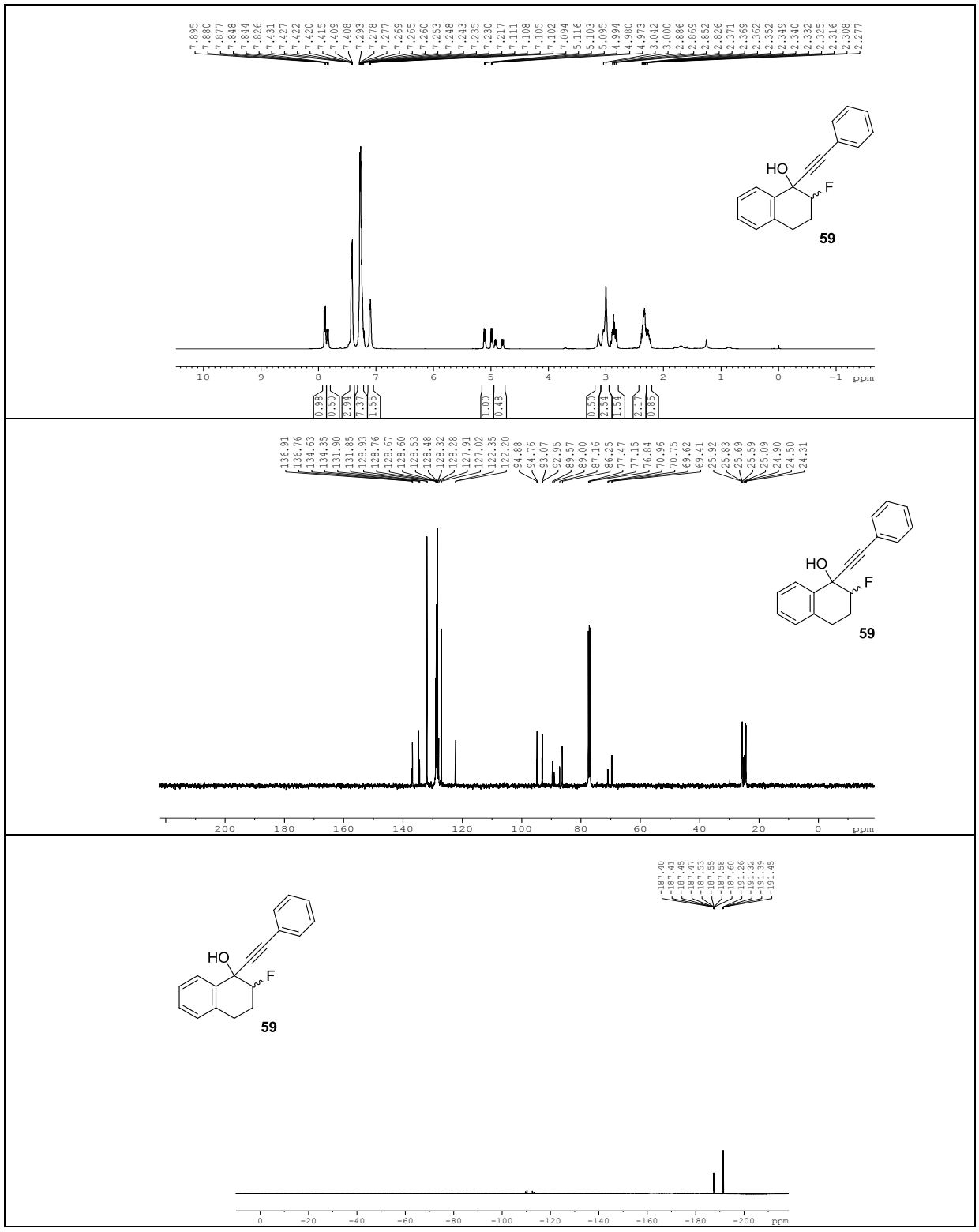


Figure 33. ^{1}H, ^{13}C and ^{19}F NMR spectra of **59**

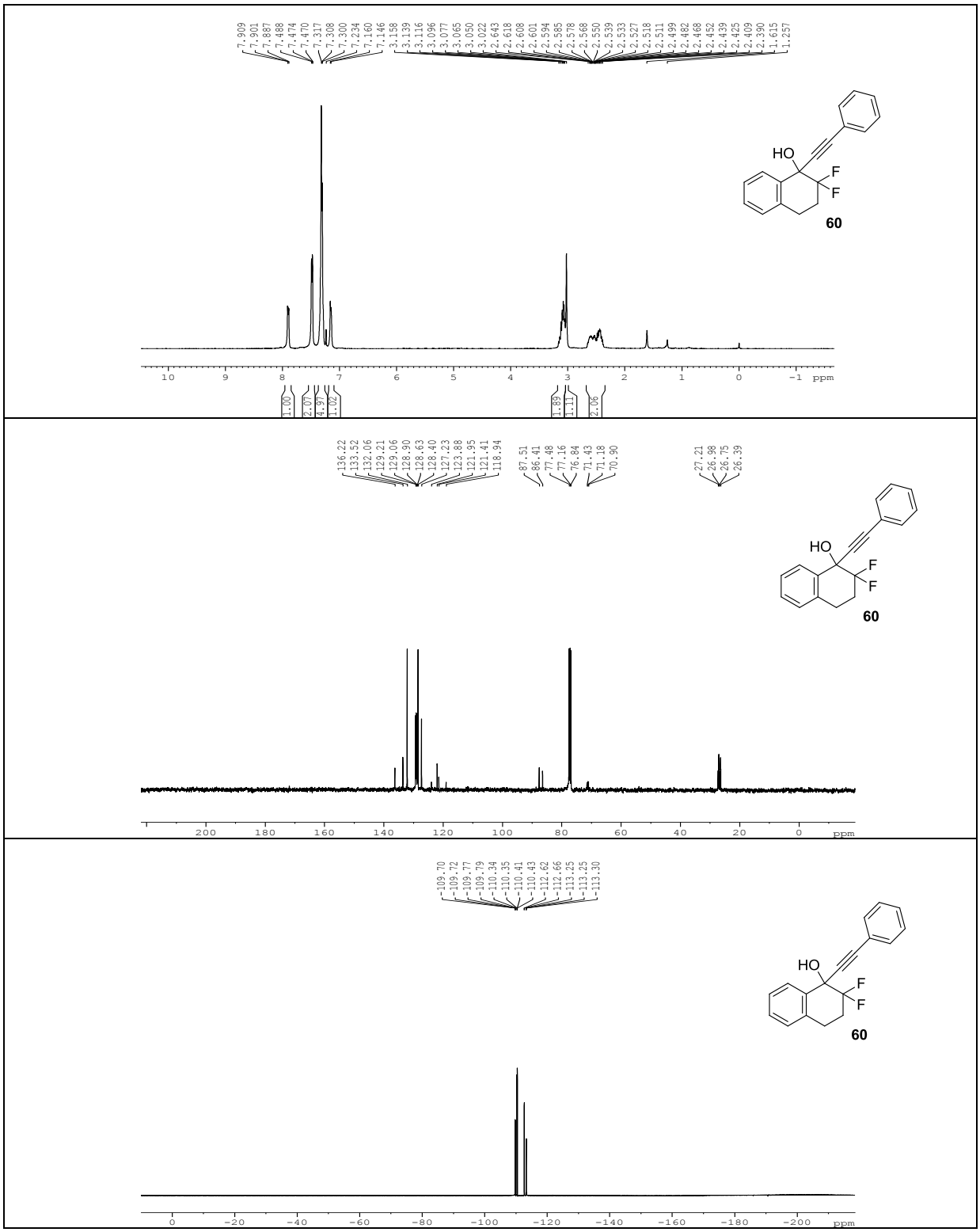


Figure 34. ^{1}H, ^{13}C and ^{19}F NMR spectra of **60**

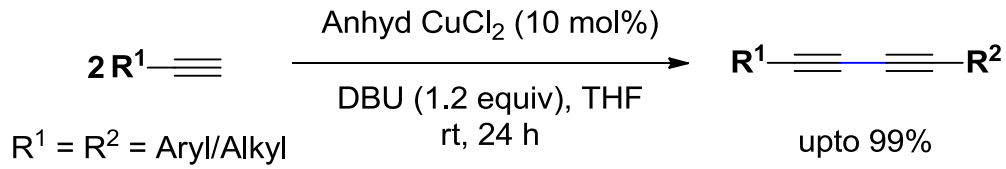
Crystal data and structure refinement of 55a

Identification code	nnk 36	
Empirical formula	C_{21} H_{17} F O_2	
Formula weight	320.35	
Temperature	293(2) K	
Wavelength	1.54184 Å	
Crystal system	'Monoclinic'	
Space group	'P121/n1'	
Unit cell dimensions	a = 15.0819(3) Å	α= 90°.
	b = 5.99560(10) Å	β= 102.275(2)°.
	c = 18.5268(4) Å	γ = 90°.
Volume	1636.99(6) $Å^3$	
Z	4	
Density (calculated)	1.300 Mg/m^3	
Absorption coefficient	0.734 mm^{-1}	
F(000)	672	
Crystal size	0.25 x 0.15 x 0.12 mm^3	
Theta range for data collection	3.44 to 71.43°.	
Index ranges	-18<=h<=16, -3<=k<=7, -22<=l<=19	
Reflections collected	5092	
Independent reflections	3107 [R(int) = 0.0121]	
Completeness to theta = 25.00°	100.0 %	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3107 / 0 / 217	
Goodness-of-fit on F^2	1.053	
Final R indices [I>2sigma(I)]	R1 = 0.0426, wR2 = 0.1199	
R indices (all data)	R1 = 0.0476, wR2 = 0.1260	
Largest diff. peak and hole	0.187 and -0.243 $e.Å^{-3}$	

Chapter 3

Copper(II)-Catalyzed Homo- and Heterocoupling of Terminal Alkynes

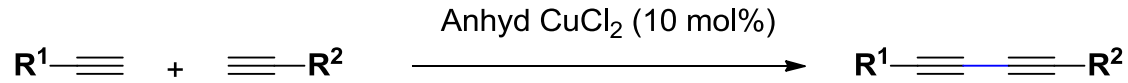
Homocoupling



$R^1 = R^2$ = Aryl/Alkyl

upto 99%

Heterocoupling



$R^1 = R^2$ = Aryl/Alkyl

upto 74%

3.1 Introduction

Construction of C-C bond stands fundamental in organic synthesis. In spite of development of several methods for C-C bond formations, coupling reactions are most significant and play a vital role in building complex structures in an elegant manner. Out of them, coupling of terminal alkynes figures out to be special because, the introduction of C-C triple bond as functional group in organic compounds has considerable applications due to its presence in variety of natural products and bio-active molecules,[1] π-conjugated scaffolds, oligomers/polymers,[2] materials having non-linear optical properties and molecular recognition properties.[3]

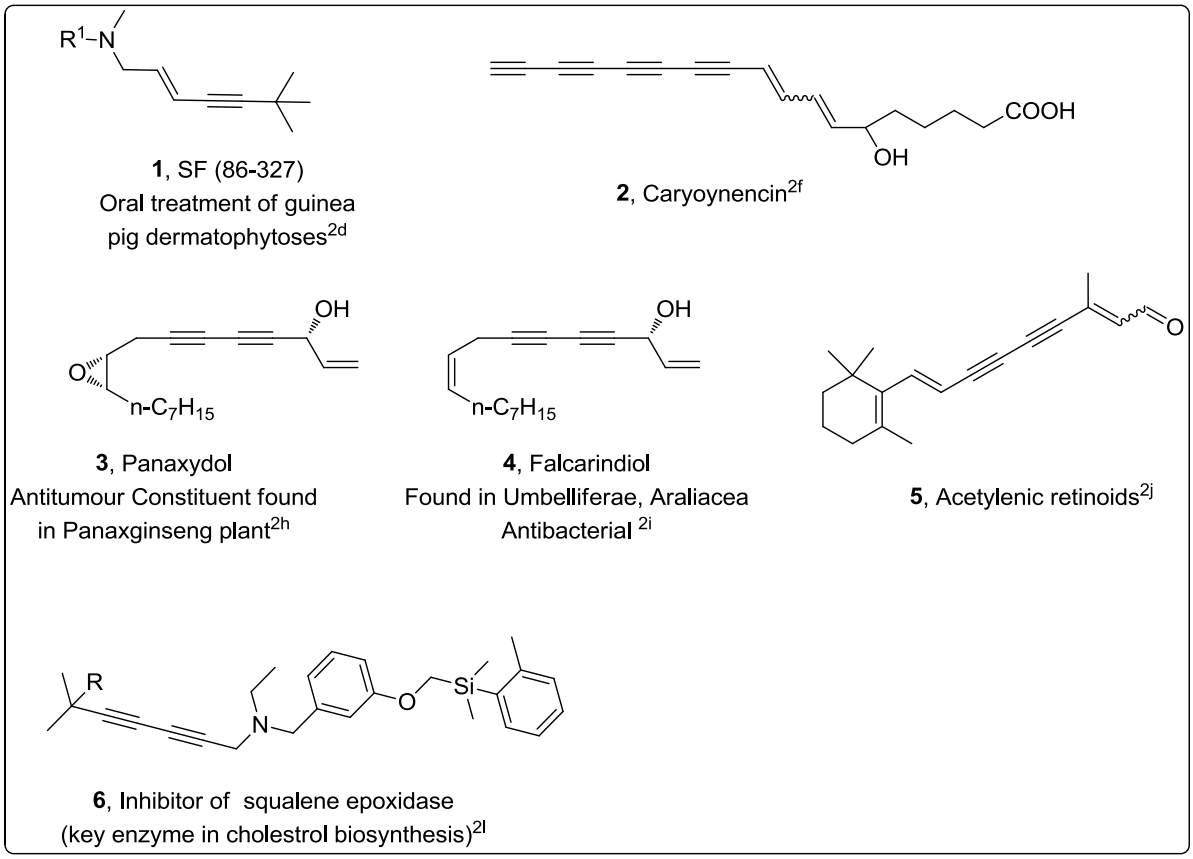


Figure 1. Representative examples of bioactive molecules prepared by alkyne coupling

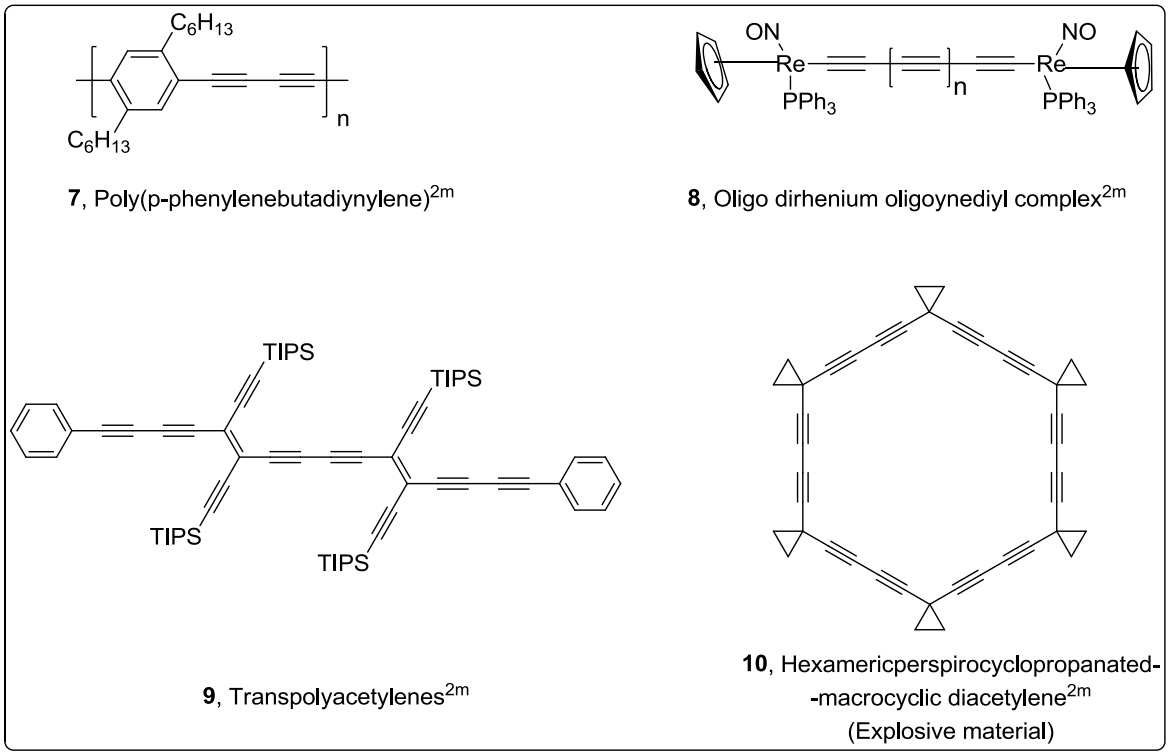
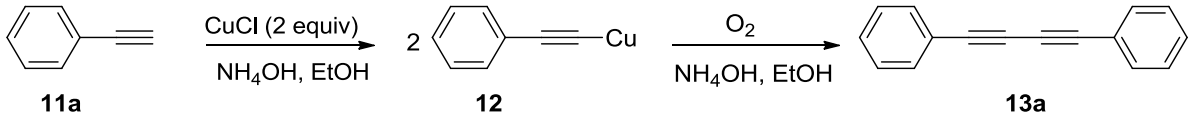


Figure 2. Representative examples of organic materials prepared by alkyne coupling

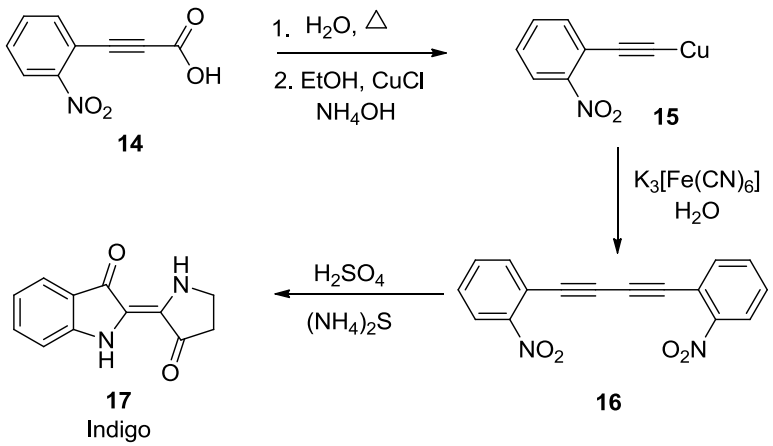
3.2 General methods for the synthesis of diynes

The historic pathway for homocoupling of alkynes was laid by Carl Glaser in 1869, who discovered the dimerization of phenylacetylene in the presence of stoichiometric amount of CuCl and ammonia solution in ethanol in two steps (Scheme 1).[4] First step is the formation of copper acetylide (**12**) which could be isolated. Then it undergoes oxidative coupling in presence of molecular oxygen. But the major drawback is isolation of copper acetylide which is difficult to isolate and is often explosive before oxidation.



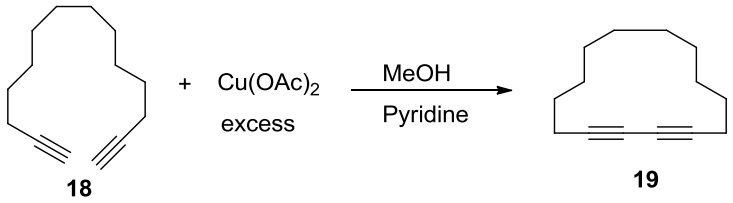
Scheme 1. Homocoupling described by Glaser

Later in 1882, Baeyer utilized this methodology for the synthesis of indigo using potassium ferricyanide as oxidant and showed that molecular oxygen was not necessary (Scheme 2).[5]



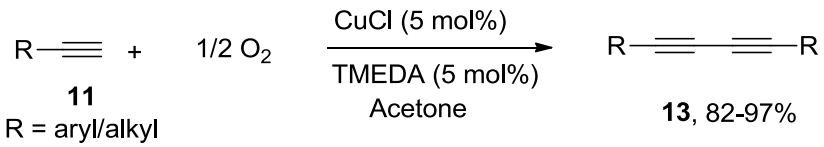
Scheme 2. Synthesis of indigo using Glaser coupling

Another breakthrough in acetylenic coupling was achieved by Eglinton and Galbraith in 1956, by using Cu^{II} salt in methanolic pyridine (Scheme 3).[6] It was proved as one of the best method for the preparation of unsaturated macrocycles[7] and annulenes.[8]



Scheme 3. Eglinton and Galbraith method for preparing macrocycles

For the first time use of ligands in homocoupling was introduced by Hay. Bidentate *N*,*N*,*N*′,*N*′ tetramethylethylenediamine (TMEDA) was used along with CuCl. The advantage of this method is the solubility of reactive copper species and usage of catalytic amount of ligand. The standard condition for Hay coupling is CuCl, O_2, TMEDA (Scheme 4).[9]

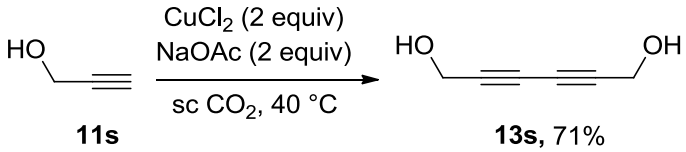


Scheme 4. Hay method of alkyne homocoupling

After these initial developments on acetylenic coupling, studies directed towards finding better condition for alkyne couplings have taken over. In this regard catalysts based on many metals like Pd,[10] Ag,[11] Ni,[12] and Co[13] were found to effect the alkyne

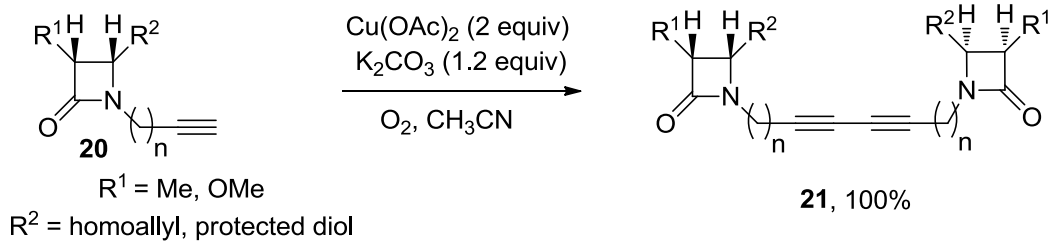
homocoupling. Still copper catalysts were found to be more effective. The main advantages of using copper catalysts are: they are non toxic, easy to handle, wide availability and low costs. Keeping the Cu^{I} as the catalyst, different bases and additives have been found to furnish the coupling products.[14] Supported catalysts like Cu-Al-LDH (LDH = Layered double hydroxide),[15] Al_2O_3,[16] Cu^{I}-Zeolite,[17] $Cu(OH)_x/TiO_2$,[18] and copper nanoparticles have been found to effect the alkyne coupling reaction.[19] In addition alkynyl boranes,[20] alkynyl stannes[21] and alkynyl silanes[21d] have also been used as coupling partners to make unsymmetrical diynes. Even ionic liquids have shown positive effect for effective alkyne coupling.[22] As described above, there are many reports for Cu^{I}-catalyzed homocoupling reactions but only few reports are there that involve Cu^{II}.[23]

Jiang and co-workers demonstrated the use of super critical carbondioxide for Glaser coupling with 2 equivalents of each Cu^{II} and solid NaOAc (Scheme 5). The advantage of this method is getting good yields with aliphatic alkynes and avoiding amine bases.[24]



Scheme 5. Glaser coupling in super critical CO_2

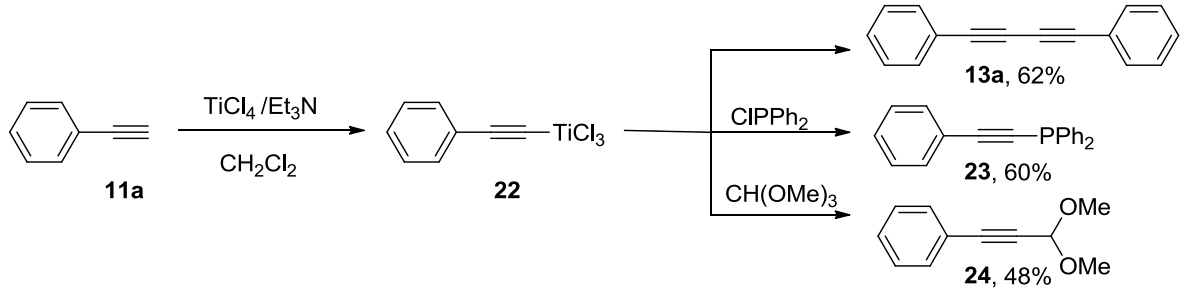
Rodríguez and co-workers reported a novel homocoupling of alkynyl β-lactams (**20**) using 2 equivalents of $Cu(OAc)_2$ to give a new class of compounds bis(β-lactams)-1,3-diynes (**21**) which can serve as building blocks for amino acid synthesis (Scheme 6).[25]



Scheme 6. Coupling of alkynyl β-lactams

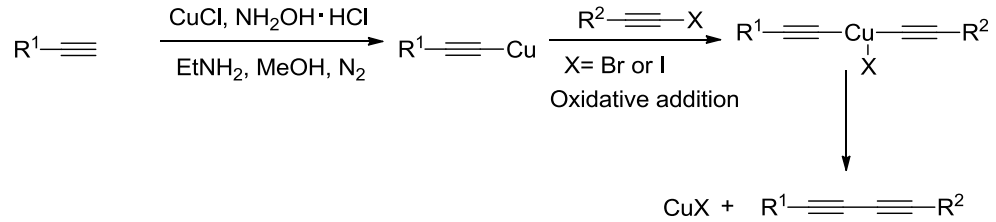
An interesting $TiCl_4$ (2 equiv)/Et_3N (3 equiv) system was used by Periasamy and co-workers for the coupling of terminal alkynes. Different electrophiles such as halodiphenylphospines, trimethyl orthoformate were reacted with in situ generated titanium

acetylide (**22**) to get respective products as shown in Scheme 7.[26] Less studied titanium acetylides have been diversely utilized to synthesize interesting alkynyl products.



Scheme 7. Coupling of alkynes using $TiCl_4$

The Glaser coupling and above mentioned methods provides a good platform for the homocoupling of terminal alkynes, but fails in the synthesis of unsymmetrical diynes by heterocoupling using two different terminal alkynes. The main problem in heterocoupling is the formation of predominant homocoupled products. To overcome this, Cadiot-Chodkiewicz reacted haloalkyne with terminal alkyne using stoichiometric Cu^I salt and suitable base (Scheme 8).[27] This method was successful in synthesizing large number of unsymmetrical diynes and can tolerate a wide range of functional groups. In their study they found that hydrophilic groups such as –OH, $-NH_2$, and carboxyl groups as part of terminal alkynes favoured heterocoupling, when compared to the reactions involving unsubstituted terminal alkynes. They also found that bromoalkynes are apt than iodo-and chloroalkynes for heterocoupling. Even now this method is used for the synthesis of unsymmetrical diynes containing natural products.

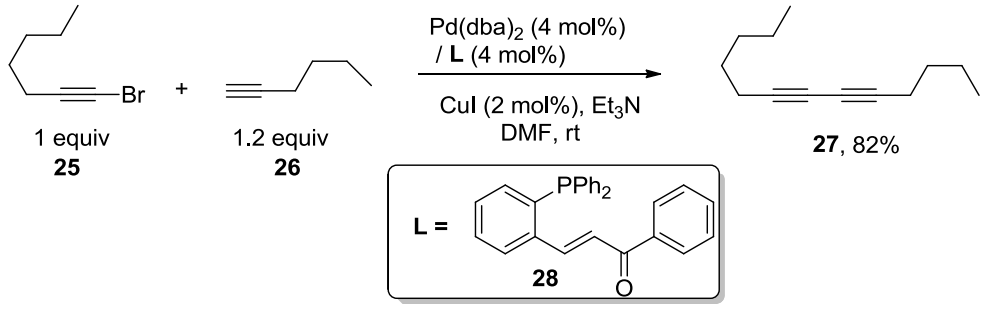


Scheme 8. Cadiot-Chodkiewicz heterocoupling

After the discovery of Cadiot-Chodkiewicz heterocoupling, many alternate methods emerged using the same concept with some variations to improve the yield and reaction conditions. There are few reports on palladium-catalyzed alkyne heterocoupling as well.[10]

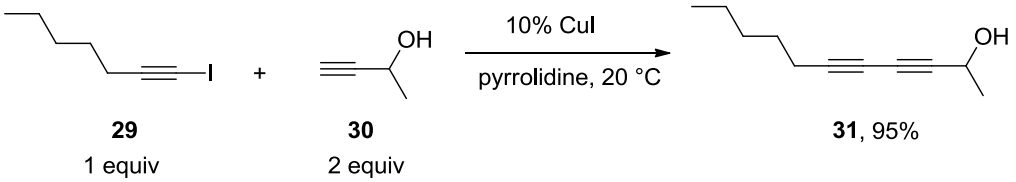
Negishi and co-workers reported a two step procedure for the preparation of unsymmetrical diynes using $Pd(PPh_3)_4$ catalyst.[28]

A fascinating approach for the preparation of unsymmetric diynes was reported by Lei *et al*. (Scheme 9). This group used palladium catalyst along with a designed ligand (**28**) which facilitates the reductive elimination. This approach succeeds in selective formation of cross-coupled products. Coupling of aliphatic alkyne (**26**) and aliphatic alkynyl bromide (**25**) was achieved smoothly which is difficult with other methods. Without Cu^I the reaction failed to give the products. Usage of expensive Pd catalysts and ligands is the drawback of the approach.[29]



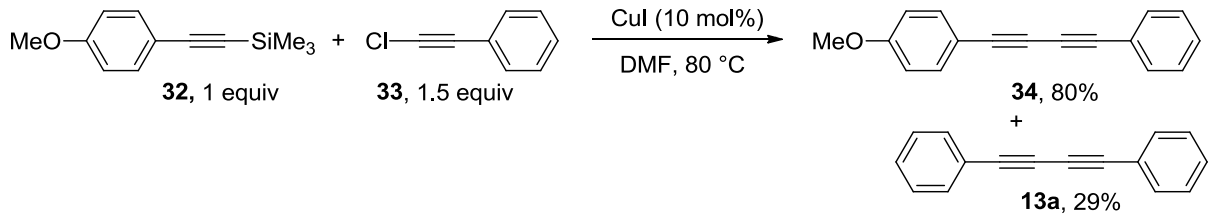
Scheme 9. Palladium-catalyzed preparation of unsymmetrical diynes

In 1996, Alami *et al.* demonstrated an efficient method for the heterocoupling of alkynes using iodoalkynes and CuI. The authors found that base plays an important role in the reaction outcome. Bases like piperidine, pyrrolidine, ethylamine and isopropyl amine were screened, and pyrrolidine was found to be the best. Moreover, less reactive terminal alkynes gave excellent yields (Scheme 10).[30]



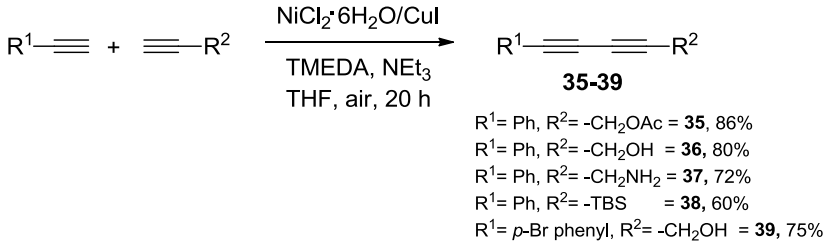
Scheme 10. Heterocoupling of alkynes using iodoalkynes and CuI

Mori and co-workers reported an excellent method for heterocoupling of alkynes using CuI with alkynylsilanes and less reactive chloroalkynes, which is in sharp contrast with Cadiot-Chodkiewicz coupling. Interesting feature of this reaction is that it does-not require base (Scheme 11).[31]



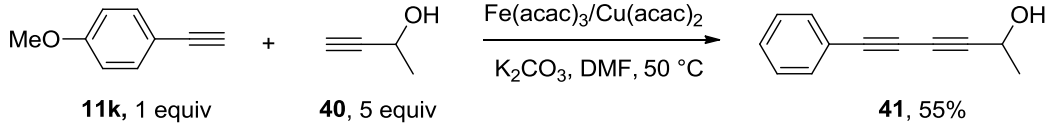
Scheme 11. Heterocoupling of alkynylsilanes with chloroalkynes

In 2009, Lei group, for the first time used nickel catalyst and oxygen (air) for oxidative coupling of alkynes (Scheme 12). In this method 5 mol% of $NiCl_2 \cdot 6H_2O$ and 5 mol% CuI are used. The role of the copper is to generate the acetylide and then on oxidative coupling with Ni gives dialkynyl Ni intermediate which on reductive elimination gives the product of heterocoupling.[32]



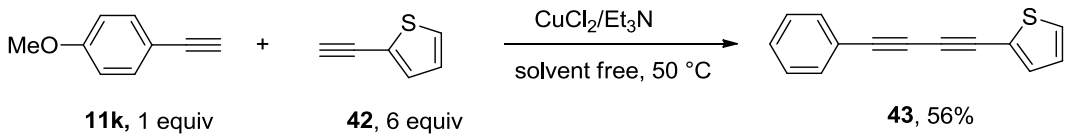
Scheme 12. Ni-catalyzed heterocoupling of terminal alkynes

A bimetallic catalytic system $Fe(acac)_3$ (10 mol%)/$Cu(acac)_2$ (0.1 mol%) was used for homo- and heterocoupling of terminal alkynes in presence of 2 equiv of K_2CO_3 by Chen group. Interesting feature of this method is initially Cu-acetylide is formed and then on reductive elimination gives Cu^I and the desired product. This Cu^I is oxidized to Cu^{II} by Fe^{III}, O_2 reoxidizes Fe^{II} to Fe^{III}. Hence the role of Fe-catalyst is as oxidant only and not catalyst for this reaction (Scheme 13).[33]



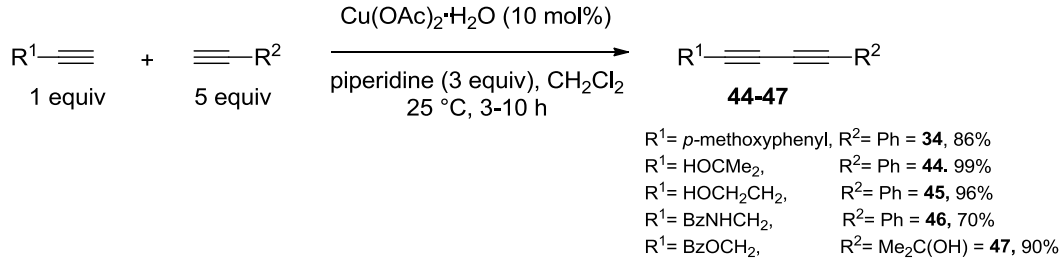
Scheme 13. Bimetallic Fe/Cu-catalyzed heterocoupling of terminal alkynes

Greener approach without using a solvent was accounted by the same group using $CuCl_2$ (3 mol%)/Et_3N (3 mol%) catalytic system. The catalyst was recycled for 5 times with slight decrease in efficiency (Scheme 14).[34]



Scheme 14. Solvent free heterocoupling

Kesavan and co-workers reported an efficient homo-and heterocoupling of alkynes with $Cu(OAc)_2 \cdot H_2O$ and demonstrated that no external oxygen source is required for the transformation. For the first time a detailed study on influence of bases on Cu^{II} salts for homocoupling of terminal alkynes was demonstrated. A wide range of substrates containing hydroxyl, amido and fluoro substituents were coupled in excellent yields (Scheme 15).[35]



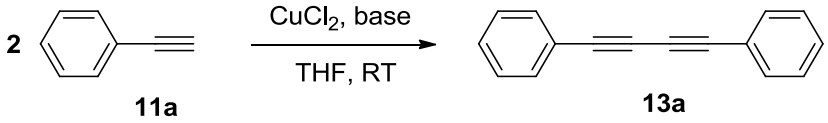
Scheme 15. Copper acetate monohydrate-catalyzed heterocoupling

Although the reported methods are good for homocoupling of terminal alkynes still there is a scope for improving the condition for heterocoupling of terminal alkynes because they are straight forward and many compounds having material and biological importance can easily be made by these coupling reactions.

3.3 Results and Discussion

We focused on developing a Cu^{II}-based catalytic system to effect the alkyne homo- and heterocoupling because Cu^{II} salts are comparatively cheaper and easier to handle than Cu^{I} salts. We studied the anhydrous $CuCl_2$-catalyzed homocoupling of terminal alkynes with the intention of employing the optimized catalytic system in alkyne heterocoupling. For the reaction screening, phenylacetylene (**11a**) was chosen as the substrate. The homocoupling of phenylacetylene was studied with $CuCl_2$ in tetrahydrofuran (THF) using different bases. It was found that, among the bases studied, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) worked well to effect the 1,3-diyne **13a** formation, while 1,4-diazabicyclo[2.2.2]octane (DABCO) being slightly less effective. The outcome of the screening of bases is given in Table 1.

Table 1. Influence of bases in the $CuCl_2$-catalyzed dimerization of phenylacetylene



Entry	Base	Equiv	$CuCl_2$ (mol %)	Time	Isolated yield (%)
1	Et_3N	1.5	10	24	82
2	TMEDA	1.5	10	24	42
3	DABCO	1.5	10	24	90
4	DABCO	1.0	10	24	88
5	DABCO	1.0	5	24	51
6	DBU	1.5	10	24	90
7	**DBU**	**1.2**	**10**	**24**	**92**
8	DBU	1.0	5	24	82
9	DBU	5	5	24	80
10	DBU	10	5	24	20

THF: tetrahydrofuran, TMEDA: *N*,*N*,*N*′,*N*′ -tetramethylethylenediamine, DABCO: 1,4-diazabicyclo[2.2.2]octane, DBU: 1,8 diazabicyclo[5.4.0]undec-7-ene.

It is important to note that DBU was reported to be the best base in a study to evaluate the influence of bases in the Cu^I-catalyzed homocoupling of terminal alkynes.[14i] From electrochemical studies, Fontaine *et al*. have shown that there is poor stabilization of the Cu^{II} state in the Cu^{II}/Cu^I redox established in the complex formed between $CuBr_2$ and DBU.[14n] Perhaps, the stabilized Cu^I state, which is required to form the alkynyl copper species, could be one of the reasons for the better efficiency of DBU in our reaction involving Cu^{II} species. Furthermore, the alkynyl copper species can undergo facile oxidation to an alkynyl radical by Cu^{II}, which reduces itself to Cu^I. This might also facilitate the reaction in the presence of DBU. Next, we studied the effect of solvents in the $CuCl_2$ /DBU-catalyzed dimerization of phenylacetylene (Table 2). For these reactions 10 mol% of $CuCl_2$ and 1.2 equiv of DBU were used in different solvents having a wide range of polarities. Among the solvents studied, toluene and THF worked very well. A slightly higher yield of **13a** was noticed in the reaction

that was carried out in THF (**92%**). Nitromethane and methanol resulted in very poor yields as shown in Table 2.

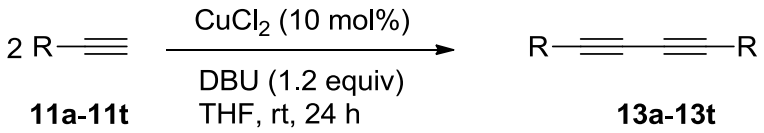
Table 2. Effect of solvent in the $CuCl_2$/diazabicyclo[5.4.0]undec-7-ene (DBU)-catalyzed dimerization of phenylacetylene

Entry	Solvent	Isolated yield (%) **13a**
1	CH_2Cl_2	28
2	CH_3NO_2	19
3	DCE	78
4	DMF	79
5	DMSO	46
6	Acetone	66
7	Hexane	69
8	Toluene	90
9	**THF**	**92**
10	CH_3CN	85
11	CH_3OH	12

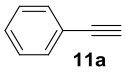
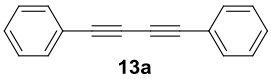
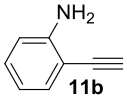
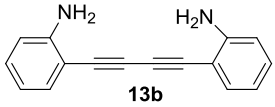
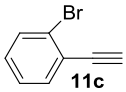
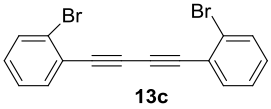
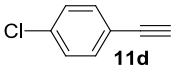
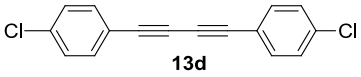
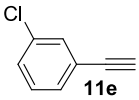
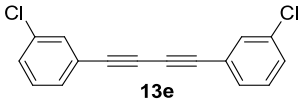
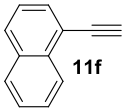
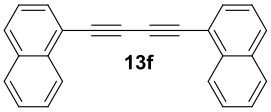
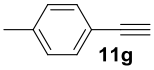
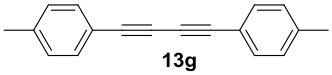
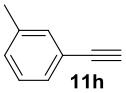
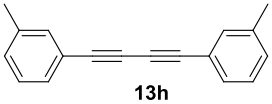
DCE: 1,2-dichloroethane**,** DMF: *N*,*N*-dimethylformamide, DMSO: dimethyl sulfoxide, THF: tetrahydrofuran.

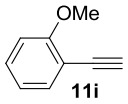
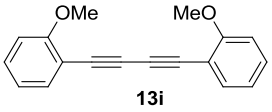
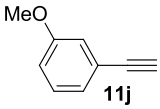
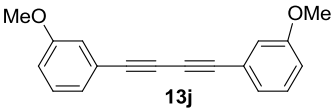
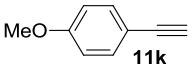
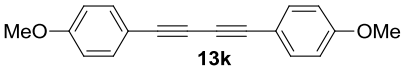
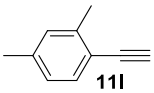
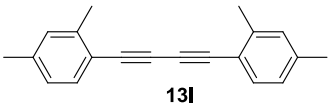
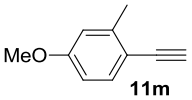
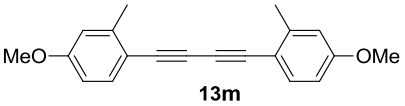
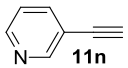
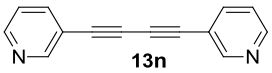
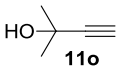
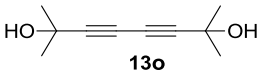
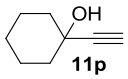
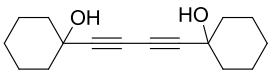
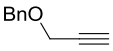
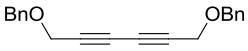
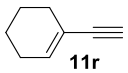
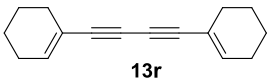
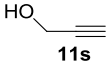
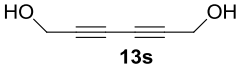
Hence the system $CuCl_2$ (10 mol%)/DBU (1.2 equiv) in THF was chosen for the study of substrate scope. A wide range of terminal alkynes were subjected to homocoupling using $CuCl_2$/DBU in THF system.[36] The results are presented in Table 3.

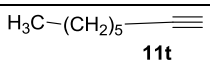
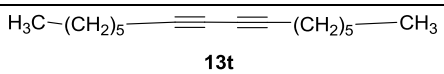
Table 3. Results of homocoupling of different terminal alkynes using $CuCl_2$/DBU in tetrahydrofuran[a]



11a-11t **13a-13t**

Entry	Alkyne	Product	Yield[b]
1	 **11a**	 **13a**	92
2	 **11b**	 **13b**	83
3	 **11c**	 **13c**	96
4	 **11d**	 **13d**	95
5	 **11e**	 **13e**	65
6	 **11f**	 **13f**	84
7	 **11g**	 **13g**	99
8	 **11h**	 **13h**	98

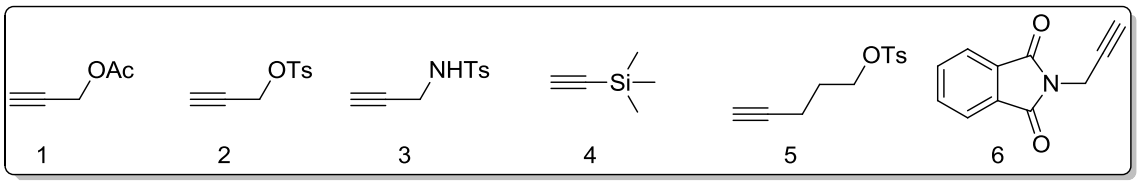
Entry	Alkyne	Product	Yield[b]
9	 **11i**	 **13i**	72
10	 **11j**	 **13j**	70
11	 **11k**	 **13k**	84
12	 **11l**	 **13l**	76
13	 **11m**	 **13m**	91
14	 **11n**	 **13n**	55
15	 **11o**	 **13o**	98
16	 **11p**	 **13p**	90
17	 **11q**	 **13q**	70
18	 **11r**	 **13r**	88
19	 **11s**	 **13s**	68

Entry	Alkyne	Product	Yield[b]
20	 **11t**	 **13t**	55

[a]All the reactions were carried out with anhydrous $CuCl_2$ (10 mol %) and DBU (1.2 equiv) in tetrahydrofuran for 24 h under open air, [b] % Isolated yield.

The substrates include substituted aryl, heteroaryl, alkyl, and hydroxylalkyl alkynes. All the substrates underwent smooth dimerization resulting in yields ranging from good to excellent. The reactions do not require bubbling of air through the reaction mixture and could be carried out in an open flask at room temperature. The yields of the products are comparable and in some cases are greater than those obtained in reported systems. Arylalkynes having substituents such as Cl, Br, OMe, and NH_2 tolerate the reaction conditions. Aliphatic alkynes having a tertiary alcohol function resulted in good yields (entries 15 and 16, Table 3). However, the yield with simple oct-1-yne was poor (entry 20, Table 3). Unfortunately, the substrates shown below (Table 4) did not work under our reaction conditions.

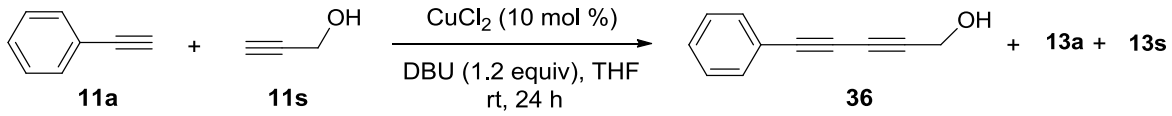
Table 4. Unsuccessful substrates



After successfully carrying out the $CuCl_2$/DBU-catalyzed homocoupling of terminal alkynes, the applicability of this catalytic system was tested in terminal alkyne heterocoupling. With this intention, the coupling of phenylacetylene (**11a**) with equimolar amount of propargyl alcohol (**11s**) was attempted using $CuCl_2$/DBU in THF. The reaction resulted in all three possible coupled products **36**, **13a**, and **13s** (Table 5). The heterocoupled product **3** was obtained only in 38% yield. It improved to 45% when three equivalents of phenylacetylene with respect to propargyl alcohol were used. However, when the reaction was carried out under an air-filled balloon the yield increased significantly to 61% (entry 3, Table 5). A similar trend was observed when propargyl alcohol was used in a three-fold

excess of phenylacetylene (entries 4 and 5, Table 5). The highest yield was obtained when five equivalents of propargyl alcohol was used with respect to phenylacetylene. Reactions carried out under reflux (entry 7, Table 5) and sonication (entry 8, Table 5) did not improve the yield of the heterocoupled product. Only a slight improvement of yield was noticed when 20 mol% of $CuCl_2$ was used (entry 9, Table 5).

Table 5. Heterocoupling of phenylacetylene with propargyl alcohol at different molar ratios



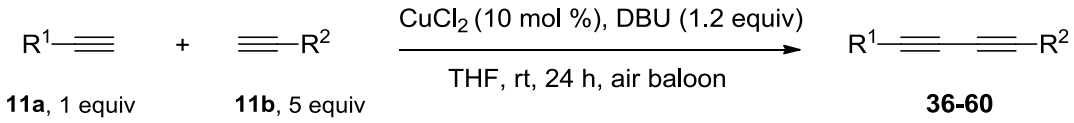
Entry	11a (equiv)	11s (equiv)	$CuCl_2$ (mol %)	DBU (equiv)	Yield (%)[c]		
					36	**13a**	**13s**
1[a]	1	1	10	1.2	38	40	18
2[a]	3	1	10	1.2	45	69	18
3[b]	3	1	10	1.2	61	39	12
4[a]	1	3	10	1.2	44	21	21
5[b]	1	3	10	1.2	63	22	15
6[b]	**1**	**5**	**10**	**1.2**	**65**	**20**	**18**
7[b,d]	1	5	10	1.2	17	13	15
8[b,e]	1	5	10	1.2	37	17	37
9[b,f]	1	5	20	1.2	70	17	18

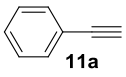
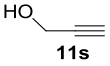
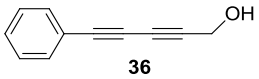
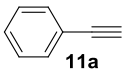
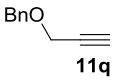
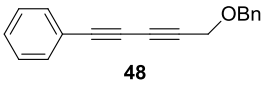
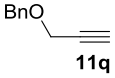
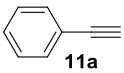
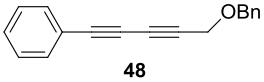
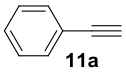
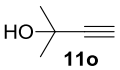
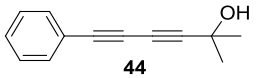
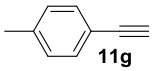
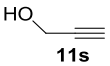
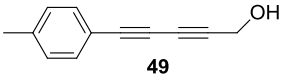
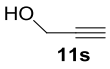
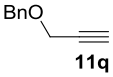
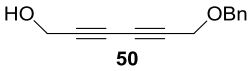
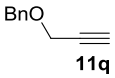
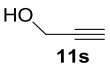
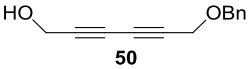
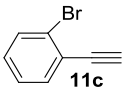
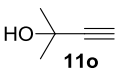
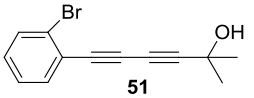
[a]The reactions were carried out in an open flask. [b]The reactions were carried out under an air-filled balloon. [c]Isolated yield. [d]Reaction was carried out at reflux. [e]Reaction was carried out under sonication, [f]20 mol% of $CuCl_2$ was used.

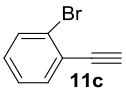
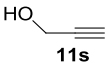
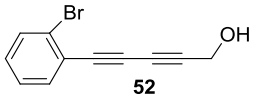
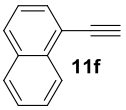
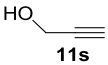
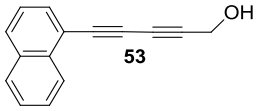
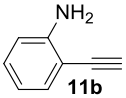
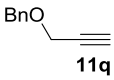
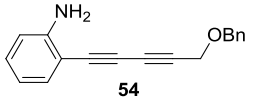
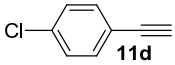
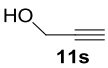
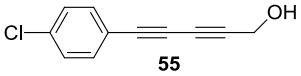
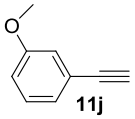
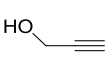
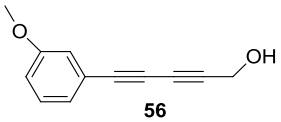
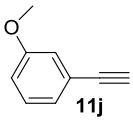
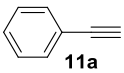
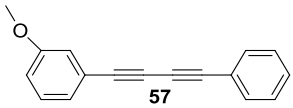
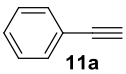
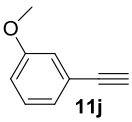
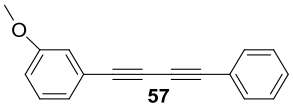
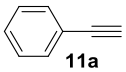
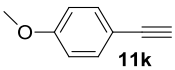
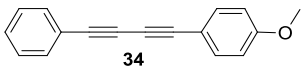
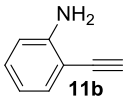
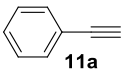
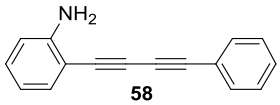
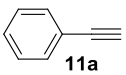
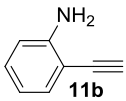
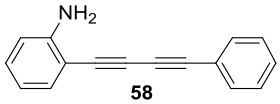
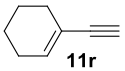
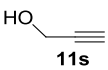
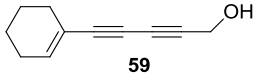
The scope of $CuCl_2$-catalyzed heterocoupling using DBU as base was tested with different pairs of terminal alkynes. In these reactions, one of the alkyne reactants was taken in five-fold excess of the other. The reactions were carried out at room temperature under an air-filled balloon. Although the role of oxygen in this reaction is not very clear, it can be

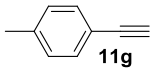
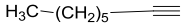
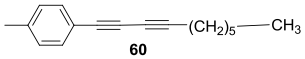
proposed that it is needed to oxidize the Cu^{I} species which will be formed after the initial Eglinton coupling using Cu^{II} present in catalytic amount. Furthermore, the thus formed Cu^{I} may form an acetylide with a terminal alkyne which will require oxygen to give the 1,3-diyne by oxidative coupling. The outcome of different heterocoupling reactions is presented in Table 6.

Table 6. Scope of $CuCl_2$/DBU system in alkyne heterocoupling using $CuCl_2$/(DBU) in tetrahydrofuran



Entry	R^1	R^2	Product	Yield[a] [%]
1	 **11a**	 **11s**	 **36**	65
2	 **11a**	 **11q**	 **48**	72
3	 **11q**	 **11a**	 **48**	43
4	 **11a**	 **11o**	 **44**	74
5	 **11g**	 **11s**	 **49**	58
6	 **11s**	 **11q**	 **50**	51
7	 **11q**	 **11s**	 **50**	61
8	 **11c**	 **11o**	 **51**	62

Entry	R^1—	R^2—	Product	Yield[a] [%]
9	 **11c**	 **11s**	 **52**	55
10	 **11f**	 **11s**	 **53**	68
11	 **11b**	 **11q**	 **54**	45
12	 **11d**	 **11s**	 **55**	74
13	 **11j**	 **11s**	 **56**	48
14[b]	 **11j**	 **11a**	 **57**	48
15[b]	 **11a**	 **11j**	 **57**	51
16[b]	 **11a**	 **11k**	 **34**	45
17[b]	 **11b**	 **11a**	 **58**	28
18[b]	 **11a**	 **11b**	 **58**	54
19[b]	 **11r**	 **11s**	 **59**	35

Entry	R^1—	—R^2	Product	Yield[a] [%]
20	 **11g**	$H_3C-(CH_2)_5$—  **11t**	 **60**	55

[a]Isolated yield. [b]Reaction was carried out for 48 h. (DBU: diazabicyclo[5.4.0]undec-7-ene, THF: tetrahydrofuran).

All the reactions were carried out for 24 h except for the reactions presented in entries 14–19 (Table 6), which were carried out for 48 h. The reactions between arylalkynes with aliphaticalkynes underwent smooth coupling to yield unsymmetrically substituted 1,3-diynes in good yields. Substituted 1,3-diynes with −Br and $-NH_2$ on one aryl ring could also be made without any difficulties (entries 8, 9, 11, 12, 17, and 18, Table 6). These functional groups can be utilized for further synthetic elaborations using transition-metal-catalyzed coupling methods. Even two different aryl alkynes could also be coupled in moderate efficiencies (entries 14–18, Table 6). Selected reactions were repeated by taking the coupling partners in exactly opposite molar ratios. The results are presented in Table 6 (entries 2 and 3, 6 and 7, 14 and 15, 17 and 18). From these experiments it is clear that the results are not a result of strategic choice of alkyne used in excess. However, it indicates that the yields are higher when the electron-rich alkyne is used in excess i.e., five equivalents.

3.4 Conclusion

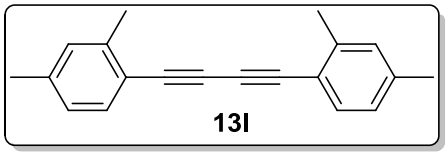
A simple protocol for making symmetrically and unsymmetrically substituted 1, 3-diynes using catalytic $CuCl_2$/DBU at room temperature has been developed. The scope of the homo-and heterocoupling was shown with a wide range of terminal alkynes. The protocol has very good functional group tolerance such as -NH_2, -OH, and -Br. Several unsymmetrical diynes synthesized are new to the literature. The unsymmetrically substituted 1, 3-diynes could serve as important building blocks. The role of DBU in this Cu^{II}-catalysed coupling of terminal alkynes is believed to be its ability to stabilize the Cu^{I} state in the Cu^{II}/Cu^{I} redox system.

3.5 Experimental section

General Experimental Procedure for the $CuCl_2$-Catalyzed Homocoupling of Alkynes

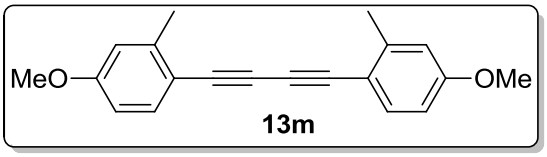
To a solution of terminal alkyne **11a** (100 mg, 0.98 mmol) in THF (5 mL), $CuCl_2$ (13 mg, 0.098 mmol) was added and the mixture was allowed to stir at room temperature for 10 min. DBU (179 mg, 1.176 mmol) was added to the reaction mixture which was allowed to stir vigorously at room temperature in open atmosphere. After 24 h the reaction mixture was concentrated under reduced pressure and the residue was purified by column chromatography on silica gel using hexanes/ethyl acetate as eluents to obtain pure **13a** (92%).

1,4-bis(2,4-Dimethylphenyl)buta-1,3-diyne (13l):



IR (Neat, cm^{-1}): 2916, 2854, 2143, 1591, 846, 750, 682, 462. ^1H NMR (400 MHz, $CDCl_3$): δ 7.16 (s, 4H), 7.0 (s, 2H), 2.31 (s, 12H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.0, 131.2, 130.1, 121.5, 81.7, 73.4, 21.1. Anal. Calcd. $C_{16}H_{18}$: C 92.98 ; H 7.02 ; Found: C 92.85; H 7.10.

1,4-bis(4-Methoxy-2-methylphenyl)buta-1,3-diyne (13m):



IR (Neat, cm^{-1}): 2974, 2137, 1896, 1597, 1564, 1491, 1460, 1307, 1236, 1163, 1095, 1033, 823, 688, 590, 489.^1H NMR (400 MHz, $CDCl_3$): δ 7.43 (d, *J* = 8.4 Hz, 2H), 6.75 (s, 2H), 6.69 (dd, *J* = 8.4, 4.4 Hz, 2H), 3.85 (s, 6H), 2.47 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.1, 143.5, 134.4, 115.2, 114.1, 111.4, 80.8, 76.5, 55.3, 21.0. Anal. Calcd. for $C_{20}H_{18}O_2$: C 82.73 ; H 6.25. Found: C 82.65 ; H 6.31.

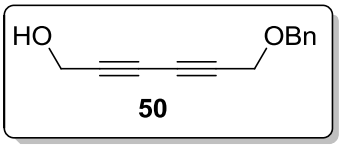
General Experimental Procedure for the $CuCl_2$-Catalyzed Heterocoupling of Alkyne

5-Phenylpenta-2,4-diyn-1-ol (36)

To a solution of phenylacetylene (**11a**) (100 mg, 0.98 mmol) and propargyl alcohol (**11s**) (274 mg, 4.90 mmol) in THF (5 mL), was added $CuCl_2$ (13 mg, 0.098 mol %) and the mixture allowed to stir at room temperature for 10 min. DBU (178 mg, 1.176 mmol) was added to the reaction mixture which was then stirred vigorously under an air-filled balloon at

room temperature. The reaction was monitored by TLC. After completion of the reaction, the mixture was concentrated under reduced pressure and the residue was purified by column chromatography on silica gel using hexanes/ethyl acetate (1/5 v/v) as eluent to obtain pure **36** in 65% yield δ 7.49–7.47 (m, 2H), 7.37–7.25 (m, 3H), 4.41 (s, 2H), 2.24 (bs, 1H). δ 132.6, 129.4, 128.4, 121.39, 8.51, 78.6, 73.2, 70.4, 51.6.

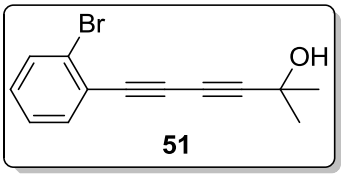
6-(Benzyloxy)hexa-2,4-diyn-1-ol (50)



50

IR (Neat, cm^{-1}): 3389, 3036, 2928, 2249, 2179, 1454, 1026, 738, 698. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35–7.28 (m, 5H), 4.60 (s, 2H), 4.32 (s, 2H), 4.23 (s, 2H), 2.09 (bs, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 136.9, 128.5, 128.2, 128.1, 77.2, 75.8, 71.8, 70.5, 69.9, 57.5, 51.4. Anal. Calcd. for $C_{13}H_{12}O_2$: C 77.98, H 6.04. Found: C 77.85, H 6.12.

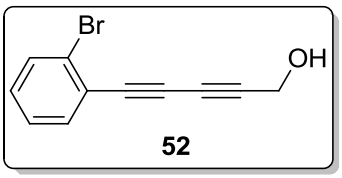
2-Bromophenyl)-2-methylhexa-3,5-diyn-2-ol (51)



51

IR (Neat, cm^{-1}): 3294, 2235, 2150, 1466, 1163. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.57 (d, *J* =7.6 Hz, 1H), 7.51 (t, *J* = 6.0 Hz, 1H), 7.26–7.20 (m, 2H), 2.27 (bs, 1H), 1.60 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 134.5, 132.6, 130.3, 127.1, 126.2, 123.9, 88.2, 76.8, 66.9, 65.8, 31.1. Anal. Calcd. for $C_{13}H_{11}OBr$: C 59.34, H 4.21. Found: C 59.55, H 4.18.

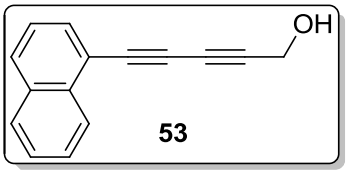
5-(2-Bromophenyl)penta-2,4-diyn-1-ol (52)



52

IR (Neat, cm^{-1}): 3341, 3069, 2920, 2856, 2245, 1585, 1556, 1469, 1433, 1109, 1014, 754, 686.^{1}H NMR (400 MHz, $CDCl_3$): δ 7.58 (d, *J* = 7.2 Hz, 1H), 7.51 (dd, *J* = 6.0 Hz, 1.6 Hz, 1H), 7.29–7.19 (m, 2H), 4.44 (s, 2H), 2.01 (bs, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 134.5, 132.5, 130.4, 127.1, 126.3, 123.7, 82.0, 70.2, 51.6. Anal. Calcd. for $C_{11}H_7OBr$: C 56.20, H 3.00. Found: C 56.31, H 3.07.

5-(Napthalen-1-yl)penta-2,4-diyn-1-ol (53)

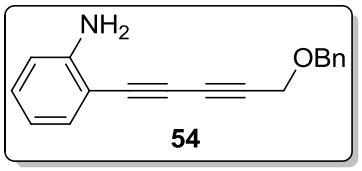


53

IR (Neat, cm^{-1}): 3364, 3059, 2916, 2856, 2233, 1356, 1028, 798, 771. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.28 (d, *J* = 8.4 Hz, 1H), 7.84 (dd, *J* = 8.0 Hz, 3.2 Hz, 2H), 7.73 (d, *J* = 7.2 Hz,

1H), 7.57 (dt, *J* = 6.8 Hz, 1.2 Hz, 1H), 7.51 (dt, *J* = 6.8 Hz, 1.2 Hz, 1H), 7.40 (t, *J* = 8.0 Hz, 1H), 4.47 (s, 2H), 2.04 (bs, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 133.9, 133.1, 132.2, 129.9, 128.3, 127.3, 126.7, 125.9, 125.2, 119.0, 81.5, 77.8, 76.9, 70.6, 51.7. Anal. Calcd. for $C_{15}H_{10}O$: C 87.36, H 4.89. Found: C 87.25, H 4.82.

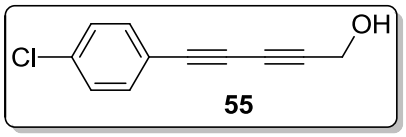
2-(5-(Benzyloxy)penta-1,3-diynyl)benzenamine (54)



54

IR (Neat, cm^{-1}): 3470, 3373, 3030, 2856, 2233, 2141, 1614, 1454, 1354, 1257, 750.^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39 (d, *J* = 4.0 Hz, 4H), 7.33 (d, *J* = 6.8 Hz, 2H), 7.16 (t, *J* = 7.6 Hz, 1H), 6.68 (t, *J* = 7.2 Hz, 2H), 4.66 (s, 2H), 4.35 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 149.8, 137.2, 133.3, 130.8, 128.5, 128.2, 128.1, 117.9, 114.4, 105.7, 79.9, 78.5, 75.3, 71.8, 71.2, 57.8. Anal. Calcd. for $C_{18}H_{15}ON$: C 82.73, H 5.79, N 5.36. Found: C 82.58, H 5.71, N 5.32.

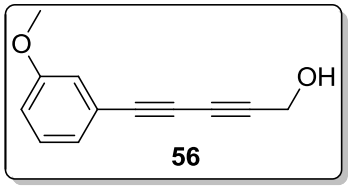
5-(4-Chlorophenyl)penta-2,4-diyn-1-ol (55)



55

IR (Neat, cm^{-1}): 3443, 2241, 1589, 1487, 1087, 1012, 823, 522.^{1}H NMR (400 MHz, Acetone-D_6): δ 7.55 (d, *J* = 8.4 Hz, 2H), 7.44 (d, *J* = 8.4 Hz, 2H), 4.50 (t, *J* = 6.0 Hz, 1H), 4.36 (d, *J* = 6.0 Hz, 2H). ^{13}C NMR (100 MHz, Acetone-D_6): δ 135.1, 133.9, 128.9, 120.1, 83.5, 75.9, 74.2, 67.9, 50.1. Anal. Calcd. for $C_{11}H_7ClO$: C 69.31, H 3.70. Found: C 69.45, H 3.65.

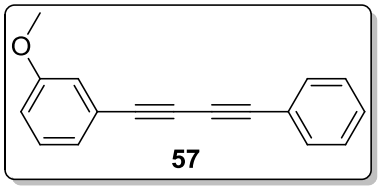
5-(3-Methoxyphenyl)penta-2,4-diyn-1-ol (56)



56

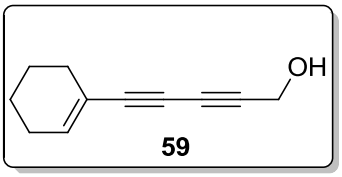
IR (Neat, cm^{-1}): 3462, 2918, 2839, 2239, 1577, 1458, 785. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.26–7.20 (m, 1H), 7.09 (d, *J* = 7.6 Hz, 1H), 7.01 (s, 1H), 6.93 (d, *J* = 8.0 Hz, 1H), 4.42 (s, 2H), 3.79 (s, 3H), 2.10 (bs, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.3, 129.6, 125.2, 122.3, 117.2, 116.2, 80.5, 78.5, 72.9, 70.4, 55.3, 51.6. Anal. Calcd. for $C_{12}H_{10}O_2$: C 77.40, H 5.41. Found: C 77.32, H 5.45.

1-Methoxy-3-(phenylbuta-1,3-diynyl)benzene (57)



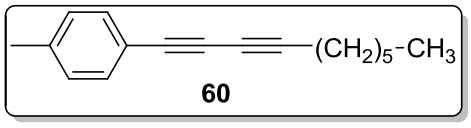
IR (Neat, cm^{-1}): 2208, 2141, 1597, 1504, 1487, 1249, 1028, 690, 530. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.53–7.51 (m, 2H), 7.37–7.31 (m, 3H), 7.26–7.22 (m, 1H), 7.12 (d, *J* = 7.6 Hz, 1H), 7.04 (s, 1H), 6.92 (dd, *J* = 2.8 Hz, 2.4 Hz, 1H), 3.80 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.3, 132.5, 129.6, 129.3, 128.5, 125.1, 122.7, 121.8, 117.1, 116.1, 81.6, 81.5, 73.9, 73.7, 55.3. Anal. Calcd. for $C_{17}H_{12}O$: C 87.90, H 5.21. Found: C 87.85, H 5.26.

5-Cyclohexenylpenta-2,4-diyn-1-ol (59)



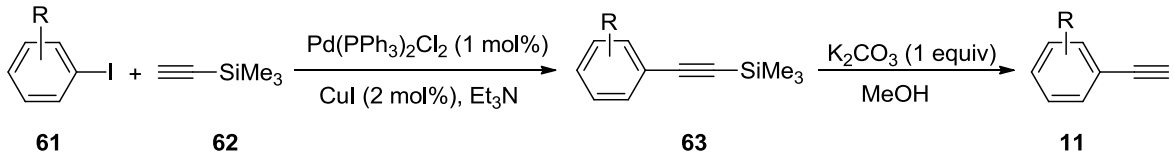
IR (Neat, cm^{-1}): 3389, 2930, 2235, 1664, 1435, 1350, 1016. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.29 (m, 1H), 4.31 (s, 2H), 2.17–2.10 (m, 4H), 1.84 (bs, 1H), 1.62–1.58 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 139.3, 119.4, 80.7, 79.4, 70.7, 70.6, 51.7, 28.5, 25.9, 22.0, 21.2. Anal. Calcd. for $C_{11}H_{12}O$: C 82.46, H 7.55. Found: C 82.33, H 7.61.

1-(Deca-1,3-diynyl)-4-methylbenzene (60)



IR (Neat, cm^{-1}): 2930, 2854, 2243, 2152, 1604, 1508, 1456, 1180, 1116, 1020, 815, 723. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36 (d, *J* = 8.0 Hz, 2H), 7.10 (d, *J* = 8.0 Hz, 2H), 2.36–2.34 (m, 5H), 1.60–1.55 (m, 2H), 1.46–1.38 (m, 2H), 1.34–1.28 (m, 4H), 0.89 (t, *J* = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 139.1, 132.4, 129.1, 119.0, 84.5, 74.9, 73.8, 65.2, 31.3, 28.6, 28.3, 22.5, 21.5, 19.6, 14.1. Anal. Calcd. for $C_{17}H_{20}$: C 91.01, H 8.99. Found: C 91.12, H 8.85.

3.5.1 Preparation of alkynes:



61 **62** **63** **11**

R = H, *o*-NH_2, *o*-Br, *p*-Cl, *m*-Cl, *o*-Cl, *m*-Me, *p*-Me, *o*-OMe, *m*-OMe, *p*-OMe

Using the literature procedures aryl substituted alkynes are synthesized by initial Sonagashira coupling followed by deprotection to furnish the aryl alkynes.[37]

Iodoalkyne and trimethylsilylacetylene was taken in a clean and dry rb flask and distilled trimethyl amine was added to it. Then $Pd(PPh_3)_2Cl_2$, CuI was added to it and stirred overnight under nitrogen atmosphere at 60 ˚C. The reaction was cooled to room temperature and filtered through celite, the resulting solution was concentrated under reduced pressure and residue was purified by column chromatography using silica gel. The purified product (**63**) was subjected to deprotection of trimethylsilyl acetylene with 1 equiv of K_2CO_3 in MeOH. Reaction mixture was washed thrice with saturated NH_4Cl and resulting mixture was extracted thrice with ethyl acetate. The resulting organic layer was washed with water, brine and dried over Na_2SO_4. The filtrate was concentrated using rotavapour and residue was purified by column chromatography on silica gel to get the pure products (**11**).

3.6 References:

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1995, *36*, 7841. (f) Yamaguchi, M.; Park, H-J.; Hirama, M.; Torisu, K.; Nakamura, S.; Minami, T.; Nishihara, H.; Hiraoka, T. *Bull. Chem. Soc. Jpn.* **1994**, *67*, 1717. (g) Gardner, J. N.; Jones, E. R. H.; Leeming, P. R.; Stephenson, J. S. *J. Chem. Soc.* **1960**, 691. (h) Fujimoto, Y.; Satoh, M.; Takeuchi, N.;. Kirisawa, M. *Chem.Pharm. Bull*. **199**1, *39*, 521. (i) Zheng, G.; Lu, W.; Cai, J. *J. Nat. Prod.* **1999**, 6*2*, 626. (j) Krause, N.; Hopj, H.; Ernst, L. *Liebig Ann. Chem.* **1986**, 1398. (k) Ottow, E.; Rohde, R.; Schewede, W.; Wiechert, R. *Tetrahedron Lett.* **1993**, *34*, 5253. (l) Gotteland, J-P.; Brunel, I.; Gendre, F.; Desire, J.; Delhon, A.; Junquero, D.; Oms, P.; Halazy, S. *J. Med. Chem.* **1995**, *38*, 3207. (m) for clear understanding see ref 1(d).

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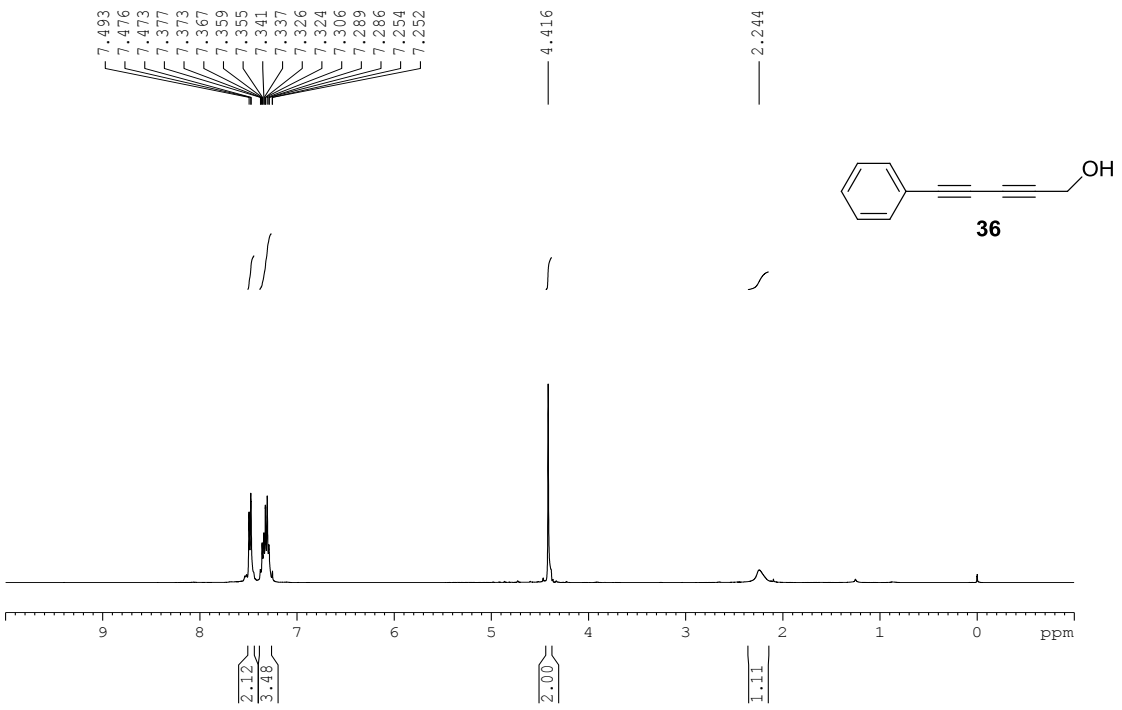

Figure 3. ^{1}H NMR spectrum of **36**

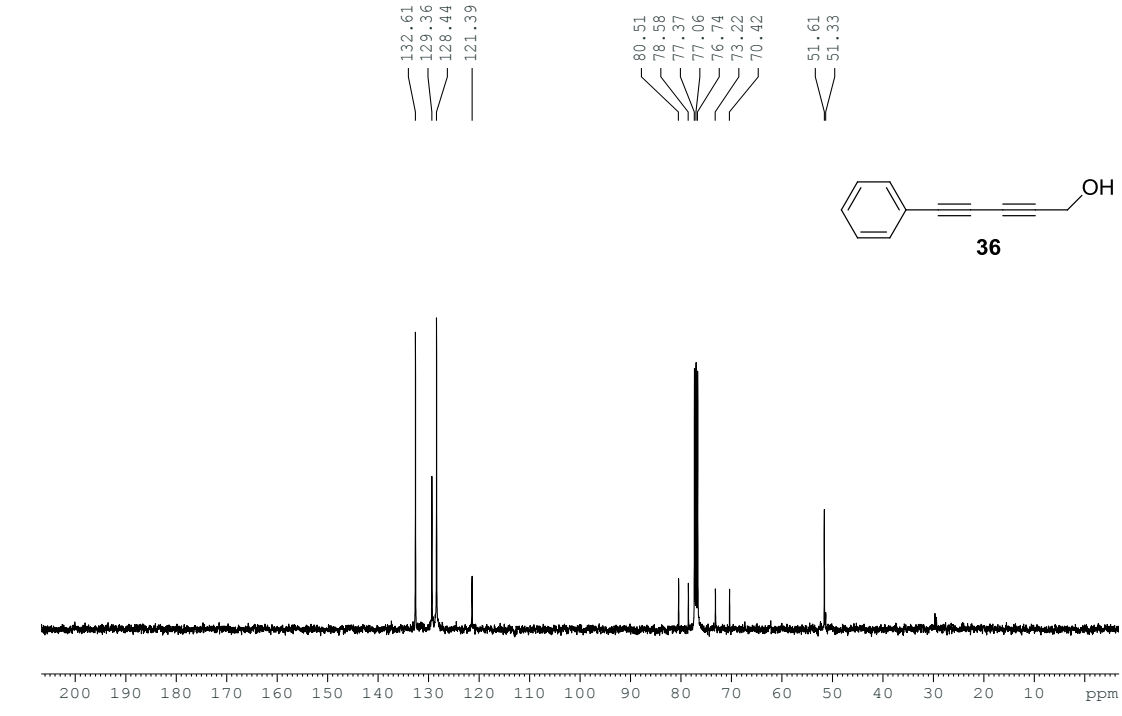

Figure 4. ^{13}C NMR spectrum of **36**

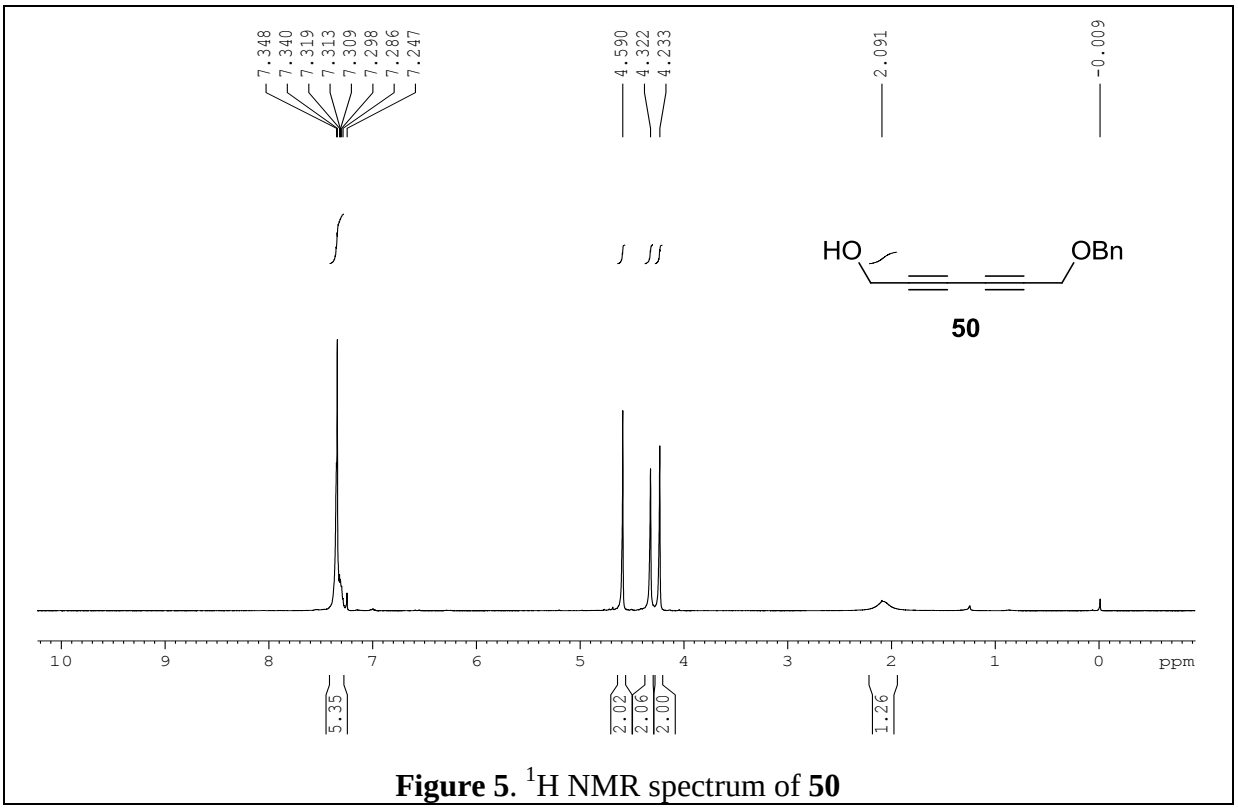

Figure 5. ^{1}H NMR spectrum of **50**

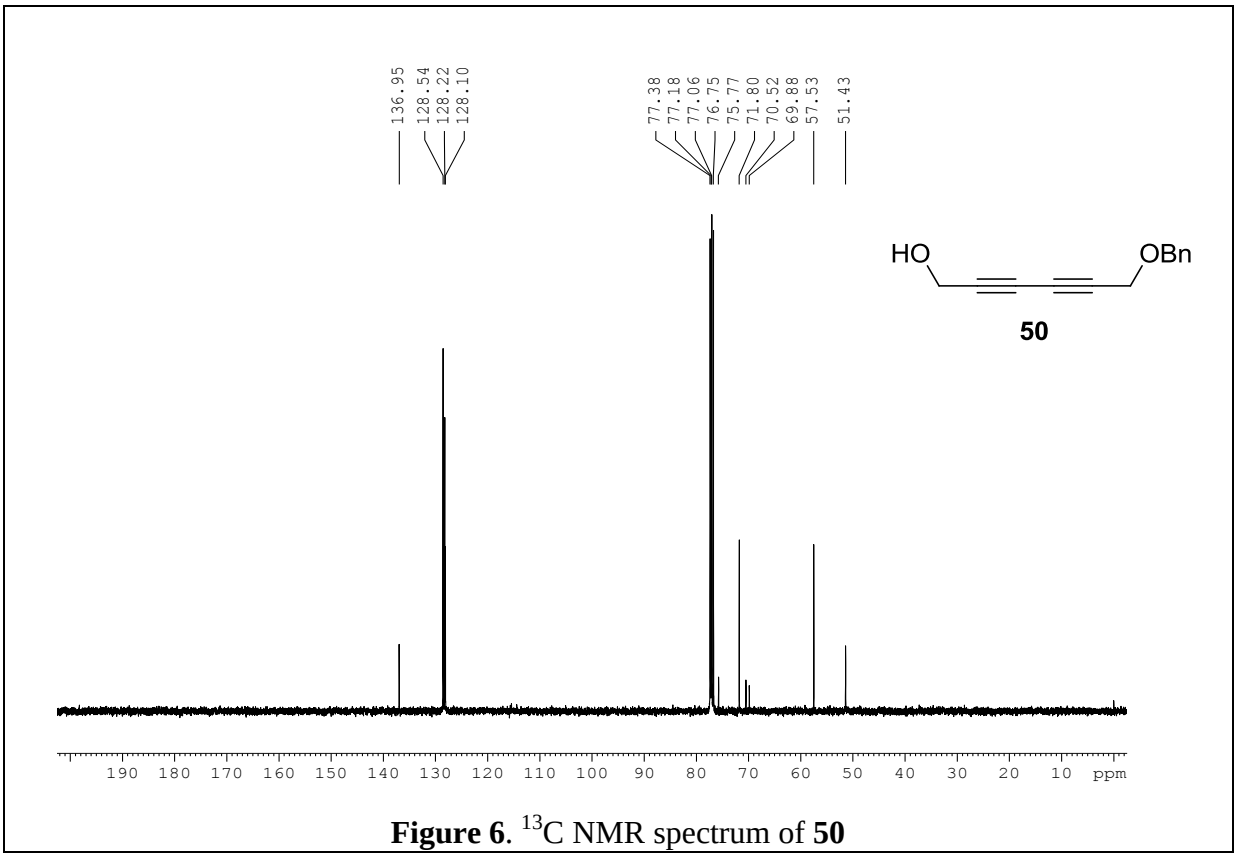

Figure 6. ^{13}C NMR spectrum of **50**

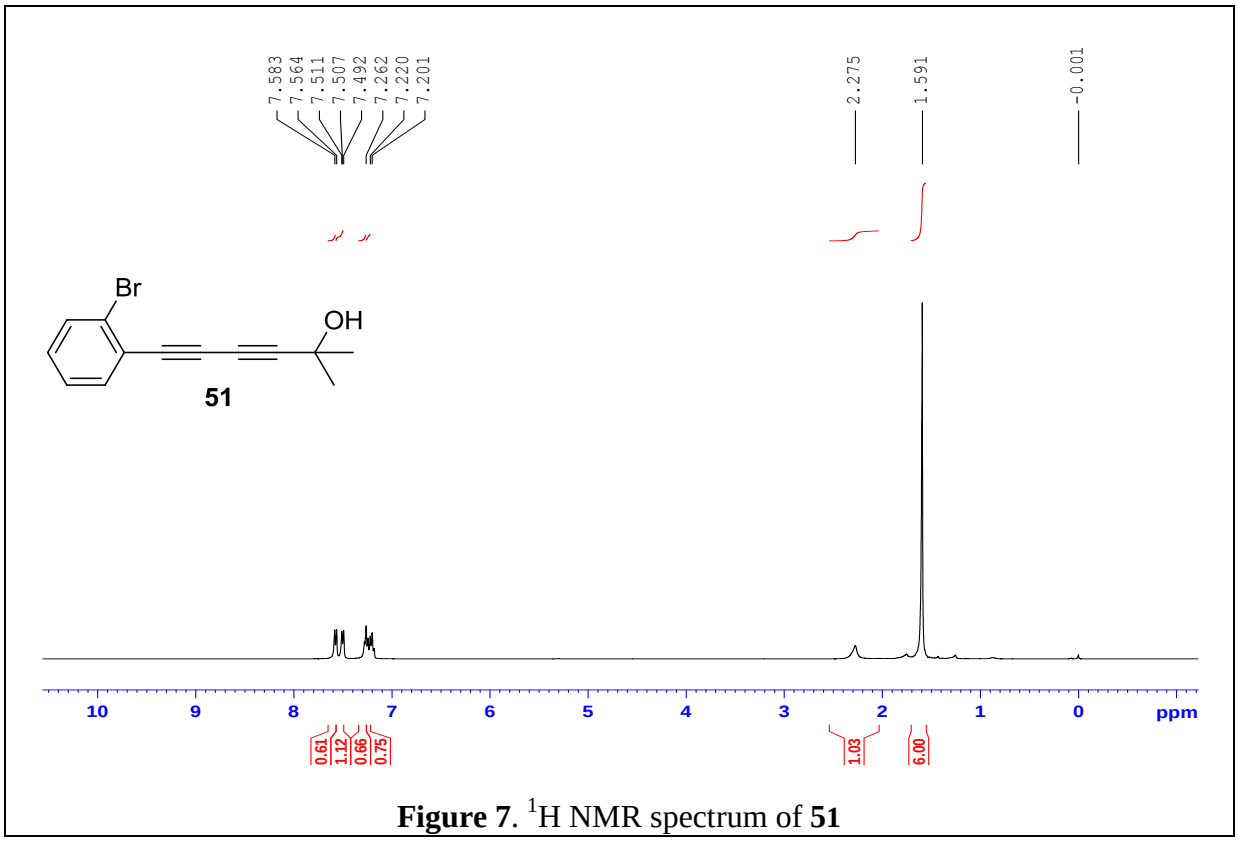

Figure 7. ^{1}H NMR spectrum of **51**

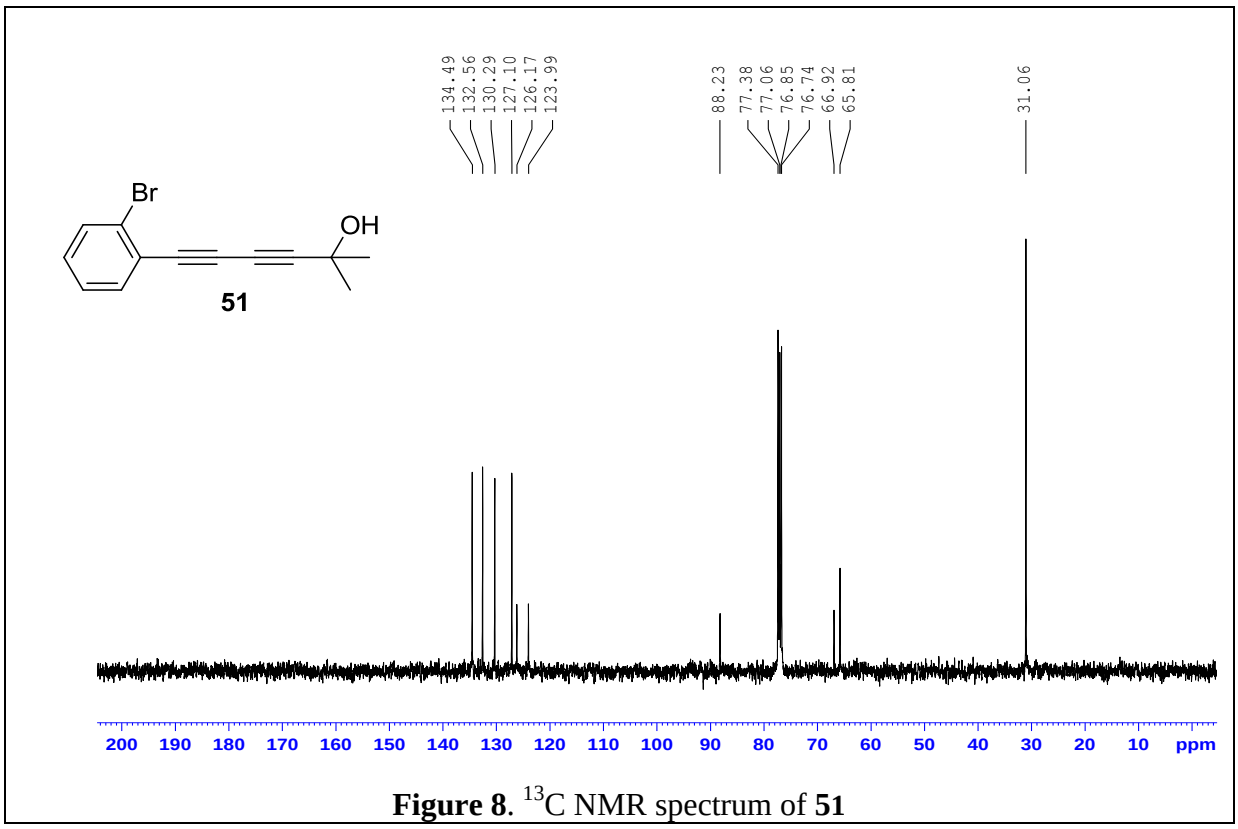

Figure 8. ^{13}C NMR spectrum of **51**

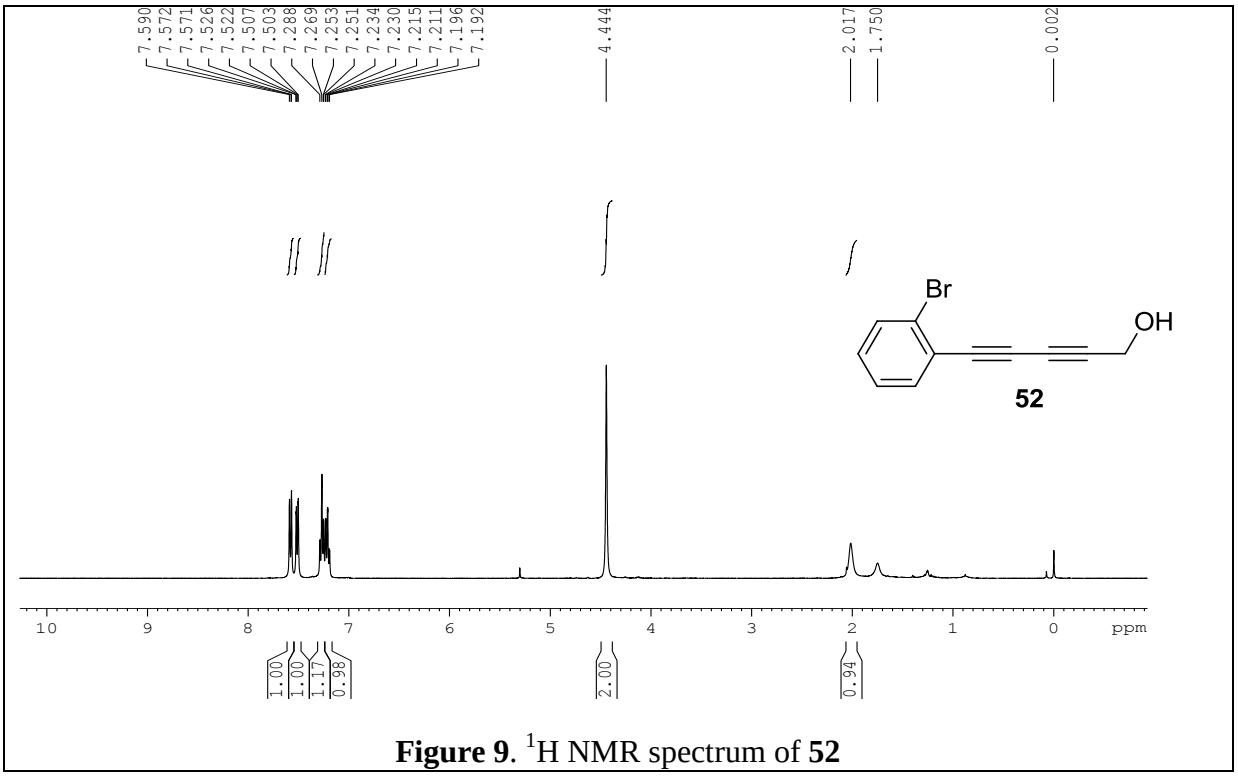

Figure 9. ^{1}H NMR spectrum of **52**

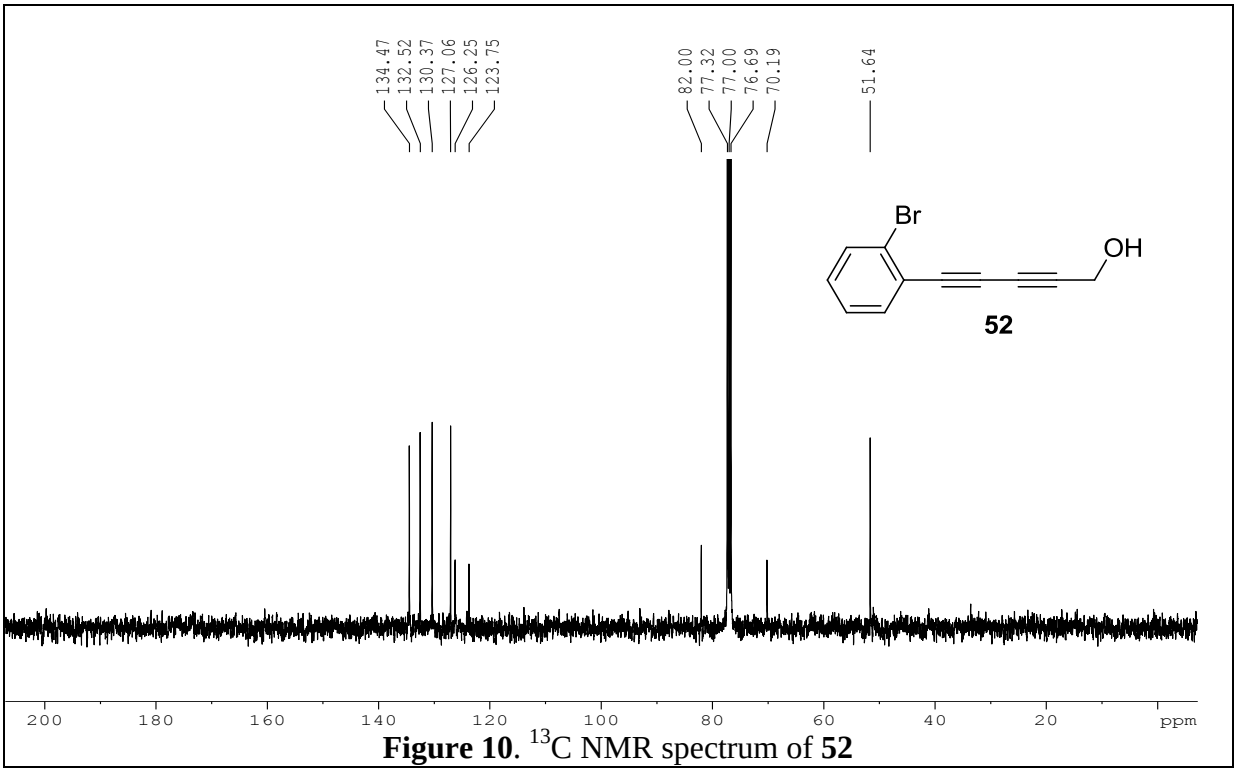

Figure 10. ^{13}C NMR spectrum of **52**

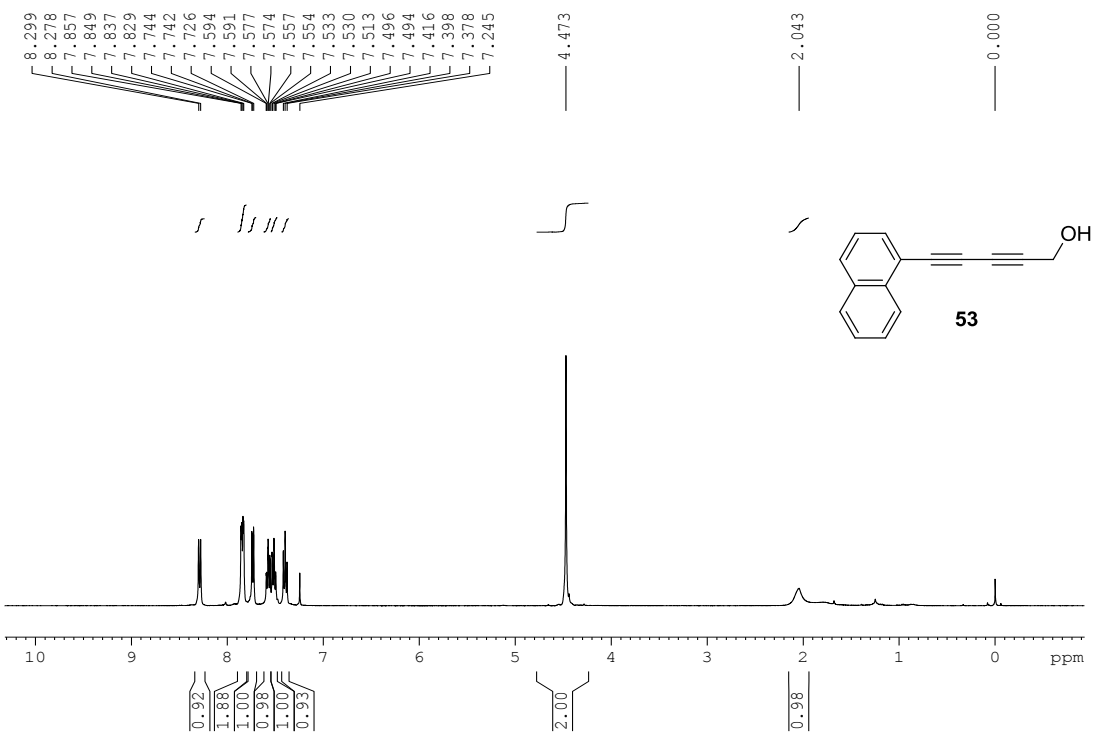

Figure 11. ^{1}H NMR spectrum of **53**

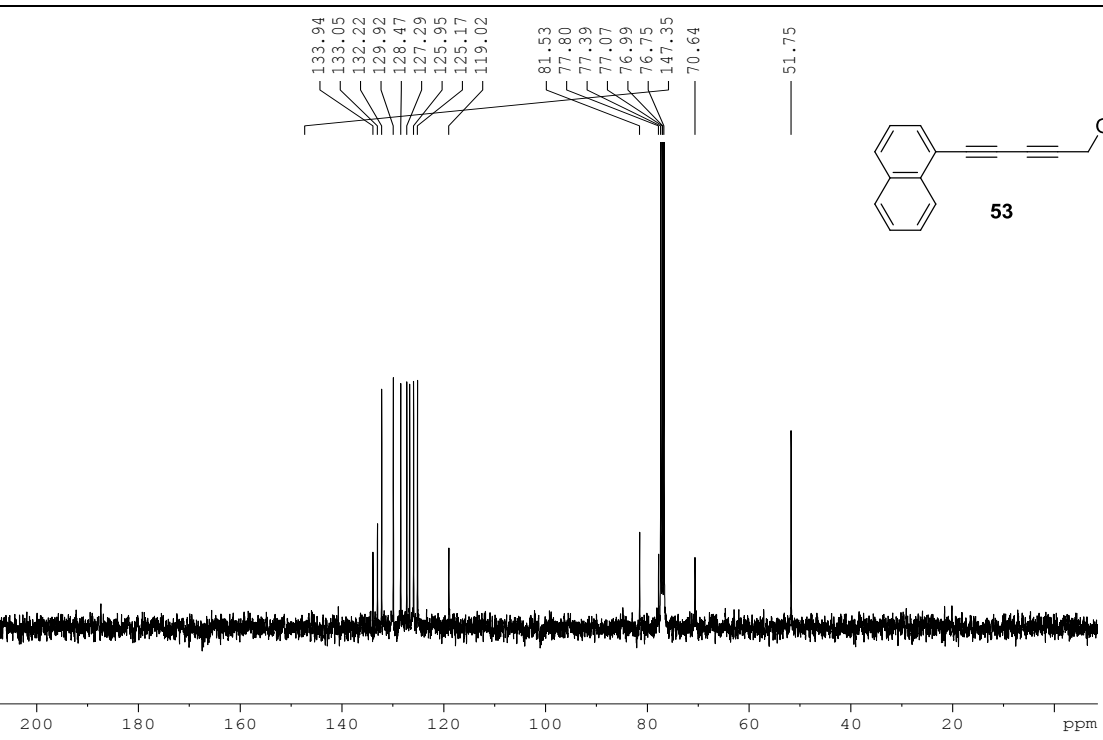

Figure 12. ^{13}C NMR spectrum of **53**

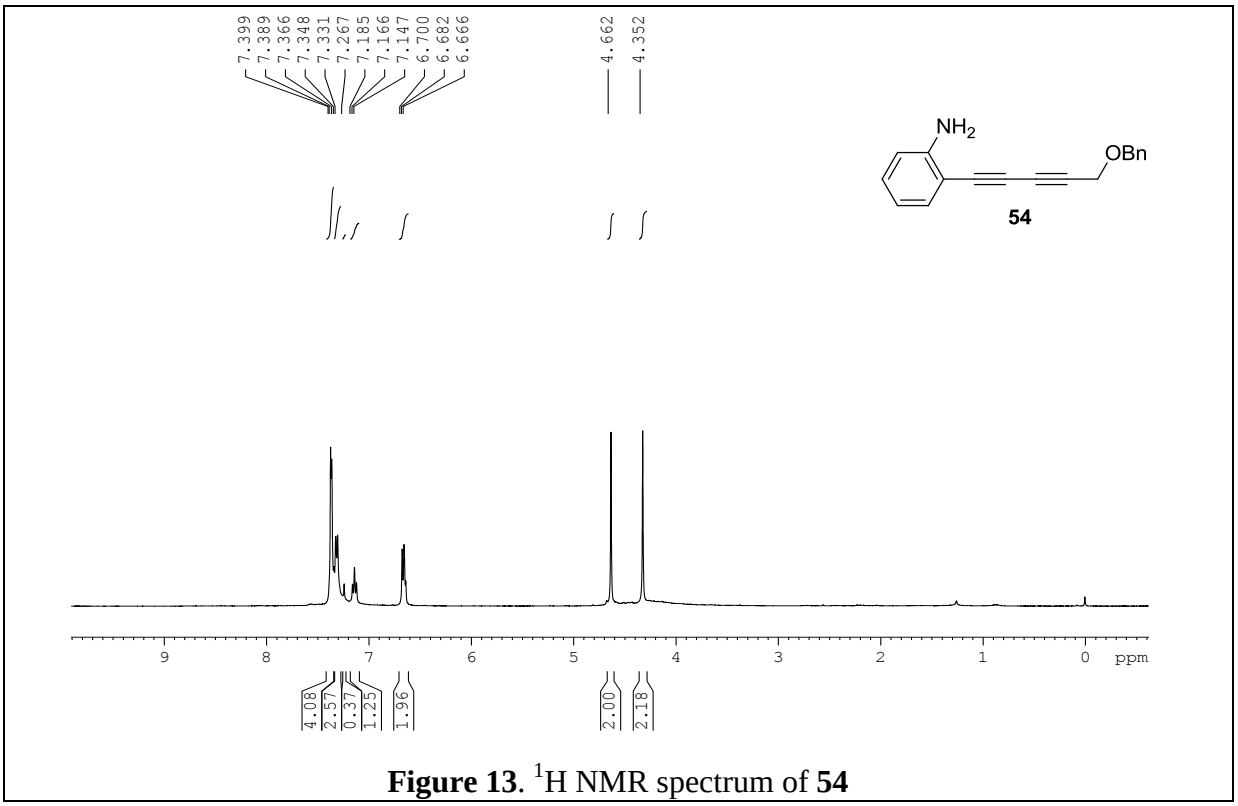

Figure 13. ^{1}H NMR spectrum of **54**

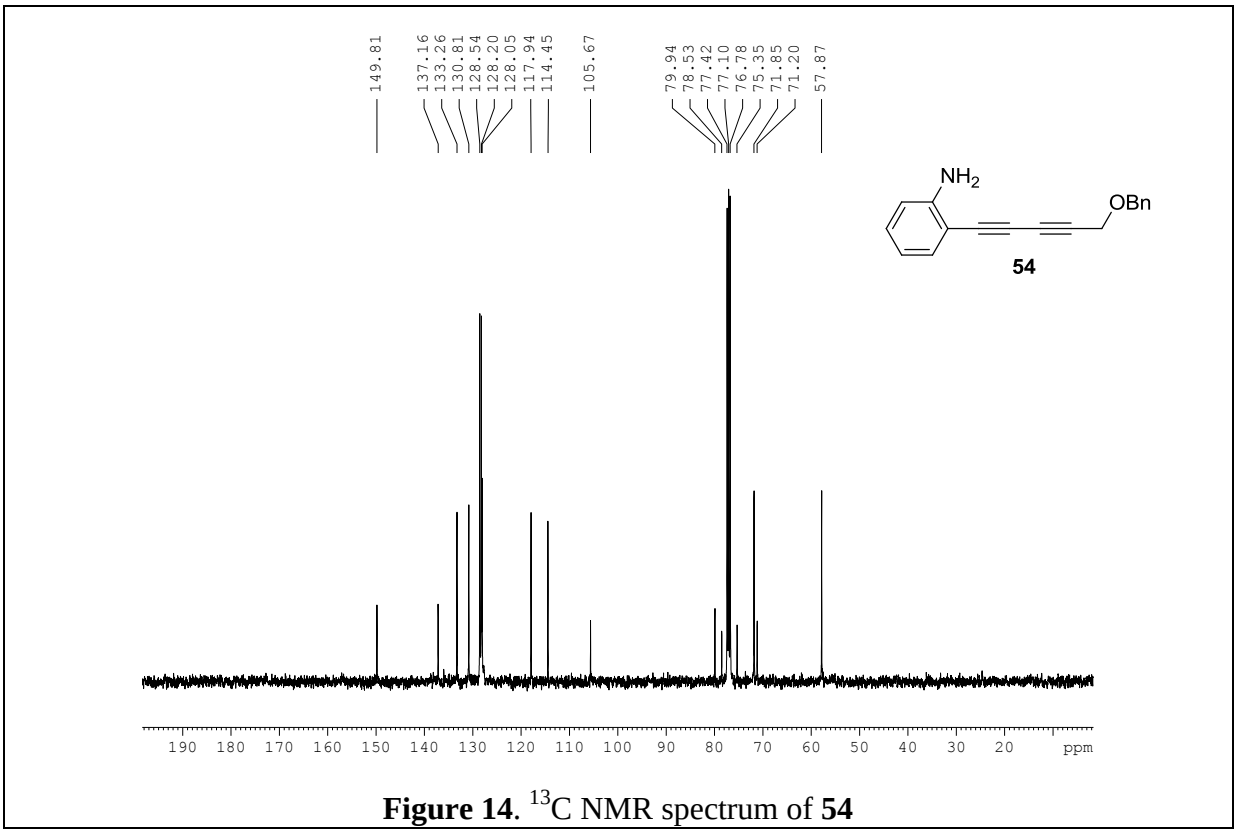

Figure 14. ^{13}C NMR spectrum of **54**

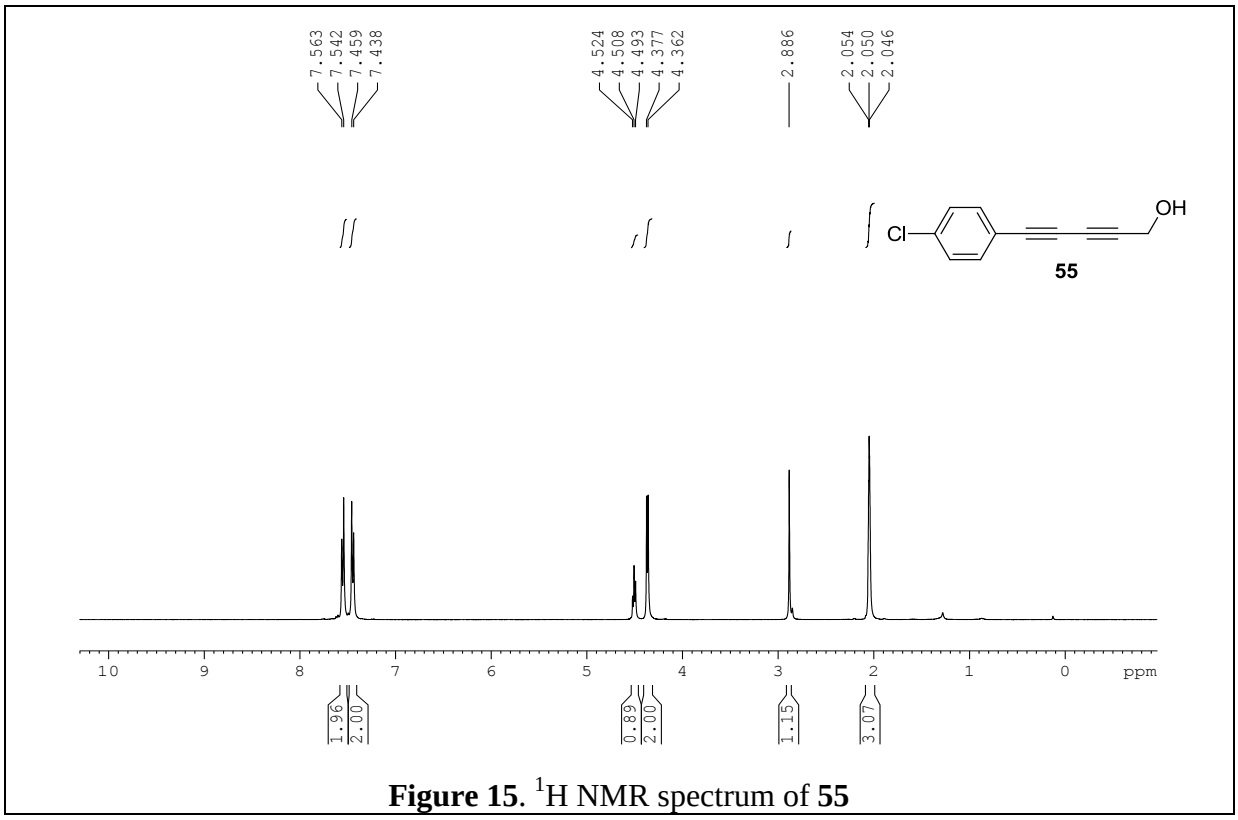

Figure 15. ^{1}H NMR spectrum of **55**

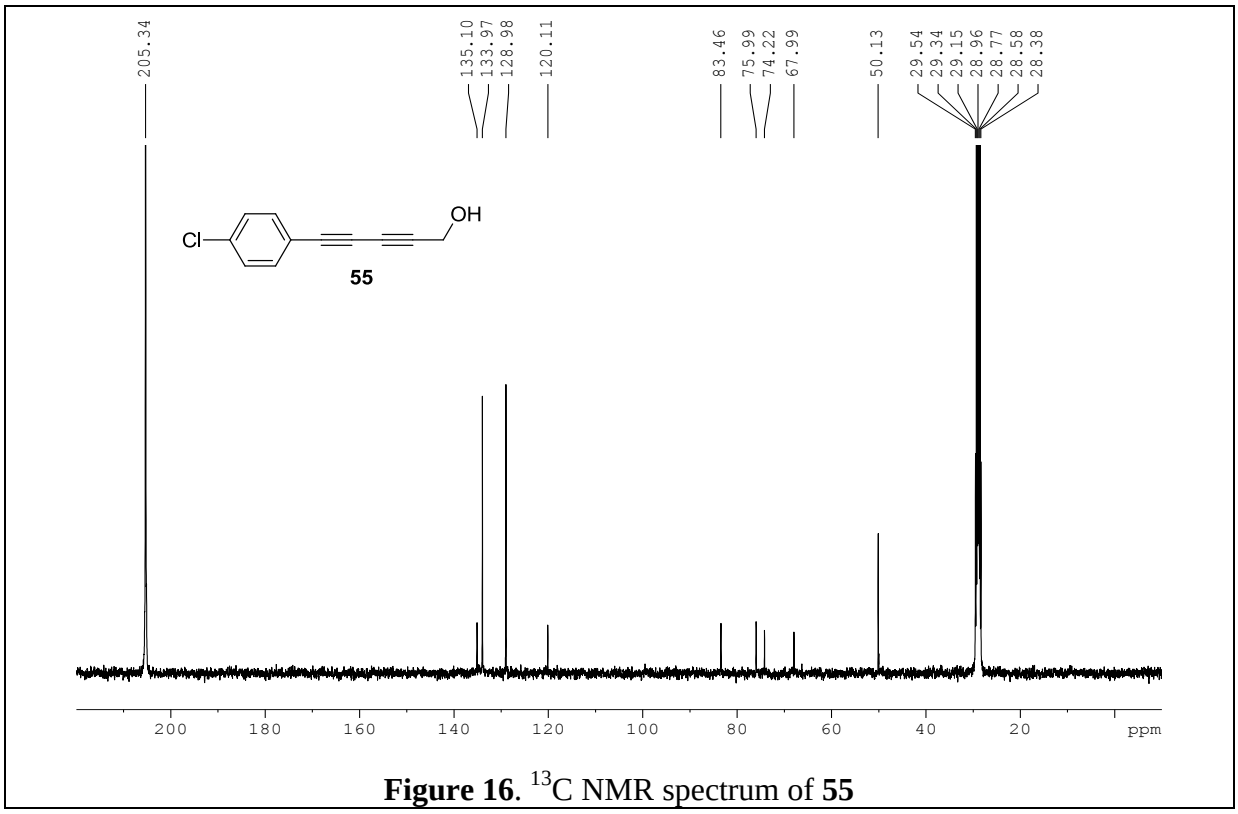

Figure 16. ^{13}C NMR spectrum of **55**

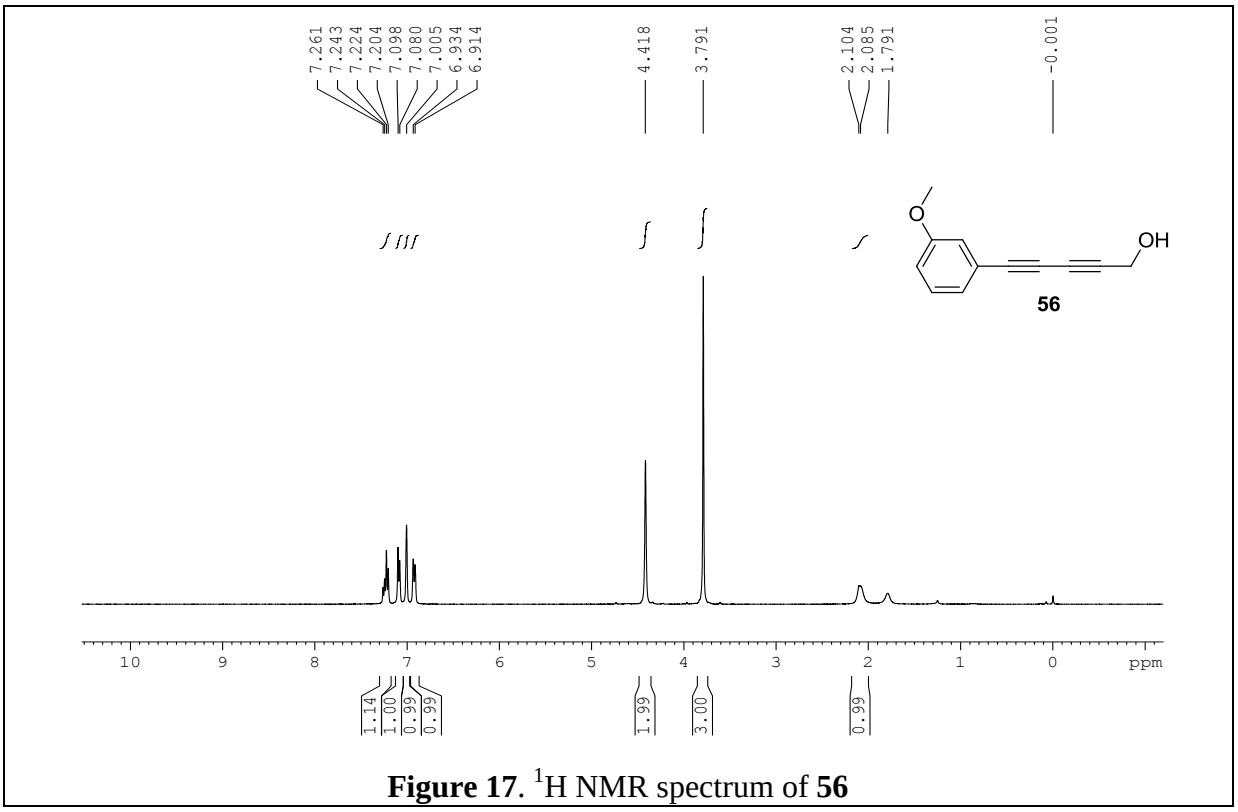

Figure 17. ^{1}H NMR spectrum of **56**

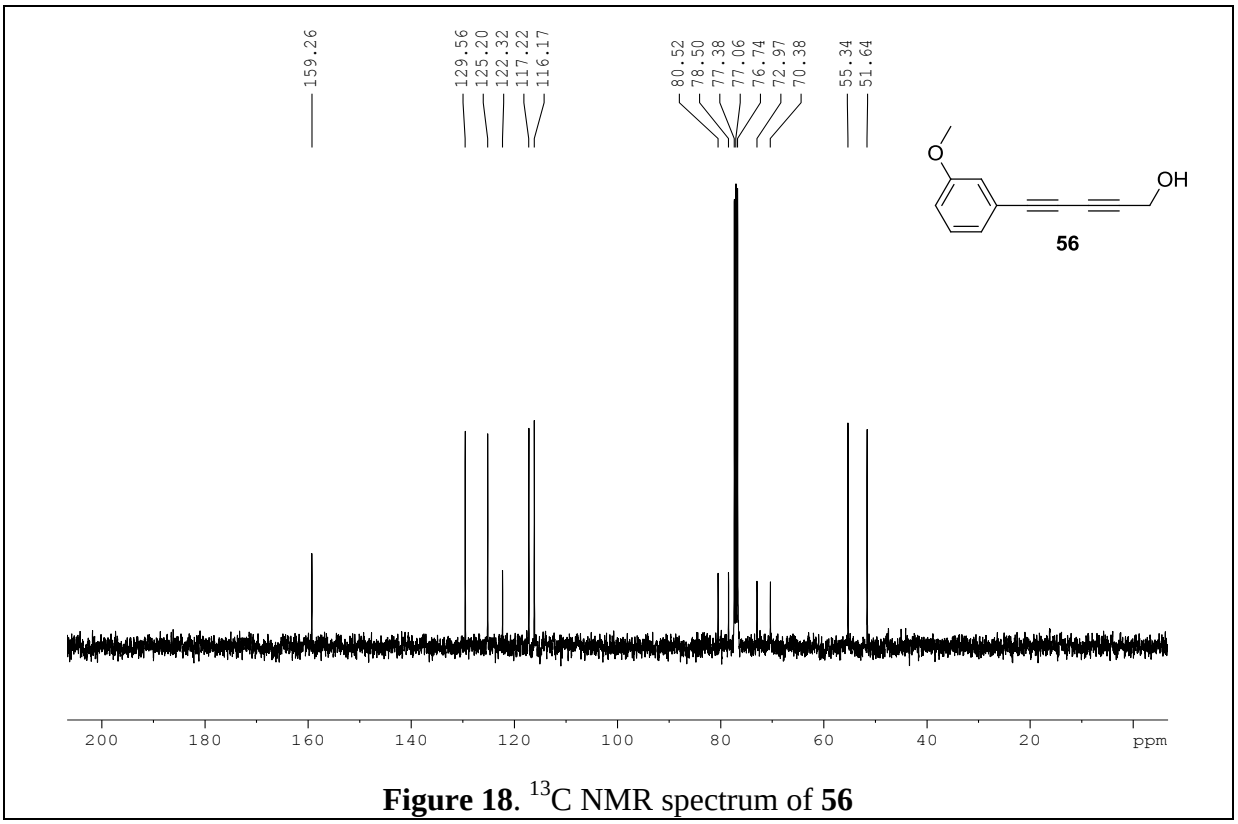

Figure 18. ^{13}C NMR spectrum of **56**

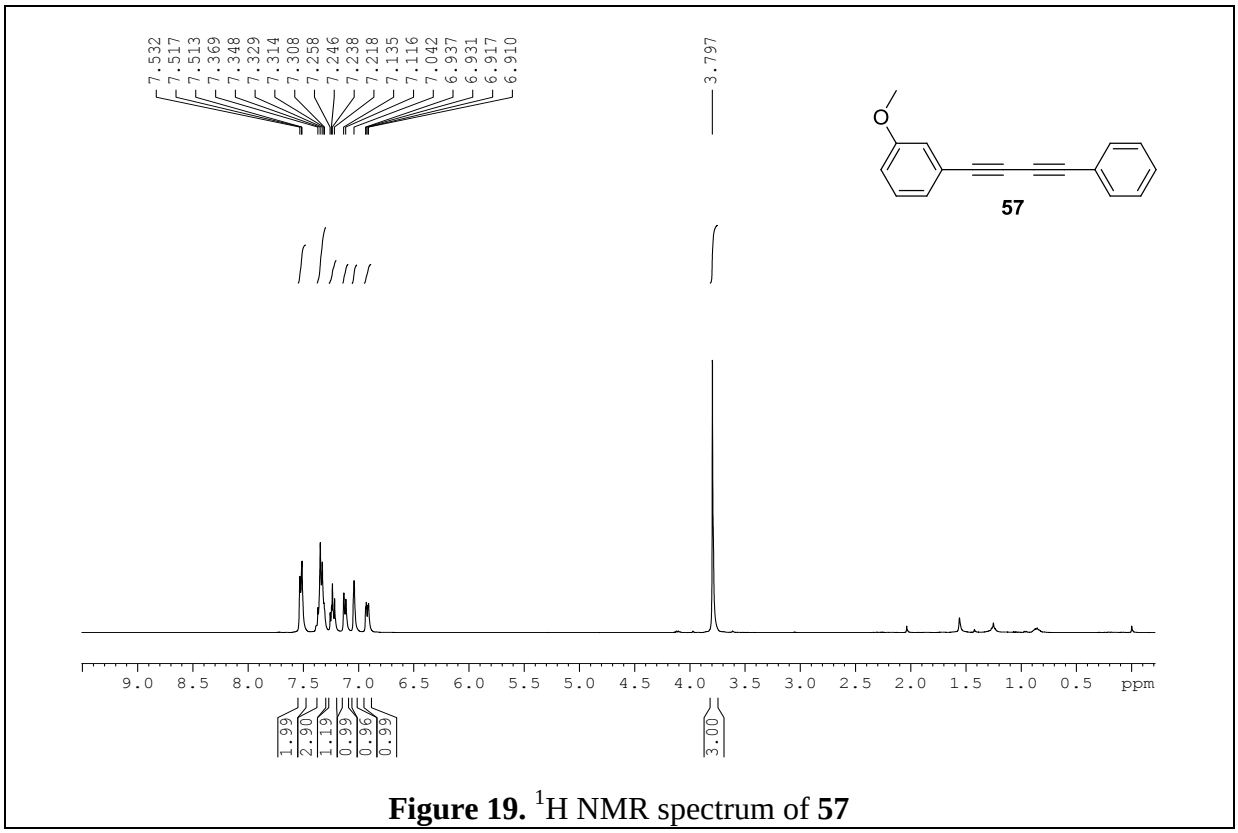

Figure 19. ^{1}H NMR spectrum of **57**

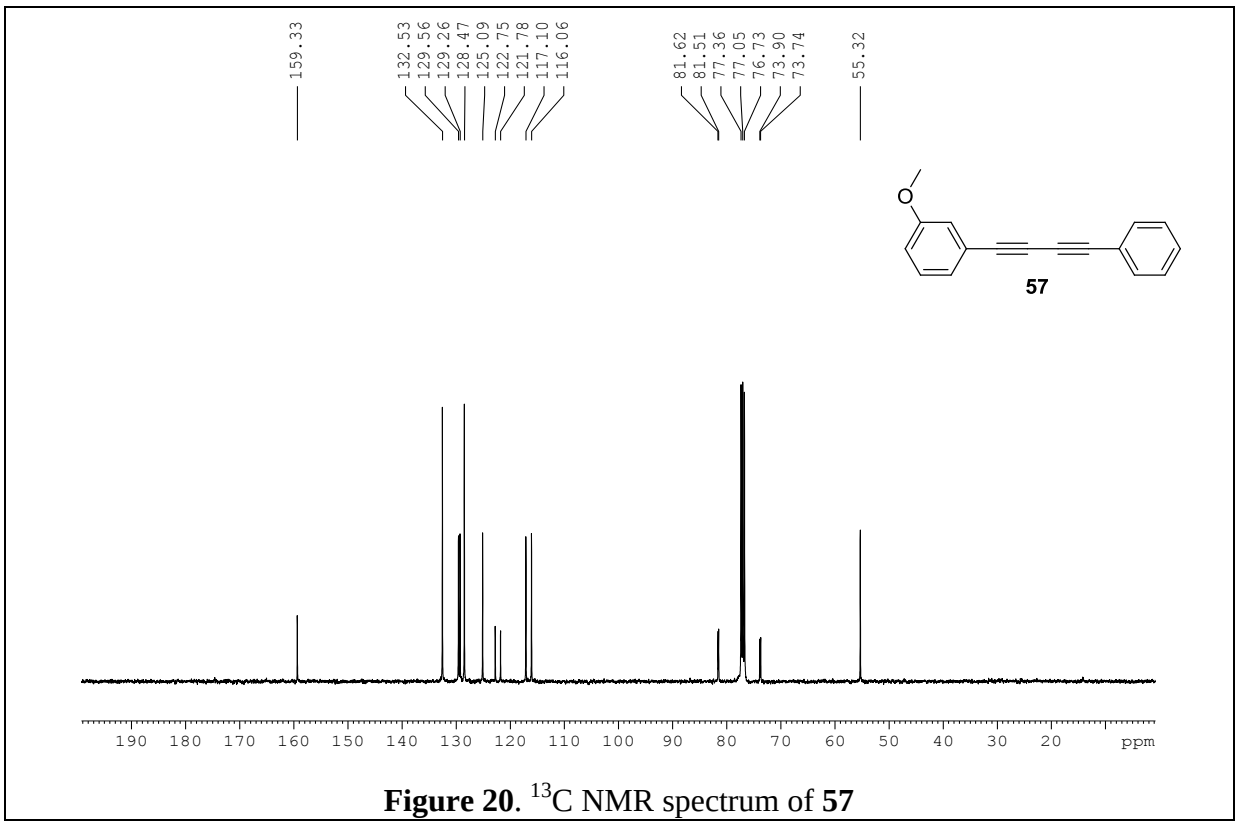

Figure 20. ^{13}C NMR spectrum of **57**

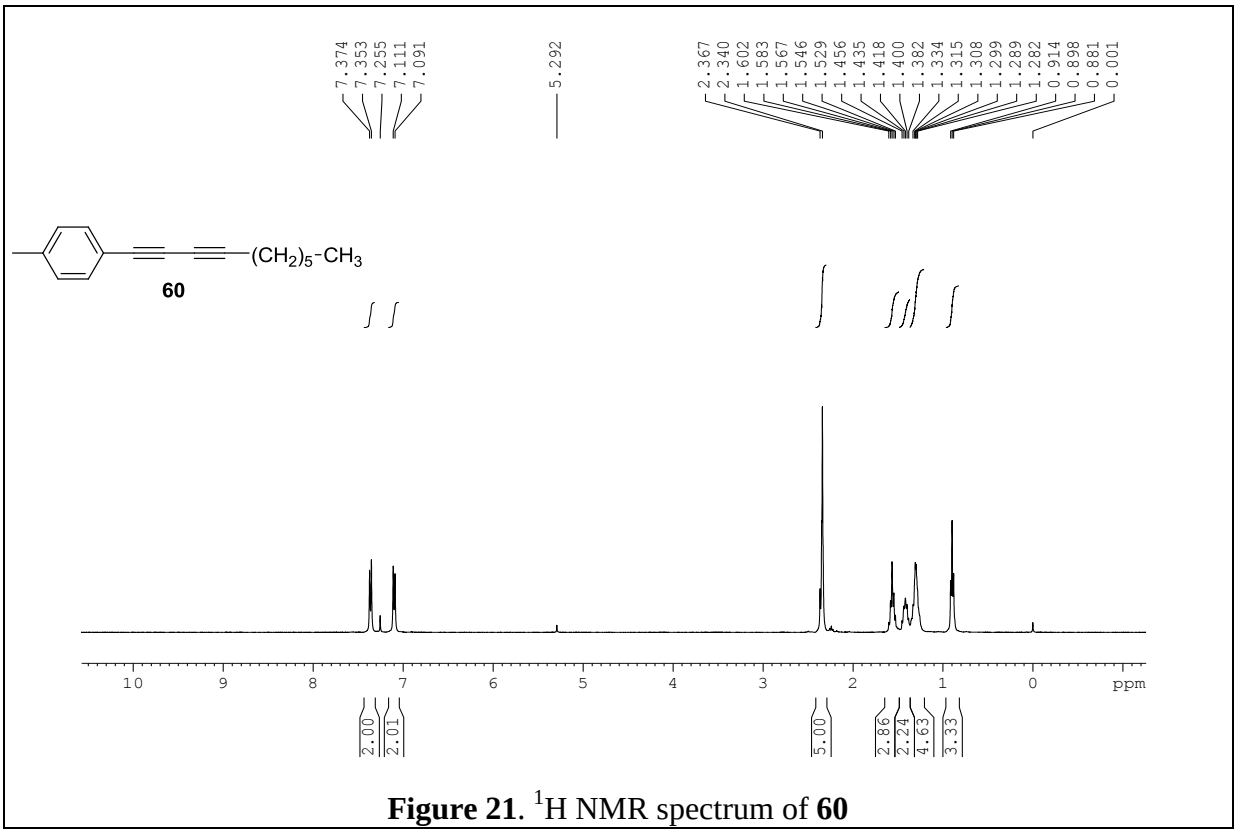

Figure 21. ^{1}H NMR spectrum of **60**

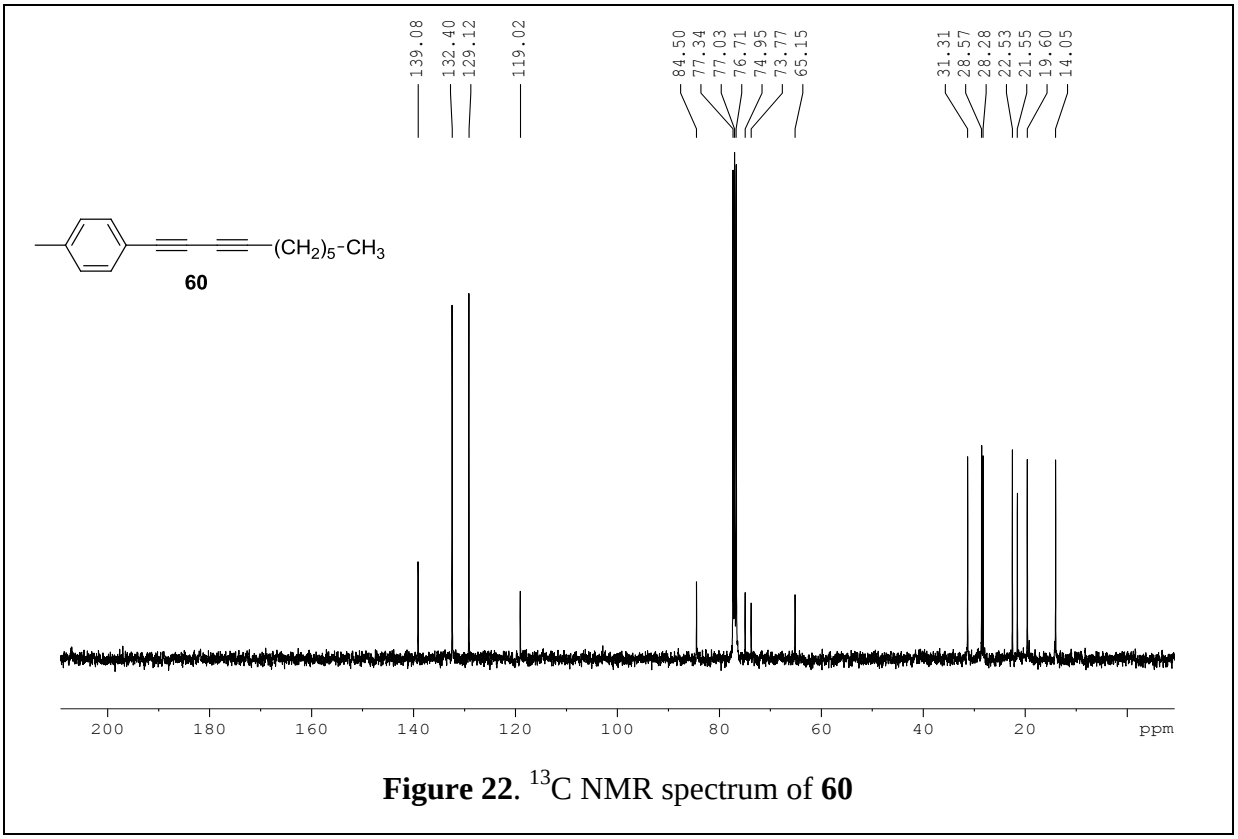

Figure 22. ^{13}C NMR spectrum of **60**

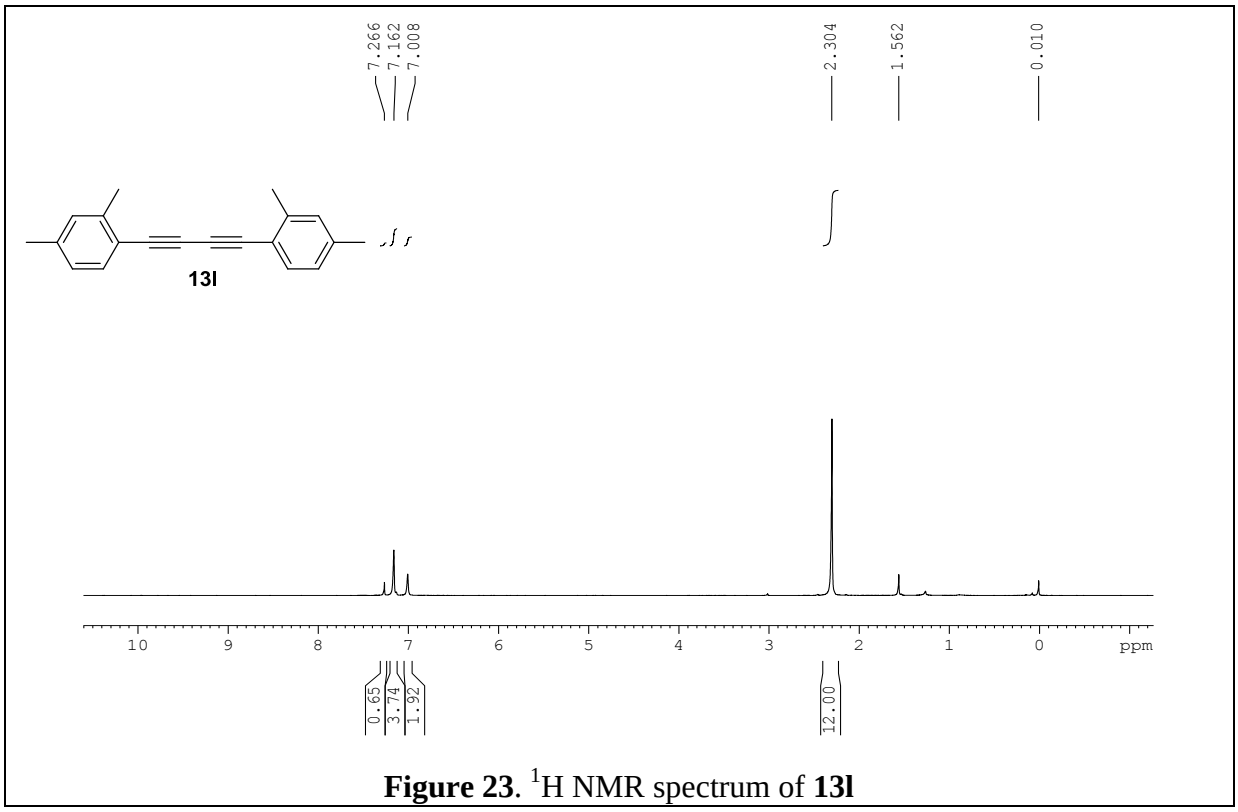

Figure 23. ^{1}H NMR spectrum of **13l**

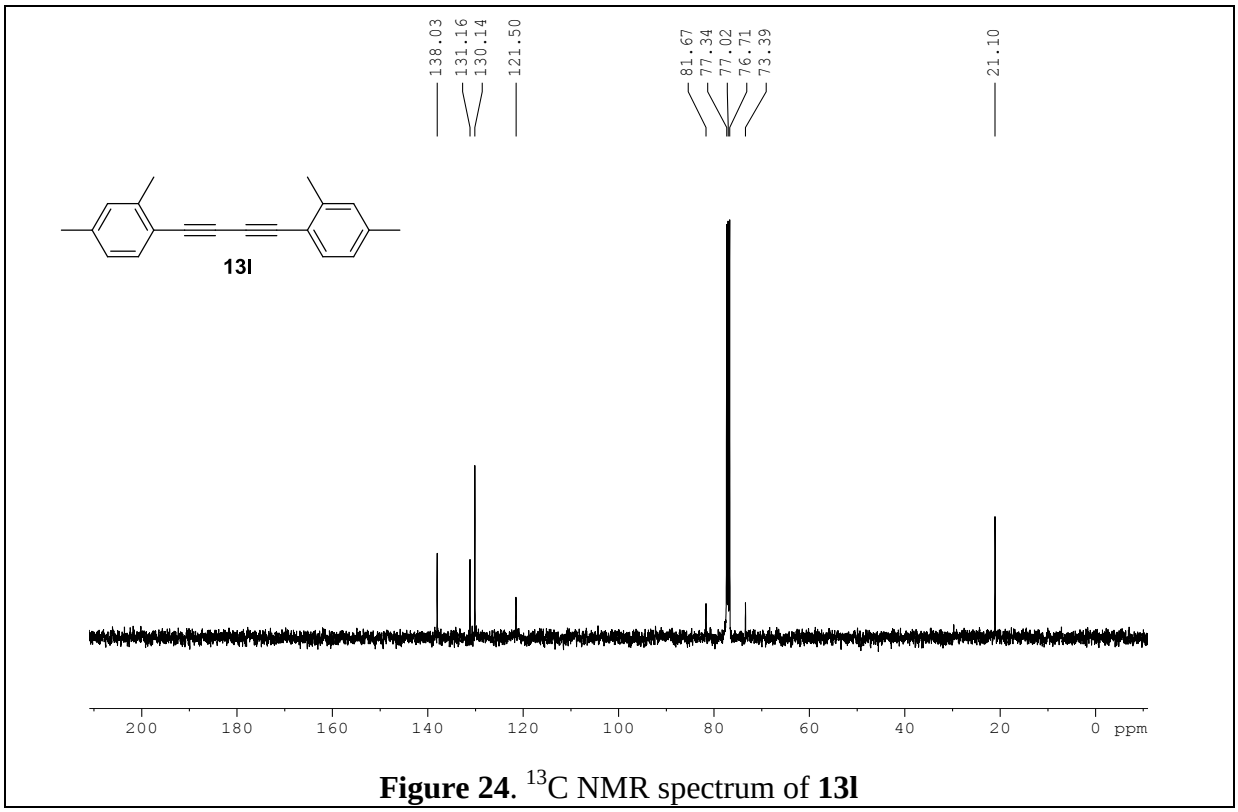

Figure 24. ^{13}C NMR spectrum of **13l**

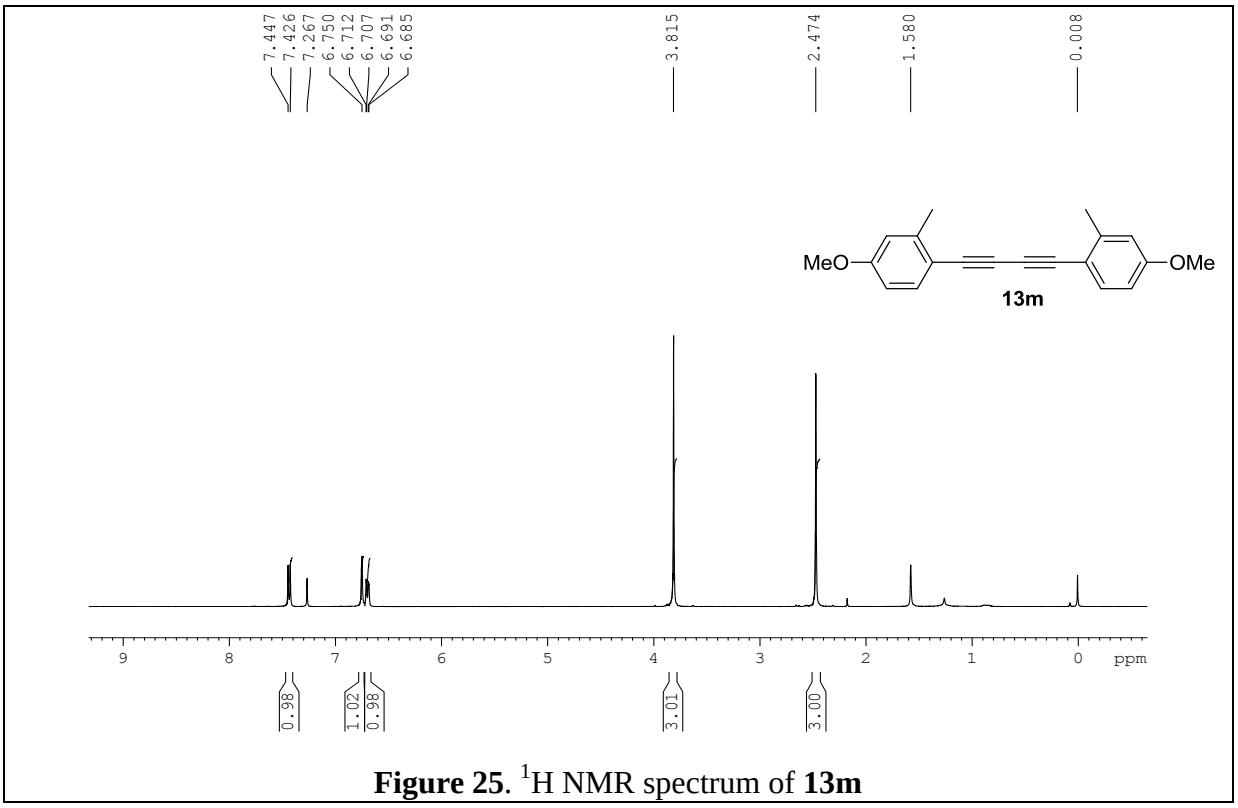

Figure 25. ^{1}H NMR spectrum of **13m**

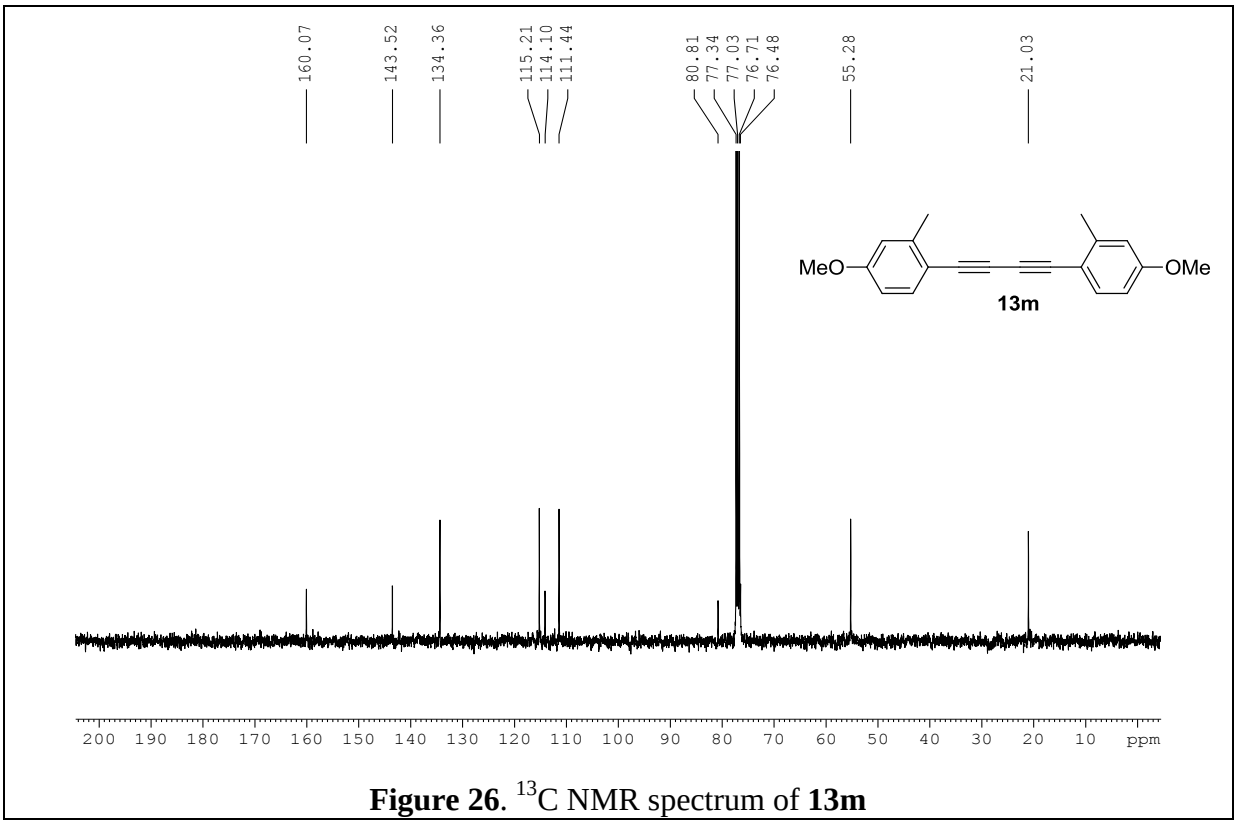

Figure 26. ^{13}C NMR spectrum of **13m**

List of Publications

1. Homo and Heterocoupling of Terminal Alkynes Using Catalytic $CuCl_2$ and DBU

   Balamurugan, R.; **Naveen**, **N**.; Manojveer, S.; Nama, M. V. *Aust. J. Chem.* **2011**, *64*, 567

2. Triflic Acid-Promoted Direct α-Alkylation of Unactivated Ketones Using Alcohols *via* In Situ Formed Acetals

   Koppolu, S. R.; **Naveen**, **N**.; Balamurugan, R. *J. Org. Chem.* **2014**, *79*, 6069.

3. Silver-Catalyzed Direct α-Alkylation of Unactivated Ketones Using Propargyl and Allyl Alcohols

   Naveen, **N**.; Koppolu, S. R.; Balamurugan, R. *Manuscript to be submitted.*

4. Metal-Free Electrophilic Fluorination of Tertiary Propargyl Alcohols Using Selectfluor

   Naveen, **N**.; Balamurugan, R. *Manuscript to be submitted.*

5. Silver-Catalyzed Meyer-Schuster Rearrangement and Electrophilic Iodination

   Naveen, **N**.; Balamurugan, R. *Manuscript under preparation.*

Oral and Poster Presentations

1. Oral presentation was given titled "Lewis/Brønsted Acids-Catalyzed Direct α-Alkylation of Unactivated Ketones" at CHEMFEST-Feb 2013, 10^{th} in-house symposium held at University of Hyderabad, Hyderabad.