Nucleophilic Carbene Catalysis in Chemoselective & Aerobic Oxidation Reactions

A thesis submitted for the partial fulfilment of

the degree of Doctor of Philosophy

by

T RAMANJANEYULU BANDARU

Department of Chemical Sciences

Indian Institute of Science Education and Research (IISER) Mohali

Sector 81, Knowledge City, S. A. S. Nagar, Manauli PO, Mohali, 140306. Punjab, India.

December 2015

Dedicated to

My parents

DECLARATION

The work presented in this thesis titled "***Nucleophilic Carbene Catalysis in Chemoselective & Aerobic Oxidation Reactions*****"** has been carried out by me under the supervision of **Dr. R. Vijaya Anand** in the Department of Chemical Sciences, Indian Institute of Science Education and Research (IISER) Mohali, Mohali.

This work has not been submitted in part or full for a degree, diploma or a fellowship to any other university or institute.

Whenever contributions of others are involved, every effort is made to indicate this clearly with due acknowledgements of collaborative work and discussions. This thesis is a bona fide record of original work done by me and all sources listed within have been detailed in the bibliography.

T RAMANJANEYULU BANDARU

Date:

Place:

In my capacity as the supervisor of the candidate's thesis work, I certify that the above statements by the candidate are true to the best of my knowledge.

Dr. R. Vijaya Anand

Assistant Professor

Department of Chemical Sciences

Indian Institute of Science Education and Research Mohali

Date:

Place:

ACKNOWLEDGEMENTS

It gives me immense pleasure to express my profound gratitude to my graduate supervisor **Dr. R. Vijaya Anand**, for giving me a wonderful opportunity to work with him and I eternally thank him to have been a part of his group from the very beginning. I sincerely thank him for giving me a good opportunity to work in the field of organic synthesis, especially in the area of organocatalysis. I am grateful to him for teaching me the basic experimental techniques, valuable guidance, constant encouragement and motivation throughout my Ph.D. work and without which this long journey would have not been possible. I enjoyed as a Ph.D. student in his laboratory during my doctoral study. I will always remain thankful to him and consider myself privileged to associate with him.

Further, I thank my research progress committee members Dr. S. Arulananda Babu and Dr. Sripada S. V. Ramasastry for their valuable suggestions and for spending their valuable time for me during the yearly assessment of my research work.

It is my privilege to thank IISER Mohali director, Professor N. Sathyamurthy, for providing the space to work, and very good infrastructural facilities.

I acknowledge IISER Mohali for NMR, HRMS, FT-IR and other facilities. Next, I sincerely thank to all the faculty members of the Department of Chemical Sciences for facilitating the use of various departmental instruments and their useful suggestions.

I wish to thank Dr. P. Balanarayan, Dr. Sugumar Venkataramani, Dr. Sanjay Singh, and Dr. Satya Prakash Singh for their help and useful discussions to understand the reaction mechanism.

I would like to express my heart full thanks to my labmembers Mr. Virsinha V. Reddy, Mr. Panjab Arde, Mr. Sriram Mahesh, Mr. Abhijeet S. Jadhav, Mr. Prithwish Goswami, Dr. Ch. Asim Kumar, Mr. Y. Mahesh, Mr. P. Manish, Mr. Chaman Lal, Mr. Akhil for maintaining healthy environment and useful discussions in the lab which helped me in learning and conceptual understanding during the course of my research further, I thank all summer trainees who worked for short time projects in our lab.

A special thank to my friends Mr. Chennakesava Reddy, Mr. V. Rajkumar, Mr. N. A. Aslam, Dr. Gurpreet Kaur, Mr. K. Maheswararao, Dr. Billa Prashanth, Mr. P. Ramarao, Mr. S. V. Subbarao. Additionally, I wish to thank my friends Dr. G. V. Ramesh, Dr. G. D. Prasad, Dr.

A. Satish Kumar, Mr. K. Trimurthulu, Mr. N. Ramesh, Mr. K. Ramakrishna, Mr. Y. Pavan Kumar, Dr. J. Krishna and other friends. I am also thankful to Mr. Triveni, Mr. Balbir for their help on time related to research. Of course, Mr. Mangat, Mr. Bahadur lab assistants of chemistry teaching lab were acknowledged for their help. I also wish to thank to all my friends in IISER Mohali.

I would like to express my heart full thanks to my well wishers Mr. A. Adinarayana Murthy (Guru Swamy), Ms. A. V. Satya Vani, Mr. A. Surya Prabhakar, and Ms. A. Sailaja for their valuable suggestions and encouragement to achieve my goals.

I am grateful to the Council of Scientific Industrial Research (CSIR) and IISER Mohali for my fellowship during my doctoral study. I wish to thank to IIT Kanpur for timely providing the HRMS data. Additionally, I also would like to thank to Department of Science and Technology (DST), India and IISER Mohali for funding and enabling me to complete my Ph.D.

Finally, I would like to express my sincere thank to my parents and my family members for their motivation and support for accomplishing my dream to obtain the highest degree.

Abstract

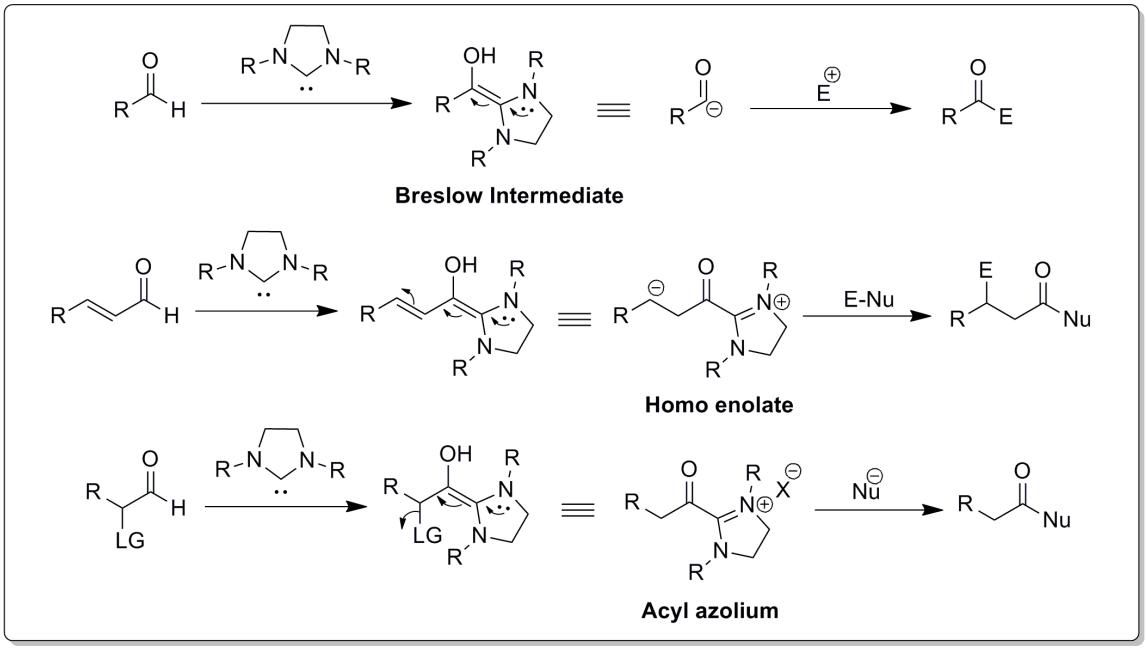
This thesis work is divided in to two parts, **Part A** and **Part B**. Part A deals with chemoselective transformations catalyzed by nucleophilic carbenes and Part B deals on the organic transformations under oxidative N-heterocyclic carbene (NHC) catalysis.

PART A: Chemoselective transformations catalyzed by nucleophilic carbenes

Part A is divided in to three chapters.

Chapter 1: **General introduction on the N-heterocyclic carbene (NHC) catalysis:**

This chapter covers a concise review about the history, the modes of activation of N-heterocyclic carbenes toward carbonyl groups and applications of N-heterocyclic carbenes in organocatalysis. Scheme 1 portrays the different modes of activation of NHC toward various carbonyl compounds.

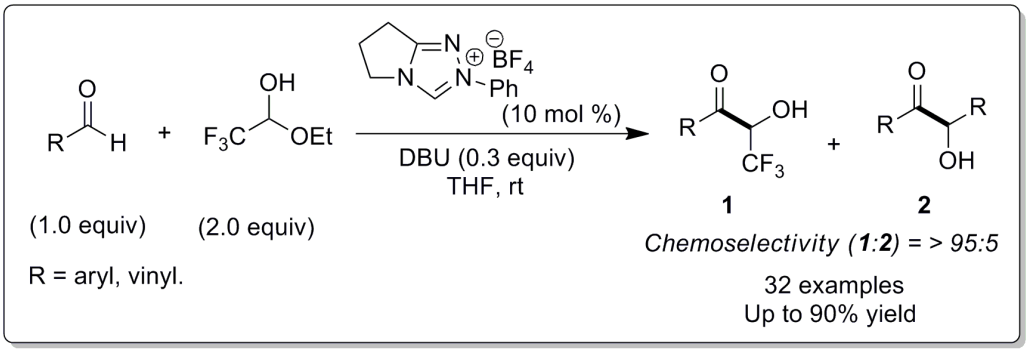


Scheme 1: Different modes of activation of NHC toward various carbonyl compounds

Chapter 2**: Chemoselective synthesis of trifluoromethylated acyloins using NHC as an organocatalyst:**

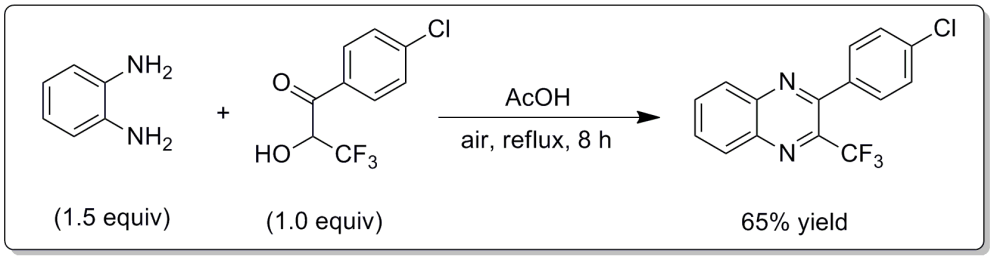
Although NHC catalyzed intermolecular homodimerization of aldehydes is well documented in the literature, intermolecular crossed acyloin condensation still remains as a challenge because of the mismatch between the reactivity of aldehyde and the coupling partner. Choosing a right coupling partner is crucial in the crossed acyloin condensation, otherwise the reaction would lead

to four different acyloins including two homodimerized products. A very few successful reports are available in the literature for the intermolecular crossed acyloin condensation in which the coupling partner was aldehyde or ketone. But so far, no reports are available using hemiacetals as an "aldehyde equivalent" (as a coupling partner) in intermolecular crossed acyloin condensation. This chapter deals with N-heterocyclic carbene (NHC) catalyzed a highly chemoselective intermolecular crossed acyloin reaction of various aldehydes with trifluoroacetaldehyde ethyl hemiacetal (as a coupling partner) leading to trifluoromethylated acyloins. Trifluoroacetaldehyde ethyl hemiacetal is relatively stable and commercially available (as 90% aq. solution). Moreover, this particular hemiacetal introduces trifluoromethyl group in the acyloin product, which could be easily transformed to pharmaceutically important trifluoromethyl containing heterocycles or drugs. The substrate scope for this reaction was evaluated using a wide range of aromatic aldehydes, and almost in all cases, the required trifluoromethyl containing acyloins were obtained in good to excellent yields with >95:5 high chemoselectivity (Scheme 2).



Scheme 2: NHC catalyzed intermolecular crossed acyloin condensation

To show the synthetic utility of this methodology, one of the crossed acyloin product was converted into trifluoromethyl containing quinoxoline (Scheme 3).

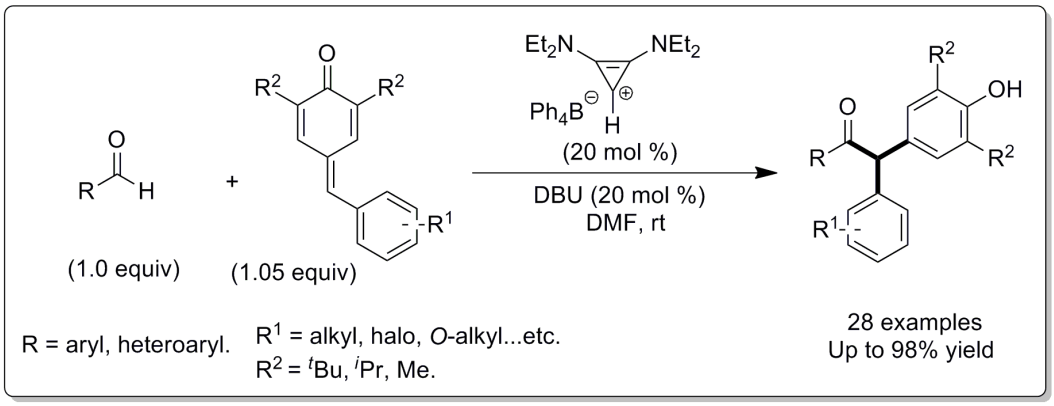


Scheme 3: Synthesis of trifluoromethyl containing quinoxoline derivative

An enantioselective version of the intermolecular crossed acyloin reaction between *p*-chlorobenzaldehyde and trifluoroacetaldehyde ethyl hemiacetal was also performed in the presence of a few chiral NHCs as a catalyst under various reaction conditions. In one of the reaction conditions, the crossed acyloin product was obtained with the maximum of 30% *ee*.

***Chapter 3*: Bis(amino)cyclopropenylidene (BAC) catalyzed chemoselective synthesis of α,α'-diarylated ketones:**

This chapter describes a brief introduction about the synthesis, stability, reactivity and applications of bis(amino)cyclopropenylidenes (BACs) in organometallic chemistry[4] as well as in organocatalysis. It has been realized that the NHCs based on a heterocyclic core such as thiazole, triazole, imidazole etc. are dominating in organocatalysis due to their unmatched nucleophilicity and high stability. On the other hand, bis(amino)cyclopropenylidene, which is a smallest aromatic compound with an inherent carbene center, was found to be a promising non-heterocyclic based candidate in terms of reactivity towards metals and carbonyl compounds. Though bis(amino)cyclopropenylidenes have been widely explored as a ligand in organometallic chemistry,[4] only a few reports are available in the literature on the application of bis(amino)cyclopropenylidenes as organocatalyst. This chapter also describes a mild and efficient method for the synthesis of α,α'-diarylated ketones via intermolecular 1,6-conjugate addition of aromatic aldehydes to *p*-quinone methides (*p*-QMs) using bis(amino)cyclopropenylidene as an organocatalyst. The versatility of this protocol has been portrayed using a wide range of aromatic and heteroaromatic aldehydes as well as *p*-QMs, and in all the cases, the corresponding α,α'-diarylated ketones were obtained in moderate to good yields under the optimized reaction conditions (Scheme 4). A plausible mechanism has also been proposed for this transformation.



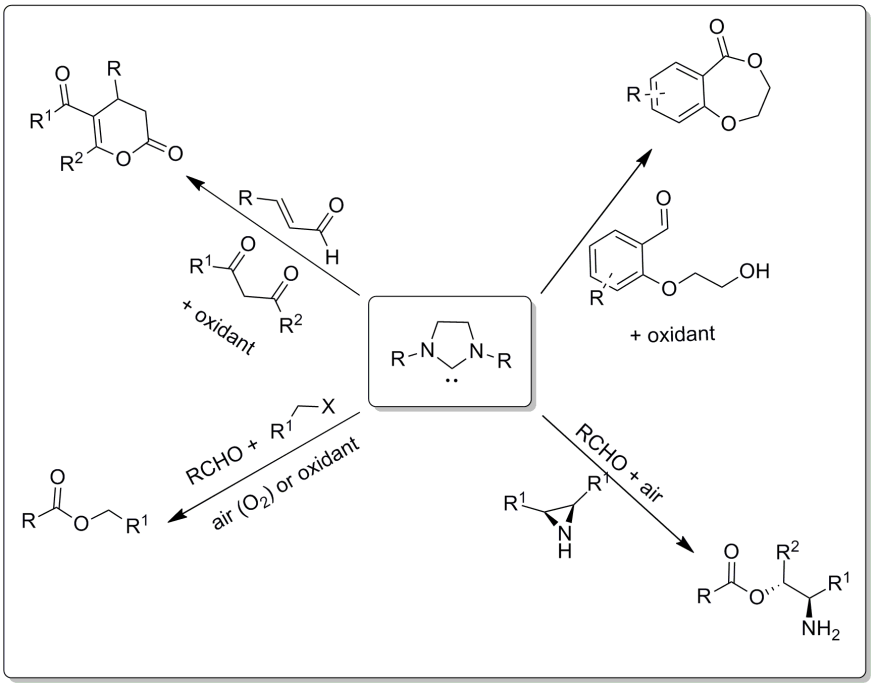
Scheme 4: Bis(amino)cyclopropenylidene catalyzed synthesis of α,α'-diarylated ketones

PART B: Organic transformations under oxidative N-heterocyclic carbene catalysis

Part B is divided in to three chapters.

***Chapter 1*: General introduction on the oxidative N-heterocyclic carbene (NHC) catalysis:**

Chapter 1 covers a general introduction about the oxidative N-heterocyclic carbene catalysis, a sub-area of N-heterocyclic carbene (NHC), which is emerging as one of the dominant methods for the construction of carbon–heteroatom (C–O, C–N) bonds. A few NHC catalyzed oxidative transformations is shown in scheme 5.



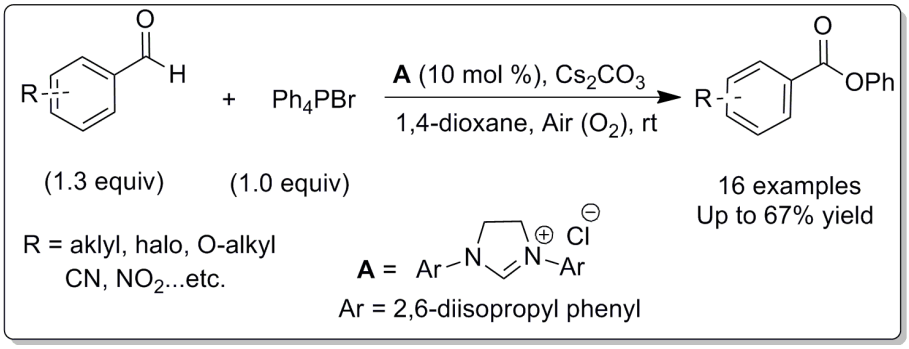
Scheme 5: A few NHC-catalyzed oxidative transformations

***Chapter 2*: Aerobic oxidation reactions under oxidative NHC catalysis**

Chapter 2 is sub-divided in to two parts.

(a) Tetraphenylphosphonium bromide as a phenyl source for the synthesis of phenyl esters under oxidative NHC catalysis:

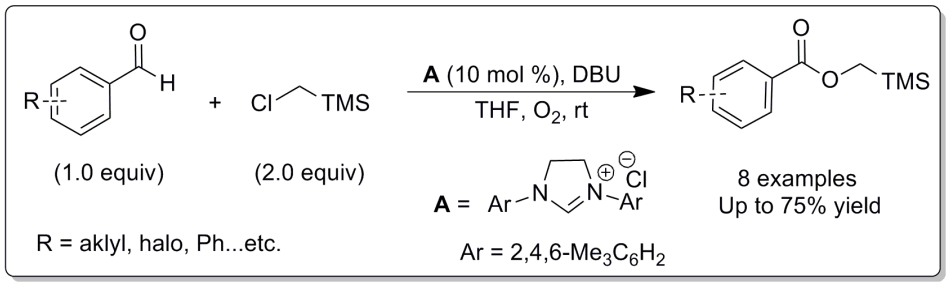
This part deals with the synthesis of aromatic esters from aromatic aldehydes using Ph_4PBr as a phenyl source through oxidative NHC catalysis. Although Ph_4PBr has been utilized as a phenyl source for Pd-catalyzed coupling reactions, it has not been explored in esterification reactions. The optimization was carried out between *p*-chlorobenzaldehyde and Ph_4PBr using different NHCs under different reaction conditions, and the NHC derived from SIPr.HCl (**A**) was found to be the best catalyst for this transformation (Scheme 6). The substrate scope and the mechanism for this reaction are discussed in detail.



Scheme 6: Synthesis of phenyl esters under oxidative NHC catalysis

(b) Synthesis of trimethylsilylmethyl esters under oxidative NHC catalysis:

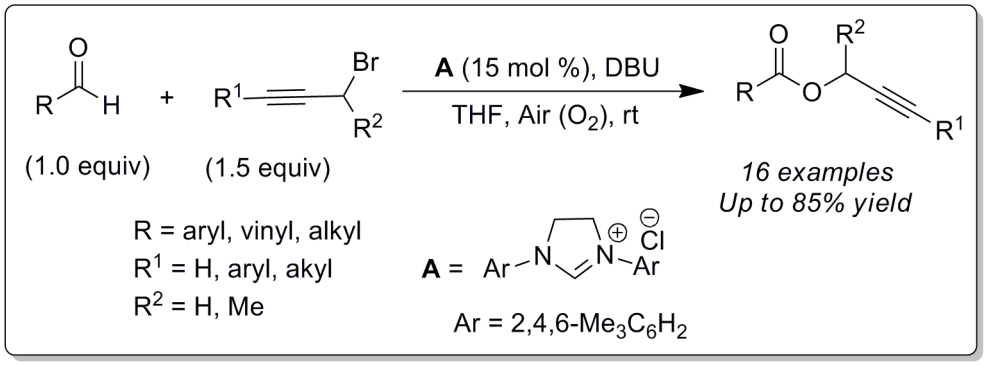
The synthesis of trimethylsilyl methyl esters starting from aromatic aldehydes and chloromethyl trimethylsilane under aerobic oxidative NHC catalysis has been described in this part. Out of many NHCs screened, the one derived from SIMes.HCl (**A)** was found to be the best. A wide range of aromatic aldehydes have been converted to their corresponding trimethylsilyl methyl esters in moderate yields under the reaction conditions (Scheme 7).



Scheme 7: Synthesis of trimethylsilyl methyl esters under oxidative NHC catalysis

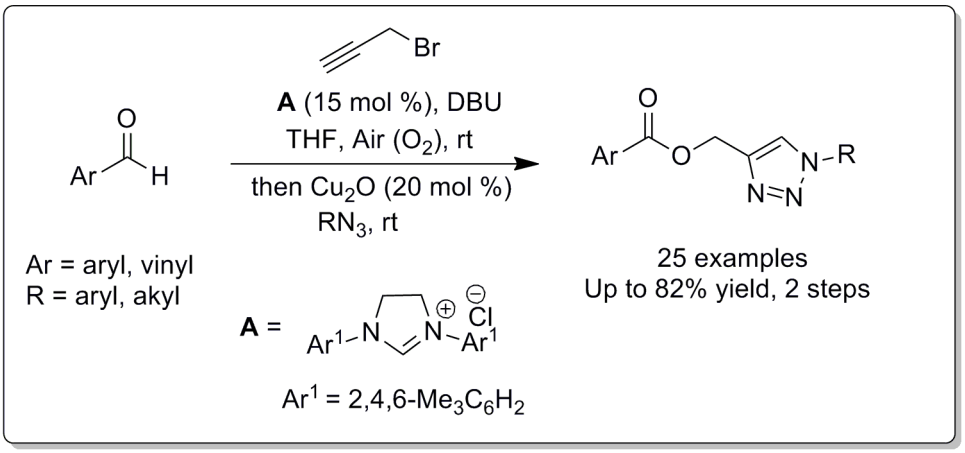
***Chapter 3*: Combining oxidative NHC catalysis with click chemistry to access 1,2,3-triazole derivatives:**

This chapter deals with the one-pot synthesis of 1,2,3-triazole derivatives by merging oxidative NHC catalysis with click chemistry. Before exploring the one-pot process for the synthesis of 1,2,3-triazoles, it was necessary to optimize the first step, *i.e*. propargyl ester formation. Thus, the esterification reaction was optimized under aerobic conditions and the substrate scope was evaluated using a wide range of aldehydes and propargyl bromides (Scheme 8).



Scheme 8: NHC catalyzed oxidative esterification of aldehydes with propargyl bromides

This protocol was then elaborated for the one pot synthesis of 1,2,3-triazole derivatives by combining with copper catalyzed click chemistry. This one-pot method was found to be versatile as a wide range of 1,2,3-triazole derivatives have been generated in good yields (Scheme 9).



Scheme 9: One-pot synthesis of 1,2,3-triazole derivatives

LIST OF ABBREVIATIONS

τ	:	retention time
Ac	:	acetyl
ACN	:	acetonitrile
AcOH	:	acetic acid
aq	:	aqueous
ATR	:	Attenuated Total Reflectance
brd	:	broad doublet
brs	:	broad singlet
°C	:	degree celcius
calcd	:	calculated
$CDCl_3$	:	chloroform-d
cm	:	centimeter
d	:	doublet
DBU	:	1,8-diazabicyclo[5.4.0]undec-7-ene
DCE	:	dichloroethane
DCM	:	dichloromethane
dd	:	doublet of doublets
dr	:	diasteriomeric ratio
dt	:	doublet of triplets
DME	:	dimethoxyethane
DMF	:	*N*,*N'*-dimethyl formamide
DMSO	:	dimethyl sulfoxide
dq	:	doublet of quartets
ee	:	enantiomeric excess
equiv	:	equivalents
er	:	enantiomeric ratio
ESI	:	electron spray ionization
FT-IR	:	Fourier transforms infrared spectroscopy
h	:	hour(s)

HRMS	:	High-resolution Mass Spectrum
Hz	:	Hertz
^{i}Pr	:	iso propyl
IR	:	infrared
J	:	coupling constant
m	:	multiplet
Mes	:	mesityl
mg	:	milli gram(s)
MHz	:	mega hertz
min	:	minute(s)
mL	:	milliliter(s)
mmol	:	millimole(s)
m.p.	:	melting point
M.S.	:	molecular sieves
m/z	:	mass/charge
NHC	:	N-heterocyclic carbene
NMR	:	Nuclear Magnetic Resonance
q	:	quartet
qd	:	quartet of doublets
rt	:	room temperature
s	:	singlet
sept	:	septet
t	:	triplet
^{t}Bu	:	*tert*-butyl
^{t}BuOK	:	potassium-*tert*-butoxide
td	:	triplet of doublets
tert	:	tertiary
THF	:	tetrahydrofuran
TMS	:	Tetramethylsilane

Contents

PART-A

Chemoselective transformations catalyzed by nucleophilic carbenes

Chapter 1

General introduction on the N-heterocyclic carbene (NHC) catalysis

1.1. Introduction

Carbenes are neutral species that feature a divalent carbon atom with six valence electrons, two of which are in non-bonding orbitals. These non-bonding pair of electrons can be either spin paired (singlet **1a**) or have parallel spins in different orbitals (triplet **1b**), depending on the electronic structure of the carbene (Figure 1). Nucleophilic heterocyclic carbene, often referred as N-heterocyclic carbene (NHC), is a special class of carbenes, in which the carbene center is directly attached to one or two heteroatoms. Most of the well-studied NHCs are based on five-membered heterocycles derived from imidazolium or thiazolium or triazolium salts. The computational and X-ray analysis suggest that the N-heterocyclic carbenes (NHCs) are singlet carbenes as the non-bonding pair of electrons of the carbene carbon occupies a sigma orbital (sp^2 hybridized orbital) with spin paired.[1] The stability of these singlet carbenes is influenced by electronic as well as steric factors. The non-bonding lone pair of electrons present in the heteroatom *pushes* the electron density towards the empty *p* orbital of the carbene carbon (π-donation) and at the same time the electronegative heteroatom(s) *pulls* the electron density from the carbene center through the sigma bond (σ-withdrawal). This *push-pull effect* is the major factor responsible for the stability of NHCs. The steric bulk from the substituents (alkyl or aryl) present on the adjacent nitrogen atom(s) to the carbene carbon provides the kinetic stability to the carbene carbon. A combination of these two factors is responsible for the overall stability of N-heterocyclic carbenes.[1] Indeed, the donation of lone pair of electrons from both nitrogen atoms

into the empty P_z orbital of carbene carbon is so strong, so the NHC **1c** can also be effectively described by its Zwitterionic resonance structure (Figure 2).

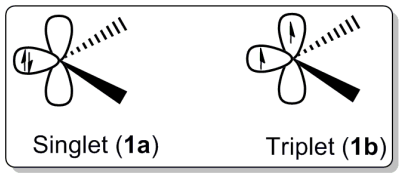


Figure 1. Electronic states accessible to carbene species

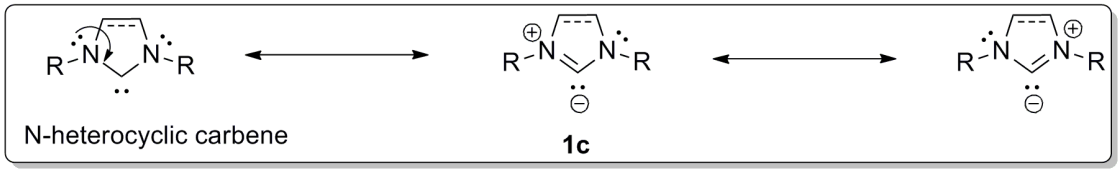


Figure 2. Alternative Zwiterionic resonance structures of N-heterocyclic carbene

Many different types of NHCs have been prepared including with a number of them are isolable in stable form and storable for a long time under inert conditions. In fact, some of the imidazolium and imidazolinium based NHCs are commercially available. In most of the reported cases, the NHC is generated *in-situ* during the reaction by the treatment of a base with the NHC precursors, usually imidazolium or triazolium salts. Some of the NHC precursors based on different heterocyclic core (**2a**–**2f**) are shown in Figure 3**.**

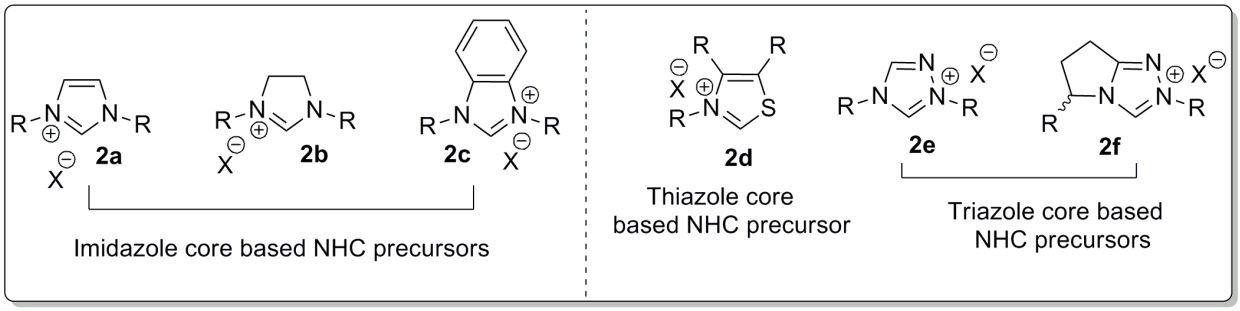


Figure 3

Owing to the exceptional electronic properties such as strong σ-donating ability and weak π-accepting character, NHCs have been well explored as non-labile ligands in the area of organometallic chemistry.[2,3] It has been realized that those unique electronic properties of NHC also help in improving the thermal stability of their metal complexes. As a result, till date, a wide

range of NHC-metal complexes has been prepared and their properties/applications have been well studied. Some of the most studied NHC-metal complexes[3] (**3a–3d**) are shown in figure 4.

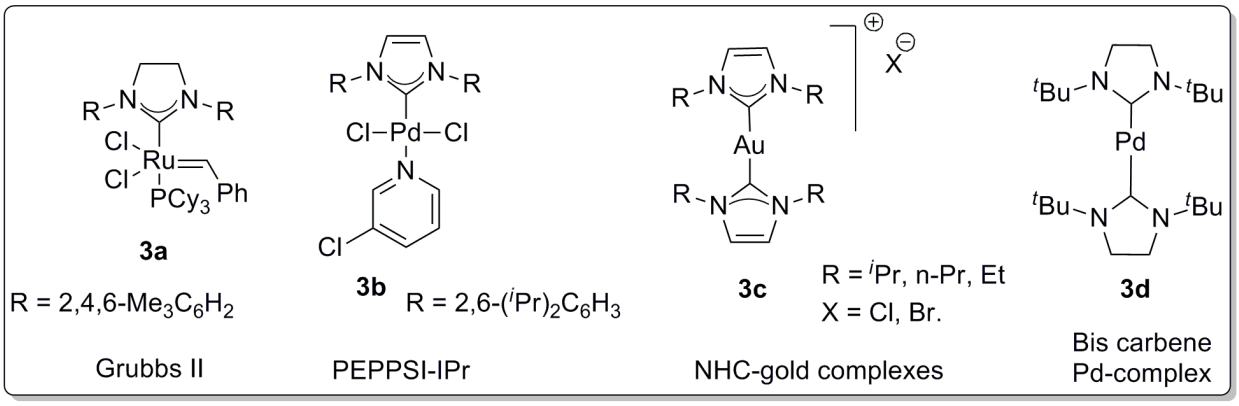


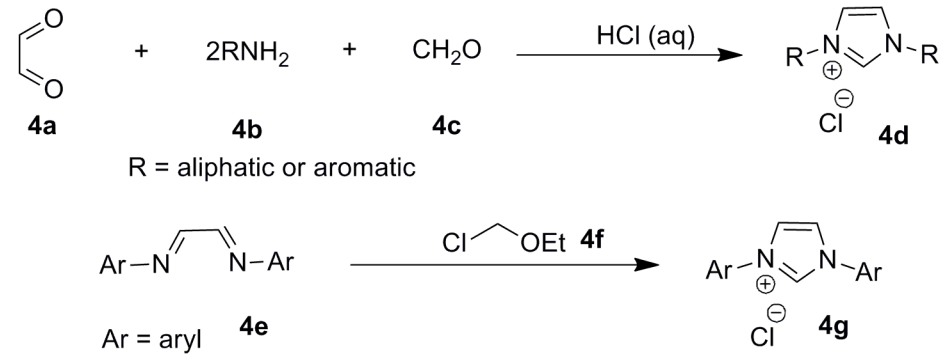
Figure 4

1.2. Synthesis of NHC precursors

A great interest has been made in the development of NHCs derived from five-membered heterocycles such as imidazolium or imidazolidinium or triazolium salts. Some of the literature reports for the synthesis of various NHC precursors are discussed below.

(a). Synthesis of symmetrical imidazolium based NHC precursors

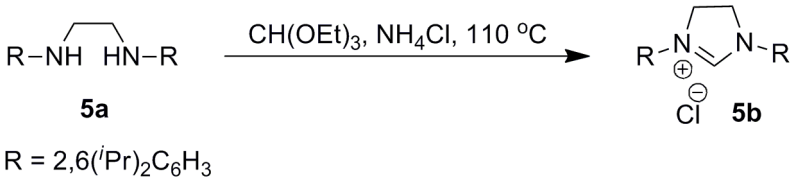
The most common one-pot method for the synthesis of symmetrical imidazolium salts (**4d**) involves the condensation of glyoxal (**4a**), primary amine **4b** and formaldehyde (**4c**) in the presence of aqueous HCl. Another method is also available in literature for the synthesis of symmetrical NHC precursor **4g** *via* cyclisation of diimine **4e** with ethoxy methyl chloride (**4f**) (Scheme 1).[4]



Scheme 1

(b). Synthesis of imidazolidinium based NHC precursor

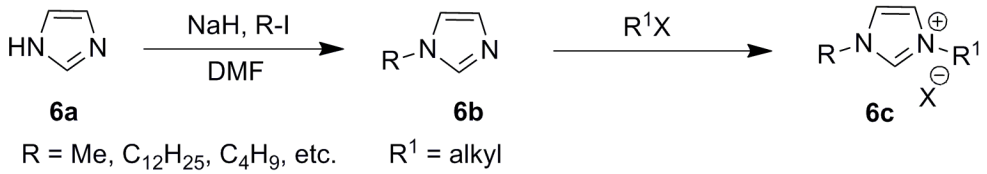
Smith and co-workers reported the synthesis of symmetrical imidazolidinium core containing NHC precursor **5b** by following a modified procedure reported by Arduengo *et al.*[5] which basically involves the reaction between *N*,*N*'-bis(2,6-diisopropyl phenyl amino)ethane (**5a)** and triethylorthoformate in the presence of NH_4Cl at elevated temperature (Scheme 2).[6]



Scheme 2

(c). Synthesis of unsymmetrical NHC precursor

The research groups of Breslow[7] and Yamamoto[8] independently developed a simple two step method for the synthesis of unsymmetrical imidazole-based NHC precursors **6c**.

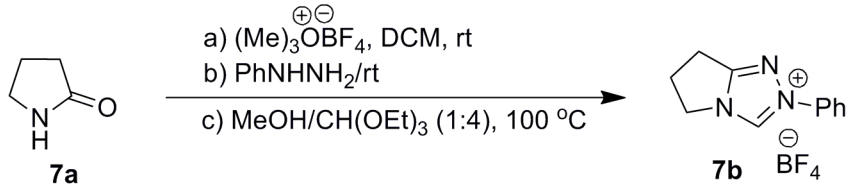


Scheme 3

The synthetic sequence involved mono alkylation of imidazole (**6a**) with suitable electrophile followed by treating with second electrophile to afford corresponding imidazole-based NHC precursor **6c** (Scheme 3).

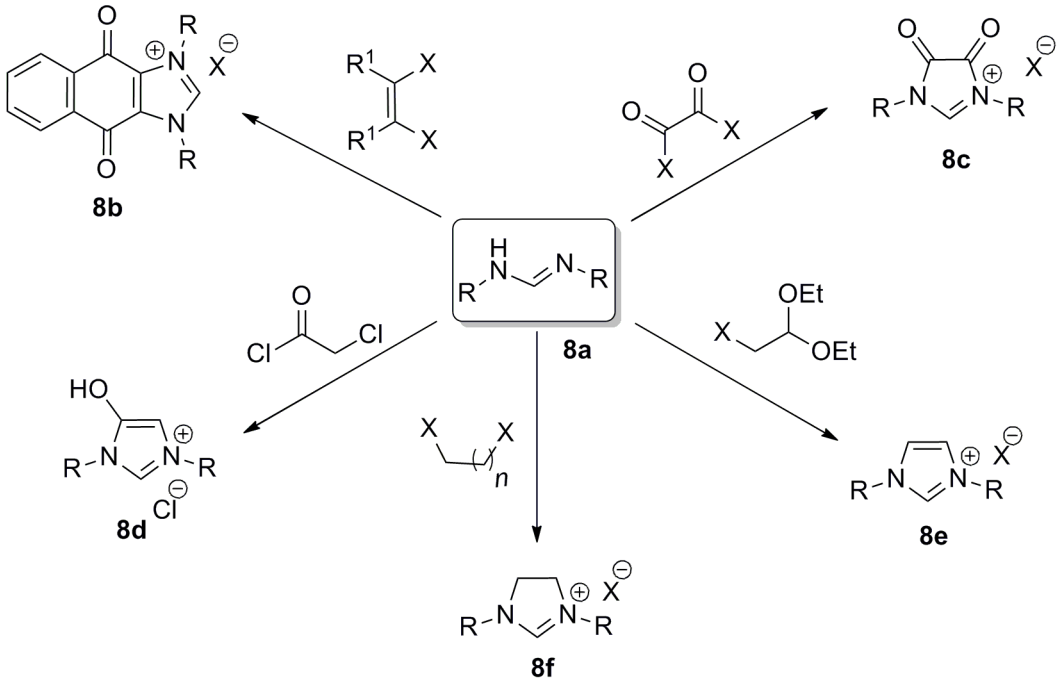
(d). Synthesis of bicyclic triazole based NHC precursor

Smith and co-workers reported a one-pot protocol for the synthesis of triazole core based NHC precursor.[6] In this procedure, a mixture of 2-pyrrolidinone (**7a**) and trimethyloxonium tetrafluoro borate in DCM was stirred to form iminium ether salt *in-situ*, which was treated with phenyl hydrazine followed by cyclization with triethylorthoformate to provide the triazolium based NHC precursor **7b** (Scheme 4).



Scheme 4

(e). Other imidazole based NHC precursors

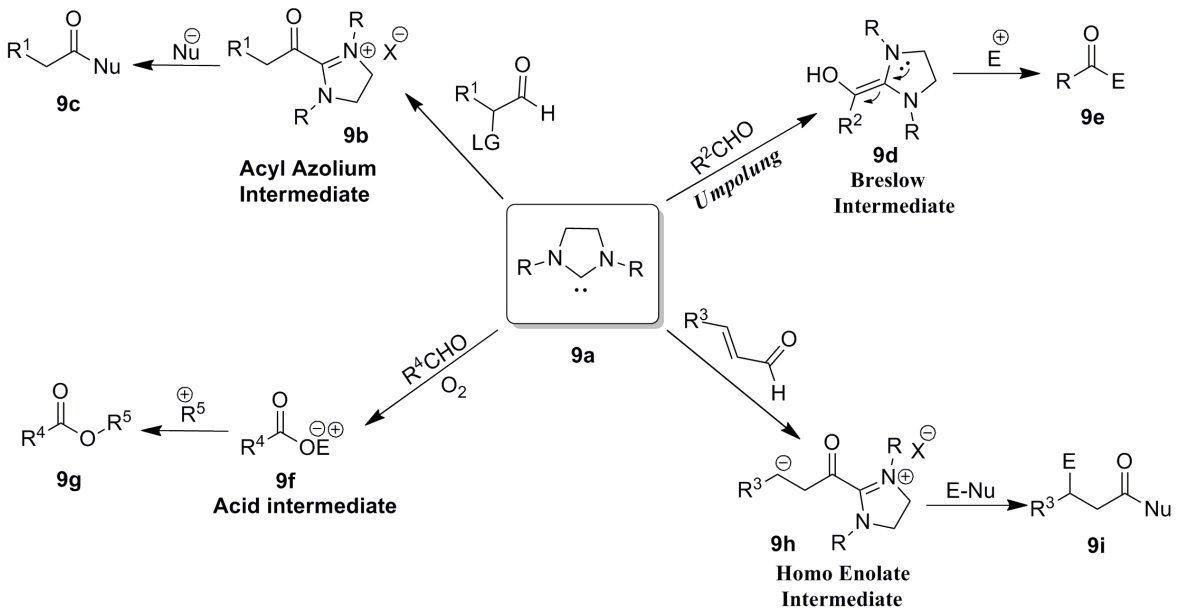


Scheme 5

Several methods have been developed by many research groups for the synthesis of imidazole-based NHC precursors (**8b**–**8f**) through the reactions of formamidines **8a** with various appropriate electrophiles, which are shown in scheme 5.[9]

1.3. NHCs in organocatalysis

Apart from serving as ligands in organometallic chemistry, the catalytic activity of NHCs has also been explored in a wide range of organic transformations.[1c] As a result, in the past two decades, NHC catalyzed transformations have become one of the major sub-areas of organocatalysis. Due to the ability to activate carbonyl compounds through diverse activation modes, NHCs have been employed as catalyst for the development of many new chemical transformations. Some of the activation modes of NHCs are shown in scheme 6.



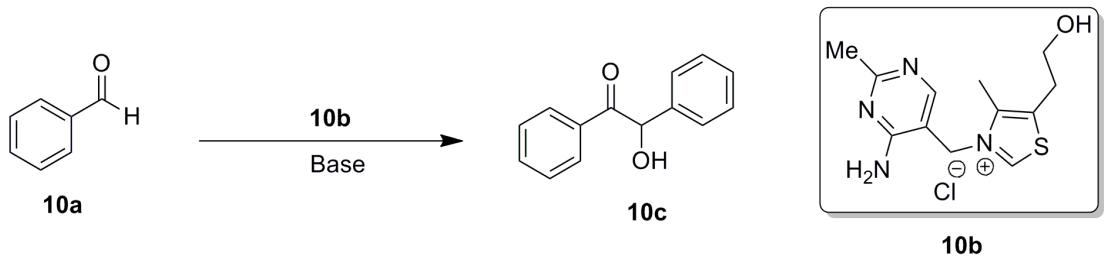
Scheme 6

1.4. Literature review on NHC catalyzed transformations

A few of the N-heterocyclic carbene catalyzed transformations are discussed in this section.

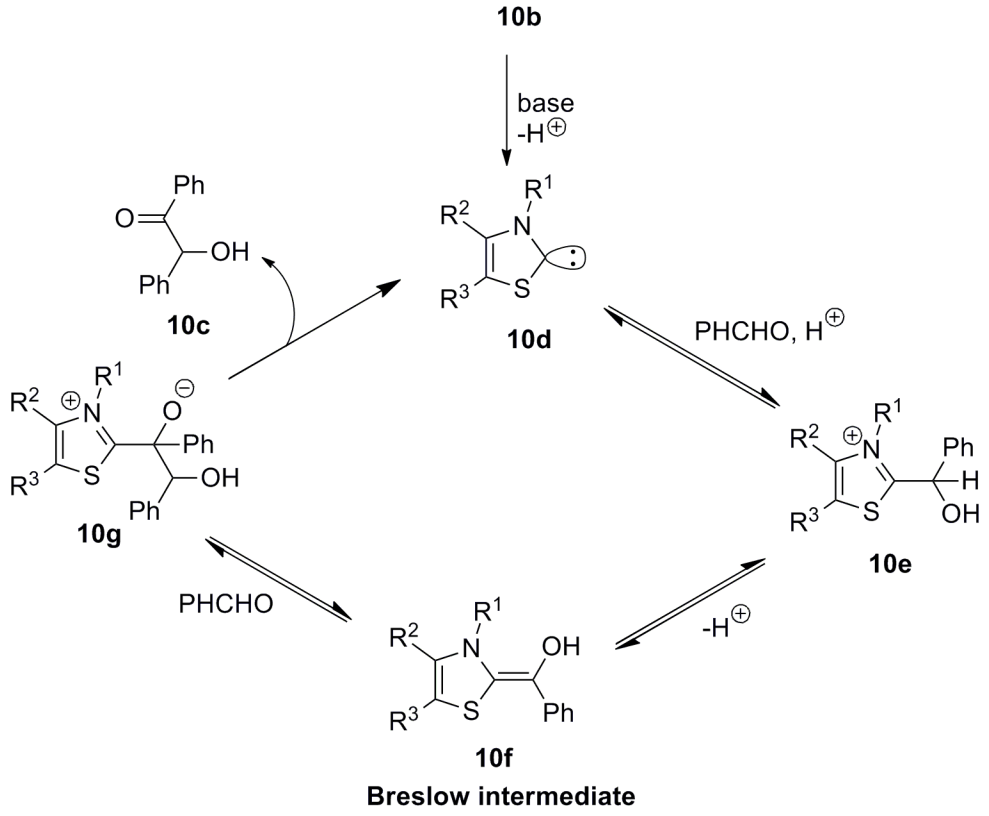
1.4.1. Benzoin reaction

Since the first isolation of stable N-heterocyclic carbenes (NHCs) independently by Arduengo[10a] and Bertrand research groups,[10b] a great interest has been developed among scientists to understand the nature and reactivity of NHCs in the innovation of new chemical transformations. In 1943, Ugai *et al.* discovered that the classical benzoin condensation[11a] was catalyzed by thiamine (**10b**) in the presence of base. However, unfortunately, the mechanism was not well understood at that time. Later, Breslow proposed mechanism[11b] for this transformation which involves acyl anion equivalent (**10f**) and is analogous to the cyanide catalyzed benzoin condensation[12] (Scheme 7).



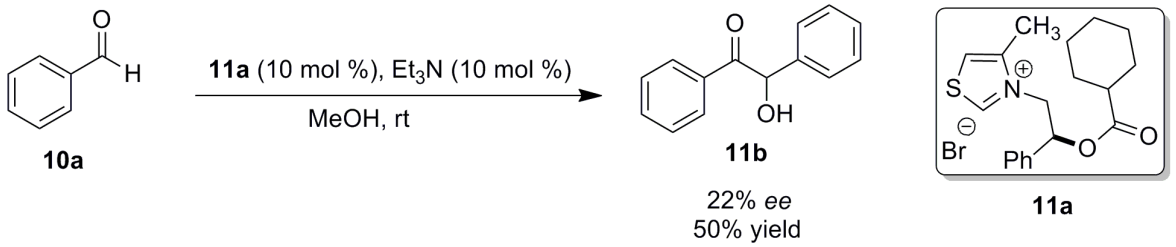
Scheme 7

The Breslow mechanism, which is the most accepted mechanism for this transformation till date, involves the abstraction of the acidic proton from thiamine (**10b**) by a base to generate the nucleophilic carbene **10d**, which reacts with aldehyde **10a** followed by proton migration produces Breslow intermediate (**10f**). The Breslow intermediate and its analogue were recently isolated and characterized by X-ray and NMR analysis by Berkessel and Rovis groups,[13] respectively. Nucleophilic attack of Breslow intermediate (**10f**) to another aldehyde produces another tetrahedral intermediate **10g**, which then decomposes to α-hydroxy ketone **10c** with the expulsion of carbene **10d**. The catalytic cycle of the benzoin condensation is shown in scheme 8.



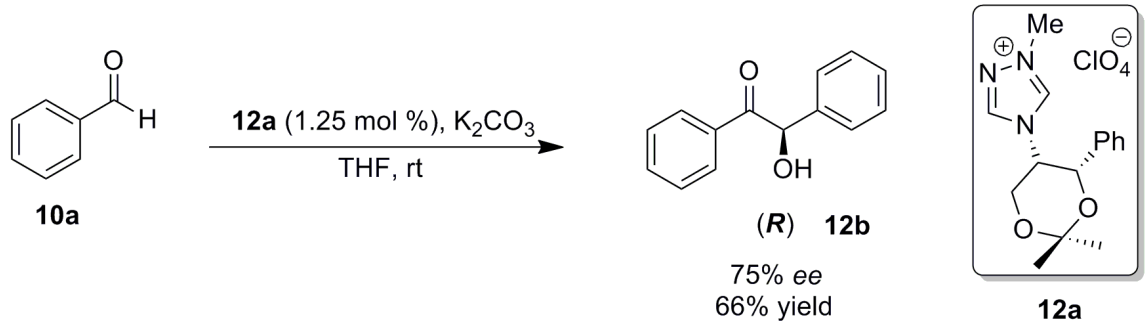
Scheme 8

The first enantioselective benzoin reaction was reported by Sheehan's group in 1966.[14a] A chiral thiazolium based NHC precursor **11a** was used to induce chirality in benzoin, and eventually the benzoin (**11b**) was obtained in a maximum of 22% *ee* (Scheme 9).



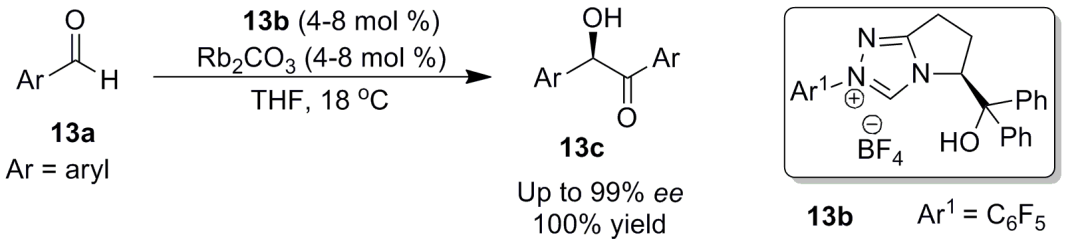
Scheme 9

A few years later, the same research group developed another thiazolium based NHC catalyst for this transformation and, in this case, the *ee* was improved to the maximum of 55%, although the chemical yield of the benzoin was very low (only 6%).[14b] After this seminal contribution by Sheehan's group, several other research groups, modified the catalyst to improve the yield as well as the enantioselectivity of the homo-benzoin products to some extent.[15] The real breakthrough in the asymmetric benzoin reaction was realized after Enders group demonstrated the utility of chiral triazole based NHCs in this reaction.[16] The chiral non-racemic triazolium salt **12a** was found to be the best catalyst for this reaction and the corresponding benzoin (**12b**) was obtained in 66% yield with 75% *ee* (Scheme 10). This discovery laid the foundation for the development of chiral triazolium based NHCs for transformations such as homo-benzoin reaction, cross-acyloin/benzoin reactions, etc.[17–19]



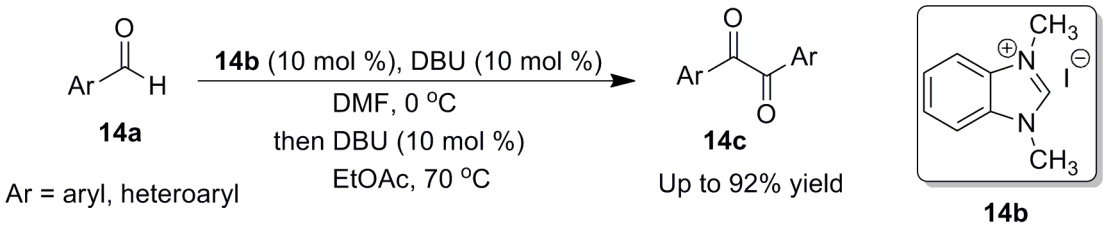
Scheme 10

Connon and co-workers demonstrated an asymmetric benzoin reaction of aryl aldehydes **13a** using a triazolium salt **13b**, which contains a free hydroxyl substituent, as a precatalyst.[20] They also proposed that the hydroxyl group helps in improving the enantioselectivity to a great extent (Scheme 11).



Scheme 11

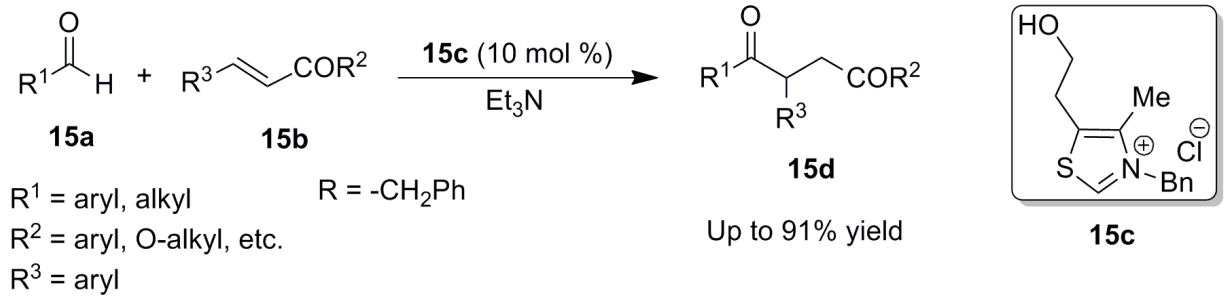
Sakaguchi and co-workers developed a facile one-pot procedure to access the benzils from aldehydes through NHC catalysis.[21] This one-pot method was found to be a versatile method to generate various benzils **14c** from aldehydes **14a** under the optimized reaction conditions. This reaction proceeds *via* an initial benzoin condensation in the presence of catalytic amount of NHC derived from benzimidazolium salt **14b** and DBU at 0 °C, followed by heating the reaction mixture at 70 °C in the presence of DBU, and EtOAc as solvent under air atmosphere, and the corresponding 1,2-diketones **14c** were obtained in good yields (Scheme 12).



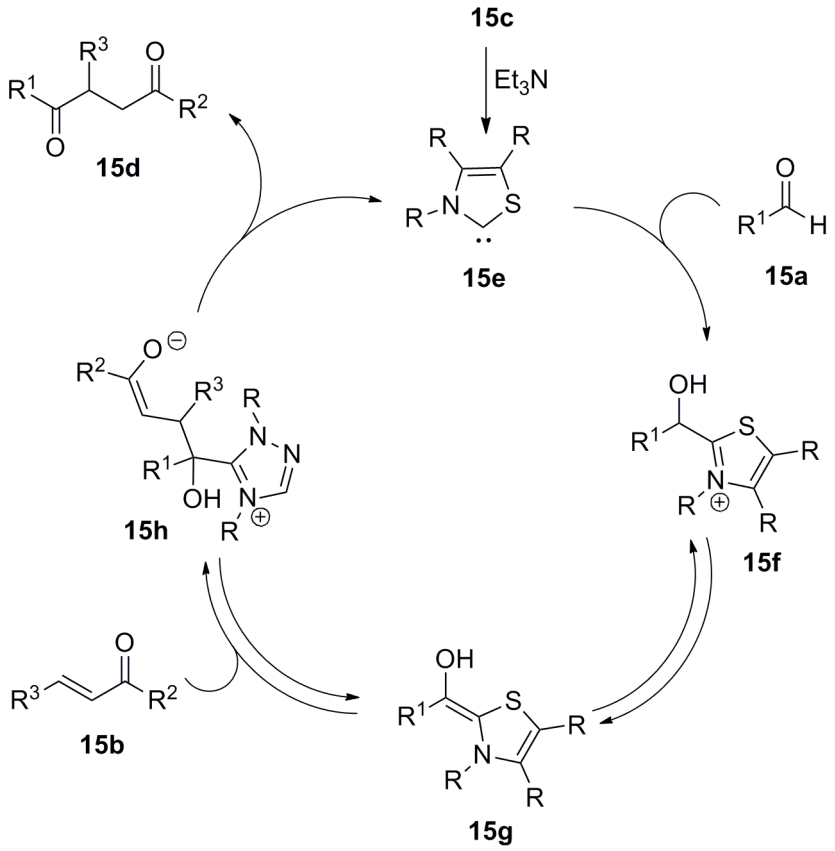
Scheme 12

1.4.2. Stetter reaction

In late 1970s, Stetter and co-workers succeeded in transferring the concept of thiazolium catalyzed acyl anion equivalent addition to an acceptor bearing an activated double bond **15b**, resulting in 1,4-bifunctional molecules **15d** (Scheme 13).[22]



Scheme 13



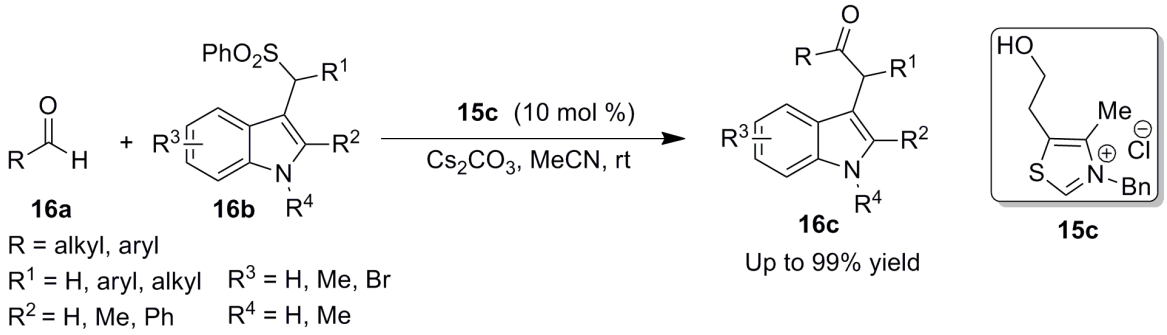
Scheme 14

A possible mechanism has also been proposed for this transformation, which was very close to that of the benzoin reaction. Initially, the carbene **15e** reacts with the aldehyde **15a** and generates the Breslow intermediate (**15g**), which then undergoes a 1,4-addition into a Michael acceptor **15b** to generate the 1,4-dicarbonyl compound **15d** (Scheme 14).

The first asymmetric Stetter reaction was investigated by Enders group using a chiral NHC derived from the corresponding thiazolium salt.[23] Consequently, much efforts has been made for both intramolecular[24] as well as intermolecular[25] Stetter reactions using a variety of achiral/chiral NHCs by employing various Michael acceptors such as α,β-unsaturated ketones, α,β-unsaturated esters, etc. A few NHC catalyzed intermolecular Stetter reactions are discussed in this section.

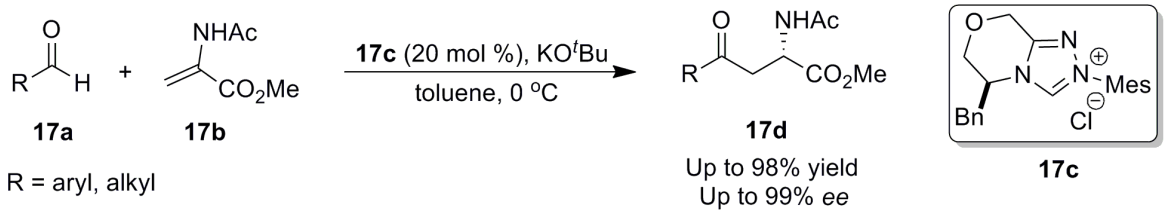
You's group reported the intermolecular Stetter reaction between aldehydes and aryl sulfonyl-indoles using a thiazolium based NHC **15c** as a catalyst.[26] The reaction proceeds *via in-situ* formation of α,β-unsaturated iminium ion from aryl sulfonyl-indoles **16b**, which eventually act

as the Michael acceptor. The 1,4-umpolung addition of aldehyde **16a** to the iminium ion resulted the corresponding indole derivatives **16c** in good yields (Scheme 15).



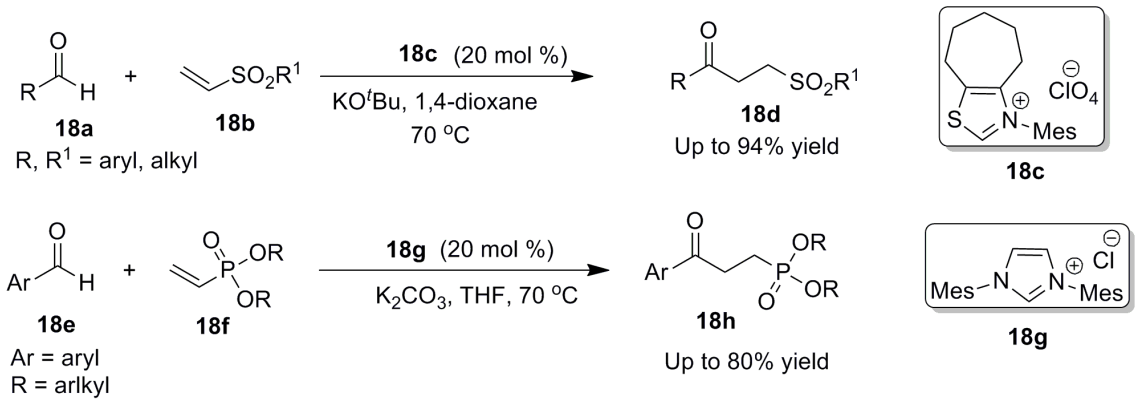
Scheme 15

Recently, Glorius and co-workers developed an NHC **17c** catalyzed highly enantioselective intermolecular Stetter reaction between aryl aldehydes **17a** and methyl 2-acetamido acrylate **17b**.[27] The corresponding unnatural α-amino acid derivatives **17d** were obtained in good yields with excellent enantioselectivity (Scheme 16).



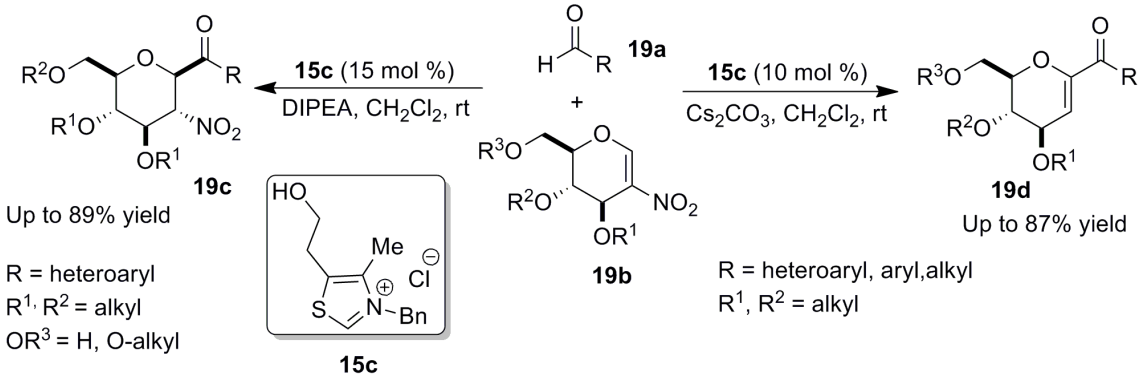
Scheme 16

Biju and co-workers have shown the scope of intermolecular Stetter reaction with other Michael acceptors such as vinyl sulfones and vinyl phosphonates. Using vinyl sulfones **18b** as Michael acceptors, variety of β-sulphonyl ketones **18d** could be accessed through 1,4-addition of umpolung of aldehydes employing the right choice of the NHC precursor **18c** and base.[28a] Biju's group also developed a method to access keto phosphonate derivatives **18h** through Michael reaction aldehydes **18e** with vinyl phosphonates **18f** (Scheme 17).[28b]



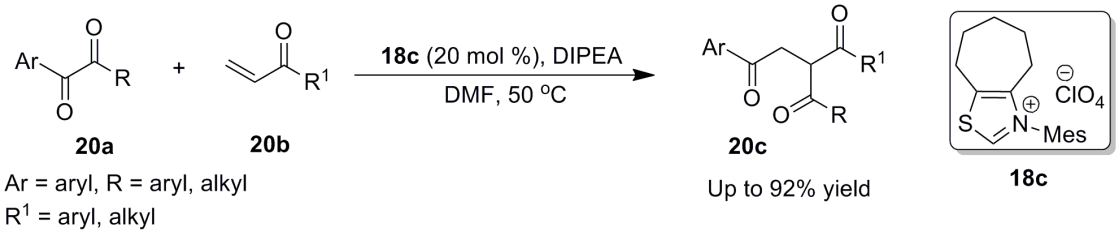
Scheme 17

Another interesting application of NHC catalysis in carbohydrate chemistry has been reported by Liu group which deals the reaction of aldehydes **19a** with 2-nitroglucal **19b** as a Michael acceptor.[29] It was found that the amine bases led to the formation of aldehyde addition products **19c**, whereas the use of carbonate bases resulted in the corresponding enone products **19d** *via* elimination of nitrous acid (Scheme 18).



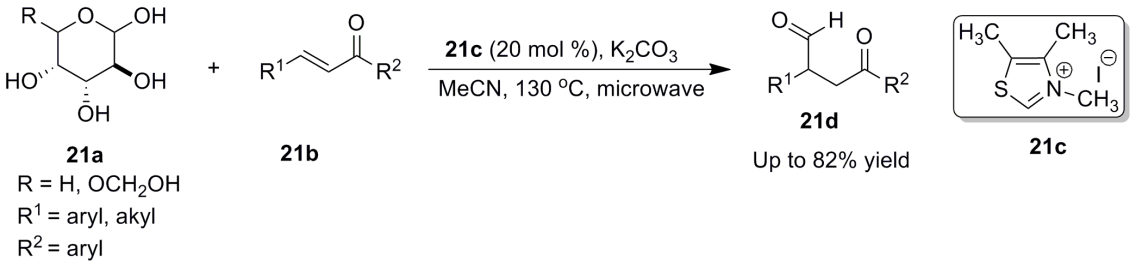
Scheme 18

Very recently, Takaki and co-workers have reported the Stetter reaction, in which benzils were employed as aldehyde equivalents (donors).[30] Thiazole-based NHC **18c** was found to be the best catalyst for the 1,2-double acylation of enones **20b** with aromatic 1,2-diketones **20a** (Scheme 19).



Scheme 19

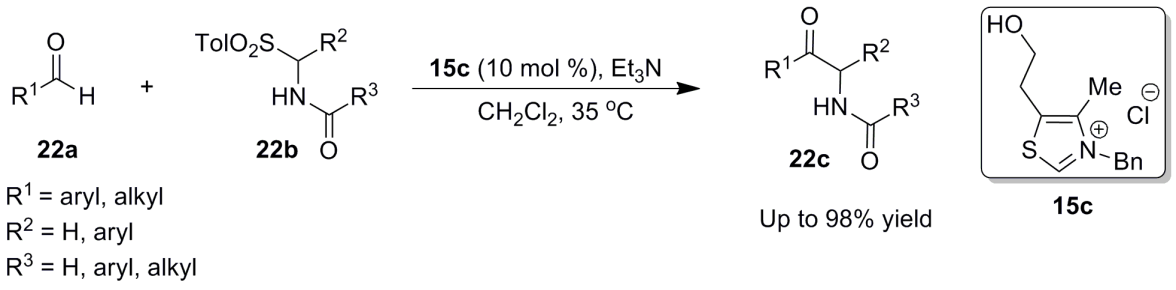
Chi and co-workers have described the NHC catalyzed 1,4-hydroformylation of enones through the activation of carbohydrate to form formaldehyde acylanion equivalents.[31] This reaction proceeds through an initial addition of NHC to the carbohydrate to generate formaldehyde acylanion equivalents, which then undergoes 1,4-addition to the chalcone **21b** to generate the 1,4-dicarbonyl product **21d** (Scheme 20).



Scheme 20

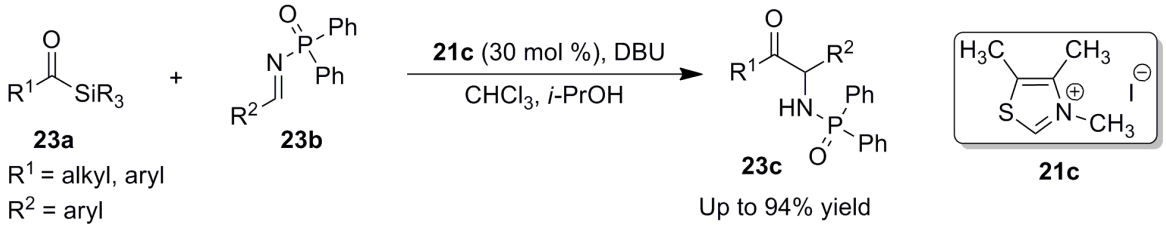
1.4.3. Aza-Benzoin reaction

Imines are also found to be competent coupling partners in intermolecular cross-benzoin condensation, leading to formation of valuable α-amino ketone derivatives. In 2001, Murry, Frantz, and co-workers reported the first NHC catalyzed Aza-benzoin reaction between aldehydes **22a** and *N*-acylimines.[32] These *N*-acylimines were generated *in-situ* from aryl sulfonyl amides **22b**. The proposed mechanism was analogous to that of the benzoin reaction *via in-situ* generation of the Breslow intermediate followed by attack on the *N*-acylimine acceptor (Scheme 21).



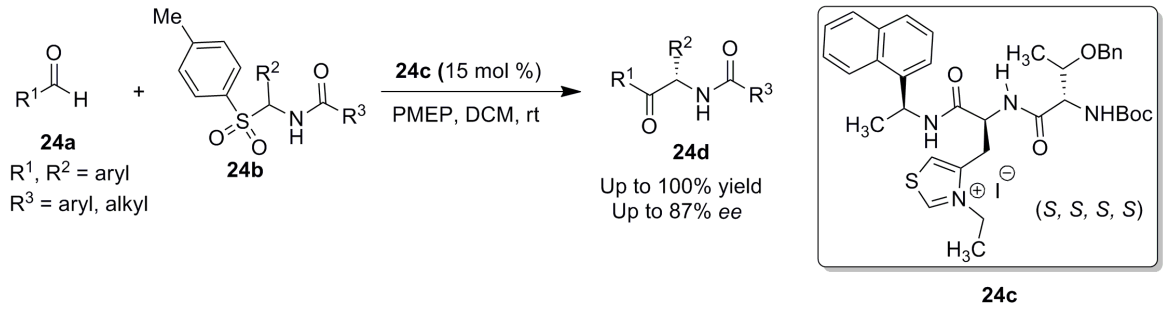
Scheme 21

Another NHC **21c** catalyzed addition of acylsilanes (as aldehyde equivalent) to imines has been developed independently by the groups of Mattson and Scheidt.[33] Under NHC catalyzed conditions, various *N*-phosphinylated amino ketones **23c** were synthesized from the reaction of acylsilanes **23a** with *N*-phosphinylated amines **23b** (Scheme 22).



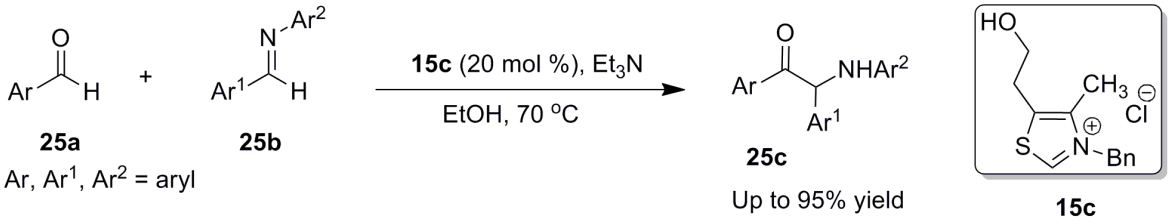
Scheme 22

Miller and co-workers have demonstrated an asymmetric variant of the Aza-benzoin reaction. The NHC derived from chiral peptidic thiazolium salt **24c** was found to be the best catalyst in the presence of pentamethyl piperidine (PEMP) as a base for the reaction between various aldehydes **24a** and aryl sulfonyl amides **24b**, and the corresponding products **24d** were obtained in good yields and good enantioselectivities (Scheme 23).[34]



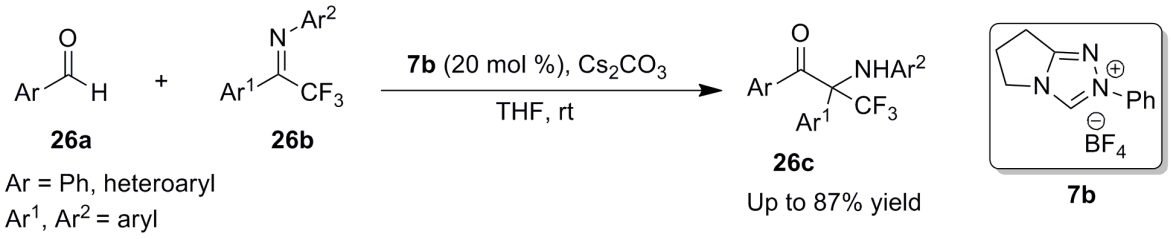
Scheme 23

You and co-workers have successfully shown the coupling of aldehydes with unactivated imines. The cross-coupling reaction was carried out between aldehydes **25a** and imines **25b** using thiazolium salt **15c** as a precatalyst, and the α-keto amines **25c** were formed in good yields (Scheme 24).[35]



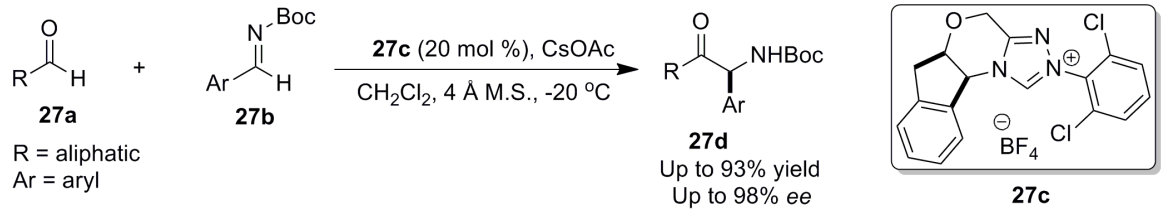
Scheme 24

Enders and coworkers expanded the cross Aza-benzoin reaction using trifluoromethyl ketimine as a coupling partner. By employing an achiral triazolium salt **7b** as a precatalyst, various heteroaromatic aldehydes **26a** combined with trifluoromethyl ketimines **26b** to form the aza-benzoin products **26c** in moderate to good yields (Scheme 25).[36]



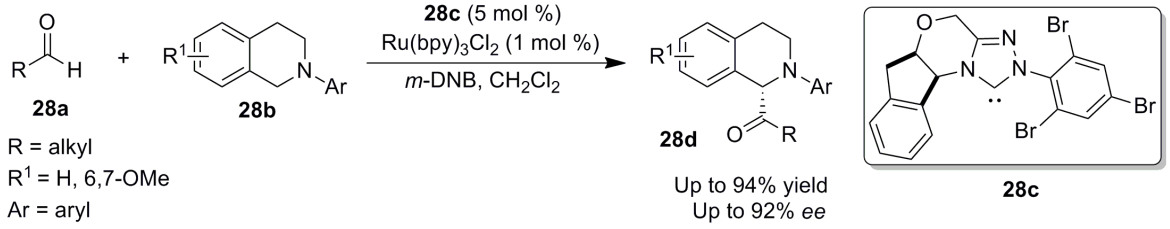
Scheme 25

DiRocco and Rovis described the enantioselective reaction of aliphatic aldehydes **27a** with *N*-Boc imines **27b**.[37] They found that the both straight-chain, as well as branched aliphatic aldehydes, gave the corresponding products **27d** with a high degree of stereo control (Scheme 26).



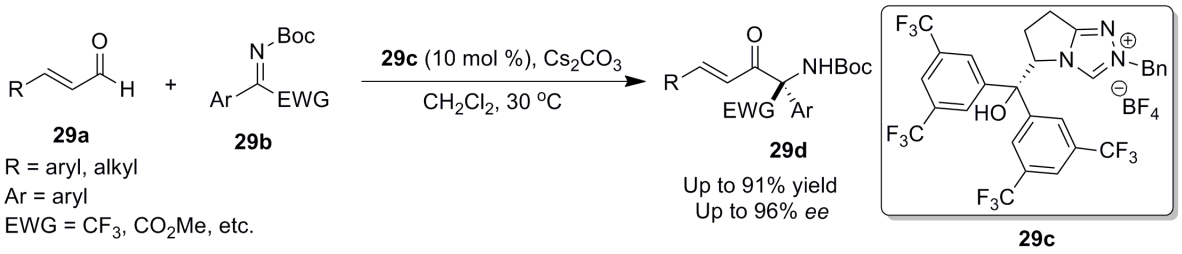
Scheme 26

Recently, Rovis group developed the aza-benzoin reaction between aliphatic aldehydes **28a** and *N*-phenyl tetrahydro isoquinoline derivatives **28b** by combining the NHC catalysis with photo-redox catalysis.[38] Photo-redox catalysis was used to generate highly reactive iminium ion as an electrophile *in-situ* from tertiary amine. The acylated products **28d** were obtained in moderate to good yields with high enantioselectivities (Scheme 27).



Scheme 27

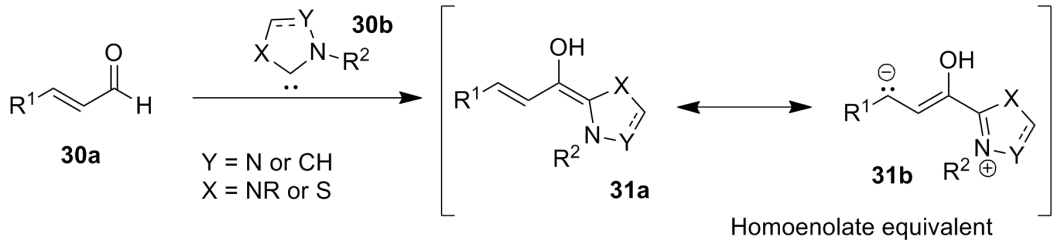
Ye and co-workers have reported NHC catalyzed enantioselective cross coupling of enals with trifluoromethyl ketones and imines.[39] The chiral NHC derived from triazolium salt **29c** was found to be effective for the reaction between various α,β-unsaturated aldehydes **29a** and electron withdrawing groups containing imines **29b**, and the α-aminoacid derivatives **29d** were obtained in good yields with excellent enantioselectivity (Scheme 28).



Scheme 28

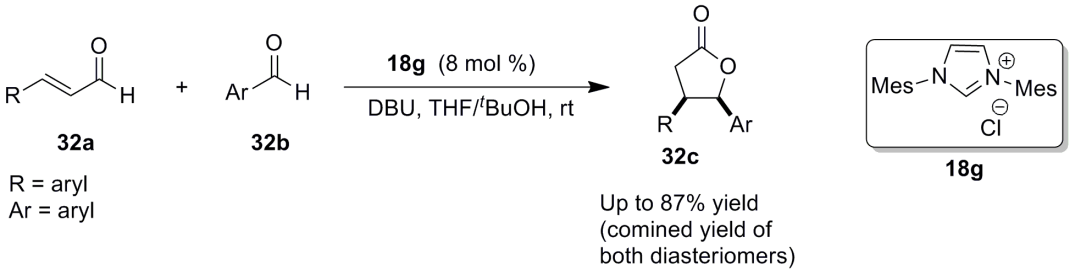
1.4.4. NHC derived homoenolate

It is well documented in the literature that when NHC (**30b**) reacts with an α,β-unsaturated aldehyde **30a**, a conjugated intermediate, which is often called as homoenolate **31b**, will be generated. The conjugation of the system allows the transfer of the nucleophilic properties of the Breslow intermediate to the β-position, thus generating a dipole type system (Scheme 29).

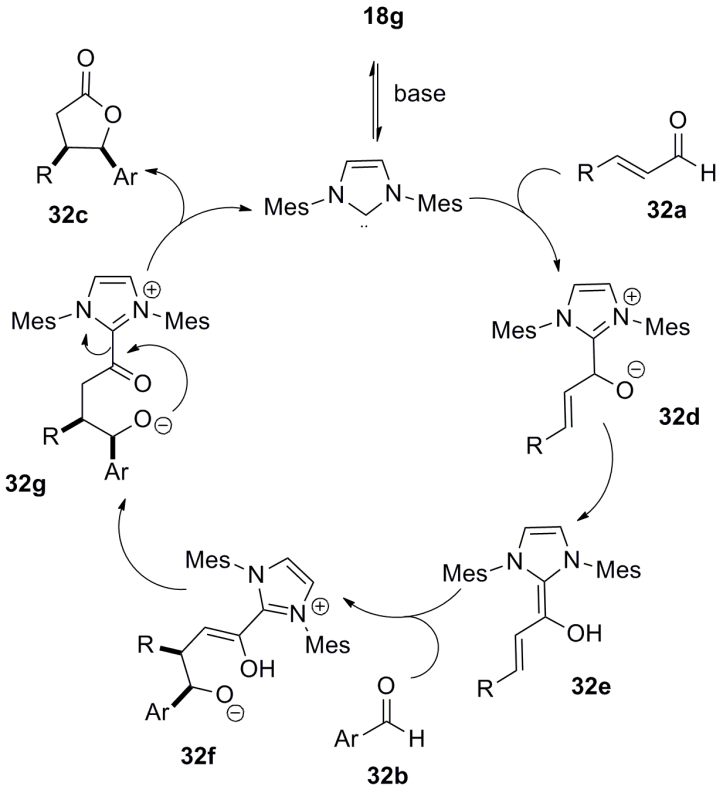


Scheme 29

The research groups Glorius and Bode independently, for the first time, implemented the concept of NHC-catalyzed generation of homoenolate equivalents for the synthesis of γ-lactones through annulation reaction between enals (α,β-unsaturated aldehyde) and aryl aldehydes. After these seminal contributions, many other research groups have successfully applied the homoenolate chemistry in redox reactions, and some of those transformations will be discussed in this section. Bode's and Glorius' protocol involves the coupling of a variety of aryl enals **32a** with aryl aldehydes **32b** using IMes.HCl (**18g**) as a NHC precursor, and the γ-lactones **32c** were obtained in moderate to good yields with good diastereoselectivity (Scheme 30).[40a,b]



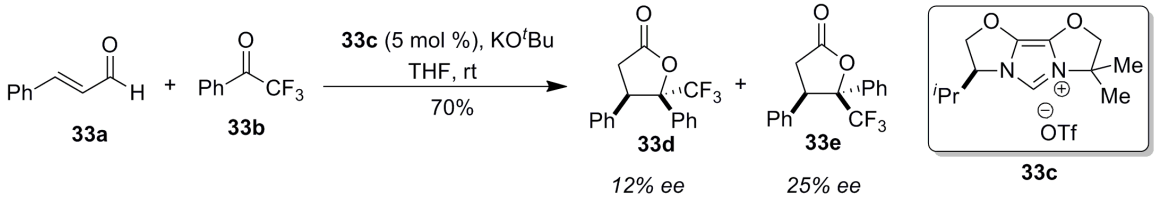
Scheme 30



Scheme 31

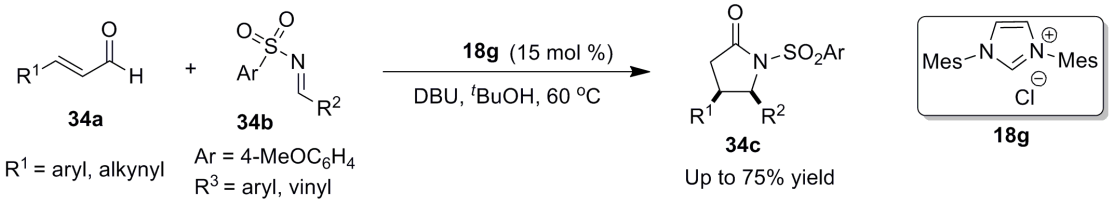
The postulated reaction mechanism proceeds *via* the formation of homoenolate equivalent, which then adds to the aldehyde to generate an acyl azolium intermediate **32g**. The intramolecular nucleophilic attack of the alkoxide anion to the acyl azolium intermediate forms the γ-lactone product **32c** and liberates the carbene catalyst (Scheme 31).

Glorius' group has extended this methodology for the synthesis of trifluoromethyl group containing γ-lactones (**33d & 33e**) from enals **33a** and trifluoromethyl ketones **33b**. His group has also developed an enantioselective version of this transformation using a chiral NHC **33c**.[40c] However, the diastereoselectivity and enantioselectivity of the γ-lactones **33d** and **33e** were very poor (Scheme 32).



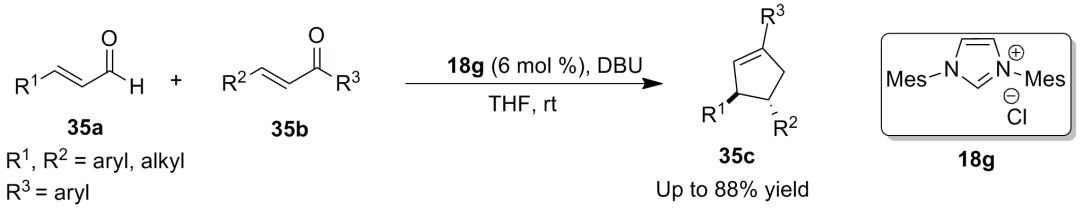
Scheme 32

In 2005, Bode has demonstrated the utility of homoenolate chemistry for the synthesis of nitrogen-containing heterocycles. Under NHC catalyzed conditions, various γ-lactams **34c** were prepared through the [3+2]-cycloaddition of enals **34a** with imines **34b**.[41] The diastereoselectivity in this reaction was found to be moderate to good depending on the substituents (*dr* from 1.7:1 to 10:1). However, the scope of the N-substituted imine **34b** was limited only to a 4-methoxy phenyl sulfonamide (Scheme 33).



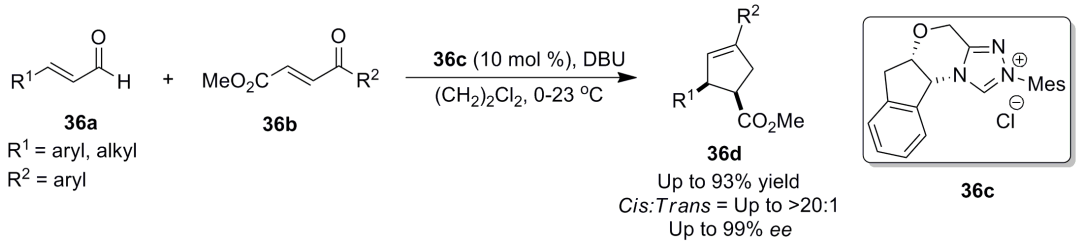
Scheme 33

Another interesting cyclopentannulation methodology was developed by Nair and co-workers employing the homoenolate concept.[42] In this case, IMes.HCl (**18g**) was used as a precursor and under the basic conditions, the homoenolate derived from NHC and enal **35a** reacted smoothly with chalcones **35b** in a highly chemoselective manner and produced 1,3,4-trisubstituted cyclopentenes **35c** in good yields (Scheme 34).



Scheme 34

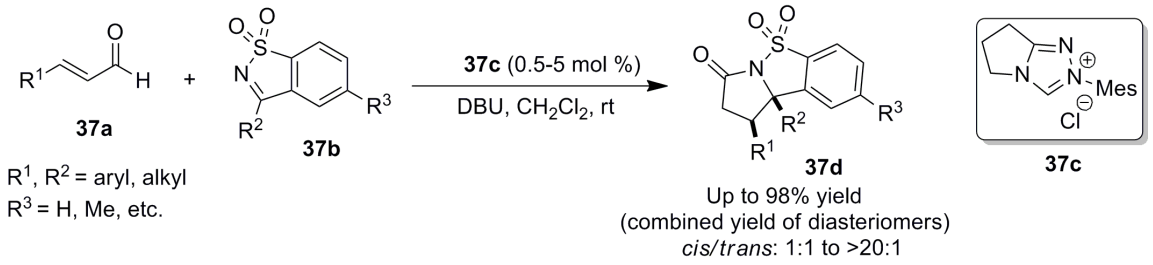
Shortly after the report of Nair's group, Bode and co-workers reported an enantioselective version of the cyclopentannulation reaction of enals with 4-oxoenoates using chiral triazolium salt **36c** as a precatalyst.[43]



Scheme 35

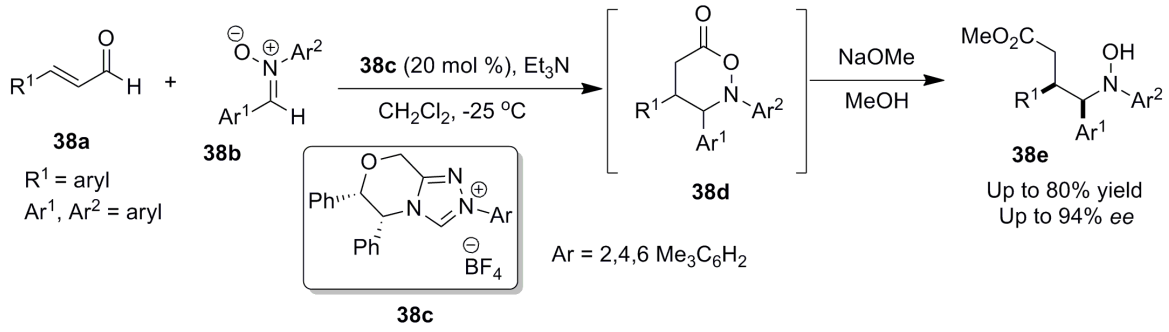
Surprisingly, in contrast to Nair's observation, only cis-substituted cyclopentenes **36d** were obtained with excellent diastereomeric as well as enantiomeric ratios (Scheme 35).

The homoenolate annulation protocol has also been extended to cyclic sulfonyl ketimines **37b** by Bode's group.[44] Triazole-based NHC **37c** was used for this purpose and they could access fused γ-lactams **37d** in good yields with moderate diastereoselectivity (1:1 to >20:1) (Scheme 36).



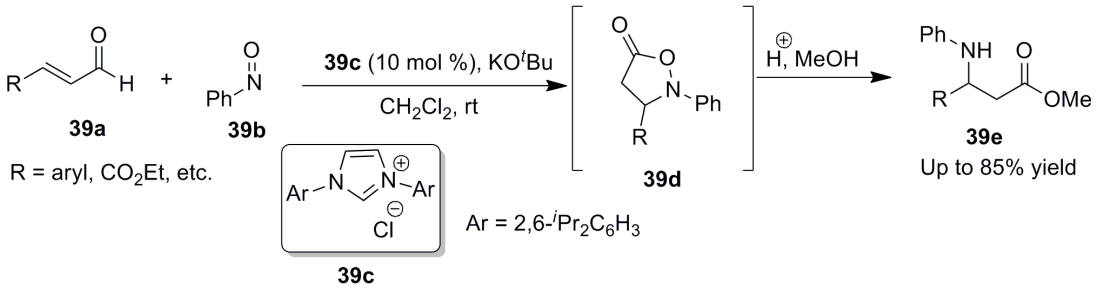
Scheme 36

Scheidt and co-workers utilized the conjugated NHC catalyzed umpolung reaction for the synthesis of enantiomerically pure γ-amino acid derivatives.[45] This reaction proceeds *via* the homoenolate addition to the nitrones **38b** followed by intramolecular cyclization to form **38d**, which then undergoes alcoholysis to generate the γ-amino acid derivatives **38e** (Scheme 37).



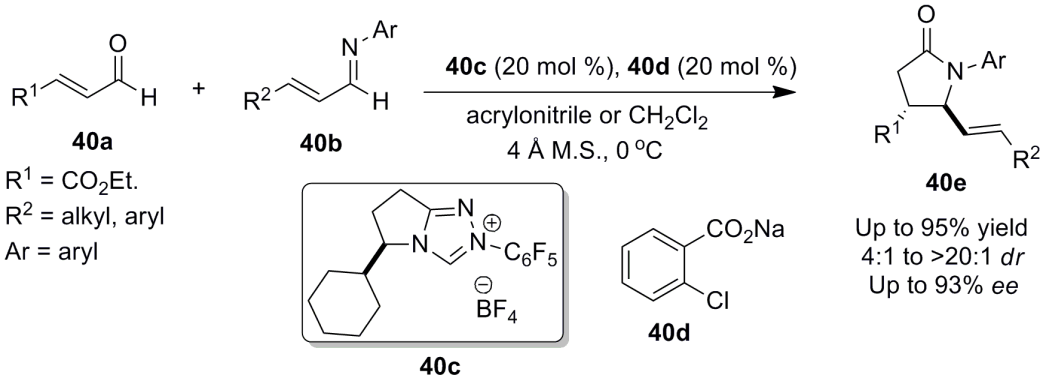
Scheme 37

Ying and co-workers demonstrated that even nitroso compounds **39b** could act as electrophiles in the NHC catalyzed redox reactions.[46] This transformation was employed for the synthesis of isoxazolidinone derivatives **39d** which could be further elaborated to the synthesis of β-amino esters **39e** upon treatment of product **39d** with methanol and acid. A wide range of β-amino acid esters **39e** were obtained in moderate to good yields (Scheme 38).



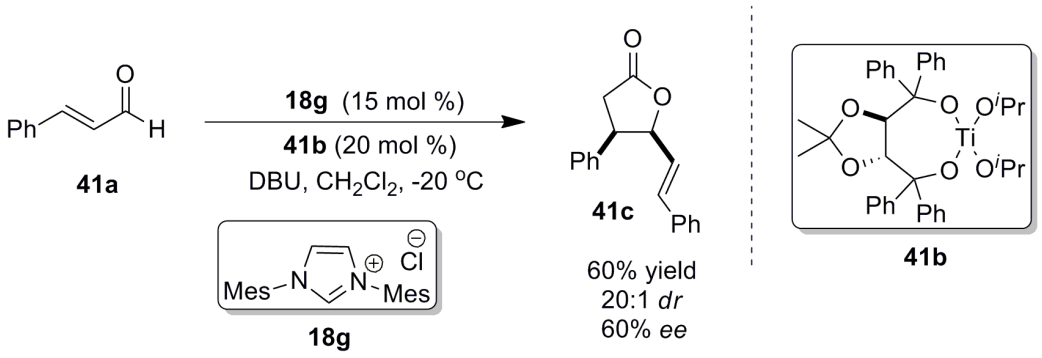
Scheme 38

Rovis and co-workers reported a co-operative NHC/Brønsted acid catalytic system for the synthesis of γ-lactams through cyclization of enals with aza-dienes.[47] A variety of enals **40a** and aza-dienes **40b** derived from α,β-unsaturated aldehydes were reacted in the presence of chiral triazole salt **40c** as NHC precursor, base **40d**, and the corresponding trans-γ-lactams **40e** were obtained in good yields with excellent enantioselectivity (Scheme 39).



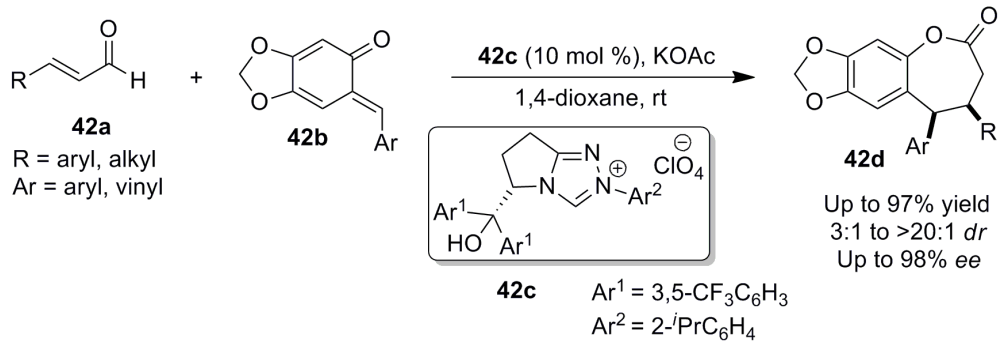
Scheme 39

A different strategy has been employed by Scheidt group for an achiral NHC **18g** catalyzed enantioselective dimerization of cinnamaldehyde (**41a**) to γ-lactone **41c** using Ti-based external chiral Lewis acid **41b**.[48] The diastereoselectivity of cis:trans **41c** was found to be 20:1 and the enantioselectivity of the cis-product was up to the maximum of 60% *ee* (Scheme 40).



Scheme 40

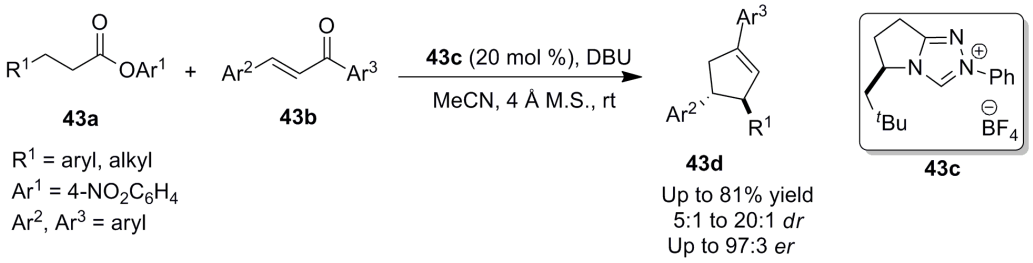
Another method has been developed by Ye and co-workers for an enantioselective formal [3 + 4] annulation of enals **42a** with *o*-quinone methides **42b** through triazole-based NHC **42c** catalysis.[49] Using this method, a variety of 7-membered fused lactones **42d** were obtained with modest to excellent diastereo- and enantioselectivities (Scheme 41).



Scheme 41

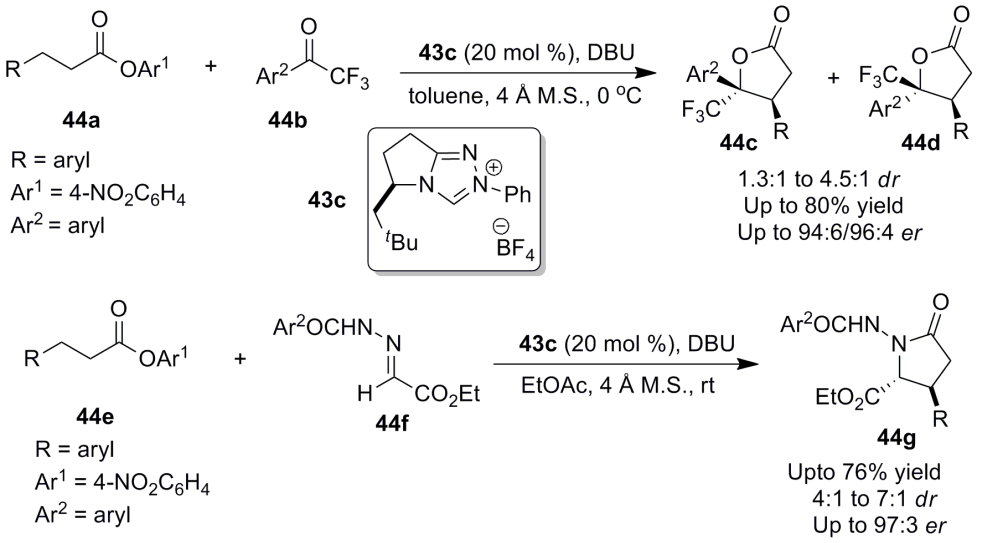
Functionalization of nonreactive β-carbon of a saturated ester:

Recently, Chi and co-workers have shown that it is possible to generate the homoenolate equivalents from the saturated esters as well. Their group developed NHC catalyzed coupling of electron-deficient saturated esters with bis-aryl ketones to get substituted cyclopentene products.[50] By employing a triazole based chiral NHC **43c**, various saturated esters **43a** were treated with bis-aryl ketones **43b**, and the corresponding cyclopentene products **43d** were obtained in moderate to good yields with good diastereo- and enantioselectivities (Scheme 42).



Scheme 42

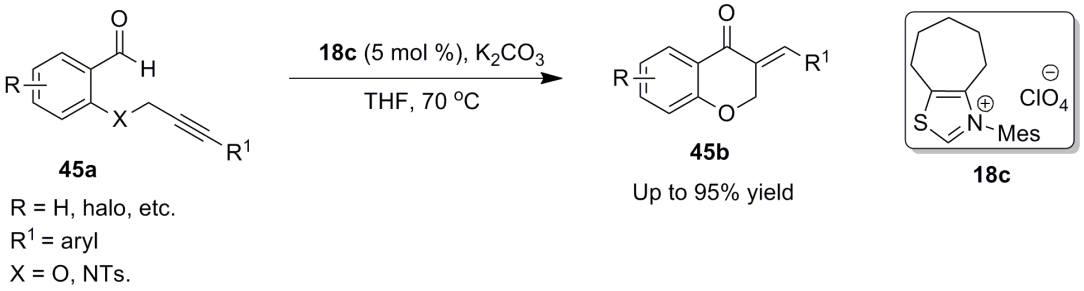
This methodology has also been elaborated to CF_3/aryl ketones **44b** and hydrazones **44f** as electrophiles to furnish γ-lactones (**44c & 44d**) and γ-lactams **44g** respectively, with moderate to good diastereoselectivities and excellent enantioselectivities (Scheme 43).



Scheme 43

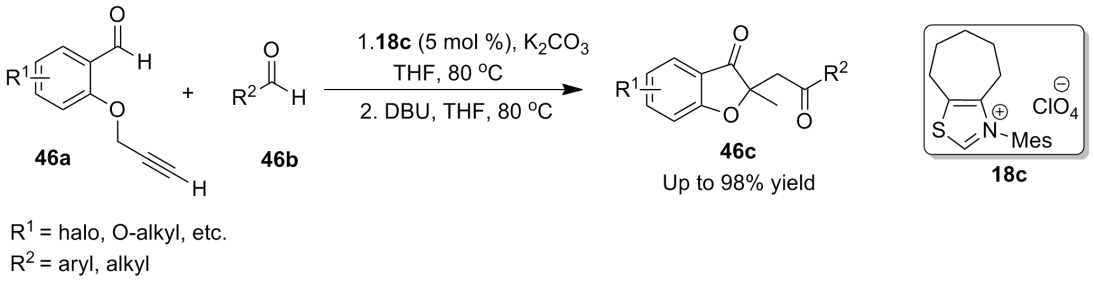
1.4.5. Hydroacylation of double and triple bonds

The acylanion addition reaction has not only been explored with enones but also with unactivated alkynes or olefins as electrophiles. After the initial findings by She and Pan,[51] Glorius and co-workers developed NHC (**18c**) catalyzed intramolecular hydroacylation of unactivated alkynes **45a** to access α,β-unsaturated ketones **45b** with exocyclic alkene in good yields (Scheme 44).[52]



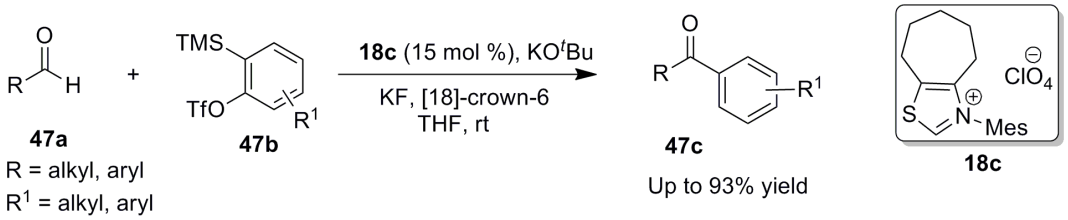
Scheme 44

A similar protocol has been developed by Zeitler and co-workers for the synthesis of benzofuranones **46c** through an one-pot cascade process, by combining the NHC catalysis with simple base catalysis.[53] The reaction sequence involves hydroacylation/Stetter reaction followed by a retro-Michael, 1,3-H shift and finally oxa-Michael cascade rearrangement promoted by DBU (Scheme 45).



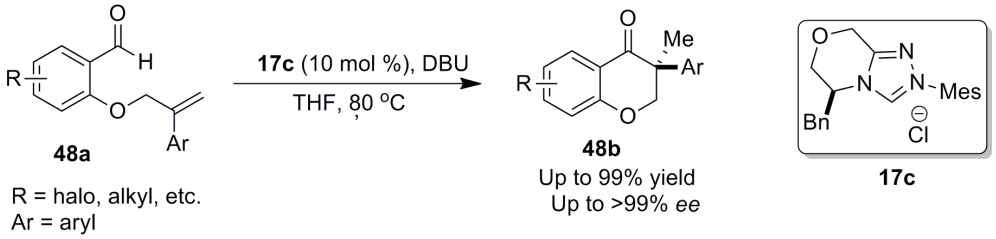
Scheme 45

In addition to the intramolecular hydroacylation, the intermolecular version has also been developed by Glorius and co-workers.[54] His group demonstrated the NHC **18c** catalyzed coupling of aldehydes **47a** with arynes derived from their precursors **47b** leading to corresponding ketones **47c** (Scheme 46).



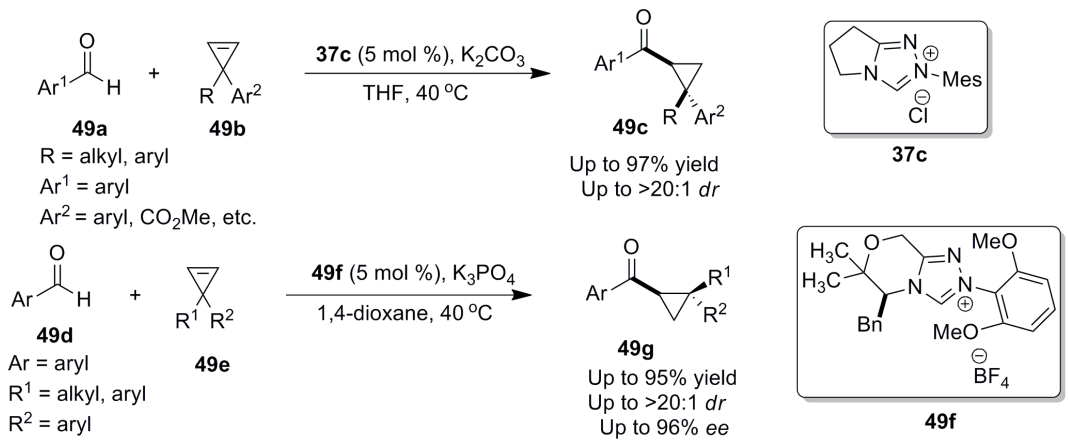
Scheme 46

Later, Glorius' group also reported a chiral triazolium based NHC **17c** catalyzed enantioselective intramolecular hydroacylation of tethered styrenes **48a**, resulting in the chromonone products **48b** in good yields with excellent selectivity (Scheme 47).[55]



Scheme 47

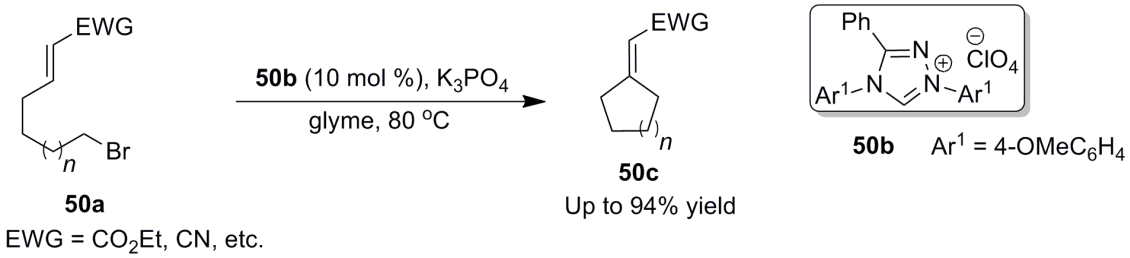
Shortly thereafter, achiral triazole-based NHC **37c** catalyzed hydroacylation of cyclopropenes **49c** has been reported by Glorius and co-workers.[56] This protocol has been further elaborated to an enantioselective version as well. Using a chiral triazolium based NHC **49f**, the expected cyclopropyl ketones **49g** were obtained in excellent enantioselectivities (Scheme 48).



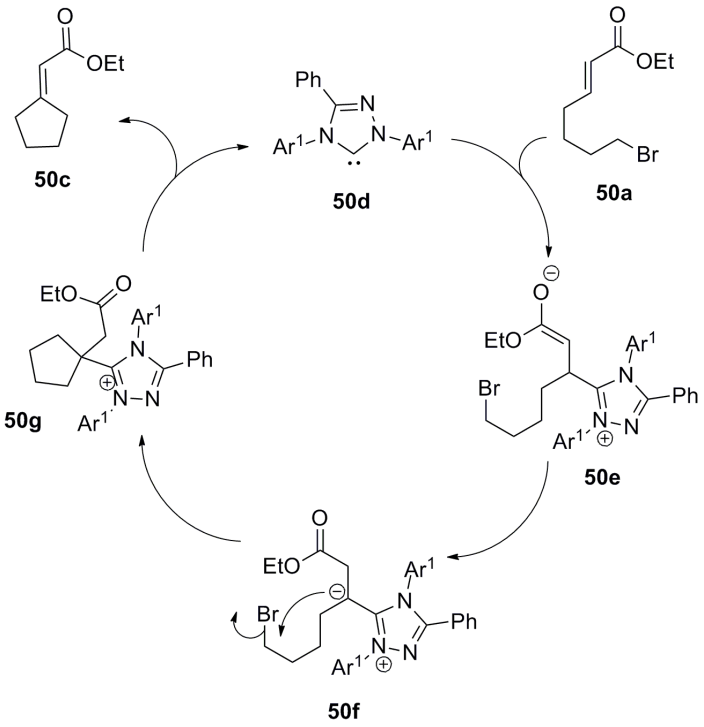
Scheme 48

1.4.6. Umpolung of Michael Acceptors

The conjugate addition of the NHC to Michael acceptors has also been reported to result in β-functionalization. In 2006, Fu and co-workers demonstrated an intramolecular Heck-type cyclization with alkyl halides **50a** through NHC catalysis **50b** (Scheme 49).[57] The proposed mechanism proceeds through an initial addition of NHC to Michael acceptor **50a** to generate a formal deoxy-Breslow intermediate, followed by intramolecular alkylation then removal of the proton to generate the carbene and product **50c** (Scheme 50).

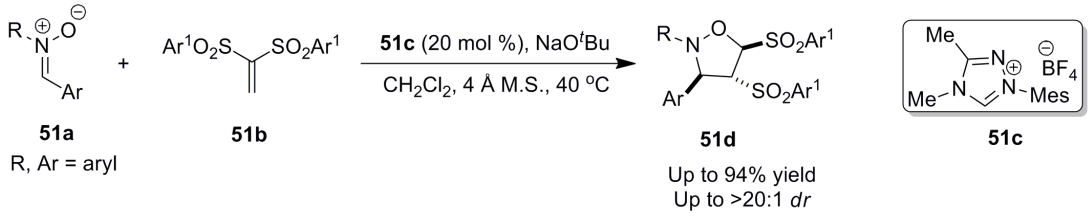


Scheme 49



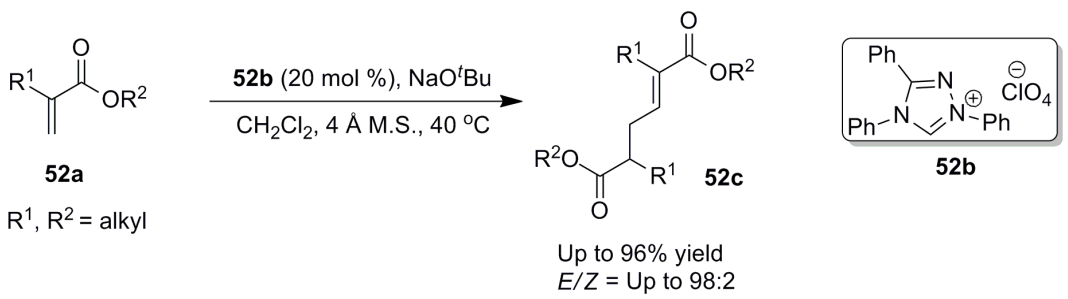
Scheme 50

Scheidt and co-workers utilized vinyl sulfones **51b** as a Michael acceptor to generate deoxy-Breslow intermediate followed by cyclization with nitrones **51a** to give isoxazolines **51d**.[58] Interestingly, only one diastereomer was generated (measured by ^{1}H NMR) under the employed reaction conditions (Scheme 51).



Scheme 51

The dimerization of acrylates **52a** under NHC **52b** catalyzed conditions has been reported independently by Matsuoka and Glorius (Scheme 52).[59] After these seminal contributions, several methodologies have been developed for the β-coupling of acrylates to form dimers, trimers, and tetramers. This reactivity has also been exploited in polymerization reactions.[60]



Scheme 52

1.5. References

[1] (a) Tomioka, H. *Acc. Chem. Res*. **1997,** *30*, 315. (b) Bourissou, D.; Guerret, O.; Gabbaï, F. P.; Bertrand, G. *Chem. Rev*. **2000**, *100*, 39 and references therein. (c) For an overview of N-heterocyclic carbenes, see: (i) Enders, D.; Niemeier, O.; Henseler, A. *Chem. Rev.* **2007**, *107*, 5606. (ii) Biju, A. T.; Kuhl, N.; Glorius, F. *Acc. Chem. Res*. **2011**, *44*, 1182. (iii) Nair, V.; Menon, R. S.; Biju, A. T.; Sinu, C. R.; Paul, R. R.; Jose, A.; Sreekumar, V. *Chem. Soc. Rev*. **2011**, *40*, 5336. (iv) Campbell, C. D.; Ling, K. B.; Smith, A. D. In *N-Heterocyclic Carbenes in Transition Metal Catalysis and Organocatalysis*, Vol. 32; Cazin, C. S. J., Ed.; Springer; Dordrecht, 2011; p 262. (v) Mahatthananchai, J.; Bode, J. W. *Acc. Chem. Res*. **2013**, *47*, 696. (vi) Nelson, D. J.; Nolan, S. P. *Chem. Soc. Rev.* **2013**, *42*, 6723. (vii) Ryan, S. J.; Candish, L.; Lupton, D. W. *Chem. Soc. Rev*. **2013**, *42*, 4906. (viii) O'Bryan, E. A.; Scheidt, K. A. "Acyloin Coupling Reactions," in *Comprehensive Organic Synthesis II.* Vol 3; Marek, I., Knochel, P. Eds.; 2014; p 621. (ix) Flanigan, D. M.; Romanov-Michailidis, F.; White, N. A.; Rovis, T. *Chem. Rev*. **2015**, *115*, 9307.

[2] (a) Wanzlick, H. W.; Kleiner, H. J. *Angew. Chem.* **1961**, *73*, 493. (b) Wanzlick, H. W. *Angew. Chem., Int. Ed.* **1962**, *1*, 75. (c) Wanzlick, H. W.; Esser, F.; Kleiner, H. J. *Chem. Berr.* **1963**, *96*, 1208. (d) Herrmann, W. A. *Angew. Chem., Int. Ed.* **2002**, *41*, 1290. (e) Perry, C. M.; Burgess, K. *Tetrahedron Asymmetry* **2003**, *14*, 951. (f) Díez-González, S.; Marion, N.; Nolan, S. P. *Chem. Rev.* **2009,** *109*, 3612.

[3] (a) Weskamp, T.; Schattenmann, W. C.; Spiegler, M.; Herrmann, W. A. *Angew. Chem., Int. Ed.* **1998**, *37*, 2490. (b) Özdemir, I.; Denizci, A.; Öztürk, H. T.; Cetinkaya, B. *Appl. Organometal. Chem.* **2004**, *18*, 318. (c) Nasielski, J.; Hadei, N.; Achonduh, G.; Kantchev, E. S. B.; O'Brien, C. J.; Lough, A.; Organ, M. G. *Chem.—Eur. J.* **2010**, *16*, 10844.

[4] (a) Arduengo, A. J. U. S. Patent 5, **1991,** 077, 414. (b) Hintermann, L. *Beilstein J. Org. Chem.* **2007**, *3*, 1.

[5] Arduengo, III, A. J.; Krafczyk, R.; Schmutzler, R. *Tetrahedron* **1999**, *55*, 14523.

[6] Thomson, J. E.; Campbell, C. D.; Concellon, C.; Duguet, N.; Rix, K.; Slawin, A. M. Z.; Smith, A. D. *J. Org. Chem.* **2008**, *73*, 2784.

[7] Zhao, H.; Foss, Jr, F. W.; Breslow, R. *J. Am. Chem. Soc.* **2008**, *130*, 12590.

[8] Kamijo, S.; Yamamoto, Y. *Chem.—Asian J.* **2007**, *2*, 568.

[9] (a) Bertogg, A.; Camponovo, F.; Togni, A. *Eur. J. Inorg. Chem.* **2005**, 347. (b) Sanderson, M. D.; Kamplain, J. W.; Bielawski, C. W. *J. Am. Chem. Soc.* **2006**, *128*, 16514. (c) Jazzar, R.; Liang, H.; Donnadieu, B.; Bertrand, G. *J. Organomet. Chem.* **2006**, *691*, 3201. (d) Kuhn, K. M.; Grubbs, R. H. *Org. Lett.* **2008**, *10*, 2075. (e) César, V.; Lugan, N.; Lavigne, G. *J. Am. Chem. Soc.* **2008**, *130*, 11286. (f) Benhamou, L.; César, V.; Gornitzka, H.; Lugan, N.; Lavigne, G. *Chem. Commun.* **2009**, 4720.

[10] (a) Arduengo, A. J., III; Harlow, R. L.; Kline, M. *J. Am. Chem. Soc.* **1991**, *113*, 361. (b) Igau, A.; Grutzmacher, H.; Baceiredo, A.; Bertrand, G. *J. Am. Chem. Soc.* **1988**, *110*, 6463.

[11] (a) Ugai, T.; Tanaka, S.; Dokawa, S. *J. Pharm. Soc. Jpn*. **1943**, *63*, 296. (b) Breslow, R. *J. Am. Chem. Soc.* **1958**, *80*, 3719.

[12] (a) Wöhler, F.; Liebig, J. *Ann. Pharm.* **1832**, *3*, 249. (b) Lapworth, A. *J. Am. Chem. Soc.* **1903**, *83*, 995.

[13] (a) Berkessel, A.; Elfert, S.; Yatham, V. R.; Neudörfl, J.-M.; Schlörer, N. E.; Teles, J. H. *Angew. Chem., Int. Ed.* **2012**, *51*, 12370. (b) DiRocco, D. A.; Oberg, K. M.; Rovis, T. *J. Am. Chem. Soc.* **2012**, *134*, 6143.

[14] (a) Sheehan, J. C.; Hunnemann, D. H. *J. Am. Chem. Soc.* **1966**, *88*, 3666. (b) Sheehan, J. C.; Hara, T. *J. Org. Chem.* **1974**, *39*, 1196.

[15] (a) Tagaki, W.; Tamura, Y.; Yano, Y. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 478. (b) Zhao, C.; Chen, S.; Wu, P.; Wen, Z. *Huaxue Xuebao* **1988**, *46*, 784. (c) Martí, J.; Castells, J.; LópezCalahorra, F. *Tetrahedron Lett.* **1993**, *34*, 521. (d) Dvorak, C. A.; Rawal, V. H. *Tetrahedron Lett.* **1998**, *39*, 2925.

[16] Enders, D.; Breuer, K.; Teles, J. H. *Helv. Chim. Acta.* **1996**, *79*, 1217.

[17] (a) Knight, R. L.; Leeper, F. J. *Tetrahedron Lett.* **1997**, *38*, 3611. (b) Gerhard, A. U.; Leeper, F. J. *Tetrahedron Lett.* **1997**, *38*, 3615. (c) Demir, A. S.; Pohl, M.; Janzen, E.;

Müller, M. *J. Chem. Soc., Perkin Trans.* **2001,** *1*, 633. (d) Iwamoto, K.-I.; Hamaya, M.; Hashimoto, N.; Kimura, H.; Suzuki, Y.; Sato, M. *Tetrahedron Lett.* **2006**, *47*, 7175. (e) Baragwanath, L.; Rose, C. A.; Zeitler, K.; Connon, S. J. *J. Org. Chem.* **2009**, *74*, 9214. (f) Mao, H.; An, S. L.; Kim, S. M.; Yang, J. W. *Bull. Korean Chem. Soc.* **2011**, *32*, 4408.

[18] (a) Stetter, H.; Schreckenberg, M. *Angew. Chem., Int. Ed.* **1973**, *12*, 81. (b) Böhler, P.; Tamm, C. *Fortschr. Chem. Org. Naturst.* **1981**, *40*, 105. (c) Hachisu, Y.; Bode, J. W.; Suzuki, K. *Ad*v. *Synth. Catal.* **2004**, *346*, 1097. (d) Kerr, M. S.; Read de Alaniz, J.; Rovis, T. *J. Org. Chem.* **2005**, *70*, 5725. (e) Takikawa, H.; Hachisu, H.; Bode, J. W.; Suzuki, K. *Angew. Chem., Int. Ed.* **2006**, *45*, 3492. (f) Enders, D.; Niemeier, O.; Raabe, G. *Synlett* **2006**, 2431.

[19] (a) Matsumoto, T.; Ohishi, M.; Inoue, S. *J. Org. Chem*. **1985**, *50*, 603. (b) Dünkelmann, P.; Kolter-Jung, D.; Nitsche, A.; Demir, A. S.; Siegert, P.; Lingen, B.; Baumann, M.; Pohl, M.; Müller, M. *J. Am. Chem. Soc*. **2002**, *124*, 12084. (c) Enders, D.; Grossmann, A.; Fronert, J.; Raabe, G. *Chem. Commun*. **2010**, *46*, 6282. (d) Kuhl, N.; Glorius, F. *Chem. Commun*. **2011**, *47*, 573. (e) Jin, M. Y.; Kim, S. M.; Han, H.; Ryu, D. H.; Yang, J. W. *Org. Lett*. **2011**, *13*, 880. (f) Rose, C. A.; Gundala, S.; Fagan, C.-L.; Franz, J. F.; Connon, S. J.; Zeitler, K. *Chem. Sci*. **2012**, *3*, 735. (g) Langdon, S. M.; Wilde, M. M. D.; Thai, K.; Gravel, M. *J. Am. Chem. Soc*. **2014**, *136*, 7539.

[20] Baragwanath, L.; Rose, C. A.; Zeitler, K.; Connon, S. J. *J. Org. Chem.* **2009**, *74*, 9214.

[21] Shimakawa, Y.; Morikawa, T.; Sakaguchi, S. *Tetrahedron Lett.* **2010**, *51*, 1786.

[22] Stetter, H.; Kuhlmann, H. *Chem. Ber*. **1976**, *109*, 2891.

[23] Enders, D.; Breuer, K.; Raabe, G.; Runsink, J.; Teles, J. H.; Melder, J.-P.; Ebel, K.; Brode, S. *Angew. Chem., Int. Ed. Engl.***1995**, *34*, 1021.

[24] (a) Ciganek, E. *Synthesis* **1995**, 1311. (b) Kerr, M. S.; Read de Alaniz, J.; Rovis, T. *J. Am Chem. Soc.* **2002**, *124*, 10298. (c) Hachisu, Y.; Bode, J. W.; Suzuki, K. *J. Am. Chem. Soc.* **2003**, *125*, 8432. (d) Nakamura, T.; Hara, O.; Tamura, T.; Makino, K.; Hamada, Y. *Synlett* **2005**, 155. (e) Mennen, S. M.; Blank, J. T.; Tran-Dubé, M. B.; Imbriglio, J. E.; Miller, S. J. *Chem. Commun.* **2005**, 195. (f) Matsumoto, Y.; Tomoika, K. *Tetrahedron Lett.* **2006**, *47*, 5843. (g) Zeitler, K.; Mager, I. *Adv. Synth. Catal.* **2007**, *349*, 1851. (h) McErlean, C. S. P.; Willis, A. C. *Synlett* **2009**, 233. (i) Rong, Z.-Q.; Li, Y.; Yang, G.-Q.; You, S.-L. *Synlett*

2011, 1033. (j) Jia, M.-Q.; Li, Y.; Rong, Z.-Q.; You, S.-L. *Org. Biomol. Chem.* **2011**, *9*, 2072. (k) Wang, Z.; Yu, Z.; Wang, Y.; Shi, D. *Synthesis* **2012**, 1559.

[25] (a) Stetter, H.; Lorenz, G. *Chem. Ber.* **1985**, *118*. 1115. (b) Linghu, X.; Johnson, J. S. *Angew. Chem., Int. Ed.* **2003**, *42*, 2534. (c) Mattson, A. E.; Bharadwaj, A. R.; Scheidt, K. A. *J. Am. Chem. Soc.* **2004**, *126*, 2314. (d) Linghu, X.; Bausch, C. C.; Johnson, J. S. *J. Am. Chem. Soc.* **2005**, *127*, 1833. (e) Myers, M. C.; Bharadwaj, A. R.; Milgram, B. C.; Scheidt, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 14675. (f) Mattson, A. E.; Bharadwaj, A. R.; Zuhl,A. M.; Scheidt, K. A. *J. Org. Chem.* **2006**, *71*, 5715. (g) Mattson, A. E.; Zuhl, A. M.; Reynolds, T. E.; Scheidt, K. A. *J. Am. Chem. Soc.* **2006**, *128*, 4932.

[26] Li, Y.; Shi, F.-Q.; He, Q.-L.; You, S.-L. *Org. Lett.* **2009**, *11*, 3182.

[27] Jousseaume, T.; Wurz, N. E.; Glorius, F. *Angew. Chem., Int. Ed.* **2011**, *50*, 1410.

[28] (a) Bhunia, A.; Yetra, S. R.; Bhojgude, S. S.; Biju, A. T. *Org. Lett.* **2012**, *14*, 2830. (b) Patra, A.; Bhunia, A.; Biju, A. T. *Org. Lett.* **2014**, *16*, 4798.

[29] Vedachalam, S.; Tan, S. M.; Teo, H. P.; Cai, S.; Liu, X.-W. *Org. Lett.* **2012**, *14*, 174.

[30] Takaki, K.; Ohno, A.; Hino, M.; Shitaoka, T.; Komeyama, K.; Yoshida, H. *Chem. Comm.* **2014**, 12285.

[31] Zhang, J.; Xing, C.; Tiwari, B.; Chi, Y. R. *J. Am. Chem. Soc.* **2013**, *135*, 8113.

[32] Murry, J. A.; Frantz, D. E.; Soheili, A.; Tillyer, R.; Grabowski, E. J. J.; Reider, P. J. *J. Am. Chem. Soc.* **2001**, *123*, 9696.

[33] Mattson, A. E.; Scheidt, K. A. *Org. Lett.* **2004**, *6*, 4363.

[34] Mennen, S. M.; Gipson, J. D.; Kim, Y. R.; Miller, S. J. *J. Am. Chem. Soc.* **2005**, *127*, 1654.

[35] Li, G.-Q.; Dai, L.-X.; You, S.-L. *Chem. Commun.* **2007**, 852.

[36] Enders, D.; Henseler, A.; Lowins, S. *Synthesis* **2009**, 4125.

[37] DiRocco, D. A.; Rovis, T. *Angew. Chem., Int. Ed.* **2012**, *51*, 5904.

[38] DiRocco, D. A.; Rovis, T. *J. Am. Chem. Soc.* **2012**, *134*, 8094.

[39] Sun, L.-H.; Liang, Z.-Q.; Jia, W.-Q.; Ye, S. *Angew. Chem., Int. Ed.* **2013**, *52*, 5803.

[40] (a) Sohn, S. S.; Rosen, E. L.; Bode, J. W. *J. Am. Chem. Soc.* **2004**, *126*, 14370. (b) Burstein, C.; Glorius, F. *Angew. Chem., Int. Ed.* **2004**, *43*, 6205. (c) Burstein, C.; Tschan, S.; Xie, X.; Glorius, F. *Synthesis* **2006**, 2418.

[41] He, M.; Bode, J. W. *Org. Lett.* **2005**, *7*, 3131.

[42] Nair, V.; Vellalath, S.; Poonoth, M.; Suresh, E. *J. Am. Chem. Soc.* **2006**, *128*, 8736.

[43] Chiang, P.-C.; Kaeobamrung, J.; Bode, J. W. *J. Am. Chem. Soc.* **2007**, *129*, 3520.

[44] Rommel, M.; Fukuzumi, T.; Bode, J. W. *J. Am. Chem. Soc.* **2008**, *130*, 17266.

[45] Phillips, E. M.; Reynolds, T. E.; Scheidt, K. A. *J. Am. Chem. Soc.* **2008**, *130*, 2416.

[46] Seayad, J.; Patra, P. K.; Zhang, Y.; Ying, J. Y. *Org. Lett.* **2008**, *10*, 953.

[47] Zhao, X.; DiRocco, D. A.; Rovis, T. *J. Am. Chem. Soc.* **2011**, *133*, 12466.

[48] Cohen, D. T.; Scheidt, K. A. *Chem. Sci.* **2012**, *3*, 53.

[49] Lv, H.; Jia, W.-Q.; Sun, L.-H.; Ye, S. *Angew. Chem., Int. Ed.* **2013**, *52*, 8607.

[50] Fu, Z.; Xu, J.; Zhu, T.; Leong, W. W. Y.; Chi, Y. R. *Nat. Chem.* **2013**, *5*, 835.

[51] He, J.; Zheng, J.; Liu, X.; She, X.; Pan, X. *Org. Lett.* **2006**, *8*, 4637.

[52] Biju, A. T.; Wurz, N. E.; Glorius, F. *J. Am. Chem. Soc.* **2010**, *132*, 5970.

[53] Franz, J. F.; Fuchs, P. J. W.; Zeitler, K. *Tetrahedron Lett.* **2011**, *52*, 6952.

[54] Biju, A. T.; Glorius, F. *Angew. Chem., Int. Ed.* **2010**, *49*, 9761.

[55] Piel, I.; Steinmetz, M.; Hirano, K.; Fröhlich, R.; Grimme, S.; Glorius, F. *Angew. Chem., Int. Ed.* **2011**, *50*, 4983.

[56] (a) Bugaut, X.; Liu, F.; Glorius, F. *J. Am. Chem. Soc.* **2011**, *133*, 8130. (b) Liu, F.; Bugaut, X.; Schedler, M.; Fröhlich, R.; Glorius, F. *Angew. Chem., Int. Ed.* **2011**, *50*, 12626.

[57] Fischer, C.; Smith, S. W.; Powell, D. A.; Fu, G. C. *J. Am. Chem. Soc.* **2006**, *128*, 1472.

[58] Atienza, R. L.; Roth, H. S.; Scheidt, K. A. *Chem. Sci.* **2011**, 1772.

[59] (a) Matsuoka, S.-I.; Ota, Y.; Washio, A.; Katada, A.; Ichioka, K.; Takagi, K.; Suzuki, M. *Org. Lett.* **2011**, *13*, 3722. (b) Biju, A. T.; Padmanaban, M.; Wurz, N. E.; Glorius, F. *Angew. Chem., Int. Ed.* **2011**, *50*, 8412.

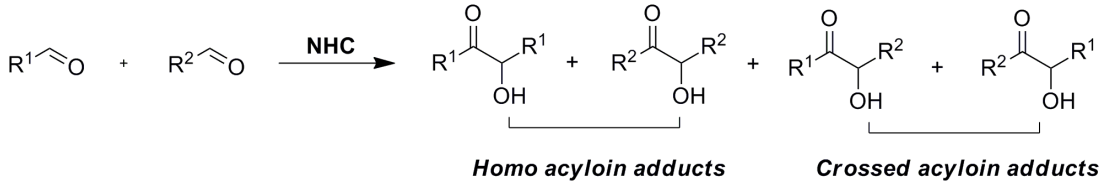
[60] (a) Zhang, Y.; Schmitt, M.; Falivene, L.; Caporaso, L.; Cavallo, L.; Chen, E. Y.-X. *J. Am. Chem. Soc.* **2013**, *135*, 17925. (b) Chen, X.-Y.; Ye, S. *Org. Biomol. Chem.* **2013**, *11*, 7991. (c) He, J.; Zhang, Y.; Chen, E. Y.-X. *Synlett* **2014**, 1534. (d) Hong, M.; Chen, E. Y.-X. *Angew. Chem., Int. Ed.* **2014**, *53*, 11900.

Chapter 2

Chemoselective synthesis of trifluoromethylated acyloins using NHC as an organocatalyst

2.1. Introduction

Although the distinctive reactivity of N-heterocyclic carbenes (NHCs) has been well investigated for the intermolecular homo-dimerization of aldehydes (Benzoin and acyloin condensation), the intermolecular cross-benzoin/acyloin condensations remain challenging due to a mismatch between the reactivity of aldehyde and the coupling partner (usually another aldehyde or aldehyde equivalent). Choosing a right coupling partner is a crucial task in the crossed acyloin reaction; otherwise, the reaction would lead to four different acyloins including two homo-dimerized products (Scheme 1).

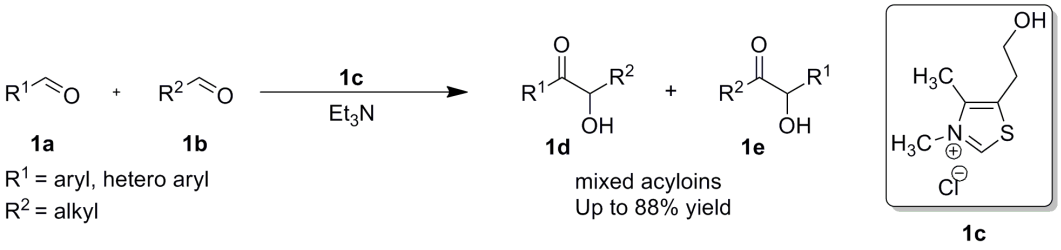


Scheme 1

In order to execute the cross-benzoin/acyloin reaction chemoselectively, the coupling partner must be chosen in such a way that it must not react with the NHC, and at the same time, its reactivity towards Breslow intermediate must be more than that of the aldehyde. Based on this concept, many successful reports have been appeared in the literature for the intramolecular benzoin reactions as well as the intra/intermolecular Stetter reactions. But, only a few reports are available in the literature for the intermolecular crossed acyloin type reactions between aldehydes and different aldehydes or ketones or α-ketoesters (including enantioselective

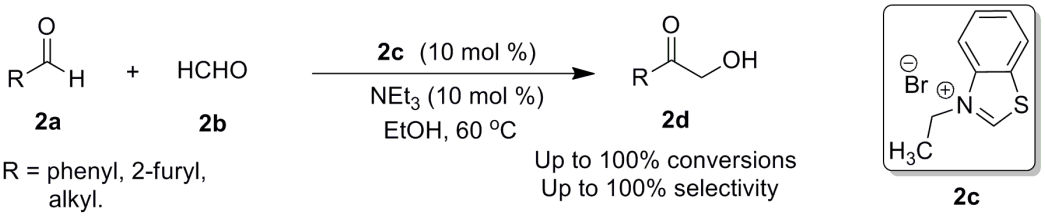
reactions) to give their corresponding crossed acyloins chemoselectively. Some of the intermolecular crossed acyloin type reactions are discussed as follows.

The first intermolecular crossed acyloin condensation was reported by the Stetter group in 1977.[1] The reaction was performed between two dissimilar aldehydes by employing thiazolium salt **1c** as a carbene precursor and Et_3N as a base. In this case, both the heterodimerized products **1d** and **1e** were obtained in major products along with homoacyloin products as minor products. However, when one of the aldehydes was used in excess, one of the dissymmetric acyloins was obtained in major quantities (Scheme 2).



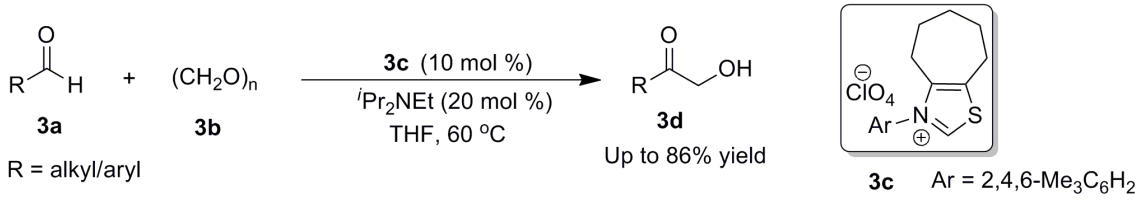
Scheme 2

A few years later, Inoue's group reported a cross coupling reaction between aliphatic or aromatic aldehydes **2a** and paraformaldehyde (**2b**) leading to α-hydroxy ketones **2d** using an NHC derived from 3-ethylbenzo-thiazolium bromide (**2c**) in the presence of Et_3N (Scheme 3).[2]



Scheme 3

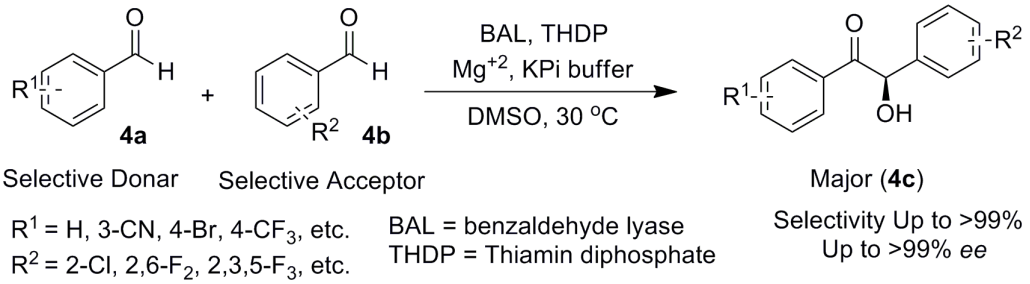
Recently, Glorius group developed a competent approach for highly chemoselective hydroxymethylation of aldehydes through NHC catalysis.[3]



Scheme 4

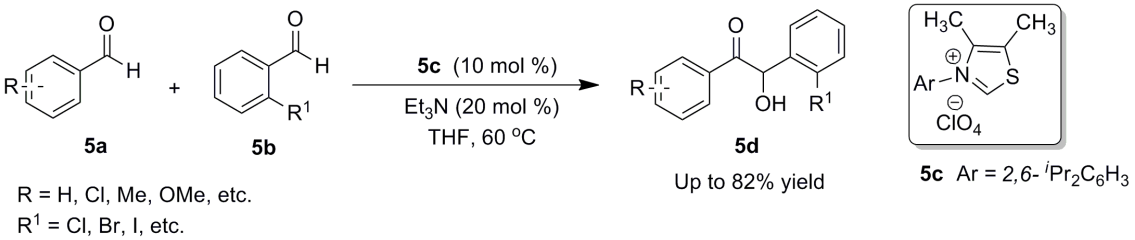
The reactions were performed between various aldehydes **3a** and paraformaldehyde **3b** in the presence of NHC derived from a thiazolium salt **3c**, and in all those cases, the corresponding 2-hydroxymethyl ketone derivatives **3d** were obtained in moderate to good yields (Scheme 4).

Müller and co-workers demonstrated the first asymmetric cross-benzoin reaction through enzymatic cross-coupling of aromatic aldehydes using ThDP-dependent benzaldehyde lyase (BAL) as catalyst.[4] The cross-coupling reaction between non-ortho substituted aromatic aldehydes **4a** and ortho substituted aromatic aldehydes **4b** was explored by taking advantage of the aldehydes donor-acceptor behavior. The ortho substituted aromatic aldehydes were chosen as acceptors by taking advantage of their inability to form symmetrical benzoins. A series of experiments were carried out by combining identified selective donors with selective acceptors using BAL catalyst, and the mixed benzoin **4c** was obtained with the high level of enantioselectivity (Scheme 5).



Scheme 5

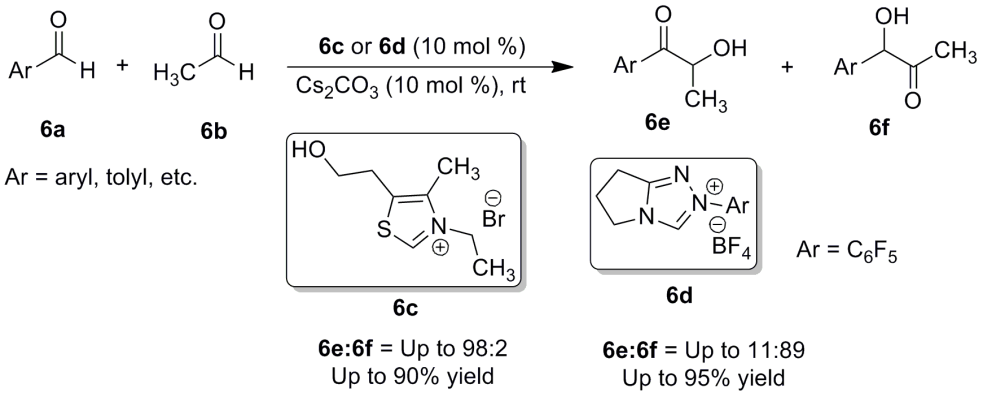
Another intermolecular cross-benzoin condensation reaction was developed by Glorius and co-workers using a new NHC derived from thiazolium salt **5c**.[5a] The cross-benzoin reactions of various non-*ortho*-substituted aromatic aldehydes **5a** with various *ortho*-substituted aromatic aldehydes **5b** were explored and the corresponding unsymmetrically substituted benzoins were formed chemoselectively **5d** in moderate to good yields (in most of the cases). The formation of homodimerized product was also observed in small quantities along with the formation of unsymmetrically substituted benzoin product in some of the examples (Scheme 6).



Scheme 6

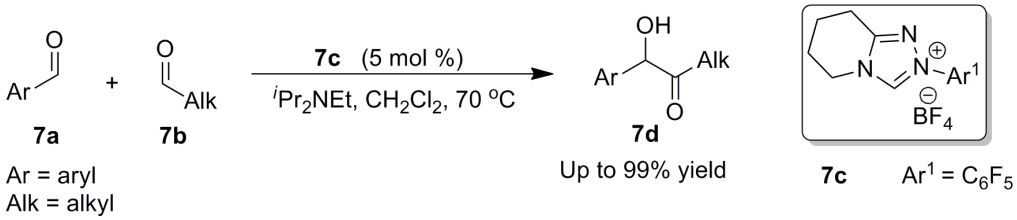
The investigation for the origin of chemoselectivity was reported by the research groups of Smith and O' Donoghue through kinetic analysis.[5b] It is evident from the kinetic analysis data that the nucleophilic addition into benzaldehydes bearing a 2-heteroatom substituent is particularly faster as compared to the nucleophilic addition into the non-*ortho*-substituted aromatic aldehydes. But, the origin of this phenomenon is unclear.

Another interesting methodology was reported by Yang's group, who showed that the choice of NHC is the crucial factor for switching the regioselectivity in crossed acyloin condensation between aromatic aldehydes **6a** with acetaldehyde (**6b**).[6] They found that thiazolium based NHC **6c** prefers aromatic aldehydes and forms the corresponding Breslow intermediate, which then reacts with acetaldehyde to give the product **6e**. On the other hand, triazolium based NHC **6d** preferentially reacts with acetaldehyde and generates another Breslow intermediate, which then reacts with aromatic aldehydes to generate the cross benzoin product **6f** (Scheme 7).



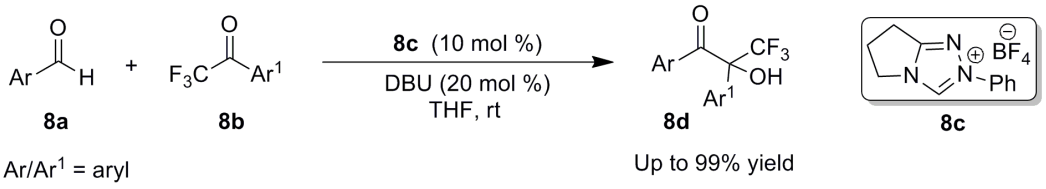
Scheme 7

In 2014, Gravel and co-workers developed a highly chemoselective cross-benzoin reaction between aromatic **7a** and aliphatic **7b** aldehydes using a NHC derived from piperidinone based triazolium salt **7c**.[7] They found that this particular NHC prefers aliphatic aldehydes over aromatic aldehydes, and the cross acyloin/benzoin products **7d** were obtained in excellent yield and selectivity (Scheme 8).



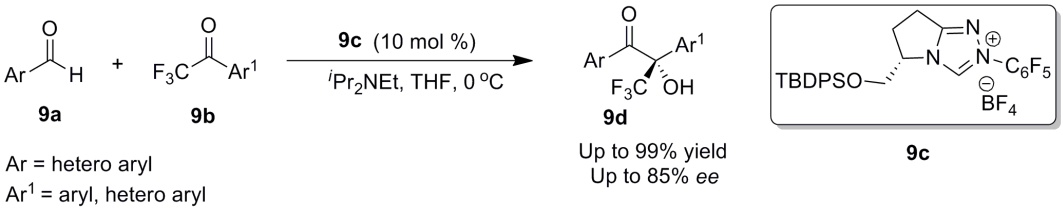
Scheme 8

Enders group reported NHC catalyzed the chemoselective cross-benzoin reaction of aromatic aldehydes **8a** with trifluoromethyl ketones **8b**.[8a] Using this protocol a wide range of α-hydroxyl α-trifluoromethyl ketones bearing quaternary center **8d** were obtained in good to excellent yields with high level of chemoselectivity (Scheme 9).



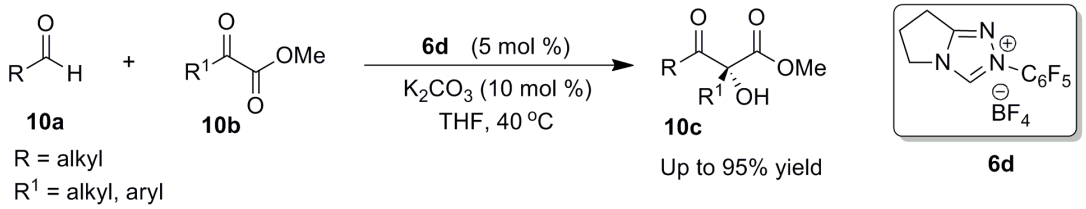
Scheme 9

In addition, to that Enders group also developed an asymmetric cross-benzoin-type reaction between heteroaromatic aldehydes **9a** and trifluoromethyl ketones **9b** using a new chiral NHC derived from triazolium salt **9c**.[8b] Various heteroaromatic aldehydes were treated with different aromatic trifluoromethyl ketones by employing chiral triazolium salt as a precatalyst **9c** and the corresponding α-hydroxyl-α-trifluoromethyl ketones **9d** were obtained in good to excellent yields and moderate to good enantioselectivities (Scheme 10).



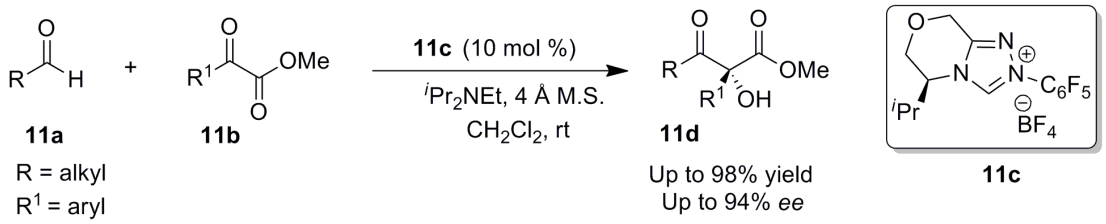
Scheme 10

Recently, the groups of Connon and Zeitler jointly disclosed a highly chemoselective crossed acyloin condensation between various aldehydes and α-ketoesters through NHC catalysis.[9a] A wide range of aliphatic aldehydes **10a** were treated with various α-keto esters **10b** by employing triazolium salt **6d** as a carbene precursor and the corresponding crossed acyloins containing a quaternary stereo centre **10c** were obtained in good to excellent yields with a high level of chemoselectivity (Scheme 11).



Scheme 11

An enantioselective version of the above mentioned methodology was reported by Gravel and co-workers employing a chiral NHC **11c**.[9b] The reaction worked very well and the cross-benzoin products **11d** were obtained in excellent yields and enantioselectivity (Scheme 12).



Scheme 12

2.2. Results and discussion

The literature reports clearly reveal that there are only a few successful reports available for the highly chemoselective crossed acyloin/benzoin reactions. While working on the similar NHC catalyzed transformations, we envisioned that the chemoselectivity could be enhanced if an "aldehyde equivalent" is used as a coupling partner instead of another aldehyde in intermolecular crossed acyloin/benzoin condensation. Since "hemiacetal" is considered to be the best aldehyde equivalent, we thought to explore this reactive compound as a coupling partner. However, the main problem is that most of the hemiacetals are not stable and can't be isolated. Surprisingly, $CF_3CH(OH)OEt$, a hemiacetal of trifluoroacetaldehyde, is found to be relatively stable and commercially available (as 90% aq. solution). Another advantage of this particular hemiacetal is that, it installs the trifluoromethyl group in the cross-acyloin product, which could be easily converted to biologically important trifluoromethyl containing heterocycles or drugs.[10] A few of the trifluoromethyl group containing biologically active compounds are shown in fig. 1.

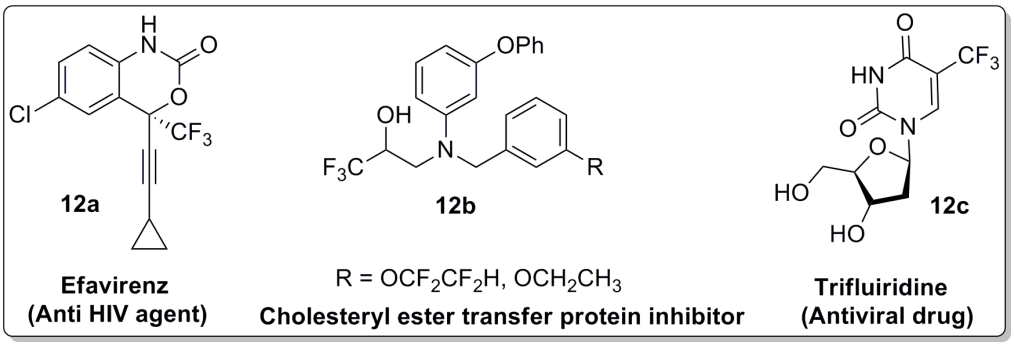
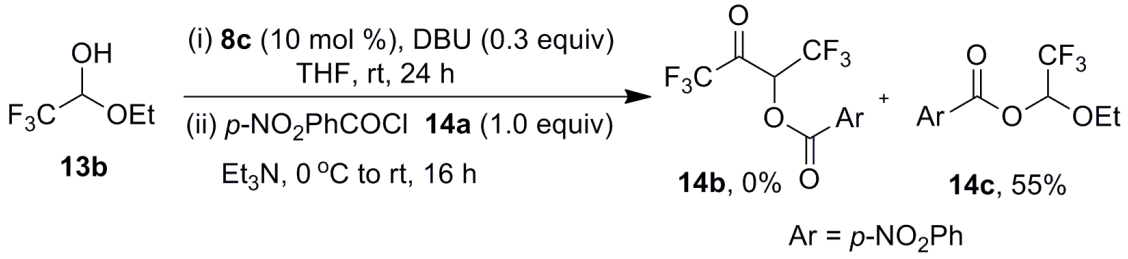


Figure 1

Although $CF_3CH(OH)OEt$ was used as an aldehyde equivalent in some of the transformations,[11] surprisingly so far, it was not explored in intermolecular cross-acyloin condensation.

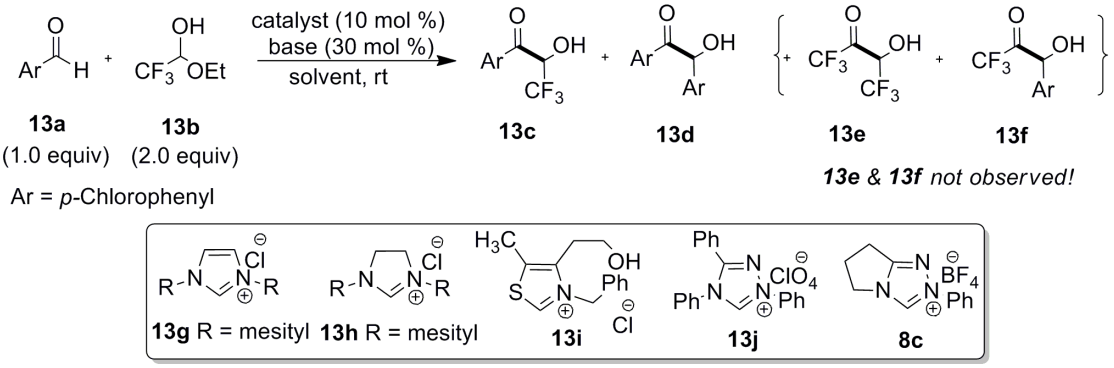
The optimization studies were carried out using *p*-chlorobenzaldehyde (**13a**) and a variety of NHC precursors (**8c**, **13g**–**13j**) under different reaction conditions (Table 1). Initially, we carried out an experiment using **13g** as a catalyst (entry 1) and the anticipated crossed acyloin adduct **13c** was formed only in 7% yield. Indeed, this result was encouraging because the crossed acyloin product **13c** was formed in a chemoselective manner, albeit the yield was quite low. Screening of other NHCs **13i** & **13j** didn't give promising results as a considerable amount of **13d** was obtained and/or the yield of **13c** was low (entries 3 & 4). Intriguingly, when the reaction was performed using NHC **8c** as a precatalyst and DBU as a base, the desired crossed acyloin **13c** was obtained in 90% yield with high chemoselectivity (entry 5). Further optimization studies were performed using **8c** as a precatalyst by altering base or solvent (entries 6–12). But in all those cases, the yield of desired product was inferior when compared to entry 5. A noteworthy observation was that the other possible products **13e** and **13f** were not formed under the reaction conditions. The acyloins **13e** and **13f** are possible only if trifluoroacetaldehyde is produced during the reaction. To have a better understanding of this observation, an experiment was carried out in which $CF_3CH(OH)OEt$ was subjected to self-acyloin condensation using **8c** as a precatalyst followed by esterification with *p*-nitro benzoyl chloride (**14a**) under basic conditions (Scheme 13).

Interestingly, in this case, the acyloin ester **14b** was not observed; instead, the acetal ester **14c** was isolated in 55% yield. This experiment suggests that $CF_3CH(OH)OEt$ doesn't decompose to trifluoroacetaldehyde under the reaction conditions, which also explains why **13e** & **13f** were not observed in any of the reaction conditions tried (Table 1).[12]



Scheme 13

Table 1. Optimization Studies[a]

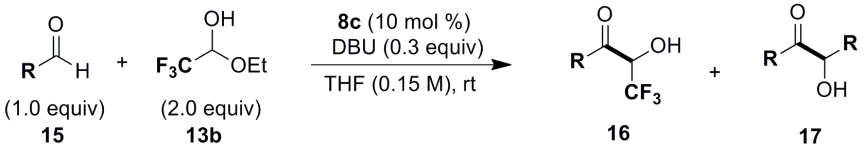


Entry	Catalyst	Base	Solvent	Time [h]	13c:13d[b]	Yield 13c [%][c]
1	**13g**	DBU	THF	24	> 95:5	7
2	**13h**	DBU	THF	15	--	0
3	**13i**	DBU	THF	15	73:27	22
4	**13j**	DBU	THF	24	> 95:5	33
5	**8c**	**DBU**	**THF**	**4**	**> 95:5**	**90**
6	**8c**	K^{t}OBu	THF	6	> 95:5	68
7	**8c**	Cs_2CO_3	THF	6	> 95:5	76
8	**8c**	Et_3N	THF	8	> 95:5	62
9	**8c**	DBU	DCM	26	> 95:5	40
10	**8c**	DBU	DME	10	> 95:5	80
11	**8c**	DBU	DMF	10	> 95:5	82
12	**8c**	DBU	1,4-dioxane	12	> 95:5	82

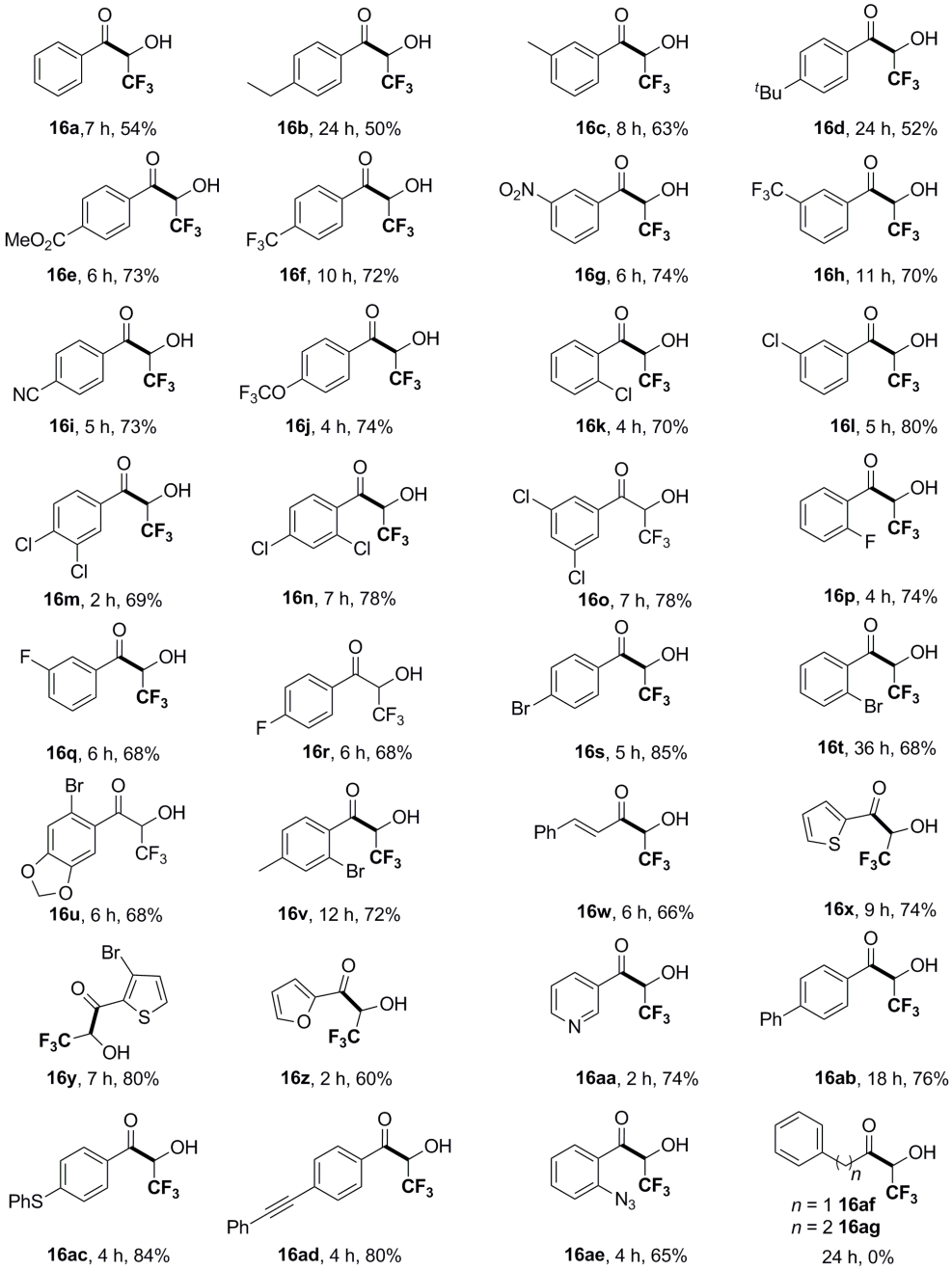
[a]Reaction conditions: 0.15 M of **13a** in solvent; Use of 2.0 equivalents of **13b** with respect to **13a** was found to be optimal; [b]Ratio determined by ^{1}H-NMR analysis of the crude mixture after work-up; [c]Isolated yield; rt = 23–26 $^\circ$C.

Having optimized conditions in hand (entry 5, Table 1), we shifted our attention in evaluating the substrate scope. As shown in scheme 14, a wide range of aromatic aldehydes (**15a–15z** & **15aa–15ag**) were treated with $CF_3CH(OH)OEt$ under standard reaction condition. In all the cases, the expected crossed acyloin adducts were obtained in moderate to good yields with high levels of chemoselectivity (> 95:5). A general observation was that the yields of products (**16b**–**16d**) in the cases of electron rich aldehydes were found to be a bit inferior when compared to that of electron poor aldehydes (**16e**–**16i**). Interestingly, in the cases of halo-and dihalo-substituted aryl aldehydes (**15k**–**15s**), the desired acyloin products (**16k**–**16s**) were obtained in good yields. Even highly hindered aldehydes such as *ortho*-bromo substituted aromatic aldehydes (**15t**–**15v**)

Scheme 14. Substrate Scope[a]



Chemoselectivity (**16**:**17**) = > 95:5[b]



[a]Yields reported are isolated yields; [b]Ratio determined by ^{1}H NMR analysis of the crude mixture after work-up; rt 23–26 °C.

underwent smooth conversion to the corresponding products (**16t**–**16v**) in good yields. This methodology also worked very well for hetero-aromatic aldehydes as well (Examples **16x**–**16z** and **16aa**). In the case of aliphatic aldehydes such as phenylacetaldehyde (**15af**) and hydrocinnamaldehyde (**15ag**) complex mixtures were obtained. But, cinnamaldehyde was efficiently converted to the acyloin **16w** in 66% yield.

We also tried to elaborate this methodology to other cyclic hemiacetals (such as carbohydrate derivative **18a** and lactol **18b**) as well as acyclic acetals **18c** (Figure 2). Unfortunately, none of them reacted with **13a** under standard reaction conditions to give the crossed acyloin products. In all those cases, only benzoin **13d** was observed.

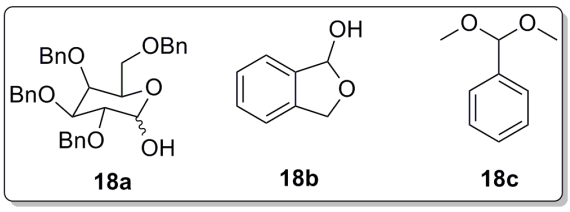
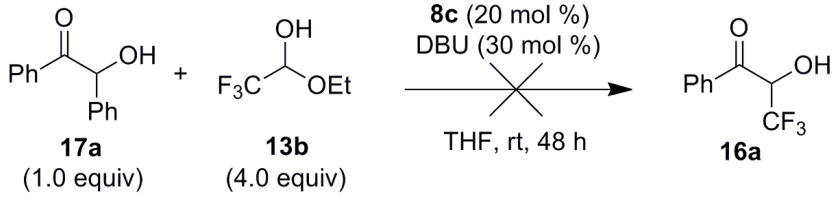


Figure 2

It is obvious from the outcome of the reaction that the Breslow intermediate reacts with $CF_3CH(OH)OEt$ chemoselectively to deliver the crossed acyloin product. To understand the reaction in detail, a few experiments were performed.

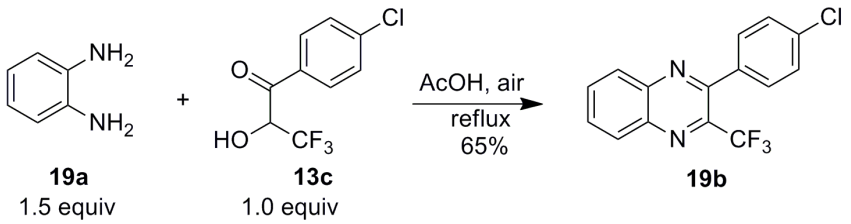
In a typical crossover experiment (Scheme 15), benzoin (**17a**) was treated with excess of **13b** under the standard reaction condition and the reaction was monitored by ^{1}H NMR spectroscopy, but the crossed acyloin product **13c** was not detected even after two days. This experiment clearly indicates that benzoin (**17a**) didn't undergo retro-benzoin reaction under the reaction condition. This result also suggests that the formation of **17a** is irreversible.



Scheme 15

In another experiment, the standard reaction (Table 1, entry 5) was monitored by ^{1}H NMR spectroscopy. In this case, the formation of product **13c** was observed prior (within 5 minutes) to the formation of **13d**. The above experiments clearly show that the chemoselectivity outcome of the reaction is controlled by kinetic factors.

To demonstrate the synthetic utility of the products, one of the trifluoromethyl containing crossed acyloin products **13c** was refluxed with a bit excess of *o*-phenylenediamine (**19a**) in acetic acid and the CF_3-containing quinoxoline **19b** was obtained in 65% yield (Scheme 16).[13]

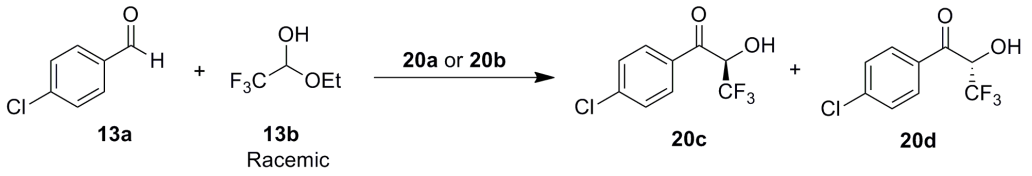


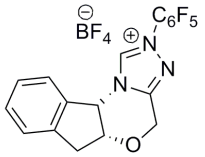
Scheme 16

Enantioselective intermolecular cross-acyloin condensation between aromatic aldehyde and trifluoroacetaldehyde ethyl hemiacetal

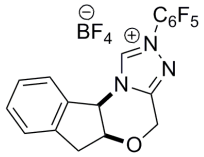
An enantioselective cross-acyloin reaction was performed between *p*-chlorobenzaldehyde (**13a**) and trifluoroacetaldehyde ethyl hemiacetal (**13b**) using chiral NHCs **20a** and **20b** under different reaction conditions. A few of the conditions are shown in table 2. Initially, reactions were carried using chiral NHC **20a** under different reaction conditions (entry 1–3). Unfortunately, only the racemic products were obtained in all the cases. A few reactions also tried using chiral NHC **20b** under different reaction conditions. Using NHC **20b,** DBU as a base, two reactions were carried out in THF and DCM at 0 $^{\circ}$C, and the racemic mixture was observed in both the cases (entry 4 & 5). Interestingly, when the reaction was carried out using NHC **20b**, DBU as a base in THF at rt, the product was obtained in 30% *ee* (entry 6). Using NHC **20b**, few more reactions were also performed by altering base and solvent at rt (entry 7 & 8). But unfortunately, none of the cases gave the enantioselectivity. Since we didn't get the high level of enantioselectivity, we didn't precede further.

Table 2. Optimization Studies[a]





20a



20b

Entry[a]	Catalyst	Base	Solvent	Temp (°C)	Conv (%)[b]	*ee* (%)[c]
1	**20a**	DBU	THF	0	50	0
2	**20a**	DBU	DCM	rt	50	0
3	**20a**	$^{i}Pr_2NEt$	THF	rt	40	0
4	**20b**	DBU	THF	0	50	0
5	**20b**	DBU	DCM	0	40	0
6	**20b**	DBU	THF	rt	60	30
7	**20b**	$^{i}Pr_2NEt$	THF	rt	40	0
8	**20b**	DBU	1,4-dioxane	rt	50	0

[a]Reaction conditions: 0.14 M of **13a** in solvent; rt = 23–26 °C. [b]Conversion was observed by TLC; [c]*ee* was determined by HPLC.

2.3. Conclusion

In conclusion, a highly chemoselective crossed acyloin condensation of aromatic aldehydes with $CF_3CH(OH)OEt$ was developed through NHC catalysis. In almost all the cases, the trifluoromethylated crossed acyloins were obtained in moderate to good yields with high chemoselectivity under the mild reaction conditions. This methodology was also tried to elaborate to an asymmetric version using chiral NHCs. Unfortunately, the corresponding crossed acyloin product was observed with max 30% *ee*.

2.4. Experimental sections

General Information

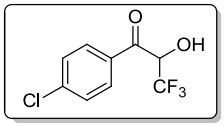
Most of the reagents and starting materials used were purchased from commercial sources and used as such. NHC precursors (**13j**, **8c**) were prepared according to the literature procedure.[14] Chiral NHC precursors (**20a & 20b**) were purchased from commercial sources and used as such. ^{1}H, ^{13}C and ^{19}F (proton decoupled) spectra were recorded in $CDCl_3$ (400, 100 and 376 MHz respectively) on Brucker FT-NMR spectrometer. Chemical shifts (δ) values are reported in parts per million relative to TMS and the coupling constants (J) are reported in Hz. Trifluoromethyl benzene was used as internal standard for ^{19}F spectra. High-resolution mass spectra were recorded on Waters Q-TOF Premier-HAB213 spectrometer. FT IR spectra were recorded on a Brucker FT-IR spectrometer equipped with a PIKE MIRacle ATR. Thin layer chromatography was performed on Merck silica gel 60 F_{254} TLC plates. Column chromatography was carried out through silica gel (100-200 mesh) using EtOAc/hexane as an eluent. Water HPLC system was used to determine the enantiomeric excess. Optical rotations were recorded on a Rudolph APIII/2W.

General procedure for the NHC catalyzed intermolecular crossed acyloin condensation of aromatic aldehydes with trifluoroacetaldehyde ethyl hemiacetal

1,8-Diazabicyclo[5.4.0]undec-7-ene (10 mg, 0.066 mmol) was added to a suspension of NHC **8c** (6 mg, 0.022 mmol), aldehyde (0.22 mmol) and trifluoroacetaldehyde ethyl hemiacetal (**13b**) (90% aq. solution, 57 μL, 0.44 mmol) in dry THF (1.5 mL) at room temperature (23–26 °C) and the resulting suspension was stirred at the same temperature until most of the aldehyde was consumed (by TLC). The solvent was removed under reduced pressure and the residue was purified through silica gel column using 5% EtOAc/Hexane mixture as an eluent.

Characterization data of compounds (13c, 16a–16z & 16aa–16ae):

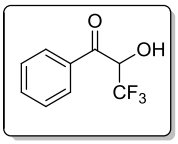
1-(4-chlorophenyl)-3,3,3-trifluoro-2-hydroxypropan-1-one (13c):[15]



White solid; Yield 90% (47.2 mg); m.p. 76–78 °C; FT IR (ATR) 3442, 1686 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$), δ 7.93 (d, J = 8.6 Hz, 2H), 7.52 (d, J = 8.6

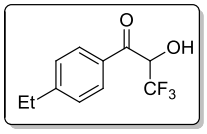
Hz, 2H), 5.42–5.35 (m, 1H), 4.29 (d, J = 8.2 Hz, 1H [OH]); ^{13}C NMR (100 MHz, $CDCl_3$), δ 192.1, 142.3, 131.7, 130.9, 129.6, 122.3 (q, $^1J_{C\text{-}F}$ = 282.6 Hz), 71.1 (q, $^2J_{C\text{-}F}$ = 30.6 Hz); ^{19}F NMR (376 MHz, $CDCl_3$), δ −73.81.

3,3,3-trifluoro-2-hydroxy-1-phenylpropan-1-one (16a):[16]



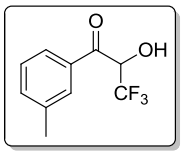
White solid; Yield 54% (24.0 mg); m.p. 82–84 °C; FT IR (ATR) 3368, 1683 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$), δ 7.99 (d, J = 7.4 Hz, 2H), 7.73–7.69 (m, 1H), 7.58–7.53 (m, 2H), 5.46–5.39 (m, 1H), 4.28 (d, J = 8.3 Hz, 1H [OH]); ^{13}C NMR (100 MHz, $CDCl_3$), δ 193.2, 135.5, 133.5, 129.6, 129.1, 122.5 (q, $^1J_{C\text{-}F}$ = 282.4 Hz), 71.1 (q, $^2J_{C\text{-}F}$ = 31.2 Hz); ^{19}F NMR (376 MHz, $CDCl_3$), δ −73.83; HRMS (ESI): *m/z* calcd for $C_9H_6F_3O_2$ $[M-H]^+$: 203.0320; found: 203.0325.

1-(4-ethylphenyl)-3,3,3-trifluoro-2-hydroxypropan-1-one (16b):



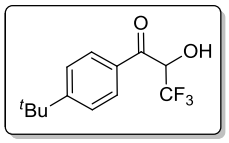
White solid; Yield 50% (25.5 mg); m.p. 66–68 °C; FT IR (ATR) 3446, 1676 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$), δ 7.91 (d, J = 8.3 Hz, 2H), 7.36 (d, J = 8.3 Hz, 2H), 5.43–5.36 (m, 1H), 4.31 (brd, J = 8.1 Hz, 1H [OH]), 2.75 (q, J = 7.6 Hz, 2H), 1.28 (t, J = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$), δ 192.5, 153.1, 131.2, 129.9, 128.7, 122.6 (q, $^1J_{C\text{-}F}$ = 284.4 Hz), 70.9 (q, $^2J_{C\text{-}F}$ = 31.4 Hz), 29.3, 15.1; ^{19}F NMR (376 MHz, $CDCl_3$), δ −73.94; HRMS (ESI): *m/z* calcd for $C_{11}H_{12}F_3O_2$ $[M+H]^+$: 233.0789; found: 233.0782.

3,3,3-trifluoro-2-hydroxy-1-(m-tolyl)propan-1-one (16c):



Semi solid; Yield 63% (30.0 mg); FT IR (ATR) 3442, 1686 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$), δ 7.79 (s, 1H), 7.78–7.74 (m, 1H), 7.53–7.49 (m, 1H), 7.43 (t, J = 7.6 Hz, 1H), 5.44–5.38 (m, 1H), 4.28 (brd, J = 8.0 Hz, 1H [OH]), 2.45 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$), δ 193.3, 139.2, 136.3, 133.5, 130.0, 129.0, 126.9, 122.5 (q, $^1J_{C\text{-}F}$ = 282.9 Hz), 71.1 (q, $^2J_{C\text{-}F}$ = 31.1 Hz), 21.5; ^{19}F NMR (376 MHz, $CDCl_3$), δ −73.87; HRMS (ESI): *m/z* calcd for $C_{10}H_{10}F_3O_2$ $[M+H]^+$: 219.0633; found: 219.0635.

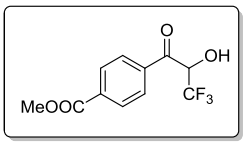
1-[4-(*tert*-butyl)phenyl]-3,3,3-trifluoro-2-hydroxypropan-1-one (16d):



Yellow oil; Yield 52% (29.5 mg); FT IR (ATR) 3446, 1683 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$), δ 7.93 (d, J = 8.4 Hz, 2H), 7.55 (d, J = 8.4 Hz, 2H), 5.43–5.38 (m, 1H), 4.30 (d, J = 6.2 Hz, 1H [OH]), 1.36 (s, 9H); ^{13}C NMR

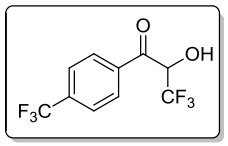
(100 MHz, $CDCl_3$), δ 192.5, 159.7, 130.8, 129.7, 126.2, 122.5 (q, $^1J_{C\text{-}F}$ = 282.7 Hz), 70.9 (q, $^2J_{C\text{-}F}$ = 31.3 Hz), 35.6, 31.1; ^{19}F NMR (376 MHz, $CDCl_3$), δ −73.90; HRMS (ESI): *m/z* calcd for $C_{13}H_{16}F_3O_2$ $[M+H]^+$: 261.1102; found: 261.1098.

Methyl 4-(3,3,3-trifluoro-2-hydroxypropanoyl)benzoate (16e):



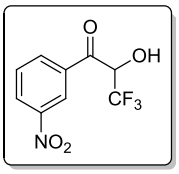
White solid; Yield 73% (42.0 mg); m.p. 85–87 °C; FT IR (ATR) 3481, 1724, 1693 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$), δ 8.20 (d, *J* = 8.7 Hz, 2H), 8.04 (d, *J* = 8.7 Hz, 2H), 5.48–5.41 (m, 1H), 4.21 (d, *J* = 8.4 Hz, 1H [OH]), 3.97 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$), δ 193.1, 165.8, 136.6, 135.9, 130.2, 129.5, 122.3 (q, $^1J_{C\text{-}F}$ = 282.8 Hz), 71.5 (q, $^2J_{C\text{-}F}$ = 31.3 Hz), 52.9; ^{19}F NMR (376 MHz, $CDCl_3$), δ −73.68; HRMS (ESI): *m/z* calcd for $C_{11}H_8F_3O_4$ $[M-H]^+$: 261.0375; found: 261.0359.

3,3,3-trifluoro-1-[4-(trifluoromethyl)phenyl]-2-hydroxypropan-1-one (16f):



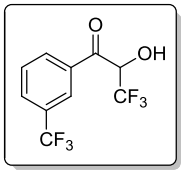
White solid; Yield 72% (43.0 mg); m.p. 58–60 °C; FT IR (ATR) 3310, 1697 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$), δ 8.10 (d, *J* = 8.3 Hz, 2H), 7.82 (d, *J* = 8.3 Hz, 2H), 5.47–5.41 (m, 1H), 4.20 (brd, *J* = 7.4 Hz, 1H [OH]); ^{13}C NMR (100 MHz, $CDCl_3$), δ 192.8, 136.5 (q, $^2J_{C\text{-}F}$ = 32.8 Hz), 136.2, 129.9, 126.2 (q, $^3J_{C\text{-}F}$ = 3.7 Hz), 123.3 (q, $^1J_{C\text{-}F}$ = 271.2 Hz), 122.3 (q, $^1J_{C\text{-}F}$ = 282.1 Hz), 71.6 (q, $^2J_{C\text{-}F}$ = 31.4 Hz); ^{19}F NMR (376 MHz, $CDCl_3$), δ −63.45, −73.62; HRMS (ESI): *m/z* calcd for $C_{10}H_5F_6O_2$ $[M-H]^+$: 271.0194; found: 271.0187.

3,3,3-trifluoro-2-hydroxy-1-(3-nitrophenyl)propan-1-one (16g):



Pale yellow oil; Yield 74% (40.4 mg); FT IR (ATR) 3453, 1699, 1532 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$), δ 8.81–8.80 (m, 1H), 8.54 (ddd, *J* = 8.2, 2.2, 1.0 Hz, 1H), 8.32 (d, *J* = 8.0 Hz, 1H), 7.79 (t, *J* = 8.0 Hz, 1H), 5.52 (q, *J* = 6.6 Hz, 1H), 4.20 (brs, 1H [OH]); ^{13}C NMR (100 MHz, $CDCl_3$), δ 191.9, 148.7, 134.9, 134.8, 130.6, 129.4, 124.4, 122.2 (q, $^1J_{C\text{-}F}$ = 281.3 Hz), 71.74 (q, $^2J_{C\text{-}F}$ = 30.6 Hz); ^{19}F NMR (376 MHz, $CDCl_3$), δ −73.61; HRMS (ESI): *m/z* calcd for $C_9H_5F_3NO_4$ $[M-H]^+$: 248.0171; found: 248.0163.

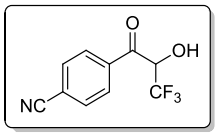
3,3,3-trifluoro-1-[3-(trifluoromethyl)phenyl]-2-hydroxypropan-1-one (16h):



Yellow oil; Yield 70% (41.6 mg); FT IR (ATR) 3453, 1697 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$), δ 8.24 (s, 1H), 8.16 (d, *J* = 7.9 Hz, 1H), 7.96 (d, *J* = 7.9 Hz, 1H), 7.72 (t, *J* = 7.9 Hz, 1H), 5.48–5.41 (m, 1H), 4.24 (d, *J* = 8.4 Hz, 1H [OH]); ^{13}C NMR (100 MHz, $CDCl_3$), δ 192.4, 134.0, 132.65–132.63 (m), 132.0 (q, $^2J_{C\text{-}F}$ = 33.5 Hz), 131.74

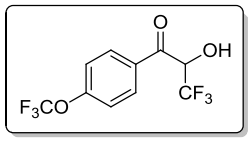
(q, $^{3}J_{C\text{-}F}$ = 3.5 Hz), 129.9, 126.4 (q, $^{2}J_{C\text{-}F}$ = 3.8 Hz), 123.4 (q, $^{1}J_{C\text{-}F}$ = 271.3 Hz), 122.3 (q, $^{1}J_{C\text{-}F}$ = 282.2 Hz), 71.5 (q, $^{2}J_{C\text{-}F}$ = 31.4 Hz); ^{19}F NMR (376 MHz, $CDCl_3$), δ −63.03, −73.69; HRMS (ESI): *m/z* calcd for $C_{10}H_5F_6O_2$ $[M-H]^+$: 271.0194; found: 271.0189.

4-(3,3,3-trifluoro-2-hydroxypropanoyl)benzonitrile (16i):



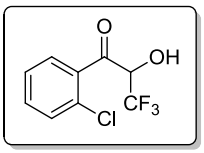
White solid; Yield 73% (36.6 mg); m.p. 82–84 °C; FT IR (ATR) 3436, 2237, 1699 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$), δ 8.08 (d, *J* = 8.4 Hz, 2H), 7.87–7.85 (m, 2H), 5.45–5.38 (m, 1H), 4.13 (d, *J* = 8.4 Hz, 1H [OH]); ^{13}C NMR (100 MHz, $CDCl_3$), δ 192.6, 136.4, 132.9, 129.9, 122.2 (q, $^{1}J_{C\text{-}F}$ = 282.9 Hz), 118.6, 117.4, 71.7 (q, $^{2}J_{C\text{-}F}$ = 31.4 Hz); ^{19}F NMR (376 MHz, $CDCl_3$), δ −73.56; HRMS (ESI): *m/z* calcd for $C_{10}H_5F_3NO_2$ $[M-H]^+$: 228.0272; found: 228.0282.

3,3,3-trifluoro-2-hydroxy-1-[4-(trifluoromethoxy)phenyl]propan-1-one (16j):



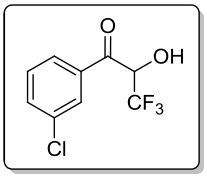
White solid; Yield 74% (46.9 mg); m.p. 50–52 °C; FT IR (ATR) 3311, 1695 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$), δ 8.06 (d, *J* = 8.8 Hz, 2H), 7.39–7.36 (m, 2H), 5.43–5.36 (m, 1H), 4.22 (d, *J* = 8.4 Hz, 1H [OH]); ^{13}C NMR (100 MHz, $CDCl_3$), δ 191.8 (q, $^{3}J_{C\text{-}F}$ = 1.5 Hz) , 154.35–154.30 (m), 132.8, 131.4, 122.4 (q, $^{1}J_{C\text{-}F}$ = 281.7 Hz), 120.3 (q, $^{1}J_{C\text{-}F}$ = 257.4 Hz), 120.59–120.56 (m), 71.2 (q, $^{2}J_{C\text{-}F}$ = 31.3 Hz); ^{19}F NMR (376 MHz, $CDCl_3$), δ −57.59, −73.82; HRMS (ESI): *m/z* calcd for $C_{10}H_5F_6O_3$ $[M-H]^+$: 287.0143; found: 287.0140.

1-(2-chlorophenyl)-3,3,3-trifluoro-2-hydroxypropan-1-one (16k):



Colorless oil; Yield 70% (36.5 mg); FT IR (ATR) 3446, 1709 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$), δ 7.55–7.48 (m, 3H), 7.43–7.39 (m, 1H), 5.58–5.51 (m, 1H), 4.17 (d, *J* = 7.4 Hz, 1H [OH]); ^{13}C NMR (100 MHz, $CDCl_3$), δ 195.7, 134.9, 133.9, 132.1, 131.1, 130.2, 127.4, 122.3 (q, $^{1}J_{C\text{-}F}$ = 282.1 Hz), 74.2 (q, $^{2}J_{C\text{-}F}$ = 31.2 Hz); ^{19}F NMR (376 MHz, $CDCl_3$), δ −73.71; HRMS (ESI): *m/z* calcd for $C_9H_5ClF_3O_2$ $[M-H]^+$: 236.9930; found: 236.9929.

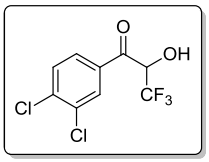
1-(3-chlorophenyl)-3,3,3-trifluoro-2-hydroxypropan-1-one (16l):[15]



Orange solid; Yield 80% (42.0 mg); m.p. 52–54 °C; FT IR (ATR) 3449, 1691 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$), δ 7.96 (t, *J* = 1.8 Hz, 1H), 7.84 (d, *J* = 7.8 Hz, 1H), 7.67 (ddd, *J* = 8.0, 2.2, 1.0 Hz, 1H), 7.50 (t, *J* = 7.8 Hz, 1H), 5.42–5.35 (m, 1H), 4.23 (d, *J* = 8.4 Hz, 1H [OH]); ^{13}C NMR (100 MHz, $CDCl_3$), δ 192.4, 135.6,

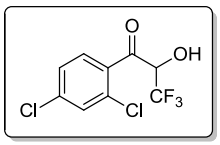
135.3, 135.0, 130.4, 129.4, 127.6, 122.3 (q, $^{1}J_{C\text{-}F}$ = 282.5 Hz), 71.3 (q, $^{2}J_{C\text{-}F}$ = 31.3 Hz); ^{19}F NMR (376 MHz, $CDCl_3$), δ −73.75; HRMS (ESI): *m/z* calcd for $C_9H_5ClF_3O_2$ $[M-H]^+$: 236.9930; found: 236.9921.

1-(3,4-dichlorophenyl)-3,3,3-trifluoro-2-hydroxypropan-1-one (16m):



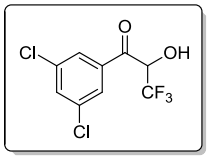
White solid; Yield 69% (41.4 mg); m.p. 53–55 °C; FT IR (ATR) 3298, 1694 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$), δ 8.08 (d, *J* = 2.1 Hz, 1H), 7.81–7.78 (m, 1H), 7.64 (d, *J* = 8.2 Hz, 1H), 5.38–5.31 (m, 1H), 4.15 (d, *J* = 8.4 Hz, 1H [OH]); ^{13}C NMR (100 MHz, $CDCl_3$), δ 191.5, 140.5, 134.3, 132.9, 131.3, 128.4, 128.4, 122.2 (q, $^{1}J_{C\text{-}F}$ = 282.8 Hz), 71.38 (q, $^{2}J_{C\text{-}F}$ = 31.4 Hz); ^{19}F NMR (376 MHz, $CDCl_3$), δ −73.74; HRMS (ESI): *m/z* calcd for $C_9H_4Cl_2F_3O_2$ $[M-H]^+$: 270.9540; found: 270.9542.

1-(2,4-dichlorophenyl)-3,3,3-trifluoro-2-hydroxypropan-1-one (16n):



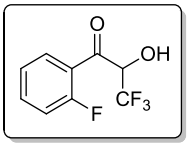
Yellow solid; Yield 78% (46.8 mg); m.p. 52–54 °C; FT IR (ATR) 3280, 1699 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$), δ 7.52 (d, *J* = 1.9 Hz, 1H), 7.47 (d, *J* = 8.4 Hz, 1H), 7.39 (dd, *J* = 8.4, 1.9 Hz, 1H), 5.52 (q, *J* = 7.0 Hz, 1H), 4.18 (brs, 1H [OH]); ^{13}C NMR (100 MHz, $CDCl_3$), δ 194.6, 139.9, 133.2, 133.1, 131.3, 131.1, 127.9, 122.3 (q, $^{1}J_{C\text{-}F}$ = 282.5 Hz), 74.2 (q, $^{2}J_{C\text{-}F}$ = 30.8 Hz); ^{19}F NMR (376 MHz, $CDCl_3$), δ −73.68; HRMS (ESI): *m/z* calcd for $C_9H_4Cl_2F_3O_2$ $[M-H]^+$: 270.9540; found: 270.9545.

1-(3,5-dichlorophenyl)-3,3,3-trifluoro-2-hydroxypropan-1-one (16o):



Colorless oil; Yield 62% (37.2 mg); m.p. 57–59 °C; FTIR (ATR) 3460, 1698 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$), δ 7.81–7.84 (d, *J* = 2.0 Hz, 2H), 7.68 (t, *J* = 2.0 Hz, 1H), 5.38–5.28 (m, 1H), 4.12 (d, *J* = 8.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$), δ 191.6, 136.4, 135.8, 135.0, 127.8, 122.2 (q, *J* = 282.8 Hz), 71.6 (q, *J* = 31.6 Hz); ^{19}F NMR (376 MHz, $CDCl_3$), δ −73.65; HRMS (ESI): *m/z* calcd for $C_9H_4Cl_2F_3O_2$ $[M-H]^+$: 270.9540; found: 270.9542.

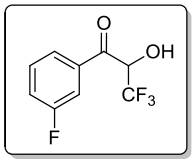
3,3,3-trifluoro-1-(2-fluorophenyl)-2-hydroxypropan-1-one (16p):



White solid; Yield 74% (36.0 mg); m.p. 61–63 °C; FT IR (ATR) 3447, 1682 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$), δ 7.94–7.89 (m, 1H), 7.70–7.64 (m, 1H), 7.34–7.30 (m, 1H), 7.26–7.19 (m, 1H), 5.51–5.44 (m, 1H), 4.24 (dd, *J* = 8.2, 1.3 Hz, 1H [OH]); ^{13}C NMR (100 MHz, $CDCl_3$), δ 191.75–191.67 (m), 162.4 (d, $^{1}J_{C\text{-}F}$ = 249.5 Hz), 137.1 (d, $^{4}J_{C\text{-}F}$ = 9.4 Hz), 131.3 (d, $^{6}J_{C\text{-}F}$ = 1.5 Hz), 125.2 (d, $^{5}J_{C\text{-}F}$ = 3.0 Hz), 122.5 (q, $^{1}J_{C\text{-}F}$ =

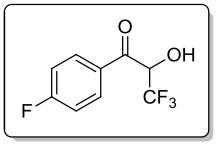
283.2 Hz), 122.3 (d, $^{3}J_{C\text{-}F}$ = 12.7 Hz), 117.0 (d, $^{2}J_{C\text{-}F}$ = 23.6 Hz), 74.7 (qd, $^{2}J_{C\text{-}F}$ = 30.6, 11.1 Hz); ^{19}F NMR (376 MHz, $CDCl_3$), δ −74.77 (d, $J_{F\text{-}F}$ = 7.1 Hz), −108.87 (q, $J_{F\text{-}F}$ = 7.4 Hz); HRMS (ESI): *m/z* calcd for $C_9H_5F_4O_2$ $[M-H]^+$: 221.0226; found: 221.0223.

3,3,3-trifluoro-1-(3-fluorophenyl)-2-hydroxypropan-1-one (16q):



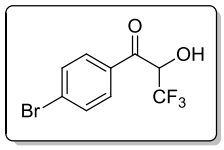
Yellow solid; Yield 68% (33.0 mg); m.p. 66–68 °C; FT IR (ATR) 3452, 1692 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$), δ 7.76 (d, J = 7.8 Hz, 1H), 7.70–7.66 (m, 1H), 7.57–7.52 (m, 1H), 7.43–7.38 (m, 1H), 5.41–5.34 (m, 1H), 4.20 (d, J = 8.4 Hz, 1H [OH]); ^{13}C NMR (100 MHz, $CDCl_3$), δ 192.4, 162.9 (d, $^{1}J_{C\text{-}F}$ = 247.7 Hz), 135.4 (d, $J_{C\text{-}F}$ = 7.0 Hz), 130.9 (d, $J_{C\text{-}F}$ = 7.3 Hz), 125.4 (d, $J_{C\text{-}F}$ = 1.7 Hz), 122.6 (q, $J_{C\text{-}F}$ = 22.5 Hz), 122.3 (q, $^{1}J_{C\text{-}F}$ = 281.6 Hz), 116.2 (d, $J_{C\text{-}F}$ = 22.5 Hz), 71.4 (q, $^{2}J_{C\text{-}F}$ = 31.6 Hz); ^{19}F NMR (376 MHz, $CDCl_3$), δ −73.76, −110.40; HRMS (ESI): *m/z* calcd for $C_9H_5F_4O_2$ $[M-H]^+$: 221.0226; found: 221.0220.

3,3,3-trifluoro-1-(4-fluorophenyl)-2-hydroxypropan-1-one (16r):



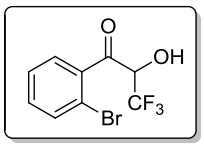
Pale yellow solid; Yield 65% (31.8 mg); m.p. 52–54 °C; FTIR (ATR) 3445, 1687 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$), δ 8.09–8.00 (m, 2H), 7.29–7.19 (m, 2H), 5.42–5.34 (m, 1H), 4.27 (d, J = 8.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$), δ 191.6, 167.2 (d, J = 256.3 Hz), 132.5 (d, J = 10.9 Hz), 129.9 (d, J = 4.3 Hz), 122.42 (q, J = 280.8 Hz), 116.6 (d, J = 21.6 Hz), 71.1 (q, J = 30.4 Hz); ^{19}F NMR (376 MHz, $CDCl_3$), δ −73.89, −100.35; HRMS (ESI): *m/z*: calcd for $C_9H_5F_4O_2$ $[M-H]^+$: 221.0226; found: 221.0222.

1-(4-Bromophenyl)-3,3,3-trifluoro-2-hydroxypropan-1-one (16s):[15]



White solid; Yield 85% (52.9 mg); m.p. 85–87 °C; FT IR (ATR) 3327, 1678 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$), δ 7.85 (d, J = 8.7 Hz, 2H), 7.70 (d, J = 8.7 Hz, 2H), 5.37 (q, J = 6.6 Hz, 1H), 4.25 (brs, 1H [OH]); δ ^{13}C NMR (100 MHz, $CDCl_3$), δ 192.3, 132.6, 132.1, 131.2, 130.9, 122.3 (q, $^{1}J_{C\text{-}F}$ = 282.3 Hz), 71.2 (q, $^{2}J_{C\text{-}F}$ = 31.4 Hz); ^{19}F NMR (376 MHz, $CDCl_3$), δ −73.80; HRMS (ESI): *m/z* calcd for $C_9H_5BrF_3O_2$ $[M-H]^+$: 280.9425; found: 280.9428.

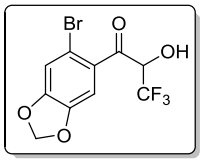
1-(2-bromophenyl)-3,3,3-trifluoro-2-hydroxypropan-1-one (16t):



Orange semi solid; Yield 68% (42.2 mg); FT IR (ATR) 3439, 1709 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$), δ 7.71–7.68 (m, 1H), 7.46–7.41 (m, 3H), 5.54–5.45 (m, 1H), 4.15 (brd, J = 5.8 Hz, 1H [OH]); ^{13}C NMR (100 MHz, $CDCl_3$), δ

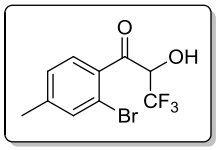
196.6, 137.0, 134.4, 133.7, 130.0, 127.8, 122.3 (q, $^{1}J_{C\text{-}F}$ = 282.5 Hz), 119.9, 73.9 (q, $^{2}J_{C\text{-}F}$ = 31.0 Hz); ^{19}F NMR (376 MHz, $CDCl_3$), δ −73.38; HRMS (ESI): *m/z* calcd for $C_9H_5BrF_3O_2$ $[M-H]^+$: 280.9425; found: 280.9428.

1-(6-bromobenzo[d][1,3]dioxol-5-yl)-3,3,3-trifluoro-2-hydroxypropan-1-one (16u):



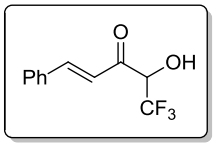
Pale yellow solid: Yield 67% (48.2 mg); FTIR (ATR) 3432, 1704 cm^{-1}; m.p. (82–84 °C); ^{1}H NMR (400 MHz, $CDCl_3$), δ 7.11 (s, 1H), 6.94 (s, 1H), 6.11 (q, *J* = 1.3 Hz, 2H), 5.57–5.47 (m, 1H), 4.15 (d, *J* = 7.6 Hz, 1H), δ ^{13}C NMR (100 MHz, $CDCl_3$), δ 194.7, 152.0, 147.8, 129.7, 122.4 (q, *J* = 282.8 Hz), 114.6, 113.6, 109.9, 103.1, 73.4 (q, *J* = 30.7 Hz); ^{19}F NMR (376 MHz, $CDCl_3$), δ −73.66; HRMS (ESI): *m/z* calcd for $C_{10}H_5BrF_3O_4$ $[M-H]^+$: 324.9323; found: 324.9314.

1-(3-bromo-4-methylphenyl)-3,3,3-trifluoro-2-hydroxypropan-1-one (16v):



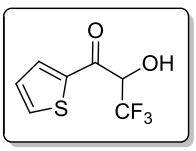
Yellow oil; Yield 72% (47.0 mg); FT IR (ATR) 3436, 1703 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$), δ 7.53 (brs, 1H), 7.37 (d, *J* = 7.9 Hz, 1H), 7.26–7.23 (m, 1H), 5.55–5.48 (m, 1H), 4.17 (brd, *J* = 7.4 Hz, 1H [OH]), 2.41 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$), δ 195.6, 145.3, 135.2, 133.7, 130.3, 128.5, 122.4 (q, $^{1}J_{C\text{-}F}$ = 282.8 Hz), 120.3, 73.5 (q, $^{2}J_{C\text{-}F}$ = 30.5 Hz), 21.4; ^{19}F NMR (376 MHz, $CDCl_3$), δ −73.53; HRMS (ESI): *m/z* calcd for $C_{10}H_9BrF_3O_2$ $[M+H]^+$: 296.9738; found: 296.9739.

(E)-5,5,5-trifluoro-4-hydroxy-1-phenylpent-1-en-3-one (16w):



Pale yellow solid; Yield 66% (33.4 mg); m.p. 85–87 °C; FT IR (ATR) 3398, 1689 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$), δ 7.91 (d, *J* = 15.8 Hz, 1H), 7.65–7.59 (m, 2H), 7.51–7.42 (m, 3H), 6.99 (dd, *J* = 15.8, 1.0 Hz, 1H), 4.82–4.70 (m, 1H [OH]), 4.25 (d, *J* = 6.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$), δ 190.8 (q, $^{3}J_{C\text{-}F}$ = 1.5 Hz), 148.0, 133.6, 132.2, 129.4, 129.3, 122.8 (q, $^{1}J_{C\text{-}F}$ = 281.5 Hz), 119.94–119.86 (m), 74.1 (q, $^{2}J_{C\text{-}F}$ = 30.9 Hz); ^{19}F NMR (376 MHz, $CDCl_3$), δ −74.07; HRMS (ESI): *m/z* calcd for $C_{11}H_8F_3O_2$ $[M-H]^+$: 229.0476; found: 229.0481.

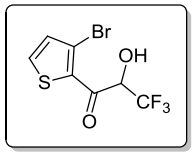
3,3,3-trifluoro-2-hydroxy-1-(thiophen-2-yl)propan-1-one (16x):[16]



Yellow solid; Yield 74% (34.2 mg); m.p. 107–109 °C; FT IR (ATR) 3353, 1655 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$), δ 7.89 (dd, *J* = 4.9, 1.1 Hz, 1H), 7.87–7.86 (m, 1H), 7.26–7.24 (m, 1H), 5.23–5.17 (m, 1H), 4.16 (brd, *J* = 8.3 Hz, 1H [OH]); ^{13}C NMR (100 MHz, $CDCl_3$), δ 184.7 (q, $^{3}J_{C\text{-}F}$ = 1.5 Hz), 139.7, 137.7, 135.68–135.62

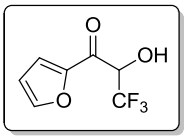
(m), 129.0, 122.4 (q, $^{1}J_{C\text{-}F}$ = 282.8 Hz), 72.1 (q, $^{2}J_{C\text{-}F}$ = 30.4 Hz); ^{19}F NMR (376 MHz, $CDCl_3$), δ −74.52.

1-(3-bromothiophen-2-yl)-3,3,3-trifluoro-2-hydroxypropan-1-one (16y):



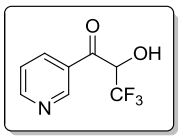
Pale yellow oil; Yield 80% (50.8 mg); FT IR (ATR) 3440, 1655, 3110 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$), δ 7.73 (d, J = 5.2 Hz, 1H), 7.20 (d, J = 5.2 Hz, 1H), 5.73–5.66 (m, 1H), 4.20 (d, J = 9.2 Hz, 1H [OH]); ^{13}C NMR (100 MHz, $CDCl_3$), δ 185.3, 135.6, 134.5, 134.3, 122.4 (q, $^{1}J_{C\text{-}F}$ = 284.3 Hz), 118.3, 72.2 (q, $^{2}J_{C\text{-}F}$ = 30.7 Hz); ^{19}F NMR (376 MHz, $CDCl_3$), δ −74.25; HRMS (ESI): *m/z* calcd for $C_7H_3BrF_3O_2S$ $[M-H]^+$: 286.8989; found: 286.8973.

3,3,3-trifluoro-1-(furan-2yl)-2-hydroxypropan-1-one (16z):



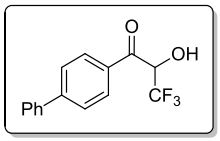
White solid; Yield 60% (25.6 mg); m.p. 140–142 °C; FT IR (ATR) 3399, 1674 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$), δ 7.77 (dd, J = 1.6, 0.6 Hz, 1H), 7.48 (d, J = 3.7 Hz, 1H), 6.69 (dd, J = 3.7, 1.6 Hz, 1H), 5.24–5.17 (m, 1H), 4.07 (d, J = 8.8 Hz, 1H [OH]); ^{13}C NMR (100 MHz, $CDCl_3$), δ 180.4, 150.0, 149.2, 122.5 (q, $^{1}J_{C\text{-}F}$ = 282.5 Hz), 122.0, 113.5, 71.4 (q, $^{2}J_{C\text{-}F}$ = 32.0 Hz); ^{19}F NMR (376 MHz, $CDCl_3$), δ −74.89; HRMS (ESI): *m/z* calcd for $C_7H_4F_3O_3$ $[M-H]^+$: 193.0113; found: 193.0107.

3,3,3-trifluoro-2-hydroxy-1-(pyridin-3-yl)propan-1-one (16aa):[15]



White solid; Yield 74% (33.4 mg); m.p. 120–122 °C; FT IR (ATR) 3016, 1705 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$), δ 9.20 (d, J = 2.2 Hz, 1H), 8.90 (dd, J = 4.8, 1.7 Hz, 1H), 8.28 (dt, J = 8.0, 2.2 Hz, 1H), 7.54 (ddd, J = 8.0, 4.8, 0.9 Hz, 1H), 5.41 (q, J = 6.6 Hz, 1H), 4.23 (d, J = 1.7 Hz, 1H [OH]); ^{13}C NMR (100 MHz, $CDCl_3$), δ 192.5 (q, $^{3}J_{C\text{-}F}$ = 1.4 Hz), 155.3, 150.5, 136.8, 129.4, 124.1, 122.3 (q, $^{1}J_{C\text{-}F}$ = 282.1 Hz), 71.8 (q, $^{2}J_{C\text{-}F}$ = 31.3 Hz); ^{19}F NMR (376 MHz, $CDCl_3$), δ −73.72; HRMS (ESI): *m/z* calcd for $C_8H_5F_3NO_2$ $[M-H]^+$: 204.0272; found: 204.0263.

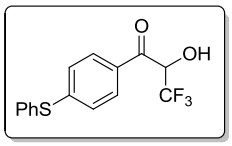
1-[(1,1'-biphenyl)-4-yl]-3,3,3-trifluoro-2-hydroxypropan-1-one (16ab):



White solid; Yield 76% (46.8 mg); m.p. 136–138 °C; FT IR (ATR) 3379, 1685 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$), δ 8.07 (d, J = 8.3 Hz, 2H), 7.77 (d, J = 8.3 Hz, 2H), 7.66–7.63 (m, 2H), 7.52–7.42 (m, 3H), 5.49–5.42 (m, 1H), 4.32 (d, J

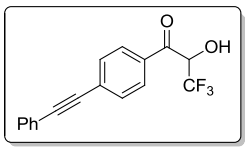
= 8.3 Hz, 1H [OH]); ^{13}C NMR (100 MHz, $CDCl_3$), δ 192.6, 148.3, 139.3, 132.0, 130.3, 129.3, 129.0, 127.7, 127.5, 122.5 (q, $^1J_{C\text{-}F}$ = 283.7 Hz), 71.09 (q, $^2J_{C\text{-}F}$ = 31.5 Hz); ^{19}F NMR (376 MHz, $CDCl_3$), δ −73.81; HRMS (ESI): *m/z* calcd for $C_{15}H_{10}F_3O_2$ $[M-H]^+$: 279.0633; found: 279.0632.

3,3,3-trifluoro-2-hydroxy-1-(4-(phenylthio)propan-1-one (16ac):



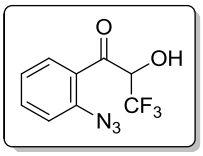
White solid; Yield 84% (57.5 mg); m.p. 135–137 °C; FT IR (ATR) 3432, 1668 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$), δ 7.82 (d, *J* = 8.6 Hz, 2H), 7.57–7.55 (m, 2H), 7.48–7.44 (m, 3H), 7.19 (d, *J* = 8.6 Hz, 2H), 5.36–5.29 (m, 1H), 4.28 (dd, *J* = 8.3, 1.8 Hz, 1H [OH]); ^{13}C NMR (100 MHz, $CDCl_3$), δ 191.7, 149.6, 135.1, 130.3, 130.1, 130.0, 130.0, 129.8, 126.5, 122.5 (q, $^1J_{C\text{-}F}$ = 282.9 Hz), 70.8 (q, $^2J_{C\text{-}F}$ = 31.3 Hz); ^{19}F NMR (376 MHz, $CDCl_3$), δ −73.95; HRMS (ESI): *m/z* calcd for $C_{15}H_{10}F_3O_2S$ $[M-H]^+$: 311.0354; found: 311.0355.

3,3,3-trifluoro-2-hydroxy-1-(4-(phenylethynyl)phenyl)propan-1-one (16ad):



Pale yellow solid; Yield 80% (53.5 mg); m.p. 137–139 °C; FT IR (ATR) 3458, 1680, 2226 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$), δ 7.97 (d, *J* = 8.6 Hz, 2H), 7.68 (d, *J* = 8.6 Hz, 2H), 7.59–7.54 (m, 2H), 7.42–7.36 (m, 3H), 5.45–5.38 (m, 1H), 4.27 (d, *J* = 8.4 Hz, 1H [OH]); ^{13}C NMR (100 MHz, $CDCl_3$), δ 192.3, 132.3, 132.1, 132.0, 130.8, 129.6, 129.3, 128.7, 122.4 (q, $^1J_{C\text{-}F}$ = 282.8 Hz), 122.4, 94.7, 88.3, 71.1 (q, $^2J_{C\text{-}F}$ = 31.1 Hz); ^{19}F NMR (376 MHz, $CDCl_3$), δ −73.81; HRMS (ESI): *m/z* calcd for $C_{17}H_{10}F_3O_2$ $[M-H]^+$: 303.0633; found: 303.0630.

1-(2-azidophenyl)-3,3,3-trifluoro-2-hydroxypropan-1-one (16ae):

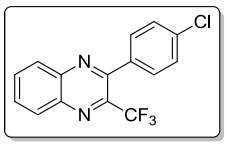


Pale yellow solid; Yield 65% (35.0 mg); m.p. 90–92 °C; FT IR (ATR) 3441, 2129, 1687 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$), δ 7.71–7.69 (m, 1H), 7.66–7.62 (m, 1H), 7.29–7.24 (m, 2H), 5.89–5.83 (m, 1H), 4.23 (brd, *J* = 6.7 Hz, 1H [OH]); ^{13}C NMR (100 MHz, $CDCl_3$), δ 194.55–194.50 (m), 140.0, 135.1, 131.4, 126.9, 125.3, 122.6 (q, $^1J_{C\text{-}F}$ = 282.9 Hz), 119.2, 74.4 (q, $^2J_{C\text{-}F}$ = 29.9 Hz); ^{19}F NMR (376 MHz, $CDCl_3$), δ −74.22; HRMS (ESI): *m/z* calcd for $C_9H_5F_3NO_2$ $[M-H-N_2]^+$: 216.0272; found 216.0271.

Synthesis of 2-(4-chlorophenyl)-3-(trifluoromethyl) quinoxoline (19b):[17]

To a mixture of 1-(4-chlorophenyl)-3,3,3-trifluoro-2-hydroxypropan-1-one **13c** (30 mg, 0.13 mmol) and *o*-phenylenediamine **19a** (21 mg, 0.19 mmol) was added AcOH (1.0 ml). After

refluxing the resultant mixture for 8 h, AcOH was removed under vacum and residue was purified through silica gel column using 5% EtOAc/Hexane mixture as an eluent to afford quinoxoline (**19b**).



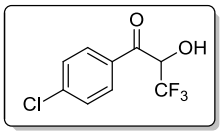
White solid: Yield 65% (44.0 mg); m.p. 146–148 °C; FT IR (ATR) 1185, 1130, 1070 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$), δ 8.29–8.27 (m, 1H), 8.22–8.20 (m, 1H), 8.00–7.89 (m, 2H), 7.59 (d, J = 8.5 Hz, 2H), 7.51 (d, J = 8.5 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$), δ 151.6, 142.7, 141.2 (q, $^{2}J_{C\text{-}F}$ = 34.3 Hz), 139.6, 136.1, 135.9, 133.0, 131.6, 130.47–130.42 (m), 129.9, 129.5, 128.8, 121.5 (q, $^{1}J_{C\text{-}F}$ = 274.7 Hz); ^{19}F NMR (376 MHz, $CDCl_3$), δ −61.65; HRMS (ESI): *m/z* calcd for $C_{15}H_9ClF_3N_2$ $[M+H]^+$: 309.0406; found: 309.0404.

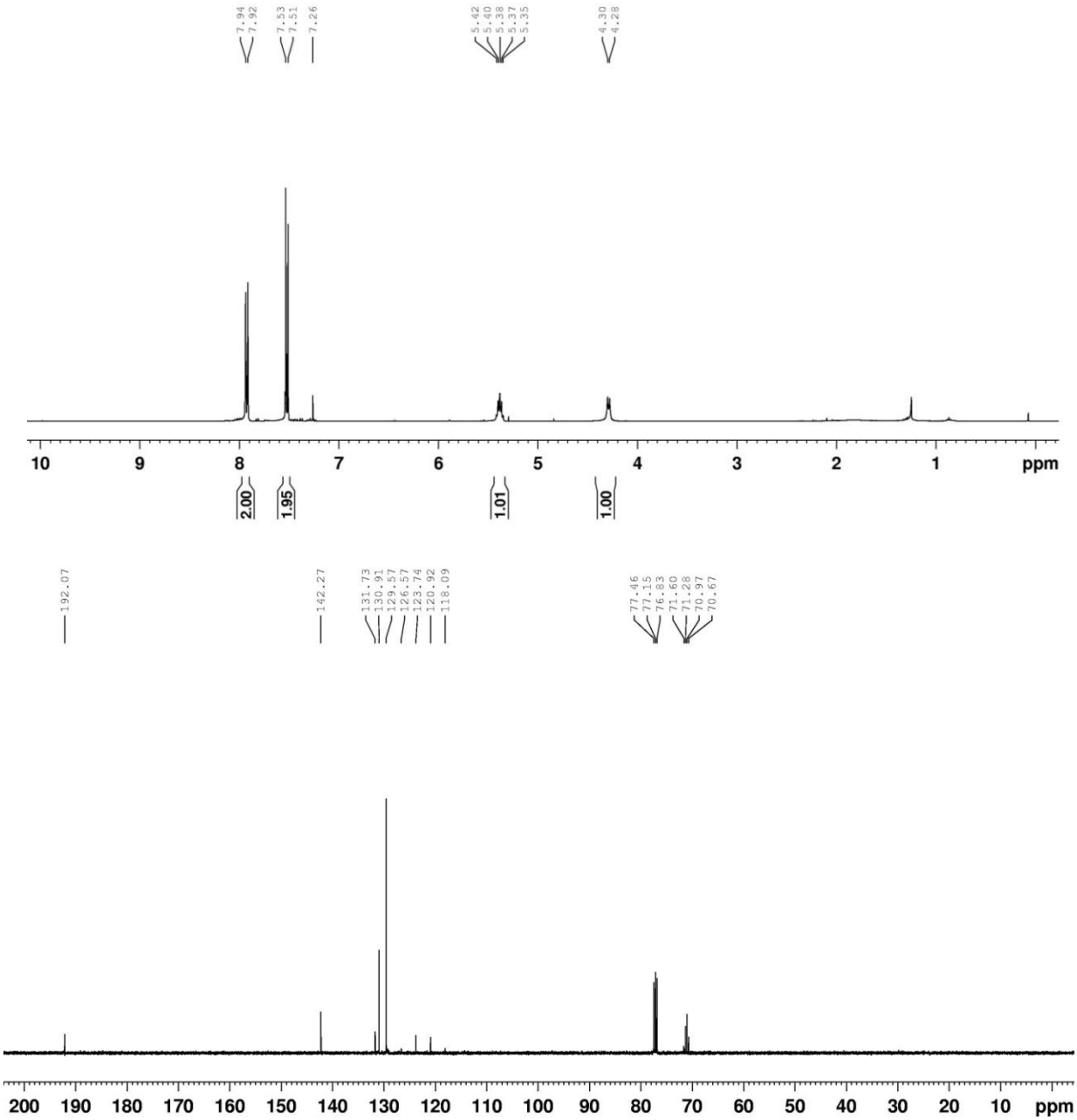
Procedure for the chiral NHC catalyzed intermolecular crossed acyloin condensation of *p*-chlorobenzaldehyde with trifluoroacetaldehyde ethyl hemiacetal

1,8-Diazabicyclo[5.4.0]undec-7-ene (6 mg, 0.042 mmol) was added to a suspension of chiral NHC **20a** or **20b** (6.5 mg, 0.014 mmol), *p*-chlorobenzaldehyde **13a** (20 mg, 0.14 mmol) and trifluoroacetaldehyde ethyl hemiacetal **13b** (90% aq. solution, 56 μL, 0.42 mmol) in dry THF (1.0 mL) at room temperature (23–26 °C) and the resulting suspension was stirred at indicated temperature and time. After completion of the reaction, the solvent was removed under reduced pressure and extracted with EtOAc and water, and the resulting organic layer was removed under reduced pressure. Then the residue was dissolved in 9:1 *n*-Hexane/2-Propanol (HPLC grade solvent), and filtered. 20 μL of sample was injected in HPLC system, 9:1 *n*-hexane/2-propanol (1.0 mL/min) mixture was eluted through CHIRALPAK® IA Column, and 30% *ee* was observed. τ_{min} = 8.5 (major), 9.1 (minor). **Optical rotation:** $[\alpha]_D^{23}$ = +6.6 (*c* 0.07, $CHCl_3$), at 589 nm for a sample with 30% *ee*.

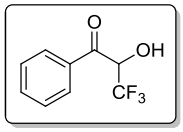
Spectra of compounds (**13c**, **16a–16z**, **16aa–16ae** & **19b**)

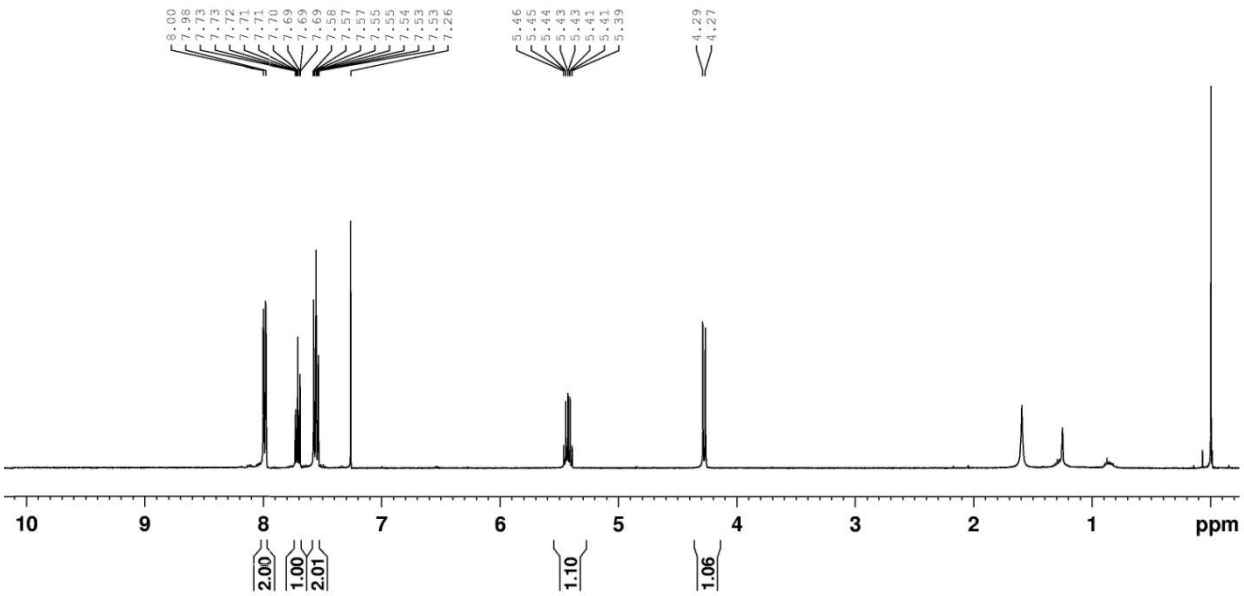
^{1}H, ^{13}C NMR Spectra of **13c**

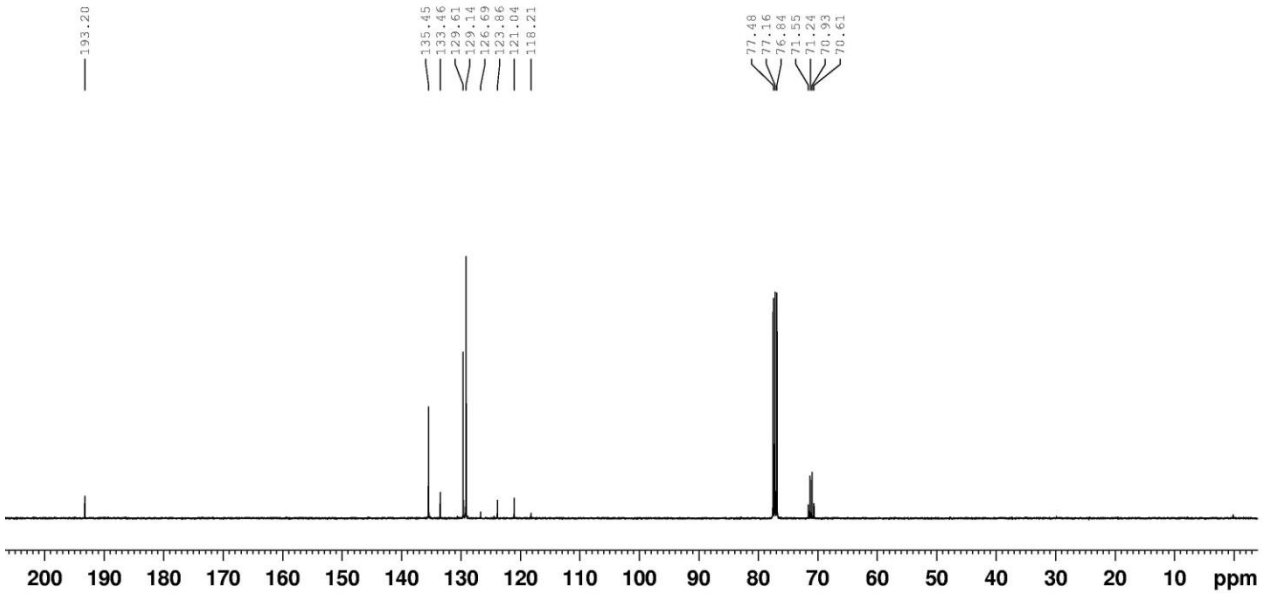




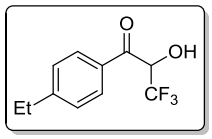
^{1}H, ^{13}C NMR Spectra of **16a**

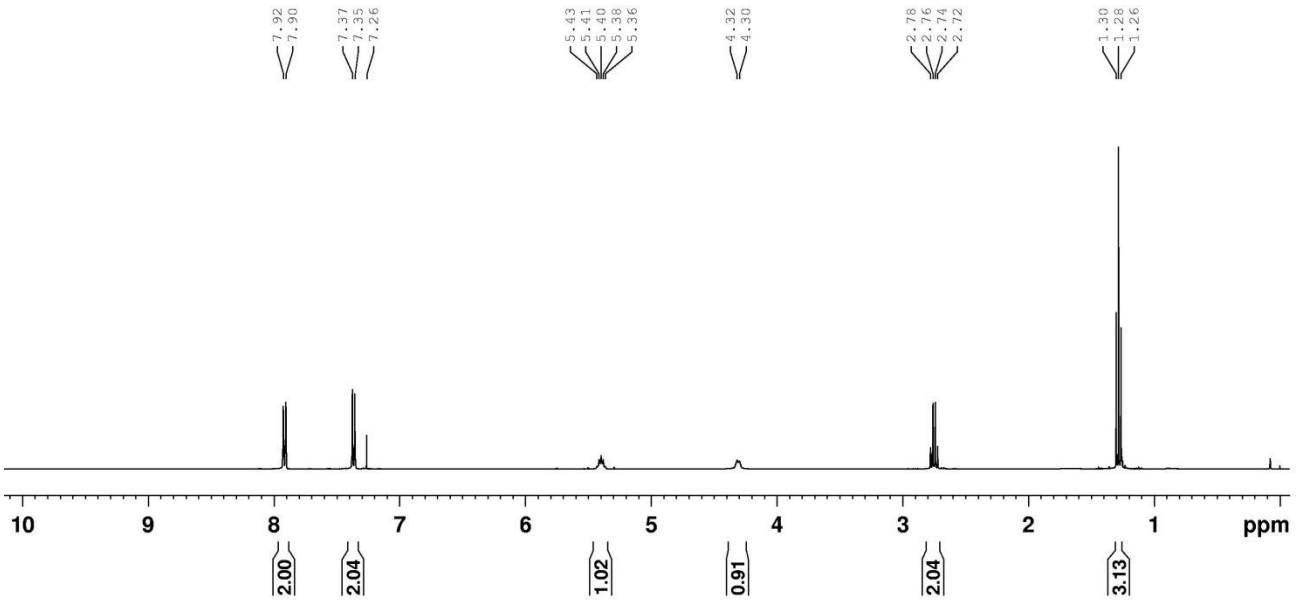


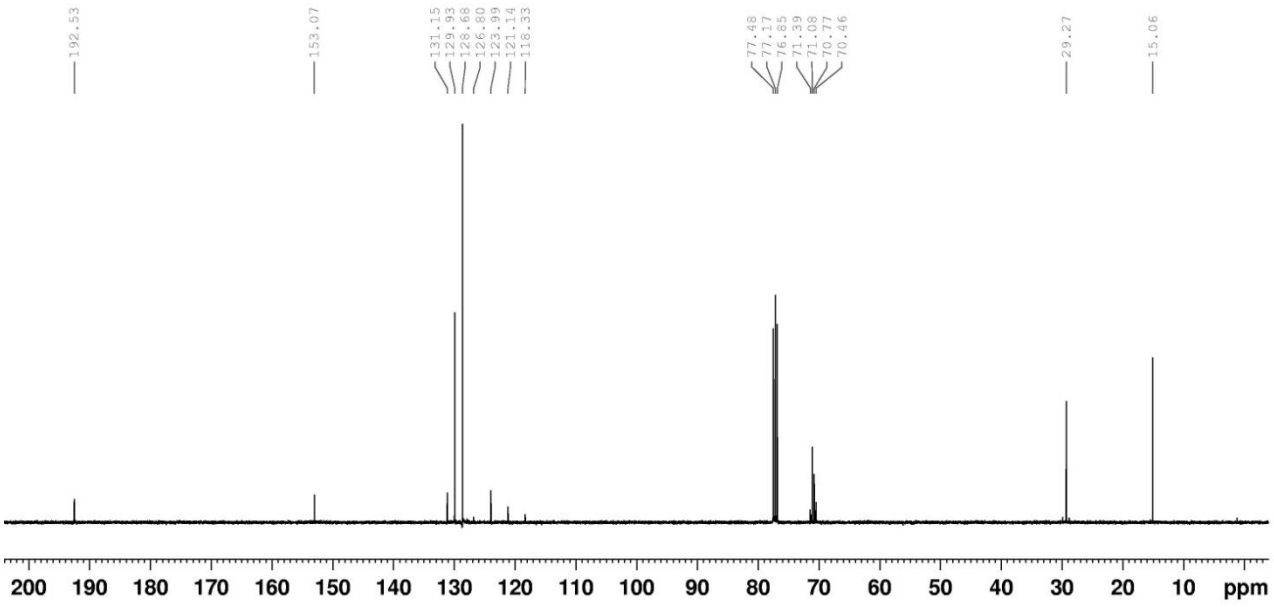




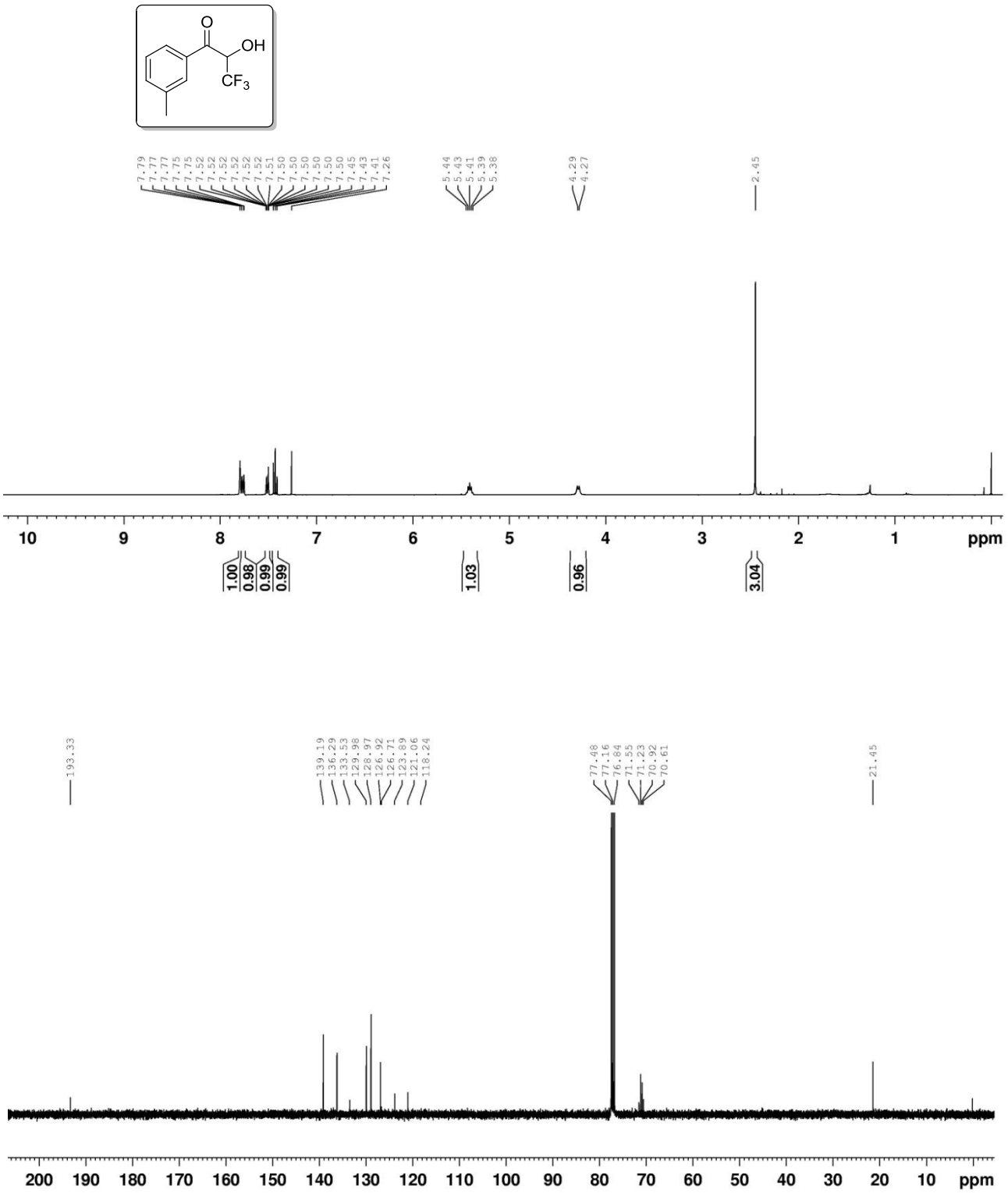
^{1}H, ^{13}C NMR Spectra of **16b**



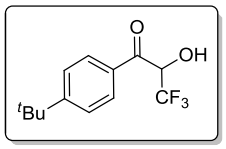


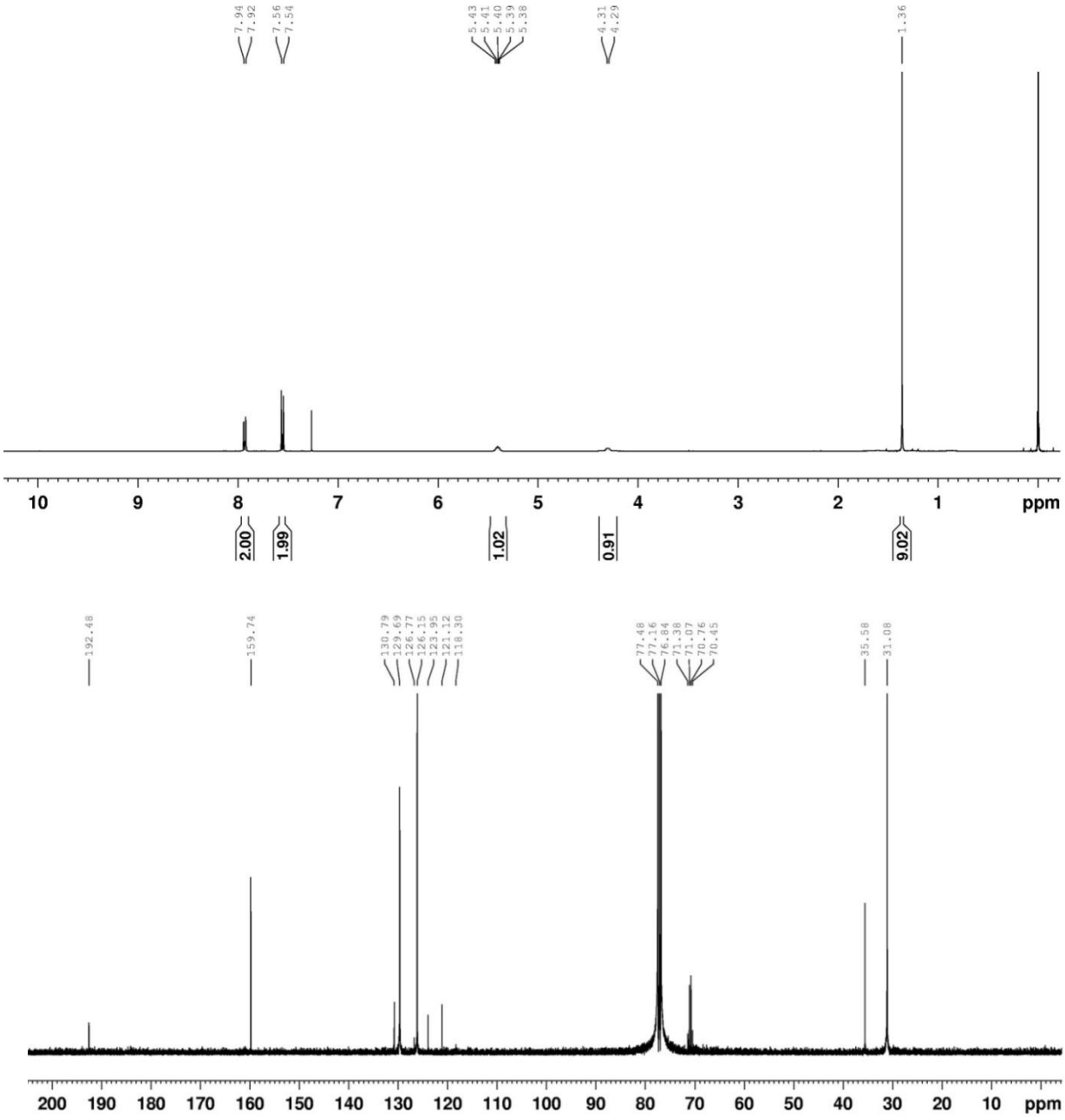


^{1}H, ^{13}C NMR Spectra of **16c**

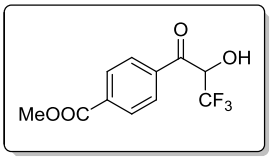


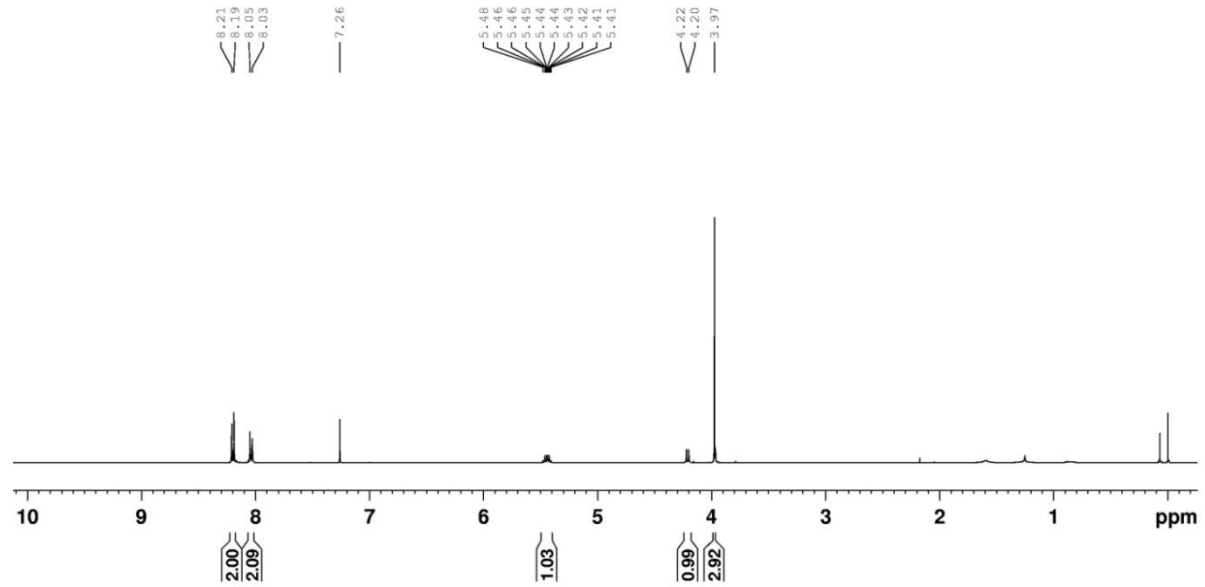
^{1}H, ^{13}C NMR Spectra of **16d**

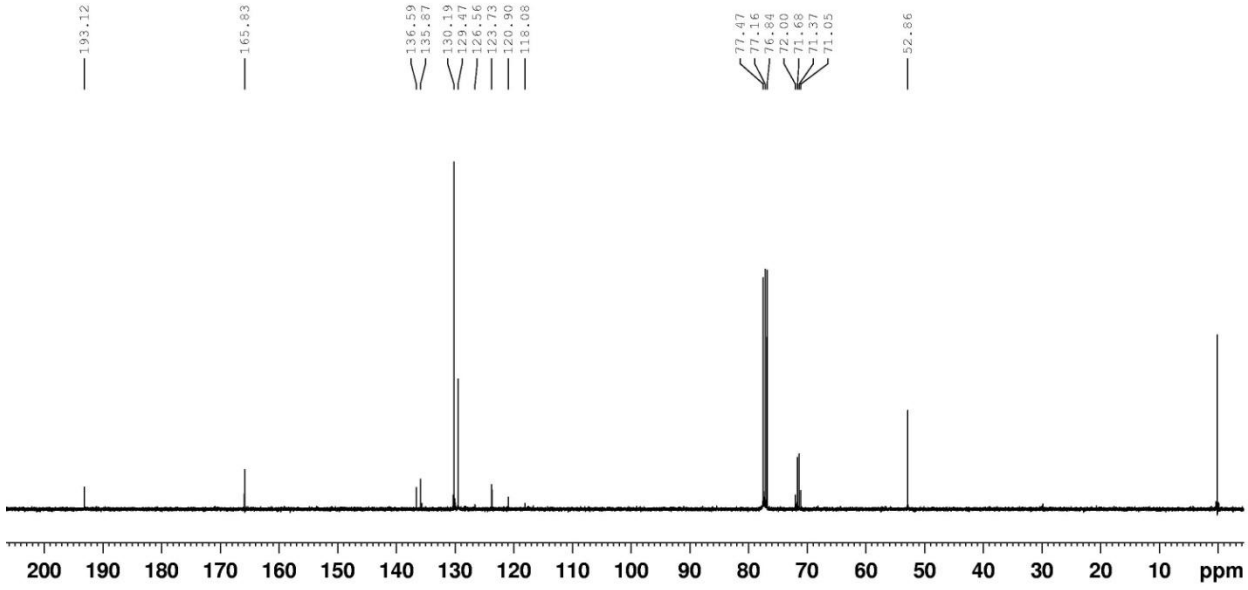




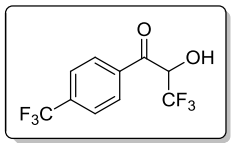
^{1}H, ^{13}C NMR Spectra of **16e**

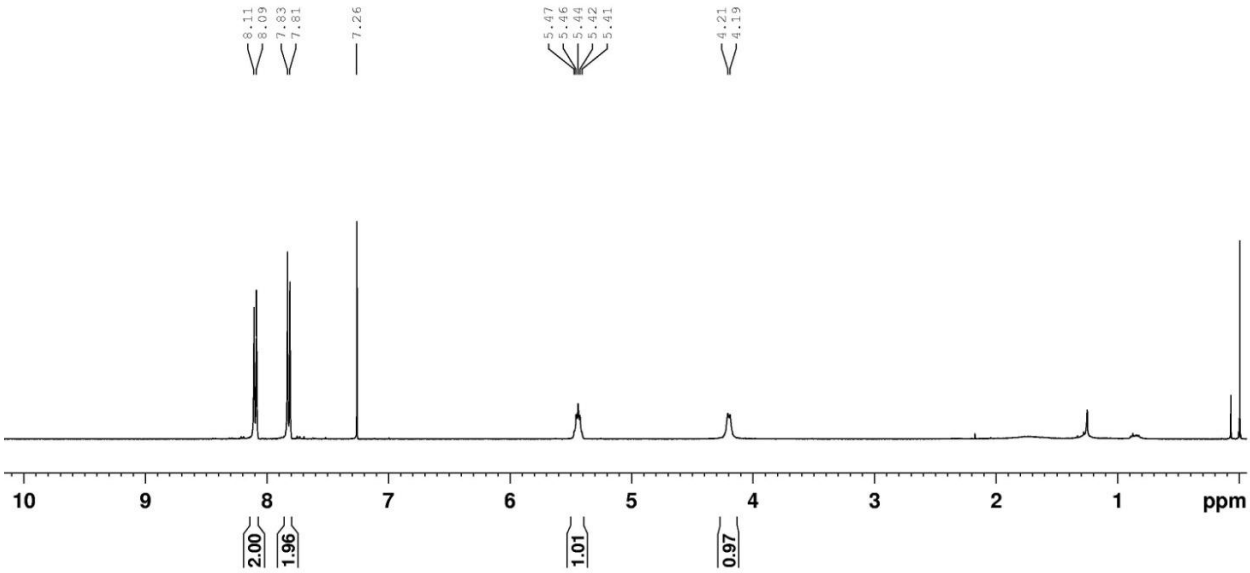


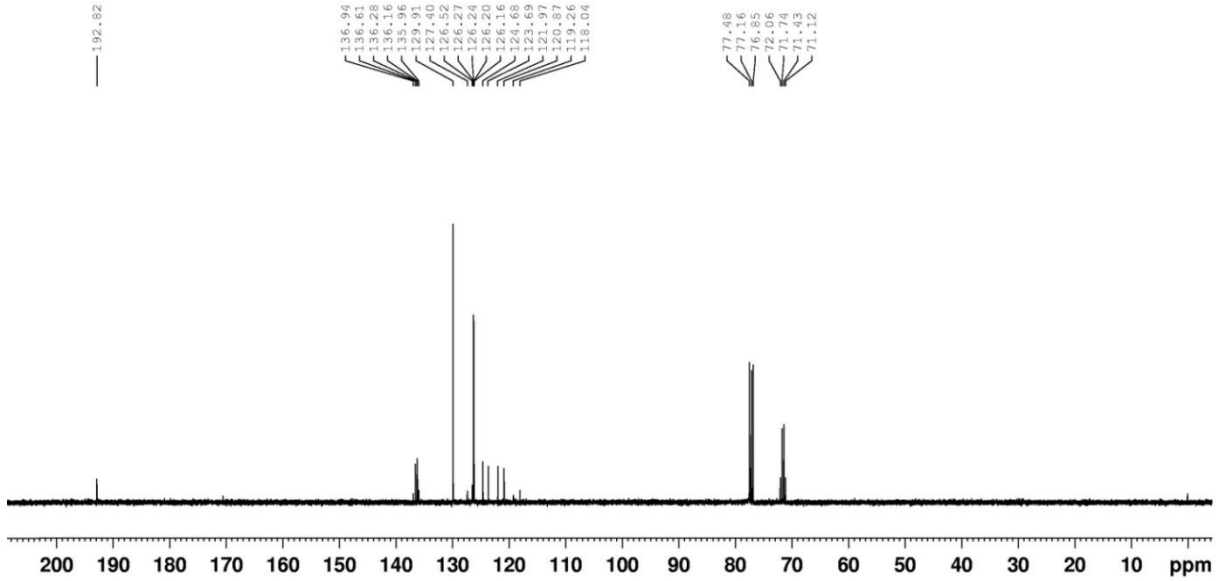




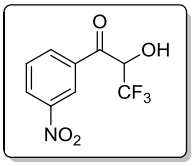
^{1}H, ^{13}C NMR Spectra of **16f**

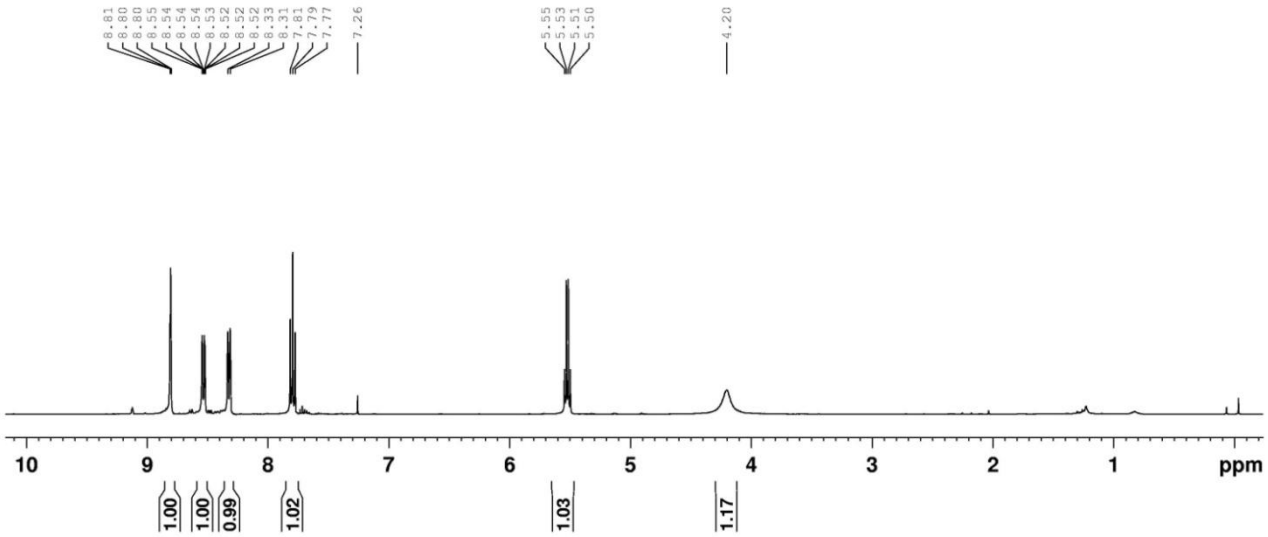


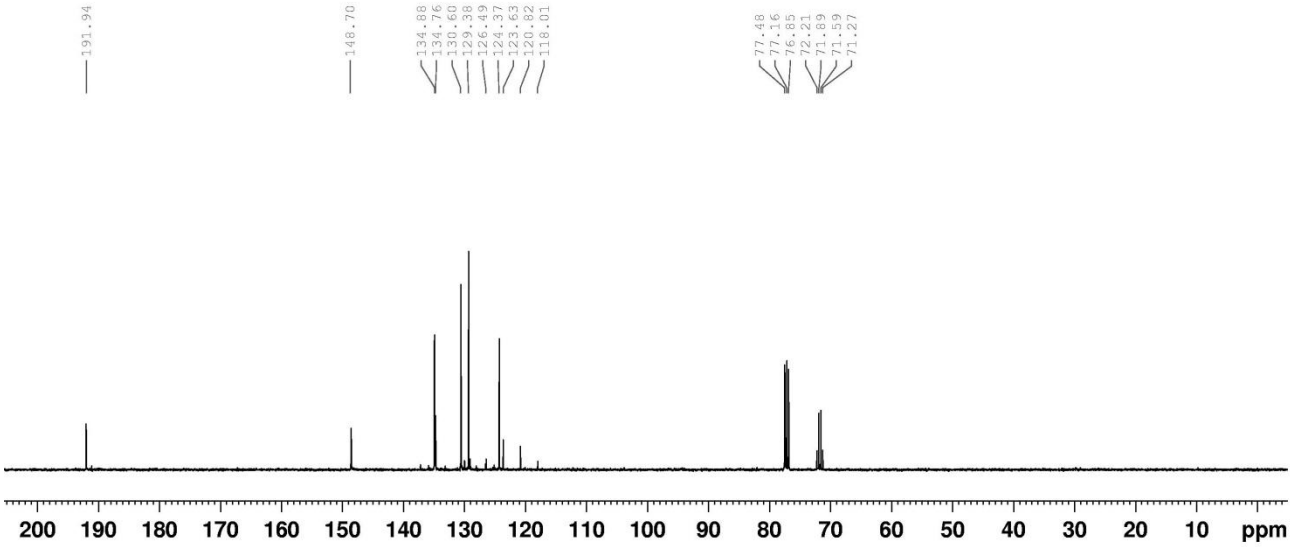




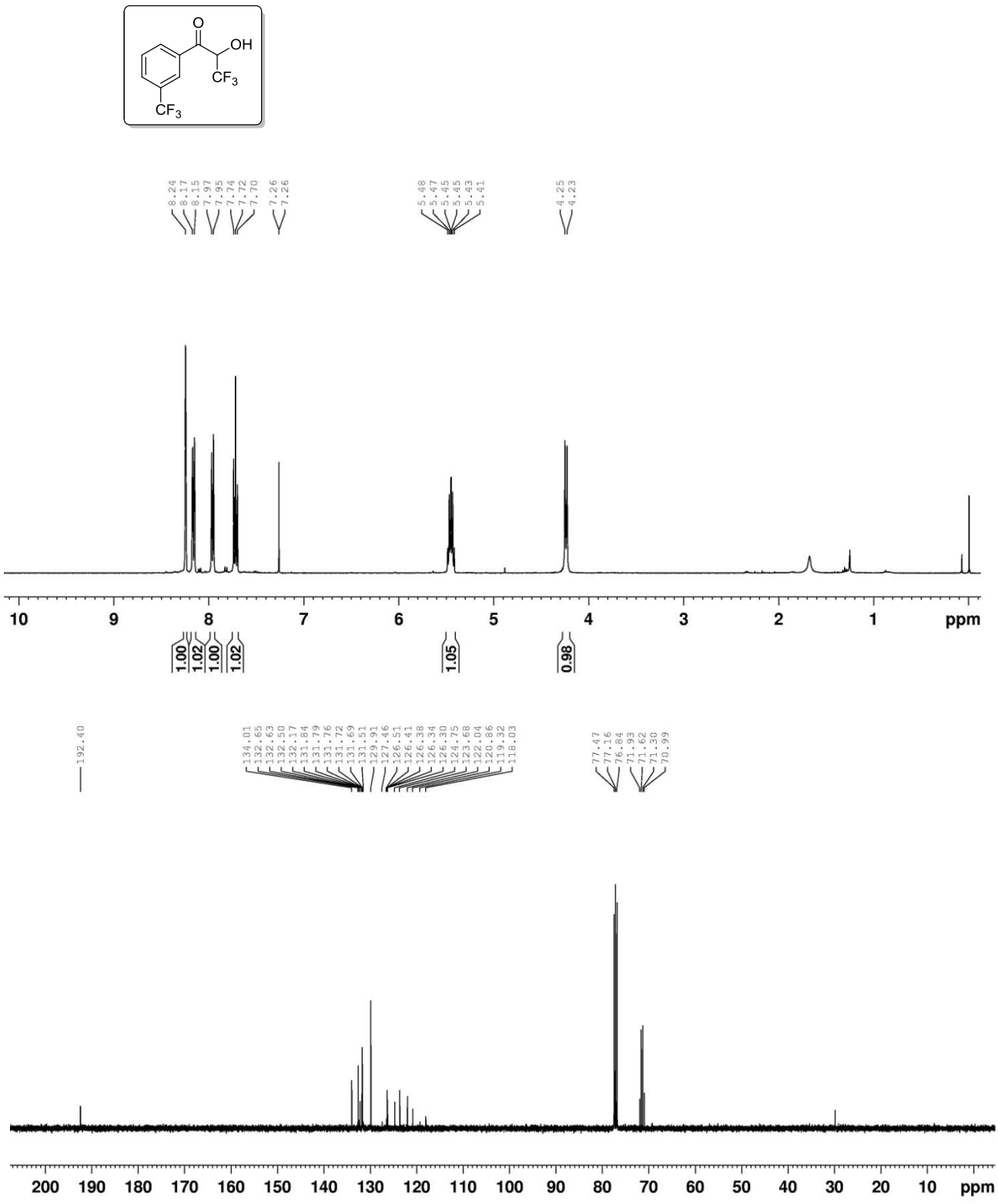
^{1}H, ^{13}C NMR Spectra of **16g**



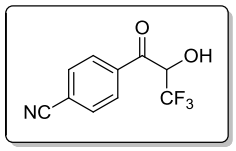


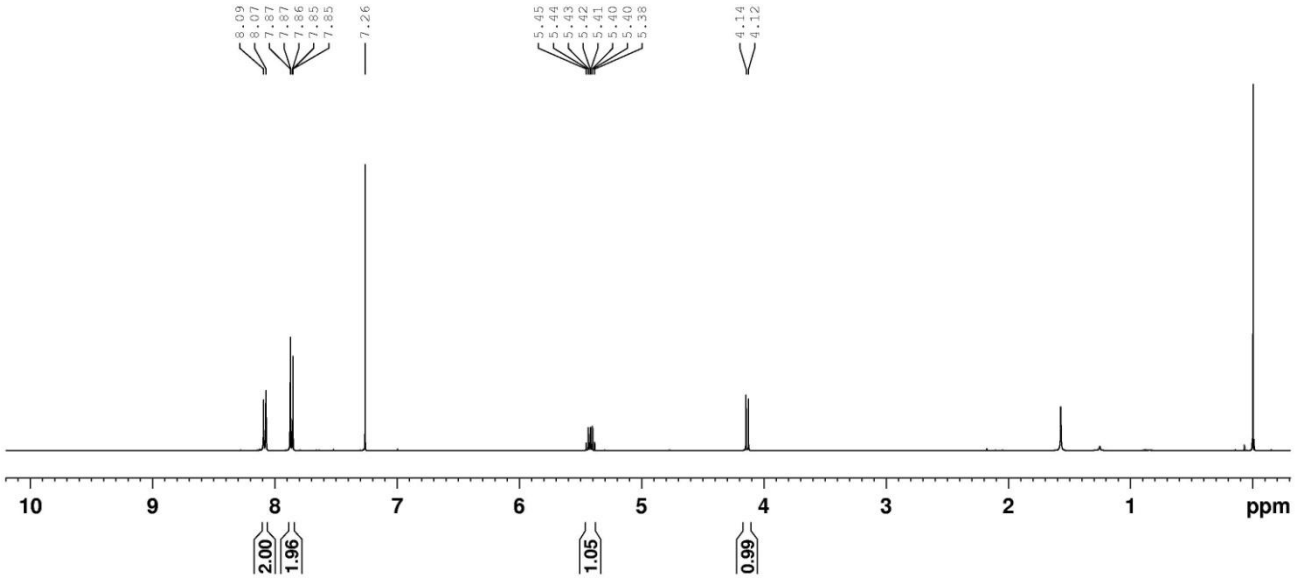


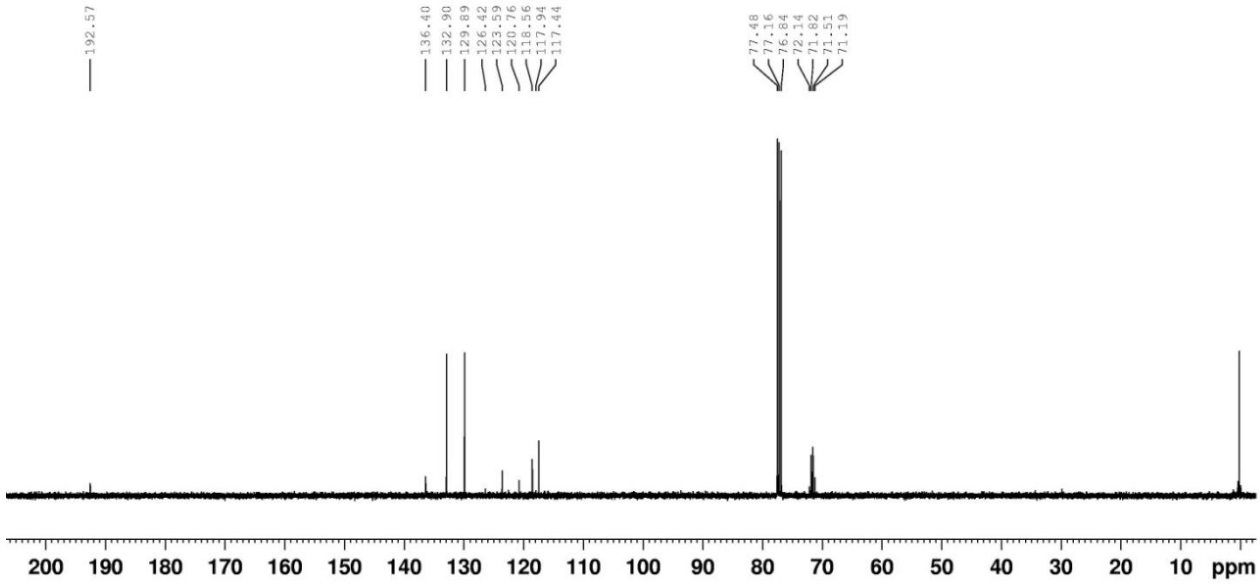
^{1}H, ^{13}C NMR Spectra of **16h**



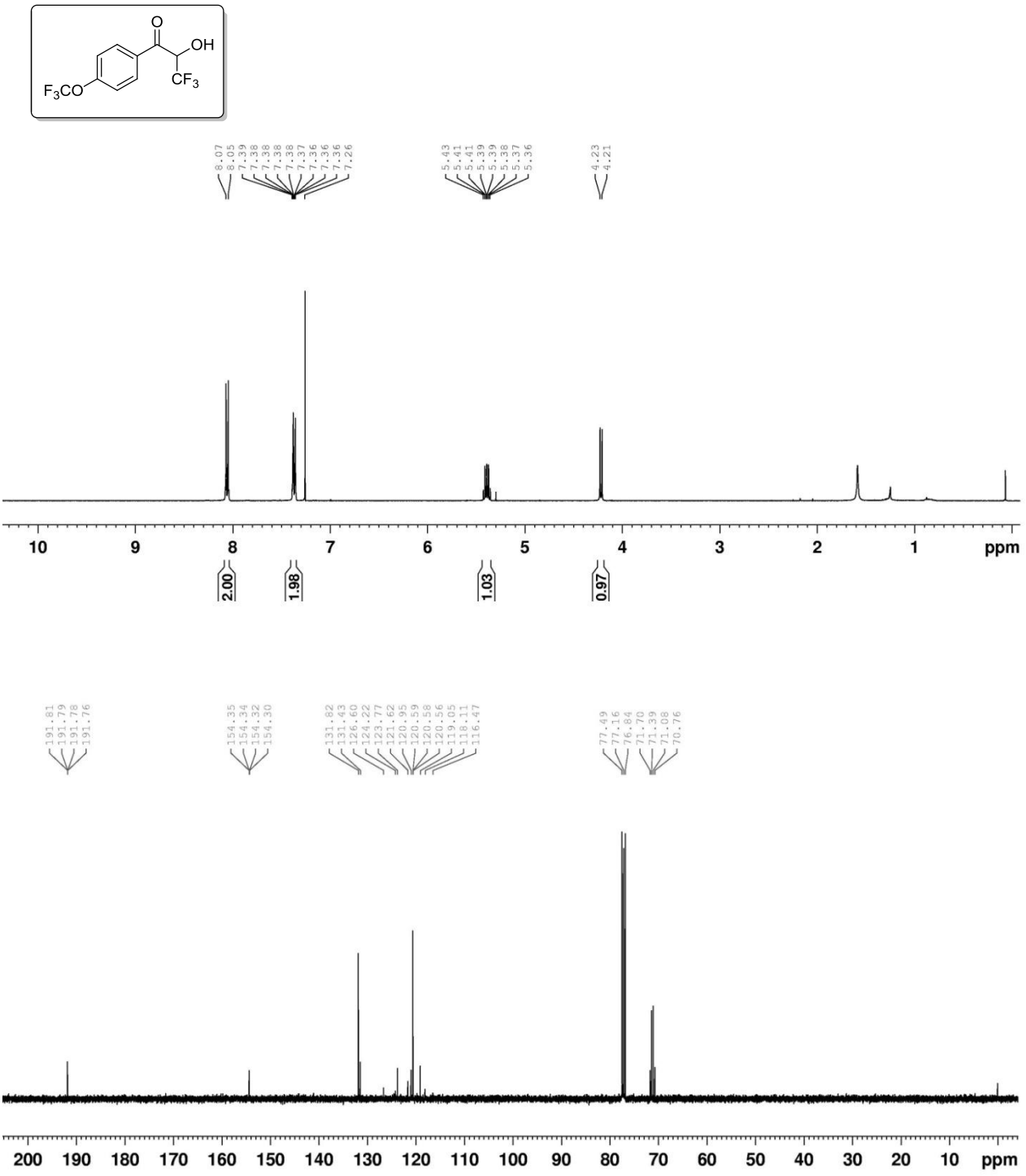
^{1}H, ^{13}C NMR Spectra of **16i**



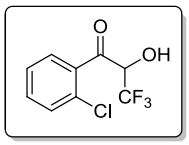


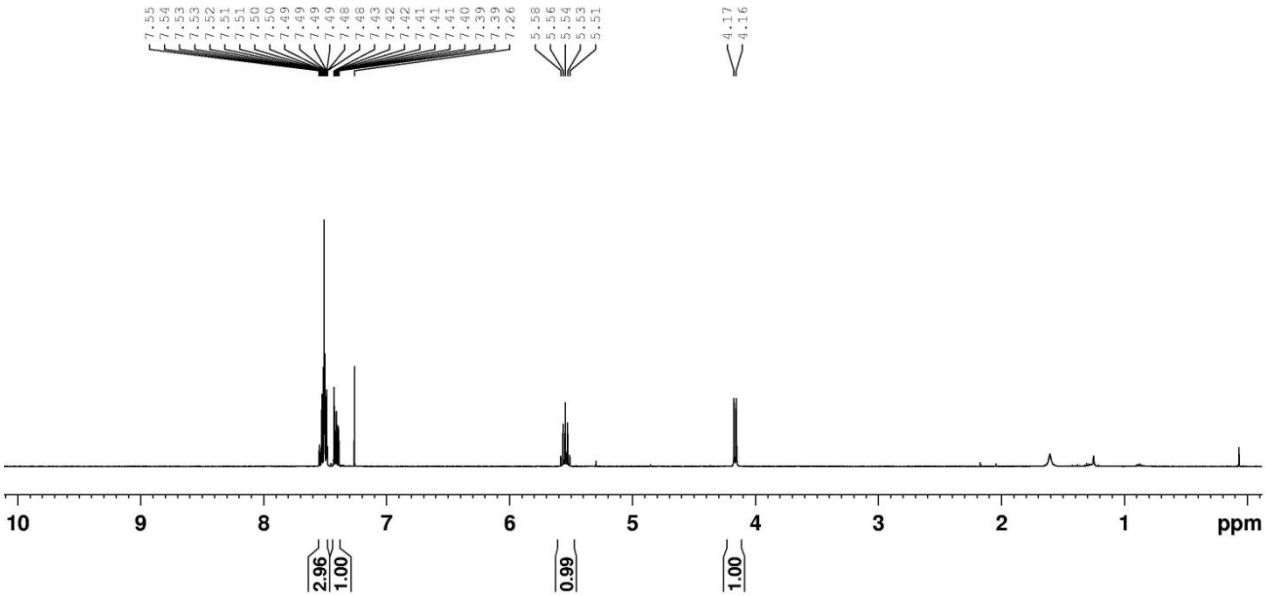


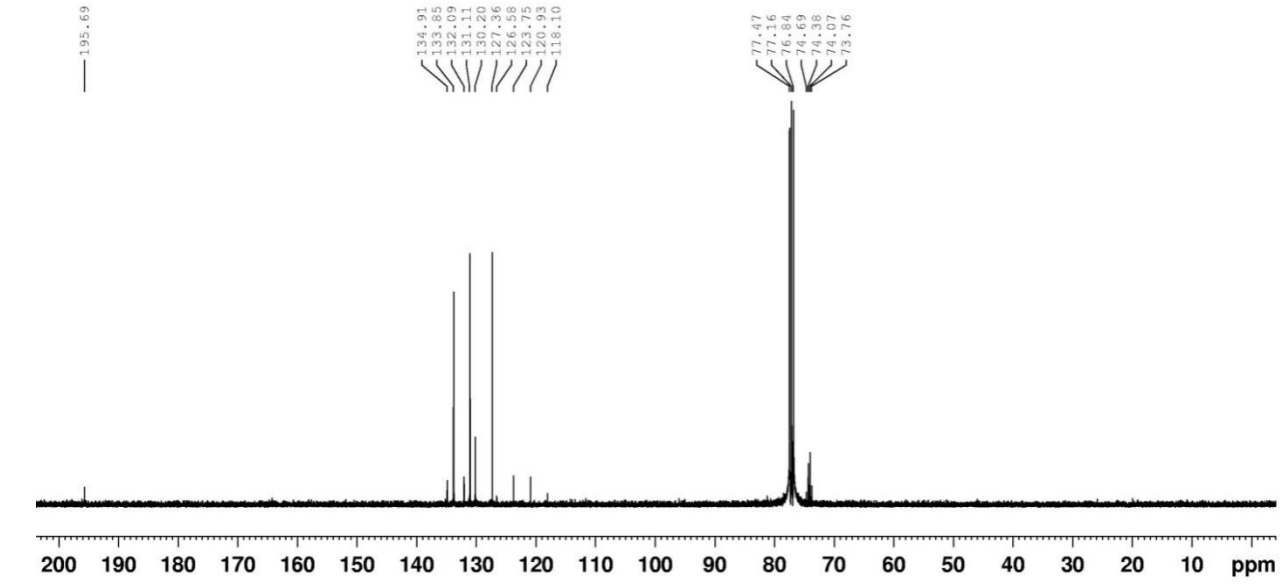
^{1}H, ^{13}C NMR Spectra of **16j**



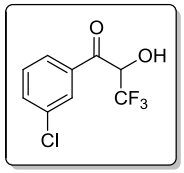
^{1}H, ^{13}C NMR Spectra of **16k**

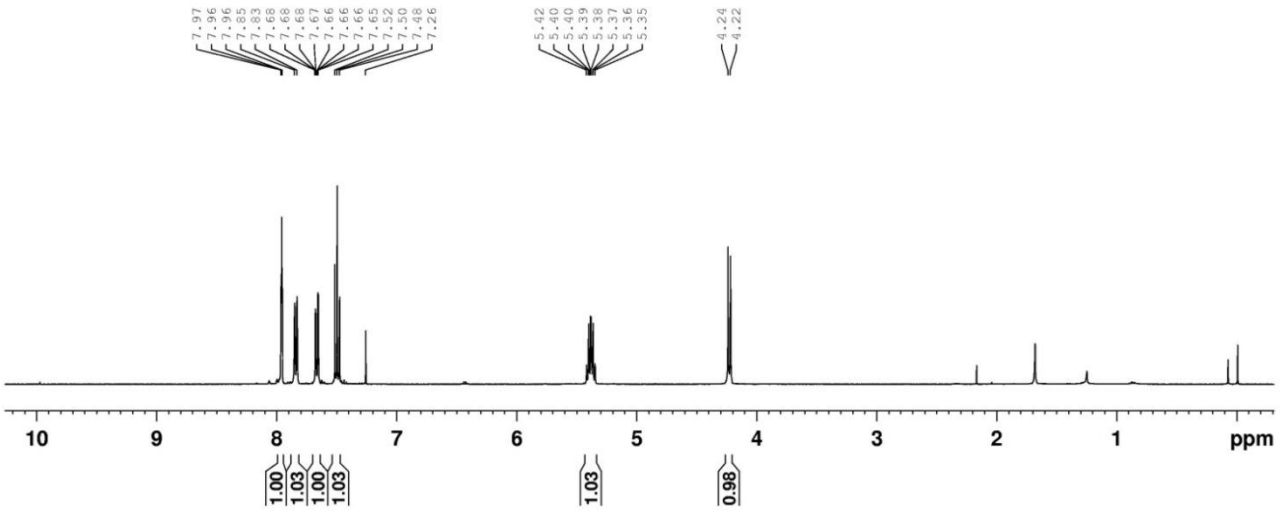


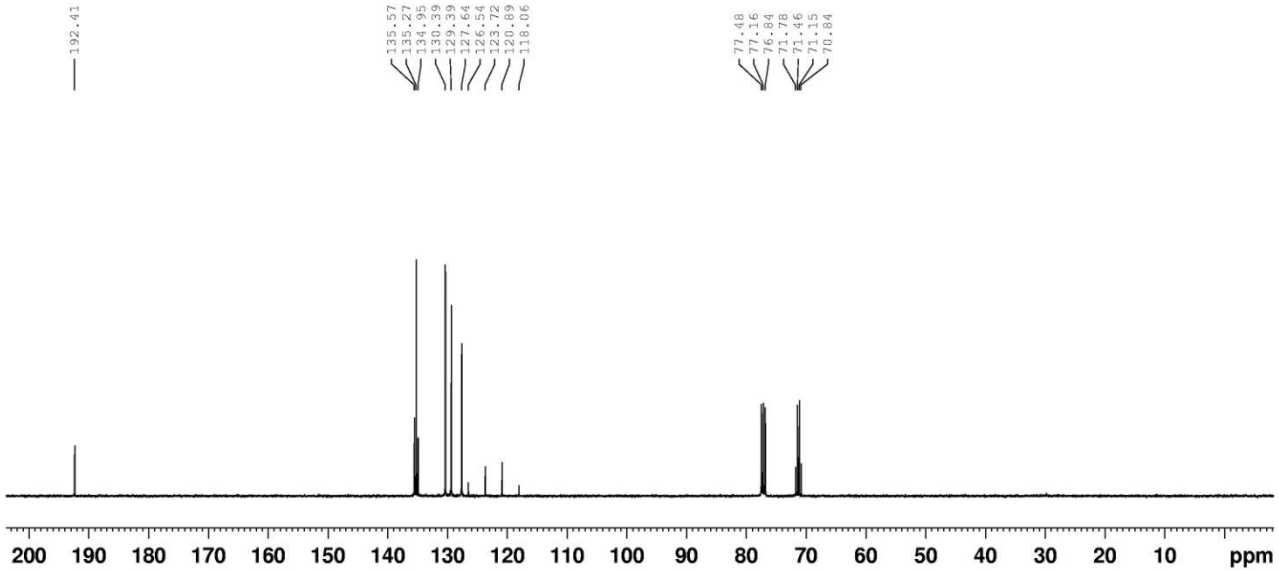




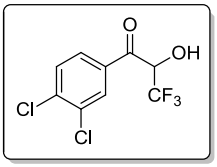
^{1}H, ^{13}C NMR Spectra of **16l**

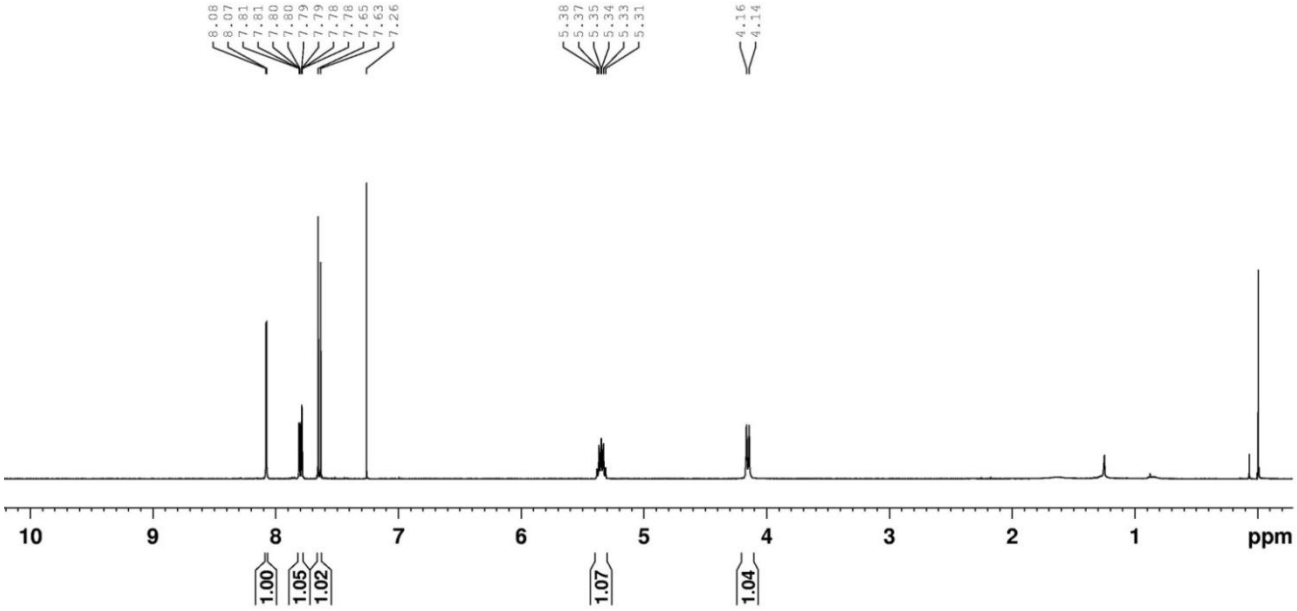


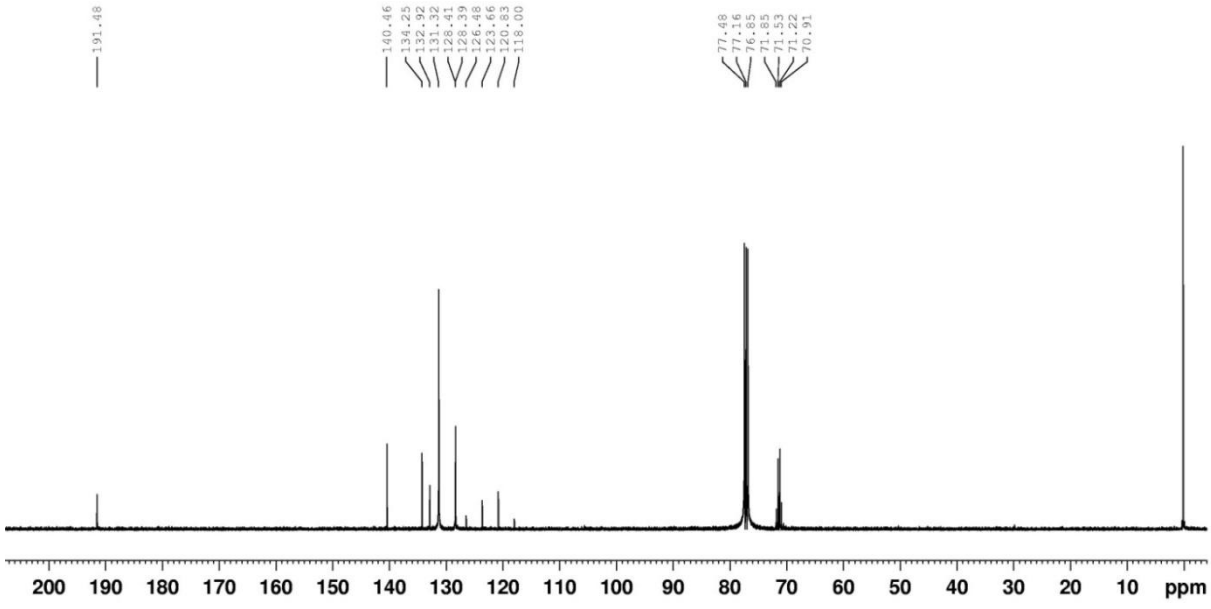




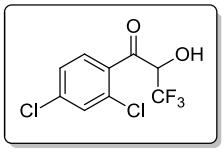
^{1}H, ^{13}C NMR Spectra of **16m**

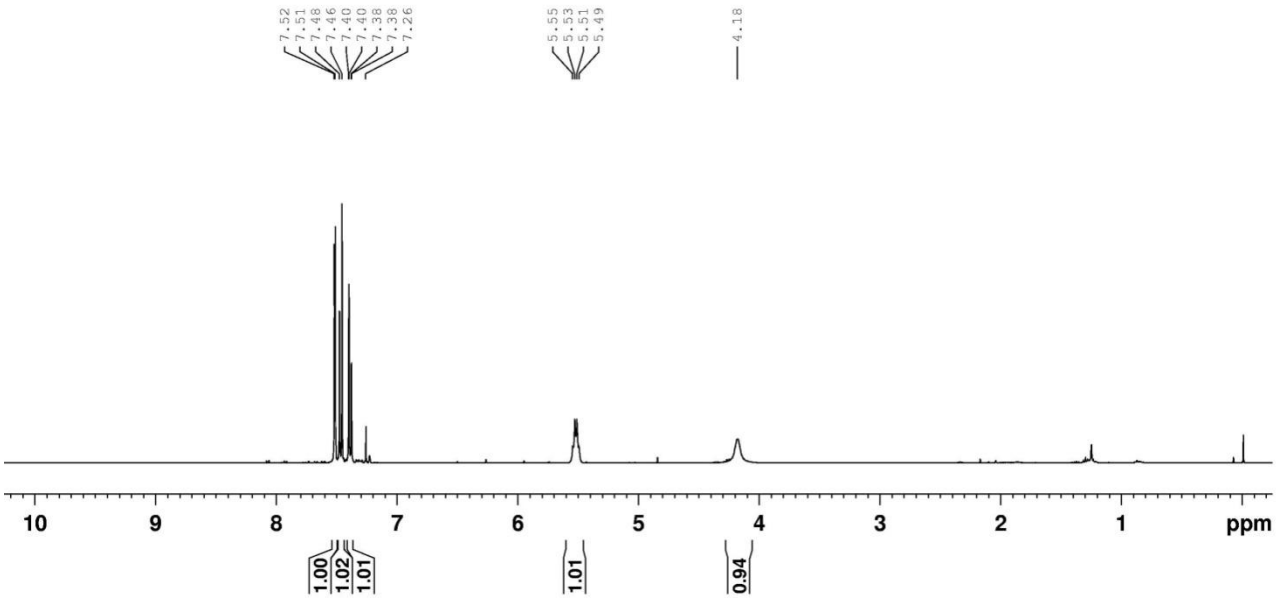


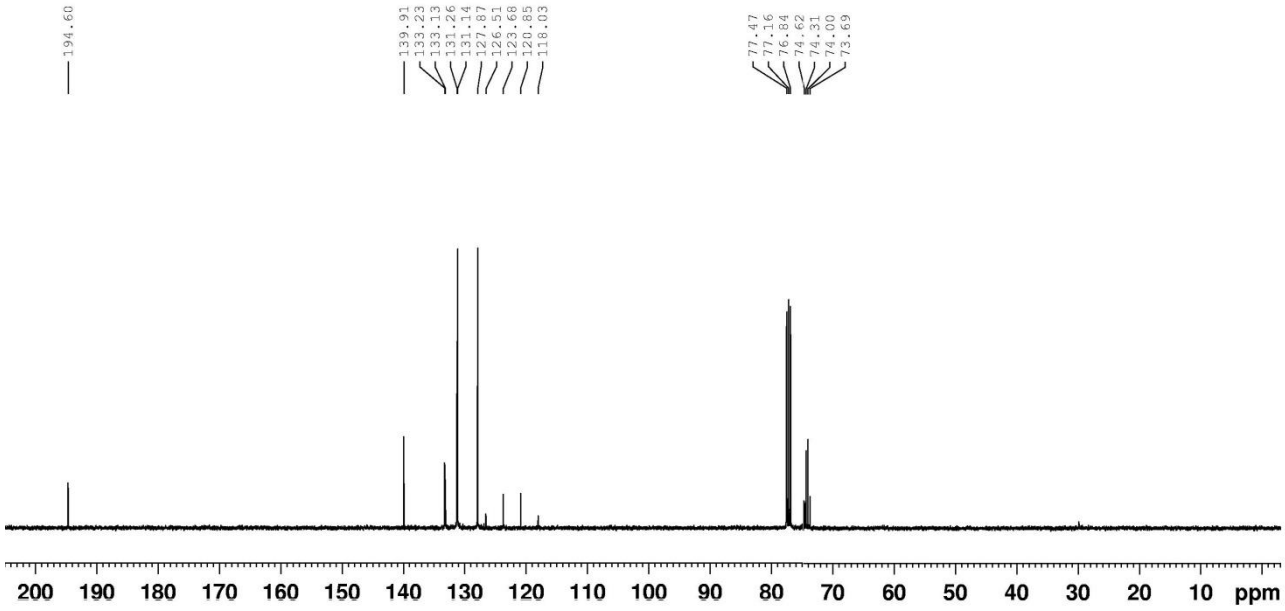




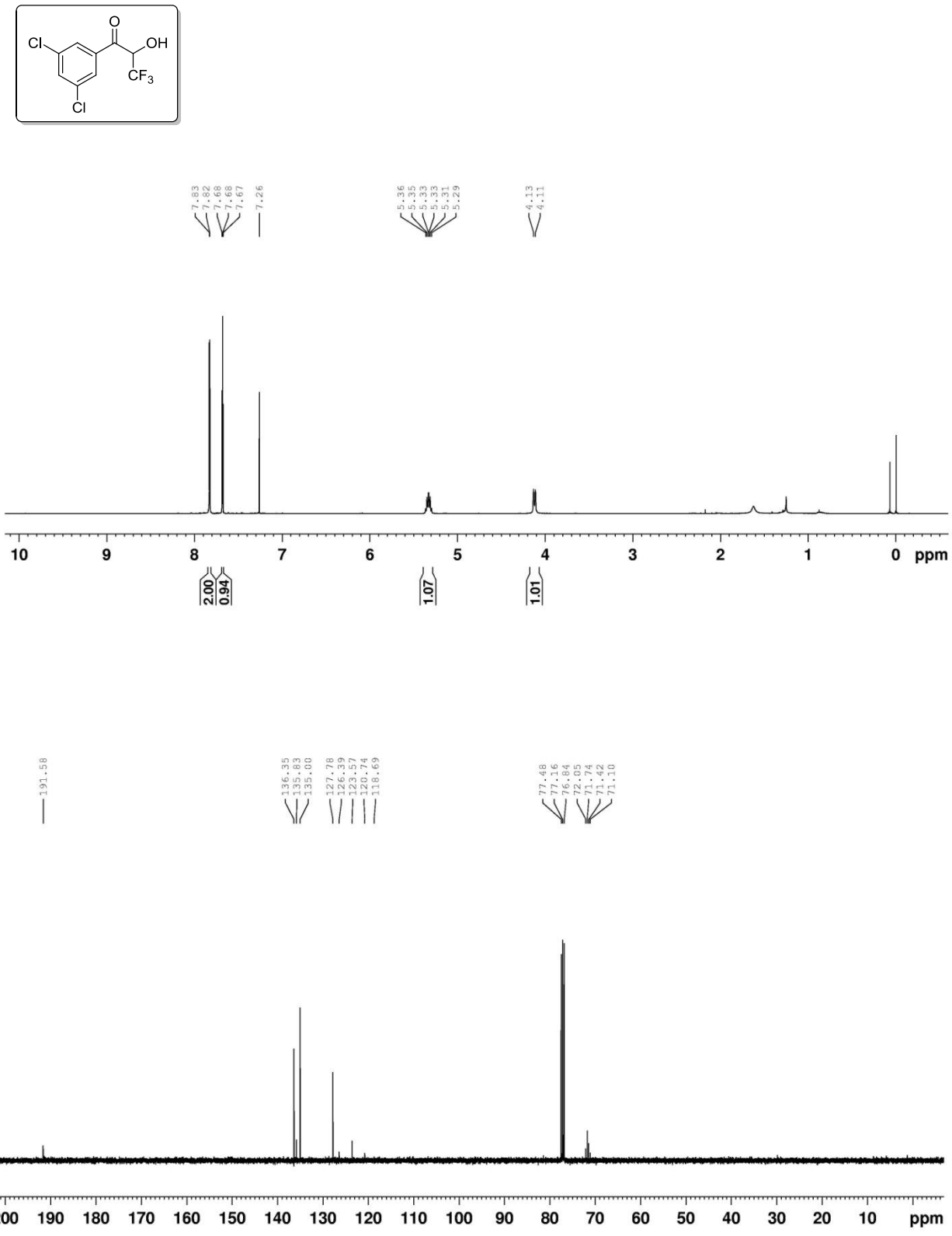
^{1}H, ^{13}C NMR Spectra of **16n**



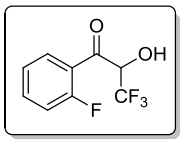


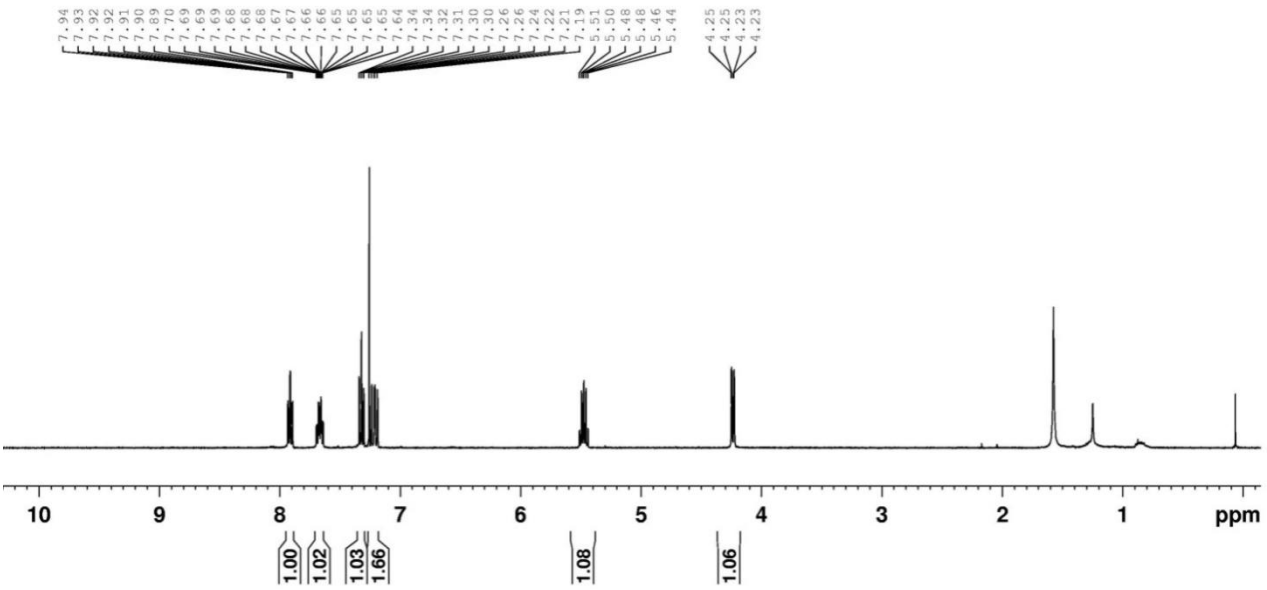


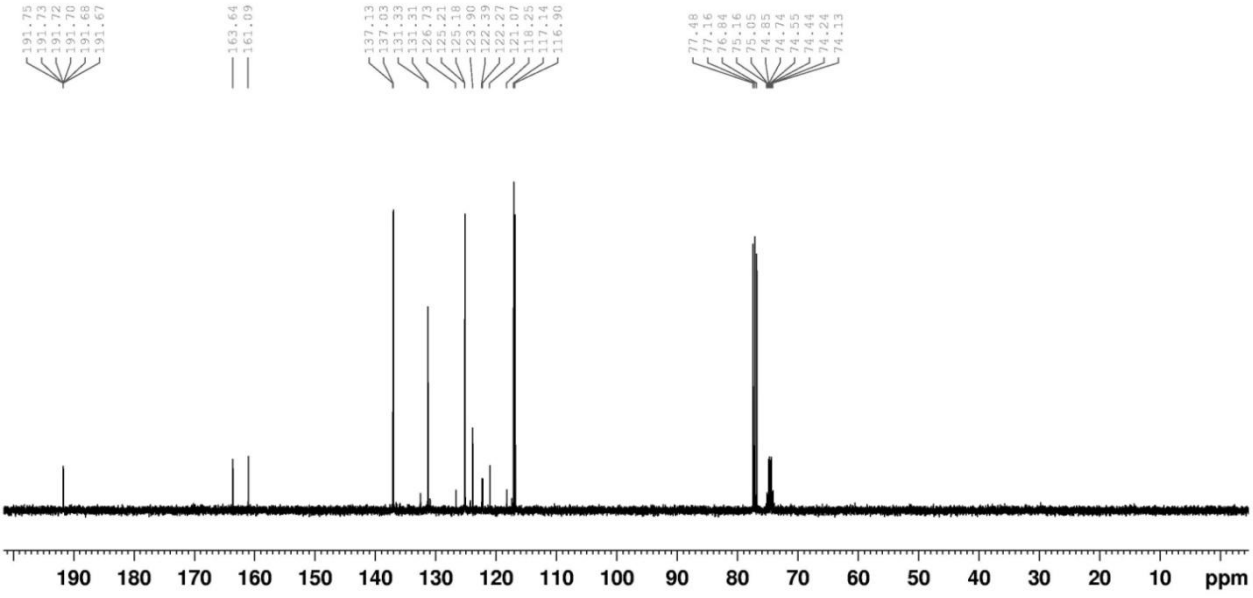
^{1}H, ^{13}C NMR Spectra of **16o**



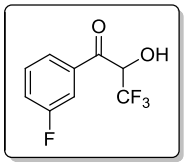
^{1}H, ^{13}C NMR Spectra of **16p**

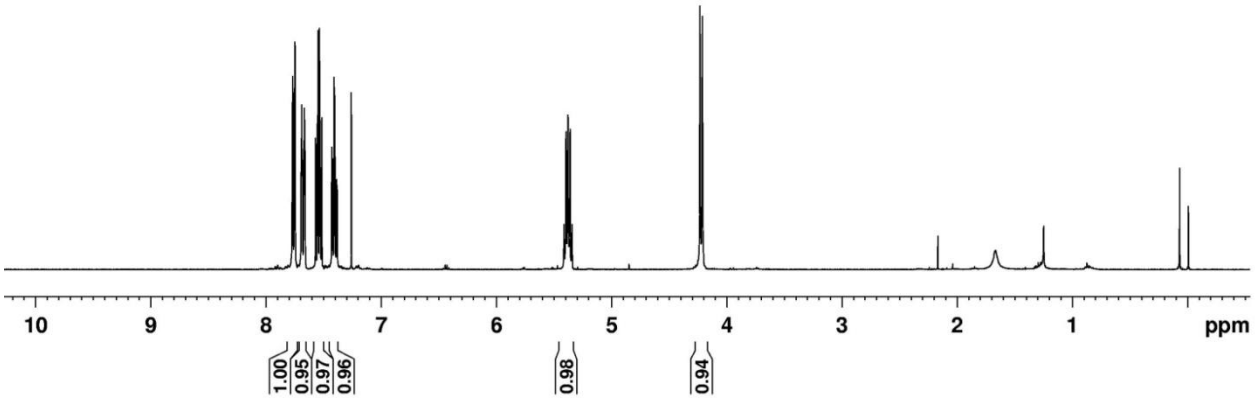


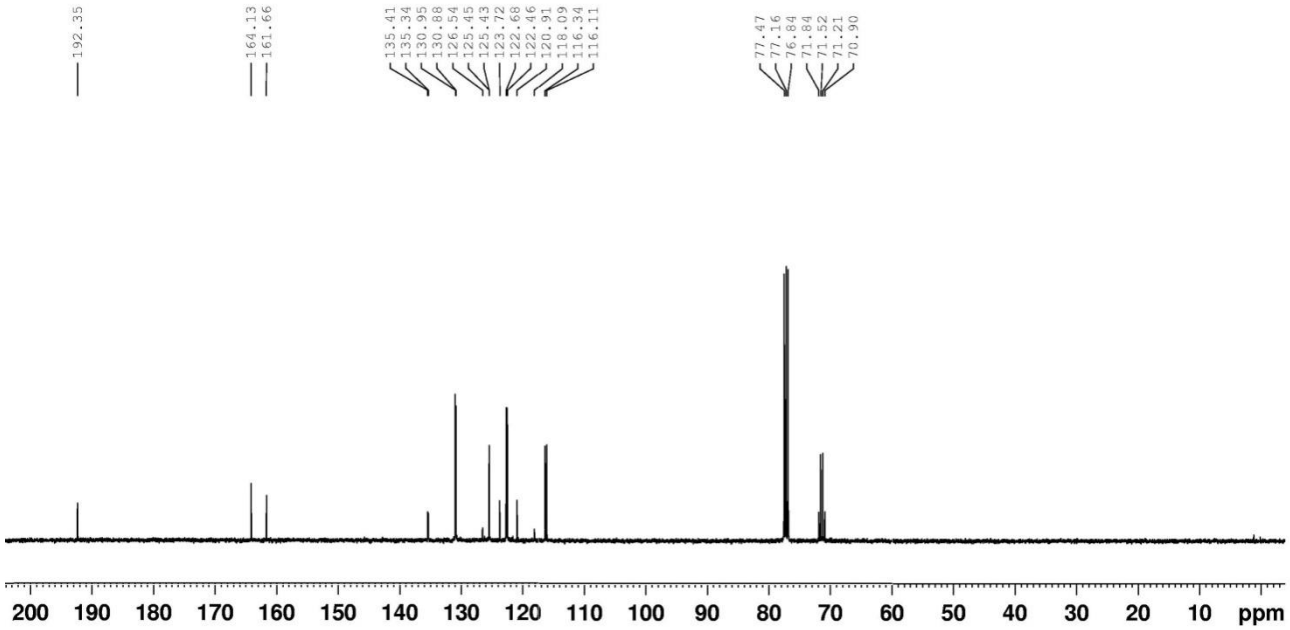




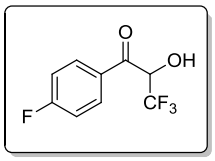
^{1}H, ^{13}C NMR Spectra of **16q**

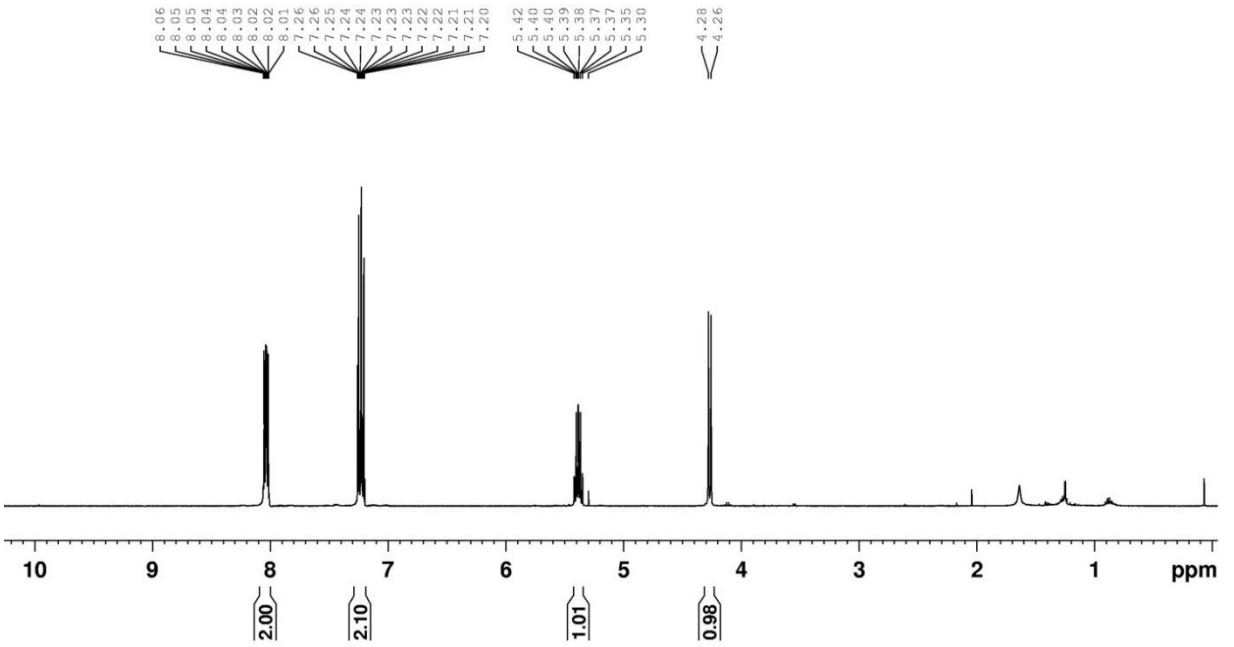


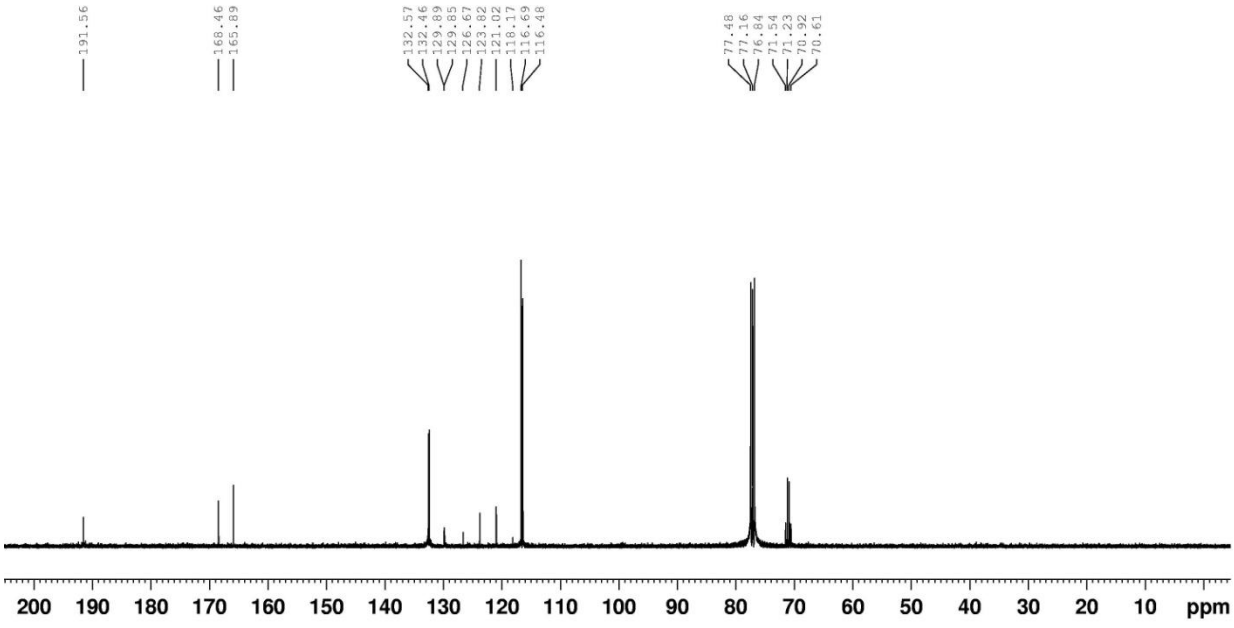




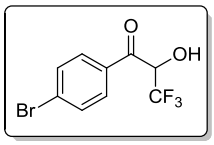
^{1}H, ^{13}C NMR Spectra of **16r**

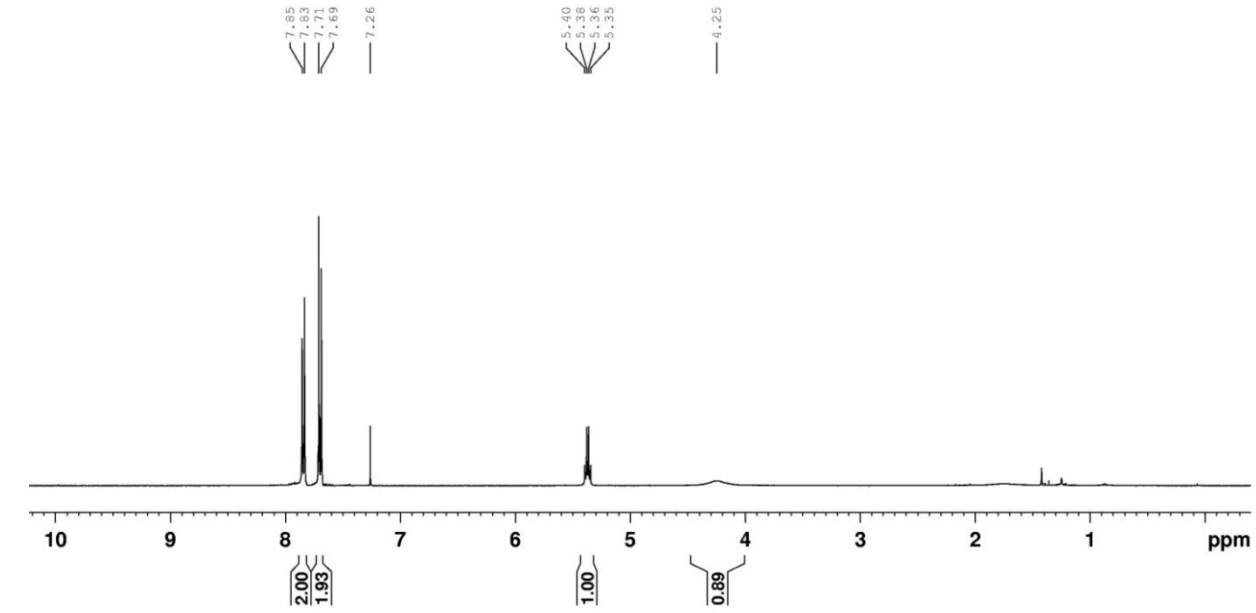


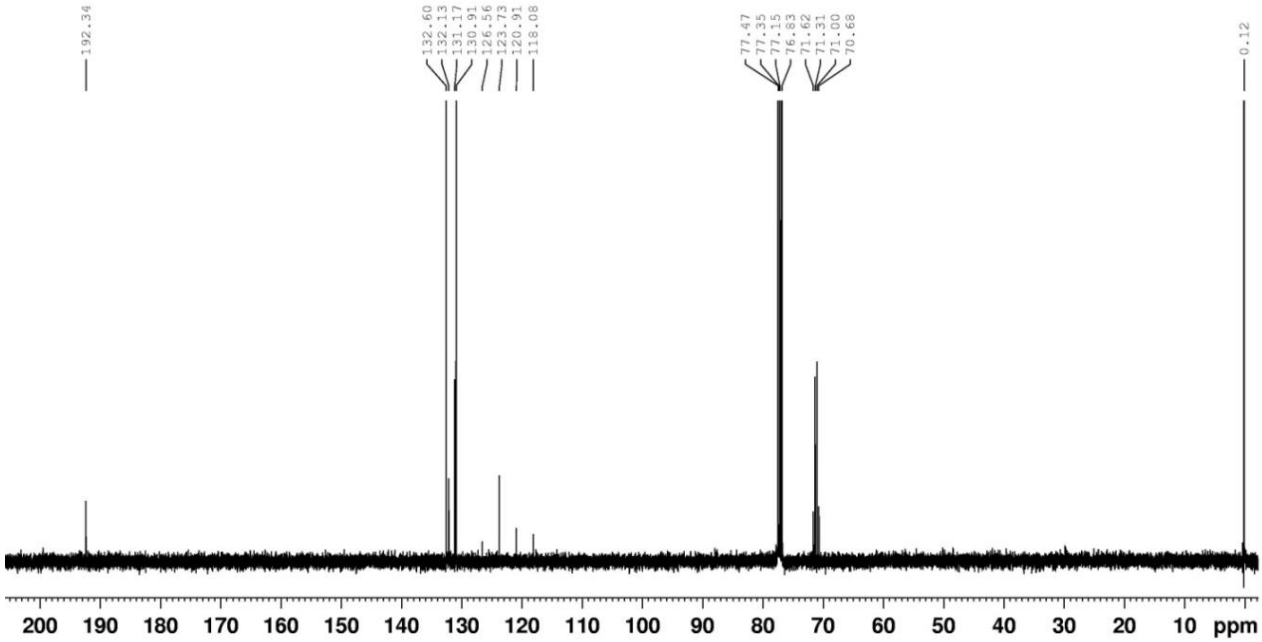




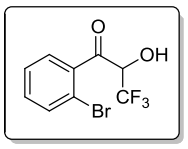
^{1}H, ^{13}C NMR Spectra of **16s**

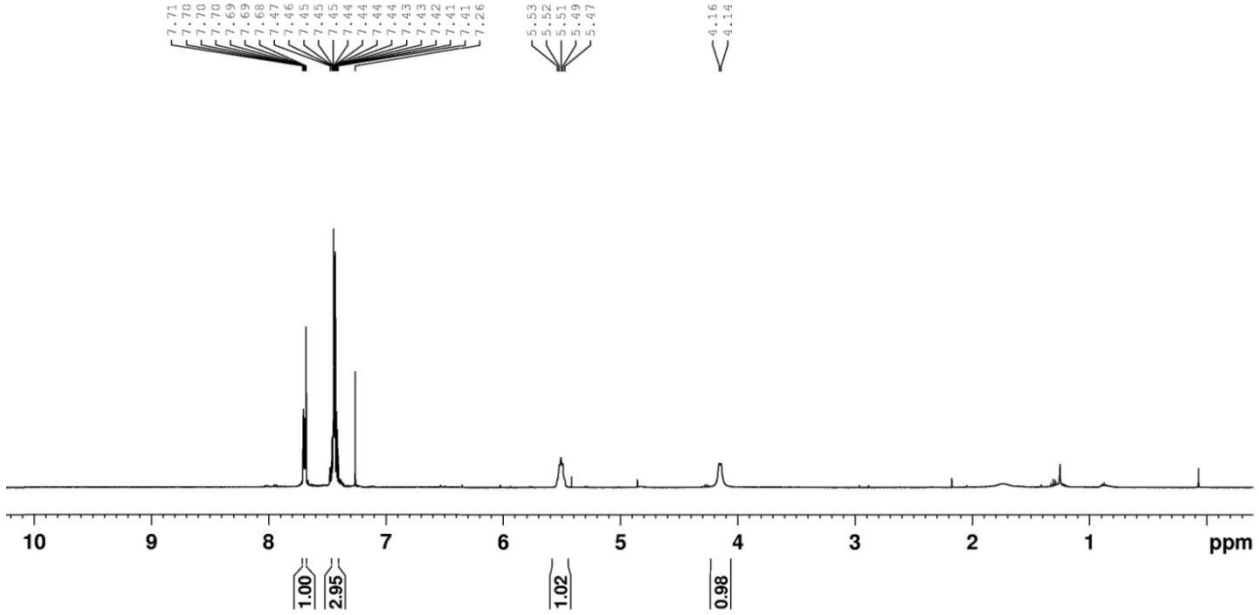


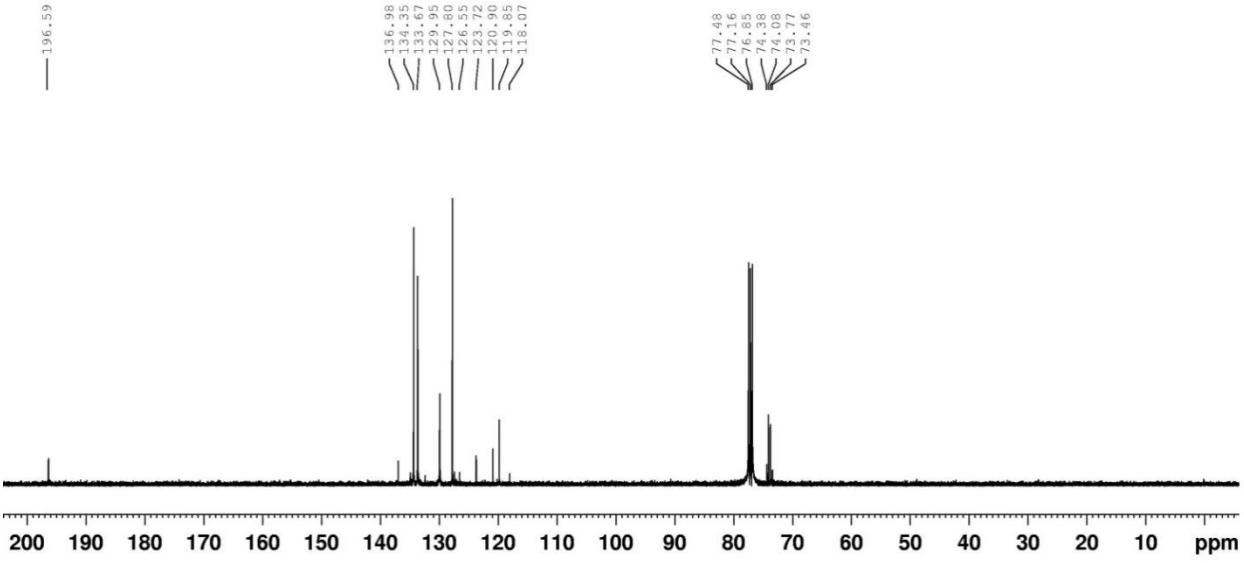




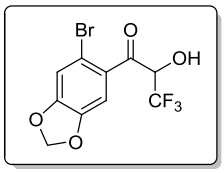
^{1}H, ^{13}C NMR Spectra of **16t**

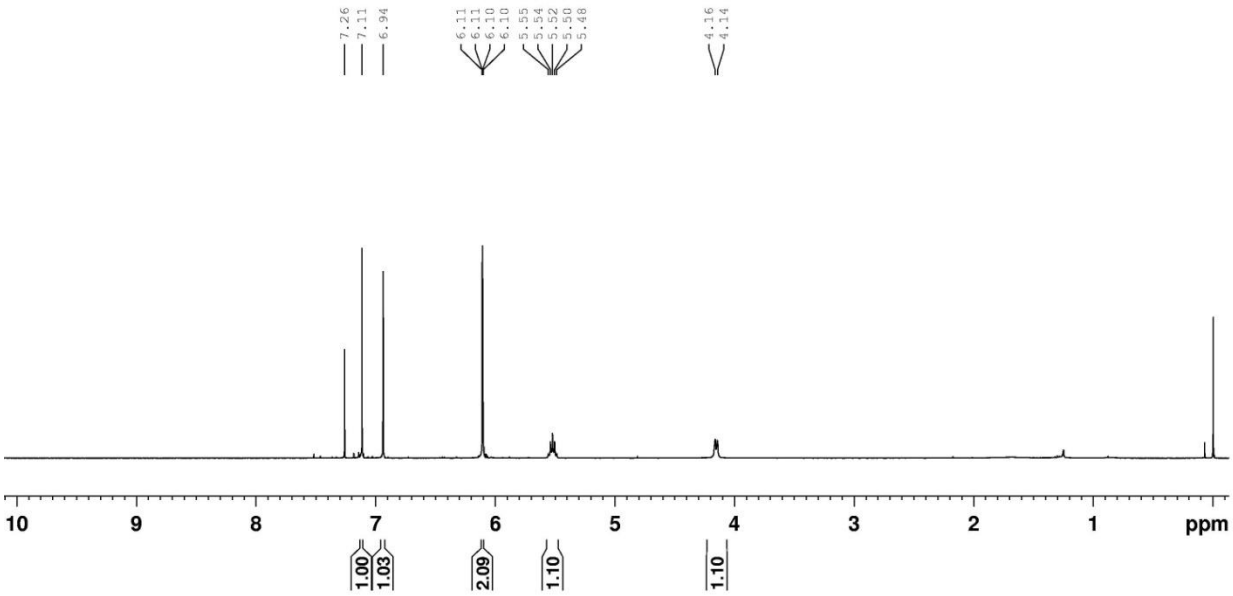


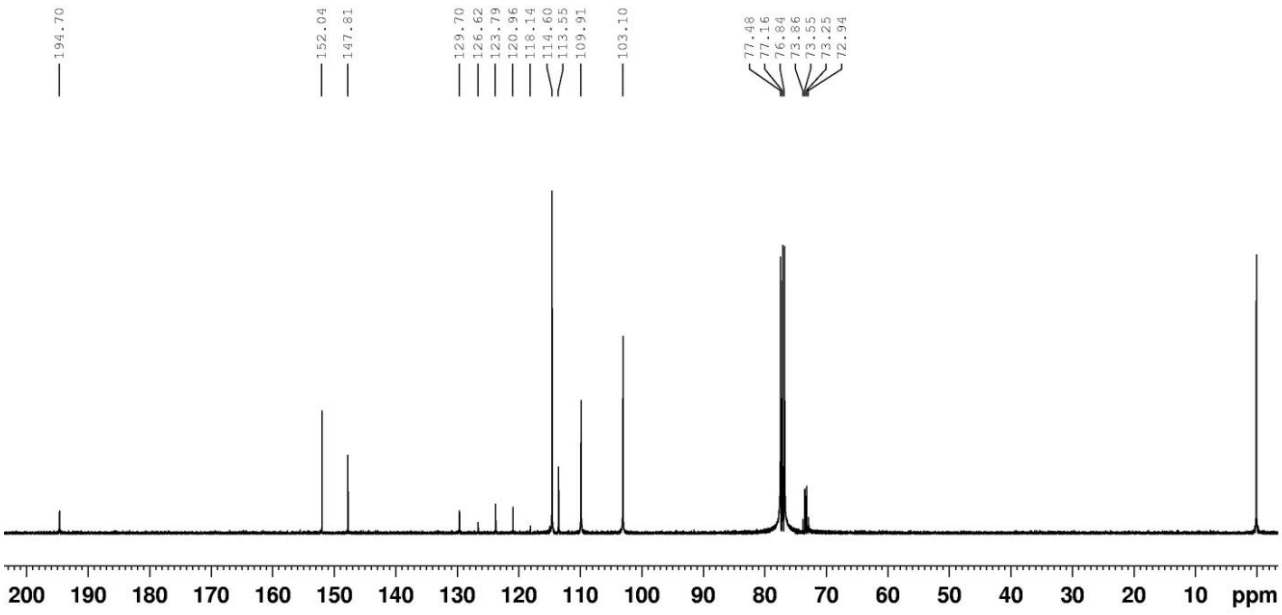




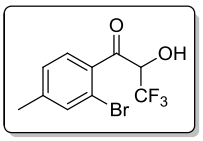
^{1}H, ^{13}C NMR Spectra of **16u**

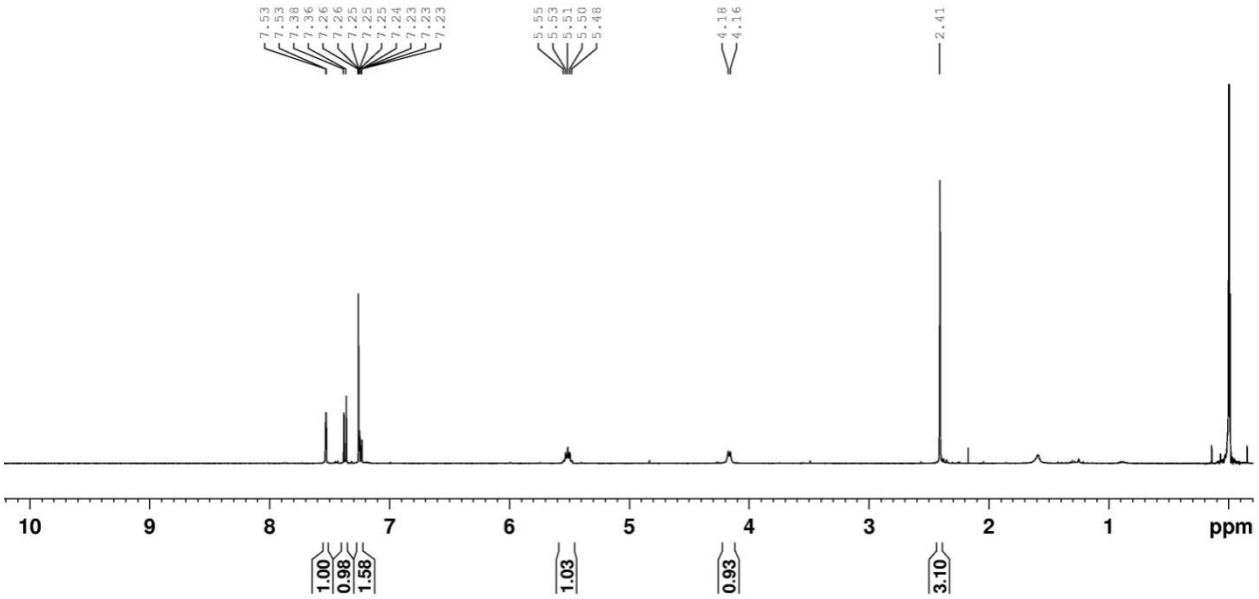


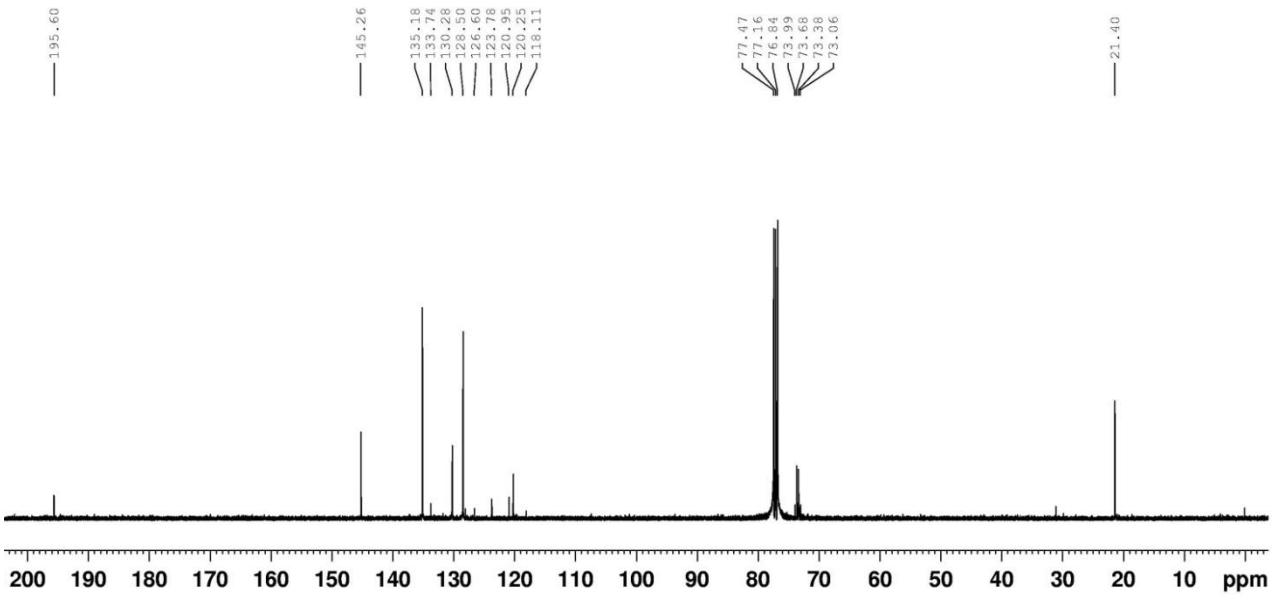




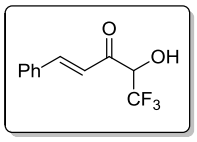
^{1}H, ^{13}C NMR Spectra of **16v**

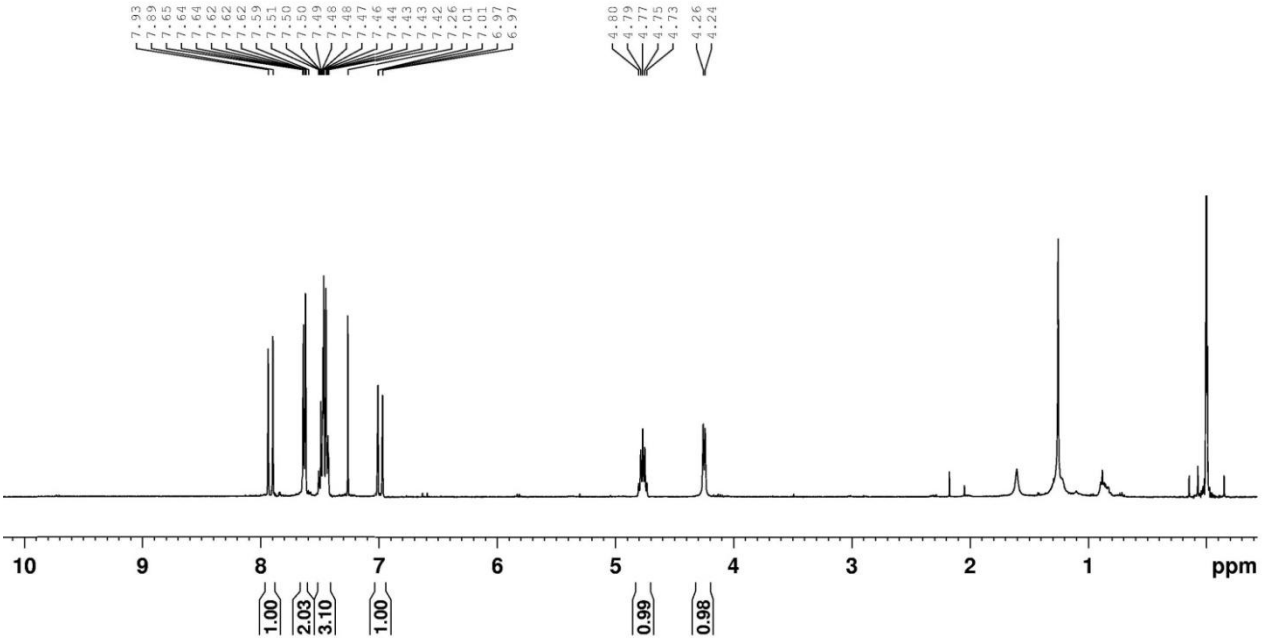


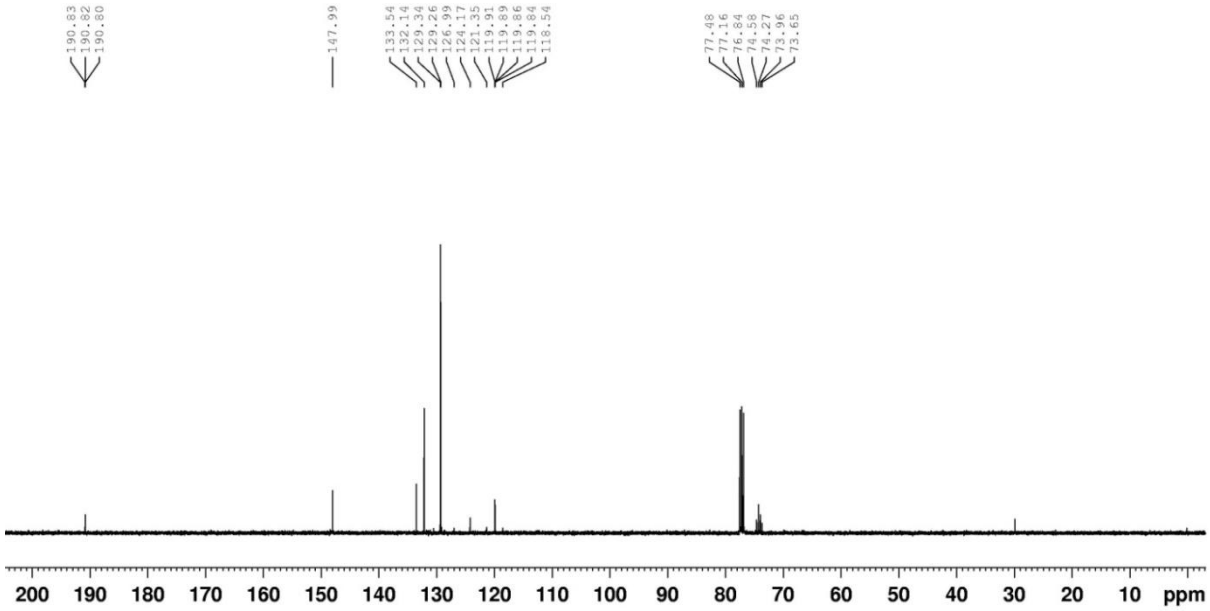




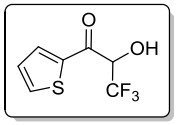
^{1}H, ^{13}C NMR Spectra of **16w**

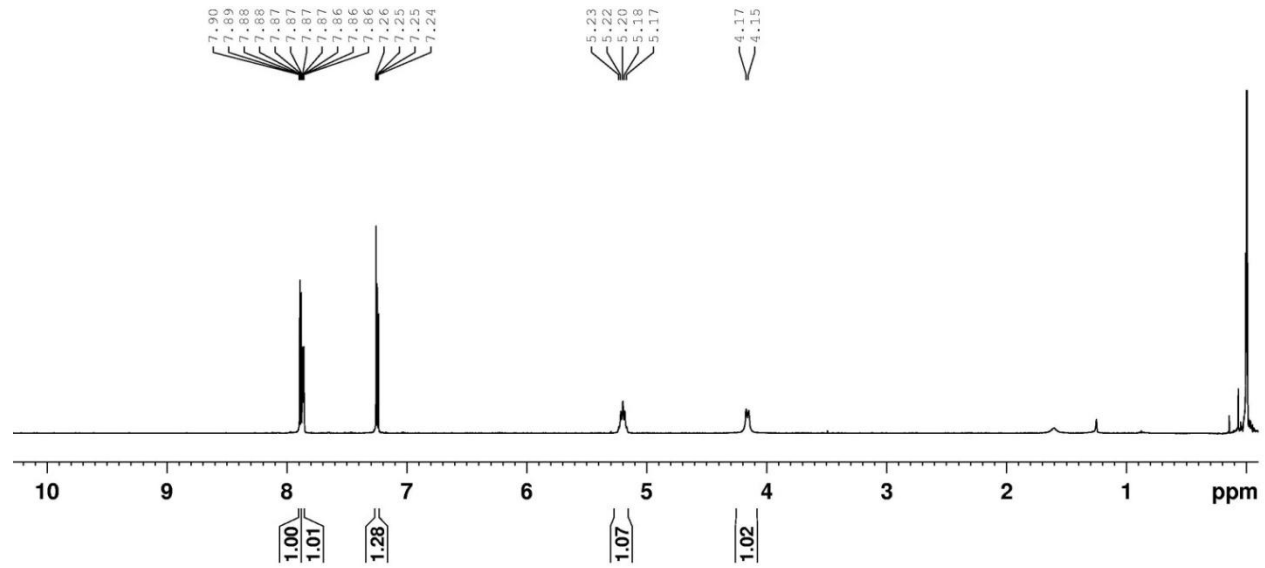


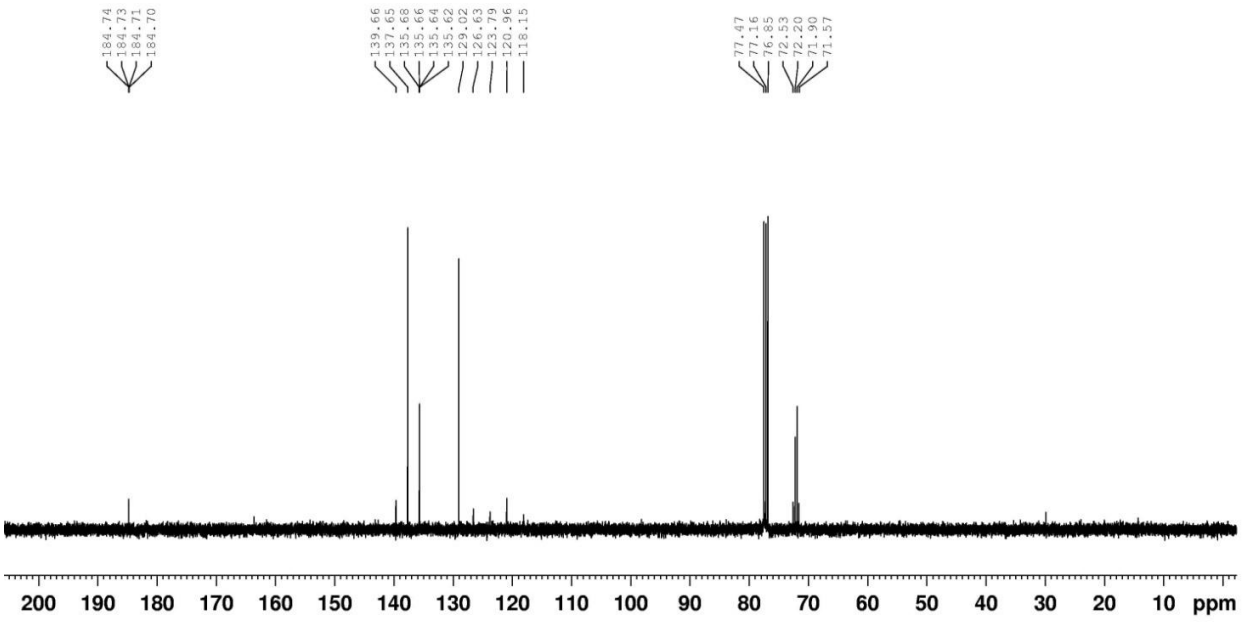




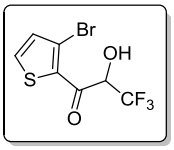
^{1}H, ^{13}C NMR Spectra of **16x**

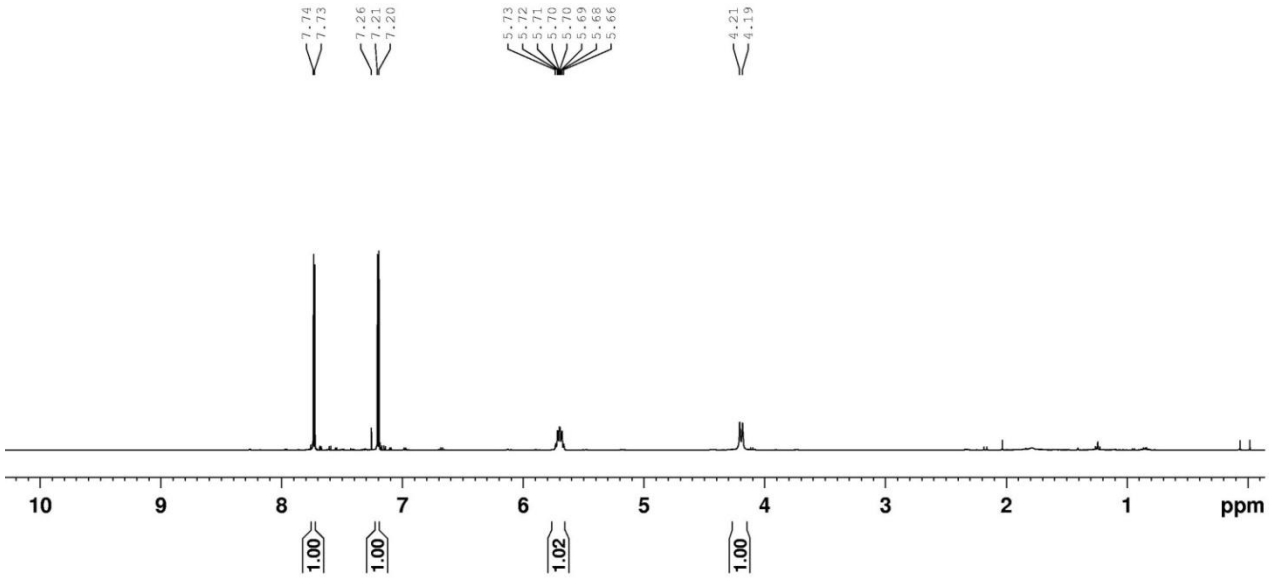


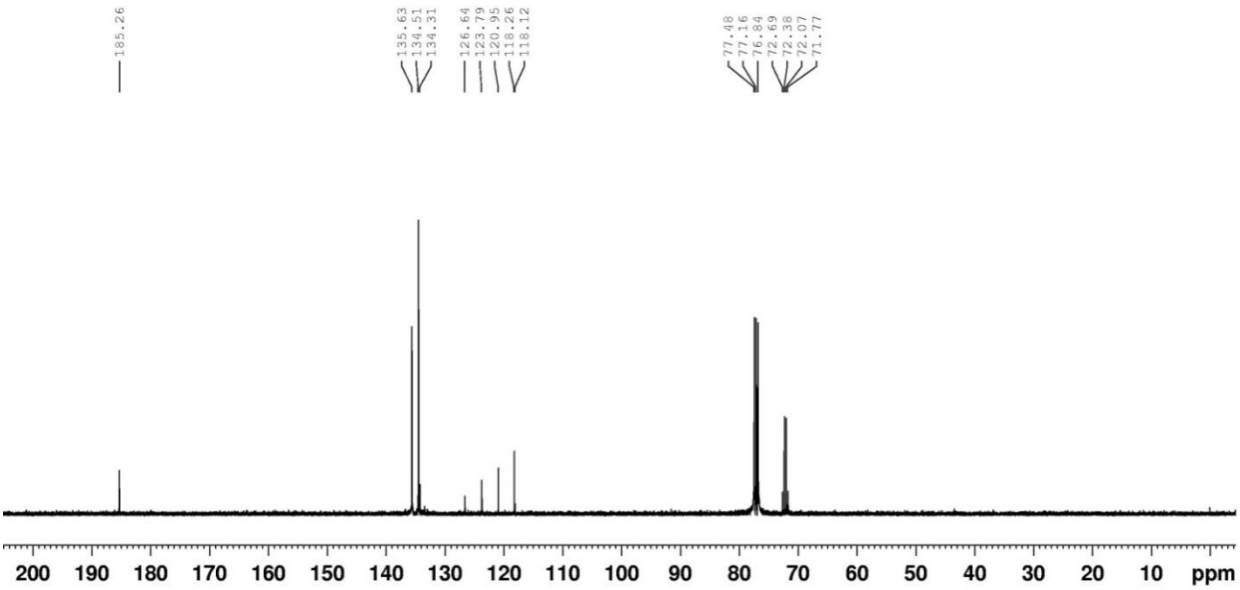




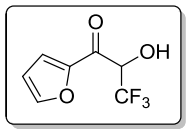
^{1}H, ^{13}C NMR Spectra of **16y**

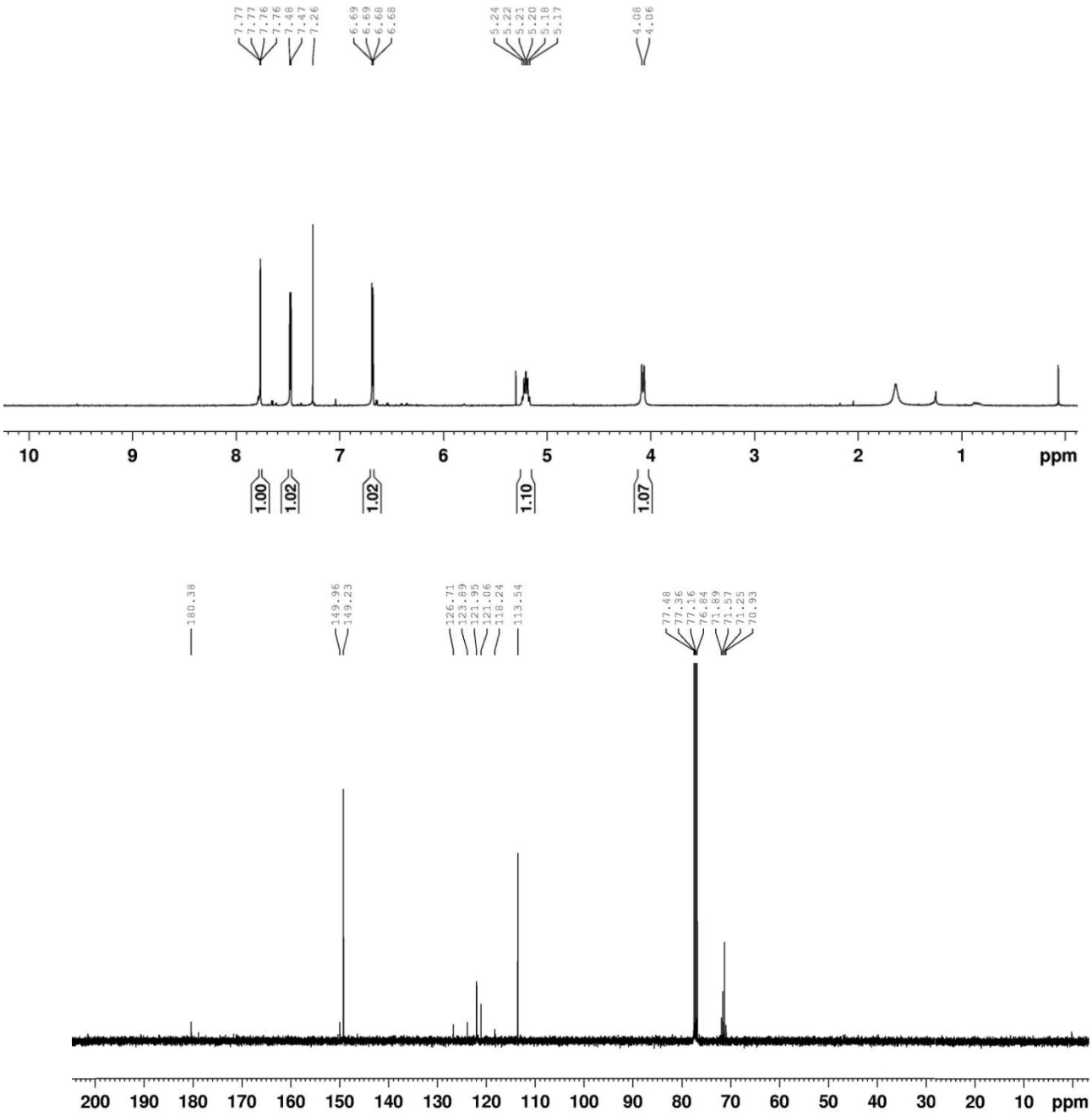




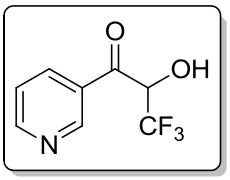


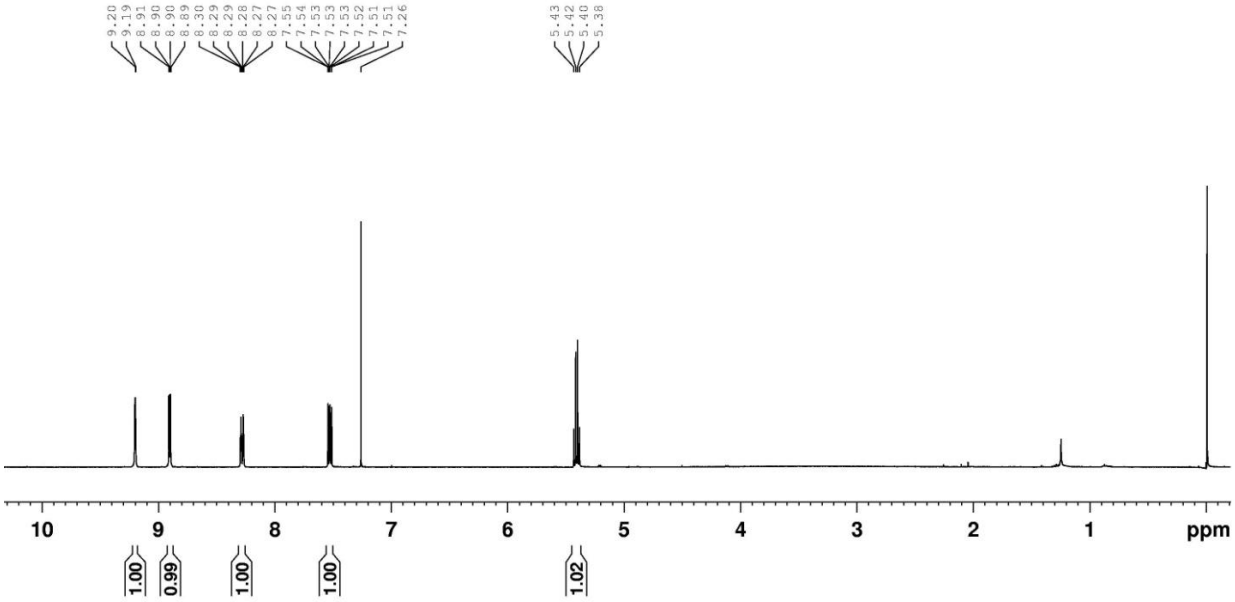
^{1}H, ^{13}C NMR Spectra of **16z**

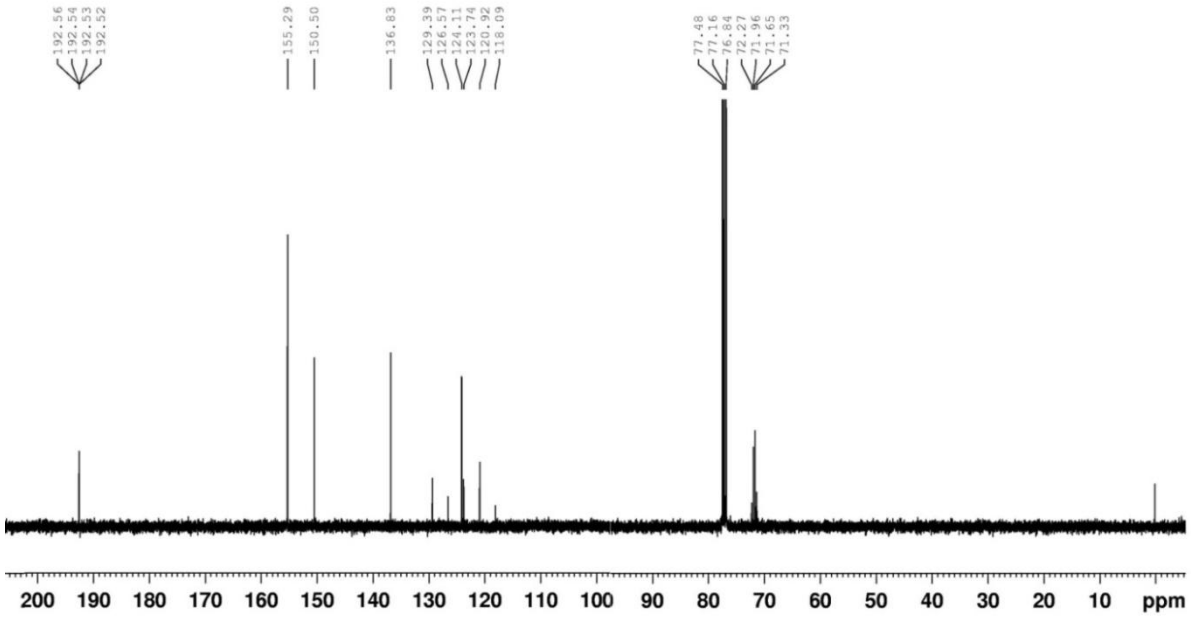




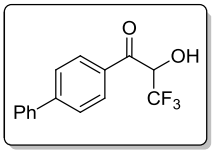
^{1}H, ^{13}C NMR Spectra of **16aa**

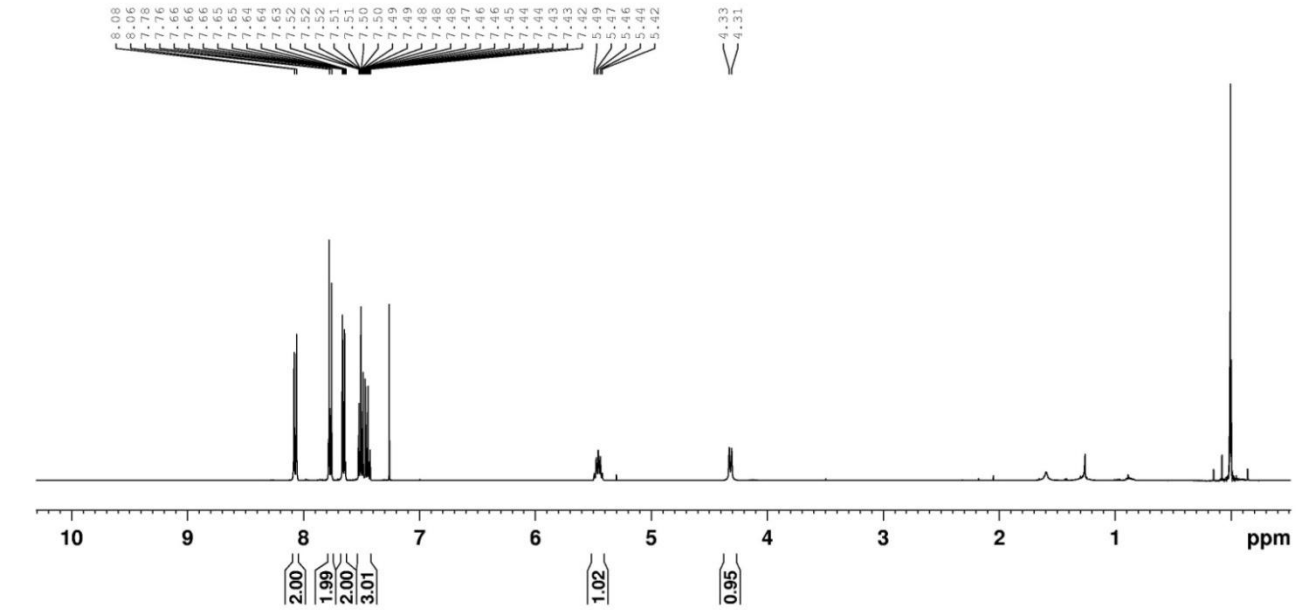


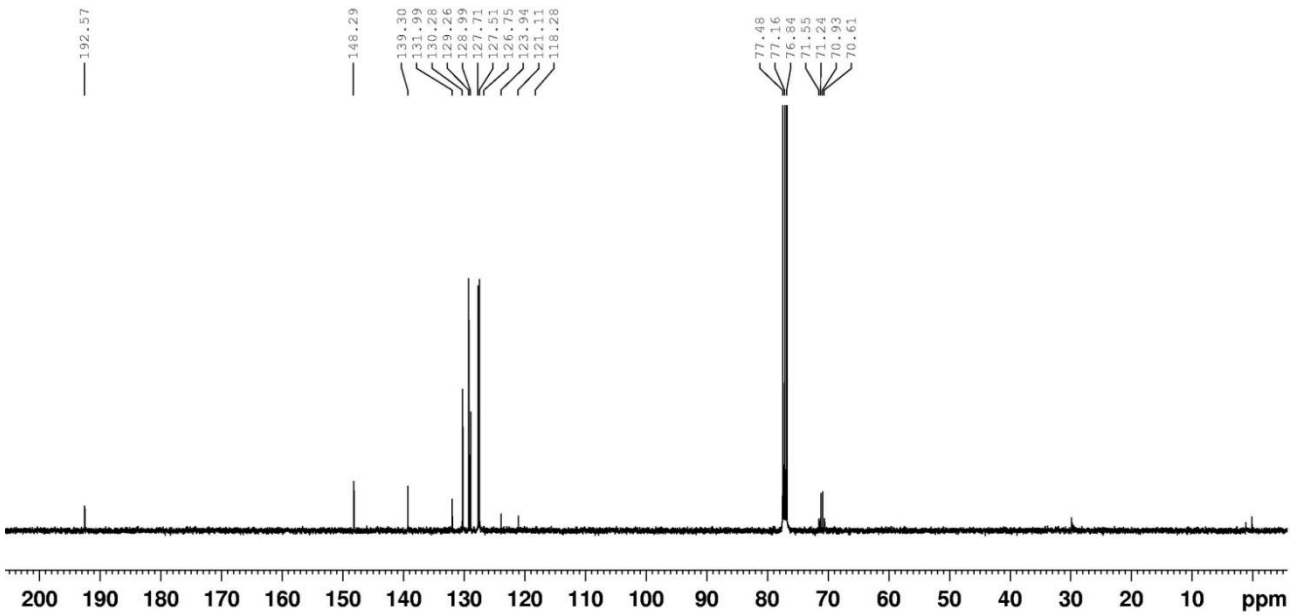




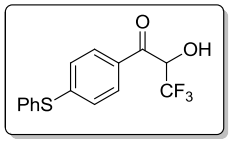
^{1}H, ^{13}C NMR Spectra of **16ab**

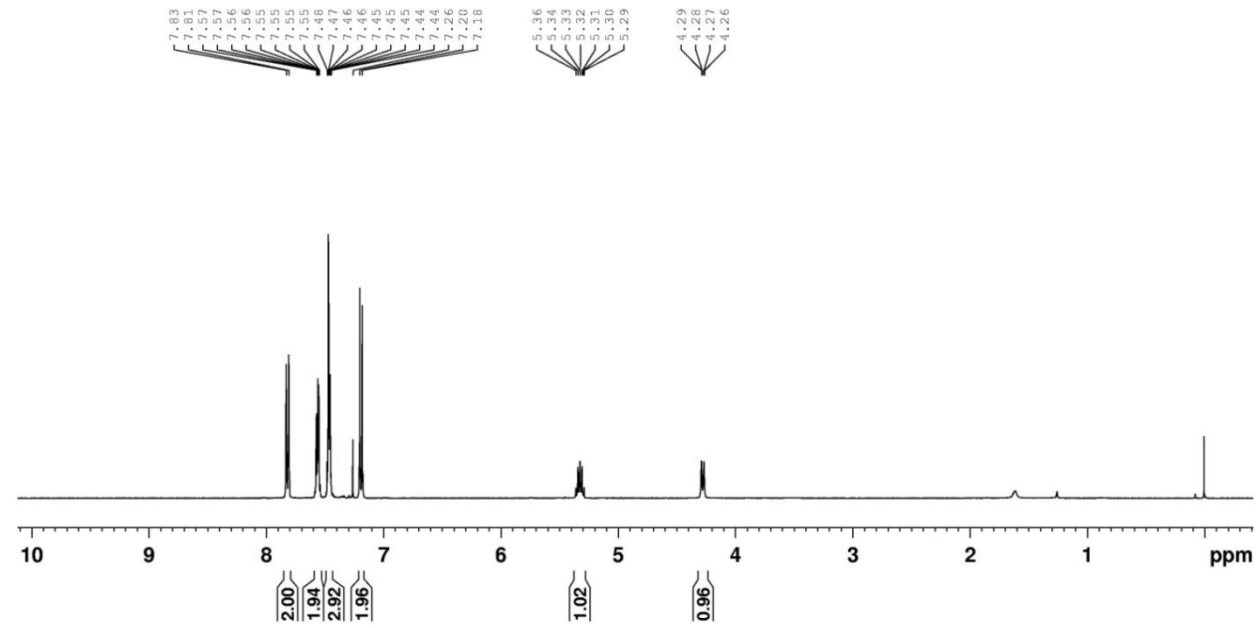


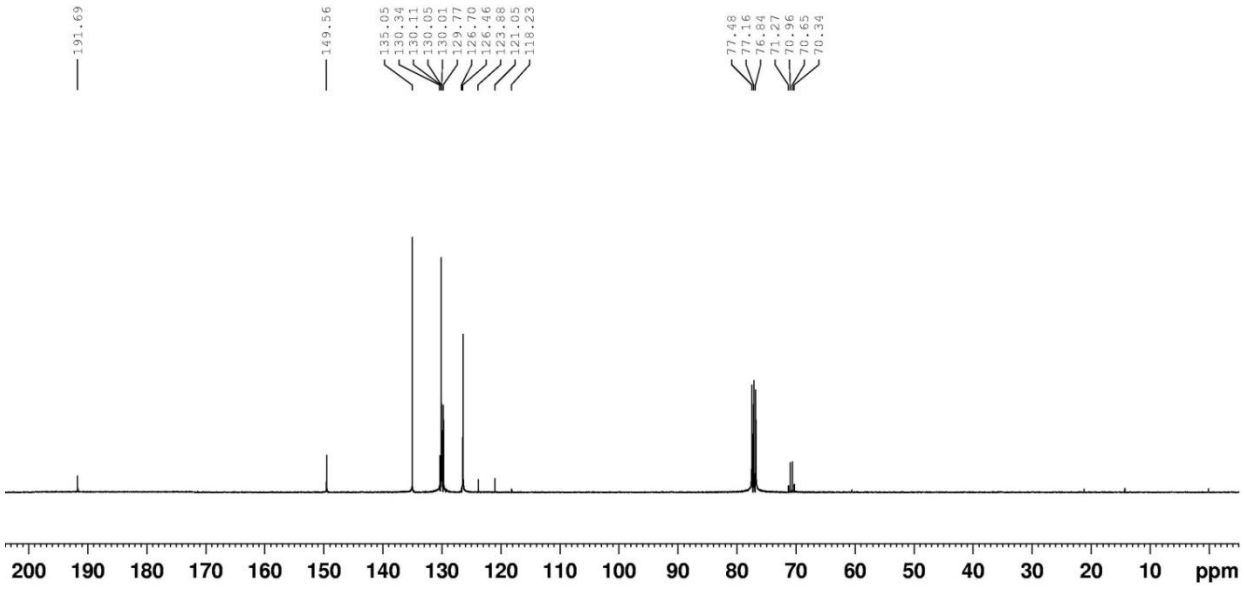




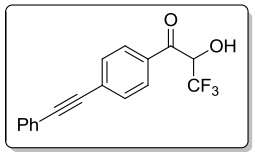
^{1}H, ^{13}C NMR Spectra of **16ac**

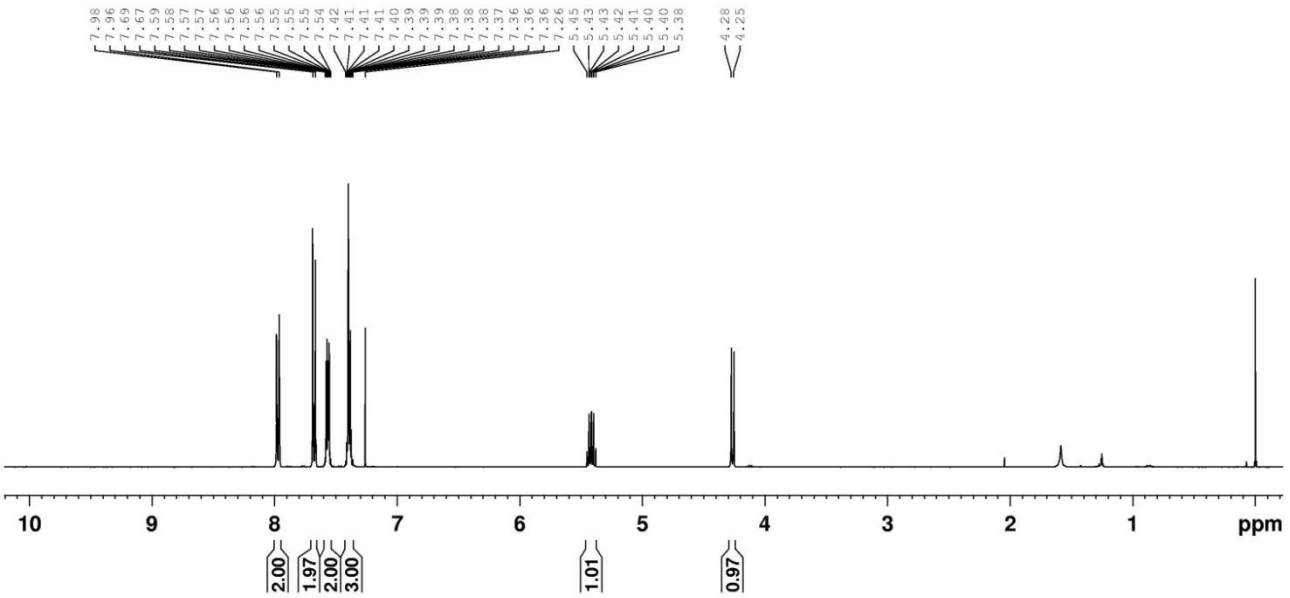


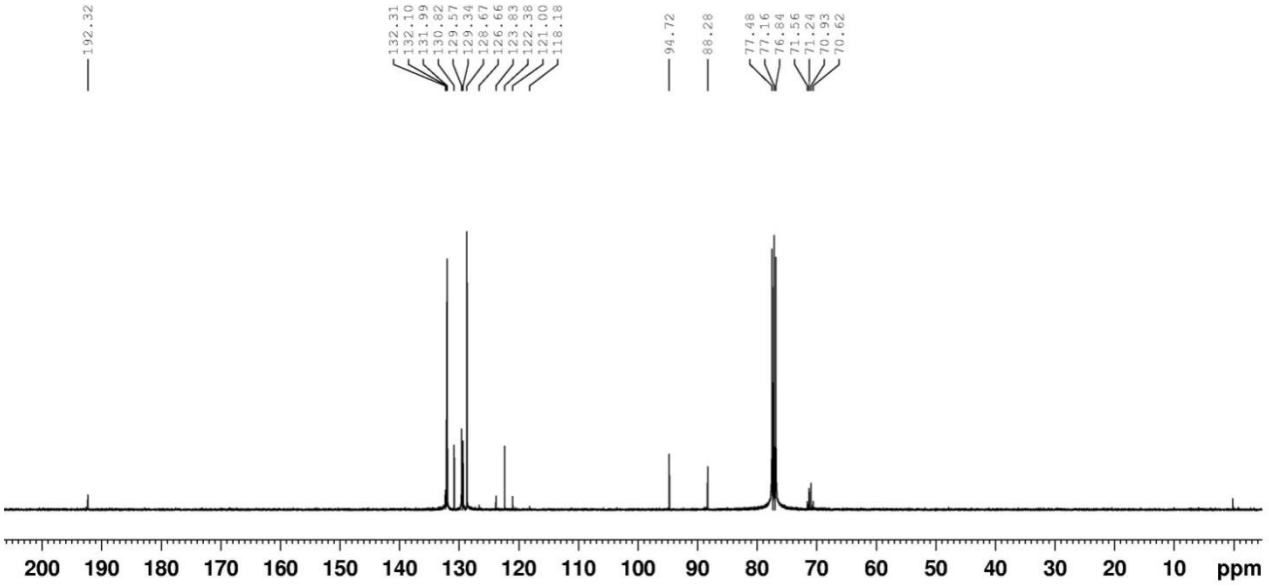




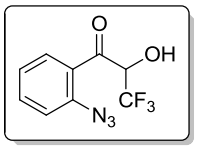
^{1}H, ^{13}C NMR Spectra of **16ad**

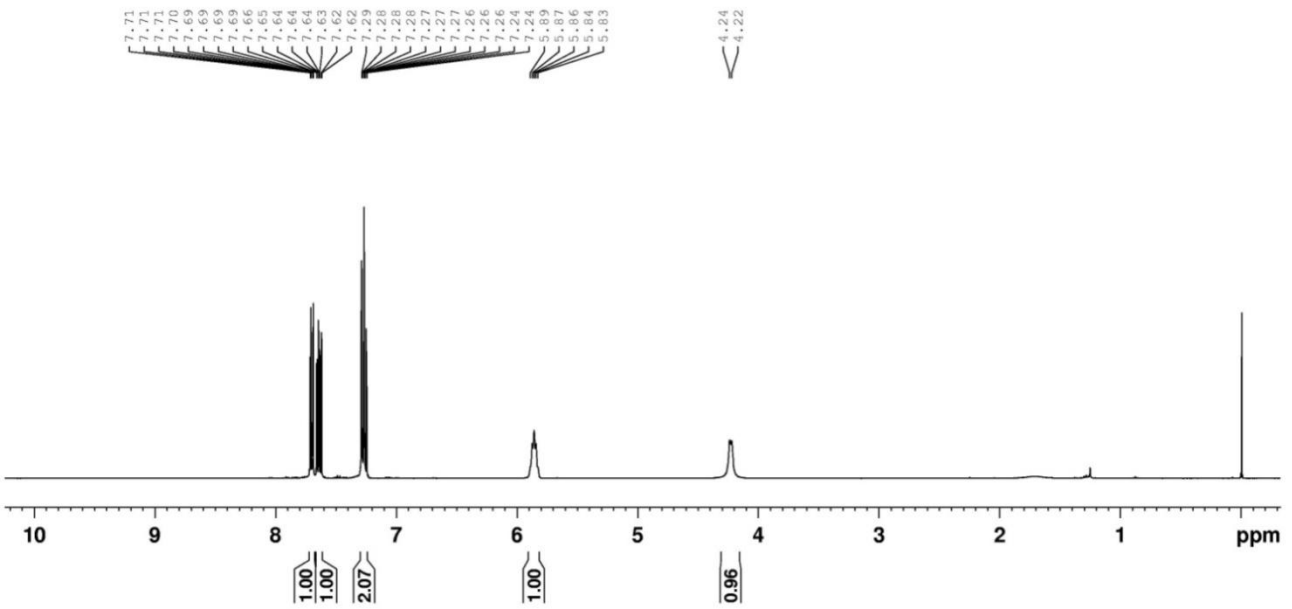


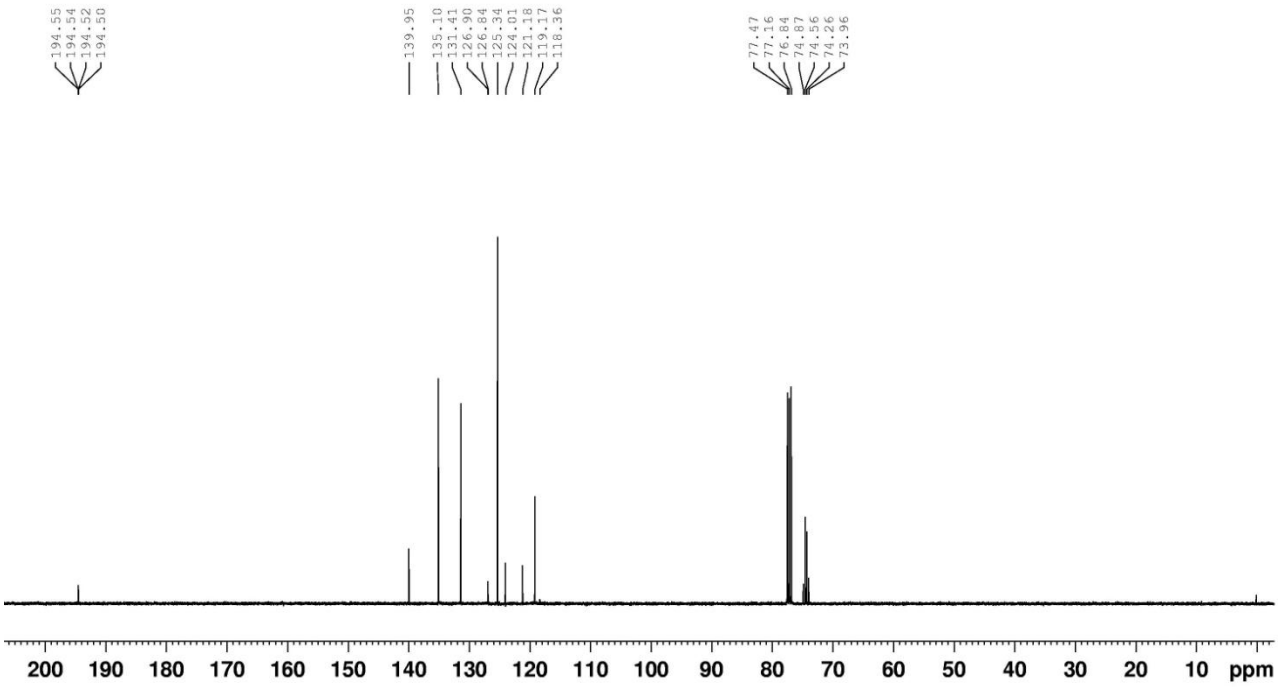




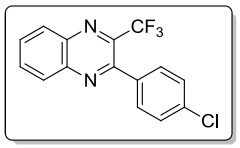
^{1}H, ^{13}C NMR Spectra of **16ae**

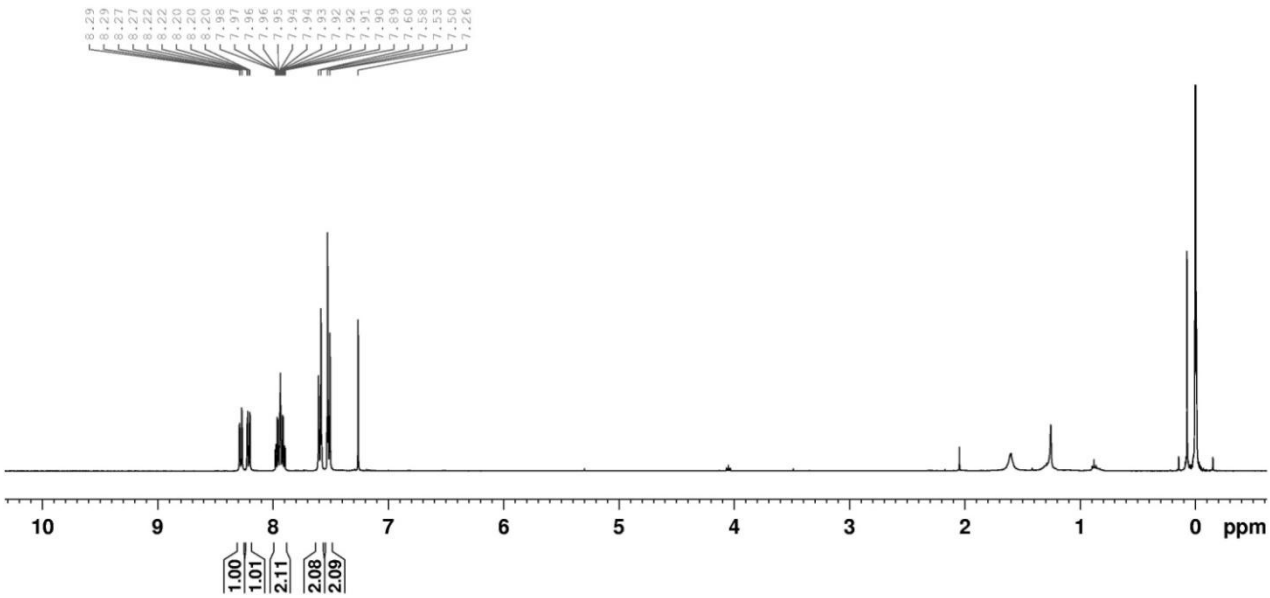


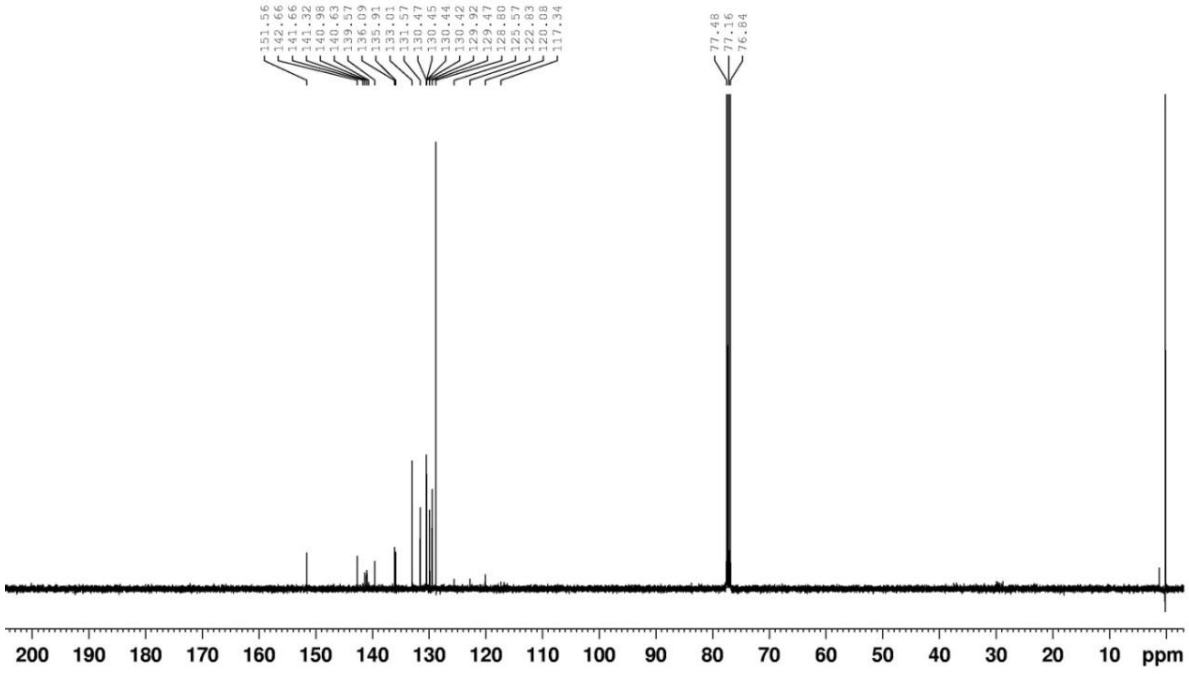




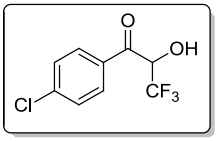
^{1}H, ^{13}C NMR Spectra of **19b**

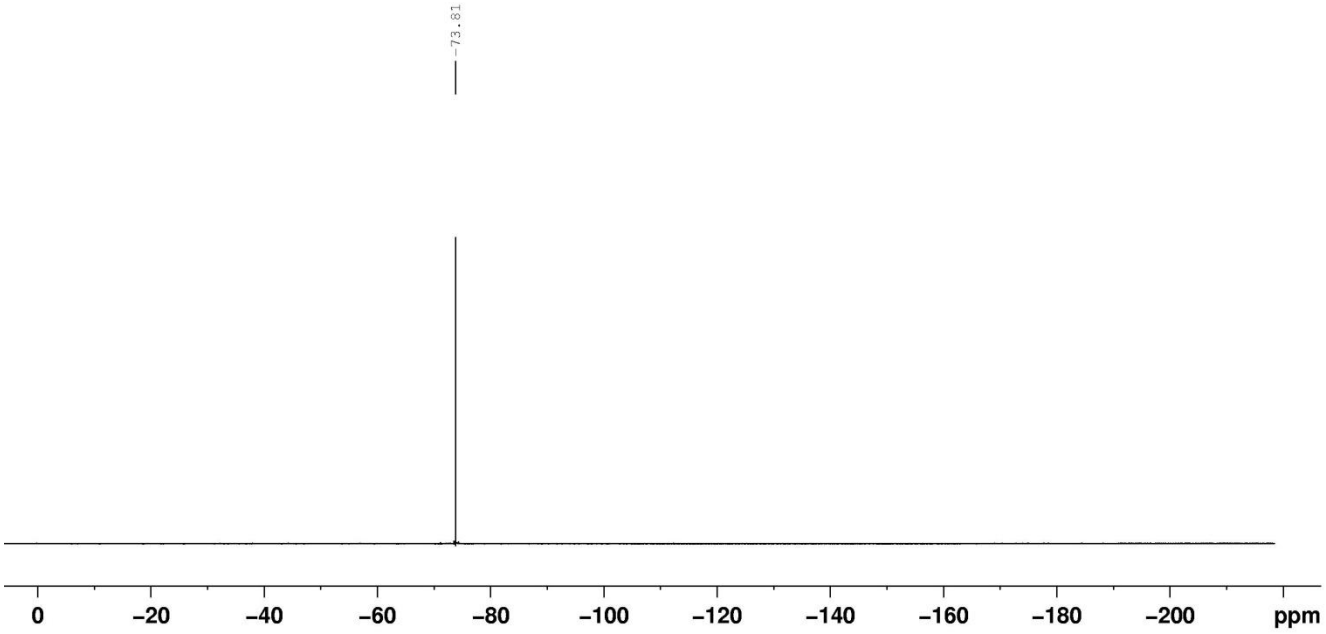




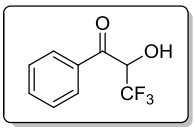


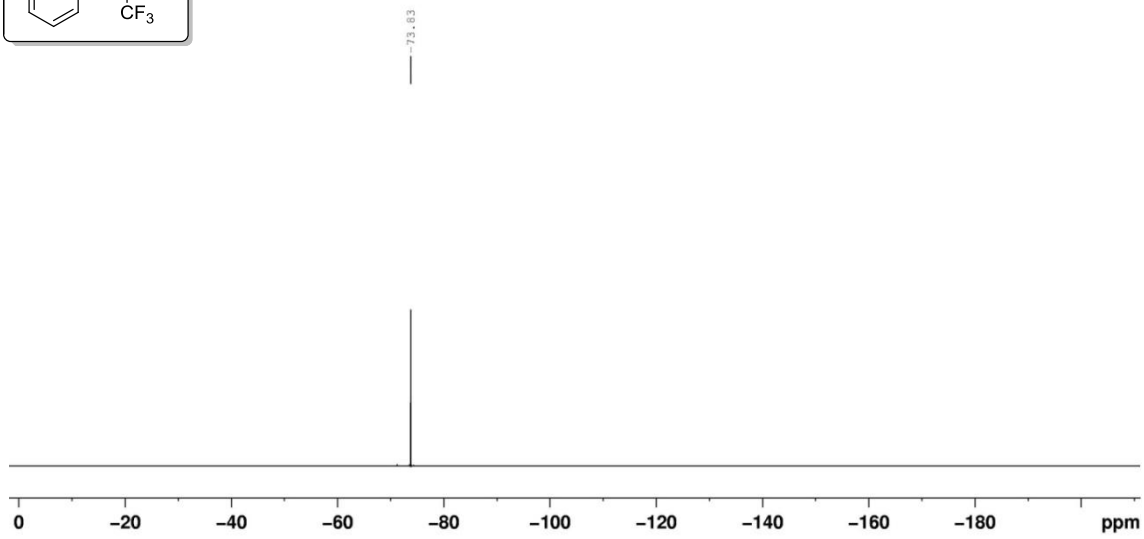
^{19}F NMR Spectra of **13c**



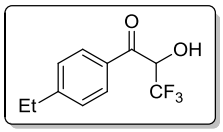


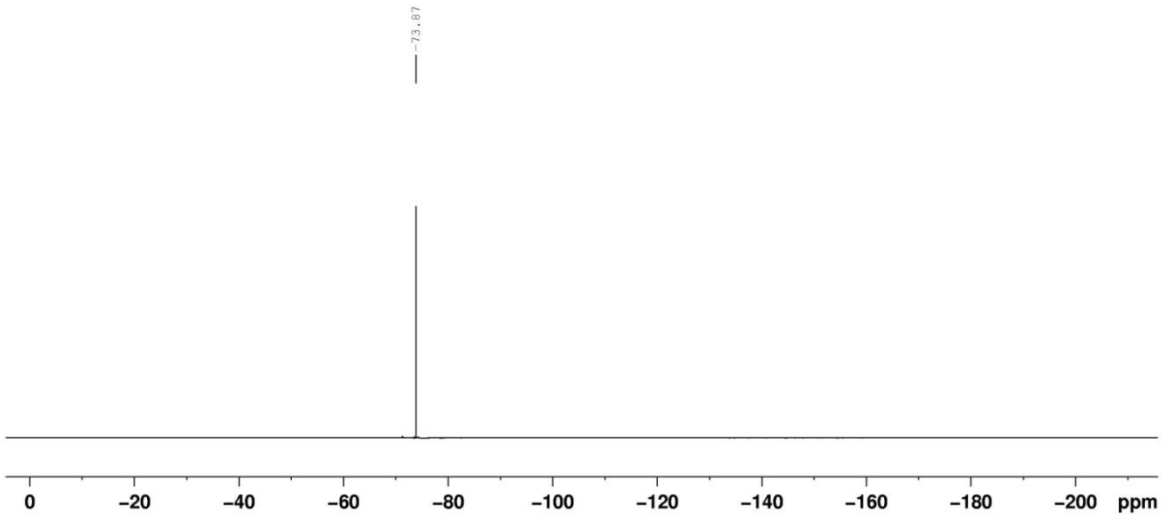
^{19}F NMR Spectra of **16a**



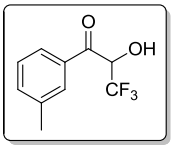


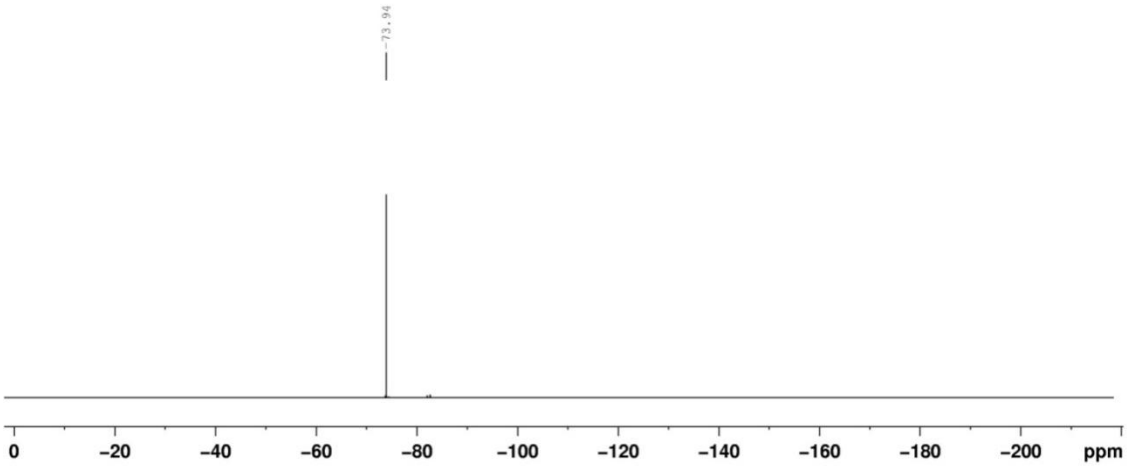
^{19}F NMR Spectra of **16b**



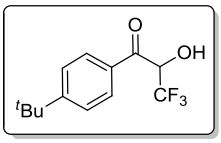


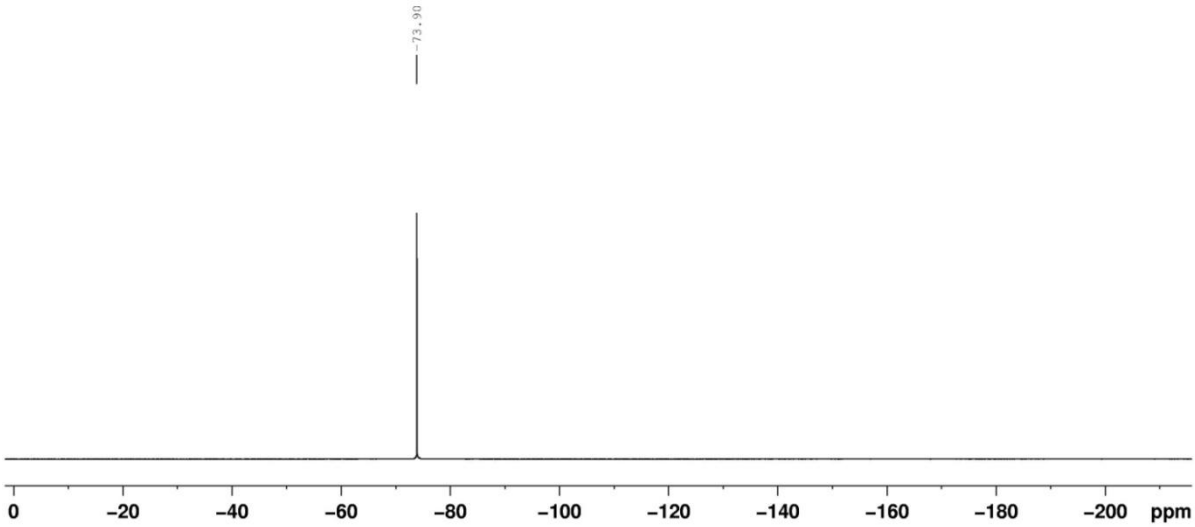
^{19}F NMR Spectra of **16c**



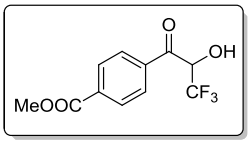


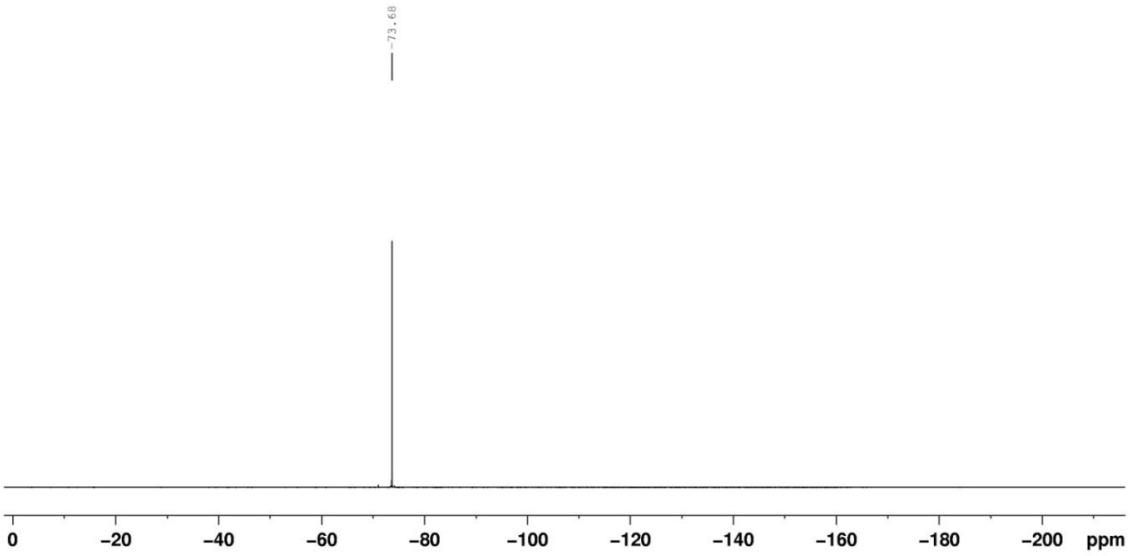
^{19}F NMR Spectra of **16d**



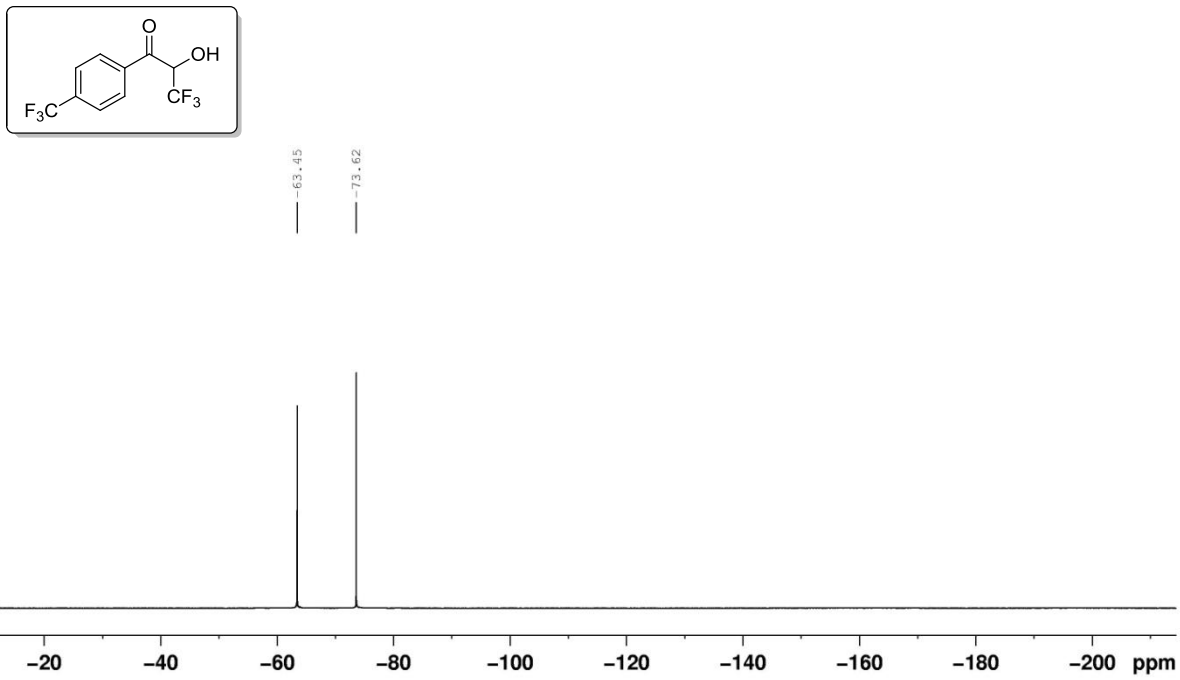


^{19}F NMR Spectra of **16e**

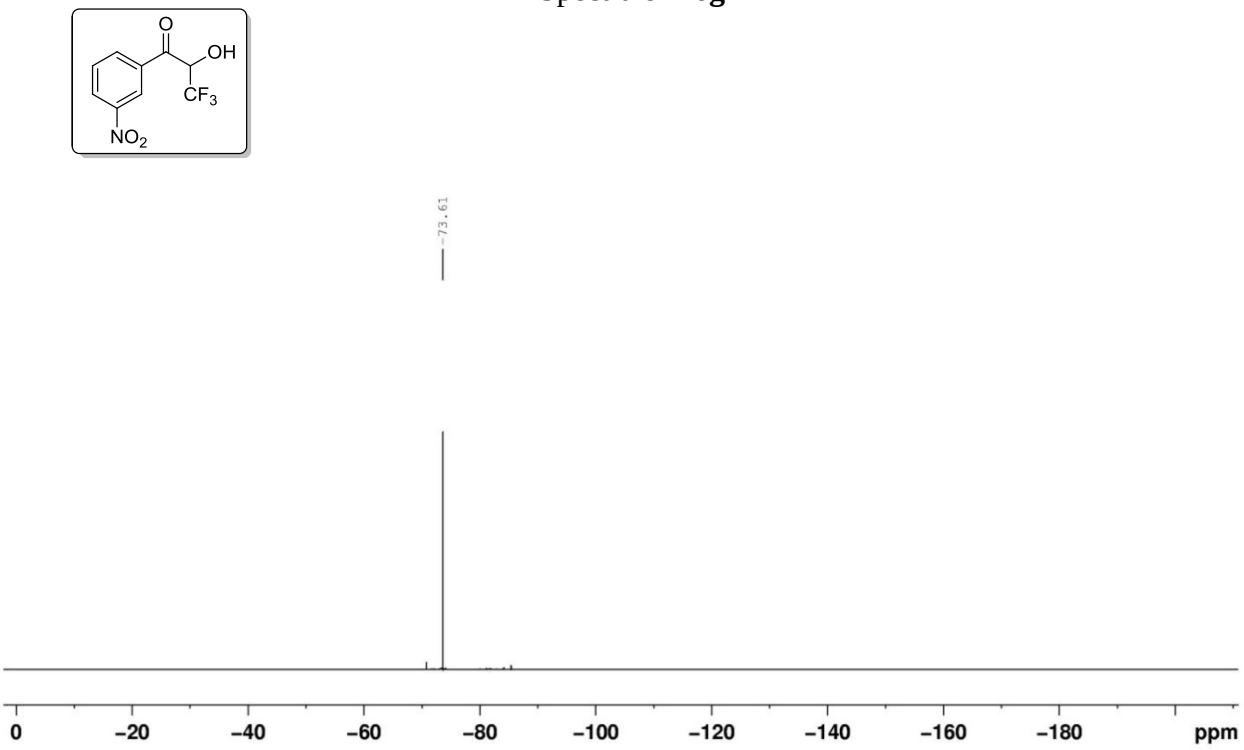




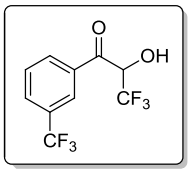
^{19}F NMR Spectra of **16f**

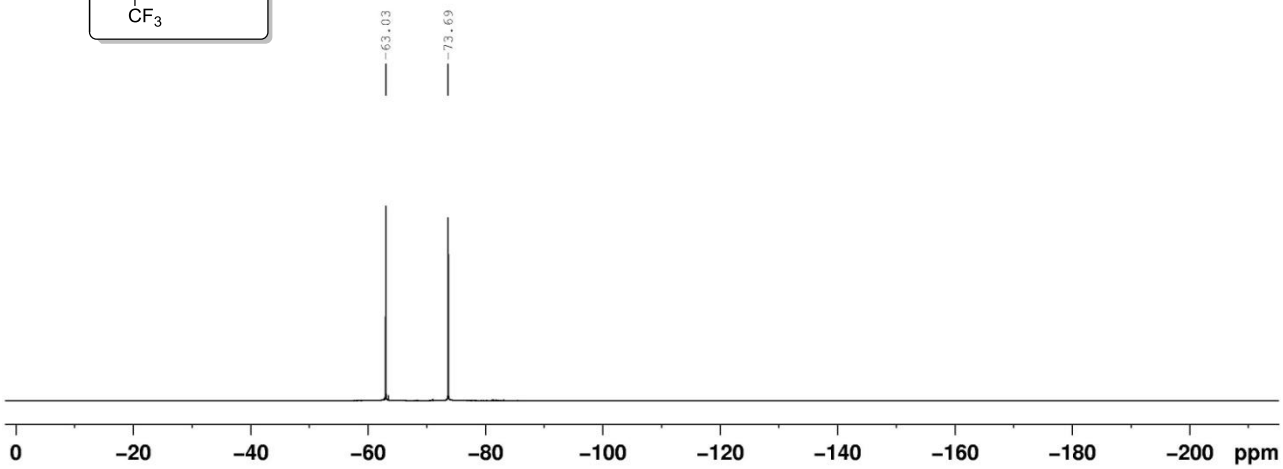


^{19}F NMR Spectra of **16g**

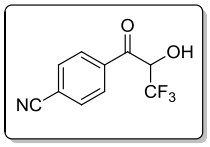


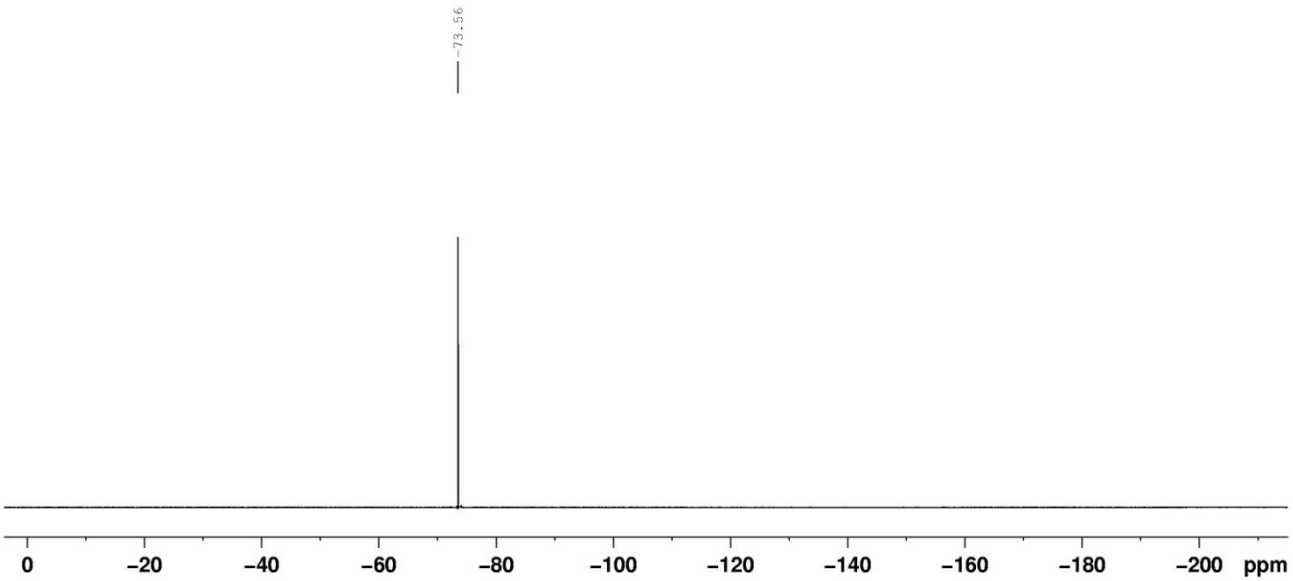
^{19}F NMR Spectra of **16h**



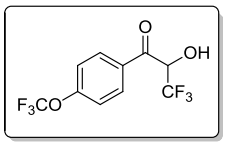


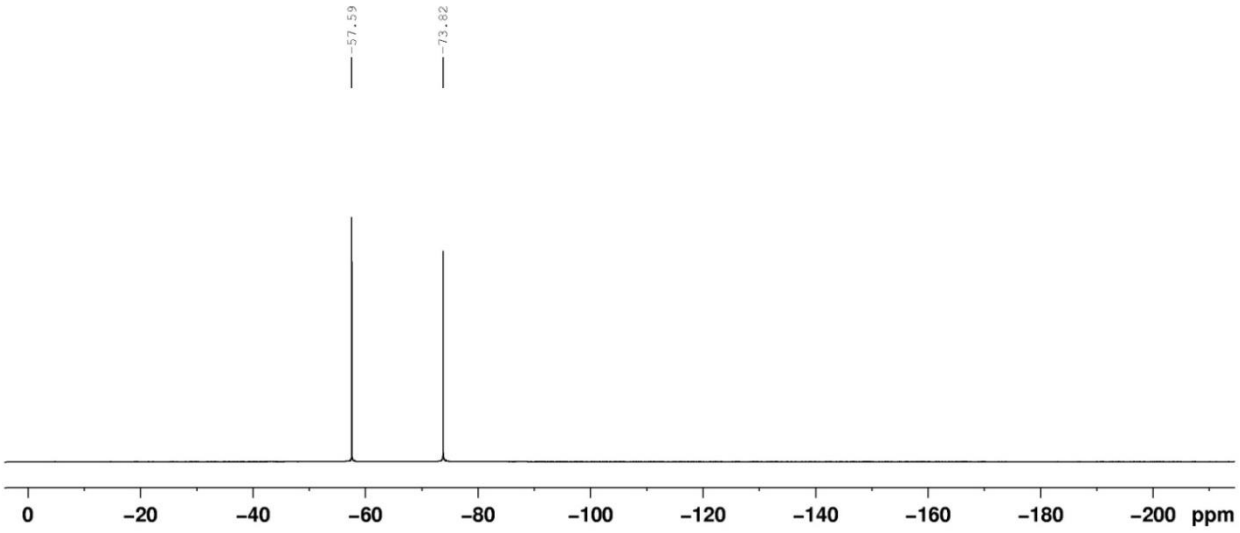
^{19}F NMR Spectra of **16i**



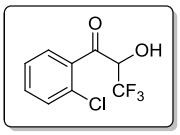


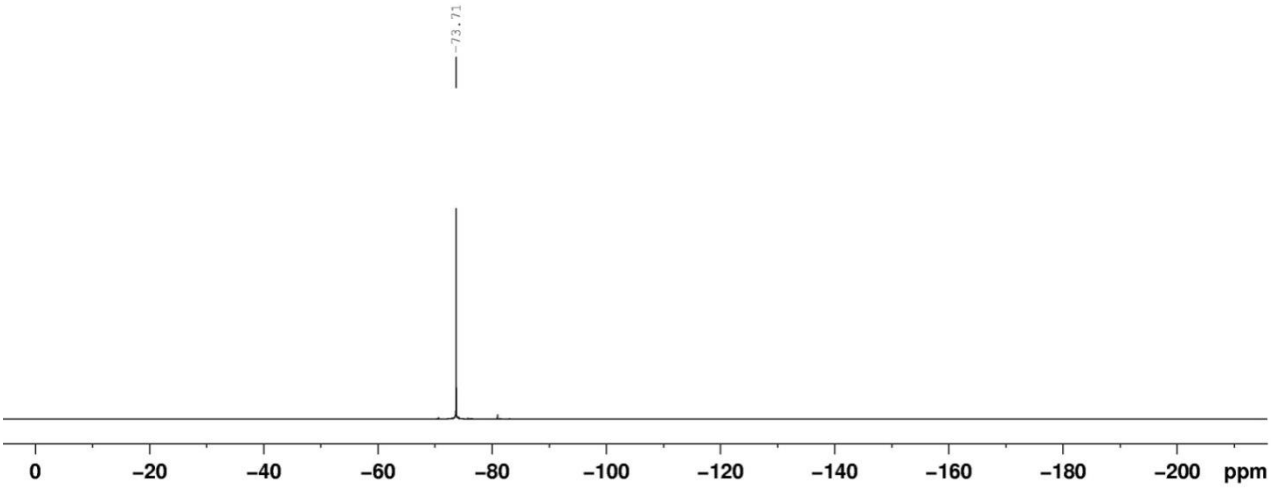
^{19}F NMR Spectra of **16j**



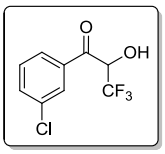


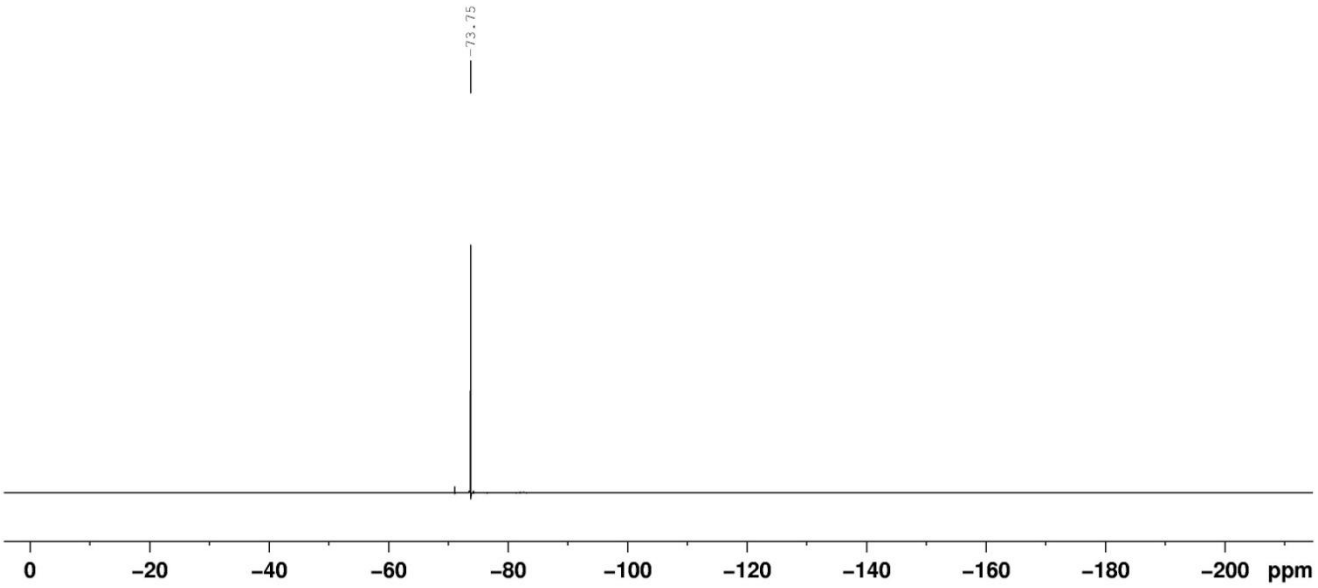
^{19}F NMR Spectra of **16k**



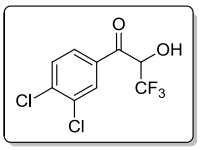


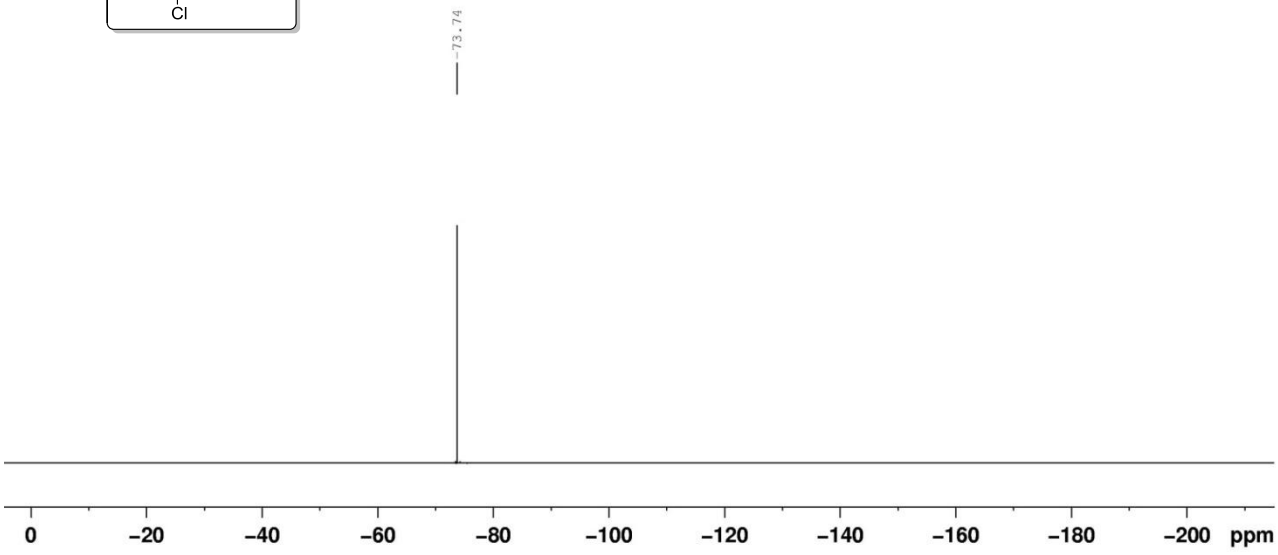
^{19}F NMR Spectra of **16l**



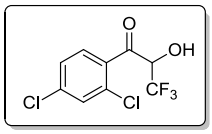


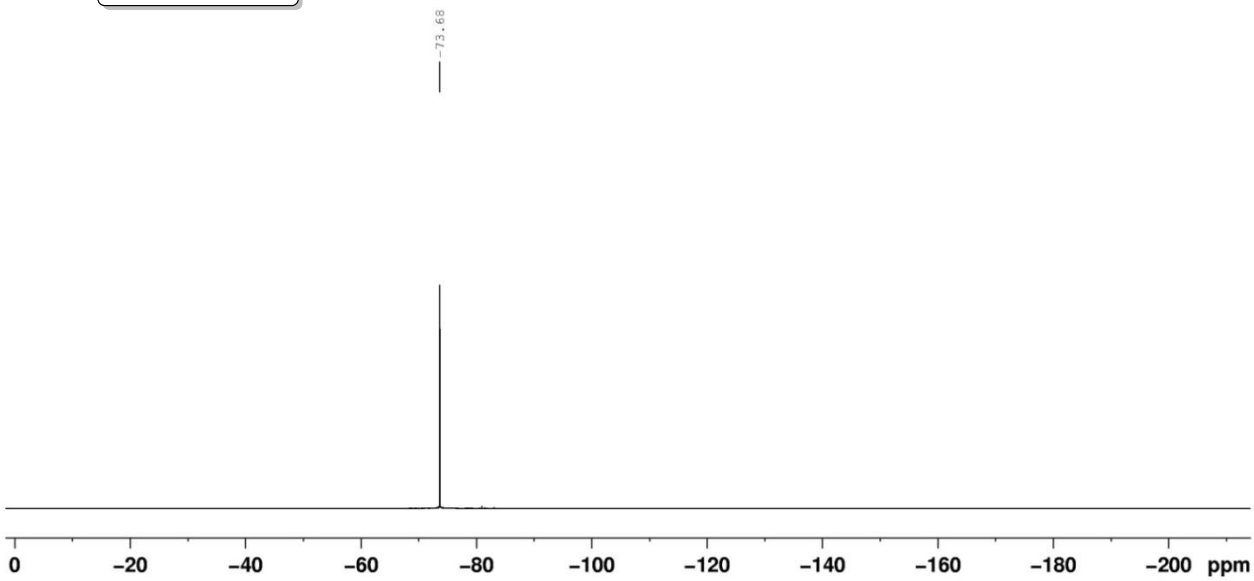
^{19}F NMR Spectra of **16m**



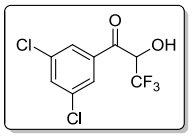


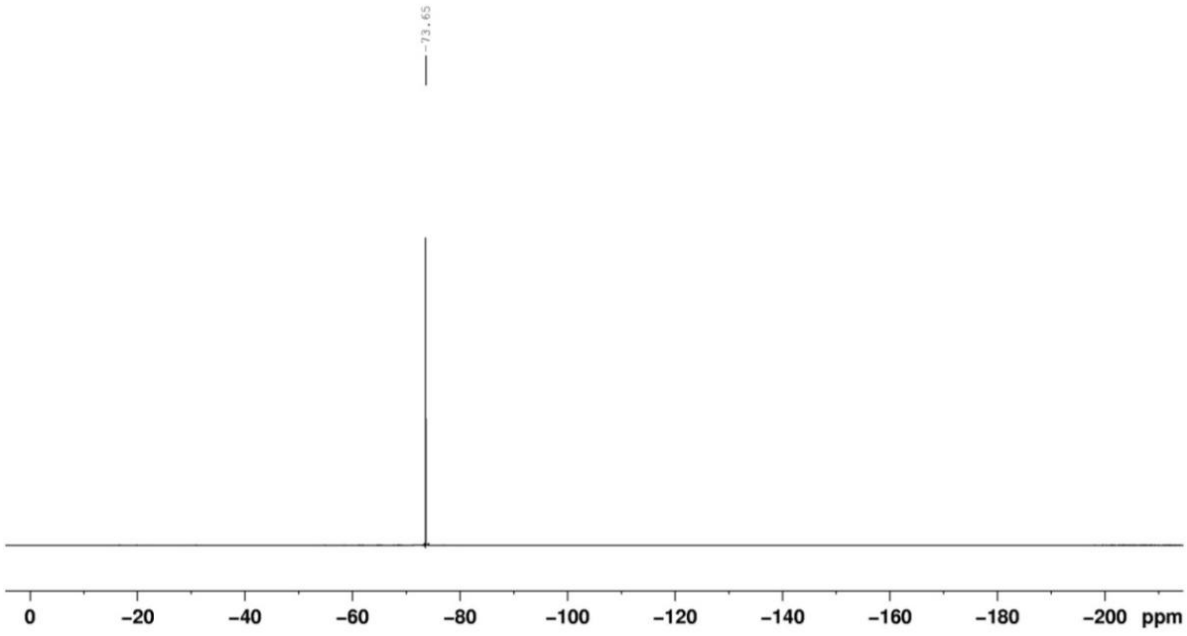
^{19}F NMR Spectra of **16n**



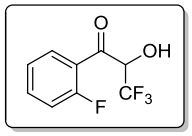


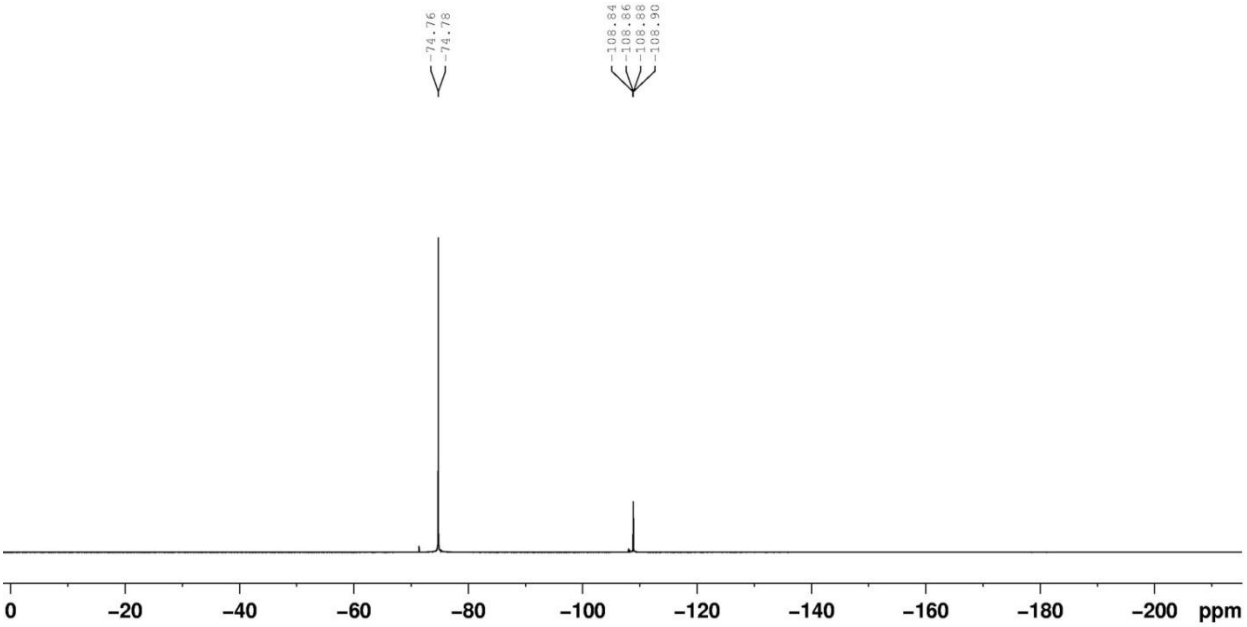
^{19}F NMR Spectra of **16o**



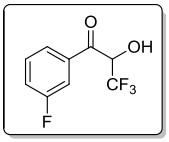


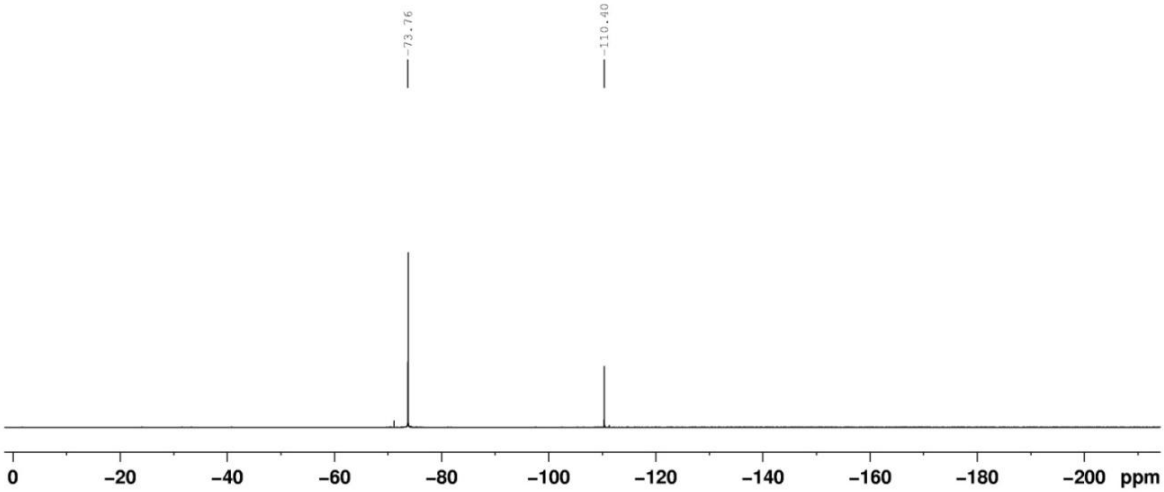
^{19}F NMR Spectra of **16p**



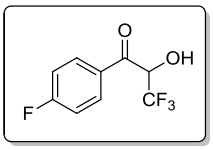


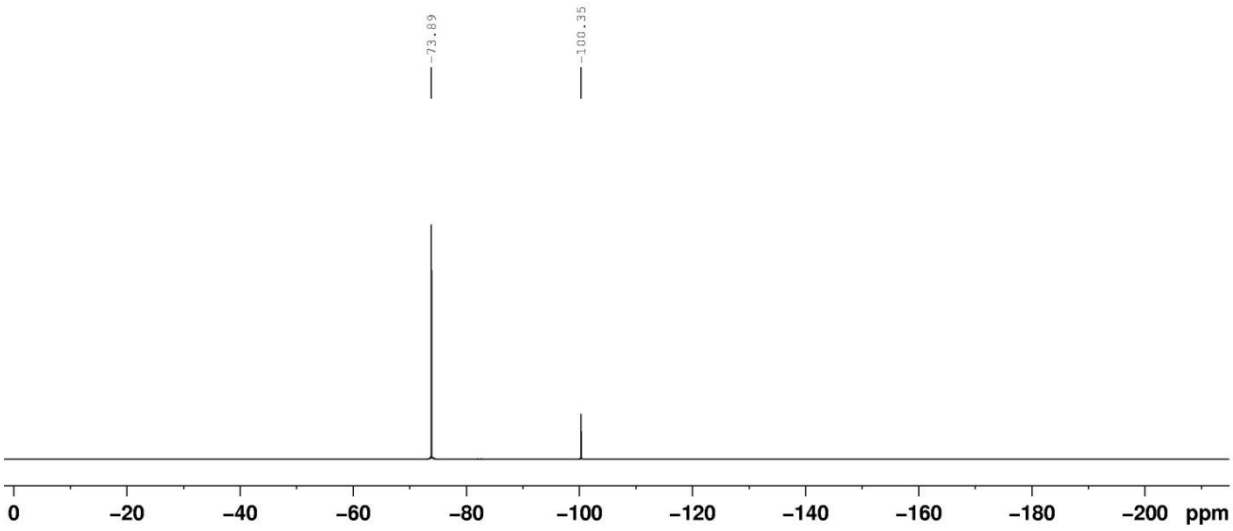
^{19}F NMR Spectra of **16q**



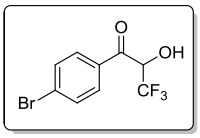


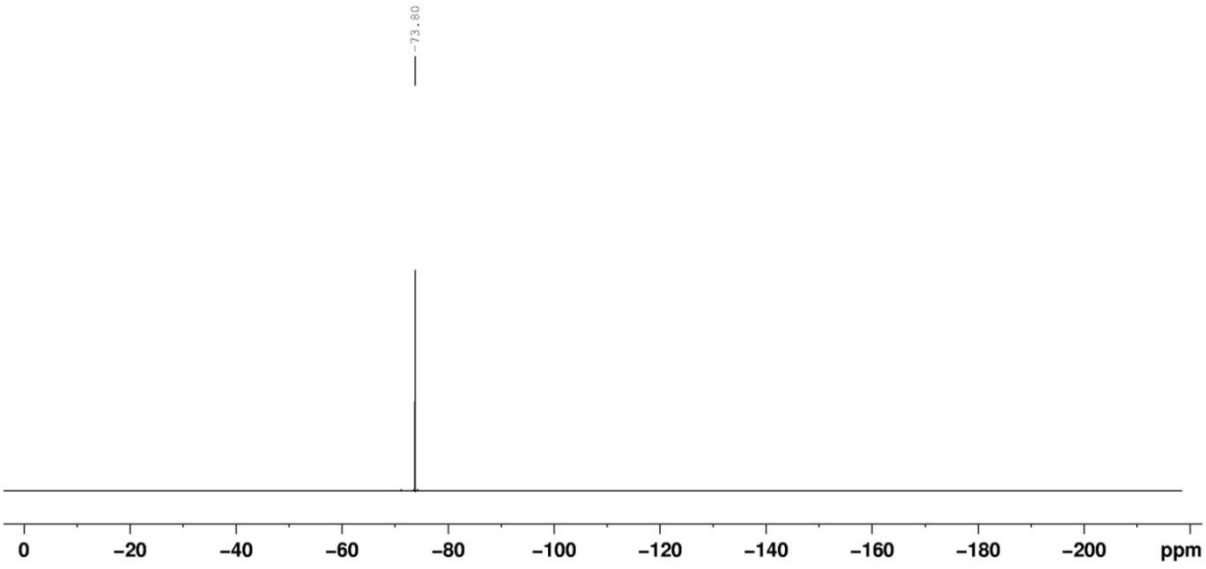
^{19}F NMR Spectra of **16r**



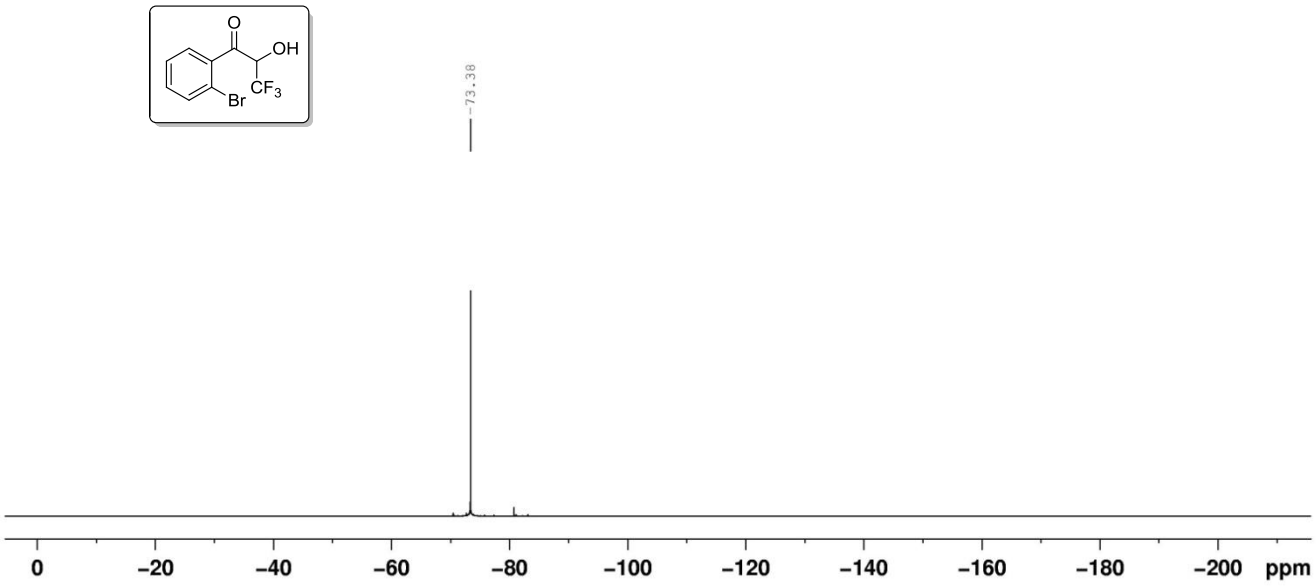


^{19}F NMR Spectra of **16s**

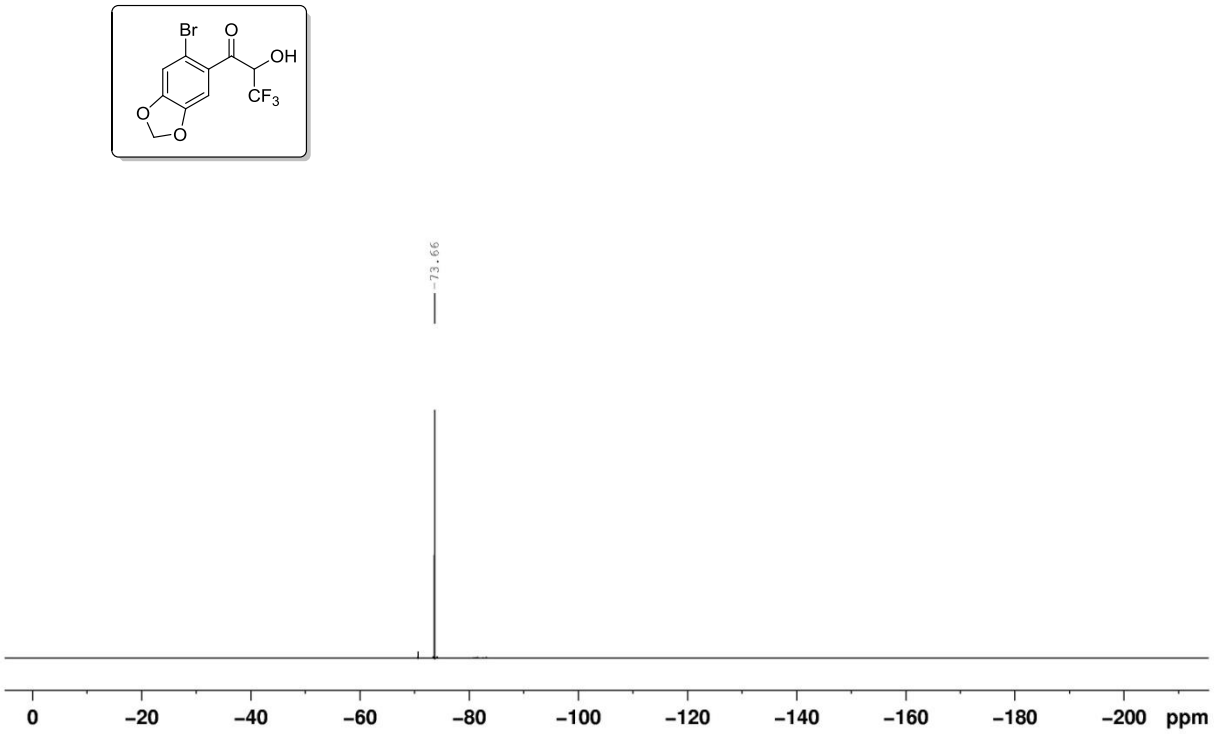




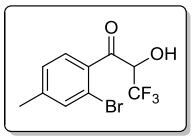
^{19}F NMR Spectra of **16t**

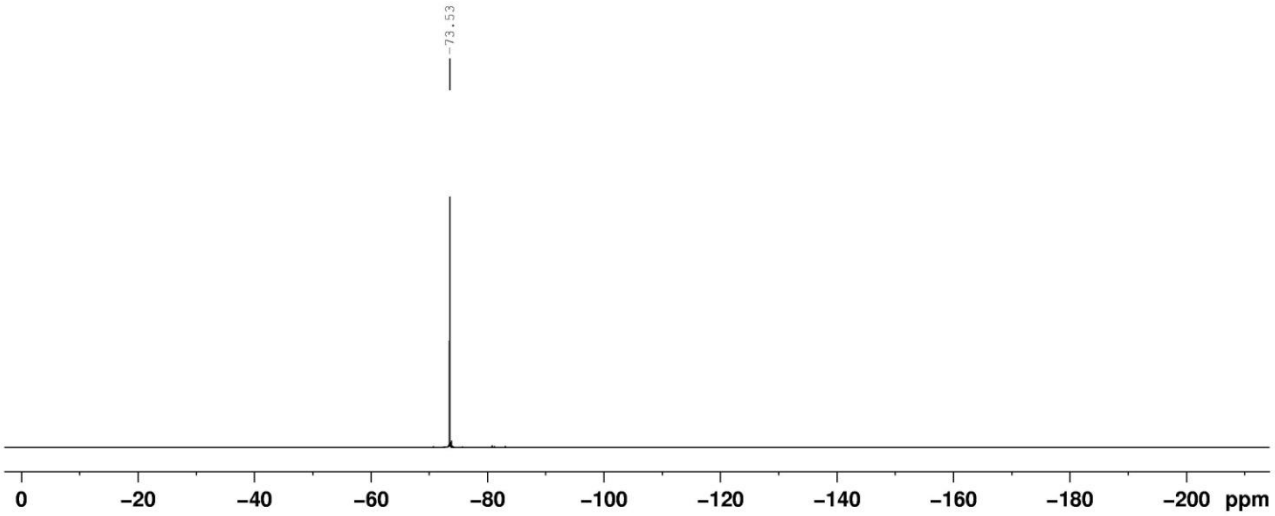


^{19}F NMR Spectra of **16u**

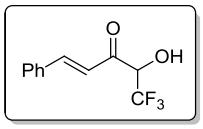


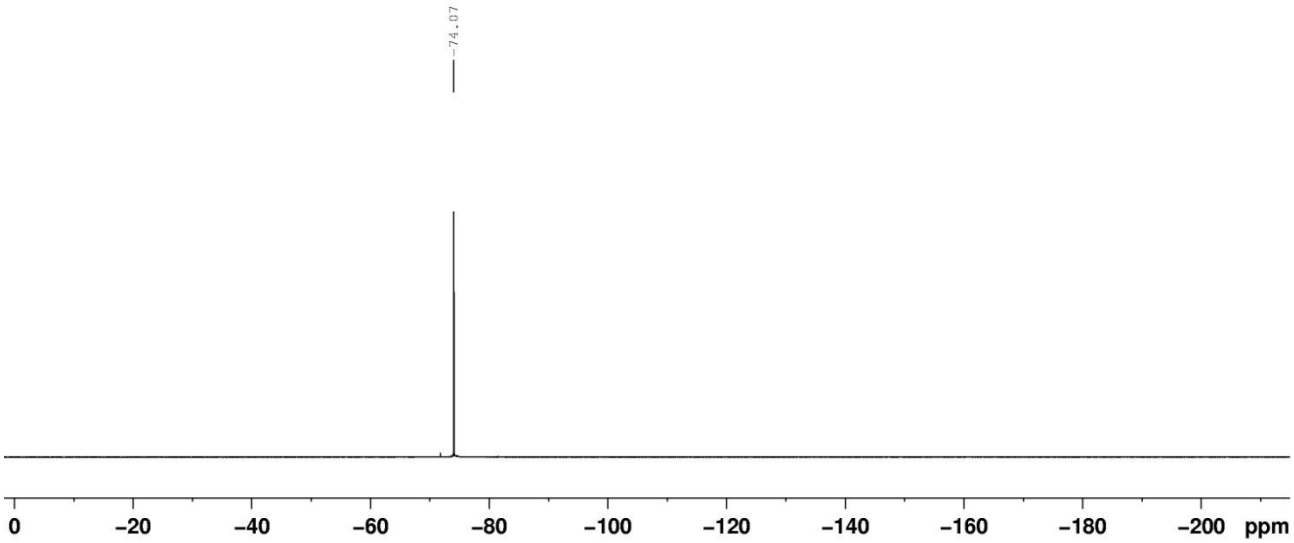
^{19}F NMR Spectra of **16v**



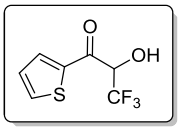


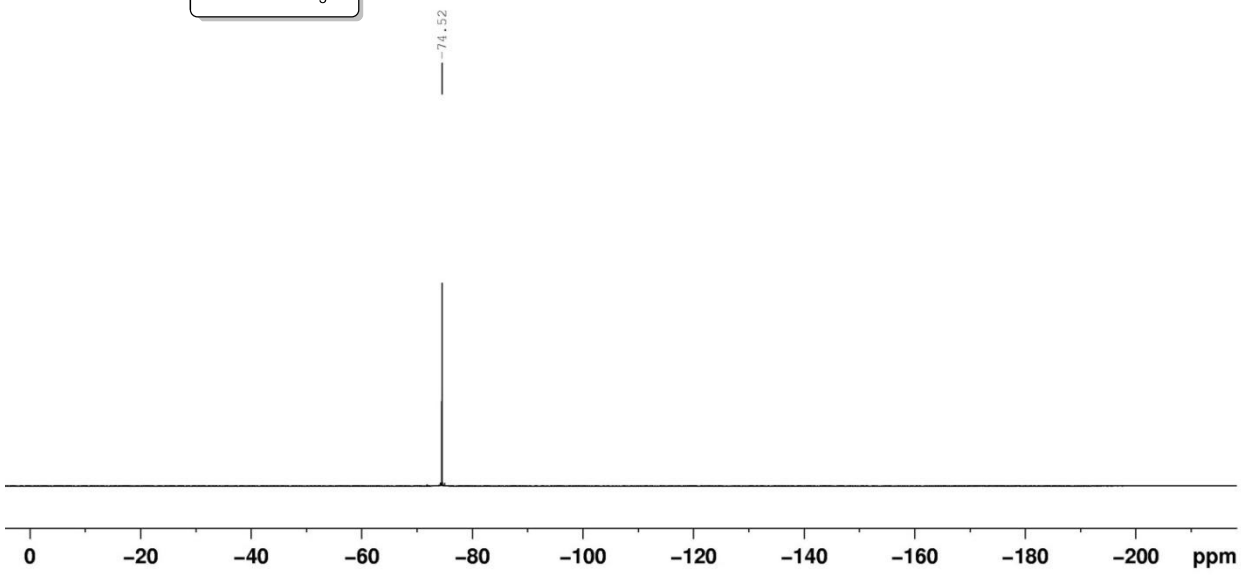
^{19}F NMR Spectra of **16w**



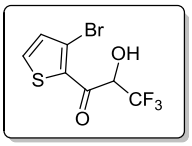


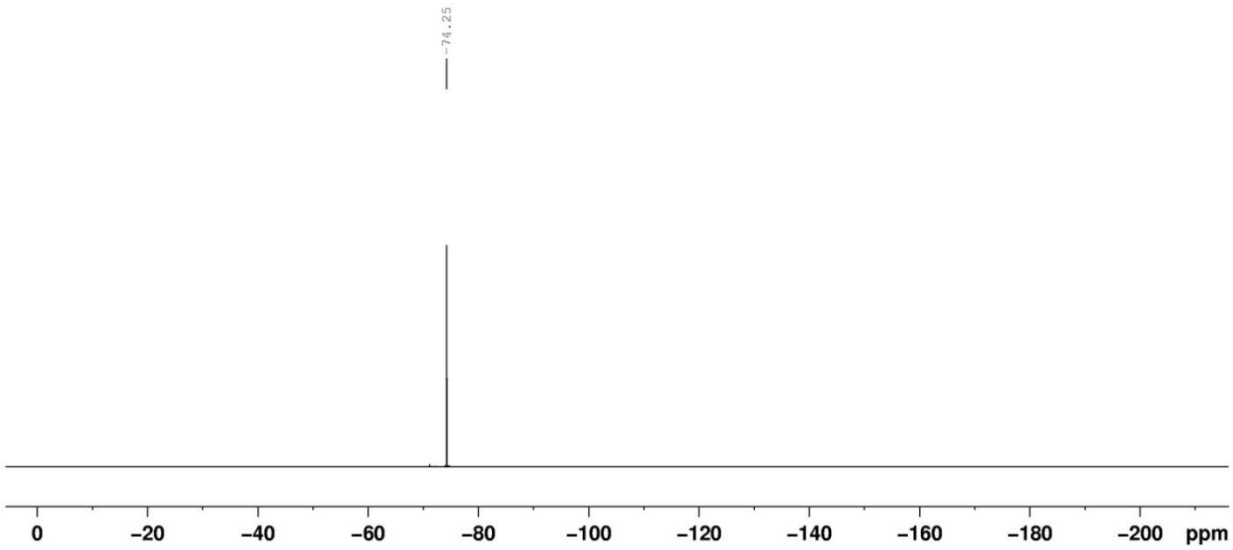
^{19}F NMR Spectra of **16x**



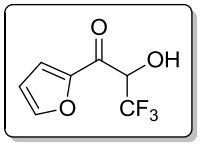


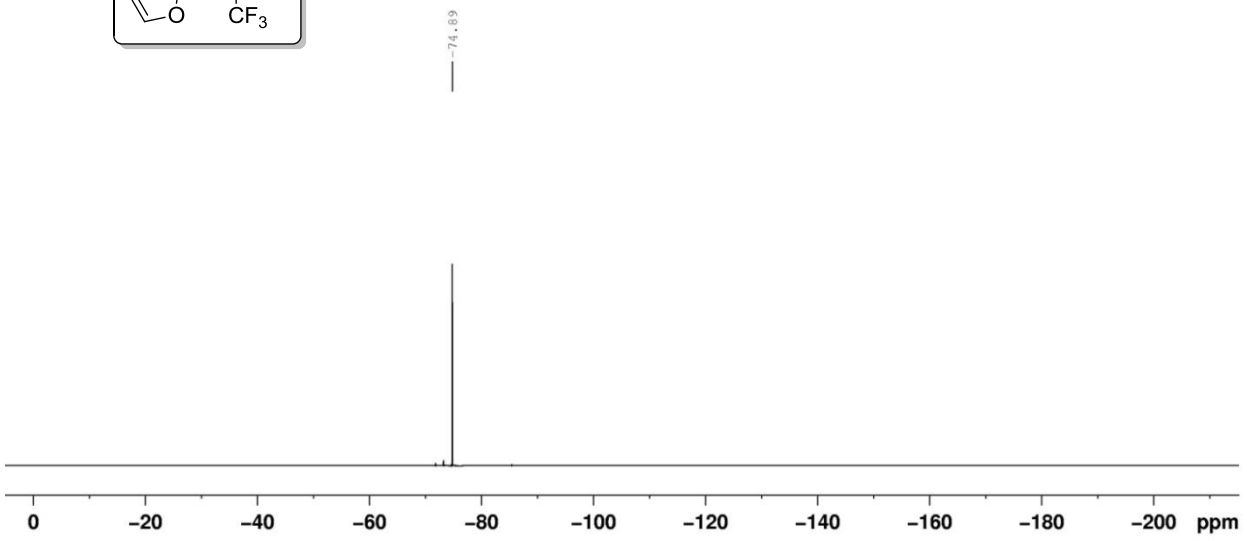
^{19}F NMR Spectra of **16y**



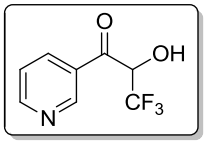


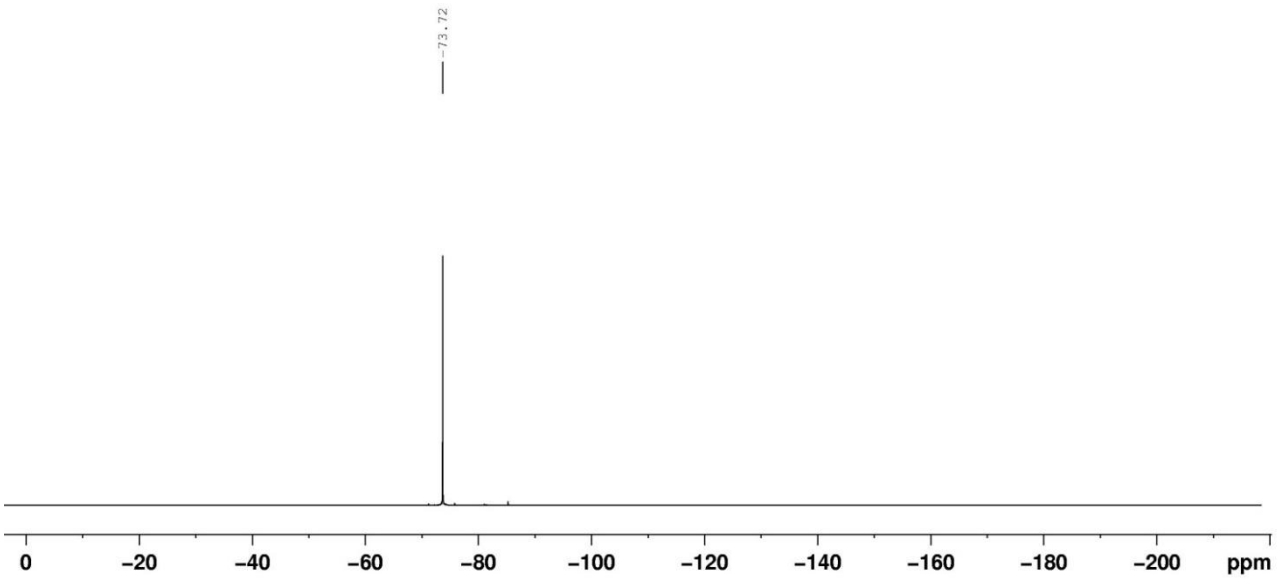
^{19}F NMR Spectra of **16z**



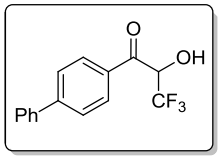


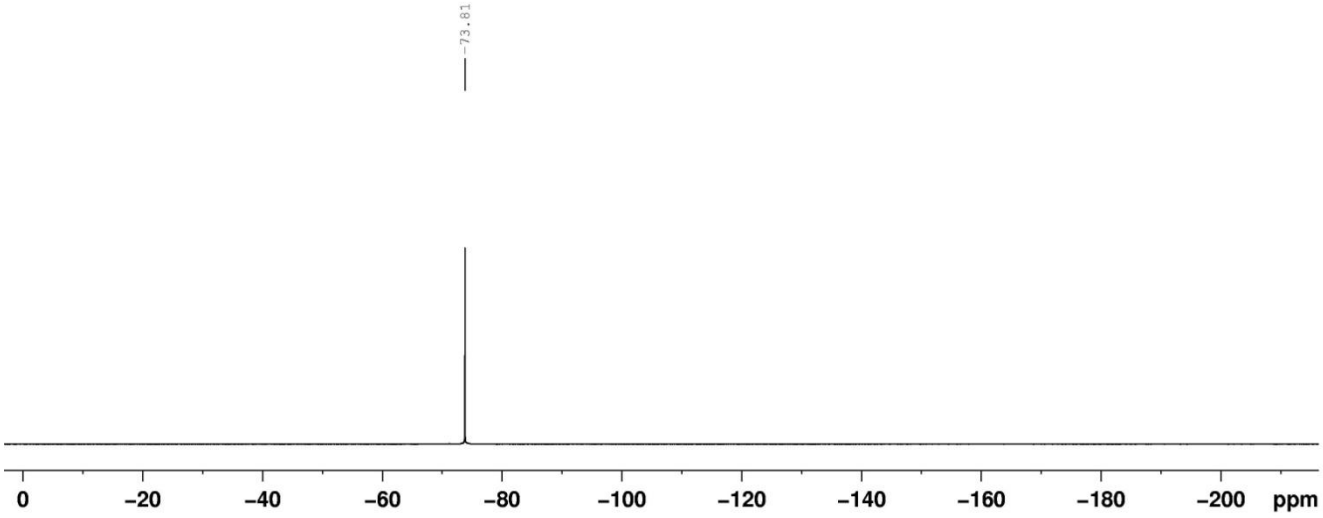
^{19}F NMR Spectra of **16aa**



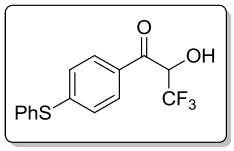


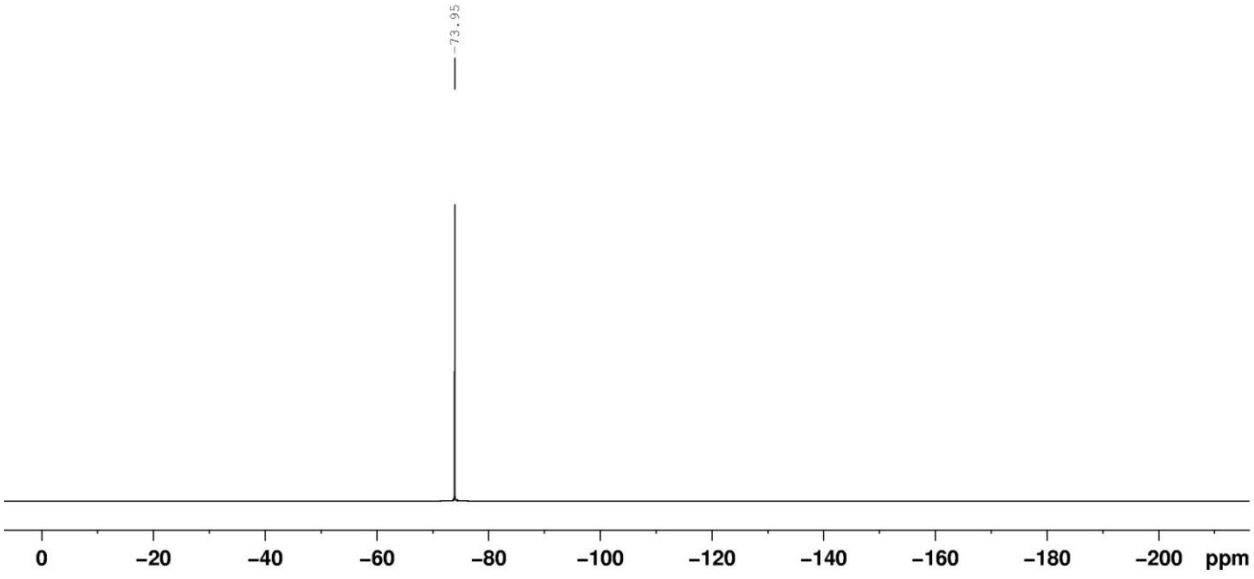
^{19}F NMR Spectra of **16ab**



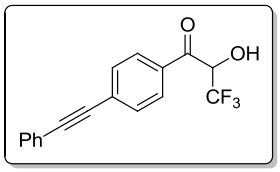


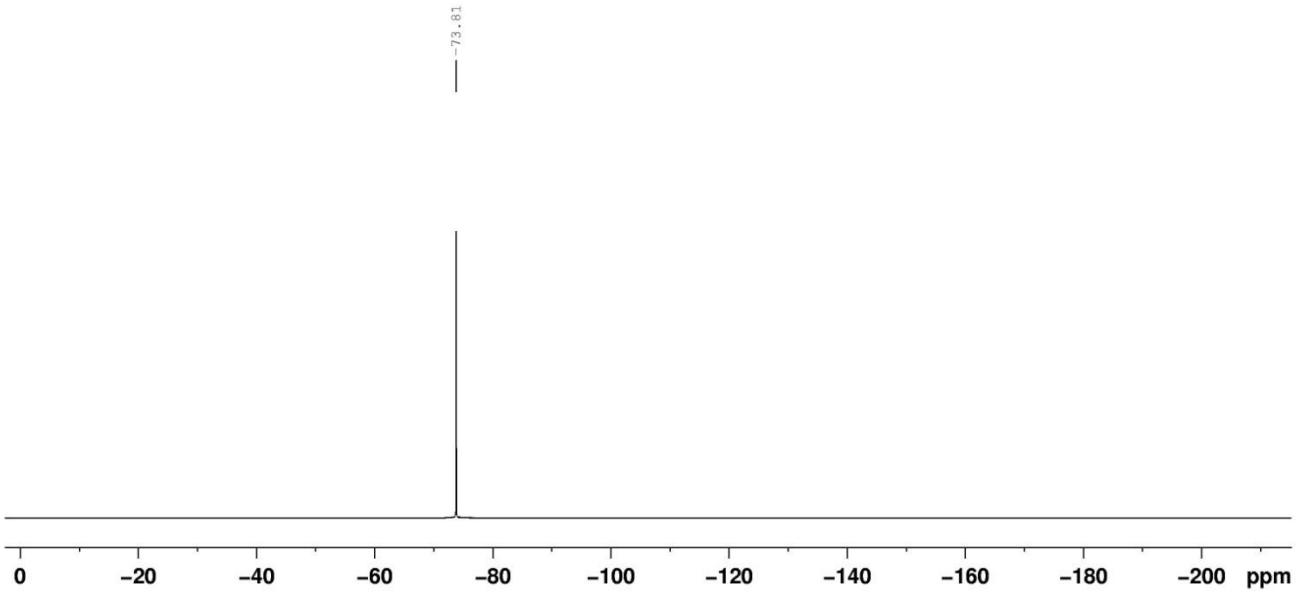
^{19}F NMR Spectra of **16ac**



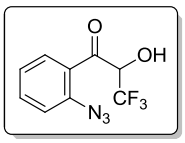


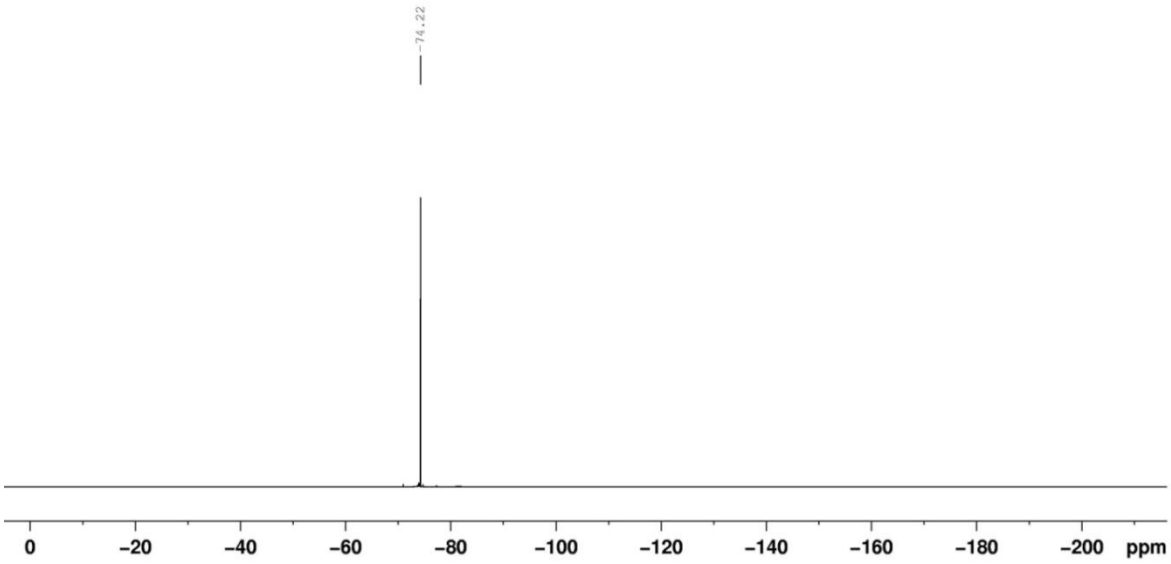
^{19}F NMR Spectra of **16ad**



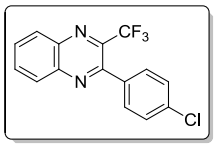


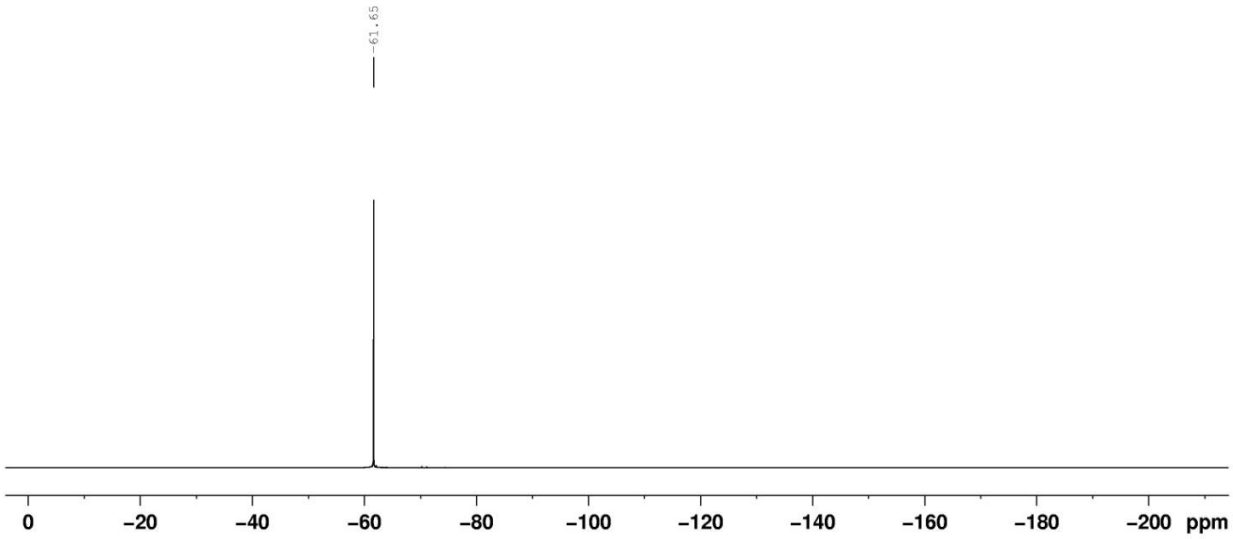
^{19}F NMR Spectra of **16ae**



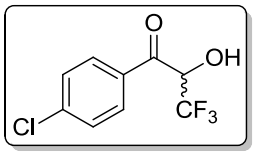


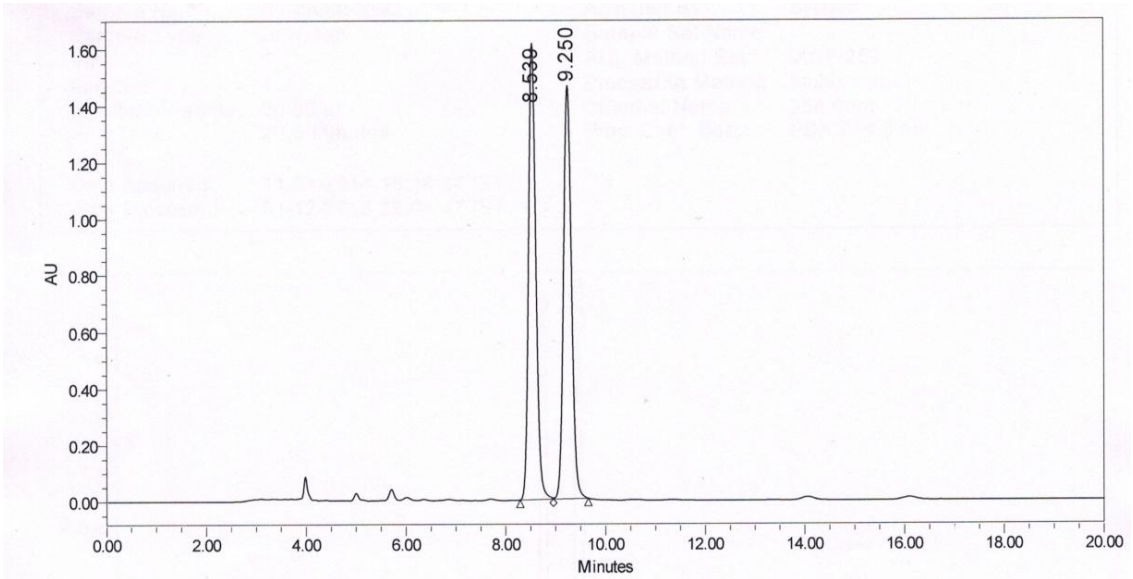
^{19}F NMR Spectra of **19b**





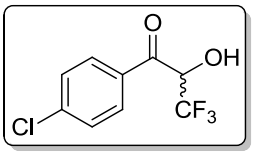
Spectra for racemic compound (13c)

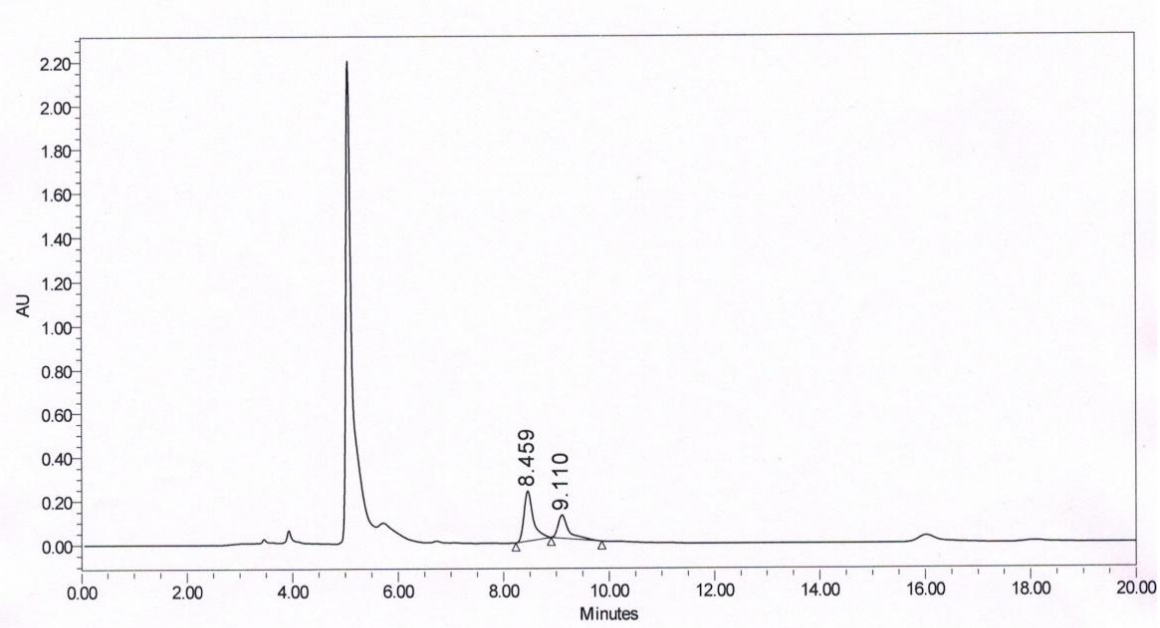




	RT	Area	% Area	Height
1	8.539	16444660	50.31	1614593
2	9.250	16240034	49.69	1462477

Spectra of sample with 30% *ee* (20a & 20b)





	RT	Area	% Area	Height
1	8.459	2778103	65.36	227834
2	9.110	1472245	34.64	106186

2.5. REFERENCES

[1] Stetter, H.; Dämbkes, G. *Synthesis* **1977**, 403.

[2] Matsumoto, T.; Ohishi, M.; Inoue, S. *J. Org. Chem*. **1985**, *50*, 603.

[3] Kuhl, N.; Glorius, F. *Chem. Commun*. **2011**, *47*, 573.

[4] Dünkelmann, P.; Kolter-Jung, D.; Nitsche, A.; Demir, A. S.; Siegert, P.; Lingen, B.; Baumann, M.; Pohl, M.; Müller, M. *J. Am. Chem. Soc*. **2002**, *124*, 12084.

[5] (a) Piel, I.; Pawelczyk, M. D.; Hirano, K.; Fröhlich, R.; Glorius, F. *Eur. J. Org. Chem*. **2011**, 5475. (b) Collett, C. J.; Massey, R. S.; Taylor, J. E.; Maguire, O. R.; O' Donoghue, A. C.; Smith, A. D. *Angew. Chem., Int. Ed*. **2015**, *54*, 6887.

[6] Jin, M. Y.; Kim, S. M.; Han, H.; Ryu, D. H.; Yang, J. W. *Org. Lett*. **2011**, *13*, 880.

[7] Langdon, S. M.; Wilde, M. M. D.; Thai, K.; Gravel, M. *J. Am. Chem. Soc*. **2014**, *136*, 7539.

[8] (a) Enders, D.; Henseler, A. *Adv. Synth. Catal*. **2009**, *351*, 1749. (b) Enders, D.; Grossmann, A.; Fronert, J.; Raabe, G. *Chem. Commun*. **2010**, *46*, 6282.

[9] (a) Rose, C. A.; Gundala, S.; Fagan, C.-L.; Franz, J. F.; Connon, S. J.; Zeitler, K. *Chem. Sci*. **2012**, *3*, 735. (b) Thai, K.; Langdon, S. M.; Bilodeau, F.; Gravel, M. *Org. Lett*. **2013**, *15*, 2214.

[10] (a) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev*. **2008**, *37*, 320. (b) For more reviews, see: (i) Yale, H. L. *J. Med. Pharm. Chem*. **1959**, *1*, 121. (ii) Müller, K.; Faeh, C.; Diederich, F. *Science* **2007**, *317*, 1881. (iii) Filler, R.; Saha, R. *Future Med. Chem*. **2009**, *1*, 777. (iv) Wang, J.; Sánchez-Roselló, M.; Aceña, J. L.; del Pozo, C.; Sorochinsky, A. E.; Fustero, S.; Soloshonok, V. A.; Liu, H. *Chem. Rev*. **2014**, *114*, 2432.

[11] (a) Loh, T.-P.; Li, X.-R. *Chem. Commun*. **1996**, 1929. (b) Poras, H.; Matsutani, H.; Yaruva, J.; Kusumoto, T.; Hiyama, T. *Chem. Lett*. **1998**, 665. (c) Loh, T.-P.; Li, X.-R. *Tetrahedron* **1999**, *55*, 5611. (d) Sakumo, K.; Kuki, N.; Kuno, T.; Takagi, T.; Koyama, M.; Ando, A.; Kumadaki, I. *J. Fluorine Chem*. **1999**, *93*, 165. (e) Kumadaki, I.; Jonoshita, S.; Harada, A.; Omote, M.; Ando, A. *J. Fluorine Chem*. **1999**, *97*, 61. (f) Ingrassia, L.; Mulliez, M. *Synthesis* **1999**, 1731. (g) Gong, Y.; Kato, K. *J. Fluorine Chem*. **2001**, *108*, 83.

[12] Another conceivable explanation for the outcome of the reaction is that even if trifluoroacetaldehyde is present in the solution, the Breslow intermediate derived from it is expected to have a poor nucleophilicity; therefore, it may not react with another molecule of trifluoroacetaldehyde to give **13e**.

[13] Islami, M. R.; Hassani, Z. *ARKIVOC* **2008**, *15*, 280.

[14] (a) Enders, D.; Breuer, K.; Kallfass, U.; Balensiefer, T. *Synthesis* **2003**, 1292. (b) Thomson, J. E.; Campbell, C. D.; Concellon, C.; Duguet, N.; Rix, K.; Slawin, A. M. Z.; Smith, A. D. *J. Org. Chem.* **2008**, *73*, 2784.

[15] Maekawa, H.; Kudo, M.; Nishiyama, Y.; Shimizu, K.; Abe, M. *Tetrahedron* **2014**, *70*, 2081.

[16] Singh, R. P.; Leitch, J. M.; Twamley, B.; Shreeve, J. M. *J. Org. Chem.* **2001**, *66*, 1436.

[17] Yang, Z.-J.; Liu, C.-Z.; Hu, B.-L.; Deng, C.-L.; Zang, X.-G. *Chem. Commun.* **2014**, *50*, 14554.

Chapter 3

Bis(amino)cyclopropenylidene (BAC) catalyzed chemoselective synthesis of α,α-diarylated ketones

3.1. Introduction on bis(amino)cyclopropenylidene (BAC)

It has been realized that the NHCs based on a heterocyclic core such as thiazole, triazole, imidazole, etc. are dominating in organocatalysis due to their unmatched nucleophilicity[1] as well as high stability.[2] On the other hand, the scope of non-heterocyclic based carbenes for the umpolung type activation of carbonyl compounds is very limited although their organometallic complexes are well studied.[3] However, bis(amino)cyclopropenylidenes (BACs), another type of nucleophilic carbenes derived from cyclopropenium salts, were found to be a promising non-heterocyclic based candidate in terms of reactivity towards metals as well as carbonyl compounds. Unlike N-heterocyclic carbenes, BACs do not require a heteroatom(s) adjacent to the electron-deficient carbene carbon center to confer stability. Indeed, the stability of these cyclopropenylidenes could be attributed to the push-pull effect of the two amino substituents that were attached to the ring.[4] Another important factor that contributes to the stability of the carbenes is the σ-aromaticity of the cyclopropene ring.[4] Although the synthesis and structural properties of bis(amino)cyclopropenylidene salts have been exploited in 1970s by Weiss and Yoshida groups[5] independently, their applications have been realized very recently, particularly in organometallic chemistry.[6] Figure 1 illustrates the general structures of N-heterocyclic carbene **1a** and bis(amino)cyclopropenylidene **1b**.

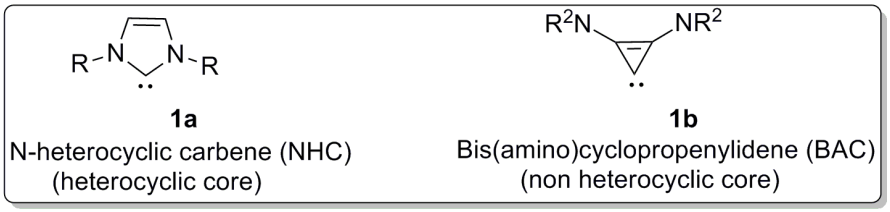


Figure 1

3.2. Literature review on BAC

In a seminal report, Bertrand and co-workers demonstrated the first isolation of bis(diisopropylamino)cyclopropenylidene (**2a**).[7] This particular BAC **2a** was found to be highly air-sensitive and possessed a reasonable thermal stability. BAC **2a** was thoroughly characterized by NMR techniques and X-ray analysis. A general comparison between BAC **2a** and NHC **2b** is shown in figure 2.

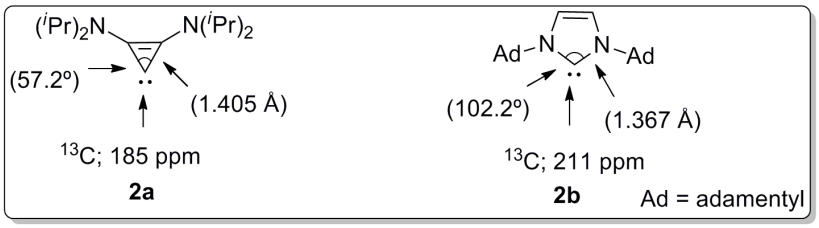
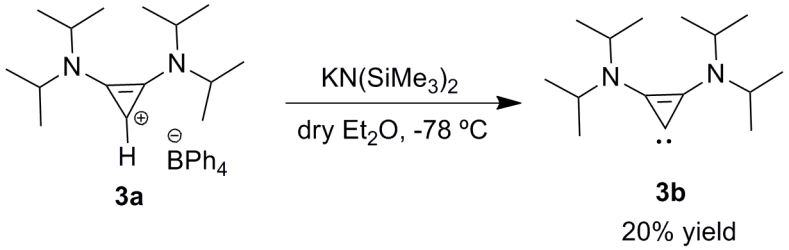


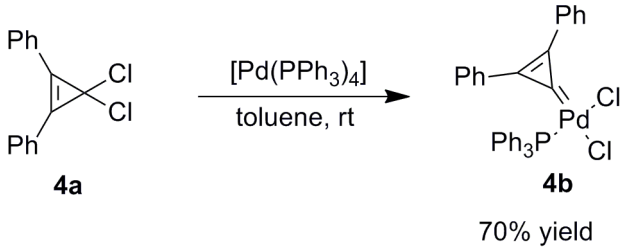
Figure 2

Bis(diisopropylamino)cyclopropenylidene (**3b**) was isolated by the reaction of an equimolar mixture of bis(diisopropylamino)cyclopropenylidene tetraphenylborate salt (**3a**) and $KN(SiMe_3)_2$ in dry Et_2O at −78 °C, and the resulting free carbene **3b** was isolated in 20% yield (Scheme 1).



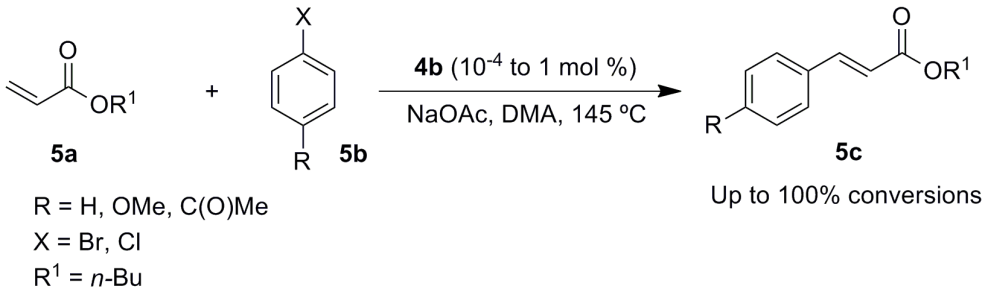
Scheme 1

After the successful isolation of BAC by Bertrand's group, several reports appeared in the literature on the application of BAC as a ligand in organometallic chemistry. Wass and co-workers reported the synthesis of 2,3-diphenylcyclopropenylidene supported palladium complex **4b**, and its applications in Heck and Suzuki coupling reactions.[8]



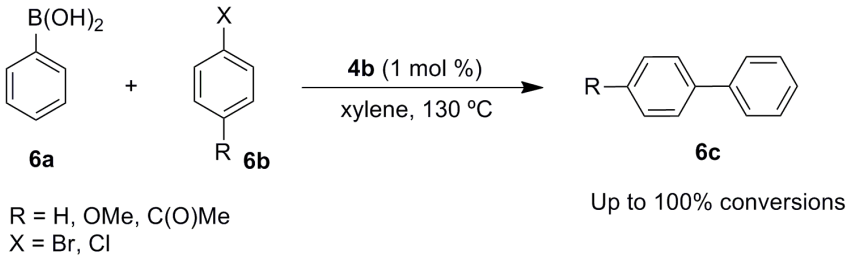
Scheme 2

This Pd-complex **4b** was readily prepared by the reaction of 1,1-dichoro-2,3-diphenylcyclopropene (**4a**) and [$Pd(PPh_3)_4$] in toluene at rt, and the desired complex **4b** was obtained in 70% yield (Scheme 2). Then the catalytic activity of Pd-complex **4b** was examined in cross-coupling reaction of *n*-butyl acrylate (**5a**) with various aryl halides **5b** in the presence of NaOAc as a base at high temperature (145 °C), and a quantitative conversion of corresponding starting material **5b** was observed in most of the cases (Scheme 3).



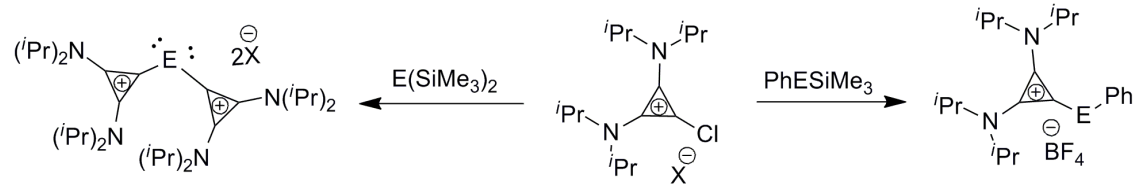
Scheme 3

The catalytic activity of this Pd-BAC complex **4b** has also been explored in Suzuki coupling reaction of phenyl boronic acid **6a** with various aryl halides **6b** in the presence of K_2CO_3 as a base at high temperature (130 °C). In most of the cases, quantitative conversion of corresponding starting materials was observed (Scheme 4).



Scheme 4

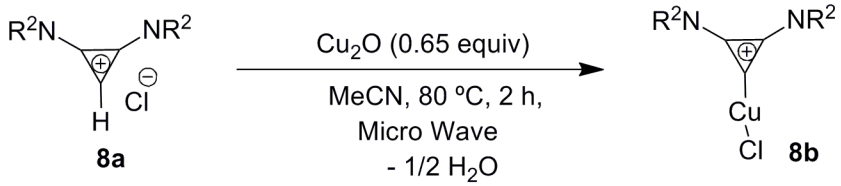
Recently, Alcarazo and co-workers demonstrated the synthesis and structural characterization of cyclopropenylidene stabilized S (II), Se (II) and Te (II) mono (**7c**–**7e**) and dications (**7f**–**7k**), by gentle heating of suspensions containing 1-chloro-2,3-bis(diisopropylamino)cyclopropenium salts **7a** or **7b** with $PhEMe_3$ and $E(SiMe_3)_2$ (E = S, Se, Te). The corresponding mono cations (**7c**–**7e**), the dications (**7f**–**7k**) were obtained in moderate to good yields (Scheme 5).[9]



7f; E = S, X = BF_4, 85% **7g**; E = S, X = TfO, 88%
7h; E = Se, X = BF_4, 66% **7i**; E = Se, X = TfO, 70%
7J; E = Te, X = BF_4, 32% **7k**; E = Te, X = TfO, 48%

Scheme 5

The first example of CuCl(BAC) **8b** complex (BAC = bis(diisopropylamino)cyclopropenylidene) was reported by Cazin and co-workers.[10] The synthesis of the BAC–Cu^I complex **8b** was achieved by the reaction of cyclopropenium chloride **8a** with Cu_2O in CH_3CN under microwave heating (80 °C) conditions (Scheme 6).

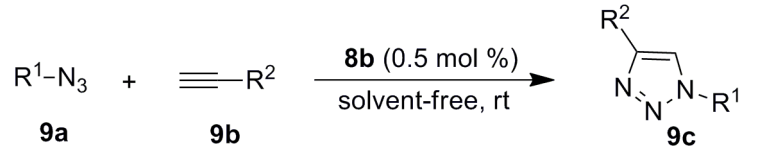


8a
R = isopropyl

8b
92% yield

Scheme 6

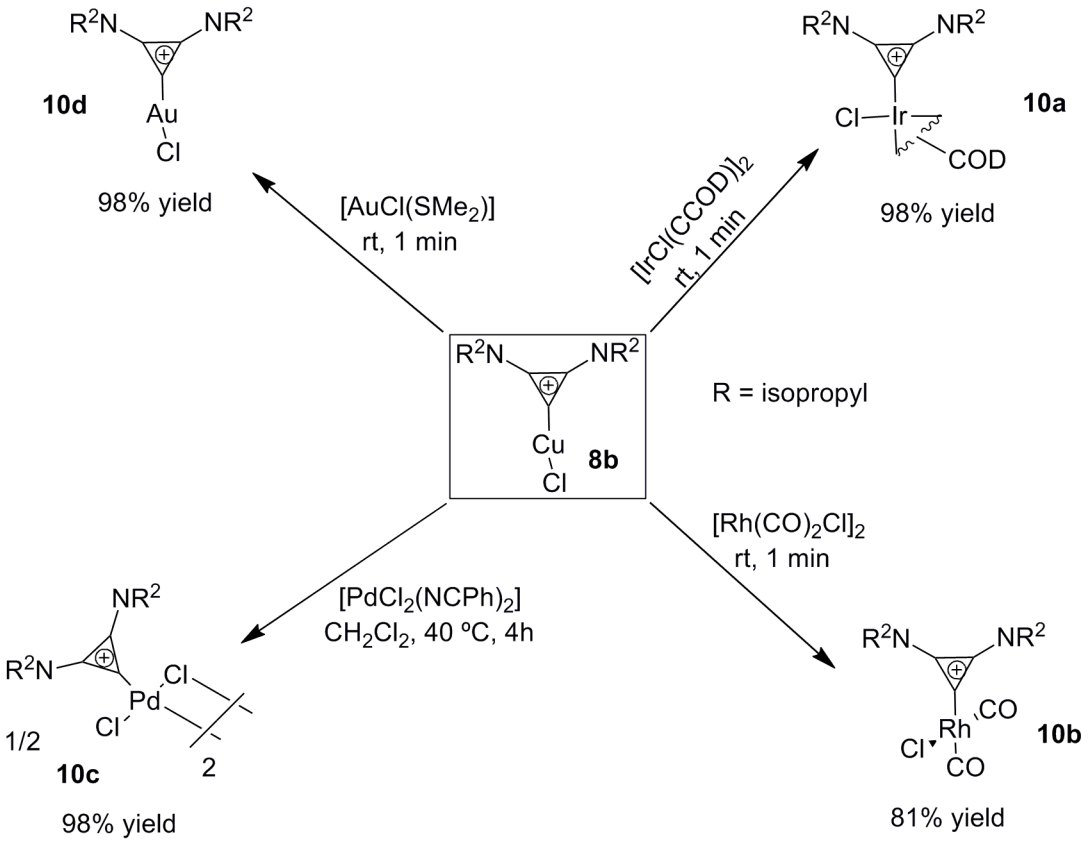
Then the catalytic activity of this complex has been evaluated in 1,2,3-triazole formation *via* the [3+2]-cycloaddition of azides with alkynes. A variety of alkynes (**9b**) were treated with various azides (**9a**) using the catalytic amount of [CuCl(BAC)] complex **8b** under a solvent free condition at rt, and the corresponding 1,2,3-triazole derivatives **9c** were obtained in good to excellent yields (Scheme 7).



9a **9b**
R_1, R_2 = alkyl, aryl

9c
Up to 96% yield

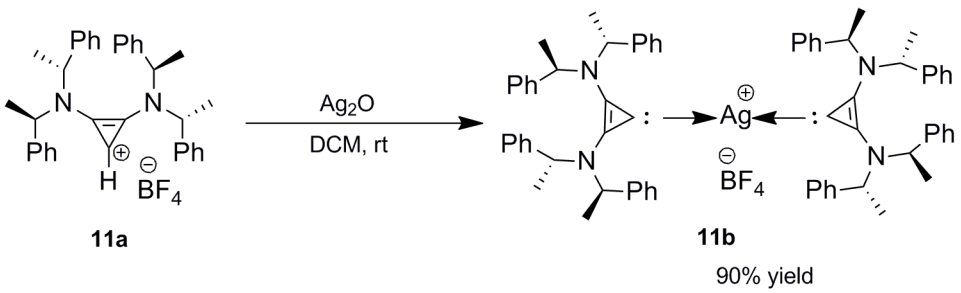
Scheme 7



Scheme 8

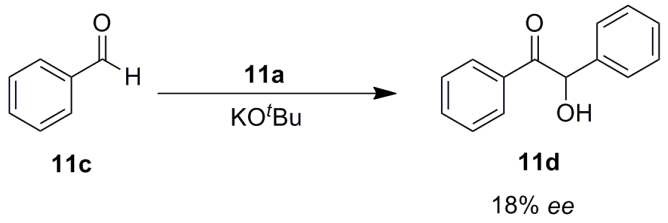
Apart from the catalytic applications, this metal complex has also been utilized for the synthesis of other metal-cyclopropenylidene complexes such as Au, Pd, Ir and Rh BAC complexes (**10a**–**10d**) *via* transmetallation reaction. Interestingly, in all those cases, the transmetallation reaction occurred quantitatively and selectively (Scheme 8).

Tamm and co-workers demonstrated the synthesis and isolation of the chiral bis[bis(*R*-1-phenylethyl)amino]cyclopropenylidene as well as its dicarbene-silver complex **11b**, which was prepared by the treatment of the chiral cyclopropenylium salt **11a** with Ag_2O in the presence of catalytic amount of Me_4BF_4 in CH_2Cl_2 (Scheme 9).[11]



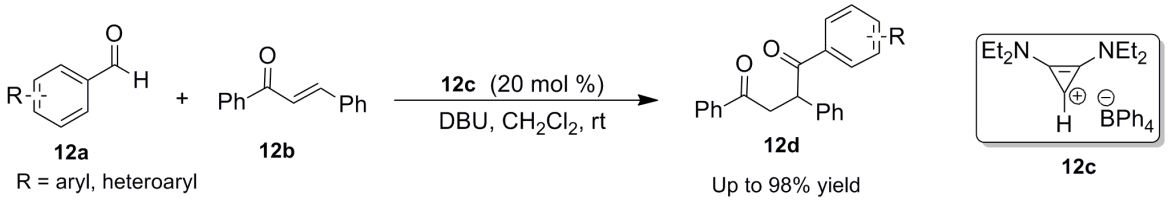
Scheme 9

Bis[bis(R-1-phenylethyl)amino]cyclopropenylidene (**11a**) has also been employed as an organocatalyst for an enantioselective benzoin reaction. However, the product benzoin (**11c**) was formed only with 18% *ee* (Scheme 10). The authors have explained that the low enantioselectivity was probably due to the rapid rotation of the chiral amino groups.



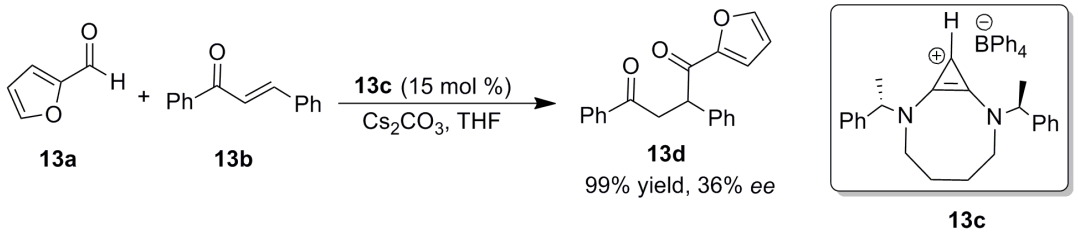
Scheme 10

Recently, Gravel and co-workers described bis(amino)cyclopropenylidiene salt **12c** as a precatalyst for a highly chemo-selective intermolecular Stetter reaction.[12] Interestingly, in those cases, the formation of benzoin products were not observed during the course of the reactions, which was in contrast to analogous reactions using thiazolium and triazolium salts as precatalysts (Scheme 11).



Scheme 11

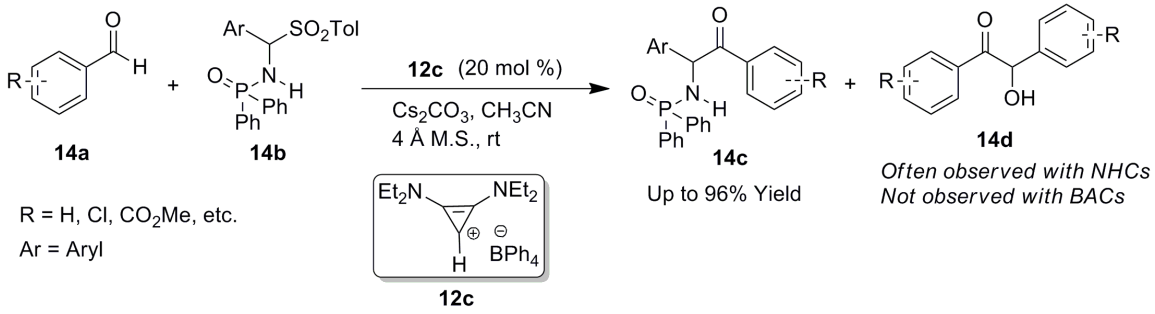
This protocol was elaborated to enantioselective Stetter reaction between furfural (**13a**) and chalcone **13b** using a chiral precatalyst **13c**. In this case, although the chemical yield of the Stetter product was excellent, the enantioselectivity of the product was only 36% (Scheme 12).



Scheme 12

Gravel's group also reported bis(amino)cyclopropenylidene catalyzed aza-benzoin reaction between aldehydes and imines.[13] When the reaction was carried out between various aromatic aldehydes **14a** and phosphinoyl imines **14b** using **12c** as a precatalyst, the aza-benzoin products

14c were obtained in a highly chemoselective manner. Interestingly, in any of these cases, the homobenzoin product was not observed (Scheme 13).



Scheme 13

Apart from these three reports, no other reports are available in the literature for the application of bis(amino)cyclopropenylidenes in organocatalysis.

3.3. Results and discussion

While working on NHC catalyzed chemo-selective transformations,[14] we became interested in developing an efficient method for the synthesis of α,α'-diarylated ketones using BAC as a catalyst *via* intermolecular 1,6-conjugate addition of aldehydes to *p*-quinone methides (*p*-QMs). The α-arylated and α,α'-diarylated ketones are very useful building blocks for many biologically important natural and unnatural compounds.[15] The most popular approach to access α-arylated and α,α'-diarylated carbonyl compounds involves transition metal catalyzed cross coupling reaction between an enolizable carbonyl compound and a suitable aryl coupling partner.[16] A few metal free coupling reactions were also reported for the synthesis of α-arylated carbonyl compounds.[17] Glorius and co-workers reported an efficient method for the synthesis of α,α'-diarylated carbonyl compounds through NHC catalyzed cross coupling between aromatic aldehydes and activated alkyl halides.[18] Recently, Mayr and co-workers reported kinetic studies involving the reaction of NHCs with *p*-quinone methides to characterize the relative nucleophilicities of NHCs.[19] The groups of Scheidt[20] and Ye[21] independently reported the synthesis of enantio-enriched benzo-fused lactones through chiral NHC catalyzed 1,4-addition of homo enolates to *o*-quinone methides. Recently, McErlean and co-workers reported NHC catalyzed intramolecular vinylogous Stetter reaction of aldehydes with 1,6-acceptors.[22] However, the synthesis of α,α'-diarylated ketones *via* 1,6-conjugate addition of aldehydes to *p*-quinone

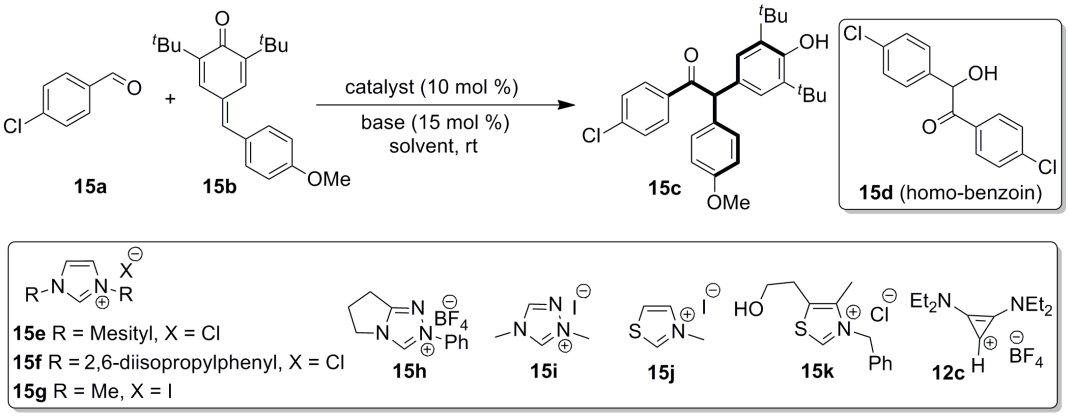
methides[23] using NHC or bis-(amino)cyclopropenylidene as a catalyst remains unprecedented, which triggered us to investigate this transformation in detail.

Optimization studies were carried out using *p*-chlorobenzaldehyde (**15a**) and *p*-quinone methide **15b** under various conditions (Table 1). Our initial attempts using conventional imidazolinium (**15e**–**16g**) as well as triazolium (**15h** & **15i**) based NHC precatalysts didn't give encouraging results as the expected product **15c** was not obtained in any of the cases (entries 1–5). Interestingly, even homo-benzoin product **15d** was not observed in all those cases. Since the reaction between NHC and *p*-QM to form an adduct has already been reported,[19] we presume that NHC prefers to react with **15b** over **15a**, so the NHC is probably not available to react with **15a** to generate either the desired product **15c** or the homo-benzoin product **15d** during the reaction. However, surprisingly, when the reaction was carried out using thiazolium salts such as **15j** or **15k** as a precatalyst, the expected product **15c** was obtained in 10% and 73% yields, respectively, after 36 h (entry 6 & 7). Interestingly, when **12c** was used as a precatalyst in DMF, **15c** was obtained in 90% yield in 3 h (entry 8). This result clearly indicates that the carbene derived from **12c** prefers to react with **15a** over **15b**.

Another possibility is that the reaction between **12c** and **15b** could be reversible under the reaction conditions. Further optimization experiments were performed using different bases (entries 9–11) and also in different solvents (entries 12–15). But in all these experiments, the yield of **15c** was found to be lower when compared to entry 8. Gratifyingly, when the reaction was carried out with 20 mol % of **12c** and 20 mol % of DBU in DMF, the product **15c** was isolated in 98% yield in 1.5 h (entry 16). Careful monitoring of the standard reaction in DMSO-d_6 by ^{1}H NMR spectroscopy revealed that the homo-benzoin product **15d** was observed in small quantities along with **15c** (ratio **15a**:**15d**:**15c** = 1:0.3:1.5) within five minutes after addition of all the reagents and the catalyst precursor **12c**. But, interestingly, the concentration of **15d** was decreasing as the reaction progressed and we couldn't detect even trace amounts of **15d** after completion of the reaction. This observation clearly suggests that the formation of **15d** is reversible under the standard reaction condition.[24] The observation of benzoin and retro-benzoin reactivity with this catalyst is in contrast to observations by Gravel and co-workers,[12,13] however the reaction conditions were different in their case. The reversible formation of **15d** was further confirmed by a crossover experiment, in which the homo-benzoin **15d** (as an aldehyde

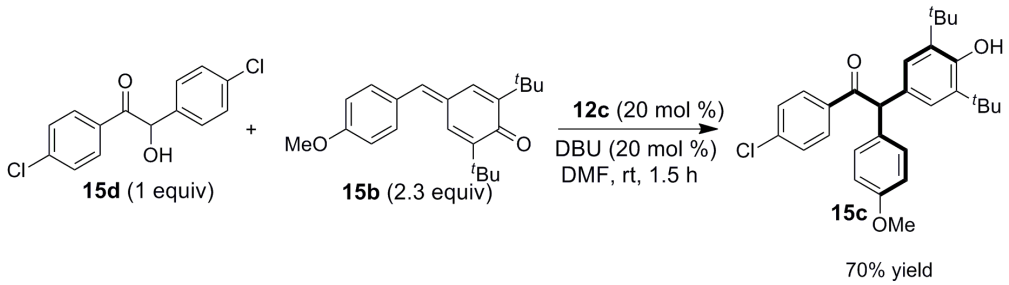
equivalent) was treated with 2.3 equivalents of **15b** under standard conditions. In this case, as expected, **15d** was converted into **15c** in 70% yield in 1.5 h (Scheme 14).

Table 1. Optimization Studies[a]



Entry	Catalyst	Base	Solvent	Time [h]	Yield 15c [%][b]
1	**15e**	DBU	DMF	24	0
2	**15f**	DBU	DMF	24	0
3	**15g**	DBU	DMF	24	0
4	**15h**	DBU	DMF	24	0
5	**15i**	DBU	DMF	24	0
6	**15j**	DBU	DMF	36	10
7	**15k**	DBU	DMF	36	73
8	**12c**	DBU	DMF	3	90
9	**12c**	Cs_2CO_3	DMF	6	40
10	**12c**	$^{i}Pr_2NEt$	DMF	18	0
11	**12c**	KO^{t}Bu	DMF	12	22
12	**12c**	DBU	PhMe	48	42
13	**12c**	DBU	THF	24	60
14	**12c**	DBU	DMSO	3	60
15	**12c**	DBU	1,4-dioxane	48	37
16[c]	**12c**	**DBU**	**DMF**	**1.5**	**98**

[a]Reaction conditions: 0.16 M of **15a** in solvent; Use of 1.05 equiv of **15b** was found to be optimal; [b]Isolated yield; [c]20 mol % of **12c** and 20 mol % of DBU were used; rt = 25–28 °C; DBU = 1,8 diazabicyclo[5.4.0]undec-7-ene.



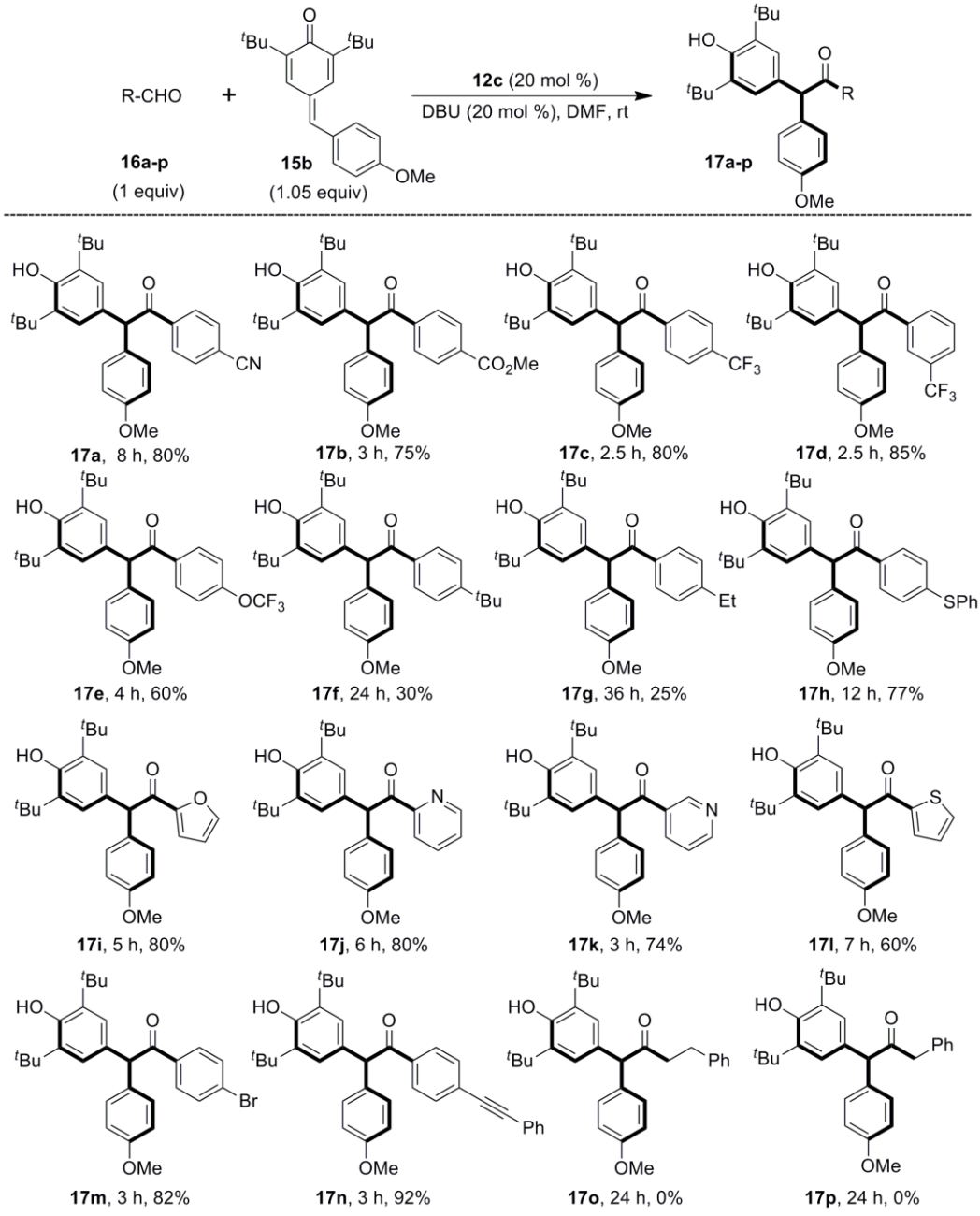
Scheme 14

Then, the substrate scope of this transformation was examined using *p*-quinone methide **15b** and a wide range of aromatic as well as heteroaromatic aldehydes (**16a**–**16p**) (Scheme 15) under the optimal conditions (entry 16, Table 1). As represented in scheme 2, this methodology worked well for electron poor aromatic aldehydes (**16a**–**16e**), and the desired α,α'-diarylated ketones (**17a**–**17e**) were obtained in moderate to good yields (60–85%) in short reaction times.

However, in the cases of election rich aldehydes, such as 4-*tert*-butylbenzaldehyde (**16f**) and 4-ethylbenzaldehyde (**16g**), the reaction was sluggish and the products (**17f** & **17g**) were obtained in lower yields. Surprisingly, 4-phenylmercapto benzaldehyde (**16h**) gave the corresponding α,α'-diarylated ketone (**17h**) in 77% yield. This methodology was further elaborated to heteroaromatic aldehydes (**16i**–**16l**) and in all those cases; the expected products (**17i**–**17l**) were isolated in good yields. Under the standard conditions, 4-bromobenzaldehyde (**16m**) and 4-alkynyl benzaldehyde (**16n**) underwent smooth transformation to their corresponding α,α'-diarylated ketones **17m** and **17n** in 82 and 92% yields, respectively. Unfortunately, in the cases of aliphatic aldehydes, such as hydrocinnamaldehyde (**16o**) and 2-phenyl acetaldehyde (**16p**), only decomposition of the reaction mixture was observed.

The substrate scope of this methodology was also extended using various *p*-quinone methides (**18a**–**18n**), derived from electron rich as well as electron poor aromatic aldehydes, and the results are summarized in scheme 16. The reaction worked pretty well in the cases of *p*-QMs derived from electron rich aromatic aldehydes (**18a**–**18d**) and the desired products (**19a**–**19d**) were obtained in reasonably good yields. In the case of *p*-QM derived from moderately electron poor aromatic aldehyde, such as 2-fluorobenzaldehyde (**18e**), the α,α'-diarylated ketone **19e** was obtained in 73% isolated yield. Similarly, *o*-bromo substituted *p*-QM **18f** also underwent smooth conversion to the corresponding product **19f** in 60% yield. Pleasingly, in the cases of *p*-QMs derived from benzaldehyde (**18g**) and other aryl-substituted benzaldehydes (**18h** & **18i**), the corresponding α,α'-diarylated ketones (**19g**–**19i**) were obtained in good yields (82–88%).

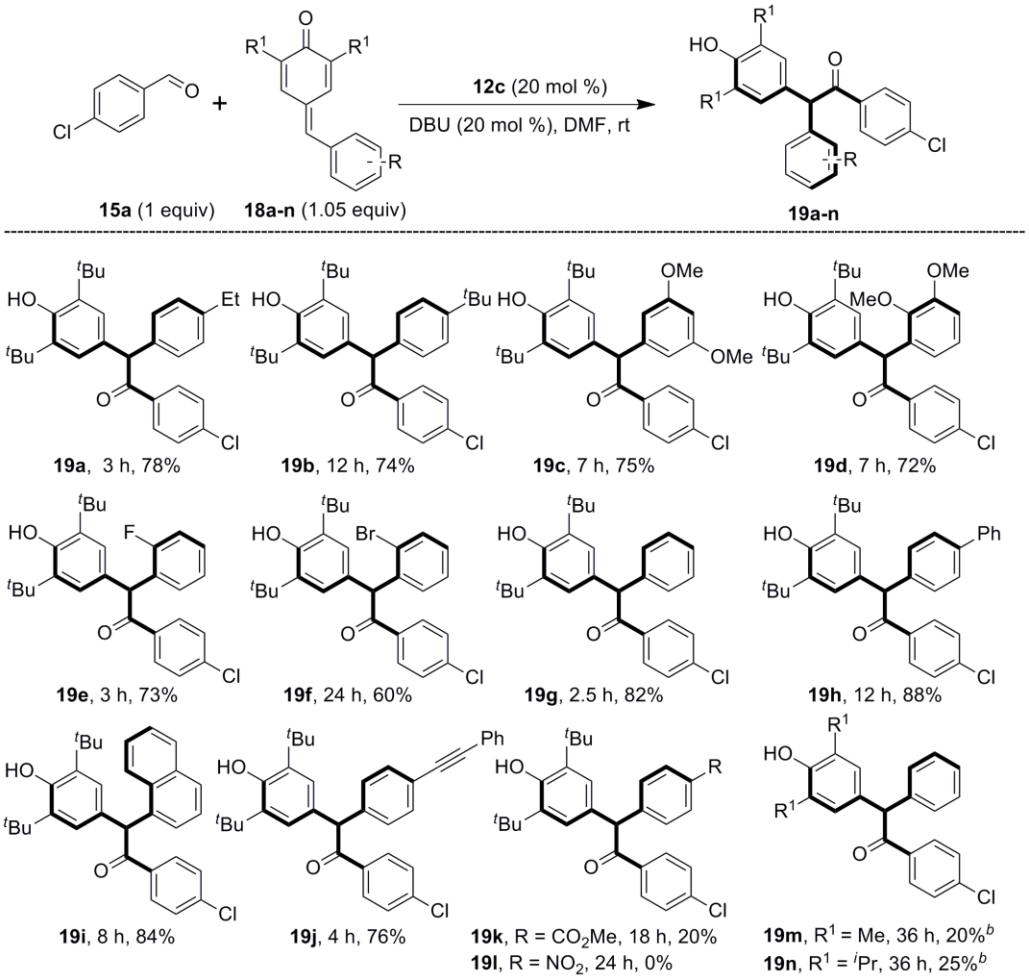
Scheme 15. Substrate Scope[a]



[a]Reaction conditions: 0.16 M of aldehyde **16** in solvent. rt = 25–28 ˚C.

The product **19j** was isolated in 76% yield under the standard condition when **18j** was used as a substrate. In the case of *p*-QM derived from electron deficient aldehyde such as **18k**, the reaction was sluggish and the product **19k** was obtained only in 20% yield. Unfortunately, no product (**19l**) was observed in the case of *p*-QM derived from 4-nitrobenzaldehyde (**18l**).

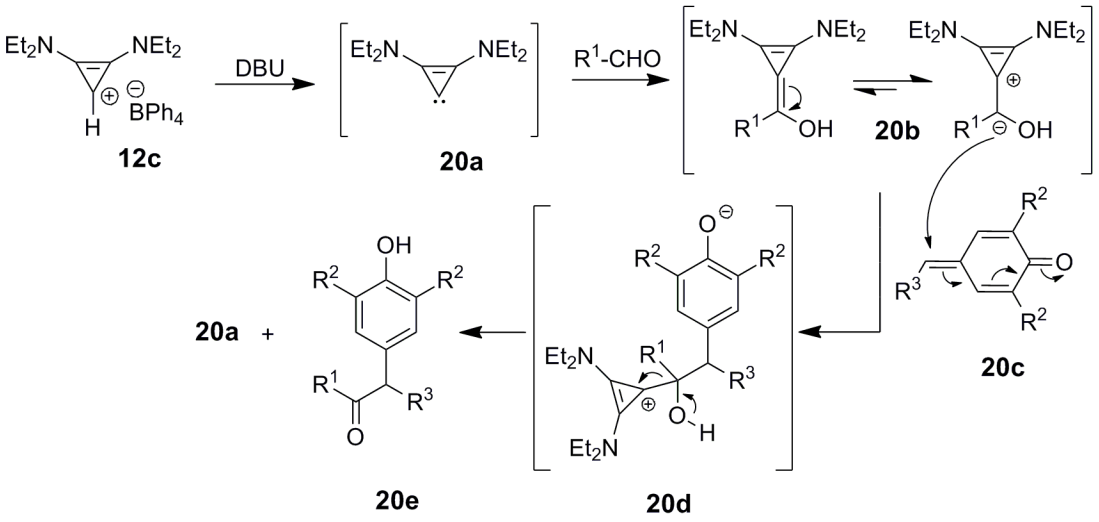
Scheme 16. Substrate Scope[a]



[a]Reaction conditions: 0.16 M of **15a** in solvent; [b]1,2-dichloroethane was used as a solvent. rt = 25–28 ˚C.

The substrate scope for this transformation was also elaborated with *p*-QMs derived from other phenols such as 2,6-dimethylphenol (**18m**) and 2,6-diisopropylphenol (**18n**). In both cases, the expected products **19m** and **19n** were obtained in 20 and 25% yields, respectively, after 36 h.

Based on the outcome of this transformation, a plausible mechanism has been proposed (Scheme 17). In the initial step, DBU abstracts the acidic proton from **12c** and generates the carbene **20a**, which reacts with aldehyde to produce an intermediate **20b**, which is similar to the Breslow intermediate.[25] Intermediate **20b** then reacts with *p*-QM **20c** to form another intermediate **20d**, which decomposes to the product **20e** with the expulsion of carbene **20a**.



Scheme 17

3.4. Conclusion

In conclusion, we have demonstrated the scope of bis(amino)cyclopropenylidene as an organocatalyst for the synthesis of α,α'-diarylated ketones through the extended conjugate addition of umpolung of aromatic aldehydes to *p*-quinone methides. The versatility of this protocol has been portrayed using a wide range of aromatic and heteroaromatic aldehydes as well as *p*-QMs.

3.5. Experimental Sections

General Information

All reactions were carried out under argon atmosphere employing flame-dried glass wares. Most of the reagents and starting materials used were purchased from commercial sources and used as such. Bis(amino)cyclopropenylidene (BAC) precursor (1**2c**)[12] and NHC precursors (**15e**–**15j**)[26] were prepared according to the literature procedure. All *para*-quinone methides used in this transformation were prepared by following a literature procedure.[23h,23j] Dry *N*,*N'*-dimethyl formamide (DMF) was stored under argon over activated 4 Å molecular sieves and used after degasification using argon. ^{1}H, ^{13}C and ^{19}F (proton decoupled) spectra were recorded in $CDCl_3$ on Brucker FT-NMR spectrometer (400, 100 and 376 MHz respectively). Chemical shifts (δ) values are reported in parts per million relative to tetramethylsilane by using residual solvent signal ($CHCl_3$) as reference (7.26 ppm) and the coupling constants (J) are reported in Hz. Trifluoromethyl benzene was used as internal standard for ^{19}F spectra. High-resolution mass

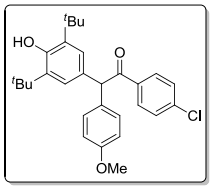
spectra were recorded on Waters Q-TOF Premier-HAB213 spectrometer. FT-IR spectra were recorded on a Brucker FT-IR spectrometer equipped with a PIKE MIRacle ATR. Melting points were measured on Stuart melting point apparatus and are uncorrected. Thin layer chromatography was performed on Merck silica gel 60 F_{254} TLC plates. Column chromatography was carried out through silica gel (100-200 mesh) using EtOAc/hexane as an eluent.

General procedure for bis(amino)cyclopropenylidene-catalyzed 1,6-conjugate addition of aldehydes to *para*-quinone methides

1,8-Diazabicyclo[5.4.0]undec-7-ene (2.5 μL, 0.016 mmol) was added to a suspension of BAC precursor **12c** (8 mg, 0.016 mmol), aldehyde (0.078 mmol, 1.0 equiv.) and *para*-quinone methide (0.082 mmol, 1.05 equiv.) in dry DMF (0.5 mL) under argon atmosphere at room temperature and the resulting suspension was stirred until most of the aldehyde was consumed. The reaction mixture was then acidified with aqueous HCl (2.0 N) and extracted with dichloro methane (3x10 mL). The combined organic layers were washed with water, brine solution, dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated under *vacuo* and the residue was purified through silica gel column using <5% EtOAc/hexane mixture as an eluent.

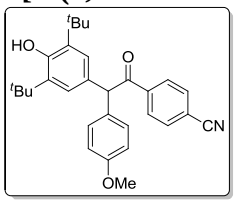
Characterization of compounds (15c, 17a–17p & 19a–19n):

1-(4-chlorophenyl)-2-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-2-(4-methoxyphenyl)ethanone (15c):



Yellow soild; Yield 98% (35.6 mg); m.p. 148–150 °C; FT IR (ATR) 3630, 2958, 2922, 2853, 1673 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), δ 7.94 (d, J = 8.6 Hz, 2H), 7.38 (d, J = 8.6 Hz, 2H), 7.19 (d, J = 8.7 Hz, 2H), 7.03 (s, 2H), 6.87 (d, J = 8.7 Hz, 2H), 5.82 (s, 1H), 5.14 (s, 1H), 3.78 (s, 3H), 1.39 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$), δ 198.0, 158.7, 153.0, 139.2, 136.0, 135.6, 131.6, 130.5, 130.2, 129.5, 128.9, 125.8, 114.2, 58.7, 55.3, 34.5, 30.4; HRMS (ESI): *m/z* calcd for $C_{29}H_{32}ClO_3$ $[M-H]^+$: 463.2040; found: 463.2050.

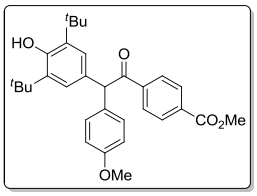
4-[2-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-2-(4-methoxyphenyl)acetyl] benzonitrile (17a):



Yellow solid; Yield 80% (28.4 mg); m.p. 152–154 °C; FT IR (ATR) 3626, 2954, 2921, 2853, 2226, 1692 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), δ 8.05 (d, J = 8.7 Hz, 2H), 7.70 (d, J = 8.6 Hz, 2H), 7.17 (d, J = 8.7 Hz, 2H), 7.00 (s,

2H), 6.87 (d, *J* = 8.8 Hz, 2H), 5.80 (s, 1H), 5.16 (s, 1H), 3.78 (s, 3H), 1.38 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$), δ 197.9, 158.9, 153.2, 140.4, 136.2, 132.5, 130.9, 130.2, 129.4, 128.9, 125.8, 118.1, 116.0, 114.4, 59.2, 55.4, 34.5, 30.4; HRMS (ESI): *m/z* calcd for $C_{30}H_{32}NO_3$ $[M-H]^+$: 454.2382; found: 454.2386.

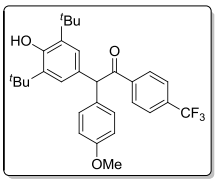
Methyl{4-[2-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-2-(4-methoxyphenyl)acetyl]}benzoate



(17b):

Yellow solid; Yield 75% (28.6 mg); m.p. 170–172 °C; FT IR (ATR) 3617, 2952, 2922, 2853, 1720, 1683 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$), δ 8.07–8.01 (m, 4H), 7.20 (d, *J* = 8.7 Hz, 2H), 7.03 (s, 2H), 6.86 (d, *J* = 8.7 Hz, 2H), 5.86 (s, 1H), 5.14 (s, 1H), 3.92 (s, 3H), 3.78 (s, 3H), 1.38 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$), δ 198.8, 166.4, 158.8, 153.1, 140.7, 136.1, 133.6, 131.4, 130.2, 129.9, 129.4, 128.9, 125.8, 114.3, 59.1, 55.4, 52.6, 34.5, 30.4; HRMS (ESI): *m/z* calcd for $C_{31}H_{37}O_5$ $[M+H]^+$: 489.2641; found: 489.2630.

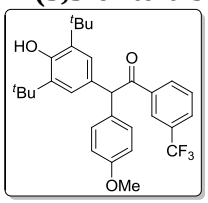
2-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-2-(4-methoxyphenyl)-1-[4(trifluoromethyl)phenyl]



ethanone (17c):

Yellow solid; Yield 80% (31.1 mg); m.p. 146–148 °C; FT IR (ATR) 3622, 2955, 2920, 2852,1679 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$), δ 8.08 (d, *J* = 8.2 Hz, 2H), 7.67 (d, *J* = 8.2 Hz, 2H), 7.20 (d, *J* = 8.7 Hz, 2H), 7.03 (s, 2H), 6.87 (d, *J* = 8.8 Hz, 2H), 5.85 (s, 1H), 5.16 (s, 1H), 3.78 (s, 3H), 1.39 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$), δ 198.3, 158.8, 153.1, 140.1–140.0 (m), 136.2, 134.08 (q, J_{C-F} = 32.2 Hz), 131.2, 130.2, 129.3, 129.2, 125.8, 125.78–125.66 (m), 123.7 (q, J_{C-F} = 271.1 Hz), 114.3, 59.1, 55.4, 34.5, 30.4; ^{19}F NMR (376 MHz, $CDCl_3$), δ −63.10; HRMS (ESI): *m/z* calcd for $C_{30}H_{32}F_3O_3$ $[M-H]^+$: 497.2304; found: 497.2315.

2-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-2-(4-methoxyphenyl)-1-[3-(trifluoromethyl)phenyl]

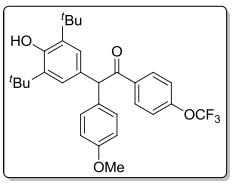


ethanone (17d):

Yellow solid; Yield 85% (33.1 mg); m.p. 128–130°C; FT IR (ATR) 3637, 2957, 2921, 2854, 1681 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$), δ 8.25 (s, 1H), 8.16 (d, *J* = 7.8 Hz, 1H), 7.74 (d, *J* = 7.8 Hz, 1H), 7.54 (t, *J* = 7.8 Hz, 1H), 7.22 (d, *J* = 8.7 Hz, 2H), 7.06 (s, 2H), 6.88 (d, *J* = 8.7 Hz, 2H), 5.85 (s, 1H), 5.16 (s, 1H), 3.79 (s, 3H), 1.39 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$), δ 197.8, 158.8, 153.2, 137.8, 136.3, 132.2–132.1 (m), 131.2, 131.1 (q, J_{C-F} =

32.6 Hz), 130.2, 129.3, 129.3–129.2 (m), 129.1, 126.0–125.9 (m), 125.9, 123.8 (q, J_{C-F} = 271.6 Hz), 114.3, 59.0, 55.4, 34.5, 30.4; ^{19}F NMR (376 MHz, $CDCl_3$), δ −62.83; HRMS (ESI): *m/z* calcd for $C_{30}H_{32}F_3O_3$ $[M-H]^+$: 497.2304; found: 497.2313.

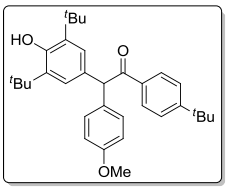
2-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-2-(4-methoxyphenyl)-1-[4-(trifluoromethoxy)phenyl]



ethanone (17e):

Yellow solid; Yield 60% (24.1 mg); m.p. 128–130 °C;FT IR (ATR) 3606, 2954, 2922, 2853, 1681 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$), δ 8.04 (d, *J* = 9.0 Hz, 2H), 7.24–7.21 (m, 2H), 7.19 (d, *J* = 8.7 Hz, 2H), 7.02 (s, 2H), 6.87 (d, *J* = 8.8 Hz, 2H), 5.82 (s, 1H), 5.14 (s, 1H), 3.78 (s, 3H), 1.38 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$), δ 197.7, 158.8, 153.1, 152.42–152.37 (m), 136.1, 135.5, 131.5, 131.1, 130.2, 129.5, 125.8, 120.4, 120.4 (q, J_{C-F} = 257.2 Hz), 114.3, 58.8, 55.4, 34.5, 30.4; ^{19}F NMR (376 MHz, $CDCl_3$), δ −57.56; HRMS (ESI): *m/z* calcd for $C_{30}H_{32}F_3O_4$ $[M-H]^+$: 513.2253; found: 513.2236.

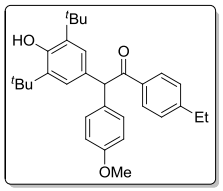
1-[4-(*tert*-butyl)phenyl]-2-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-2-(4-methoxyphenyl)



ethanone (17f):

Yellow solid; Yield 30% (11.4 mg); m.p. 152–154 °C; FT IR (ATR) 3633, 2999, 2968, 2870, 1677 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$), δ 7.96 (d, *J* = 8.5 Hz, 2H), 7.43 (d, *J* = 8.5 Hz, 2H), 7.23 (d, *J* = 8.7 Hz, 2H), 7.05 (s, 2H), 6.85 (d, *J* = 8.7 Hz, 2H), 5.89 (s, 1H), 5.11 (s, 1H), 3.78 (s, 3H), 1.39 (s, 18H), 1.31 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$), δ 198.8, 158.6, 156.5, 152.9, 135.8, 134.7, 132.1, 130.2, 130.1, 129.0, 125.9, 125.6, 114.2, 58.4, 55.3, 35.2, 34.5, 31.2, 30.4; HRMS (ESI): *m/z* calcd for $C_{33}H_{41}O_3$ $[M-H]^+$: 485.3056; found: 485.3071.

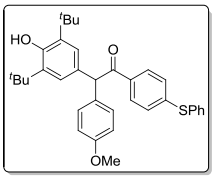
2-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-1-(4-ethylphenyl)-2-(4-methoxyphenyl)ethanone



(17g):

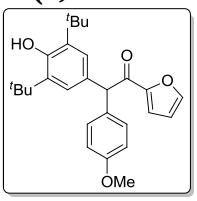
Yellow solid; Yield 25% (8.9 mg); m.p. 126–128 °C; FT IR (ATR) 3636, 2956, 2911, 2872, 1679 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$), δ 7.94 (d, *J* = 8.4 Hz, 2H), 7.24–7.21 (m, 4H), 7.05 (s, 2H), 6.85 (d, *J* = 8.8 Hz, 2H), 5.88 (s, 1H), 5.11 (s, 1H), 3.77 (s, 3H), 2.67 (q, *J* = 7.6 Hz, 2H), 1.38 (s, 18H), 1.23 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$), δ 198.8, 158.6, 152.9, 149.8, 135.8, 135.0, 132.1, 130.2, 130.1, 129.3, 128.2, 125.9, 114.1, 58.4, 55.4, 34.5, 30.4, 29.0, 15.3; HRMS (ESI): m/z calcd for $C_{31}H_{37}O_3$ $[M-H]^+$: 457.2743; found: 457.2751.

2-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-2-(4-methoxyphenyl)-1-[4-(phenylthio)phenyl] ethanone (17h):



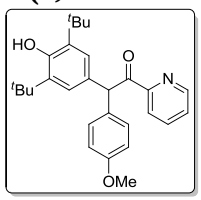
Yellow solid; Yield 77% (32.4 mg); m.p. 158–160 °C; FT IR (ATR) 3630, 2954, 2918, 2871, 1677 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), δ 7.87 (d, J = 8.6 Hz, 2H), 7.49–7.46 (m, 2H), 7.40–7.37 (m, 3H), 7.18 (d, J = 8.7 Hz, 2H), 7.14 (d, J = 8.6 Hz, 2H), 7.01 (s, 2H), 6.84 (d, J = 8.7 Hz, 2H), 5.80 (s, 1H), 5.11 (s, 1H), 3.77 (s, 3H), 1.38 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$), δ 198.2, 158.6, 152.9, 144.7, 135.9, 134.5, 134.1, 132.1, 131.9, 130.2, 129.9, 129.8, 129.6, 128.9, 127.4, 125.8, 114.2, 58.4, 55.3, 34.5, 30.4; HRMS (ESI): *m/z* calcd for $C_{35}H_{37}SO_3$ $[M-H]^+$: 537.2463; found: 537.2467.

2-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-1-(furan-2-yl)-2-(4-methoxyphenyl)ethanone (17i):



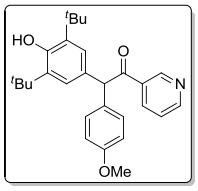
Yellow solid; Yield 80% (26.2 mg); m.p. 150–152 °C; FT IR (ATR) 3593, 2953, 2921, 2853, 1675 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), δ 7.56–7.55 (m, 1H), 7.29 (d, J = 8.7 Hz, 2H), 7.24 (d, J = 3.6 Hz, 1H), 7.15 (s, 2H), 6.87 (d, J = 8.7 Hz, 2H), 6.49 (dd, J = 3.6, 1.7 Hz, 1H), 5.74 (s, 1H), 5.16 (s, 1H), 3.78 (s, 3H), 1.41 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$), δ 188.2, 158.7, 153.0, 152.8, 146.6, 135.9, 131.4, 130.2, 129.3, 125.8, 118.2, 114.0, 112.4, 58.0, 55.3, 34.5, 30.4; HRMS (ESI): *m/z* calcd for $C_{27}H_{31}O_4$ $[M-H]^+$: 419.2222; found: 419.2207.

2-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-2-(4-methoxyphenyl)-1-(pyridin-2-yl)ethanone (17j):



Yellow solid; Yield 80% (26.9 mg); m.p. 128–130 °C; FT IR (ATR) 3633, 2954, 2922, 2854, 1695 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), δ 8.68 (ddd, J = 4.8, 1.7, 0.9 Hz, 1H), 8.07 (dt, J = 7.9, 1.0 Hz, 1H), 7.79 (td, J = 7.6, 1.7 Hz, 1H), 7.41 (ddd, J = 7.5, 4.8, 1.2 Hz, 1H), 7.33 (d, J = 8.6 Hz, 2H), 7.19 (s, 2H), 6.83 (d, J = 8.8 Hz, 2H), 6.78 (s, 1H), 5.09 (s, 1H), 3.76 (s, 3H), 1.39 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$), δ 200.5, 158.5, 153.6, 152.8, 149.0, 137.0, 135.7, 132.0, 130.5, 129.9, 127.0, 126.2, 123.1, 114.0, 55.3, 54.7, 34.5, 30.5; HRMS (ESI): *m/z* calcd for $C_{28}H_{32}NO_3$ $[M-H]^+$: 430.2382; found: 430.2373.

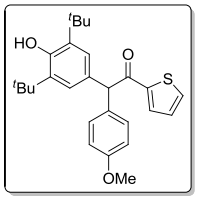
2-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-2-(4-methoxyphenyl)-1-(pyridin-3-yl)ethanone (17k):



Yellow solid; Yield 74% (24.9 mg); m.p. 157–159 °C; FT IR (ATR) 3624, 2954, 2920, 2853, 1668 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), δ 9.20 (d, J = 1.5 Hz, 1H), 8.70 (dd, J = 4.6, 1.2 Hz,1H), 8.25 (dt, J = 8.0, 1.8 Hz, 1H), 7.37 (dd, J = 8.0,

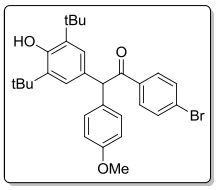
4.8 Hz, 1H), 7.20 (d, *J* = 8.7 Hz, 2H), 7.04 (s, 2H), 6.87 (d, *J* = 8.7 Hz, 2H), 5.82 (s, 1H), 5.17 (s, 1H), 3.78 (s, 3H), 1.39 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$), δ 198.0, 158.8, 153.2, 153.1, 150.5, 136.4, 136.2, 132.6, 131.0, 130.2, 129.0, 125.8, 123.7, 114.3, 59.2, 55.4, 34.5, 30.4; HRMS (ESI): *m/z* calcd for $C_{28}H_{34}NO_3$ $[M+H]^+$: 432.2539; found: 432.2542.

2-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-2-(4-methoxyphenyl)-1-(thiophen-2-yl)ethanone (17l):



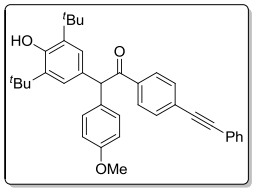
Yellow solid; Yield 60% (20.4 mg); m.p. 126–128 °C; FT IR (ATR) 3593, 2954, 2915, 2870, 1661 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$), δ 7.76 (dd, *J* = 3.8, 1.0 Hz, 1H), 7.59 (dd, *J* = 4.9, 1.0 Hz, 1H), 7.28–7.26 (m, 2H), 7.11 (s, 2H), 7.08 (dd, *J* = 4.9, 3.8 Hz, 1H), 6.86 (d, *J* = 8.7 Hz, 2H), 5.71 (s, 1H), 5.14 (s, 1H), 3.78 (s, 3H), 1.39 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$), δ 192.0, 158.7, 153.0, 144.6, 135.9, 133.9, 132.7, 131.8, 130.1, 129.6, 128.2, 125.8, 114.1, 59.8, 55.4, 34.5, 30.4; HRMS (ESI): *m/z* calcd for $C_{27}H_{31}SO_3$ $[M-H]^+$: 435.1994; found: 435.1974.

1-(4-bromophenyl)-2-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-2-(4-methoxyphenyl)ethanone (17m):



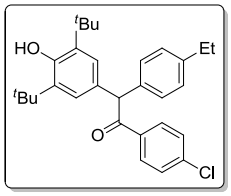
Yellow solid; Yield 82% (32.6 mg); m.p. 156–158 °C; FT IR (ATR) 3625, 2853, 2921, 2852, 1673 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$), δ 7.86 (d, *J* = 8.6 Hz, 2H), 7.54 (d, *J* = 8.6 Hz, 2H), 7.19 (d, *J* = 8.7 Hz, 2H), 7.02 (s, 2H), 6.86 (d, *J* = 8.7 Hz, 2H), 5.81 (s, 1H), 5.14 (s, 1H), 3.78 (s, 3H), 1.39 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$), δ 198.2, 158.7, 153.0, 136.0, 135.9, 131.9, 131.5, 130.6, 130.2, 129.5, 128.0, 125.8, 114.2, 58.7, 55.4, 34.5, 30.4; HRMS (ESI): *m/z* calcd for $C_{29}H_{34}BrO_3$ $[M+H]^+$: 509.1691; found: 509.1703.

2-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-2-(4-methoxyphenyl)-1-[4-(phenylethynyl)phenyl] ethanone (17n):



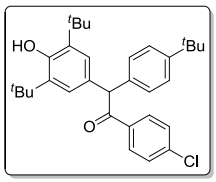
Yellow solid; Yield 92% (38.1 mg); m.p. 122–124 °C; FT IR (ATR) 3630, 2953, 2922, 2853, 2213, 1668 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$), δ 7.98 (d, *J* = 8.6 Hz, 2H), 7.56–7.52 (m, 4H), 7.38–7.35 (m, 3H), 7.21 (d, *J* = 8.7 Hz, 2H), 7.05 (s, 2H), 6.87 (d, *J* = 8.7 Hz, 2H), 5.87 (s, 1H), 5.13 (s, 1H), 3.78 (s, 3H), 1.39 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$), δ 198.5, 158.7, 153.0, 136.4, 136.0, 131.9, 131.8, 131.7, 130.2, 129.7, 129.0, 128.9, 128.6, 127.9, 125.9, 122.8, 114.2, 92.7, 88.8, 58.7, 55.4, 34.5, 30.4; HRMS (ESI): *m/z* calcd for $C_{37}H_{37}O_3$ $[M-H]^+$: 529.2743; found: 529.2726.

1-(4-chlorophenyl)-2-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-2-(4-ethylphenyl)ethanone (19a):



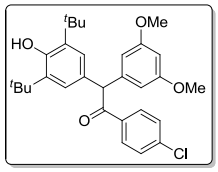
Yellow solid; Yield 78% (28.2 mg); m.p.168–170 °C; FT IR (ATR) 3636, 2955, 2922, 2853, 1671 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), δ 7.94 (d, J = 8.7 Hz, 2H), 7.37 (d, J = 8.7 Hz, 2H), 7.20–7.14 (m, 4H), 7.05 (s, 2H), 5.83 (s, 1H), 5.13 (s, 1H), 2.61 (q, J = 7.6 Hz, 2H), 1.38 (s, 18H), 1.21 (t, J = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$), δ 197.9, 153.1, 143.1, 139.2, 136.7, 136.0, 135.6, 130.5, 129.4, 129.0, 128.9, 128.3, 125.9, 59.2, 34.5, 30.4, 28.6, 15.5; HRMS (ESI): *m/z* calcd for $C_{30}H_{36}ClO_2$ $[M+H]^+$: 463.2404; found: 463.2394.

2-[4-(*tert*-butyl)phenyl]-1-(4-chlorophenyl)-2-(3,5-di-*tert*-butyl-4-hydroxyphenyl)ethanone (19b):



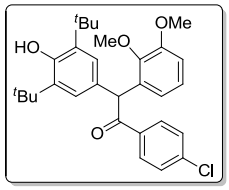
Yellow solid; Yield 74% (28.4 mg); m.p.170–172 °C; FT IR (ATR) 3637, 2953, 2921, 2852, 1660 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), δ 7.94 (d, J = 8.7 Hz, 2H), 7.38 (d, J = 8.7 Hz, 2H), 7.33 (d, J = 8.5 Hz, 2H), 7.20 (d, J = 8.3 Hz, 2H), 7.07 (s, 2H), 5.83 (s, 1H), 5.14 (s, 1H), 1.39 (s, 18H), 1.29 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$), δ 197.9, 153.1, 149.9, 139.3, 136.5, 136.1, 135.7, 130.5, 129.3, 129.0, 128.7, 125.9, 125.7, 59.1, 34.6, 34.5, 31.5, 30.4; HRMS (ESI): *m/z* calcd for $C_{32}H_{38}ClO_2$ $[M-H]^+$: 489.2560; found: 489.2548.

1-(4-chlorophenyl)-2-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-2-(3,5-dimethoxyphenyl)ethanone (19c):



Yellow solid; Yield 75% (29.0 mg); m.p.118–120 °C; FT IR (ATR) 3628, 2956, 2918, 2872, 1681cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), δ 7.94 (d, J = 8.6 Hz, 2H), 7.38 (d, J = 8.6 Hz, 2H), 7.06 (s, 2H), 6.44 (d, J = 2.2 Hz, 2H), 6.34 (t, J = 2.2 Hz, 1H), 5.77 (s, 1H), 5.15 (s, 1H), 3.74 (s, 6H), 1.39 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$), δ 197.4, 161.0, 153.2, 141.6, 139.4, 136.0, 135.5, 130.5, 129.0, 128.8, 125.9, 107.3, 99.1, 59.7, 55.4, 34.5, 30.4; HRMS (ESI): *m/z* calcd for $C_{30}H_{34}ClO_4$ $[M-H]^+$: 493.2146; found: 493.2162.

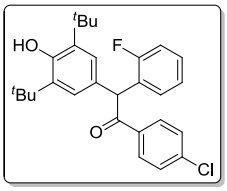
1-(4-chlorophenyl)-2-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-2-(2,3-dimethoxyphenyl) ethanone (19d):



Yellow solid; Yield 72% (27.8 mg); m.p.120–122 °C; FT IR (ATR) 3636, 2954, 2921, 2853, 1682 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), δ 7.97 (d, J = 8.7 Hz, 2H), 7.37 (d, J = 8.7 Hz, 2H), 7.09 (s, 2H), 6.97 (t, J = 8.0 Hz, 1H), 6.84 (dd, J = 8.2, 1.4 Hz, 1H), 6.60 (dd, J = 7.8, 1.4 Hz, 1H), 6.23 (s, 1H), 5.14 (s, 1H), 3.85 (s, 3H), 3.67 (s, 3H), 1.39 (s,

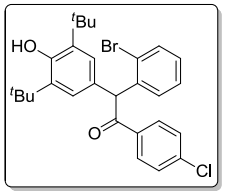
18H); ^{13}C NMR (100 MHz, $CDCl_3$), δ 198.1, 153.1, 152.6, 146.0, 139.1, 136.1, 135.6, 134.6, 130.3, 128.9, 127.9, 126.5, 123.9, 121.5, 111.6, 60.5, 55.9, 53.0, 34.5, 30.5; HRMS (ESI): *m/z* calcd for $C_{30}H_{34}ClO_4$ $[M-H]^+$: 493.2146; found: 493.2158.

1-(4-chlorophenyl)-2-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-2-(2-fluorophenyl)ethanone (19e):



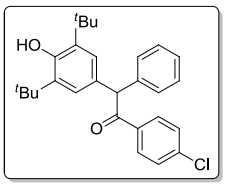
Yellow solid; Yield 73% (25.8 mg); m.p.163–165 °C; FT IR (ATR) 3624, 2953, 2921, 2853, 1687 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$), δ 7.94 (d, J = 8.6 Hz, 2H), 7.38 (d, J = 8.6 Hz, 2H), 7.26–7.21 (m, 1H), 7.10–7.03 (m, 5H), 6.13 (s, 1H), 5.19 (s, 1H), 1.39 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$), δ 196.9, 160.3 (d, $J_{C\text{-}F}$ = 243.7 Hz), 153.4, 139.4, 136.5, 135.2, 130.6 (d, $J_{C\text{-}F}$ = 3.8 Hz), 130.4, 129.0, 128.9 (d, $J_{C\text{-}F}$ = 8.2 Hz), 127.4 (d, $J_{C\text{-}F}$ = 14.6 Hz), 126.9, 126.2, 124.3 (d, $J_{C\text{-}F}$ = 3.7 Hz), 115.3 (d, $J_{C\text{-}F}$ = 22.3 Hz), 52.0 (d, $J_{C\text{-}F}$ = 2.7 Hz), 34.5, 30.4; ^{19}F NMR (376 MHz, $CDCl_3$), δ −116.75; HRMS (ESI): *m/z* calcd for $C_{28}H_{29}ClFO_2$ $[M-H]^+$: 451.1840; found: 451.1828.

2-(2-bromophenyl)-1-(4-chlorophenyl)-2-(3,5-di-*tert*-butyl-4-hydroxyphenyl)ethanone (19f):



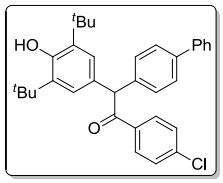
Yellow solid; Yield 60% (24.1 mg); m.p. 156–158°C; FT IR (ATR) 3623, 2953, 2921, 2869, 1677 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$), δ 7.96 (d, J = 8.7 Hz, 2H), 7.58 (dd, J = 7.9, 1.3 Hz, 1H), 7.39 (d, J = 8.7 Hz, 2H), 7.23 (dd, J = 7.6, 1.3 Hz, 1H), 7.13 (td, J = 7.7, 1.8 Hz, 1H), 7.05 (s, 2H), 7.03 (dd, J = 7.8, 1.7 Hz, 1H), 6.26 (s, 1H), 5.20 (s, 1H), 1.39 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$), δ 197.0, 153.4, 139.9, 139.3, 136.5, 135.5, 132.9, 131.1, 130.4, 129.0, 128.8, 127.7, 126.9, 126.4, 125.0, 59.1, 34.5, 30.4; HRMS (ESI): *m/z* calcd for $C_{28}H_{29}BrClO_2$ $[M-H]^+$: 511.1039; found: 511.1043.

1-(4-chlorophenyl)-2-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-2-phenyl ethanone (19g):



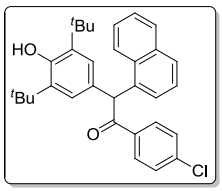
Yellow solid; Yield 82% (27.8 mg); m.p. 166–168 °C; FT IR (ATR) 3622, 2953, 2921, 2853, 1683 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$), δ 7.94 (d, J = 8.6 Hz, 2H), 7.38 (d, J = 8.6 Hz, 2H), 7.34–7.31 (m, 2H), 7.28–7.23 (m, 3H), 7.04 (s, 2H), 5.87 (s, 1H), 5.15 (s, 1H), 1.38 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$), δ 197.7, 153.1, 139.5, 139.3, 136.1, 135.6, 130.5, 129.2, 129.1, 129.0, 128.8, 127.2, 125.9, 59.5, 34.5, 30.4; HRMS (ESI): *m/z* calcd for $C_{28}H_{30}ClO_2$ $[M-H]^+$: 433.1934; found: 433.1922.

2-[(1,1'-biphenyl)-4-yl]-1-(4-chlorophenyl)-2-(3,5-di-*tert*-butyl-4-hydroxyphenyl)ethanone (19h):



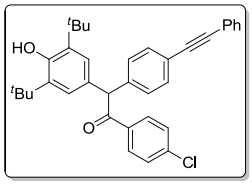
Yellow solid; Yield 88% (35.1 mg); m.p. 168–170 °C; FT IR (ATR) 3615, 2954, 2921, 2852, 1689 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), δ 7.97 (d, J = 8.7 Hz, 2H), 7.58–7.54 (m, 4H), 7.44–7.38 (m, 4H), 7.36–7.31 (m, 3H), 7.09 (s, 2H), 5.91 (s, 1H), 5.16 (s, 1H), 1.40 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$), δ 197.7, 153.2, 140.9, 140.0, 139.4, 138.7, 136.2, 135.6, 130.5, 129.5, 129.1, 129.0, 128.9, 127.5, 127.4, 127.2, 125.9, 59.2, 34.5, 30.4; HRMS (ESI): *m/z* calcd for $C_{34}H_{34}ClO_2$ $[M-H]^+$: 509.2247; found: 509.2233.

1-(4-chlorophenyl)-2-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-2-(naphthalen-1-yl)ethanone (19i):



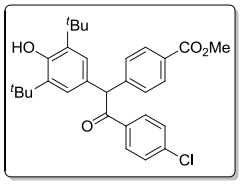
Yellow solid; Yield 84% (31.8 mg); m.p. 125–127 °C; FT IR (ATR) 3633, 2954, 2918, 2850, 1686 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), δ 8.00–7.87 (m, 4H), 7.78 (d, J = 8.2 Hz, 1H), 7.52–7.48 (m, 2H), 7.41–7.34 (m, 3H), 7.16 (d, J = 7.0 Hz, 1H), 7.07 (s, 2H), 6.56 (s, 1H), 5.16 (s, 1H), 1.37 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$), δ 197.7, 153.2, 139.4, 136.1, 135.9, 135.3, 134.3, 131.5, 130.4, 129.3, 129.1, 128.1, 127.8, 127.1, 126.8, 126.5, 125.8, 125.6, 123.2, 56.0, 34.5, 30.4; HRMS (ESI): *m/z* calcd for $C_{32}H_{32}ClO_2$ $[M-H]^+$: 483.2091; found: 483.2084.

1-(4-chlorophenyl)-2-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-2-[4-(phenylethynyl)phenyl] ethanone (19j):



Yellow solid; Yield 76% (31.7 mg); m.p. 180–182 °C; FT IR (ATR) 3628, 2954, 2921, 2852, 1681 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), δ 7.93 (d, J = 8.6 Hz, 2H), 7.52–7.48 (m, 4H), 7.39 (d, J = 8.6 Hz, 2H), 7.34–7.32 (m, 3H), 7.26–7.24 (m, 2H), 7.02 (s, 2H), 5.87 (s, 1H), 5.17 (s, 1H), 1.39 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$), δ 197.5, 153.2, 139.8, 139.5, 136.2, 135.4, 132.1, 131.7, 130.5, 129.2, 129.1, 128.8, 128.5, 128.4, 125.9, 123.3, 122.2, 89.8, 89.3, 59.3, 34.5, 30.4; HRMS (ESI): *m/z* calcd for $C_{36}H_{34}ClO_2$ $[M-H]^+$: 533.2247; found: 533.2262.

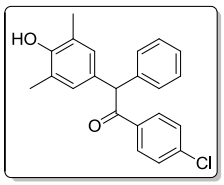
Methyl{4-[2-(4-chlorophenyl)-1-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-2-oxoethyl]}benzoate (19k):



Yellow solid; Yield 20% (7.7 mg); m.p. 164–166 °C; FT IR (ATR) 3616, 2956, 2921, 2853, 1710, 1688 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), δ 7.99 (d, J

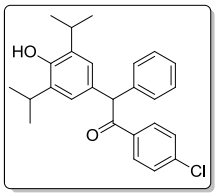
= 8.5 Hz, 2H), 7.92 (d, *J* = 8.7 Hz, 2H), 7.38 (d, *J* = 8.7 Hz, 2H), 7.33 (d, *J* = 8.2 Hz, 2H), 7.02 (s, 2H), 5.91 (s, 1H), 5.17 (s, 1H), 3.89 (s, 3H), 1.38 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$), δ 197.2, 167.0, 153.3, 144.9, 139.7, 136.4, 135.3, 130.5, 130.1, 129.3, 129.1, 129.0, 128.5, 125.8, 59.4, 52.3, 34.5, 30.4; HRMS (ESI): *m/z* calcd for $C_{30}H_{32}ClO_4$ $[M-H]^+$: 491.1989; found: 491.1997.

1-(4-chlorophenyl)-2-(4-hydroxy-3,5-dimethylphenyl)-2-phenylethanone (**19m**):



Yellow color semi solid; Yield 20% (5.5 mg); FT IR (ATR) 3459, 2953, 2919, 2850, 1677 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$), δ 7.93 (d, *J* = 8.6 Hz, 2H), 7.37 (d, *J* = 8.6 Hz, 2H), 7.34–7.30 (m, 2H), 7.25–7.21 (m, 3H), 6.86 (s, 2H), 5.83 (s, 1H), 4.59 (s, 1H), 2.19 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$), δ 197.6, 151.6, 139.5, 139.4, 135.2, 130.5, 130.2, 129.3, 129.1, 129.0, 128.8, 127.2, 123.6, 59.0, 16.2; HRMS (ESI): m/z calcd for $C_{22}H_{18}ClO_2$ $[M-H]^+$: 349.0995; found: 349.0990.

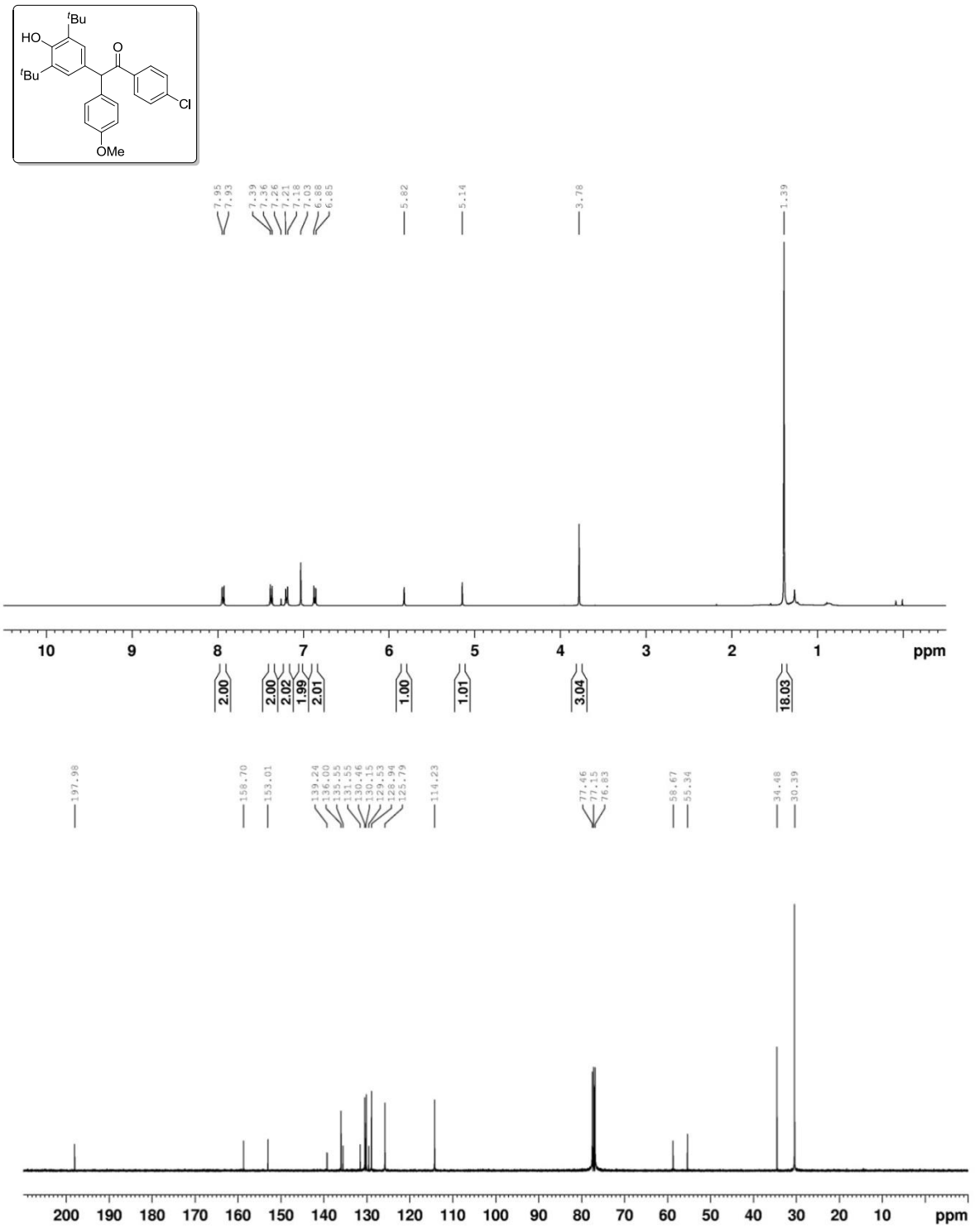
1-(4-chlorophenyl)-2-(4-hydroxy-3,5-diisopropylphenyl)-2-phenylethanone (**19n**):



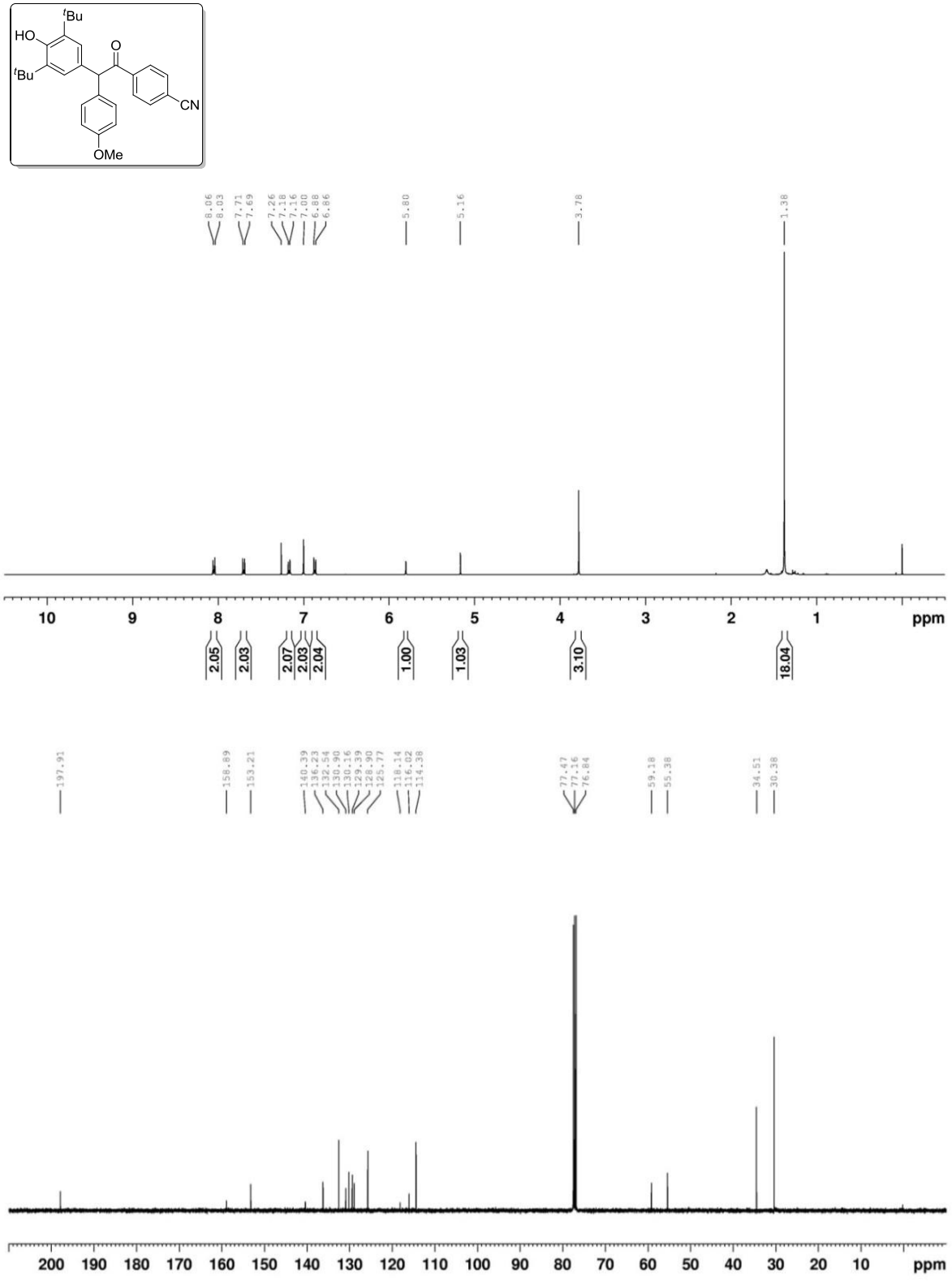
Yellow solid; Yield 25% (7.9 mg); m.p. 138–140 °C; FT IR (ATR) 3503, 2960, 2926, 2868, 1679 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$), δ 7.93 (d, *J* = 8.6 Hz, 2H), 7.37 (d, *J* = 8.6 Hz, 2H), 7.34–7.30 (m, 2H), 7.24–7.22 (m, 3H), 6.92 (s, 2H), 5.88 (s, 1H), 4.75 (s, 1H), 3.09 (sept, *J* = 6.9 Hz, 2H), 1.22 (d, *J* = 6.9 Hz, 2H), 1.19 (d, *J* = 6.9 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$), δ 197.7, 149.4, 139.5, 139.3, 135.5, 134.1, 130.5, 130.3, 129.1, 129.0, 128.8, 127.2, 124.5, 59.5, 27.5, 22.8, 22.75; HRMS (ESI): *m/z* calcd for $C_{26}H_{28}ClO_2$ $[M+H]^+$: 407.1778; found: 407.1784.

Spectra of compounds (**15c**, **17a–17p** & **19a–19n**)

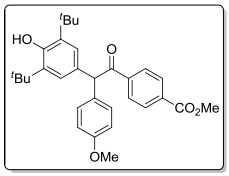
^{1}H, ^{13}C NMR Spectra of **15c**

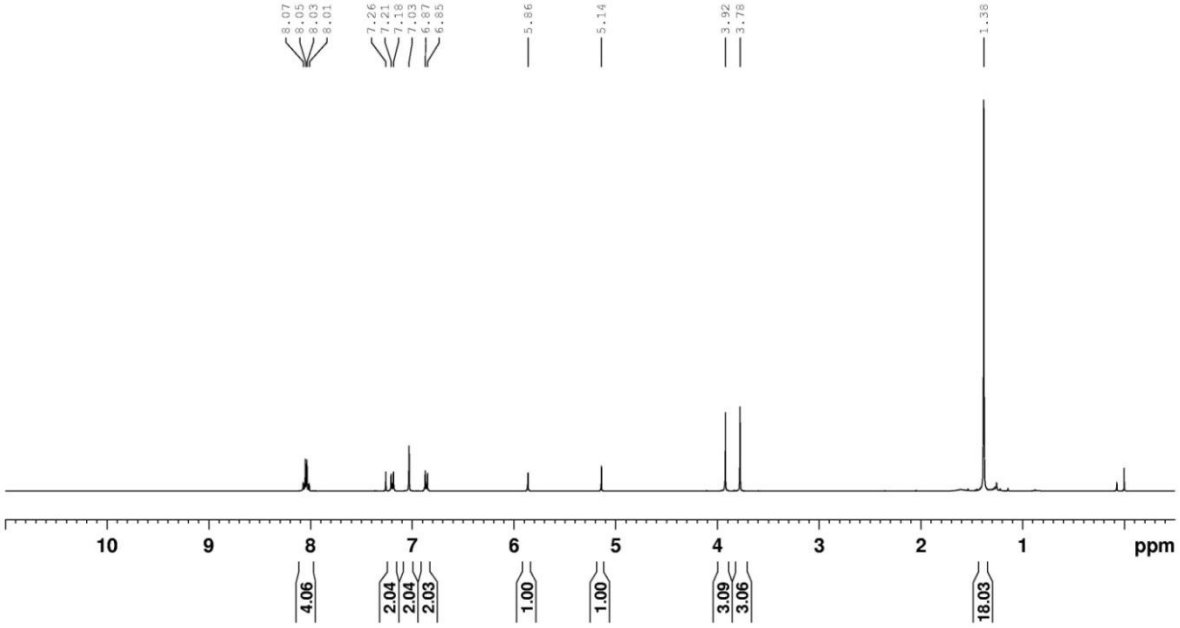


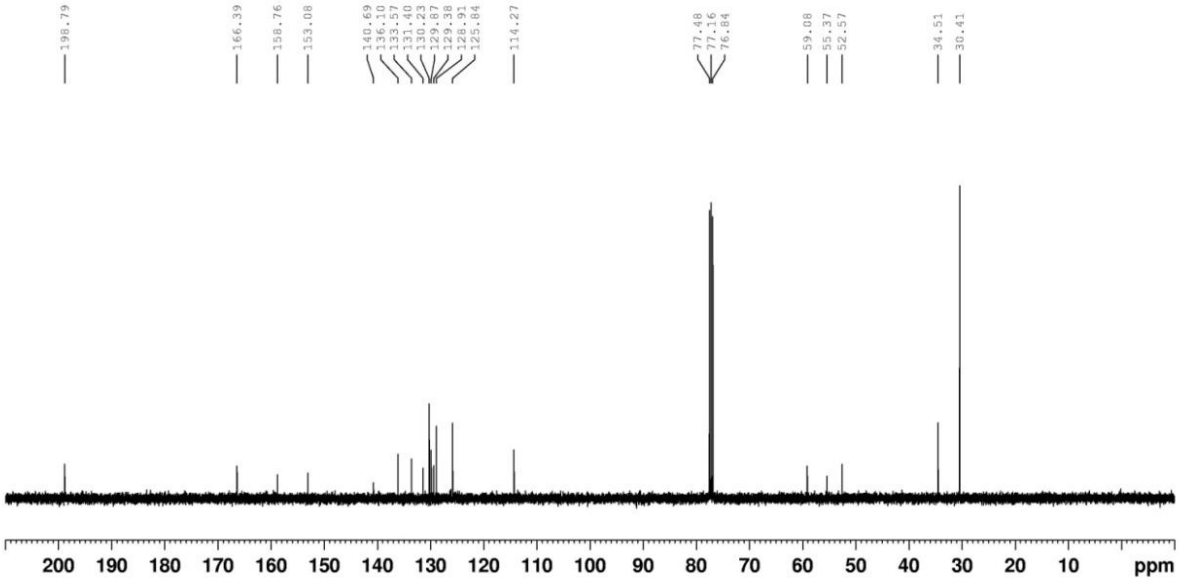
^{1}H, ^{13}C NMR Spectra of **17a**



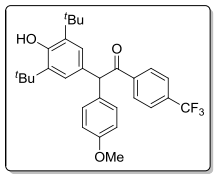
^{1}H, ^{13}C NMR Spectra of **17b**

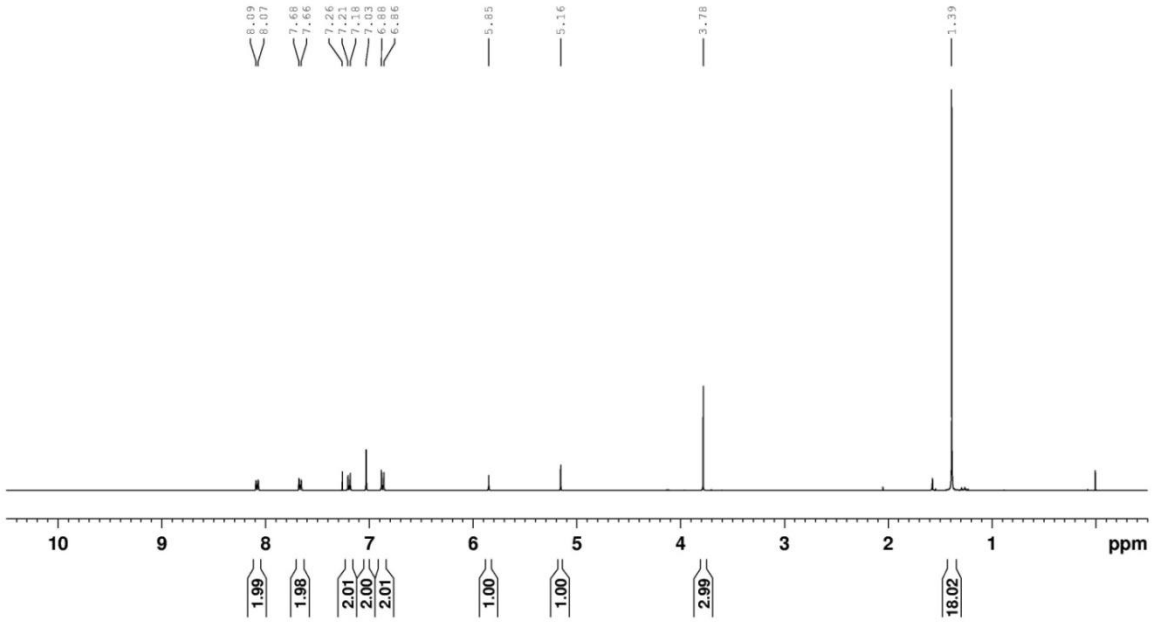


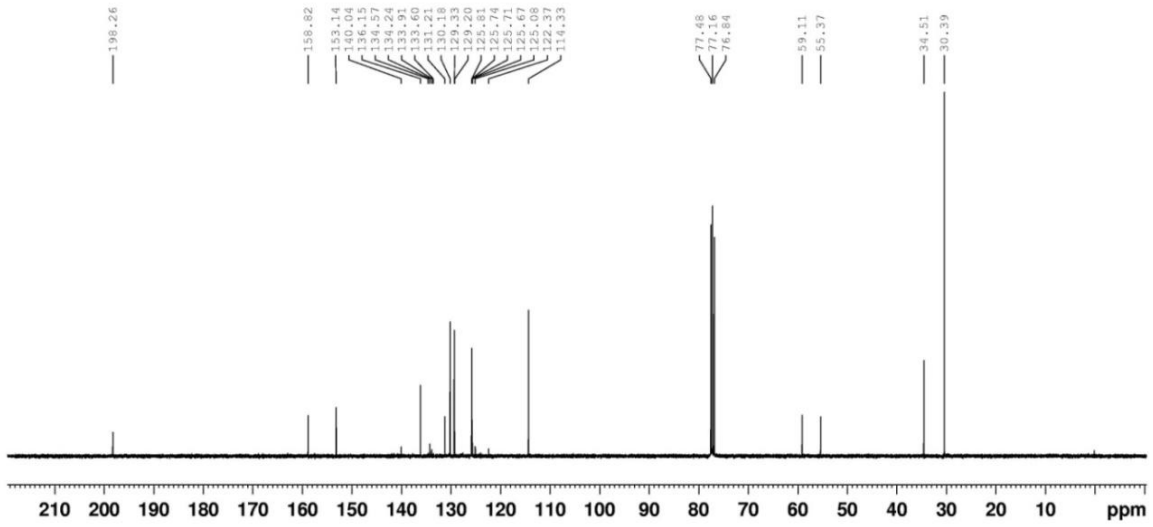




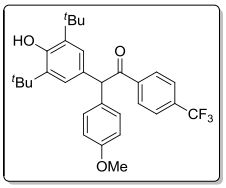
^{1}H, ^{13}C NMR Spectra of **17c**

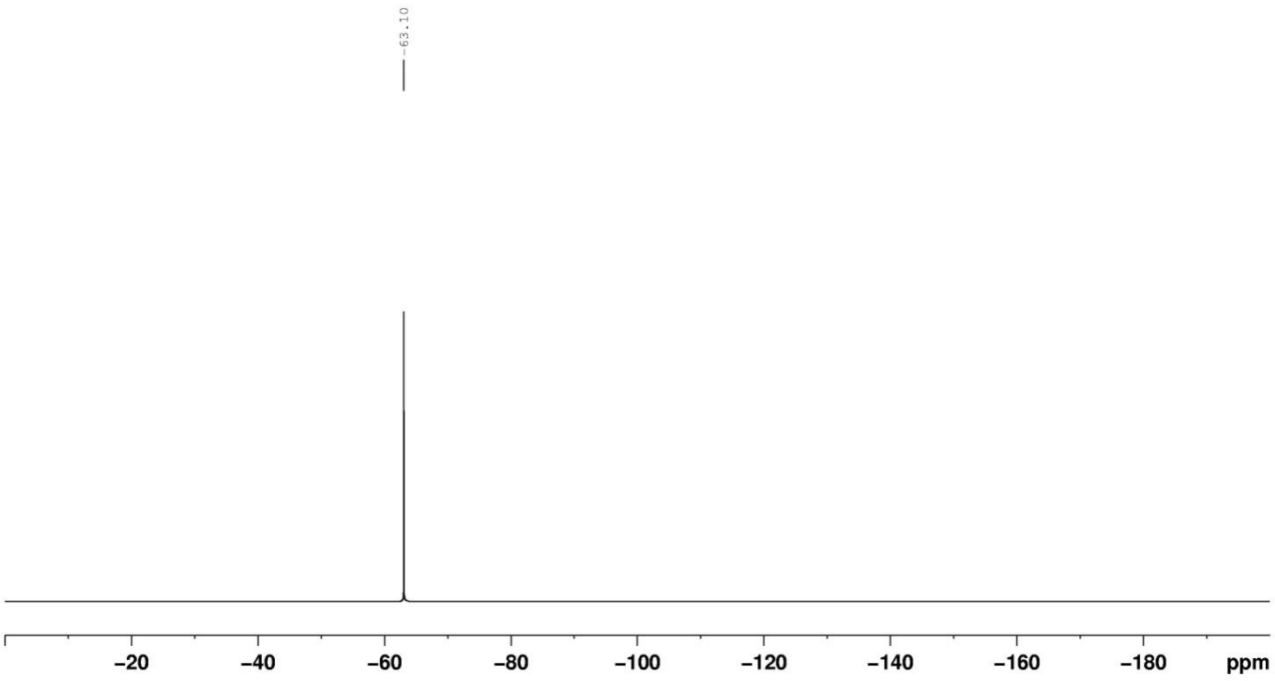




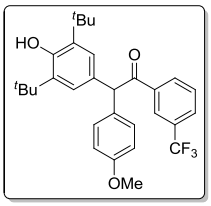


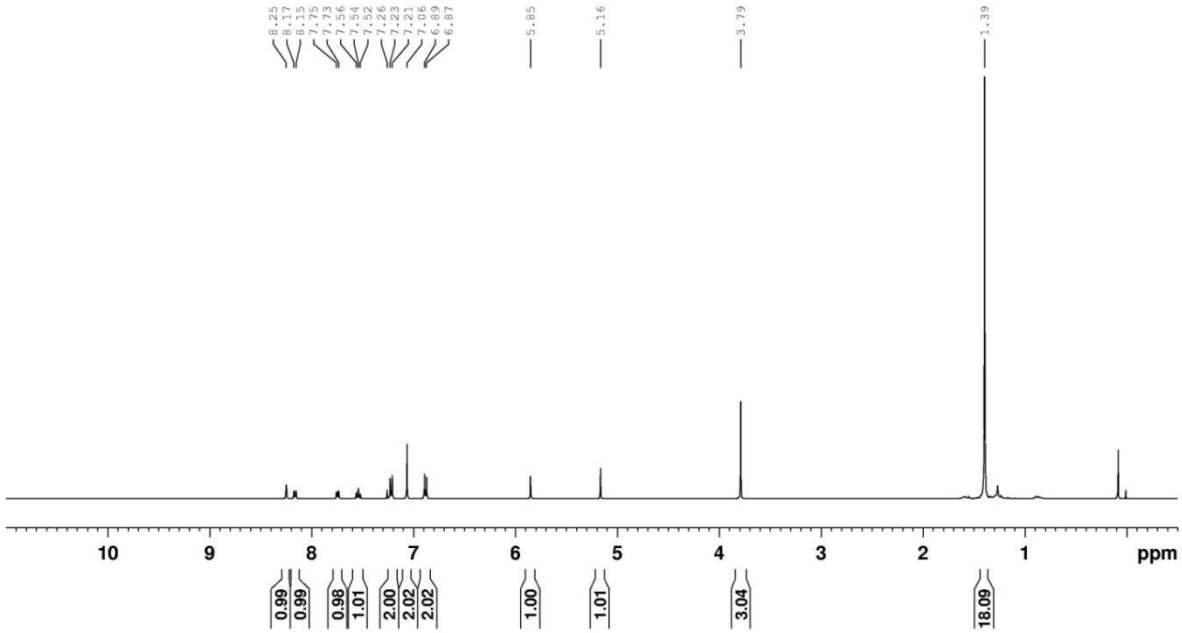
^{19}F NMR Spectra of **17c**

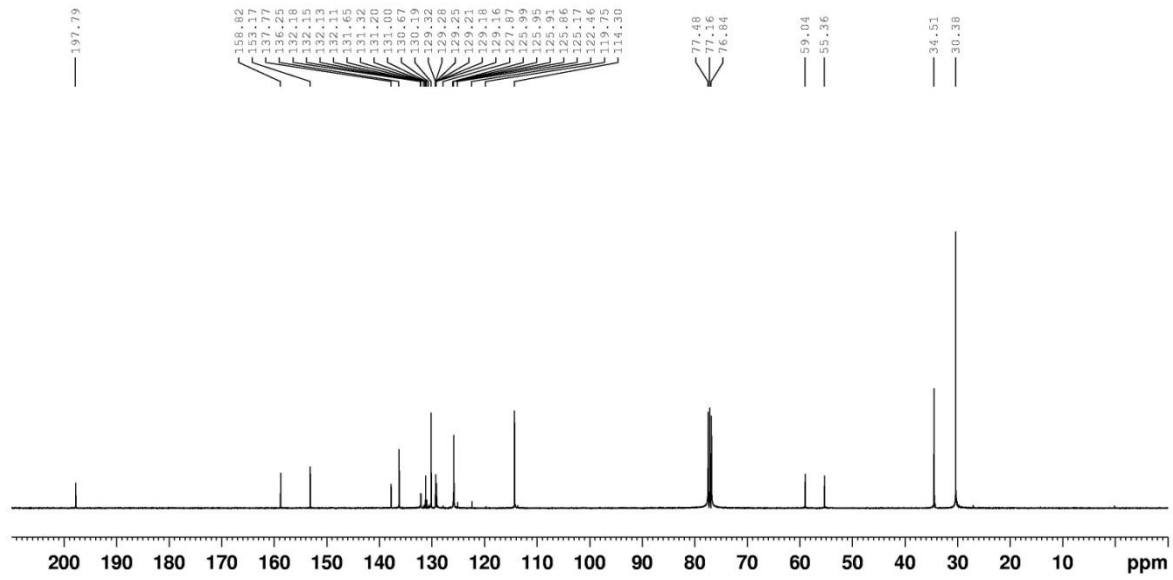




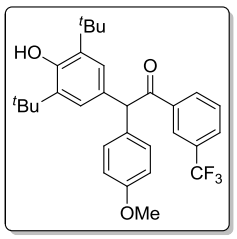
^{1}H, ^{13}C NMR Spectra of **17d**

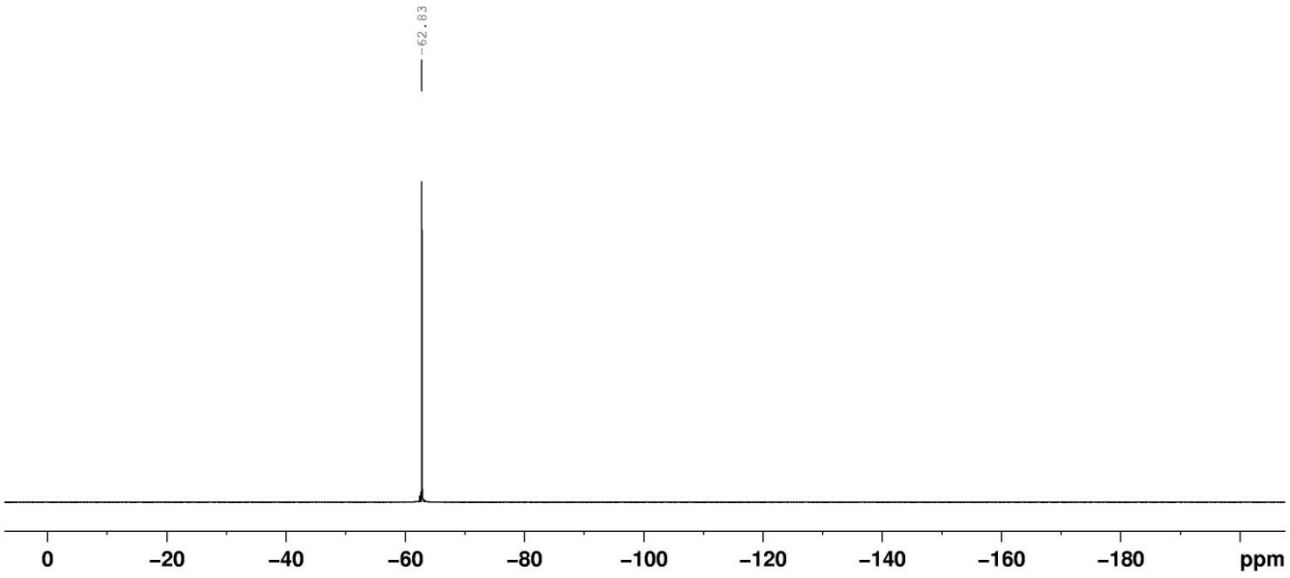




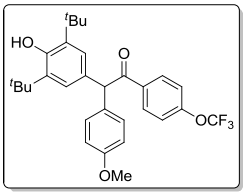


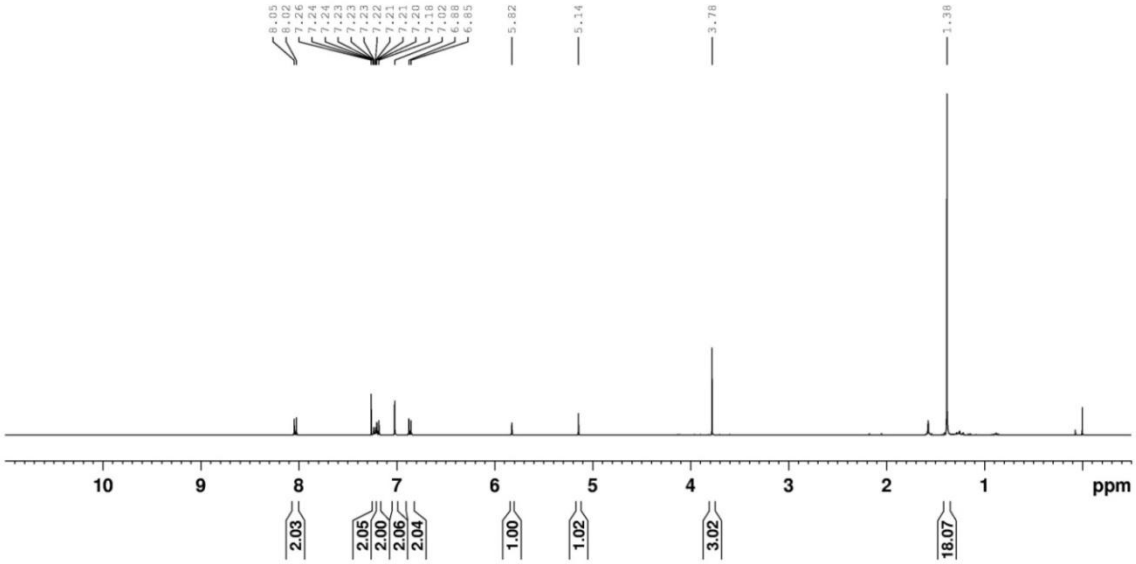
^{19}F NMR Spectra of **17d**

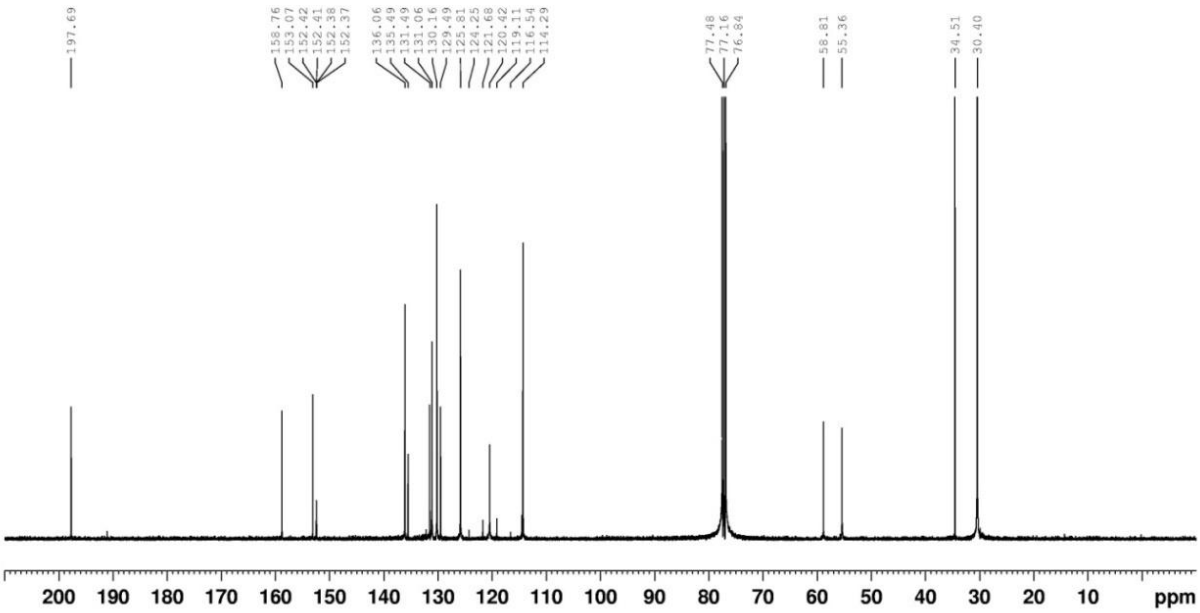




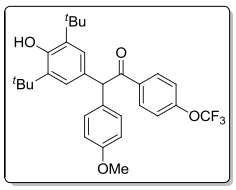
^{1}H, ^{13}C NMR Spectra of **17e**

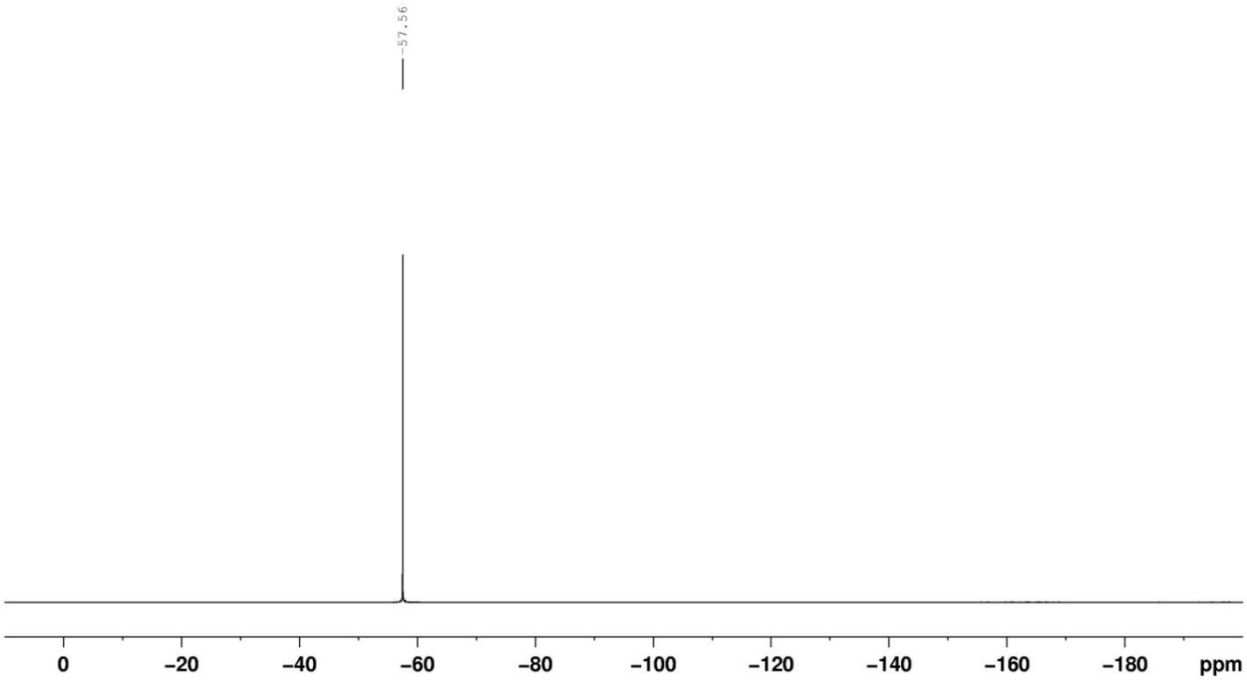




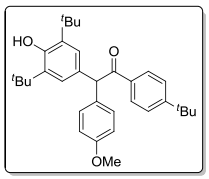


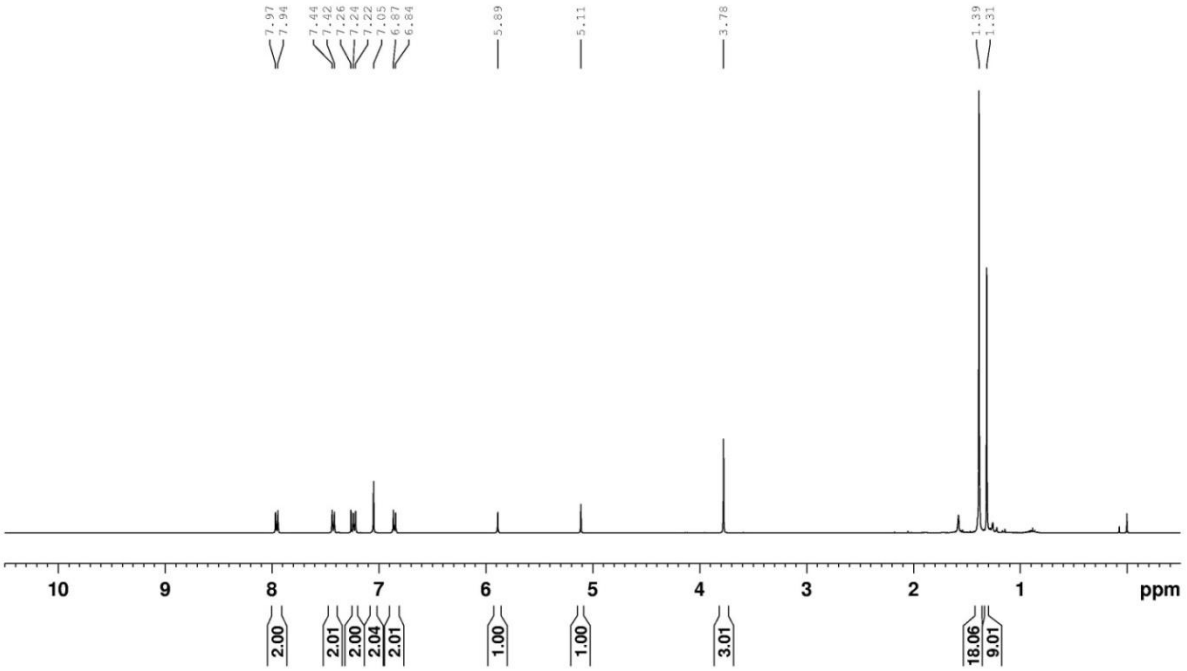
^{19}F NMR Spectra of **17e**

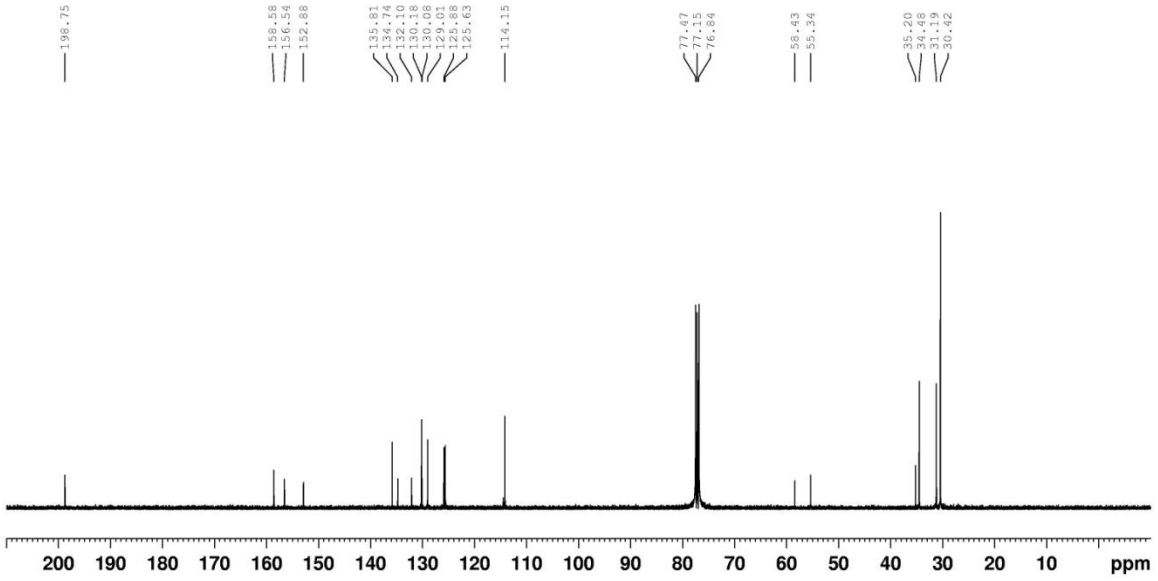




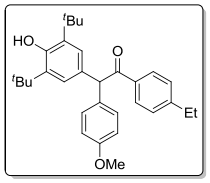
^{1}H, ^{13}C NMR Spectra of **17f**

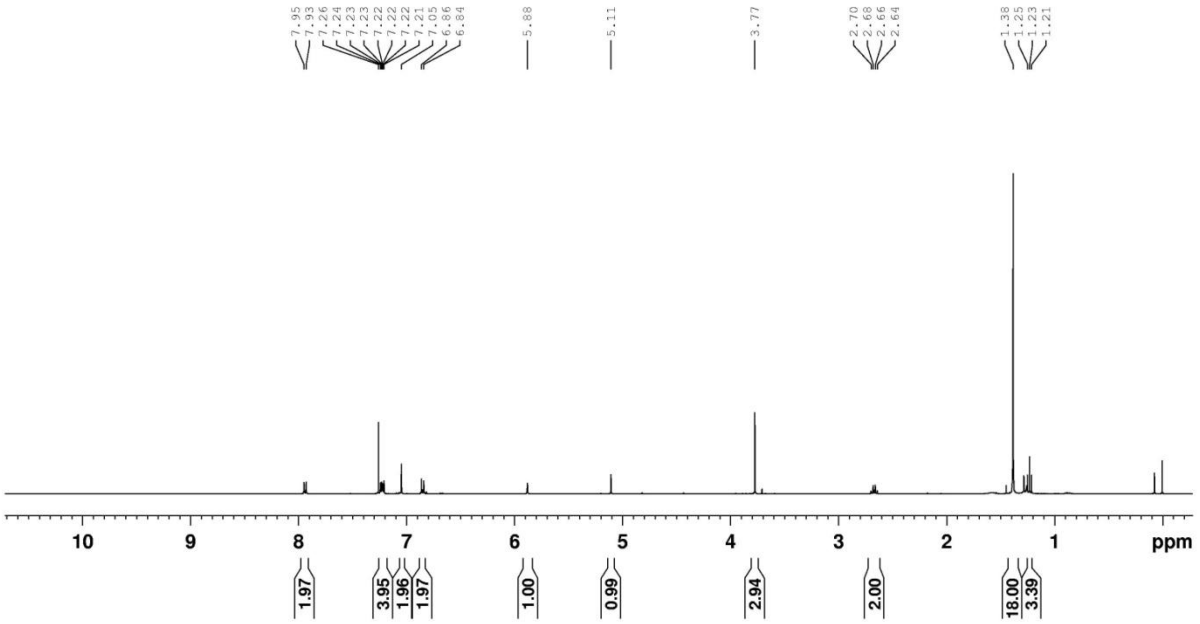


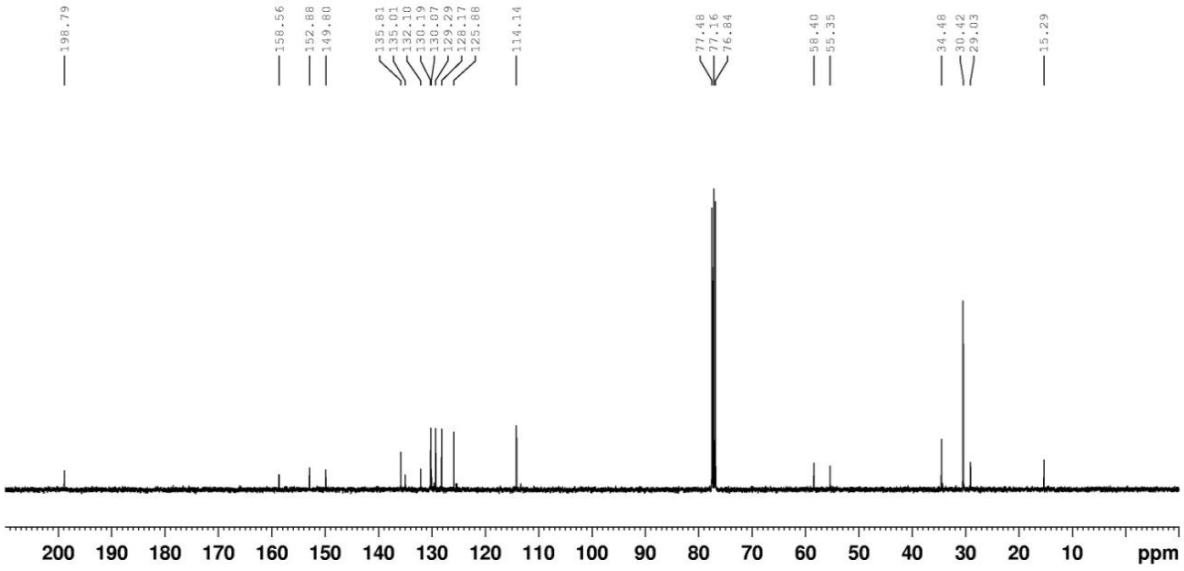




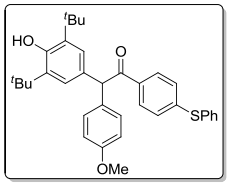
^{1}H, ^{13}C NMR Spectra of **17g**

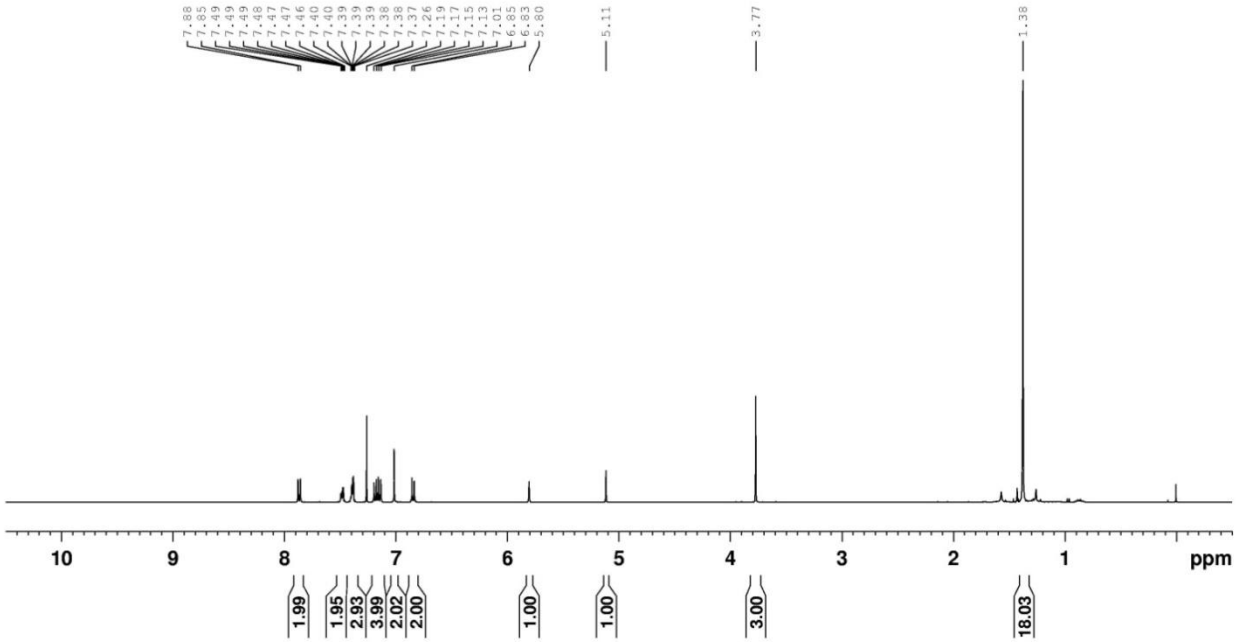


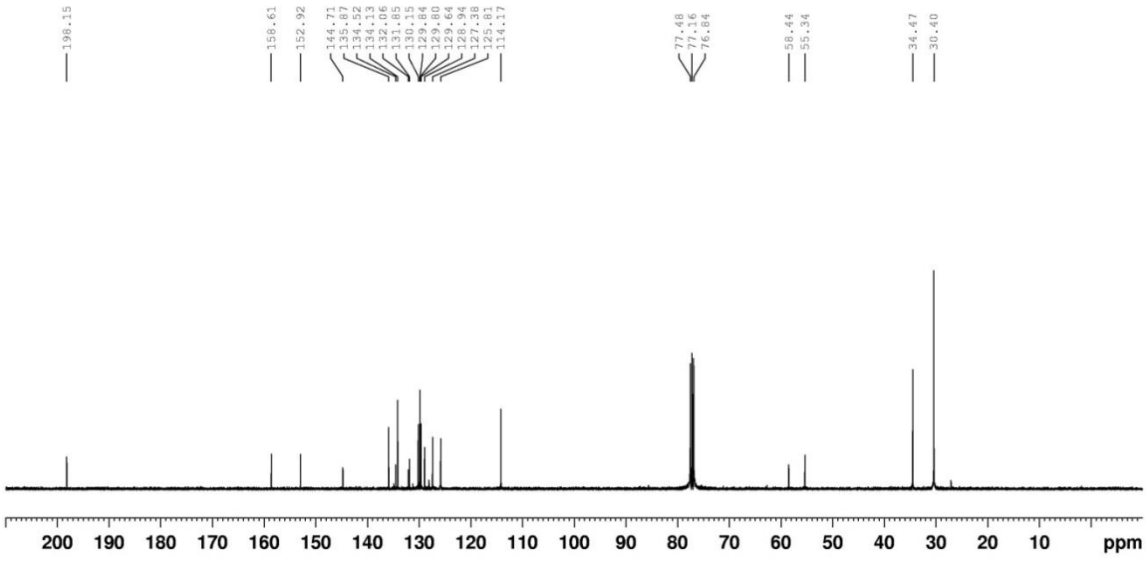




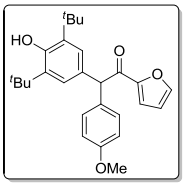
^{1}H, ^{13}C NMR Spectra of **17h**

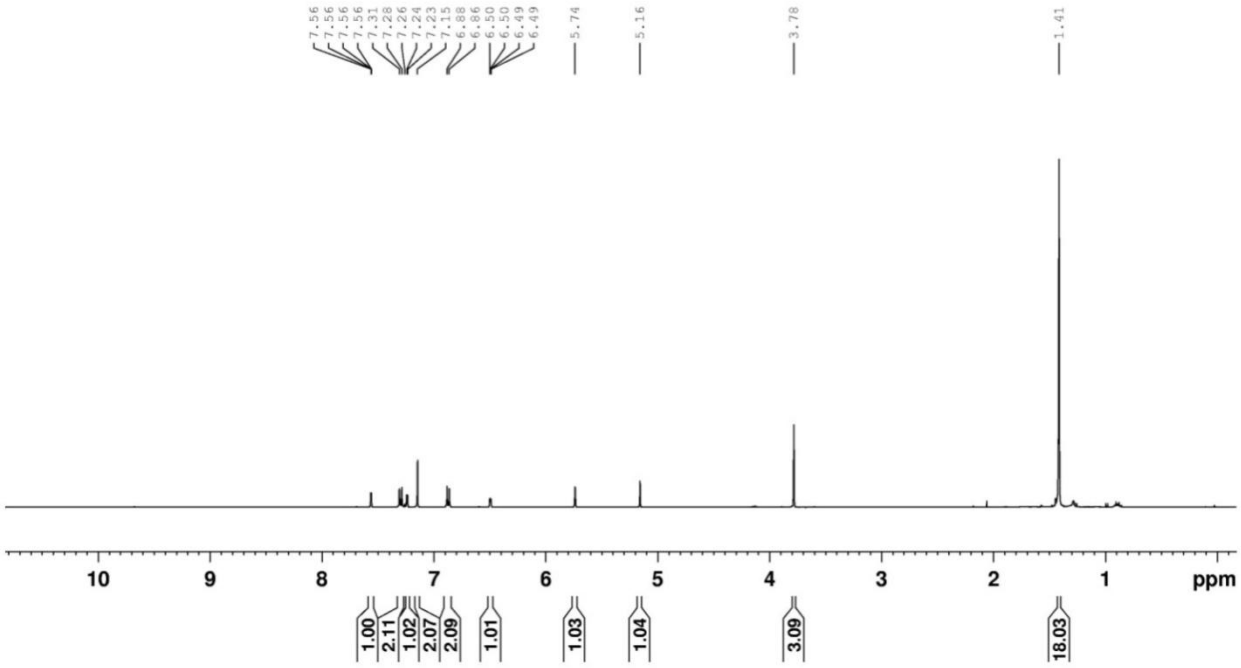


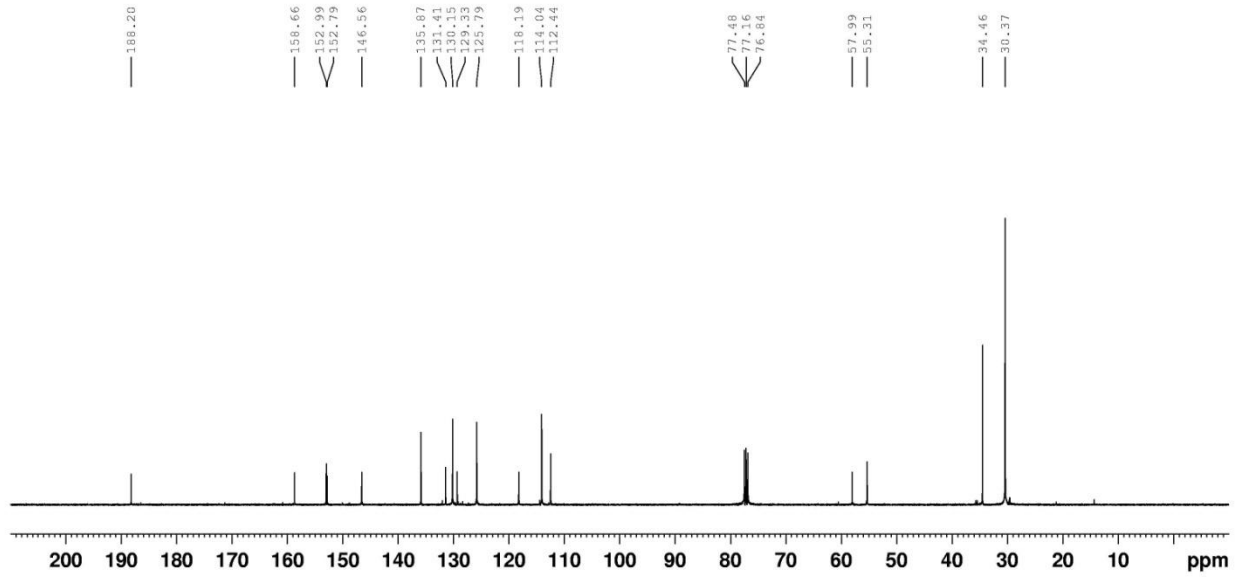




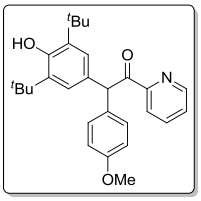
^{1}H, ^{13}C NMR Spectra of **17i**

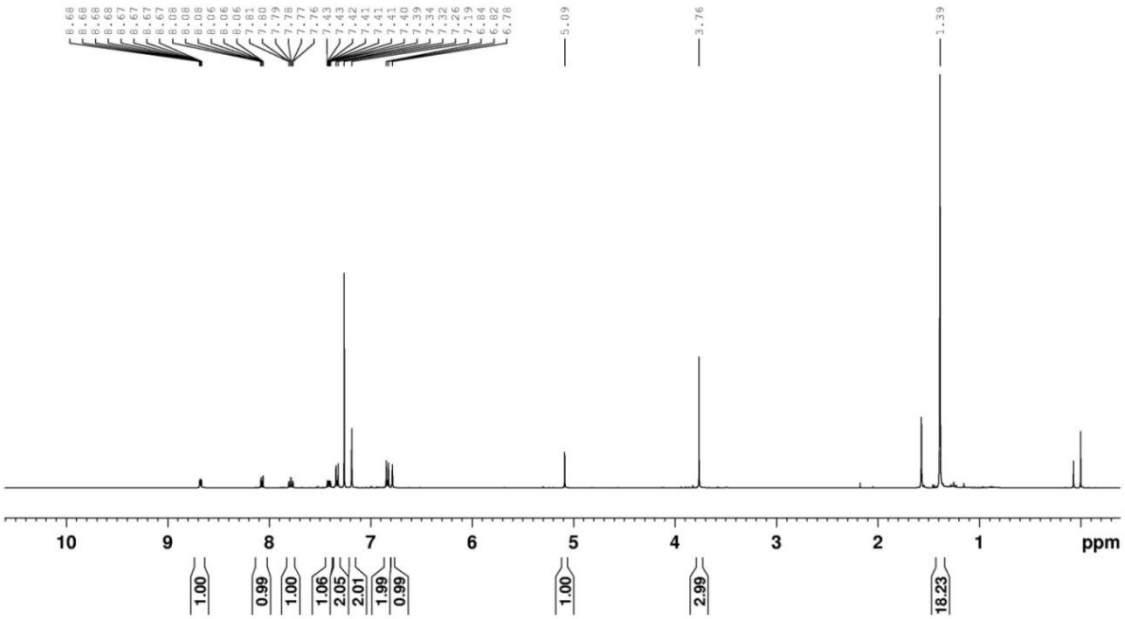


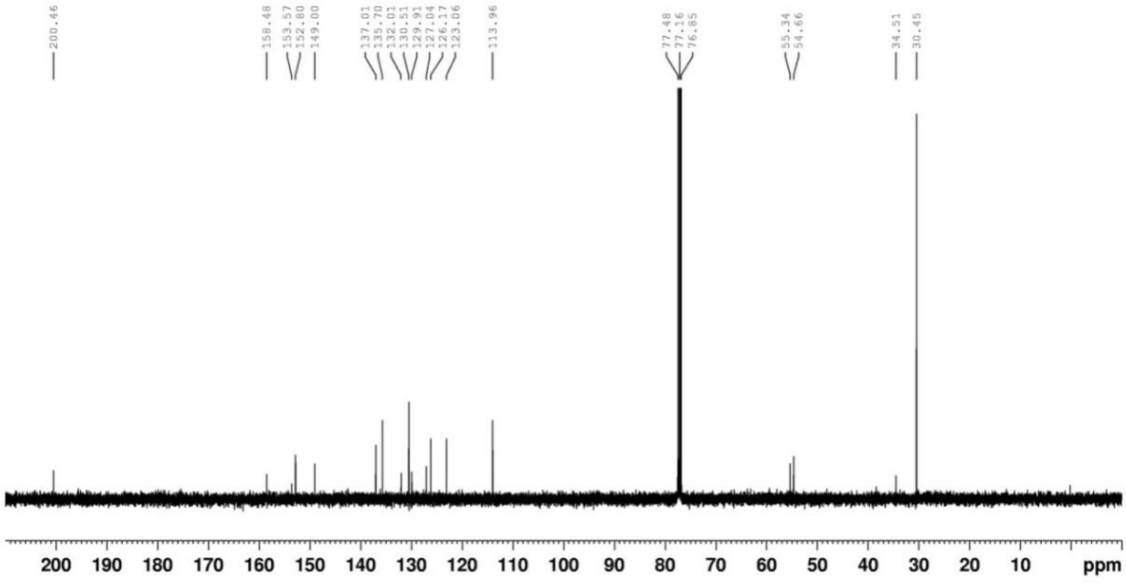




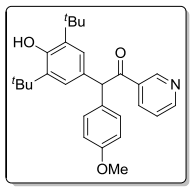
^{1}H, ^{13}C NMR Spectra of **17j**

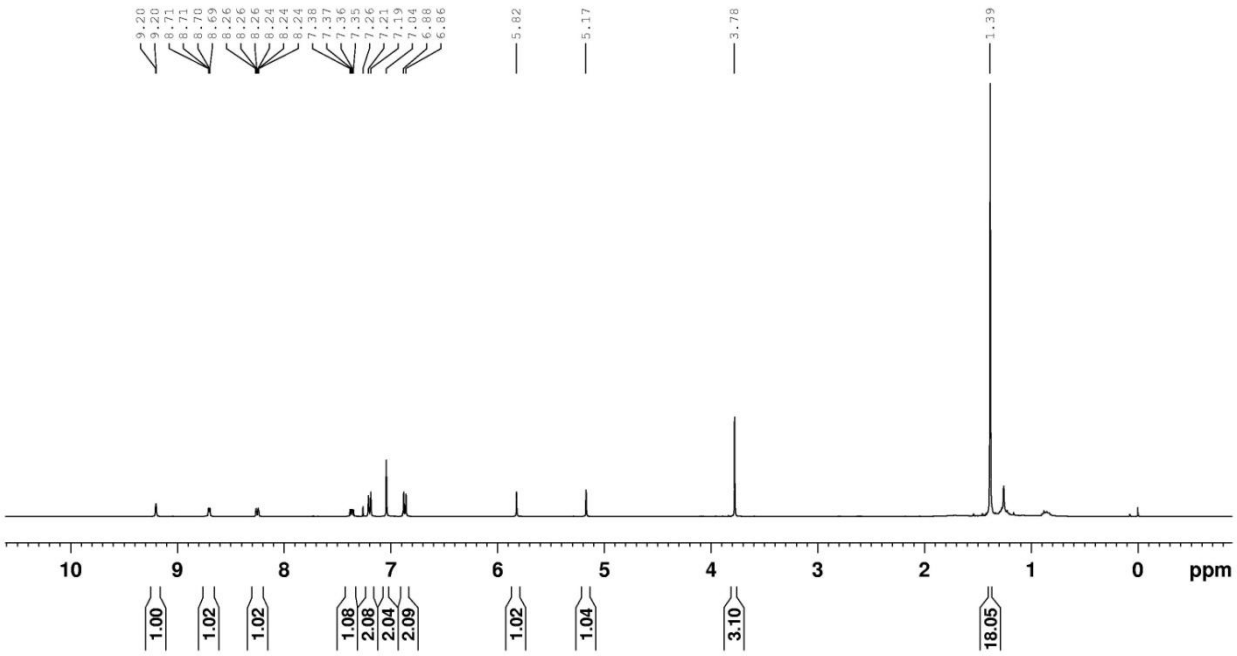


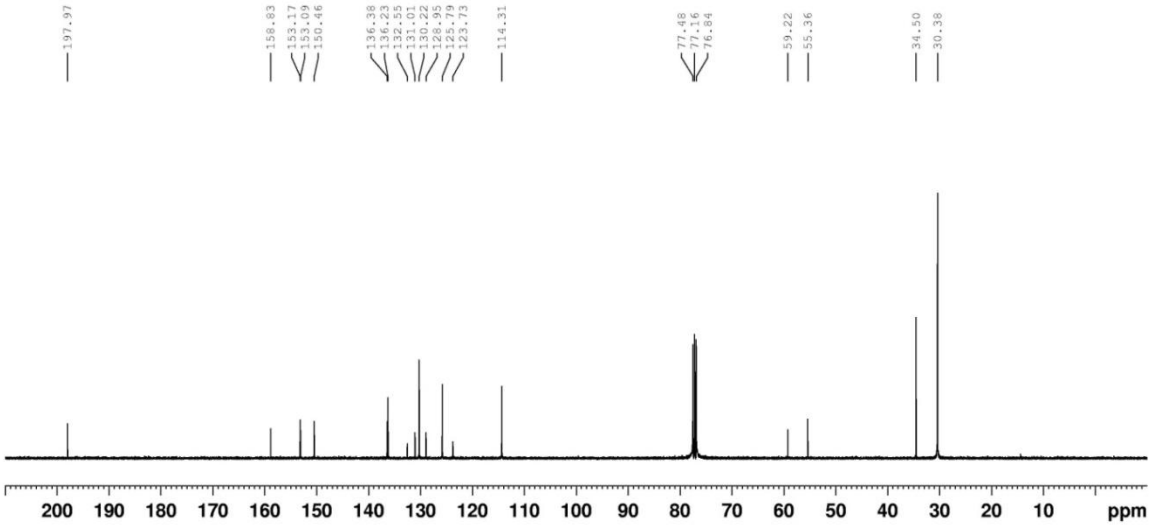




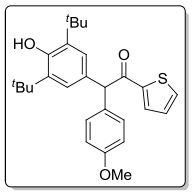
^{1}H, ^{13}C NMR Spectra of **17k**

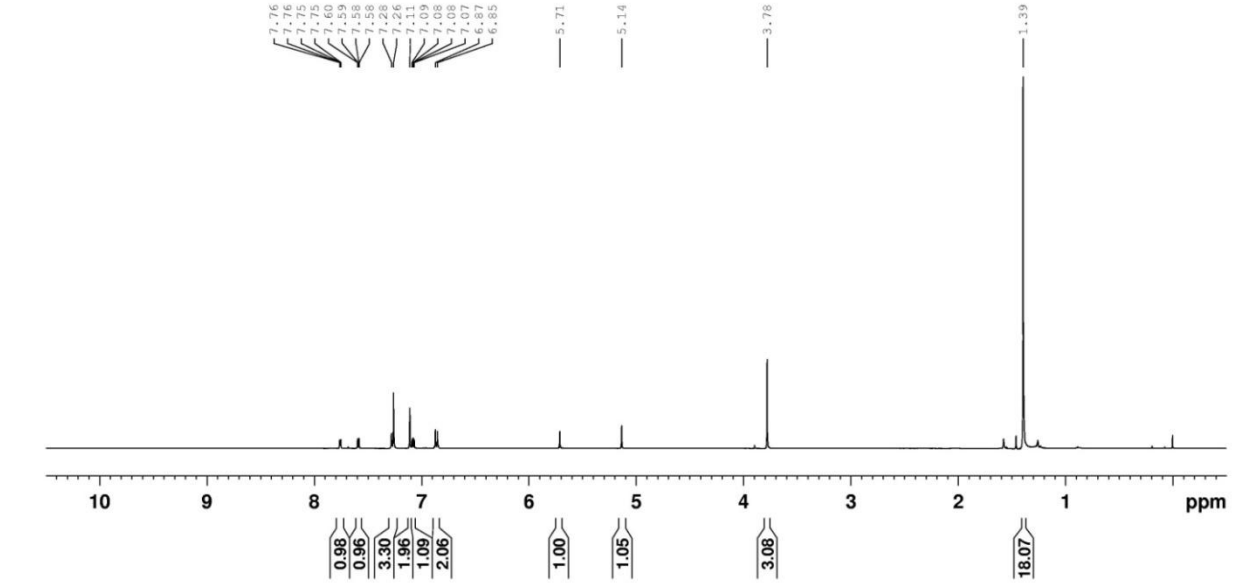


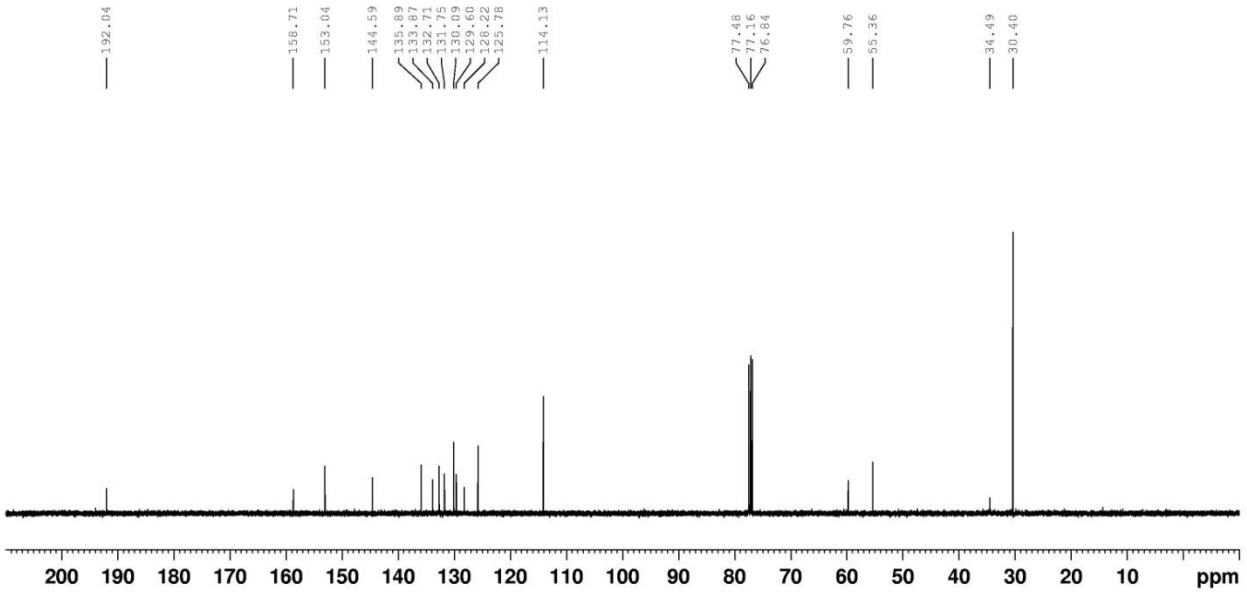




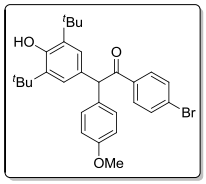
^{1}H, ^{13}C NMR Spectra of **17l**

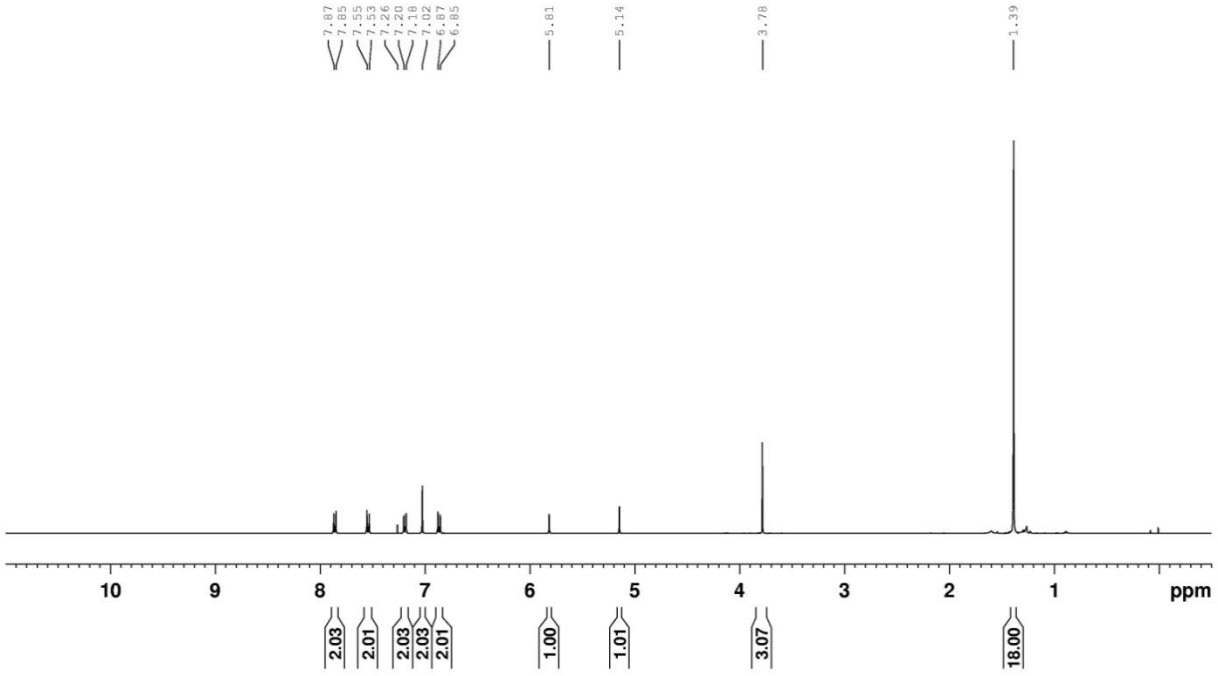


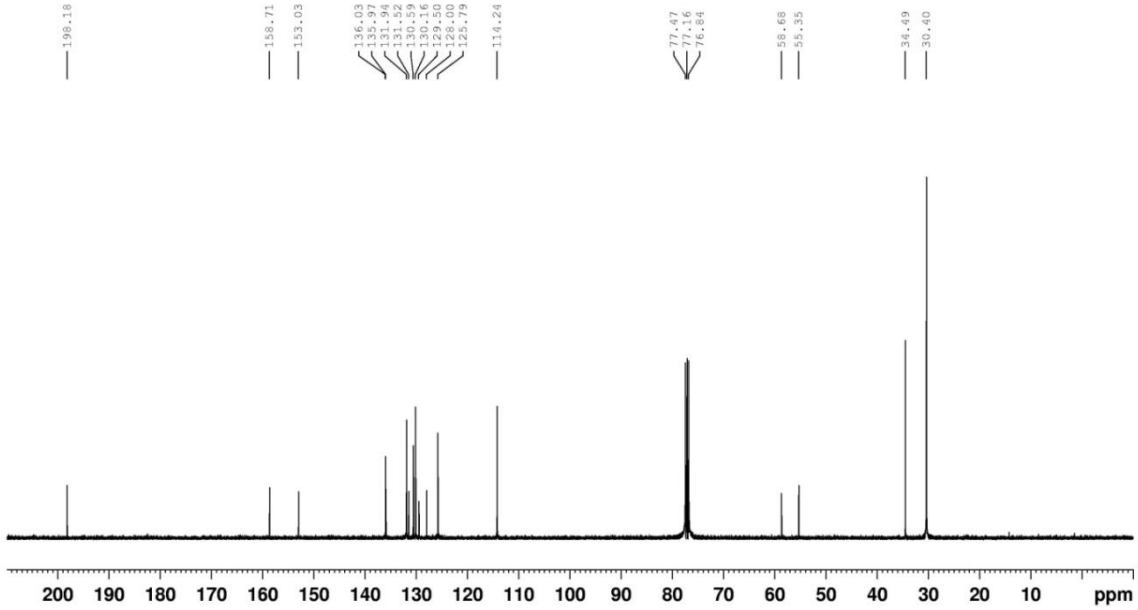




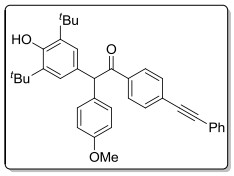
^{1}H, ^{13}C NMR Spectra of **17m**

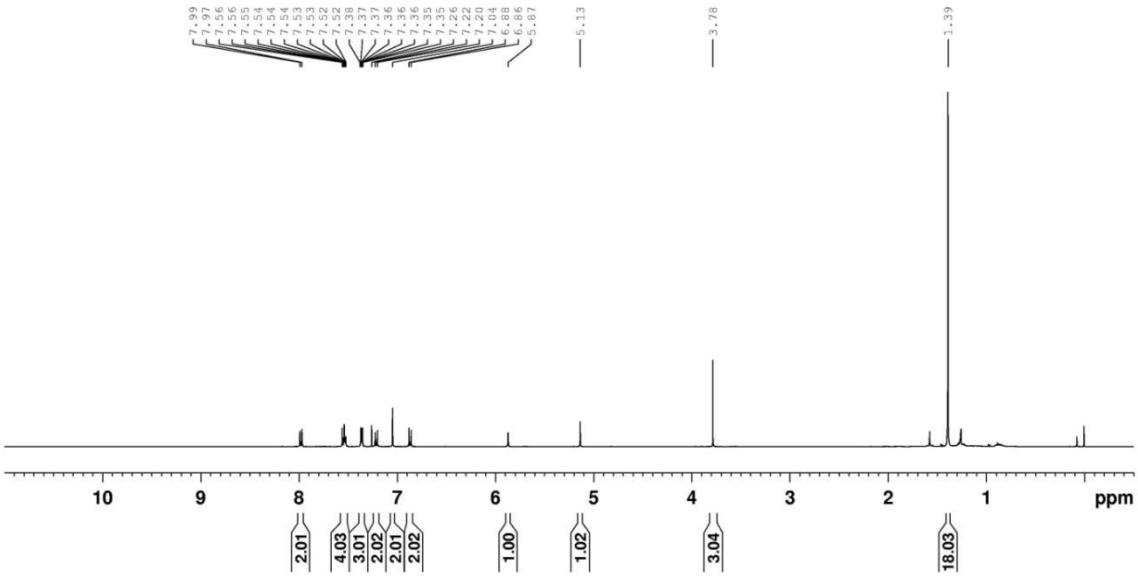


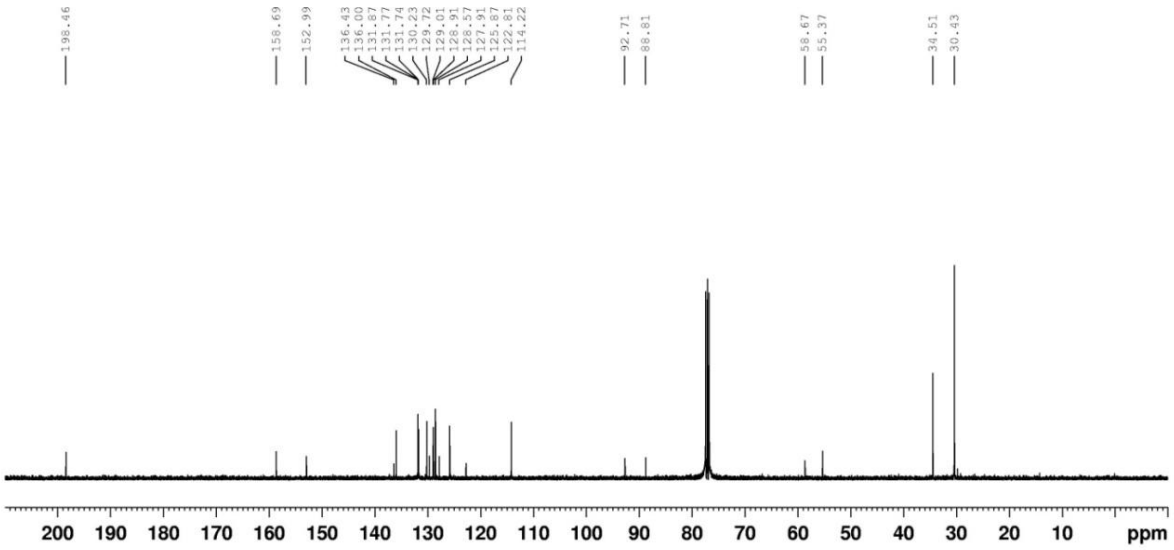




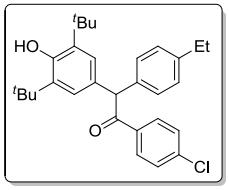
^{1}H, ^{13}C NMR Spectra of **17n**

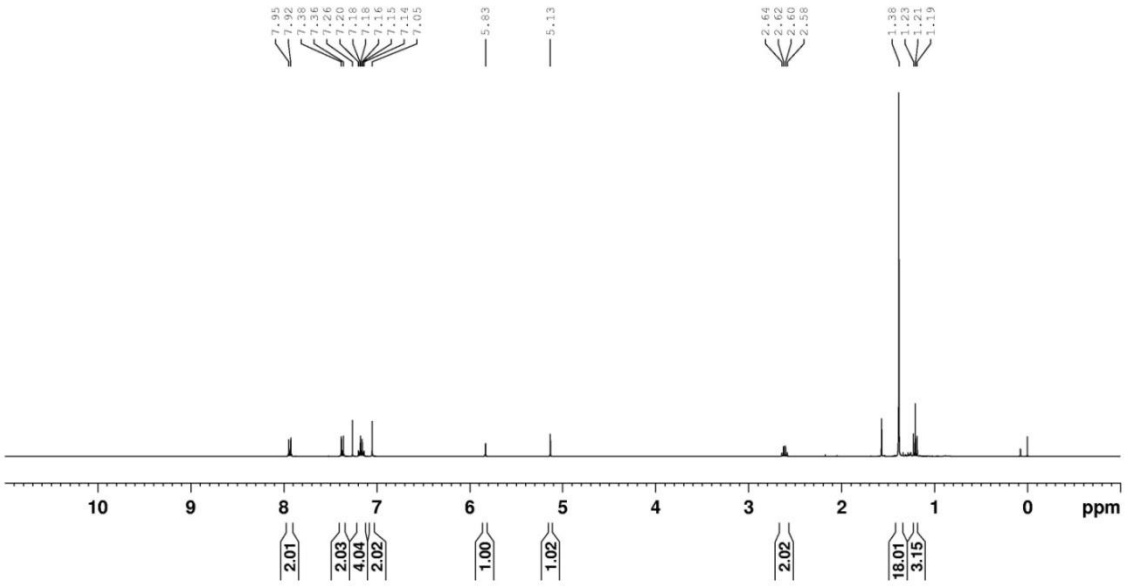


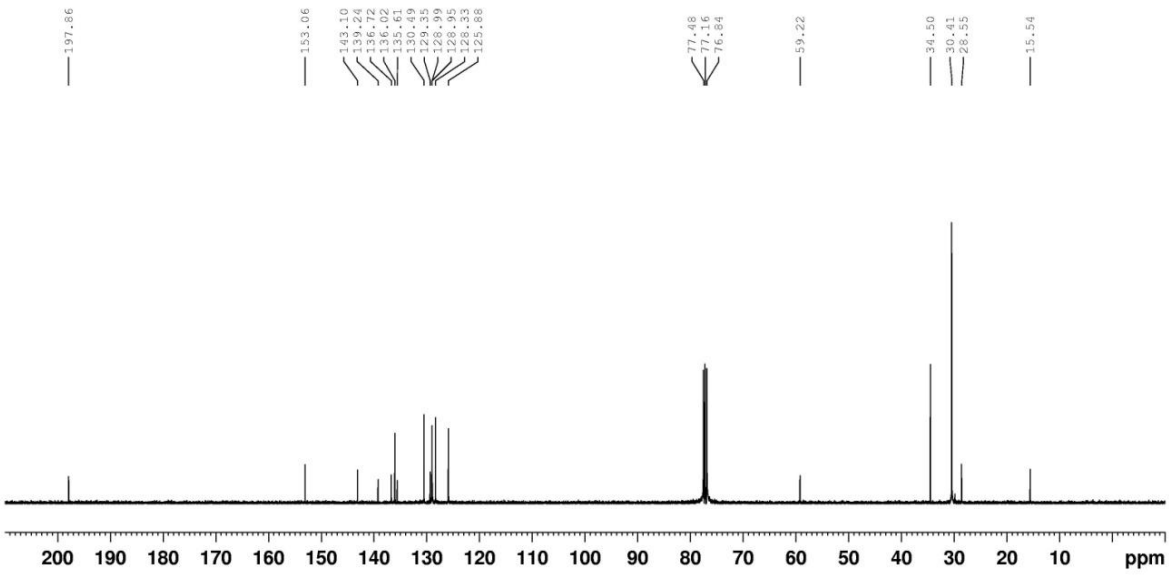




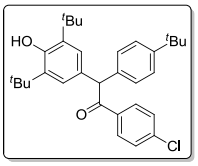
^{1}H, ^{13}C NMR Spectra of **19a**

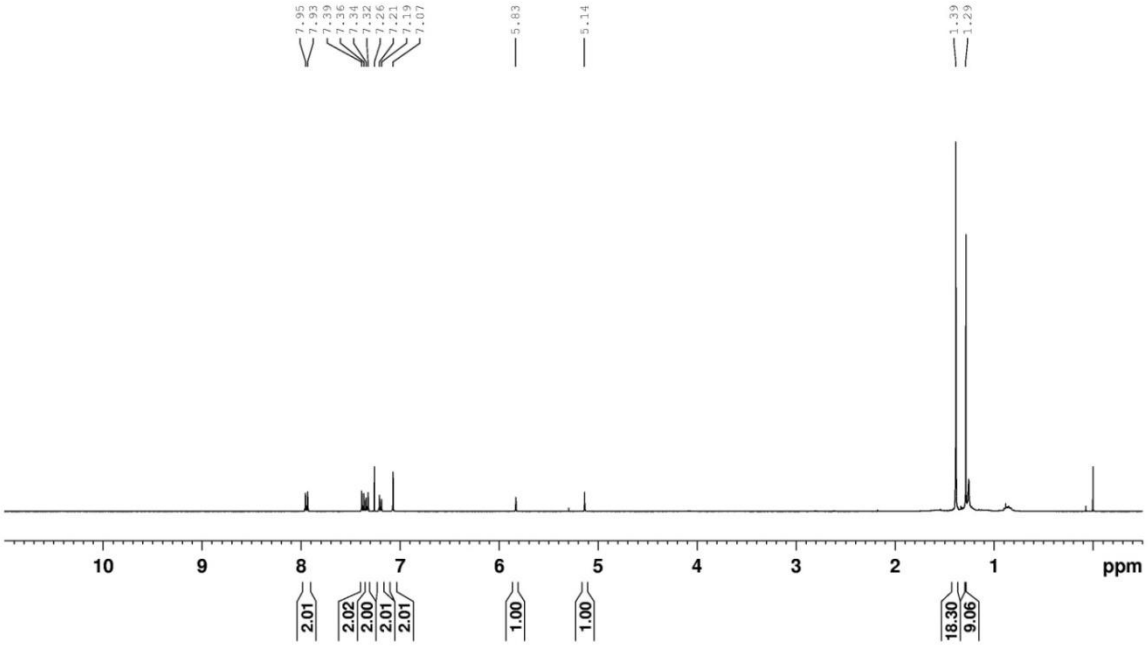


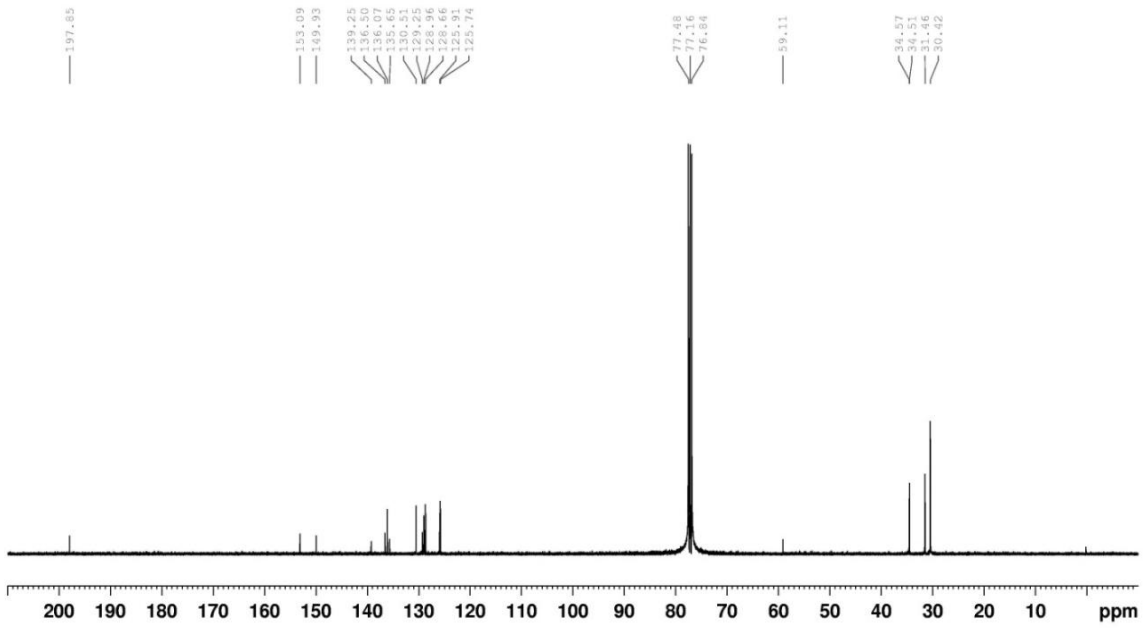




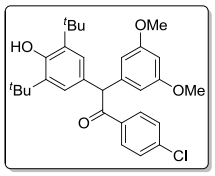
^{1}H, ^{13}C NMR Spectra of **19b**

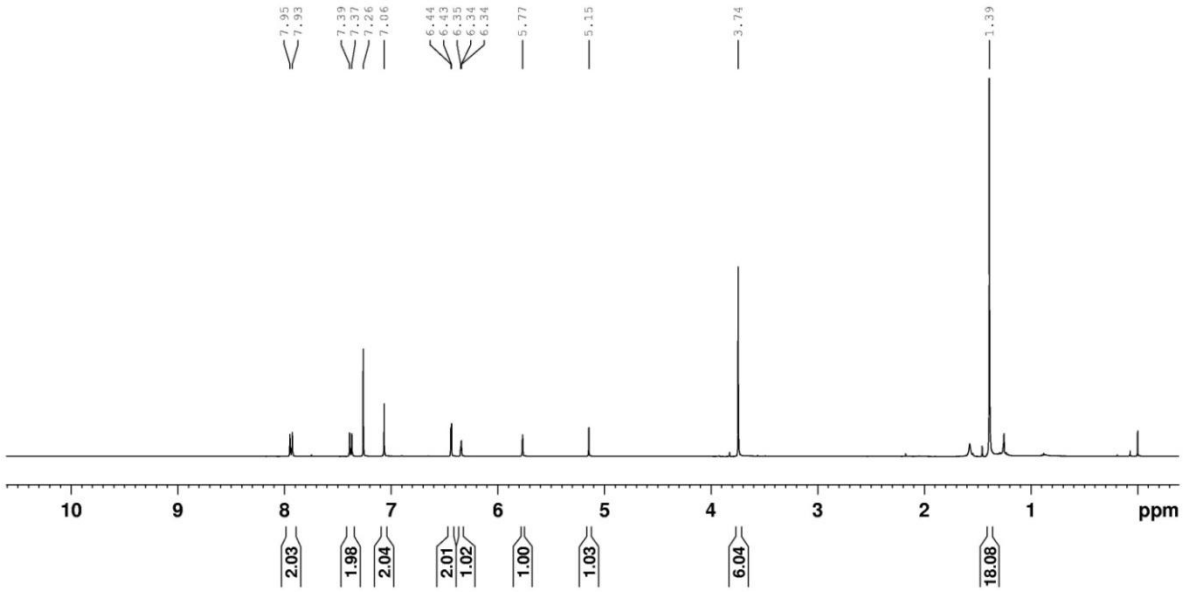


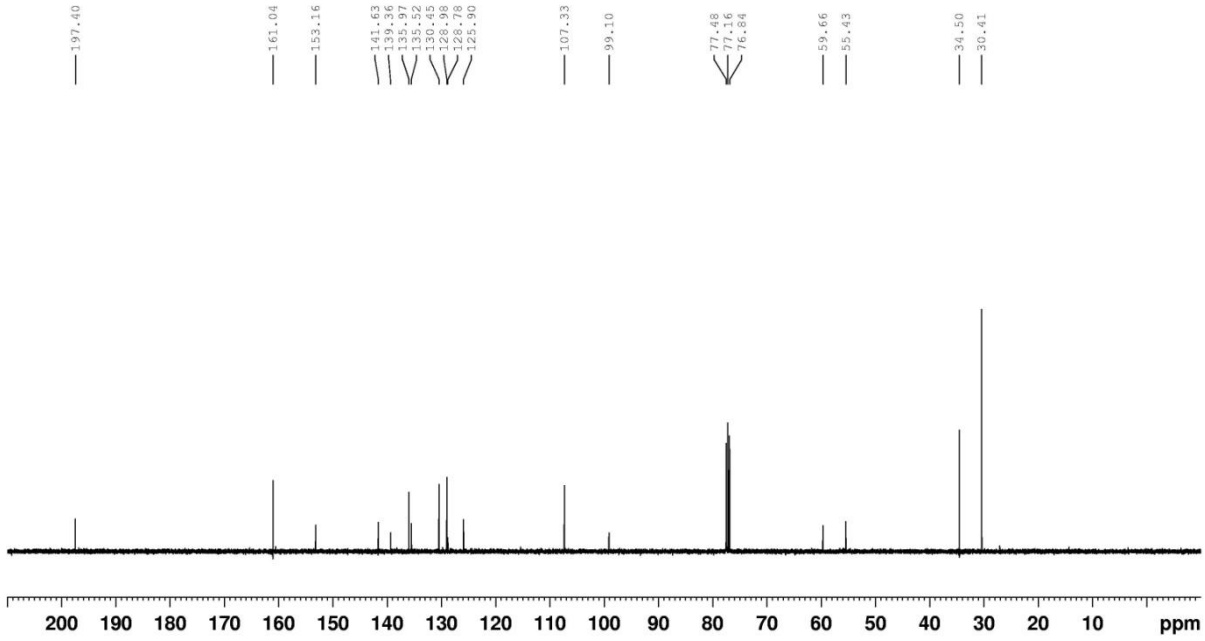




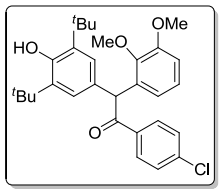
^{1}H, ^{13}C NMR Spectra of **19c**

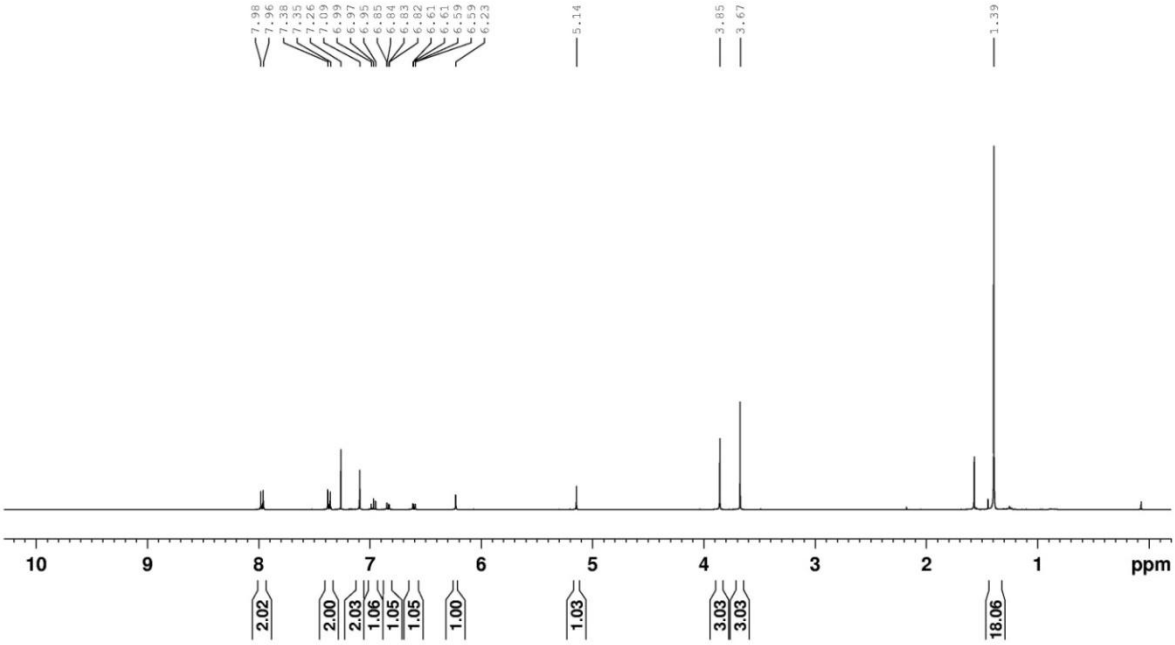


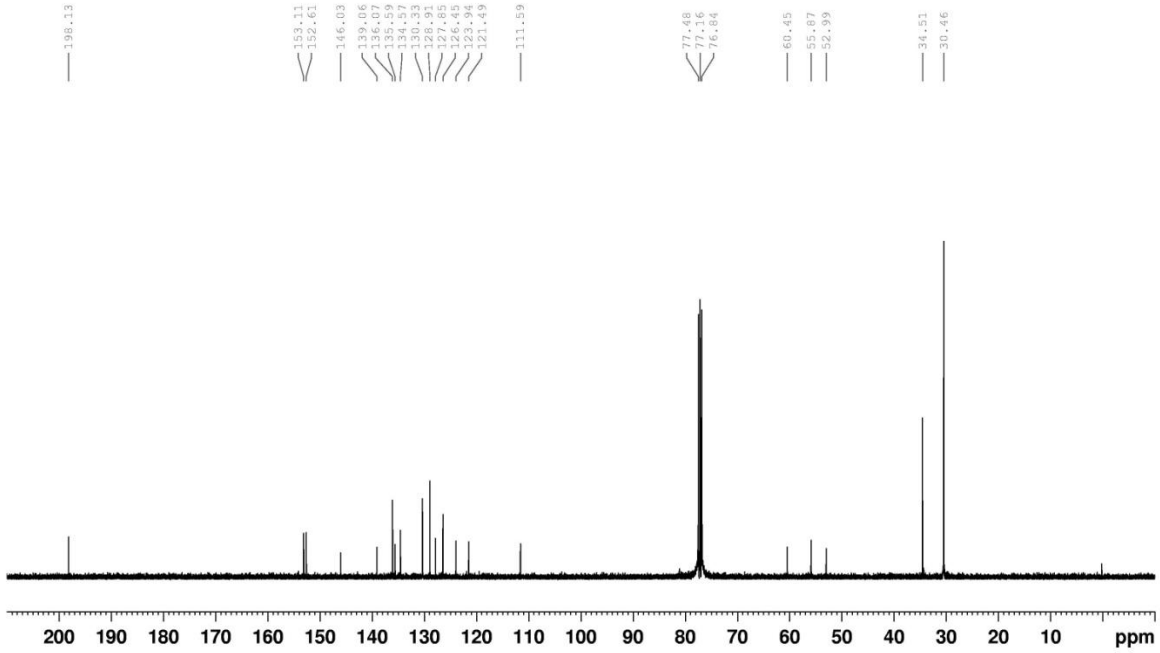




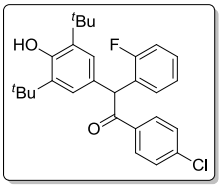
^{1}H, ^{13}C NMR Spectra of **19d**

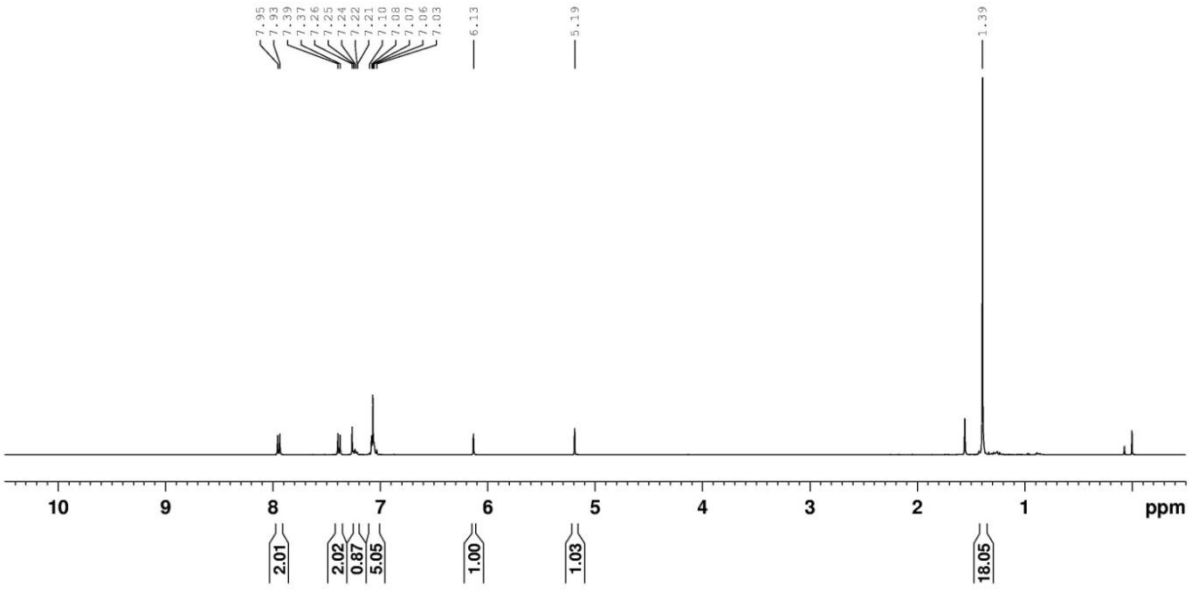


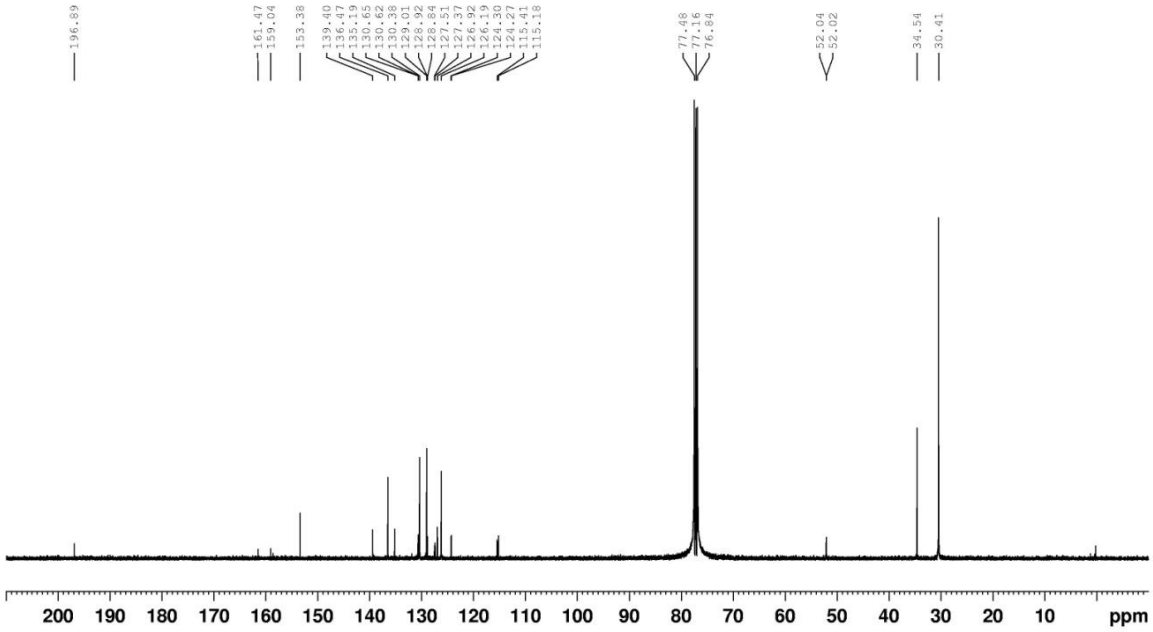




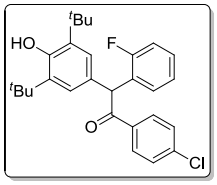
^{1}H, ^{13}C NMR Spectra of **19e**

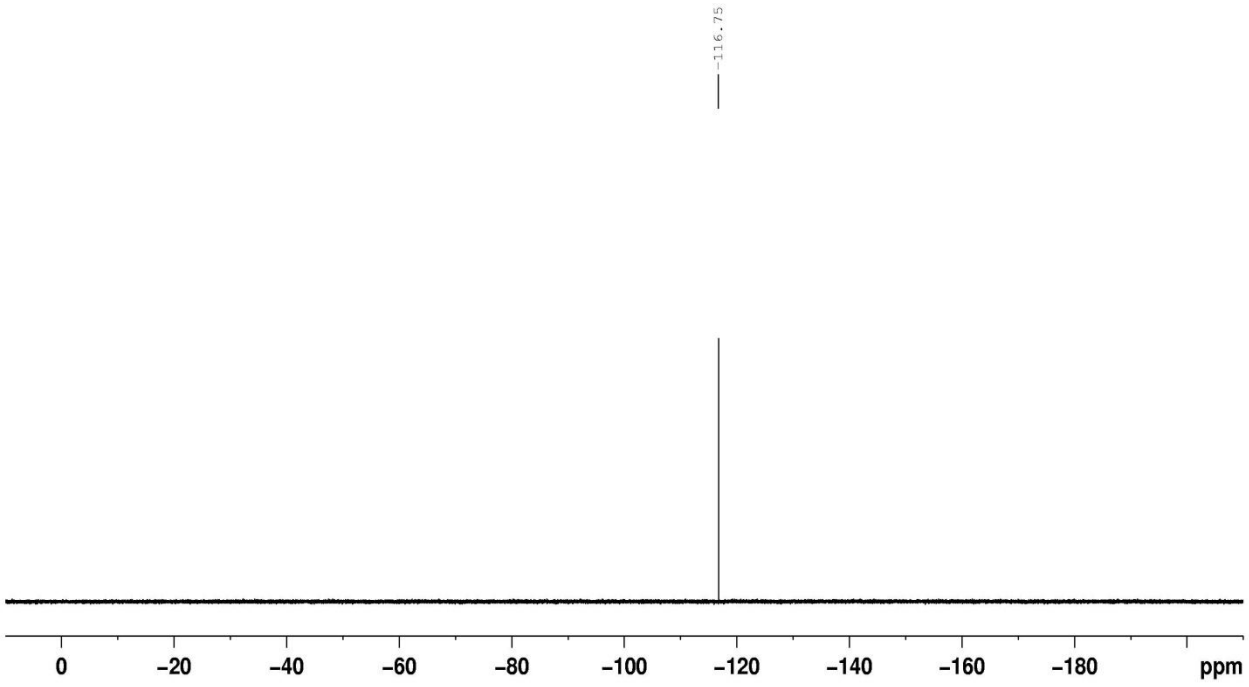




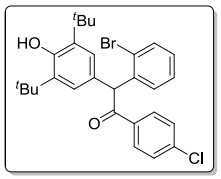


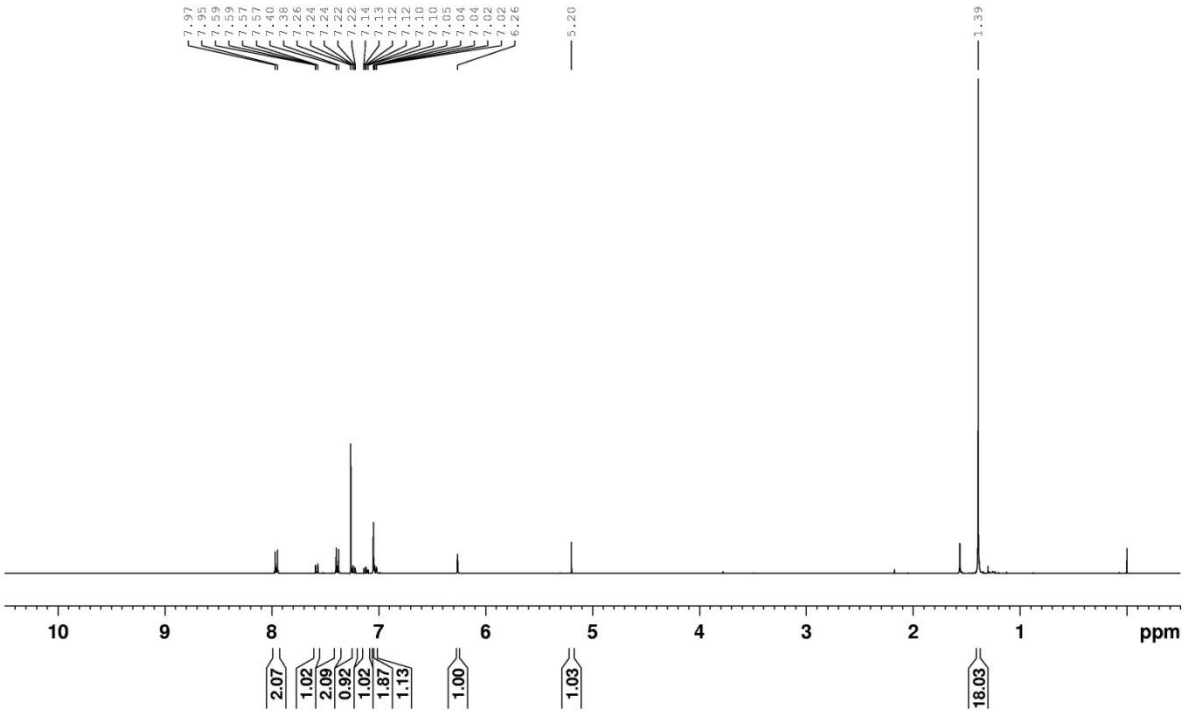
^{19}F NMR Spectra of **19e**

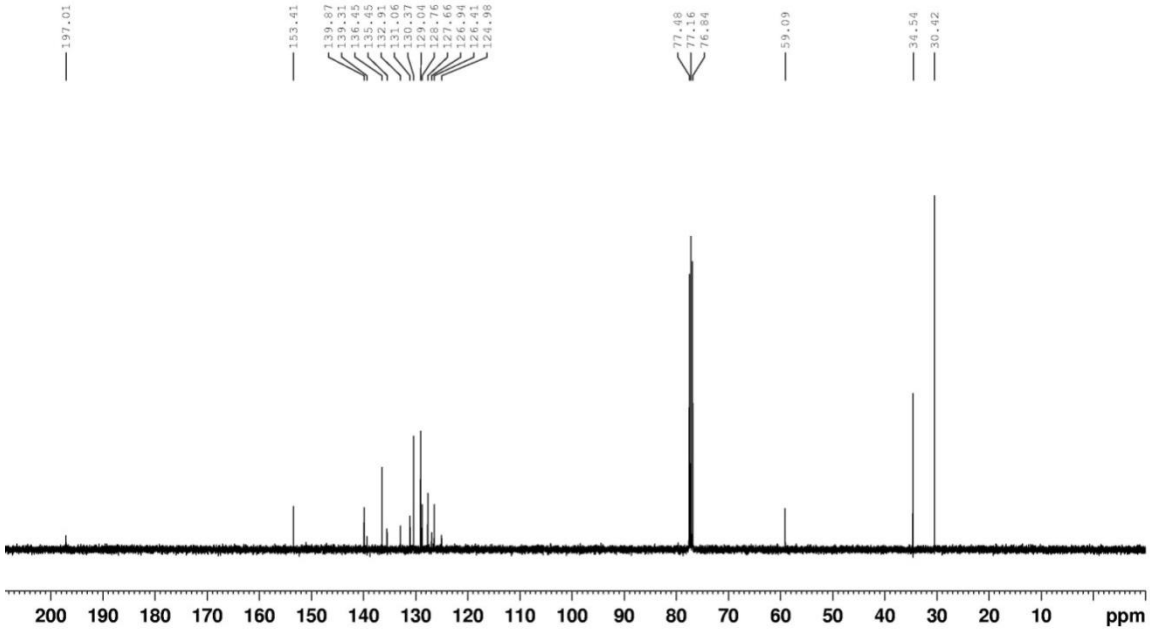




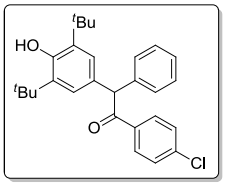
^{1}H, ^{13}C NMR Spectra of **19f**

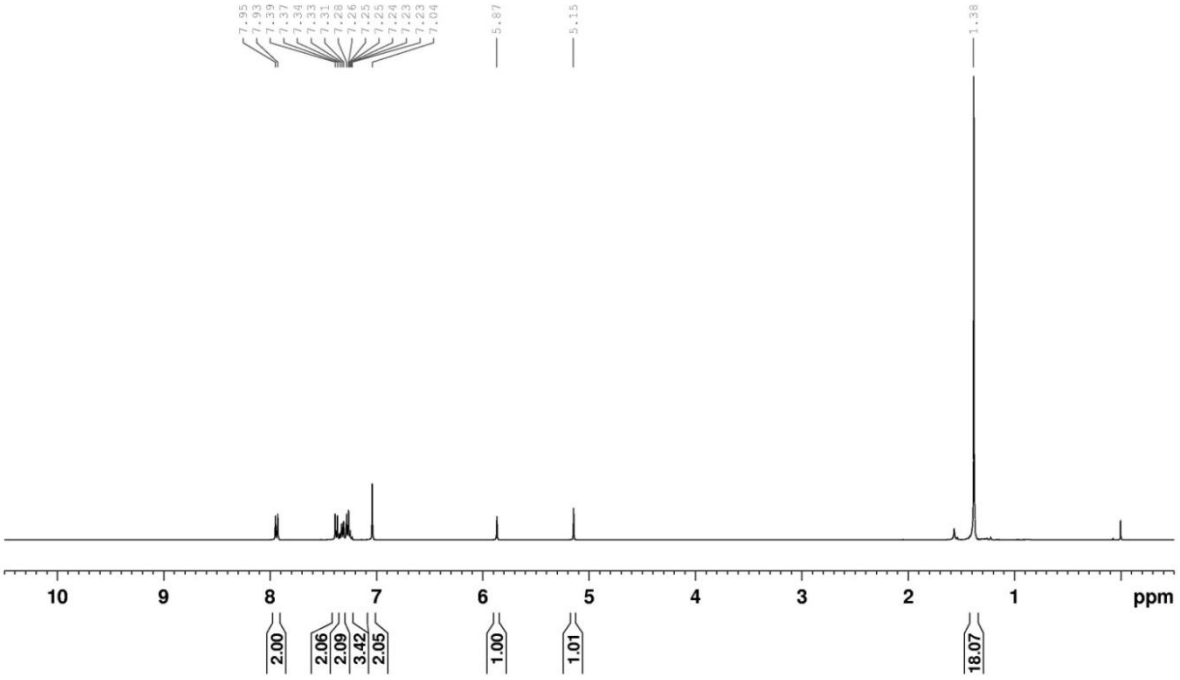


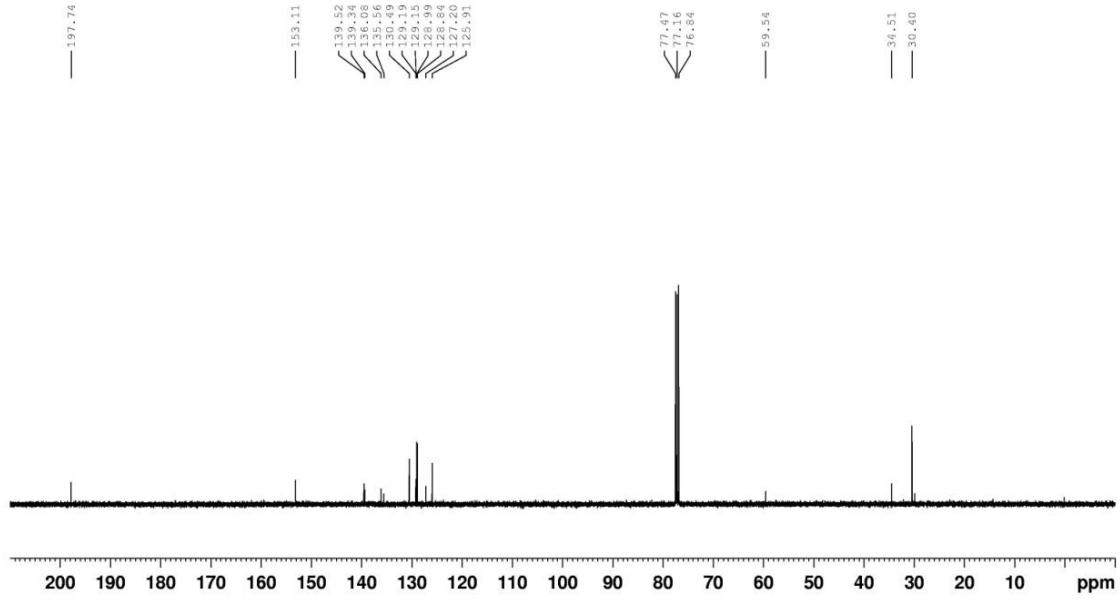




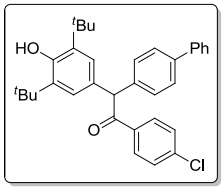
^{1}H, ^{13}C NMR Spectra of **19g**

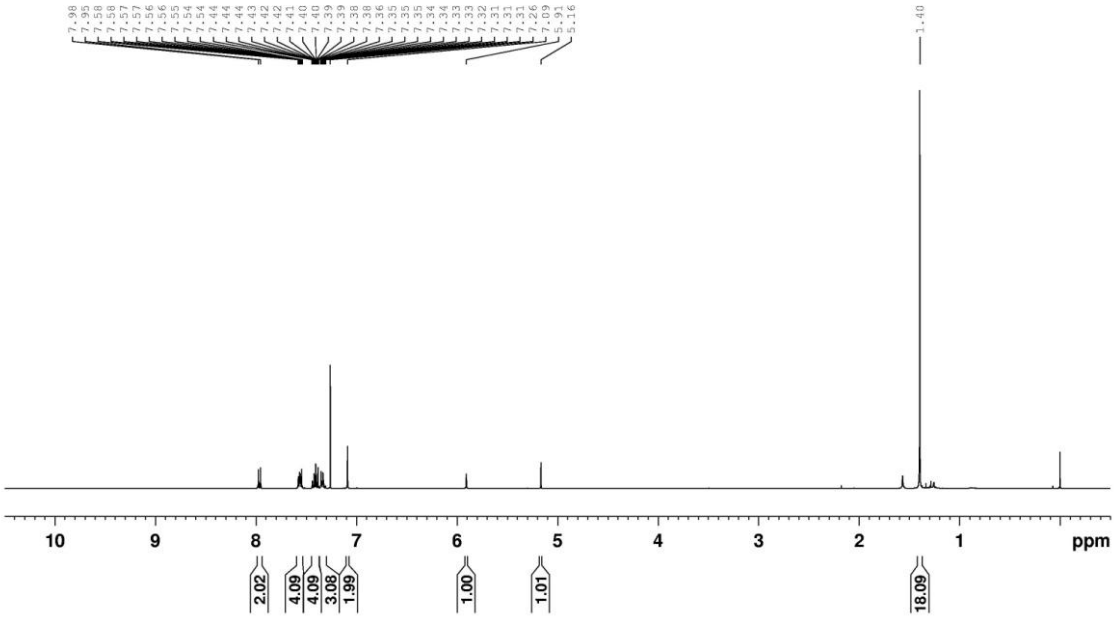


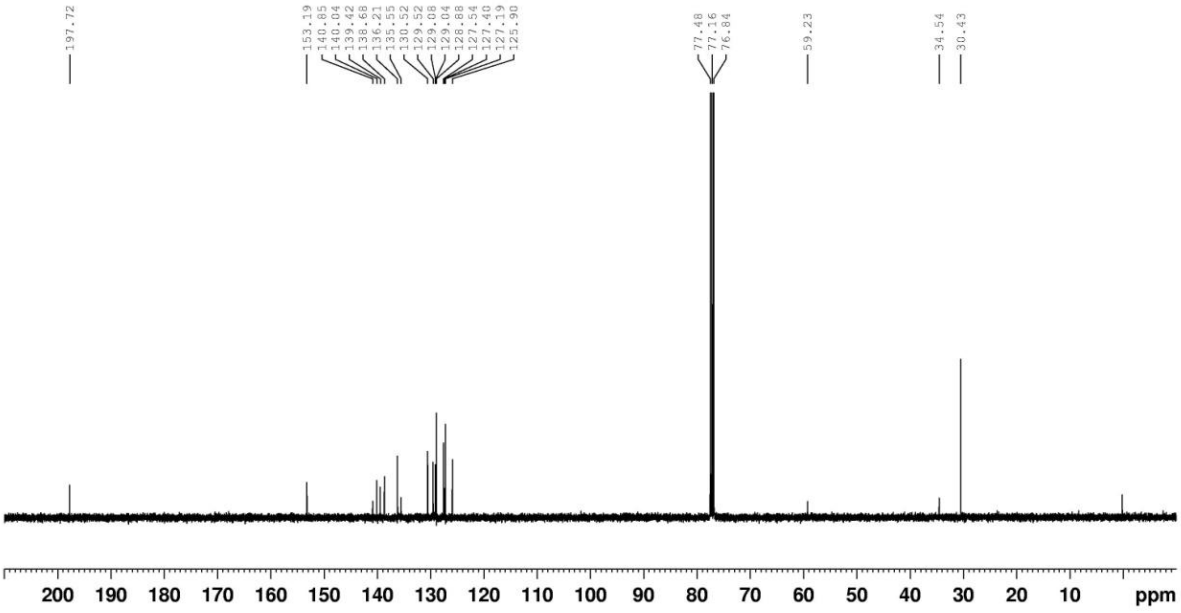




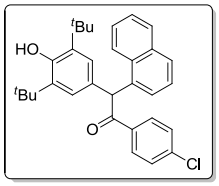
^{1}H, ^{13}C NMR Spectra of **19h**

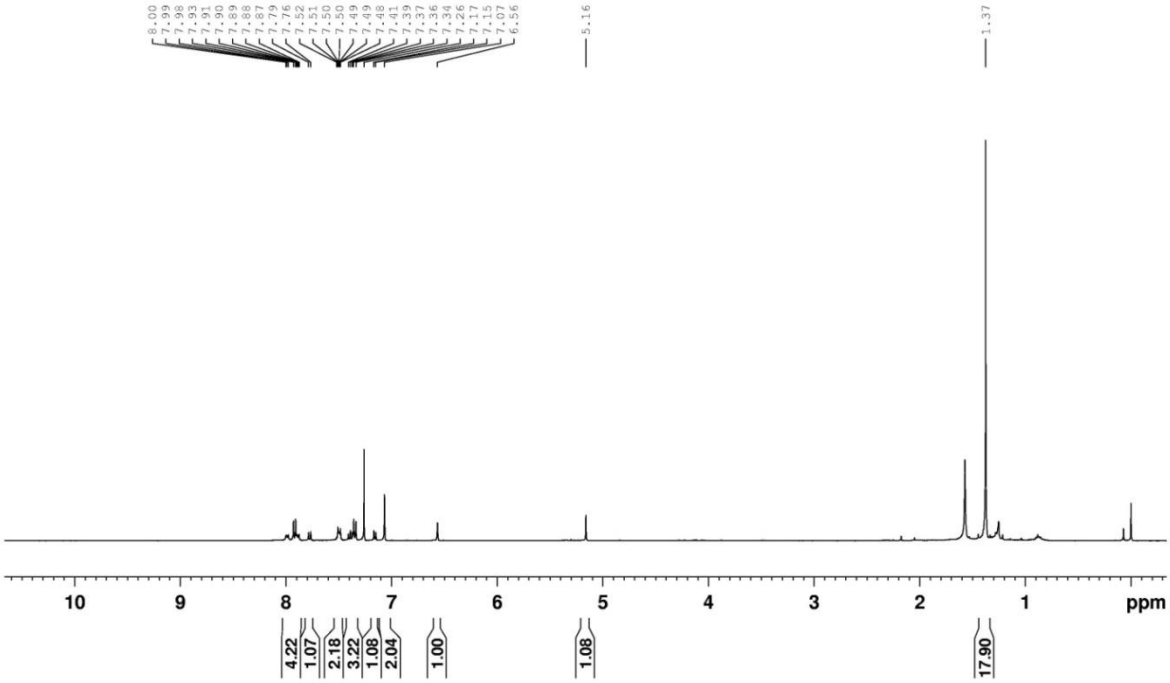


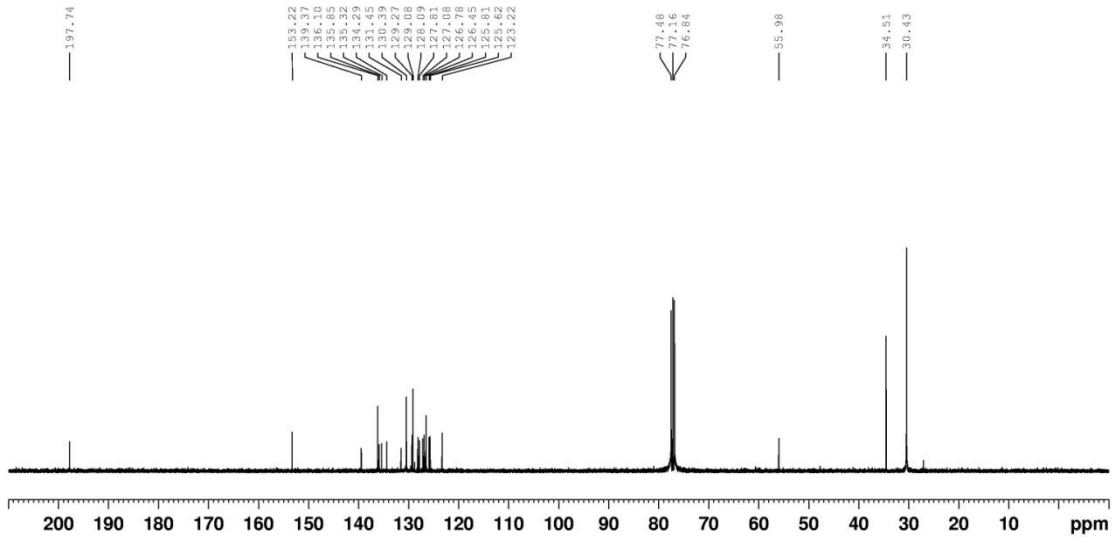




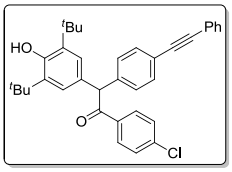
^{1}H, ^{13}C NMR Spectra of **19i**

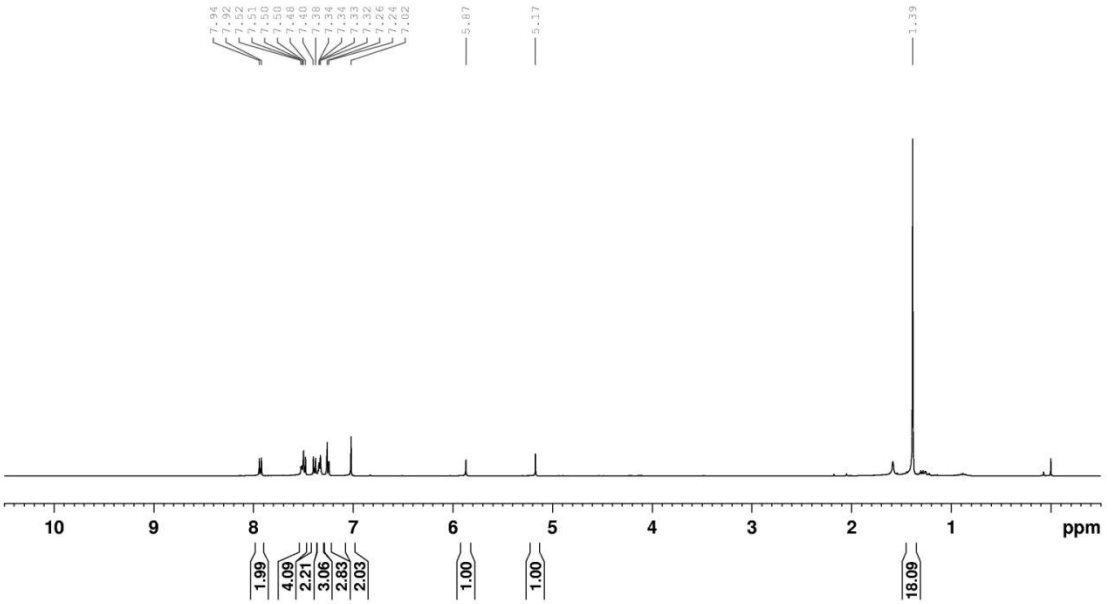


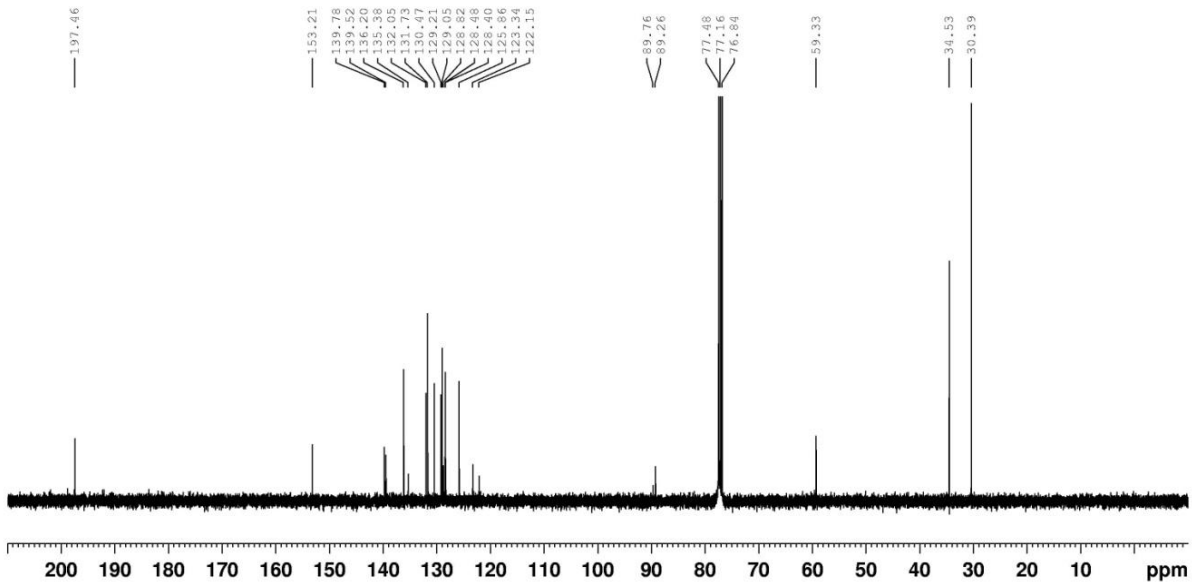




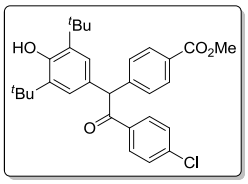
^{1}H, ^{13}C NMR Spectra of **19j**

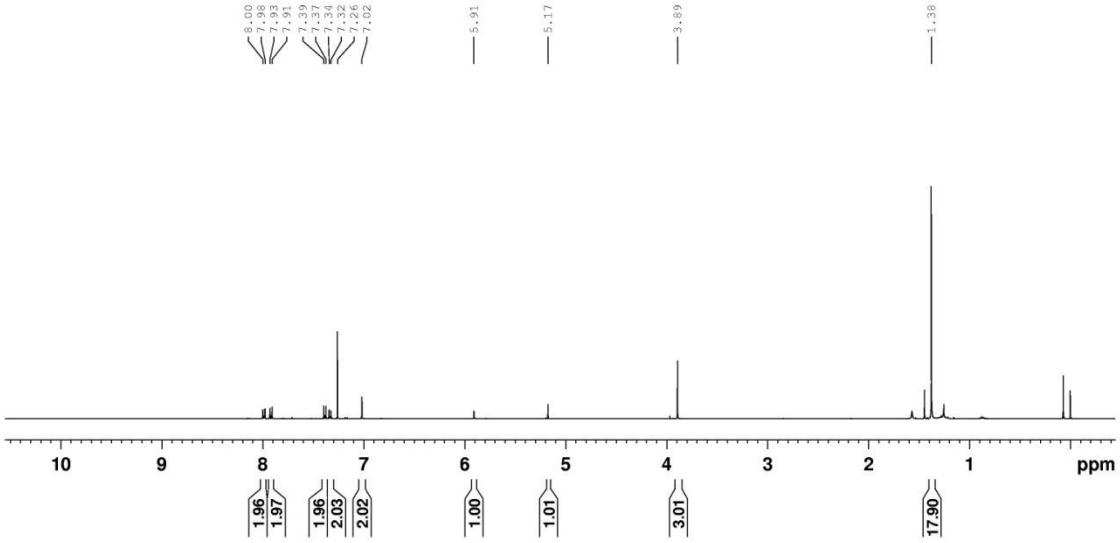


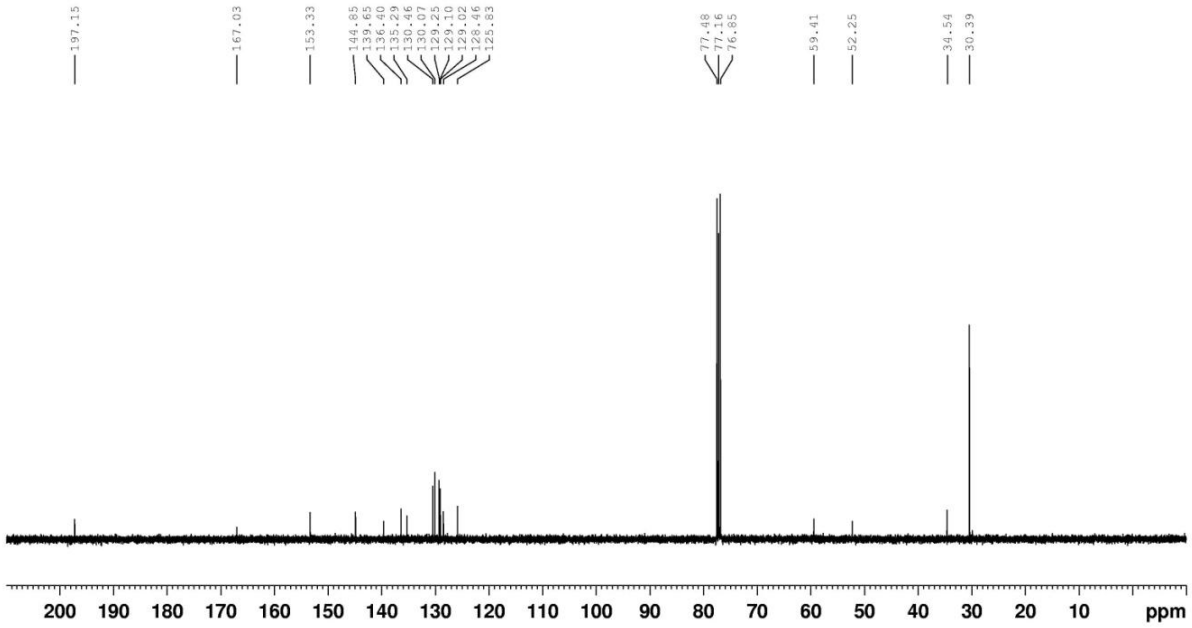




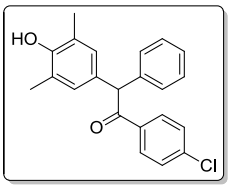
^{1}H, ^{13}C NMR Spectra of **19k**

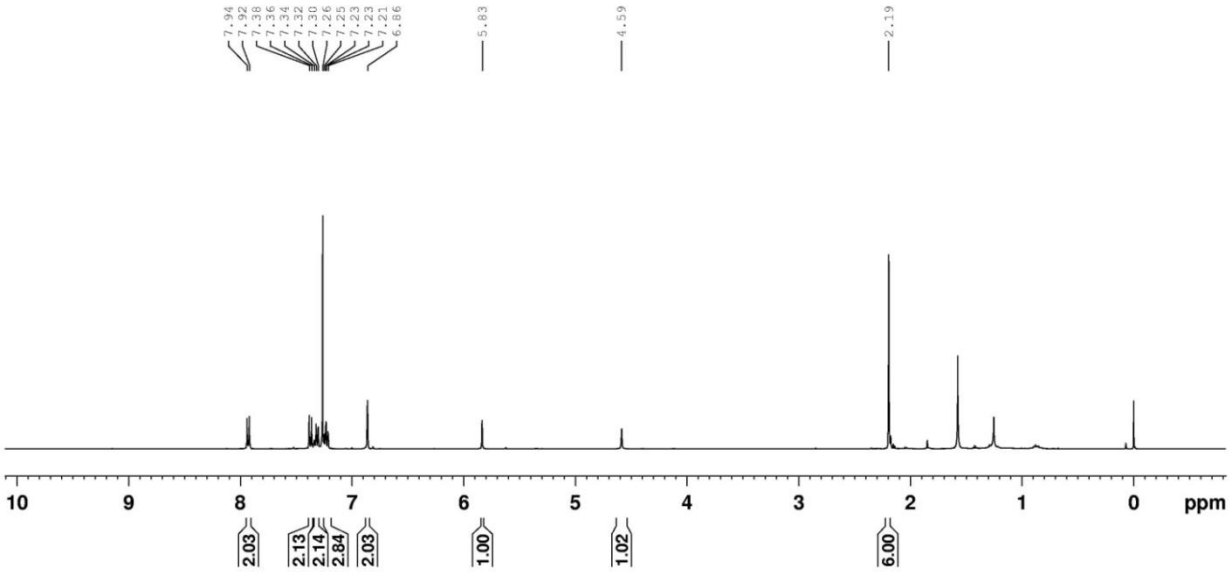


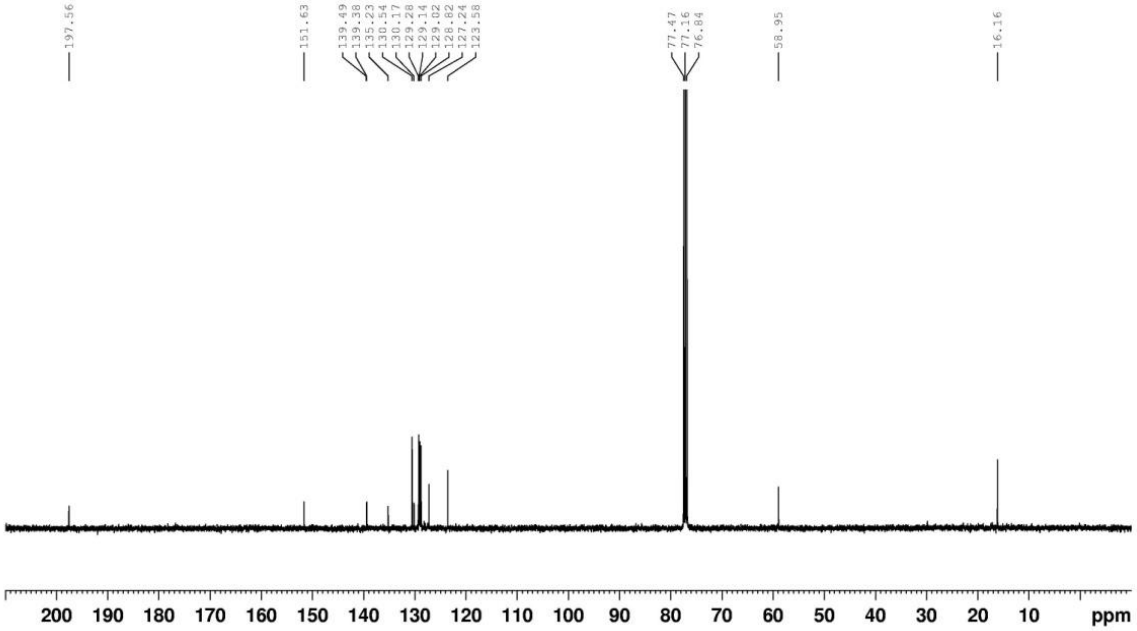




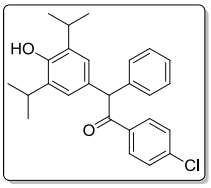
^{1}H, ^{13}C NMR Spectra of **19m**

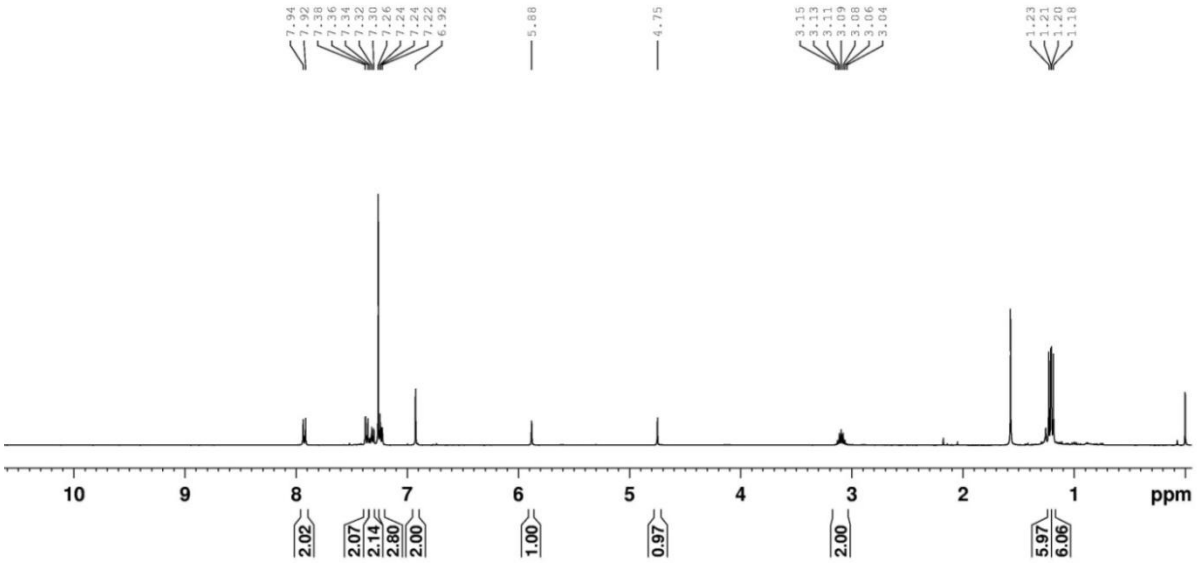


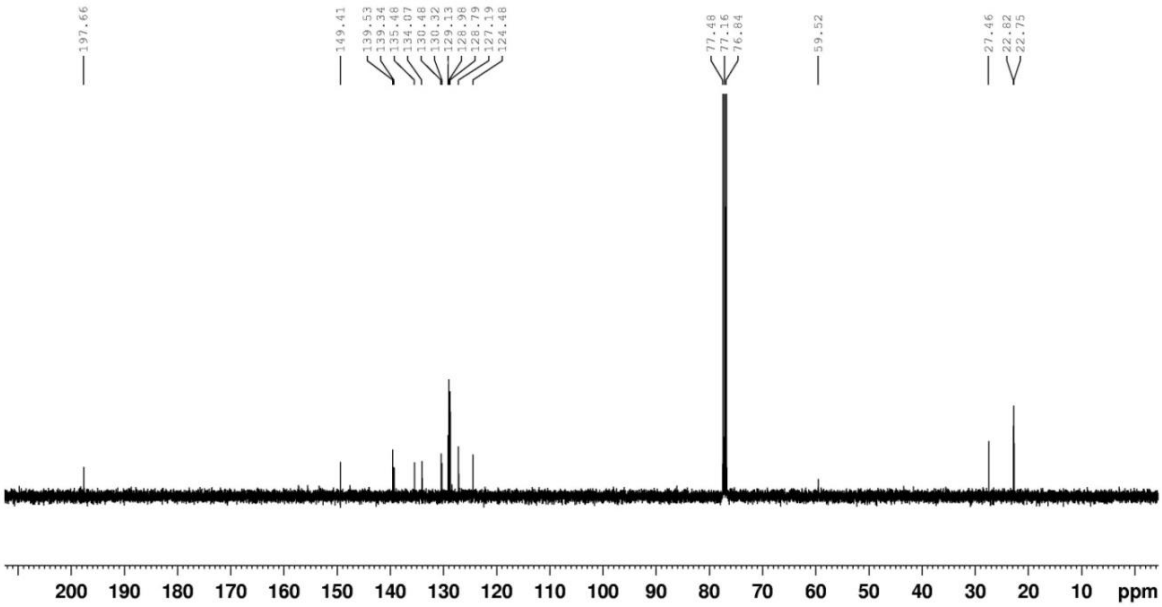




^{1}H, ^{13}C NMR Spectra of **19n**







3.6. References

[1] For recent reviews, see: (a) Enders, D.; Niemeier, O.; Henseler, A. *Chem. Rev*. **2007**, *107*, 5606. (b) Phillips, E. M.; Chan, A.; Scheidt, K. A. *Aldrichimica Acta* **2009**, *42*, 55. (c) Moore, J. L.; Rovis, T. *Top. Curr. Chem*. **2010**, *291*, 77. (d) Chiang, P.-C.; Bode, J. W. In N-*Heterocyclic Carbenes: From Laboratory Curiosities to Efficient Synthetic Tools*; Díez-González, S., Ed.; Royal Society of Chemistry: Cambridge, U. K., 2010; p 339. (e) Chiang, P.-C.; Bode, J. W. *TCI MAIL* **2011**, *149*, 2. (f) Biju, A. T.; Kuhl, N.; Glorius, F. *Acc. Chem. Res*. **2011**, *44*, 1182. (g) Nair, V.; Menon, R. S.; Biju, A. T.; Sinu, C. R.; Paul, R. R.; Jose, A.; Sreekumar, V. *Chem. Soc. Rev*. **2011**, *40*, 5336. (h) Campbell, C. D.; Ling, K. B.; Smith, A. D. In N-*Heterocyclic Carbenes in Transition Metal Catalysis and Organocatalysis*, Vol. 32; Cazin, C. S. J., Ed.; Springer; Dordrecht, 2011; p 262. (i) Bugaut, X.; Glorius, F. *Chem. Soc. Rev*. **2012**, *41*, 3511. (j) Izquierdo, J.; Hutson, G. E.; Cohen, D. T.; Scheidt, K. A. *Angew. Chem., Int. Ed*. **2012**, *51*, 11686. (k) Ryan, S. J.; Candish, L.; Lupton, D. W. *Chem. Soc. Rev*. **2013**, *42*, 4906. (l) Thai, K.; Sánchez-Larios, E.; Gravel, M. in *Comprehensive Enantioselective Organocatalysis: Catalysts, Reactions, and Applications*; Dalko, P. I., Ed.; Wiley-VCH: Weinheim, Germany, 2013; p 477. (m) Hopkinson, M. N.; Richter, C.; Schedler, M.; Glorius, F. *Nature* **2014**, *510*, 485. (n) Flanigan, D. M.; Romanov-Michailidis, F.; White, N. A.; Rovis, T. *Chem. Rev*. **2015**, *115*, 9307.

[2] (a) Arduengo, A. J., III; Dias, H. V. R.; Harlow, R. L.; Kline, M. *J. Am. Chem. Soc*. **1992**, *114*, 5530. (b) Heinemann, C.; Müller, T.; Apeloig, Y.; Schwarz, H. *J. Am. Chem. Soc*. **1996**, *118*, 2023. (c) Arduengo, A. J., III *Acc. Chem. Res*. **1999**, *32*, 913. (d) Bourissou, D.; Guerret, O.; Gabbaï, F. P.; Bertrand, G. *Chem. Rev*. **2000**, *100*, 39. (e) Crudden, C. M.; Allen, D. P. *Coord. Chem. Rev*. **2004**, *248*, 2247.

[3] (a) Canac, Y.; Soleilhavoup, M.; Conejero, S.; Bertrand, G. *J. Organomet. Chem*. **2004**, *689*, 3857. (b) Vignolle, J.; Cattoën, X.; Bourissou, D. *Chem. Rev*. **2009**, *109*, 3333.

[4] (a) Johnson, L. E.; DuPré, D. B. *J. Phys. Chem. A* **2007**, *111*, 11066. (b) Johnson, L. E.; DuPré, D. B. *J. Phys. Chem. A* **2008**, *112*, 7448.

[5] (a) Yoshida, Z.; Konishi, H.; Sawada, S.; Ogoshi, H. *J. Chem. Soc., Chem. Commun*., **1977**, 850. (b) Weiss, R.; Priesner, C.; Wolf, H. *Angew. Chem., Int. Ed. Engl*. **1978**, *17*, 446. (c) Konishi, H.; Matsumoto, S.; Kamitori, Y.; Ogoshi, H.; Yoshida, Z. *Chem. Lett*. **1978**, 241.

(d) Weiss, R.; Hertel, M.; Wolf, H. *Angew. Chem., Int. Ed. Engl*. **1979**, *18*, 473. (e) Yoshida, Z. *Pure Appl. Chem*. **1982**, *54*, 1059.

[6] (a) Komatsu, K.; Kitagawa, T. *Chem. Rev*. **2003**, *103*, 1371. (b) Herrmann, W. A.; Őfele, K.; Taubmann, C.; Herdtweck, E.; Hoffmann, S. D. *J. Organomet. Chem*. **2007**, *692*, 3846. (c) Kuchenbeiser, G.; Donnadieu, B.; Bertrand, G. *J. Organomet. Chem*. **2008**, *693*, 899. (d) Kuchenbeiser, G.; Soleilhavoup, M.; Donnadieu, B.; Bertrand, G. *Chem.—Asian. J*. **2009**, *4*, 1745. (e) Őfele, K.; Tosh, E.; Taubmann, C.; Herrmann, W. A. *Chem. Rev.* **2009**, *109*, 3408. (f) Melaimi, M.; Soleilhavoup, M.; Bertrand, G. *Angew. Chem., Int. Ed*. **2010**, *49*, 8810. (g) Malik, H. A.; Sormunen, G. J.; Montgomery, J. *J. Am. Chem. Soc*. **2010**, *132*, 6304. (h) Rodrigo, S. K.; Guan, H. *J. Org. Chem*. **2012**, *77*, 8303.

[7] (a) Lavallo, V.; Canac, Y.; Donnadieu, B.; Schoeller, W. W.; Bertrand, G. *Science* **2006**, *312*, 722. (b) Lavallo, V.; Ishida, Y.; Donnadieu, B.; Bertrand, G. *Angew. Chem., Int. Ed*. **2006**, *45*, 6652.

[8] Wass, D. F.; Haddow, M. F.; Hey, T. W.; Orpen, A. G.; Russell, C. A.; Wingad, R. L.; Green, M. *Chem. Commun*. **2007**, 2704.

[9] Kozma, Á.; Petuškova, J.; Lehmann, C. W.; Alcarazo, M. *Chem. Commun*. **2013**, *49*, 4145.

[10] Bidal, Y. D.; Lesieur, M.; Melaimi, M.; Cordes, D. B.; Slawin, A. M. Z.; Bertrand, G.; Cazin, C. S. J. *Chem. Commun.* **2015**, *51*, 4778.

[11] Holschumacher, D.; Hrib, C. G.; Jones, P. G.; Tamm, M. *Chem. Commun*. **2007**, 3661.

[12] Wilde, M. M. D.; Gravel, M. *Angew. Chem., Int. Ed*. **2013**, *52*, 12651.

[13] Wilde, M. M. D.; Gravel, M. *Org. Lett*. **2014**, *16*, 5308.

[14] Ramanjaneyulu, B. T.; Mahesh, S.; Anand, R. V. *Org. Lett*. **2015**, *17*, 6.

[15] (a) Muratake, H.; Hayakawa, A.; Natsume, M. *Tetrahedron Lett*. **1997**, *38*, 7577. (b) Lu, M. C.; Wung, W. E.; Shih, L. B.; Callejas, S.; Gearien, J. E.; Thompson, E. B. *J. Med. Chem*. **1987**, *30*, 273. (c) Wang, J.-Q.; Miller, M. A.; Mock, B. H.; Lopshire, J. C.; Groh, W. J.; Zipes, D. P.; Hutchins, G. D.; Zheng, Q.-H. *Bioorg. Med. Chem. Lett*. **2005**, *15*, 4510.

[16] (a) Palucki, M.; Buchwald, S. L. *J. Am. Chem. Soc*. **1997**, *119*, 11108. (b) Hamann, B. C.; Hartwig, J. F. *J. Am. Chem. Soc*. **1997**, *119*, 12382. (c) For selected reviews, see: (i) Lloyd-Jones, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 953. (ii) Culkin, D. A.; Hartwig, J. F. *Acc. Chem. Res.* **2003**, *36*, 234. (iii) Burtoloso, A. C. B. *Synlett* **2009**, 320. (iv) Bellina, F.; Rossi, R. *Chem. Rev*. **2010**, *110*, 1082. (v) Johansson, C. C. C.; Colacot, T. J. *Angew. Chem., Int.*

Ed. **2010**, *49*, 676. (vi) Danoun, G.; Tlili, A.; Monnier, F.; Taillefer, M. *Angew. Chem., Int. Ed*. **2012**, *51*, 12815.

[17] (a) Baran, P. S.; Richter, J. M. *J. Am. Chem. Soc*. **2004**, *126*, 7450. (b) Tambar, U. K.; Stoltz, B. M. *J. Am. Chem. Soc*. **2005**, *127*, 5340. (c) Baran, P. S.; Richter, J. M.; Lin, D. W. *Angew. Chem., Int. Ed.* **2005**, *44*, 609. (d) Xia, J.; Brown, L. E.; Konopelski, J. P. *J. Org. Chem*. **2007**, *72*, 6885. (e) Mohanan, K.; Coquerel, Y.; Rodriguez, J. *Org. Lett*. **2012**, *14*, 4686. (f) Huang, X.; Patil, M.; Farès, C.; Thiel, W.; Maulide, N. *J. Am. Chem. Soc*. **2013**, *135*, 7312. (g) More, N. Y.; Jeganmohan, M. *Org. Lett*. **2014**, *16*, 804.

[18] Padmanaban, M.; Biju, A. T.; Glorius, F. *Org. Lett*. **2011**, *13*, 98.

[19] Maji, B.; Breugst, M.; Mayr, H. *Angew. Chem., Int. Ed*. **2011**, *50*, 6915.

[20] (a) Izquierdo, J.; Orue, A.; Scheidt, K. A. *J. Am. Chem. Soc*. **2013**, *135*, 10634. (b) Lee, A.; Scheidt, K. A. *Chem. Commun*. **2015**, *51*, 3407.

[21] Lv, H.; Jia, W.-Q.; Sun, L.-H.; Ye, S. *Angew. Chem., Int. Ed*. **2013**, *52*, 8607.

[22] Law, K. R.; McErlean, C. S. P. *Chem.—Eur. J*. **2013**, *19*, 15852.

[23] For selected examples of other transformations where *p*-quinone methides were used as electrophiles, see: (a) Hart, D. J.; Cain, P. A.; Evans, D. A. *J. Am. Chem. Soc*. **1978**, *100*, 1548. (b) Angle, S. R.; Turnbull, K. D. *J. Am. Chem. Soc*. **1989**, *111*, 1136. (c) Angle, S. R.; Arnaiz, D. O. *J. Org. Chem*. **1992**, *57*, 5937. (d) Baik, W.; Lee, H. J.; Jang, J. M.; Koo, S.; Kim, B. H. *J. Org. Chem*. **2000**, *65*, 108. (e) Breugst, M.; Mayr, H. *J. Am. Chem. Soc*. **2010**, *132*, 15380. (f) Nigst, T. A.; Ammer, J.; Mayr, H. *Angew. Chem., Int. Ed*. **2012**, *51*, 1353. (g) Breugst, M.; Bautista, F. C.; Mayr, H. *Chem.—Eur. J*. **2012**, *18*, 127. (h) Chu, W.-D.; Zhang, L.-F.; Bao, X.; Zhao, X.-H.; Zeng, C.; Du, J.-Y.; Zhang, G.-B.; Wang, F.-X.; Ma, X.-Y.; Fan, C.-A. *Angew. Chem., Int. Ed*. **2013**, *52*, 9229. (i) Caruana, L.; Kniep, F.; Johansen, T. K.; Poulsen, P. H.; Jørgensen, K. A. *J. Am. Chem. Soc*. **2014**, *136*, 15929. (j) Reddy, V.; Anand, R. V. *Org. Lett*. **2015**, *17*, 3390.

[24] For selected prior reports on similar kind of observations, see: (a) Chiang, P.-C.; Kaeobamrung, J.; Bode, J. W. *J. Am. Chem. Soc.* **2007**, *129*, 3520. (b) Enders, D.; Han, J.; Henseler, A. *Chem. Commun.* **2008**, 3989. (c) Enders, D.; Henseler, A. *Adv. Synth. Catal.* **2009**, *351*, 1749.

[25] Breslow, R. *J. Am. Chem. Soc*. **1958**, *80*, 3719.

[26] (a) Thomson, J. E.; Campbell, C. D.; Concellon, C.; Duguet, N.; Rix, K.; Slawin, A. M. Z.; Smith, A. D. *J. Org. Chem*. **2008**, *73*, 2784. (b) Zhao, H.; Foss, Jr, F. W.; Breslow, R. *J. Am. Chem. Soc.* **2008**, *130*, 12590. (c) Ueng, S.-H.; Fensterbank, L.; Lacôte, E.; Malacria, M.; Curran, D. P. *Org. Lett.* **2010**, *12*, 3002. (d) Diba, A. K.; Noll, C.; Richter, M.; Gieseler, M. T.; Kalesse, M. *Angew. Chem., Int. Ed.* **2010**, *49*, 8367.

PART-B

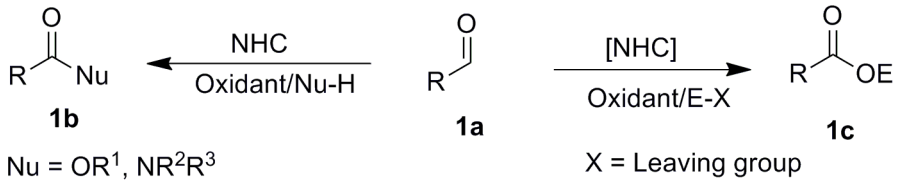
Organic transformations under oxidative N-heterocyclic carbene (NHC) catalysis

Chapter 1

General introduction on the oxidative N-heterocyclic carbene catalysis

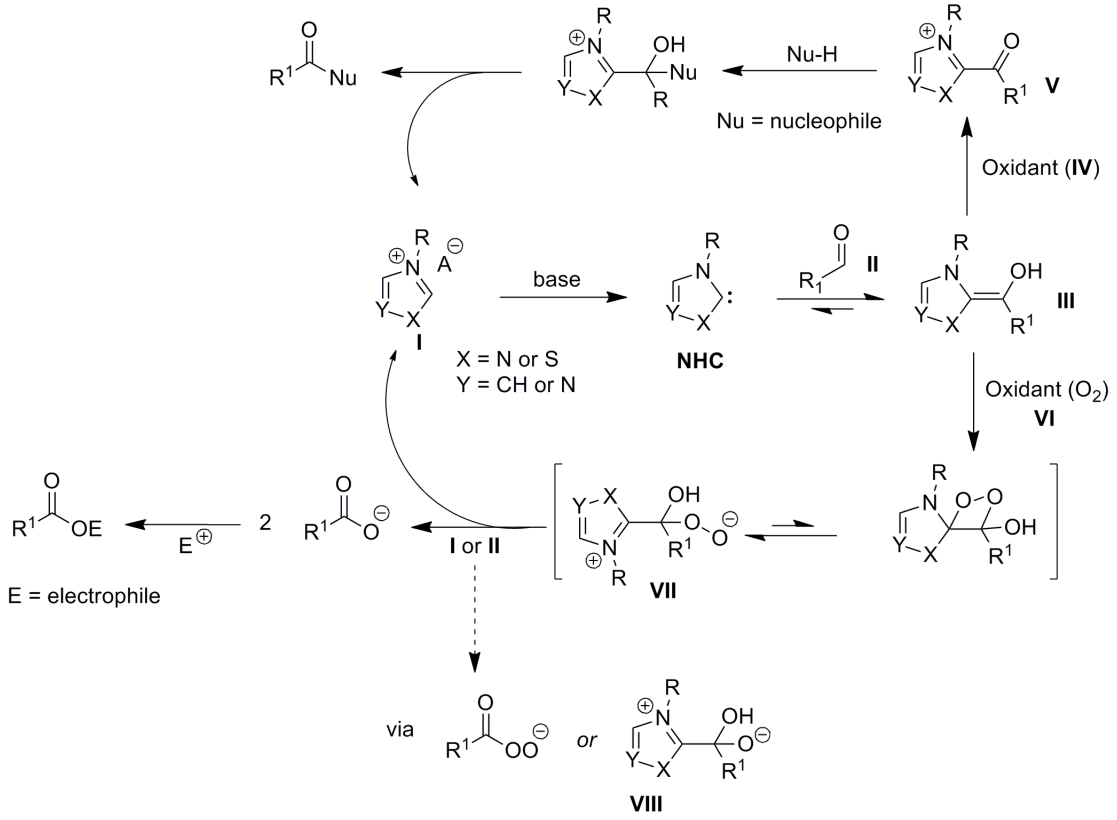
1.1. Introduction

Over the past decade, much efforts have been devoted to the development of oxidative NHC catalysis, an interesting sub-area of NHC catalysis for the construction of carbon–heteroatom bonds (C-O, C-N), where NHC was used in combination with external oxidants. Many interesting and important protocols have been developed by employing a variety of NHCs in the presence of various oxidation agents (Scheme 1).[1a]



Scheme 1

These oxidative NHC-catalyzed reactions generally proceed *via* an initial formation of Breslow intermediate **III** from NHC **I** and aldehyde **II** followed by oxidation. These oxidation reactions can either occur in two different path ways. Path **A** involves oxidation *via* transfer of two electrons from Breslow intermediate to the oxidant **IV** resulting in the formation of an electrophilic acyl azoliumion intermediate **V**, which can react with nucleophiles with the elimination of azolium ion. Whereas Path **B** involves oxidation *via* oxygen atom transfer from the oxidant **VI**, generally molecular oxygen, to the Breslow intermediate resulting zwitterionic peroxide intermediate **VII** or azolium carboxylate species **VIII**, which then react with suitable electrophiles. Many fundamental oxidation reactions have been reported through oxidative NHC catalysis, which are believed to follow either one of the mechanistic path ways as shown in scheme 2.



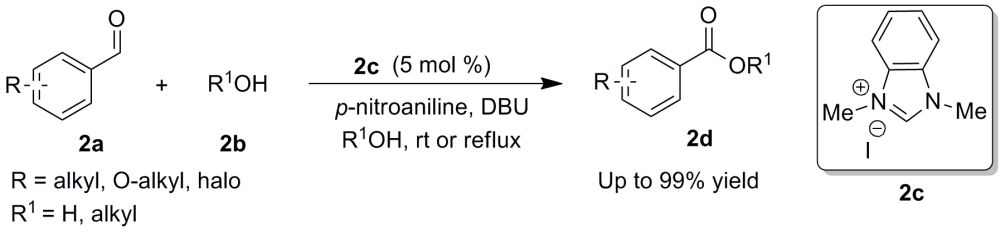
Scheme 2

1.2. Literature review

This remarkable oxidative NHC catalysis has been successfully applied in fundamental transformations such as esterification, acid formation, lactone formation, and lactam formation, etc. Some of the NHC catalyzed oxidative transformations are discussed below.

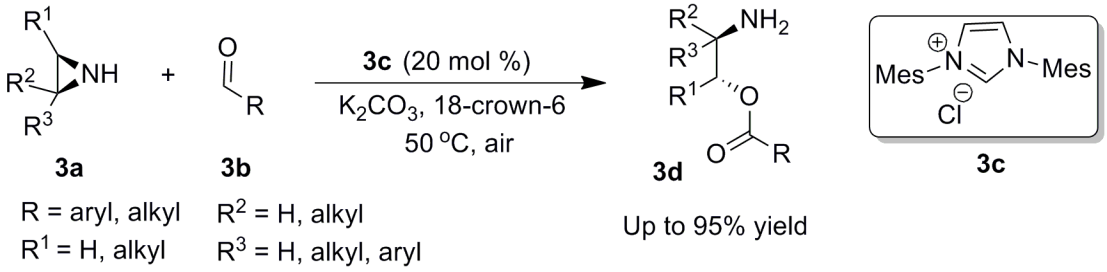
1.2.1. Construction of C-O bond through oxidative NHC catalysis

In 1997, Miyashita and co-workers reported the oxidative arylation with aromatic aldehydes with aliphatic alcohols through NHC catalysis.[1b] By employing the 1,3-dimethyl benzimidazolium iodide (**2c**) as NHC precursor and *p*-nitroaniline as an external oxidant, various aldehydes (**2a**) were treated with different aliphatic alcohols (**2b**), and the corresponding alkyl esters **2d** were obtained in good yields (Scheme 3).



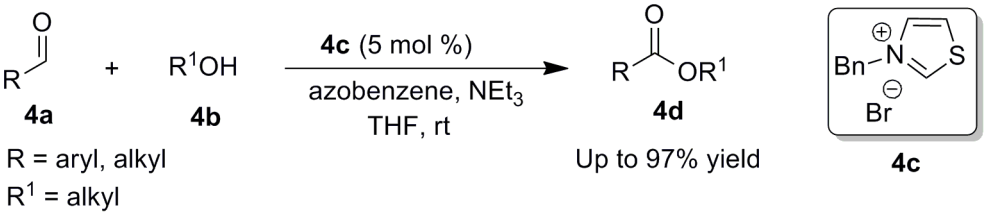
Scheme 3

Synthesis of carboxylates of 1,2-amino alcohols from aziridines **3a** and aldehydes **3b** through oxidative NHC **3c** catalysis has been reported by Chen and co-workers in 2006.[2] This oxidative method afforded the carboxylates of 1,2-amino alcohols **3d** in moderate to good yields (Scheme 4).



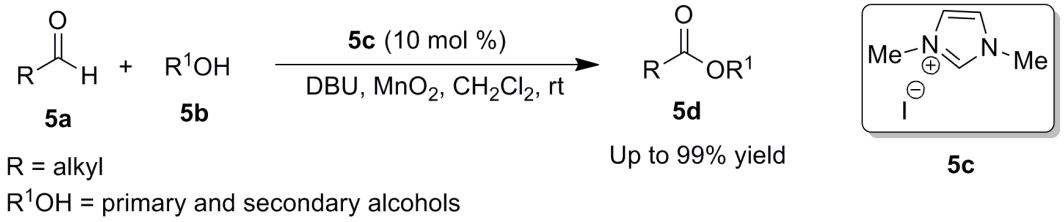
Scheme 4

A direct method was developed by Connon and co-workers for the oxidative esterification of aldehydes (**4a**) with primary and secondary alcohols (**4b**) using 3-benzyl thiazolium bromide **4c** as a NHC precursor.[3] In this case, azobenzene was used as an external oxidant. This method allowed to access alkyl esters (**4d**) in moderate to good yields (Scheme 5).



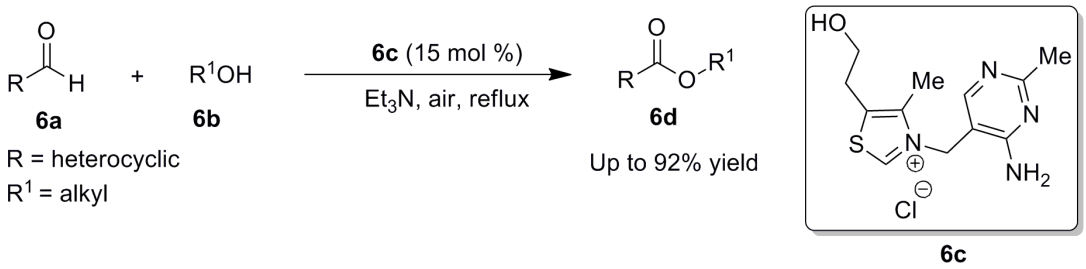
Scheme 5

In 2008, Scheidt and co-workers reported NHC catalyzed oxidative method for the conversion of aliphatic aldehydes (**5a**) to esters (**5d**).[4] Manganese (IV) oxides was used as an oxidant. In this case, the corresponding aliphatic esters **5d** were obtained in good to excellent yields within short reaction times (Scheme 6).



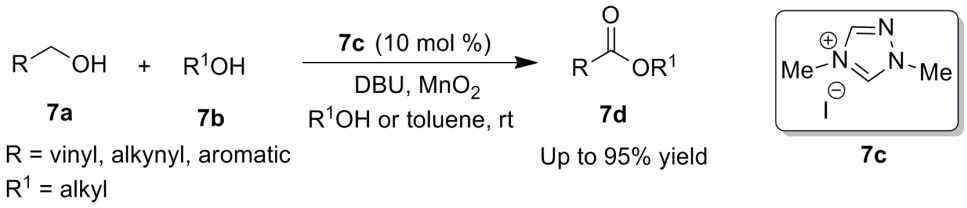
Scheme 6

Later the Goswami and co-workers reported a modified procedure for the synthesis of esters containing heterocyclic core starting from hetero aromatic aldehydes (**6a**) and alcohols (**6b**).[5] A wide range of hetero aromatic aldehydes, particularly electron withdrawing hetero aromatic aldehydes, were converted to their corresponding esters (**6d**) in high yield (Scheme 7).



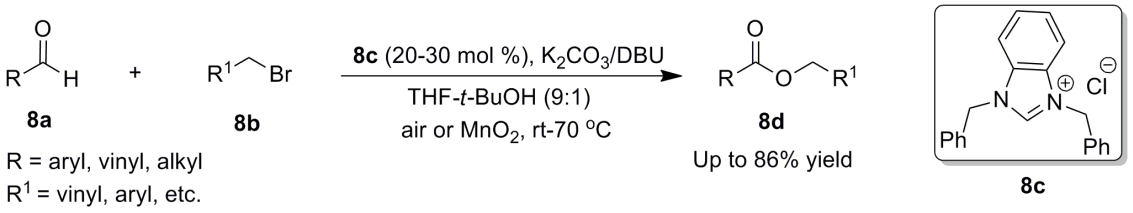
Scheme 7

Scheidt and co-workers extended the oxidative NHC catalysis for the one-pot oxidative esterification of benzylic alcohols with other alcohols to synthesize benzoate esters **7d** (Scheme 8).[6] Initially, MnO_2 oxidizes the benzyl alcohol **7a** into benzaldehyde, which then undergoes usual oxidative esterification reaction with another alcohol **7b**.



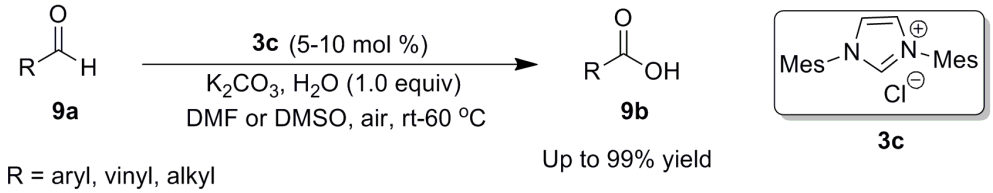
Scheme 8

In 2011, Liu and co-workers described the esterification of various aromatic and α,β-unsaturated aldehydes with cinnamyl bromides or benzyl halides through oxidative NHC catalysis.[7] A wide range of aldehydes **8a** were treated with various cinnamyl bromides **8b** or benzyl halides **8b** in the presence of 1,3-dibenzyl benzimidazolium chloride (**8c**) serves as NHC precursor, in combination with K_2CO_3/DBU as bases, and air as an oxidant (Scheme 9).



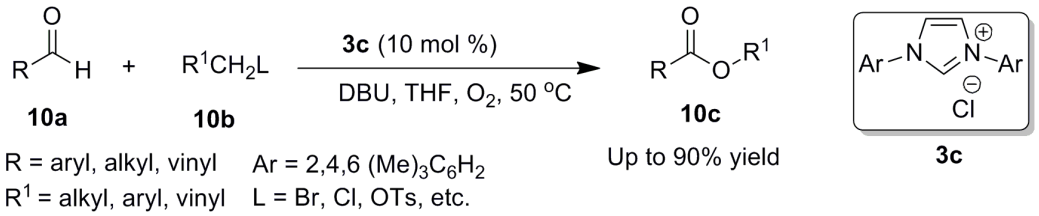
Scheme 9

Bode and co-workers developed a protocol for the conversion of various aldehydes to their corresponding acids under aerobic oxidative NHC conditions. IMes.HCl **3c** was used as precatalyst for this purpose.[8] Aromatic aldehydes **9a** were converted to corresponding acids **9b** in reasonable isolated yields, where as cinnamaldehyde was converted to cinnamic acid in quantitative yield. However, this protocol did not work well in the cases of aliphatic and sterically hindered aldehydes, as the respected acids were obtained in lower yields under the optimized reaction conditions (Scheme 10).



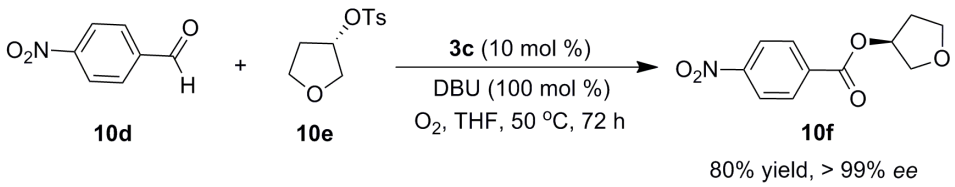
Scheme 10

Recently, Hui and co-workers reported an alternative method for a direct oxidative esterification of various aldehydes **10a** with various alkyl halides (or tosylates) **10b** in the presence of NHC derived from 1,3-dimesityl imidazolium chloride (**3c**) under oxygen atmosphere (Scheme 11).[9]



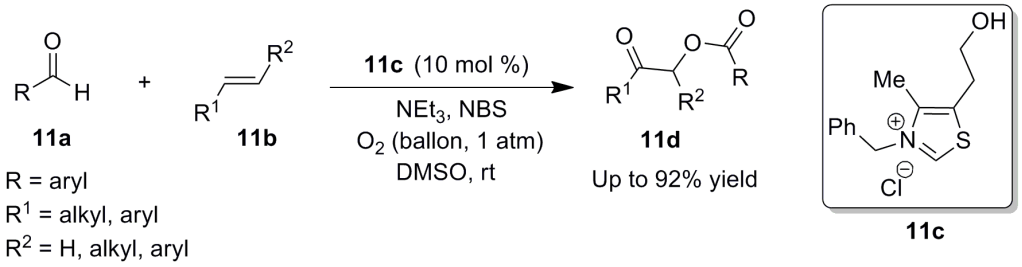
Scheme 11

When the reaction was performed between 4-nitrobenzaldehyde (**10d**) and (*S*)-tetrahydrofuran-3-yl-4-methylbenzenesulfonate **10e** as starting materials, the product (*R*)-tetrahydrofuran-3-yl-4-nitrobenzoate **10f** was obtained in 80% yield with more than 99% *ee* under the optimized reaction conditions. This experiment clearly suggested that the oxidative esterification of the aldehyde with alkyl 4-methylbenzenesulfonate was a typical S_N2 reaction under the NHC-catalyzed reaction conditions (Scheme 12).



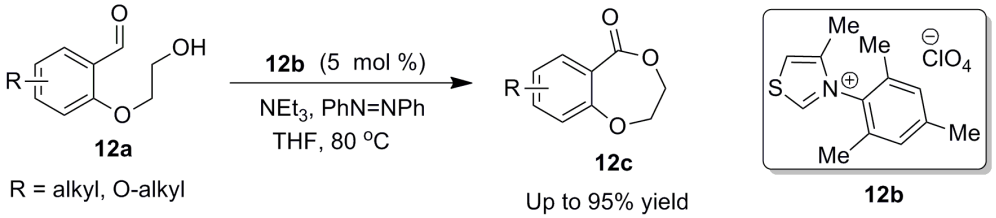
Scheme 12

A novel organocatalytic oxidative process was developed by Sudalai and co-workers for the synthesis of α-acyloxy ketones.[10] A variety of aromatic aldehydes **11a** was treated with various olefins **11b** in the presence of thiazolium salt **11c** as an NHC precursor in combination with NBS/DMSO/O_2 as oxidants. In this case, the corresponding α-acyloxy ketones **11d** were obtained in good to excellent yields (Scheme 13).



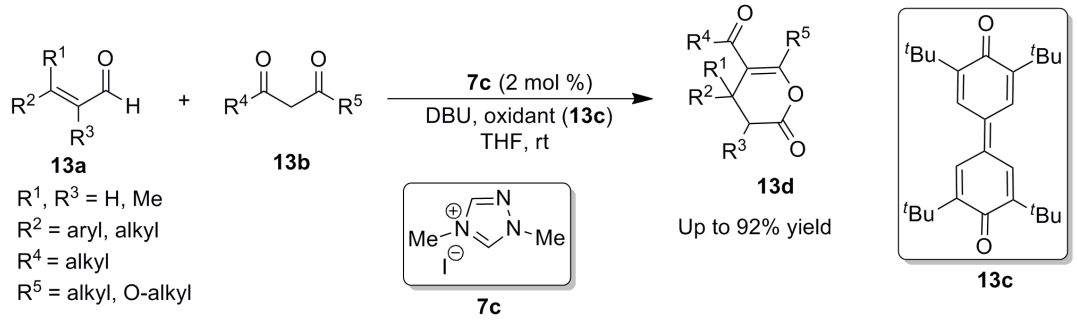
Scheme 13

Rose and Zeitler efficiently applied oxidative NHC method for the synthesis of lactones **12c** through intramolecular oxidative cyclization.[11] A variety of benzodioxepinones **12c** were synthesized in good yields by using NHC derived from 3-mesitylthiazolium perchlorate (**12b**) and azobenzene as an oxidant in THF (Scheme 14).



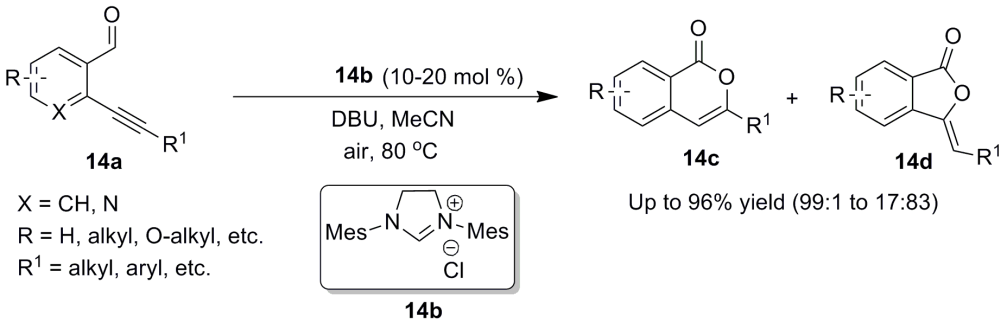
Scheme 14

Studer group demonstrated a novel method for the synthesis of various dihydropyranones (**13d**) from cinnamaldehydes (**13a**) and 1,3-dicarbonyl compounds **13b** through oxidative NHC catalysis.[12] A variety of substituted cinnamaldehydes were treated with 1,3-dicarbonyl compounds in the presence of triazolium based NHC **7c** and quinone derivative **13c** as an oxidant in combination with DBU (Scheme 15).



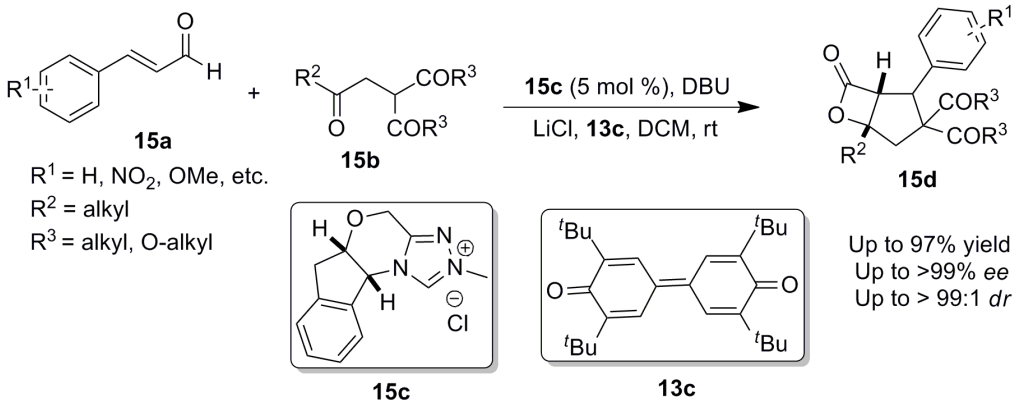
Scheme 15

A regio and stereoselective method for the synthesis of isocoumarins and/or phthalides through oxidative cyclization of 2-alkynylbenzaldehydes has been reported by Youn and co-workers through oxidative NHC catalysis.[13] Depending on the substituents in the alkyne portion **14a**, the products phthalides (**14d**) and/or isocoumarins (**14c**) were obtained in moderate to excellent yields with good regioselectivities (Scheme 16).



Scheme 16

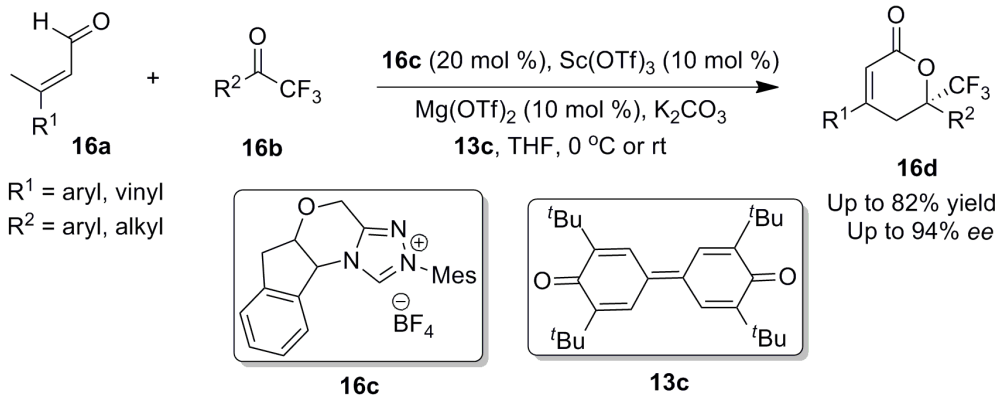
Very recently, Studer and co-workers have developed an oxidative method for the synthesis of highly substituted β-lactones from enals and β-diketones or β-ketoesters or malonates.[14] Reactions were carried out between enals **15a** with β-diketones or malonates **15b** bearing a β-oxyalkyl substituent at the α-position under oxidative conditions employing the chiral triazolium based NHC **15c** as a precatalyst, and quinone derivative as an oxidant, the corresponding β-lactones **15d** were obtained with excellent diastereo- and enantioselectivities (Scheme 17).



Scheme 17

γ-Functionalization of Enals through oxidative NHC catalysis:

An interesting report was published by Chi and co-workers who demonstrated the γ-functionalization of α,β-unsaturated aldehydes through oxidative NHC catalysis for the first time.[15] An enantioselective γ-addition of enals to activated ketones was developed by combining NHC/Lewis acid co-operative catalysis under oxidative conditions. A variety of α,β-unsaturated aldehydes **16a** bearing methyl substitution at β-position were treated with various ketones (**16b**) in the presence of chiral NHC **16c** derived from triazolium salt, $Sc(OTf)_3$/$Mg(OTf)_2$ as Lewis acids, **13c** as an oxidant, and the corresponding α,β-unsaturated γ-lactones **16d** were obtained in good yields with high *ee* values (Scheme 18).

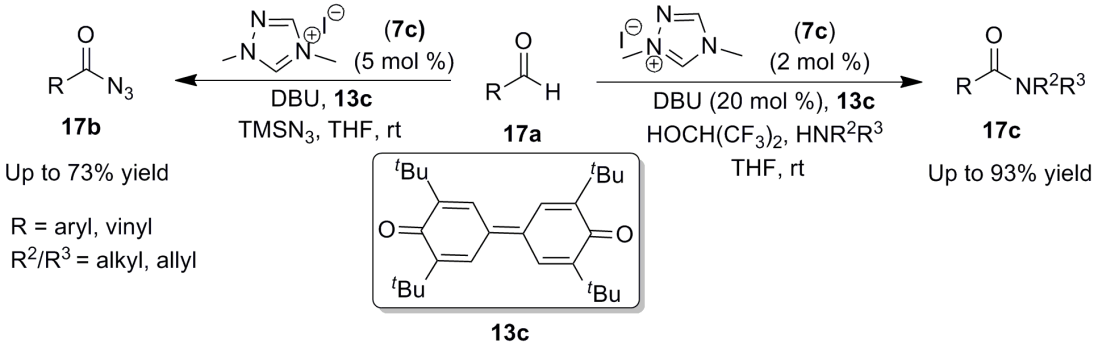


Scheme 18

1.2.2. Construction of C-N bond through oxidative NHC catalysis

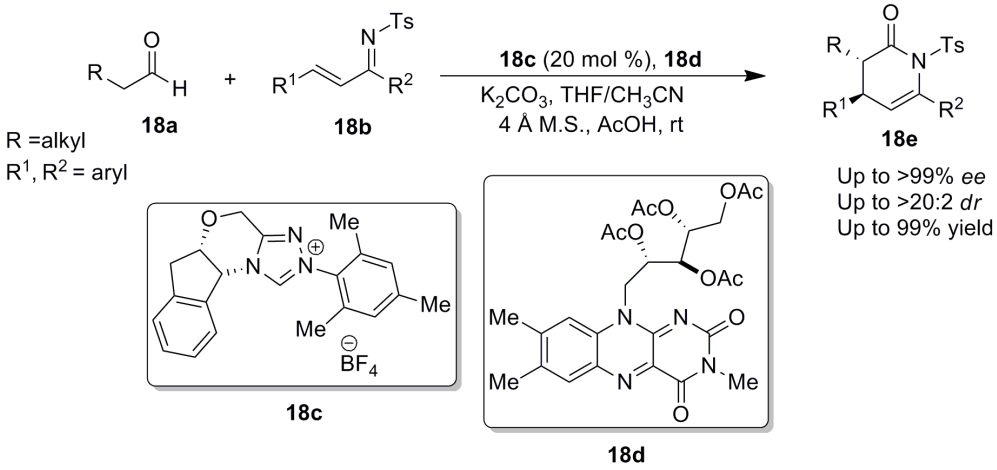
Oxidative NHC catalysis has also been applied to the construction of C-N bonds. A few of the reports are described in this section.

Studer and co-workers disclosed a highly efficient one-pot amidation of aldehydes through NHC catalyzed oxidative esterification followed by amidation.[16] Both aromatic and unsaturated aldehydes (**17a**) have been converted to their corresponding amides (**17c**) in moderate to excellent yields under the optimized reaction conditions. This oxidative NHC process has also been successfully applied for the azidation of aromatic aldehydes with trimethylsilylazide under the similar reaction conditions (Scheme 19).



Scheme 19

In another report, Rovis and co-workers demonstrated a novel protocol for the asymmetric oxidative hetero Diels-alder reactions of aliphatic aldehydes with α,β unsaturated ketimines through NHC catalysis.[17]

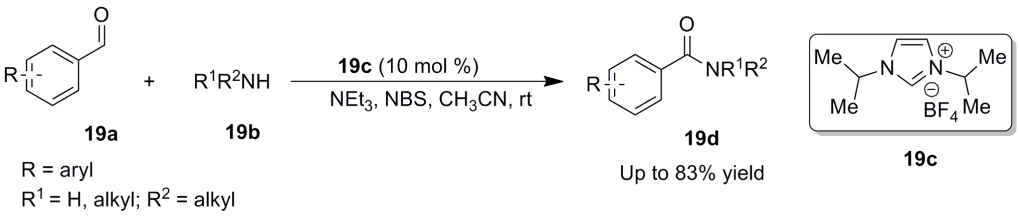


Scheme 20

Simple aliphatic aldehydes **18a** were treated with α,β unsaturated ketimines **18b** by employing the chiral NHC **18c** derived from triazolium salt and a chiral oxidant **18d**. In this case, the corresponding *trans*-lactams **18e** were obtained with high enantioselectivities (Scheme 20).

Very recently, Maheswari and co-workers reported NHC catalyzed oxidative amidation of aromatic aldehydes with primary and secondary amines.[18] Various aromatic aldehydes **19a** were

treated with amines (both 1° and 2°) **19b** in the presence of NHC **19c** using NBS as an oxidant and the corresponding amides **19d** were obtained in moderate to good yields (Scheme 21).



Scheme 21

1.3. References

[1] (a) For reviews, see: (i) Knappke, C. E. I.; Imami, A.; von Wangelin, A. J. *ChemCatChem* **2012**, *4*, 937. (ii) Sarkar, S. D.; Biswas, A.; Samanta, R. C.; Studer, A. *Chem.—Eur. J.* **2013**, *19*, 4664 and references cited therein. (b) Miyashita, A.; Suzuki, Y.; Nagasaki, I.; Ishiguro, C.; Iwamoto, K.-I.; Higashino, T. *Chem. Pharm. Bull.* **1997**, *45*, 1254.

[2] Liu, Y.-K.; Yue, L.; Li, B.-J.; Chen, Y.-C.; Wu, Y.; Ding, L.-S. *Org. Lett*. **2006**, *8*, 1521.

[3] Noonan, C.; Baragwanath, L.; Connon, S. J. *Tetrahedron. Lett.* **2008**, *49*, 4003.

[4] Maki, B. E.; Scheidt, K. A. *Org. Lett*. **2008**, *10*, 4331.

[5] Goswami, S.; Hazra, A. *Chem. Lett.* **2009**, *38*, 484.

[6] Maki, B. E.; Chan, A.; Phillips, E. M.; Scheidt, K. A. *Tetrahedron* **2009**, *65*, 3102.

[7] Maji, B.; Vedachalam, S.; Ge, X.; Cai, S.; Liu, X.-W. *J. Org. Chem*. **2011**, *76*, 3016.

[8] Chiang, P.-C.; Bode, J. W. *Org. Lett*. **2011**, *13*, 2422.

[9] Xin, Y.-C.; Shi, S.-H.; Xie, D.-D.; Hui, X.-P.; Hu, P.-F. *Eur. J. Org. Chem*. **2011**, *32*, 6527.

[10] Reddi, R. N.; Malekar, P. V.; Sudalai, A. *Org. Biomol. Chem.* **2013**, *11*, 6477.

[11] Rose, C. A.; Zeitler, K. *Org. Lett*. **2010**, *12*, 4552.

[12] Sarkar, S. D.; Studer, A. *Angew. Chem., Int. Ed*. **2010**, *49*, 9266.

[13] Park, J. H.; Bhilare, S. V.; Youn, S. W. *Org. Lett*. **2011**, *13*, 2228.

[14] Bera, S.; Samanta, R. C.; Daniliuc, C. G.; Studer, A. *Angew. Chem., Int. Ed.* **2014**, *53*, 1.

[15] Mo, J.; Chen, X.; Chi, Y. R. *J. Am. Chem. Soc.* **2012**, *134*, 8810.

[16] Sarkar, S. D.; Studer, A. *Org. Lett*. **2010**, *12*, 1992.

[17] Zhao, X.; Ruhl, K. E.; Rovis, T. *Angew. Chem., Int. Ed.* **2012**, 51, 12330.

[18] Alanthadka, A.; Maheswari, C. U. *Adv. Synth. Catal.* **2015**, *357*, 1199.

Chapter 2

2. Aerobic oxidation reactions under oxidative NHC catalysis

This chapter is sub-divided into two parts; (a) and (b).

(a) Tetraphenylphosphonium bromide as a phenyl source for the synthesis of phenyl esters under oxidative NHC catalysis

(b) Synthesis of trimethylsilylmethyl esters under oxidative NHC catalysis

(a) Tetraphenylphosphonium bromide as a phenyl source for the synthesis of phenyl esters under oxidative NHC catalysis

2.1. Introduction

Tetraphenylphosphonium salts have gained momentous attention due to their wide range of applications as ion-pair extractants for the extraction of heavy metals,[1] herbicides,[2] ionic liquids,[3] conducting materials[4] and as phase transfer catalysts.[5] Some of the tetraphenylphosphonium salts have been used as molecular probes for imaging tumors.[6] Apart from these applications, tetraphenylphosphonium bromide has also been used as an additive in few metal catalyzed cross-coupling reactions.[7] However, only a few reports are available in the literature, where tetraphenylphosphonium salts were used as a phenyl transfer reagents. Yamamoto and co-workers reported arylation of electron deficient olefins with Ph_4PCl through Palladium catalysis.[8] Recently, Chang's group described that tetraphenylphosphonium salts could be effectively used as a phenyl source for Palladium catalyzed Heck, Suzuki-Miyura and Sonagashira coupling reactions.[9] Surprisingly, apart from the above mentioned reports, tetraphenylphosphonium salts have not been utilized a phenyl source in any other organic transformations.

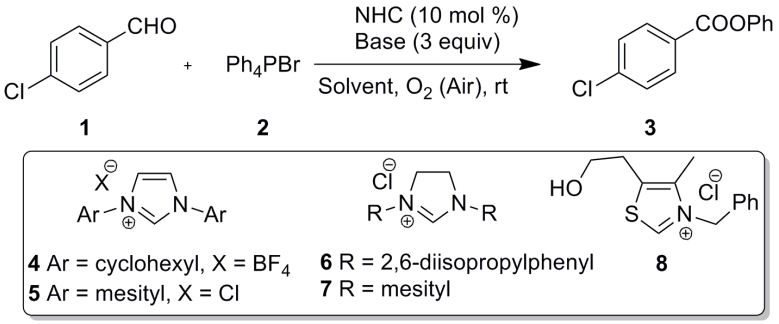
2.2. Results and discussion

Recently, the research groups of Wu's and Gois reported independently the synthesis of aryl esters from aromatic aldehydes and aryl boronic acids which involve Pd and Fe-NHC complexes as catalyst respectively.[10] Our group reported an efficient and metal-free method for the direct synthesis of aryl esters from aromatic aldehydes and aryl boronic acids under oxidative N-heterocyclic carbene catalysis.[11] 1,3-bis(2,6-diisopropylphenyl)imidazolinium chloride was found to be the better precatalyst for this transformations.

While developing an organocatalytic method for the preparation of aryl esters, we came across a few alternative aryl sources, especially phenyl transfer agents, which include tetraphenylphosphonium salts. Since Ph_4PBr is commercially available and has not been utilized for esterification reactions so far, we decided to study it as a phenyl source in the oxidative esterification reaction.

The optimization studies were carried out with 4-chlorobenzaldehyde as a model substrate and Ph_4PBr as a phenyl source. A variety of NHC precursors (**4**–**8**) were screened for this oxidative esterification reaction under different conditions (Table 1). All these reactions were carried out under aerobic conditions. Our initial attempt in the optimization studies using NHC precursor **4** was disappointing, as the anticipated product **3** was not observed even after 24 h (entry 1, Table 1). However, when the experiment was executed using **5** as a catalyst, the expected ester **3** was obtained in 20% yield (entry 2).

Table 1. Optimization Studies[a]



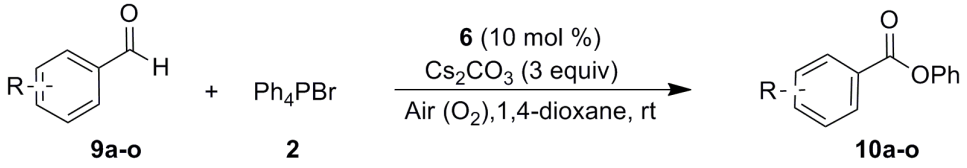
Entry	NHC	Base	Solvent	Time [h]	Yield [%][b]
1	**4**	Cs_2CO_3	1,4 dioxane	24	0
2	**5**	Cs_2CO_3	1,4 dioxane	26	20
3	**6**	**Cs_2CO_3**	**1,4 dioxane**	**4**	**67**
4	**7**	Cs_2CO_3	1,4 dioxane	36	56
5	**8**	Cs_2CO_3	1,4 dioxane	24	Trace
6	**6**	K_2CO_3	1,4 dioxane	36	23
7	**6**	$^{i}Pr_2NEt$	1,4 dioxane	24	0
8	**6**	$KO^{t}Bu$	1,4 dioxane	24	Trace
9	**6**	Cs_2CO_3	Toluene	14	44
10	**6**	Cs_2CO_3	THF	4	56
12	**6**	Cs_2CO_3	DME	5	33
13	**6**	Cs_2CO_3	DCM	30	24

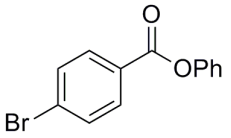
[a]Reaction conditions: **1**:**2** = 1.3:1 equivalents in 0.15 M solvent; [b]Isolated yield of **3**. rt = 32–35°C.

Encouraged by this result, we performed the optimization studies with a few more NHC precursors and different bases, and the results are compiled in Table 1. Out of few conditions tried, the best was found as indicated in entry 3 (Table 1). NHC precursor **6** was used as a catalyst, and the phenyl ester **3** was obtained in 67% yield after 4 h at rt.

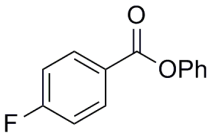
After having found an appropriate reaction condition, we focused our attention on the scope of this transformation. Consequently, a variety of aromatic aldehydes (**9a**–**9o**) were subjected to the oxidative esterification reaction with Ph_4PBr under optimized conditions, and the results are collected in scheme 1. In most of the cases, the required esters were obtained in moderate yields. Halogenated aromatic aldehydes such as 4-bromobenzaldehyde and 4-fluorobenzaldehyde gave the corresponding esters (**10a** and **10b)** in 47 and 55% yields, respectively. In the case of benzaldehyde (**9c**), phenyl benzoate (**10c**) was obtained in 41% yield after 14 h. Electron-poor aromatic aldehydes such as 4-formylbenzonitrile (**9d**) and 3-nitrobenzaldehyde (**9f**) gave the esters **10d** and **10f** in 33 and 32% yields, respectively. The yield of the ester **10e** is slightly better in the case of methyl 4-formylbenzoate. This methodology worked relatively better in the cases of electron-rich aromatic aldehydes (**10g**, **10j** and **10k**). 4-(Trifluoromethyl)-benzaldehyde (**9h)** was also converted to the product **10h** in 55% yield. In the case of alkyl- and aryl-substituted benzaldehydes such as 4-ethylbenzaldehyde (**9i**) and 4-phenylbenzaldehyde (**9n**), the reaction was very slow, and the esters **10i** and **10n** were obtained in 38 and 39% yields, respectively after 48h. A few heteroaromatic aldehydes, such as furfural (**9l**) and thiophene-2-carboxaldehyde (**9m**) provided the corresponding esters **10l** and **10m** in 48 and 50% yields, respectively. 3-Fluorobenzaldehyde (**9o**) gave the corresponding ester **10o** in 40% yield in 5h. Aliphatic aldehydes, such as dihydrocinnamaldehyde and cyclohexane carboxaldehyde failed to give the desired products; instead, the starting materials were decomposed, since the reaction medium was highly basic. Almost in all the cases, a considerable amount of the corresponding acid was also formed along with ester. This could be due to the competitive oxidation of aldehydes to acids under oxidative NHC catalyzed conditions.[12] It is also known that Ph_4PBr decomposes under strong basic conditions.[13] These are probably the reasons why lower yields were obtained in most of the cases.

Scheme 1. Substrate Scope[a]

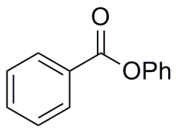




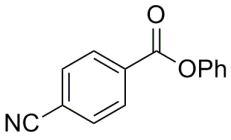
10a, 36 h, 47%



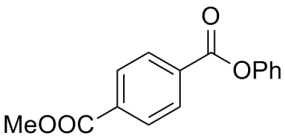
10b, 5 h, 55%



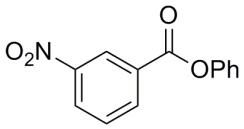
10c, 14 h, 41%



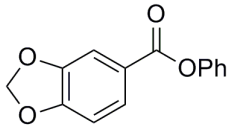
10d, 12 h, 33%



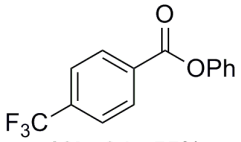
10e, 5 h, 43%



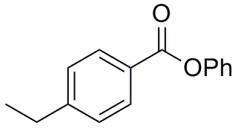
10f, 6 h, 32%



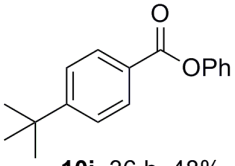
10g, 28 h, 58%



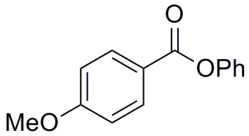
10h, 9 h, 55%



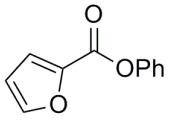
10i, 48 h, 38%



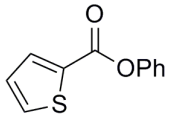
10j, 36 h, 48%



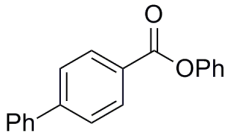
10k, 48 h, 43%



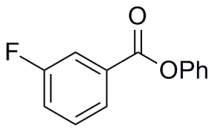
10l, 3 h, 48%



10m, 48 h, 50%



10n, 48 h, 39%

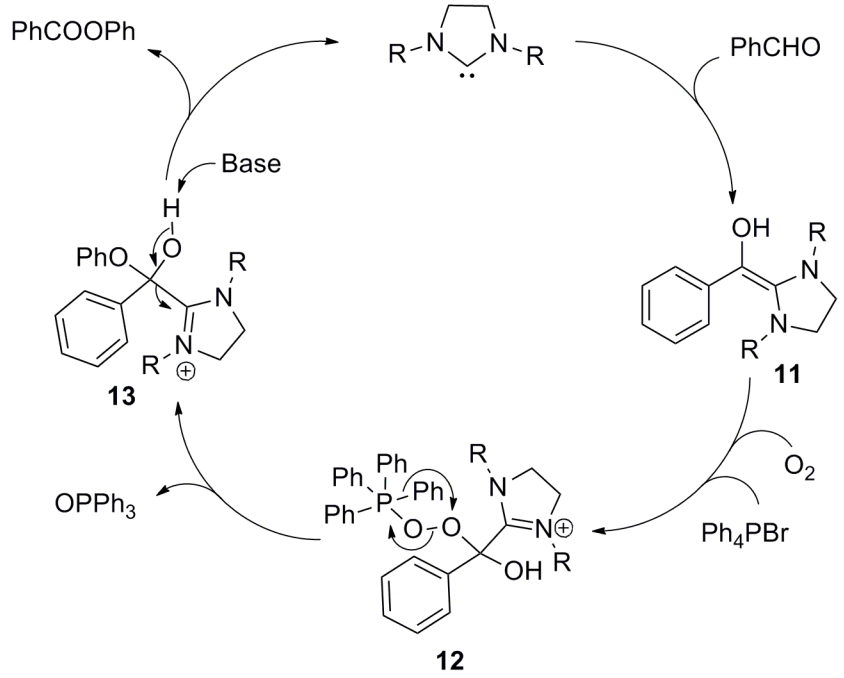


10o, 5 h, 40%

[a]Reaction conditions: **9**:**2** = 1.3:1 equivalents; 0.15 M of **2** in 1,4-dioxane; rt = 32–35 °C.

At this stage, our attention was shifted towards understanding the mechanism of this reaction. Careful monitoring of the reaction between 4-chlorobenzaldehyde and Ph_4PBr under the standard conditions revealed that triphenylphosphine oxide (Ph_3PO) and 4-chlorobenzoic acid were the by-products. Since 4-chlorobenzoic acid was observed in the reaction, we initially thought the reaction proceeds *via* acid, which then reacts with Ph_4PBr under basic conditions to give the product and Ph_3PO. To confirm this, an experiment was performed by treating 4-chlorobenzoic

acid with Ph_4PBr in 1,4-dioxane using 3.0 equiv. of Cs_2CO_3 as a base. However, the phenyl ester **3** was not observed even after 24 h at room temperature. This clearly indicates that the reaction does not proceed *via* the acid intermediate. Another possible intermediate for this reaction could be PhOH, which might be formed by the decomposition of Ph_4PBr under oxidative conditions. Although PhOH formation was not observed (by TLC) in our experiments, we carried out an experiment, in which Ph_4PBr was exposed to NHC and air (O_2) in 1,4-dioxane under basic condition. However, PhOH was not detected even after stirring the reaction mixture for a prolonged period at room temperature. It is evident from the above mentioned experiments that the reaction involves neither PhCOOH nor PhOH as an intermediate. Based on these observations, we propose a concerted mechanism, which is depicted in the scheme 2.

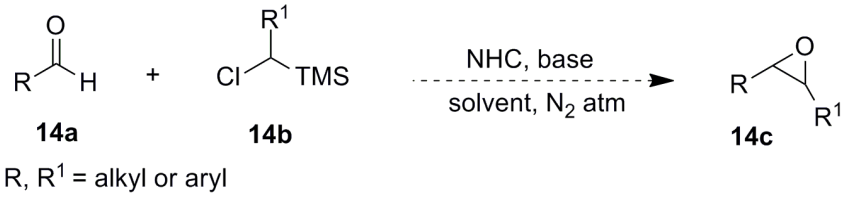


Scheme 2

We presume that the Breslow intermediate (**11**), formed by the reaction of PhCHO (**9c**) with NHC, reacts with O_2 and Ph_4PBr in a concerted manner to give intermediate **12**, which decomposes readily to intermediate **13** with the expulsion of Ph_3PO. On deprotonation, intermediate **13** releases the product along with NHC.

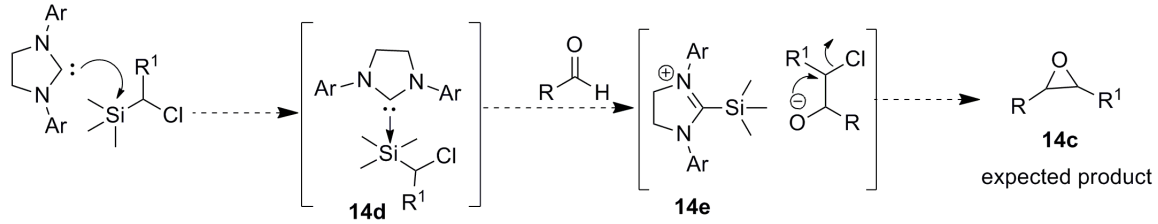
(b) Synthesis of trimethylsilylmethyl esters under oxidative NHC catalysis

Epoxides are very versatile building blocks in the synthesis of pharmaceutically important compounds as well as in natural products.[14] Although there are many methods available in the literature for the synthesis of epoxides,[15] including enantioselective epoxidation reactions,[16] only a handful reports are available in the literature for the direct synthesis of epoxides from aldehydes and (chloromethyl)trimethylsilane using CsF as a silyl activator.[17] However, these methods required sensitive reagents and harsh reaction conditions. We became interested in developing an efficient organocatalytic method for the direct synthesis of epoxides **14c** from aldehydes **14a** and (chloromethyl) trimethylsilane (**14b**) using NHC as an organo catalyst (Scheme 3).



Scheme 3

Since the activation of silicon compounds by N-heterocyclic carbenes has been already well documented in the literature,[18] we envisioned NHC could activate the chloromethyltrimethyl-silane to form a hypervalent silicon species **14d**. The intermediate **14d** then may react with the aldehyde to generate another intermediate **14e**, which may subsequently undergo nucleophilic substitution to deliver the epoxide **14c** (Scheme 4).

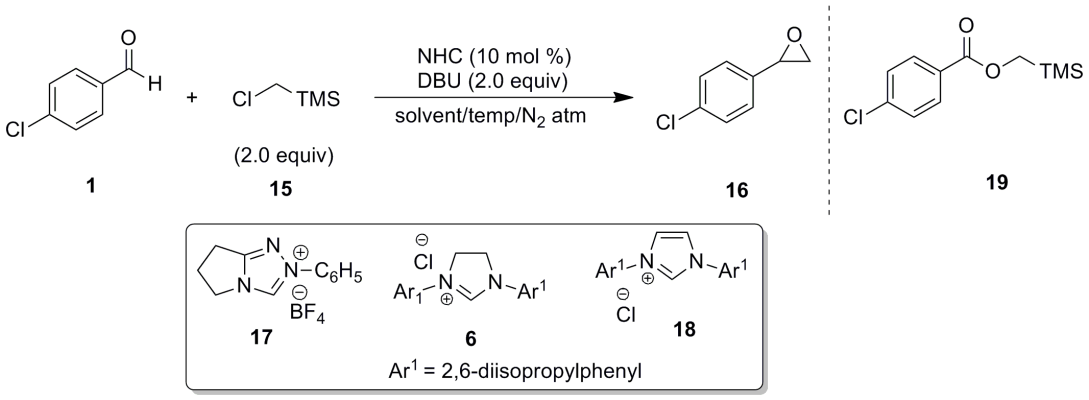


Scheme 4

Optimization studies were carried out using *p*-chlorobenzaldehyde (**1**) and (chloromethyl) trimethylsilane (**15**) under different reaction conditions employing different NHCs. Unfortunately, none of the cases gave the desired product; instead homo-benzoin was observed

in some of the cases. The reaction conditions tried are disclosed in Table 2. Interestingly, when the reaction was carried out using NHC **18** in the presence of DBU under reaction conditions (entry 5), a new spot was observed on TLC, which was found to be the ester **19**. The ester product **19**, which was isolated in 10% yield, is possible only if oxygen is present in the system. To conform it, a reaction was carried out under an open atmosphere using NHC **6** under same reaction conditions (entry 6). In this case, the yield of the ester **19** was increased to 20%.

Table 2. Optimization Studies[a]



Entry	NHC	Base	Solvent	Temp (°C)	Time [h]	Yield of 19 [%][c]
1	**17**	DBU	THF	rt/N_2	12	NR
2	**6**	DBU	THF	rt/N_2	12	NR
3	**18**	DBU	Toluene	60/N_2	6	NR
4	**6**	DBU	Toluene	60/N_2	6	10[b]
5	**18**	DBU	THF	rt/N_2	12	10
6	**18**	DBU	THF	rt/air	12	20

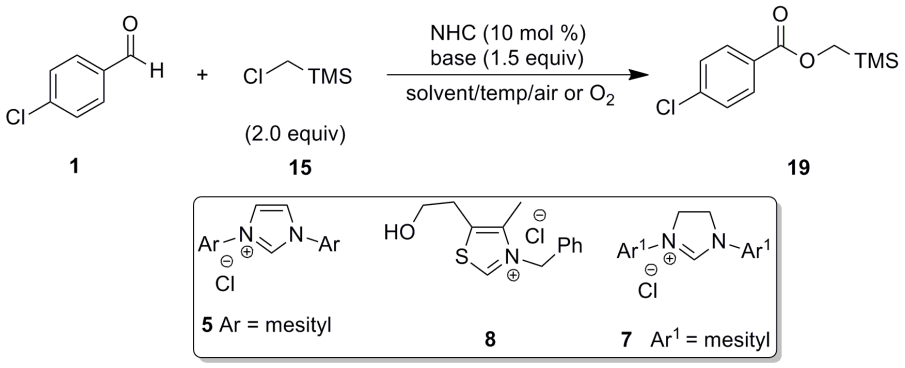
[a]Reaction conditions: 0.3 M of **1** in solvent; [b]homo-benzoin was isolated; [c]**19** was isolated; NR = no reaction.

Since silicon-containing compounds were found to be versatile synthons in many organic transformations as well as in the synthesis of natural products,[19] we have decided to explore this oxidative esterification method, which would be useful in the synthesis of a variety of trimethylsilylmethyl esters.

The optimization studies were carried out using different NHC precursors under different reaction conditions. All reactions were carried out in an open atmosphere to make sure that sufficient oxygen is available for the oxidation reaction (Table 3). When reactions were

performed using NHCs **5**, **7**, and **8** at room temperature under air conditions, the ester **19** was obtained in lower yield (entries 1–3). But interestingly, when a reaction was performed at 60 ºC in the presence of NHC precursor **7**, ester **19** was obtained in 60% yield (entry 4). By maintaining the temperature (60 ºC), another reaction was carried out under oxygen (O_2 balloon) atmosphere using NHC **7**. In this case, the yield of the ester **19** was improved to 75% (entry 5). Further optimization studies were carried out using different NHCs (entries 6–8), bases (entries 9–11) and also in different solvents (entries 12 & 13). But in all those cases, ester **19** was obtained in low yield when compared to entry 5.

Table 3. Optimization Studies[a]

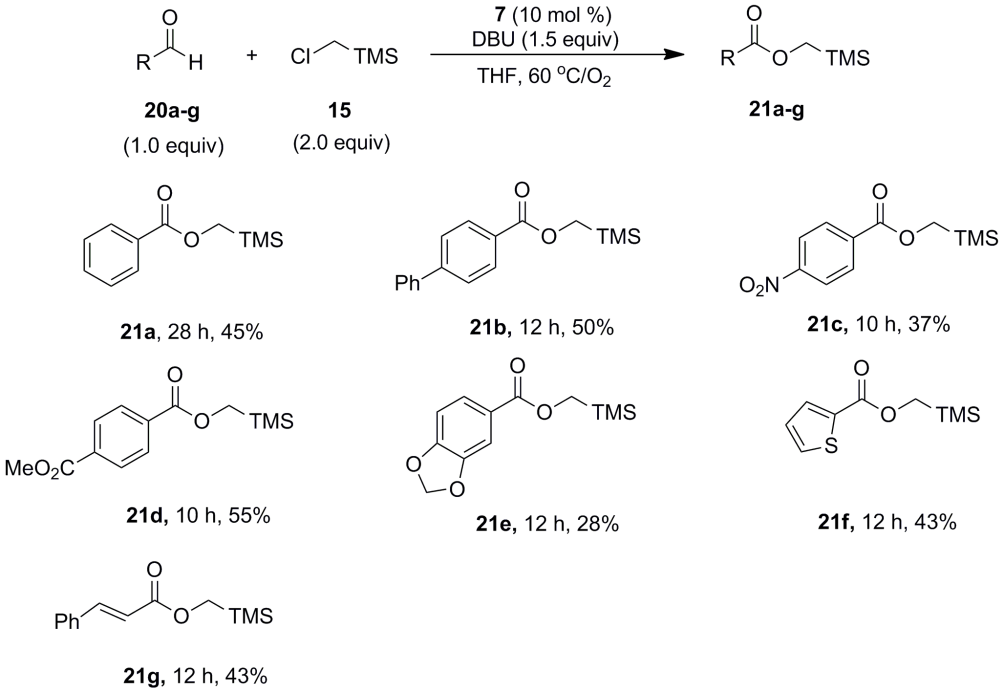


Entry	NHC	Base	Solvent	Temp (°C)	Time [h]	Yield of 19 [%][b]
1	**5**	DBU	THF	rt/air	12	20
2	**8**	DBU	THF	rt/air	12	12
3	**7**	DBU	THF	rt/air	12	30
4	**7**	DBU	THF	60/air	8	60
5	**7**	**DBU**	**THF**	**60/(O_2)**	**6**	**75**
6	**18**	DBU	THF	60/(O_2)	12	39
7	**5**	DBU	THF	60/(O_2)	12	60
8	**8**	DBU	THF	60/(O_2)	12	20
9	**7**	$^{i}Pr_2NEt$	THF	60/(O_2)	12	10
10	**7**	Cs_2CO_3	THF	60/(O_2)	12	NR
11	**7**	K_2CO_3	THF	60/(O_2)	12	NR
12	**7**	DBU	ACN	60/(O_2)	12	29
13	**7**	DBU	Toluene	60/(O_2)	12	40

[a]Reaction conditions: 0.3 M of **1** in the solvent; [b]**19** was isolated; NR = no reaction.

Having the optimized condition (entry 5) in hand, a variety of aldehydes was subjected to standard condition and the results are summarized in scheme 5. It is evident from scheme 5 that a variety of trimethylsilylmethyl benzoate derivatives could be easily accessed from various aldehydes in moderate yields (in most of the cases). Benzaldehyde (**20a**) and 4-phenyl benzaldehydes (**20b**) underwent smooth conversion and the corresponding esters **21a** & **21b** were obtained in 45% and 50% yields, respectively. Electron withdrawing group containing aldehydes such as **20c** and **20d** gave better yields, as compared to electron donating group containing aldehyde **20e**. Thiophene 2-carboxaldehyde (**20f**) was also converted to its corresponding ester **21f** in 43% yield. In the case of cinnamaldehyde (**20g**), the product **21g** was obtained in 43% yield under the reaction conditions. Unfortunately, in most of the examples, the required esters were obtained in moderate yields.

Scheme 5. Substrate Scope[a]



[a]Reaction conditions: 0.3 M of **20** in solvent, and yields reported are isolated yields.

2.3. Conclusions

(1) We have developed an alternative method for the direct synthesis of phenyl esters from aromatic aldehydes and Ph_4PBr under oxidative NHC catalysis. Although the yield of the esters was moderate in most of the cases, Ph_4PBr was investigated, for the first time, as a phenyl source in this methodology.

(2) An alternative method was also developed for the direct synthesis of trimethylsilylmethyl esters from aldehydes and chloromethyltrimethylsilane through oxidative NHC catalysis. Although moderate yields were obtained in some of the cases, we believe that this methodology would be useful to access the variety of trimethylsilylmethyl esters.

2.4. Experimental sections

General information

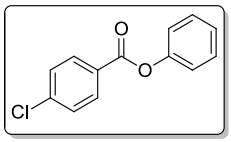
Most of the reagents and starting materials used were purchased from commercial sources and used as such. NHC precursors (**5–7, 17 & 18**) were prepared according to the literature procedure.[20] ^{1}H, ^{13}C spectra were recorded in $CDCl_3$ on Brucker FT-NMR spectrometer (400, 100 and 376 MHz respectively). Chemical shifts (δ) values are reported in parts per million relative to tetramethylsilane by using residual solvent signal ($CHCl_3$) as reference (7.26 ppm) and the coupling constants (J) are reported in Hz. High-resolution mass spectra (HRMS) for compounds (**19** & **21a**–**21g**) were recorded on Waters Q-TOF Premier-HAB213 spectrometer. FT-IR spectra for compounds (**3 & 10a**–**10o**) were recorded on a Perkin-Elmer FT IR spectrometer using KBr and are reported in cm^{-1}. FT IR spectra for compounds (**19** & **21a**–**21g**) were recorded on a Brucker FT IR spectrometer equipped with a PIKE MIRacle ATR. Melting points for all compounds were measured on Stuart melting point apparatus and are uncorrected. Thin layer chromatography was performed on Merck silica gel 60 F_{254} TLC plates. Column chromatography was carried out through silica gel (100-200 mesh) using hexane/EtOAc as an eluent.

General experimental procedure for the oxidative esterification of aromatic aldehydes with Ph_4PBr

Aromatic aldehyde (0.37 mmol) was added to a suspension of tetraphenylphosponium bromide (**2**) (0.29 mmol), **6** (0.029 mmol) and cesium carbonate (0.86 mmol) in 1,4-dioxane (2 ml) at room temperature (32–35 °C). After completion of the reaction, the reaction mass was filtered, washed with EtOAc (10 ml) and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure, and the residue was purified through silica gel column using hexane/EtOAc (5%) as an eluent to give the pure ester.

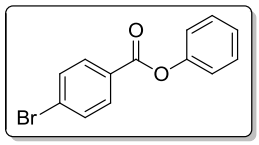
Characterization data of products (3 & 10a–10o):

Phenyl 4-chlorobenzoate (**3**):[11]



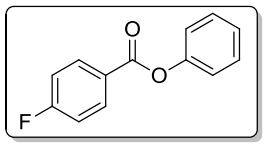
White solid; Yield 67% (45.2 mg); m.p. 104–106 °C; FT IR (KBr): 1732 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), δ 8.15 (d, J = 8.7 Hz, 2H), 7.49 (d, J = 8.7 Hz, 2H), 7.47–7.42 (m, 2H), 7.31–7.27 (m, 1H), 7.23–7.19 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$), δ 164.5, 150.9, 140.3, 131.7, 129.7, 129.1, 128.2, 126.2, 121.8.

Phenyl 4-bromobenzoate (**10a**):[11]



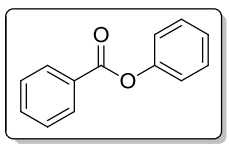
White solid; Yield 47% (37.8 mg); m.p. 117–118 °C; FT IR (KBr): 1731 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), δ 8.07 (d, J = 8.6 Hz, 2H), 7.66 (d, J = 8.6 Hz, 2H), 7.46–7.41 (m, 2H), 7.31–7.27 (m, 1H), 7.22–7.20 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$), δ 164.7, 150.9, 132.1, 131.8, 129.7, 129.0, 128.6, 126.2, 121.8.

Phenyl 4-fluorobenzoate (**10b**):[10b]



White solid; Yield 55% (34.5 mg); m.p. 63–65 °C; FT IR (KBr): 1734 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), δ 8.26–8.21 (m, 2H), 7.46–7.41 (m, 2H), 7.30–7.26 (m, 1H), 7.22–7.16 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$), δ 166.3 (d, J = 250.5 Hz), 164.4, 151.0, 132.9 (d, J = 9.4 Hz), 129.7, 128.9, 126.0 (d, J = 19.2 Hz), 121.8, 115.9 (d, J = 21.8 Hz).

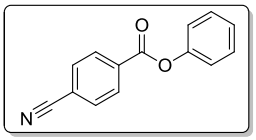
Phenyl benzoate (**10c**):[11]



White solid; Yield 41% (23.6 mg); m.p. 66–68 °C; FT IR (KBr): 1731 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), δ 8.24–8.21 (m, 2H), 7.67–7.63 (m, 1H), 7.54–7.51 (m, 2H), 7.47–7.42 (m, 2H), 7.31–7.27 (m, 1H), 7.24–7.21 (m,

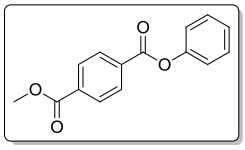
2H); ^{13}C NMR (100 MHz, $CDCl_3$), δ 165.3, 151.1, 133.7, 130.3, 129.7, 129.6, 128.7, 126.0, 121.9.

Phenyl 4-cyanobenzoate (**10d**):[11]



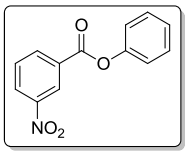
White solid; Yield 33% (21.4 mg); m.p. 94–96 °C; FT IR (KBr): 1742, 2365 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$), δ 8.31 (d, J = 8.7 Hz, 2H), 7.83 (d, J = 8.7 Hz, 2H), 7.48–7.44 (m, 2H), 7.33–7.29 (m, 1H), 7.24–7.20 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$), δ 163.7, 150.7, 133.6, 132.6, 130.8, 129.8, 126.5, 121.6, 118.0, 117.6.

Methyl phenyl terephthalate (**10e**):[11]



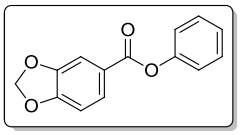
White solid; Yield 43% (32.0 mg); m.p. 106–108 °C; FT IR (KBr): 1734 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$), δ 8.27 (d, J = 8.6 Hz, 2H), 8.18 (d, J = 8.6 Hz, 2H), 7.47–7.42 (m, 2H), 7.32–7.28 (m, 1H), 7.24–7.21 (m, 2H), 4.0 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$), δ 166.4, 164.6, 150.9, 134.6, 133.5, 130.3, 129.9, 129.7, 126.3, 121.7, 52.7.

Phenyl 3-nitrobenzoate (**10f**):[21]



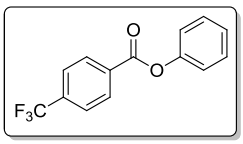
Pale yellow solid; Yield 32% (22.6 mg); m.p. 156–158 °C; FT IR (KBr): 1728, 2923 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$), δ 9.05–9.04 (m, 1H), 8.55–8.49 (m, 2H), 7.76–7.72 (m, 1H), 7.49–7.44 (m, 2H), 7.34–7.3 (m, 1H), 7.26–7.22 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$), δ 163.1, 150.6, 148.5, 135.9, 131.5, 130.3, 129.8, 128.1, 126.6, 125.3, 121.6.

Phenyl benzo[d][dioxole-5-carboxylate (**10g**):[11]



White solid; Yield 58% (40.7 mg); m.p. 80–82 °C; FT IR (KBr): 1715 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$), δ 7.83 (dd, J = 8.2, 1.7 Hz, 1H), 7.62 (d, J = 1.7, 1H), 7.45–7.40 (m, 2H), 7.29–7.24 (m, 1H), 7.21–7.18 (m, 2H), 6.91 (d, J = 8.1 Hz, 1H), 6.08 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$), δ 164.7, 152.3, 151.1, 148.1, 129.6, 126.4, 126.0, 123.6, 121.9, 110.1, 108.3, 102.1.

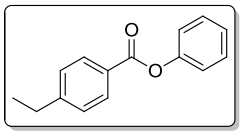
Phenyl 4-(trifluoromethyl)benzoate (**10h**):[21]



Pale yellow solid; Yield 55% (42.5 mg); m.p. 81–83 °C; FT IR (KBr): 1733 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$), δ 8.33 (d, J = 8.04 Hz, 2H), 7.79 (d, J =

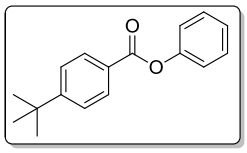
8.12 Hz, 2H), 7.48–7.43 (m, 2H), 7.33–7.29 (m, 1H), 7.25–7.21 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$), δ 164.2, 150.8, 135.2 (q, J = 32.9 Hz), 133.0 (q, J = 1.4 Hz), 130.7, 129.8, 126.4, 125.8 (q, J = 3.66 Hz), 123.7 (q, J = 270.6 Hz), 121.7.

Phenyl 4-ethylbenzoate (**10i**):[11]



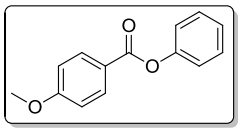
White solid; Yield 38% (24.9 mg); m.p. 62–63 °C; FT IR (KBr): 1726 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$), δ 8.13 (d, J = 8.1 Hz, 2H), 7.45–7.41 (m, 2H), 7.34 (d, J = 8.0 Hz, 2H), 7.29–7.26 (m, 1H), 7.22 (d, J = 8.0 Hz, 2H), 2.75 (q, J = 7.6 Hz, 2H), 1.29 (t, J = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$), δ 165.4, 151.2, 150.7, 130.5, 129.6, 128.2, 127.2, 125.9, 121.9, 29.2, 15.4.

Phenyl 4(tert-butyl)benzoate (**10j**):[22]



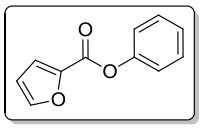
White solid; Yield 48% (35.4 mg); m.p. 142–146 °C; FT IR (KBr): 1729 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$), δ 8.18 (d, J = 8.4 Hz, 2H), 7.57 (d, J = 8.4 Hz, 2H), 7.49–7.45 (m, 2H), 7.33–7.24 (m, 3H), 1.41 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$), δ 165.3, 157.5, 151.2, 130.2, 129.6, 126.9, 125.9, 125.7, 121.9, 35.3, 31.3.

Phenyl 4-methoxybenzoate (**10k**):[11]



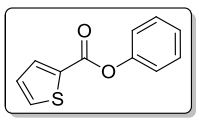
White solid; Yield 43% (28.5 mg); m.p. 75–77 °C; FT IR (KBr): 1727 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$), δ 8.14 (d, J = 8.8 Hz, 2H), 7.42–7.39 (m, 2H), 7.26–7.22 (m, 1H), 7.20–7.18 (m, 2H), 6.97 (d, J = 8.8 Hz, 2H), 3.88 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$), δ 165.9, 164.0, 151.2, 132.4, 129.6, 125.9, 122.0, 121.9, 114.0, 55.7.

Phenyl furan-2-carboxylate (**10l**):[11]



White solid; Yield 48% (26.2 mg); m.p. 54–56 °C; FT IR (KBr): 1736 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$), δ 7.68 (dd, J = 1.7, 0.8, 1H), 7.45–7.40 (m, 2H), 7.39 (dd, J = 3.5, 0.8 Hz, 1H), 7.30–7.25 (m, 1H), 7.23–7.20 (m, 2H), 7.60 (dd, J = 3.5, 1.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$), δ 157.1, 150.3, 147.3, 144.2, 129.7, 126.2, 121.8, 119.6, 112.3.

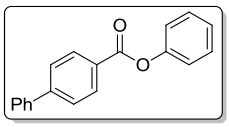
Phenyl thiophene-2-carboxylate (**10m**):[11]



Semi solid; Yield 50% (29.6 mg); FT IR (KBr): 1738 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$), δ 7.99 (dd, J = 3.8, 1.3 Hz, 1H), 7.67 (dd, J = 5.0, 1.3 Hz, 1H),

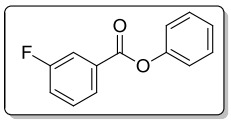
7.45–7.40 (m, 2H), 7.30–7.25 (m, 1H), 7.24–7.21 (m, 2H), 7.18 (dd, J = 5.0, 3.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$), δ 160.7, 150.7, 134.8, 133.6, 133.1, 129.6, 128.2, 126.1, 121.8.

Phenyl [1,1'-biphenyl]-4-carboxylate (**10n**):[11]



White solid; Yield 39% (31.0 mg); m.p. 158–160 °C; FT IR (KBr): 1731 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$), δ 8.28 (d, J = 8.2 Hz, 2H), 7.74 (d, J = 8.2 Hz, 2H), 7.67 (d, J = 7.7 Hz, 2H), 7.52–7.41 (m, 5H), 7.31–7.24 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$), δ 165.2, 151.2, 146.5, 140.0, 130.9, 129.7, 129.1, 128.5, 128.4, 127.5, 127.4, 126.0, 121.9.

Phenyl 3-fluorobenzoate (**10o**):[11]



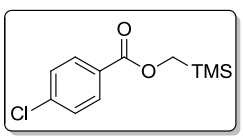
White solid; Yield 40% (25.1 mg); m.p. 58–59 °C; FT IR (KBr): 1736 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$), δ 8.02–8.00 (m, 1H), 7.91–7.87 (m, 1H), 7.37–7.27 (m, 2H), 7.23–7.20 (m, 2H), 7.53–7.42 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$), δ 164.1 (d, J = 25.4), 161.5, 150.9, 131.9 (d, J = 3.8 Hz), 130.4 (d, J = 7.8 Hz), 129.7, 126.3, 126.1 (d, J = 3.1 Hz), 121.7, 120.9 (d, J = 21.2 Hz), 117.2 (d, J = 22.9 Hz).

General procedure for the synthesis of trimethylsilylmethyl esters (19 & 21a–21g) through oxidative NHC catalysis

1,8-Diazabicyclo[5.4.0]undec-7-ene (98 mg, 0.65 mmol) was added to a suspension of NHC precursor **7** (0.043 mmol, 0.1 equiv), aldehyde (0.43 mmol, 1.0 equiv) and (chloromethyl)-trimethylsilane (0.85 mmol, 2.0 equiv) in dry THF (1.5 mL) under oxygen ballon atmosphere at room temperature and the resulting suspension was stirred at 60 °C in the presence of oxygen balloon until most of the aldehyde was consumed (TLC). After completion of the reaction, the reaction mixture was cooled to rt then the solvent was removed carefully under rotavac (water bath at 40 °C, vacuum at 250 mbar). The residue was purified through silica gel column using hexane as an eluent.

Characterization data of compounds (19 & 21a–21g):

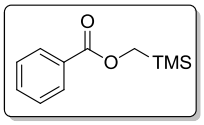
(trimethylsilyl)methyl 4-chlorobenzoate (19):



Colorless liquid; Yield 75% (78.3 mg); FT IR (ATR) 1719 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$), δ 7.95 (d, J = 8.4 Hz, 2H), 7.40 (d, J = 8.4 Hz, 2H), 4.00 (s, 2H), 0.14 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$), δ 166.6, 139.2,

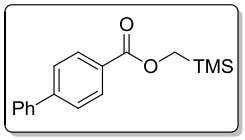
131.0, 129.2, 128.8, 58.6, −2.9; HRMS (ESI): *m/z* calcd for $C_{10}H_{12}ClO_2Si$ $[M-CH_3]^+$: 227.0295; found: 227.0300.

(trimethylsilyl)methyl benzoate (21a):



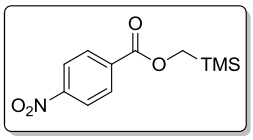
Colorless liquid; Yield 45% (40.3 mg); FT IR (ATR) 1722 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), δ 8.04–8.02 (m, 2H), 7.57–7.53 (m, 1H), 7.46–7.42 (m, 2H), 4.01 (s, 2H), 0.15 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$), δ 167.6, 132.8, 130.8, 129.6, 128.5, 58.3, −2.8; HRMS (ESI): *m/z* calcd for $C_{11}H_{17}O_2Si$ $[M+H]^+$: 209.0998; found: 209.0998.

(trimethylsilyl)methyl (1,1'-biphenyl)-4-carboxylate (21b):



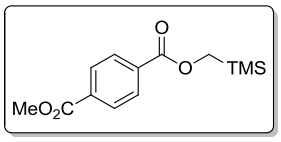
Colorless liquid; Yield 50% (61.2 mg); FT IR (ATR) 1718 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), δ 8.10 (d, J = 8.7 Hz, 2H), 7.67–7.62 (m, 4H), 7.49–7.45 (m, 2H), 7.40 (t, J = 7.4 Hz, 1H), 4.04 (s, 2H), 0.17 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$), δ 167.4, 145.6, 140.2, 130.1, 129.5, 129.1, 128.2, 127.4, 127.2, 58.4, −2.8; HRMS (ESI): *m/z* calcd for $C_{17}H_{20}O_2SiNa$ $[M+Na]^+$: 307.1130; found: 307.1129.

(trimethylsilyl)methyl 4-nitrobenzoate (21c):



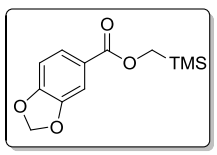
White solid; Yield 37% (40.3 mg); m.p. 68–70 °C; FT IR (ATR) 1735, 1533 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), δ 8.29 (d, J = 8.4 Hz, 2H), 8.18 (d, J = 8.5 Hz, 2H), 4.08 (s, 2H), 0.16 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$), δ 165.6, 150.5, 136.1, 130.7, 123.7, 59.5, −2.8; HRMS (ESI): *m/z* calcd for $C_{11}H_{15}NO_4SiNa$ $[M+Na]^+$: 276.0668; found: 276.0661.

Methyl[(trimethylsilyl)methyl] terephthalate (21d):



White solid; Yield 55% (63.0 mg); m.p. 78–80 °C; FT IR (ATR) 1719, 1708 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), δ 8.11–8.06 (m, 4H), 4.04 (s, 2H), 3.94 (s, 3H), 0.15 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$), δ 166.7, 166.5, 134.5, 133.8, 129.7, 129.6, 58.9, 52.6, −2.8; HRMS (ESI): *m/z* calcd for $C_{12}H_{15}O_4Si$ $[M-CH_3]^+$: 251.0740; found: 251.0740.

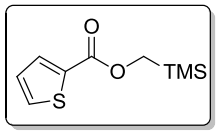
(trimethylsilyl)methyl benzo[d][1,3]dioxole-5-carboxylate (21e):



Colorless liquid; Yield 28% (30.4 mg); FT IR (ATR) 1712 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), δ 7.63 (dd, J = 8.3, 1.8 Hz, 1H), 7.44 (d, J = 2.0 Hz, 1H), 6.83 (d, J = 8.3 Hz, 1H), 6.03 (s, 2H), 3.96 (s, 2H), 0.13 (s, 9H); ^{13}C NMR

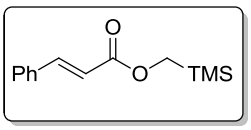
(100 MHz, $CDCl_3$), δ 166.9, 151.5, 147.8, 125.3, 124.8, 109.5, 108.1, 101.8, 58.2, −2.9; HRMS (ESI): *m/z* calcd for $C_{12}H_{17}O_4Si$ $[M+H]^+$: 253.0896; found: 253.0903.

(trimethylsilyl)methyl thiophene-2-carboxylate (21f):



Colorless liquid; Yield 43% (39.6 mg); FT IR (ATR) 1719 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), δ 7.78 (dd, *J* = 3.8, 1.3 Hz, 1H), 7.53 (dd, *J* = 5.0 1.2 Hz, 1H), 7.1 (dd, *J* = 5.0, 3.7 Hz, 1H), 4.0 (s, 2H), 0.14 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$), δ 163.2, 134.3, 133.2, 132.1, 127.8, 58.5, −2.9; HRMS (ESI): *m/z* calcd for $C_8H_{11}O_2SSi$ $[M-CH_3]^+$: 199.0249; found: 199.0244.

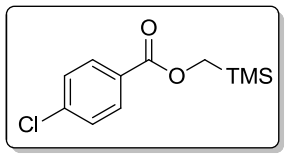
(trimethylsilyl)methyl cinnamate (21g):

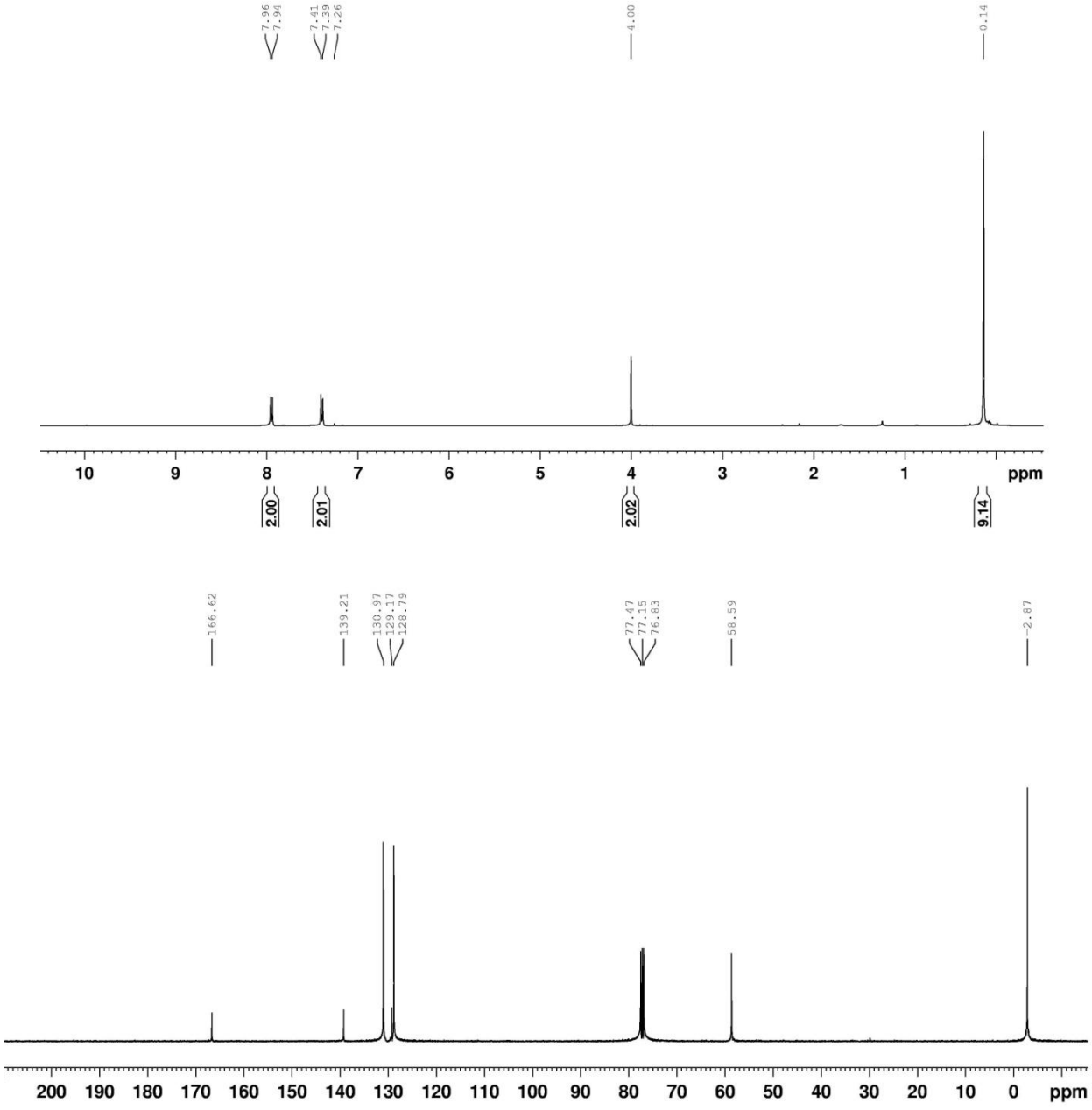


Colorless liquid; Yield 43% (43.3 mg); FT IR (ATR) 1711, 1638 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), δ 7.67 (d, *J* = 16.0 Hz, 1H), 7.54–7.52 (m, 2H), 7.38–7.37 (m, 3H), 6.46 (d, *J* = 16.0 Hz, 1H), 3.91 (s, 2H), 0.12 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$), δ 168.0, 144.4, 134.6, 130.3, 129.0, 128.2, 118.4, 58.0, −2.9; HRMS (ESI): *m/z* calcd for $C_{12}H_{15}O_2Si$ $[M-CH_3]^+$: 219.0841; found: 219.0807.

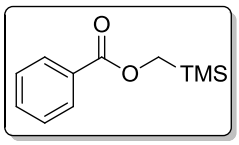
Spectra of compounds (19 & 21a–21g)

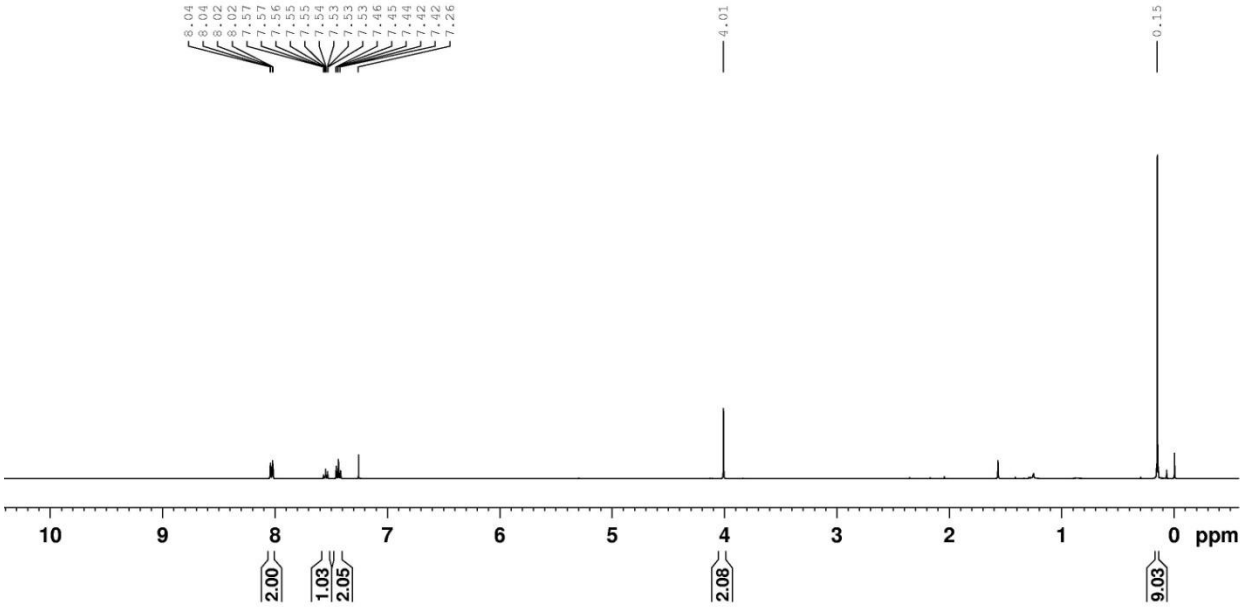
^{1}H, ^{13}C NMR Spectra of **19**

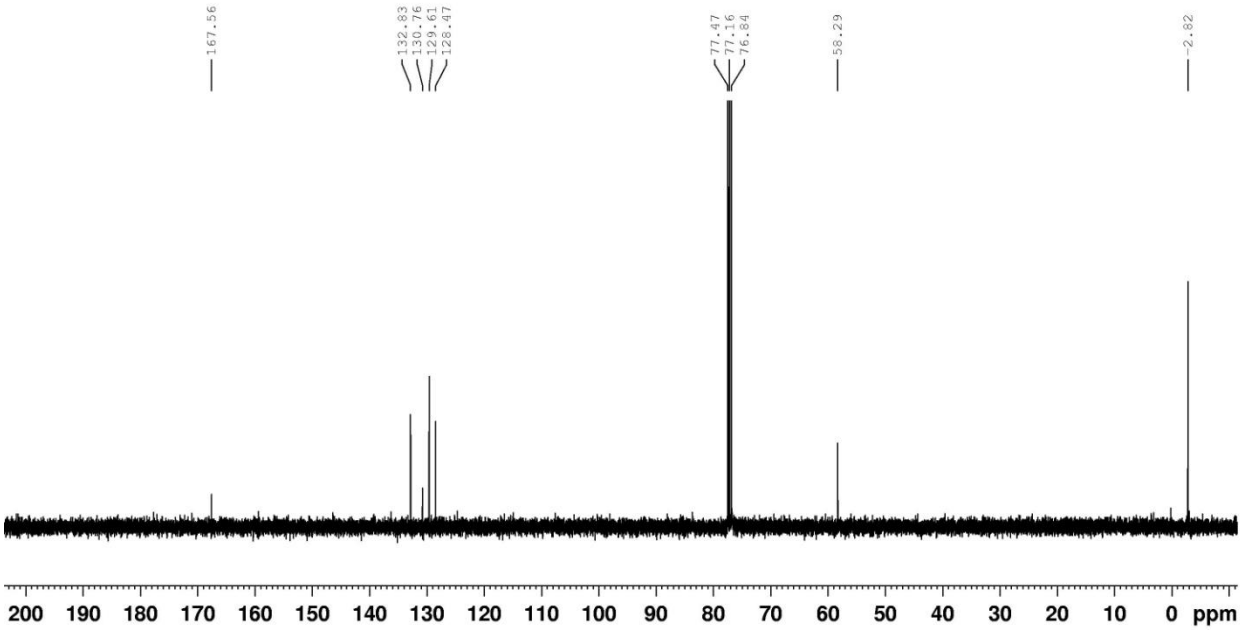




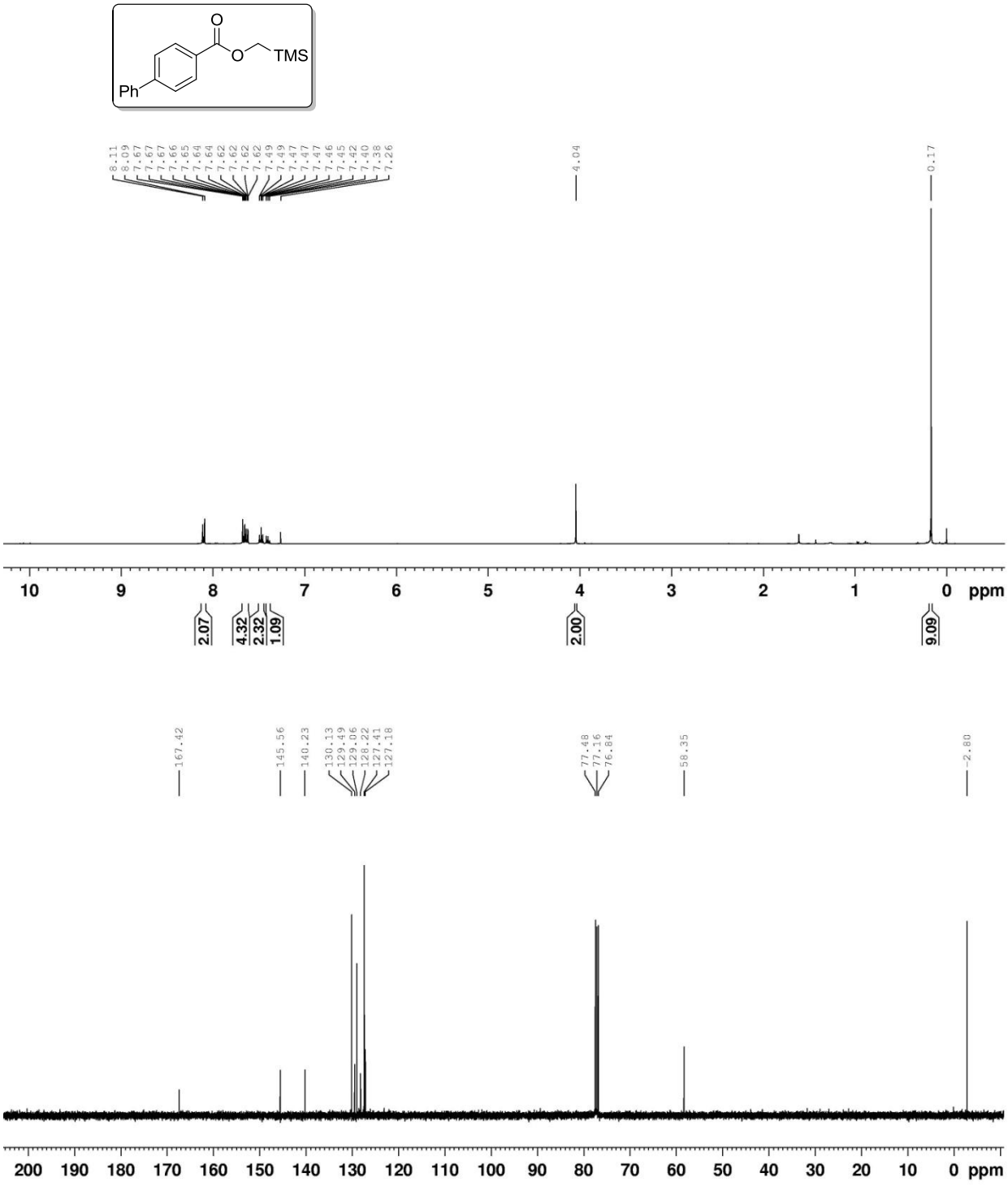
^{1}H, ^{13}C NMR Spectra of **21a**



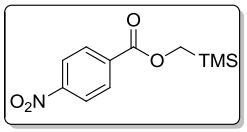


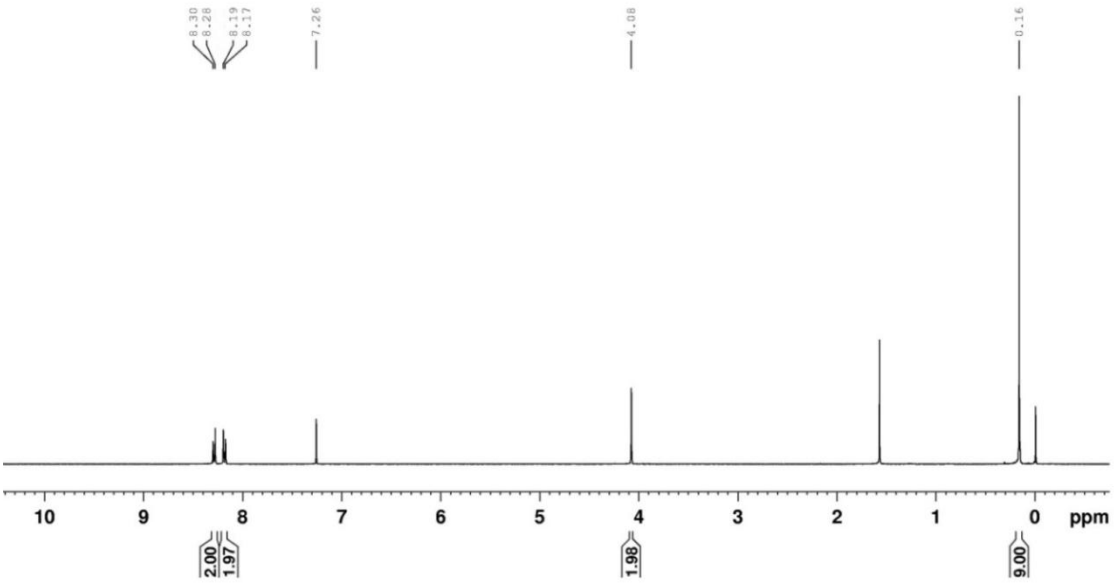


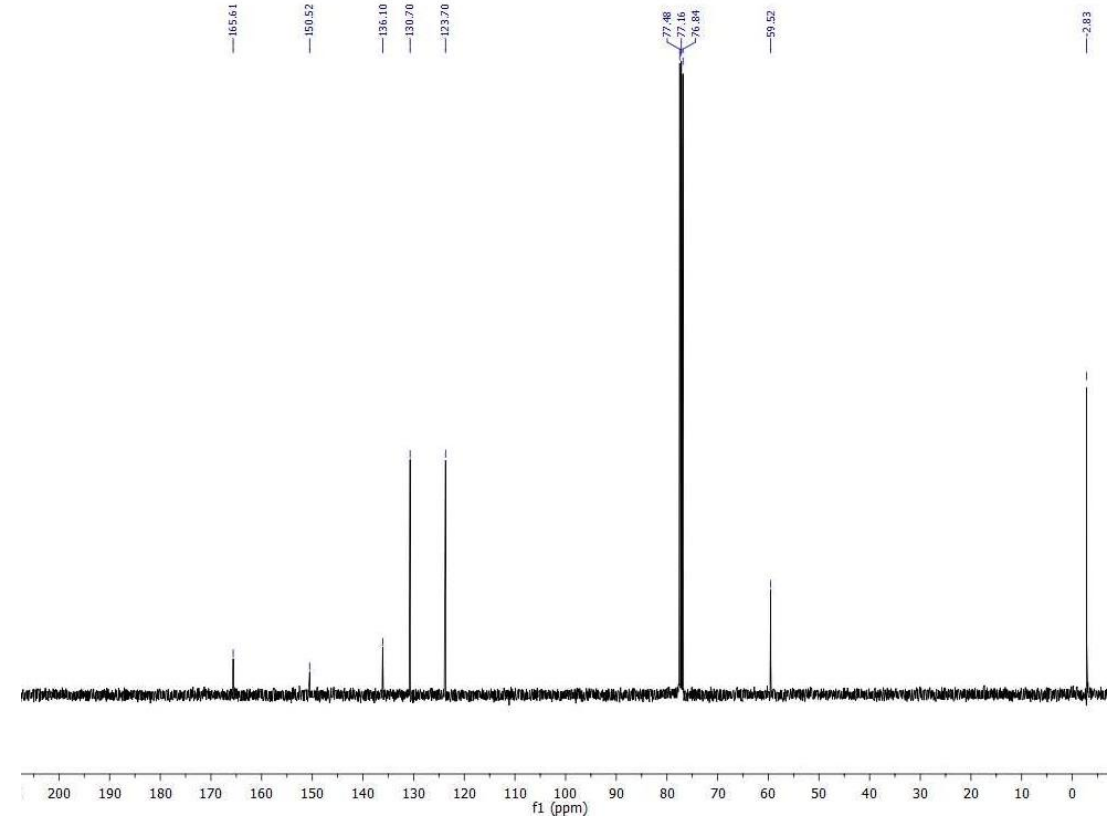
^{1}H, ^{13}C NMR Spectra of **21b**



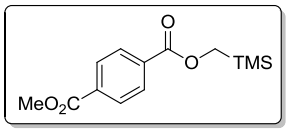
^{1}H, ^{13}C NMR Spectra of **21c**

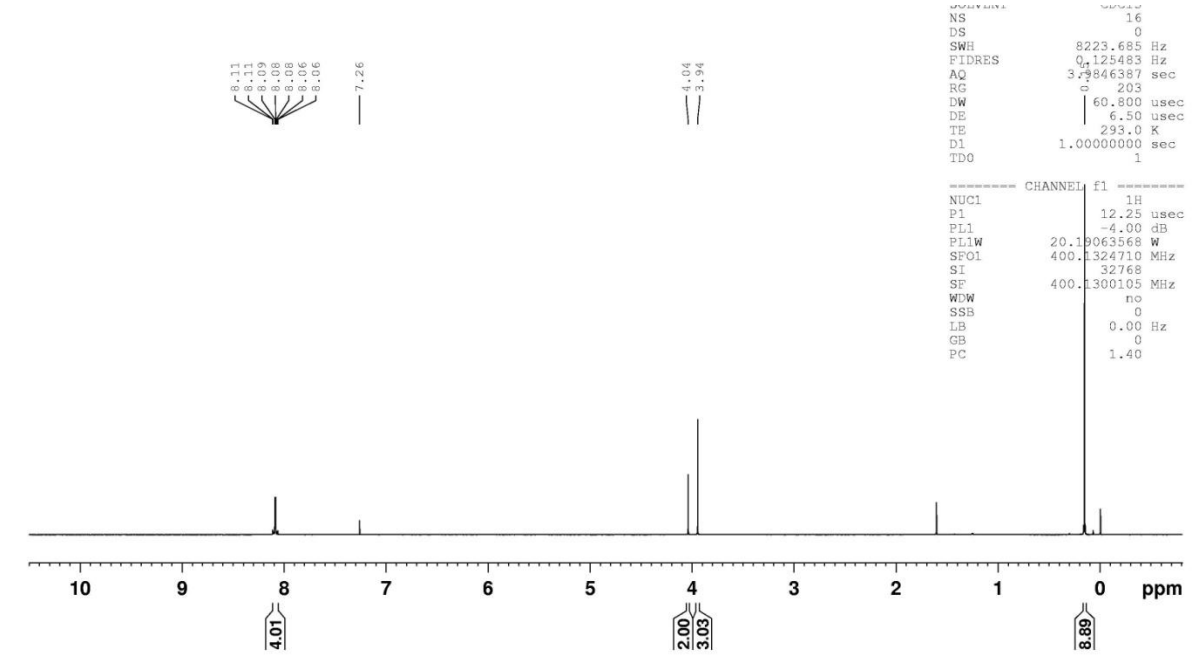


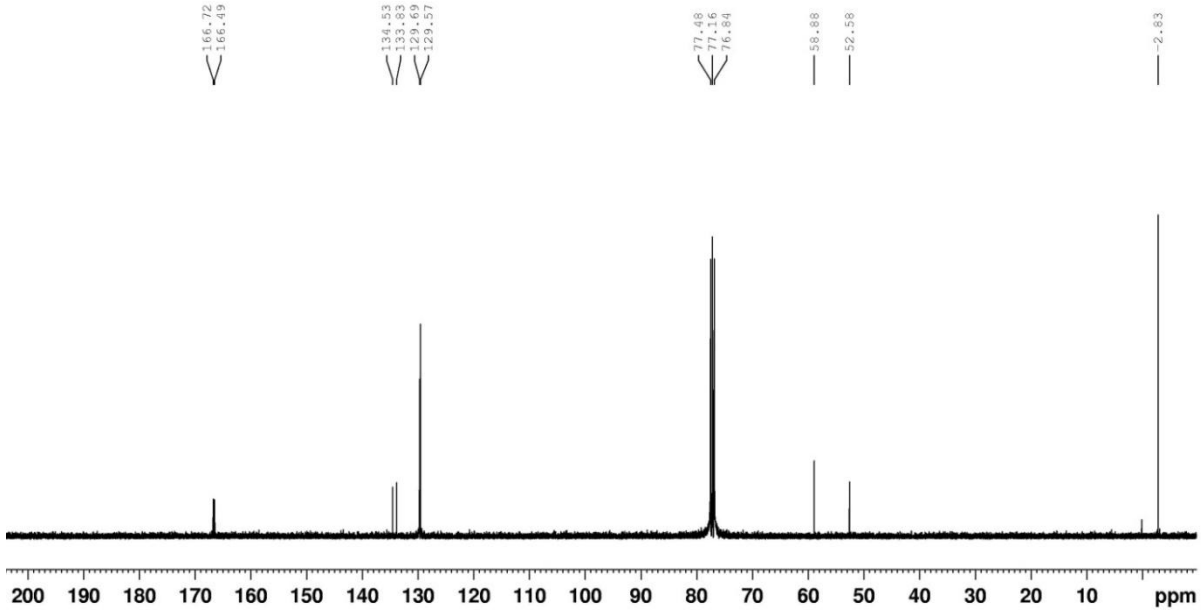




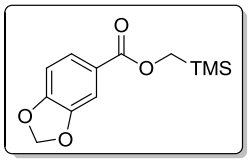
^{1}H, ^{13}C NMR Spectra of **21d**

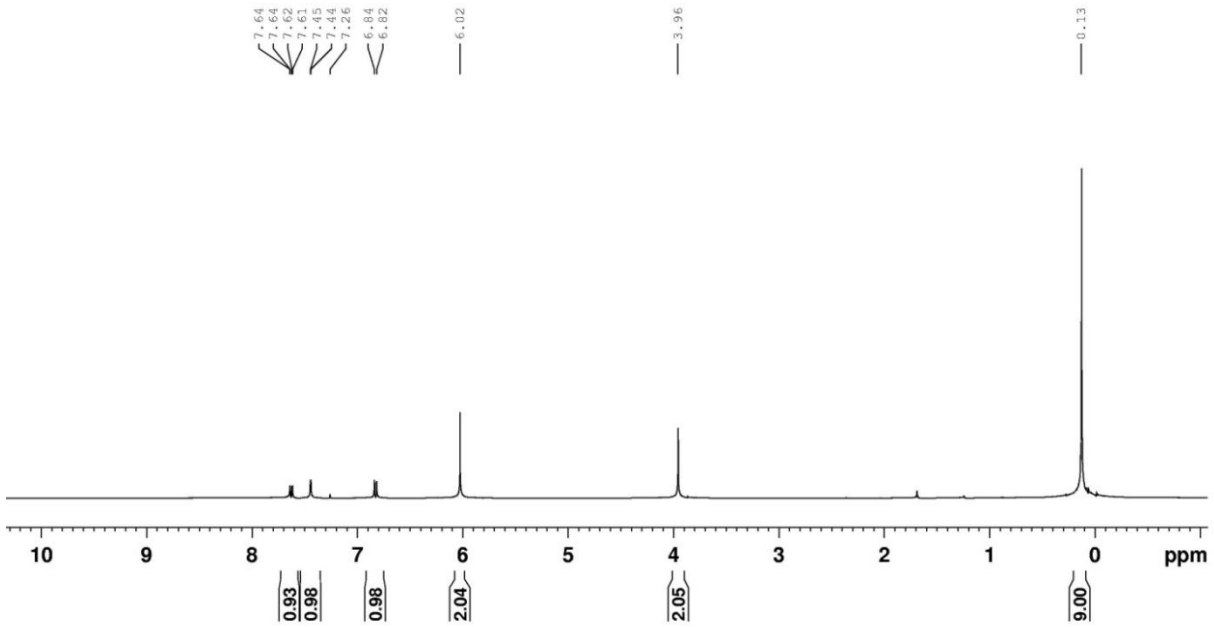


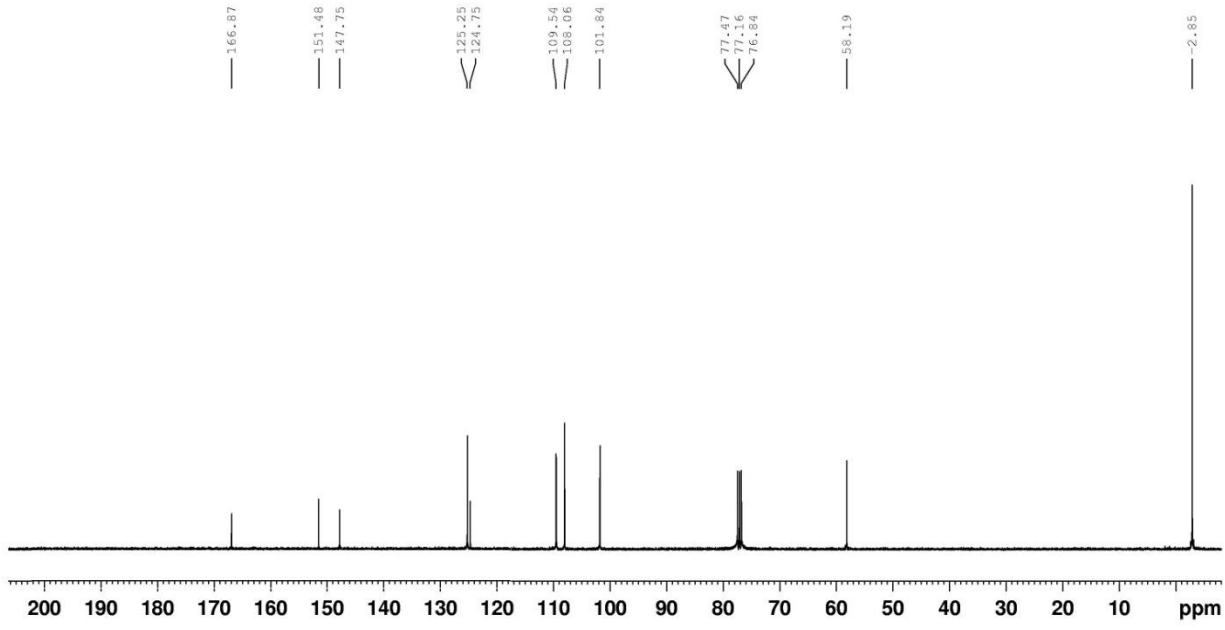




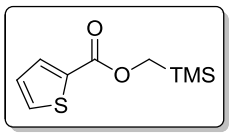
^{1}H, ^{13}C NMR Spectra of **21e**

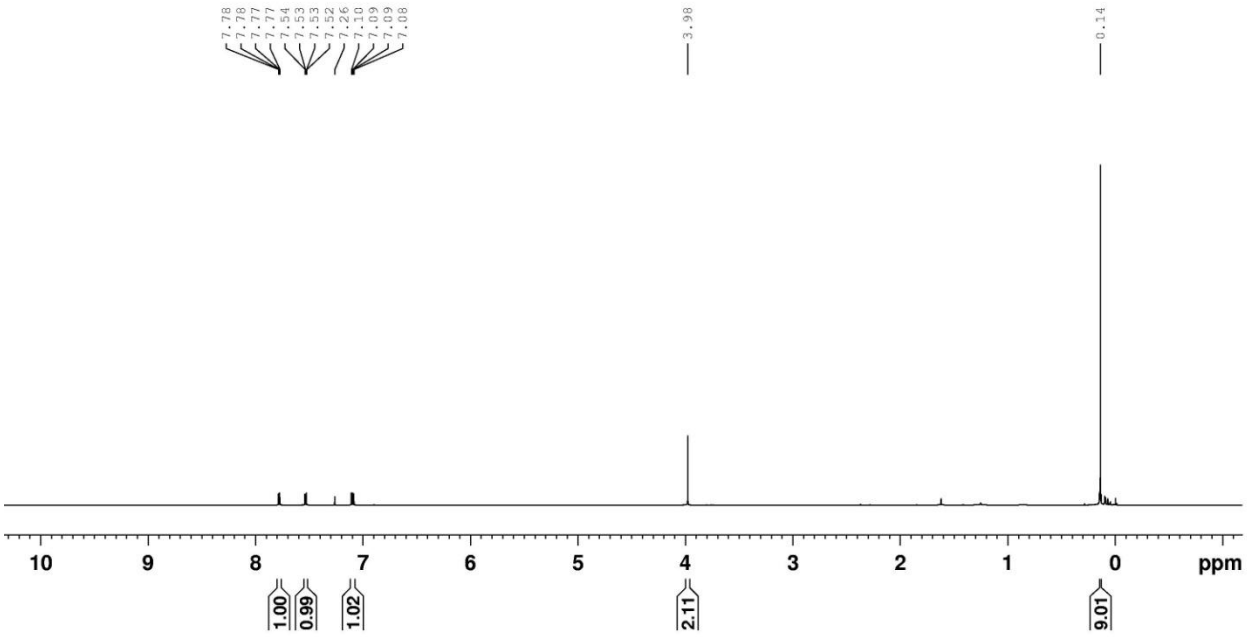


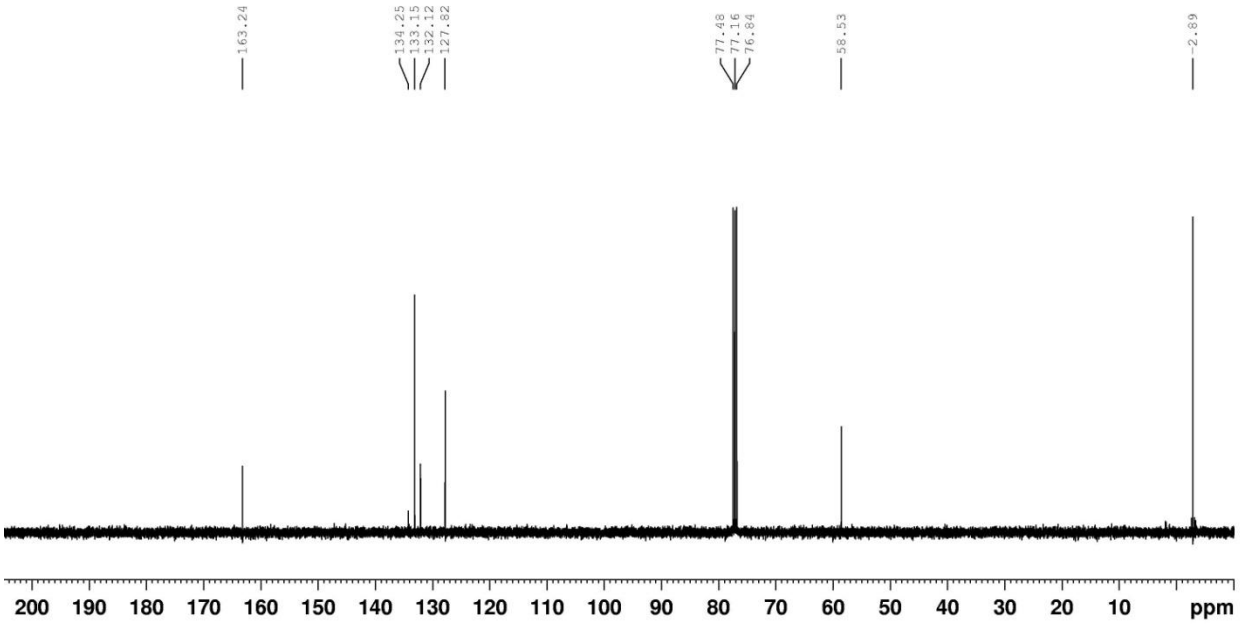




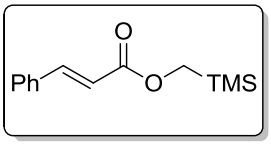
^{1}H, ^{13}C NMR Spectra of **21f**

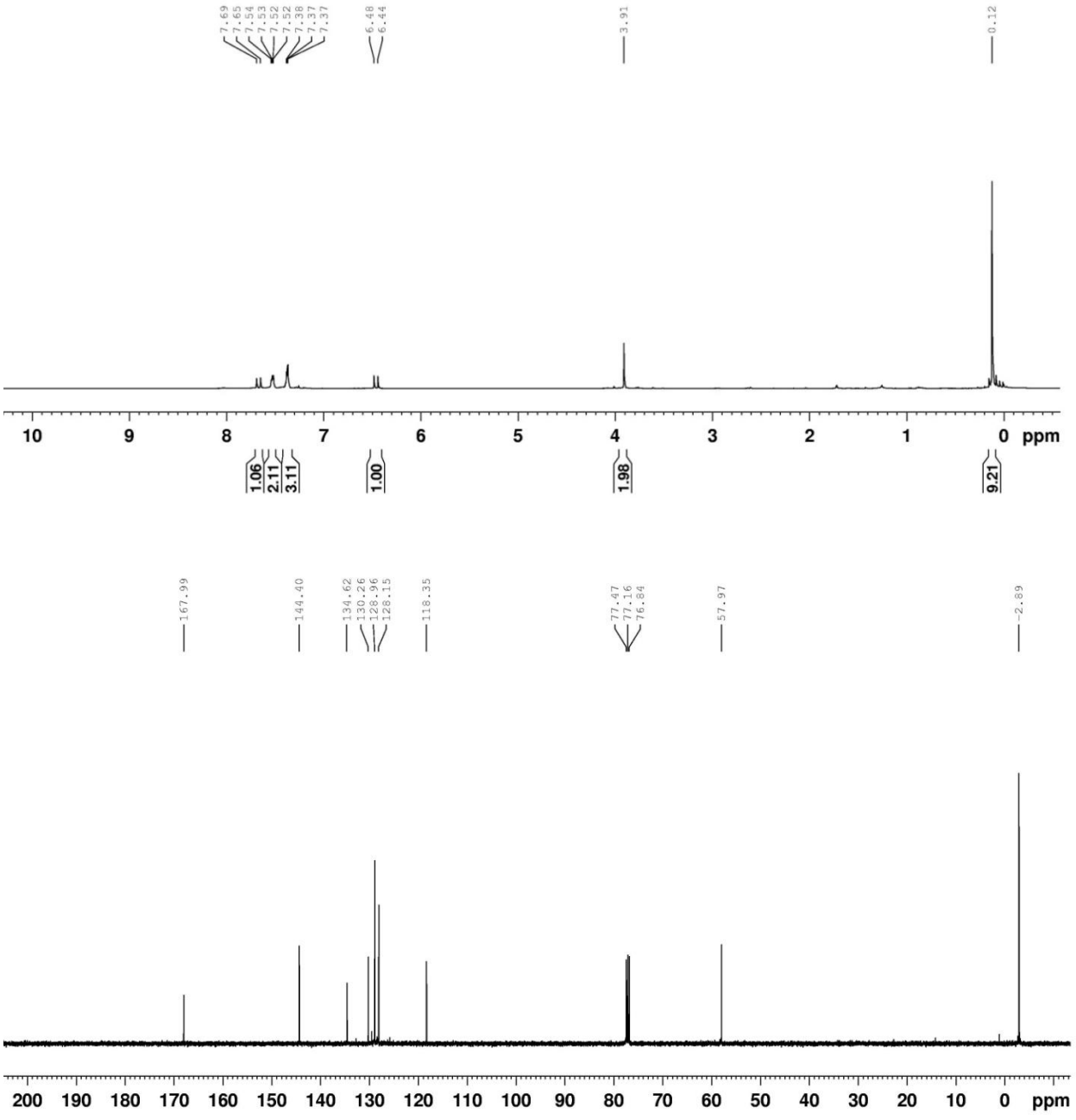






^{1}H, ^{13}C NMR Spectra of **21g**





2.5. References

[1] Kopunec, R.; Abudeab, F. N.; Skrašková, S. *J. Radio- anal. Nucl. Chem.* **1998**, *230*, 51.

[2] Large, G. B.; Buren, L. L. US Patent 4341549, July 27, 1982.

[3] Del Sesto, R. E.; Koppisch, A. T.; Lovejoy, K. S.; Purdy, G. M. US Patent Appl. 20120138789 A1, Jun 7, 2012.

[4] Zhao, Y.; Freeman, G. R. *J. Phy. Chem*. **1996**, *100*, 17568.

[5] (a) Yoshida, Y.; Kimura, Y.; Tomoi, M. *Chem. Lett*. **1990**, 19, 769. (b) Manabe, K. *Tetrahedron Lett*. **1998**, *39*, 5807.

[6] Min, J.-J.; Biswal, S.; Deroose, C.; Gambhir, S. S. *J. Nucl. Med*. **2004**, *45*, 636.

[7] (a) Reetz, M. T.; Lohmer, G.; Schwickardi, R. *Angew. Chem., Int. Ed*. **1998**, *37*, 481. (b) Herrmann, W. A.; Böhm, V. P. W. *J. Organomet. Chem*. **1999**, *572*, 141. (c) Verma, R. S.; Naicker, K. P. *Tetrahedron Lett*. **1999**, *40*, 439. (d) Böhm, V. P. W.; Herrmann, W. A. *Chem.—Eur. J*. **2000**, *6*, 1017.

[8] Sakamoto, M.; Shimizu, I.; Yamamoto, A. *Chem. Lett*. **1995**, *24*, 1101.

[9] Hwang, L. K.; Na, Y.; Lee, J.; Do, Y.; Chang, S. *Angew. Chem., Int. Ed*. **2005**, *44*, 6166.

[10] (a) Qin, C.; Wu, H.; Chen, J.; Liu, M.; Cheng, J.; Su, W.; Ding, J. *Org. Lett.* **2008**, *10*, 1537. (b) Rosa, J. N.; Reddy, R. S.; Candeias, N. R.; Cal, P. M. S. D.; Gois, P. M. P. *Org. Lett*. **2010**, *12*, 2686.

[11] Arde, P.; Ramanjaneyulu, B. T.; Reddy, V.; Saxena, A.; Anand, R. V. *Org. Biomol. Chem*. **2012**, *10*, 848.

[12] (a) Chiang, P. C.; Bode, J. W. *Org. Lett*. **2011**, *13*, 2422. (b) Li, Y.; Du, W.; Deng, W. P. *Tetrahedron* **2012**, *68*, 3611.

[13] Aldridge, S.; Warwick, P.; Evans, N.; Vines, S. *Chemosphere*. **2007**, *66*, 672.

[14] (a) Takao, K.-I.; Sasaki, T.; Kozaki, T.; Yanagisawa, Y.; Tadano, K.-I.; Kawashima, A.; Shinonaga, H. *Org. Lett.* **2001**, *3*, 4291. (b) Wipf, P.; Grenon, M. *Can. J. Chem.* **2006**, *84*, 1226.

[15] (a) Hioki, K.; Tani, S.; Sato, Y. *Synthesis* **1995**, 649. (b) Concellón, J. M.; Cuerco, H.; Fernandez-Fano, R. *Tetrahedron* **2001**, *57*, 8983. (c) Jana, N. K.; Verkade, J. G.; *Org. Lett.* **2003**, *5*, 3787. (d) Kavanagh, S. A.; Piccinini, A.; Fleming, E. M.; Connon, S. J. *Org. Biomol. Chem.* **2008**, *6*, 1339. (e) Piccinini, A.; kavanagh, S. A.; Connon, P. B.; Connon, S. J. *Org. Lett.* **2010**, *12*, 608.

[16] (a) Helder, R.; Hummelen, J. C.; Laane, R. W. P. M.; Wiering, J. S.; Wynberg, H.; *Tetrahedron Lett.* **1976**, 1831. (b) Wang, Z.-X.; Tu, Y.; Frohn, M.; Zhang, J.-R.; Shi, Y. *J. Am. Chem. Soc.* **1997**, *119*, 11224. (c) O'Brien, P.; Childs, A. C.; Ensor, G. J.; Hill, C. L.; Kirby, J. P.; Dearden, M. J.; Oxenford, S. J.; Rosser, C. M. *Org. Lett.* **2003**, *5*, 4955. (d) Piccinini, A.; kavanagh, S. A.; Connon, S. J. *Chem. Comm.* **2012**, *48*, 7814. (e) He, J.; Ling, J.; Chiu, P. *Chem. Rev.* **2014**, *114*, 8037.

[17] (a) Kessar, S. V.; Singh, P.; Venugopal, D. *Indian J. Chem. Sect B.* **1987**, *26B*, 605. (b) Kessar, S. V.; Singh, P.; Kaur, N. P.; Chawla, U.; Shukla, K.; Aggarwal, P.; Venugopal, D. *J. Org. Chem.* **1991**, *56*, 3908.

[18] (a) Fukuda, Y.; Maeda, Y.; Ishii, S.; Kondo, K.; Aoyama, T. *Synthesis* **2006**, 589. (b) Du, G.-F.; He, L.; Gu, C.-Z.; Dai, B. *Synlett* **2010**, 2513. (c) Zhao, Q.; Curran, D. P.; Malacria, M.; Fensterbank, L.; Goddard, J.-P.; Laccôte, E. *Chem.—Eur. J.* **2011**, *17*, 9911. (d) Fuchter, M. J. *Chem.—Eur. J.* **2010**, *16*, 12286.

[19] (a) Langkopf, E.; Schinzer, D. *Chem. Rev.* **1995**, *95*, 1375. (b) Yamane, M.; Uera, K.; Narasaka, K. *Chem. Lett.* **2004**, *33*, 424. (c) Iwanami, K.; Seo, H.; Tobita, Y.; Oriyama, T. *Synthesis* **2005**, 0183. (d) Sa-ei, K.; Montgomery, J. *Org. Lett.* **2006**, *8*, 4441. (e) Safa, K. D.; Samani, S. P.; Tofangdarzadeh, S.; Hassanpour, A. *J. Organomet. Chem.* **2008**, *693*, 2004.

[20] Thomson, J. E.; Campbell, C. D.; Concellon, C.; Duguet, N.; Rix, K.; Slawin, A. M. Z.; Smith, A. D. *J. Org. Chem.* **2008**, *73*, 2784.

[21] Zhang, M.; Zhang, S.; Zhang, G.; Chen, F.; Cheng, J. *Tetrahedron Lett*. **2011**, *52*, 2480.

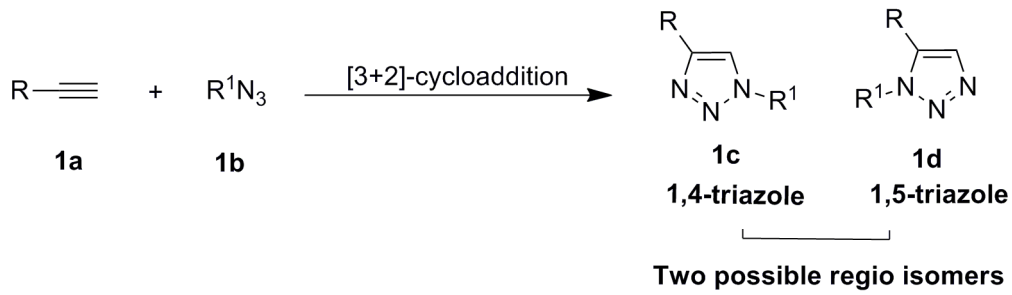
[22] Jacques, B.; Devaux, J.; Legras, R. *Macromolecules* **1996**, *29*, 3129.

Chapter 3

Combining oxidative NHC catalysis with the click chemistry to access 1,2,3-triazole derivatives

3.1. Introduction

In 2001, Sharpless was first introduced the term "click chemistry" to describe reactions defined by a set of stringent criteria: ''*The reaction must be modular, wide in scope, give very high yields, generate only inoffensive by-products that can be removed by non-chromatographic methods, and be stereospecific (but not necessarily enantioselective). The required process characteristics include simple reaction conditions, readily available starting materials and reagents, the use of no solvents or a solvent that is benign (such as water) or easily removed, and simple product isolation*.''[1a] To date, Huisgen cycloaddition (1,3-Dipolar cycloaddition) reaction between an azide and alkyne was one of the reactions to fulfill the above criteria, many known reactions e.g. Diels-Alder reactions, dipolar cycloaddition reactions, nucleophilic addition and substitution reactions fulfill these criteria to some extent. Although Huisgen discovered [3+2]-cycloaddition reaction in the 1960s, it didn't attract much attention at that time, because the reaction required high temperature and pressure.[1b] At the beginning of the 20th century, Sharpless and Meldal developed a mild and efficient copper (I) catalyzed 1,3-dipolar cycloaddition reaction between alkynes and azides to afford 1,2,3-triazoles in high regioselectivity.[2] The [3+2]-cycloaddition reaction between a terminal alkyne **1a** and an azide **1b** is schematically represented in scheme 1.



Scheme 1

After the discovery, the click chemistry has been widely exploited in the synthesis of biologically active and pharmaceutically important compounds apart from the synthesis of 1,2,3-triazoles.[3] A few of the 1,2,3-triazoles containing medicinally active compounds[3] (**2a**–**2f**) are shown in figure 1.

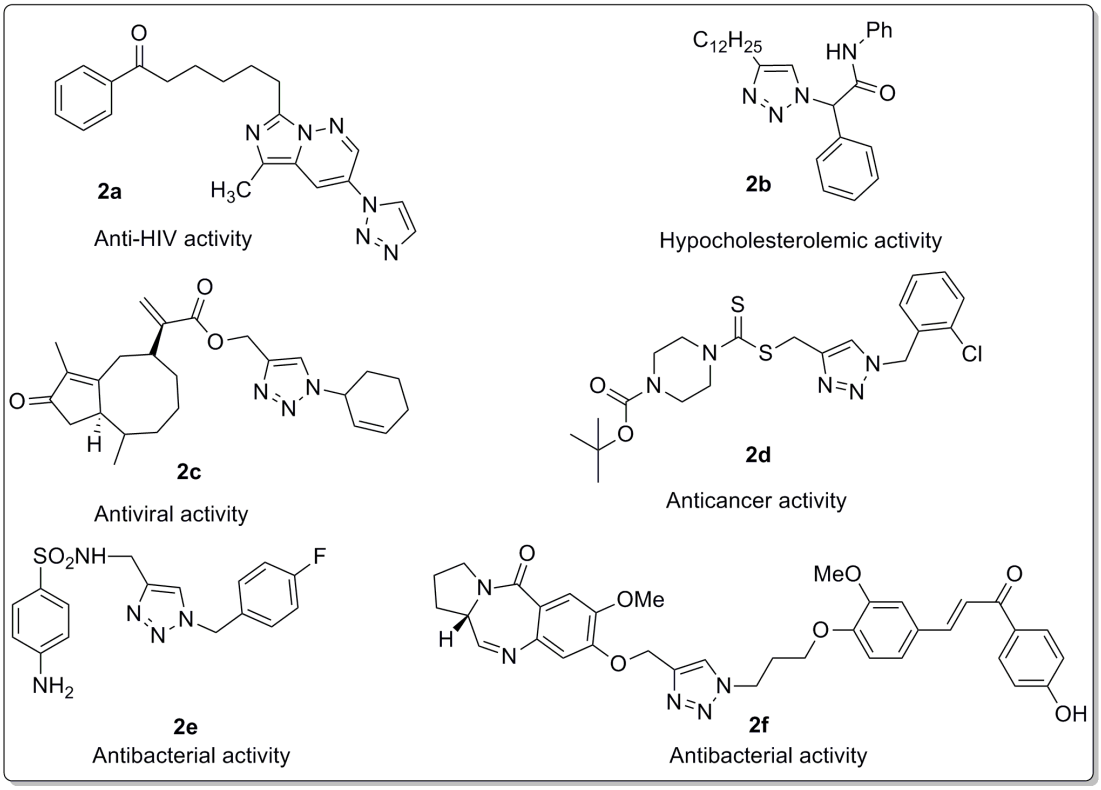
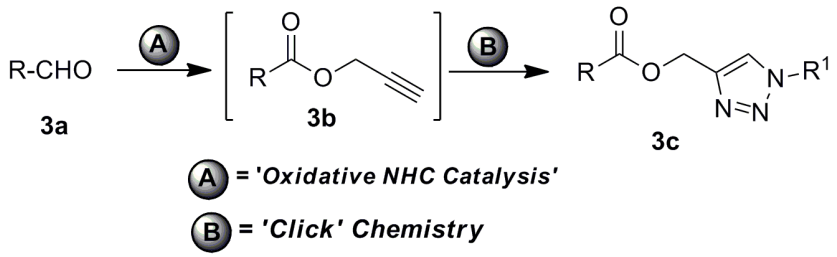


Figure 1

3.2. Results and Discussion

Since the 1,2,3-triazole derivatives are considered to be an important compounds, we became interested to develop a mild and efficient one-pot method for the direct conversion of aldehydes to 1,2,3-triazole derivatives by combining oxidative NHC catalysis with click chemistry.

Recently, we developed a mild and an efficient organocatalytic route for the esterification of aromatic aldehydes to aryl esters by using aryl boronic acids through oxidative NHC catalysis.[4] Although aryl esters were obtained in excellent yields, this method was not able to access aliphatic esters because aliphatic boronic acids didn't react with the aldehydes under the reaction conditions. So, we became interested to develop a competent method for the synthesis of aliphatic esters, particularly propargyl esters **3b**, because these esters could be derivatized in a straightforward manner to afford worthwhile compounds **3c** by using 'click' chemistry (Scheme 2).[5]



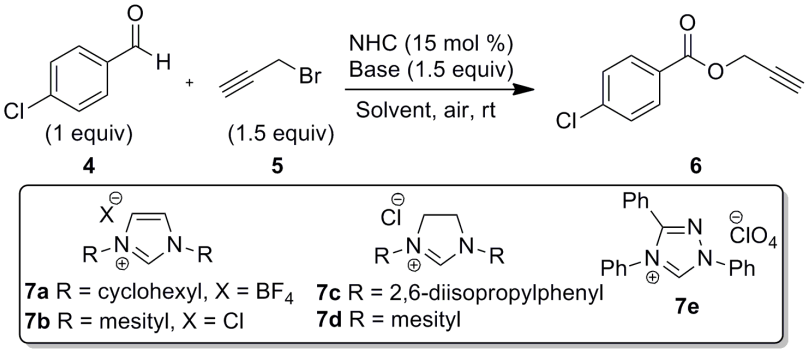
Scheme 2

Before exploring the one-pot process for the synthesis of 1,2,3-triazoles, we considered it necessary to optimize the first step, that is, the formation of the propargyl ester. Thus, we performed optimization studies for the first step by using *para*-chlorobenzaldehyde (**4**) and propargyl bromide (**5**) under oxidative NHC-catalyzed conditions. All of the reactions were conducted in an open atmosphere to ensure that sufficient oxygen is available for the oxidation reaction to take place. The results of the optimization studies are shown in Table 1.

A variety of NHCs (**7a**–**7e**) was used for this transformation. After careful screening, NHC **7d** was found to be the best catalyst and the conditions shown in Table 1, entry 4 was found to be the best conditions for this transformation. Next, because this particular oxidative esterification is not yet appeared in the literature, we examined the scope of this reaction with a variety of aldehydes, and the results are summarized in scheme 3.

Scheme 3 shows that range of propargyl esters of aromatic acids could be easily accessed using this method in good yields. Electron-poor aldehydes (**8d**–**8f**) reacted at faster rates than electron-rich aldehydes **8h** and benzaldehyde (**8c**). To our surprise, and in contrast to the literature report, cinnamaldehyde gave its corresponding propargyl ester **9i** in 72% yield under the standard conditions. Of course, the reaction condition was slightly different in the reported case.[6] This methodology also worked efficiently in the case of aliphatic aldehydes, such as

Table 1. Optimization Studies[a]

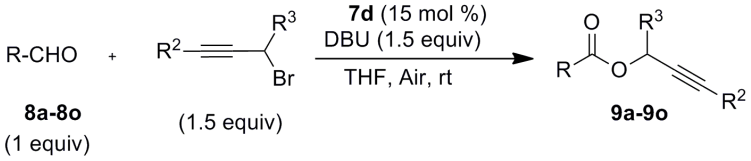


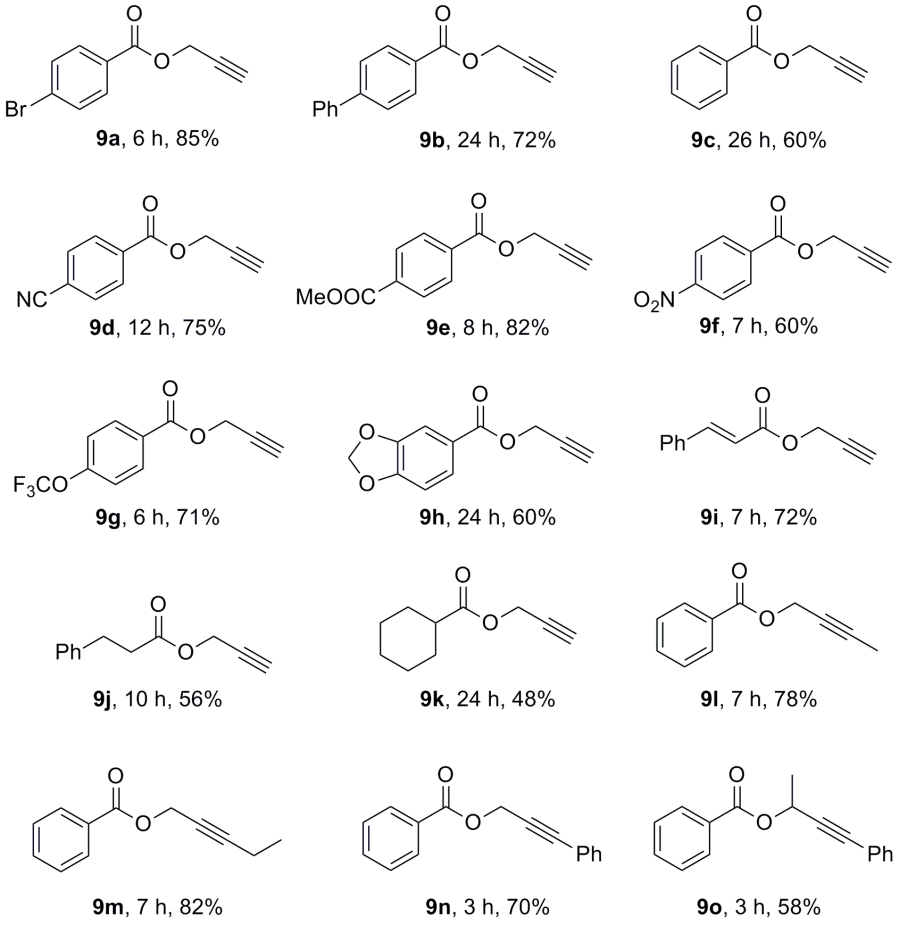
Entry[a]	NHC	Base	Solvent	Time [h]	Yield of 6 [%][b]
1	**7a**	DBU	THF	24	<5
2	**7b**	DBU	THF	24	12
3	**7c**	DBU	THF	24	40
4	**7d**	**DBU**	**THF**	**3**	**82**
5	**7e**	DBU	THF	24	10
6	**7d**	Li_2CO_3	THF	15	NR
7	**7d**	Cs_2CO_3	THF	14	10
8	**7d**	Et_3N	THF	24	5
9	**7d**	DBU	Toluene	15	67
10	**7d**	DBU	MeCN	15	28
11	**7d**	DBU	DME	15	60
12	**7d**	DBU	DMF	15	10
13	**7d**	DBU	DCE	15	25
14	**7d**	DBU	1,4-dioxane	15	54

[a]Reaction conditions: 0.1 M of **4** in solvent; rt = 32–35 °C; [b]Isolated yield; NR = No Reaction.

hydrocinnamaldehyde (**8j**) and cyclohexane carboxaldehyde (**8k**), and the corresponding esters **8j** and **8k** were obtained in moderate yields. The scope of the reaction was extended to internal (**9l**–**9n**) and secondary propargyl bromides **9o** by treating with benzaldehyde as a model substrate. In all those cases, the required propargyl esters (**9l**–**9o**) were isolated in satisfactory yields.

Scheme 3. Substrate scope in oxidative esterification reaction of aldehydes with propargyl bromide[a]





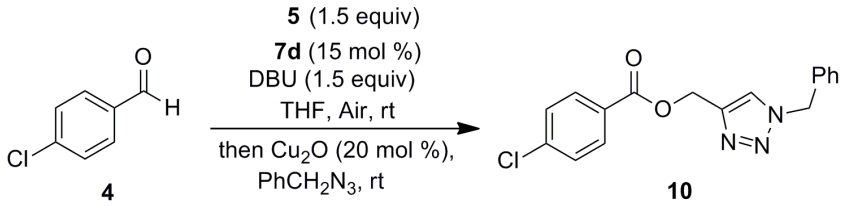
[a]Reaction conditions: 0.1 M of R-CHO in THF, rt = 32–35 °C.

Encouraged by the outcomes in propargyl ester formation, we shifted our attention towards developing a one-pot protocol for the synthesis of 1,2,3-triazole derivatives[7] from aldehydes by combining the oxidative NHC catalysis with copper-catalyzed 'click' chemistry.

The standardization experiments were carried out using benzyl azide and a copper catalyst, which were added straight away to the reaction mixture after the first step was complete (by TLC), and the results are summarized in Table 2. It is evident from the optimization studies that the required 1,2,3-triazole derivative was formed in all the reaction conditions tried (Table 2).

But, the yield of **10** was highest when 2 equivalents of azide and 20 mol % of cuprous oxide were used (entry 5) and, thus picked as a standard condition. No product was observed without a copper catalyst.

Table 2. Optimization Studies of one-pot reaction



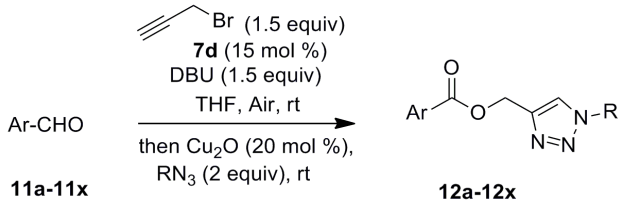
Entry[a]	Equiv. of Azide	Solvent	Time [h] [steps 1+2]	Yield [%][b]
1[c]	1.3	THF+H_2O (1 mL)	3 + 10	49
2[c]	1.5	THF+H_2O (1 mL)	3 + 6	55
3[c]	2	THF+H_2O (1 mL)	3 + 3	60
4	1.5	THF	3 + 16	65
5	**2**	**THF**	**3 + 12**	**78**
6[d]	2	THF	3 + 24	65
7[e]	2	THF	3 + 10	44

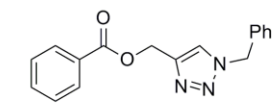
[a]Reaction conditions: 0.1 M of **4** in THF, rt = 32–35 °C. [b]Isolated yield of **10** over 2 steps. [c]Water was added along with copper catalyst. [d]CuI (20 mol %) was used instead of Cu_2O. [e]$CuSO_4.5H_2O$ (10 mol %) and sodium ascorbate (20 mol %) were used instead of Cu_2O.

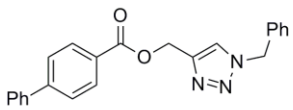
This optimized condition was investigated for making a wide range of substituted 1,2,3-triazoles employing a variety of aromatic aldehydes and azides (Scheme 4). The scope of this one-pot methodology has been realized, as shown in scheme 4, and 1,2,3-triazole derivatives were obtained in moderate to good yields in a regio-selective manner. Electron poor aldehydes (**11d**, **11e** and **11g**), except *p*-nitrobenzaldehyde (**11f**), were transformed to the desired products at relatively faster rate than electron rich aldehydes (**11h**–**11j**).

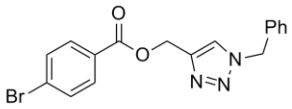
This method was also effective in converting few hetero-aromatic aldehydes to their corresponding 1,2,3-triazole derivatives **12k** and **12l** in moderate yields. Not only with benzyl azide, was this method found to be equally effective for aromatic as well as other azides (Examples **12q**–**12x**).

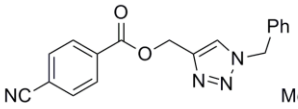
Scheme 4. Substrate Scope of One-Pot reaction[a]

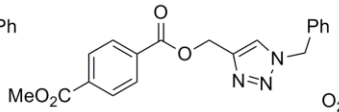


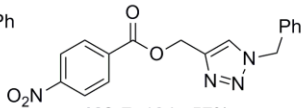

12a, 26+11 h, 60%

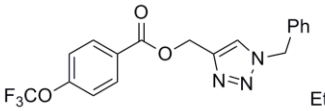

12b, 24+15 h, 60%

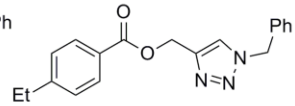

12c, 6+18 h, 80%

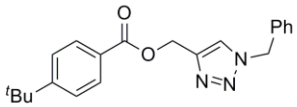

12d, 12+13 h, 62%

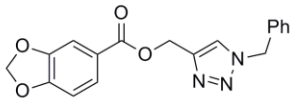

12e, 8+13 h, 70%

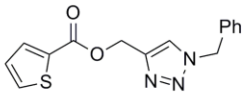

12f, 7+18 h, 57%

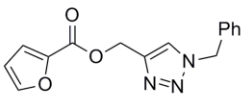

12g, 6+14 h, 70%

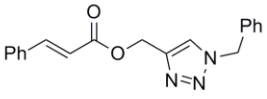

12h, 24+17 h, 54%

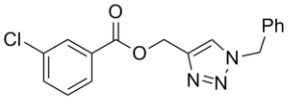

12i, 24+17 h, 59%

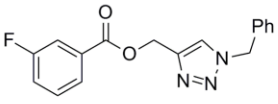

12j, 24+18 h, 58%

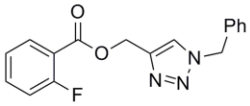

12k, 28+36 h, 48%

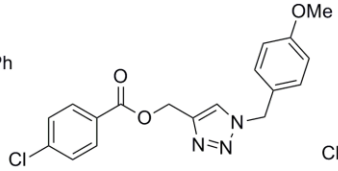

12l, 9+14 h, 52%

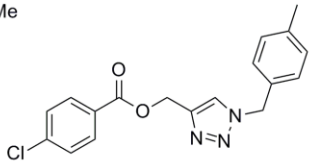

12m, 7+28 h, 65%

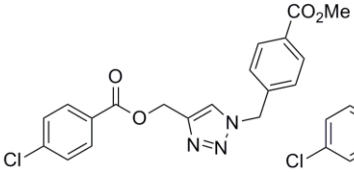

12n, 13+12 h, 78%

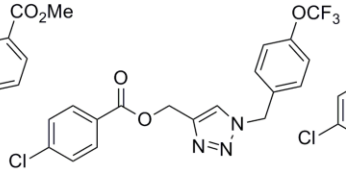

12o, 13+14 h, 73%

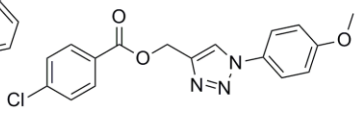

12p, 7+13 h, 62%

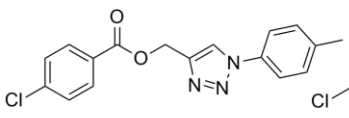

12q, 3+36 h, 55%

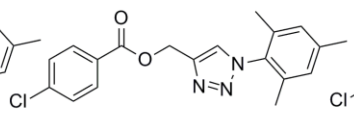

12r, 3+15 h, 67%

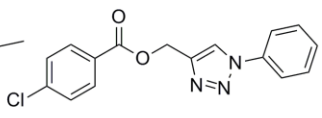

12s, 3+20 h, 80%


12t, 3+15 h, 82%


12u, 3+42 h, 52%


12v, 3+42 h, 69%


12w, 3+42 h, 65%

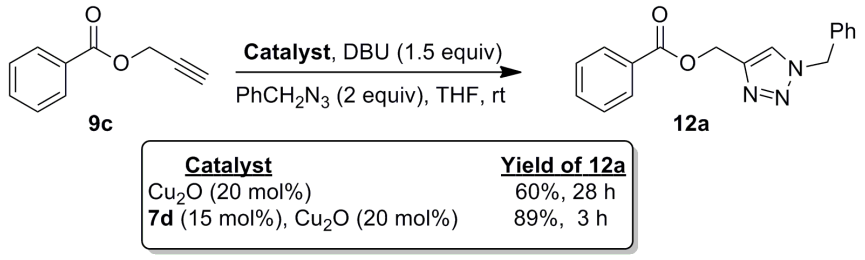

12x, 3+40 h, 60%

[a]Reaction conditions: 0.1 M of Ar-CHO in THF, rt = 32–35 ˚C.

Since NHC catalyzed oxidation of aldehydes to their respective acids is precedented in the literature,[8] we anticipated that the first step in our methodology proceeds through the initial formation of acid followed by alkylation with propargyl bromide.

To confirm this, few experiments were performed. In one of the experiments, *p*-chlorobenzaldehyde (**4**) was treated with the catalytic amount of **7d** and DBU (1.5 equiv) under open air, and the product *p*-chlorobenzoic acid was isolated in 80% yield within 3 h. In another experiment, *p*-chlorobenzoic acid was reacted with propargyl bromide (**5**) (1.5 equiv) in the presence of DBU (1.5 equiv), and the propargyl ester **6** was formed almost in quantitative yield in 5 h. Based on these experimental observations, we strongly believe that the reaction proceeds through oxidation of aldehyde to acid followed by propargylation.

Another interesting point was observed during the standardization of this methodology. As shown in scheme 3, benzaldehyde was converted to its propargyl ester **9c** in 60% yield. At the same time, under the one-pot reaction conditions, benzaldehyde gave the 1,2,3-triazole derivative **12a** in 60% over all yield. This clearly implies that the triazole formation step is almost quantitative in this case. But, when the propargyl ester **9c** was directly treated with cuprous oxide and benzyl azide without **7d**, the product **12a** was obtained only in 60% yield even after 28 h (Scheme 5). The reaction rate and the yield of **12a** were increased by the addition of 15 mol % of **7d** to the reaction mixture (Scheme 5). Based on these observations, we presume that NHC also influences the triazole formation step probably by forming a complex with copper catalyst, thereby increasing its catalytic activity.[9]



[a]Reaction conditions: 0.1 M of **9c** in THF, rt = 32–35 °C.

Scheme 5

3.3. Conclusion

In conclusion, a one-pot method was developed for the synthesis of 1,2,3-triazole derivatives by combining the oxidative NHC catalysis with 'click' chemistry. This methodology could be utilized for the synthesis of a diverse range of 1,2,3-triazole derivatives under mild reaction conditions starting from aldehydes. Since one-pot synthesis is an integral part of sustainable chemistry, we believe, the methodology would find some applications in near future.

3.4. Experimental sections

General information

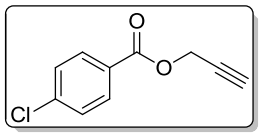
Most of the reagents and starting materials used were purchased from commercial sources and used as such. NHC precursor **7e** was prepared according to the literature procedure.[10] All the organic azides used in this methodology were prepared following a literature procedure.[11] ^{1}H and ^{13}C spectra were recorded in $CDCl_3$ on 400 MHz Brucker FT-NMR spectrometer. Chemical shifts values are reported in parts per million relative to TMS. High resolution mass spectra were recorded on Waters Q-TOF Premier-HAB213 spectrometer. FT-IR spectra were recorded on a Brucker FT-IR spectrometer equipped with a PIKE MIRacle ATR. Thin layer chromatography was performed on Merck silica gel 60 F_{254} TLC plates using EtOAc/Hexane as an eluent. Column chromatography was carried out through silica gel (100-200 mesh).

General procedure for the NHC catalyzed aerobic oxidation of aryl aldehydes with propargyl bromides

Aldehyde (0.6 mmol) was added to a suspension of NHC **7d** (0.09 mmol) and DBU (0.9 mmol) in THF (6 mL) at room temperature (32–35 $^{\circ}C$) and stirred for half an hour. Propargyl bromide (**5**) (80% solution in toluene, 0.9 mmol) was added to the reaction mixture in a drop-wise manner, and the resulting suspension was stirred until most of the aldehyde was consumed (by TLC). The reaction mass was then filtered, washed with EtOAc (10 mL) and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure, and the residue was purified through silica gel column using EtOAc/Hexane mixture as an eluent.

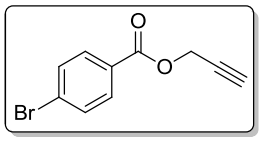
Characterization data of compounds (6 & 9a–9o):

Prop-2-yn-1-yl-4-chloro benzoate (**6**):[12]



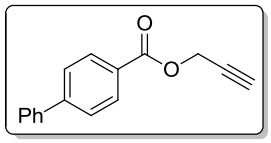
Colorless oil; Yield 82% (95.8 mg); FT IR (ATR) 3299 (≡CH), 2131 (C≡C), 1722 (C=O) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$), δ 8.00 (d, J = 8.72 Hz, 2H), 7.42 (d, J = 8.72 Hz, 2H), 4.92 (d, J =2.48 Hz, 2H), 2.53 (t, J = 2.48 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$), δ 165.0, 139.9, 131.2, 128.8, 127.8, 77.5, 75.2, 52.7.

Prop-2-yn-1-yl-4-bromo benzoate (**9a**):[13]



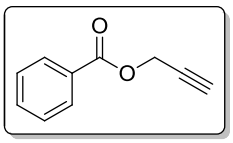
Colorless oil; Yield 85% (121.9 mg); FT IR (ATR) 3297 (≡CH), 2130 (C≡C), 1721 (C=O) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$), δ 7.93 (d, J = 8.72 Hz, 2H), 7.59 (d, J = 8.72 Hz, 2H), 4.92 (d, J = 2.48 Hz, 2H), 2.53 (t, J = 2.48 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$), δ 165.1, 131.8, 131.3, 128.6, 128.3, 77.5, 75.3, 52.7.

Prop-2-yn-1-yl-4-Phenyl benzoate (9b):



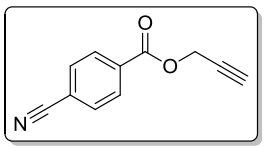
White solid; Yield 72% (102.1 mg); m.p. 106-107 °C; FT IR (ATR) 3250 (≡CH), 2121 (C≡C), 1713 (C=O) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$), δ 8.14 (d, J = 8.60 Hz, 2H), 7.68 (d, J = 8.60 Hz, 2H), 7.64–7.61 (m, 2H), 7.50–7.45 (m, 2H), 7.43 –7.38 (m, 1H), 4.95 (d, J = 2.48 Hz, 2H), 2.54 (t, J = 2.48 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$), δ 165.7, 146.1, 139.9, 130.4, 129.0, 128.3, 128.1, 127.3, 127.1, 77.8, 75.0, 52.5; HRMS (ESI); *m/z* calcd for $C_{16}H_{13}O_2$ $[M+H]^+$: 237.0915; found: 237.0916.

Prop-2-yn1-yl benzoate (9c):[12]



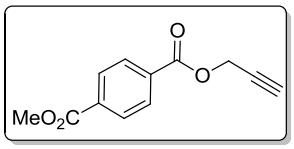
Colorless oil; Yield 60% (57.7 mg); FT IR (ATR) 3296 (≡CH), 2130 (C≡C), 1720 (C=O) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$), δ 8.09–8.06 (m, 2H), 7.61–7.56 (m, 1H), 7.48–7.43 (m, 2H), 4.93 (d, J = 2.44 Hz, 2H), 2.52 (t, J = 2.48 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$), δ 165.8, 133.4, 129.8, 129.4, 128.5, 77.7, 75.0, 52.5.

Prop-2-yn-1-yl-4-cyano benzoate (9d):[13]



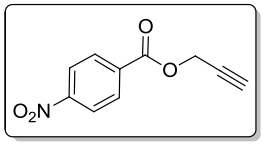
White solid; Yield 75% (83.3 mg); m.p. 96–97 °C; FT IR (ATR) 3267 (≡CH), 2360 (C≡N), 2230 (C≡C), 1728 (C=O) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$), δ 8.18 (d, J = 8.72 Hz, 2H), 7.76 (d, J = 8.72 Hz, 2H), 4.96 (d, J = 2.48 Hz, 2H), 2.55 (t, J = 2.48 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$), δ 164.2, 133.2, 132.3, 130.3, 117.9, 116.8, 77.2, 75.7, 53.2.

Methyl prop-2-yn-1-yl terephthalate (9e):[14]



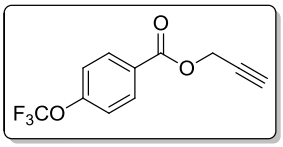
White solid; Yield 75% (104.5 mg); m.p. 88–89 °C; FT IR (ATR) 3248 (≡CH), 2130 (C≡C), 1720 (C=O) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), δ 8.08–8.03 (m, 4H), 4.88 (d, J = 2.48 Hz, 2H), 3.95 (s, 3H), 2.48 (t, J = 2.48 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$), δ 166.2, 165.0, 134.3, 133.1, 129.8, 129.6, 77.2, 75.4, 52.9, 52.5;

Prop-2-yn-1-yl-4-nitro benzoate (9f):[12]



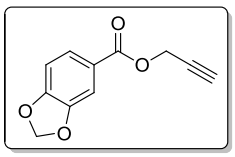
Pale yellow solid; Yield 60% (73.9 mg); m.p. 96–97 °C; FT IR (ATR) 3288 (≡CH), 2132 (C≡C), 1720 (C=O) 1608, 1523 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), δ 8.31 (d, J = 9.04 Hz, 2H), 8.23 (d, J = 9.04 Hz, 2H), 4.97 (d, J = 2.48 Hz, 2H), 2.56 (t, J = 2.48 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$), δ 164.0, 150.8, 134.7, 131.0, 123.7, 77.4, 75.8, 53.3.

Prop-2- yn-1-yl-4-trifluoro methoxy benzoate (9g):[15]



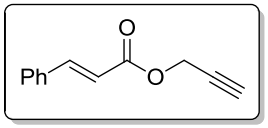
Colorless oil; Yield 71% (104.0 mg); FT IR (ATR) 3306 (≡CH), 2132 (C≡C), 1727 (C=O), cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), δ 8.14–8.10 (m, 2H), 7.29–7.26 (m, 2H), 4.93 (d, J = 2.48 Hz, 2H), 2.53 (t, J = 2.48 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$), δ 164.6, 152.9 (d, J_{C-F} = 2.0 Hz), 131.9, 127.8, 120.3 (q, J_{C-F} = 257 Hz), 120.3, 77.4, 75.3, 52.7.

Prop-2-yn-1-yl-3,4-methylene dioxy benzoate (**9h**):



Off white solid; Yield 60% (73.5 mg); m.p. 59–60 °C; FT IR (ATR) 3245 (≡CH), 2128 (C≡C), 1708 (C=O) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), δ 7.68 (dd, J = 8.20, 1.68 Hz, 1H), 7.48 (d, J = 1.68 Hz, 1H), 6.84 (d, J = 8.20 Hz, 1H), 6.04 (s, 2H), 4.88 (d, J = 2.44 Hz, 2H), 2.52 (t, J = 2.45 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$), δ 165.2, 152.0, 147.8, 125.8, 123.3, 109.7, 108.1, 101.9, 77.8, 75.0, 52.4; HRMS (ESI): *m/z* calcd for $C_{11}H_9O_4$ $[M + H]^+$: 205.0501; found: 205.0504.

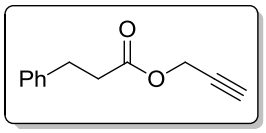
Prop-2-yn-1-yl cinnamate (9i):[12]



Colorless oil; Yield 72% (80.5 mg); FT IR (ATR) 3293 (≡CH), 2129 (C≡C), 1712 (C=O) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), δ 7.75 (d, J = 16.0 Hz, 1H), 7.55–7.51 (m, 2H), 7.41-7.38 (m, 3H), 6.47 (d, J = 16.0 Hz, 1H),

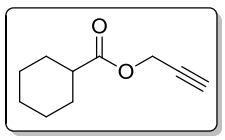
4.82 (d, J = 2.48 Hz, 2H), 2.52 (t, J = 2.48 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$), δ 166.1, 146.0, 134.2, 130.6, 129.0, 128.2, 117.0, 77.8, 74.9, 52.1.

Prop-2-yn-1-yl 3-phenylpropanoate (9j):[12]



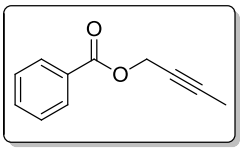
Colorless oil; Yield 56% (63.2 mg); FT IR (ATR) 3288 (≡CH), 2126 (C≡C), 1740 (C=O) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$), δ 7.32–7.28 (m, 2H), 7.23–7.20 (m, 3H), 4.69 (d, J = 2.48 Hz, 2H), 2.98 (t, J = 7.56 Hz, 2H), 2.69 (t, J = 7.56 Hz, 2H), 2.48 (t, J = 2.48 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$), δ 172.2, 140.3, 128.7, 128.4, 126.5, 77.8, 75.0, 52.1, 35.7, 30.9.

Prop-2-yn-1-yl cyclohexanecarboxylate (9k):[16]



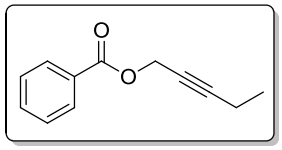
Colorless oil; Yield 48% (47.9 mg); FT IR (ATR) 3292 (≡CH), 2131 (C≡C), 1736 (C=O) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$), δ 4.66 (d, J = 2.48, 2H), 2.45 (t, J = 2.48 Hz, 1H), 2.38–2.31 (m, 1H), 1.93–1.25 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$), δ 175.4, 78.1, 74.8, 51.8, 43.0, 29.0, 25.8, 25.5.

But-2-yn-1-yl benzoate (9l):[17]



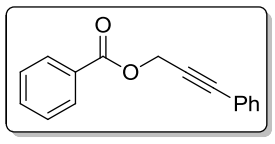
Colorless oil; Yield 78% (81.5 mg); FT IR (ATR) 2240 (C≡C), 1721 (C=O) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$), δ 8.09–8.06 (m, 2H), 7.59–7.55 (m, 1H), 7.47–7.42 (m, 2H), 4.89 (q, J = 2.44 Hz, 2H), 1.88 (t, J = 2.44 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$), δ 166.1, 133.3, 129.9, 129.8, 128.5, 83.4, 73.4, 53.4, 3.8.

Pent-2-yn-1-yl benzoate (9m):[18]



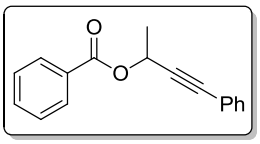
Colorless oil; Yield 82% (92.6 mg); FT IR (ATR) 2242 (C≡C), 1721 (C=O) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$), δ 8.09–8.06 (m, 2H), 7.59–7.54 (m, 1H), 7.46–7.42 (m, 2H), 4.91 (t, J = 2.20 Hz, 2H), 2.26 (qt, J = 7.54, 2.20 Hz, 2H), 1.15 (t, J = 7.54 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$), δ 166.1, 133.2, 130.2, 129.9, 128.5, 89.1, 73.5, 53.4, 13.7, 12.6.

3-Phenylprop-2-yn-1-yl benzoate (9n):[19]



Colorless oil; Yield 60% (85.1 mg); FT IR (ATR) 2130 (C≡C), 1722 (C=O) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$), δ 8.13–8.10 (m, 2H), 7.60–7.56 (m, 2H), 7.50–7.44 (m, 5H), 7.34–7.33 (m, 1H), 5.17 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$), δ 166.1, 133.4, 132.1, 130.0, 129.9, 128.9, 128.6, 128.4, 122.3, 86.7, 83.2, 53.5.

4-Phenylbut-3-yn-2-yl benzoate (9o):[19]



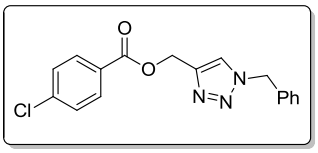
Colorless oil; Yield 58% (87.1 mg); FT IR (ATR) 2229 (C≡C), 1722 (C=O) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), δ 8.13–8.10 (m, 2H), 7.60–7.56 (m, 1H), 7.49–7.44 (m, 4H), 7.33–7.29 (m, 3H), 5.95 (q, J = 6.68 Hz, 1H), 1.73 (d, J = 6.68 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$), δ 165.7, 133.3, 132.0, 130.1, 129.9, 128.7, 128.5, 128.4, 127.8, 87.6, 84.9, 61.5, 21.8.

General procedure for the NHC catalyzed one-pot synthesis of 1,2,3-triazole derivatives (12a–12x)

Aromatic aldehyde (0.6 mmol) was added to a suspension of NHC **7d** (0.09 mmol) and DBU (0.9 mmol) in THF (6 mL) at room temperature (32–35 °C) and stirred for half an hour. Propargyl bromide (**5**) (80% solution in toluene, 0.9 mmol) was added in a dropwise manner and the resulting suspension was stirred until most of the aldehyde was consumed (by TLC). Cuprous oxide (0.12 mmol) and azide (1.2 mmol) were added in the same reaction mass and the stirring was continued until most of the propargyl ester, which was formed in the first step, was consumed. The reaction mass was then filtered, washed with EtOAc (10 mL) and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the residue was purified through silica gel column using EtOAc/Hexane mixture as an eluent.

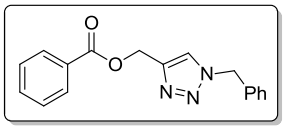
Characterization of compounds (10 & 12a–12x)

(1-benzyl-1H-1,2,3-triazol-4-yl)methyl-4-chlorobenzoate (10):



Pale yellow solid; Yield 78% (153.4 mg); m.p. 114–115 °C; FT IR (ATR) 1719 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), δ 7.95 (d, J = 8.64 Hz, 2H), 7.60 (s, 1H), 7.40–7.35 (m, 5H), 7.31–7.27 (m, 2H), 5.53 (s, 2H), 5.43 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$), δ 165.6, 143.1, 139.7, 134.3, 131.2, 129.2, 128.9, 128.8, 128.2, 128.1, 123.9, 58.2, 54.3; HRMS (ESI): *m/z* calcd for $C_{17}H_{14}ClN_3O_2$ $[M+Na]^+$: 350.0673; found: 350.0678.

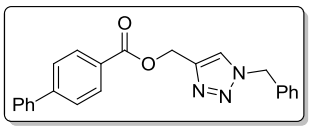
(1-benzyl-1H-1,2,3-triazol-4-yl)methyl benzoate (12a):[20]



White solid; Yield 60% (105.6 mg); m.p. 122–123 °C; FT IR (ATR) 1710 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), δ 8.02 (dd, J = 8.48, 1.40 Hz, 2H), 7.61 (s, 1H), 7.57–7.53 (m, 1H), 7.43–7.34 (m, 5H), 7.31–7.27 (m, 2H), 5.53 (s, 2H), 5.44

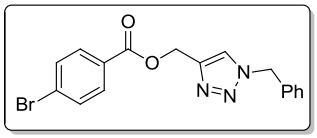
(s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$), δ 166.5, 143.4, 134.4, 133.2, 129.8, 129.7, 129.2, 128.9, 128.4, 128.2, 123.9, 58.1, 54.3.

(1-benzyl-1H-1,2,3-triazol-4-yl)methyl[1,1'-biphenyl]-4-carboxylate (12b):



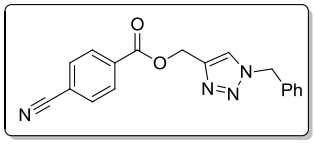
Golden yellow solid; Yield 60% (133.0 mg); m.p. 153–154 °C; FT IR (ATR) 1714 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$), δ 8.11 (d, J = 8.56 Hz, 2H), 7.66 (d, J = 8.59 Hz, 2H), 7.65–7.62 (m, 3H), 7.51–7.46 (m, 2H), 7.44–7.37 (m, 4H), 7.35–7.30 (m, 2H), 5.56 (s, 2H), 5.50 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$), δ 166.4, 145.9, 143.4, 139.9, 134.4, 130.3, 129.2, 129.0, 128.9, 128.4, 128.2, 128.2, 127.3, 127.1, 123.9, 58.1, 54.3; HRMS (ESI); *m/z* calcd for $C_{23}H_{20}N_3O_2$ $[M+H]^+$: 370.1555; found: 370.1551.

(1-benzyl-1H-1,2,3-triazol-4-yl)methyl-4-bromobenzoate (12c):



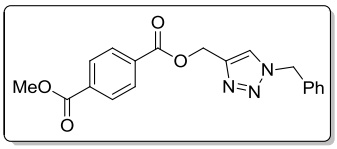
White solid; Yield 80% (178.7 mg); m.p. 114–115 °C; FT IR (ATR) 1730 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$), δ 7.87 (d, J = 8.64 Hz, 2H), 7.60 (s, 1H), 7.55 (d, J = 8.64 Hz, 2H), 7.41–7.36 (m, 3H), 7.30–7.27 (m, 2H), 5.53 (s, 2H), 5.43 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$), δ 165.8, 143.0, 134.3, 131.8, 131.3, 129.2, 128.9, 128.6, 128.4, 128.2, 123.9, 58.2, 54.3; HRMS (ESI); *m/z* calcd for $C_{17}H_{15}BrN_3O_2$ $[M+H]^+$: 372.0347; found: 372.0343.

(1-benzyl-1H-1,2,3-triazol-4-yl)methyl 4-cyanobenzoate (12d):



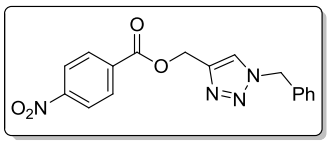
Pale orange solid; Yield 62% (118.4 mg); m.p. 131–132 °C; FT IR (ATR) 2231, 1719 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$), δ 8.12 (d, J = 8.60 Hz, 2H), 7.71 (d, J = 8.60 Hz, 2H), 7.60 (s, 1H), 7.41–7.35 (m, 3H), 7.32–7.265 (m, 2H), 5.53 (s, 2H), 5.46 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$), δ 164.8, 142.6, 134.2, 133.5, 132.2, 130.3, 129.2, 129.0, 128.2, 124.0, 118.0, 116.6, 58.6, 54.3; HRMS (ESI): *m/z* calcd for $C_{18}H_{15}N_4O_2$ $[M+H]^+$: 319.1195; found: 319.1197.

(1-benzyl-1H-1,2,3-triazol-4-yl)methyl methyl terephthalate (12e):



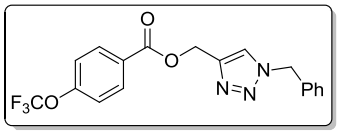
Off white solid; Yield 70% (147.6 mg); m.p. 140–141 °C; FT IR (ATR) 2231, 1716 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$), δ 8.08 (s, 4H), 7.62 (s, 1H), 7.40–7.36 (m, 3H), 7.30–7.28 (m, 2H), 5.54 (s, 2H), 5.46 (s, 2H), 3.94 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$), δ 166.2, 165.7, 142.9, 134.3, 134.1, 133.5, 129.8, 129.6, 129.2, 128.9, 128.2, 124.0, 58.4, 54.3, 52.5; HRMS (ESI): *m/z* calcd for $C_{18}H_{17}N_3O_4$ $[M+H]^+$: 352.1297; found: 352.1299.

(1-benzyl-1H-1,2,3-triazol-4-yl)methyl 4-nitrobenzoate (12f):



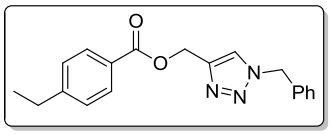
Pale yellow solid; Yield 57% (115.7 mg); m.p. 140–141 °C; FT IR (ATR) 1719, 1519, 1347 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), δ 7.88 (d, J = 8.64 Hz, 2H), 7.60 (s, 1H), 7.55 (d, J = 8.68 Hz, 2H), 7.41–7.34 (m, 3H), 7.31–7.27 (m, 2H), 5.53 (s, 2H), 5.43 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$), δ 164.6, 150.7, 135.1, 134.2, 130.9, 129.2, 129.0, 128.2, 123.6, 77.3, 58.8, 54.6, 54.4; HRMS (ESI): *m/z* calcd for $C_{17}H_{15}N_4O_4$ $[M+H]^+$: 339.1093; found: 339.1092.

(1-benzyl-1H-1,2,3-triazol-4-yl)methyl-4-(trifluoromethoxy)benzoate (12g):



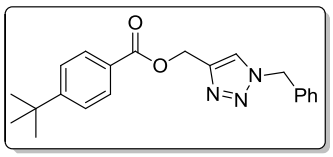
Pale yellow solid; Yield 70% (158.5 mg); m.p. 110–111 °C; FT IR (ATR) 1719 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), δ 8.06 (d, J = 8.96 Hz, 2H), 7.60 (s, 1H), 7.41–7.34 (m, 3H), 7.31–7.23 (m, 4H), 5.53 (s, 2H) 5.44 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$), δ 165.3, 152.8, 143.0, 134.3, 131.8, 129.3, 129.2, 128.9, 128.2, 128.1, 123.9, 120.3, 58.3, 54.3; HRMS (ESI): *m/z* calcd for $C_{18}H_{15}F_3N_3O_3$ $[M+H]^+$: 378.1065; found: 378.1067.

(1-benzyl-1H-1,2,3-triazol-4-yl)methyl 4-ethylbenzoate (12h):



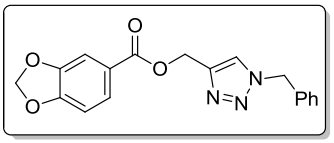
Pale yellow solid; Yield 54% (104.1 mg); m.p. 98–99 °C; FT IR (ATR) 1702 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), δ 7.93 (d, J = 8.32 Hz, 2H), 7.60 (s, 1H), 7.40–7.35 (m, 3H), 7.30–7.26 (m, 2H), 7.23 (d, J = 8.32 Hz, 2H), 5.52 (s, 2H), 5.43 (s, 2H), 2.68 (q, J = 7.64 Hz, 2H), 1.23 (t, J = 7.64 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$), δ 166.5, 150.2, 143.5, 134.4, 129.9, 129.2, 128.9, 128.2, 127.9, 127.2, 123.8, 57.9, 54.3, 29.0, 15.2; HRMS (ESI): *m/z* calcd for $C_{18}H_{16}N_3O_4$ $[M+H]^+$: 322.1555; found: 322.1552.

(1-benzyl-1H-1,2,3-triazol-4-yl)methyl 4-(tert-butyl) benzoate (12i):



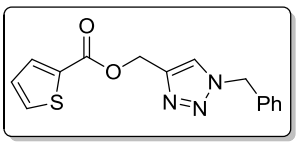
Pale yellow solid; Yield 59% (123.7 mg); m.p. 98–99 °C; FT IR (ATR) 1708 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), δ 7.95 (d, J = 8.64 Hz, 2H), 7.60 (s, 1H), 7.43 (d, J = 8.64 Hz, 2H), 7.40–7.35 (m, 3H), 7.29–7.26 (m, 2H), 5.52 (s, 2H), 5.43 (s, 2H), 1.32 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$), δ 166.5, 156.9, 143.5, 134.4, 129.6, 129.2, 128.9, 128.2, 126.9, 125.4, 123.8, 57.9, 54.3, 35.1, 31.1; HRMS (ESI): *m/z* calcd for $C_{21}H_{24}N_3O_2$ $[M+H]^+$: 350.1868; found: 350.1862.

(1-benzyl-1H-1,2,3-triazol-4-yl)methylbenzo[d][1,3]dioxole-5-carboxylate (12j):



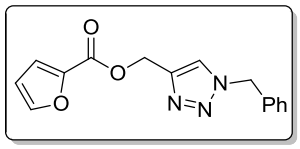
Off white solid; Yield 60% (121.4 mg); m.p. 148–149 °C; FT IR (ATR) 1711 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$), δ 7.63 (dd, J = 8.20, 1.72 Hz, 1H), 7.59 (s, 1H), 7.44 (d, J = 1.68 Hz, 1H), 7.41–7.35 (m, 3H), 7.30–7.27 (m, 2H), 6.81 (d, J = 8.12 Hz, 1H), 6.02 (s, 2H), 5.52 (s, 2H), 5.40 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$), δ 165.8, 151.8, 147.7, 143.4, 134.4, 129.2, 128.9, 128.2, 125.7, 123.8, 123.7, 109.6, 108.0, 101.8, 58.0, 54.3; HRMS (ESI): *m/z* calcd for $C_{18}H_{16}N_3O_4$ $[M+H]^+$: 338.1141; found: 338.1142.

(1-benzyl-1H-1,2,3-triazol-4-yl)methyl thiophene-2-carboxylate (12k):



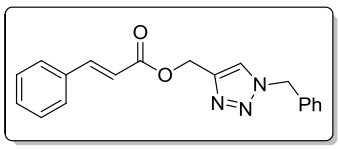
Off white solid; Yield 48% (86.2 mg); m.p. 85–86 °C; FT IR (ATR) 1707 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$), δ 7.78 (dd, J = 3.78, 1.24 Hz, 1H), 7.61 (s, 1H), 7.55 (dd, J = 5.0, 1.24 Hz, 1H), 7.40–7.34 (m, 3H), 7.30–7.26 (m, 2H), 7.07 (dd, J = 5.0, 3.80 Hz, 1H), 5.52 (s, 2H), 5.41 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$), δ 162.1, 143.2, 134.4, 133.9, 133.2, 132.9, 129.2, 128.9, 128.2, 127.8, 124.0, 58.2, 54.3; HRMS (ESI): *m/z* calcd for $C_{15}H_{14}N_3O_2S$ $[M+H]^+$: 300.0806; found: 300.0804.

(1-benzyl-1H-1,2,3-triazol-4-yl)methyl furan-2-carboxylate (12l):



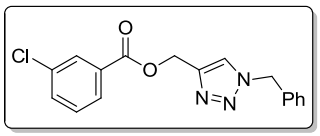
Pale brown solid; Yield 48% (81.6 mg); m.p. 84–85 °C; FT IR (ATR) 1702 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$), δ 7.62 (s, 1H), 7.55 (s, 1H), 7.39–7.34 (m, 3H), 7.28–7.26 (m, 2H), 7.17–7.16 (m, 1H), 6.48–6.47 (m, 1H), 5.51 (s, 2H), 5.40 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$), δ 158.5, 146.7, 144.1, 143.0, 134.3, 129.2, 128.9, 128.2, 124.1, 118.6, 111.9, 57.9, 54.3; HRMS (ESI): *m/z* calcd for $C_{15}H_{14}N_3O_3$ $[M+H]^+$: 284.1035; found: 284.1034.

(1-benzyl-1H-1,2,3-triazol-4-yl)methyl cinnamate (12m):



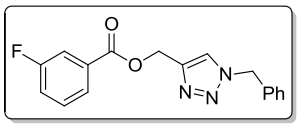
White solid; Yield 65% (124.6 mg); m.p. 123–124 °C; FT IR (ATR) 1715 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$), δ 7.69 (d, J = 16.00 Hz, 1H), 7.58 (s, 1H), 7.52–7.47 (m, 2H), 7.41–7.35 (m, 6H), 7.30–7.27 (m, 2H), 6.42 (d, J = 16.04 Hz, 1H), 5.53 (s, 2H), 5.33 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$), δ 166.8, 145.6, 134.4, 134.2, 130.5, 129.2, 128.9, 128.9, 128.2, 128.2, 123.7, 117.5, 77.2, 57.7, 54.3; HRMS (ESI): *m/z* calcd for $C_{19}H_{18}N_3O_2$ $[M+H]^+$: 320.1399; found: 320.1399.

(1-benzyl-1H-1,2,3-triazol-4-yl)methyl 3-chlorobenzoate (12n):



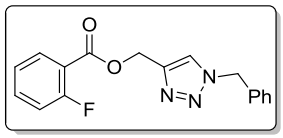
Pale orange solid; Yield 78% (153.4 mg); m.p. 104–105 °C; FT IR (ATR) 1721 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), δ 7.99 (t, J = 1.84 Hz, 1H), 7.91–7.89 (m, 1H), 7.60 (s, 1H), 7.51 (ddd, J = 8.0, 2.20, 1.84 Hz, 1H), 7.40–7.26 (m, 6H), 5.53 (s, 2H), 5.44 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$), δ 165.3, 143.0, 134.6, 134.3, 133.2, 131.4, 129.8, 129.7, 129.2, 128.9, 128.2, 127.9, 123.9, 58.4, 54.3; HRMS (ESI): *m/z* calcd for $C_{17}H_{15}ClN_3O_2$ $[M+H]^+$: 328.0853; found: 328.0855.

(1-benzyl-1H-1,2,3-triazol-4-yl)methyl 3-fluorobenzoate (12o):



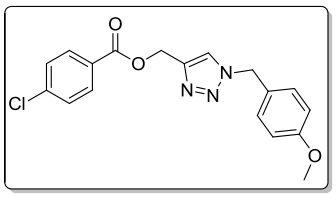
White solid; Yield 73% (136.4 mg); m.p. 126-127 °C; FT IR (ATR) 1716 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), δ 7.83–7.80 (m, 1H), 7.71–7.68 (m, 1H), 7.60 (s, 1H), 7.42–7.35 (m, 4H), 7.31–7.22 (m, 3H), 5.53 (s, 2H), 5.45 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$), δ 165.3–161.2 (d, J_{C-F} = 407 Hz), 163.7, 143.0, 134.3, 131.9 (d, J_{C-F} = 8 Hz), 130.1 (d, J_{C-F} = 7 Hz), 129.2, 128.9, 128.2, 125.5 (d, J_{C-F} = 3 Hz), 123.9, 120.3 (d, J_{C-F} = 21 Hz) , 116.6 (d, J_{C-F} = 24 Hz), 58.4, 54.3; HRMS (ESI): *m/z* calcd for $C_{17}H_{15}ClN_3O_2$ $[M+H]^+$: 328.0853; found: 328.0855.

(1-benzyl-1H-1,2,3-triazol-4-yl)methyl 2-fluorobenzoate (12p):



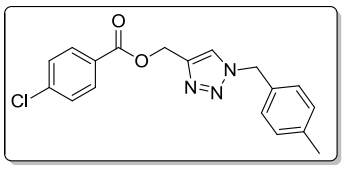
Pale yellow oil; Yield 62% (115.8 mg); FT IR (ATR) 1717 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), δ 7.94–7.90 (m, 1H), 7.63 (s, 1H), 7.54–7.48 (m, 1H), 7.40–7.26 (m, 5H), 7.20–7.09 (m, 2H), 5.53 (s, 2H), 5.45 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$), δ 164.0 (d, J_{C-F} = 3 Hz), 163.4–160.8 (d, J_{C-F} = 318 Hz), 143.2, 134.9 (d, J_{C-F} = 9 Hz), 134.4, 132.2, 129.2, 128.9, 128.2, 124.0, 123.9 (d, J_{C-F} = 7 Hz), 118.2, 117.0 (d, J_{C-F} = 22 Hz), 58.4, 54.3; HRMS (ESI): *m/z* calcd for $C_{17}H_{15}FN_3O_2$ $[M+H]^+$: 312.1148; found: 312.1146.

(1-(4-methoxybenzyl)-1H-1,2,3-triazol-4-yl)methyl-4-chlorobenzoate (12q):



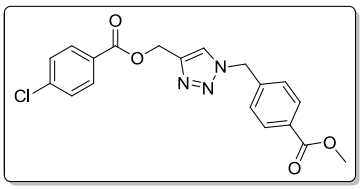
Off white solid; Yield 55% (118.1 mg); m.p. 119–120 °C; FT IR (ATR) 1716 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), δ 7.96 (d, J = 8.60 Hz, 2H), 7.56 (s, 1H), 7.38 (d, J = 8.60 Hz, 2H), 7.24 (d, J = 8.64 Hz, 2H), 6.89 (d, J = 8.64 Hz, 2H), 5.46 (s, 2H), 5.41 (s, 2H), 3.80 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$), δ 165.6, 160.0, 143.0, 139.7, 131.2, 129.8, 128.7, 128.2, 126.3, 123.7, 114.5, 58.2, 55.4, 53.9; HRMS (ESI): *m/z* calcd for $C_{17}H_{15}ClN_3O_3$ $[M+H]^+$: 358.0958; found: 358.0965.

(1-(4-methylbenzyl)-1H-1,2,3-triazol-4-yl)methyl-4-chlorobenzoate (12r):



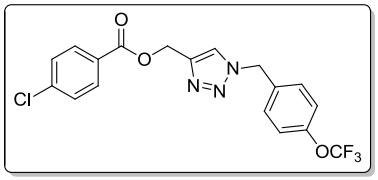
Pale yellow solid; Yield 67% (137.4 mg); m.p. 110–111 °C; FT IR (ATR) 1719 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), δ 7.95 (d, J = 8.64 Hz, 2H), 7.57 (s, 1H), 7.38 (d, J = 8.64 Hz, 2H), 7.18 (s, 4H), 5.48 (s, 2H), 5.42 (s, 2H) 2.35 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$), δ 165.6, 143.0, 139.7, 138.9, 131.3, 131.2, 129.9, 128.7, 128.3, 128.2, 123.8, 58.2, 54.1, 21.2; HRMS (ESI): *m/z* calcd for $C_{17}H_{15}ClN_3O_2$ $[M+H]^+$: 342.1009; found: 342.1008.

(1-(4-(methoxycarbonyl)benzyl)-1H-1,2,3-triazol-4-yl)methyl 4-chlorobenzoate (12s):



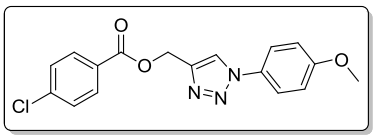
Off white solid; Yield 82% (189.8 mg); m.p. 175–176 °C; FT IR (ATR) 1723, 1709 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), δ 8.03 (d, J = 8.38 Hz, 2H), 7.94 (d, J = 8.68 Hz, 2H), 7.64 (s, 1H), 7.39 (d, J = 8.68 Hz, 2H), 7.32 (d, J = 8.42 Hz, 2H), 5.58 (s, 2H), 5.44 (s, 2H), 3.91 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$), δ 166.4, 165.6, 143.4, 139.8, 139.1, 131.2, 130.7, 130.4, 128.8, 128.1, 127.9, 124.1, 58.2, 53.8, 52.4; HRMS (ESI): *m/z* calcd for $C_{19}H_{17}ClN_3O_4$ $[M+H]^+$: 386.0907; found: 386.0901.

(1-(4-(trifluoromethoxy)benzyl)-1H-1,2,3-triazol-4-yl)methyl 4-chlorobenzoate (12t):



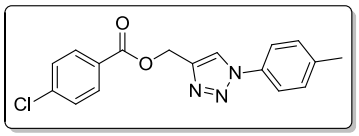
Pale brown solid; Yield 80% (197.6 mg); m.p. 155–156 °C; FT IR (ATR) 1712 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), δ 7.95 (d, J = 8.68 Hz, 2H), 7.64 (s, 1H), 7.39 (d, J = 8.72 Hz, 2H), 7.32 (d, J = 8.72 Hz, 2H), 7.23–7.21 (m, 2H) 5.53 (s, 2H) 5.44 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$), δ 165.6, 149.5, 143.3, 139.8, 133.0, 131.1, 129.7, 128.8, 128.1, 124.0, 121.6, 119.1, 58.1, 53.4; HRMS (ESI): *m/z* calcd for $C_{18}H_{14}ClF_3N_3O_3$ $[M+H]^+$: 412.0676; found: 412.0678.

(1-(4-methoxyphenyl)-1H-1,2,3-triazol-4-yl)methyl-4-chlorobenzoate (12u):



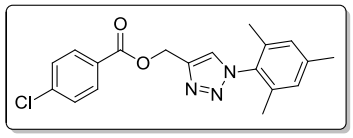
Pale yellow solid; Yield 52% (107.3 mg); m.p. 132–133 °C; FT IR (ATR) 1714 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), δ 8.04 (s, 1H), 8.00 (d, J = 8.72 Hz, 2H), 7.65 (d, J = 9.08 Hz, 2H), 7.41 (d, J = 8.72 Hz, 2H), 7.02 (d, J = 9.08 Hz, 2H), 5.54 (s, 2H), 3.87 (s, 3H); $^{13}CNMR$ (100 MHz, $CDCl_3$), δ 165.7, 160.0, 143.2, 139.8, 131.2, 128.8, 128.2, 122.5, 122.3, 114.8, 77.2, 58.2, 55.7; HRMS (ESI): *m/z* calcd for $C_{17}H_{15}ClN_3O_3$ $[M+H]^+$: 344.0802; found: 344.0808.

(1-(p-tolyl)-1H-1,2,3-triazol-4-yl)methyl- 4-chlorobenzoate (12v):



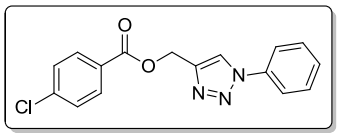
Pale brown solid; Yield 69% (135.7 mg); m.p. 73–74 °C; FT IR (ATR) 1708 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), δ 8.09 (s, 1H), 7.98 (d, J = 8.68 Hz, 2H), 7.60 (d, J = 8.44 Hz, 2H), 7.39 (d, J = 8.68 Hz, 2H), 7.30 (d, J = 8.08 Hz, 2H), 5.53 (s, 2H), 2.41 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$), δ 165.7, 139.8, 139.2, 134.6, 131.2, 130.3, 129.3, 128.8, 128.2, 122.4, 120.6, 58.2, 21.1; HRMS (ESI): *m/z* calcd for $C_{17}H_{15}ClN_3O_2$ $[M+H]^+$: 328.0853; found: 328.0850.

(1-mesityl-1H-1,2,3-triazol-4-yl)methyl-4-chlorobenzoate (12w):



Pale yellow solid; Yield 65% (138.8 mg); m.p. 132–133 °C; FT IR (ATR) 1730 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), δ 8.00 (d, J = 8.68 Hz, 2H), 7.74 (s, 1H), 7.40 (d, J = 8.68 Hz, 2H), 6.98 (s, 2H), 5.56 (s, 2H), 2.34 (s, 3H), 1.94 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$), δ 165.6, 142.5, 140.2, 139.7, 135.0, 133.2, 131.2, 129.1, 128.8, 128.2, 125.9, 58.4, 21.1, 17.3; HRMS (ESI): *m/z* calcd for $C_{19}H_{19}ClN_3O_2$ $[M+H]^+$: 356.1166; found: 356.1162.

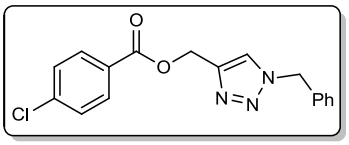
(1-phenyl-1H-1,2,3-triazol-4-yl)methyl-4-chlorobenzoate (12x):

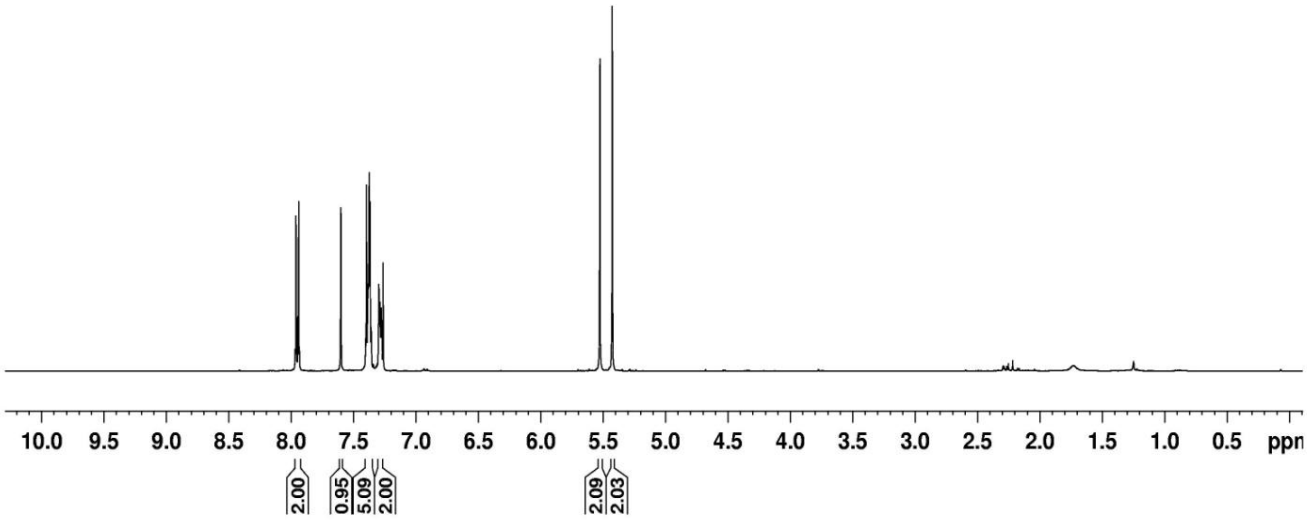


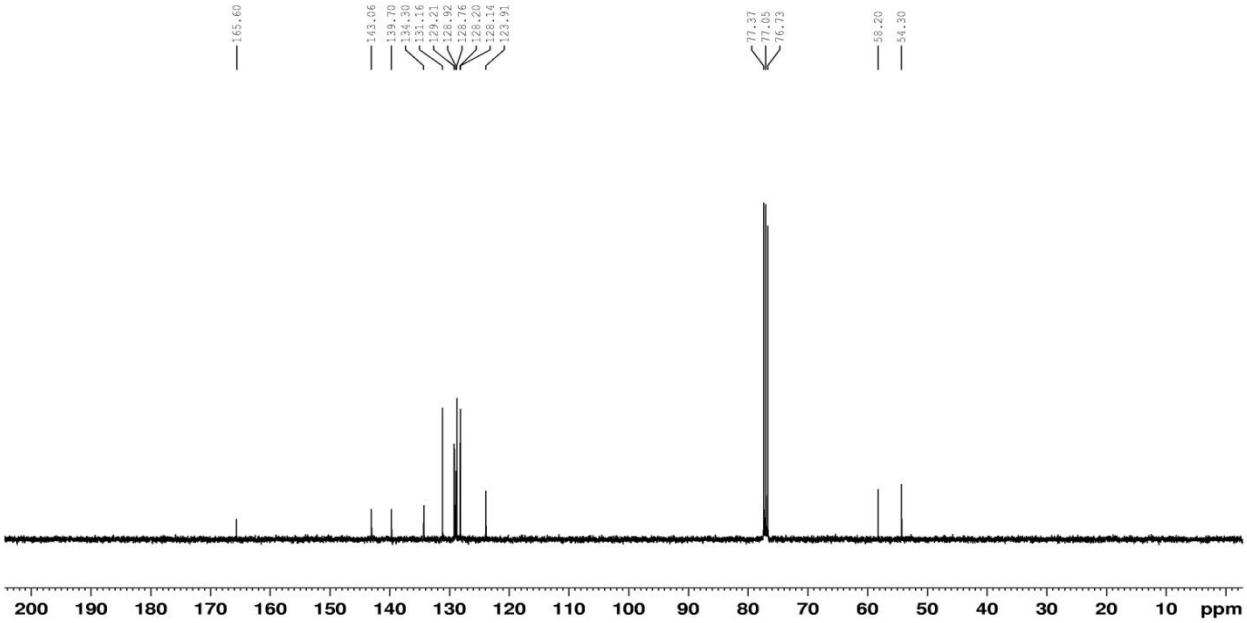
Pale brown solid; Yield 60% (112.9 mg); m.p. 84–85 °C; FT IR (ATR) 1718 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), δ 8.14 (s, 1H), 7.98 (d, J = 8.72 Hz, 2H), 7.74–7.72 (m, 2H), 7.54–7.49 (m, 2H), 7.46–7.42 (m, 1H), 7.44 (d, J = 8.72 Hz, 2H), 5.54 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$), δ 165.7, 143.4, 139.8, 131.2, 129.8, 129.3, 129.0, 128.8, 128.1, 122.4, 120.6, 58.2; HRMS (ESI): *m/z* calcd for $C_{16}H_{13}ClN_3O_2$ $[M+H]^+$: 314.0696; found: 314.0693.

Spectra of compounds (10 & 12a–12x)

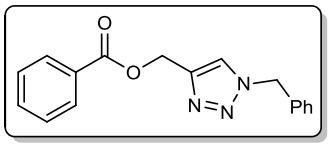
^{1}H, ^{13}C NMR Spectra of **10**

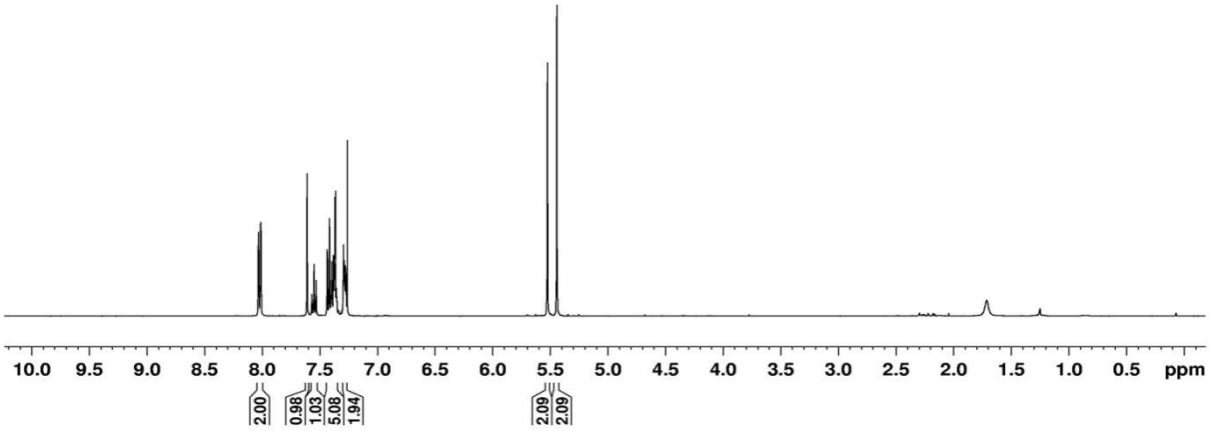


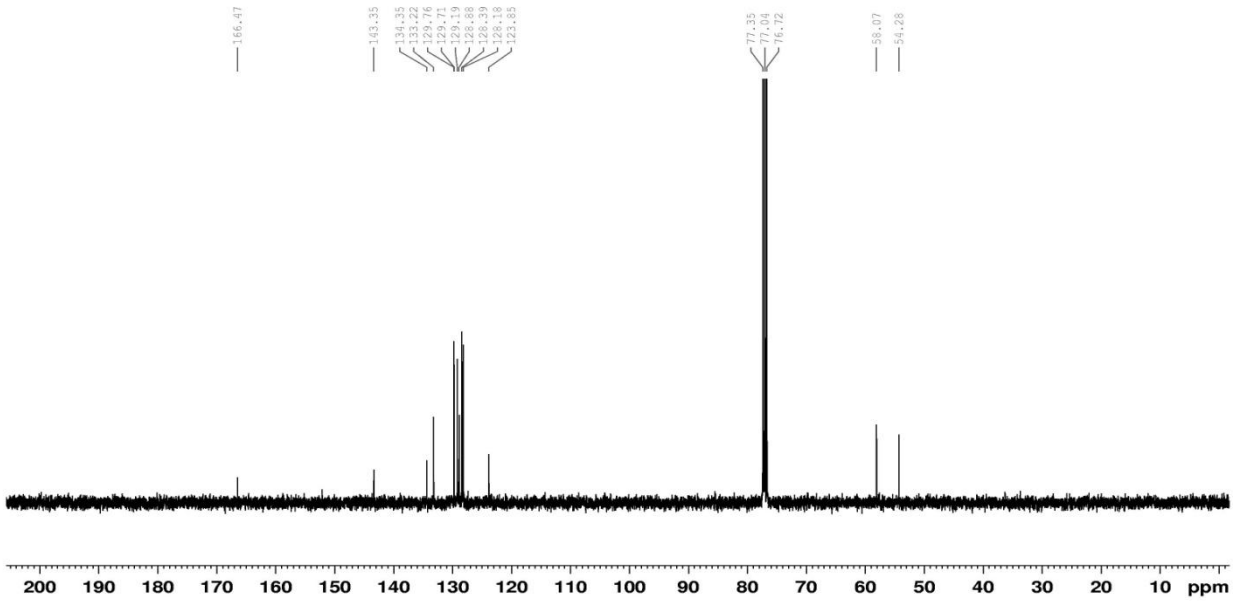




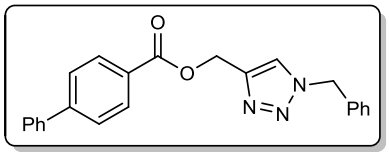
^{1}H, ^{13}C NMR Spectra of **12a**

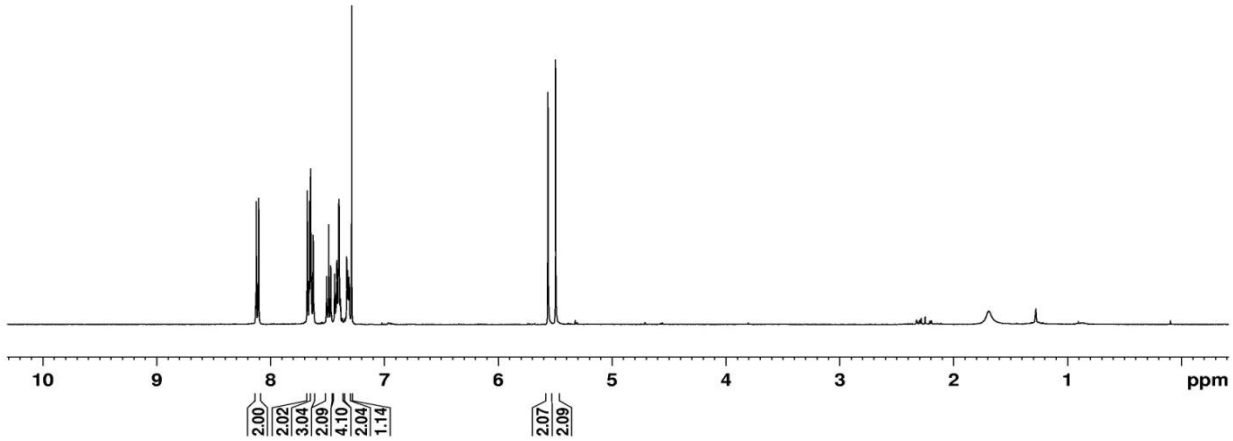


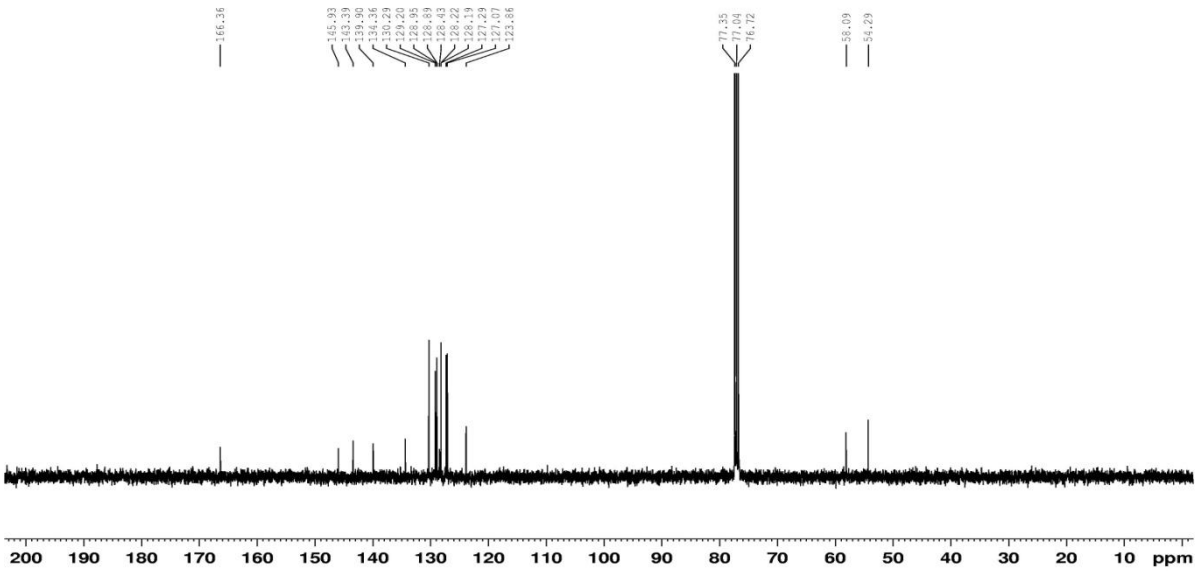




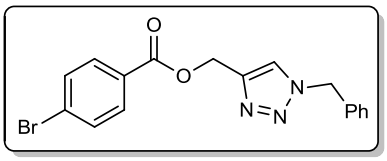
^{1}H, ^{13}C NMR Spectra of **12b**

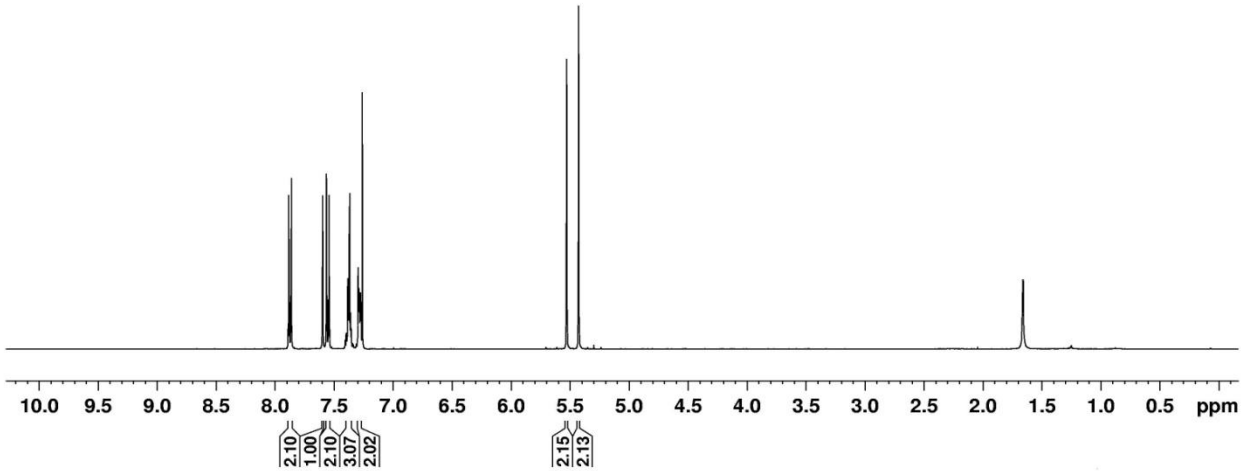


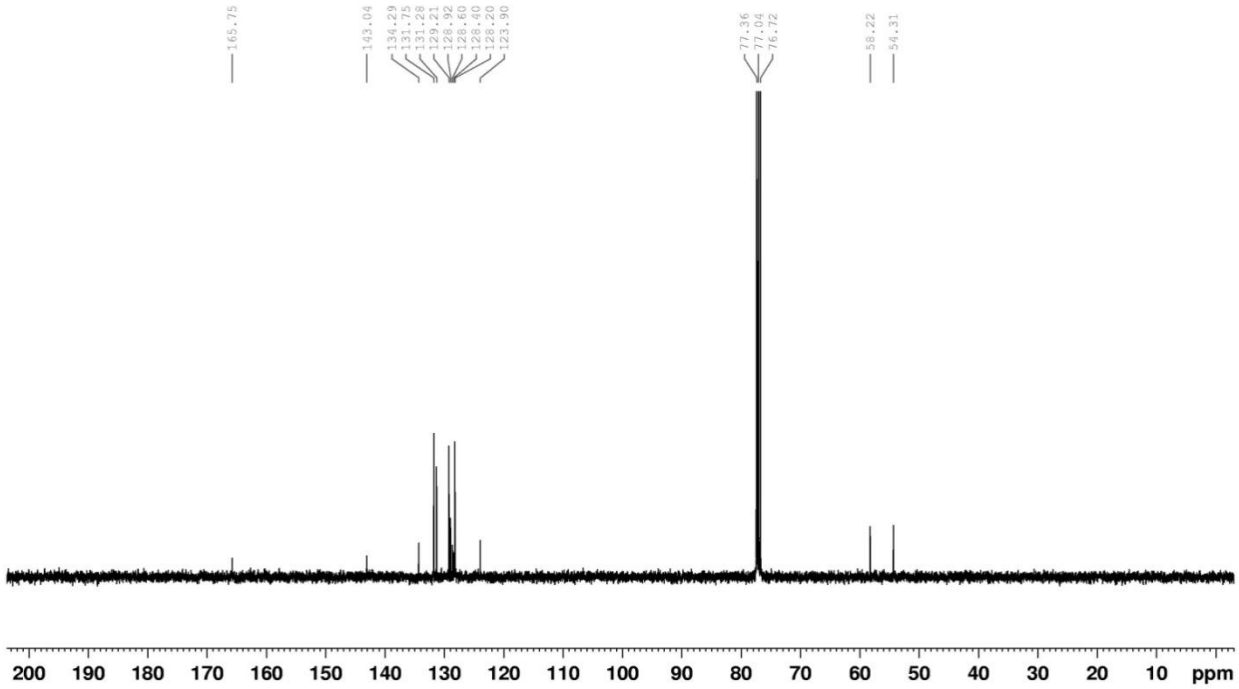




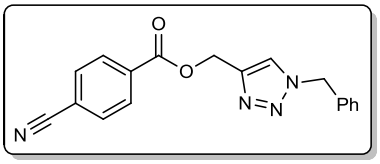
^{1}H, ^{13}C NMR Spectra of **12c**

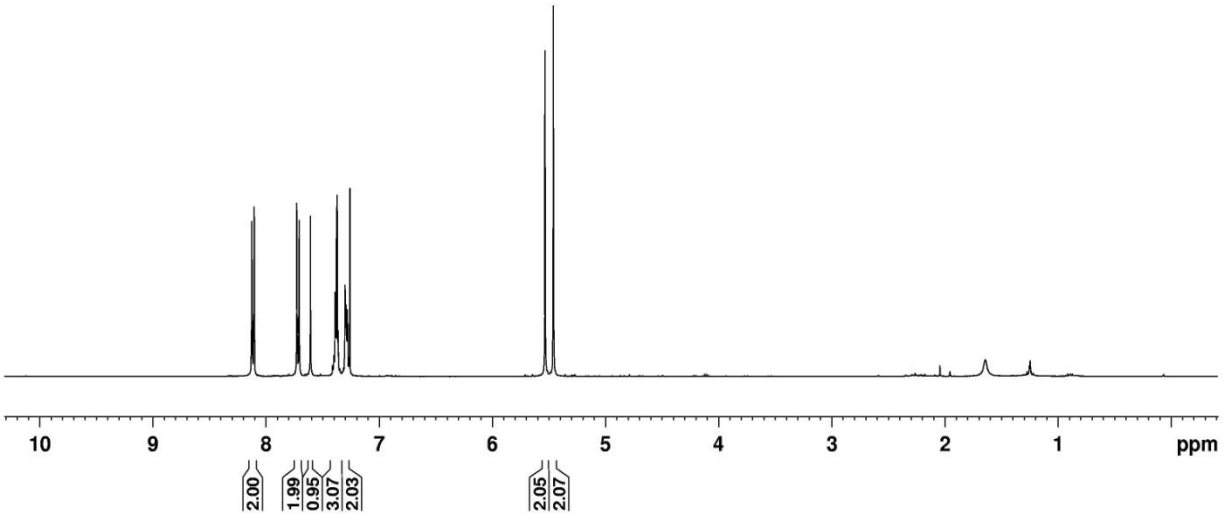


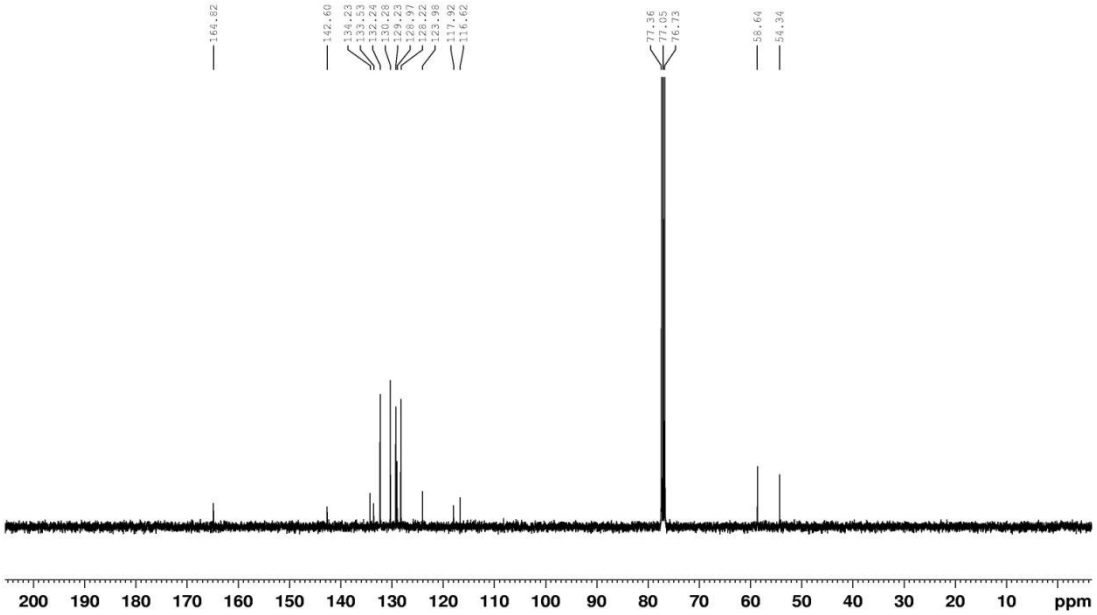




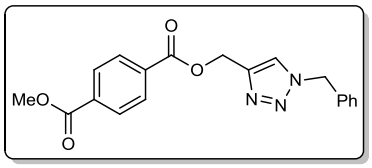
^{1}H, ^{13}C NMR Spectra of **12d**

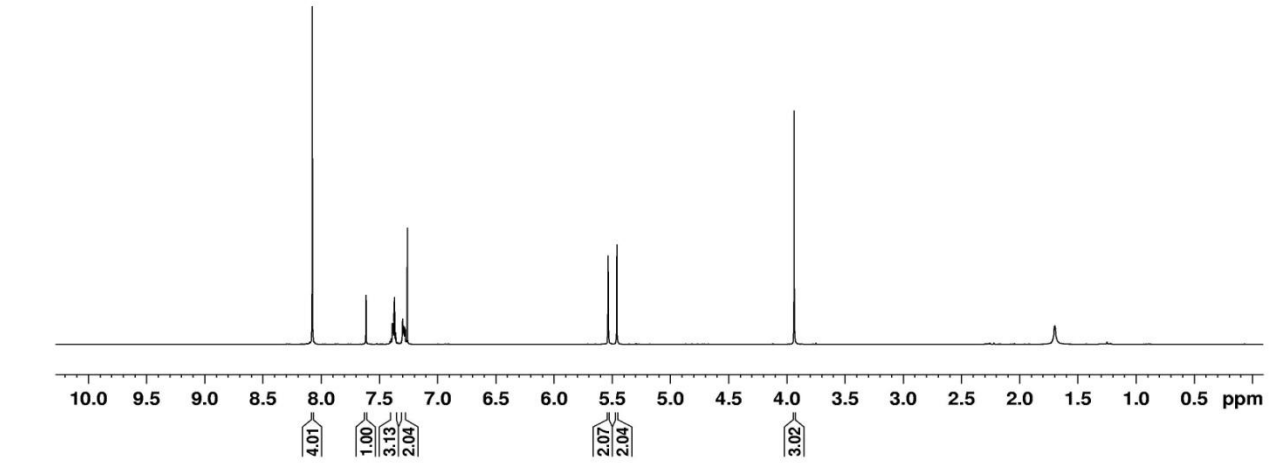


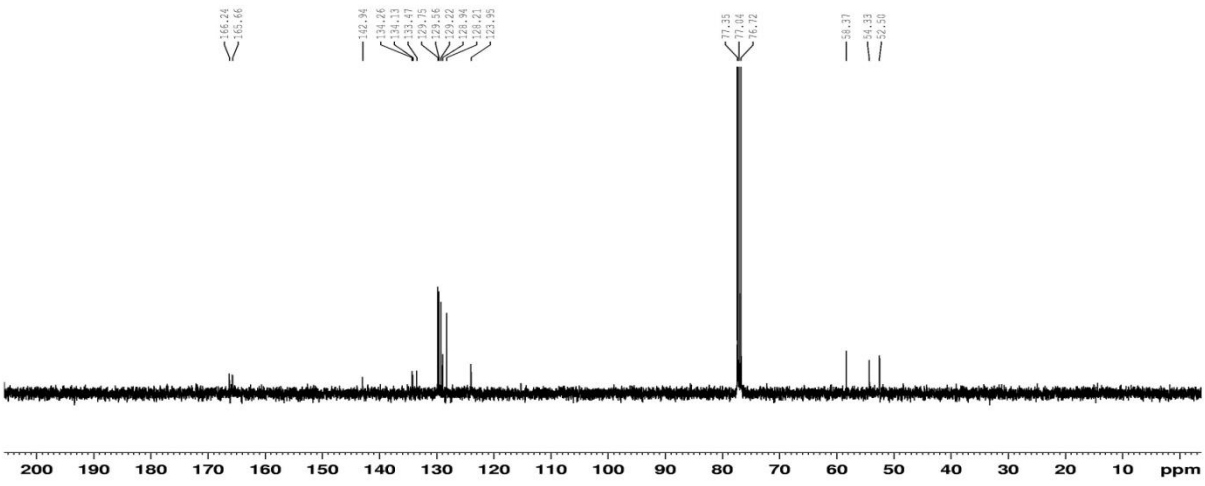




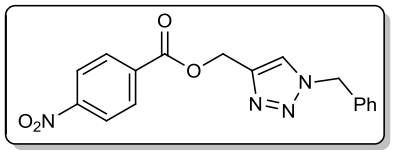
^{1}H, ^{13}C NMR Spectra of **12e**

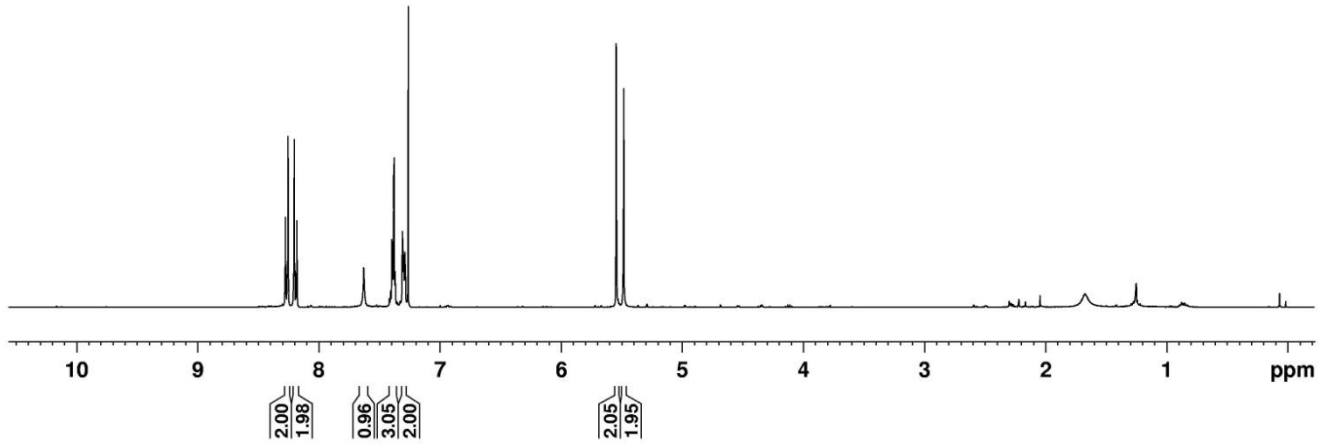


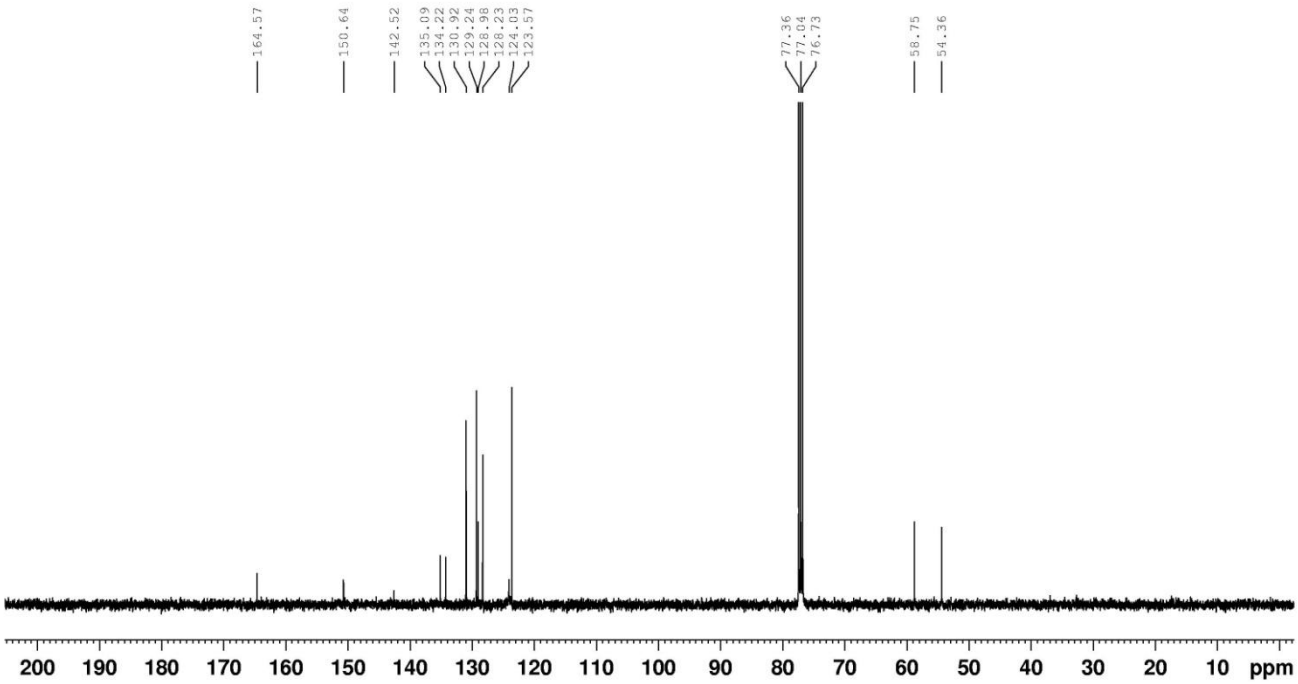




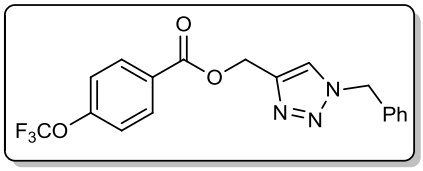
^{1}H, ^{13}C NMR Spectra of **12f**

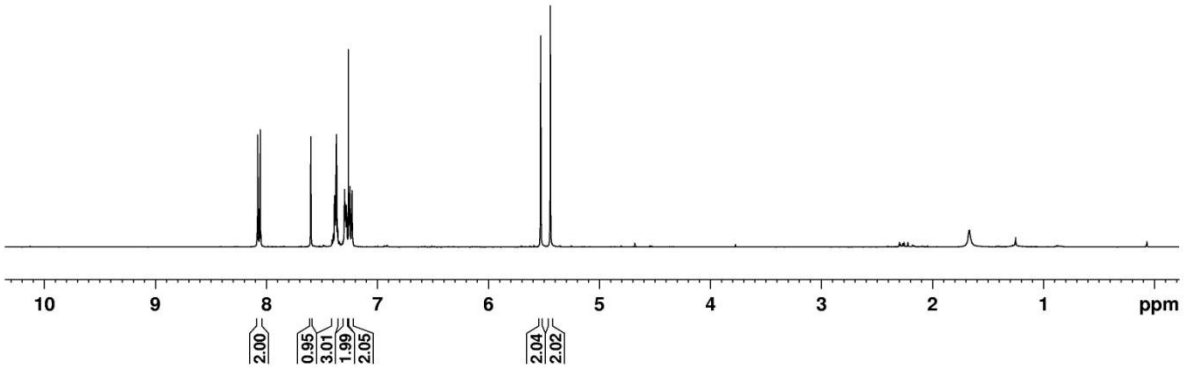


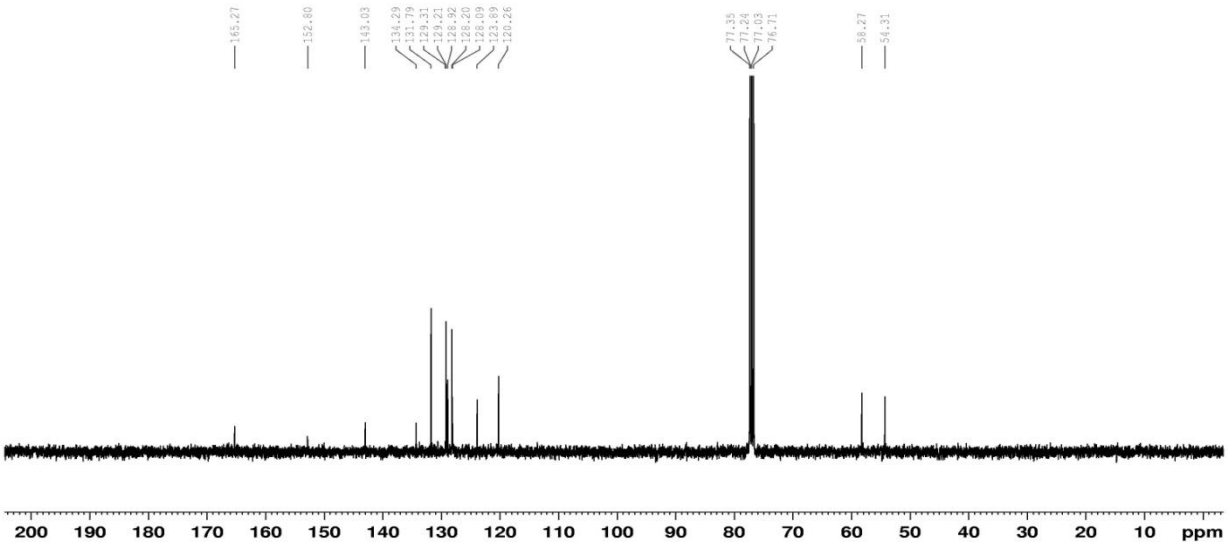




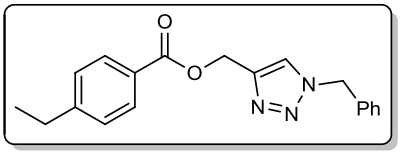
^{1}H, ^{13}C NMR Spectra of **12g**

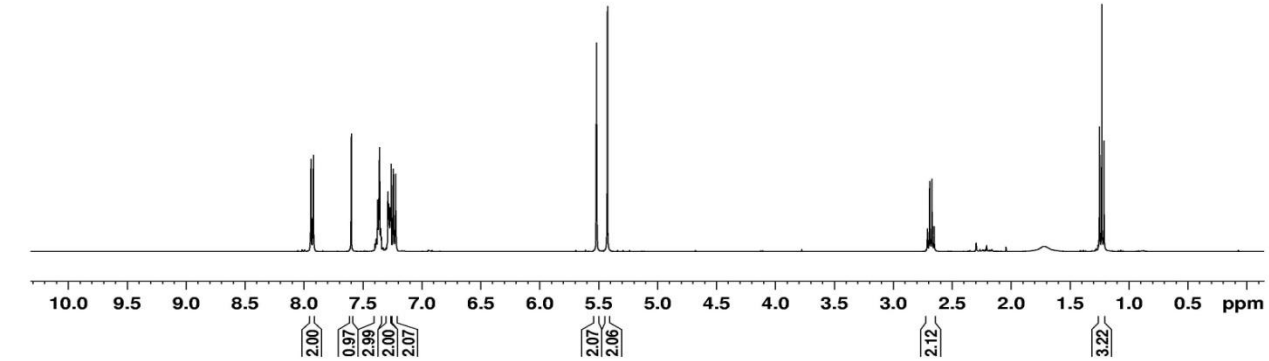


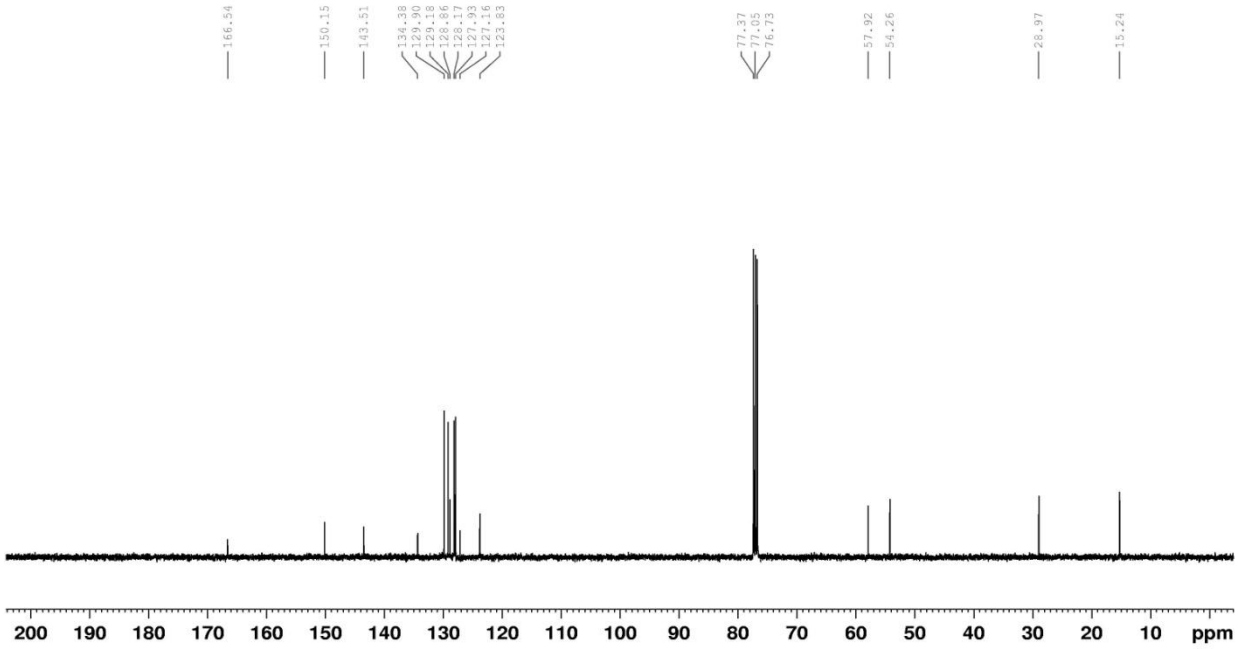




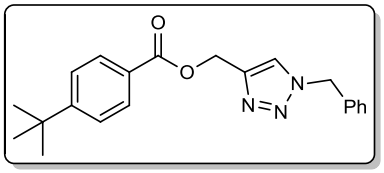
^{1}H, ^{13}C NMR Spectra of **12h**

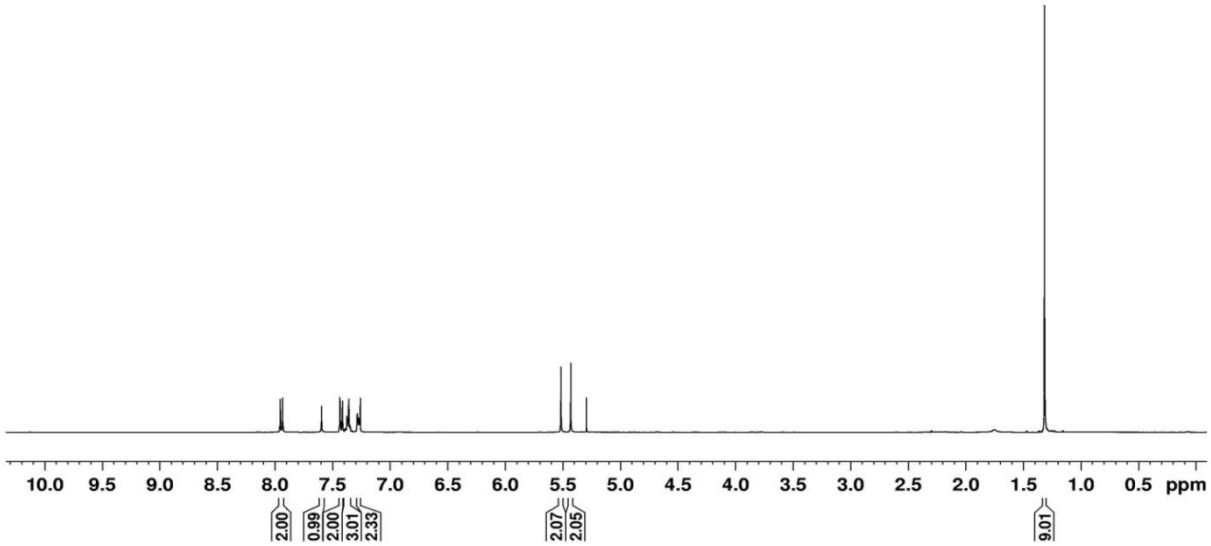


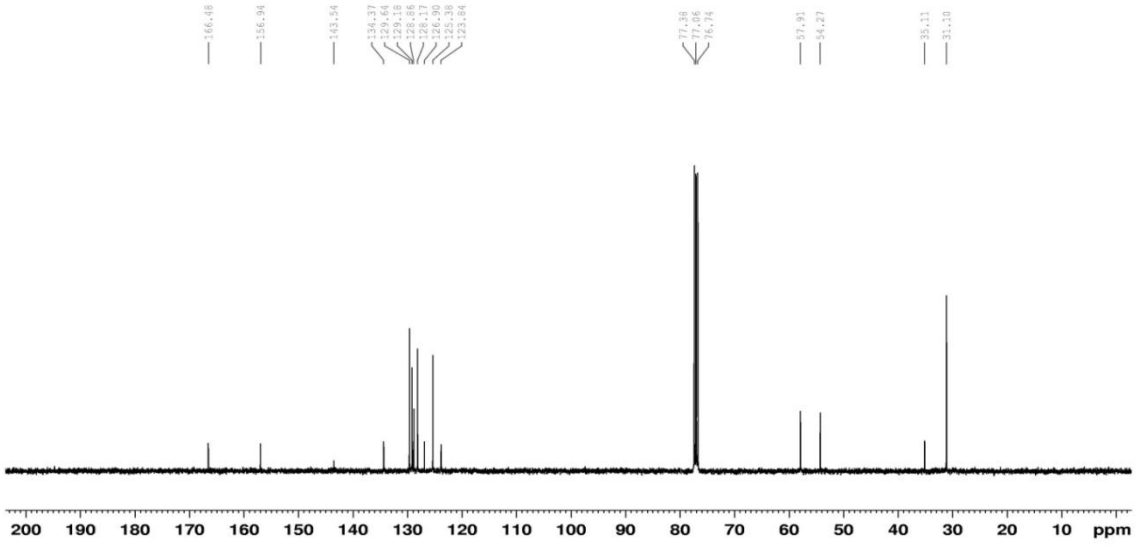




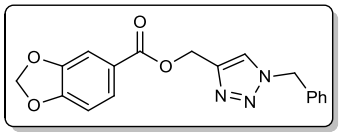
^{1}H, ^{13}C NMR Spectra of **12i**

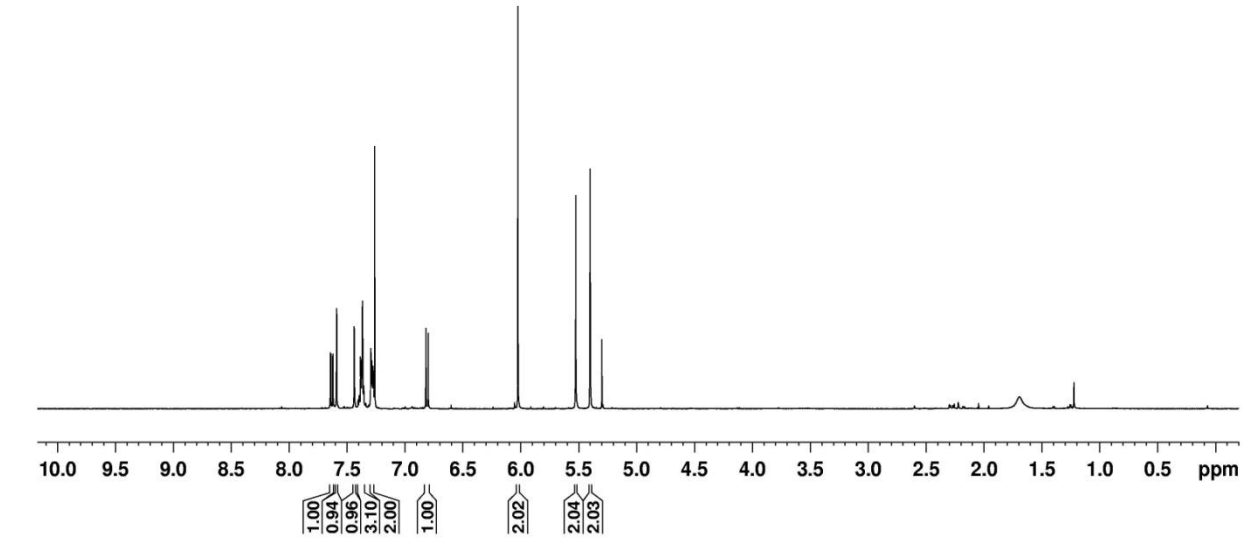


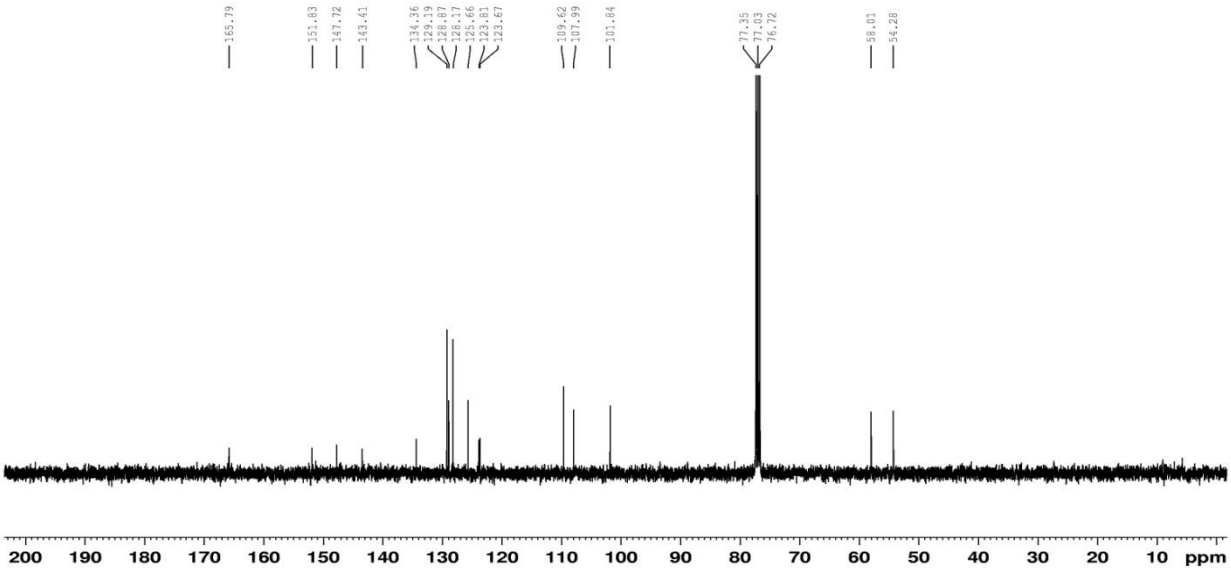




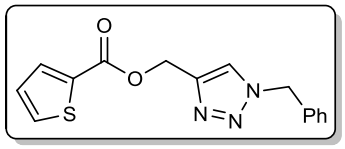
^{1}H, ^{13}C NMR Spectra of **12j**

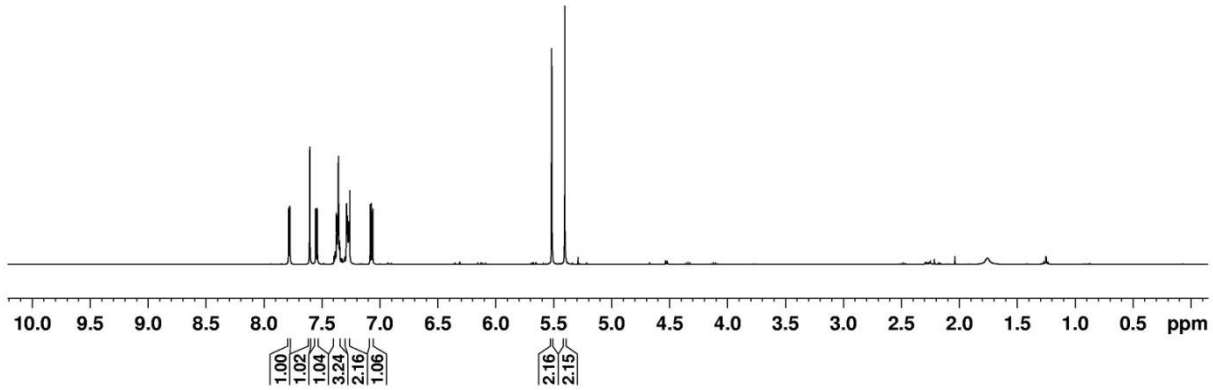


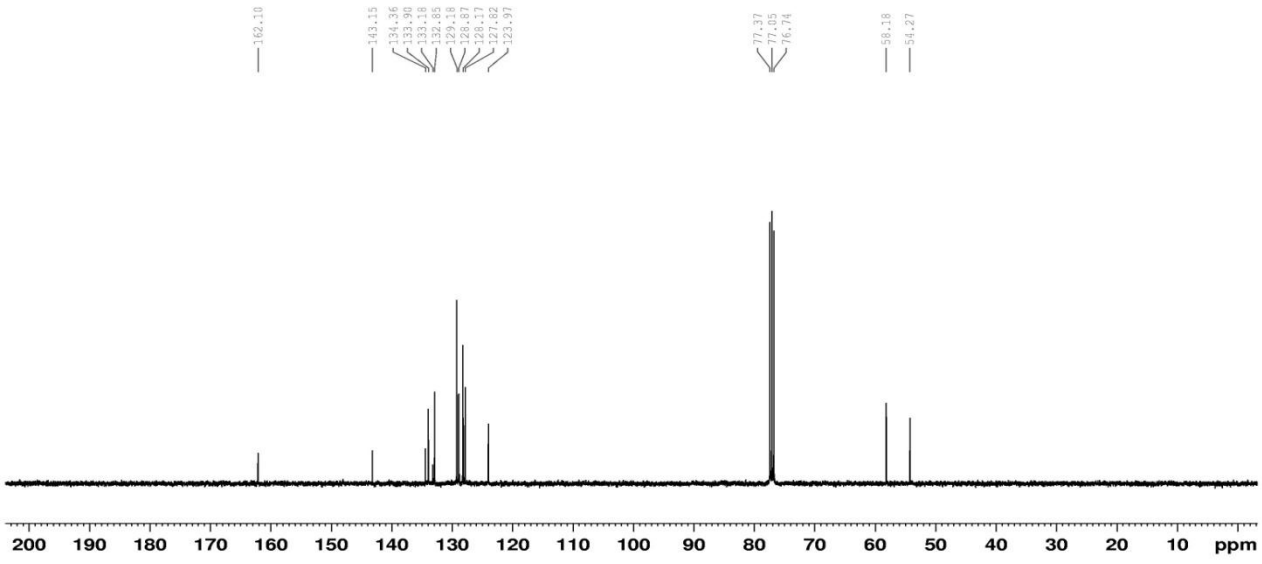




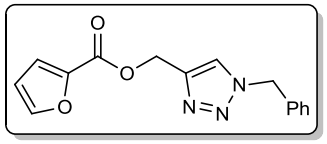
^{1}H, ^{13}C NMR Spectra of **12k**

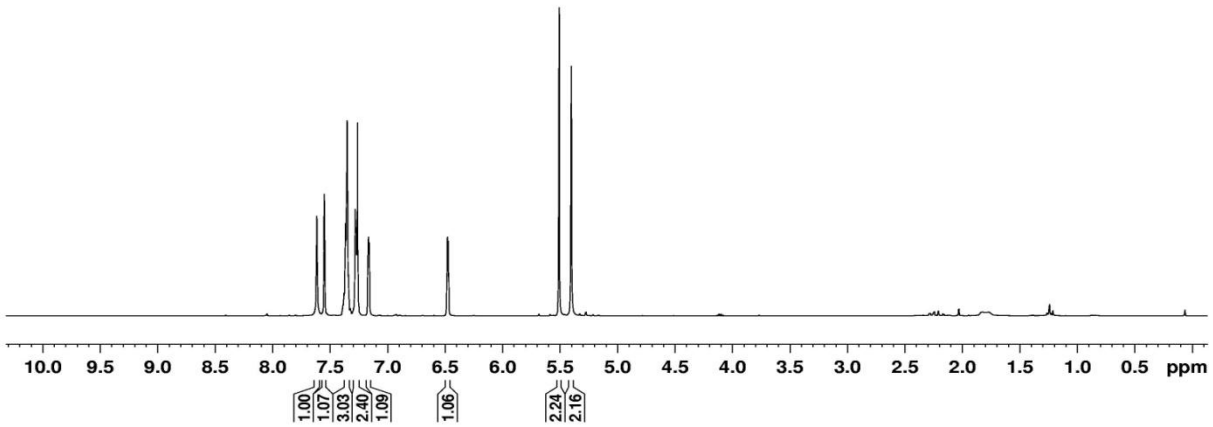


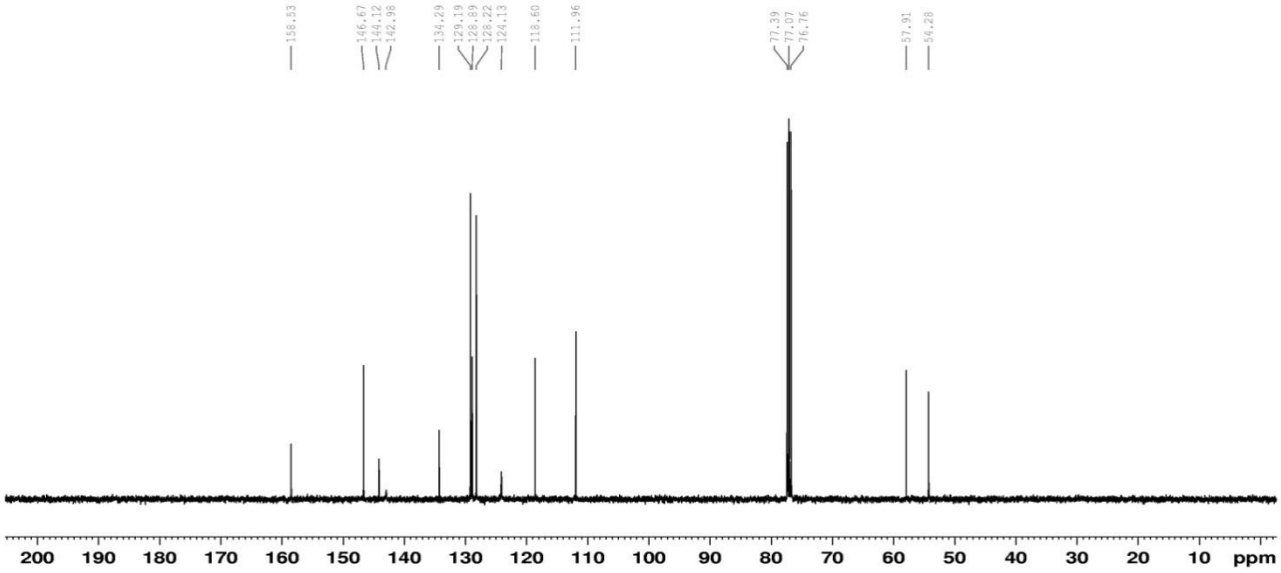




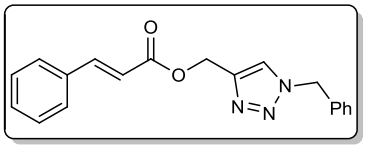
^{1}H, ^{13}C NMR Spectra of **12l**

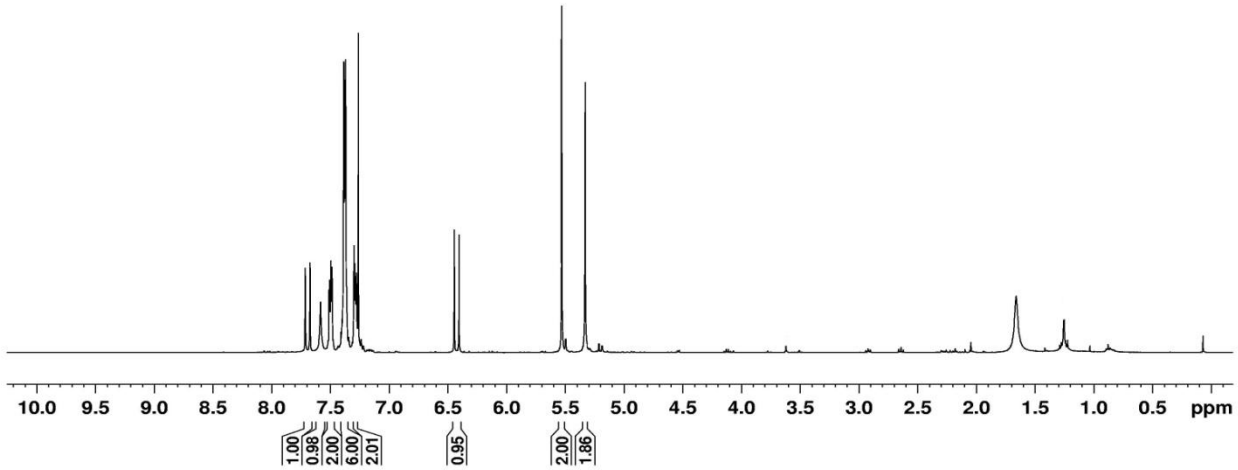


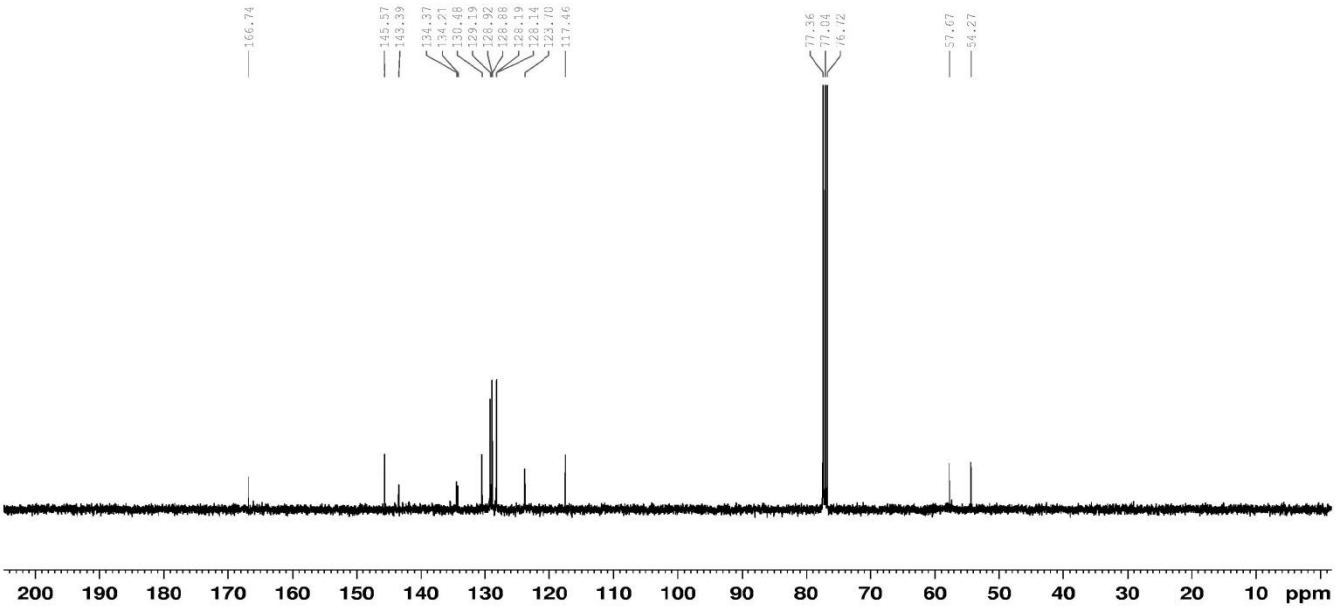




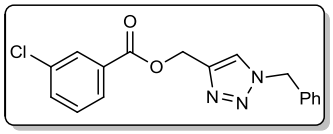
^{1}H, ^{13}C NMR Spectra of **12m**

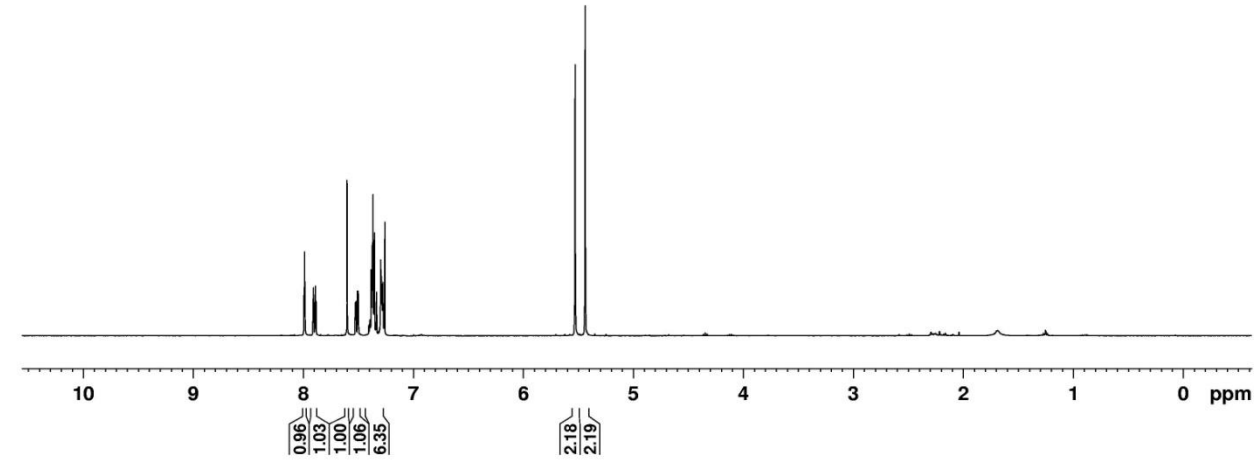


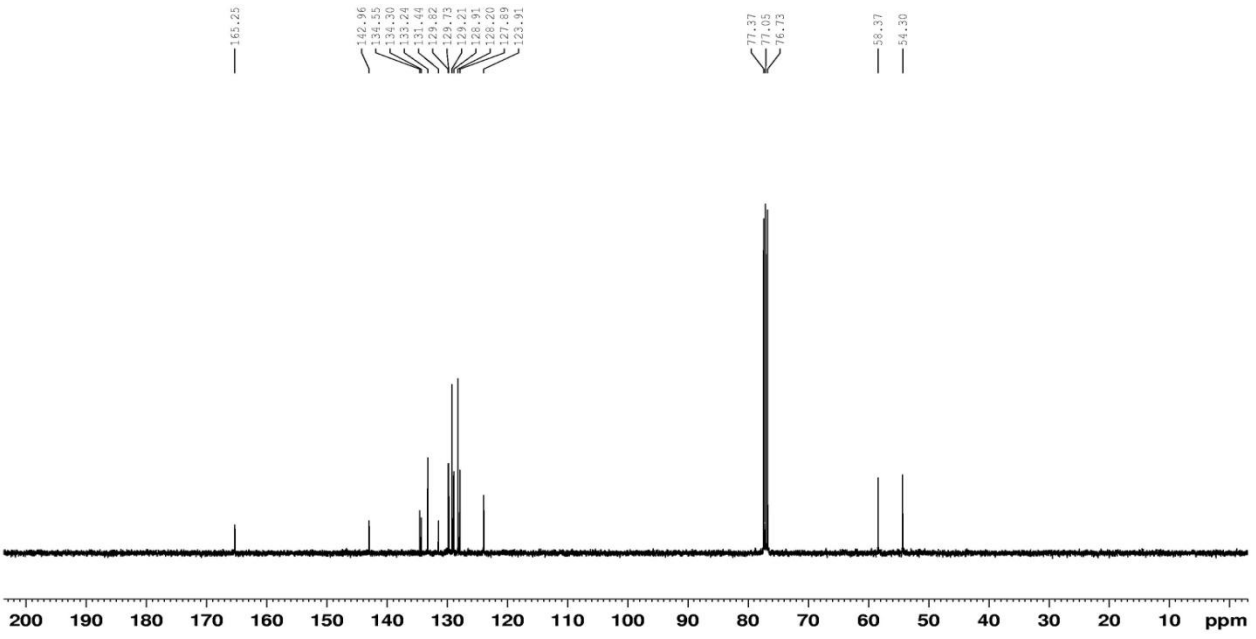




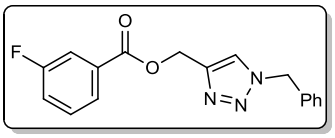
^{1}H, ^{13}C NMR Spectra of **12n**

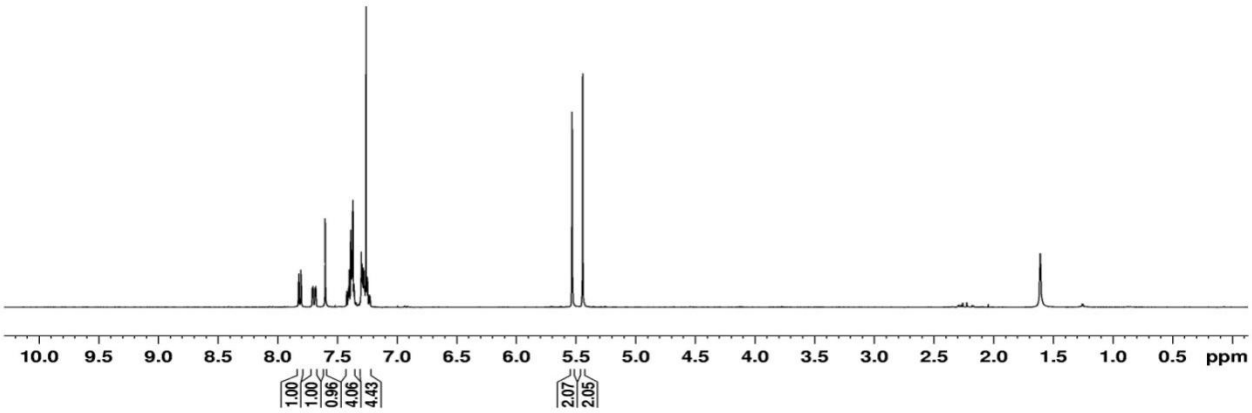


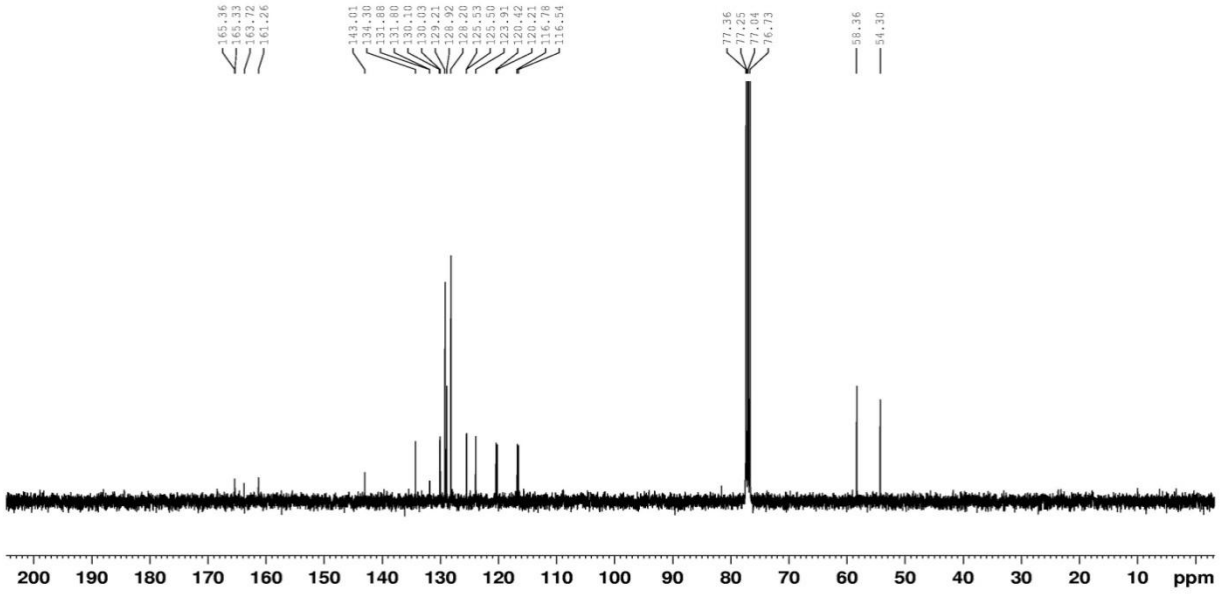




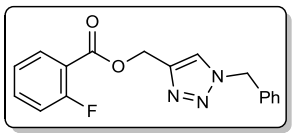
^{1}H, ^{13}C NMR Spectra of **12o**

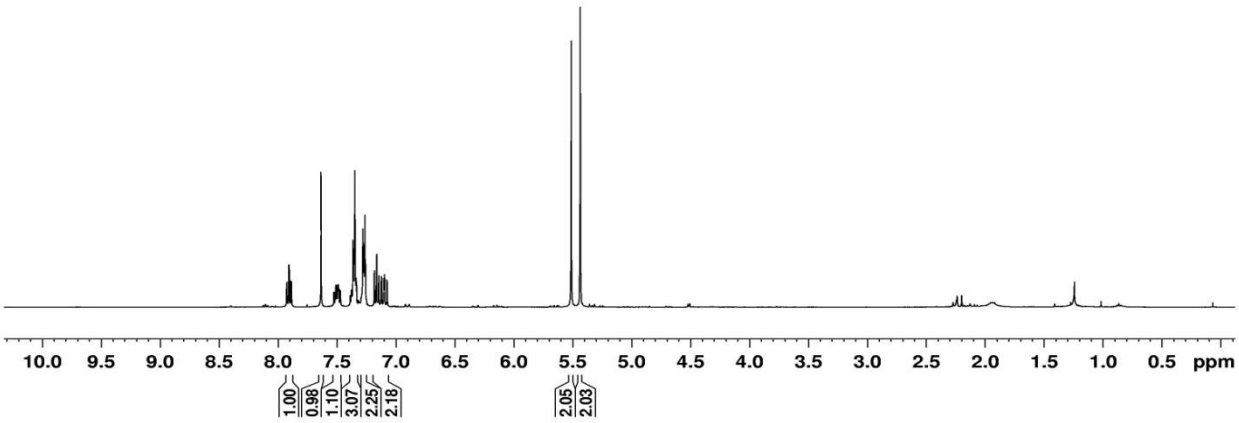


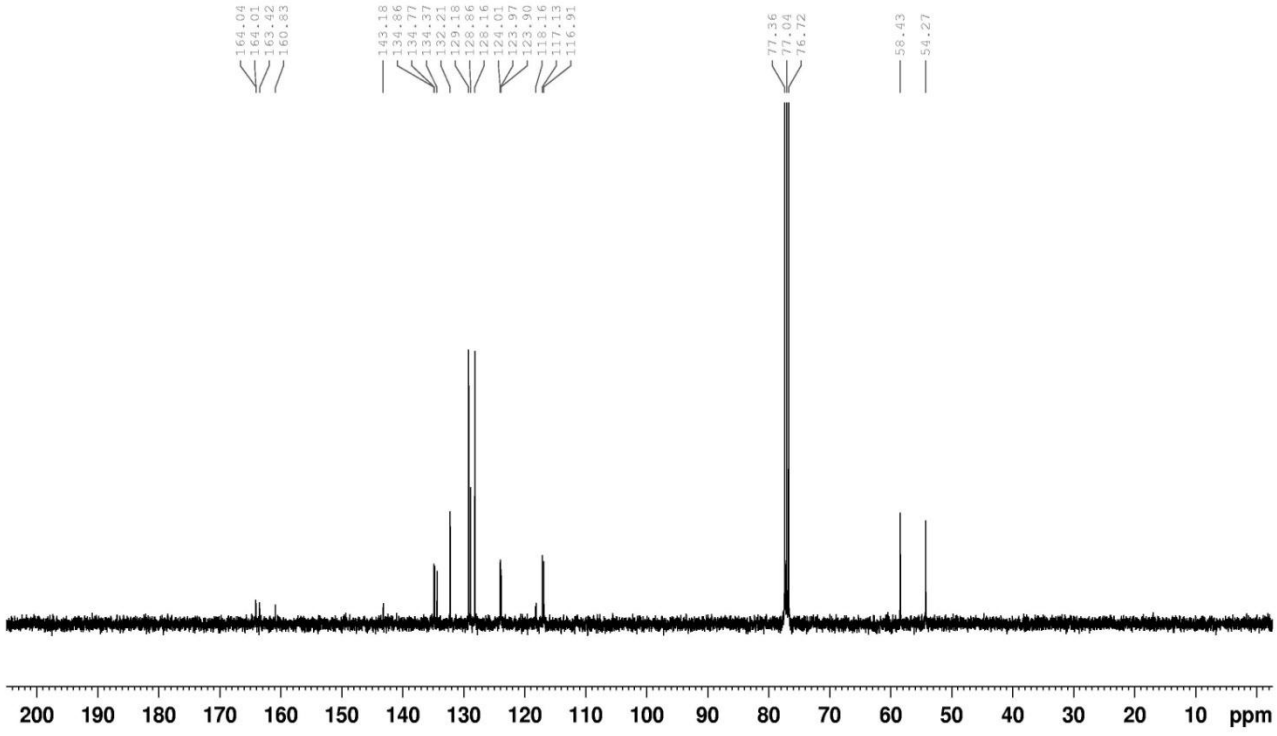




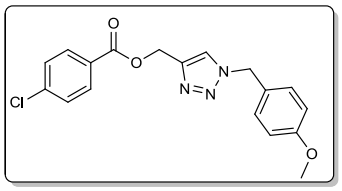
^{1}H, ^{13}C NMR Spectra of **12p**

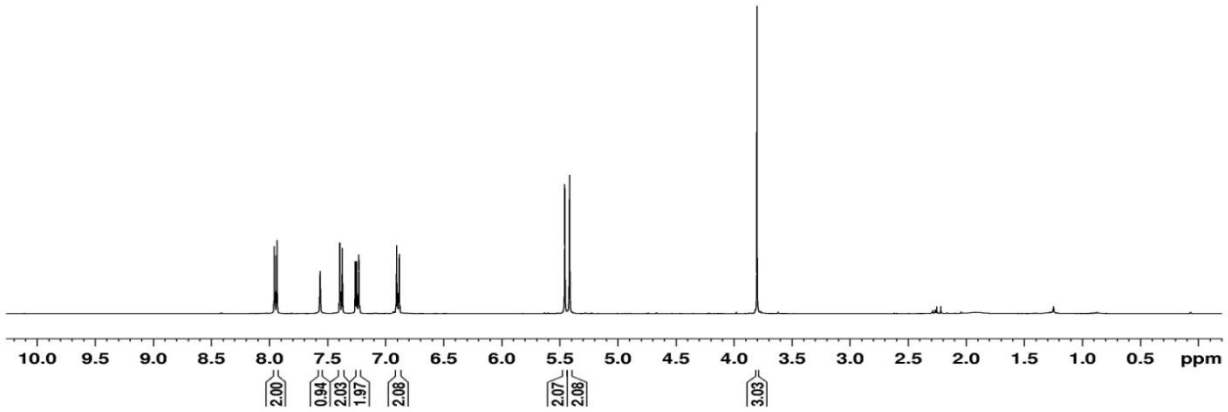


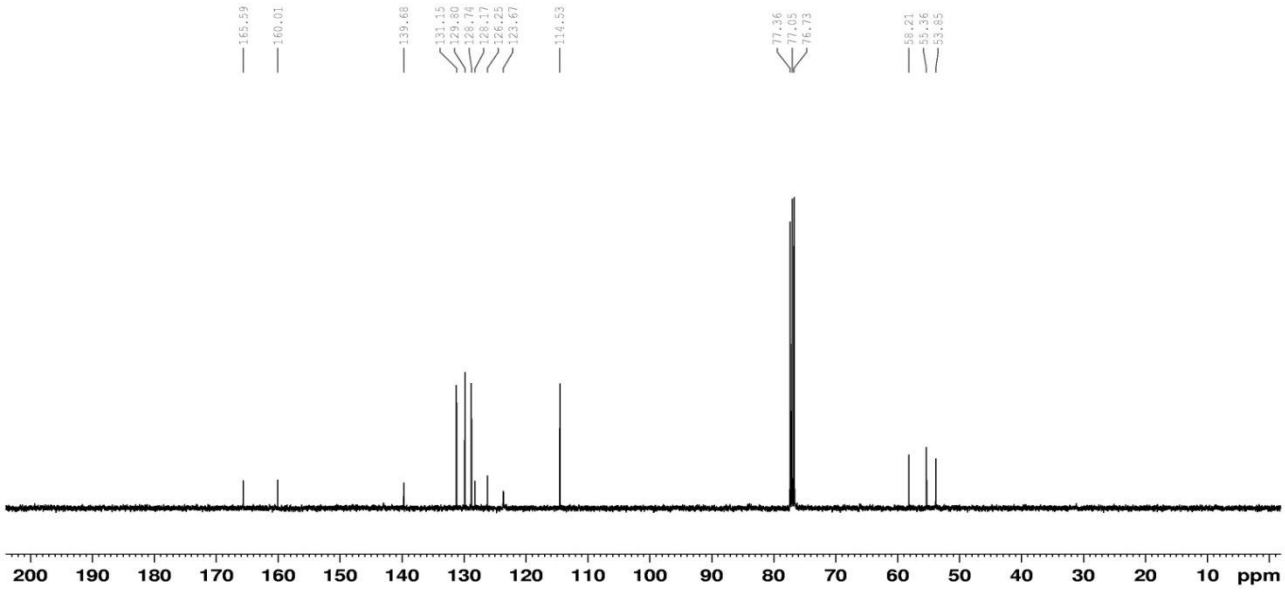




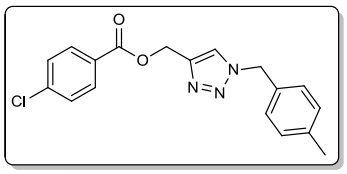
^{1}H, ^{13}C NMR Spectra of **12q**

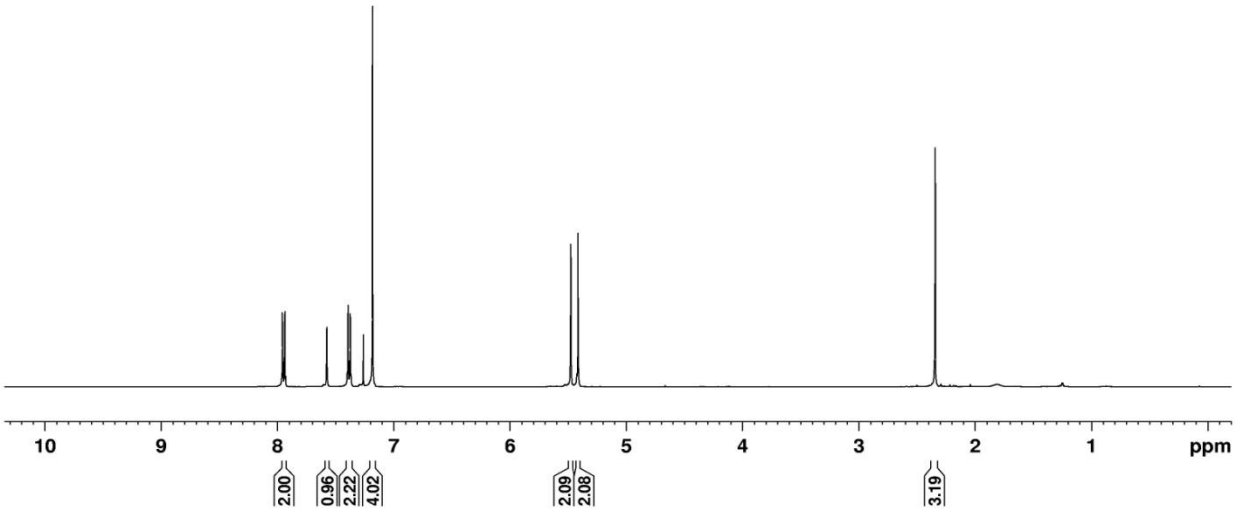


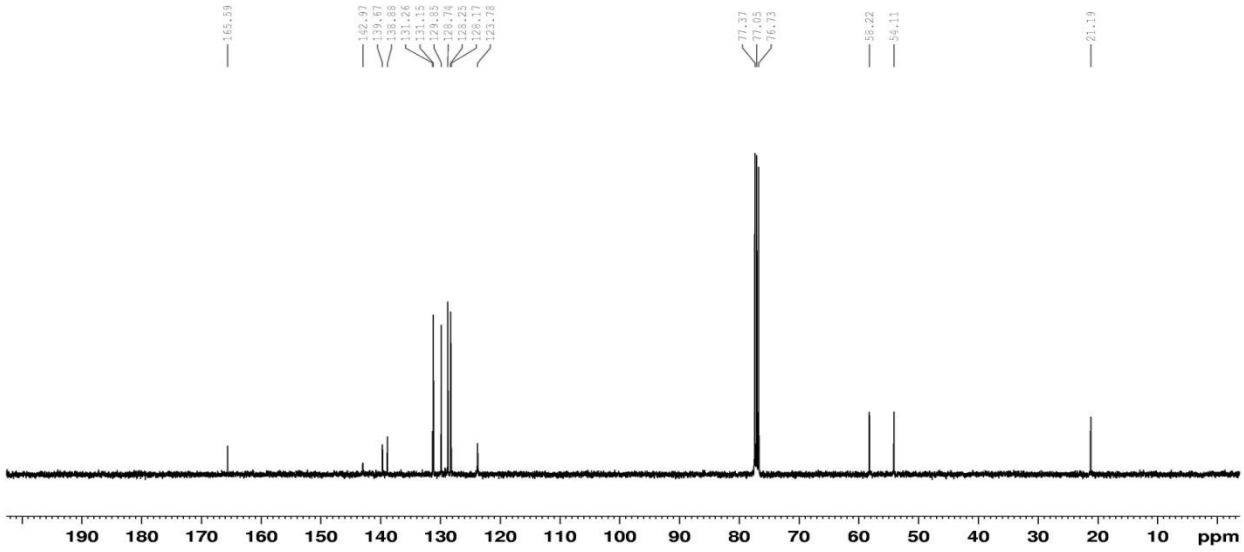




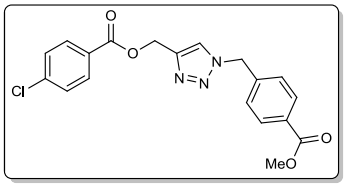
^{1}H, ^{13}C NMR Spectra of **12r**

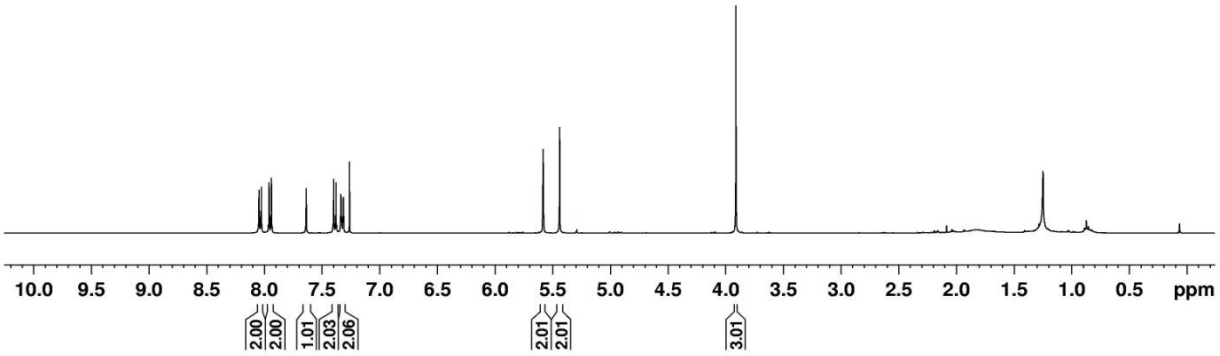


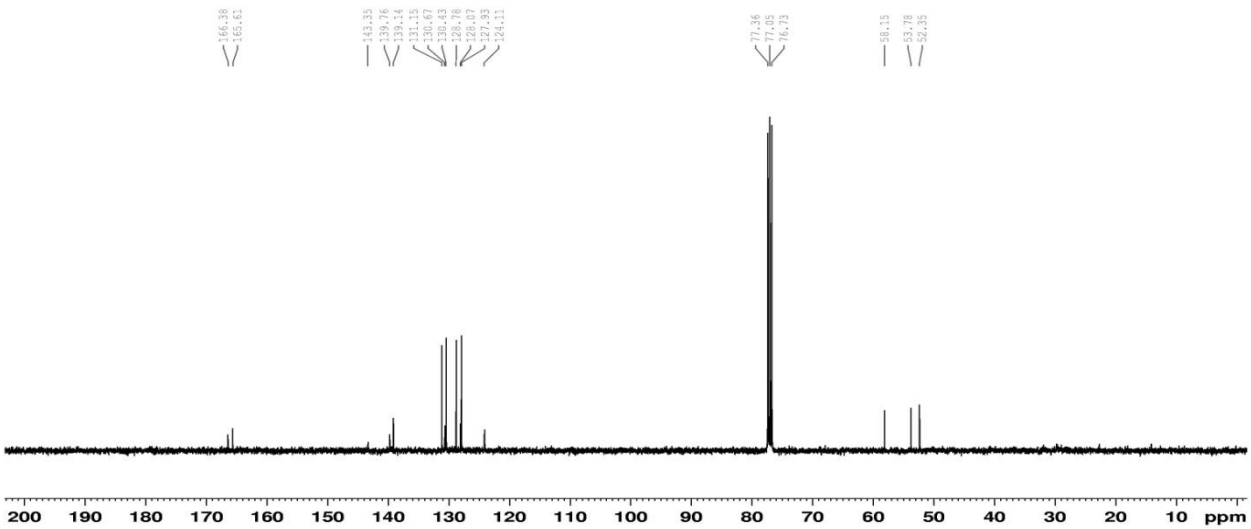




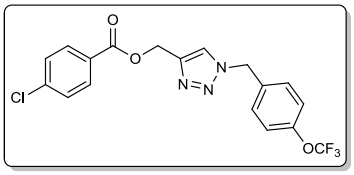
^{1}H, ^{13}C NMR Spectra of **12s**

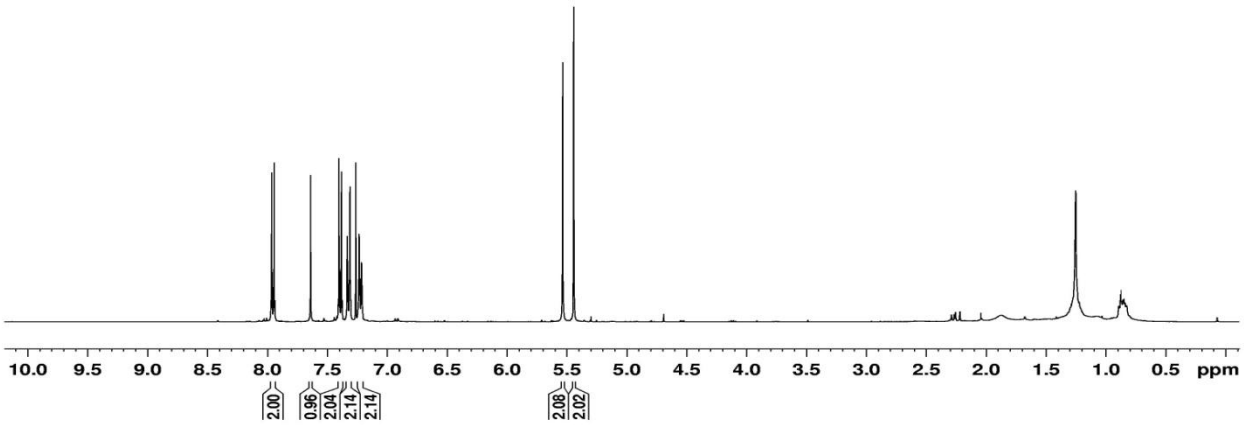


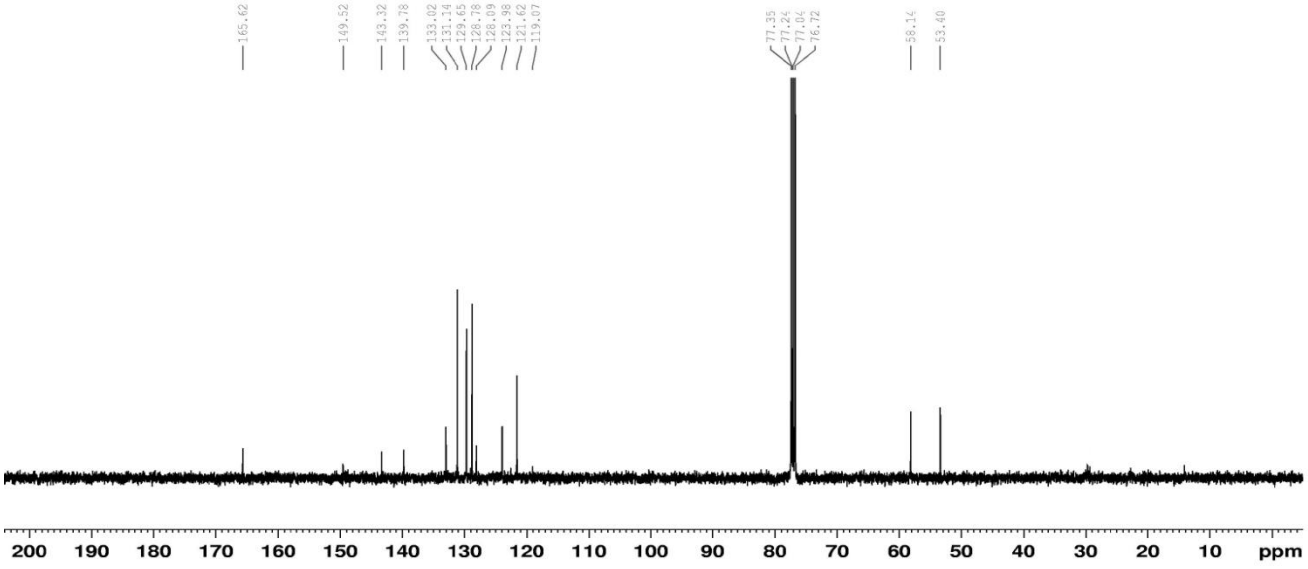




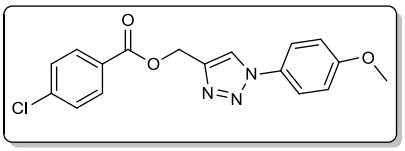
^{1}H, ^{13}C NMR Spectra of **12t**

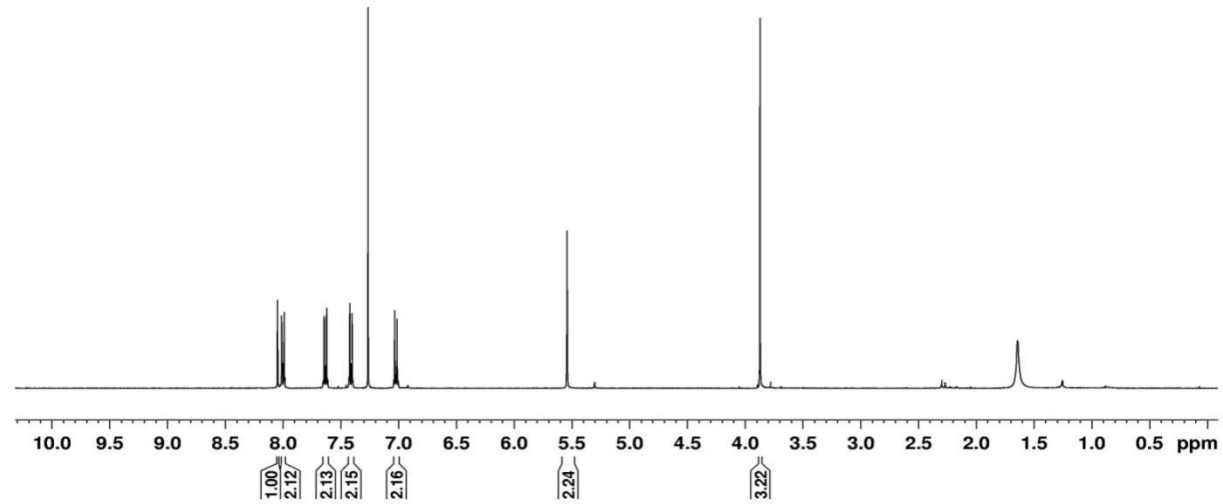


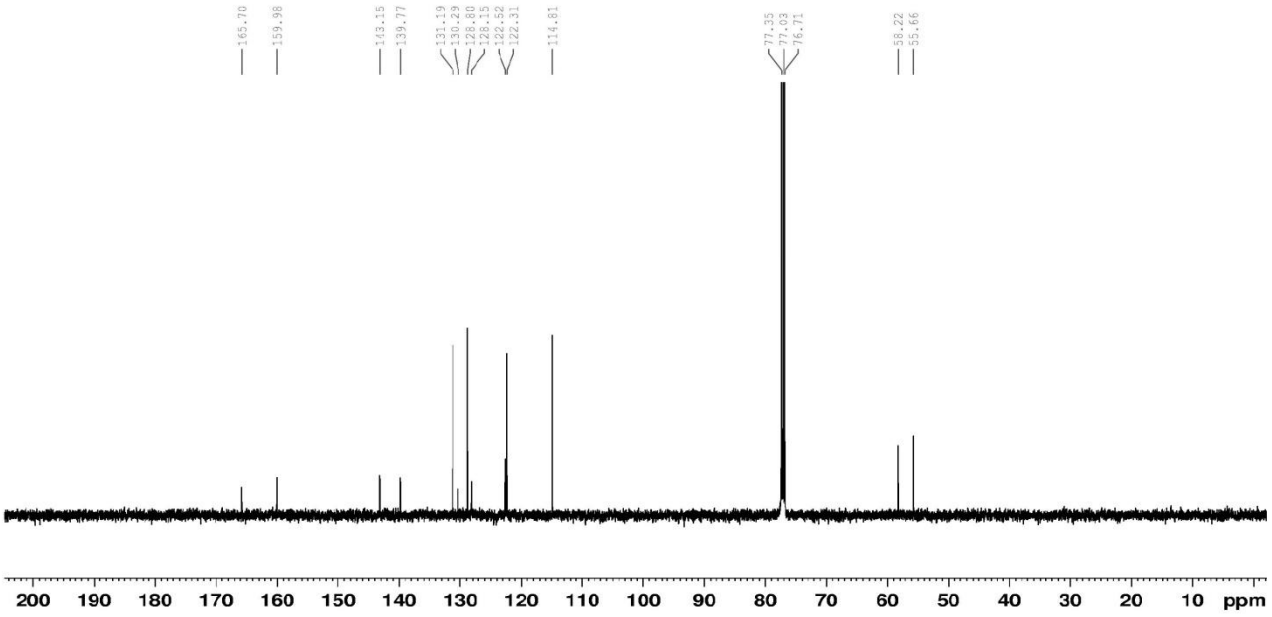




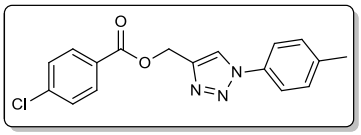
^{1}H, ^{13}C NMR Spectra of **12u**

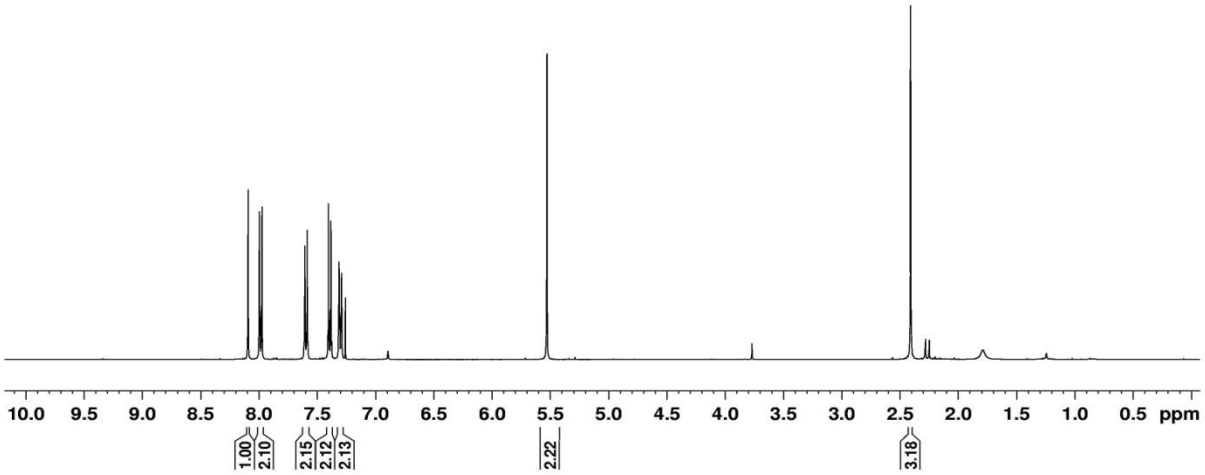


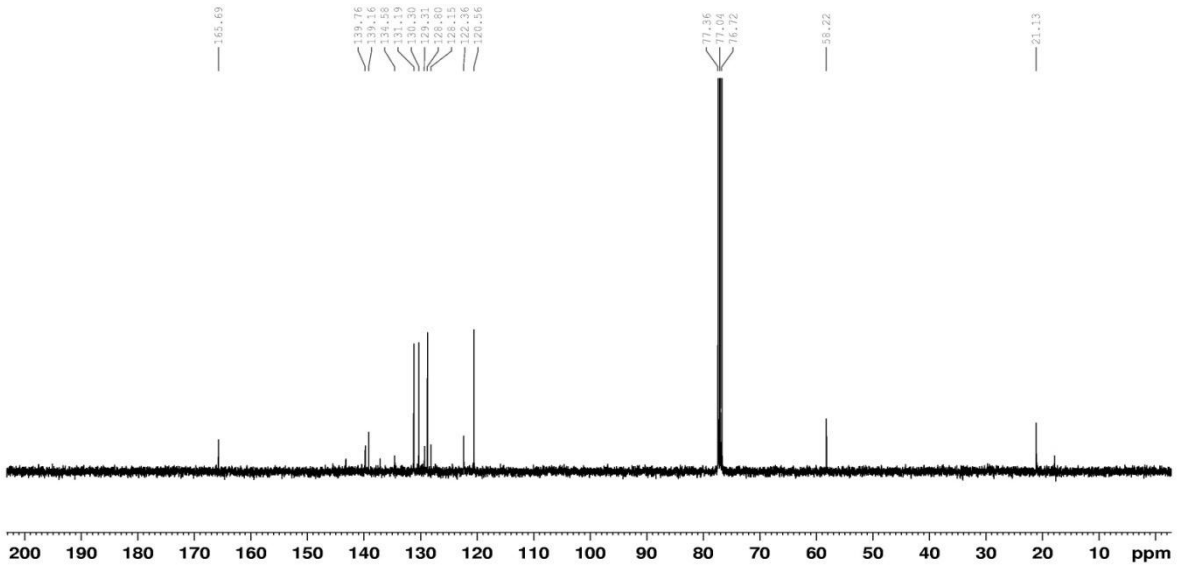




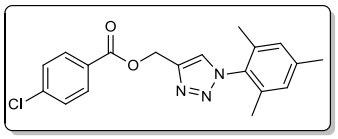
^{1}H, ^{13}C NMR Spectra of **12v**

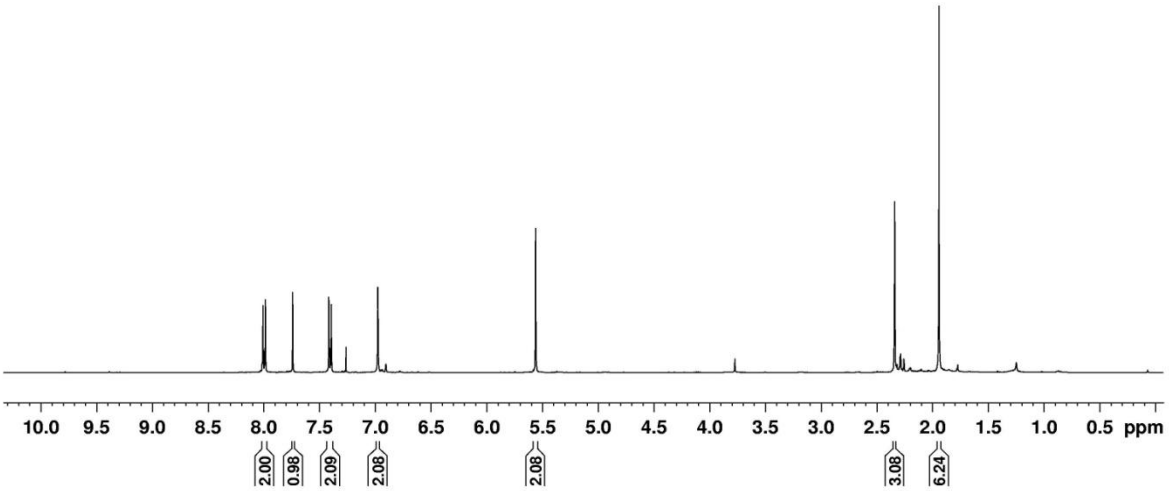


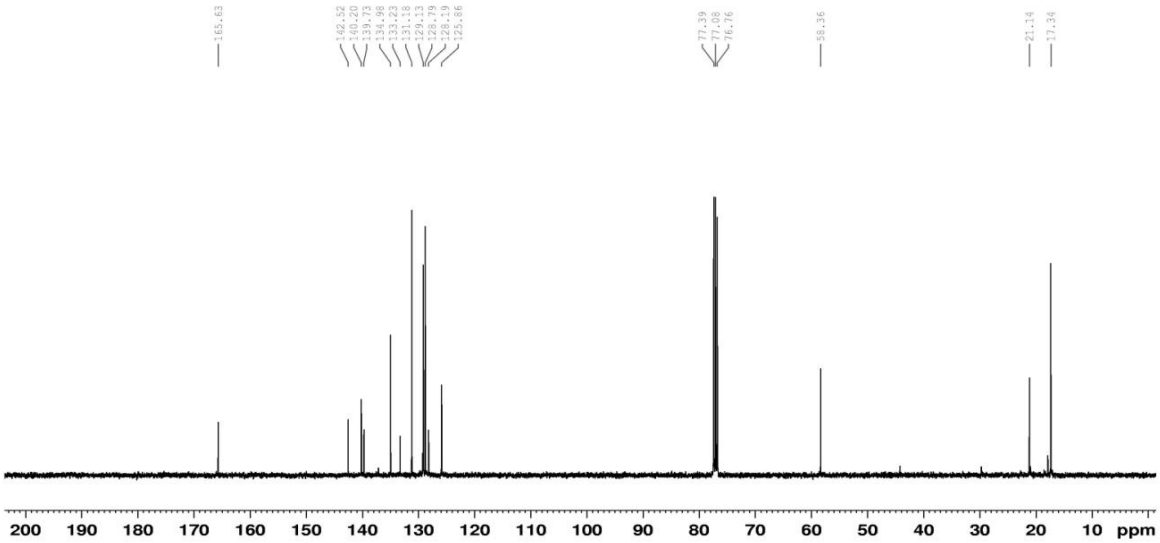




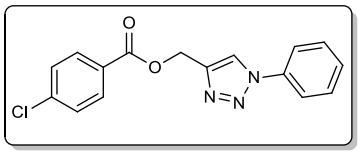
^{1}H, ^{13}C NMR Spectra of **12w**

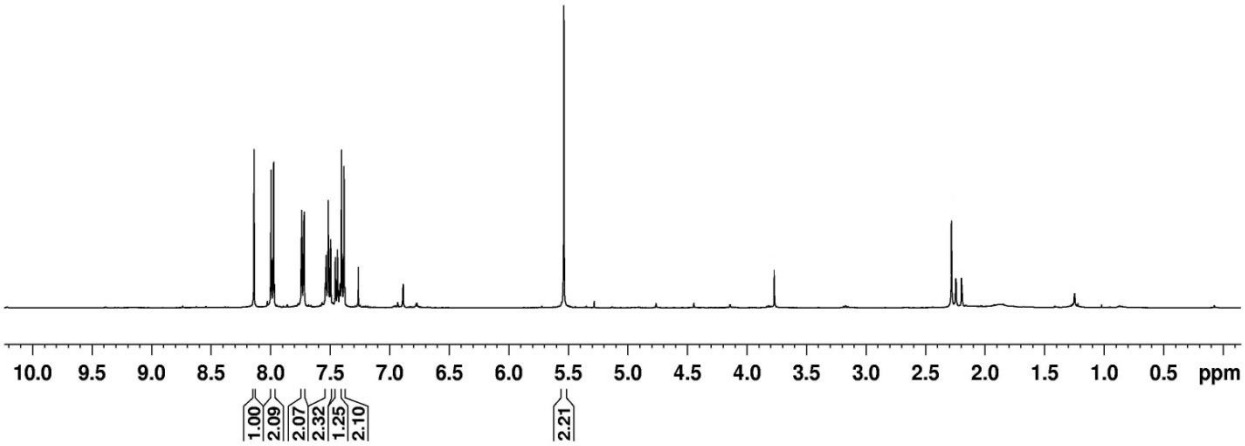


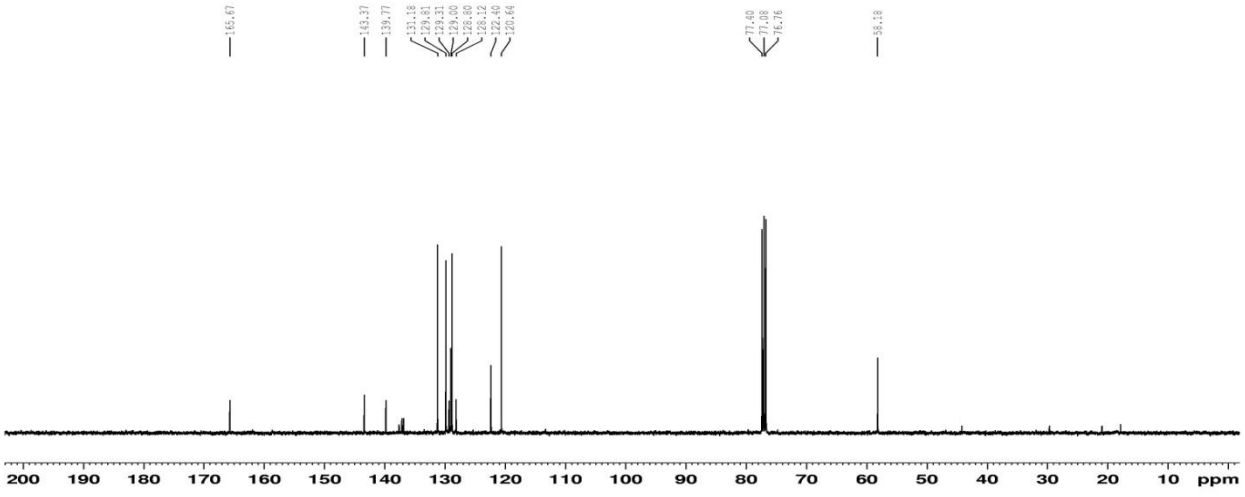




^{1}H, ^{13}C NMR Spectra of **12x**







3.5. References

[1] (a) Kolb, H.; Finn, M.; Sharpless, K. *Angew. Chem., Int. Ed.* **2001**, *40*, 2004. (b) Huisgen, R. *Angew. Chem., Int. Ed.* **1963**, *2*, 565.

[2] For reviews: (a) Tornoe, C.; Christensen, C.; Meldal, M. *J. Org. Chem.* **2002**, *67*, 3057. (b) Rostovtsev, V.; Green, L.; Fokin, V.; Sharpless, K. *Angew. Chem., Int. Ed.* **2002**, *41*, 2596. (c) Meldal, M.; Tornøe, C. W.; *Chem. Rev*. **2008**, *108*, 2952. (d) For special issues on click chemistry: (i) Kolb, H. C.; Sharpless, K. B.; *Drug Discovery Today* **2003**, *8*, 1128. (ii) Binder, W. H.; Sachsenhofer, R.; *Macromol. Rapid Commun*. **2007**, *28*, 15. (iii) Lutz, J.-F. *Angew. Chem., Int. Ed.* **2007**, *46*, 1018. (iv) Moses, J. E.; Moorhouse, A. D. *Chem. Soc. Rev*. **2007**, *36*, 1249. (v) Mamidyala, S. K.; Finn, M. G. *Chem. Soc. Rev*. **2010**, *39*, 1252. (vi) Finn, M. G.; Fokin, V. V. *Chem. Soc. Rev*. **2010**, *39*, 1231. (vii) Pedersen, D. S.; Abell, A. *Eur. J. Org. Chem*. **2011**, 2399.

[3] Haider, S.; Alam, M. S.; Hamid, H. *Inflamm. & Cell Signal.* **2014**, *1*, e95.

[4] Arde, P.; Ramanjaneyulu, B. T.; Reddy, V.; Saxena, A.; Anand, R. V. *Org. Biomol. Chem*. **2012**, *10*, 848. For recent reviews on sequential catalysis by two different catalysts, see: (a) Shao, Z.; Zhang, H. *Chem. Soc. Rev*. **2009**, *38*, 2745. (b) Zhong, C.; Shi, X. *Eur. J. Org. Chem*. **2010**, 2999. (c) Zhou, J. *Chem.—Asian J*. **2010**, *5*, 422. (d) Piovesana, S.; Schietroma, D. M. S.; Bella, M. *Angew. Chem. Int. Ed*. **2011**, *50*, 6216. (e) Loh, C. C. J.; Enders, D. *Chem.—Eur. J*. **2012**, *18*, 10212. (f) Patil, N. T.; Shinde, V. S.; Gajula, B. *Org. Biomol. Chem*. **2012**, *10*, 211.

[5] Maji, B.; Vedachalam, S.; Ge, X.; Cai, S.; Liu, X.W. *J. Org. Chem*. **2011**, *76*, 3016.

[6] (a) Feldman, A. K.; Colasson, B.; Folkin. V. *Org. Lett*. **2004**, *6*, 3897. (b) Barral, K.; Moorhouse, A. D.; Moses, J. E. *Org. Lett*. **2007**, *9*, 1809.

[7] (a) Chiang, P.-C.; Bode, J. W. *Org. Lett*. **2011**, *13*, 2422. (b) Li, Y.; Du, W.; Deng, W. P. *Tetrahedron* **2012**, *68*, 3611.

[8] For NHC-Cu catalyzed click chemistry, see: (a) Díez-González, S.; Correa, A.; Cavallo, L.; Nolan, S. P. *Chem.—Eur. J*. **2006**, *12*, 7558. (b) Nakamura, T.; Terashima, T.; Ogata, K.; Fukuzawa, S. *Org. Lett*. **2011**, *13*, 620.

[9] Enders, D.; Breuer, K.; Kallfass, U.; Balensiefer. T. *Synthesis* **2003**, 1292.

[10] (a) Anderson, J.; Madsen, U.; Björkling, F.; Liang, X. *Synlett* **2005**, 2209. (b) Shen, J.; Woodward, R.; Kedenburg, J. P.; Liu, X.; Chen, M.; Fang, L.; Sun, D.; Wang, P. G. *J. Med. Chem*. **2008**, *51*, 7417.

[11] Chakraborti, A. K.; Singh, B.; Chankeshwara, S. V.; Patel, A. R. *J. Org. Chem*. **2009**, *74*, 5967.

[12] Raj, V. P.; Sudalai, A. *Tetrahedron Lett*. **2005**, *46*, 8303.

[13] Punna, S.; Meunier, S.; Finn, M. G. *Org. Lett*. **2004**, *6*, 2777.

[14] Hofmeister, P.; Buerstinghaus, R.; Adolphi, H.; *U.S. patent*, US4642368, 1987.

[15] Zoser, B. S. *U.S. patent*, US0265269, 2007.

[16] Ram, R. N.; Soni, V. K.; Gupta, D. K. *Tetrahedron* **2012**, *68*, 9068.

[17] Wu, X.-F.; Neumann, H.; Beller, M. *Chem. Comm.* **2011**, *47*, 7959.

[18] Alvarez, L. X.; Christ, M. L.; Sorokin, A. B. *Applied Catalysis A: General* **2007**, *325*, 303.

[19] Buckley, B. R.; Dann, S. E.; Heaney, H.; Stubbs, E. C. *Eur. J. Org. Chem*. **2011**, 770.

List of Publications

- **Ramanjaneyulu, B. T.**; Mahesh, S.; Anand, R. V.* *Org. Lett.* **2015**, *17*, 6-9.
  Title: N-Heterocyclic Carbene Catalyzed Highly Chemoselective Intermolecular Crossed Acyloin Condensation of Aromatic Aldehydes with Trifluoroacetaldehyde Ethyl Hemiacetal
- **Ramanjaneyulu, B. T.**; Mahesh, S.; Anand, R. V.* *Org. Lett.* **2015**, *17*, 3952-3955.
  Title: Bis(amino)cyclopropenylidene (BAC) Catalyzed 1,6-Conjugate Addition of Aromatic Aldehydes to *para*-Quinone Methides: Expedient Access to α,α'-Diarylated Ketones
- **Ramanjaneyulu, B. T.**; Pareek, M.; Reddy, V.; Anand, R. V.* *Helv. Chim. Acta.* **2014**, *97*, 431-437.
  Title: Direct Esterification of Aromatic Aldehydes with Tetraphenylphosphonium Bromide under Oxidative N-Heterocyclic Carbene Catalysis
- **Ramanjaneyulu, B. T.**; Reddy, V.; Arde, P.; Mahesh, S.; Anand, R. V.* *Chem.—Asian J.* **2013**, *8*, 1489-1496.
  Title: Combining Oxidative N-Heterocyclic Carbene Catalysis with Click Chemistry: A Facile One-pot Approach to 1,2,3-Triazole Derivatives
- Mahesh, S.; Pareek, M.; **Ramanjaneyulu, B. T.**; Kaur, G.; Anand, R. V.* *Indian. J. Chem. Sec A.* **2013**, *52A*, 1086-1092.
  Title: Base Mediated 5-Endo-Dig Cyclization of N-Propargyl Proline derivatives: A Facile Entry to Pyrrolizidine Scaffolds
- Arde, P.; **Ramanjaneyulu, B. T.**; Reddy, R.; Saxena, A.; Anand, R. V.* *Org. Biomol. Chem.* **2012**, *10*, 848-851.
  Title: N-Heterocyclic Carbene Catalyzed Aerobic Oxidation of Aromatic Aldehydes to Aryl Esters using Boronic acids.

Presentations/Conferences

- Participated and presented a poster in the **Nature Inspired Initiatives in Chemical Trends (NIICT) conference held in IICT Hyderabad, Hyderabad** during 2-5th March 2014, India.
- Participated and presented an oral presentation in **Junior National Organic Symposium Trust (8th J-NOST) conference held in IIT Guwahati, Guwahati** during 15-17th, Dec 2012, India.
- Participated in **Junior National Organic Symposium Trust (7th J-NOST) conference held in IISER Mohali, Mohali** during 15-18th, Dec 2011, India.
- Participated in **Junior National Organic Symposium Trust (6th J-NOST) conference held in University of Hyderabad, Hyderabad** during 28-31st, January 2011, India.

Curriculum Vitae

Name: **T RAMANJANEYULU BANDARU**

Date of Birth: **07/06/1985**

Education

- M.Sc. (2008) Organic Chemistry with 61.0% of Marks from Acharya Nagarjuna University, Andhra Pradesh, India.
- B.Sc. (2006) (Mathematics, Physics, Chemistry) with 58.5% of Marks from Andhra University, Andhra Pradesh, India.

Awards/ Fellowships received

- **CSIR-JRF** with all India **37th** Rank in **CSIR-UGC NET** (Council of Scientific and Industrial Research-University Grants Commission National Eligibility Test examination in 2009.
- Awarded Junior Research Fellowship by Council of Scientific and Industrial Research (**CSIR**), India, 2010-2011.
- Awarded Senior Research Fellowship by Council of Scientific and Industrial Research (**CSIR**), India, 2012-2014.
- Qualified in Graduate Aptitude Test in Engineering (**GATE**) in Jan-2009 with percentile 89.5, a national level examination, India.