Organocatalytic and Lewis Acid Catalyzed Nucleophilic Addition Reactions of *para*-Quinone Methides and Cyclopropenones

A thesis submitted for the partial fulfilment of

the degree of Doctor of Philosophy

by

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Dedicated

To

My beloved parents

Declaration

The work presented in this thesis titled ***"Organocatalytic and Lewis Acid Catalyzed Nucleophilic Addition Reactions of para-Quinone Methides and Cyclopropenones"*** 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, Punjab.

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 bonafide record of original work done by me and all sources listed within have been detailed in the bibliography.

Prithwish Goswami

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

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Department of Chemical Sciences

Indian Institute of Science Education and Research, Mohali

Date:

Place:

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Abstract

The research work carried out in this thesis is mainly focused on the organocatalytic and/or Lewis acid catalyzed nucleophilic addition reactions of *para*-quinone methides and cyclopropenones with various nucleophiles. This thesis is divided into four chapters. Chapter 1 deals with the *N*-heterocyclic carbene catalyzed synthesis of *α*-aryl nitriles. Chapter 2 demonstrates a new catalytic activity of bis(amino)cyclopropenylidene (BAC) for the cross vinylogous Rauhut-Currier reaction between enones and *p*-quinone methides (*p*-QMs). Chapter 3 involves a 100% atom-economical approach for the synthesis of unsymmetrical diaryl(2-indolyl)methanes through 1,6-conjugate addition of C3-substituted indoles to *p*-quinone methides. Chapter 4 describes a mild organocatalytic approach for the synthesis of *O*-acylated phenols/alcohols and *N*-acylated indoles through the ring opening of cyclopropenones with phenols/alcohols and indoles, respectively.

***Chapter 1:* *N*-heterocyclic carbene catalyzed 1,6-conjugate addition of Me_3Si-CN to *para*-quinone methides and fuchsones: Access to *α*-arylated nitriles**

In this chapter, a straightforward approach for the synthesis of *α*-aryl nitriles is described. *α*-aryl nitriles are important structural scaffolds, often found in many biologically significant natural products and pharmaceuticals. Several of them display important therapeutic applications such as potent mAchR antagonist, anti-diarrheal, anti-protozoal activities (Figure 1). In addition, *α*-aryl nitriles serve as a key precursor for the synthesis of drug candidates. Furthermore, the nitrile moieties are valuable building blocks for the synthesis of amines, amides, carboxaldehydes, carboxylic acids and different *N*- containing heterocycles.

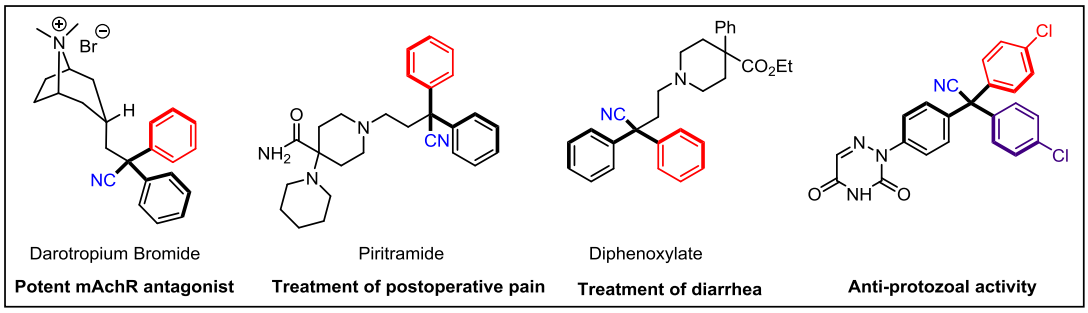
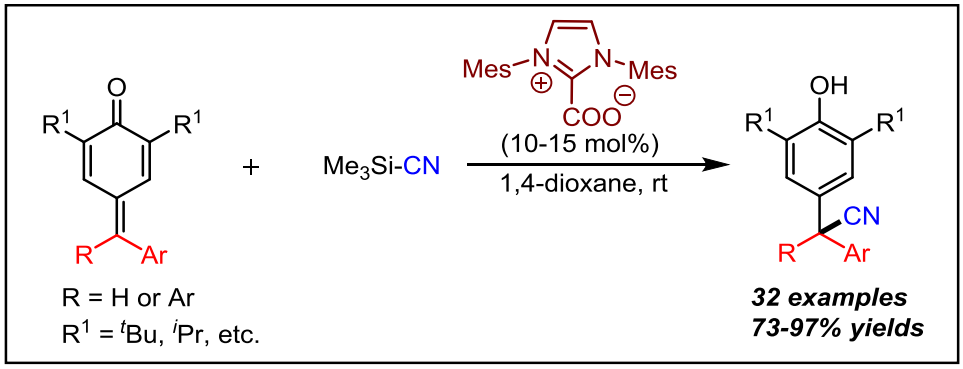


Figure 1. Some biologically significant *α*-aryl nitriles

Although there are many elegant metal catalyzed approaches known for the synthesis of *α*-aryl nitriles, most of them involve expensive metal catalysts or ligands. In addition,

some of the reported methods required toxic cyanide source. Therefore, developing an organocatalytic and atom-economic approach for the synthesis of α-aryl nitriles would be highly demanding. While working on *N*-heterocyclic carbene catalyzed organic transformations, we envisioned that it is possible to synthesize α-aryl nitriles through 1,6-conjugate addition of Me_3Si-CN to *para*-quinone methides using NHC as a catalyst. Under the optimized conditions, a wide range of *p*-QMs were reacted with Me_3Si-CN and, in most of the cases, the corresponding α-diaryl nitriles were obtained in excellent yields. Further, this concept was elaborated to access α-triaryl nitriles by employing fuchsones as 1,6-acceptor (Scheme 1).

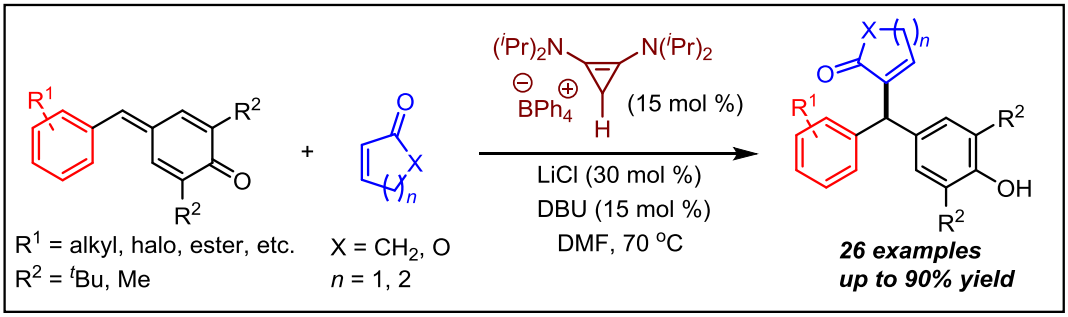


Scheme 1. Synthesis of α-aryl nitriles from *p*-QMs and fuchsones

Chapter 2: **Bis(amino)cyclopropenylidene (BAC) catalyzed Rauhut-Currier reaction between *α,β*-unsaturated carbonyl compounds and *para*-quinone methides**

In this chapter, a new catalytic activity of bis-(amino)cyclopropenylidene (BAC) for the cross vinylogous Rauhut-Currier reaction has been demonstrated. In recent years, nucleophilic carbene catalysis has emerged as a powerful tool for many organic transformations. Especially, the nucleophilic carbene catalysis has been extensively explored in the areas of organocatalysis and organometallic chemistry. As a result, recently, apart from *N*-heterocyclic carbene (NHC) catalysis, the syntheses of other non-heterocyclic based carbenes have drawn significant interest by many research groups. In this context, bis-(amino)cyclopropenylidenes (BACs), derived from cyclopropenium salts, have gained tremendous attention due to their unique reactivity towards carbonyl compounds. Unfortunately, until the recent past, the application of bis-(amino)cyclopropenylidene was limited only to organometallic chemistry. However, after the pioneering work by Bertrand and co-workers to isolate a bis-(amino)cyclopropenylidene in a stable form, this particular area of chemistry has drawn attention to some extent from the scientific community. But,

surprisingly, the organocatalytic application of BACs is still in immature state. Thus, we became interested in this research area. Recently, we have utilized BAC as an organocatalyst for the intermolecular cross vinylogous Rauhut-Currier reaction between *α,β*-unsaturated carbonyl compounds and *para*-quinone methides. This methodology worked well with the catalytic amount of BAC, and the respective R-C adducts were obtained in moderate to good yields. Interestingly, sensitive functional groups such as, ester and nitrile were well-tolerated under the reaction conditions. However, unfortunately, this methodology was limited to cyclic enones as acyclic enones failed to react under the optimized conditions (Scheme 2).



Scheme 2. BAC-catalyzed intermolecular Rauhut-Currier reaction

Chapter 3: **$Bi(OTf)_3$ catalyzed solvent free approach to unsymmetrical diaryl(2-indolyl)methanes through 1,6-conjugate addition of 3-substituted indoles to *para*-quinone methides**

This chapter describes a straight-forward approach for the synthesis of unsymmetrical diaryl(2-indolyl)methanes via a direct C2-functionalization of indoles with *para*-quinone methides. C2-functionalized indoles are important architectural motifs, widely found in various pharmaceuticals and natural products. Especially, C-2 substituted diarylindolylmethanes display interesting biological activities such as anti-protozoal, antibacterial, antispasmodic, anti-inflammatory activities, etc (Figure 2).

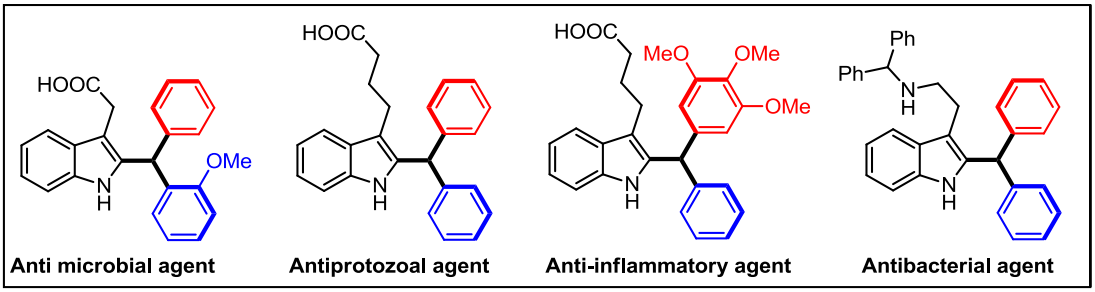
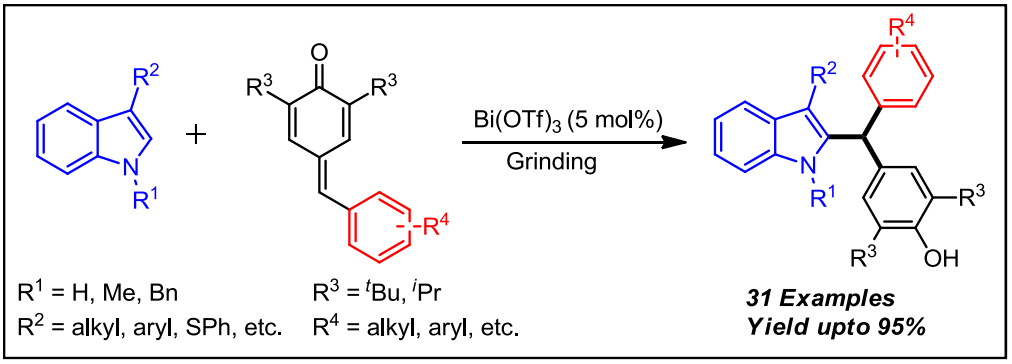


Figure 2. Some important biologically active diaryl(2-indolyl)methanes

It has been well documented that the C3 position of indole is most reactive towards any electrophile. Therefore, direct C2-functionalization of indoles is difficult due to relatively low nucleophilicity of the C2 position. Despite this drawback, several approaches have been reported for the synthesis of C2-functionalized of indoles by manipulating the reaction conditions. Although most of the previously known methods show excellent substrate scope and functional group tolerance, the involvement of highly toxic metal catalysts or expensive catalysts made their practical uses unattractive. Moreover, some of the reactions needed harsh conditions. Notably, none of the hitherto known methods could achieve 100% atom-economy. Therefore, developing an environmentally benign, 100% atom-economical protocol for the direct C-2 functionalization of indoles is highly desirable and challenging. While working on the 1,6-conjugate addition of different nucleophiles to *p*-QMs, we envisioned that we could achieve C-2 functionalized indoles through a vinylogous Michael addition of 3-substituted indoles to *p*-quinone methides. Optimization studies revealed that this methodology worked efficiently under solvent free grinding conditions and, out of several Lewis acids screened, $Bi(OTf)_3$ was found to be the best catalyst to drive the transformation. Under the optimized conditions, a wide range of 3-substituted indoles and *p*-QMs were reacted to afford the corresponding diaryl(2-indolyl)methanes in good to excellent yields. Various sensitive functional groups like Boc, Ts, Cbz, acid and ester were found to be stable under the optimized conditions (Scheme 3).



Scheme 3. Synthesis of unsymmetrical diaryl(2-indolyl)methanes

Chapter 4: **Organocatalytic *O*-acylation of phenols/alcohols and *N*-acylation of indoles with cyclopropenones**

In this chapter, a 100% atom-economical approach for the synthesis of *O*-acylated phenols/alcohols and *N*-acylated indoles is described. *O*-acylated phenols/alcohols and *N*-acylated indoles are an important architectural motif, often found in numerous biologically

significant molecules and pharmaceuticals. Several of them exhibit important medicinal applications (Figure 3). In addition, *O*-acylated phenols and *N*-acylated indoles can serve as key intermediates in the synthesis of complex molecules.

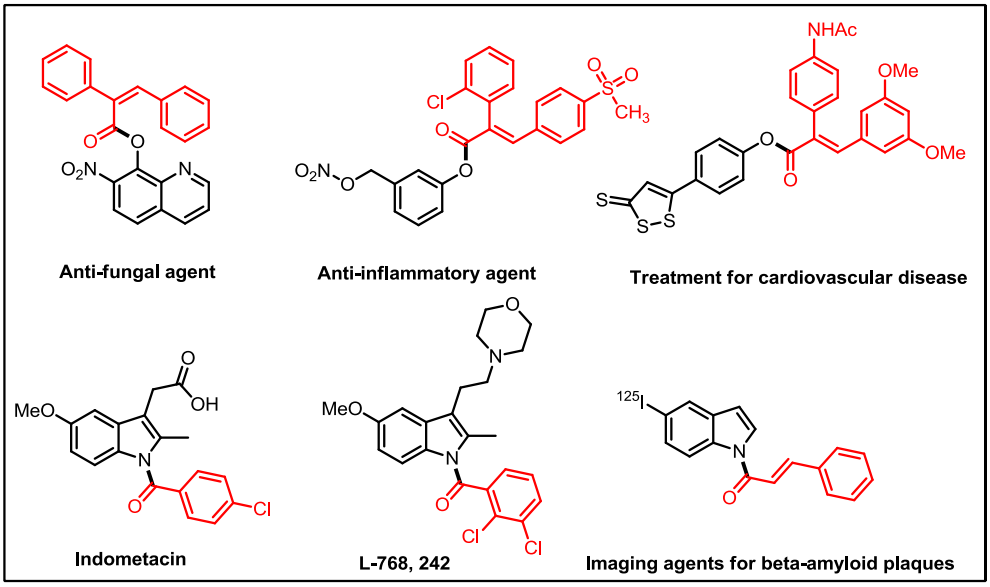
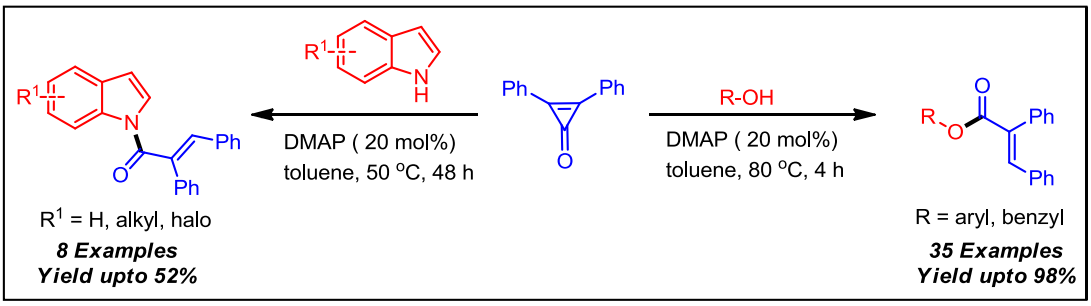


Figure 3. Biologically active *O*-acyl phenols and *N*-acyl indoles

The most common method for the acylation reaction involves a reaction between phenols/alcohols/indoles with acylating agents in presence of a stoichiometric amount of a base. However, the use of sensitive and hazardous acylating agents restrict the practical applications of this strategy. Moreover, the presence of stoichiometric amount of base limits the functional group tolerances. Therefore, developing an alternative and more efficient method for the synthesis of *O*-acylated phenols/alcohols and *N*-acylated indoles, especially under organocatalytic conditions would be more attractive and highly desired. While working on organocatalytic transformations, we envisaged that we could access *O*-acylated phenols/alcohols and *N*-acylated indoles through a ring opening reaction of cyclopropenones with phenols/alcohols and indoles, respectively. Optimization studies revealed that DMAP was the best catalyst to drive the transformation. Under the optimized conditions, a wide range of phenols was reacted with diphenylcyclopropenone to afford the corresponding *O*-acylated phenols in good to excellent yields. Apart from phenols, the substrate scopes was also demonstrated by treating various aliphatic alcohols with diphenylcyclopropenone under the optimized conditions and the resultant *O*-acylated alcohols were obtained in moderate to good yields. Interestingly benzoin and secondary benzyl alcohols were reacted efficiently under the catalytic conditions. To demonstrate the synthetic utility of this methodology, *N*-

acylation reaction of indoles were also examined. Under the optimized conditions, different *N*-acylated indoles were observed in moderate yields. However, the reactions were found to be very sluggish. Unfortunately, other cyclopropenones failed to react under the optimized conditions (Scheme 4).



Scheme 4. Synthesis of *O*-acylated phenols and *N*-acylated indoles

Abbreviations

ACN	Acetonitrile
AcOH	Acetic acid
Ac_2O	Acetic anhydride
Aq	Aqueous
$B_2(pin)_2$	Bis(pinacolato)diboron
Brs	Broad singlet
Bn	Benzyl
BAC	Bis(amino)cyclopropenylidene
$CHCl_3$	Chloroform
CCl_4	Carbon tetrachloride
CSA	Camphorsulfonic acid
Clcd	Calculated
Cy `	Cyclohexyl
Cbz	Carboxybenzyl
CO	Carbon monoxide
CsOAc	Caesium acetate
Cs_2CO_3	Cesium carbonate
Cm	Centimetre
δ	Chemical shift
$CDCl_3$	Chloroform-D
J	Coupling constant
CPME	Cyclopentyl methyl ether
DCE	Dichloroethane
DCM	Dichloromethane
Et_2O	Diethyl ether
°C	Degree celsius
dr	Diastereomeric ratio
DMA	Dimethylacetamide
DMAP	4-Dimethylaminopyridine
DME	Dimethoxyethane
DMSO	Dimethyl sulfoxide
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene

DBN	1,5-Diazabicyclo[4.3.0]non-5-ene
d	Doublet
dd	Doublet of doublet
ddd	Doublet of doublet of doublet
dt	Doublet of triplets
dtbbpy	4,4′-Di-*tert*-butyl-2,2′-dipyridyl
DTBP	Di-*tert*-butyl peroxide
EWG	Electron withdrawing
ESI	Electrospray ionization
ee	Enantiomeric excess
er	Enantiomeric ratio
EtOH	Ethanol
EtOAc	Ethylacetate
Equiv	Equivalents
FT-IR	Fourier transform infrared spectroscopy
Hz	Hertz
HRMS	High-resolution Mass Spectrum
HPLC	High Performance Liquid Chromatography
H	Hour(s)
i-Pr	*iso*-Propyl
LHMDS	Lithium bis(trimethylsilyl)amide
LDA	Lithium diisopropylamide
^{t}BuOLi	Lithium-*tert*-butoxide
m/z	Mass/Charge
MHz	Megahertz
m.p.	Melting point
Mes	Mesityl
MeOH	Methanol
Mg	Milligram(s)
ml	Milliliter(s)
mmol	Millimole(s)
min	Minute(s)
µL	Microliter (s)
µm	Micrometre (s)

M.S.	Molecular sieves
m	Multiplet
DMF	*N*,*N*'-Dimethyl formamide
NHC	N-heterocyclic carbene
NMO	N-Methylmorpholine N-oxide
NMP	*N*-Methyl-2-pyrrolidone
NMR	Nuclear Magnetic Resonance
n-Pr	Propyl
^{t}BuOK	Potassium-*tert*-butoxide
$POCl_3$	Phosphoryl chloride
P-TSA	*p*-Toluene sulfonic acid
q	Quartet
R_f	Retention factor
rt	Room temperature
sept	Septet
s	Singlet
NaH	Sodium hydride
^{t}Bu	*tert*-Butyl
tert	Tertiary
Boc	*tert*-Butyloxycarbonyl
TBAB	Tetrabutylammonium bromide
TPAP	Tetrapropylammonium perruthenate
THF	Tetrahydrofuran
TMS	Tetramethylsilane
TBS	*tert*-Butyldimethylsilane
TFA	Trifluoroacetic acid
TFE	2,2,2-Trifluoroethanol
t	Triplet
td	Triplet of doublets
tt	Triplet of triplet
UV	Ultraviolet
Vis	Visible

Contents

Chapter 1

1. *N*-Heterocyclic carbene catalyzed 1,6-conjugate addition of Me_3Si-CN to *para*-quinone methides and fuchsones: Access to *α*-arylated nitriles

In this chapter, the NHC-catalyzed 1,6-conjugate addition of Me_3Si-CN to *para*-quinone methides and fuchsones has been discussed. This chapter also covers a general introduction and reactions on NHC-catalyzed activation of silicon nucleophiles.

1.1 Introduction

In the recent past, *N*-Heterocyclic carbenes (NHCs) have been extensively explored in the areas of organocatalysis[1] and organometallic chemistry.[2] Owing to their unique structural and electronic properties, NHCs display different and interesting reactivity pattern. Due to presence of free sp^2-type lone pair, NHC could act as an extremely strong *σ*-donor and thus can stabilize low-valent *p*-block elements through its strong *σ*-donation and weak *π*-back-bonding interactions.[3] The best example for this is the formation of hypervalent complexes of NHCs with tetravalent silicon compounds.[4] The strong *σ*-donation of NHCs towards the empty *p*-orbital of Si, through a hypervalent complex, makes the NHC-Si bond more stronger than Si-C bond of organosilicon reagents. This extra stability of NHC-Si bond is the driving force for the facile cleavage of Si-C bond of organosilicon reagents (Figure 1).

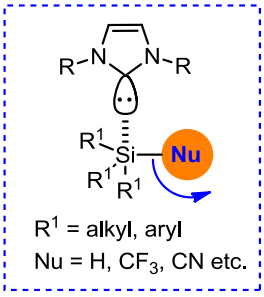


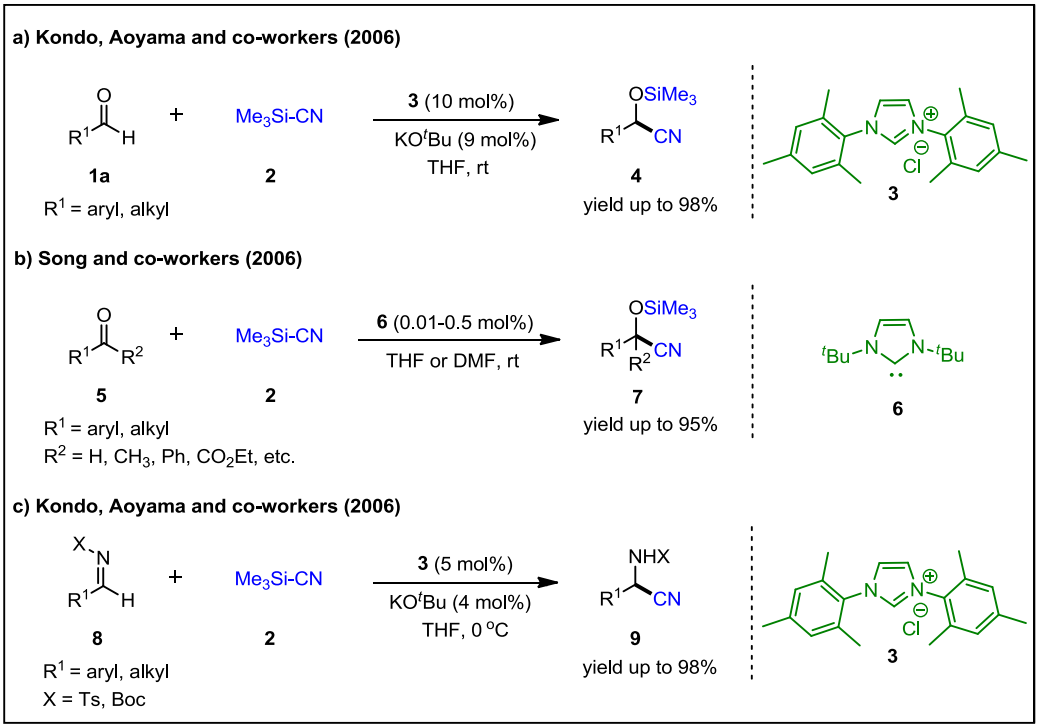
Figure 1

This concept has been utilized for many organic transformations and a few of them are discussed in this section.

1.2 Literature reports on NHC-catalyzed activation of silicon nucleophiles:

1.2.1 NHC-catalyzed 1, 2-addition reactions

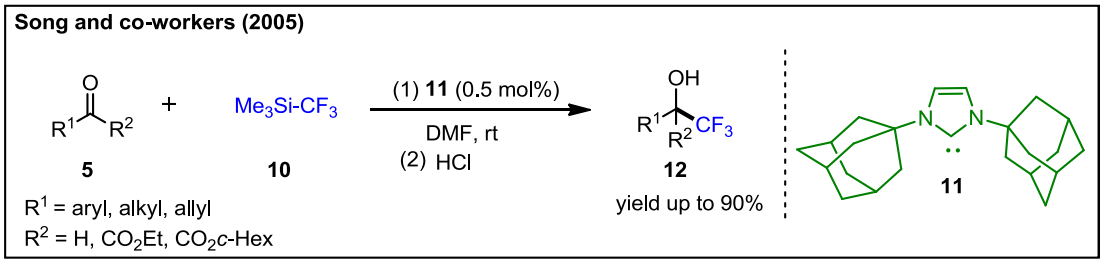
Kondo, Aoyama and co-workers, for the first time in 2006, described the NHC catalyzed Me_3Si-CN (**2**) addition to aldehydes (**1a**) to access cyanohydrins derivatives (**4**) [a, Scheme 1].[5a] Free IMes carbene was generated in situ by the treatment of the imidazolium salt (**3**) with KO^{t}Bu. Later, Song and co-workers investigated the cyanosilylation reaction of carbonyl compounds (**5**) by using pre-isolated NHCs (**6**) [b, Scheme 1].[5b] It was found that the reaction underwent smoothly even at very low catalyst loading (0.01-0.5 mol %) and the corresponding trimethylsilylated cyanohydrins (**7**) were isolated in very good to excellent yields. Kondo, Aoyama and co-workers extended this activation approach for the Strecker reaction between Me_3Si-CN (**2**) and aldimines (**8**).[6] The resultant α-aminonitriles (**9**) were obtained in excellent yields (c, Scheme 1).



Scheme 1: NHC-catalyzed 1, 2-cyanosilylation of carbonyl compounds and imines

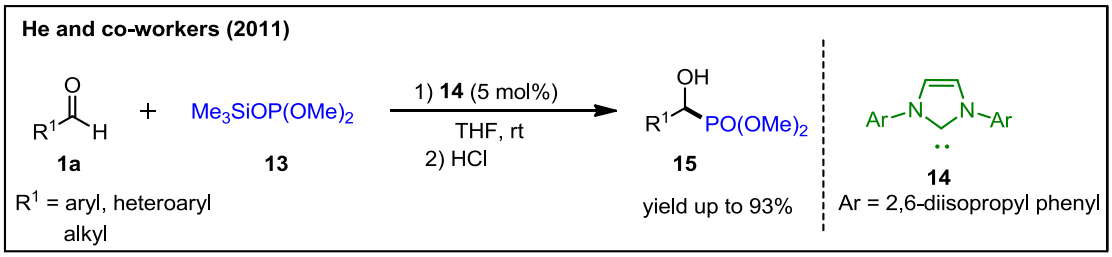
Song and co-workers disclosed an NHC-catalyzed trifluoromethylation reaction of carbonyl compounds (**5**) leading to trifluoromethyl containing compounds.[7] In this case, the Ruppert's reagent (**10**) was used as trifluoromethyl source to obtain different trifluoromethyl containing alcohols (**12**). Both enolizable as well as nonenolizable aldehydes and α-ketoesters

underwent smooth transformation with the Ruppert's reagent. Moreover, the chemoselective trifluoromethylation of aldehydes over ketones could be attained under controlled conditions. (Scheme 2).



Scheme 2: NHC-catalyzed trifluoromethylation of aldehydes and ketones

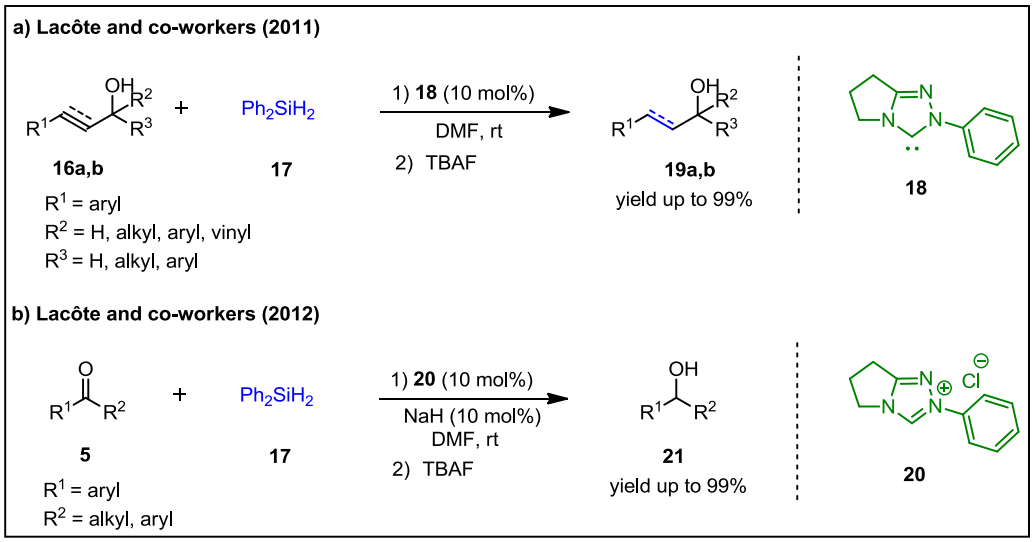
He and co-workers developed an efficient NHC-catalyzed Pudovik-type reaction for the hydrophosphonylation of aldehydes.[8] A wide range of aldehydes (**1a**) were treated with dimethyl trimethylsilyl phosphite (**13**) in presence of 5 mol% of IPr NHC (**14**) to produce a variety of *α*-hydroxyphosphonate derivatives (**15**) [Scheme 3].



Scheme 3: NHC-catalyzed Pudovik-type reaction

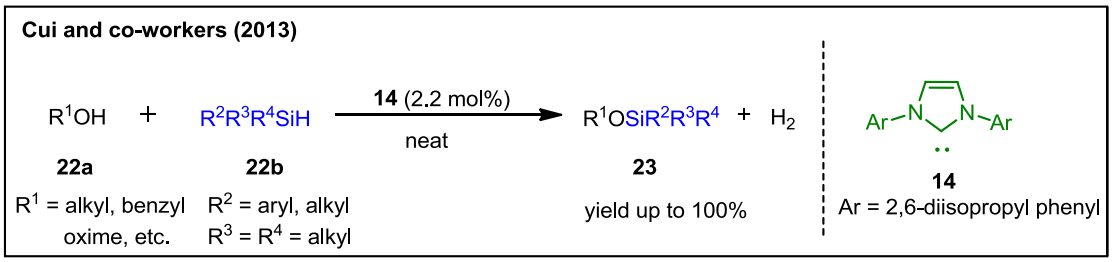
1.2.2 NHC-catalyzed hydrosilylation reactions

Lacôte and co-workers described an interesting NHC-catalyzed protocol for the hydrosilylation of nonactivated olefins and alkynes (**16a,b**). Moreover, the chemoselective reduction of styryl and propargylic alcohols (**16a,b**) with dihydrosilanes (**17**) was achieved.[9a] The reduced alcohols (**19a,b**) were isolated in excellent yields under mild reaction condition (a, Scheme 4). Later, the same group extended this concept for the chemo- and regioselective reduction of carbonyl compounds (**5**).[9b] The resultant alcohols (**21**) were isolated in good to excellent yields. Sensitive functional groups such as epoxide and cyclopropene containing substrates also underwent smooth conversion under the standard conditions (b, Scheme 4).



Scheme 4: NHC-catalyzed hydrosilylation of olefins and carbonyl compounds

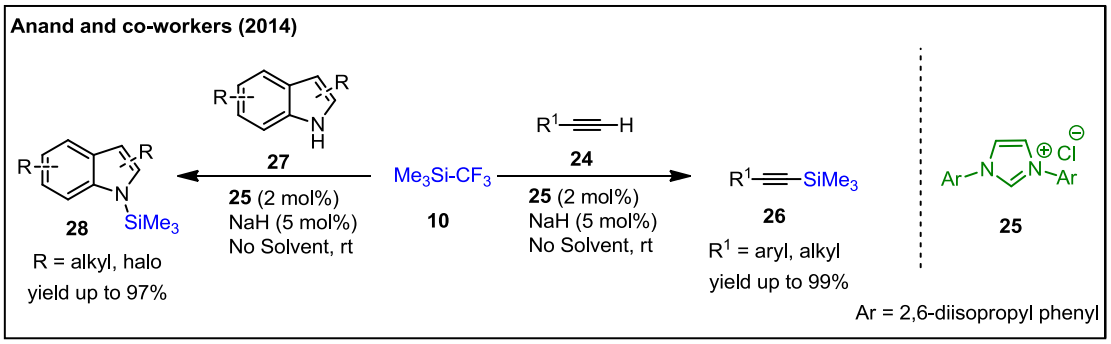
Cui's group disclosed a fascinating solvent free NHC-catalyzed dehydrogenative coupling approach for the synthesis of silyl ethers.[10] A variety of alcohols (**22a**) were reacted with different silanes (**22b**) in presence of 2.2 mol% IPr NHC (**14**) to provide the respective silyl ethers (**23**) in excellent yields. Interestingly, in case of diphenylprolinol, the chemoselective silylation of only hydroxyl group was observed (Scheme 5).



Scheme 5: NHC-catalyzed dehydrogenative coupling of silanes with hydroxyl compounds

1.2.3 NHC-catalyzed trimethylsilylation of terminal alkynes and indoles

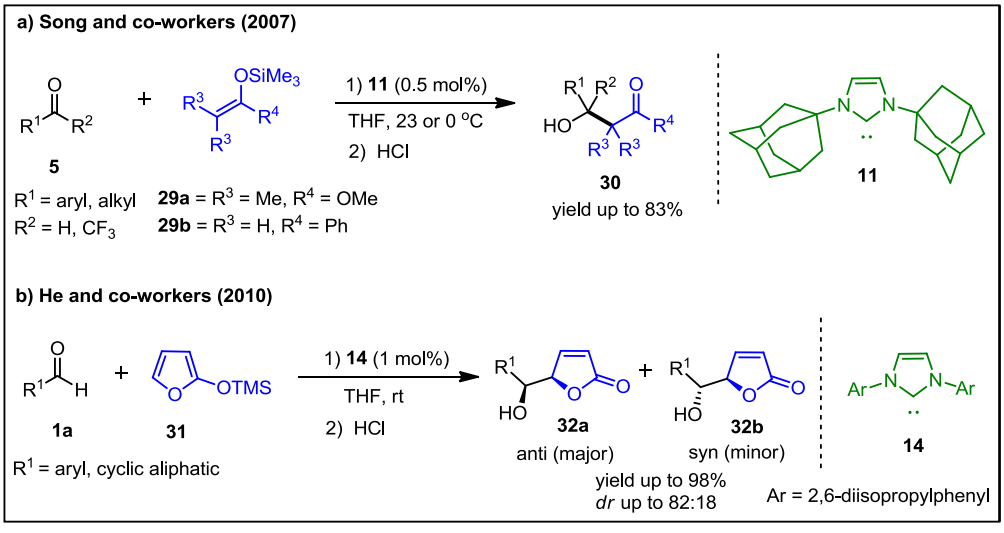
Very recently, Anand and co-workers reported an NHC-catalyzed trimethylsilylation of terminal acetylenes (**24**) using Ruppert's reagent (**10**) under solvent and fluoride free conditions.[11] A wide range of terminal acetylenes containing aromatic as well as aliphatic substituent were reacted with Ruppert's reagent in the presence of 2 mol% of NHC precursor (**25**) and 5 mol% of NaH. In all the cases, the corresponding silylated acetylenes (**26**) were isolated in excellent yields. It was also shown that the byproduct, fluoroform, could be further utilized for the regeneration of Ruppert's reagent (**10**). Further, this methodology was extended to the chemospecific *N*-silylation of indoles (**27**) [Scheme 6].



Scheme 6: NHC-catalyzed trimethylsilylation of terminal acetylenes and indoles

1.2.4 NHC-catalyzed Mukaiyama aldol type reactions

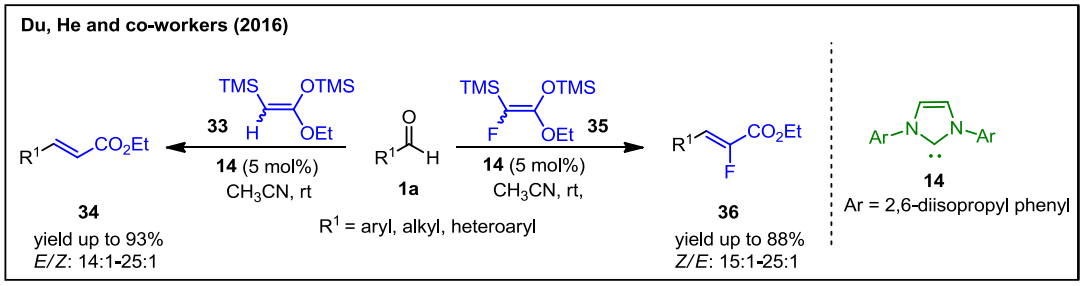
Song and co-workers demonstrated a novel NHC-catalyzed Mukaiyama aldol reaction.[12a] A wide range of aldehydes and activated ketones (**5**) were treated with trimethylsilyl ketene acetal (**29a**) at room temperature in presence of 0.5 mol% NHC (**11**) to afford the resultant aldol adducts (**30**) in moderate to good yields (a, Scheme 7). Later He's group accomplished an efficient NHC catalyzed vinylogous Mukaiyama aldol reaction between aldehydes (**1a**) and 2-(trimethylsililoxy)furan (**31**).[12b] The reaction worked efficiently even at very low catalyst loading and, almost all the cases, the corresponding vinylogous Mukaiyama aldol adducts (**32a,b**) were obtained in excellent yields with anti-selectivity (b, Scheme 7).



Scheme 7: NHC-catalyzed Mukaiyama Aldol reaction

Du, He and co-workers extended the concept of Mukaiyama aldol reaction for the synthesis of functionalized olefins through an *N*-heterocyclic carbene catalyzed Peterson type

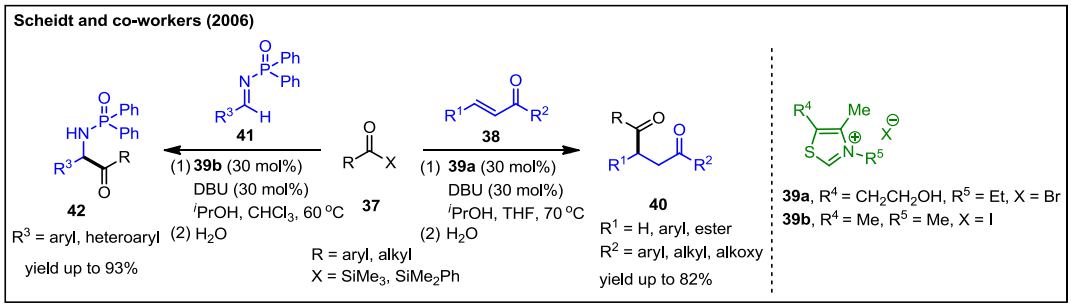
olefination reaction of aldehydes (**1a**) and silyl ketene acetals (**33**).[13] Under the optimized reaction conditions, most of aromatic aldehydes and aliphatic aldehydes reacted efficiently to produce their corresponding olefins (**34**) with excellent yields and very good *E*-selectivity. Further, this methodology was elaborated for the synthesis of fluoroolefines (**36**) as well (Scheme 8).



Scheme 8: NHC-catalyzed Peterson type olefination reaction

1.2.5 NHC-catalyzed reaction of acylsilanes with imines and enones

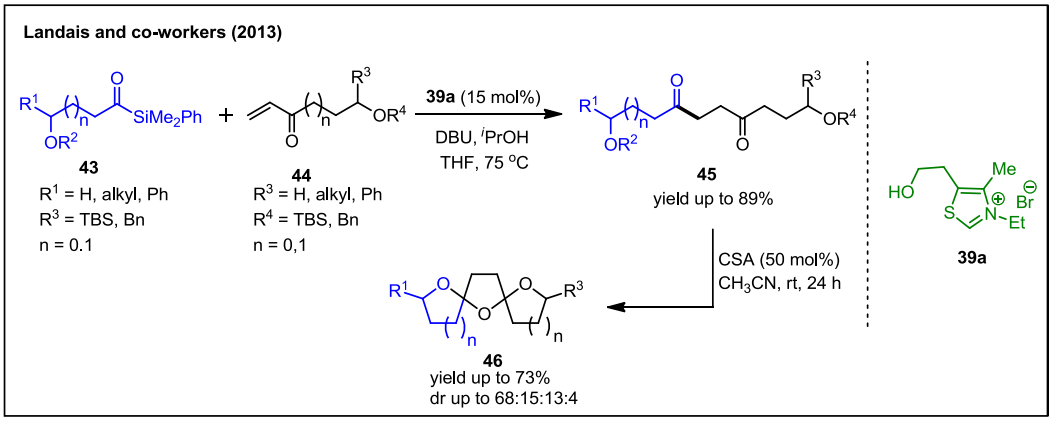
Scheidt and co-workers reported an NHC catalyzed acyl anion addition to chalcones (**38**) and *N*-phosphinoylimines (**41**).[14] Acylsilanes (**37**) were utilized for the generation of acyl anions. The carbonyl anion addition to enones and imines led to the formation of 1,4-diketones (**40**) and *N*-phosphinoyl-*α*-aminoketones (**42**), respectively in good to excellent yields (Scheme 9).



Scheme 9: NHC-catalyzed addition of acylsilanes to chalcones and imines

Landais and co-workers described a NHC-catalyzed sila-Stetter/ketalization approach for the synthesis of bis-spiroacetals.[15] In the first step, a wide range of silyl ether substituted acylsilanes (**43)** and silyl ether substituted enones (**44**) were reacted with catalytic amount of NHC precursor (**39a**) to obtain the corresponding 1,4-diketones (**45**) in good to excellent yields. After successfully synthesizing the 1,4-diketones, the spiroacetalization cascade reactions were performed in the next step. When different 1,4-diketones (**45**) were treated

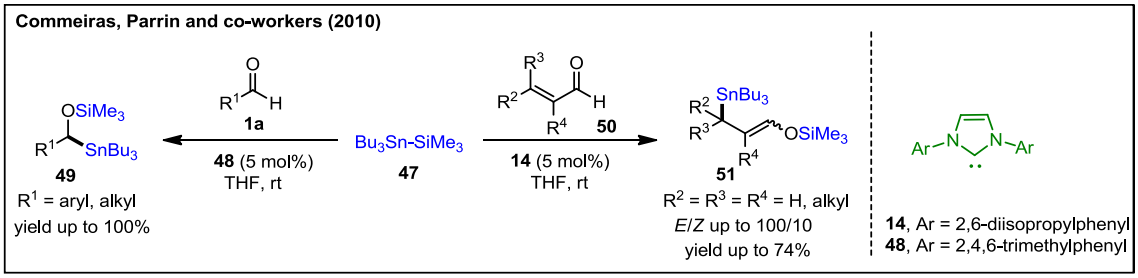
with 50 mol% CSA (camphorsulfonic acid), the required bis-spiroacetals (**46**) were isolated in moderate to good yields with very good diastereoselectivity (Scheme 10).



Scheme 10: NHC-catalyzed Sila-Stetter-Ketalization cascade

1.2.6 NHC-catalyzed stannylsilylation reactions

Commeiras, Parrin and co-workers accomplished an efficient NHC catalyzed stannylsilylation of aldehydes and enals.[16] For this purpose, tributyl(trimethylsilyl)stannane ($Bu_3SnSiMe_3$) (**47**) has been utilized as a tin source. Wide range aldehydes (**1a**) underwent stannylsilylation reaction to produce *α*-silyloxyalkylstannanes (**49**) derivatives. In case of enals, only aliphatic substituted acrolein derivatives (**50**) underwent this transformation smoothly and the resultant *γ*-silyloxyallylstannanes (**51**) were obtained in good yields with excellent *E* selectivity. The formation of pentavalent silicon complex was proved by NMR experiments (Scheme 11).

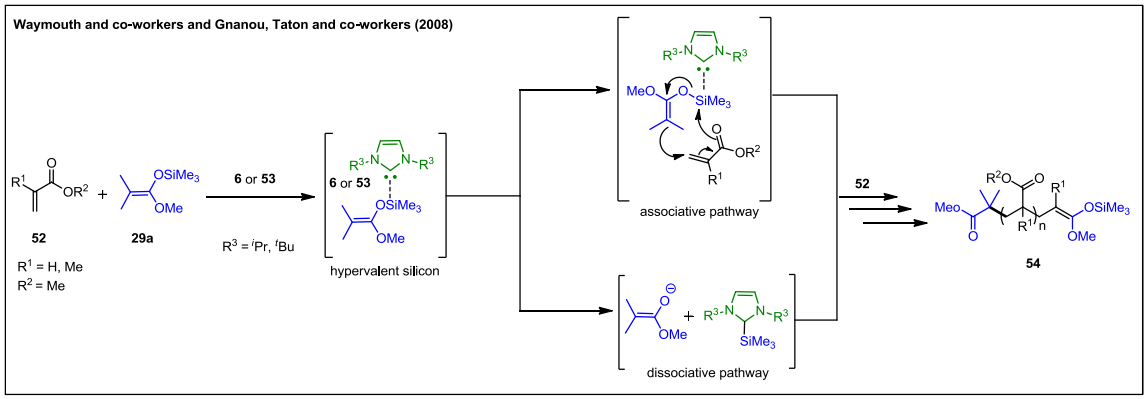


Scheme 11: NHC-catalyzed stannylsilylation reaction

1.2.7 NHC-catalyzed polymerization reactions

Waymouth[17] and Taton's[18] group independently discovered a fascinating NHC-catalyzed group-transfer polymerization (GTP) reaction for the polymerization of methyl methacrylates (**52**) and silylketene acetals (**29a**) through the replication of Mukaiyama-

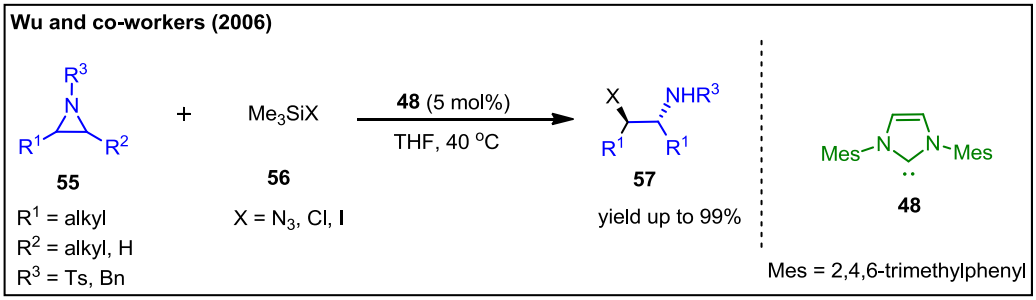
Michael reactions. According to previous literature reports, it is believed that NHC activates the silyl ketene acetals to initiate the group transfer polymerization reaction. However, both the groups postulated two different plausible pathways for the polymerization reaction. According to Waymouth's hypothesis, reaction follows a dissociative pathway. Based on kinetic studies, they assumed that imidazolium enolates initiates the GTP reaction. Whereas, Taton and co-workers believed that the reaction goes through an associative pathway. Based on on ^{13}C and ^{29}Si NMR studies they overruled the formation of enolate intermediate. They proposed that the reaction proceeds through the formation of hypervalent silicon-NHC complex (Scheme 12).



Scheme 12: NHC-catalyzed group-transfer polymerization

1.2.8 NHC-catalyzed ring-opening reactions of aziridines with silicon nucleophiles

Wu and co-workers demonstrated a NHC catalyzed aziridine ring opening reaction.[19] A wide range of silyl nucleophiles such as $TMSN_3$, TMSCl, TMSI (**56**) were activated by NHC (**48**) and reacted with aziridines (**55**), and the corresponding ring opening products (**57**) were obtained in up to 99% yield with anti-selectivity (Scheme 13).



Scheme 13: NHC-catalyzed ring-opening of aziridines

1.3. Introduction and Literature reports on the synthesis of *α*-Aryl nitriles

1.3.1 Introduction

α-Aryl nitriles are considered as valuable architectural scaffolds in synthetic organic chemistry due to their presence in many pharmaceuticals and biologically active natural products.[20] Many of the *α*-diaryl and *α*-triaryl nitriles exhibit exciting biological and therapeutic applications. Some of the selected biologically important *α*-Aryl nitriles are shown in figure 2. For example, darotropium bromide (**58**) can act as a very potent mAchR antagonist and used for treatment of COPD.[21a] Piritramide (**59**)[21b] and diphenoxylate (**60**)[21c] hold important applications in medicinal chemistry and have been commercialized for the treatment of postoperative pain and diarrhea, respectively. Apart from these, *α*-triaryl nitrile derivative **61** was found to inhibit the growth of protozoa.[21d] In addition, *α*-Aryl nitriles serve as key precursors in drug synthesis.[22] Furthermore, the nitrile scaffolds are valuable building blocks for the synthesis of amines, amides, carboxaldehydes, carboxylic acids and different *N*- containing heterocycles.[23]

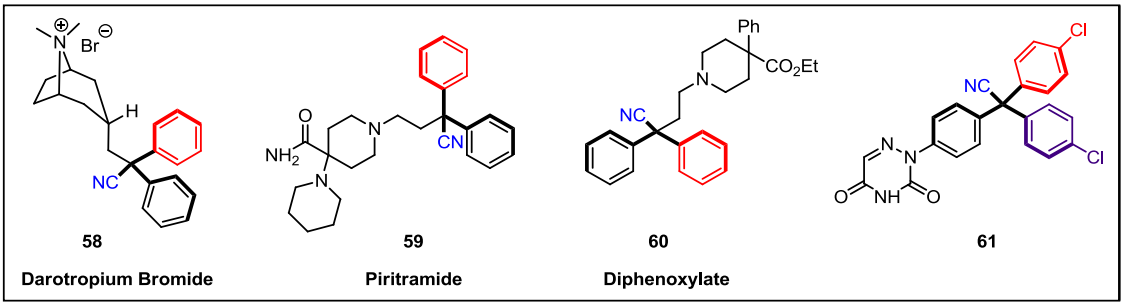
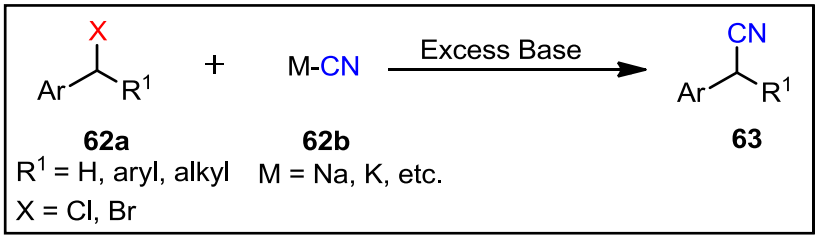


Figure 2: Important biologically active *α*-Aryl nitriles

1.3.2 Literature reports on the synthesis of *α*-Aryl nitriles

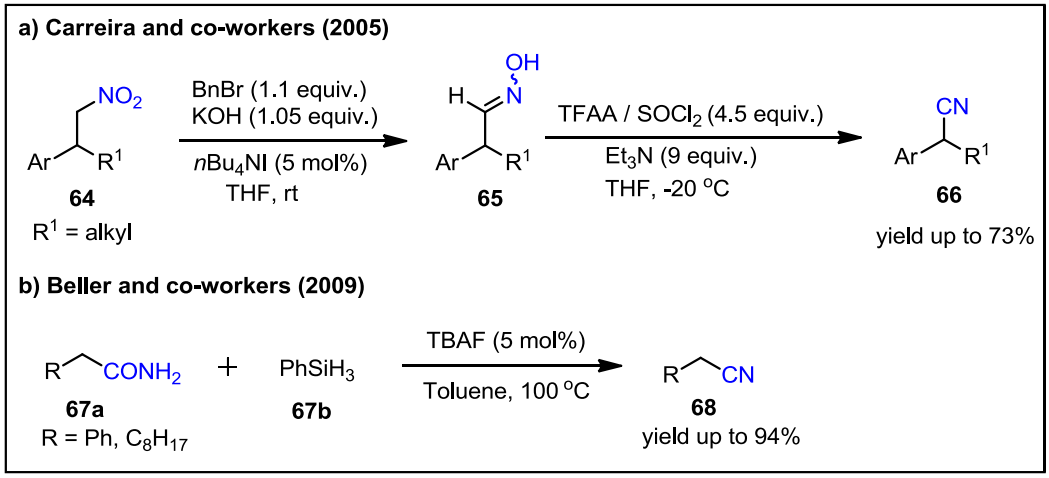
Due to their widespread applications in various fields, several approaches have been developed for the synthesis of *α*-Aryl nitriles. The general route for the synthesis of *α*-aryl



Scheme 14: General method for the synthesis of *α*-Aryl nitriles

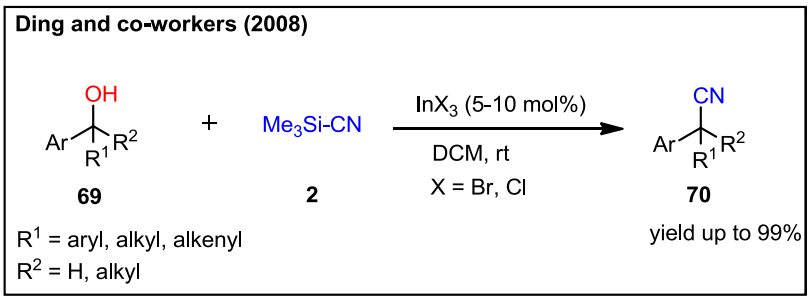
nitriles includes a nucleophilic substitution of benzyl halides with alkali metal cyanides or ammonium cyanides (Scheme 14).[24] However, the uses of toxic alkali metal salts and excess amount of base limits the synthetic utility of these methods. To overcome these limitations many alternative approaches have been emerged by many research groups.

Carreira and co-workers demonstrated a one-pot metal free transformation of nitroalkanes into nitriles through the dehydration of aldoximes.[25a] A variety of organonitro compounds (**64**) were treated with benzyl bromide, KOH and catalytic amounts of nBu$_4$NI at room temperature to get the corresponding aldoximes intermediate (**65**). Further, the addition of TFAA or $SOCl_2$ and Et_3N led directly to organonitriles (**66**) in good yields. This result revealed that the mixture of TFAA or $SOCl_2$ and Et_3N could act as efficient dehydrating agent for the dehydration of aldoximes to nitriles (a, Scheme 15). Later in 2009, Beller's group reported a fluoride-catalyzed dehydration of amides (**67a**) to nitriles (**68**) for the first time.[25b] Readily available TBAF was used as a catalyst and phenylsilane (**67b**) was used as a dehydrating reagent (b, Scheme 15).



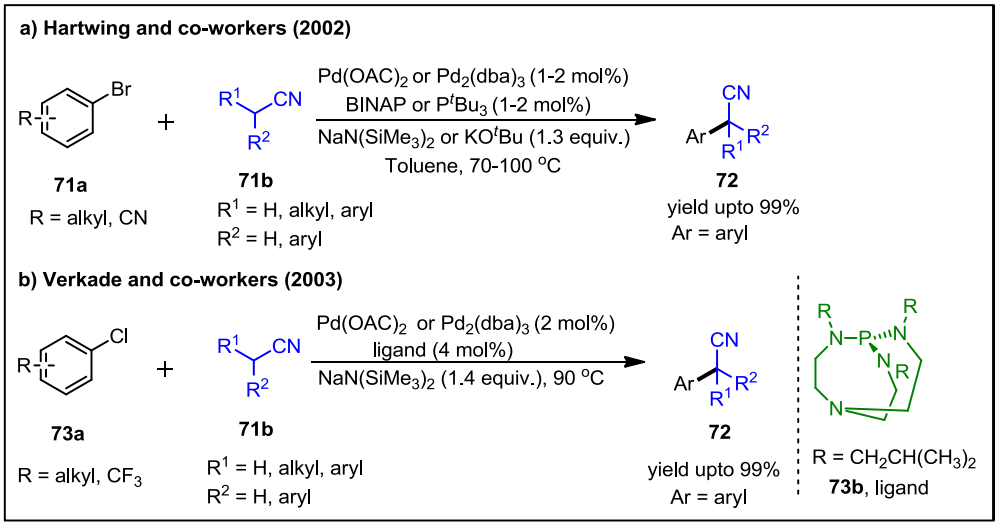
Scheme 15: Dehydration of aldoximes and amides

Ding and co-workers discovered a Lewis acid catalyzed addition of Me_3Si-CN to diarylcarbinols.[26] A variety of α-aryl alcohols (**69**) were treated with Me_3Si-CN (**2**) using InX_3 (X = Br or Cl) as a catalyst, and the resultant α-aryl nitriles (**70**) were isolated in good to excellent yields. It is worth mention that this catalytic method was found to be very suitable for the synthesis of key nitrile precursors for some medicinally important compounds (Scheme 16).



Scheme 16: Lewis acid catalyzed addition of Me_3Si-CN to diarylalcohols

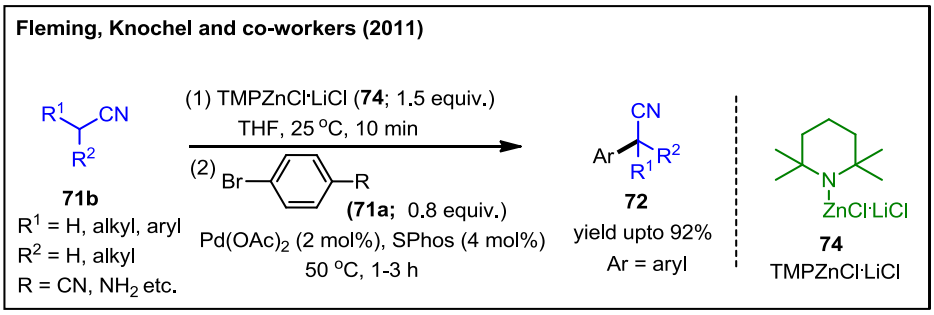
Recently transition-metal catalyzed approaches have also been developed by many research groups. For example, Hartwig and co-workers described a palladium catalyzed *α*-arylation of nitriles for the synthesis of *α*-aryl nitriles.[27a] A wide range of aryl bromides (**71a**) and unactivated nitriles (**71b**) were subjected under the standard conditions and the resultant *α*-arylated nitriles (**72**) were isolated in good yields (a, Scheme 17). Later, Verkade's group reported similar methodology using aryl chlorides as coupling partner.[27b] Bicyclic proazaphosphatranes (**73b**) was utilized as ligand. An array of nitriles (**71b**) was treated with a wide range of aryl chlorides (**73a**) under the optimized conditions and the subsequent *α*-aryl nitriles (**72**) were obtained in excellent yields (b, Scheme 17).



Scheme 17: Palladium catalyzed *α*-arylation of nitriles

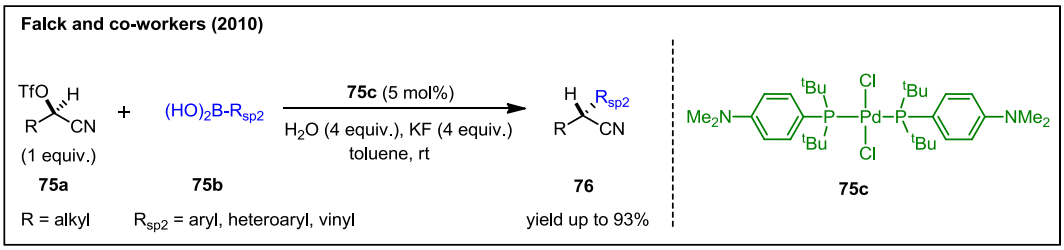
Recently, Fleming, Knochel and co-workers disclosed a slightly modified procedure for the palladium catalyzed *α*-arylation of benzylic nitriles and aliphatic nitriles (**71b**) with aryl bromides (**71a**) using TMPZnCl·LiCl (**74**) as a kinetically active base.[28] Remarkably,

various functional groups such as NH_2, CN and CO_2Et substitutions in aryl bromides were well tolerated during the reaction (Scheme 18).



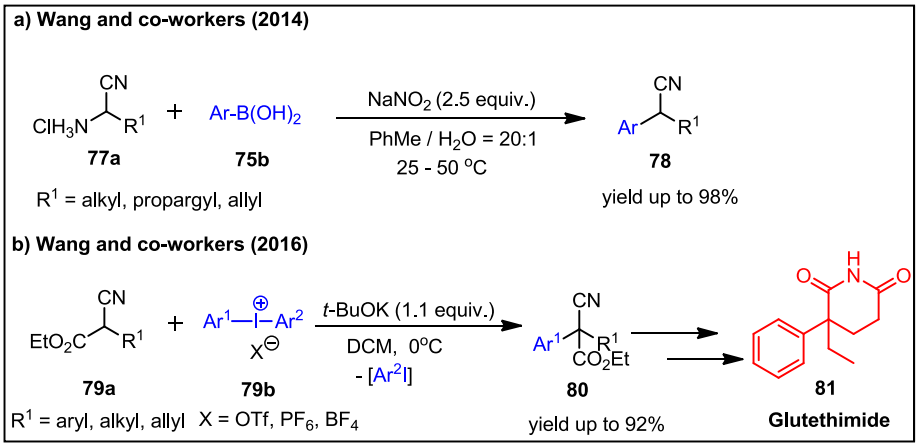
Scheme 18: Palladium catalyzed α-arylation of nitriles with TMPZnCl·LiCl

Falck and co-workers accomplished a fascinating stereospecific Suzuki cross-coupling reaction of boronic acids and α-cyanohydrin triflates for the formation of α-aryl nitriles.[29] Various boronic acids (**75b**) were coupled with α-cyanohydrin triflates (**75a**) in presence of palladium catalyst (**75c**) to afford the corresponding α-aryl nitriles (**76**) in good to excellent yields (Scheme 19).



Scheme 19: Palladium catalyzed Suzuki cross-coupling of alkyl α-cyanohydrin triflates

Apart from the above-mentioned methods, a few metal free protocols are also known in the literature. Wang's group demonstrated a transition metal free deaminative coupling of arylboronic acids with α-aminoacetonitriles for the synthesis of α-aryl nitriles (**78**).[30a] A wide range of α-aminoacetonitriles derivatives (**77a**) and arylboronic acids (**75b**) were examined under the optimized conditions (a, Scheme 20). Later in 2016, Han, Wang and co-workers disclosed a transition metal free direct arylation of 2-substituted cyanoacetates (**79a**) with diaryliodonium salts (**79b**) for the synthesis of α-aryl nitriles.[30b] This approach involves *tert*-butoxide mediated arylation of various cyanoacetates to furnish subsequent α-aryl nitriles (**80**) in up to 92% yield. To show the synthetic utility of the current protocol, it was elaborated for the synthesis of glutethimide (**81**) [b, Scheme 20].



Scheme 20: Transition metal free approaches towards *α*-aryl nitriles

1.4 Background

Although most of the above-mentioned hitherto known approaches provide good substrate scope, the harsh reaction conditions and the use of expensive metal catalysts or ligands make these transformations practically unattractive. In addition, the synthesis of prefunctionalized starting materials and the tedious workup procedures or the use stoichiometric activating agents restrict their practical application. Therefore, developing an alternative and more efficient method for the synthesis of *α*-aryl nitriles, especially under organocatalytic conditions would be more attractive and highly desired.

While working on *N*-heterocyclic carbene catalyzed organic transformations, we envisioned that it is possible to synthesize *α*-aryl nitriles through 1,6-conjugate addition of Me_3Si-CN to *para*-quinone methides using NHC as a catalyst (Figure 2).

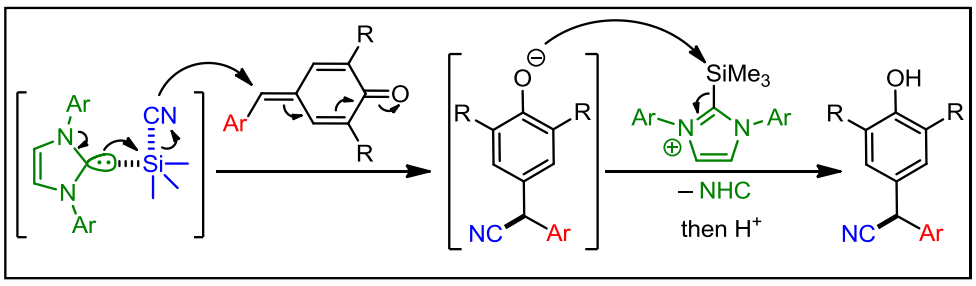
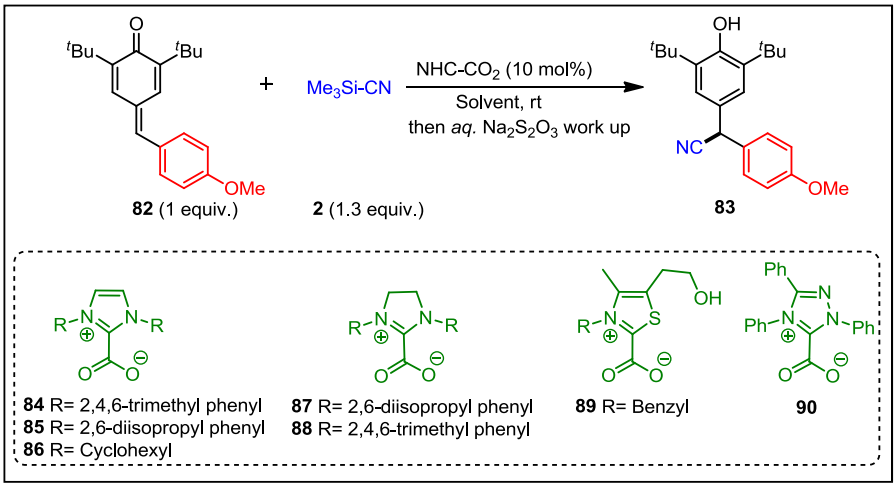


Figure 2: Our hypothesis for the synthesis of *α*-arylated nitriles

1.5 Results and Discussions

To optimize the reaction condition, a readily available *p*-QM **82** was treated with Me_3Si-CN (**2**) in presence of wide range of NHC-CO_2 adducts (**84-90**) as pre-catalysts and the results are summarized in Table 1.

Table 1: Optimization studies[a]

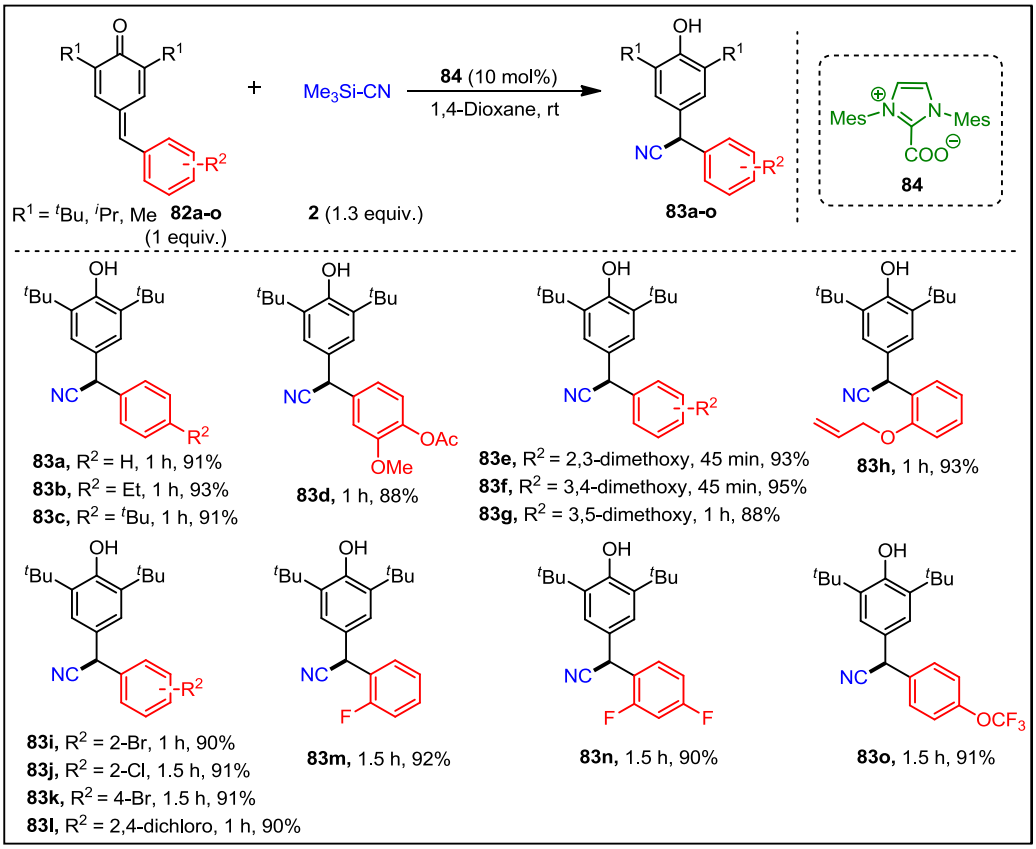


entry	precatalyst	solvent	time [h]	yield of **83** (%)
1	**84**	DCM	24	N. D.
2	**84**	THF	24	trace
3	**84**	Et_2O	24	27
4	**84**	DCE	24	33
5	**84**	PhMe	24	50
6	**84**	DMSO	3	80
7	**84**	MeCN	24	45
8	**84**	DMF	3	85
9	**84**	^{t}BuOH	24	60
10	**84**	**1,4-dioxane**	**1**	**97**
11	**85**	1,4-dioxane	4	85
12	**86**	1,4-dioxane	6	88
13	**87**	1,4-dioxane	6	90
14	**88**	1,4-dioxane	4	91
15	**89**	1,4-dioxane	24	trace
16	**90**	1,4-dioxane	24	trace
17	-	1,4-dioxane	24	0

[a]Reaction conditions: All reactions were carried out with **82** (0.062 mmol), **2** (0.081 mmol) in solvent (0.5 mL). Yields reported are isolated yields.

It is well known in the literature that the generation of NHC-CO_2 adduct could be efficiently utilized as NHC precursor, since the formation of NHC-CO_2 adduct is reversible in solution at ambient conditions,[31] Another advantage is that, one can perform the reaction under neutral conditions without using any external base. In addition, these solid NHC-CO_2 adducts are air and moisture stable and very easy to handle. Due to these fundamental advantages, we have decided to use NHC-CO_2 adducts as pre-catalyts for this transformation. However, our initial attempt in presence of pre-catalyst **84** was highly discouraging as no product was observed when the reaction was performed in CH_2Cl_2 at room temperature (entry 1). Changing the solvent from CH_2Cl_2 to THF did not affect much as only trace amounts of α-diaryl nitrile **83** was obtained (entry 2). Surprisingly, when Et_2O was used as a solvent, **83** could be isolated in 27% yield (entry 3). Encouraged by this observation, the solvent screening were performed using different solvents (entries 4-10), and it was found that 1,4-dioxane was the best to drive the reaction, as the desired product **83** was observed in 97% yield in just 1 h (entry 10).[32] The optimization studies were extended using other imidazolium based NHC pre-catalysts **85-88** in 1,4-dioxane (entries 11-14) at rt. However, in all those cases, the isolated yield of **83** was found to be inferior when compared to entry 10. Surprisingly, thiazolium (**89**) and triazolium (**90**) based NHC pre-catalysts failed to drive this transformation (entries 15 & 16). As expected, in the absence of NHC pre-catalyst the product formation was not observed, which clearly suggests that NHC is essential to drive this transformation (entry 17).

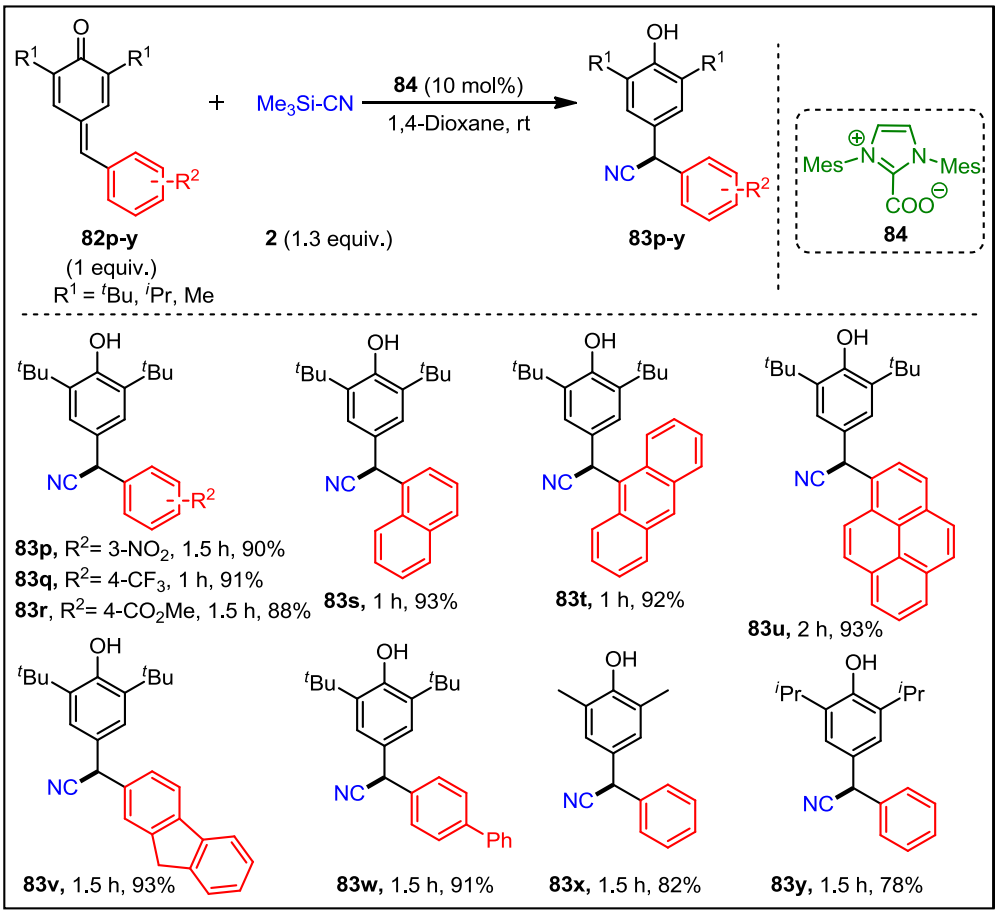
With the optimized reaction conditions in hand (entry 10, Table 1), the substrate scope and limitations were evaluated using a wide range of *p*-quinone methides (**82a-o**), and the results are summed up in Schemes 21 and 22. It is evident from Scheme 21 that this methodology worked very well for the *p*-QMs (**82a-h**), derived from electron-donating aromatic aldehydes, as most of them underwent smooth transformation under the catalytic condition and provided the corresponding α-diaryl nitriles (**83a-h**) in good to excellent yields (88-95%) within a very short period of time. It was also observed that the *p*-QMs (**82i-n**), derived from halo-substituted aromatic aldehydes, reacted efficiently under the optimized conditions to produce the resultant products **83i-n** in very high yields. Interestingly, this catalytic method was found to be very robust in case of *p*-QM (**82o**), derived from 4-(trifluoromethoxy)benzaldehyde, as the subsequent α-diaryl nitrile (**83o**) was isolated in 91% yield (Scheme 21).



[a]Reaction conditions: All reactions were carried out with 20 mg scale of **82(a-o)** in 0.5 mL of solvent. Yields reported are isolated yields.

Scheme 21: Synthesis of *α*-diaryl nitriles[a]

Delightfully, the *p*-QMs (**82p-r**), substituted with electron-poor arenes, were also viable substrates for this transformation as various functional groups such as nitro group, trifluoromethyl group and ester group were well tolerated under the optimized conditions, and the respective *α*-diaryl nitriles **83p-r** were observed in very good yields (Scheme 22).The generality of this concept was further investigated with *p*-QMs (**82s-u**) [derived from sterically hindered aromatic aldehydes], and in all those cases, the successive products (**83s-u**) were obtained in >90% yields. This reaction also underwent efficiently in case of *p*-QMs synthesized from fluorene-2-carboxaldehyde (**82v**) and biphenyl-4-carboxaldehyde (**82w**) to produce the desired *α*-diaryl nitriles (**83v-w**) in excellent yields. Further, this methodology was elaborated to other *p*-QMs **82x** & **82y**, derived from 2,6-dimethylphenol and 2,6-diisopropylphenol, respectively, and in both the cases, the required *α*-diaryl nitriles **83x** & **83y** were obtained in good yields (Scheme 22).

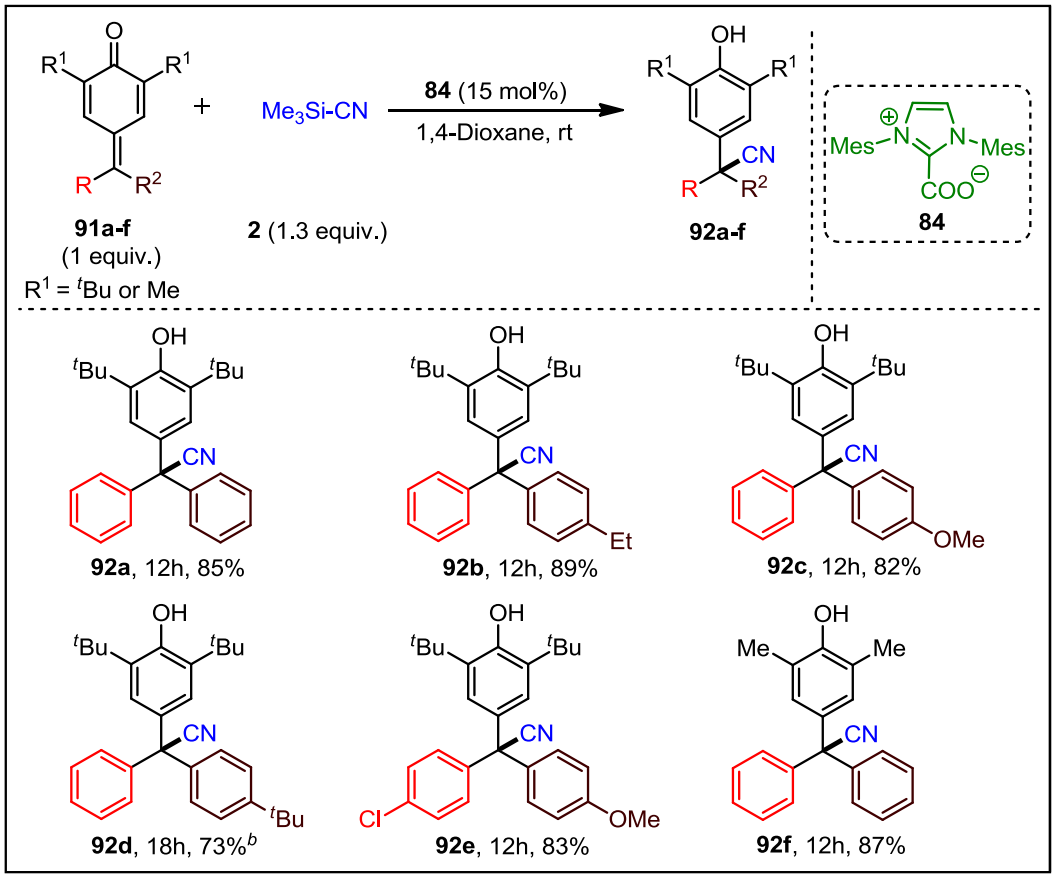


[a]Reaction conditions: All reactions were carried out with 20 mg scale of **82(p-y)** in 0.5 mL of solvent. Yields reported are isolated yields.

Scheme 22: Synthesis of *α*-diaryl nitriles[a]

Next, we shifted our attention to access *α*-triaryl nitriles by employing fuchsones as 1,6-Michael acceptors. Interesting thing is that this method would allow us to access α-triaryl nitriles, which otherwise is very difficult to prepare. In this context, fuchsone **91a**[33] was treated with Me_3Si-CN under the optimized conditions (entry 10, Table 1). However, in this particular case, the reaction was found to be very sluggish as only 48% of **92a** was isolated. We believe that this could be due to the steric influence of the additional aryl group at the sixth position of fuchsone, which basically shield the electrophilic centre of **91a**, and makes it a less reactive toward Me_3Si-CN. Surprisingly, by increasing the catalyst loading to 15 mol% and increasing the reaction time to 12 h, substantial improvement in the yield of **92a** was observed (85%). Thus, further exploration of the substrate scope with various fuchsones (**91b-f**) was performed with 15 mol% of the catalyst loading and, the results are summarized in Scheme 23. It is noteworthy to mention that most of the fuchsones (**91b-e**), derived from

the corresponding aryl ketones and 2,6-di(*tert*-butyl)phenol, underwent smooth transformation under the modified reaction conditions, and the resultant *α*-triaryl nitriles (**92b-e**) were obtained in very good yields (73-89%). Interestingly, 2,6-dimethyl substituted fuchsone (**91f**), derived from benzophenone and 2,6-dimethylphenol, also reacted efficiently with Me_3Si-CN and provided **92f** in 87% yield (Scheme 23).

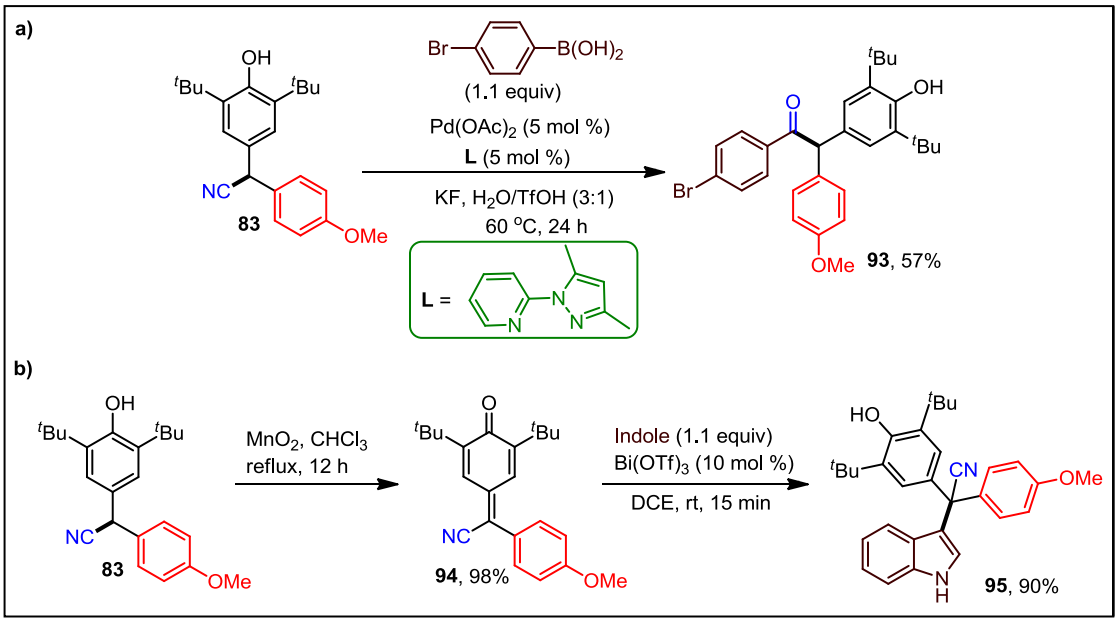


[a]Reaction conditions: All reactions were carried out with 20 mg scale of **91a-f** in 0.5 mL of solvent. [b]Reaction was carried out at 80 °C Yields reported are isolated yields.

Scheme 23: Synthesis of *α*-triaryl nitriles[a]

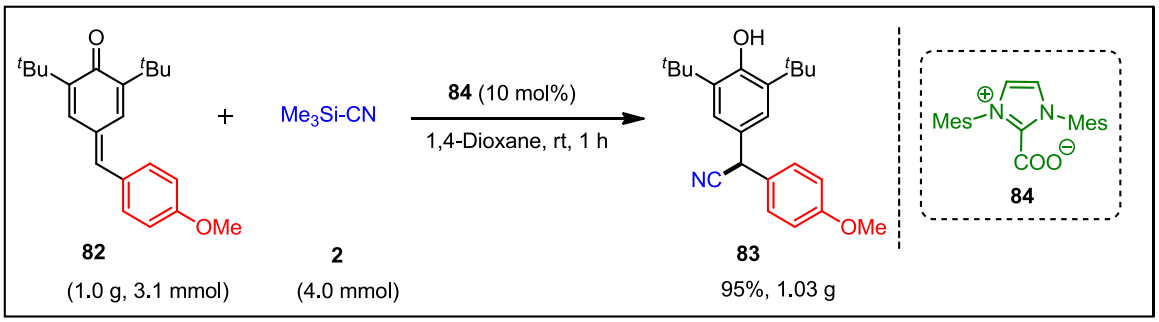
To show the synthetic application of the current protocol, few derivatization reactions were performed with one of the *α*-diaryl nitriles. When, **83** was subjected to palladium catalyzed oxidative addition with 4-bromophenyl boronic acid, the corresponding *α,α'*-diaryl ketone **93**[34] was obtained in 57% yield (a, Scheme 24). In another experiment, **83** was treated with activated MnO_2 to get the 6-cyano-*p*-quinone methide **94** in quantitative yield. Similar types of cyanated *p*-quinone methides are used as a chemical tool for assessing haemolytic anaemia induced by naphthoquinones.[35] Further, the 6-cyano-*p*-quinone methide **94** was

subjected to nucleophilic addition with indole to furnish a leuconitrile[36] dye analogue **95** in 90% yield (b, Scheme 24).



Scheme 24: Synthetic elaborations of *α*-diaryl nitrile **83**

To show the scalability and robustness of the present methodology, a large scale reaction was also performed with **82**. When a mixture of 3.1 mmol of **82** and 4 mmol of Me_3Si-CN (**2**) were reacted with NHC–CO_2 adduct **84** under the optimized conditions, the corresponding *α*-diaryl nitrile **83** was obtained in 95% yield, which clearly indicates the generality of this transformation (Scheme 25).



Scheme 25: Gram scale synthetis of *α*-diaryl nitrile **83**

1.6 Conclusion

In this chapter we have disclosed, for the first time, an organocatalytic protocol for the construction of *α*-aryl nitriles through NHC catalysed 1,6-conjugate addition of Me_3Si-CN to

p-quinone methides.[37] Through this method, a wide range of α-diaryl and α-triaryl nitriles were obtained in good to excellent yields under mild conditions.

1.7 Experimental Section

General methods

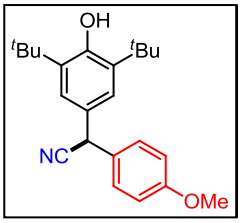
All reactions were carried out under an argon atmosphere in an oven dried vials. Commercially available AR grade 1,4– dioxane was used without further distillation. Most of the reagents and starting materials were purchased from commercial sources and used as such. All *p*-quinone methides were prepared by following a literature procedure.[38] NHC precursors were prepared according to the literature procedure.[31a,f] Melting points were recorded on SMP20 melting point apparatus and are uncorrected. ^{1}H, ^{13}C and ^{19}F spectra were recorded in $CDCl_3$ (400, 100 and 376 MHz respectively) on Bruker FT–NMR spectrometer. Chemical shift (δ) values are reported in parts per million relative to TMS and the coupling constants (J) are reported in Hz. High resolution mass spectra were recorded on Waters Q–TOF Premier–HAB213 spectrometer. FT-IR spectra were recorded on a Perkin-Elmer FTIR spectrometer. Thin layer chromatography was performed on Merck silica gel 60 F_{254} TLC pellets and visualized by UV irradiation, $KMnO_4$ stain. Column chromatography was carried out through silica gel (100–200 mesh) using EtOAc/hexane as an eluent.

General procedure for the 1,6–conjugate addition of Me_3Si-CN to *p*–quinone methides:

1,4– dioxane (0.5 mL) was added to a mixture of *p*-quinone methide (0.062 mmol), Me_3Si-CN (0.081 mmol) and NHC–CO_2 adduct **84** (0.0062 mmol) under argon atmosphere and the resulting mixture was stirred at room temperature. After the reaction was complete (based on TLC analysis), the mixture was quenched with 5 mL of aqueous sodium thiosulfate and extracted with Et_2O (3 x 5 mL). The combined organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was then purified through a silica gel column using EtOAc/Hexane mixture as an eluent to get the pure product.

Characterization data of compounds (83, 83a-83y):

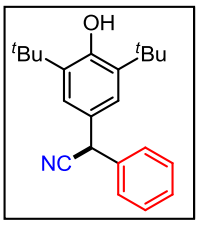
2-{3,5-di-*tert*-butyl-4-hydroxyphenyl}-2-(4-methoxyphenyl)acetonitrile (83)



The reaction was performed at 0.062 mmol scale of *p*-quinone methide **(82)**; R_f = 0.5 (10% EtOAc in hexane); pale yellow solid (21.1 mg, 97%

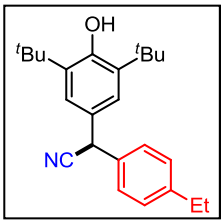
yield); m.p. = 101–102 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (d, J = 8.8 Hz, 2H), 7.10 (s, 2H), 6.90 (d, J = 8.8 Hz, 2H), 5.26 (s, 1H), 5.03 (s, 1H), 3.81 (s, 3H), 1.41 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.3, 153.7, 136.6, 128.9, 128.6, 126.9, 124.5, 120.7, 114.5, 55.4, 41.8, 34.5, 30.3; FT-IR (thin film, neat): 3630, 2958, 2923, 2878, 2240, 1612, 1512, 1435, 1362, 1305, 1251, 1180, 1156, 1122, 1034, 881, 834, 772 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{23}H_{28}NO_2$ $[M–H]^+$: 350.2120; found : 350.2135.

2-{3,5-di-*tert*-butyl-4-hydroxyphenyl}-2-phenylacetonitrile (83a)



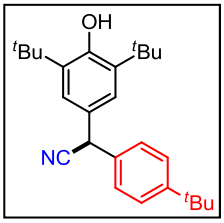
The reaction was performed at 0.068 mmol scale of *p*-quinone methide **(82a)**; R_f = 0.5 (10% EtOAc in hexane); orange solid (19.8 mg, 91% yield); m.p. = 108–110 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41–7.36 (m, 4H), 7.35–7.30 (m, 1H), 7.11 (s, 2H), 5.27 (s, 1H), 5.07 (s, 1H), 1.41 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.8, 136.8, 136.6, 129.2, 128.1, 127.8, 126.6, 124.6, 120.5, 42.7, 34.6, 30.3; FT-IR (thin film, neat): 3631, 2959, 2922, 2874, 2244, 1599, 1437, 1393, 1362, 1318, 1237, 1155, 1125, 1026, 881, 748, 698, 613 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{22}H_{26}NO$ $[M–H]^+$: 320.2014; found : 320.2001.

2-{3,5-di-*tert*-butyl-4-hydroxyphenyl}-2-(4-ethylphenyl)acetonitrile (83b)



The reaction was performed at 0.062 mmol scale of *p*-quinone methide **(82b)**; R_f = 0.5 (10% EtOAc in hexane); orange gummy solid (20.2 mg, 93% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (d, J = 8.1 Hz, 2H), 7.21 (d, J = 8.1 Hz, 2H), 7.12 (s, 2H), 5.26 (s, 1H), 5.04 (s, 1H), 2.66 (q, J = 7.6 Hz, 2H), 1.42 (s, 18H), 1.24 (t, J = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.7, 144.2, 136.7, 133.8, 128.6, 127.7, 126.8, 124.6, 120.7, 42.3, 34.5, 30.3, 28.6, 15.6; FT-IR (thin film, neat): 3637, 2963, 2929, 2874, 2241, 1513, 1435, 1392, 1364, 1320, 1238, 1157, 1022, 932, 890, 839, 772, 661, 630 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{24}H_{30}NO$ $[M–H]^+$: 348.2327; found : 348.2315.

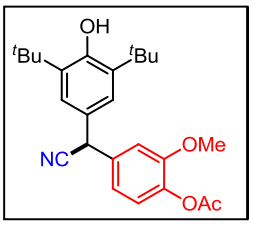
2-[4-(*tert*-butyl)phenyl]-2-{3,5-di-*tert*-butyl-4-hydroxyphenyl}acetonitrile (83c)



The reaction was performed at 0.057 mmol scale of *p*-quinone methide **(82c)**; R_f = 0.5 (10% EtOAc in hexane); orange gummy solid (19.6 mg, 91% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (d, J = 8.3 Hz, 2H), 7.29–7.26 (m, 2H), 7.12 (s, 2H), 5.25 (s, 1H), 5.03 (s, 1H), 1.41 (s, 18H), 1.31 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.7, 151.1, 136.7, 133.6, 127.4, 126.7, 126.1,

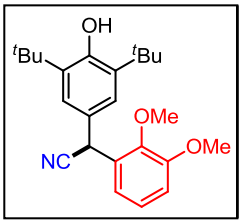
124.6, 120.7, 42.3, 34.7, 34.6, 31.4, 30.3; FT-IR (thin film, neat): 3636, 2961, 2921, 2871, 2251, 1615, 1511, 1435, 1364, 1321, 1239, 1157, 1123, 1020, 913, 839, 772, 658 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{26}H_{34}NO$ $[M–H]^+$: 376.2640; found : 376.2624.

4-[cyano{3,5-di-*tert*-butyl-4-hydroxyphenyl}methyl]-2-methoxyphenyl acetate (83d)



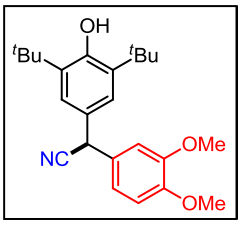
The reaction was performed at 0.052 mmol scale of *p*-quinone methide **(82d)**; R_f = 0.3 (10% EtOAc in hexane); orange gummy solid (18.8 mg, 88% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.11 (s, 2H), 7.03 (d, *J* = 8.1 Hz, 1H), 6.95 (d, *J* = 1.9 Hz, 1H), 6.90 (dd, *J* = 8.2, 1.9 Hz, 1H), , 5.29 (s, 1H), 5.05 (s, 1H), 3.82 (s, 3H), 2.31 (s, 3H), 1.42 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.0, 153.9, 151.5, 139.5, 136.8, 135.2, 126.1, 124.6, 123.3, 120.3, 120.1, 111.8, 56.1, 42.4, 34.6, 30.2, 20.8; FT-IR (thin film, neat): 3624, 2958, 2924, 2855, 2240, 1765, 1605, 1509, 1461, 1434, 1366, 1270, 1198, 1147, 1123, 1031, 901, 884, 764, 747 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{25}H_{30}NO_4$ $[M–H]^+$: 408.2175; found : 408.2158.

2-{3,5-di-*tert*-butyl-4-hydroxyphenyl}-2-(2,3-dimethoxyphenyl)acetonitrile (83e)



The reaction was performed at 0.056 mmol scale of *p*-quinone methide **(82e)**; R_f = 0.4 (10% EtOAc in hexane); orange solid (20 mg, 93% yield); m.p. = 91–93 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16 (s, 2H), 7.07 (t, *J* = 8.0 Hz, 1H), 6.99 (d, *J* = 7.6 Hz, 1H), 6.89 (d, *J* = 8.1 Hz, 1H), 5.46 (s, 1H), 5.22 (s, 1H), 3.87 (s, 3H), 3.79 (s, 3H), 1.41 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.5, 152.8, 146.2, 136.5, 130.7, 126.5, 124.6, 124.4, 120.8, 120.5, 112.5, 60.8, 55.9, 36.6, 34.5, 30.3; FT-IR (thin film, neat): 3633, 2958, 2922, 2875, 2240, 1588, 1482, 1433, 1362, 1277, 1236, 1159, 1122, 1072, 1006, 883, 772, 747, 667 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{24}H_{30}NO_3$ $[M–H]^+$: 380.2226; found : 380.2212.

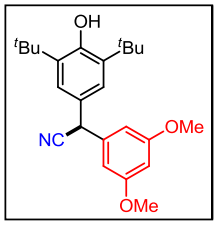
2-{3,5-di-*tert*-butyl-4-hydroxyphenyl}-2-(3,4-dimethoxyphenyl)acetonitrile (83f)



The reaction was performed at 0.056 mmol scale of *p*-quinone methide **(82f)**; R_f = 0.4 (10% EtOAc in hexane); yellow solid (20.3 mg, 95% yield); m.p. = 160–162 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.11 (s, 2H), 6.91–6.88 (m, 1H), 6.86–6.84 (m, 2H), 5.26 (s, 1H), 5.03 (s, 1H), 3.88 (s, 3H), 3.86 (s, 3H), 1.41 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.7, 149.4, 148.9, 136.7, 128.9, 126.7, 124.5, 120.6, 120.2, 111.4, 110.9, 56.1, 56.0, 42.1, 34.5, 30.3; FT-IR (thin film, neat): 3631, 2958, 2917, 2876, 2838, 2240, 1595, 1516, 1434, 1263, 1239, 1185,

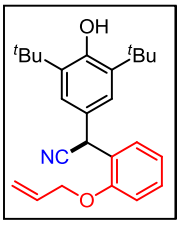
1144, 1027, 911, 809, 734 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{24}H_{30}NO_3$ $[M–H]^+$: 380.2226; found : 380.2213.

2-{3,5-di-*tert*-butyl-4-hydroxyphenyl}-2-(3,5-dimethoxyphenyl)acetonitrile (83g)



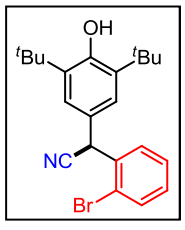
The reaction was performed at 0.056 mmol scale of *p*-quinone methide **(82g)**; R_f = 0.4 (10% EtOAc in hexane); orange solid (18.8 mg, 88% yield); m.p. = 151–153 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.11 (s, 2H), 6.49 (d, *J* = 2.1 Hz, 2H), 6.39 (t, *J* = 2.1 Hz, 1H), 5.26 (s, 1H), 4.97 (s, 1H), 3.78 (s, 6H), 1.41 (s, 18H).; ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.3, 153.8, 138.7, 136.7, 126.2, 124.6, 120.3, 106.1, 99.8, 55.6, 42.8, 34.6, 30.3; FT-IR (thin film, neat): 3633, 2957, 2920, 2873, 2842, 2241, 1589, 1523, 1438, 1269, 1239, 1188, 1145, 1030, 915, 811, 736 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{24}H_{30}NO_3$ $[M–H]^+$: 380.2226; found : 380.2211.

2-[2-(allyloxy)phenyl]-2-{3,5-di-*tert*-butyl-4-hydroxyphenyl}acetonitrile (83h)



The reaction was performed at 0.057 mmol scale of *p*-quinone methide **(82h)**; R_f = 0.3 (10% EtOAc in hexane); yellow gummy solid (20 mg, 93% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41(dd, *J* = 7.6, 1.6 Hz, 1H), 7.30–7.26 (m, 1H), 7.21 (s, 2H), 6.99 (td, *J* = 7.6, 1.0 Hz, 1H), 6.90 (d, *J* = 8.2 Hz, 1H), 6.08–6.00 (m, 1H), 5.51 (s, 1H), 5.39 (dq, *J* = 17.3, 1.6 Hz, 1H), 5.30 (dq, *J* = 10.6, 1.4 Hz, 1H), 5.23 (s, 1H), 4.64–4.55 (m, 2H), 1.42 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.0, 153.5, 136.3, 132.9, 129.4, 128.8, 126.3, 125.7, 124.6, 121.3, 120.7, 117.8, 112.1, 69.1, 36.5, 34.5, 30.3; FT-IR (thin film, neat): 3633, 2959, 2920, 2874, 2243, 1599, 1492, 1454, 1435, 1248, 1158, 1122, 1001, 753 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{25}H_{30}NO_2$ $[M–H]^+$: 376.2277; found : 376.2262.

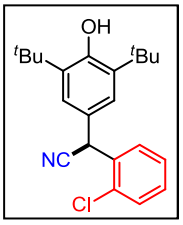
2-(2-bromophenyl)-2-{3,5-di-*tert*-butyl-4-hydroxyphenyl}acetonitrile (83i)



The reaction was performed at 0.054 mmol scale of *p*-quinone methide **(82i)**; R_f = 0.5 (10% EtOAc in hexane); orange solid (19.3 mg, 90% yield); m.p. = 118–120 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (dd, *J* = 8.0, 0.8 Hz, 1H), 7.54 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.37 (td, *J* = 7.6, 0.8 Hz, 1H), 7.22–7.18 (m, 3H), 5.58 (s, 1H), 5.28 (s, 1H), 1.42 (s, 18H).; ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.8, 136.7, 136.3, 133.5, 129.9, 128.4, 125.2, 124.6, 123.6, 120.0, 41.9, 34.6, 30.3; FT-IR (thin film, neat): 3635, 2958, 2923, 2874, 2243, 1633, 1571, 1439, 1392, 1263, 1241, 1157, 1126, 1025,

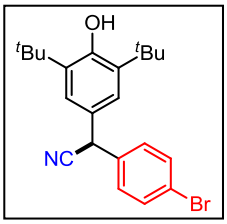
884, 759 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{22}H_{25}BrNO$ $[M–H]^+$: 398.1120; found : 398.1106.

2-(2-chlorophenyl)-2-{3,5-di-*tert*-butyl-4-hydroxyphenyl}acetonitrile (83j)



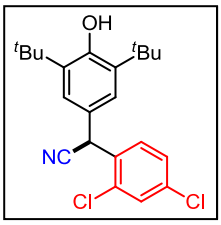
The reaction was performed at 0.061 mmol scale of *p*-quinone methide **(82j)**; R_f = 0.5 (10% EtOAc in hexane); orange solid (19.7 mg, 91% yield); m.p. = 100–102 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (dd, *J* = 7.6, 1.7 Hz, 1H), 7.42 (dd, *J* = 7.7, 1.5 Hz, 1H), 7.35–7.31 (m, 1H), 7.30–7.26 (m, 1H), 7.20 (s, 2H), 5.58 (s, 1H), 5.30 (s, 1H), 1.43 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.8, 136.7, 134.5, 133.1, 130.1, 129.62, 129.61, 127.8, 125.1, 124.6, 119.9, 39.4, 34.5, 30.2; FT-IR (thin film, neat): 3634, 2960, 2917, 2875, 2244, 1474, 1435, 1393, 1363, 1322, 1239, 1208, 1157, 1123, 1052, 1038, 910, 884, 793, 754, 734, 712, 661, 642, 613 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{22}H_{25}ClNO$ $[M–H]^+$: 354.1625; found : 354.1608.

2-(4-bromophenyl)-2-{3,5-di-*tert*-butyl-4-hydroxyphenyl}acetonitrile (83k)



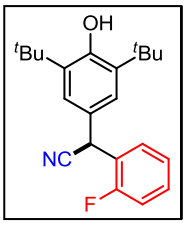
The reaction was performed at 0.054 mmol scale of *p*-quinone methide **(82k)**; R_f = 0.5 (10% EtOAc in hexane); orange solid (19.5 mg, 91% yield); m.p. = 153–155 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (d, *J* = 8.5 Hz, 2H), 7.24 (d, *J* = 8.4 Hz, 2H), 7.08 (s, 2H), 5.29 (s, 1H), 5.02 (s, 1H), 1.42 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.9, 136.9, 135.7, 132.3, 129.4, 126.0, 124.5, 122.2, 119.9, 42.1, 34.6, 30.2; FT-IR (thin film, neat): 3632, 2960, 2921, 2874, 2244, 1488, 1435, 1402, 1393, 1363, 1321, 1239, 1156, 1123, 1074, 1012, 909, 890, 881, 812, 772, 734, 716, 654, 615 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{22}H_{25}BrNO$ $[M–H]^+$: 398.1120; found : 398.1105.

2-{3,5-di-*tert*-butyl-4-hydroxyphenyl}-2-(2,4-dichlorophenyl)acetonitrile (83l)



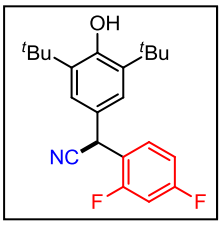
The reaction was performed at 0.055 mmol scale of *p*-quinone methide **(82l)**; R_f = 0.6 (10% EtOAc in hexane); white solid (19.3 mg, 90% yield); m.p. = 130–132 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45-7.43 (m, 2H), 7.31 (dd, *J* = 8.4, 2.1 Hz, 1H), 7.14 (s, 2H), 5.49 (s, 1H), 5.30 (s, 1H), 1.41 (s, 18H);^{13}C NMR (100 MHz, $CDCl_3$) δ 154.0, 136.8, 134.9, 133.9, 133.3, 130.5, 130.0, 128.1, 124.6, 124.5, 119.5, 39.1, 34.6, 30.2; FT-IR (thin film, neat): 3633, 2960, 2923, 2876, 2248, 1588, 1563, 1472, 1435, 1385, 1239, 1156, 1122, 1050, 1028, 994, 910, 875, 734 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{22}H_{24}Cl_2NO$ $[M–H]^+$: 388.1235; found : 388.1219.

2-{3,5-di-*tert*-butyl-4-hydroxyphenyl}-2-(2-fluorophenyl)acetonitrile (83m)



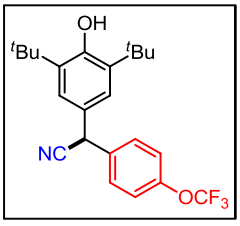
The reaction was performed at 0.064 mmol scale of *p*-quinone methide **(82m)**; R_f = 0.5 (10% EtOAc in hexane); orange solid (20 mg, 92% yield); m.p. = 95–97 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (td, J = 7.6, 1.6 Hz, 1H), 7.35–7.30 (m, 1H), 7.21 (td, J = 7.6, 1.0 Hz, 1H), 7.18 (s, 2H), 7.12–7.07 (m, 1H), 5.39 (s, 1H), 5.29 (s, 1H), 1.43 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.8 (d, $J_{C\text{-}F}$ = 246.5 Hz), 153.8, 136.7, 130.2 (d, $J_{C\text{-}F}$ = 8.2 Hz), 129.2 (d, $J_{C\text{-}F}$ = 2.9 Hz), 125.3, 124.9 (d, $J_{C\text{-}F}$ = 3.7 Hz), 124.4, 124.2 (d, $J_{C\text{-}F}$ = 14.0 Hz), 119.6, 116.0 (d, $J_{C\text{-}F}$ = 21.2), 36.1 (d, $J_{C\text{-}F}$ = 2.8 Hz), 34.5, 30.2; ^{19}F NMR (376 MHz, $CDCl_3$) δ –117.3; FT-IR (thin film, neat): 3632, 2958, 2918, 2875, 2240, 1608, 1584, 1511, 1436, 1362, 1301, 1256, 1182, 1122, 1095, 1038, 875, 854, 743, 674 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{22}H_{26}FNO$ $[M–H]^+$: 338.1920; found : 338.1907.

2-{3,5-di-*tert*-butyl-4-hydroxyphenyl}-2-(2,4-difluorophenyl)acetonitrile (83n)



The reaction was performed at 0.061 mmol scale of *p*-quinone methide **(82n)**; R_f = 0.6 (5% EtOAc in hexane); brown solid (19.5 mg, 90% yield); m.p. = 111–113 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45–7.39 (m, 1H), 7.13 (s, 2H), 6.95–6.90 (m, 1H), 6.89–6.83 (m, 1H), 5.31 (s, 1H), 5.29 (s, 1H), 1.42 (s, 18H);^{13}C NMR (100 MHz, $CDCl_3$) δ 162.9 (dd, $J_{C\text{-}F}$ = 248.9, 10.9 Hz), 160.0 (dd, $J_{C\text{-}F}$ = 249.2, 11.9 Hz), 153.9, 136.9, 130.1 (dd, $J_{C\text{-}F}$ = 9.8, 4.5 Hz), 125.0, 124.3, 120.4 (dd, $J_{C\text{-}F}$ = 14.2, 3.9 Hz), 119.4, 112.2 (dd, $J_{C\text{-}F}$ = 21.5, 3.8 Hz), 104.6 (t, $J_{C\text{-}F}$ = 25.3 Hz), 35.7 (d, $J_{C\text{-}F}$ = 3.1 Hz), 34.6, 30.2; ^{19}F NMR (376 MHz, $CDCl_3$) δ –109.26 (d, J = 7.9 Hz), –112.83 (d, J = 7.9 Hz); FT-IR (thin film, neat): 3636, 2961, 2917, 2876, 2246, 1622, 1607, 1505, 1434, 1363, 1322, 1288, 1239, 1143, 967, 852, 772, 735, 540 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{22}H_{25}F_2NO$ $[M–H]^+$: 356.1826; found : 356.1817.

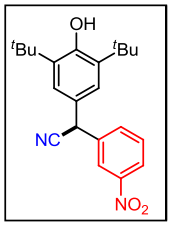
2-{3,5-di-*tert*-butyl-4-hydroxyphenyl}-2-[4-(trifluoromethoxy)phenyl]acetonitrile (83o)



The reaction was performed at 0.053 mmol scale of *p*-quinone methide **(82o)**; R_f = 0.5 (10% EtOAc in hexane); white solid (19.5 mg, 91% yield); m.p. = 87–89 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (d, J = 8.64 Hz, 2H), 7.23 (d, J = 8.3 Hz, 2H), 7.08 (s, 2H), 5.30 (s, 1H), 5.07 (s, 1H), 1.41 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.0, 149.0 (q, $J_{C\text{-}F}$ = 1.6 Hz), 137.0, 135.3, 129.3, 126.0, 124.6, 121.6, 120.5 (q, $J_{C\text{-}F}$ = 256 Hz), 120.0, 42.0, 34.6, 30.2; ^{19}F NMR (376 MHz, CDCl3) δ –57.9; FT-IR (thin film, neat): 3636, 2962, 2918, 2877, 2244, 1509,

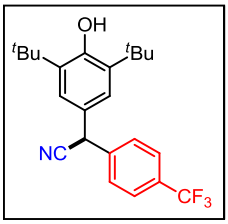
1435, 1376, 1352, 1262, 1222, 1211, 1167, 1123, 1021, 853, 774 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{23}H_{25}F_3NO_2$ $[M–H]^+$: 404.1837; found : 404.1821.

2-{3,5-di-*tert*-butyl-4-hydroxyphenyl}-2-[3-nitrophenyl]acetonitrile (83p)



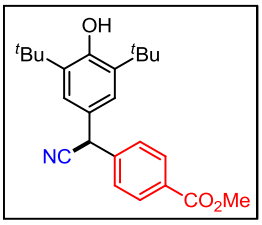
The reaction was performed at 0.059 mmol scale of *p*-quinone methide **(82p)**; R_f = 0.4 (10% EtOAc in hexane); orange gummy solid (19.4 mg, 90% yield); *the product was found to be unstable as some amount of decomposition was observed during purification*; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22–8.19 (m, 2H), 7.75 (d, J = 7.9 Hz, 1H), 7.61–7.57 (m, 1H), 7.09 (s, 2H), 5.33 (s, 1H), 5.16 (s, 1H), 1.41 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.3, 148.7, 138.8, 137.3, 133.7, 130.3, 125.2, 124.6, 123.3, 122.9, 119.3, 42.3, 34.6, 30.2; FT-IR (thin film, neat): 3385, 2963, 2922, 2851, 2243, 1588, 1534, 1434, 1349, 1239, 1158, 1122, 879, 741 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{22}H_{25}N_2O_3$ $[M–H]^+$: 365.1865; found : 365.1851.

2-{3,5-di-*tert*-butyl-4-hydroxyphenyl}-2-[4-(trifluoromethyl)phenyl]acetonitrile (83q)



The reaction was performed at 0.055 mmol scale of *p*-quinone methide **(82q)**; R_f = 0.5 (10% EtOAc in hexane); orange solid (19.6 mg, 91% yield); m.p. = 135–137 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (d, J = 8.2 Hz, 2H), 7.50 (d, J = 8.4 Hz, 2H), 7.10 (s, 2H), 5.31 (s, 1H), 5.11 (s, 1H), 1.41 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.1, 140.6 (apparent q, $J_{C\text{-}F}$ = 1.1 Hz), 137.1, 130.5 (q, $J_{C\text{-}F}$ = 32.5 Hz), 128.1, 126.2 (q, $J_{C\text{-}F}$ = 3.7 Hz), 125.7, 124.6, 124.0 (q, $J_{C\text{-}F}$ = 270.5 Hz), 119.7, 42.5, 34.6, 30.2; ^{19}F NMR (376 MHz, CDCl3) δ –62.63; FT-IR (thin film, neat): 3639, 2961, 2920, 2876, 2243, 1620, 1436, 1327, 1276, 1263, 1243, 1167, 1132, 1070, 1019, 882, 849, 764, 750 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{23}H_{25}F_3NO$ $[M–H]^+$: 388.1888; found : 388.1873.

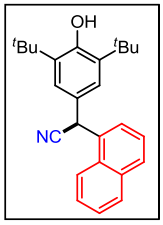
Methyl 4-[cyano{3,5-di-*tert*-butyl-4-hydroxyphenyl}methyl]benzoate (83r)



The reaction was performed at 0.045 mmol scale of *p*-quinone methide **(82r)**; R_f = 0.3 (10% EtOAc in hexane); orange gummy solid (15 mg, 88% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, J = 8.4 Hz, 2H), 7.45 (d, J = 8.2 Hz, 2H), 7.08 (s, 2H), 5.29 (s, 1H), 5.11 (s, 1H), 3.92 (s, 3H), 1.40 (s, 18H);^{13}C NMR (100 MHz, $CDCl_3$) δ 166.6, 154.0, 141.4, 136.9, 130.5, 130.0, 127.8, 125.9, 124.6, 119.8, 52.4, 42.6, 34.6, 30.2; FT-IR (thin film, neat): 3633, 2957, 2932, 2879, 2243, 1725, 1616, 1435, 1362, 1312, 1284, 1240, 1184, 1156, 1114, 1021, 886,

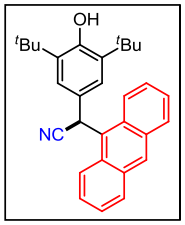
861, 775, 742, 708 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{24}H_{28}NO_3$ $[M–H]^+$: 378.2069; found : 378.2053.

2-{3,5-di-*tert*-butyl-4-hydroxyphenyl}-2-(naphthalene-1-yl)acetonitrile (83s)



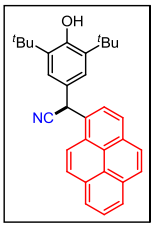
The reaction was performed at 0.058 mmol scale of *p*-quinone methide **(82s)**; R_f = 0.3 (10% EtOAc in hexane); yellow solid (20 mg, 93% yield); m.p. = 153–155 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (d, *J* = 7.7 Hz, 1H), 7.93–7.90 (m, 1H), 7.87 (d, *J* = 8.2 Hz, 1H), 7.60 (d, *J* = 7.0 Hz, 1H), 7.57–7.49 (m, 3H), 7.16 (s, 2H), 5.78 (s, 1H), 5.25 (s, 1H), 1.38 (s, 18H);^{13}C NMR (100 MHz, $CDCl_3$) δ 153.7, 136.7, 134.1, 131.7, 130.6, 129.3, 129.2, 127.0, 126.8, 126.2, 125.64, 125.58, 124.8, 123.2, 120.6, 39.6, 34.5, 30.2; FT-IR (thin film, neat): 3628, 2959, 2919, 2875, 2242, 1599, 1512, 1435, 1397, 1362, 1321, 1239, 1156, 1122, 881, 777, 668 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{26}H_{28}NO$ $[M–H]^+$: 370.2171; found : 370.2158.

2-(anthracen-9-yl)-2-{3,5-di-*tert*-butyl-4-hydroxyphenyl}acetonitrile (83t)



The reaction was performed at 0.051 mmol scale of *p*-quinone methide **(82t)**; R_f = 0.4 (15% EtOAc in hexane); orange gummy solid (19.7 mg, 92% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56 (s, 1H), 8.22 (d, *J* = 8.7 Hz, 2H), 8.08 (dd, *J* = 7.8 Hz, 2H), 7.56–7.48 (m, 4H), 7.14 (s, 2H), 6.67 (s, 1H), 5.21 (s, 1H), 1.29 (s, 18H);^{13}C NMR (100 MHz, $CDCl_3$) δ 153.4, 136.6, 131.7, 130.0, 129.64, 129.6, 127.0, 125.7, 125.6, 125.3, 124.1, 123.8, 120.7, 35.1, 34.5, 30.2; FT-IR (thin film, neat): 3633, 2960, 2924, 2879, 2243, 1625, 1534, 1435, 1366, 1319, 1254, 1222, 1158, 1122, 910, 888, 777, 731 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{30}H_{32}NO$ $[M+H]^+$: 422.2484; found : 422.2469.

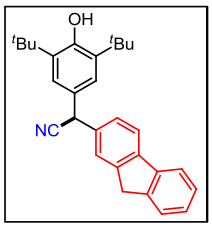
2-{3,5-di-*tert*-butyl-4-hydroxyphenyl}-2-(pyren-1-yl)-acetonitrile (83u)



The reaction was performed at 0.048 mmol scale of *p*-quinone methide **(82u)**; R_f = 0.3 (15% EtOAc in hexane); orange solid (19.8 mg, 93% yield); m.p. = 203–205 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24–8.23 (m, 1H), 8.22–8.20 (m, 3H), 8.16 (d, *J* = 5.5 Hz, 1H), 8.15–8.12 (m, 1H), 8.09 (d, *J* = 5.6 Hz, 2H), 8.04 (t, *J* = 7.7 Hz, 1H), 7.22 (s, 2H), 6.11 (s, 1H), 5.25 (s, 1H), 1.36 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.7, 136.8, 131.5, 131.4, 130.7, 129.1, 128.7, 128.3, 128.1, 127.5, 126.5, 126.41, 126.37, 126.0, 125.7, 125.31, 125.30, 124.74, 124.70, 122.2, 120.9, 39.9, 34.6, 30.3; FT-IR (thin film, neat): 3621, 2958, 2924, 2873, 2240, 1595, 1434, 1362, 1318, 1236, 1147,

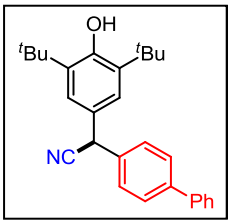
1123, 911, 843, 734 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{32}H_{30}NO$ $[M–H]^+$: 444.2327; found : 444.2309.

2-{3,5-di-*tert*-butyl-4-hydroxyphenyl}-2-(9*H*-fluoren-2-yl)acetonitrile (83v)



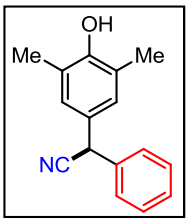
The reaction was performed at 0.052 mmol scale of *p*-quinone methide **(82v)**; R_f = 0.3 (10% EtOAc in hexane); yellow solid (19.2 mg, 93% yield); m.p. = 185–187 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79–7.76 (m, 2H), 7.55 (d, *J* = 7.6 Hz, 2H), 7.41–7.30 (m, 3H), 7.15 (s, 2H), 5.26 (s, 1H), 5.15 (s, 1H), 3.91 (s, 2H), 1.42 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.8, 144.3, 143.5, 141.8, 141.1, 136.8, 134.9, 127.2, 127.0, 126.9, 126.6, 125.2, 124.6, 124.5, 120.7, 120.4, 120.2, 42.8, 37.1, 34.6, 30.3; FT-IR (thin film, neat): 3627, 2957, 2925, 2872, 2241, 1456, 1434, 1364, 1320, 1238, 1153, 1122, 910, 750, 732 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{29}H_{30}NO$ $[M–H]^+$: 408.2327; found : 408.2311.

2-[{1,1'-biphenyl}-4-yl]-2-(3,5-di-*tert*-butyl-4-hydroxyphenyl)acetonitrile (83w)



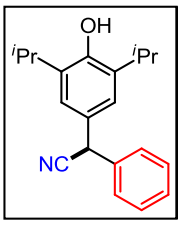
The reaction was performed at 0.054 mmol scale of *p*-quinone methide **(82w)**; R_f = 0.4 (10% EtOAc in hexane); yellow solid (18.8 mg, 91% yield); m.p. = 142–144 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62–7.57 (m, 4H), 7.46–7.42 (m, 4H), 7.38–7.34 (m, 1H), 7.14 (s, 2H), 5.27 (s, 1H), 5.10 (s, 1H), 1.42 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.8, 141.1, 140.4, 136.8, 135.6, 129.0, 128.2, 127.9, 127.7, 127.2, 126.5, 124.6, 120.4, 42.4, 34.6, 30.3; FT-IR (thin film, neat): 3633, 2963, 2910, 2876, 2240, 1583, 1511, 1437, 1401, 1364, 1301, 1256, 1182, 1122, 1095, 1035, 874, 827, 743, 674 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{28}H_{30}NO$ $[M–H]^+$: 396.2327; found : 396.2311.

2-{4-hydroxy-3,5-dimethylphenyl}-2-phenylacetonitrile (83x)



The reaction was performed at 0.095 mmol scale of *p*-quinone methide **(82x)**; R_f = 0.3 (10% EtOAc in hexane); orange solid (18.5 mg, 82% yield); m.p. = 99–101 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41–7.30 (m, 5H), 6.96 (s, 2H), 5.11 (s, 1H), 5.04 (s, 1H), 2.23 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.3, 136.4, 129.2, 128.1, 127.9, 127.6, 127.2, 124.1, 120.3, 41.9, 16.1; FT-IR (thin film, neat): 3468, 2969, 2921, 2850, 2248, 1490, 1454, 1369, 1327, 1302, 1281, 1246, 1196, 1147, 874, 699 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{16}H_{14}NO$ $[M–H]^+$: 236.1075; found : 236.1067.

2-{4-hydroxy-3,5-diisopropylphenyl}-2-phenylacetonitrile (83y)



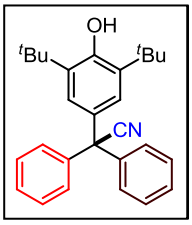
The reaction was performed at 0.075 mmol scale of *p*-quinone methide **(82y)**; R_f = 0.4 (10% EtOAc in hexane); white solid (17.2 mg, 78% yield); m.p. = 100–102 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40–7.29 (m, 5H), 7.00 (s, 2H), 5.09 (s, 1H), 4.95 (s, 1H), 3.14 (sept, J = 6.8 Hz, 2H), 1.25 (s, 6H), 1.23 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.1, 136.6, 134.6, 129.2, 128.1, 127.70, 127.67, 123.1, 120.4, 42.5, 27.4, 22.7; FT-IR (thin film, neat): 3480, 2964, 2931, 2871, 2246, 1495, 1469, 1385, 1364, 1315, 1288, 1201, 1152, 1075, 881, 741, 699 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{20}H_{22}NO$ $[M–H]^+$: 292.1701; found : 292.1695.

General procedure for the 1,6–conjugate addition of Me_3Si-CN to fuchsones:

1,4– dioxane (0.5 mL) was added to a mixture of fuchsone (0.054 mmol), Me_3Si-CN (0.070 mmol) and NHC–CO_2 adduct **84** (0.0081 mmol) under argon atmosphere and the resulting mixture was stirred at room temperature. After the reaction was complete (based on TLC analysis), the mixture was quenched with 5 mL of aqueous sodium thiosulfate and extracted with Et_2O (3 x 5 mL).The combined organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was then purified through a silica gel column using EtOAc/Hexane mixture as an eluent to get the pure product.

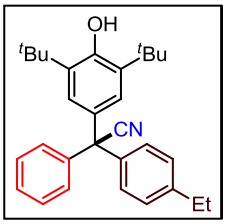
Characterization data of compounds (92a-92f):

2-{3,5-di-*tert*-butyl-4-hydroxyphenyl}-2,2-diphenylacetonitrile (92a)



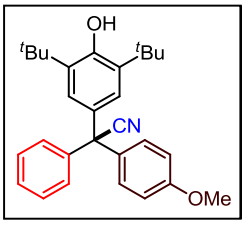
The reaction was performed at 0.054 mmol scale of fuchsone **(91a)**; R_f = 0.5 (10% EtOAc in hexane); orange gummy solid (18.2 mg, 85% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37–7.31 (m, 6H), 7.23–7.20 (m, 4H), 6.95 (s, 2H), 5.28 (s, 1H), 1.33 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.6, 141.1, 135.9, 130.5, 128.9, 128.6, 128.0, 125.9, 124.0, 57.4, 34.6, 30.3; FT-IR (thin film, neat): 3633, 2957, 2923, 2871, 2852, 2240, 1602, 1493, 1436, 1366, 1320, 1240, 1161, 1124, 1031, 913, 773, 700 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{28}H_{30}NO$ $[M–H]^+$: 396.2327; found : 396.2313.

2-{3,5-di-*tert*-butyl-4-hydroxyphenyl}-2-(4-ethylphenyl)-2-phenylacetonitrile (92b)



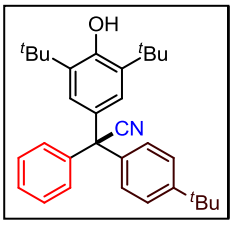
The reaction was performed at 0.050 mmol scale of fuchsone **(91b)**; R_f = 0.5 (10% EtOAc in hexane); orange gummy solid (19.0 mg, 89% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36–7.29 (m, 3H), 7.23–7.21 (m, 2H), 7.17 (d, J = 8.5 Hz, 2H), 7.11 (d, J = 8.4 Hz, 2H), 6.96 (s, 2H), 5.27 (s, 1H), 2.65 (q, J = 7.6 Hz, 2H), 1.34 (s, 18H), 1.24 (t, J = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.5, 144.1, 141.4, 138.3, 135.8, 130.7, 128.9, 128.8, 128.5, 128.1, 128.0, 125.9, 124.1, 57.1, 34.6, 30.3, 28.5, 15.6; FT-IR (thin film, neat): 3634, 2958, 2924, 2855, 2239, 1492, 1437, 1369, 1260, 1019, 754 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{30}H_{34}NO$ $[M–H]^+$: 424.2640; found : 424.2624.

2-{3,5-di-*tert*-butyl-4-hydroxyphenyl}-2-(4-methoxyphenyl)-2-phenylacetonitrile (92c)



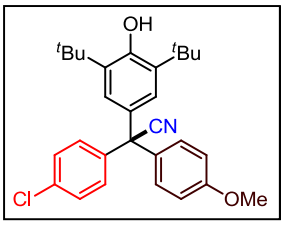
The reaction was performed at 0.050 mmol scale of fuchsone **(91c)**; R_f = 0.4 (10% EtOAc in hexane); yellow solid (17.5 mg, 82% yield); m.p. = 165–167 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37–7.29 (m, 3H), 7.23–7.21 (m, 2H), 7.12 (d, J = 8.9 Hz, 2H), 6.97 (s, 2H), 6.87 (d, J = 8.9 Hz, 2H), 5.28 (s, 1H), 3.81 (s, 3H), 1.34 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.2, 153.5, 141.4, 135.9, 133.2, 130.8, 130.1, 128.8, 128.6, 127.9, 125.8, 124.2, 113.9, 56.7, 55.5, 34.6, 30.3; FT-IR (thin film, neat): 3638, 2957, 2906, 2857, 2237, 1509, 1439, 1276, 1263, 1038, 750 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{29}H_{32}NO_2$ $[M–H]^+$: 426.2433; found : 426.2418.

2-[4-(*tert*-butyl)phenyl]-2-{3,5-di-*tert*-butyl-4-hydroxyphenyl}-2-phenylacetonitrile (92d)



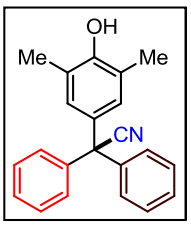
The reaction was performed at 0.047 mmol scale of fuchsone **(91d)**; R_f = 0.5 (10% EtOAc in hexane); orange gummy solid (15.5 mg, 73% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36–7.29 (m, 5H), 7.23–7.21 (m, 2H), 7.11 (d, J = 8.6 Hz, 2H), 6.95 (s, 2H), 5.26 (s, 1H), 1.33 (s, 18H), 1.32 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.5, 151.0, 141.4, 138.0, 135.8, 130.7, 128.9, 128.5, 127.9, 125.9, 125.5, 124.1, 57.0, 34.7, 34.6, 31.4, 30.3; FT-IR (thin film, neat): 3636, 2962, 2913, 2869, 2237, 1599, 1436, 1393, 1363, 1321, 1239, 1157, 1123, 1020, 911, 825, 760, 735, 700, 683, 659, 567 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{32}H_{38}NO$ $[M–H]^+$: 452.2953; found : 452.2937.

2-[4-chlorophenyl]-2-{3,5-di-*tert*-butyl-4-hydroxyphenyl}-2-(4-methoxyphenyl)acetonitrile (92e)



The reaction was performed at 0.046 mmol scale of fuchsone **(91e)**; R_f = 0.5 (10% EtOAc in hexane); yellow solid (17.6 mg, 83% yield); m.p. = 146–148 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (d, J = 8.7 Hz, 2H), 7.17 (d, J = 8.7 Hz, 2H), 7.11 (d, J = 8.9 Hz, 2H), 6.96 (s, 2H), 6.88 (d, J = 8.9 Hz, 2H), 5.31 (s, 1H), 3.82 (s, 3H), 1.35 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.3, 153.6, 140.1, 136.1, 134.0, 132.6, 130.3, 130.2, 130.0, 128.7, 125.6, 123.7, 114.0, 56.3, 55.5, 34.6, 30.3; FT-IR (thin film, neat): 3638, 2959, 2914, 2844, 2236, 1511, 1492, 1439, 1362, 1253, 1015, 750 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{29}H_{31}ClNO_2$ $[M–H]^+$: 460.2043; found : 460.2027.

2-{4-hydroxy-3,5-dimethylphenyl}-2,2-diphenylacetonitrile (92f)



The reaction was performed at 0.069 mmol scale of fuchsone **(91f)**; R_f = 0.4 (10% EtOAc in hexane); white solid (19.0 mg, 87% yield); m.p. = 186–188 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38–7.33 (m, 6H), 7.25–7.22 (m, 4H), 6.80 (s, 2H), 4.90 (s, 1H), 2.19 (s, 6H).; ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.2, 140.7, 131.5, 129.1, 128.9, 128.7, 128.1, 124.0, 123.4, 56.9, 16.3; FT-IR (thin film, neat): 3457, 2924, 2852, 2240, 1489, 1448, 1205, 1144, 1031, 863, 754, 699 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{22}H_{18}NO$ $[M–H]^+$: 312.1388; found : 312.1376.

Procedure for the synthesis of *α,α′*-diarylated ketones 93

Reaction was carried out according to a literature procedure:[39] To an oven dried round bottom flask, diarylnitrile **83** (30 mg, 0.085 mmol), 4-bromophenylboronic acid (20.6 mg, 0.10 mmol), $Pd(OAc)_2$ (1 mg, 0.0043 mmol), ligand (0.7 mg, 0.0043 mmol) and KF (14.8 mg, 0.26 mmol) were added. Then H_2O (0.2 mL) and TfOH (0.07 mL) were added into it and the resultant mixture was stirred at 60 ^{o}C under air for 24 h. The reaction mixture was then neutralized with saturated $NaHCO_3$ at 0 ^{o}C and extracted with diethyl ether (5 mL x 2). Combined organic layer was washed with brine, dried over sodium sulphate and concentrated. Then residue was purified by silica gel column chromatography (using EtOAc/hexane as eluent) to afford corresponding product **93** (24 mg, 57%) as a yellow solid. ^{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 = 8.6 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, 135.98, 131.9, 131.5, 130.6, 130.2, 129.5, 128.0, 125.8, 114.3, 58.7, 55.4, 34.5, 30.4.

Procedure for the synthesis of 6-cyano-*p*-quinone methide 94

Reaction was carried out according to a literature procedure:[40] Activated MnO_2 (57 mg, 0.66 mmol) was added to a solution of diarylnitrile **83** (23 mg, 0.066 mmol) in $CHCl_3$ (2.5 mL) and the reaction mixture was refluxed for 12 h. The crude product was filtered through a pad of celite and concentrated under reduced pressure. The residue was then purified through a silica gel column (using EtOAc/hexane as eluent) to afford the corresponding product **94** (22 mg, 98%) as an orange solid; m. p. = 142–144 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, J = 1.7 Hz, 1H), 7.46 (d, J = 8.6 Hz, 2H), 7.26 (s, 1H), 7.02 (d, J = 8.6 Hz, 2H), 3.88 (s, 3H), 1.34 (s, 9H), 1.24 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 186.5, 161.5, 151.2, 151.1, 139.6, 132.2, 130.1, 127.6, 125.3, 120.0, 118.2, 114.7, 55.7, 35.9, 35.8, 29.6 (2C) ; FT-IR (thin film, neat): 2960, 2913, 2869, 2206, 1615, 1601, 1504, 1457, 1388, 1365, 1300, 1260, 1179, 1088, 1031, 913, 882, 836, 733, 632 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{23}H_{28}NO_2$ $[M+H]^+$: 350.2120; found : 350.2105.

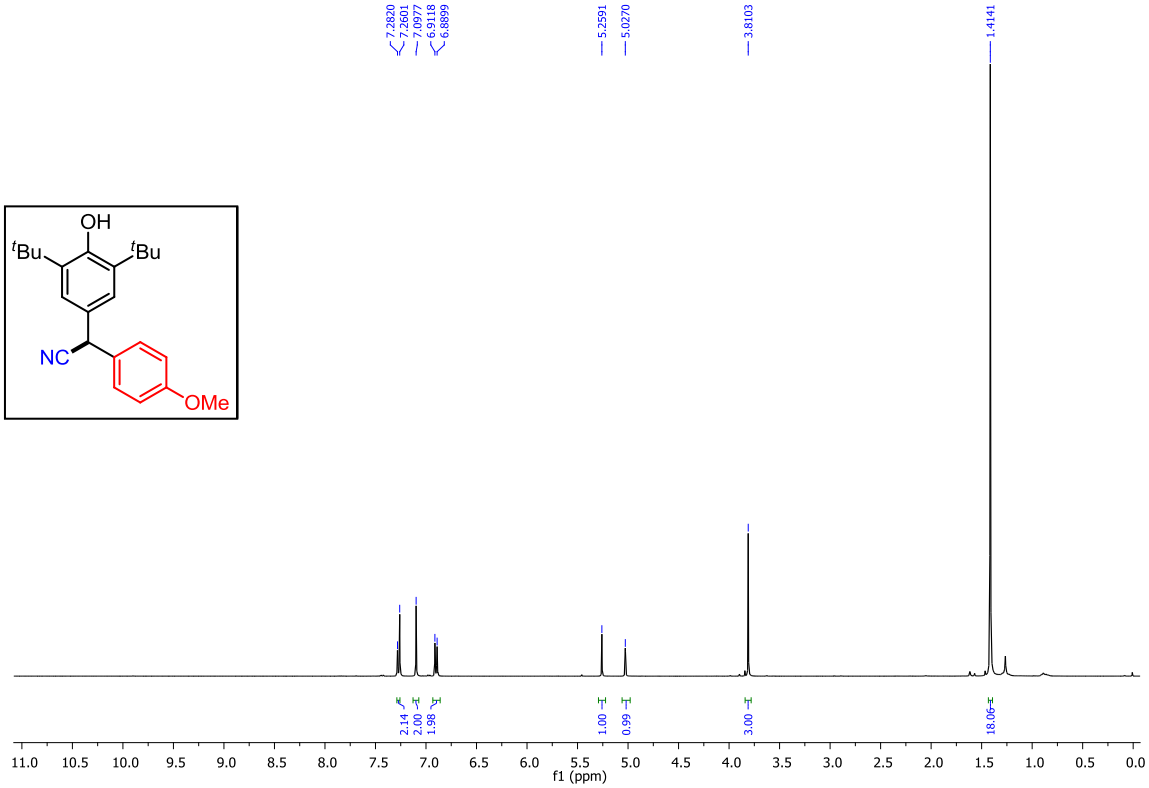
Procedure for the synthesis of leuconitrile analogue 95

To an oven dried round-bottom flask, **94** (20 mg, 0.057 mmol), Indole (7.4 mg, 0.063 mmol), and $Bi(OTf)_3$ (3.7 mg, 0.0057 mmol) were added. DCE (0.5 mL) was then added into the mixture and the resultant mixture was stirred at room temperature under argon. After completion of the reaction (15 min, based on TLC), water was added to the reaction mixture and extracted with EtOAc (2 x 5 mL). Combined organic layer was washed with brine, dried over sodium sulphate and concentrated. Then residue was purified by silica gel column chromatography (using EtOAc/hexane as eluent) to afford corresponding product **95** (24 mg, 90%) as orange gummy solid. *The product was found to be unstable as some amount of decomposition was observed during purification*. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (brs, 1H), 7.37 (d, J = 8.1 Hz, 1H), 7.32–7.29 (m, 2H), 7.26 (d, J = 3.3 Hz, 1H), 7.20 (t, J = 7.5 Hz, 1H), 7.14 (s, 2H), 7.03 (t, J = 7.5 Hz, 1H), 6.86 (d, J = 8.7 Hz, 2H), 6.51 (d, J = 2.3 Hz, 1H), 5.25 (s, 1H), 3.81 (s, 3H), 1.34 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.1, 153.4, 137.0, 135.8, 134.1, 132.5, 130.6, 129.5, 125.4, 125.1, 123.1, 122.8, 121.0, 120.3, 117.7, 113.8, 111.4, 55.4, 50.4, 34.6, 30.3; FT-IR (thin film, neat): 3636, 2957, 2923, 2853, 2239, 1639, 1510, 1455, 1435, 1360, 1305, 1252, 1218, 1111, 1036, 819, 772, 746 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{31}H_{33}N_2O_2$ $[M–H]^+$: 465.2542; found : 465.2524.

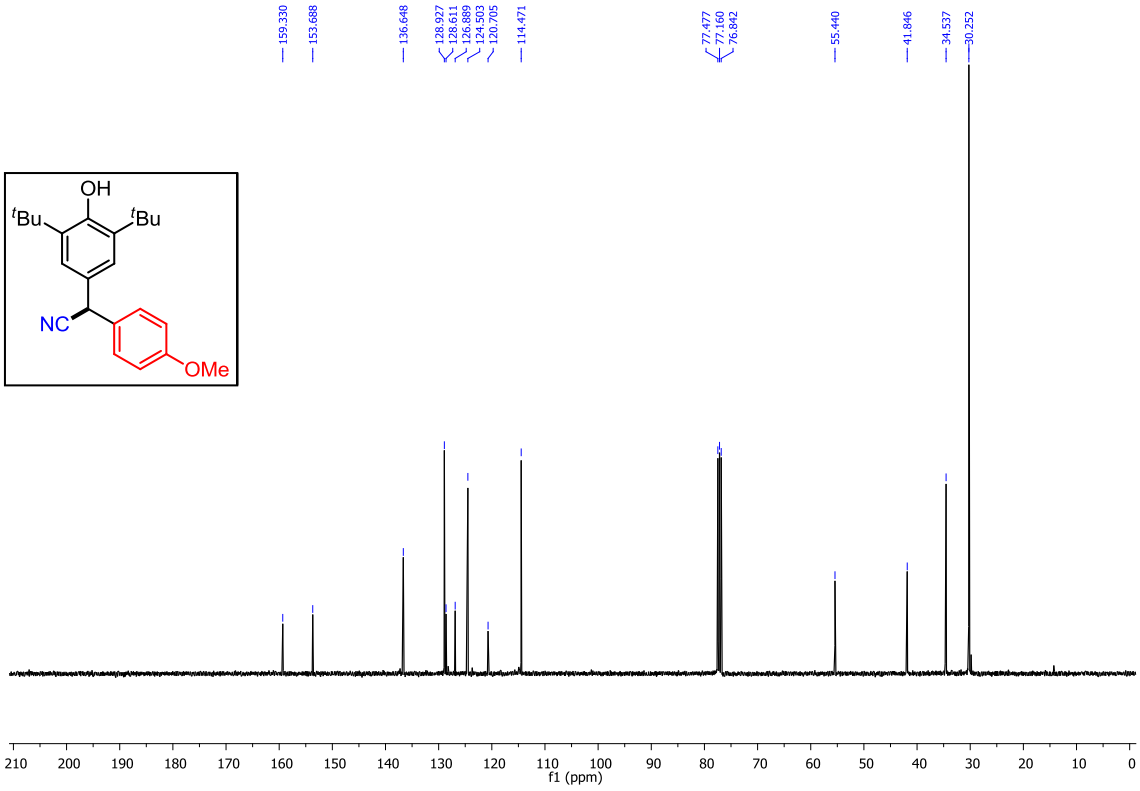
Procedure for gram scale synthesis of 83

1,4– dioxane (24 mL) was added to a mixture of *p*-quinone methide **82** (3.1 mmol), Me_3Si-CN (4 mmol, 0.51 mL) and NHC–CO_2 adduct **84** (0.31 mmol) under argon atmosphere and the resulting mixture was stirred at room temperature. After the reaction was complete (based on TLC analysis), the mixture was quenched with 15 mL of aqueous sodium thiosulfate and extracted with Et_2O (3 x 20 mL). The combined organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was then purified through a silica gel column using EtOAc/Hexane mixture as an eluent to get the pure product.

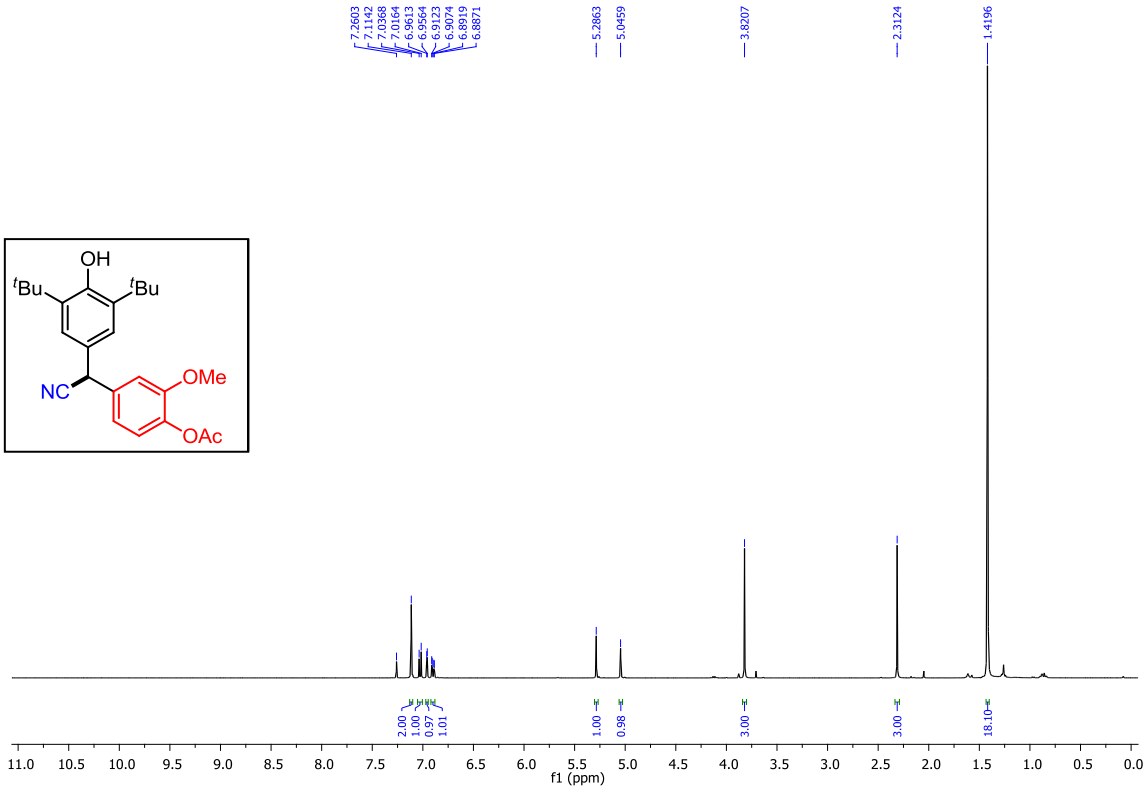
^{1}H NMR spectrum of **83**



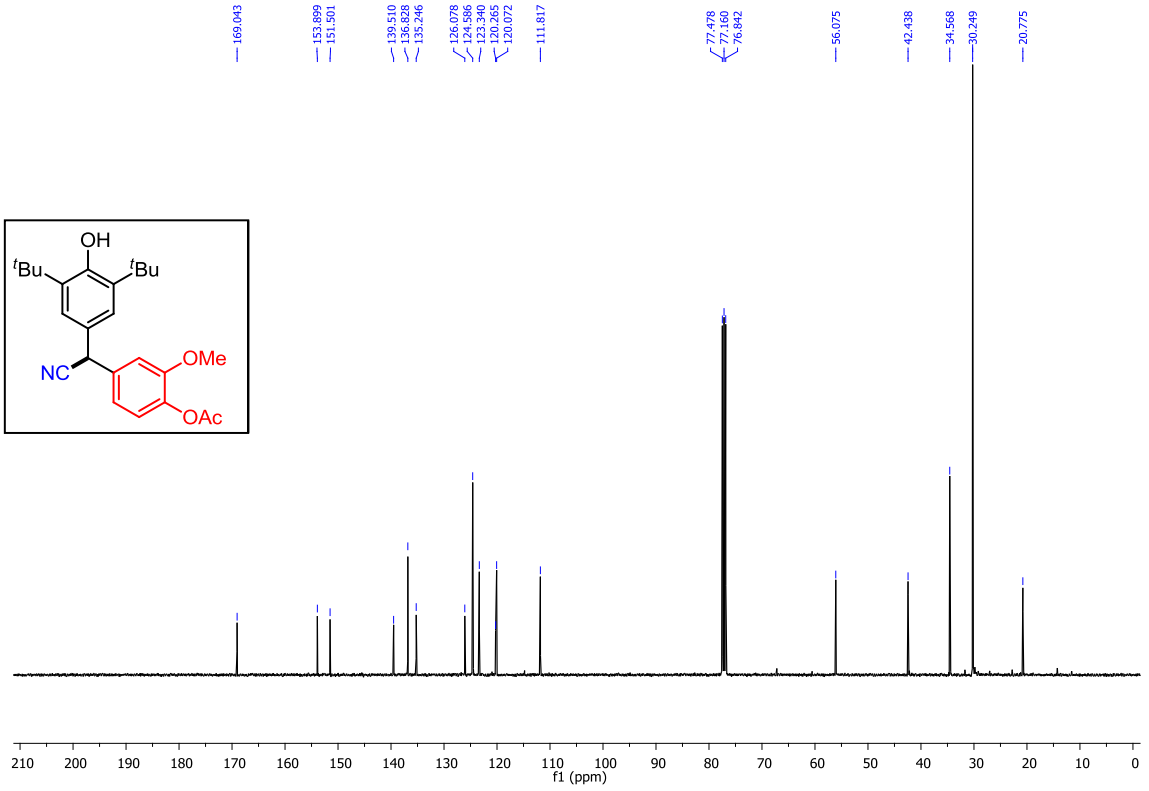
^{13}C NMR spectrum of **83**



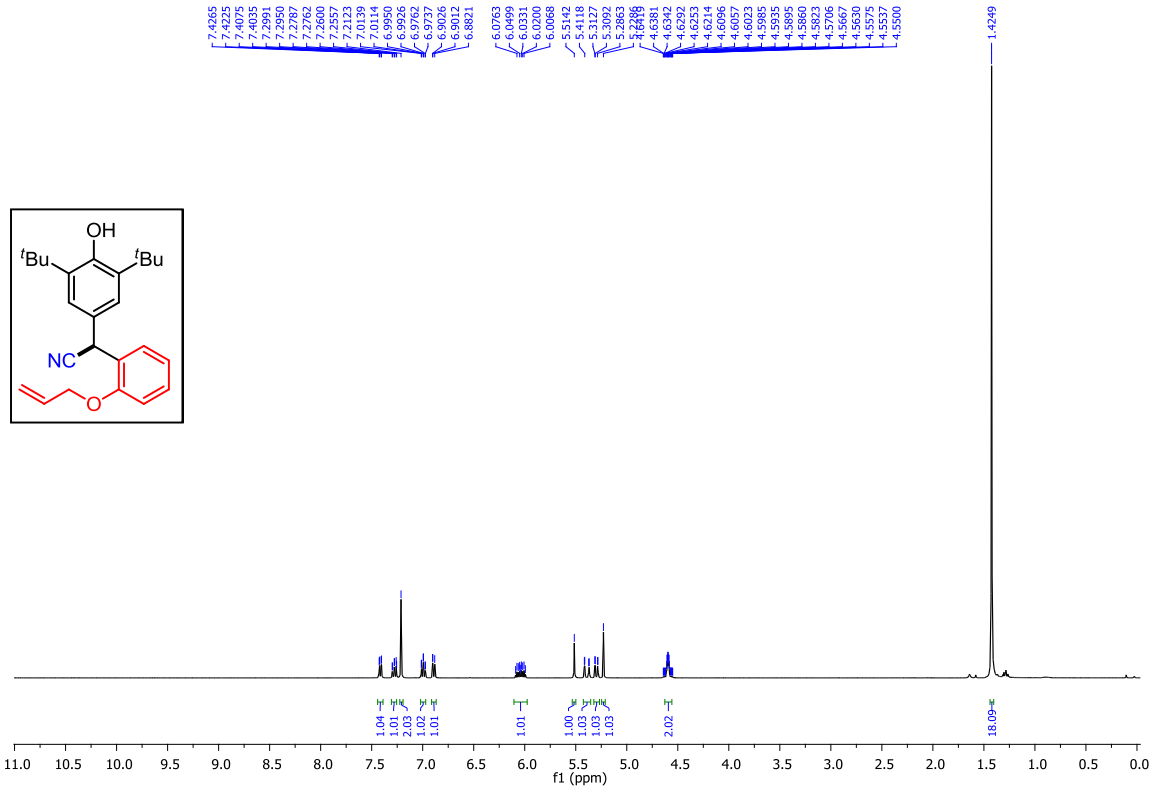
^{1}H NMR spectrum of **83d**



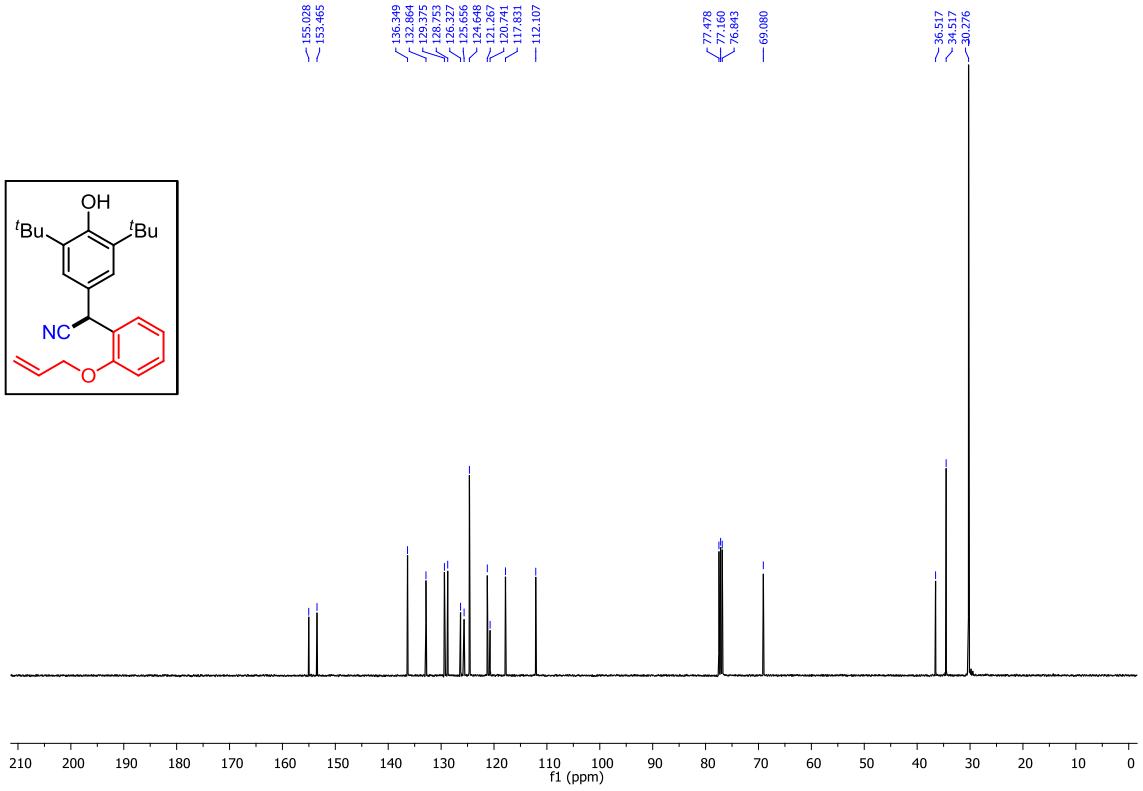
^{13}C NMR spectrum of **83d**



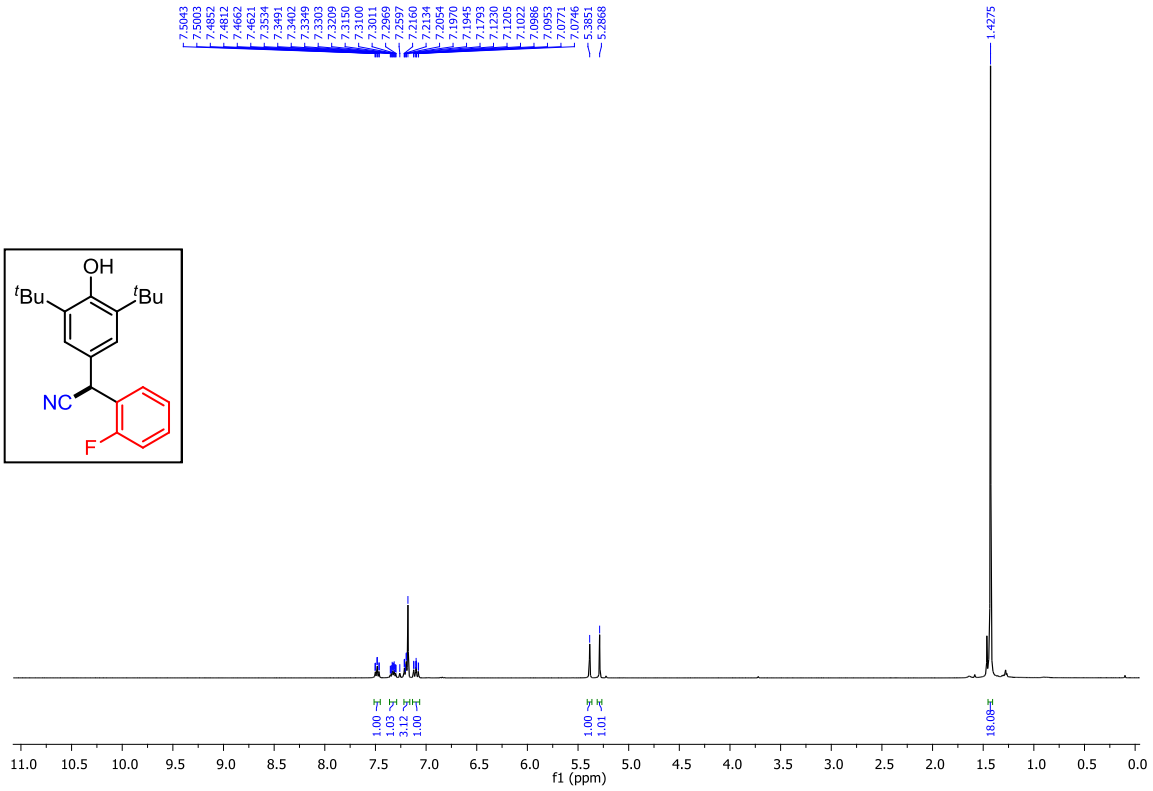
^{1}H NMR spectrum of **83h**



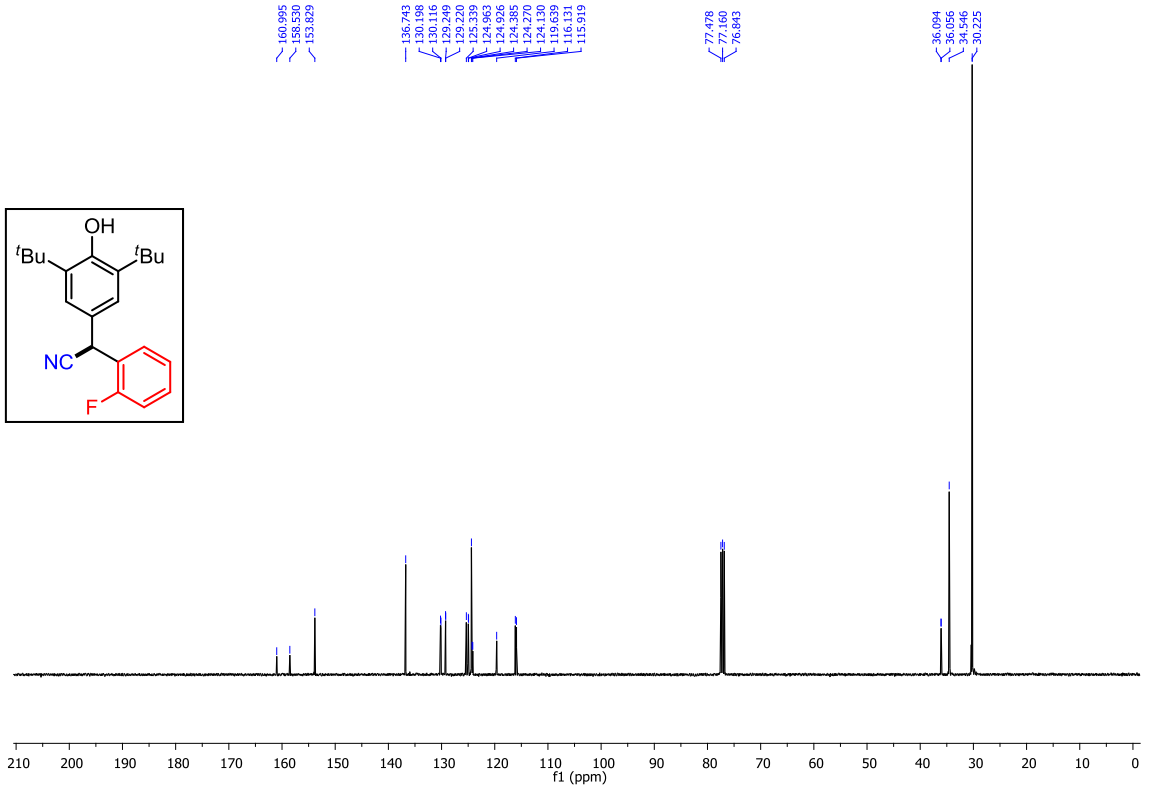
^{13}C NMR spectrum of **83h**



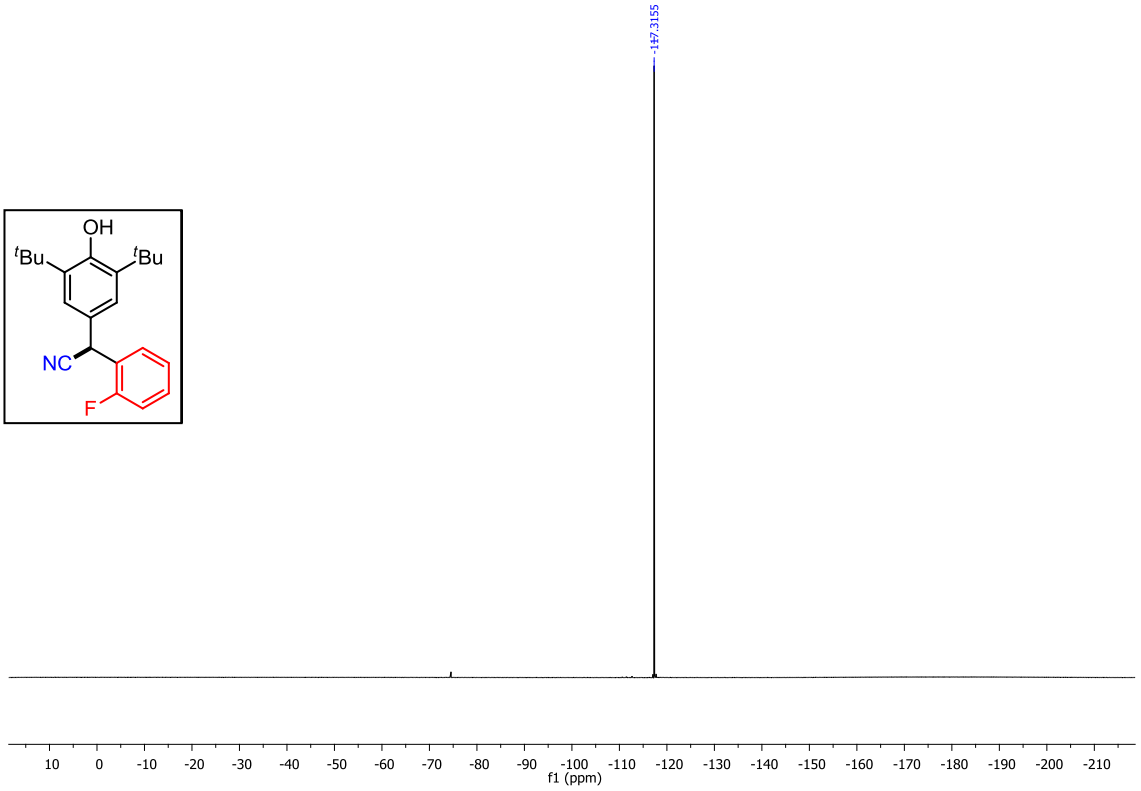
^{1}H NMR spectrum of **83m**



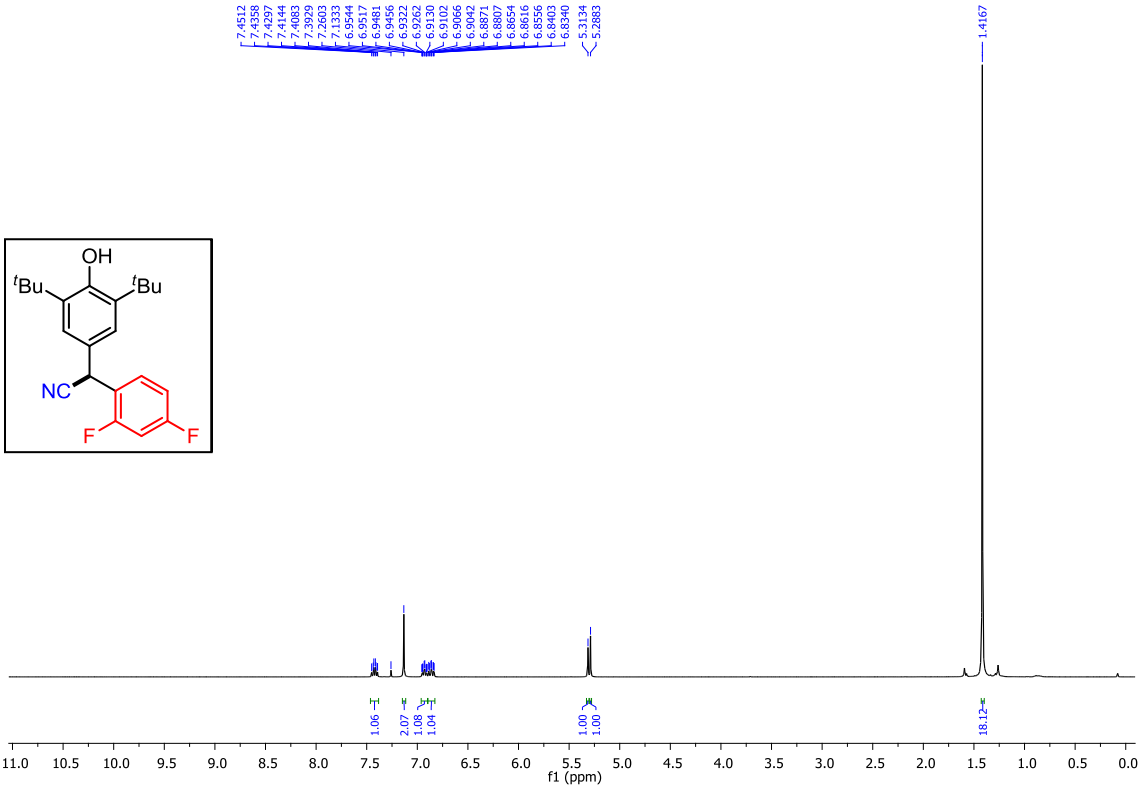
^{13}C NMR spectrum of **83m**



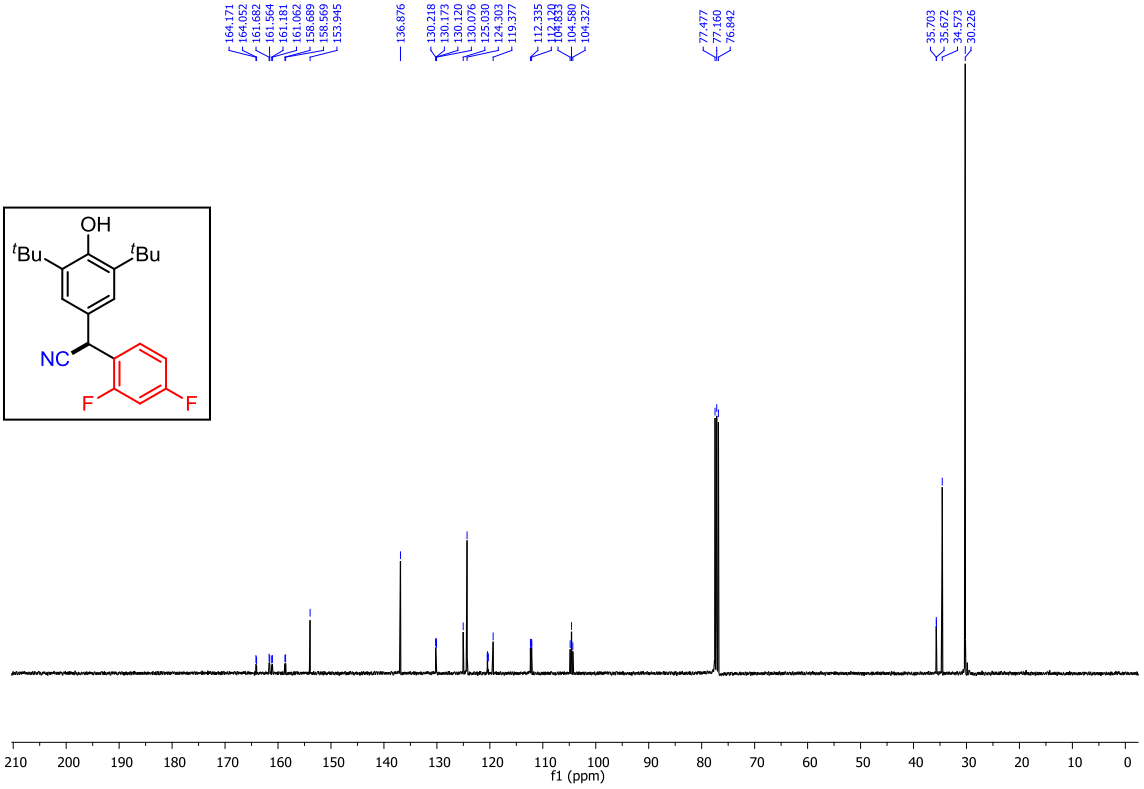
^{19}F NMR spectrum of **83m**



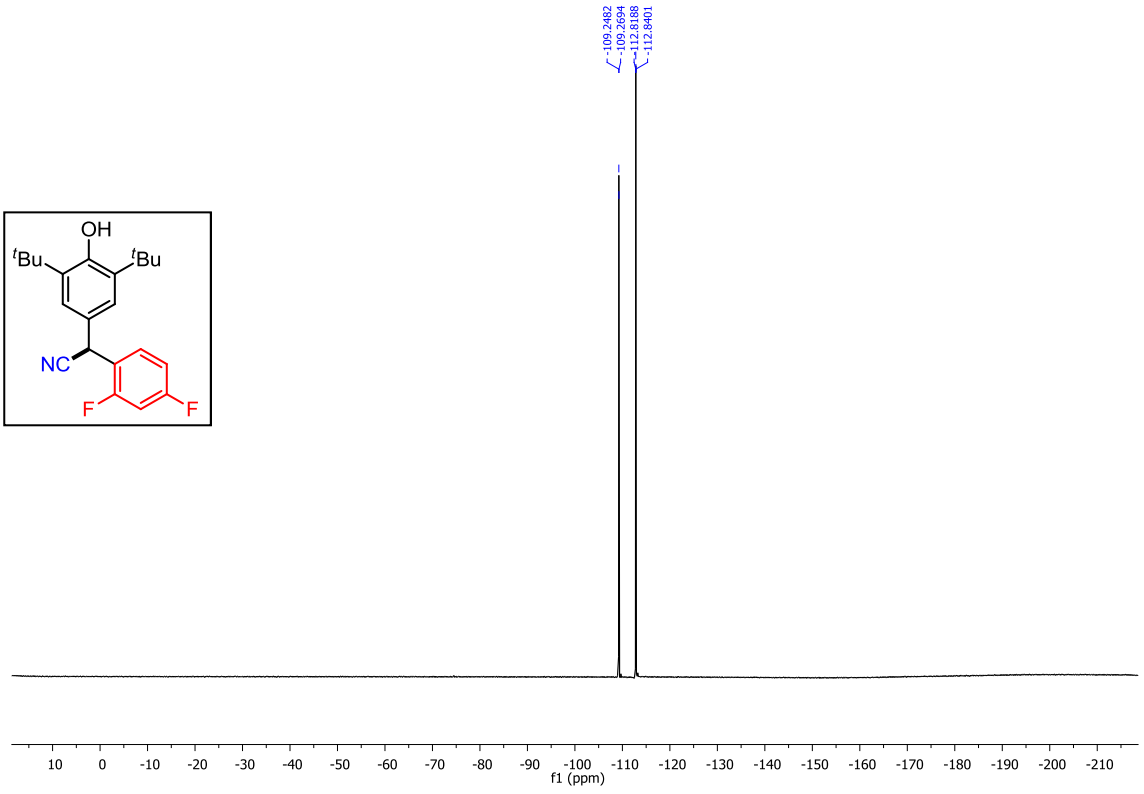
^{1}H NMR spectrum of **83n**



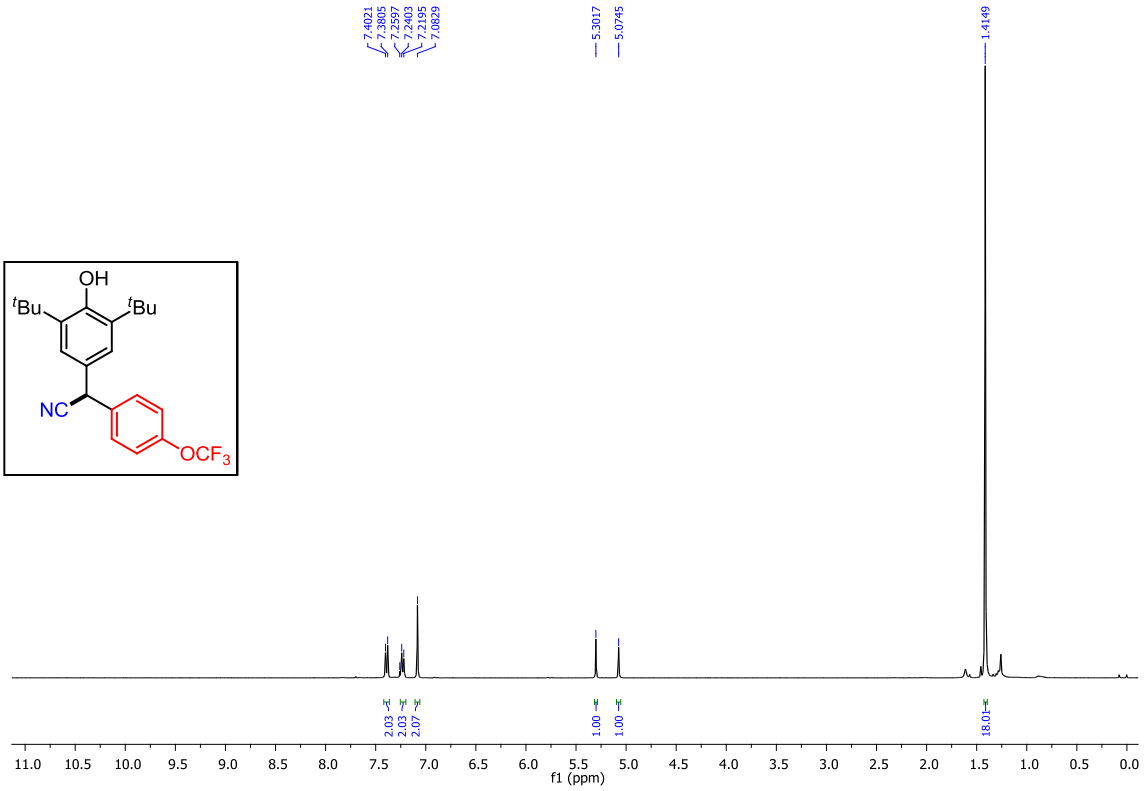
^{13}C NMR spectrum of **83n**



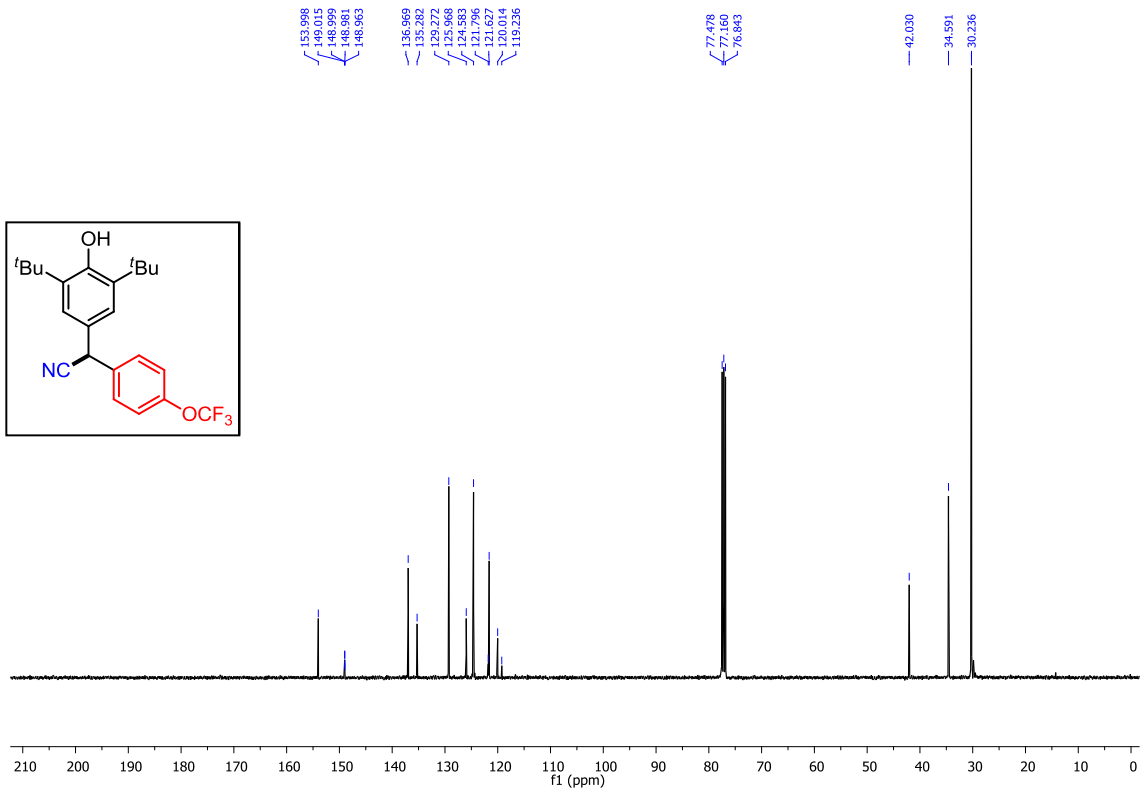
^{19}F NMR spectrum of **83n**



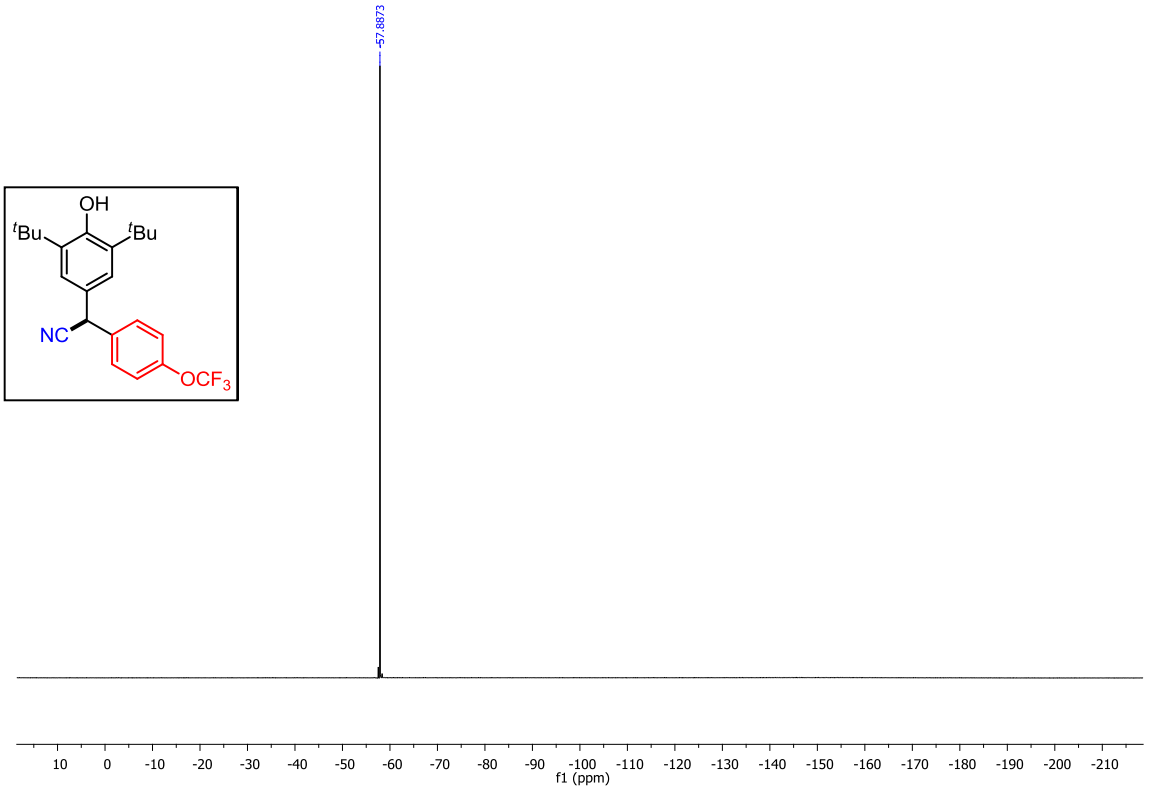
^{1}H NMR spectrum of **83o**



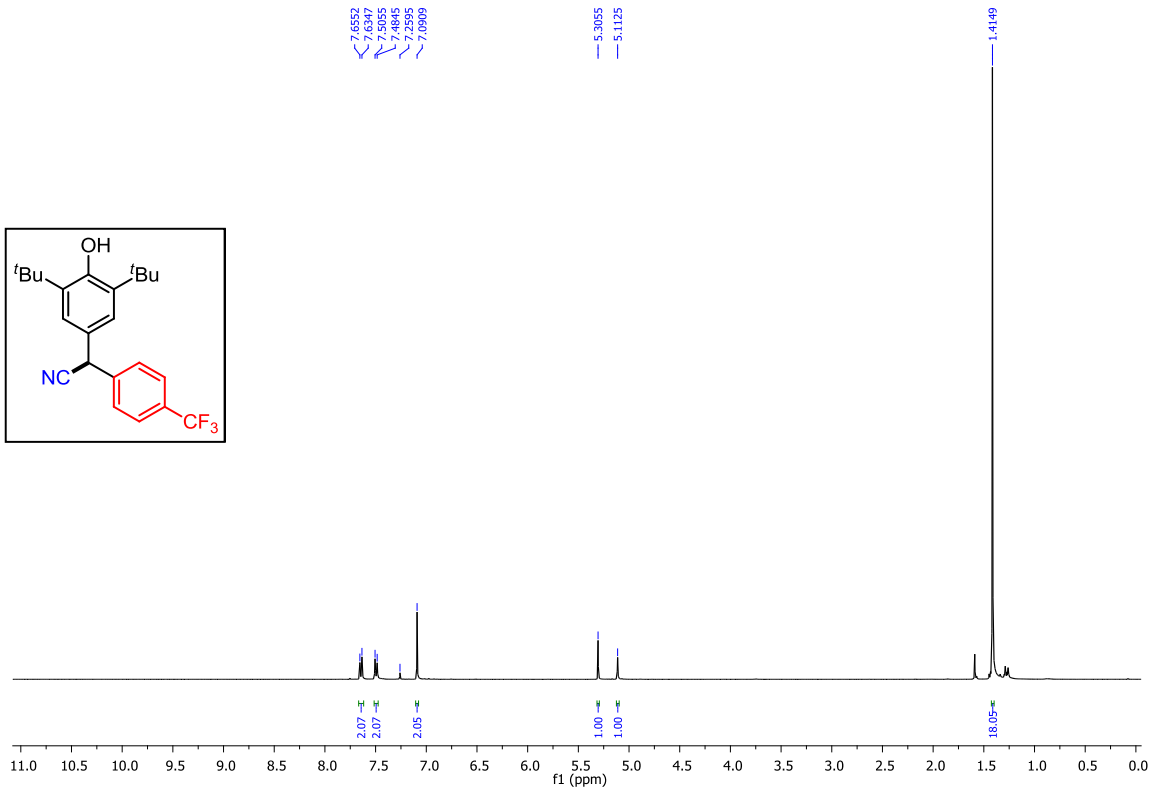
^{13}C NMR spectrum of **83o**



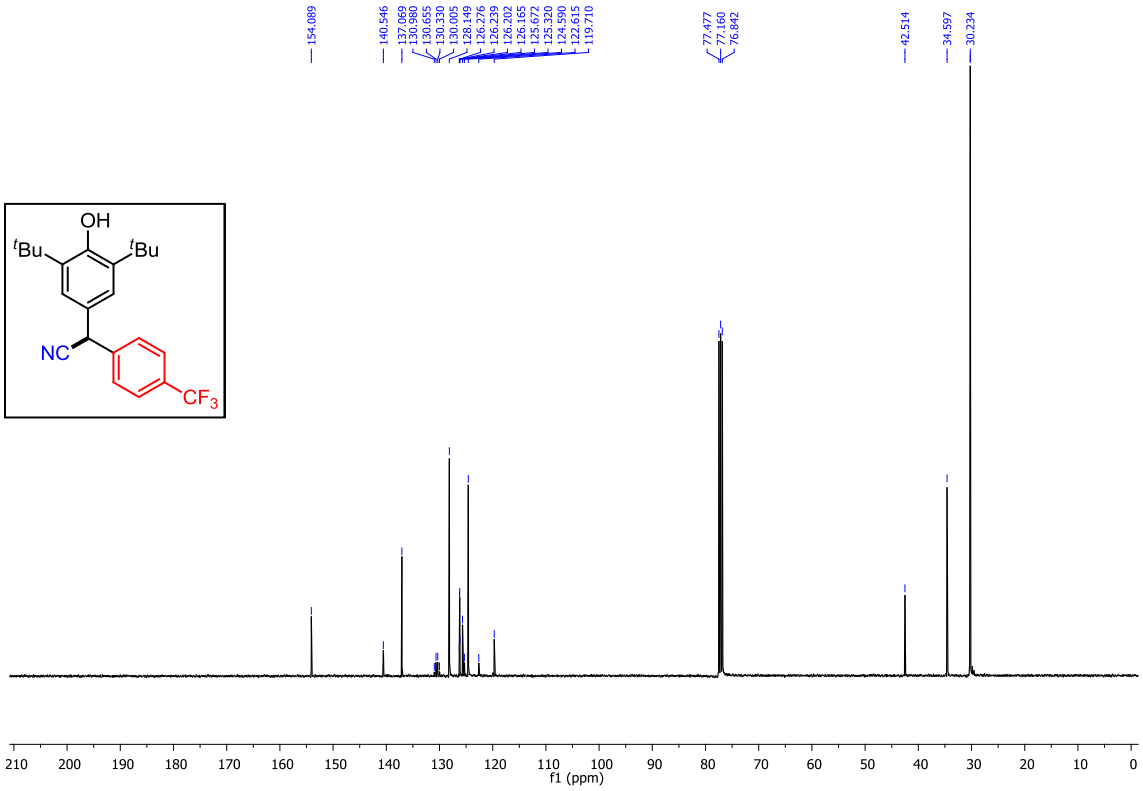
^{19}F NMR spectrum of **83o**



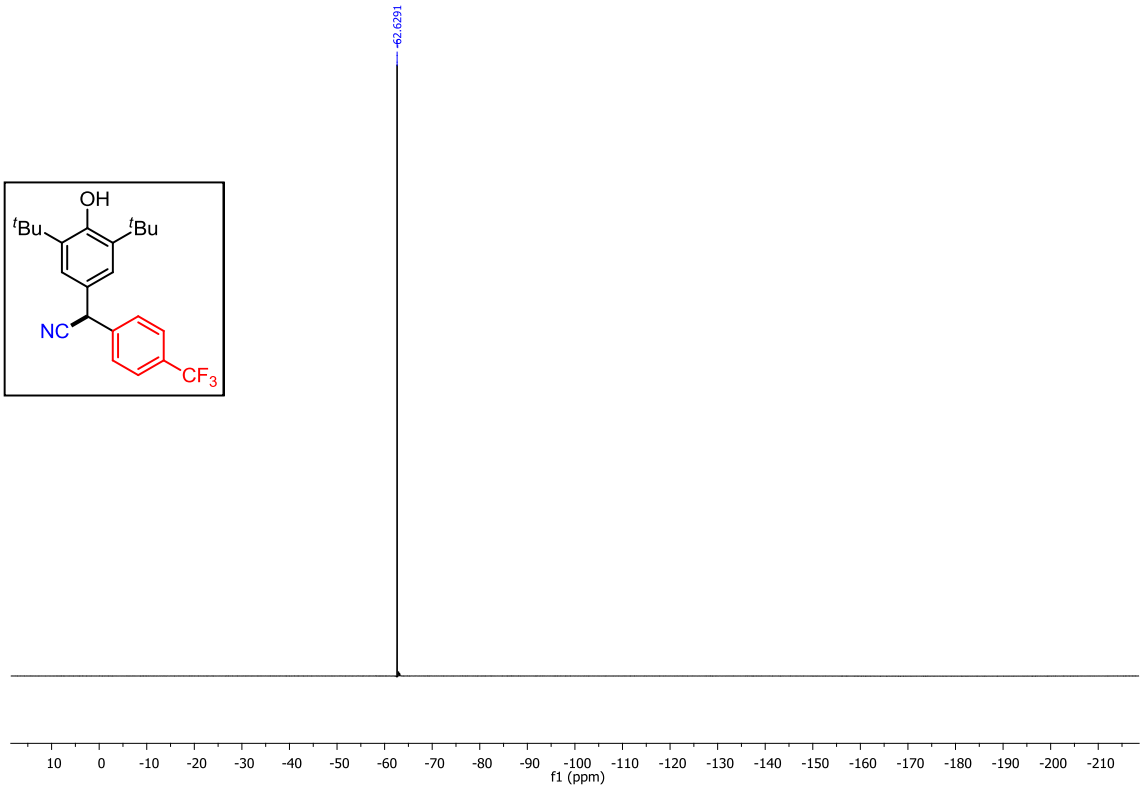
^{1}H NMR spectrum of **83q**



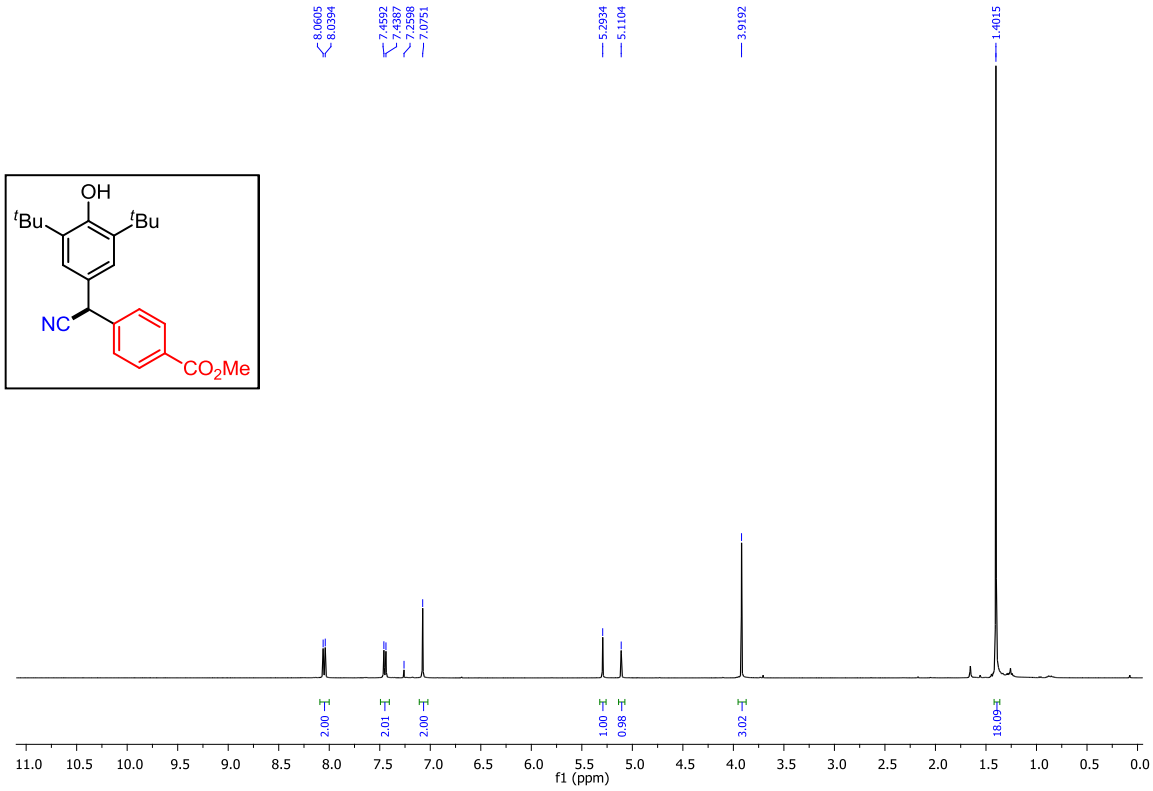
^{13}C NMR spectrum of **83q**



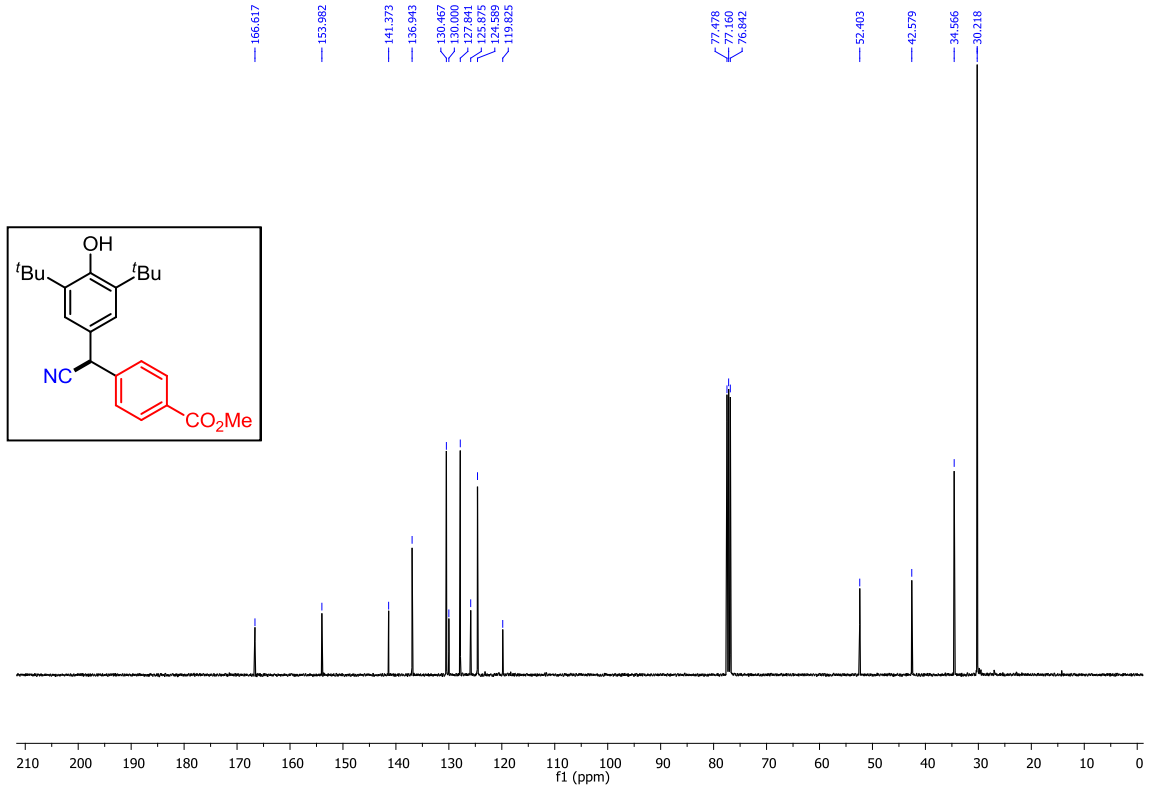
^{19}F NMR spectrum of **83q**



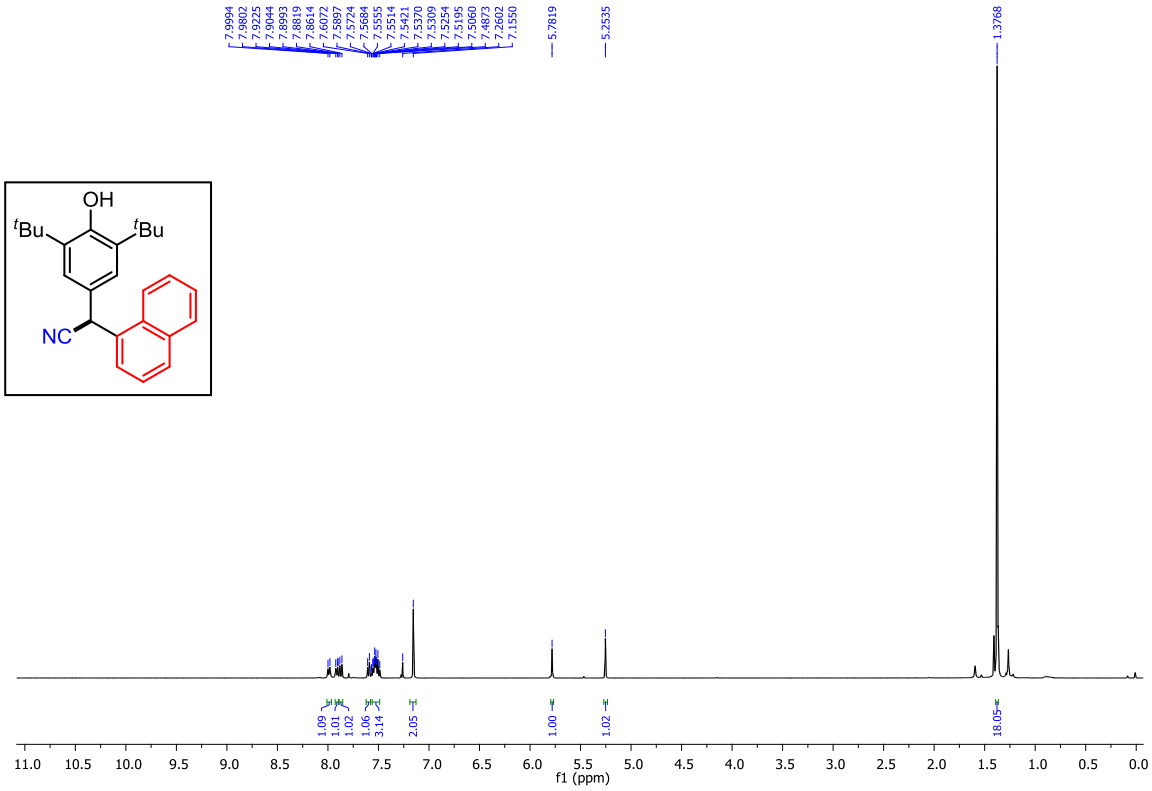
^{1}H NMR spectrum of **83r**



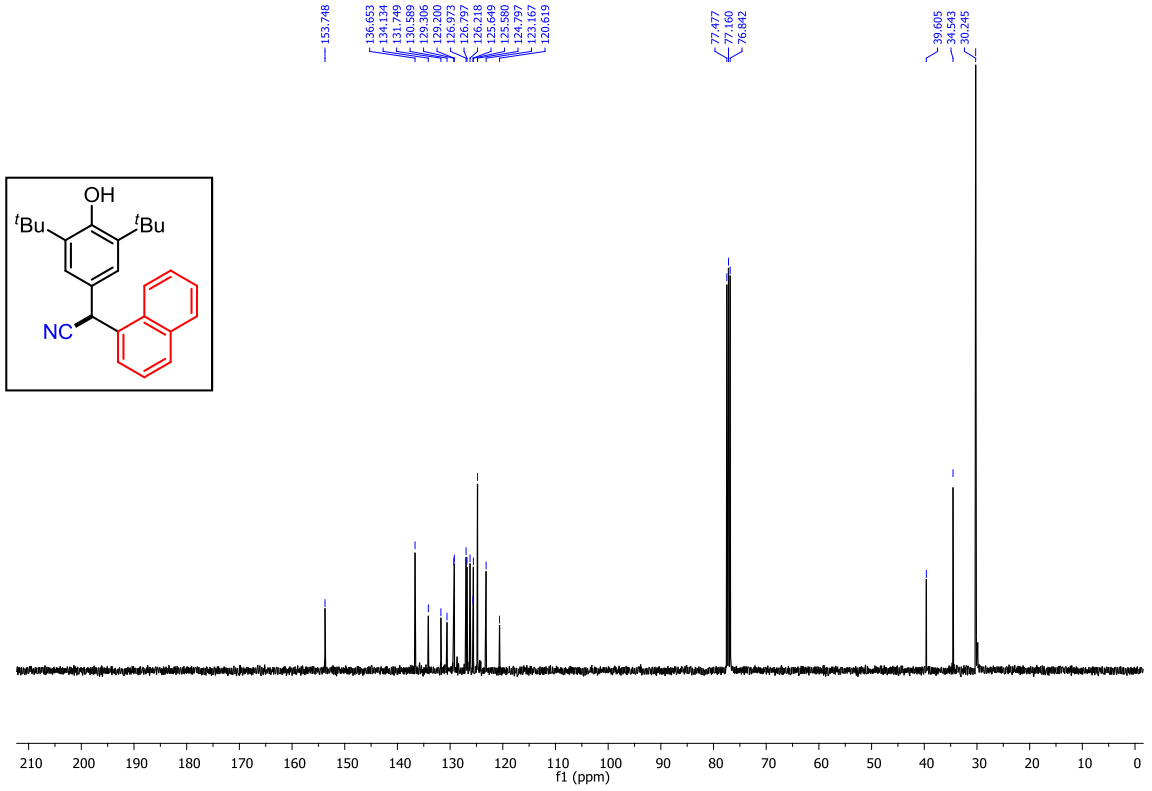
^{13}C NMR spectrum of **83r**



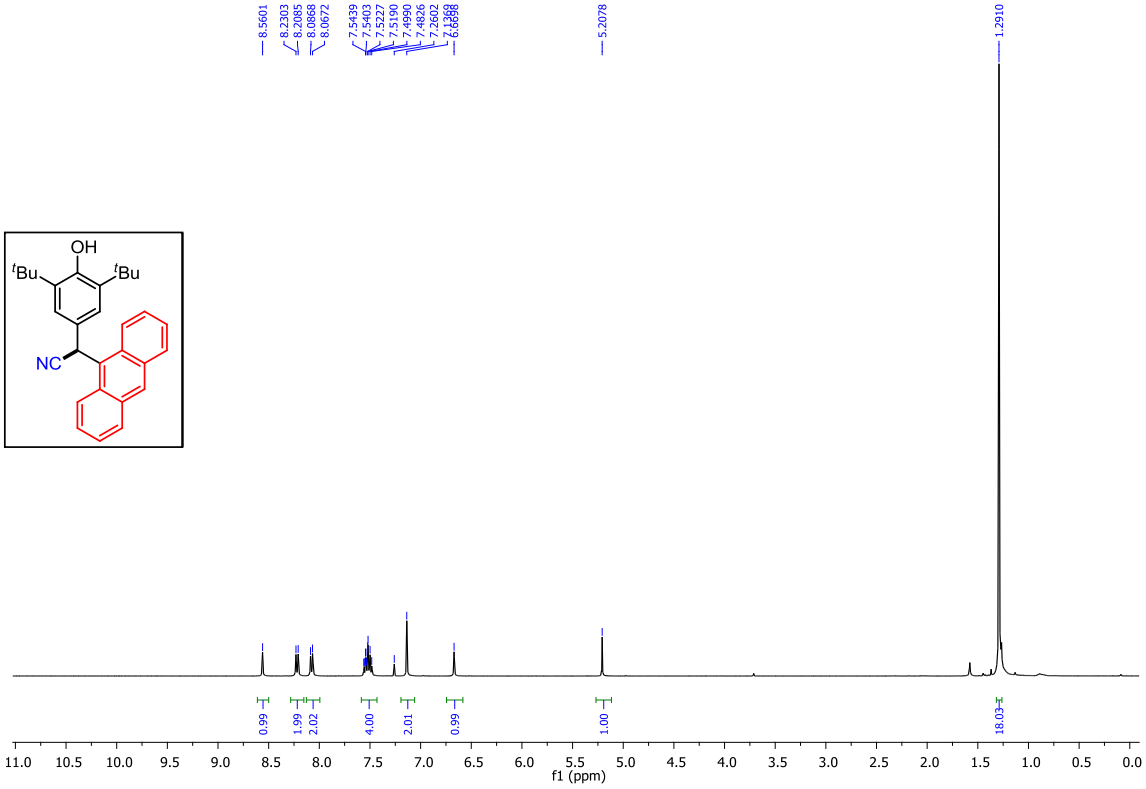
^{1}H NMR spectrum of **83s**



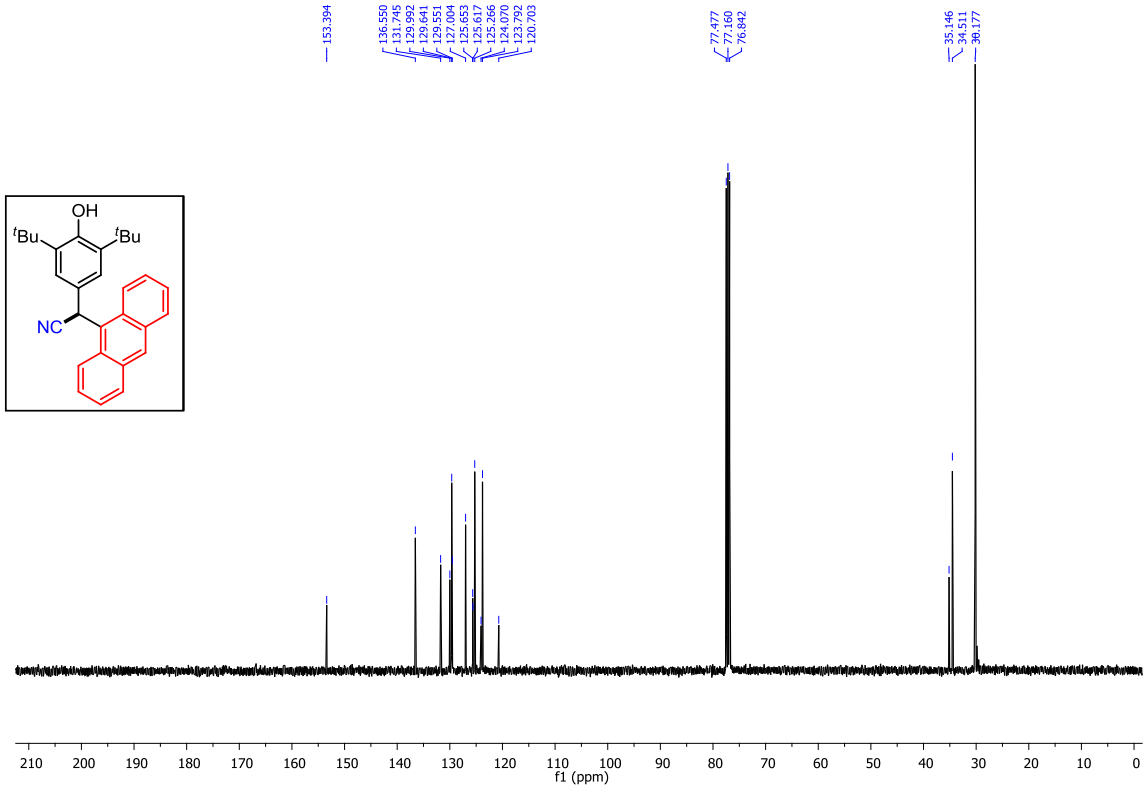
^{13}C NMR spectrum of **83s**



^{1}H NMR spectrum of **83t**



^{13}C NMR spectrum of **83t**



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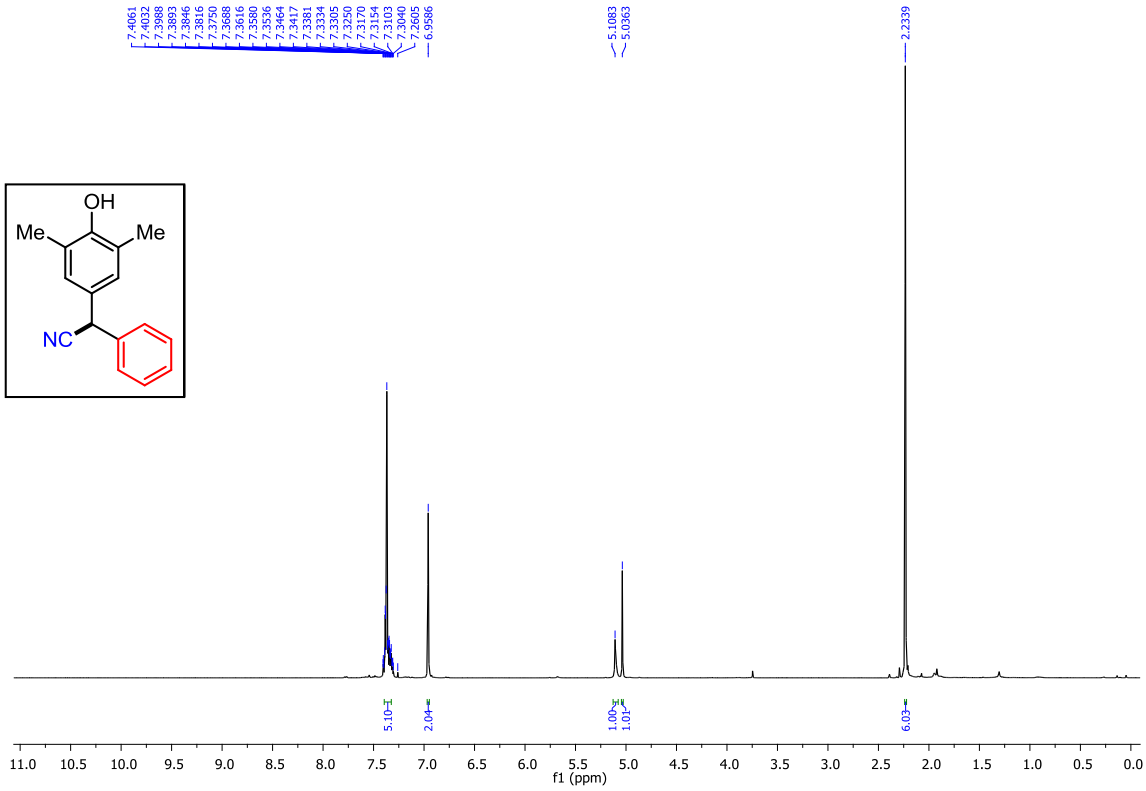
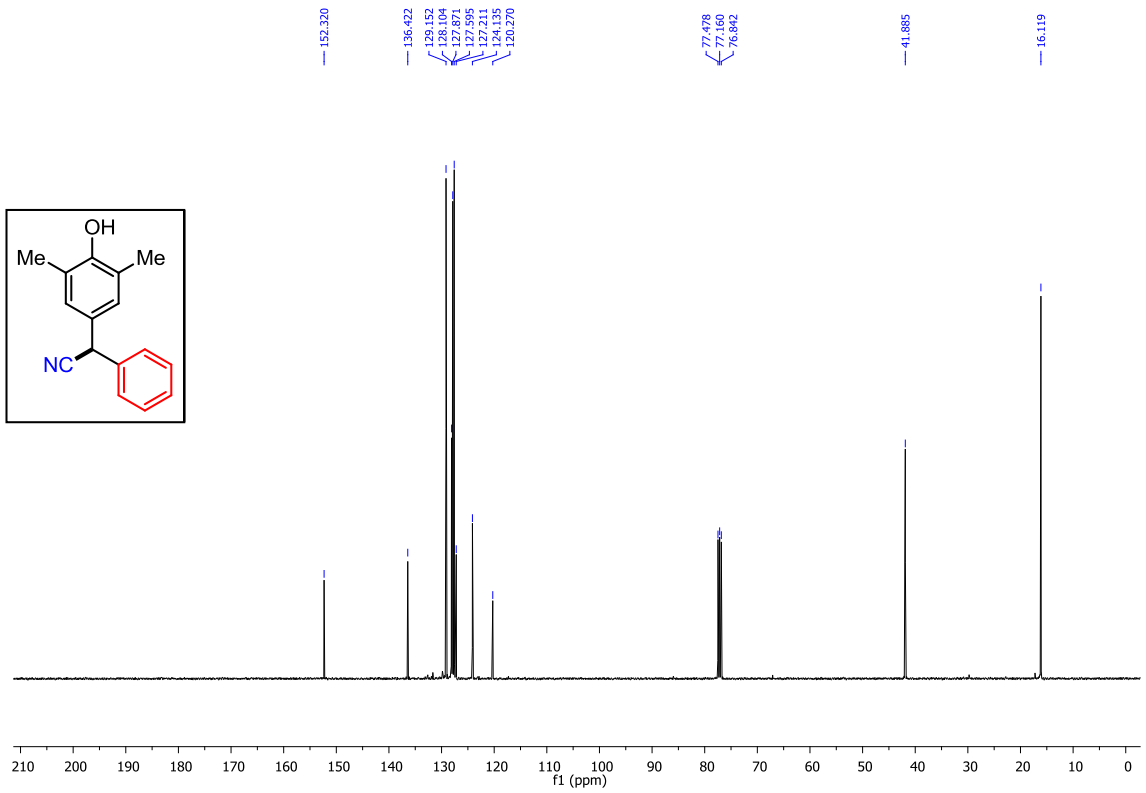
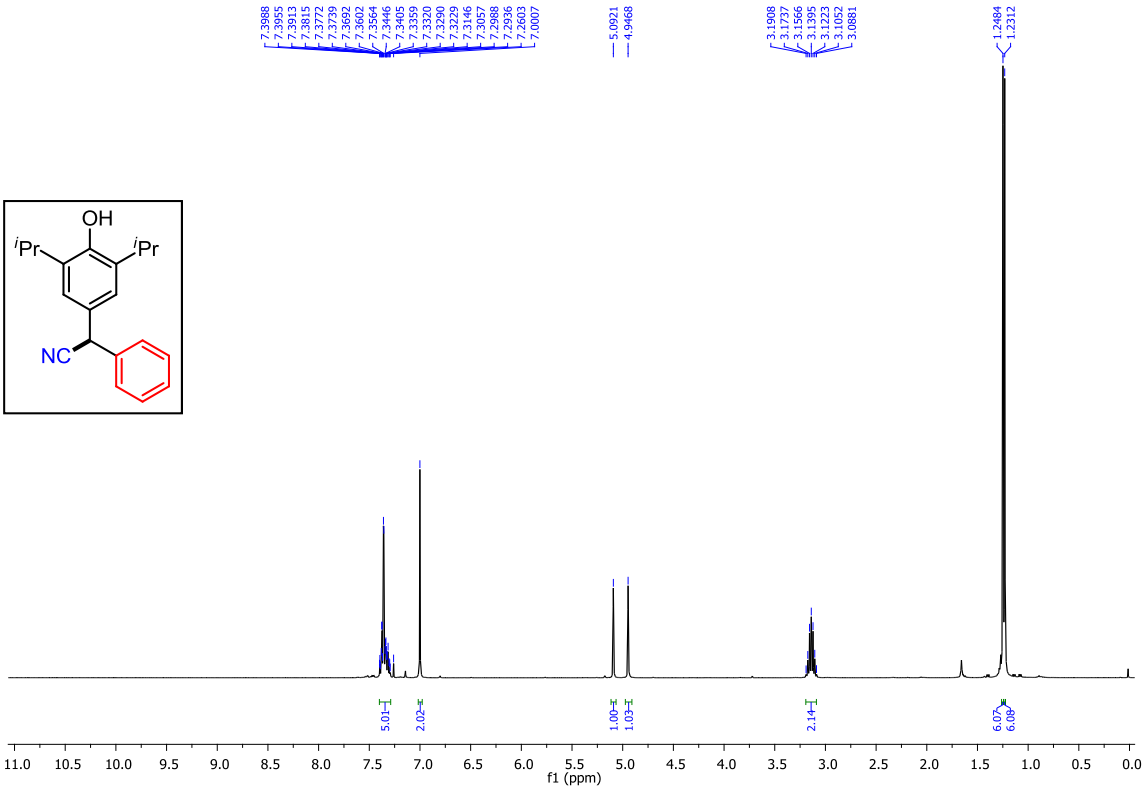


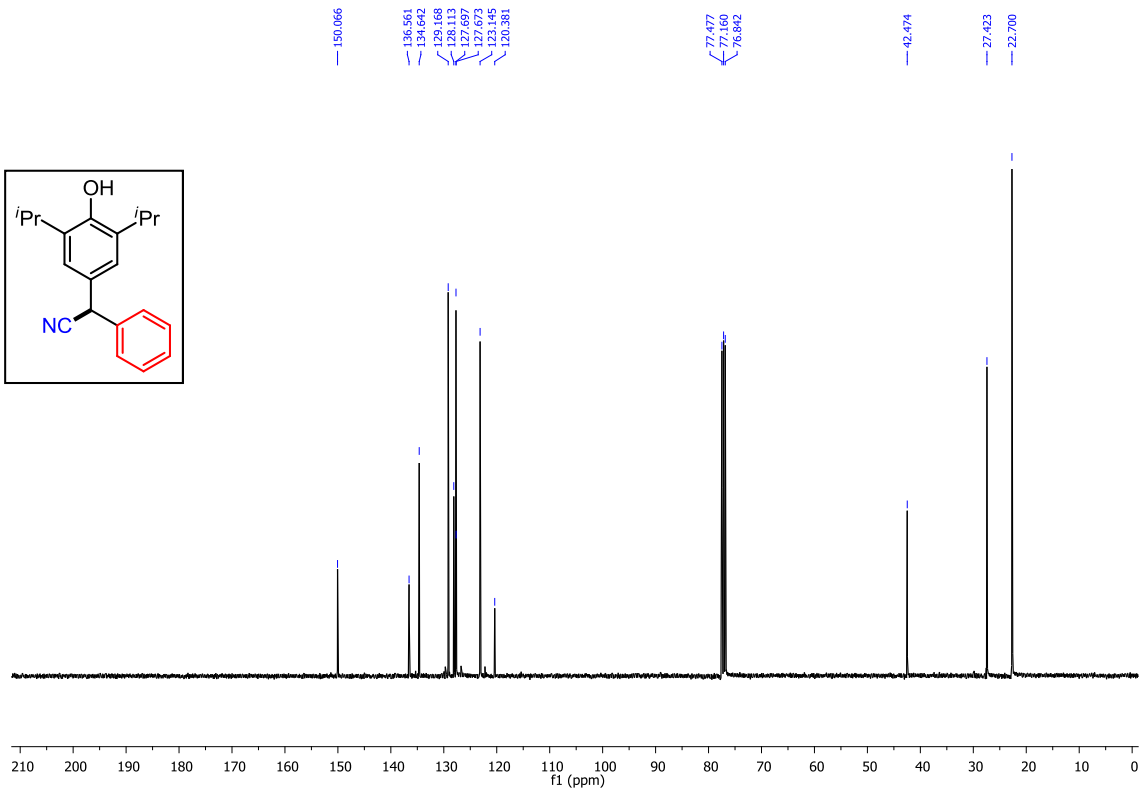
^{13}C NMR spectrum of **83x**



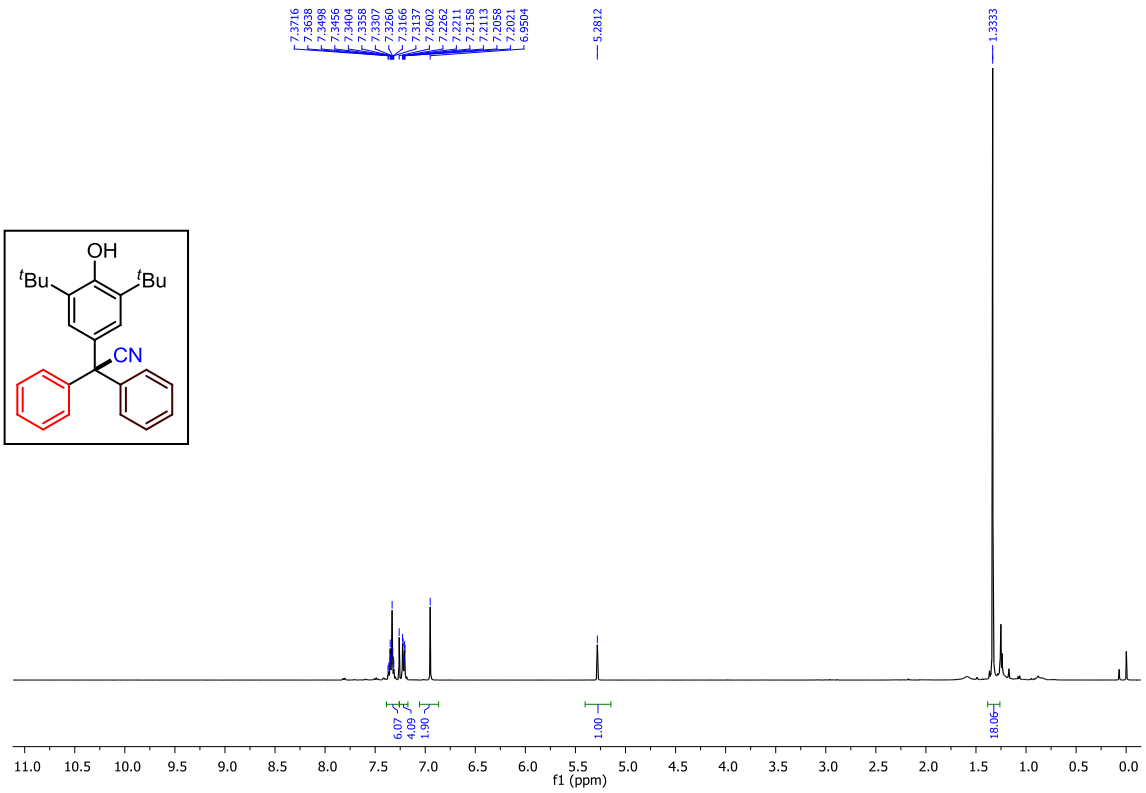
^{1}H NMR spectrum of **83y**



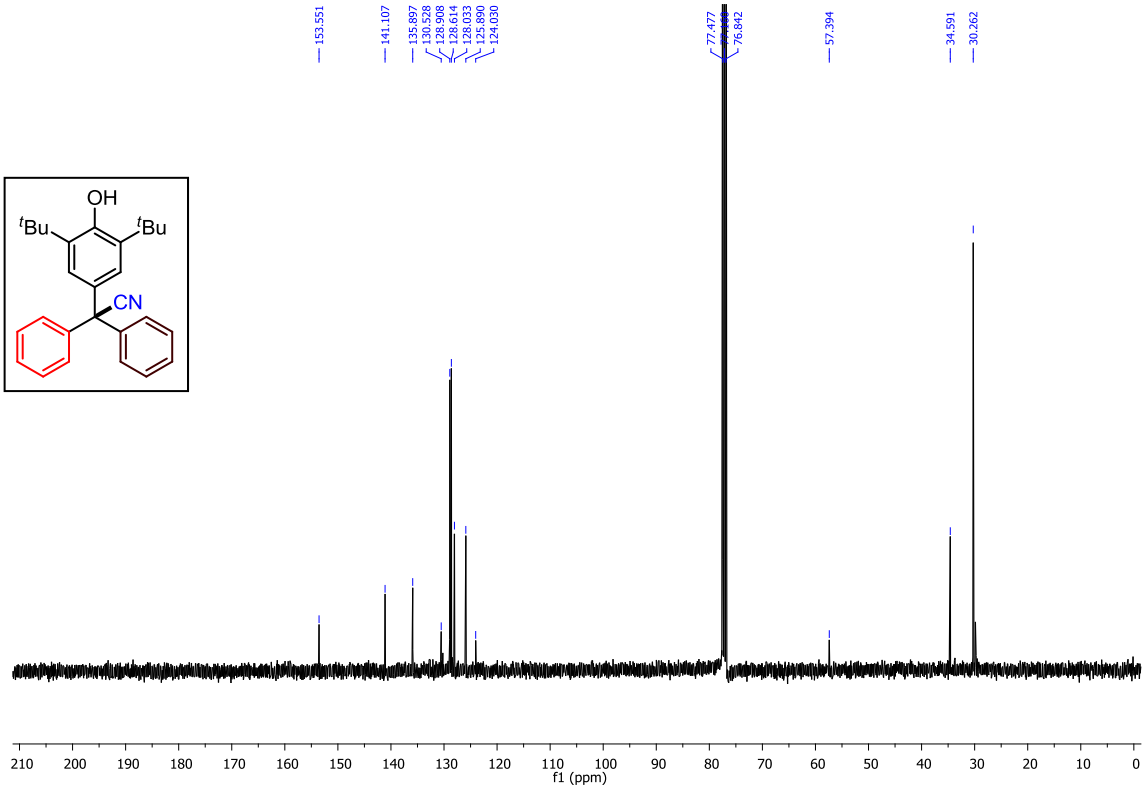
^{13}C NMR spectrum of **83y**



^{1}H NMR spectrum of **92a**



^{13}C NMR spectrum of **92a**



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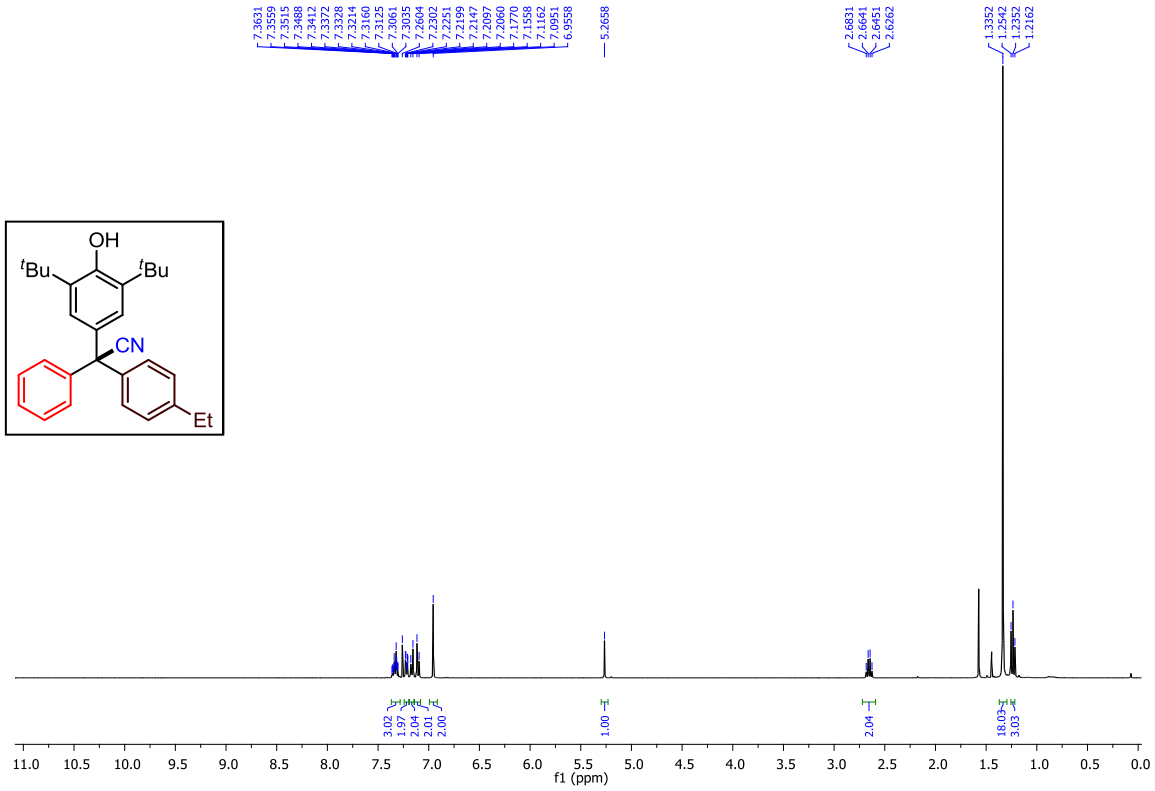

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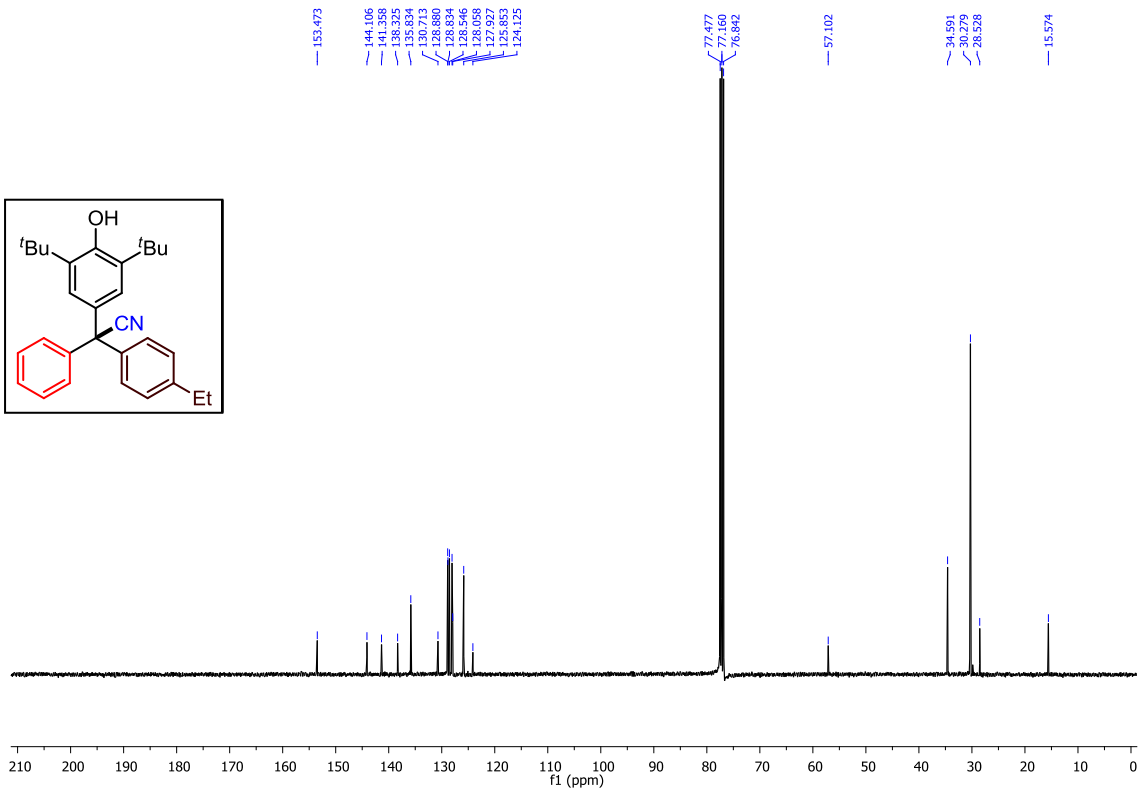

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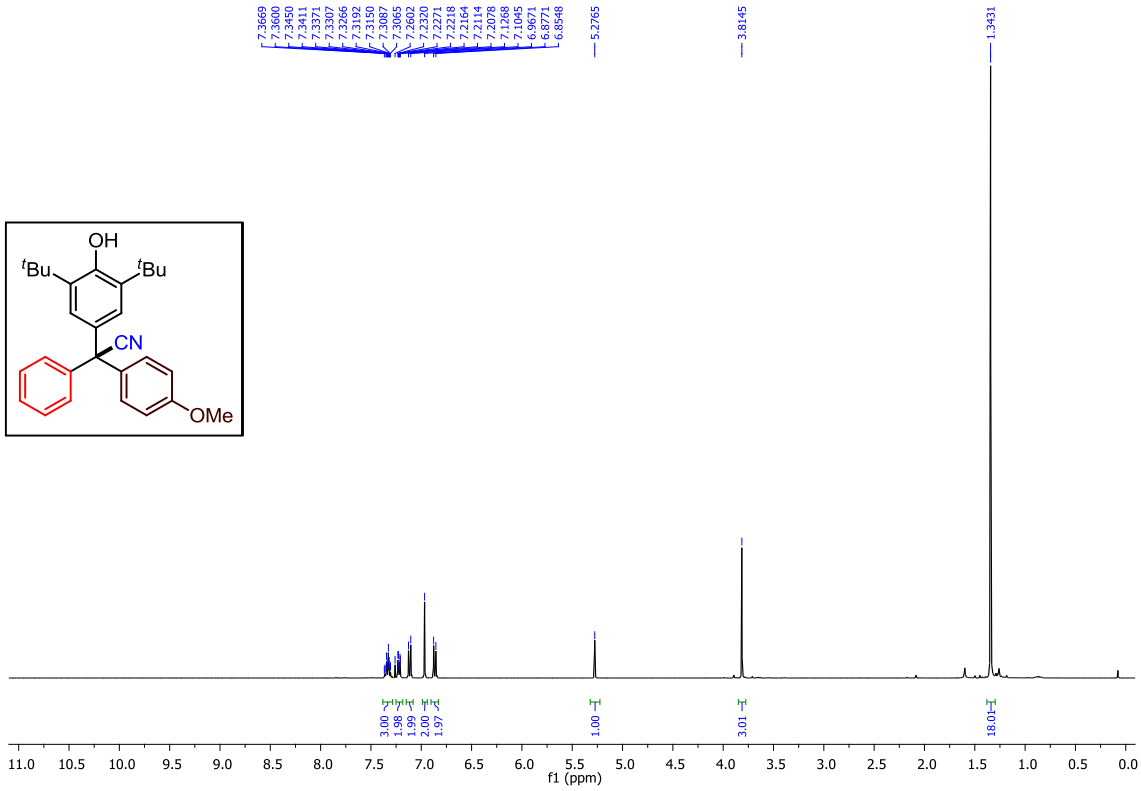
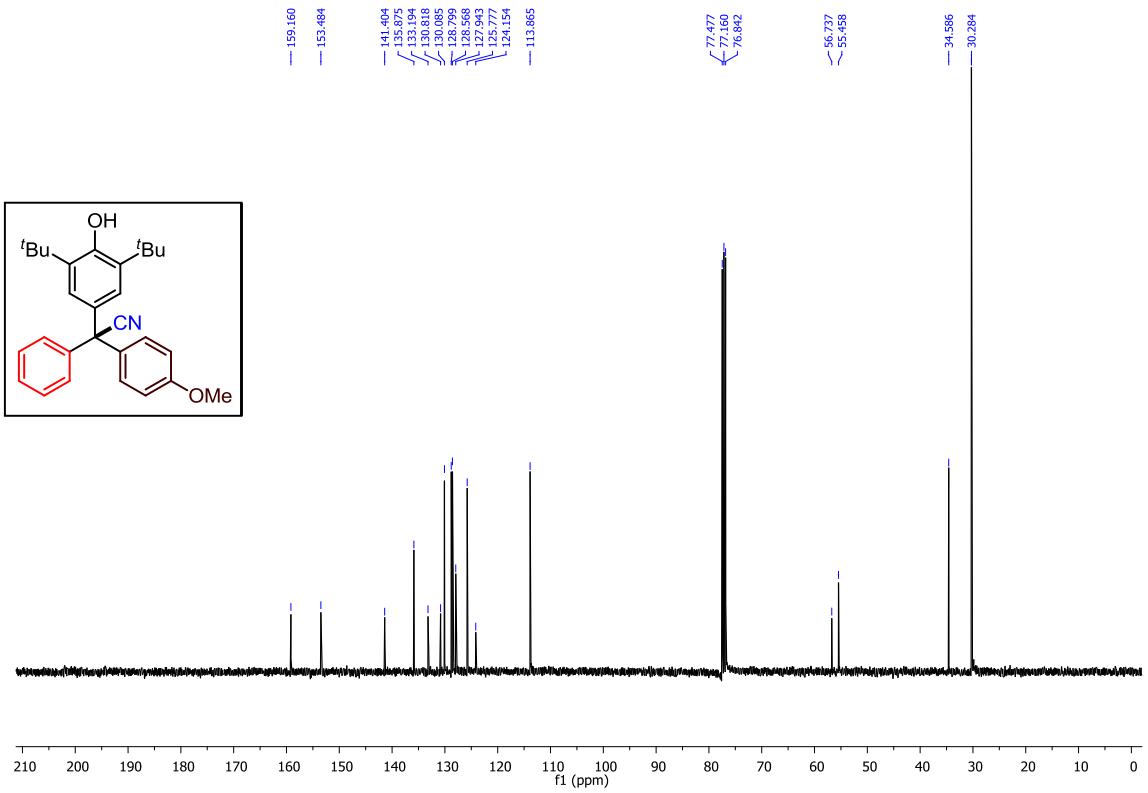
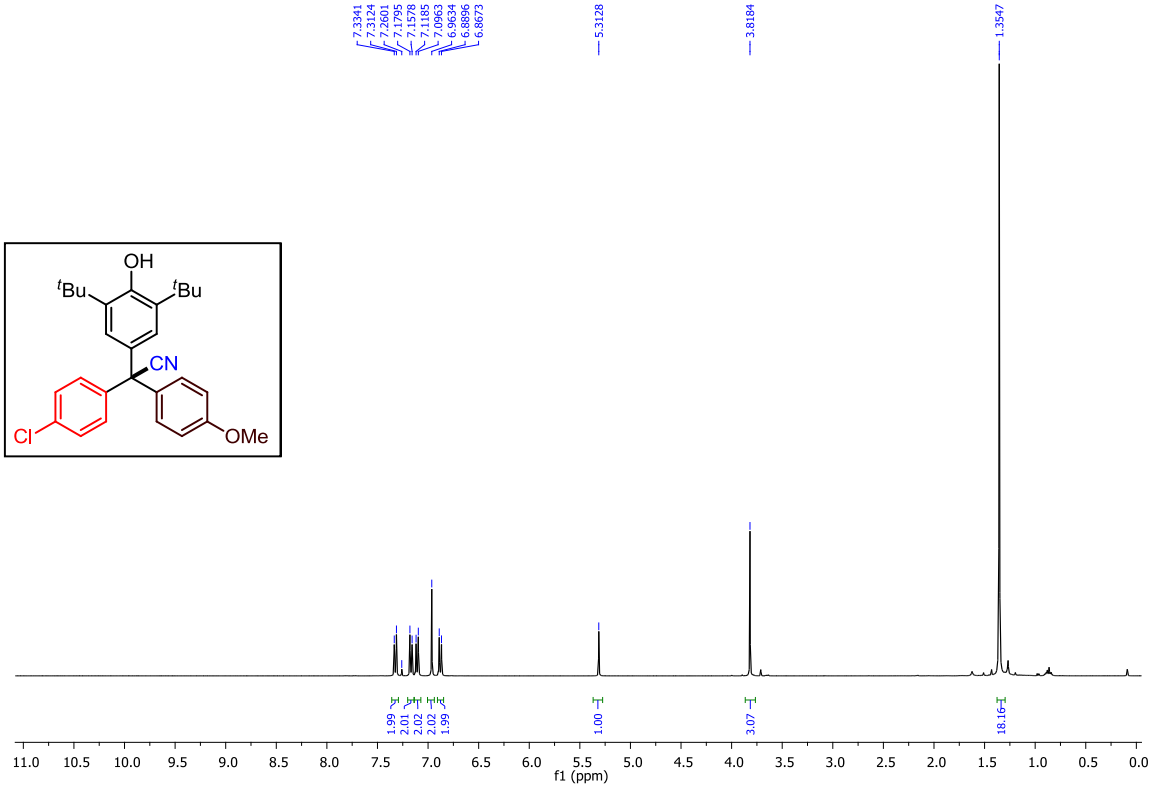


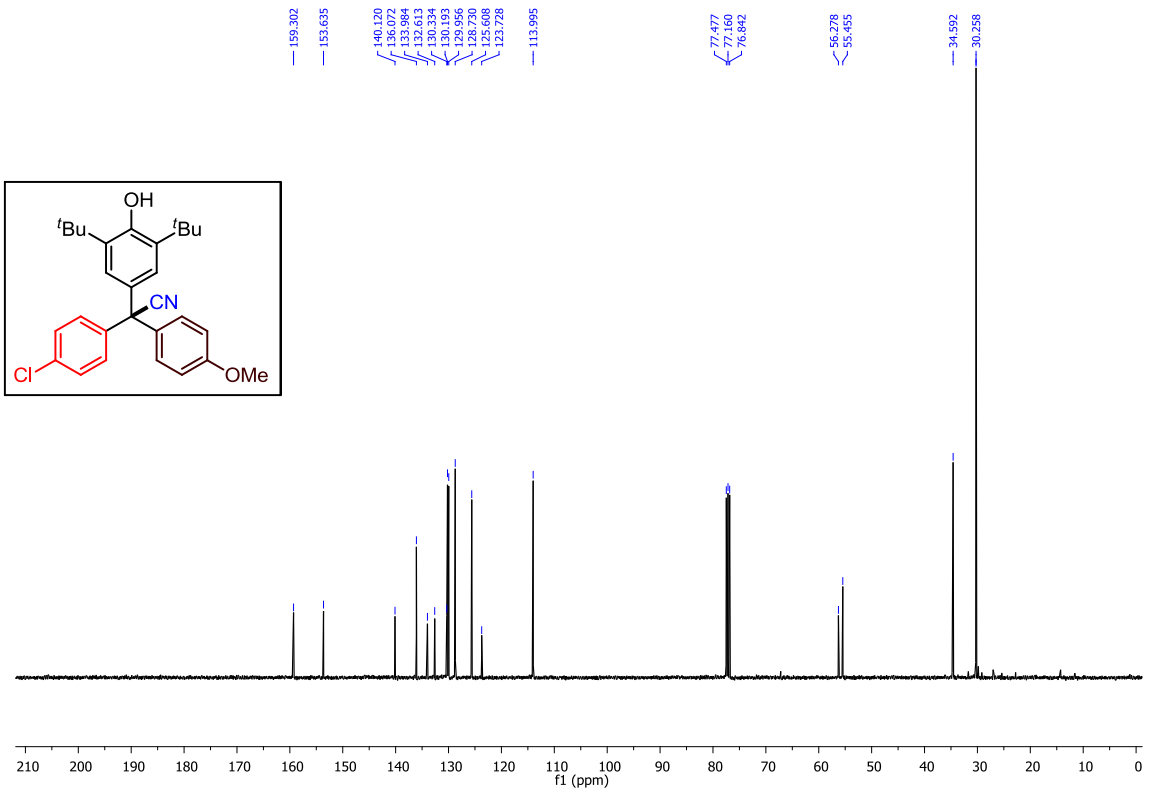
^{13}C NMR spectrum of **92c**



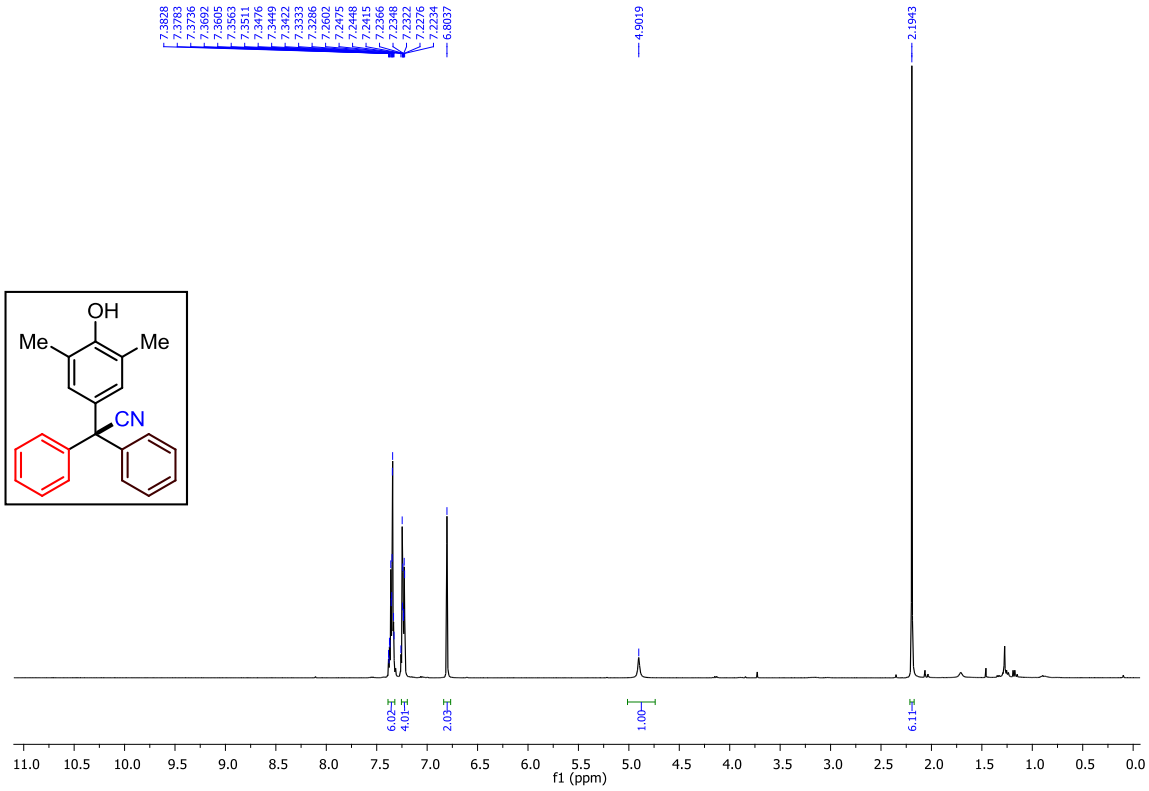
^{1}H NMR spectrum of **92e**



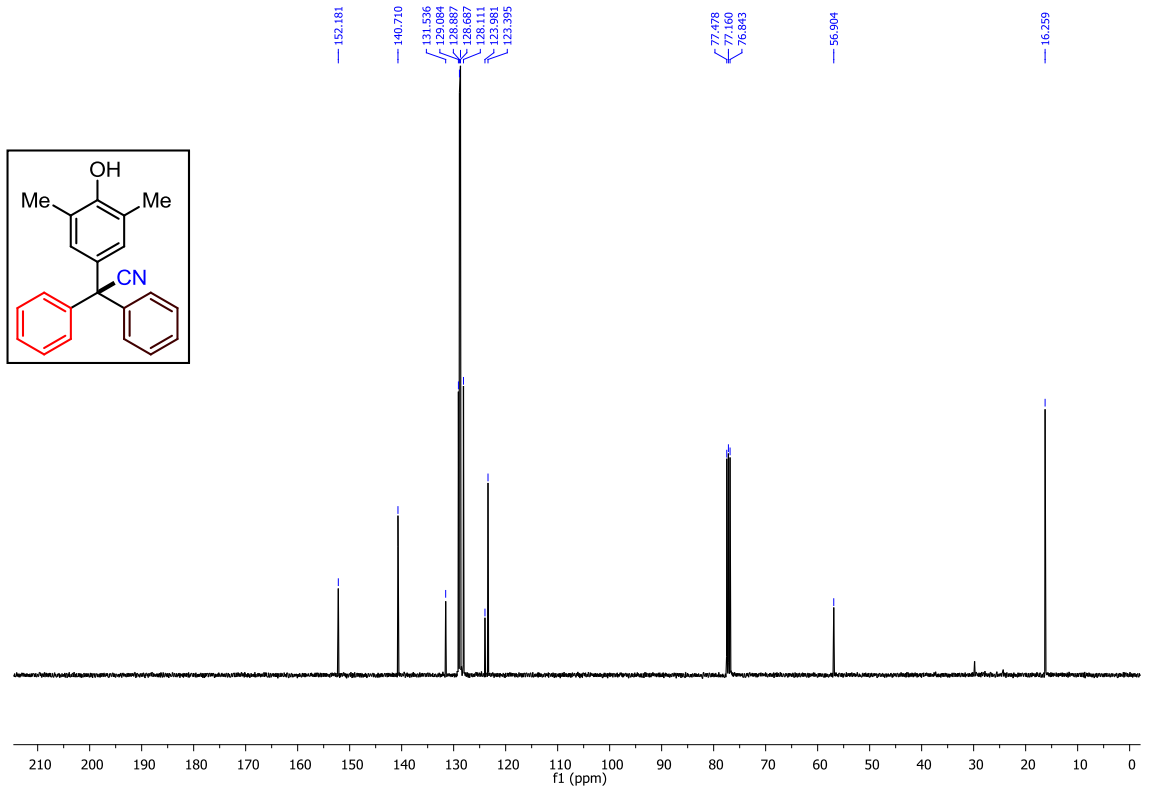
^{13}C NMR spectrum of **92e**



^{1}H NMR spectrum of **92f**



^{13}C NMR spectrum of **92f**



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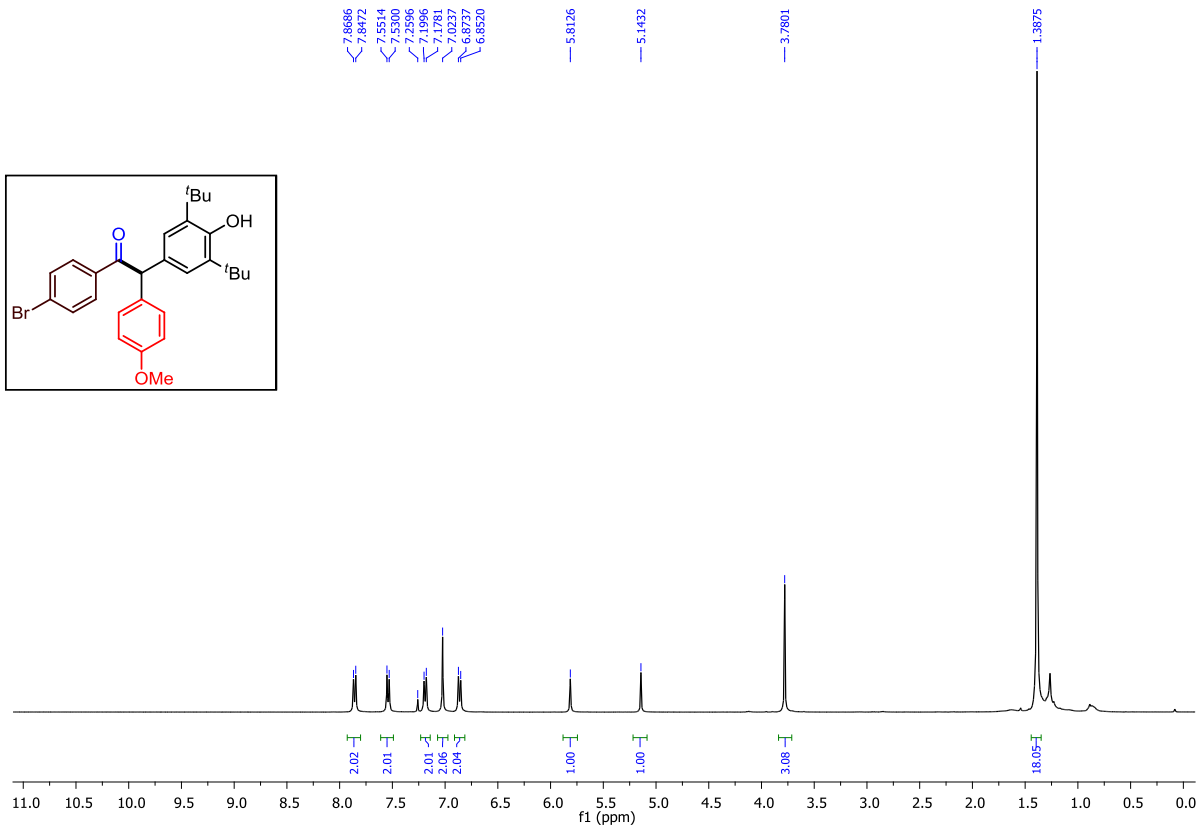

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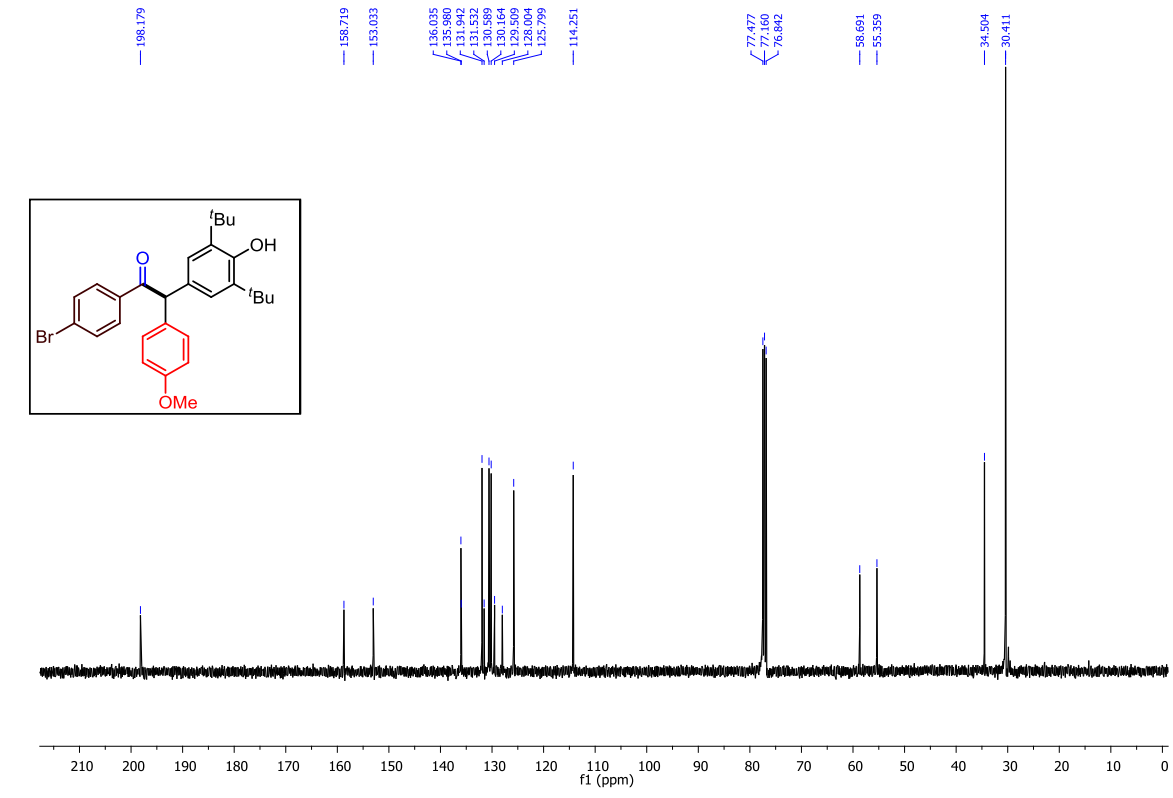

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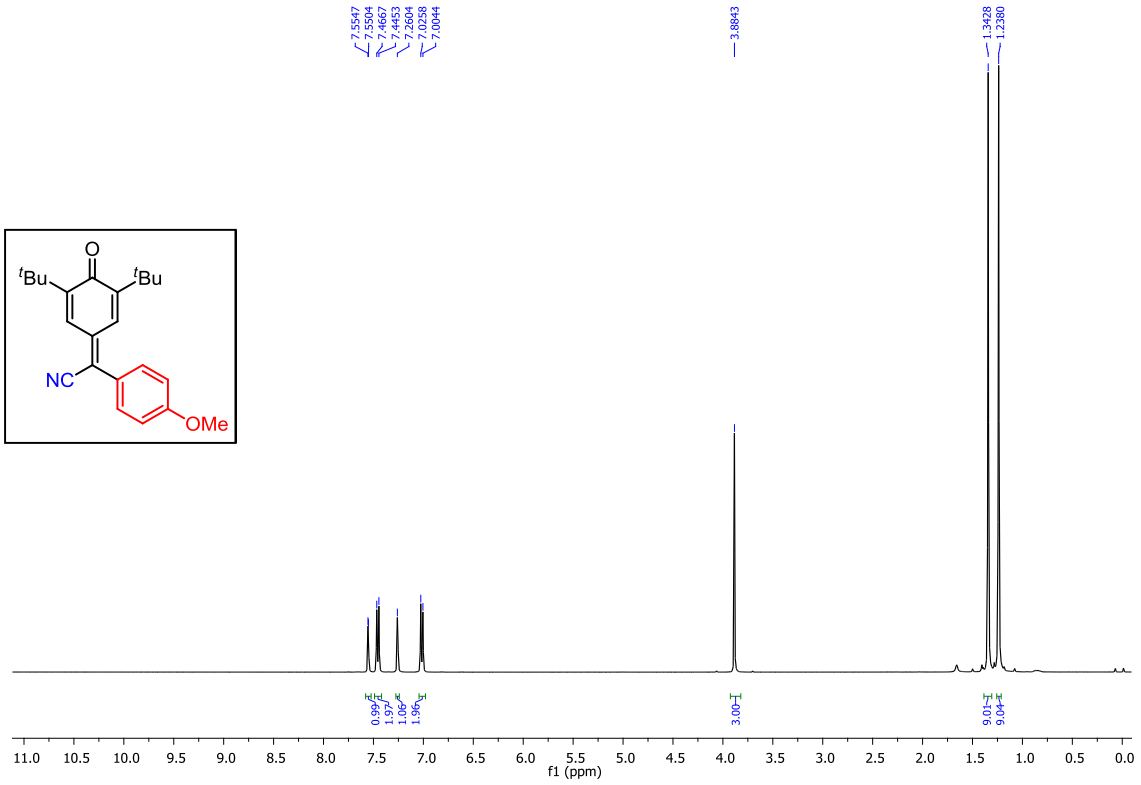

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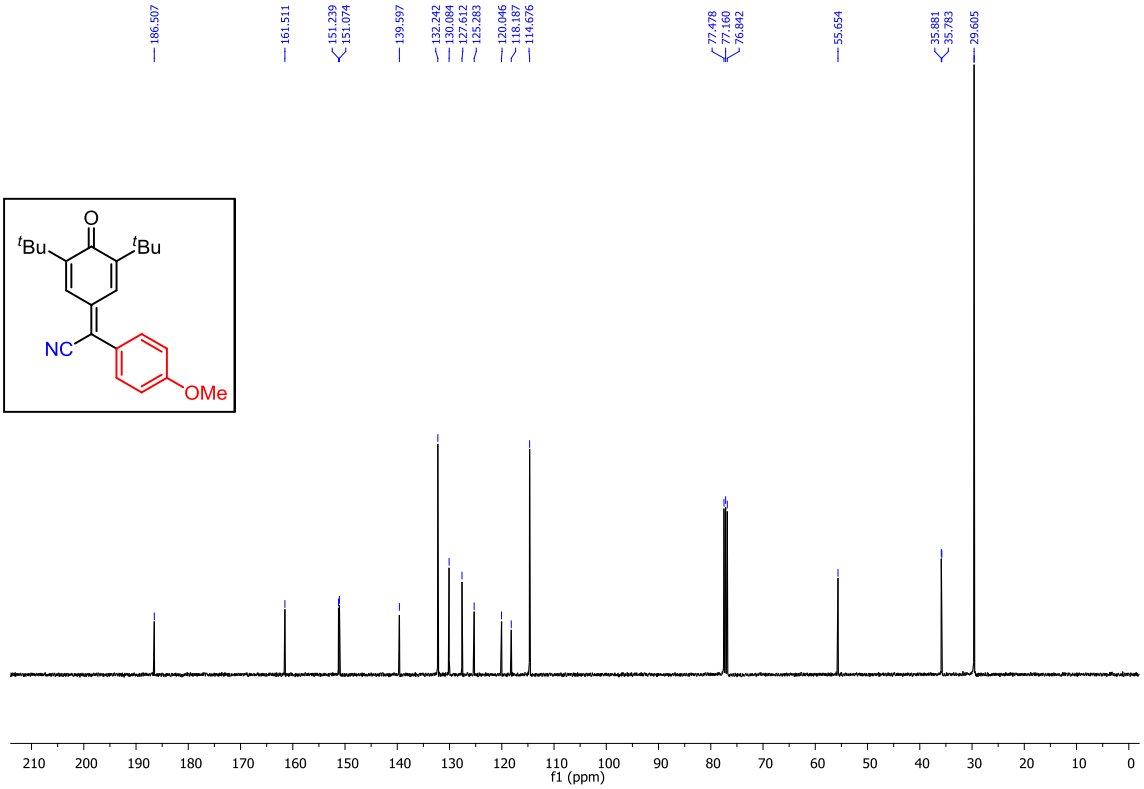

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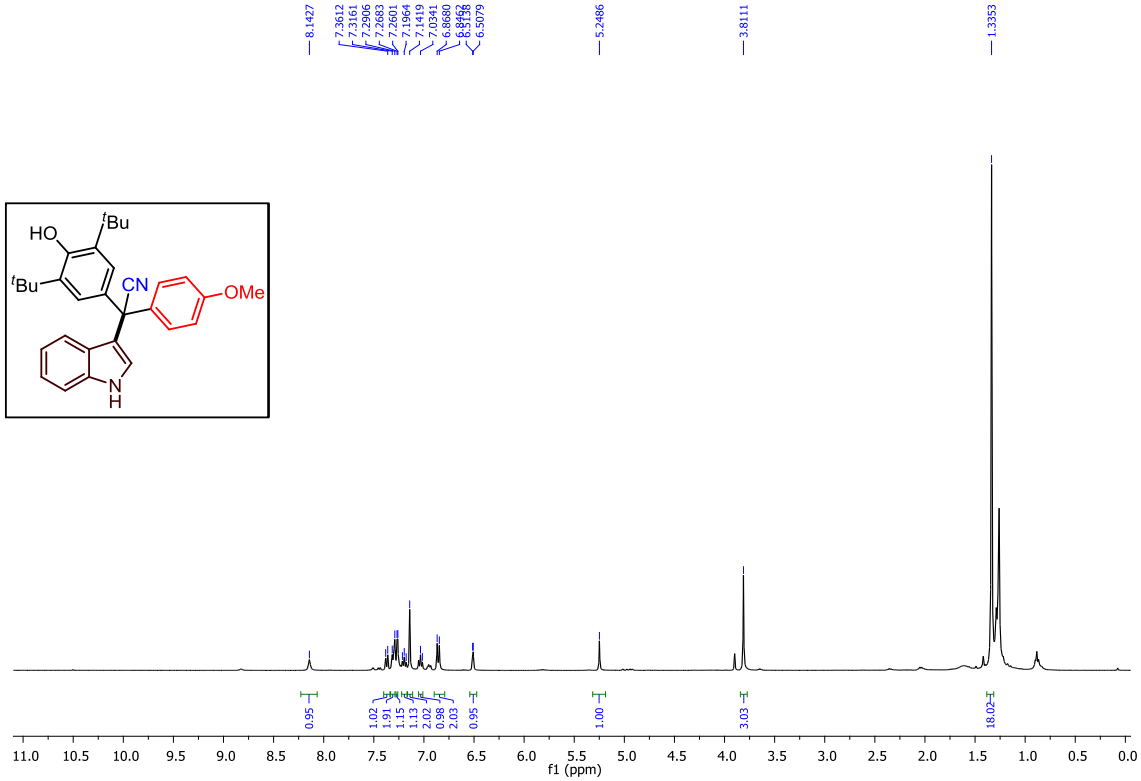

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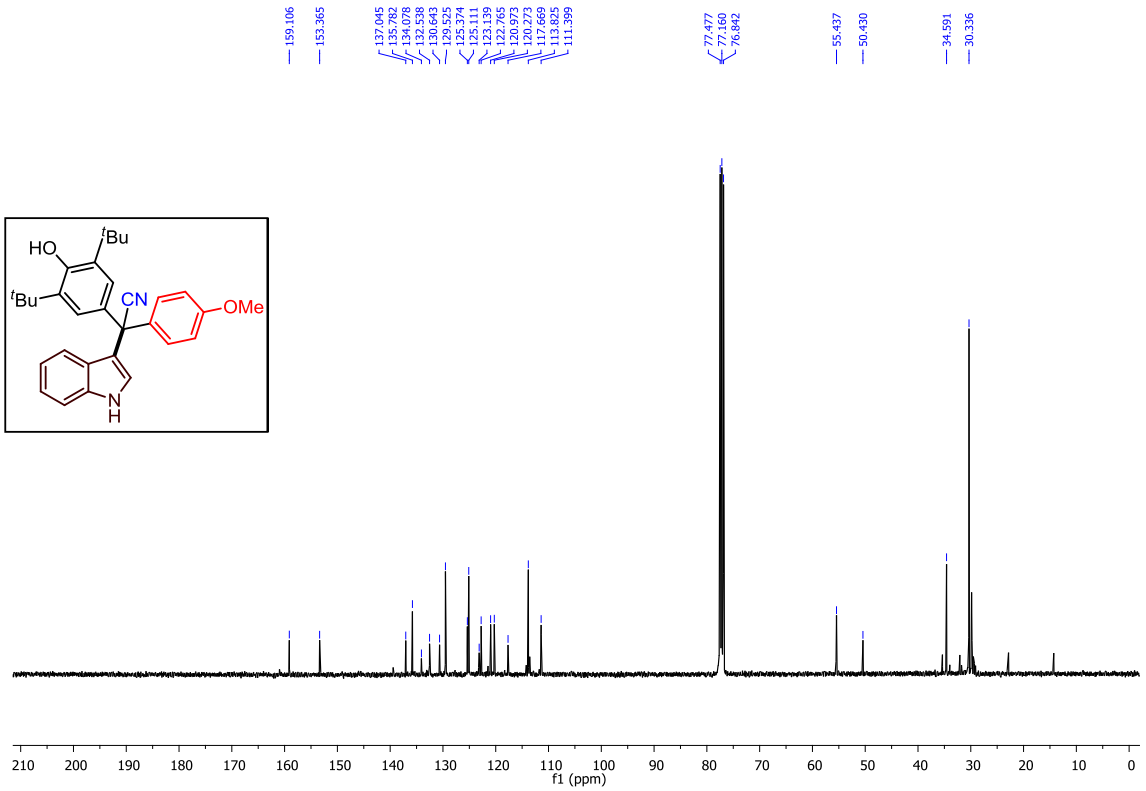

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Chapter 2

2. Bis-(amino)cyclopropenylidene catalyzed Rauhut–Currier reaction between *α,β*-unsaturated carbonyl compounds and *para*-quinone methides

This chapter describes a straight-forward organocatalytic approach for the vinylogous Rauhut–Currier reaction between *α,β*-unsaturated carbonyl compounds and *para*-quinone methides. This chapter also includes a literature review on bis-(amino)cyclopropenylidenes (BACs) and vinylogous Rauhut-Currier reaction.

2.1 Introduction on Bis-(amino)cyclopropenylidenes (BACs)

Recently, nucleophilic carbene catalysis implies as a powerful synthetic tool for many organic transformations.[1] Especially, *N*-Heterocyclic carbene catalysis became highly valuable for the construction of different carbon-carbon as well as carbon-heteroatom bond in organic transformations.[2] In recent years, apart from NHCs, other non-heterocyclic based carbenes have drawn significant interest by many research groups. In this context, bis-(amino)cyclopropenylidenes (BACs), derived from cyclopropenium salts have gained some attention due to its unique reactivity towards carbonyl compounds. The stability of BAC is attributed to the σ-aromaticity of the cyclopropene ring and the push-pull effect of the two amino groups present in the ring.[3] BAC displays extremely strong σ-donor ability and parallel π-acceptor ability like NHCs.[4] Yoshida and Weiss groups independently reported the synthesis and structural properties of bis-(amino)cyclopropenylidene salts in late 1970s.[5] At that point of time, the application of bis-(amino)cyclopropenylidene was limited only to the organometallic chemistry.[6]

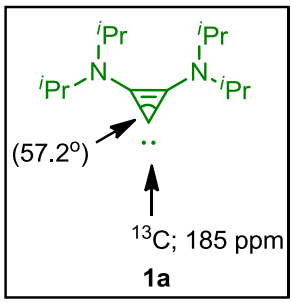


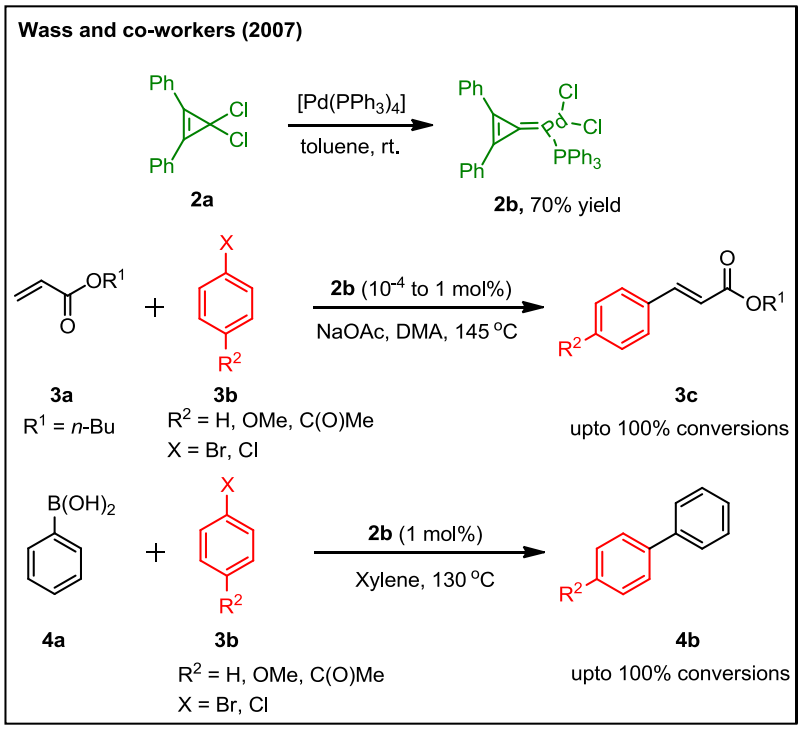
Figure 1: Free bis-(diisopropylamino)cyclopropenylidene **1a**

However, the chemistry of bis-(amino)cyclopropenylidene attained great consideration after the pioneering work by Bertrand and co-workers in 2006.[7] Bertrand's group isolated the free bis-(diisopropylamino)cyclopropenylidene (**1a**, Figure 1) in stable form and the structure of **1a** was unambiguously confirmed by X-ray and NMR analysis. Interestingly, the carbene bond angle was found to be 57.2°.

2.2 Literature reports on bis-(amino)cyclopropenylidene (BAC)-catalyzed transformations

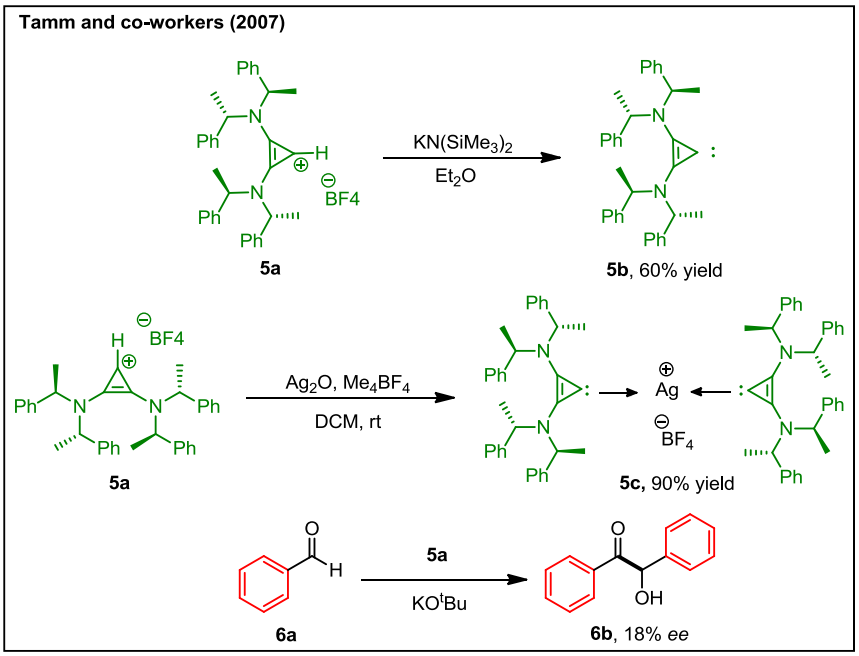
2.2.1 Applications of cyclopropenylidenes and bis-(amino)cyclopropenylidenes as ligands in organometallic chemistry

Wass and co-workers described a palladium-cyclopropenylidene complex catalyzed Heck and Suzuki coupling reactions.[8] The Pd-cyclopropenylidene complex (**2b**) was generated by the reaction of 1,1-dichloro-2,3-diphenylcyclopropene (**2a**) and $Pd(PPh_3)_4$. The catalytic activity of the Pd-complex (**2b**) was further investigated for the Heck and Suzuki cross coupling reactions of aryl halides. It was found that all the reactions underwent smoothly at very low catalyst loading (10^{-4} to 1 mol %) and, in most of the cases, almost 100% conversions were observed (Scheme 1).



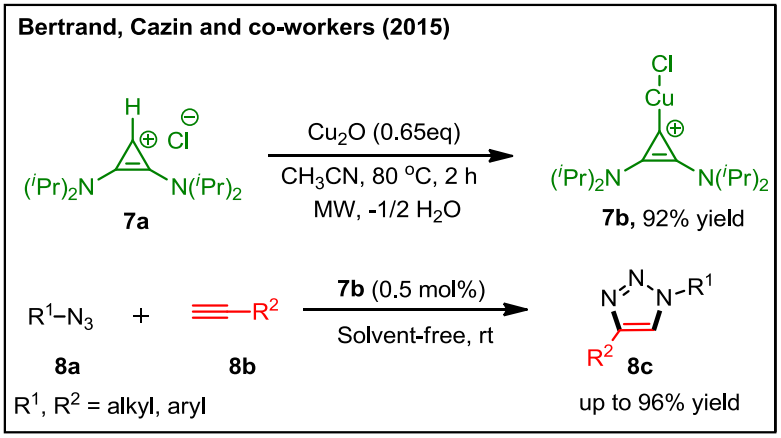
Scheme 1: Pd-cyclopropenylidene complex catalyzed Heck and Suzuki cross coupling reactions

Tamm and co-workers isolated the free chiral carbene bis[bis(*R*-1-phenylethyl)amino]cyclopropenylidene (**5b**) and its dicarbene-silver-complex (**5c**) for the first time.[9] Free chiral carbene (**5b**) was generated in 60% isolated yield after the deprotonation of chiral cyclopropenylium salt (**5a**) with $KN(SiMe_3)_2$. Further, the chiral cyclopropenylium salt (**5a**) was reacted with Ag_2O in the presence of catalytic amount of Me_4BF_4 and the chiral dicarbene-silver-complex (**5c**) was obtained in 90% yield. Later, this novel chiral cyclopropenylium salt (**5a**) was tested for the asymmetric benzoin condensation reaction of benzaldehyde (**6a**). Unfortunately, in this case, the respective benzoin (**6b**) was obtained only in 18% *ee* (Scheme 2).



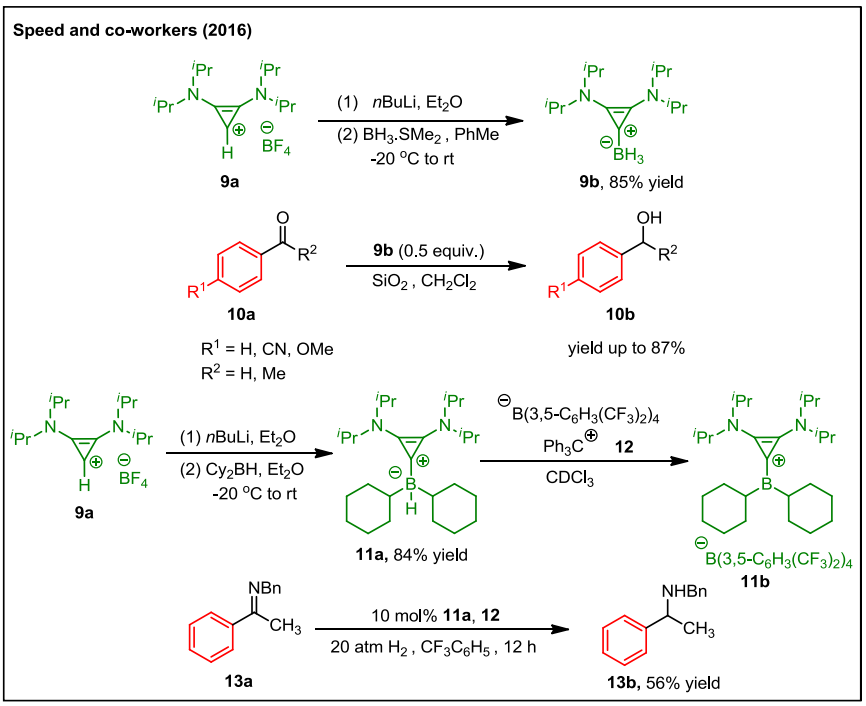
Scheme 2: Synthesis of chiral diaminocyclopropenylidene and its silver complex

Bertrand, Cazin and co-workers reported a first example of BAC-Cu^I complex.[10] Diisopropylcyclopropenium chloride (**7a**) was treated with Cu_2O under microwave condition to get the [CuCl(BAC)] complex (**7b**) in 92% yield. After the synthesis of BAC-Cu^I complex, the catalytic activity of **7b** was examined for the "Click reaction" of terminal alkynes and azides. A variety of alkynes (**8b**) underwent [3+2] cycloaddition reaction with azides (**8a**) in the presence of 0.5 mol% of [CuCl(BAC)] complex (**7b**) and, in all the cases, the resultant 1,2,3-triazole derivatives (**8c**) were isolated in excellent yields. Mild reaction conditions (room temperature and solvent-free) and low catalyst loading are the key features of this reaction (Scheme 3).



Scheme 3: [CuCl(BAC)] complex catalyzed "Click reaction" of alkynes and azides

Speed and co-workers discovered a neutral borane-bis(amino)cyclopropenylidene carbene adduct for the first time.[11] Diisopropylcyclopropenium tetrafluoroborate salt (**9a**) was treated with butyllithium and borane dimethyl sulphide to get the corresponding BAC carbene-borane adduct (**9b**) in 85% yield. This adduct (**9b**) was found to be bench stable. The application of the carbene-borane adduct was evaluated for the reduction of carbonyl compounds.



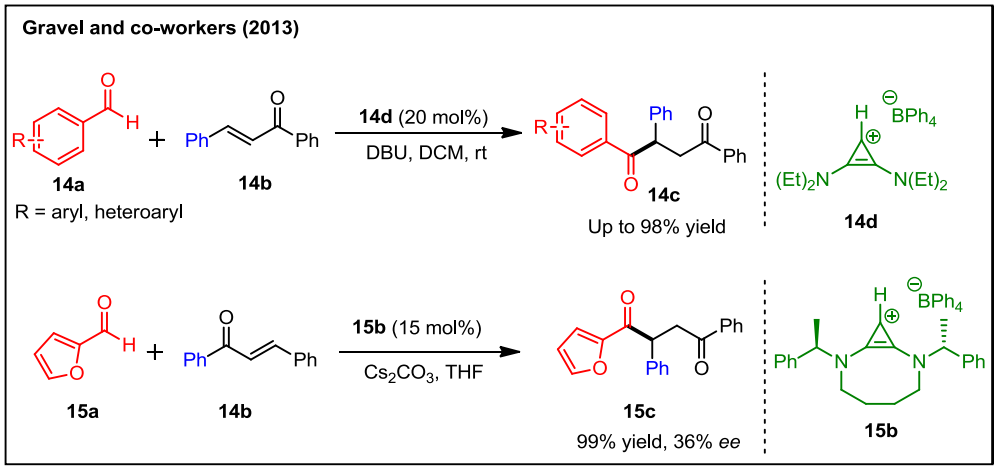
Scheme 4: Synthesis of BAC-borane complex

It was found that 0.5 equiv. of **9b** failed to reduce the carbonyl compounds (**10a**). However, the mixture of **9b** and silica gel were capable to reduce the carbonyl compounds. Later, the

concept was extended for the synthesis of bis(diisopropylamino)cyclopropenylidene-dicyclohexylborane adduct (**11a**). The combination of **11a** and trityl tetrakis[3,5-(trifluoromethyl)phenyl]borate **12** was found to catalyze the reduction of benzyl imines (**13a**). The combination of **11a** and **12** resulted in the formation of borenium carbocation intermediate **11b**, which was identified by ^{11}B NMR analysis. The authors have explained that this in situ formed borenium carbocation **11b** is actually responsible for the catalytic reduction of benzyl imines (Scheme 4).

2.2.2 Bis-(amino)cyclopropenylidene (BAC) catalyzed synthetic transformations

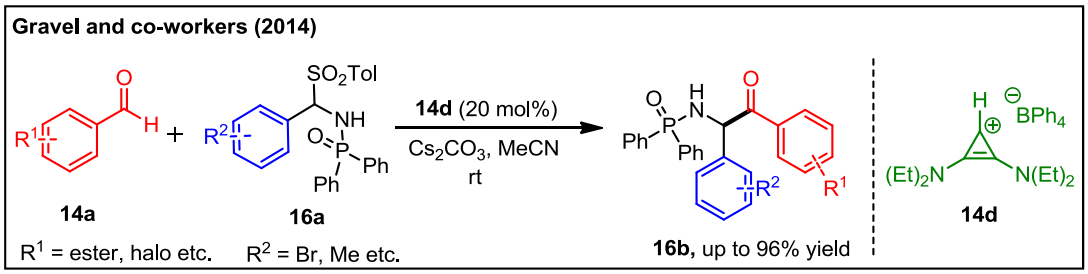
In 2013, Gravel and co-workers reported a BAC-catalyzed highly chemoselective Stetter reaction.[12] A variety of aromatic aldehydes (**14a**) were treated with chalcones (**14b**) in presence of 20 mol% of BAC precursor (**14d**) and, almost in all the cases, the corresponding products (**14c**) were isolated in good to excellent yields. It is noteworthy to mention that the formation of competing benzoin dimerized product was not observed in any of the BAC catalyzed reactions. In one of the experiments, chiral BAC precatalyst (**15b**) was utilized for the enantioselective Stetter reaction between furfural (**15a**) and chalcone (**14b**). However, although the product (**15c**) was obtained in 99% yield, the enantioselectivity was found to be very low [36% *ee*] (Scheme 5).



Scheme 5: BAC catalyzed Stetter reaction

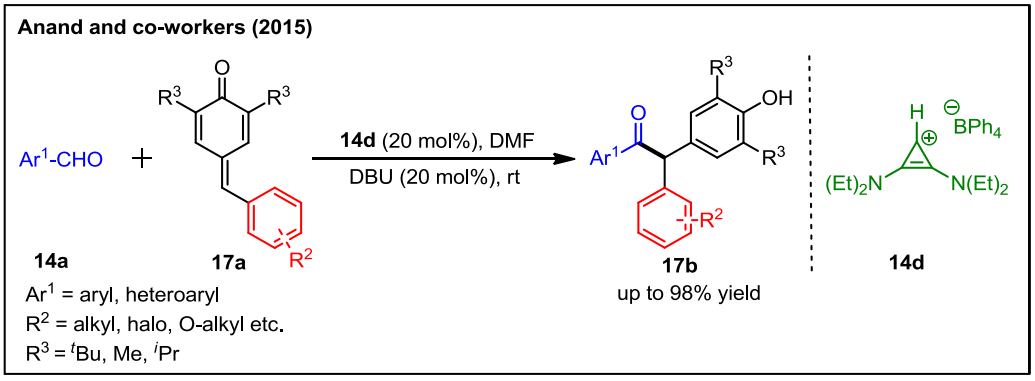
Later in 2014, Gravel's group also demonstrated an aza-benzoin reaction between aromatic aldehydes and imines using BAC as an organocatalyst.[13] A wide range of aromatic aldehydes (**14a**) and phosphinoyl imines (**16a**) were reacted at room temperature in presence of 20 mol% BAC (**14d**) to afford the resultant chemoselective cross aza-benzoin adducts

(**16b**) in moderate to good yields. Interestingly, the formation of homobenzoin adducts was not observed under the reaction conditions (Scheme 6).



Scheme 6: BAC catalyzed aza-benzoin reaction

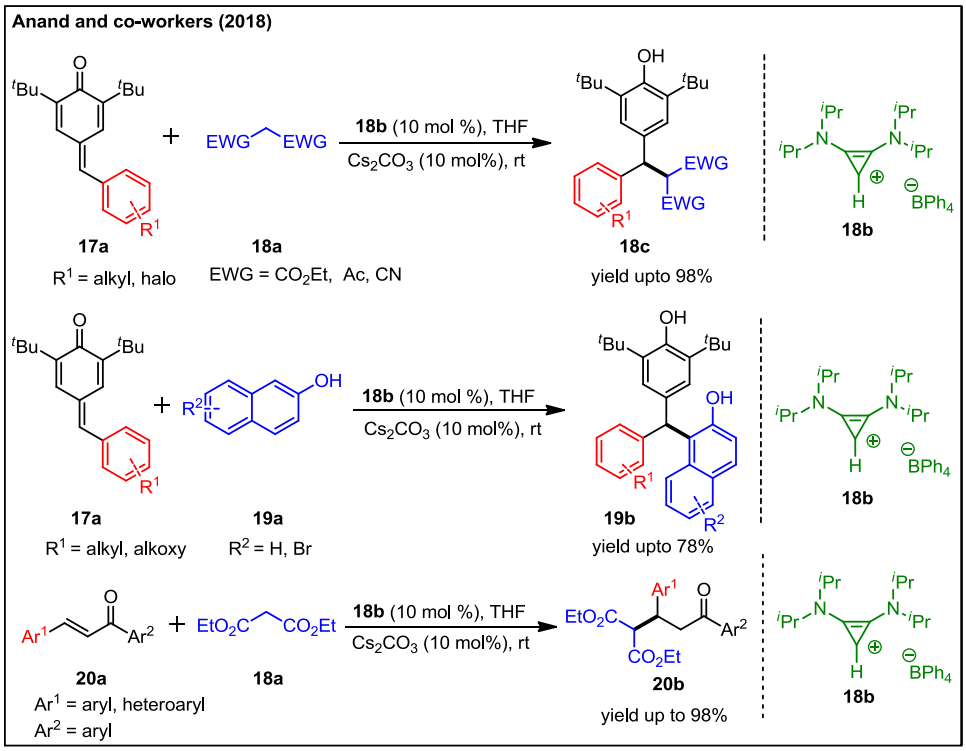
Later, Anand and co-workers accomplished an efficient method for the synthesis of *α,α′*-diarylated ketones through the 1,6-conjugate addition of aromatic aldehydes and *p*-QMs using BAC as an organocatalyst.[14] The scope of various aromatic as well as heteroaroamtic aldehydes (**14a**) were examined for the vinylogous Stetter reaction under the optimized conditions. In case of electron-rich aromatic aldehydes, the reaction was found to be very sluggish as the respective products were obtained in poor yields. However electron-poor and heteroaromatic aldehydes furnished the resultant products in good to excellent yields. Notably, most of the *p*-QMs (**17a**) derived from electron-rich as well as sterically hindered aromatic aldehydes reacted smoothly and the corresponding *α,α′*-diarylated ketones (**17b**) were obtained in high yields. The extremely mild reaction condition, excellent functional groups tolerance and 100% atom-economy are the salient features of this transformation (Scheme 7).



Scheme 7: BAC catalyzed vinylogous stetter reaction of *p*-QMs and aromatic aldehydes

Very recently, Anand and co-workers utilized BAC as a non-covalent Brønsted base catalyst for the 1,6-conjugate addition of carbon nucleophiles to enones and *p*-QMs.[15] This is

the first time that BAC has been utilized as a Brønsted base catalyst. A broad range of *p*-QMs (**17a**) were treated with different active methylene compounds (**18a**) in presence of 10 mol% BAC pre-catalyst (**18b**) and, the resultant 1,6-conjugate adducts (**18c**) were isolated in excellent yields. Further, to expand the substrate scope, 1,6-conjugate addition of 2-naphthols (**19a**) to different *p*-QMs (**17a**) was also examined and, in those cases, the unsymmetrical triaylmethanes (**19b**) were produced in good yields. The concept of this methodology was further extended for the 1,4-conjugate addition of diethyl malonate (**18a**) to different chalcone derivatives (**20a**) and the corresponding 1,4-adducts (**20b**) were obtained in excellent yields (Scheme 8).



Scheme 8: BAC as Brønsted base catalyst for the conjugate addition reactions

2.3 Literature review on vinylogous Rauhut-Currier reaction

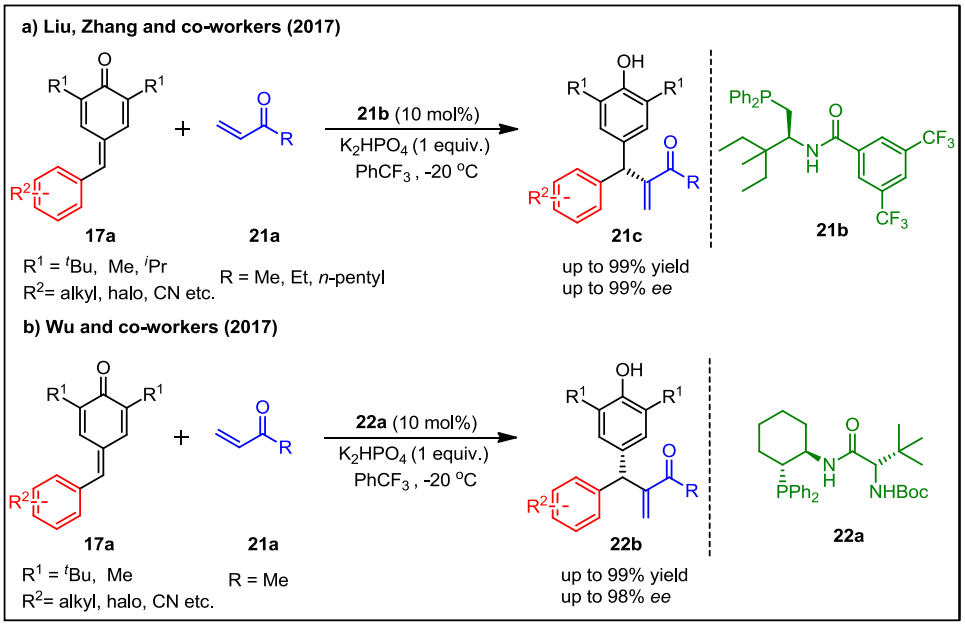
2.3.1 Introduction

The Rauhat-Currier (R-C) reaction,[16] also recognized as vinylogous Morita-Baylis-Hillman reaction, is unquestionably referred as one of the atom-economical and most powerful practical methods to build carbon-carbon bonds in complex molecules.[17] R-C reaction narrates the coupling between two electron deficient olefins. Due to the wide-spread applications, the R-C reaction gained tremendous attention from different research groups. In

this regard, the intramolecular R-C reaction has appeared as the most popular and well explored approach to construct densely functionalized carbocylic molecules.[18] On the other hand, intermolecular R-C reactions[19] are relatively limited due to lack of substrate scope and chemoselectivity issues. It is known that electron deficient olefins can dimerize under the intermolecular R-C reaction condition leading to the formation of homo-dimerized as well as hetero-dimerized R-C adducts. Therefore, the formation of highly chemoselective hetero-dimerized R-C adducts over other products becomes a main concern. The situation is more difficult in the case of intermolecular vinylogous R-C reaction (i.e. the reaction between 1,4-enone with 1,6-dienone) as additional chemo-selectivity issues will come up due to 1,4- and 1,6-reactivity of the 1,6-dienone. Therefore, controlling the reactivity of 1,4-enone as well as 1,6-dienone to get the desired product in a highly chemo-selective manner is a monumental task. Surprisingly, despite the above-mentioned issues, some reports are available for the intramolecular as well as intermolecular vinylogous R-C reactions. A few of them are discussed below.

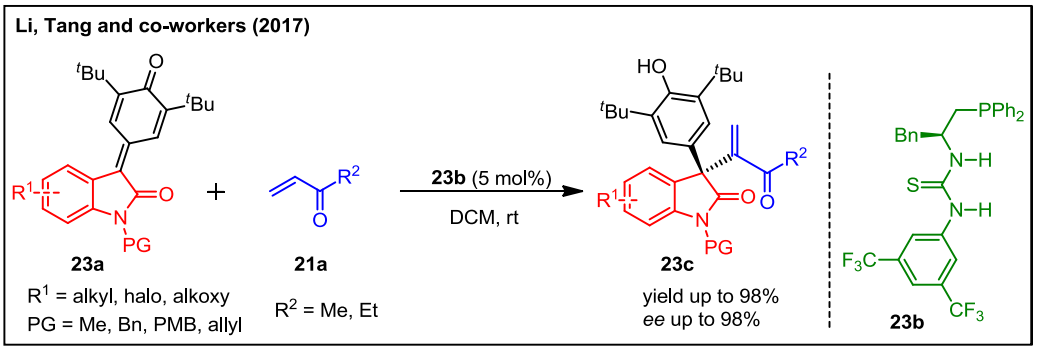
2.3.2 Literature reports on vinylogous Rauhut-Currier reactions

Liu, Zhang and co-workers described a chiral phosphine catalyzed enantioselective intermolecular cross-vinylogous Rauhut-Currier reaction of vinyl ketones and *para*-quinone methides.[20] This is the first report on the enantioselective vinylogous Rauhut-Currier reaction to an extended conjugated system. A variety of chiral amide-phosphine bifunctional catalysts were prepared and their catalytic activity was further examined. A wide range of *p*-QMs (**17a**) and alkyl vinyl ketones (**21a**) were reacted in presence of 10 mol% of chiral phosphine catalyst (**21b**) and the 1,6- conjugate addition products (**21c**) were observed in very high yields with very high *ee* (up to 99% yield and 99% *ee*). The reaction mechanism and the transition states for the enantioselective pathway were further investigated through DFT calculations (a, Scheme 9). At the same time, Wu and co-workers reported the similar type of methodology using chiral phosphine-amide catalyst.[21] All the *p*-QMs (**17a**) used in this transformation reacted efficiently with methyl vinyl ketone (**21a**) and the subsequent products (**22b**) were obtained in excellent yields and *ee*. Unfortunately other vinyl ketones did not react under the optimized conditions. Interestingly, the interaction between phosphine-amide catalyst and MVK was proved by ^{31}P NMR spectroscopic analysis (b, Scheme 9).



Scheme 9: Asymmetric intermolecular vinylogous R-C reaction of vinyl ketones and *p*-QMs

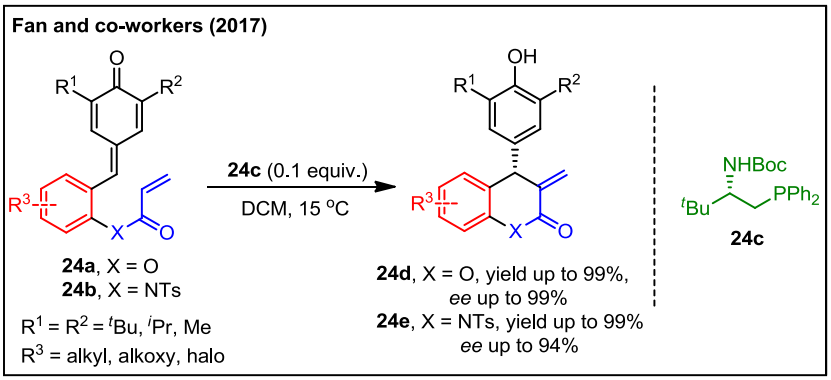
Li, Tang and co-workers developed a bifunctional phosphine catalyzed cross vinylogous Rauhat-Currier reaction of isatins derived *p*-QMs and vinyl ketones.[22] This method provides an easy route for the synthesis of 3,3-disubstituted oxindoles. An array of isatins derived *p*-QMs (**23a**) was reacted with aliphatic vinyl ketones (**21a**) in presence of chiral bifunctional phosphine (**23b**). In all the cases, the corresponding 3,3-disubstituted oxindoles (**23c**) were furnished in excellent yields and enantioselectivities (Scheme 10).



Scheme 10: Asymmetric intermolecular vinylogous R-C reaction of vinyl ketones and isatins derived *p*-QMs

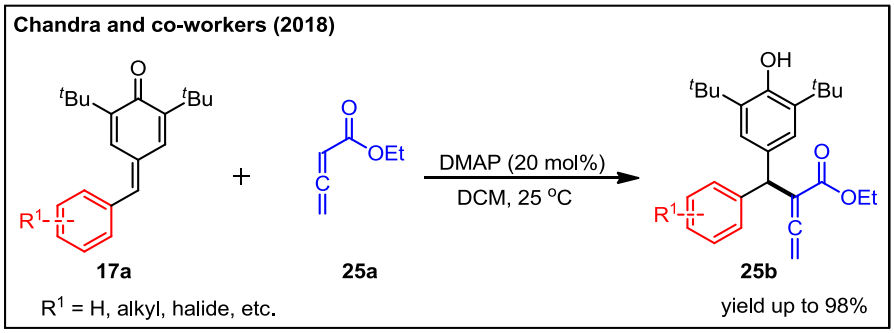
Recently Fan's group disclosed a chiral-bifunctional phosphine catalyzed intramolecular vinylogous Rauhut-Currier reaction of *p*-QMs.[23] An amino acid derived chiral phosphine (**24c**) was utilized as catalyst for this transformation. A wide range of *p*-QM esters (**24a**) and *p*-QM amides (**24b**) were reacted in the presence of chiral phosphine catalyst (**24c**)

to provide 4-aryl hydrocoumarins (**24d**) and 4-aryl hydroquinolin-2-ones (**24e**), respectively in excellent yields and enantioselectivities (Scheme 11).



Scheme 11: Asymmetric intramolecular vinylogous R-C reaction *p*-QMs

Chandra and co-workers reported DMAP catalyzed vinylogous Rauhut-Currier reaction of *p*-QMs and allenoates.[24] When *p*-QMs (**17a**) were reacted with 2,3-butadienoates (**25a**) in presence of 20 mol% of DMAP, the resultant vinylogous R-C adducts (**25b**) were obtained in high to excellent yields. Electron-donating and halo-substituted *p*-QMs underwent smooth transformation. But, surprisingly, the electron-poor *p*-QMs failed to react under the reaction conditions. Unfortunately, the substrate scope in case of allenoates was limited to only ethyl 2,3-butadienoate (Scheme 12).



Scheme 12: Intramolecular vinylogous R-C reaction *p*-QMs with allenoates

2.4 Background

Although the above-mentioned vinylogous R-C reactions are elegant, most of them involve phosphine catalysis. Interestingly, the nucleophilic carbene catalysis for this kind transformation remains unexplored. While developing new synthetic approach using *p*-quinone methides (*p*-QMs) as 1,6-acceptors, we envisioned that it is possible to perform the

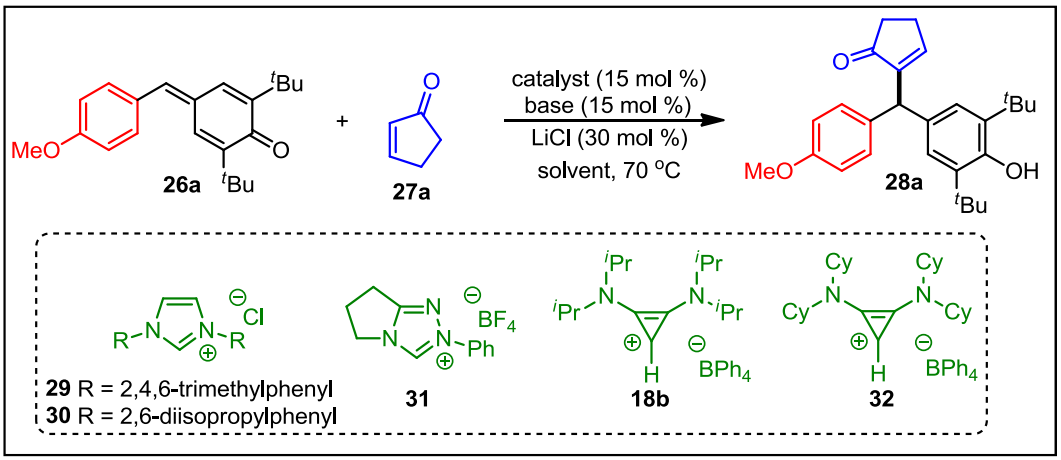
R-C reaction between 1,4-enones with *p*-QMs using BAC as organocatalyst. Since the catalytic application of BAC is still under explored, we thought of investigating whether BAC could be utilized as a catalyst for this transformation or not.

2.5 Results and Discussions

The optimization studies for the reaction between *p*-QM (**26a**) and 2-cyclopentenone (**27a**) were carried out under various conditions using a wide range of NHC (**29**-**31**) and BAC (**18b** & **32**) precursors (Table 1). The initial experiments were carried out using NHC precursors (**29**-**31**) in DMF at room temperature. In those experiments, 15 mol% DBU was utilized for the generation of free NHC. However, in all those cases, the expected R-C adduct **28a** was not observed (entries 1-3). The use of bis-(diisopropylamino)cyclopropenylidene precursor **18b** did not help as no reaction was observed when the reaction was carried in DMF at room temperature (entry 4). However, when the reaction was performed in presence of **29** as a catalyst using 30 mol% of LiCl as an additive at room temperature, a trace amount of product formation was observed (entry 5). Delightfully, when the reaction was carried out at 70 ^{o}C in presence of **29** as a catalyst precursor and 30 mol% LiCl as an additive, the expected R-C adduct **28a** was obtained in 55% yield in 36 h (entry 6). With this encouraging result in hand, the catalyst screening was investigated in DMF solvent at 70 ^{o}C. It was found that the other NHC catalysts, derived from their corresponding precursors (**30** & **31**), were not beneficial in this reaction as the corresponding R-C adduct **28a** was observed only in 55 and 58% respectively (entries 7 & 8). Gratifyingly, when BAC precursor **18b** was used as a catalyst, **28a** was isolated in 90% yield (entry 9). Bis-(dicyclohexylamino)cyclopropenylidene precursor (**32**) was found to be less superior than BAC precursor **18b** to catalyze the transformation as **28a** was obtained only in 75% isolated yield (entry 10). Further screening of solvents revealed that THF and toluene were not appropriate to drive the reaction as no product was detected in both the cases (entry 11 & 12). When DMSO was used as solvent, the R-C adduct (**28a**) was produced only in 75% yield after 24 h (entry 13). Other inorganic bases such as sodium hydride, cesium carbonate and potassium carbonate led to the formation of the R-C adduct **28a** in lower yields (entries 14-16). These observations clearly show that DMF is the suitable solvent and DBU is the best base for this transformation. It is noteworthy to mention that no product was detected in the absence of carbene precursor, which demonstrates the requirement of carbene catalyst in this

transformation (entry 17). Moreover, the reaction did not work in the absence of base (entry 18).

Table 1. Catalyst screen and optimization[a]

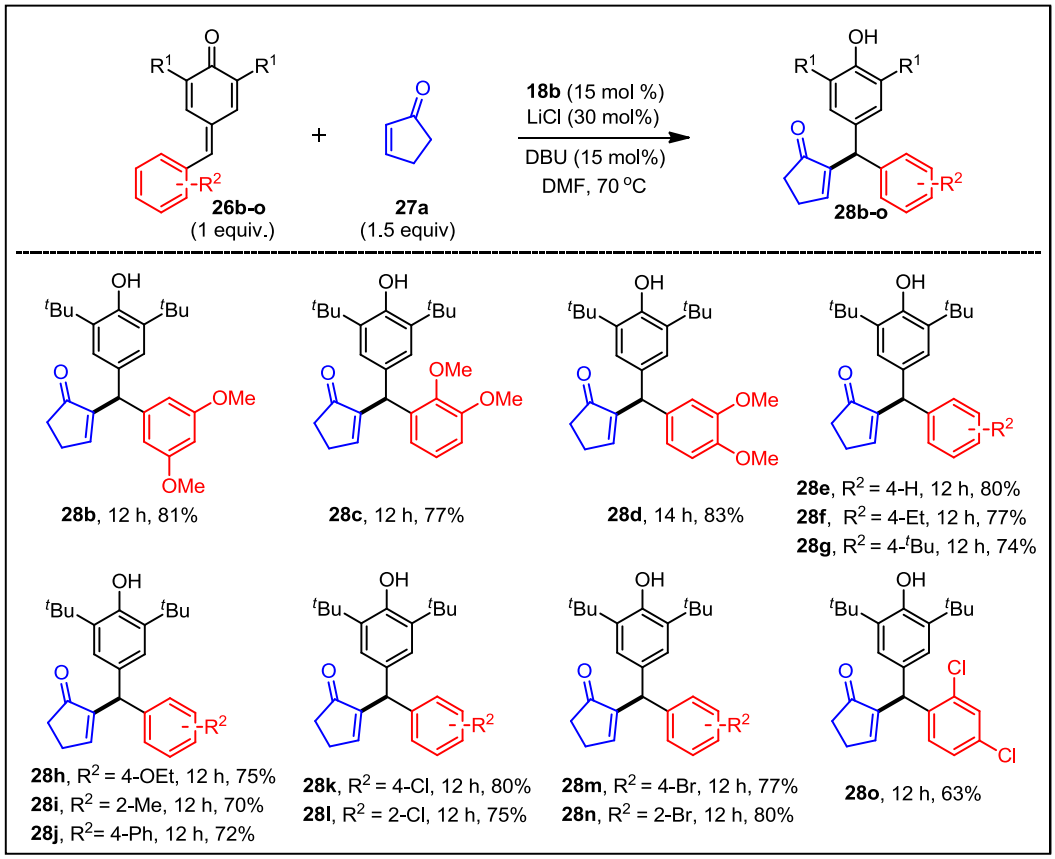


entry	catalyst	solvent	base	time (h)	yield (%)
1[b]	**29**	DMF	DBU	48	nr
2[b]	**30**	DMF	DBU	48	nr
3[b]	**31**	DMF	DBU	48	nr
4[b]	**18b**	DMF	DBU	48	nr
5	**29**	DMF	DBU	48	<10
6	**29**	DMF	DBU	36	55
7	**30**	DMF	DBU	36	55
8	**31**	DMF	DBU	36	58
9	**18b**	**DMF**	**DBU**	**12**	**90**
10	**32**	DMF	DBU	24	75
11	**18b**	THF	DBU	24	nr
12	**18b**	PhMe	DBU	24	nr
13	**18b**	DMSO	DBU	24	75
14	**18b**	DMF	NaH	48	45
15	**18b**	DMF	Cs_2CO_3	48	30
16	**18b**	DMF	K_2CO_3	48	17
17	**-**	DMF	DBU	36	nd
18	**18b**	DMF	-	24	nr

[a]Reaction conditions: All reactions were carried out with **26a** (0.1233 mmol) and **27a** (0.185 mmol) in solvent (1.5 mL). [b]Reaction was carried out at room temperature without using LiCl. [c]Reaction was carried out with 3.1 mmol of **26a**.

After successfully optimizing the reaction conditions, we shifted our attention to investigate the scope and limitations of this transformation using a diverse range of *p*-QMs (**26b-y**) and the results are included in Schemes 13 & 14.

It is evident from Scheme 13 that the electronic nature of the aryl ring present in *p*-QMs barely influences the reactivity pattern. Most of the *p*-QMs (**26b-j**), derived from electron-rich aromatic aldehydes, reacted efficiently with **27a** under the optimized conditions to furnish the corresponding R-C adducts (**28b-j**) in good to excellent yields (70-83% yields). Delightfully, the present method was found to be robust in case of *p*-QMs (**26k-o**) synthesized from halo-substituted aromatic aldehydes and the respective products **28k-o** were formed in good yields (63-80% yields) [Scheme 13].

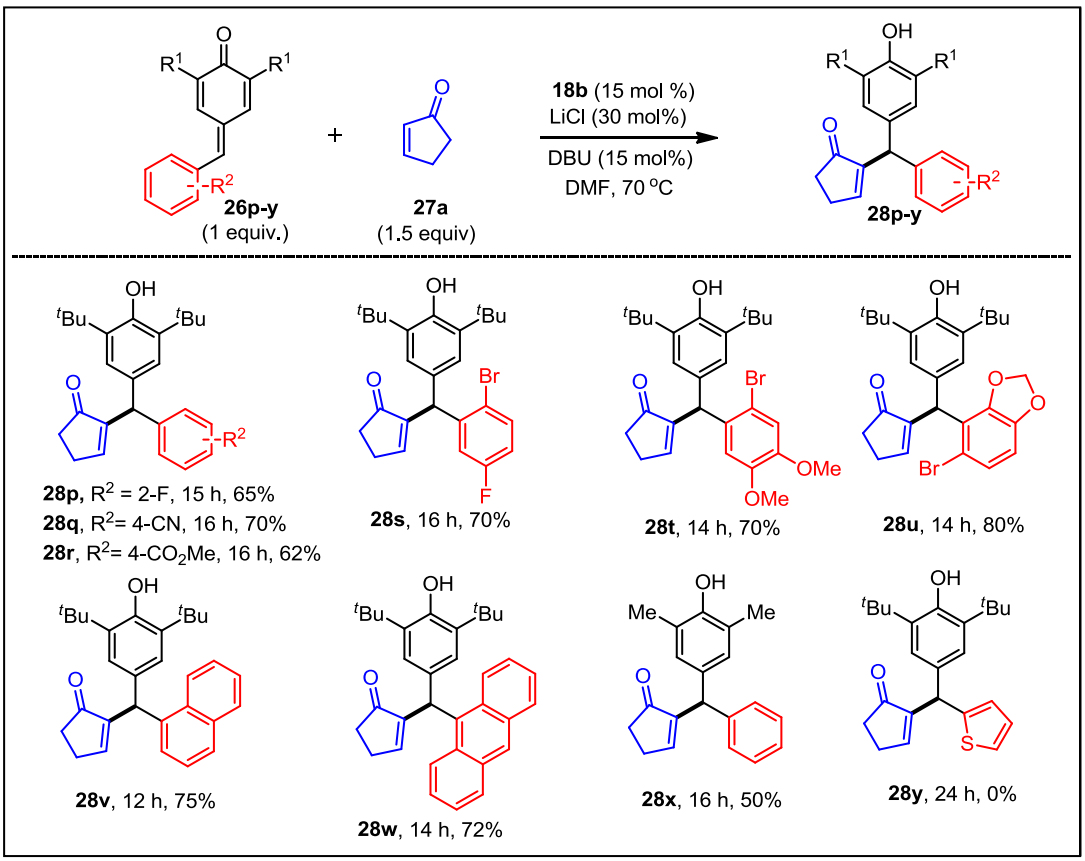


[a]Reaction conditions: All reactions were carried out with 40 mg scale of **26(b-o)** in 1.5 mL of solvent. Yields reported are isolated yields.

Scheme 13: Substrate scope with different *p*-quinone methides[a]

Moreover, the generality of this protocol was also investigated using *p*-QMs (**26p-r**) bearing an electron-withdrawing substituent at the aromatic ring under the optimized reaction conditions. In all those cases, the respective products **28p-r** was obtained in good yields (62-70% yields). Sensitive functional groups such as nitrile and ester were found to be compatible under the optimized conditions. Even sterically hindered *p*-QMs (**26s-w**) were found to be

suitable substrates, affording the successive products **28s-w** in the range of 70-80% yields. Furthermore, *p*-QM (**26x**) derived from 2,6-dimethylphenol also reacted under the optimized conditions and the resultant R-C adduct **28x** was isolated in 50% yield. Unfortunately, *p*-QM (**26y**) derived from thiophene-2-carboxaldehyde, failed to react under the optimized conditions (Scheme 14).

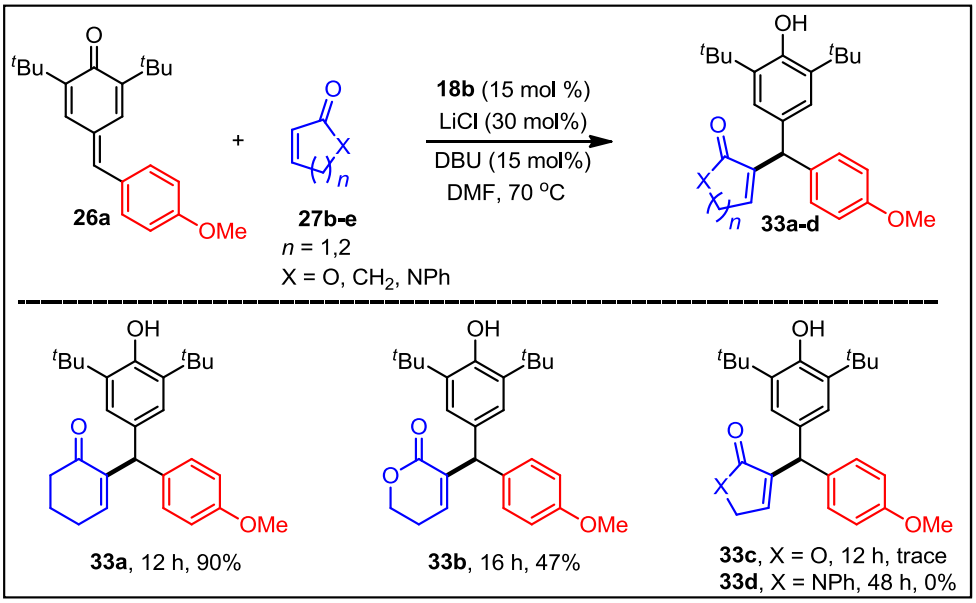


[a]Reaction conditions: All reactions were carried out with 40 mg scale of **26(p-y)** in 1.5 mL of solvent. Yields reported are isolated yields.

Scheme 14: Substrate scope with different *p*-quinone methides[a]

Next, we studied the substrate scope and limitations of enones for this transformation (Scheme 15). Initially, the scope of other cyclic enones was examined. In the case of 2-cyclohexen-1-one (**27b**), the R-C adduct **33a** was produced in 90% yield. Surprisingly, 5,6-dihydro-2H-pyran-2-one (**27c**), which is not explored in R-C reaction so far, furnished the corresponding lactone **33b** in 47% yield. However, 2-(5H)-furanone (**27d**) and *α,β*-unsaturated lactam (**27e**) failed to react with **26a** under the standard conditions. Unfortunately, the current protocol was limited only to cyclic enone systems. The acyclic

enones such as, vinyl ketones, acrylates and acrylamides did not participate in the reaction. Not only in our case, the substrate scope is the main concern in most of the hitherto known reports available in the literature on the intermolecular R-C[19] as well as intermolecular vinylogous R-C reactions.[20,21,22,24]

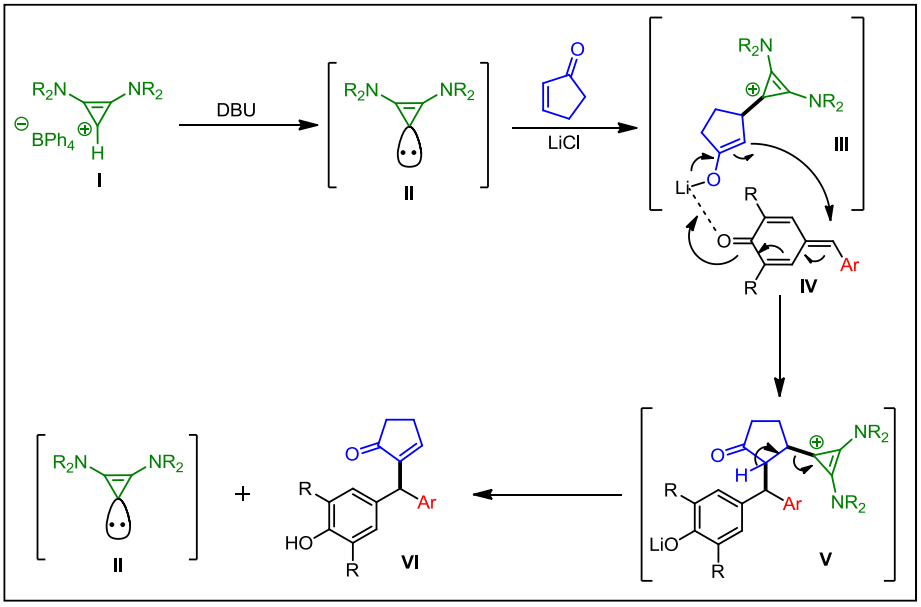


[a]Reaction conditions: All reactions were carried out with 0.1233 mmol of **26a** and 0.185 mmol of **27**(**b-e**) in 1.5 mL of DMF. Yields reported are isolated yields.

Scheme 15. Substrate scope and limitations of enones[a]

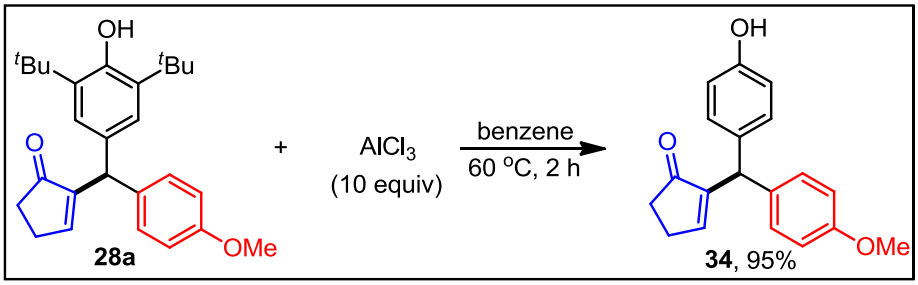
Based on the outcome of the reaction, we proposed a plausible mechanism for this transformation (Scheme 16). Initially, DBU abstracts the acidic proton from **I** and generates the free carbene intermediate **II**, which reacts to 2-cyclopentenone in a Michael fashion to produce the enolate intermediate **III**. We hypothesize that LiCl plays an important role in stabilizing the enolate **III**.[25] It is also believed that Li co-ordinates with the carbonyl of *p*-QM (**IV**) to bring it to the close proximity of intermediate **III**. As a result, enolate **III** reacts with **IV** and produces another intermediate **V**, which further decomposes to the product **VI** with the expulsion of catalyst **II**. In order to get the clear insight of the mechanism further, an experiment was carried out with **27a** (1 equiv), BAC precursor **18b** (1 equiv), and DBU (1 equiv) in CH_3CN at 60 °C (without *p*-quinone methide **26a**). After an hour of stirring, the ESI-MS spectrum was recorded for the crude reaction mixture. Interestingly, in the ESI-MS spectrum, a peak at *m*/*z* 319.2 was observed, which actually corresponds to the intermediate

[**III** + H]$^+$. This clearly implies that BAC is acting as a nucleophile and also proves that the reaction is taking place through the formation of intermediate **III**.



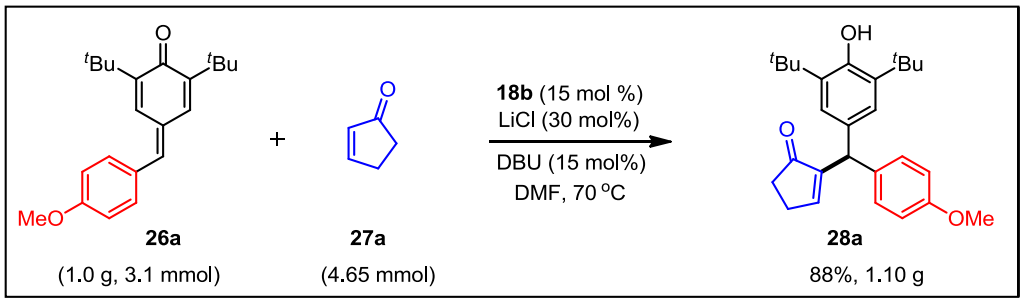
Scheme 16. Plausible mechanism of the BAC catalyzed R-C reaction

One of the drawbacks of using *p*-QMs as 1,6-acceptor is the presence of *t*-butyl groups in the products, which eventually limiting the substrate scope of *p*-QMs. In fact, the presence of *t*-Bu groups cannot be avoided as they stabilize the *p*-QMs moiety. Moreover, the bulky *t*-Bu groups block the C-4 position of the *p*-QMs and as a result only highly regioselective 1,6-conjugate addition reactions are observed. The good thing is that one can easily remove the *t*-Bu groups selectively by treating with excess amount of $AlCl_3$.[20,21] In order to further expand the substrate scope of the current protocol, **28a** was treated with excess of $AlCl_3$ in benzene at 60 ^oC, and as expected, the desired de-*tert*-butylated product **34** was isolated in 95% yield in 2 h (Scheme 17).



Scheme 17. De-*tert*-butylation of **28a** using $AlCl_3$

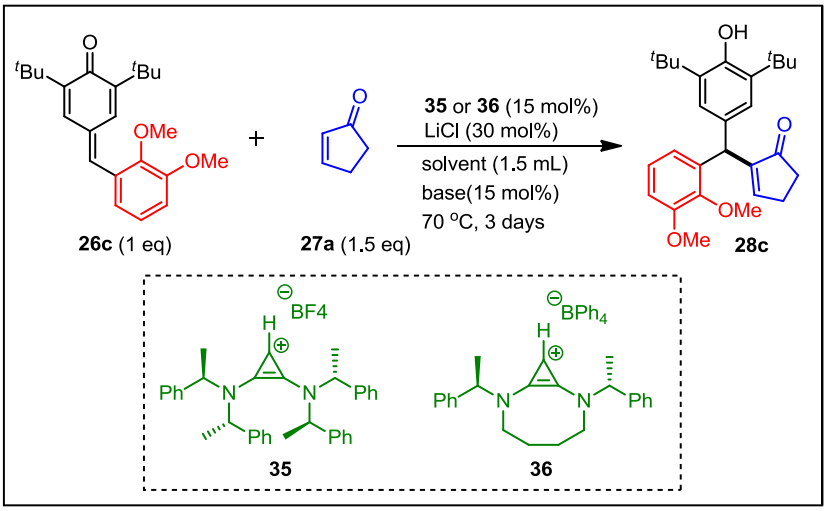
To show the generality of the current protocol, a gram scale reaction was also perfomed with **26a**. When a mixture of 3.1 mmol of **26a** and 4.65 mmol of **27a** were reacted under the optimized conditions, the corresponding R-C adduct **28a** was obtained in 88% yield, which clearly proves the robustness of this transformation (Scheme 18).



Scheme 18. Gram scale synthesis of **28a**

2.6 Attempted enantioselective R-C reaction using chiral BAC catalysts

Table 2: Optimization studies using chiral BAC precursor[a]



entry	catalyst	base	solvent	yield of **28c** [%]	*ee* [%][c]
1[b]	**35**	DBU	DMF	0	0
2[b]	**36**	DBU	DMF	0	0
3	**35**	DBU	DMF	25	0
4	**36**	DBU	DMF	30	0

[a]Reaction conditions: All reactions were carried out with **26c** (0.12 mmol), **27a** (0.18 mmol) in solvent (1.5 mL). [b]Reaction was carried out at room temperature. Yields reported are isolated yields. [c]*ee* was determined by HPLC.

Next, we shifted our attention to develop an entioselective method for the R-C reaction using chiral a BAC catalyst. For this purpose, a few enantioselective reactions of *p*-QM **26c** were attempted using chiral BAC precursors **35** & **36** and the results are shown in Table 2. When the reaction was performed at room temperature using **35** & **36** as catalyst precursors, respectively, the product **28c** was not observed (entries 1 & 2). Interestingly, when the same reactions were conducted under the optimized conditions, the desired R-C adduct **28c** was obtained in 25 and 30% yields respectively. However, unfortunately, the product **28c** was obtained as a racemic mixture in both the cases (entries 3 & 4). It was also observed that the reaction was very sluggish in both the cases and a considerable amount of starting material **26c** was recovered after the reaction.

2.7 Conclusion

In this chapter, we have described bis-(amino)cyclopropenylidene (BAC) catalyzed intermolecular Rauhut-Currier (R-C) reaction between 1,4-enones and *p*-quinone methides.[26] A new catalytic application of bis-(amino)cyclopropenylidene (BAC) has been demonstrated. Various unsymmetrical vinyl diarylmethanes could be accessed in moderate to good yields.

2.8 Experimental Section

General Informations

All reactions were carried out under an argon atmosphere in an oven dried round bottom flask. All the solvents were distilled before use and stored under argon atmosphere. Most of the reagents and starting materials and NHC precursors **29** & **30** were purchased from commercial sources and used as such. All *p*-quinone methides were prepared by following a literature procedure.[27] NHC precursor **31** was prepared according to the literature procedure.[28] BAC precursors were prepared according to known literature procedure.[7a,9,12] Melting points were recorded on SMP20 melting point apparatus and are uncorrected. ^{1}H, ^{13}C and ^{19}F spectra were recorded in $CDCl_3$ (400, 100 and 376 MHz respectively) on Bruker FT–NMR spectrometer. Chemical shift (δ) values are reported in parts per million relative to TMS and the coupling constants (J) are reported in Hz. High resolution mass spectra were recorded on Waters Q–TOF Premier–HAB213 spectrometer. FT-IR spectra were recorded on a Perkin-Elmer FTIR spectrometer. Thin layer chromatography was performed on Merck silica gel 60 F_{254} TLC pellets and visualized by UV irradiation and $KMnO_4$ stain. Column

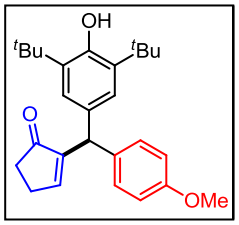
chromatography was carried out through silica gel (100–200 mesh) using EtOAc/hexane as an eluent. *Notes: It was found that if solvent was not dried properly or the exposure of the reaction mixture to air or moisture led to the formation of other uncharacterized compounds along with the R-C adduct. It was also found that most of the R-C adducts were less stable, as some amounts of decomposition observed during the purification by column chromatography.*

General procedure for the BAC catalyzed R-C reaction of *α,β*-unsaturated carbonyl Compounds with *p*–quinone methides:

Freshly distilled DMF (1.5 mL) was added to a mixture of *p*-quinone methide (40 mg, 0.1233 mmol), 2-cyclopentenone (15.2 mg, 0.185 mmol), catalyst **18b** (10.3 mg, 0.0185 mmol) and LiCl (1.6 - 1.8 mg, 0.037 - 0.04 mmol) under argon atmosphere. DBU (2.82 mg, 0.0185 mmol) was then added into it. The reaction mixture was degassed for 20 mins by purging argon and stirred at 70 ^{o}C. After the reaction was complete (based on TLC analysis), the mixture was quenched with 5 mL of distilled water and extracted with Et_2O (3 x 5 mL). The combined organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was then purified through a silica gel column using EtOAc/Hexane mixture as an eluent to get the pure product.

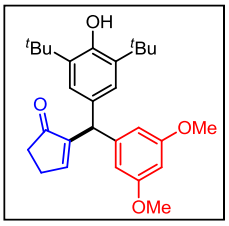
Characterization data of compounds (28a-28x):

2-[{3,5-di-*tert*-butyl-4-hydroxyphenyl}(4-methoxyphenyl)methyl]cyclopent-2-enone (28a)



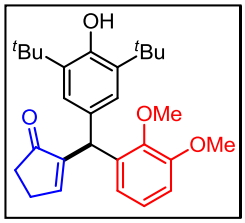
The reaction was performed with a 40 mg scale (0.1233 mmol) of *p*-quinone methide **(26a)**; R_f = 0.2 (10% EtOAc in hexane); brown solid (45.1 mg, 90% yield); m.p. = 152–154 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16 – 7.15 (m, 1H), 7.05 (d, J = 8.6 Hz, 2H), 6.91 (s, 2H), 6.82 (d, J = 8.8 Hz, 2H), 5.07 (s, 1H), 5.03 (s, 1H), 3.78 (s, 3H), 2.62 – 2.60 (m, 2H), 2.48 – 2.46 (m, 2H), 1.38 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.5, 160.0, 158.1, 152.3, 150.0, 135.7, 134.9, 132.8, 129.6, 125.2, 113.8, 55.4, 46.4, 35.1, 34.5, 30.5, 26.6; FT-IR (thin film, neat): 3639, 2957, 2925, 2870, 1704, 1612, 1511, 1464, 1435, 1360, 1300, 1251, 1177, 1120, 1038, 911, 837, 742 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{27}H_{34}NaO_3$ $[M+Na]^+$: 429.2406; found: 429.2390.

2-[{3,5-di-*tert*-butyl-4-hydroxyphenyl}(3,5-dimethoxyphenyl)methyl]cyclopent-2-enone (28b)



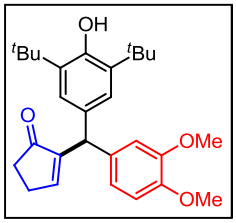
The reaction was performed with a 40 mg scale (0.113 mmol) of *p*-quinone methide **(26b)**; R_f = 0.2 (20% EtOAc in hexane); orange solid (39.9 mg, 81% yield); m.p. = 186–188 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19 – 7.18 (m, 1H), 6.93 (s, 2H), 6.30 (s, 3H), 5.07 (s, 1H), 4.99 (s, 1H), 3.74 (s, 6H), 2.62 – 2.60 (m, 2H), 2.47 – 2.45 (m, 2H), 1.38 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.4, 160.7, 160.2, 152.5, 149.4, 145.3, 135.7, 132.0, 125.3, 107.2, 98.1, 55.4, 47.3, 35.0, 34.5, 30.5, 26.6; FT-IR (thin film, neat): 3636, 2956, 2916, 2874, 2836, 1703, 1596, 1461, 1434, 1347, 1317, 1298, 1233, 1204, 1157, 1122, 1068, 913, 753, 730 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{28}H_{36}NaO_4$ $[M+Na]^+$: 459.2511; found : 459.2501.

2-[{3,5-di-*tert*-butyl-4-hydroxyphenyl}(2,3-dimethoxyphenyl)methyl]cyclopent-2-enone (28c)



The reaction was performed with a 40 mg scale (0.113 mmol) of *p*-quinone methide **(26c)**; R_f = 0.2 (20% EtOAc in hexane); orange gummy solid (38.0 mg, 77% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15 (brs, 1H), 6.95 (t, *J* = 8.0 Hz, 1H), 6.92 (s, 2H), 6.79 (d, *J* = 8.1 Hz, 1H), 6.57 (d, *J* = 7.7 Hz, 1H), 5.41 (s, 1H), 5.03 (s, 1H), 3.84 (s, 3H), 3.68 (s, 3H), 2.60 – 2.59 (m, 2H), 2.46 – 2.44 (m, 2H), 1.37 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.2, 159.9, 153.0, 152.3, 149.4, 146.8, 137.1, 135.5, 131.9, 125.4, 123.5, 120.9, 110.7, 60.5, 55.8, 40.8, 35.1, 34.4, 30.5, 26.5; FT-IR (thin film, neat): 3639, 2957, 2928, 2874, 1704, 1625, 1585, 1479, 1434, 1362, 1280, 1236, 1221, 1164, 1122, 1075, 1054, 1007, 912, 807, 732 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{28}H_{36}NaO_4$ $[M+Na]^+$: 459.2511; found : 459.2525.

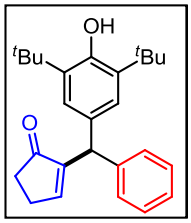
2-[{3,5-di-*tert*-butyl-4-hydroxyphenyl}(3,4-dimethoxyphenyl)methyl]cyclopent-2-enone (28d)



The reaction was performed with a 40 mg scale (0.113 mmol) of *p*-quinone methide **(26d)**; R_f = 0.2 (20% EtOAc in hexane); orange gummy solid (40.9 mg, 83% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15 – 7.149 (m, 1H), 6.92 (s, 2H), 6.78 (d, *J* = 8.2 Hz, 1H), 6.69 (d, *J* = 1.9 Hz, 1H), 6.64 (dd, *J* = 8.2, 2.0 Hz, 1H), 5.07 (s, 1H), 5.01 (s, 1H), 3.85 (s, 3H), 3.81 (s, 3H), 2.62 – 2.61 (m, 2H), 2.48 – 2.44 (m, 2H), 1.38 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.5,

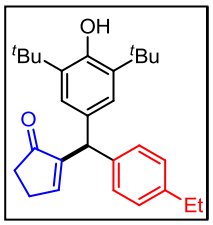
159.9, 152.4, 150.0, 148.8, 147.6, 135.7, 135.3, 132.5, 125.2, 120.5, 112.4, 111.0, 56.0, 55.9, 46.7, 35.1, 34.5, 30.5, 26.6; FT-IR (thin film, neat): 3638, 2957, 2928, 2874, 2840, 1703, 1626, 1591, 1514, 1464, 1435, 1360, 1235, 1196, 1141, 1121, 1029, 913, 809, 791, 733 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{28}H_{36}NaO_4$ $[M+Na]^+$: 459.2511; found : 459.2506.

2-[{3,5-di-*tert*-butyl-4-hydroxyphenyl}(phenyl)methyl]cyclopent-2-enone (28e)



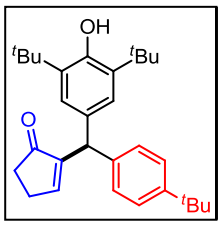
The reaction was performed with a 40 mg scale (0.136 mmol) of *p*-quinone methide **(26e)**; R_f = 0.2 (10% EtOAc in hexane); orange gummy solid (40.9 mg, 80% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 – 7.26 (m, 2H), 7.20 (d, *J* = 7.0 Hz, 1H), 7.17 (s, 1H), 7.14 (d, *J* = 7.6 Hz, 2H), 6.92 (s, 2H), 5.08 (brs, 2H), 2.62 (brs, 2H), 2.49 – 2.47 (m, 2H), 1.38 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.4, 160.2, 152.4, 149.7, 142.7, 135.7, 132.4, 128.7, 128.4, 126.4, 125.3, 47.1, 35.0, 34.5, 30.4, 26.6; FT-IR (thin film, neat): 3385, 2957, 2923, 2854, 1737, 1703, 1597, 1462, 1434, 1261, 1123, 1098, 1047, 860, 803, 795, 753, 707 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{26}H_{32}NaO_2$ $[M+Na]^+$: 399.2300; found : 399.2283.

2-[{3,5-di-*tert*-butyl-4-hydroxyphenyl}(4-ethylphenyl)methyl]cyclopent-2-enone (28f)



The reaction was performed with a 40 mg scale (0.124 mmol) of *p*-quinone methide **(26f)**; R_f = 0.2 (10% EtOAc in hexane); orange gummy solid (38.6 mg, 77% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18 (s, 1H), 7.10 (d, *J* = 7.3 Hz, 2H), 7.04 (d, *J* = 7.2 Hz, 2H), 6.93 (s, 2H), 5.05 (s, 1H), 5.04 (s, 1H), 2.61 (q, *J* = 7.4 Hz, 4H), 2.47 – 2.45 (m, 2H), 1.38 (s, 18H), 1.21 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.5, 160.0, 152.4, 149.9, 142.2, 140.0, 135.7, 132.6, 128.5, 127.9, 125.3, 46.8, 35.1, 34.5, 30.5, 28.5, 26.6, 15.6; FT-IR (thin film, neat): 3645, 2959, 2925, 2855, 1705, 1511, 1466, 1435, 1361, 1235, 1198, 1155, 1121, 909, 812, 769, 644 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{28}H_{36}NaO_2$ $[M+Na]^+$: 427.2613; found : 427.2596.

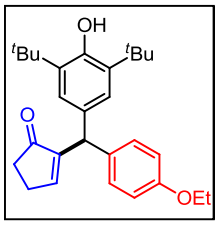
2-[{4-(*tert*-butyl)phenyl}(3,5-di-*tert*-butyl-4-hydroxyphenyl)methyl]cyclopent-2-enone (28g)



The reaction was performed with a 40 mg scale (0.114 mmol) of *p*-quinone methide **(26g)**; R_f = 0.3 (10% EtOAc in hexane); orange gummy solid (36.5 mg, 74% yield); *The product was found to be unstable as some*

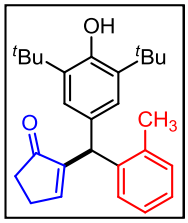
amount of decomposition was observed during purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (d, J = 8.3 Hz, 2H), 7.20 (brs, 1H), 7.05 (d, J = 8.2 Hz, 2H), 6.94 (s, 2H), 5.06 (s, 1H), 5.05 (s, 1H), 2.61 – 2.60 (m, 2H), 2.47 – 2.45 (m, 2H), 1.38 (s, 18H), 1.29 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.5, 159.9, 152.4, 149.9, 149.0, 139.8, 135.6, 132.5, 128.2, 125.4, 125.3, 46.7, 35.0, 34.5, 31.5, 30.5, 29.8, 26.6; FT-IR (thin film, neat): 3646, 2958, 2927, 2873, 1705, 1616, 1435, 1365, 1237, 1199, 1160, 1125, 1025, 812, 773 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{30}H_{40}NaO_2$ $[M+Na]^+$: 455.2926; found : 455.2908.

2-[{3,5-di-*tert*-butyl-4-hydroxyphenyl}(4-ethoxyphenyl)methyl]cyclopent-2-enone (28h)



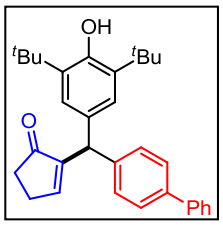
The reaction was performed with a 40 mg scale (0.118 mmol) of *p*-quinone methide **(26h)**; R_f = 0.2 (15% EtOAc in hexane); orange solid (37.2 mg, 75% yield); m.p. = 144–146 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.147 – 7.145 (m, 1H), 7.03 (d, J = 8.5 Hz, 2H), 6.90 (s, 2H), 6.80 (d, J = 8.6 Hz, 2H), 5.06 (s, 1H), 5.02 (s, 1H), 4.00 (q, J = 6.9 Hz, 2H), 2.61 – 2.60 (m, 2H), 2.47 – 2.45 (m, 2H), 1.41 – 1.37 (m, 3H), 1.37 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.5, 160.0, 157.5, 152.3, 150.1, 135.7, 134.8, 132.8, 129.6, 125.3, 114.4, 63.5, 46.3, 35.1, 34.5, 30.5, 26.6, 15.0; FT-IR (thin film, neat): 3642, 2957, 2925, 2855, 1705, 1611, 1510, 1435, 1392, 1362, 1300, 1246, 1177, 1155, 1118, 1049, 924, 806, 740 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{28}H_{36}NaO_3$ $[M+Na]^+$: 443.2562; found : 443.2545.

2-[{3,5-di-*tert*-butyl-4-hydroxyphenyl}(*o*-tolyl)methyl]cyclopent-2-enone (28i)



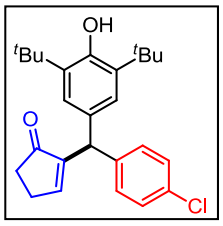
The reaction was performed a 40 mg scale (0.13 mmol) of *p*-quinone methide **(26i)**; R_f = 0.2 (10% EtOAc in hexane); pale yellow solid (35.5 mg, 70% yield); m.p. = 128–130 ^{o}C; *The product was found to be unstable as some amount of decomposition was observed during purification*. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14 – 7.12 (m, 1H), 7.11 – 7.09 (m, 2H), 7.07 (brs, 1H), 6.91 – 6.88 (m, 1H), 6.86 (s, 2H), 5.18 (s, 1H), 5.06 (s, 1H), 2.61 (brs, 2H), 2.49 – 2.47 (m, 2H), 2.26 (s, 3H), 1.37 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.8, 164.6, 152.1, 142.4, 136.9, 135.3, 134.3, 130.9, 130.8, 127.2, 126.4, 125.9, 125.3, 49.6, 47.1, 34.4, 33.9, 30.4, 20.2; FT-IR (thin film, neat): 3648, 2957, 2928, 2867, 1706, 1633, 1598, 1488, 1469, 1436, 1358, 1237, 1195, 1157, 1122, 753 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{27}H_{34}NaO_2$ $[M+Na]^+$: 413.2457; found : 413.2465.

2-[(1,1'-biphenyl)-4-yl{3,5-di-*tert*-butyl-4-hydroxyphenyl}methyl]cyclopent-2-enone (28j)



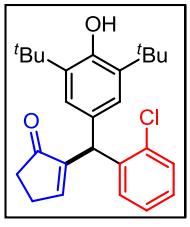
The reaction was performed with a 40 mg scale (0.108 mmol scale of *p*-quinone methide **(26j)**; R_f = 0.3 (10% EtOAc in hexane); brown gummy solid (35.2 mg, 72% yield); *The product was found to be unstable as some amount of decomposition was observed during purification*. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, J = 7.2 Hz, 2H), 7.51 (d, J = 8.2 Hz, 2H), 7.42 (t, J = 7.4 Hz, 3H), 7.33 (d, J = 7.2 Hz, 1H), 7.22 – 7.20 (m, 2H), 6.96 (s, 2H), 5.12 (s, 1H), 5.09 (s, 1H), 2.65 – 2.64 (m, 2H), 2.51 – 2.48 (m, 2H), 1.39 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.4, 160.2, 152.5, 149.7, 141.9, 141.1, 139.2, 135.8, 132.3, 129.0, 128.8, 127.21, 127.16, 127.13, 125.4, 46.9, 35.1, 34.5, 30.5, 26.7; FT-IR (thin film, neat): 3387, 2955, 2923, 2853, 1701, 1643, 1601, 1486, 1459, 1434, 1402, 1384, 1365, 1152, 1092, 796, 762, 742 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{32}H_{36}NaO_2$ $[M+Na]^+$: 475.2613; found : 475.2632.

2-[(4-chlorophenyl){3,5-di-*tert*-butyl-4-hydroxyphenyl}methyl]cyclopent-2-enone (28k)



The reaction was performed with a 40 mg scale (0.122 mmol) scale of *p*-quinone methide **(26k)**; R_f = 0.2 (10% EtOAc in hexane); brown solid (40 mg, 80% yield); m.p. = 137–139 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (d, J = 8.4 Hz, 2H), 7.15 (brs, 1H), 7.06 (d, J = 8.4 Hz, 2H), 6.87 (s, 2H), 5.10 (s, 1H), 5.03 (s, 1H), 2.63 – 2.62 (m, 2H), 2.49 – 2.47 (m, 2H), 1.37 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.2, 160.4, 152.6, 149.4, 141.3, 135.9, 132.2, 131.9, 130.0, 128.6, 125.2, 46.6, 35.0, 34.5, 30.4, 26.7; FT-IR (thin film, neat): 3640, 2958, 2923, 2877, 2866, 1704, 1490, 1435, 1363, 1236, 1199, 1154, 1092, 1015, 913, 814, 791, 743 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{26}H_{32}ClO_2$ $[M+H]^+$: 411.2091; found : 411.2074.

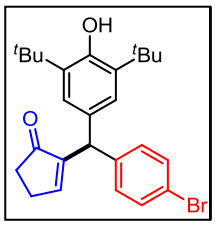
2-[(2-chlorophenyl){3,5-di-*tert*-butyl-4-hydroxyphenyl}methyl]cyclopent-2-enone (28l)



The reaction was performed with a 40 mg scale (0.122 mmol) of *p*-quinone methide **(26l)**; R_f = 0.2 (10% EtOAc in hexane); pale yellow solid (37.5 mg, 75% yield); m.p. = 173–175 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.34 (m, 1H), 7.16 – 7.14 (m, 2H), 7.05 (brs, 1H), 6.97 – 6.94 (m, 1H), 6.90 (s, 2H), 5.44 (s, 1H), 5.09 (s, 1H), 2.62 (brs, 2H), 2.49 – 2.47 (m, 2H), 1.38 (s, 18H).; ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.8, 160.2, 152.6, 148.6, 140.8, 135.7, 134.3, 130.3, 129.9, 129.6, 127.7, 126.6, 125.6, 44.3, 35.1, 34.5, 30.4, 26.6; FT-IR (thin film, neat): 3644, 2958, 2928,

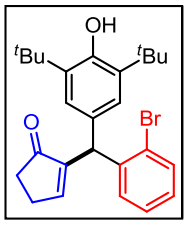
2874, 1705, 1629, 1473, 1435, 1358, 1237, 1202, 1160, 1122, 1058, 1039, 913, 741 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{26}H_{31}ClNaO_2$ $[M+Na]^+$: 433.1910; found : 433.1931.

2-[(4-bromophenyl){3,5-di-*tert*-butyl-4-hydroxyphenyl}methyl]cyclopent-2-enone (28m)



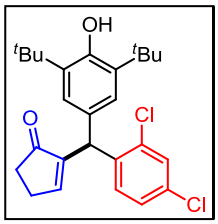
The reaction was performed with a 40 mg scale (0.107 mmol) of *p*-quinone methide **(26m)**; R_f = 0.2 (10% EtOAc in hexane); brown solid (37.5 mg, 77% yield); m.p. = 133–135 ^oC; ^1H NMR (400 MHz, $CDCl_3$) δ 7.39 (d, *J* = 8.4 Hz, 2H), 7.16 – 7.15 (m, 1H), 7.00 (d, *J* = 8.4 Hz, 2H), 6.88 (s, 2H), 5.11 (s, 1H), 5.02 (s, 1H), 2.63 – 2.62 (m, 2H), 2.49 – 2.47 (m, 2H), 1.38 (s, 18H).; ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.2, 160.4, 152.6, 149.3, 141.8, 135.9, 131.8, 131.5, 130.4, 125.2, 120.3, 46.7, 35.0, 34.5, 30.4, 26.7; FT-IR (thin film, neat): 3386, 2961, 2924, 2854, 1737, 1596, 1464, 1401, 1260, 1123, 1098, 1035, 860, 803, 749 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{26}H_{30}BrO_2$ $[M–H]^–$: 453.1429; found : 453.1409.

2-[(2-bromophenyl){3,5-di-*tert*-butyl-4-hydroxyphenyl}methyl]cyclopent-2-enone (28n)



The reaction was performed with a 40 mg scale (0.107 mmol) of *p*-quinone methide **(26n)**; R_f = 0.2 (10% EtOAc in hexane); orange gummy solid (39 mg, 80% yield); ^1H NMR (400 MHz, $CDCl_3$) δ 7.54 (dd, *J* = 7.9, 1.0 Hz, 1H), 7.20 (td, *J* = 7.6, 0.9 Hz, 1H), 7.08 – 7.04 (m, 2H), 6.94 (dd, *J* = 7.7, 1.4 Hz, 1H), 6.90 (s, 2H), 5.42 (s, 1H), 5.09 (s, 1H), 2.62 – 2.59 (m, 2H), 2.50 – 2.47 (m, 2H), 1.38 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.8, 160.3, 152.6, 148.6, 142.5, 135.7, 133.2, 130.3, 129.9, 128.0, 127.2, 125.7, 125.2, 46.9, 35.0, 34.5, 30.4, 26.7; FT-IR (thin film, neat): 3644, 3386, 2957, 2924, 2858, 1705, 1596, 1465, 1435, 1237, 1157, 1121, 1025, 803, 754, 646 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{26}H_{30}BrO_2$ $[M–H]^–$: 453.1429; found : 453.1446.

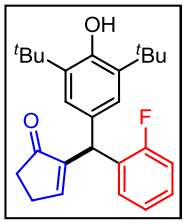
2-[{3,5-di-*tert*-butyl-4-hydroxyphenyl}(2,4-dichlorophenyl)methyl]cyclopent-2-enone (28o)



The reaction was performed with a 40 mg scale (0.11 mmol) of *p*-quinone methide **(26o)**; R_f = 0.2 (10% EtOAc in hexane); orange gummy solid (30.9 mg, 63% yield); ^1H NMR (400 MHz, $CDCl_3$) δ 7.37 (d, *J* = 1.8 Hz, 1H), 7.14 (dd, *J* = 8.4, 1.9 Hz, 1H), 7.06 (brs, 1H), 6.89 (d, *J* = 8.4 Hz, 1H), 6.87 (s, 2H), 5.37 (s, 1H), 5.11 (s, 1H), 2.63 – 2.62 (m, 2H), 2.49 – 2.48 (m, 2H), 1.38 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.7, 160.4, 152.7, 148.2, 139.5, 135.9, 135.0,

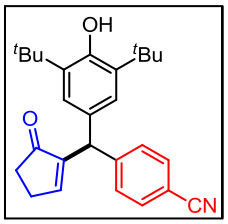
132.7, 130.4, 129.8, 129.7, 126.9, 125.5, 44.0, 35.0, 34.5, 30.4, 26.7; FT-IR (thin film, neat): 3644, 2957, 2924, 2871, 1707, 1629, 1591, 1564, 1469, 1436, 1366, 1237, 1202, 1160, 1122, 1103, 852, 776 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{26}H_{29}Cl_2O_2$ $[M–H]^-$: 443.1545; found : 443.1528.

2-[{3,5-di-*tert*-butyl-4-hydroxyphenyl}(2-fluorophenyl)methyl]cyclopent-2-enone (28p)



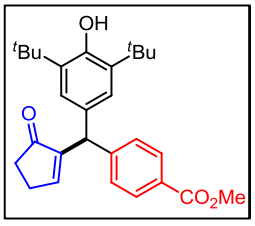
The reaction was performed with a 40 mg scale (0.128 mmol) scale of *p*-quinone methide **(26p)**; R_f = 0.2 (10% EtOAc in hexane); orange gummy solid (32.8 mg, 65% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 – 7.16 (m, 1H), 7.14 – 7.13 (m, 1H), 7.06 – 7.00 (m, 2H), 6.99 – 6.96 (m, 1H), 6.92 (s, 2H), 5.31 (s, 1H), 5.09 (s, 1H), 2.62 – 2.61 (m, 2H), 2.48 (t, *J*= 4.6 Hz, 2H),1.38 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.0, 160.7 (d, J_{C-F} = 245.3 Hz), 160.2, 152.6, 148.6, 135.8, 130.7, 130.0 (d, J_{C-F} = 14.3 Hz), 129.8 (d, J_{C-F} = 4.0 Hz), 128.2 (d, J_{C-F} = 8.2 Hz), 125.3, 123.9 (d, J_{C-F} = 3.5 Hz), 115.6 (d, J_{C-F} = 22.0 Hz), 40.5 (d, J_{C-F} = 3.0 Hz), 35.1, 34.5, 30.4, 26.6; ^{19}F NMR (376 MHz, $CDCl_3$) δ –116.2; FT-IR (thin film, neat): 3381, 2965, 2924, 2854, 1710, 1596, 1489, 1459, 1433, 1268, 1226, 1121, 1047, 807, 772, 738, 700 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{26}H_{31}FNaO_2$ $[M+Na]^+$: 417.2206; found : 417.2223.

4-[{3,5-di-*tert*-butyl-4-hydroxyphenyl}(5-oxocyclopent-1-en-1-yl)methyl]benzonitrile (28q)



The reaction was performed with a 40 mg scale (0.125 mmol) of *p*-quinone methide **(26q)**; R_f = 0.2 (20% EtOAc in hexane); orange solid (35.2 mg, 70% yield); m.p. = 175–177 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (d, *J* = 7.7 Hz, 2H), 7.24 (d, *J* = 7.8 Hz, 2H), 7.16 (brs, 1H), 6.85 (s, 2H), 5.13 (s, 1H), 5.09 (s, 1H), 2.65 (brs, 2H), 2.50 – 2.48 (m, 2H), 1.37 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.0, 160.9, 152.8, 148.6, 148.3, 136.1, 132.3, 131.1, 129.4, 125.2, 119.1, 110.3, 47.4, 35.0, 34.5, 30.4, 26.8; FT-IR (thin film, neat): 3644, 2962, 2924, 2855, 2231, 1705, 1610, 1503, 1437, 1362, 1240, 1199, 1157, 1120, 753 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{27}H_{30}NO_2$ $[M–H]^-$: 400.2277; found : 400.2258.

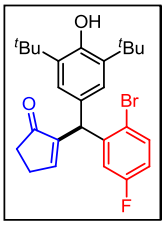
Methyl 4-[{3,5-di-*tert*-butyl-4-hydroxyphenyl}(5-oxocyclopent-1-en-1-yl)methyl] benzoate (28r)



The reaction was performed with a 40 mg scale (0.113 mmol) of *p*-quinone methide **(26r)**; R_f = 0.2 (20% EtOAc in hexane); orange solid

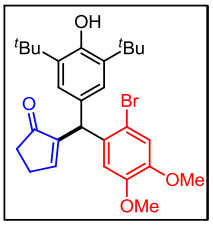
(30.6 mg, 62% yield); m.p. = 124–126 ^{o}C; *The product was found to be unstable as some amount of decomposition was observed during purification* ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, J = 7.8 Hz, 2H), 7.20 (d, J = 7.9 Hz, 2H), 7.16 (s, 1H), 6.88 (s, 2H), 5.11 (s, 2H), 3.89 (s, 3H), 2.63 (brs, 1H), 2.49 – 2.48 (m, 2H), 1.37 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.2, 167.2, 160.6, 152.6, 149.1, 148.1, 135.9, 131.7, 129.8, 128.7, 128.3, 125.3, 52.2, 47.3, 35.0, 34.5, 30.4, 26.7; FT-IR (thin film, neat): 3392, 2959, 2925, 2861, 1723, 1709, 1614, 1435, 1402, 1280, 1114, 1050, 1022, 863, 772, 712 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{28}H_{34}NaO_4$ $[M+Na]^+$: 457.2355; found : 457.2361.

2-[{2-bromo-5-fluorophenyl}(3,5-di-*tert*-butyl-4-hydroxyphenyl)methyl]cyclopent-2-enone (28s)



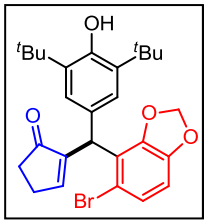
The reaction was performed with a 40 mg scale (0.102 mmol) of *p*-quinone methide **(26s)**; R_f = 0.2 (10% EtOAc in hexane); orange solid (33.9 mg, 70% yield); m.p. = 158–160 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (dd, J = 8.7, 5.5 Hz, 1H), 7.064 – 7.062 (m, 1H), 6.88 (s, 2H), 6.81 (td, J = 8.1, 3.0 Hz, 1H), 6.67 (dd, J = 9.9, 3.0 Hz, 1H), 5.35 (s, 1H), 5.12 (s, 1H), 2.64 – 2.63 (m, 2H), 2.51 – 2.48 (m, 2H), 1.38 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.6, 162.0 (d, $J_{C\text{-}F}$ = 244.6 Hz), 160.4, 152.8, 148.1, 144.9 (d, $J_{C\text{-}F}$ = 6.8 Hz), 136.0, 134.3 (d, $J_{C\text{-}F}$ = 8.0 Hz), 129.6, 125.6, 119.2 (d, $J_{C\text{-}F}$ = 3.0 Hz), 117.0 (d, $J_{C\text{-}F}$ = 23.6 Hz), 115.1 (d, $J_{C\text{-}F}$ = 22.5 Hz), 47.1, 35.0, 34.5, 30.4, 26.7; ^{19}F NMR (376 MHz, CDCl3) δ –114.6; FT-IR (thin film, neat): 3640, 2960, 2925, 2859, 1707, 1581, 1464, 1436, 1407, 1365, 1251, 1237, 1199, 1150, 1028, 807, 775, 598 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{26}H_{30}BrFNaO_2$ $[M+Na]^+$: 495.1311; found : 495.1330.

2-[{2-bromo-4,5-dimethoxyphenyl}(3,5-di-*tert*-butyl-4-hydroxyphenyl)methyl]cyclopent-2-enone (28t)



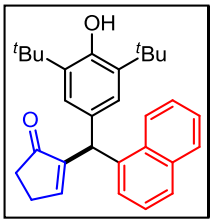
The reaction was performed with a 40 mg scale (0.0923 mmol) of *p*-quinone methide **(26t)**; R_f = 0.2 (20% EtOAc in hexane); orange solid (33.3 mg, 70% yield); m.p. = 183–185 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.07 (s, 1H), 7.02 (s, 1H), 6.93 (s, 2H), 6.48 (s, 1H), 5.33 (s, 1H), 5.10 (s, 1H), 3.84 (s, 3H), 3.66 (s, 3H), 2.621 – 2.617 (m, 2H), 2.50 – 2.47 (m, 2H), 1.38 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.9, 159.9, 152.6, 148.6, 148.0, 135.8, 134.6, 130.5, 125.5 (2C), 115.9, 114.9, 113.1, 56.3, 56.0, 46.6, 35.1, 34.5, 30.4, 26.6; FT-IR (thin film, neat): 3641, 2960, 2925, 2856, 1705, 1602, 1504, 1466, 1436, 1379, 1260, 1206, 1160, 1035, 810, 754 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{28}H_{35}BrNaO_4$ $[M+Na]^+$: 537.1616; found : 537.1596.

2-[{5-bromobenzo[*d*][1,3]dioxol-4-yl}(3,5-di-*tert*-butyl-4-hydroxyphenyl)methyl]-cyclo-pent-2-enone (28u)



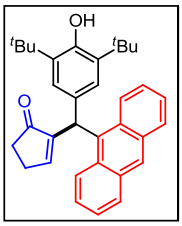
The reaction was performed with a 40 mg scale (0.096 mmol) of *p*-quinone methide **(26u)**; R_f = 0.2 (15% EtOAc in hexane); pale yellow solid (38.4 mg, 80% yield); m.p. = 208–210 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.08 – 7.078 (m, 1H), 7.01 (s, 1H), 6.88 (s, 2H), 6.45 (s, 1H), 5.94 – 5.93 (m, 2H), 5.33 (s, 1H), 5.09 (s, 1H), 2.63 – 2.62 (m, 2H), 2.50 – 2.47 (m, 2H), 1.38 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.8, 160.2, 152.6, 148.6, 147.2, 146.8, 135.9, 135.8, 130.4, 125.5, 115.3, 113.2, 109.8, 101.7, 46.7, 35.1, 34.5, 30.4, 26.7; FT-IR (thin film, neat): 3387, 2956, 2924, 2854, 1704, 1597, 1504, 1477, 1435, 1375, 1314, 1235, 1157, 1113, 1039, 936, 757 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{27}H_{30}BrO_4$ $[M–H]^-$: 497.1327; found : 497.1347.

2-[{3,5-di-*tert*-butyl-4-hydroxyphenyl}(naphthalene-1-yl)methyl]cyclopent-2-enone (28v)



The reaction was performed with a 40 mg scale (0.116 mmol) of *p*-quinone methide **(26v)**; R_f = 0.2 (10% EtOAc in hexane); orange solid (37.1 mg, 75% yield); m.p. = 195–197 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 – 7.98 (m, 1H), 7.86 – 7.83 (m, 1H), 7.72 (d, *J* = 8.2 Hz, 1H), 7.47 – 7.45 (m, 2H), 7.38 – 7.34 (m, 1H), 7.04 – 7.00 (m, 2H), 6.97 (s, 2H), 5.86 (s, 1H), 5.09 (s, 1H), 2.59 – 2.57 (m, 2H), 2.52 – 2.51 (m, 2H), 1.38 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.1, 160.9, 152.6, 149.6, 139.6, 135.8, 134.1, 131.7, 131.2, 128.8, 127.3, 126.2, 125.9, 125.7, 125.6, 125.3, 124.2, 42.9, 35.1, 34.5, 30.5, 26.6; FT-IR (thin film, neat): 3444, 3022, 3007, 2960, 2923, 2873, 1737, 1710, 1702, 1627, 1598, 1435, 1375, 1260, 1237, 1121, 1040, 919, 796, 758, 668 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{30}H_{34}NaO_2$ $[M+Na]^+$: 449.2457; found : 449.2440.

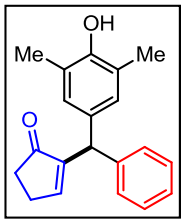
2-[(anthracen-9-yl){3,5-di-*tert*-butyl-4-hydroxyphenyl}methyl]cyclopent-2-enone (28w)



The reaction was performed with a 40 mg scale (0.101 mmol) of *p*-quinone methide **(26w)**; R_f = 0.2 (10% EtOAc in hexane); orange gummy solid (34.8 mg, 72% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.42 (s, 1H), 8.19 (d, *J* = 9.0 Hz, 2H), 8.00 (d, *J* = 8.4 Hz, 2H), 7.42 – 7.38 (m, 2H), 7.34 – 7.31 (m, 2H), 7.26 (s, 1H), 6.81 (s, 2H), 6.68 (s, 1H), 5.00 (s, 1H), 2.71 – 2.55 (m, 2H), 2.51 – 2.41 (m, 2H), 1.24 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.9, 160.9, 151.9, 148.7, 135.6, 134.7, 132.7, 132.1, 130.7, 129.3, 127.6, 126.0, 125.2, 124.7, 124.6, 40.4, 34.8, 34.4, 30.3, 26.8; FT-

IR (thin film, neat): 3639, 2957, 2925, 2871, 1703, 1623, 1436, 1404, 1361, 1318, 1236, 1196, 1157, 1121, 910, 886, 853, 784, 731 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{34}H_{36}NaO_2$ $[M+Na]^+$: 499.2613; found : 499.2595.

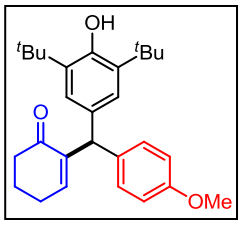
2-[{4-hydroxy-3,5-dimethylphenyl}(phenyl)methyl]cyclopent-2-enone (28x)



The reaction was performed with a 40 mg scale (0.190 mmol) of *p*-quinone methide **(26x)**; R_f = 0.2 (20% EtOAc in hexane); pale yellow solid (27.8 mg, 50% yield); m.p. = 147–149 ^oC; *The product was found to be unstable as some amount of decomposition was observed during purification*. ^1H NMR (400 MHz, $CDCl_3$) δ 7.29 – 7.26 (m, 3H), 7.21 – 7.18 (m, 1H), 7.14 – 7.10 (m, 2H), 6.72 (s, 2H), 5.03 (s, 1H), 4.54 (s, 1H), 2.63 – 2.61 (m, 2H), 2.49 – 2.47 (m, 2H), 2.18 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.4, 160.5, 151.0, 149.4, 142.6, 133.4, 128.8, 128.7, 128.5, 126.5, 123.1, 46.6, 35.1, 26.6, 16.2; FT-IR (thin film, neat): 3640, 2988, 2924, 2855, 1693, 1598, 1489, 1275, 1270, 1195, 1153, 913, 769, 750 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{20}H_{20}NaO_2$ $[M+Na]^+$: 315.1361; found : 315.1352.

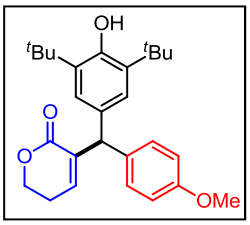
Characterization data of compounds (33a & 33b):

2-[{3,5-di-*tert*-butyl-4-hydroxyphenyl}(4-methoxyphenyl)methyl]cyclohex-2-enone (33a)



The reaction was performed with a 40 mg scale (0.1233 mmol) of *p*-quinone methide **(26a)**; R_f = 0.2 (10% EtOAc in hexane); orange solid (46.7 mg, 90% yield); m.p. = 143–145 ^oC; ^1H NMR (400 MHz, $CDCl_3$) δ 7.01 (d, *J* = 8.0 Hz, 2H), 6.86 (s, 2H), 6.81 (d, *J* = 7.8 Hz, 2H), 6.41 (t, *J* = 3.8 Hz, 1H), 5.38 (s, 1H), 5.05 (s, 1H), 3.78 (s, 3H), 2.47 – 2.44 (m, 2H), 2.40 – 2.39 (m, 2H), 2.01 (quint, *J* = 6.2 Hz, 2H), 1.38 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.4, 157.9, 152.1, 147.4, 143.5, 135.5, 135.4, 133.0, 130.0, 125.6, 113.6, 55.3, 48.3, 38.9, 34.5, 30.5, 26.3, 23.1; FT-IR (thin film, neat): 3386, 2961, 2924, 2850, 1733, 1672, 1597, 1510, 1434, 1260, 1119, 1038, 803 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{28}H_{36}NaO_3$ $[M+Na]^+$: 443.2562; found : 443.2579.

3-[{3,5-di-*tert*-butyl-4-hydroxyphenyl}(4-methoxyphenyl)methyl]-5,6-dihydro-2*H*-pyran-2-one (33b)



The reaction was performed with a 40 mg scale (0.1233 mmol) of *p*-quinone methide **(26a)**; R_f = 0.2 (20% EtOAc in hexane); pale yellow

solid (24.5 mg, 47% yield); m.p. = 199–201 ^{o}C; *The product was found to be unstable as some amount of decomposition was observed during purification*. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.05 (d, J = 8.5 Hz, 2H), 6.90 (s, 2H), 6.83 (d, J = 8.6 Hz, 2H), 6.24 (t, J = 3.6 Hz, 1H), 5.37 (s, 1H), 5.08 (s, 1H), 4.42 – 4.32 (m, 2H), 3.79 (s, 3H), 2.46 – 2.45 (m, 2H), 1.38 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.7, 158.2, 152.5, 140.7, 137.3, 135.7, 134.3, 131.9, 130.1, 125.6, 113.9, 66.2, 55.4, 50.1, 34.5, 30.5, 24.8; FT-IR (thin film, neat): 3386, 2957, 2923, 2854, 1724, 1609, 1511, 1435, 1249, 1114, 1043, 803, 757, 734 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{27}H_{34}NaO_4$ $[M+Na]^+$: 445.2355; found : 445.2373.

General procedure for de-tert-butylation of 28a

To a solution of **28a** (40 mg, 0.098 mmol) in dry benzene (2.5 mL), was added $AlCl_3$ (132 mg, 0.984 mmol) under argon atmosphere. The reaction mixture was stirred at 60 ^{o}C for 2 h and then quenched with 10 mL of distilled water. It was extracted with EtOAc (3 x 10 mL) and the combined organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was then purified through a silica gel column using EtOAc/Hexane mixture as an eluent to get the pure product **34** (27.5 mg, 95%) as white solid. m.p. = 173–175 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.132 – 7.129 (m, 1H), 7.00 (d, J = 8.6 Hz, 2H), 6.92 (d, J = 8.4 Hz, 2H), 6.81 (d, J = 8.6 Hz, 2H), 6.68 (d, J = 8.5 Hz, 2H), 5.88 (s, 1H), 5.03 (s, 1H), 3.77 (s, 3H), 2.62 – 2.58 (m, 2H), 2.50 – 2.48 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.1, 161.1, 158.2, 154.6, 149.7, 134.5, 133.9, 129.7, 129.6, 115.4, 113.9, 55.4, 45.8, 35.2, 26.7; FT-IR (thin film, neat): 3357, 3034, 2951, 2925, 2853, 2833, 1683, 1610, 1510, 1442, 1248, 1173, 1110, 1033 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{19}H_{18}NaO_3$ $[M+Na]^+$: 317.1154; found : 317.1140.

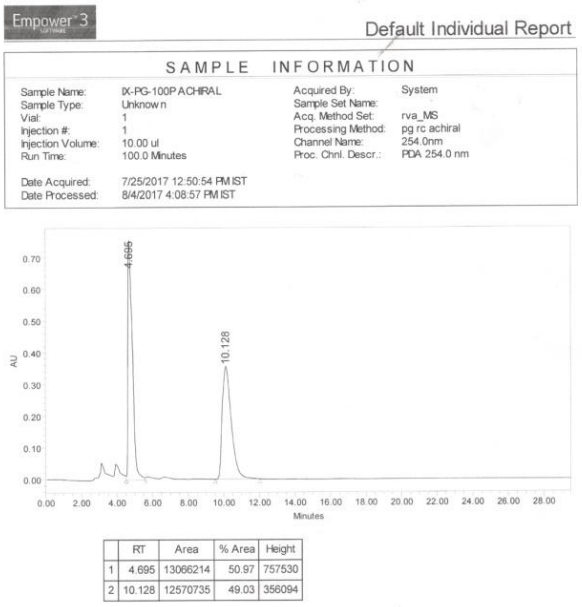
General procedure for gram scale synthesis of 28a

Freshly distilled DMF (35 mL) was added to a mixture of *p*-quinone methide **26a** (1 gm, 3.1 mmol), 2-cyclopentenone (**27a**) [382 mg, 4.65 mmol], catalyst **18b** (258 mg, 0.465 mmol) and LiCl (39.5 mg, 0.93 mmol) under argon atmosphere. DBU (71 mg, 0.465 mmol) was then added into it. The reaction mixture was degassed for 20 mins by purging argon and stirred at 70 ^{o}C until **26a** was completely consumed (by TLC analysis). The mixture was then quenched with 40 mL of distilled water and extracted with Et_2O (3 x 40 mL). The combined organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was then purified through a silica gel column using EtOAc/Hexane mixture as an eluent to get the pure product.

General procedure for the attempted enantioselective R-C reaction of 26c using chiral BAC catalysts

Freshly distilled solvent (1.5 mL) was added to a mixture of *p*-quinone methide **26c** (43 mg, 0.12 mmol), 2-cyclopentenone **27a** (14.8 mg, 0.18 mmol), chiral catalyst **35** (10.3 mg, 0.018 mmol) or **36** (11.7 mg, 0.018 mmol) and LiCl (1.5 mg, 0.036 mmol) under argon atmosphere. Base (0.018 mmol) was then added into it and the resulting mixture was degassed for 20 mins by purging argon and stirred at 70 ^{o}C under argon atmosphere for 3 days. Then the mixture was quenched with 5 mL of distilled water and extracted with Et_2O (3 x 5 mL). The combined organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was then purified through a silica gel column using EtOAc/Hexane mixture as an eluent to get the pure product. HPLC analysis was performed using Diacel Chiralpak AD-H column (90:10 *n*-Hexane/2-Propanol, 1.0 mL/min, 254 nm).

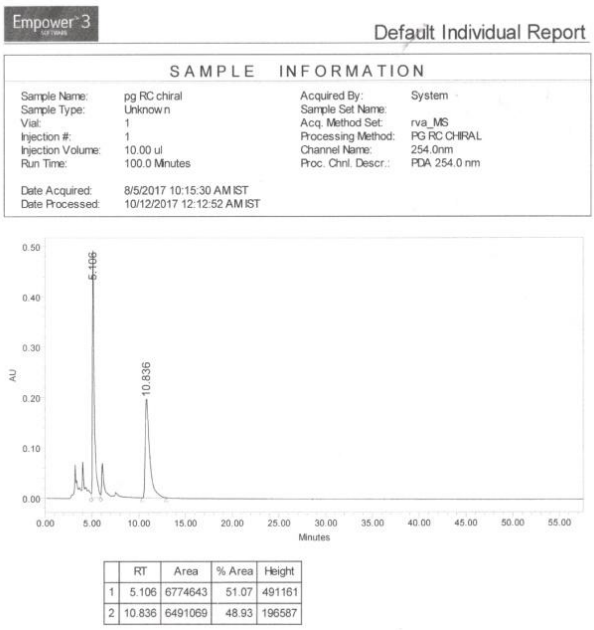
HPLC data for compound 28c (racemic)



	RT	Area	% Area	Height
1	4.695	13086214	50.97	757530
2	10.128	12570735	49.03	356094

HPLC analysis was performed using Diacel Chiralpak AD-H column (90:10 *n*-Hexane/2-Propanol, 1.0 mL/min, 254 nm)

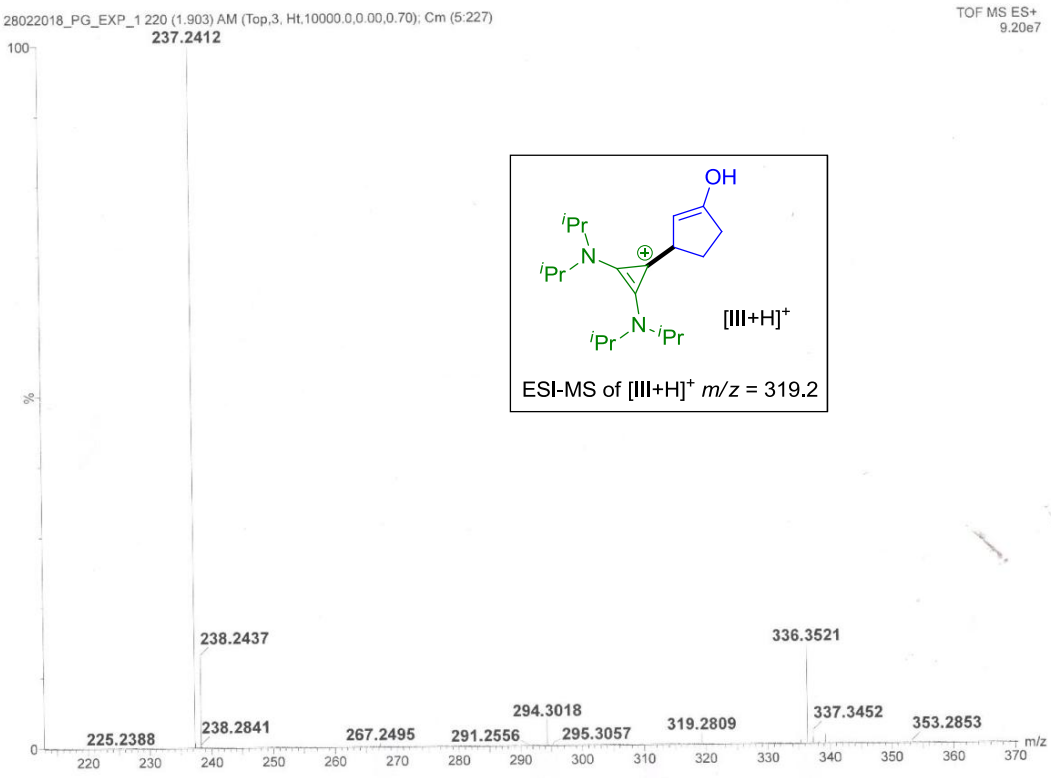
HPLC data for compound 28c (using chiral BAC 36)



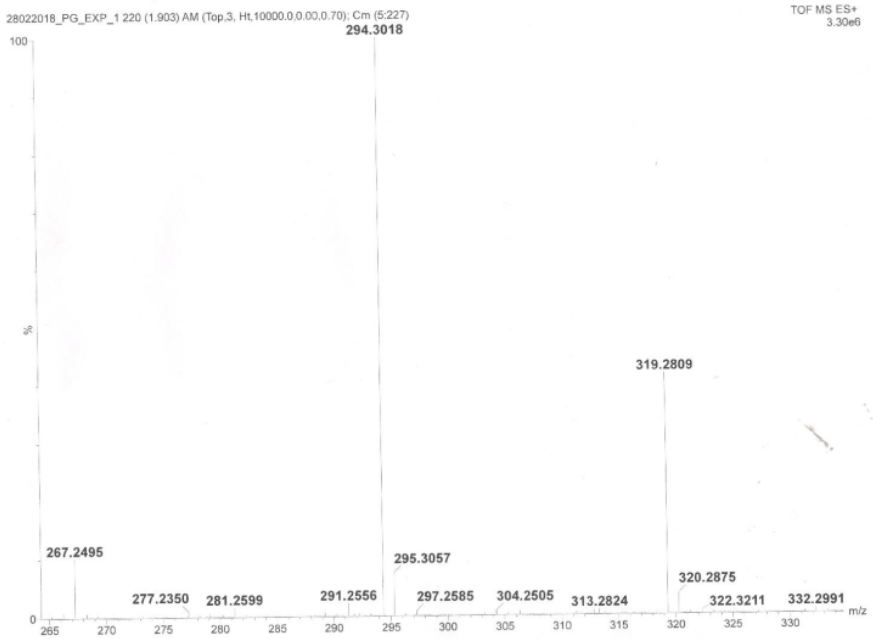
	RT	Area	% Area	Height
1	5.106	6774643	51.07	491161
2	10.836	6491069	48.93	196587

HPLC analysis was performed using Diacel Chiralpak AD-H column (90:10 *n*-Hexane/2-Propanol, 1.0 mL/min, 254 nm)

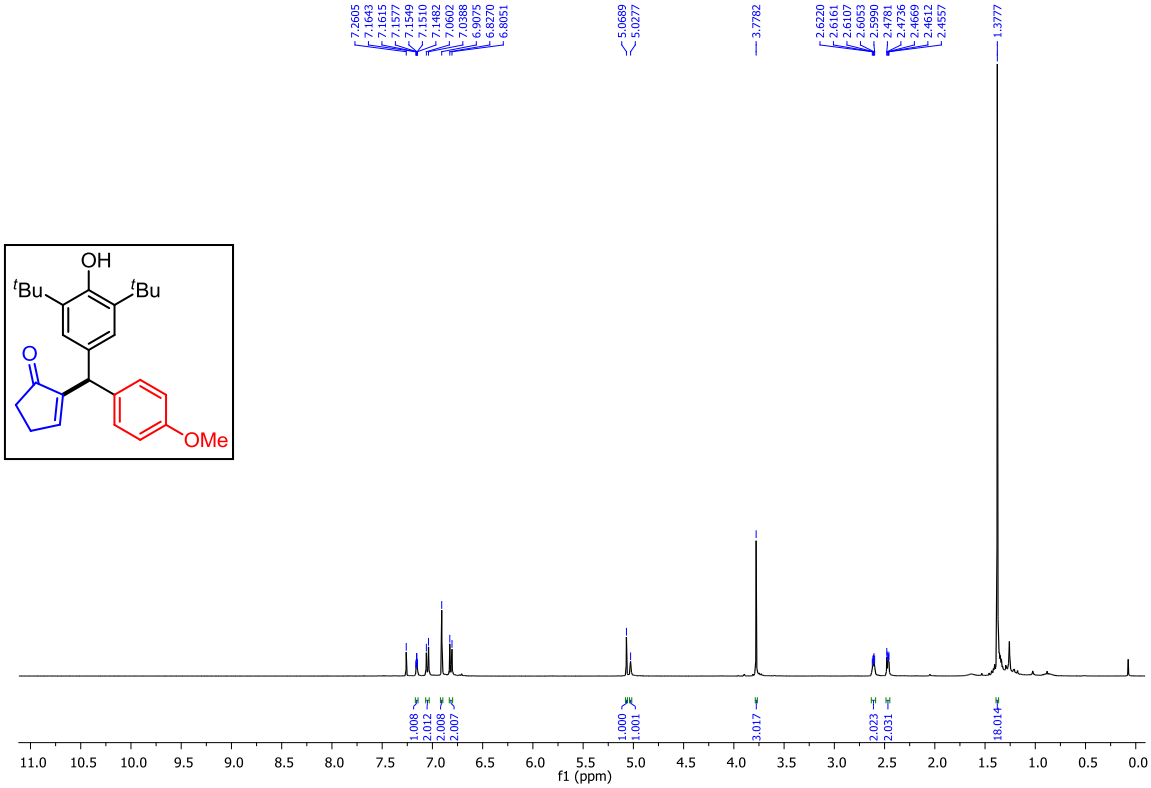
ESI-MS analysis for mechanism study



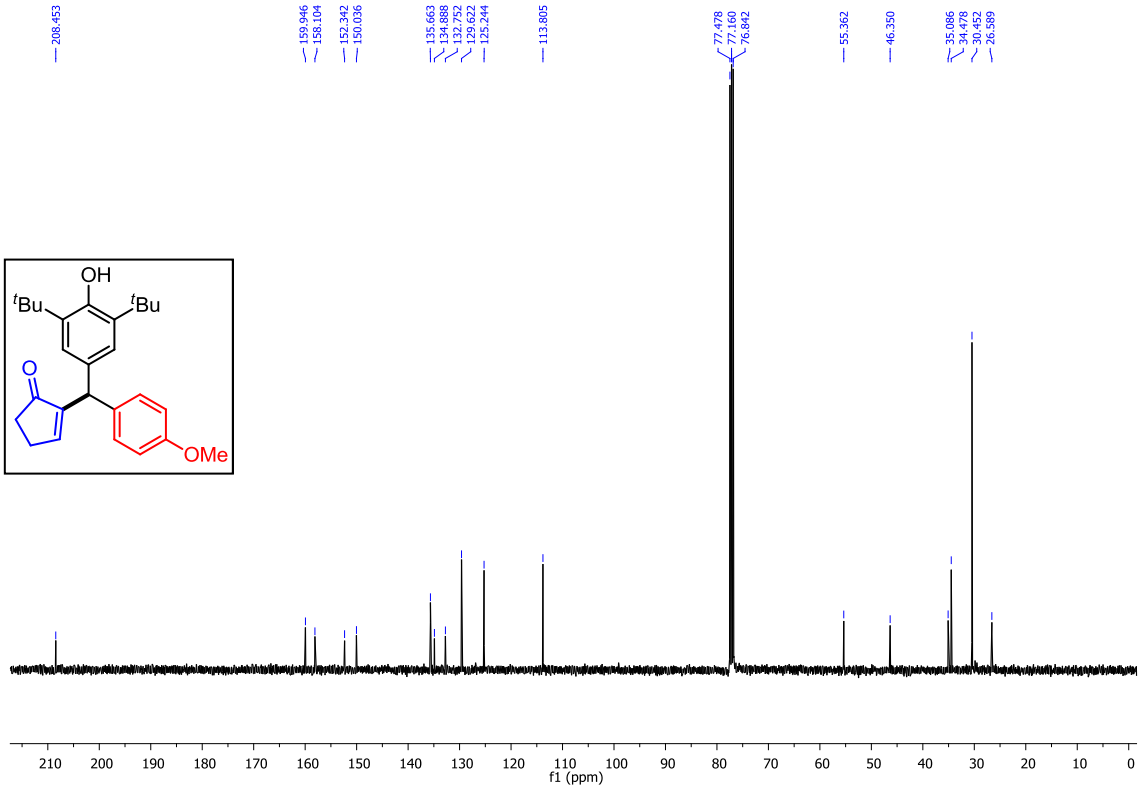
Expanded part



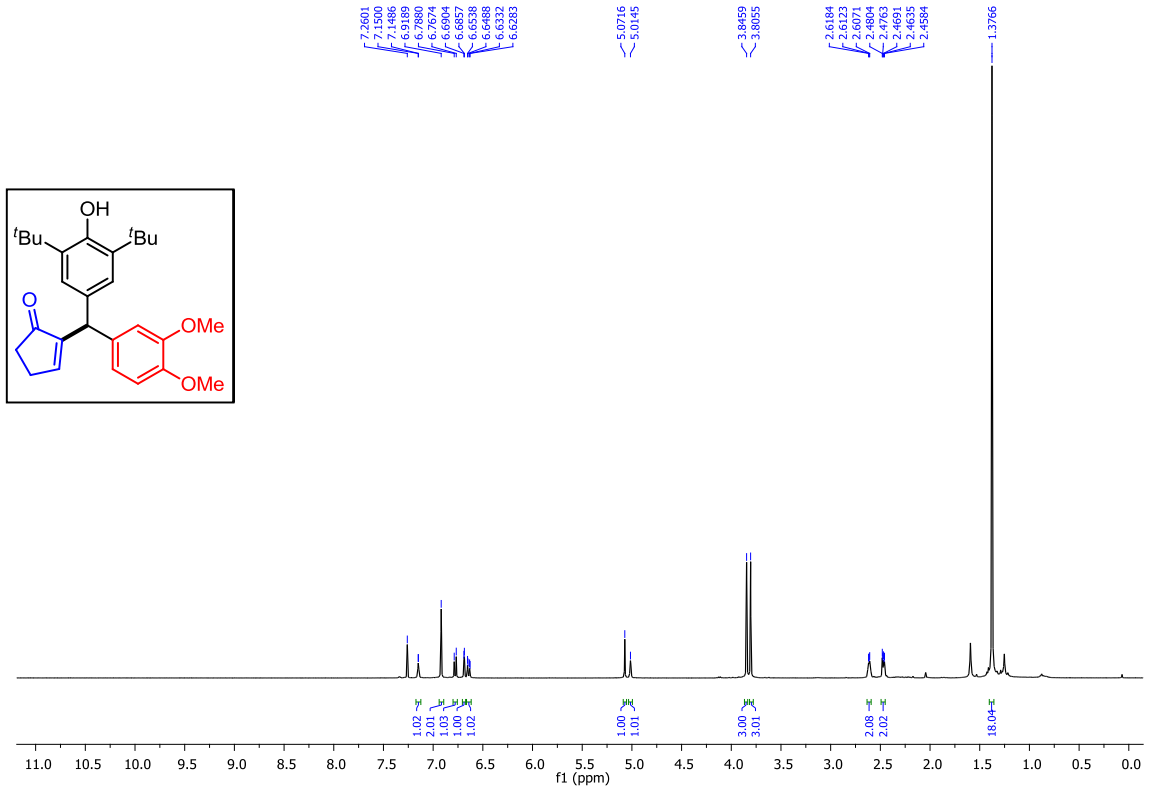
^{1}H NMR spectrum of **28a**



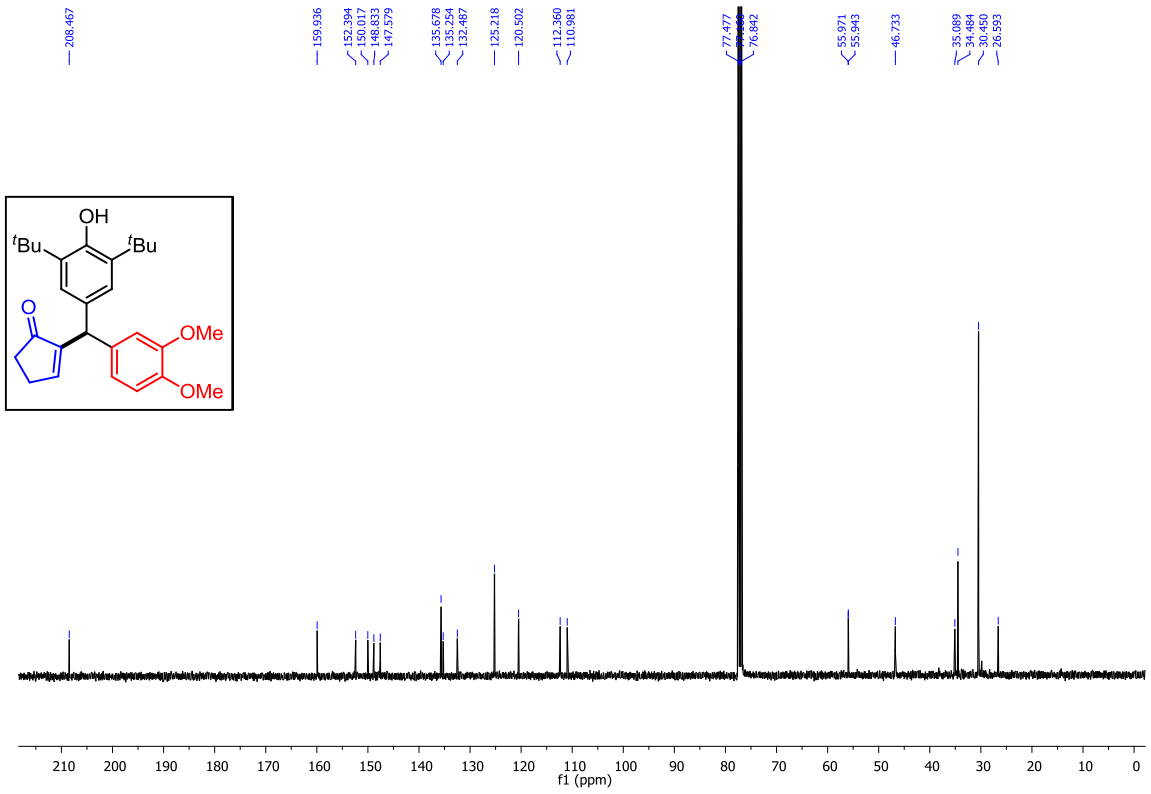
^{13}C NMR spectrum of **28a**



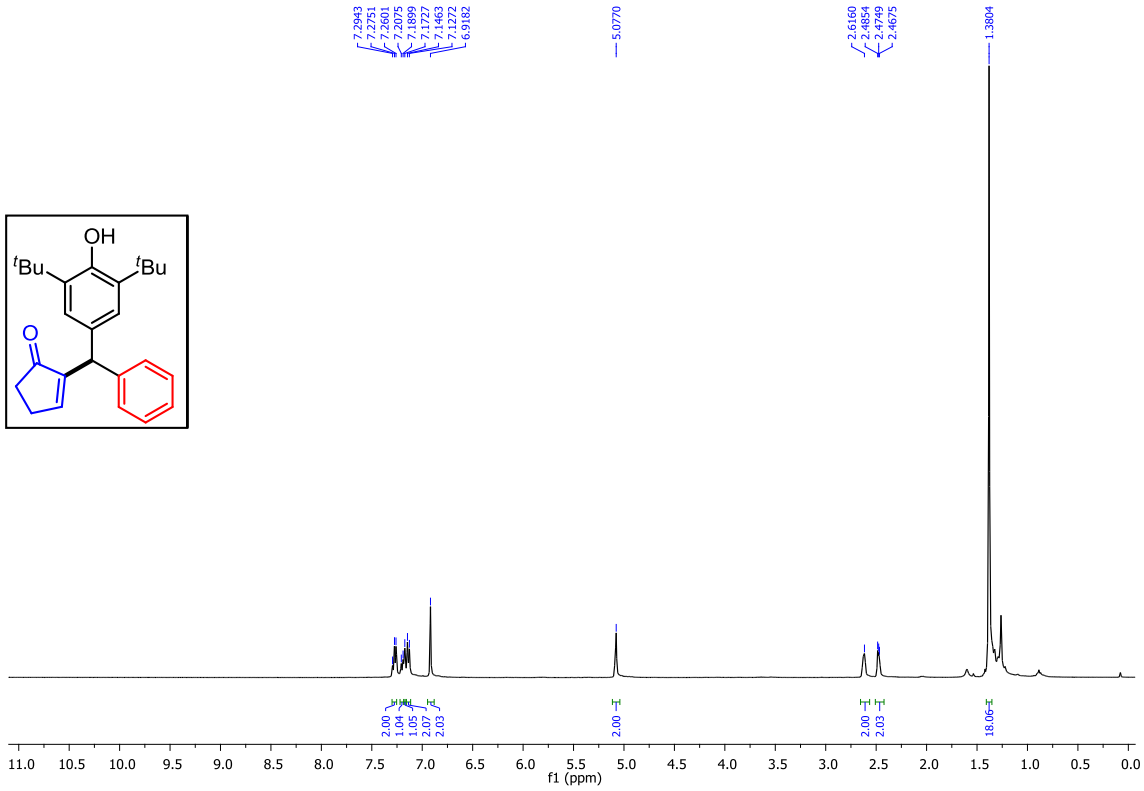
^{1}H NMR spectrum of **28d**



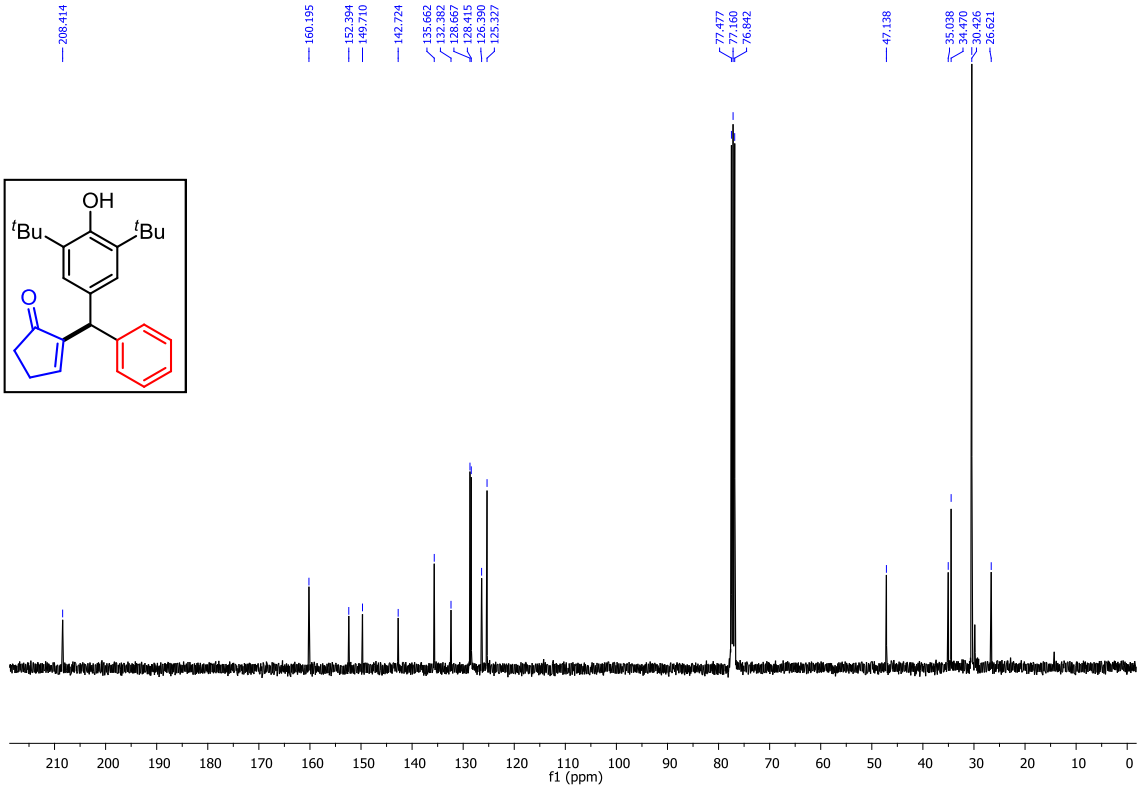
^{13}C NMR spectrum of **28d**



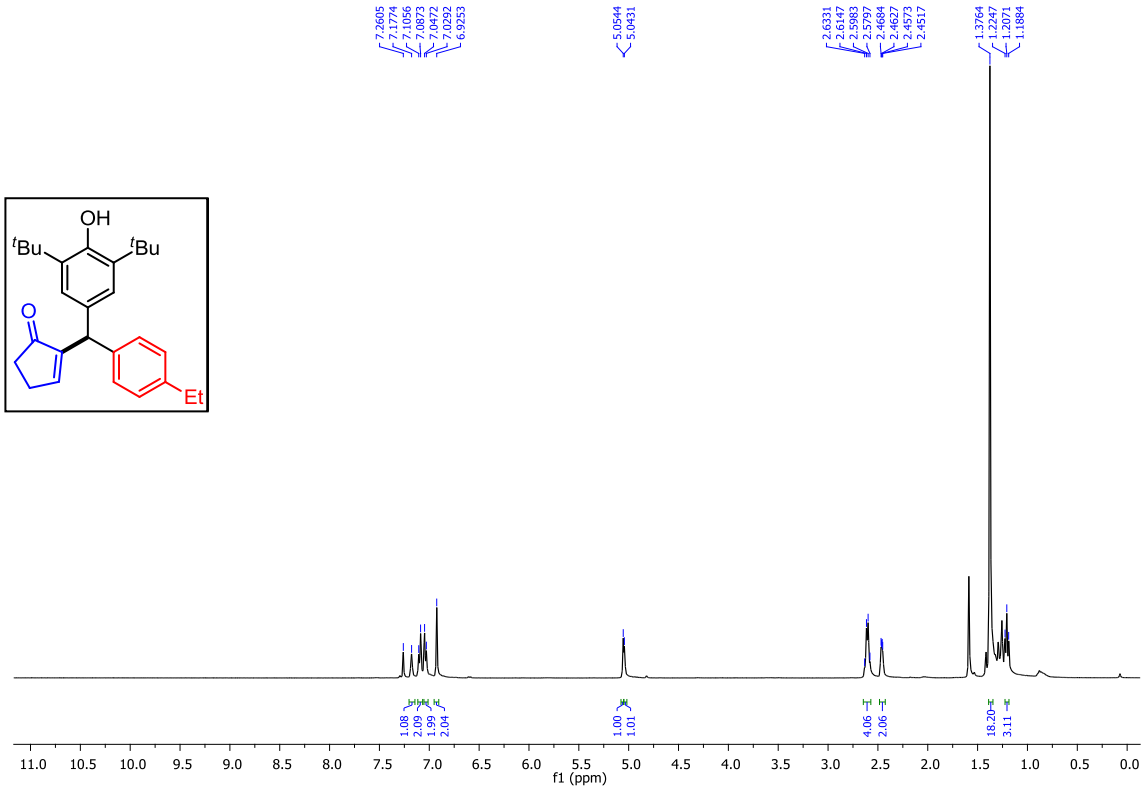
^{1}H NMR spectrum of **28e**



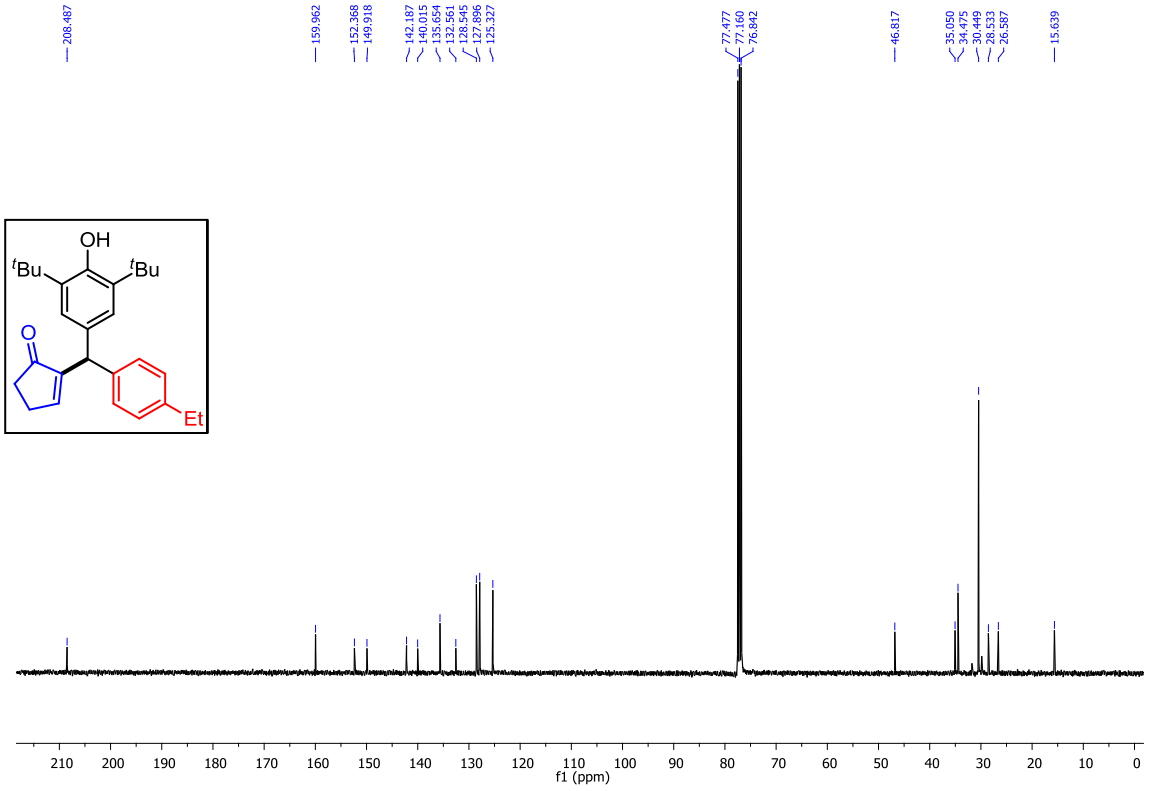
^{13}C NMR spectrum of **28e**



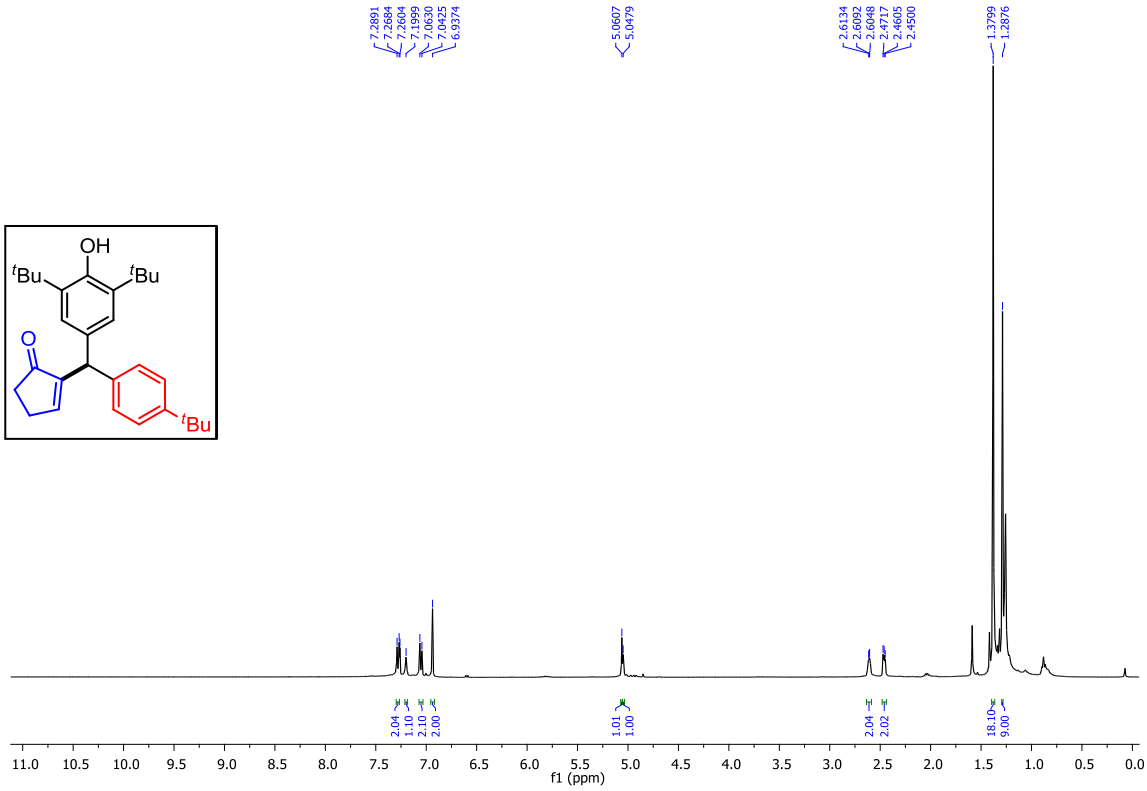
^{1}H NMR spectrum of **28f**



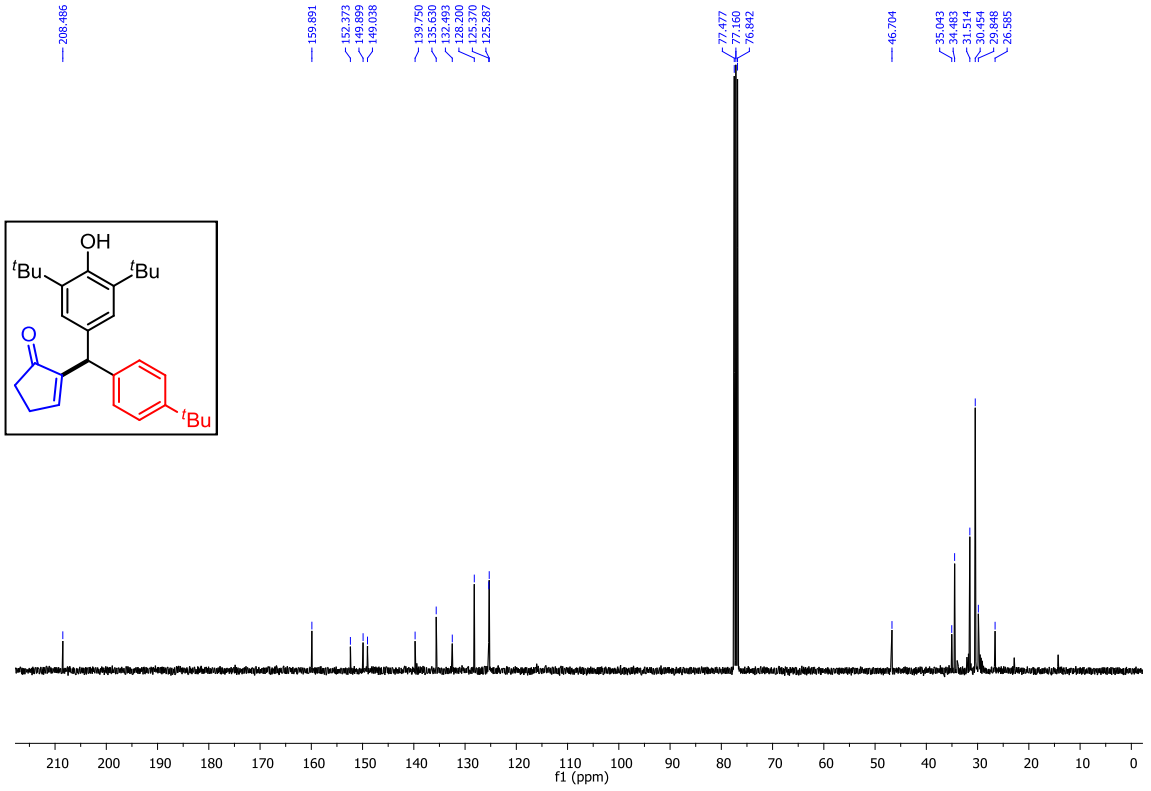
^{13}C NMR spectrum of **28f**



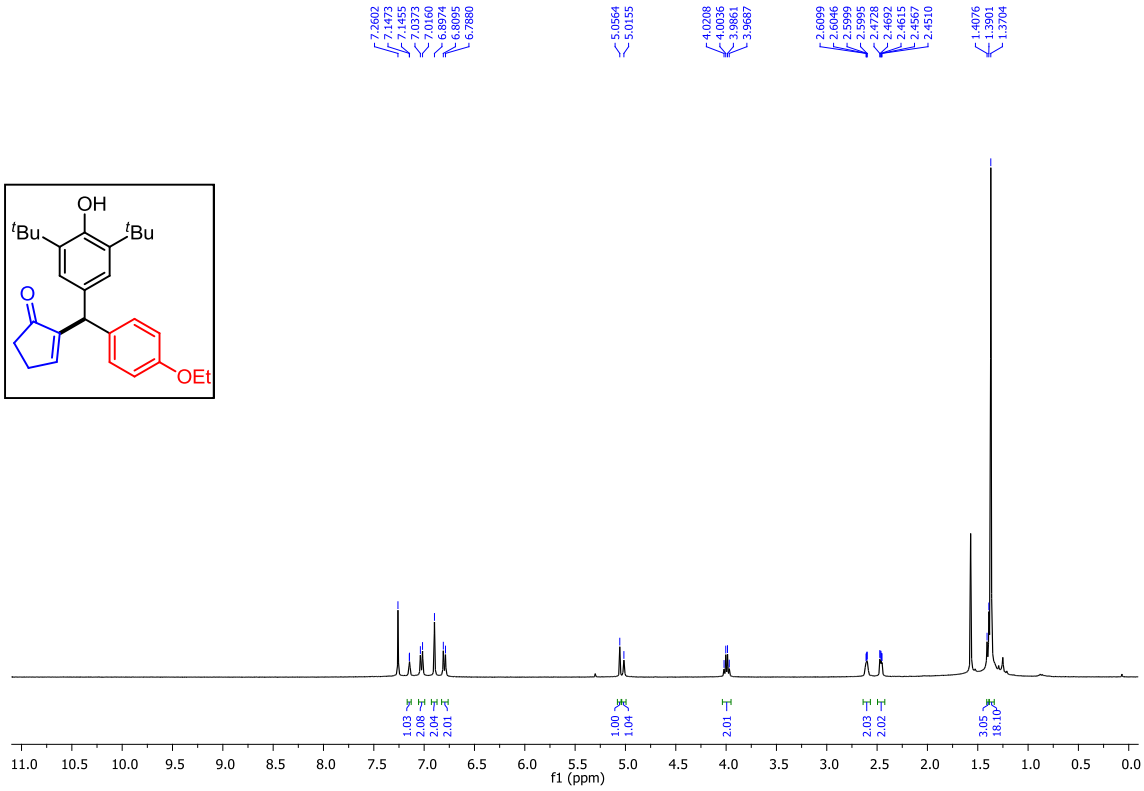
^{1}H NMR spectrum of **28g**



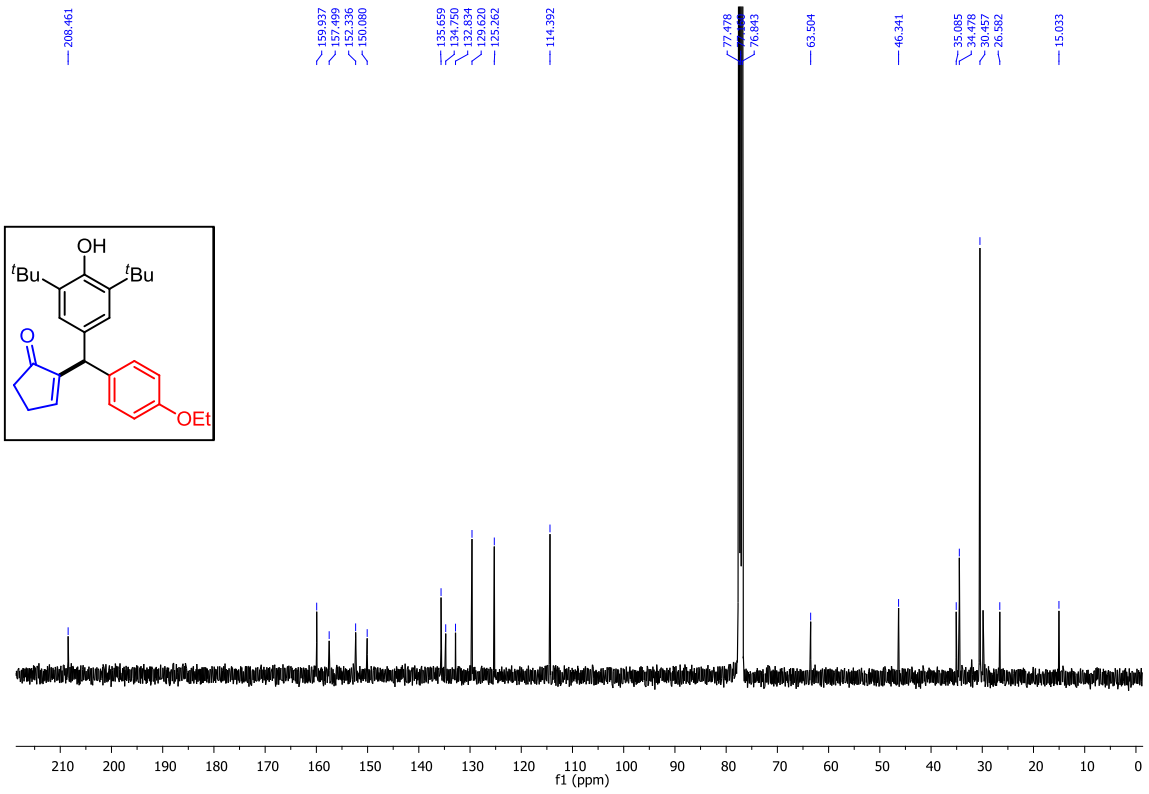
^{13}C NMR spectrum of **28g**



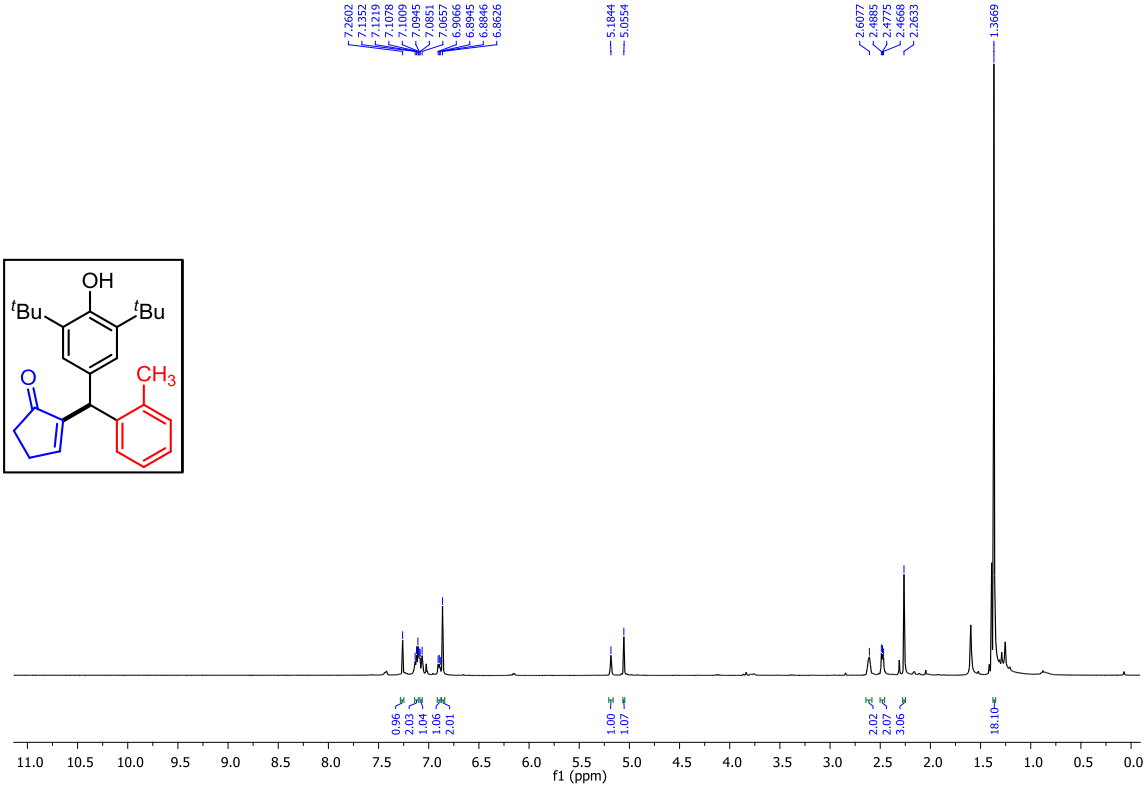
^{1}H NMR spectrum of **28h**



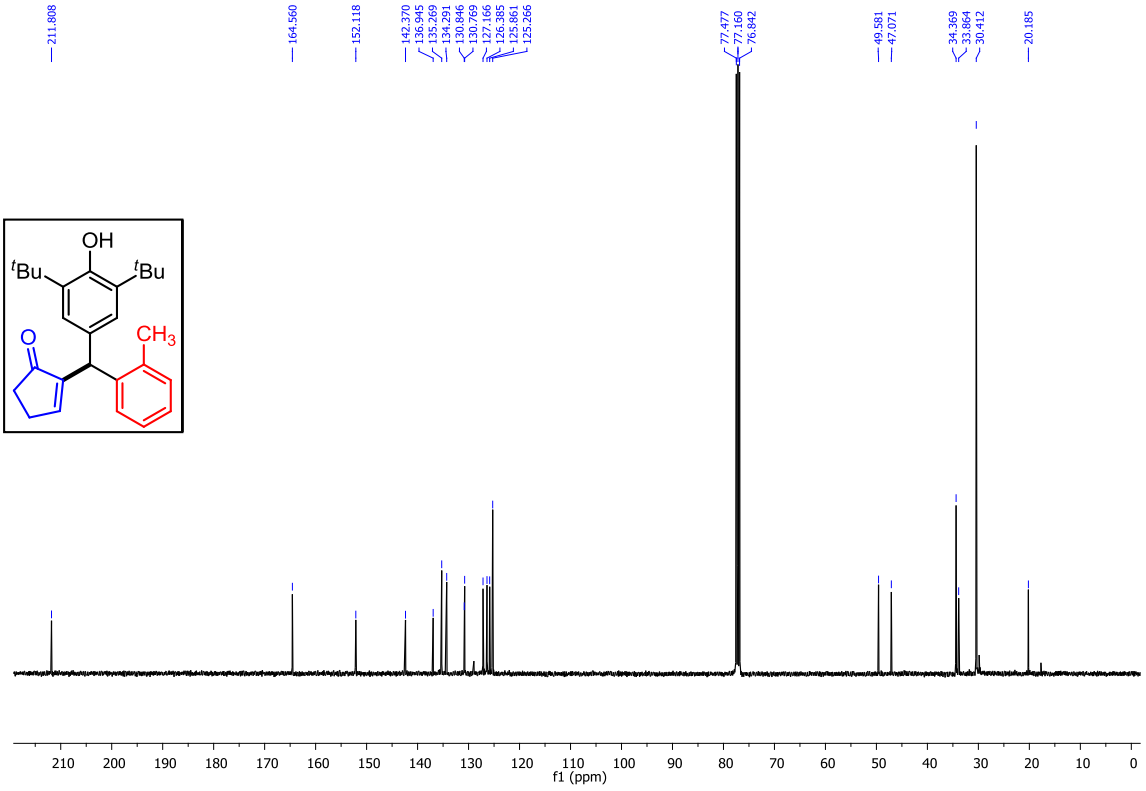
^{13}C NMR spectrum of **28h**



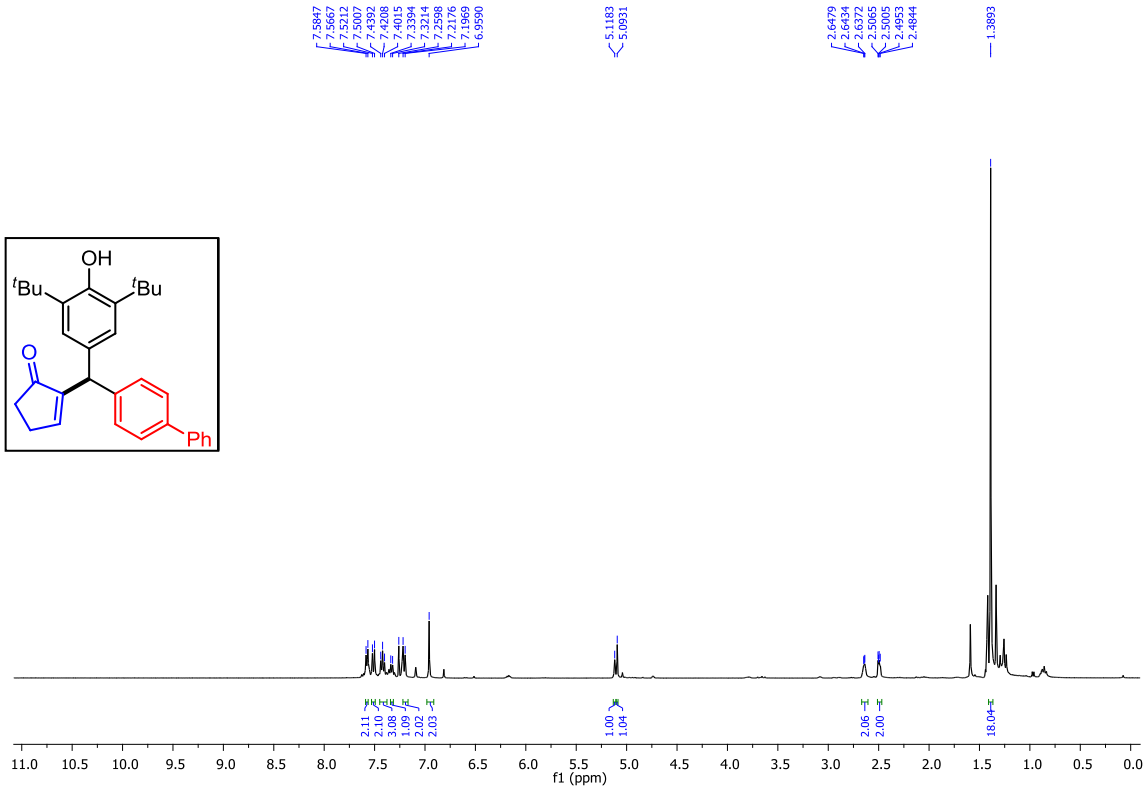
^{1}H NMR spectrum of **28i**



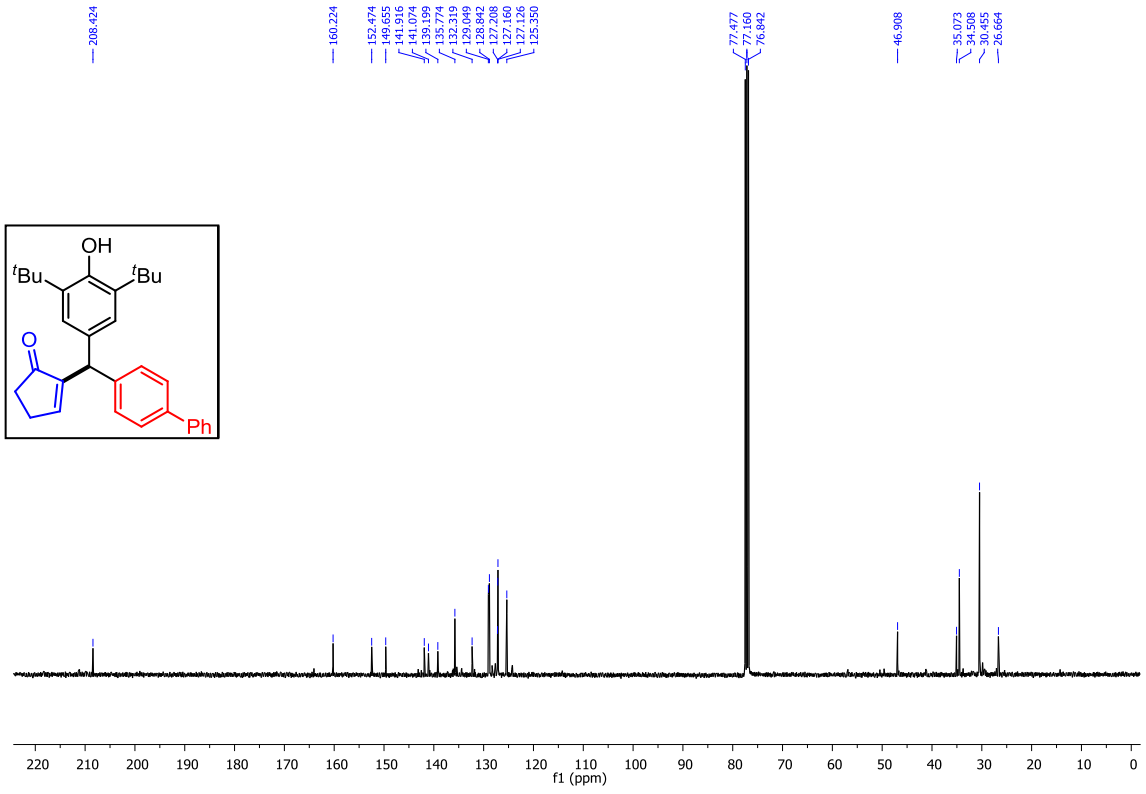
^{13}C NMR spectrum of **28i**



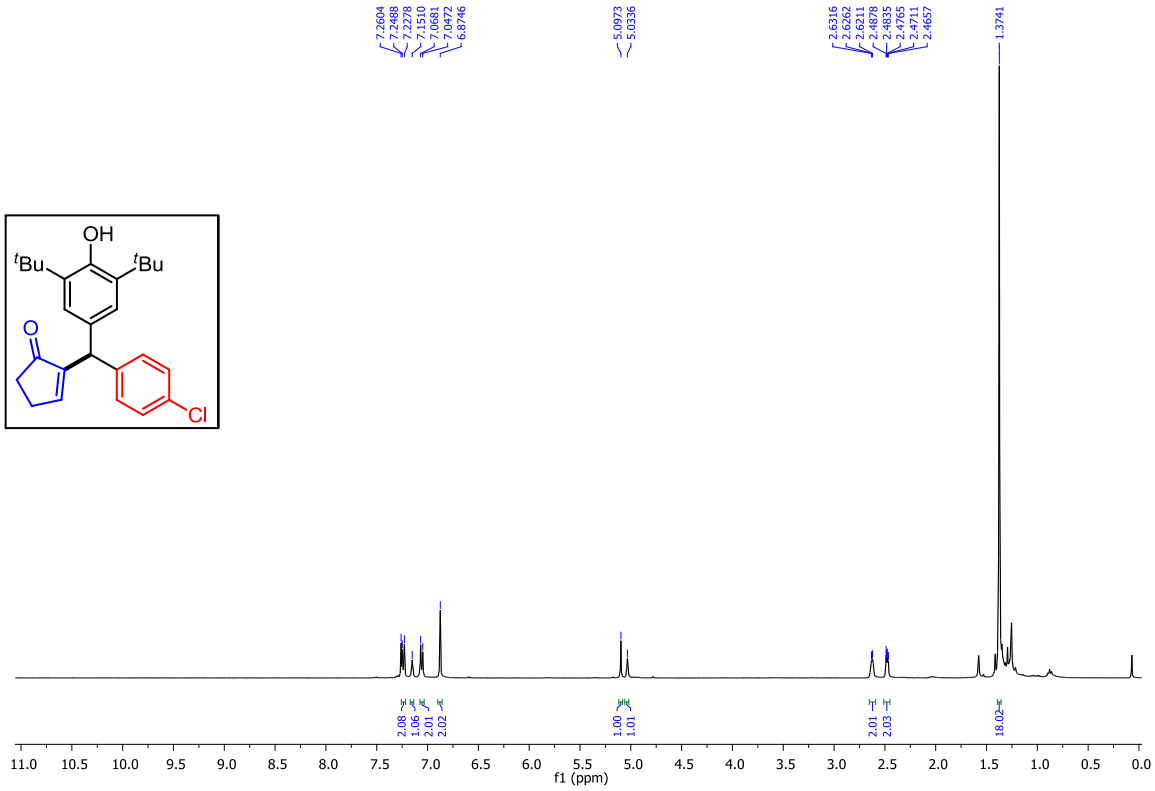
^{1}H NMR spectrum of **28j**



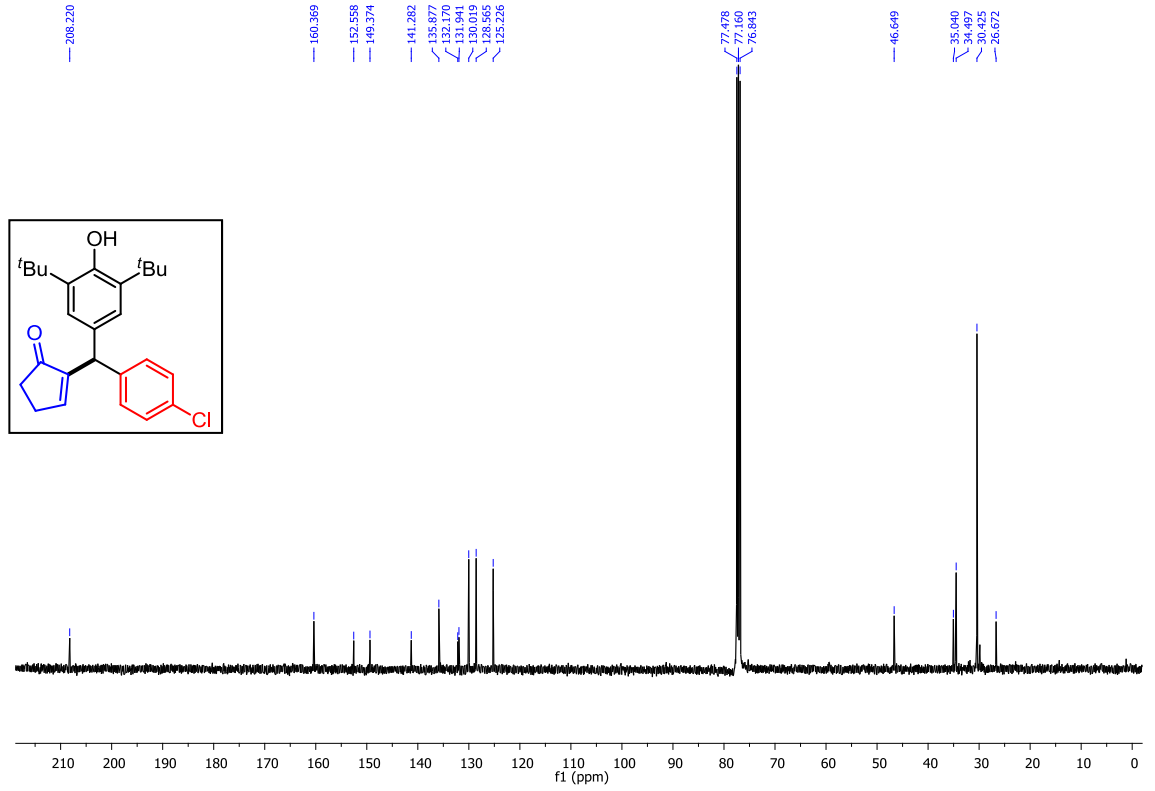
^{13}C NMR spectrum of **28j**



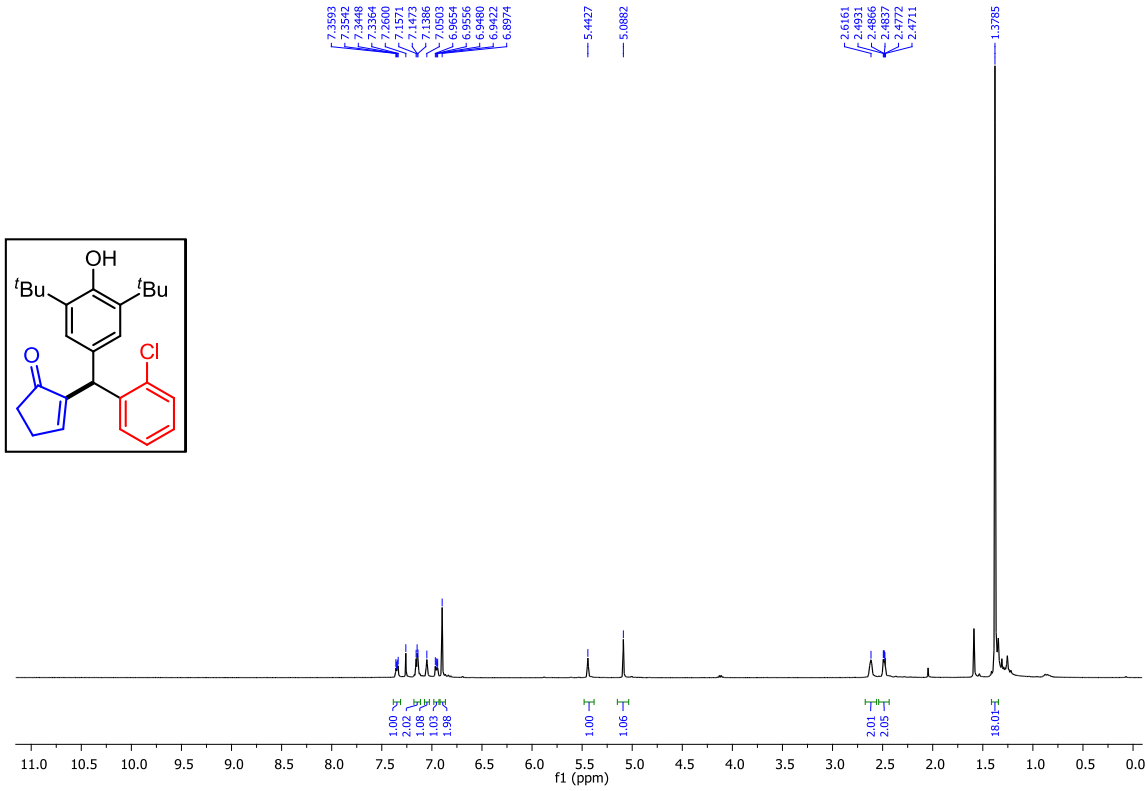
^{1}H NMR spectrum of **28k**



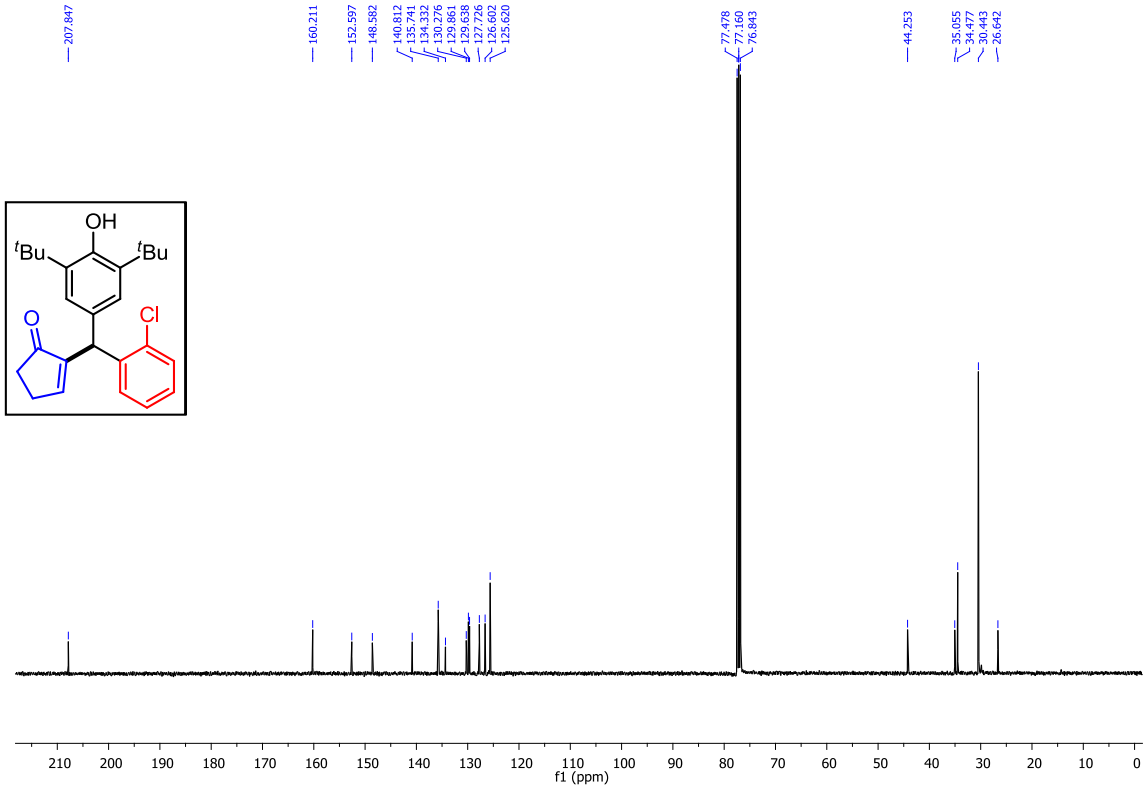
^{13}C NMR spectrum of **28k**



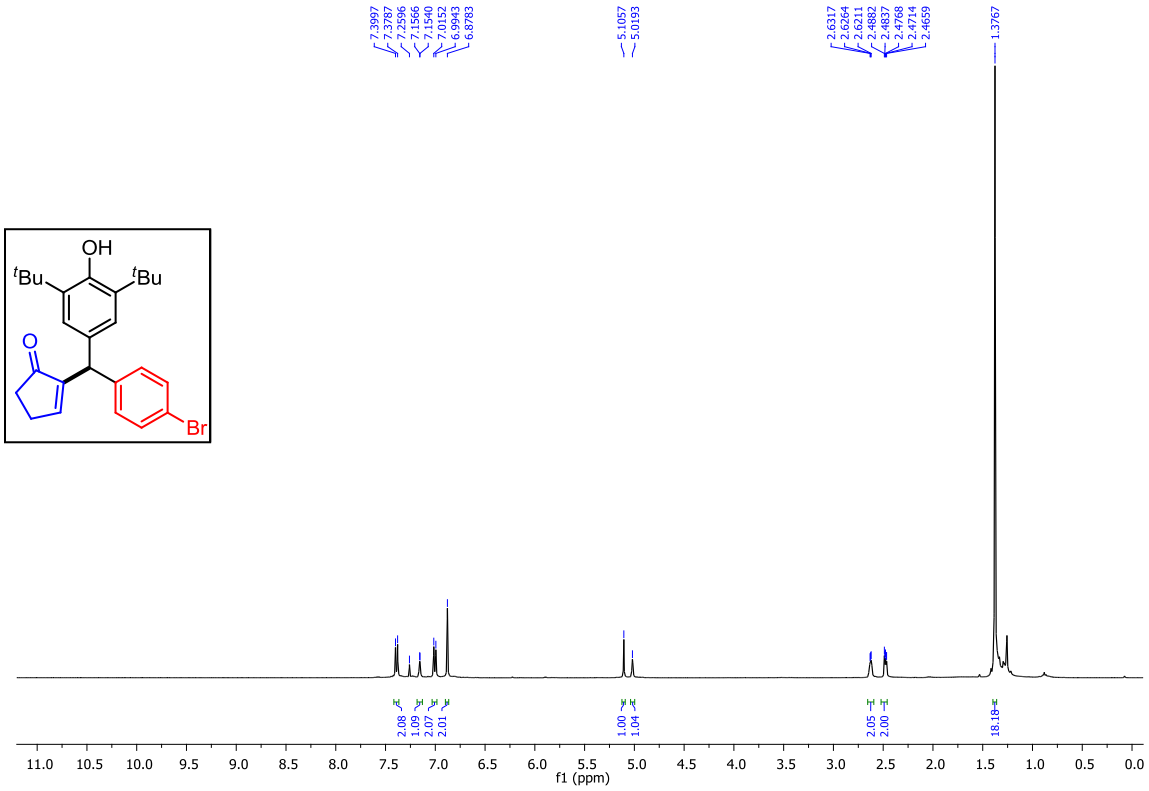
^{1}H NMR spectrum of **28l**



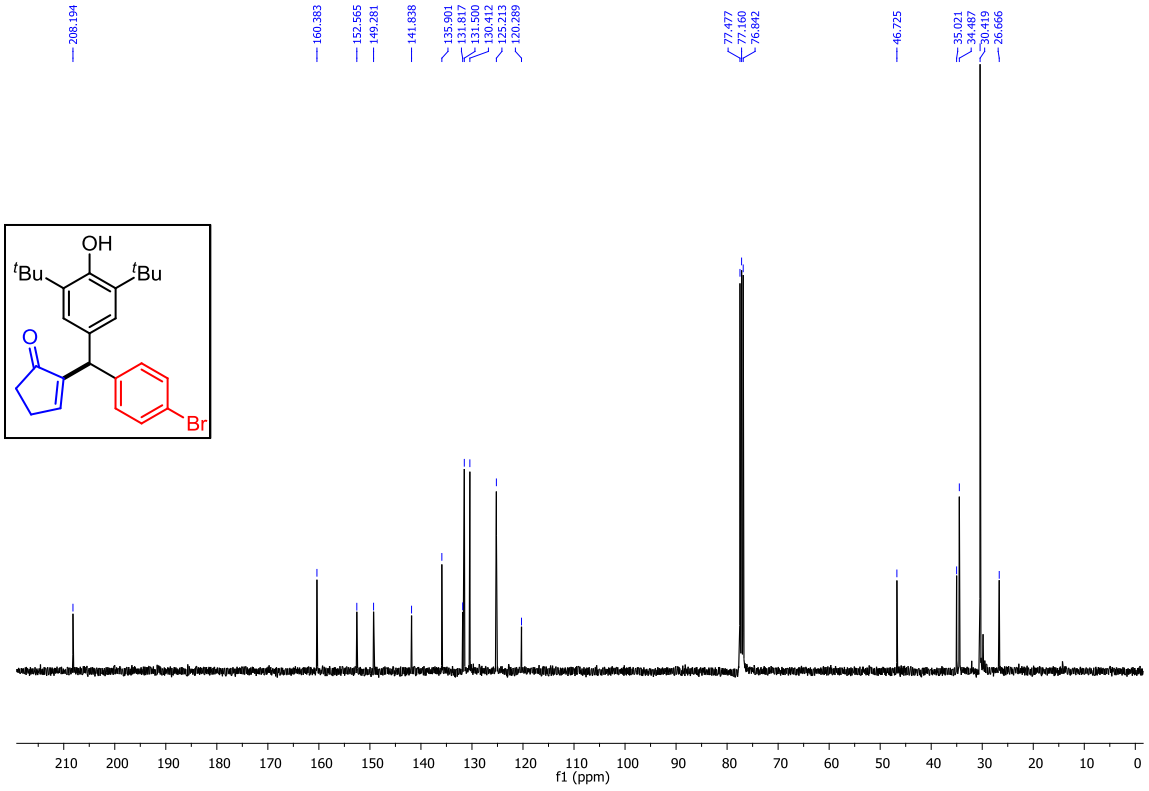
^{13}C NMR spectrum of **28l**



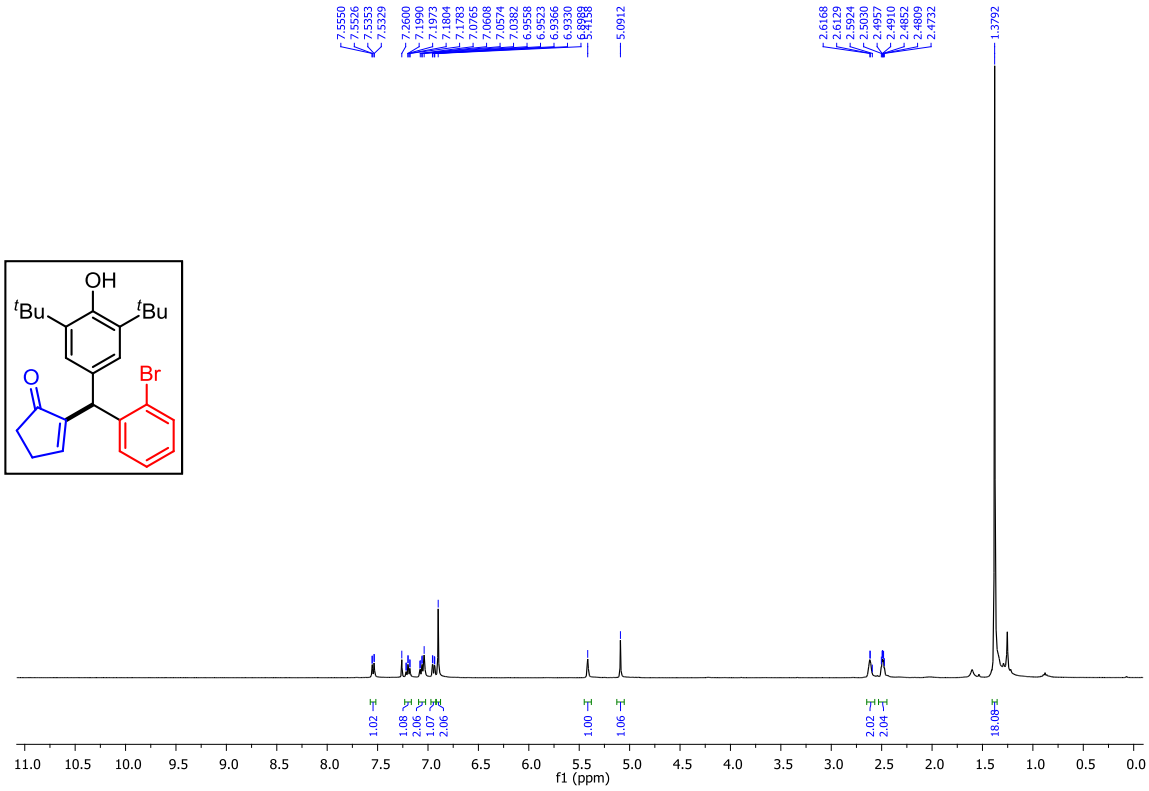
^{1}H NMR spectrum of **28m**



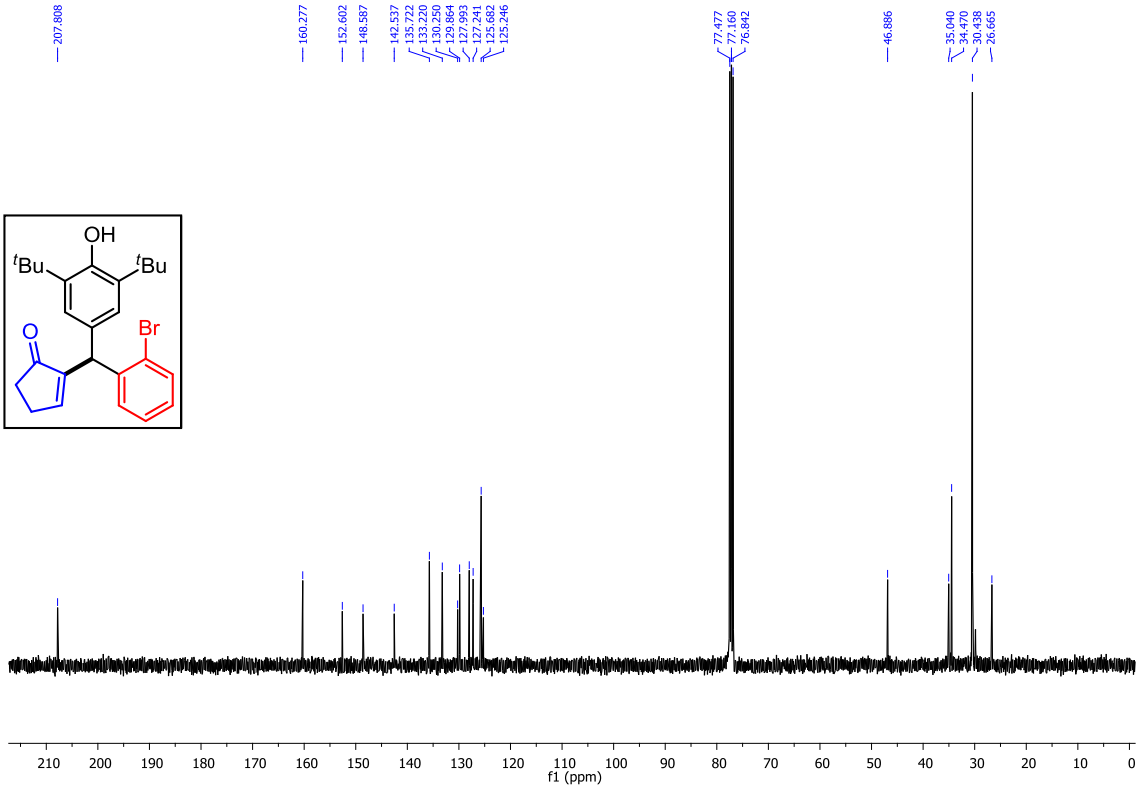
^{13}C NMR spectrum of **28m**



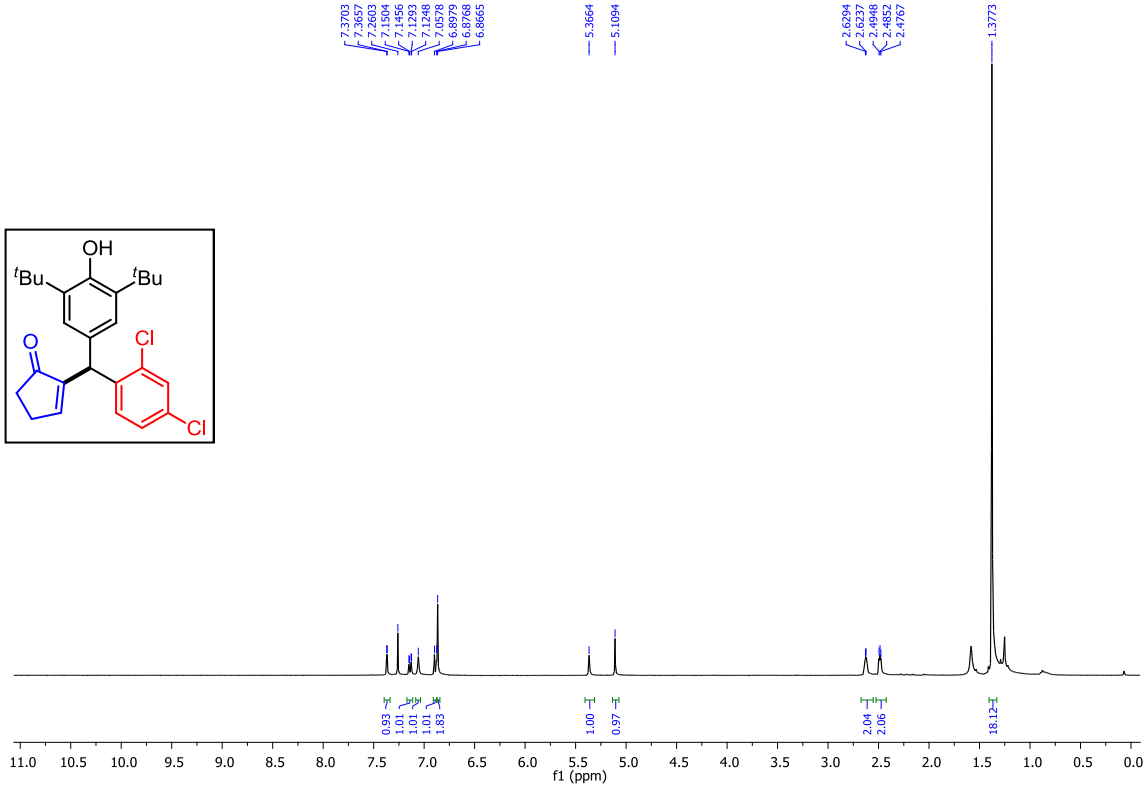
^{1}H NMR spectrum of **28n**



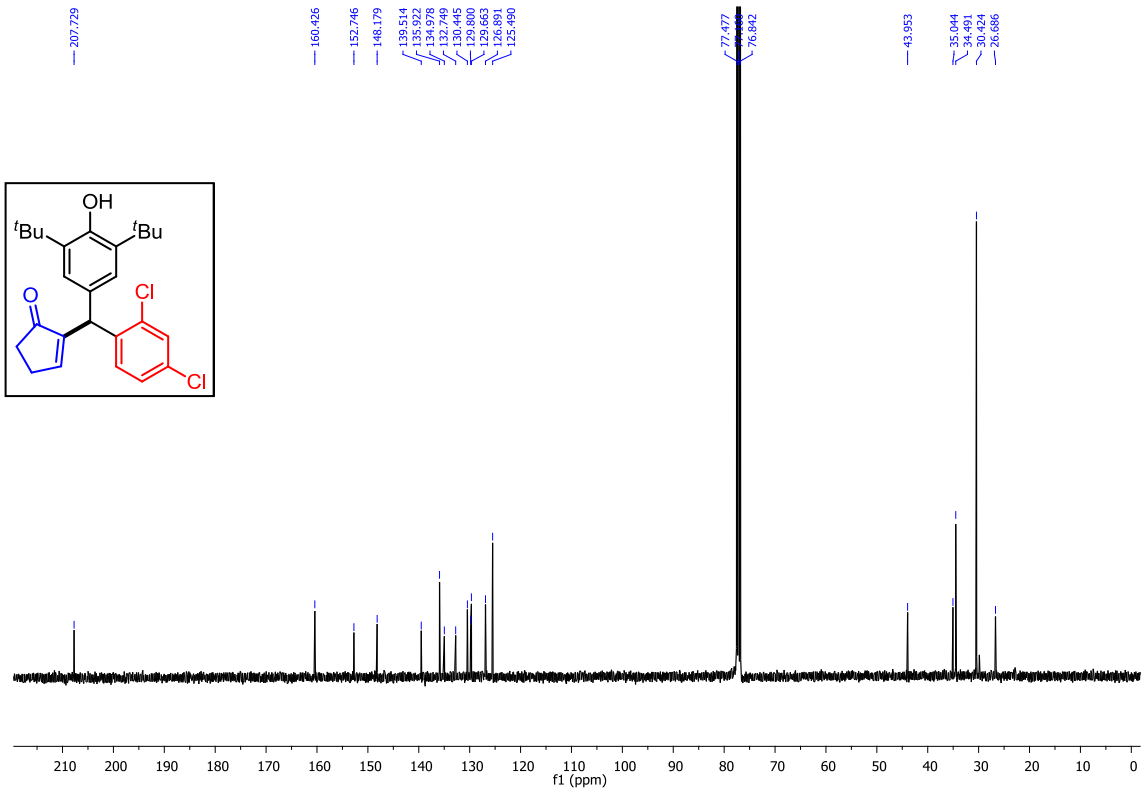
^{13}C NMR spectrum of **28n**



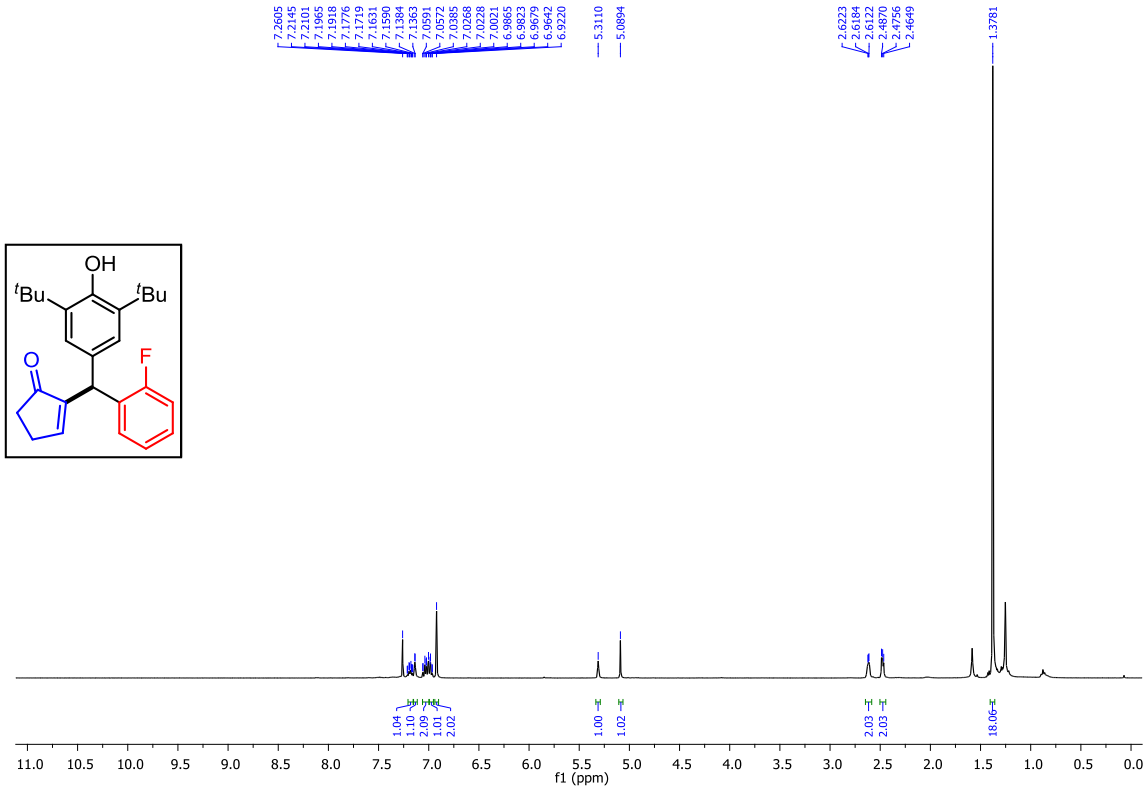
^{1}H NMR spectrum of **28o**



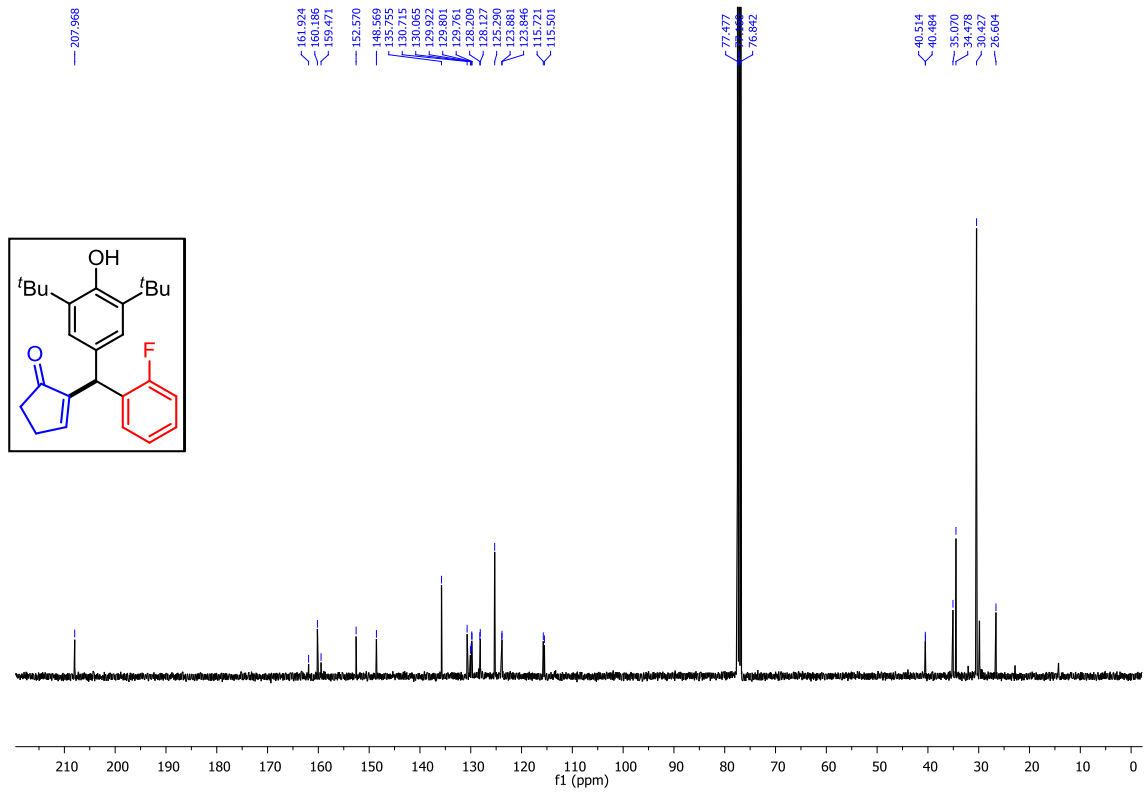
^{13}C NMR spectrum of **28o**



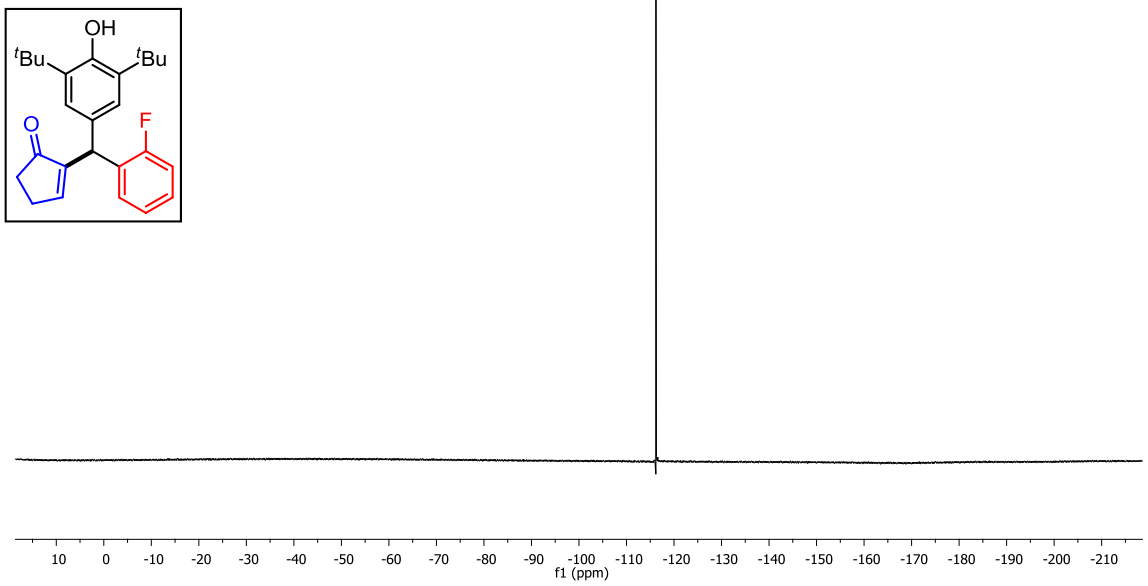
^{1}H NMR spectrum of **28p**



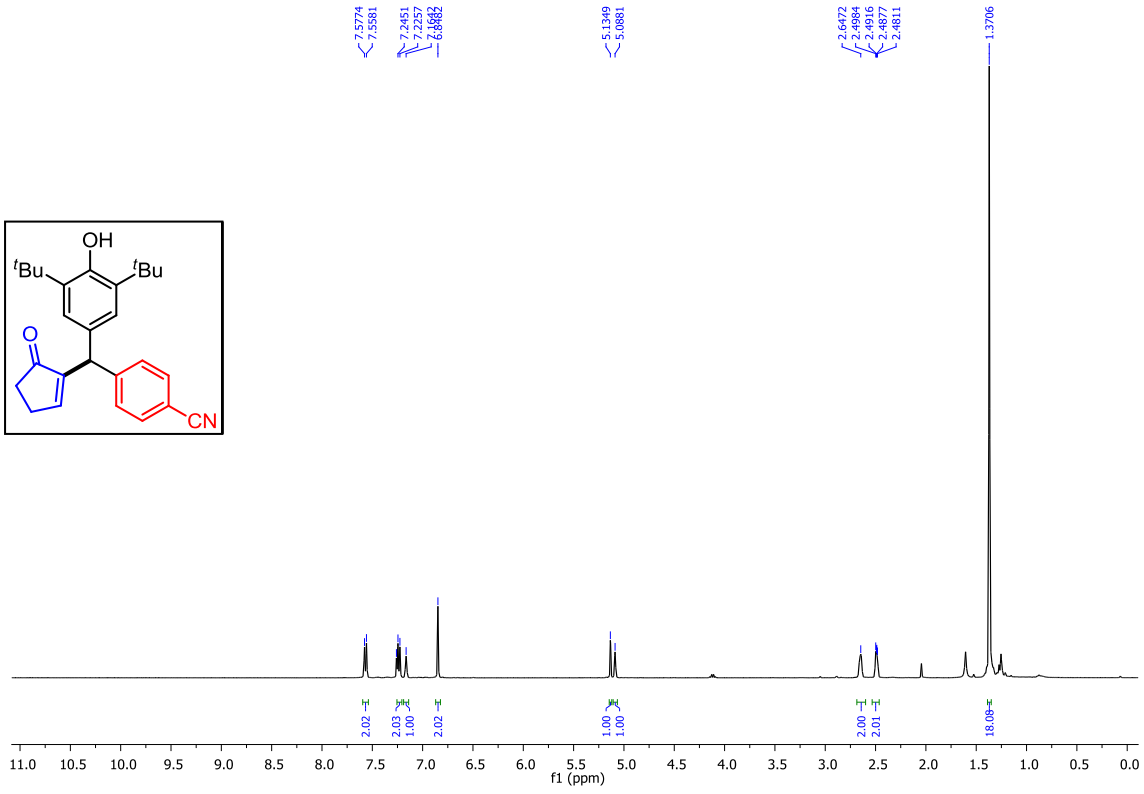
^{13}C NMR spectrum of **28p**



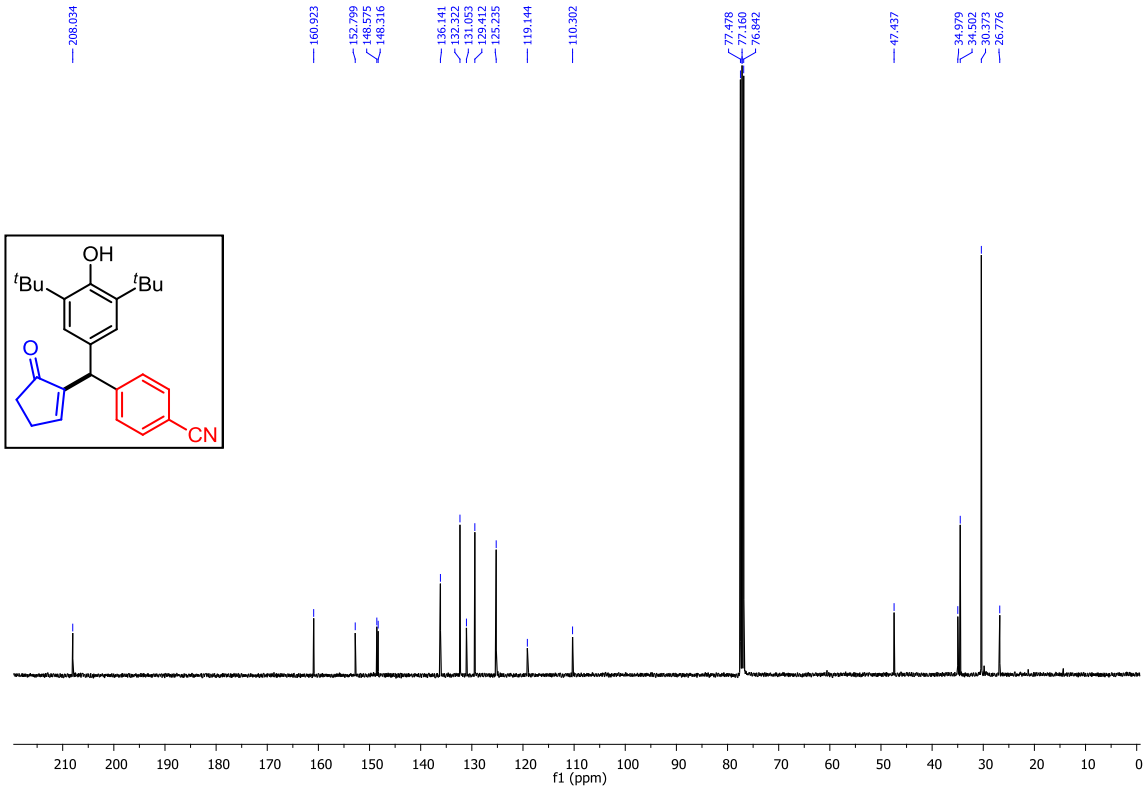
^{19}F NMR spectrum of **28p**



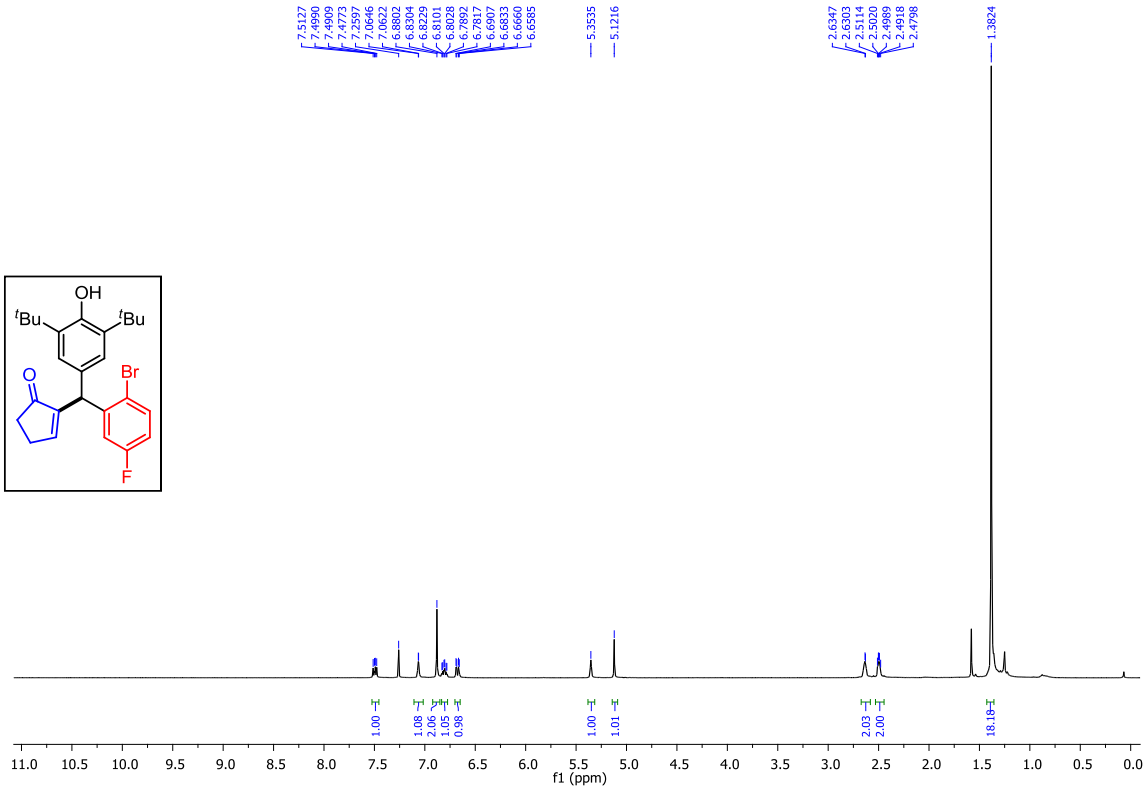
^{1}H NMR spectrum of **28q**



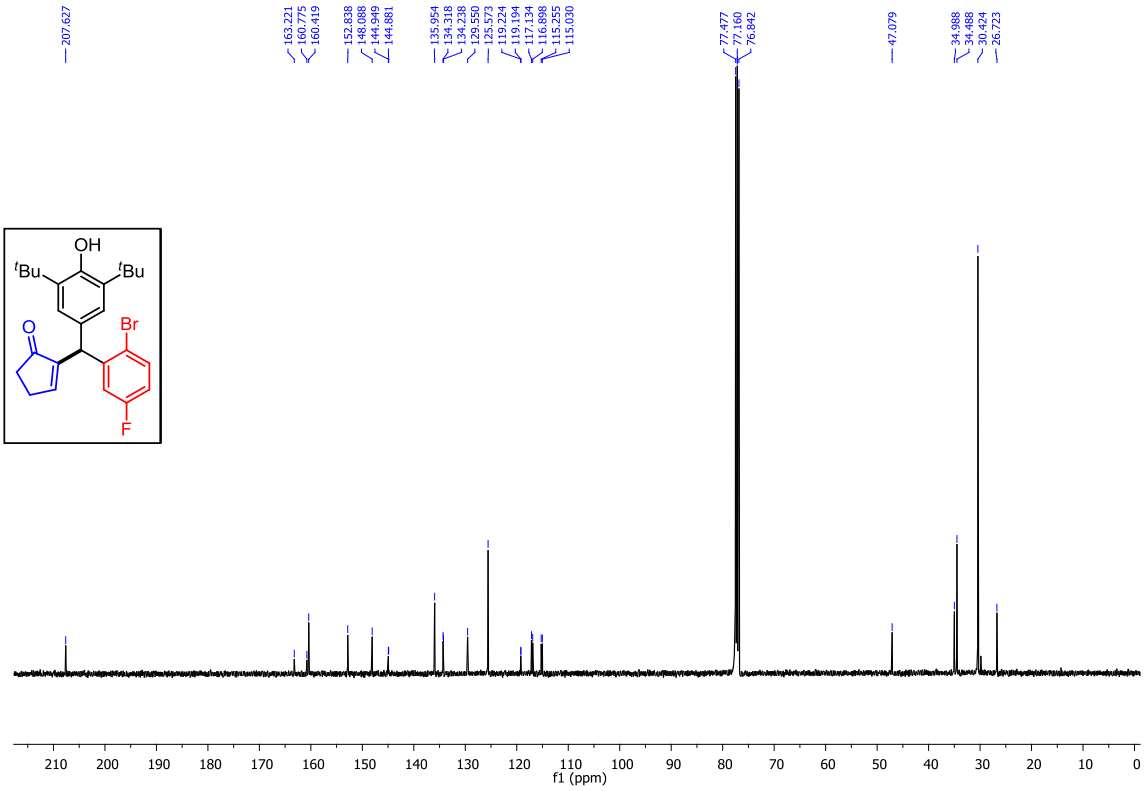
^{13}C NMR spectrum of **28q**



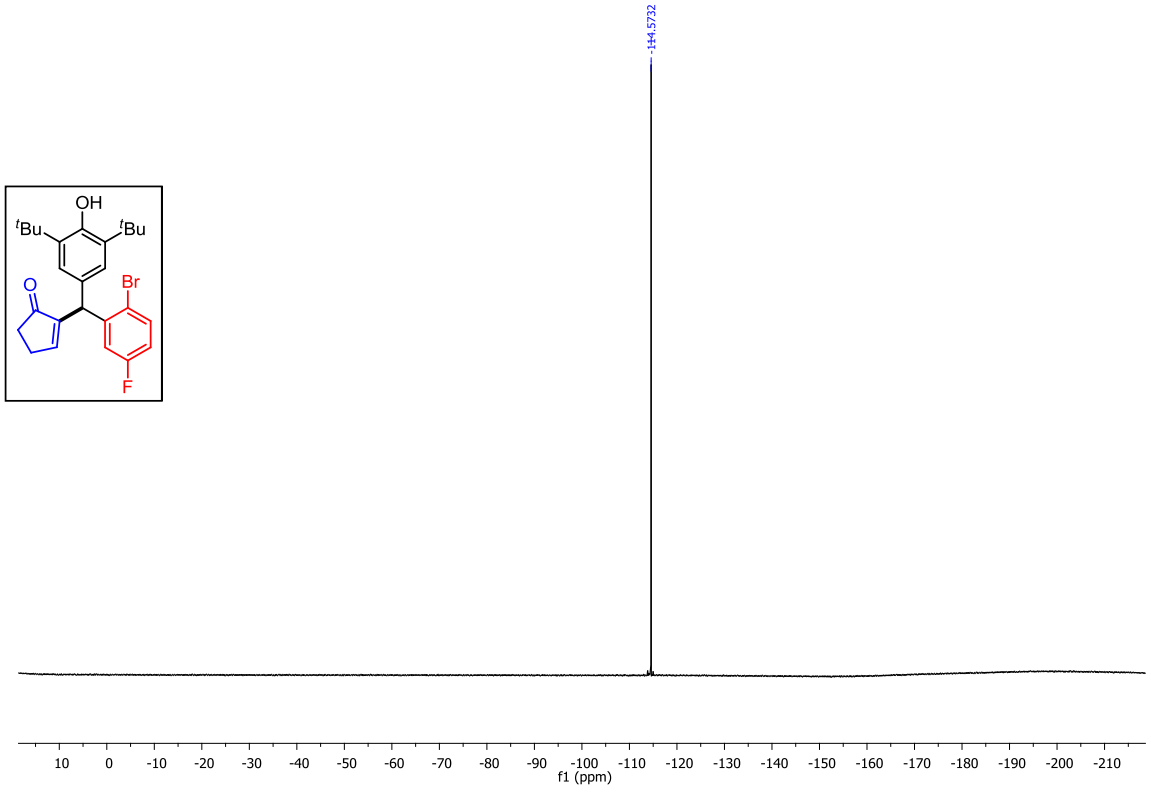
^{1}H NMR spectrum of **28s**



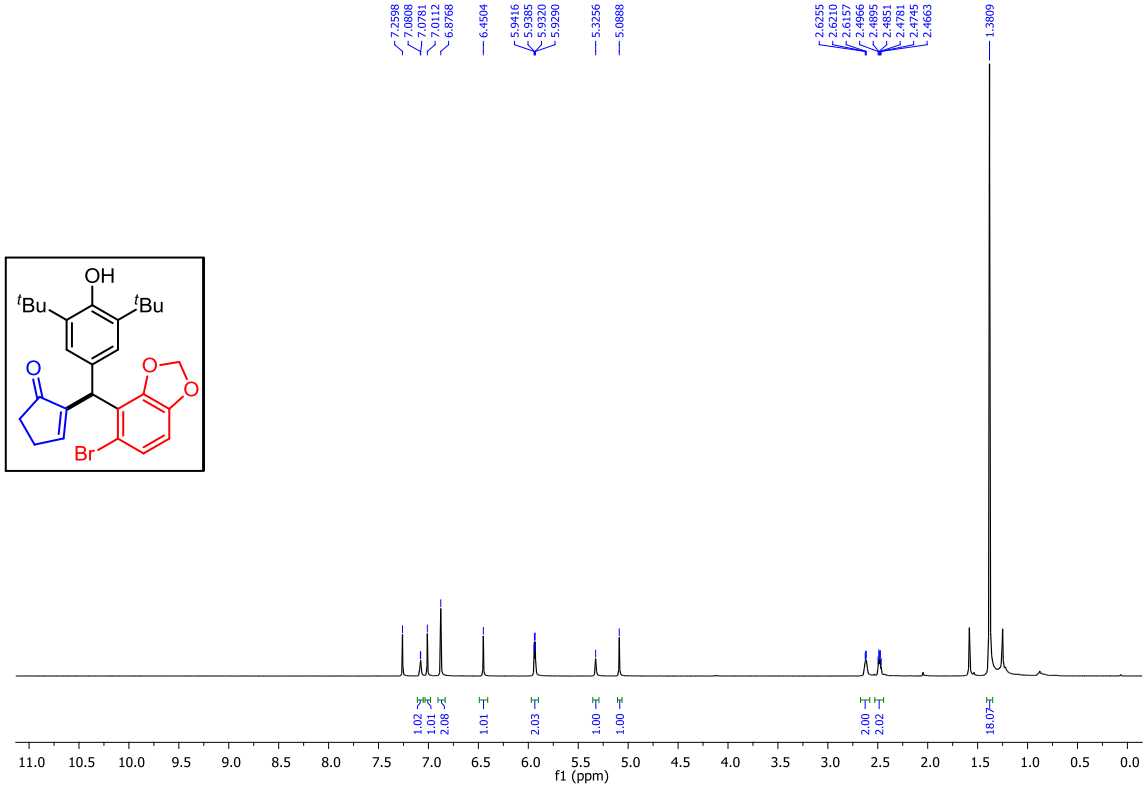
^{13}C NMR spectrum of **28s**



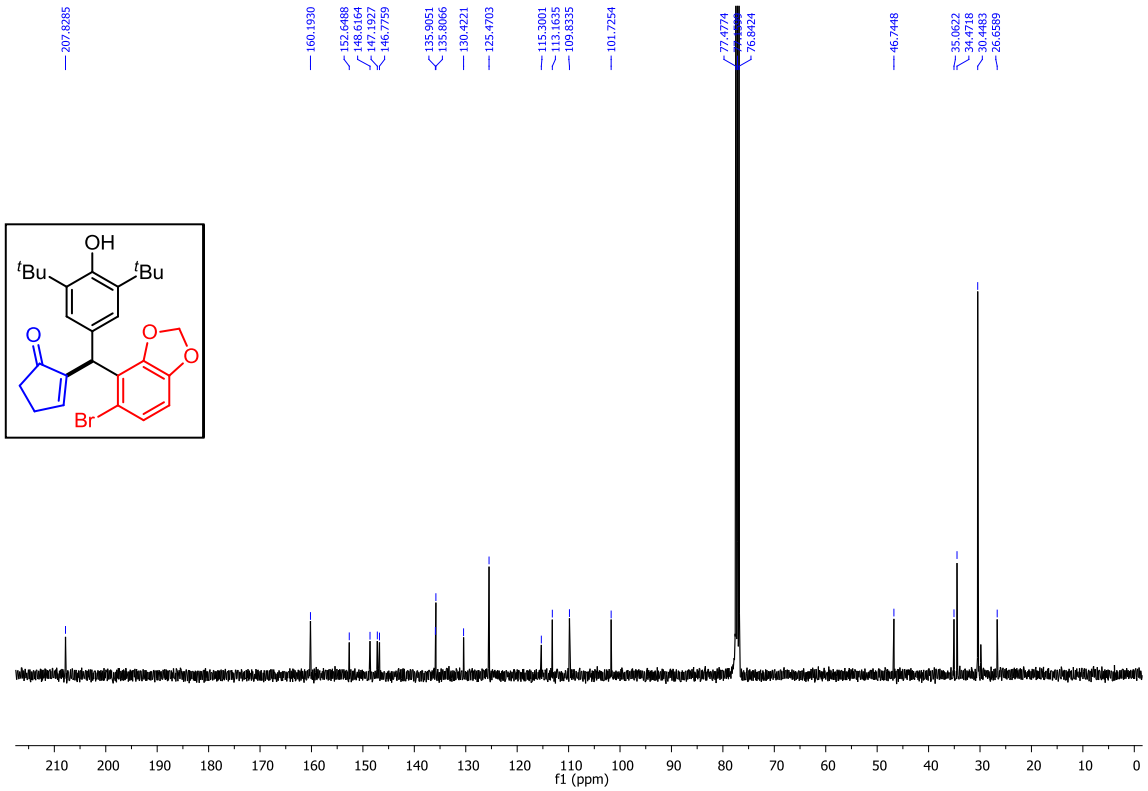
^{19}F NMR spectrum of **28s**



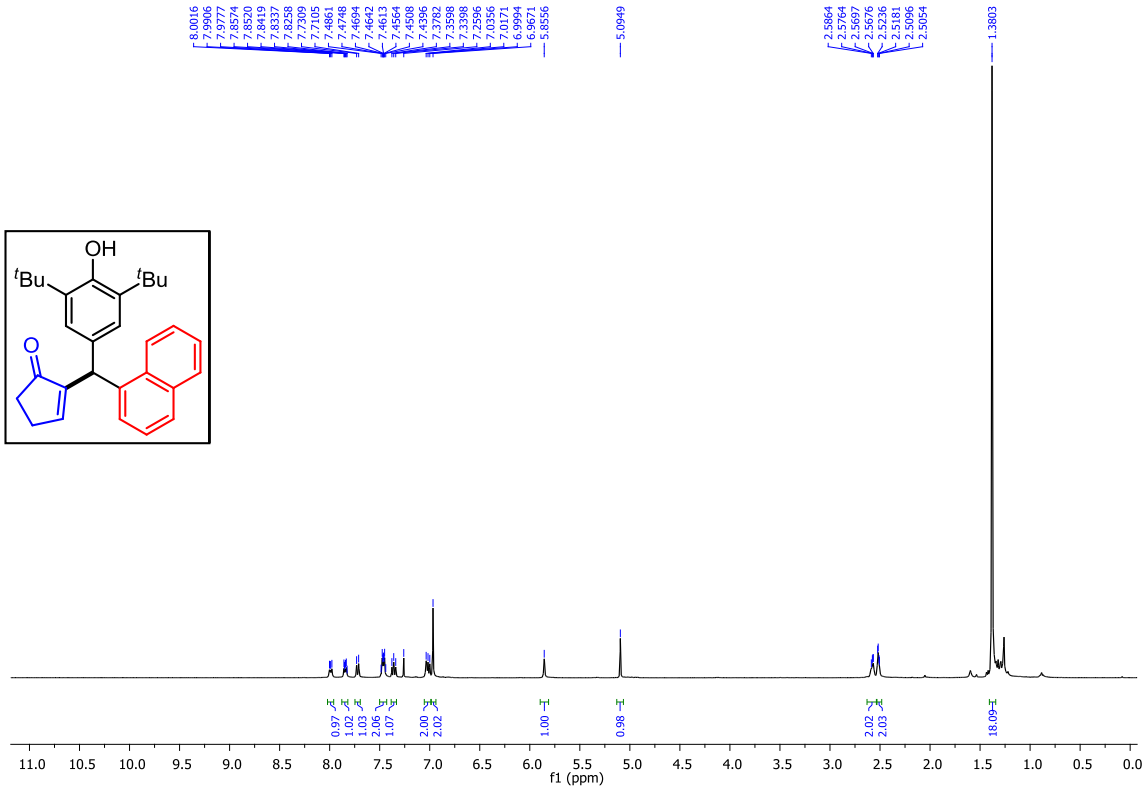
^{1}H NMR spectrum of **28u**



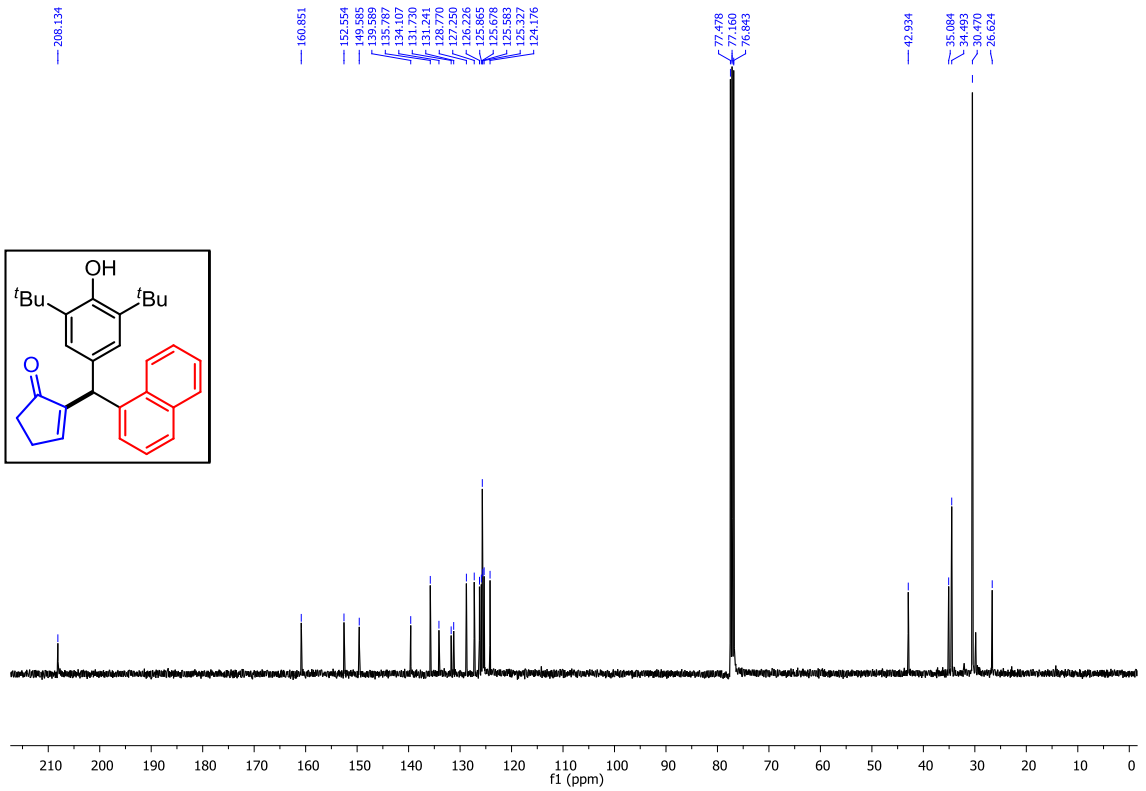
^{13}C NMR spectrum of **28u**



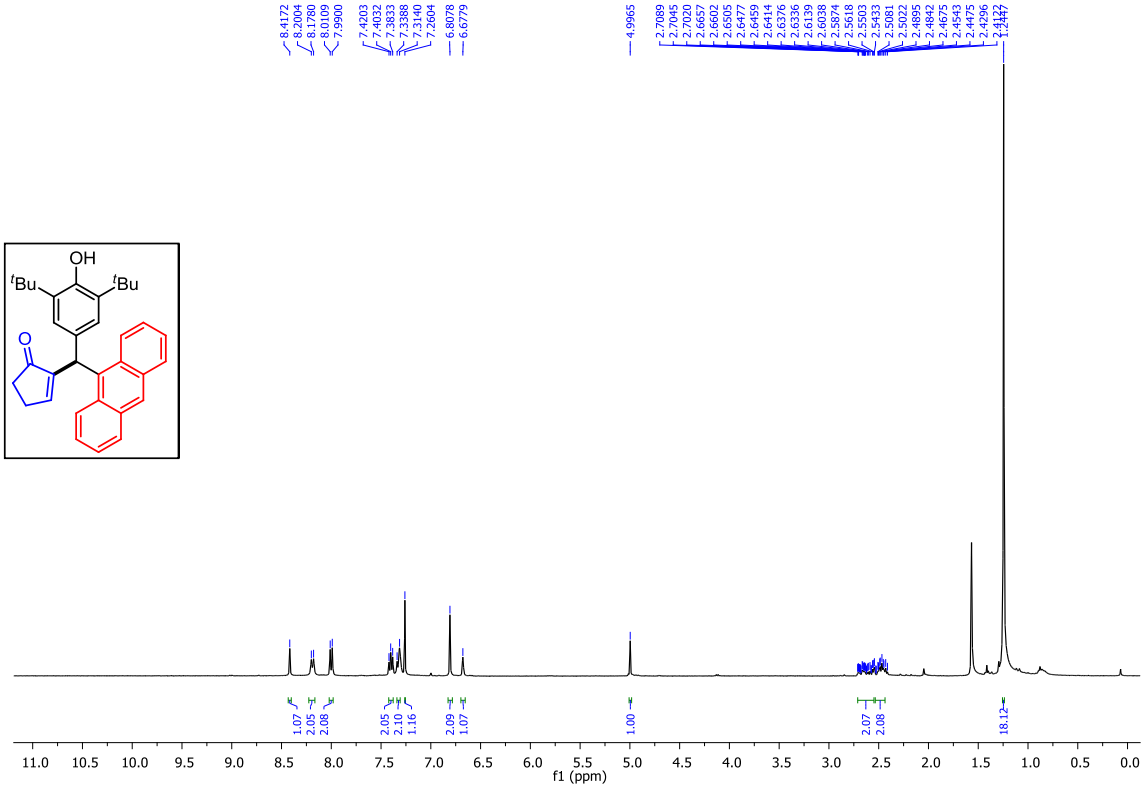
^{1}H NMR spectrum of **28v**



^{13}C NMR spectrum of **28v**



^{1}H NMR spectrum of **28w**



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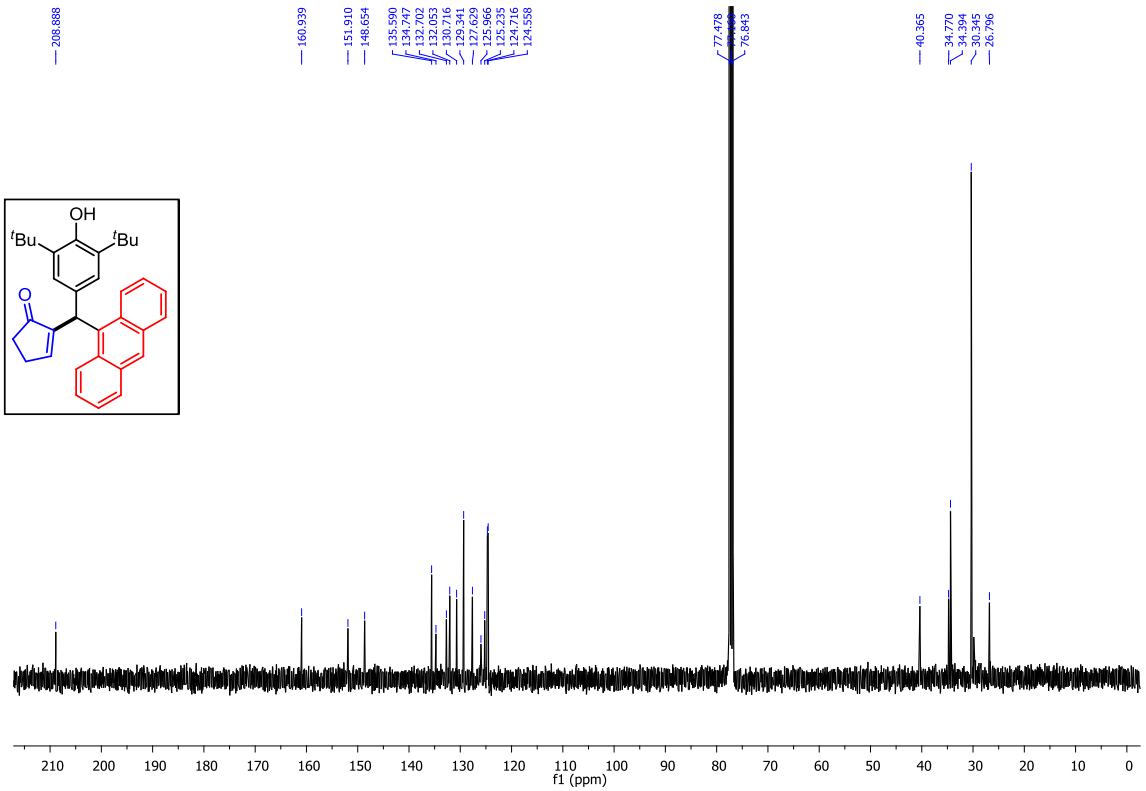
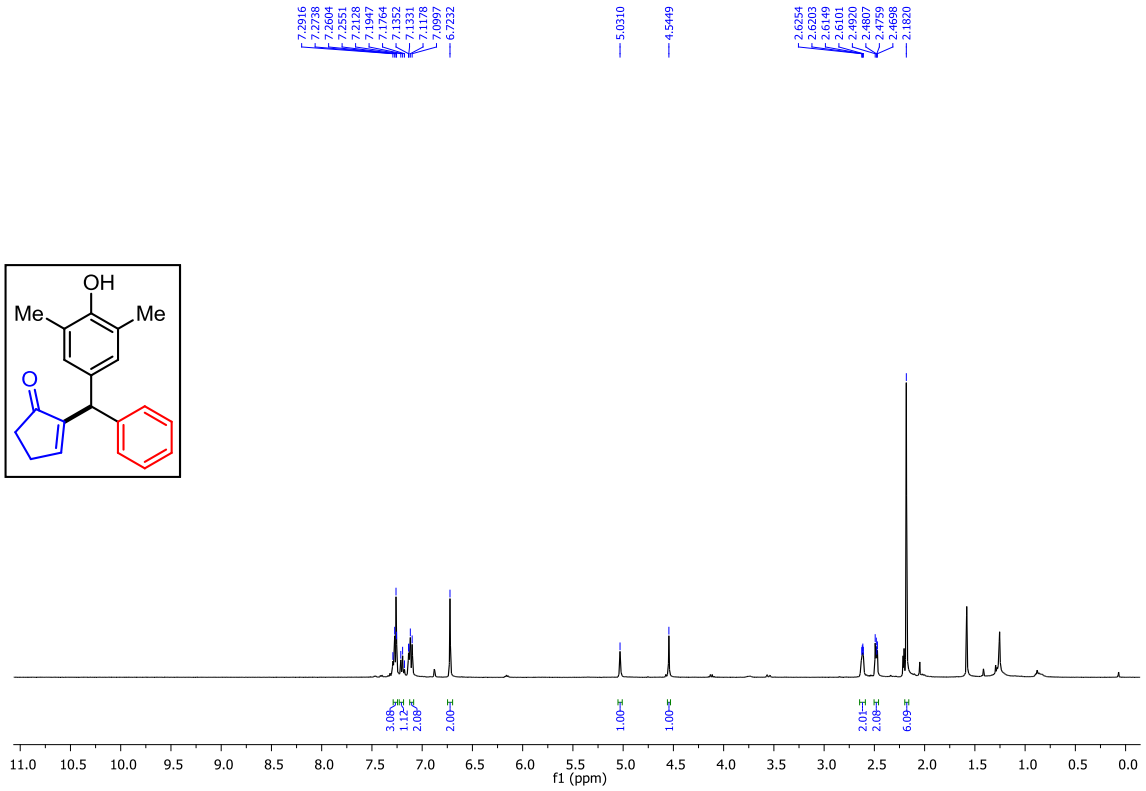


^{1}H NMR spectrum of **28x**



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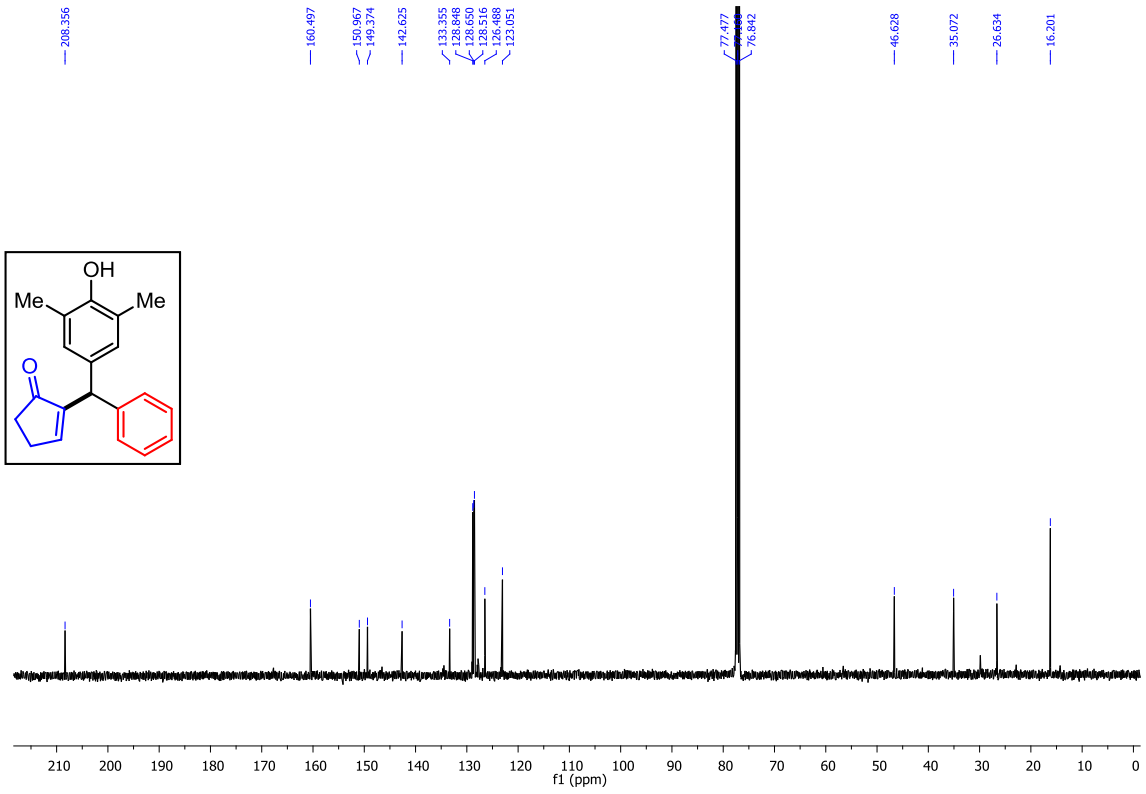
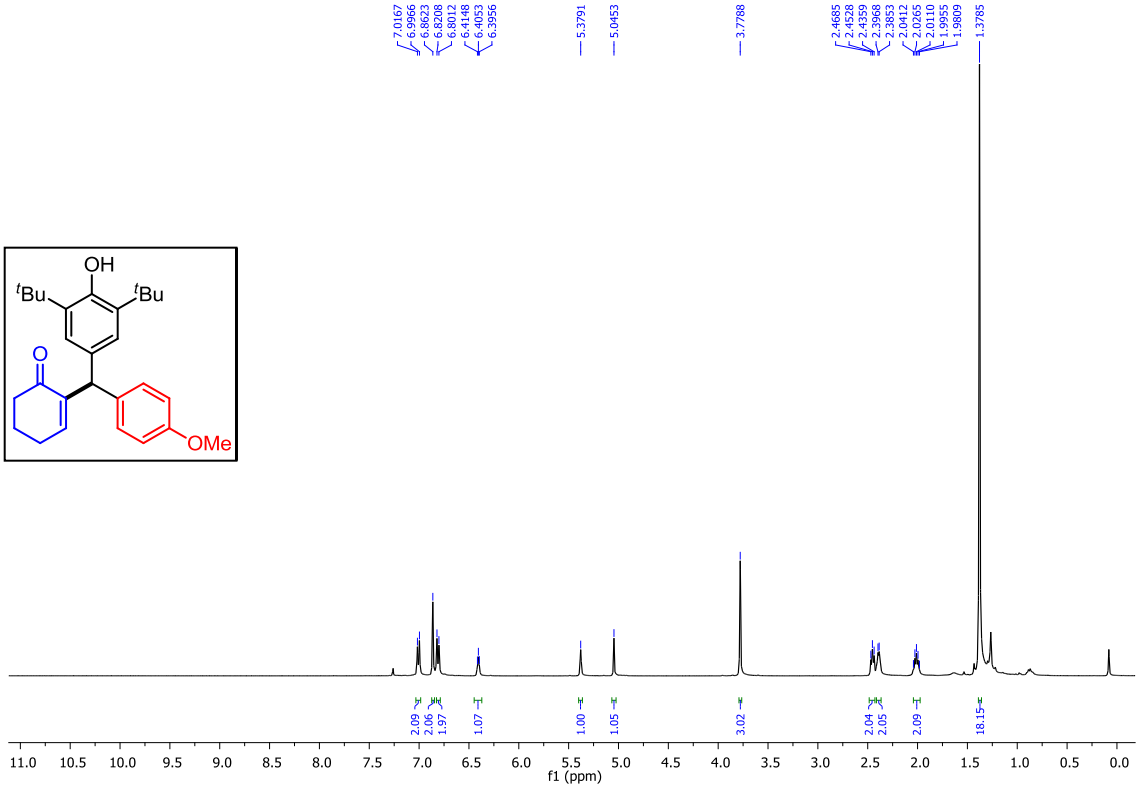


^{1}H NMR spectrum of **33a**



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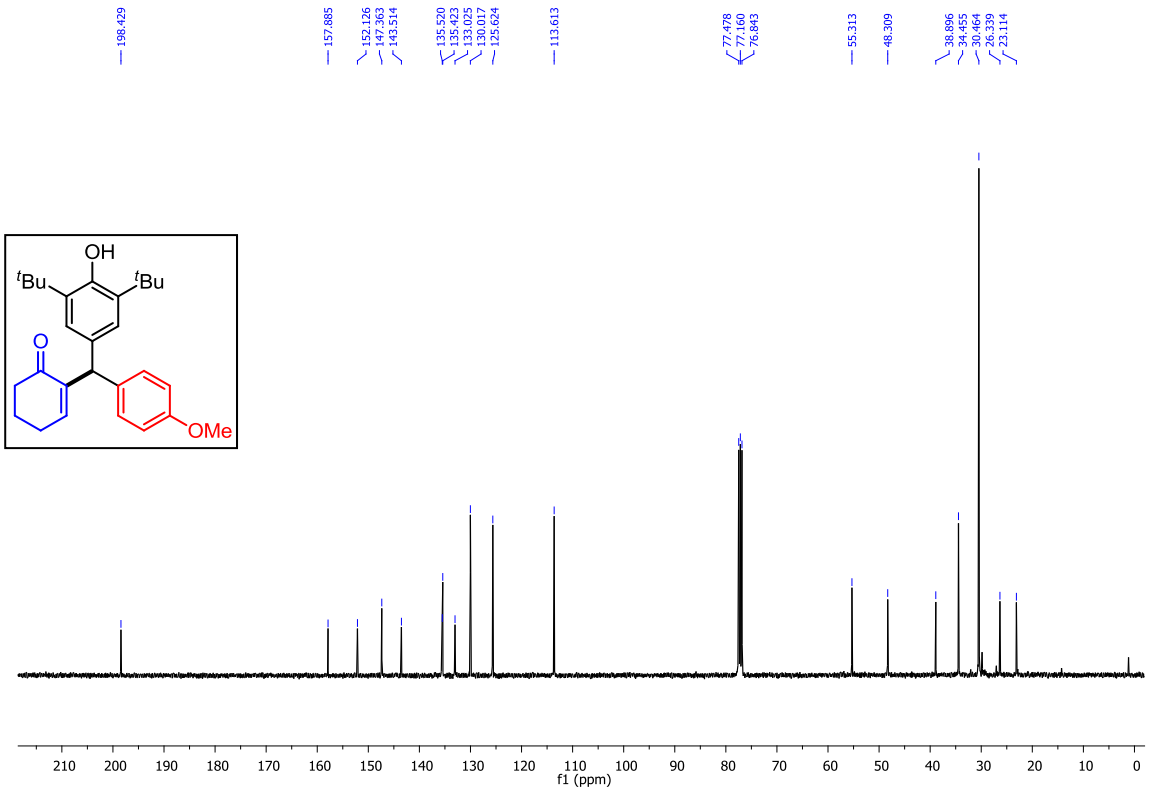

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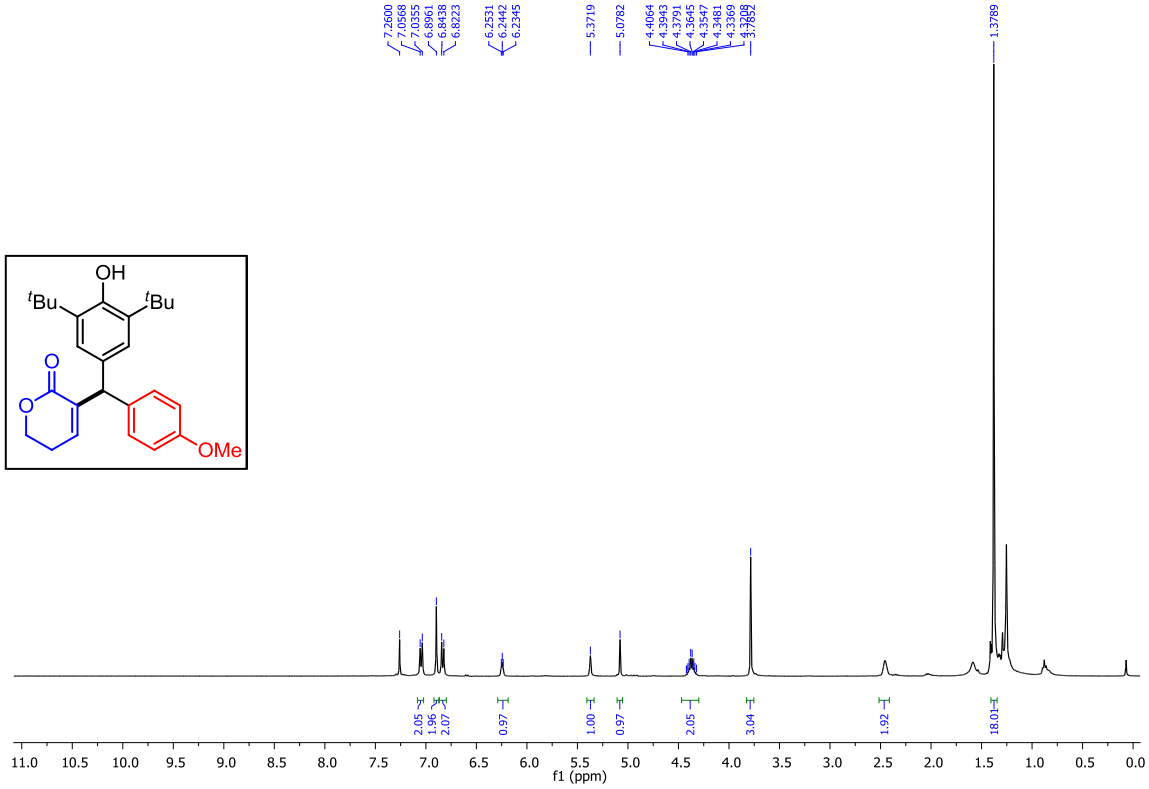
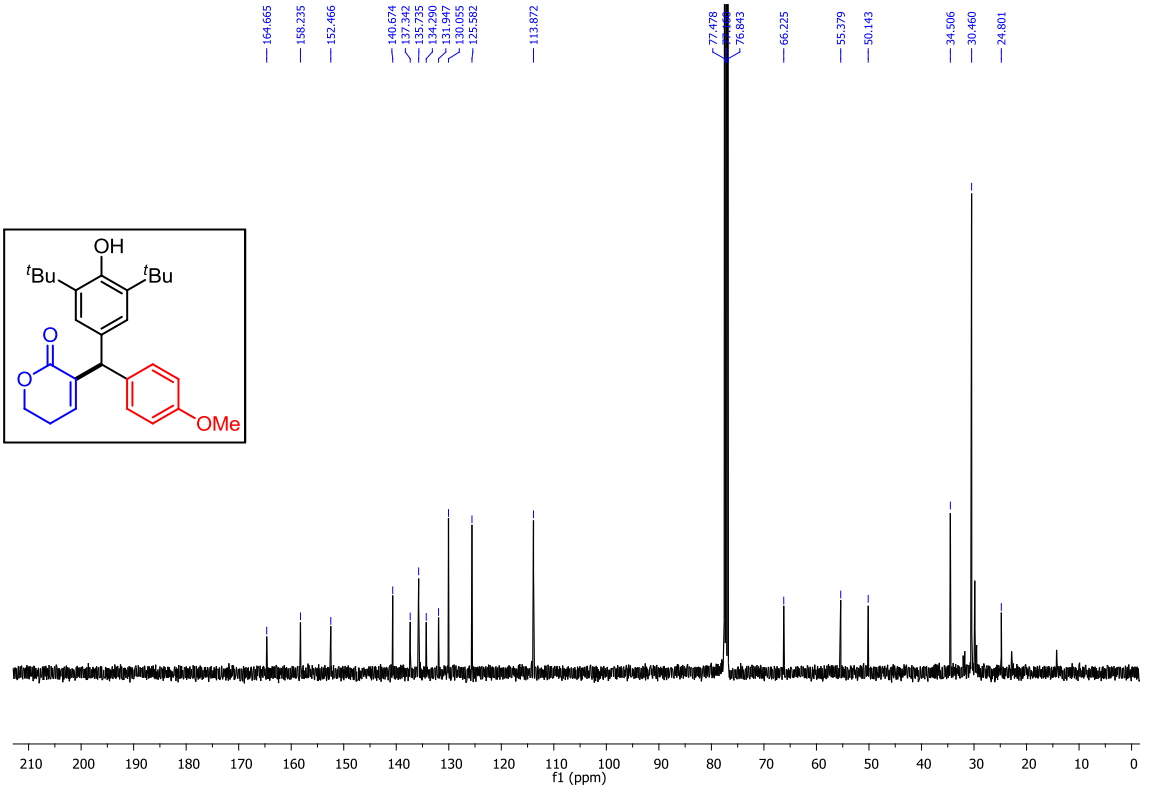
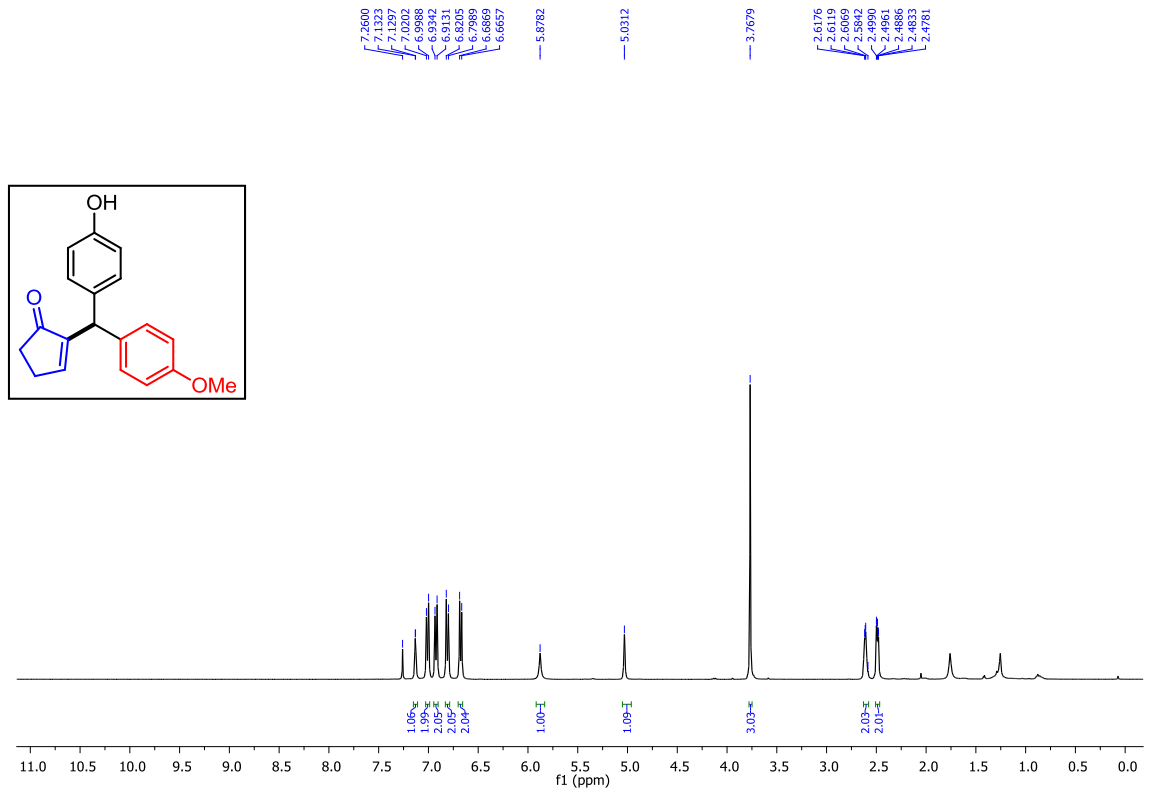


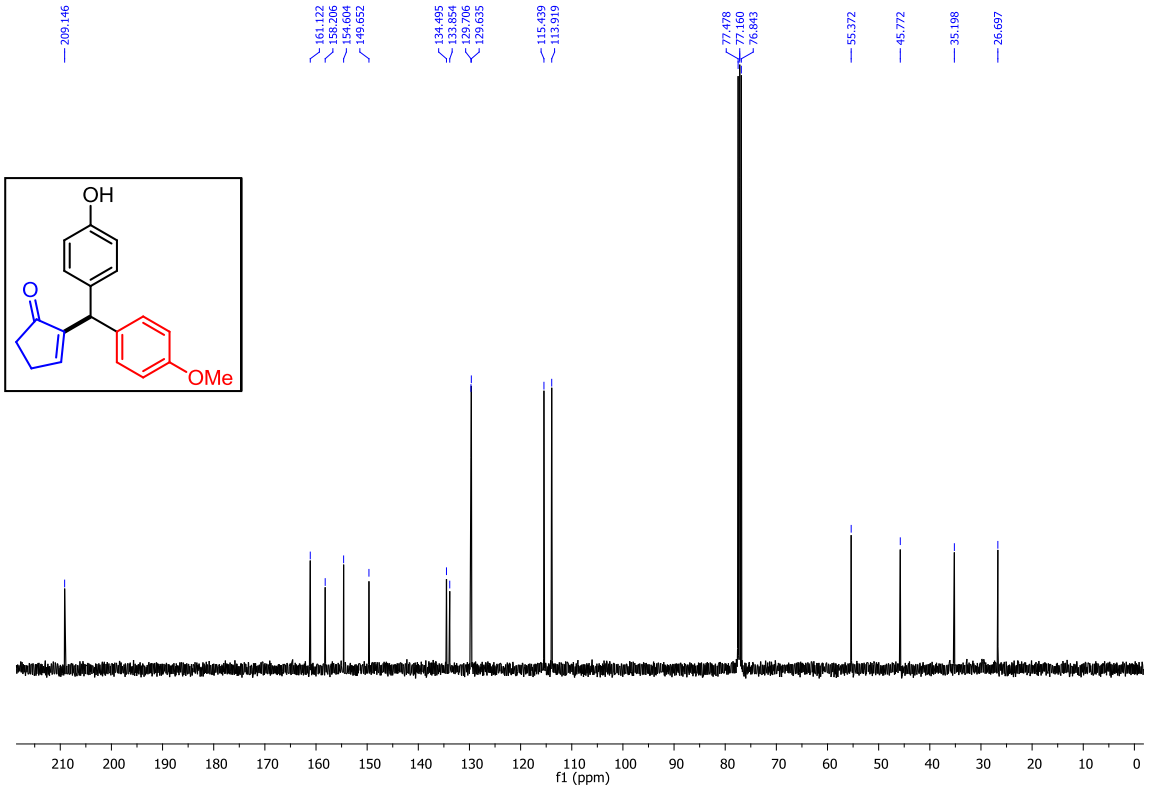
^{13}C NMR spectrum of **33b**



^{1}H NMR spectrum of **34**



^{13}C NMR spectrum of **34**



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Chapter 3

3. $Bi(OTf)_3$ catalyzed solvent free approach to unsymmetrical diaryl(2-indolyl)methanes through 1,6-conjugate addition of 3-substituted indoles to *para*-quinone methides

This chapter describes a straightforward approach for the synthesis of unsymmetrical diaryl(2-indolyl)methanes via a direct C2-functionalization of indoles with *para*-quinone methides. This chapter also covers a brief literature review on different strategies for the synthesis of triarylmethanes and C2-functionalized indoles

3.1 Introduction

Triarylmethanes have emerged as important and integral scaffolds in many pharmaceuticals and biologically active natural molecules.[1] Several of them exhibits important therapeutic applications (Figure 1).[2] For example, Triarylmethanes **1a**, **1b** and **1c** possess remarkable biological activities and being explored as anti-breast cancer,[2b] anti-viral[2c] and anti-TB agents,[2d] respectively. Compound **1d** displayed impressive anti-fungal activity.[3a] Furthermore, triarylmethanes **1e** and **1f** possess significant cytotoxic activity against renal cancer cells[3b] and lungs cancer cells,[3c] respectively.

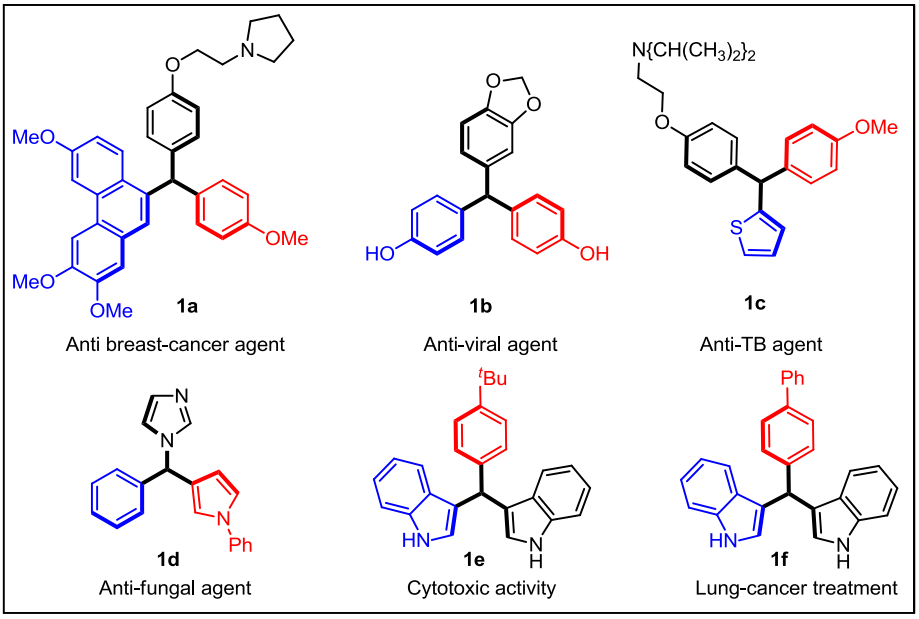


Figure 1. Some biologically significant triarylmethanes

Besides the medicinal applications, triarylmethanes have also found remarkable applications in dye industry[4] and materials science.[4b] Some of the triarylmethane derivatives have been utilized as metal ion sensors[5] and fluorescent probes.[6] In addition, in bio-organic chemistry, triarylmethanes are utilized for the synthesis of polyamide nucleic acid equivalents.[7] These significant applications of triarylmethanes have attracted the scientific community towards the development of different easily accessible routes. Some of the literature reports are discussed in this section.

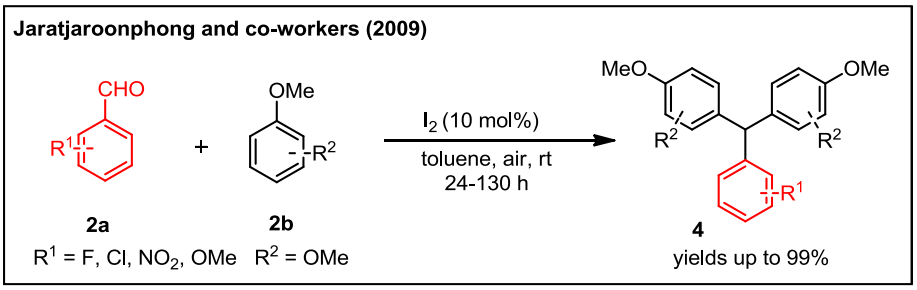
3.2 Synthesis of Triarylmethanes

3.2.1 Lewis acid/Bronsted acid catalyzed Friedel-Crafts approach

Xu and co-workers reported a solvent free Lewis acid catalyzed Friedel-Crafts alkylation approach for the synthesis of triarylmethanes.[8] A wide range of aromatic aldehydes (**2a**) containing electron-poor and electron-rich substituents were reacted with electron-rich arenes (**2b**) in presence of catalytic amount of $AlCl_3$ to undergo a Friedel-Crafts alkylation reaction and the resultant triarylmethanes (**3**) were isolated in moderate to good yields (Scheme 1).

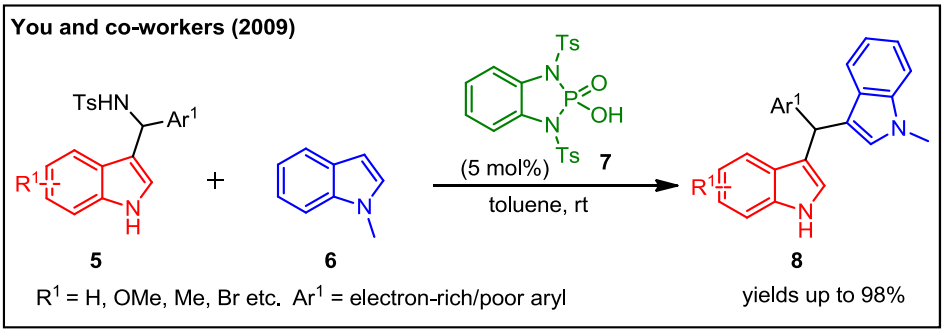
Scheme 1: Synthesis of triarylmethanes through Friedel-Crafts alkylation

Later, Jaratjaroonphong's group disclosed molecular iodine catalyzed mild and efficient Friedel-Crafts alkylation reaction for the synthesis of triarylmethanes.[9] A wide range of electron rich arenes (**2b**) and aromatic aldehydes (**2a**) were reacted in presence of 10 mol% of iodine under open flask conditions. Almost in all the cases, the corresponding triarylmethanes (**4**) were isolated in good to excellent yields. Both electron-rich and electron-poor aromatic aldehydes were tolerated under the optimized conditions (Scheme 2).



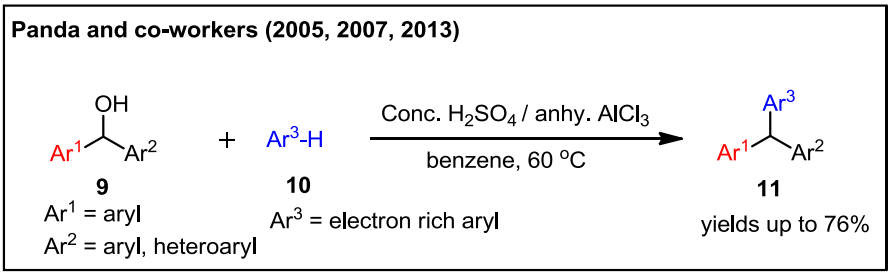
Scheme 2: Lewis acid catalyzed synthesis of triarylmethanes

You and co-workers described a Brønsted acid catalyzed Friedel-Crafts alkylation reaction for the synthesis of unsymmetrical triarylmethanes.[10] Varieties of α-(3-indolyl)benzylamines (**5**) underwent Friedel-Crafts alkylation reaction with *N*-methylindole (**6**) in presence of catalytic amount of phosphorodiamidic acid (**7**) to afford the corresponding triarylmethanes (**8**) in good to excellent yields (Scheme 3).



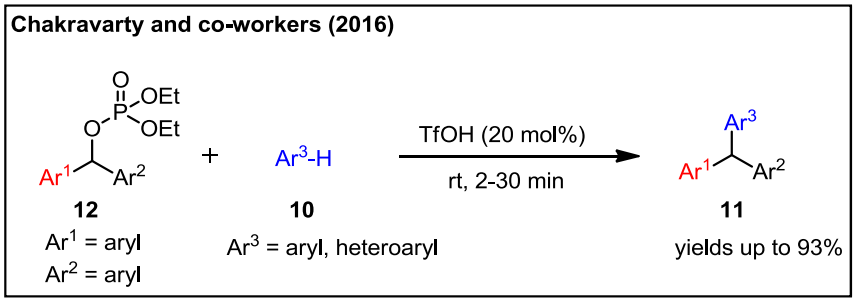
Scheme 3: Brønsted acid catalyzed Friedel-Crafts alkylation approach

Panda and co-workers developed a Friedel-Craft alkylation of diarylcarbinols for the synthesis of unsymmetrical triarylmethanes.[11] Different diarylcarbinols (**9**) reacted with electron-rich arenes (**10**) in presence of conc. H_2SO_4/anhy.$AlCl_3$ to furnish the corresponding triarylmethanes (**11**) in good yields (Scheme 4).



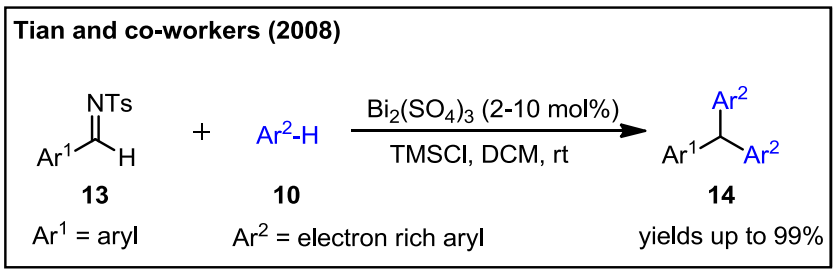
Scheme 4: Brønsted acid catalyzed synthesis of triarylmethanes

Later, Chakravarty and co-workers reported a triflic acid catalyzed Friedel-Crafts benzylation reaction of secondary benzylic phosphates and arenes.[12] A wide range of electron-rich and electron-poor secondary benzylic phosphates (**12**) reacted efficiently with arenes (**10**) to produce the subsequent unsymmetrical triarylmethanes (**11**) in good to excellent yields. Interestingly, no external solvent was required for this transformation (Scheme 5).



Scheme 5: Friedel-Crafts benzylation of phosphates with arenes

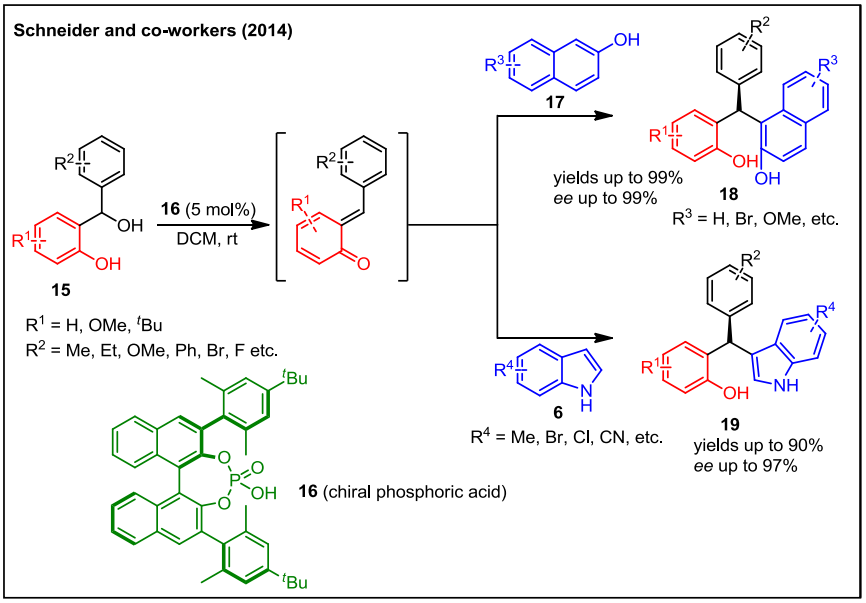
In 2008, Tian's group observed a bismuth catalyzed Friedel-Crafts alkylation approach for the synthesis of symmetrical triarylmethanes.[13] A wide range of *N*-tosylimines (**13**), derived from aromatic aldehydes, were reacted efficiently with electron-rich arenes (**10**) to produce the resultant symmetrical triarylmethanes (**14**) in a highly regioselective manner (Scheme 6).



Scheme 6: Bi-catalyzed Friedel-Crafts reactions for the synthesis of symmetrical triarylmethanes

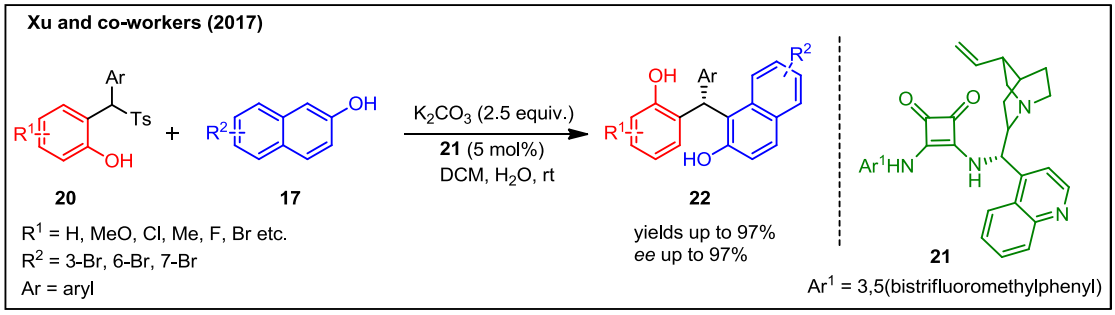
Very recently, quinone methides (QMs) are being utilized as very good precursor for the synthesis of triarylmethane derivatives. For example, Schneider's group accomplished a fascinating approach for the synthesis of chiral triaylmethanes using chiral phosphoric acid as a hydrogen bonding catalyst.[14] A library of 2-naphthols (**17**) and indoles (**6**) were subjected to Friedel-Crafts alkylation reaction with *o*-quinone methides precursors (**15**), respectively

under the optimized conditions and, in most of the cases, the resultant triarylmethanes (**18** & **19**) were isolated in good to excellent yields with excellent *ee* (Scheme 7).



Scheme 7: Chiral phosphoric acid catalyzed synthesis of unsymmetrical triarylmethanes

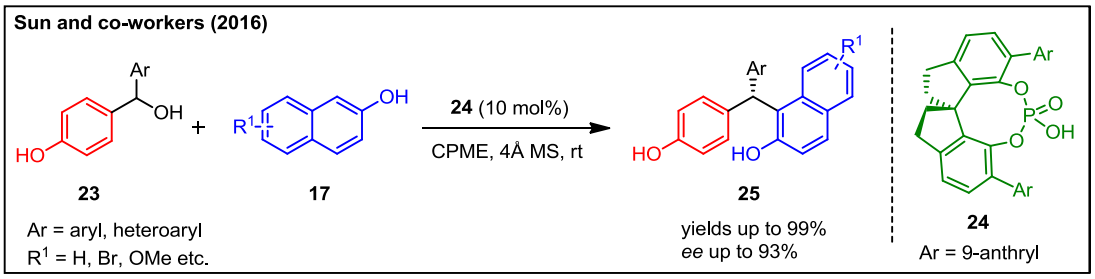
Very recently, another interesting methodology was disclosed by Xu and co-workers for the synthesis of enantiomerically-enriched triarylmethanes using a chiral bifunctional amine-squaramide catalyst.[15] An array of 2-[phenyl(tosyl)methyl]phenol derivatives (**20**) were reacted with 2-naphthols (**17**) in presence of chiral catalyst (**21**) in an oil-water biphasic medium to furnish the triarylmethanes (**22**) in good to excellent yields with excellent *ee*. The authors believe that oil-water biphasic medium is actually increasing the effectiveness of the catalytic medium (Scheme 8).



Scheme 8: Synthesis of chiral triarylmethanes in oil-water phase

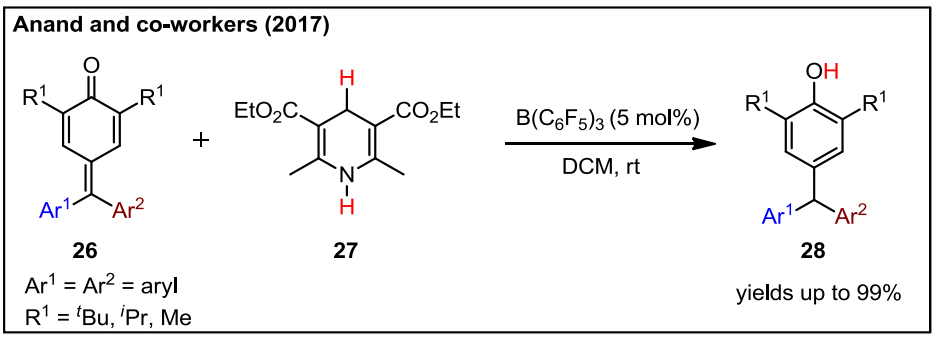
Sun and co-workers developed a chiral phosphoric acid catalyzed synthesis of enantiomerically enriched triarylmethanes from an *in situ* generated *para*-quinone methides.[16]

In presence of chiral phosphoric acid (**24**), 2-naphthols (**17**) underwent 1,6-conjugate addition reactions to *in situ* generated *p*-QMs from a variety of 4-hydroxybenzyl alcohols (**23**) to afford the chiral triarylmethanes (**25**) in excellent yields with very good enantioselectivity (Scheme 9).



Scheme 9: Chiral Brønsted acid catalyzed synthesis of triarylmethanes

Very recently, Anand and co-workers disclosed an interesting approach for the synthesis of triarylmethanes through a transfer hydrogenation of fuchsones.[17] In this method, $B(C_6F_5)_3$ was used as Lewis acid to activate the carbonyl oxygen of fuchsones (**26**). Further, the hydride transfer from the Hantzsch ester (**27**) to the fuchsones in 1,6-fashion led to the formation of triarylmethanes (**28**) in excellent yields (Scheme 10).



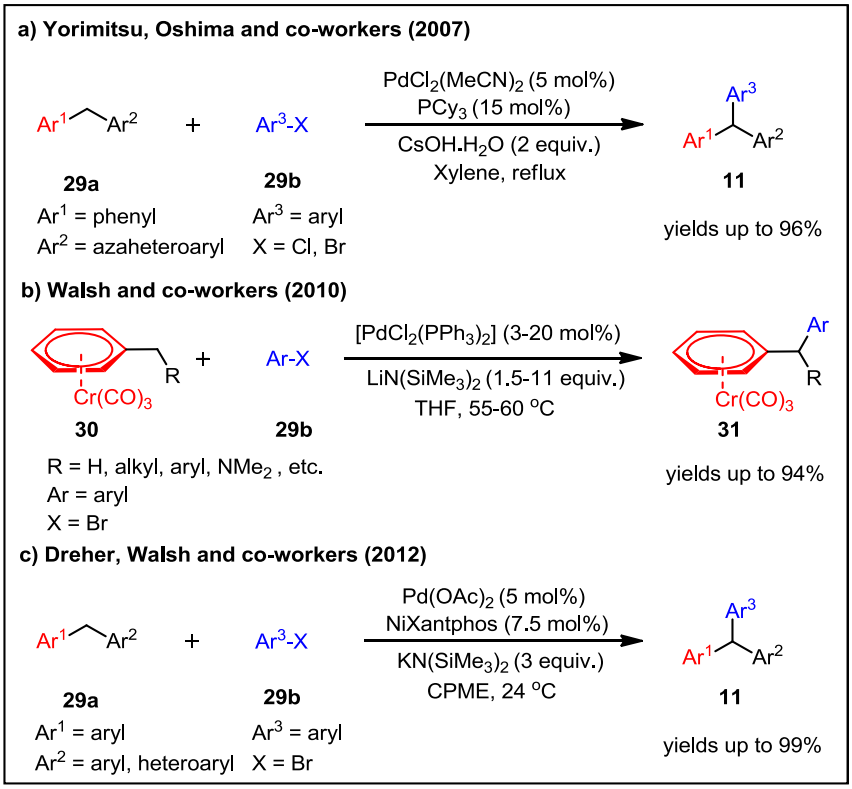
Scheme 10: Reduction of fuchsones for the synthesis of triarylmethanes

3.2.2 Transition metal catalyzed cross-coupling approach for the synthesis of triarylmethanes

Although most of Lewis or Brønsted acid catalyzed approaches are elegant, they suffer from few drawbacks such as poor regioselectivity, harsh reaction conditions and the requirement of electron-rich arenes or heteroarenes. Therefore, to overcome these drawbacks, recently, the transition metal catalyzed cross coupling approach has gained substantial attention from many research groups. Moreover, the transition metal catalyzed cross coupling

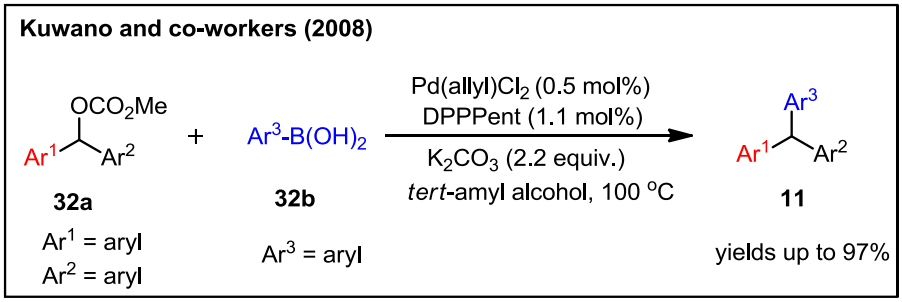
approaches turn out to be more useful methods for the synthesis of complex unsymmetrical triarylmethanes.[18] A few of them are discussed in this section.

Yorimitsu, Oshima and co-workers reported a palladium catalyzed arylation of aryl(azaaryl)methanes (**29a**) with aryl halides (**29b**) for the first time.[19a] various unsymmetrical triarylmethanes (**11**) were obtained good to excellent yields (a, Scheme 11). Walsh and co-workers observed a palladium catalyzed cross coupling between aryl bromides (**29b**) and tricarbonylchromium activated benzylic derivatives (**30**) for the synthesis of diaryl, triaryl, polyarylated methanes (**31**) (b, Scheme 11).[19b] Later, the same group extended this protocol for the synthesis of triarylmethanes through cross coupling of diarylmethanes (**29a**) and aryl halides (**29b**). Different functional groups such as acetal, amide, phenol, and acetyl were well tolerated under the reaction conditions (c, Scheme 11).[19c]



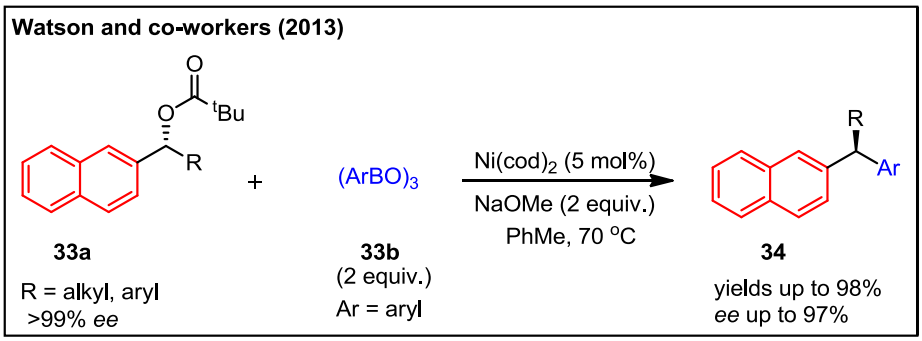
Scheme 11: Pd-catalyzed cross coupling approach for the synthesis of triarylmethanes

Another interesting approach was discovered by Kuwano and co-workers for the synthesis of unsymmetrical triarylmethanes via a Suzuki-Miyaura cross coupling reaction.[20] Varities of diarylmethyl carbonates (**32a**) were coupled with arylboronic acid (**32b**) under the optimized conditions to furnish the unsymmetrical triarylmethanes (**11**) in good yields (Scheme 12)



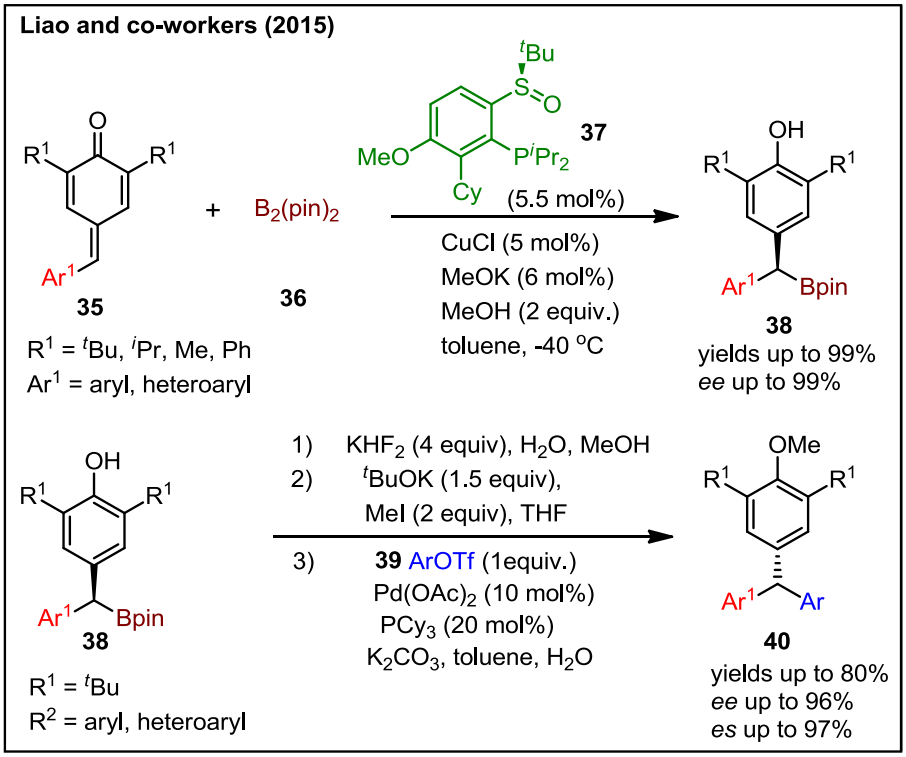
Scheme 12: Pd-catalyzed Suzuki-Miyaura cross coupling approach

Another interesting approach was discovered by Watson and co-workers for the stereospecific synthesis of triarylmethanes.[21] Nickel catalyzed cross coupling reaction between benzylic pivalates (**33a**) and arylboroxines (**33b**) afforded a variety of diarylmethane and triarylmethanes (**34**) in good to excellent yields with excellent *ee* (Scheme 13).



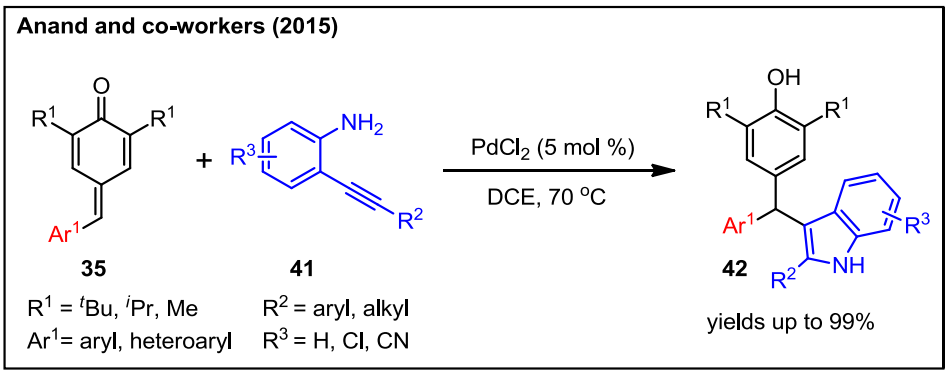
Scheme 13: Ni-catalyzed asymmetric synthesis of triarylmethanes

Recently, transition metal catalyzed cross coupling approaches have also applied for the synthesis of triarylmethanes using *p*-QMs as 1,6-acceptor. For example, Liao and co-workers demonstrated a copper-catalyzed asymmetric 1,6-conjugate addition of diborane (**36**) to *p*-QMs (**35**) to access *gem*-diarylmethyl boronates (**38**) in excellent yields and enantioselectivity. Further the chiral *gem*-diarylmethyl boronates (**38**) were subjected to stereospecific Suzuki-Miyaura cross-coupling with aryl triflates (**39**). Notably, in most of the cases, the desired enantioenriched traiarylmethanes (**40**) were observed in excellent yields and excellent enantioselectivity. Various functional groups such as carbonyl, nitro, formyl, alkoxy were well tolerated under the Suzuki-Miyaura cross-coupling conditions (Scheme 14).[22]



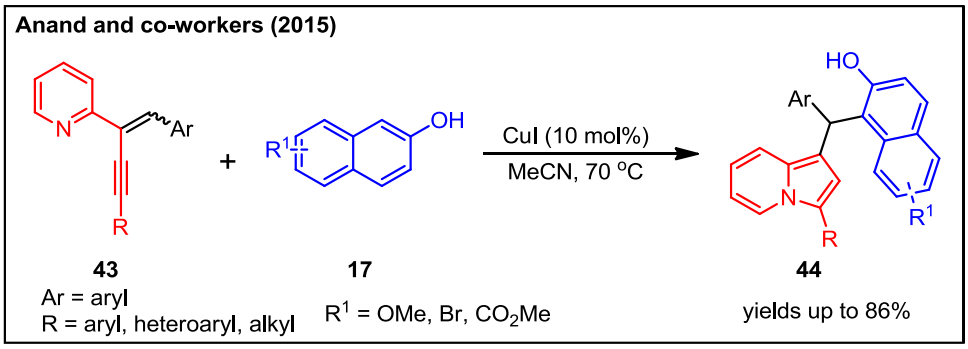
Scheme 14: Asymmetric synthesis of triarylmethanes from *p*-QMs

Anand and co-workers discovered an another interesting one-pot approach for the synthesis of unsymmetrical triarylmethanes through a palladium catalyzed annulation of *o*-alkynylanilines (**41**) followed by 1,6-conjugate addition to *p*-QMs (**35**). It is noteworthy to mention that, this reaction underwent smoothly without protection of amino group of *o*-alkynylanilines. Most of the unsymmetrical diarylindolylmethanes (**42**) were isolated in good to excellent yields. Various functional group tolerance, mild reaction conditions, 100% atom economical approach made this transformation very attractive (Scheme 15).[23]



Scheme 15: Pd-catalyzed domino approach for synthesis of triarylmethanes from *p*-QMs

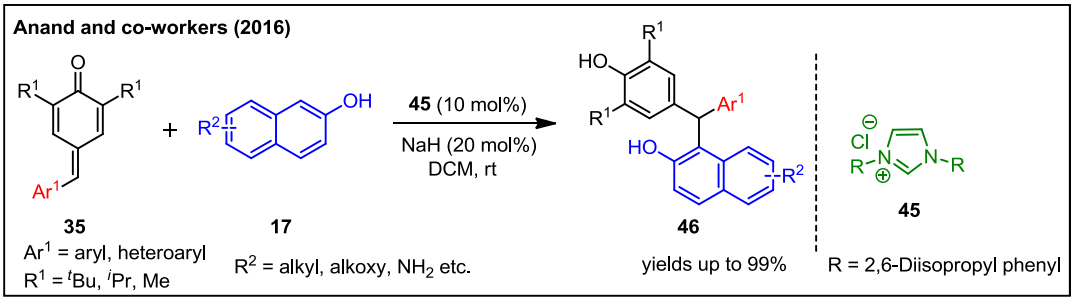
The same group also developed another domino cyclization approach for the synthesis of unsymmetrical triarylmethanes.[24] Copper catalyzed cyclization of 2-(2-enynyl)pyridines (**43**) followed by addition of 2-naphthols (**17**) produced a library of indolizine-containing triarylmethanes (**44**) in good yields. Various functional groups such as alkoxy, trifluoromethoxy, ester, halo etc. were well tolerated under the reaction condition (Scheme 16).



Scheme 16: Cu-catalyzed indolizine-based triarylmethane synthesis

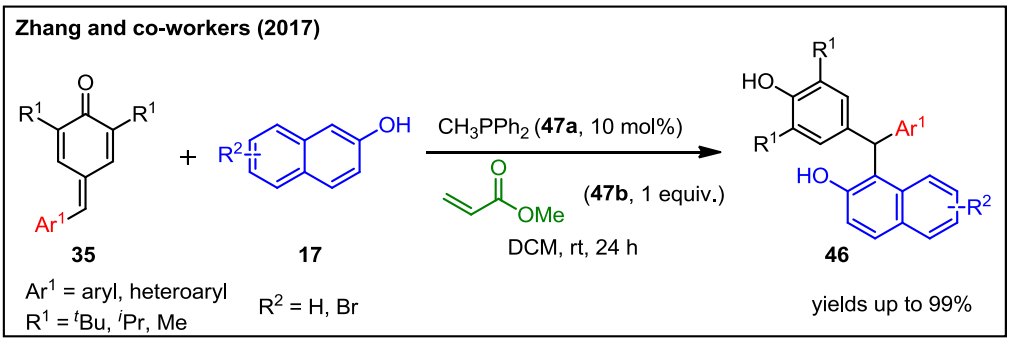
3.2.3 Organocatalytic approaches for the synthesis of triarylmethanes

Apart from Lewis or Brønsted acid catalyzed Fridel-Crafts alkylation approach and transition metal catalyzed cross coupling approaches, there are few organocatalytic approaches known in the literature for the synthesis of unsymmetrical triarylmethanes. For example, Anand and co-workers reported an *N*-heterocyclic carbene catalyzed 1,6-conjugate addition of 2-naphthols (**17**) to *p*-QMs (**35**) for the synthesis of unsymmetrical triarylmethanes.[25] In this method, the *N*-heterocyclic carbene derived from **45** was used as a Brønsted base. An array of unsymmetrical triarylmethanes (**46**) was synthesized in good to excellent yields (Scheme 17).



Scheme 17: *N*-heterocyclic carbene catalyzed synthesis of unsymmetrical triarylmethanes

Very recently, Zhang and co-workers demonstrated an interesting approach for the synthesis of unsymmetrical triarylmethanes.[26] Phosphine catalyzed 1,6-conjugate addition of 2-naphthols (**17**) to *p*-QMs (**35**) was developed and the desired unsymmetrical triarylmethanes (**46**) were isolated in good to excellent yields. Notably, for the first time, phophine has been utilized for the Friedel-Crafts reaction. The authors have explained that the combination of phosphine (**47a**) and methyl acrylate (**47b**) generates an active species *in situ*, which actually catalyzes the reaction (Scheme 18).

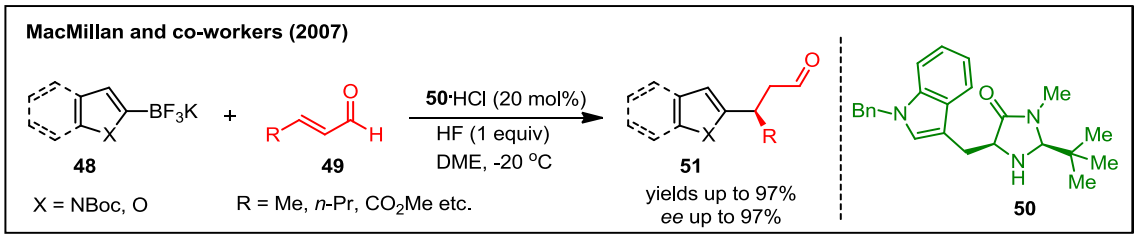


Scheme 18: Phosphine-catalyzed synthesis of unsymmetrical triarylmethanes

3.3 Literature overview on C2-functionalization of indoles

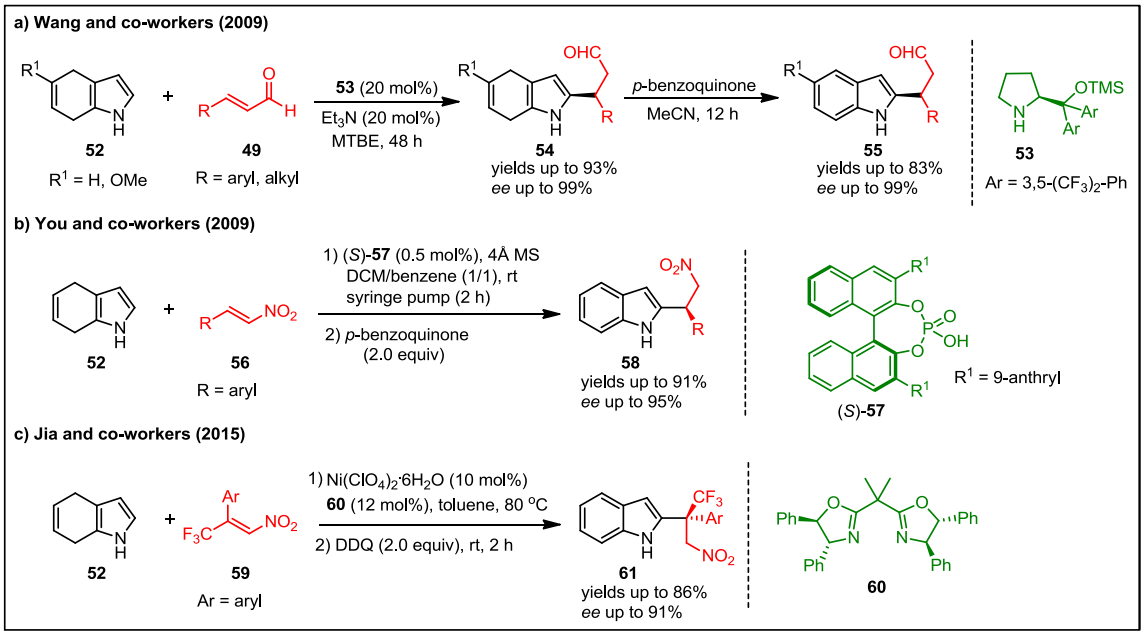
C2-functionalized indoles are important class of compounds, widely found in many pharmaceutically active molecules and natural products.[27] Due to this, several approaches have been reported for the synthesis of C2-functionalized indoles.[28] It has been well documented that the C3 position of indole is more reactive (nucleophilic) towards any electrophile. Nevertheless, the direct C2-functionalization of indoles is not a usual transformation, because the nucleophilicity at C2 position of indoles is relatively low when compared to that of C3 position. However, despite this concern, many reports are available for the direct C2 functionalization of indoles. The most common strategy for the C2-functionalization of indole is intramolecular Pictet-Spengler reaction of C3-substituted indoles.[29] Apart from this protocol, a few other methods are reported for the C2-functionalization of indoles. A few of them are discussed in this section.

MacMillan and co-workers discovered an organocatalytic addition of 2-indolyltrifluoroborate salts (**48**) to enals (**49**) for the formation of C2-substituted indoles (**51**).[30] Interestingly, this reaction proceeded without any substitution at C3-position of the indole. The synthetic utility of this methodology was further demonstrated using other heterocycles such as 2-formyl furans and benzofurans (Scheme 19).



Scheme 19: Organocatalytic C2-functionalization of indole

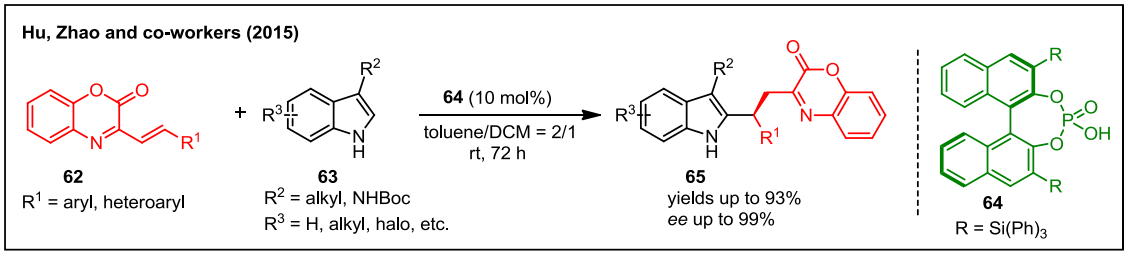
Wang and co-workers demonstrated an organocatalytic asymmetric Friedel-Crafts alkylation of 4,7-dihydroindoles (**52**) with *α,β*-unsaturated aldehydes (**49**), followed by a successive oxidation of the products with *p*-benzoquinone to produce the C2-substituted indoles (**55**) in very good to excellent yields and high *ee* (a, Scheme 20).[31a] At the same time, You's group reported a chiral phosphoric acid catalyzed enantioselective Friedel-Crafts alkylation of 4,7-dihydroindole (**52**) with nitroolefins (**56**), followed by oxidation of the resultant products to get C2-substituted indoles (b, Scheme 20).[31b] Later, Jia and co-workers extended the concept for Friedel-Crafts alkylation of 4,7-dihydroindole (**52**) with CF_3-containing nitoolefins (**59**) for the synthesis of CF_3-containing 2-alkylated indoles (**61**) using $Ni(ClO_4)_2$–bisoxazoline as a catalyst (c, Scheme 20).[31c]



Scheme 20: Organocatalytic Friedel-Crafts alkylation of 4,7-dihydroindoles

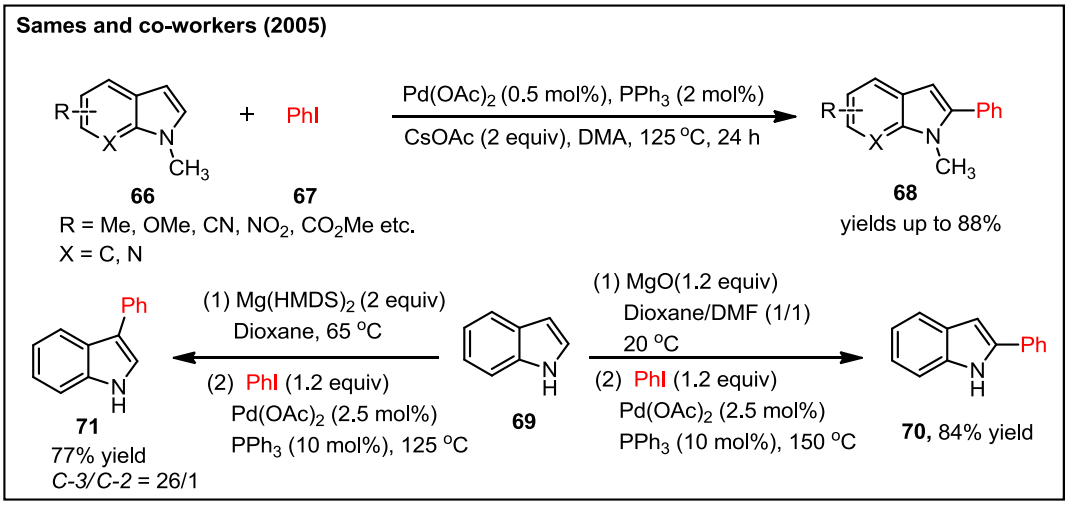
Hu, Zhao and co-workers accomplished another fascinating method for the synthesis of C2-substituted indoles using a chiral phosphoric acid as a Brönsted acid.[32] A wide range of

β,*γ*-unsaturated *α*-ketimino esters (**62**) were treated with 3-substituted indoles (**63**) to produce a C2-substituted indoles (**65**) in good to excellent yields with excellent *ee* (Scheme 21).



Scheme 21: Brønsted acid-catalyzed C-2 functionalization of indoles

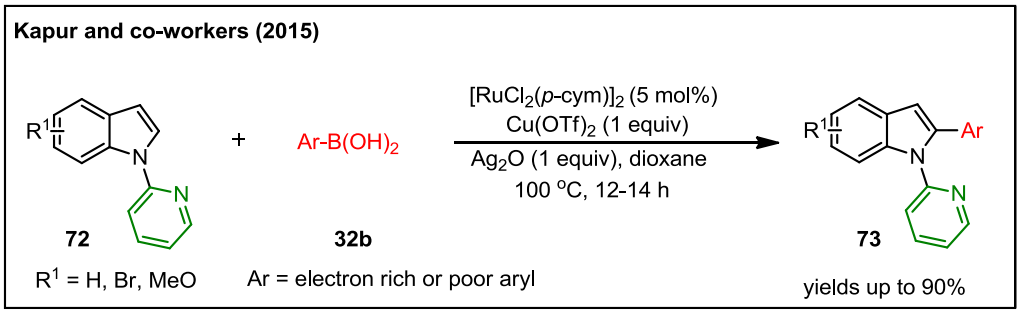
A few transition metal catalyzed coupling reactions are also known in the literature for the C-2 functionalization of indoles. For example, Sames and co-workers developed a palladium catalyzed regioselective C-2 and C-3 arylation of indoles.[33] Kinetic studies indicated that reaction proceeds through an electrophilic palladation of indole followed by 1,2-migration of palladium intermediate to produce C-2 arylated products. Electron-rich as well as electron-poor substituent *N*-methylindoles (**66**) participated in the reaction. Notably, azaindoles were tolerated under the optimized conditions. In case of N-H free indoles (**69**) regioselectivity was controlled by using different magnesium salt. When MgO was used, only C-2 arylated product (**70**) was observed as a sole product. On the other hand, C-3 arylated product (**71**) was observed when $Mg(HMDS)_2$ was used (Scheme 22).



Scheme 22: Pd-catalyzed regioselective arylation of indoles

Kapur and co-workers demonstrated another important approach for the heteroatom directed regioselective C-2 arylation of indoles.[34] An array of *N*-pyridylindoles (**72**) were

treated with aryl boronic acid (**32b**) in presence of catalytic amount ruthenium catalyst and the corresponding C-2 arylated indoles (**73**) were obtained in good to excellent yields (Scheme 23).



Scheme 23: Ru-catalyzed heteroatom-directed regioselective C-2 arylation of indoles

3.4 Background

Although most of the above mentioned methods showed excellent substrate scope and functional group tolerance, the involvement of highly toxic metal catalysts or expensive catalysts made those protocols practically unattractive. Moreover, none of those methods are 100% atom economical. Therefore, developing an environmentally benign, 100% atom economical for the direct C-2 functionalization of indoles is highly desirable. While working on the 1,6-conjugate addition of different nucleophiles to *p*-QMs, we envisioned that one could get direct C-2 functionalized indoles through a vinylogous Michael addition of 3-substituted indoles to *p*-quinone methides.

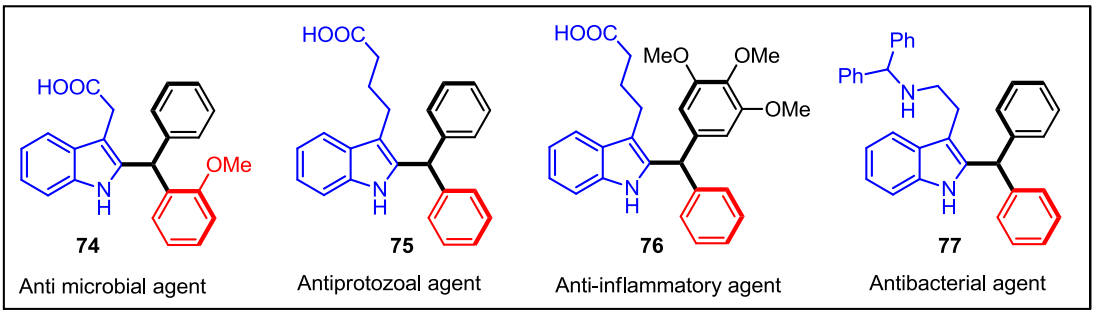
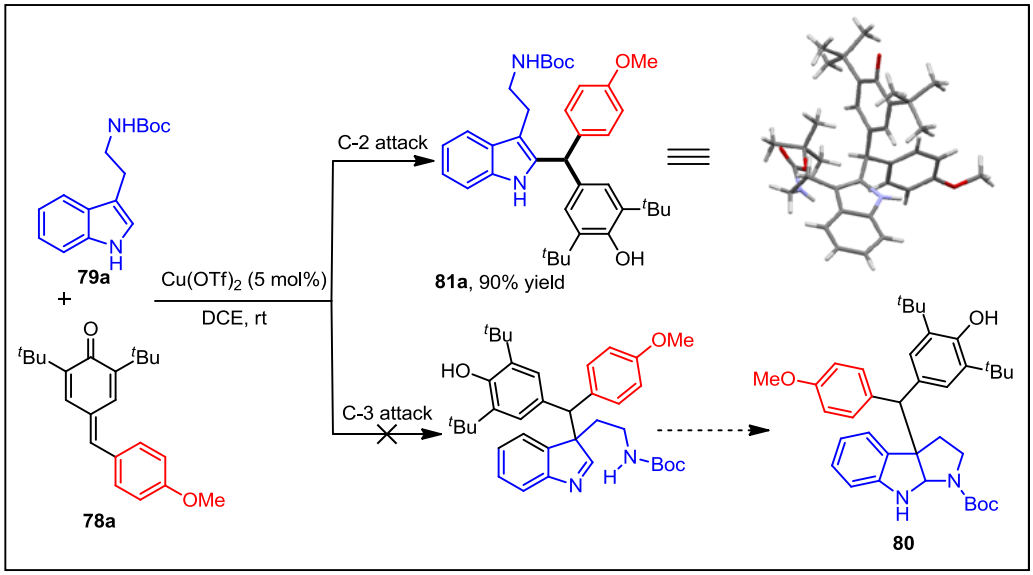


Figure 2. Some important biologically active diaryl(2-indolyl)methanes

Moreover, this method will allow to access diaryl(2-indolyl)methanes in one-step. Many of the diaryl(indolyl)methane derivatives exhibit important therapeutic applications,[35,36] especially, some of the C-2 substituted diaryl(indolyl)methanes display anti-protozoal, antibacterial, antispasmodic and anti-inflammatory activities (Figure 2).[36]

3.5 Results and Discussions

Initially, to optimize the reaction conditions, we carried out a reaction between *p*-quinone methide **78a** and Boc-protected tryptamine **79a** in presence of catalytic amount of $Cu(OTf)_2$ in DCE. Basically, we thought that **78a** would undergo nucleophilic attack with **79a** at C-3 position to generate a dearomatized intermediate, which would potentially undergo cyclization to form a stable pyrroloindoline scaffold **80**.[37] However, in our case, instead of **80**, a diaryl(2-indolyl)methane **81a** was obtained as a sole product in 90% yield (Scheme 9 & entry 1, Table 1). The structure of **81a** was unambiguously confirmed by NMR as well as X-ray analysis (Scheme 24). Since many diaryl(2-indolyl)methanes possess important therapeutic applications, we decided to investigate this transformation in detail.

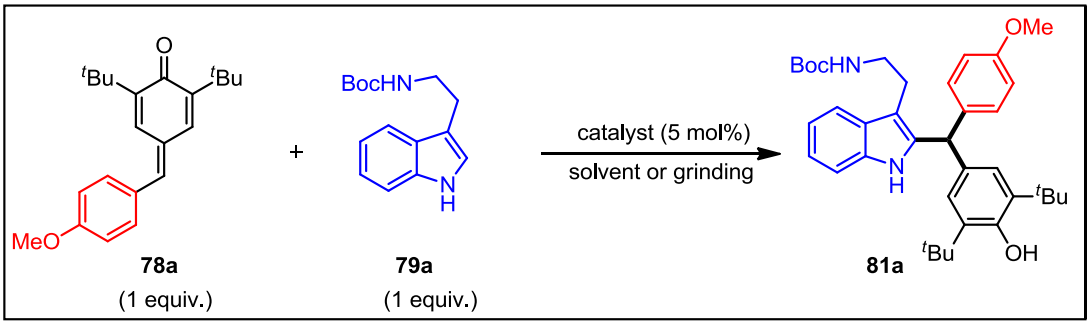


Scheme 24: Our initial observation

Further, to optimize the reaction conditions, *p*-QM **78a** was reacted with Boc-protected tryptamine **79a** in presence of 5 mol% of $Cu(OTf)_2$ (5 mol %) in THF solvent (entry 2, Table 1). The expected diaryl(2-indolyl)methane **81a** was isolated in 91% yield in 24 h. Later, when the reaction was carried out in toluene as a solvent, the reaction was completed within 6 h, and the desired product was obtained in 90% yield (entry 3, Table 1). The catalyst screening (entries 4-7, Table 1) using DCE as a solvent revealed that $Bi(OTf)_3$ was the best catalyst to drive the transformation, as the expected product **81a** was observed in 92% yield in just 15 min in that case (entry 7, Table 1). Notably, main group triflates $Mg(OTf)_2$ and LiOTf failed to catalyze the transformation (entries 8 & 9, Table 1).

Since the solvent-free reactions have gained enormous attention in recent years, we became interested to develop this methodology under solvent free conditions.

Table 1: Optimization studies[a]



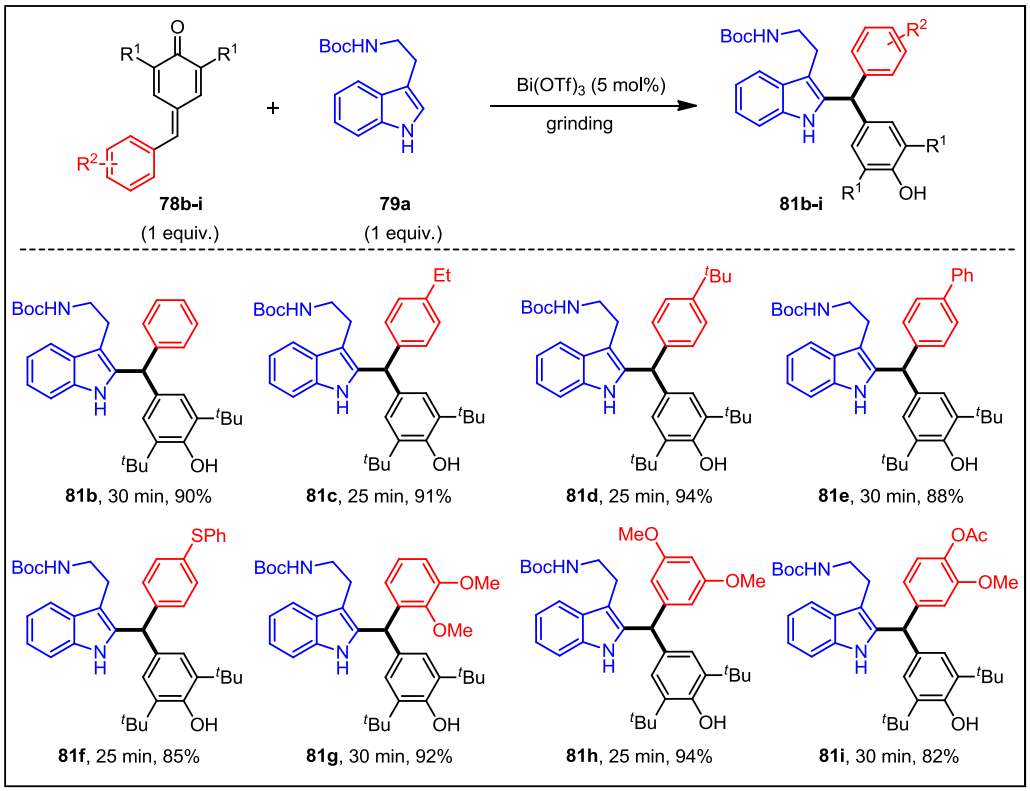
entry	catalyst	solvent	time	yield of **81a** (%)
1	$Cu(OTf)_2$	DCE	25 min	90
2	$Cu(OTf)_2$	THF	24 h	91
3	$Cu(OTf)_2$	PhMe	06 h	90
4	CuOTf.PhMe	DCE	30 min	91
5	$Ce(OTf)_3$	DCE	30 min	90
6	$Yb(OTf)_3$	DCE	30 min	87
7	$Bi(OTf)_3$	DCE	15 min	92
8	$Mg(OTf)_2$	DCE	48 h	trace
9	LiOTf	DCE	48 h	trace
10	**$Bi(OTf)_3$**	-	**15 min**	**95**
11	$BiBr_3$	-	30 min	80
12	Bi_2O_3	-	30 min	trace
13	$Ce(OTf)_3$	-	30 min	80
14	$FeCl_3$	-	30 min	82
15	$FeCl_2$	-	40 min	trace
16	$Fe(OAc)_2$	-	30 min	trace
17	$FeTiO_3$	-	30 min	trace
18	$Fe(acac)_2$	-	30 min	trace
19	$Fe(acac)_3$	-	30 min	trace
20	-	-	45 min	-

[a]Reaction conditions: All reactions were carried out with **78a** (0.062 mmol), **79a** (0.062 mmol) and 5 mol% of the catalyst in solvent (1 mL) or without solvent. Yields reported are isolated yields.

Delightfully, our first attempt itself provided a satisfactory result as **81a** was furnished in 95% yield in just 15 min, when the reaction between **78a** and **79a** was performed using a mortar and pestle grinder using $Bi(OTf)_3$ as a catalyst (entry 10,

Table 1). Under similar conditions, $BiBr_3$ was found to be less superior than $Bi(OTf)_3$ as only 80% yield of product was obtained in 30 min (entry 11, Table 1). However, Bi_2O_3 failed to catalyze the transformation (entry 12, Table 1). When the reaction was carried out in $Ce(OTf)_3$ and $FeCl_3$ respectively, similar yields were observed in both the cases (entries 13 & 14, Table 1). Other iron complexes were found to be not suitable to drive this transformation (entries 15 to 19, Table 1). Moreover, no product formation was observed when the solvent-free grinding reaction was performed without a catalyst (entry 20, Table 1). This observation clearly shows that catalyst is essential to drive the reaction.

With the optimized reaction conditions in hand (entry 10, Table 1), we then shifted our attention to evaluate the substrate scope and limitations of this methodology using a variety of *p*-quinone methides, and the results are summarized in Schemes 25 & 26.



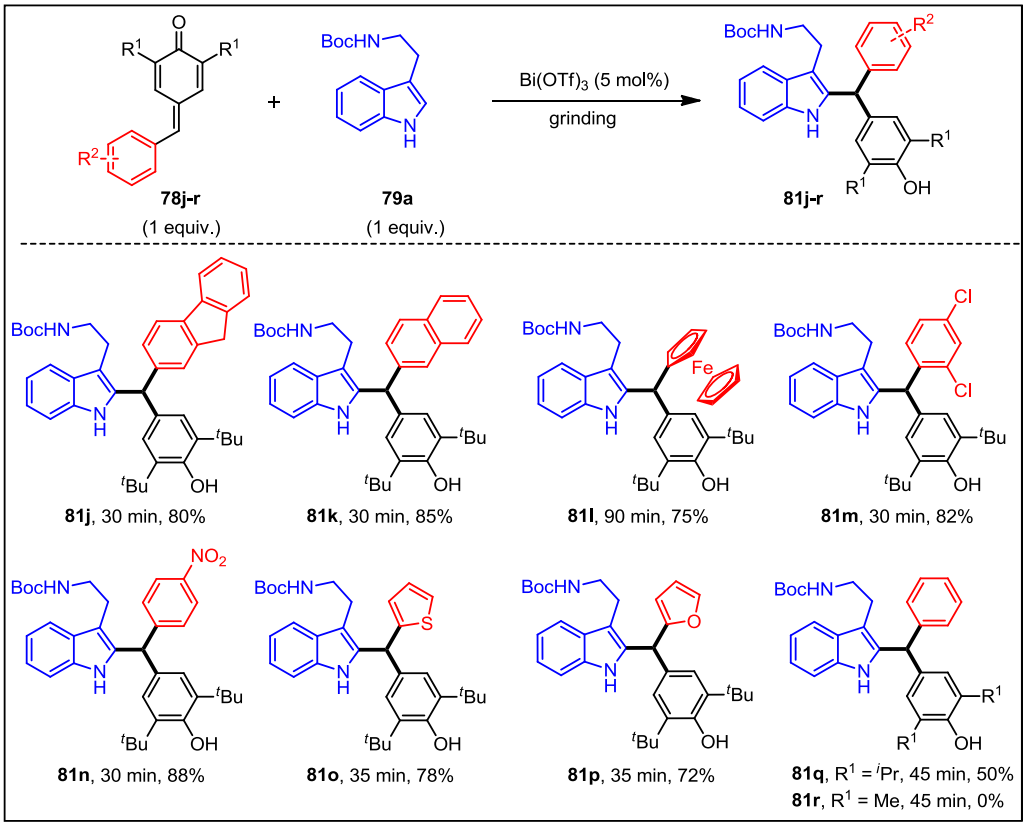
[a]Reaction conditions: All reactions were carried out with 0.062 mmol of **78(b-i)** without solvent. Yields reported are isolated yields.

Scheme 25: Substrate scope for different *p*-QMs[a]

It is obvious from Scheme 25 that electron-rich arenes substituted *p*-QMs were suitable substrates for this transformation, as most of them (**78b-i**) reacted smoothly under the

catalytic conditions and furnished the resultant diaryl(2-indolyl)methanes (**81b-i**) in good to excellent yields (82-94%) within a very short period of time (Scheme 25).

It was also observed that all the *p*-QMs (**78j-l**), derived from fused aromatic aldehydes, reacted efficiently under the optimized conditions to produce the subsequent diaryl(2-indolyl)methanes (**81j-l**) in very high yields (75-85%). Interestingly, this catalytic method was found to be very robust in case of *p*-QM (**78m**) synthesized from 2,4-dichlorobenzaldehyde and the produced diaryl(2-indolyl)methane (**81m**) was isolated in 82% yield. Delightfully, even strong electron-poor arenes substituted *p*-QM (**78n**) reacted efficiently to afford the resultant diaryl(2-indolyl)methane (**81n**) in 88% yield. Heteroaryl substituent *p*-QMs (**78o-p**) were also tolerated under the optimized conditions and produced the expected diaryl(2-indolyl)methanes (**81o** & **81p**) up to 78% yields (Scheme 26).



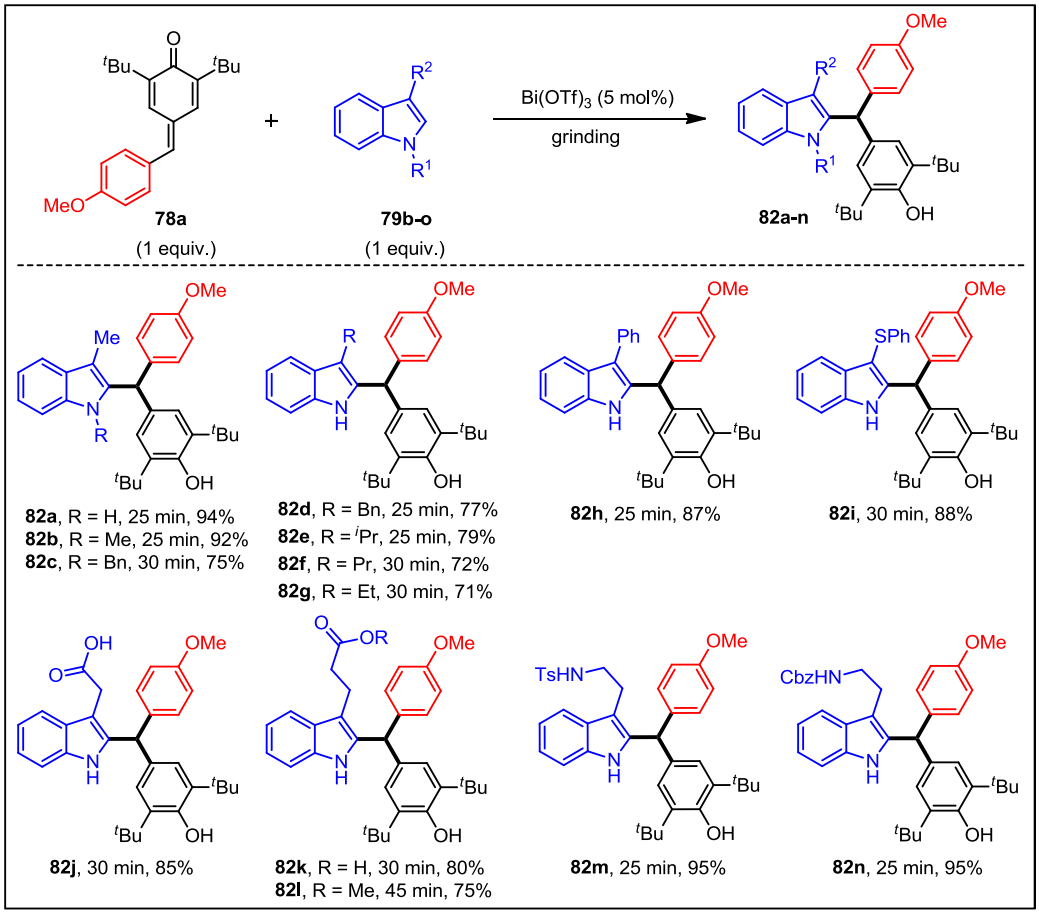
[a]Reaction conditions: All reactions were carried out with 0.062 mmol of **78(j-r)** without solvent. Yields reported are isolated yields.

Scheme 26: Substrate scope for different *p*-QMs[a]

Notably, when the reaction was carried out with *p*-QM (**78q**) derived from 2,6-diisopropylphenol, the required product (**81q**) was obtained only in 50% yield. Unfortunately,

p-QM (**78r**) derived from 2,6-dimethylphenol, failed to react under the optimized conditions (Scheme 26).

The generality of the substrate scope was further examined by treating a wide range of 3-substituted indoles (**79b–o**) with *p*-QM (**78a**) under the optimized conditions (Scheme 27). It is noteworthy to mention that both 3-alkyl- and 3-aryl-substituted indoles reacted efficiently under the optimized conditions. For example, 3-methyl indole (**79b**) and *N*-protected 3-methyl indoles (**79c** & **79d**) produced the desired products (**82a–c**) in good to excellent yields (75–94%).



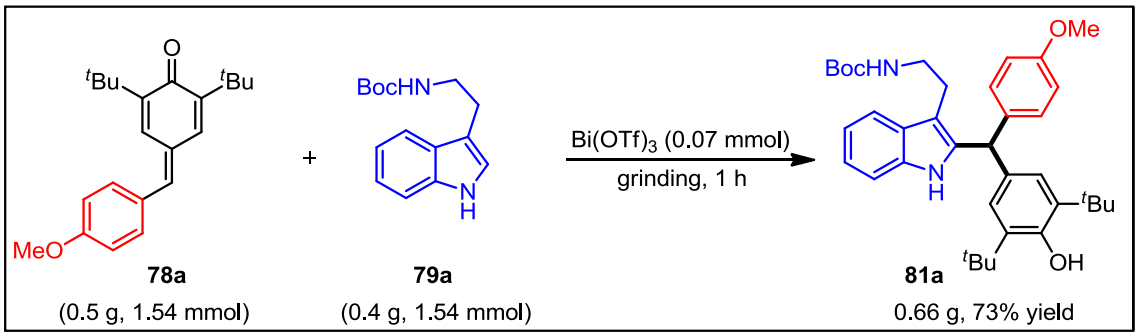
[a]Reaction conditions: All reactions were carried out with 0.062 mmol of **78a** without solvent. Yields reported are isolated yields.

Scheme 27: Substrate scope using different 3-substituted indoles[a]

Delightfully, other 3-alkyl substituted indoles (**79e–h**) also afforded the subsequent diarylindolylmethanes (**82d–g**) in good yields. Moreover, 3-phenyl indole (**79i**) and 3-thiophenyl indole (**79j**) were converted to their respective products (**82h-i**) with excellent yields. Indole-3-acetic acid (**79k**) was also reacted smoothly and the required

diarylindolylmethane (**82j**) was obtained in 85% yield. Other indole derivatives such as indole-3-propionic acid (**79l**) and its methyl ester (**79m**) also participated in the reaction and the corresponding products (**82k-l**) were isolated in good yields. Tosyl- and Cbz-protected tryptamines (**79n-o**) were also well tolerated in the reaction and produced the corresponding products (**82m-n**) in excellent yields (Scheme 27).

The scalability of the protocol was further demonstrated by carrying out a large-scale reaction of **78a** under the optimized conditions. When 0.5 g of **78a** (1.54 mmol) was reacted with 0.4 g of **79a** (1.54 mmol) in presence of $Bi(OTf)_3$ (0.07 mmol, 50.5 mg), the corresponding diaryl(2-indolyl)methane **81a** was isolated in 73% yield (0.66 g) after 1 h. This clearly shows the robustness of the current protocol (Scheme 28).



Scheme 28: Gram scale synthesis of diaryl(2-indolyl)methane **81a**

3.6 Conclusion

In this chapter we have described a mild catalytic protocol for the synthesis of unsymmetrical diaryl(2-indolyl)methanes under solvent-free grinding conditions.[38] The utility of the inexpensive and nontoxic $Bi(OTf)_3$ catalyst makes this protocol environmentally benign and practically viable. A 100% atom economy, broad substrate scopes and various functional group tolerances are the salient features of this transformation.

3.7 Experimental Section

General methods

All solvent free reactions were carried out using a pestle and mortar. Most of the reagents and starting materials were purchased from commercial sources and used without further purification. All *p*-quinone methides were prepared by following a literature procedure.[39] All 3-substituted (aliphatic and aromatic) indoles were prepared by following a

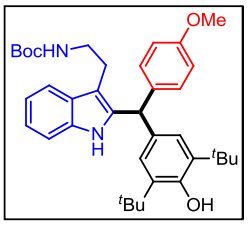
general literature procedure.[40] Thiophenyl substituted indole was prepared according to literature procedure.[41] Melting points were recorded on SMP20 melting point apparatus and are uncorrected. ^{1}H, ^{13}C spectra were recorded in $CDCl_3$ (400, 100 MHz respectively) on Bruker FT-NMR spectrometer. Chemical shift (δ) values are reported in parts per million relative to TMS (for ^{1}H and ^{13}C). High resolution mass spectra were recorded on Waters Q-TOF Premier-HAB213 spectrometer. FT-IR spectra were recorded on a Perkin–Elmer FTIR spectrometer. Single crystal X-ray data was collected using XtaLabmini X-ray diffractometer. Thin layer chromatography was performed on Merck silica gel 60 F_{254} TLC pellets. Column chromatography was carried out through silica gel (100-200 mesh) using EtOAc/hexane as an eluent.

General procedure for the synthesis of C2 substituted diarylindolylmethanes:

A mixture of *p*-quinone methide (0.062 mmol), 3-substituted indole (0.062 mmol) and $Bi(OTf)_3$ (0.0031 mmol) was grinded using a pestle and mortar. After the reaction was complete (based on TLC analysis), the mixture was diluted with EtOAc and concentrated under reduced pressure. The residue was then purified through a silica gel column using EtOAc/Hexane mixture as an eluent to get the pure product.

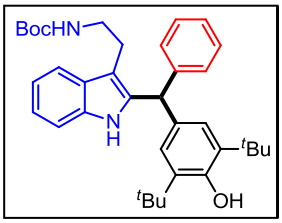
Characterization data of compounds (81a-81q):

***Tert*-butyl[2-{2-((3,5-di-*tert*-butyl-4-hydroxyphenyl)(4-methoxyphenyl)methyl)-1H-indol-3-yl}ethyl]carbamate (81a)**



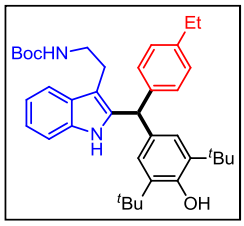
The reaction was performed at 0.062 mmol scale of *p*-quinone methide **(78a)**; R_f = 0.4 (10% EtOAc in hexane); orange solid (35 mg, 95% yield); m.p. = 126–128 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61–7.59 (m, 2H), 7.27–7.25 (m, 1H), 7.16–7.10 (m, 2H), 7.09 (d, J = 8.6 Hz, 2H), 6.94 (s, 2H), 6.84 (d, J = 8.7 Hz, 2H), 5.64 (s, 1H), 5.18 (s, 1H), 4.49 (brs, 1H), 3.81 (s, 3H), 3.32–3.18 (m, 2H), 2.88 (t, J = 6.4 Hz, 2H), 1.43 (s, 9H), 1.38 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.3, 156.0, 152.7, 137.9, 136.1, 135.3, 134.9, 132.6, 129.9, 129.1, 125.5, 121.4, 119.5, 118.7, 114.0, 110.8, 109.3, 79.1, 55.3, 47.7, 40.9, 34.5, 30.4, 28.6, 24.9; FT-IR (thin film, neat): 3625, 3462, 2959, 2928, 1699, 1610, 1510, 1460, 1435, 1366, 1249, 1176, 1035, 743 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{37}H_{48}N_2NaO_4$ $[M+Na]^+$: 607.3512; found : 607.3524.

Tert-butyl[2-{2-((3,5-di-_tert_-butyl-4-hydroxyphenyl)(phenyl)methyl)-1H-indol-3-yl}ethyl]carbamate (81b)



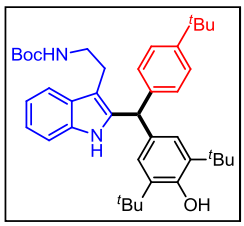
The reaction was performed at 0.062 mmol scale of *p*-quinone methide **(78b)**; R_f = 0.3 (10% EtOAc in hexane); orange solid (31 mg, 90% yield); m.p. = 193–195 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61–7.59 (m, 2H), 7.32–7.27 (m, 2H), 7.25–7.22 (m, 2H), 7.17 (d, *J* = 7.1 Hz, 2H), 7.14–7.08 (m, 2H), 6.94 (s, 2H), 5.68 (s, 1H), 5.18 (s, 1H), 4.46 (brs, 1H), 3.30–3.19 (m, 2H), 2.94–2.88 (m, 2H), 1.42 (s, 9H), 1.37 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.0, 152.7, 142.9, 137.5, 136.1, 135.3, 132.3, 129.1, 128.9, 128.7, 126.8, 125.6, 121.4, 119.5, 118.8, 110.8, 109.5, 79.1, 48.5, 40.9, 34.5, 30.4, 28.6, 24.9; FT-IR (KBr): 3623, 3470, 3365, 2963, 2867, 1676, 1598, 1517, 1494, 1462, 1435, 1365, 1284, 1244, 1170, 991, 743 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{36}H_{46}N_2NaO_3$ $[M+Na]^+$: 577.3406; found : 577.3419.

Tert-butyl[2-{2-((3,5-di-_tert_-butyl-4-hydroxyphenyl)(4-ethylphenyl)methyl)-1H-indol-3-yl}ethyl]carbamate (81c)



The reaction was performed at 0.062 mmol scale of *p*-quinone methide **(78c)**; R_f = 0.4 (10% EtOAc in hexane); orange solid (33 mg, 91% yield); m.p. = 138–140 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60–7.57 (m, 2H), 7.25 (d, *J* = 6.92 Hz, 1H), 7.14–7.06 (m, 6H), 6.94 (s, 2H), 5.63 (s, 1H), 5.15 (s, 1H), 4.47 (brs, 1H), 3.31–3.16 (m, 2H), 2.86 (t, *J* = 6.4 Hz, 2H), 2.64 (q, *J* = 7.6 Hz, 2H), 1.42 (s, 9H), 1.36 (s, 18H), 1.23 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.0, 152.7, 142.7, 139.9, 137.8, 136.0, 135.3, 132.6, 129.1, 128.9, 128.1, 125.6, 121.4, 119.5, 118.7, 110.8, 109.4, 79.1, 48.2, 40.9, 34.5, 30.4 (2C), 28.6, 24.9, 15.7; FT-IR (thin film, neat): 3640, 3458, 2959, 2924, 2863, 2855, 1698, 1508, 1459, 1437, 1390, 1365, 1238, 1167, 741 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{38}H_{49}N_2O_3$ $[M-H]^+$: 581.3743; found : 581.3730.

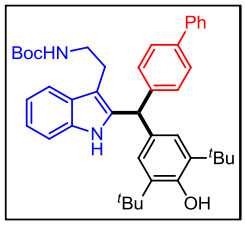
Tert-butyl[2-{2-((4-(_tert_-butyl)phenyl)(3,5-di-_tert_-butyl-4-hydroxyphenyl)methyl)-1H-indol-3-yl}ethyl]carbamate (81d)



The reaction was performed at 0.062 mmol scale of *p*-quinone methide **(78d)**; R_f = 0.3 (15% EtOAc in hexane); orange solid (35.6 mg, 94% yield); m.p. = 116–118 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (s, 1H), 7.61 (d, *J* = 7.3 Hz, 1H), 7.34 (d, *J* = 8.3 Hz, 2H), 7.27 (d, *J* = 7.7 Hz,

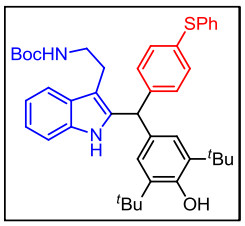
1H), 7.16–7.09 (m, 4H), 6.98 (s, 2H), 5.66 (s, 1H), 5.18 (s, 1H), 4.52 (brs, 1H), 3.31–3.15 (m, 2H), 2.89 (t, J = 6.3 Hz, 2H), 1.45 (s, 9H), 1.39 (s, 18H), 1.34 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.0, 152.6, 149.6, 139.6, 137.8, 136.1, 135.3, 132.6, 129.1, 128.6, 125.6, 125.5, 121.3, 119.4, 118.7, 110.8, 109.5, 79.1, 48.1, 41.0, 34.6, 34.5, 31.5, 30.4, 28.6, 24.9; FT-IR (KBr): 3640, 3457, 3417, 2962, 2867, 1699, 1510, 1460, 1435, 1392, 1366, 1237, 1168, 1121, 742 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{40}H_{54}N_2NaO_3$ $[M+Na]^+$: 633.4032; found : 633.4047.

Tert-butyl[2-{2-([1,1'-biphenyl]-4-yl(3,5-di-_tert_-butyl-4-hydroxyphenyl)methyl)-1H-indol-3-yl}ethyl]carbamate (81e)



The reaction was performed at 0.062 mmol scale of *p*-quinone methide **(78e)**; R_f = 0.3 (15% EtOAc in hexane); pale yellow solid (34.5 mg, 88% yield); m.p. = 149–151 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (brs, 1H), 7.62–7.60 (m, 3H), 7.56 (d, J = 8.2 Hz, 2H), 7.47–7.43 (m, 2H), 7.37–7.33 (m, 1H), 7.30–7.24 (m, 3H), 7.18–7.10 (m, 2H), 6.99 (s, 2H), 5.73 (s, 1H), 5.20 (s, 1H), 4.52 (brs, 1H), 3.34–3.20 (m, 2H), 2.91 (t, J = 6.4 Hz, 2H), 1.42 (s, 9H), 1.39 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.0, 152.8, 141.9, 140.8, 139.6, 137.4, 136.2, 135.3, 132.2, 129.4, 129.1, 128.9, 127.4, 127.3, 127.1, 125.6, 121.5, 119.5, 118.8, 110.9, 109.6, 79.1, 48.2, 40.9, 34.5, 30.4, 28.6, 24.9; FT-IR (thin film, neat): 3635, 3446, 2956, 2925, 2869, 2857, 1699, 1487, 1459, 1434, 1365, 1237, 1166, 908, 736 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{42}H_{50}N_2NaO_3$ $[M+Na]^+$: 653.3719; found : 653.3708.

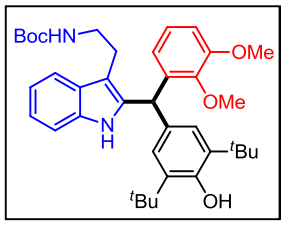
Tert-butyl[2-{2-((3,5-di-_tert_-butyl-4-hydroxyphenyl)(4-(phenylthio)phenyl)methyl)-1H-indol-3-yl}ethyl]carbamate (81f)



The reaction was performed at 0.062 mmol scale of *p*-quinone methide **(78f)**; R_f = 0.3 (10% EtOAc in hexane); orange solid (35 mg, 85% yield); m.p. = 65–67 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59–7.58 (m, 2H), 7.30–7.28 (m, 6H), 7.26–7.20 (m, 2H), 7.16–7.08 (m, 4H), 6.91 (s, 2H), 5.66 (s, 1H), 5.18 (s, 1H), 4.48 (brs, 1H), 3.29–3.20 (m, 2H), 2.87 (t, J = 6.6 Hz, 2H), 1.42 (s, 9H), 1.36 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.0, 152.8, 142.2, 137.1, 136.2, 135.3, 133.7, 132.0, 131.8, 130.6, 129.9, 129.3 (2C), 129.0, 127.0, 125.6, 121.6, 119.6, 118.8, 110.9, 109.7, 79.2, 48.0, 40.9, 34.5, 30.4, 28.6, 24.9; FT-IR (thin film, neat): 3636, 3454,

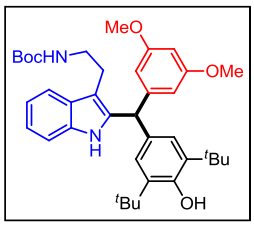
2956, 2925, 2869, 2855, 1699, 1489, 1459, 1435, 1392, 1366, 1237, 1167, 909, 737 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{42}H_{50}N_2NaO_3S$ $[M+Na]^+$: 685.3440; found : 685.3430.

Tert-butyl[2-{2-((3,5-di-_tert_-butyl-4-hydroxyphenyl)(2,3-dimethoxyphenyl)methyl)-1H-indol-3-yl}ethyl]carbamate (81g)



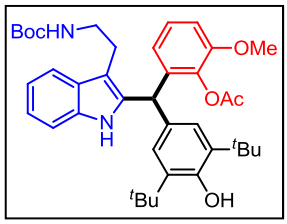
The reaction was performed at 0.062 mmol scale of *p*-quinone methide **(78g)**; R_f = 0.15 (20% EtOAc in hexane); orange solid (35 mg, 92% yield); m.p. = 83–85 ^oC; ^1H NMR (400 MHz, $CDCl_3$) δ 8.34 (s, 1H), 7.57 (d, J = 7.5 Hz, 1H), 7.27 (d, J = 9.24 Hz, 1H), 7.13–7.05 (m, 2H), 6.99 (t, J = 8.0 Hz, 1H), 6.90 (s, 2H), 6.84 (d, J = 8.0 Hz, 1H), 6.75 (d, J = 7.4 Hz, 1H), 5.85 (s, 1H), 5.10 (s, 1H), 4.49 (brs, 1H), 3.86 (s, 3H), 3.33 (s, 3H), 3.28–3.23 (m, 2H), 2.97–2.84 (m, 2H), 1.41 (s, 9H), 1.33 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.1, 153.2, 152.4, 146.6, 137.6, 137.0, 135.9, 135.3, 132.9, 128.9, 125.0, 124.2, 122.2, 121.3, 119.2, 118.7, 111.4, 110.8, 109.3, 79.0, 60.1, 55.9, 43.8, 41.0, 34.4, 30.4, 28.6, 24.9; FT-IR (KBr): 3638, 3452, 3397, 2951, 2925, 2855, 1702, 1585, 1509, 1461, 1435, 1366, 1276, 1168, 1070, 1005, 739 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{38}H_{50}N_2NaO_5$ $[M+Na]^+$: 637.3618; found : 637.3627.

Tert-butyl[2-{2-((3,5-di-_tert_-butyl-4-hydroxyphenyl)(3,5-dimethoxyphenyl)methyl)-1H-indol-3-yl}ethyl]carbamate (81h)



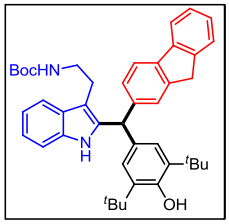
The reaction was performed at 0.062 mmol scale of *p*-quinone methide **(78h)**; R_f = 0.35 (20% EtOAc in hexane); brown solid (35.8 mg, 94% yield); m.p. = 68–70 ^oC; ^1H NMR (400 MHz, $CDCl_3$) δ 7.63 (s, 1H), 7.58 (d, J = 7.4 Hz, 1H), 7.25 (d, J = 8.12 Hz, 1H), 7.15–7.07 (m, 2H), 6.95 (s, 2H), 6.35 (s, 3H), 5.59 (s, 1H), 5.16 (s, 1H), 4.49 (brs 1H), 3.73 (s, 6H), 3.30–3.20 (m, 2H), 2.88 (t, J = 6.0 Hz, 2H), 1.42 (s, 9H), 1.37 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.0, 156.1, 152.7, 145.3, 137.2, 136.1, 135.3, 132.1, 129.1, 125.5, 121.4, 119.5, 118.7, 110.9, 109.6, 107.4, 98.5, 79.1, 55.4, 48.7, 41.0, 34.5, 30.4, 28.6, 24.9; FT-IR (KBr): 3631, 3455, 3408, 2958, 2929, 2871, 1700, 1596, 1503, 1460, 1434, 1366, 1238, 1157, 1066, 739 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{38}H_{50}N_2NaO_5$ $[M+Na]^+$: 637.3618; found : 637.3630.

4-[(3-(2-{(*tert*-butoxycarbonyl)amino}ethyl)-1H-indol-2-yl)(3,5-di-*tert*-butyl-4-hydroxyphenyl)methyl]-2-methoxyphenyl acetate (81i).



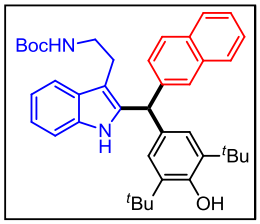
The reaction was performed at 0.062 mmol scale of *p*-quinone methide **(78i)**; R_f = 0.3 (20% EtOAc in hexane); orange gummy solid (33 mg, 82% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (s, 1H), 7.59 (d, J = 7.5 Hz, 1H), 7.27 (d, J = 9.08 Hz, 1H), 7.16–7.08 (m, 2H), 6.96 (t, J = 3.9 Hz, 3H), 6.80 (s, 1H), 6.70 (d, J = 8.1 Hz, 1H), 5.65 (s, 1H), 5.18 (s, 1H), 4.53 (brs, 1H), 3.71 (s, 3H), 3.26–3.18 (m, 2H), 2.86–2.83 (m, 2H), 2.31 (s, 3H), 1.42 (s, 9H), 1.37 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.3, 156.1, 152.8, 151.1, 141.7, 138.5, 137.2, 136.2, 135.3, 132.0, 129.0, 125.6, 122.8, 121.5, 121.2, 119.5, 118.8, 113.3, 110.9, 109.8, 79.1, 56.0, 48.5, 41.0, 34.5, 30.4, 28.5, 25.0, 20.8; FT-IR (thin film, neat): 3388, 2957, 2924, 2852, 1765, 1698, 1604, 1507, 1460, 1366, 1269, 1198, 1178, 1122, 1040, 748 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{39}H_{50}N_2NaO_6$ $[M+Na]^+$: 665.3567; found : 665.3541.

***Tert*-butyl[2-{2-((3,5-di-*tert*-butyl-4-hydroxyphenyl)(9H-fluoren-2-yl)methyl)-1H-indol-3-yl}ethyl]carbamate (81j).**



The reaction was performed at 0.062 mmol scale of *p*-quinone methide **(78j)**; R_f = 0.4 (20% EtOAc in hexane); orange solid (32 mg, 80% yield); m.p. = 84–86 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, J = 7.5 Hz, 1H), 7.72 (d, J = 7.9 Hz, 1H), 7.65–7.61 (m, 2H), 7.54 (d, J = 7.4 Hz, 1H), 7.40–7.35 (m, 2H), 7.32–7.28 (m, 2H), 7.20–7.11 (m, 3H), 6.99 (s, 2H), 5.77 (s, 1H), 5.19 (s, 1H), 4.49 (brs, 1H), 3.85 (s, 2H), 3.34–3.20 (m, 2H), 2.96–2.85 (m, 2H), 1.40 (s, 9H), 1.37 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.0, 152.8, 143.8, 143.5, 141.6, 141.5, 140.4, 137.7, 136.2, 135.3, 132.5, 129.1, 127.6, 126.9, 126.7, 125.7, 125.6, 125.2, 121.4, 120.0, 119.9, 119.5, 118.8, 110.9, 109.5, 79.1, 48.6, 40.9, 37.0, 34.5, 30.4, 28.5, 24.9; FT-IR (thin film, neat): 3638, 3456, 2957, 2925, 2873, 2857, 1699, 1504, 1457, 1435, 1392, 1365, 1242, 1167, 738 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{43}H_{49}N_2O_3$ $[M-H]^+$: 641.3743; found : 641.3726.

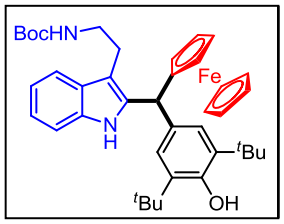
***Tert*-butyl[2-{2-((3,5-di-*tert*-butyl-4-hydroxyphenyl)(naphthalene-2-yl)methyl)-1H-indol-3-yl}ethyl]carbamate (81k).**



The reaction was performed at 0.062 mmol scale of *p*-quinone methide **(78k)**; R_f = 0.3 (10% EtOAc in hexane); orange solid (31.8 mg, 85%

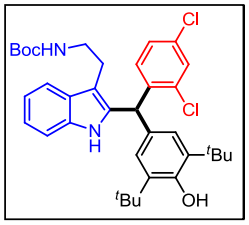
yield); m.p. = 100–102 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (d, J = 8.2 Hz, 1H), 7.88 (d, J = 7.6 Hz, 1H), 7.79 (d, J = 8.2 Hz, 1H), 7.64–7.63 (m, 1H), 7.57 (s, 1H), 7.49–7.34 (m, 3H), 7.23–7.21 (m, 1H), 7.14–7.11 (m, 2H), 7.07 (d, J = 7.1 Hz, 1H), 6.93 (s, 2H), 6.36 (s, 1H), 5.17 (s, 1H), 4.39 (brs, 1H), 3.23–3.11 (m, 2H), 2.86 (t, J = 6.3 Hz, 2H), 1.41 (s, 9H), 1.33 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.0, 152.8, 138.8, 137.5, 136.2, 135.2, 134.0, 132.2, 131.8, 128.8, 127.9, 126.9, 126.5, 125.8, 125.7, 125.5, 125.3, 124.1, 121.3, 119.5, 118.9, 110.8, 109.3, 79.1, 45.2, 40.7, 34.5, 30.4, 28.6, 25.1; FT-IR (thin film, neat): 3636, 3454, 2956, 2924, 2872, 2852, 1699, 1508, 1460, 1434, 1390, 1365, 1238, 1167, 741 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{40}H_{47}N_2O_3$ $[M-H]^+$: 603.3587; found : 603.3575.

[2-{(3-(2-{(*tert*-butoxycarbonyl)amino}ethyl)-1H-indol-2-yl)(3,5-di-*tert*-butyl-4-hydroxyphenyl)methyl)methyl}cyclopenta-2,4-dien-1-yl](cyclopenta-2,4-dien-1-yl)iron (81l).



The reaction was performed at 0.062 mmol scale of *p*-quinone methide **(78l)**; R_f = 0.3 (10% EtOAc in hexane); brown solid (32 mg, 75% yield); m.p. = 97–99 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93(brs, 1H), 7.54 (d, J = 7.4 Hz, 1H), 7.28–7.26 (m, 1H), 7.14–7.06 (m, 4H), 5.26 (s, 1H), 5.15 (s, 1H), 4.45 (brs, 1H), 4.21 (s, 2H), 4.14 (s, 2H), 4.04 (s, 5H), 3.23–3.07 (m, 2H), 2.94–2.80 (m, 2H), 1.47 (s, 9H), 1.43 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.0, 152.5, 138.7, 135.8, 134.9, 133.6, 129.1, 125.1, 121.2, 119.3, 118.6, 110.7, 108.2, 90.9, 79.1, 69.0, 68.8, 68.4, 68.2, 68.0, 43.5, 41.0, 34.5, 30.5, 28.6, 24.9; FT-IR (thin film, neat): 3643, 3374, 2956, 2923, 2852, 1692, 1461, 1377, 1363, 1166, 748 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{40}H_{50}FeN_2O_3$ $[M-H]^+$: 661.3093; found : 661.3077.

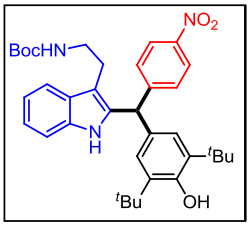
***Tert*-butyl[2-{2-((3,5-di-*tert*-butyl-4-hydroxyphenyl)(2,4-dichlorophenyl)methyl)-1H-indol-3-yl}ethyl]carbamate (81m).**



The reaction was performed at 0.062 mmol scale of *p*-quinone methide **(78m)**; R_f = 0.3 (10% EtOAc in hexane); orange solid (31 mg, 82% yield); m.p. = 93–95 ^{o}C**)**; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, J = 7.5 Hz, 1H), 7.53 (s, 1H), 7.42 (d, J = 2.0 Hz, 1H), 7.27 (d, J = 7.2 Hz, 1H), 7.17–7.09 (m, 3H), 6.96 (d, J = 8.4 Hz, 1H), 6.85 (s, 2H), 5.96 (s, 1H), 5.21 (s, 1H), 4.43 (brs, 1H), 3.24–3.19 (m, 2H), 2.87–2.72 (m, 2H), 1.42 (s, 9H), 1.36 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.0, 153.0, 139.5, 136.4, 135.8, 135.2, 134.8, 133.3, 131.2, 130.0, 129.7,

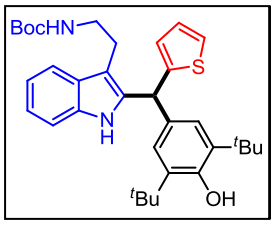
129.1, 127.3, 125.4, 121.7, 119.8, 119.0, 110.9, 109.9, 79.2, 45.3, 40.6, 34.5, 30.4, 28.6, 25.1; FT-IR (thin film, neat): 3640, 3451, 2956, 2924, 2868, 2852, 1697, 1504, 1460, 1434, 1366, 1238, 1168, 744 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{36}H_{43}Cl_2N2O3$ $[M-H]^+$: 621.2651; found : 621.2637.

Tert-butyl[2-{2-((3,5-di-_tert_-butyl-4-hydroxyphenyl)(4-nitrophenyl)methyl)-1H-indol-3-yl}ethyl]carbamate (81n)



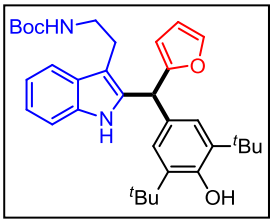
The reaction was performed at 0.062 mmol scale of *p*-quinone methide **(78n)**; R_f = 0.3 (10% EtOAc in hexane); orange solid (32 mg, 88% yield); m.p. = 184–186 ^oC; ^1H NMR (400 MHz, $CDCl_3$) δ 8.16 (d, *J* = 8.8 Hz, 2H), 7.64 (brs, 1H), 7.61 (d, *J* = 7.7 Hz, 1H), 7.35 (d, *J* = 8.5 Hz, 2H), 7.30 (d, *J* = 7.6 Hz, 1H), 7.20–7.16 (m, 1H), 7.15–7.11 (m, 1H), 6.90 (s, 2H), 5.80 (s, 1H), 5.27 (s, 1H), 4.54 (brs, 1H), 3.28–3.27 (m, 2H), 2.87 (t, *J* = 5.8 Hz, 2H), 1.41 (s, 9H), 1.38 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.0, 153.2, 150.7, 146.8, 136.6, 135.7, 135.5, 130.9, 129.8, 128.8, 125.5, 123.9, 122.0, 119.9, 118.9, 111.0, 110.2, 79.3, 48.2, 40.9, 34.5, 30.3, 28.5, 25.0; FT-IR (thin film, neat): 3628, 3406, 2954, 2924, 2870, 2853, 1699, 1520, 1456, 1435, 1346, 1238, 1163, 748 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{36}H_{44}N_3O_5$ $[M-H]^+$: 598.3281; found : 598.3289.

Tert-butyl[2-{2-((3,5-di-_tert_-butyl-4-hydroxyphenyl)(thiophen-2-yl)methyl)-1H-indol-3-yl}ethyl]carbamate (81o)



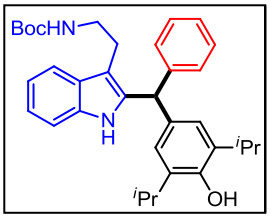
The reaction was performed at 0.062 mmol scale of *p*-quinone methide **(78o)**; R_f = 0.4 (10% EtOAc in hexane); orange solid (27 mg, 78% yield); m.p. = 190–192 ^oC; ^1H NMR (400 MHz, $CDCl_3$) δ 7.79 (brs, 1H), 7.60 (d, *J* = 7.6 Hz, 1H), 7.30–7.28 (m, 1H), 7.23 (dd, *J* = 5.1, 1.2 Hz, 1H), 7.16 (td, *J* = 7.1, 1.3 Hz, 1H), 7.11 (td, *J* = 7.8, 1.4 Hz, 1H), 7.07 (s, 2H), 6.96 (dd, *J* = 5.1, 3.5 Hz, 1H), 6.82 (d, *J* = 3.4 Hz, 1H), 5.86 (s, 1H), 5.21 (s, 1H), 4.54 (brs, 1H), 3.41–3.15 (m, 2H), 2.95 (t, *J* = 6.5 Hz, 2H), 1.43 (s, 9H), 1.40 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.0, 153.0, 146.6, 137.1, 136.2, 135.3, 132.3, 128.8, 126.9, 126.4, 125.0, 124.9, 121.7, 119.6, 118.8, 110.9, 109.5, 79.1, 43.8, 41.0, 34.5, 30.4, 28.6, 24.9; FT-IR (KBr): 3624, 3468, 3361, 2963, 2867, 1676, 1517, 1434, 1241, 1170, 742 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{34}H_{44}N_2NaO_3S$ $[M+Na]^+$: 583.2970; found : 583.2965.

Tert-butyl[2-{2-((3,5-di-_tert_-butyl-4-hydroxyphenyl)(furan-2-yl)methyl)-1H-indol-3-yl}ethyl]carbamate (81p)



The reaction was performed at 0.062 mmol scale of *p*-quinone methide **(78p)**; R_f = 0.3 (10% EtOAc in hexane); orange solid (24 mg, 72% yield); m.p. = 109–111 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (brs, 1H), 7.60 (d, J = 7.7 Hz, 1H), 7.42–7.41 (m, 1H), 7.30 (d, J = 7.8 Hz, 1H), 7.16 (td, J = 7.1, 1.2 Hz, 1H), 7.11 (td, J = 7.9, 1.2 Hz, 1H), 6.97 (s, 2H), 6.35 (dd, J = 3.1, 1.9 Hz, 1H), 6.16 (d, J = 3.1 Hz, 1H), 5.66 (s, 1H), 5.19 (s, 1H), 4.62 (brs, 1H), 3.48–3.22 (m, 2H), 3.03–2.88 (m, 2H), 1.44 (s, 9H), 1.38 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.1, 155.1, 153.0, 142.3, 136.2, 135.6, 135.1, 130.5, 128.5, 124.7, 121.8, 119.5, 118.8, 110.9, 110.4, 109.6, 108.1, 79.1, 42.1, 41.1, 34.5, 30.3, 28.6, 24.8; FT-IR (thin film, neat): 3639, 3407, 2955, 2924, 2871, 2853, 1698, 1460, 1377, 1364, 1168, 1082, 772 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{34}H_{44}N_2NaO_4$ $[M+Na]^+$: 567.3199; found : 567.3188.

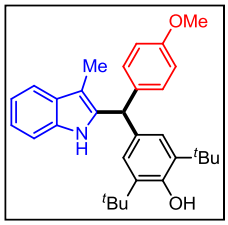
***tert*-butyl[2-{2-((4-hydroxy-3,5-diisopropylphenyl)(phenyl)(methyl)-1H-indol-3-yl}ethyl]carbamate (81q)**



The reaction was performed at 0.062 mmol scale of *p*-quinone methide **(78q)**; R_f = 0.3 (15% EtOAc in hexane); orange gummy solid (17 mg, 50% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60–7.59 (m, 2H), 7.33–7.29 (m, 2H), 7.25–7.22 (m, 1H), 7.16–7.08 (m, 4H), 6.82 (s, 2H), 5.71 (s, 1H), 4.89 (s, 1H), 4.47 (s, 1H), 3.32–3.20 (m, 2H), 3.12 (sept, J = 6.9 Hz, 2H), 2.88 (t, J = 6.4 Hz, 2H), 1.42 (s, 9H), 1.19 (d, J = 8.3 Hz, 6H), 1.17 (d, J = 8.3 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.0, 149.1, 142.8, 137.4, 135.3, 134.1, 133.7, 129.0, 128.9, 128.7, 126.9, 124.2, 121.5, 119.5, 118.8, 110.9, 109.5, 79.1, 48.3, 40.8, 29.9, 28.6, 27.5, 22.8, 22.78; FT-IR (thin film, neat): 3414, 2957, 2924, 2852, 1694, 1461, 1366, 1275, 1167, 749 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{34}H_{42}N_2NaO_3$ $[M+Na]^+$: 549.3093; found : 549.3070.

Characterization data of compounds (82a-82n):

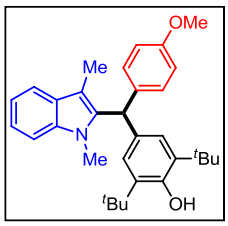
2,6-di-_tert_-butyl-4-[(4-methoxyphenyl){3-methyl-1H-indol-2-yl}methyl]phenol (82a)



The reaction was performed at 0.062 mmol scale of *p*-quinone methide **(78a)**; R_f = 0.5 (5% EtOAc in hexane); orange solid (26 mg, 94% yield); m.p. = 168–170 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57–7.55 (m, 1H),

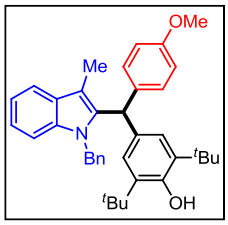
7.52 (brs, 1H), 7.27–7.25 (m, 1H), 7.16–7.12 (m, 2H), 7.09 (d, *J* = 8.4 Hz, 2H), 7.00 (s, 2H), 6.86 (d, *J* = 8.6 Hz, 2H), 5.65 (s, 1H), 5.18 (s, 1H), 3.82 (s, 3H), 2.18 (s, 3H), 1.41 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.2, 152.6, 136.6, 136.0, 135.1, 135.0, 132.7, 130.0, 129.8, 125.7, 121.1, 119.1, 118.4, 113.8, 110.6, 107.8, 55.4, 47.9, 34.5, 30.4, 8.8; FT-IR (KBr): 3616, 3418, 2953, 2924, 2855, 1610, 1584, 1509, 1462, 1432, 1247, 1157, 747 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{31}H_{38}NO_2$ $[M+H]^+$: 456.2903; found : 456.2906.

2,6-di-*tert*-butyl-4-[(1,3-dimethyl-1H-indol-2-yl){4-methoxyphenyl}methyl]phenol (82b)



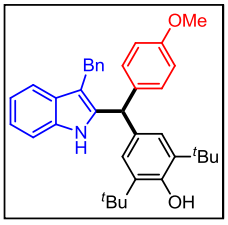
The reaction was performed at 0.062 mmol scale of *p*-quinone methide **(78a)**; R_f = 0.6 (5% EtOAc in hexane); yellow solid (27mg, 92% yield); m.p. = 162–164 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, *J* = 7.8 Hz, 1H), 7.27–7.25 (m, 1H), 7.23–7.19 (m, 1H), 7.14–7.10 (m, 1H), 7.06 (d, *J* = 8.5 Hz, 2H), 6.99 (s, 2H), 6.85 (d, *J* = 8.8 Hz, 2H), 5.77 (s, 1H), 5.16 (s, 1H), 3.82 (s, 3H), 3.54 (s, 3H), 1.86 (s, 3H), 1.39 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.1, 152.4, 137.9, 136.7, 135.8, 134.4, 132.1, 130.2, 129.1, 126.1, 121.0, 118.5, 118.3, 113.7, 108.6, 108.4, 55.4, 47.5, 34.5, 30.5, 30.4, 9.2; FT-IR (thin film, neat): 3640, 2955, 2924, 2869, 2853, 1609, 1510, 1468, 1436, 1245, 1176, 737 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{32}H_{40}NO_2$ $[M+H]^+$: 470.3059; found : 470.3045.

4-[(1-benzyl-3-methyl-1H-indol-2-yl){4-methoxyphenyl}methyl]-2,6-di-*tert*-butylphenol (82c)



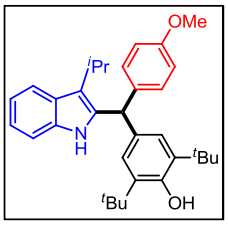
The reaction was performed at 0.062 mmol scale of *p*-quinone methide **(78a)**; R_f = 0.5 (5% EtOAc in hexane); yellow solid (25mg, 75% yield); m.p. = 103–105 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59–7.56 (m, 1H), 7.25–7.16 (m, 4H), 7.15–7.10 (m, 2H), 6.98 (d, *J* = 8.6 Hz, 2H), 6.91 (d, *J* = 6.6 Hz, 2H), 6.82 (s, 2H), 6.80 (d, *J* = 8.8 Hz, 2H), 5.53 (s, 1H), 5.31 (d, *J* = 17.4 Hz, 1H), 5.17 (d, *J* = 17.4 Hz, 1H), 5.07 (s, 1H), 3.80 (s, 3H), 1.78 (s, 3H), 1.31 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.2, 152.3, 138.7, 138.2, 136.6, 135.7, 133.9, 132.3, 130.2, 129.4, 128.8, 127.2, 125.9, 125.8, 121.4, 118.8, 118.4, 113.8, 109.2, 109.1, 55.4, 47.4, 46.9, 34.4, 30.4, 9.3; FT-IR (thin film, neat): 3643, 2954, 2923, 2870, 2853, 1609, 1510, 1463, 1455, 1377, 1249, 908, 736 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{38}H_{44}NO_2$ $[M+H]^+$: 546.3372; found : 546.3360.

4-[(3-benzyl-1H-indol-2-yl){4-methoxyphenyl}methyl]-2,6-di-*tert*-butylphenol (82d)



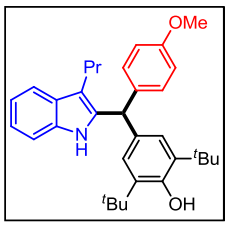
The reaction was performed at 0.062 mmol scale of *p*-quinone methide **(78a)**; R_f = 0.3 (5% EtOAc in hexane); brown solid (25 mg, 77% yield); m.p. = 144–146 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (s, 1H), 7.43 (d, *J* = 7.8 Hz, 1H), 7.27 (d, *J* = 6.8 Hz, 1H), 7.20–7.17 (m, 2H), 7.13–7.09 (m, 4H), 7.06–7.02 (m, 3H), 6.91 (s, 2H), 6.82 (d, *J* = 8.7 Hz, 2H), 5.60 (s, 1H), 5.14 (s, 1H), 4.04 (d, *J* = 3.6 Hz, 2H), 3.80 (s, 3H), 1.35 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.3, 152.6, 141.6, 137.8, 136.0, 135.4, 134.7, 132.8, 130.0, 129.3, 128.5, 128.3, 125.7, 125.6, 121.3, 119.4, 118.9, 113.9, 111.0, 110.7, 55.4, 47.6, 34.5, 30.4, 30.2; FT-IR (thin film, neat): 3633, 3456, 2956, 2925, 2870, 2857, 1609, 1510, 1459, 1435, 1247, 1178, 1034, 909, 738 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{37}H_{42}NO_2$ $[M+H]^+$: 532.3216; found : 532.3210.

2,6-di-*tert*-butyl-4-[(3-isopropyl-1H-indol-2-yl){4-methoxyphenyl}methyl]phenol (82e)



The reaction was performed at 0.062 mmol scale of *p*-quinone methide **(78a)**; R_f = 0.4 (5% EtOAc in hexane); orange solid (23.5 mg, 79% yield); m.p. = 124–126 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, *J* = 7.4 Hz, 1H), 7.41 (s, 1H), 7.25–7.23 (m, 1H), 7.12–7.04 (m, 4H), 6.94 (s, 2H), 6.83 (d, *J* = 8.7 Hz, 2H), 5.68 (s, 1H), 5.15 (s, 1H), 3.81 (s, 3H), 3.16 (sept, *J* = 7.0 Hz, 1H), 1.37 (s, 18H), 1.31 (d, *J* = 7.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.2, 152.6, 136.0, 135.7, 135.3, 135.2, 133.1, 130.0, 127.5, 125.6, 120.7, 120.3, 118.8, 118.3, 113.8, 111.0, 55.4, 47.7, 34.5, 30.4, 26.1, 23.1, 22.8; FT-IR (thin film, neat): 3637, 3456, 2958, 2926, 2869, 1609, 1510, 1458, 1434, 1248, 1177, 1035, 909, 739 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{33}H_{42}NO_2$ $[M+H]^+$: 484.3216; found : 484.3210.

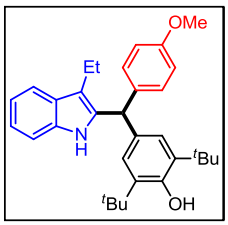
2,6-di-*tert*-butyl-4-[(4-methoxyphenyl){3-propyl-1H-indol-2-yl}methyl]phenol (82f)



The reaction was performed at 0.062 mmol scale of *p*-quinone methide **(78a)**; R_f = 0.6 (5% EtOAc in hexane); orange gummy solid (21 mg, 72% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, *J* = 7.5 Hz, 1H), 7.62 (s, 1H), 7.30 (d, *J* = 7.3 Hz, 1H), 7.20–7.14 (m, 4H), 7.06 (s, 2H), 6.92–6.90 (m, 2H), 5.73 (s, 1H), 5.23 (s, 1H), 3.86 (s, 3H), 2.84–2.68 (m, 2H), 1.68–1.61 (m, 2H), 1.46 (s, 18H), 0.97 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.2, 152.5, 136.7, 136.0, 135.4, 135.1, 133.1, 130.0, 129.2, 125.6, 121.0, 119.0, 118.8, 113.8, 112.9, 110.7, 55.3, 47.6, 34.5, 30.4, 26.5, 23.8, 14.4; FT-IR (thin film, neat): 3638, 3458, 3399, 2957, 2933, 2869,

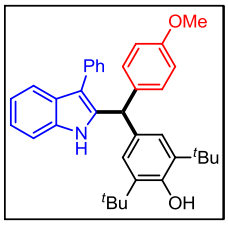
1609, 1510, 1459, 1435, 1247, 1177, 1035, 740 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{33}H_{42}NO_2$ $[M+H]^+$: 484.3216; found : 484.3200.

2,6-di-*tert*-butyl-4-[{3-ethyl-1H-indol-2-yl}(4-methoxyphenyl)methyl]phenol (82g)



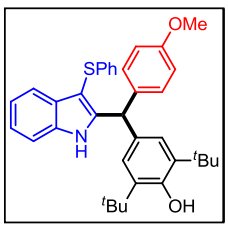
The reaction was performed at 0.062 mmol scale of *p*-quinone methide **(78a)**; R_f = 0.5 (5% EtOAc in hexane); orange solid (20.5 mg, 71% yield); m.p. = 145–147 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72–7.70 (m, 1H), 7.64 (s, 1H), 7.34–7.32 (m, 1H), 7.22–7.20 (m, 4H), 7.10 (s, 2H), 6.95 (d, *J* = 8.3 Hz, 2H), 5.78 (s, 1H), 5.27 (s, 1H), 3.88 (s, 3H), 2.82 (q, *J* = 7.4 Hz, 2H), 1.50 (s, 18H), 1.23 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.2, 152.6, 136.1, 136.0, 135.4, 135.2, 133.0, 130.0, 128.8, 125.6, 121.0, 119.0, 118.6, 114.5, 113.8, 110.7, 55.3, 47.7, 34.5, 30.4, 17.6, 15.3; FT-IR (thin film, neat): 3639, 3458, 3406, 2961, 2871, 1610, 1510, 1459, 1435, 1302, 1248, 1178, 1037, 909, 836, 736 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{32}H_{40}NO_2$ $[M+H]^+$: 470.3059; found : 470.3045.

2,6-di-*tert*-butyl-4-[(4-methoxyphenyl){3-phenyl-1H-indol-2-yl}methyl]phenol (82h)



The reaction was performed at 0.062 mmol scale of *p*-quinone methide **(78a)**; R_f = 0.3 (5% EtOAc in hexane); reddish brown solid (28 mg, 87% yield); m.p. = 137–139 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (s, 1H), 7.71 (d, *J* = 7.8 Hz, 1H), 7.47–7.45 (m, 2H), 7.43–7.39 (m, 2H), 7.35–7.31 (m, 2H), 7.20 (td, *J* = 7.1, 1.2 Hz, 1H), 7.15 (td, *J* = 8.0, 1.2 Hz, 1H), 7.10 (d, *J* = 8.6 Hz, 2H), 6.96 (s, 2H), 6.86 (d, *J* = 8.8 Hz, 2H), 5.71 (s, 1H), 5.16 (s, 1H), 3.82 (s, 3H), 1.38 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.2, 152.6, 137.3, 136.0, 135.6, 135.4, 135.3, 133.2, 130.0, 129.8, 128.5, 128.2, 126.1, 125.6, 121.8, 120.0, 119.5, 115.1, 113.9, 110.9, 55.4, 47.5, 34.5, 30.4; FT-IR (thin film, neat): 3633, 3449, 2956, 2925, 2870, 2857, 1603, 1510, 1457, 1435, 1249, 1178, 1034, 743, 702 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{36}H_{40}NO_2$ $[M+H]^+$: 518.3059; found : 518.3049.

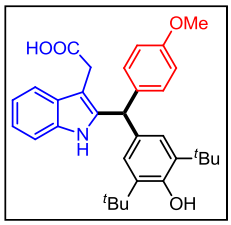
2,6-di-*tert*-butyl-4-[(4-methoxyphenyl){3-(phenylthio)-1H-indol-2-yl}methyl]phenol (82i)



The reaction was performed at 0.062 mmol scale of *p*-quinone methide **(78a)**; R_f = 0.4 (10% EtOAc in hexane); orange solid (30 mg, 88% yield); m.p. = 164–166 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (s, 1H), 7.63 (d, *J* = 7.8 Hz, 1H), 7.36 (d, *J* = 8.0 Hz, 1H), 7.25–7.21 (m, 1H), 7.18–7.15 (m,

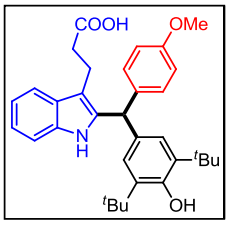
1H), 7.12–7.09 (m, 4H), 7.04–7.00 (m, 3H), 6.99 (s, 2H), 6.83 (d, *J* = 8.8 Hz, 2H), 6.04 (s, 1H), 5.17 (s, 1H), 3.80 (s, 3H), 1.38 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.3, 152.7, 147.0, 139.1, 136.1, 135.7, 134.1, 132.1, 130.4, 130.0, 128.6, 125.8, 125.6, 124.6, 122.5, 120.9, 119.5, 113.9, 111.3, 99.9, 55.4, 47.4, 34.4, 30.4; FT-IR (thin film, neat): 3633, 3444, 2956, 2922, 2868, 2852, 1510, 1455, 1434, 1248, 1178, 741 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{36}H_{38}NO_2S$ $[M-H]^+$: 548.2623; found : 548.2627.

2-[2-{(3,5-di-*tert*-butyl-4-hydroxyphenyl)(4-methoxyphenyl)methyl}-1H-indol-3-yl]acetic acid (82j)



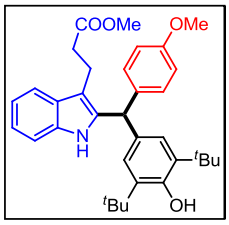
The reaction was performed at 0.062 mmol scale of *p*-quinone methide **(78a)**; R_f = 0.3 (30% EtOAc in hexane); orange solid (26 mg, 85% yield); m.p. = 88–90 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (s, 1H), 7.57–7.55 (m, 1H), 7.27–7.25 (m, 1H), 7.16–7.12 (m, 2H), 7.10 (d, *J* = 8.6 Hz, 2H), 6.98 (s, 2H), 6.84 (d, *J* = 8.7 Hz, 2H), 5.70 (s, 1H), 5.17 (s, 1H), 3.78 (s, 3H), 3.62-3.53 (m, 2H), 1.36 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.0, 158.4, 152.8, 138.8, 136.2, 135.0, 134.3, 132.2, 130.0, 128.9, 125.6, 121.6, 119.8, 118.5, 114.0, 110.9, 104.4, 55.4, 47.9, 34.5, 30.4, 30.1; FT-IR (KBr): 3631, 3395, 2963, 2926, 2855, 1709, 1609, 1510, 1461, 1435, 1261, 1096, 1021, 800 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{32}H_{38}NO_4$ $[M+H]^+$: 500.2801; found : 500.2809.

3-[2-{(3,5-di-*tert*-butyl-4-hydroxyphenyl)(4-methoxyphenyl)methyl}-1H-indol-3-yl]propanoic acid (82k)



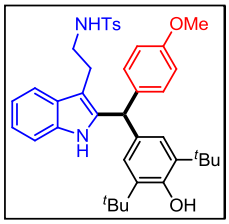
The reaction was performed at 0.062 mmol scale of *p*-quinone methide **(78a)**; R_f = 0.3 (30% EtOAc in hexane); brown solid (25 mg, 80% yield); m.p. = 169–171 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56–7.54 (m, 2H), 7.27–7.24 (m, 1H), 7.15–7.10 (m, 2H), 7.07 (d, *J* = 8.7 Hz, 2H), 6.94 (s, 2H), 6.83 (d, *J* = 8.8 Hz, 2H), 5.68 (s, 1H), 5.16 (s, 1H), 3.79 (s, 3H), 2.99 (t, *J* = 8.0 Hz, 2H), 2.50–2.37 (m, 2H), 1.36 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.2, 158.3, 152.7, 137.5, 136.1, 135.2, 134.8, 132.7, 130.0, 128.6, 125.6, 121.3, 119.4, 118.3, 114.0, 110.9, 110.4, 55.4, 47.7, 35.5, 34.5, 30.4, 19.7; FT-IR (thin film, neat): 3635, 3459, 2959, 2928, 2867, 1708, 1603, 1512, 1434, 1248, 1177, 1035, 913, 741 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{33}H_{40}NO_4$ $[M+H]^+$: 514.2957; found : 514.2964.

Methyl 3-[2-{(3,5-di-*tert*-butyl-4-hydroxyphenyl)(4-methoxyphenyl)methyl}-1H-indol-3-yl]propanoate (82l)



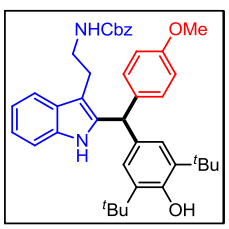
The reaction was performed at 0.062 mmol scale of *p*-quinone methide **(78a)**; R_f = 0.4 (20% EtOAc in hexane); brown solid (24.5 mg, 75% yield); m.p. = 144–146 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57–7.55 (m, 2H), 7.26–7.25 (m, 1H), 7.15–7.10 (m, 2H), 7.08 (d, *J* = 7.7 Hz, 2H), 6.96 (s, 2H), 6.84 (d, *J* = 8.6 Hz, 2H), 5.72 (s, 1H), 5.16 (s, 1H), 3.81 (s, 3H), 3.62 (s, 3H), 3.01 (t, *J* = 7.9 Hz, 2H), 2.50–2.37 (m, 2H), 1.38 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.0, 158.3, 152.7, 137.4, 136.1, 135.2, 134.9, 132.8, 130.0, 128.6, 125.6, 121.3, 119.4, 118.4, 113.9, 110.9, 110.7, 55.4, 51.6, 47.5, 34.7, 34.5, 30.4, 19.9; FT-IR (thin film, neat): 3633, 3454, 3394, 2955, 2923, 2872, 1730, 1609, 1510, 1460, 1435, 1248, 1177, 741 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{34}H_{40}NO_4$ $[M-H]^+$: 526.2957; found : 526.2963.

N-[3-(2-{(3,5-di-*tert*-butyl-4-hydroxyphenyl)(4-methoxyphenyl)methyl}-1H-indol-3-yl)ethyl]-4-methylbenzenesulfonamide (82m)



The reaction was performed at 0.062 mmol scale of *p*-quinone methide **(78a)**; R_f = 0.2 (20% EtOAc in hexane); orange solid (38 mg, 95% yield); m.p. = 149–151 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (s, 1H), 7.54 (d, *J* = 8.3 Hz, 2H), 7.37 (d, *J* = 7.9 Hz, 1H), 7.24 (d, *J* = 8.0 Hz, 1H), 7.18 (d, *J* = 7.9 Hz, 2H), 7.14–7.10 (m, 1H), 7.06–7.00 (m, 3H), 6.91 (s, 2H), 6.82 (d, *J* = 8.8 Hz, 2H), 5.57 (s, 1H), 5.17 (s, 1H), 4.16 (t, *J* = 6.2 Hz, 1H), 3.80 (s, 3H), 3.08–3.03 (m, 2H), 2.87–2.84 (m, 2H), 2.38 (s, 3H), 1.36 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.4, 152.8, 143.2, 138.3, 137.0, 136.3, 135.2, 134.8, 132.4, 129.8, 129.7, 128.6, 127.1, 125.5, 121.5, 119.7, 118.3, 114.1, 110.9, 107.8, 55.4, 47.6, 43.2, 34.5, 30.4, 25.0, 21.7; FT-IR (KBr): 3619, 3454, 3407, 2957, 1610, 1510, 1460, 1435, 1248, 1326, 1159, 813, 743 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{39}H_{47}N_2O_4S$ $[M+H]^+$: 639.3257; found : 639.3240.

Benzyl[3-(2-{(3,5-di-*tert*-butyl-4-hydroxyphenyl)(4-methoxyphenyl)methyl}-1H-indol-3-y)ethyl]carbamate (82n)



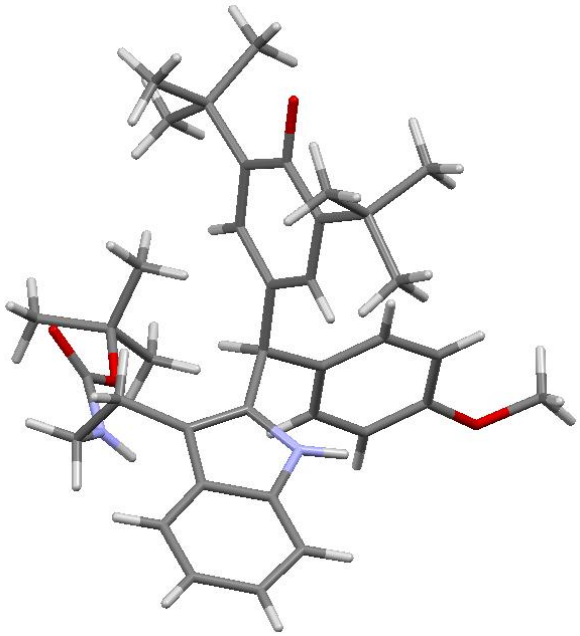
The reaction was performed at 0.062 mmol scale of *p*-quinone methide **(78a)**; R_f = 0.2 (20% EtOAc in hexane); orange solid (36 mg, 95% yield); m.p. = 161–163 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (s, 1H), 7.59 (d, *J*

= 7.5 Hz, 1H), 7.34–7.25 (m, 6H), 7.16–7.10 (m, 2H), 7.06 (d, *J* = 8.4 Hz, 2H), 6.95 (s, 2H), 6.82 (d, *J* = 8.4 Hz, 2H), 5.63 (s, 1H), 5.17 (s, 1H), 5.08 (s, 2H), 4.67 (brs, 1H), 3.77 (s, 3H), 3.33–3.30 (m, 2H), 2.91 (t, *J* = 6.6 Hz, 2H), 1.37 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.4, 156.4, 152.7, 138.0, 136.8, 136.2, 135.3, 134.8, 132.6, 129.9, 129.0, 128.6, 128.2, 128.1, 125.5, 121.4, 119.6, 118.6, 114.0, 110.9, 108.9, 66.6, 55.3, 47.7, 41.3, 34.5, 30.4, 24.9; FT-IR (KBr): 3596, 3439, 3378, 2954, 2924, 2854, 1715, 1611, 1583, 1509, 1459, 1436, 1304, 1259, 1242, 1176, 1074, 746 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{40}H_{46}N_2NaO_4$ $[M+Na]^+$: 641.3355; found : 641.3379.

General procedure for the gram scale synthesis of 81a:

A mixture of *p*-quinone methide **78a** (0.5 g, 1.54 mmol), 3-substituted indole **79a** (0.4 g, 1.54 mmol) and $Bi(OTf)_3$ (50.5 mg, 0.07 mmol) was grinded using a pestle and mortar. After 1 h, the mixture was diluted with EtOAc and concentrated under reduced pressure. The residue was then purified through a silica gel column using EtOAc/Hexane mixture as an eluent to get the pure product **81a**.

X-ray Crystal structure of compound 81a[42]



X-ray Crystal structure determination of compound 81a

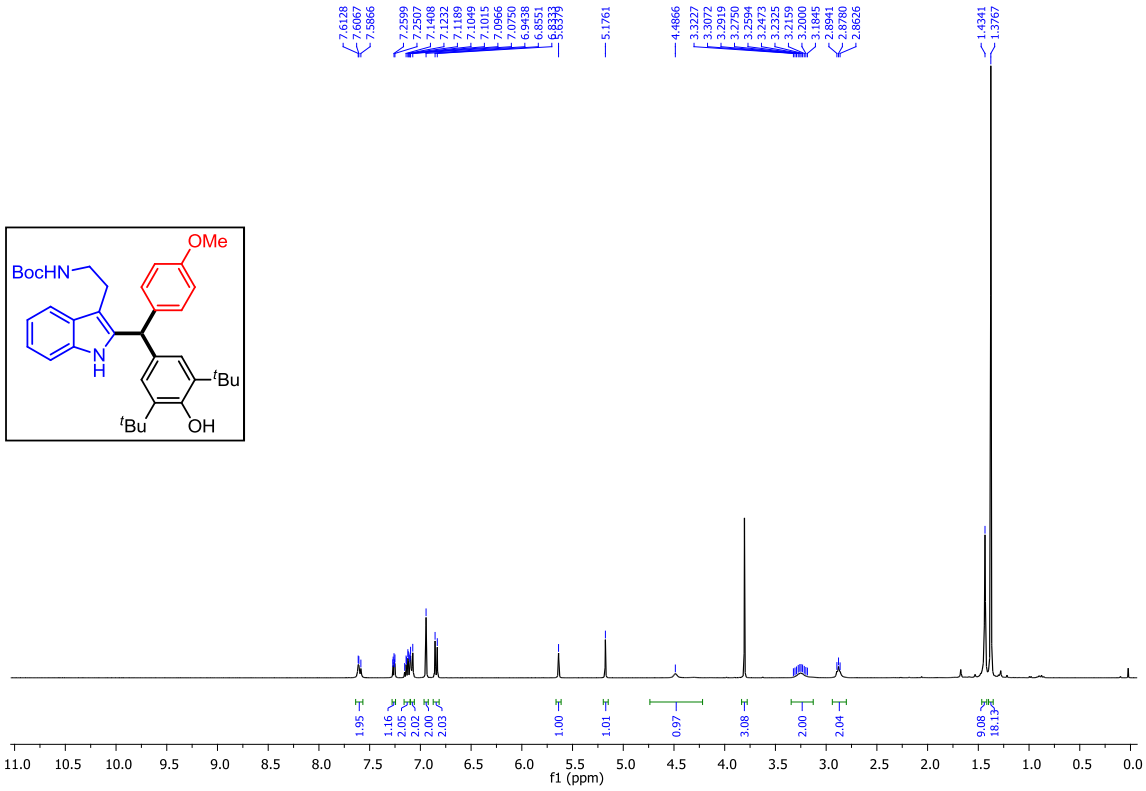
Crystal Data for $C_{37}H_{48}N_2O_4$ (*M* =582.79 g/mol): triclinic, space group P-1 (no. 2), *a* = 14.974(3) Å, *b* = 15.630(3) Å, *c* = 17.976(3) Å, α = 94.469(6), β = 108.213(6), γ = 101.712(4)°, *V* = 3867.5(12) Å^3, *Z* = 4, *T* = 293 K, μ(Mo Kα) = 0.065 mm^{-1}, *Dcalc* =

1.0043 g/cm^3, 35619 reflections measured (6.06° ≤ 2Θ ≤ 50.7°), 14116 unique (R_{int} = 0.0743, R_{sigma} = 0.0975) which were used in all calculations. The final R_1 was 0.1231 (I>=2u(I)) and wR_2 was 0.3515 (all data).

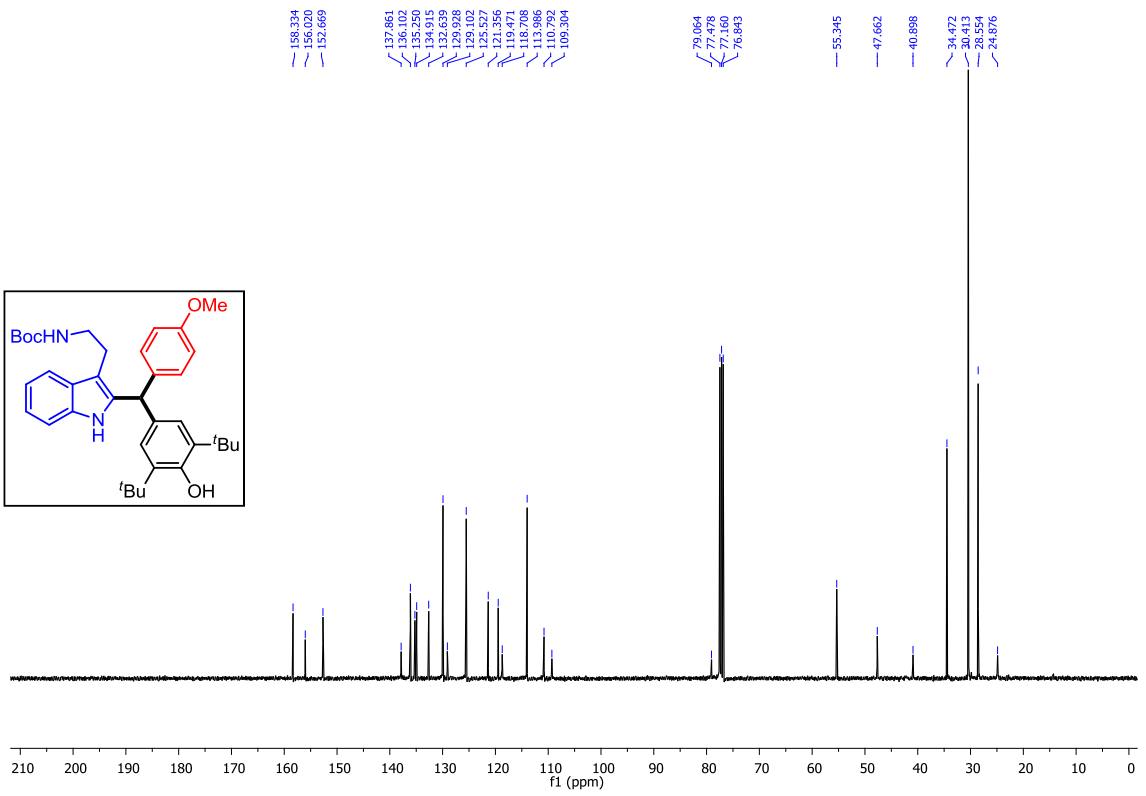
Crystal data and structure refinement for compound 81a

Identification code	**81a**
Empirical formula	$C_{37}H_{48}N_2O_4$
Formula weight	584.79
Temperature/K	293
Crystal system	triclinic
Space group	P-1
a/Å	14.974(3)
b/Å	15.630(3)
c/Å	17.976(3)
α/°	94.469(6)
β/°	108.213(6)
γ/°	101.712(4)
Volume/Å^3	3867.5(12)
Z	4
ρ_{calc}g/cm^3	1.0043
μ/mm^{-1}	0.065
F(000)	1264.6
Crystal size/mm^3	0.2 × 0.2 × 0.2
Radiation	Mo Kα (λ = 0.71073)
2Θ range for data collection/°	6.06 to 50.7
Index ranges	-18 ≤ h ≤ 18, -18 ≤ k ≤ 18, -21 ≤ l ≤ 21
Reflections collected	35619
Independent reflections	14116 [R_{int} = 0.0743, R_{sigma} = 0.0975]
Data/restraints/parameters	14116/0/796
Goodness-of-fit on F^2	1.540
Final R indexes [I>=2σ (I)]	R_1 = 0.1231, wR_2 = 0.3055
Final R indexes [all data]	R_1 = 0.2144, wR_2 = 0.3515
Largest diff. peak/hole / e Å^{-3}	1.01/-0.43

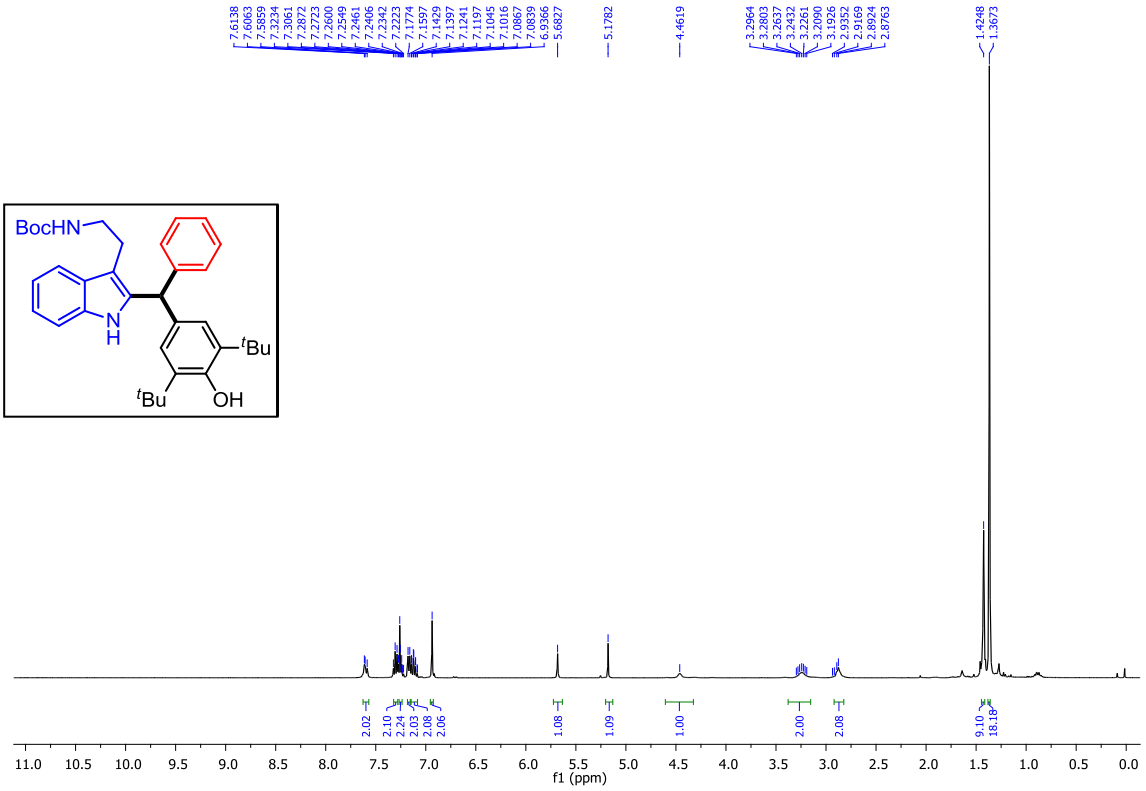
^{1}H NMR spectrum of **81a**



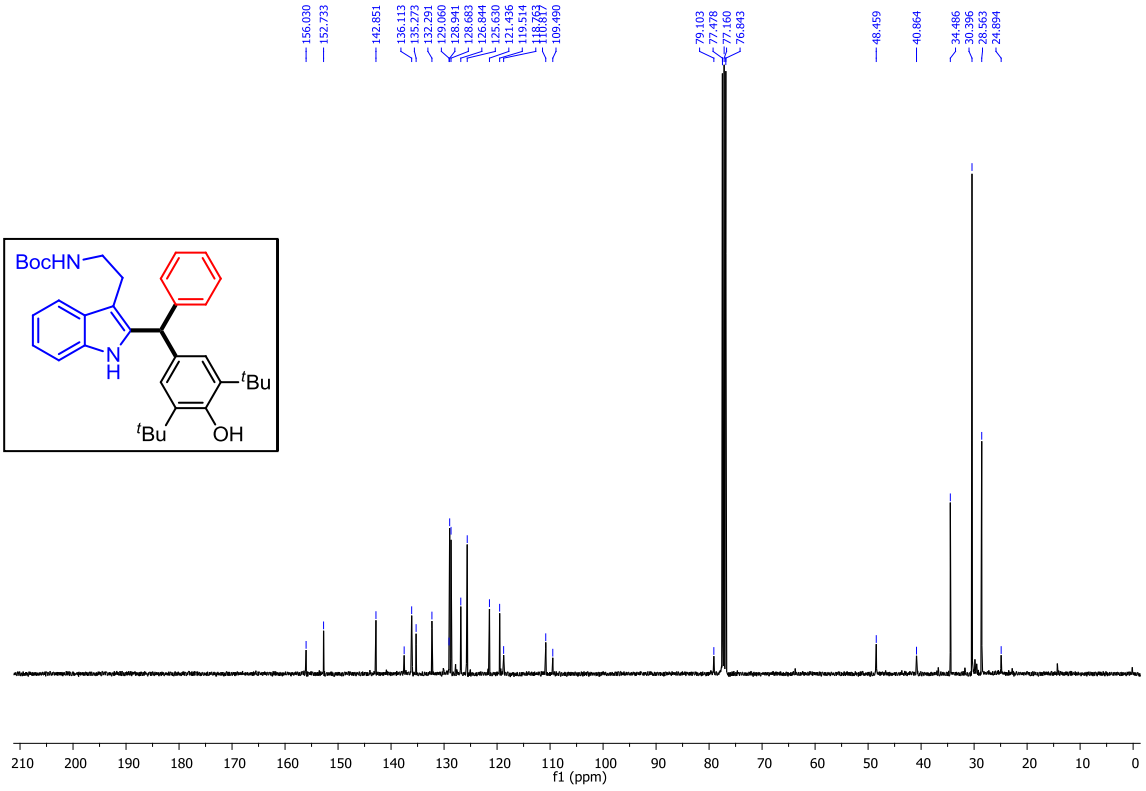
^{13}C NMR spectrum of **81a**



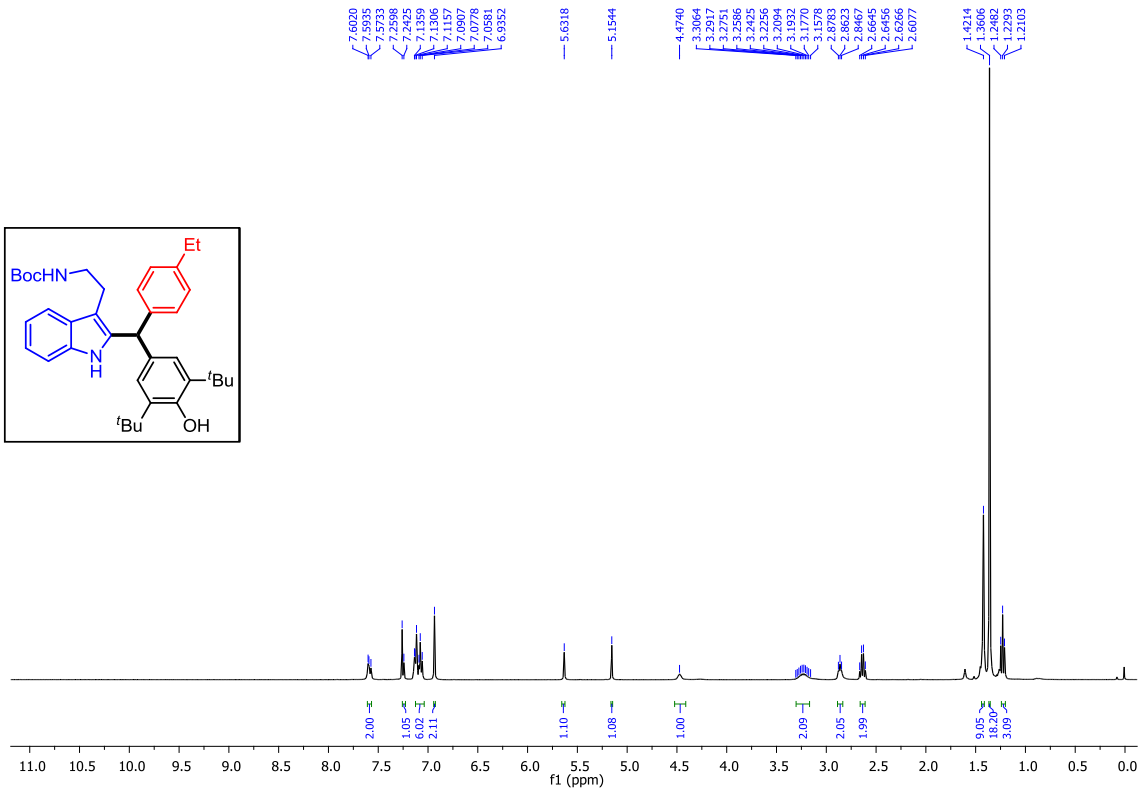
^{1}H NMR spectrum of **81b**



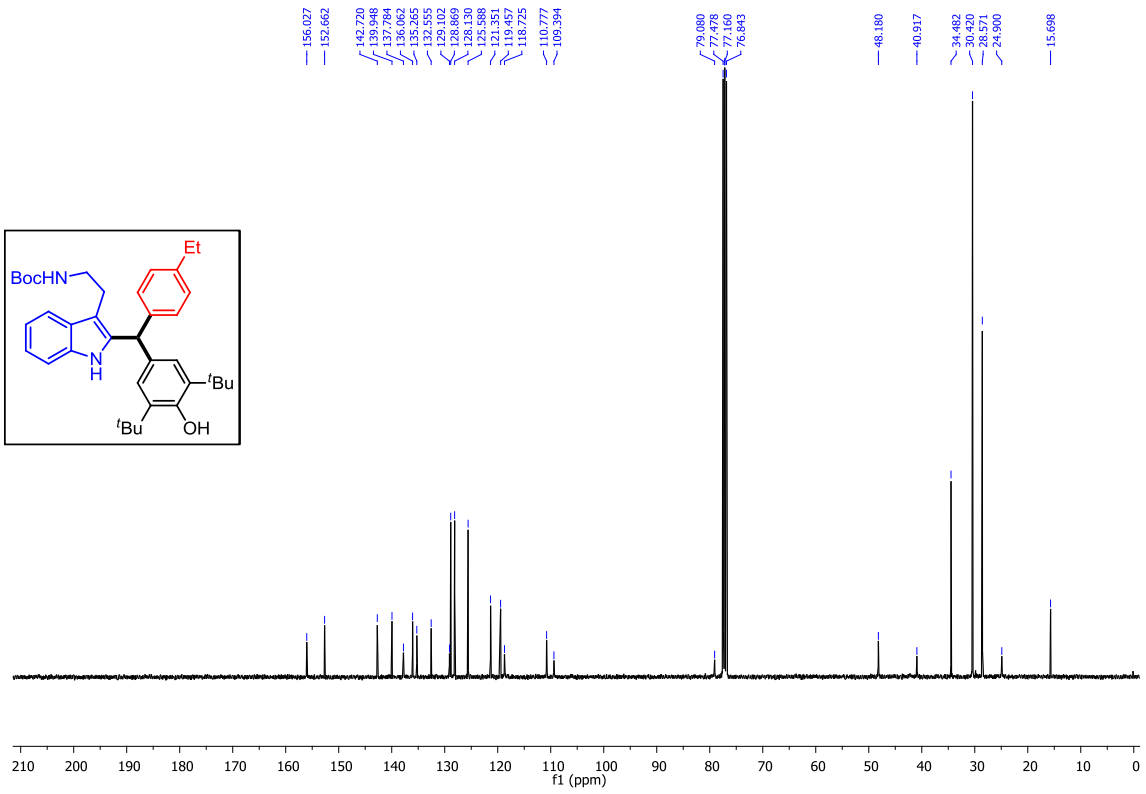
^{13}C NMR spectrum of **81b**



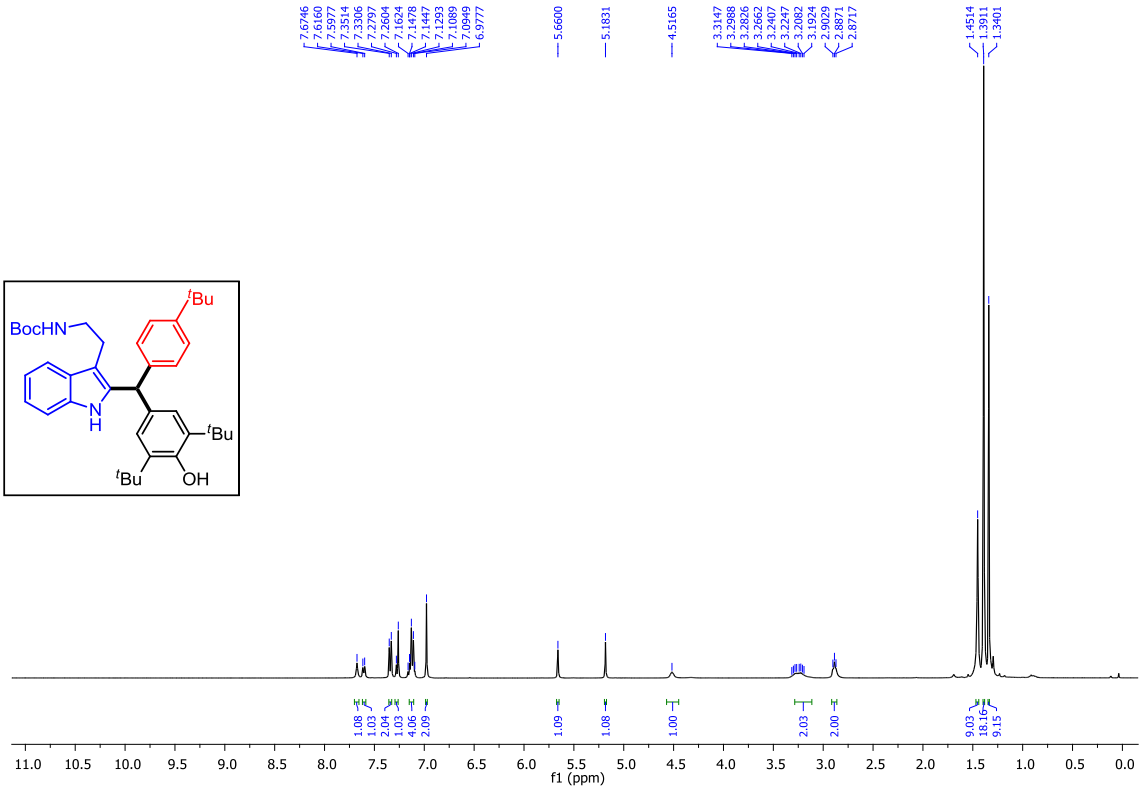
^{1}H NMR spectrum of **81c**



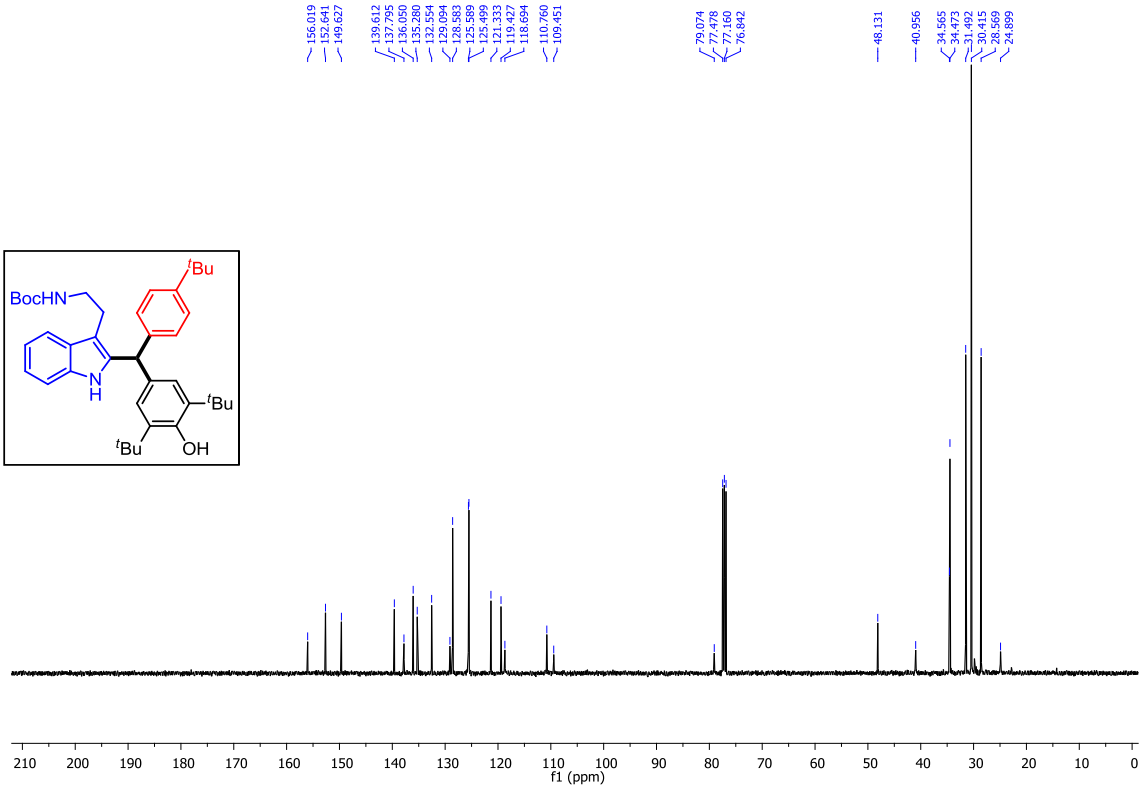
^{13}C NMR spectrum of **81c**



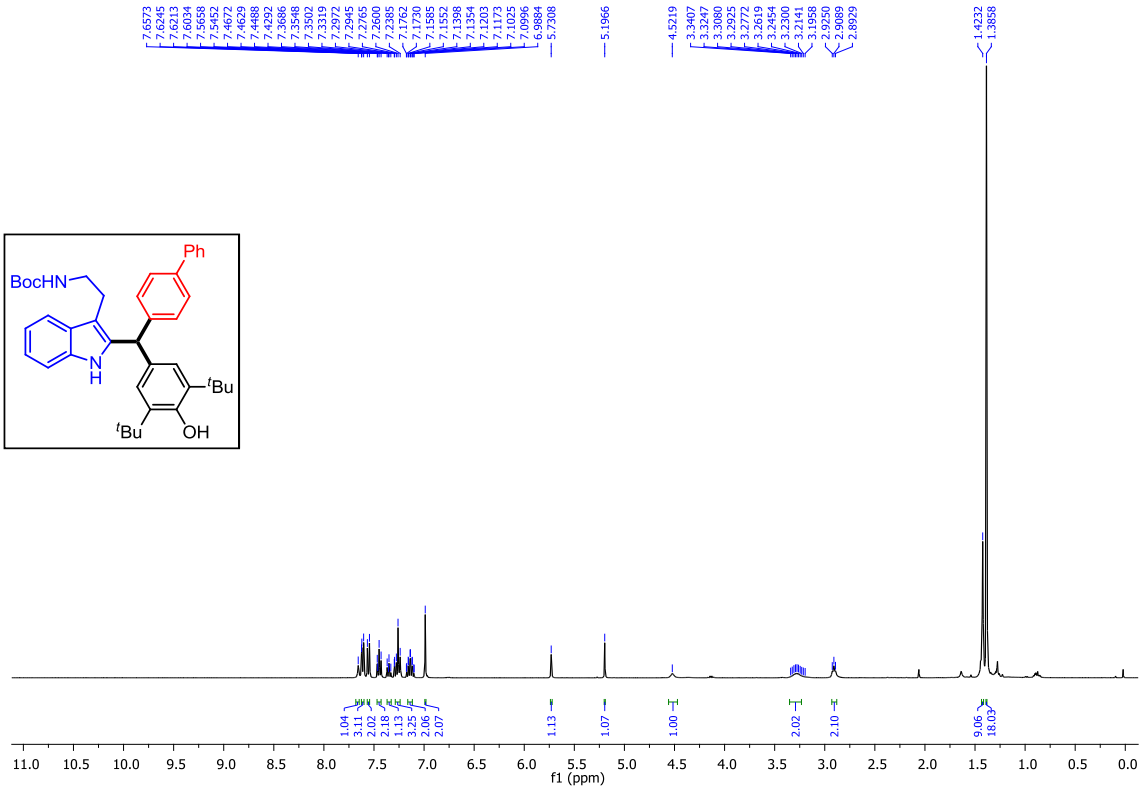
^{1}H NMR spectrum of **81d**



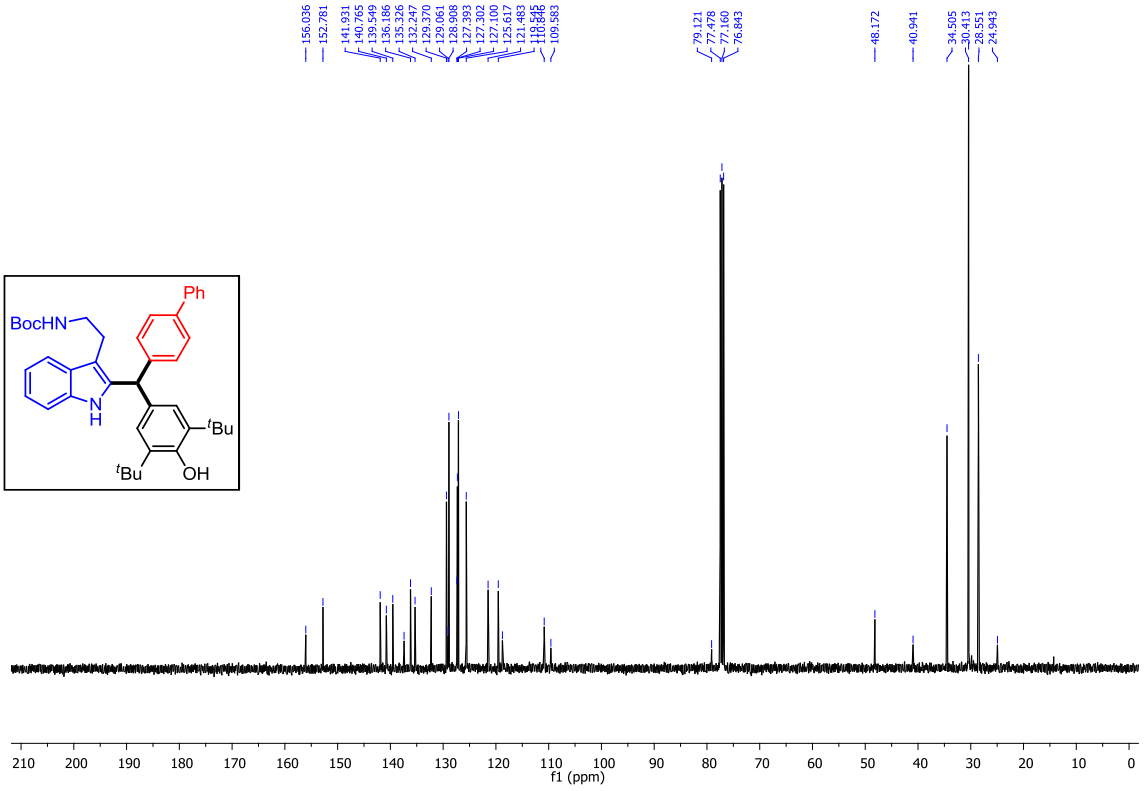
^{13}C NMR spectrum of **81d**



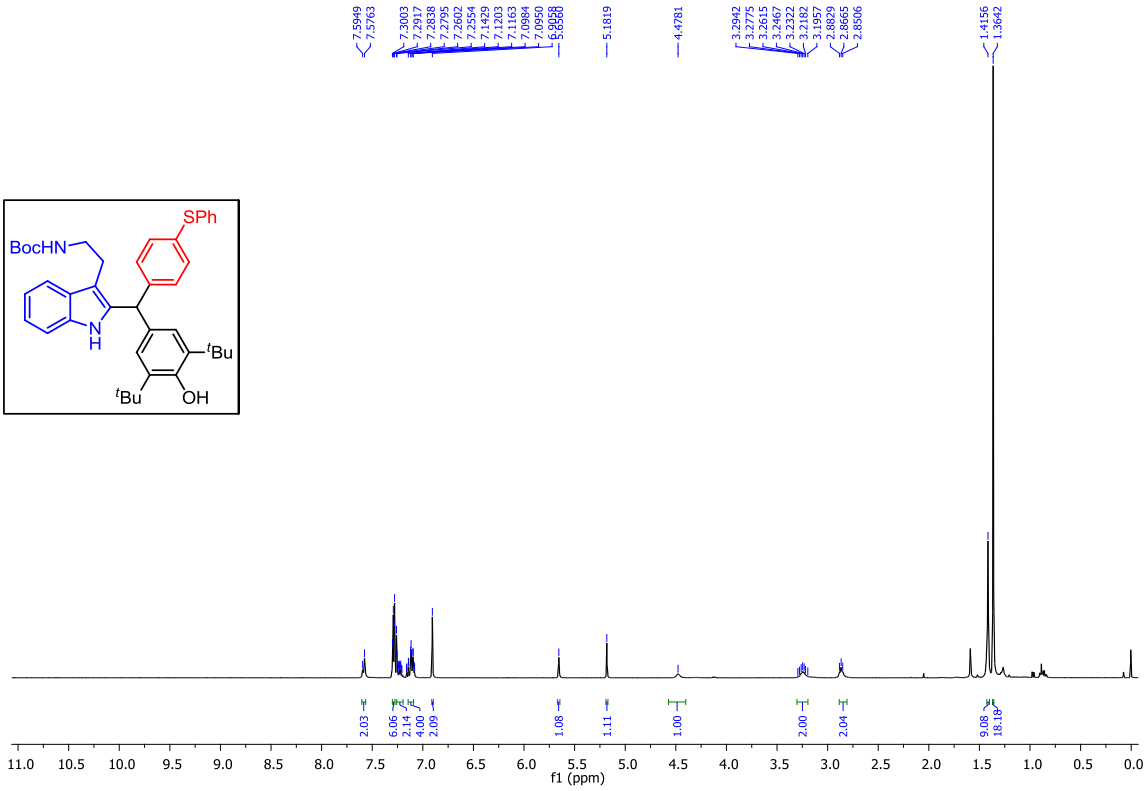
^{1}H NMR spectrum of **81e**



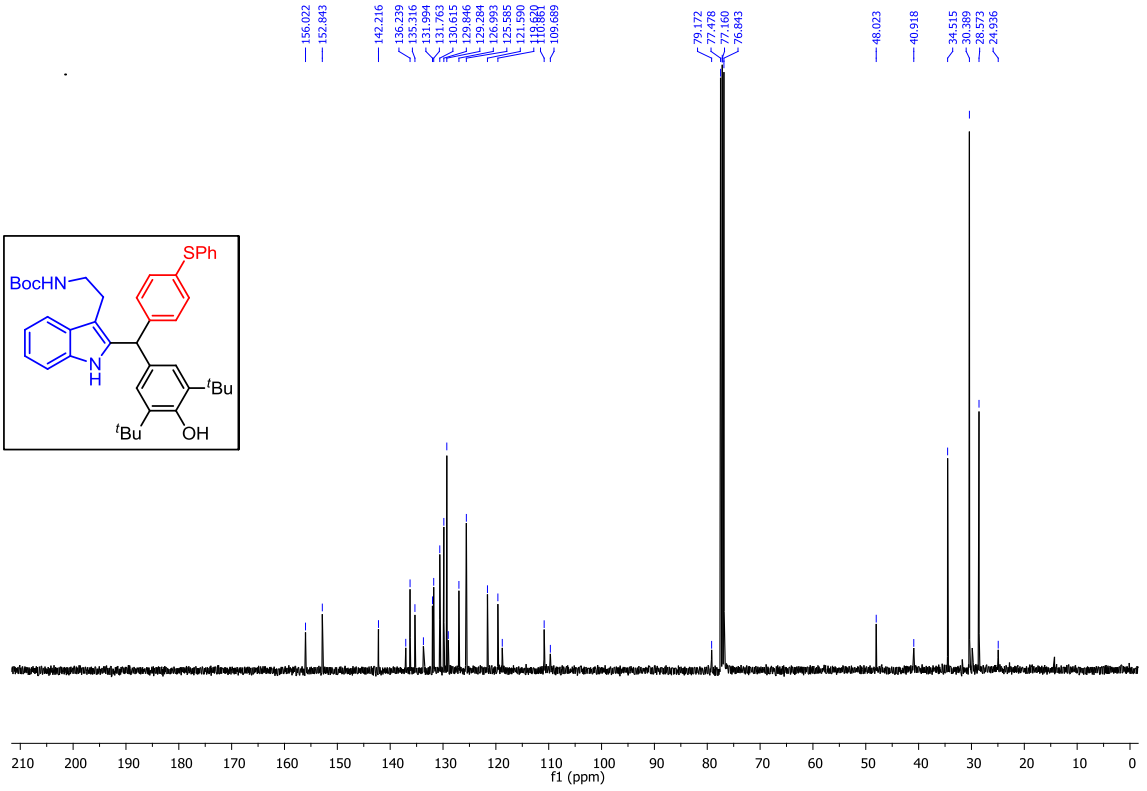
^{13}C NMR spectrum of **81e**



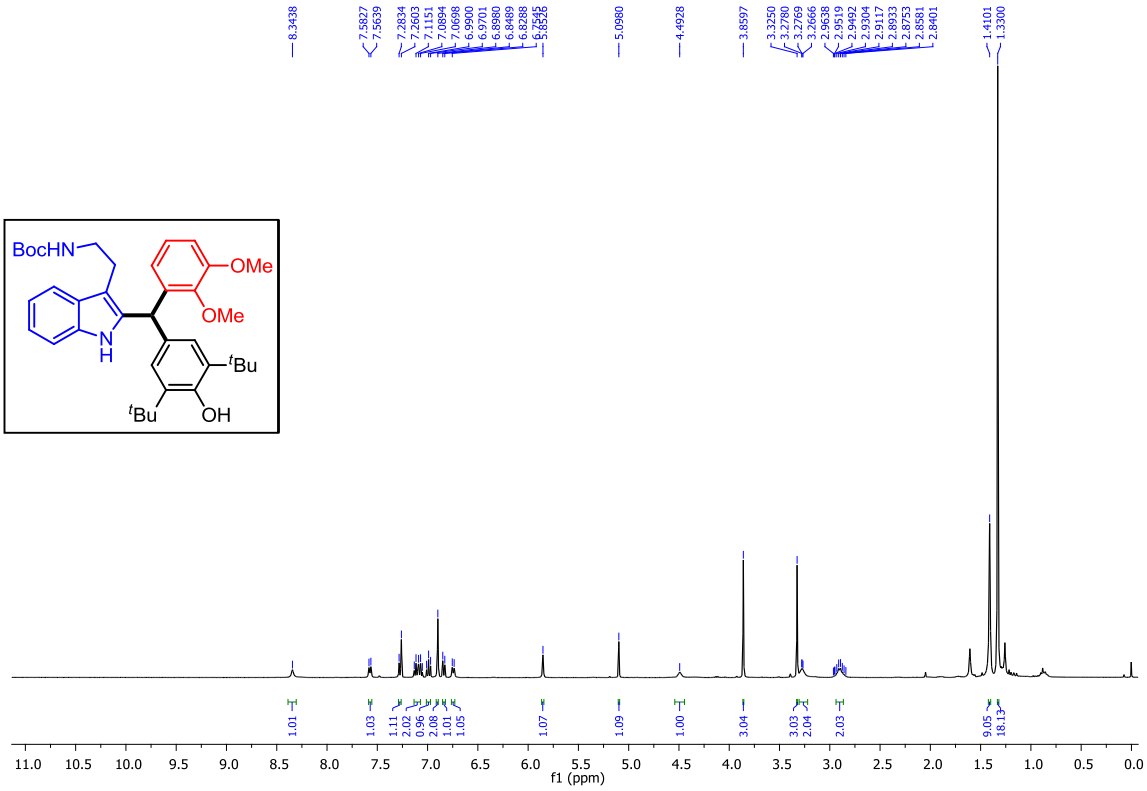
^{1}H NMR spectrum of **81f**



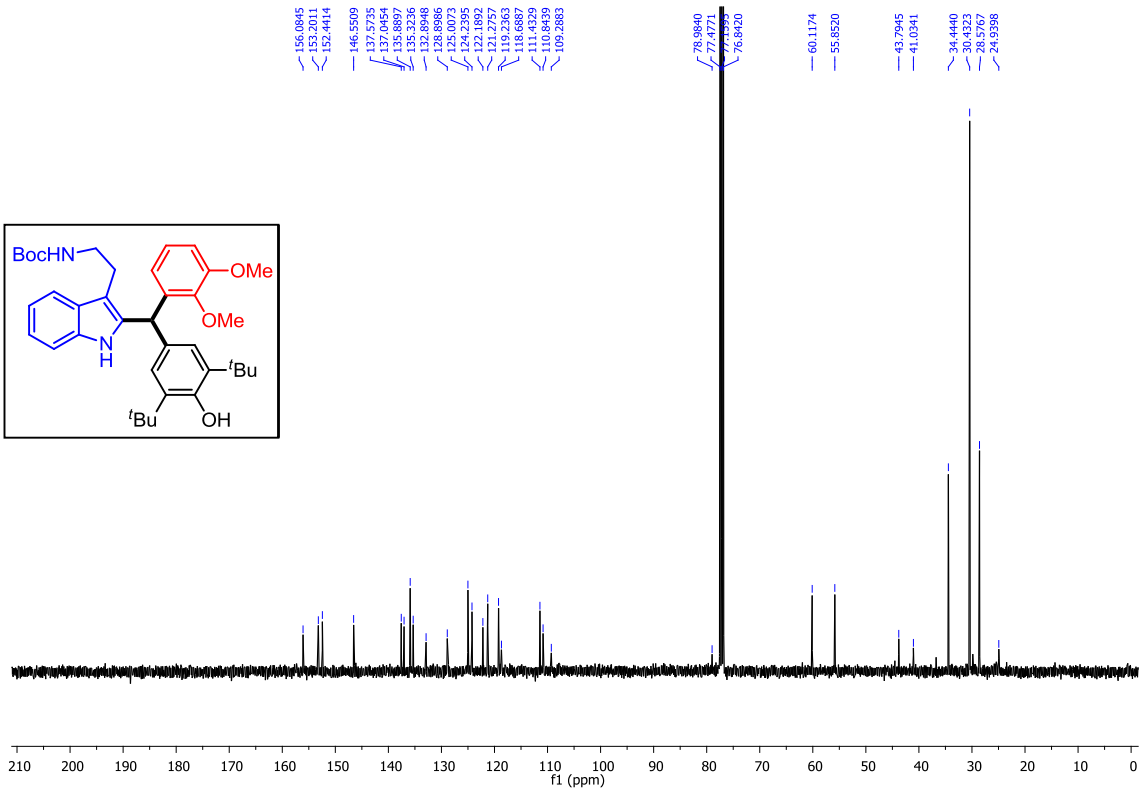
^{13}C NMR spectrum of **81f**



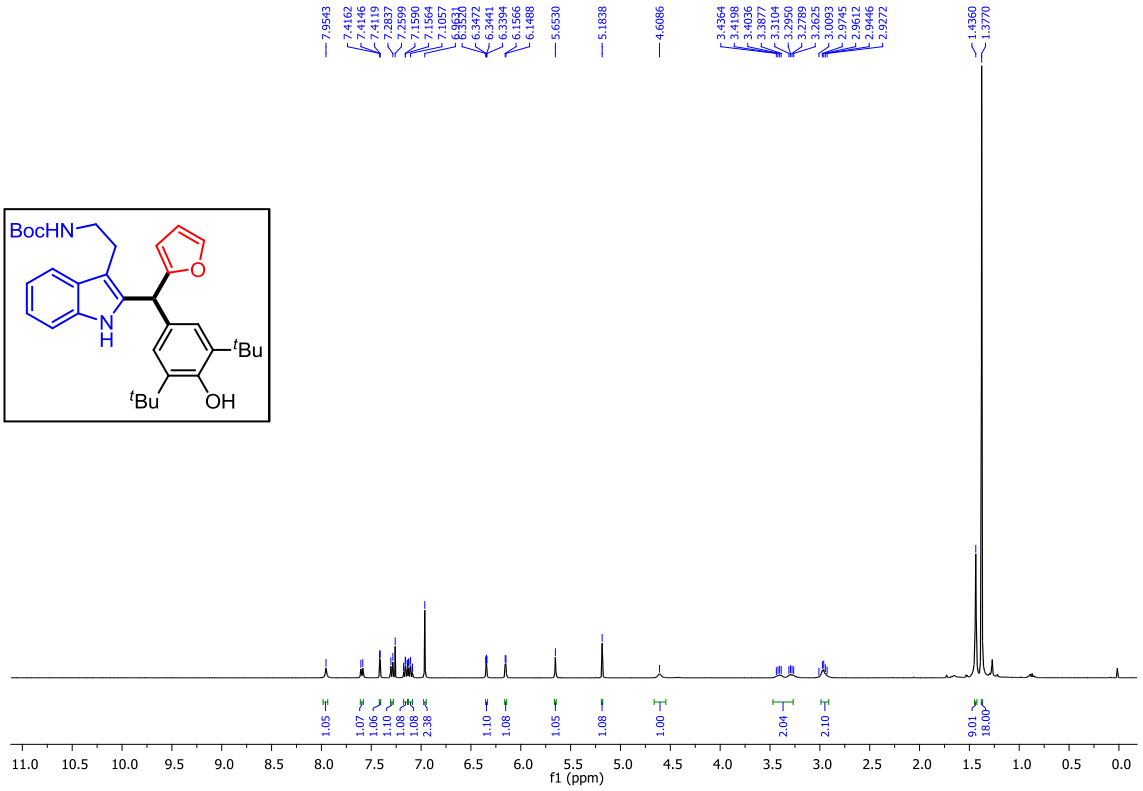
^{1}H NMR spectrum of **81g**



^{13}C NMR spectrum of **81g**



^{1}H NMR spectrum of **81p**



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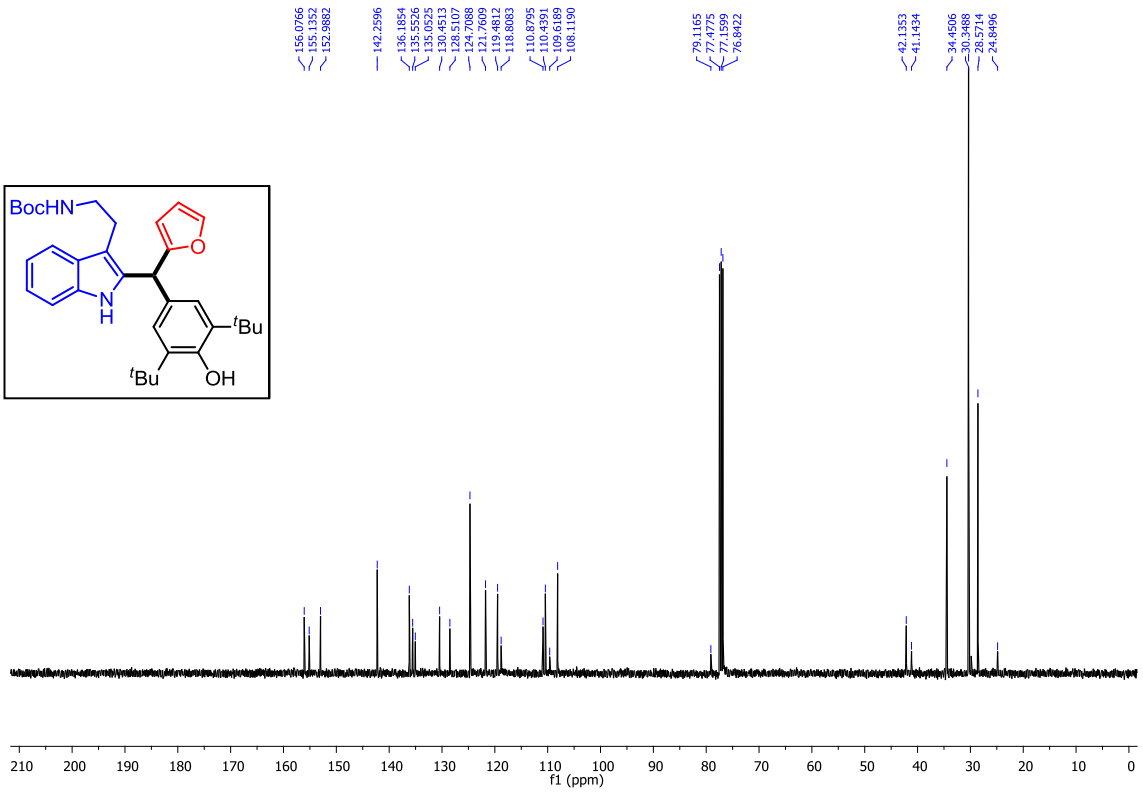

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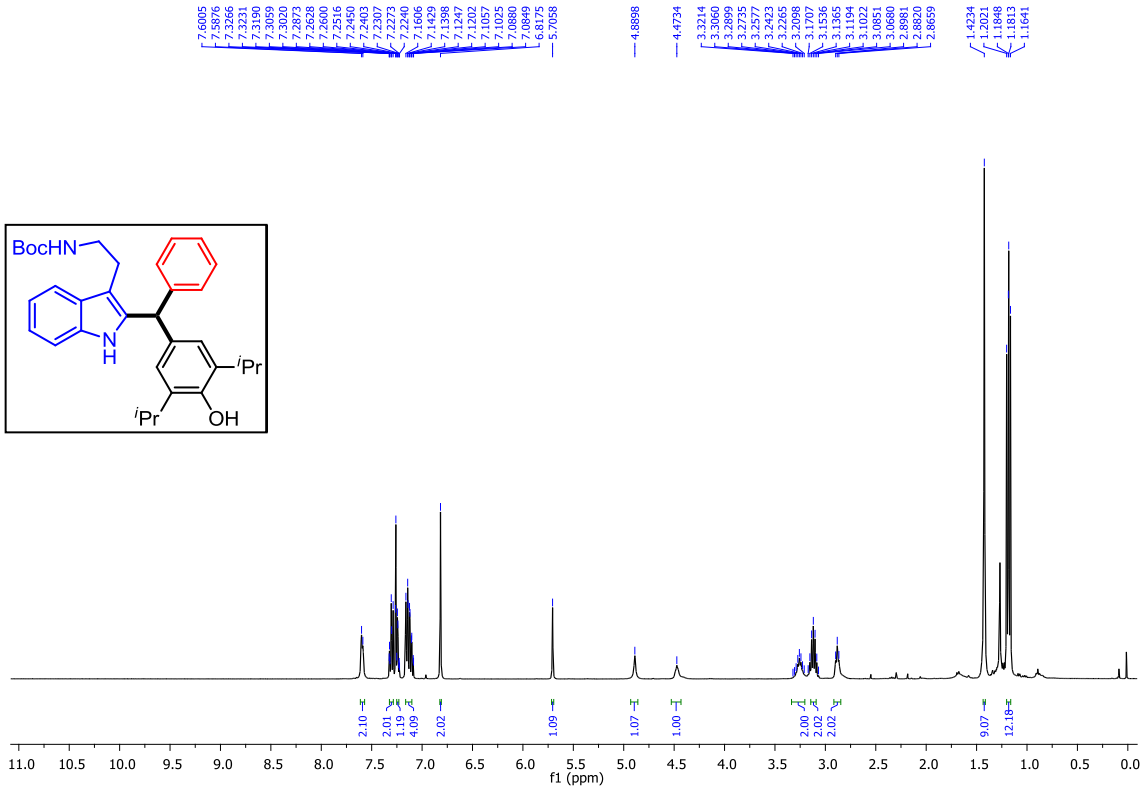

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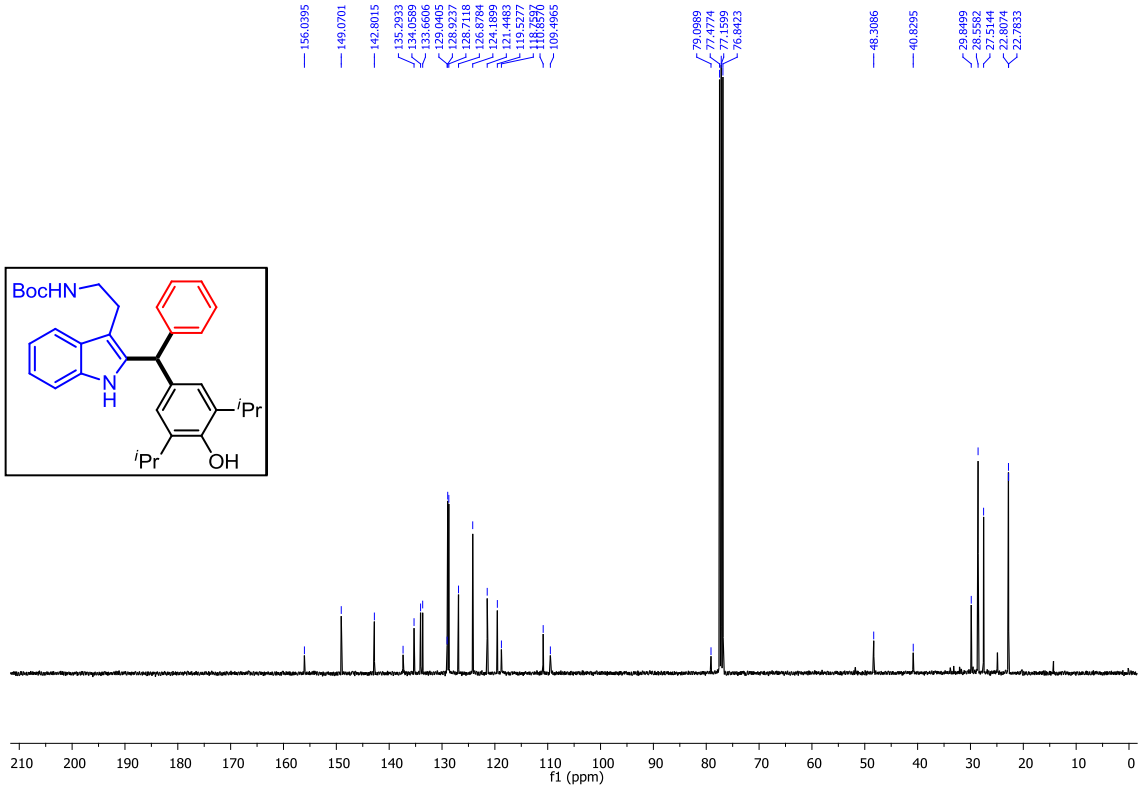

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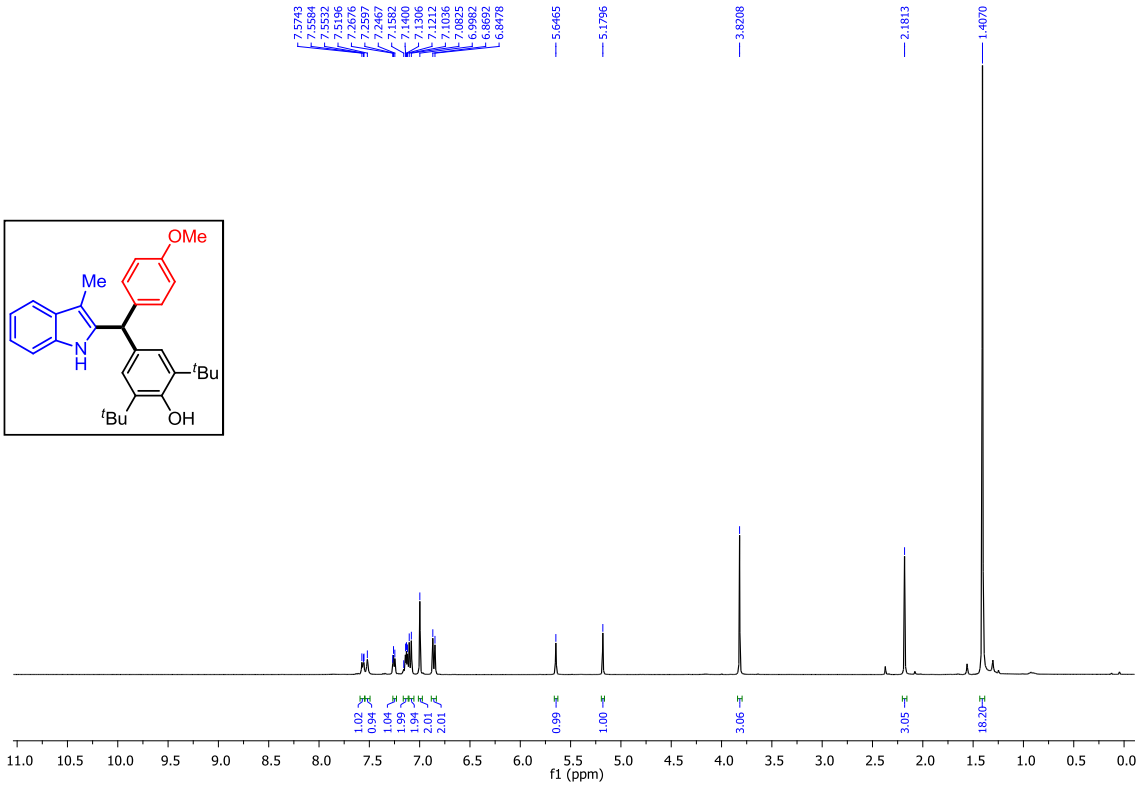
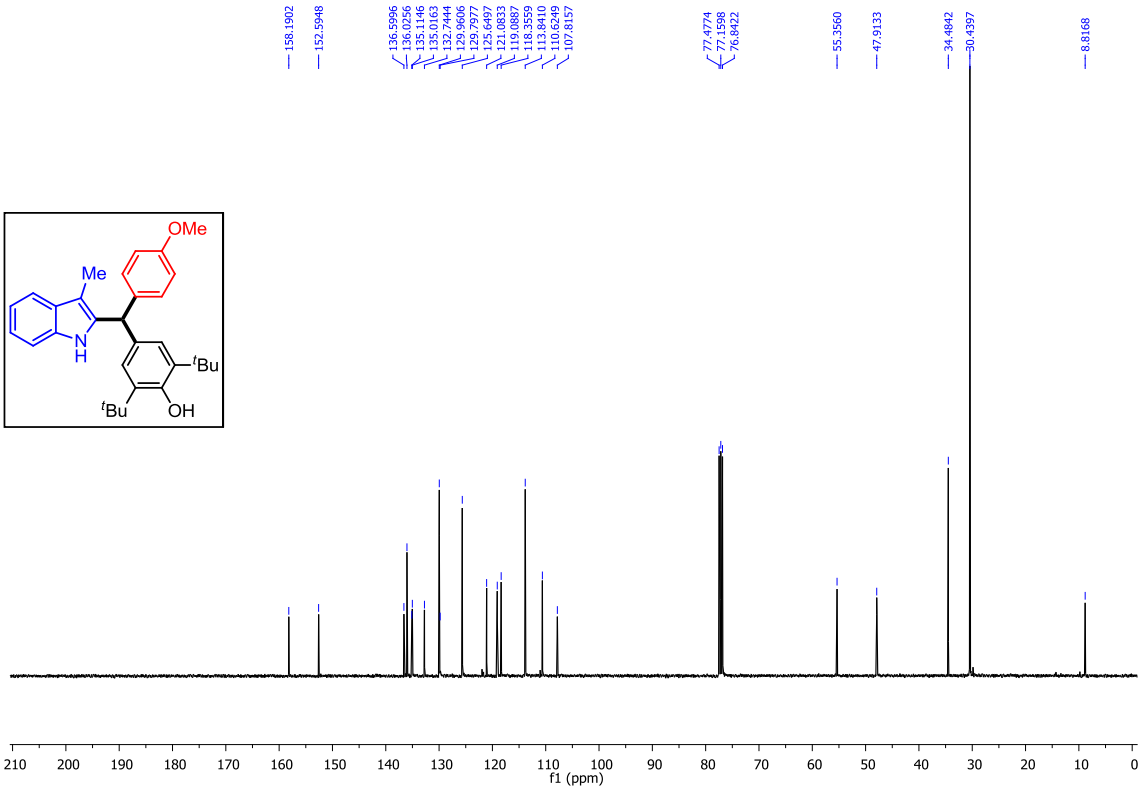
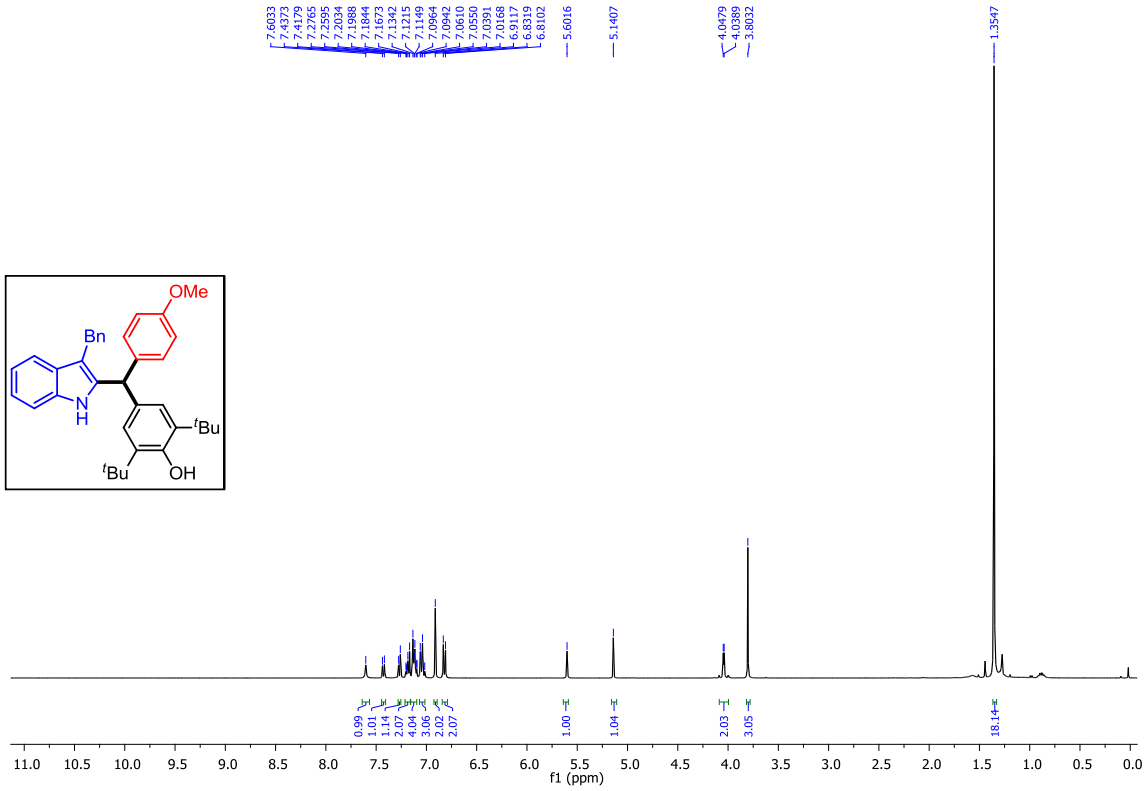


^{13}C NMR spectrum of **82a**



^{1}H NMR spectrum of **82d**



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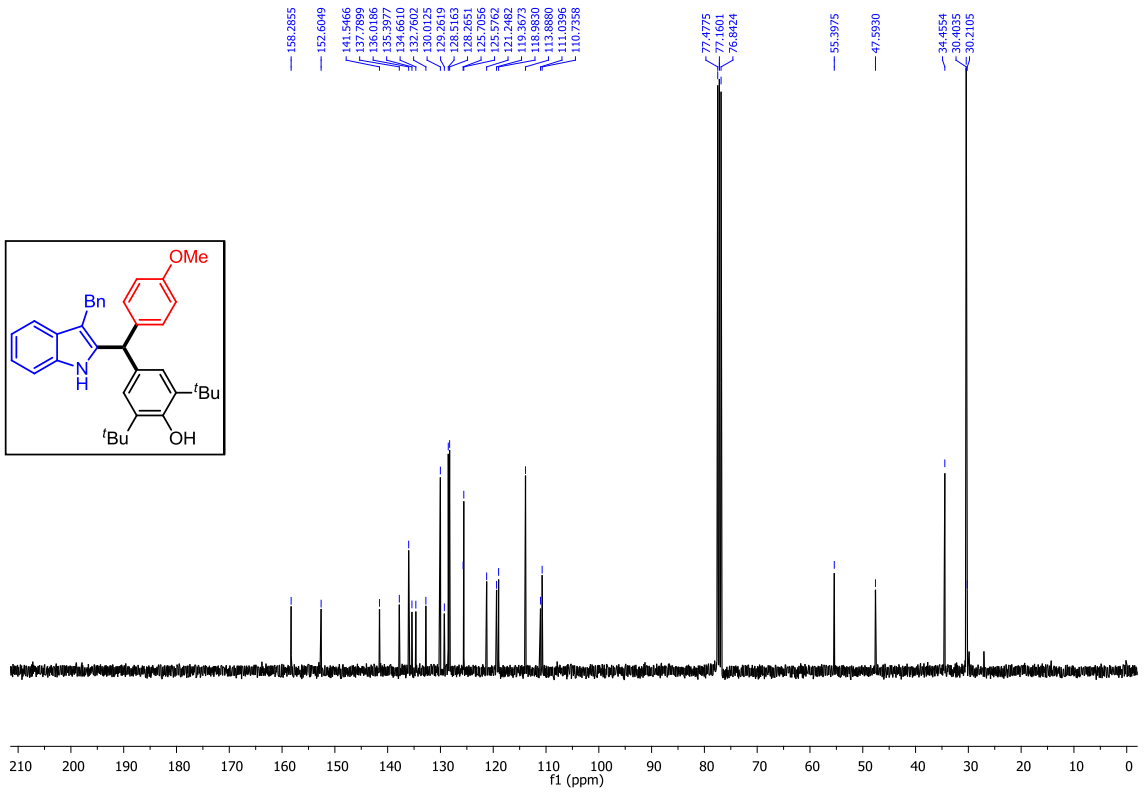

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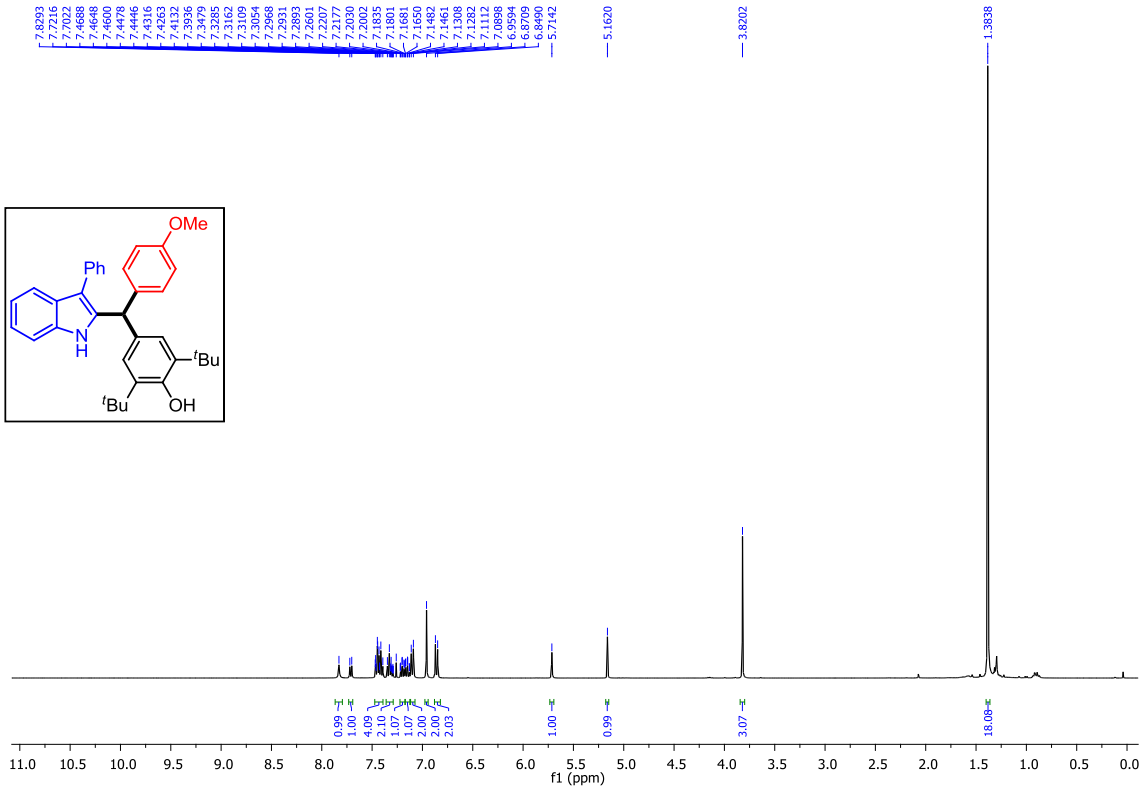

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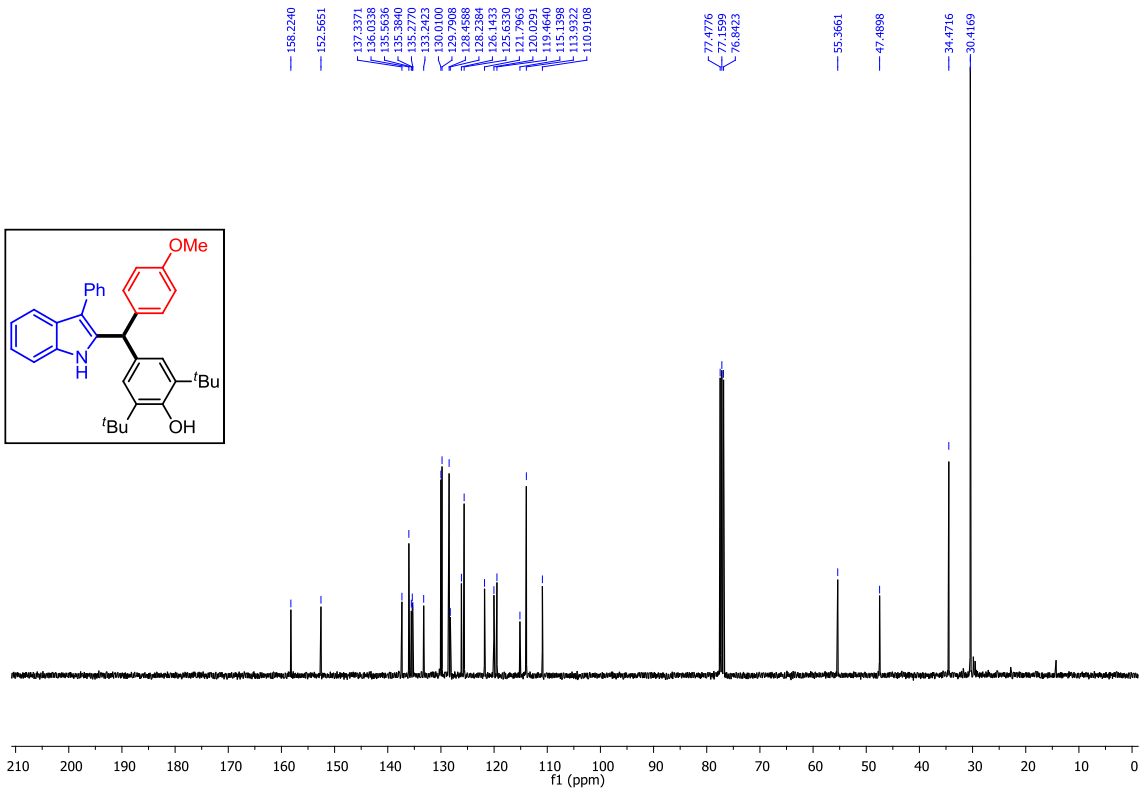

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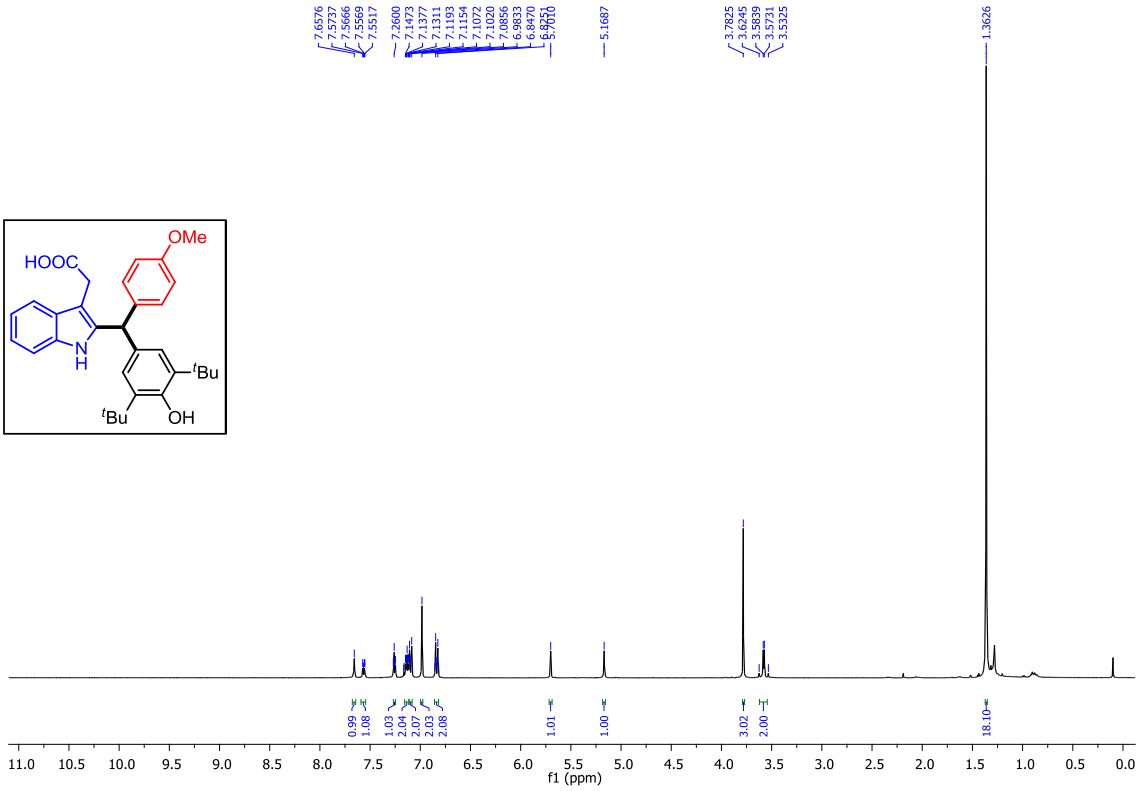

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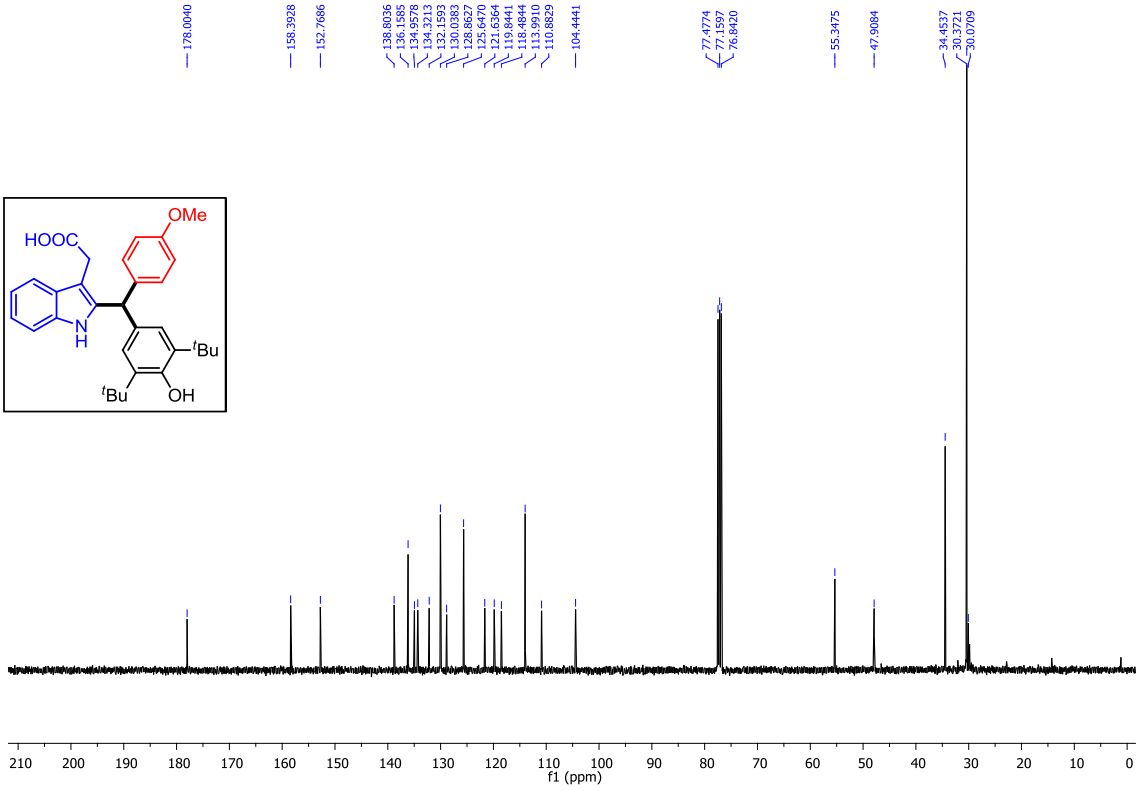

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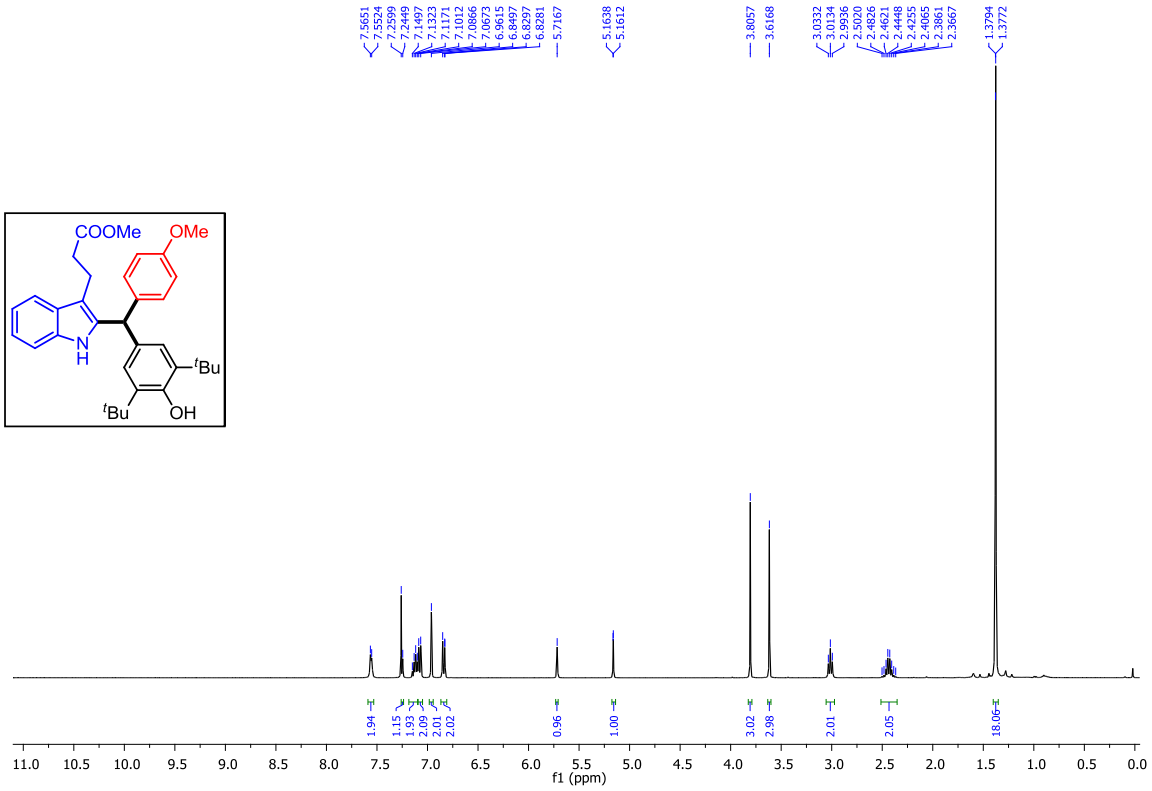

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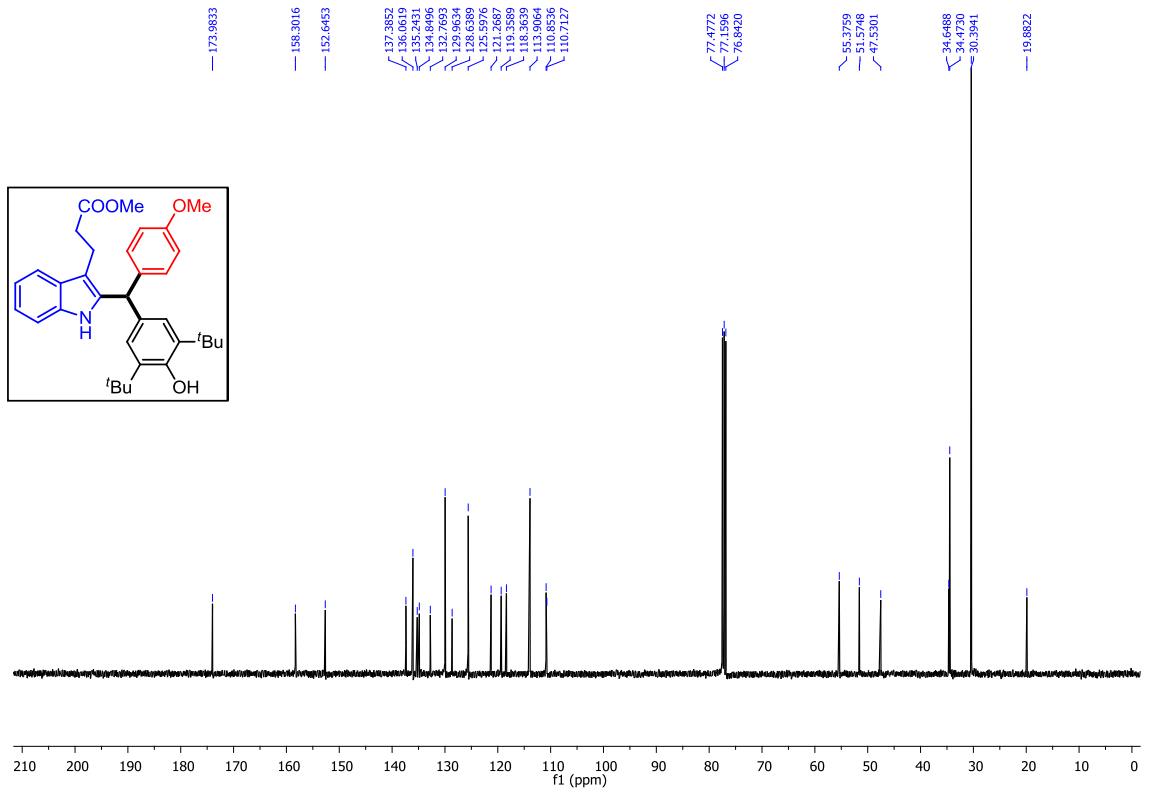
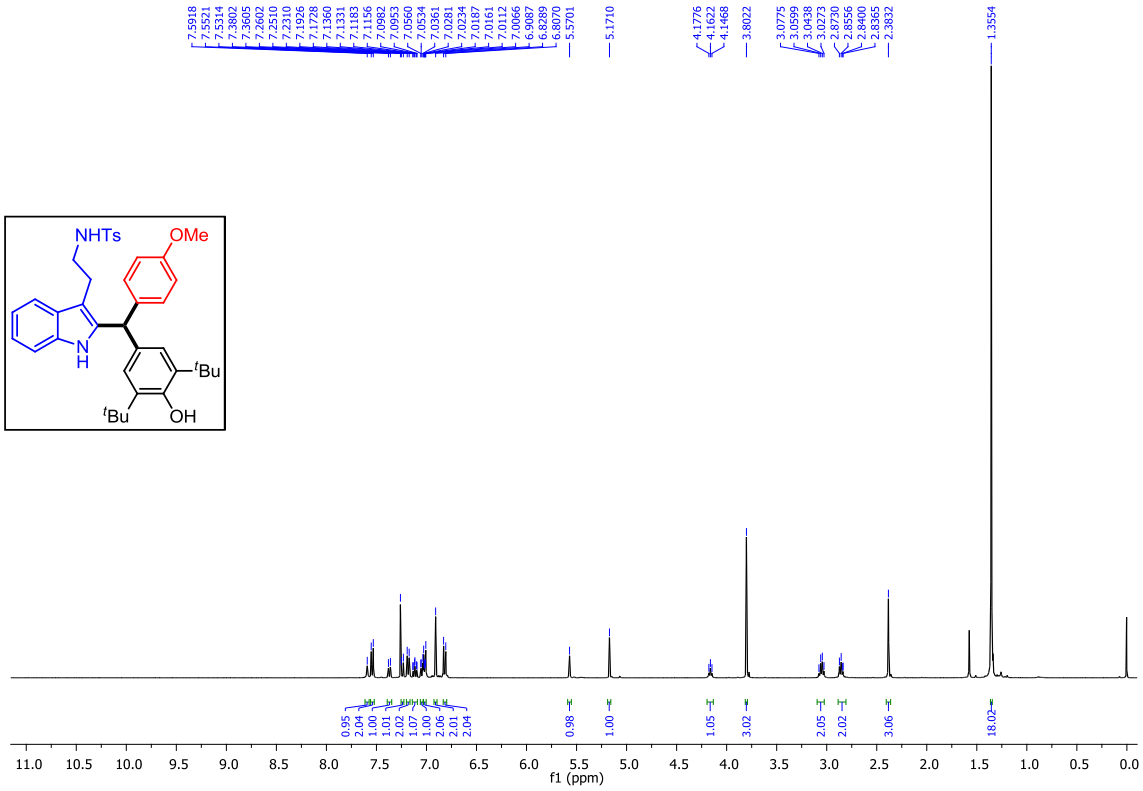


^{1}H NMR spectrum of **82m**



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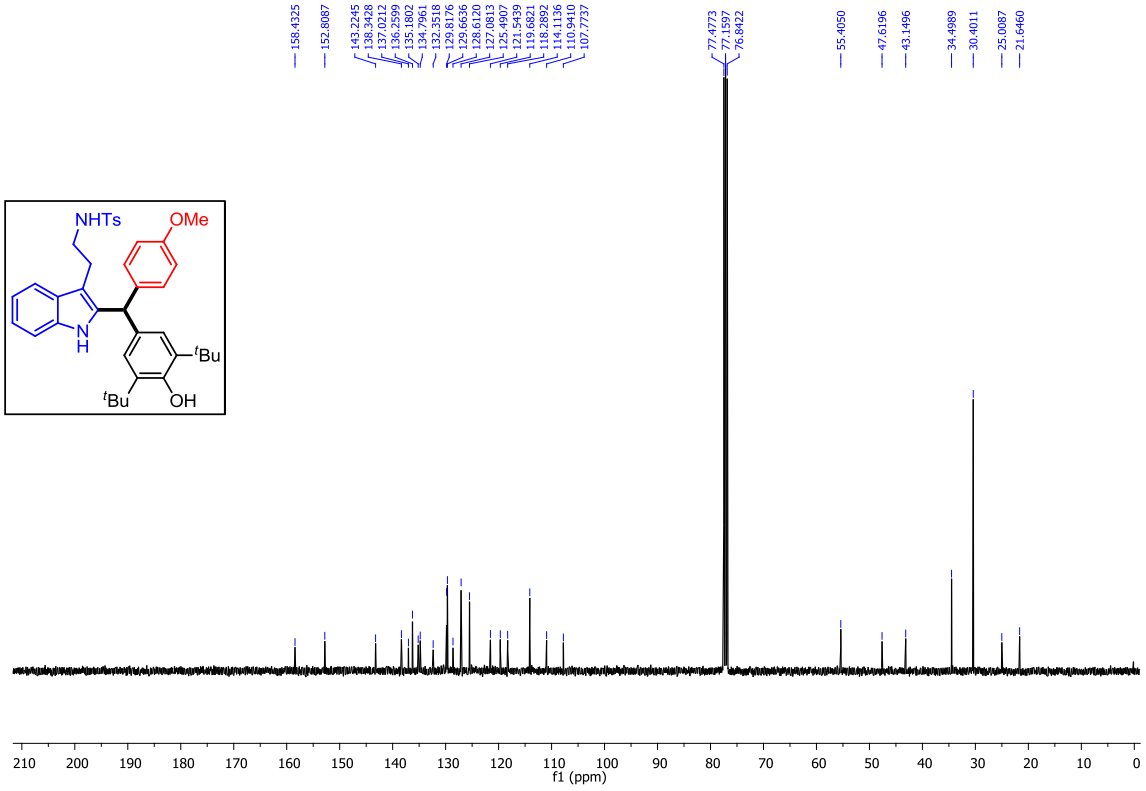

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Chapter 4

4. Organocatalytic *O*-acylation of phenols/alcohols and *N*-acylation of indoles with cyclopropenones

In this chapter, a 100% atom-economical approach for the synthesis of *O*-acylated phenols/alcohols and *N*-acylated indoles is described. This chapter also covers a brief literature review on different strategies reported for the synthesis of *O*-acyl phenols/alcohols and *N*-acyl indoles.

4.1 Introduction

O-acylated phenols/alcohols and *N*-acylated indoles are an important architectural motifs, often found in numerous biologically significant molecules and pharmaceuticals.[1] Several of them exhibit important medicinal applications (Figure 1).[2] For example, *O*-acyl phenols **1a**, **1b** possess remarkable biological activities and being explored as anti-fungal,[2a] anti-inflammatory agents,[2b] respectively. Compound **1c** is used for the treatment for cardiovascular disease.[2c]

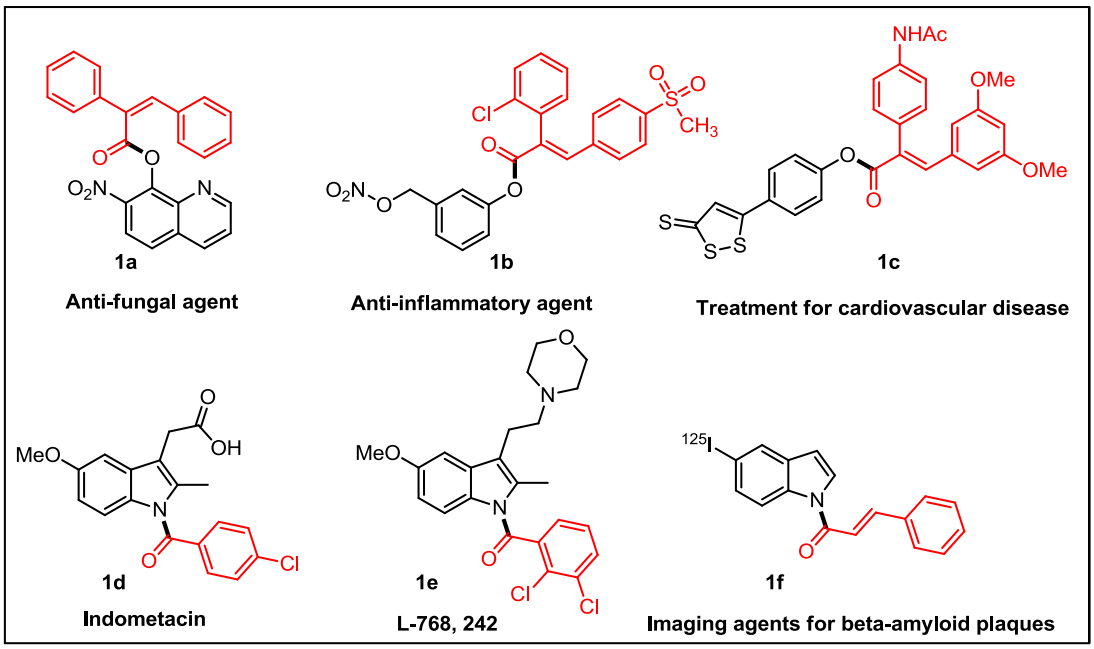


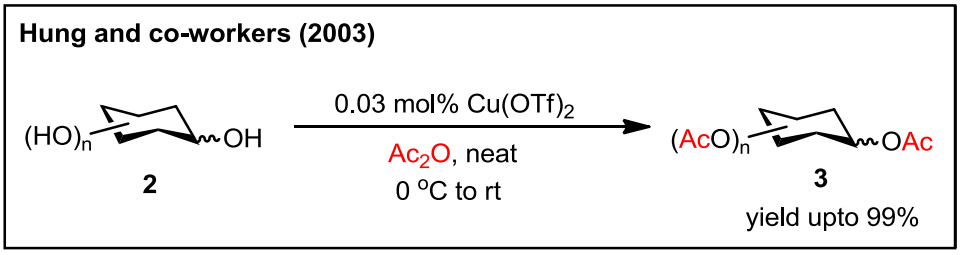
Figure 1. Biologically active *O*-acyl phenols and *N*-acyl indoles

Similarly, indometacin (**1d**), which is an *N*-acyl indole, is being used as a non-steroidal anti-inflammatory and antipyretic drug.[2d] Another *N*-acyl indole derivative **1e** (L-768,242) displayed good selectivity towards hCB2 receptror.[2e] In addition, **1f** is used as imaging agents for beta amyloid plaques.[2f] Besides the medicinal applications, *O*-acylated phenols and *N*-acylated indoles can serve as key intermediates in the synthesis of complex molecules.[3] These significant applications of these compounds have attracted the scientific community towards the development of divergent and viable synthetic routes. Some of the literature reports are discussed in this section.

4.2 Synthesis of *O*-acyl phenols/alcohols and *N*-acyl indoles

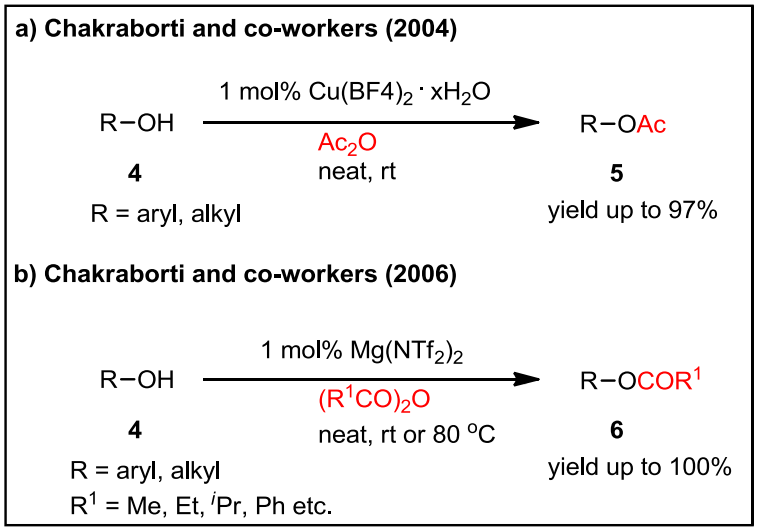
The most common method for the acylation reaction involves a reaction between phenols/alcohols/indoles with acylating agents in presence of a stoichiometric amount of a base.[4] However, the use of sensitive and hazardous acylating agents restrict the practical applications of this strategy. Moreover, the presence of stoichiometric amount of base limits the functional group tolerances. To overcome these limitations, many alternative approaches have been emerged.

Hung and co-workers reported a $Cu(OTf)_2$ catalyzed per-*O*-acetylation of hexoses.[5] Interestingly, the reaction worked efficiently under solvent-free conditions (Scheme 1).



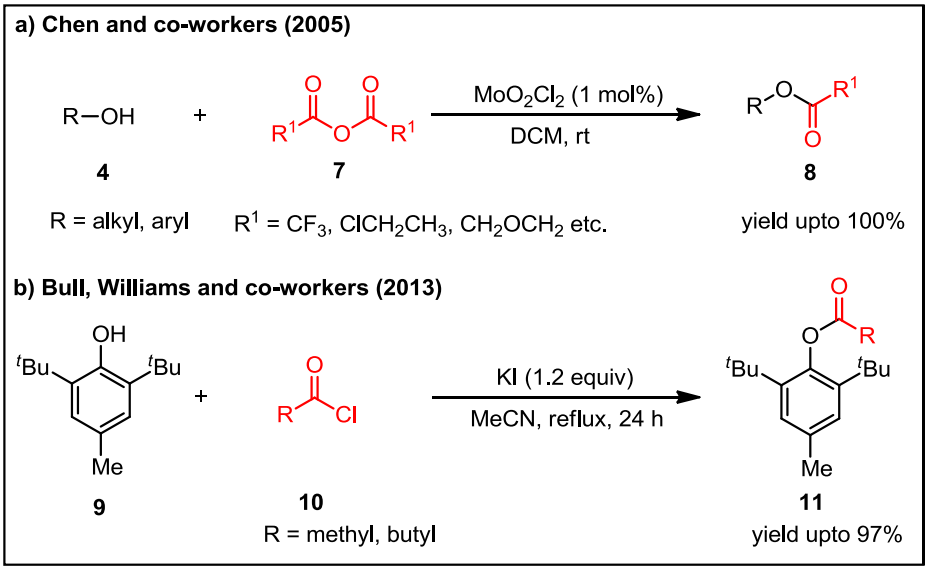
Scheme 1: Synthesis of per-*O*-acetyl hexoses

Later, Chakraborti's group disclosed a solvent-free, mild and efficient acetylation approach for phenols and alcohols.[6a] Catalytic amounts of Cu(II) tetrafluoroborate was found to be sufficient to drive the transformation (a, Scheme 2). Furthermore, the same group described magnesium bistrifluoromethanesulfonimide as an efficient catalyst for acylation reactions of alcohols and phenols. In case of acid-sensitive alcohols, chemoselective acylation could be achieved (b, Scheme 2).[6b]



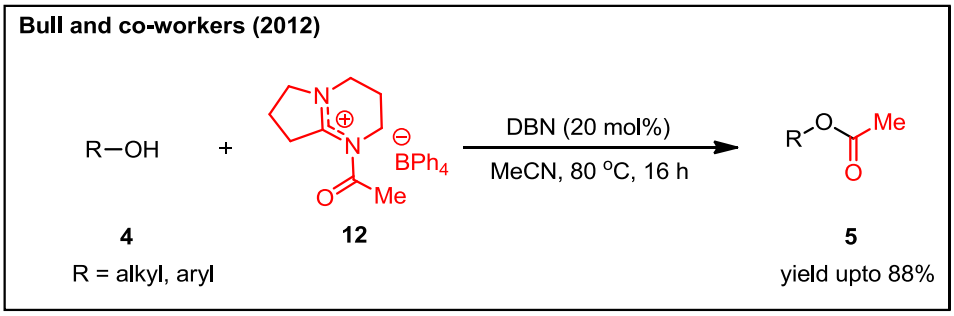
Scheme 2: Lewis acid-catalyzed acylation of phenols and alcohols

Chen and co-workers demonstrated a dioxomolybdenum dichloride catalyzed acylation of alcohols (a, Scheme 3).[7a] Later, Bull, Williams and co-workers reported a KI mediated acylation reaction of sterically hindered phenols. However, with 2,6-di-*tert*-butylphenol, *C*-acylation at the *para*-position of phenol was observed (b, Scheme 3).[7b]



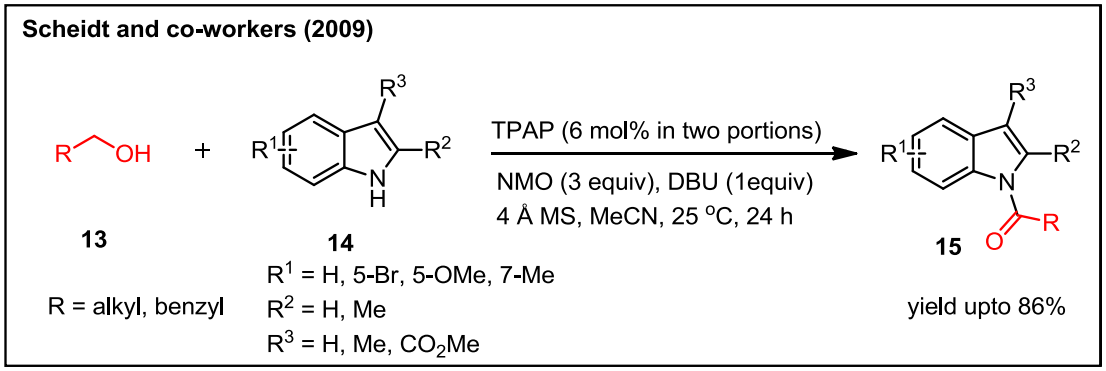
Scheme 3: Synthesis of *O*-acyl alcohols and phenol

Bull and co-workers also developed the acylation of alcohols using *N*-acyl 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) tetraphenylborate salt (**12**) as an acylating agent. Interestingly, in case of diols, regioselective acetylation of primary alcohol was observed over secondary alcohol functionality (Scheme 4).[8]



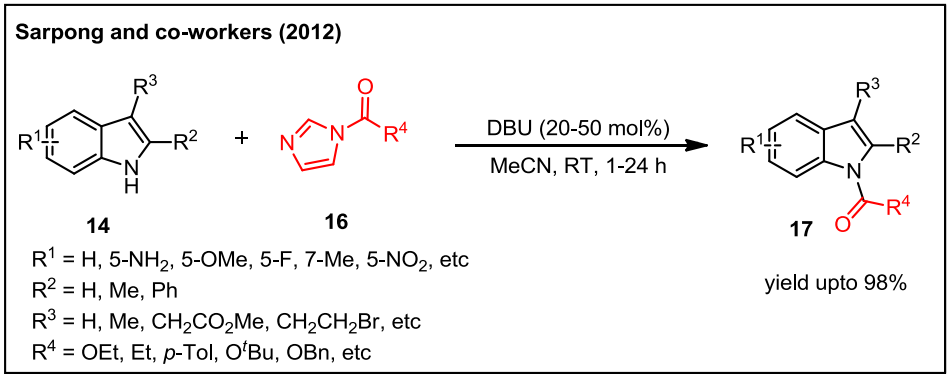
Scheme 4: DBN catalyzed *O*-acetylation of alcohols and phenols

Scheidt and co-workers reported a dehydrogenative coupling between primary alcohols (**13**) and indoles (**14**) for the synthesis of *N*-acyl indoles. Tetrapropyl ammonium perruthenate was found to be an efficient catalyst for the dehydrogenative process (Scheme 5).[9]



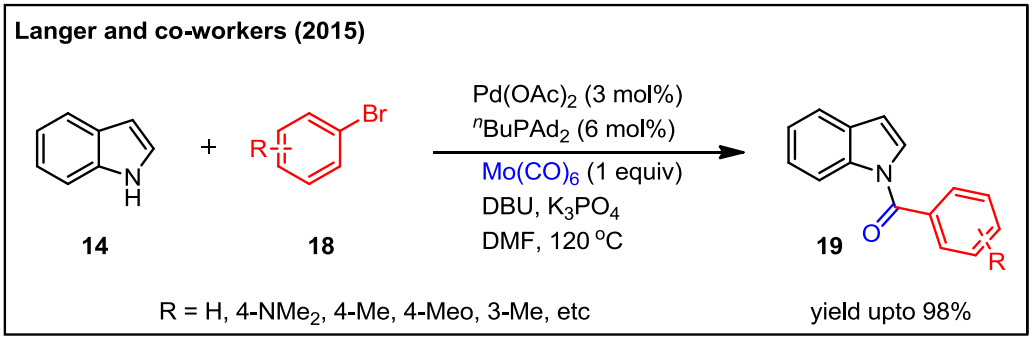
Scheme 5: Synthesis of *N*-acyl indoles under dehydrogenative coupling condition

Sarpong and co-workers developed a DBU catalyzed chemoselective *N*-acylation of indoles.[10] A wide range of indoles (**14**) were reacted with carbonylazoles (**16**) to produce the corresponding *N*-acyl indoles (**17**) in good to excellent yields (Scheme 6).



Scheme 6: DBU catalyzed chemoselective synthesis of *N*-acyl indoles

Very recently, Langer's group accomplished a palladium-catalyzed amino-carbonylation approach for the synthesis of *N*-benzoyl indoles.[11] $Mo(CO)_6$ was used as a carbon monoxide precursor (Scheme 7).



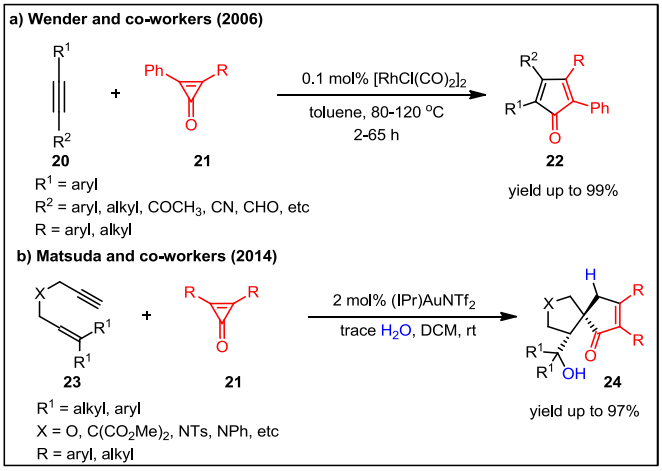
Scheme 7: Palladium-catalyzed aminocarbonylation of indoles

4.3 Background

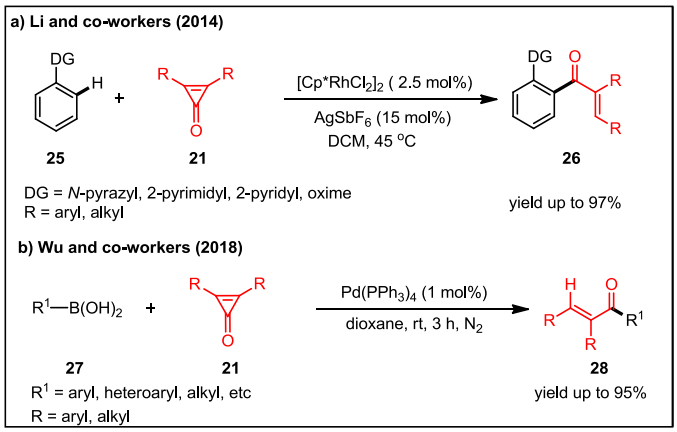
Although most of the above-mentioned hitherto known approaches show good substrate scope, the use of expensive metal catalysts or ligands make these transformations practically unattractive. In addition, the synthesis of prefunctionalized acylating agents and the tedious workup procedures restrict their practical application. Therefore, developing an alternative and 100% atom economical method for the synthesis of esters and *N*-acyl indoles especially under organocatalytic conditions would be more attractive and highly desired.

In recent years, cyclopropenones have been utilized in many organic transformations. For example, Wender and co-workers reported a Rh-catalyzed [3+2] cycloaddition reaction between alkynes (**20**) and cyclopropenones (**21**) for the synthesis of cyclopentadienones (**22**) [a, Scheme 8].[12a] Later, Matsuda and co-workers extended this concept for the synthesis of spirocyclic cyclopentenones (**24**) via gold catalyzed spiro-annulation of cyclopropenones (**21**) and enynes (**23**) [b, Scheme 8].[12b] Li and co-workers demonstrated an efficient Rh catalyzed coupling of cyclopropenones (**21**) and arenes (**25**) to synthesize chalcones (**26**) [a, Scheme 9].[13a] Very recently, Wu and co-workers observed a palladium catalyzed cross coupling between organo boronic acid (**27**) and cyclopropenones (**21**) to furnish *α,β*-diaryl unsaturated ketones (**28**) [b, Scheme 9].[13b] Lin and co-workers established [3+2] annulation of cyclopropenones (**21**) and *β*-ketoesters (**29**) to provide a highly substituted butenolides (**30**).[14a] Catalytic amount of DBU was found to be sufficient to drive the transformation (a, Scheme 10). Further, Lu, Du and co-workers discovered a DMAP catalyzed ring-opening

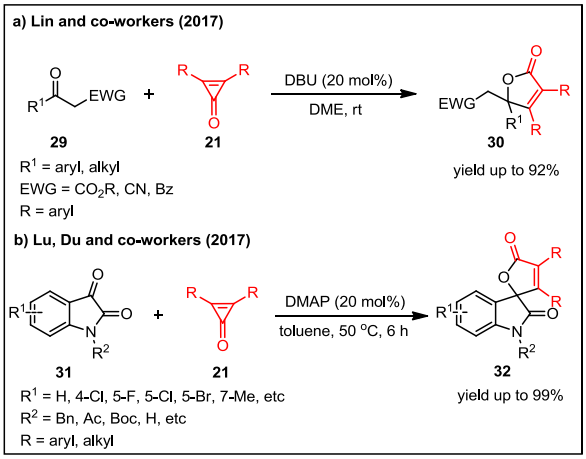
formal [3+2] annulations of cyclopropenones (**21**) with isatins (**31**) to access spirooxindoles (**32**) [b, Scheme 10].[14b]



Scheme 8: Metal catalyzed annulation reactions with cyclopropenones



Scheme 9: Metal catalyzed cross coupling reactions with cyclopropenones



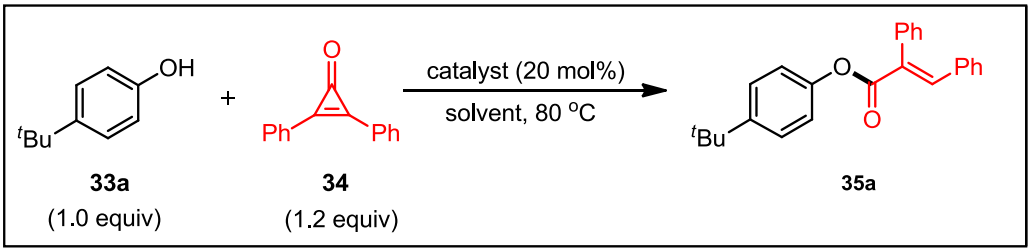
Scheme 10: Organocatalytic annulation reactions with cyclopropenones

While working on organocatalytic transformations, we envisaged that we could access esters and *N*-acyl indoles through a ring opening reaction of cyclopropenones with phenols/alcohols and indoles, respectively.

4.4 Results and Discussions

Optimization studies were carried out using 4-*tert*-butyl phenol (**33a**) and diphenylcyclopropenone (**34**) as model substrates under various conditions, and the results are summarized in Table 1. The initial experiments were carried out using DMAP as a catalyst at room temperature. However, in both the cases, the expected ester **35a** was not observed when 1,4-dioxane or DMSO was used as a solvent (entries 1 & 2).

Table 1: Optimization studies[a]

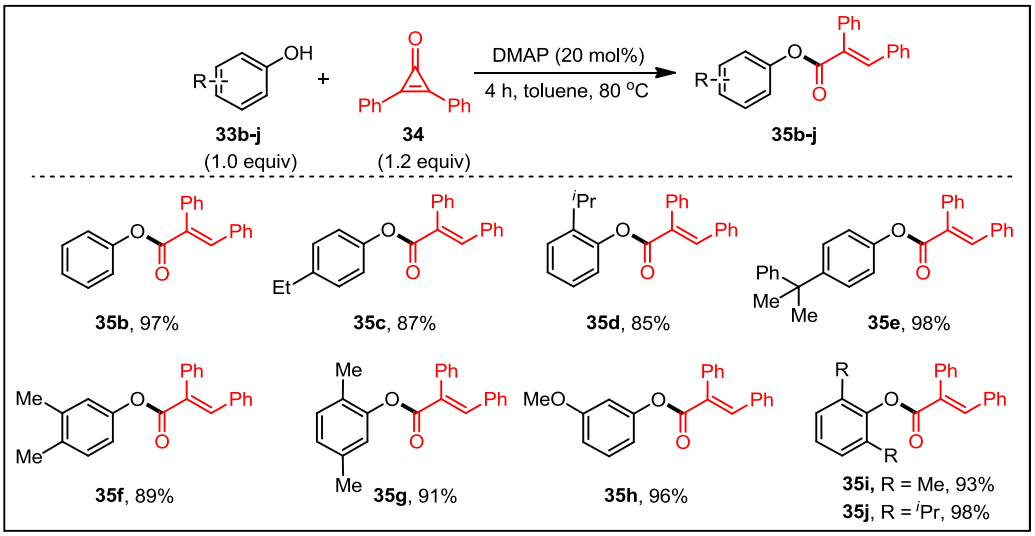


entry	catalyst	solvent	time (h)	yield of **35a** (%)
1[b]	DMAP	1,4-dioxane	24	nr
2[b]	DMAP	DMSO	24	nr
3[b]	DMAP	THF	24	53
4[b]	DMAP	MeCN	24	63
5[b]	DMAP	DMF	24	65
6[b]	DMAP	DCM	24	65
7[b]	DMAP	PhMe	24	70
8[c]	DMAP	PhMe	6	80
9	**DMAP**	**PhMe**	**4**	**91**
10	DABCO	PhMe	24	62
11	DBU	PhMe	24	45
12	DBN	PhMe	24	20
13	K_2CO_3	PhMe	24	10
14	Cs_2CO_3	PhMe	24	10
15	-	PhMe	48	13

[a]Reaction conditions: All reactions were carried out with **33a** (30 mg, 0.20 mmol) and **34** (0.24 mmol) in solvent (1.5 mL). [b]Reaction was carried out at room temperature. [c]Reaction was carried out at 50 °C. Yields reported are isolated yields.

Delightfully, when the reaction was performed in THF at room temperature, **35a** was isolated in 53% yield after 24 h (entry 3). With this encouraging result in hand, the solvent screening was investigated at room temperature. It was found that toluene was the appropriate solvent to drive the transformation as the desired ester **35a** was obtained in 70% yield after 24 h (entries 4-7). Interestingly, when the reaction was carried out at 50 ^{o}C, **35a** was obtained in 80% yield in 6 h (entry 8). Gratifyingly, further increasing the temperature to 80 ^{o}C, the yield of **35a** could be improved the maximum of 91% in just 4 h (entry 9). The optimization studies were extended using other organic bases in toluene (entries 10-12) at 80 ^{o}C. However, in all those cases, the isolated yield of **35a** was found to be inferior when compared to entry 9. Other inorganic bases such as potassium carbonate and cesium carbonate led to the formation of **35a** in very poor yields even after 24 h (entries 13 & 14). These observations clearly show that DMAP is the best catalyst for this transformation. Moreover, when the reaction was performed in the absence of catalyst, only 13% of **35a** was observed even after 48 h, which clearly indicates that catalyst is driving the reaction (entry 15).

With the optimized reaction conditions in hand (entry 9, Table 1), the substrate scope and limitations of this methodology was investigated using a variety of phenols, and the results are summarized in Schemes 11 & 12.

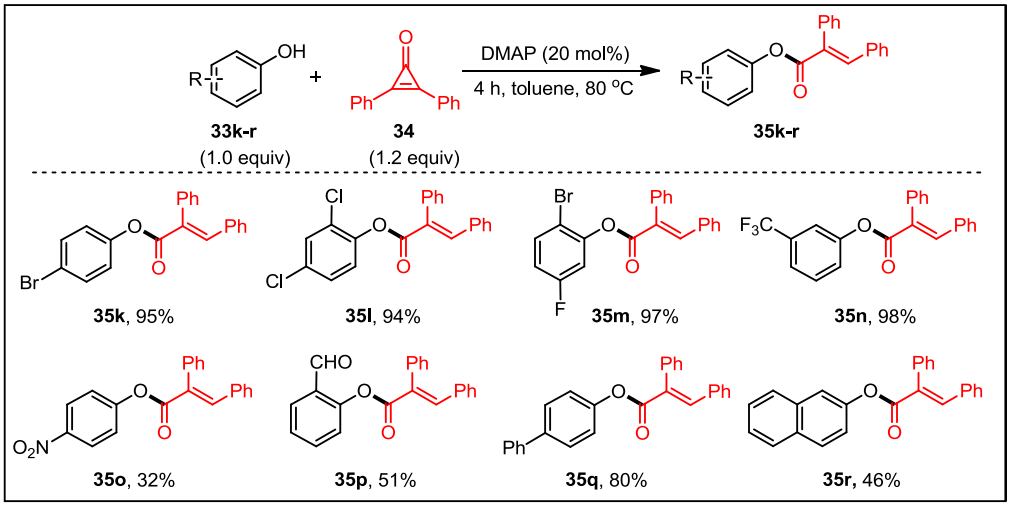


[a]Reaction conditions: All reactions were carried out with 30 mg scale of **33(b-j)** in 1.5 mL of solvent. Yields reported are isolated yields.

Scheme 11: Substrate scope for different phenols[a]

It is evident from Scheme 11 that phenols, substituted with electron-rich substituents (**33b-h**), underwent smooth transformations under the optimized conditions and furnished the respective esters (**35b-h**) in good to excellent yields (85-98%). Interestingly, sterically hindered phenols such as, 2,6-dimethyl phenol (**33i**) and 2,6-diisopropyl phenol (**33j**) also reacted efficiently to furnish the corresponding products **35i** & **35j** in excellent yields. (Scheme 11).

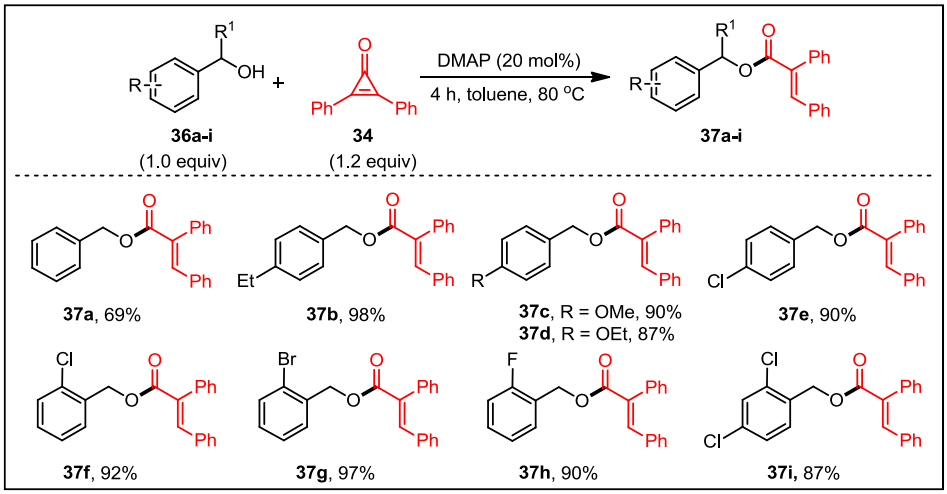
Moreover, this catalytic method was found to be very robust in the case of halo substituted phenols (**33k-m**) and, in those cases, the corresponding products **35k-m** were isolated in the range of 94-97% yields. Delightfully, moderately electron-poor substituted phenol (**33n**) was also converted to the required product **35n** in 98% yield. However, in case of strong electron-poor substituted phenols **33o-p**, the reactions were found to be very sluggish as the products (**35o-p**) were observed in moderate yields in both the cases. 4-Phenyl phenol (**33q**) and 2-naphthol (**33r**) also provided the desired products **35q** & **35r** in moderate to good yields (Scheme 12).



[a]Reaction conditions: All reactions were carried out with 30 mg scale of **33(k-r)** in 1.5 mL of solvent. Yields reported are isolated yields.

Scheme 12: Substrate scope for different phenols[a]

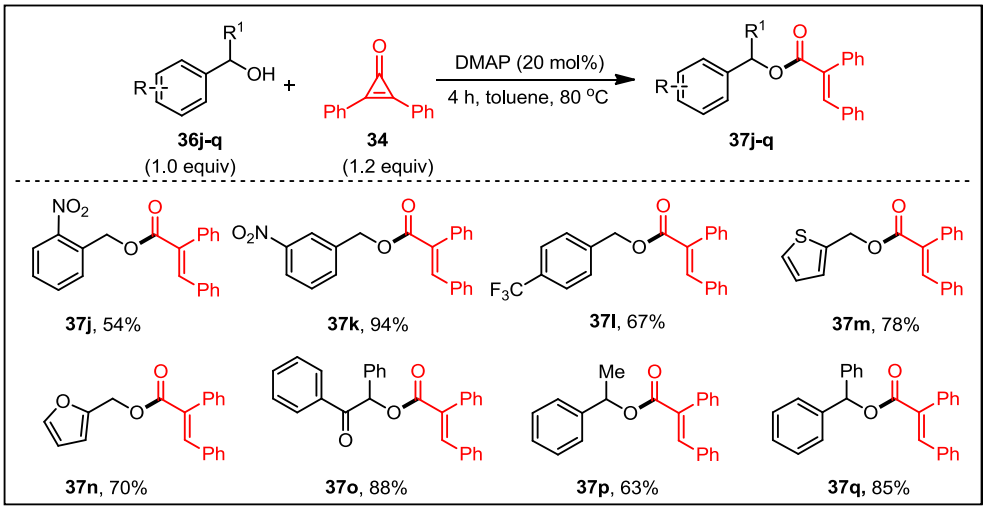
The generality of the substrate scope was further examined by treating a wide range of primary and secondary aliphatic alcohols (**36a–q**) with diphenylcyclopropenone (**34**) under the optimized conditions and the results are summarized in Schemes 13 & 14.



[a]Reaction conditions: All reactions were carried out with 30 mg scale of **36(a-i)** in 1.5 mL of solvent. Yields reported are isolated yields.

Scheme 13: Substrate scope using different aliphatic alcohols[a]

It is obvious from the Scheme 13 that the electron-rich aryl-substituted aliphatic alcohols (**36a-d**) reacted efficiently under the optimized conditions and the corresponding esters **37a-d** were isolated in good to excellent yields (69-98%). It is also observed that alcohols substituted with halogen substituents (**36e-i**) underwent smooth transformations to produce the corresponding products **37e-i** in excellent yields. (Scheme 13).

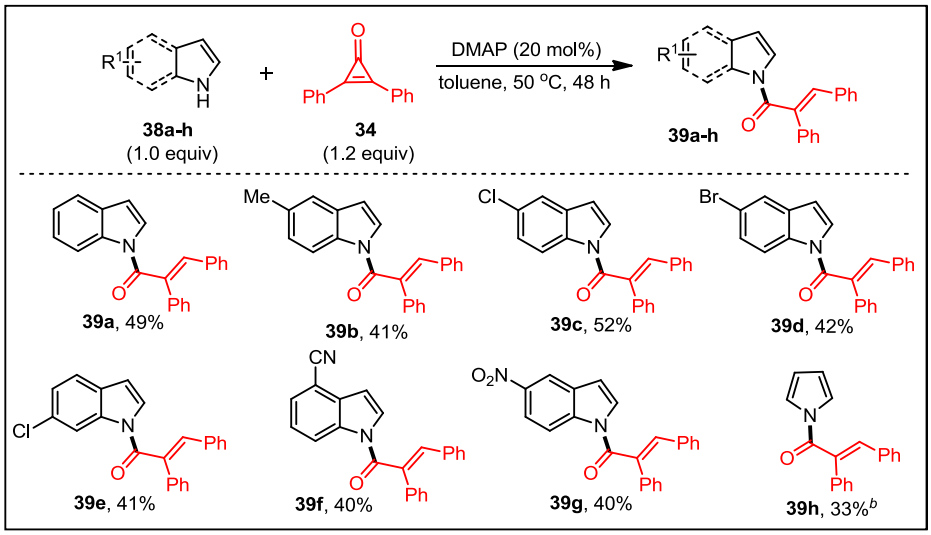


[a]Reaction conditions: All reactions were carried out with 30 mg scale of **36(j-q)** in 1.5 mL of solvent. Yields reported are isolated yields.

Scheme 14: Substrate scope using different aliphatic alcohols[a]

Delightfully, electron-poor aliphatic alcohols (**36j-l**) also provided the respective esters **37j-l** in moderate to good yields (54-94%). Moreover, heteroaryl substituents aliphatic alcohols **36m** and **36n** were also acylated to provide **37m** and **37n** in 78 and 70% yields, respectively. It is noteworthy to mention that secondary alcohols such as benzoin (**36o**), 1-phenylethanol (**36p**) and diphenylmethanol (**36q**) were also converted to the corresponding products **37o-q** in the range of 63-88% yields (Scheme 14).

To demonstrate the synthetic utility of this methodology, *N*-acylation reaction of indoles were also examined. However, under the optimized conditions for alcohols and phenols (entry 9, Table 1), a complex mixture was observed. Interestingly, by decreasing the reaction temperature to 50 ^{o}C, the reaction was found to be slow and the expected *N*-acyl indole **39a** was obtained in 49% yield after 48 h. Further, the substrate scopes were carried out at 50 ^{o}C. 5-Methyl indole (**38b**) also reacted under the modified reaction conditions and the corresponding *N*-acyl indole **39b** was isolated in 41% yield. Halo-substituted indoles (**38c-e**) were also converted to their respective *N*-acylated products (**39c-e**) in moderate yields. Electron-poor indoles, such as **38f** & **38g** underwent reaction with **34** and provided the desired products **39f** & **39g** in 40% yields, respectively. Interestingly, pyrrole (**38h**) was also participated in the reaction and gave the *N*-acyl pyrrole **39h** in 33% yield (Scheme 15).



[a]Reaction conditions: All reactions were carried out with 30 mg scale of **38(a-g)** in 1.5 mL of solvent. Yields reported are isolated yields. [b]Reaction was carried out in 20 mg scale of **38h** in 1.5 mL of solvent.

Scheme 15: Synthesis of *N*-acyl indoles[a]

4.5 Conclusion

In this chapter, we have described a mild organocatalytic protocol for the synthesis of *O*-acyl phenols and alcohols.[15] The generality of the concept was further demonstrated by performing the *N*-acylation of indoles. Diphenylcyclopropenone has been utilized as an acylating agent. A 100% atom economy and various functional group tolerances are the key features of this transformation.

4.6 Experimental Section

General methods

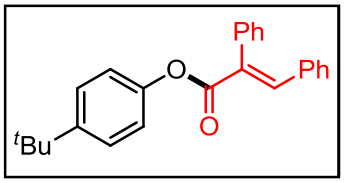
All reactions were carried out under an argon atmosphere in an oven dried round bottom flask. All the solvents were distilled before use and stored under argon atmosphere. Most of the reagents and starting materials were purchased from commercial sources and used as such. All benzyl alcohols were prepared according to the literature procedure.[16] Melting points were recorded on SMP20 melting point apparatus and are uncorrected. ^{1}H, ^{13}C and ^{19}F spectra were recorded in $CDCl_3$ (400, 100 and 376 MHz respectively) on Bruker FT–NMR spectrometer. Chemical shift (δ) values are reported in parts per million relative to TMS and the coupling constants (J) are reported in Hz. High resolution mass spectra were recorded on Waters Q–TOF Premier–HAB213 spectrometer. FT-IR spectra were recorded on a Perkin-Elmer FTIR spectrometer. Thin layer chromatography was performed on Merck silica gel 60 F_{254} TLC pellets and visualized by UV irradiation and $KMnO_4$ stain. Column chromatography was carried out through silica gel (100–200 mesh) using EtOAc/hexane as an eluent.

General procedure for the synthesis of *O*-acyl phenols:

Toluene (1.5 mL) was added to a mixture of phenol (30 mg, 0.20 mmol), diphenylcyclopropenone (49.5 mg, 0.24 mmol) and DMAP (4.9 mg, 0.04 mmol) under argon atmosphere. The reaction mixture was stirred at 80 ^{o}C. After 4 h, the mixture was quenched with 5 mL of distilled water and extracted with EtOAc (3 x 5 mL). The combined organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was then purified through a silica gel column using EtOAc/Hexane mixture as an eluent to get the pure product.

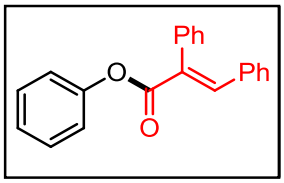
Characterization data of compounds (35a-35r):

(*E*)-4-(*tert*-butyl)phenyl 2,3-diphenylacrylate (35a)



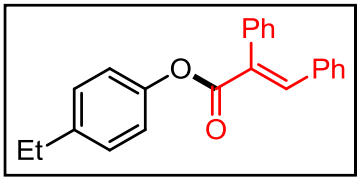
The reaction was performed at 0.20 mmol scale of **33a**; R_f = 0.4 (5% EtOAc in hexane); white solid (64.8 mg, 91% yield); m. p. =134–136 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (s, 1H), 7.43 – 7.37 (m, 5H), 7.35 – 7.33 (m, 2H), 7.27 – 7.17 (m, 3H), 7.13 – 7.11 (m, 2H), 7.08 (d, *J* = 8.8 Hz, 2H), 1.33 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.7, 148.9, 148.6, 141.9, 135.7, 134.6, 132.2, 130.9, 130.0, 129.5, 128.8, 128.4, 128.1, 126.4, 121.0, 34.6, 31.6; FT-IR (thin film, neat): 2959, 1720, 1506, 1239, 1201 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{25}H_{24}NaO_2$ $[M+Na]^+$: 379.1682; found : 379.1674.

(*E*)-phenyl 2,3-diphenylacrylate (35b)



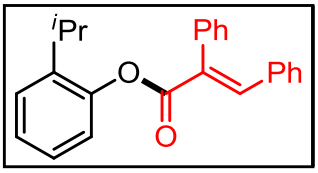
The reaction was performed at 0.319 mmol scale of **33b**; R_f = 0.4 (5% EtOAc in hexane); white solid (92.8 mg, 97% yield); m. p. = 145–147 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (s, 1H), 7.49 – 7.40 (m, 7H), 7.31 – 7.28 (m, 2H), 7.26 – 7.21 (m, 4H), 7.19 – 7.17 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.4, 151.2, 142.1, 135.5, 134.5, 132.0, 130.9, 129.9, 129.5, 129.4, 128.8, 128.4, 128.1, 125.8, 121.7; FT-IR (thin film, neat): 3051, 1720, 1494, 1236, 1156 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{21}H_{16}NaO_2$ $[M+Na]^+$: 323.1048; found : 323.1041.

(*E*)-4-ethylphenyl 2,3-diphenylacrylate (35c)



The reaction was performed at 0.245 mmol scale of **33c**; R_f = 0.4 (5% EtOAc in hexane); white solid (70.0 mg, 87% yield); m. p. = 115–117 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (s, 1H), 7.47 – 7.39 (m, 5H), 7.30 – 7.21 (m, 5H), 7.18 – 7.15 (m, 2H), 7.12 (d, *J* = 8.5 Hz, 2H), 2.70 (q, *J* = 7.6 Hz 2H), 1.29 (t, *J* a= 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.6, 149.1, 141.9, 141.7, 135.6, 134.5, 132.1, 130.9, 129.9, 129.4, 128.8, 128.7, 128.3, 128.1, 121.4, 28.4, 15.7; FT-IR (thin film, neat): 3056, 2933, 1725, 1497, 1235, 1162 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{23}H_{20}NaO_2$ $[M+Na]^+$: 351.1361; found : 351.1351.

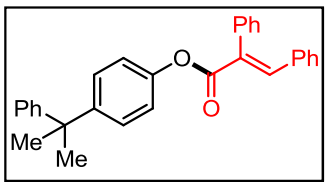
(*E*)-2-isopropylphenyl 2,3-diphenylacrylate (35d)



The reaction was performed at 0.220 mmol scale of **33d**; R_f = 0.3 (5% EtOAc in hexane); white solid (64.0 mg, 85% yield); m. p. = 118–120 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (s, 1H), 7.47 – 7.45 (m, 1H), 7.44 – 7.38 (m, 4H), 7.35 – 7.32 (m, 1H), 7.30 –

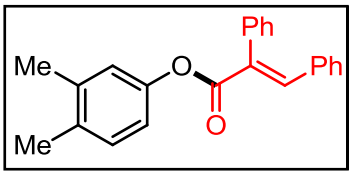
7.20 (m, 5H), 7.17 – 7.14 (m, 3H), 3.03 (hept, J = 6.9 Hz, 1H), 1.19 (d, J = 6.9 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.5, 148.7, 142.0, 140.1, 135.8, 134.5, 132.1, 131.0, 129.8, 129.6, 128.9, 128.4, 128.1, 126.63, 126.60, 126.2, 122.3, 27.7, 22.9; FT-IR (thin film, neat): 2965, 1727, 1489, 1211, 1154 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{24}H_{23}O_2$ $[M+H]^+$: 343.1698; found : 343.1681.

(*E*)-4-(2-phenylpropan-2-yl)phenyl 2,3-diphenylbut-2-enoate (35e)



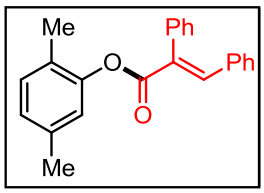
The reaction was performed at 0.141 mmol scale of **33e**; R_f = 0.4 (5% EtOAc in hexane); white solid (57.8 mg, 98% yield); m. p. = 140–142 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.1 (s, 1H), 7.45 – 7.39 (m, 3H), 7.37 – 7.35 (m, 2H), 7.32 – 7.30 (s, 1H), 7.28 – 7.25 (m, 6H), 7.23 – 7.19 (m, 3H), 7.15 – 7.13 (m, 2H), 7.08 (d, J = 8.7 Hz 2H), 1.71 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.5, 150.5, 149.0, 148.2, 142.0, 135.6, 134.5, 132.1, 130.9, 129.9, 129.5, 128.8, 128.4, 128.13, 128.09, 127.9, 126.9, 125.8, 121.0, 42.8, 30.9; FT-IR (thin film, neat): 2970, 1727, 1501, 1202, 1170 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{30}H_{27}O_2$ $[M+H]^+$: 419.2011; found : 419.1999.

(*E*)-3,4-dimethylphenyl 2,3-diphenylacrylate (35f)



The reaction was performed at 0.245 mmol scale of **33f**; R_f = 0.3 (5% EtOAc in hexane); white solid (71.7 mg, 89% yield); m. p. = 137–139 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (s, 1H), 7.47 – 7.44 (m, 1H), 7.43 – 7.41 (m, 2H), 7.40 – 7.38 (m, 2H), 7.30 – 7.26 (m, 1H), 7.24 – 7.21 (m, 2H), 7.18 – 7.15 (m, 3H),6.99 (d, J = 2.3 Hz, 1H), 6.94 (dd, J = 8.1, 2.4 Hz, 1H), 2.30 (s, 3H), 2.29 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.7, 149.1, 141.8, 137.8, 135.7, 134.6, 134.0, 132.2, 130.8, 130.3, 129.9, 129.4, 128.8, 128.3, 128.0, 122.6, 118.7, 19.9, 19.3; FT-IR (thin film, neat): 3053, 2957, 1726, 1502, 1243, 1187 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{23}H_{20}NaO_2$ $[M+H]^+$: 351.1361; found : 351.1353.

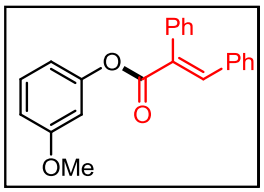
(*E*)-2,5-dimethylphenyl 2,3-diphenylacrylate (35g)



The reaction was performed at 0.245 mmol scale of **33g**; R_f = 0.3 (5% EtOAc in hexane); pale yellow gummy solid (73.1 mg, 91% yield); ^{1}H NMR (400 MHz, $CDCl_3$), δ 8.10 (s, 1H), 7.48 – 7.445 (m, 1H), 7.441 – 7.39 (m, 4H), 7.30 – 7.26 (m, 1H), 7.25 – 7.21 (m, 2H), 7.17 – 7.13 (m, 3H), 6.99 – 6.97 (m, 2H), 2.36 (s, 3H), 2.18 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.3, 149.6, 141.9, 136.8, 135.8, 134.5, 132.1, 130.9, 130.8, 129.8, 129.5, 128.8, 128.4, 128.1, 126.8, 126.7,

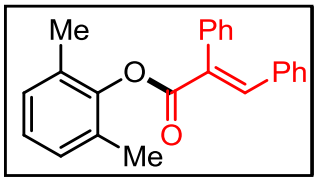
122.2, 21.0, 16.0; FT-IR (thin film, neat): 3056, 2925, 1726, 1507, 1229, 1156 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{23}H_{20}NaO_2$ $[M+Na]^+$: 351.1361; found : 351.1359.

(*E*)-3-methoxyphenyl 2,3-diphenylacrylate (35h)



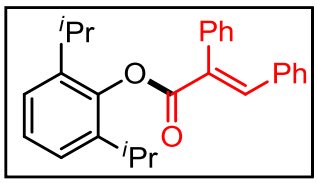
The reaction was performed at 0.242 mmol scale of **33h**; R_f = 0.2 (5% EtOAc in hexane); white solid (76.4 mg, 96% yield); m. p. = 110–112 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (s, 1H), 7.47 – 7.41 (m, 3H), 7.39 – 7.37 (m, 2H), 7.31(t, *J* = 8.2 Hz, 1H), 7.28 – 7.25 (m, 1H), 7.24 – 7.20 (m, 2H), 7.16 – 7.14 (m, 2H), 6.81 (td, *J* = 8.2, 2.3 Hz, 2H), 6.76 (t, *J* = 2.2 Hz, 1H); 3.81 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.3, 160.5, 152.2, 142.1, 135.5, 134.4, 131.9, 130.9, 129.9, 129.8, 129.5, 128.8, 128.3, 128.1, 113.9, 111.8, 107.6, 55.5; FT-IR (thin film, neat): 2937, 2839, 1726, 1610, 1229, 1156 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{22}H_{18}NaO_3$ $[M+Na]^+$: 353.1154; found : 353.1171.

(*E*)-2,6-dimethylphenyl 2,3-diphenylacrylate (35i)



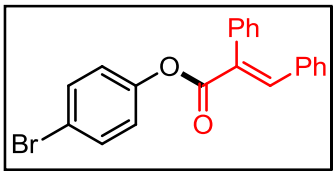
The reaction was performed at 0.245 mmol scale of **33i**; R_f = 0.3 (5% EtOAc in hexane); colorless gummy solid (74.8 mg, 93% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (s, 1H), 7.49 – 7.46 (m, 1H), 7.45 – 7.40 (m, 4H), 7.30 – 7.26 (m, 1H), 7.25 – 7.21 (m, 1H), 7.18 – 7.16 (m, 2H), 7.11 – 7.05 (m, 3H), 2.22 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.7, 148.6, 141.9, 135.9, 134.5, 131.9, 131.0, 130.2, 129.7, 129.6, 128.9, 128.6, 128.4, 128.1, 125.8, 16.5; FT-IR (thin film, neat): 2924, 1725, 1476, 1235, 1159 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{23}H_{21}O_2$ $[M+H]^+$: 329.1542; found : 329.1526.

(*E*)-2,6-diisopropylphenyl 2,3-diphenylacrylate (35j)



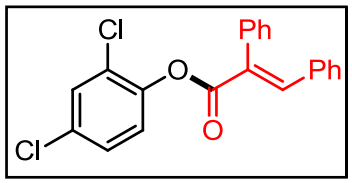
The reaction was performed at 0.168 mmol scale of **33j**; R_f = 0.4 (5% EtOAc in hexane); white solid (64.1 mg, 98% yield); m. p. = 118–120 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (s, 1H), 7.48 – 7.451 (m, 1H), 7.446 – 7.44 (m, 1H), 7.43 – 7.39 (m, 3H), 7.30 – 7.26 (m, 1H), 7.25 – 7.21 (m, 3H), 7.20 – 7.16 (m, 4H), 2.98 (hept, *J* = 6.9 Hz, 2H), 1.28 (d, *J* = 6.5 Hz, 6H), 1.15 (d, *J* = 6.5 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.6, 146.4, 141.9, 140.3, 136.0, 134.5, 132.1, 131.0, 129.7, 129.6, 128.9, 128.4, 128.1, 126.5, 123.9, 27.9, 24.0, 22.6; FT-IR (thin film, neat): 2966, 1726, 1448, 1230, 1160 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{27}H_{29}O_2$ $[M+H]^+$: 385.2168; found : 385.2150.

(*E*)-4-bromophenyl 2,3-diphenylacrylate (35k)



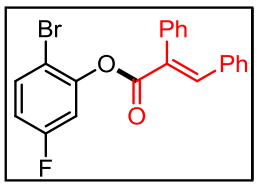
The reaction was performed at 0.173 mmol scale of **33k**; R_f = 0.3 (5% EtOAc in hexane); white solid (62.3 mg, 95% yield); m. p. = 158–160 ºC; ^{1}H NMR (400 MHz, $CDCl_3$), δ 8.07 (s, 1H), 7.51 (d, J = 8.9 Hz, 2H), 7.46 – 7.432 (m, 1H), 7.427 – 7.40 (m, 2H), 7.36 – 734 (m, 2H), 7.29 – 7.25 (m, 1H), 7.23 – 7.19 (m, 2H), 7.14 – 7.12 (m, 2H), 7.07 (d, J = 8.9 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.1, 150.2, 142.6, 135.4, 134.3, 132.5, 131.6, 130.9, 129.9, 129.7, 128.9, 128.4, 128.2, 123.5, 118.9; FT-IR (thin film, neat): 3059, 1727, 1484, 1197, 1150 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{21}H_{15}BrNaO_2$ $[M+Na]^+$: 401.0153; found : 401.0146.

(*E*)-2,4-dichlorophenyl 2,3-diphenylacrylate (35l)



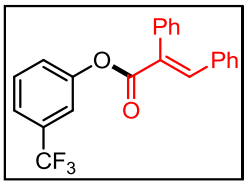
The reaction was performed at 0.184 mmol scale of **33l**; R_f = 0.4 (5% EtOAc in hexane); white solid; (63.9 mg, 94% yield); m. p. = 100–102 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (s, 1H), 7.47 (d, J = 2.4 Hz, 1H), 7.46 – 7.44 (m, 1H), 7.43 – 7.41 (m, 2H), 7.40 – 7.38 (m, 2H), 7.30 – 7.25 (m, 2H), 7.23 – 7.19 (m, 2H), 7.17 – 7.13 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.4, 146.3, 143.3, 135.2, 134.3, 131.8, 131.06, 131.0, 130.1, 130.0, 129.8, 128.9, 128.4, 128.3, 127.9 (2C), 124.8; FT-IR (thin film, neat): 3061, 1736, 1474, 1209, 1143 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{21}H_{14}Cl_2NaO_2$ $[M+Na]^+$: 391.0269; found : 391.0252.

(*E*)-2-bromo-5-fluorophenyl 2,3-diphenylacrylate (35m)



The reaction was performed at 0.157 mmol scale of **33m**; R_f = 0.4 (5% EtOAc in hexane); colorless gummy solid (60.5 mg, 97% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (s, 1H), 7.56 (dd, J = 8.9, 5.8 Hz, 1H) 7.46 – 7.38 (m, 5H), 7.29 – 7.25 (m, 1H), 7.23 – 7.19 (m, 2H), 7.14 – 7.12 (m, 2H), 7.02 (dd, J = 8.8, 2.9 Hz, 1H) 6.89 (ddd, J = 8.8, 7.8, 2.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.2, 156.0, 145.4, 143.5, 135.1, 134.1, 131.1 (2C), 130.0, 129.9, 129.1, 128.53, 128.47, 125.3, 122.6; ^{19}F NMR (376 MHz, $CDCl_3$) δ –112.05; FT-IR (thin film, neat): 2964, 1736, 1477, 1261, 1222 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{21}H_{14}BrFNaO_2$ $[M+Na]^+$: 419.0059; found : 419.0040.

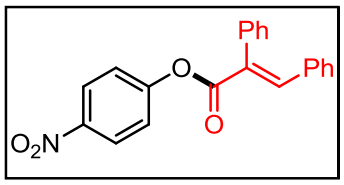
(*E*)-3-(trifluoromethyl)phenyl 2,3-diphenylacrylate (35n)



The reaction was performed at 0.185 mmol scale of **33n**; R_f = 0.4 (5% EtOAc in hexane); white solid (64.9 mg, 98% yield); m. p. = 94–96 ºC;

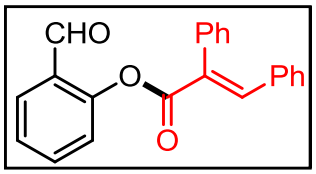
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (s, 1H), 7.53 – 7.51 (m, 2H), 7.47 – 7.444 (m, 2H), 7.439 – 7.41 (m, 2H), 7.40 – 7.35 (m, 3H), 7.30 – 7.26 (m, 1H), 7.24 – 7.20 (m, 2H), 7.15 – 7.13 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.1, 151.3, 142.9, 135.3, 134.3, 132.0 (d, $J_{C\text{-}F}$ = 32.7 Hz), 131.4, 131.0, 130.0, 129.9, 129.8, 129.0, 128.5, 128.3, 125.4, 123.7 (d, $J_{C\text{-}F}$ = 270.8 Hz), 122.6 (d, $J_{C\text{-}F}$ = 3.8 Hz), 119 (d, $J_{C\text{-}F}$ = 3.8 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ –62.56; FT-IR (thin film, neat): 3062, 1730, 1327, 1449, 1327, 1145 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{22}H_{15}F_3NaO_2$ $[M+Na]^+$: 391.0922; found : 391.0903.

(*E*)-4-nitrophenyl 2,3-diphenylacrylate (35o)



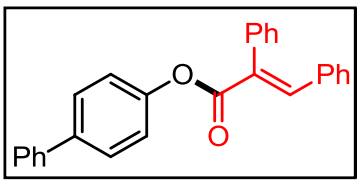
The reaction was performed at 0.216 mmol scale of **33o**; R_f = 0.2 (5% EtOAc in hexane); white solid; (23.8 mg, 32% yield); m. p. = 169–171 ºC; ^{1}H NMR (400 MHz, $CDCl_3$), δ 8.3 (d, J = 9.1 Hz, 2H), 8.07 (s, 1H), 7.46 – 7.41 (m, 3H), 7.32 – 7.32 (m, 4H), 7.30 – 7.26 (m, 1H), 7.23 – 7.19 (m, 2H), 7.13 – 7.11 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.5, 156.0, 145.4, 143.5, 135.1, 134.1, 131.1 (2C), 130.0, 129.9, 129.1, 128.53, 128.47, 125.3, 122.6; FT-IR (thin film, neat): 3081, 1724, 1518, 1230, 1143 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{21}H_{15}NNaO_4$ $[M+Na]^+$: 368.0899; found : 368.0888.

(*E*)-2-formylphenyl 2,3-diphenylacrylate (35p)



The reaction was performed at 0.246 mmol scale of **33p**; R_f = 0.2 (10% EtOAc in hexane); white solid (41.0 mg, 51% yield); m. p. = 127–129 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.09 (s, 1H), 8.12 (s, 1H), 7.91 (d, J = 7.7 Hz, 1H), 7.64 (t, J = 7.8 Hz, 1H), 7.47 – 7.36 (m, 6H), 7.32 (d, J = 8.2 Hz, 1H), 7.27 (d, J = 6.6 Hz, 1H), 7.21 (t, J = 7.5 Hz, 2H), 7.15 (d, J = 7.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.7, 166.1, 152.5, 143.2, 135.35, 135.3, 134.2, 131.2, 131.1, 130.2, 129.83, 129.79, 129.0, 128.4, 128.3, 128.1, 126.3, 123.4; FT-IR (thin film, neat): 3066, 1730, 1698, 1198, 1146 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{22}H_{16}NaO_3$ $[M–H]^-$: 351.0997; found : 351.1011.

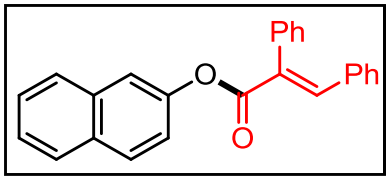
(*E*)-[1,1'-biphenyl]-4-yl 2,3-diphenylacrylate (35q)[17]



The reaction was performed at 0.176 mmol scale of **33q**; R_f = 0.3 (5% EtOAc in hexane); white solid (54.2 mg, 80% yield); m. p. = 184–186 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (s, 1H), 7.64 – 7.59 (m, 4H), 7.48 – 7.46 (m, 2H), 7.45 – 7.42 (m, 3H), 7.41 – 7.37 (m, 3H), 7.28 – 7.21 (m, 5H), 7.16 – 7.15 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.5, 150.7, 142.3,

140.5, 138.9, 135.6, 134.5, 132.0, 130.9, 130.0, 129.6, 128.89, 128.88, 128.4, 128.2, 127.4, 127.2, 122.0; FT-IR (thin film, neat): 2919, 1723, 1487, 1235, 1151 cm^{-1}.

(*E*)-naphthalen-2-yl 2,3-diphenylacrylate (35r)



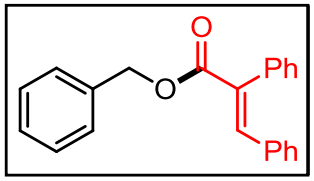
The reaction was performed at 0.208 mmol scale of **33r**; R_f = 0.5 (10% EtOAc in hexane); white solid (33.4 mg, 46% yield); m. p. = 162–164 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (s, 1H), 7.88 – 7.85 (m, 2H), 7.81 (d, J = 7.7 Hz, 1H), 7.64 (s, 1H), 7.52 – 7.39 (m, 7H), 7.32 – 7.30 (m, 1H), 7.27 – 7.25 (m, 1H), 7.21 (t, J = 7.4 Hz, 2H), 7.14(d, J = 7.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.7, 148.9, 142.3, 135.6, 134.5, 133.9, 132.0, 131.5, 131.0, 130.0, 129.6, 129.4, 128.9, 128.4, 128.2, 127.9, 127.8, 126.6, 125.8, 121.4, 118.7; FT-IR (thin film, neat): 2932, 1724, 1268, 1164 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{25}H_{18}NaO_2$ $[M+H]^+$: 373.1204; found : 373.1216.

General procedure for the synthesis of *O*-acyl alcohols:

Toluene (1.5 mL) was added to a mixture of alcohol (30 mg, 0.277 mmol), diphenylcyclopropenone (68.6 mg, 0.332 mmol) and DMAP (6.8 mg, 0.055 mmol) under argon atmosphere. The reaction mixture was stirred at 80 °C. After 4 h, the mixture was quenched with 5 mL of distilled water and extracted with EtOAc (3 x 5 mL). The combined organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was then purified through a silica gel column using EtOAc/Hexane mixture as an eluent to get the pure product.

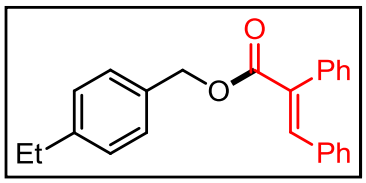
Characterization data of compounds (37a-37q):

(*E*)-benzyl 2,3-diphenylacrylate (37a)[18]



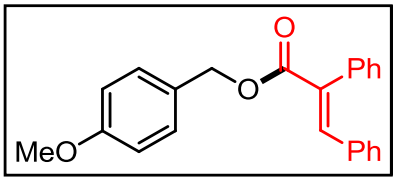
The reaction was performed at 0.277 mmol scale of **36a**; R_f = 0.3 (5% EtOAc in hexane); pale yellow gummy solid (58.0 mg, 69% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (s, 1H), 7.44 – 7.40 (m, 3H), 7.39 – 7.34 (m, 5H), 7.30 – 7.27 (m, 2H), 7.24 – 7.16 (m, 3H), 7.10 – 7.08 (m, 2H), 5.31 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.6, 140.7, 136.3, 135.9, 134.6, 132.6, 130.7, 129.9, 129.1, 128.7, 128.5, 128.2, 128.1, 127.90, 127.86, 66.8; FT-IR (thin film, neat): 3032, 1710, 1450, 1239, 1168 cm^{-1}.

(*E*)-4-ethylbenzyl 2,3-diphenylacrylate (37b)



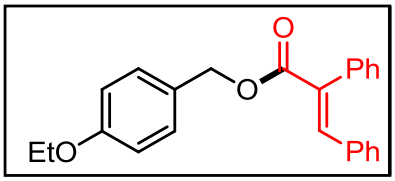
The reaction was performed at 0.221 mmol scale of **36b**; R_f = 0.5 (10% EtOAc in hexane); colorless gummy solid (74.1 mg, 98% yield); ^{1}H NMR (400 MHz, $CDCl_3$), δ 7.95 (s, 1H), 7.46 – 7.42 (m, 3H), 7.35 – 7.31 (m, 4H), 7.27 – 7.25 (m, 3H), 7.23 – 7.19 (m, 2H), 7.12 (d, *J* = 7.7 Hz, 2H), 5.31 (s, 2H), 2.72 (q, *J* = 7.6 Hz, 2H), 1.31 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.7, 144.2, 140.6, 135.9, 134.7, 133.5, 132.6, 130.7, 129.9, 129.1, 128.7, 128.2 128.13, 128.06, 127.9, 67.0, 28.7, 15.7; FT-IR (thin film, neat): 2965, 1711, 1623, 1449, 1239, 1168 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{24}H_{22}NaO_2$ $[M+Na]^+$: 365.1517; found : 365.1528.

(*E*)-4-methoxybenzyl 2,3-diphenylacrylate (37c)



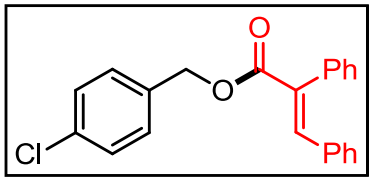
The reaction was performed at 0.217 mmol scale of **36c**; R_f = 0.2 (5% EtOAc in hexane); colorless gummy solid (67.3 mg, 90% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 – 7.88 (m, 1H), 7.39 – 7.38 (m, 3H), 7.32 (d, *J* = 8.2 Hz, 2H), 7.26 – 7.25 (m, 2H), 7.21 – 7.15 (m, 3H), 7.07 (d, *J* = 7.0 Hz, 2H), 6.91 (d, *J* = 8.2 Hz, 2H), 5.23 (s, 2H), 3.82 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.7, 159.5, 140.5, 135.9, 134.7, 132.6, 130.7, 129.87, 129.86, 129.1, 128.7, 128.4, 128.2, 113.9, 127.9, 66.7, 53.3; FT-IR (thin film, neat): 2956, 1708, 1515, 1240, 1168 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{23}H_{20}NaO_3$ $[M+Na]^+$: 367.1310; found : 367.1301.

(*E*)-4-ethoxybenzyl 2,3-diphenylacrylate (37d)



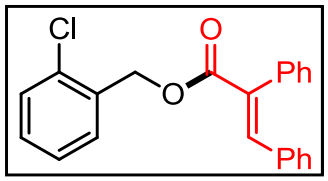
The reaction was performed at 0.197 mmol scale of **36d**; R_f = 0.3 (5% EtOAc in hexane); pale yellow gummy solid (61.4 mg, 87% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (s, 1H), 7.40 – 7.36 (m, 3H), 7.30 (d, *J* = 8.7 Hz, 2H), 7.26 – 7.23 (m, 2H), 7.22 – 7.19 (m, 1H), 7.18 – 7.14 (m, 2H), 7.08 – 7.05 (m, 2H), 6.89 (d, *J* = 8.7 Hz, 2H), 5.22 (s, 2H), 4.05 (q, *J* = 7.0 Hz, 2H), 1.43 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.7, 158.9, 140.5, 135.9, 134.7, 132.7, 130.7, 129.89, 129.87, 129.1, 128.7, 128.25 128.23, 127.9, 114.5, 66.7, 63.5, 14.9; FT-IR (thin film, neat): 2981, 1708, 1617, 1514, 1238, 1168 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{24}H_{22}NaO_3$ $[M+Na]^+$: 381.1467; found : 381.1482.

(*E*)-4-chlorobenzyl 2,3-diphenylacrylate (37e)



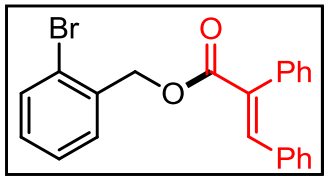
The reaction was performed at 0.210 mmol scale of **36e**; R_f = 0.2 (5% EtOAc in hexane); white solid (66.4 mg, 90% yield); m. p. = 96–98 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (s, 1H), 7.43 – 7.38 (m, 3H), 7.34 (d, *J* = 8.4 Hz, 2H), 7.28 – 7.25 (m, 4H), 7.23 – 7.15 (m, 3H), 7.08 (d, *J* = 7.3 Hz, 2H), 5.24 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.5, 141.0, 135.8, 134.7, 134.5, 133.9, 132.3, 130.7, 129.8, 129.3, 129.27, 128.7 (2C), 128.3, 128.0, 66.8; FT-IR (thin film, neat): 3058, 1711, 1494, 1239, 1167 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{22}H_{17}ClNaO2$ $[M+Na]^+$: 371.0815; found : 371.0804.

(*E*)-2-chlorobenzyl 2,3-diphenylacrylate (37f)



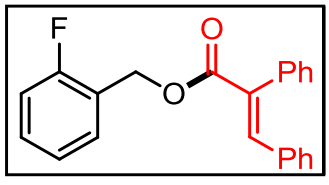
The reaction was performed at 0.211 mmol scale of **36f**; R_f = 0.5 (5% EtOAc in hexane); white solid (61.3 mg, 92% yield);); m. p. = 85–87 ºC, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (s, 1H), 7.43 – 7.40 (m, 4H), 7.32 – 7.29 (m, 3H), 7.27 – 7.22 (m, 3H), 7.18 (t, *J* = 7.6, 2H), 7.10 (d, *J* = 7.8 Hz, 2H), 5.39 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.4, 141.0, 135.8, 134.6, 133.9, 133.3, 132.3, 130.8, 129.9, 129.5, 129.29, 129.27, 128.7, 128.3, 128.0, 126.9, 64.2; FT-IR (thin film, neat): 3060, 1712, 1447, 1239, 1167 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{22}H_{18}ClO_2$ $[M+H]^+$: 349.0995; found : 349.1000.

(*E*)-2-bromobenzyl 2,3-diphenylacrylate (37g)



The reaction was performed at 0.160 mmol scale of **36g**; R_f = 0.5 (5% EtOAc in hexane); white solid (61.6mg, 97% yield); m. p. = 81–83 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (s, 1H), 7.58 (d, *J* = 7.9 Hz, 1H), 7.43 – 7.38 (m, 3H), 7.30 – 7.28 (m, 4H), 7.25 – 7.16 (m, 4H), 7.09 (d, *J* = 7.7 Hz, 2H), 5.35 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.4, 141.0, 135.8, 135.5, 134.6, 132.8, 132.3, 130.8, 129.9, 129.5, 129.4, 129.3, 128.7, 128.3, 128.0, 127.5, 123.0, 66.4; FT-IR (thin film, neat): 3060, 1713, 1446, 1239, 1167 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{22}H_{18}BrO_2$ $[M+H]^+$: 393.0490; found : 393.0502.

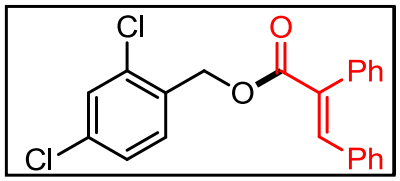
(*E*)-2-fluorobenzyl 2,3-diphenylacrylate (37h)



The reaction was performed at 0.238 mmol scale of **36h**; R_f = 0.3 (10% EtOAc in hexane); pale yellow solid (71.2 mg, 90 % yield); m. p. = 112–114 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (s, 1H), 7.43 – 7.38 (m, 3H), 7.36 – 7.31 (m, 2H), 7.30 – 7.28 (m, 2H), 7.25 – 7.21 (m, 1H), 7.20 –

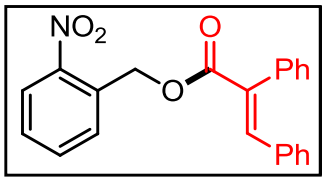
7.14 (m, 3H), 7.12 – 7.08 (m, 3H), 5.37 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.5, 160.9 (d, $J_{C\text{-}F}$ = 46.6 Hz), 140.9, 135.8, 134.6, 132.3, 130.7, 130.2 (d, $J_{C\text{-}F}$ = 3.8 Hz), 130.0 (d, $J_{C\text{-}F}$ = 8.1 Hz), 129.9, 129.2, 128.7, 128.3, 127.9, 124.2(d, $J_{C\text{-}F}$ = 3.7 Hz), 123.4 (d, $J_{C\text{-}F}$ = 14.3 Hz), 115.4 (d, $J_{C\text{-}F}$ = 20.9 Hz), 60.9 (d, $J_{C\text{-}F}$ = 4.4 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ – 117.80; FT-IR (thin film, neat): 3058, 1711, 1495, 1239, 1167 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{22}H_{18}FO_2$ $[M+H]^+$: 333.1291; found : 333.1305.

(*E*)-2,4-dichlorobenzyl 2,3-diphenylacrylate (37i)



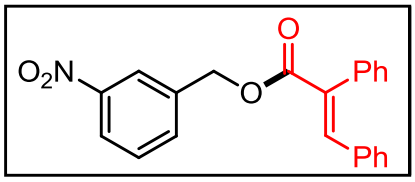
The reaction was performed at 0.169 mmol scale of **36i**; R_f = 0.5 (10% EtOAc in hexane); white solid (56.5 mg, 87 % yield); m. p. = 129–131 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (s, 1H), 7.42 – 7.39 (m, 4H), 7.29 – 7.26 (m, 2H), 7.25 – 7.20 (m, 3H), 7.17 (t, *J* = 7.6 Hz, 2H), 7.09 (d, *J* = 7.7 Hz, 2H), 5.31 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.3, 141.2, 135.7, 134.48, 134.46, 134.0, 132.6, 132.1, 130.8, 130.2, 129.8, 129.4, 128.8 (2C), 128.3, 128.0, 127.2, 63.6; FT-IR (thin film, neat): 2924, 1711, 1494, 1612, 1240, 1168 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{22}H_{16}Cl_2NaO2$ $[M+Na]^+$: 405.0425; found : 405.0441.

(*E*)-2-nitrobenzyl 2,3-diphenylacrylate (37j)



The reaction was performed at 0.196 mmol scale of **36j**; R_f = 0.3 (10% EtOAc in hexane); white solid (38.1 mg, 54% yield); m. p. = 107–109 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (d, *J* = 8.2 Hz, 1H), 7.92 (s, 1H), 7.57 (t, *J* = 7.5 Hz, 1H), 7.47 – 7.38 (m, 5H), 7.28 – 7.26 (m, 2H), 7.22 (d, *J* = 7.2 Hz, 1H), 7.17 (t, *J* = 7.7 Hz, 2H), 7.08 (d, *J* = 7.7 Hz, 2H), 5.65 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.2, 147.4, 141.5, 135.8, 134.4, 133.9, 132.6, 132.0, 130.9, 129.8, 129.5, 128.9, 128.7, 128.4, 128.1, 126.7, 125.1, 63.7; FT-IR (thin film, neat): 3060, 1715, 1529, 1239, 1167 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{22}H_{17}NNaO_4$ $[M+Na]^+$: 382.1055; found : 382.1073.

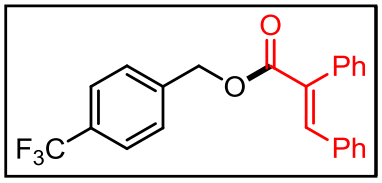
(*E*)-3-nitrobenzyl 2,3-diphenylacrylate (37k)



The reaction was performed at 0.196 mmol scale of **36k**; R_f = 0.2 (10% EtOAc in hexane); pale yellow gummy solid (66.1 mg, 94% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17 – 7.15 (m, 2H), 7.93 (s, 1H), 7.64 – 7.62 (m, 1H), 7.54 – 7.49 (m, 1H), 7.45 – 7.39 (m, 3H), 7.28 – 7.26 (m, 2H), 7.24 – 7.21 (m, 1H), 7.19 – 7.15 (m, 2H), 7.09 – 7.07 (m, 2H), 5.34 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.4, 148.4, 141.5, 138.4, 135.6, 134.4, 133.4, 131.9, 130.8, 129.7, 129.6, 129.5 128.9, 128.3, 128.1, 123.0, 122.4, 65.3; FT-IR (thin film,

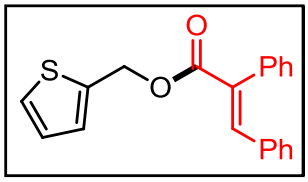
neat): 3062, 1706, 1623, 1534, 1352, 1239, 1166 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{22}H_{17}NNaO_4$ $[M+Na]^+$: 382.1055; found : 382.1038.

(*E*)-4-(trifluoromethyl)benzyl 2,3-diphenylacrylate (37l)



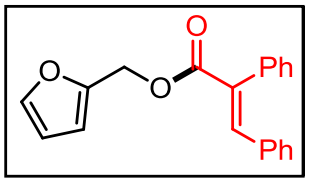
The reaction was performed at 0.170 mmol scale of **36l**; R_f = 0.3 (5% EtOAc in hexane); pale yellow gummy solid (43.7 mg, 67% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (s, 1H), 7.62 (d, *J* = 8.0 Hz, 2H), 7.43 – 7.40 (m, 5H) 7.28 – 7.26 (m, 2H), 7.23 (d, *J* = 7.1 Hz, 1H), 7.18 (t, *J* = 7.4 Hz, 2H), 7.08 (d, *J* = 7.7 Hz, 2H), 5.32 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.5, 141.3, 140.3, 135.8, 134.5, 132.2, 130.8, 130.2 (q, $J_{C\text{-}F}$ = 32.5 Hz), 129.8, 129.4, 128.8, 128.4, 128.1, 127.8, 125.6 (q, $J_{C\text{-}F}$ = 3.7 Hz), 124.2 (d, $J_{C\text{-}F}$ = 270.8 Hz), 65.9; ^{19}F NMR (376 MHz, $CDCl_3$) δ –62.51; FT-IR (thin film, neat): 3060, 1713, 1494, 1623, 1240, 1167 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{23}H_{17}F_3NaO_2$ $[M+Na]^+$: 405.1078; found : 405.1065.

(*E*)-thiophen-2-ylmethyl 2,3-diphenylacrylate (37m)



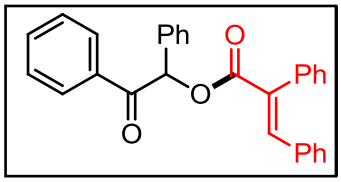
The reaction was performed at 0.263 mmol scale of **36m**; R_f = 0.4 (5% EtOAc in hexane); pale yellow gummy solid (70.1 mg, 78% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (s, 1H), 7.42 – 7.38 (m, 3H), 7.34 (dd, *J* = 5.1, 1.2 Hz, 1H), 7.28 – 7.25 (m, 2H), 7.24 – 7.21 (m, 1H), 7.20 – 7.13 (m, 3H), 7.09 – 7.07 (m, 2H), 7.01 (dd, *J* = 5.1, 3.5 Hz, 1H), 5.45 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.5, 141.0, 138.3, 135.7, 134.6, 132.3, 130.7, 129.9, 129.2, 128.7 (2C), 128.2, 128.0, 127.9, 126.8, 61.3; FT-IR (thin film, neat): 3059, 1707, 1622, 1444, 1236, 1166 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{20}H_{16}NaO_2S$ $[M+Na]^+$: 343.0769; found : 343.0753.

(*E*)-furan-2-ylmethyl 2,3-diphenylacrylate (37n)



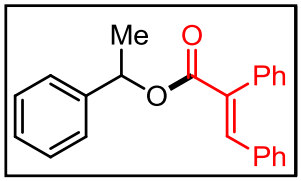
The reaction was performed at 0.306 mmol scale of **36n**; R_f = 0.3 (5% EtOAc in hexane); pale yellow gummy solid (43.4 mg, 70% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (s, 1H), 7.444 – 7.438 (m, 1H), 7.38 – 7.34 (m, 3H), 7.25 – 7.22 (m, 2H), 7.21 – 7.13 (m, 3H), 7.06 – 7.03 (m, 2H), 6.44 (d, *J* = 3.2 Hz, 1H), 6.38 – 6.37 (m, 1H), 5.22 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.5, 149.8, 143.2, 140.9, 135.7, 134.6, 132.3, 130.7, 129.9, 129.2, 128.7, 128.3 128.0, 110.73, 110.65, 58.8; FT-IR (thin film, neat): 3059, 1711, 1499, 1237, 1166 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{20}H_{16}NaO_3$ $[M+Na]^+$: 327.0997; found : 327.0983.

(*E*)-2-oxo-1,2-diphenylethyl 2,3-diphenylacrylate (37o)



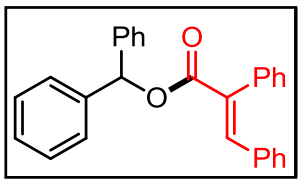
The reaction was performed at 0.141 mmol scale of **36o**; R_f = 0.2 (10% EtOAc in hexane); white solid (52.4 mg, 88% yield); m. p. = 136–138 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, J = 6.3, Hz, 3H), 7.52 (t, J = 7.4, Hz, 1H), 7.46 (d, J = 6.9 Hz, 2H), 7.42 (d, J = 7.6 Hz, 2H), 7.38 (d, J = 6.9 Hz, 3H), 7.36 – 7.32 (m, 5H), 7.24 – 7.21 (m, 1H), 7.17 (t, J = 7.5 2H), 7.10 (d, J = 7.6 Hz, 2H), 6.99 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.3, 167.3, 141.5, 135.5, 134.8, 134.6, 133.7, 133.5, 131.8, 130.9, 130.0, 129.3, 129.2, 129.1, 129.0, 128.71, 128.68, 128.30, 128.28, 128.0, 78.4; FT-IR (thin film, neat): 3061, 1698, 1449, 1234, 1167 cm^{-1} HRMS (ESI): *m/z* calcd for $C_{29}H_{22}NaO_3$ $[M+Na]^+$: 441.1467; found : 441.1475.

(*E*)-1-phenylethyl 2,3-diphenylacrylate (37p)



The reaction was performed at 0.246 mmol scale of **36p**; R_f = 0.4 (5% EtOAc in hexane); pale yellow gummy solid (50.5 mg, 63% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (s, 1H), 7.42 – 7.36 (m, 4H), 7.35 – 7.30 (m, 4H), 7.29 – 7.25 (m, 2H), 7.24 – 7.21 (m, 1H), 7.20 – 7.16 (m, 2H), 7.11 – 7.09 (m, 2H), 6.06 (q, J = 6.6 1H), 1.59 (d, J = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.1, 142.0, 140.4, 136.0, 134.7, 133.0, 130.7, 129.9, 129.1, 128.6, 128.5, 128.3, 127.83, 127.80, 126.0, 73.2, 22.7; FT-IR (thin film, neat): 2982, 1708, 1494, 1624, 1449, 1243, 1171 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{23}H_{20}NaO_2$ $[M+Na]^+$: 351.1361; found : 351.1373.

(*E*)-benzhydryl 2,3-diphenylacrylate (37q)



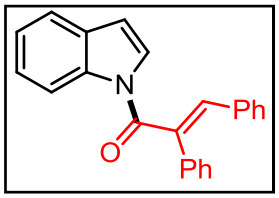
The reaction was performed at 0.163 mmol scale of **36q**; R_f = 0.4 (5% EtOAc in hexane); pale yellow solid (54.2 mg, 85% yield); m. p. = 110–112 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (s, 1H), 7.47 – 7.42 (m, 3H), 7.37 – 7.34 (m, 2H), 7.33 – 7.32 (m, 6H), 7.31 – 7.27 (m, 4H), 7.25 – 7.17 (m, 3H), 7.13 – 7.11 (m, 2H) 7.03 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.8, 140.9, 140.6, 136.0, 134.6, 132.7, 130.8, 129.9, 129.3, 128.7, 128.6, 128.3, 127.92, 127.86, 127.0, 77.6; FT-IR (thin film, neat): 3032, 1711, 1625, 1495, 1239, 1167 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{28}H_{22}NaO_2$ $[M+Na]^+$: 413.1517; found : 413.1533.

General procedure for the synthesis of *N*-acyl indoles:

Toluene (1.5 mL) was added to a mixture of indole (30 mg, 0.26 mmol), diphenylcyclopropenone (63.4 mg, 0.312 mmol) and DMAP (6.4 mg, 0.052 mmol) under argon atmosphere. The reaction mixture was stirred at 80 ^{o}C. After 4 h, the mixture was quenched with 5 mL of distilled water and extracted with EtOAc (3 x 5 mL). The combined organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was then purified through a silica gel column using EtOAc/Hexane mixture as an eluent to get the pure product.

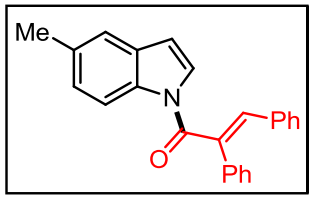
Characterization data of compounds (39a-39h):

(*E*)-1-(1H-indol-1-yl)-2,3-diphenylprop-2-en-1-one (39a)



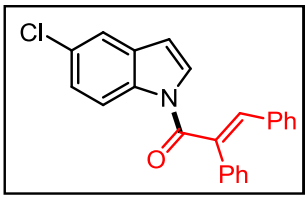
The reaction was performed at 0.26 mmol scale of **38a**; R_f = 0.4 (5% EtOAc in hexane); brown gummy solid (40.6 mg, 49% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.53 (d, J = 8.2 Hz, 1H), 7.58 (d, J = 7.7 Hz, 1H), 7.52 (d, J = 3.8 Hz, 1H), 7.42 – 7.38 (m, 3H), 7.36 – 7.31 (m, 4H), 7.29 – 7.26 (m, 1H), 7.24 – 7.22 (m, 2H), 7.21 – 7.19 (m, 2H), 7.13 (s, 1H), 6.58 (d, J = 3.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.2, 136.4, 136.1, 136.0, 135.3, 134.6, 130.9, 130.0, 129.3, 129.2, 128.9, 128.7, 128.5, 127.1, 125.1, 124.1, 121.0, 116.8, 108.9; FT-IR (thin film, neat): 3053, 1677, 1449, 1333 cm^{-1} HRMS (ESI): *m/z* calcd for $C_{23}H_{18}NO$ $[M+H]^+$: 324.1388; found : 324.1400.

(*E*)-1-(5-methyl-1H-indol-1-yl)-2,3-diphenylprop-2-en-1-one (39b)



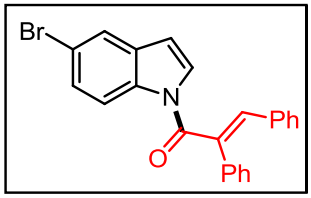
The reaction was performed at 0.23 mmol scale of **38b**; R_f = 0.5 (5% EtOAc in hexane); pale yellow gummy solid (31.6 mg, 41% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.38 (d, J = 8.4 Hz, 1H), 7.46 (d, J = 3.8 Hz, 1H), 7.40 – 7.38 (m, 2H), 7.36 – 7.32 (m, 4H), 7.25 – 7.16 (m, 6H), 7.10 (s, 1H), 6.50 (d, J = 3.7 Hz, 1H), 2.46 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.1, 136.5, 135.9, 135.4, 134.7, 133.7, 131.2, 130.0, 129.3, 129.2, 128.9, 128.6, 128.5, 127.2, 126.4, 124.3, 120.9, 116.4, 108.8, 21.6; FT-IR (thin film, neat): 3064, 1679, 1465, 1330 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{24}H_{20}NO$ $[M+H]^+$: 338.1545; found : 338.1560.

(*E*)-1-(5-chloro-1H-indol-1-yl)-2,3-diphenylprop-2-en-1-one (39c)



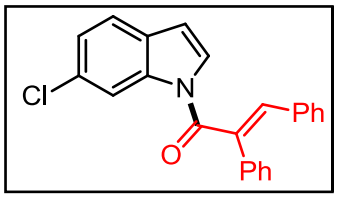
The reaction was performed at 0.197 mmol scale of **38c**; R_f = 0.4 (5% EtOAc in hexane); pale yellow gummy solid (36.8 mg, 52% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.42 (d, J = 8.8 Hz, 1H), 7.52 (dd, J = 9.8, 1.8 Hz, 2H), 7.39 – 7.32 (m, 6H), 7.25 – 7.21 (m, 3H), 7.18 (d, J = 7.1 Hz, 2H), 7.13 (s, 1H), 6.50 (d, J = 3.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.1, 136.7, 136.0, 135.2, 134.43, 134.37, 132.1, 130.0, 129.6, 129.30, 129.26, 129.1, 128.8, 128.6, 128.3, 125.3, 120.6, 117.7, 108.1; FT-IR (thin film, neat): 2919, 1681, 1445, 1328 cm^{-1} $C_{23}H_{17}ClNO$ $[M+H]^+$: 358.0999; found : 358.0983.

(*E*)-1-(5-bromo-1H-indol-1-yl)-2,3-diphenylprop-2-en-1-one (39d)



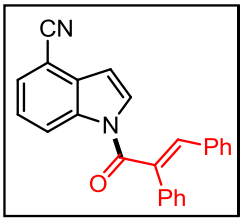
The reaction was performed at 0.153 mmol scale of **38d**; R_f = 0.5 (5% EtOAc in hexane); pale yellow gummy solid (25.9 mg, 42% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.37 (d, J = 8.8 Hz, 1H), 7.70 – 7.69 (m, 1H), 7.49 – 7.46 (m, 2H), 7.39 – 7.33 (m, 5H), 7.26 – 7.23 (m, 3H), 7.21 – 7.17 (m, 2H), 7.13 (s, 1H), 6.49 (d, J = 3.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.1, 136.7, 136.0, 135.2, 134.7, 134.4, 132.6, 130.0, 129.29, 129.26, 129.1, 128.8, 128.6, 128.2, 128.0, 123.6, 118.1, 117.4, 108.0; FT-IR (thin film, neat): 2924, 1687, 1444, 1327, 1194 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{23}H_{17}BrNO$ $[M+H]^+$: 402.0494; found : 402.0507**.**

(*E*)-1-(6-chloro-1H-indol-1-yl)-2,3-diphenylprop-2-en-1-one (39e)



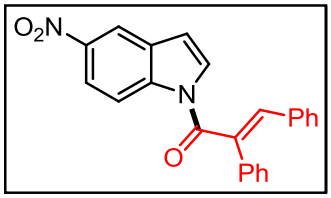
The reaction was performed at 0.197 mmol scale of **38e**; R_f = 0.3 (5% EtOAc in hexane); pale yellow gummy solid (29.0 mg, 41% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.74 (s, 1H), 7.54 – 7.51 (m, 2H), 7.42 – 7.38 (m, 3H), 7.37 – 7.33 (m, 3H), 7.31 – 7.28 (m, 1H), 7.26 – 7.20 (m, 5H), 6.40 (d, J = 3.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.9, 136.6, 135.6, 135.4, 134.7, 131.3, 131.1, 129.6, 129.3, 129.0, 128.97, 128.9, 128.4, 127.1, 126.0, 125.0, 121.6, 117.2, 109.5; FT-IR (thin film, neat): 2924, 1688, 1427, 1329 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{23}H_{17}ClNO$ $[M+H]^+$: 358.0999; found : 358.0982**.**

(*E*)-1-(2,3-diphenylacryloyl)-1H-indole-4-carbonitrile (39f)



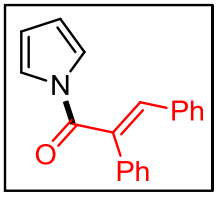
The reaction was performed at 0.211 mmol scale of **38f**; R_f = 0.2 (10% EtOAc in hexane); colorless gummy solid (29.4 mg, 40% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.72 (d, J = 8.4 Hz, 1H), 7.64 – 7.62 (m, 2H), 7.53 – 7.38 (m, 3H), 7.36 (s, 3H), 7.31 – 7.27 (m, 1H), 7.24 – 7.17 (m, 5H), 6.77 (d, J = 3.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.2, 137.8, 135.9, 135.6, 135.0, 134.2, 132.7, 130.2, 129.6, 129.4, 129.3, 129.0, 128.6, 128.5, 126.1, 125.1, 121.3, 117.8, 106.8, 103.9; FT-IR (thin film, neat): 2998, 2227, 1689, 1424, 1380 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{24}H_{15}N_2O$ $[M–H]^-$: 347.1184; found : 347.1168**.**

(*E*)-1-(5-nitro-1H-indol-1-yl)-2,3-diphenylprop-2-en-1-one (39g)



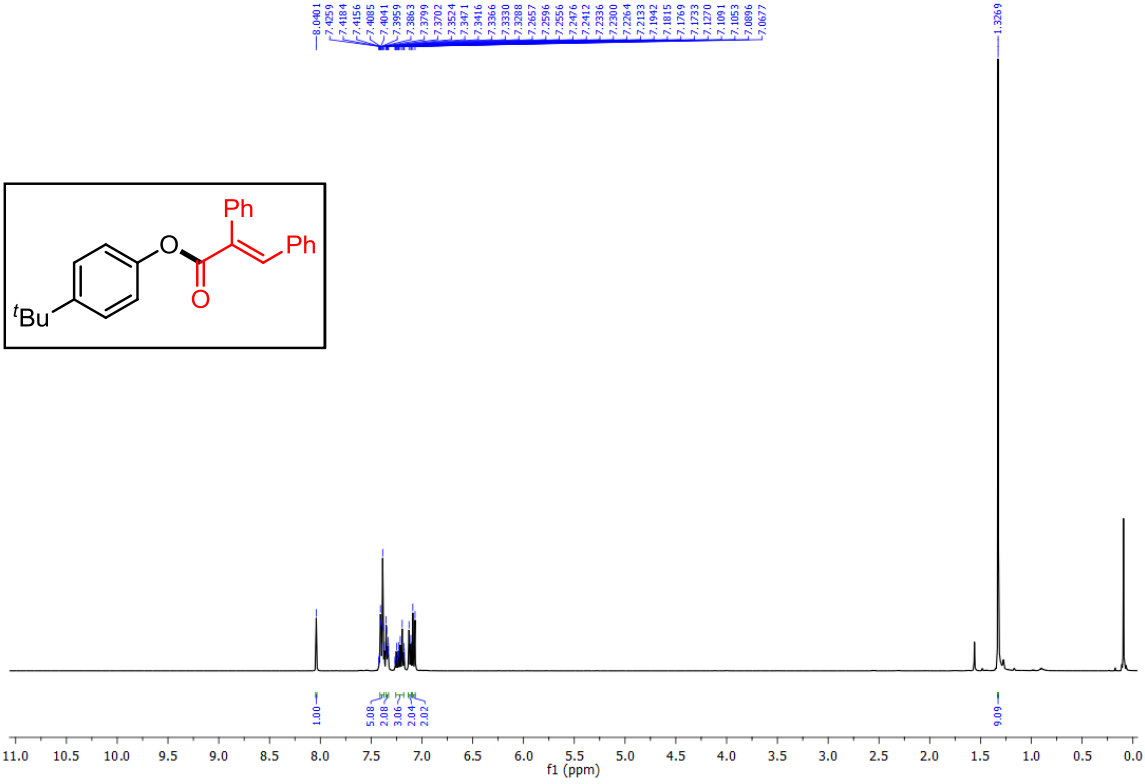
The reaction was performed at 0.185 mmol scale of **38g**; R_f = 0.2 (5% EtOAc in hexane); pale yellow gummy solid (27.3 mg, 40% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.59 (d, J = 9.2 Hz, 1H), 8.48 (d, J = 2.2 Hz, 1H), 8.26 (dd, J = 9.2, 2.3 Hz, 1H), 7.62 (d, J = 3.8 Hz, 1H), 7.55 – 7.52 (m, 1H), 7.41 (d, J = 7.5 Hz, 1H), 7.37 (s, 3H), 7.33 (s, 1H), 7.24 – 7.19 (m, 5H), 6.68 (d, J = 3.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.1, 144.5, 138.1, 135.5, 134.9, 134.1, 132.0, 130.7, 130.2, 129.9, 129.4, 129.3, 129.0, 128.6, 128.3, 126.1, 120.3, 117.2, 109.0; FT-IR (thin film, neat): 3059, 1695, 1522, 1446, 1309, 1188 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{23}H_{17}N_2O_3$ $[M+Na]^+$: 369.1239; found : 369.1227.

(*E*)-2,3-diphenyl-1-(1H-pyrrol-1-yl)prop-2-en-1-one (39h)

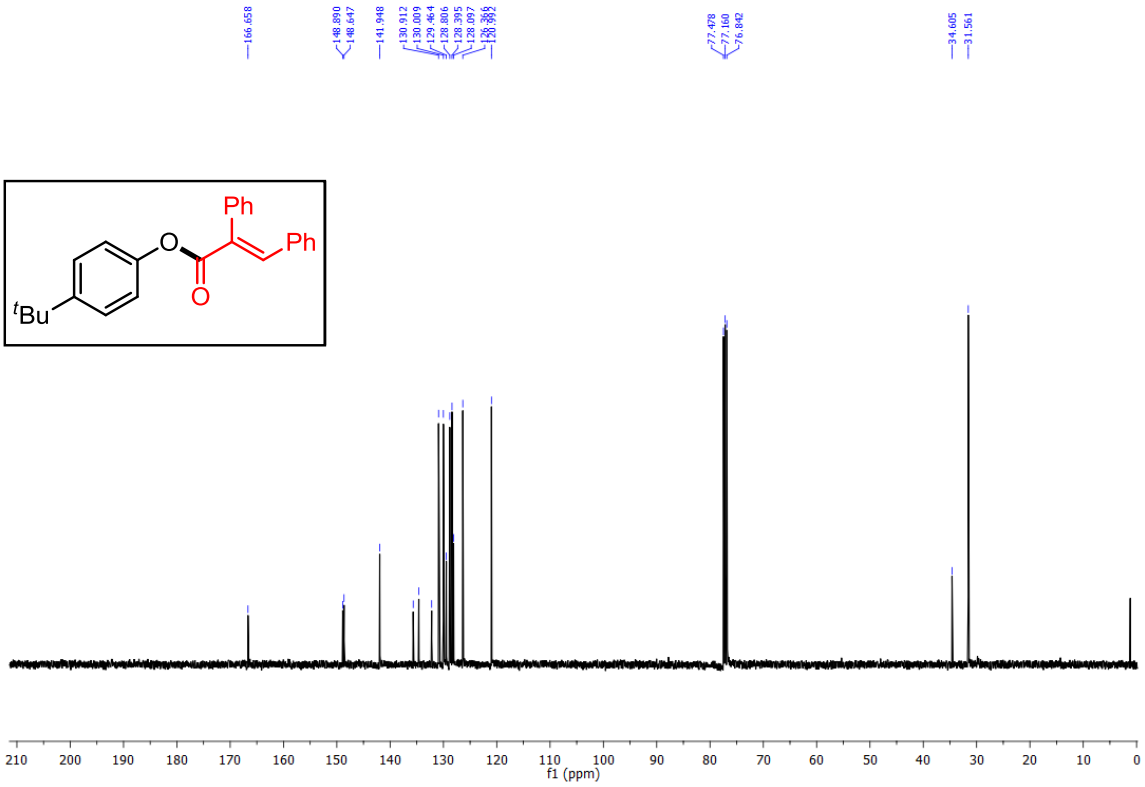


The reaction was performed at 0.298 mmol scale of **38h**; R_f = 0.5 (5% EtOAc in hexane); pale yellow gummy solid (26.9 mg, 33% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (s, 1H), 7.34 – 7.30 (m, 6H), 7.22 – 7.20 (m, 2H), 7.18 – 7.15 (m, 2H), 7.11 – 7.10 (m, 1H), 7.04 – 7.02 (m, 2H), 6.24 (t, J = 2.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.0, 141.9, 135.5, 134.4, 130.7, 129.9, 129.7, 129.3, 129.2, 128.6, 128.3, 128.2, 127.9, 120.8, 113.1; FT-IR (thin film, neat): 1674, 1426, 1276 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{19}H_{16}NO$ $[M+H]^+$: 274.1232; found : 274.1220.

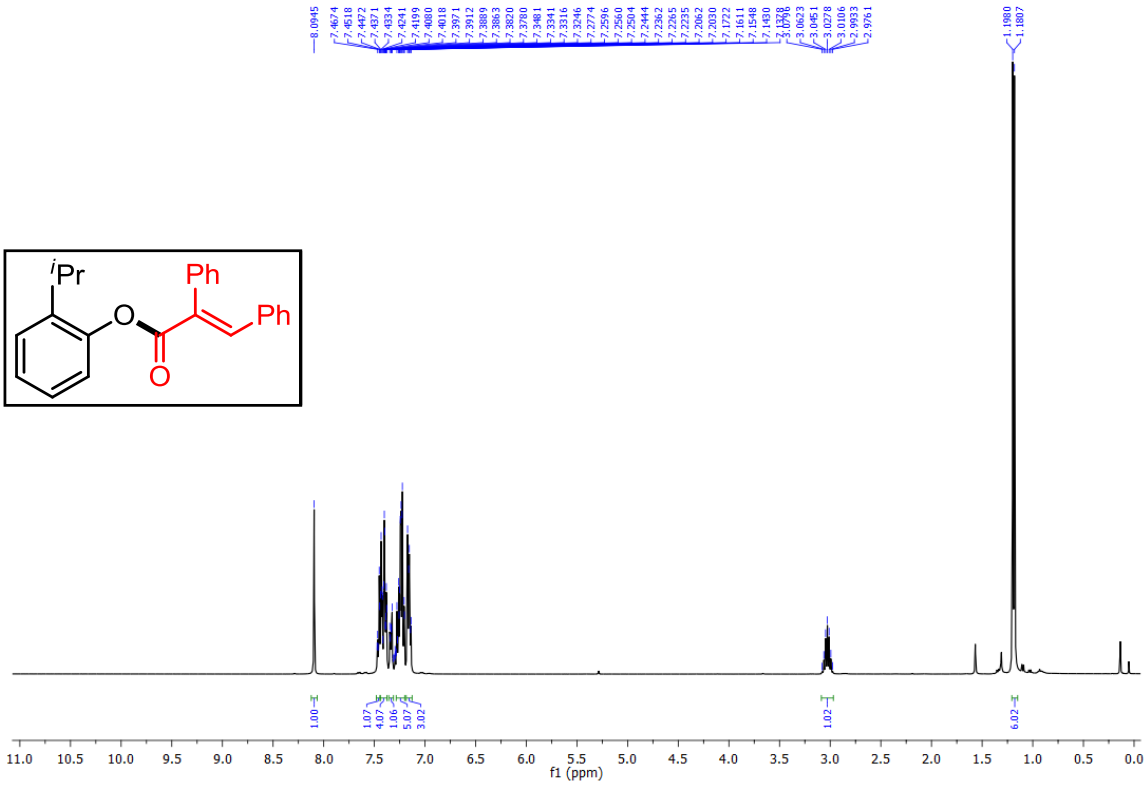
^{1}H NMR spectrum of **35a**



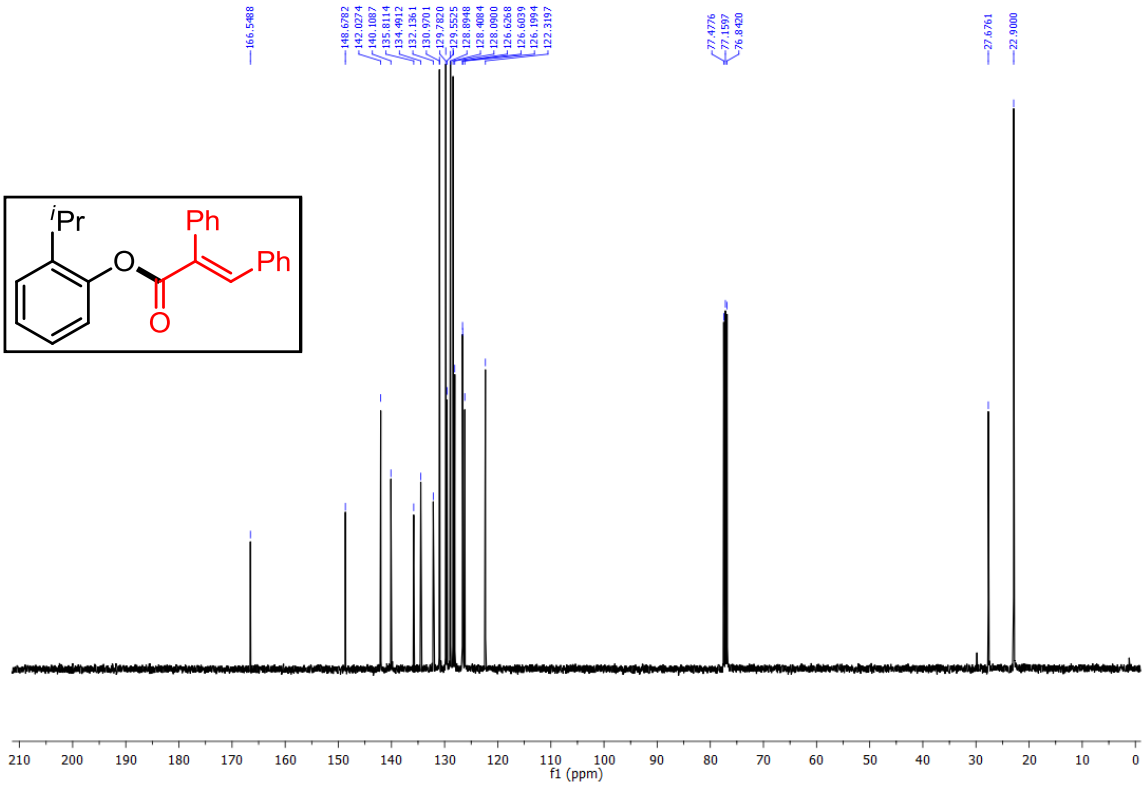
^{13}C NMR spectrum of **35a**



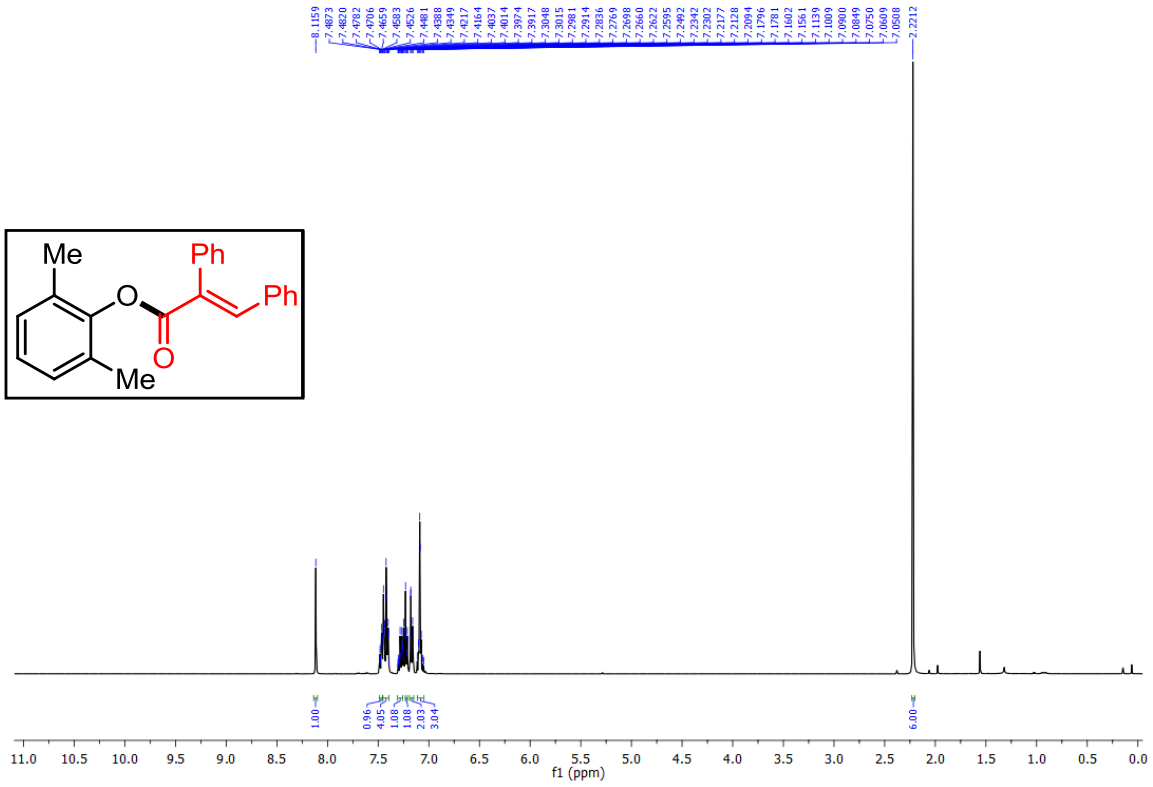
^{1}H NMR spectrum of **35d**



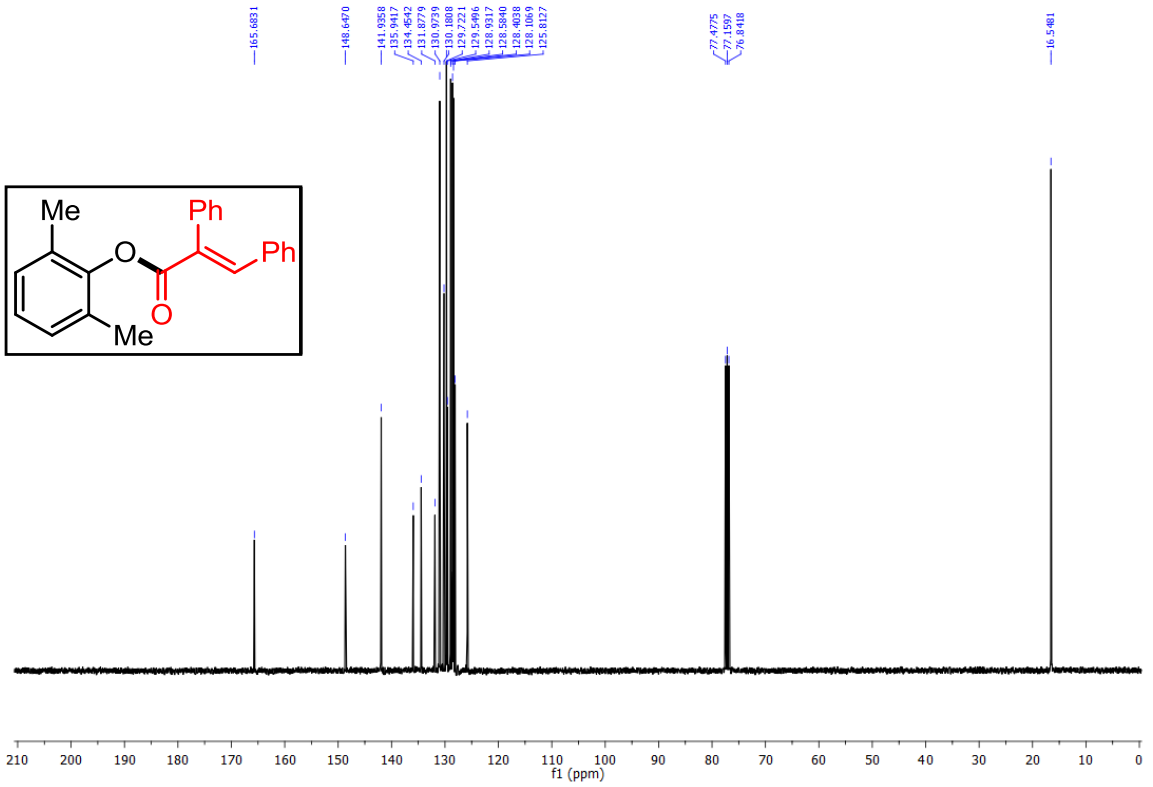
^{13}C NMR spectrum of **35d**



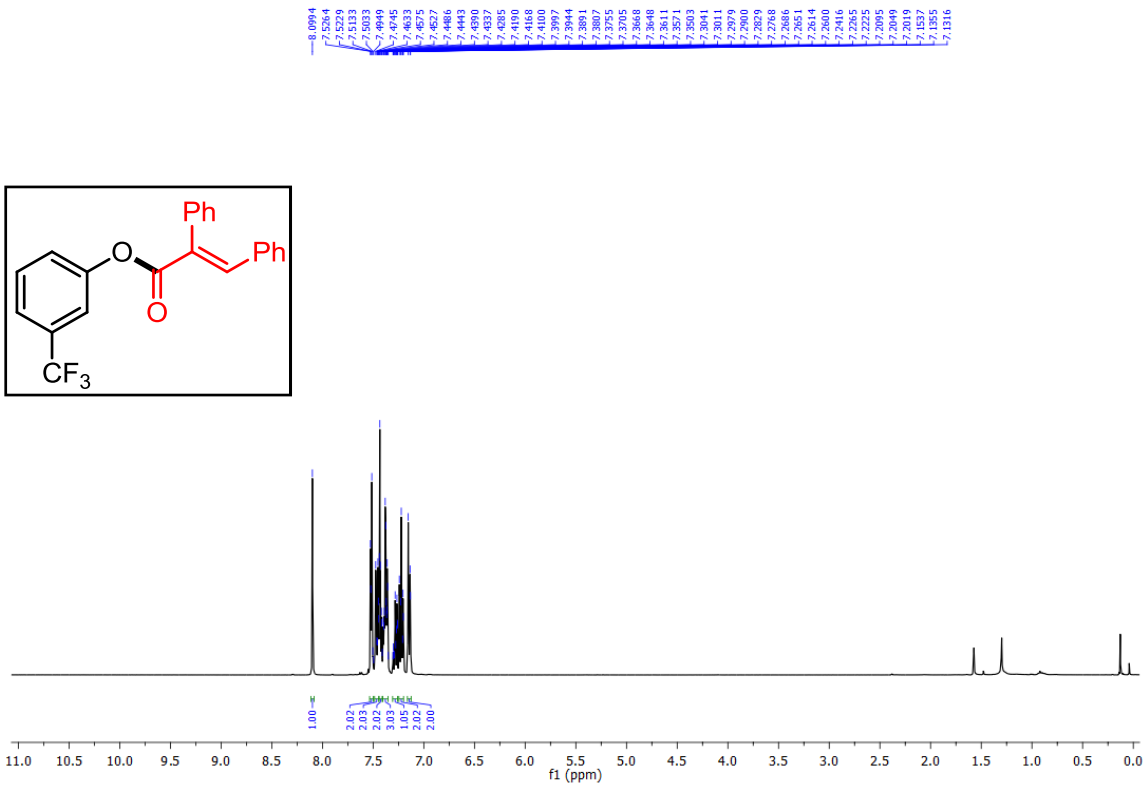
^{1}H NMR spectrum of **35i**



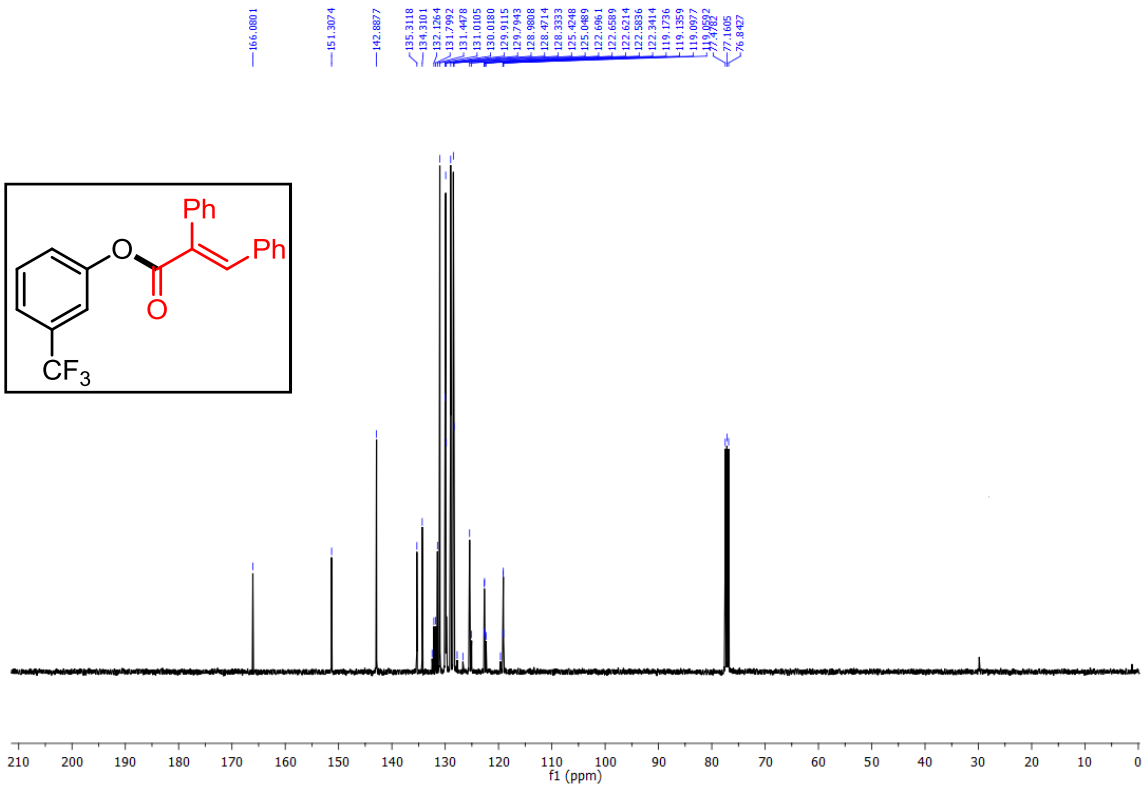
^{13}C NMR spectrum of **35i**



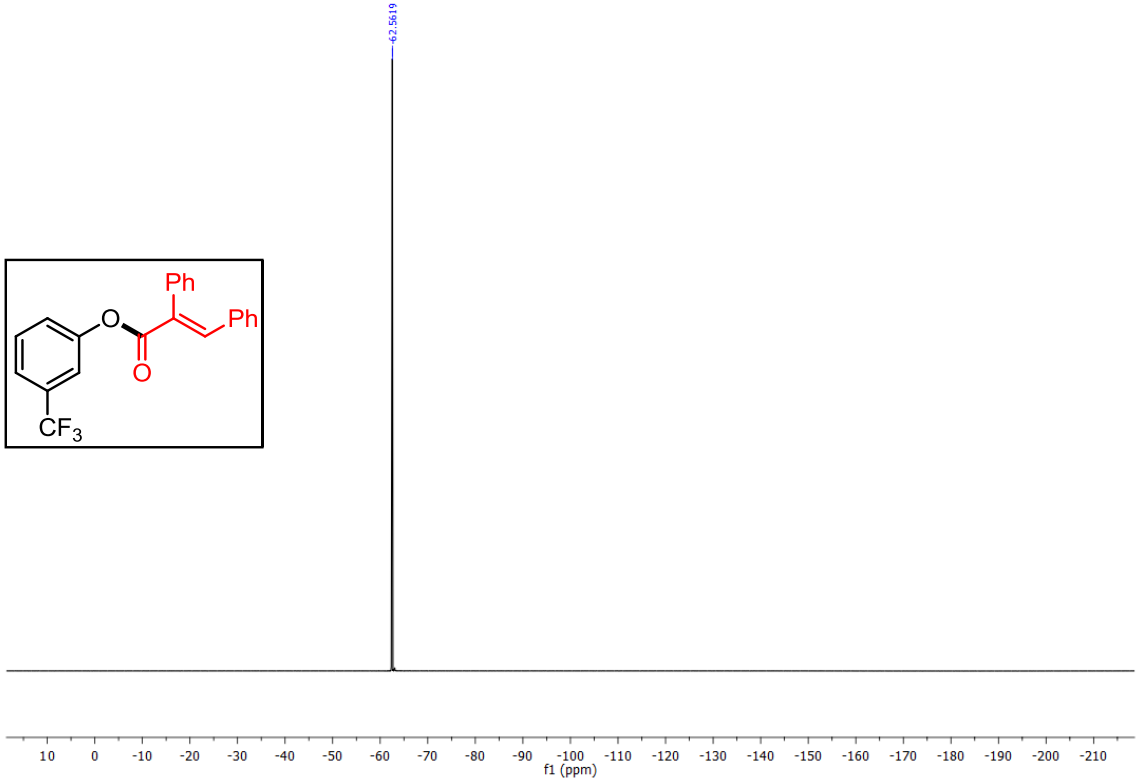
^{1}H NMR spectrum of **35n**



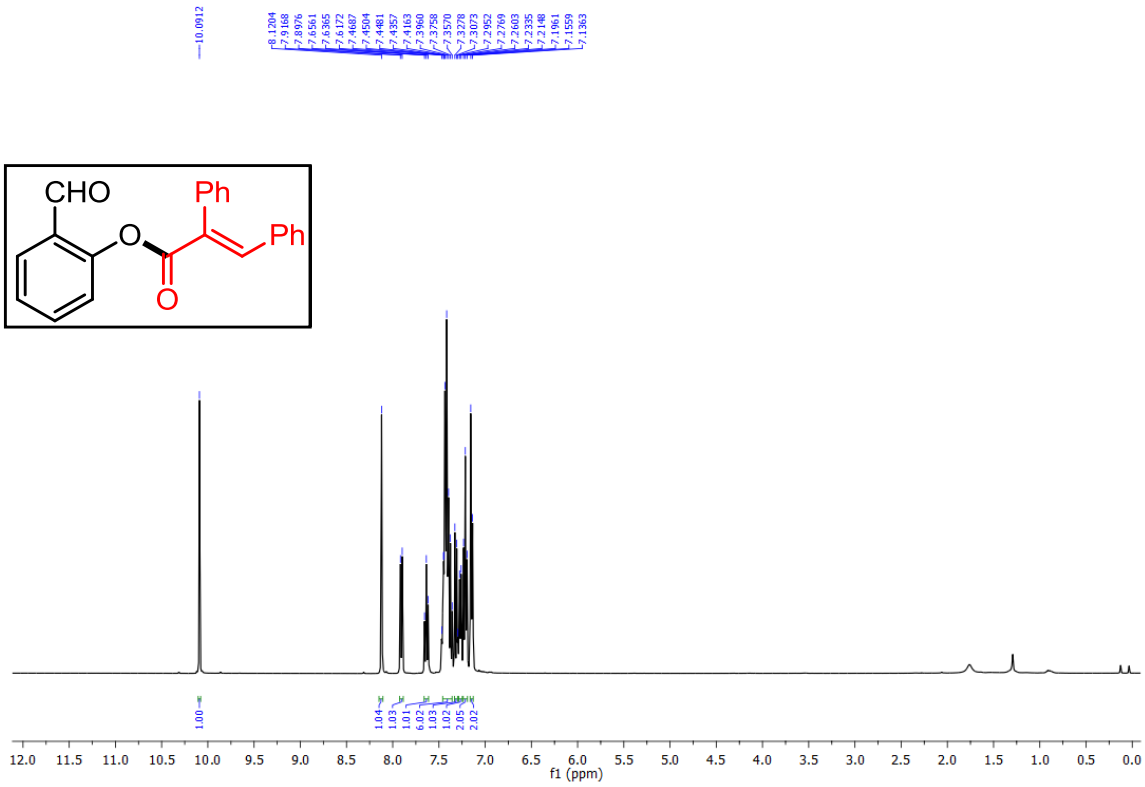
^{13}C NMR spectrum of **35n**



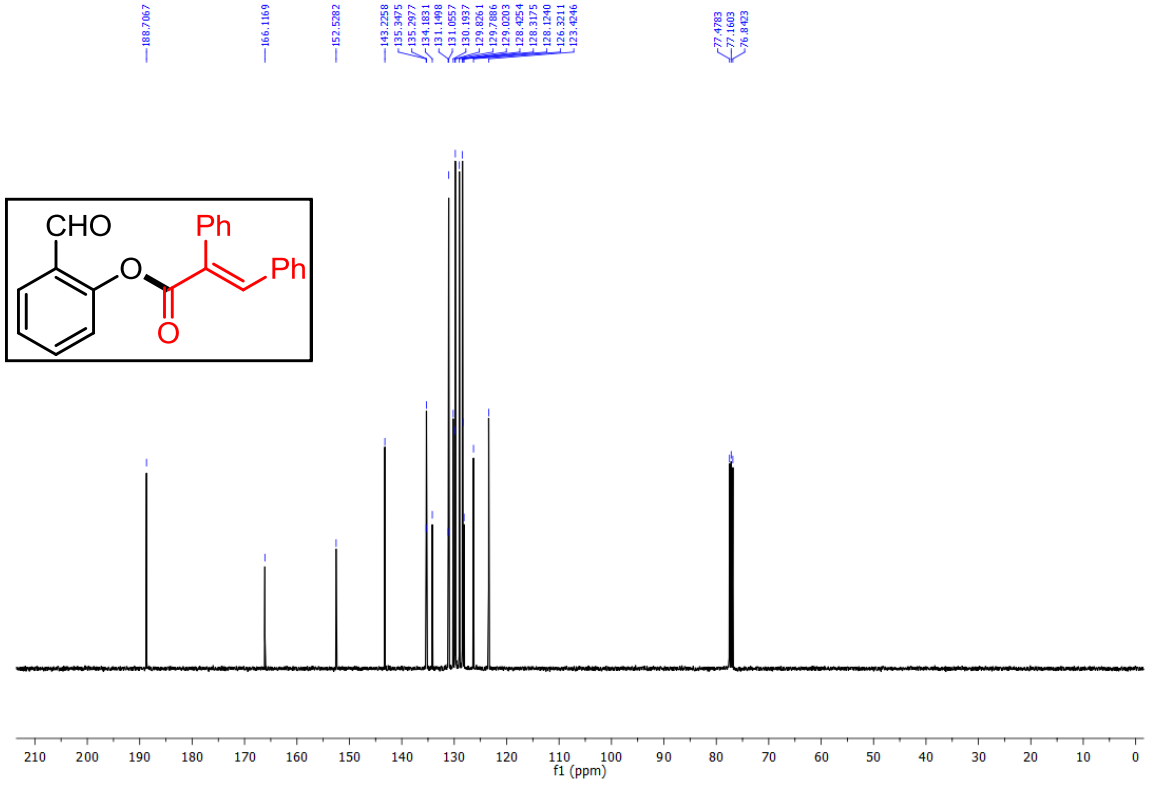
^{19}F NMR spectrum of **35n**



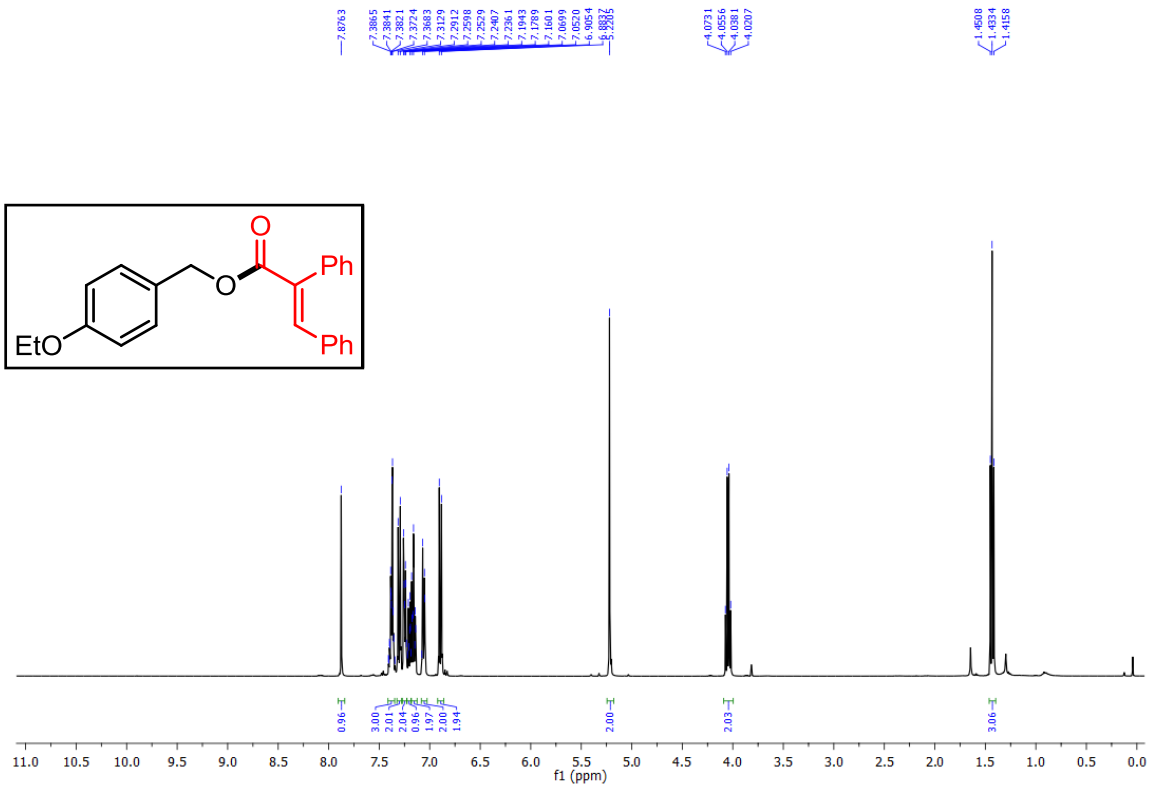
^{1}H NMR spectrum of **35p**



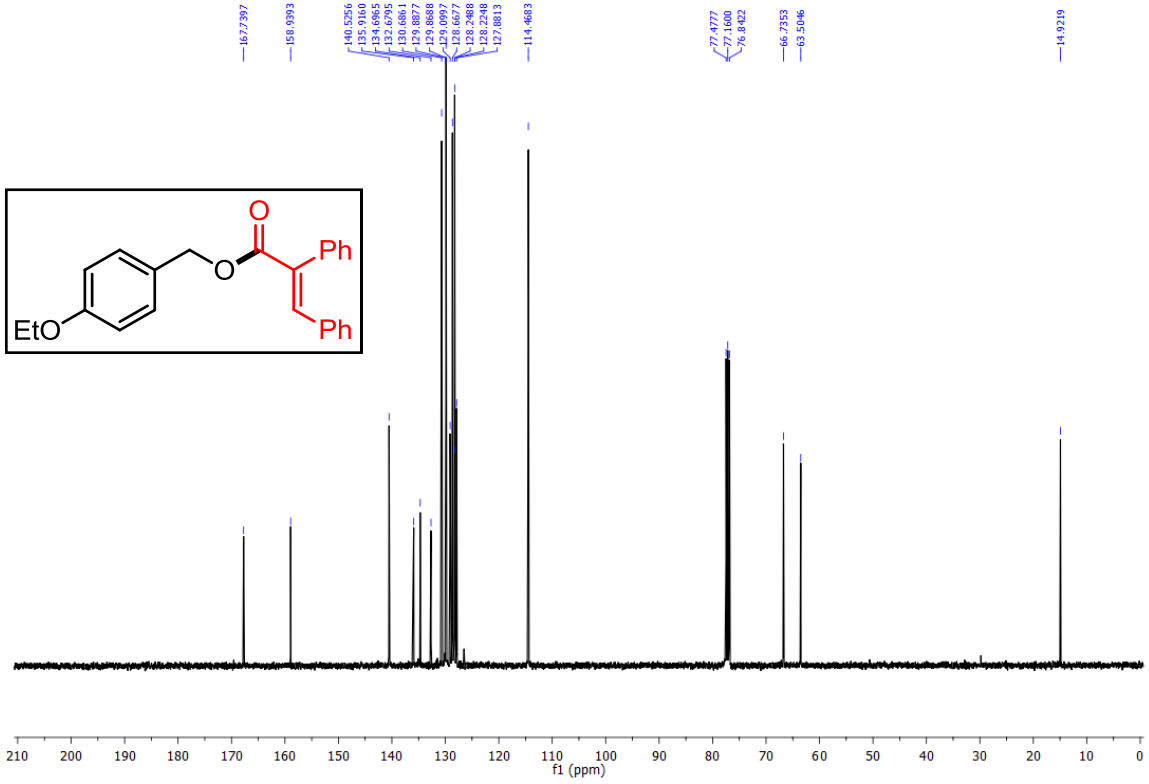
^{13}C NMR spectrum of **35p**



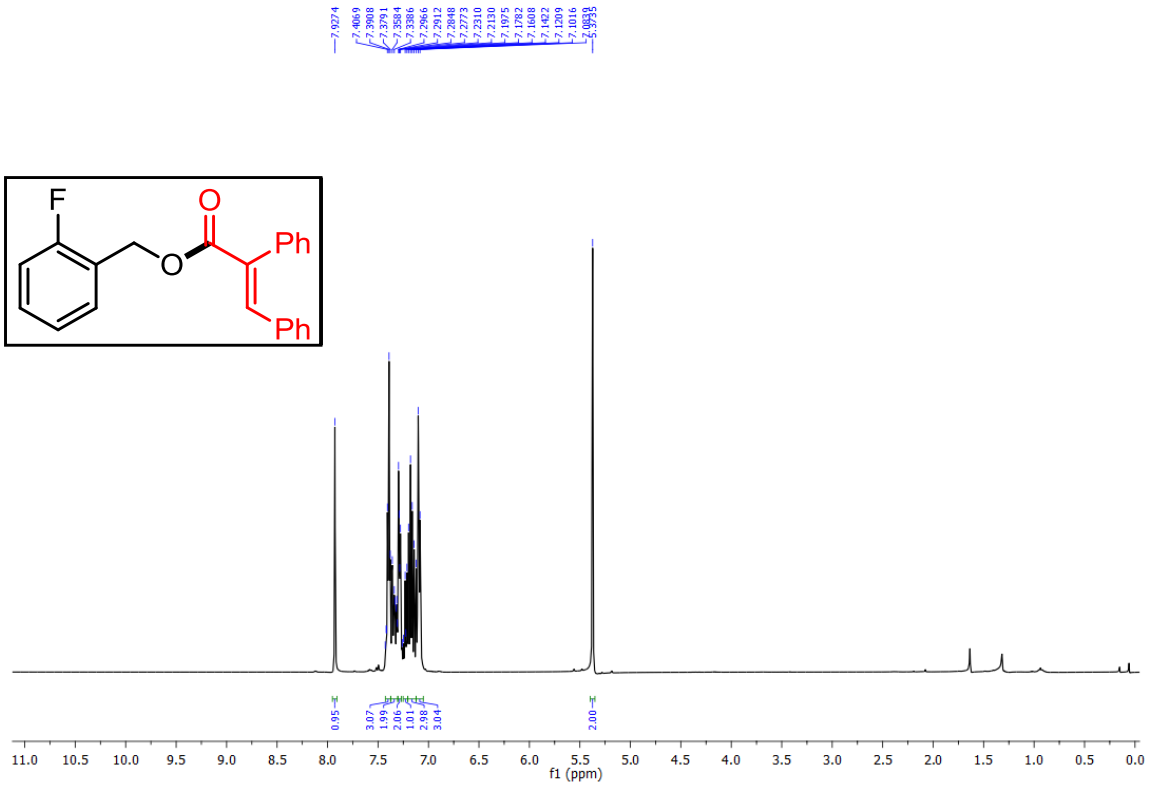
^{1}H NMR spectrum of **37d**



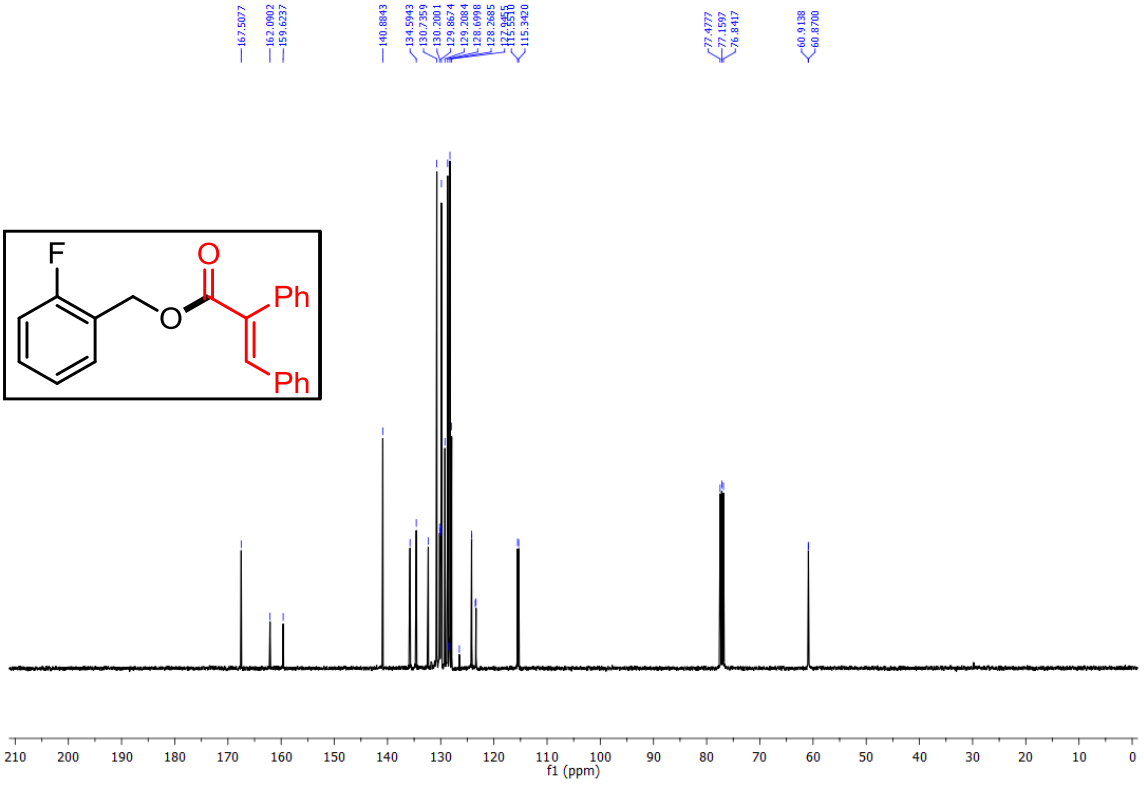
^{13}C NMR spectrum of **37d**



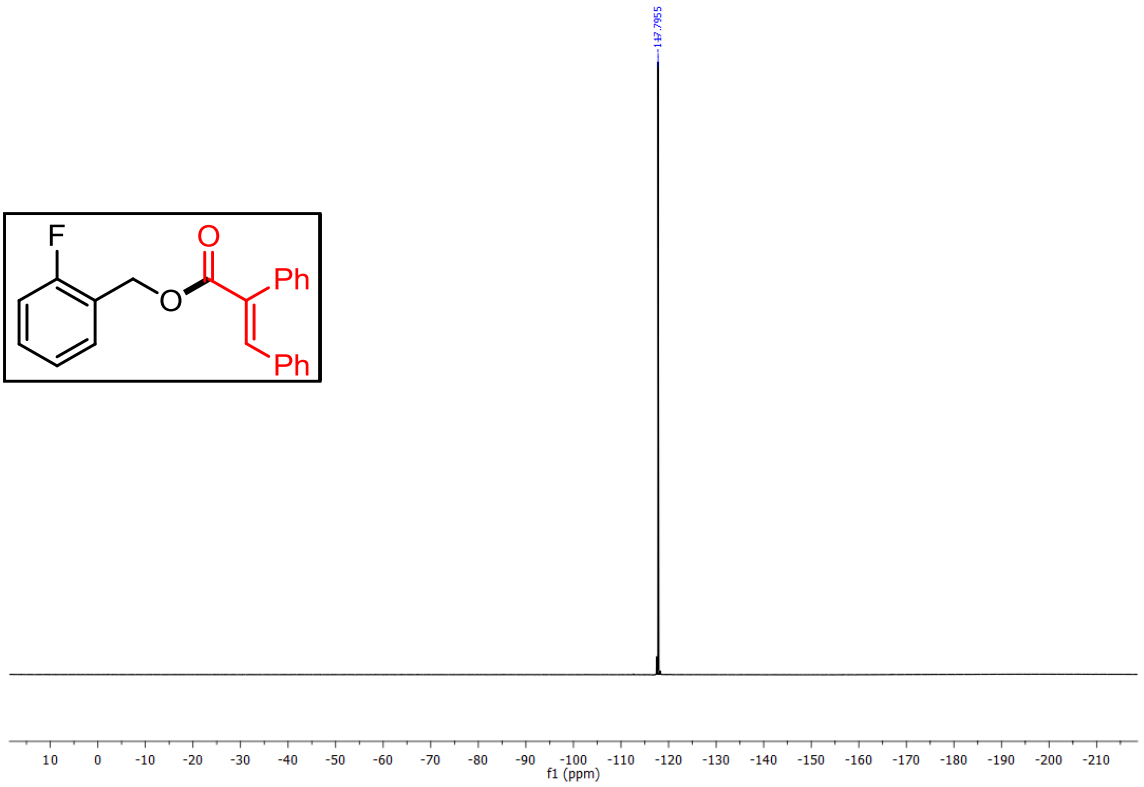
^{1}H NMR spectrum of **37h**



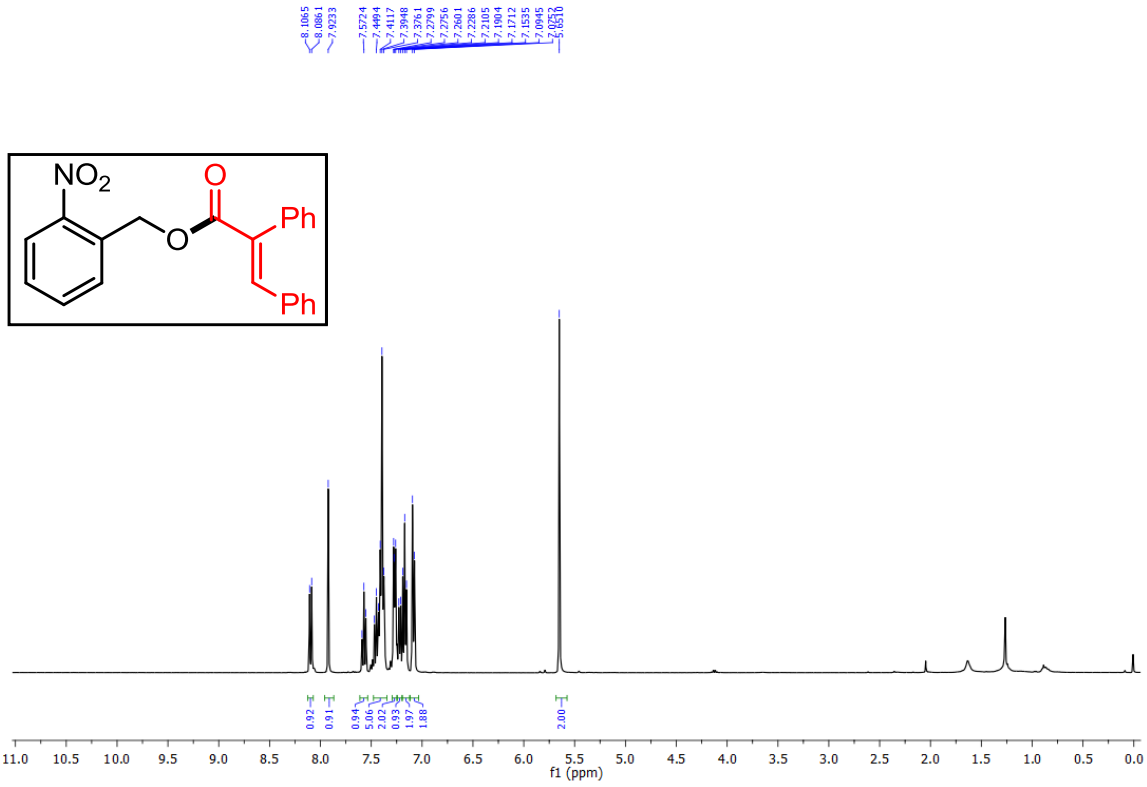
^{13}C NMR spectrum of **37h**



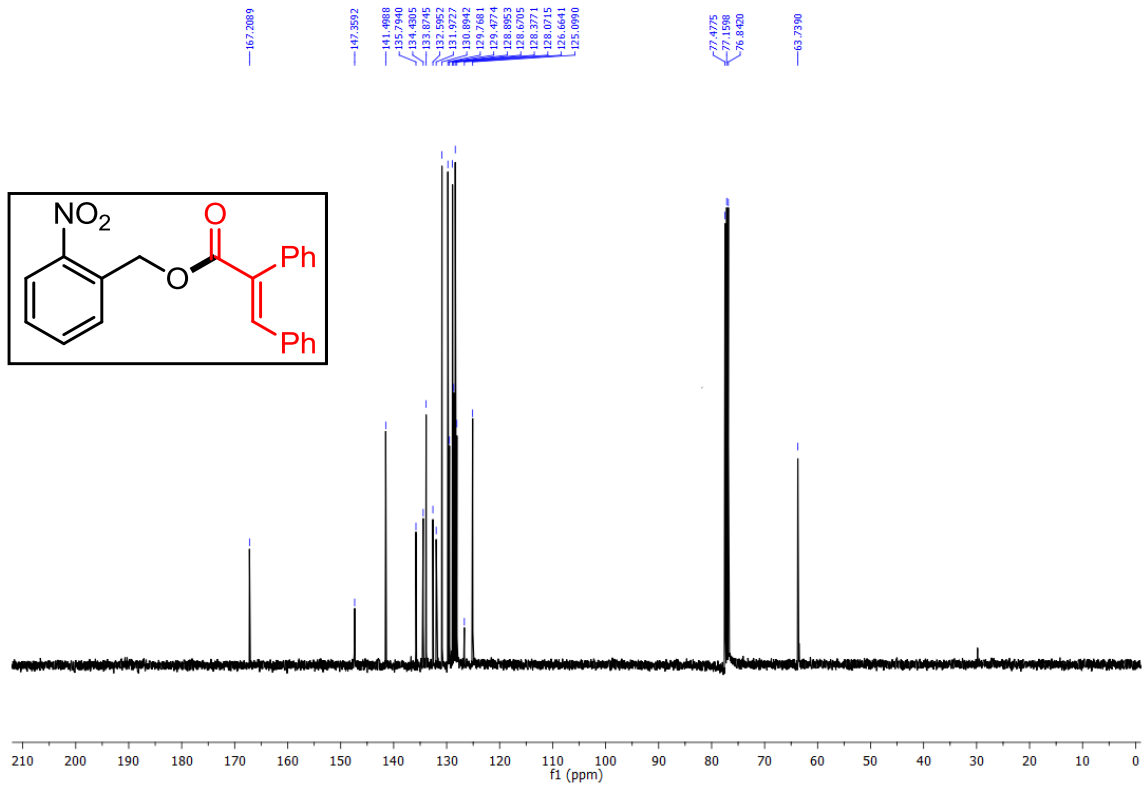
^{19}F NMR spectrum of **37h**



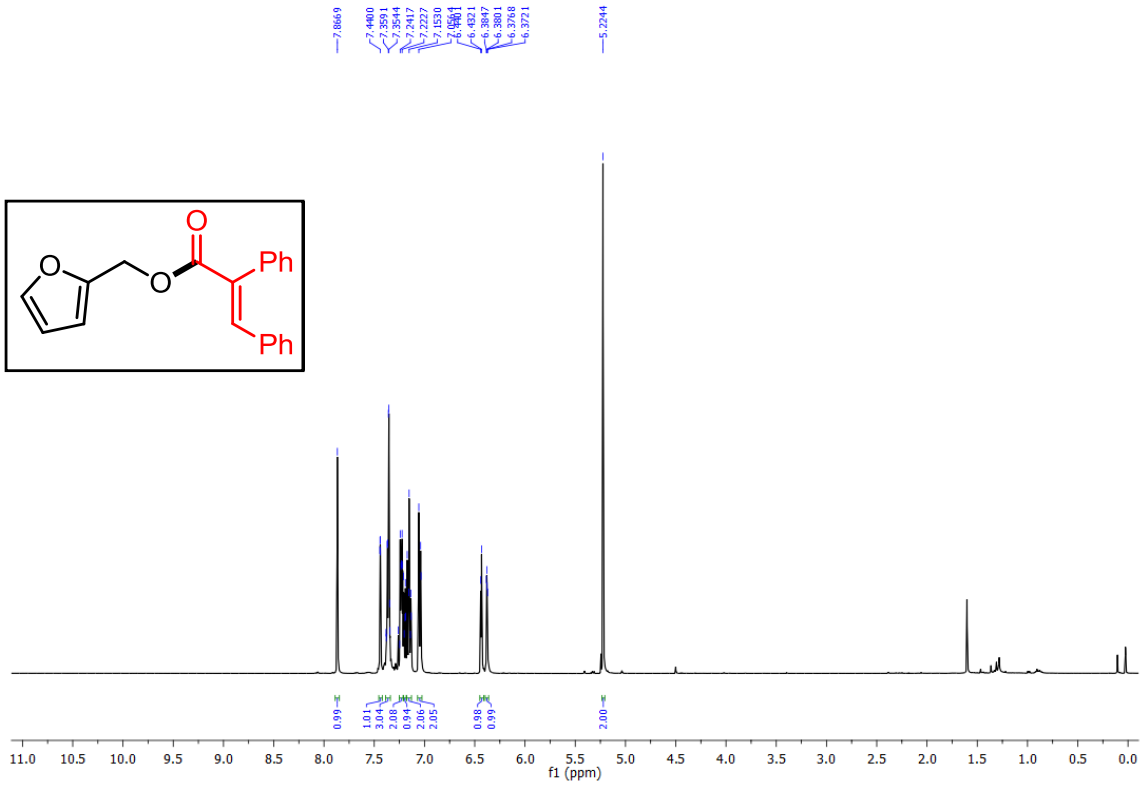
^{1}H NMR spectrum of **37j**



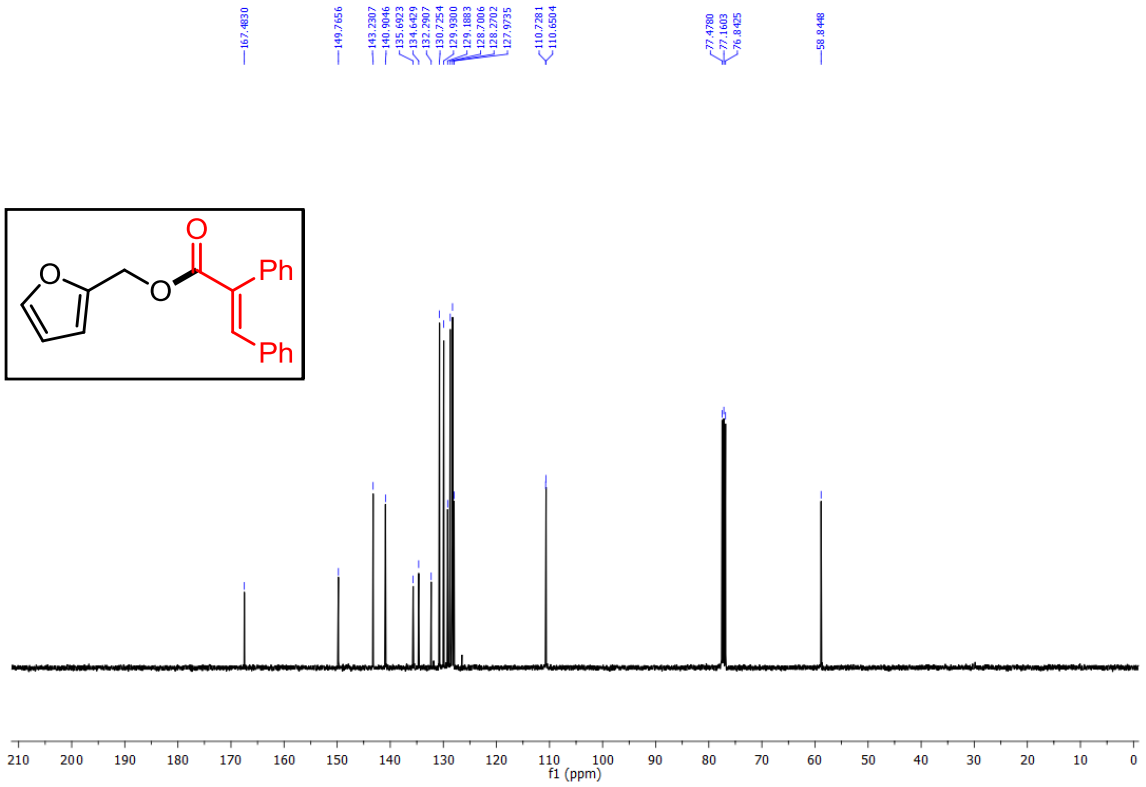
^{13}C NMR spectrum of **37j**



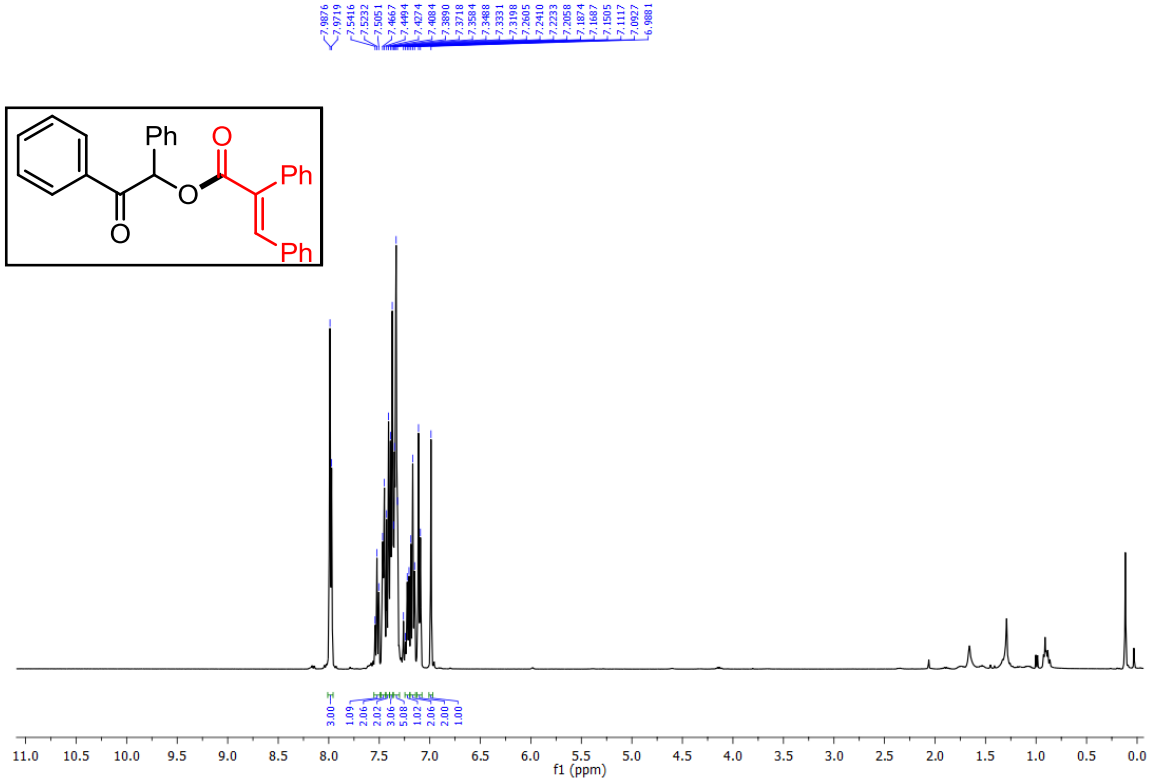
^{1}H NMR spectrum of **37n**



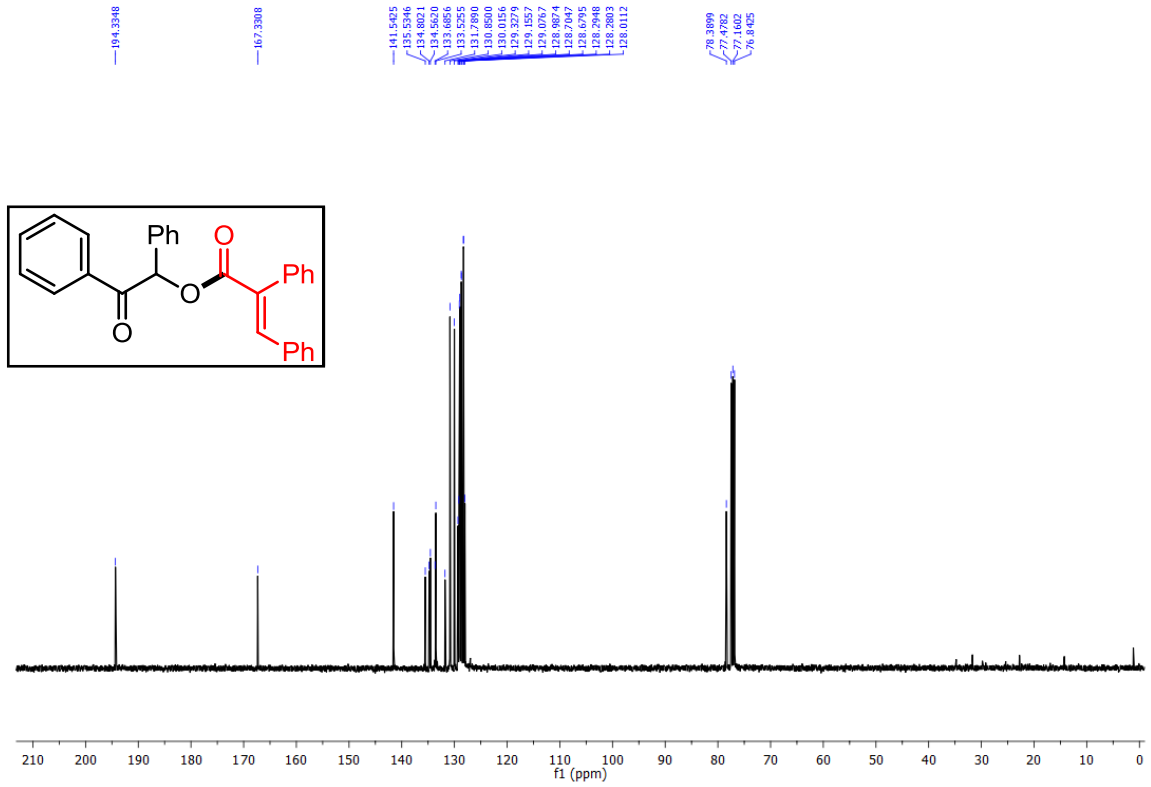
^{13}C NMR spectrum of **37n**



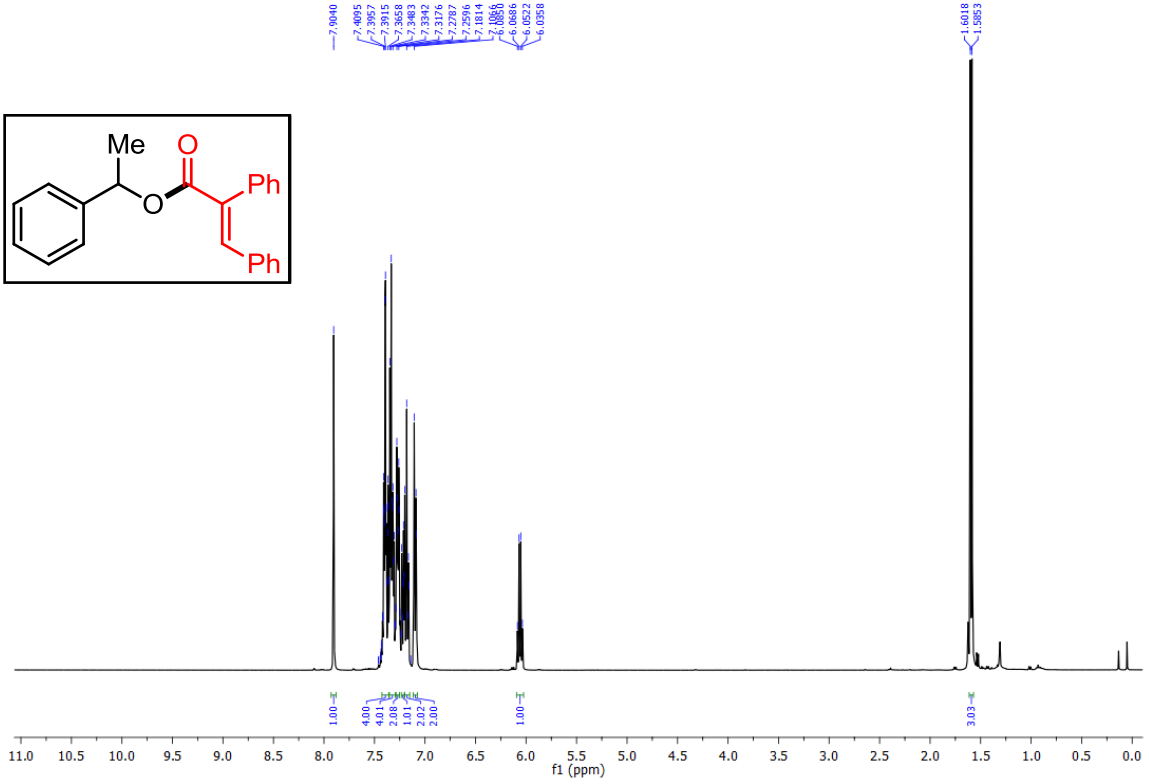
^{1}H NMR spectrum of **37o**



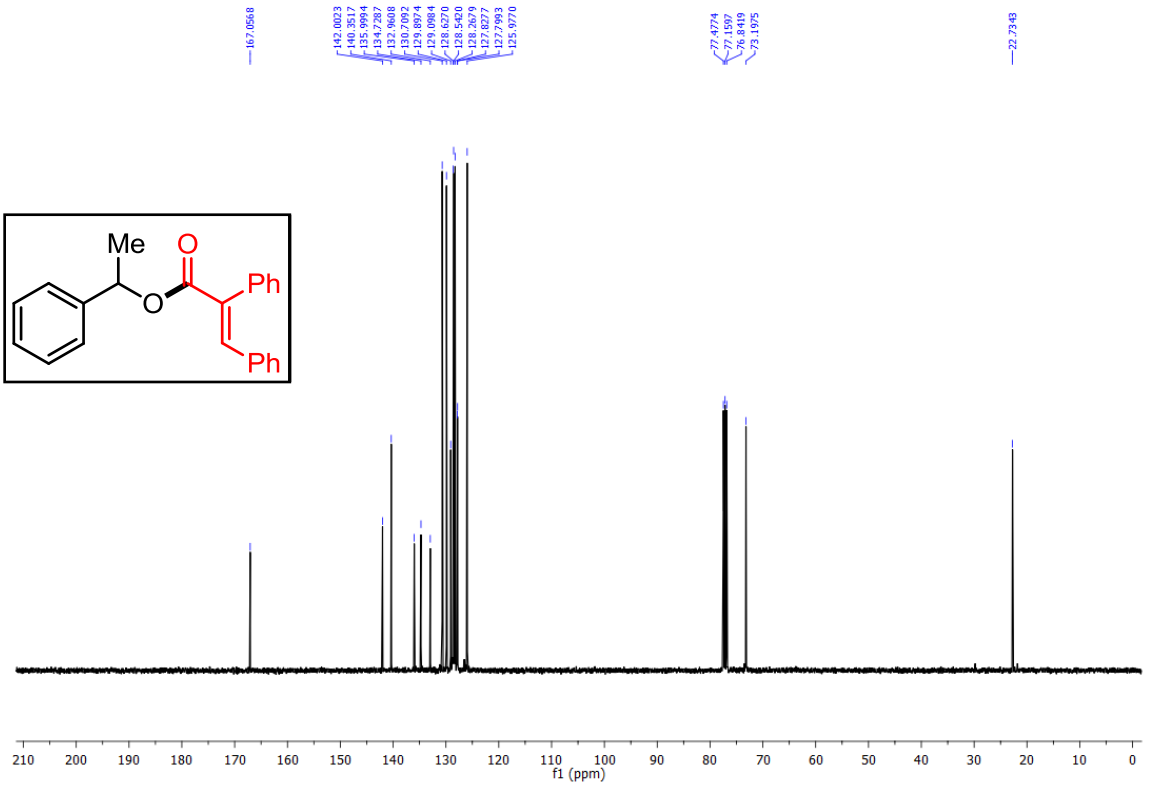
^{13}C NMR spectrum of **37o**



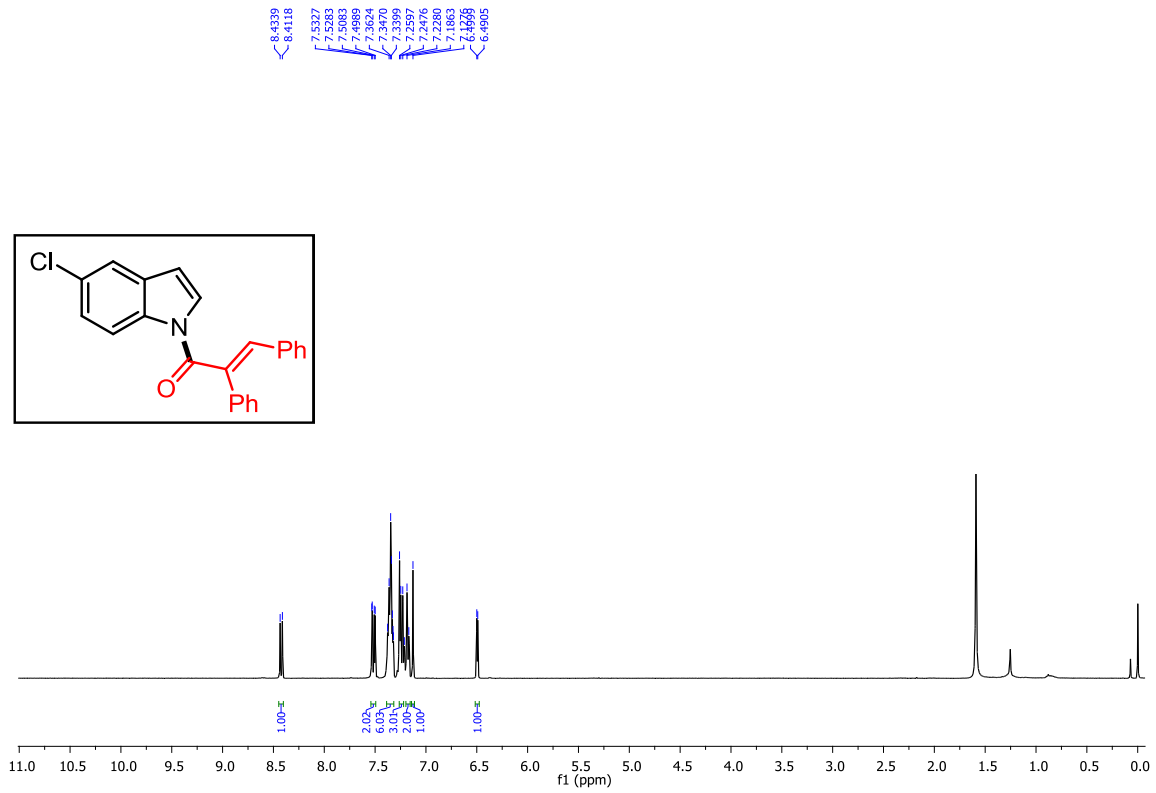
^{1}H NMR spectrum of **37p**



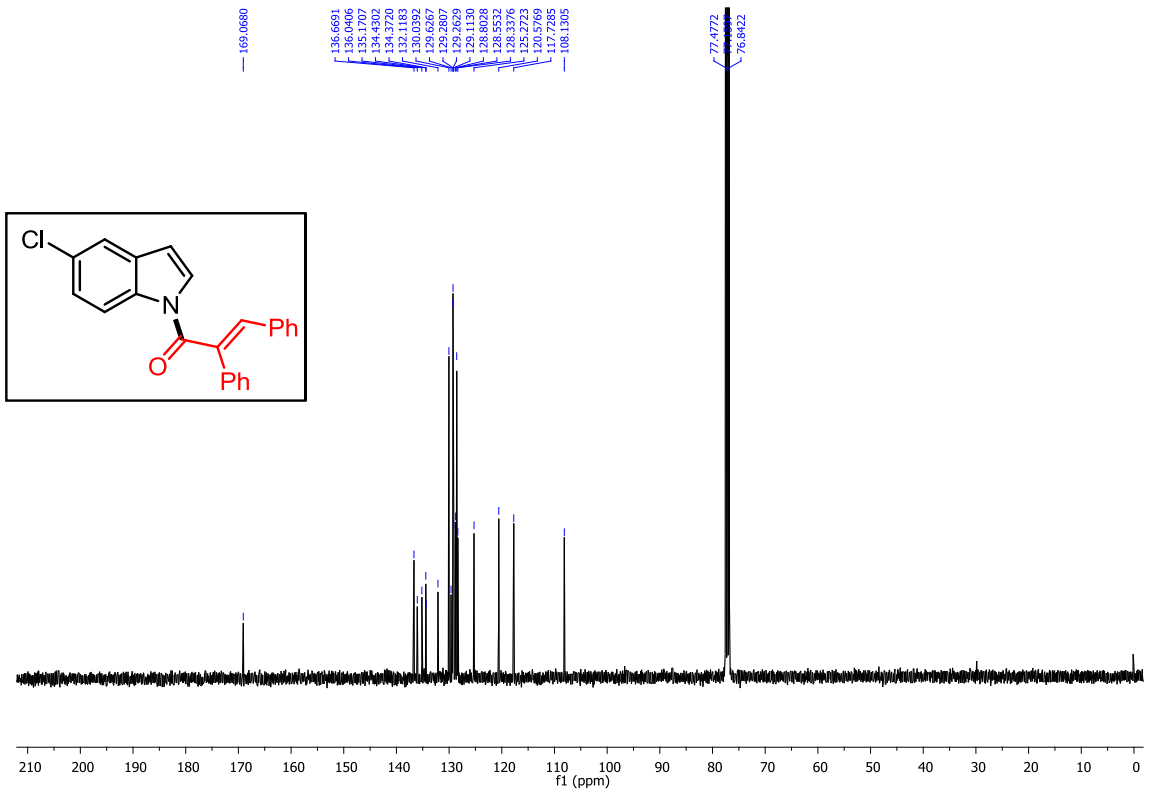
^{13}C NMR spectrum of **37p**



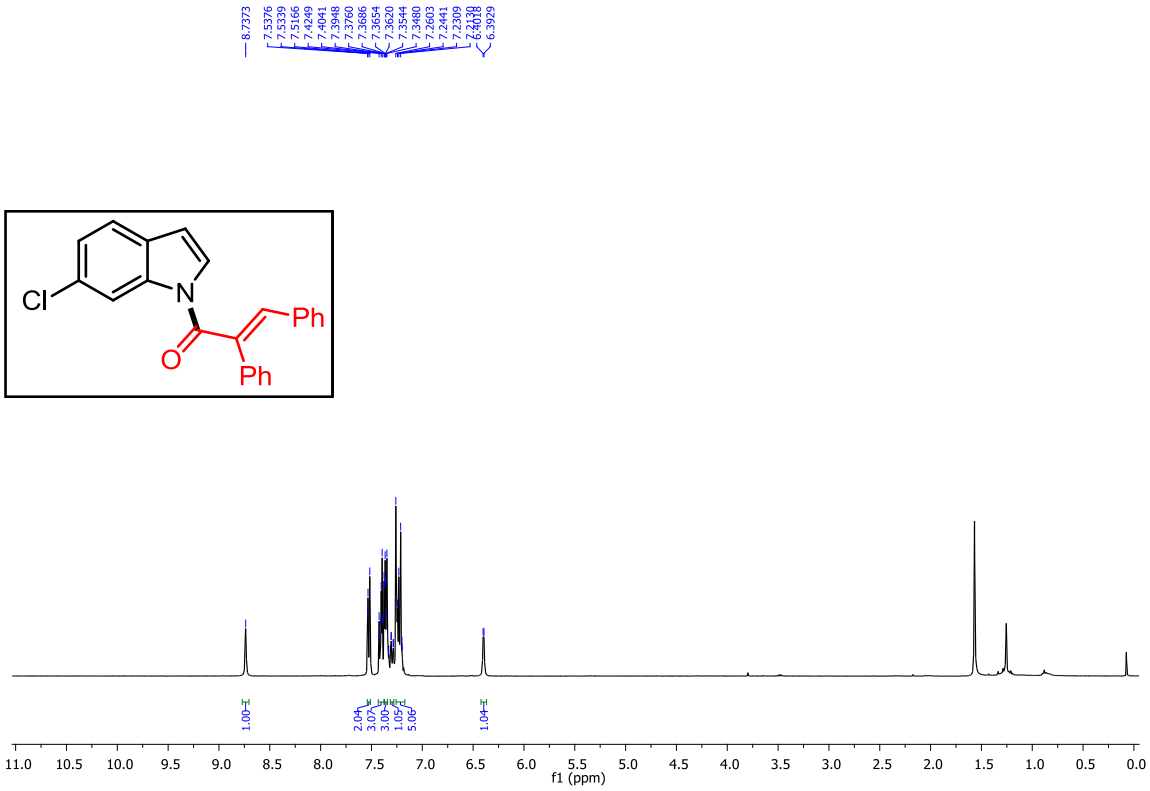
^{1}H NMR spectrum of **39c**



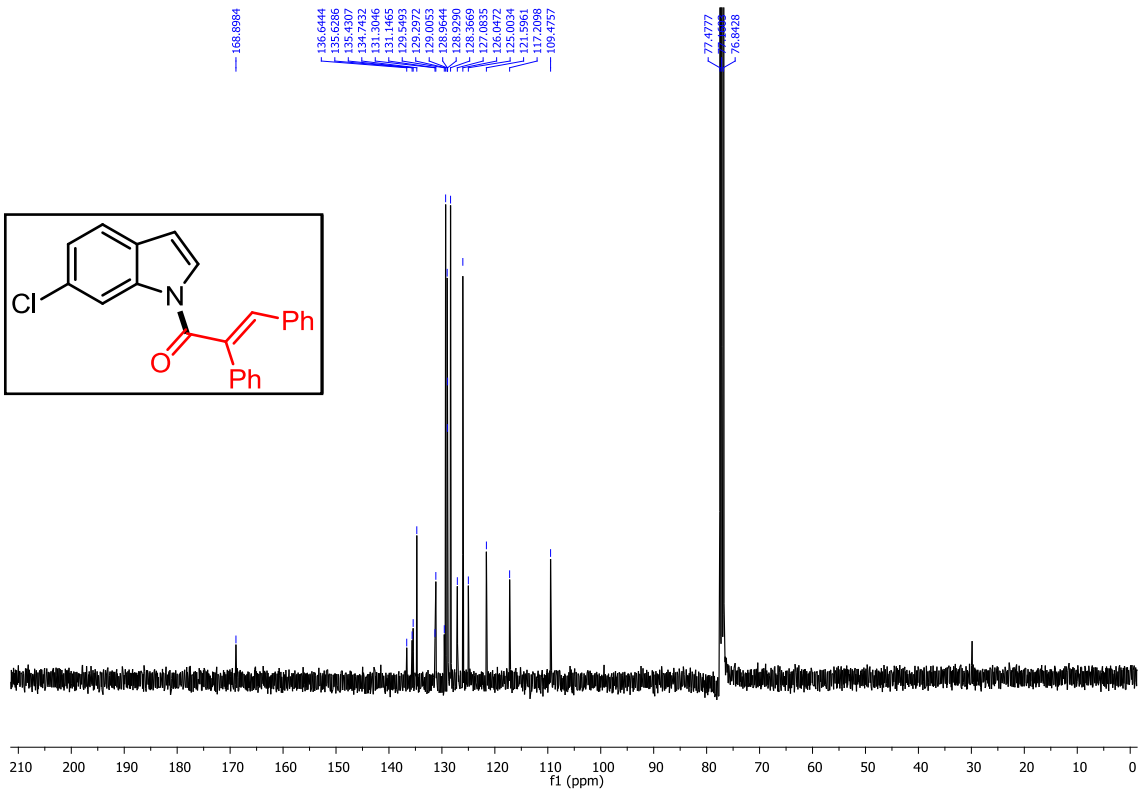
^{13}C NMR spectrum of **39c**



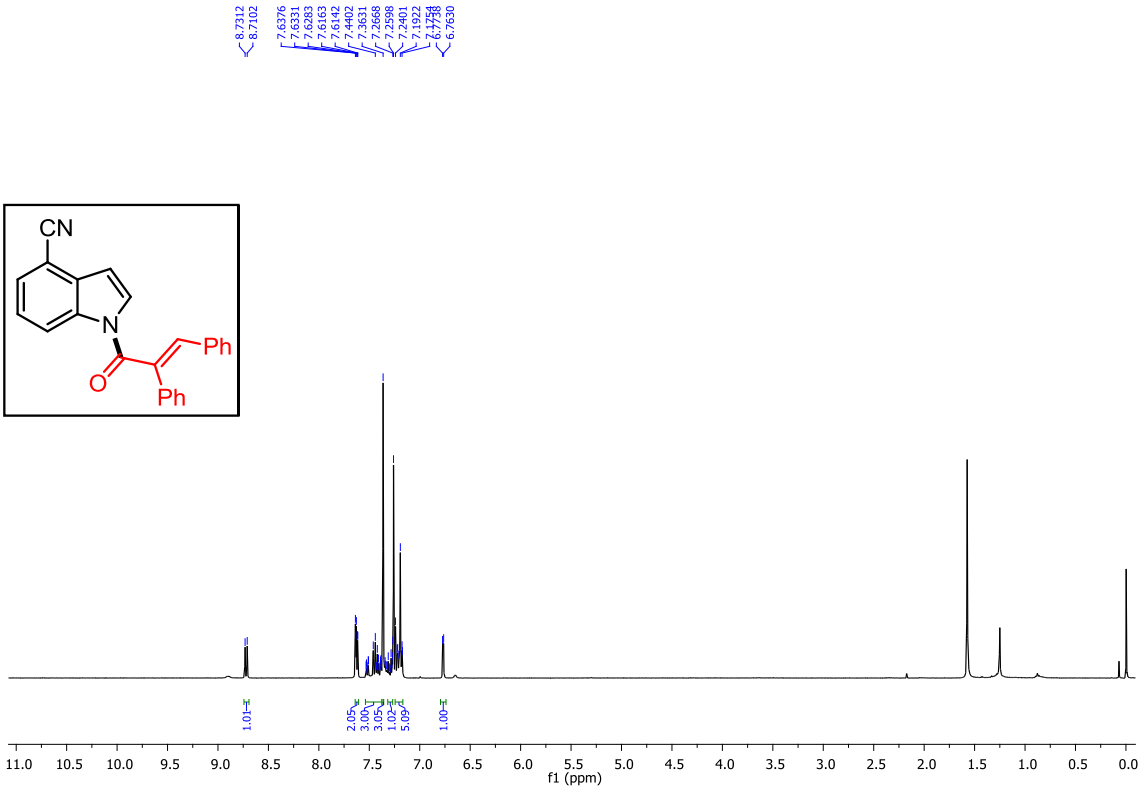
^{1}H NMR spectrum of **39e**



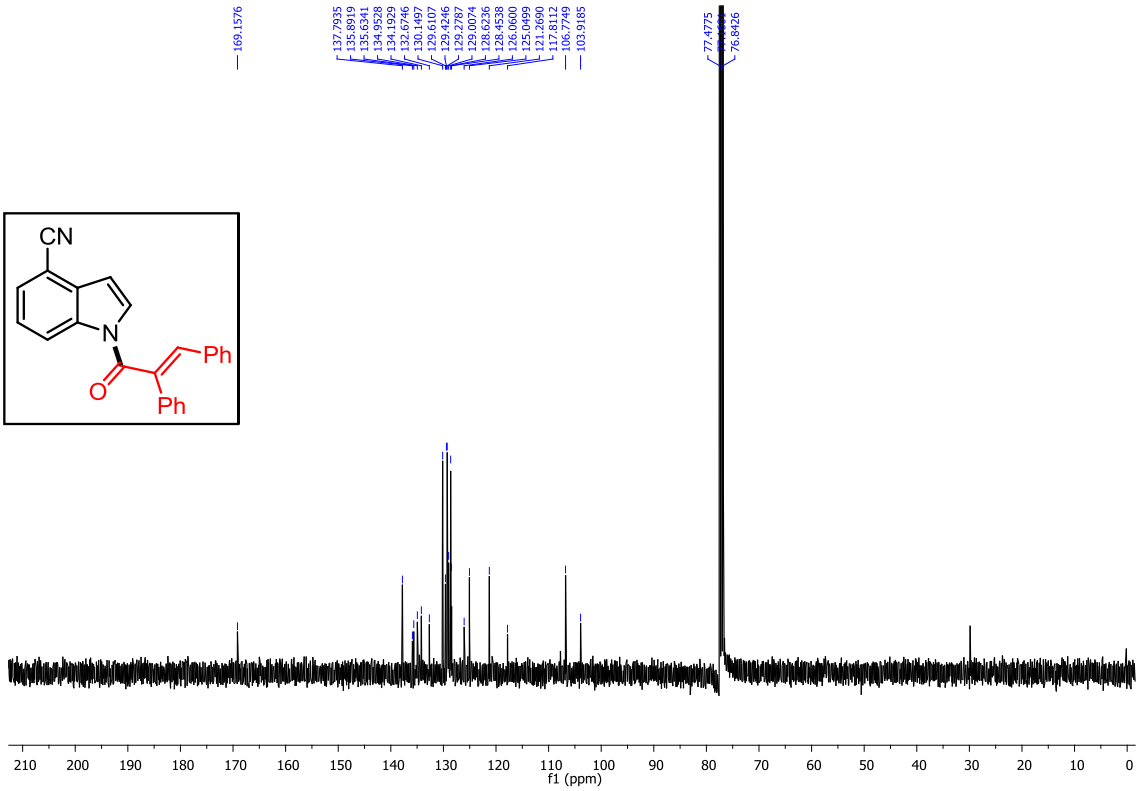
^{13}C NMR spectrum of **39e**



^{1}H NMR spectrum of **39f**



^{13}C NMR spectrum of **39f**



4.7 References

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List of Publications

1. "*N-Heterocyclic carbene catalyzed 1,6-conjugate addition of Me_3Si-CN to para-quinone methides and fuchsones: Access to α-arylated nitriles*"
   Goswami, P.; Singh, G.; Anand, R. V. *Org. Lett.* **2017**, *19*, 1982.

2. "*Bis(amino)cyclopropenylidene catalyzed Rauhut-Currier reaction between α,β-unsaturated carbonyl compounds and para-quinone methides*"
   Goswami, P.; Sharma, S.; Singh, G.; Anand, R. V. *J. Org. Chem.* **2018**, *83*, 4213.

3. "*$Bi(OTf)_3$ catalyzed solvent free approach to unsymmetrical diaryl(2-indolyl)methanes through 1,6-conjugate addition of 3-substituted indoles to para-quinone methides*"
   Goswami, P.; Anand, R. V. *Chemistry Select* **2016**, *1*, 2556.

4. "*A One-pot approach to 2,3-diarylbenzo[b]furans through N-heterocyclic carbene catalyzed 1,6-conjugate addition followed by acid mediated dehydrative cyclization*"
   Singh, G.; **Goswami, P.**; Sharma, S.; Anand, R. V. *J. Org. Chem.* **2018**, *83*, 10546.

5. "*Exploring bis-(amino)cyclopropenylidene as a non-covalent Brønsted base catalyst in conjugate addition reactions*"
   Singh, G.; **Goswami, P.**; Anand, R. V. *Org. Biomol. Chem.* **2018**, *16*, 384.

6. "*Organocatalytic O-acylation of phenols/alcohols and N-acylation of indoles with cyclopropenones*"
   Goswami, P.[†]; Singh, G.[†]; Kumar, S.; Anand, R. V. (Manuscript under preparation)
   (†These authors contributed equally to this work)

Conferences/Symposia

- Participated in the *National Seminar on Crystallography 43A* held at the Department of Chemistry, Indian Institute of Science Education and Research (IISER) Mohali, S. A. S. Nagar Mohali, India (28-30th March, 2014).
- Presented a poster on "$Bi(OTf)_3$ Catalyzed 1,6- conjugate addition of 3-substituted indoles to *p*-quinone methides under solvent free condition: an atom economic approach to C2-substituted unsymmetrical diarylindolylmethanes" Goswami, P.; Anand, R. V. in the *11th Junior National Organic Symposium (J-NOST)* held at the Department of Chemistry, School of Chemical Sciences, NISER Bhubaneswar, India, (14-17th December, 2015).
- Presented a poster on "Synthesis of arylated acetonitriles via *N*-heterocyclic carbene catalyzed 1,6- conjugate addition of TMSCN to *para*-quinone methides" Goswami, P.; Anand, R. V. in the *12th Junior National Organic Symposium (J-NOST)* held at Department of Chemistry, CSIR-Central Drug Research Institute, Lucknow, India, (24-27th November, 2016).
- Presented a poster on "*p*-Quinone methides (*p*-QMs) as versatile intermediates in the synthesis of various diarylmethane derivatives" Goswami. P.; Anand, R. V. in the *21st International conference on organic synthesis (ICOS 21)* held at the Department of Chemistry, Indian Institute of Technology (IIT) Bombay, Mumbai, India (11-16thDecember, 2016).
- Participated in the 24th *National Conference on Liquid Crystals* held at the Department of Chemistry, Indian Institute of Science Education and Research (IISER) Mohali, S. A. S. Nagar Mohali, India (11-13th October, 2017).
- Delivered a talk entitled "Bis(amino)cyclopropenylidene catalyzed Rauhut-Currier reaction between α,β-unsaturated carbonyl compounds and *para*-quinone methides" Goswami, P.; Anand, R. V. in the *13th Junior National Organic Symposium (J-NOST)* held at School of Chemistry, Banaras Hindu University, Varanasi,, India, (9-12th November, 2017).
- Participated in the *Royal Society of Chemistry Roadshow* held at Indian Institute of Science Education and Research (IISER) Mohali, S. A. S. Nagar, Mohali, India (14th November, 2017).

- Presented a poster on "*N*-heterocyclic carbene catalyzed 1,6-conjugate addition of Me_3Si-CN to *para*-quinone methides and fuchsones: easy access to α-arylated nitriles" Goswami, P.; Anand, R. V. in the *Contemporary Facets in Organic Synthesis* (CFOS) held at the Department of Chemistry, Indian Institute of Technology (IIT) Roorkee, India (22-24th December, 2017).
- Participated in the *ACS on campus India Roadshow* held at Indian Institute of Science Education and Research (IISER) Mohali, S. A. S. Nagar, Mohali, India (9th February, 2018).

Prithwish Goswami-Curriculum Vitae

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Education

2014-2018: Ph.D. in Synthetic Organic Chemistry (Indian Institute of Science Education and Research (IISER) Mohali, Punjab, India

2012-2014: M.S. in Chemistry (Indian Institute of Science Education and Research (IISER) Mohali, Punjab, India

2008-2011: B. Sc. Honours in Chemistry **(**Ramakrishna Mission Residential College, Narendrapur, Affiliated under the University of Calcutta), 700103, West Bengal, India.

Doctoral Detail

Thesis Title: "Organocatalytic and Lewis Acid Catalyzed Nucleophilic Addition Reactions of *para*-Quinone Methides and Cyclopropenones"

Supervisor: Dr. R. Vijaya Anand, Associate Professor, IISER Mohali, India

Awards and Scholarships

- Qualified the Joint Admission Test for M. Sc. (IIT JAM): All India rank (546) held in February 2012.
- Awarded an Institute fellowship for pursuing MS degree from Indian Institute of Science Education and Research (IISER) Mohali from August 2012 to May 2014.
- Awarded Merit Certificate for Academic Excellence from Indian Institute of Science Education and Research (IISER) Mohali in 2013 and 2014.
- Awarded Junior Research Fellowship and Senior Research Fellowship from Indian Institute of Science Education and Research (IISER) Mohali from August 2014 to July 2018.

- Received the Best Poster Award from the organizers of the *"Contemporary Facets in Organic Synthesis (CFOS 2017)"* conference held at Indian Institute of Technology (IIT) Roorkee during 22-24th Dec, 2017.

Research and Instrumental Skills

- Firsthand experience in setting up a synthetic organic chemistry lab and designing projects.
- Excellent knowledge in the synthesis of *N*-heterocyclic carbene (NHC) and Bis-(amino)cyclopropenylidene (BAC) precursors, and their applications in organocatalysis.
- Good knowledge of organic and organometallic chemistry.
- Experience in the isolation, purification and characterization of a wide range of organic compounds by, modern chromatographic and spectroscopic (IR, UV, NMR, and HRMS) techniques. Proficiency in handling IR, 400 MHz NMR, HPLC and Biotage-Isolera One flash column chromatography.
- Excellent practical skills in handling air/moisture sensitive reagents/reactions and gram/milligram scale reactions.