Exploring New Synthetic Transformations Employing *p*-Quinone Methides as Versatile Acceptors in 1,6-Addition Reactions

by

Mr. Sachin Rohidas Shirsath
10CC17J26007

A thesis submitted to the
Academy of Scientific & Innovative Research
for the award of the degree of

DOCTOR OF PHILOSOPHY
in
SCIENCE

Under the supervision of
Dr. M. Muthukrishnan

CSIR-National Chemical Laboratory, Pune

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August-2022

Certificate

This is to certify that the work incorporated in this Ph.D. thesis entitled, "*Exploring New Synthetic Transformations Employing p-Quinone Methides as Versatile Acceptors in 1,6-Addition Reactions*" submitted by *Mr. Sachin R. Shirsath* to the Academy of Scientific and Innovative Research (AcSIR) in fulfillment of the requirements for the award of the Degree of *Doctor of Philosophy in Science*, embodies original research work carried-out by the student. We, further certify that this work has not been submitted to any other University or Institution in part or full for the award of any degree or diploma. Research material(s) obtained from other source(s) and used in this research work has/have been duly acknowledged in the thesis. Image(s), illustration(s), figure(s), table(s) etc., used in the thesis from other source(s), have also been duly cited and acknowledged.

Mr. Sachin R. Shirsath
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Date: 02/08/2022

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I Mr. Sachin Rohidas Shirsath, a Ph. D. student of the Academy of Scientific and Innovative Research (AcSIR) with Registration No. 10CC17J26007 hereby undertake that, the thesis entitled "*Exploring New Synthetic Transformations Employing p-Quinone Methides as Versatile Acceptors in 1,6-Addition Reactions*" has been prepared by me and that the document reports original work carried out by me and is free of any plagiarism in compliance with the UGC Regulations on *"Promotion of Academic Integrity and Prevention of Plagiarism in Higher Educational Institutions (2018)"* and the CSIR Guidelines for "*Ethics in Research and in Governance (2020)".*

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Name:

Date:

Place:

Signature of the Supervisor

Name: Dr. M. Muthukrishnan

Date: 02/08/2022

Place: Pune

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DECLARATION

The research work embodied in this thesis has been carried out at CSIR–National Chemical Laboratory, Pune under the supervision of **Dr. M. Muthukrishnan**, Organic Chemistry Division, CSIR–National Chemical Laboratory, Pune – 411 008. This work is original and has not been submitted in part or full, for any degree or diploma of this or any other university.

August, 2022

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Dedicated to

My Beloved Family

With Lots of Love

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--- Sachin R. Shirsath

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Units

°C	Degree centigrade
cm	Centimetre
mg	Milligram
h	Hour
Hz	Hertz
µL	Microlitre
mL	Millilitre
min	Minutes
MHz	Megahertz
mmol	Millimole
ppm	Parts per million

Chemical Notations

AcOH	Acetic acid
Ac_2O	Acetic anhydride
AgSbF6	Silver hexafluoro antimonite
Ag_2O	Silver oxide
AIBN	Azobisisobutyronitrile
$AlCl_3$	Aluminum chloride
AgOTf	Silver trifluoromethanesulfonate
$AgSbF_6$	Silver hexafluoroantimonate
$AgNTf_2$	Silver(I) bis(trifluoromethanesulfonyl)amide
$AuCl_3$	Gold(III) chloride
aq.	Aqueous
$BF_3.OEt_2$	Boron trifluoride diethyl etherate
BHT	Butylated hydroxytoluene
$Bi(OTf)_3$	Bismuth(III) trifluoromethanesulfonate
Boc	*tert*-butyloxycarbonyl
*n*BuLi	*n*-Butyl lithium
^{t}BuNC	*tert*-Butyl isocyanide
Cat.	Catalytic
Conc.	Concentrated
CO	Carbon monoxide
CN	Cyanide
$Cu(OTf)_2$	Copper(II) trifluoromethanesulfonate
$Cu(acac)_2$	Copper(II) acetylacetonate
DCM	Dichloromethane
DCE	Dichloroethane
DMF	*N,N*-Dimethylformamide
DMAP	*N,N′*-Dimethyl aminopyridine

DMSO	Dimethyl sulfoxide
DBU	1,8-Diazabicyclo(5.4.0)undec-7-ene
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
Et_2AlCl	Diethylaluminium chloride
Et_2O	Diethyl ether
EtOAc	Ethyl acetate
$FeCl_3$	Iron(III) chloride
$Fe(acac)_3$	Tris(acetylacetonato) iron(III)
fac-Ir(ppy)$_3$	*fac*-Tris(2-phenylpyridine)iridium(III)
HBF_4	Fluoroboric acid
H_2	Hydrogen
H_2O	Water
$InCl_3$	Indium(III) chloride
K_2CO_3	Potassium carbonate
$LiAlH_4$	Lithium aluminium hydride
Mg	Magnesium
Me_3SiCN	Trimethylsilyl cyanide
$Mo(CO)_6$	Molybdenum hexacarbonyl
$Mn(acac)_2$	Manganese(II) acetylacetonate
NaOH	Sodium hydroxide
$NaHCO_3$	Sodium bicarbonate
NH_4Cl	Ammonium chloride
Na_2SO_4	Sodium sulfate
NBS	*N*-Bromosuccinimide
NIS	*N*-Iodosuccinimide
NHC	*N*-Heterocyclic Carbene
NMP	N-Methyl-2-pyrrolidone
$Ni(cod)_2$	Bis(cyclooctadiene)nickel(0)
Pd/C	Palladium on carbon
PPh_3AuCl	Chloro(triphenylphosphine)gold(I)
$Pd(PPh_3)_4$	Tetrakis(triphenylphosphine)palladium(0)
$Pd_2(dba)_3$	Tris(dibenzylideneacetone)dipalladium(0)
$P(Cy)_3$	Tricyclohexylphosphine
$PhSiH_3$	Phenylsilane
$PhSO_2Na$	Sodium benzenesulfinate
$Sc(OTf)_3$	Scandium trifluoromethanesulfonate
SPhos	Dicyclohexyl(2′,6′-dimethoxy[1,1′-biphenyl]-2-yl)phosphane
TBACl	Tetrabutylammonium chloride
TBS	*tert*-butyldimethylsilyl
THF	Tetrahydrofuran
$TiCl_4$	Titanium tetrachloride

TFA	Trifluoroacetic acid
TEMPO	2,2,6,6-Tetramethylpiperidine-1-oxyl
$TMSN_3$	Trimethylsilyl azide
TosMIC	*p*-Toluenesulfonylmethyl isocyanide
XPhos	Dicyclohexyl[2′,4′,6′-tris(propan-2-yl)[1,1′-biphenyl]-2-yl]phosphane
$ZnCl_2$	Zinc chloride
$Zn(CN)_2$	Zinc cyanide

Other Notations

calcd	Calculated
δ	Chemical shift
J	Coupling constant in NMR
DEPT	Distortionless Enhancement by Polarization Transfer
dr	Diastereomeric excess
ee	Enantiomeric excess
equiv.	Equivalents
ESI	Electrospray ionization Mass spectrometry
HPLC	High Pressure Liquid Chromatography
HMBC	Heteronuclear Multiple Bond Correlation
COSY	Homonuclear Correlation Spectroscopy
HRMS	High Resolution Mass Spectrometry
IR	Infra Red
m/*z*	Mass-to-charge ratio
mp	Melting Point
NMR	Nuclear Magnetic Resonance
NOESY	Nuclear Overhauser Effect Spectroscopy
ORTEP	Oak Ridge Thermal Ellipsoid Plot
rt	Room temperature
TLC	Thin layer chromatography

Abbreviation Used for NMR Spectral Information

br	broad	s	singlet
d	doublet	t	triplet
q	quartet	quint	quintet
sept	septet	m	multiplet
dd	doublet of doublets		
ddd	doublet of doublet of doublets		

- ✓ All reagents, starting materials, and solvents were obtained from commercial suppliers and used as such without further purification.
- ✓ All the moisture and air sensitive reactions have been carried out in anhydrous solvents under argon atmosphere in oven-dried glassware. Solvents were distilled and dried using standard protocols.
- ✓ Petroleum ether refers to the fraction collected in the boiling range 60-80 °C. Organic layers after every extraction were dried over anhydrous sodium sulfate.
- ✓ Air-sensitive reagents and solutions were transferred *via* syringe or cannula and were introduced to the apparatus *via* rubber septa.
- ✓ TLC was performed on E-Merck pre-coated 60 F254 plates and the visualization was accomplished either by exposing to UV light, iodine adsorbed on silica or by immersion in *p*-anisaldehyde (in ethanol), vanillin (in ethanol), KMnO4 (in ethanol) and ninhydrin (in ethanol) followed by heating with a heat gun for ~15 sec.
- ✓ All evaporations were carried out under reduced pressure on the Heidolph rotary evaporator below 50 °C unless otherwise specified.
- ✓ Column chromatography was performed on silica gel (100-200 or 230-400 mesh size).
- ✓ Deuterated solvents for NMR spectroscopic analyses were used as received. ^{1}H NMR spectra were recorded on AV-200 MHz, AV-400 MHz, JEOL AL-400 (400 MHz) and DRX–500 MHz spectrometer.
- ✓ ^{13}C NMR spectra were recorded on AV-50 MHz, AV-100 MHz, JEOL AL-100 (100 MHz) and DRX-125 MHz spectrometers. ^{19}F NMR spectra were recorded on AV-376 MHz.
- ✓ Chemical shifts (δ) reported are referred to as internal reference tetramethylsilane (TMS). Chemical shifts have been expressed in ppm units relative to TMS, using the residual solvent peak as a reference standard. Coupling constants were measured in Hertz.
- ✓ All the melting points are uncorrected and were recorded using a scientific melting point apparatus (Buchi B-540).

- ✓ High-resolution mass spectra (HRMS) were recorded on a Thermo Scientific Q-Exactive, Accela 1250 pump. EI mass spectra were recorded on Finnigan MAT-1020 spectrometer at 70 *eV* using a direct inlet system.
- ✓ Infrared (IR) spectra were recorded on a FT-IR spectrometer as a thin film.
- ✓ Chemical nomenclature (IUPAC) and structures were generated using Chem Bio Draw Ultra 20.0 software.
- ✓ The compound, scheme, figure and table numbers given in each section of the chapter only refer to the particular section of the chapter.


Synopsis
Report

Synopsis of the Thesis to be submitted to the Academy of Scientific and Innovative Research for Award of the Degree of Doctor of Philosophy in Chemistry	
Name of the Candidate	Mr. Sachin Rohidas Shirsath
Degree Enrollment No. & Date	Ph. D. in Chemical Sciences, 10CC17J26007, January 2017
Title of the Thesis	Exploring New Synthetic Transformations Employing *p*-Quinone Methides as Versatile Acceptors in 1,6-Addition Reactions.
Research Supervisor	Dr. M. Muthukrishnan
Research Co-Supervisor (if any)	--

Introduction:

Quinone methide framework is one of the important class of compounds that occur in nature both as fungal metabolites and wood pigments and serve as intermediates in numerous biological and chemical processes. In particular, *para*-quinone methides (*p*-QMs) structural isomer of quinone methides is ubiquitous structural motifs found in a wide variety of biologically active natural products.[1] *p*-QMs consist cyclohexadiene moiety in *para*-conjugation with a carbonyl group and olefinic moieties. Due to its unique reactivity, *p*-QMs have been widely explored in organic synthesis to access many unsymmetrical di- and triarylmethane derivatives, variety of carbocycles, spirocyclic compounds, heterocycles, etc. The proposed thesis describes the development of new scalable methods of *p*-QMs for the synthesis of various structurally diverse molecules.

Statement of the problem:

Vinylogous conjugate addition is a powerful tool in synthetic organic chemistry for generating complex organic molecules. During the past few years, *p*-QMs have been widely explored as vinylogous acceptors in various 1,6-addition and annulation reactions.[2] Despite the significant progress achieved, we believe that many opportunities and challenges are still remaining for further exploration in this field. For example, 1,6-addition/annulation reactions, radical addition using *O*-, *S*-, *P*-, or *N*-centered compounds as radical donors, and asymmetric construction of new chemical bonds with *p*-QMs have yet to be investigated. Considering the significance of *p*-quinone methide chemistry in organic synthesis, as part of this thesis work, we carried out the novel transformations employing *p*-QMs to access a variety of biologically significant and structurally intriguing molecules.

Objectives:

- Exploration of new synthetic transformations employing *p*-QMs as Michael acceptor to synthesize structurally diverse diarylmethane units.
- Development of metal-catalyzed electrophilic cascade cyclization of heteroatomic nucleophiles with alkynamine followed by trapping with electrophilic acceptor *p*-QMs for the construction substituted dihydropyrroles.
- To explore the reactivity of *tert*-butyl isocyanide and other substituted isocyanides in presence of various Lewis acids for vinylogous conjugate addition reaction with *p*-QMs as an electrophile.
- Development of radical ring-opening of cyclopropanols in the presence of single electron oxidant and its addition reaction with *p*-QMs to access highly functionalized organic compounds.

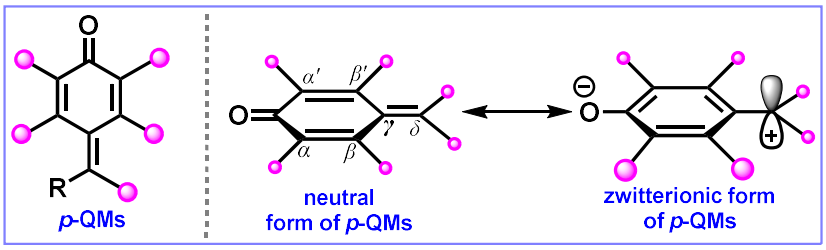
Methodology:

The work embodied in the present thesis has been divided into four chapters, mainly focusing on exploring new chemical transformations employing *p*-QMs as versatile Michael acceptors in nucleophilic 1,6- addition reactions. The first chapter (Section I) introduces *p*-quinone methide chemistry and its significance in organic synthesis. Section II of this chapter describes the development of silver-catalyzed cascade cyclization/1,6-conjugate addition of homopropargyl sulfonamides with *p*-QMs to synthesize diverse 3-diarylmethine substituted dihydropyrroles. The second chapter deals with the Lewis acid mediated 1,6-conjugate addition of *tert*-butyl isocyanide and other substituted isocyanides to *p*-QMs for accessing α-arylated nitriles and amides, respectively. The iron-mediated tandem ring opening/1,6-conjugate addition of cyclopropanols with *p*-QMs to access γ, γ -diaryl ketones has been described in the third chapter. The fourth chapter describes the 1,6-conjugate addition initiated formal [4+2] annulation of *p*-QMs with sulfonyl allenols to synthesize spiro[5.5]undeca-1,4-dien-3-one scaffolds. The details are given below.

***Chapter 1*: *para*-Quinone methides (*p*-QMs): A Versatile acceptor for the synthesis of structurally diverse molecules**

***Section I*: A brief introduction to *p*-quinone methide chemistry**

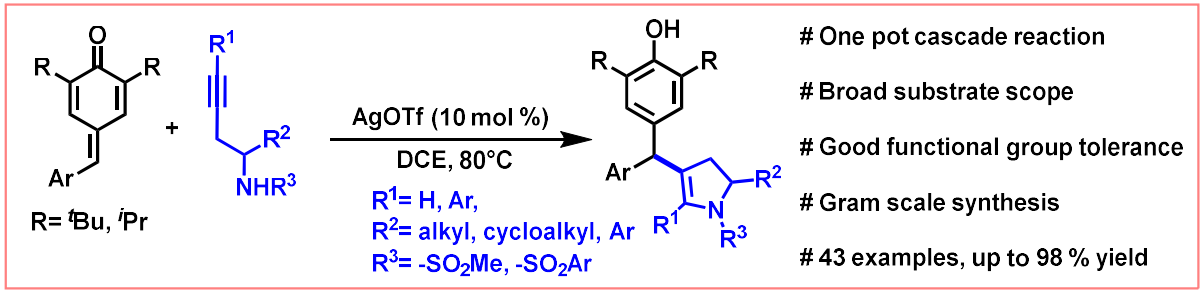
p-QMs are highly reactive dearomatized intermediates widely featured in potential bioactive triterpenoids such as Celastrol, Pristimerin and natural products like Kendomycin and



Taxodone.[3] *p*-QMs plays a vital role as a key intermediate in various medicinal and biological processes, such as lignin biosynthesis, adrenergic receptors, enzyme inhibition, DNA alkylation and cross-linking. *p*-QMs undergo resonance stabilization between neutral and zwitterionic structures and display intrinsic chemical reactivity as acceptors for 1,6-addition reactions, including Michael and radical addition. This section deals with a brief account of the significant organic transformations reported in the literature utilizing *p*-QMs.

***Section II*: Silver-catalyzed cascade cyclization/1,6-conjugate addition of homopropargyl sulfonamides to *p*-quinone methides: An approach to diverse 3-diarylmethine substituted dihydropyrroles**

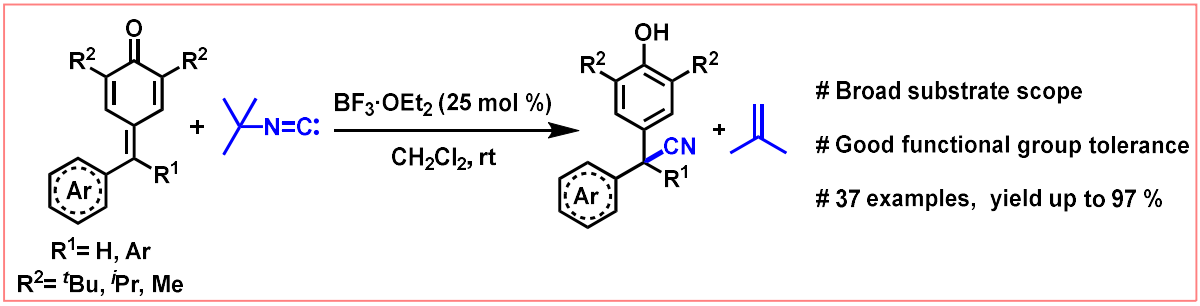
Substituted dihydropyrroles are an important framework present in a plethora of natural products and pharmaceutical agents, and further, they serve as versatile building blocks in the synthesis of complex organic molecules. Of particular importance are the diarylmethine substituted dihydropyrroles that are present in several bioactive agents used to treat several disorders such as overactive bladder (Darifenacin), epilepsy, inflammation, etc.[4] In recent years, the metal catalyzed electrophilic cyclization of heteroatomic nucleophiles with alkynes has emerged as a general and efficient protocol for the construction of a wide variety of heterocycles. Notably, for the construction of substituted dihydropyrroles, catalytic cascade cyclization of alkynamine followed by trapping with suitable electrophiles would be an ideal and extremely useful strategy. Despite the merit of these elegant approaches, still most of the methods require a dual catalytic system for substrate activation, prolonged reaction duration, and limited substrate scope. Therefore, the development of a rapid, catalytic, and one-pot strategy to access these kinds of pyrrole derivatives is of high value.



In this section, we have described an simple and efficient strategy for the synthesis of 3-diarylmethine substituted dihydropyrroles *via* silver catalyzed cascade cyclization/1,6-conjugate addition of homopropargyl sulfonamides to *p*-QMs. In this reaction silver catalyst plays a dual role, *ie* Ag (I) activates homopropargyl sulfonamide for cycloisomerization as well as activates *p*-QMs in 1,6-conjugate addition. The salient features of this reaction include readily accessible starting materials, mild reaction conditions, good functional group tolerance and scalability. This simple strategy may provide a general approach to the synthesis of highly substituted dihydropyrrole derivatives in a rapid manner.

***Chapter 2*: Lewis acid catalyzed 1,6-conjugate addition of isocyanides to *p*-quinone methides for accessing *α*-arylated nitriles and amides**

***Section I*: Accessing *α*-arylated nitriles *via* $BF_3{\cdot}OEt_2$ catalyzed cyanation of *para*-quinone methides using *tert*-butyl isocyanide as a cyanide source**

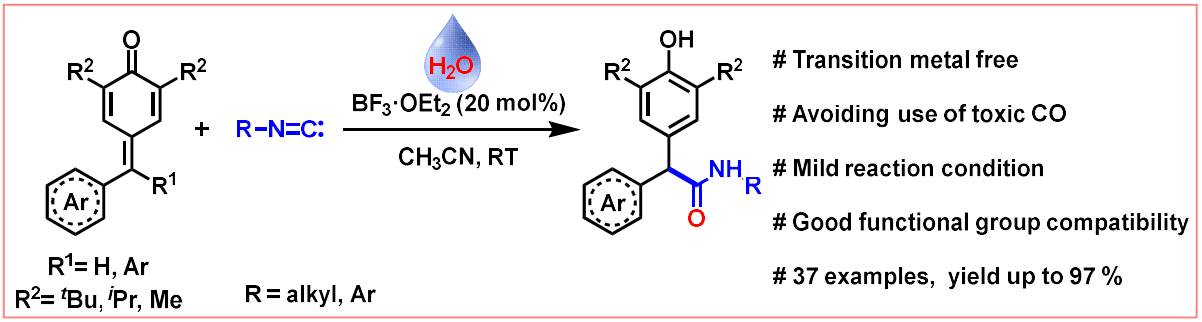


The synthesis of nitrile-containing organic frameworks, in particular α-arylated nitrile compounds, is of great importance, as these structures exist in several natural products, a vast range of functional molecules relevant to pharmaceuticals, agrochemicals, and functional materials.[5] For instance, more than 30 nitrile-containing drugs have been approved for the treatment of depression, breast cancer, and Parkinson's disease, while 20 more are in clinical trials. On the other hand, they are valuable precursors in organic synthesis to prepare carboxylic acids, amides, aldehydes, ketones, amidines, amines, *N*-containing heterocycles etc. Consequently, several synthetic approaches toward the synthesis of *α*-arylated nitriles have been explored and that mainly involves the nucleophilic substitution of a benzylic halide, dehydration of aldoximes/amides, addition of cyanide to diarylcarbinols, coupling reactions of nitriles with aryl halides, and others. However, most of these methods suffer from drawbacks such as harsh reaction conditions, expensive catalysts, usage of notorious toxic cyanide sources, etc. Therefore, the development of a robust strategy for the synthesis of diverse functional-group rich *α*-aryl nitriles is highly desirable.

In this section, a $BF_3{\cdot}OEt_2$ catalyzed 1,6-addition of *tert*-butyl isocyanide to *p*-QMs and fuchsones for the synthesis of *α*-diaryl and *α*-triaryl nitriles has been described. This protocol allows *α*-diaryl- and *α*-triaryl nitriles to be accessed in good to excellent yields (up to 97%) and with a broad substrate scope, which could be further functionalized to give a versatile set of products. This is the first example wherein *tert*-butyl isocyanide has been used as a cyanide source for the 1,6-conjugate addition reaction of *p*-QMs.

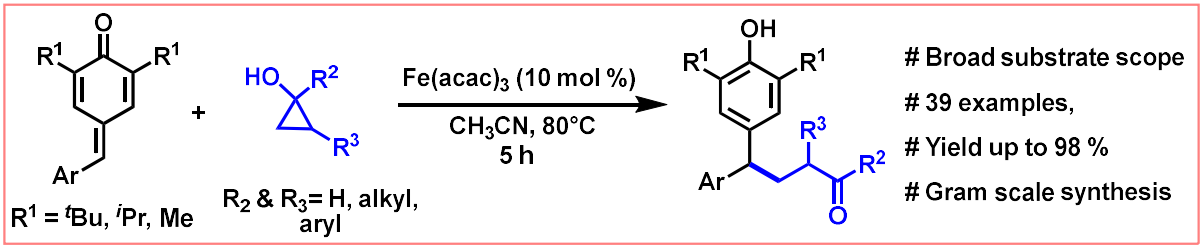
***Section II*: Metal-Free Aminocarbonylation of *p*-Quinone Methides with Isocyanides: Synthesis of Sterically Hindered *α*-Arylated Acetamides**

α-Arylated acetamide is an important class of organic compounds and is an integral part of several drugs, natural products, and bulk chemicals.[6] Due to their ubiquitous nature, it has attracted wide attention among synthetic organic chemists to access α-arylated acetamide, particularly with restricted steric hindrance. Previous approaches for α-Arylated acetamide mainly focused on transition-metal-catalyzed aminocarbonylation between benzylic electrophiles and amine, carbon monoxide or isocyanides. Most of these method requires transition metal catalysts, toxic carbon monoxide, harsh reaction conditions etc. On the other hand, isocyanides are a highly versatile C1 building block and have widespread applications in organic, medicinal, and combinatorial chemistry. They have been used as efficient CO surrogates and readily available C1 synthon for carbonylation reactions, multicomponent reactions, heterocycle synthesis etc.[7] Therefore, exploring novel protocol to prepare α-arylated acetamides from easily accessible starting material under mild reaction condition is highly attractive. In continuation of our cyanation work described in the previous section, this section deals with the aminocarbonylation of *p*-QMs and fuchsones with isocyanides for the synthesis of *α*-arylated acetamides.



***Chapter 3*: Iron mediated tandem ring opening/1,6-conjugate addition of cyclopropanols with *p*-quinone methides: New access to *γ*, *γ* -diaryl ketones**

γ,*γ*-Diarylketones and their derivatives are frequently encountered in numerous bioactive molecules and natural products. Furthermore, compounds possessing *γ*,*γ*-diaryl ketone motif are known integrin receptor inhibitors, nitric oxide donors and serve as a precursor for antidepressant drug Zoloft.[8] Despite the significance, in contrast to their structural analogues such as *α*,*α*- and *β*,*β*-diaryl ketones which could be easily prepared through several methods, surprisingly synthetic strategies to access *γ*,*γ*-diaryl ketones are rare and considered to be challenging. The development of simple and efficient strategy to access these *γ*,*γ*-diarylketones from easily accessible starting material is ideal and highly desirable.

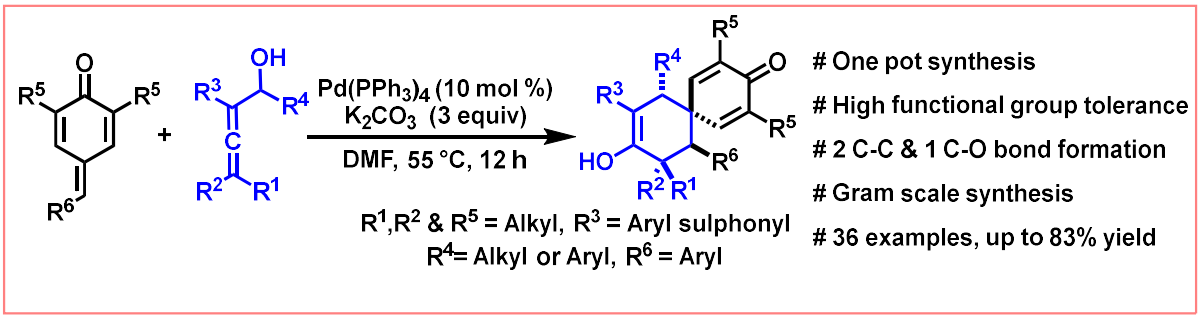


The development of Iron (III) promoted tandem ring opening/1,6-conjugate addition of cyclopropanols to *p*-QMs to access *γ*, *γ*-diaryl ketones is the content of this chapter. This reaction is quite efficient and delivers the desired *γ*, *γ*-diarylated ketones in high to excellent yields. The reaction proceeds *via* generation of the *β*-keto alkyl radical from C−C bond cleavage of the alkoxyl radical species and its 1,6-addition to *p*-QMs to deliver *γ*, *γ* -diarylated ketones. An inexpensive and environmentally friendly catalyst, ease of operation, broad substrate scope, and scalability are the salient features of this methodology. The products are versatile building block and the utility of the reaction have been demonstrated by converting them into several useful products.

***Chapter 4*: 1,6-Conjugate addition initiated formal [4+2] annulation of *p*- quinone Methides with sulfonyl allenols: An unique access to spiro[5.5]undeca-1,4-dien-3-one scaffolds**

The ubiquity of spirocyclohexadienone framework in a plethora of natural products and pharmaceuticals constitutes the efficient construction of this core of significant interest. Spiro[5.5]undeca-1,4-dien-3-ones, an important subclass of spirocyclohexadienones is regarded as a privileged structural scaffold that are abundantly present in natural products such as tatanan B-C, laurencenone A-D and other similar bioactive molecules.[9] Indeed, these scaffolds exhibits various biological activities such as anti-biofouling activity, antiproliferative activity, cytotoxicity against HeLa and Hep-2 human carcinoma cell lines and antifungal activities. Besides, they are useful intermediates in the synthesis of several natural products. Several strategies exist in

the literature for the efficient construction of spirocyclohexadienone core, however, the methods available for the preparation of spiro[5.5]undeca-1,4-dien-3-one core remains elusive.



In this chapter, we devised a new one pot strategy to prepare carbocyclic spiro[5.5]undeca-1,4-dien-3-ones *via* conjugate addition induced formal [4+2] annulation of sulfonyl allenols with *p*-QMs. The reaction features a broad substrate scope and good functional group tolerance, allowing efficient access to a wide variety of highly substituted spiro[5.5]undeca-1,4- dien-3-ones in good yields. Notably, the present strategy provides straightforward access to spiro[5.5]undeca-1,4-dien-3-one skeleton prevalent in several biologically relevant natural products.

Summary/Conclusion:

In summary, different chemical transformations involving *p*-QMs such as 1,6-nucleophilic addition, radical- addition and annulation reactions have been explored in this thesis. These transformations clearly show that *p*-QMs can serve as highly reactive and versatile synthons providing direct access to various biologically relevant molecules by acting as Michael acceptors or radical acceptors. We have developed a strategy for the synthesis of 3-diarylmethine substituted dihydropyrroles *via* silver catalyzed cascade cyclization/1,6-conjugate addition of homopropargyl sulfonamides to *p*-QMs. Further, we have reported cyanation of *para*-quinone methides using *tert*-butyl isocyanide as a cyanide source for the synthesis of *α*-arylated nitriles for the first time. In addition, we also demonstrated 1,6-conjugate addition of substituted isocyanides to *para*-quinone methides for accessing potentially useful α-arylated acetamides. Next, scalable Iron (III) promoted tandem ring opening/1,6-conjugate addition of cyclopropanols to *p*-quinone methides to access *γ*, *γ*-diaryl ketones have been developed. Finally, in the fourth chapter, we demonstrated a facile one pot strategy to prepare carbocyclic spiro[5.5]undeca-1,4-dien-3-ones *via* conjugate addition induced formal [4+2] annulation of sulfonyl allenols with *p*-QMs.

Future directions:

Developing a new enantioselective chemical transformations, green and environmentally friendly strategies such as photocatalysis or electrocatalysis employing *p*-QMs can be another orientation for further developments. In future, efforts will be anticipated on these aspects. In addition, we believe that our synthesized 3-diarylmethine substituted dihydropyrroles, α-arylated nitriles and amides, *γ*, *γ*-diarylated ketones and spiro[5.5]undeca-1,4-dien-3-ones derivatives would find enormous application in medicinal chemistry. So, the study related to the bioactivity of these compounds would be undertaken further in our laboratory.

Publications:

1. **Shirsath, S. R.**; Shinde, G. H.; Shaikh, A. C.; Muthukrishnan, M., Accessing α-Arylated Nitriles via $BF_3 \cdot OEt_2$ Catalyzed Cyanation of *para*-Quinone Methides Using *tert*-Butyl Isocyanide as a Cyanide Source. *J. Org. Chem.* **2018**, *83*, 12305-12314.
2. Ghotekar, G. S.; **Shirsath, S. R.**; Shaikh, A. C.; Muthukrishnan, M., 1, 6-Conjugate addition initiated formal [4+ 2] annulation of *p*-quinone methides with sulfonyl allenols: a unique access to spiro [5.5] undeca-1, 4-dien-3-one scaffolds. *Chem. Commun.* **2020,** *56*, 5022-5025.
3. **Shirsath, S. R.**; Ghotekar, G. S.; Bahadur, V.; Gonnade, R. G.; Muthukrishnan, M., Silver-Catalyzed Cascade Cyclization/1,6-Conjugate Addition of Homopropargyl Sulfonamides to *p*-Quinone Methides: An Approach to Diverse 3-Diarylmethine Substituted Dihydropyrroles. *J. Org. Chem.,* **2020,** *85*, 15038-15050.
4. **Shirsath, S. R**.; Chandgude. S. M., Muthukrishnan, M., Iron Catalyzed Tandem Ring Opening/1,6-Conjugate Addition of Cyclopropanols with *p*-Quinone Methides: New Access to γ, γ-Diaryl Ketones. *Chem. Commun.* **2021,** *57*, 13582–13585.

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Carvalho da Silva, F. *para*-Quinone Methides as Acceptors in 1,6-Nucleophilic Conjugate Addition Reactions for the Synthesis of Structurally Diverse Molecules. *Eur. J. Org. Chem*., **2020**, *2020*, 2650–2692.

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CHAPTER-1

para-Quinone Methides (*p*-QMs): A Versatile Acceptors for the Synthesis of Structurally Diverse Molecules

Section I

A Brief Introduction to *p*-Quinone Methide Chemistry

Section II

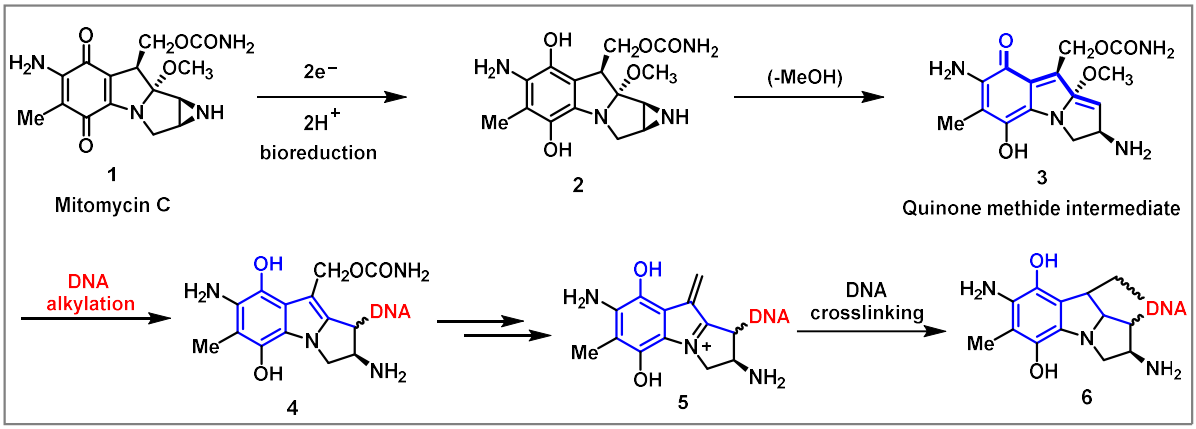
Silver-Catalyzed Cascade Cyclization/1,6-Conjugate Addition of Homopropargyl Sulfonamides to *p*-Quinone Methides: An Approach to Diverse 3-Diarylmethine Substituted Dihydropyrroles

Section-I:

A Brief Introduction to *p*-Quinone Methide Chemistry

1.1.1 Introduction

Quinone methides (QMs) are an important structural framework in organic synthesis. In addition, they serve as valuable intermediates in numerous biological and chemical processes. A large number of quinone methides have been isolated as fungal metabolites, wood pigments and insect pigments.[1] Furthermore, quinone methides have been implicated as intermediates in oxidative phosphorylation and in the biosynthesis of chromans, lignin, and alkaloids.[2] They are highly reactive electrophilic transient intermediates thought to be formed either by tautomeric rearrangement of quinones or by oxidation of phenols in a large number of biological processes such as DNA-alkylation and enzyme inhibition.[3] Regarding enzyme inhibition, they have been shown to particularly inhibit *β*- lactamase, serine hydrolase, phosphatase and ribonuclease.[4] The most famous example is mitomycin C, a clinically used anticancer drug and its mode of action involves bioreduction of mitomycin C to give compound **2**. Further, loss of methanol from compound **2** followed by aziridine ring-opening generate quinone methide intermediate **3**, which is the active species responsible for alkylation of DNA causing cross-linkage (Scheme 1.1.1).[3b]



Scheme 1.1.1. Mechanism of mitomycin C with DNA

Generally, quinone methides are classified into three isomeric forms, *o*-, *m*-, and *p*-quinone methides (also known as *o*-, *m*-, and *p*-QMs), having cyclohexadiene core in conjugation with the carbonyl group (Fig. 1.1.1). *meta*-Quinone methide is a resonance hybrid of two canonical forms, one of which is a zwitterionic form stabilized by aromatic conjugation, enhancing its polarity and increasing reactivity. Among the quinone methides, 1,4-quinone methi-

des, also called *p*-quinone methides (*p*-QMs), are dearomatized intermediates in organic synthesis discovered more than a century with remarkable applications in a variety of synthetic transformations. Unlike benzoquinones, they are highly polarized molecules and transient reactive intermediates capable to undergo facile 1,6-addition reactions driven by the aromatization process. Structurally *p*-quinone methides have a cyclohexadiene core affixed with a carbonyl residue, and exocyclic methylene disposed in a *para* fashion.

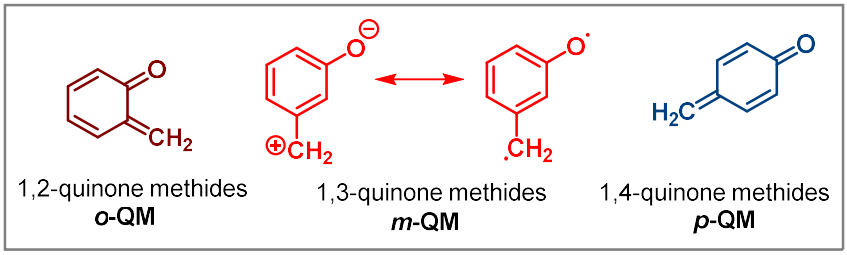


Fig. 1.1.1. Isomeric structures of quinone methides

p-Quinone methides (*p*-QMs) are important structural moieties widely featured in many potential bioactive triterpenoids such as celastrol **9**, pristimerin **10** (anti-oxidant and anti-inflammatory), 4-epi-parvifloran **11** (antiproliferative agents), natural products like kendomycin **7** (anti-tumor and anti-bacterial) and taxodone **8** (anti-cancer) etc. (Fig. 1.1.2).[5] Importantly, *p*-QMs are widely used as reactive intermediates to synthesize drug molecules such as DPP-IV inhibitors, thrombin inhibitors, antibacterials, (+)-BW37U86, melanins, and so on.[6] Moreover, it can be used as an effective DNA crosslinking agent and directed alkylation reagent.[7]

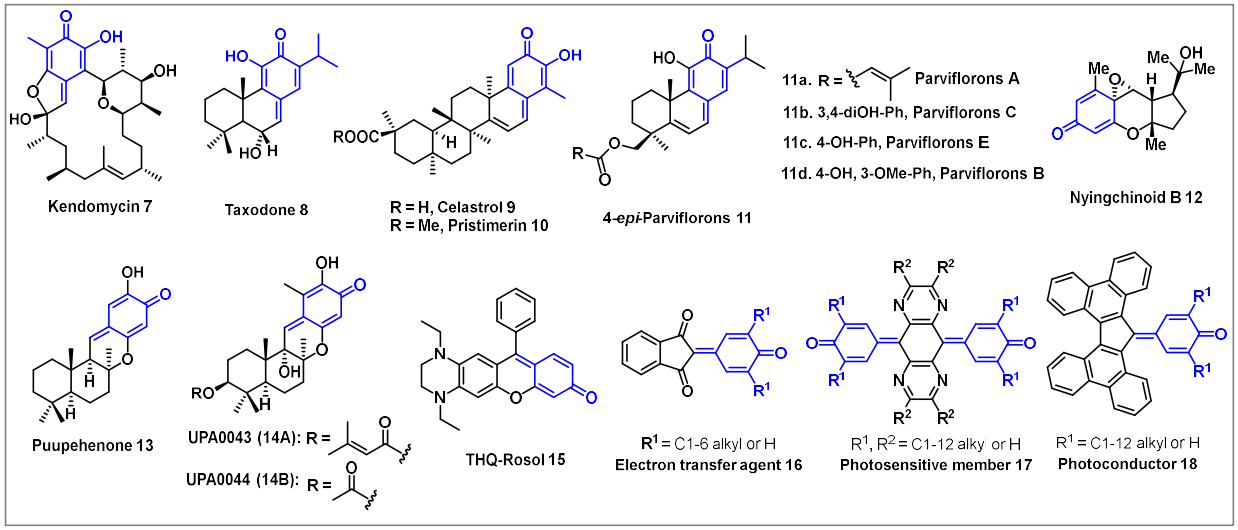


Fig. 1.1.2. Representative bioactive compounds containing *p*-QMs core.

Further, puupehenones (marine natural product) **13** and its derivatives show various biological activities such as antitumor, antiviral, and anti-HIV. Its antibiotic derivatives UPA0043

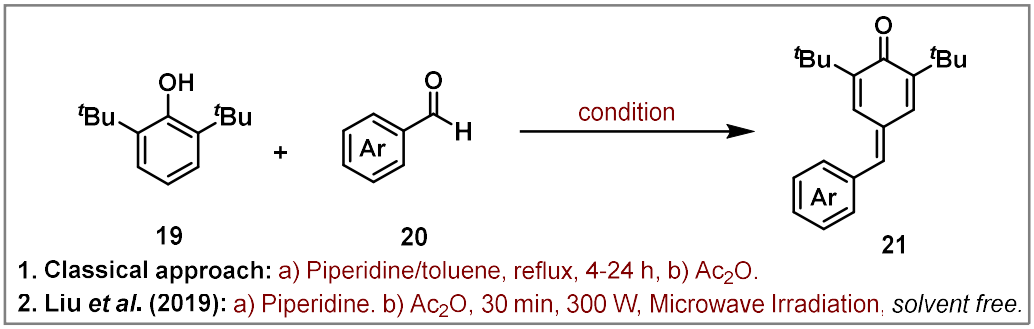
(**14A**) and UPA0044 (**14B**) exhibit significant cytotoxic and antifungal activities.[5d] Among the *p*-QMs family, the 2,6-di-*tert*- butyl-7-substituted quinone methides are essential due to their distinctive properties such as stability, antipolymerant and antioxidant characteristics.[8] Most of the bioactive compounds shown in Fig. 1.1.2 have a common *p*-quinone-methide system that is thought to be responsible for their biological activities.

1.1.2 Methods for the Preparation of *p*-Quinone Methides

The *p*-QMs are neutral molecules, and their stability is directly related to the presence of bulky substituents in the 2 and 6 positions. Consequently, most of the methods described in the literature are for the synthesis of *p*-QMs with bulky *tert*-butyl groups in the 2 and 6 positions. Following are a few general protocols for the synthesis of some stable and unstable *p*-QMs.

a) Classical approach to stable *p*-QMs synthesis:

Synthesis of stable 2,6-di-*tert*-butyl group substituted *p*-QMs generally involves classical base promoted condensation reaction between phenols **19** and aromatic aldehydes **20**.[9] Recently, Liu and co-workers have developed a solvent-free microwave-promoted synthesis of stable aryl-substituted *p*-QMs from aromatic aldehydes **20** and 2,6-di-*tert*-butyl-phenol **19** in a short reaction time (Scheme 1.1.2).[10]

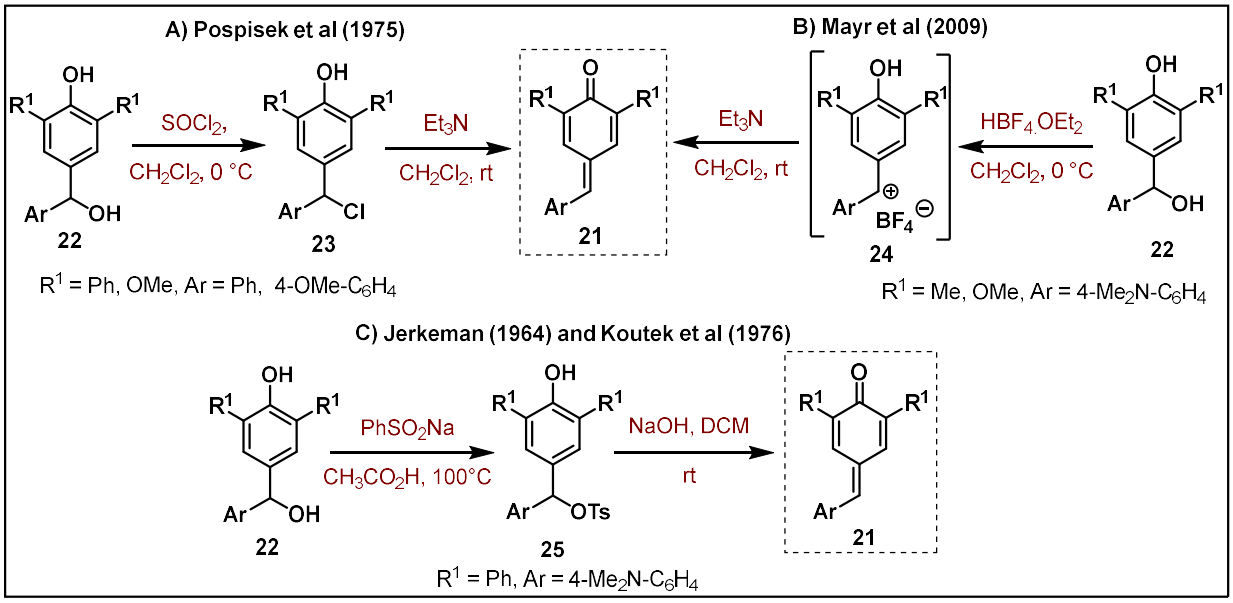


Scheme 1.1.2. Synthesis of stable *p*-QMs

b) Synthesis *p*-QMs using benzyl alcohols:

The synthesis of 2,6-dimethyl, 2,6-dimethoxy, and 2,6-diphenyl substituted *p*-QMs can be prepared using 4-hydroxy-substituted benzhydrols as a starting material. As shown in Scheme 1.1.3A, in 1975, Pospisek and co-workers[11] reported the preparation *p*-QMs by converting benzyl alcohols **22** into benzhydryl chlorides **23** in thionyl chloride followed by base treatment to give *p*-QMs **21**. Similarly, Mayr *et al*. converted benzyl alcohols **22** in the presence of ethereal HBF_4 in dichloromethane to give a cationic intermediate **24**, which provides the *p*-QMs

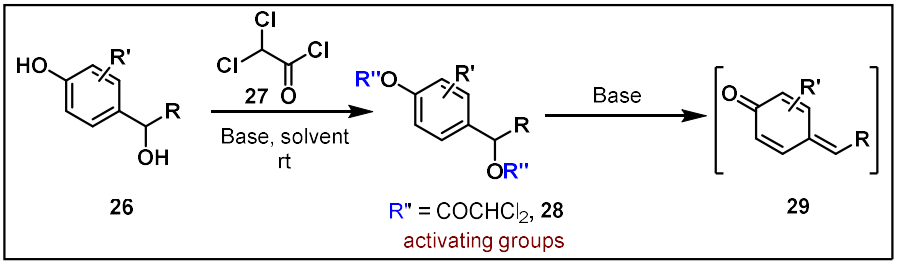
21 on treatment with triethylamine (Scheme 1.1.3B).[12] Jerkeman *et al*. in 1964 and Koutek *et al*. in 1976 individually converted benzyl alcohols **22** into sulfone **25** by refluxing with $PhSO_2Na$ in aqueous acetic acid, which gives *p*-QM **21** after treatment with sodium hydroxide (Scheme 1.1.3C).[13]



Scheme 1.1.3. Synthesis *p*-QMs using benzyl alcohols

c) *In situ* generation of *p*-QMs:

In contrast to the synthesis of stable *p*-QMs, *in situ* generation of *ortho*-unsubstituted *p*-QMs considerably improve these scaffolds' structural variety. During past few years, several research groups unveiled numerous synthetic methodologies by generating highly reactive *ortho*-unsubstituted *p*-QMs *in situ*.[14-15] As shown in Scheme 1.1.4, benzyl alcohol **26** in the presence of protecting group such as 2,2-dichloroacetyl chloride **27** gives bis(dichloroacetates) of 4-(hydroxymethyl)phenols derivative **28**. Further, compound **28** on treatment with base provided *p*-QM **29** *in situ*.[15b]



Scheme 1.1.4. *In situ* synthesis *p*-QMs from activated 4-(Hydroxymethyl)phenols **26**

1.1.3 Chemistry of *p*-Quinone Methides

The olefinic and carbonyl moieties in the *p*-QMs form a unique assembly that undergoes resonance stabilisation between neutral (**30**) and zwitterionic structures (**31**) (Figure 1.1.2a). Due to this, *p*-QMs exhibit electrophilic character at the δ position and display intrinsic chemical reactivity as versatile acceptors for 1,6-addition reactions such as Michael and radical addition (Figure 1.1.2b). The inherent reactivity of *p*-QMs is governed by the strong aromatic driving force that has led to many nucleophilic 1,6-conjugate addition reactions and provided several derivatized phenolic products.

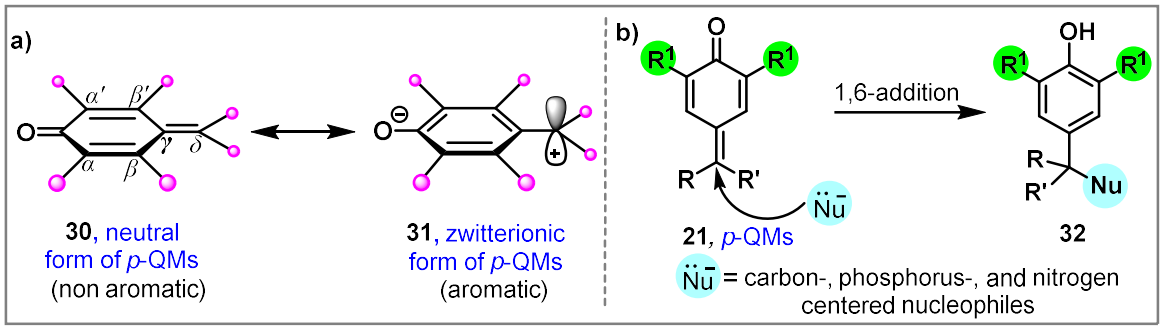


Fig. 1.1.2. a) Resonance structures of *p*-QMs. b) Nucleophilic 1,6-addition with *p*-QMs.

During the last few years, *p*-QM chemistry has encountered an unprecedented resurgence and has been widely explored as an acceptor in diverse 1,6-addition and various annulation reactions. Various reactions of *p*-QMs such as catalyst-free 1,6-addition, base promoted 1,6-addition, Lewis acid-promoted 1,6-addition, metal-catalyzed 1,6-addition, NHC-catalyzed 1,6-addition, radical-enabled 1,6-addition, asymmetric 1,6-addition and variety of 1,6-addition/annulation reactions has been studied extensively.[16] Because of their unique reactivity, they have been effectively used to obtain a wide range of unsymmetrical di- and triarylmethane derivatives, a variety of carbocycles, spirocyclic compounds, heterocycles, and so on. Importantly, contributions from the group of Fan,[17] Jørgensen,[18] Vijaya Anand,[19] Tortosa,[20] Enders,[21] Lin,[22] Cui,[23] Li,[24] Shi,[25] and many others[26] are really commendable. Our group has also demonstrated a few synthetic transformations employing *p*-QMs chemistry.[27]

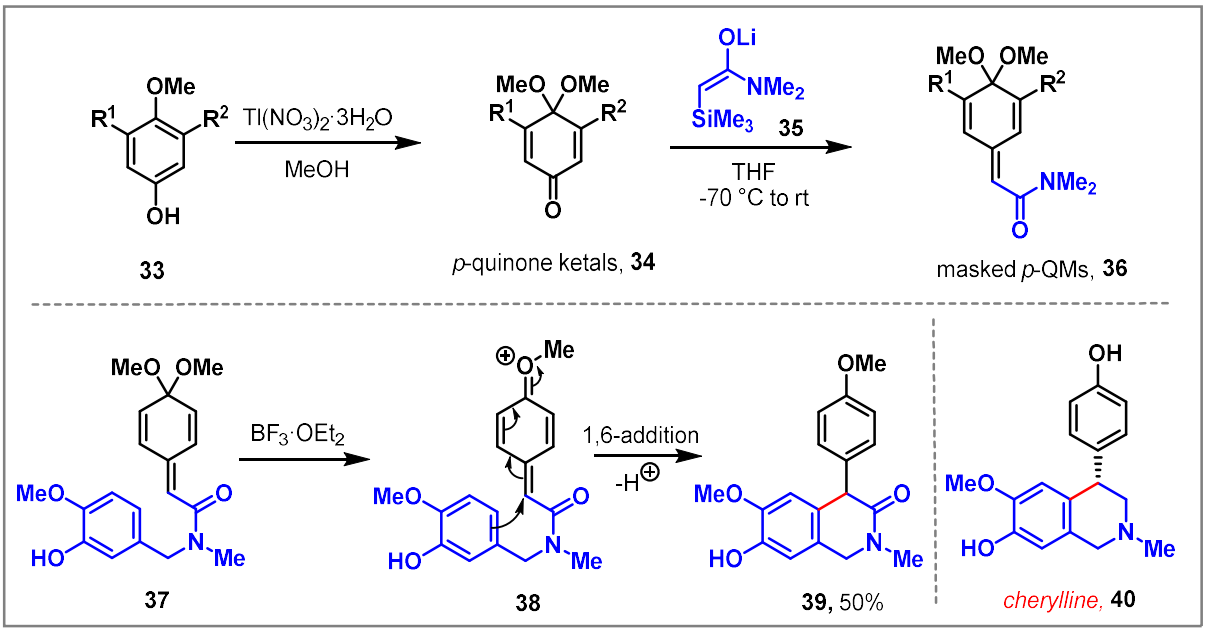
Despite the enormous progress achieved, several opportunities and challenges remain for further research studies in this field. For example, 1,6-addition/annulation reactions, use of *O*-, *S*-, *P*-, or *N*-centered radicals in radical addition with *p*-QMs, and asymmetric construction of new chemical bonds. Furthermore, the development of new reactions, alternative catalysis, multicomponent reactions, green and sustainable chemical reactions of *p*-QMs are rarely report-

ed and need to be investigated. Further, excellent reviews have recently appeared in the literature, providing more insight into its reactivity and thus signifying the importance of chemistry *p*-quinone methides.[16] The present thesis uncovers some of the new intriguing transformations of *p*-QMs such as Lewis acid-catalyzed 1,6-addition, radical addition and dearomative spirocyclization reactions for the synthesis of various biologically relevant and structurally diverse molecules. This section deals with the literature reports of only selected reactions of *p*-QMs pertinent to the present work.

1.1.4 Reactivity of *p*-Quinone Methides

1.1.4.1 Lewis acid mediated 1,6-addition:

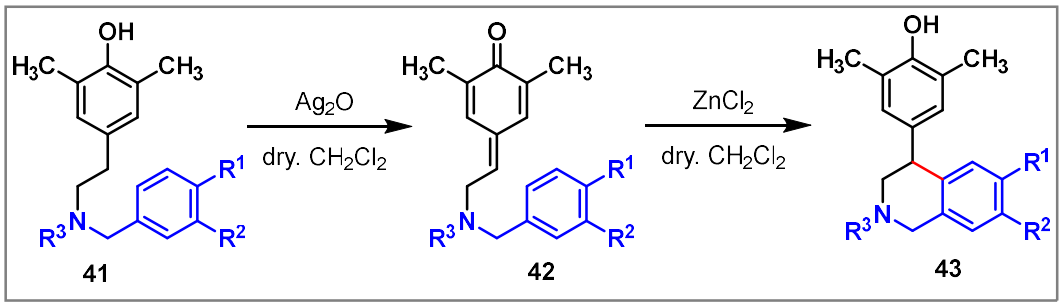
Lewis acid-mediated 1,6-addition reactions of nucleophilic and electrophilic reactants to *p*-QMs has emerged as an important research area that offers an effective strategy for accessing divesre range of polysubstituted diarylmethane derivatives.



Scheme 1.1.5. Synthesis of masked *p*-QMs and the total synthesis of cherylline.

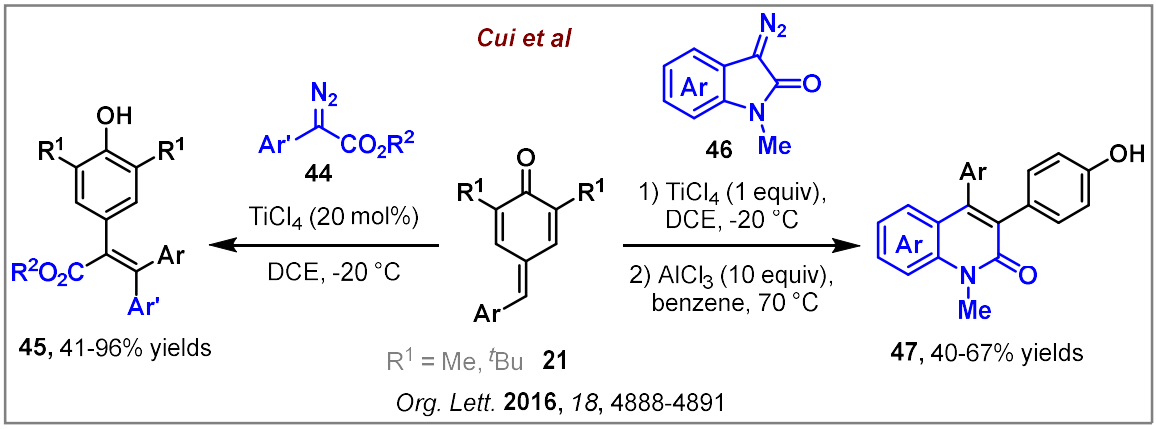
In 1978, Evans and co-workers,[28a] during the total synthesis of cherylline **40,** an Amaryllidaceae alkaloid, proposed that *p*-quinone methide could be a pivotal intermediate to achieve their desired target molecule. The group developed a method for the synthesis of masked *p*-quinone methides **36** from *p*-quinone ketals **34** and *α*-trimethylsilylamides enolate **35** (Scheme 1.1.5). The masked *p*-QMs **36** were not isolable and formed *in situ*. They successfully showed the application of these masked *p*-QMs in the total synthesis of cherylline **40**. The reaction of

masked *p*-QM **36** proceeds *via* dienone-phenol rearrangement to afford intermediate **38** and its subsequent $BF_3{\cdot}OEt_2$ catalyzed intramolecular 1,6-nucleophilic addition of aryl ring, offering lactam, 4-aryl-tetrahydroisoquinoline **39** a key intermediate in the total synthesis of cherylline **40**. In 2004, on a similar line, Raju *et al.*[28b] reported zinc chloride mediated synthesis of 4-aryl-1,2,3,4-tetrahydroisoquinolines **43** from *in situ* generated *p*-QMs **42**. The phenol compound **41** was oxidized with Ag_2O in dry CH_2Cl_2 at room temperature to give *p*-QM intermediate **42,** which was subjected to $ZnCl_2$ promoted 1,6-addition to deliver the corresponding tetrahydroisoquinolines derivatives **43** (Scheme 1.1.6).



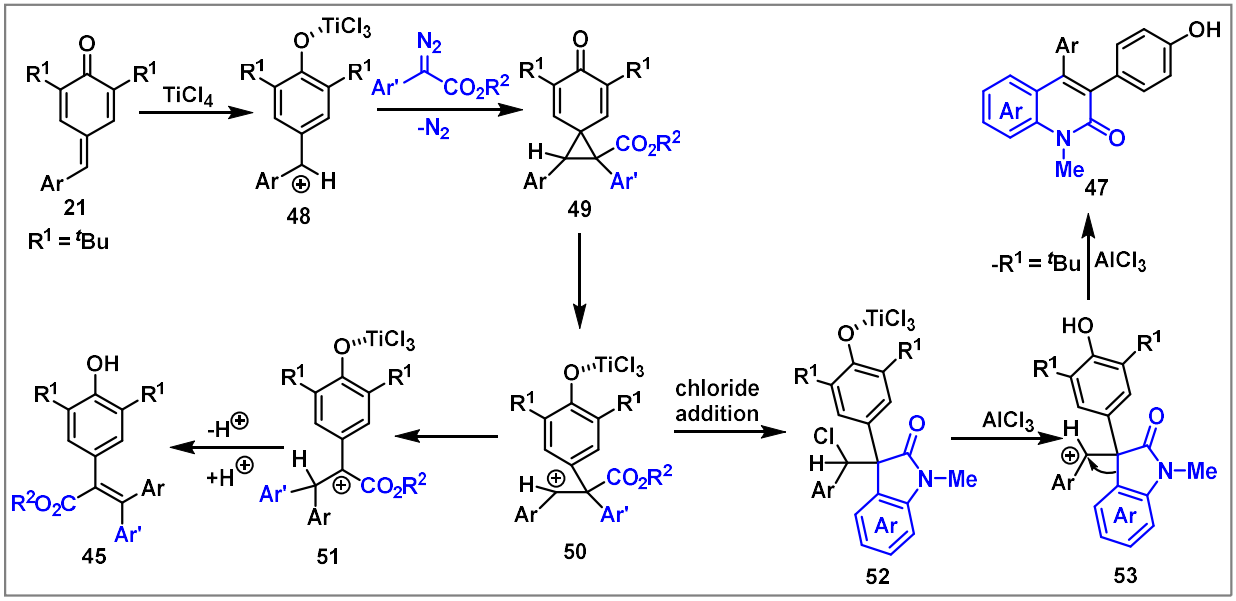
Scheme 1.1.6. Synthesis of 4-aryl-1,2,3,4-tetrahydroisoquinolines from *p*-QMs.

In 2016, Cui *et al.*[28c] disclosed the $TiCl_4$-catalyzed metathesis reaction of diazo compounds with *p*-QMs **21,** affording the tetrasubstituted alkenes and quinolinones derivatives. At -20 °C, *p*-QMs **21** react with *α*-aryl diazoesters **44**, allowing aryl group migration to offer a diverse range of functionalized tetrasubstituted alkenes **45**. Further, authors also showed $TiCl_4$ promoted one-pot metathesis reaction of *p*-QMs **21** with diazooxindole **46** toward quinolinone synthesis **47**. Moreover, to understand the reaction mechanism, ^{13}C-labeling experiments were performed (Scheme 1.1.7).



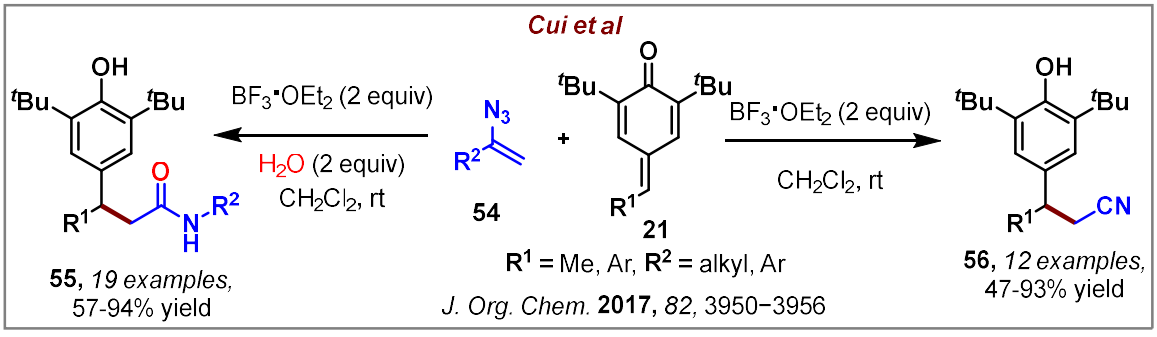
Scheme 1.1.7. $TiCl_4$-catalyzed metathesis of *p*-QMs with diazo compounds.

In the proposed mechanism, *p*-QM **21** activates first by $TiCl_4$ to give cationic intermediate **48,** which underwent cyclopropanation with diazo compound by N_2 extrusion to form intermediate **49**. Next, this quinone system is activated by Lewis acid to deliver cationic intermediate **50.** At this stage, when diazoester **44** was used, intermediate **50** undergoes aryl ring migration followed by hydrogen elimination, giving to tetrasubstituted alkene **45**. Further, when diazooxindoles **46** was used, intermediate **50** underwent chloride addition followed by $AlCl_3$ mediated de-*tert*-butylation and ring expansion, giving the quinolinones product **47** (Scheme 1.1.8).



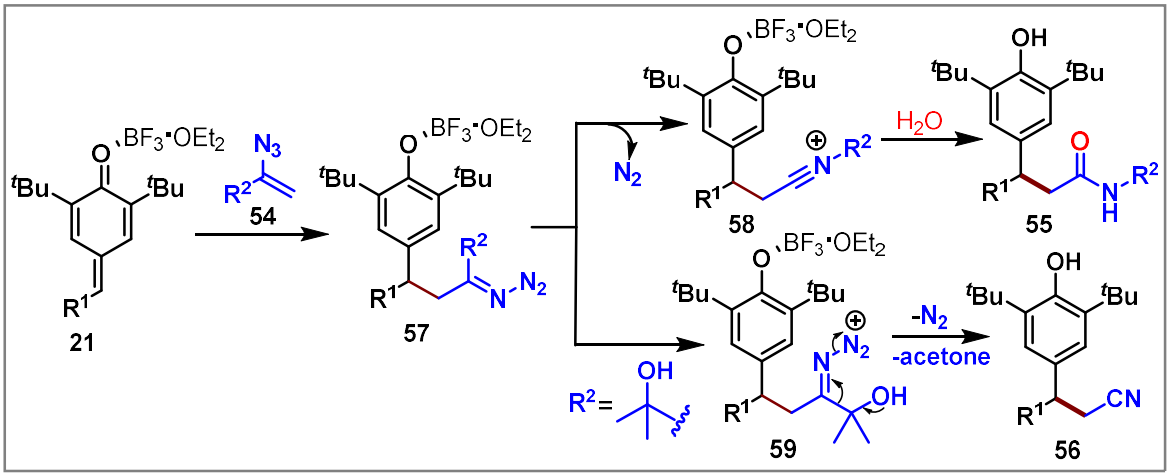
Scheme 1.1.8. Mechanism of the metathesis reaction.

The same group in 2017 reported the $BF_3{\cdot}OEt_2$ mediated reaction of vinyl azides and *p*-quinone methides (*p*-QMs) **21** for the synthesis of amides **55** and nitriles **56**. This reaction is initiated by activating *p*-QMs and then nucleophilic attack by vinyl azides **54**, leading to the synthesis of amides and nitriles. In this reaction, vinyl azide serves as both amide and nitrile precursor (Scheme 1.1.9).[28d]



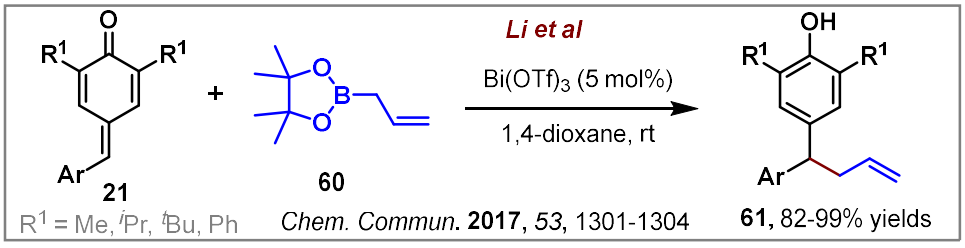
Scheme 1.1.9. $BF_3{\cdot}OEt_2$ mediated reaction of vinyl Azides and *p*-QMs.

The reaction mechanism involves activation of *p*-QMs **21** by $BF_3{\cdot}OEt_2$ followed by the attack of vinyl azides **54** generating the intermediate **57.** At this stage, vinyl azides with phenyl- and alkyl-substitution, intermediate **57** underwent Schmidt rearrangement to give nitrilium ion **58,** which in the presence of H_2O leads to the amide product **55**. If vinyl azide with R^2 = tertiary alcohol was used, intermediate **59** undergoes elimination of nitrogen gas and acetone instead of Schmidt rearrangement to give nitrile product **56** (Scheme 1.1.10).



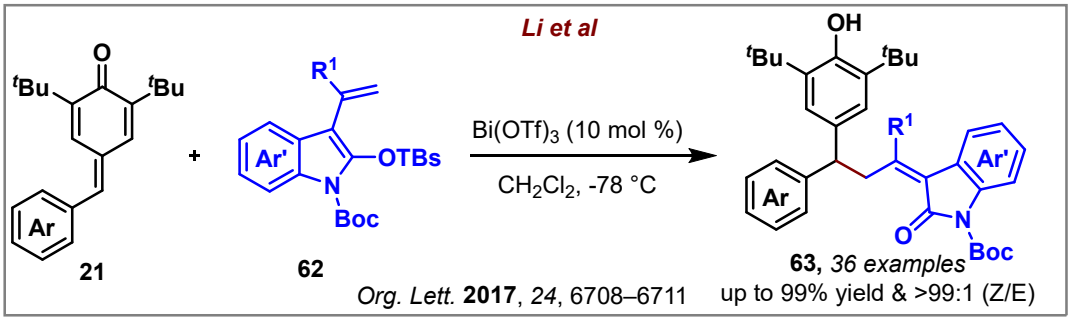
Scheme 1.1.10. Mechanism for the reaction between *p*-QMs and vinyl azide.

Li *et al.*[28e] in 2017 developed efficient bismuth(III) triflate catalyzed 1,6-addition of allyl boronic acid pinacol ester **60** with *p*-quinone methides **21**. Under mild reaction conditions, this method produces valuable allyl group substituted diarylmethane products **61** in high yields (Scheme 1.1.11).



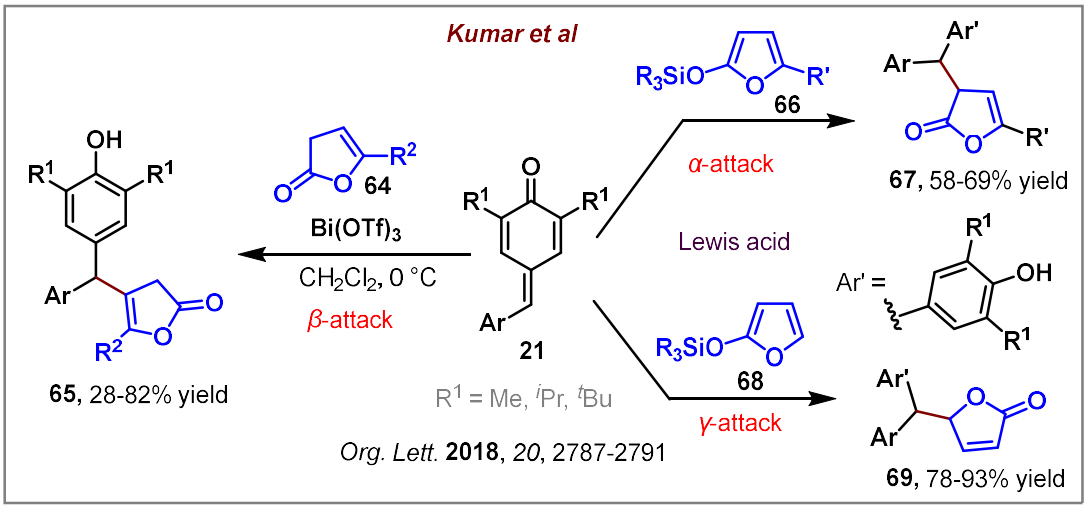
Scheme 1.1.11. $Bi(OTf)_3$-catalyzed allylation of *p*-QMs.

In 2017, the same group reported the $Bi(OTf)_3$-catalyzed vinylogous diastereoselective 1,6-conjugate addition of *p*-QMs **21** with 3-propenyl- 2-silyloxyindoles **62** (Scheme 1.1.12).[28f] This reaction provides access to the wide range of vinylogous 1,6-addition adducts **63** with high diastereoselectivities and in good yields. Mechanistically, the Lewis acid binds to the oxygen atom of **62**, activating the carbonyl group to nucleophilic attack. This Lewis acid coordination assists the leaving of the TBS group and the formation of enol to attack *p*-QMs.



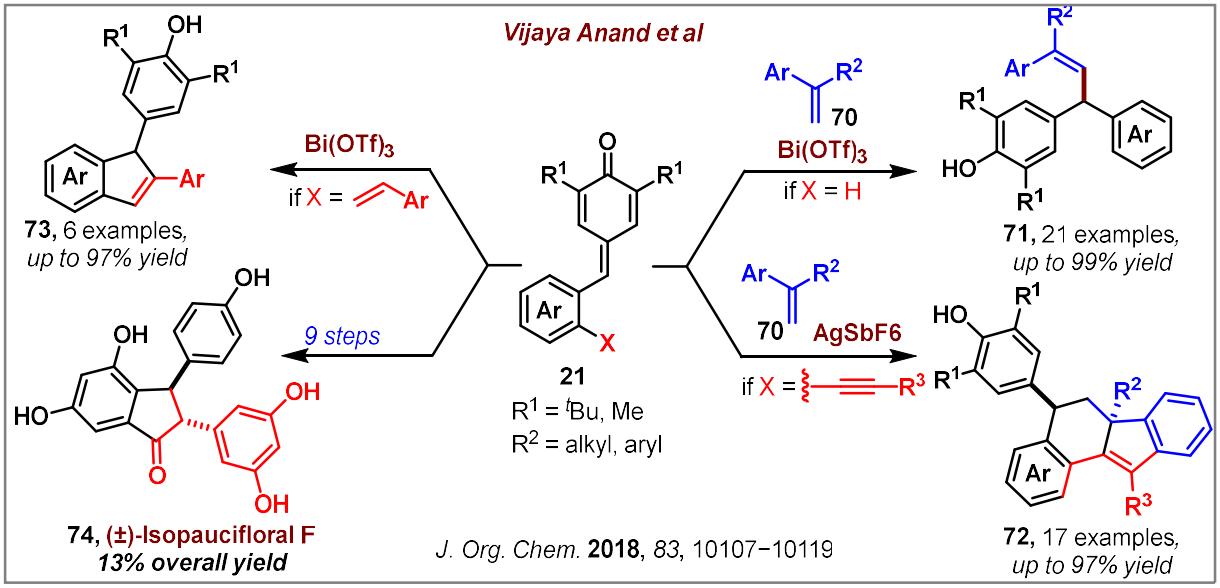
Scheme 1.1.12. $Bi(OTf)_3$-catalyzed 1,6-addition of *p*-QMs with 3-propenyl-2-silyloxyindoles.

In 2018, Kumar *et al.*[28g] disclosed selective nucleophilic addition of *α*-, *β*-, and *γ*-positions of butenolides **64/66/68** with *p*-QMs **21** by employing $Bi(OTf)_3$ or $BF_3{\cdot}OEt_2$ as a catalyst**.** This reaction allows the synthesis of diversely substituted butenolide-derived diarylmethane units **65/67/69** embedded in various natural products belonging to the lignan secolignan families in moderate to good yields (Scheme 1.1.13). Further, one of the most important findings of the study was butenolides enol ester reactivity. Mild reaction conditions and broad substrate scope are the salient features of this method.



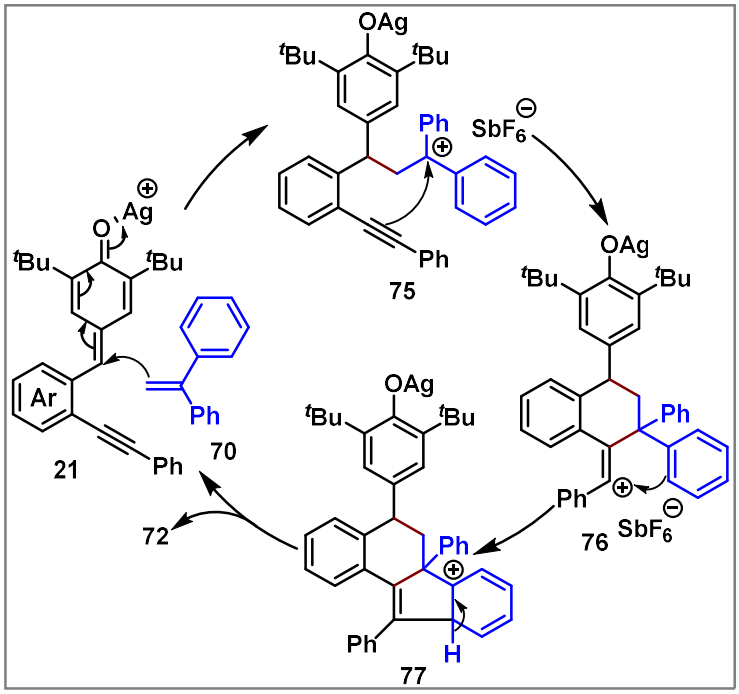
Scheme 1.1.13. $Bi(OTf)_3$-catalyzed selective 1,6-addition of *p*-QMs and butenolides.

In 2018, Vijaya Anand and co-workers reported an efficient Lewis acid-catalyzed protocol for intermolecular 1,6-hydroolefination of *p*-quinone methides with styrenes to access vinyl diarylmethanes and indene derivatives. Importantly, this intramolecular hydroolefination reaction was applied to the total synthesis of (±)-isopaucifloral F. In addition, this method was also employed for the synthesis of various dihydrobenzo[*a*]fluorene derivatives *via* reaction between 2-alkynyl group substituted *p*-QMs and styrenes in good yields and with excellent diastereose lectivity (Scheme 1.1.14).[28h]



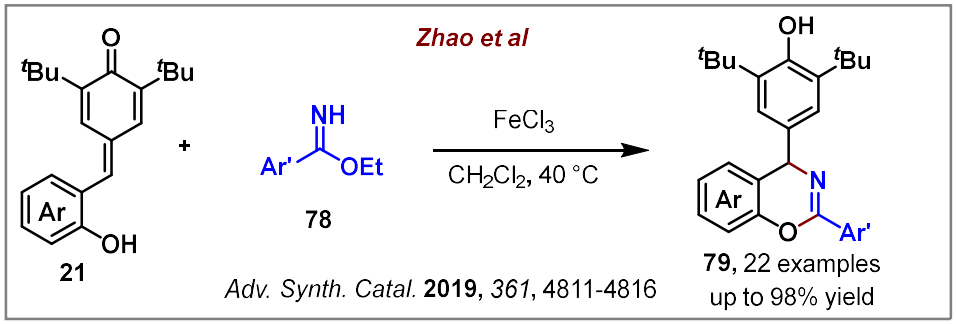
Scheme 1.1.14. 1,6-hydroolefination and cascade cyclization of *p*-QMs with styrenes.

The mechanism rationale of this hydroolefination/cyclization process is illustrated in Scheme 1.1.15. Initially, the carbonyl group of 2-alkynyl group substituted *p*-QM **21** will be activated by the silver catalyst, followed by 1,6- addition reaction of olefin **70** produces reactive carbocation intermediate **75**. Further, the intramolecular attack of alkyne leads to another carbocation intermediate **76**. Then, intramolecular Friedel-Crafts type cyclization of intermediate **76** gives another carbocation intermediate **77**, which undergoes aromatization to deliver product **72.**



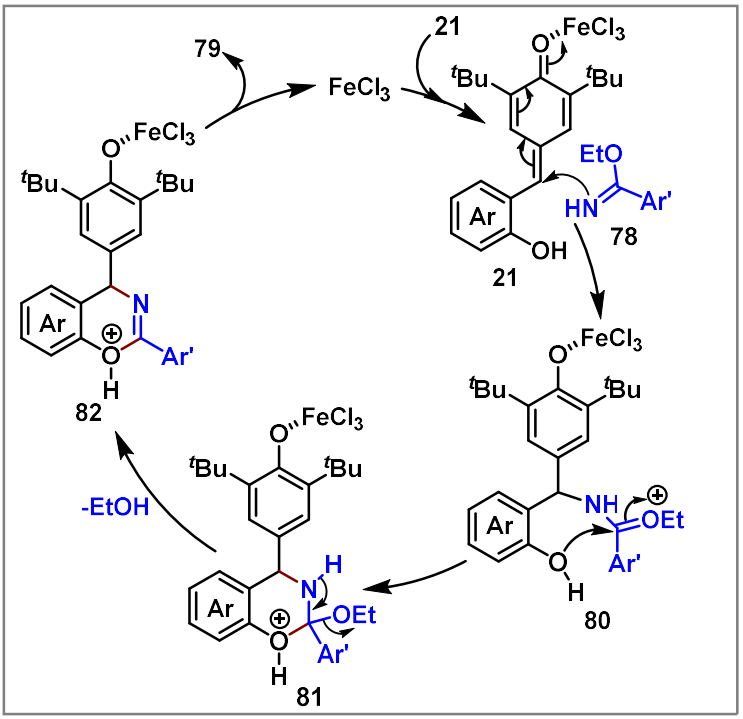
Scheme 1.1.15. Mechanism of 1,6-hydroolefination and cyclization of *p*-QMs with styrenes.

Zhao *et al*. in 2019 documented the $FeCl_3$-catalyzed 1,6-addition/intramolecular cyclization reaction imidates **78** to *ortho*-hydroxyphenyl-substituted *p*-QMs **21** to prepare divesre 2,4-diaryl-1,3- benzoxazines **79** derivatives. This reaction gives easy access to 2,4-diaryl-1,3-benzoxazines **79** in moderate to excellent yields under mild conditions and with good functional tolerance (Scheme 1.1.16).[28i]



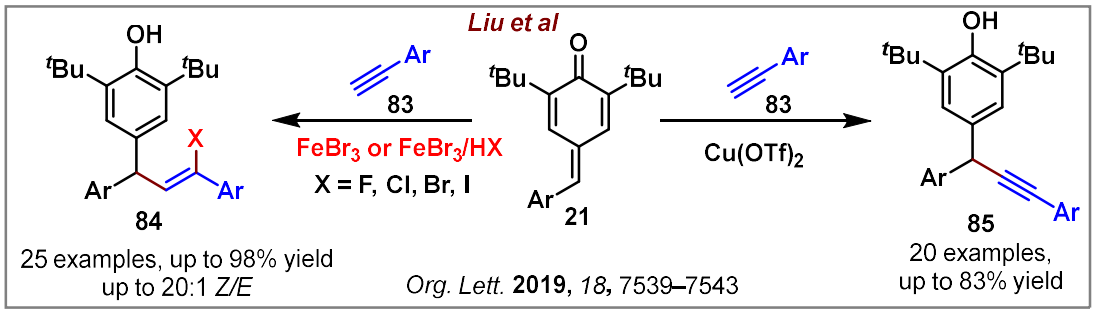
Scheme 1.1.16. 1,6-addition/intramolecular cyclization *p*-QMs with imidates.

Mechanistically, this transformation involves activation of *p*-QMs **21** by $FeCl_3$ and the attack of imidates **78** to form intermediate **80**. Subsequent intramolecular attack of the oxygen atom of the phenol generates a cyclized intermediate **81**, followed by the elimination of EtOH produces intermediate **82**. Finally, intermediate **82** undergoes a protonation to furnish the product **79** and releases the $FeCl_3$ catalyst (Scheme 1.1.17).

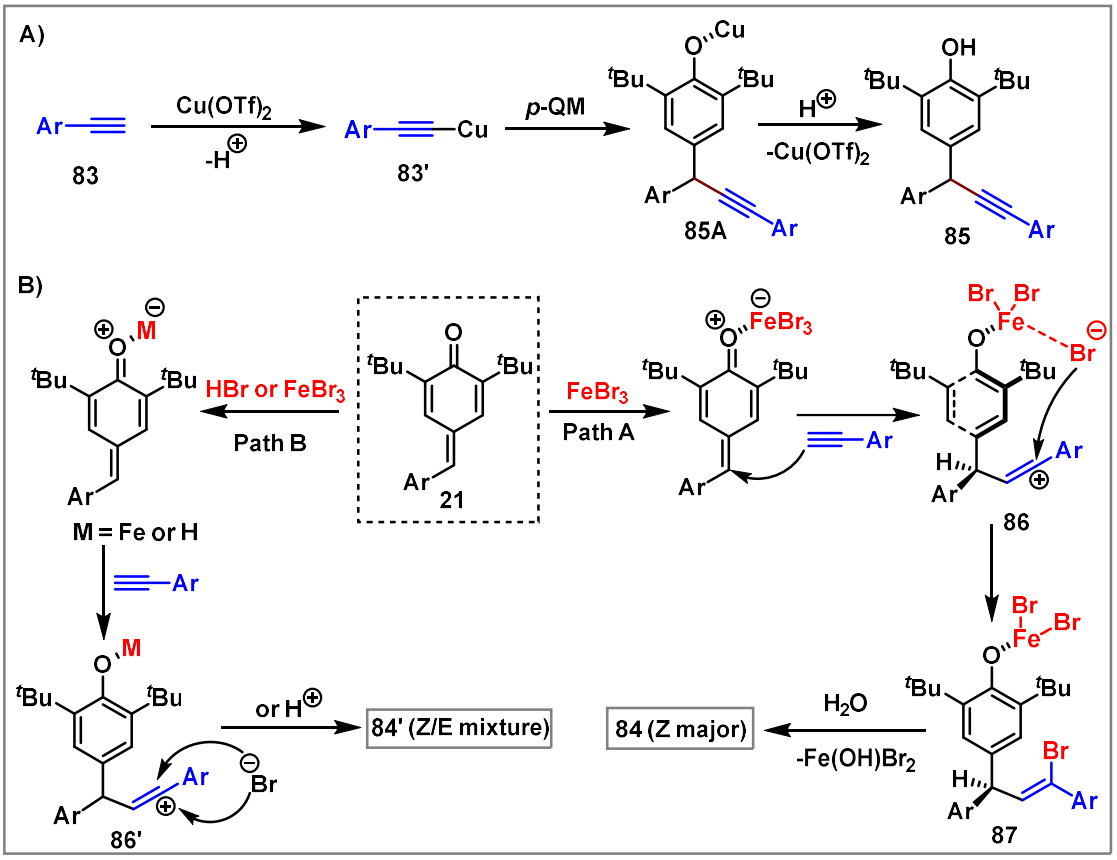


Scheme 1.1.17. Mechanism of reaction between *ortho*-hydroxyphenyl *p*-QMs with imidates.

In 2019, Liu and co-workers demonstrated chemodivergent catalyst-controlled 1,6-addition of *p*-QMs **21** and alkynes **83**, resulting in diverse alkynyl- and vinyl-substituted diarymethanes derivatives **84**/**85**.[28j] In the presence of $Cu(OTf)_2$ the direct 1,6-addition of alkynes with *p*-QMs take place to give the products **85**. While, in the presence of iron, the three components reaction of *p*-QMs, alkynes, and halogens from iron salts or added HX acid deliver the vinyl-substituted diarylmethane adduct **84**. The salient features of this reaction include controllable chemoselectivity, mild reaction conditions, inexpensive catalysts, and good substrate scopes (Scheme 1.1.18).



Scheme 1.1.18. Chemodivergent 1,6-addition of alkynes with *p*-QMs.



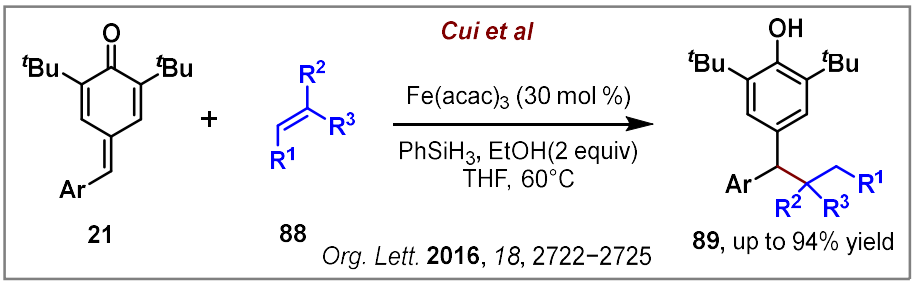
Scheme 1.1.19. Mechanism of chemodivergent1,6-addition alkynes with *p*-QMs.

The mechanism of this transformation is outlined in Scheme 1.1.19. Initially, $Cu(OTf)_2$-activate the terminal alkyne **83** to generate the intermediate **83'**, which then attacked *p*-QMs **21** to give intermediate **85A**. The protonation of this intermediate leads to product **85,** and the catalyst $Cu(OTf)_2$ is regenerated. For Fe-promoted three-component reaction, the author proposed two pathways. In the absence of HBr, $FeBr_3$-coordinated *p*-QMs **21** followed by the attack of alkyne **83** gives vinyl cation **86**. Then these intimate ion pair **86** undergoes the intramolecular addition of bromide anion produces intermediate **87**. Further, the hydrolysis of **87** formed the product **84** with major Z-isomer and released $Fe(OH)Br_2$ (Path-A). Under path B, *p*-QMs **21** binds with Fe or protonation, followed by an attack of the π electron of alkyne **83** leads to the vinyl cation **86'**. Finally, intermediate **86'** underwent the addition of bromide anion to yield the product **84'** as a Z/E mixture.

1.1.4.2 Radical enabled 1,6-addition

The development of radical cascade reactions of unsaturated acceptors permits the construction of multiple carbon-carbon and carbon-heteroatom bonds. It has become a crucial synthetic strategy for preparing valuable entities. The unsaturated compounds like alkene and alkyne moieties have been established as versatile radical acceptors. Similarly, in recent years *p*-QMs have proven to be versatile radical acceptors to construct a wide range of valuable products.

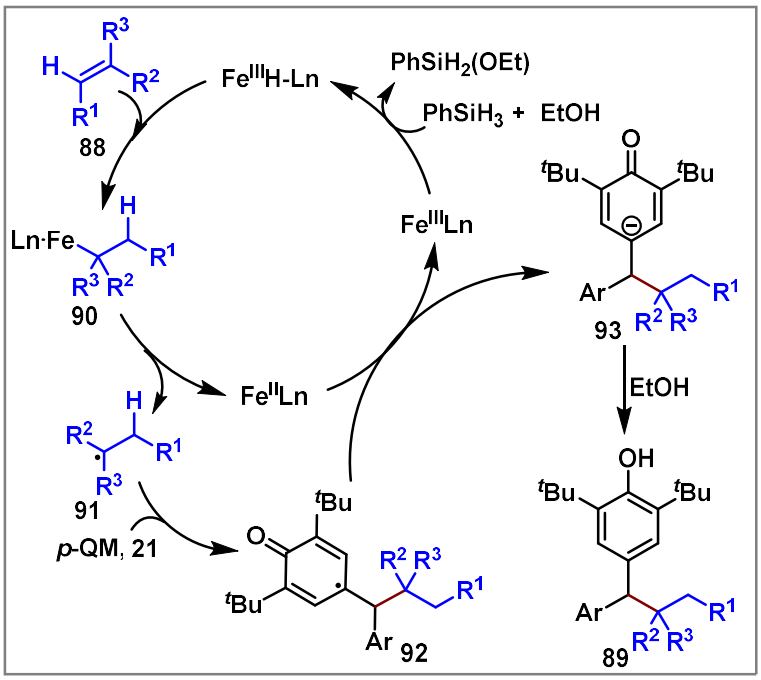
In 2016, the Cui group[29a] reported a Fe-catalyzed hydroalkylation of *p*-quinone methides **21** using alkene **88** for the synthesis of various phenol derivatives. This radical-induced reaction was carried out at 60 °C using $Fe(acac)_3$, $PhSiH_3$, 2 equiv. of EtOH in THF as a solvent producing the respective phenol products **89** in 30-94% yields. In this reaction, a wide range of terminal and internal olefins were tolerated to convert into alkyl radicals and their subsequent addition to *p*-QMs to produce various alkyl group substituted diarylmethane unit (Scheme 1.1.20).



Scheme 1.1.20. Fe-catalyzed hydroalkylation of alkenes with *p*-QMs.

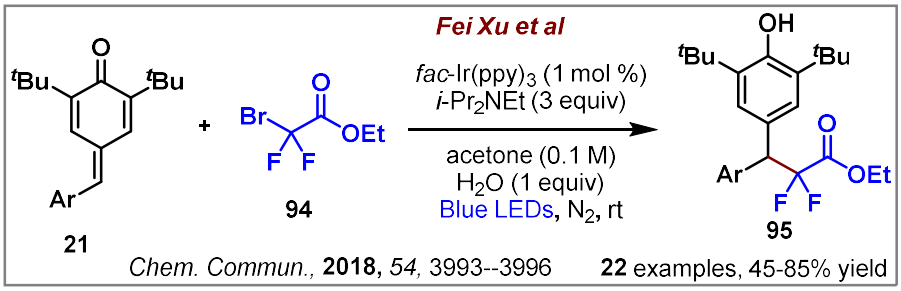
The mechanism involves converting Fe(III) to Fe(III)-hydride species by a reaction between phenyl silane and ethanol. Then this hydride species undergo regioselective addition to

olefin **88** to generate intermediate **90**. Further, dissociation of **90** gives alkyl radical **91** and Fe(II) species. Next, this alkyl radical is trapped by *p*-QMs **21** to generate intermediate **92**. Finally, the single-electron transfer gives anionic intermediate **93,** followed by its protonation and isomerization, leads to the product **89** and regeneration of the Fe(III) catalyst (Scheme 1.1.21).



Scheme 1.1.21. The mechanism for the hydroalkylation of alkenes with *p*-QMs.

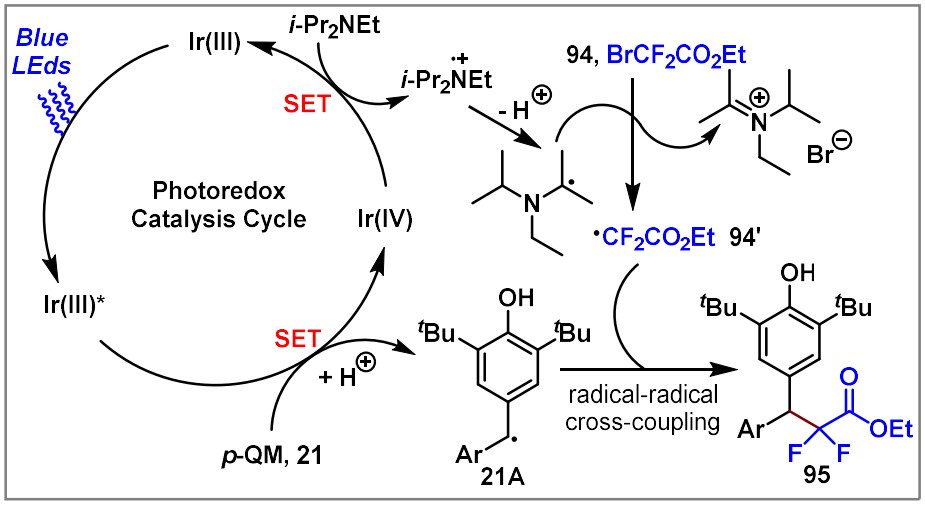
Fei Xu and co-workers demonstrated a photocatalytic radical cross-coupling reaction of *p*-QMs **21** and ethyl bromodifluoroacetate **94** to access difluoroalkylated diarylmethane compounds **95**. The reaction features high efficiency and broad functional group compatibility. Notably, the reaction was mediated by a diarylmethyl radical intermediate generated from the single electron reduction and subsequent protonation of *p*-QMs (Scheme 1.1.22).[29b]



Scheme 1.1.22. Visible light-mediated synthesis of difluoroalkylated diarylmethanes.

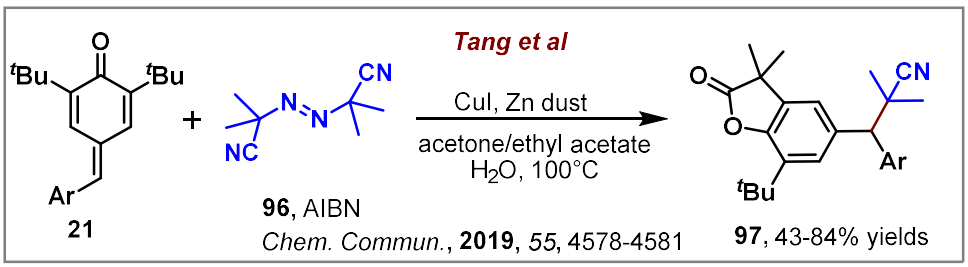
The proposed mechanism for this radical-radical cross-coupling reaction is depicted in Scheme 1.1.23. Upon absorption of visible light, the excited [*fac*-Ir(III)(ppy)$_3$]* engages in sin-

gle electron transfer (SET) with *p*-QM **21,** followed by a protonation process to give the *p*-QM diarylmethyl radical intermediate **21A** and the oxidized [*fac*-Ir(IV)(ppy)$_3$]$^+$. Then SET process occurs between DIPEA and [*fac*-Ir(IV)(ppy)$_3$]$^+$ giving radical cation of DIPEA and closing the photocatalytic cycle. Next, deprotonation of DIPEA radical cation gives *α*-aminoalkyl radical (a strong reducing agent) that can easily reduce ethyl bromodifluoroacetate **94** to generate corresponding radical intermediate **94'**. Finally, a radical–radical cross-coupling of *p*-QM radical intermediate **21A** and **94'** deliver diarylmethane product **95**.



Scheme 1.1.23. Mechanism of radical reaction of *p*-QMs and ethyl bromodifluoroacetate.

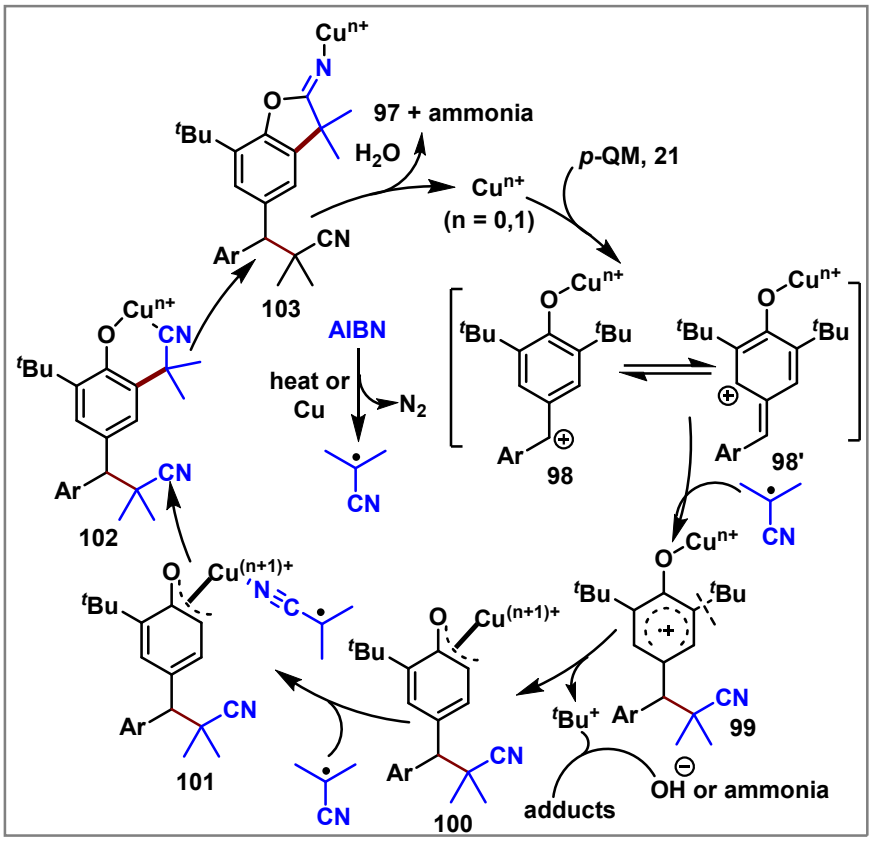
In 2019, Tang and group[29c] reported a Cu-catalyzed radical cascade reaction between *p*-QMs **21**, AIBN **96** and H_2O for accessing benzofuran-2(3H)-one scaffold **97** in one-pot. This reaction proceeds through 1,6-conjugate addition/ aromatization of cyanoalkyl radical, *α*-cyanoalkylation by C-^{t}Bu bond cleavage followed by cyano-insertion/cyclization/hydrolysis. This reaction sequence provides divesre cyano-substituted benzofuran-2(3H)-ones and 2,3-dialkylating derivatives with good functional tolerance and yields (Scheme 1.1.24).



Scheme 1.1.24. Cu-catalyzed radical cascade between *p*-QMs, AIBN and water.

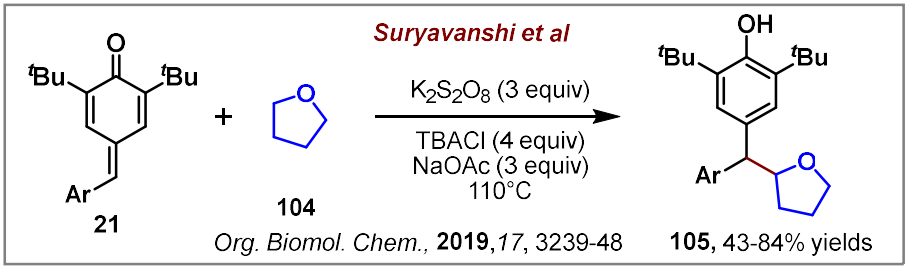
This radical cascade transformation involves the formation of isobutyronitrile radical upon heating or Cu catalysis from AIBN. Initially, the Cu^{n+} coordinate to the *p*-QM **21,** forming

intermediate **98',** which underwent 1,6-addition with an isobutyronitrile radical, generating the radical cation **99**. Then, in the presence of *in situ* generated nucleophile (e.g., hydroxide and ammonia), removing one of the *t*-butyl groups *via* a retro-Friedel–Crafts process gives Cu-complex **100**. Subsequently, coordination of the isobutyronitrile radical to the intermediate **100** to form an intermediate **101,** followed by radical cross-coupling with the adjacent allyl-like Cu species, generate intermediate **102** *via* SET (single-electron-transfer) reduction of $Cu^{(n+1)+/}Cu^{n+}$. Finally, cyanoinsertion/ cyclization of **102** and hydrolysis of **103** give the benzofuran-2(3H)-ones **97** and Cu^{n+} for the next catalytic cycle (Scheme 1.1.25).



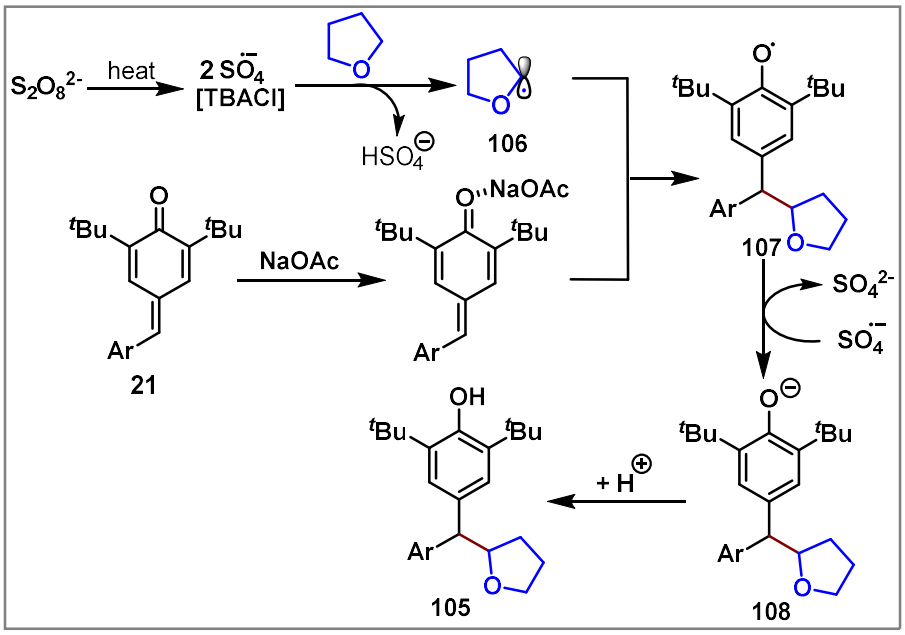
Scheme 1.1.25. Mechanism of radical cascade between *p*-QMs, AIBN and water.

In 2019, Suryavanshi and co-workers[29d] reported radical 1,6-addition of cyclic ethers **104** with *p*-quinone methides **21** under the metal-free condition to afford cyclic ethers substituted diarylmethane or triarylmethane phenols **105**. Additionally, the reaction of isatin-derived *p*-QMs and various fuchsone derivatives were also studied as 1,6-acceptor substrates with cyclic ethers to deliver related products in good yields (Scheme 1.1.26).



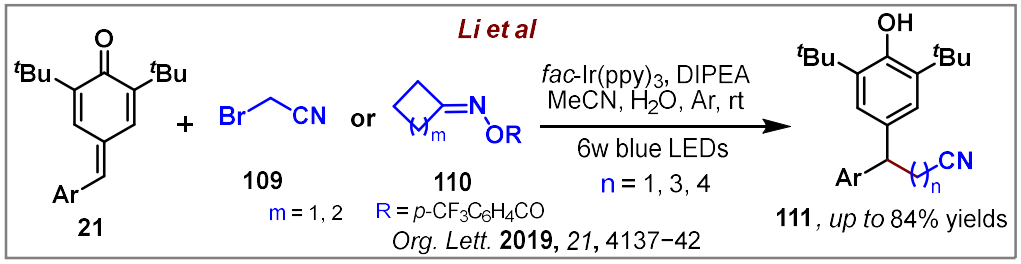
Scheme 1.1.26. Radical 1,6-addition between cyclic ethers and *p*-QMs.

The mechanism of this reaction comprises formation of sulfate anion radical by the decomposition of persulfate and is stabilized by TBACl. Then the abstraction of the proton of THF by a sulfate anion radical generates *α*-oxyalkyl radical **106** followed by its 1,6-addition with activated *p*-QMs producing the radical intermediate **107**. Finally, single-electron transfer from the sulfate radical anion to the intermediate **107** gives anionic intermediate **108,** which on protonation gives rise to the desired product **105** (Scheme 1.1.27).



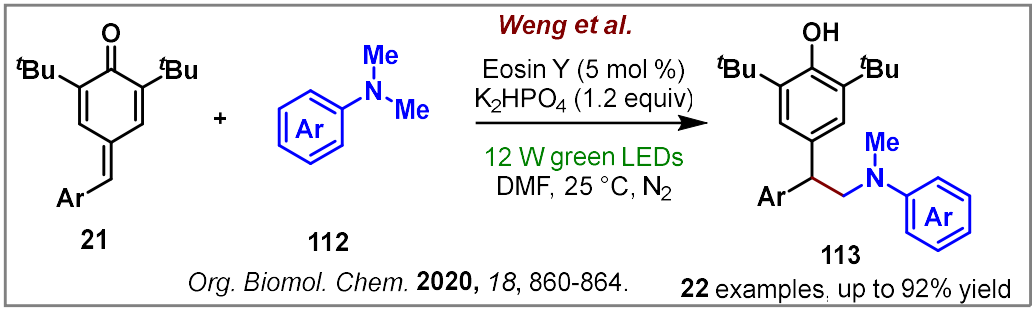
Scheme 1.1.27. Mechanism of radical 1,6-addition of cyclic ethers with *p*-QMs.

In 2019, Li and co-workers[29e] developed a simple photocatalytic radical cyanoalkylation of *p*-QMs **21** employing cyanoalkylating reagents **109** or **110** to access cyanoalkylated diarylmethane compounds **111** under mild conditions (Scheme 1.1.28). The reaction is very efficient and has a wide range of functional group compatibility. The synthetic utility of this methodology has been demonstrated in the efficient synthesis of GPR40 agonists, which play a crucial role in FA-induced glucose-sensitive insulin secretion. This radical cyanoalkylation process follows a similar mechanism described in Scheme 1.1.23.



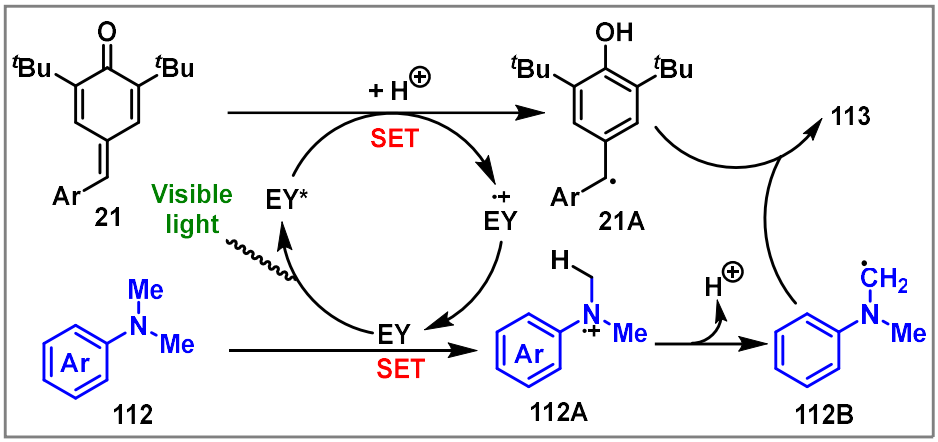
Scheme 1.1.28. Photocatalytic radical cyanoalkylation of *p*-QMs.

Recently, Weng and co-workers demonstrated a visible light-mediated radical-radical cross-coupling reaction of *p*-QMs **21** with *N*-substituted anilines **112** for the efficient synthesis of 2,2-diarylethylamines **113**. This reaction features metal-free, redox-neutral and mild reaction conditions with broad functional group compatibility (Scheme 1.1.29).[29f]



Scheme 1.1.29. Radical cross-coupling between *p*-QMs and *N*-substituted anilines.

The mechanism of this radical cross-coupling reaction is illustrated in Scheme 1.1.30. Initially, upon irradiation of visible light, EY produces long-lived excited-stated EY*, which on single electron transfer (SET) with *p*-QM **21**, followed by a protonation, generates diarylmethyl radical intermediate **21A** and the oxidized $EY^{\bullet+}$. Next, this oxidized photocatalyst converts the

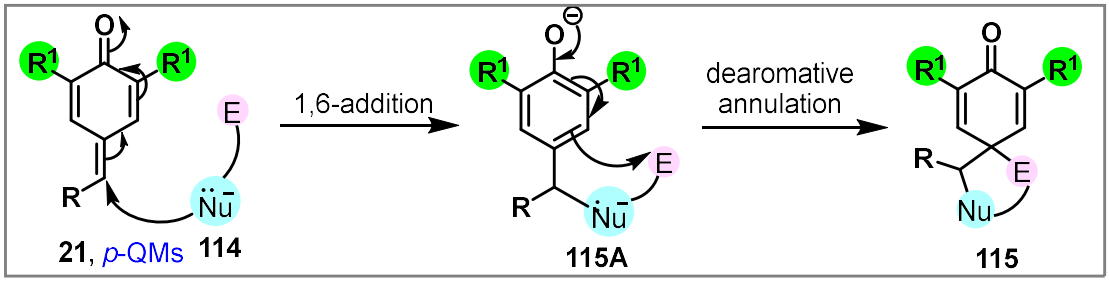


Scheme 1.1.30. Mechanism of radical cross-coupling of *p*-QMs with *N*-substituted anilines.

neutral amine **112** into the radical cation **112A**. Finally, deprotonation of **112A** gives *α*-aminoalkyl radical **112B,** which on direct coupling with radical intermediate **21A**, provides the corresponding product **113**.

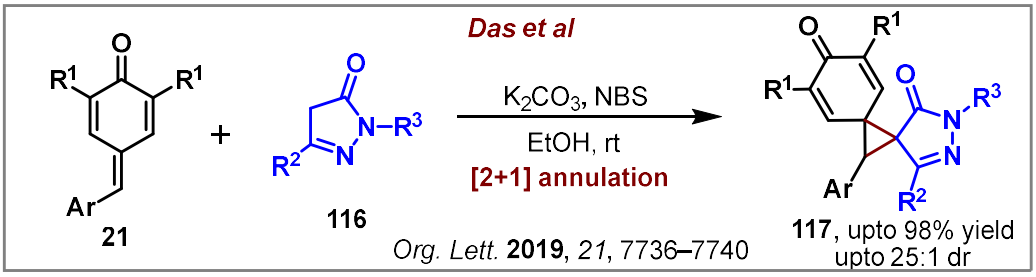
1.1.4.3 1,6-Addition/annulation of *p*-QMs :

Recently, *p*-quinone methides (*p*-QMs) have emerged as one of the most desirable components to access spiro-cyclohexadienones structural core. As discussed above, the 1,6-addition reactions of *p*-QMs are driven by the aromatization of the cyclohexadiene moiety, which has been extensively studied and well documented in the literature. In contrast, the spirocyclization reactions of *p*-QMs are comparatively less studied due to the requirement of the dearomatization process. The reaction of *p*-QMs with prefunctionalized nucleophiles **114** having additional functional sites undergoes spiro-cyclization to deliver spiro-cyclohexadienones core (Scheme 1.1.31). In these approaches, the carbon atom at the *para*-position to phenolic hydroxyl exhibit sufficient nucleophilicity (as in intermediate **115A**) and thus can undergo dearomative ring-closing giving rise to the [2+n] spirocyclization reactions. In the past few years, significant annulations such as [2+1], [3+2] and [4+2] spiro-cyclization reactions have been developed employing *p*-QMs. Few selective approaches to [2+n] spirocyclization reactions that have been discussed are as follows.



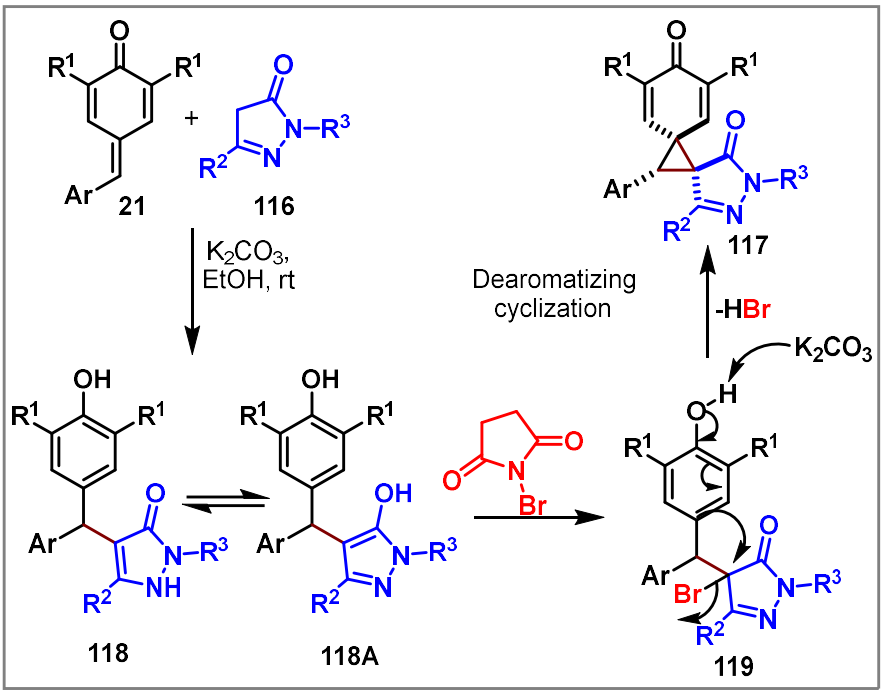
Scheme 1.1.31. 1,6-addition/annulation reactions of *p*-QMs.

In 2019, Das and co-workers[30a] demonstrated diastereoselective formal 1,6-conjugate addition-induced [2+1] annulation reaction of *p*-quinone methides **21** and pyrazolones **116**. This



Scheme 1.1.32. [2+1] annulation of *p*-quinone methides and pyrazolones.

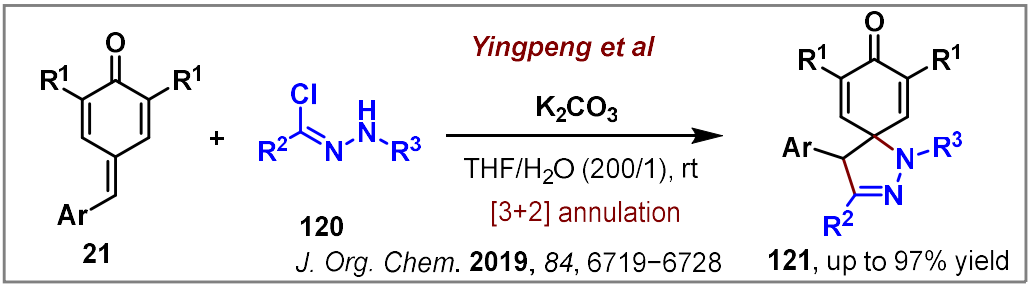
reaction produced various bis-spiro[cyclohexadienone-cyclopropane-pyrazolone] derivatives **117** under basic conditions in good yield and with good diastereoselectivities (Scheme 1.1.32).



Scheme 1.1.33. Mechanism of bis-spirocyclization of *p*-QMs and pyrazolones.

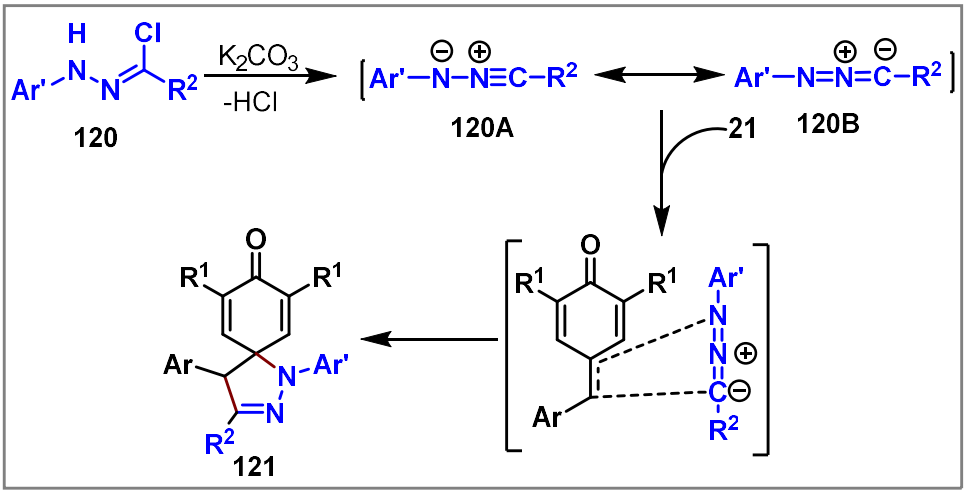
The possible mechanism for this bis-spirocyclization is shown in Scheme 1.1.33. Firstly, under basic conditions 1, 6-addition of pyrazolone **116** with *p*-QM **21** generates the intermediate **118** (and its tautomer **118A**). Further, the bromination of intermediate **118A** with NBS produces the pyrazolone substituted phenol compound **119,** followed by an intramolecular dearomatization ring closing generate the final product **117.**

In the same year, Yingpeng and group[30b] reported [3 + 2] cycloaddition between *p*-QMs **21** and nitrile imines **120** for synthesizing spiro-pyrazoline-cyclohexadienones derivatives. This protocol is tolerant to various functional groups with a broad substrate scope giving access to spiropyrazoline-cyclohexadienone products **121** in good to excellent yields (Scheme 1.1.34).



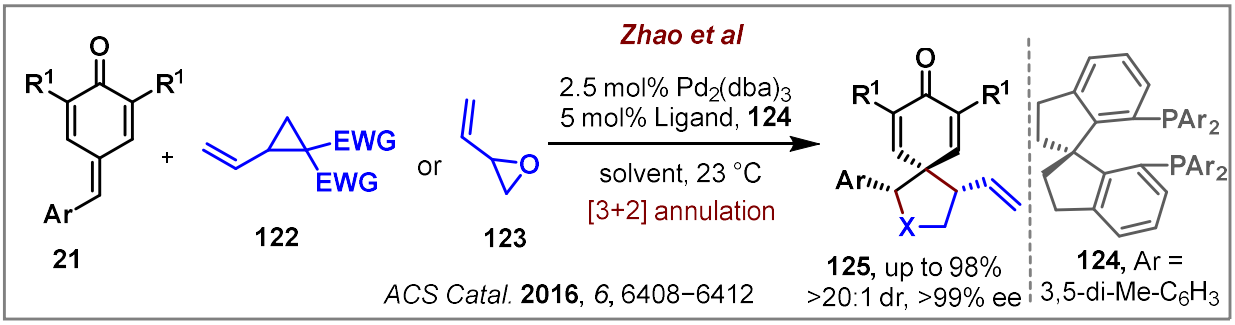
Scheme 1.1.34. [3+2] cycloaddition between *p*-QMs and nitrile imines.

The mechanism of this process involves one step cycloaddition reaction. Initially, dehydrochlorination of hydrazonoyl chloride **120** with base K_2CO_3 gives nitrile imine with two canonical forms, **120A** and **120B**. Of these two forms, **120B** reacts with *p*-QMs **21** and produces the desired product **121** (Scheme 1.1.35).



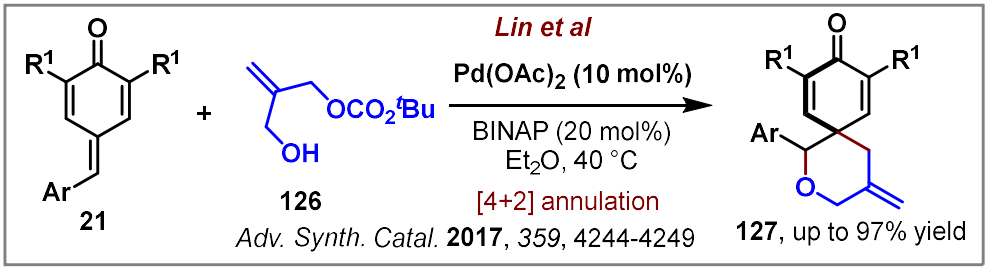
Scheme 1.1.35. Mechanism of [3+2] cycloaddition of *p*-QMs and nitrile imines.

In 2016, Zhao *et al.*[30c] reported an unprecedented stereoselective Pd-catalyzed formal [3 + 2] cycloaddition reaction of *p*-QMs **21** with cyclopropanes/vinyl epoxides **122** or **123** to afford diverse spiro[4.5]decanes **125** derivatives (Scheme 1.1.36). This protocol gives access to spiro[4.5]decanes products **125** with excellent stereocontrol from readily available starting materials, commercially available catalysts at ambient temperature.



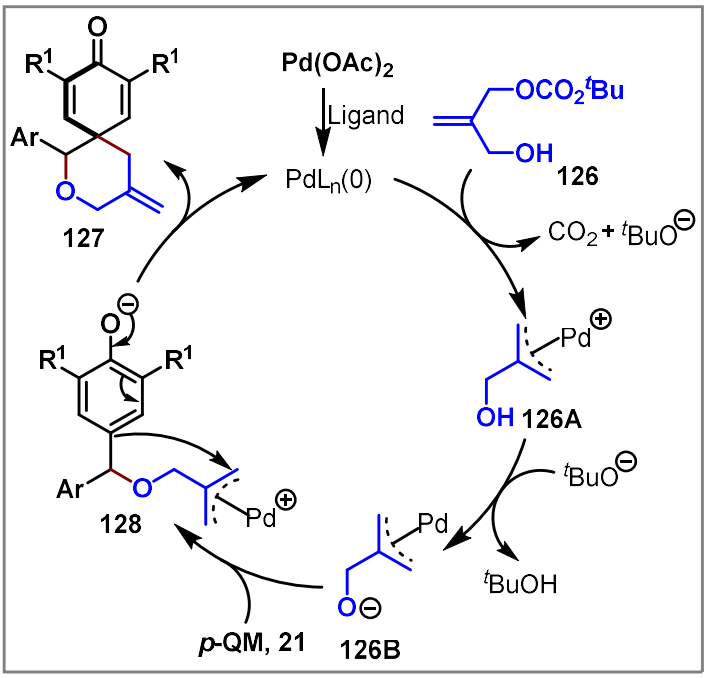
Scheme 1.1.36. Stereoselective Pd-catalyzed formal [3 + 2] cycloaddition reaction of *p*-QMs.

In 2017, Lin and co-workers reported Pd-catalyzed oxa-[4+2] annulation reaction between *p*-QMs **21** and allyl carbonates **126** bearing a nucleophilic alcohol side chain. This protocol provided an efficient strategy for constructing 2-oxaspiro-cyclohexadienones derivatives **127** *via* 1,6-conjugated addition induced allylation in moderate to good yields (Scheme 1.1.37).[30d]



Scheme 1.1.37. Stereoselective Pd-catalyzed formal [3 + 2] cycloaddition reaction of *p*-QMs.

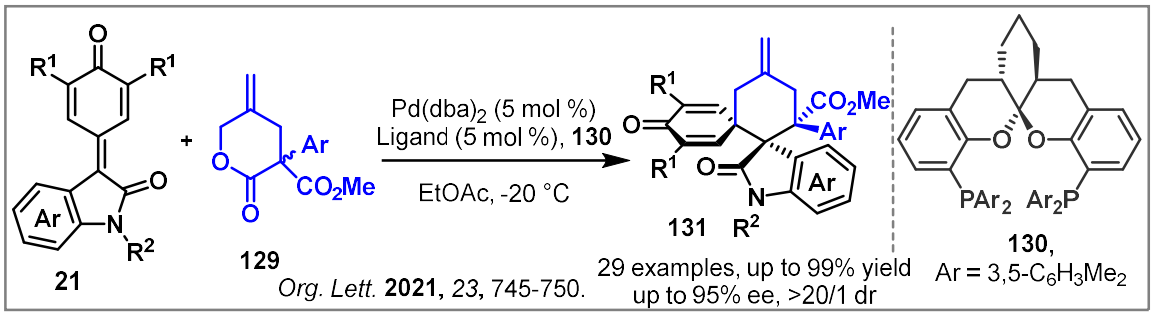
The proposed mechanism comprises the initial oxidative addition of allylic carbonate **126** to Pd(0) species that generates π-allyl- Pd-complex **126A** along with the liberation of *tert*-butoxy anion and carbon dioxide. Next, the deprotonation of the hydroxyl group by *tert*-butoxy anion gives oxygen anion intermediate **126B**. Then, oxygen anion underwent 1,6-conjugate addition to *p*-QM **21,** producing intermediate **128**, followed by dearomatization ring closure provides the product **127** and regenerates the Pd-catalyst for the next catalytic cycle (Scheme 1.1.38).



Scheme 1.1.38. Mechanism of oxa-[4+2] annulation of *p*-QMs and allyl carbonates.

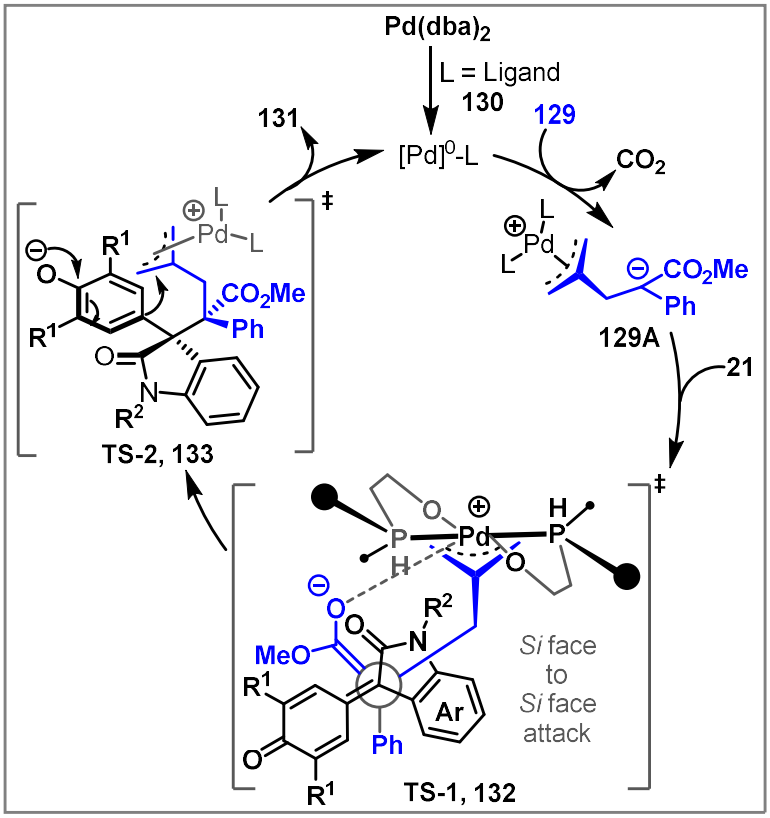
Recently, Fan and co-workers developed Pd-catalyzed first diastereo and enantioselective [4 + 2] annulation between isatin-derived *p*-QMs **21** and aryl-substituted γ-methylidene-δ-valerolactones (GMDVs) **129**. Importantly, this method provides an effective and selective approach for the construction of chiral cyclohexadienone-fused cyclohexyl spirooxindoles derivatives **131** comprising three highly congested contiguous quaternary centers in bispirocyclic

skeleton, of which two are vicinal to each other (Scheme 1.1.39).[30e]



Scheme 1.1.39. Pd-catalyzed asymmetric [4 + 2] annulation reaction of GMDVs and *p*-QMs.

The mechanism for this Pd-catalyzed asymmetric [4 + 2] annulation reaction of GMDVs and *p*-QMs is depicted in Scheme 1.1.40. Initially, Pd(0)-mediated decarboxylative oxidative addition to GMDV **129** generates 1,4-zwitterionic intermediate **129A.** Further, due to the C2-like symmetric backbone of ligand **130,** an enantioselective 1,6-conjugate addition *via* **TS-1**, the *Si* face of intermediate **129A** to the *Si* face of the *p*-QM **21**, takes place. Finally, the intramolecular dearomative ring-closing in **TS-2** yields the required cyclohexyl spirooxindole **131** and a Pd(0) catalyst for the next catalytic cycle.



Scheme 1.1.40. Mechanism of asymmetric [4 + 2] annulation reaction of GMDVs and *p*-QMs.

1.1.5 Conclusion:

In conclusion, the chemistry of *p*-quinone methides has contributed to rapid advances in synthetic organic chemistry and provided access to new molecules needed to explore hitherto unexplained and undiscovered processes in the molecular realm. Despite the significant achievement, we still believe that a window of opportunities exists to employ *p*-QMs in various synthetic applications such as developing new reactions, use of alternative catalysts, green and sustainable chemistry and so on. The present thesis unveiled the unique reactivity of *p*-QMs and developed new synthetic chemical transformations to achieve diverse, structurally intriguing, complex and biologically relevant molecules.

1.1.6 References

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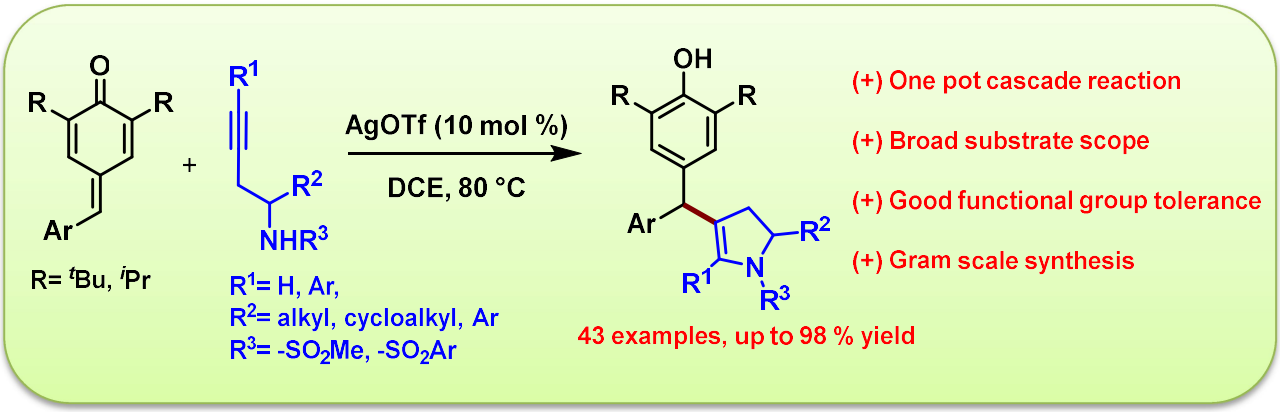
Section-II

Silver Catalyzed Cascade Cyclization/1,6-Conjugate Addition of Homopropargyl Sulfonamides to *p*-Quinone Methides: An Approach to Diverse 3-Diarylmethine Substituted Dihydropyrroles

A silver catalyzed cycloisomerization/1,6-conjugate addition of homopropargyl sulfonamides to *p*-quinone methides to access diverse diarylmethine substituted dihydropyrroles has been disclosed in this section. The reaction pathway involves an intramolecular cascade cyclization of homopropargyl sulfonamides to generate a highly reactive dihydropyrrole intermediate *in situ* followed by conjugate addition with *p*-quinone methides. This method provides an efficient and scalable route to the synthesis of 3-diarylmethine substituted dihydropyrroles in one pot.



J. Org. Chem., **2020,** *85*, 15038–15050

1.2.1 Introduction

Nitrogen-containing five-membered heterocycles such as pyrroles, dihydropyrroles and pyrrolidines are found in many bioactive natural products, as well as pharmaceuticals, pesticides and functional materials.[1,2] In five-membered heterocycles, 2,3-dihydropyrroles, also called 2-pyrrolines, are important frameworks present in many natural products and pharmaceutical agents (Figure 1.2.1).[3] For example, pyrrolobenzodiazepines sibiromycin **I** and anthramycin **II** produced by actinomycetes are potent DNA alkylating agents with significant antineoplastic and antitumor properties.[4a] Further, spirotryprostatin B compound **III** isolated from the fungus *Aspergillus fumigatus* inhibits cell cycle progression in mammalian cells.[4b] Meropenem (SM-7338) **IV** is a broad-spectrum antibiotic active against gram-positive and negative bacteria.[4c] Recently, in combination with vaborbactam, it has been approved by the FDA to treat complicated urinary tract infections in adults.[4d] In addition, 2,3-dihydropyrroles have been widely employed as a versatile building blocks in the synthesis of natural products and other complex molecules.[5]

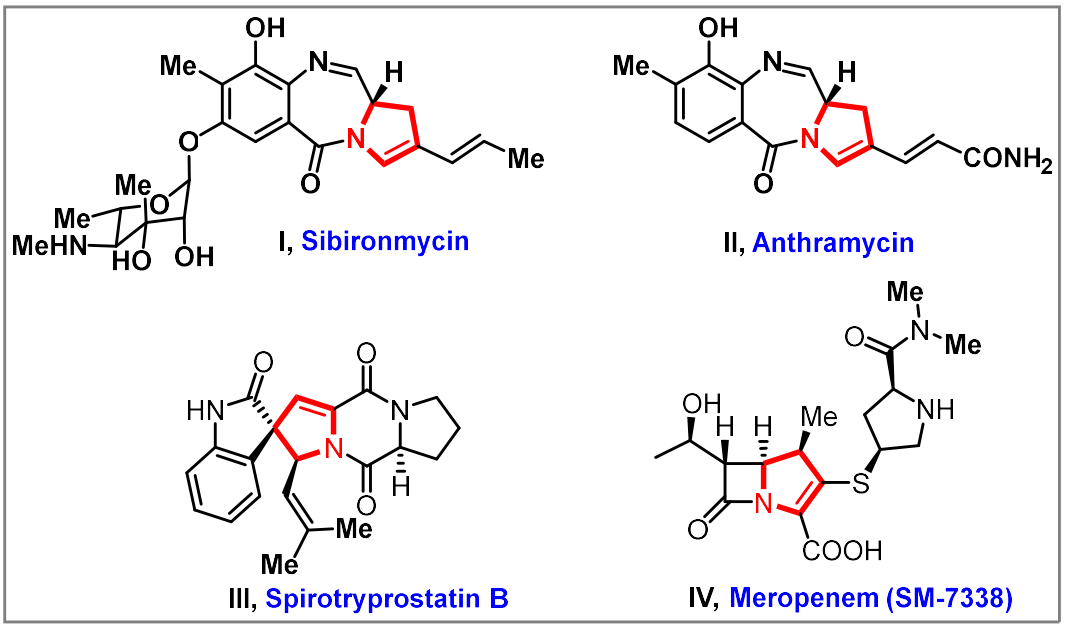


Figure 1.2.1. Representative examples of natural products containing dihydropyrrole units.

Of particular interest, 3-diarylmethine substituted dihydropyrroles are an important subclass of pyrroles that are present in several bioactive agents used to treat several disorders such as the overactive bladder (Darifenacin), epilepsy, inflammation etc. (Figure 1.2.2).[6] Therefore, the development of a rapid, catalytic and one pot strategy to access these kinds of pyrrole derivatives is of high value. In recent years, the metal-catalyzed electrophilic cyclization of heteroa-

tomic nucleophiles with alkynes has emerged as a general and efficient protocol for constructing a wide variety of heterocycles. Notably, catalytic cascade cyclization of alkynyl sulfonamides followed by trapping with suitable electrophiles would be an ideal and valuable strategy for the construction of substituted dihydropyrrole.[7-10] Following are a few reports on the electrophilic cascade cyclization and subsequent trapping with electrophiles in the synthesis of complex heterocyclic scaffolds.

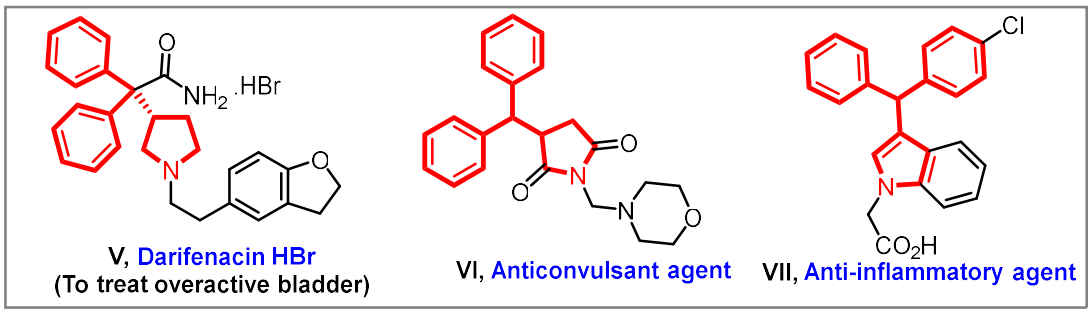
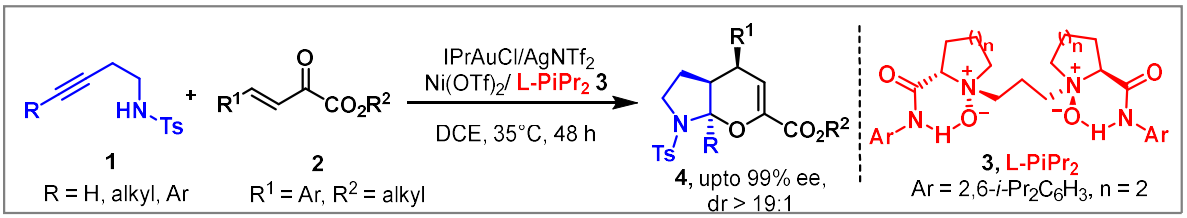


Figure 1.2.2. Bioactive molecules with the 3-diarylmethine substituted dihydropyrrole unit.

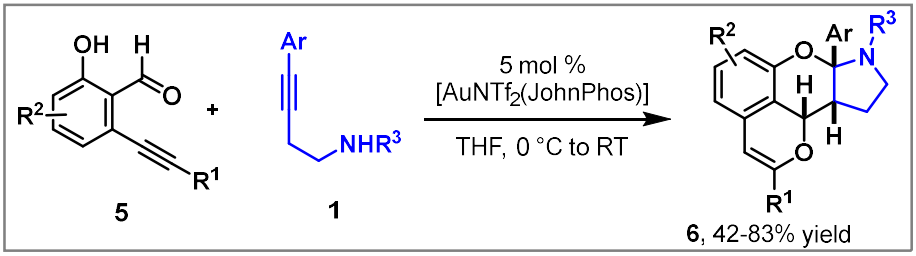
1.2.2 Literature Precedence on Strategies Involving Cyclization of Alkynamide in the Synthesis of Complex Heterocyclic Scaffolds

Feng and co-workers[10a] in 2018 developed an efficient catalytic asymmetric cascade cyclization/inverse-electron-demand hetero-Diels-Alder reaction of *β,γ*-unsaturated *α*-ketoesters **2** with alkynamides **1**. This reaction provides a wide range of fused bicyclic *N, O*-acetals or *O, O*-acetals derivatives **4** with a chiral quaternary carbon centre. For this transformation, they utilized a bimetallic catalyst system with achiral gold(I) catalyst and chiral *N, N'*-dioxide/Ni(II) catalyst **3** (Scheme 1.2.1).



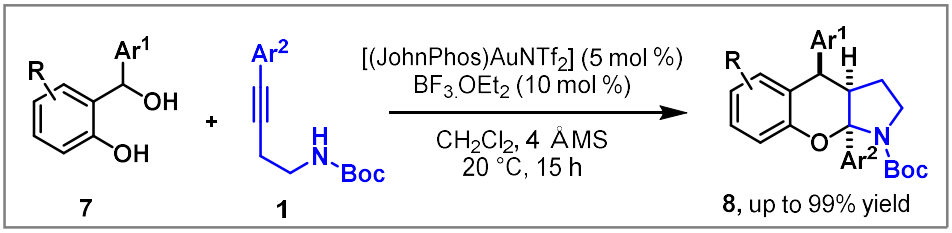
Scheme 1.2.1. Asymmetric cyclization/ inverse-electron-demand hetero-Diels-Alder reaction.

In 2016, Rodriguez and co-workers reported a gold-catalyzed cascade reaction of *ortho*-alkynyl salicylaldehydes **5** and alkynamides **1** towards functionalized complex polycyclic compounds **6**.[10b] The reaction proceeds through a double cycloisomerization reaction and subsequent formal [4+2] cycloaddition. Interestingly, in this reaction, the gold catalyst promotes the *in situ* formation of both the diene and dienophile (Scheme 1.2.2).



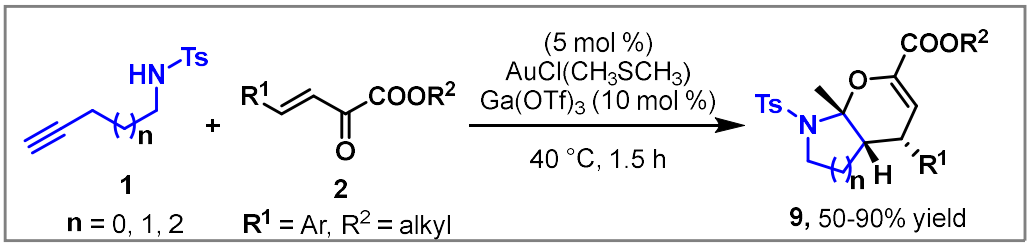
Scheme 1.2.2. Gold(I)-catalyzed formal [4+2] cycloaddition reaction

In 2018, the same group[10c] demonstrated dual Gold/Lewis acid-catalyzed simultaneous generation and cycloaddition of *o*-quinone methides **7** with alkynamide **1** to synthesize structurally complex hexahydrochromeno[2,3-*b*]pyrrole derivatives **8** (Scheme 1.2.3). This reaction proceeds *via* cycloaddition of the two reactive intermediates formed *in situ*, one is the cyclic enamine, 2,3-dihydropyrrole, and the other is *o*-quinone methide to deliver respective fused tricyclic pyrrole derivatives **8**.



Scheme 1.2.3. Gold(I)-catalyzed formal [4+2] cycloaddition reaction.

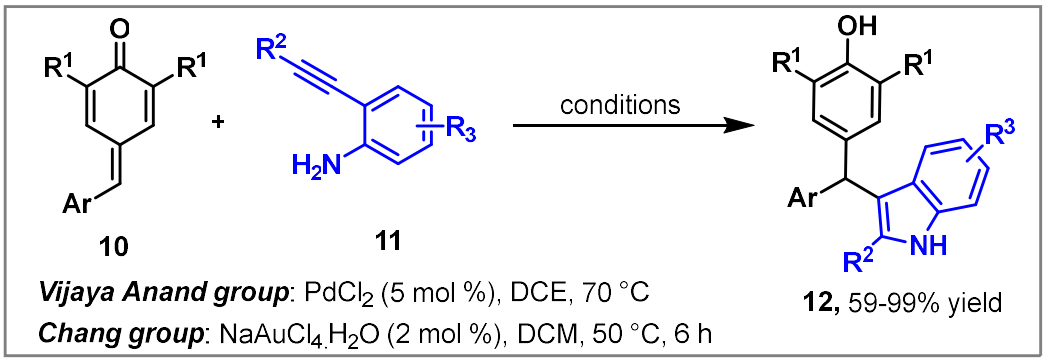
In 2013, Xu and co-workers[10d] reported a one-pot sequential gold/Lewis acid-catalyzed intramolecular hydroamination of alkynamide **1** and its inverse-electron-demand hetero-Diels-Alder reaction with unsaturated *β*-ketone ester **2**. This reaction delivers various biologically important complex racemic bicyclo[4.*n*.0] aminals derivatives **9** with high efficiency under mild reaction conditions. This reaction was performed by a combination of a π-acid with σ-metal Lewis acid (Scheme 1.2.4).



Scheme 1.2.4. Sequential Gold/Lewis acid-catalyzed hetero-Diels-Alder reaction.

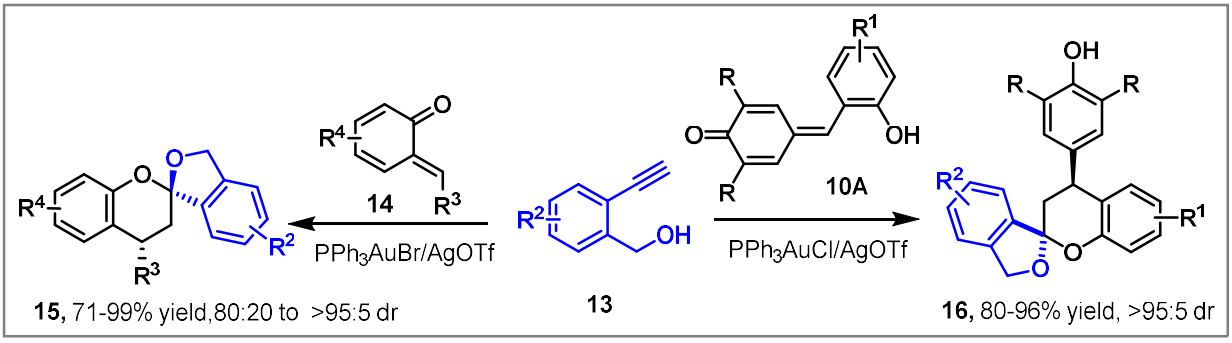
Vijaya Anand[10e] and Chang group[10f] independently reported one-pot metal catalyzed efficient protocol to construct unsymmetrical diarylindolylmethanes derivatives **12** through dom-

ino electrophilic cyclization of *o*-alkynyl anilines **11** followed by its conjugate addition to *p*-quinone methides **10**. Notably, both the method does not require any protection of the amino group of *o*-alkynylanilines (Scheme 1.2.5).



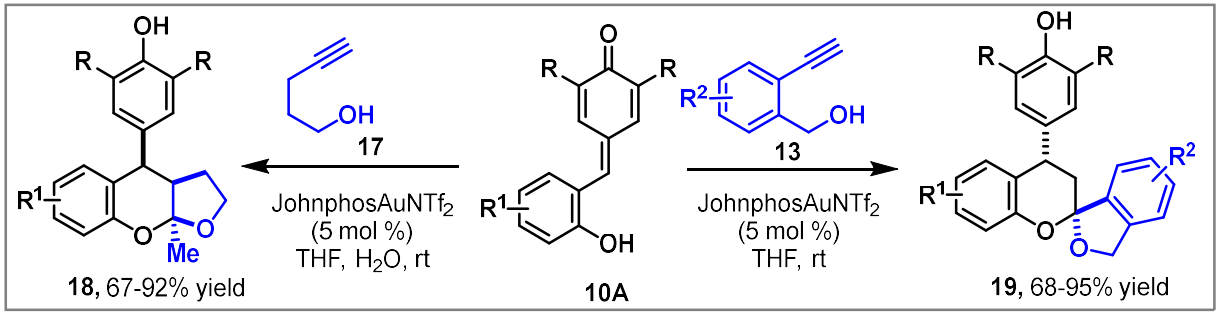
Scheme 1.2.5. Metal catalyzed tandem reaction of 2-alkynylanilines with *p*-quinone methides.

In 2018, Shi group[10g] reported gold-catalyzed oxa-[4+2] cyclization between *o*-QMs **14** or **10A** with alkynyl benzyl alcohols **13** to prepare spiroacetal products **15** or **16**. This [4+2] cyclization provides corresponding spiro-derivatives in high yields (up to 99%) and with good diastereoselectivities (up to >95:5 dr). This method uses electron-rich alkynyl benzyl alcohols and *p*-QMs derivatives as reaction partners. Under gold catalysis, this approach is beneficial in settling challenges embedded in oxa- [4+2] cyclization reaction (Scheme 1.2.6).



Scheme 1.2.6. [4+2] Cyclizations of alkynyl benzyl alcohols with quinone methides.

In 2020 Xu and co-workers[10h] reported an efficient gold (I)- catalyzed domino cyclization reaction between alkynyl alcohols **13** or **17** and *p*-QMs **10A** to construct fused ketal **18** and spiro ketals **19**. This method allows the synthesis of divergent complex polycyclic fused- and spiro-ketals derivatives in good yields under mild conditions from readily available starting materials. In this reaction, water plays an important role in promoting intermediate isomerization and produces the desired products with high chemoselectivity (Scheme 1.2.7).

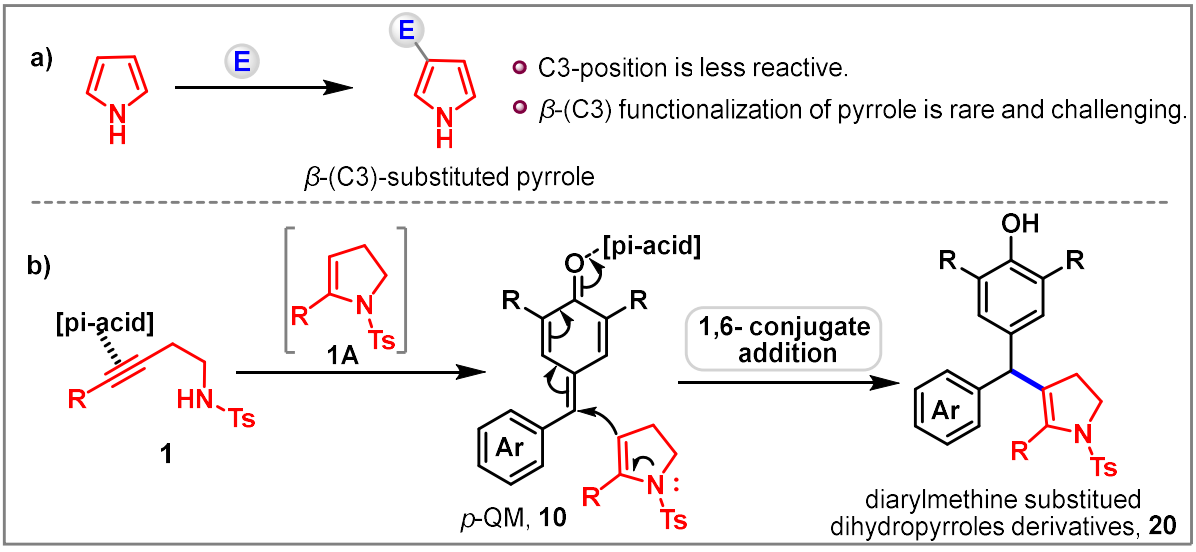


Scheme 1.2.7. oxa-[4+2] cyclizations of alkynyl benzyl alcohols with quinone methides.

1.2.3 Present Work

1.2.3.1 Statement of the Problem

Most of the approaches discussed above for cascade cyclization of alkynamine and trapping with suitable electrophiles to achieve various complex heterocycles possess certain limitations such as the requirement of a dual catalytic system for substrate activation, prolonged reaction duration, limited substrate scope, etc. In addition, due to the mitigated nucleophilicity of pyrroles, selective access to *β*-(C3)-substituted pyrrole is difficult and often challenging (Scheme 1.2.8a).[11] Therefore, the development of a new intermolecular approach to 3-diarylmethine substituted dihydropyrroles *via* cascade cyclization of alkynamine and its 1,6-addition to *p*-QMs is significant from a diversity-oriented synthesis point of view.



Scheme 1.2.8. Hypothesis on cyclization of alkynamine and its 1,6-addition with *p*-QMs.

As discussed in the previous section, the chemistry of *p*-quinone methides (*p*-QMs) has been well recognized and widely used in organic synthesis due to their unique 1,6-reactivity toward a variety of nucleophiles.[12-14] Inspired by the emerging importance of cascade/domino reactions

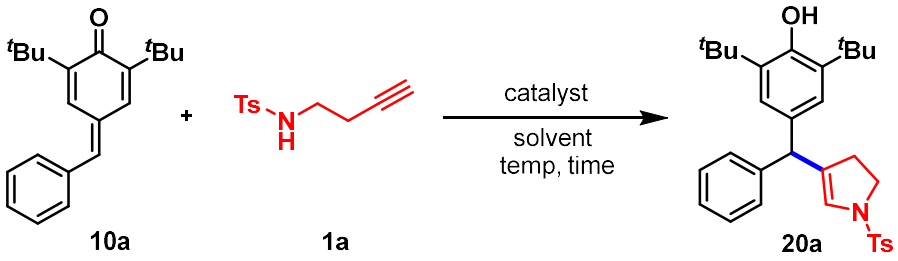
involving alkynols and alkynamines and the chemistry of *p*-QMs, we envisioned that intramolecular cyclization of an appropriately substituted homopropargylic amide **1** activated by a suitable π-acid would generate reactive dihydropyrrole intermediate **1A** *in situ*. Subsequent, conjugate addition of this dihydropyrrole intermediate from the *β*-position to *p*-QM **10** could result in straightforward access to *β*-diarylmethine substituted dihydropyrroles **20** in one pot (Scheme 1.2.8b). To the best of our knowledge, Lewis acid-catalyzed cycloisomerization/1,6-Conjugate addition of homopropargyl sulfonamides to *p*-quinone methides to access diarylmethine substituted dihydropyrroles has not been reported yet.

1.2.4 Results and Discussion

1.2.4.1 Optimization of Reaction Conditions

The present studies were initiated by selecting *p*-quinone methide **10a** and alkynamide **1a** as model substrates under variable reaction conditions (Table 1.2.1). An initial experiment of **10a** and **1a** was conducted in the presence of 10 mol% PPh_3AuCl as a catalyst in DCE solvent at room temperature. The reaction was not fruitful, as no consumption of starting material was observed even after 24 h (Table 1.2.1, entry 1). To our delight, when a reaction was performed with $AuCl_3$ as a catalyst in DCE, the expected product **20a** was isolated in 34% yield (Table 1.2.1, entry 2). The formation of the desired product **20a** was confirmed from its ^1H, ^{13}C NMR and HRMS analysis. The typical ^1H signal at δ 5.09 (s, 1H) corresponds to the phenolic (-OH). The disappearance of signals for **1a** at δ 1.99 (t, 1H) of terminal alkyne proton, δ 5.04 (t, 1H) of NH proton and the appearance of a methine (-CH) signal of diarylmethyl phenol at δ 5.77 (d, 1H) indicates the formation of 1,6-addition adduct **20a**. Furthermore, the constitution of **20a** has been confirmed as $C_{32}H_{40}NO_3S$ (calculated value 518.2723) by the HRMS $[M+H]^+$ found as 518.2719. With this structure confirmation and next to improve the yield of the product **20a,** the effect of various catalysts, solvent, temperature etc., was studied. Interestingly, when AgOTf was used as a catalyst, the yield of the product improved to 54% (Table 1.2.1, entry 3). Superior results were obtained at a reaction temperature of 80 °C (Table 1.2.1, entries 4–6) with AgOTf catalyst. Further, we observed that lowering the catalyst loading resulted in a decreased yield of the product (Table 1.2.1, entry 7). Next, we examined various silver salts and Lewis acids to determine the best catalyst for this transformation. Among the Lewis acid catalysts examined, we found that AgOTf is the best choice of catalyst (Table 1.2.1, entries 8–13). Evaluation of different solvents revealed that DCE exhibited the best results (Table 1.2.1, entries 5, 14-18).

Table 1.2.1. Optimization of the reaction conditions[a,b]



entry	catalyst	solvent	temp (°C)	time (h)	yield (%)
1	PPh_3AuCl	DCE	rt	24 h	N.R
2	$AuCl_3$	DCE	rt	24 h	34
3	AgOTf	DCE	rt	24 h	54
4	AgOTf	DCE	60	12 h	63
5	**AgOTf**	**DCE**	**80**	**12 h**	**90**
6	AgOTf	DCE	100	12 h	82
7	AgOTf	DCE	80	12 h	69[c]
8	AgSbF6	DCE	80	12 h	68
9	$AgNTf_2$	DCE	80	12 h	48
10	$AgNO_3$	DCE	80	12 h	52
11	$Sc(OTf)_3$	DCE	80	12 h	N.R.
12	$Bi(OTf)_3$	DCE	80	12 h	N.R.
13	$Cu(OTf)_2$	DCE	80	12 h	42
14	AgOTf	$CHCl_3$	60	12 h	65
15	AgOTf	toluene	80	12 h	53
16	AgOTf	THF	80	12 h	trace
17	AgOTf	1,4-dioxane	80	12 h	69
18	AgOTf	CH_3CN	80	12 h	trace
19	-	DCE	80	12 h	N.R.

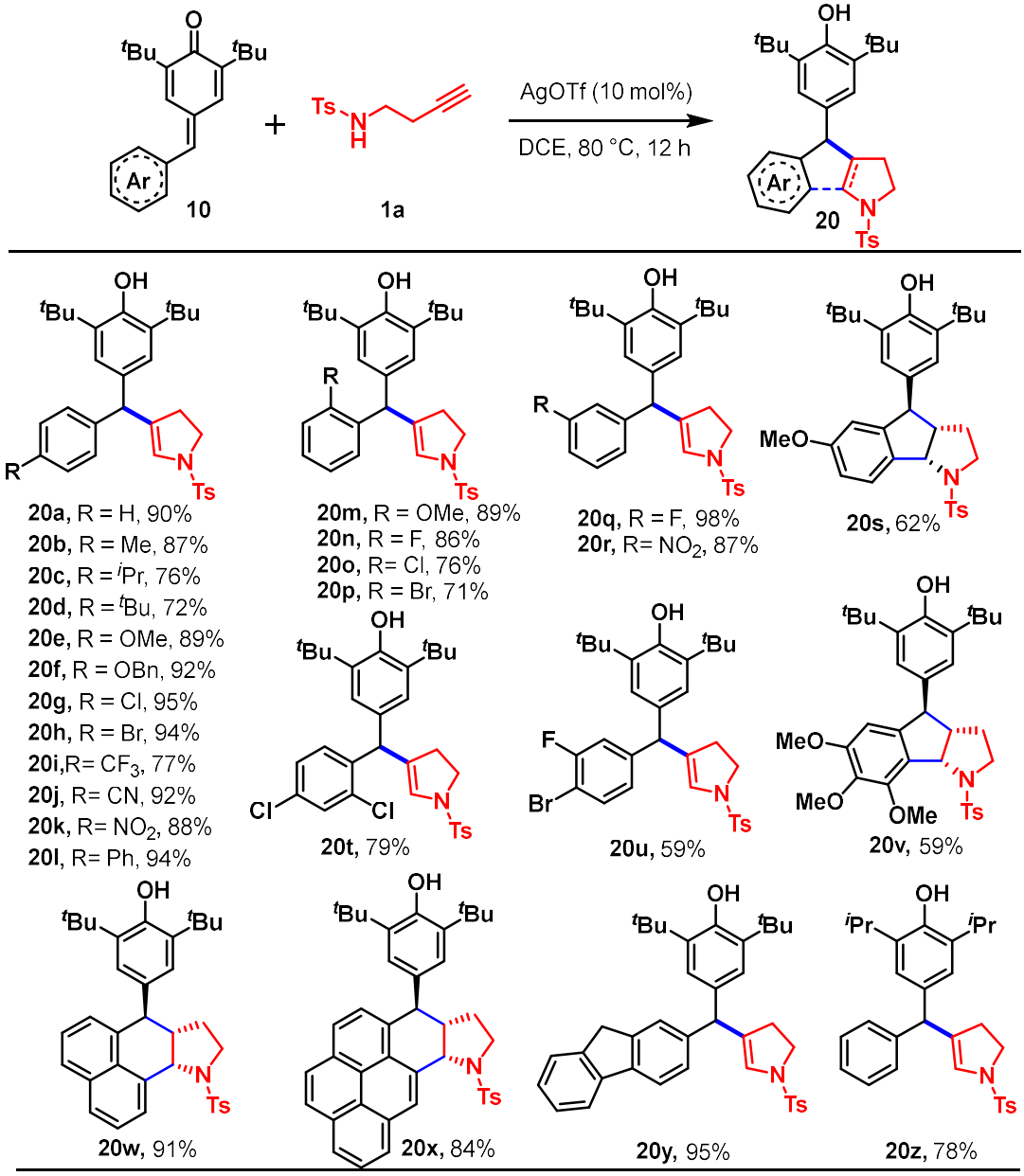
[a]All reactions were performed using with 0.17 mmol **10a**, 0.22 mmol **1a**, 10 mol% catalyst, dry DCE (2.0 mL). [b]Isolated yields, [c]5 mol % catalyst was used. N.R. = no reaction.

No product was detected when the reaction was performed without the catalyst (Table 1.2.1, entry 19). On the basis of all of these results, 10 mol% of AgOTf, 1 equiv. of **10a**, and 1.3 equiv of **1a** in DCE solvent at 80 °C were selected as the optimized conditions.

1.2.4.2 Scope of the Reaction: Substituents on the *p*-QMs

With the above optimal conditions in hand, we then examined the scope with respect to the *p*-QMs and the results are listed in Table 1.2.2.

Table 1.2.2. Scope of the reaction: Substituents on the *p*-QMs[a,b]



[a]Reaction conditions: 0.17 mmol **10a-10z**, 0.22 mmol **1a**, 10 mol% catalyst, dry DCE (2.0 mL), 12 h; [b]Isolated yields.

To our delight, a wide range of *p*-QMs were tolerated, and all the reactions proceeded smoothly to deliver the desired products in good to excellent yields. *p*-QMs bearing *ortho-, meta-* or *para*-substituted, electron-donating or electron-withdrawing groups on the phenyl ring reacted smoothly with homopropargyl sulfonamide **1a**, affording the desired products **20a–20r** in good to excellent yields. Further, di-substitution on phenyl ring also gives corresponding products in good yields (59-79%) under the same conditions (**20t-20u**). In the case of 3-methoxy and 3,4,5-trimethoxy-substituted *p*-QMs (**10s, 10v**), [3 + 2] annulation products with tricyclic core (**20s, 20v**) were obtained in 62% and 59% respectively. Similarly, when sterically hindered *p*-QMs (**10w-10x**) were used under this reaction condition, we observed unexpected [4 + 2] annulation products hexahydronaphthoindolyl and hexahydropyrenoindolyl phenols in good yields (**20w-20x**). The formation of these polycyclic products can be attributed to the annulation of the iminium ion formed after an initial β-attack. Moreover, fluorenyl substituted *p*-QM also underwent a smooth transformation to afford the desired product **20y** in 95 % yield. In addition, *p*-QM with isopropyl substitution at C2 and C6 positions could also work well with this strategy (**20z**). The structures of **20e** and **20w** were determined unambiguously by a single-crystal X-ray analysis. The configurations of the other products **(20s, 20v and 20x)** were assigned by analogy.

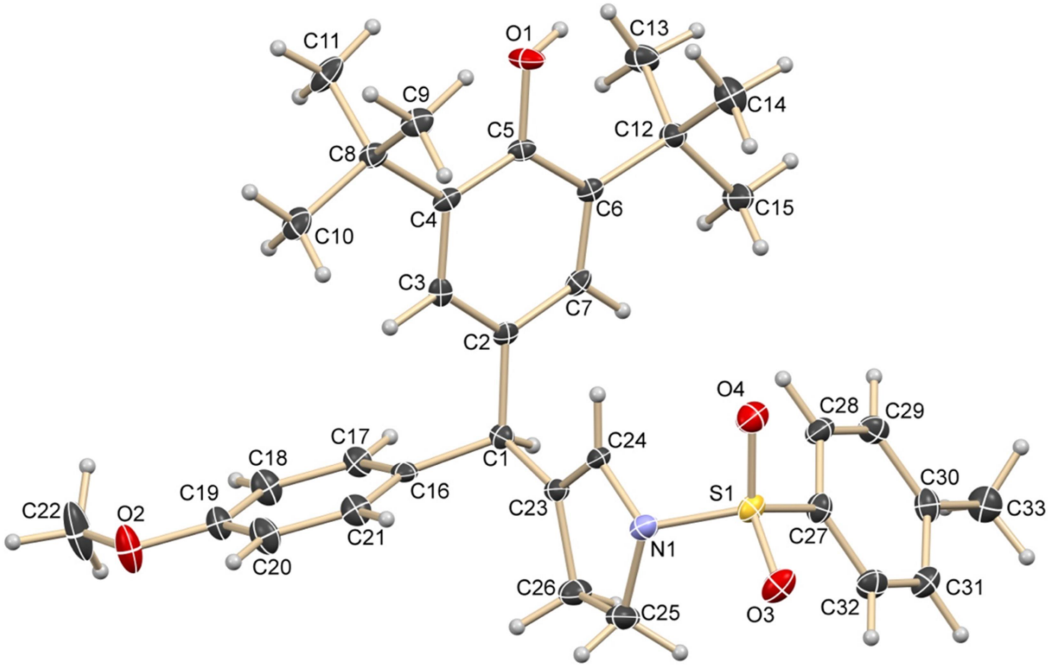


Fig. 1.2.3. ORTEP drawing (50% probability ellipsoids) of **20e** (**CCDC1969572**)

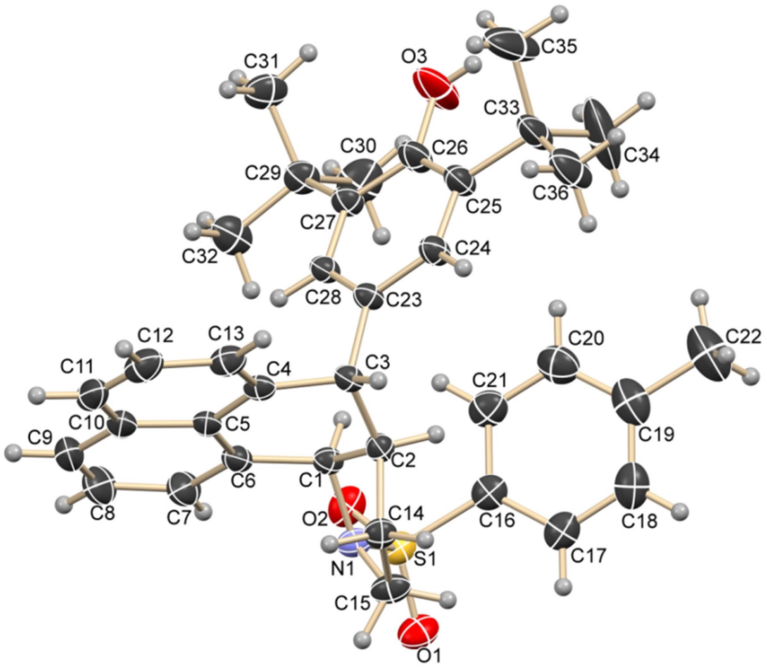
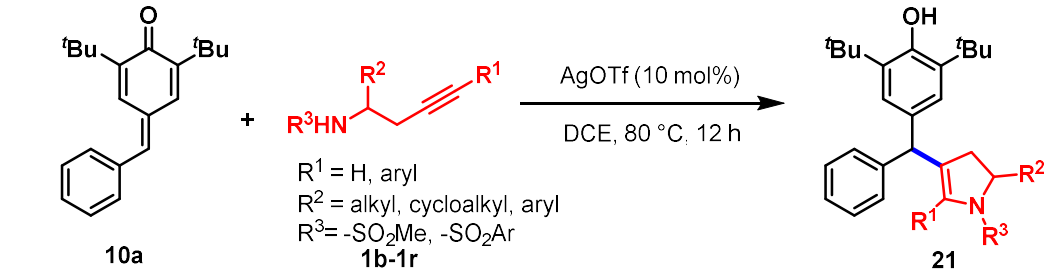


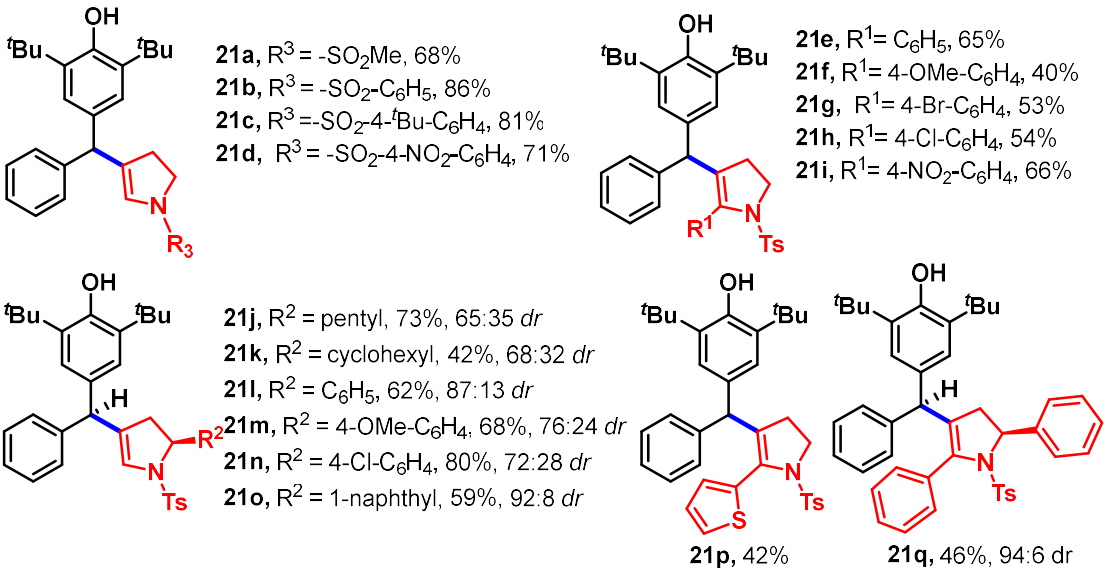
Fig. 1.2.4. ORTEP drawing (30% probability ellipsoids) of **20w** (**CCDC2013163**)

1.2.4.3 Scope of the Reaction: Substituents on the Homopropargyl Sulfonamides

Next, the scope of homopropargyl sulfonamides was investigated under the standard reaction condition (Table 1.2.3). As shown in Table 1.2.3, various *N*-substitution on homopropargyl sulfonamides underwent a smooth transformation to their corresponding products **(21a-21d)** in moderate to good yields. Moreover, we tested different substitutions on the aryl alkyne part of homopropargyl sulfonamides. We found that electron- donating and withdrawing groups on the phenyl ring were tolerable to get the desired products **(21e-21i)** in moderate to good yields. Furthermore, the scope of the substrate investigation was extended to substituents **(-R^2)** of homopropargyl sulfonamide and found that alkyl, and cycloalkyl substituted homopropargyl sulfonamides underwent a smooth transformation to afford corresponding products **(21j-21k)** in 73, 42% respectively with moderate diastereomeric ratios. In addition, substrates with various aryl substitutions also gave corresponding products **(21l-21o)** with 59-80% yields and good dr. Notably, the furyl ring-derived dihydropyrrole precursor **(1q)** was also compatible with furnishing the desired product **(21p)** in a 42% yield. Interstigly, trisubstituted dihydropyrrole precursor **(1r)** also works well to result in highly substituted diarylmethine dihydropyrrole derivative **(21q)** in 46% yield with 94:6 dr. The relative configuration of **21k** was assigned unambiguously *via* single-crystal X-ray analysis. The configurations of the other products (**21j**, **21l-21o**, **21q**) were assigned by analogy.

Table 1.2.3. Scope of the reaction: Substituents on the homopropargyl sulfonamides[a,b]





[a]All reactions were performed using with 0.17 mmol **10a**, 0.22 mmol **1b-2r**, 10 mol% catalyst, dry DCE (2.0 mL), 12 h, isolated yields; [b]The dr values were determined by ^{1}H NMR analysis.

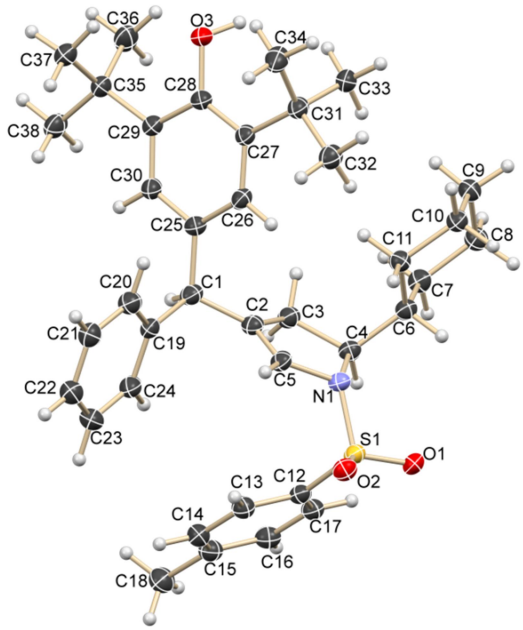
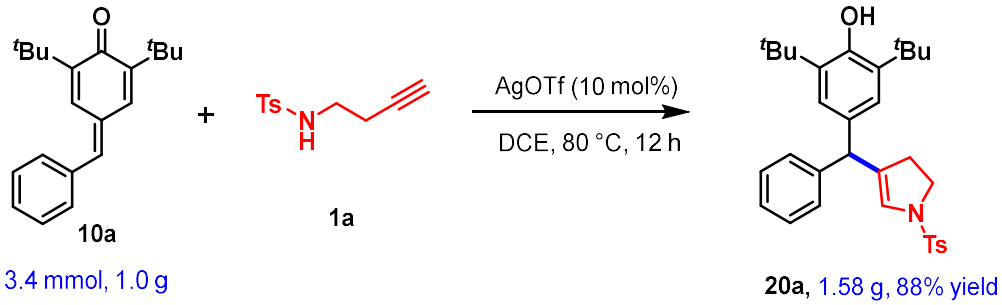


Fig. 1.2.5. ORTEP drawing (50% probability ellipsoids) of **21k** (**CCDC2035515**)

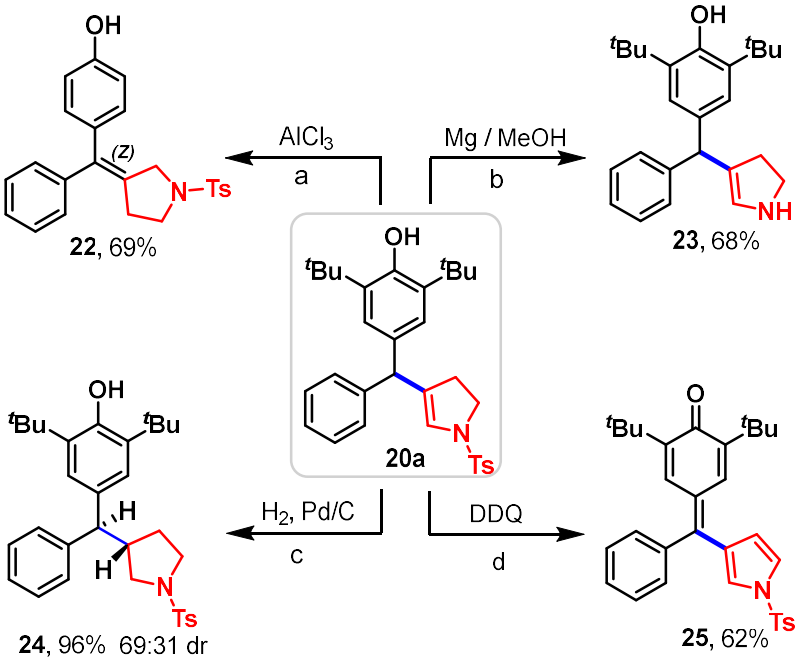
1.2.4.4 Gram-Scale Experiment and Product Transformations:

To demonstrate the synthetic utility of this reaction, a gram scale reaction (3.4 mmol) was carried out under the optimal conditions and afforded **10a** in 88 % yield (Scheme 1.2.9A).



Scheme 1.2.9A. Gram scale preparation

The synthetic applicability of this protocol was also demonstrated by carrying out the transformations of compound **20a** (Scheme 1.2.9B). Compound **20a** on de-*tert*-butylation reaction with aluminium chloride afforded 3-diphenylmethylene pyrrolidine derivative **22** in 69 % yield.



[a]Reaction conditions: (a) $AlCl_3$ (10 equiv), benzene, 40 °C, 1 h. (b) Mg/MeOH, rt, 5 h. (c) H_2 (balloon), Pd/C, EtOAc, rt, 5 h. (d) DDQ, toluene, 100 °C, 12 h.

Scheme 1.2.9B. Product transformations

Moreover, the tosyl protecting group of compound **20a** was readily removed using magnesium turnings in methanol solution. Upon hydrogenation using Pd/C, compound **20a** led to a pyrrolidine derivative **24** in excellent yield. The relative configuration of **24** was unambiguously de-

termined by the single crystal X-ray analysis. Compound **10a** was further converted to a pyrrole substituted *p*-quinone **25** with DDQ oxidation in a 62% yield.

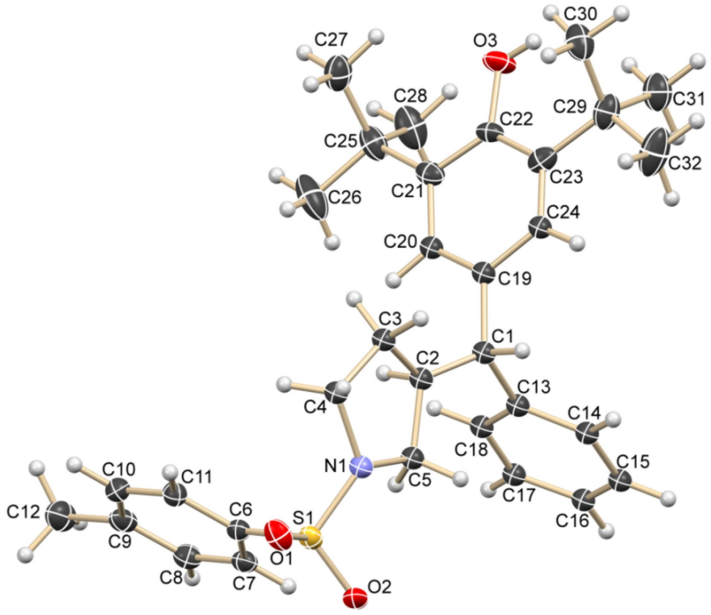
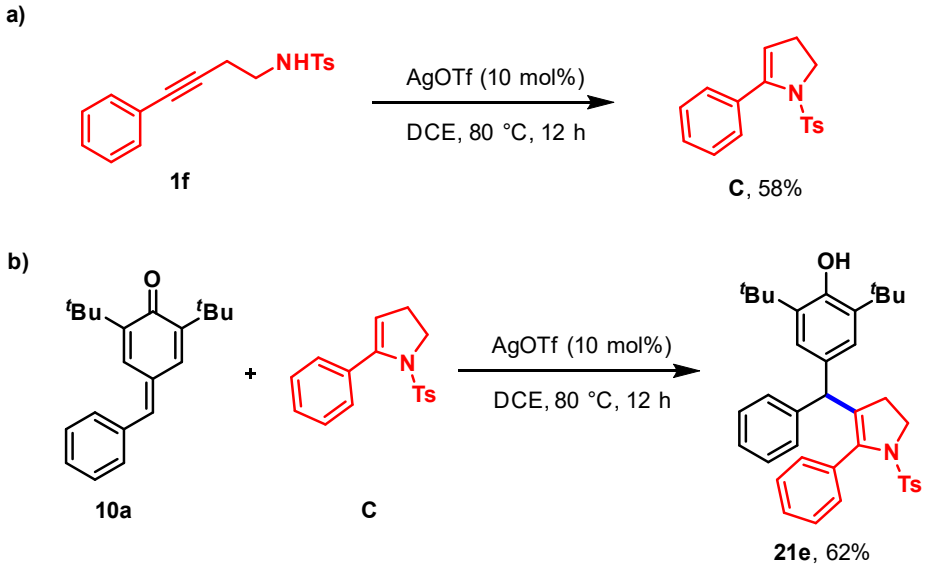


Fig. 1.2.6. ORTEP drawing (50% probability ellipsoids) of **24** (**CCDC2035514**)

1.2.4.5 Control Experiments and Plausible Reaction Mechanism:

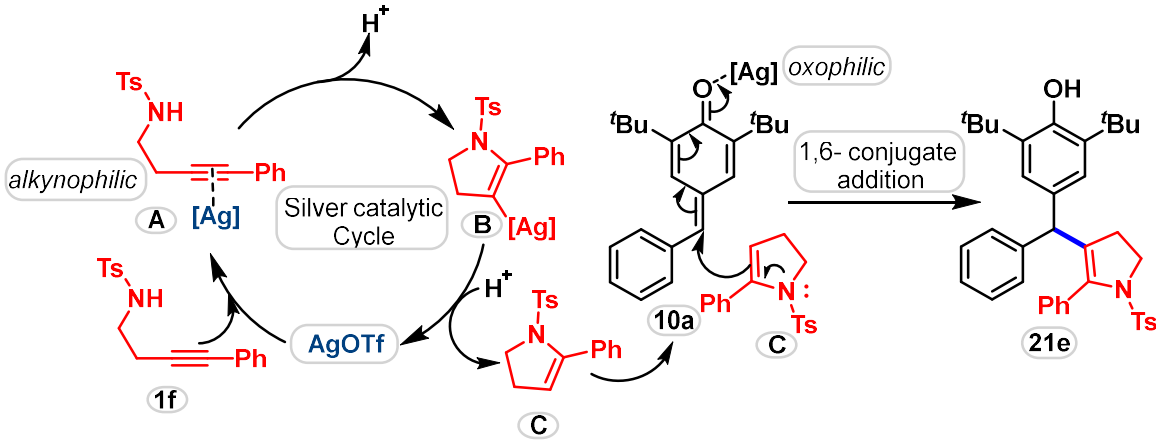
To understand the reaction pathway, some control experiments were carried out. The reaction of phenyl substituted homopropargyl sulfonamide **1f** in the absence of *p*-QM **10a** under standard reaction conditions provided the 2,3-dihydropyrrole intermediate **C** in 58% yield



Scheme 1.2.10. Control experiments

(Scheme 1.2.10a). Further intermediate **C** was allowed to react with *p*-QM **10a,** with standard reaction conditions afforded **21e** in 62% yield (Scheme 1.2.10b). These results imply that the reaction proceeds *via* silver catalyzed hydroamination of alkynyl amine to generate a 2,3-dihydropyrrole intermediate *in situ* and its subsequent 1,6-conjugate addition with *p*-QM **10** provides the desired products **20**/**21**.

Based on the control experiments and according to the literature,[10a] a plausible mechanism for this Ag(I) catalyzed cascade cyclization/1,6-conjugate addition reaction is depicted in scheme 1.2.11 (compound **21e** as an example). Initially, the silver catalyst coordinated with the alkynamide **1f** to form a π- alkyne complex **A,** followed by 5-endo-dig cyclization affording the σ-silver complex **B.** Further, the protodemetalation of **B** generates the key cyclic intermediate 2,3-dihydropyrrole **C** *in situ* and releases the silver catalyst into the catalytic cycle. Simultaneously, *p*-QMs **10a** was activated by oxophilic silver catalyst followed by 1,6-conjugate addition with the reactive 2,3-dihydropyrrole to form the desired product **21e**.



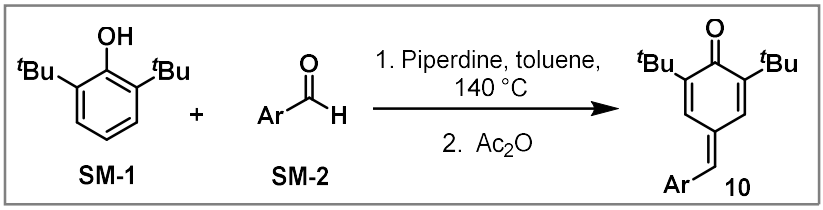
Scheme 1.2.11. A plausible mechanism

2.4 Conclusion

In conclusion, in this section, we have developed a simple and efficient strategy for the synthesis of 3-diarylmethine substituted dihydropyrroles *via* silver catalyzed cascade cyclization/1,6-conjugate addition of homopropargyl sulfonamides to *p*-QMs, for the first time. In this reaction, silver catalyst plays a dual role, *i.e.* Ag (I) activates homopropargyl sulfonamide for cycloisomerization and *p*-QM's for 1,6-conjugate addition. The salient features of this reaction include readily accessible starting materials, mild reaction conditions, good functional group tolerance and scalability. We believe this simple strategy may provide ageneral approach to the synthesis of highly substituted dihydropyrrole derivatives in a rapid manner.

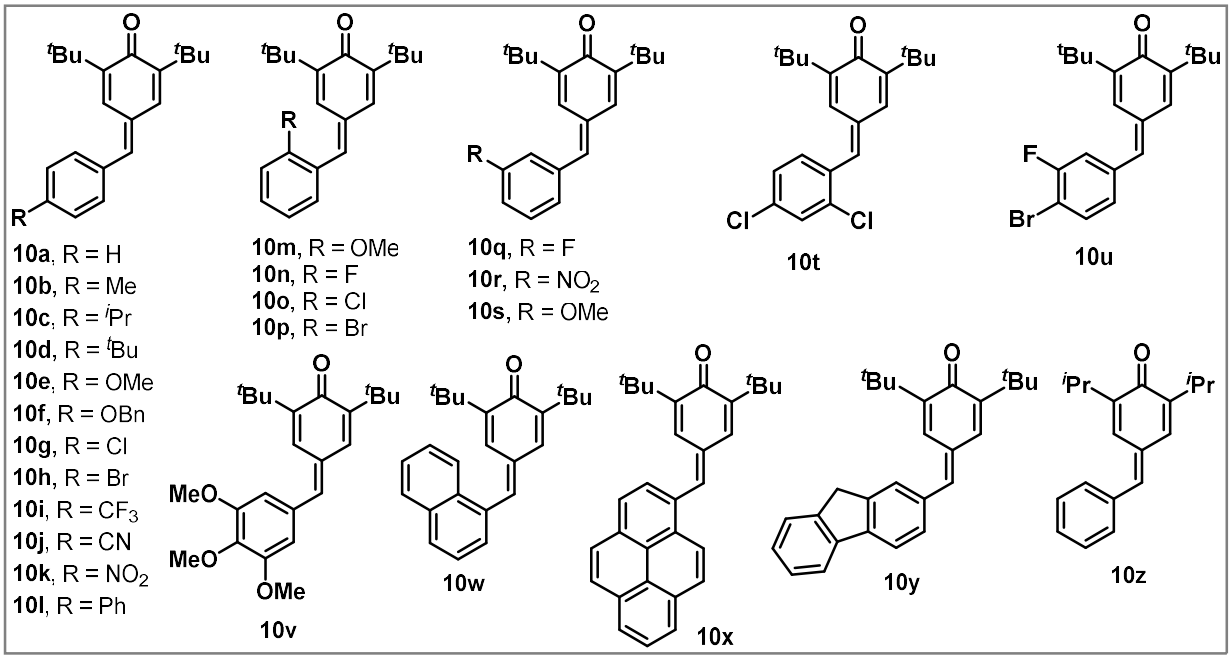
1.2.5 Experimental Section

1.2.5.1 General Procedure for the Preparation of *p*-Quinone Methides (*p*-QMs):



Scheme 1.2.12. Preparation of *p*-quinone methides

2,6-di-*tert*-butylphenol (20 mmol) and 1.0 equiv of aldehyde (20 mmol) were dissolved in toluene (0.25 M) and the mixture was heated to 140 °C in a Dean−Stark apparatus (oil bath). Piperidine (2.0 equiv, 40 mmol) was added dropwise over 1 h, and the reaction mixture was re-fluxed for 6-12 h. After cooling just below the boiling point of the mixture, acetic anhydride (2.0 equiv, 40 mmol) was added and stirring was continued for 15 min. Then the reaction mixture was poured into ice-water, extracted with DCM (3 x 200 mL), and dried over Na_2SO_4, the solvent was evaporated, and the residue was dried in vacuo. The crude products were purified by flash column chromatographyusing using petroleum ether as eluent, affording the desired *p*-QMs **10**.



The *p*-quinone methides (**10a-10y**)[15a] were prepared by following above general procedure. *p*-QM (**10z**) was prepared by following literature procedures.[15b]

1.2.5.1 Synthesis of Homopropargyl Sulfonamides:

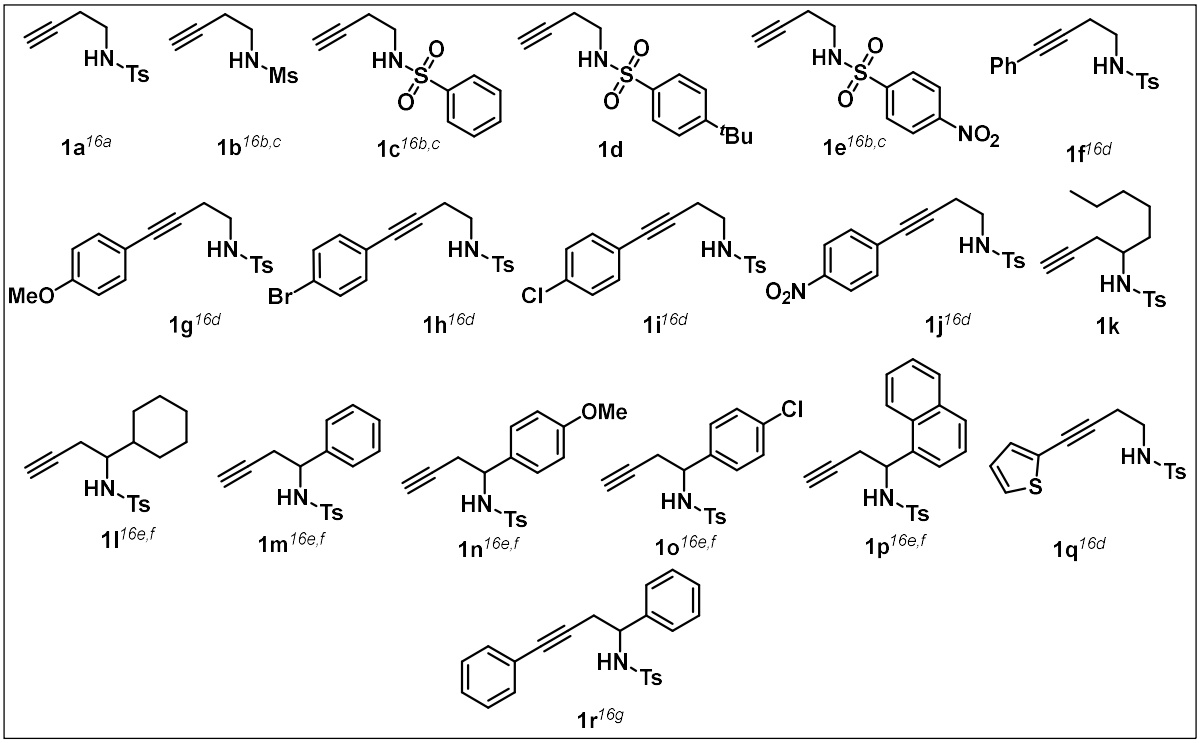
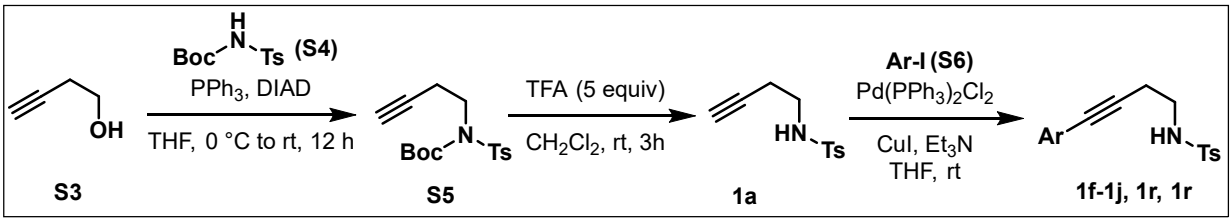


Fig. 1.2.7. Structures of homopropargyl sulfonamides used in this study.

Preparation of Homopropargyl Sulfonamides (1a, 1f-1j, 1q and 1r):

*Synthesis of tert-Butyl tosylcarbamate (**S4**)*:

A solution of Boc_2O (13.2 mL, 57.5 mmol) in DCM (15 mL) was added dropwise at room temperature to a solution of NEt_3 (7.6 mL, 55.0 mmol), DMAP (0.6 g, 5.0 mmol) and *p*-toluenesulfonamide (8.55 g, 50.0 mmol) in dichloromethane (60 mL). The colorless reaction mixture was stirred at room temperature for 5 h. After completion the solvent was removed under vacuum, the residue was diluted with ethyl acetate (60 mL) and 1N HCl (40 mL). An organic layer was washed with water, brine and then dried over Na_2SO_4 and concentrated on a rotary evaporator to give a white solid. Crystallization from hot hexane (50 mL) gave **S4** (12.2 g, 90%).



Scheme 1.2.13. Preparation of homopropargyl sulfonamides (**1a**, **1f-1j, 1q and 1r**)

Procedure for the Preparation of **1a**:

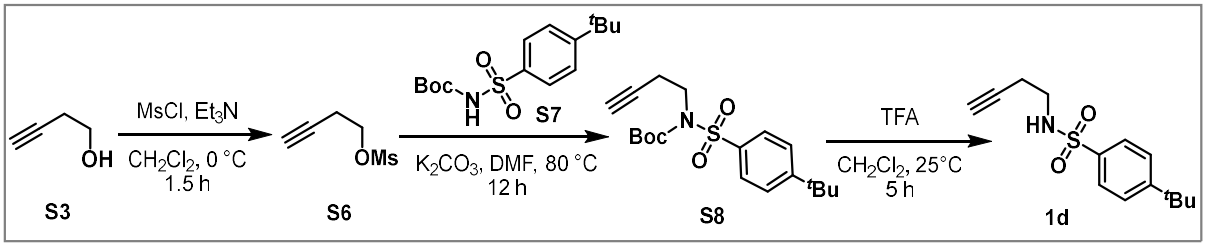
Step-1: A solution of triphenylphosphine (1.44 g, 5.5 mmol), but-3-yn-1-ol **S3** (0.39 g, 5 mmol) and **S4** (1.35g, 5 mmol) in dry THF (15 mL) was stirred for 10 minutes. Diethyl azodicarboxylate (0.96 g, 5.5 mmol) was then added at 0 ^{o}C. The reaction mixture was stirred at room temperature for 12 h. The solvent was removed by a rotary evaporator and the residue was purified by silica gel flash chromatography (1:10 ethyl acetate/ petroleum ether) to afford the desired substrate **S5** (1.49 g, 84%).

Step-2: To a solution of **S5** (1 g, 3.1 mmol) in DCM (5 mL) was added TFA (1.15 mL, 15.5 mmol) and the mixture was stirred at room temperature for 3 h. The reaction was quenched by saturated aqueous $NaHCO_3$ solution and was extracted with DCM. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under vacuo. The residue was purified by flash chromatography (1:5 ethyl acetate/ petroleum ether) to afford the desired substrate **1a** (0.66 g, 95%).

Preparation of Homopropargyl Sulfonamide (**1f-1j, 1q and 1r**):

To a three-necked flask were added $Pd(PPh_3)_2Cl_2$ (5 mol %), CuI (10 mol %), **1a** (1.0 equiv), Et_3N (10 equiv) and THF. After degassing with argon and four evacuation/backfill-cycles with argon, **S6** (1.2 equiv) in THF was added dropwise. The reaction mixture was stirred at room temperature. When the reaction was complete as monitored by TLC, saturated NH_4Cl solution was added to the resulting mixture. After separation of the organic layer, the water layer was extracted with ethyl acetate. The combined organic layer was dried over anhydrous Na_2SO_4, filtered, concentrated in vacuo and purified via column chromatography on silica gel (petroleum ether/ethyl acetate) to afford the desired product **1f-1j, 1q and 1r.**

Synthesis of N-(but-3-yn-1-yl)-4-(tert-butyl)benzenesulfonamide (1d):



Scheme 1.2.14. Preparation of homopropargyl sulfonamides **1d**

*But-3-yn-1-yl methanesulfonate (**S6**)*:

To a solution of 3-butynol (1.5 g, 21.4 mmol, 1 equiv), triethylamine (2.5 mL, 32.1 mmol, 1.5

equiv) in dichloromethane (75 mL) were added methanesulfonyl chloride (2.05 mL, 26.7 mmol, 1.25 equiv) in dichloromethane (15 mL) dropwise for a period of 30 minutes at 0 °C. The mixture was stirred at 0 °C for 45 min, quenched with water (50 mL), and extracted with additional dichloromethane (2 x 25 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The resulting residue was distilled under vacuum (bp ~50 °C, ca. 1 torr) to give but-3-yn-1-yl methanesulfonate as a colorless liquid which was used directly in the next step.

*tert-butyl ((4-(tert-butyl)phenyl)sulfonyl)carbamate (**S7**)*:

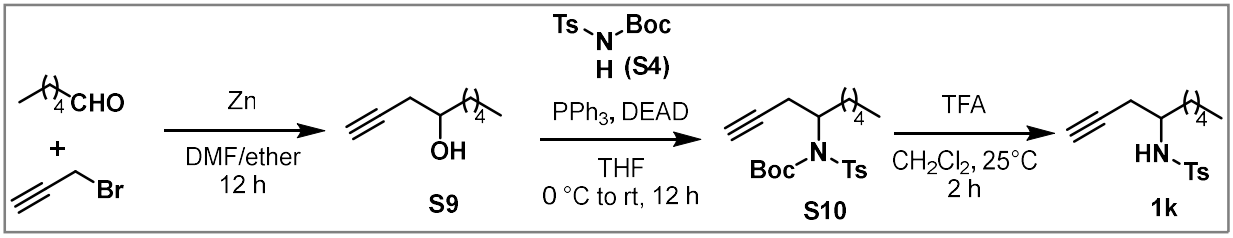
To a solution of 4-(*tert*-butyl)benzenesulfonamide (0.70 g, 3.28 mmol, 1.0 equiv), triethylamine (0.50 mL, 68 mmol, 1.12 equiv), DMAP (0.33 mmol, 0.10 equiv) in dichloromethane (10 mL) were added $(Boc)_2O$ (0.85 mL, 3.68 mmol, 1.12 equiv) dissolved in dichloromethane (5 mL) at room temperature. The reaction mixture was stirred at room temperature for 5 h. After completion, the solvent was removed under reduced pressure, and the residue was extracted with ethyl acetate (30 mL x 3) and 1N HCl (20 mL x 3). Combined organic layers were washed with water, brine and dried (Na_2SO_4) and concentrated under reduced pressure to afford crude compound as a white solid. Crystallization from hot hexane (5 mL) gave **S7**, which was used without further purification in the next step.

To a solution of **S6** (0.3 g, 2.03 mmol, 1 equiv), **S7** (0.76 g, 2.43 mmol, 1.2 equiv) in DMF (10 mL) were added K_2CO_3 (0.42 g, 3.04 mmol, 1.5 equiv) and the reaction mixture was stirred at 85 °C in an oil bath for 12 h. After completion, the reaction mixture was cooled to room temperature, filtered through a bed of Celite, and concentrated under reduced pressure. The resulting residue was dissolved in ethyl acetate (30 mL), washed with 1 M HCl (15 mL x 3), $NaHCO_3$ (15 mL x 3), brine and dried (Na_2SO_4). The solvent was removed under reduced pressure, and the residue was used directly in the next step.

To a solution of *tert*-butyl but-3-yn-1-yl((4-(*tert*-butyl)phenyl)sulfonyl)carbamate (**S8**) (0.5 g, 1.37 mmol, 1.0 equiv) in dichloromethane (15 mL) was added TFA (0.52 mL, 6.85 mmol, 5.0 equiv) and the reaction mixture was stirred at room temperature for 5 h. After completion, the reaction was quenched by adding sat. aq. $NaHCO_3$ and extracted with DCM (25 mL x 3). The combined organic layers were washed with water, brine and dried (Na_2SO_4). The solvent was removed under reduced pressure and the residue was purified by column chromatography over silica gel (petroleum ether: ethyl acetate = 17:3) to afford **1d** as a white solid.

Homopropargyl sulfonamides (**1b**, **1c** and **1e**) were prepared by following above procedure described for the preparation of **1d**.

Synthesis of of 4-methyl-N-(non-1-yn-4-yl)benzenesulfonamide (1k):



Scheme 1.2.15. Preparation of homopropargyl sulfonamides **1k**

Non-1-yn-4-ol (**S9**): To a 100 mL round-bottom flask fitted with a reflux condenser was added hexanal (0.5 g, 5.0 mmol, 1 equiv) in ether/ DMF (1:1, 20 mL, tech grade, not anhydrous) and propargyl bromide (0.49 mL, 6.5 mmol, 1.3 equiv). An activated zinc powder (0.98 g, 15 mmol, 3 equiv) was then added portion-wise over 10 min. (Caution! Very freshly activated zinc can produce very exothermic reactions). The reaction mixture was stirred at room temperature for 12 h. After completion (by TLC), the reaction mixture was slowly quenched with saturated NH_4Cl (50 mL) and allowed to stir for 30 min. The resulting mixture was decanted into a separatory funnel, and the organic layer was separated. The aqueous layer was extracted with ether (30 mL x 3), and the combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was used without further purification in the next step.

tert-butyl non-1-yn-4-yl(tosyl)carbamate (**S10**): To a solution of non-1-yn-4-ol (0.5 g, 3.57 mmol, 1 equiv), triphenylphosphine (1.03 g, 3.92 mmol, 1.1 equiv), *N*-Boc-toluenesulfonamide **S4** (1.06 g, 3.92 mmol, 1.1 equiv) in dry THF (15 mL) were added diethyl azodicarboxylate (0.64 mL, 3.92 mmol, 1.1 equiv) at 0 °C and the reaction mixture was stirred at room temperature for 12 h. After completion, the solvent was removed under reduced pressure. The residue was further purified by flash column chromatography over silica gel (petroleum ether:ethyl acetate, 40:1) to provide *tert*-butyl non-1-yn-4-yl(tosyl)carbamate **S10** as a pale yellow liquid.

To a solution of **S10** (0.5 g, 1.27 mmol, 1equiv**)** in DCM (15 mL was added TFA (0.49 mL, 6.35 mmol, 5 equiv) and the reaction mixture was stirred at room temperature for 2 h. The reaction mixture was quenched by the addition of sat. aq. $NaHCO_3$ and the aqueous layer was extracted with dichloromethane (15 mL x 3). The combined organic layers were washed with

brine, dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by column chromatography over silica gel (petroleum ether:ethyl acetate, 9:1) to afford (**1k**) as a colorless liquid. Homopropargyl sulfonamides (**1l-1p**) were prepared by following above procedure described for the preparation of **1k**.

1.2.5.2 General Procedure for the Synthesis of 3-Diarylmethine Substituted Dihydropyrroles:

To a screw-capped vial with a triangular-shaped Teflon stir bar were added *p*-QM's **10** (0.17 mmol, 1 equiv.), homopropargyl sulfonamide **1** (0.22 mmol, 1.3 equiv), AgOTf (10 mol %) and dry DCE (2.0 mL). The reaction mixture was stirred at 80 °C in an oil bath for 12 h. After completion of the reaction (detected by TLC), the solvent was concentrated under reduced pressure, and the residue was subjected to flash silica gel chromatography (petroleum ether:ethyl acetate = 19:1) to afford 3-diarylmethine substituted dihydropyrroles **20/21.**

1.2.5.3 Control Experiments Procedure:

(a) Procedure for the synthesis of C: To a screw-capped vial with a triangular-shaped Teflon stir bar were added homopropargyl sulfonamide **1f** (0.050 g, 0.17 mmol, 1.0 equiv), AgOTf (10 mol %) and dry DCE (2.0 mL). The reaction mixture was stirred at 80 °C in an oil bath for 12 h. After completion of the reaction (detected by TLC), the solvent was concentrated under reduced pressure and the residue was subjected to flash silica gel chromatography (petroleum ether:ethyl acetate = 1:1) to afford 5-phenyl-1-tosyl-2,3-dihydro-1H-pyrrole **C** (0.029 g, 58%).

(b) Procedure for the synthesis of 21e: To a screw-capped vial with a triangular-shaped Teflon stir bar were added *p*-QM's **10a** (0.10 mmol, 1 equiv), dihydropyrrole **C** (0.046 g, 0.15 mmol, 1.5 equiv), AgOTf (10 mol %) and dry DCE (2.0 mL). The reaction mixture was stirred at 80 °C in an oil bath for 12 h. After completion of the reaction (detected by TLC), the solvent was concentrated under reduced pressure, and the residue was purified by flash chromatography on silica gel column (petroleum ether:ethyl acetate = 19:1) to afford the product **21e** (0.037 g, 62%).

1.2.5.4 Procedure for Product Transformations:

(a) Procedure for the synthesis of 22: To a solution of **20a** (0.050 g, 0.097 mmol) in dry benzene (3 mL) was added $AlCl_3$ (0.128 g, 0.97 mmol) under argon atmosphere, and the resulting mixture was stirred at 40 °C in an oil bath for 1 h. The reaction mixture was then quenched with

10 mL of ice-cold water and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was subjected to column chromatography on silica gel using petroleum ether:ethyl acetate=4:1 mixture as an eluent to afford **22** (0.027 g, 69%).

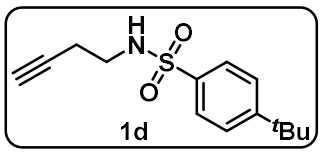
(b) Procedure for the synthesis of 23: To a solution of **20a** (0.100 g, 0.19 mmol) in methanol (5 mL) was added Mg powder (0.023g, 0.97 mmol). The resulting suspension was stirred at room temperature for 5 h. After completion, the reaction mixture was passed through a pad of celite and concentrated under reduced pressure. The residue was chromatographed on neutral aluminium oxide (petroleum ether:ethyl acetate = 17:3) to afford **23** (0.048 g, 68 %).

(c) Procedure for the synthesis of 24: To a solution of **20a** (0.050 g, 0.097 mmol) in ethyl acetate (7 mL) was added 10 % Pd/C (0.01 g, 0.0097 mmol), and the reactants were degassed and filled with hydrogen gas while stirring magnetically. After 5 h, the solution was filtered through a pad of Celite and concentrated under reduced pressure. The residue was chromatographed on silica gel (petroleum ether:ethyl acetate = 17:3) to afford **24** (0.048 g, 96%).

(d) Procedure for the synthesis of 25: To a solution of **20a** (0.050 g, 0.097 mmol) in toluene (2 mL) was added DDQ (0.044 g, 0.193 mmol). The reaction mixture was stirred at 100 °C in an oil bath for 12 h. After completion, the reaction mixture was diluted with CH_2Cl_2 (10 mL) and washed with sat. $NaHCO_3$ followed by brine, dried (Na_2SO_4), and concentrated under reduced pressure. The resulting crude was purified by column chromatography on silica gel (petroleum ether:ethyl acetate = 19:1) to afford **25** (0.031 g, 62%).

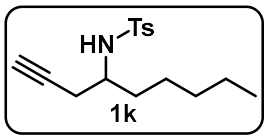
1.2.5.5 Characterization Data of Compounds 1d, 1k, 20a-20z, 21a-21q, 22-25 and C:

***N*-(but-3-yn-1-yl)-4-(*tert*-butyl)benzenesulfonamide (1d)**



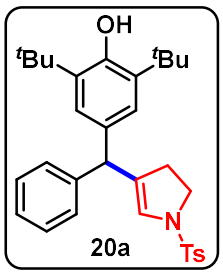
The product **1d** was obtained in 77% yield (280 mg, White solid); **mp** = 81-82 °C; R_f = 0.40 (petroleum ether:ethyl acetate = 4:1); **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 7.82 – 7.76 (m, 2H), 7.54 – 7.48 (m, 2H), 5.19 (t, *J* = 5.4 Hz, 1H), 3.10 (q, *J* = 6.6 Hz, 2H), 2.35 (td, *J* = 6.8, 2.5 Hz, 2H), 1.97 (t, *J* = 2.6 Hz, 1H), 1.32 (s, 9H) ; **^{13}C{^{1}H} NMR (100 MHz,$CDCl_3$) δ** = 156.4, 136.6, 126.8, 126.1, 80.3, 70.7, 41.6, 35.0, 31.0, 19.8; **HRMS (ESI$^+$)** *m/z*: $[M + H]^+$ calcd for $C_{14}H_{20}NO_2S$ 266.1209; found 266.1213.

4-methyl-N-(non-1-yn-4-yl)benzenesulfonamide (**1k**):



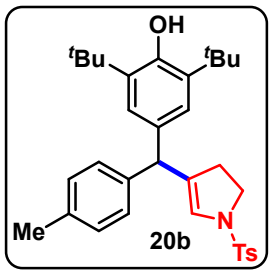
The product **1k** was obtained in 86% yield (322 mg, colorless liquid); R_f = 0.65 (petroleum ether:ethyl acetate = 4:1); **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 7.78 (d, *J* = 7.9 Hz, 2H), 7.28 (d, *J* = 7.9 Hz, 2H), 5.13 (d, *J* = 8.5 Hz, 1H), 3.40 – 3.21 (m, 1H), 2.41 (s, 3H), 2.27 (dd, *J* = 5.3, 2.5 Hz, 2H), 1.96 (t, *J* = 2.5 Hz, 1H), 1.56 – 1.43 (m, 2H), 1.22 – 1.06 (m, 6H), 0.79 (t, *J* = 6.9 Hz, 3H) ; **^{13}C{^{1}H} NMR (100 MHz,$CDCl_3$) δ** = 143.2, 137.9, 129.5, 126.9, 79.6, 71.2, 51.7, 33.7, 31.1, 25.0, 22.3, 21.3, 13.7; **HRMS (ESI$^+$)** *m/z*: $[M + H]^+$ calcd for $C_{16}H_{24}NO_2S$ 294.1522; found 294.1523.

2,6-di-*tert*-butyl-4-(phenyl(1-tosyl-4,5-dihydro-1H-pyrrol-3-yl)methyl)phenol (20a):

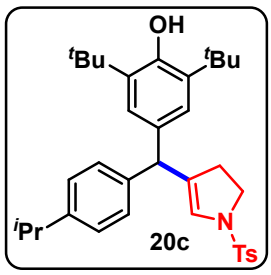


The product **20a** was obtained in 90% yield (81 mg, White solid); **mp** = 177-178 °C; R_f = 0.50 (petroleum ether:ethyl acetate = 4:1); **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 7.61 (dd, *J* = 8.3, 1.8 Hz, 2H), 7.35 (d, *J* = 8.2 Hz, 2H), 7.28 – 7.17 (m, 3H), 7.06 – 6.97 (m, 2H), 6.81 (s, 2H), 5.77 (d, *J* = 1.5 Hz, 1H), 5.09 (s, 1H), 4.53 (s, 1H), 3.60 – 3.45 (m, 2H), 2.48 (s, 3H), 2.32 (t, *J* = 8.9 Hz, 2H), 1.35 (s, 18H); **^{13}C{^{1}H} NMR (100 MHz,$CDCl_3$) δ** = 152.3, 143.7, 141.8, 135.6, 132.4, 131.7, 131.1, 129.6, 128.5, 128.3, 128.1, 127.8, 126.5, 124.9, 51.0, 48.2, 34.3, 31.9, 30.3, 21.6; **HRMS (ESI$^+$)** *m/z*: $[M + H]^+$ calcd for $C_{32}H_{40}NO_3S$ 518.2723; found 518.2719.

2,6-Di-*tert*-butyl-4-(p-tolyl(1-tosyl-4,5-dihydro-1H-pyrrol-3-yl)methyl)phenol (20b):



The product **20b** was obtained in 87% yield (75 mg, White solid); **mp** = 181-182 °C; R_f = 0.55 (petroleum ether:ethyl acetate = 4:1); **^{1}H NMR (500 MHz, $CDCl_3$) δ** = 7.62 (d, *J* = 8.1 Hz, 2H), 7.34 (d, *J* = 8.0 Hz, 2H), 7.05 (d, *J* = 7.8 Hz, 2H), 6.90 (d, *J* = 7.9 Hz, 2H), 6.81 (s, 2H), 5.77 (d, *J* = 1.0 Hz, 1H), 5.07 (s, 1H), 4.49 (s, 1H), 3.61 – 3.43 (m, 2H), 2.48 (s, 3H), 2.32 (s, 3H), 2.30 (t, 2H), 1.35 (s, 18H); **^{13}C{^{1}H} NMR (125 MHz,$CDCl_3$) δ** = 152.3, 143.7, 138.9, 136.0, 135.6, 132.5, 131.9, 131.3, 129.6, 129.0, 128.3, 128.0, 127.8, 124.9, 50.7, 48.2, 34.3, 31.9, 30.3, 21.6, 21.0; **HRMS (ESI$^+$)** *m/z*: $[M + H]^+$ calcd for $C_{33}H_{42}NO_3S$ 532.2880; found 532.2881.

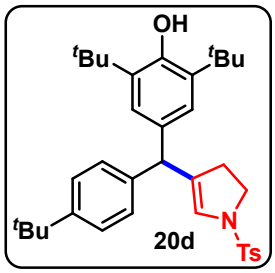


2,6-Di-*tert*-butyl-4-((4-isopropylphenyl)(1-tosyl-4,5-dihydro-1H-pyrrol-3-yl)methyl)phenol (20c):

The product **20c** was obtained in 76% yield (63 mg, White solid); **mp** = 197-198 °C; R_f = 0.55 (petroleum ether:ethyl acetate = 4:1); **^{1}H NMR (500 MHz, $CDCl_3$) δ** = 7.63 (d, *J* = 8.1 Hz, 2H), 7.36 (d, *J* = 7.9 Hz,

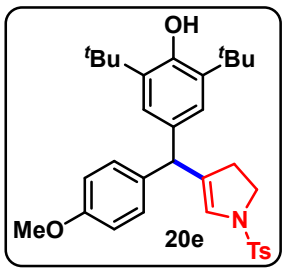
2H), 7.10 (d, *J* = 8.0 Hz, 2H), 6.94 (d, *J* = 8.0 Hz, 2H), 6.82 (s, 2H), 5.80 (d, *J* = 1.0 Hz, 1H), 5.07 (s, 1H), 4.49 (s, 1H), 3.60 – 3.46 (m, 2H), 2.88 (spt, *J* = 6.9 Hz, 1 H), 2.49 (s, 3H), 2.32 (t, 2H), 1.36 (s, 18H), 1.24 (d, *J* = 6.9 Hz, 6H); **$^{13}C\{^1H\}$ NMR (125 MHz,$CDCl_3$) δ** = 152.3, 147.0, 143.7, 139.2, 135.6, 132.6, 132.0, 131.3, 129.6, 128.3, 127.9, 127.8, 126.3, 124.9, 50.7, 48.2, 34.3, 33.6, 32.0, 30.3, 24.0, 21.6; **HRMS (ESI$^+$)** *m/z*: $[M + H]^+$ calcd for $C_{35}H_{46}NO_3S$ 560.3193; found 560.3189.

2,6-Di-*tert*-butyl-4-((4-(tert-butyl)phenyl)(1-tosyl-4,5-dihydro-1H-pyrrol-3-yl)methyl)phenol (20d):



The product **20d** was obtained in 72% yield (59 mg, White solid); **mp** = 222-223 °C; ***R*$_f$** = 0.60 (petroleum ether:ethyl acetate = 4:1); **^1H NMR (500 MHz, $CDCl_3$) δ** = 7.63 (d, *J* = 8.2 Hz, 2H), 7.35 (d, *J* = 8.1 Hz, 2H), 7.25 (d, *J* = 8.3 Hz, 2H), 6.94 (d, *J* = 8.3 Hz, 2H), 6.82 (s, 2H), 5.80 (d, *J* = 1.5 Hz, 1H), 5.07 (s, 1H), 4.49 (s, 1H), 3.57-3.46 (m, 2H), 2.48 (s, 3H), 2.37 – 2.25 (m, 2H), 1.35 (s, 18H), 1.30 (s, 9H) ; **$^{13}C\{^1H\}$ NMR (125 MHz,$CDCl_3$) δ** = 152.3, 149.2, 143.7, 138.8, 135.5, 132.5, 132.0, 131.3, 129.6, 128.0, 127.8, 125.1, 124.9, 50.6, 48.2, 34.3, 34.3, 32.0, 31.3, 30.3, 21.6; **HRMS (ESI$^+$)** *m/z*: $[M + H]^+$ calcd for $C_{36}H_{48}NO_3S$ 574.3349; found 574.3349.

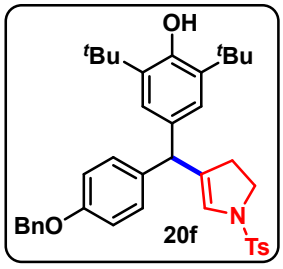
2,6-Di-*tert*-butyl-4-((4-methoxyphenyl)(1-tosyl-4,5-dihydro-1H-pyrrol-3-yl)methyl)phenol (20e):



The product **20e** was obtained in 89% yield (75 mg, White solid); **mp** = 166-167 °C; ***R*$_f$** = 0.40 (petroleum ether:ethyl acetate = 4:1); **^1H NMR (500 MHz, $CDCl_3$) δ** = 7.62 (d, *J* = 8.2 Hz, 2H), 7.35 (d, *J* = 8.0 Hz, 2H), 6.93 (d, *J* = 8.6 Hz, 2H), 6.80 (s, 2H), 6.79 (d, *J* = 8.6 Hz, 2H), 5.76 (d, *J* = 1.4 Hz, 1H), 5.07 (s, 1H), 4.48 (s, 1H), 3.79 (s, 3H), 3.60 – 3.45 (m, 2H), 2.48 (s, 3H), 2.31 (t, *J* = 8.9 Hz, 2H), 1.36 (s, 18H); **$^{13}C\{^1H\}$ NMR (125 MHz,$CDCl_3$) δ** = 158.1, 152.3, 143.7, 135.6, 134.0, 132.5, 132.1, 131.5, 129.6, 129.4, 128.0, 127.8, 124.8, 113.7, 55.2, 50.2, 48.2, 34.3, 31.9, 30.3, 29.4, 21.6; **HRMS (ESI$^+$)** *m/z*: $[M + Na]^+$ calcd for $C_{33}H_{41}NO_4SNa$ 570.2649; found 570.2640.

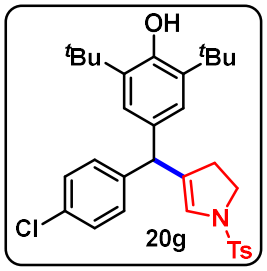
4-((4-(Benzyloxy)phenyl)(1-tosyl-4,5-dihydro-1H-pyrrol-3-yl)methyl)-2,6-di-*tert*-butyl phenol (20f):

The product **20f** was obtained in 92% yield (72 mg, White solid); **mp** = 167-168 °C; ***R*$_f$** = 0.45 (petroleum ether:ethyl acetate =4:1); **^1H NMR (500 MHz, $CDCl_3$) δ** = 7.62 (d, *J* = 8.0 Hz, 2H),



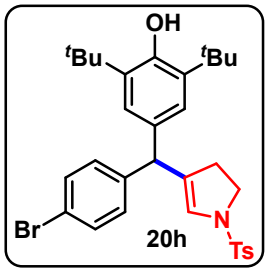
7.44 (d, *J* = 7.4 Hz, 2H), 7.39 (t, *J* = 7.5 Hz, 2H), 7.34 (d, *J* = 7.9 Hz, 3H), 6.93 (d, *J* = 8.4 Hz, 2H), 6.87 (d, *J* = 8.4 Hz, 2H), 6.81 (s, 2H), 5.77 (s, 1H), 5.08 (s, 1H), 5.05 (s, 2H), 4.49 (s, 1H), 3.60 – 3.46 (m, 2H), 2.48 (s, 3H), 2.32 (t, *J* = 8.8 Hz, 2H), 1.36 (s, 18H); **$^{13}C\{^{1}H\}$ NMR (125 MHz,$CDCl_3$) δ** = 157.4, 152.3, 143.7, 137.1, 135.6, 134.4, 132.6, 132.0, 131.4, 129.6, 129.5, 128.6, 128.0, 127.9, 127.8, 127.5, 124.9, 114.7, 70.0, 50.2, 48.2, 34.2, 31.9, 30.3, 21.6; **HRMS (ESI$^+$)** *m/z*: $[M + Na]^+$ calcd for $C_{39}H_{45}NO_4SNa$ 646.2962; found 646.2958.

2,6-Di-*tert*-butyl-4-((4-chlorophenyl)(1-tosyl-4,5-dihydro-1H-pyrrol-3-yl)methyl)phenol (20g):



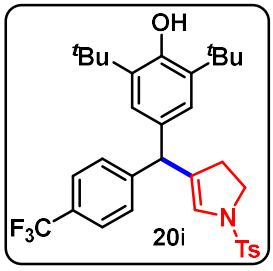
The product **20g** was obtained in 95% yield (80 mg, White solid); **mp** = 169-170 °C; R_f = 0.48 (petroleum ether:ethyl acetate =4:1); **^{1}H NMR (500 MHz, $CDCl_3$) δ** = 7.62 (d, *J* = 8.2 Hz, 2H), 7.35 (d, *J* = 8.1 Hz, 2H), 7.22 (d, *J* = 8.4 Hz, 2H), 6.95 (d, *J* = 8.4 Hz, 2H), 6.79 (s, 2H), 5.79 (d, *J* = 1.4 Hz, 1H), 5.11 (s, 1H), 4.52 (s, 1H), 3.61 – 3.47 (m, 2H), 2.49 (s, 3H), 2.32 (t, *J* = 8.9 Hz, 2H), 1.36 (s, 18H); **$^{13}C\{^{1}H\}$ NMR (125 MHz,$CDCl_3$) δ** =152.5, 143.8, 140.5, 135.8, 132.5, 132.2, 131.2, 130.4, 129.8, 129.6, 128.5, 128.4, 127.8, 124.8, 50.4, 48.1, 34.2, 31.9, 30.3, 21.6; **HRMS (ESI$^+$)** *m/z*: $[M + H]^+$ calcd for $C_{32}H_{39}ClNO_3S$ 552.2334; found 552.2337.

4-((4-Bromophenyl)(1-tosyl-4,5-dihydro-1H-pyrrol-3-yl)methyl)-2,6-di-*tert*-butylphenol (20h)



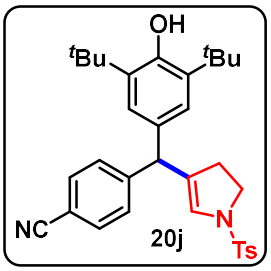
The product **20h** was obtained in 94% yield (75 mg, White solid); **mp** = 158-159 °C; R_f = 0.47 (petroleum ether:ethyl acetate =4:1); **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 7.61 (d, *J* = 7.8 Hz, 2H), 7.36 (t, *J* = 8.7 Hz, 4H), 6.89 (d, *J* = 7.9 Hz, 2H), 6.78 (s, 2H), 5.78 (s, 1H), 5.11 (s, 1H), 4.50 (s, 1H), 3.53 (m, 2H), 2.49 (s, 3H), 2.31 (t, *J* = 8.6 Hz, 2H), 1.35 (s, 18H); **$^{13}C\{^{1}H\}$ NMR (100 MHz,$CDCl_3$) δ** = 152.5, 143.8, 141.1, 135.8, 132.5, 131.4, 131.1, 130.3, 130.2, 129.6, 128.4, 127.8, 124.8, 120.3, 50.4, 48.1, 34.3, 31.9, 30.3, 21.6; **HRMS (ESI$^+$)** *m/z*: $[M + H]^+$ calcd for $C_{32}H_{39}BrNO_3S$ 596.1829; found 596.1821.

2,6-Di-*tert*-butyl-4-((1-tosyl-4,5-dihydro-1H-pyrrol-3-yl)(4(trifluoromethyl)phenyl)methyl) phenol (20i):



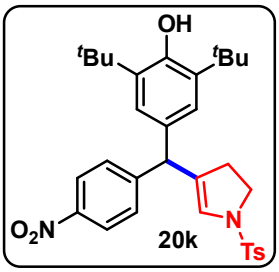
The product **20i** was obtained in 77% yield (62 mg, White solid); **mp** = 179-180 °C; R_f = 0.42 (petroleum ether:ethyl acetate = 4:1); **^{1}H NMR (500 MHz, $CDCl_3$) δ** = 7.62 (d, *J* = 8.1 Hz, 2H), 7.51 (d, *J* = 8.1 Hz, 2H), 7.36 (d, *J* = 8.0 Hz, 2H), 7.14 (d, *J* = 8.0 Hz, 2H), 6.79 (s, 2H), 5.81 (d, *J* = 1.0 Hz, 1H), 5.13 (s, 1H), 4.60 (s, 1H), 3.62 – 3.48 (m, 2H), 2.49 (s, 3H), 2.33 (t, *J* = 8.9 Hz, 2H), 1.36 (s, 18H) ; **^{13}C{1H} NMR (125 MHz,$CDCl_3$) δ** = 152.6, 146.1, 143.9, 136.0, 132.6, 130.8, 129.8, 129.7, 128.8, 128.6, 127.8, 125.30 (q, $J_{C\text{-}F}$ = 3.8 Hz), 124.9, 50.8, 48.1, 34.3, 31.9, 30.3, 21.6; **^{19}F NMR (376 MHz, CDCl3) δ** = -62.35; **HRMS (ESI$^+$)** m/z: [M + H]+ calcd for $C_{33}H_{39}F_3NO_3S$ 586.2597; found 586.2598.

4-((3,5-Di-*tert*-butyl-4-hydroxyphenyl)(1-tosyl-4,5-dihydro-1H-pyrrol-3-yl)methyl) benzonitrile (20j):



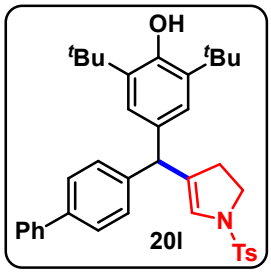
The product **20j** was obtained in 92% yield (78 mg, White solid); **mp** = 201-202 °C; R_f = 0.42 (petroleum ether:ethyl acetate = 4:1); **^{1}H NMR (500 MHz, $CDCl_3$) δ** = 7.61 (d, *J* = 8.2 Hz, 2H), 7.55 (d, *J* = 8.2 Hz, 2H), 7.35 (d, *J* = 8.1 Hz, 2H), 7.14 (d, *J* = 8.2 Hz, 2H), 6.76 (s, 2H), 5.79 (d, *J* = 1.3 Hz, 1H), 5.15 (s, 1H), 4.59 (s, 1H), 3.62 – 3.47 (m, 2H), 2.49 (s, 3H), 2.33 (t, *J* = 8.9 Hz, 2H), 1.35 (s, 18H); **^{13}C{^{1}H} NMR (125 MHz,$CDCl_3$) δ** = 152.7, 147.6, 143.9, 136.1, 132.5, 132.2, 130.3, 129.7, 129.3, 129.1, 128.9, 127.8, 124.8, 118.8, 110.5, 51.0, 48.1, 34.3, 31.9, 30.2, 21.6; **HRMS (ESI$^+$)** *m/z*: [M + H]$^+$ calcd for $C_{33}H_{39}N_2O_3S$ 543.2676; found 543.2681.

2,6-Di-*tert*-butyl-4-((4-nitrophenyl)(1-tosyl-4,5-dihydro-1H-pyrrol-3-yl)methyl)phenol (20k):



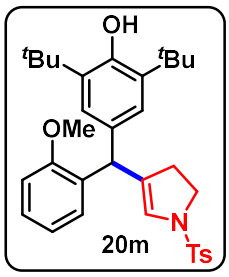
The product **20k** was obtained in 88% yield (73 mg, White solid); **mp** = 211-212 °C; R_f = 0.40 (petroleum ether:ethyl acetate = 4:1); **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 8.12 (d, *J* = 8.6 Hz, 2H), 7.62 (d, *J* = 8.2 Hz, 2H), 7.36 (d, *J* = 8.1 Hz, 2H), 7.19 (d, *J* = 8.8 Hz, 2H), 6.77 (s, 2H), 5.80 (d, *J* = 1.2 Hz, 1H), 5.17 (s, 1H), 4.65 (s, 1H), 3.64 – 3.48 (m, 2H), 2.50 (s, 3H), 2.35 (t, *J* = 8.9 Hz, 2H), 1.35 (s, 18H); **^{13}C{^{1}H} NMR (100 MHz,$CDCl_3$) δ** = 152.8, 149.7, 146.6, 144.0, 136.1, 132.4, 130.2, 129.7, 129.3, 129.1, 129.0, 127.8, 124.8, 123.7, 50.8, 48.01, 34.3, 31.9, 30.2, 21.6; **HRMS (ESI$^+$)** *m/z*: [M + H]$^+$ calcd for $C_{32}H_{39}N_2O_5S$ 563.2574; found 563.2574.

4-([1,1'-Biphenyl]-4-yl(1-tosyl-4,5-dihydro-1H-pyrrol-3-yl)methyl)-2,6-di-*tert*-butylphenol (20l):



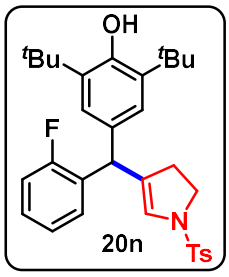
The product **20l** was obtained in 94% yield (75 mg, White solid); **mp** = 206-207 °C; R_f = 0.43 (petroleum ether:ethyl acetate = 4:1); **^{1}H NMR (500 MHz, $CDCl_3$) δ** = 7.65 (d, *J* = 8.0 Hz, 2H), 7.60 (d, *J* = 7.5 Hz, 2H), 7.50 (d, *J* = 8.0 Hz, 2H), 7.45 (t, *J* = 7.6 Hz, 2H), 7.35 (dd, *J* = 14.8, 7.6 Hz, 3H), 7.11 (d, *J* = 8.0 Hz, 2H), 6.87 (s, 2H), 5.86 (s, 1H), 5.11 (s, 1H), 4.59 (s, 1H), 3.67 – 3.44 (m, 2H), 2.50 (s, 3H), 2.37 (t, *J* = 8.7 Hz, 2H), 1.38 (s, 18H); **^{13}C{^{1}H} NMR (125 MHz,$CDCl_3$) δ** = 152.4, 143.7, 141.1, 140.8, 139.4, 135.7, 132.6, 131.7, 130.9, 129.6, 128.9, 128.7, 128.2, 127.8, 127.2, 127.0, 127.0, 124.9, 50.7, 48.2, 34.3, 32.0, 30.3, 21.6; **HRMS (ESI$^+$)** *m/z*: $[M + H]^+$ calcd for $C_{38}H_{44}NO_3S$ 594.3036; found 594.3027.

2,6-Di-*tert*-butyl-4-((2-methoxyphenyl)(1-tosyl-4,5-dihydro-1H-pyrrol-3-yl)methyl)phenol (20m):



The product **20m** was obtained in 89% yield (75 mg, White solid); **mp** = 114-115 °C; R_f = 0.40 (petroleum ether:ethyl acetate = 4:1); **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 7.62 (d, *J* = 8.1 Hz, 2H), 7.34 (d, *J* = 8.0 Hz, 2H), 7.23 – 7.12 (m, 1H), 6.85 (s, 2H), 6.80 (m, 3H), 5.72 (s, 1H), 5.05 (s, 1H), 4.97 (s, 1H), 3.75 (s, 3H), 3.64 – 3.40 (m, 2H), 2.48 (s, 3H), 2.32 (t, *J* = 8.7 Hz, 2H), 1.36 (s, 18H); **^{13}C{^{1}H} NMR (100 MHz,$CDCl_3$) δ** = 156.8, 152.2, 143.6, 135.4, 132.6, 131.6, 131.0, 130.5, 129.6, 128.8, 127.8, 127.6, 127.5, 125.1, 120.2, 110.6, 55.5, 48.2, 43.1, 34.3, 32.2, 30.3, 21.6; **HRMS (ESI$^+$)** *m/z*: $[M + H]^+$ calcd for $C_{33}H_{42}NO_4S$ 548.2829; found 548.2827.

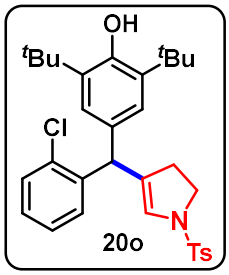
2,6-Di-*tert*-butyl-4-((2-fluorophenyl)(1-tosyl-4,5-dihydro-1H-pyrrol-3-yl)methyl)phenol (20n):



The product **20n** was obtained in 86% yield (70 mg, White solid); **mp** = 140-141 °C; R_f = 0.52 (petroleum ether:ethyl acetate = 4:1); **^{1}H NMR (500 MHz, $CDCl_3$) δ** = 7.61 (d, *J* = 8.0 Hz, 2H), 7.34 (d, *J* = 7.9 Hz, 2H), 7.19 (dd, *J* = 12.9, 6.6 Hz, 1H), 7.01 (t, *J* = 8.2 Hz, 2H), 6.88 (d, *J* = 7.5 Hz, 1H), 6.85 (s, 2H), 5.78 (s, 1H), 5.10 (s, 1H), 4.85 (s, 1H), 3.63 – 3.45 (m, 2H), 2.47 (s, 3H), 2.34 (t, *J* = 8.8 Hz, 2H), 1.36 (s, 18H); **^{13}C{^{1}H} NMR (125 MHz,$CDCl_3$) δ** = 161.5 (d, J_{C-F} = 247 Hz), 152.5, 143.7, 135.8, 132.5, 130.4, 129.7, 129.6, 129.5, 129.5, 129.2 (d, J_{C-F} = 14.31 Hz), 128.3, 128.2 (d, J_{C-F} = 8.58 Hz), 127.8, 124.9, 123.8 (d,

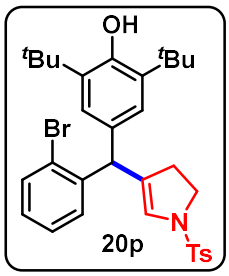
$J_{C\text{-}F}$ = 3.81 Hz), 115.4 (d, $J_{C\text{-}F}$ = 22.89 Hz), 48.2, 43.2, 34.3, 32.0, 30.3, 21.6; **^{19}F NMR (376 MHz, $CDCl_3$) δ** = -117.79; **HRMS (ESI$^+$)** *m/z*: $[M + H]^+$ calcd for $C_{32}H_{39}FNO_3S$ 536.2629; found 536.2631.

2,6-Di-*tert*-butyl-4-((2-chlorophenyl)(1-tosyl-4,5-dihydro-1H-pyrrol-3-yl)methyl)phenol (20o):



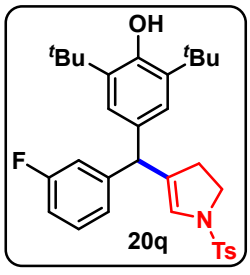
The product **20o** was obtained in 76% yield (64 mg, White solid); **mp** = 151-152 °C; R_f = 0.51 (petroleum ether:ethyl acetate = 4:1); **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 7.61 (d, *J* = 8.3 Hz, 2H), 7.40 – 7.30 (m, 3H), 7.19 – 7.08 (m, 2H), 6.88 – 6.85 (m, 1H), 6.85 (s, 2H), 5.74 (d, *J* = 1.5 Hz, 1H), 5.13 (s, 1H), 4.98 (s, 1H), 3.56 (m, 2H), 2.48 (s, 3H), 2.36 (t, *J* = 8.8 Hz, 2H), 1.37 (s, 18H) ; **^{13}C{^{1}H} NMR (100 MHz,$CDCl_3$) δ** = 152.5, 143.7, 139.8, 135.7, 134.1, 132.4, 130.1, 129.6, 129.5, 129.5, 128.5, 127.8, 126.6, 125.2, 48.1, 47.1, 34.2, 32.1, 30.3, 21.6; **HRMS (ESI$^+$)** *m/z*: $[M + H]^+$ calcd for $C_{32}H_{39}ClNO_3S$ 552.2334; found 552.2337.

4-((2-Bromophenyl)(1-tosyl-4,5-dihydro-1H-pyrrol-3-yl)methyl)-2,6-di-*tert*-butylphenol (20p):



The product **20p** was obtained in 71% yield (57 mg, White solid); **mp** = 140-141 °C; R_f = 0.50 (petroleum ether:ethyl acetate = 4:1); **^{1}H NMR (500 MHz, $CDCl_3$) δ** = 7.60 (d, *J* = 8.1 Hz, 2H), 7.37 (t, *J* = 5.5 Hz, 1H), 7.34 (d, *J* = 8.0 Hz, 2H), 7.12 (dd, *J* = 8.3, 1.8 Hz, 1H), 6.81 (s, 2H), 6.78 (d, *J* = 8.4 Hz, 1H), 5.74 (d, *J* = 0.6 Hz, 1H), 5.13 (s, 1H), 4.91 (s, 1H), 3.55 (m, 2H), 2.48 (s, 3H), 2.35 (t, *J* = 8.8 Hz, 2H), 1.36 (s, 18H); **^{13}C{^{1}H} NMR (125 MHz,$CDCl_3$) δ** = 152.5, 143.7, 141.6, 135.8, 133.0, 132.6, 130.2, 129.7, 129.4, 128.7, 128.1, 127.8, 127.3, 125.3, 125.2, 49.9, 48.1, 34.3, 32.2, 30.3, 21.6; **HRMS (ESI$^+$)** *m/z*: $[M + H]^+$ calcd for $C_{32}H_{39}BrNO_3S$ 596.1829; found 596.1833.

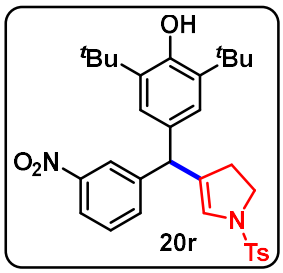
2,6-Di-*tert*-butyl-4-((3-fluorophenyl)(1-tosyl-4,5-dihydro-1H-pyrrol-3-yl)methyl)phenol (20q):



The product **20q** was obtained in 98% yield (80 mg, White solid); **mp** = 166-167 °C; R_f = 0.52 (petroleum ether:ethyl acetate = 4:1); **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 7.63 (d, *J* = 7.9 Hz, 2H), 7.37 (d, *J* = 7.8 Hz, 2H), 7.27 – 7.18 (m, 1H), 6.90 (t, *J* = 7.7 Hz, 1H), 6.85 – 6.78 (m, 3H), 6.68 (d, *J* = 9.9 Hz, 1H), 5.79 (s, 1H), 5.13 (s, 1H), 4.53 (s, 1H), 3.61 – 3.48 (m, 2H), 2.49 (s, 3H), 2.33 (t, *J* = 8.7 Hz, 2H), 1.37 (s, 18H); **^{13}C{^{1}H} NMR (100 MHz,$CDCl_3$) δ** =

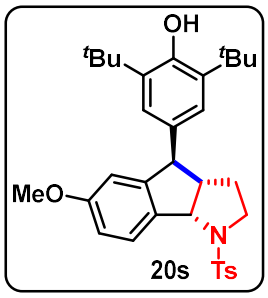
162.9 (d, $J_{C\text{-}F}$ = 245.83 Hz), 152.5, 144.7 (d, $J_{C\text{-}F}$ = 6.17 Hz), 143.9, 135.8, 132.3, 130.7 (d, $J_{C\text{-}F}$ = 74.75 Hz), 129.8, 129.7, 128.5, 127.8, 124.8, 124.2 (d, $J_{C\text{-}F}$ = 1.54 Hz), 115.2 (d, $J_{C\text{-}F}$ = 22.35 Hz), 113.4 (d, $J_{C\text{-}F}$ = 21.58 Hz), 50.7, 48.1, 34.3, 31.9, 30.2, 21.6; **^{19}F NMR (376 MHz, $CDCl_3$) δ** = -113.19 ; **HRMS (ESI$^+$)** *m/z*: $[M + H]^+$ calcd for $C_{32}H_{39}FNO_3S$ 536.2629; found 536.2632.

2,6-Di-*tert*-butyl-4-((3-nitrophenyl)(1-tosyl-4,5-dihydro-1H-pyrrol-3-yl)methyl)phenol (20r):



The product **20r** was obtained in 87% yield (72 mg, White solid); **mp** = 151-152 °C; R_f = 0.35 (petroleum ether:ethyl acetate = 4:1); **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 8.08 (d, *J* = 7.7 Hz, 1H), 7.95 (s, 1H), 7.61 (d, *J* = 8.1 Hz, 2H), 7.41 (m, 4H), 6.81 (s, 2H), 5.79 (s, 1H), 5.16 (s, 1H), 4.64 (s, 1H), 3.63 – 3.46 (m, 2H), 2.50 (s, 3H), 2.35 (t, *J* = 8.3 Hz, 2H), 1.36 (s, 18H); **^{13}C{^{1}H} NMR (100 MHz,$CDCl_3$) δ** = 152.8, 148.4, 144.4, 144.1, 136.1, 134.53, 132.1, 130.2, 129.8, 129.3, 129.1, 127.7, 124.8, 123.3, 121.7, 50.7, 48.1, 34.3, 31.9, 30.2, 21.6; **HRMS (ESI$^+$)** *m/z*: $[M + H]^+$ calcd for $C_{32}H_{39}N_2O_5S$ 563.2574; found 563.2575.

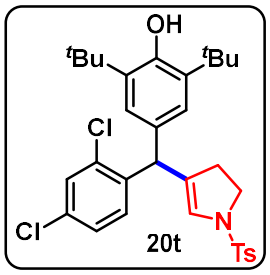
2,6-Di-*tert*-butyl-4-(6-methoxy-1-tosyl-1,2,3,3a,4,8b-hexahydroindeno[1,2-b]pyrrol-4-yl)phenol (20s):



The product **20s** was obtained in 62% yield (52 mg, White solid); **mp** = 79-80 °C; R_f = 0.40 (petroleum ether:ethyl acetate = 4:1); **^{1}H NMR (500 MHz, $CDCl_3$) δ** = 7.78 (d, *J* = 8.2 Hz, 2H), 7.75 (d, *J* = 8.5 Hz, 1H), 7.31 (d, *J* = 8.1 Hz, 2H), 6.87 (dd, *J* = 8.4, 2.3 Hz, 1H), 6.81 (s, 2H), 6.54 (d, *J* = 2.0 Hz, 1H), 5.27 (d, *J* = 7.5 Hz, 1H), 5.09 (s, 1H), 4.00 (d, *J* = 3.3 Hz, 1H), 3.85 – 3.77 (m, 1H), 3.75 (s, 3H), 3.50 – 3.41 (m, 1H), 3.41 – 3.31 (m, 1H), 2.77 (m, 1H), 2.42 (s, 3H), 1.87 – 1.71 (m, 2H), 1.39 (s, 18H) ;**^{13}C{^{1}H} NMR (125 MHz,$CDCl_3$) δ** = 160.4, 152.3, 146.8, 143.3, 136.0, 135.3, 135.0, 134.0, 129.7, 127.6, 127.6, 123.9, 114.2, 110.1, 67.5, 55.4, 55.2, 53.3, 48.9, 34.3, 30.9, 30.2, 21.4; **DEPT 135 (125 MHz, $CDCl_3$) δ** = 129.7, 127.7, 127.6, 123.9, 114.2, 110.2, 67.6, 55.4, 55.2, 53.4, 48.9, 31.0, 30.3, 21.5; **HRMS (ESI$^+$)** *m/z*: $[M + H]^+$ calcd for $C_{33}H_{42}NO_4S$ 548.2829; found 548.2839.

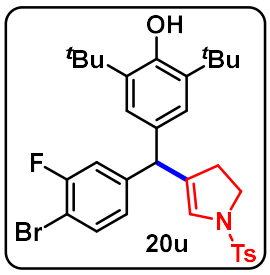
2,6-Di-*tert*-butyl-4-((2,4-dichlorophenyl)(1-tosyl-4,5-dihydro-1H-pyrrol-3-yl)methyl) phenol (20t):

The product **20t** was obtained in 79 % yield (64 mg, White solid); **mp** = 147-148 °C; R_f = 0.48 (petroleum ether:ethyl acetate = 4:1); **^{1}H NMR (500 MHz, $CDCl_3$) δ** = 7.60 (d, *J* = 8.2 Hz, 2H), 7.38 (d, *J* = 2.1 Hz, 1H), 7.34 (d, *J* = 8.1 Hz, 2H), 7.11 (dd, *J* = 8.4, 2.1 Hz, 1H), 6.80 (s,



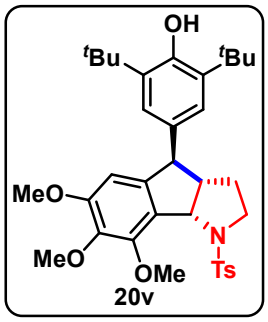
2H), 6.78 (d, J = 8.4 Hz, 1H), 5.74 (d, J = 1.4 Hz, 1H), 5.13 (s, 1H), 4.91 (s, 1H), 3.55 (td, J = 9.2, 3.1 Hz, 2H), 2.48 (s, 3H), 2.35 (t, J = 8.9 Hz, 2H), 1.36 (s, 18H); **^{13}C{^{1}H} NMR (125 MHz,CDCl$_3$) δ** = 152.7, 143.8, 138.6, 135.9, 134.8, 132.8, 132.5, 130.3, 129.7, 129.7, 129.4, 128.8, 127.8, 127.0, 125.1, 48.1, 46.8, 34.3, 32.1, 30.3, 21.6; **HRMS (ESI$^+$)** *m/z*: $[M + H]^+$ calcd for $C_{32}H_{38}Cl_2NO_3S$ 586.1944; found 586.1926.

4-((4-Bromo-3-fluorophenyl)(1-tosyl-4,5-dihydro-1H-pyrrol-3-yl)methyl)-2,6-di-*tert*-butylphenol (20u):



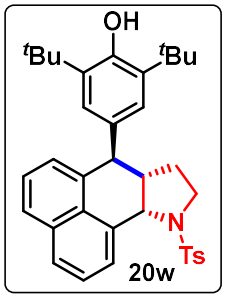
The product **20u** was obtained in 59 % yield (47 mg, White solid); **mp** = 163-164 °C; R_f = 0.50 (petroleum ether:ethyl acetate = 4:1); **^{1}H NMR (400 MHz, CDCl$_3$) δ** = 7.62 (d, J = 8.1 Hz, 2H), 7.41 (dd, J = 10.3, 5.2 Hz, 1H), 7.36 (d, J = 8.0 Hz, 2H), 6.78 (s, 2H), 6.73 (dd, J = 7.5, 3.0 Hz, 2H), 5.80 (d, J = 1.2 Hz, 1H), 5.14 (s, 1H), 4.50 (s, 1H), 3.62 – 3.47 (m, 2H), 2.49 (s, 3H), 2.32 (t, J = 8.8 Hz, 2H), 1.36 (s, 18H); **^{13}C{^{1}H} NMR (100 MHz,CDCl$_3$) δ** = 159.0 (d, $J_{C\text{-}F}$ = 247.28 Hz), 152.7, 144.1, 144.1, 136.0, 133.2, 132.3, 130.5, 129.7, 128.7, 127.8, 125.4 (d, $J_{C\text{-}F}$ = 3.83 Hz), 124.7, 116.4 (d, $J_{C\text{-}F}$ = 22.05 Hz), 106.8 (d, $J_{C\text{-}F}$ = 20.13 Hz), 50.3, 48.1, 34.3, 31.8, 30.2, 21.6; **^{19}F NMR (376 MHz, CDCl$_3$) δ =** -107.33; **HRMS (ESI$^+$)** *m/z*: $[M + H]^+$ calcd for $C_{32}H_{38}BrFNO_3S$ 614.1734; found 614.1734.

2,6-Di-*tert*-butyl-4-(6,7,8-trimethoxy-1-tosyl-1,2,3,3a,4,8b-hexahydroindeno[1,2-b]pyrrol-4-yl)phenol (20v):



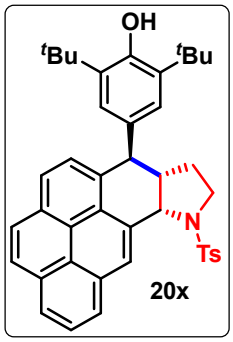
The product **20v** was obtained in 59 % yield (47 mg, White solid); **mp** = 172-173 °C; R_f = 0.37 (petroleum ether:ethyl acetate = 4:1); **^{1}H NMR (400 MHz, CDCl$_3$) δ** = 7.81 (d, J = 8.2 Hz, 2H), 7.27 (d, J = 8.4 Hz, 2H), 6.76 (s, 2H), 6.26 (s, 1H), 5.72 (d, J = 7.2 Hz, 1H), 5.09 (s, 1H), 4.04 (s, 3H), 3.96 (d, J = 3.5 Hz, 1H), 3.87 (s, 3H), 3.74 (s, 3H), 3.66 (m, 1H), 3.23 – 3.10 (m, 1H), 2.75 – 2.60 (m, 1H), 2.40 (s, 3H), 1.63-1.50 (m, 2H), 1.38 (s, 18H); **^{13}C{^{1}H} NMR (100 MHz,CDCl$_3$) δ** = 155.1, 152.4, 151.2, 143.1, 142.0, 141.7, 136.9, 136.0, 135.5, 129.6, 127.5, 125.9, 123.8, 103.5, 67.5, 61.2, 60.8, 57.5, 56.1, 52.6, 47.7, 34.3, 32.1, 30.3, 21.5; **DEPT 135 (100 MHz, CDCl$_3$) δ** = 129.6, 127.5, 123.8, 103.5, 67.5, 61.2, 60.8, 57.5, 56.1, 52.6, 47.6, 32.1, 30.2, 21.4; **HRMS (ESI$^+$)** *m/z*: $[M + H]^+$ calcd for $C_{35}H_{46}NO_6S$ 608.3040; found 608.3046.

2,6-Di-*tert*-butyl-4-(10-tosyl-7,7a,8,9,10,10a-hexahydronaphtho[1,8-fg]indol-7-yl)phenol (20w):



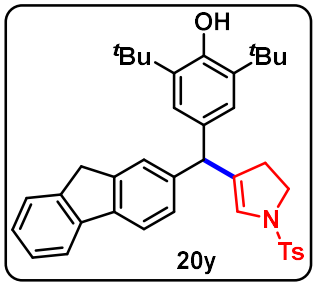
The product **20w** was obtained in 91% yield (75 mg, White solid); **mp** = 201-202 °C; R_f = 0.51(petroleum ether:ethyl acetate = 4:1); **^{1}H NMR (500 MHz, $CDCl_3$) δ** = 8.16 (d, *J* = 6.3 Hz, 1H), 7.84 (d, *J* = 7.6 Hz, 1H), 7.78 (d, *J* = 7.9 Hz, 1H), 7.62 (d, *J* = 7.1 Hz, 3H), 7.40 (t, *J* = 6.9 Hz, 1H), 7.25 (d, *J* = 7.0 Hz, 1H), 7.20 (d, *J* = 7.1 Hz, 2H), 6.47 (s, 2H), 5.09 (s, 1H), 5.05 (s, 1H), 4.24 (s, 1H), 3.38 (t, *J* = 9.4 Hz, 1H), 3.34 – 3.23 (m, 1H), 2.42 (s, 3H), 1.95 (s, 2H), 1.41-1.37 (m, 1H), 1.28 (s, 18H) ; **^{13}C{^{1}H} NMR (125 MHz,$CDCl_3$) δ** = 152.0, 143.2, 136.2, 135.6, 135.1, 132.9, 132.5, 129.7, 128.3, 127.5, 127.3, 127.2, 126.9, 126.2, 125.6, 123.5, 59.0, 47.4, 46.3, 44.7, 34.2, 30.4, 30.1, 29.2 , 21.5; **DEPT 135 (125 MHz, $CDCl_3$) δ** = δ 129.7, 127.5, 127.4, 127.3, 127.2, 126.9, 126.2, 125.6, 123.5, 58.9, 47.4, 46.2, 44.7, 34.2, 30.1, 29.2, 21.5; **HRMS (ESI$^+$)** *m/z*: $[M + H]^+$ calcd for $C_{36}H_{42}NO_3S$ 568.2880; found 568.2875.

2,6-Di-*tert*-butyl-4-(11-tosyl-8,8a,9,10,11,11a-hexahydropyreno[1,10-fg]indol-8-yl)phenol (20x):



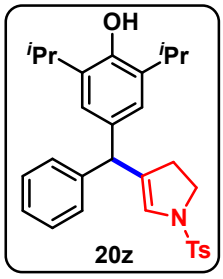
The product **20x** was obtained in 84% yield (64 mg, White solid); **mp** = 216-217 °C; R_f = 0.52 (petroleum ether:ethyl acetate = 4:1); **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 8.78 (d, *J* = 1.3 Hz, 1H), 8.34 (d, *J* = 7.5 Hz, 1H), 8.21 (d, *J* = 7.5 Hz, 1H), 8.14 – 8.11 (m, 1H), 8.09 (s, 1H), 8.07 (s, 1H), 8.05 (s, 1H), 7.78 (d, *J* = 7.7 Hz, 1H), 7.67 (d, *J* = 8.2 Hz, 2H), 7.19 (d, *J* = 8.1 Hz, 2H), 6.61 (s, 2H), 5.35 (d, *J* = 5.9 Hz, 1H), 5.10 (s, 1H), 4.52 (s, 1H), 3.55 – 3.30 (m, 2H), 2.41 (s, 3H), 2.10 – 1.93 (m, 2H), 1.73 – 1.62 (m, 1H), 1.29 (s, 18H); **^{13}C{^{1}H} NMR (100 MHz,$CDCl_3$) δ** = 152.0, 143.2, 136.5, 135.7, 135.0, 131.3, 131.1, 131.0, 130.8, 130.1, 129.6, 128.5, 128.0, 127.4, 127.3, 126.9, 126.1, 125.7, 125.4, 125.1, 124.8, 124.2, 124.1, 123.8, 59.1, 47.3, 46.8, 45.1, 34.2, 30.2, 29.3, 21.5; **DEPT 135 (100 MHz, $CDCl_3$) δ** = 129.8, 128.7, 128.2, 127.5, 127.5, 127.1, 126.3, 125.6, 125.2, 124.9, 124.0, 123.9, 59.3, 47.5, 47.0, 45.3, 30.3, 29.5, 21.6; **HRMS (ESI$^+$)** *m/z*: $[M + H]^+$ calcd for $C_{42}H_{44}NO_3S$ 642.3036; found 642.3040.

4-((9H-Fluoren-2-yl)(1-tosyl-4,5-dihydro-1H-pyrrol-3-yl)methyl)-2,6-di-*tert*-butylphenol (20y):



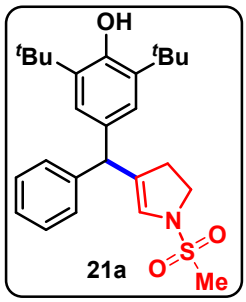
The product **20y** was obtained in 95% yield (75 mg, White solid); **mp** = 190-191 °C; R_f = 0.52 (petroleum ether:ethyl acetate = 4:1); **^{1}H NMR (500 MHz, $CDCl_3$) δ** = 7.74 (d, *J* = 7.5 Hz, 1H), 7.64 (dd, *J* = 11.3, 8.1 Hz, 3H), 7.52 (d, *J* = 7.4 Hz, 1H), 7.35 (d, *J* = 7.9 Hz, 3H), 7.27 (t, *J* = 7.3 Hz, 1H), 7.23 (s, 1H), 7.02 (d, *J* = 7.7 Hz, 1H), 6.85 (s, 2H), 5.82 (s, 1H), 5.09 (s, 1H), 4.61 (s, 1H), 3.82 (s, 2H), 3.62 – 3.46 (m, 2H), 2.49 (s, 3H), 2.35 (t, *J* = 8.7 Hz, 2H), 1.36 (s, 18H); **^{13}C{^{1}H} NMR (125 MHz,$CDCl_3$) δ** = 152.3, 143.7, 143.5, 143.2, 141.5, 140.5, 140.2, 135.7, 132.6, 132.1, 131.2, 129.6, 128.1, 127.9, 127.1, 126.7, 126.5, 125.3, 125.0, 125.0, 119.6, 119.6, 51.1, 48.2, 36.9, 34.3, 32.0, 30.3, 21.6; **HRMS (ESI$^+$)** *m/z*: $[M + H]^+$ calcd for $C_{39}H_{44}NO_3S$ 606.3036; found 606.3038.

2,6-Di-isopropyl-4-(phenyl(1-tosyl-4,5-dihydro-1H-pyrrol-3-yl)methyl)phenol (20z):



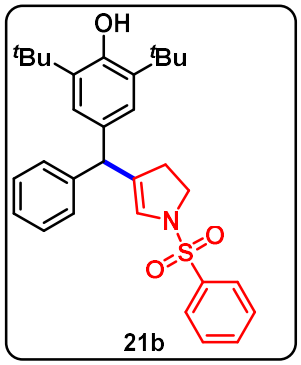
The product **20z** was obtained in 78% yield (72 mg, White solid); **mp** = 125-126 °C; R_f = 0.40 (petroleum ether:ethyl acetate = 4:1); **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 7.62 (d, *J* = 8.2 Hz, 2H), 7.36 (d, *J* = 8.0 Hz, 2H), 7.28 – 7.18 (m, 3H), 7.01 (d, *J* = 6.9 Hz, 2H), 6.71 (s, 2H), 5.77 (d, *J* = 1.4 Hz, 1H), 4.73 (s, 1H), 4.55 (s, 1H), 3.61 – 3.46 (m, 2H), 3.16 – 3.04 (m, 2H), 2.49 (s, 3H), 2.32 (t, *J* = 8.9 Hz, 2H), 1.18 (d, *J* = 4.9 Hz, 6H), 1.17 (d, *J* = 5.0 Hz, 6H); **^{13}C{^{1}H} NMR (100 MHz,$CDCl_3$) δ** = 148.6, 143.8, 141.8, 133.5, 132.9, 132.4, 131.1, 129.6, 128.4, 128.3, 128.3, 127.9, 126.5, 123.5, 50.8, 48.2, 31.9, 27.1, 22.7, 22.7, 21.6; **HRMS (ESI$^+$)** *m/z*: $[M + H]^+$ calcd for $C_{30}H_{36}NO_3S$ 490.2410; found 490.2409.

2,6-Di-*tert*-butyl-4-((1-(methylsulfonyl)-4,5-dihydro-1H-pyrrol-3-yl)(phenyl)methyl)phenol (21a):



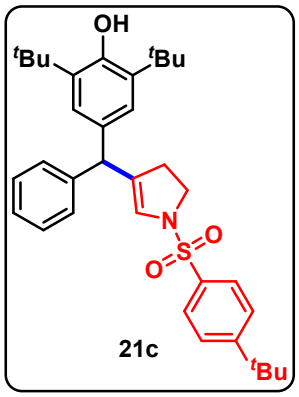
The product **21a** was obtained in 68% yield (51 mg, White solid); **mp** = 165-166 °C; R_f = 0.40 (petroleum ether:ethyl acetate = 4:1); **^{1}H NMR (500 MHz, $CDCl_3$) δ** = 7.29 (t, *J* = 7.1 Hz, 2H), 7.26 – 7.19 (m, 1H), 7.16 (d, *J* = 7.3 Hz, 2H), 6.95 (s, 2H), 5.77 (s, 1H), 5.12 (s, 1H), 4.65 (s, 1H), 3.74 (m, 2H), 2.82 (s, 3H), 2.60 (t, *J* = 8.9 Hz, 2H), 1.39 (s, 18H) ; **^{13}C{^{1}H} NMR (125 MHz,$CDCl_3$) δ** = 152.4, 142.0, 135.7, 131.6, 130.6, 128.4, 127.3, 126.6, 125.0, 51.1, 48.5, 34.4, 34.3, 32.3, 30.3; **HRMS (ESI$^+$)** *m/z*: $[M + H]^+$ calcd for $C_{26}H_{36}NO_3S$ 442.2410; found 442.2406.

2,6-Di-*tert*-butyl-4-(phenyl(1-(phenylsulfonyl)-4,5-dihydro-1H-pyrrol-3-yl)methyl)phenol (21b):



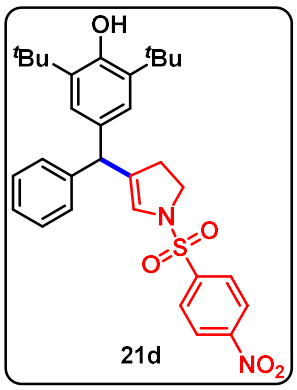
The product **21b** was obtained in 86% yield (73 mg, White solid); **mp** = 155-156 °C; R_f = 0.40 (petroleum ether:ethyl acetate = 4:1); **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 7.74 (d, *J* = 7.4 Hz, 2H), 7.65 (t, *J* = 7.4 Hz, 1H), 7.55 (t, *J* = 7.6 Hz, 2H), 7.21 (m ,3H), 7.01 (d, *J* = 7.1 Hz, 2H), 6.82 (s, 2H), 5.79 (s, 1H), 5.10 (s, 1H), 4.53 (s, 1H), 3.63 – 3.48 (m, 2H), 2.32 (t, *J* = 8.9 Hz, 2H), 1.36 (s, 18H); **^{13}C{^{1}H} NMR (100 MHz,$CDCl_3$) δ** = 152.3, 141.7, 135.6, 135.5, 132.9, 131.7, 131.3, 129.0, 128.4, 128.3, 127.9, 127.7, 126.5, 124.9, 51.0, 48.2, 34.3, 31.9, 30.3; **HRMS (ESI$^+$)** *m/z*: $[M + H]^+$ calcd for $C_{31}H_{38}NO_3S$ 504.2567; found 504.2566.

2,6-Di-*tert*-butyl-4-((1-((4-(tert-butyl)phenyl)sulfonyl)-4,5-dihydro-1H-pyrrol-3-yl)(phenyl) methyl)phenol (21c):



The product **21c** was obtained in 81% yield (77 mg, White solid); **mp** = 192-193 °C; R_f = 0.40 (petroleum ether:ethyl acetate = 4:1); **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 7.66 (d, *J* = 8.4 Hz, 2H), 7.56 (d, *J* = 8.7 Hz, 2H), 7.28 – 7.15 (m, 3H), 7.07 – 6.99 (m, 2H), 6.83 (s, 2H), 5.80 (d, *J* = 1.4 Hz, 1H), 5.10 (s, 1H), 4.55 (s, 1H), 3.61 – 3.47 (m, 2H), 2.35 (t, *J* = 8.9 Hz, 2H), 1.39 (s, 9H), 1.37 (s, 18H) ; **^{13}C{^{1}H} NMR (100 MHz,$CDCl_3$) δ** =156.6, 152.3, 141.7, 135.5, 132.5, 131.8, 130.8, 128.5, 128.3, 128.1, 127.6, 126.5, 125.9, 124.9, 51.0, 48.1, 35.2, 34.3, 32.0, 31.1, 30.3; **HRMS (ESI$^+$)** *m/z*: $[M + H]^+$ calcd for $C_{35}H_{46}NO_3S$ 560.3193; found 560.3194.

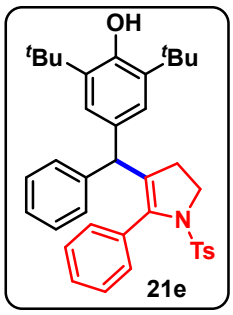
2,6-Di-*tert*-butyl-4-((1-((4-nitrophenyl)sulfonyl)-4,5-dihydro-1H-pyrrol-3-yl) (phenylmethyl)phenol (21d):



The product **21d** was obtained in 71% yield (66 mg, White solid); **mp** = 212-213 °C; R_f = 0.40 (petroleum ether:ethyl acetate = 4:1); **^{1}H NMR (500 MHz, $CDCl_3$) δ** = 8.39 (d, *J* = 8.0 Hz, 2H), 7.91 (d, *J* = 8.0 Hz, 2H), 7.27 (t, *J* = 7.2 Hz, 2H), 7.25 – 7.20 (m, 1H), 7.04 (d, *J* = 7.3 Hz, 2H), 6.81 (s, 2H), 5.80 (s, 1H), 5.12 (s, 1H), 4.56 (s, 1H), 3.59 (m, 2H), 2.38 (t, *J* = 8.8 Hz, 2H), 1.35 (s, 18H); **^{13}C{^{1}H} NMR (125**

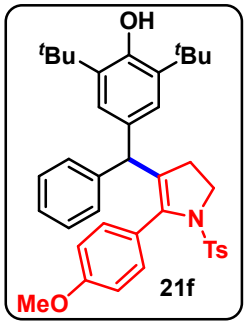
MHz,$CDCl_3$) δ = 152.5, 150.2, 141.6, 141.4, 135.8, 132.7, 131.2, 128.8, 128.4, 128.3, 126.9, 126.7, 124.8, 124.2, 51.0, 48.2, 34.3, 31.9, 30.2; **HRMS (ESI^+)** *m/z*: $[M + H]^+$ calcd for $C_{31}H_{37}N_2O_5S$ 549.2418; found 549.2434.

2,6-Di-*tert*-butyl-4-(phenyl(2-phenyl-1-tosyl-4,5-dihydro-1H-pyrrol-3-yl)methyl)phenol (21e):

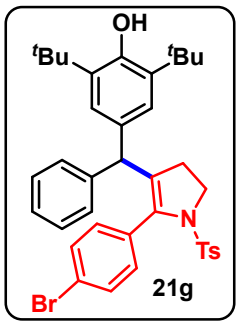


The product **21e** was obtained in 65 % yield (65 mg, White solid); **mp** = 170-171 °C; R_f = 0.40 (petroleum ether:ethyl acetate = 4:1); **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 7.54 (d, *J* = 8.2 Hz, 2H), 7.46 – 7.36 (m, 5H), 7.25 – 7.13 (m, 5H), 6.86 (dd, *J* = 6.7, 2.7 Hz, 2H), 6.66 (s, 2H), 5.07 (s, 1H), 4.94 (s, 1H), 4.04-3.98 (m, 1H), 3.91-3.83 (m, 1H), 2.43 (s, 3H), 2.14 – 1.99 (m, 2H), 1.31 (s, 18H); **^{13}C{^{1}H} NMR (100 MHz,$CDCl_3$) δ** = 152.1, 143.4, 142.0, 138.4, 135.4, 134.3, 132.7, 132.2, 131.3, 129.4, 128.5, 128.4, 128.1, 127.9, 127.8, 126.2, 125.1, 50.1, 48.5, 34.2, 30.2, 29.6, 21.6; **HRMS (ESI^+)** *m/z*: $[M + H]^+$ calcd for $C_{38}H_{44}NO_3S$ 594.3036; found 594.3025.

2,6-Di-*tert*-butyl-4-((2-(4-methoxyphenyl)-1-tosyl-4,5-dihydro-1H-pyrrol-3-yl)(phenyl) methyl)phenol (21f):



The product **21f** was obtained in 40% yield (40 mg, White solid); **mp** = 218-219 °C; R_f = 0.40 (petroleum ether:ethyl acetate = 4:1); **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 7.53 (d, *J* = 8.1 Hz, 2H), 7.36 (d, *J* = 8.6 Hz, 2H), 7.19 (d, *J* = 8.7 Hz, 5H), 6.93 (d, *J* = 8.6 Hz, 2H), 6.85 (d, *J* = 3.5 Hz, 2H), 6.66 (s, 2H), 5.07 (s, 1H), 4.92 (s, 1H), 4.00 (m, 1H), 3.85 (s, 3H), 2.43 (s, 3H), 2.05 (dd, *J* = 11.4, 6.6 Hz, 2H), 1.32 (s, 18H); **^{13}C{^{1}H} NMR (100 MHz,$CDCl_3$) δ** = 159.6, 152.0, 143.4, 142.2, 138.1, 135.4, 134.5, 132.5, 130.7, 130.1, 129.4, 128.5, 128.0, 127.8, 126.1, 125.0, 124.9, 113.3, 55.2, 50.0, 48.7, 34.2, 30.2, 29.6, 21.6; **HRMS (ESI^+)** *m/z*: $[M + H]^+$ calcd for $C_{39}H_{46}NO_4S$ 624.3142; found 624.3143.

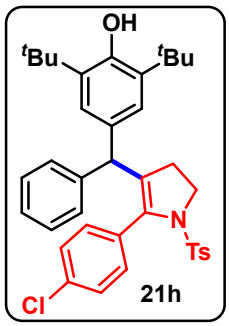


4-((2-(4-Bromophenyl)-1-tosyl-4,5-dihydro-1H-pyrrol-3- yl)(phenyl) methyl)-2,6-di-*tert*-butylphenol (21g):

The product **21g** was obtained in 53% yield (60 mg, gummy solid); R_f = 0.40 (petroleum ether:ethyl acetate = 4:1); **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 7.51 (d, *J* = 8.2 Hz, 3H), 7.28 (d, *J* = 8.4 Hz, 2H), 7.23 – 7.17 (m, 4H), 6.81 (dd, *J* = 6.0, 2.5 Hz, 2H), 6.62 (s, 2H), 5.07 (s, 1H), 4.86 (s, 1H), 4.04 – 3.94 (m, 1H), 3.91 – 3.78 (m, 1H), 2.44 (s, 3H), 2.12 – 1.99 (m, 2H), 1.30 (s, 18H); **^{13}C{^{1}H}**

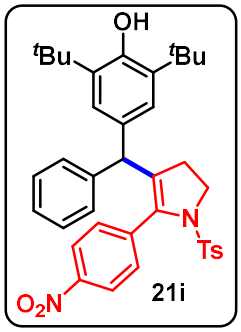
NMR (100 MHz,$CDCl_3$) δ = 152.2, 143.7, 141.9, 137.3, 135.6, 134.3, 132.1, 131.6, 131.2, 130.9, 130.1, 129.5, 128.4, 128.2, 127.8, 126.3, 125.0, 122.6, 50.0, 48.7, 34.2, 30.2, 29.99, 21.6; **HRMS (ESI$^+$)** *m/z*: $[M + H]^+$ calcd for $C_{38}H_{43}BrNO_3S$ 672.2142; found 672.2150.

2,6-Di-*tert*-butyl-4-((2-(4-chlorophenyl)-1-tosyl-4,5-dihydro-1H-pyrrol-3yl)(phenyl)methyl) phenol (21h):



The product **21h** was obtained in 54% yield (57 mg, White solid); **mp** = 192-193 °C; R_f = 0.40 (petroleum ether:ethyl acetate = 4:1); **^{1}H NMR (500 MHz, $CDCl_3$) δ** = 7.52 (d, *J* = 7.6 Hz, 2H), 7.36 (s, 4H), 7.21 (s, 5H), 6.82 (s, 2H), 6.63 (s, 2H), 5.08 (s, 1H), 4.87 (s, 1H), 4.00 (dd, *J* = 15.9, 10.0 Hz, 1H), 3.86 (dd, *J* = 20.9, 10.1 Hz, 1H), 2.44 (s, 3H), 2.08 (s, 2H), 1.31 (s, 18H); **^{13}C{^{1}H} NMR (125 MHz,$CDCl_3$) δ** = 152.2, 143.7, 141.9, 137.2, 135.6, 134.4, 134.3, 132.1, 132.0, 131.2, 130.7, 129.5, 128.4, 128.2, 128.2, 127.8, 126.3, 125.0, 50.0, 48.7, 34.2, 30.2, 29.9, 21.6; **HRMS (ESI$^+$)** *m/z*: $[M + H]^+$ calcd for $C_{38}H_{43}ClNO_3S$ 628.2647; found 628.2640.

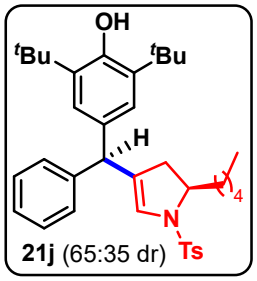
2,6-Di-*tert*-butyl-4-((2-(4-nitrophenyl)-1-tosyl-4,5-dihydro-1H-pyrrol-3-yl)(phenyl)methyl) phenol (21i):



The product **21i** was obtained in 66% yield (71 mg, White solid); **mp** = 238-239 °C; R_f = 0.40 (petroleum ether:ethyl acetate = 4:1); **^{1}H NMR (400 MHz, $CDCl_3$) δ** = δ 8.25 (d, *J* = 8.8 Hz, 2H), 7.60 (d, *J* = 8.8 Hz, 2H), 7.52 (d, *J* = 8.2 Hz, 2H), 7.25 – 7.19 (m, 5H), 6.79 (d, *J* = 7.6 Hz, 2H), 6.60 (s, 2H), 5.09 (s, 1H), 4.87 (s, 1H), 4.02 (m, 1H), 3.88 (m, 1H), 2.46 (s, 3H), 2.19 – 2.07 (m, 2H), 1.30 (s, 18H); **^{13}C{^{1}H} NMR (100 MHz,$CDCl_3$) δ** =152.4, 147.5, 144.0, 141.5, 139.6, 136.3, 135.8, 135.2, 134.0, 131.8, 130.1, 130.0, 129.7, 128.3, 127.8, 126.6, 125.0, 123.3, 50.1, 48.9, 34.2, 30.6, 30.2, 21.7; **HRMS (ESI$^+$)** *m/z*: $[M + H]^+$ calcd for $C_{38}H_{43}N_2O_5S$ 639.2887; found 639.2872.

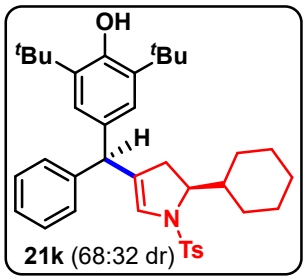
2,6-Di-*tert*-butyl-4-((5-pentyl-1-tosyl-4,5-dihydro-1H-pyrrol-3-yl)(phenyl)methyl)phenol (21j):

The product **21j** was obtained in 73% yield (73 mg, White solid); 65:35 dr; **mp** = 164-165 °C; R_f = 0.40 (petroleum ether:ethyl acetate = 4:1); **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 7.60 (t, *J* = 7.3 Hz, 3.30H), 7.35 (d, *J* = 8.0 Hz, 1.77H), 7.27 (dd, *J* = 14.3, 6.4 Hz, 4.86H), 7.24 – 7.14 (m, 3.10H), 7.09 (d, *J* = 7.3 Hz, 2.14H), 6.87 (s, 2.27H), 6.77 (s, 2.01H), 5.76 (s, 1H), 5.64 (s, 0.54H), 5.09 (s, 0.56H), 5.08 (s, 0.95H), 4.53 (s, 1.03H), 4.44 (s, 0.59H), 3.81 – 3.63 (m,



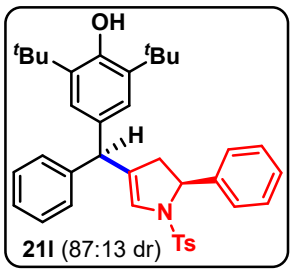
1.72H), 2.50 (s, 1.61H), 2.45 (s, 3.15H), 2.35 – 2.21 (m, 1.78H), 2.02 – 1.90 (m, 1.80H), 1.90 – 1.78 (m, 1.80H), 1.64-1.59 (m, 2.40H), 1.39 (s, 10.47H), 1.35 (s, 18.06H), 0.87 (t, J = 6.6 Hz, 5.08H); **^{13}C{^{1}H} NMR (100 MHz,CDCl$_3$) δ** = 152.4, 152.3, 143.5, 143.4, 142.1, 141.8, 135.8, 135.6, 133.7, 133.6, 132.2, 132.0, 130.9, 130.1, 129.5, 129.5, 128.6, 128.4, 128.4, 128.2, 127.9, 127.8, 127.6, 126.5, 126.4, 125.0, 124.9, 61.1, 61.1, 51.3, 51.0, 38.3, 38.0, 36.7, 36.4, 34.4, 34.3, 31.7, 31.6, 30.4, 30.3, 29.4, 24.5, 24.4, 22.6, 21.7, 21.6, 14.1, 14.0; **HRMS (ESI$^+$)** *m/z*: [M + H]$^+$ calcd for $C_{37}H_{50}NO_3S$ 588.3506; found 588.3504.

2,6-Di-*tert*-butyl-4-((5-cyclohexyl-1-tosyl-4,5-dihydro-1H-pyrrol-3-yl)(phenyl)methyl) phenol (21k):



The product **21k** was obtained in 42% yield (42 mg, White solid); 68:32 dr; **mp** = 178-179 °C; ***R$_f$*** = 0.40 (petroleum ether:ethyl acetate = 4:1); **^{1}H NMR (400 MHz, CDCl$_3$) δ** = 7.61 (d, J = 8.1 Hz, 3.02H), 7.36 (d, J = 8.1 Hz, 1H), 7.28 (dd, J = 11.7, 7.2 Hz, 4.69H), 7.20 (dd, J = 15.4, 6.7 Hz, 2.50H), 7.06 (d, J = 7.2 Hz, 2.20H), 6.87 (s, 1.90H), 6.78 (s, 2.13H), 5.81 (s, 1H), 5.62 (s, 0.48H), 5.10 (s, 0.48H), 5.08 (s, 1H), 4.56 (s, 1.06H), 4.41 (s, 0.49H), 3.68-3.59 (m, 1.62H), 2.52 (s, 1.38H), 2.46 (s, 3.02H), 2.16 – 1.96 (m, 3.27H), 1.86 – 1.61 (m, 9.04H), 1.40 (s, 8.01H), 1.35 (s, 18.04H), 1.30-1.19 (m, 4.42H), 1.10-0.95 (m, 3.15H); **^{13}C{^{1}H} NMR (100 MHz,CDCl$_3$) δ** = 152.4, 152.2, 143.5, 143.4, 142.0, 141.6, 135.7, 135.5, 133.6, 133.6, 133.3, 131.9, 131.6, 131.3, 129.5, 129.4, 128.6, 128.3, 128.2, 128.1, 127.9, 127.8, 127.6, 126.5, 126.4, 125.0, 124.9, 65.3, 65.3, 51.4, 51.0, 42.5, 42.2, 34.7, 34.3, 34.2, 33.6, 30.3, 28.9, 28.7, 26.7, 26.5, 26.1, 25.8, 21.6, 21.6; **HRMS (ESI$^+$)** *m/z*: [M + H]$^+$ calcd for $C_{38}H_{50}NO_3S$ 600.3506; found 600.3503.

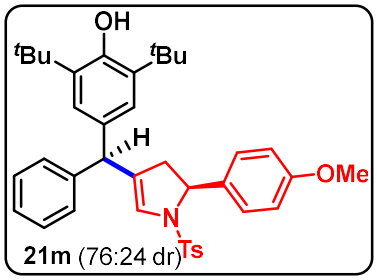
2,6-Di-*tert*-butyl-4-(phenyl(5-phenyl-1-tosyl-4,5-dihydro-1H-pyrrol-3-yl)methyl)phenol (21l):



The product **21l** was obtained in 62% yield (63 mg, White solid); 87:13 dr; **mp** = 209-210 °C; ***R$_f$*** = 0.40 (petroleum ether:ethyl acetate = 4:1); **^{1}H NMR (400 MHz, CDCl$_3$) δ** = 7.62 (t, J = 8.6 Hz, 2.33H), 7.37 – 7.28 (m, 7.19H), 7.28 – 7.22 (m, 3.92H), 7.20 (t, J = 7.3 Hz, 1.38H), 7.09 (d, J = 7.2 Hz, 2.06H), 6.95 (d, J = 6.8 Hz, 0.30H), 6.87 (s, 0.30H), 6.79 (s, 2.08H), 5.99 (d, J = 1.3 Hz, 0.99H), 5.88 (d, J = 1.3 Hz, 0.12H), 5.28 (s,

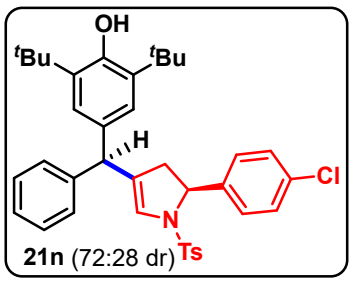
0.18H), 5.07 (s, 1.16H), 4.81 (dd, *J* = 10.8, 5.6 Hz, 0.13H), 4.74 (dd, *J* = 10.8, 6.2 Hz, 1.02H), 4.58 (s, 1.02H), 4.47 (s, 0.13H), 2.75 (dd, *J* = 16.3, 10.5 Hz, 1.10H), 2.51 (s, 0.45H), 2.46 (s, 3.06H), 2.30 (dd, *J* = 16.3, 6.2 Hz, 1.18H), 1.36 (s, 3.11H), 1.33 (s, 18H); **$^{13}C\{^1H\}$ NMR (100 MHz,$CDCl_3$) δ** = 152.3, 143.6, 142.8, 141.7, 135.6, 133.6, 131.7, 129.6, 129.4, 128.6, 128.5, 128.5, 128.3, 128.2, 128.0, 127.8, 127.7, 127.4, 126.5, 126.1, 126.1, 124.9, 63.7, 50.9, 42.6, 34.2, 30.3, 21.6; **HRMS (ESI$^+$)** *m/z*: $[M + H]^+$ calcd for $C_{38}H_{44}NO_3S$ 594.3036; found 594.3033.

2,6-Di-*tert*-butyl-4-((5-(4-methoxyphenyl)-1-tosyl-4,5-dihydro-1H-pyrrol-3-yl)(phenyl) methyl)phenol (21m):



The product **21m** was obtained in 68% yield (72 mg, White solid); 76:24 dr; **mp** = 174-175 °C; R_f = 0.40 (petroleum ether:ethyl acetate = 4:1); **^1H NMR (500 MHz, $CDCl_3$) δ** = 7.60 (t, *J* = 8.2 Hz, 2.67H), 7.35 (d, *J* = 7.6 Hz, 0.75H), 7.32 – 7.16 (m, 9.23H), 7.09 (d, *J* = 7.4 Hz, 2.15H), 6.95 (d, *J* = 7.1 Hz, 0.75H), 6.87 (s, 0.71H), 6.83 (d, *J* = 7.6 Hz, 2.70H), 6.79 (s, 2.08H), 5.96 (s, 0.96H), 5.86 (s, 0.30H), 5.07 (s, 1.36H), 4.75 (dd, *J* = 10.3, 5.6 Hz, 0.31H), 4.68 (dd, *J* = 9.5, 7.1 Hz, 1.01H), 4.58 (s, 1.01H), 4.47 (s, 0.32H), 3.78 (s, 4.03H), 2.70 (dt, *J* = 20.5, 10.4 Hz, 1.32H), 2.50 (s, 0.97H), 2.45 (s, 3H), 2.29 (dd, *J* = 16.2, 5.4 Hz, 1.41H), 1.36 (s, 6.58H), 1.33 (s, 18.03H); **$^{13}C\{^1H\}$ NMR (125 MHz,$CDCl_3$) δ** = 158.9, 152.4, 152.3 143.6, 143.6, 142.1, 141.7, 135.7, 135.6, 135.1, 134.9, 133.7, 133.6, 131.8, 131.3, 130.6, 129.6, 129.5, 129.3, 128.6, 128.3, 128.2, 128.1, 127.9, 127.8, 127.6, 127.4, 127.3, 126.5, 125.0, 124.9, 113.9, 113.9, 63.4, 63.1, 52.2, 51.1, 50.9, 42.8, 42.5, 34.3, 34.2, 30.3, 21.6; **HRMS (ESI$^+$)** *m/z*: $[M + H]^+$ calcd for $C_{39}H_{46}NO_4S$ 624.3142; found 624.3143.

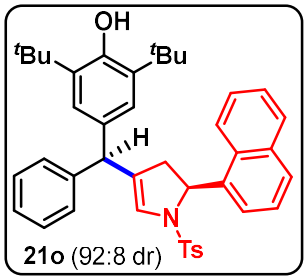
2,6-Di-*tert*-butyl-4-((5-(4-chlorophenyl)-1-tosyl-4,5-dihydro-1H-pyrrol-3-yl)(phenyl) methyl)phenol (21n):



The product **21n** was obtained in 80% yield (85 mg, White solid); 72:28 dr; **mp** = 204-205 °C; R_f = 0.40 (petroleum ether:ethyl acetate = 4:1); **^1H NMR (400 MHz, $CDCl_3$) δ** = 7.61 (t, *J* = 7.6 Hz, 2.75H), 7.38 (d, *J* = 8.0 Hz, 0.84H), 7.32 (d, *J* = 8.1 Hz, 2.35H), 7.30 – 7.17 (m, 9.85H), 7.09 (d, *J* = 7.1 Hz, 2.11H), 6.94 (d, *J* = 6.5 Hz, 0.80H), 6.85 (s, 0.76H), 6.78 (s, 2.01H), 5.98 (s, 0.98H), 5.86 (s, 0.37H), 5.10 (s, 1.42H), 4.78 (dd, *J* = 10.8, 5.7 Hz, 0.41H), 4.71 (dd, *J* = 10.8, 6.3 Hz,

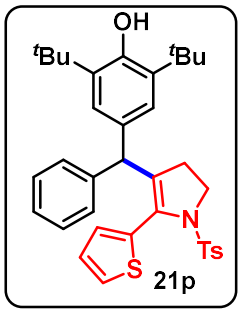
1.03H), 4.58 (s, 1.02H), 4.47 (s, 0.39H), 2.80 – 2.68 (m, 1.45H), 2.52 (s, 1.18H), 2.48 (s, 3H), 2.26 (dd, *J* = 16.2, 6.0 Hz, 1.38H), 1.36 (s, 6.43H), 1.34 (s, 18.07H); **$^{13}C\{^1H\}$ NMR (100 MHz,$CDCl_3$) δ** = 152.4, 152.3, 143.9, 143.8, 141.9, 141.5, 141.4, 141.3, 135.7, 135.6, 133.3, 133.2, 133.1, 131.5, 131.1, 130.7, 129.7, 129.6, 129.4, 128.7, 128.5, 128.4, 128.3, 128.0, 127.8, 127.7, 127.6, 127.6, 127.5, 126.6, 126.6, 124.9, 124.8, 63.0, 62.8, 51.0, 50.8, 42.6, 42.4, 34.2, 30.2, 21.6; **HRMS (ESI^+)** *m/z*: $[M + H]^+$ calcd for $C_{38}H_{43}ClNO_3S$ 628.2647; found 628.2651.

2,6-Di-*tert*-butyl-4-((5-(naphthalen-1-yl)-1-tosyl-4,5-dihydro-1H-pyrrol-3-yl)(phenyl) methyl)phenol (21o):



The product **21o** was obtained in 59% yield (65 mg, White solid); 92:8 dr; **mp** = 233-234 °C; R_f = 0.40 (petroleum ether:ethyl acetate = 4:1); **^1H NMR (400 MHz, $CDCl_3$) δ** = 7.89 – 7.83 (m, 1.25H), 7.78 (d, *J* = 7.8 Hz, 2.25H), 7.75 – 7.61 (m, 3.58H), 7.53 – 7.41 (m, 3.79H), 7.31 (d, *J* = 8.0 Hz, 2.39H), 7.28 – 7.15 (m, 4.07H), 7.08 (d, *J* = 7.1 Hz, 2.02H), 6.83 (s, 0.28H), 6.78 (s, 2.01H), 6.14 (s, 0.97H), 5.42 (dd, *J* = 10.9, 6.1 Hz, 1H), 5.07 (s, 0.93H), 5.05 (s, 0.08H), 4.59 (s, 1.02H), 2.96 (dd, *J* = 15.6, 11.5 Hz, 1.10H), 2.55 (s, 0.28H), 2.48 (s, 3.01H), 2.31 (dd, *J* = 16.3, 5.9 Hz, 1.20H), 2.05 (dd, *J* = 8.5, 3.4 Hz, 0.19H), 1.32 (s, 18.05H), 1.29 (s, 1.64H); **$^{13}C\{^1H\}$ NMR (100 MHz,$CDCl_3$) δ** = 152.3, 143.7, 141.7, 137.8, 135.6, 134.1, 133.5, 131.7, 129.8, 129.7, 129.7, 129.1, 128.6, 128.4, 128.2, 128.0, 127.7, 126.5, 125.9, 125.6, 125.3, 124.9, 123.9, 122.9, 61.5, 50.8, 42.3, 34.2, 30.3, 29.4, 21.6; **HRMS (ESI^+)** *m/z*: $[M + H]^+$ calcd for $C_{42}H_{46}NO_3S$ 644.3193; found 644.3198.

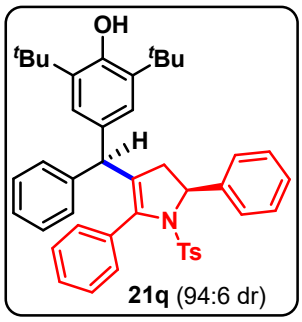
2,6-Di-*tert*-butyl-4-(phenyl(2-(thiophen-2-yl)-1-tosyl-4,5-dihydro-1H-pyrrol-3-yl)methyl) phenol (21p):



The product **21p** was obtained in 42% yield (43 mg, Brown solid); **mp** = 156-157 °C; R_f = 0.40 (petroleum ether:ethyl acetate = 4:1); **^1H NMR (500 MHz, $CDCl_3$) δ** = 7.58 (d, *J* = 8.1 Hz, 2H), 7.42 (d, *J* = 5.0 Hz, 1H), 7.22 (dd, *J* = 5.0, 1.4 Hz, 3H), 7.16 (d, *J* = 3.4 Hz, 1H), 7.13 (d, *J* = 8.0 Hz, 2H), 7.05 (dd, *J* = 4.7, 3.9 Hz, 1H), 6.93 – 6.89 (m, 2H), 6.71 (s, 2H), 5.14 (s, 1H), 5.08 (s, 1H), 4.01 (ddd, *J* = 13.7, 9.1, 5.0 Hz, 1H), 3.86 (dt, *J* = 12.4, 9.5 Hz, 1H), 2.39 (s, 3H), 2.05 – 1.88 (m, 2H), 1.33 (s, 18H); **$^{13}C\{^1H\}$ NMR (125 MHz,$CDCl_3$) δ** = 152.2, 143.5, 141.7, 135.6, 134.3, 134.2, 134.0, 132.3, 131.9, 129.4, 128.6, 128.5, 128.1,

127.8, 126.9, 126.5, 126.3, 125.1, 50.2, 48.8, 34.3, 30.3, 29.9, 21.6; **HRMS (ESI$^+$)** *m/z*: [M + H]$^+$ calcd for $C_{36}H_{42}NO_3S_2$ 600.2601; found 600.2585.

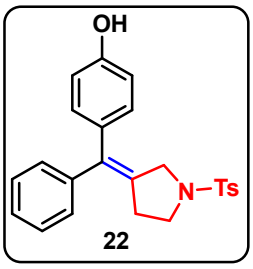
2,6-Di-*tert*-butyl-4-((2,5-diphenyl-1-tosyl-4,5-dihydro-1H-pyrrol-3-yl)(phenyl)methyl) phenol (21q):



21q (94:6 dr)

The product **21q** was obtained in 46% yield (52 mg, Brown solid); 94:6 dr; **mp** = 219-220 °C; R_f = 0.40 (petroleum ether:ethyl acetate = 4:1); **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 7.65 (d, *J* = 8.2 Hz, 2H), 7.49 (dd, *J* = 10.1, 5.0 Hz, 0.34H), 7.43 – 7.35 (m, 5.22H), 7.35 – 7.26 (m, 3.07H), 7.26 – 7.17 (m, 6.06H), 7.14 – 7.09 (m, 2.01H), 6.98 (dd, *J* = 15.1, 7.5 Hz, 0.25H), 6.86 (dd, *J* = 6.5, 5.1 Hz, 2.10H), 6.62 (d, *J* = 6.9 Hz, 0.15H), 6.43 (s, 2H), 5.24 (d, *J* = 8.3 Hz, 1.06H), 5.14 (s, 0.07H), 5.06 (s, 1.02H), 5.00 (s, 0.99H), 4.93 (s, 0.07H), 2.62 (dd, *J* = 16.6, 9.4 Hz, 1.09H), 2.52 (s, 3H), 2.36 (s, 0.21H), 2.18 (dd, *J* = 16.7, 1.1 Hz, 1.03H), 1.39 (s, 1.15H), 1.16 (s, 18.06H); **^{13}C{^{1}H} NMR (100 MHz,$CDCl_3$) δ** = 152.1, 143.5, 142.5, 141.3, 137.2, 135.5, 134.9, 133.0, 132.2, 130.9, 129.6, 128.9, 128.6, 128.5, 128.5, 128.1, 128.1, 127.8, 127.4, 126.3, 126.0, 125.1, 63.1, 48.6, 36.5, 34.1, 30.3, 30.1, 21.7; **HRMS (ESI$^+$)** *m/z*: [M + H]$^+$ calcd for $C_{44}H_{48}NO_3S$ 670.3349; found 670.3356.

4-(Phenyl(1-tosyl-4,5-dihydro-1H-pyrrol-3-yl)methyl)phenol (22):

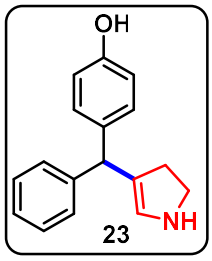


22

The product **22** was obtained in 69% yield (27 mg, Brown solid); **mp** = 164-165 °C; R_f = 0.40 (petroleum ether:ethyl acetate = 4:1); **^{1}H NMR (500 MHz, $CDCl_3$) δ** = 7.61 (d, *J* = 8.2 Hz, 2H), 7.46 (t, *J* = 7.4 Hz, 2H), 7.40 (dd, *J* = 8.6, 7.5 Hz, 2H), 7.33 – 7.28 (m, 2H), 7.23 (d, *J* = 7.4 Hz, 1H), 7.21 – 7.15 (m, 4H), 4.27 (t, *J* = 5.9 Hz, 1H), 3.33 (s, 2H), 3.15 (dd, *J* = 13.1, 6.8 Hz, 2H), 2.66 (t, *J* = 6.9 Hz, 2H), 2.39 (s, 3H); **^{13}C{^{1}H} NMR (125 MHz,$CDCl_3$) δ** = 145.7, 143.4, 142.3, 141.9, 139.4, 136.6, 134.7, 129.6, 129.0, 128.7, 127.5, 127.0, 126.4, 124.7, 123.6, 119.9, 42.6, 40.2, 28.8, 21.5; **HRMS (ESI$^+$)** *m/z*: [M + H]$^+$ calcd for $C_{24}H_{24}NO_3S$ 406.1471; found 406.1464.

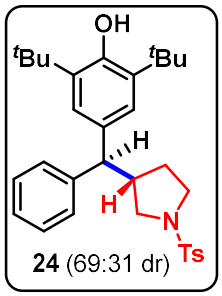
2,6-Di-*tert*-butyl-4-((4,5-dihydro-1H-pyrrol-3-yl)(phenyl)methyl)phenol (23):

The product **23** was obtained in 68% yield (48 mg, White solid); **mp** = 85-86 °C; R_f = 0.40 (petroleum ether:ethyl acetate = 4:1); **^{1}H NMR (500 MHz, $CDCl_3$) δ** = 7.35 (s, 1H), 7.28 (d, *J* = 19.8 Hz, 4H), 7.20 (d, *J* = 3.2 Hz, 1H), 7.07 (d, *J* = 13.7 Hz, 2H), 5.15 (d, *J* = 10.7 Hz, 1H), 3.92 (s, 1H), 3.75 (dd, *J* = 24.8, 9.3 Hz, 2H), 3.65 (d, *J* = 8.2 Hz, 1H), 2.07 – 1.93 (m, 1H), 1.42



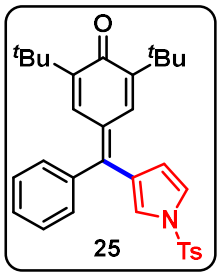
(s, 18H); **$^{13}C\{^1H\}$ NMR (125 MHz,$CDCl_3$) δ** = 170.1, 169.8, 152.3, 152.2, 144.0, 143.8, 136.0, 135.7, 133.8, 133.7, 128.6, 128.4, 127.9, 126.4, 126.2, 124.3, 124.3, 61.0, 60.9, 54.9, 54.8, 34.3, 30.3, 27.8, 27.7; **HRMS (ESI^+)** *m/z*: $[M + H]^+$ calcd for $C_{25}H_{34}NO$ 364.2635; found 364.2635.

2,6-Di-*tert*-butyl-4-(phenyl(1-tosylpyrrolidin-3-yl)methyl)phenol (24):



The product **24** was obtained in 96% yield (48 mg, White solid); 69:31 dr; **mp** = 157-158 °C; R_f = 0.40 (petroleum ether:ethyl acetate = 4:1); **^1H NMR (400 MHz, $CDCl_3$) δ** = 7.71 (t, *J* = 7.1 Hz, 3.06H), 7.36 (d, *J* = 7.9 Hz, 3.35H), 7.33 – 7.23 (m, 3.83H), 7.19 (dd, *J* = 14.8, 7.4 Hz, 4.52H), 6.99 (s, 1H), 6.96 (s, 2.13H), 5.09 (s, 0.45H), 5.05 (s, 1H), 3.50 – 3.37 (m, 3.38H), 3.32-3.16 (m, 3.29H), 2.91-2.29 (m, 3.24H), 2.48 (s, 4.88H), 1.82 – 1.70 (m, 1.63H), 1.44 (s, 9.28H), 1.40 (s, 18H); **$^{13}C\{^1H\}$ NMR (100 MHz,$CDCl_3$) δ** = 152.4, 152.2, 144.0, 143.9, 143.3, 143.3, 135.8, 135.7, 133.8, 133.8, 133.7, 129.6, 129.6, 128.6, 128.5, 127.6, 127.5, 127.5, 126.4, 126.3, 123.9, 123.8, 55.9, 55.8, 52.9, 52.7, 47.9, 47.7, 43.8, 43.6, 34.3, 34.2, 31.0, 30.9, 30.3, 30.2, 21.5.; **HRMS (ESI^+)** *m/z*: $[M + H]^+$ calcd for $C_{32}H_{42}NO_3S$ 520.2880; found 520.2890.

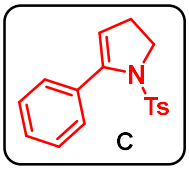
2,6-Di-*tert*-butyl-4-(phenyl(1-tosyl-1H-pyrrol-3-yl)methylene)cyclohexa-2,5-dien-1-one (25):



The product **25** was obtained in 62% yield (31 mg, Yellow solid); **mp** = 181-182 °C; R_f = 0.40 (petroleum ether:ethyl acetate = 4:1); **^1H NMR (400 MHz, $CDCl_3$) δ** = 7.79 (d, *J* = 8.3 Hz, 2H), 7.46 – 7.37 (m, 4H), 7.34 (d, *J* = 8.3 Hz, 2H), 7.21 (m, 3H), 7.16 (t, *J* = 1.8 Hz, 1H), 6.99 (d, *J* = 2.6 Hz, 1H), 6.23 (dd, *J* = 3.0, 1.5 Hz, 1H), 2.45 (s, 3H), 1.27 (s, 9H), 1.18 (s, 9H); **$^{13}C\{^1H\}$ NMR (100 MHz,$CDCl_3$) δ** = 186.1, 148.2, 147.4, 146.9, 145.7, 140.0, 135.5, 131.8, 131.6, 130.9, 130.2, 129.3, 129.3, 128.9, 127.9, 127.1, 123.6, 121.2, 116.4, 35.3, 35.2, 29.6, 29.4, 21.7; **HRMS (ESI^+)** *m/z*: $[M + H]^+$ calcd for $C_{32}H_{36}NO_3S$ 514.2410; found 514.2427.

5-phenyl-1-tosyl-2,3-dihydro-1H-pyrrole (C):

The product **C** was obtained in 58% yield (29 mg, Yellow solid); **mp** = 121-122 °C; R_f = 0.40 (petroleum ether:ethyl acetate = 3:2); **^1H NMR (500 MHz, $CDCl_3$) δ** = 7.72 (d, *J* = 7.3 Hz, 2H), 7.52 (d, *J* = 8.2 Hz, 2H), 7.39 (t, *J* = 7.4 Hz, 1H), 7.31 (t, *J* = 7.6 Hz, 2H), 7.17 (d, *J* = 8.0



Hz, 2H), 4.91 (dt, J = 10, 1.7 Hz, 1H), 4.10 (m, 1H), 3.54 (m, 1H), 2.74 (m, 1H), 2.48 – 2.40 (m, 1H), 2.38 (s, 3H); **$^{13}C\{^1H\}$ NMR (125 MHz,$CDCl_3$) δ** = 166.5, 145.2, 134.3, 132.7, 130.7, 129.5, 128.9, 128.6, 128.2, 72.2, 59.6, 27.7, 21.5; **HRMS (ESI$^+$)** *m/z*: $[M + H]^+$ calcd for $C_{17}H_{18}NO_2S$ 300.1053; found 300.1052.

1.2.4.6 X-Ray Crystallography Data of Compounds 20e, 20w, 21k and 24:

The single crystal suitable for single-crystal X-ray diffraction analysis were selected using Leica polarizing microscope (S8 APO). X-ray intensity data measurements of compounds **20e**, **20w, 21k and 24** were carried out on a Bruker D8 VENTURE Kappa Duo PHOTON II CPAD diffractometer equipped with Incoatech multilayer mirrors optics. The intensity measurements for **20e** was carried out at 100(2) K temperature with Mo micro-focus sealed tube diffraction source (MoK_α= 0.71073 Å) and for compounds **20w, 21k & 24** the intensity measurements were carried out at 300(2) K temperature for **20w** and 100(2) K temperature for **21k & 24** with Cu micro-focus sealed tube diffraction source (CuK_α= 1.54178 Å). The X-ray generator was operated at 50 kV and 1.4 mA (for **20e**) and 50 kV and 1.1 mA (for **20w, 21k & 24**). A preliminary set of cell constants and an orientation matrix for the compound **20e** was calculated from three sets of 36 frames, and for the compounds **20w, 21k & 24** were calculated from two matrix sets of 40 frames (each matrix run consists of 20 frames). Data were collected with ωa scan width of 0.5° at different settings of φ and 2θ with a frame time of 15 secs (for **20e**) and 20 secs (for **20w, 21k & 24**), keeping the sample-to-detector distance fixed at 5.00 cm. The X-ray data collection was monitored by the APEX3 program (Bruker, 2016).[17] All the data were corrected for Lorentzian, polarization and absorption effects using SAINT and SADABS programs (Bruker, 2016)[17]. Using the APEX3 (Bruker) program suite, the structure was solved with the ShelXS-97 (Sheldrick, 2008)[18] structure solution program, using direct methods. The model was refined with a version of ShelXL-2013 (Sheldrick, 2015)[19] for the compound **20e** & **20w** and ShelXL-2018/3 (Sheldrick, 2015)[19] for the compounds **21k and 24** for using Least Squares minimization. All the hydrogen atoms were placed in a geometrically idealized position and constrained to ride on their parent atoms. An *ORTEP* III[20] view of the compound was drawn with 50% probability displacement ellipsoids (for **20e, 21k and 24**) and 30% probability displacement ellipsoids (for **20w**), and H atoms are shown as small spheres of arbitrary radii. PLATON/SQUEEZE[21] was used to correct the diffraction data for the contribution from disor-

dered lattice solvent (ethanol) molecules. The solvent-accessible void volume per unit cell was 409 $Å^3$ (13%), and Electron Count/unit Cell was 104 e/$Å^3$, estimated by PLATON. This electron count corresponds to four disordered ethanol molecules present in the unit cell. However, they have been included in SFAC and UNIT instructions to get the correct molecular formula of the asymmetric unit, formula weight, crystal density and *F*(000).

Crystal data of 20e: $C_{33}H_{41}NO_4S$, CH_3CH_2OH, M = 593.79, colorless block, 0.22 x 0.18 x 0.08 mm^3, monoclinic, space group $P2_1/c$, a = 6.0532(3) Å, b = 21.7105(13) Å, c = 24.7967(14) Å, β = 92.467(2)°, V = 3255.7(3) $Å^3$, Z = 4, T = 100(2) K, $2\theta_{max}$= 52°, D_{calc} (g cm^{-3}) = 1.211, $F(000)$ = 1280, μ (mm^{-1}) = 0.141, 49041 reflections collected, 6390 unique reflections (R_{int} = 0.0907, R_{sig} = 0.0569), 5057 observed ($I > 2\sigma(I)$) reflections, multi-scan absorption correction, T_{min} = 0.970, T_{max} = 0.989, 361 refined parameters, Good of Fit = S = 1.121, $R1$ = 0.0726, $wR2$ = 0.1294 (all data R = 0.0987, $wR2$ = 0.1391), maximum and minimum residual electron densities; $\Delta\rho_{max}$ = 0.381, $\Delta\rho_{min}$= -0.408 (e $Å^{-3}$), CCDC No. 1969572.

Crystal data of 20w: $C_{36}H_{41}NO_3S$, M = 567.76, colorless block, 0.301 x 0. 070 x 0.050 mm^3, monoclinic, non centrosymmetric space group *Pc*, a = 11.225(4) Å, b = 9.871(3) Å, c = 14.581(4) Å, β = 102.443(13)°, V = 1577.6(8) $Å^3$, Z = 2, T = 300(2) K, $2\theta_{max}$= 150°, D_{calc} (g cm^{-3}) = 1.195, $F(000)$ = 608, μ (mm^{-1}) = 1.181, 7939 reflections collected, 5323 unique reflections (R_{int} = 0.0293, R_{sig} = 0.0574), 5059 observed ($I > 2\sigma(I)$) reflections, multi-scan absorption correction, T_{min} = 0.718, T_{max} = 0.943, 378 refined parameters, Good of Fit = S = 1.039, $R1$ = 0.0365, $wR2$ = 0.0949 (all data R = 0.0385, $wR2$ = 0.0972), maximum and minimum residual electron densities; $\Delta\rho_{max}$ = 0.150, $\Delta\rho_{min}$= -0.156 (e $Å^{-3}$), CCDC No. 2013163.

Crystal data of 21k: A single crystal of compound **21k**, molecular formula $C_{38}H_{49}NO_3S$, approximate dimensions 0.011 mm x 0.056 mm x 0.067 mm, was used for the X-ray crystallographic analysis. The integration of the data using a monoclinic unit cell yielded a total of 97010 reflections to a maximum θ angle of 68.46° (0.83 Å resolution), of which 5821 were independent (average redundancy 16.666, completeness = 93.9%, R_{int} = 23.56%, R_{sig} = 8.91%) and 3252 (55.87%) were greater than $2\sigma(F^2)$. The final cell constants of a = 6.1610(2) Å, b = 22.1547(6) Å, c =24.6418(7) Å, β = 92.253(2)°, volume = 3360.89(17) $Å^3$, are based upon the refinement of the XYZ-centroids of reflections above 20

σ(I). The calculated minimum and maximum transmission coefficients (based on crystal size) are 0.9280 and 0.9880. The structure was solved and refined using the Bruker SHELXTL Software Package, using the space group $P2_1/c$, with Z = 4 for the formula unit, $C_{38}H_{49}NO_3S$. The final anisotropic full-matrix least-squares refinement on F^2 with 400 variables converged at R1 = 6.01%, for the observed data and wR2 = 18.42% for all data. The goodness-of-fit was 0.989. The largest peak in the final difference electron density synthesis was 0.235 $e^-/Å^3$, and the largest hole was -0.314 $e^-/Å^3$ with an RMS deviation of 0.062 $e^-/Å^3$. Based on the final model, the calculated density was1.185 g/cm^3 and F(000), 1296 e^-, CCDC No. 2035515.

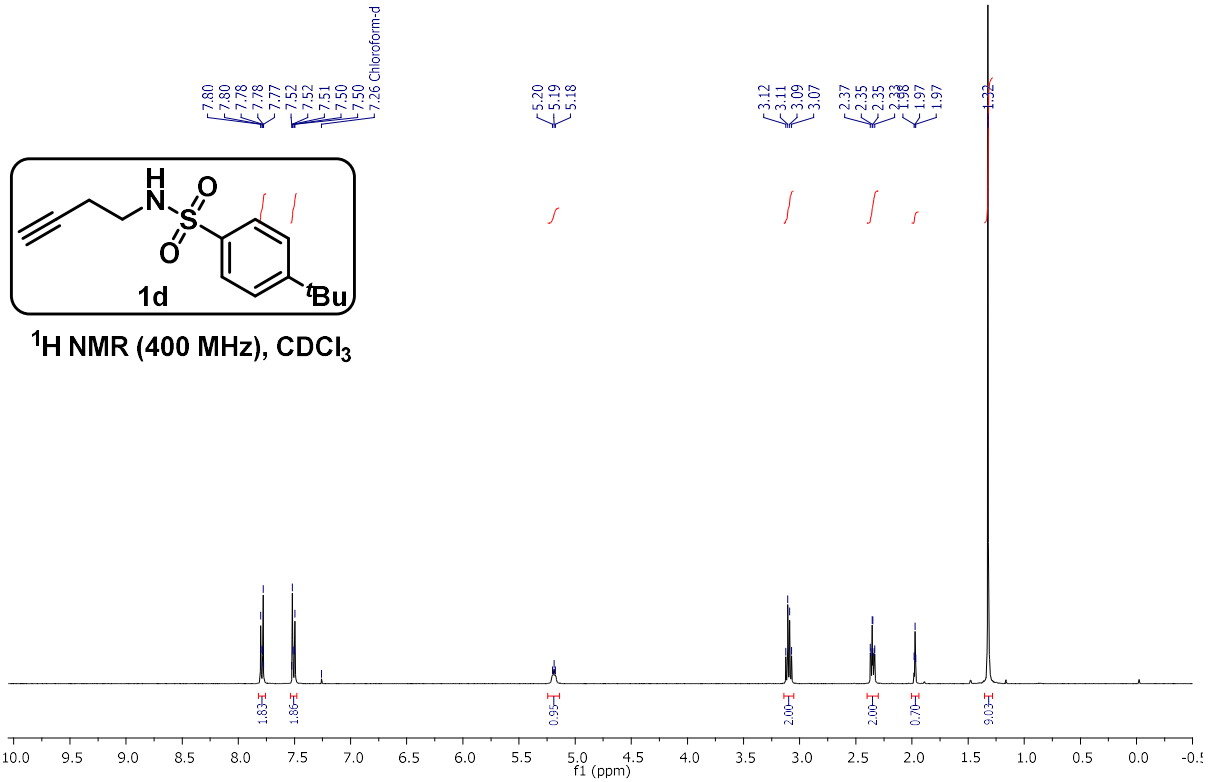
Crystal data of 24: A single crystal of compound **24**, molecular formula $C_{32}H_{41}NO_3S$, approximate dimensions 0.013 mm x 0.059 mm x 0.068 mm, was used for the X-ray crystallographic analysis. The integration of the data using a triclinic unit cell yielded a total of 133642 reflections to a maximum θ angle of 74.52° (0.80 Å resolution), of which 11677 were independent (average redundancy 11.445, completeness = 99.5%, R_{int} = 10.34%, R_{sig} = 4.25%) and 7826 (67.02%) were greater than $2\sigma(F^2)$. The final cell constants of a = 9.6543(2) Å, b = 15.9905(4) Å, c =19.2656(5) Å, α = 76.296(2)°, β = 85.046(2)°, γ = 85.567(2)°, volume = 2873.74(12) $Å^3$, are based upon the refinement of the XYZ-centroids of reflections above 20 σ(I). The calculated minimum and maximum transmission coefficients (based on crystal size) are 0.9200 and 0.9840. The structure was solved and refined using the Bruker SHELXTL Software Package, using the space group *P*-1, with Z = 4 for the formula unit, $C_{32}H_{41}NO_3S$. The final anisotropic full-matrix least-squares refinement on F^2 with 635 variables converged at R1 = 7.47%, for the observed data and wR2 = 23.16% for all data. The goodness-of-fit was 1.028. The largest peak in the final difference electron density synthesis was 0.519 $e^-/Å^3$, and the largest hole was -0.796 $e^-/Å^3$ with an RMS deviation of 0.071 $e^-/Å^3$. Based on the final model, the calculated density was 1.201g/cm^3 and F(000), 1120 e^-, CCDC No. 2035514.

Crystal Data Table:

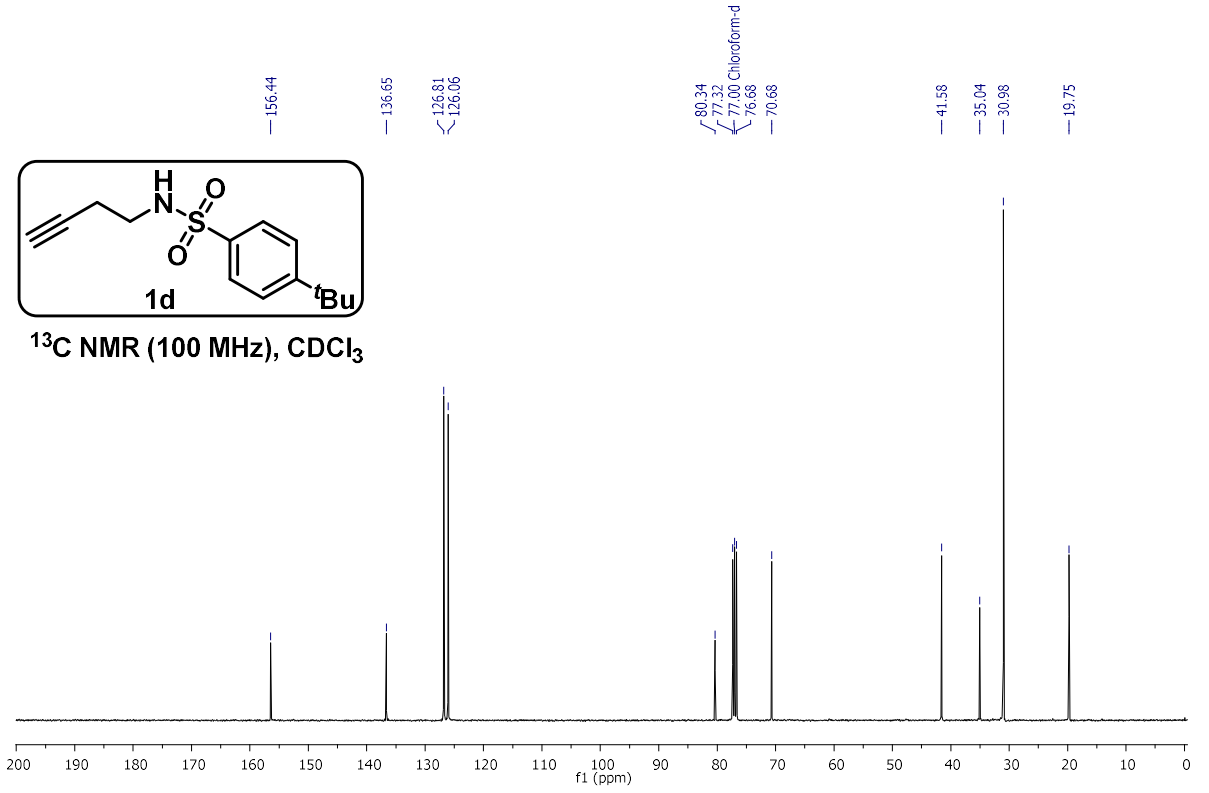
Crystal data	**20e**	**20w**	**21k**	**24**
Mol. Formula	$C_{33}H_{41}NO_4S$	$C_{36}H_{41}NO_3S$	$C_{38}H_{49}NO_3S$	$C_{32}H_{41}NO_3S$
Formula Weight	593.79	567.76	599.84	519.72
Solvent of recrystallization	Ethanol (slow evapora-tion method)	Ethanol (slow evapora-tion method)	Ethanol (slow evapora-tion method)	Ethanol (slow evapora-tion method)
Crystal size (mm)	0.220 × 0.180 × 0.080	0.301 × 0.070 × 0.050	0.067 × 0.056 × 0.011	0.068 × 0.059 × 0.013
Wavelength (Å)	0.71073	1.54178	1.54178	1.54178
Temp. (K)	100(2)	300(2)	100(2)	100(2)
Crystal System	Monoclinic	Monoclinic	Monoclinic	Triclinic
Space group	$P2_1/c$	Pc	$P2_1/c$	P-1
a/Å	6.0532(3)	11.225(4)	6.1610(2)	9.6543(2)
b/Å	21.7105(13)	9.871(3)	22.1547(6)	15.9905(4)
c/Å	24.7967(14)	14.581(4)	24.6418(7)	19.2656(5)
α/°	90	90	90	76.296(2)
β/°	92.467(2)	102.443(13)	92.253(2)	85.046(2)
γ/°	90	90	90	85.567(2)
V/Å^3	3255.7(3) Å^3	1577.6(8)	3360.88(17)	2873.74(12)
Z, D_{calc}/g cm^{-1}	4, 1.211	2, 1.195	4, 1.185	4,1.201
μ/mm^{-1}	0.141	1.181	1.131	1.247
F (000)	1280	608	1296	1120
θ range/°	3.099 to 26.0°.	4.479 to 74.995	2.683 and 68.462	2.366 to 74.522
Index ranges	-7 ≤ h ≤ 7, -26 ≤k ≤ 26, -30 ≤ l ≤ 30	-14 ≤ h ≤ 12, -10 ≤ k ≤12, -18 ≤ l ≤ 18	-7 ≤ h ≤ 7, -26 ≤ k ≤26, -29 ≤ l ≤ 29	-12 ≤ h ≤ 12, -19 ≤ k ≤19, -23 ≤ l ≤ 24
Absor. correction	multi-scan	multi-scan	multi-scan	multi-scan
Refln. collected	49041	7939	97010	133642
Unique Refln.	6390	5323	5821	11677
Observed Refln.	5037	5059	3252	7826
R_{int}	0.0907	0.0293	0.2356	0.1034
R_{sig}	0.0569	0.0574	0.0891	0.0425

Completeness to θ_{max}	99.8 %	96.4%	94.0%	99.5%
Max. and min. transmission	0.989 and 0.970	0.150 and 0.156	0.988 and 0.928	0.984 and 0.920
Refinement method	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2
Data / restraints / parameters	6390 / 0 / 361	5323 / 2 / 378	5821 / 0 / 400	11677 / 10 / 634
Final R indices [I>2sigma(I)]	R1 = 0.0726, wR2 = 0.1294	R1 = 0.0365, wR2 = 0.0949	R1 = 0.0601, wR2 = 0.1407	R1 = 0.0753, wR2 = 0.1862
R indices (all data)	R1 = 0.0987, wR2 = 0.1391	R1 = 0.0385, wR2 = 0.0972	R1 = 0.1264, wR2 = 0.1842	R1 = 0.1176, wR2 = 0.2317
Goodness-of-fit on F^2	1.121	1.039	0.989	1.048
$\Delta\rho_{max}$, $\Delta\rho_{min}$ ($eÅ^{-3}$)	0.381, -0.408	0.567, -0.327	0.235, -0.314	0.514, -0.804
Flack parameter	-	0.039(9)	-	-
CCDC. No.	1969572	2013163	2035515	2035514

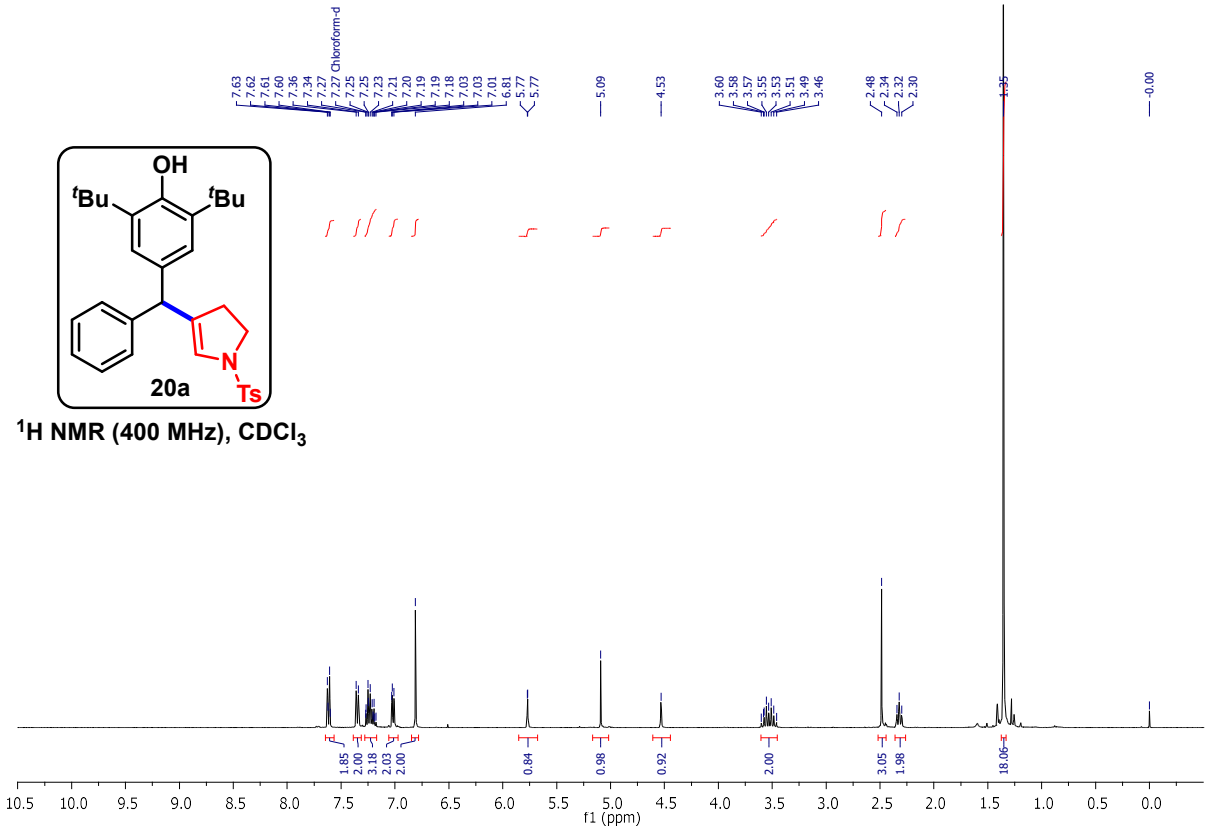
1.2.6 Spectral Data:



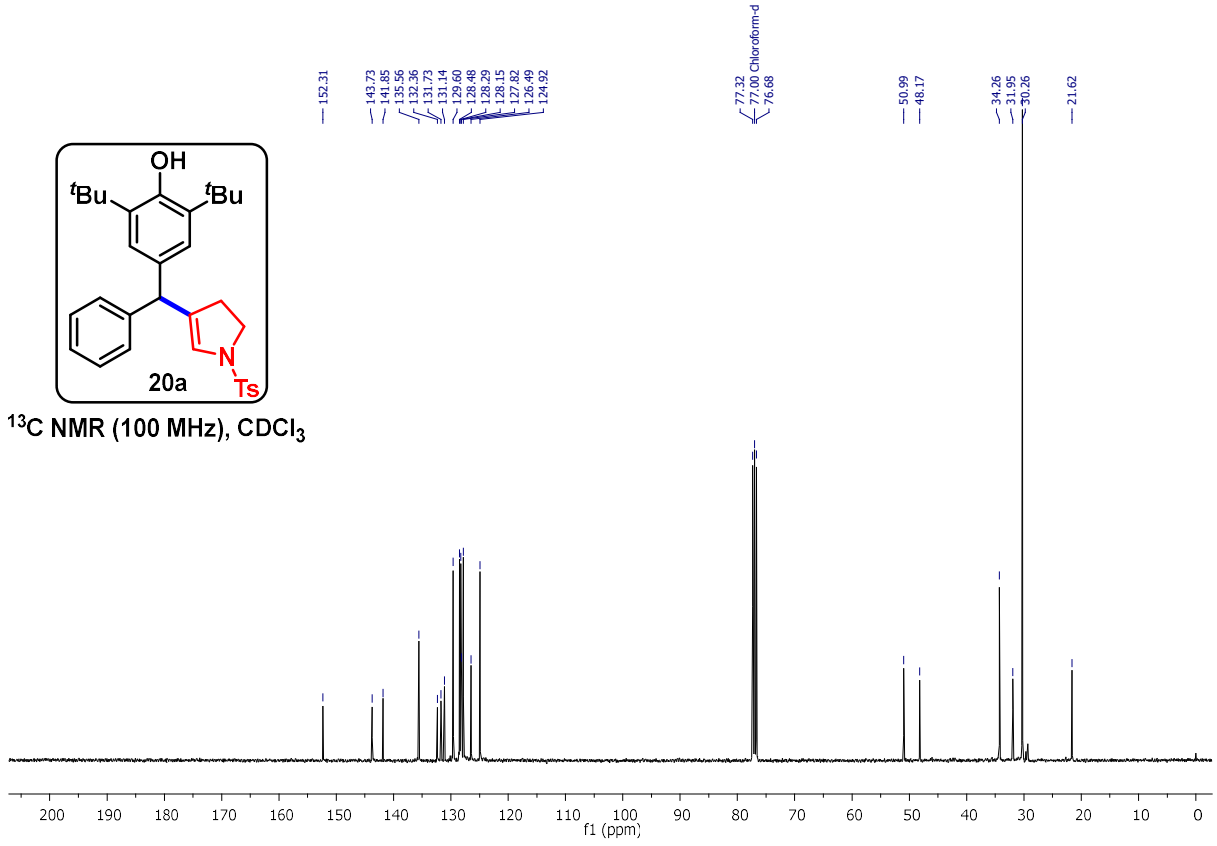
^{1}H NMR (400 MHz), $CDCl_3$



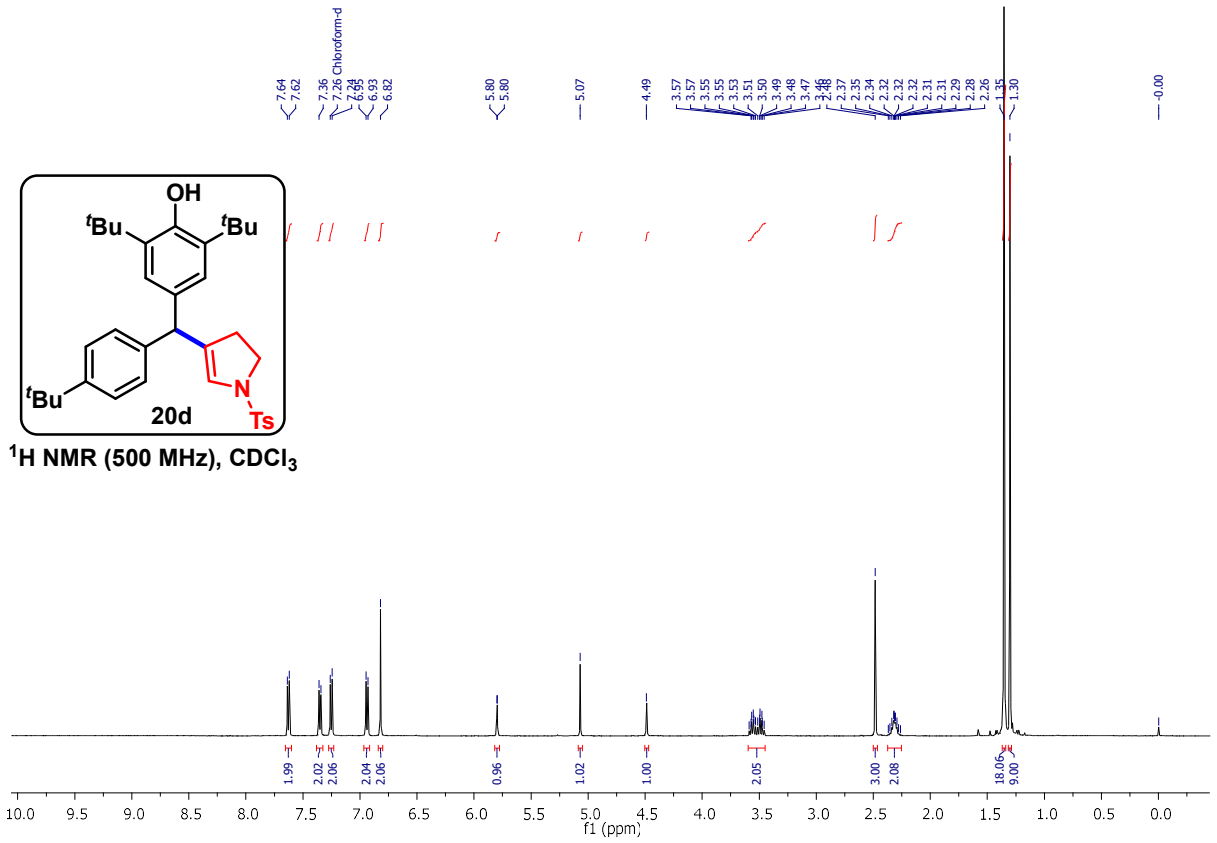
^{13}C NMR (100 MHz), $CDCl_3$



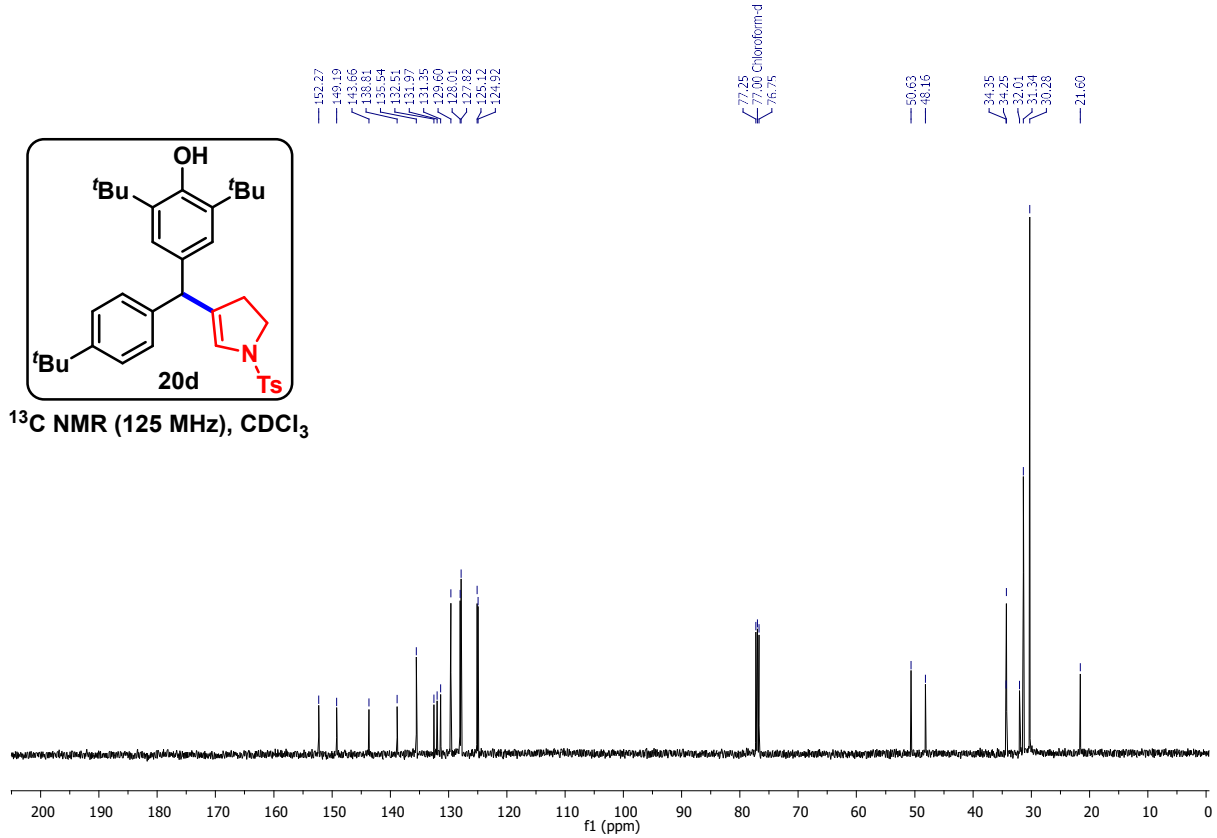
^{1}H NMR (400 MHz), $CDCl_3$



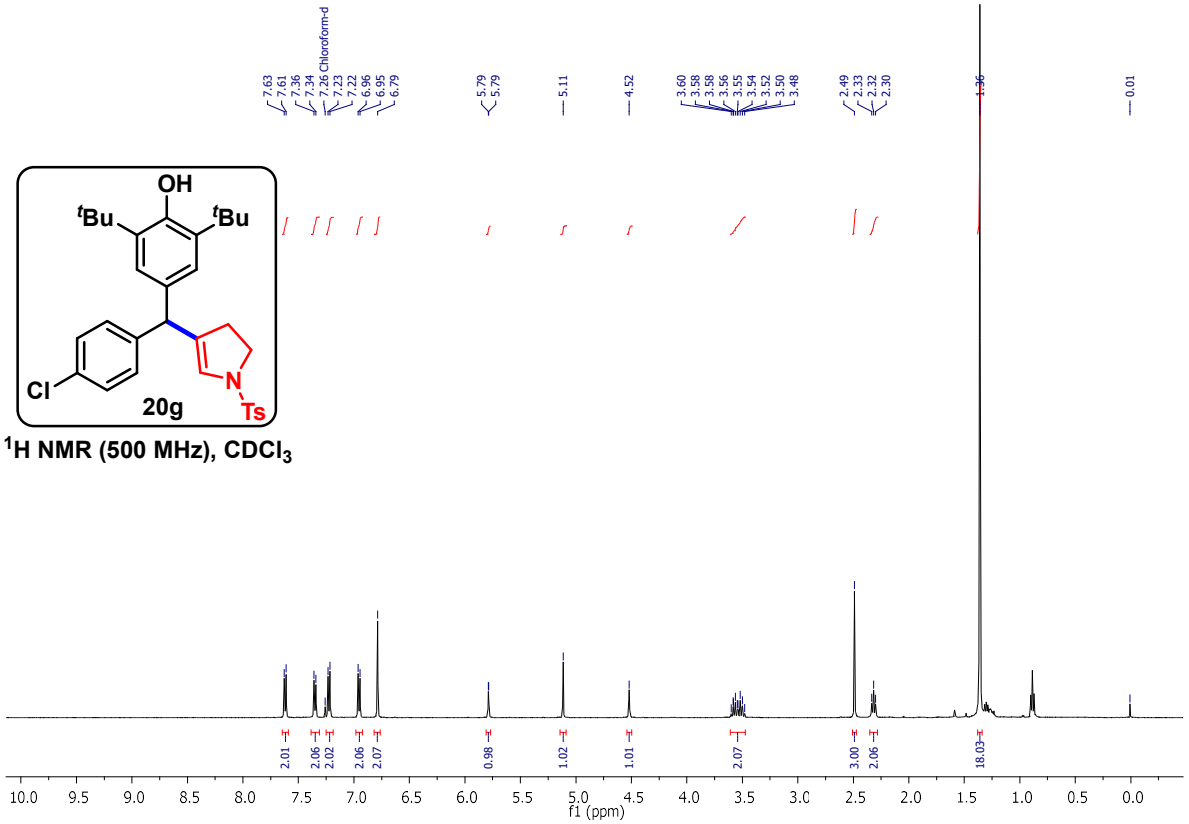
^{13}C NMR (100 MHz), $CDCl_3$



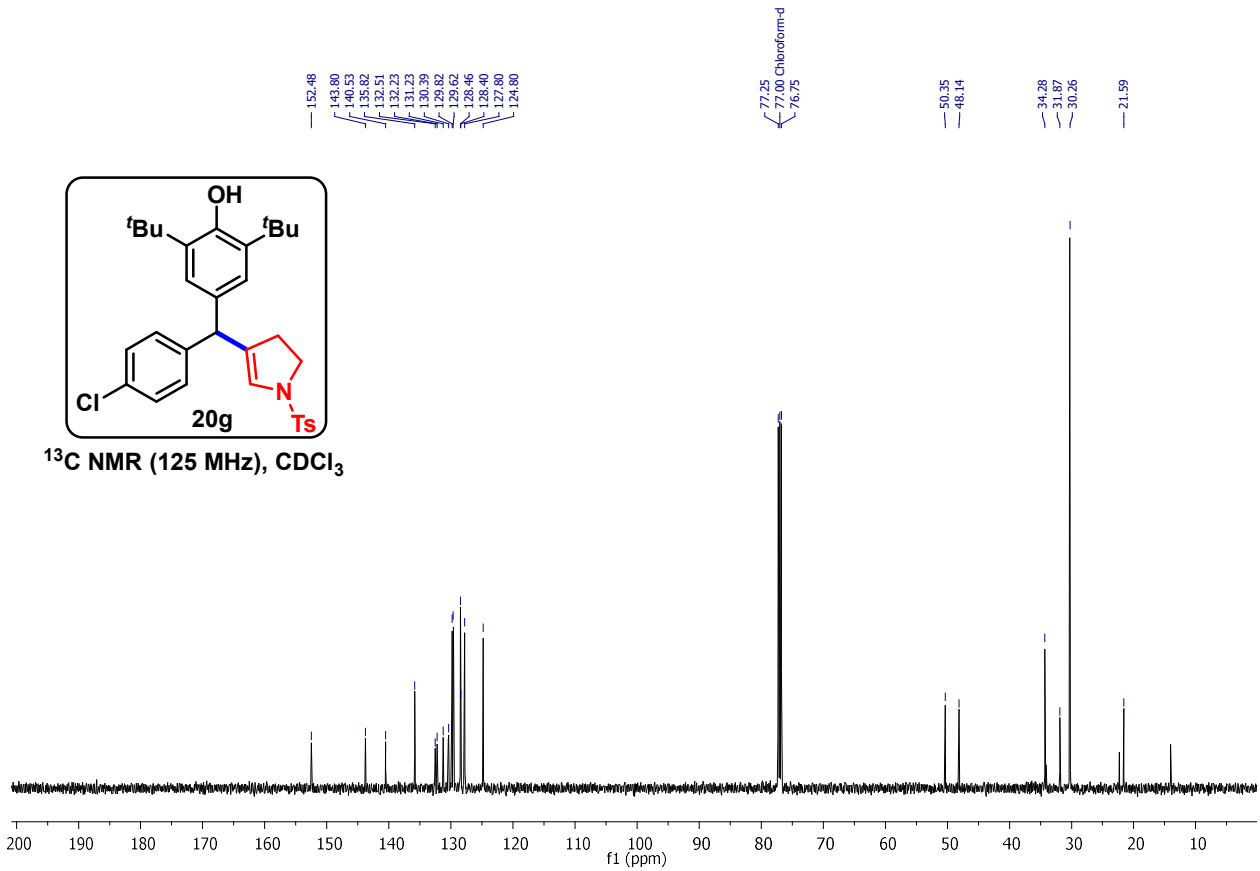
^{1}H NMR (500 MHz), $CDCl_3$



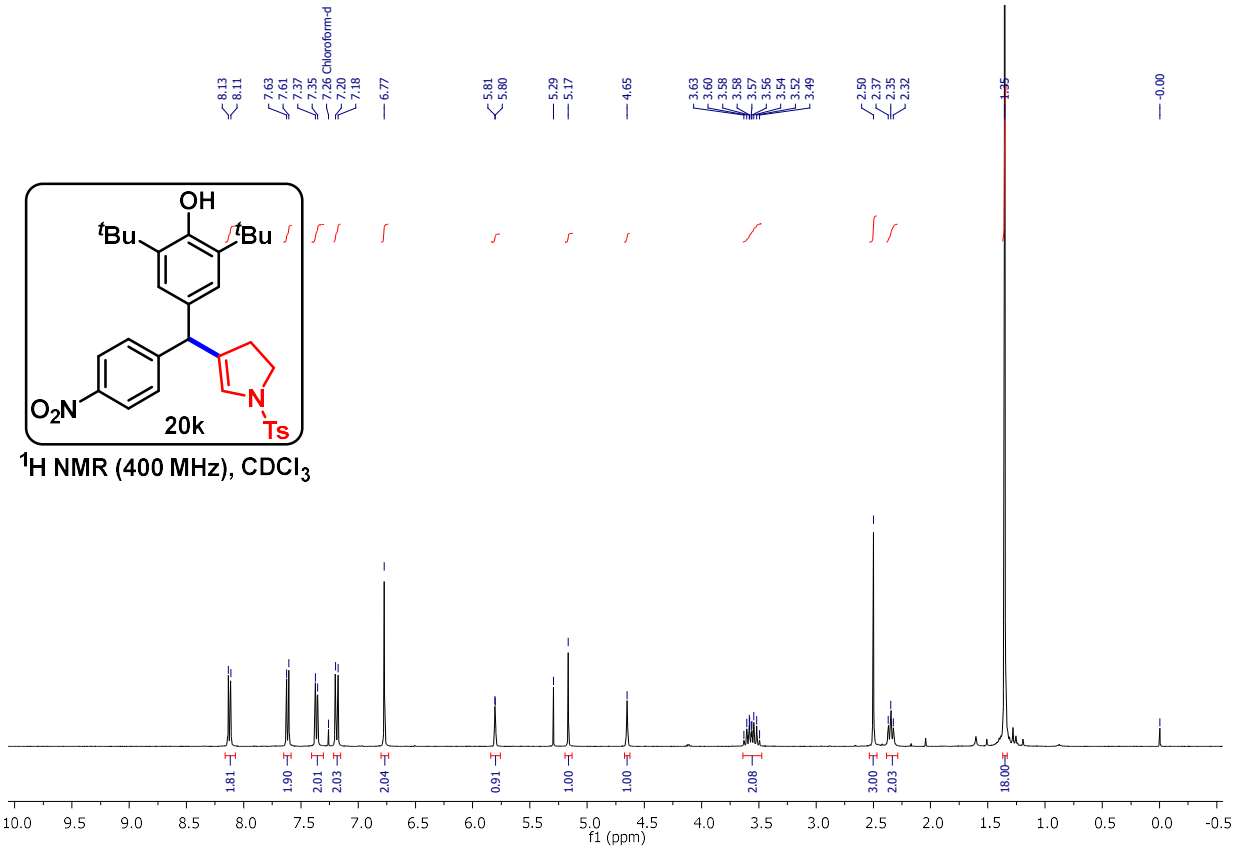
^{13}C NMR (125 MHz), $CDCl_3$

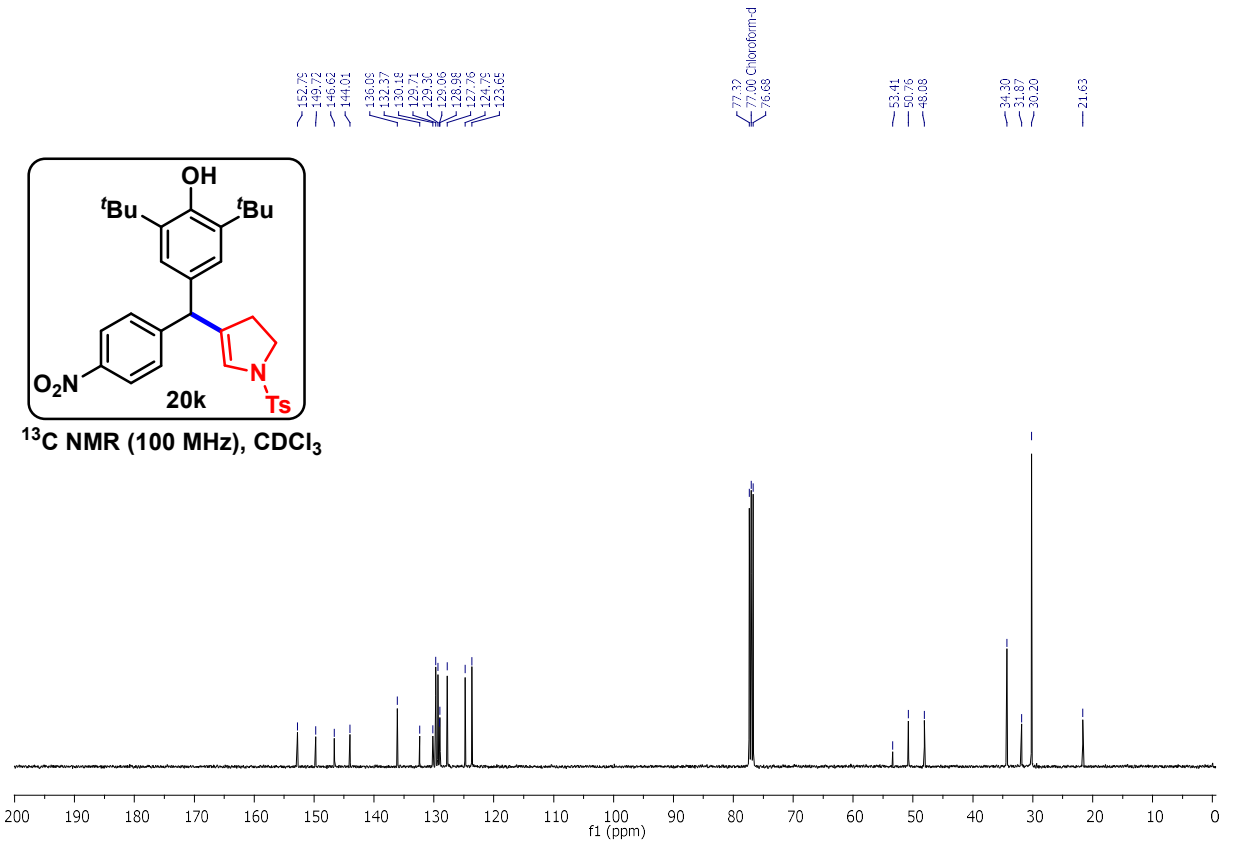


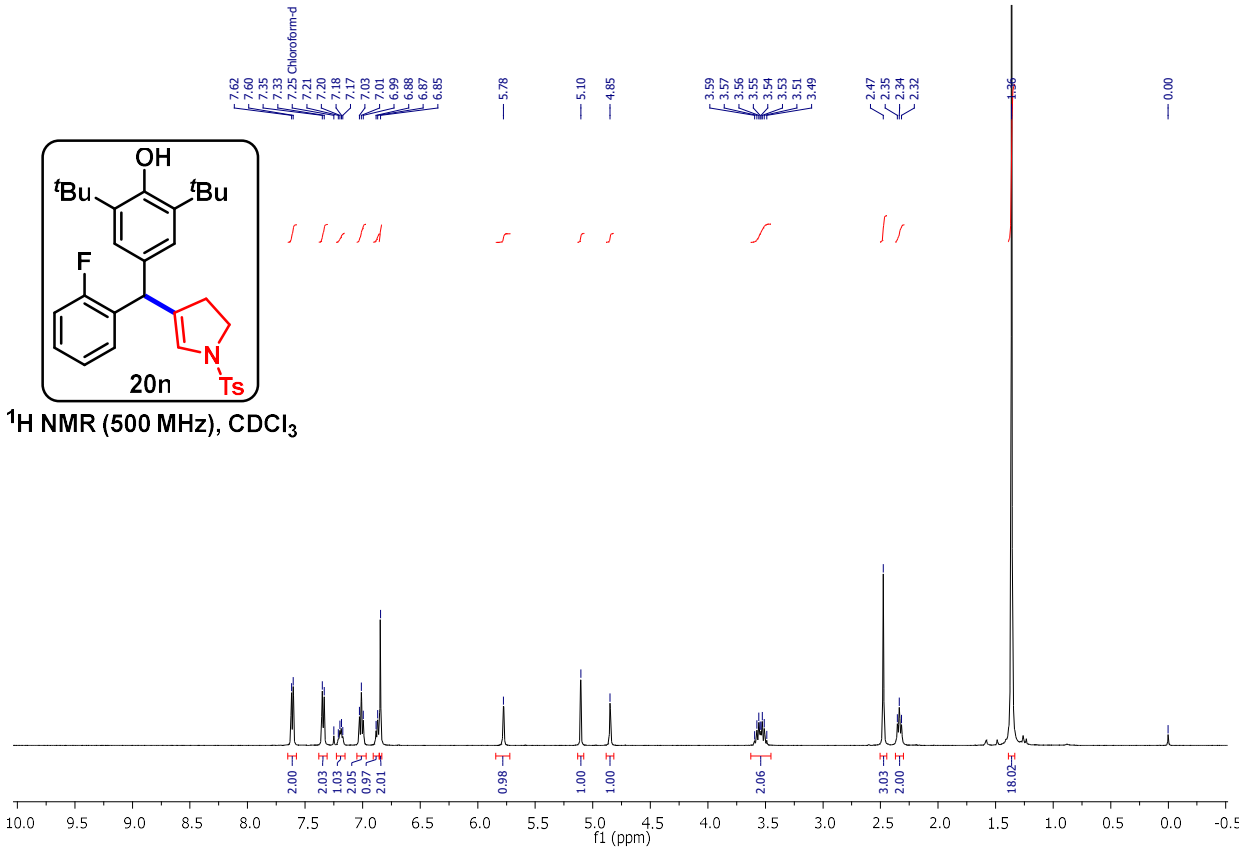
^{1}H NMR (500 MHz), $CDCl_3$



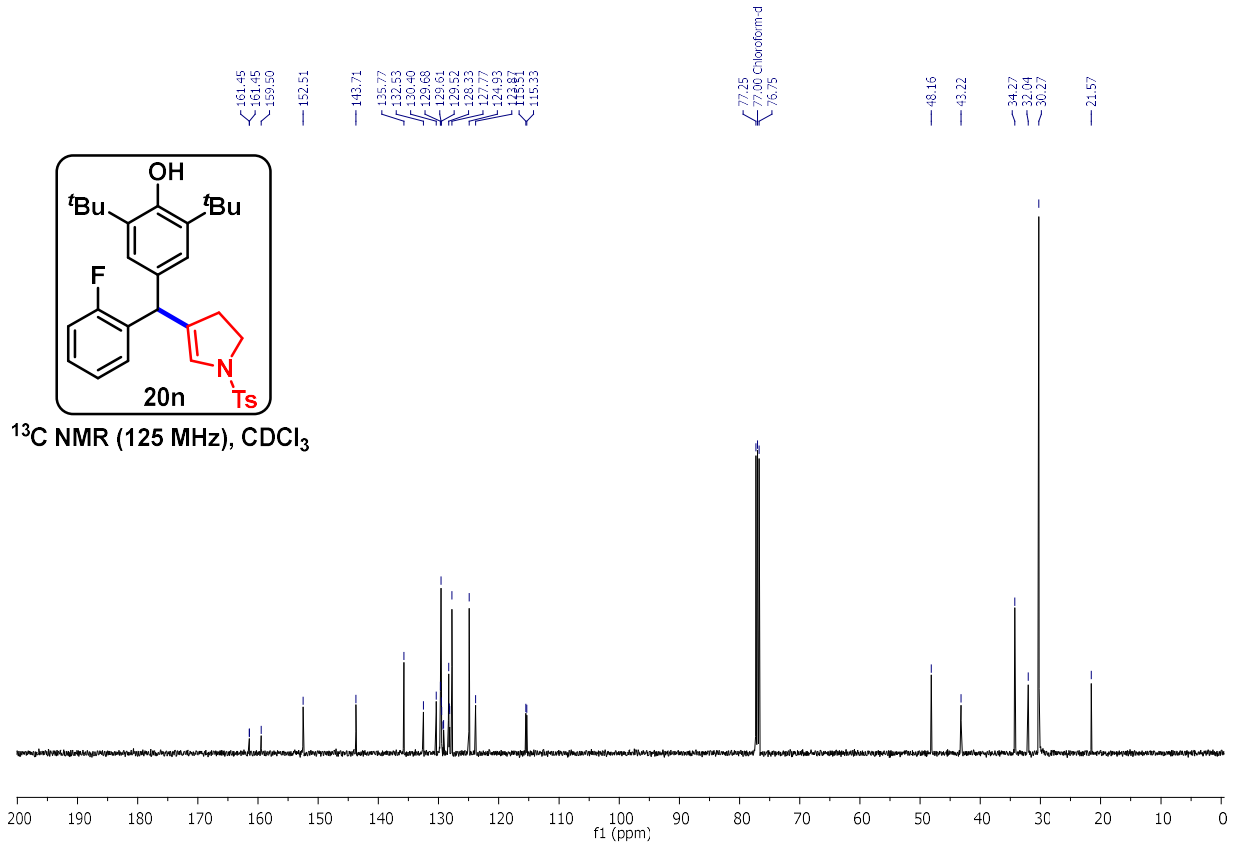
^{13}C NMR (125 MHz), $CDCl_3$


OH
tBu
tBu
O2N
N
Ts
20k
1H NMR (400 MHz), CDCl3
f1 (ppm)

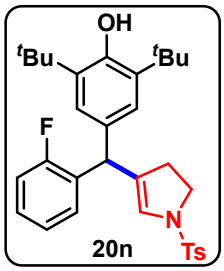

OH
tBu
tBu
O2N
N
Ts
20k
13C NMR (100 MHz), CDCl3
f1 (ppm)



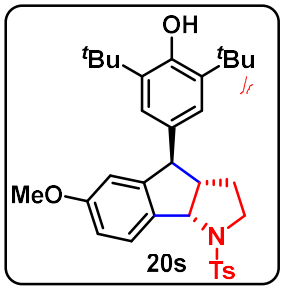
^{1}H NMR (500 MHz), $CDCl_3$



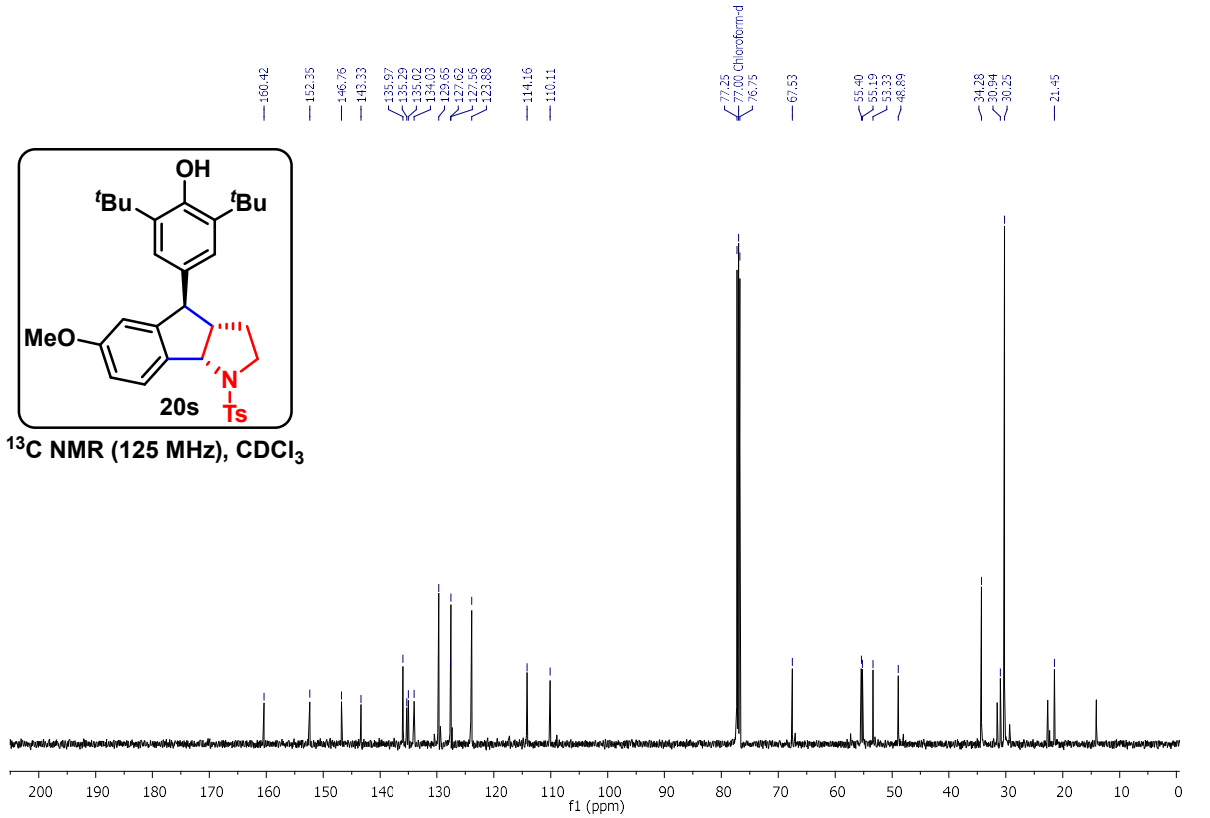
^{13}C NMR (125 MHz), $CDCl_3$



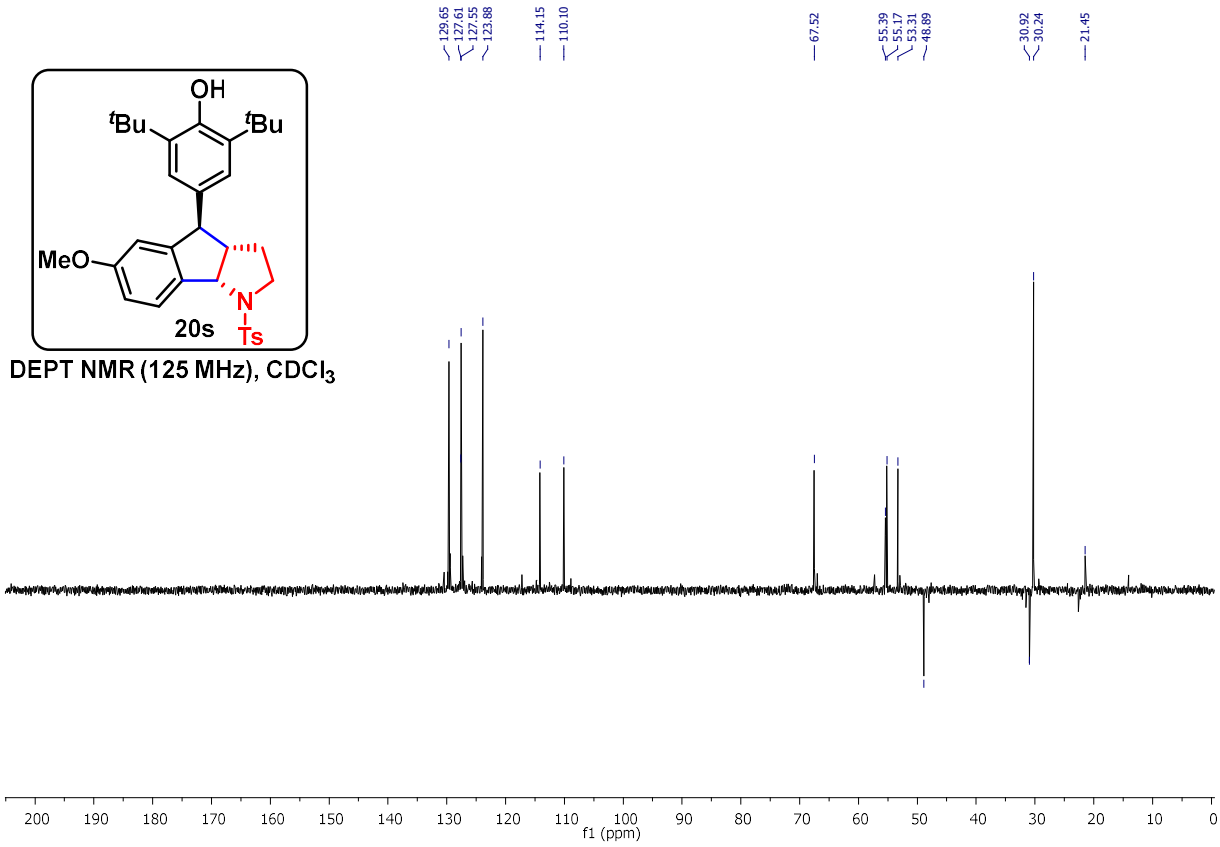
^{19}F NMR (376 MHz), $CDCl_3$



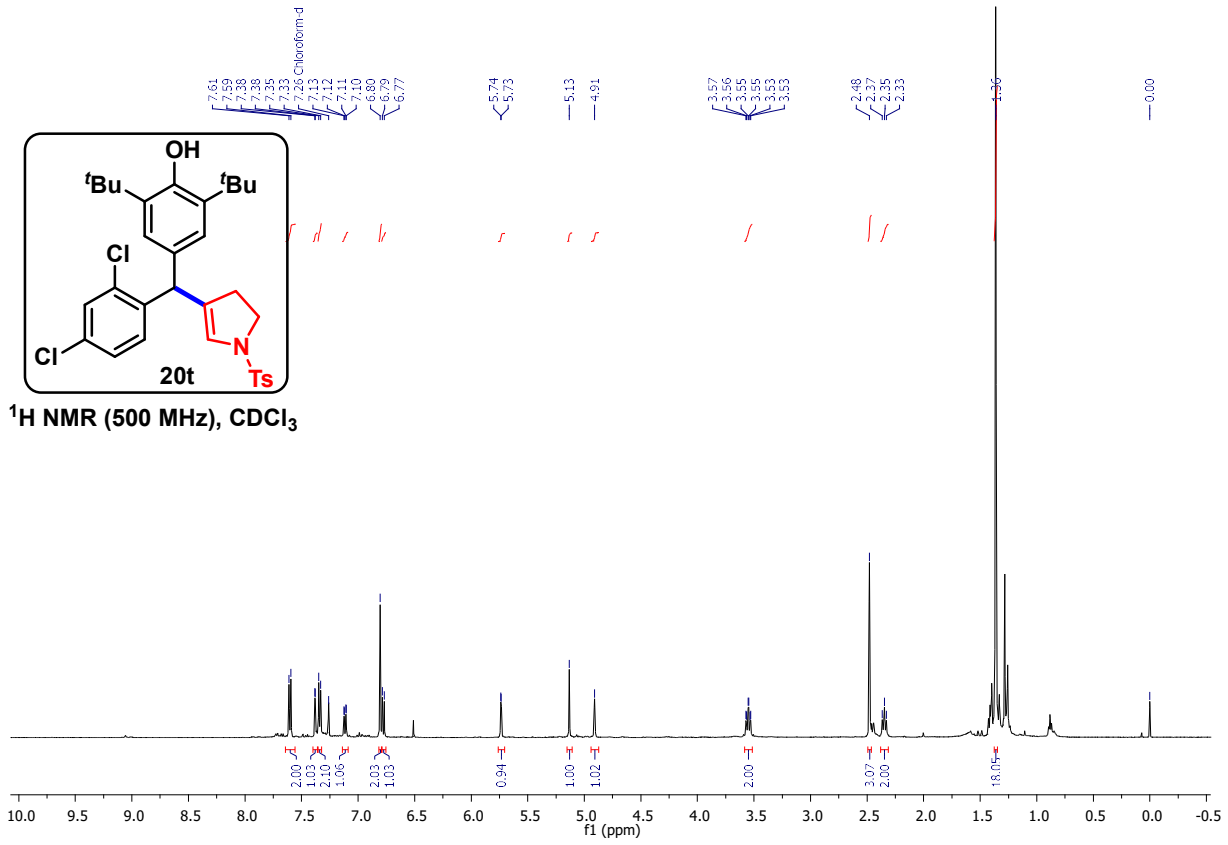
^{1}H NMR (500 MHz), $CDCl_3$



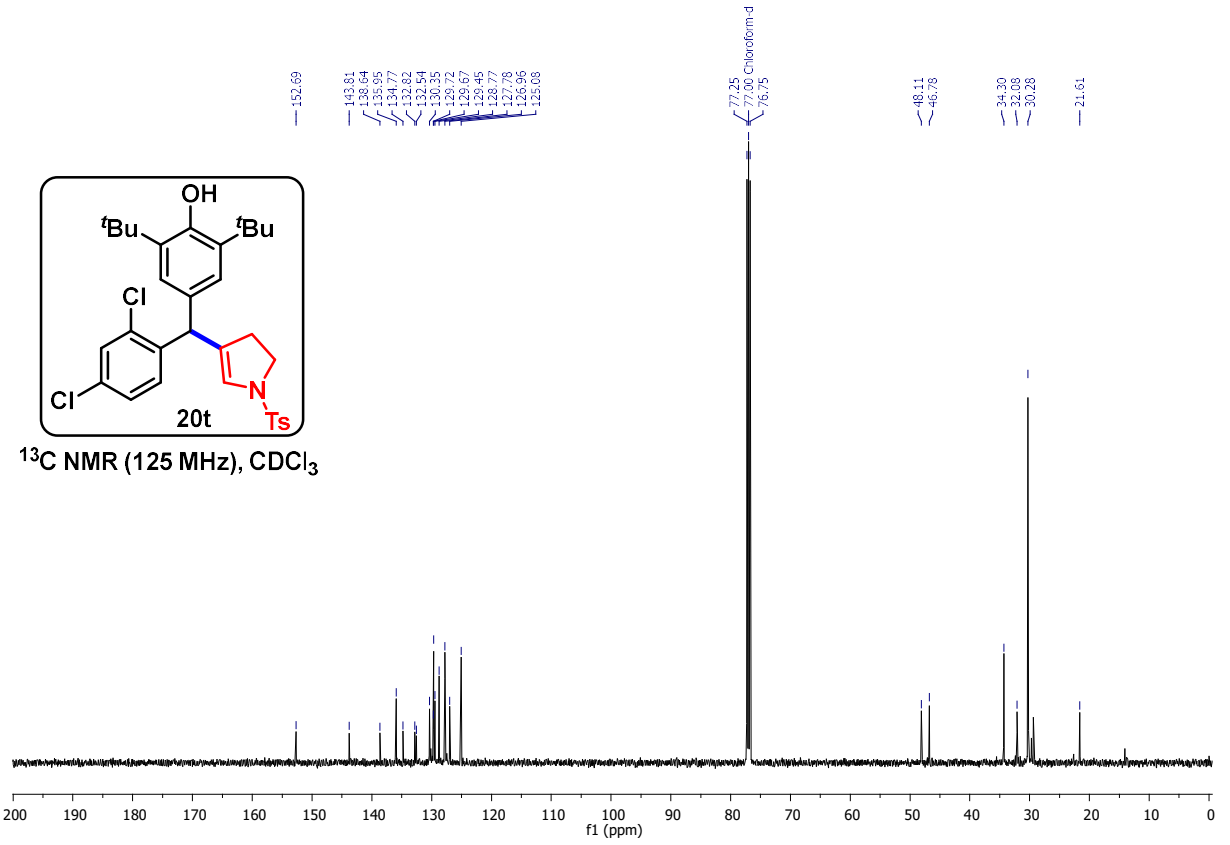
^{13}C NMR (125 MHz), $CDCl_3$



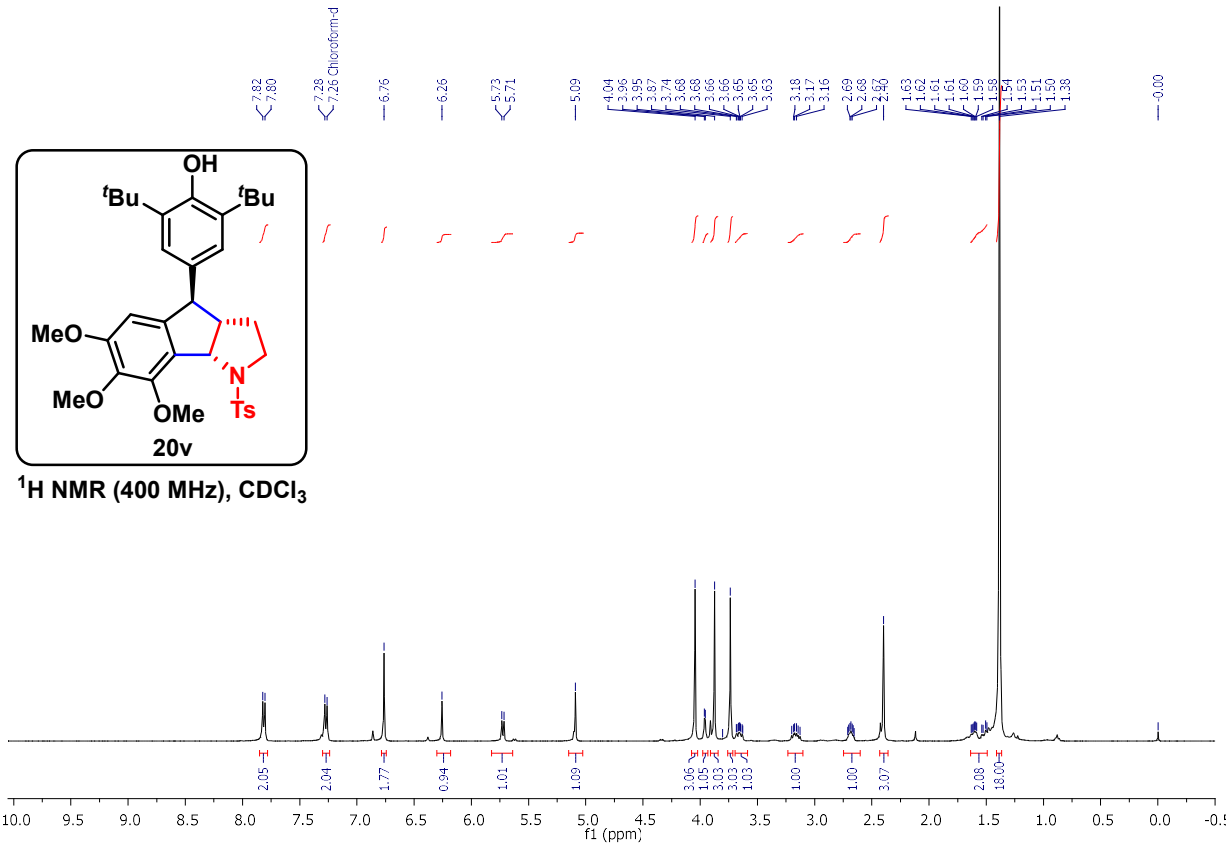
DEPT NMR (125 MHz), $CDCl_3$



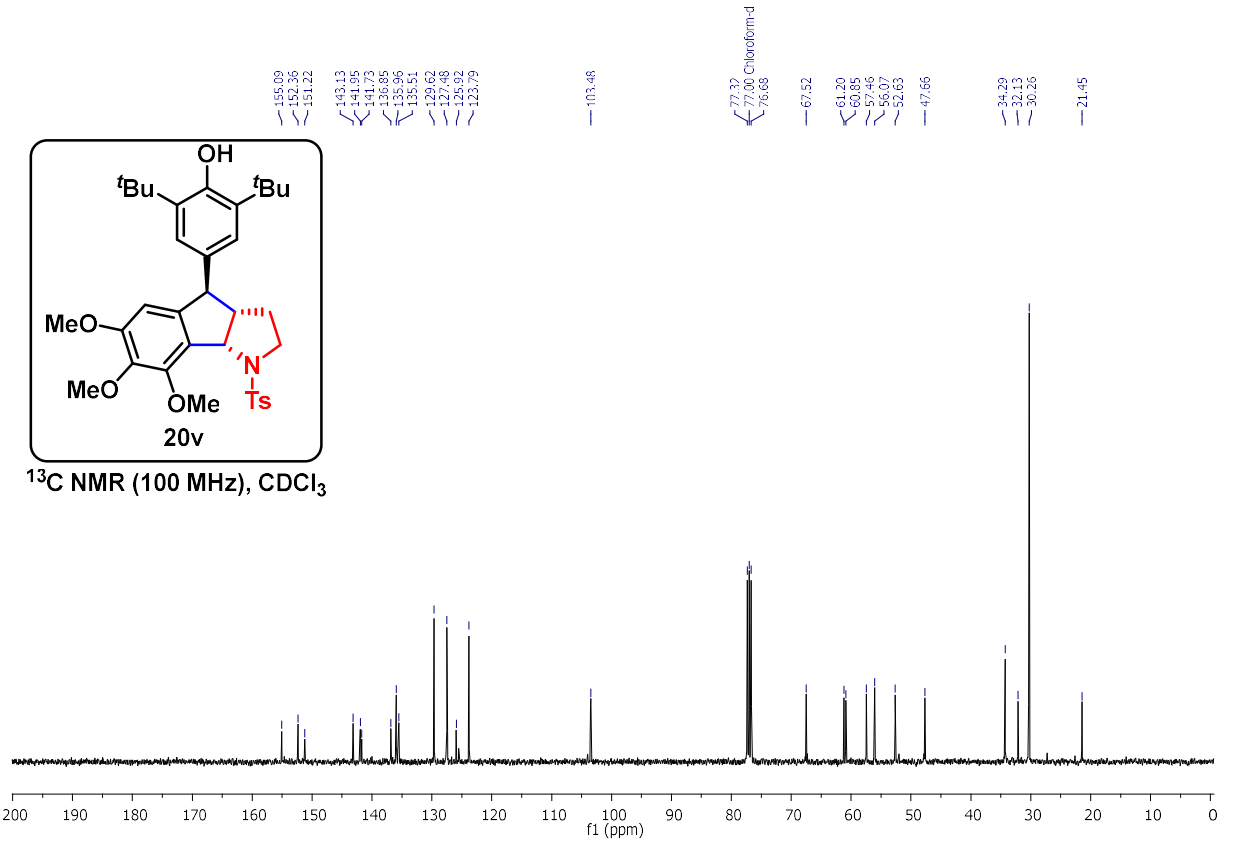
^{1}H NMR (500 MHz), $CDCl_3$



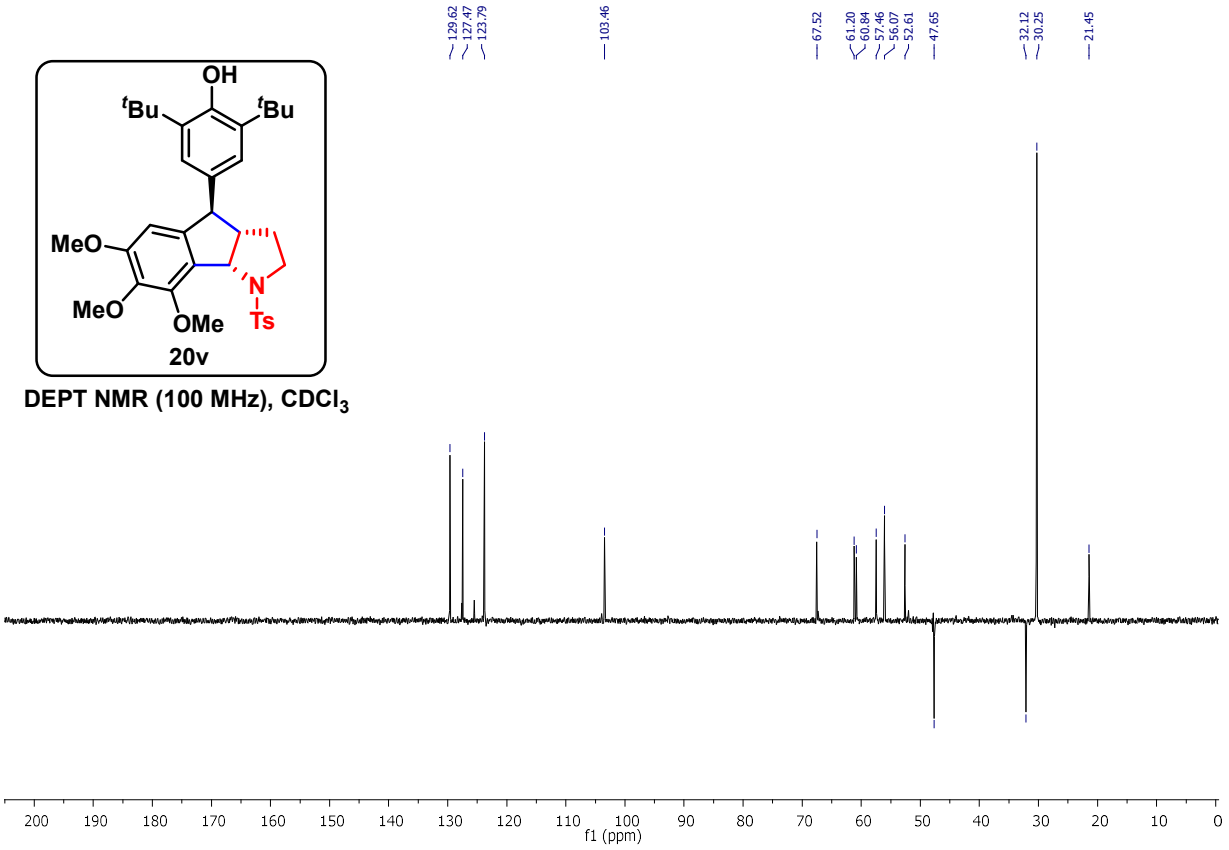
^{13}C NMR (125 MHz), $CDCl_3$



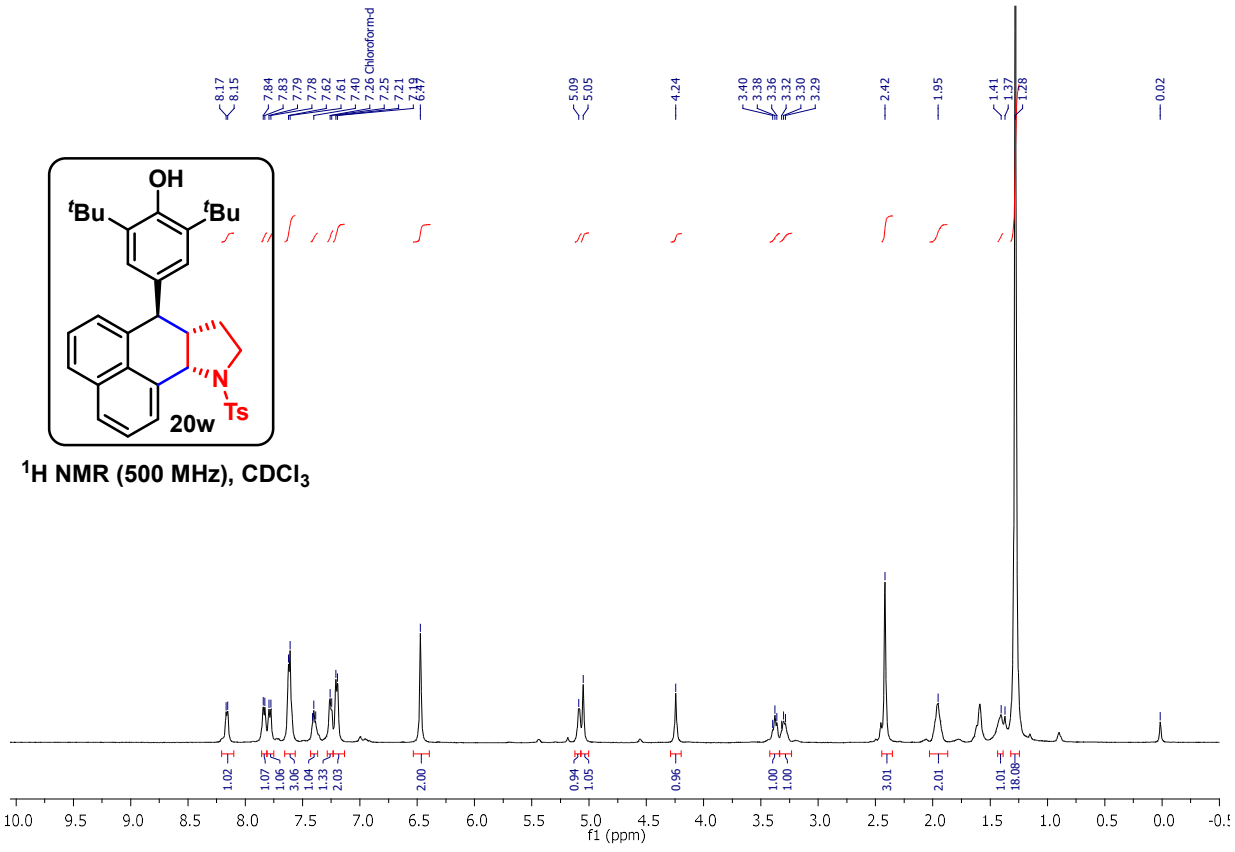
^{1}H NMR (400 MHz), $CDCl_3$



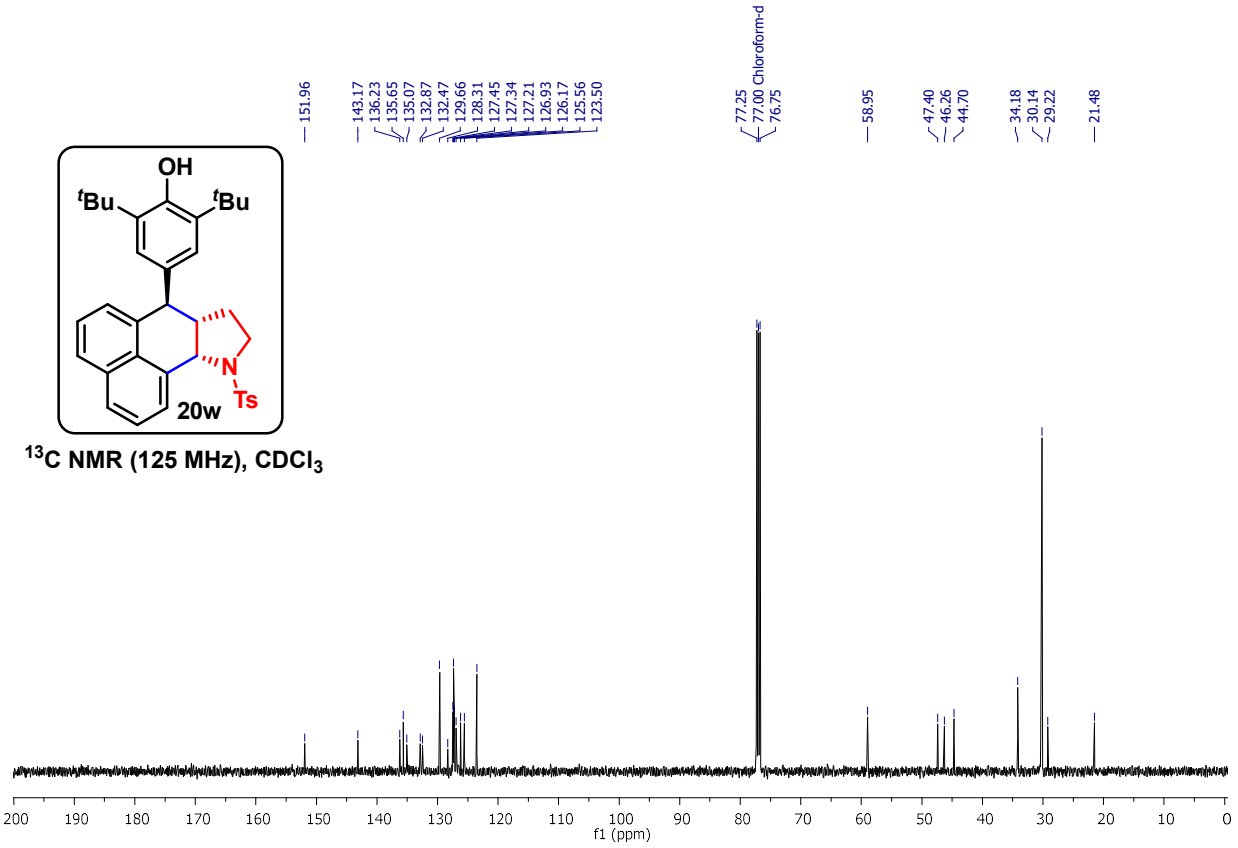
^{13}C NMR (100 MHz), $CDCl_3$



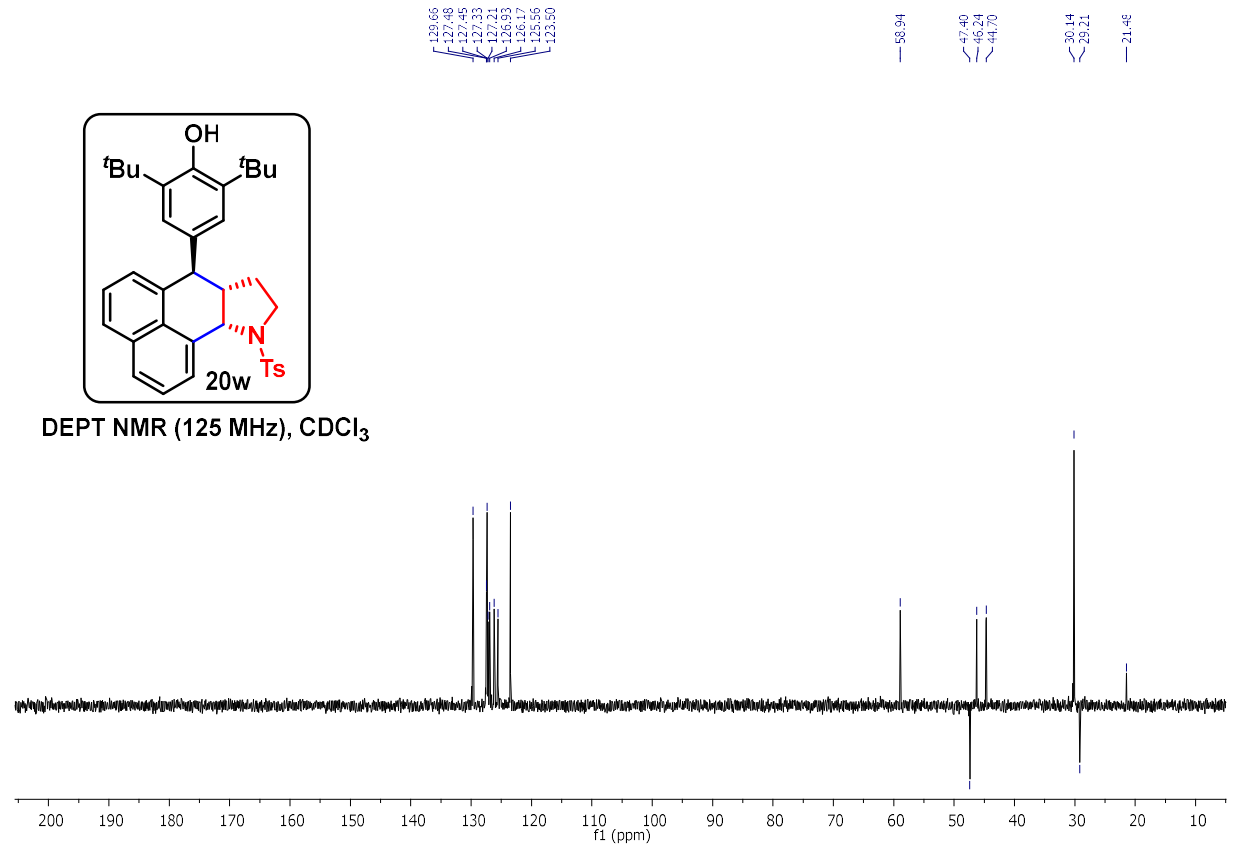
DEPT NMR (100 MHz), $CDCl_3$



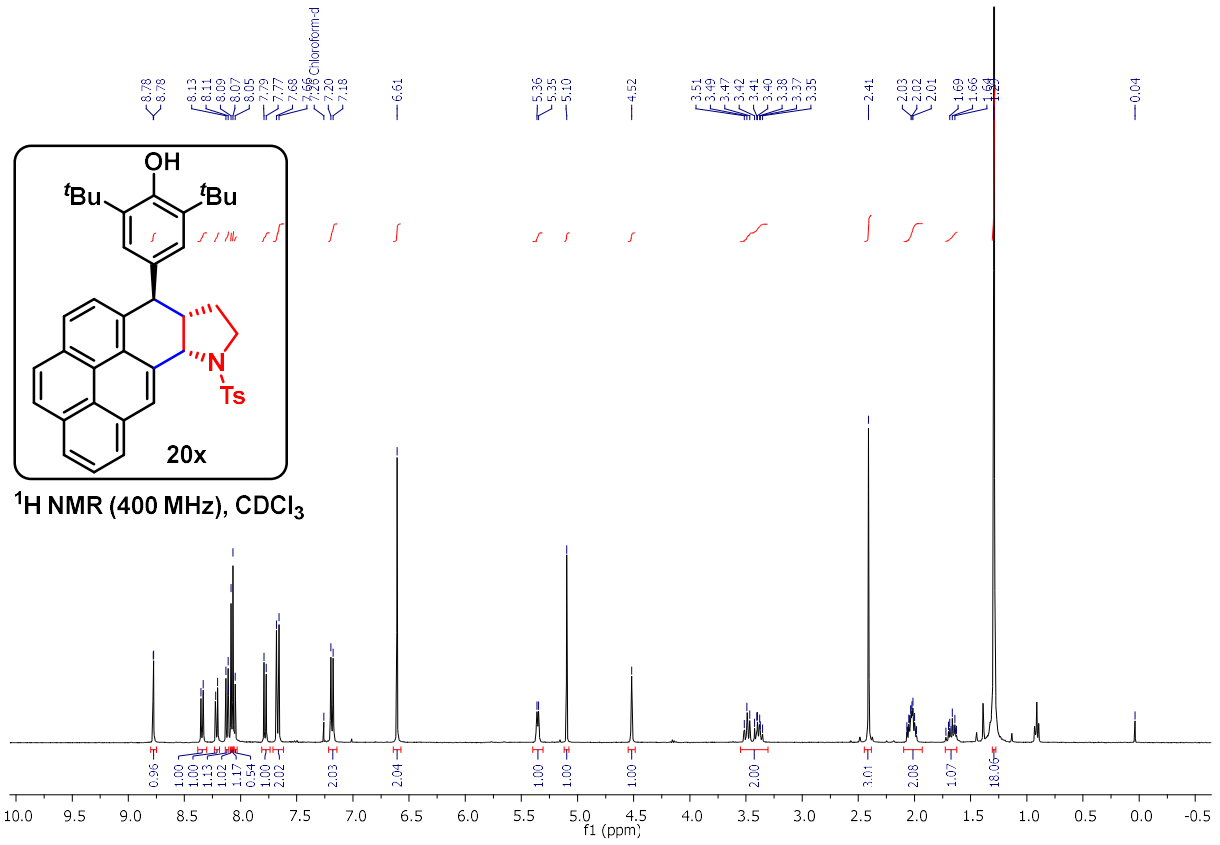
^1H NMR (500 MHz), $CDCl_3$



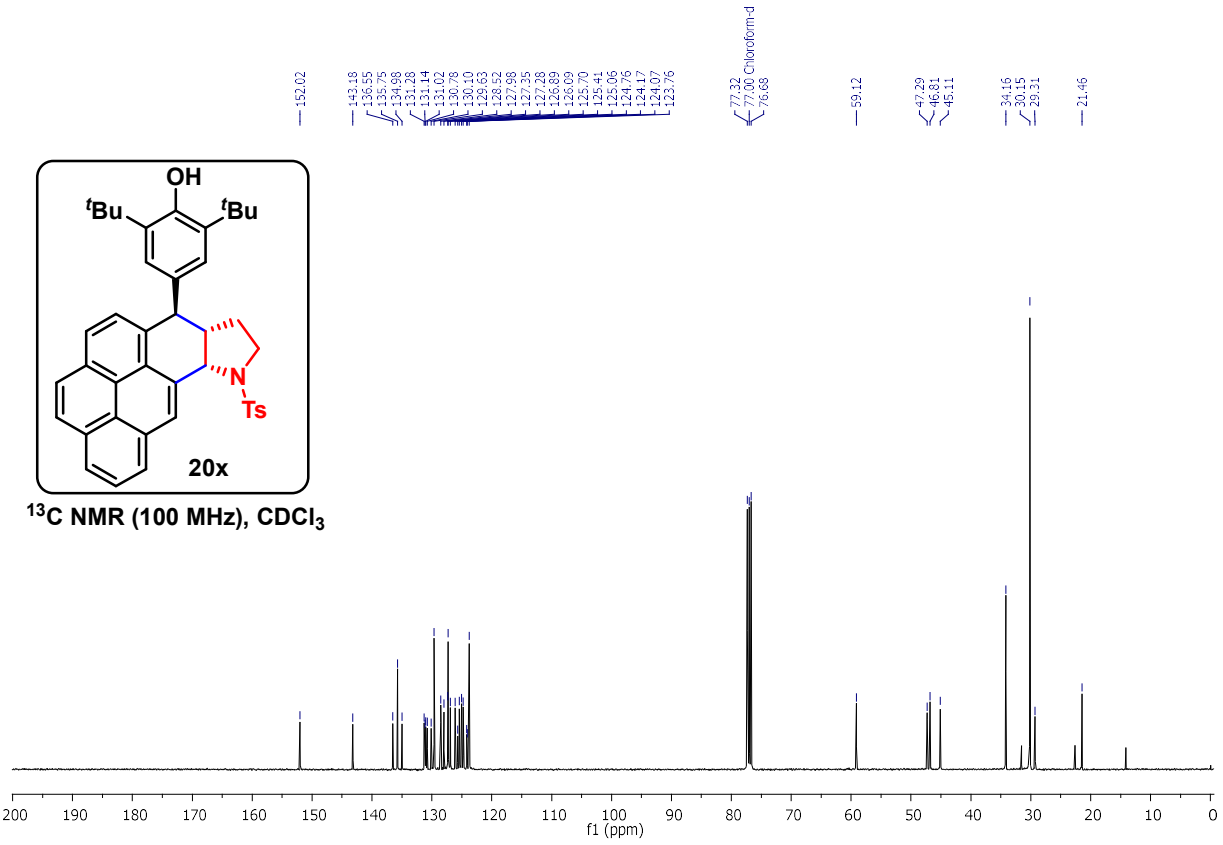
^{13}C NMR (125 MHz), $CDCl_3$



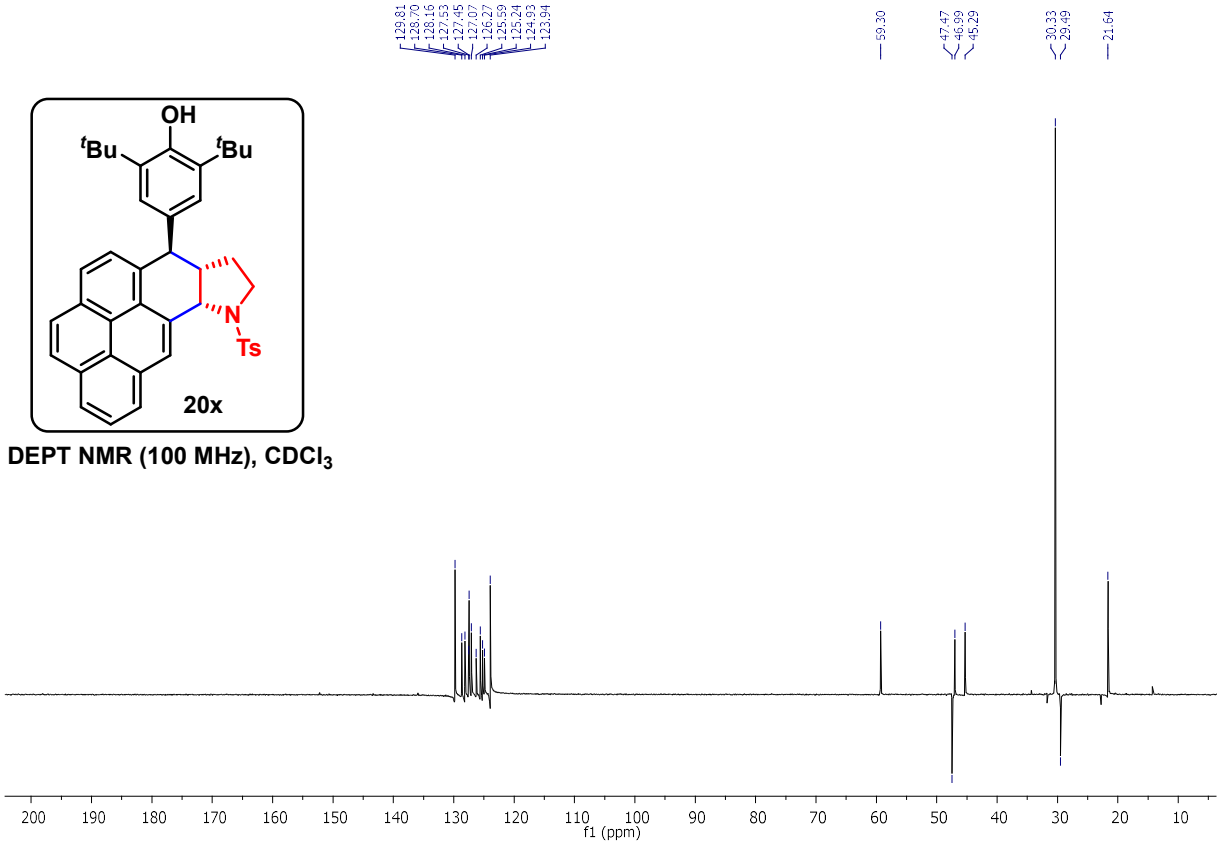
DEPT NMR (125 MHz), $CDCl_3$



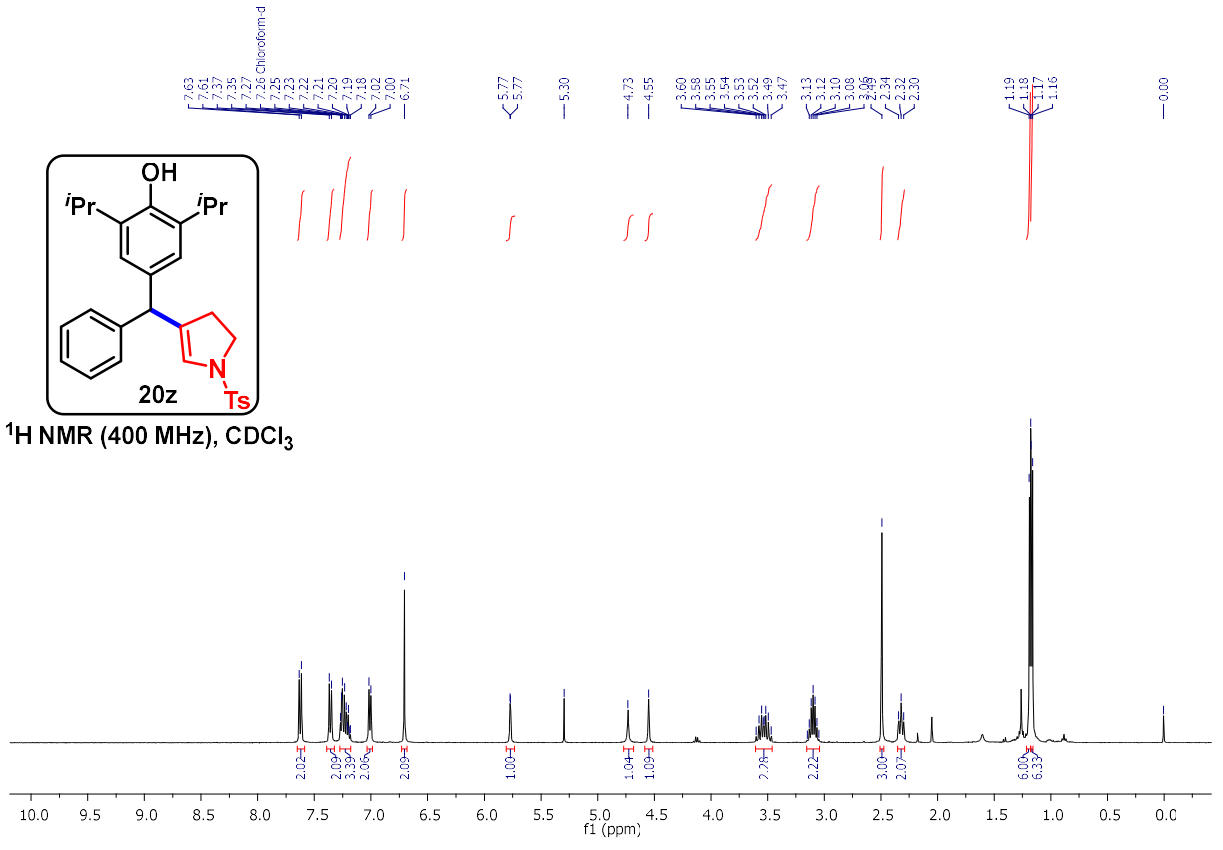
^{1}H NMR (400 MHz), $CDCl_3$



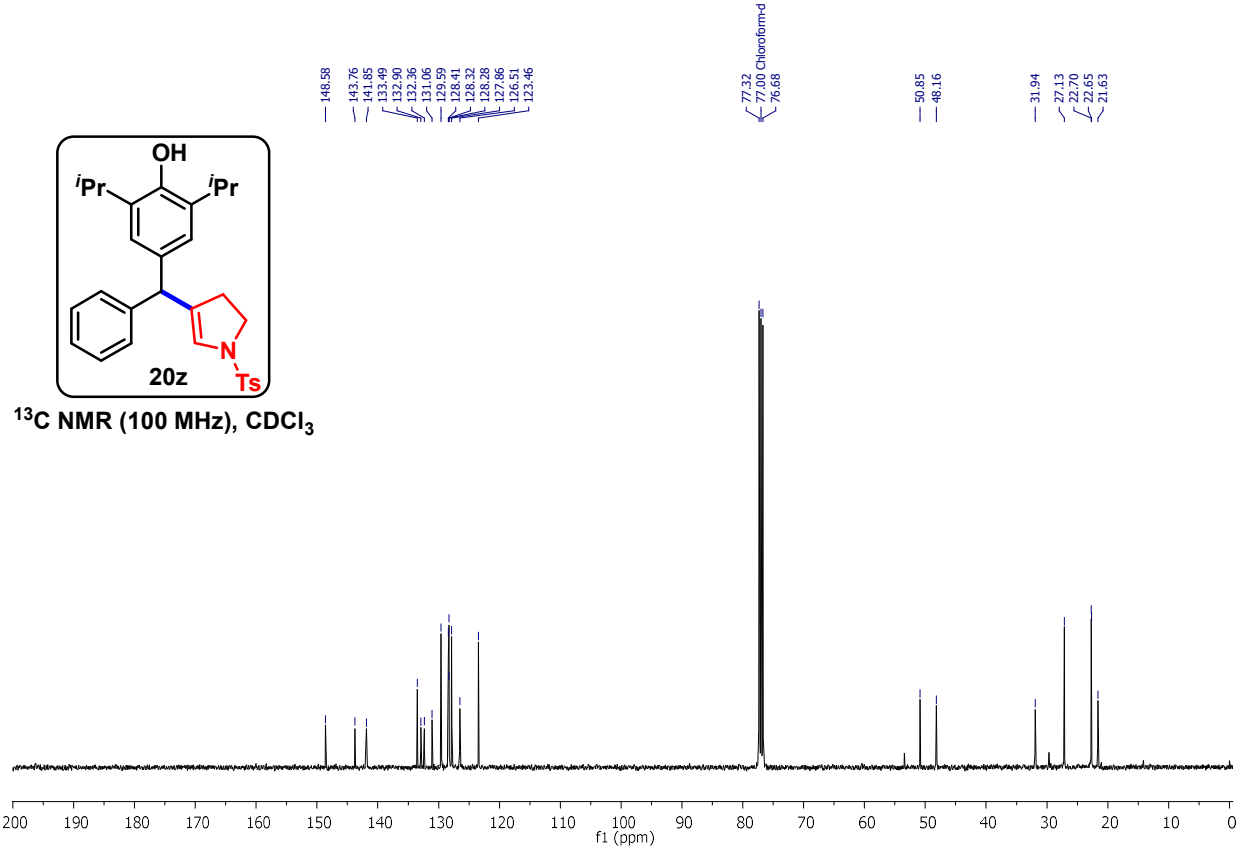
^{13}C NMR (100 MHz), $CDCl_3$



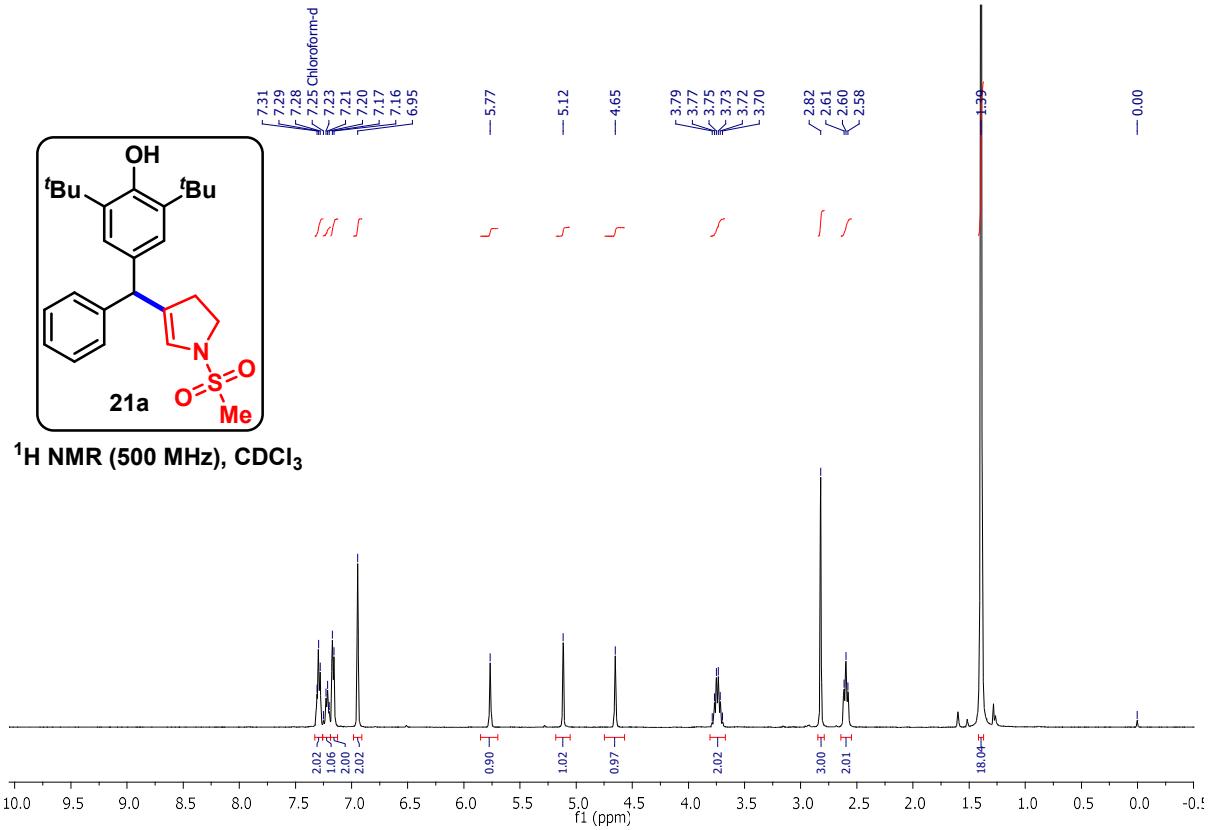
DEPT NMR (100 MHz), $CDCl_3$



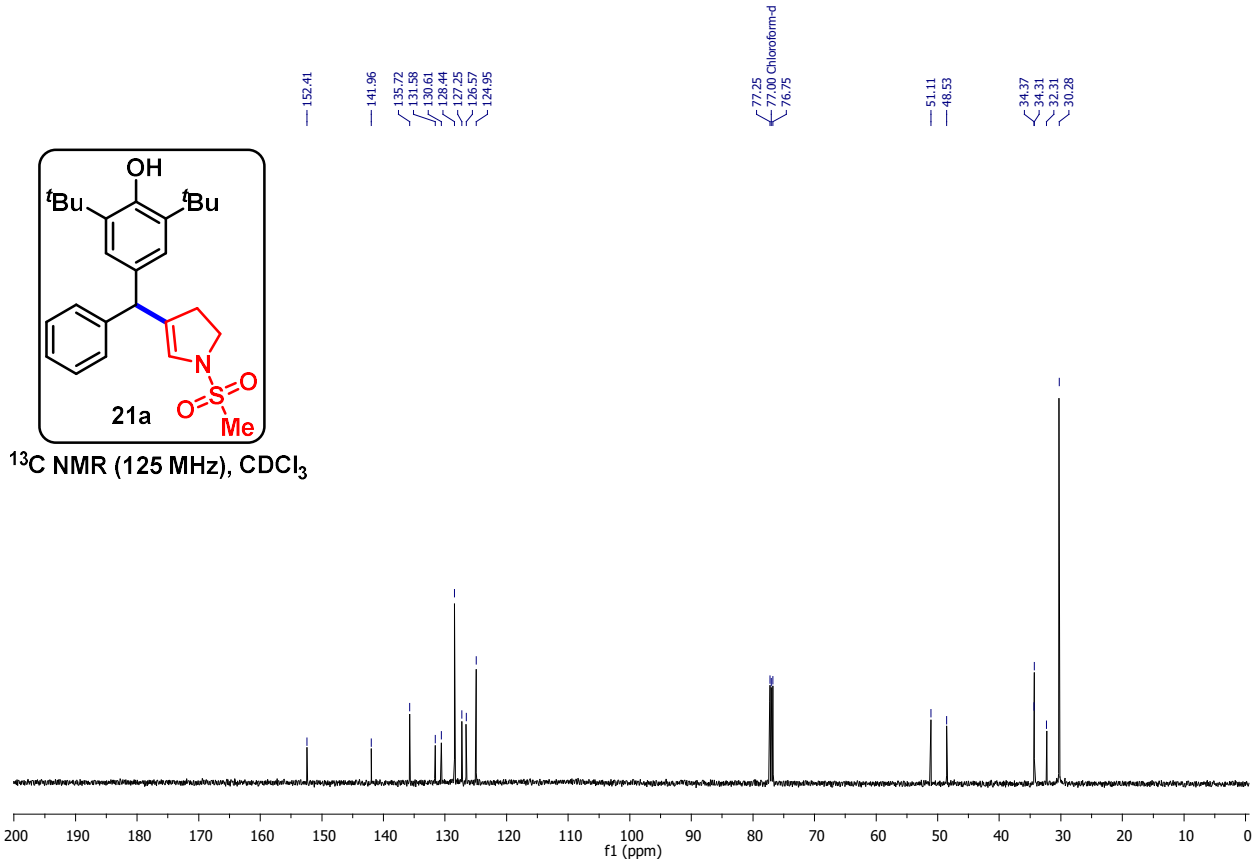
^{1}H NMR (400 MHz), $CDCl_3$



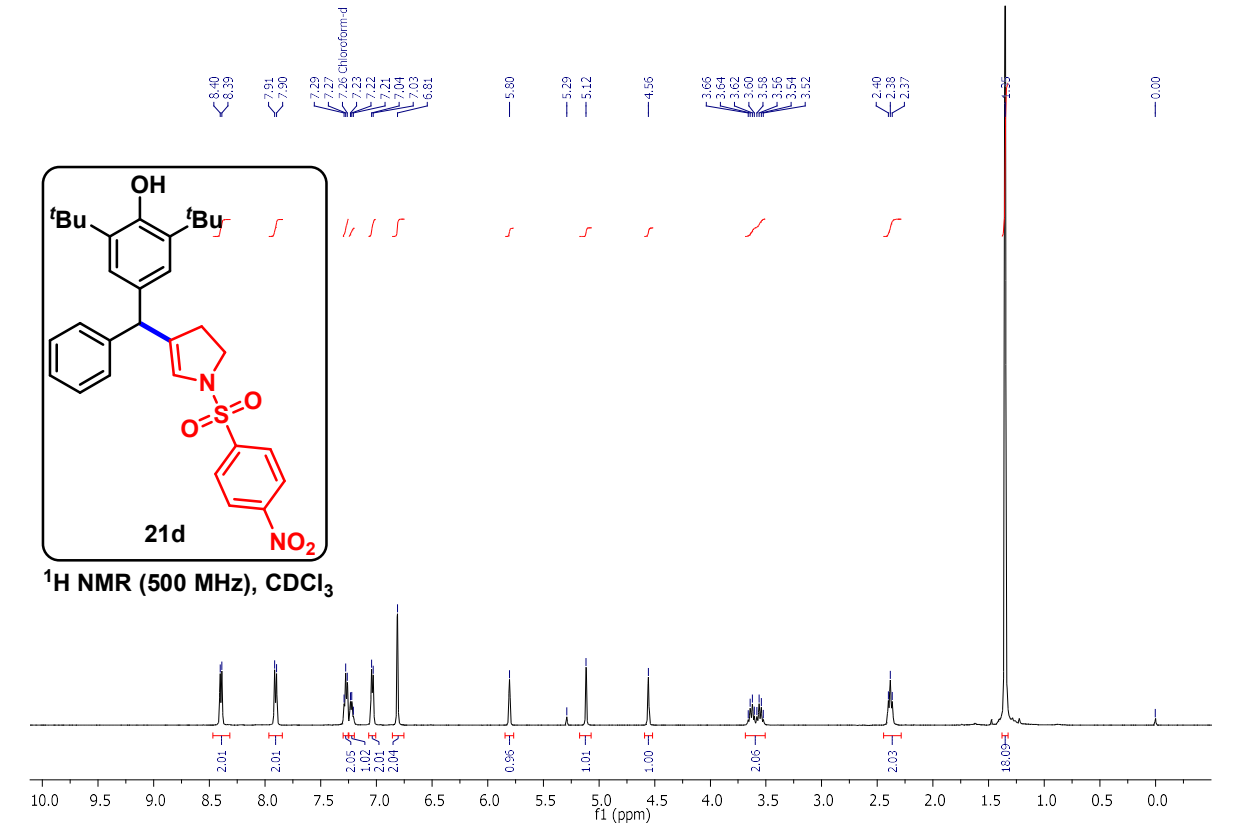
^{13}C NMR (100 MHz), $CDCl_3$



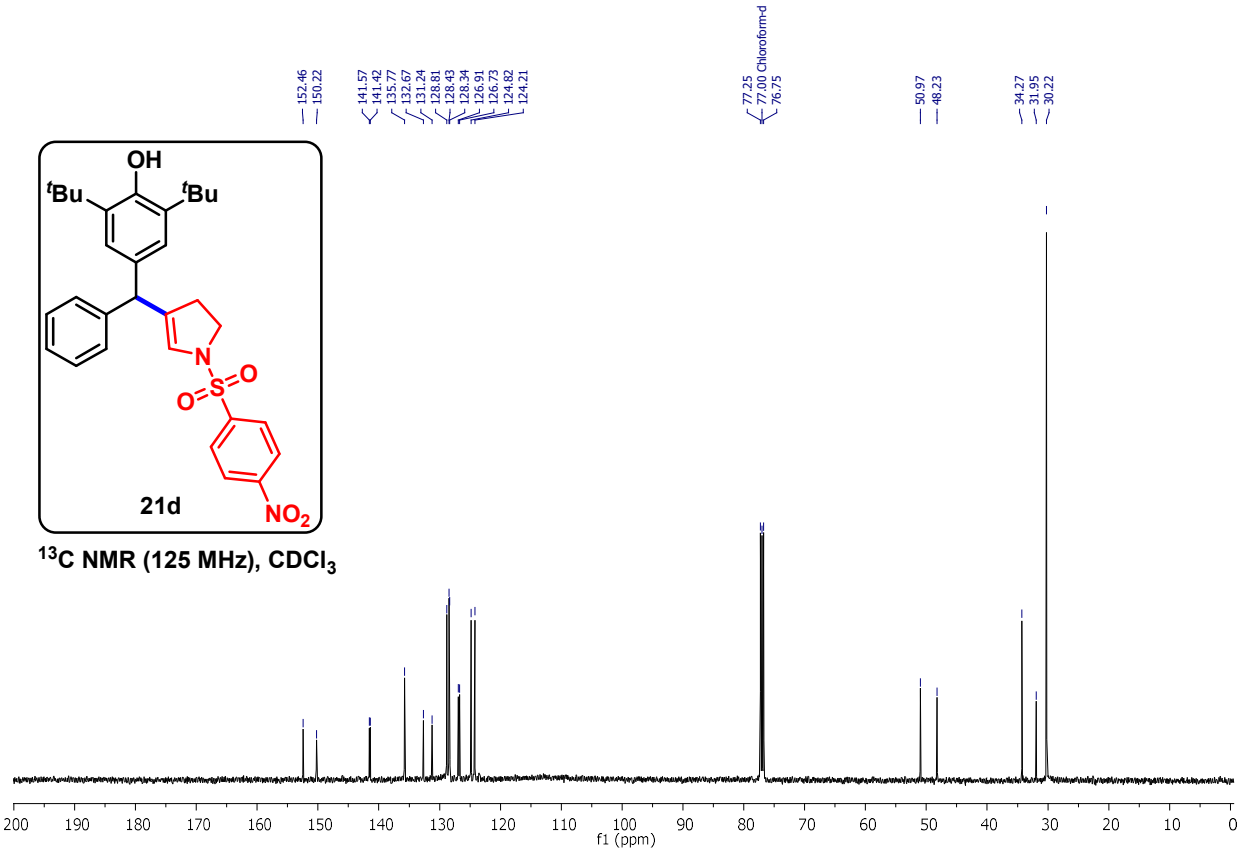
^{1}H NMR (500 MHz), $CDCl_3$



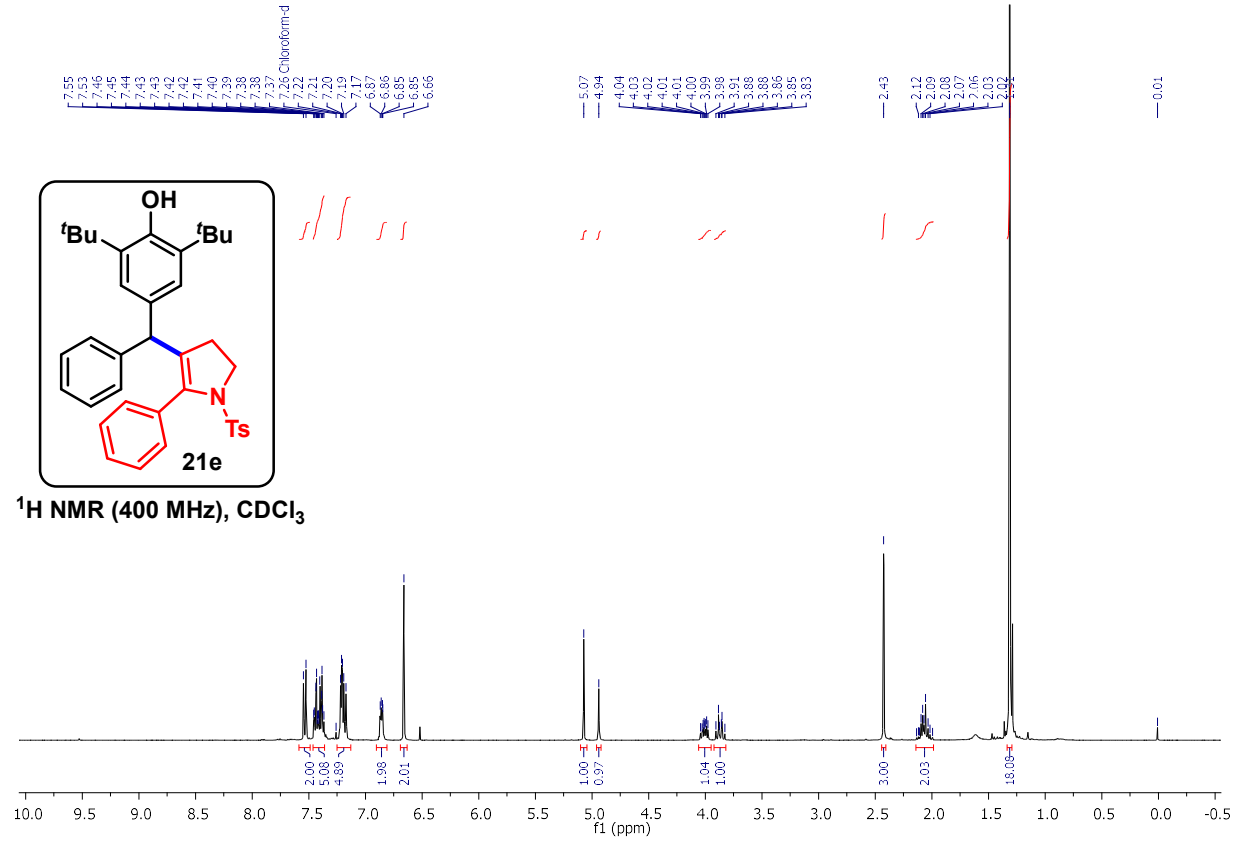
^{13}C NMR (125 MHz), $CDCl_3$



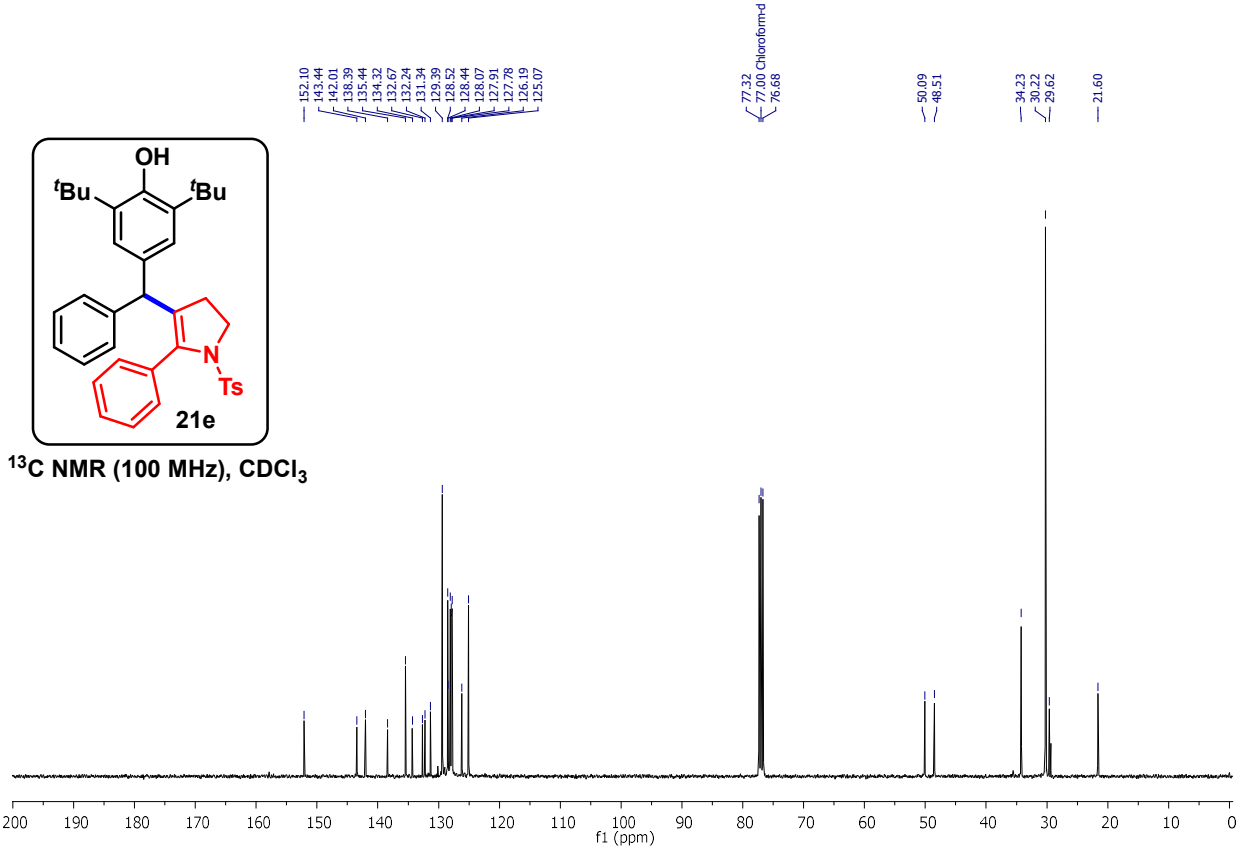
^{1}H NMR (500 MHz), $CDCl_3$

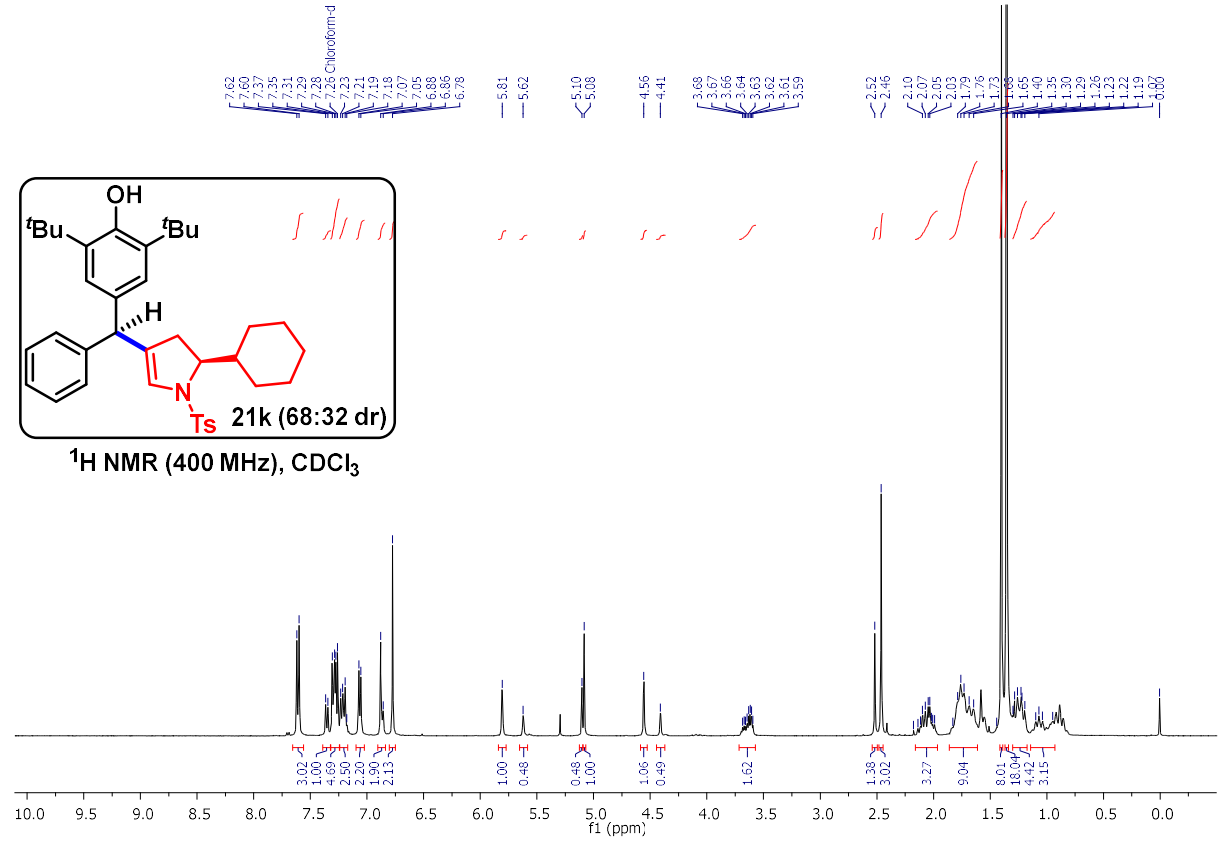


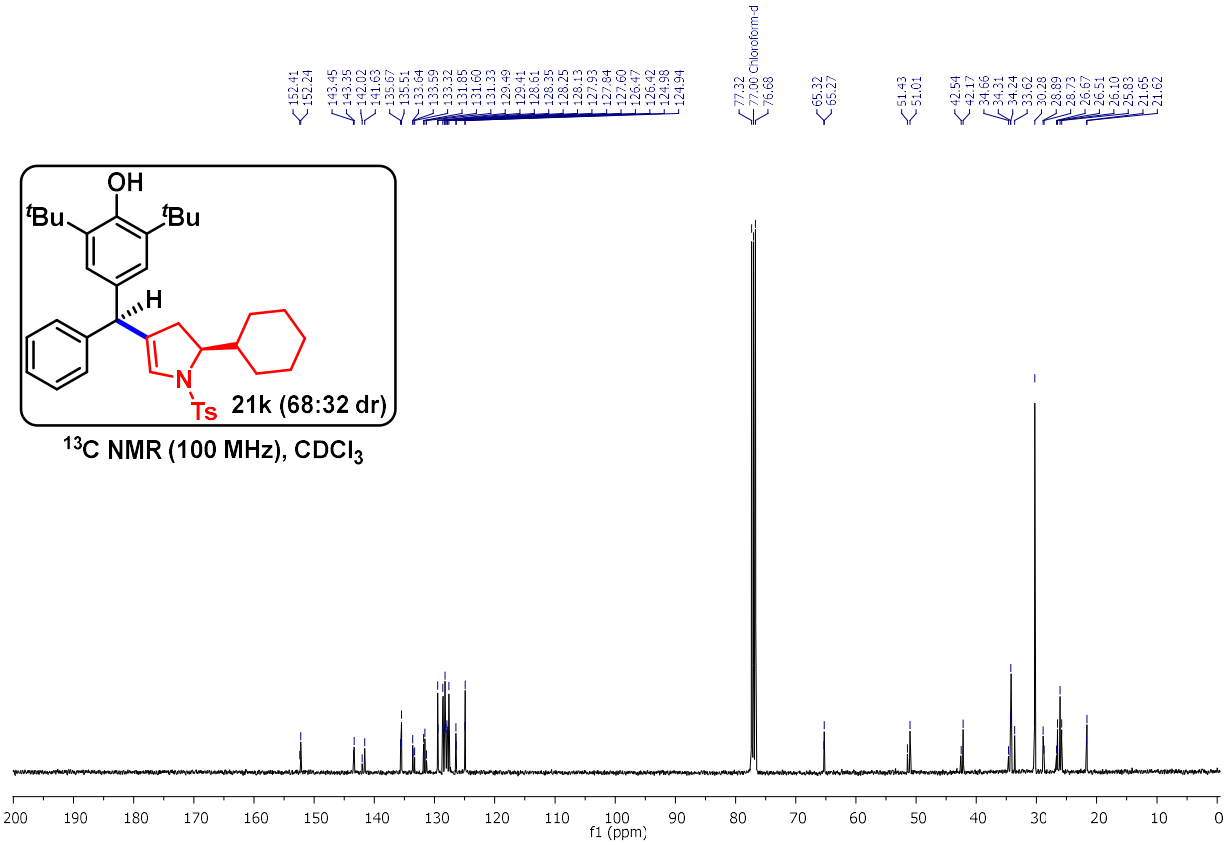
^{13}C NMR (125 MHz), $CDCl_3$

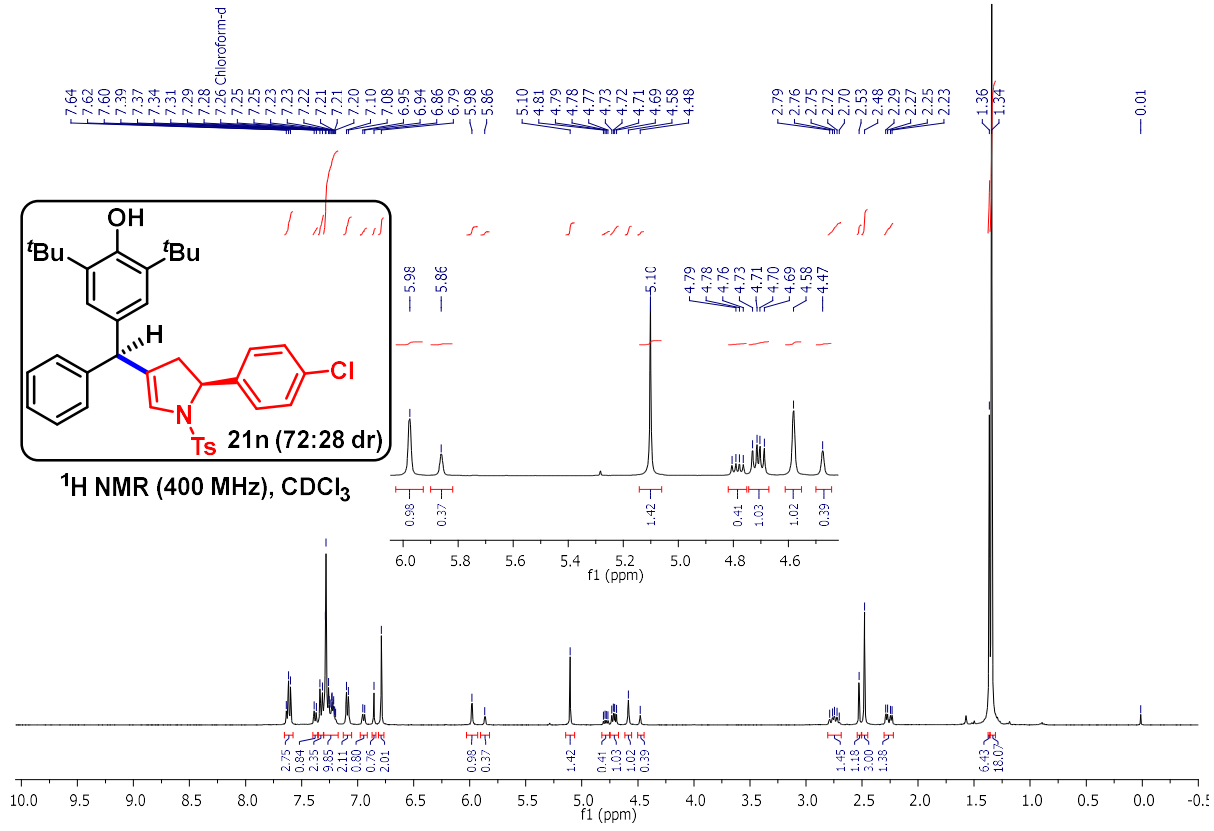


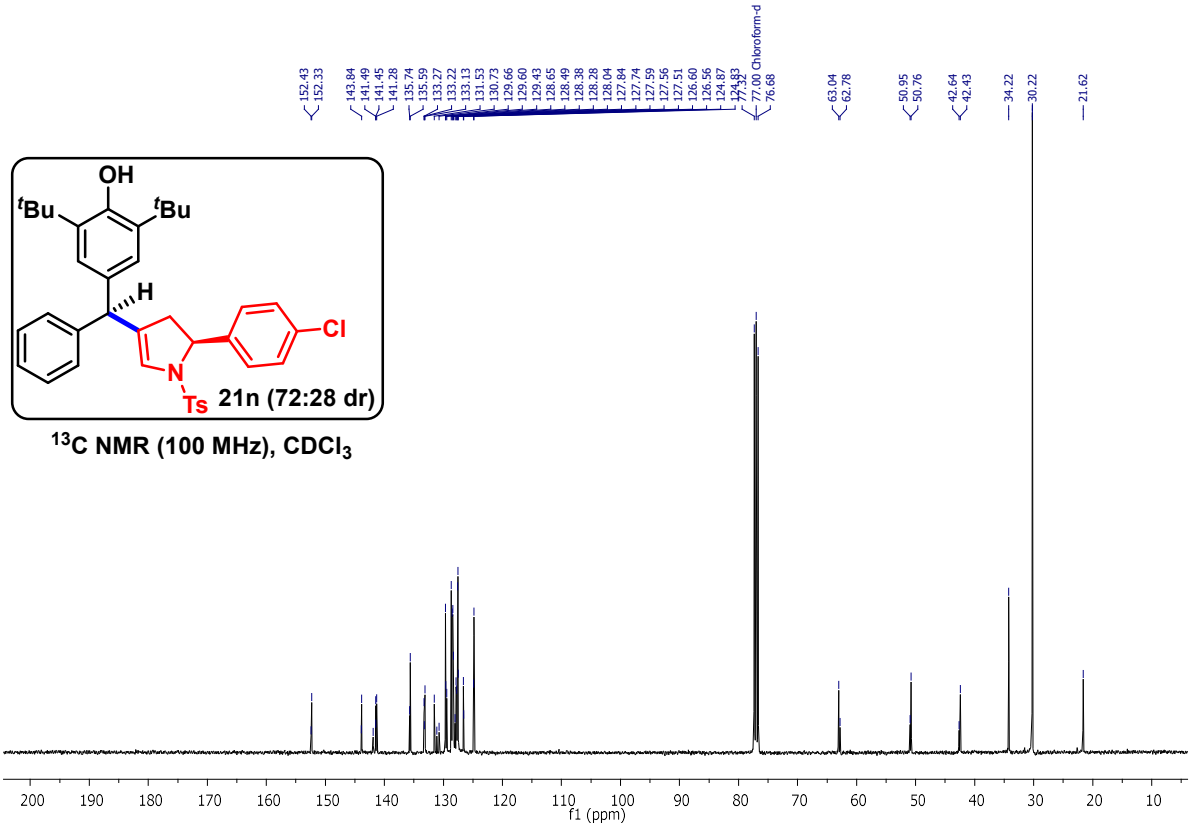
^{1}H NMR (400 MHz), $CDCl_3$

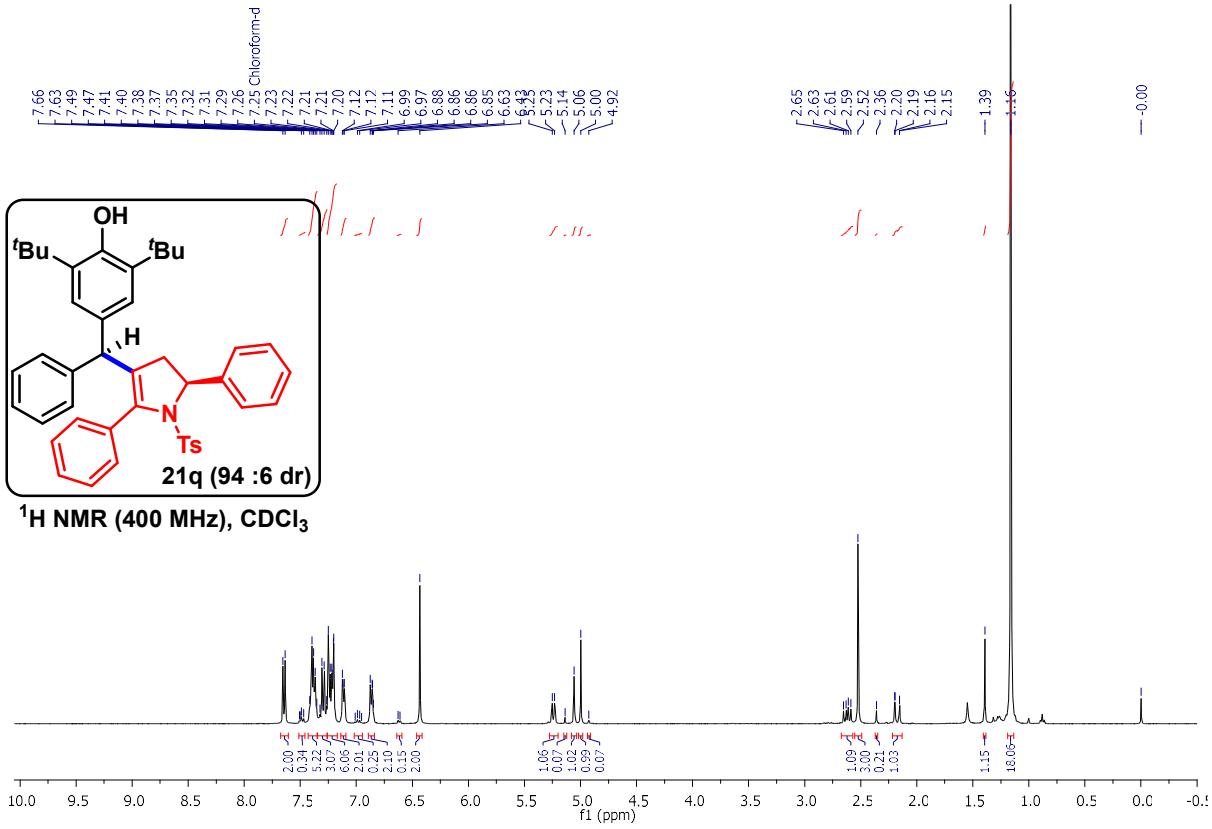

OH
tBu
tBu
N
Ts
21e
13C NMR (100 MHz), CDCl3
f1 (ppm)

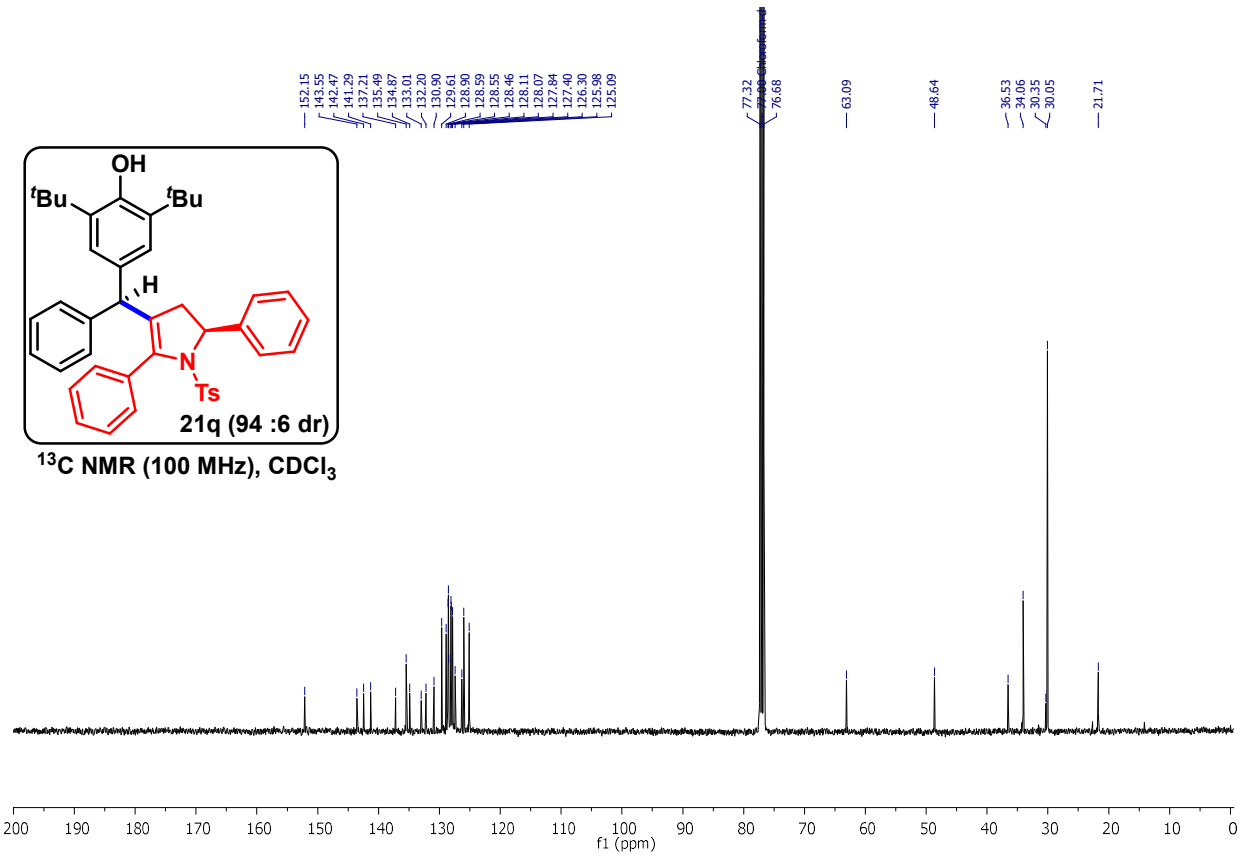

OH
tBu
tBu
H
N
Ts
21k (68:32 dr)
1H NMR (400 MHz), CDCl3
f1 (ppm)


OH
tBu
tBu
H
N
Ts
21k (68:32 dr)
13C NMR (100 MHz), CDCl3
f1 (ppm)

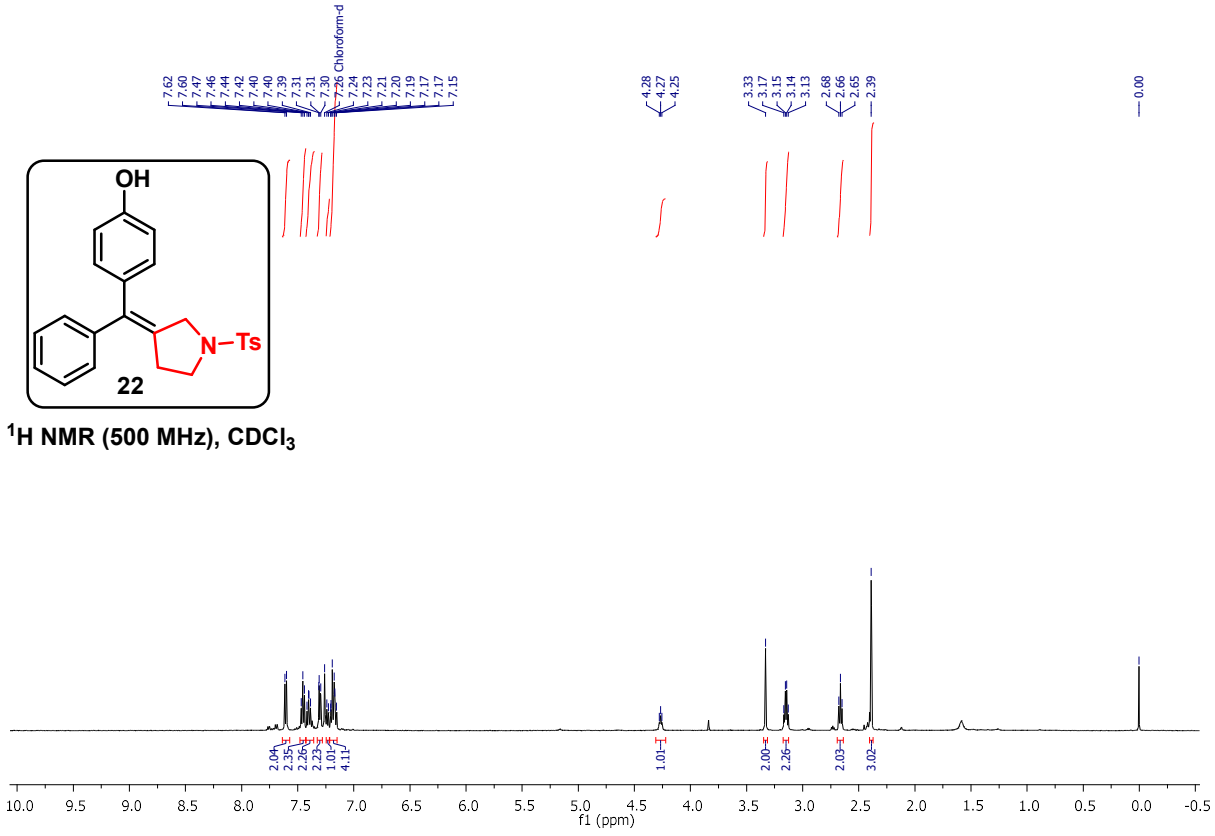

OH
tBu
tBu
H
Cl
N
Ts
21n (72:28 dr)
1H NMR (400 MHz), CDCl3
f1 (ppm)


OH
tBu
tBu
H
Cl
N
Ts
21n (72:28 dr)
13C NMR (100 MHz), CDCl3
f1 (ppm)

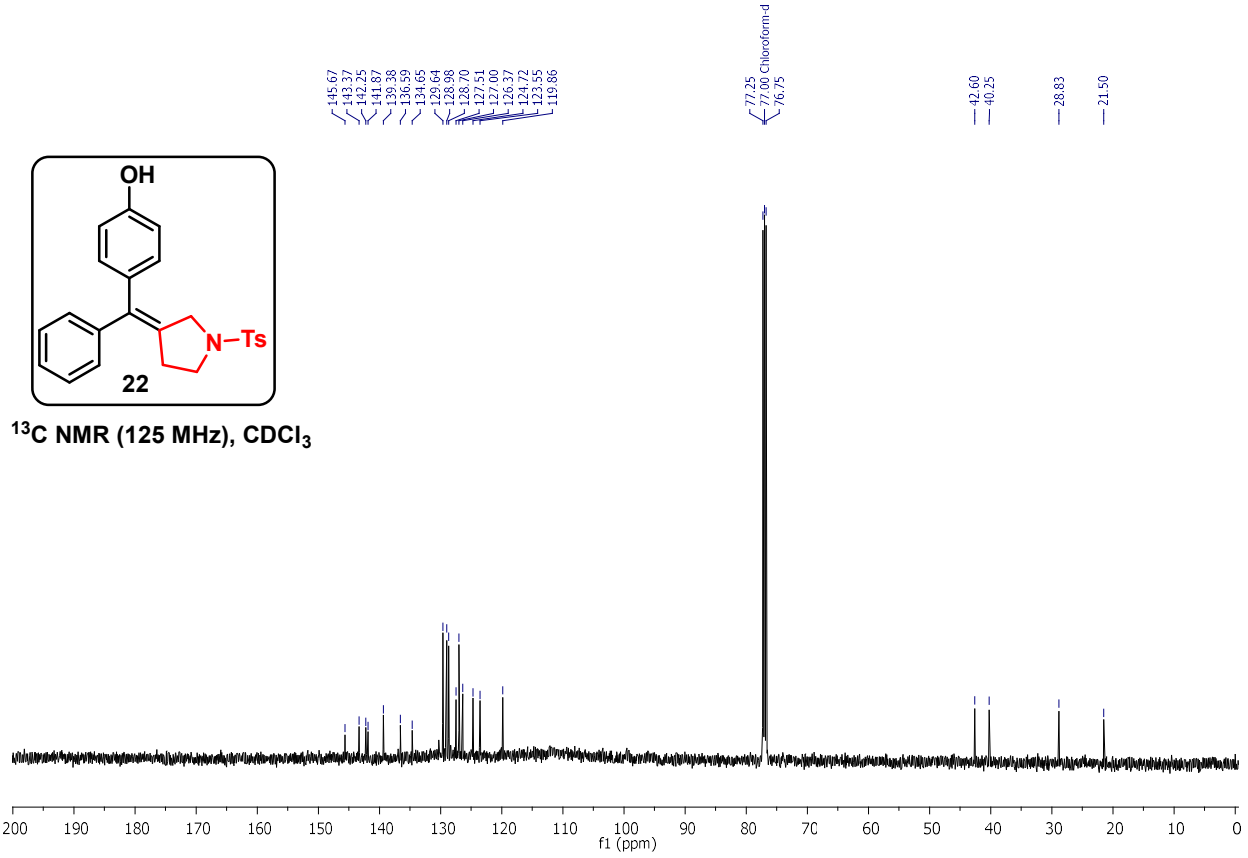

OH
tBu
tBu
H
N
Ts
21q (94 :6 dr)
1H NMR (400 MHz), CDCl3
f1 (ppm)



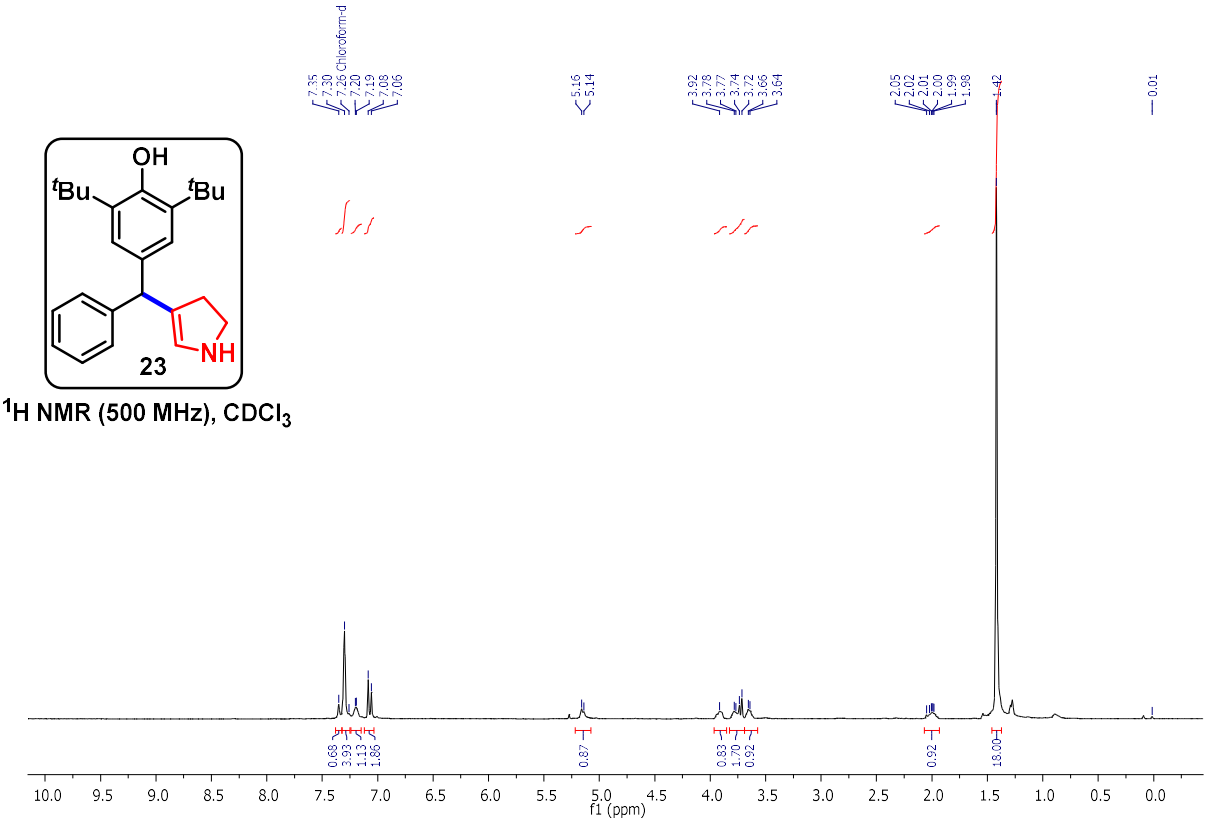
^{13}C NMR (100 MHz), $CDCl_3$



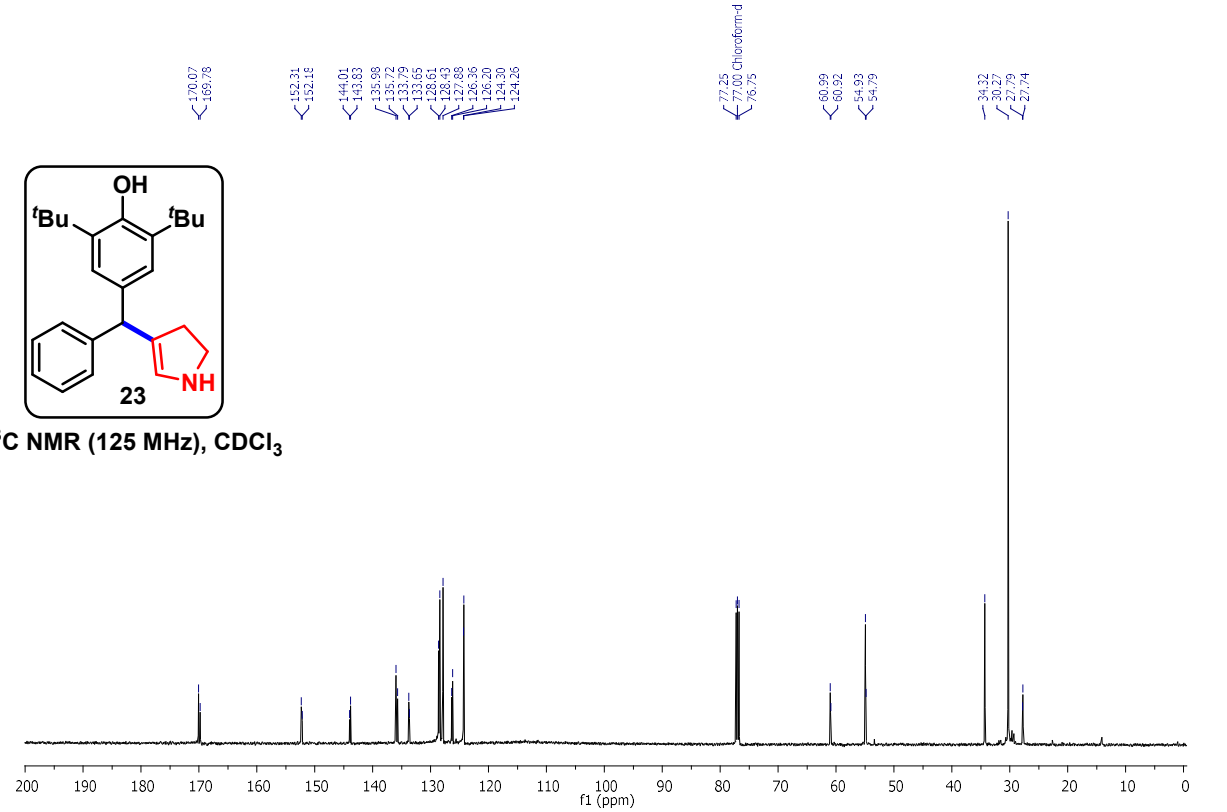
^{1}H NMR (500 MHz), $CDCl_3$



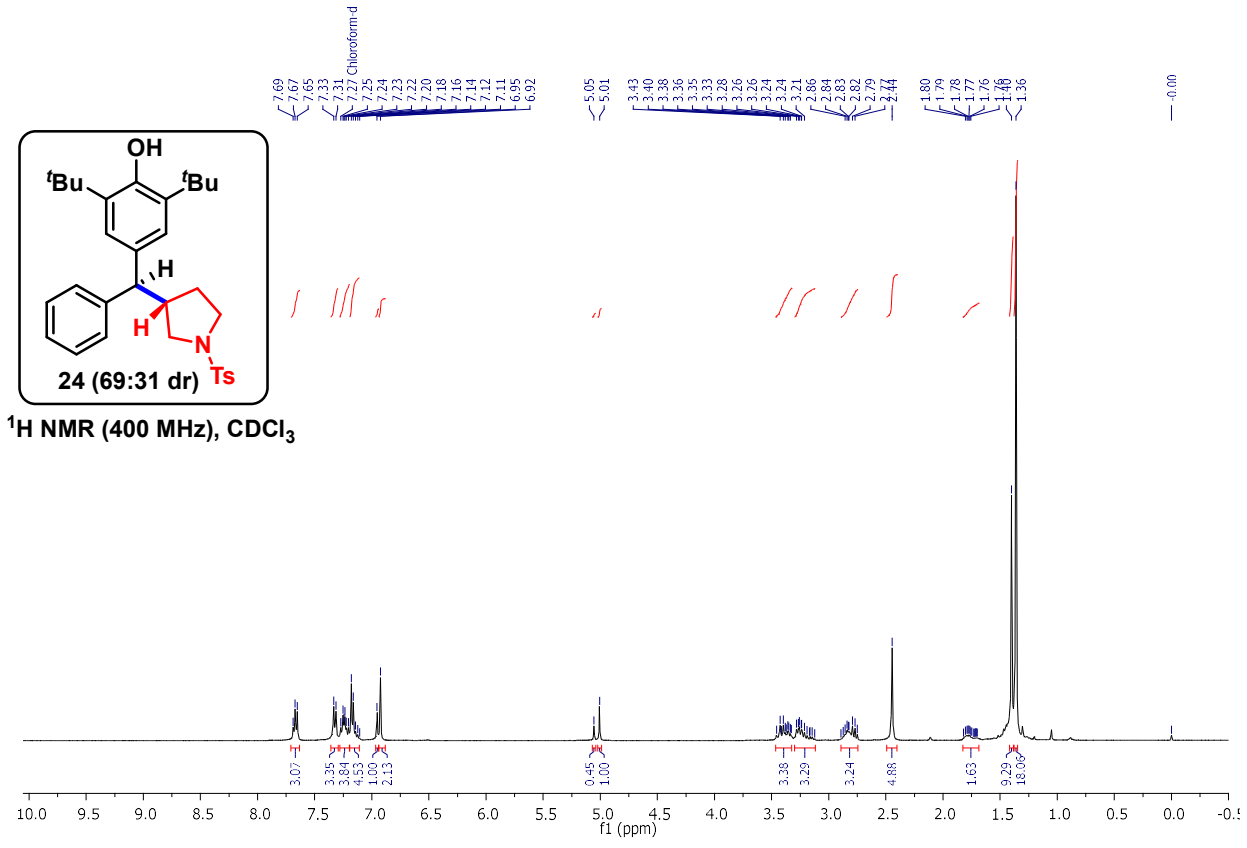
^{13}C NMR (125 MHz), $CDCl_3$



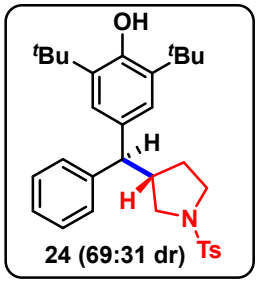
^{1}H NMR (500 MHz), $CDCl_3$



^{13}C NMR (125 MHz), $CDCl_3$

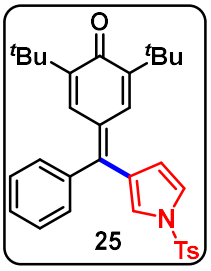


^{1}H NMR (400 MHz), $CDCl_3$



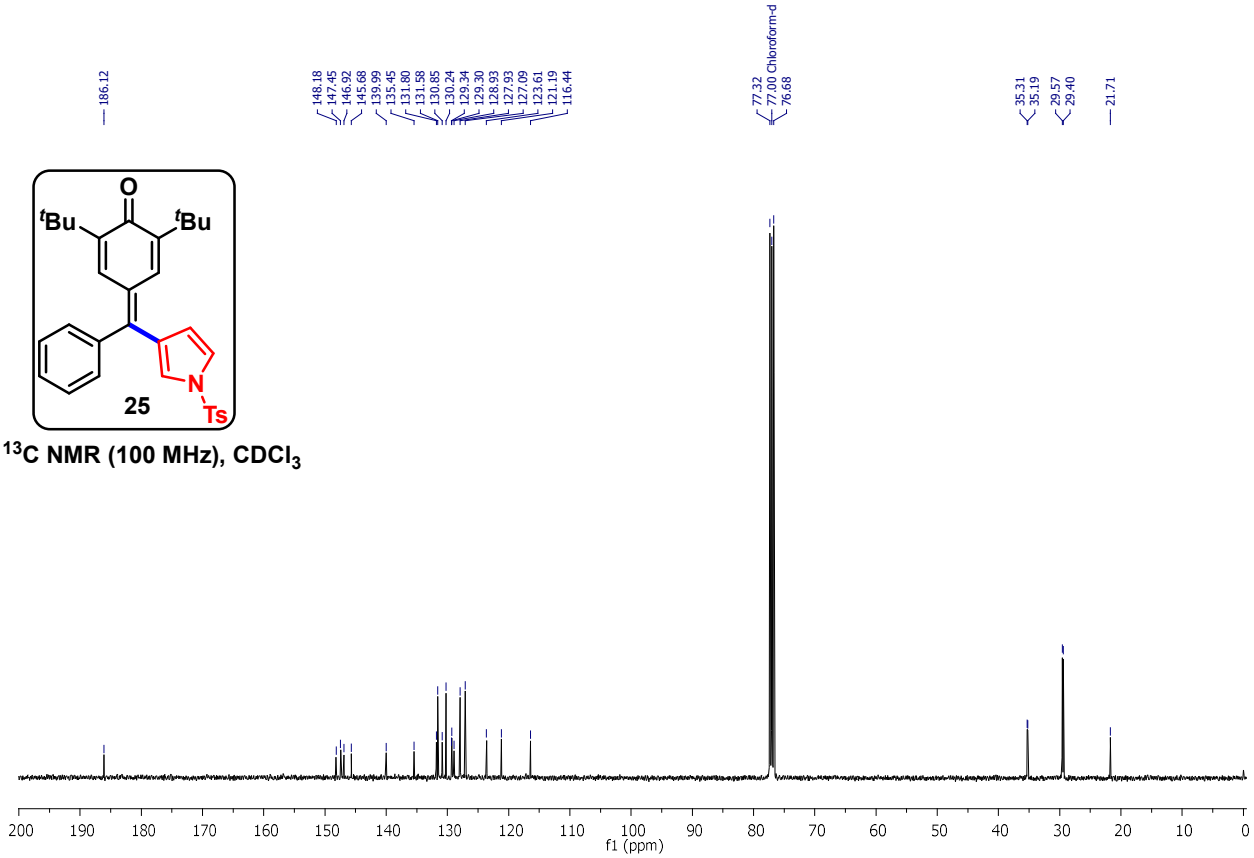
24 (69:31 dr)

^{13}C NMR (100 MHz), $CDCl_3$

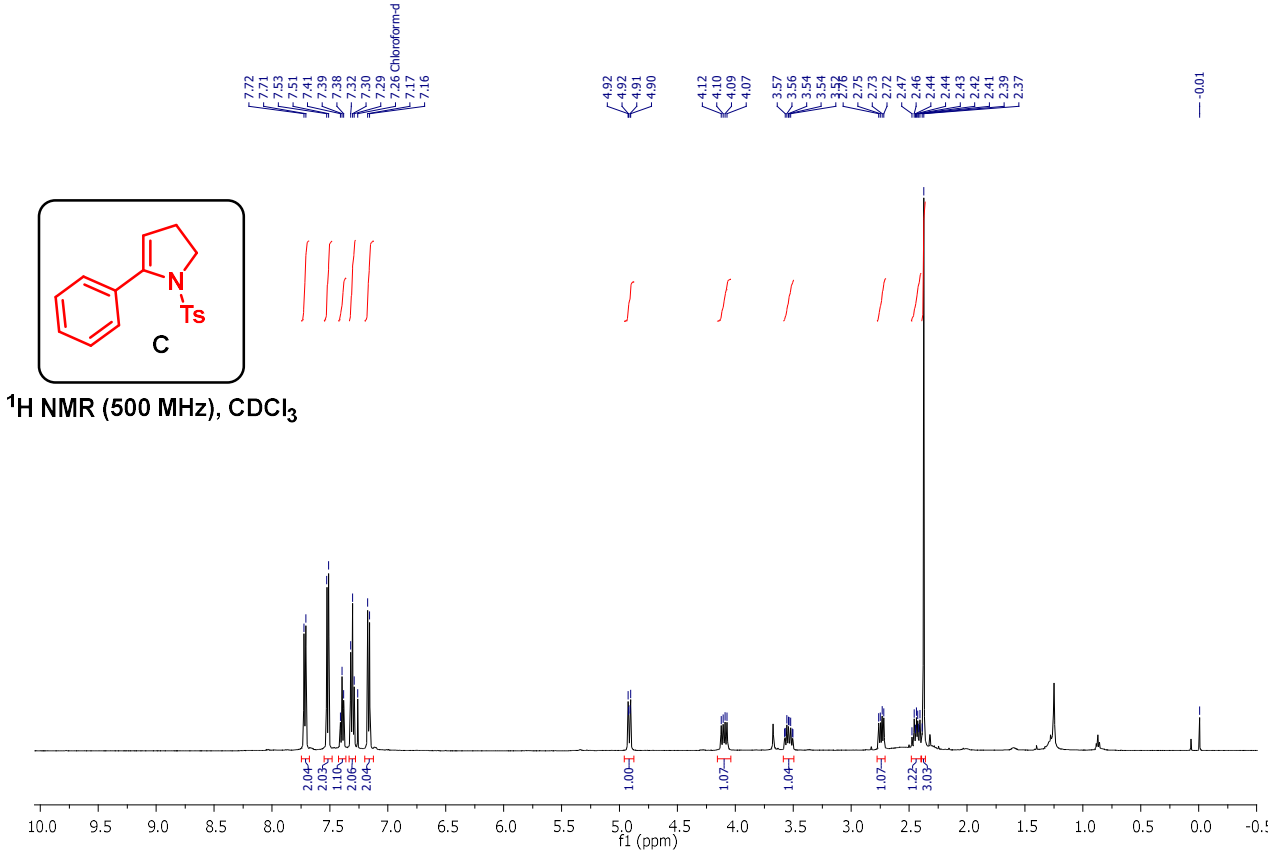


25

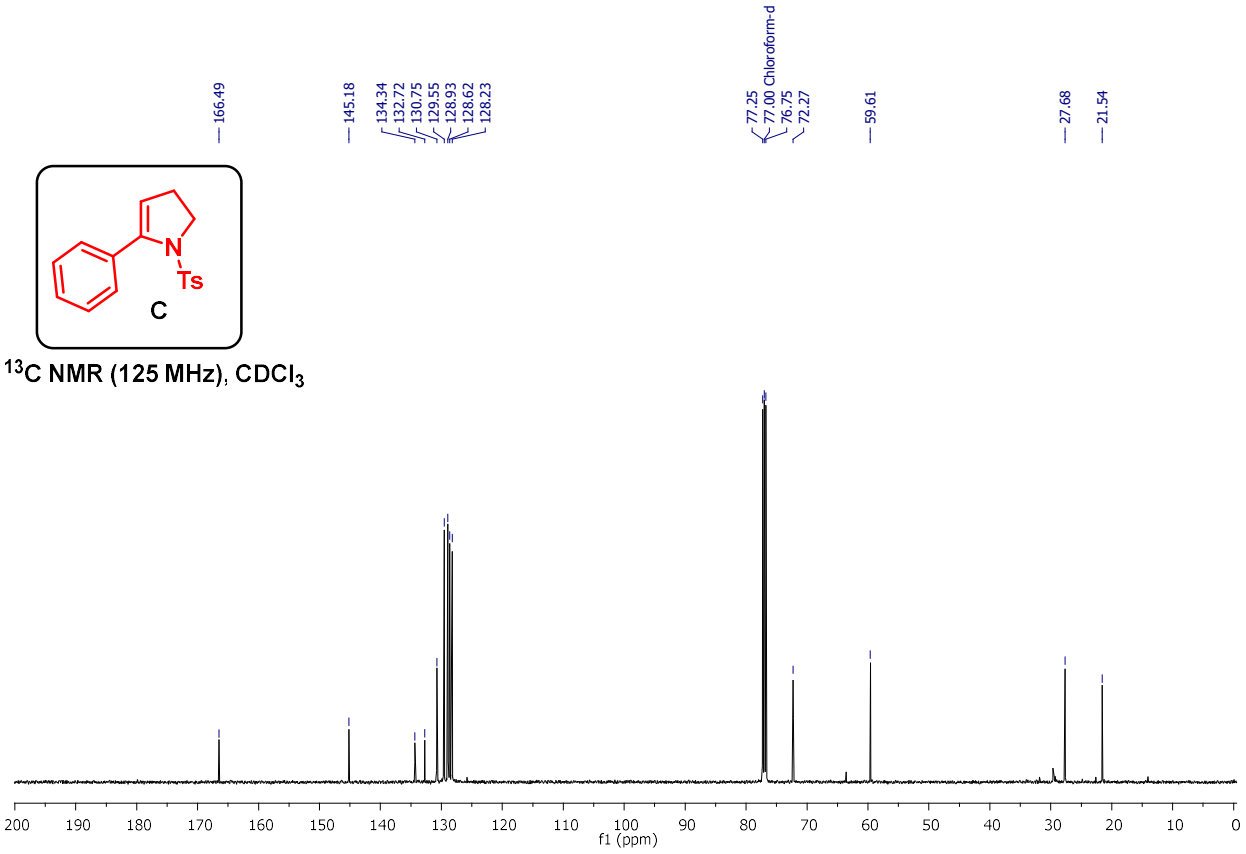
^{1}H NMR (400 MHz), $CDCl_3$



^{13}C NMR (100 MHz), $CDCl_3$



^{1}H NMR (500 MHz), $CDCl_3$



1.2.7 References

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CHAPTER-2

Lewis Acid Catalyzed 1,6-Conjugate Addition of Isocyanides to *p*-Quinone Methides for Accessing *α*-Arylated Nitriles and Amides.

Section I

Accessing *α*-Arylated Nitriles via $BF_3 \cdot OEt_2$ Catalyzed Cyanation of *para*-Quinone Methides Using *tert*-Butyl Isocyanide as a Cyanide Source

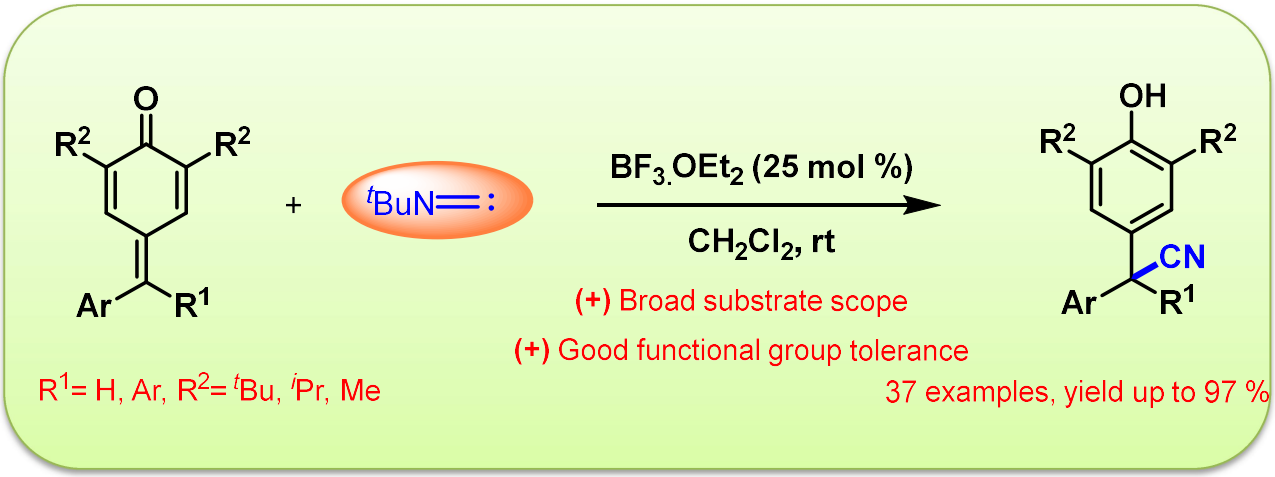
Section II

Metal-Free Aminocarbonylation of *p*-Quinone Methides with Isocyanides: Synthesis of Sterically Hindered *α*-Arylated Acetamides.

Section-I

Accessing *α*-Arylated Nitriles via $BF_3{\cdot}OEt_2$ Catalyzed Cyanation of *para*-Quinone Methides Using *tert*-Butyl Isocyanide as a Cyanide Source

In this section, $BF_3{\cdot}OEt_2$ catalyzed 1,6-conjugate addition of *tert*-butyl isocyanide to *para*-quinone methides and fuchsones for the synthesis of α-diaryl and *α*-triaryl nitriles has been reported. This protocol allows *α*-diaryl- and *α*-triaryl nitriles to be accessed in good to excellent yields and with a broad substrate scope, which could be further functionalized to give a versatile set of products. This is the first example wherein *tert*-butyl isocyanide has been used as a cyanide source for the 1,6-conjugate addition reaction.



J. Org. Chem., **2018**, *83*, 12305−12314

2.1.1 Introduction

The nitrile functional group is a very important functional group in organic chemistry. In addition, it is a highly important synthon in many natural products, dyes, herbicides, agrochemicals, functional materials and various fine chemicals.[1] They also play a significant role in drug design because of their unique electron-withdrawing and hydrogen bond acceptor properties.[2] For instance, nearly 30 nitrile-containing drugs are in the market for various diseases, and many nitrile-containing leads are in clinical development.[3] The synthesis of nitrile-containing organic frameworks, particularly α-arylated nitrile compounds, is of great importance, as these structures exist in several natural products, a vast range of functional molecules relevant to pharmaceuticals, agrochemicals, and functional materials (Figure 2.1.1).[4] For example, verapamil (**I**) is used clinically for the treatment of chronic obstructive pulmonary disease and hypertension, anastrozole (**II**) has been approved for the treatment of breast cancer, darotropium bromide (**III**) has been identified as a very potent mAchR antagonist. Diphenoxylate (**IV**) and piritramide (**V**) are other α-diaryl nitrile-based drugs used to treat diarrhea and postoperative pain, respectively. α-Triaryl nitrile derivative (**VI**) displays significant inhibitory activity against the growth of protozoa.

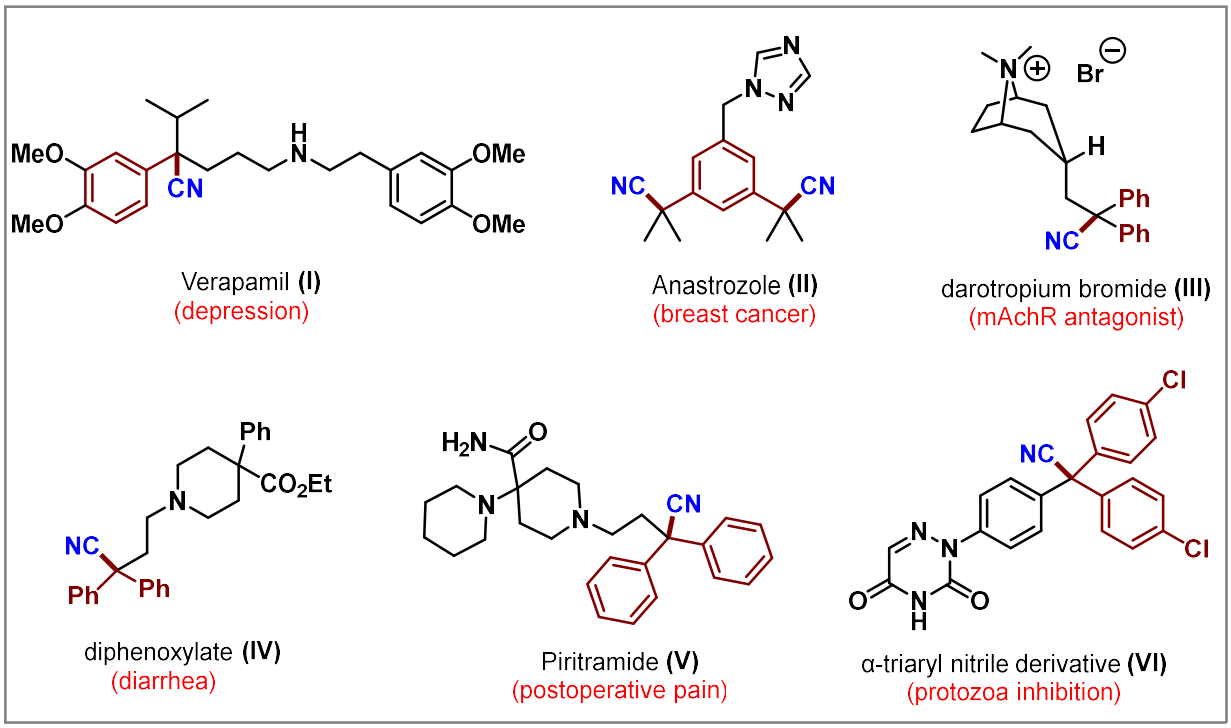


Figure 2.1.1. Representative biologically important *α*-arylated nitriles.

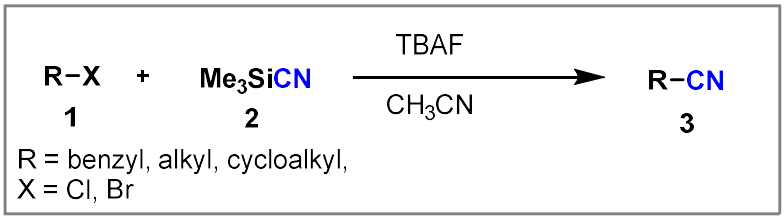
Besides the therapeutic importance, they are valuable precursors in organic synthesis for the preparation of carboxylic acids, amides, aldehydes, ketones, amidines, amines, *N*-containing

heterocycles, etc.[5] or as directing groups for remote C−H activation through weak coordination.[6] Their importance in chemistry and biology has consistently stimulated the development of methodologies for their synthesis. Consequently, several synthetic approaches toward the synthesis of *α*-arylated nitriles have been developed, mainly involving the nucleophilic substitution of a benzylic halides,[7] coupling reactions of nitriles with aryl halides,[8] addition of cyanide to diarylcarbinols,[9] dehydration of aldoximes/amides[10] and other methods.[11-13] Some of the selective approaches toward the synthesis of α-arylated nitriles are described below.

2.1.2 Literature Precedence on the Synthesis of *α*-Arylated Nitriles:

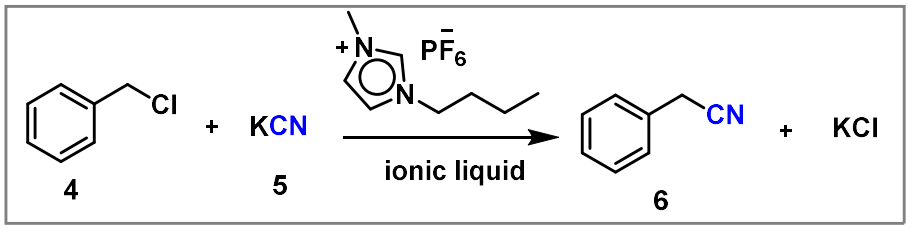
a) Nucleophilic Substitution of a Benzylic Halide:

In 1999, DeShong and co-workers reported the synthesis of α-arylated or alkylated nitriles **3** *via* nucleophilic cyanide displacement of benzyl or alkyl halides or pseudohalides **1** with trimethylsilyl cyanide **2** and tetrabutylammonium fluoride. This reaction proceeds through *in situ* generations of cyanosilicate derivatives under mild reaction conditions (Scheme 2.1.1).[7a]



Scheme 2.1.1. Cyanide displacement *via* hypervalent silicate intermediates

Eckert *et al.* in 2001 reported ionic liquids catalyzed synthesis of benzyl cyanide **6** through the nucleophilic substitution by the cyanide on benzyl chloride **4**, replacing phase transfer catalyzed biphasic system. This reaction employs ionic liquid as both catalyst and environmentally benign solvent (Scheme 2.1.2).[7b]

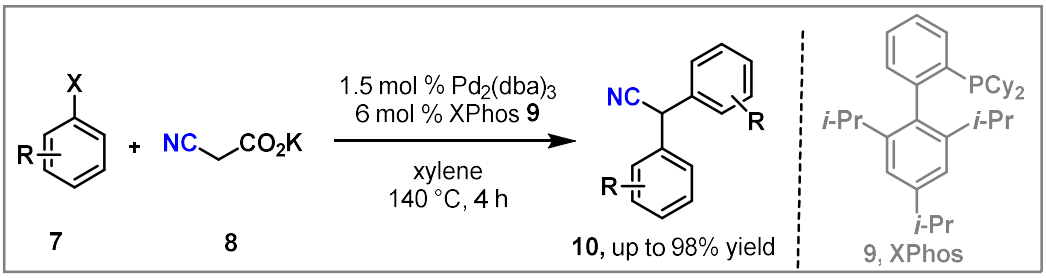


Scheme 2.1.2. Ionic liquid catalyzed cyanide displacement of benzyl chloride.

b) Coupling Reactions of Nitriles with Aryl Halides:

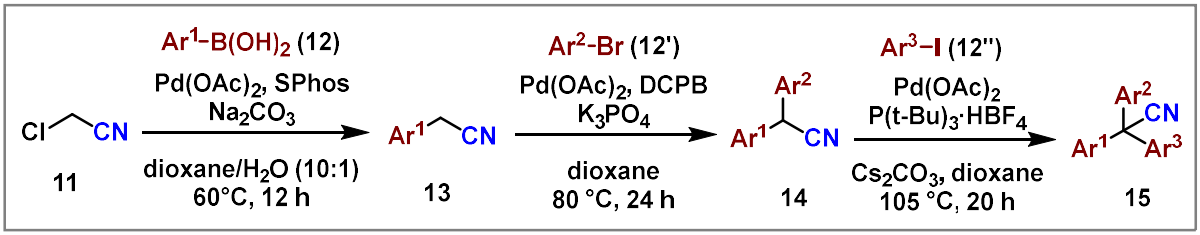
In 2011, Kwong and co-workers developed a palladium-catalyzed decarboxylative coupling of potassium cyanoacetate **8** with aryl bromides or chlorides **7** (Scheme 2.1.3).[8a] The reaction conditions feature the absence of other strong inorganic bases and provide ester functional

group tolerance. With $Pd_2(dba)_3$ and XPhos ligand **9** as the catalyst, α-diaryl nitriles **10** can be obtained in good yields.



Scheme 2.1.3. Pd-catalyzed arylation of potassium cyanoacetate

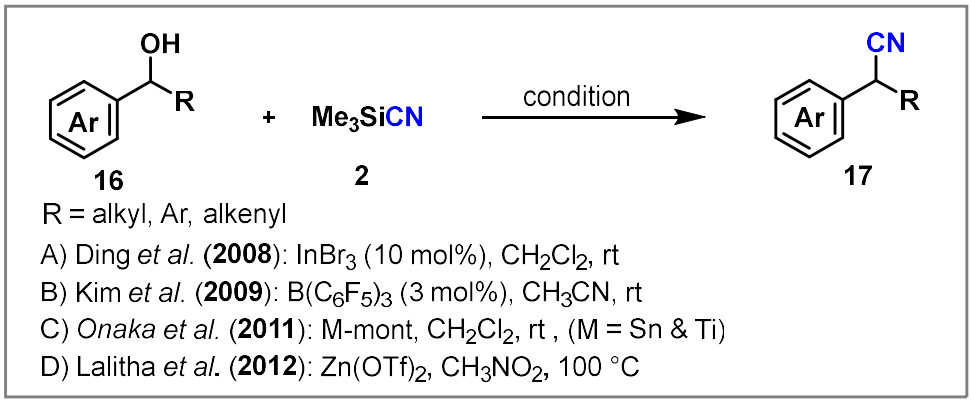
Crudden *et al*. in 2015 reported the selective three-step protocol for the synthesis of un-symmetrical sterically hindered α-tri-aryl nitriles **15** *via* sequential Pd-catalyzed arylations of chloroacetonitrile **11** (Scheme 2.1.4).[8b] This method enables Pd-catalyzed selective installation of three aryl groups *via* Suzuki−Miyaura cross-coupling reaction followed by back-to-back C−H arylations to afford α-tri-aryl nitriles **15** with no over-arylation at any step.



Scheme 2.1.4. Pd-catalyzed sequential arylation of acetonitriles.

c) Addition of Cyanide to Diarylcarbinols or Masked Diarylcarbinols or with *p*-QMs:

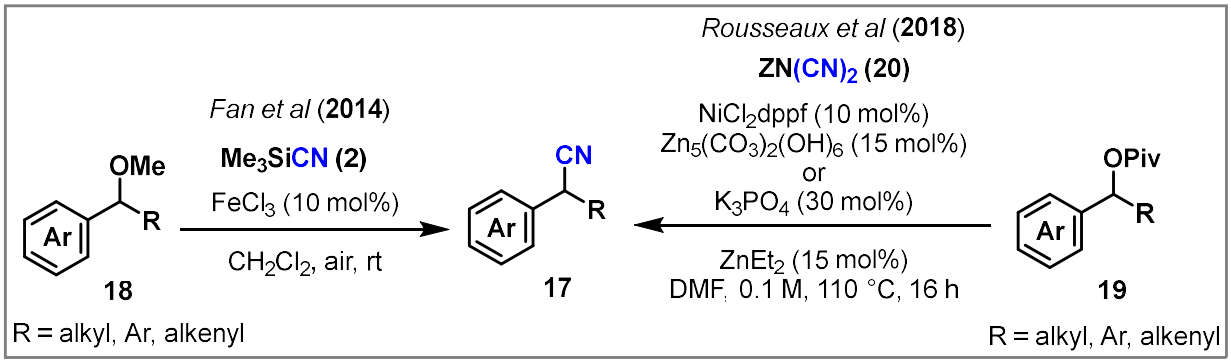
In 2008 Ding *et al*. and Kim *et al*. in 2009, individually developed direct cyanation of benzylic or allylic alcohols **16** under Lewis acid catalysis (Scheme 2.1.5A and 2.1.5B).[9a,b] This method converted a variety of α-aryl alcohols to the corresponding nitriles **17** in good to excellent yields.



Scheme 2.1.5. Direct cyanation of benzylic alcohols using Me_3SiCN.

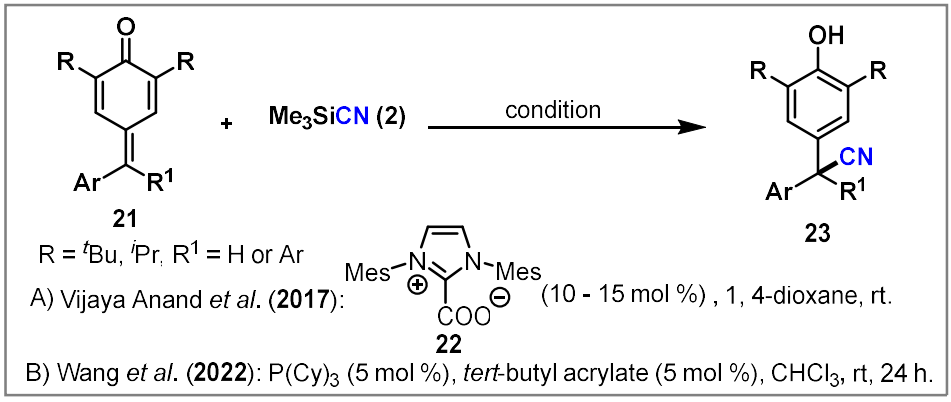
Onaka *et al.* in 2011 reported Brønsted acid montmorillonite catalyzed cyanation of various secondary or tertiary benzylic and allylic alcohols **16** with Me_3SiCN **2** to prepare α-arylated nitriles in good to excellent yields (Scheme 2.1.5C).[9c] Similarly, in 2012, Lalitha and co-workers developed $Zn(OTf)_2$ catalyzed cyanation of benzylic alcohols **16** with Me_3SiCN **2** as a cyanation agent for the synthesis of a variety of *α*-arylated nitriles **17** in good to excellent yields (Scheme 2.1.5D).[9d]

In 2014, Fan and co-workers developed an iron-catalyzed Csp^3 ether bond cleavage with C–C bond formation in the reaction of *π*-activated ethers **18** with Me_3SiCN **2** for the synthesis of diverse *α*-arylated nitriles **17** (Scheme 2.1.6).[10a] On similar lines, in 2018, Rousseaux and group reported nickel-catalyzed cyanation reaction of benzylic and allylic pivalate esters **19** using an air-stable Ni(II) precatalyst and substoichiometric quantities of $Zn(CN)_2$ **20** as a cyanide source (Scheme 2.1.6). [10b]



Scheme 2.1.6. Synthesis of α-arylated nitriles from the benzylic ether or pivalate esters.

In 2017, Vijaya Anand and co-workers developed an efficient *N*-heterocyclic carbene (NHC) **22** catalyzed 1,6-conjugate addition of cyanide to *p*-quinone methides (*p*-QMs) **1** and fuchsones for accessing a wide range of *α*-diaryl and *α*-triaryl nitriles derivatives **23** (Scheme 2.1.7A).[11a]



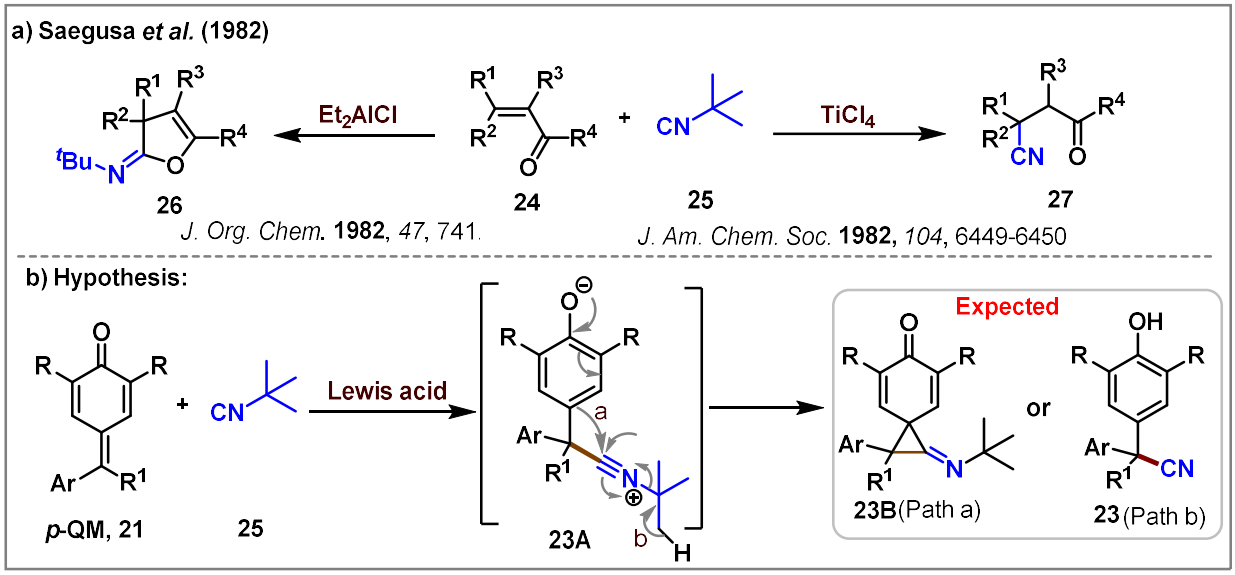
Scheme 2.1.7. 1,6-Cyanation reaction of *p*-QMs and fushones using Me_3SiCN

Similarly, very recently, Wang *et al*. reported an efficient *in situ* generation of phosphonium salt Lewis base catalyst by combining $P(Cy)_3$ and *tert*-butyl acrylate and its application in promoting 1,6-cyanation reaction of *p*-QMs and fushones (Scheme 2.1.7B).[11b] Both the methods delivered a diverse range of *α*-diaryl and *α*-triaryl nitriles **23** in high yields and relied on Me_3SiCN as a cyanide source and NHC or phosphonium salt catalyst to activate Me_3SiCN.

2.1.3 Present Work

2.1.3.1 Statement of the Problem

Most of the methods described above for the synthesis of *α*-arylated nitriles suffer from certain drawbacks such as harsh reaction conditions, expensive catalysts and the usage of notorious toxic cyanide sources etc. Therefore, developing a robust strategy aiming at synthesising diverse functional group-rich *α*-aryl-nitriles is highly desirable. On the other hand, isocyanides are useful C1 building blocks in organic synthesis and have a wide variety of applications in medicinal chemistry and materials science.[14] In particular, *tert*-butyl isocyanide is a highly interconvertible isocyanide found in various applications as a versatile C1 source in synthetic organic chemistry. The easily cleavable *tert*-butyl group makes it a useful cyano and CO source. Significantly, in recent years *tert*-butyl isocyanide has been efficiently utilized as an alternative "CN" source under transition metal catalysis avoiding the use of toxic metal cyanides.[15,16.]



Scheme 2.1.8. Hypothesis of 1,6-addition of *tert*-butyl isocyanide to *p*-QMs

In 1982, Saegusa *et al*.[17a] reported organoaluminum (Et_2AlCl) promoted cycloaddition of isocyanides to *α,β*-unsaturated carbonyl compounds to produce unsaturated *N*-substituted iminolactones **26**. In a similar line, the same group in 1982 described a $TiCl_4$-mediated conjugate hy-

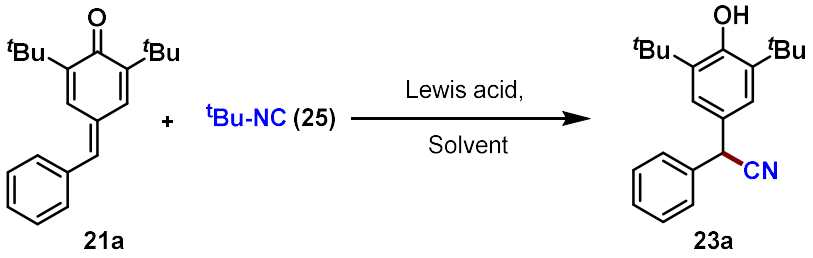
drocyanation of activated *α,β*-unsaturated carbonyl compounds with *tert*-butyl isocyanide **25** to give *β*-cyano ketone derivatives **27**.[17b] Inspired by this work, we envisioned that the reaction of *p*-quinone methide (*p*-QMs) **21** with *tert*-butyl isocyanide **25** in the presence of appropriate Lewis acid could lead to the formation of spiro-product **23B** (path a) or *α*-diaryl nitrile **23** (path b). With this aim, we chose to explore *tert*-butyl isocyanide as an alternate and safe cyanide source,[18] avoiding the use of toxic cyanides for the 1,6-conjugate addition reaction of *p*-QM. In this section, we describe the amenability of *tert*-butyl isocyanide as a source of cyanide for the successful preparation of *α*-diaryl and *α*-triaryl nitriles from *p*-QMs. To the best of our knowledge, this is the first example wherein *tert*-butyl isocyanide has been used as a cyanide source for the 1,6-conjugate addition reactions.

2.1.4 Results and Discussion

2.1.4.1 Optimization of Reaction Conditions

We began our optimization studies with *p*-quinone methide **21a**, which contains removable *t*-Bu groups at the ortho positions and *tert*-butyl isocyanide **25** as a source of cyanide under variable reaction conditions (Table 2.1.1). An initial experiment was conducted with **21a** and **25** in the presence of 20 mol% $Sc(OTf)_3$ as a catalyst in CH_2Cl_2 solvent at room temperature. Gratifyingly, the desired product **23a** was isolated in a 36% yield after 30 mins (Table 2.1.1, entry 1). The structure of compound **23a** was characterized with the help of spectral and analytical data and completely matched with the product. In the ^1H NMR spectra of compound **23a**, signal at δ 5.07 (s, 1H) is due to methine proton (-CH), and a signal at δ 5.26 (s, 1H) corresponds to the phenolic (-OH). In addition, the appearance of typical carbon signals at δ 120.3 is due to nitrile functionalities, and the signal at δ 42.5 is attributed to the methine carbon. Further, the HRMS (ESI-TOF) m/z: $[M–H]^-$ the peak of **23a** at 320.2024 corresponds to formula $C_{22}H_{26}NO$ (calculated value 320.2009), confirms the structure of **23a**. With this structure confirmation and encouraged by the initial result, we next screened various Lewis acid catalysts, such as $Bi(OTf)_3$, $BF_3.(OEt)_2$, $Yb(OTf)_3$, $TiCl_4$, $InCl_3$ and $Cu(OTf)_2$ (Table 2.1.1, entries 2-7) to define the best catalyst for this transformation. Among the above Lewis acid catalysts examined, $BF_3.(OEt)_2$ was found to be the most effective one to give the desired product **23a** in 64% yield (Table 2.1.1, entry 3). The reaction conditions were further optimized by varying solvents such as THF, Et_2O, CH_3CN, & DMSO and the results revealed that CH_2Cl_2 was superior to other solvents. (Table 2.1.1, entry 3 vs entries 8-11). Interestingly, increasing the equivalents of ^{t}BuNC to 1.3 equiv., the desired product formation was observed in 76% yield (Table 2.1.1, entry 12). Next

Table 2.1.1. Optimization of reaction conditions[a,b]



Entry	Cat.	^{t}Bu-NC (equiv)	Solvent	Yield (%), 23a
1	$Sc(OTf)_3$	1.0	CH_2Cl_2	36
2	$Bi(OTf)_3$	1.0	CH_2Cl_2	42
3	$BF_3.OEt_2$	1.0	CH_2Cl_2	64
4	$Yb(OTf)_3$	1.0	CH_2Cl_2	<10
5	$TiCl_4$	1.0	CH_2Cl_2	14
6	$InCl_3$	1.0	CH_2Cl_2	trace
7	$Cu(OTf)_2$	1.0	CH_2Cl_2	32
8	$BF_3.OEt_2$	1.0	THF	trace
9	$BF_3.OEt_2$	1.0	Et_2O	27
10	$BF_3.OEt_2$	1.0	CH_3CN	41
11	$BF_3.OEt_2$	1.0	DMSO	n.r.
12	$BF_3.OEt_2$	1.3	CH_2Cl_2	76
13	$BF_3.OEt_2$	1.3	CH_2Cl_2	59[b]
14	**$BF_3.OEt_2$**	**1.3**	**CH_2Cl_2**	**90[c]**
15	$BF_3.OEt_2$	1.3	CH_2Cl_2	88[d]
16	$BF_3.OEt_2$	1.5	CH_2Cl_2	92[c]
17	--	1.3	CH_2Cl_2	n.r.[e]

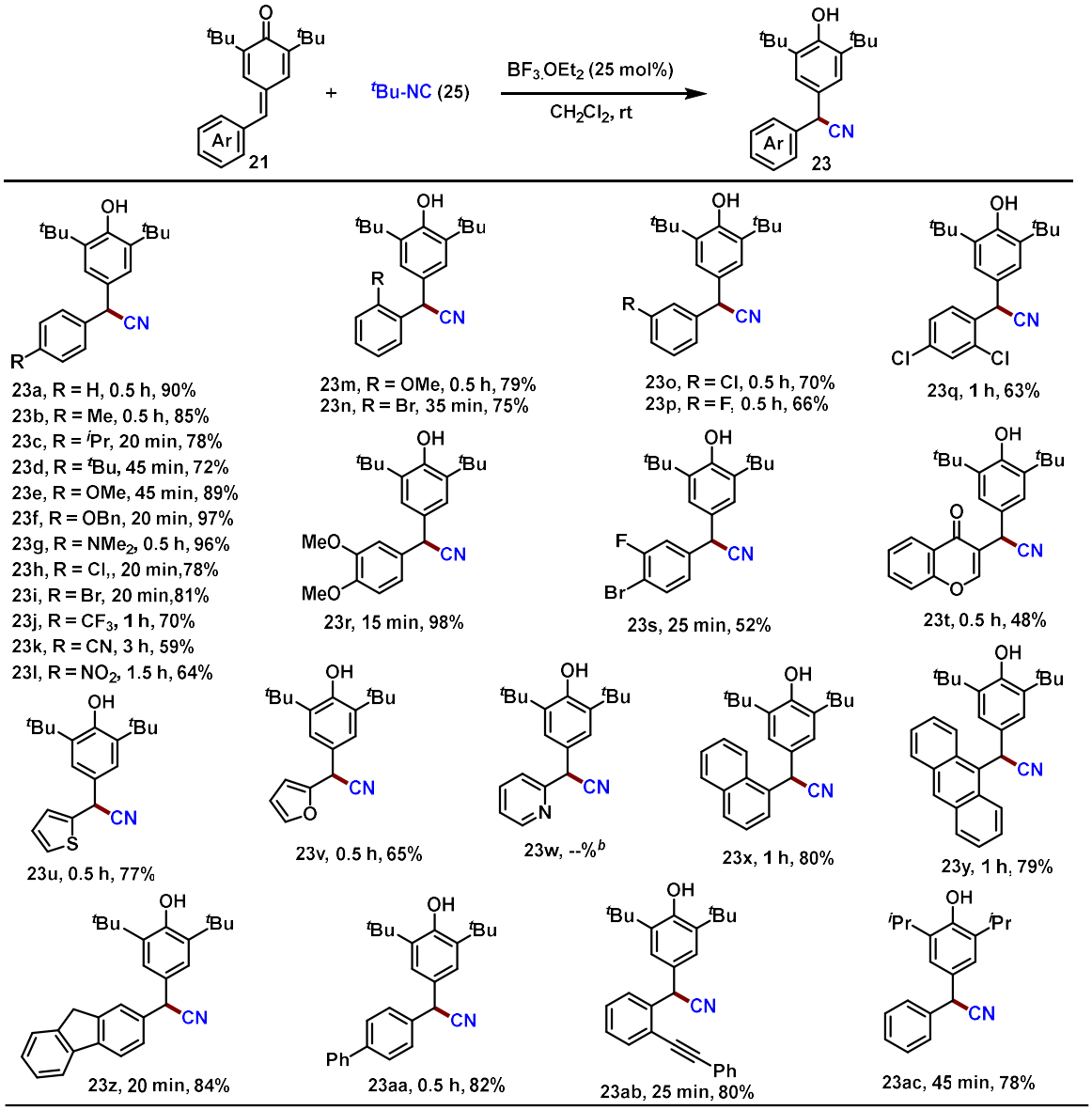
[a]Performed with *p*-QMs **21a** (0.1 mmol), [t]BuNC **25** (0.1 mmol) and 20 mol % of Lewis acid in solvent (1 mL) at room temperature. [b]10 mol% of $BF_3.OEt_2$ was used, [c]25 mol% of $BF_3.OEt_2$ was used, [d]30 mol% of $BF_3.OEt_2$ was used [e]Without catalyst.

we examined the effect of catalyst loading, and it was observed that 25 mol% of $BF_3.(OEt)_2$ appears ideal for this reaction as it provides the desired product in 90% yield (Table 2.1.1, entry 12-14). Further, increasing catalyst loading and variation in the stoichiometric quantity of ^{t}BuNC did not have much impact on the reaction efficiency (Table 2.1.1, entry 15,16). No product was detected when the reaction was performed without the catalyst (Table 2.1.1, entry 17).

2.1.4.2 Scope of the Reaction: Substituents on the *p*-QMs

With the optimized reaction conditions in hand, we next explored the scope of the reaction with respect to *p*-quinone methides (*p*-QMs) (Table 2.1.2). It has been observed that a broad

Table 2.1.2. Substrate scope of the reaction with *p*-QMs[a]



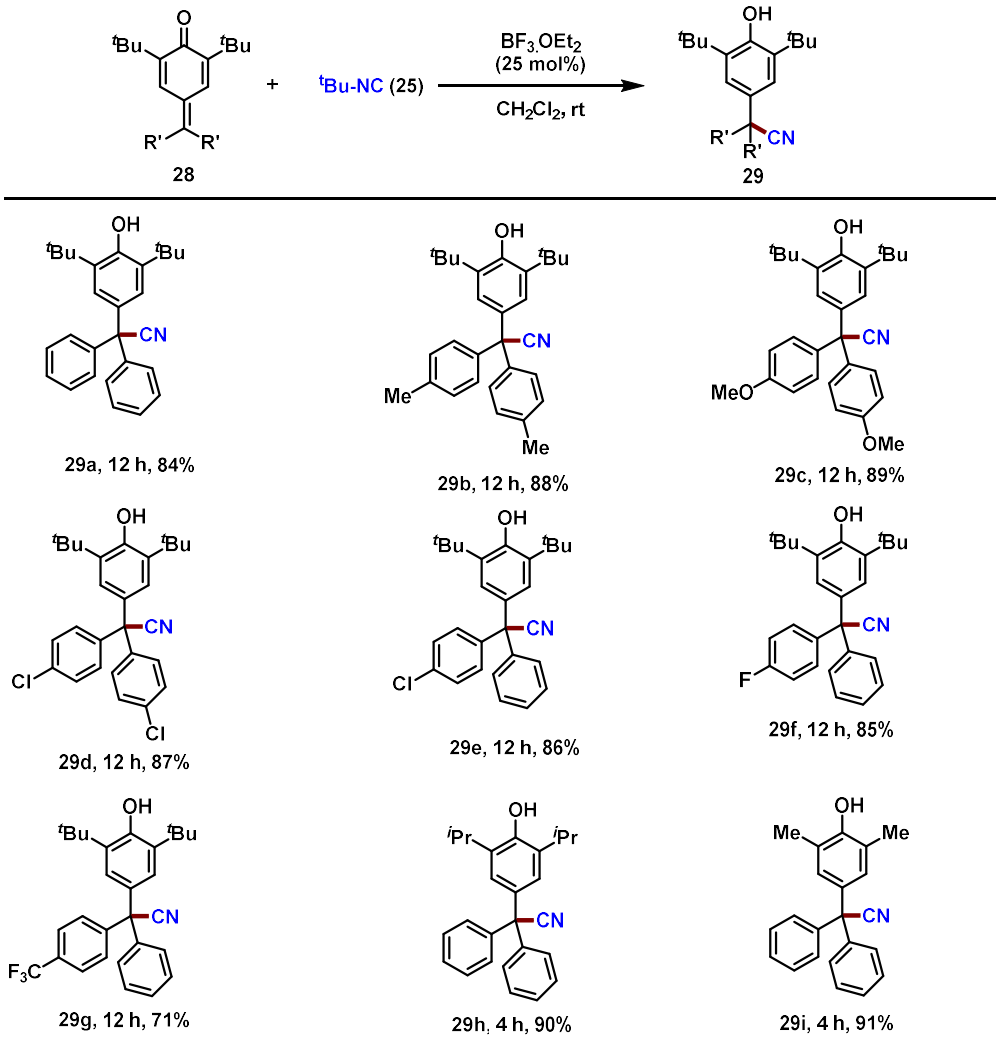
[a]Performed with *p*-QMs **21** (0.1 mmol) ^{t}Bu-NC **25** (0.13 mmol) and $BF_3.OEt_2$ (25 mol %) in CH_2Cl_2 (1 mL) at room temperature. [b]No desired product formation.

range of *p*-QMs reacted with *tert*-butyl isocyanide to furnish the corresponding products (**23a-23ac**) in 48−97% yields. Both electron-donating (R = -Me, -OMe, -NMe_2) and electron-withdrawing groups (R = -CN, -NO_2) at the para, ortho or meta positions of the benzene rings were well tolerated, offering the desired products in good to excellent yields (**23a-23p**). The halo-substituted *p*-QMs are also well-tolerated to yield the desired product in moderate to good yields. Furthermore, di-substitution on the benzene ring of *p*-QMs was also found to be suitable substrates, and the corresponding products (**23q-23s**) were isolated under optimal conditions. Interestingly, *p*-QM (**21t**) derived from the chromone-3-carboxaldehyde also works well to result in the desired cyano-addition product **23t** in 48% yield. Heterocyclic substituted *p*-QMs, like furan and thiophene, were also amenable to this protocol and generated the corresponding cyano products in good yields (65 & 77%, **23u-23v**). However, pyridyl ring bearing *p*-QM failed to afford the desired product (**23w**). Notably, the sterically hindered naphthyl, anthracenyl, fluorenyl, and biphenyl substitution-bearing *p*-QMs were also susceptible in this process to furnish the desired cyano-product (**23x-23aa**) in good yields (79-84%). It is noteworthy to mention that the alkyne group tethered *p*-QM was also well tolerated under optimized reaction conditions to afford the desired product (**23ab)** in good yield (80%). Additionally, *p*-QM (**21ac)** bearing two isopropyl groups at the ortho position was also well-tolerated to afford the product **23ac** in a 78% yield.

2.1.4.3 Scope of the Reaction with Different Fuchsones

Next, we examined the scope of this cyanation reaction with respect to fuchsones as a 1,6-acceptor (Table 2.1.3). Due to more steric hindrance and low reactivity of fuchsones, their 1,6-addition reactions are rare. Interestingly, under this protocol, various fuchsones also efficiently underwent a 1,6-conjugate addition reaction with *tert*-butyl isocyanide under the optimized reaction conditions to produce *α*-triaryl nitriles (**29a-29i**) in excellent yields. It should be noted that, in general, the synthesis of *α*-triaryl nitriles requires multistep processes, and it is often difficult to access these compounds due to steric constraints.[8b] Fuchsones possessing both electron-donating (-Me, -OMe) (**28b-28c**), halo-substituted (-F, -Cl) (**28d-28f**) and electron-withdrawing group (-CF_3) (**28g**) were well tolerated to afford the desired *α*-triaryl nitriles. Fuchsones bearing electron-donating groups at the *para* positions showed higher reactivity than those bearing electron-withdrawing groups. Other fuchsones derived from 2,6-di-isopropyl phenol (**28h**) and 2,6-dimethylphenol (**28i**) also underwent a smooth transformation to their corresponding *α*-triaryl nitriles **29h** and **29i** in 90 and 91% yields, respectively.

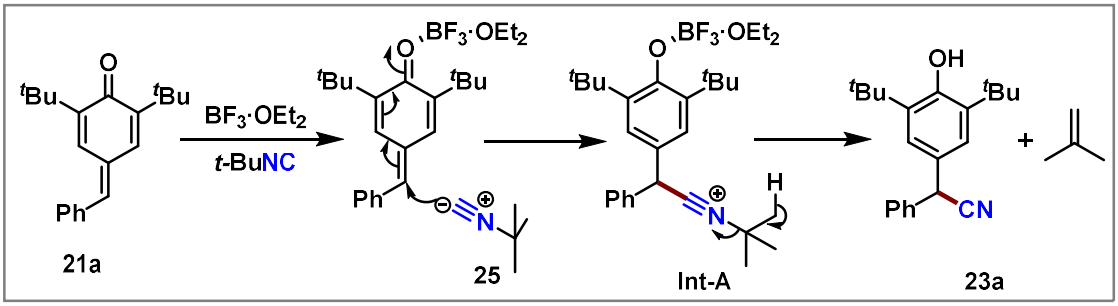
Table 2.1.3. Substrate scope with different fuchsones[a]



[a]Performed with fuchsones **28** (0.1 mmol) ^{t}Bu-NC **25** (0.15 mmol) and $BF_3.OEt_2$ (25 mol %) in CH_2Cl_2 (1 mL) at room temperature.

2.1.4.4 Plausible Reaction Mechanism

A plausible reaction mechanism for this transformation is depicted in Scheme 2.1.9.[19.]



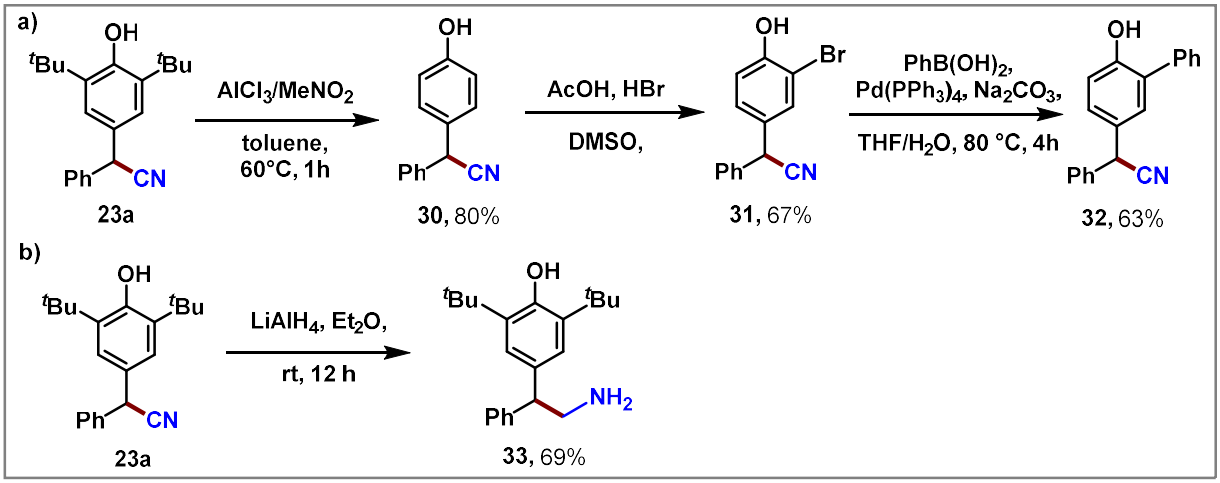
Scheme 2.1.9. Plausible reaction mechanism

The *p*-QMs were activated by Lewis acid $BF_3 \cdot Et_2O$, forming a highly electrophilic methylenic

carbon. Subsequent nucleophilic attack by *tert*-butyl isocyanide **25** generates zwitterionic nitrilium ion intermediate **A**. The nitrilium ion **A** undergoes a loss of isobutylene, resulting in the formation of the desired 1,6-conjugate addition product **23a**.

2.1.4.5 Useful Transformations of Compound 23a

To further investigate the synthetic utility of this work, a few useful transformations of **23a** was carried out as depicted in Scheme 2.1.10. The bulky *tert*-butyl group could easily be removed *via* an $AlCl_3$-mediated retro-Friedel–Crafts reaction to afford the deprotected product **30** in 80% yield. The bromination of phenol **30** at the *ortho*-position using HBr in AcOH resulted in bromophenol **31** in a 67% yield. The bromide functionality can be easily transformed to other functional groups. For example, a Suzuki coupling was performed on compound **31** to give the coupling biphenyl product **32** in a 63% yield. Also, the cyano product **23a** could be easily transformed into amine **33** upon reduction using $LiAlH_4$.



Scheme 2.1.10. Transformations of compound **23a**

2.1.5 Conclusion

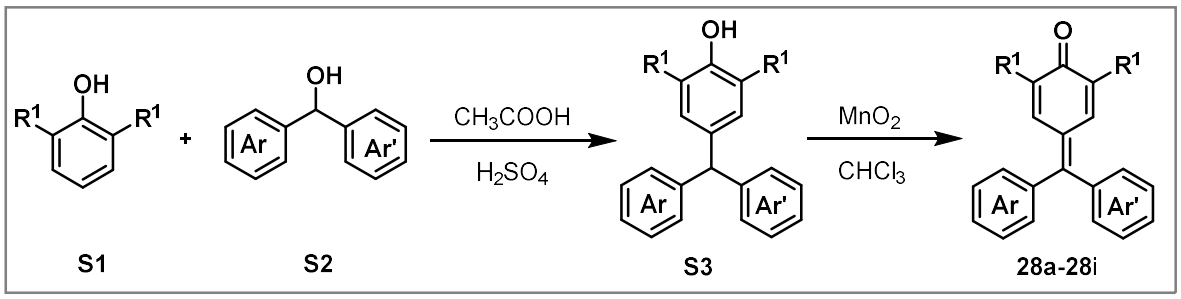
In conclusion, a $BF_3{\cdot}OEt_2$ catalyzed 1,6- conjugate addition of *tert*-butyl isocyanide to *p*-quinone methides and fuchsones for the synthesis of α-diaryl and α- triaryl nitriles have been developed. This method allows facile access to a diverse range of α-diaryl and α-triaryl nitriles in good to excellent yields and with a broad substrate scope. This is the first example where *tert* butyl isocyanide has been used as a cyanide source for the 1,6-conjugate addition reaction under Lewis acid catalysis. Importantly, these cyano-products could be readily functionalized further to obtain a diverse set of useful products. Future studies in this direction are required to develop an asymmetric version and biological evaluations of the synthesized compounds.

2.1.6 Experimental Section

2.1.6.1 Experimental Procedures:

All the *p*-quinone methides were prepared as per the procedure described in the section **1.2.5.1** of the chapter **1.**

A] General Procedure for the Preparation of Fuchsones (28a-28i):[20]



Scheme 2.1.11. Preparation of Fuchsones

Step-1: In a 100 mL round bottom flask phenol **S1** (1 equiv) and diarylmethanol **S2** (1 equiv) was added 20 mL of acetic acid and stirred the reaction mixture for 5 min. Then, to this reaction mixture conc. H_2SO_4 (1 equiv) was added dropwise and the reaction mixture was kept at room temperature. After completion of the reaction (detected by TLC), the reaction was quenched by saturated aqueous $NaHCO_3$ solution and was extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under vacuo. The crude residue was purified by flash chromatography to afford the desired triarylmethane intermediate **S3.**

Step-2: To a solution of **S3** (1 equiv) in $CHCl_3$ (5 mL) was added MnO_2 (15 equiv) and the reaction mixture was stirred at room temperature for 12 h. After completion of the reaction (detected by TLC), the reaction mixture was filtered through Celite, and the filtrate was concentrated under vacuum. The crude products were purified by silica gel flash column to afford the desired fuchsones as as yellow solids.

B] General Procedure for $BF_3.OEt_2$ Mediated Cyanation of *p*-Quinone Methides:

In a 5 mL reaction vial *tert*-butyl isocyanide **25** (0.22 mmol, 25 µL, 1.3 equiv) was added to the mixture of *p*-QM **21** (0.17 mmol, 1 equiv) and DCM (1 mL). Then $BF_3.Et_2O$ (0.042 mmol, 5 µL, 0.25 equiv) was added via syringe, and the reaction mixture was kept at room temperature for ~0.5 h. After the reaction was complete (detected by TLC), the solvent was removed under reduced pressure, and the residue was directly loaded on a silica gel column and eluted using EtOAc/hexane mixture to obtain pure α-arylated nitrile **(23)**.

C] Procedure for Product Transformations

a) Procedure for synthesis of 30:

Dry $MeNO_2$ (16 mL, 0.22 mmol) and $AlCl_3$ (40 mg, 0.75 mmol) were added to a flame-dried glass flask under an atmosphere of nitrogen. The mixture was stirred for 30 min, and then **23a** (50 mg, 0.15 mmol) in toluene (4 mL) was added. After stirring at 60 °C for 1 h, the mixture was cooled to 0 °C and ice water was added to quench the $AlCl_3$. The mixture was extracted with EtOAc (3 × 15 mL), the combined organic layers were dried (anhyd Na_2SO_4) and concentrated under reduced pressure, followed by column chromatography purification to afford the desired product **30** as a white solid in 80% yield.

b) Procedure for synthesis of 31:

To a stirred solution of **30** (50 mg, 0.24 mmol), HBr (45%, 0.8 mL) and AcOH (0.5 mL), was added DMSO (0.25 mL) dropwise. The reaction progress was monitored by TLC. After completion of the reaction, the system was extracted with ethyl acetate (3X10 mL). The organic layers were combined, washed with brine (10 mL), dried with anhydrous Na_2SO_4 and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by 200– 300 mesh silica gel column chromatography (n-hexane/ethyl acetate=10:1) to give the brominated product **31** as a yellow gummy solid in 67 % yield.

c) Procedure for synthesis of 32:

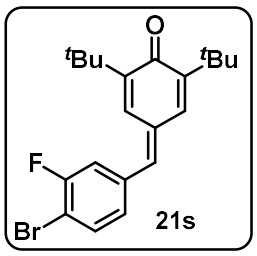
To a solution of **31** (30 mg, 0.10 mmol) in THF/H_2O (2 mL, 9:1) were added $Pd(PPh_3)_4$ (11 mg, 0.010 mmol), phenylboronic acid (25 mg, 0.20 mmol), and Na_2CO_3 (22 mg, 0.15 mmol). The resulting mixture was stirred at 80°C for 4 h under N_2. Water (10 mL) was added, and the system was extracted with CH_2Cl_2 (3X10 mL). The combined organic layers were dried with anhydrous Na_2SO_4 and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by 200–300 mesh silica gel column chromatography (n-hexane/ethyl acetate=10:1) to give the coupling product **32** as a yellow gummy solid in 63 % yield.

d) Procedure for the synthesis of 33:

A round bottom flask was charged with $LiAlH_4$ (12 mg, 0.311 mmol) and anhydrous diethyl ether (4 mL). To the above suspension was added **23a** (50 mg, 0.155 mmol) dissolved in diethyl ether (1 mL) dropwise. The resulting suspension was stirred for 12 h at room temperature. The reaction mixture was cooled at 0 °C and water was cautiously added until gas evolution ceased, the aqueous layer was extracted with ether (10 ml x 2). The combined organic layer was washed with brine and dried over Na_2SO_4. After evaporation of the organic solvent, the crude amine was purified by using flash column chromatography (MeOH:DCM 3:97) as a viscous yellow liquid (**33**, 35 mg, 69 %).

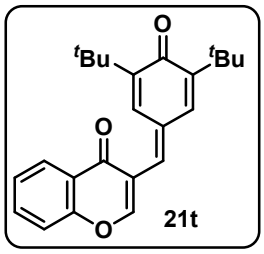
2.1.6.2 Characterization Data of Compounds 21s, 21t, 23, 28, 29 and 30-33:

4-(4-bromo-3-fluorobenzylidene)-2,6-di-*tert*-butylcyclohexa-2,5-dien-1-one (21s):



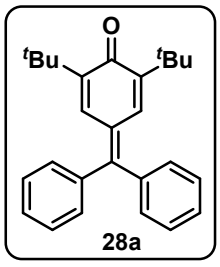
Yellow solid, 320 mg, 48% yield; mp = 118-120 °C; R_f= 0.85(petroleum ether/ethyl acetate = 99/01); **^{1}H NMR (200 MHz, $CDCl_3$) δ** = 7.63 (t, J = 7.7 Hz, 1 H), 7.40 (d, J = 2.3 Hz, 1 H), 7.20 (dd, J = 1.8, 9.4 Hz, 1 H), 7.10 (dd, J = 1.4, 8.3 Hz, 1 H), 7.03 (s, 1 H), 6.97 (d, J = 2.3 Hz, 1 H), 1.32 (s, 9 H), 1.29 (s, 9 H), **^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$) δ** =186.5, 160.3- 157.9 (d, J = 248.6 Hz), 152.8, 150.2, 148.5, 138.9-138.9 (d, J =2.9 Hz), 137.1 (d, J =7.3 Hz), 135.9, 134.6, 133.9-133.8 (d, J = 3.7 Hz), 133.1, 126.9 (d, J = 3.7 Hz), 126.8, 124.0, 117.8-117.5 (d, J = 23.4 Hz), 110.0-109.8 (d, J = 20.5 Hz), 35.5, 35.1, 34.4, 30.3, 29.7, 29.5, 29.5; **^{19}F NMR (376 MHz, $CDCl_3$) δ** = –106.33; **HRMS (ESI-TOF)** m/z: $[M+H]^+$ calcd for $C_{21}H_{25}BrFO$ 391.1067; found 391.1071.

3-((3,5-di-*tert*-butyl-4-oxocyclohexa-2,5-dien-1-ylidene)methyl)-4H-chromen-4-one (21t):

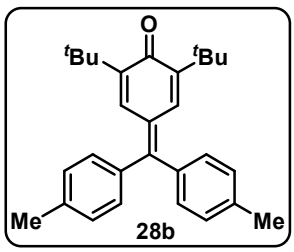


Yellow solid, 332 mg, 54% yield; mp = 190-192 °C; R_f= 0.85 (petroleum ether/ethyl acetate = 99/01); **^{1}H NMR (200 MHz, $CDCl_3$) δ** = 8.37 - 8.20 (dd, J = 8.0 Hz, 1.2 Hz, 1 H), 8.07 (s, 1 H), 7.81 - 7.68 (m, 1 H), 7.57 - 7.42 (m, 2 H), 7.32 (d, J = 1.8 Hz, 1 H), 7.17 (s, 1 H), 7.08 (d, J = 2.0 Hz, 1 H), 1.32 (s,9 H), 1.31 (s,9 H); **^{13}C{^{1}H} NMR (50 MHz,$CDCl_3$) δ** = 186.9, 176.3, 156.1, 155.2, 149.8, 148.0, 134.6, 134.3, 133.1, 131.9, 126.4, 126.3, 125.9, 123.8, 121.2, 118.3, 35.5, 35.0, 29.5, 29.4; **HRMS (ESI-TOF)** m/z: $[M–H]^-$ calcd for $C_{24}H_{25}O_3$ 361.1798; found 361.1797.

2,6-di-*tert*-butyl-4-(diphenylmethylene)cyclohexa-2,5-dien-1-one (28a):



Yellow solid, 635 mg, 63% yield; mp = 173-175 °C; R_f= 0.85 (petroleum ether/ethyl acetate = 99/01); **^{1}H NMR (200 MHz, $CDCl_3$) δ** = 7.39 - 7.30 (m, 6 H), 7.19 - 7.13 (m, 4 H), 7.11 (s, 2 H), 1.16 (s, 18 H); **^{13}C{^{1}H} NMR (50 MHz,$CDCl_3$) δ** = 186.2, 155.9, 147.5, 140.8, 131.9, 129.7, 129.1, 128.0, , 35.3, 29.5; **HRMS (ESI-TOF)** m/z: $[M+H]^+$ calcd for $C_{27}H_{31}O$ 371.2369; found 371.2369.

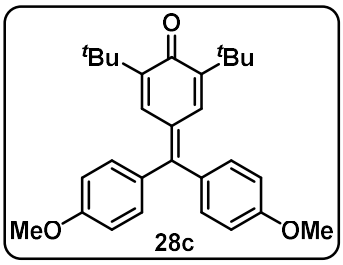


2,6-di-*tert*-butyl-4-(di-*p*-tolylmethylene)cyclohexa-2,5-dien-1-one (28b):

Yellow solid, 660 mg, 68% yield; mp = 177-179 °C; R_f= 0.85 (petroleum ether/ethyl acetate = 99/01); **^{1}H NMR (200 MHz, $CDCl_3$) δ** = 7.24

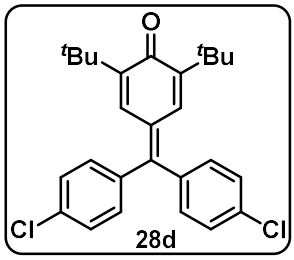
- 7.08 (m, 10 H), 2.42 (s, 6 H), 1.25 (s, 18 H); **$^{13}C\{^1H\}$ NMR (50 MHz,$CDCl_3$) δ** = 186.1, 156.8, 147.0, 139.4, 138.1, 132.3, 132.1, 129.2, 128.7, 35.2, 29.5, 21.4; **HRMS (ESI-TOF)** m/z: $[M+H]^+$ calcd for $C_{29}H_{35}O$ 399.2682; found 399.2674.

4-(*bis*(4-methoxyphenyl)methylene)-2,6-di-*tert*-butylcyclohexa-2,5-dien-1-one (28c) :



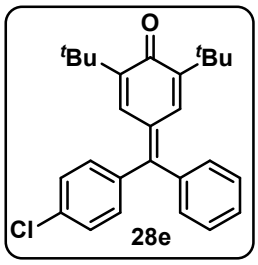
Yellow solid, 610 mg, 68% yield; mp = 174-176 °C; R_f= 0.60 (petroleum ether/ethyl acetate = 97/03); **^1H NMR (200 MHz, $CDCl_3$) δ** = 7.23 - 7.11 (m, 6 H), 6.93 (d, *J* = 8.8 Hz, 4 H), 3.88 (s, 6 H), 1.26 (s, 18 H); **$^{13}C\{^1H\}$ NMR (50 MHz, $CDCl_3$) δ** = 186.0, 160.7, 156.5, 146.6, 134.0, 133.4, 132.4, 128.5, 113.4, 55.4, 35.2, 29.5; **HRMS (ESI-TOF)** m/z: $[M+H]^+$ calcd for $C_{29}H_{35}O_3$ 431.2581; found 431.2575.

4-(bis(4-chlorophenyl)methylene)-2,6-di-*tert*-butylcyclohexa-2,5-dien-1-one (28d) :



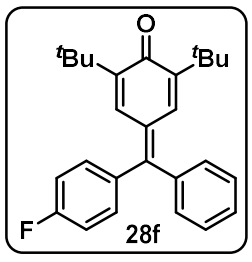
Yellow solid, 550 mg, 62% yield; mp = 215-217 °C; R_f= 0.70 (petroleum ether/ethyl acetate = 98/02); **^1H NMR (200 MHz, $CDCl_3$) δ=** 7.39 (d, *J* = 8.6 Hz, 4 H), 7.15 (d, *J* = 8.5 Hz, 4 H), 7.10 (s, 2 H), 1.23 (s, 18 H); **$^{13}C\{^1H\}$ NMR (50 MHz, $CDCl_3$) δ** = 186.0, 152.4, 148.1, 138.8, 135.6, 133.1, 131.2, 130.3, 128.5, 35.3, 29.5; **HRMS (ESI-TOF)** m/z: $[M+H]^+$ calcd for $C_{27}H_{29}Cl_2O$ 439.1590; found 439.1579.

2,6-di-*tert*-butyl-4-((4-chlorophenyl)(phenyl)methylene)cyclohexa-2,5-dien-1-one (28e) :



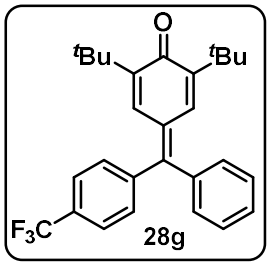
Yellow solid, 580 mg, 59% yield; mp = 189-191 °C; R_f= 0.75 (petroleum ether/ethyl acetate = 99/01); **^1H NMR (400 MHz, $CDCl_3$) δ** = 7.47 - 7.33 (m, 5 H), 7.25 - 7.12 (m, 6 H), 1.25 (s, 9 H), 1.23 (s, 9 H); **$^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ** = 186.1, 154.1, 147.9, 147.7, 140.4, , 133.1, 131.8, 131.7, 131.3, 130.0, 129.3, 128.3, 128.1, 35.3, 35.3, 29.5, 29.4; **HRMS (ESI-TOF)** m/z: $[M+H]^+$ calcd for $C_{27}H_{30}ClO$ 405.1980; found 405.1973.

2,6-di-*tert*-butyl-4-((4-fluorophenyl)(phenyl)methylene)cyclohexa-2,5-dien-1-one (28f) :



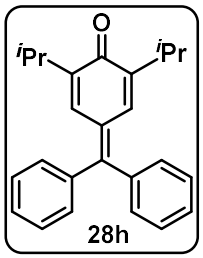
Yellow solid, 560 mg, 57% yield; mp = 186-188 °C; R_f= 0.75 (petroleum ether/ethyl acetate = 99/01); **^1H NMR (400 MHz, $CDCl_3$) δ** = 7.51 - 7.36 (m, 3 H), 7.27 - 7.19 (m, 4 H), 7.17 - 7.05 (m, 4 H), 1.24 (s, 9 H), 1.23 (s, 9 H); **$^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ** = 186.1, 164.4-161.9 (d, J = 251.23 Hz), 154.5, 147.7- 147.6 (d, J = 13.10 Hz), 140.6, 136.8, 133.8-133.7 (d, J = 7.71 Hz), 131.9, 131.8, 131.5, 129.8, 129.3, 128.1, 125.9, 115.3-115.1(d, J = 21.58 Hz), 35.3, 30.3, 29.5, 29.5; **^{19}F NMR (376 MHz, $CDCl_3$) δ** = –111.28; **HRMS (ESI-TOF)** m/z: $[M+H]^+$ calcd for $C_{27}H_{30}FO$ 389.2275; found 389.2269.

2,6-di-*tert*-butyl-4-(phenyl(4-(trifluoromethyl)phenyl)methylene)cyclohexa-2,5-dien-1-one (28g) :



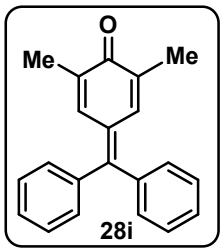
Yellow solid, 490 mg, 55% yield; mp = 191-193 °C; R_f= 0.75 (petroleum ether/ethyl acetate = 99/01); **^{1}H NMR (200 MHz, $CDCl_3$) δ** = 7.67 (d, *J* = 8.1 Hz, 2 H), 7.47 - 7.33 (m, 5 H), 7.21 (dd, *J* = 2.5, 6.3 Hz, 3 H), 7.08 (d, *J* = 2.4 Hz, 1 H), 1.23 (s, 18 H); **^{13}C{^{1}H} NMR (50 MHz, $CDCl_3$) δ** = 186.1, 153.3, 148.2 (d, J= 5.8 Hz), 144.4, 140.2, 131.8 (d, J= 12.4 Hz), 131.2 (d, J= 27.8 Hz), 130.6, 129.4, 128.2, 124.9 (d, J= 3.2 Hz), 35.4, 29.5; **^{19}F NMR (376 MHz, $CDCl_3$) δ** = –62.64; **HRMS (ESI-TOF)** m/z: $[M+H]^+$ calcd for $C_{28}H_{30}F_3O$ 439.2243; found 439.2231.

4-(diphenylmethylene)-2,6-diisopropylcyclohexa-2,5-dien-1-one (28h) :



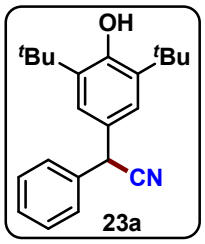
Yellow solid, 560 mg, 61% yield; mp = 147-148 °C; R_f= 0.75 (petroleum ether/ethyl acetate = 99/01); **^{1}H NMR (200 MHz, $CDCl_3$) δ** = 7.56 - 7.35 (m, 6 H), 7.29 - 7.19 (m, 4 H), 7.12 (s, 2 H), 3.18 (spt, *J* = 6.9 Hz, 2 H), 1.06 (d, *J* = 6.8 Hz, 12 H) **^{13}C{^{1}H} NMR (50 MHz, $CDCl_3$) δ** = 185.0, 156.5, 145.5, 140.7, 132.1, 131.7, 130.0, 129.3, 128.0, 26.8, 22.0; **HRMS (ESI-TOF)** m/z: $[M+H]^+$ calcd for $C_{25}H_{27}O$ 343.2056; found 343.2057.

4-(diphenylmethylene)-2,6-dimethylcyclohexa-2,5-dien-1-one (28i) :



Yellow solid, 480 mg, 57% yield; mp = 180-183 °C; R_f= 0.75 (petroleum ether/ethyl acetate = 99/01); **^{1}H NMR (200 MHz, $CDCl_3$) δ** = 7.46 - 7.39 (m, 5 H), 7.31 - 7.17 (m, 5 H), 7.16 (s, 2 H), 2.02 (s, 6 H) ; **^{13}C{^{1}H} NMR (50 MHz, $CDCl_3$) δ** = 187.1, 156.5, 140.6, 135.7, 135.4, 131.9, 129.8, 129.3, 128.0, 16.7 ; **HRMS (ESI-TOF)** m/z: $[M+H]^+$ calcd for $C_{21}H_{19}O$ 287.1430; found 287.1433.

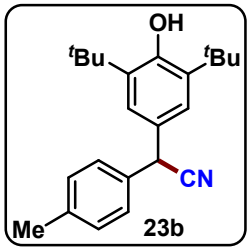
2-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-2-phenylacetonitrile (23a) :



White solid, 49 mg, 90 % yield; mp = 108–110 °C; R_f= 0.50 (petroleum ether/ethyl acetate = 95/05); **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 7.41 - 7.30 (m, 5 H), 7.10 (s, 2 H), 5.26 (s, 1 H), 5.07 (s, 1 H), 1.41 (s, 18 H); **^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ** = 153.6, 136.6, 136.4, 129.0, 128.0, 127.6, 126.5, 124.5, 120.3, 42.5, 34.4, 30.1; **HRMS (ESI-TOF)** m/z: $[M–H]^-$ calcd for $C_{22}H_{26}NO$ 320.2009; found 320.2024.

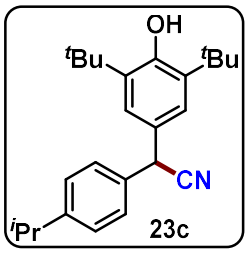
2-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-2-(p-tolyl)acetonitrile (23b) :

Yellow solid, 46 mg, 85% yield; mp = 107-109 °C; R_f= 0.50 (petroleum ether/ethyl acetate =



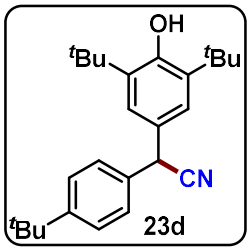
95/05); **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 7.25 (d, J= 8.2, 2H), 7.18 (d, J= 8.2, 2H), 7.10 (s, 2 H), 5.24 (s, 1 H), 5.03 (s, 1 H), 2.35 (s, 3 H), 1.41 (s, 18 H) ; **^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ** = 153.6, 137.7, 136.5, 133.5, 129.7, 127.5, 126.7, 124.4, 120.5, 42.2, 34.4, 30.1, 21.0; **HRMS (ESI-TOF)** m/z: $[M–H]^-$ calcd for $C_{23}H_{28}NO$ 334.2165; found 334.2178.

2-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-2-(4-isopropylphenyl)acetonitrile (23c) :



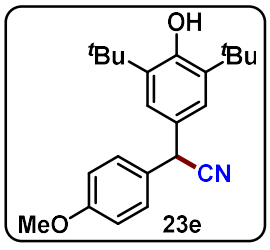
Yellow solid, 42 mg, 78% yield; mp = 70-72 °C; ***R*$_f$** = 0.40 (petroleum ether/ethyl acetate = 95/05); **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 7.28 (d, J= 8.4, 2H), 7.22 (d, J= 8.4, 2H), 7.12 (s, 2 H), 5.25 (s, 1 H), 5.03 (s, 1 H), 2.91 (spt, J = 6.9 Hz, 1 H), 1.42 (s, 18 H), 1.24 (d, J = 6.9 Hz, 6 H); **^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ =** 153.6, 148.7, 136.6, 133.8, 127.5, 127.1, 126.7, 124.5, 120.6, 42.2, 34.4, 33.8, 30.3, 30.2, 23.9; **HRMS (ESI-TOF)** m/z: $[M–H]^-$ calcd for $C_{25}H_{32}NO$ 362.2478; found 362.2494.

2-(4-(*tert*-butyl)phenyl)-2-(3,5-di-tert-butyl-4-hydroxyphenyl)acetonitrile (23d) :



Yellow gummy solid, 39 mg, 72 % yield; ***R*$_f$** = 0.40 (petroleum ether/ethyl acetate = 95/05); **^{1}H NMR (200 MHz, $CDCl_3$) δ** = 7.39 (d, J = 8.4 Hz, 2 H), 7.28 (d, J = 8.2 Hz, 2 H), 7.12 (s, 2 H), 5.25 (s, 1 H), 5.03 (s, 1 H), 1.42 (s, 18 H), 1.32 (s, 9 H); **^{13}C{^{1}H} NMR (50 MHz, $CDCl_3$) δ** = 153.6, 150.9, 136.5, 133.5, 127.2, 126.6, 125.9, 124.5, 120.5, 42.1, 34.5, 34.4, 31.2, 30.1**;** **HRMS (ESI-TOF)** m/z: $[M–H]^-$ calcd for $C_{26}H_{34}NO$ 376.2635; found 376.2650.

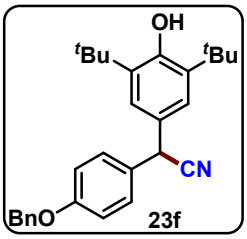
2-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-2-(4-methoxyphenyl)acetonitrile (23e) :



Pale yellow solid, 48 mg, 89% yield; mp = 96-97 °C; ***R*$_f$** = 0.30 (petroleum ether/ethyl acetate = 95/05); **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 7.28 (d, J = 8.2 Hz, 2 H), 7.10 (s, 2 H), 6.91 (d, J = 8.2 Hz, 2 H), 5.26 (s, 1 H), 5.04 (s, 1 H), 3.83 (s, 3 H), 1.43 (s, 18 H); **^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ** = 159.3, 153.6, 136.6, 128.8, 128.5, 126.8, 124.4, 120.6, 114.4, 55.3, 41.8, 34.4, 30.2; **HRMS (ESI-TOF)** m/z: $[M–H]^-$ calcd for $C_{23}H_{28}NO_2$ 350.2115; found 350.2130.

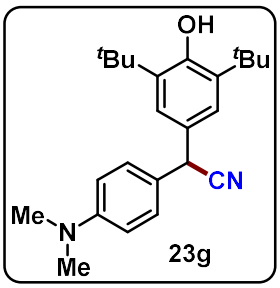
2-(4-(benzyloxy)phenyl)-2-(3,5-di-*tert*-butyl-4-hydroxyphenyl)acetonitrile (23f) :

White solid, 52 mg, 97% yield; mp = 86-88°C; ***R*$_f$** = 0.25 (petroleum ether/ethyl acetate = 95/05); **^{1}H NMR (500 MHz, $CDCl_3$) δ** = 7.43 (d, J = 7.2 Hz ,2 H), 7.39 (t, J = 7.2 Hz, 2 H), 7.33 (t, J = 7.2 Hz ,1 H), 7.28 (d, J = 8.8 Hz, 2 H), 7.10 (s, 2 H), 6.98 (d, J = 8.8 Hz, 2 H), 5.25 (s, 1 H), 5.07 (s, 2 H), 5.02 (s, 1 H), 1.42 (s, 18 H) ; **^{13}C{^{1}H} NMR (50 MHz, $CDCl_3$) δ** =



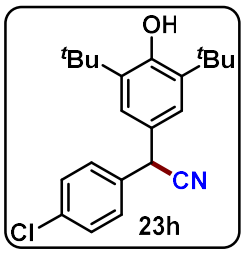
158.4, 153.5, 136.7, 136.5, 128.8, 128.6, 128.0, 127.4, 126.7, 124.4, 120.5, 115.3, 70.0, 41.7, 34.4, 30.1; **HRMS (ESI-TOF)** m/z: $[M–H]^-$ calcd for $C_{29}H_{32}NO_2$ 426.2428; found 426.2444.

2-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-2-(4-(dimethylamino)phenyl)acetonitrile (23g) :



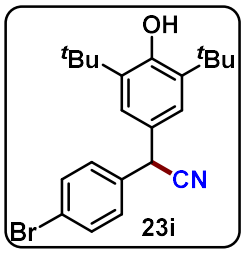
Light pink solid, 52 mg, 96% yield; mp = 138-140 °C; R_f = 0.50 (petroleum ether/ethyl acetate = 95/05); **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 7.20 (d, J = 7.9 Hz, 2 H), 7.12 (s, 2 H), 6.72 (d, J = 8.5 Hz, 2 H), 5.23 (s, 1 H), 4.99 (s, 1 H), 2.96 (s, 6 H), 1.42 (s, 18 H); **^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ** = 153.4, 149.9, 136.4, 128.3, 127.2, 124.3, 120.9, 112.8, 41.7, 40.6, 34.4, 30.1; **HRMS (ESI-TOF)** m/z: $[M–H]^-$ calcd for $C_{24}H_{31}N_2O$ 363.2449; found 363.2431.

2-(4-chlorophenyl)-2-(3,5-di-*tert*-butyl-4-hydroxyphenyl)acetonitrile (23h) :



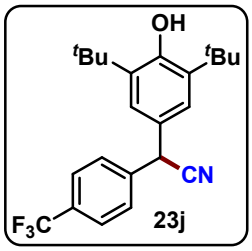
Yellow gummy solid, 42 mg, 78% yield; R_f = 0.50 (petroleum ether/ethyl acetate = 95/05); **^{1}H NMR (200 MHz, $CDCl_3$) δ** = 7.36 (d, J = 8.8 Hz ,2 H), 7.28 (d, J = 8.8 Hz ,2 H), 7.07 (s, 2 H), 5.28 (s, 1 H), 5.03 (s, 1 H), 1.41 (s, 18 H); **^{13}C{^{1}H} NMR (50 MHz, $CDCl_3$) δ** = 153.8, 136.8, 135.0, 134.0, 129.3, 129.0, 126.0, 124.4, 119.9, 42.0, 34.5, 30.1; **HRMS (ESI-TOF)** m/z: $[M–H]^-$ calcd for $C_{22}H_{25}ClNO$ 354.1619; found 354.1633.

2-(4-bromophenyl)-2-(3,5-di-*tert*-butyl-4-hydroxyphenyl)acetonitrile (23i) :



Yellow solid, 43 mg, 81% yield; mp = 150-152 °C; R_f = 0.50 (petroleum ether/ethyl acetate = 95/05); **^{1}H NMR (200 MHz, $CDCl_3$) δ** = 7.51 (d, J = 8.4 Hz, 2 H), 7.24 (d, J = 8.4 Hz, 2 H), 7.08 (s, 2 H), 5.29 (s, 1 H), 5.02 (s, 1 H), 1.42 (s, 18 H); **^{13}C{^{1}H} NMR (50 MHz, $CDCl_3$) δ** = 153.8, 136.8, 135.5, 132.2, 129.3, 125.9, 124.4, 122.1, 119.8, 42.0, 34.4, 30.1; **HRMS (ESI-TOF)** m/z: $[M–H]^-$ calcd for $C_{22}H_{25}BrNO$ 398.1114; found 398.1130.

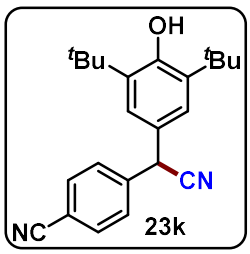
2-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-2-(4-(trifluoromethyl)phenyl)acetonitrile (23j) :



White solid, 37 mg, 70% yield; mp = 133-135 °C; R_f = 0.50 (petroleum ether/ethyl acetate = 95/05); **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 7.64 (d, J = 8.2 Hz, 2 H), 7.49 (d, J = 8.2 Hz, 2 H), 7.09 (s, 2 H), 5.30 (s, 1 H), 5.11 (s, 1 H), 1.41 (s, 18 H); **^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ** = 153.9, 140.4, 136.9, 128.0, 126.9 (q, J= 3.8 Hz), 125.5, 124.4, 119.5, 42.4, 34.4, 30.1;

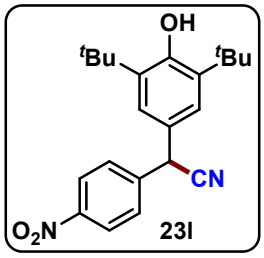
^{19}F NMR (376 MHz, $CDCl_3$) δ = –62.66; **HRMS (ESI-TOF)** m/z: $[M–H]^-$ calcd for $C_{23}H_{25}F_3NO$ 388.1883; found 388.1902.

4-(cyano(3,5-di-*tert*-butyl-4-hydroxyphenyl)methyl)benzonitrile (23k) :



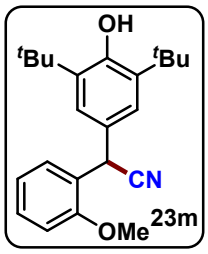
White solid, 32 mg, 59% yield; mp = 144-145 °C; R_f = 0.40 (petroleum ether/ethyl acetate = 95/05); **^{1}H NMR (200 MHz, $CDCl_3$) δ** = 7.69 (d, J = 8.3 Hz, 2 H), 7.49 (d, J = 8.2 Hz, 2 H), 7.05 (s, 2 H), 5.32 (s, 1 H), 5.10 (s, 1 H), 1.40 (s, 18 H); **^{13}C{^{1}H} NMR (50 MHz, $CDCl_3$) δ** = 154.1, 141.6, 137.1, 132.9, 128.5, 125.1, 124.5, 119.2, 112.2, 42.6, 34.5, 30.1; **HRMS (ESI-TOF)** m/z: $[M–H]^-$ calcd for $C_{23}H_{25}N_2O$ 345.1961; found 345.1976.

2-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-2-(4-nitrophenyl)acetonitrile (23l) :



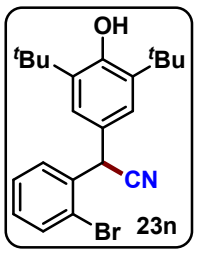
Off white solid, 34 mg, 64% yield; mp = 113-114 °C; R_f = 0.30 (petroleum ether/ethyl acetate = 95/05); **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 8.27 - 8.22 (d, J = 9.2 Hz, 2 H), 7.58 - 7.53 (d, J = 8.7 Hz, 2 H), 7.07 (s, 2 H), 5.33 (s, 1 H), 5.15 (s, 1 H), 1.41 (s, 18 H); **^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ** = 154.1, 147.6, 143.4, 137.1, 128.6, 125.0, 124.4, 124.3, 119.1, 42.3, 34.4, 30.0; **HRMS (ESI-TOF)** m/z: $[M–H]^-$ calcd for $C_{22}H_{25}N_2O_3$ 365.1860; found 365.1871.

2-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-2-(2-methoxyphenyl)acetonitrile (23m) :



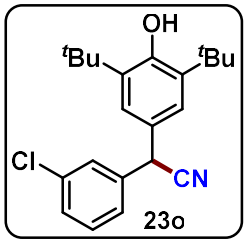
Off white solid, 43 mg, 79% yield; mp = 107-108 °C; R_f = 0.40 (petroleum ether/ethyl acetate = 95/05); **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 7.32 (d, J = 7.9 Hz, 1 H), 7.28 (m, 1 H), 7.17 (s, 2 H), 6.94 (t, J = 7.6 Hz, 1 H), 6.89 (d, J = 8.5 Hz, 1 H), 5.45 (s, 1 H), 5.29 (s, 1 H), 3.87 (s, 3 H), 1.40 (s, 18 H); **^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ** = 156.0, 153.4, 136.2, 129.3, 128.6, 126.1, 125.3, 124.5, 121.0, 120.6, 110.8, 55.5, 36.1, 34.4, 30.2; **HRMS (ESI-TOF)** m/z: $[M–H]^-$ calcd for $C_{23}H_{28}NO_2$ 350.2115; found 350.2129.

2-(2-bromophenyl)-2-(3,5-di-*tert*-butyl-4-hydroxyphenyl)acetonitrile (23n) :



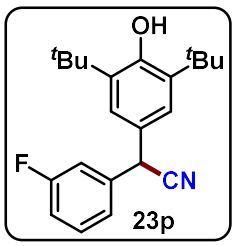
White solid, 40 mg, 75% yield; mp = 109-110 °C; R_f = 0.65 (petroleum ether/ethyl acetate = 95/05); **^{1}H NMR (200 MHz, $CDCl_3$) δ** = 7.60 (d, J = 8.1 Hz, 1 H), 7.53 (dd, J = 1.3, 7.8 Hz, 1 H), 7.37 (t, J = 7.5 Hz, 1 H), 7.23 (d, J = 1.5 Hz, 1 H), 7.18 (s, 2 H), 5.56 (s, 1 H), 5.26 (s, 1 H), 1.41 (s, 18 H); **^{13}C{^{1}H} NMR (50 MHz, $CDCl_3$) δ** = 153.7, 136.5, 136.2, 133.3, 129.8, 129.7, 128.3, 125.1, 124.5, 123.5, 119.8 , 41.8, 34.4, 30.1; **HRMS (ESI-TOF)** m/z: $[M–H]^-$ calcd for $C_{22}H_{25}BrNO$ 398.1114; found 398.1133.

2-(3-chlorophenyl)-2-(3,5-di-*tert*-butyl-4-hydroxyphenyl)acetonitrile (23o) :



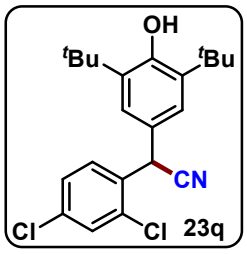
Yellow gummy solid, 38 mg,70% yield; R_f = 0.50 (petroleum ether/ethyl acetate = 95/05); **^{1}H NMR (200 MHz, $CDCl_3$) δ** = 7.41 - 7.32 (m, 2 H), 7.32 - 7.20 (m, 2 H), 7.09 (s, 2 H), 5.30 (s, 1 H), 5.03 (s, 1 H), 1.42 (s, 18 H); **^{13}C{^{1}H} NMR (50 MHz, $CDCl_3$) δ** = 153.9, 138.3, 136.8, 134.9, 130.3, 128.3, 127.8, 125.8, 125.7, 124.4, 119.7, 42.2, 34.4, 30.1; **HRMS (ESI-TOF)** m/z: $[M–H]^-$ calcd for $C_{22}H_{25}ClNO$ 354.1619; found 354.1633.

2-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-2-(3-fluorophenyl)acetonitrile (23p) :



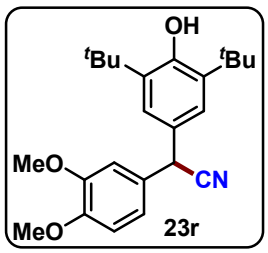
Yellow gummy solid, 36 mg, 66% yield; R_f = 0.50(petroleum ether/ethyl acetate = 95/05); **^{1}H NMR (500 MHz, $CDCl_3$) δ** = 7.38 (dt, *J* = 6.1, 8.0 Hz, 1 H), 7.20 (d, *J* = 7.6 Hz, 1 H), 7.12 (s, 2 H), 7.10 - 7.01 (m, 2 H), 5.31 (s, 1 H), 5.08 (s, 1 H), 1.44 (s, 18 H); **^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ** = 162.9 (d, *J* = 247.0 Hz), 153.9, 138.8 (d, *J* = 6.8 Hz), 136.8, 130.6 (d, *J* = 7.6 Hz), 125.8, 124.5, 123.3 (d, *J* = 2.8 Hz), 119.8, 115.0 (d, *J* = 20.9 Hz), 114.8 (d, *J* = 22.8 Hz), 42.2, 34.4, 30.1; **^{19}F NMR (376 MHz, $CDCl_3$) δ** = –111.57; **HRMS (ESI-TOF)** m/z: $[M–H]^-$ calcd for $C_{22}H_{25}FNO$ 338.1915; found 338.1928.

2-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-2-(2,4-dichlorophenyl)acetonitrile (23q) :



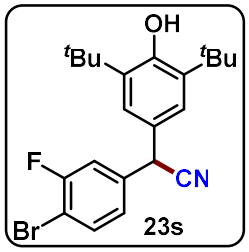
White solid, 36 mg, 63% yield; mp = 120-122 °C; R_f = 0.40 (petroleum ether/ethyl acetate = 95/05); **^{1}H NMR (200 MHz, $CDCl_3$) δ** = 7.47 - 7.43 (d, J = 2.2 Hz, 1 H), 7.42 (d, J = 6.1 Hz, 1 H), 7.34 - 7.27 (dd, J = 8.3 Hz, 2.2 Hz, 1 H), 7.13 (s, 2 H), 5.48 (s, 1 H), 5.29 (s, 1 H), 1.41 (s, 18 H); **^{13}C{^{1}H} NMR (50 MHz, $CDCl_3$) δ** = 153.9, 136.7, 134.8, 133.7, 133.2, 130.3, 129.8, 128.0, 124.5, 124.4, 119.3, 38.9, 34.4, 30.1; **HRMS (ESI-TOF)** m/z: $[M–H]^-$ calcd for $C_{22}H_{24}Cl_2NO$ 388.1229; found 388.1245.

2-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-2-(3,4-dimethoxyphenyl)acetonitril (23r) :



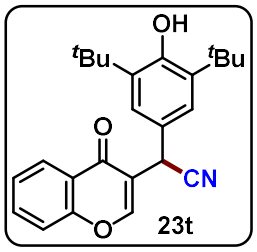
White solid, 52 mg, 98% yield; mp = 130-131 °C; R_f = 0.30 (petroleum ether/ethyl acetate = 90/10); **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 7.10 (s, 2 H), 6.92 - 6.79 (m, 3 H), 5.26 (s, 1 H), 5.02 (s, 1 H), 3.86 (s, 3 H), 3.88 (s, 3 H), 1.41 (s, 18 H); **^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ** = 153.6, 149.3, 148.7, , 136.6, 128.7, 126.5, 124.3, 120.5, 120.1, 111.3, 110.7, 55.9, 42.0, 34.4, 30.1; **HRMS (ESI-TOF)** m/z: $[M–H]^-$ calcd for $C_{24}H_{30}NO_3$ 380.2220; found 380.2236.

2-(4-bromo-3-fluorophenyl)-2-(3,5-di-*tert*-butyl-4-hydroxyphenyl)acetonitrile (23s) :



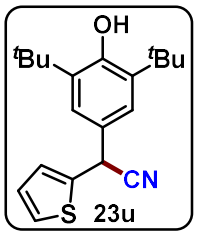
Off white solid, 28 mg, 52% yield; mp = 78-80 °C; R_f = 0.50 (petroleum ether/ethyl acetate = 95/05); **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 7.56 (t, J = 7.8 Hz, 1 H), 7.14 - 7.02 (m, 4 H), 5.31 (s, 1 H), 5.01 (s, 1 H), 1.41 (s, 18 H); **^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ** = 160.4-158.0 (d, J= 248.9 Hz), 154.0, 138.2-138.1 (d, J= 6.9 Hz), 137.0, 134.1, 125.3, 124.4, 119.3, 116.1-115.8 (d, J= 23.8 Hz), 108.9-108.7 (d, J= 20.8 Hz), 41.9, 34.5, 30.1; **^{19}F NMR (376 MHz, $CDCl_3$) δ** = –105.37; **HRMS (ESI-TOF)** m/z: $[M–H]^-$ calcd for $C_{22}H_{24}BrFNO$ 416.1040; found 416.1020.

2-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-2-(4-oxo-4H-chromen-3-yl)acetonitrile (23t) :



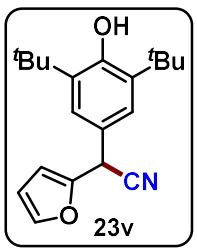
Off white solid, 26 mg, 48% yield; mp = 135-137 °C; R_f = 0.30 (petroleum ether/ethyl acetate = 95/05); **^{1}H NMR (200 MHz, $CDCl_3$) δ** = 8.24 (dd, J = 1.4, 8.0 Hz, 1 H), 7.98 (s, 1 H), 7.76 - 7.63 (m, 1 H), 7.51 - 7.38 (m, 2 H), 7.26 (s, 2 H), 5.42 (s, 1 H), 5.30 (s, 1 H), 1.43 (s, 18 H); **^{13}C{^{1}H} NMR (50 MHz, $CDCl_3$) δ** = 175.1, 156.3, 154.0, 153.9, 136.8, 134.2, 126.1, 125.6, 124.5, 124.1, 123.6, 122.0, 119.2, 118.2, 34.4, 32.8, 30.1; **HRMS (ESI-TOF)** m/z: $[M–H]^-$ calcd for $C_{25}H_{26}NO_3$ 388.1907; found 388.1919.

2-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-2-(thiophen-2-yl)acetonitrile (23u) :



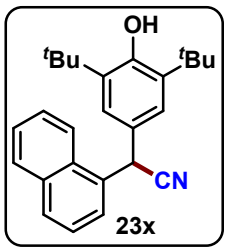
Orange gummy solid, 42 mg, 77% yield; R_f = 0.40 (petroleum ether/ethyl acetate = 95/05); **^{1}H NMR (200 MHz, $CDCl_3$) δ** = 7.30 - 7.24 (m, 1 H), 7.18 (s, 2 H), 7.12 - 7.03 (m, 1 H), 7.03 - 6.93 (m, 1 H), 5.30 (s, 1 H), 5.28 (s, 1 H), 1.43 (s, 18 H) ; **^{13}C{^{1}H} NMR (50 MHz, $CDCl_3$) δ** = 154.0, 139.4, 136.7, 127.0, 126.4, 126.1, 124.3, 119.4, 37.9, 34.4, 30.1; **HRMS (ESI-TOF)** m/z: $[M–H]^-$ calcd for $C_{20}H_{24}NOS$ 326.1573; found 326.1587.

2-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-2-(furan-2-yl)acetonitrile (23v) :



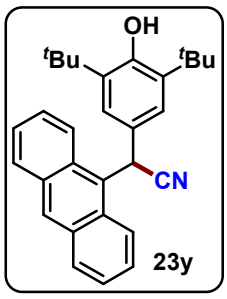
Orange gummy solid, 36 mg, 65% yield; R_f = 0.30 (petroleum ether/ethyl acetate = 95/05); **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 7.41 (s, 1 H), 7.15 (s, 2 H), 6.35 (dd, *J* = 2.0, 3.1 Hz, 1 H), 6.33 - 6.19 (d, *J* = 3.2, 1 H), 5.30 (s, 1 H), 5.11 (s, 1 H), 1.43 (s, 18 H); **^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ** = 154.0, 148.5, 143.2, 136.7, 124.4, 123.6, 118.1, 110.7, 108.3, 36.7, 34.4, 30.1; **HRMS (ESI-TOF)** m/z: $[M–H]^-$ calcd for $C_{20}H_{24}NO_2$ 310.1802; found 310.1815.

2-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-2-(naphthalen-1-yl)acetonitrile (23x) :



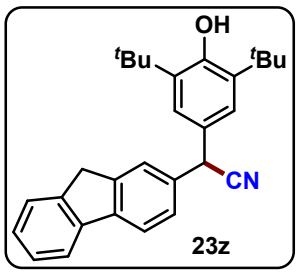
Off white solid, 43 mg, 80% yield; mp = 144-145 °C; R_f = 0.40 (petroleum ether/ethyl acetate = 95/05); **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 7.99 (d, J = 7.9 Hz, 1 H), 7.94 - 7.85 (m, 2 H), 7.60 (d, J = 7.3 Hz, 1 H), 7.57 - 7.48 (m, 3 H), 7.15 (s, 2 H), 5.78 (s, 1 H), 5.24 (s, 1 H), 1.38 (s, 18 H); **^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ** = 153.6, 136.5, 134.0, 131.6, 130.5, 129.2, 129.1, 126.8, 126.7, 126.1, 125.5, 125.4, 124.6, 123.0, 120.5, 39.5, 34.4, 30.1; **HRMS (ESI-TOF)** m/z: $[M–H]^-$ calcd for $C_{26}H_{28}NO$ 370.2165; found 370.2184.

2-(anthracen-9-yl)-2-(3,5-di-*tert*-butyl-4-hydroxyphenyl)acetonitrile (23y) :



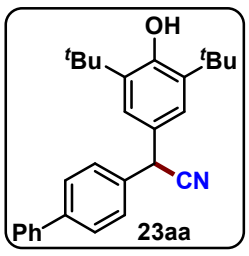
Yellow solid, 42 mg, 79% yield; mp = 193-195 °C; R_f = 0.50 (petroleum ether/ethyl acetate = 95/05); **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 8.56 (s, 1 H), 8.21 (d, J = 8.4 Hz, 2 H), 8.07 (dd, J = 7.6 Hz 2 H), 7.61 - 7.43 (m, 4 H), 7.13 (s, 2 H), 6.67 (s, 1 H), 5.20 (s, 1 H), 1.29 (s, 18 H); **^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ** = 153.3, 136.5, 131.6, 129.9, 129.5, 129.4, 126.8, 125.6, 125.5, 125.1, 123.9, 123.7, 120.5, 35.0, 34.4, 30.0; **HRMS (ESI-TOF)** m/z: $[M+Na]^+$ calcd for $C_{30}H_{31}NONa$ 444.2298, found 444.2299.

2-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-2-(9H-fluoren-3-yl)acetonitrile (23z) :



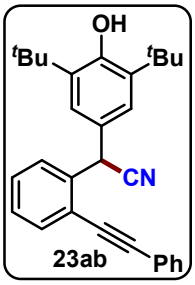
White solid, 45 mg, 84% yield; mp = 187-189 °C; R_f = 0.30 (petroleum ether/ethyl acetate = 95/05); **^{1}H NMR (200 MHz, $CDCl_3$) δ** = 7.78 (d, J = 8.2 Hz, 2 H), 7.60 - 7.51 (m, 2 H), 7.45 - 7.27 (m, 3 H), 7.15 (s, 2 H), 5.27 (s, 1 H), 5.15 (s, 1 H), 3.91 (s, 2 H), 1.42 (s, 18 H); **^{13}C{^{1}H} NMR (50 MHz, $CDCl_3$) δ** = 153.6, 144.1, 143.4, 141.6, 140.9, 136.6, 134.8, 127.0, 126.8, 126.8, 126.4, 125.1, 124.4, 124.3, 120.5, 120.2, 120.0, 42.6, 36.9, 34.4, 30.1; **HRMS (ESI-TOF)** m/z: $[M–H]^-$ calcd for $C_{29}H_{30}NO$ 408.2322; found 408.2334.

2-([1,1'-biphenyl]-4-yl)-2-(3,5-di-*tert*-butyl-4-hydroxyphenyl)acetonitrile (23aa) :



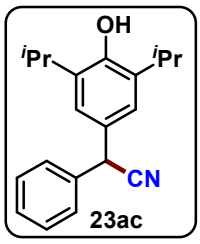
White solid, 44 mg, 82% yield; mp = 133-135 °C; R_f = 0.50 (petroleum ether/ethyl acetate = 95/05); **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 7.68 - 7.54 (m, 4 H), 7.53 - 7.31 (m, 5 H), 7.16 (s, 2 H), 5.29 (s, 1 H), 5.12 (s, 1 H), 1.44 (s, 18 H); **^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ** = 153.7, 140.9, 140.2, 136.7, 135.4, 128.8, 128.0, 127.7, 127.6, 127.0, 126.4, 124.5, 120.3, 42.2, 34.4, 30.1; **HRMS (ESI-TOF)** m/z: $[M–H]^-$ calcd for $C_{28}H_{30}NO$ 396.2322; found 396.2334.

2-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-2-(2-(phenylethynyl)phenyl)acetonitrile (23ab) :



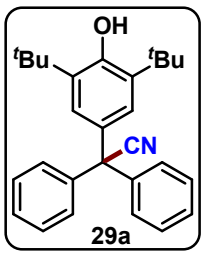
Off white solid, 43 mg, 80% yield; mp = 64-66 °C; R_f = 0.40 (petroleum ether/ethyl acetate = 95/05); **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 7.61 - 7.54 (m, 2 H), 7.52 (dd, *J* = 2.7, 6.5 Hz, 2 H), 7.42 - 7.29 (m, 5 H), 7.24 (s, 2 H), 5.73 (s, 1 H), 5.22 (s, 1 H), 1.36 (s, 18 H)**; ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$) δ** = 153.6, 138.4, 136.5, 132.6, 131.6, 129.2, 128.8, 128.4, 128.0, 127.8, 126.1, 124.3, 122.5, 122.2, 120.2, 95.2, 86.8, 40.5, 34.4, 30.1; **HRMS (ESI-TOF)** m/z: $[M–H]^-$ $C_{30}H_{30}NO$ 420.2322; found 420.2336.

2-(4-hydroxy-3,5-diisopropylphenyl)-2-phenylacetonitrile (23ac) :



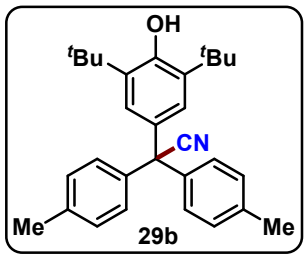
White solid, 43 mg, 78% yield; mp = 99-100 °C; R_f = 0.50 (petroleum ether/ethyl acetate = 90/10); **^{1}H NMR (500 MHz, $CDCl_3$) δ** = 7.39 - 7.28 (m, 5 H), 6.99 (s, 2 H), 5.08 (s, 1 H), 4.97 (br. s., 1 H), 3.13 (spt, *J* = 6.8 Hz, 2 H), 1.23 (d, *J* = 6.9 Hz, 12 H); **^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ** = 149.9, 136.4, 134.6, 129.8, 129.0, 127.9, 127.5, 123.0, 120.2, 42.3, 27.3, 22.5; **HRMS (ESI-TOF)** m/z: $[M–H]^-$ calcd for $C_{20}H_{22}NO$ 292.1696; found 292.1710.

2-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-2,2-diphenylacetonitrile (29a):



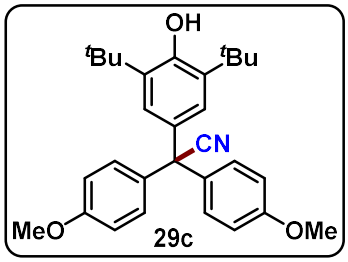
Off white solid, 43 mg, 80% yield; mp = 137-138 °C; R_f = 0.60 (petroleum ether/ethyl acetate = 98/02); **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 7.35 (m, 6 H), 7.23 (d, *J*=6.10 Hz, 4 H), 6.97 (s, 2 H), 5.29 (s, 1 H), 1.35 (s, 18 H); **^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ** = 153.7, 141.3, 136.1, 130.7, 129.1, 128.8, 128.2, 126.1, 124.2, 57.6, 34.8, 30.4; **HRMS (ESI-TOF)** m/z: $[M–H]^-$ calcd for $C_{28}H_{30}NO$ 396.2322; found 396.2338.

2-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-2,2-di-*p*-tolylacetonitrile (29b):



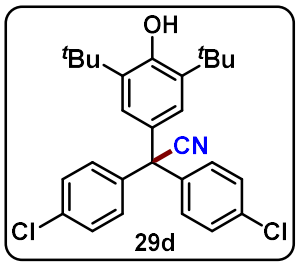
Off white solid, 45 mg, 84% yield; mp = 141-143 °C; R_f = 0.70 (petroleum ether/ethyl acetate = 98/02); **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 7.13 (d, *J*=7.93 Hz, 4 H), 7.09 (d, *J*=7.93 Hz, 4 H), 6.97 (s, 2 H), 5.25 (s, 1 H), 2.35 (s, 6 H), 1.34 (s, 18 H); **^{13}C{^{1}H} NMR (100 MHz,$CDCl_3$) δ** = 153.6, 138.6, 137.8, 136.0, 131.0, 129.4, 128.9, 126.0, 124.4, 57.0, 34.8, 30.5, 21.3; **HRMS (ESI-TOF)** m/z: $[M–H]^-$ calcd for $C_{30}H_{34}NO$ 424.2635; found 424.2653.

2-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-2,2-*bis*(4-methoxyphenyl)acetonitrile (29c):



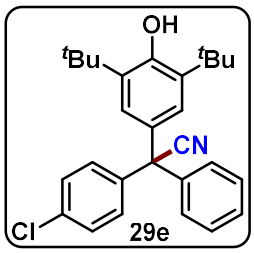
Yellow solid, 43 mg, 81% yield; mp = 135-136 °C; R_f = 0.40 (petroleum ether/ethyl acetate = 95/05); **^{1}H NMR (400 MHz, CDCl$_3$) δ** = 7.12 (d, *J*=8.54 Hz, 4 H) 6.98 (s, 2 H) 6.86 (d, *J*=8.55 Hz, 4 H) 5.27 (s, 1 H) 3.81 (s, 6 H) 1.35 (s, 18 H); **^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$) δ** = 159.0, 153.3, 135.7, 133.4, 131.0, 129.8, 125.5, 124.1, 113.7, 55.9, 55.3, 34.4, 30.1; **HRMS (ESI-TOF)** m/z: [M–H]$^-$ calcd for $C_{30}H_{34}NO_3$ 456.2533; found 456.2552.

2,2-*bis*(4-chlorophenyl)-2-(3,5-di-*tert*-butyl-4-hydroxyphenyl)acetonitrile (29d):



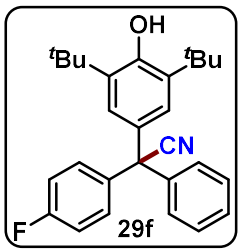
Off white solid, 44 mg, 83% yield; mp = 166-168 °C; R_f = 0.50 (petroleum ether/ethyl acetate = 95/05); **^{1}H NMR (200 MHz, CDCl$_3$) δ** = 7.34 (d, *J*=8.84 Hz, 4 H) 7.14 (d, *J*=8.84 Hz, 4 H) 6.93 (s, 2 H) 5.33 (s, 1 H) 1.34 (s, 18 H); **^{13}C{^{1}H} NMR (50 MHz, CDCl$_3$) δ** = 153.7, 139.2, 136.2, 134.2, 130.0, 129.5, 128.8, 125.4, 123.0, 56.3, 34.5, 30.1; **HRMS (ESI-TOF)** m/z: [M–H]$^-$ calcd for $C_{28}H_{28}Cl_2NO$ 464.1542; found 464.1562.

2-(4-chlorophenyl)-2-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-2-phenylacetonitrile (29e):



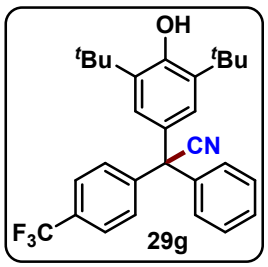
Off white solid, 44 mg, 82% yield; mp = 117-118 °C; R_f = 0.50 (petroleum ether/ethyl acetate = 98/02); **^{1}H NMR (400 MHz, CDCl$_3$) δ** = 7.39 - 7.36 (m, 1 H), 7.36 - 7.33 (m, 3 H), 7.33 - 7.31 (m, 1 H), 7.22 (d, J = 1.8 Hz, 1 H), 7.20 (d, J = 1.8 Hz, 1 H), 7.19 - 7.17 (m, 1 H), 7.17 - 7.14 (m, 1 H), 6.95 (s, 2 H), 5.31 (s, 1 H), 1.35 (s, 18 H); **^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$) δ** = 153.6, 140.4, 139.7, 136.0, 134.0, 130.1, 129.9, 128.6, 128.6, 128.1, 125.6, 123.4, 56.8, 34.4, 30.1; **HRMS (ESI-TOF)** m/z: [M–H]$^-$ calcd for $C_{28}H_{29}ClNO$ 430.1932; found 430.1949.

2-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-2-(4-fluorophenyl)-2-phenylacetonitrile (29f):



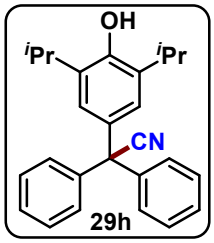
Off white solid, 43 mg, 80% yield; mp = 134-136 °C; R_f = 0.50 (petroleum ether/ethyl acetate = 98/02); **^{1}H NMR (500 MHz, CDCl$_3$) δ** = 7.37 (m, 3 H), 7.22 (m, 4 H), 7.06 (m, 2 H), 6.97 (s, 2 H), 5.33 (s, 1 H), 1.38 (s, 18 H); **^{13}C{^{1}H} NMR (125 MHz, CDCl$_3$) δ** = 163.2-161.2 (d, J = 247.96 Hz), 153.5, 140.8, 136.9, 136.0, 130.6-130.5 (d, J = 7.63 Hz), 130.3, 128.6 (d, J =6.6 Hz), 128.0, 125.6, 123.7, 115.5-115.3 (d, J = 21.93 Hz), 56.7, 34.5, 30.1; **^{19}F NMR (376 MHz, CDCl$_3$) δ** = –114.16; **HRMS (ESI-TOF)** m/z: [M–H]$^-$ calcd for $C_{28}H_{29}FNO$ 414.2228; found 414.2248.

2-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-2-phenyl-2-(4-(trifluoromethyl)phenyl)acetonitrile (29g) :



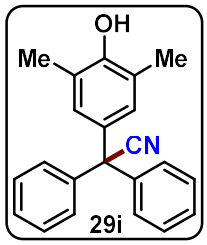
Off white solid, 40 mg, 75% yield; mp = 128-129 °C; R_f = 0.40 (petroleum ether/ethyl acetate = 98/02); **^{1}H NMR (200 MHz, $CDCl_3$) δ** = 7.62 (d, J = 8.2 Hz, 2 H), 7.37 (d, J = 7.1 Hz, 5 H), 7.26 - 7.12 (m, 2 H), 6.94 (s, 2 H), 5.33 (s, 1 H), 1.34 (s, 18 H); **^{13}C{^{1}H} NMR (50 MHz, $CDCl_3$) δ** = 153.7, 145.1, 140.1, 136.2, 129.6, 129.2, 128.7, 128.7, 128.3, 125.6, 125.5, 125.4, 123.2, 34.5, 30.1; **^{19}F NMR (376 MHz, $CDCl_3$) δ** = –62.65; **HRMS (ESI-TOF)** m/z: $[M–H]^-$ calcd for $C_{29}H_{29}F_3NO$ 464.2196; found 464.2210.

2-(4-hydroxy-3,5-diisopropylphenyl)-2,2-diphenylacetonitrile (29h) :



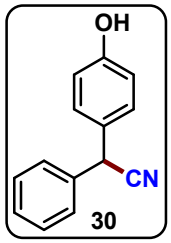
White solid, 48 mg, 90% yield; mp = 149-151 °C; R_f = 0.50 (petroleum ether/ethyl acetate = 95/05); **^{1}H NMR (500 MHz, $CDCl_3$) δ** = 7.44 - 7.30 (m, 6 H), 7.29 - 7.10 (m, 4 H), 6.85 (s, 2 H), 4.95 (s, 1 H), 3.12 (spt, *J* = 6.8 Hz, 2 H), 1.16 (d, *J* = 6.8 Hz, 12 H); **^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ** = 149.7, 140.9, 133.8, 131.7, 128.7, 128.5, 127.9, 124.2, 123.8, 57.1, 27.3, 22.5; **HRMS (ESI-TOF)** m/z: $[M–H]^-$ calcd for $C_{26}H_{26}NO$ 368.2009; found 368.2022.

2-(4-hydroxy-3,5-dimethylphenyl)-2,2-diphenylacetonitrile (29i) :



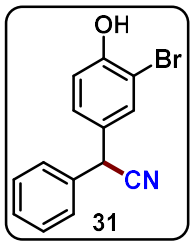
White solid, 50 mg, 91% yield; mp = 177-178 °C; R_f = 0.50 (petroleum ether/ethyl acetate = 95/05); **^{1}H NMR (500 MHz, $CDCl_3$) δ** = 7.42 - 7.34 (m, 6 H), 7.31 - 7.20 (m, 4 H), 6.83 (s, 2 H), 4.90 (s, 1 H), 2.22 (s, 6 H) ; **^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ** = 152.0, 140.6, 131.5, 129.0, 128.7, 128.5, 128.0, 123.8, 123.2, 56.8, 16.1; **HRMS (ESI-TOF)** m/z: $[M–H]^-$ calcd for $C_{22}H_{18}NO$ 312.1383; found 312.1395.

2-(4-hydroxyphenyl)-2-phenylacetonitrile (30) :



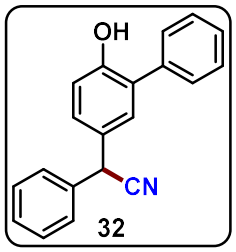
White solid, 26mg, 80% yield; mp = 106-108 °C; R_f = 0.65 (petroleum ether/ethyl acetate = 80/20); **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 7.39 - 7.30 (m, 5 H), 7.17 (d, J = 8.4 Hz, 2 H), 6.83 (d, J = 9.2 Hz, 2 H), 5.91 (br. s., 1 H), 5.09 (s, 1 H) ; **^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ** = 155.7, 135.9, 129.1, 129.0, 128.2, 127.6, 127.5, 120.0, 116.0, 41.7 ; **HRMS (ESI-TOF)** m/z: $[M–H]^-$ calcd for $C_{14}H_{10}NO$ 208.0757; found 208.0763.

2-(3-bromo-4-hydroxyphenyl)-2-phenylacetonitrile (31) :



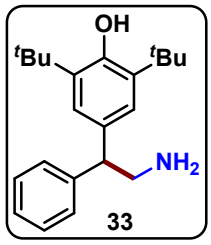
Yellow gummy solid, 46 mg, 67% yield; R_f = 0.50 (petroleum ether/ethyl acetate = 80/20); **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 7.49 - 7.43 (m, 1 H), 7.36 (d, J = 4.0 Hz, 5 H), 7.20 (d, J = 8.7 Hz, 1 H), 7.01 (d, J = 8.3 Hz, 1 H), 6.01 (br. s., 1 H), 5.08 (s, 1 H); **^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ** = 152.3, 135.4, 131.2, 129.3, 128.6, 128.5, 127.6, 116.7, 110.7, 41.4; **HRMS (ESI-TOF)** m/z: $[M-H]^-$ calcd for $C_{14}H_9BrNO$ 285.9862; found 285.9876.

2-(6-hydroxy-[1,1'-biphenyl]-3-yl)-2-phenylacetonitrile (32) :



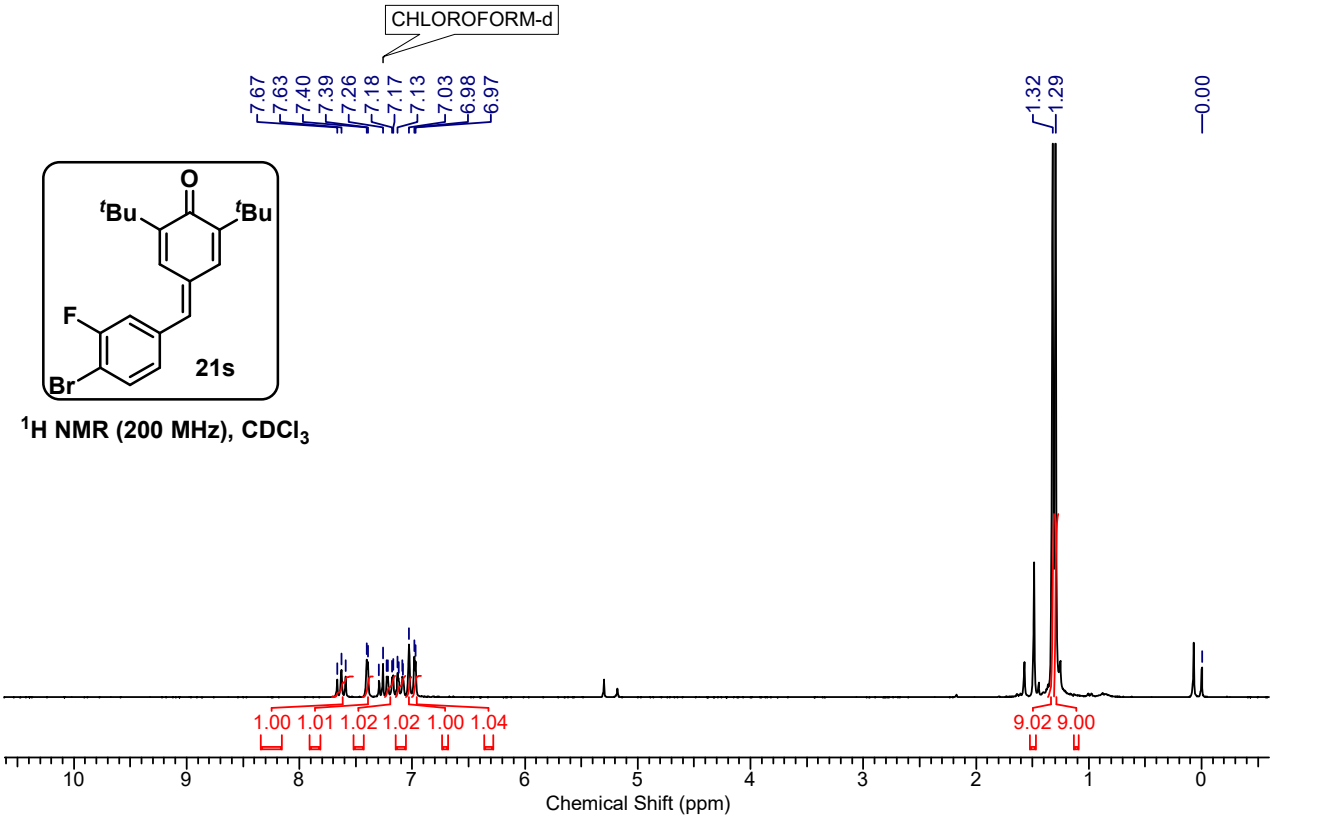
Yellow gummy solid, 31 mg, 63% yield; R_f = 0.55 (petroleum ether/ethyl acetate = 80/20); **^{1}H NMR (200 MHz, $CDCl_3$) δ** = 7.53 - 7.41 (m, 5 H), 7.37 (s, 5 H), 7.23 (s, 1 H), 7.19 (d, J = 2.3 Hz, 1 H), 6.98 (d, J = 9.0 Hz, 1 H), 5.33 (s, 1 H), 5.12 (s, 1 H); **^{13}C{^{1}H} NMR (50 MHz, $CDCl_3$) δ** = 152.4, 136.2, 136.1, 129.5, 129.4, 129.2, 129.0, 128.8, 128.5, 128.3, 128.2, 128.2, 127.6, 119.8, 116.6, 41.9; **HRMS (ESI-TOF)** m/z: $[M-H]^-$ calcd for $C_{20}H_{14}NO$ 284.1070; found 284.1081.

4-(2-amino-1-phenylethyl)-2,6-di-*tert*-butylphenol (33) :

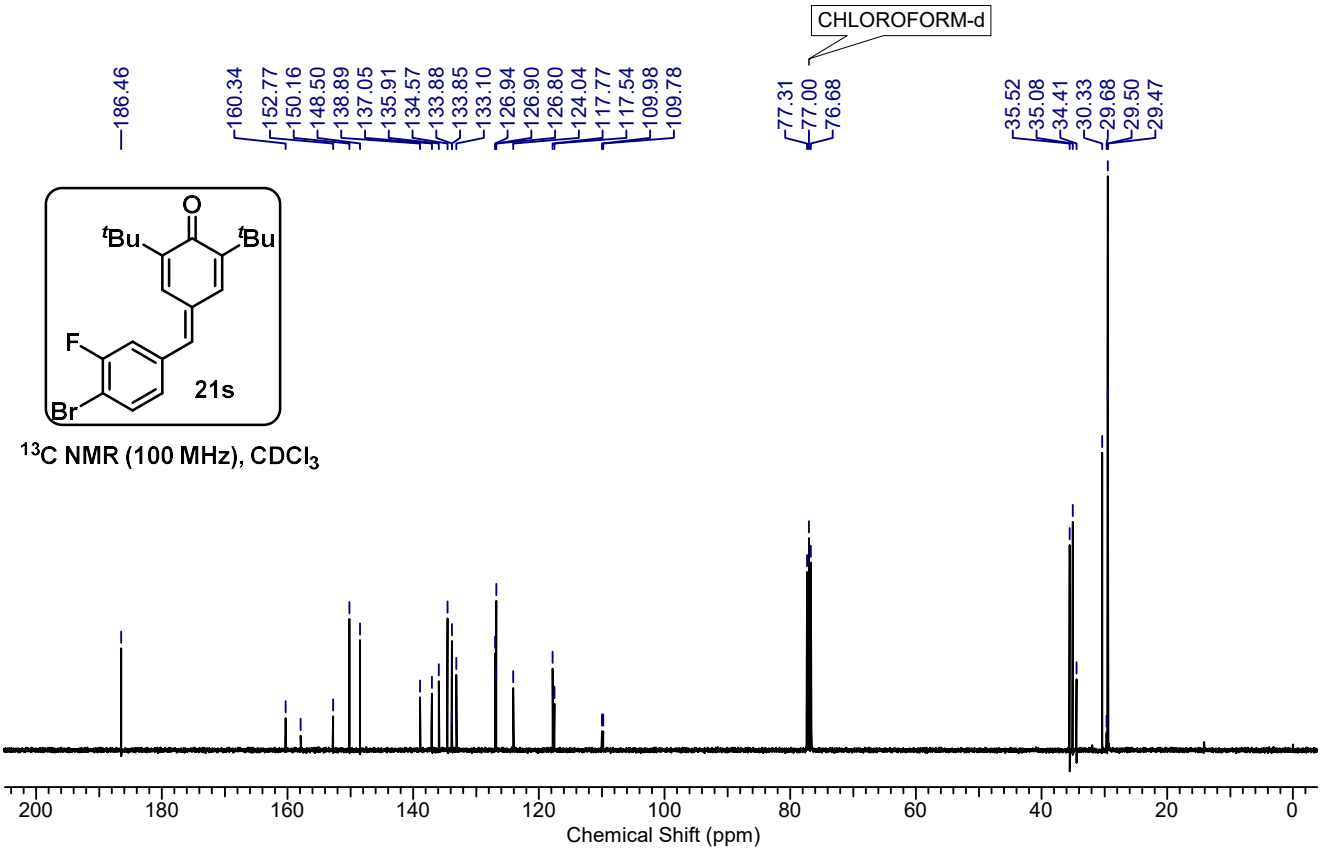


Viscous yellow liquid, 35 mg, 69% yield; R_f = 0.55 (petroleum ether/ethyl acetate = 80/20); **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 7.32 - 7.24 (m, 4 H), 7.21 - 7.16 (m, 1 H), 7.03 (s, 2 H), 3.88 (t, *J* = 7.6 Hz, 1 H), 3.26 (d, *J* = 7.6 Hz, 2 H), 1.40 (s, 18 H); **^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$) δ** = 152.3, 143.2, 135.9, 133.0, 128.5, 128.1, 126.3, 124.4, 55.2, 47.5, 34.3, 30.3; **HRMS (ESI-TOF)** m/z: $[M+H]^+$ calcd for $C_{22}H_{32}NO$ 326.2478; found 326.2480.

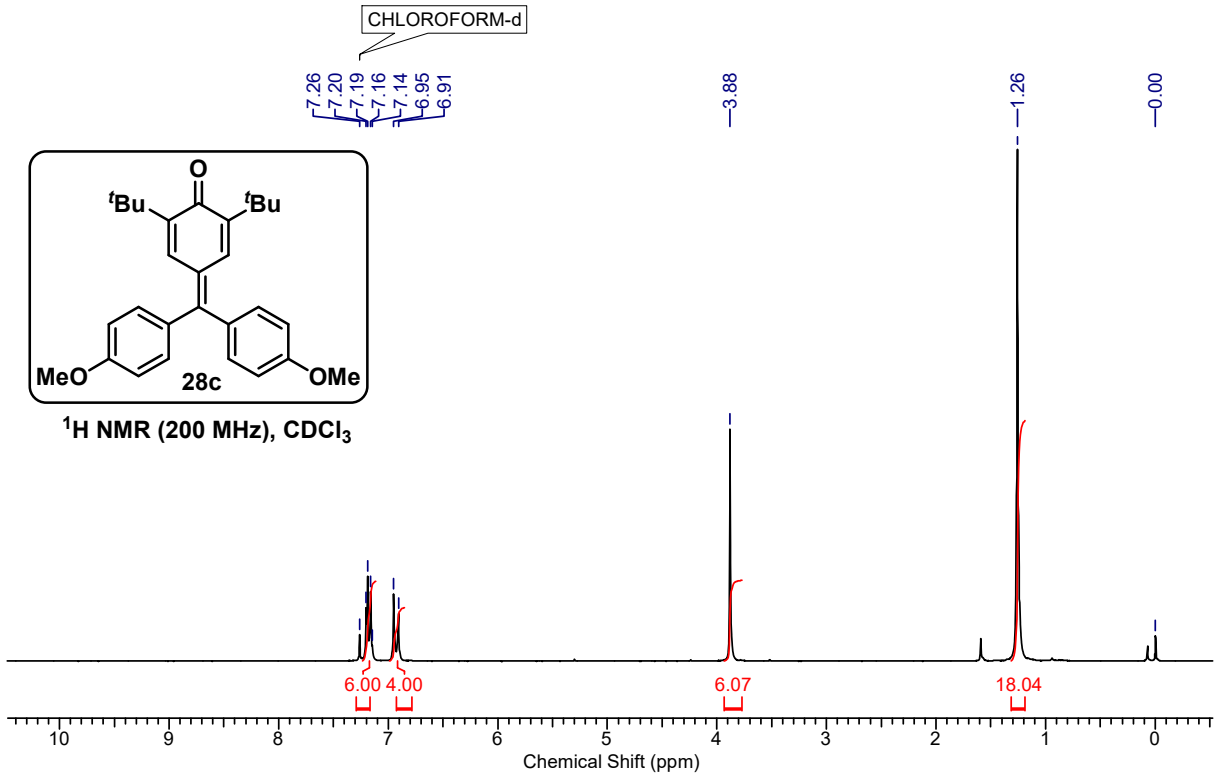
2.1.7 Spectral data

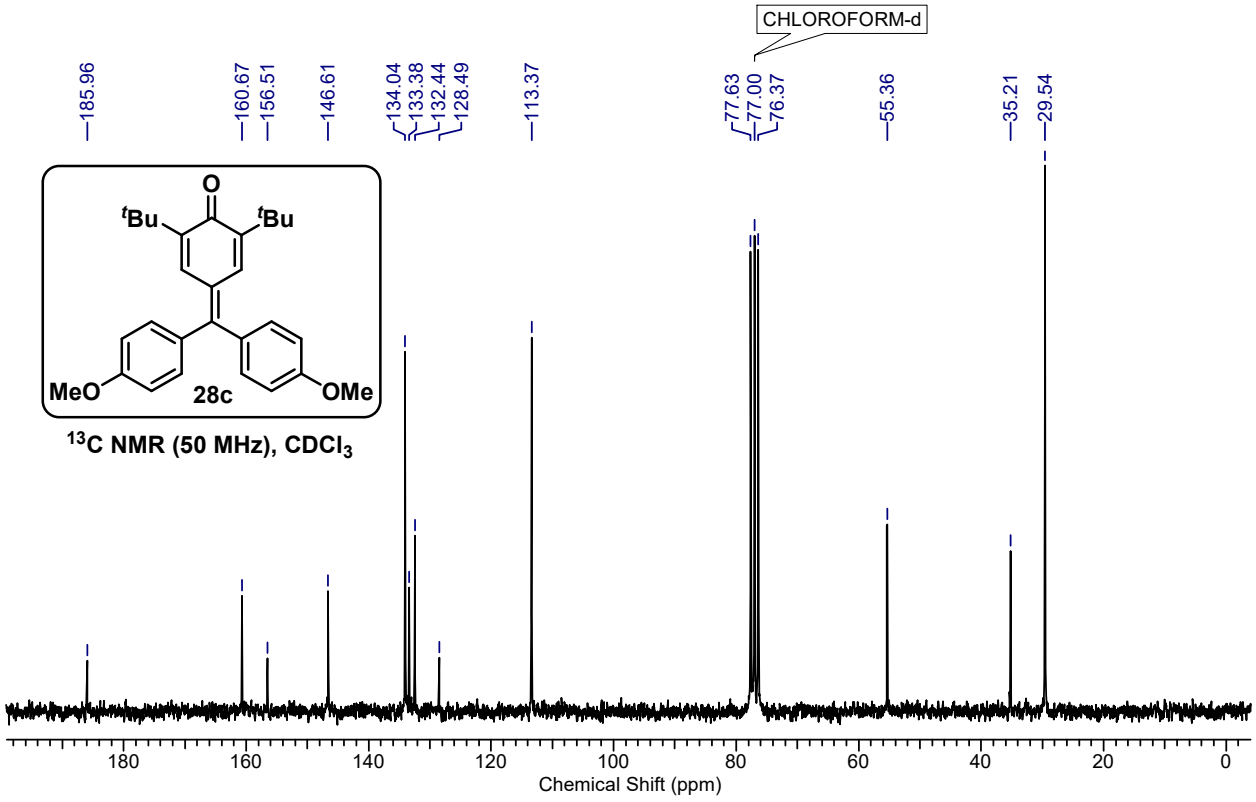


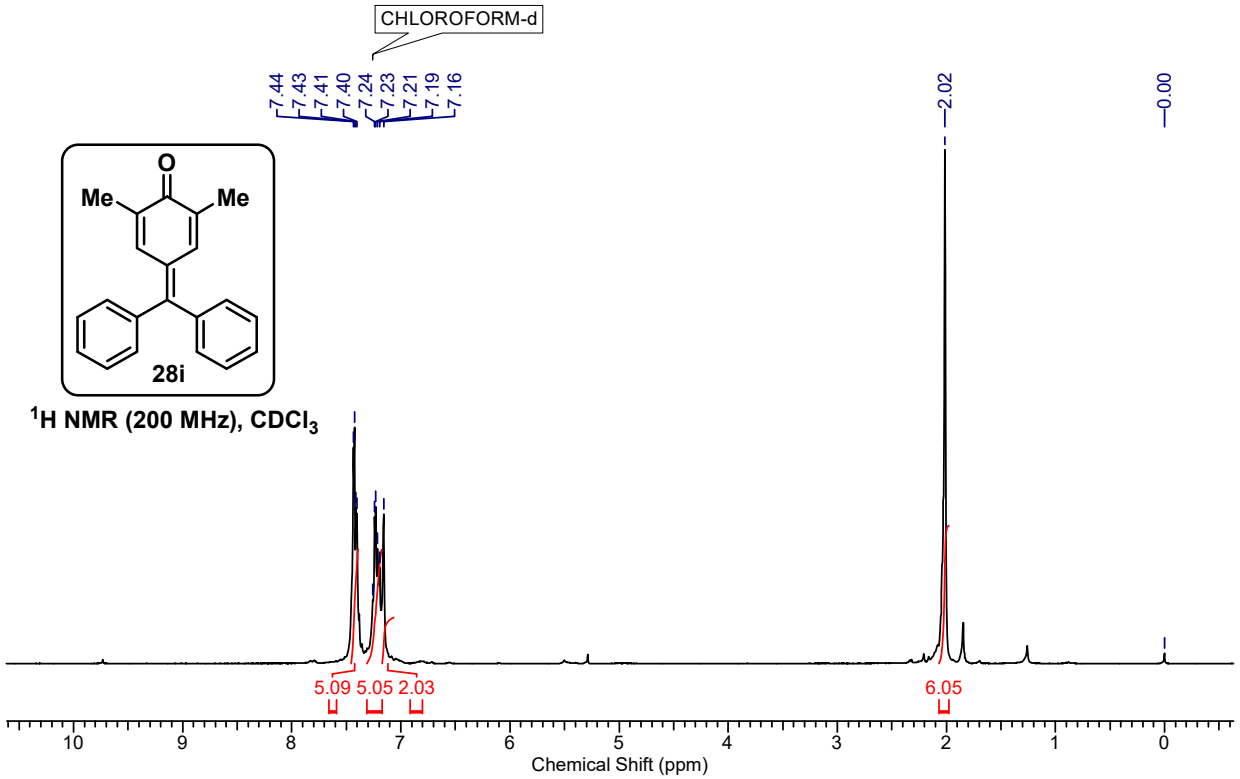
^{1}H NMR (200 MHz), $CDCl_3$

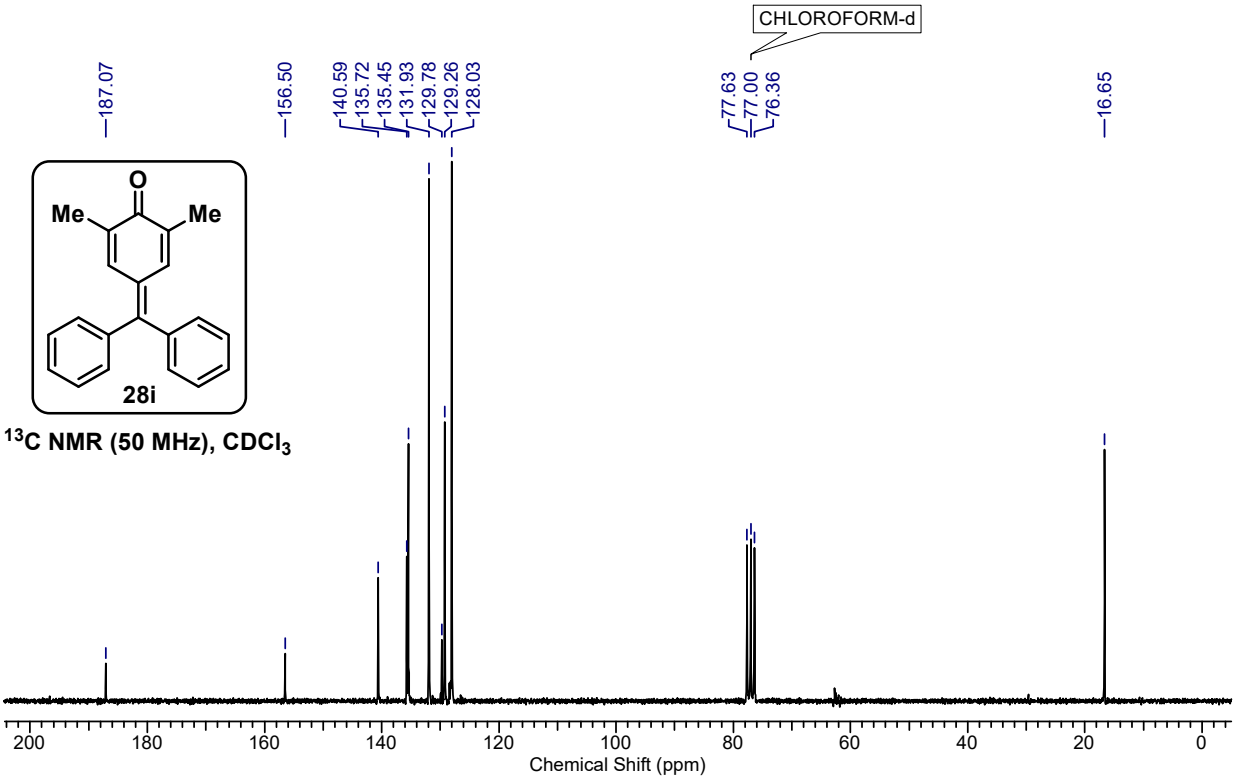


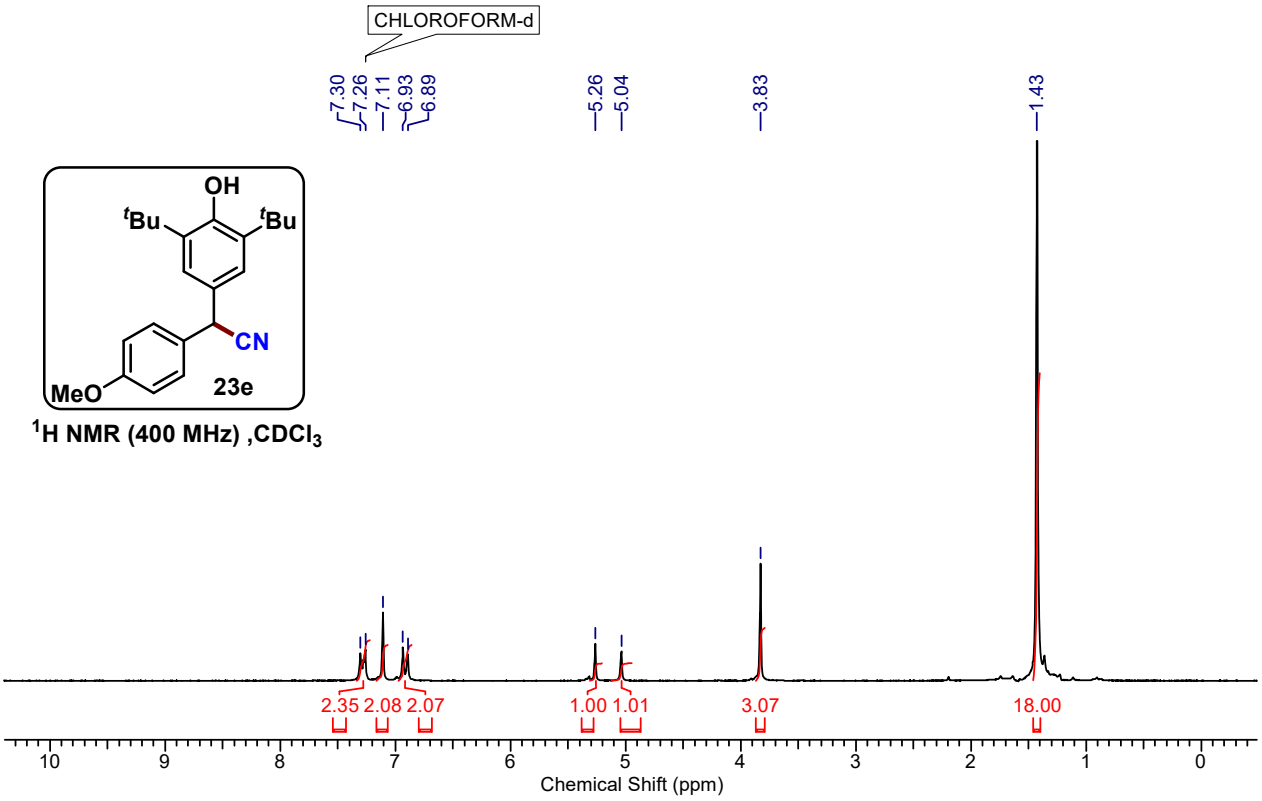
^{13}C NMR (100 MHz), $CDCl_3$


CHLOROFORM-d
7.26
7.20
7.19
7.16
7.14
6.95
6.91
3.88
1.26
0.00
O
tBu
tBu
MeO
OMe
28c
1H NMR (200 MHz), CDCl3
6.00
4.00
6.07
18.04
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

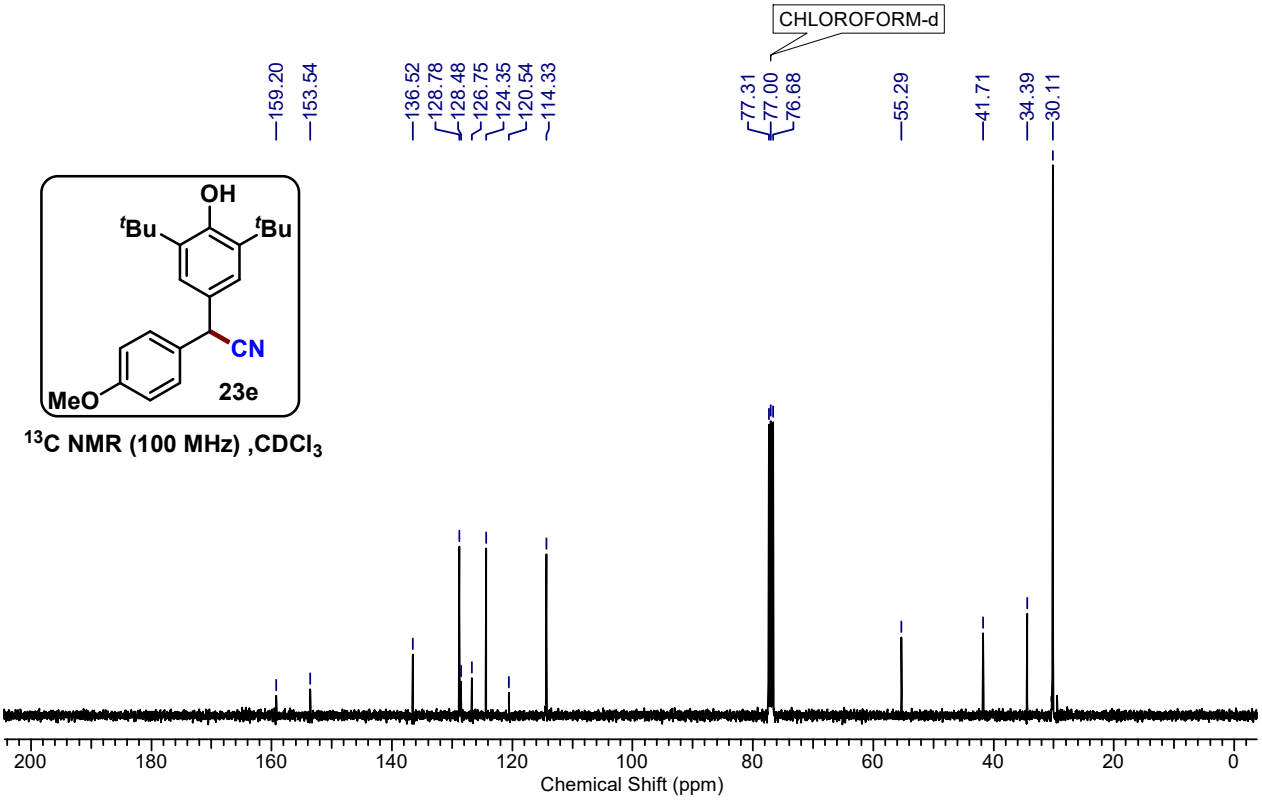

CHLOROFORM-d
185.96
160.67
156.51
146.61
134.04
133.38
132.44
128.49
113.37
77.63
77.00
76.37
55.36
35.21
29.54
O
tBu
tBu
MeO
OMe
28c
13C NMR (50 MHz), CDCl3
180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)


CHLOROFORM-d
7.44
7.43
7.41
7.40
7.24
7.23
7.21
7.19
7.16
2.02
0.00
O
Me
Me
28i
^{1}H NMR (200 MHz), CDCl$_3$
5.09
5.05
2.03
6.05
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

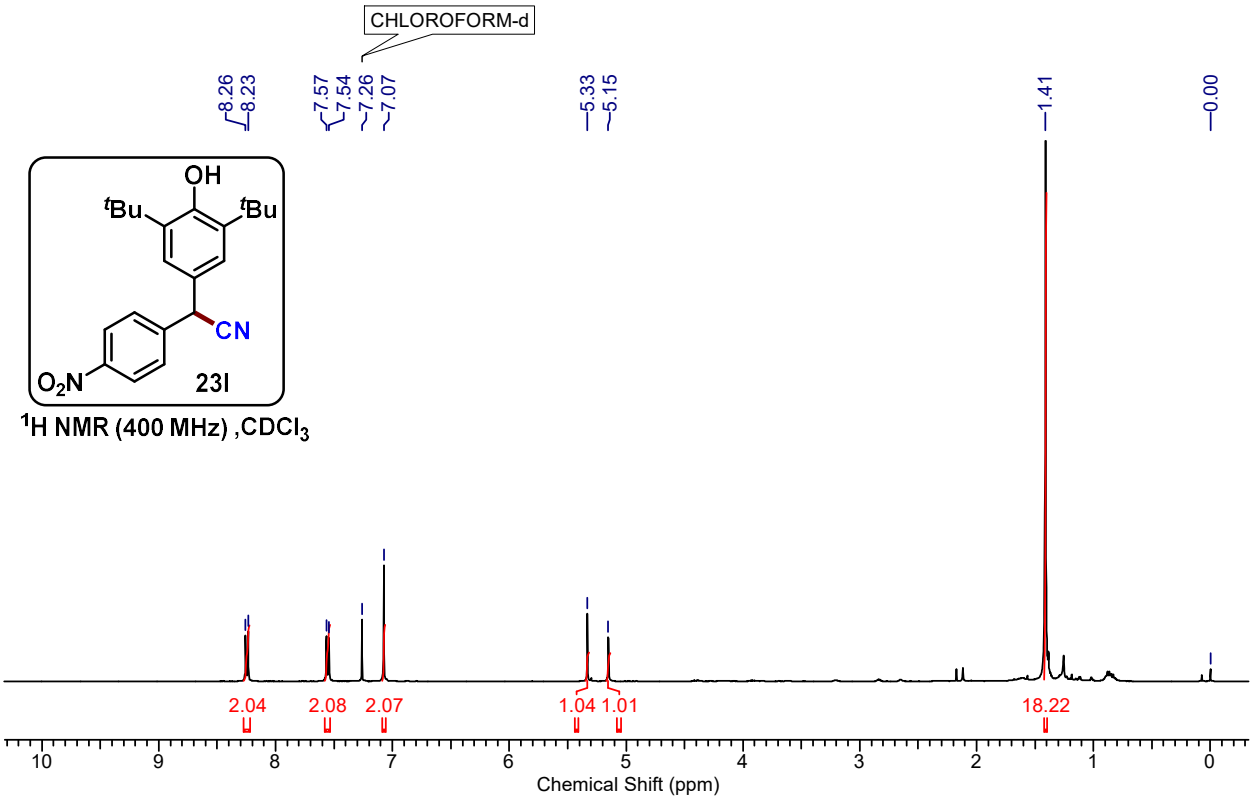

CHLOROFORM-d
187.07
156.50
140.59
135.72
135.45
131.93
129.78
129.26
128.03
77.63
77.00
76.36
16.65
O
Me
Me
28i
^{13}C NMR (50 MHz), CDCl$_3$
200
180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)



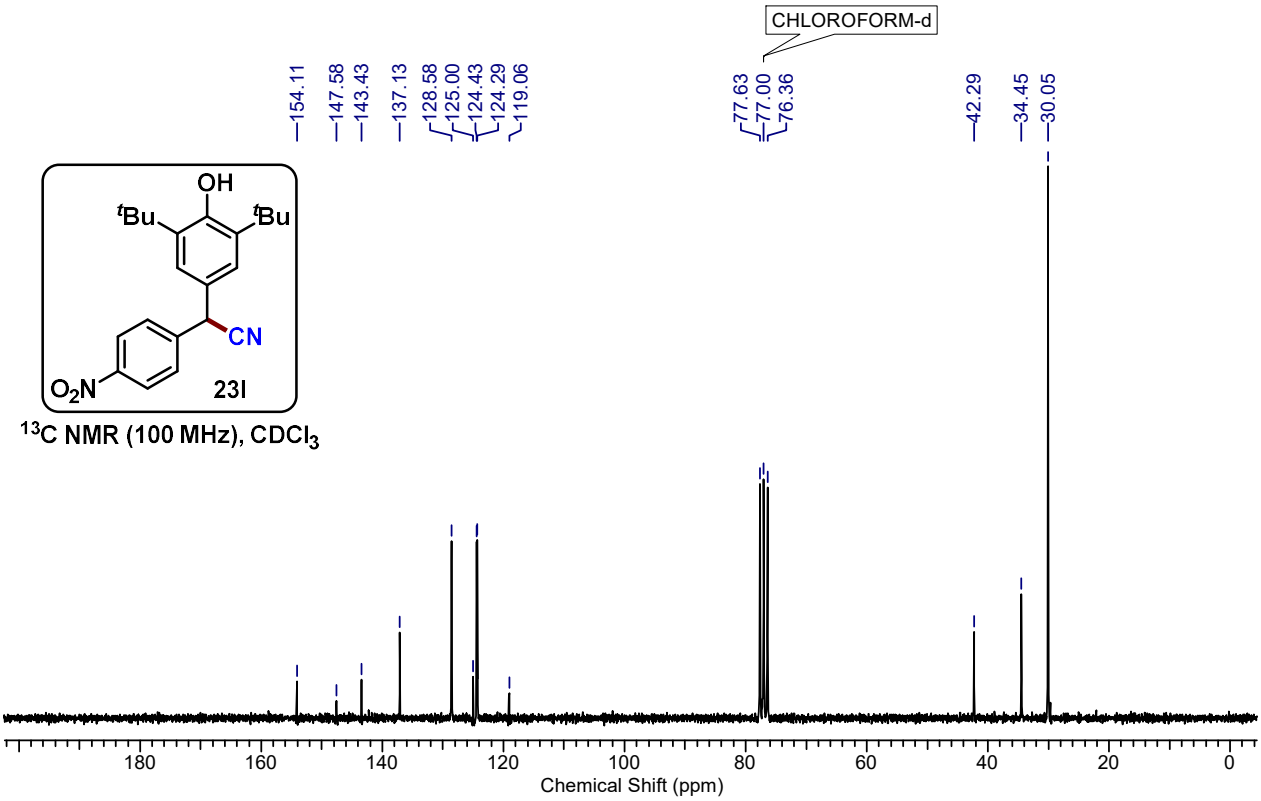
^{1}H NMR (400 MHz) ,$CDCl_3$



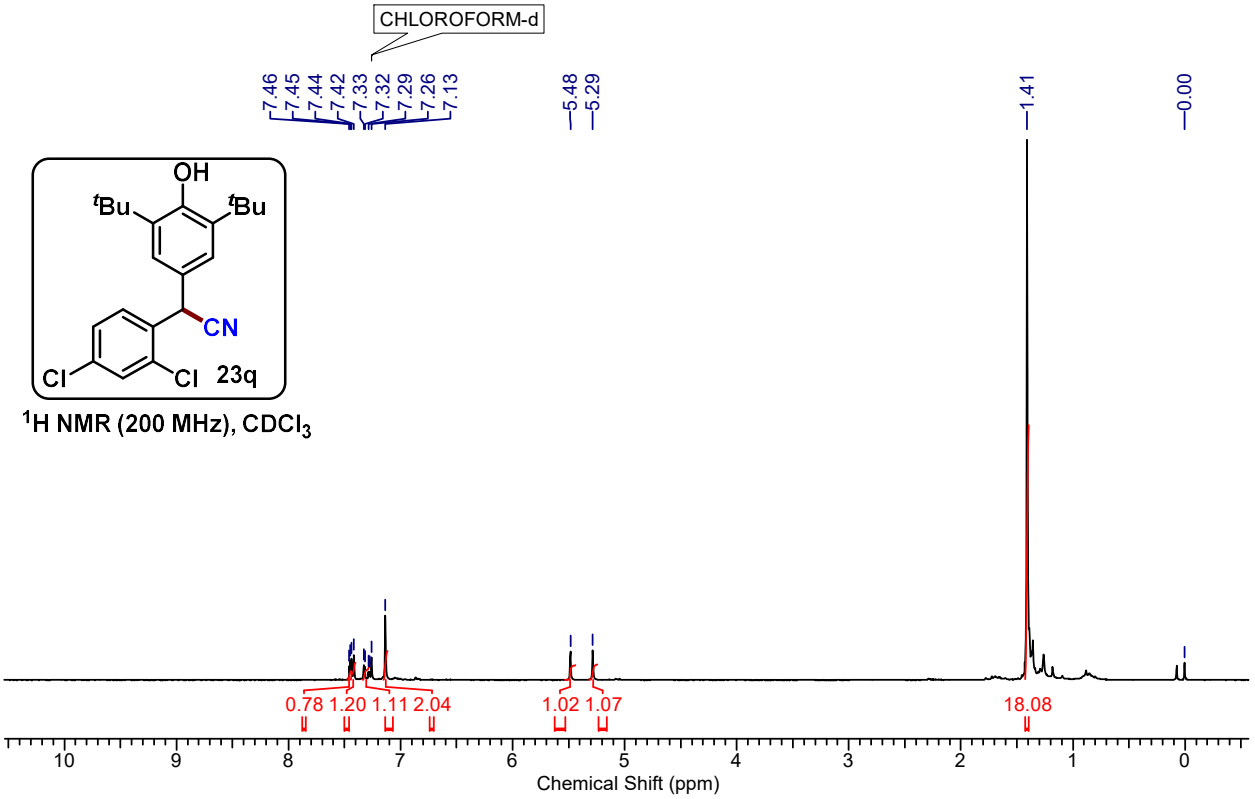
^{13}C NMR (100 MHz) ,$CDCl_3$



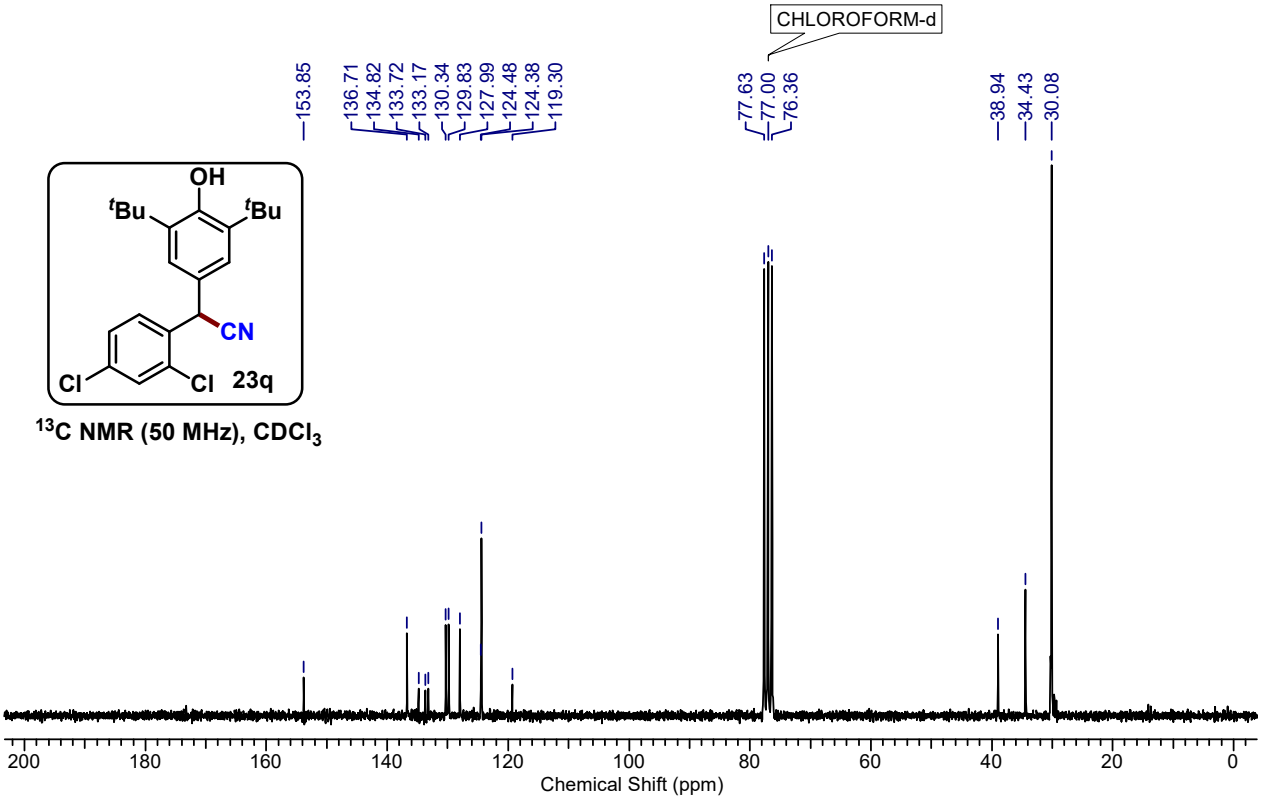
^{1}H NMR (400 MHz) ,$CDCl_3$



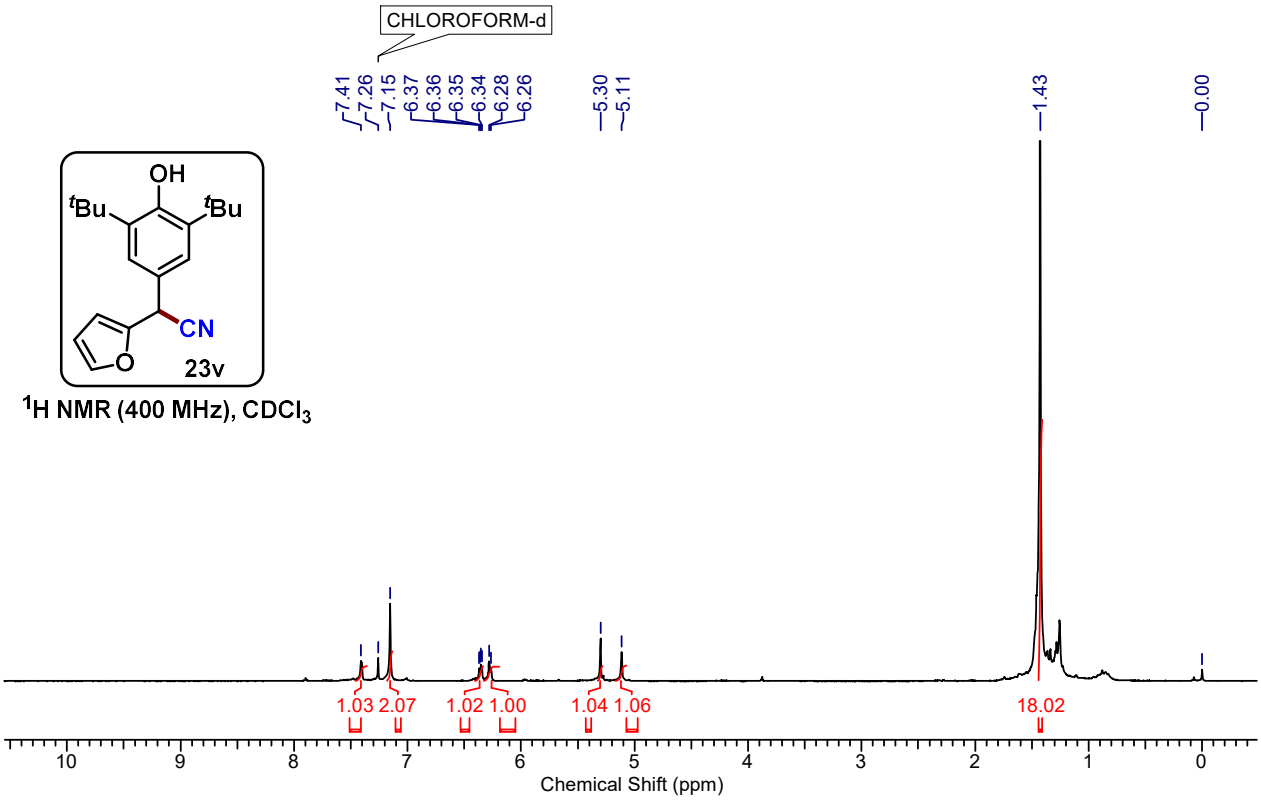
^{13}C NMR (100 MHz), $CDCl_3$



^{1}H NMR (200 MHz), $CDCl_3$



^{13}C NMR (50 MHz), $CDCl_3$



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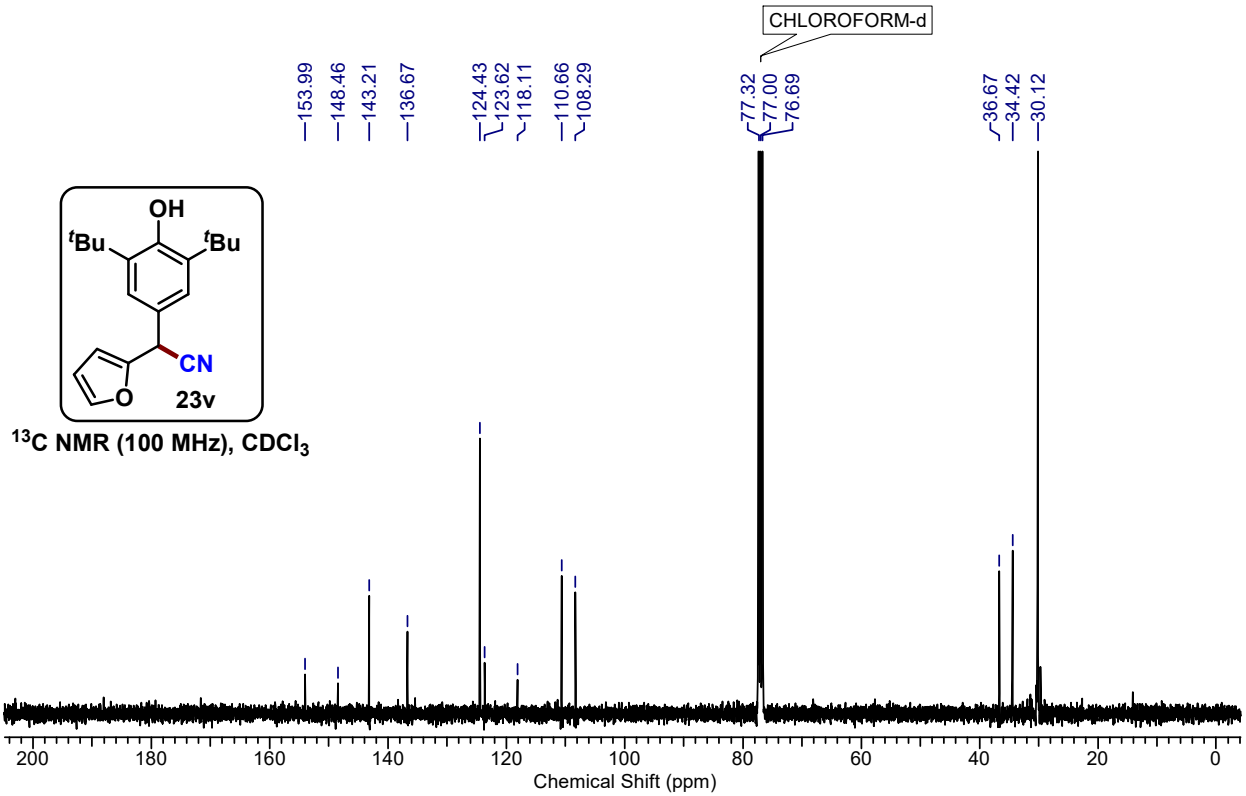
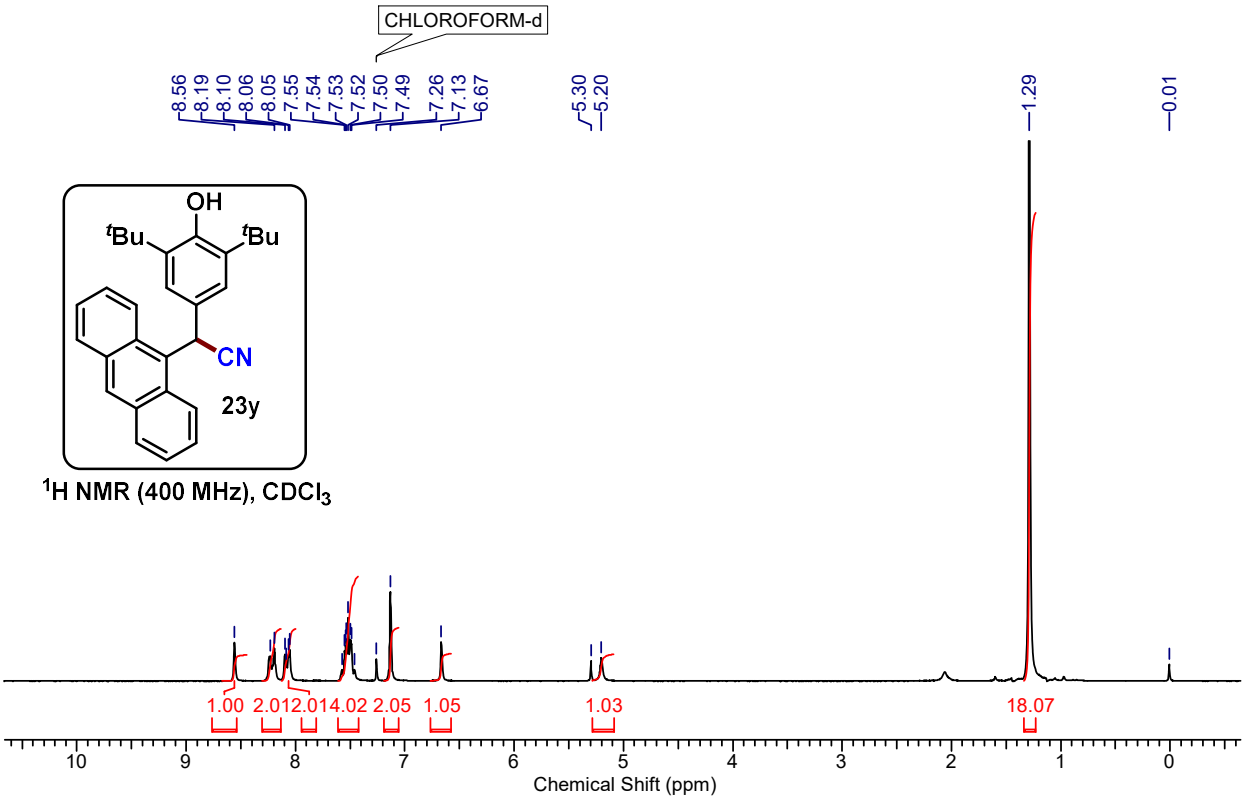
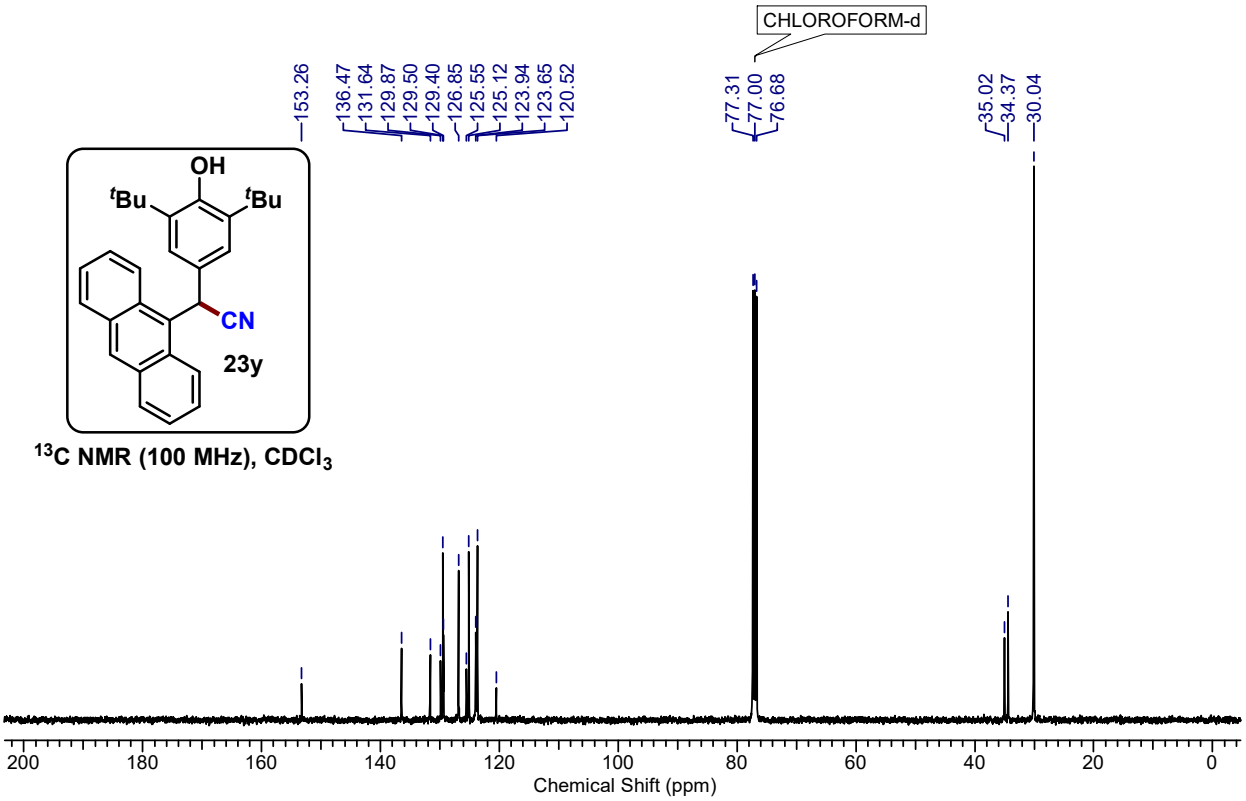


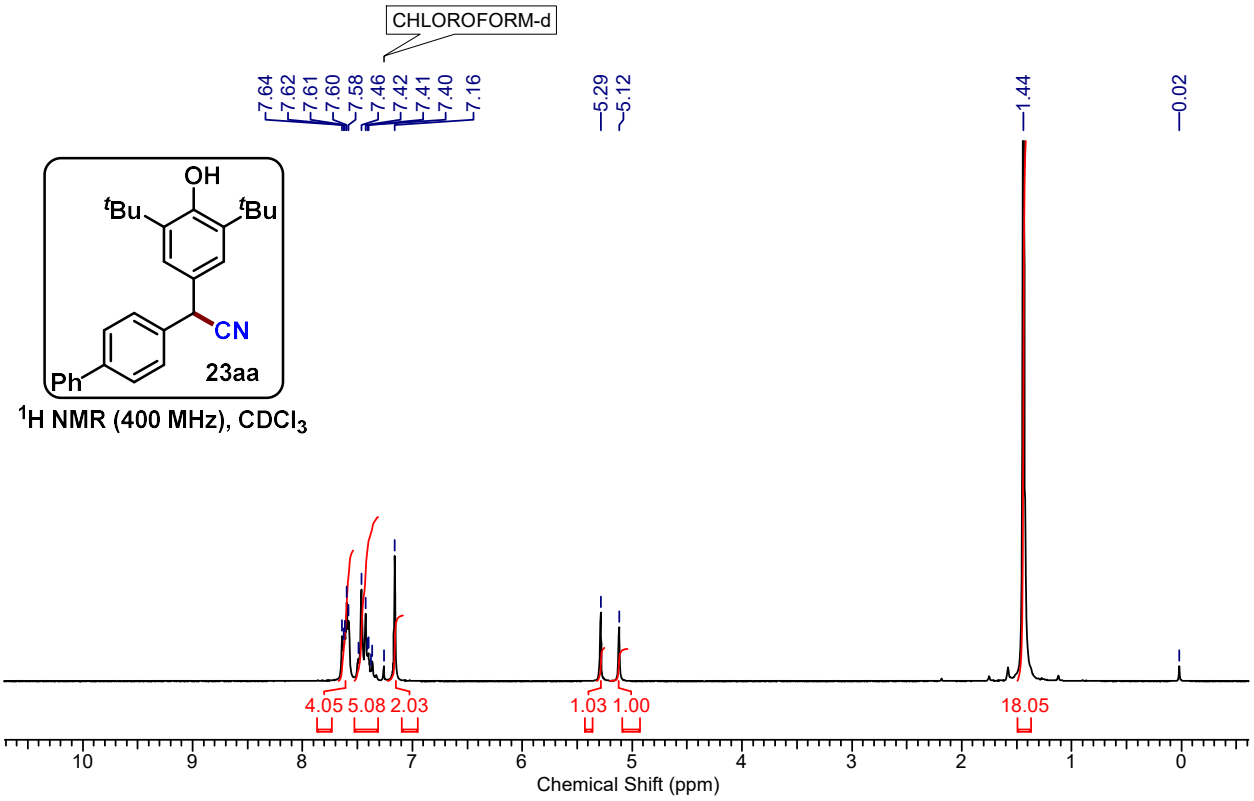
^{13}C NMR (100 MHz), $CDCl_3$



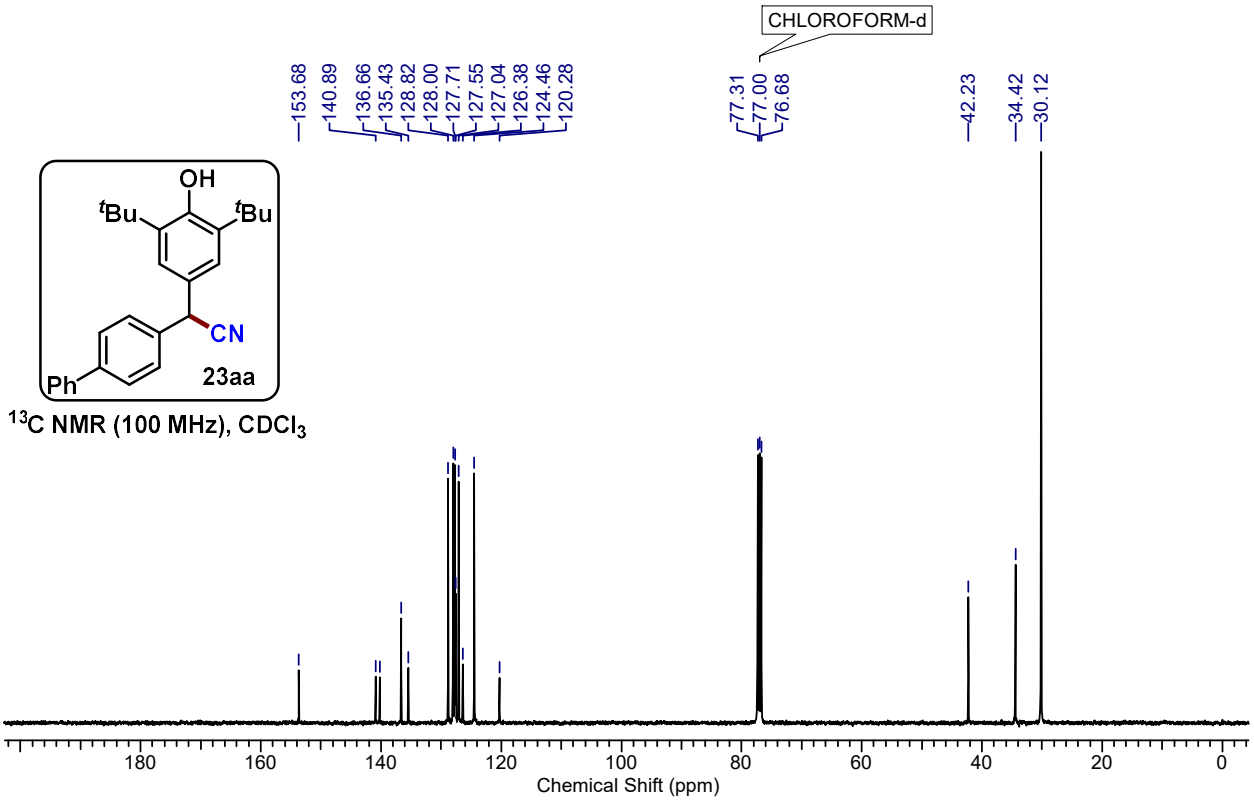
^{1}H NMR (400 MHz), $CDCl_3$



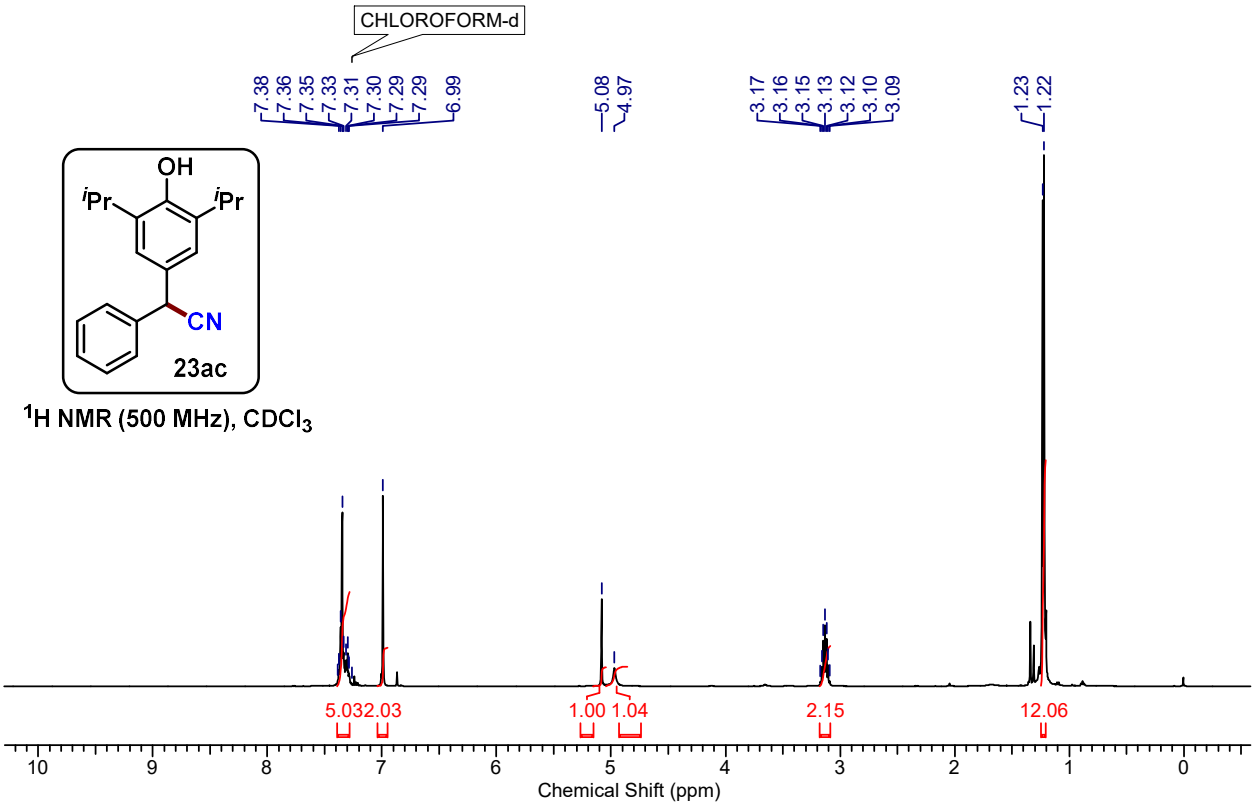
^{13}C NMR (100 MHz), $CDCl_3$



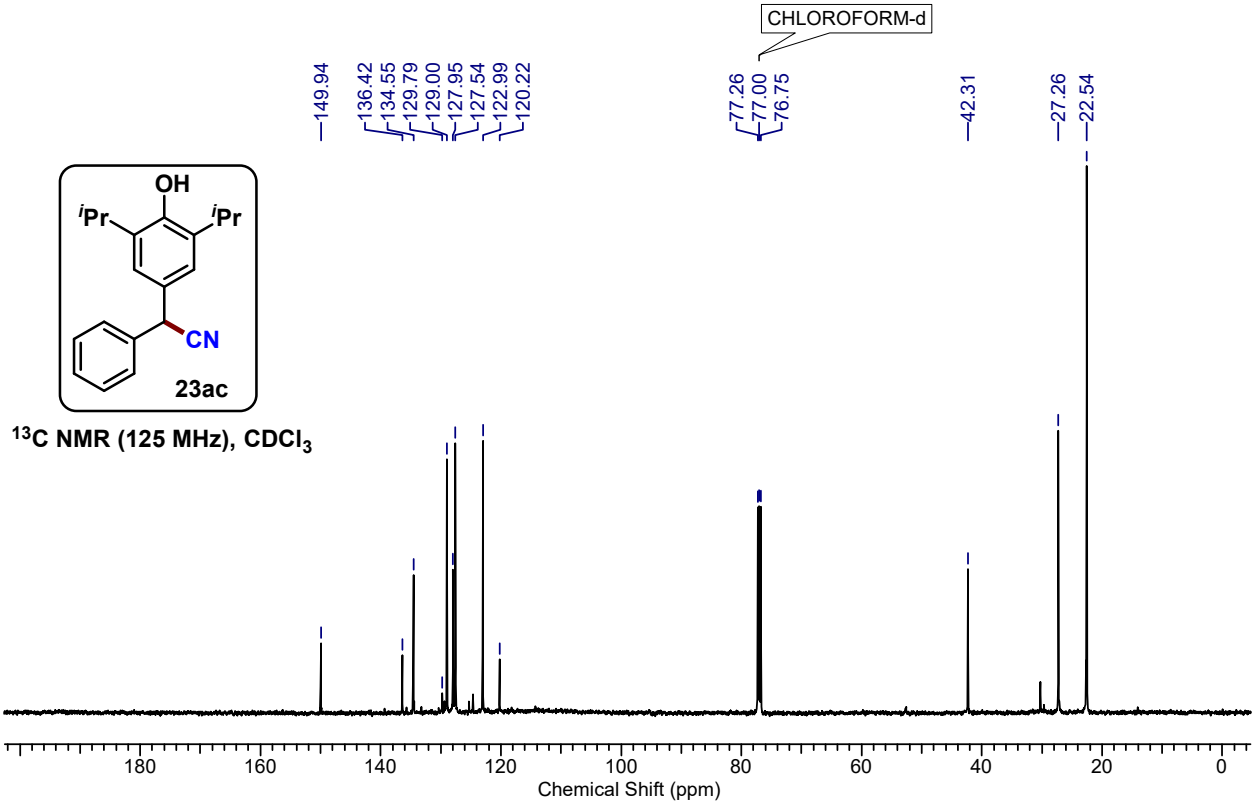
^{1}H NMR (400 MHz), $CDCl_3$



^{13}C NMR (100 MHz), $CDCl_3$



^{1}H NMR (500 MHz), $CDCl_3$



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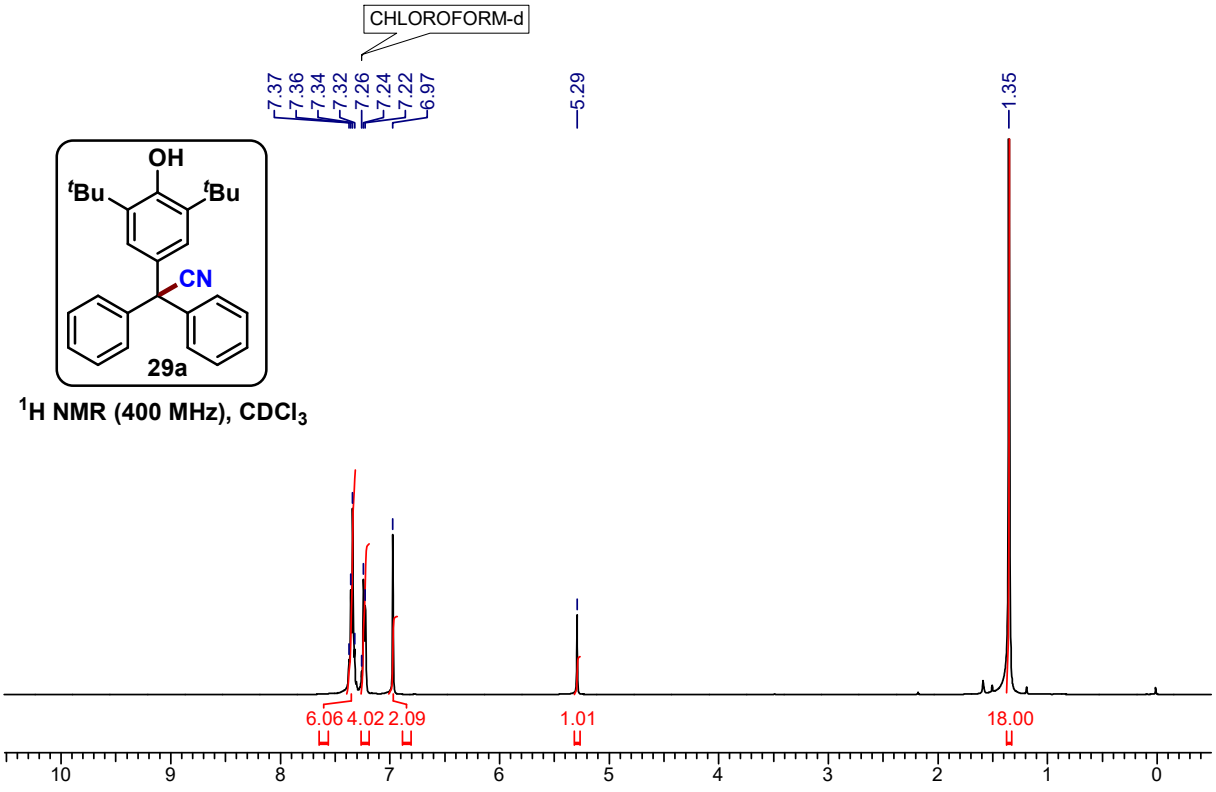
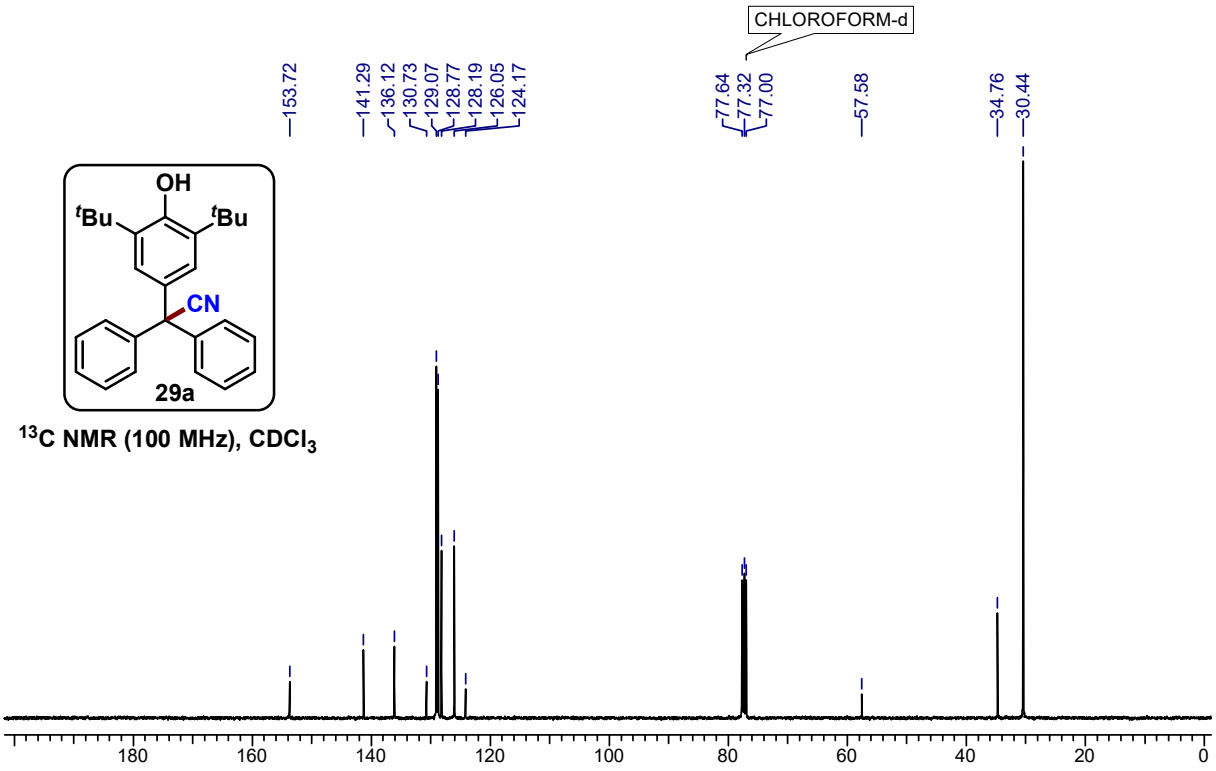
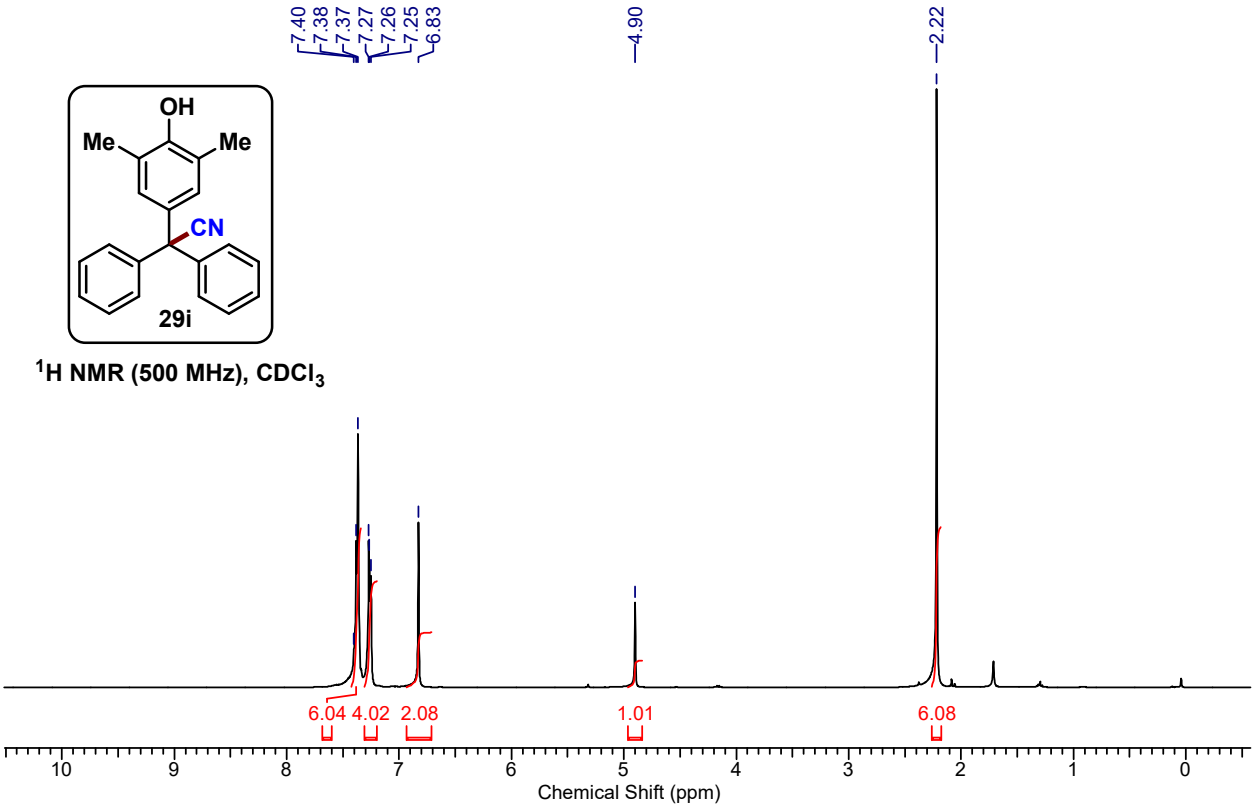


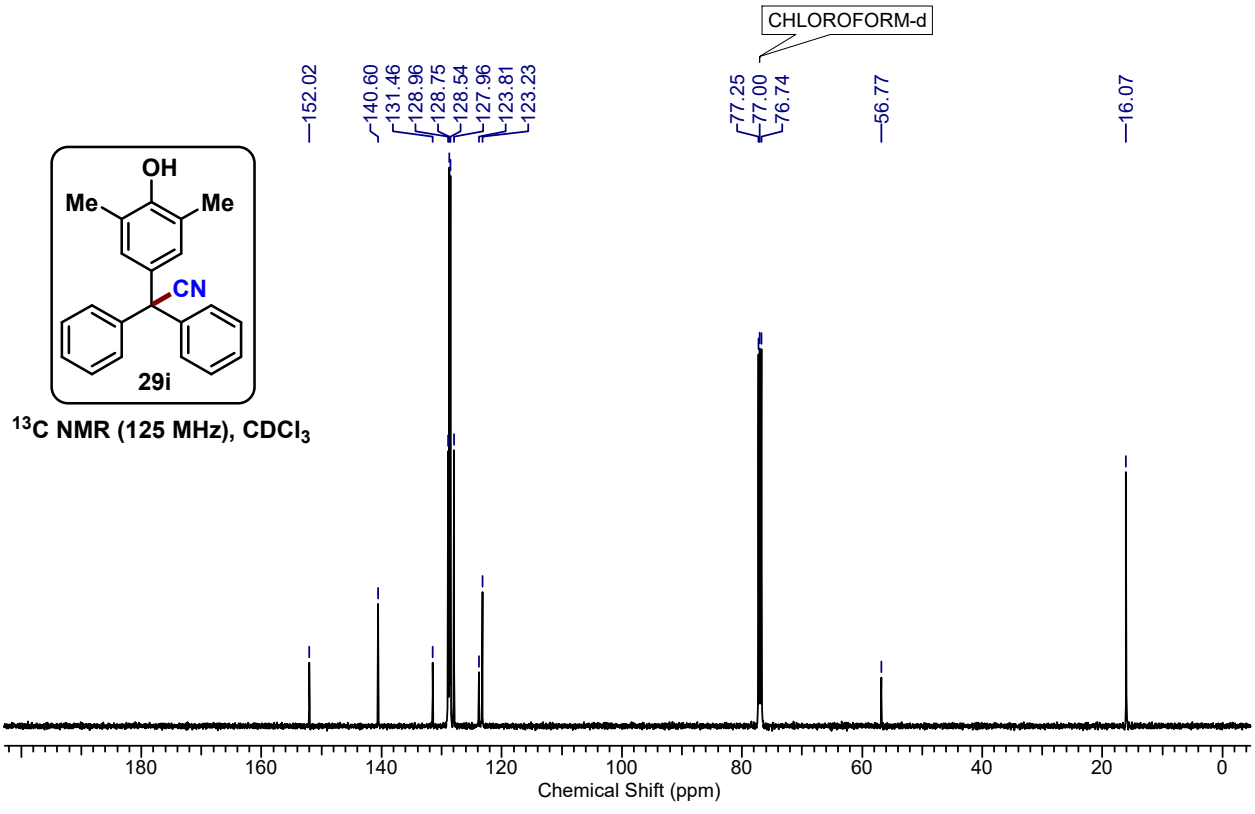
^{1}H NMR (400 MHz), $CDCl_3$



^{13}C NMR (100 MHz), $CDCl_3$



^{1}H NMR (500 MHz), $CDCl_3$



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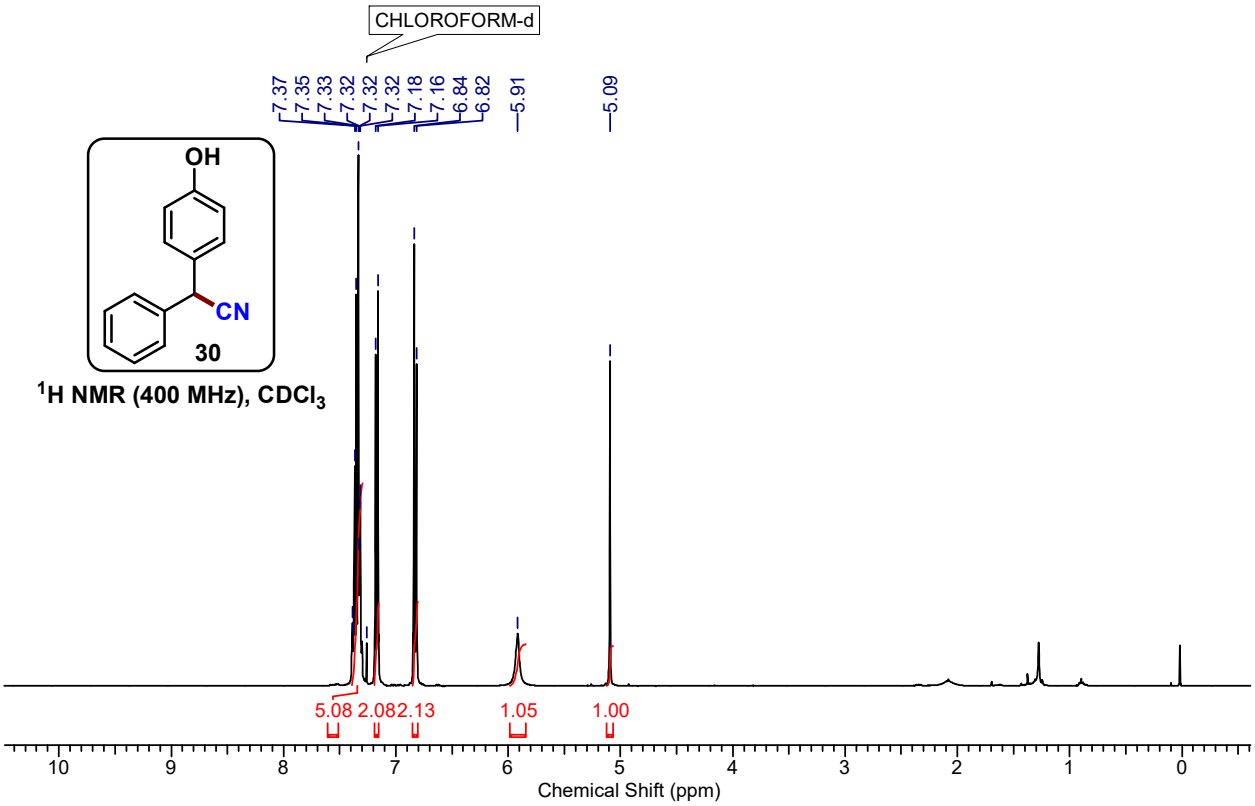
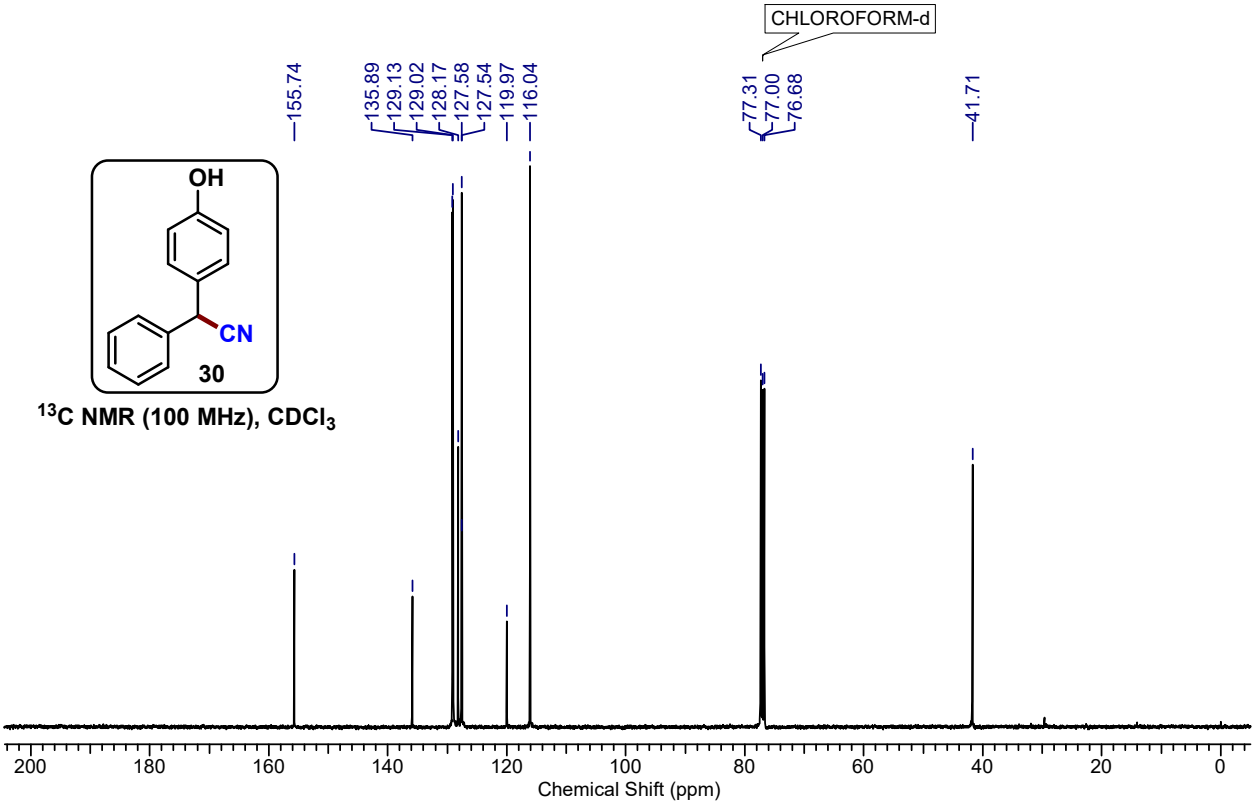
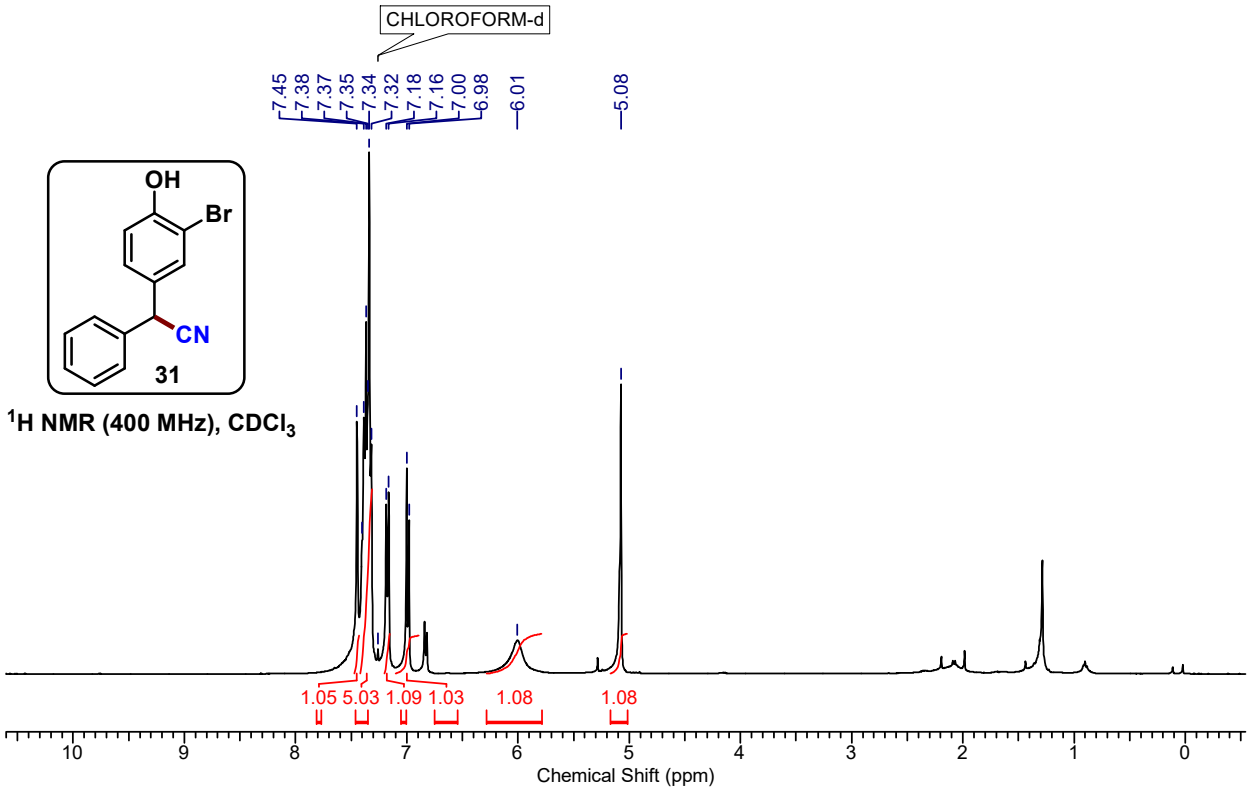


^{1}H NMR (400 MHz), $CDCl_3$



^{13}C NMR (100 MHz), $CDCl_3$



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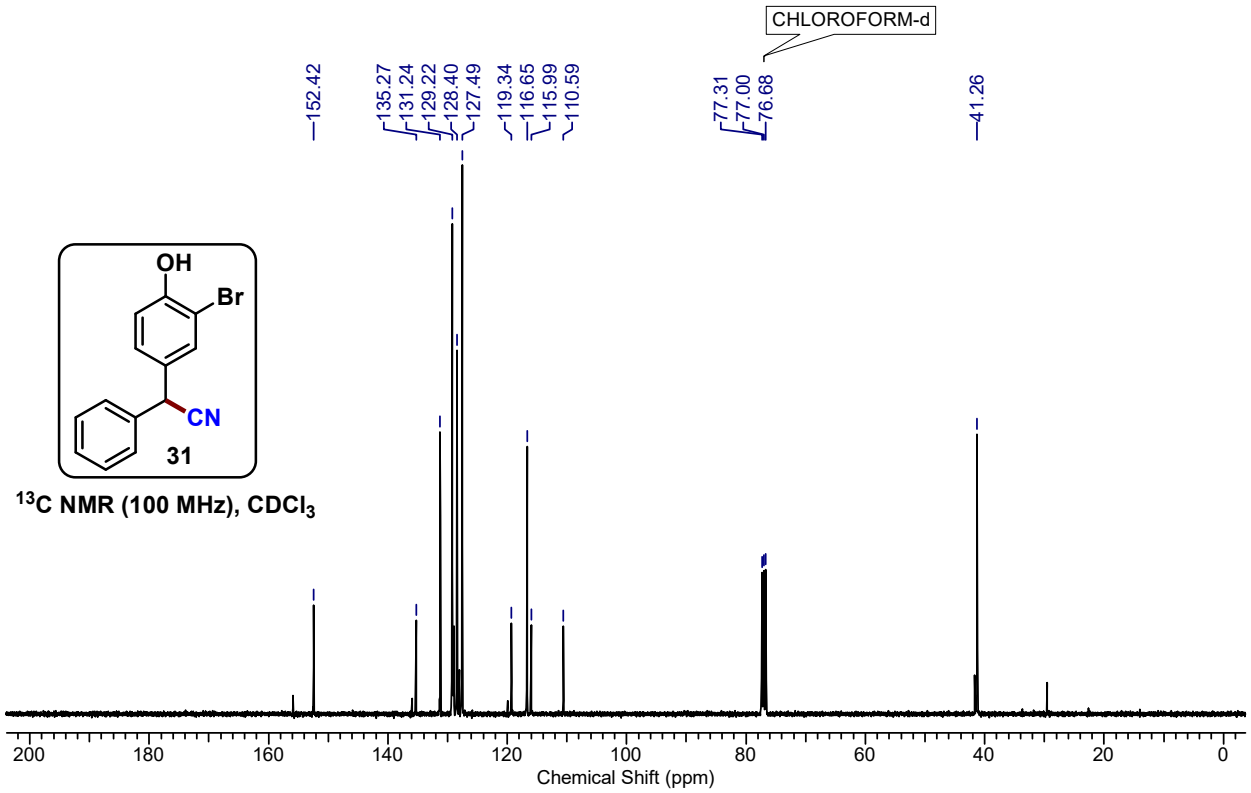

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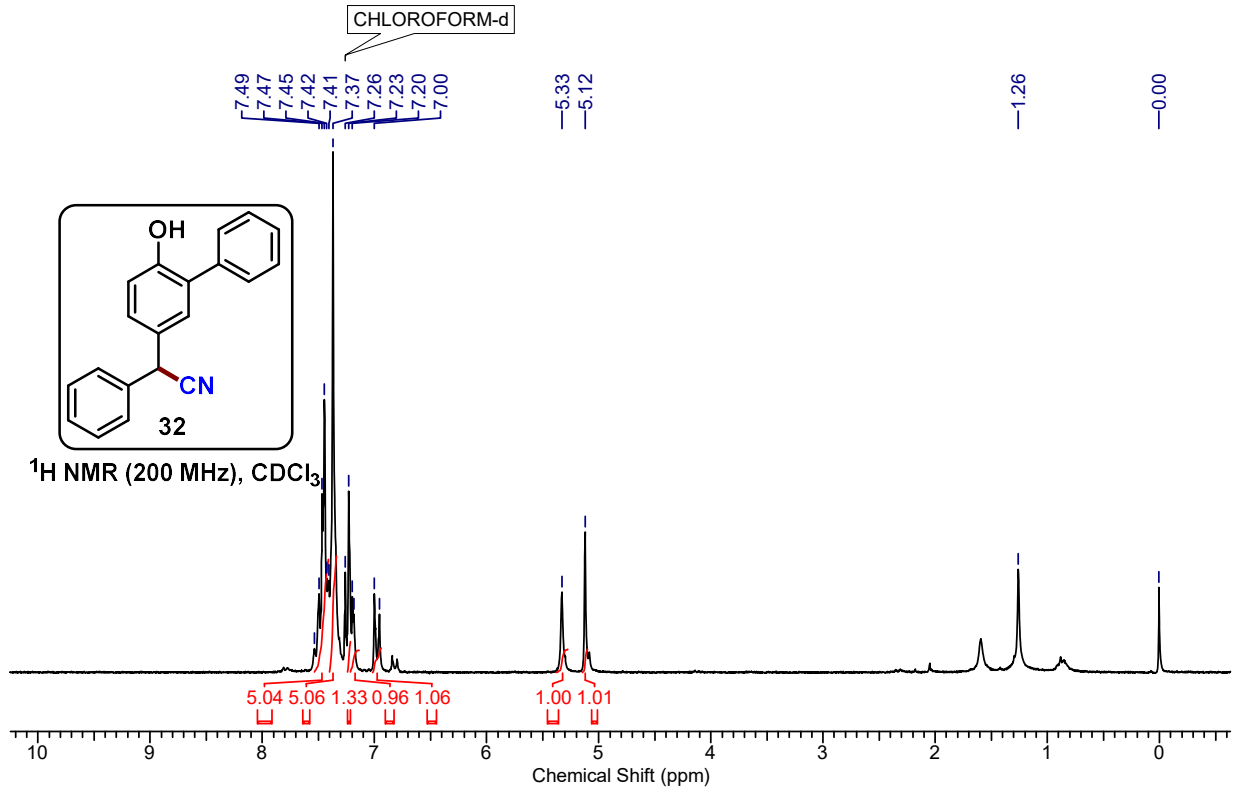
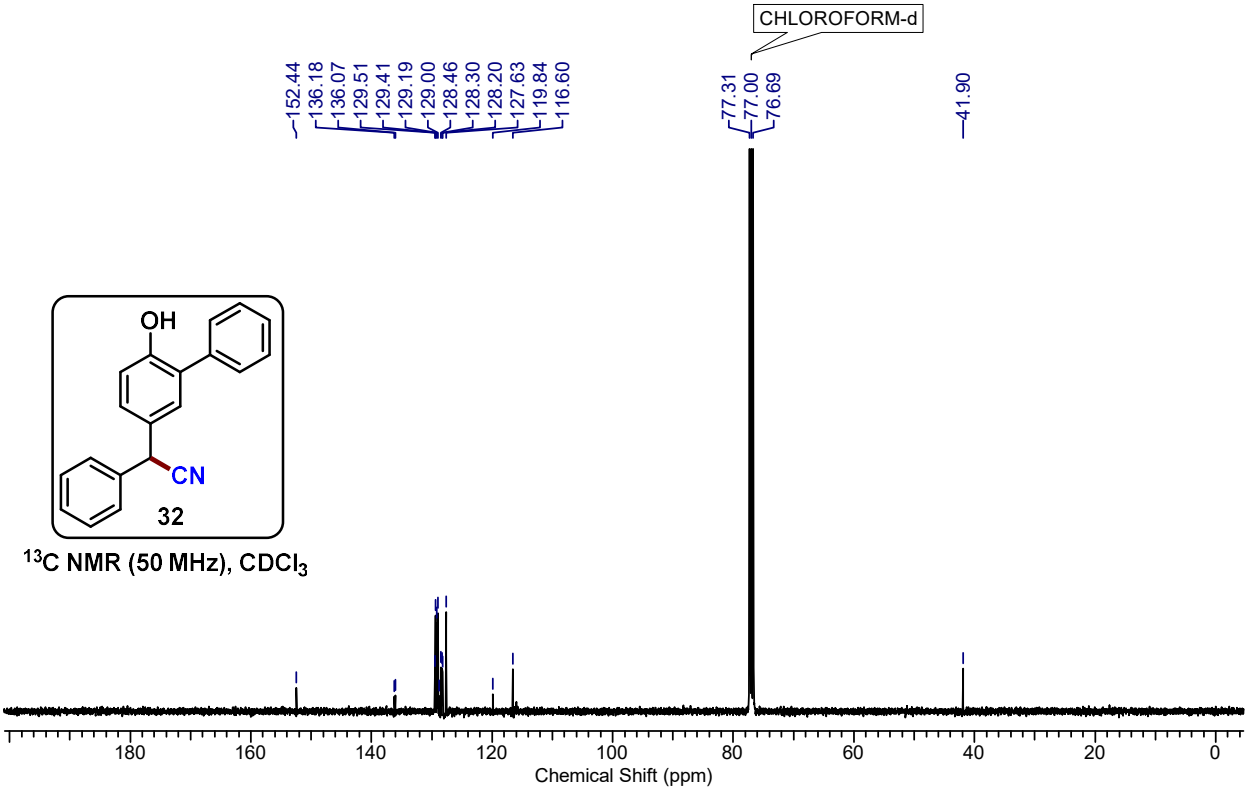
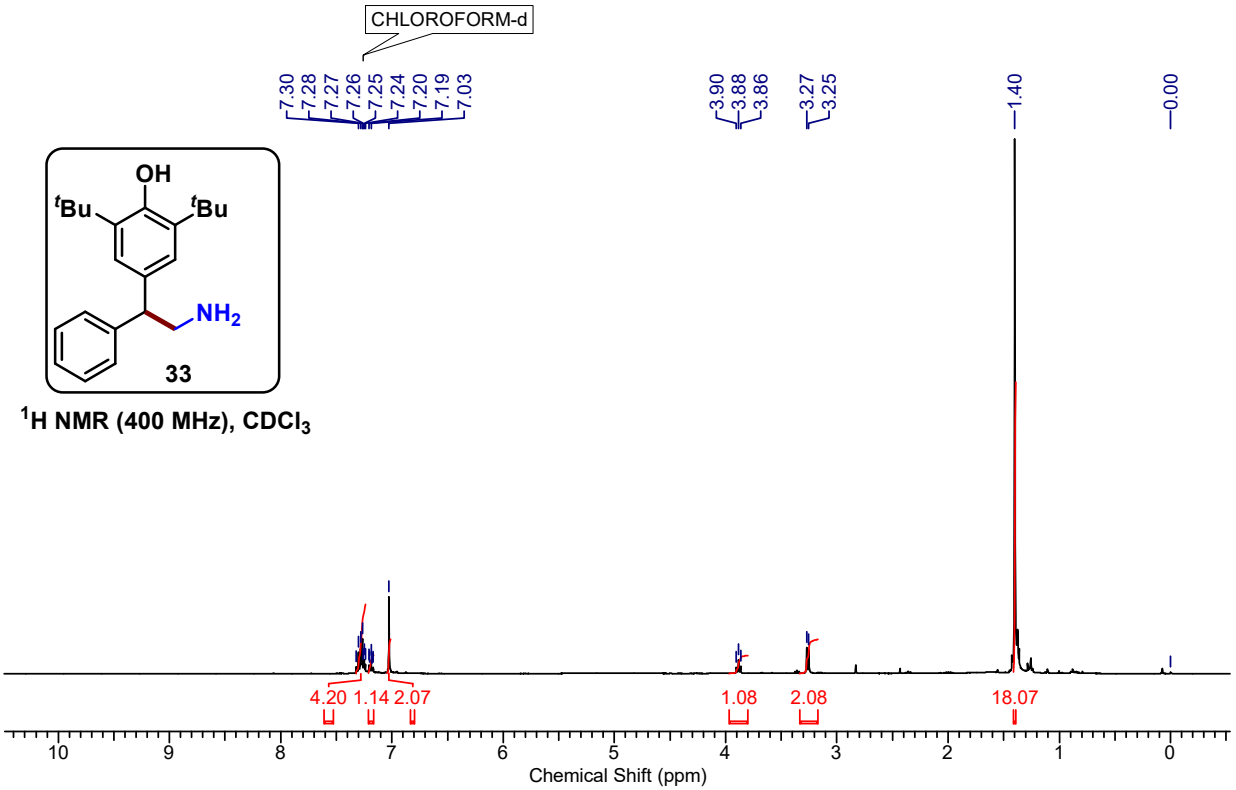
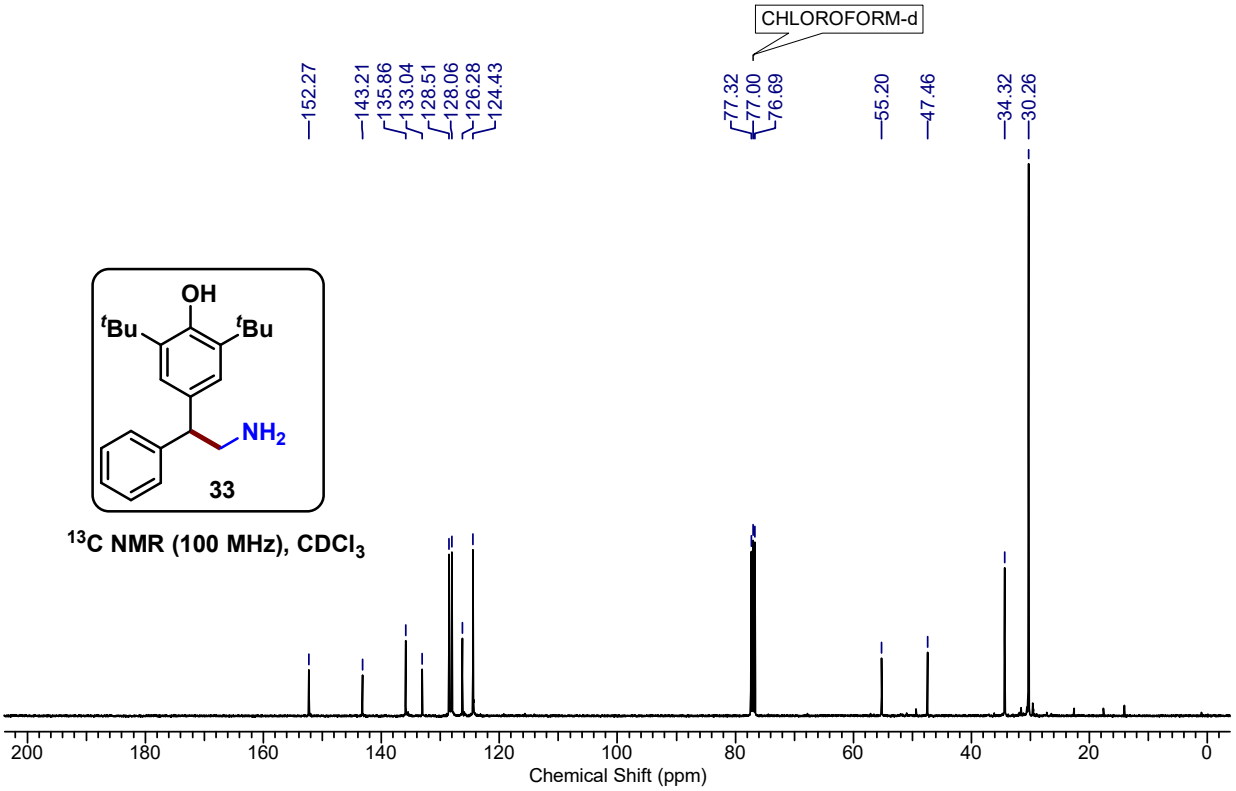

CHLOROFORM-d
7.49
7.47
7.45
7.42
7.41
7.37
7.26
7.23
7.20
7.00
5.33
5.12
1.26
0.00
OH
CN
32
^{1}H NMR (200 MHz), CDCl$_3$
5.04 5.06 1.33 0.96 1.06
1.00 1.01
10 9 8 7 6 5 4 3 2 1 0
Chemical Shift (ppm)

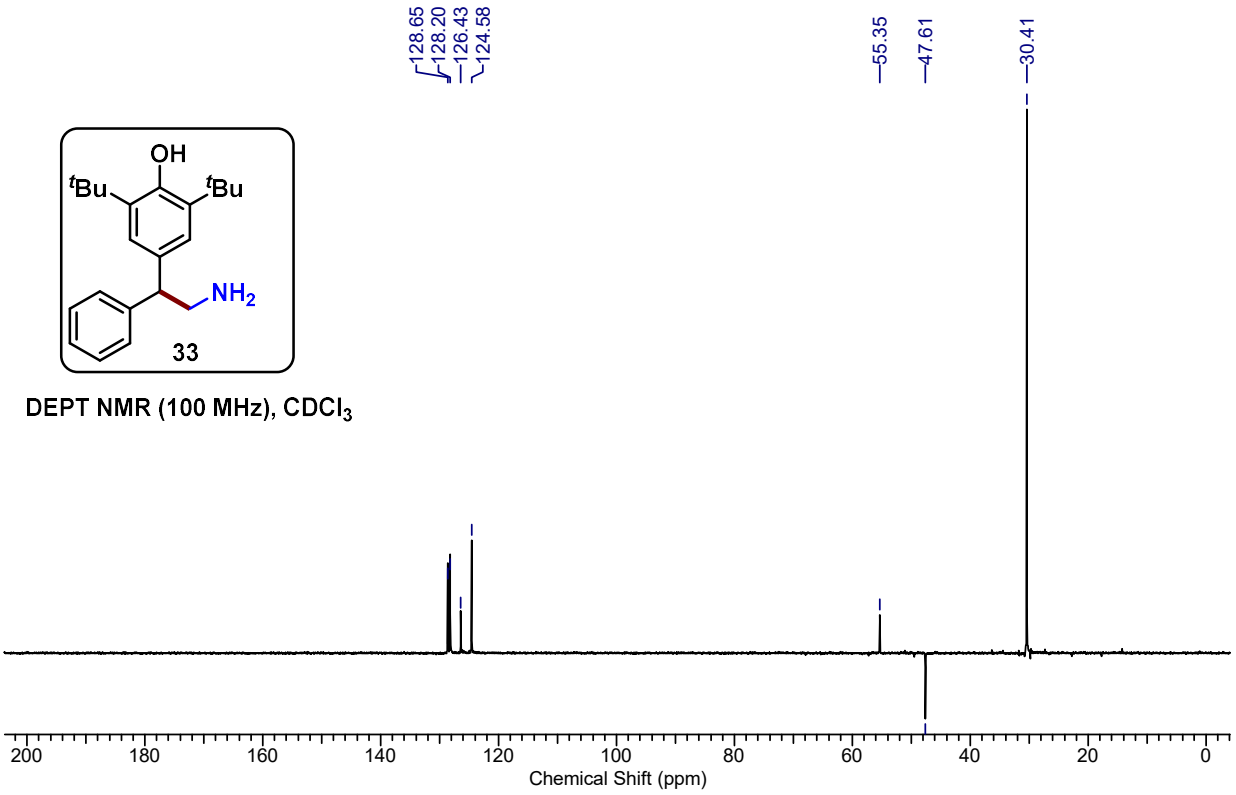

CHLOROFORM-d
152.44
136.18
136.07
129.51
129.41
129.19
129.00
128.46
128.30
128.20
127.63
119.84
116.60
77.31
77.00
76.69
41.90
OH
CN
32
^{13}C NMR (50 MHz), CDCl$_3$
180 160 140 120 100 80 60 40 20 0
Chemical Shift (ppm)



^{1}H NMR (400 MHz), $CDCl_3$



^{13}C NMR (100 MHz), $CDCl_3$



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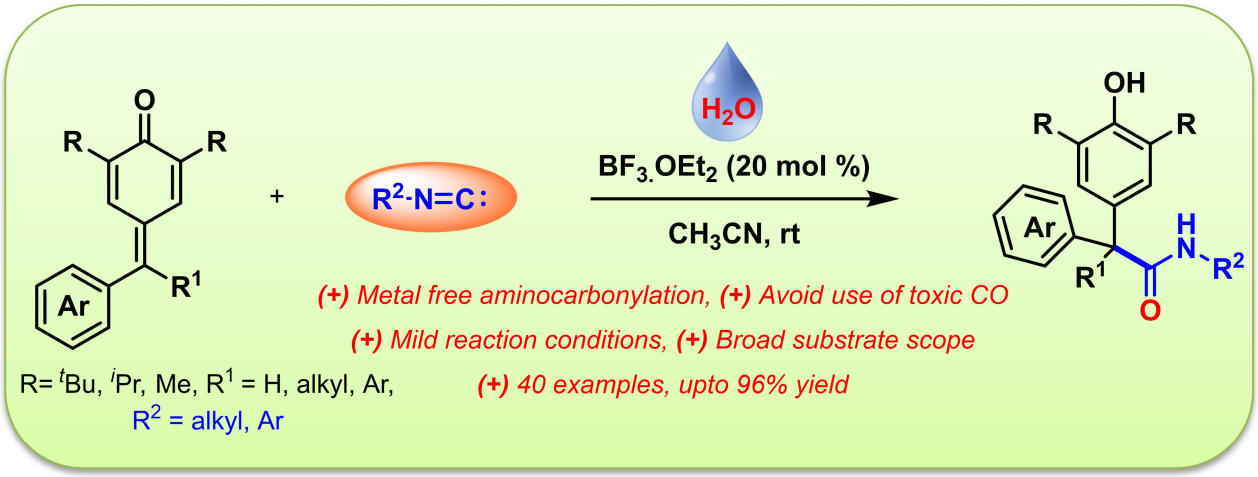
Section-II

Metal-Free Aminocarbonylation of *p*-Quinone Methides with Isocyanides: Synthesis of Sterically Hindered *α*-Arylated Acetamides.

This section deals with the metal-free aminocarbonylation reaction of *p*-quinone methide using isocyanides to access sterically hindered *α*-arylated acetamides. The synthesis of sterically hindered *α*-arylated acetamides generally requires a multistep reaction sequence and is also difficult to access due to steric constraints. The present protocol allows the synthesis of sterically hindered *α*-arylated acetamides in moderate to high yields *via* $BF_3.OEt_2$ catalyzed 1,6-addition of isocyanides to *p*-QMs. Important highlights of the present transformation are transition metal-free conditions, avoiding the use of toxic carbon monoxide, broad substrate scope, mild reaction conditions, and operational simplicity.



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(https://doi.org/10.1002/asia.202200642)

2.2.1 Introduction

Amide functionality represents one of the most important structural motifs found ubiquitously in fine chemicals, bioactive molecules (e. g., peptides and proteins), natural products and pharmaceuticals.[1] In the pharmaceutical industry, the formation of the amide group is pivotal and one of the frequently encountered reactions. Recent surveys demonstrate that the amide bond is present in more than 25% of pharmaceuticals, while amide bond-forming reactions represent the most common reaction performed by medicinal chemists.[2] In addition, amides are important synthetic intermediates in organic chemistry and also employed as reaction partners in diverse transformations, representing the source for both the carbonyl and the amine group.[3] As a type of important amide, α-arylated acetamides have gained considerable attention because of their significant applications in natural products, drugs and crop protection agents. This structural motif is found in several pharmacological and biologically active natural products and drug molecules (Figure 2.2.1).[4,5]

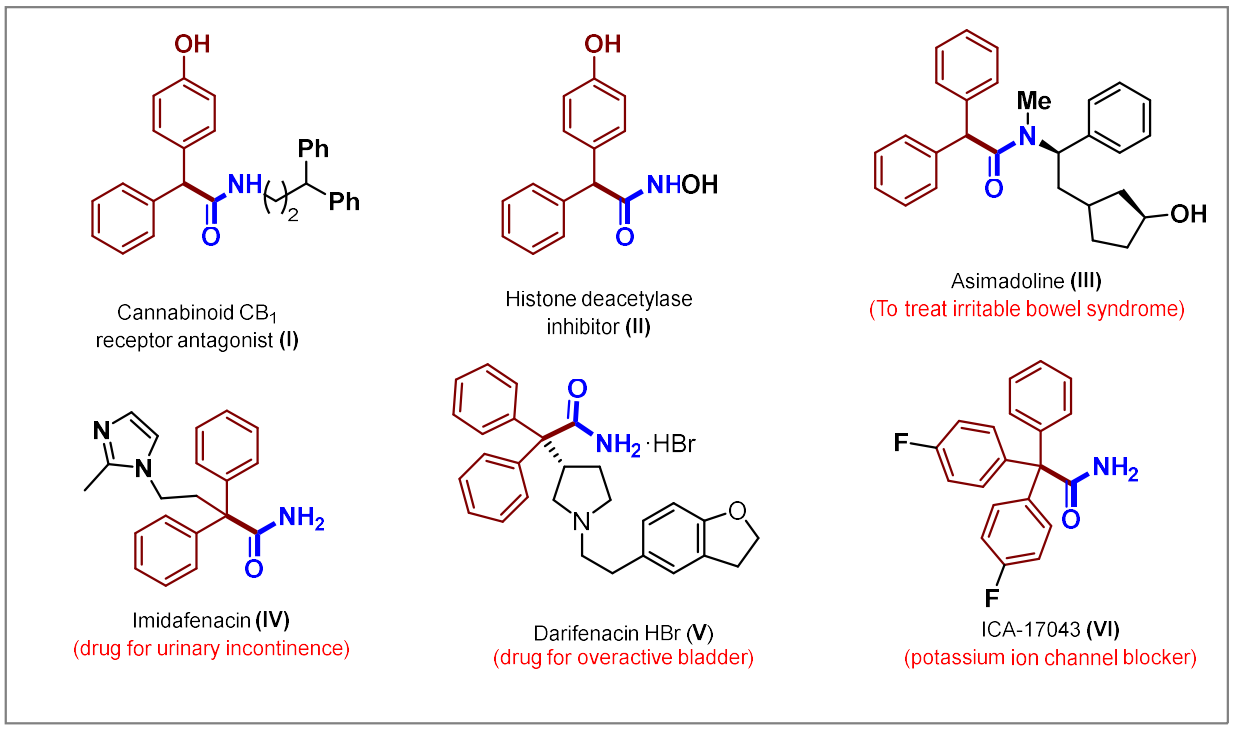


Figure 2.2.1. Selected bioactive compounds and drugs containing α, α-diaryl amide moiety.

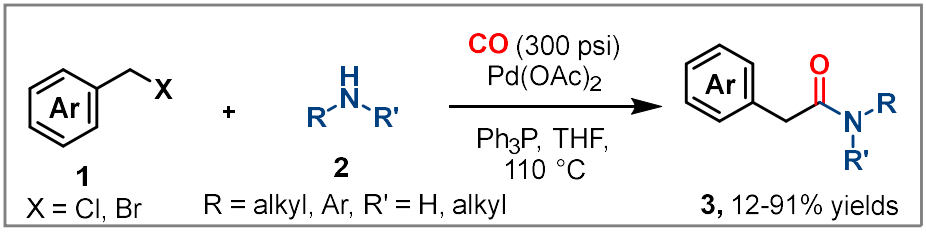
For example, compound **I** is the cannabinoid CB1 receptor inverse agonist and compound **II** is known to possess histone deacetylase inhibitory activity. Asimadoline (EMD-61753) **III** is an experimental drug which acts as a peripherally selective κ-opioid receptor (KOR) agonist and is used to treat peripheral pain such as arthritis. Imidafenacin **IV** and darif-

enacin **V** are muscarinic receptor blockers used to treat urinary incontinence (overactive bladder syndrome). Bis(4-fluorophenyl)phenyl acetamide) ICA-17043 compound **VI** is a potassium ion channel blocker used for the chronic treatment of patients with sickle cell disease (SCD). Therefore, the developments of novel methods for the synthesis of α-arylated acetamides have attracted the attention of researchers. Given the increasing importance of α-arylated acetamides, many methods for their preparation have long been developed and sought after. The conventional way of making α-arylated acetamides is based on the coupling reaction of activated acids with amines in the presence of a coupling agent, which produces enormous waste and therefore increases the cost of industrial production. In a pioneering study, Heck and co-workers reported the palladium-catalyzed aminocarbonylation of aryl halides with amines and carbon monoxide to prepare arylated amides.[6] Subsequently, several research groups contributed significantly to this approach to make α-arylated acetamides *via* transition metal-catalyzed aminocarbonylation protocols employing electrophiles such as benzyl halides or benzyl pseudohalides with amines or nitroarenes, and CO or $Mo(CO)_6$ as a C1 building block.[7-10] Therefore, the aminocarbonylation reactions offer a promising alternative to synthesising α-arylated acetamides. Some of the effective approaches toward the synthesis of arylacetamides have been discussed below.

2.2.2 Literature Precedence on the Synthesis of α-Arylated Acetamides:

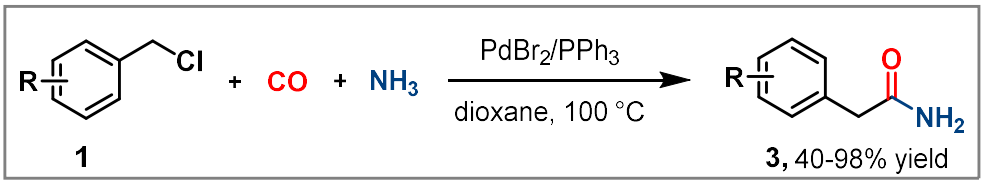
a) Aminocarbonylation of Benzyl Halides or Benzyl (pseudo)halides:

Troisi and co-workers in 2010[7a] reported Pd-catalyzed aminocarbonylation reaction between benzyl halides **1** and primary or secondary amines **2** under CO pressure to access arylacetamides derivatives in one pot. The reaction proceeds *via* the generation of acyl palladium halide, which undergoes an acylic nucleophilic substitution from the amine (Scheme 2.2.1).



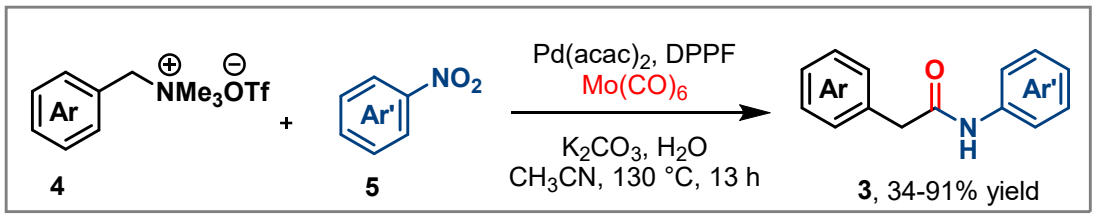
Scheme 2.2.1. Pd-catalyzed aminocarbonylation of benzyl halides and amines

Beller and co-workers[7b] in 2012 reported Pd-catalyzed aminocarbonylation of benzyl chlorides **1** using ammonia and carbon monoxide. This protocol allows the synthesis of a variety of α-mono arylated acetamides **3** in good to excellent yields. Notably, an inexpensive palladium catalyst system is successfully applied for this atom-efficient methodology (Scheme 2.2.2).



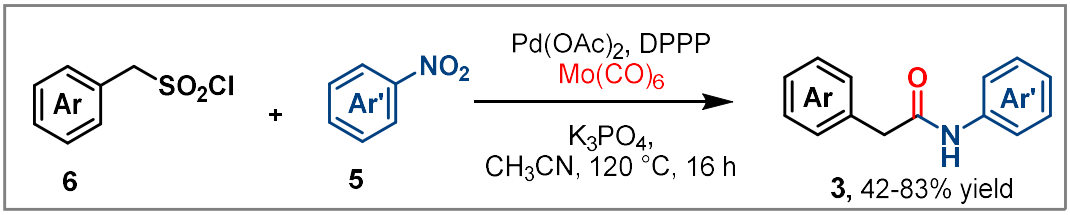
Scheme 2.2.2. Pd-catalyzed aminocarbonylation of benzyl chlorides and ammonia

In 2021, Peng and co-workers[7c] developed palladium-catalyzed reductive aminocarbonylation of benzylic ammonium triflates **4** with nitroarenes **5** for the synthesis of *α*-mono arylated acetamides **3**. Under standard reaction conditions, a range of substituted arylacetamides was prepared in moderate to good yields *via* Csp^3-N bond cleavage of benzylic ammonium triflates and its coupling with nitroarenes (Scheme 2.2.3).



Scheme 2.2.3. Pd-catalyzed amidation of benzylic ammonium triflates with nitroarenes

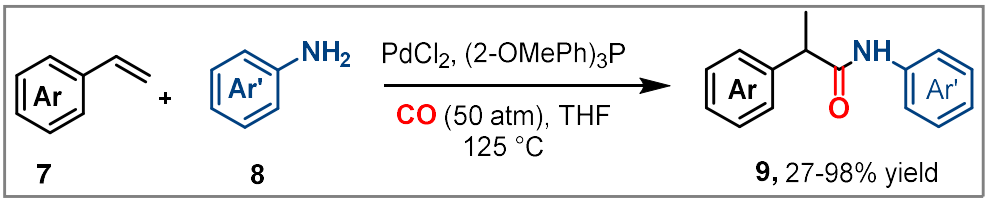
Recently, Wu and co-workers reported Pd-catalyzed reductive desulfonative aminocarbonylation reaction of benzylsulfonyl chlorides **6** and nitroarenes **5** to construct variety of *α*-mono arylated acetamides **3**. In this aminocarbonylation protocol, benzylsulfonyl chlorides served as efficient $C(sp^3)$ electrophiles, whereas nitroarenes acted as aniline sources and $Mo(CO)_6$ acted as both a reductant and CO source (Scheme 2.2.4).[7d]



Scheme 2.2.4. Pd-catalyzed aminocarbonylation of benzylsulfonyl chlorides and nitroarenes.

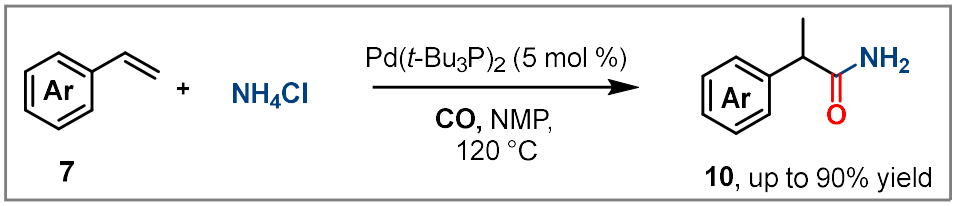
b) Aminocarbonylation *via* CO Insertion of Styrene:

In 2014, Dyson *et al.*[8a] reported an efficient synthesis of *α*-arylated acetamides *via* the Pd-catalyzed aminocarbonylation of styrene with CO and amines. A wide range of aromatic amines could be efficiently transformed in good yield and with high regioselectivity (Scheme 2.2.5).



Scheme 2.2.5. Pd-catalyzed aminocarbonylation of styrene.

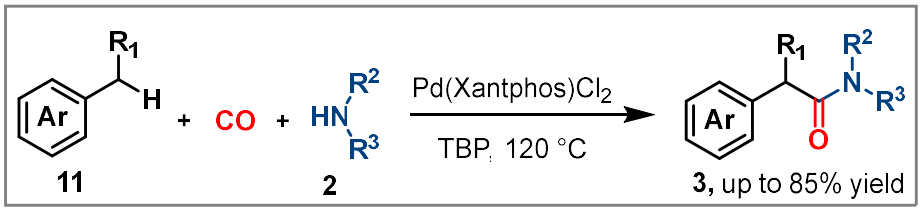
In 2018, Huang *et al.*[8b] in 2018 developed palladium-catalyzed hydroaminocarbonylation of alkenes with NH_4Cl as a surrogate of ammonia in the presence of CO for the synthesis of *α*-arylated acetamides derivatives. This protocol allows the synthesis of a wide range of linear or branched primary amides in high yields with good to excellent regioselectivities. Importantly, this is the first example of the direct conversion of NH_4Cl to primary aliphatic amides in the absence of base (Scheme 2.2.6).



Scheme 2.2.6. Pd-catalyzed aminocarbonylation of styrene.

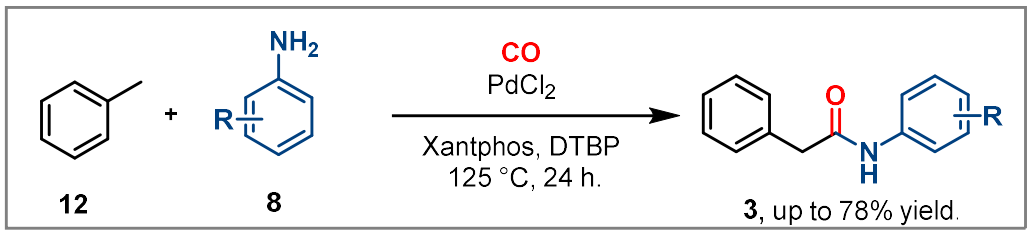
c) Aminocarbonylation of Benzylic C(sp^3)–H Bond Activation:

In 2013, Huang and co-workers[9b] reported a synthetic method for *α*-arylated acetamides *via* palladium-catalyzed oxidative aminocarbonylation reaction *via* C(sp^3)-H activation. This C-H activation protocol can also synthesize the 2-arylpropanamides, which serve as precursors for many important marketed drugs (Scheme 2.2.7).



Scheme 2.2.7. Pd-catalyzed aminocarbonylation *via* C(sp^3)–H bond activation

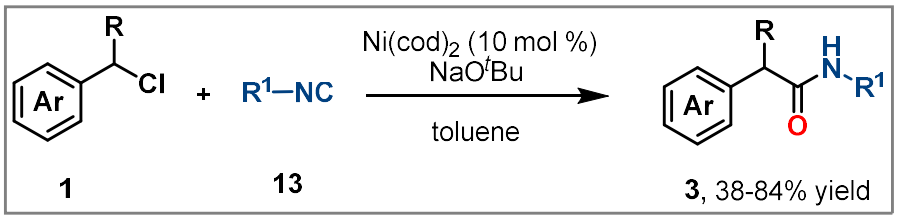
In 2014, Dyson *et al.*[9c] documented an efficient Pd-catalyzed oxidative carbonylation reaction of C-H bonds of toluene **12** with CO and substituted anilines for the synthesis of *α*-arylated acetamides **3**. The method represents a practical and efficient approach for the synthesis of substituted *α*-aryl substituted acetamides from aryl alkanes (Scheme 2.2.8).



Scheme 2.2.8. Pd-catalyzed aminocarbonylation *via* C(sp^3)–H bond functionalization

d) Aminocarbonylation of Benzylic Chlorides with Isocyanides:

In 2020, Chen and co-workers[10] reported the nickel-catalyzed aminocarbonylation of secondary benzyl chlorides **1** with isocyanides **13** to access *α*-arylated acetamide derivatives **3**. The reaction features wide functional group tolerance under mild conditions, highlighted by the tolerance of various aromatic halides (−Cl, −Br, −I) and heteroaromatic rings (pyridine and pyrazine) (Scheme 2.2.9).



Scheme 2.2.9. Aminocarbonylation of secondary benzyl chlorides with isocyanides.

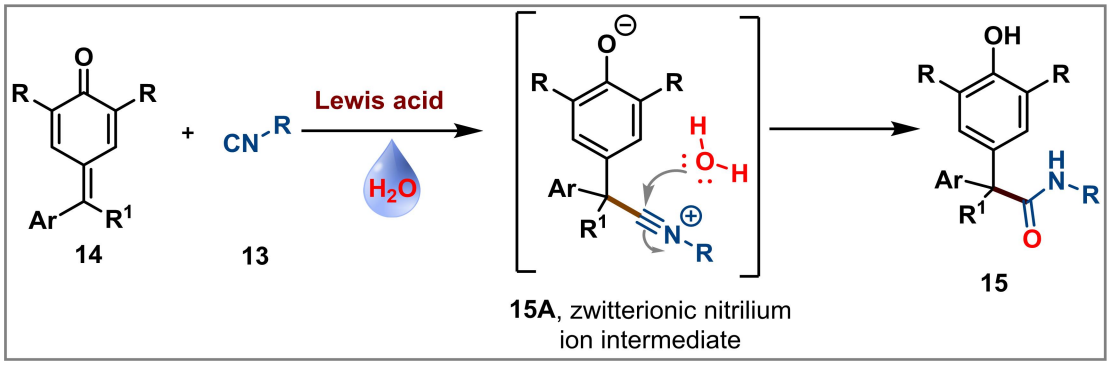
2.2.3 Present Work

2.2.3.1 Statement of the Problem

Despite these significant achievements, most of the methods described above provide only mono *α*-aryl-substituted acetamides. Further, they suffer from certain drawbacks such as the usage of transition metal catalysts, toxic carbon monoxide and harsh reaction conditions. However, in contrast with the synthesis of simple mono *α*-arylated acetamides, methods available for the preparation of *α*-arylated acetamides with restricted steric hindrance such as *α*-di/triaryl acetamides are rare and considered to be challenging.[10] Therefore, developing simple, transition metal-free methods for the preparation of *α*-arylated acetamides, especially with restricted steric hindrance, would be worthwhile.

On the other hand, isocyanides are considered a highly versatile C1 building block with widespread application in organic synthesis, medicinal, and material chemistry.[11] Due to its classical carbene-like reactivity, isocyanides have been used in various multicomponent reactions to synthesize a wide variety of heterocyclic compounds.[12] In addition, they have also been

used in Lewis (Brønsted) acid-catalyzed isocyanide insertion and transition-metal enabled isocyanide insertion reactions.[13] Intrigued by these developments, we speculated that 1,6-addition of isocyanides **13** to *p*-quinone methides **14** in the presence of Lewis acid would form a zwitterionic intermediate **15A** and its subsequent trapping with water would accomplish the formation of sterically hindered *α*-arylated acetamides **15** (Scheme 2.2.10). Although the reactivity of isocyanides with *p*-QMs has been investigated, however, to the best of our knowledge, there is no report on aminocarbonylation of *p*-QMs employing isocyanides.[14-15] Herein, we describe the successful realization of this simple process of aminocarbonylation of *p*-QMs with isocyanides under the mild, metal-free condition to obtain sterically hindered *α*-arylacetamides.



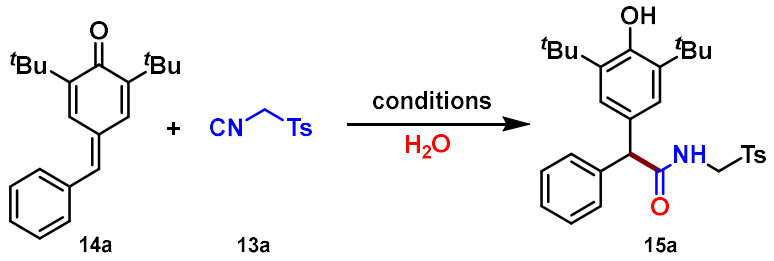
Scheme 2.2.10. Hypothesis on 1,6-amidation of *p*-QMs with isocyanides.

2.2.4 Results and Discussion

2.2.4.1 Optimization of Reaction Conditions

We started our studies by selecting *p*-quinone methide (**14a**) and TosMIC (**13a**) as a model substrates. At the beginning of the initial study, the reaction of *p*-QM (**14a**) and TosMIC (**13a**) in the presence of 20 mol % of $Bi(OTf)_3$, 5 equiv. of H_2O at room temperature in CH_3CN, the product *α*-arylated acetamides **15a** was generated in a 33% yield (Table 2.2.1, entry 1). The structure of **15a** was established with the help of ^1H and ^{13}C NMR spectral data. In the ^1H NMR spectrum of compound **15a**, the characteristic peak of diaryl methine proton (-CH) appeared as a singlet at δ 4.72 (s, 1H). The singlet of phenolic hydroxyl proton resonates at δ 5.20 (s, 1H) and a triplet of amide –NH proton due to coupling with adjacent methylene protons ($-CH_2-$) resonating at δ 6.45 (t, J = 6.5 Hz, 1H). In the ^{13}C NMR spectrum of compound **15a**, the distinguishing amide carbonyl peak appeared as a singlet at δ 171.9. Additionally, the HRMS (ESI-TOF) m/z: $[M + H]^+$ peak at 508.2512 corresponds to the formula $C_{30}H_{38}NO_4S$ (calculated value 508.2516) confirms the structure of **15a.** Now with this structure confirmation, further to

Table 2.2.1. Optimization of the reaction conditions[a,b]



Entry	Catalyst	Solvent	Time	Yields
1	$Bi(OTf)_3$	CH_3CN	1 h	33
2	$In(OTf)_3$	CH_3CN	1 h	52
3	$Sc(OTf)_3$	CH_3CN	1 h	44
4	$Yb(OTf)_3$	CH_3CN	12 h	42
5	$Cu(OTf)_2$	CH_3CN	1 h	59
6	TMSOTf	CH_3CN	1 h	83
7	**$BF_3{\cdot}OEt_2$**	**CH_3CN**	**1 h**	**89**
8	Tf_2NH	CH_3CN	1 h	57
9	$BF_3{\cdot}OEt_2$	CH_3CN	1 h	71[c]
10	$BF_3{\cdot}OEt_2$	CH_3CN	1 h	84[d]
11	$BF_3{\cdot}OEt_2$	Toluene	1 h	trace
12	$BF_3{\cdot}OEt_2$	CH_2Cl_2	1 h	26
13	$BF_3{\cdot}OEt_2$	DCE	1 h	45
14	$BF_3{\cdot}OEt_2$	CH_3NO_2	1 h	42
15	$BF_3{\cdot}OEt_2$	DMF	1 h	NR
16	--	CH_3CN	1 h	NR

[a]Reaction conditions: All reactions were carried out with **14a** (0.10 mmol), **13a** (0.15 mmol), 20 mol % of catalyst, H_2O (5 equiv) in a solvent (2.0 mL) at room temperature. [b]The yields refer to the isolated yields. [c]10 mol % of the catalyst used. [d]10 equiv of H_2O was used. NR = No reaction.

improve the yield, the reaction was conducted with various Lewis acids such as $In(OTf)_3$, $Sc(OTf)_3$, $Yb(OTf)_3$, $Cu(OTf)_2$, TMSOTf, $BF_3{\cdot}OEt_2$ and Brønsted acid Tf_2NH (Table 2.2.1, entries 2–8). As shown in Table 2.2.1, among the catalyst examined $BF_3{\cdot}OEt_2$ demonstrated the highest reactivity to catalyze the formation of *α*-Arylated acetamide product **15a** in 89% yield (Table 2.2.1, entry 7). Relatively lower yield was observed when the catalyst loading was decreased to 10 mol % (Table 2.2.1, entry 9). The yield was not improved when 10 equivalents of water were used (Table 2.2.1, entry 10). In addition, further screening of various solvents revealed that CH_3CN was the optimal reaction medium (Table 2.2.1, entries 11–15). Further, no desired product was observed in the absence of a catalyst (Table 2.2.1, entry 16). Thus, 1 equiv. of **14a**, 1.5 equiv. of **13a**, 20 mol % $BF_3{\cdot}OEt_2$ and 5 equiv. H_2O in CH_3CN at room temperature for 1 h was set as standard reaction conditions.

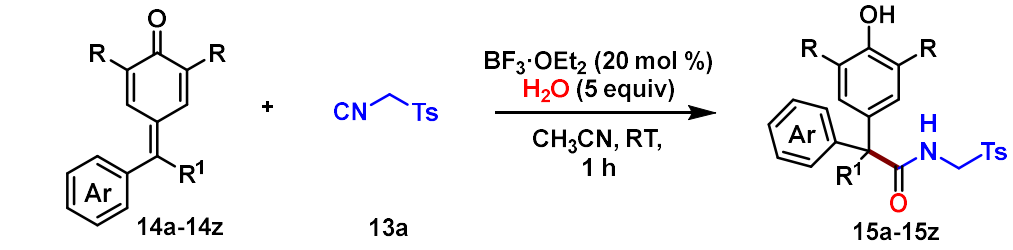
2.2.4.2 Substrate Scope of *p*-Quinone Methides:

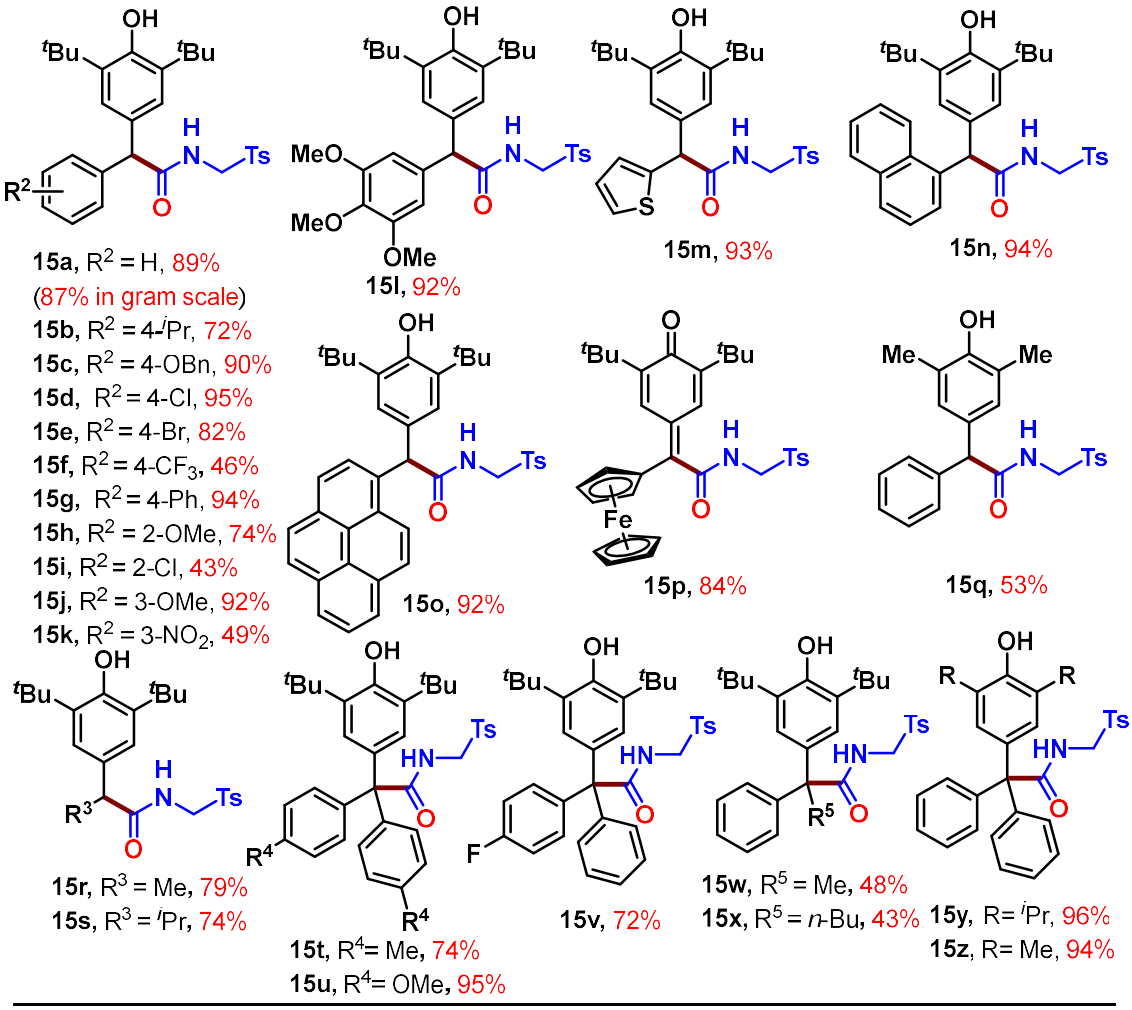
With the optimized conditions in hand, the substrate scope of *p*-quinone methides and fuchsones **(14a-14z)** was investigated. As shown in Table 2.2.2, various *p*-QMs were examined to afford the corresponding products in moderate to good yields. It was found that both electron-donating or electron-withdrawing groups at the *ortho*-, *meta*-, or *para*-position of the aryl ring of *p*-QMs were well tolerated to afford *α*-arylated acetamides (**15a−15k**) in 43−95% yields. Additionally, 3,4,5-trimethoxyphenyl substituted *p*-QM react with **13a** to deliver the corresponding product (**15l**) in a 92% yield. Furthermore, *p*-QMs derived from the thiophene ring and sterically hindered naphthyl and pyrenyl rings also reacted well to afford respective products (**15m-15o**) in good to excellent yields. Interestingly, in the case of ferrocene-derived *p*-QM, a quinone substituted arylacetamide product (**15p**) was obtained in an 84% yield.

Next, *p*-QMs with two methyl groups at the *ortho*-position and aliphatic group at the *δ*-position of the quinone methide were also well-tolerated to afford the product (**15q**-**15s**) in good yields. In addition, the scope of different fuchsones as a 1,6-acceptor has also been examined for the synthesis of sterically hindered *α*-triaryl acetamides. Generally, the synthesis of *α*-triaryl acetamides requires a multistep reaction sequence and is difficult to access due to steric constraints.[2] The reaction of fuchsone derivatives with electron-donating or withdrawing groups on the phenyl ring were readily proceeded to afford the corresponding products (**15t-15v**) in moderate to good yields (72-95%). Notably, the reaction could also be extended to methyl and butyl substituents, and the corresponding products were obtained in 48% (**15w**) and 43% (**15x**),

respectively. Finally, 2,6-di-isopropyl or 2,6-dimethyl substitution were also found to be well suited to deliver products (**15y-15z**) in good yields (94-96%).

Table 2.2.2. Substrate scope of *p*-QMs and fuchsones 14[a,b]





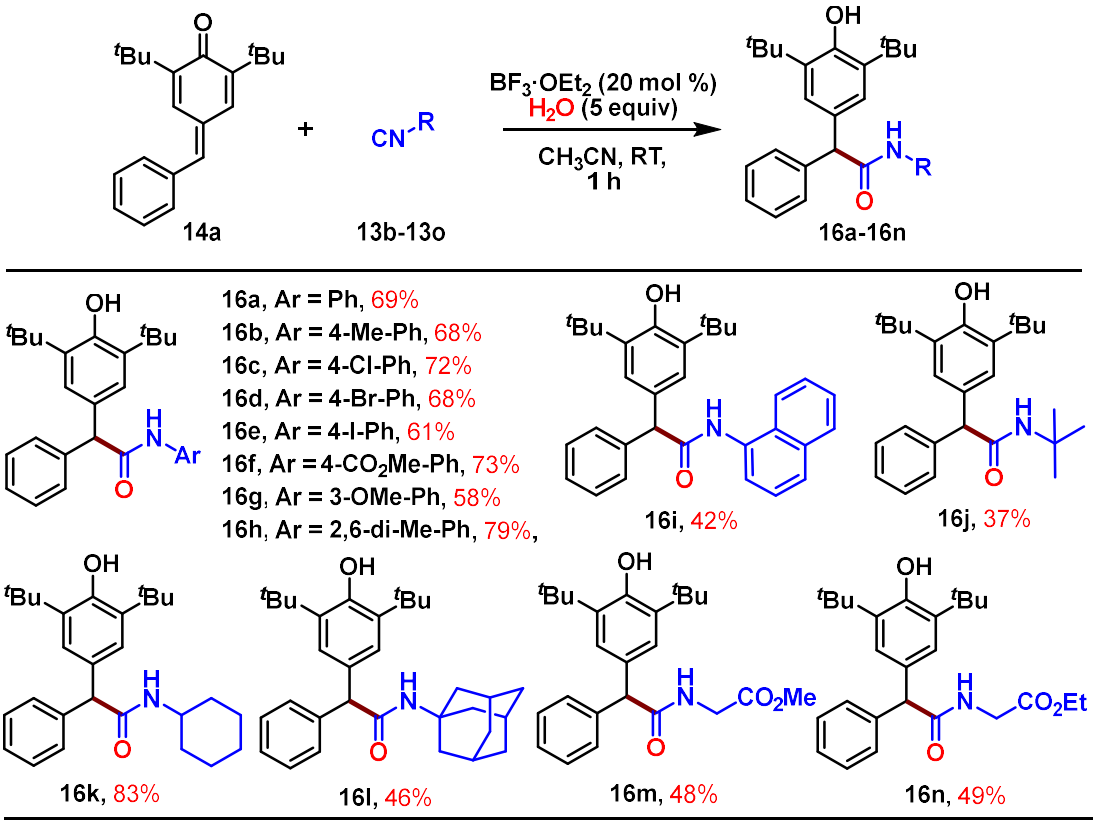
[a]All reactions were performed with **14a-14z** (0.17 mmol), **13a** (0.25 mmol), H_2O (5 equiv) and $BF_3{\cdot}OEt_2$ (20 mol%) in CH_3CN (2.0 mL) for 1 h. [b]Isolated yields.

2.2.4.3 Substrate Scope of Isocyanides:

Next, the scope of isocyanides were tested to react with *p*-QMs. Gratifyingly, various isocyanides (**13b-13o**) were well applicable in this 1,6-addition reaction to furnish the products (**16a-16n**) in moderate to good yields. As shown in Table.2.2.3, various aromatic isocyanides

bearing electron-donating or withdrawing groups were well applicable in this protocol to deliver the *α*-arylated acetamide products in the range of 58-79% yields (**16a-16h**). Further, sterically hindered 1-naphthyl isocyanide also gave the corresponding product (**16i**) in a 42% yield. The reaction of *t*-BuNC under this optimized condition delivers the desired amide product (**16j**) in 37% yields. Next, different aliphatic isocyanides such as cyclohexyl isocyanide, 1-adamantyl isocyanide and methyl or ethyl isocyanoesters are also well suitable under the optimal conditions and give products (**16k-16n**) in acceptable yields (48-83%).

Table 2.2.3. Substrate scope of isocyanides 13[a,b]

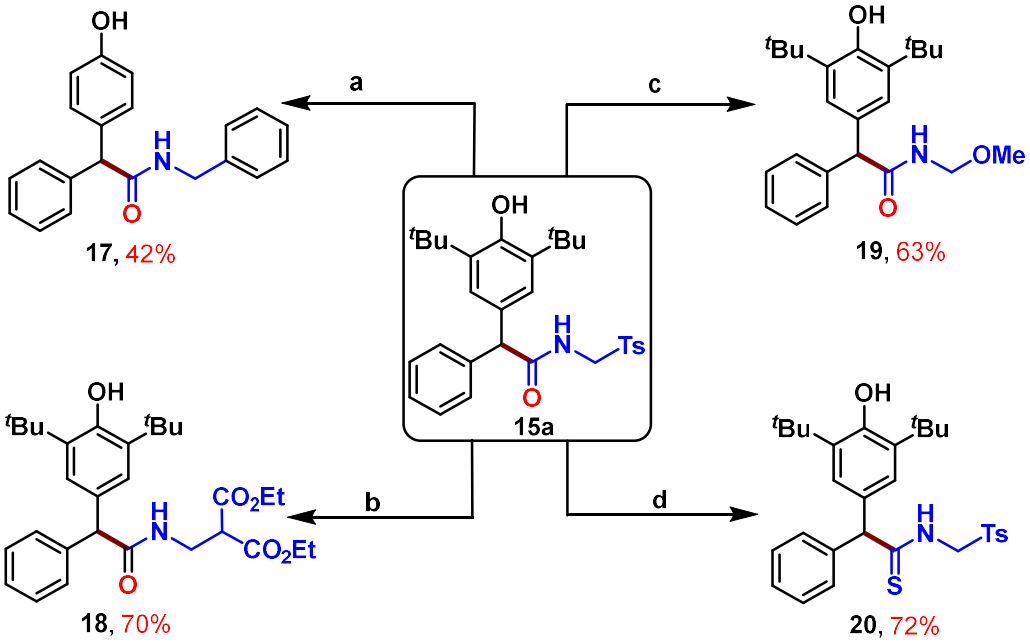


[a]All reactions were performed with **14a** (0.17 mmol), **13b-13o** (0.25 mmol), H_2O (5 equiv) and $BF_3{\cdot}OEt_2$ (20 mol%) in CH_3CN (2.0 mL) for 1 h. [b]Isolated yields.

2.2.4.4 Synthetic Utility:

To show the synthetic potential of this protocol, a gram-scale experiment was carried out. The reaction of **14a** (1.7 mmol, 0.5 g) with **13a** (2.55 mmol, 0.5 g) under the optimal conditions afforded **15a** (0.75 g) in 87% isolated yield. Next, the synthetic application of this aminocarbonylation reaction was also demonstrated by the transformation of compound **15a** (Scheme 2.2.11). For example, $AlCl_3$ mediated de-*tert*-butylation of **15a** in benzene gave product **17** in 42% yield. It is interesting to note that, due to the sulfonyl group's good leaving group

ability, the nucleophilic substitution of the tosyl group with benzene takes place along with de-*tert*-butylation. Further, the nucleophilic substitution of the tosyl group with diethyl malonate and methanol delivered the corresponding products **18-19** in good yields. Finally, thionation of **15a** led to α-arylated thioacetamide product **20** in 72% yield.



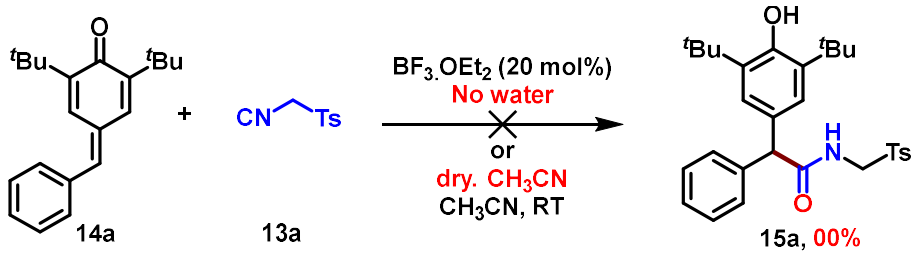
[a]Reaction conditions: a) $AlCl_3$ (6 equiv.), benzene, 60°C, 2 h; b) Cs_2CO_3 (2 equiv.), Diethyl malonate (2 equiv.), CH_2Cl_2, RT, 16 h; c) NaOH (2 equiv.), MeOH, rt, 16 h; d) Lawesson's reagent (1.5 equiv), pyridine (0.2 equiv.), PhMe reflux, 2 h.

Scheme 2.2.11. Synthetic utility[a]

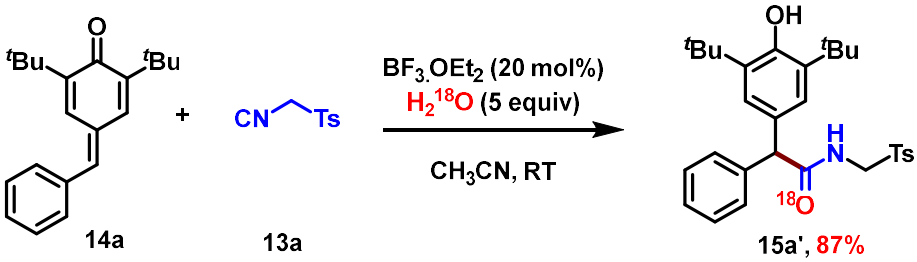
2.2.4.5 Control Experiments:

To understand the source of oxygen in this aminocarbonylation reaction few control experiments were performed. The reaction of **14a** and **13a** without water or in dry CH_3CN did not give the expected product **15a**. This indicates that water is required for an aminocarbonylation reaction (Scheme 2.2.12a). In addition, to confirm the source of oxygen, we have carried out an ^{18}O labelling experiment. The reaction of **14a** and **13a** in the presence of H_2O^{18} under standard reaction condition, the O^{18}-labelled **15a'** was isolated in an 87% yield (Scheme 2.2.12b). The formation of ^{18}O-labelled α-arylated acetamide derivatives (**15a'**) was confirmed by spectroscopic and HRMS analysis. In ^{13}C NMR, **15a'** shows two signals (δ 171.95 and 171.91 ppm) due to both labelled and unlabelled carbonyl groups (amide) of **15a'** (Figure 2.2.2). Further, the HRMS analysis confirms the formation of ^{18}O-labelled (**15a'**) (Figure 2.2.3). This proves that water is the source of carbonyl oxygen.

a) Without water or in dry. CH_3CN :



b) ^{18}O labelling experiment:



Scheme 2.2.12. Control experiments.

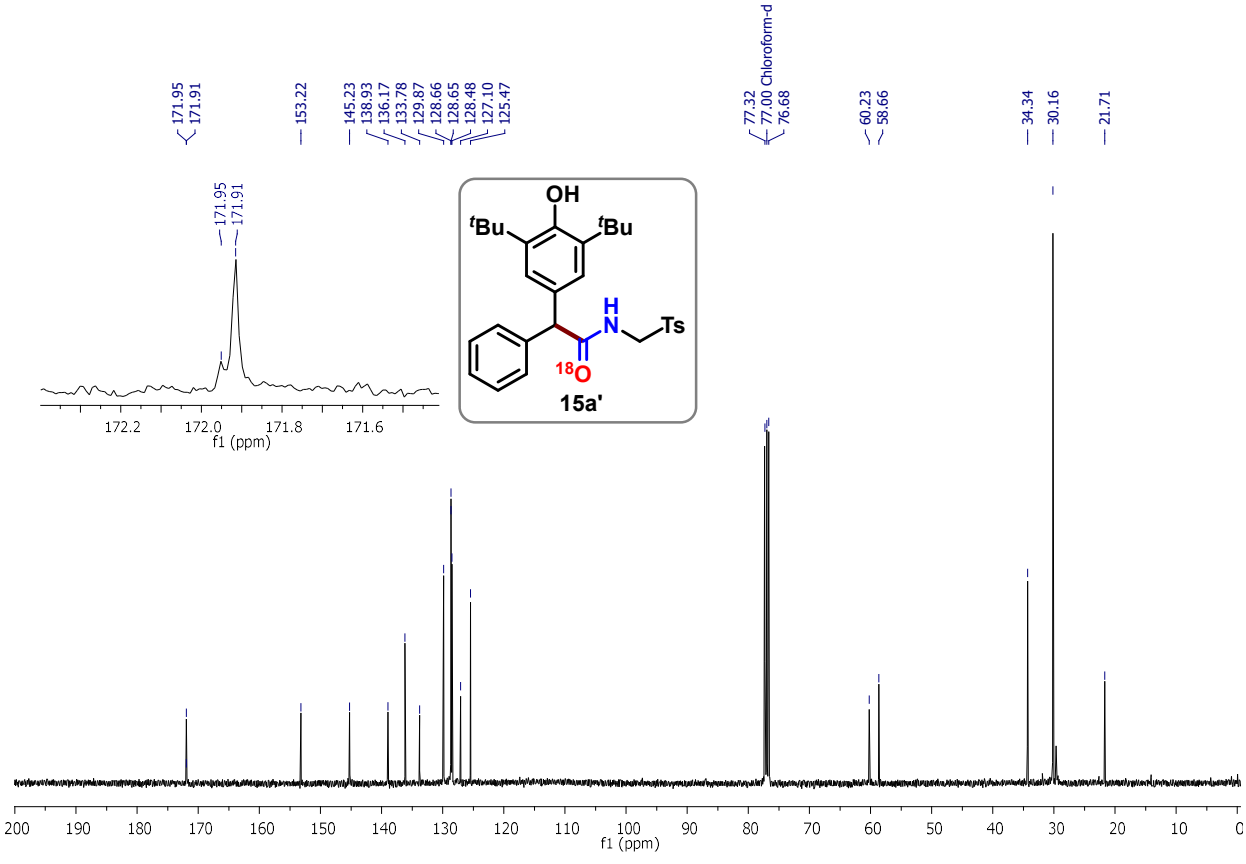


Figure 2.2.2. ^{13}C NMR spectra of ^{18}O labelled α-arylated acetamide (**15a'**).

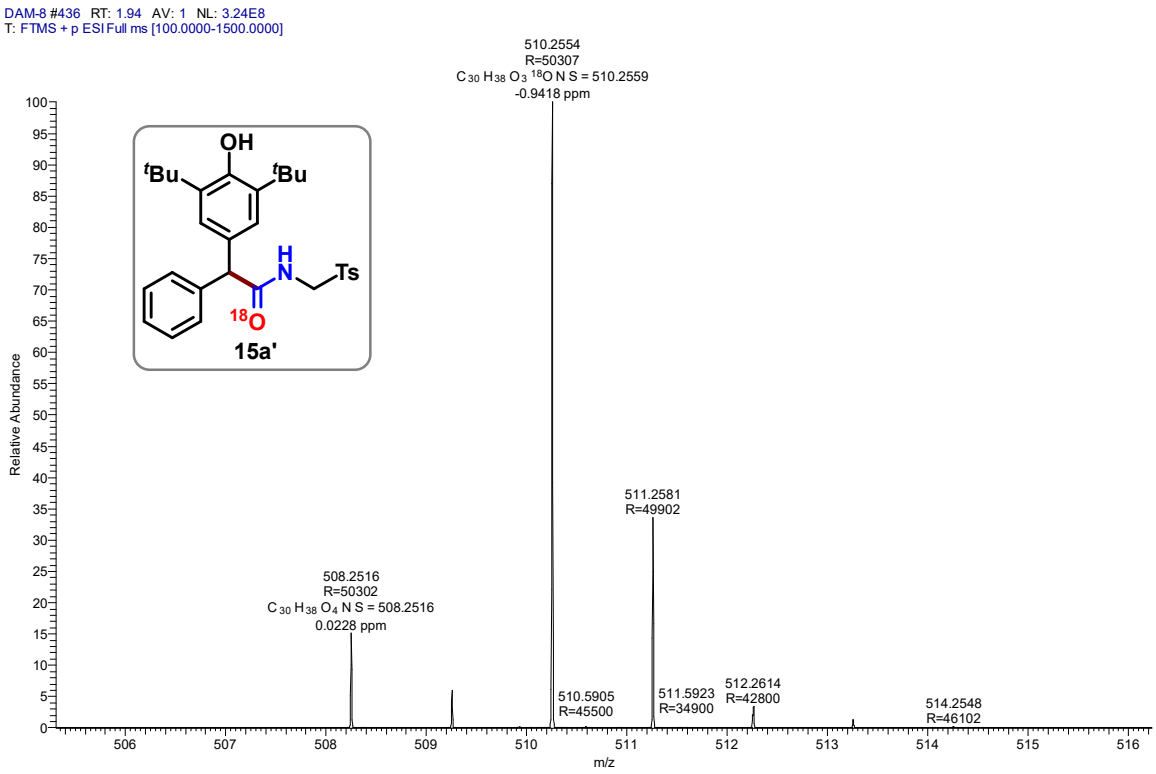
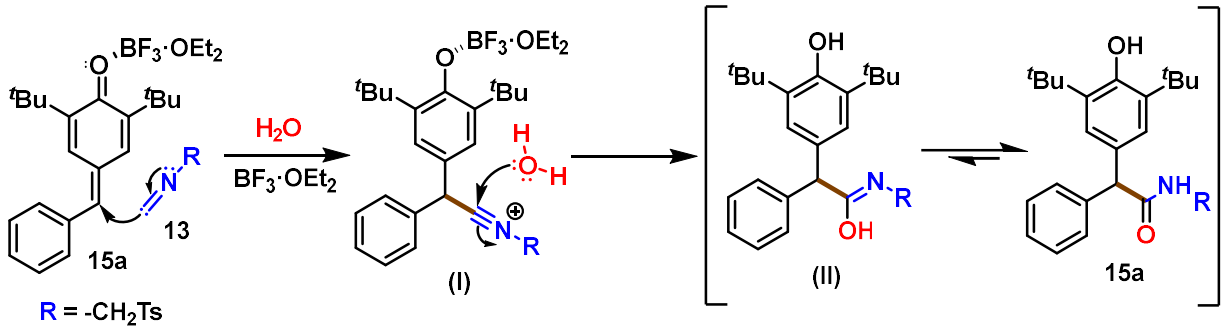


Figure 2.2.3. LC-HRMS spectra of ^{18}O labelled α-arylated acetamide (**15a'**).

2.2.4.6 Reaction Mechanism:

Based on these results and previous reports, a plausible mechanism is depicted in Scheme 2.2.13. At first, *p*-QMs were activated by Lewis acid $BF_3{\cdot}Et_2O$, resulting in the formation of electrophilic δ-methylenic carbon. Next, the nucleophilic attack by isocyanide **13** gives zwitter-ionic nitrilium ion intermediate **I**. Finally, the addition of H_2O to this intermediate produces the desired product **15a** *via* amide−iminol tautomerism of intermediate **II**.



Scheme 2.2.13. Proposed reaction mechanism.

2.2.5 Conclusion

In this section, we have developed a $BF_3.OEt_2$ catalyzed transition metal-free aminocarbonylation of *p*-quinone methide with isocyanides. This method tolerates a broad range of *p*-QMs, fuchsones and isocyanides, giving a wide range of sterically hindered *α*-arylated acetamides in good to high yields. We believe that owing to the biological significance of this scaffold, the present methodology is significant to organic and medicinal chemists working in the area of drug discovery.

2.2.6 Experimental Section

2.2.6.1 Synthesis of Isocyanides

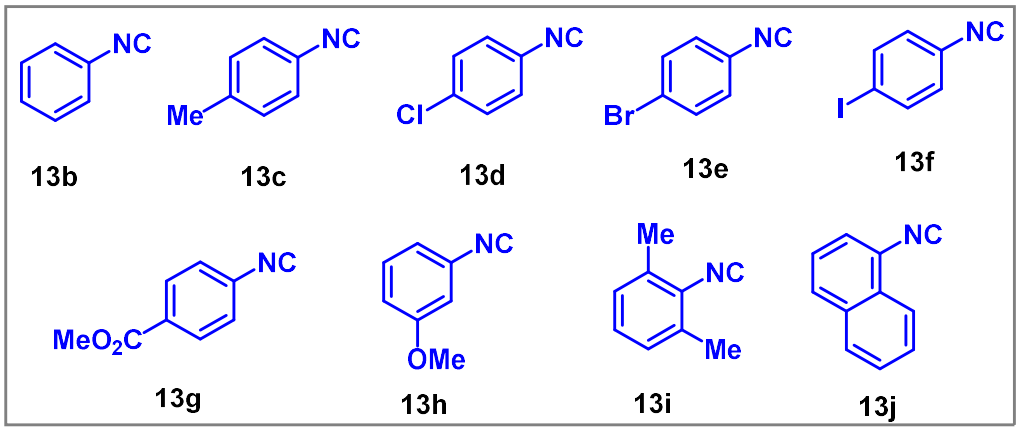
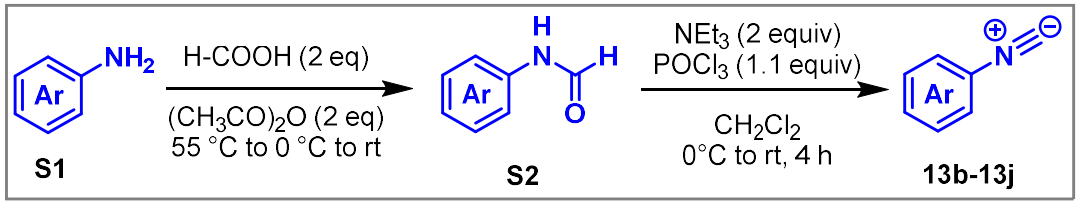


Figure 2.2.2. Structure of isocyanides used in this study.

General Procedure for the Synthesis of Isocyanides (13b-13j)[16]



Scheme 2.2.12. Preparation of isocyanides.

Step 1: To formic acid (2 equiv) was added acetic anhydride (2 equiv) and the mixture was stirred at 55 °C temperature. After stirring for 2 h, to the mixture was added the solution of substituted aniline **S1** (1.0 equiv) in THF (1.0 M) at 0 °C and the mixture was stirred at room temperature. After stirring for 2 h, the reaction was terminated by adding saturated aqueous $NaHCO_3$ (*Caution! Gas evolution*) and diluted with ethyl acetate (50 mL). The organic layer was separated and washed successively with 1M NaOH (2× 30 mL), water and brine, dried over Na_2SO_4 and evaporated. The crude product was purified by flash chromatography over silica gel

using petroleum ether/ethyl acetate as the eluent.

Step 2: To the solution of the formanilide **S2** and Et_3N (2.0 equiv) in DCM (1.0 M) was added neat $POCl_3$ (1.1 equiv) at 0 °C. After stirring at 0 °C for 30 min, the reaction was allowed to stir for additional 1 h at room temperature. Then the mixture was cooled in an ice bath eaction and basified with saturated aqueous $NaHCO_3$ (*Caution! Gas evolution*), extracted with DCM. The combined extracts were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography using petroleum ether/ethyl acetate as the eluent to afford the desired isocyanides **13b-13j**.

Note: the isonitriles are malodorous and often irritant materials. As such, they should be handled in a well-ventilated hood using appropriate safety measures.

All the *p*-quinone methides were prepared as per the procedure described in the section 1.2.5.1 of the chapter. Fuchsones **14t-14v** and **14y-14z** were prepared as per the procedure described in the section 2.1.6.1 of the chapter 2. Fuchsones **14w-14x** prepared according to reported literature procedures.[17]

2.2.6.2 Experimental Procedures:

I) General Procedure for the Synthesis of *α*-Arylated Acetamides:

The *p*-quinone methide **14** (0.17 mmol), isocyanide **13** (1.5 equiv), H_2O (5 equiv) in CH_3CN (1.8 mL) were taken into an oven-dried 5 mL screw-cap reaction vial equipped with a magnetic stir bar. Then, $BF_3{\cdot}OEt_2$ (20 mol %) dissolved in CH_3CN (0.2 mL) was added dropwise, and the reaction mixture was stirred at room temperature for 1 h. After completion of the reaction (detected by TLC), the solvent was removed under reduced pressure, and the residue was directly loaded on a silica gel column and eluted using a petroleum ether/ethyl acetate mixture to obtain pure *α*-arylated acetamide derivatives (**15** or **16**).

II) Procedure for Product Transformations:

a) Procedure for the synthesis of 17: To a solution of **15a** (0.100 g, 0.196 mmol) in benzene (3 mL) was added $AlCl_3$ (0.157 g, 1.181 mmol) under an argon atmosphere, and the resulting mixture was stirred at 60 °C for 2 h. The reaction mixture was then quenched with 10 mL of ice cold water and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was subjected to column chromatography on silica gel using a petroleum ether/ethyl acetate = 3:2 mixture as an eluent to afford **17** as a pale yellow solid (0.026 g, 42%).

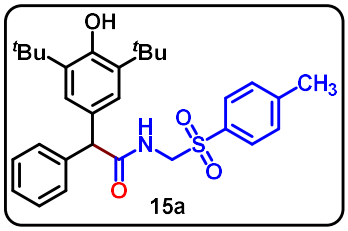
b) Procedure for preparation of 18: To a 5 mL screw-cap reaction vial were added **15a** (0.050 g, 0.098 mmol), Diethyl malonate (0.196 mmol, 0.032 g), and Cs_2CO_3 (0.196 mmol, 0.064 g) in dichloromethane (2 mL). The reaction mixture was then allowed to stir at room temperature for 16 h. After removal of solvent, the residue was directly loaded on a silica gel column and eluted using petroleum/ethyl acetate = 1:1 mixture to afford **18** in 70% yield (0.035 g).

c) Procedure for preparation of 19: To a 5 mL screw-cap reaction vial were added **15a** (0.050 g, 0.098 mmol) and NaOH (0.196 mmol, 0.016 g) in CH_3OH (2 mL). The reaction mixture was then allowed to stir at room temperature for 16 h. After removal of solvent, the residue was directly loaded on a silica gel column using petroleum/ethyl acetate = 1/1 as the eluent to afford **19** in 63% yield (0.024 g).

d) Procedure for the synthesis of 20: To a solution of **15a** (0.100 g, 0.196 mmol) in toluene (2 mL), Lawesson's reagent (0.119 g, 0.294 mmol) and pyridine (3.2 µL, 0.0393 mmol) were added, and the reaction mixture was heated at 115°C. After 2 h, the crude mixture was allowed to cool to the ambient temperature and was subsequently concentrated under reduced pressure. The crude material was purified by silica gel column chromatography using petroleum ether/ethyl acetate = 9:1 mixture as an eluent to afford 0.075 g (72%) of the title compound **20**.

2.2.6.3 Characterization of 15a-15z, 16a-16n and 17-20:

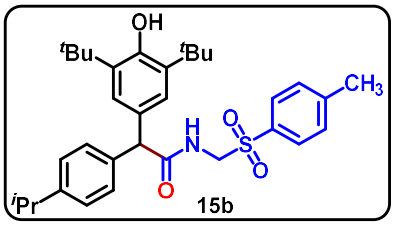
2-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-2-phenyl-*N*-(tosylmethyl)acetamide (15a):



The product **15a** was obtained in 89% yield (77 mg, White solid); **mp** = 178-179 °C; R_f = 0.64 (petroleum ether:ethyl acetate = 7:3); **IR υ_{max}(film)** = 3632, 3338, 3286, 2950, 1679, 1518, 1546, 1437, 1308, 1220, 1139, 752, 692 cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 7.67 (d, *J* = 8.2 Hz, 2H), 7.29 – 7.23 (m, 5H), 7.10 – 7.08 (m, 2H), 7.00 (s, 2H), 6.45 (t, *J* = 6.5 Hz, 1H), 5.20 (s, 1H), 4.76 – 4.63 (m, 2H), 4.72 (s, 1H), 2.42 (s, 3H), 1.39 (s, 18H) ; **^{13}C{^{1}H} NMR (100 MHz,$CDCl_3$) δ** = 171.9, 153.2, 145.2, 138.9, 136.2, 133.8, 129.9, 128.7 (2C), 128.7, 128.5, 127.1, 125.5, 60.2, 58.7, 34.4, 30.2, 21.7 ; **HRMS (ESI-TOF)** *m/z*: $[M + H]^+$ calcd for $C_{30}H_{38}NO_4S$ 508.2516; found 508.2512.

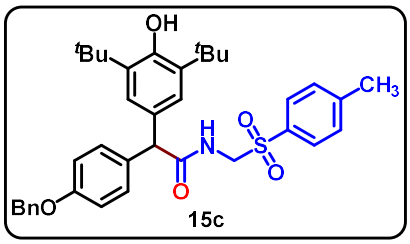
2-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-2-(4-isopropylphenyl)-*N*-(tosylmethyl)acetamide (15b):

The product **15b** was obtained in 72% yield (59 mg, White solid); **mp** = 180-181 °C; R_f = 0.71 (petroleum ether:ethyl acetate = 7:3); **IR υ_{max}(film) =** 3633, 3550, 3467, 3339, 2958, 1678,



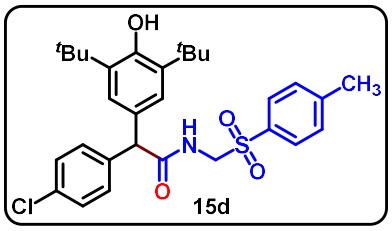
1518, 1433, 1305, 1222, 1141, 816, 756, 689 cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 7.67 (d, *J* = 8.1 Hz, 2H), 7.27 – 7.21 (d, *J* = 7.8 Hz, 2H), 7.13 (d, *J* = 8.0 Hz, 2H), 7.02 – 7.00 (m, 4H), 6.45 (t, *J* = 6.4 Hz, 1H), 5.19 (s, 1H), 4.79 – 4.59 (m, 2H), 4.68 (s, 1H), 2.88 (sept, 6.7 Hz, 1H), 2.42 (s, 3H), 1.40 (s, 18H), 1.24 (d, *J* = 6.9 Hz, 6H); **^{13}C{^{1}H} NMR (100 MHz,$CDCl_3$) δ** = 172.2, 153.2, 147.7, 145.2, 136.2, 136.2, 133.9, 129.9, 128.8, 128.7, 128.6, 126.6, 125.5, 60.3, 58.5, 34.3, 33.7, 30.2, 23.9, 21.7 ; **HRMS (ESI-TOF)** *m/z*: $[M + H]^+$ calcd for $C_{33}H_{44}NO_4S$ 550.2986; found 550.2979.

2-(4-(benzyloxy)phenyl)-2-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-*N*-(tosylmethyl)acetamide (15c):



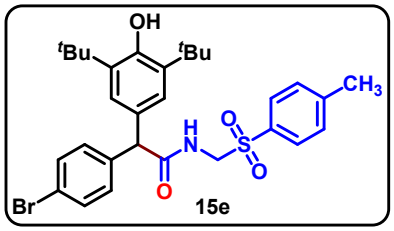
The product **15c** was obtained in 90% yield (69 mg, White solid); **mp** = 186-187 °C; R_f = 0.55 (petroleum ether:ethyl acetate = 7:3); **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 7.67 (d, *J* = 8.2 Hz, 2H), 7.45 – 7.36 (m, 4H), 7.35 – 7.30 (m, 1H), 7.23 (d, *J* = 8.0 Hz, 2H), 7.03 – 6.97 (m, 4H), 6.88 (d, *J* = 8.7 Hz, 2H), 6.46 (t, *J* = 6.6 Hz, 1H), 5.20 (s, 1H), 5.06 (s, 2H), 4.76 – 4.62 (m, 2H), 4.68 (s, 1H), 2.40 (s, 3H), 1.40 (s, 18H) ; **^{13}C{^{1}H} NMR (100 MHz,$CDCl_3$) δ** = 172.2, 157.8, 153.2, 145.2, 136.9, 136.2, 133.9, 131.3, 129.8, 129.8, 129.0, 128.7, 128.6, 128.0, 127.4, 125.4, 114.9, 70.0, 60.3, 57.9, 34.3, 30.2, 21.7 ; **HRMS (ESI-TOF)** *m/z*: $[M + H]^+$ calcd for $C_{37}H_{44}NO_5S$ 614.2935; found 614.2921.

2-(4-chlorophenyl)-2-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-*N*-(tosylmethyl)acetamide (15d):



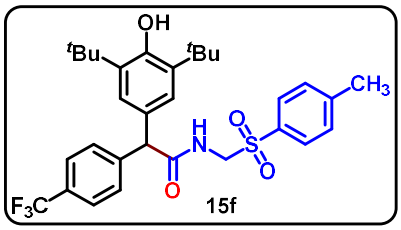
The product **15d** was obtained in 95% yield (78 mg, White solid); **mp** = 183-184 °C; R_f = 0.62 (petroleum ether:ethyl acetate = 7:3); **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 7.67 (d, *J* = 8.2 Hz, 2H), 7.22 (dd, *J* = 8.3, 4.8 Hz, 4H), 7.02 (d, *J* = 8.5 Hz, 2H), 6.98 (s, 2H), 6.63 (t, *J* = 6.6 Hz, 1H), 5.22 (s, 1H), 4.78 (dd, *J* = 14.1, 7.2 Hz, 1H), 4.69 (s, 1H), 4.61 (dd, *J* = 14.1, 6.3 Hz, 1H), 2.42 (s, 3H), 1.39 (s, 18H) ; **^{13}C{^{1}H} NMR (100 MHz,$CDCl_3$) δ** = 171.6, 153.4, 145.4, 137.6, 136.4, 133.7, 132.9, 130.0, 129.9, 128.6, 128.5, 128.3, 125.3, 60.2, 57.8, 34.4, 30.1, 21.7 ; **HRMS (ESI-TOF)** *m/z*: $[M + H]^+$ calcd for $C_{30}H_{37}ClNO_4S$ 542.2126; found 542.2121.

2-(4-bromophenyl)-2-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-*N*-(tosylmethyl)acetamide (15e):



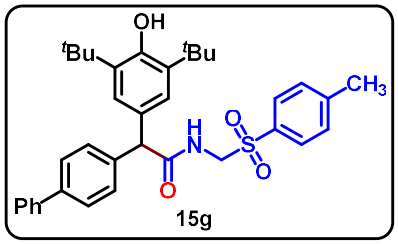
The product **15e** was obtained in 82% yield (64 mg, White solid); **mp** = 187-188 °C; R_f = 0.62 (petroleum ether:ethyl acetate = 7:3); **^{1}H NMR (400 MHz, CDCl$_3$) δ** = 7.66 (d, *J* = 8.2 Hz, 2H), 7.37 (d, *J* = 8.4 Hz, 2H), 7.23 (d, *J* = 8.1 Hz, 2H), 6.98 (s, 2H), 6.97 (d, *J* = 8.5 Hz, 2H), 6.60 (t, *J* = 6.6 Hz, 1H), 5.23 (s, 1H), 4.77 (dd, *J* = 14.1, 7.1 Hz, 1H), 4.66 (s, 1H), 4.61 (dd, *J* = 14.1, 6.2 Hz, 1H), 2.42 (s, 3H), 1.39 (s, 18H) ; **^{13}C{^{1}H} NMR (100 MHz,CDCl$_3$) δ** = 171.5, 153.4, 145.4, 138.1, 136.4, 133.7, 131.5, 130.4, 129.9, 128.6, 128.2, 125.3, 121.1, 60.2, 57.9, 34.4, 30.2, 21.7 ; **HRMS (ESI-TOF)** *m/z*: $[M + H]^+$ calcd for $C_{30}H_{37}BrNO_4S$ 586.1621; found 586.1617.

2-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-*N*-(tosylmethyl)-2-(4 (trifluoromethyl)phenyl) acetamide (15f):



The product **15f** was obtained in 46% yield (36 mg, White solid); **mp** = 185-186 °C; R_f = 0.30 (petroleum ether:ethyl acetate = 7:3); **^{1}H NMR (400 MHz, CDCl$_3$) δ** = 7.68 (d, *J* = 8.2 Hz, 2H), 7.50 (d, *J* = 8.1 Hz, 2H), 7.21 (t, *J* = 8.5 Hz, 4H), 7.01 (s, 2H), 6.61 (t, *J* = 6.5 Hz, 1H), 5.25 (s, 1H), 4.78 (dd, *J* = 14.5, 7.1 Hz, 1H), 4.76 (s, 1H), 4.63 (dd, *J* = 14.1, 6.3 Hz, 1H), 2.41 (s, 3H), 1.39 (s, 18H) ; **^{13}C{^{1}H} NMR (100 MHz,CDCl$_3$) δ** = 171.2, 153.6, 145.4, 143.1, 136.6, 133.7, 129.9, 129.0, 128.6, 127.8, 125.4, 125.3, 125.3, 125.2, 60.2, 58.3, 34.4, 30.1, 21.6 ; **^{19}F NMR (376 MHz, CDCl$_3$) δ** = -62.53 ; **HRMS (ESI-TOF)** *m/z*: $[M + H]^+$ calcd for $C_{31}H_{37}F_3NO_4S$ 576.2390; found 576.2383.

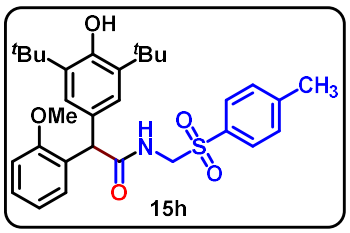
2-([1,1'-biphenyl]-4-yl)-2-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-*N*-(tosylmethyl)acetamide (15g):



The product **15g** was obtained in 94% yield (74 mg, White solid); **mp** = 209-210 °C; R_f = 0.57 (petroleum ether:ethyl acetate =7:3); **^{1}H NMR (400 MHz, CDCl$_3$) δ** = 7.70 (d, *J* = 8.2 Hz, 2H), 7.61 – 7.55 (m, 2H), 7.50 (d, *J* = 8.1 Hz, 2H), 7.44 (t, *J* = 7.6 Hz, 2H), 7.35 (t, *J* = 7.3 Hz, 1H), 7.21 (dd, *J* = 22.4, 8.1 Hz, 4H), 7.06 (s, 2H), 6.59 (t, *J* = 6.1 Hz, 1H), 5.23 (s, 1H), 4.78 (s, 1H), 4.77 (dd, *J* = 14.0, 6.0 Hz, 1H), 4.67 (dd, *J* = 14.1, 6.3 Hz, 1H), 2.39 (s, 3H), 1.41 (s, 18H) ; **^{13}C{^{1}H} NMR (100 MHz,CDCl$_3$) δ** = 172.0, 153.3, 145.2, 140.6, 139.9, 138.1, 136.3, 133.8, 129.9, 129.1, 128.8, 128.7, 128.6, 127.3, 127.2, 126.9, 125.5, 60.3, 58.4, 34.4, 30.2, 21.7 ; **HRMS (ESI-TOF)** *m/z*:

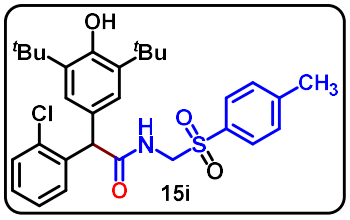
$[M + H]^+$ calcd for $C_{36}H_{42}NO_4S$ 584.2829; found 584.2822.

2-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-2-(2-methoxyphenyl)-*N*-(tosylmethyl)acetamide (15h):



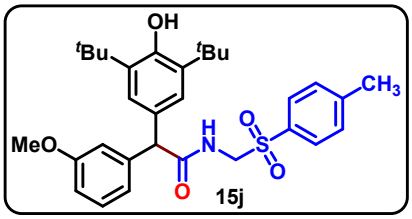
The product **15h** was obtained in 74% yield (61 mg, White solid); **mp** = 139-140 °C; R_f = 0.37 (petroleum ether:ethyl acetate = 7:3); **^{1}H NMR (500 MHz, $CDCl_3$) δ** = 7.64 (d, *J* = 8.1 Hz, 2H), 7.28 – 7.24 (m, 1H), 7.22 (d, *J* = 8.0 Hz, 2H), 7.06 (s, 2H), 6.99 (dd, *J* = 7.5, 1.3 Hz, 1H), 6.89 (dd, *J* = 15.8, 7.9 Hz, 2H), 6.50 (t, *J* = 6.0 Hz, 1H), 5.19 (s, 1H), 5.09 (s, 1H), 4.74 – 4.63 (m, 2H), 3.84 (s, 3H), 2.41 (s, 3H), 1.41 (s, 18H) ; **^{13}C{^{1}H} NMR (125 MHz,$CDCl_3$) δ** = 172.3, 156.7, 153.0, 145.0, 135.9, 134.2, 129.8, 129.7, 128.5 (2C), 128.0, 127.6, 125.8, 120.7, 110.6, 60.4, 55.6, 52.1, 34.3, 30.2, 21.7 ; **HRMS (ESI-TOF)** *m/z*: $[M + H]^+$ calcd for $C_{31}H_{40}NO_5S$ 538.2622; found 538.2620.

2-(2-chlorophenyl)-2-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-*N*-(tosylmethyl)acetamide (15i):



The product **15i** was obtained in 43% yield (35 mg, White solid); **mp** = 122-123 °C; R_f = 0.63 (petroleum ether:ethyl acetate = 7:3); **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 7.70 (d, *J* = 7.7 Hz, 2H), 7.33 (d, *J* = 7.3 Hz, 1H), 7.25 (d, *J* = 7.6 Hz, 2H), 7.20 – 7.11 (m, 2H), 7.06 (d, *J* = 7.3 Hz, 1H), 7.02 (s, 2H), 6.39 (t, *J* = 6.4 Hz, 1H), 5.23 (s, 1H), 5.16 (s, 1H), 4.75 – 4.62 (m, 2H), 2.40 (s, 3H), 1.40 (s, 18H) ; **^{13}C{^{1}H} NMR (100 MHz,$CDCl_3$) δ** = 171.4, 153.6, 145.4, 137.1, 136.6, 134.3, 134.0, 130.2, 130.1, 129.7, 128.9, 128.6, 127.4, 127.0, 125.9, 60.5, 55.2, 34.5, 30.3, 21.9 ; **HRMS (ESI-TOF)** *m/z*: $[M + H]^+$ calcd for $C_{30}H_{37}ClNO_4S$ 542.2126; found 542.2118.

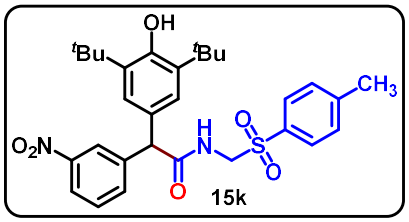
2-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-2-(3-methoxyphenyl)-*N*-(tosylmethyl)acetamide (15j):



The product **15j** was obtained in 92% yield (76 mg, White solid); **mp** = 156-157 °C; R_f = 0.48 (petroleum ether:ethyl acetate = 7:3); **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 7.66 (d, *J* = 8.2 Hz, 2H), 7.22 (dt, *J* = 16.1, 7.7 Hz, 3H), 7.02 (s, 2H), 6.80 (dd, *J* = 8.2, 2.1 Hz, 1H), 6.74 (s, 1H), 6.69 (d, *J* = 7.7 Hz, 1H), 6.51 (t, *J* = 6.6 Hz, 1H), 5.20 (s, 1H), 4.73 (dd, *J* = 14.2, 7.0 Hz, 1H), 4.69 (s, 1H), 4.63 (dd, *J* = 14.1, 6.5 Hz, 1H), 3.76 (s, 3H), 2.41 (s, 3H), 1.39 (s, 18H) ; **^{13}C{^{1}H} NMR (100 MHz,$CDCl_3$) δ** = 171.9, 159.7, 153.2, 145.2, 140.4, 136.2, 133.8, 129.9, 129.5, 128.6, 128.5, 125.4, 121.0, 114.6, 112.6, 60.3, 58.7, 55.1,

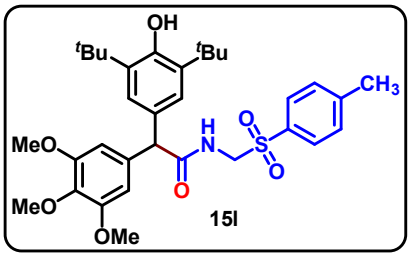
34.3, 30.2, 21.7 ; **HRMS (ESI-TOF)** *m/z*: $[M + H]^+$ calcd for $C_{31}H_{40}NO_5S$ 538.2622; found 538.2614.

2-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-2-(3-nitrophenyl)-*N*-(tosylmethyl)acetamide (15k):



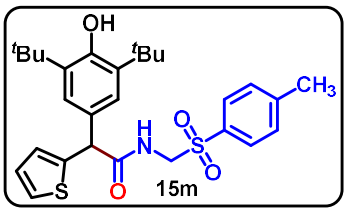
The product **15k** was obtained in 49% yield (40 mg, White solid); **mp** = 194-195 °C; R_f = 0.39 (petroleum ether:ethyl acetate = 7:3); **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 8.09 (dt, *J* = 6.6, 2.1 Hz, 1H), 8.02 (s, 1H), 7.70 (d, *J* = 8.2 Hz, 2H), 7.46 – 7.40 (m, 2H), 7.28 – 7.24 (m, 2H), 7.03 (s, 2H), 6.59 (t, *J* = 6.7 Hz, 1H), 5.30 (s, 1H), 4.79 (s, 1H), 4.75 (dd, *J* = 14.1, 7.0 Hz, 1H), 4.62 (dd, *J* = 14.1, 6.4 Hz, 1H), 2.40 (s, 3H), 1.41 (s, 18H) ; **^{13}C{^{1}H} NMR (100 MHz,$CDCl_3$) δ** = 170.9, 153.8, 148.2, 145.6, 141.2, 136.9, 134.8, 133.8, 130.0, 129.2, 128.6, 127.3, 125.4, 123.9, 122.1, 60.3, 58.0, 34.4, 30.1, 21.7 ; **HRMS (ESI-TOF)** *m/z*: $[M + H]^+$ calcd for $C_{30}H_{37}N_2O_6S$ 553.2367; found 553.2360.

2-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-*N*-(tosylmethyl)-2-(3,4,5-trimethoxyphenyl) acetamide (15l):



The product **15l** was obtained in 92% yield (72 mg, White solid); **mp** = 164-165 °C; R_f = 0.19 (petroleum ether:ethyl acetate = 7:3); **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 7.63 (d, *J* = 8.1 Hz, 2H), 7.20 (d, *J* = 8.0 Hz, 2H), 7.08 (s, 2H), 6.59 (t, *J* = 5.7 Hz, 1H), 6.52 (s, 2H), 5.21 (s, 1H), 4.72 (dd, *J* = 14.2, 6.5 Hz, 1H), 4.68 (s, 1H), 4.63 (dd, *J* = 14.0, 6.1 Hz, 1H), 3.84 (s, 3H), 3.80 (s, 6H), 2.39 (s, 3H), 1.40 (s, 18H); **^{13}C{^{1}H} NMR (100 MHz,$CDCl_3$) δ** = 172.1, 153.3, 153.2, 145.3, 137.1, 136.1, 134.4, 134.1, 129.9, 128.5, 128.5, 125.3, 106.0, 60.8, 60.5, 58.8, 56.1, 34.4, 30.2, 21.6 ; **HRMS (ESI-TOF)** *m/z*: $[M + H]^+$ calcd for $C_{33}H_{44}NO_7S$ 598.2833; found 598.2825.

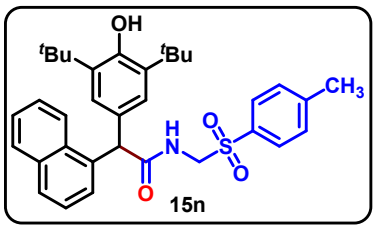
2-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-2-(thiophen-2-yl)-*N*-(tosylmethyl)acetamide (15m):



The product **15m** was obtained in 93% yield (79 mg, White solid); **mp** = 182-183 °C; R_f = 0.57 (petroleum ether:ethyl acetate = 7:3); **IR υ_{max}(film)** = 3631, 3326, 2959, 1682, 1524, 1438, 1305, 1229, 1141, 853, 754, 685 cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 7.65 (d, *J* = 8.3 Hz, 2H), 7.23 – 7.19 (m, 3H), 7.11 (s, 2H), 6.92 (dd, *J* = 5.1, 3.6 Hz, 1H), 6.79 (d, *J* = 3.5 Hz, 1H), 6.64 (t, *J* = 6.7 Hz, 1H), 5.24 (s, 1H), 4.91 (s, 1H), 4.72 (dd, *J* = 14.2, 7.0 Hz, 1H), 4.61 (dd, *J* = 14.2, 6.5 Hz, 1H), 2.39 (s, 3H), 1.41 (s, 18H) ; **^{13}C{^{1}H} NMR (100**

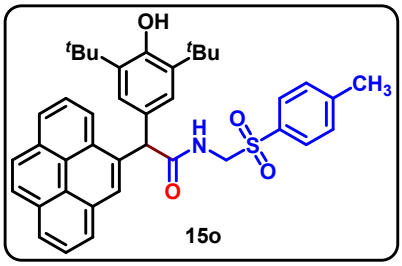
MHz,$CDCl_3$) δ = 171.0, 153.5, 145.3, 141.6, 136.3, 133.7, 129.9, 128.6 (2C), 126.5, 126.4, 125.3, 125.1, 60.4, 53.9, 34.4, 30.2, 21.7; **HRMS (ESI-TOF)** *m/z*: $[M + H]^+$ calcd for $C_{28}H_{36}NO_4S_2$ 514.2080; found 514.2076.

2-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-2-(naphthalen-1-yl)-*N*-(tosylmethyl)acetamide (15n):



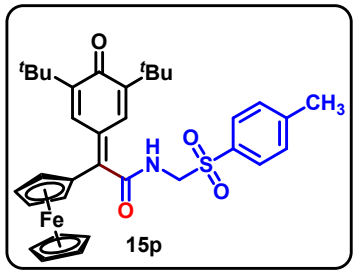
The product **15n** was obtained in 94% yield (76 mg, White solid); **mp** = 116-117 °C; R_f = 0.57 (petroleum ether:ethyl acetate = 7:3); **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 7.89 (dd, *J* = 10.7, 8.3 Hz, 2H), 7.79 (d, *J* = 8.2 Hz, 1H), 7.58 (d, *J* = 8.2 Hz, 2H), 7.52 – 7.43 (m, 2H), 7.37 (t, *J* = 7.7 Hz, 1H), 7.18 (d, *J* = 8.1 Hz, 2H), 7.13 (d, *J* = 7.1 Hz, 1H), 7.04 (s, 2H), 6.41 (t, *J* = 6.6 Hz, 1H), 5.55 (s, 1H), 5.22 (s, 1H), 4.69 (ddd, *J* = 32.7, 14.2, 6.7 Hz, 2H), 2.40 (s, 3H), 1.38 (s, 18H); **^{13}C{^{1}H} NMR (100 MHz,$CDCl_3$) δ** = 172.3, 153.3, 145.1, 136.3, 134.9, 134.0, 133.9, 131.7, 129.8, 128.9, 128.5, 128.2, 128.1, 126.5, 126.4, 125.7 (2C), 125.3, 123.4, 60.3, 55.2, 34.3, 30.2, 21.7 ; **HRMS (ESI-TOF)** *m/z*: $[M + H]^+$ calcd for $C_{34}H_{40}NO_4S$ 558.2673; found 558.2665.

2-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-2-(pyren-4-yl)-*N*-(tosylmethyl)acetamide (15o):



The product **15o** was obtained in 92% yield (69 mg, White solid); **mp** = 197-199 °C; R_f = 0.50 (petroleum ether:ethyl acetate = 7:3); **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 8.23 – 8.15 (m, 3H), 8.10 – 7.99 (m, 5H), 7.72 (d, *J* = 8.0 Hz, 1H), 7.49 (d, *J* = 8.2 Hz, 2H), 7.11 (s, 2H), 6.92 (d, *J* = 8.0 Hz, 2H), 6.55 (t, *J* = 6.3 Hz, 1H), 5.88 (s, 1H), 5.22 (s, 1H), 4.82 – 4.67 (m, 2H), 2.23 (s, 3H), 1.37 (s, 18H) ; **^{13}C{^{1}H} NMR (100 MHz,$CDCl_3$) δ** = 172.5, 153.2, 145.0, 136.3, 133.7, 132.5, 131.3, 130.6, 130.6, 129.7, 129.1, 128.6, 128.4, 128.1, 127.5, 127.4, 126.4, 126.1, 125.7, 125.4, 125.2, 125.1, 124.8, 124.7, 122.7, 60.3, 55.3, 34.4, 30.2, 21.5 ; **HRMS (ESI-TOF)** *m/z*: $[M + H]^+$ calcd for $C_{40}H_{42}NO_4S$ 632.2829; found 632.2825.

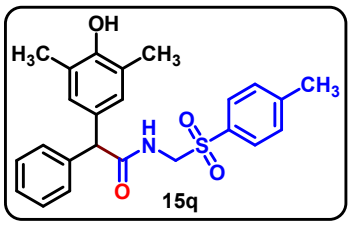
2-(3,5-di-*tert*-butyl-4-oxocyclohexa-2,5-dien-1-ylidene)-2(1(cyclopentadienyl) cyclopentadienyliron)-*N*-(tosylmethyl)acetamide (15p):



The product **15p** was obtained in 84% yield (64 mg, Violet solid); **mp** = 182-183 °C; R_f = 0.75 (petroleum ether:ethyl acetate = 7:3); **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 7.87 (d, *J* = 8.2 Hz, 2H), 7.60 (d, *J* = 2.4 Hz, 1H), 7.41 (d, *J* = 8.0 Hz, 2H), 6.97 (d, *J* = 2.4 Hz, 1H), 6.61 (t, *J* = 6.6 Hz, 1H), 4.88 (d, *J* = 6.7 Hz, 2H), 4.63 (s,

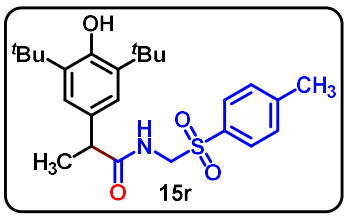
2H), 4.55 (s, 2H), 4.27 (s, 5H), 2.48 (s, 3H), 1.32 (s, 9H), 1.25 (s, 9H) ; **^{13}C{^{1}H} NMR (100 MHz,CDCl$_3$) δ** = 186.4, 167.7, 148.8, 148.1, 147.2, 145.8, 134.3, 130.3, 129.7, 128.8, 128.7, 127.7, 78.0, 72.1, 71.2, 70.8, 60.2, 35.7, 35.3, 29.6, 29.4, 21.8 ; **HRMS (ESI-TOF)** *m/z*: [M + H]$^+$ calcd for $C_{34}H_{40}FeNO_4S$ 614.2022; found 614.2011.

2-(4-hydroxy-3,5-dimethylphenyl)-2-phenyl-*N*-(tosylmethyl)acetamide (15q):



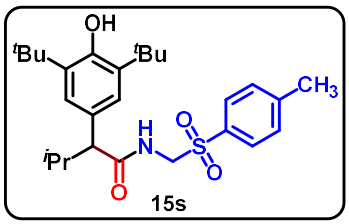
The product **15q** was obtained in 53% yield (54 mg, White solid); **mp** = 193-194 °C; ***R**$_f$* = 0.34 (petroleum ether:ethyl acetate = 7:3); **^{1}H NMR (400 MHz, CDCl$_3$) δ** = 7.68 (d, *J* = 8.1 Hz, 2H), 7.27 – 7.26 (m, 5H), 7.06 (d, *J* = 7.5 Hz, 2H), 6.75 (s, 2H), 6.43 (t, *J* = 6.1 Hz, 1H), 4.71 (d, *J* = 6.7 Hz, 2H), 4.67 (s, 1H), 2.43 (s, 3H), 2.18 (s, 6H) ; **^{13}C{^{1}H} NMR (100 MHz,CDCl$_3$) δ** = 171.7, 151.7, 145.3, 138.7, 133.7, 129.9, 129.7, 128.9, 128.8, 128.7, 128.6, 127.3, 123.5, 60.2, 58.0, 21.7, 16.0 ; **HRMS (ESI-TOF)** *m/z*: [M + H]$^+$ calcd for $C_{24}H_{26}NO_4S$ 424.1577; found 424.1562.

2-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-*N*-(tosylmethyl)propanamide (15r):



The product **15r** was obtained in 79% yield (76 mg, White solid); **mp** = 183-184 °C; ***R**$_f$* = 0.62 (petroleum ether:ethyl acetate = 7:3); **IR υ_{max}(film)** = 3631, 3340, 2962, 1678, 1529, 1442, 1305, 1224, 1141, 754, 675 cm^{-1}; **^{1}H NMR (400 MHz, CDCl$_3$) δ** = 7.67 (d, *J* = 7.5 Hz, 2H), 7.30 (d, *J* = 7.7 Hz, 2H), 7.04 (s, 2H), 6.20 (s, 1H), 5.27 (s, 1H), 4.63 (s, 2H), 3.43 (q, *J* = 6.6 Hz, 1H), 2.44 (s, 3H), 1.47 (s, 18H), 1.36 (d, *J* = 6.4 Hz, 3H) ; **^{13}C{^{1}H} NMR (100 MHz,CDCl$_3$) δ** = 174.1, 153.2, 145.2, 136.5, 134.0, 130.4, 129.8, 128.7, 124.3, 60.2, 46.8, 34.4, 30.2, 21.7, 18.2 ; **HRMS (ESI-TOF)** *m/z*: [M + H]$^+$ calcd for $C_{25}H_{36}NO_4S$ 446.2360; found 446.2344.

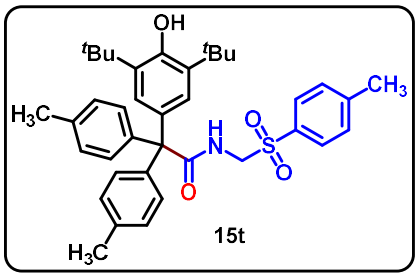
2-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-3-methyl-*N*-(tosylmethyl)butanamide (15s):



The product **15s** was obtained in 74% yield (67 mg, White solid); **mp** = 179-180 °C; ***R**$_f$* = 0.26 (petroleum ether: ethyl acetate = 4:1); **^{1}H NMR (400 MHz, CDCl$_3$) δ** = 7.65 (d, *J* = 8.3 Hz, 2H), 7.22 (d, *J* = 8.0 Hz, 2H), 6.98 (s, 2H), 6.41 (dd, *J* = 7.3, 6.1 Hz, 1H), 5.15 (s, 1H), 4.92 (dd, *J* = 14.3, 7.8 Hz, 1H), 4.41 (dd, *J* = 14.3, 5.7 Hz, 1H), 2.74 (d, *J* = 10.1 Hz, 1H), 2.38 (s, 3H), 2.22 – 2.13 (m, 1H), 1.41 (s, 18H), 0.70 (d, *J* = 6.5 Hz, 3H), 0.61 (d, *J* = 6.7 Hz, 3H); **^{13}C{^{1}H} NMR (100 MHz,CDCl$_3$) δ** = 173.0, 153.0, 145.1, 135.9, 133.9, 129.8, 128.9, 128.6, 124.8, 61.3, 60.2, 34.3, 31.0, 30.3, 21.6, 21.2, 20.2; **HRMS**

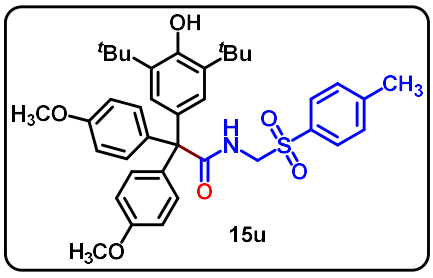
(ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{27}H_{40}NO_4S$ 474.2673; found 474.2670.

2-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-2,2-di-*p*-tolyl-*N*-(tosylmethyl)acetamide (15t):



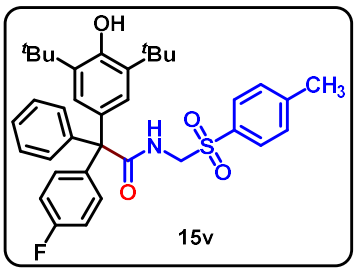
The product **15t** was obtained in 74% yield (57 mg, White solid); **mp** = 156-157 °C; R_f = 0.81 (petroleum ether:ethyl acetate = 7:3); **IR** υ_{max}**(film)** = 3648, 3539, 3404, 2966, 2925, 1680, 1498, 1437, 1318, 1231, 1142, 756, 667 cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 7.65 (d, *J* = 7.8 Hz, 2H), 7.25 (d, *J* = 7.6 Hz, 2H), 7.03 (d, *J* = 8.0 Hz, 4H), 6.98 – 6.91 (m, 6H), 6.69 (t, *J* = 6.3 Hz, 1H), 5.23 (s, 1H), 4.75 (d, *J* = 6.5 Hz, 2H), 2.45 (s, 3H), 2.32 (s, 6H), 1.34 (s, 18H) ; **^{13}C{^{1}H} NMR (100 MHz,$CDCl_3$) δ** = 173.7, 152.8, 145.0, 140.3, 136.3, 135.1, 134.2, 132.6, 130.0, 129.9 (2C), 128.7, 128.4 (2C), 127.3, 67.0, 60.6, 34.4, 30.2, 21.7, 20.9 ; **HRMS (ESI-TOF)** *m/z*: $[M + H]^+$ calcd for $C_{38}H_{46}NO_4S$ 612.3142; found 612.3132.

2-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-2,2-bis(4-methoxyphenyl)-*N*-(tosylmethyl)acetamide (15u):



The product **15u** was obtained in 95% yield (71 mg, White solid); **mp** = 186-187 °C; R_f = 0.58 (petroleum ether:ethyl acetate = 7:3); **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 7.65 (d, *J* = 7.7 Hz, 2H), 7.25 (d, *J* = 7.9 Hz, 2H), 6.95 (d, *J* = 8.1 Hz, 4H), 6.91 (s, 2H), 6.74 (d, *J* = 8.1 Hz, 4H), 6.68 (t, *J* = 6.5 Hz, 1H), 5.22 (s, 1H), 4.74 (d, *J* = 6.5 Hz, 2H), 3.78 (s, 6H), 2.44 (s, 3H), 1.32 (s, 18H) ; **^{13}C{^{1}H} NMR (100 MHz,$CDCl_3$) δ** = 173.9, 158.1, 152.8, 145.0, 135.5, 135.2, 134.2, 132.9, 131.2 (2C), 129.9 (2C), 128.6 (2C), 127.2, 113.0 (2C), 66.3, 60.6, 55.2, 34.4, 30.2, 21.7; **HRMS (ESI-TOF)** *m/z*: $[M + H]^+$ calcd for $C_{38}H_{46}NO_6S$ 644.3040; found 644.3015.

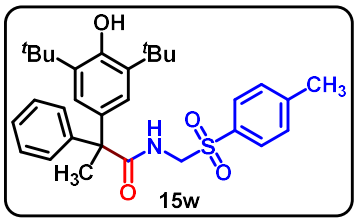
2-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-2-(4-fluorophenyl)-2-phenyl-*N*-(tosylmethyl) acetamide (15v):



The product **15v** was obtained in 72% yield (55.5 mg, White solid); **mp** = 174-175 °C; R_f = 0.81 (petroleum ether:ethyl acetate = 7:3); **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 7.65 (d, *J* = 8.2 Hz, 2H), 7.28 – 7.21 (m, 5H), 7.09 – 7.00 (m, 4H), 6.90 (d, *J* = 8.6 Hz, 2H), 6.87 (s, 2H), 6.72 (t, *J* = 6.5 Hz, 1H), 5.28 (s, 1H), 4.75 (d, *J* = 6.7 Hz, 2H), 2.44 (s, 3H), 1.33 (s, 18H) ; **^{13}C{^{1}H} NMR (100 MHz,$CDCl_3$) δ** = 173.5, 162.7, 160.3,

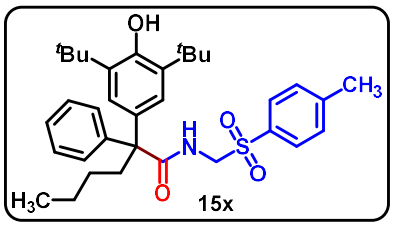
153.1, 144.0 (d, *J* = 225.1 Hz), 138.9, 138.9, 135.6, 134.2, 132.0 (d, *J* = 7.6 Hz), 131.8, 129.9, 128.6, 127.9 (d, *J* = 71.7 Hz), 127.3, 127.1, 114.4 (d, *J* = 21.4 Hz), 67.0, 60.6, 34.5, 30.2, 21.7 ; **^{19}F NMR (376 MHz, $CDCl_3$) δ** = -115.9; **HRMS (ESI-TOF)** *m/z*: $[M + H]^+$ calcd for $C_{36}H_{41}FNO_4S$ 602.2735; found 602.2729.

2-(3,5-di-tert-butyl-4-hydroxyphenyl)-2-phenyl-*N*-(tosylmethyl)propanamide (15w):



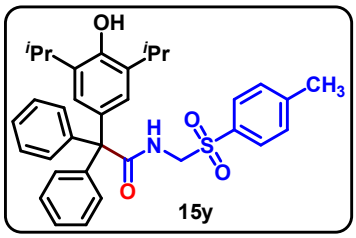
The product **15w** was obtained in 48% yield (40 mg, White solid); **mp** = 193-194 °C; ***R**$_f$* = 0.29 (petroleum ether: ethyl acetate = 4:1); **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 7.66 (d, *J* = 8.3 Hz, 2H), 7.31 (d, *J* = 8.1 Hz, 2H), 7.26 (dd, *J* = 7.0, 4.3 Hz, 3H), 7.07 – 7.02 (m, 2H), 6.95 (s, 2H), 6.21 (t, *J* = 6.6 Hz, 1H), 5.25 (s, 1H), 4.81 (dd, *J* = 14.1, 7.1 Hz, 1H), 4.58 (dd, *J* = 14.2, 6.3 Hz, 1H), 2.45 (s, 3H), 1.81 (s, 3H), 1.38 (s, 18H); **^{13}C{^{1}H} NMR (100 MHz,$CDCl_3$) δ** = 175.3, 152.9, 145.2, 144.5, 135.8, 134.2, 133.7, 129.9, 128.7, 128.2, 127.8, 126.8, 125.0, 60.4, 56.8, 34.5, 30.2, 27.1, 21.7; **HRMS (ESI-TOF)** *m/z*: $[M + H]^+$ calcd for $C_{31}H_{40}NO_4S$ 522.2673; found 522.2670.

2-(3,5-di-tert-butyl-4-hydroxyphenyl)-2-phenyl-*N*-(tosylmethyl)propanamide (15x):



The product **15x** was obtained in 43% yield (34 mg, Semi solid); ***R**$_f$* = 0.39 (petroleum ether:ethyl acetate = 4:1); **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 7.51 (d, *J* = 7.9 Hz, 2H), 7.29 – 7.24 (m, 3H), 7.21 (d, *J* = 7.8 Hz, 2H), 7.12 (d, *J* = 6.7 Hz, 2H), 7.02 (s, 2H), 6.26 (t, *J* = 6.5 Hz, 1H), 5.25 (s, 1H), 4.74 (dd, *J* = 14.1, 7.1 Hz, 1H), 4.57 (dd, *J* = 14.1, 6.4 Hz, 1H), 2.42 (s, 3H), 2.26 – 2.12 (m, 2H), 1.40 (s, 18H), 1.26 – 1.18 (m, 2H), 1.02 – 0.92 (m, 2H), 0.79 (t, *J* = 7.2 Hz, 3H) ; **^{13}C{^{1}H} NMR (100 MHz,$CDCl_3$) δ** = 174.6, 152.8, 145.0, 142.6, 135.6, 134.2, 131.8, 129.8, 128.9, 128.5, 128.0, 126.7, 125.9, 60.6, 60.4, 38.2, 34.5, 30.3, 27.1, 23.2, 21.7, 13.9; **HRMS (ESI-TOF)** *m/z*: $[M + H]^+$ calcd for $C_{30}H_{46}NO_4S$ 564.3142; found 564.3137.

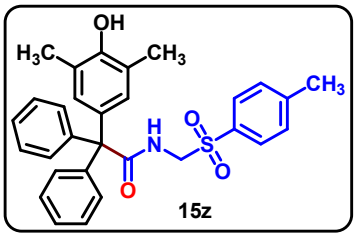
2-(4-hydroxy-3,5-diisopropylphenyl)-2,2-diphenyl-*N*-(tosylmethyl)acetamide (15y):



The product **15y** was obtained in 96% yield (78 mg, White solid); **mp** = 184-185 °C; ***R**$_f$* = 0.68 (petroleum ether:ethyl acetate = 7:3); **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 7.68 (d, *J* = 7.8 Hz, 2H), 7.25 (dd, *J* = 12.7, 4.7 Hz, 8H), 7.08 (d, *J* = 4.4 Hz, 4H), 6.81 (s, 2H), 6.74 (t, *J* = 6.1 Hz, 1H), 4.77 (d, *J* = 6.5 Hz, 2H), 3.17 – 3.04 (m, 2H), 2.46 (s, 3H), 1.14 (d, *J* = 6.8 Hz, 12H); **^{13}C{^{1}H} NMR (100 MHz,$CDCl_3$) δ** = 173.4,

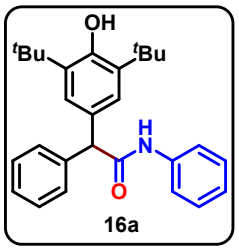
149.2, 145.1, 143.0, 134.1, 133.7, 133.3, 130.1, 129.9, 128.7, 127.7, 126.9, 125.9, 67.5, 60.6, 27.2, 22.5, 21.7 ; **HRMS (ESI-TOF)** *m/z*: $[M + H]^+$ calcd for $C_{34}H_{38}NO_4S$ 556.2516; found 556.2498.

2-(4-hydroxy-3,5-dimethylphenyl)-2,2-diphenyl-*N*-(tosylmethyl)acetamide (15z):



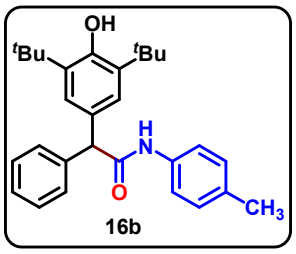
The product **15z** was obtained in 94% yield (82 mg, White solid); **mp** = 187-188 °C; R_f = 0.42 (petroleum ether:ethyl acetate = 7:3); **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 7.68 (d, *J* = 8.3 Hz, 2H), 7.29 (d, *J* = 8.0 Hz, 2H), 7.27 – 7.23 (m, 6H), 7.11 – 7.07 (m, 4H), 6.73 (s, 2H), 6.69 (t, *J* = 6.6 Hz, 1H), 4.78 (d, *J* = 6.7 Hz, 2H), 2.46 (s, 3H), 2.16 (s, 6H) ; **^{13}C{^{1}H} NMR (100 MHz,$CDCl_3$) δ** = 173.3, 151.4, 145.2, 142.8, 134.2, 133.6, 130.6, 130.1, 129.9, 128.7, 127.9, 127.0, 122.7, 67.1, 60.7, 21.7, 16.2 ; **HRMS (ESI-TOF)** *m/z*: $[M + H]^+$ calcd for $C_{30}H_{30}NO_4S$ 500.1890; found 500.1882.

2-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-*N*,2-diphenylacetamide (16a):



The product **16a** was obtained in 69% yield (48 mg, White solid); **mp** = 200-201 °C; R_f = 0.34 (petroleum ether:ethyl acetate = 9:1); **IR υ_{max}(film)** = 3646, 3398, 3329, 2962, 1664, 1530, 1438, 1316, 1240, 1163, 755, 692 cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 7.43 (d, *J* = 7.8 Hz, 2H), 7.36 – 7.32 (m, 5H), 7.30-7.24 (m, 3H), 7.11 (s, 2H), 7.08 (t, *J* = 7.4 Hz, 1H), 5.20 (s, 1H), 4.99 (s, 1H), 1.40 (s, 18H) ; **^{13}C{^{1}H} NMR (100 MHz,$CDCl_3$) δ** = 170.8, 153.2, 139.6, 137.7, 136.3, 129.5, 128.9, 128.9, 128.7, 127.2, 125.6, 124.4, 119.8, 60.1, 34.4, 30.2; **HRMS (ESI-TOF)** *m/z*: $[M + H]^+$ calcd for $C_{26}H_{38}NO_2$ 416.2584; found 416.2576.

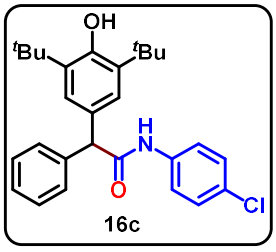
2-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-2-phenyl-*N*-(*p*-tolyl)acetamide (16b):



The product **16b** was obtained in 68% yield (50 mg, White solid); **mp** = 202-203 °C; R_f = 0.34 (petroleum ether:ethyl acetate = 9:1); **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 7.35 – 7.31 (m, 5H), 7.29 – 7.25 (m, 2H), 7.10 (s, 3H), 7.08 (s, 1H), 5.20 (s, 1H), 4.98 (s, 1H), 2.29 (s, 3H), 1.40 (s, 18H) ; **^{13}C{^{1}H} NMR (100 MHz,$CDCl_3$) δ** = 170.7, 153.1, 139.7, 136.2, 135.2, 134.0, 129.6, 129.4, 128.9, 128.7, 127.1, 125.6, 119.9, 60.1, 34.4, 30.2, 20.8; **HRMS (ESI-TOF)** *m/z*: $[M + H]^+$ calcd for $C_{29}H_{36}NO_2$ 430.2741; found 430.2734.

***N*-(4-chlorophenyl)-2-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-2-phenylacetamide (16c):**

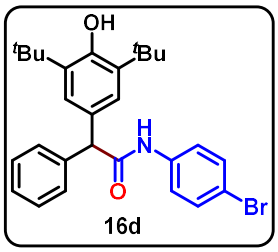
The product **16c** was obtained in 72% yield (55 mg, White solid); **mp** = 233-235 °C; R_f = 0.33 (petroleum ether:ethyl acetate = 9:1); **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 7.49 (t, *J* = 6.0 Hz, 2H),



16c

7.42 (dt, *J* = 15.0, 7.6 Hz, 6H), 7.34 (d, *J* = 8.7 Hz, 2H), 7.19 (s, 2H), 5.31 (s, 1H), 5.07 (s, 1H), 1.49 (s, 18H) ; **$^{13}C\{^1H\}$ NMR (100 MHz,$CDCl_3$) δ** = 170.9, 153.2, 139.4, 136.3, 136.3, 129.4, 129.2, 129.0, 128.8, 128.8, 127.3, 125.5, 121.0, 60.1, 34.4, 30.2; **HRMS (ESI-TOF)** *m/z*: $[M + H]^+$ calcd for $C_{28}H_{33}ClNO_2$ 450.2194; found 450.2191.

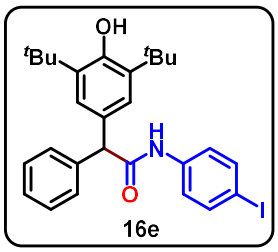
***N*-(4-bromophenyl)-2-(3,5-di-tert-butyl-4-hydroxyphenyl)-2-phenylacetamide (16d):**



16d

The product **16d** was obtained in 68% yield (57 mg, White solid); **mp** = 217-218 °C; R_f = 0.38 (petroleum ether:ethyl acetate = 9:1); **IR** υ_{max}**(film)** = 3645, 3392, 3377, 2961, 1665, 1529, 1546, 1437, 1308, 1239, 1159, 826, 755, 693 cm^{-1}; **^1H NMR (400 MHz, $CDCl_3$) δ** = 7.39 – 7.30 (m, 10 H), 7.09 (s, 2H), 5.21 (s, 1H), 4.97 (s, 1H), 1.40 (s, 18H); **$^{13}C\{^1H\}$ NMR (100 MHz,$CDCl_3$) δ** = 170.9, 153.2, 139.4, 136.8, 136.3, 131.9, 129.2, 128.8, 128.8, 127.3, 125.5, 121.3, 116.9, 60.0, 34.4, 30.2 ; **HRMS (ESI-TOF)** *m/z*: $[M + H]^+$ calcd for $C_{28}H_{33}BrNO_2$ 494.1689; found 494.1684.

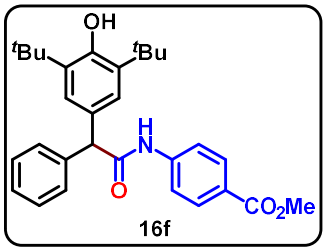
2-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-*N*-(4-iodophenyl)-2-phenylacetamide (16e):



16e

The product **16e** was obtained in 61% yield (56 mg, White solid); **mp** = 236-237 °C; R_f = 0.59 (petroleum ether:ethyl acetate = 9:1); **^1H NMR (400 MHz, $CDCl_3$) δ** = 7.60 – 7.54 (m, 2H), 7.37 (dd, *J* = 3.3, 2.1 Hz, 1H), 7.34 (dd, *J* = 5.5, 1.6 Hz, 2H), 7.32 – 7.25 (m, 3H), 7.23 (d, *J* = 8.8 Hz, 2H), 7.09 (s, 2H), 5.22 (s, 1H), 4.96 (s, 1H), 1.40 (s, 18H); **$^{13}C\{^1H\}$ NMR (100 MHz,$CDCl_3$) δ** = 170.9, 153.2, 139.3, 137.8, 137.5, 136.29, 129.2, 128.8, 128.8, 127.3, 125.5, 121.6, 87.5, 60.1, 34.4, 30.2 ; **HRMS (ESI-TOF)** *m/z*: $[M + H]^+$ calcd for $C_{28}H_{33}INO_2$ 542.1550; found 542.1546.

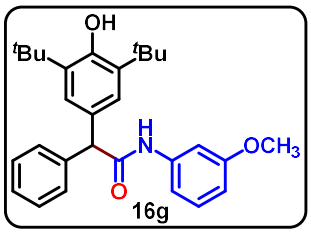
methyl 4-(2-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-2-phenylacetamido)benzoate (16f):



16f

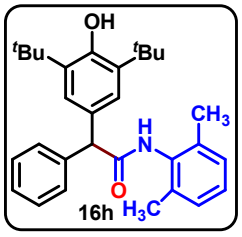
The product **16f** was obtained in 73% yield (58 mg, White solid); **mp** = 211-212 °C; R_f = 0.55 (petroleum ether:ethyl acetate = 4:1); **^1H NMR (400 MHz, $CDCl_3$) δ** = 7.96 (d, *J* = 8.7 Hz, 2H), 7.53 (dd, *J* = 7.9, 5.5 Hz, 3H), 7.37 – 7.25 (m, 5H), 7.10 (s, 2H), 5.22 (s, 1H), 4.99 (s, 1H), 3.87 (s, 3H), 1.39 (s, 18H) ; **$^{13}C\{^1H\}$ NMR (100 MHz,$CDCl_3$) δ** = 171.1, 166.5, 153.3, 141.9, 139.3, 136.4, 130.8, 129.1, 128.8, 127.4, 125.7, 125.5, 118.8, 60.2, 52.0, 34.4, 30.2 ; **HRMS (ESI-TOF)** *m/z*: $[M + H]^+$ calcd for $C_{30}H_{36}NO_4$ 474.2639; found 474.2632.

2-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-*N*-(3-methoxyphenyl)-2-phenylacetamide (16g):



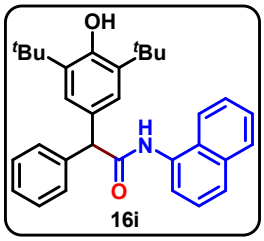
The product **16g** was obtained in 58% yield (45 mg, White solid); **mp** = 170-171 °C; R_f = 0.30 (petroleum ether:ethyl acetate = 9:1); **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 7.36 – 7.24 (m, 7H), 7.15 (s, 1H), 7.09 (s, 2H), 6.81 (d, *J* = 7.9 Hz, 1H), 6.63 (dd, *J* = 8.2, 2.2 Hz, 1H), 5.19 (bs, 1H), 4.97 (s, 1H), 3.76 (s, 3H), 1.39 (s, 18H) ; **^{13}C{^{1}H} NMR (100 MHz,$CDCl_3$) δ** = 170.9, 160.1, 153.2, 139.5, 139.0, 136.3, 129.6, 129.4, 128.9, 128.7, 127.2, 125.6, 111.7, 110.4, 105.3, 60.2, 55.3, 34.4, 30.2 ; **HRMS (ESI-TOF)** *m/z*: $[M + H]^+$ calcd for $C_{29}H_{36}NO_3$ 446.2690; found 446.2683.

2-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-*N*-(2,6-dimethylphenyl)-2-phenylacetamide (16h):



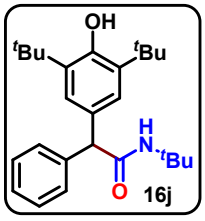
The product **16h** was obtained in 79% yield (59 mg, White solid); **mp** = 187-188 °C; R_f = 0.33 (petroleum ether:ethyl acetate = 9:1); **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 7.44 – 7.34 (m, 4H), 7.27 (dd, *J* = 14.9, 7.6 Hz, 1H), 7.16 (s, 2H), 7.08 – 7.00 (m, 3H), 6.81 (d, *J* = 10.5 Hz, 1H), 5.19 (s, 1H), 5.08 (s, 1H), 2.13 (s, 6H), 1.40 (s, 18H) ; **^{13}C{^{1}H} NMR (100 MHz,$CDCl_3$) δ** = 170.8, 153.1, 139.6, 136.3, 135.1, 134.0, 129.9, 129.1, 128.7, 128.2, 127.2, 127.2, 125.6, 59.8, 34.4, 30.2, 18.6 ; **HRMS (ESI-TOF)** *m/z*: $[M + H]^+$ calcd for $C_{30}H_{38}NO_2$ 444.2897; found 444.2889.

2-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-*N*-(naphthalen-1-yl)-2-phenylacetamide (16i):



The product **16i** was obtained in 42% yield (33 mg, White solid); **mp** = 130-131 °C; R_f = 0.26 (petroleum ether:ethyl acetate = 9:1); **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 8.17 (d, *J* = 7.5 Hz, 1H), 7.83 (d, *J* = 8.3 Hz, 2H), 7.66 (d, *J* = 8.2 Hz, 1H), 7.50 – 7.39 (m, 6H), 7.37 – 7.31 (m, 2H), 7.21 (s, 2H), 7.13 (d, *J* = 8.4 Hz, 1H), 5.30 (s, 1H), 5.22 (s, 1H), 1.44 (s, 18H); **^{13}C{^{1}H} NMR (100 MHz,$CDCl_3$) δ** = 171.2, 153.4, 139.6, 136.8, 134.0, 132.1, 129.8, 129.0, 128.8 (2C), 127.3, 126.3, 126.2, 125.9, 125.8, 125.8, 125.2, 119.6, 119.2, 60.5, 34.5, 30.2; **HRMS (ESI-TOF)** *m/z*: $[M + H]^+$ calcd for $C_{32}H_{36}NO_2$ 466.2741; found 466.2734.

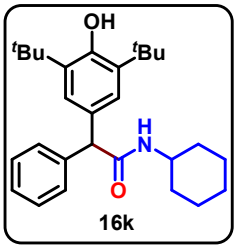
***N*-(*tert*-butyl)-2-(3,5-di-tert-butyl-4-hydroxyphenyl)-2-phenylacetamide (16j):**



The product **16j** was obtained in 37% yield (25 mg, White solid); **mp** = 165-166 °C; R_f = 0.35 (petroleum ether:ethyl acetate = 9:1); **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 7.35 – 7.28 (m, 2H), 7.26 – 7.21 (m, 3H), 7.01 (s, 2H), 5.37 (s, 1H), 5.13 (s, 1H), 4.74 (s, 1H), 1.39 (s, 18H), 1.32 (s, 9H) ; **^{13}C{^{1}H} NMR**

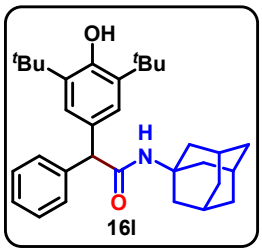
(100 MHz,$CDCl_3$) δ = 171.9, 152.8, 140.4, 135.9, 130.4, 128.8, 128.5, 126.8, 125.4, 60.0, 51.3, 34.4, 30.3, 28.7 ; **HRMS (ESI-TOF)** *m/z*: $[M + H]^+$ calcd for $C_{26}H_{38}NO_2$ 396.2897; found 396.2895.

***N*-cyclohexyl-2-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-2-phenylacetamide (16k):**



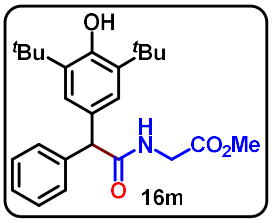
The product **16k** was obtained in 83% yield (60 mg, White solid); **mp** = 188-189 °C; R_f = 0.32 (petroleum ether:ethyl acetate = 4:1); **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 7.34 – 7.30 (m, 2H), 7.26 – 7.23 (m, 3H), 7.02 (s, 2H), 5.43 (d, *J* = 7.6 Hz, 1H), 5.15 (s, 1H), 4.82 (s, 1H), 3.90 – 3.81 (m, 1H), 1.86 (d, *J* = 11.2 Hz, 2H), 1.56 (d, *J* = 8.8 Hz, 4H), 1.39 (s, 18H), 1.15 – 1.06 (m, 4H) ; **^{13}C{^{1}H} NMR (100 MHz,$CDCl_3$) δ** = 171.7, 152.8, 140.2, 136.0, 130.0, 128.8, 128.6, 126.9, 125.5, 59.3, 48.0, 34.4, 32.8, 32.8, 30.2, 25.5, 24.5 ; **HRMS (ESI-TOF)** *m/z*: $[M + H]^+$ calcd for $C_{28}H_{40}NO_2$ 422.3054; found 422.3048.

***N*-((3s,5s,7s)-adamantan-1-yl)-2-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-2-phenylacetamide (16l):**



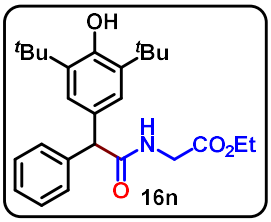
The product **16l** was obtained in 46% yield (37 mg, White solid); **mp** = 171-172 °C; R_f = 0.57 (petroleum ether:ethyl acetate = 9:1); **IR υ_{max}(film)** = 3618, 3397, 3323, 2912, 1657, 1526, 1441, 1363, 1227, 1133, 826, 757, 700 cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 7.34 – 7.28 (m, 2H), 7.27 – 7.21 (m, 3H), 7.02 (s, 2H), 5.26 (s, 1H), 5.14 (s, 1H), 4.74 (s, 1H), 2.05 (s, 3H), 1.96 (d, *J* = 2.8 Hz, 6H), 1.66 (d, *J* = 2.9 Hz, 6H), 1.40 (s, 18H) ; **^{13}C{^{1}H} NMR (100 MHz,$CDCl_3$) δ** = 171.6, 152.7, 140.5, 135.9, 130.4, 128.8, 128.5, 126.8, 125.4, 60.0, 51.9, 41.5, 36.3, 34.4, 30.3, 29.4 ; **HRMS (ESI-TOF)** *m/z*: $[M + H]^+$ calcd for $C_{32}H_{44}NO_2$ 474.3367; found 474.3363.

methyl (2-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-2-phenylacetyl)glycinate (16m):



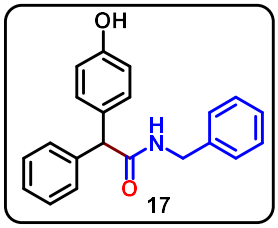
The product **16m** was obtained in 48% yield (34 mg, White solid); **mp** = 133-134 °C; R_f = 0.26 (petroleum ether:ethyl acetate = 4:1); **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 7.36 – 7.28 (m, 4H), 7.27 – 7.22 (m, 1H), 7.07 (s, 2H), 6.16 (s, 1H), 5.17 (s, 1H), 4.89 (s, 1H), 4.06 (d, *J* = 5.2 Hz, 2H), 3.72 (s, 3H), 1.39 (s, 18H) ; **^{13}C{^{1}H} NMR (100 MHz,$CDCl_3$) δ** = 172.9, 170.2, 153.0, 139.6, 136.0, 129.4, 128.8, 128.6, 127.0, 125.6, 58.9, 52.3, 41.4, 34.3, 30.2 ; **HRMS (ESI-TOF)** *m/z*: $[M + H]^+$ calcd for $C_{25}H_{34}NO_4$ 412.2482; found 412.2476.

ethyl (2-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-2-phenylacetyl)glycinate (16n):



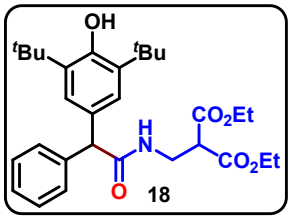
The product **16n** was obtained in 49% yield (35 mg, White solid); **mp** = 106-107 °C; R_f = 0.35 (petroleum ether:ethyl acetate = 4:1); **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 7.32 (s, 4H), 7.26 (s, 1H), 7.08 (s, 2H), 6.17 (s, 1H), 5.18 (s, 1H), 4.89 (s, 1H), 4.19 (q, J = 14.1, 7.0 Hz, 2H), 4.05 (d, J = 1.9 Hz, 2H), 1.40 (s, 18H), 1.26 (t, J = 7.1 Hz, 3H). ; **^{13}C{^{1}H} NMR (100 MHz,$CDCl_3$) δ** = 172.9, 169.7, 153.0, 139.7, 136.0, 129.5, 128.8, 128.6, 127.0, 125.6, 61.4, 58.9, 41.6, 34.3, 30.2, 14.1 ; **HRMS (ESI-TOF)** *m/z*: $[M + H]^+$ calcd for $C_{26}H_{36}NO_4$ 426.2639; found 426.2634.

2-(4-hydroxyphenyl)-2-phenyl-*N*-(tosylmethyl)acetamide (17):



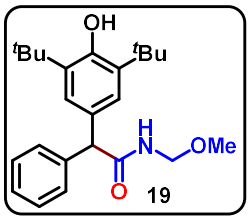
The product **17** was obtained in 42% yield (26 mg, Pale yellow solid); **mp** = 135-136 °C; R_f = 0.62 (petroleum ether:ethyl acetate = 1:1); **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 7.32 – 7.27 (m, 4H), 7.26 – 7.21 (m, 4H), 7.20 – 7.16 (m, 2H), 6.99 (d, *J* = 8.5 Hz, 2H), 6.66 – 6.62 (m, 2H), 6.10 (t, *J* = 5.7 Hz, 1H), 4.90 (s, 1H), 4.46 (d, *J* = 5.8 Hz, 2H) ; **^{13}C{^{1}H} NMR (100 MHz,$CDCl_3$) δ** = 173.2, 155.6, 139.3, 137.8, 130.2, 129.9, 128.8, 128.8, 128.7, 127.5, 127.5, 127.3, 115.9, 58.3, 43.9 ; **HRMS (ESI-TOF)** *m/z*: $[M + H]^+$ calcd for $C_{21}H_{20}NO_2$ 318.1489; found 318.1485.

Diethyl 2-((2-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-2-phenylacetamido)methyl)malonate (18):



The product **18** was obtained in 70% yield (35 mg, Sticky liquid); R_f = 0.53 (petroleum ether:ethyl acetate = 4:1); **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 7.33 – 7.29 (m, 2H), 7.26 – 7.22 (m, 3H), 7.01 (s, 2H), 6.21 (t, *J* = 5.7 Hz, 1H), 5.15 (s, 1H), 4.78 (s, 1H), 4.18 – 4.10 (m, 4H), 3.82 – 3.69 (m, 2H), 3.66 (t, *J* = 6.3 Hz, 1H), 1.39 (s, 18H), 1.22 (td, *J* = 7.1, 2.9 Hz, 6H) ; **^{13}C{^{1}H} NMR (100 MHz,$CDCl_3$) δ** = 172.8, 168.0, 168.0, 153.0, 139.8, 136.0, 129.5, 128.7, 128.5, 127.0, 125.5, 61.7, 59.2, 51.3, 38.1, 34.3, 30.2, 14.0 ; **HRMS (ESI-TOF)** *m/z*: $[M + H]^+$ calcd for $C_{30}H_{42}NO_6$ 512.3007; found 512.3002.

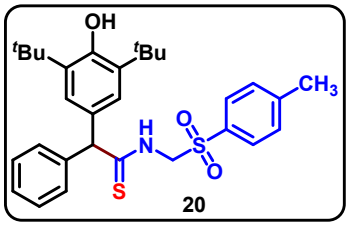
2-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-*N*-(methoxymethyl)-2-phenylacetamide (19):



The product **19** was obtained in 63% yield (24 mg, White solid); **mp** = 117-118 °C; R_f = 0.37 (petroleum ether:ethyl acetate = 4:1); **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 7.37 – 7.31 (m, 2H), 7.28 (d, *J* = 2.1 Hz, 1H), 7.26 (d, *J* = 3.0 Hz, 2H), 7.05 (s, 2H), 6.18 (t, *J* = 6.4 Hz, 1H), 5.17 (s, 1H),

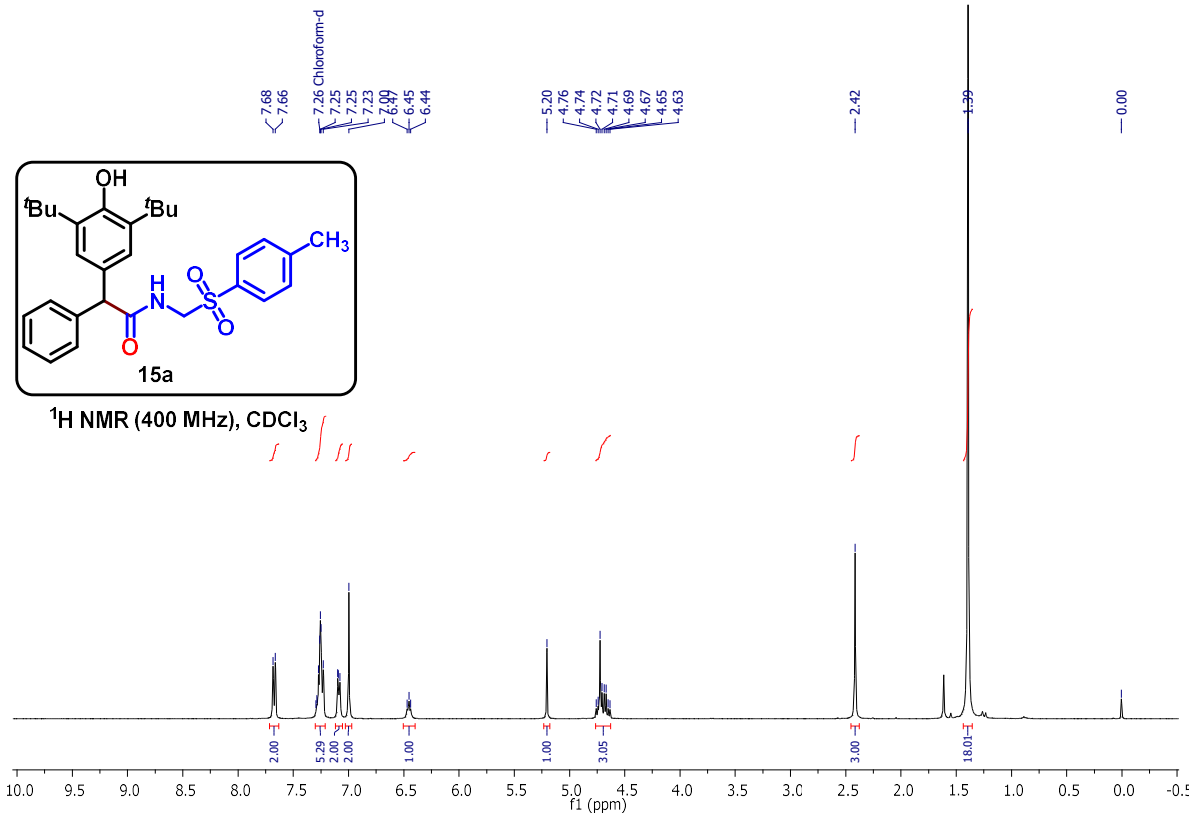
4.88 (s, 1H), 4.76 – 4.66 (m, 2H), 3.32 (s, 3H), 1.39 (s, 18H); **$^{13}C\{^1H\}$ NMR (100 MHz,$CDCl_3$) δ** = 173.6, 153.1, 139.4, 136.1, 129.3, 128.9, 128.7, 127.2, 125.5, 71.6, 59.4, 56.1, 34.4, 30.2 ; **HRMS (ESI-TOF)** *m/z*: $[M + H]^+$ calcd for $C_{24}H_{34}NO_3$ 384.2533; found 384.2527.

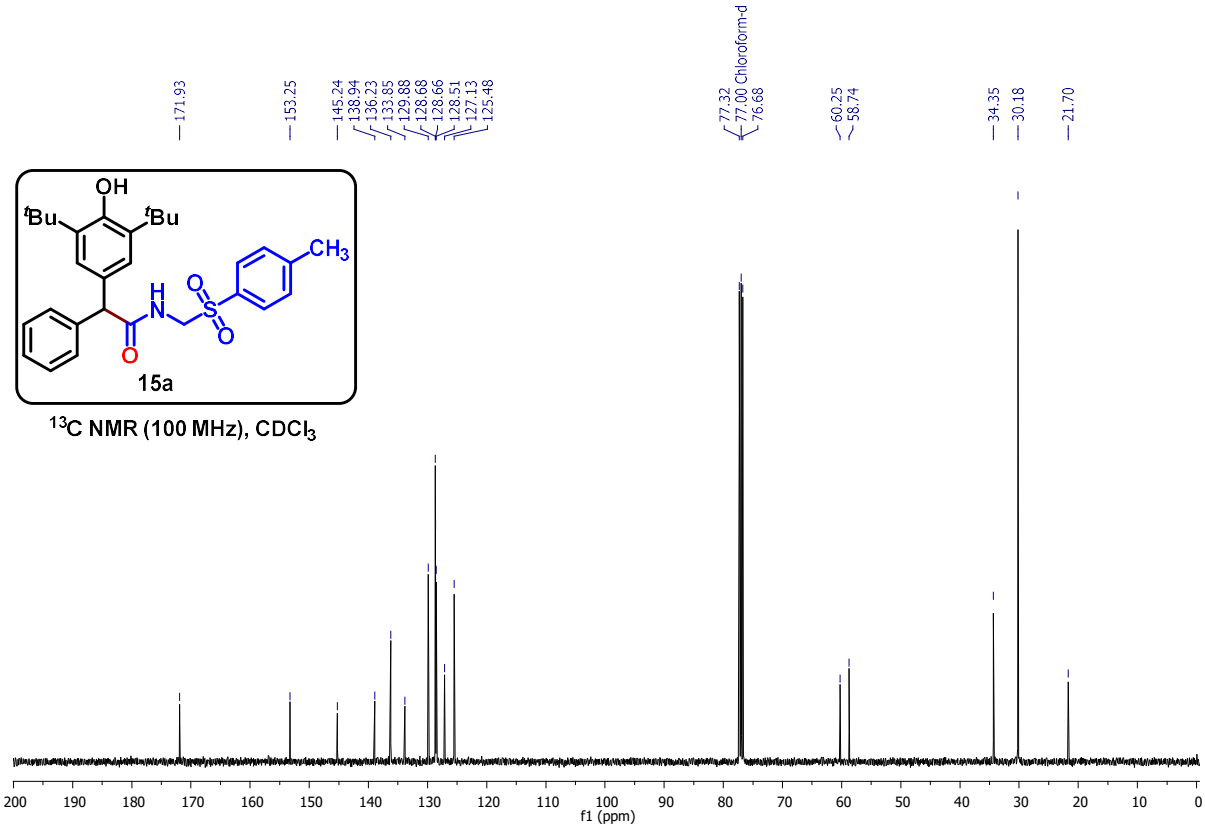
2-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-2-phenyl-*N*-(tosylmethyl)ethanethioamide (20):

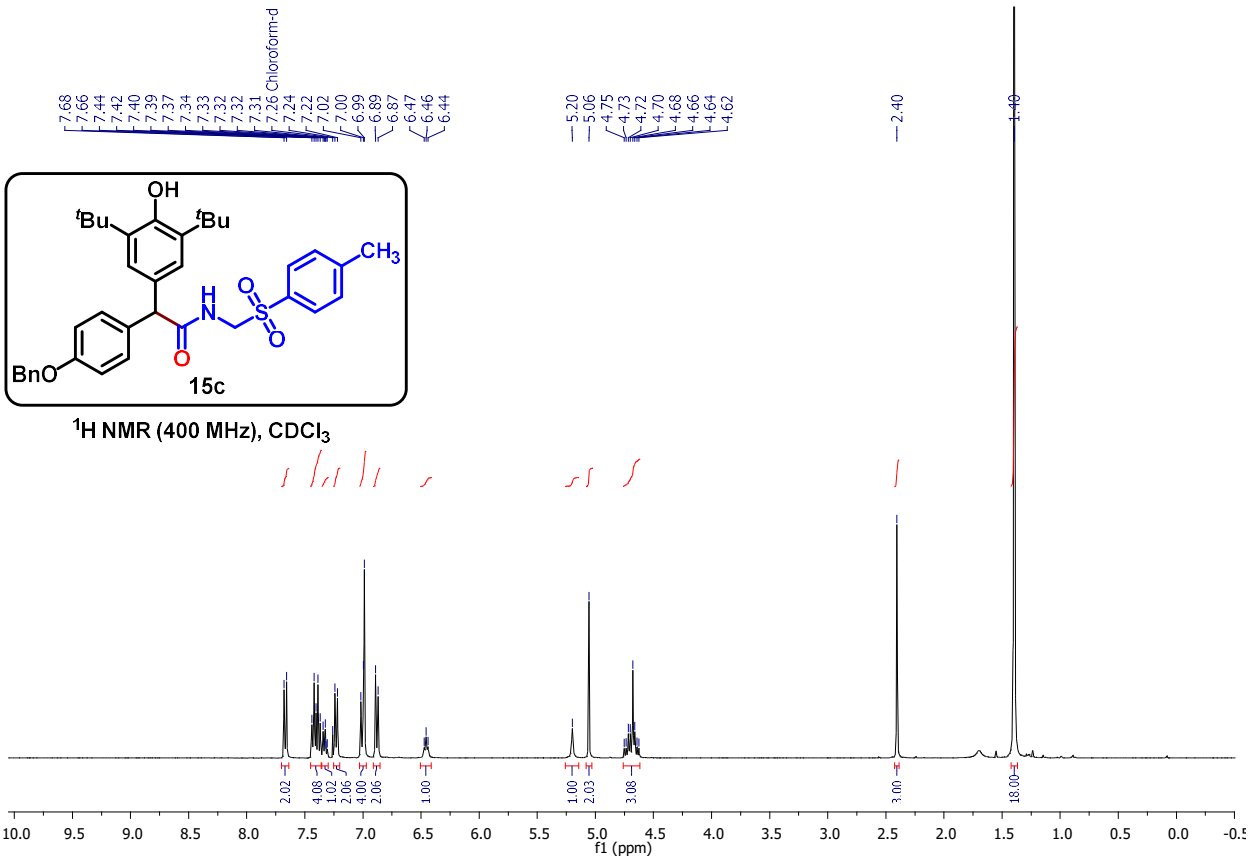


The product **20** was obtained in 72% yield (37.5 mg, White solid); **mp** = 181-182 °C; R_f = 0.59 (petroleum ether:ethyl acetate = 4:1); **IR υ_{max}(film)** = 3752, 3625, 3328, 2961, 2925, 1514, 1435, 1311, 1230, 1138, 914, 817, 756, 677 cm^{-1}; **^1H NMR (400 MHz, $CDCl_3$) δ** = 7.78 (t, *J* = 6.2 Hz, 1H), 7.62 (d, *J* = 8.3 Hz, 2H), 7.31 – 7.23 (m, 5H), 7.07 (dd, *J* = 7.4, 1.8 Hz, 2H), 6.97 (s, 2H), 5.45 (s, 1H), 5.45 – 5.39 (m, 1H), 5.28 (s, 1H), 5.12 (dd, *J* = 14.1, 5.9 Hz, 1H), 2.44 (s, 3H), 1.40 (s, 18H) ; **$^{13}C\{^1H\}$ NMR (100 MHz,$CDCl_3$) δ** = 207.3, 153.5, 145.6, 140.3, 136.5, 134.3, 130.0, 128.7, 128.7, 128.6, 128.6, 127.3, 125.8, 67.4, 64.4, 34.4, 30.1, 21.7 ; **HRMS (ESI-TOF)** *m/z*: $[M + H]^+$ calcd for $C_{30}H_{38}NO_3S_2$ 524.2288; found 524.2286.

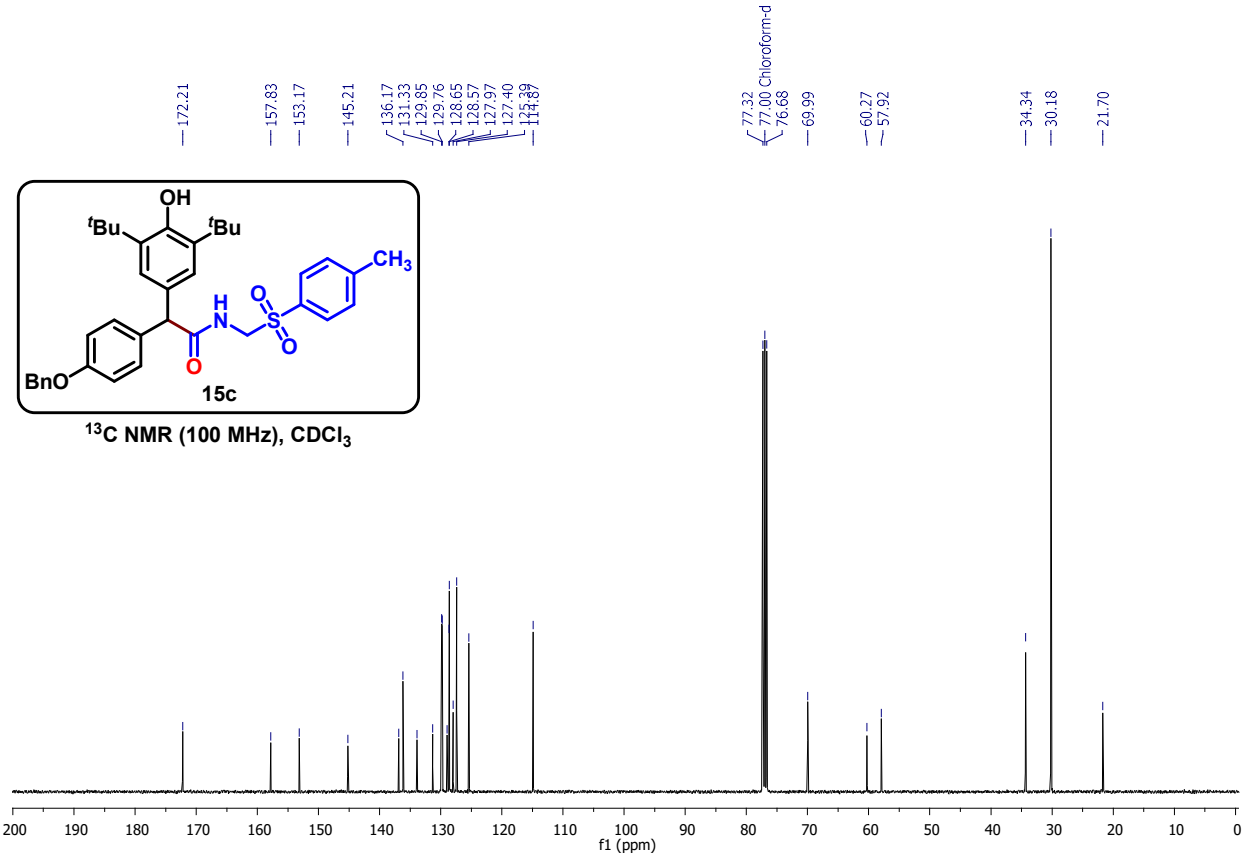
2.2.7 Spectral Data:



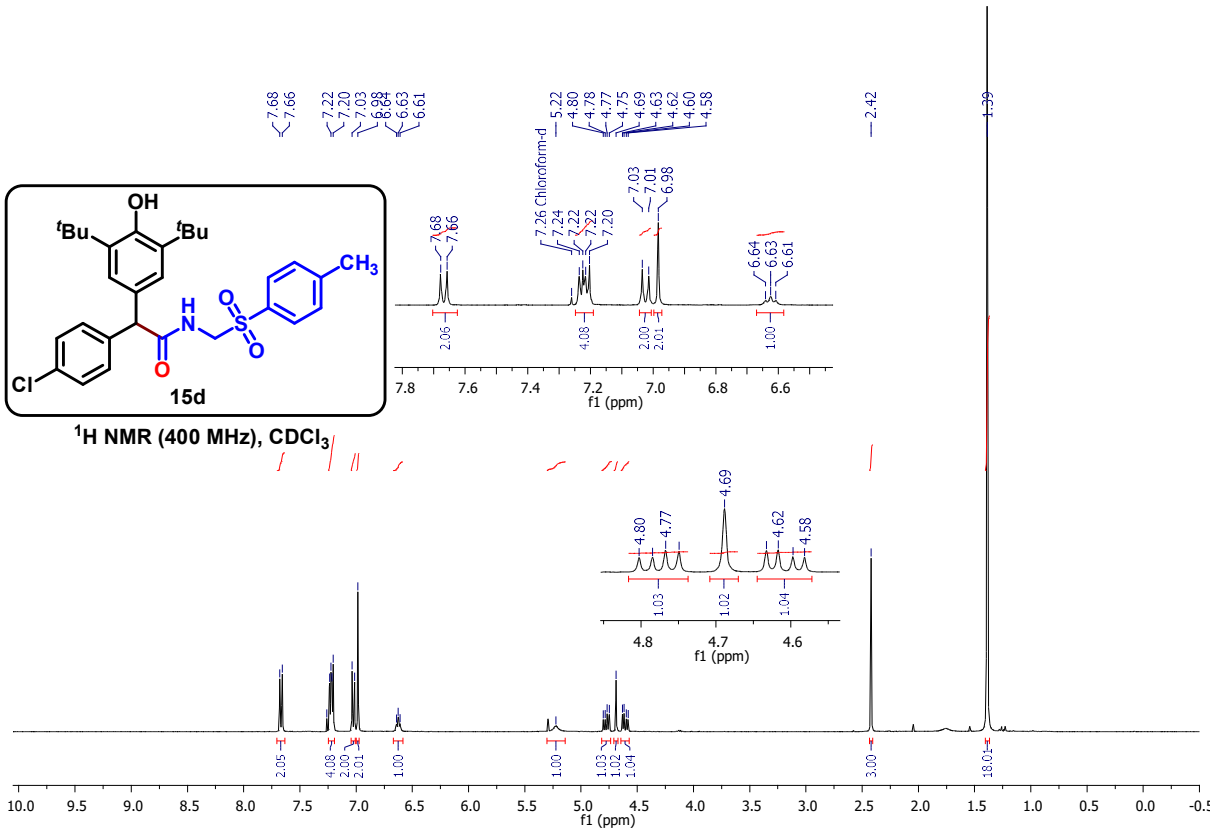


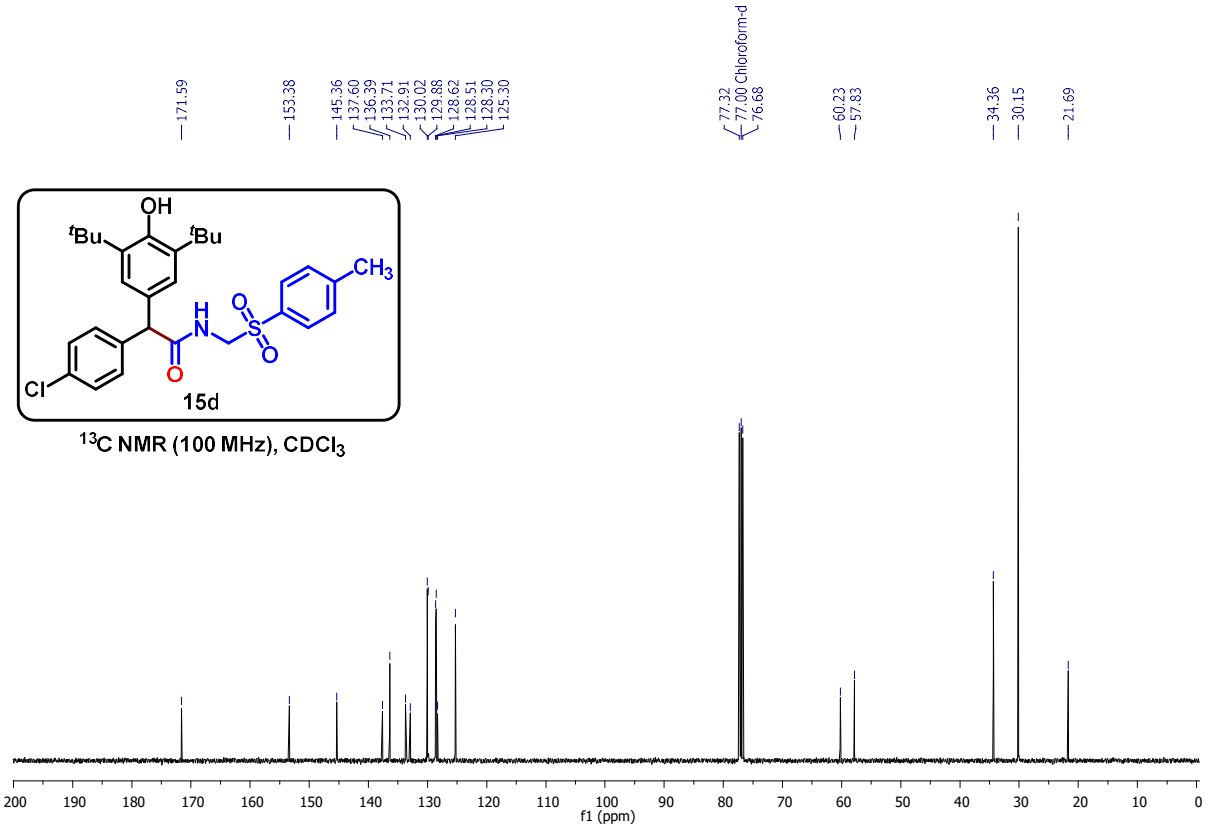


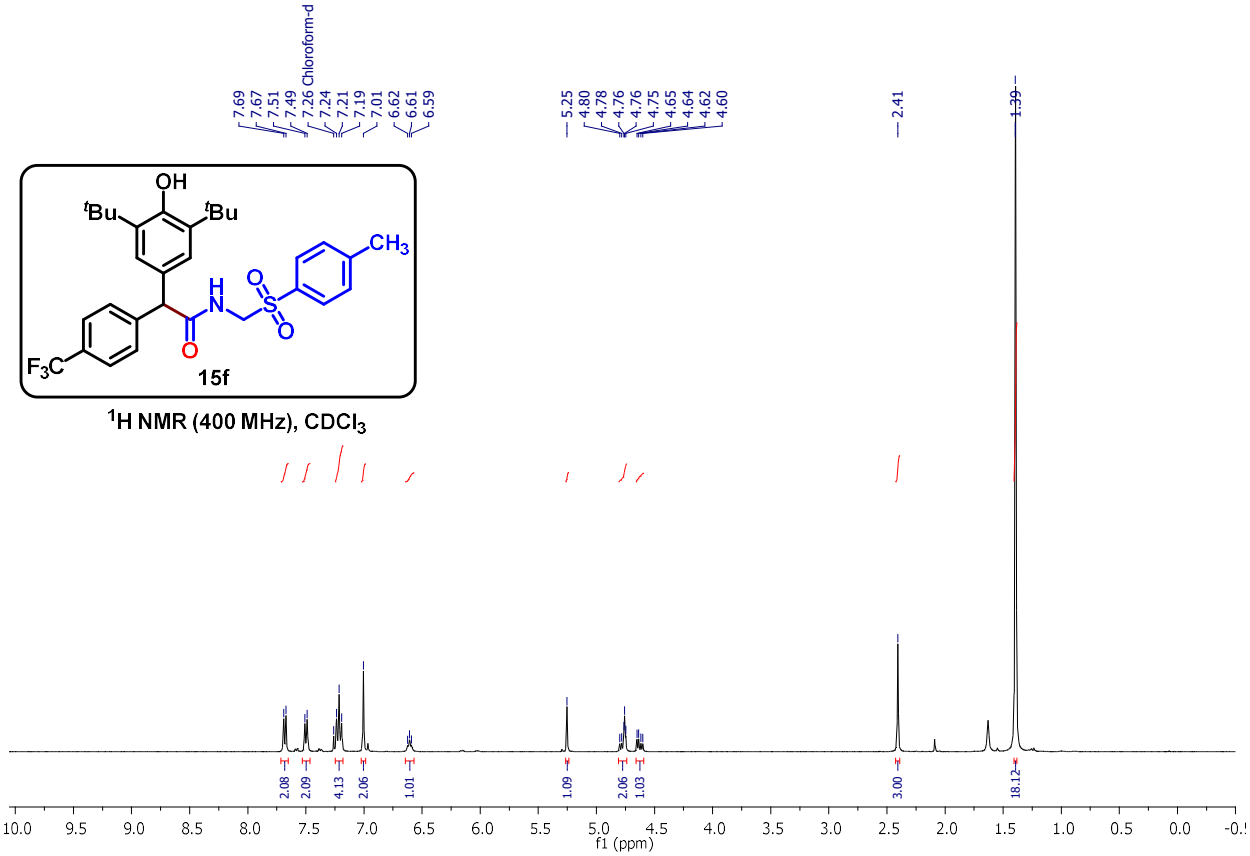
^{1}H NMR (400 MHz), $CDCl_3$



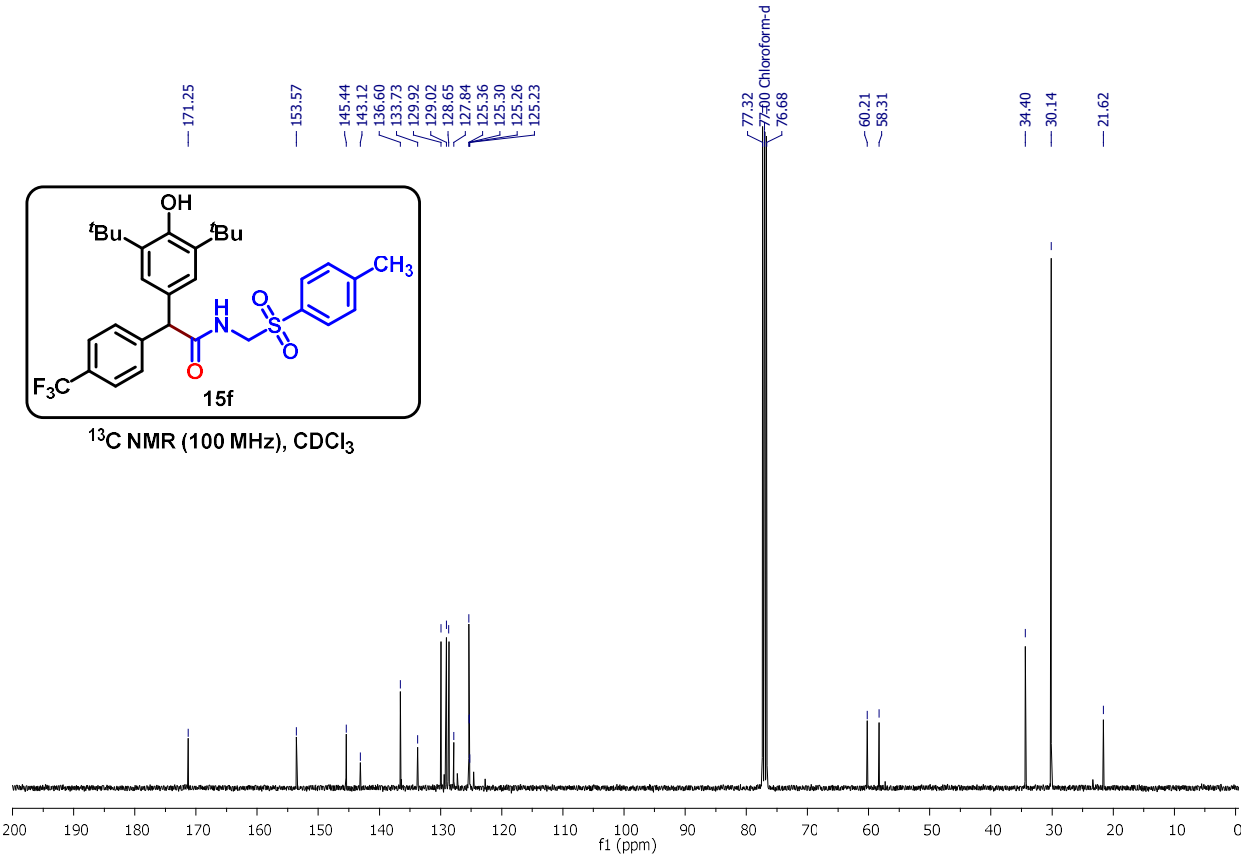
^{13}C NMR (100 MHz), $CDCl_3$


OH
tBu
tBu
CH3
H
N
O
S
O
O
Cl
15d
1H NMR (400 MHz), CDCl3
f1 (ppm)

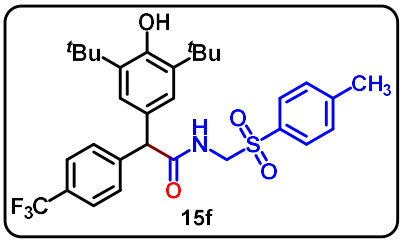

OH
tBu
tBu
CH3
H
N
O
S
O
O
Cl
15d
13C NMR (100 MHz), CDCl3
f1 (ppm)



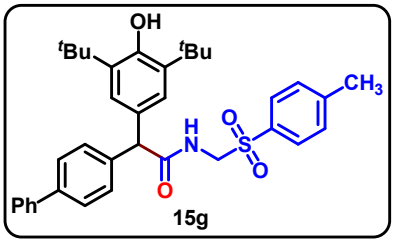
^{1}H NMR (400 MHz), $CDCl_3$



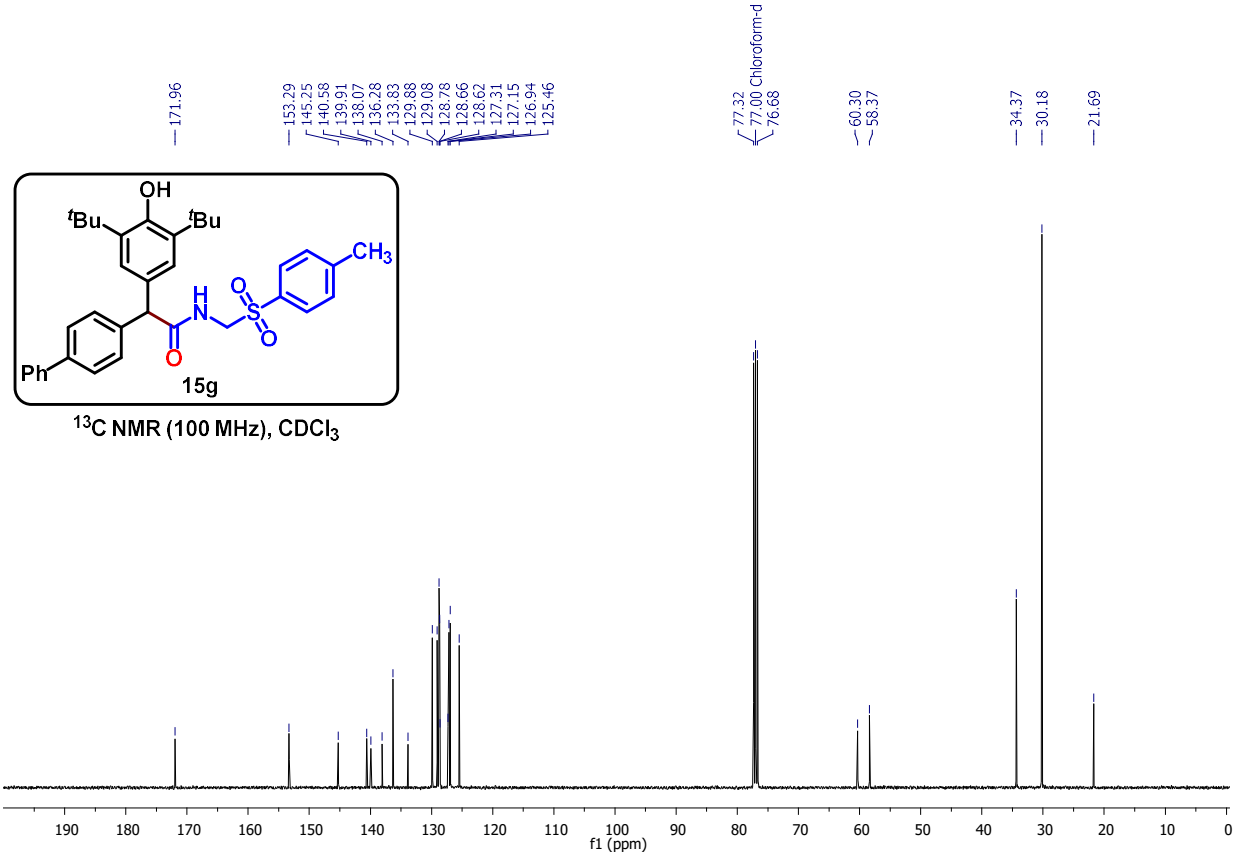
^{13}C NMR (100 MHz), $CDCl_3$

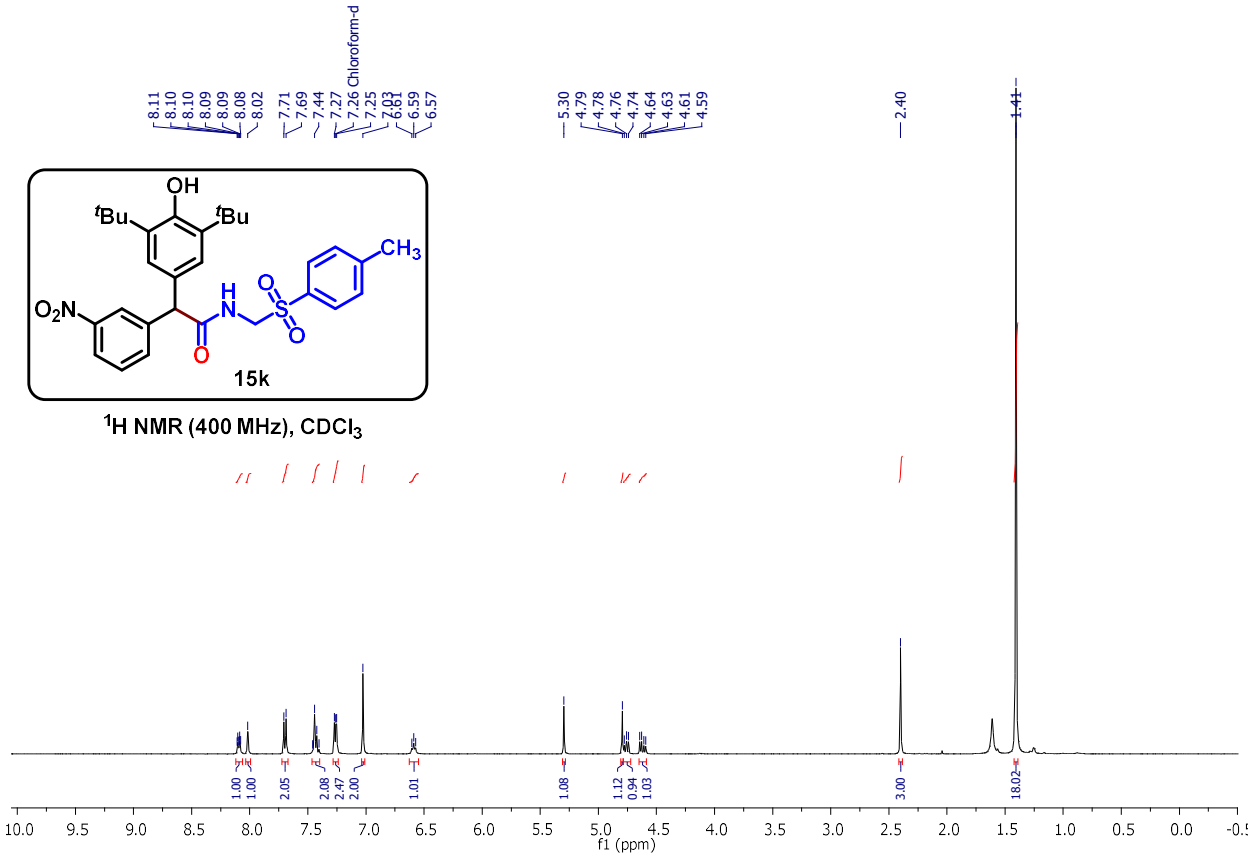


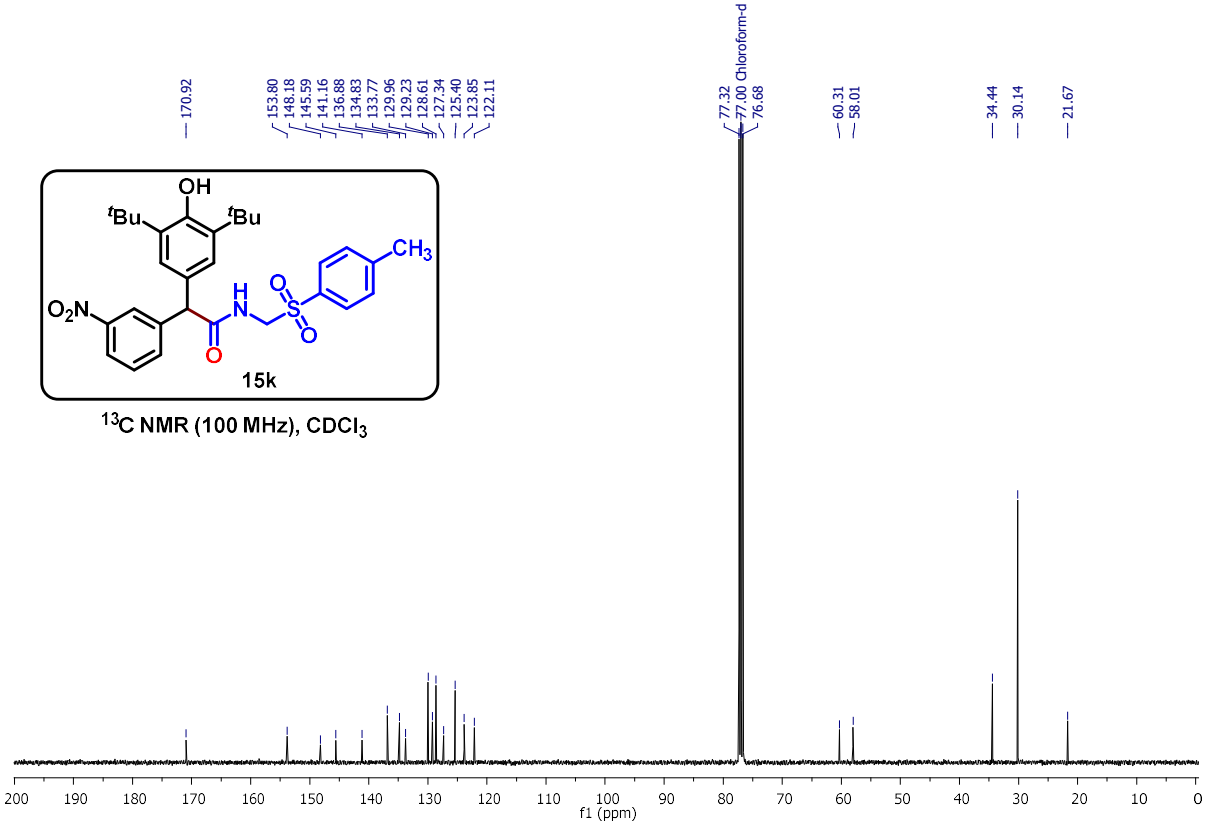
^{19}F NMR (376 MHz), $CDCl_3$

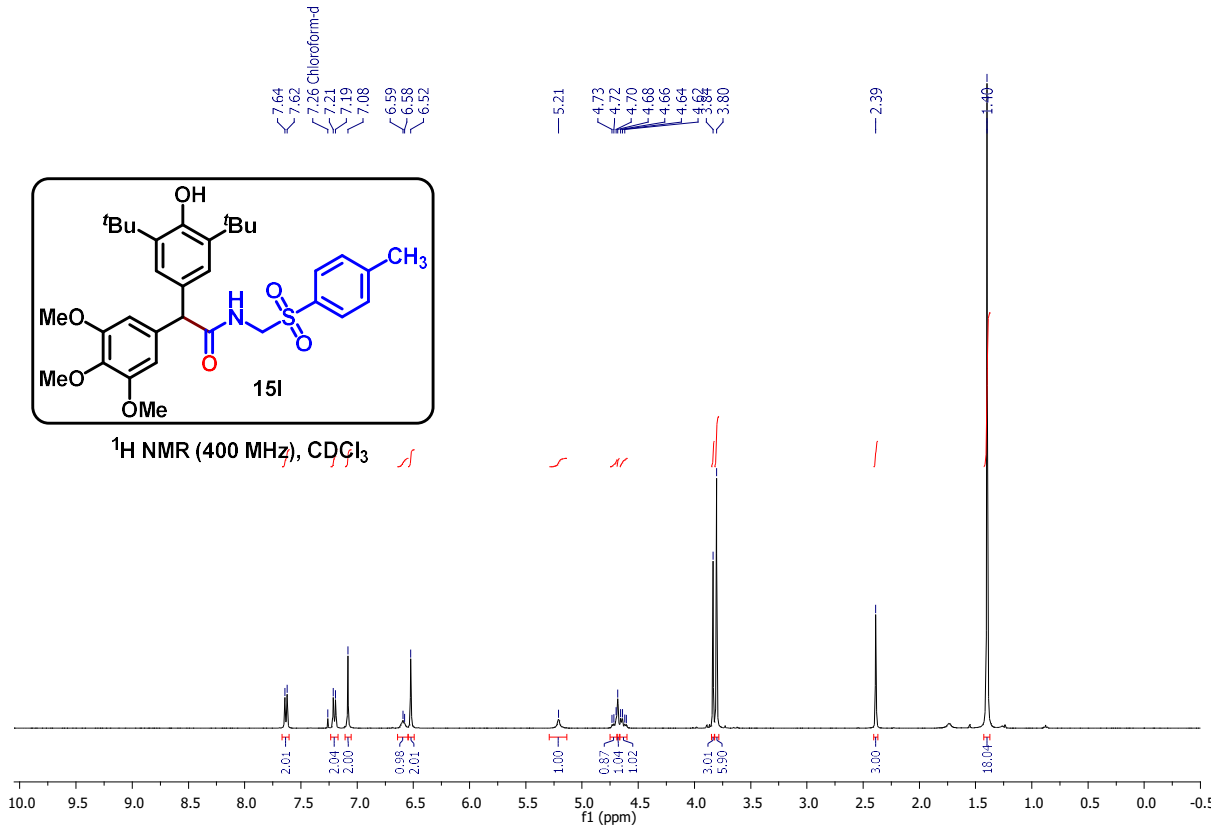


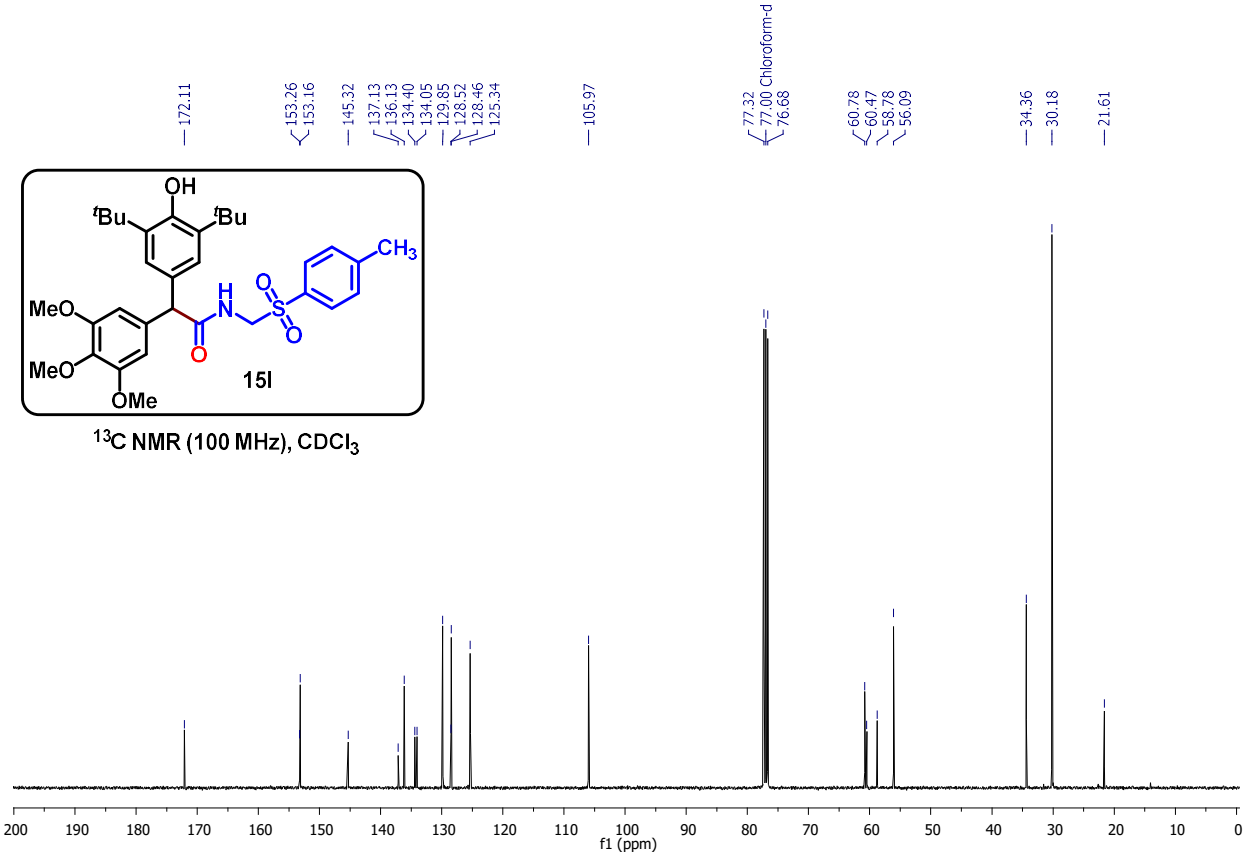
^{1}H NMR (400 MHz), $CDCl_3$


171.96
153.29
145.25
140.58
139.91
138.07
136.28
133.83
129.88
129.08
128.78
128.66
128.62
127.31
127.15
126.94
125.46
77.32
77.00 Chloroform-d
76.68
60.30
58.37
34.37
30.18
21.69
OH
tBu
tBu
CH3
H
N
O
S
O
O
Ph
15g
13C NMR (100 MHz), CDCl3
f1 (ppm)

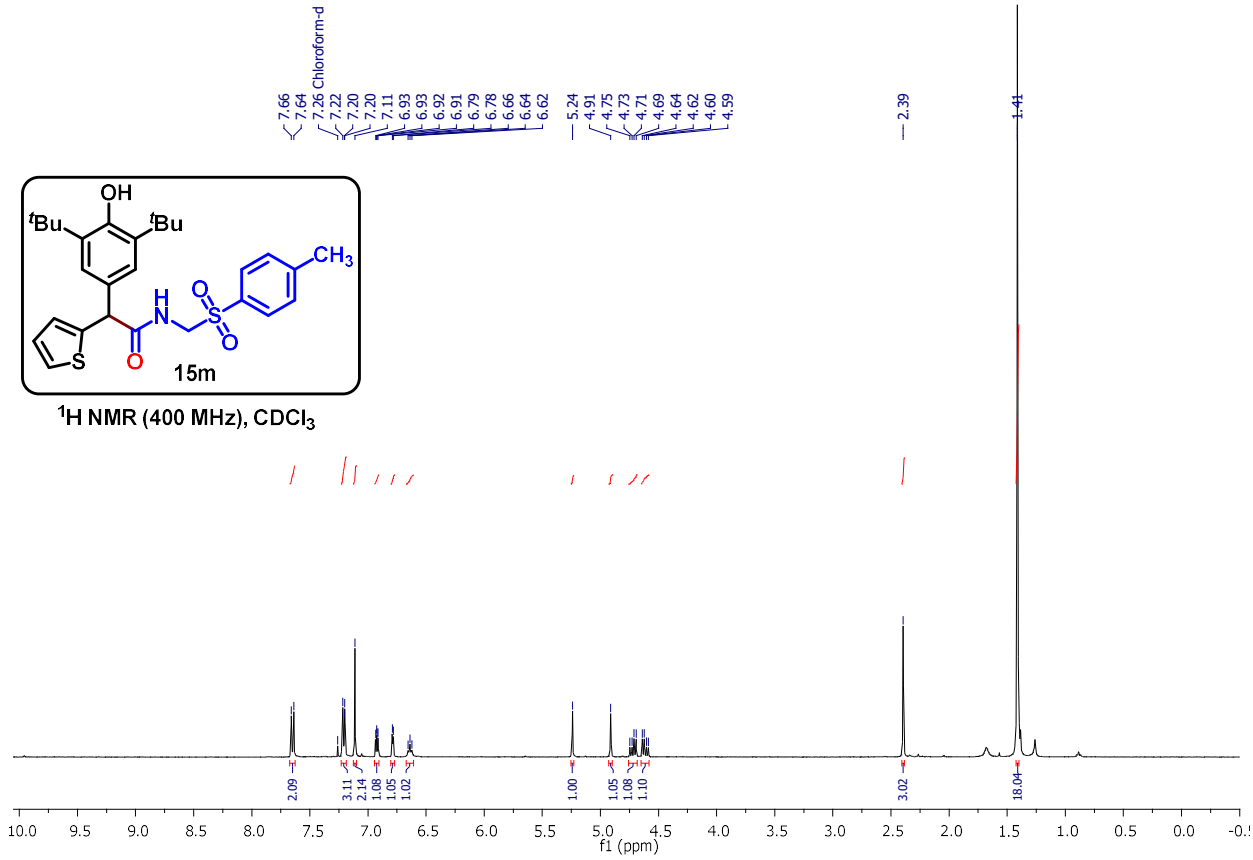

8.11
8.10
8.10
8.09
8.09
8.08
8.02
7.71
7.69
7.44
7.27
7.26 Chloroform-d
7.25
7.03
6.81
6.59
6.57
5.30
4.79
4.78
4.76
4.74
4.64
4.63
4.61
4.59
2.40
1.41
OH
tBu
tBu
CH3
O2N
H
N
O
S
O
O
15k
1H NMR (400 MHz), CDCl3
1.00
1.00
2.05
2.08
2.47
2.00
1.01
1.08
1.12
0.94
1.03
3.00
18.02
f1 (ppm)


170.92
153.80
148.18
145.59
141.16
136.88
134.83
133.77
129.96
129.23
128.61
127.34
125.40
123.85
122.11
77.32
77.00 Chloroform-d
76.68
60.31
58.01
34.44
30.14
21.67
OH
tBu
tBu
CH3
O2N
H
N
O
S
O
O
15k
13C NMR (100 MHz), CDCl3
f1 (ppm)

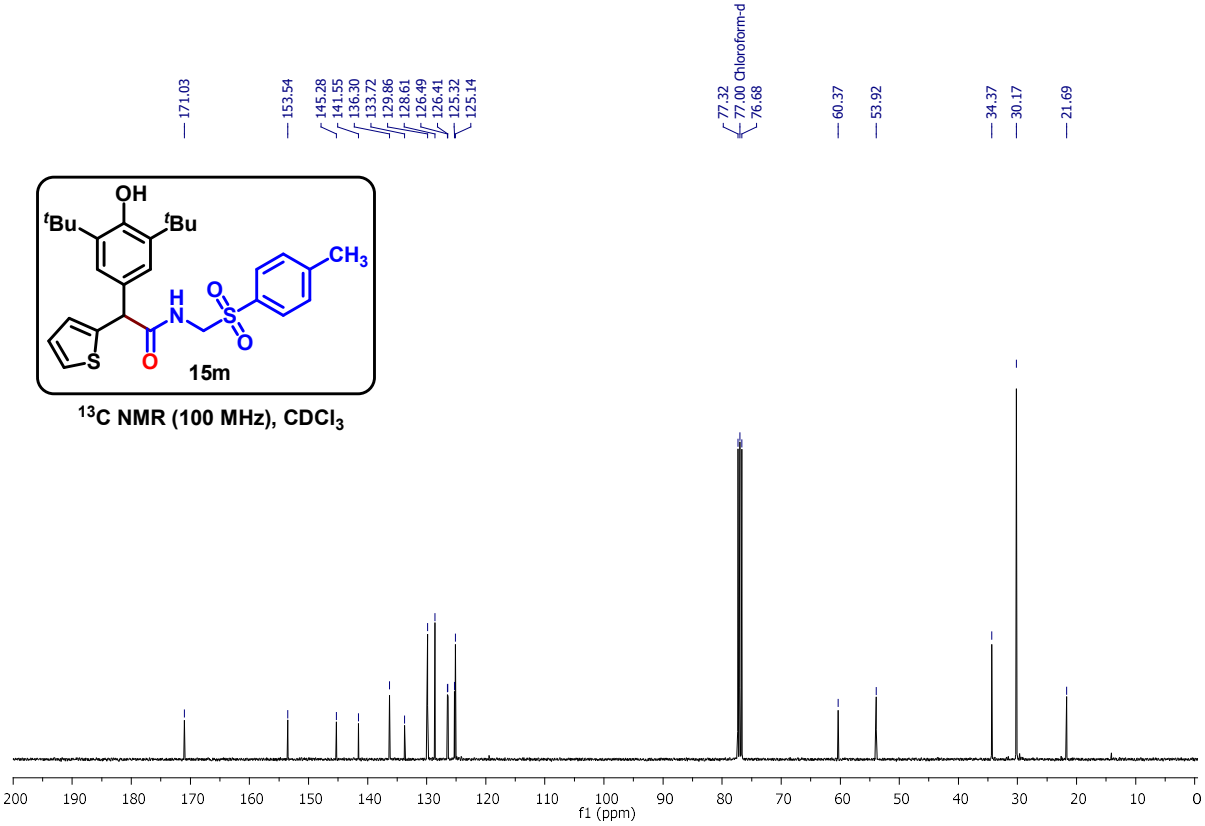

7.64
7.62
7.26 Chloroform-d
7.21
7.19
7.08
6.59
6.58
6.52
5.21
4.73
4.72
4.70
4.68
4.66
4.64
3.84
3.80
2.39
1.40
OH
tBu
tBu
CH3
MeO
MeO
OMe
H
N
O
S
O
O
15l
1H NMR (400 MHz), CDCl3
2.01
2.04
2.00
0.98
2.01
1.00
0.87
1.04
1.02
3.01
5.90
3.00
18.04
f1 (ppm)

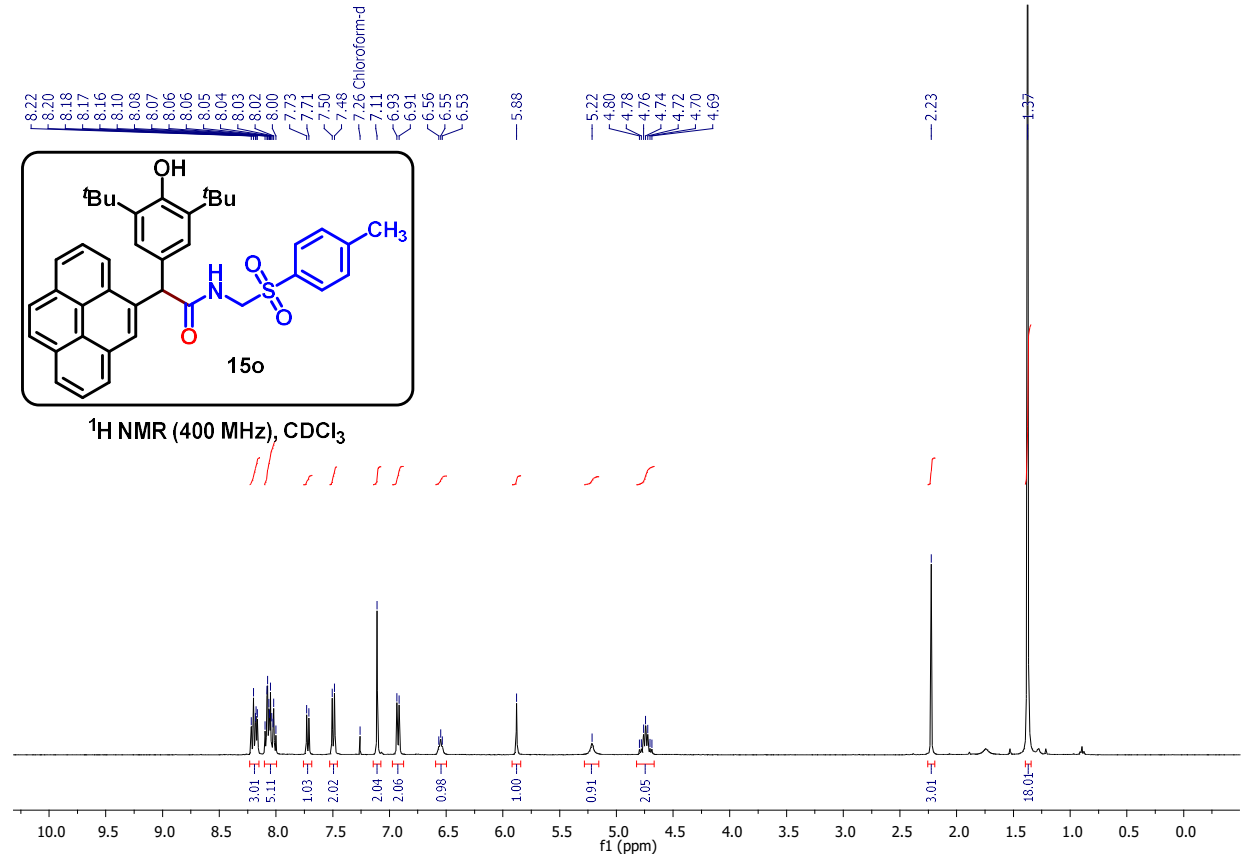


^{13}C NMR (100 MHz), $CDCl_3$



^{1}H NMR (400 MHz), $CDCl_3$


171.03
153.54
145.28
141.55
136.30
133.72
129.86
128.61
126.49
126.41
125.32
125.14
77.32
77.00 Chloroform-d
76.68
60.37
53.92
34.37
30.17
21.69
OH
tBu
tBu
CH3
H
N
O
S
O
O
S
O
15m
13C NMR (100 MHz), CDCl3
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)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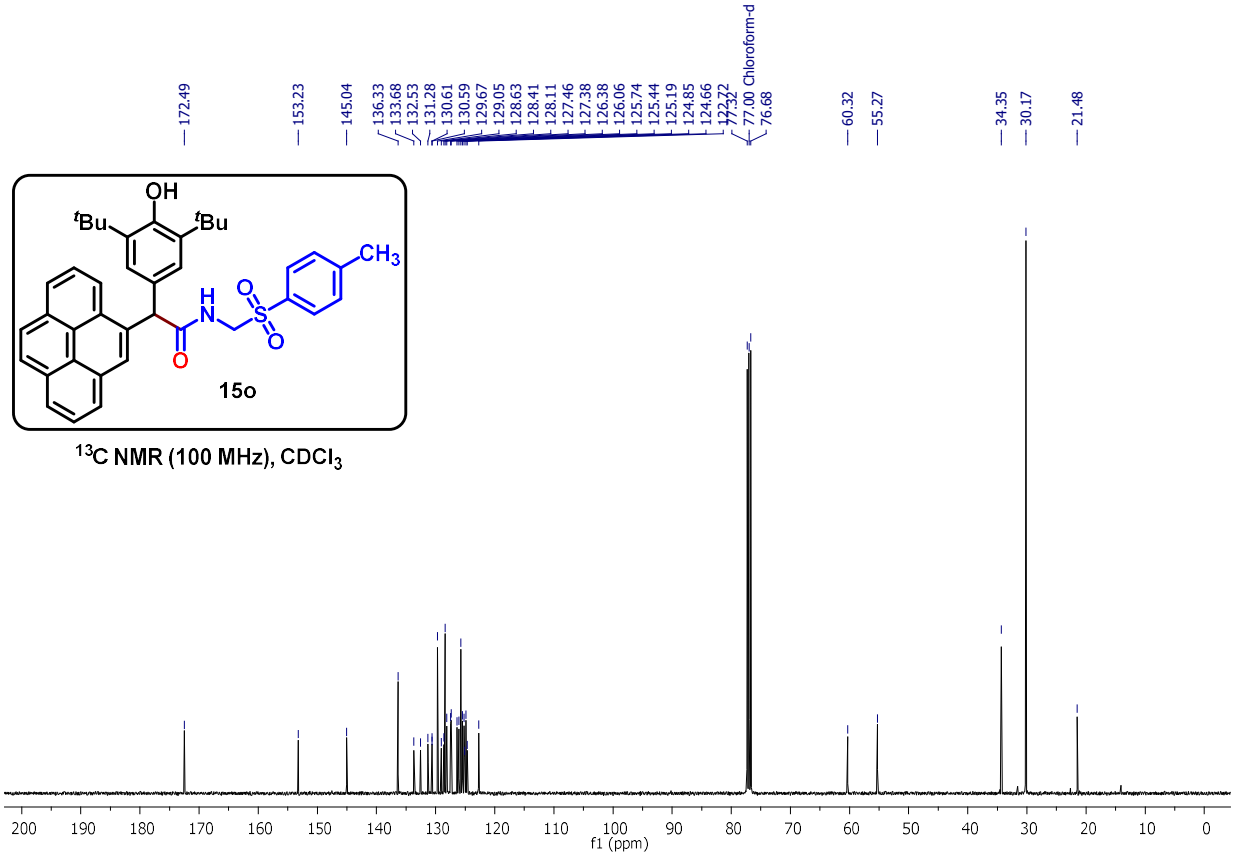
8.20
8.18
8.17
8.16
8.10
8.08
8.07
8.06
8.06
8.05
8.04
8.03
8.02
8.00
7.73
7.71
7.50
7.48
7.26 Chloroform-d
7.11
6.93
6.91
6.56
6.55
6.53
5.88
5.22
4.80
4.78
4.76
4.74
4.72
4.70
4.69
2.23
1.37
OH
tBu
tBu
CH3
H
N
O
S
O
O
15o
1H NMR (400 MHz), CDCl3
3.01
5.11
1.03
2.02
2.04
2.06
0.98
1.00
0.91
2.05
3.01
18.01
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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133.68
132.53
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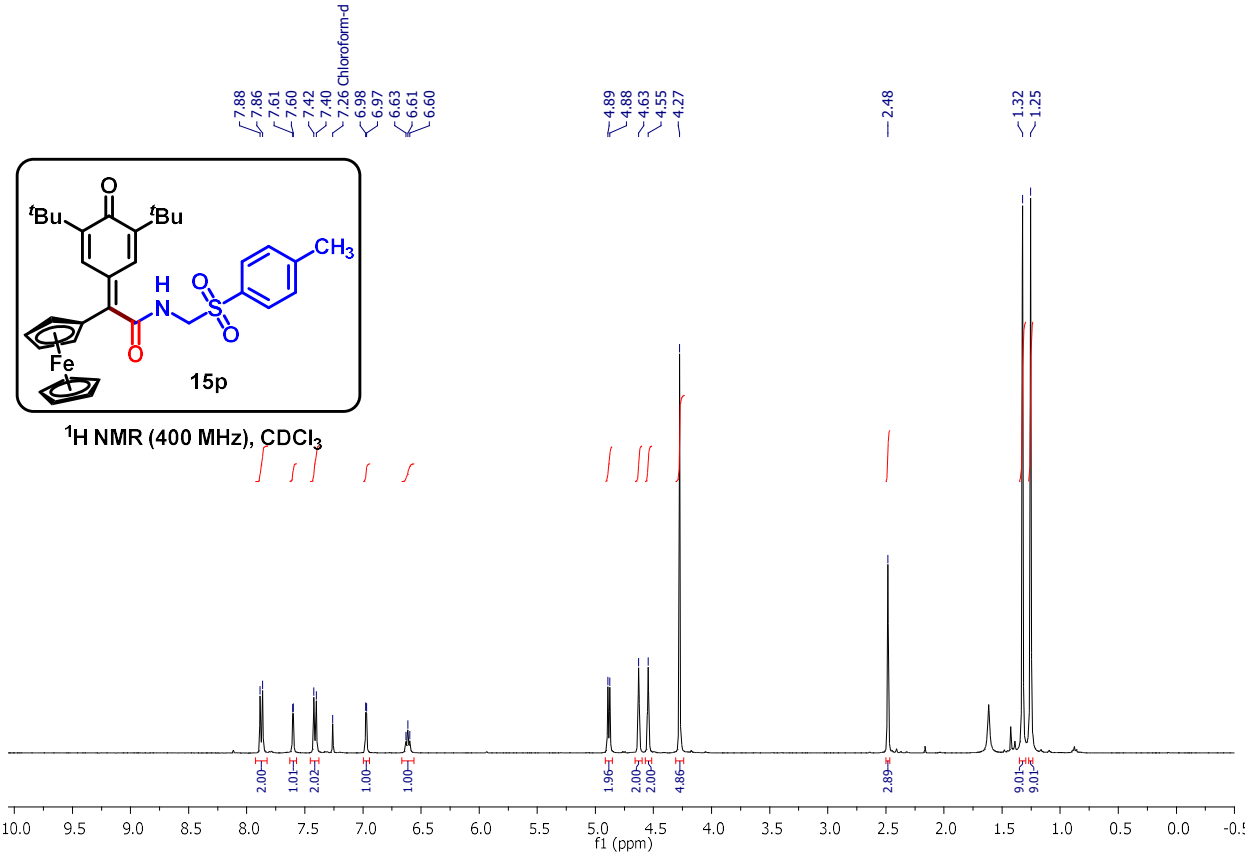
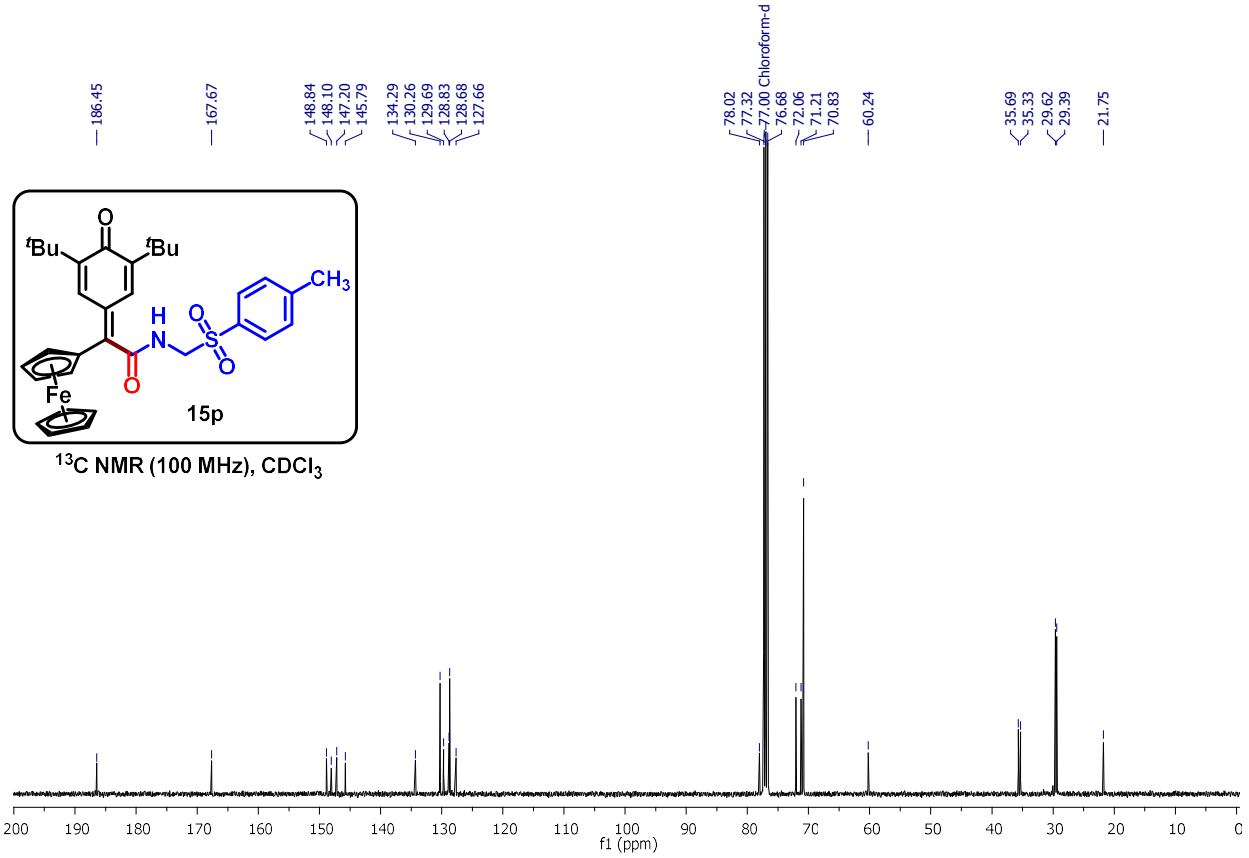
130.61
130.59
129.67
129.05
128.63
128.41
128.11
127.46
127.38
126.38
126.06
125.74
125.44
125.19
124.85
124.66
122.72
77.32
77.00 Chloroform-d
76.68
60.32
55.27
34.35
30.17
21.48
OH
tBu
tBu
CH3
H
N
O
S
O
O
15o
13C NMR (100 MHz), CDCl3
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


7.88
7.86
7.61
7.60
7.42
7.40
7.26 Chloroform-d
6.98
6.97
6.63
6.61
6.60
4.89
4.88
4.63
4.55
4.27
2.48
1.32
1.25
O
tBu
tBu
CH3
H
N
O
S
O
O
Fe
15p
1H NMR (400 MHz), CDCl3
2.00
1.01
2.02
1.00
1.00
1.96
2.00
2.00
4.86
2.89
9.01
9.01
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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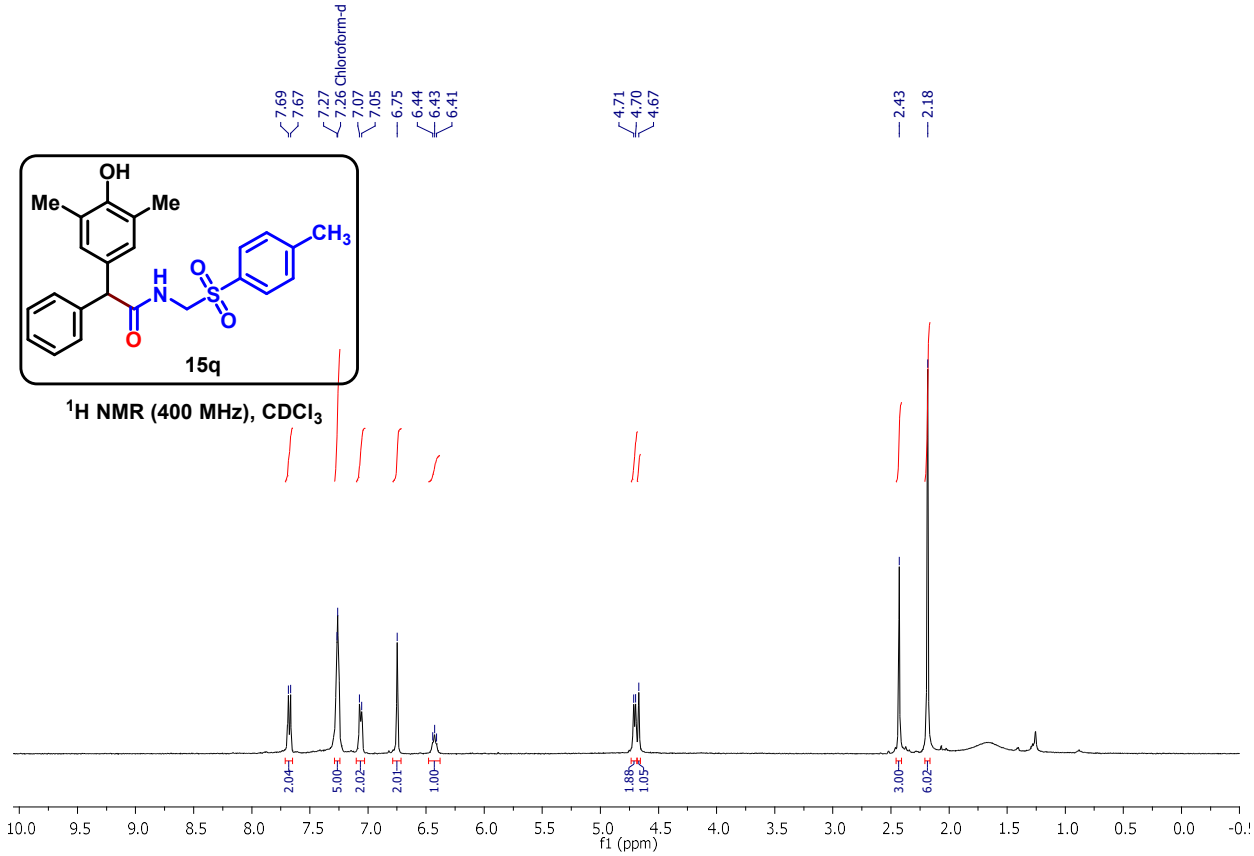
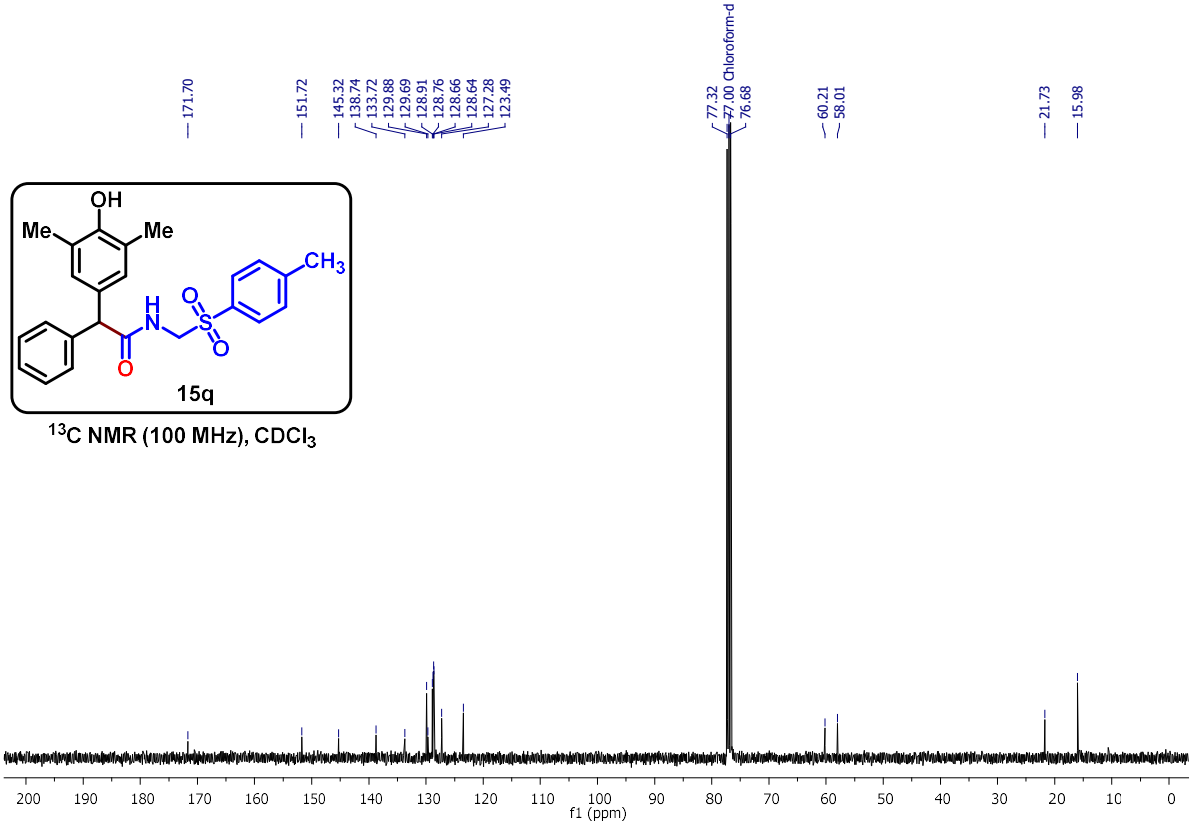
167.67
148.84
148.10
147.20
145.79
134.29
130.26
129.69
128.83
128.68
127.66
78.02
77.32
77.00 Chloroform-d
76.68
72.06
71.21
70.83
60.24
35.69
35.33
29.62
29.39
21.75
tBu
tBu
CH3
H
N
O
S
O
O
Fe
15p
13C NMR (100 MHz), CDCl3
f1 (ppm)


7.69
7.67
7.27
7.26 Chloroform-d
7.07
7.05
6.75
6.44
6.43
6.41
4.71
4.70
4.67
2.43
2.18
OH
Me
Me
CH3
H
N
O
S
O
O
15q
1H NMR (400 MHz), CDCl3
2.04
5.00
2.02
2.01
1.00
1.88
1.05
3.00
6.02
f1 (ppm)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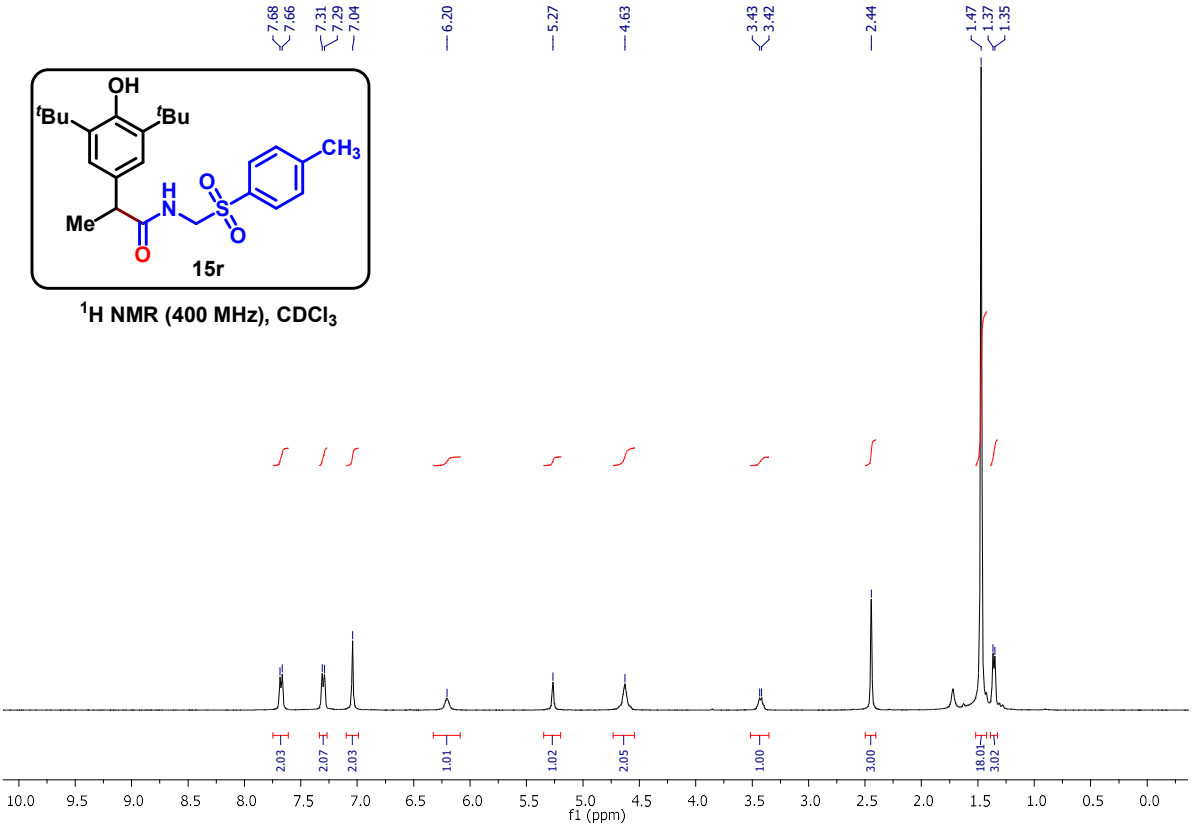
151.72
145.32
138.74
133.72
129.88
129.69
128.91
128.76
128.66
128.64
127.28
123.49
77.32
77.00 Chloroform-d
76.68
60.21
58.01
21.73
15.98
OH
Me
Me
CH3
H
N
O
S
O
O
15q
13C NMR (100 MHz), CDCl3
f1 (ppm)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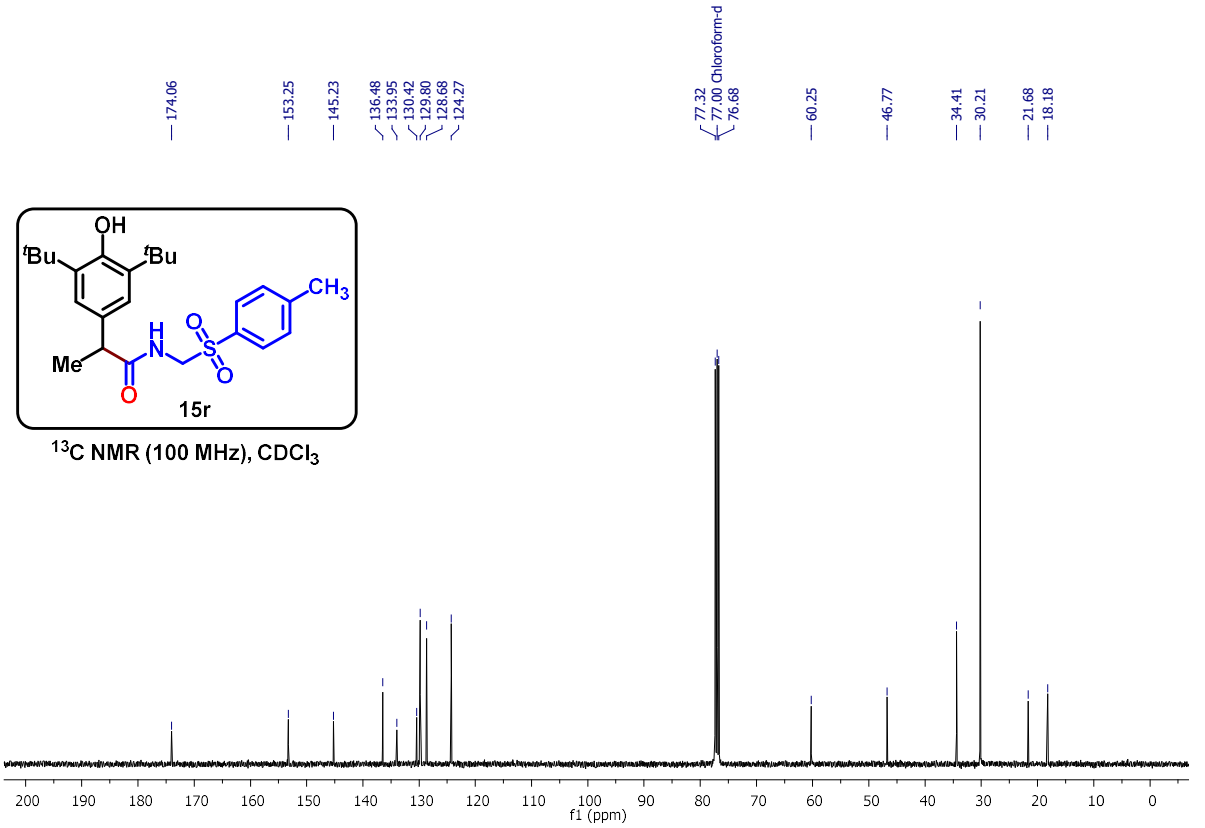
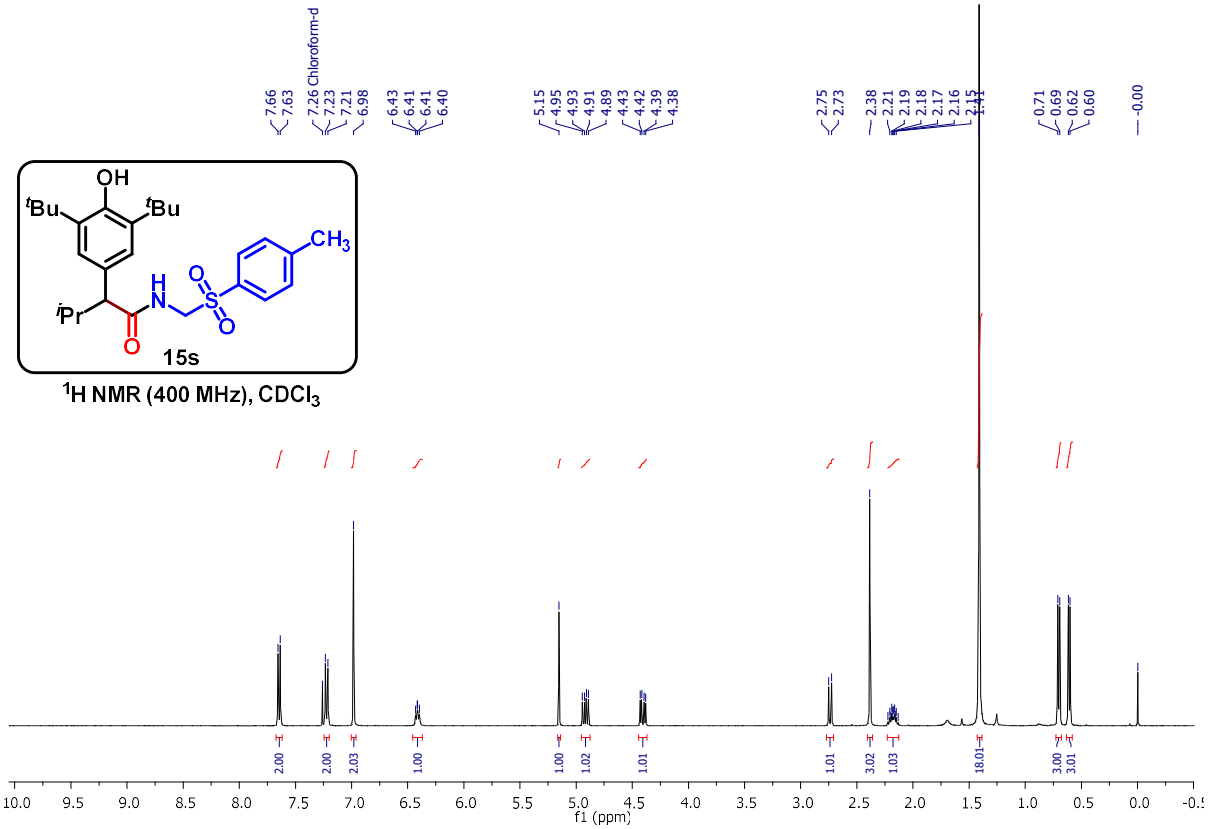
7.66
7.31
7.29
7.04
6.20
5.27
4.63
3.43
3.42
2.44
1.47
1.37
1.35
OH
tBu
tBu
CH3
Me
H
N
O
S
O
O
15r
1H NMR (400 MHz), CDCl3
2.03
2.07
2.03
1.01
1.02
2.05
1.00
3.00
18.01
3.02
f1 (ppm)


174.06
153.25
145.23
136.48
133.95
130.42
129.80
128.68
124.27
77.32
77.00 Chloroform-d
76.68
60.25
46.77
34.41
30.21
21.68
18.18
OH
tBu
tBu
CH3
H
N
O
S
O
Me
O
15r
13C NMR (100 MHz), CDCl3
f1 (ppm)


7.66
7.63
7.26 Chloroform-d
7.23
7.21
6.98
6.43
6.41
6.41
6.40
5.15
4.95
4.93
4.91
4.89
4.43
4.42
4.39
4.38
2.75
2.73
2.38
2.21
2.19
2.18
2.17
2.16
2.15
2.11
0.71
0.69
0.62
0.60
-0.00
OH
tBu
tBu
CH3
H
N
O
S
O
iPr
O
15s
1H NMR (400 MHz), CDCl3
2.00
2.00
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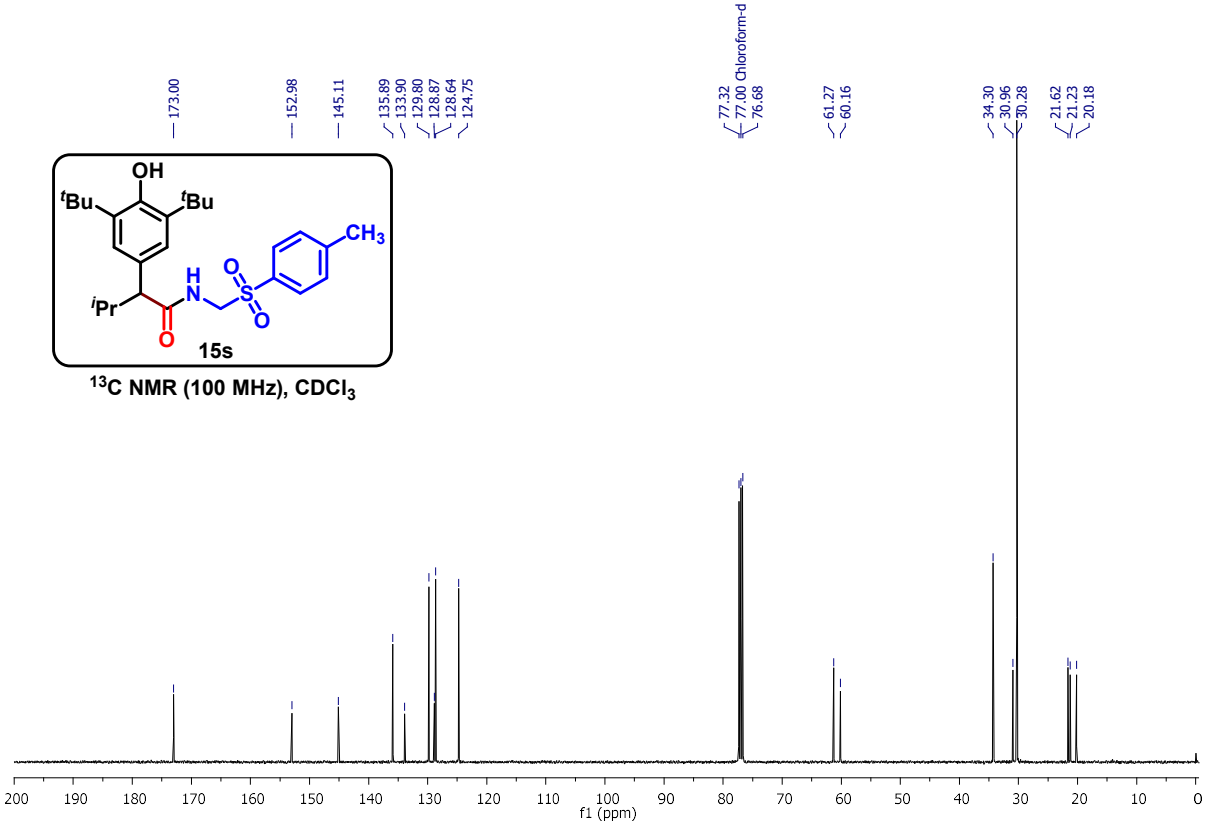
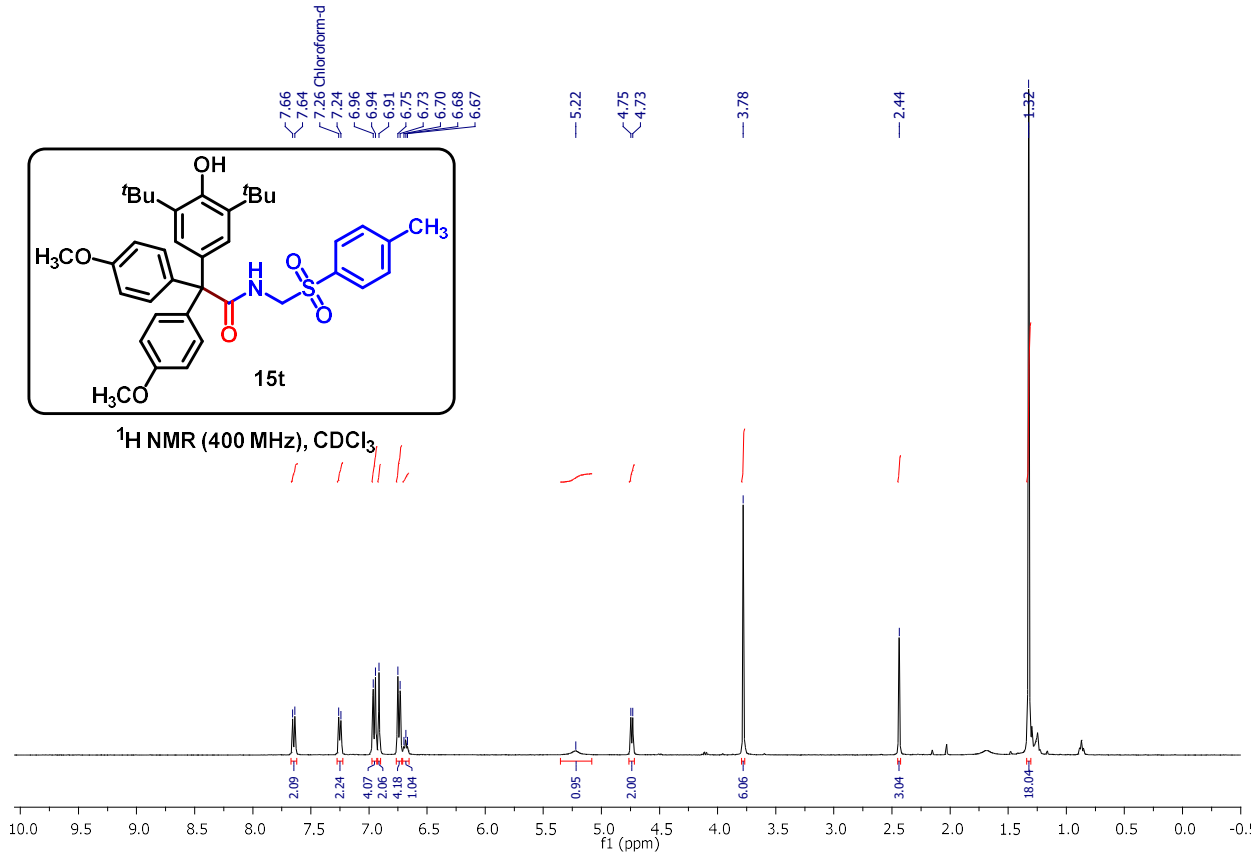
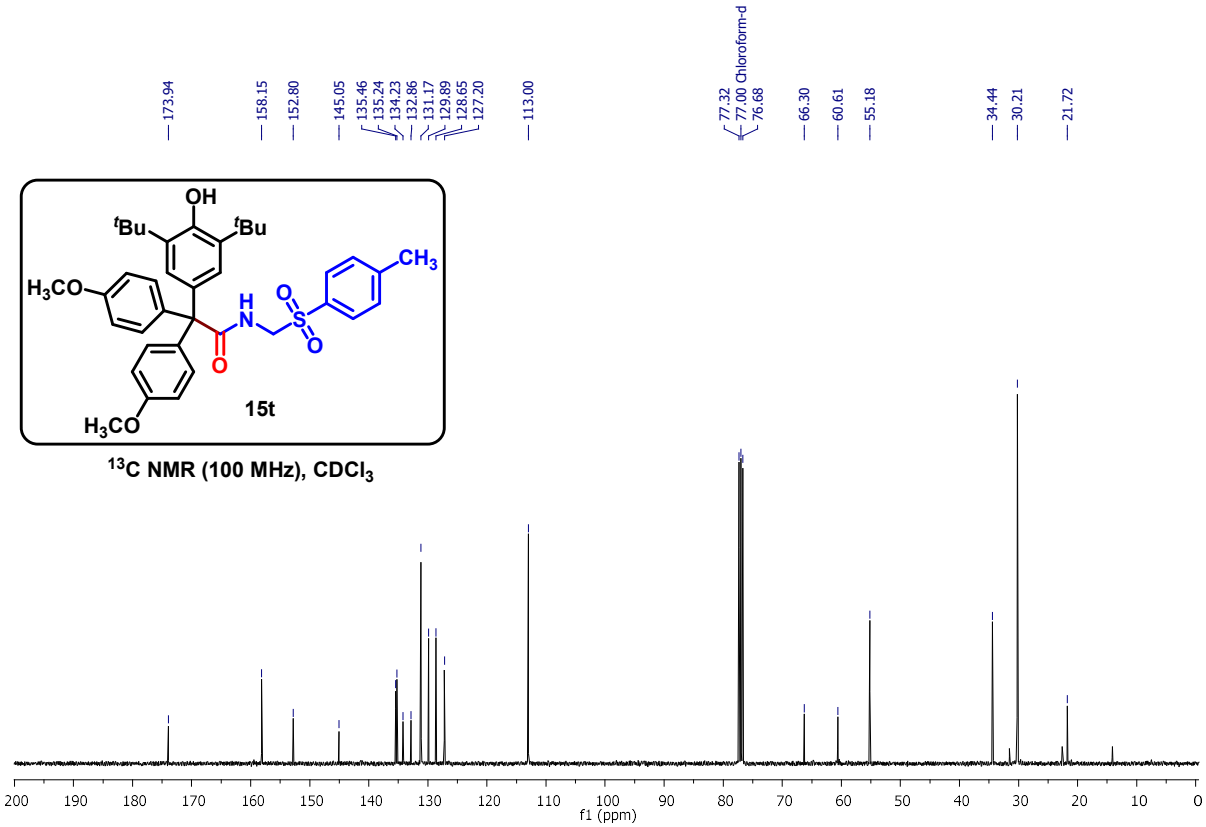
1.03
18.01
3.00
3.01
f1 (ppm)



^{13}C NMR (100 MHz), $CDCl_3$



^{1}H NMR (400 MHz), $CDCl_3$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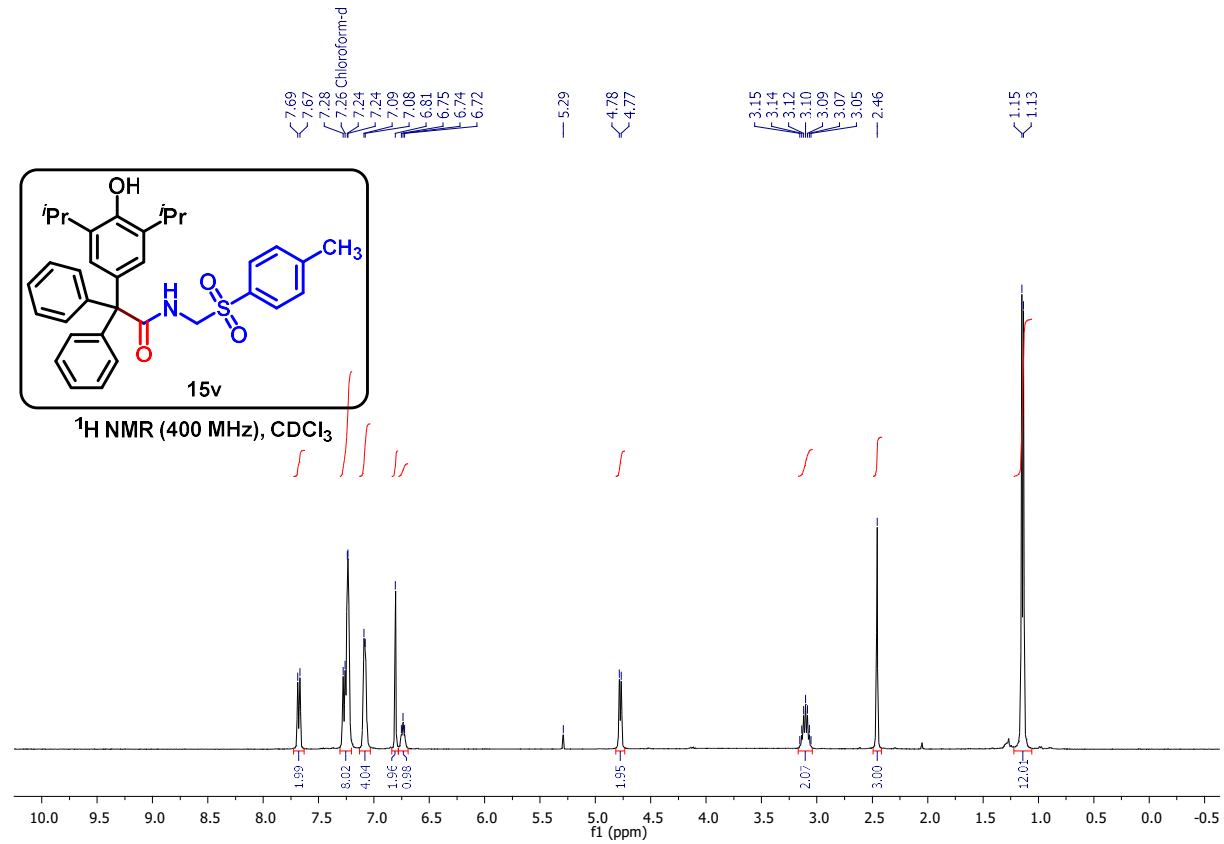
145.05
135.46
135.24
134.23
132.86
131.17
129.89
128.65
127.20
113.00
77.32
77.00 Chloroform-d
76.68
66.30
60.61
55.18
34.44
30.21
21.72
OH
tBu
tBu
H3CO
CH3
H
N
O
S
O
O
O
H3CO
15t
13C NMR (100 MHz), CDCl3
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)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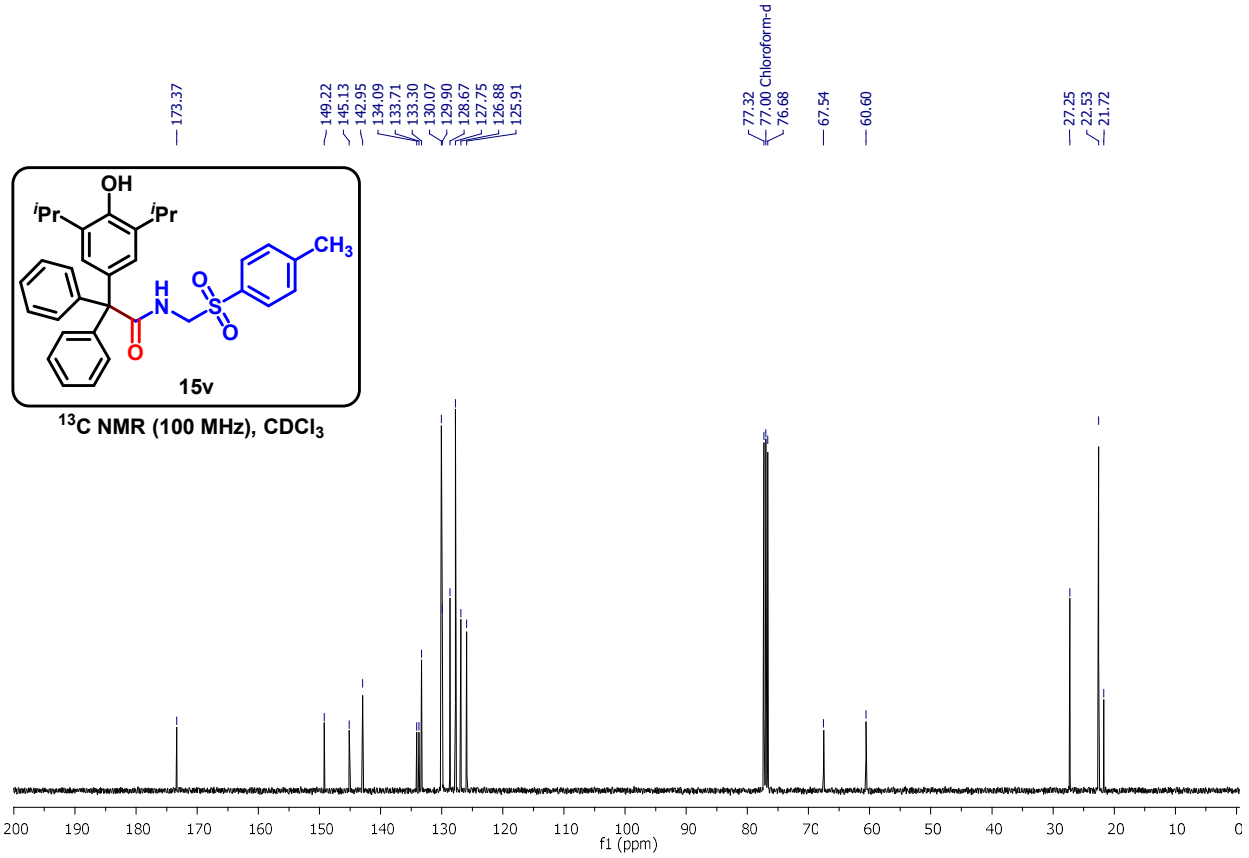
7.67
7.28
7.26 Chloroform-d
7.24
7.24
7.09
7.08
6.81
6.75
6.74
6.72
5.29
4.78
4.77
3.15
3.14
3.12
3.10
3.09
3.07
3.05
2.46
1.15
1.13
OH
iPr
iPr
CH3
H
N
O
S
O
O
O
15v
1H NMR (400 MHz), CDCl3
1.99
8.02
4.04
1.96
0.98
1.95
2.07
3.00
12.01
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)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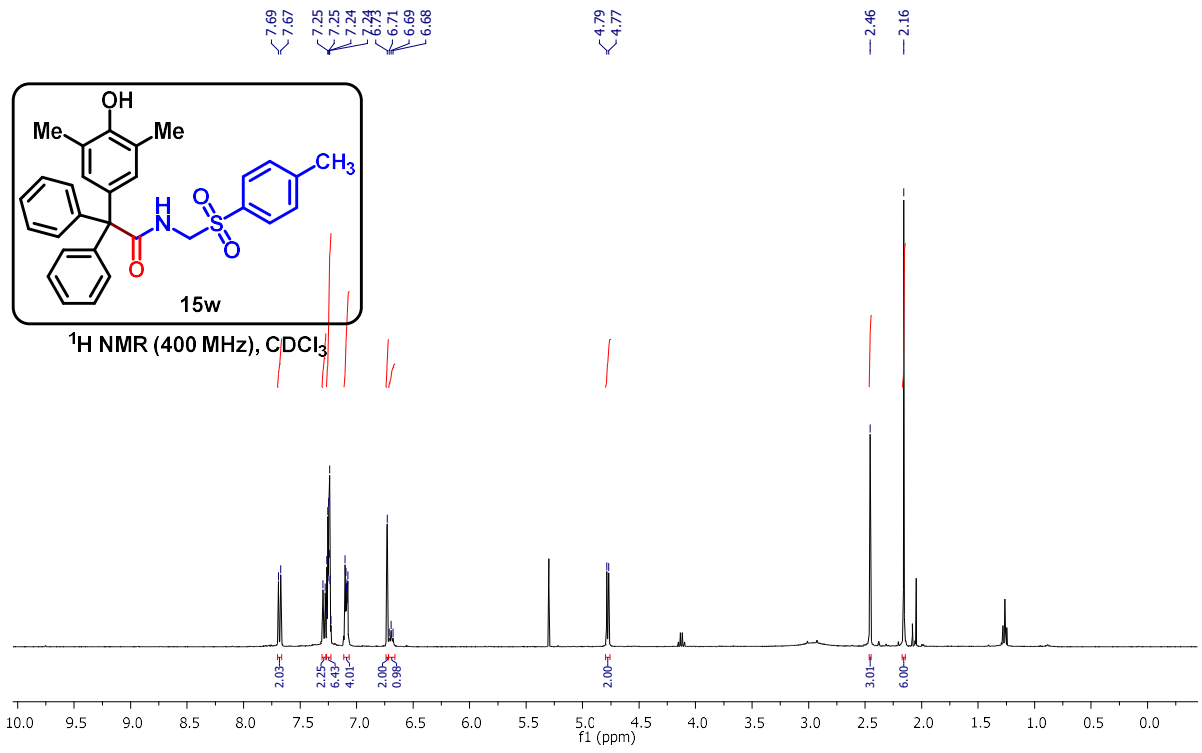
142.95
134.09
133.71
133.30
130.07
129.90
128.67
127.75
126.88
125.91
77.32
77.00 Chloroform-d
76.68
67.54
60.60
27.25
22.53
21.72
OH
iPr
iPr
CH3
H
N
O
S
O
O
O
15v
13C NMR (100 MHz), CDCl3
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)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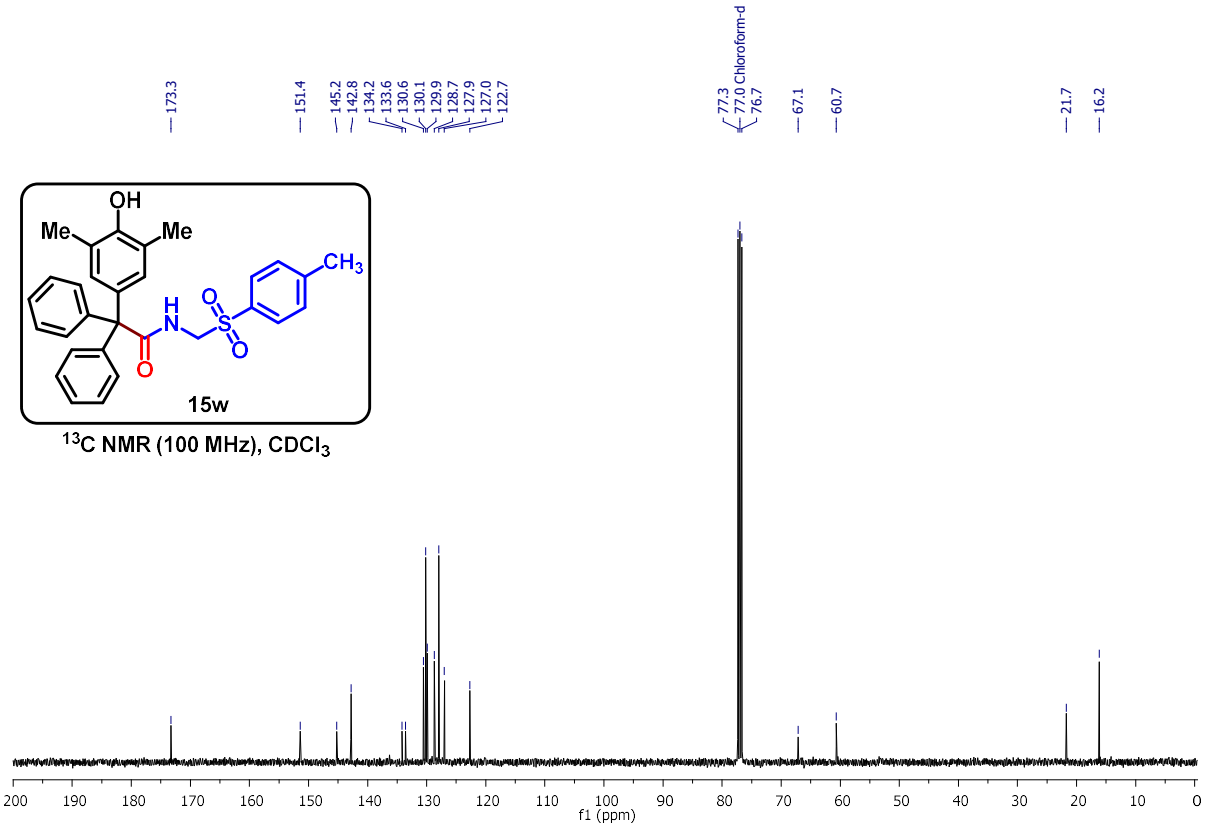
7.67
7.25
7.25
7.24
7.24
6.73
6.71
6.69
6.68
4.79
4.77
2.46
2.16
OH
Me
Me
CH3
H
N
O
S
O
O
O
15w
1H NMR (400 MHz), CDCl3
2.03
2.25
6.43
4.01
2.05
0.98
2.00
3.01
6.00
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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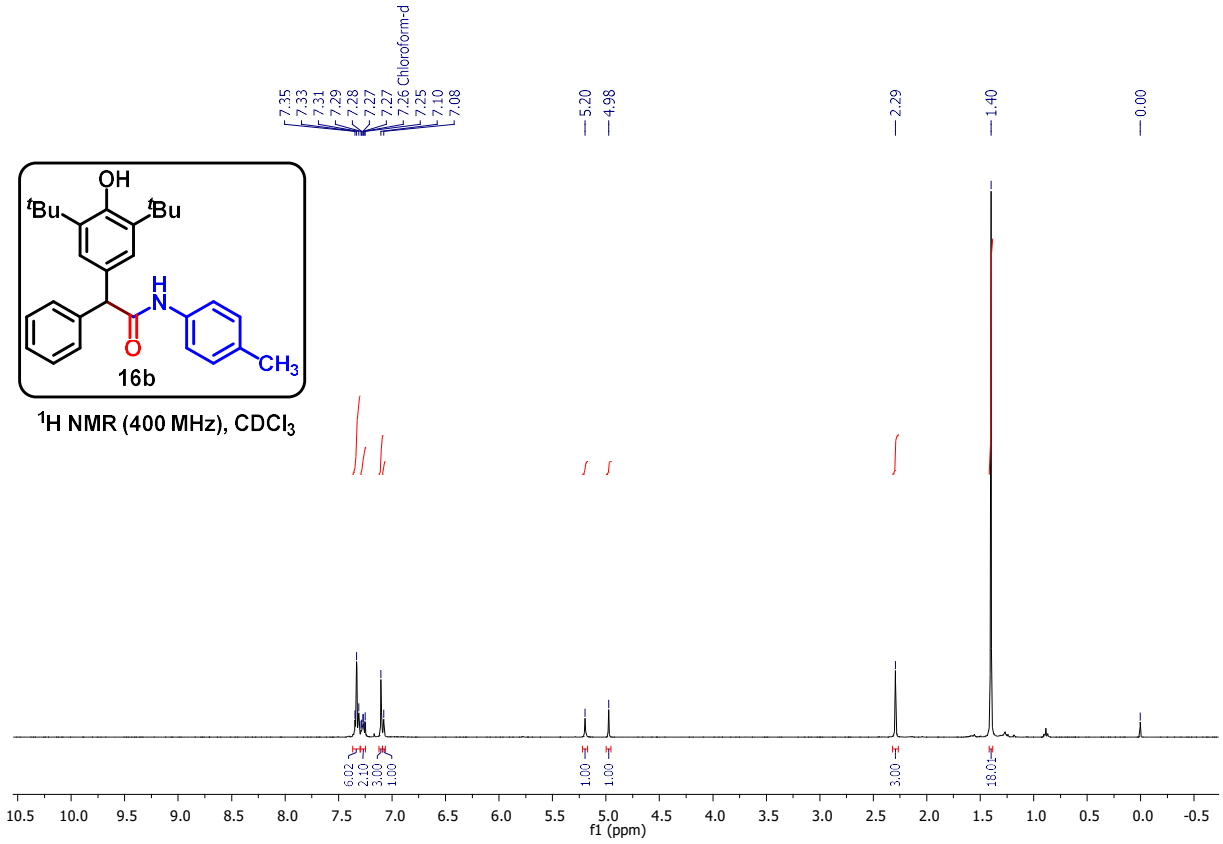
151.4
145.2
142.8
134.2
133.6
130.6
130.1
129.9
128.7
127.9
127.0
122.7
77.3
77.0 Chloroform-d
76.7
67.1
60.7
21.7
16.2
OH
Me
Me
CH3
H
N
O
S
O
O
15w
13C NMR (100 MHz), CDCl3
f1 (ppm)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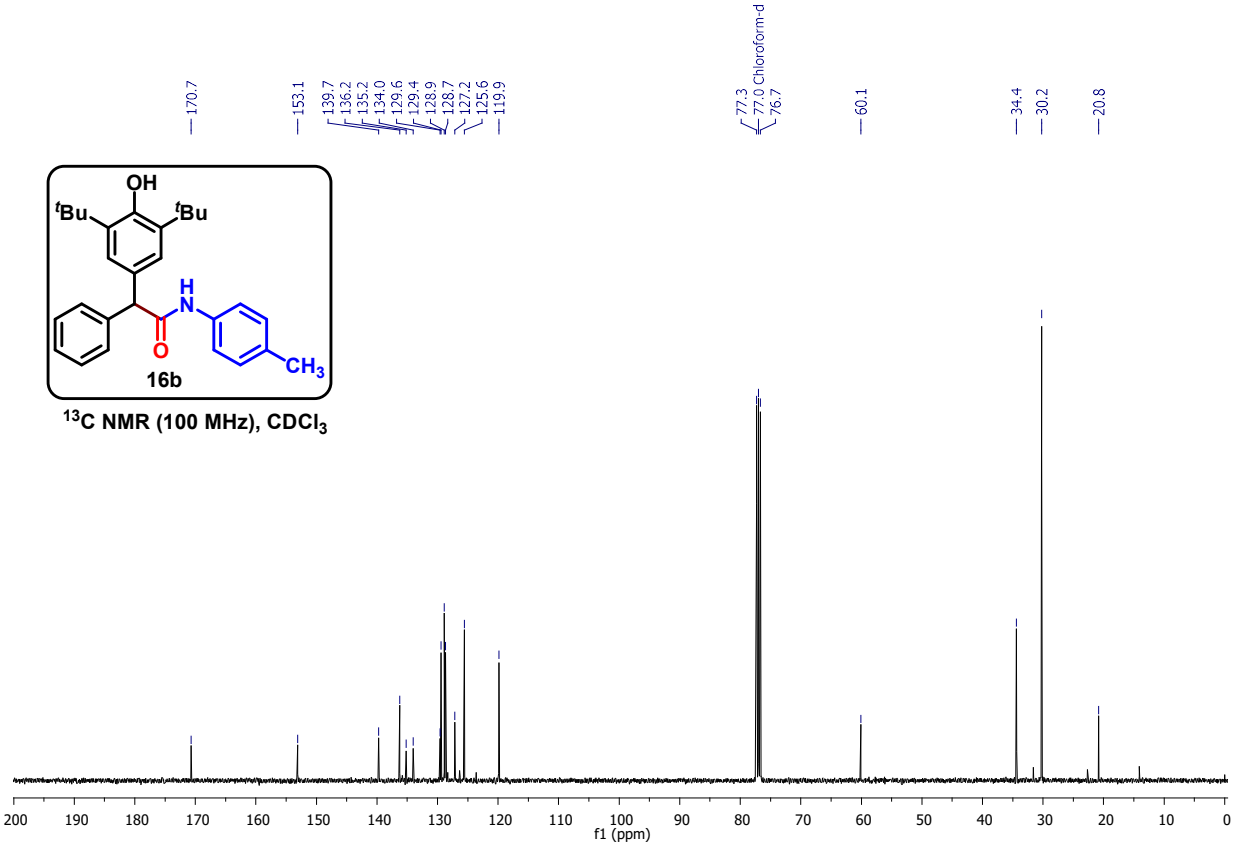
7.33
7.31
7.29
7.28
7.27
7.27
7.26 Chloroform-d
7.25
7.10
7.08
5.20
4.98
2.29
1.40
0.00
OH
tBu
tBu
H
N
O
CH3
16b
1H NMR (400 MHz), CDCl3
6.02
2.10
3.00
1.00
1.00
1.00
3.00
18.01
f1 (ppm)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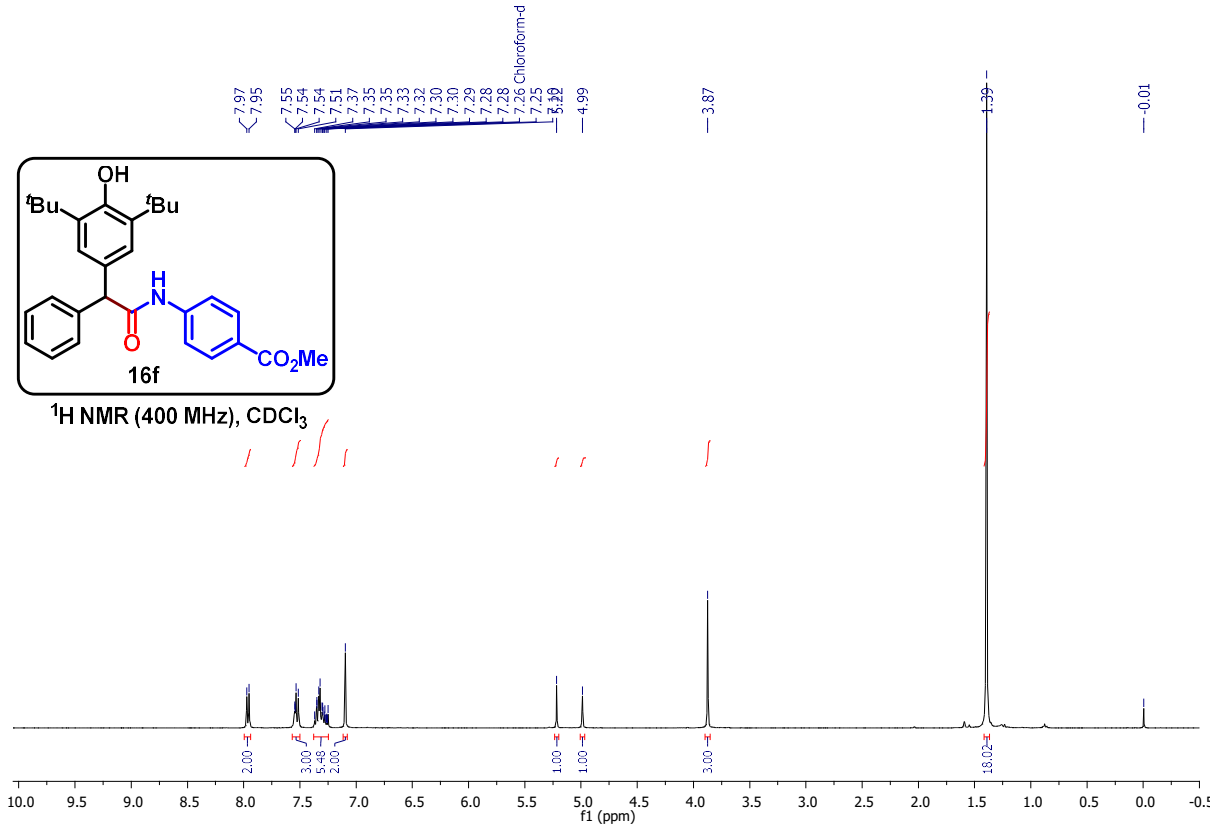
153.1
139.7
136.2
135.2
134.0
129.6
129.4
128.9
128.7
127.2
125.6
119.9
77.3
77.0 Chloroform-d
76.7
60.1
34.4
30.2
20.8
OH
tBu
tBu
H
N
O
CH3
16b
13C NMR (100 MHz), CDCl3
f1 (ppm)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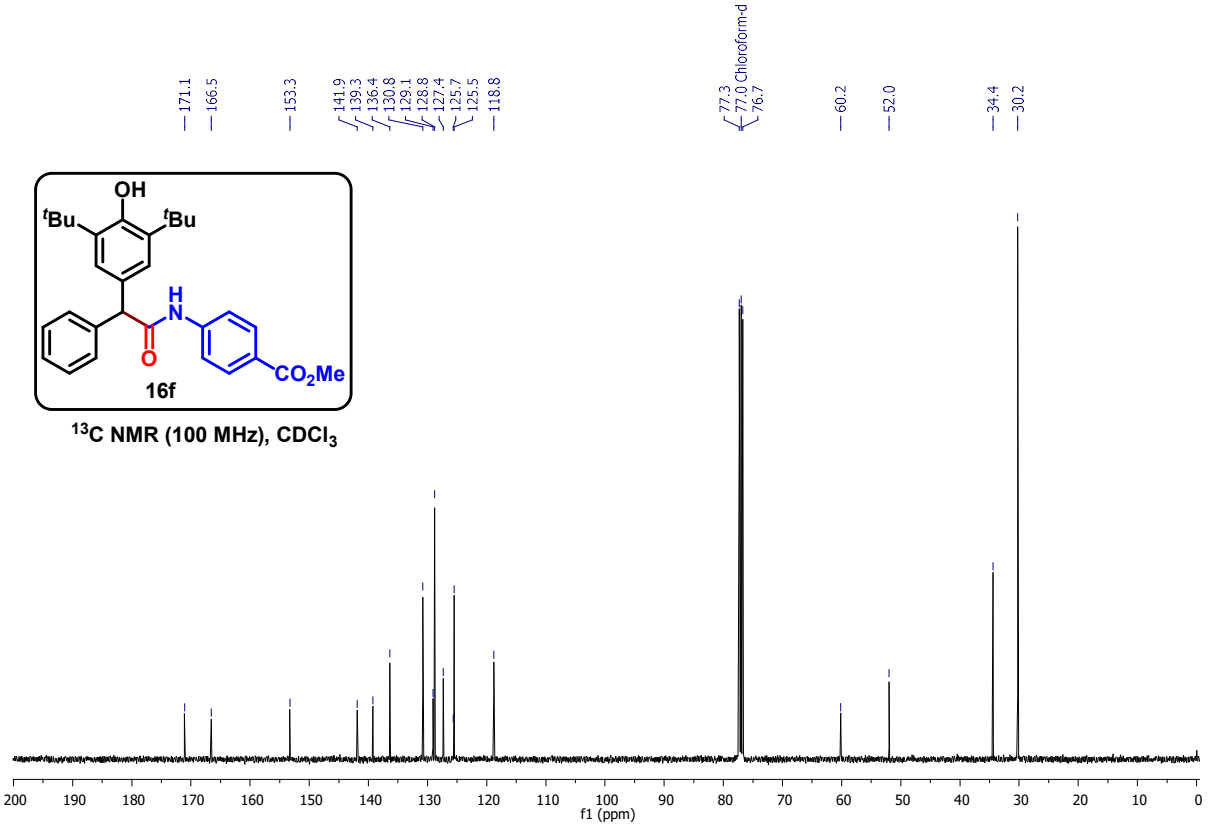
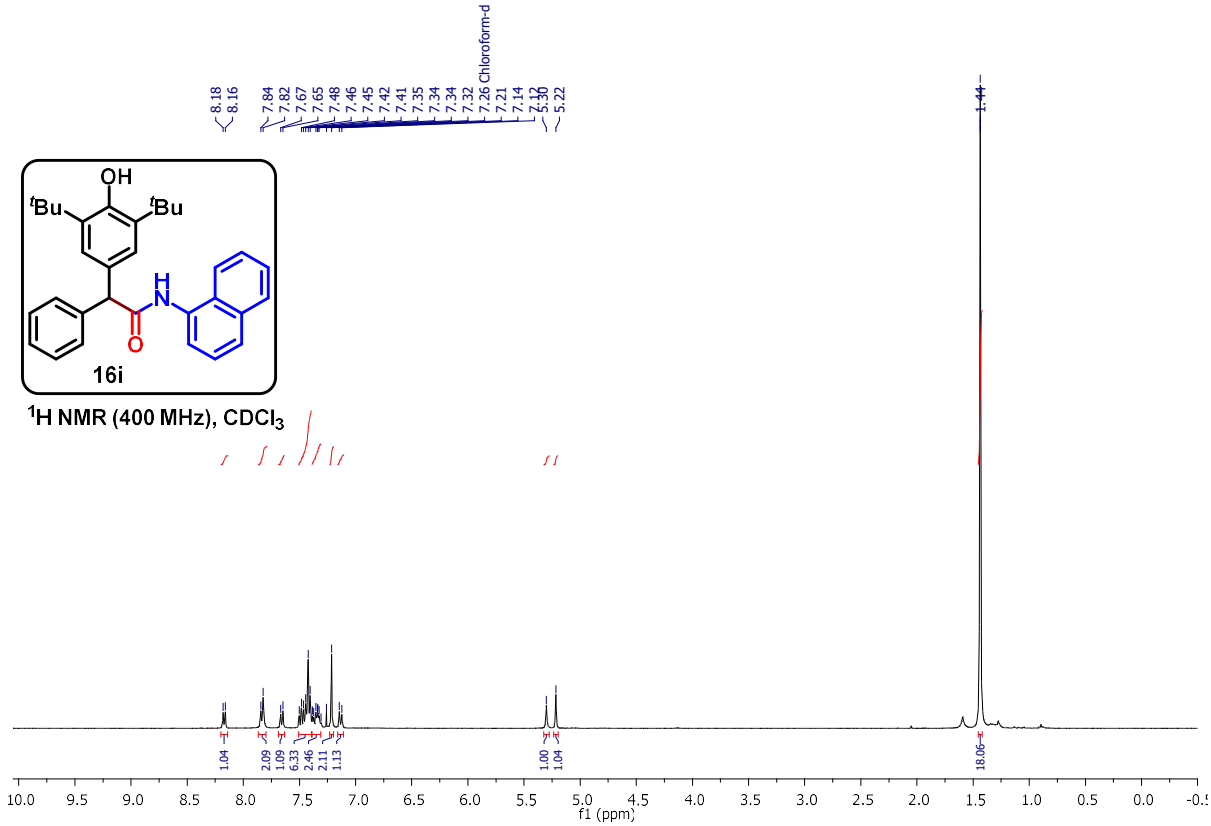
7.55
7.54
7.54
7.51
7.37
7.35
7.35
7.33
7.32
7.30
7.30
7.29
7.28
7.28
7.26 Chloroform-d
7.25
4.99
3.87
1.39
0.01
OH
tBu
tBu
H
N
O
CO2Me
16f
1H NMR (400 MHz), CDCl3
2.00
3.00
5.48
2.00
1.00
1.00
3.00
18.02
f1 (ppm)


171.1
166.5
153.3
141.9
139.3
136.4
130.8
129.1
128.8
127.4
125.7
125.5
118.8
77.3
77.0 Chloroform-d
76.7
60.2
52.0
34.4
30.2
OH
tBu
tBu
H
N
O
CO2Me
16f
13C NMR (100 MHz), CDCl3
f1 (ppm)


8.18
8.16
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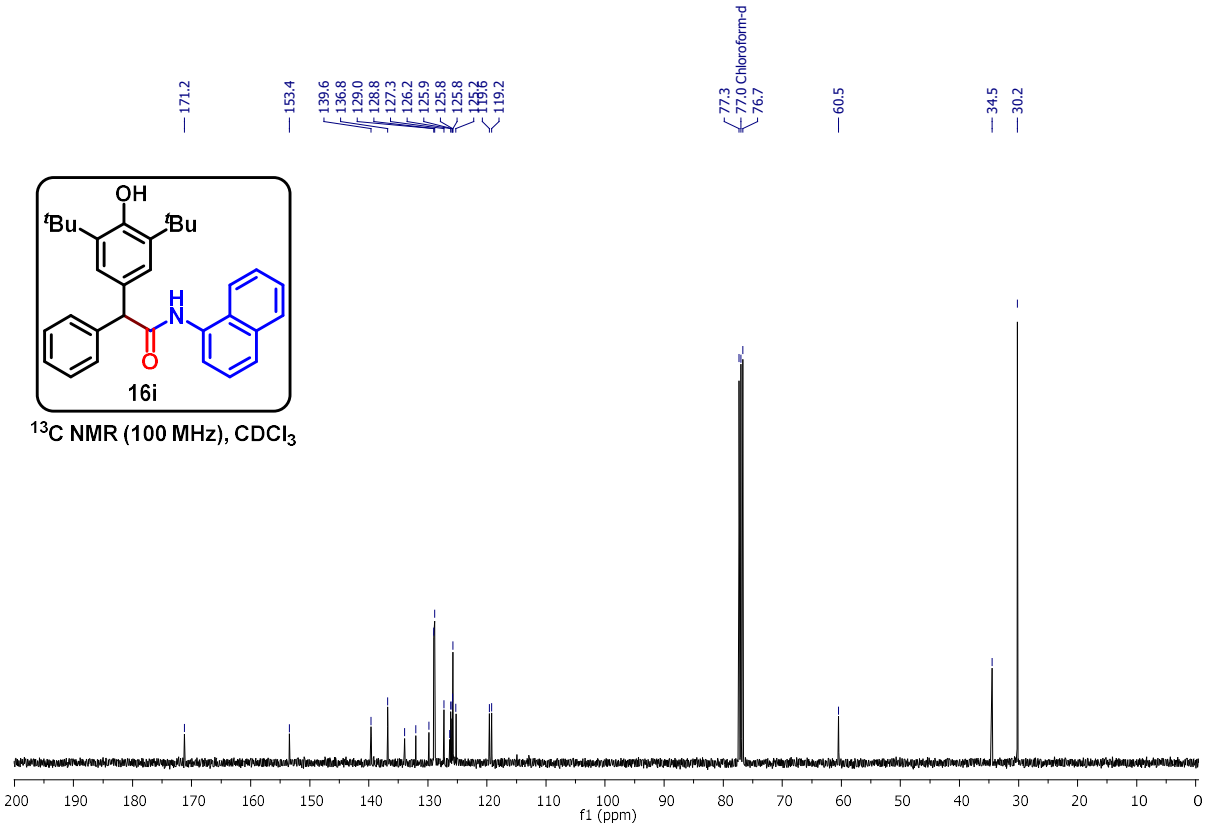
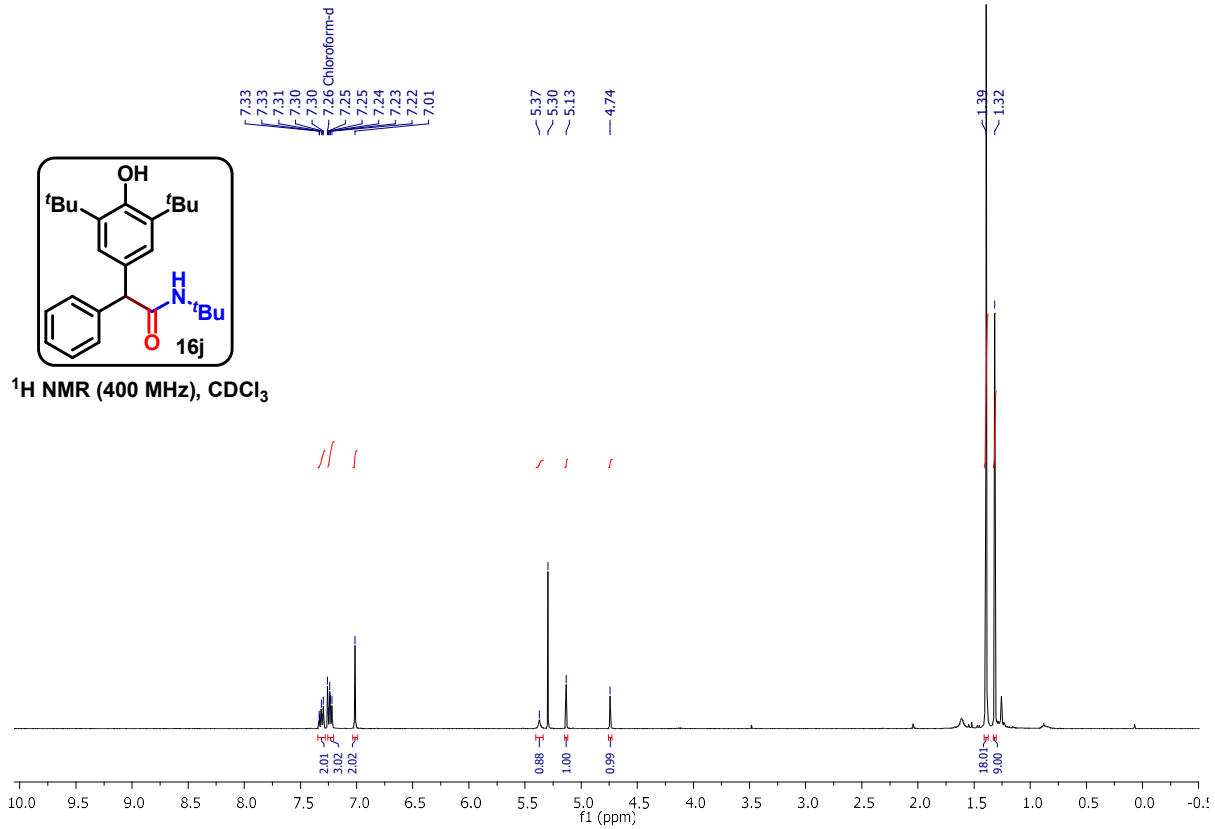
7.82
7.67
7.65
7.48
7.46
7.45
7.42
7.41
7.35
7.34
7.34
7.32
7.26 Chloroform-d
7.21
7.14
5.30
5.22
1.44
OH
tBu
tBu
H
N
O
16i
1H NMR (400 MHz), CDCl3
1.04
2.09
1.09
6.33
2.46
2.11
1.13
1.00
1.04
18.06
f1 (ppm)



^{13}C NMR (100 MHz), $CDCl_3$



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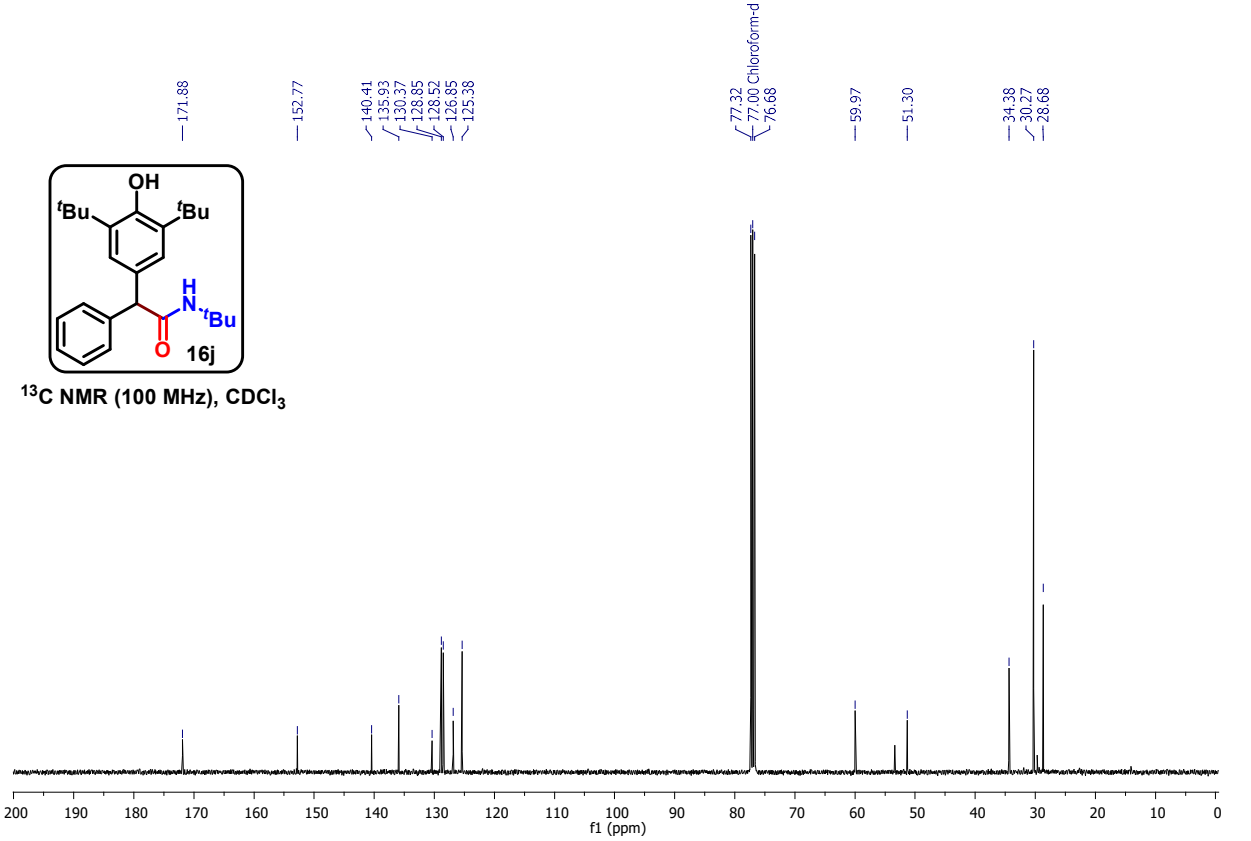
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51.30
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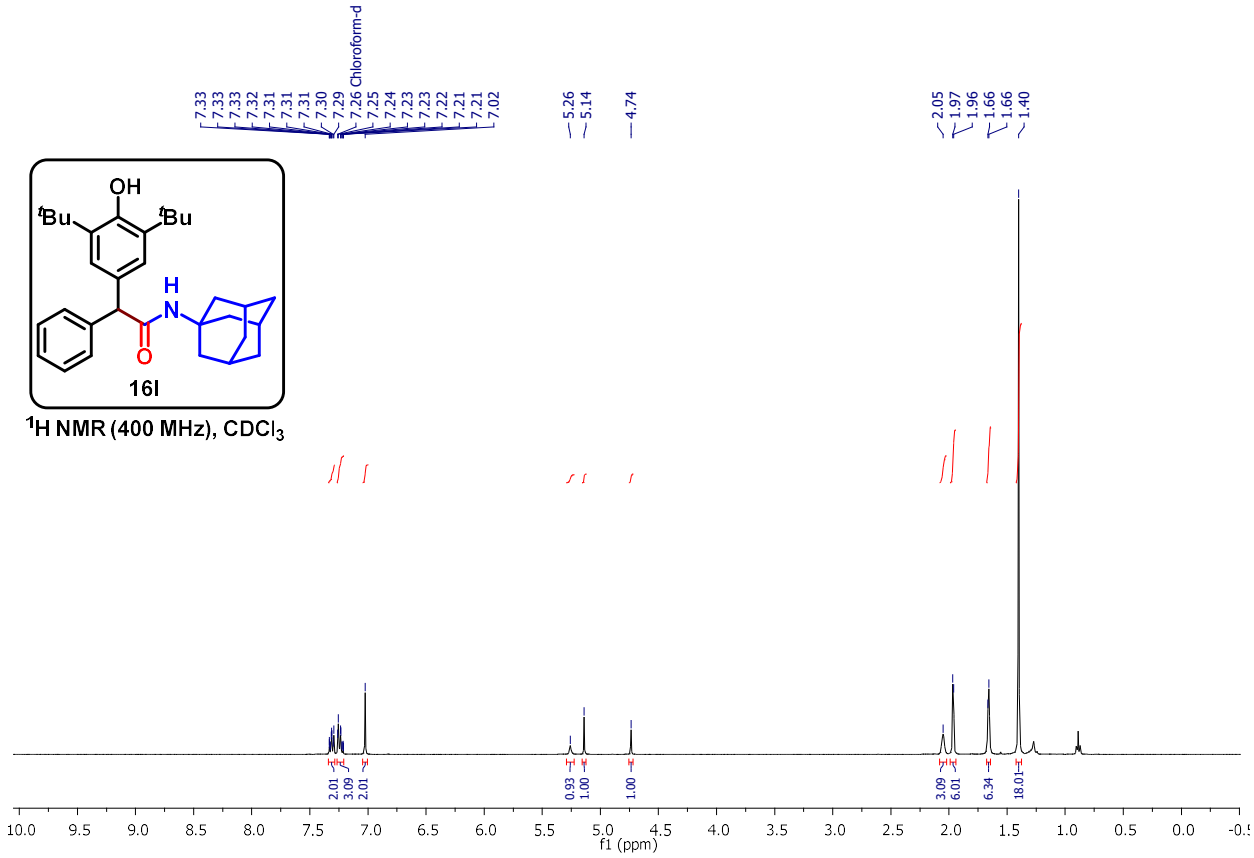
f1 (ppm)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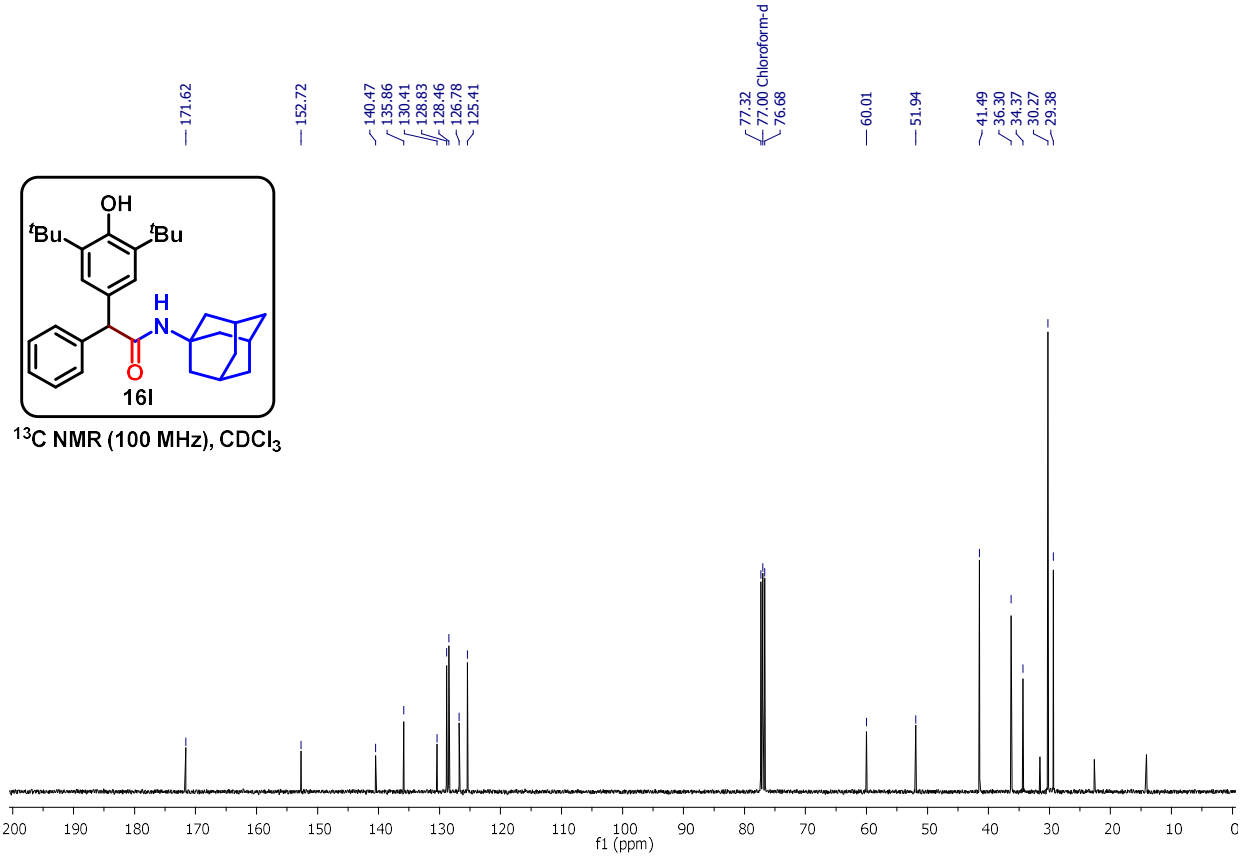

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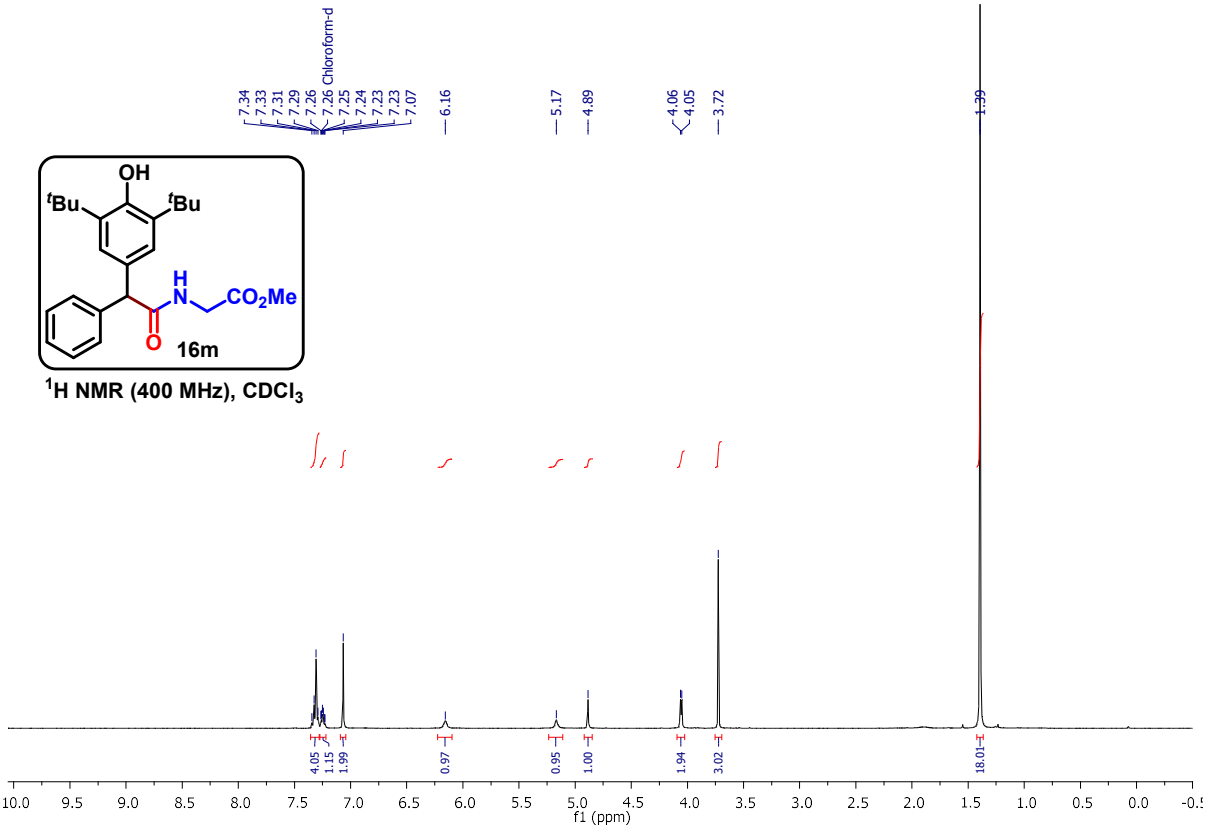

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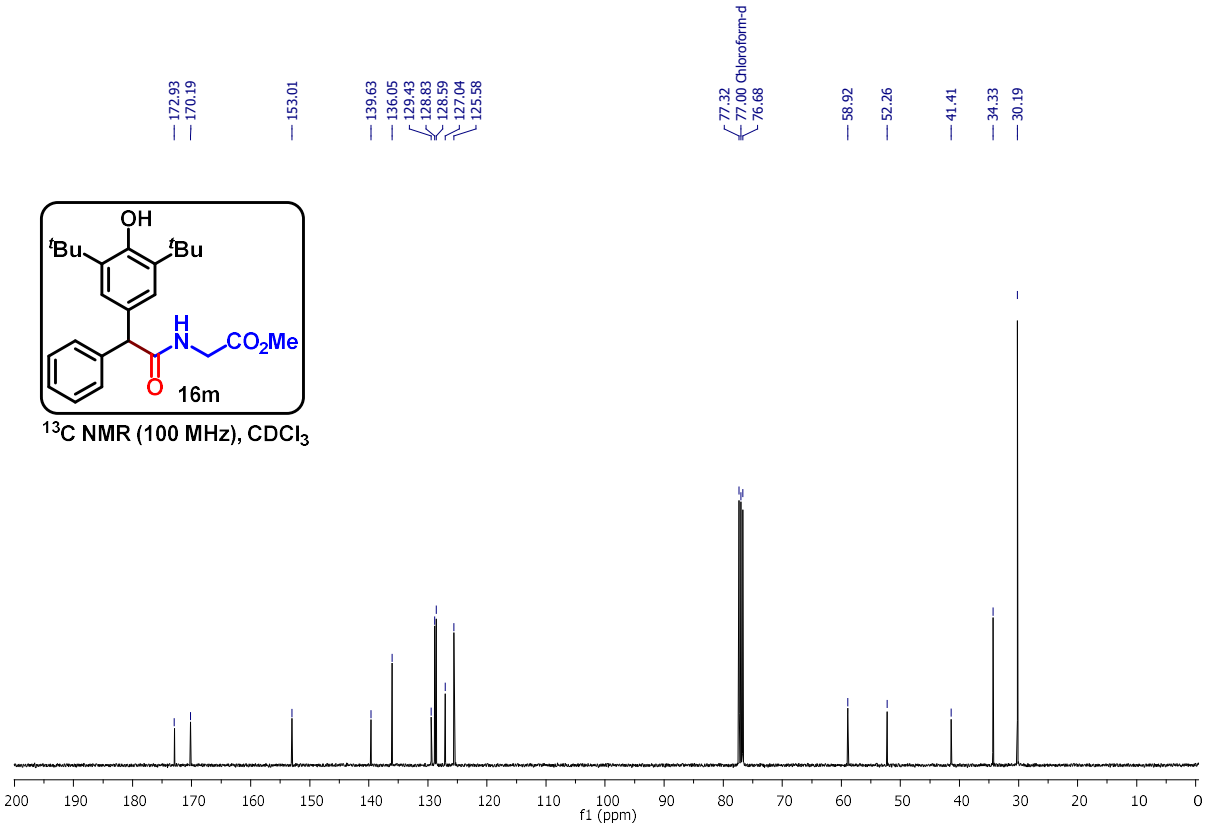
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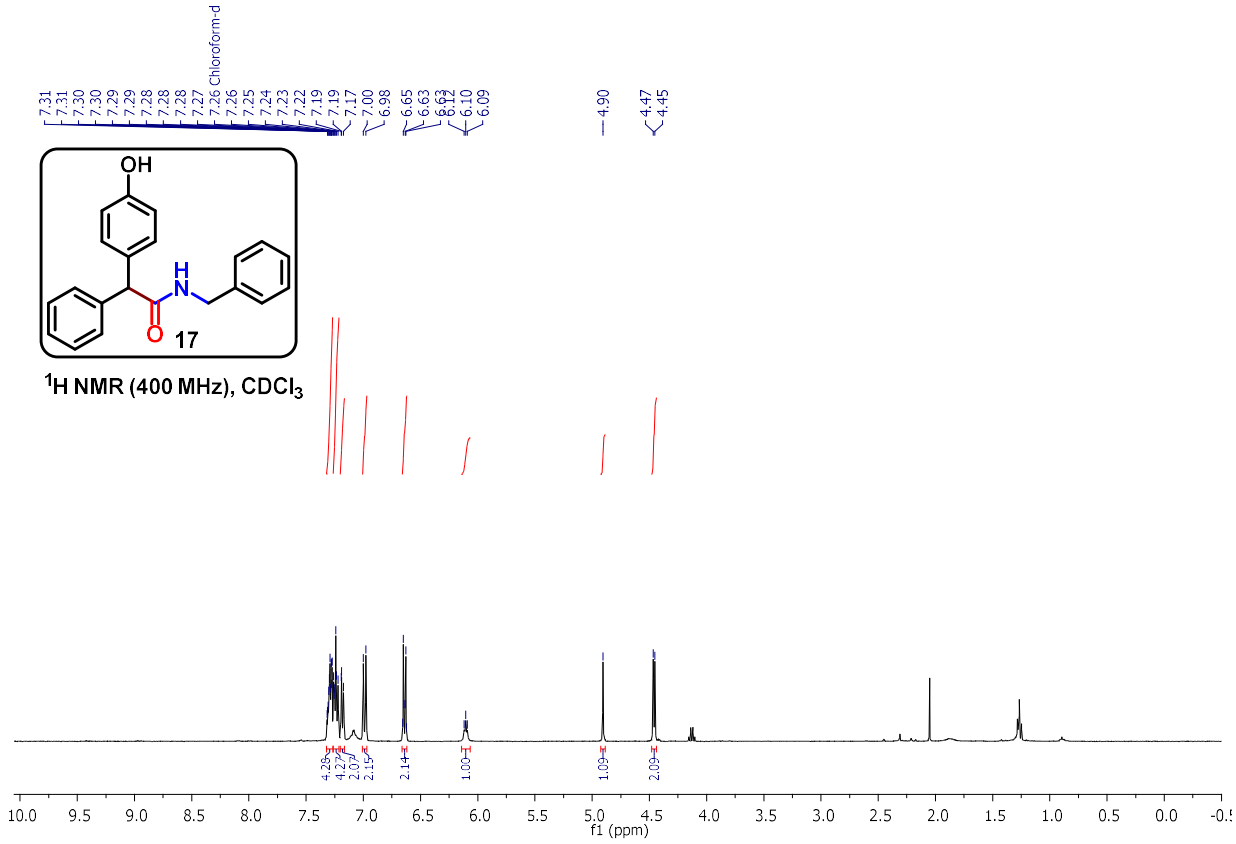
f1 (ppm)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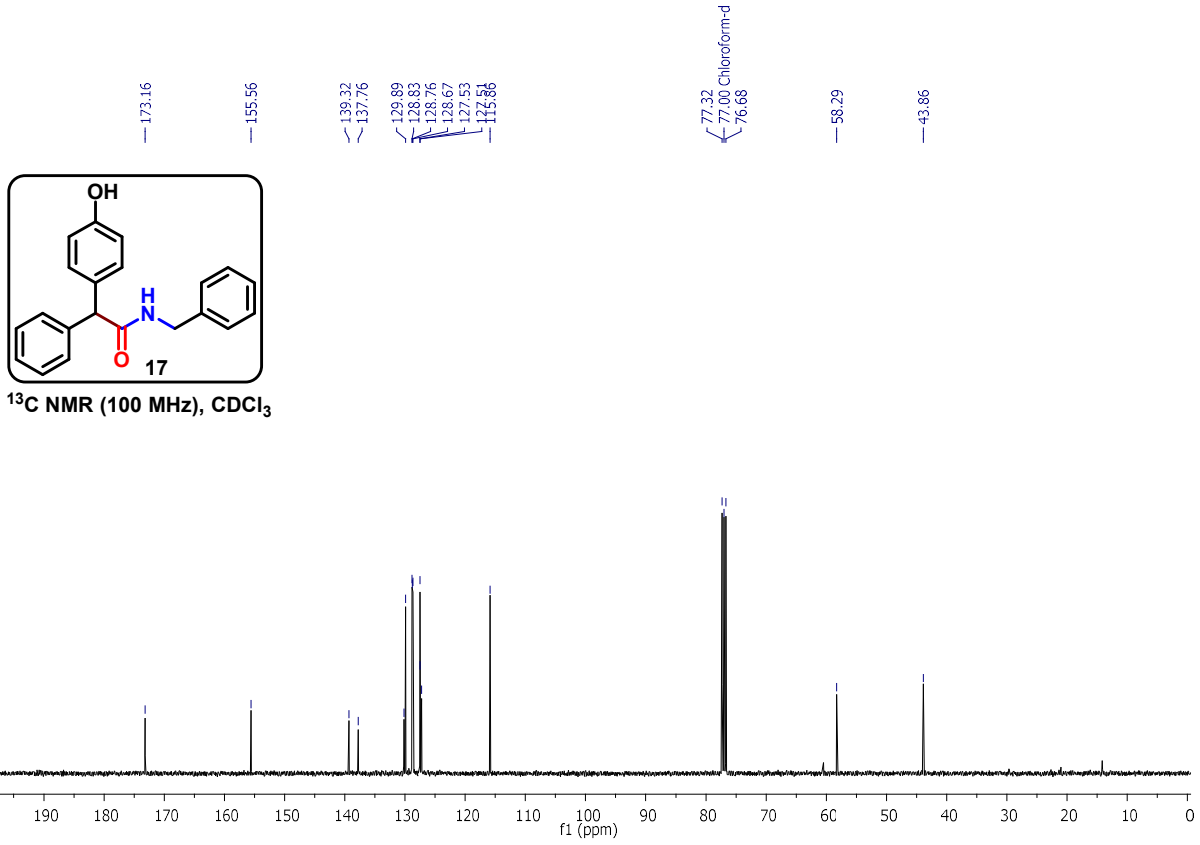
f1 (ppm)



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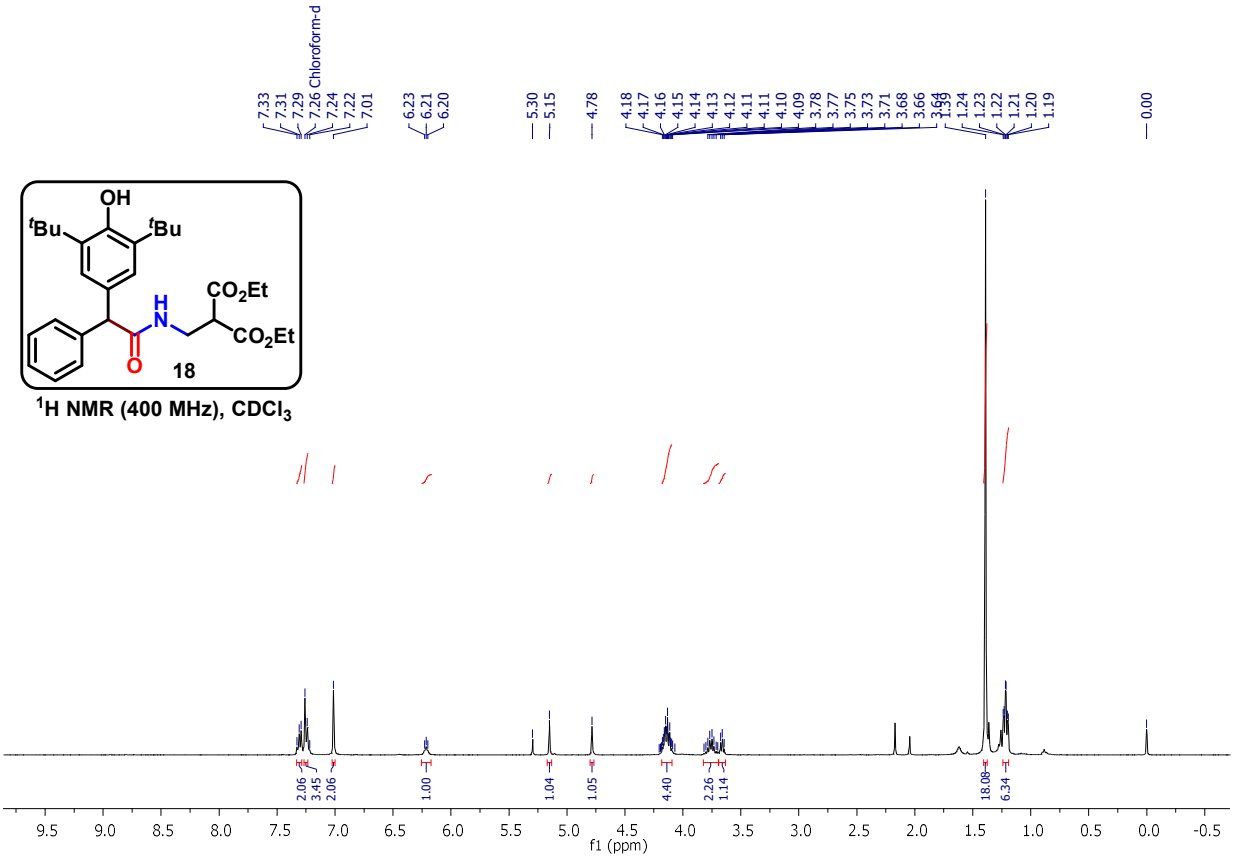

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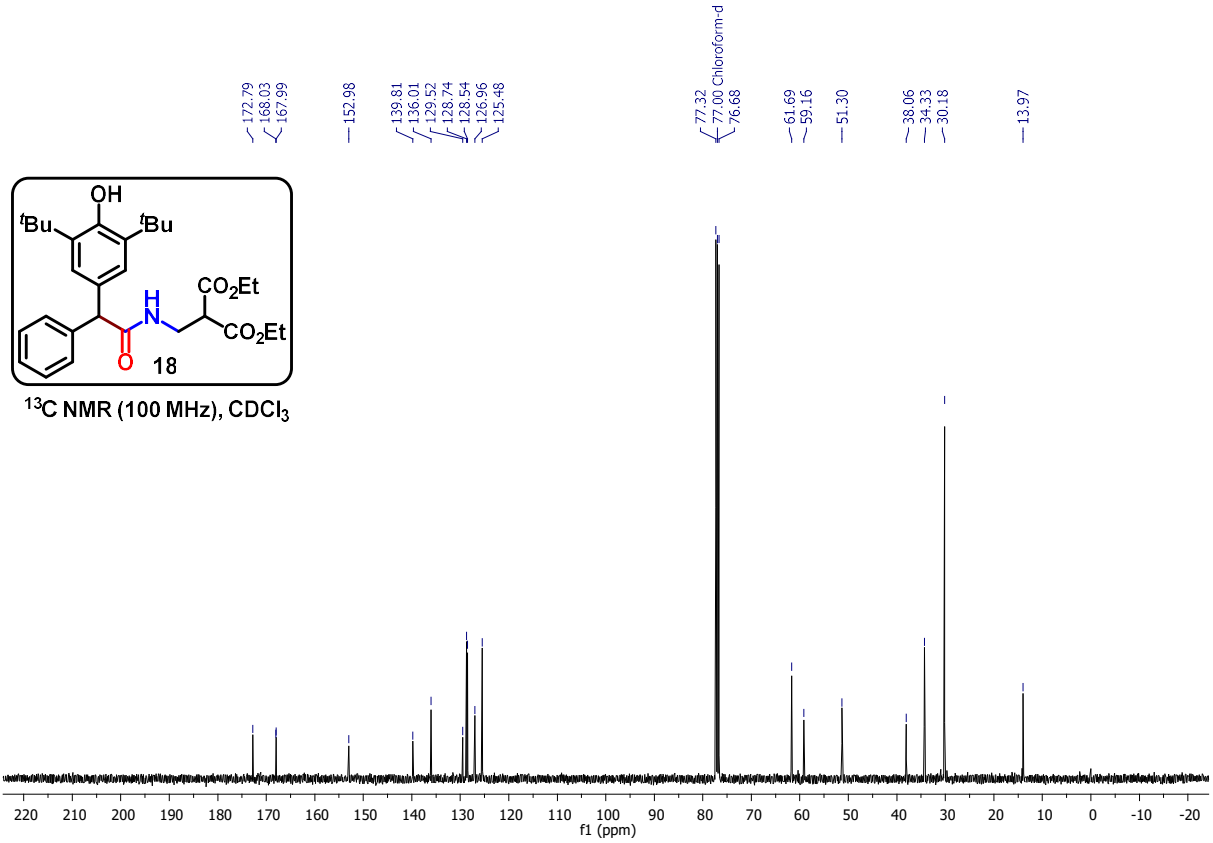
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51.30
38.06
34.33
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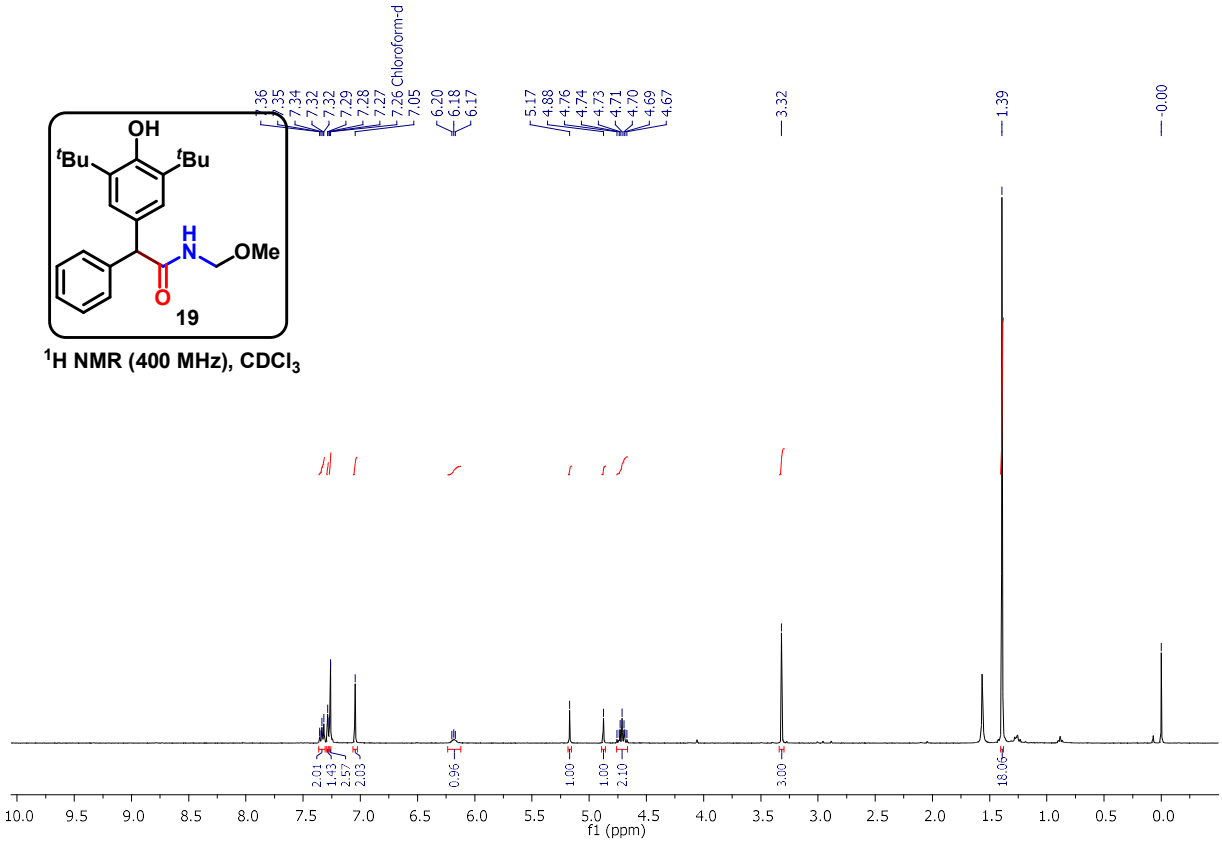
CO2Et
O
18
13C NMR (100 MHz), CDCl3
f1 (ppm)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H
N
OMe
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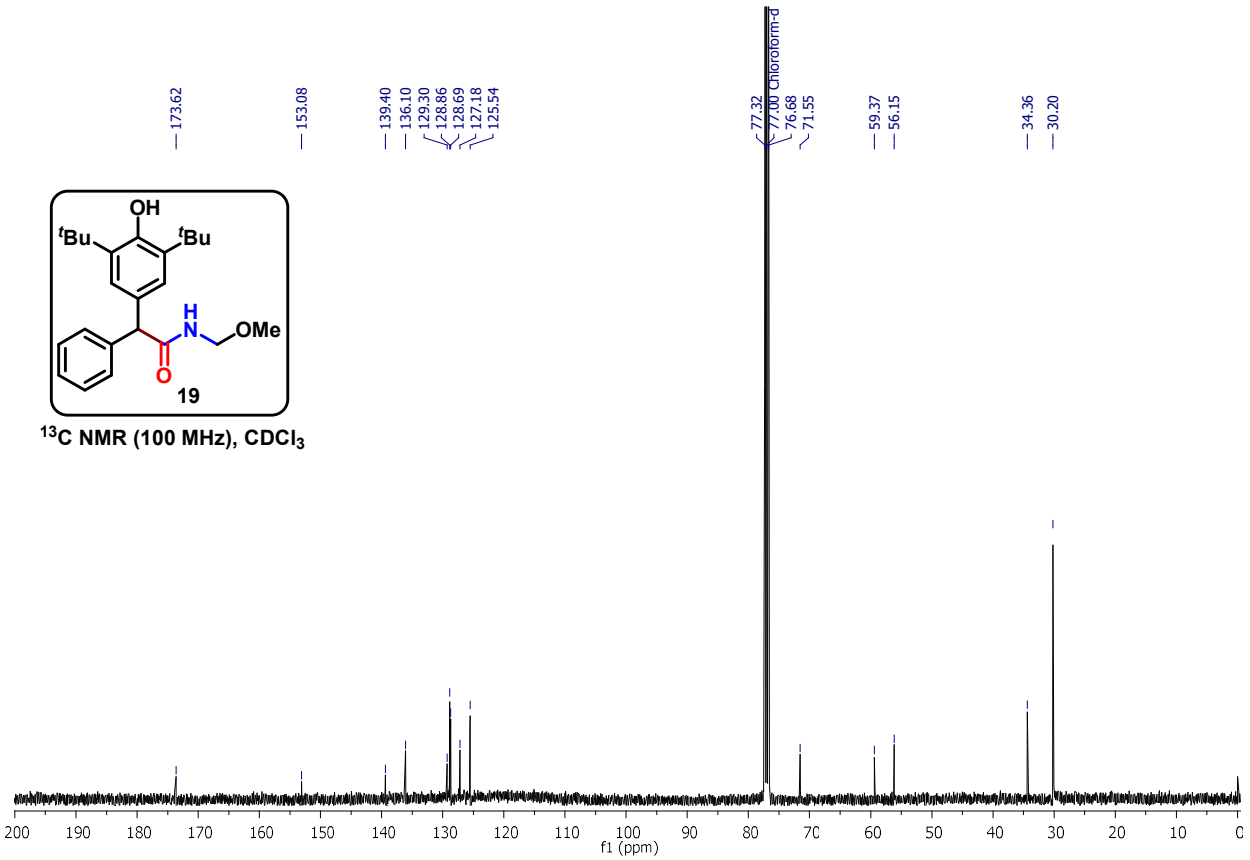
f1 (ppm)



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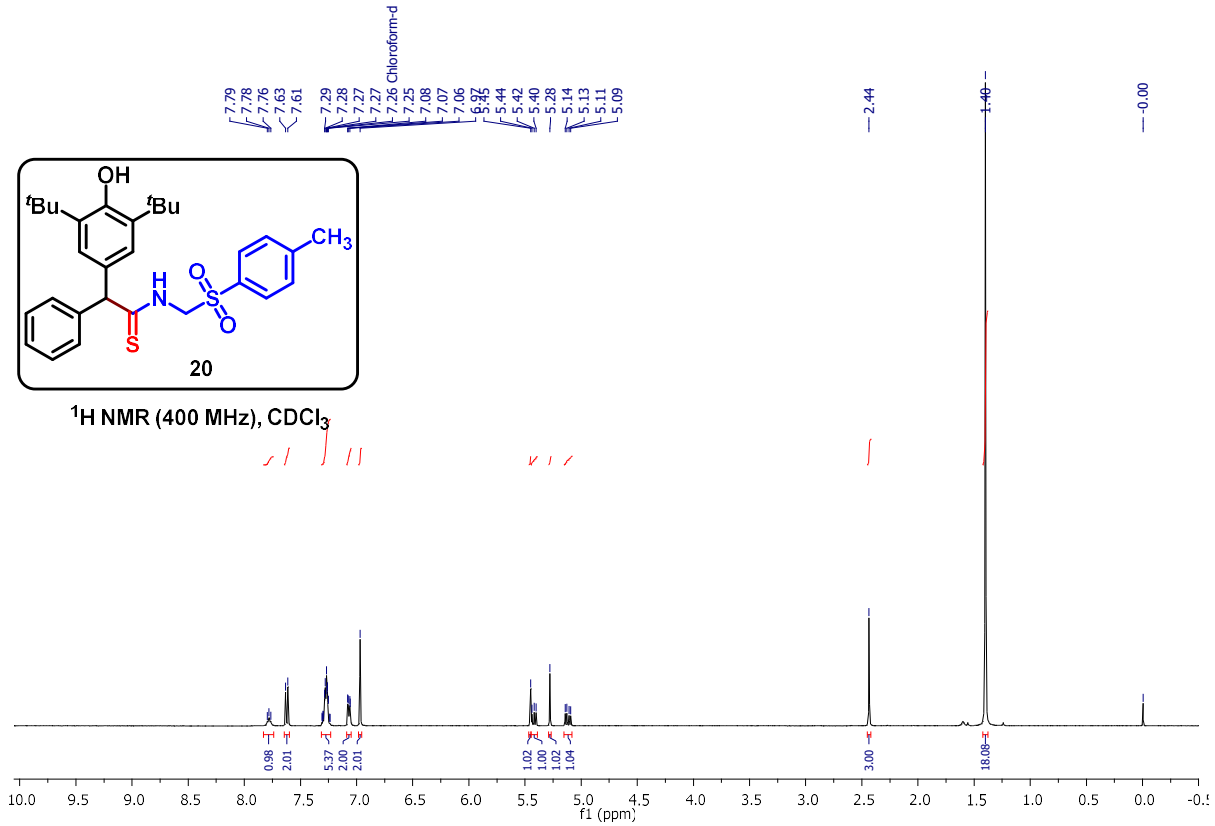

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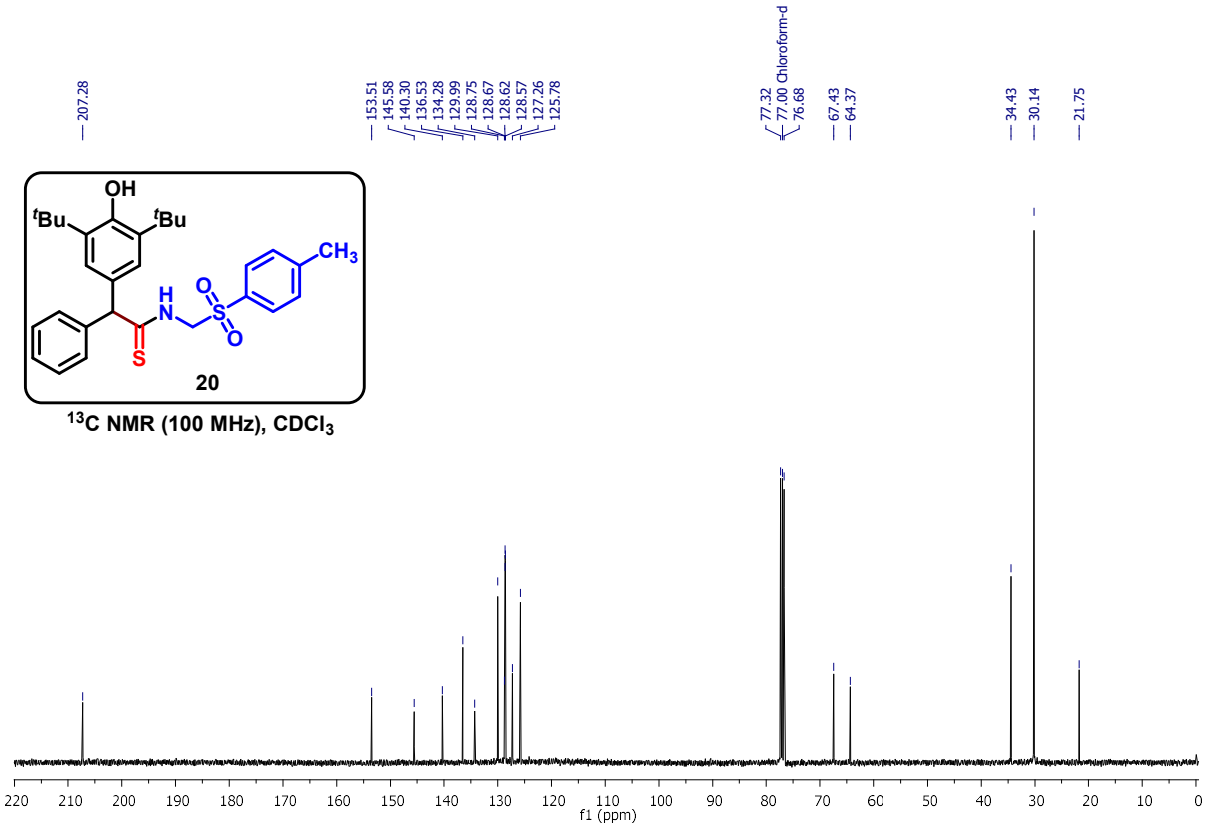

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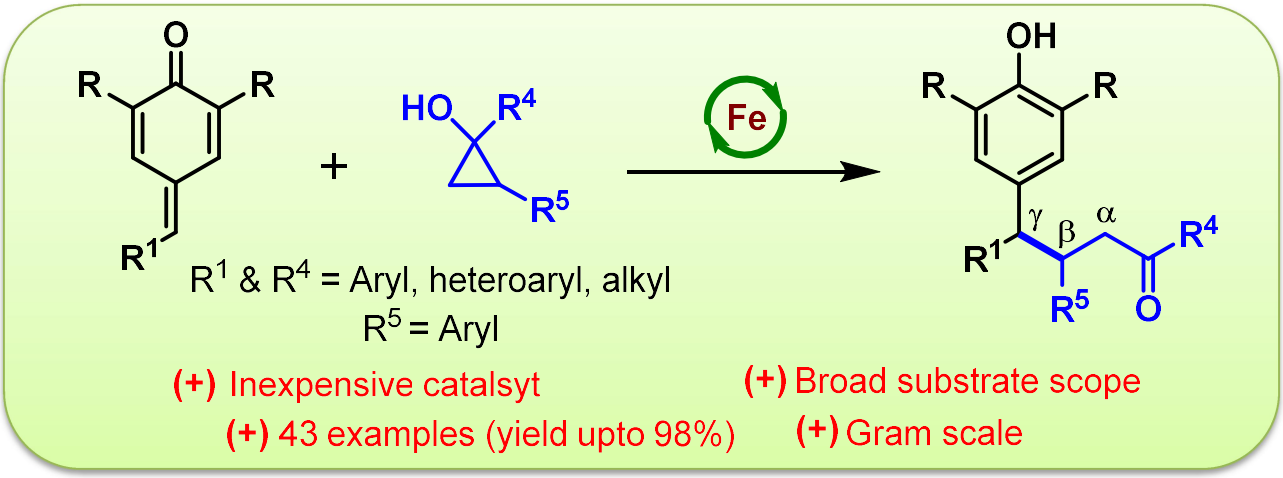
CHAPTER-3

Iron Catalyzed Tandem Ring Opening/1,6-Conjugate Addition of Cyclopropanols with *p*-Quinone Methides: New Access to *γ*, *γ*-Diaryl Ketones

Iron Catalyzed Tandem Ring Opening/1,6-Conjugate Addition of Cyclopropanols with *p*-Quinone Methides: New Access to *γ*, *γ* - Diaryl Ketones

This chapter describes an iron (III) catalyzed tandem ring opening/1,6-conjugate addition of cyclopropanols to *p*-quinone methides leading to *γ*, *γ*-diaryl ketones. This catalytic protocol provides a novel and efficient method to access *γ*, *γ*-diaryl ketone derivatives in good to excellent yields with high functional group tolerance. Importantly, *γ*, *γ*-diaryl ketone can be further functionalized to give a versatile set of useful products.



Chem. Commun., **2021**, *57*, 13582-13585.

3.1 Introduction

This work endeavors to study the iron (III) catalyzed tandem radical ring opening/1,6-conjugate addition of cyclopropanols to *p*-quinone methides leading to *γ*,*γ*-diaryl ketones. The *γ*,*γ*-diarylketone and their derivatives are frequently encountered in numerous bioactive molecules and natural products.[1] Furthermore, compounds possessing *γ*,*γ* -diaryl ketone motif are known integrin receptor inhibitors, nitric oxide donors and serve as a precursor for the antidepressant drug Zoloft (Fig 3.1).[2] Despite the significance, in contrast to their structural analogues such as *α,α*- and *β,β*-diaryl ketones, which could be easily prepared through several methods, surprisingly synthetic strategies to access *γ*,*γ*-diaryl ketones are rare and considered to be challenging.[3d] A few new approaches to address their synthesis have been reported recently, which are described below.

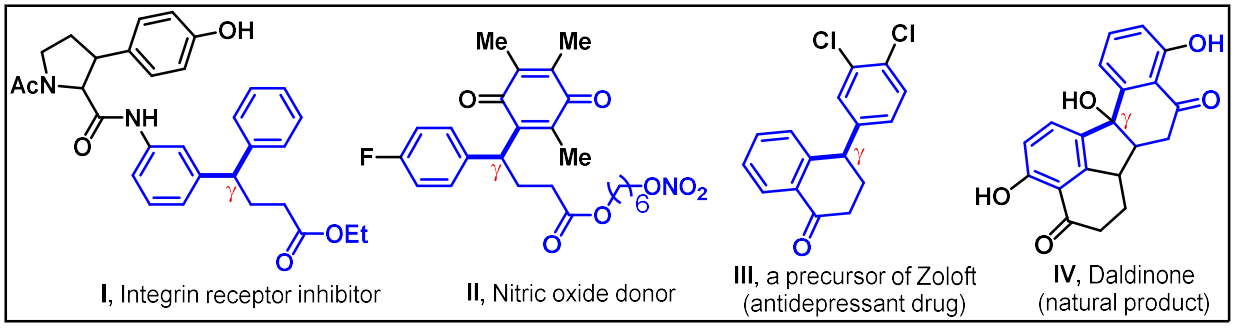
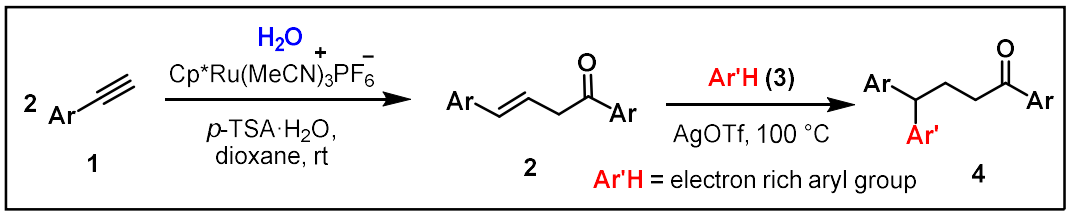


Fig. 3.1. Representative bioactive compounds possessing *γ*, *γ*- diarylketone moiety.

3.2 Literature Precedence on the Synthesis of *γ*, *γ* -Diaryl Ketones:

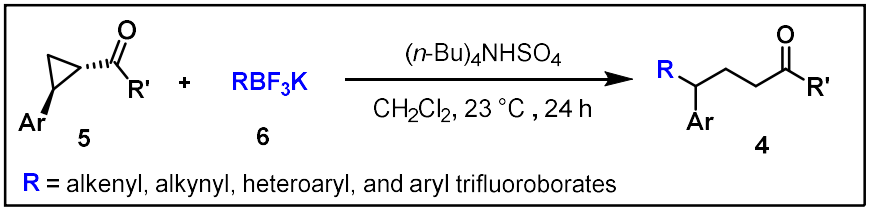
In 2009, Dixneuf and co-workers reported the regioselective synthesis of *β,γ*-unsaturated allylic ketones **2** from terminal aryl alkynes **1** employing ruthenium catalysts. In the second step, the resulting homoallyl ketones on direct regioselective intermolecular hydroarylation/Friedel–Crafts reaction with electron-rich aryl group **3** in the presence of AgOTf gives *γ*,*γ*-diarylketone derivatives **4**. Both catalytic reactions occur with high atom economy and provide an alternative approach to the synthesis of *γ*-arylated ketones (Scheme 3.1).[3a]



Scheme 3.1. Intermolecular hydroarylation of *β,γ*-unsaturated ketone.

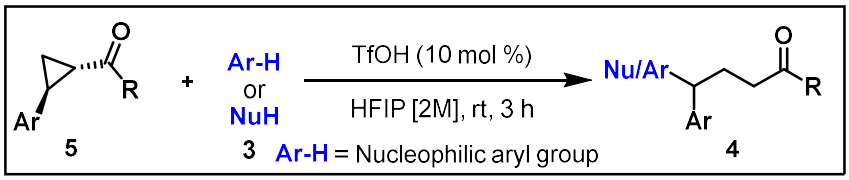
In 2016, May and co-workers reported the homoconjugate addition of alkenyl, alkynyl,

heteroaryl, and aryl trifluoroborate-based nucleophiles **6** with arylated cyclopropyl ketones **5** to construct *γ,γ*-disubstituted ketones **4**. The mechanistic investigation suggests that the reaction proceeds through ketone protonation, an intermediary carbocation, and intermolecular nucleophilic addition of trifluoroborate nucleophiles (Scheme 3.2).[3b]



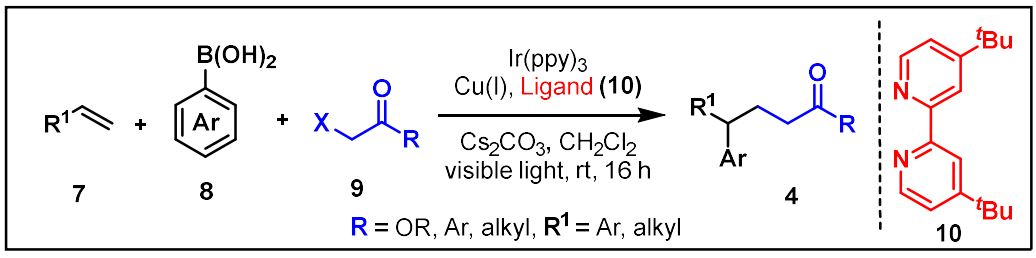
Scheme 3.2. Homoconjugate addition of organotrifluoroborates to arylated cyclopropyl ketones.

Similarly, in 2018, Moran *et al*. demonstrated Brønsted acid-catalyzed nucleophilic ring-opening of Donor-Acceptor-cyclopropanes **5** with electron-rich arenes and other nitrogen or oxygen-based nucleophiles **3**. The combination of trifluoromethanesulfonic acid (TfOH) in hexafluoroisopropanol (HFIP) acts as a highly active Brønsted acid system for the nucleophilic ring-opening of DA-cyclopropanes. This methodology provides access to *γ,γ*-disubstituted carbonyl derivatives **4** at ambient temperature under open-flask conditions (Scheme 3.3).[3c]



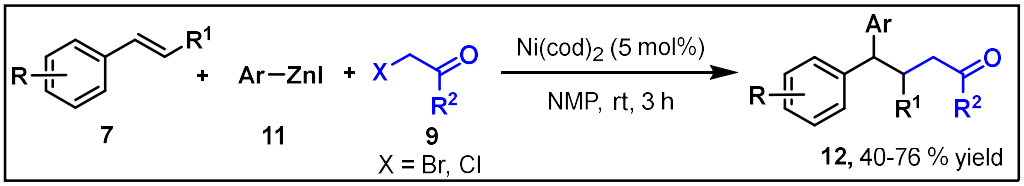
Scheme 3.3. Ring opening of DA-cyclopropanes catalyzed by a Brønsted acid.

In 2019, Shu *et al*. elegantly developed the first formal *γ*-(hetero)arylation of carbonyl compounds **9** *via* the radical relay alkylarylation of alkenes **7** under mild conditions. In this reaction use of copper and visible-light, catalysis is essential for the successful transformation, which can lead to the sequential formation of $C(sp^3)$-$C(sp^3)$ and $C(sp^3)$-$C(sp^2)$ bonds, allowing straightforward access to *γ*-arylated carbonyl compounds **4**, without directing groups or preactivation (Scheme 3.4).[3d]



Scheme 3.4. *γ*-Arylation of carbonyl compounds *via* radical relay cross-coupling reaction.

Similarly, recently Giri *et al.* reported Ni-catalyzed regioselective *α*-carbonylalkylarylation of vinylarenes **7** with *α*-halocarbonyl compounds **9** and arylzinc reagents **11**. This transformation employs $Ni(cod)_2$ as a metal catalyst and NMP as a solvent. The reaction works with primary, secondary and tertiary *α*-halocarbonyl molecules and electronically varied arylzinc reagents. The reaction provides *γ*,*γ*-diarylcarbonyl derivatives **12** with *α*-secondary, tertiary and quaternary carbon centres (Scheme 3.5).[3e]



Scheme 3.5. Ni-Catalyzed *α*-carbonylalkylarylation of vinylarenes.

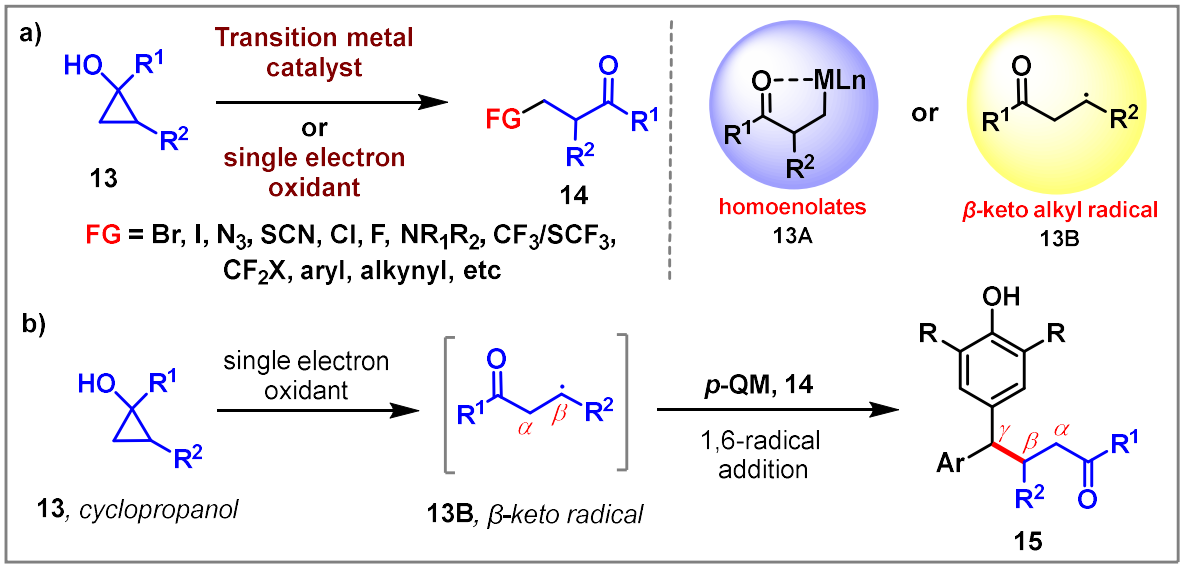
3.3. Present Work

3.3.1. Statement of the Problem

As described above, there are only a few methods available for the synthesis of *γ*, *γ*-diaryl ketones. However, there are certain disadvantages associated with these methods, such as the requirement of expensive and sensitive catalysts, harsh reaction conditions, limited substrates scope etc., hampers the superiority of these methods. Therefore, developing a simple and efficient strategy to access these *γ*, *γ*-diarylketones from easily accessible starting materials is ideal and highly desirable. On the other hand, radical addition reactions have become a very important synthetic tool in organic synthesis. Radical reactions can assemble carbon-carbon and carbon-heteroatom bonds under mild and non-basic conditions that may be compatible with a variety of functional groups.[4] With the fast development of this field, the continuous expansion of the scope of radical acceptors is in high demand.

In recent years radical ring-opening of strained cycloalkanols, especially cyclopropanols **13**, have been established as a versatile strategy in the synthesis of a wide range of highly functionalized organic compounds **14**.[5-7] Cyclopropanols are readily available compounds prepared through the Kulinkovich reaction or Simmons-Smith reaction. Due to their intrinsic ring strain, they have received significant attention as important C3 synthons. Cyclopropanols in the presence of transition metal catalyst or single electron oxidant undergo ring-opening to give either metal homoenolates **13A** or *β*-keto radicals **13B**, which can eventually provide *β*-functionalized carbonyl motifs (Scheme 3.6a). During the last decade, radical ring-opening and its *β*-functionalization have been achieved by the groups of Chiba,[8] Zhu,[9] Dai,[10] Orellena,[11] and many

others.[12] Inspired by the progress achieved in radical ring-opening of cyclopropanols and our research interest in *p*-QMs chemistry, we thought to investigate the reactivity of cyclopropanols in 1,6-addition reaction with *p*-QMs as a radical acceptor. We envisioned that the radical ring-opening of cyclopropanols **13** in the presence of single electron oxidant would generate *β*-keto radical **13B** and its subsequent 1,6-conjugate addition with *p*-QMs **14** would provide a new opportunity to access structurally important *γ*,*γ*-diarylketones derivatives **15** (Scheme 3.6b).



Scheme 3.6. Synthesis of *γ*, *γ*-diarylketones from cyclopropanols and *p*-QMs.

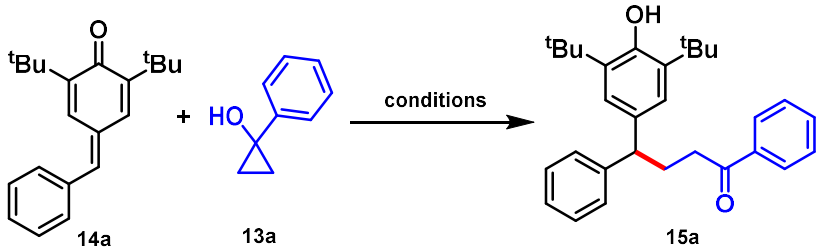
Notably, *p*-QMs have been efficiently utilized for the synthesis of *α*,*α*- and *β*,*β*-diaryl ketone derivatives.[13,14] However, reactions employing *p*-QMs that give direct access to *γ*,*γ*-diarylketones are not yet explored. In addition, in contrast to the studies on the nucleophilic 1,6-addition of *p*-QMs, the quest for the radical addition of *p*-QMs remains scarce.[15] In this chapter, the development of iron-catalyzed tandem ring opening/1,6-conjugate addition of readily accessible cyclopropanols with *p*-QM to yield the corresponding *γ*,*γ*-diarylketones is discussed. Furthermore, the versatility of the products featured further elaboration into beneficial building blocks in good yield.

3.4 Results and Discussion

3.4.1 Optimization of Reaction Conditions

At the outset, we commenced our optimization studies by employing *p*-quinone methide **14a** and 1-phenylcyclopropanol **13a** as model substrates, and the results are summarized in Table 3.1. Initially, we carried out the reaction with the single electron oxidant $Mn(acac)_2$ (10 mol %) in acetonitrile solvent at 80 °C. To our delight, we isolated the expected *γ*,*γ*-diarylcarbonyl

Table 3.1. Optimization of reaction conditions[a,b]



entry	catalyst (mol %)	solvent (mL)	temp (°C)	time (h)	yield[b] (%)
1	$Mn(acac)_2$	CH_3CN	80	16 h	60
2	$Cu(acac)_2$	CH_3CN	80	16 h	65
3	$Pd(OAc)_2$	CH_3CN	80	16 h	NR
4	$InCl_3$	CH_3CN	80	16 h	20
5	$Fe(OAc)_2$	CH_3CN	80	16 h	69
6	$Fe(OTf)_3$	CH_3CN	80	5 h	79
7	$FeCl_3$	CH_3CN	80	5 h	94
8	$Fe(NO_3)_3.9H_2O$	CH_3CN	80	5 h	54
9	**$Fe(acac)_3$**	**CH_3CN**	**80**	**5 h**	**97**
10	$Fe(acac)_3$	DCE	80	5 h	86
11	$Fe(acac)_3$	Toluene	80	5 h	81
12	$Fe(acac)_3$	THF	80	5 h	76
13	$Fe(acac)_3$	DMF	80	5 h	80
14	$Fe(acac)_3$	1,4-dioxane	80	5 h	18
15	$Fe(acac)_3$	CH_3CN	80	5 h	68[c]
16	$Fe(acac)_3$	CH_3CN	60	5 h	65
17	$Fe(acac)_3$	CH_3CN	RT	24 h	NR
18	--	CH_3CN	80	5 h	NR

[a]Unless otherwise noted, all reactions were performed with **14a** (0.17 mmol), **13a** (0.25 mmol), 10 mol % of catalyst in a solvent (2 mL). [b]Isolated yield. [c]5 mol % of catalyst was used. NR = No reaction.

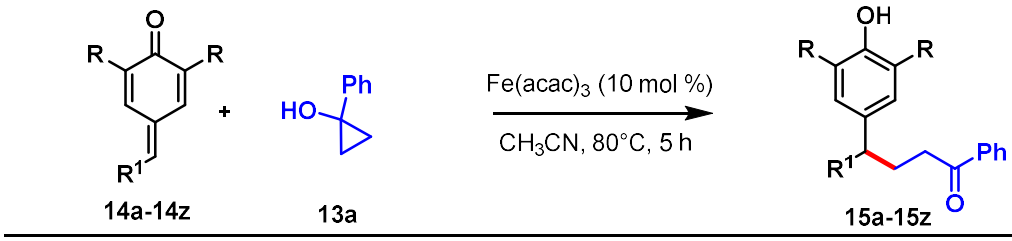
derivative **15a** in 60 % yield (Table 3.1, entry 1). The structure of product **15a** was confirmed by its ^{1}H and ^{13}C NMR spectral analysis. In the ^{1}H NMR spectrum of compound **15a,** the characteristic methine proton resonates as a triplet at δ 3.91 (t, J = 8.0 Hz, 1H) and phenolic –OH proton shows singlet at δ 5.05 (s, 1H). In the ^{13}C NMR, the characteristic signal of carbonyl carbons appeared at δ 200.3 ppm, confirming product **15a**. Further, its HRMS analysis showed *m/z*: $[M - H]^-$ 427.2641 peak calculated for molecular formula $C_{30}H_{35}O_2$ (427.2632) supports the structure. Encouraged by this desired outcome, we studied different transition metals for this transformation and found that $Fe(OAc)_2$ gave superior results (Table 3.1, entry 2-5). Further improvements to the yield could be realized by changing the catalyst to $Fe(acac)_3$ and decreasing the reaction duration to 5h (Table 3.1, entry 6-9). Subsequently, the role of different solvents was investigated, and acetonitrile was found to be the best solvent with a 97% yield of **15a** (Table 3.1, entry 9 vs entry 10-14). Lowering the catalyst loading dramatically decreases the yield of the desired product (Table 3.1, entry 15). When the temperature was decreased to 60 °C, the yield dropped significantly (Table 3.1, entry 16). Further, no product formation was observed when the reaction was carried out at room temperature or in the absence of the catalyst (Table 3.1, entry 17-18). Finally, the optimal conditions comprising the treatment of *p*-QM **14a** and cyclopropanol **13a** with 10 mol% $Fe(acac)_3$ at 80 °C in acetonitrile for 5 h to afford **15a** in 97 % yield.

3.4.2 Substrate Scope of *p*-QMs 14

With the optimized conditions in hand, we next investigated the scope of the reaction with regard to different *p*-QMs (**14**), and the results are summarized in Table 3.2. We were pleased to find that a series of *para*-, *meta*- and *ortho*- substituted *p*- QMs (**14a–14p**) underwent smooth conjugate addition with **13a** to deliver the corresponding γ,γ-diaryalated carbonyl derivative (**15a–15p**) in good to excellent yields (76–98%). Furthermore, di- and trisubstitution on the benzene ring of *p*-QMs were well tolerated, and the corresponding products (**15q–15r**) were isolated in good to excellent yields under the optimal conditions. Notably, *p*-QMs possessing heterocyclic substitution such as furan and pyridine were also amenable to this protocol and provided the corresponding products in good yields (75 and 79%, **15s–15t**). Moreover, *p*-QMs possessing sterically hindered substitution patterns such as naphthyl, pyrenyl and fluorenyl were also amenable in this process to furnish the desired γ,γ-diaryalated ketone products (**15u–15w**, 76-86%) in good yields. Furthermore, *p*-QM incorporating two isopropyl and methyl groups at the

ortho-position and a methyl group at the *para*-position of quinone methide was also well tolerated to afford the product in good yields (**15x–15z**, 63-92%). A gram-scale reaction of **14a** (3.4 mmol) with **13a** proceeded effectively to deliver the corresponding **15a** in 93% yield, which exhibits the scalability of the present method.

Table 3.2. Substrate scope of *p*-QMs **14**[a,b]



15a, R^2 = H, 97 %
(93% in gram scale)
15b, R^2 = Me, 89%
15c, R^2 = ^{i}Pr, 85%
15d, R^2 = OBn, 97%
15e, R^2 = NMe_2, 92%
15f, R^2 = Br, 84%
15g, R^2 = CN, 83%
15h, R^2 = NO_2, 79%
15i, R^2 = Ph, 98%

15j, R^2 = OMe, 78%
15k, R^2 = Cl, 79%
15l, R^2 = Br, 92%

15m, R^2= OMe, 91%
15n, R^2 = F, 90%
15o, R^2 = Cl, 89%
15p, R^2 = NO_2, 76%

15q, 98%

15r, 87%

15s, R^3 = 2-furyl, 75%
15t, R^3 = 2-pyridyl, 79%

15u, 86%

15v, 81%

15w, 76%

15x, R= ^{i}Pr, 92%
15y, R= Me, 63%

15z, 89%

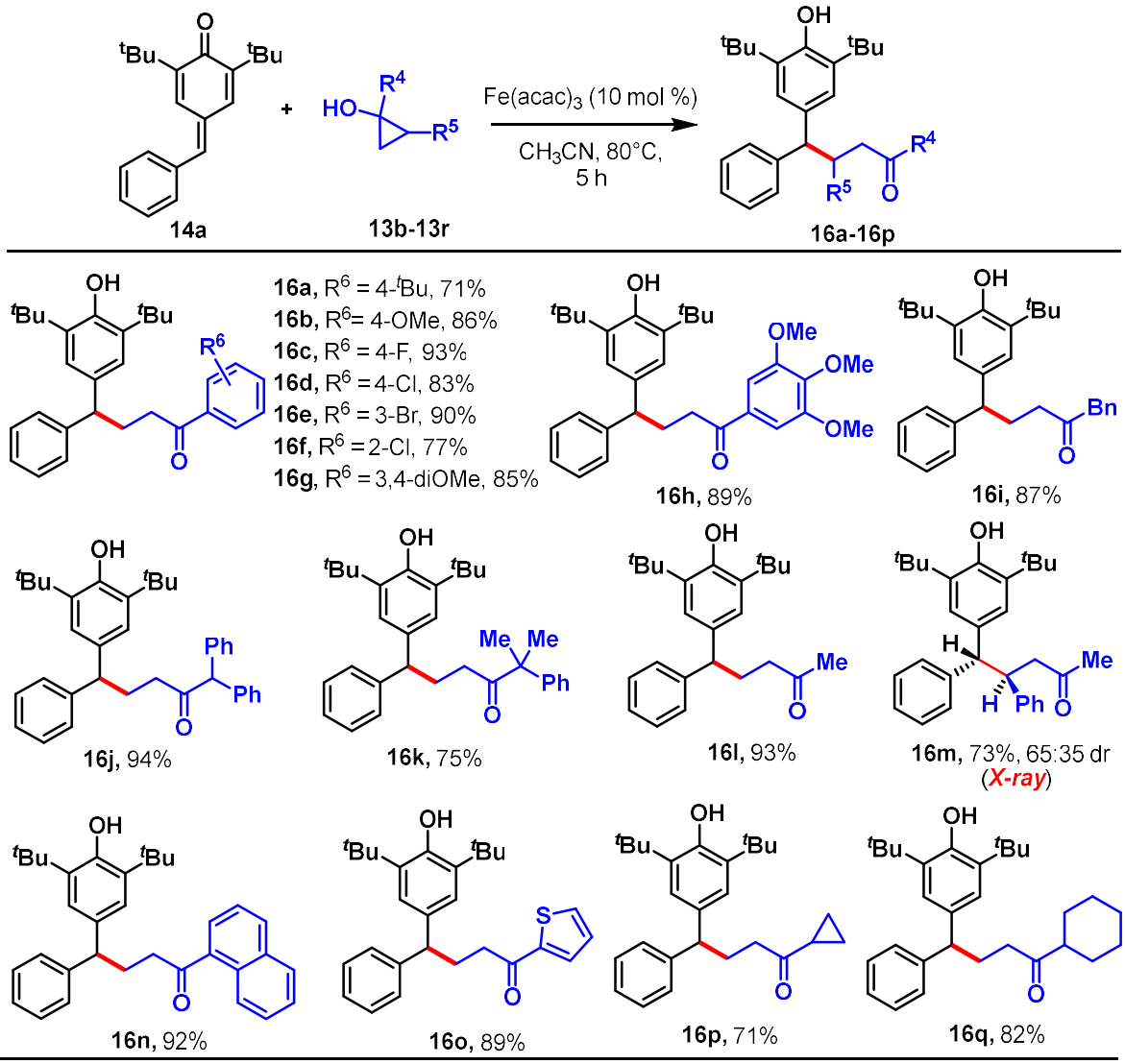
[a]All reactions were performed with **14a-14z** (0.34 mmol), **13a** (0.51 mmol) and $Fe(acac)_3$ (10 mol %) in CH_3CN (2.5 mL) for 5 h. [b]Isolated yields.

3.4.3 Substrate Scope of Cyclopropanols 13

We then examined the scope of the various substituted cyclopropanols **13**. As shown in Table 3.3, a wide range of cyclopropanols (**13b–2f**) with mono, di or tri-substitution on aromatic rings efficiently participated in the conjugate addition with **14a**

to furnish the desired *γ*,*γ*-diaryalated ketone derivatives (**16a–16h**) in good yields (71–93%). Further, alkyl substituted cyclopropanols were also proved to be viable for this conjugate addition reaction generating the desired product (**16i–16l**) in good to excellent yields. Notably, 1,2-disubstituted cyclopropanol was also participated in this transformation to provide *β*,*γ*-triaryl-substituted derivative **16m** in 73% yield with 65:35 dr. The relative configuration of **16m** was unambiguously assigned by a single crystal X-ray analysis. In addition, naphthyl and thiophene-derived cyclopropanols were compatible, affording the desired products **16n–16o** in 92% and 89% yields, respectively. Finally, cycloalkyl substituted cyclopropanols were also engaged in this conjugate addition

Table 3.3. Substrate scope of cyclopropanol **13**[a,b]



[a]All reactions were performed with **14a** (0.34 mmol), **13b-13r** (0.51 mmol) and $Fe(acac)_3$ (10 mol %) in CH_3CN (2.5 mL) for 5 h. [b]Isolated yields.

process to provide the corresponding *γ*,*γ*-diarylated ketone derivatives **16p–16q** in good yields.

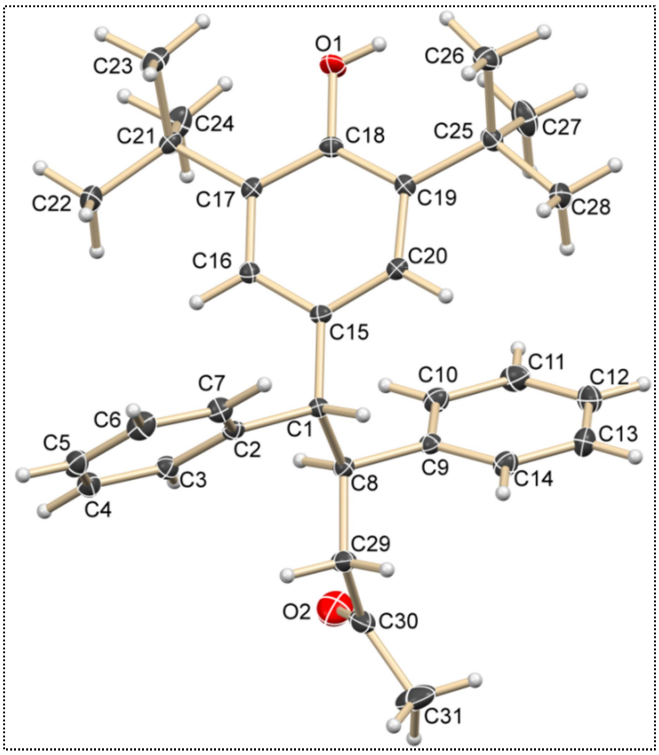
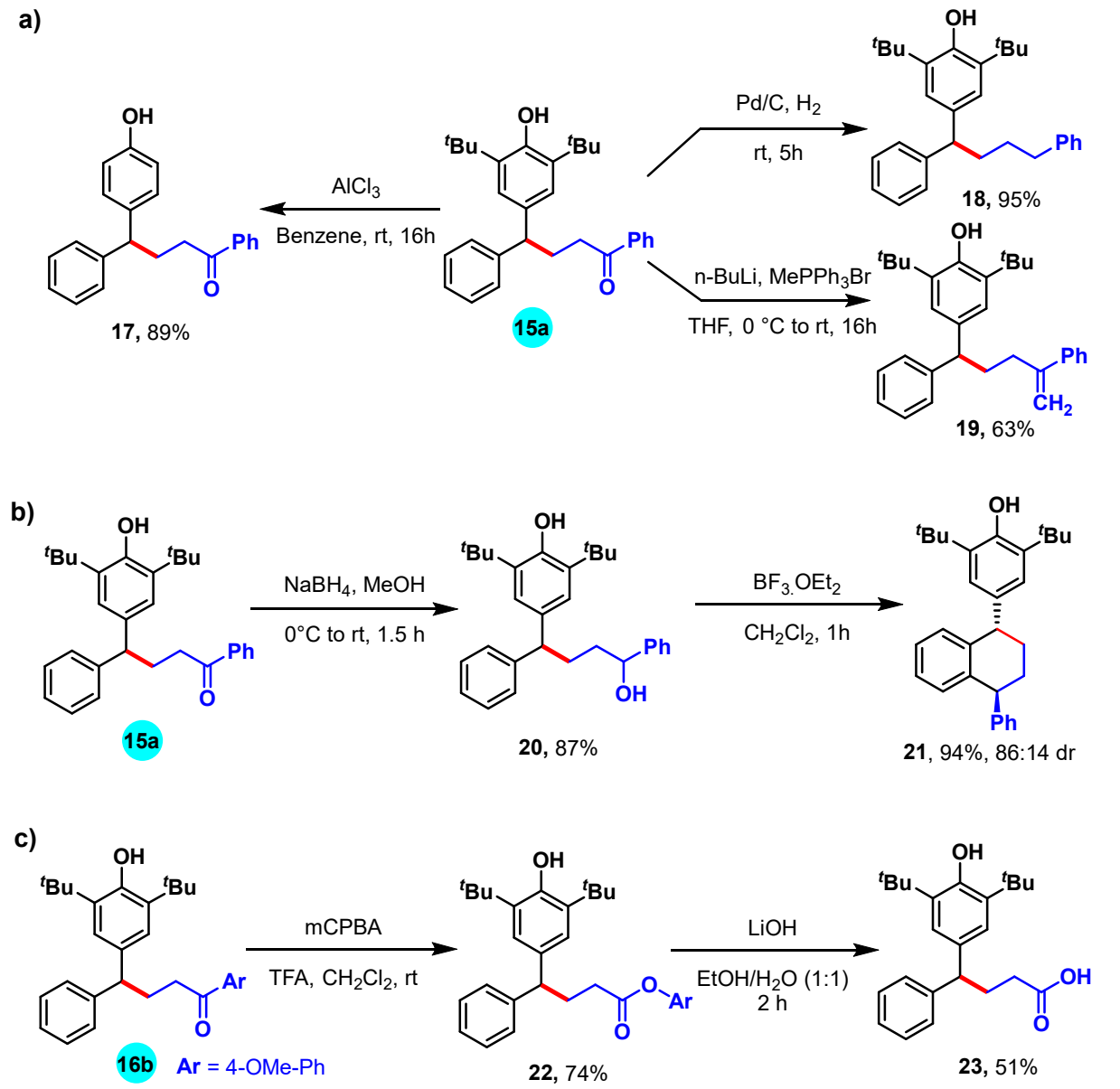


Fig. 3.2.ORTEP drawing (50% probability ellipsoids) of **16m** (**CCDC2103437**)

3.4.4 Product Transformations

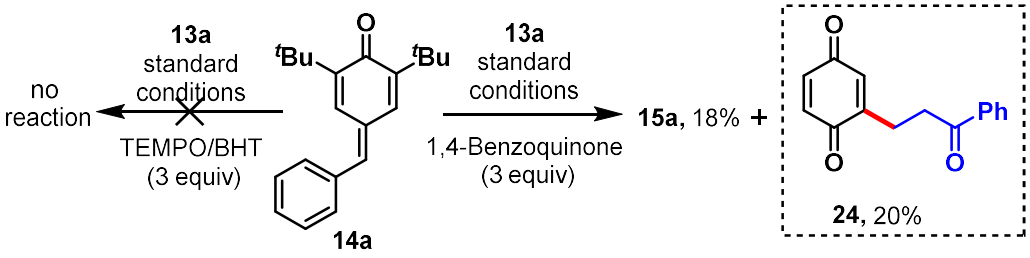
Next, the utility of this protocol has been demonstrated by carrying out several post-functionalizations of the product (Scheme 3.7a-c). De-*tert*-butylation of compound **15a** was achieved by treating with $AlCl_3$ in benzene, and the de-*tert*-butylated product **17** was obtained in 89% yield. The carbonyl group of **15a** was reduced to the corresponding methylene **18** in 95% yield upon reaction with Pd/C under H_2 pressure. Further, **15a** was converted into a terminal alkene **19** by the Wittig reaction (Scheme 3.7a). Next, reduction of **15a** with $NaBH_4$ produced intermediate **20,** and its subsequent BF_3•OEt_2 mediated Friedel–Crafts cyclization provided tetrahydronaphthalene derivative **21** in 94% yield with 86:14 d.r. It is noteworthy to mention that such basic tetrahydronaphthalene core is widely present in many pharmaceuticals and natural products (Scheme 3.7b).[16] Further, Baeyer–Villiger oxidation of **16b** in the presence of 3-chloroperoxybenzoic acid (*m*-CPBA) furnished the corresponding ester **22** in 74% yield. Subsequent hydrolysis of **22** with LiOH in EtOH/water (1:1) afforded the carboxylic acid **23** in 51% yield (Scheme 3.7c).



Scheme 3.7. Product transformations

3.4.5 Control Experiments

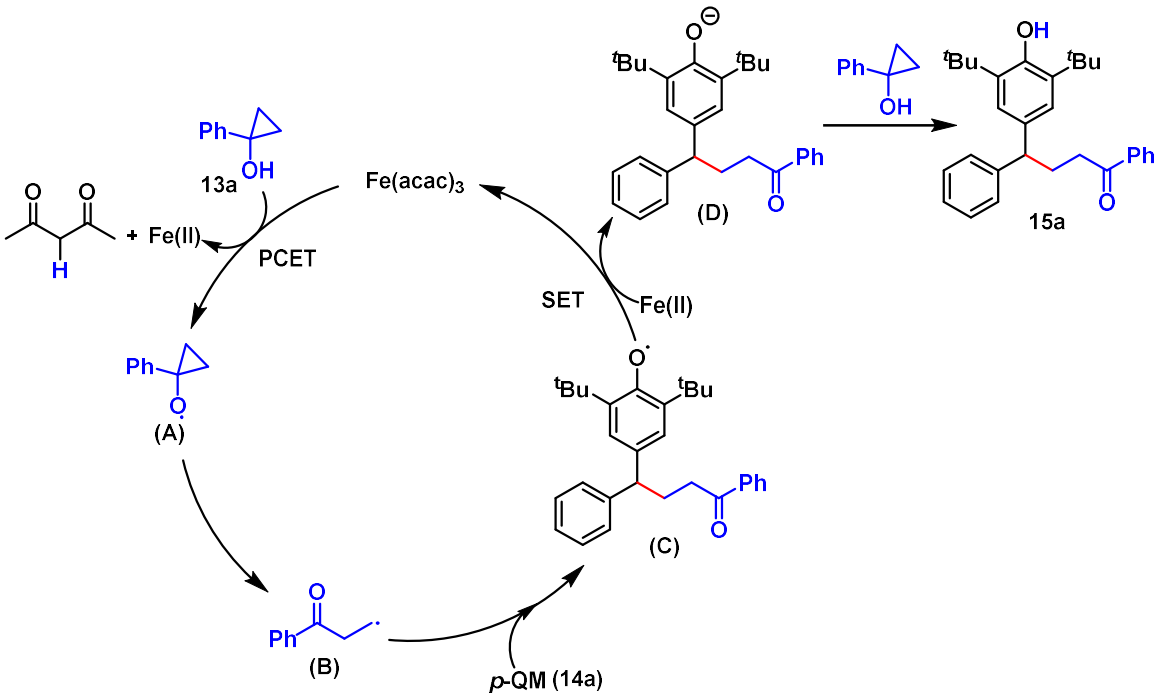
A few control experiments were performed to gain insights into the reaction mechanism. The reaction of *p*-QM **14a** with 1-phenyl cyclopropanol **13a** in the presence of TEMPO and BHT (3 equiv) under optimized conditions completely suppressed the conjugate addition. When 3 equiv 1,4-benzoquinone was added, the product **15a** was isolated in only 18% yield along with quinone derivative **24** in 20% yield. These results suggest that the cyclopropanol ring opening is seemingly proceeds *via* a radical pathway (Scheme 3.8).



Scheme 3.8. Control experiments

3.4.5 Plausible Reaction Mechanism

Based on the above control experiments and previous reports,[7f, 7h] a plausible reaction mechanism for this tandem ring opening/1,6-conjugate addition of cyclopropanol with *p*-QM is depicted in Scheme 3.9. Initially, the reaction of $Fe(acac)_3$ with cyclopropanol **13a** gives a Fe(II) species and a cyclopropanoxyl radical (**A**) through proton-coupled electron transfer (PCET). The ring opening of (**A**) driven by strain release, generates the *β*-keto radical (**B**), it then undergoes intermolecular addition to the *p*-QM (**14a**) to afford the radical intermediate (**C**). Subsequently, intermediate (**C**) is converted into a phenolate anion (D) *via* single electron transfer (SET) oxidation of Fe (II) and releasing $Fe(acac)_3$ to complete the catalytic cycle. Finally, the protonation of the intermediate (**D**) delivers the *γ*,*γ*-diarylated carbonyl derivative **15a**.



Scheme 3.9. Plausible reaction mechanism

3.5 Conclusion

In this chapter, we have developed a new and facile way of accessing *γ*,*γ*-diaryl ketones through iron-catalyzed one-pot tandem reaction of cyclopropanols with *p*-quinone methides. The ease of operation, wide substrate scope and scalability are the salient features of the current methodology. Product transformations of the *γ*,*γ*-diaryl ketone gave a number of versatile building blocks such as tetrahydronaphtahlene derivative, *γ*,*γ*-diaryl butanoic acid etc., thus demonstrating the utility of this method. Given the fundamental importance of *γ*,*γ*-diarylketone derivatives, we believe that this simple strategy may provide a general approach to the preparation of *γ*,*γ*-diarylketones in a rapid manner.

3.6 Experimental Section

All the *p*-QMs were prepared as per the procedure described in the section 1.2.5.1 of the chapter 1.

3.6.1 General Procedure for the Preparation of Cyclopropanols[17]

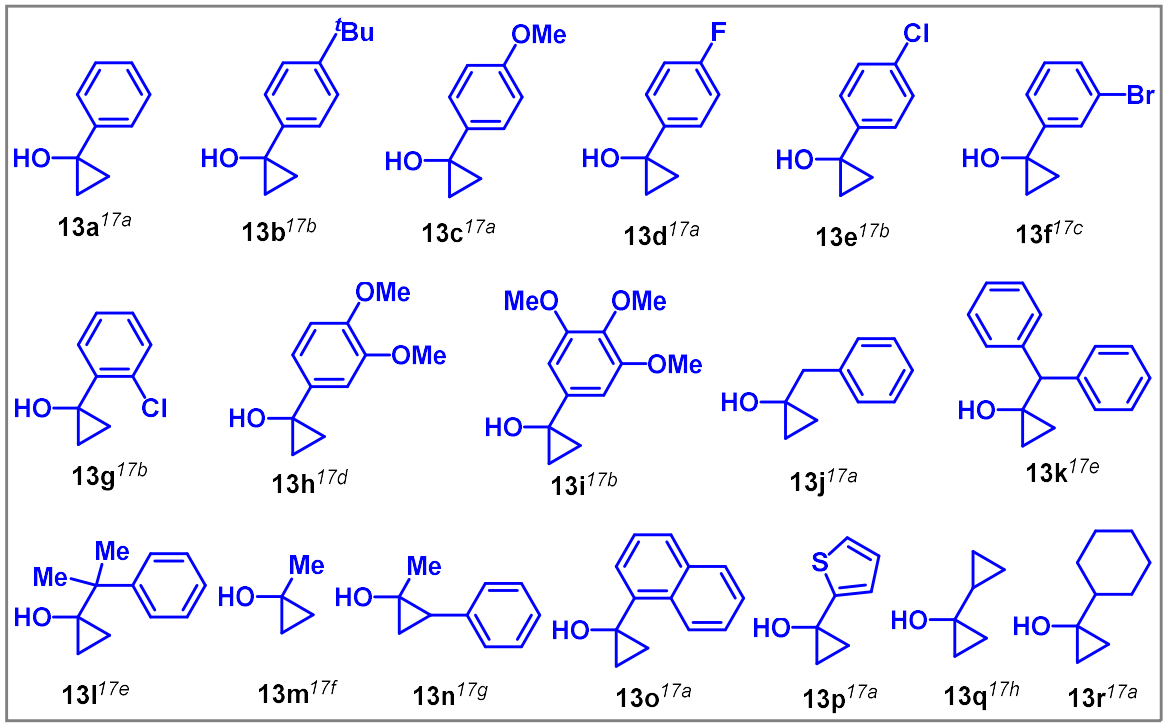
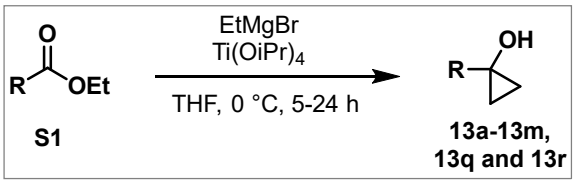


Fig. 3.3. Structures of cyclopropanols used in this study.

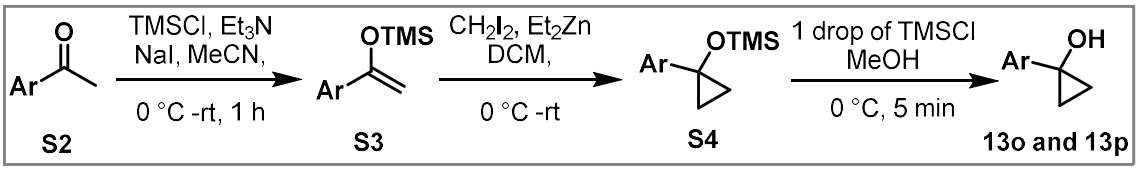
Procedure A: Kulinkovich reaction: Cyclopropanols **13a-13m**, **13q** and **13r** were prepared according to procedure A.



Scheme 3.10. Preparation of cyclopropanols *via* Kulinkovich reaction

Ethylmagnesium bromide (2.8 equiv, 2M in THF) in THF was added dropwise over 30 min at 0 °C to a solution of ester **S1** (1.0 equiv) and titanium isopropoxide (1.4 equiv) in THF under argon. The mixture was warmed to room temperature and stirred overnight. The reaction was quenched with water, and the precipitated solid was removed by filtration. The filtrate was extracted with ethyl acetate (3 × 30 mL), washed with water, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography to afford the cyclopropanols **13a-13m**, **13q** and **13r**.

b) Procedure B: Simmons–Smith reaction: Cyclopropanols **13o** and **13p** were prepared by following procedure **B**.



Scheme 3.11. Preparation of cyclopropanols *via* Simmons–Smith reaction

Step 1: An oven-dried round-bottom flask equipped with a stir bar was added sodium iodide (1.4 equiv), and the flask was flame-dried and cooled under vacuum. The flask was back-filled with argon and MeCN (20 mL) was added, followed by the desired ketone (1.0 equiv). The solution was cooled to 0 ºC, and TMSCl (1.3 equiv) was added, followed by triethylamine (1.5 equiv). The reaction was stirred at 0 ºC for 1 h under argon. The reaction mixture was extracted with petroleum ether (3 × 30 mL). The combined organic layers were washed with water, brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to yield the crude silyl enol ether **S3**.

Step 2: An oven-dried round-bottom flask equipped with a stir bar was transferred the crude silyl enol ether **S3** (1.0 equiv) under the argon. The flask was charged with anhydrous DCM (20 mL) and diiodomethane (1.2 equiv). The resulting solution was cooled to 0 ºC using an ice bath. Diethylzinc (1.2 equiv, 1.0 M in heptane) was added dropwise over 10 min. The reaction was stirred at 0 ºC for 1 h, then at room temperature until the complete conversion of the silyl enol ether was achieved as determined by TLC. The reaction was quenched with sat.

$NaHCO_3$ and extracted with DCM (3 × 30 mL). The combined organic layers were washed washed with water, brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to yield the crude trimethylsilyl cyclopropanol **S4**.

Step 3: An oven-dried round-bottom flask equipped with a stir bar was transferred the crude trimethylsilyl cyclopropanol **S4**, and MeOH (20 mL) was added. The solution was cooled to 0 ºC and TMSCl (1 drop from a 1-mL syringe) was added. The reaction was stirred at 0 ºC for 5 min. After completion, the resulting mixture was evaporated under a vacuum. The residue was purified by column chromatography on silica gel using petroleum ether/ethyl acetate to yield the desired cyclopropanols **13o** and **13p.**

Procedure for the synthesis of 13n: Titanium isopropoxide (1.36 g, 1.45 mL, 4.8 mmol, 1.0 equiv) was added to a flame-dried flask at room temperature under argon. Anhydrous THF (20 mL) was added to the flask, followed by the styrene (0.5 g, 4.8 mmol, 1.0 equiv) and EtOAc (0.69 mL, 7.2 mmol, 1.5 eq). Then freshly prepared cyclohexyl magnesium bromide (19 mL, 19.2 mmol, 4 equiv, ~1M in THF) was added dropwise over the period of 1 h at 25 ºC. The reaction was stirred overnight at room temperature, diluted with EtOAc (50 mL) and poured into NH_4Cl (50 mL). The mixture was stirred vigorously for 0.5 h to break up the emulsion and then filtered through celite. The layers were separated, and the aqueous layer was extracted twice with EtOAc (3 × 50 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash column chromatography to yield the desired cyclopropanols **13n**.

3.6.2 General Procedure for the Synthesis of *γ*, *γ* -Diaryl Ketones (15/16):

To a 5 mL oven-dried screw-capped vial equipped with a magnetic stir bar were added *p*-Quinone methide **14** (0.34 mmol), cyclopropanol derivative **13** (0.51 mmol), $Fe(acac)_3$ (10 mol%) and anhydrous CH_3CN (2.0 mL) under argon atmosphere at room temperature. The resultant reaction mixture was kept stirring at 80 °C for 8 h. After completion, the resulting mixture was evaporated under a vacuum. The residue was purified by column chromatography on silica gel using petroleum ether/ethyl acetate to give the products **15/16**.

3.6.3 Procedure for Product Transformations:

a) Procedure for the synthesis of 17: To a solution of **15a** (0.100 g, 0.233 mmol) in benzene (3 mL) was added $AlCl_3$ (0.155 g, 1.166 mmol) under an argon atmosphere, and the resulting mixture was stirred at room temperature for 16 h. The reaction mixture was then quenched with 10

mL of ice-cold water and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was subjected to column chromatography on silica gel using a petroleum ether/ethyl acetate = 20:1 mixture as an eluent to afford **17** as a yellow solid (0.066 g, 89%).

b) Procedure for the synthesis of 18: To an oven-dried 25 mL round-bottom flask equipped with a stir bar was added **15a** (0.100 g, 0.233 mmol) and 10% palladium on carbon (33.9 mg, 0.32 mmol), then MeOH (8 mL) and EtOAc (1 mL) was added under an atmosphere of H_2. The reaction was stirred at room temperature for 5 h. The solvent was removed under vacuum, and the residue was subjected to column chromatography on silica gel using petroleum ether/ethyl acetate = 20:1 as an eluent to give **18** as a white solid (0.092 g, 95% yield).

c) Procedure for the synthesis of 19: 0.1 mL of *n*-BuLi (2.5 M, 0.268 mmol) was added drop-wise to a solution of methyltriphenylphosphonium bromide (0.096 g, 0.268 mmol) in 6.0 mL of THF at 0 ºC. The reaction was stirred for about 15 min, and then **15a** (0.100 g, 0.233 mmol) in 2.0 mL of THF was added. After an additional 15 min, the ice bath was removed, and the reaction was allowed to stir at room temperature for 12 h. The reaction mixture was diluted with water (10 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude product was purified as a pale yellow solid by a silica gel column chromatography (petroleum ether/ethyl acetate = 100:1) to afford **19** (0.062 g, 63% yield).

d) Procedure for the synthesis of 20: To an oven-dried 25 mL round-bottom flask equipped with a stir bar was added **15a** (0.100g, 0.233 mmol) and MeOH (4 mL), then the mixture was cooled to 0 °C, and sodium borohydride (28.4 mg, 0.75 mmol) was added. The reaction was stirred at room temperature for 1.5 h. The reaction was then quenched with saturated ammonium chloride (10 mL) and vigorously stirred and filtered through Celite. The aqueous layer was extracted with EtOAc (2 x 15 mL), and the organic layers were combined and washed with brine (10 mL) and then dried with anhydrous Na_2SO_4. The solvent was removed under a vacuum. The residue was subjected to flash chromatography on silica gel using petroleum ether/ethyl acetate (20:1) as an eluent to give **20** as a sticky solid (0.087 g, 87% yield).

e) Procedure for the synthesis of 21: To a solution of **20** (0.100 g, 0.232 mmol) in CH_2Cl_2 (3 mL) was added $BF_3{\cdot}OEt_2$ (0.029 mL, 0.232 mmol) under an argon atmosphere, and the resulting mixture was stirred at room temperature for 1 h. The colour of the solution changed from

yellow to orange during the reaction. After completing the reaction, the solvent was removed under a vacuum. The residue was subjected to flash chromatography on silica gel using petroleum ether/ethyl acetate (100:1) as an eluent to give **21** as a white solid (0.090 g, 94% yield).

f) Procedure for the synthesis of 22: A mixture of **16b** (0.100 g, 0.218 mmol), *meta*-chloroperoxybenzoic acid (*m*CPBA, 0.150 g, 0.872 mmol), TFA (0.033 mL, 0.436 mmol) in CH_2Cl_2 (10 mL) was stirred at room temperature. Upon completion of the reaction (monitored by TLC), the mixture was diluted with CH_2Cl_2 (20 mL), washed with saturated aqueous Na_2SO_3 (1 × 30 mL) and saturated aqueous $NaHCO_3$ (1 × 30 mL). After extraction, the resulting organic layer was dried over anhydrous Na_2SO_4 and concentrated under a vacuum. The residue was purified by flash chromatography on silica gel eluting with petroleum ether/ethyl acetate (20:1) to give **22** as a white solid. (0.076 g, 74%)

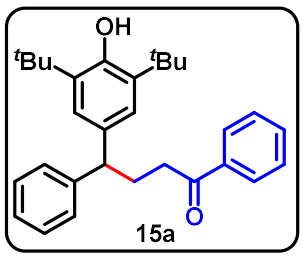
g) Procedure for the synthesis of 23: Lithium hydroxide (0.005 g, 0.211 mmol) was added to the solution of ester **22** (0.050 g, 0.105 mmol) in 10 mL of ethanol/water (4:1) mixture. The resulting solution was stirred at room temperature for 2 h, then acidified with 2 N HCl to pH 1, diluted with water (10 mL) and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under a vacuum. The residue was purified by flash chromatography on silica gel eluting with petroleum ether/ethyl acetate (9:1) to give **23** as a white solid (0.020 g, 51%).

3.6.4 Procedure for the Control Reaction:

To 5 mL screw-cap reaction vial was added *p*-quinone methide **14a** (0.100 g, 0.340 mmol), 1-phenyl cyclopropanols **13a** (0.068 g, 0.509 mmol), $Fe(acac)_3$ (0.012 g, 0.034 mmol), and 2,2,6,6-tetramethylpiperidinooxy (TEMPO) or butylated hydroxytoluene (BHT) or 1,4-benzoquinone (3 equiv). Then 2.0 mL anhydrous CH_3CN was added under nitrogen. The reaction mixture was stirred at 80 °C for 5 h, and the reaction was monitored by TLC.

3.6.5 Characterization of 15a-15z, 16a-16q and 17-24:

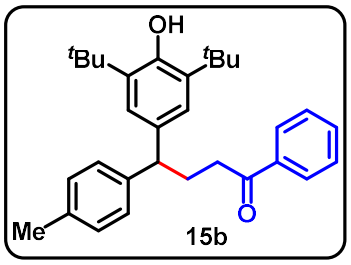
4-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-1,4-diphenylbutan-1-one (15a):



The product **15a** was obtained in 97% yield (141 mg, White solid); **mp** = 96-97 °C; R_f = 0.59 (10% EtOAc in petroleum ether); **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 7.84 – 7.82 (m, 2H), 7.51 – 7.47 (m, 1H), 7.37 (dd, *J* = 10.6, 4.6 Hz, 2H), 7.30 – 7.28 (m, 4H), 7.20 – 7.14 (m, 1H), 7.05 (s, 2H), 5.05 (s, 1H), 3.91 (t, *J* = 8.0 Hz, 1H), 2.97 – 2.84 (m,

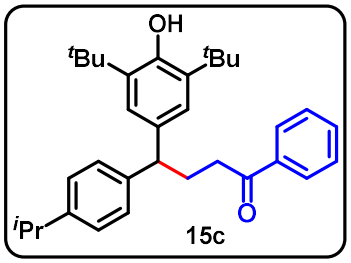
2H), 2.50 – 2.41 (m, 2H), 1.39 (s, 18H); **$^{13}C\{^{1}H\}$ NMR (100 MHz,$CDCl_3$) δ** = 200.3, 152.1, 144.8, 136.9, 135.6, 134.9, 132.8, 128.4, 128.4, 128.0, 127.8, 126.1, 124.2, 50.7, 37.1, 34.3, 30.7, 30.3; **HRMS (ESI-TOF)** *m/z*: $[M - H]^-$ calcd for $C_{30}H_{35}O_2$ 427.2632; found 427.2641.

4-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-1-phenyl-4-(p-tolyl)butan-1-one (15b):



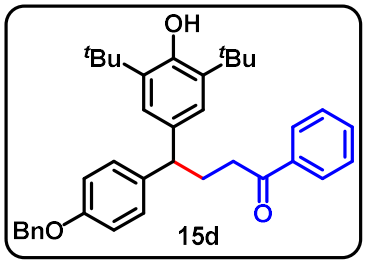
The product **15b** was obtained in 89% yield (128 mg, White solid); **mp** = 116-117 °C; R_f = 0.47 (10% EtOAc in petroleum ether);**^{1}H NMR (400 MHz, $CDCl_3$) δ** = 7.86 – 7.84 (m, 2H), 7.53 (t, *J* = 7.2 Hz, 1H), 7.41 (t, *J* = 7.6 Hz, 2H), 7.19 (d, *J* = 7.8 Hz, 2H), 7.11 (d, *J* = 7.7 Hz, 2H), 7.05 (s, 2H), 5.04 (s, 1H), 3.87 (t, *J* = 7.8 Hz, 1H), 2.91 (t, *J* = 7.3 Hz, 2H), 2.47 – 2.39 (m, 2H), 2.32 (s, 3H), 1.41 (s, 18H); **$^{13}C\{^{1}H\}$ NMR (100 MHz,$CDCl_3$) δ** = 200.4, 152.0, 141.9, 137.0, 135.6, 135.5, 135.2, 132.9, 129.1, 128.5, 128.0, 127.7, 124.2, 50.4, 37.2, 34.3, 30.8, 30.3, 21.0; **HRMS (ESI-TOF)** *m/z*: $[M - H]^-$ calcd for $C_{31}H_{37}O_2$ 441.2788; found 441.2809.

4-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-4-(4-isopropylphenyl)-1-phenylbutan-1-one (15c):



The product **15c** was obtained in 85% yield (119 mg, sticky solid); R_f = 0.62 (10% EtOAc in petroleum ether); **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 7.83 (d, *J* = 7.7 Hz, 2H), 7.50 (t, *J* = 7.6 Hz, 1H), 7.39 (t, *J* = 7.6 Hz, 2H), 7.20 (d, *J* = 8.0 Hz, 2H), 7.13 (d, *J* = 8.1 Hz, 2H), 7.05 (s, 2H), 5.03 (s, 1H), 3.86 (t, *J* = 7.9 Hz, 1H), 2.92 – 2.81 (m, 3H), 2.49 – 2.37 (m, 2H), 1.39 (s, 18H), 1.21 (d, *J* = 6.9 Hz, 6H); **$^{13}C\{^{1}H\}$ NMR (100 MHz,$CDCl_3$) δ** = 200.5, 152.1, 146.5, 142.2, 137.0, 135.6, 135.1, 132.8, 128.4, 128.0, 127.6, 126.4, 124.2, 50.5, 37.3, 34.3, 33.6, 31.0, 30.3, 24.0; **HRMS (ESI-TOF)** *m/z*: $[M - H]^-$ calcd for $C_{33}H_{41}O_2$ 469.3101; found 469.3115.

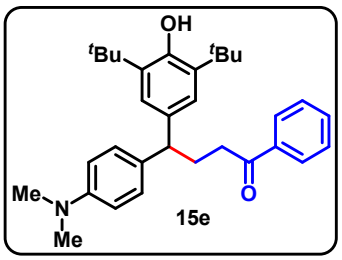
4-(4-(benzyloxy)phenyl)-4-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-1-phenylbutan-1-one (15d):



The product **15d** was obtained in 97% yield (129 mg, White solid); **mp** = 108-109 °C; R_f = 0.50 (10% EtOAc in petroleum ether); **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 7.86 (d, *J* = 7.7 Hz, 2H), 7.53 (t, *J* = 7.5 Hz, 1H), 7.48 – 7.36 (m, 6H), 7.36 – 7.28 (m, 1H), 7.22 (d, *J* = 8.6 Hz, 2H), 7.05 (s, 2H), 6.93 (d, *J* = 8.5 Hz, 2H), 5.05 (s, 3H), 3.88 (t, *J* = 7.9 Hz, 1H), 2.95 – 2.87 (m, 2H), 2.42 (dd, *J* = 12.6, 5.0 Hz, 2H), 1.42 (s, 18H); **$^{13}C\{^{1}H\}$ NMR (100 MHz,$CDCl_3$) δ** = 200.4, 157.1, 152.0, 137.3, 137.1, 137.0, 135.6, 135.3, 132.9, 128.8, 128.5, 128.5, 128.0, 127.9, 127.5, 124.2, 114.8, 70.0, 49.9, 37.2,

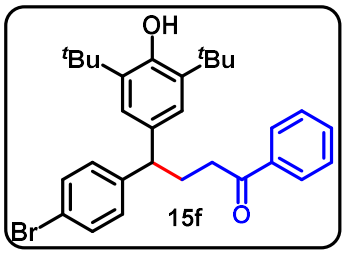
34.3, 30.9, 30.3; **HRMS (ESI-TOF)** *m/z*: [M – H]$^-$ calcd for $C_{37}H_{41}O_3$ 533.3050; found 533.3069.

4-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-4-(4-(dimethylamino)phenyl)-1-phenylbutan-1-one (15e):



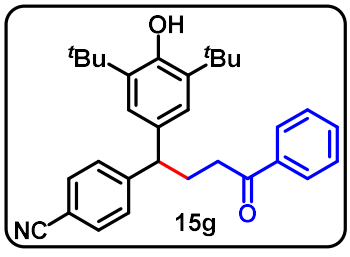
The product **15e** was obtained in 92% yield (129 mg, White solid); **mp** = 128-129 °C; R_f = 0.51 (10% EtOAc in petroleum ether); **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 7.87 (d, *J* = 7.7 Hz, 2H), 7.53 (t, *J* = 7.3 Hz, 1H), 7.42 (t, *J* = 7.6 Hz, 2H), 7.19 (d, *J* = 8.7 Hz, 2H), 7.08 (s, 2H), 6.73 (t, *J* = 5.7 Hz, 2H), 5.04 (s, 1H), 3.84 (t, *J* = 7.9 Hz, 1H), 2.93 (s, 6H), 2.93 (t, 2H), 2.49 – 2.39 (m, 2H), 1.43 (s, 18H); **^{13}C{^{1}H} NMR (100 MHz,$CDCl_3$) δ** = 200.6, 151.9, 149.1, 137.0, 135.7, 135.5, 133.0, 132.8, 128.4, 128.4, 128.0, 124.1, 112.9, 49.9, 40.7, 37.4, 34.3, 31.0, 30.3; **HRMS (ESI-TOF)** *m/z*: [M – H]$^-$ calcd for $C_{32}H_{40}NO_2$ 470.3054; found 470.3069.

4-(4-bromophenyl)-4-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-1-phenylbutan-1-one (15f):



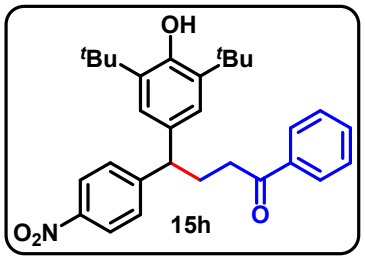
The product **15f** was obtained in 84% yield (114 mg, White solid); **mp** = 126-127 °C; R_f = 0.45 (10% EtOAc in petroleum ether); **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 7.85 (d, *J* = 7.3 Hz, 2H), 7.54 (t, *J* = 7.3 Hz, 1H), 7.42 (t, *J* = 7.8 Hz, 4H), 7.16 (d, *J* = 8.2 Hz, 2H), 7.00 (s, 2H), 5.07 (s, 1H), 3.88 (t, *J* = 7.8 Hz, 1H), 2.90 (t, *J* = 7.2 Hz, 2H), 2.43 (q, *J* = 7.5 Hz, 2H), 1.40 (s, 18H) ; **^{13}C{^{1}H} NMR (100 MHz,$CDCl_3$) δ** = 200.0, 152.3, 144.0, 136.9, 135.8, 134.3, 133.0, 131.5, 129.6, 128.5, 128.0, 124.1, 119.8, 50.1, 36.9, 34.3, 30.4, 30.3 ; **HRMS (ESI-TOF)** *m/z*: [M – H]$^-$ calcd for $C_{30}H_{34}O_2Br$ 505.1737; found 505.1758.

4-(1-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-4-oxo-4-phenylbutyl)benzonitrile (15g):



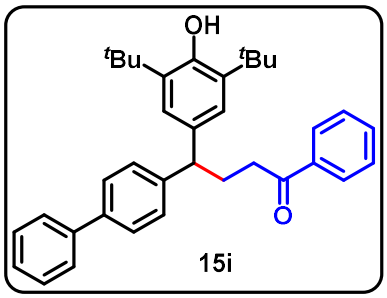
The product **15g** was obtained in 83% yield (118 mg, White solid); **mp** = 106-107 °C; R_f = 0.26 (10% EtOAc in petroleum ether); **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 7.85 (d, *J* = 7.3 Hz, 2H), 7.59 – 7.52 (m, 3H), 7.42 (dd, *J* = 13.9, 8.0 Hz, 4H), 6.99 (s, 2H), 5.13 (s, 1H), 4.00 (t, *J* = 7.9 Hz, 1H), 2.94 – 2.90 (m, 2H), 2.47 (dd, *J* = 14.7, 7.2 Hz, 2H), 1.40 (s, 18H) ; **^{13}C{^{1}H} NMR (100 MHz,$CDCl_3$) δ** = 199.7, 152.5, 150.7, 136.8, 136.1, 133.2, 133.1, 132.3, 128.6, 128.5, 127.9, 124.2, 119.0, 109.9, 50.5, 36.5, 34.3, 30.2, 29.9 ; **HRMS (ESI-TOF)** *m/z*: [M – H]$^-$ calcd for $C_{31}H_{34}NO_2$ 452.2584; found 452.2602.

4-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-4-(4-nitrophenyl)-1-phenylbutan-1-one (15h):



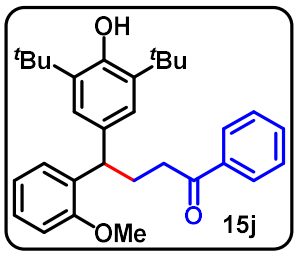
The product **15h** was obtained in 79% yield (110 mg, White solid); **mp** = 113-114 °C; R_f = 0.27 (10% EtOAc in petroleum ether); **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 8.27 – 8.14 (m, 2H), 7.85 (d, *J* = 7.3 Hz, 2H), 7.57 – 7.52 (m, 1H), 7.46 – 7.41 (m, 4H), 7.00 (s, 2H), 5.12 (d, *J* = 1.0 Hz, 1H), 4.05 (t, *J* = 7.9 Hz, 1H), 2.93 (t, *J* = 7.2 Hz, 2H), 2.49 (q, *J* = 7.3 Hz, 2H), 1.40 (s, 18H) ; **^{13}C{^{1}H} NMR (100 MHz,$CDCl_3$) δ** = 199.7, 152.9, 152.6, 146.4, 136.8, 136.2, 133.1, 133.0, 128.6, 128.6, 127.9, 124.2, 123.8, 50.4, 36.5, 34.4, 30.2, 30.0 ; **HRMS (ESI-TOF)** *m/z*: $[M - H]^-$ calcd for $C_{30}H_{34}NO_4$ 472.2482; found 472.2501.

4-([1,1'-biphenyl]-4-yl)-4-(3,5-di-tert-butyl-4-hydroxyphenyl)-1-phenylbutan-1-one (15i) :



The product **15i** was obtained in 98% yield (133 mg, White solid); **mp** = 99-100 °C; R_f = 0.39 (10% EtOAc in petroleum ether); **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 7.83 (d, *J* = 7.3 Hz, 2H), 7.56 – 7.46 (m, 5H), 7.37 (dd, *J* = 14.8, 7.8 Hz, 6H), 7.29 (dd, *J* = 14.7, 7.3 Hz, 1H), 7.08 (s, 2H), 5.05 (s, 1H), 3.95 (t, *J* = 7.9 Hz, 1H), 2.93 (t, *J* = 7.4 Hz, 2H), 2.55 – 2.42 (m, 2H), 1.40 (s, 18H); **^{13}C{^{1}H} NMR (100 MHz,$CDCl_3$) δ** = 200.3, 152.2, 144.0, 140.9, 138.9, 136.9, 135.7, 134.8, 132.9, 128.7, 128.5, 128.2, 128.0, 127.1, 127.0, 126.9, 124.2, 50.4, 37.1, 34.3, 30.7, 30.3 ; **HRMS (ESI-TOF)** *m/z*: $[M - H]^-$ calcd for $C_{36}H_{39}O_2$ 503.2945; found 503.2962.

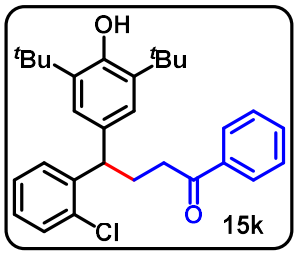
4-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-4-(2-methoxyphenyl)-1-phenylbutan-1-one (15j) :



The product **15j** was obtained in 78% yield (110 mg, White solid); **mp** = 161-162 °C; R_f = 0.56 (10% EtOAc in petroleum ether);

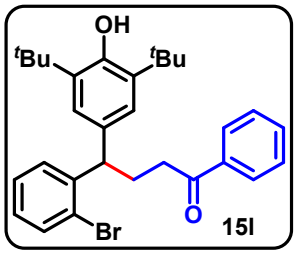
^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.85 (d, *J* = 7.6 Hz, 2H), 7.51 (t, *J* = 7.3 Hz, 1H), 7.40 (t, *J* = 7.6 Hz, 2H), 7.25 (d, *J* = 7.2 Hz, 1H), 7.17 – 7.13 (m, 1H), 7.12 (s, 2H), 6.92 (t, *J* = 7.4 Hz, 1H), 6.83 (d, *J* = 8.1 Hz, 1H), 5.02 (s, 1H), 4.40 (t, *J* = 7.9 Hz, 1H), 3.76 (s, 3H), 2.99 – 2.84 (m, 2H), 2.44 (dd, *J* = 15.2, 7.6 Hz, 2H), 1.41 (s, 18H); **^{13}C{^{1}H} NMR (100 MHz,$CDCl_3$) δ** = 200.6, 157.0, 151.9, 137.0, 135.3, 134.6, 133.4, 132.7, 128.4, 128.0, 127.6, 126.9, 124.6, 120.6, 110.6, 55.3, 42.7, 37.4, 34.3, 30.4, 29.9; **HRMS (ESI-TOF)** *m/z*: $[M - H]^-$ calcd for $C_{31}H_{37}O_3$ 457.2737; found 457.2760.

4-(2-chlorophenyl)-4-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-1-phenylbutan-1-one (15k):



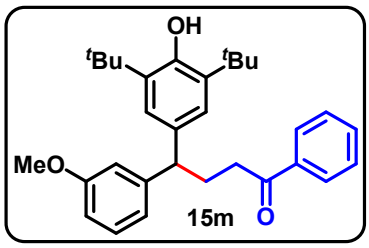
The product **15k** was obtained in 79% yield (111 mg, White solid); **mp** = 131-132 °C; R_f = 0.46 (10% EtOAc in petroleum ether); **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 7.85 (d, *J* = 7.6 Hz, 2H), 7.51 (t, *J* = 7.3 Hz, 1H), 7.42 – 7.32 (m, 4H), 7.22 (dd, *J* = 11.0, 4.3 Hz, 1H), 7.12 – 7.08 (m, 3H), 5.06 (s, 1H), 4.49 (t, *J* = 7.9 Hz, 1H), 3.02 – 2.85 (m, 2H), 2.52 – 2.37 (m, 2H), 1.40 (s, 18H); **^{13}C{^{1}H} NMR (100 MHz,$CDCl_3$) δ** = 200.0, 152.2, 142.4, 136.9, 135.6, 134.1, 133.4, 132.9, 129.6, 128.5, 128.2, 128.0, 127.2, 127.0, 124.5, 45.9, 37.0, 34.3, 30.3, 30.0 ; **HRMS (ESI-TOF)** *m/z*: [M – H]$^-$ calcd for $C_{30}H_{34}O_2Cl$ 461.2242; found 461.2269.

4-(2-bromophenyl)-4-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-1-phenylbutan-1-one (15l):



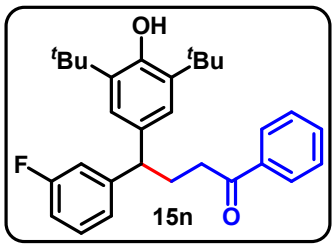
The product **15l** was obtained in 92% yield (125 mg, White solid); **mp** = 104-105 °C; R_f = 0.50 (10% EtOAc in petroleum ether); **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 7.87 – 7.85 (m, 2H), 7.54 – 7.50 (m, 2H), 7.41 (t, *J* = 7.6 Hz, 2H), 7.35 (dd, *J* = 7.7, 1.4 Hz, 1H), 7.26 (dd, *J* = 10.7, 3.9 Hz, 1H), 7.13 (s, 2H), 7.04 – 7.00 (m, 1H), 5.07 (s, 1H), 4.49 (t, *J* = 7.9 Hz, 1H), 3.04 – 2.85 (m, 2H), 2.53 – 2.38 (m, 2H), 1.41 (s, 18H) ; **^{13}C{^{1}H} NMR (100 MHz,$CDCl_3$) δ** = 200.1, 152.2, 144.1, 136.9, 135.6, 133.4, 132.9, 132.9, 128.5, 128.4, 128.0, 127.7, 127.6, 125.2, 124.5, 48.5, 37.0, 34.3, 30.3, 30.2 ; **HRMS (ESI-TOF)** *m/z*: [M – H]$^-$ calcd for $C_{30}H_{34}O_2Br$ 505.1737; found 505.1761.

4-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-4-(3-methoxyphenyl)-1-phenylbutan-1-one (15m) :



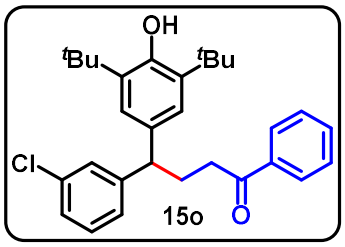
The product **15m** was obtained in 91% yield (128 mg, sticky solid); R_f = 0.50 (10% EtOAc in petroleum ether); **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 7.90 – 7.88 (m, 2H), 7.56 – 7.52 (m, 1H), 7.45 – 7.37 (m, 2H), 7.26 (dd, *J* = 9.0, 6.7 Hz, 1H), 7.12 (s, 2H), 6.95 (d, *J* = 7.6 Hz, 1H), 6.89 (d, *J* = 1.7 Hz, 1H), 6.77 (dd, *J* = 8.2, 2.3 Hz, 1H), 5.11 (s, 1H), 3.93 (t, *J* = 7.9 Hz, 1H), 3.80 (s, 3H), 2.98 – 2.94 (m, 2H), 2.53 – 2.47 (m, 2H), 1.45 (s, 18H) ; **^{13}C{^{1}H} NMR (100 MHz,$CDCl_3$) δ** = 200.3, 159.6, 152.1, 146.5, 136.9, 135.6, 134.7, 132.8, 129.3, 128.4, 128.0, 124.1, 120.2, 113.8, 111.2, 55.0, 50.8, 37.1, 34.3, 30.7, 30.3 ; **HRMS (ESI-TOF)** *m/z*: [M – H]$^-$calcd for $C_{31}H_{37}O_3$ 457.5737; found 457.2750.

4-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-4-(3-fluorophenyl)-1-phenylbutan-1-one (15n):



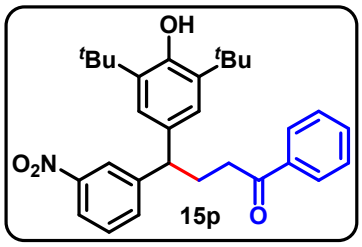
The product **15n** was obtained in 90% yield (129 mg, White solid); **mp** = 80-81 °C; R_f = 0.60 (10% EtOAc in petroleum ether); **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 7.84 (d, *J* = 7.3 Hz, 2H), 7.50 (t, *J* = 7.4 Hz, 1H), 7.39 (t, *J* = 7.6 Hz, 2H), 7.26 – 7.21 (m, 1H), 7.07 (d, *J* = 7.7 Hz, 1H), 7.02 (s, 2H), 6.98 (d, *J* = 10.3 Hz, 1H), 6.86 (td, *J* = 8.4, 1.9 Hz, 1H), 5.08 (s, 1H), 3.91 (t, *J* = 7.9 Hz, 1H), 2.90 (t, *J* = 7.1 Hz, 2H), 2.44 (q, *J* = 7.3 Hz, 2H), 1.39 (s, 18H) ; **^{13}C{^{1}H} NMR (100 MHz,$CDCl_3$) δ** = 200.0, 163.0 (d, J_{C-F} = 245.67 Hz), 152.3, 147.7 (d, J_{C-F} = 6.87 Hz), 136.9, 135.8, 134.2, 132.9, 129.9 (d, J_{C-F} = 7.63 Hz), 128.5, 128.0, 124.2, 123.5(d, J_{C-F} = 3.05 Hz), 14.7 (d, J_{C-F} = 21.36 Hz), 113.0 (d, J_{C-F} = 20.60 Hz), 50.4, 36.9, 34.3, 30.4, 30.3 ; **^{19}F NMR (376 MHz, $CDCl_3$) δ =** -113.2; **HRMS (ESI-TOF)** *m/z*: $[M - H]^-$ calcd for $C_{30}H_{34}FO_2$ 445.2537; found 445.2560.

4-(3-chlorophenyl)-4-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-1-phenylbutan-1-one (15o) :



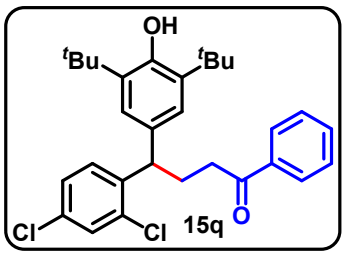
The product **15o** was obtained in 89% yield (126 mg, White solid); **mp** = 72-73 °C; R_f = 0.60 (10% EtOAc in petroleum ether); **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 7.84 (d, *J* = 7.6 Hz, 2H), 7.52 (t, *J* = 7.5 Hz, 1H), 7.41 (t, *J* = 7.7 Hz, 2H), 7.26– 7.14 (m, 4H), 7.00 (s, 2H), 5.07 (s, 1H), 3.88 (t, *J* = 7.9 Hz, 1H), 2.91 – 2.87 (m, 2H), 2.42 (dt, *J* = 13.2, 6.6 Hz, 2H), 1.39 (s, 18H); **^{13}C{^{1}H} NMR (100 MHz,$CDCl_3$) δ** = 200.0, 152.3, 147.0, 136.9, 135.9, 134.2, 134.0, 133.0, 129.7, 128.5, 128.1, 128.0, 126.3, 126.0, 124.2, 50.4, 36.9, 34.4, 30.4, 30.3; **HRMS (ESI-TOF)** *m/z*: $[M - H]^-$ calcd for $C_{30}H_{34}ClO_2$ 461.2242; found 461.2260.

4-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-4-(3-nitrophenyl)-1-phenylbutan-1-one (15p) :



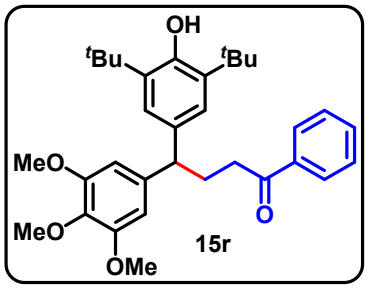
The product **15p** was obtained in 76% yield (106 mg, White solid); **mp** = 79-80 °C; R_f = 0.26 (10% EtOAc in petroleum ether); **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 8.20 – 8.19 (m, 1H), 8.06 (dd, *J* = 8.5, 1.9 Hz, 1H), 7.86 (d, *J* = 7.7 Hz, 2H), 7.65 (d, *J* = 7.7 Hz, 1H), 7.54 (dd, *J* = 10.5, 4.2 Hz, 1H), 7.49-7.34 (m, 3H), 7.04 (s, 2H), 5.15 (s, 1H), 4.07 (t, *J* = 7.9 Hz, 1H), 2.95 (t, *J* = 7.2 Hz, 2H), 2.59 – 2.45 (m, 2H), 1.42 (s, 18H) ; **^{13}C{^{1}H} NMR (100 MHz,$CDCl_3$) δ** = 199.7, 152.5, 148.3, 147.3, 136.8, 136.1, 134.0, 133.2, 133.1, 129.3, 128.5, 127.9, 124.2, 122.7, 121.3, 50.2, 36.5, 34.3, 31.8, 30.2; **HRMS (ESI-TOF)** *m/z*: $[M - H]^-$ calcd for $C_{30}H_{24}NO_4$ 472.2482; found 472.2501.

4-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-4-(2,4-dichlorophenyl)-1-phenylbutan-1-one (15q) :



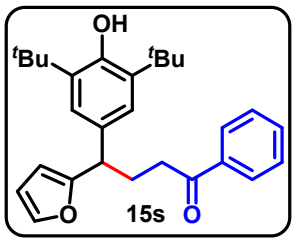
The product **15q** was obtained in 98% yield (134 mg, White solid); **mp** = 144-145 °C; R_f = 0.47 (10% EtOAc in petroleum ether); **^{1}H NMR (400 MHz, $CDCl_3$) δ** =7.85 (d, *J* = 7.7 Hz, 2H), 7.52 (t, *J* = 7.3 Hz, 1H), 7.41 (t, *J* = 7.6 Hz, 2H), 7.35 (d, *J* = 1.4 Hz, 1H), 7.26 (t, *J* = 6.6 Hz, 1H), 7.19 (dd, *J* = 8.4, 1.8 Hz, 1H), 7.05 (s, 2H), 5.07 (s, 1H), 4.43 (t, *J* = 7.8 Hz, 1H), 3.01 – 2.84 (m, 2H), 2.50 – 2.33 (m, 2H), 1.39 (s, 18H); **^{13}C{^{1}H} NMR (100 MHz,$CDCl_3$) δ** = 199.8, 152.4, 141.2, 136.8, 135.8, 134.7, 133.0, 132.8, 132.1, 129.4, 129.1, 128.5, 128.0, 127.3, 124.4, 45.5, 36.8, 34.3, 30.3, 29.8; **HRMS (ESI-TOF)** *m/z*: $[M - H]^-$ calcd for $C_{30}H_{33}O_2Cl_2$ 495.1852; found 495.1873.

4-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-1-phenyl-4-(3,4,5-trimethoxyphenyl)butan-1-one (15r):



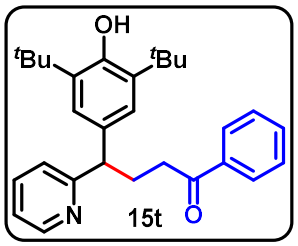
The product **15r** was obtained in 87% yield (117 mg, White solid); **mp** = 109-110 °C; R_f = 0.42 (20% EtOAc in petroleum ether); **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 7.85 (dd, *J* = 5.2, 3.3 Hz, 2H), 7.55 – 7.51 (m, 1H), 7.42 (t, *J* = 7.6 Hz, 2H), 7.09 (s, 2H), 6.52 (s, 2H), 5.08 (s, 1H), 3.86 (t, *J* = 8.0 Hz, 1H), 3.83 (s, 6H), 3.82 (s, 3H), 2.95 – 2.91 (m, 2H), 2.42 (dt, *J* = 11.6, 5.9 Hz, 2H), 1.42 (s, 18H) ; **^{13}C{^{1}H} NMR (100 MHz,$CDCl_3$) δ** = 200.4, 153.0, 152.2, 140.5, 136.9, 136.3, 135.7, 134.6, 132.9, 128.5, 128.0, 124.1, 104.8, 60.8, 56.0, 51.0, 37.0, 34.3, 31.2, 30.3 ; **HRMS (ESI-TOF)** *m/z*: $[M - H]^-$ calcd for $C_{33}H_{41}O_5$ 517.2949; found 517.2958.

4-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-4-(furan-2-yl)-1-phenylbutan-1-one (15s):



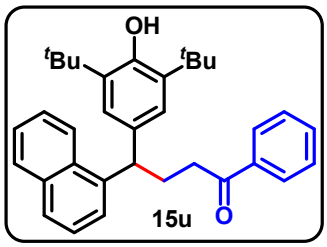
The product **15s** was obtained in 75% yield (110 mg, sticky solid); R_f = 0.44 (10% EtOAc in petroleum ether); **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 7.88 – 7.86 (m, 2H), 7.56 – 7.52 (m, 1H), 7.43 (t, *J* = 7.7 Hz, 2H), 7.34 (s, 1H), 7.04 (s, 2H), 6.31 – 6.30 (m, 1H), 6.10 (d, *J* = 3.1 Hz, 1H), 5.09 (s, 1H), 3.98 (t, *J* = 7.9 Hz, 1H), 2.94 (dt, *J* = 8.2, 6.1 Hz, 2H), 2.55 – 2.46 (m, 1H), 2.33 – 2.24 (m, 1H), 1.41 (s, 18H) ; **^{13}C{^{1}H} NMR (100 MHz,$CDCl_3$) δ** = 200.1, 157.8, 152.4, 141.2, 136.9, 135.7, 132.9, 132.7, 128.5, 128.0, 124.3, 110.0, 105.5, 44.4, 36.6, 34.3, 30.3, 29.9; **HRMS (ESI-TOF)** *m/z*: $[M - H]^-$ calcd for $C_{28}H_{33}O_3$ 417.2424; found 417.2440.

4-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-1-phenyl-4-(pyridin-2-yl)butan-1-one (15t) :



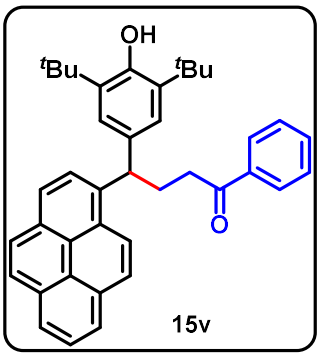
The product **15t** was obtained in 79% yield (115 mg, sticky solid); R_f = 0.41 (20% EtOAc in petroleum ether); **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 8.58 (ddd, *J* = 4.9, 1.8, 0.8 Hz, 1H), 7.89 – 7.86 (m, 2H), 7.56 (td, *J* = 7.7, 1.9 Hz, 1H), 7.53 – 7.49 (m, 1H), 7.43 – 7.39 (m, 2H), 7.21 (d, *J* = 7.9 Hz, 1H), 7.15 (s, 2H), 7.09 (ddd, *J* = 7.5, 4.9, 1.1 Hz, 1H), 5.10 (s, 1H), 4.11 (t, *J* = 7.8 Hz, 1H), 2.95 (dd, *J* = 11.1, 4.3 Hz, 2H), 2.72 – 2.63 (m, 1H), 2.53 – 2.44 (m, 1H), 1.41 (s, 18H) ; **^{13}C{^{1}H} NMR (100 MHz,$CDCl_3$) δ** = 200.3, 163.7, 152.3, 149.0, 136.9, 136.4, 135.7, 133.8, 132.8, 128.4, 128.0, 124.5, 122.9, 121.2, 52.7, 37.0, 34.3, 30.3, 30.2; **HRMS (ESI-TOF)** *m/z*: $[M - H]^-$ calcd for $C_{29}H_{34}NO_2$ 428.2584; found 428.2599.

4-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-4-(naphthalen-1-yl)-1-phenylbutan-1-one (15u):



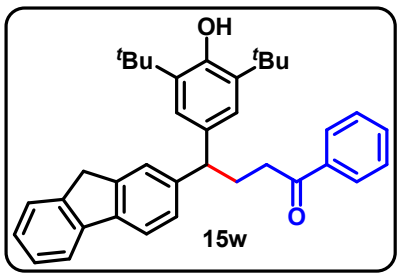
The product **15u** was obtained in 86% yield (119 mg, White solid); **mp** = 124-125 °C; R_f = 0.57 (10% EtOAc in petroleum ether); **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 8.30 (d, *J* = 8.4 Hz, 1H), 7.88 – 7.85 (m, 3H), 7.76 (d, *J* = 7.9 Hz, 1H), 7.56 – 7.46 (m, 5H), 7.40 (dd, *J* = 10.7, 4.6 Hz, 2H), 7.17 (s, 2H), 5.07 (s, 1H), 4.83 (t, *J* = 7.7 Hz, 1H), 3.05 (t, *J* = 7.5 Hz, 2H), 2.73 – 2.54 (m, 2H), 1.42 (s, 18H); **^{13}C{^{1}H} NMR (100 MHz,$CDCl_3$) δ** = 200.4, 152.1, 140.6, 136.9, 135.6, 134.4, 134.1, 132.9, 132.0, 128.8, 128.4, 128.0, 126.8, 125.8, 125.4, 125.3, 124.5, 124.0, 123.8, 45.3, 37.2, 34.3, 31.0, 30.3; **HRMS (ESI-TOF)** *m/z*: $[M - H]^-$ calcd for $C_{34}H_{37}O_2$ 477.2788; found 477.2798.

4-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-1-phenyl-4-(pyren-1-yl)butan-1-one (15v):



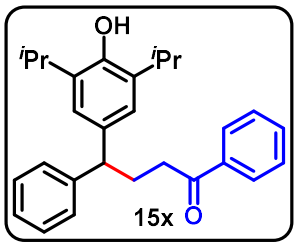
The product **15v** was obtained in 81% yield (107 mg, White solid); **mp** = 183-184 °C; R_f = 0.34 (10% EtOAc in petroleum ether); **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 8.51 (d, *J* = 9.5 Hz, 1H), 8.15 – 8.02 (m, 5H), 8.00 – 7.95 (m, 2H), 7.94 – 7.90 (m, 1H), 7.76 – 7.74 (m, 2H), 7.40 (t, *J* = 7.5 Hz, 1H), 7.29 (t, *J* = 5.5 Hz, 2H), 7.19 (s, 2H), 5.12 (t, *J* = 7.8 Hz, 1H), 5.01 (s, 1H), 3.05 – 2.92 (m, 2H), 2.78 – 2.69 (m, 2H), 1.35 (s, 18H) ; **^{13}C{^{1}H} NMR (100 MHz,$CDCl_3$) δ** = 200.3, 152.1, 138.7, 136.9, 135.7, 134.9, 132.8, 131.4, 130.7, 129.6, 128.9, 128.4, 128.3, 127.9, 127.4, 127.4, 126.8, 125.9, 125.8, 125.1, 124.9, 124.9, 124.7, 124.6, 124.5, 123.2, 45.2, 37.1, 34.3, 31.1, 30.3 ; **HRMS (ESI-TOF)** *m/z*: $[M - H]^-$ calcd for $C_{40}H_{39}O_2$ 551.2945; found 551.2971.

4-(3,5-di-*tert*-butyl-4-chlorophenyl)-4-(9H-fluoren-2-yl)-1-phenylbutan-1-one (15w) :



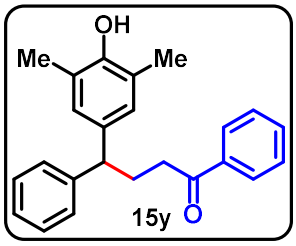
The product **15w** was obtained in 76% yield (103 mg, White solid); **mp** = 114-115 °C; R_f = 0.41 (10% EtOAc in petroleum ether); **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 7.84 (d, *J* = 7.7 Hz, 2H), 7.72 (dd, *J* = 11.9, 7.7 Hz, 2H), 7.50 (t, *J* = 6.4 Hz, 2H), 7.46 (s, 1H), 7.38 (dd, *J* = 13.2, 5.6 Hz, 2H), 7.32 (t, *J* = 7.9 Hz, 2H), 7.28 – 7.24 (m, 1H), 7.09 (s, 2H), 5.05 (d, *J* = 1.6 Hz, 1H), 3.99 (t, *J* = 7.6 Hz, 1H), 3.85 (s, 2H), 2.94 (t, *J* = 7.2 Hz, 2H), 2.50 (dd, *J* = 14.3, 7.1 Hz, 2H), 1.40 (s, 18H); **^{13}C{^{1}H} NMR (100 MHz,$CDCl_3$) δ** = 200.4, 152.1, 143.6, 143.2, 141.6, 139.8, 137.0, 135.7, 135.2, 132.9, 128.5, 128.0, 126.6, 126.5, 126.3, 125.0, 124.6, 124.2, 119.8, 119.6, 50.8, 37.2, 36.9, 34.4, 30.9, 30.3; **HRMS (ESI-TOF)** *m/z*: $[M - H]^-$ calcd for $C_{37}H_{39}O_2$ 515.2945; found 515.2963.

4-(4-hydroxy-3,5-diisopropylphenyl)-1,4-diphenylbutan-1-one (15x) :



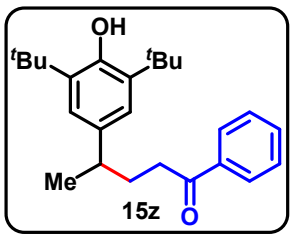
The product **15x** was obtained in 92% yield (138 mg, White solid); **mp** = 118-119 °C; R_f = 0.35 (10% EtOAc in petroleum ether); **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 7.84 – 7.82 (m, 2H), 7.51 – 7.47 (m, 1H), 7.38 (t, *J* = 7.6 Hz, 2H), 7.27 (d, *J* = 4.4 Hz, 4H), 7.16 (dq, *J* = 8.5, 4.3 Hz, 1H), 6.93 (s, 2H), 4.79 (s, 1H), 3.93 (t, *J* = 7.9 Hz, 1H), 3.16 – 3.06 (m, 2H), 2.97 – 2.84 (m, 2H), 2.53 – 2.39 (m, 2H), 1.22 (d, *J* = 2.7 Hz, 6H), 1.20 (d, *J* = 2.7 Hz, 6H) ; **^{13}C{^{1}H} NMR (100 MHz,$CDCl_3$) δ** = 200.4, 148.4, 145.0, 136.9, 136.1, 133.6, 132.9, 128.4, 128.4, 128.0, 127.7, 126.0, 122.8, 50.5, 37.1, 30.5, 27.3, 22.7; **HRMS (ESI-TOF)** *m/z*: $[M - H]^-$ calcd for $C_{28}H_{31}O_2$ 399.2319; found 399.2338.

4-(4-hydroxy-3,5-dimethylphenyl)-1,4-diphenylbutan-1-one (15y) :



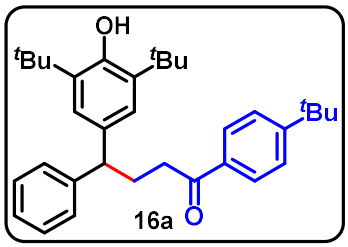
The product **15y** was obtained in 63% yield (104 mg, sticky solid); R_f = 0.26 (10% EtOAc in petroleum ether); **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 7.85 – 7.83 (m, 2H), 7.52 – 7.48 (m, 1H), 7.38 (dd, *J* = 10.6, 4.7 Hz, 2H), 7.28 – 7.26 (m, 4H), 7.16 (ddd, *J* = 8.6, 6.1, 2.8 Hz, 1H), 6.86 (s, 2H), 4.69 (s, 1H), 3.86 (t, *J* = 8.0 Hz, 1H), 2.93 – 2.89 (m, 2H), 2.44 (dd, *J* = 15.2, 7.7 Hz, 2H), 2.18 (s, 6H); **^{13}C{^{1}H} NMR (100 MHz,$CDCl_3$) δ** = 200.3, 150.6, 145.0, 136.9, 135.9, 132.9, 128.5, 128.4, 128.0, 127.9, 127.7, 126.1, 123.0, 49.8, 37.0, 30.0, 16.0; **HRMS (ESI-TOF)** *m/z*: $[M - H]^-$calcd for $C_{24}H_{23}O_2$ 343.1693; found 343.1710.

4-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-1-phenylpentan-1-one (15z) :



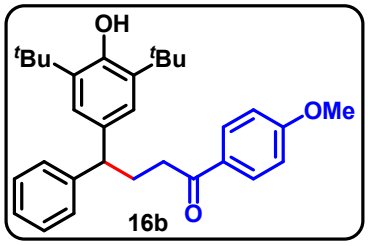
The product **15z** was obtained in 89% yield (140 mg, White solid); **mp** = 93-94 °C; R_f = 0.59 (10% EtOAc in petroleum ether); **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 7.87 – 7.84 (m, 2H), 7.55 – 7.51 (m, 1H), 7.44 – 7.40 (m, 2H), 6.98 (s, 2H), 5.05 (s, 1H), 2.92 – 2.77 (m, 2H), 2.78 – 2.67 (m, 1H), 2.07 – 1.89 (m, 2H), 1.43 (s, 18H), 1.29 (d, *J* = 7.0 Hz, 3H) ; **^{13}C{^{1}H} NMR (100 MHz,$CDCl_3$) δ** = 200.8, 151.9, 137.1, 137.0, 135.7, 132.8, 128.5, 128.0, 123.4, 39.3, 36.9, 34.4, 33.2, 30.4, 22.4 ; **HRMS (ESI-TOF)** *m/z*: [M – H]$^-$calcd for $C_{25}H_{33}O_2$ 365.2475; found 365.2493.

1-(4-(*tert*-butyl)phenyl)-4-(3,5-di-tert-butyl-4-hydroxyphenyl)-4-phenylbutan-1-one (16a) :



The product **16a** was obtained in 71% yield (117 mg, White solid); **mp** = 99-100 °C; R_f = 0.62 (10% EtOAc in petroleum ether); **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 7.81 (d, *J* = 8.3 Hz, 2H), 7.45 (d, *J* = 8.4 Hz, 2H), 7.32 (d, *J* = 4.4 Hz, 4H), 7.23 – 7.18 (m, 1H), 7.07 (s, 2H), 5.07 (s, 1H), 3.94 (t, *J* = 7.9 Hz, 1H), 2.93 – 2.90 (m, 2H), 2.48 (dd, *J* = 14.8, 7.0 Hz, 2H), 1.43 (s, 18H), 1.35 (s, 9H); **^{13}C{^{1}H} NMR (100 MHz,$CDCl_3$) δ** = 200.0, 156.5, 152.1, 144.9, 135.6, 135.0, 134.4, 128.4, 128.0, 127.9, 126.1, 125.4, 124.3, 50.7, 37.0, 35.0, 34.3, 31.0, 30.8, 30.3; **HRMS (ESI-TOF)** *m/z*: [M – H]$^-$ calcd for $C_{34}H_{43}O_2$ 483.3258; found 483.3274.

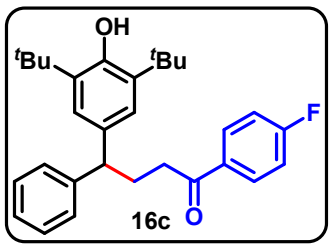
4-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-1-(4-methoxyphenyl)-4-phenylbutan-1-one (16b) :



The product **16b** was obtained in 86% yield (134 mg, White solid); **mp** = 103-104 °C; R_f = 0.35 (10% EtOAc in petroleum ether); **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 7.84 (d, *J* = 8.7 Hz, 2H), 7.30 (d, *J* = 4.3 Hz, 4H), 7.22 – 7.17 (m, 1H), 7.06 (s, 2H), 6.89 (d, *J* = 8.7 Hz, 2H), 5.06 (s, 1H), 3.92 (t, *J* = 7.9 Hz, 1H), 3.85 (s, 3H), 2.87 (td, *J* = 6.8, 2.1 Hz, 2H), 2.46 (dd, *J* = 15.0, 7.4 Hz, 2H), 1.41 (s, 18H); **^{13}C{^{1}H} NMR (100 MHz,$CDCl_3$) δ** = 198.9, 163.3, 152.1, 144.9, 135.6, 135.0, 130.3, 130.1, 128.4, 127.9, 126.1, 124.2, 113.6, 55.4, 50.8, 36.8, 34.3, 30.9, 30.3; **HRMS (ESI-TOF)** *m/z*: [M – H]$^-$ calcd for $C_{31}H_{37}O_3$ 457.2737; found 457.2750.

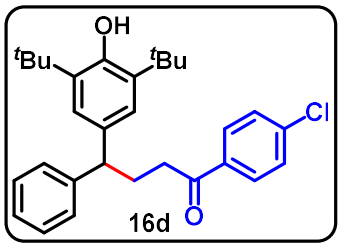
4-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-1-(4-fluorophenyl)-4-phenylbutan-1-one (16c):

The product **16c** was obtained in 86% yield (134 mg, White solid); **mp** = 82-83 °C; R_f = 0.69 (10% EtOAc in petroleum ether);



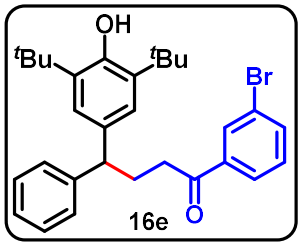
^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.89 – 7.85 (m, 2H), 7.33 – 7.30 (m, 4H), 7.23 – 7.18 (m, 1H), 7.11 – 7.08 (m, 2H), 7.06 (s, 2H), 5.07 (s, 1H), 3.92 (t, *J* = 7.9 Hz, 1H), 2.89 (td, *J* = 7.0, 2.7 Hz, 2H), 2.46 (q, *J* = 7.3 Hz, 2H), 1.41 (s, 18H); **^{13}C{^{1}H} NMR (100 MHz,$CDCl_3$) δ** = 198.7, 165.6 (d, $J_{C\text{-}F}$ = 153.99 Hz), 152.1, 144.7, 135.6, 134.8, 133.4, 133.3, 130.6 (d, $J_{C\text{-}F}$ = 8.63 Hz), 128.1 (d, $J_{C\text{-}F}$ = 62.30 Hz), 126.1, 124.2, 115.5 (d, $J_{C\text{-}F}$ = 22.04 Hz), 50.7, 37.0, 34.3, 30.7, 30.3; **^{19}F NMR (376 MHz, $CDCl_3$) δ** = -105.56; **HRMS (ESI-TOF)** *m/z*: $[M - H]^-$ calcd for $C_{30}H_{34}FO_2$ 445.2537; found 445.2560.

1-(4-chlorophenyl)-4-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-4-phenylbutan-1-one (16d) :



The product **16d** was obtained in 83% yield (131 mg, White solid); **mp** = 84-85 °C; R_f = 0.53 (10% EtOAc in petroleum ether); **^{1}H NMR (500 MHz, $CDCl_3$) δ** = 7.81 (d, *J* = 8.3 Hz, 2H), 7.40 (d, *J* = 8.5 Hz, 2H), 7.33 (d, *J* = 3.9 Hz, 4H), 7.22 (dt, *J* = 8.5, 4.1 Hz, 1H), 7.09 (s, 2H), 5.11 (s, 1H), 3.95 (t, *J* = 7.6 Hz, 1H), 2.94 – 2.91 (m, 2H), 2.50 (dd, *J* = 14.3, 7.1 Hz, 2H), 1.45 (s, 18H); **^{13}C{^{1}H} NMR (125 MHz,$CDCl_3$) δ** = 199.0, 152.1, 144.7, 139.2, 135.7, 135.2, 134.8, 129.4, 128.7, 128.4, 127.8, 126.1, 124.2, 50.7, 37.0, 34.3, 30.6, 30.3; **HRMS (ESI-TOF)** *m/z*: $[M - H]^-$ calcd for $C_{30}H_{34}ClO_2$ 461.2242; found 461.2258.

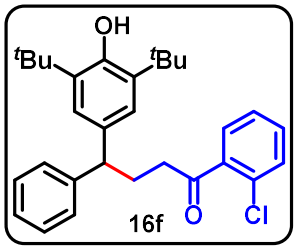
1-(3-bromophenyl)-4-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-4-phenylbutan-1-one (16e):



The product **16e** was obtained in 90% yield (155 mg, sticky solid); R_f = 0.73 (10% EtOAc in petroleum ether); **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 7.88 (t, *J* = 1.8 Hz, 1H), 7.66 – 7.63 (m, 1H), 7.55 (ddd, *J* = 8.0, 2.0, 1.0 Hz, 1H), 7.24 – 7.16 (m, 5H), 7.13 – 7.08 (m, 1H), 6.95 (s, 2H), 4.97 (s, 1H), 3.82 (t, *J* = 8.0 Hz, 1H), 2.80 (dd, *J* = 10.4, 4.9 Hz, 2H), 2.40 – 2.34 (m, 2H), 1.31 (s, 18H); **^{13}C{^{1}H} NMR (100 MHz,$CDCl_3$) δ** = 198.8, 152.1, 144.6, 138.6, 135.7, 135.6, 134.7, 131.0, 130.0, 128.5, 127.8, 126.5, 126.2, 124.2, 122.8, 50.6, 37.1, 34.3, 30.5, 30.3; **HRMS (ESI-TOF)** *m/z*: $[M - H]^-$ calcd for $C_{30}H_{34}BrO_2$ 505.1737; found 505.1761.

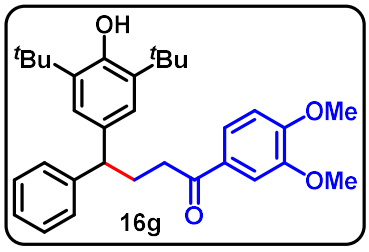
1-(2-chlorophenyl)-4-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-4-phenylbutan-1-one (16f):

The product **16f** was obtained in 77% yield (121 mg, sticky solid); R_f = 0.44 (10% EtOAc in petroleum ether); **^{1}H NMR (500 MHz, $CDCl_3$) δ** = 7.37 – 7.30 (m, 2H), 7.28 – 7.23 (m, 6H), 7.17 (td, *J* = 5.9, 2.9 Hz, 1H), 7.03 (s, 2H), 5.04 (s, 1H), 3.88 (t, *J* = 8.0 Hz, 1H), 2.92 – 2.81 (m,



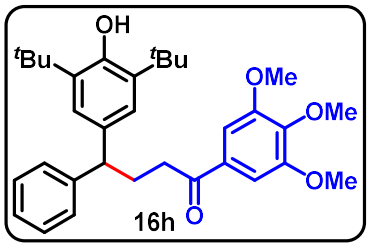
2H), 2.46 – 2.41 (m, 2H), 1.39 (s, 18H) ; **$^{13}C\{^1H\}$ NMR (125 MHz,$CDCl_3$) δ** = 203.5, 152.1, 144.7, 139.7, 135.7, 134.6, 131.4, 130.7, 130.4, 128.6, 128.4, 127.8, 126.8, 126.1, 124.3, 50.6, 41.6, 34.3, 30.4, 30.3; **HRMS (ESI-TOF)** *m/z*: $[M - H]^-$ calcd for $C_{30}H_{34}ClO_2$ 461.2243; found 461.2259.

4-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-1-(3,4-dimethoxyphenyl)-4-phenylbutan-1-one(16g) :



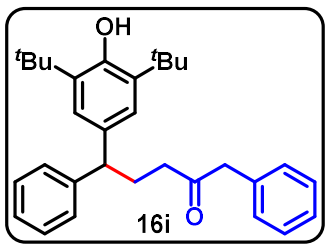
The product **16g** was obtained in 85% yield (141 mg, White solid); **mp** = 151-152 °C; R_f = 0.55 (20% EtOAc in petroleum ether); **^1H NMR (400 MHz, $CDCl_3$) δ** = 7.47 (d, *J* = 1.9 Hz, 1H), 7.40 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.28 (t, *J* = 6.5 Hz, 4H), 7.18 (dq, *J* = 8.6, 4.2 Hz, 1H), 7.04 (s, 2H), 6.80 (d, *J* = 8.4 Hz, 1H), 5.04 (s, 1H), 3.93 (s, 1H), 3.90 (s, 3H), 3.89 (s, 3H), 2.88 – 2.85 (m, 2H), 2.44 (q, *J* = 7.3 Hz, 2H), 1.39 (s, 18H); **$^{13}C\{^1H\}$ NMR (100 MHz,$CDCl_3$) δ** = 199.0, 153.0, 152.0, 148.9, 144.8, 135.6, 135.0, 130.2, 128.4, 127.8, 126.0, 124.2, 122.6, 110.0, 109.8, 55.9, 55.9, 50.7, 36.5, 34.3, 31.0, 30.3; **HRMS (ESI-TOF)** *m/z*: $[M - H]^-$ calcd for $C_{32}H_{39}O_4$ 487.2843; found 487.2857.

4-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-4-phenyl-1-(3,4,5-trimethoxyphenyl)butan-1-one (16h):



The product **16h** was obtained in 89% yield (157 mg, sticky solid); R_f = 0.54 (20% EtOAc in petroleum ether); **^1H NMR (400 MHz, $CDCl_3$) δ** = 7.31 – 7.28 (m, 4H), 7.26 (s, 1H), 7.08 (s, 2H), 7.02 (s, 2H), 5.04 (s, 1H), 3.90 (s, 1H), 3.89 (s, 3H), 3.85 (s, 6H), 2.87 (td, *J* = 7.3, 3.0 Hz, 2H), 2.44 (tdd, *J* = 10.1, 5.7, 2.8 Hz, 2H), 1.38 (s, 18H) ; **$^{13}C\{^1H\}$ NMR (100 MHz,$CDCl_3$) δ** = 199.2, 153.0, 152.1, 144.8, 135.6, 135.0, 132.3, 130.1, 128.5, 128.0, 126.1, 124.3, 105.6, 60.9, 56.2, 50.6, 36.7, 34.3, 31.0, 30.3, 29.4 ; **HRMS (ESI-TOF)** *m/z*: $[M - H]^-$ calcd for $C_{33}H_{41}O_5$ 517.2949; found 517.2960.

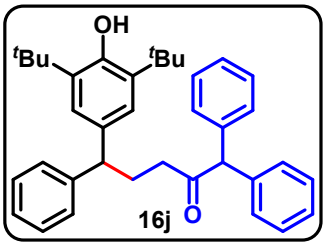
5-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-1,5-diphenylpentan-2-one (16i):



The product **16i** was obtained in 87% yield (131 mg, sticky solid); R_f = 0.60 (10% EtOAc in petroleum ether); **^1H NMR (400 MHz, $CDCl_3$) δ** = 7.30 – 7.22 (m, 5H), 7.21 – 7.14 (m, 3H), 7.14 – 7.09 (m, 2H), 6.98 (s, 2H), 5.04 (s, 1H), 3.76 (t, *J* = 7.9 Hz, 1H), 3.56 (s, 2H), 2.42 – 2.38 (m, 2H), 2.29 – 2.23 (m, 2H), 1.39 (s, 18H) ; **$^{13}C\{^1H\}$ NMR (100 MHz,$CDCl_3$) δ** = 208.2, 152.0, 144.7, 135.6, 134.8, 134.2, 129.3, 128.6,

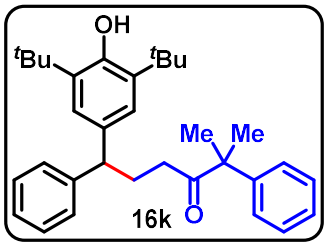
128.4, 127.8, 126.9, 126.0, 124.2, 50.4, 50.1, 40.5, 34.3, 30.3, 30.0; **HRMS (ESI-TOF)** *m/z*: [M – H]$^-$ calcd for $C_{31}H_{37}O_2$ 441.2788; found 441.2798.

5-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-1,1,5-triphenylpentan-2-one (16j):



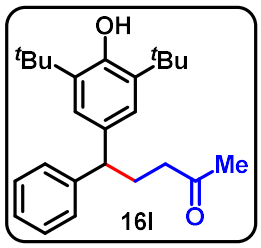
The product **16j** was obtained in 94% yield (165 mg, sticky solid); R_f = 0.56 (10% EtOAc in petroleum ether); **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 7.30 – 7.22 (m, 8H), 7.15 (dd, *J* = 8.0, 7.0 Hz, 7H), 6.97 (s, 2H), 5.03 (s, 1H), 5.00 (s, 1H), 3.77 (t, *J* = 7.9 Hz, 1H), 2.88 – 2.74 (m, 1H), 2.53 – 2.49 (m, 2H), 2.29 (dd, *J* = 14.9, 7.5 Hz, 2H), 1.37 (s, 18H) ; **^{13}C{^{1}H} NMR (100 MHz,$CDCl_3$) δ** = 208.5, 152.0, 144.6, 138.4, 138.3, 135.5, 134.7, 129.3, 128.9, 128.8, 128.6, 128.4, 127.8, 127.1, 127.0, 126.0, 124.1, 64.1, 50.3, 43.4, 41.4, 34.3, 30.3 ; **HRMS (ESI-TOF)** *m/z*: [M – H]$^-$ calcd for $C_{37}H_{41}O_2$ 517.3101; found 517.3125.

6-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-2-methyl-2,6-diphenylhexan-3-one (16k):



The product **16k** was obtained in 75% yield (120 mg, Semi-solid); R_f = 0.62 (10% EtOAc in petroleum ether); **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 7.30 – 7.25 (m, 2H), 7.23 – 7.14 (m, 5H), 7.12 – 7.07 (m, 3H), 6.90 (s, 2H), 4.99 (s, 1H), 3.64 (t, *J* = 7.3 Hz, 1H), 2.14 (d, *J* = 3.8 Hz, 4H), 1.38 (s, 3H), 1.37 (s, 3H), 1.36 (s, 18H) ; **^{13}C{^{1}H} NMR (100 MHz,$CDCl_3$) δ** = 213.1, 152.0, 144.7, 144.0, 135.5, 135.0, 128.6, 128.3, 127.8, 126.7, 126.0, 125.9, 124.2, 52.2, 50.4, 36.1, 34.3, 30.9, 30.3, 25.2, 25.1; **HRMS (ESI-TOF)** *m/z*: [M – H]$^-$ calcd for $C_{33}H_{41}O_2$ 469.3101; found 469.3123.

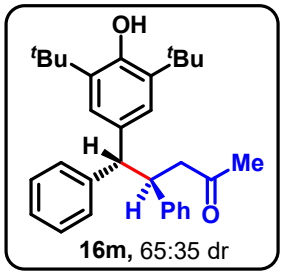
5-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-5-phenylpentan-2-one (16l):



The product **16l** was obtained in 93% yield (115 mg, White solid); **mp** = 89-90 °C; R_f = 0.62 (10% EtOAc in petroleum ether); **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 7.31 – 7.21 (m, 4H), 7.20 – 7.13 (m, 1H), 7.01 (s, 2H), 5.04 (s, 1H), 3.78 (t, *J* = 7.9 Hz, 1H), 2.38 (dd, *J* = 10.9, 5.1 Hz, 2H), 2.32 – 2.24 (m, 2H), 2.04 (s, 3H), 1.40 (s, 18H) ; **^{13}C{^{1}H} NMR (100 MHz,$CDCl_3$) δ** = ^{13}C NMR (101 MHz, $CDCl_3$) δ 208.8, 152.1, 144.7, 135.6, 134.9, 128.4, 127.8, 126.1, 124.1, 50.6, 42.2, 34.3, 30.3, 30.0, 30.0 ; **HRMS (ESI-TOF)** *m/z*: [M – H]$^-$ calcd for $C_{25}H_{33}O_2$ 365.2475; found 365.2479.

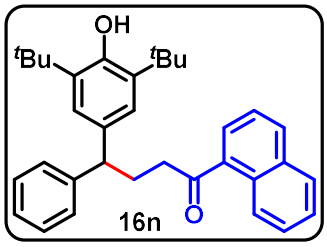
5-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-4,5-diphenylpentan-2-one (16m):

The product **16m** was obtained in 73% yield (109 mg, White solid); dr = 65:35; **mp** = 84-85 °C;



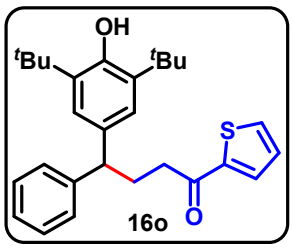
***R*$_f$** = 0.44 (10% EtOAc in petroleum ether); **^{1}H NMR (400 MHz, CDCl$_3$) δ** = 7.38 (dd, *J* = 8.1, 1.0 Hz, 1.09H$_{major\ \&\ minor}$), 7.28 (dd, *J* = 10.6, 4.9 Hz, 1.20H$_{major\ \&\ minor}$), 7.18 – 7.13 (m, 1.01H$_{major\ \&\ minor}$), 7.13 – 7.06 (m, 6.93H$_{major\ \&\ minor}$), 7.06 – 6.94 (m, 7.18H$_{major\ \&\ minor}$), 6.93 – 6.88 (m, 1.13H$_{major\ \&\ minor}$), 6.70 (s, 1.06H$_{major\ \&\ minor}$), 5.03 (s, 1H$_{major}$), 4.80 (s, 0.51H$_{minor}$), 4.06 – 3.83 (m, 3.14H$_{major\ \&\ minor}$), 2.82 – 2.59 (m, 3.12H$_{major\ \&\ minor}$), 1.77 (s, 1.58H$_{minor}$), 1.69 (s, 3.01H$_{major}$), 1.39 (s, 18H$_{major}$), 1.21 (s, 9.79H$_{minor}$) ; **^{13}C{^{1}H} NMR (100 MHz,CDCl$_3$) δ** = major diastereomer: 207.7, 152.3, 143.6, 143.4, 135.8, 133.4, 128.2, 128.0, 128.0, 127.9, 126.0, 125.6, 124.9, 58.4, 49.5, 45.9, 34.3, 30.6, 30.3 ; minor diastereomer: 207.9, 151.5, 143.4, 142.9, 134.9, 133.0, 128.7, 128.3, 128.3, 127.8, 126.4, 126.0, 124.8, 58.2, 48.8, 46.6, 34.1, 30.8, 30.1 ; **HRMS (ESI-TOF)** *m/z*: [M – H]$^-$ calcd for $C_{31}H_{37}O_2$ 441.2788; found 441.2809.

4-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-1-(naphthalen-1-yl)-4-phenylbutan-1-one (16n):



The product **16n** was obtained in 92% yield (149 mg, White solid); **mp** = 100-101 °C; ***R*$_f$** = 0.44 (10% EtOAc in petroleum ether); **^{1}H NMR (400 MHz, CDCl$_3$) δ** = 8.50 – 8.48 (m, 1H), 7.91 (d, *J* = 8.2 Hz, 1H), 7.83 (dd, *J* = 8.3, 1.0 Hz, 1H), 7.59 (dd, *J* = 7.2, 1.1 Hz, 1H), 7.54 (ddd, *J* = 8.5, 6.9, 1.6 Hz, 1H), 7.49 (ddd, *J* = 8.0, 6.9, 1.3 Hz, 1H), 7.38 (dd, *J* = 8.1, 7.3 Hz, 1H), 7.28 (dd, *J* = 8.3, 5.6 Hz, 4H), 7.17 (ddd, *J* = 8.6, 5.7, 2.8 Hz, 1H), 7.05 (s, 2H), 5.04 (s, 1H), 3.95 (t, *J* = 8.0 Hz, 1H), 3.01 – 2.97 (m, 2H), 2.55 – 2.49 (m, 2H), 1.38 (s, 18H) ; **^{13}C{^{1}H} NMR (100 MHz,CDCl$_3$) δ** = 204.7, 152.1, 144.8, 136.3, 135.7, 134.8, 133.9, 132.2, 130.0, 128.5, 128.3, 127.9, 127.7, 127.1, 126.3, 126.1, 125.7, 124.3, 50.7, 40.8, 34.3, 31.0, 30.3 ; **HRMS (ESI-TOF)** *m/z*: [M – H]$^-$ calcd for $C_{34}H_{37}O_2$ 477.2788; found 477.2814.

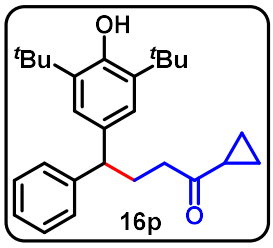
4-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-4-phenyl-1-(thiophen-2-yl)butan-1-one (16o):



The product **16o** was obtained in 89% yield (81 mg, White solid); **mp** = 97-98 °C; ***R*$_f$** = 0.41 (10% EtOAc in petroleum ether); **^{1}H NMR (400 MHz, CDCl$_3$) δ** = 7.57 (dd, *J* = 4.9, 1.1 Hz, 1H), 7.50 (dd, *J* = 3.8, 1.1 Hz, 1H), 7.29 (s, 2H), 7.28 (s, 2H), 7.21 – 7.16 (m, 1H), 7.06 – 7.04 (m, 1H), 7.04 (s, 2H), 5.05 (s, 1H), 3.90 (t, *J* = 8.0 Hz, 1H), 2.84 (dd, *J* = 8.6, 6.7 Hz, 2H), 2.49 – 2.43 (m, 2H), 1.39 (s, 18H); **^{13}C{^{1}H} NMR (100 MHz,CDCl$_3$) δ** = 193.2, 152.1, 144.7, 144.4, 135.6, 134.7, 133.4, 131.7, 128.4, 127.9, 127.9,

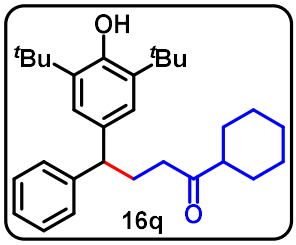
126.1, 124.3, 50.6, 37.8, 34.3, 31.0, 30.3; **HRMS (ESI-TOF)** *m/z*: [M – H]$^-$ calcd for $C_{28}H_{33}O_2S$ 433.2196; found 433.2217.

1-cyclopropyl-4-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-4-phenylbutan-1-one (16p):



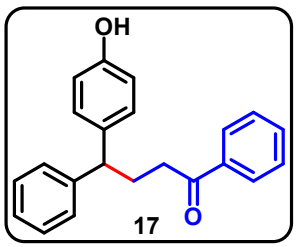
The product **16p** was obtained in 71% yield (94 mg, White solid); **mp** = 114-115 °C; R_f = 0.47 (10% EtOAc in petroleum ether); **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 7.31 – 7.24 (m, 4H), 7.19 – 7.15 (m, 1H), 7.01 (s, 2H), 5.03 (s, 1H), 3.80 (t, *J* = 7.9 Hz, 1H), 2.50 (dd, *J* = 8.3, 6.5 Hz, 2H), 2.31 (q, *J* = 7.1 Hz, 2H), 1.85 – 1.79 (m, 1H), 1.40 (s, 18H), 0.99 – 0.95 (m, 2H), 0.82 – 0.78 (m, 2H); **^{13}C{^{1}H} NMR (100 MHz,$CDCl_3$) δ** = 210.8, 152.0, 144.8, 135.6, 135.0, 128.4, 127.9, 126.0, 124.2, 50.7, 41.9, 34.3, 30.3, 30.2, 20.5, 10.6; **HRMS (ESI-TOF)** *m/z*: [M – H]$^-$ calcd for $C_{27}H_{35}O_2$ 391.2632; found 391.2649.

1-cyclohexyl-4-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-4-phenylbutan-1-one (16q):



The product **16q** was obtained in 82% yield (121 mg, Semi-solid); R_f = 0.78 (10% EtOAc in petroleum ether); **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 7.32 – 7.26 (m, 4H), 7.21 – 7.16 (m, 1H), 7.04 (s, 2H), 5.07 (s, 1H), 3.82 (t, *J* = 7.8 Hz, 1H), 2.43 – 2.36 (m, 2H), 2.34 – 2.22 (m, 3H), 1.75 – 1.73 (m, 5H), 1.43 (s, 18H), 1.29 – 1.19 (m, 5H); **^{13}C{^{1}H} NMR (100 MHz,$CDCl_3$) δ** = 214.0, 152.0, 144.9, 135.5, 134.9, 128.3, 127.8, 126.0., 124.2, 50.8, 50.6, 39.0, 34.3, 30.3, 29.9, 28.4, 25.8, 25.6, 12.6, 7.5; **HRMS (ESI-TOF)** *m/z*: [M – H]$^-$ calcd for $C_{30}H_{41}O_2$ 433.3101; found 433.3111.

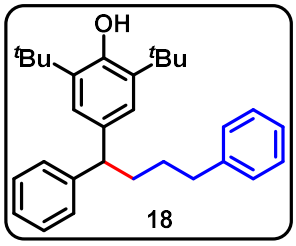
4-(4-hydroxyphenyl)-1,4-diphenylbutan-1-one (17):



The product **17** was obtained in 89% yield (66 mg, Yellow solid); **mp** = 77-78 °C; R_f = 0.56 (10% EtOAc in petroleum ether); **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 7.84 – 7.82 (m, 2H), 7.51 – 7.47 (m, 1H), 7.40 – 7.36 (m, 2H), 7.27 (d, *J* = 1.3 Hz, 3H), 7.26 (s, 4H), 7.20 – 7.14 (m, 2H), 4.01 (t, *J* = 7.9 Hz, 1H), 2.93 – 2.89 (m, 2H), 2.49 (dd, *J* = 15.0, 7.8 Hz, 2H) ; **^{13}C{^{1}H} NMR (100 MHz,$CDCl_3$) δ** = 199.9, 144.4, 136.9, 132.9, 128.5, 128.5, 127.9, 127.8, 126.3, 50.5, 36.9, 29.8.

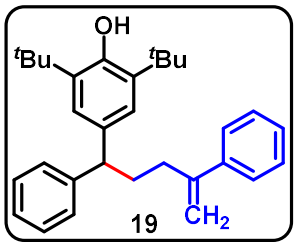
2,6-di-*tert*-butyl-4-(1,4-diphenylbutyl)phenol (18):

The product **18** was obtained in 95% yield (92 mg, sticky solid); R_f = 0.74 (10% EtOAc in petroleum ether); **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 7.35 – 7.29 (m, 6H), 7.24 – 7.18 (m, 4H), 7.08 (s, 2H), 5.08 (s, 1H), 3.89 (t, *J* = 7.8 Hz, 1H), 2.70 (t, *J* = 7.6 Hz, 2H), 2.16 – 2.07 (m, 2H), 1.70



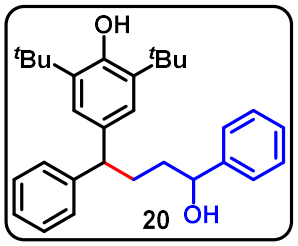
– 1.62 (m, 2H), 1.47 (s, 18H) ; **$^{13}C\{^1H\}$ NMR (100 MHz,$CDCl_3$) δ** = 151.9, 145.6, 142.5, 135.6, 135.4, 128.4, 128.3, 128.2, 127.8, 125.8, 125.6, 124.2, 51.3, 35.9, 35.8, 34.3, 30.3, 29.9 ; **HRMS (ESI-TOF)** *m/z*: $[M - H]^-$ calcd for $C_{30}H_{37}O$ 413.2839; found 413.2859.

2,6-di-*tert*-butyl-4-(1,4-diphenylpent-4-en-1-yl)phenol (19):



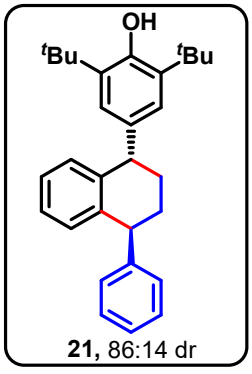
The product **19** was obtained in 63% yield (62 mg, sticky solid); R_f = 0.78 (10% EtOAc in petroleum ether); **^1H NMR (400 MHz, $CDCl_3$) δ** = 7.35 – 7.19 (m, 10H), 6.98 (s, 2H), 5.26 (s, 1H), 5.01 (s, 2H), 3.84 (t, *J* = 7.8 Hz, 1H), 2.46 – 2.42 (m, 2H), 2.13 (dd, *J* = 15.5, 7.8 Hz, 2H), 1.38 (s, 18H); **$^{13}C\{^1H\}$ NMR (100 MHz,$CDCl_3$) δ** = 151.9, 148.4, 145.3, 141.1, 135.5, 135.3, 128.3, 128.2, 127.9, 127.3, 126.1, 125.9, 124.3, 112.5, 51.0, 35.1, 34.3, 33.9, 30.3; **HRMS (ESI-TOF)** *m/z*: $[M - H]^-$ calcd for $C_{31}H_{37}O$ 425.2839; found 425.2843.

2,6-di-*tert*-butyl-4-(4-hydroxy-1,4-diphenylbutyl)phenol (20):



The product **20** was obtained in 87% yield (87 mg, sticky solid); R_f = 0.40 (10% EtOAc in petroleum ether); **^1H NMR (400 MHz, $CDCl_3$) δ** = 7.31 – 7.17 (m, 9H), 7.14 – 7.10 (m, 1H), 6.96 (d, *J* = 3.3 Hz, 2H), 5.00 (s, 1H), 4.66 – 4.62 (m, 1H), 3.78 – 3.74 (m, 1H), 2.17 – 2.06 (m, 1H), 2.01 – 1.83 (m, 2H), 1.81 – 1.70 (m, 1H), 1.70 – 1.60 (m, 1H), 1.37 (s, 18H) ; **$^{13}C\{^1H\}$ NMR (100 MHz,$CDCl_3$) δ** = 151.9, 145.4, 145.2, 144.5, 135.5, 135.4, 135.2, 128.4, 128.4, 128.3, 127.8, 127.7, 127.5, 127.5, 125.9, 125.9, 124.1, 124.1, 74.6, 74.4, 51.3, 51.2, 37.5, 37.4, 34.3, 32.4, 32.2, 30.3; **HRMS (ESI-TOF)** *m/z*: $[M - H]^-$ calcd for $C_{30}H_{37}O_2$ 429.2788; found 429.2798.

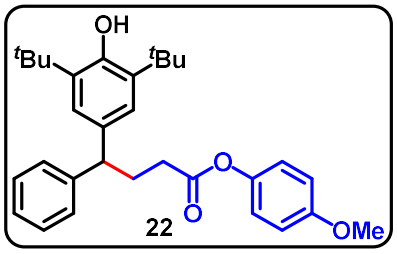
2,6-di-*tert*-butyl-4-(4-phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)phenol (21):



The product **21** was obtained in 94% yield (90 mg, White solid); dr = 86:14, **mp** = 151-152 °C; R_f = 0.78 (10% EtOAc in petroleum ether); **^1H NMR (400 MHz, $CDCl_3$) δ** = 7.32 – 7.27 (m, $2.21H_{major\ \&\ minor}$), 7.23 – 7.17 (m, $1.66H_{major\ \&\ minor}$), 7.15 (dd, *J* = 5.2, 3.2 Hz, $2.14H_{major\ \&\ minor}$), 7.07 (ddd, *J* = 13.4, 7.2, 3.1 Hz, $0.56H_{major\ \&\ minor}$), 7.03 – 6.98 (m, $2.18H_{major\ \&\ minor}$), 6.95 – 6.88 (m, $3.47H_{major\ \&\ minor}$), 6.85 – 6.83 (m, $1H_{major\ \&\ minor}$), 5.06 (s, $1H_{major}$), 5.03 (s, $0.16H_{minor}$), 4.26 – 4.19 (m,

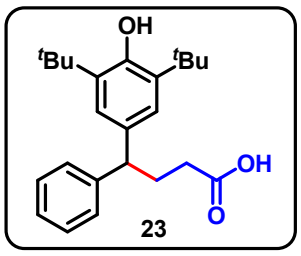
1.16H$_{major\ \&\ minor}$), 4.13 (dd, *J* = 11.0, 7.7 Hz, 1.16H$_{major\ \&\ minor}$), 2.28 – 2.17 (m, 2.15H$_{major\ \&\ minor}$), 1.95 – 1.84 (m, 2.32H$_{major\ \&\ minor}$), 1.41 (s, 20.88H$_{major\ \&\ minor}$) ; **^{13}C{^{1}H} NMR (100 MHz,CDCl$_3$) δ** = major diastereomer: 151.9, 147.7, 140.8, 139.8, 137.7, 135.5, 135.4, 129.8, 129.7, 128.8, 128.3, 126.0, 125.8, 125.7, 125.3, 46.3, 46.2, 34.3, 32.1, 31.7, 30.4 ; minor diastereomer: 151.8, 147.5, 140.5, 139.4, 138.0, 135.4, 130.5, 130.0, 128.9, 128.1, 126.1, 126.0, 125.9, 125.4, 45.6, 45.3, 34.4, 30.4, 30.1, 30.0 ; **HRMS (ESI-TOF)** *m/z*: [M – H]$^-$ calcd for $C_{30}H_{35}O$ 411.2682; found 411.2694.

4-methoxyphenyl 4-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-4-phenylbutanoate (22):



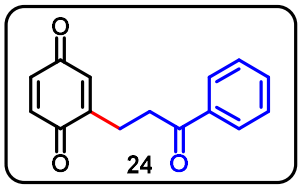
The product **22** was obtained in 74% yield (76 mg, White solid); **mp** = 82-83 °C; ***R$_f$*** = 0.44 (10% EtOAc in petroleum ether); **^{1}H NMR (400 MHz, CDCl$_3$) δ** = 7.34 (d, *J* = 4.3 Hz, 4H), 7.26 – 7.21 (m, 1H), 7.10 (s, 2H), 6.99 – 6.97 (m, 2H), 6.91 – 6.89 (m, 2H), 5.11 (s, 1H), 3.95 (t, *J* = 7.4 Hz, 1H), 3.81 (s, 3H), 2.57 – 2.46 (m, 4H), 1.45 (s, 18H) ; **^{13}C{^{1}H} NMR (100 MHz,CDCl$_3$) δ** = 172.4, 157.1, 152.1, 144.4, 144.1, 135.6, 134.5, 128.5, 127.8, 126.2, 124.2, 122.2, 114.3, 55.5, 50.7, 34.3, 33.0, 31.2, 30.3 ; **HRMS (ESI-TOF)** *m/z*: [M – H]$^-$ calcd for $C_{31}H_{37}O_4$ 473.2686; found 473.2710.

4-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-4-phenylbutanoic acid (23):



The product **23** was obtained in 51% yield (20 mg, White solid); mp = 119-120 °C; ***R$_f$*** = 0.59 (20% EtOAc in petroleum ether); **^{1}H NMR (500 MHz, CDCl$_3$) δ** = 7.30 – 7.24 (m, 5H), 7.20 – 7.16 (m, 1H), 7.01 (s, 2H), 5.05 (s, 1H), 3.83 (t, *J* = 7.5 Hz, 1H), 2.38 – 2.29 (m, 4H), 1.40 (s, 18H) ; **^{13}C{^{1}H} NMR (125 MHz,CDCl$_3$) δ** = 178.9, 152.2, 144.5, 135.7, 134.5, 128.5, 127.8, 126.2, 124.2, 50.6, 34.3, 32.5, 31.0, 30.3 ; **HRMS (ESI-TOF)** *m/z*: [M – H]$^-$ calcd for $C_{24}H_{31}O_3$ 367.2268; found 367.2279.

2-(3-oxo-3-phenylpropyl)cyclohexa-2,5-diene-1,4-dione (24):



The product **24** was obtained in 20% yield (36 mg, Yellow solid); ***R$_f$*** = 0.59 (20% EtOAc in petroleum ether); **^{1}H NMR (400 MHz, CDCl$_3$) δ** = 7.95 (d, *J* = 7.6 Hz, 2H), 7.58 (t, *J* = 7.5 Hz, 1H), 7.47 (t, *J* = 7.7 Hz, 2H), 6.79 – 6.71 (m, 2H), 6.65 (d, *J* = 1.7 Hz, 1H), 3.26 (t, *J* = 7.1 Hz, 2H), 2.88 (t, *J* = 7.0 Hz, 2H) ; **^{13}C{^{1}H} NMR (100 MHz,CDCl$_3$) δ** = 197.9, 187.5, 187.4, 148.2, 136.8, 136.4, 136.3, 133.4, 133.3, 128.7, 128.0, 36.4, 24.0 ; **HRMS (ESI-TOF)** *m/z*: [M + H]$^+$

calcd for $C_{15}H_{13}O_3$ 241.0859; found 241.0855.

3.6.6 Single Crystal Analysis Data (Compound 16m):

ORTEP view of compound **16m** showing the atom-numbering scheme. The displacement ellipsoids are drawn at the 50% probability level, and H atoms are shown as small spheres with arbitrary radii**.** X-ray intensity data measurements of compound **16m** was carried out on a Bruker D8 VENTURE Kappa Duo PHOTON II CPAD diffractometer equipped with Incoatec multilayer mirrors optics. The intensity measurements were carried out with Mo micro-focus sealed tube diffraction source (MoK_α= 0.71073 Å) at 100(2) K temperature. The X-ray generator was operated at 50 kV and 1.4 mA. A preliminary set of cell constants and an orientation matrix were calculated from three sets of 36 frames. Data were collected with ω scan width of 0.5° at different settings of φ and 2θ with a frame time of 15 secs keeping the sample-to-detector distance fixed at 5.00 cm. The X-ray data collection was monitored by APEX3 program (Bruker, 2016).[18] All the data were corrected for Lorentzian, polarization and absorption effects using SAINT[19] and SADABS programs (Bruker, 2016). Using APEX3 (Bruker) program suite, the structure was solved with the ShelXS-97[20] (Sheldrick, 2008) structure solution program, using direct methods. The model was refined with version of ShelXL-2014[21] (Sheldrick, 2014) using Least Squares minimisation. All the hydrogen atoms were placed in geometrically idealized positions and constrained to ride on their parent atoms except H-atom attached to the hydroxy group. The H-atom bound to the –OH group has been located in the difference Fourier and refined isotropically. An *ORTEP* III[22] view of the compound was drawn with 50% probability displacement ellipsoids, and H atoms are shown as small spheres of arbitrary radii. Compound **16m** having molecular formula $C_{31}H_{38}O_2$, approximate dimensions 0.090 mm × 0.110 mm × 0.150 mm, was used for the X-ray crystallographic analysis. The X-ray intensity data were measured (λ = 0.71073 Å). The integration of the data using a triclinic unit cell yielded a total of 36099 reflections to a maximum θ angle of 28.70° (0.74 Å resolution), of which 6574 were independent (average redundancy5.491, completeness = 99.7%, R_{int} = 5.00%, R_{sig} = 3.65%) and 6151 (93.57%) were greater than $2\sigma(F^2)$. The final cell constants of a = 5.8692(3) Å, b = 11.1234(7) Å, c = 20.1269(13) Å, α = 97.223(2)°, β = 90.009(2)°, γ = 101.093(2)°, volume = 1278.81(13) Å^3, are based upon the refinement of the XYZ-centroids of reflections above 20 $\sigma(I)$. The calculated minimum and maximum transmission coefficients (based on crystal size) are 0.9900 and 0.9940. The structure was solved and refined using the

Bruker SHELXTL Software Package, using the space group *P*-1, with $Z = 2$ for the formula unit, $C_{31}H_{38}O_2$. The final anisotropic full-matrix least-squares refinement on F^2 with 309 variables converged at $R1 = 4.78\%$, for the observed data and $wR2 = 12.65\%$ for all data. The goodness-of-fit (*S*) was 1.056. The largest peak in the final difference electron density synthesis was 0.392 $e^-/Å^3$, and the largest hole was -0.254 $e^-/Å^3$ with an RMS deviation of 0.053 $e^-/Å^3$. On the basis of the final model, the calculated density was 1.149 g/cm^3 and *F*(000), 480 e^-.

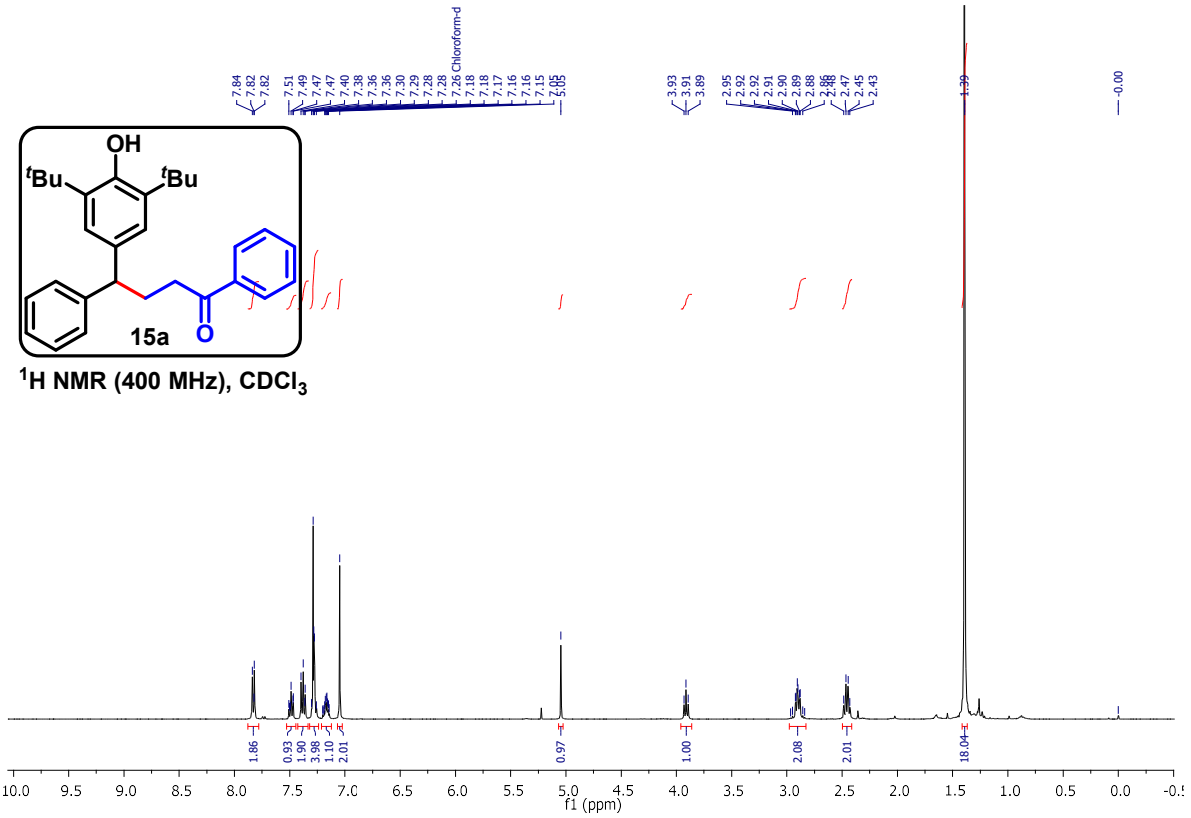
Table 3.4. Sample and crystal data for **16m**

Identification code	**16m**	
Chemical formula	$C_{31}H_{38}O_2$	
Formula weight	442.61 g/mol	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal size	0.090 x 0.110 x 0.150 mm	
Crystal system	triclinic	
Space group	P -1	
Unit cell dimensions	a = 5.8692(3) Å	α = 97.223(2)°
	b = 11.1234(7) Å	β = 90.009(2)°
	c = 20.1269(13) Å	γ = 101.093(2)°
Volume	1278.81(13) $Å^3$	
Z	2	
Density (calculated)	1.149 g/cm^3	
Absorption coefficient	0.070 mm^{-1}	
F(000)	480	

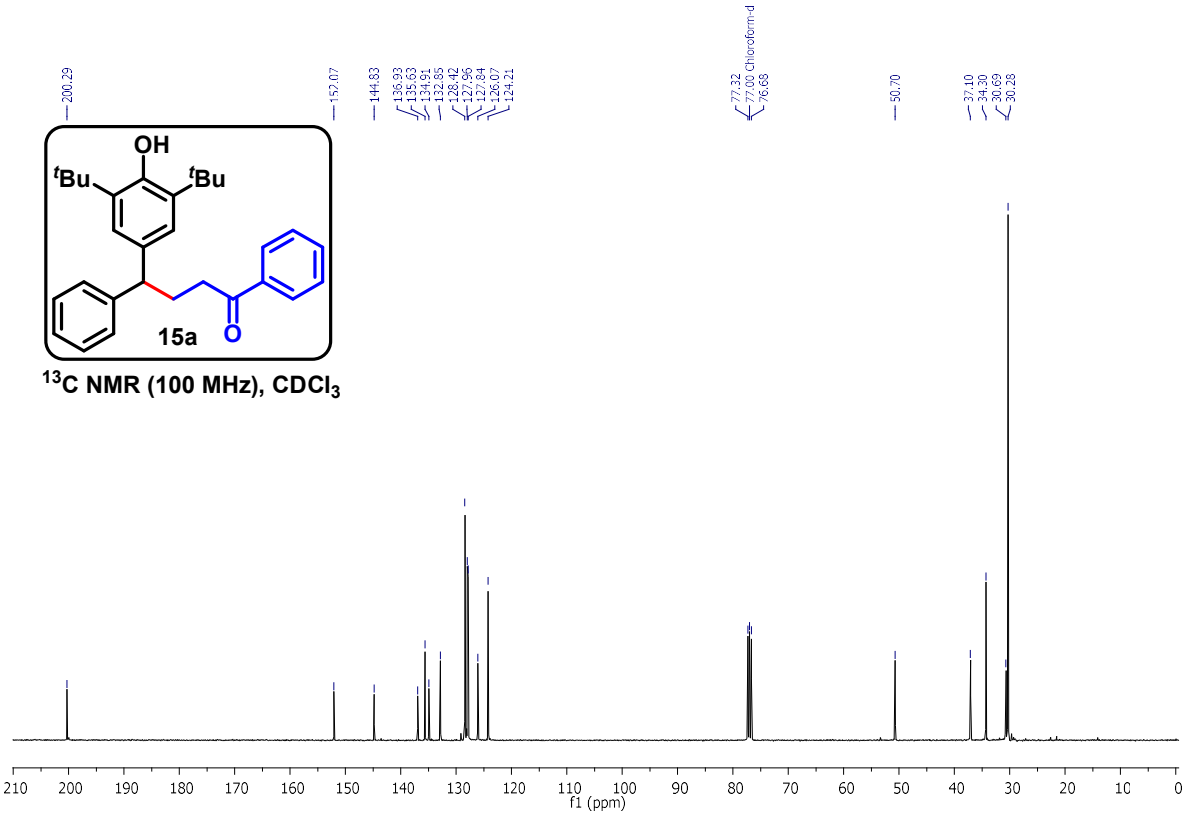
Table 3.5. Data collection and structure refinement for **16m**.

Theta range for data collection	1.88 to 28.70°	
Index ranges	-6<=h<=7, -15<=k<=14, -27<=l<=27	
Reflections collected	36099	
Independent reflections	6574 [R_{int} = 0.0500]	
Max. and min. transmission	0.9940 and 0.9900	
Structure solution technique	direct methods	
Structure solution program	SHELXT 2014/5 (Sheldrick, 2014)	
Refinement method	Full-matrix least-squares on F^2	
Refinement program	SHELXL-2018/3 (Sheldrick, 2018)	
Function minimized	$\Sigma\, w(F_o^2 - F_c^2)^2$	
Data / restraints / parameters	6574 / 0 / 309	
Goodness-of-fit on F^2	1.056	
Δ/σ_{max}	0.001	
Final R indices	6151 data; I>2σ(I)	R1 = 0.0478, wR2 = 0.1242
	all data	R1 = 0.0505, wR2 = 0.1265
Weighting scheme	$w=1/[\sigma^2(F_o^2)+(0.0575P)^2+0.6244P]$ where $P=(F_o^2+2F_c^2)/3$	
Largest diff. peak and hole	0.392 and -0.254 eÅ^{-3}	
R.M.S. deviation from mean	0.053 eÅ^{-3}	

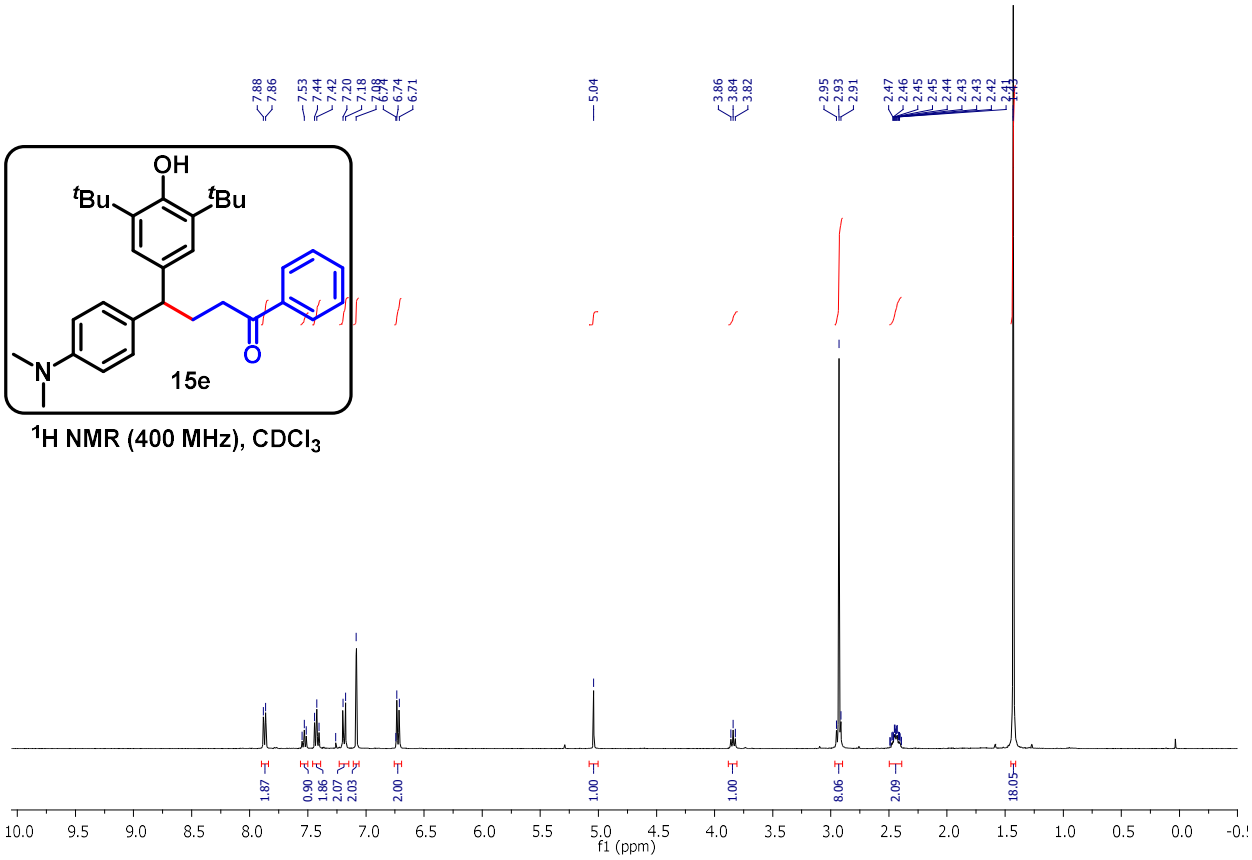
3.7 Spectral Data



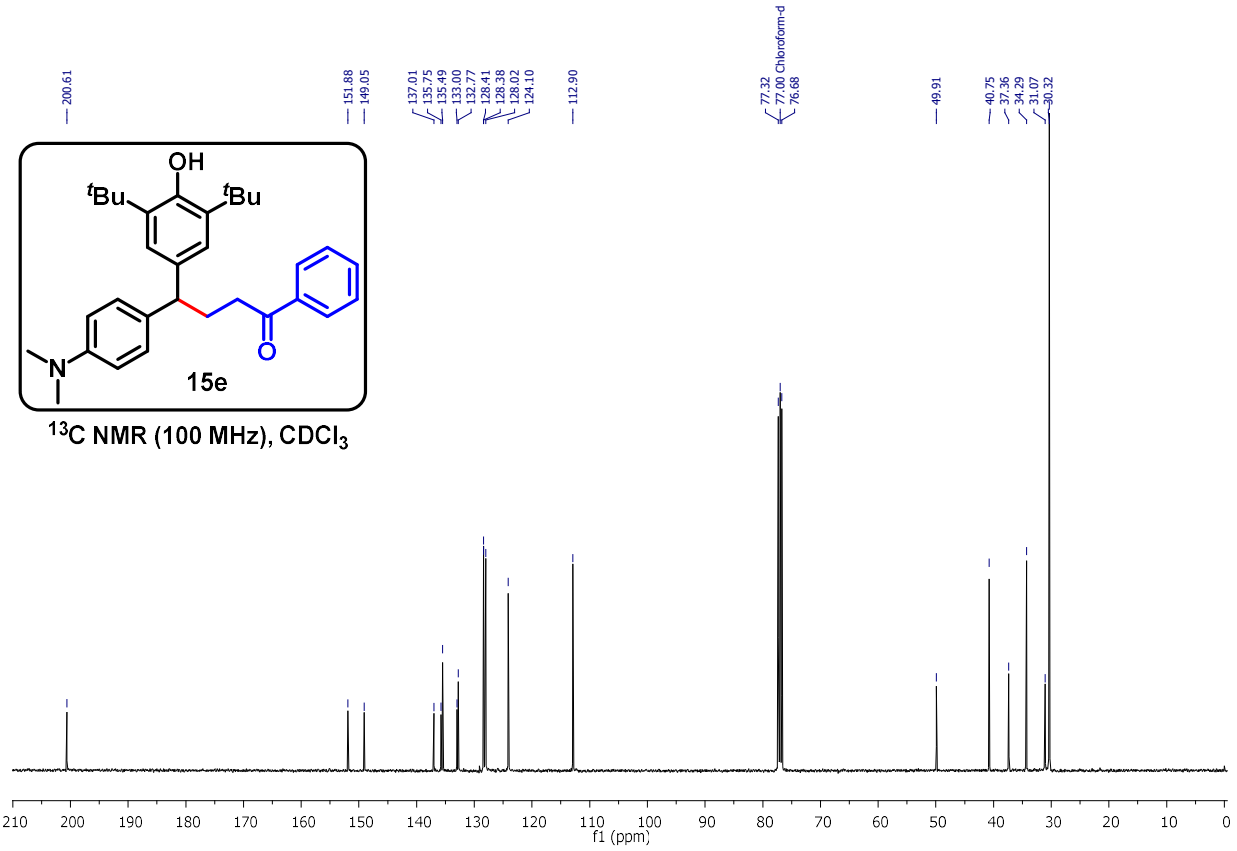
^{1}H NMR (400 MHz), $CDCl_3$



^{13}C NMR (100 MHz), $CDCl_3$



^{1}H NMR (400 MHz), $CDCl_3$



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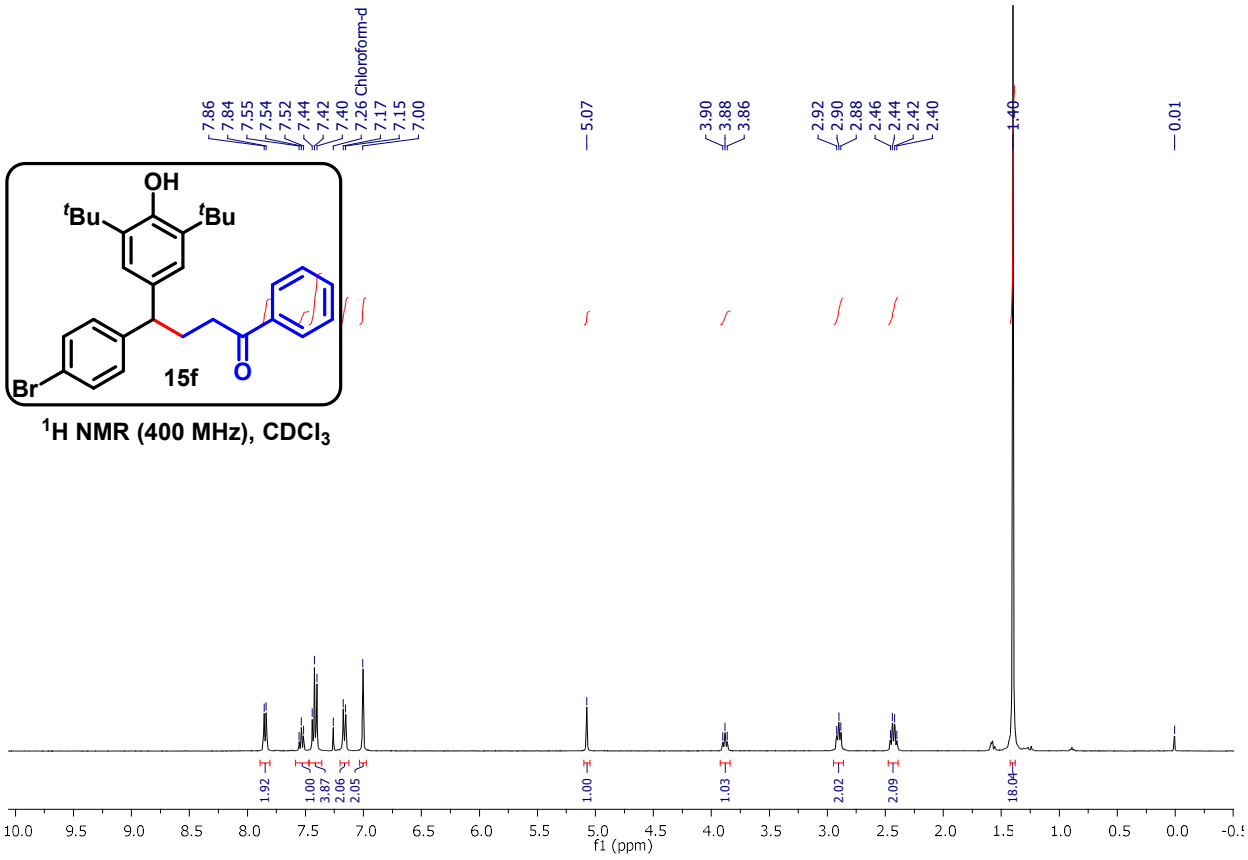

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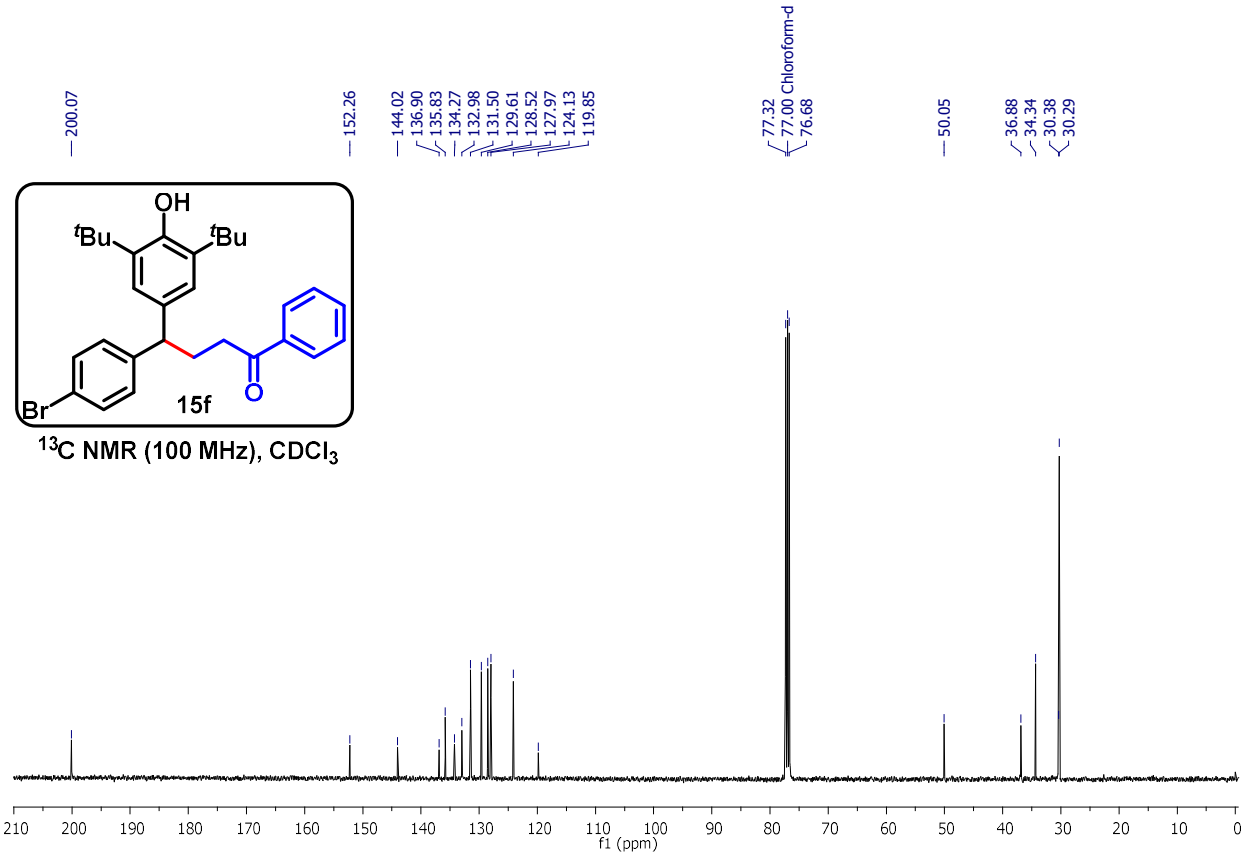
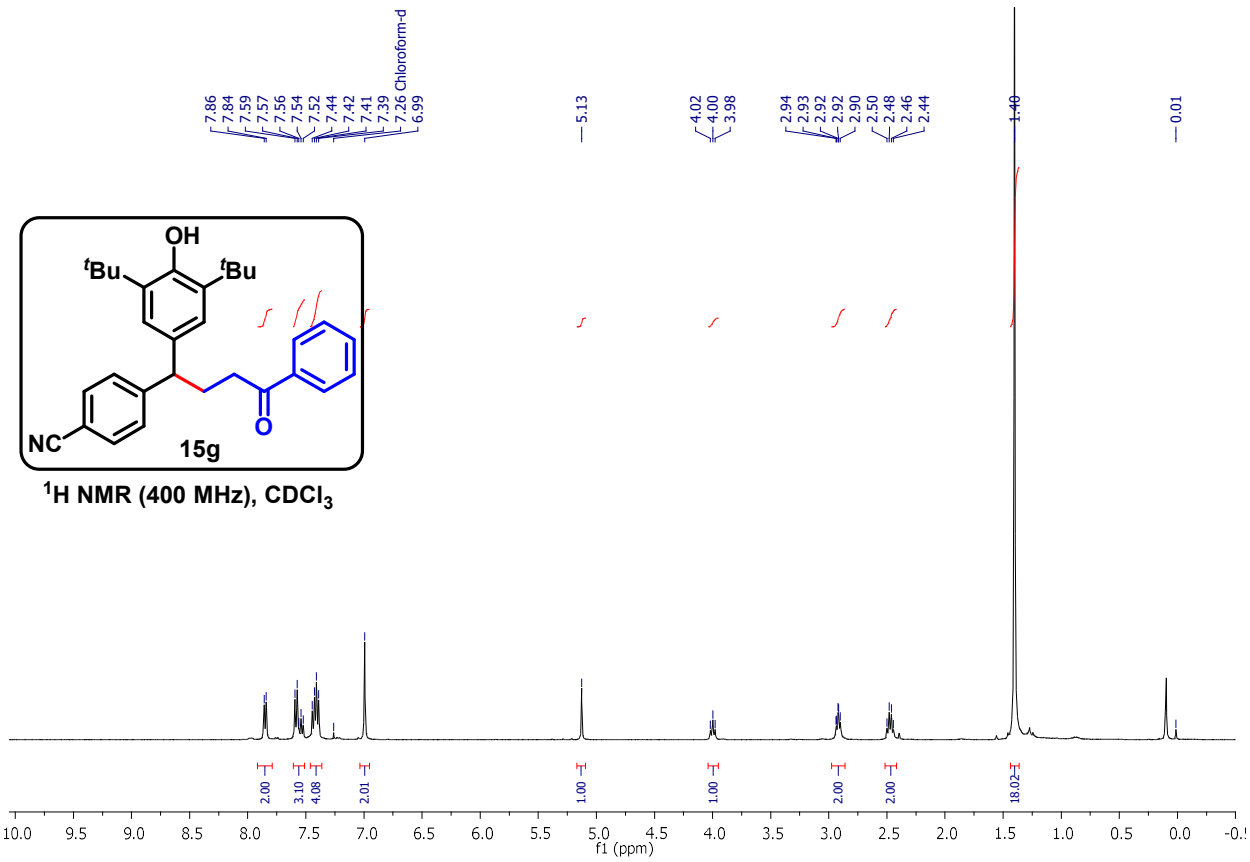
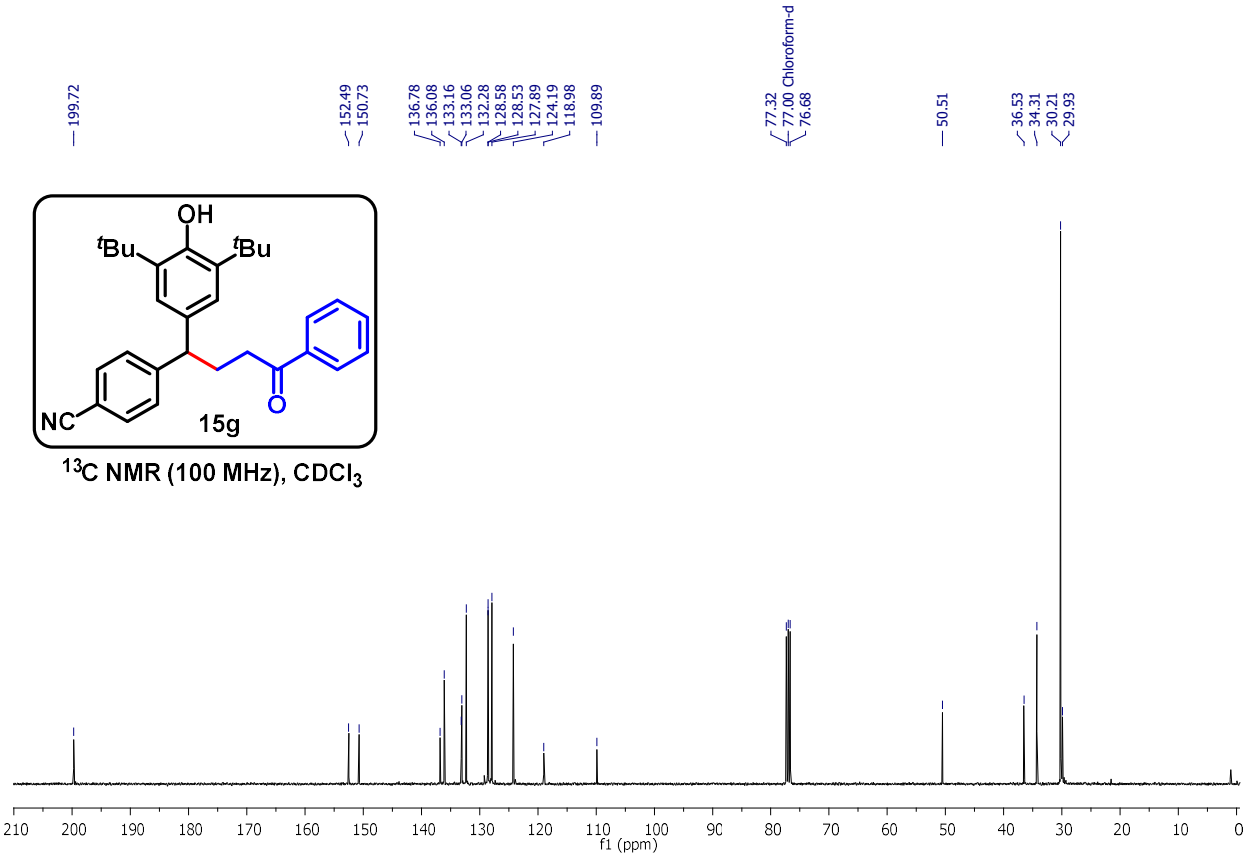


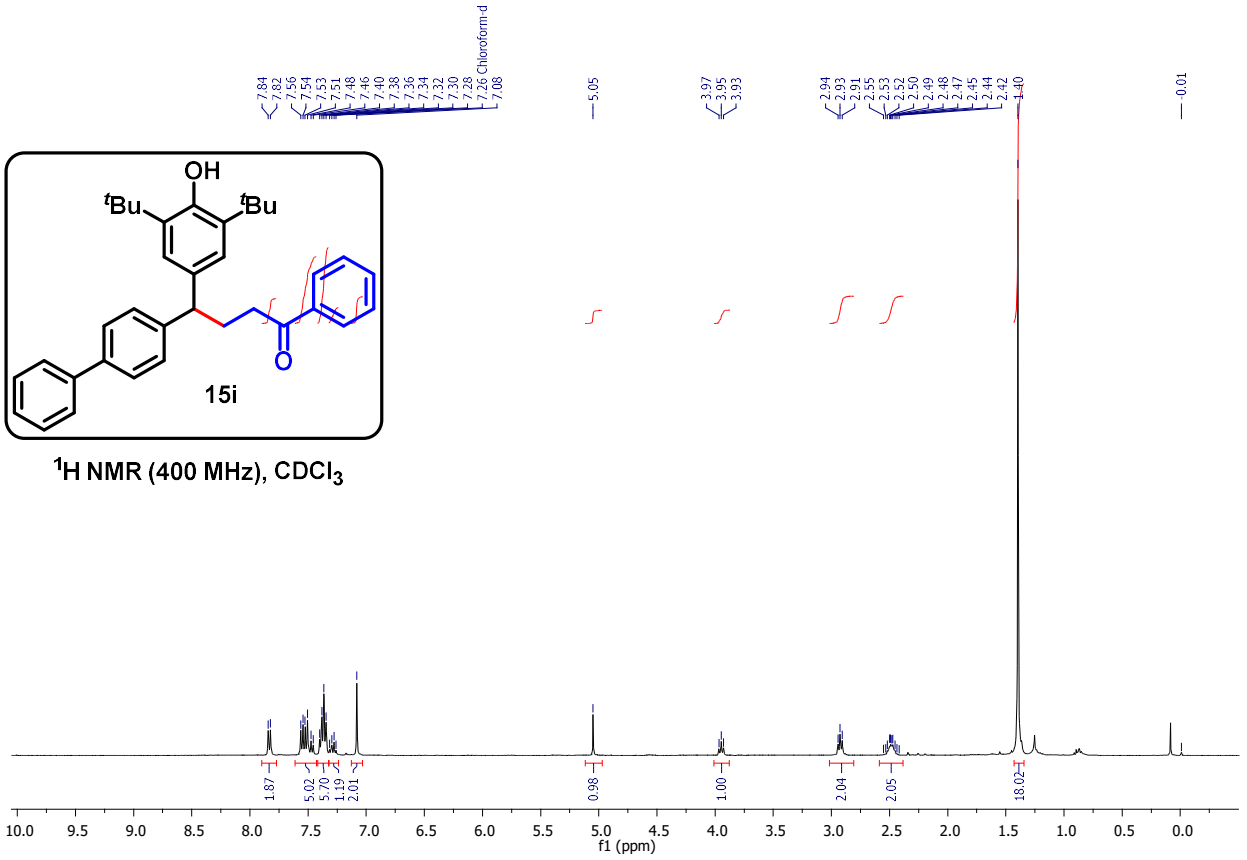
^{13}C NMR (100 MHz), $CDCl_3$



^{1}H NMR (400 MHz), $CDCl_3$



^{13}C NMR (100 MHz), $CDCl_3$



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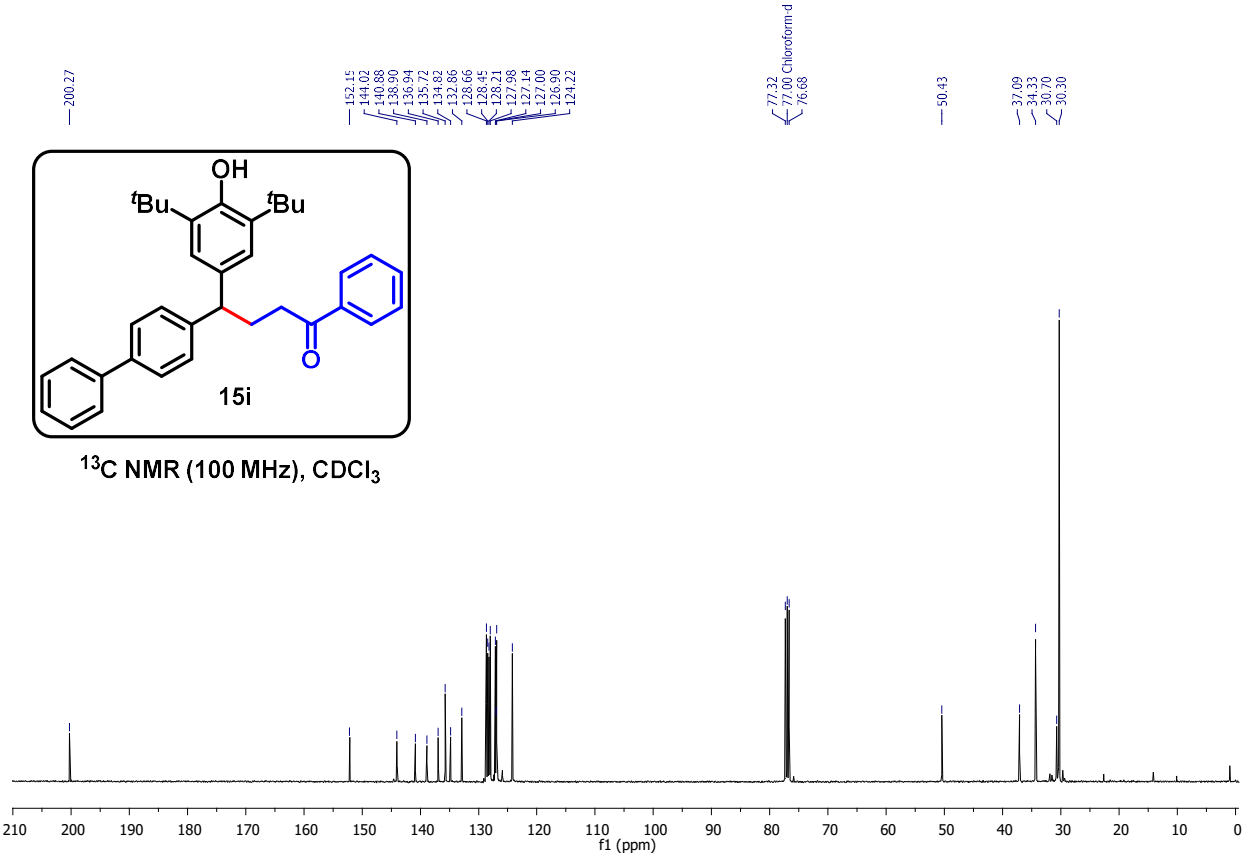
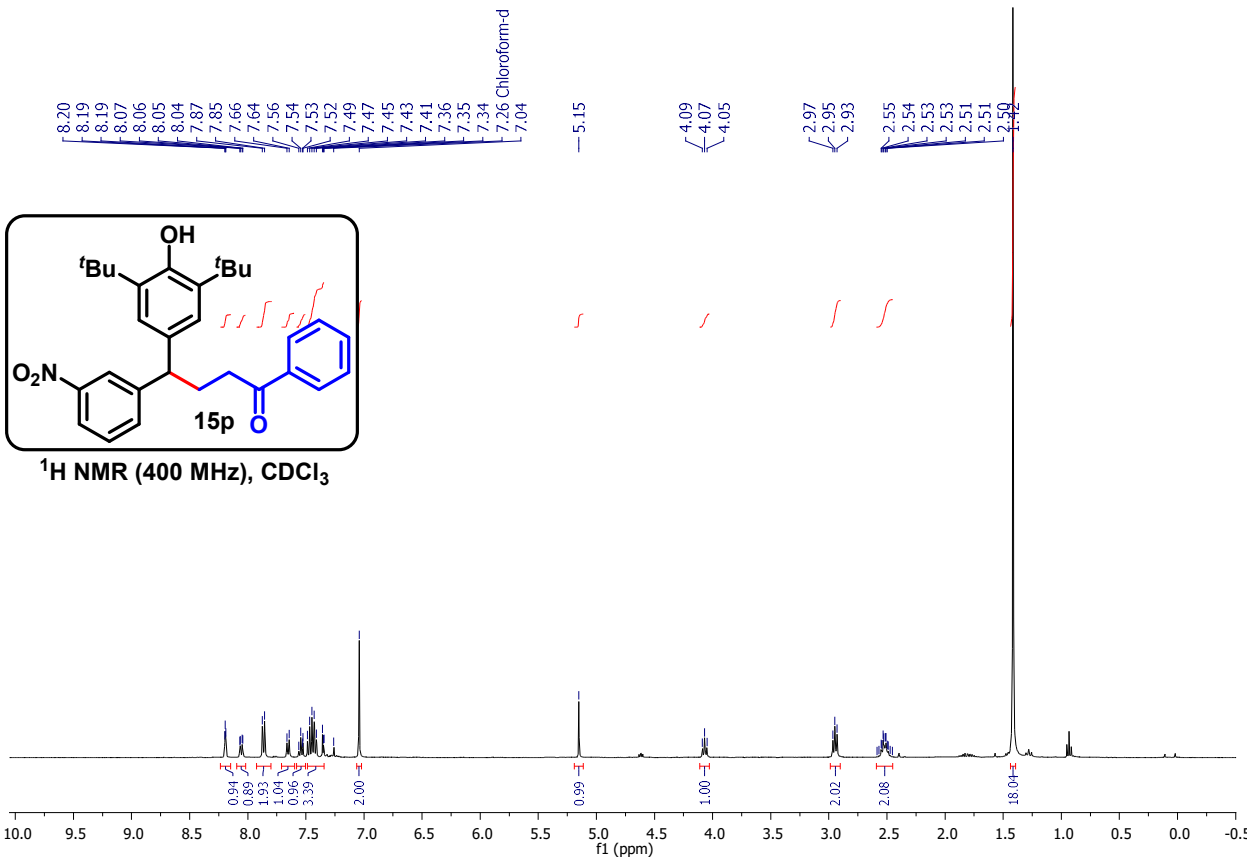
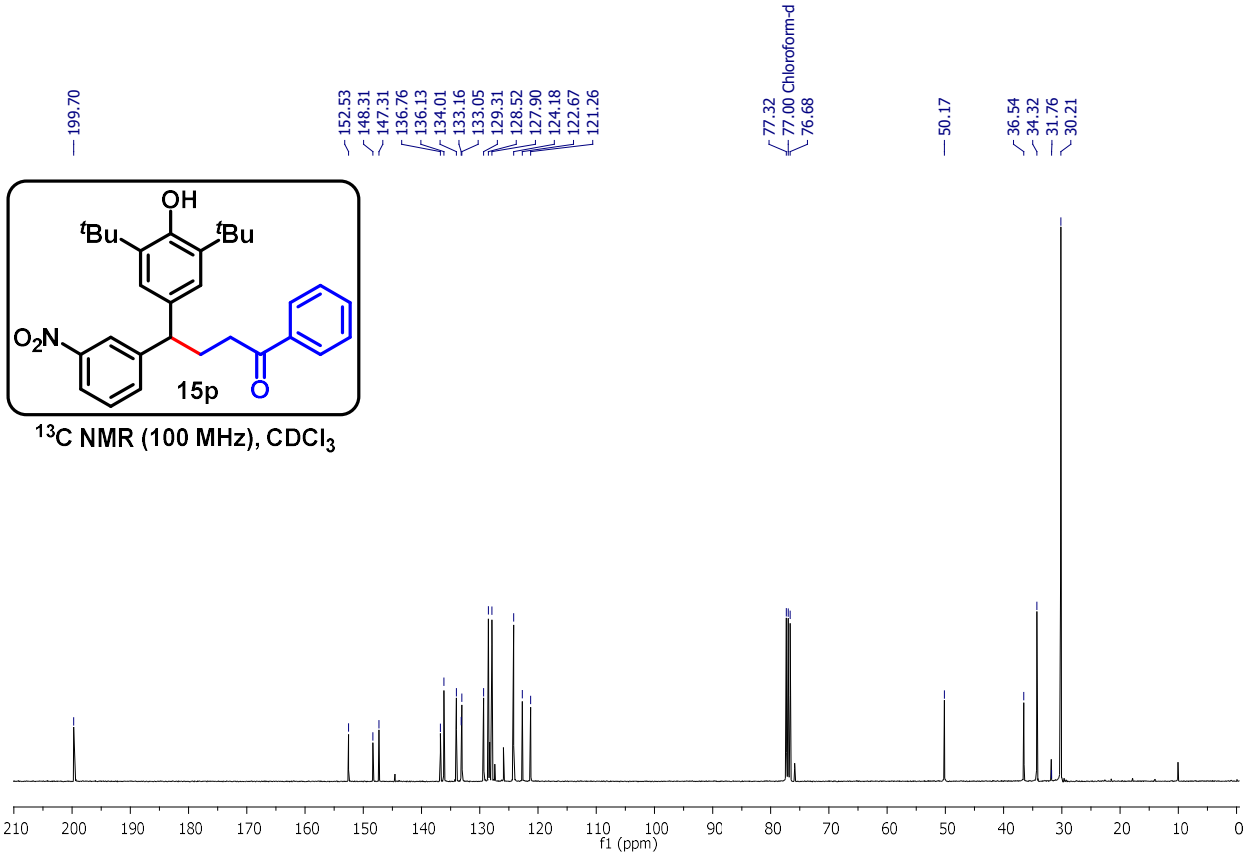


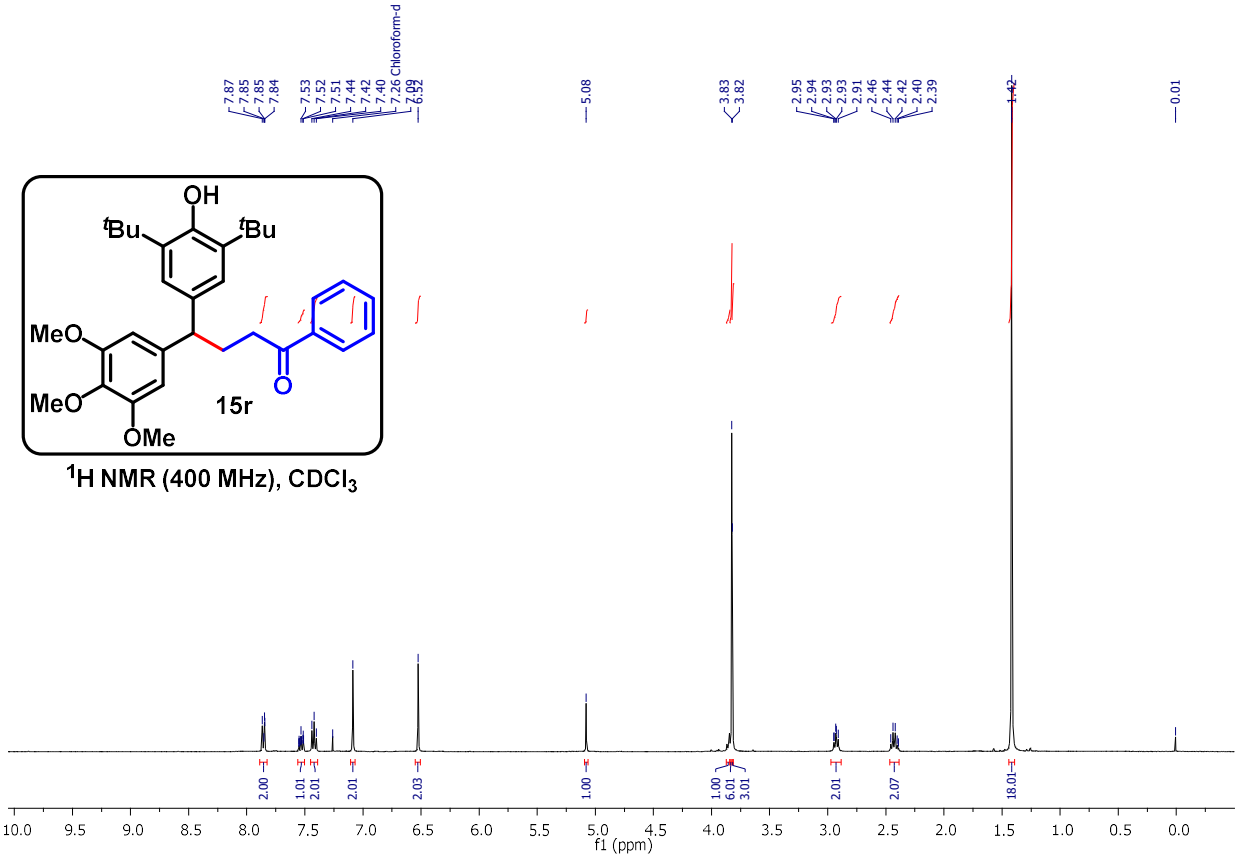
^{13}C NMR (100 MHz), $CDCl_3$



^{1}H NMR (400 MHz), $CDCl_3$



^{13}C NMR (100 MHz), $CDCl_3$



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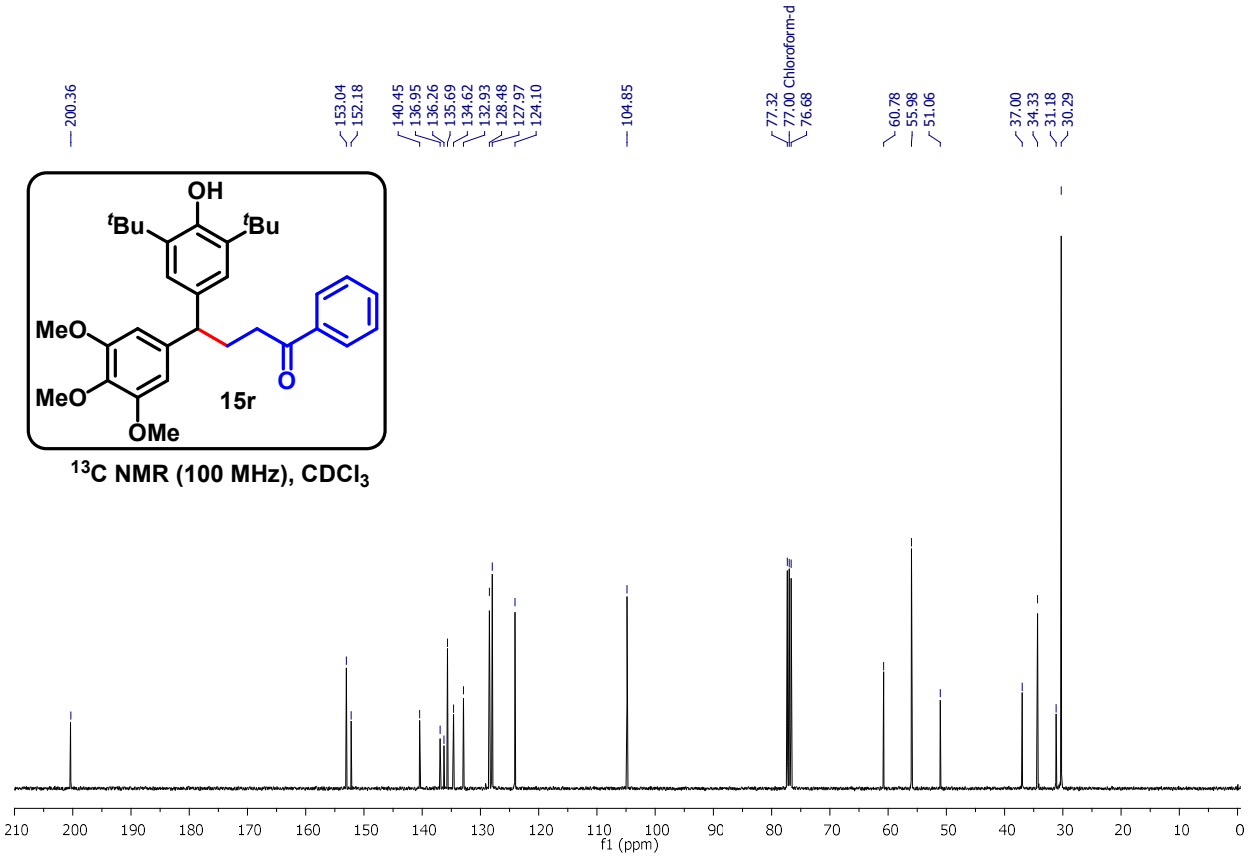

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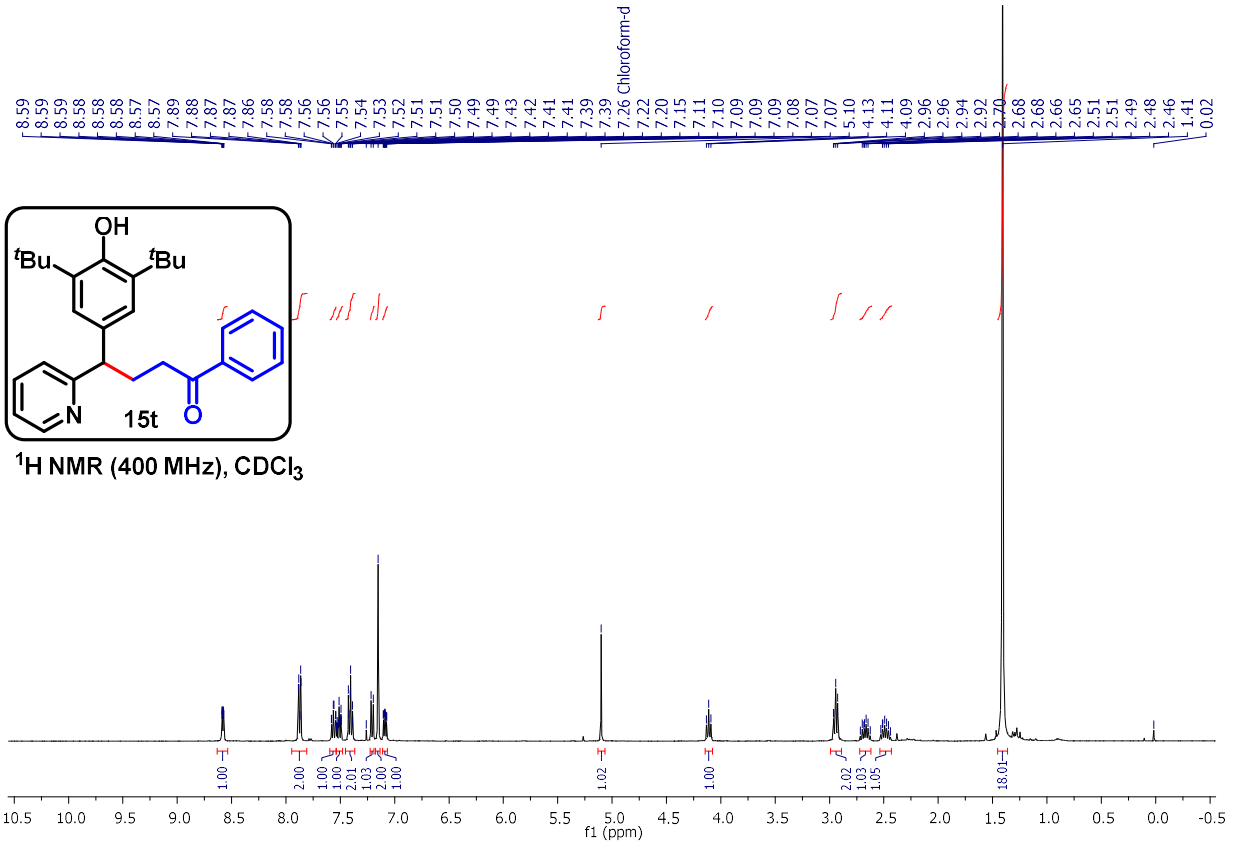

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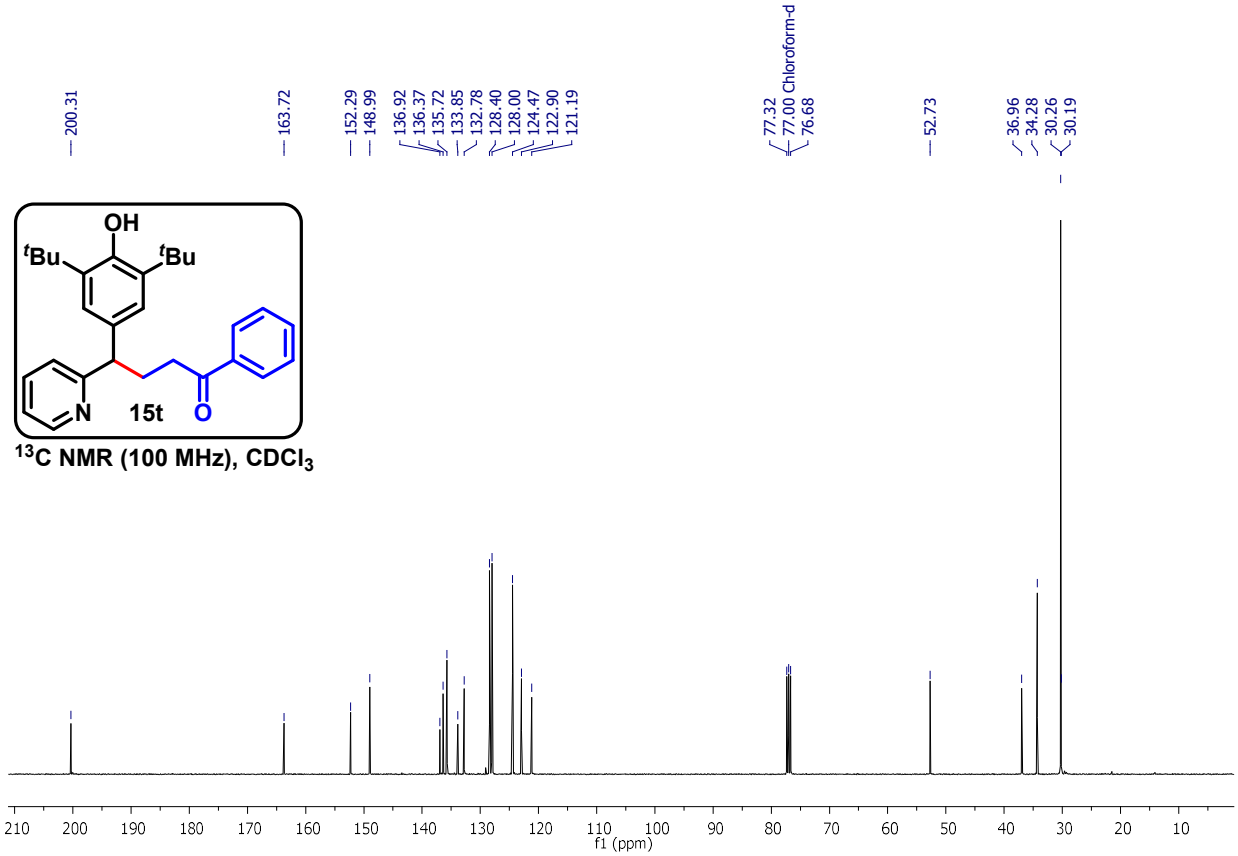

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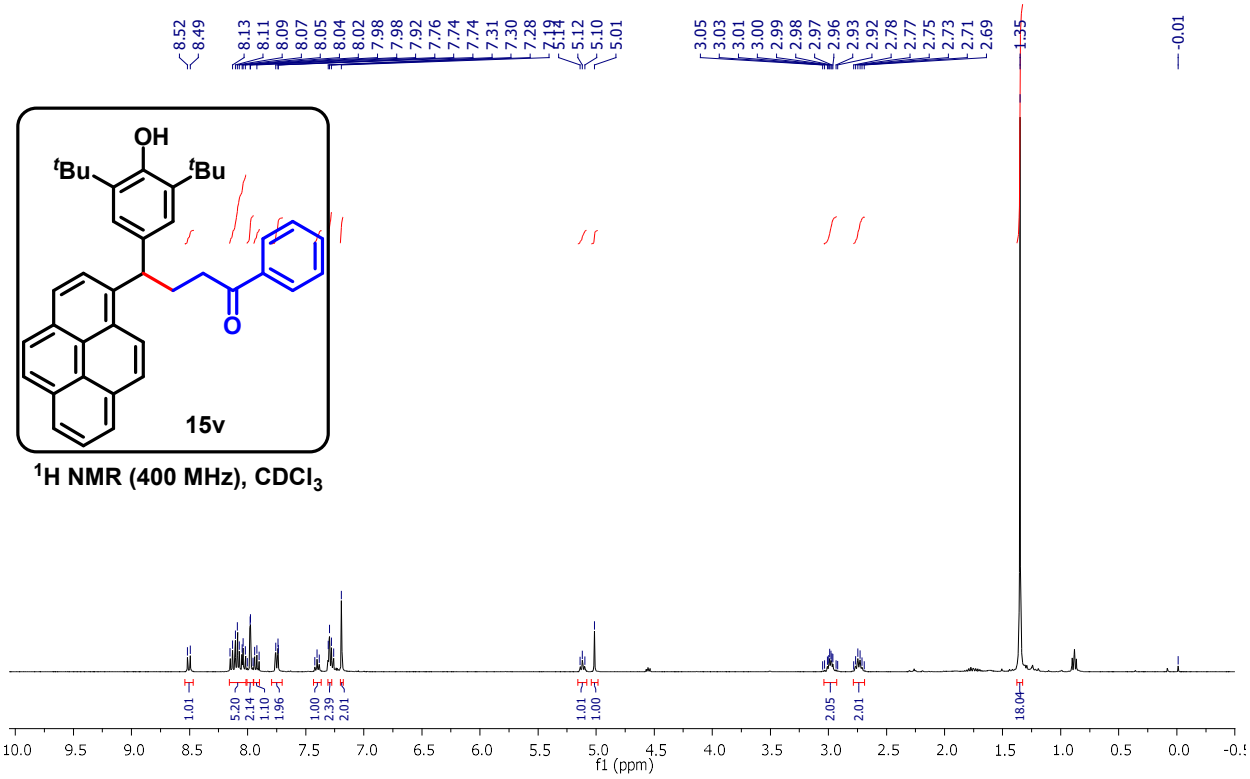

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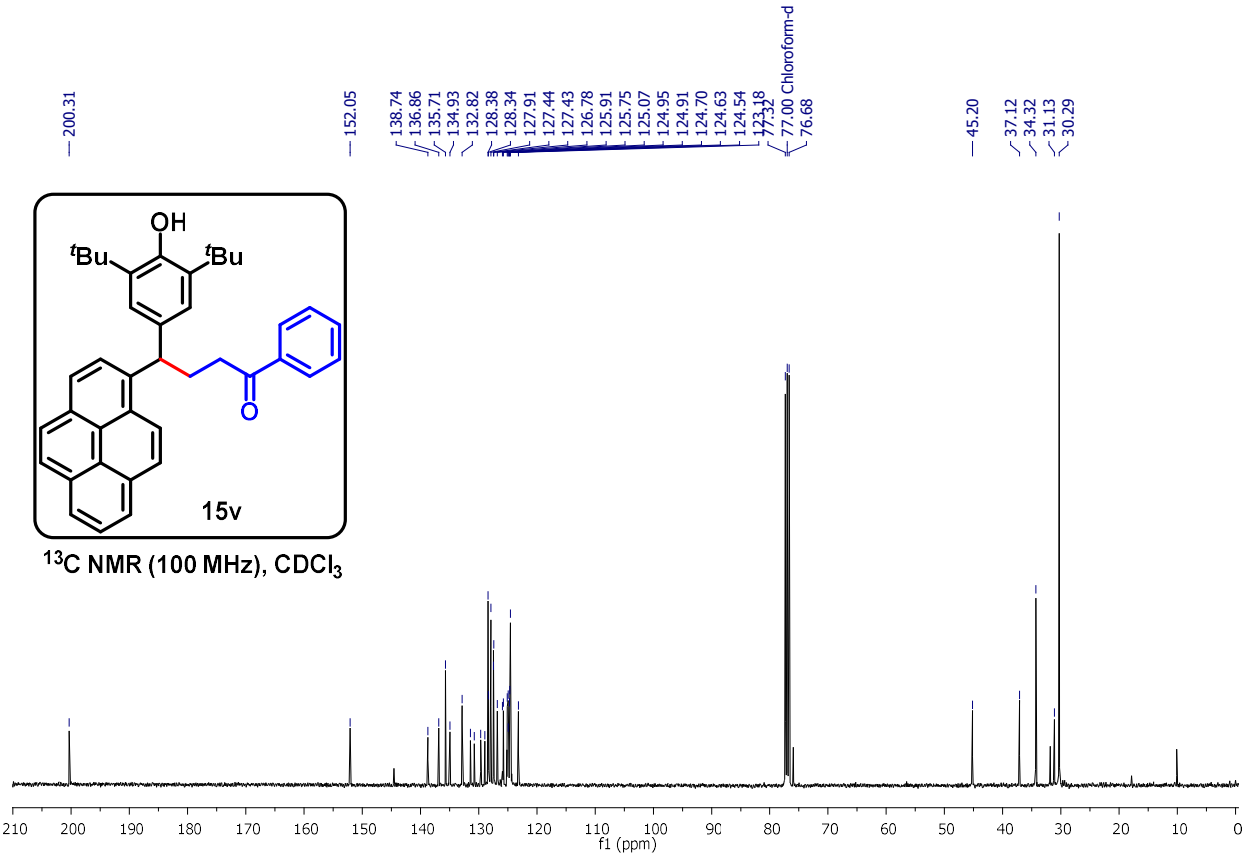

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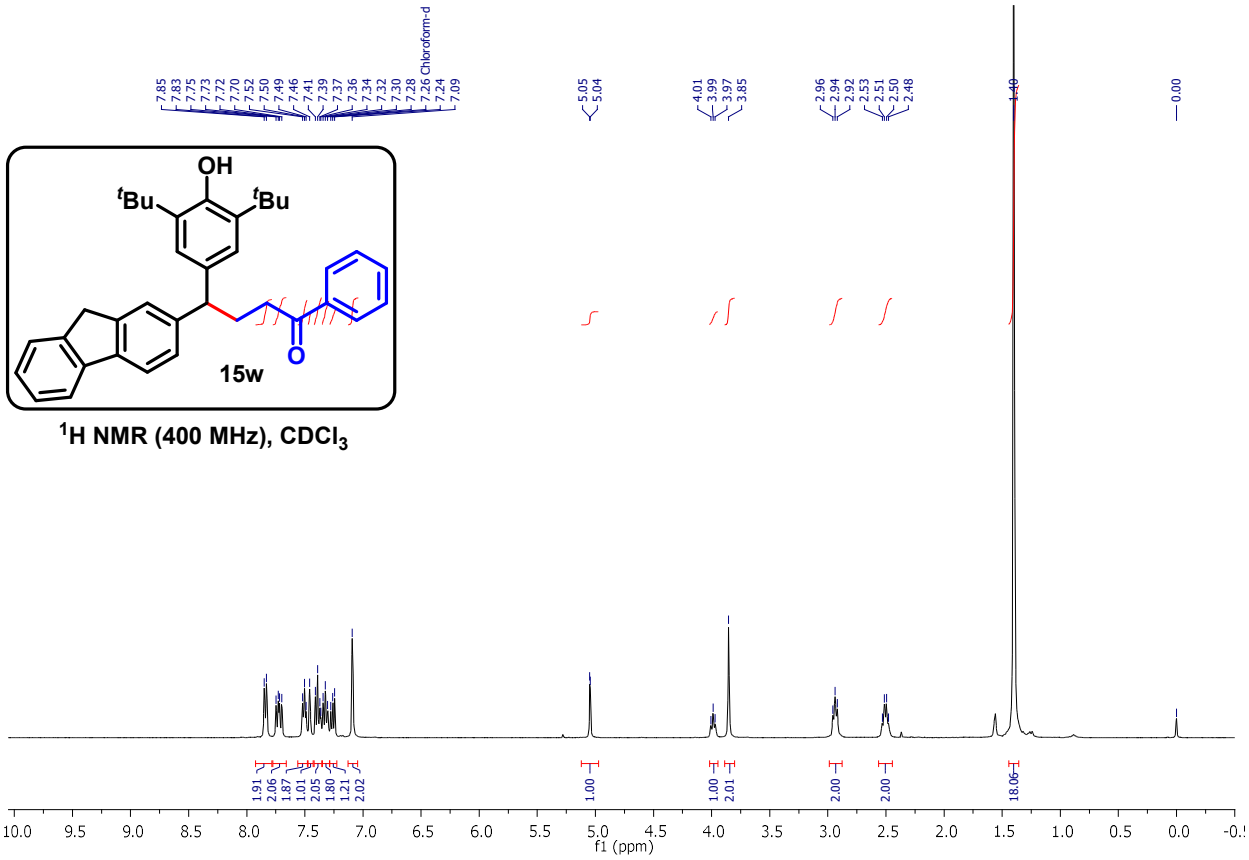

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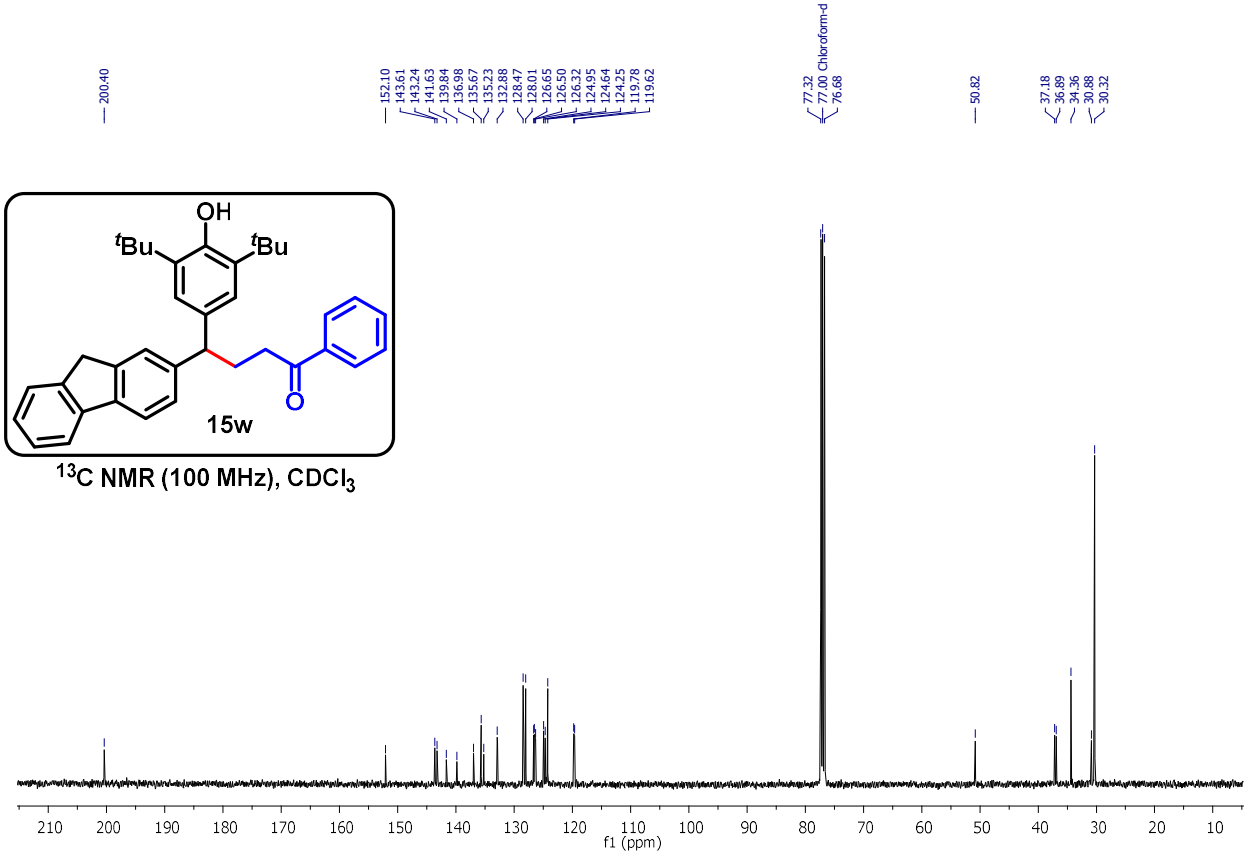
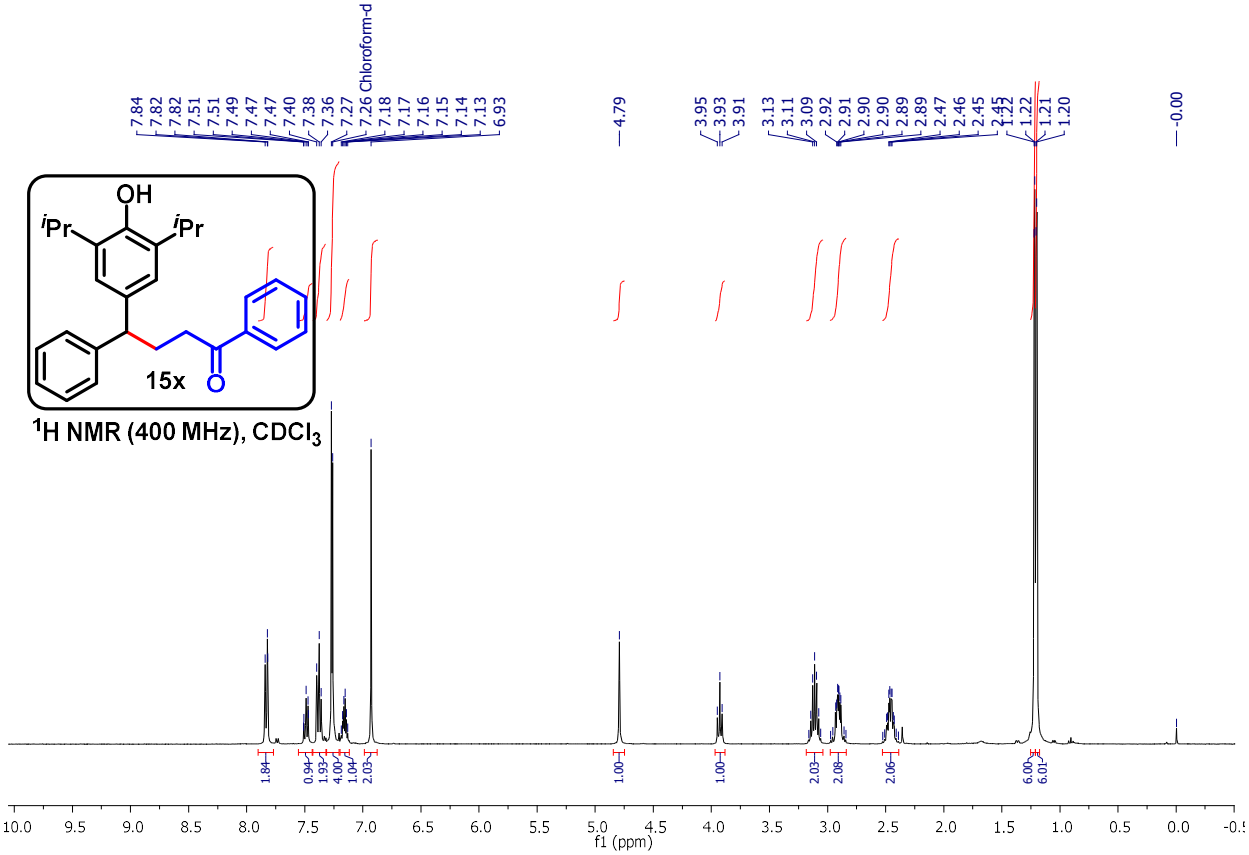


^{13}C NMR (100 MHz), $CDCl_3$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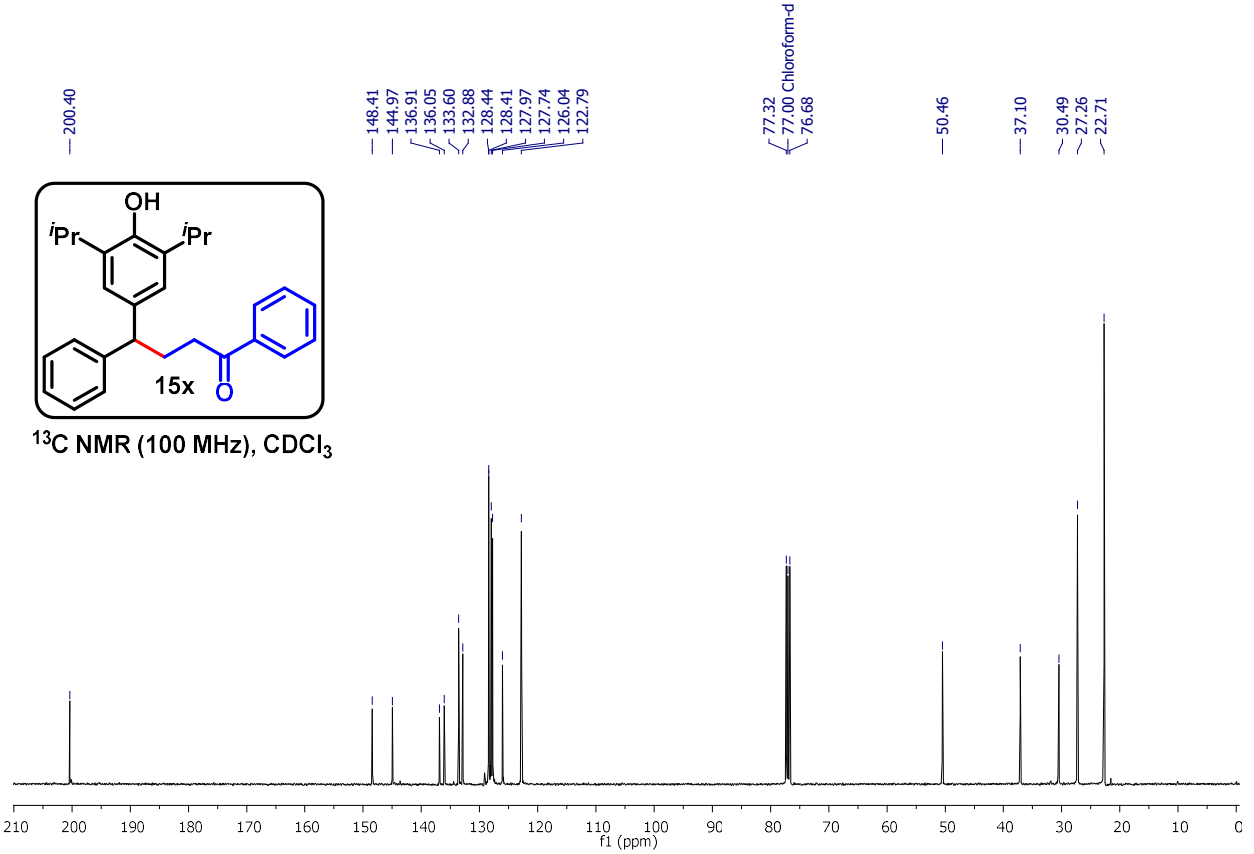
7.82
7.82
7.51
7.51
7.49
7.47
7.47
7.40
7.38
7.36
7.27
7.26 Chloroform-d
7.18
7.17
7.16
7.15
7.14
7.13
6.93
4.79
3.95
3.93
3.91
3.13
3.11
3.09
2.92
2.91
2.90
2.90
2.89
2.89
2.47
2.46
2.45
1.22
1.21
1.20
0.00
OH
iPr
iPr
15x
O
1H NMR (400 MHz), CDCl3
1.84
0.94
1.93
4.00
1.04
2.03
1.00
1.00
2.03
2.08
2.06
6.00
6.01
f1 (ppm)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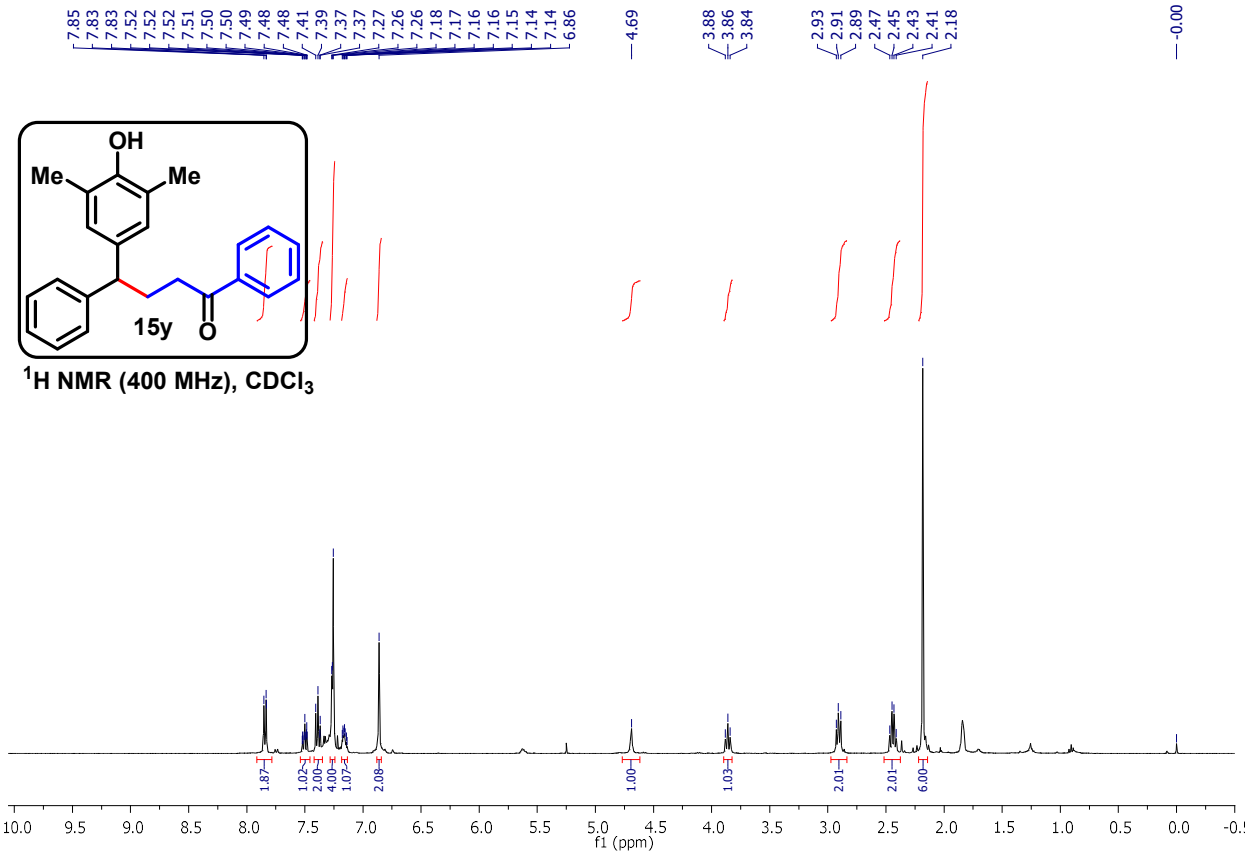
148.41
144.97
136.91
136.05
133.60
132.88
128.44
128.41
127.97
127.74
126.04
122.79
77.32
77.00 Chloroform-d
76.68
50.46
37.10
30.49
27.26
22.71
OH
iPr
iPr
15x
O
13C NMR (100 MHz), CDCl3
f1 (ppm)



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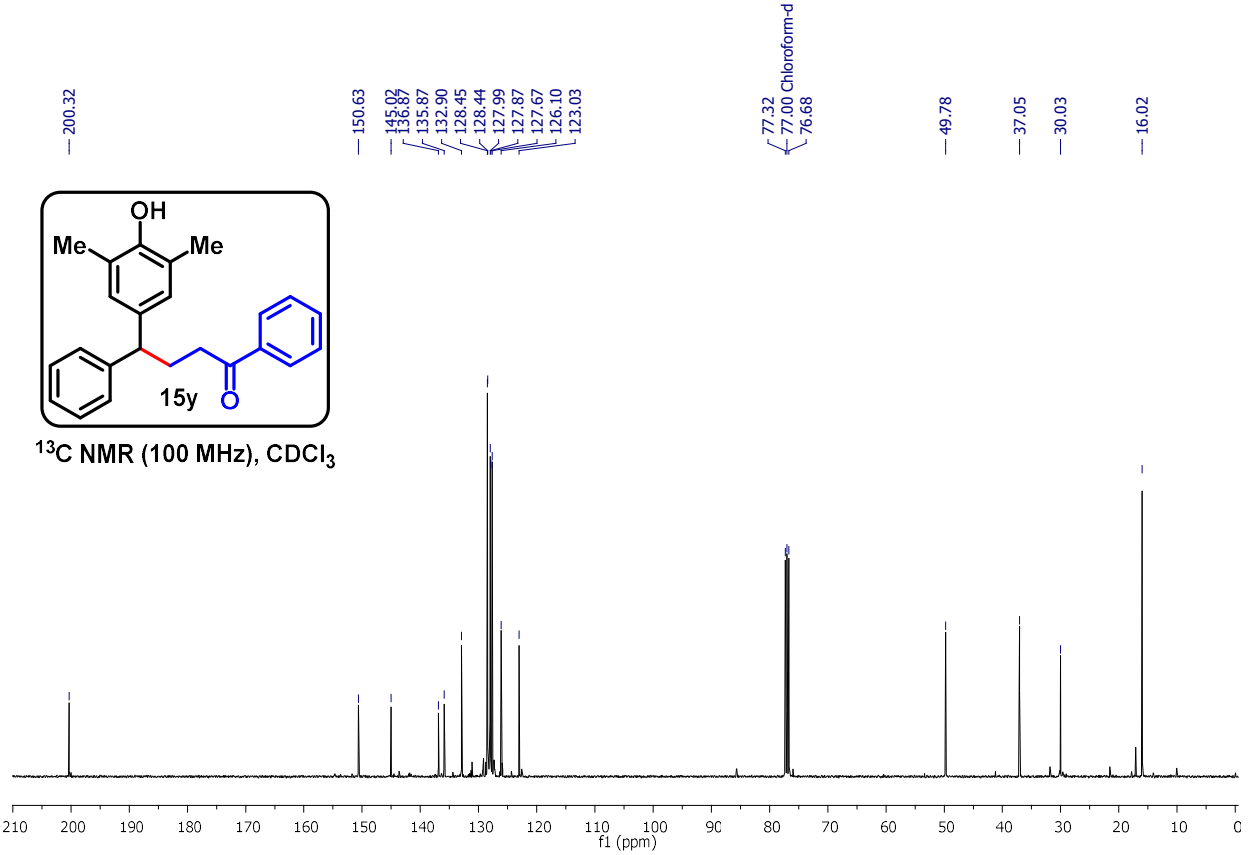
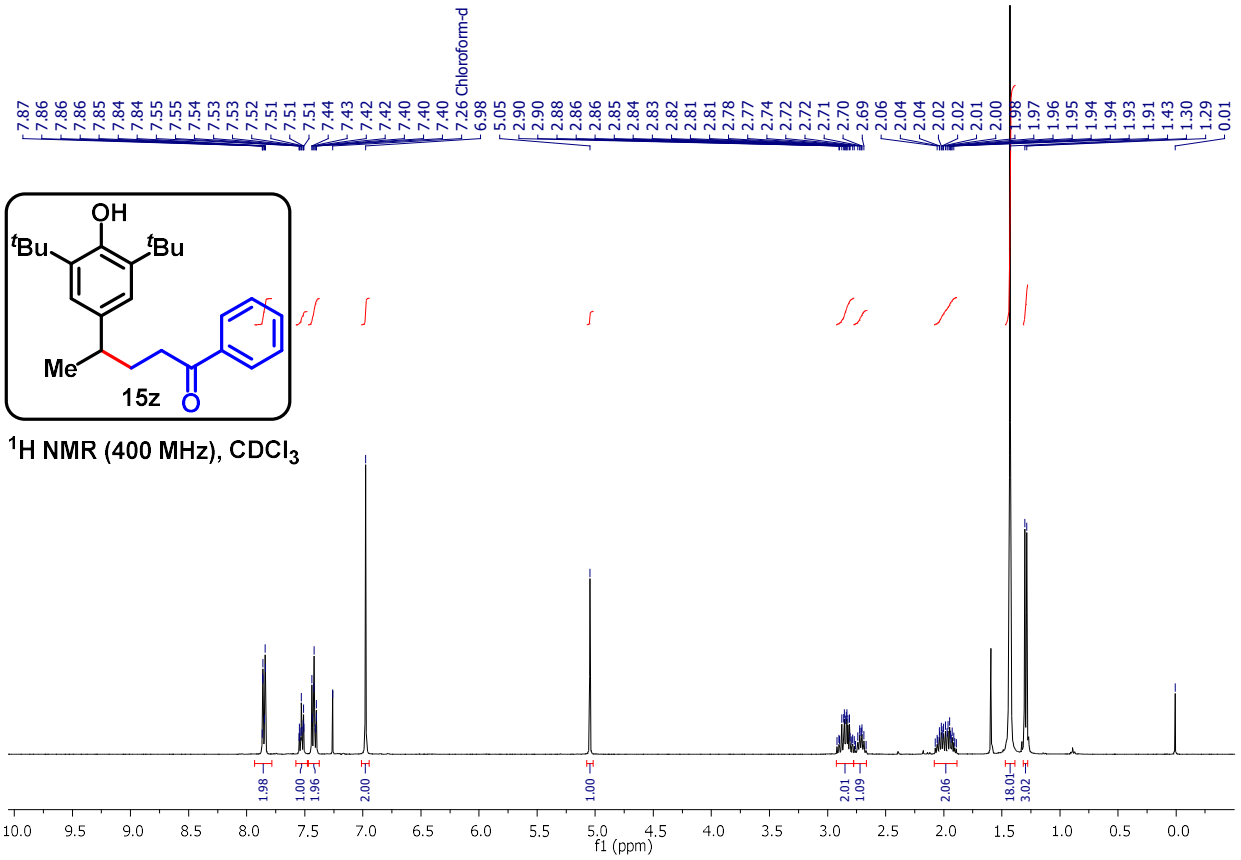


^{13}C NMR (100 MHz), $CDCl_3$



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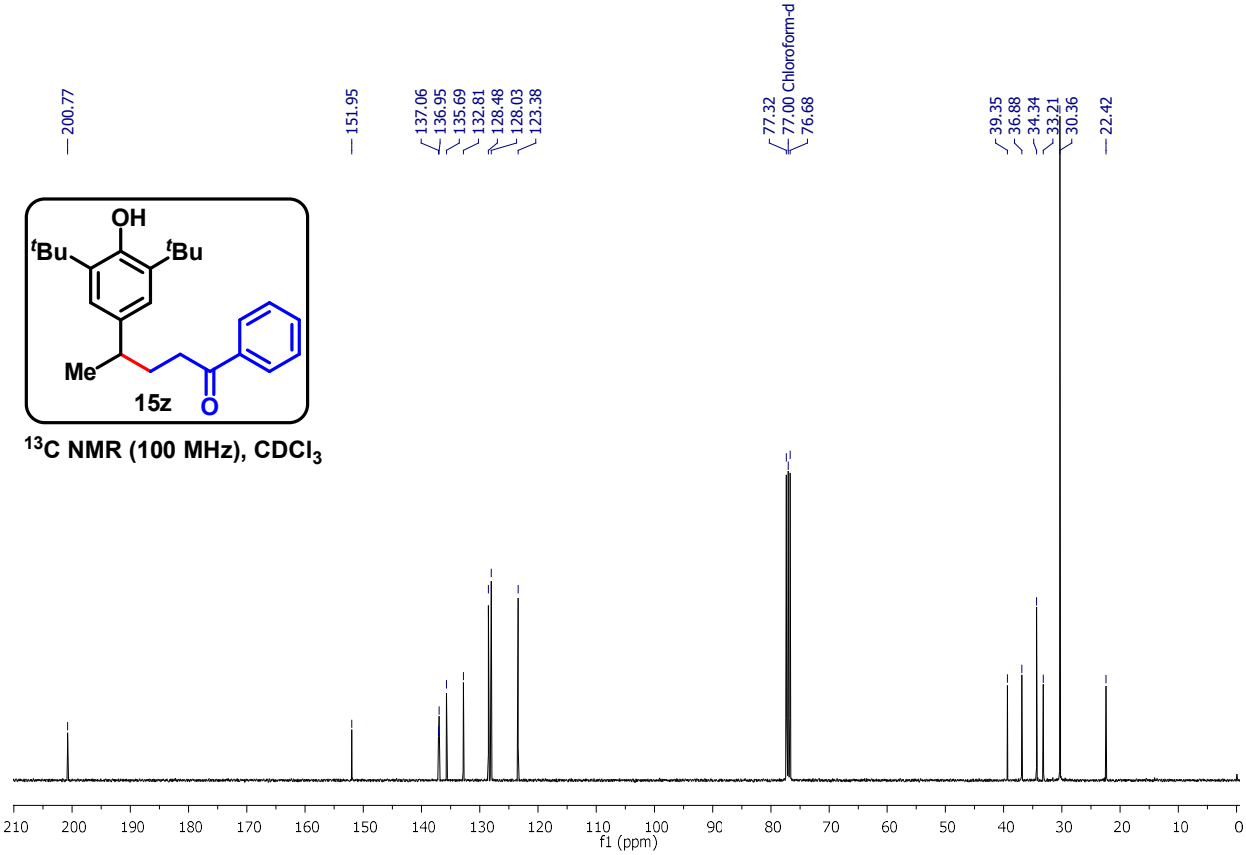
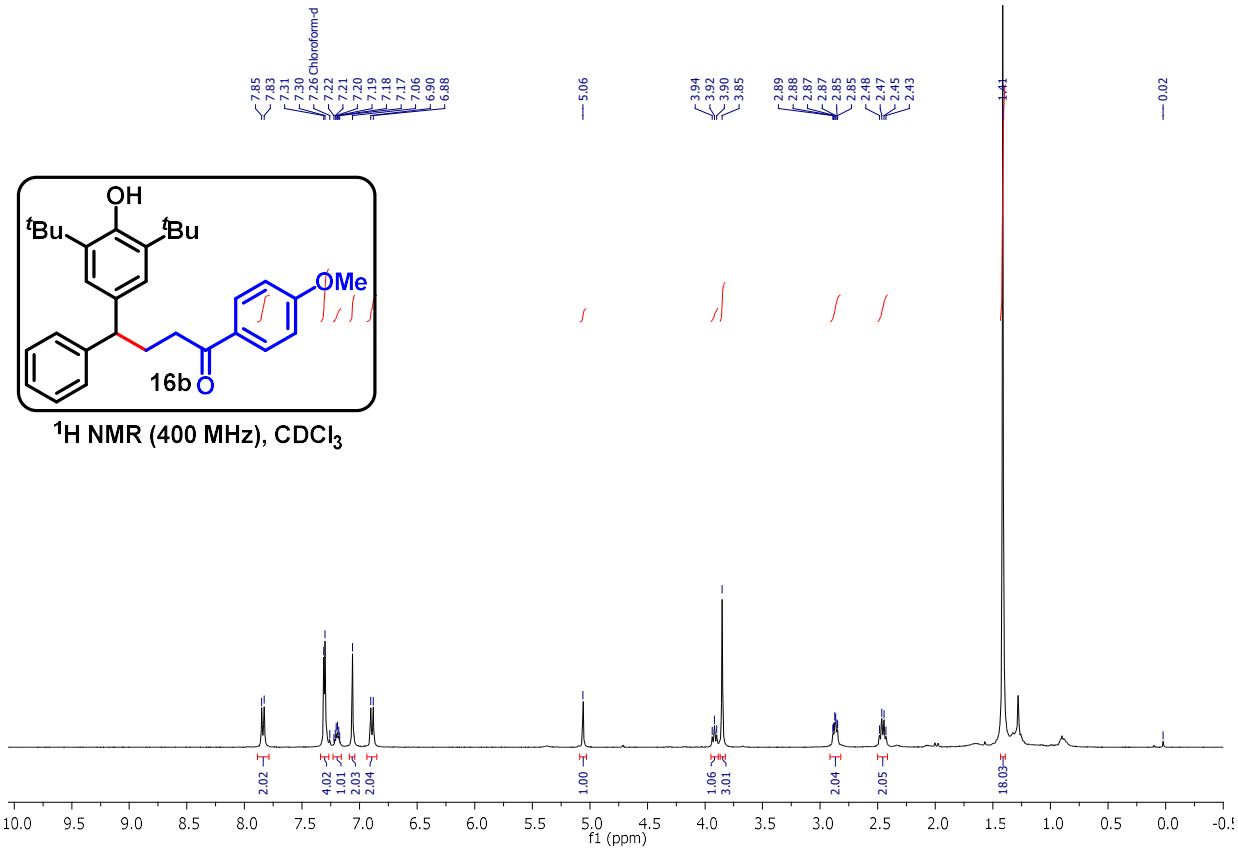
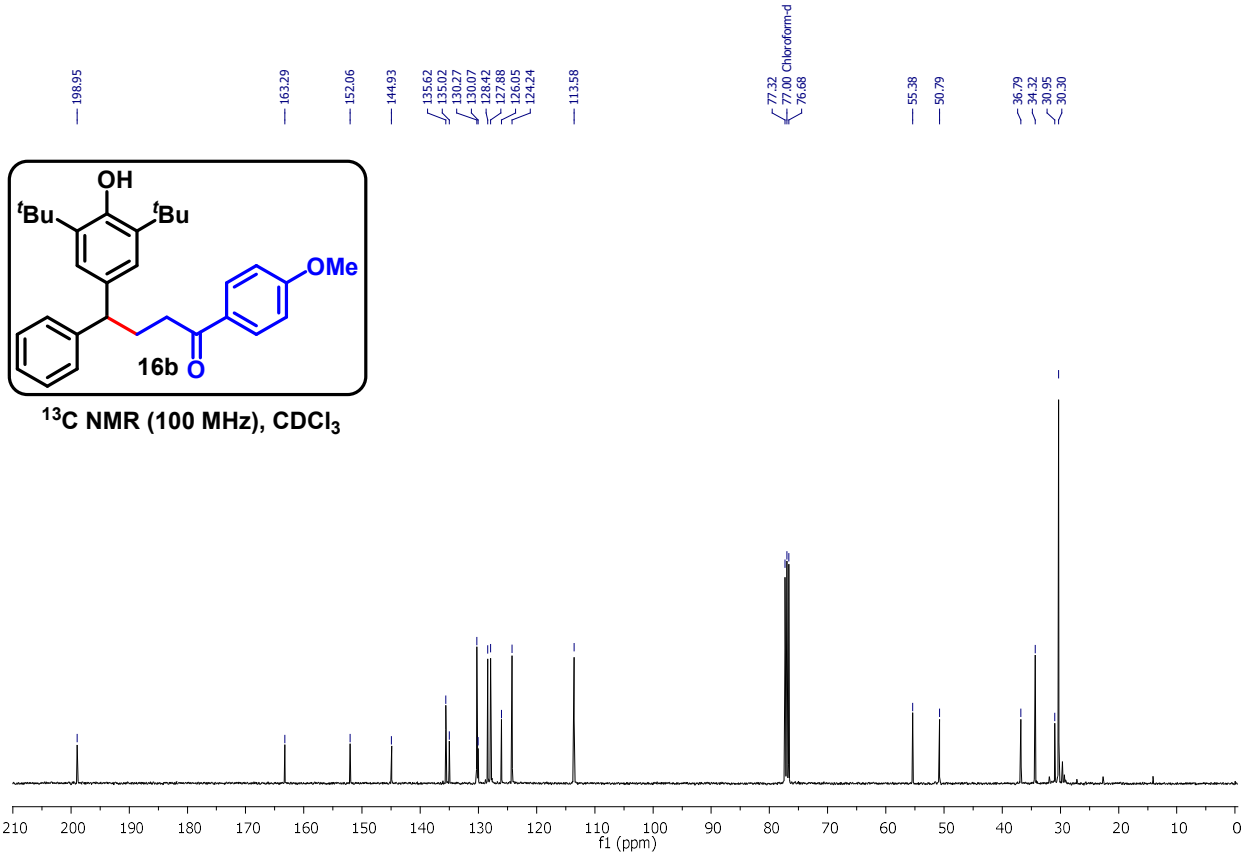


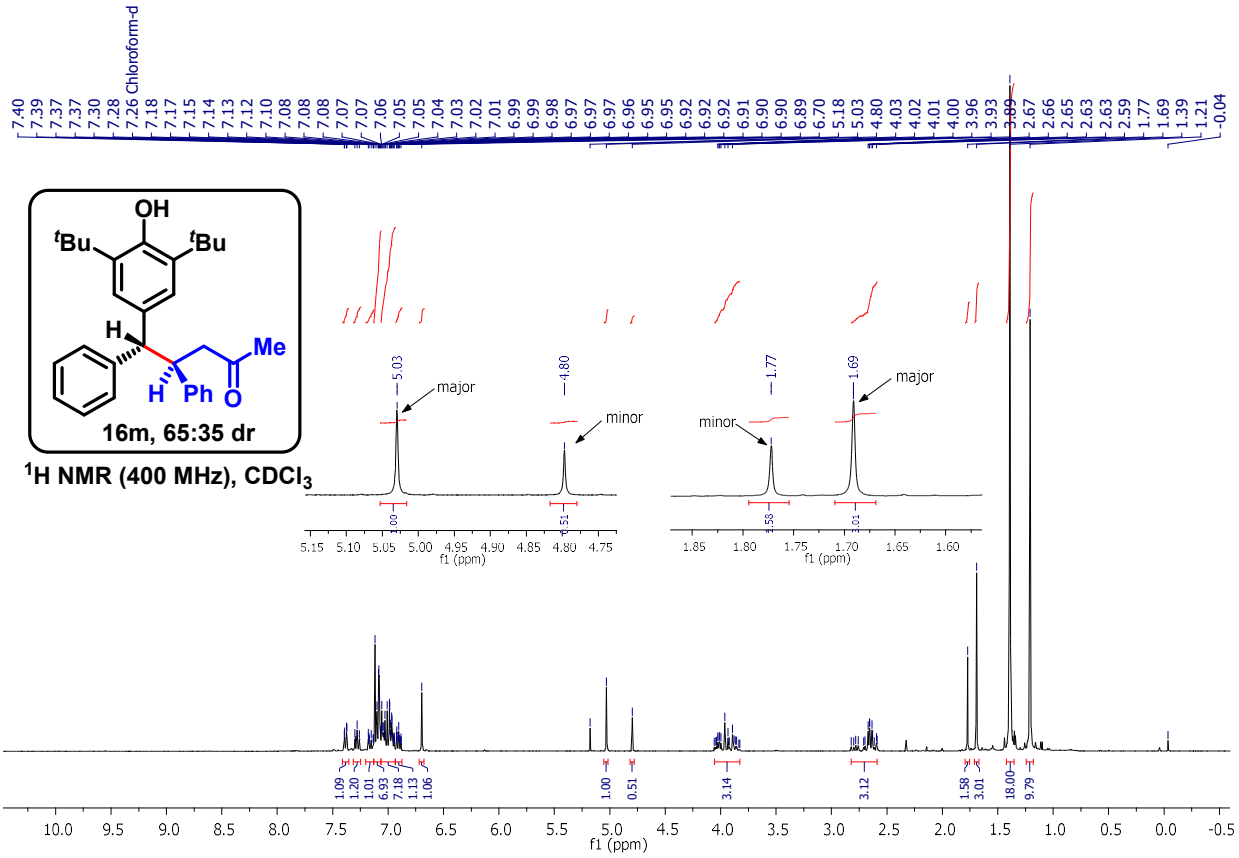
^{13}C NMR (100 MHz), $CDCl_3$



^{1}H NMR (400 MHz), $CDCl_3$



^{13}C NMR (100 MHz), $CDCl_3$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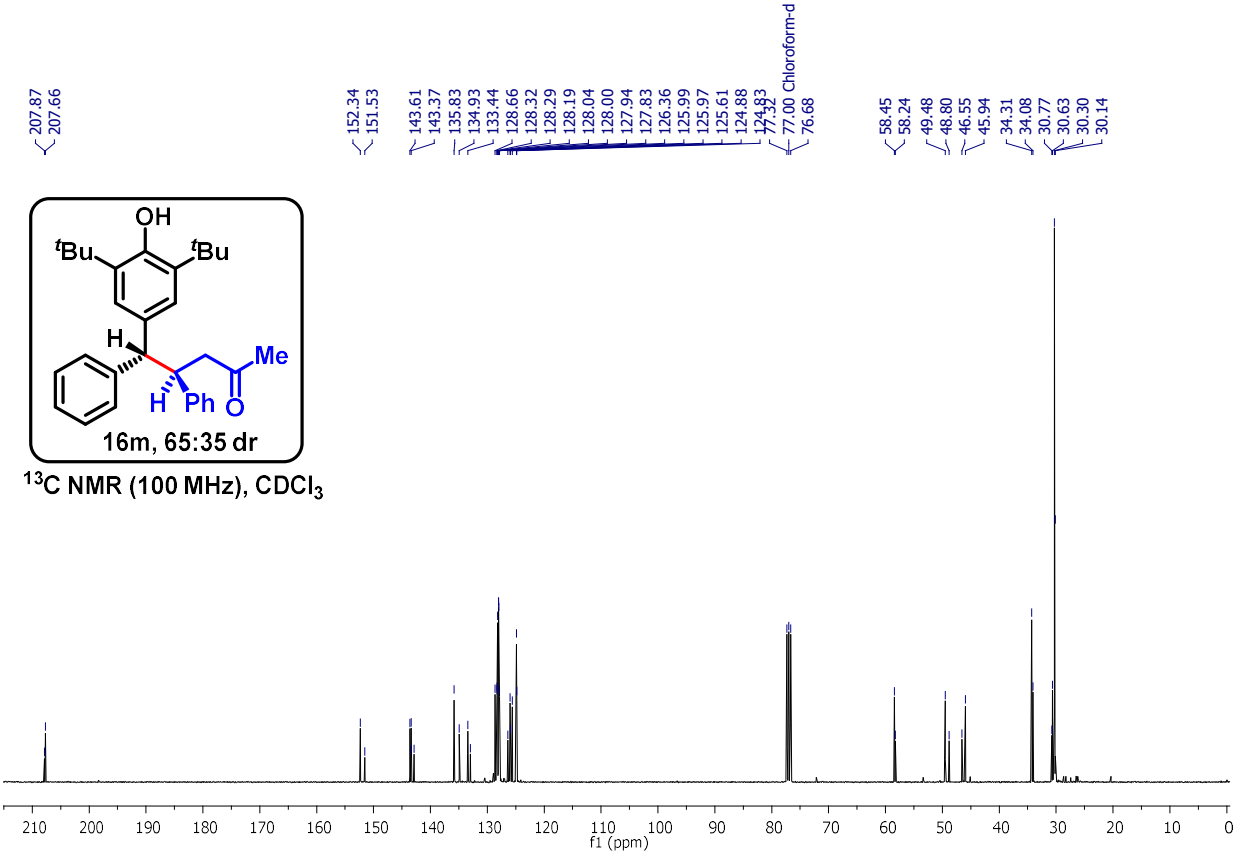
tBu
tBu
H
Me
H Ph O
16m, 65:35 dr
1H NMR (400 MHz), CDCl3
major
minor
major
minor
f1 (ppm)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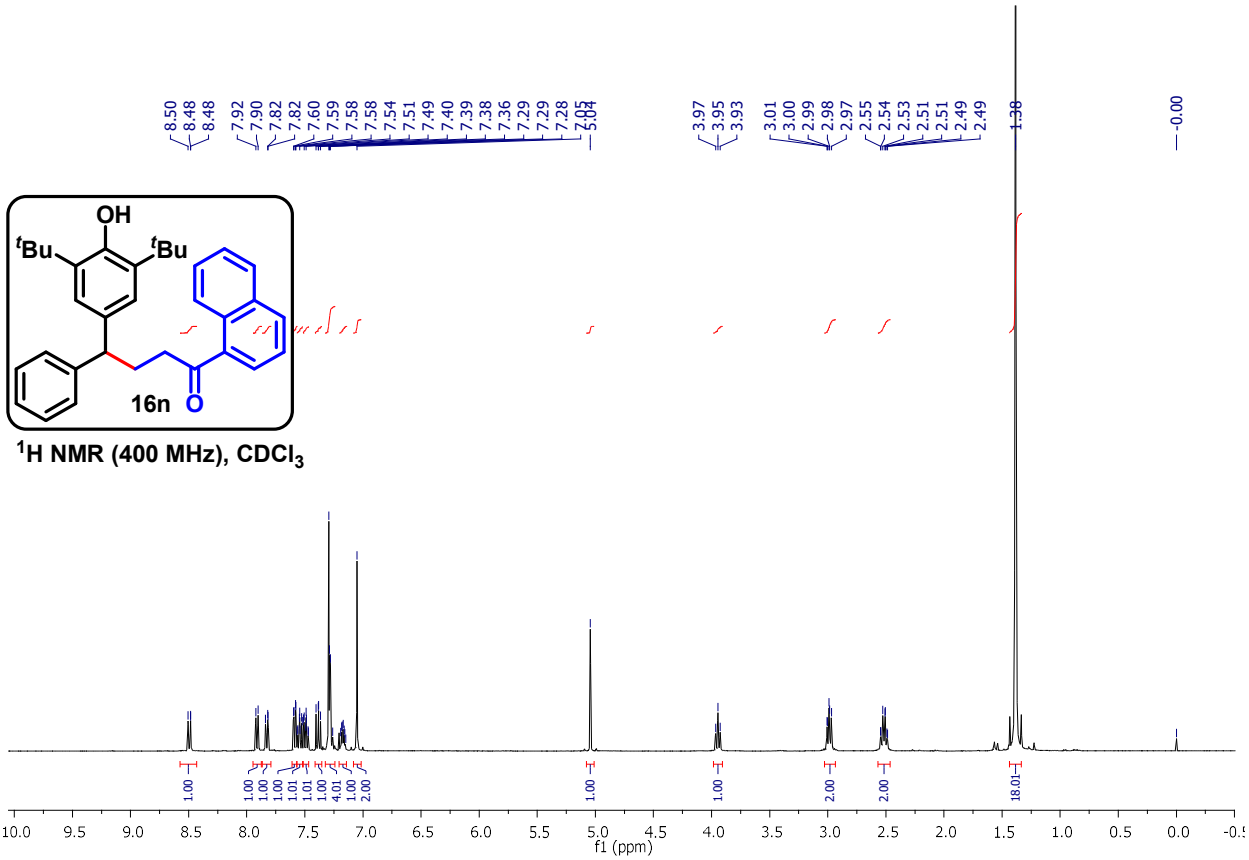
H
Me
H Ph O
16m, 65:35 dr
13C NMR (100 MHz), CDCl3
f1 (ppm)



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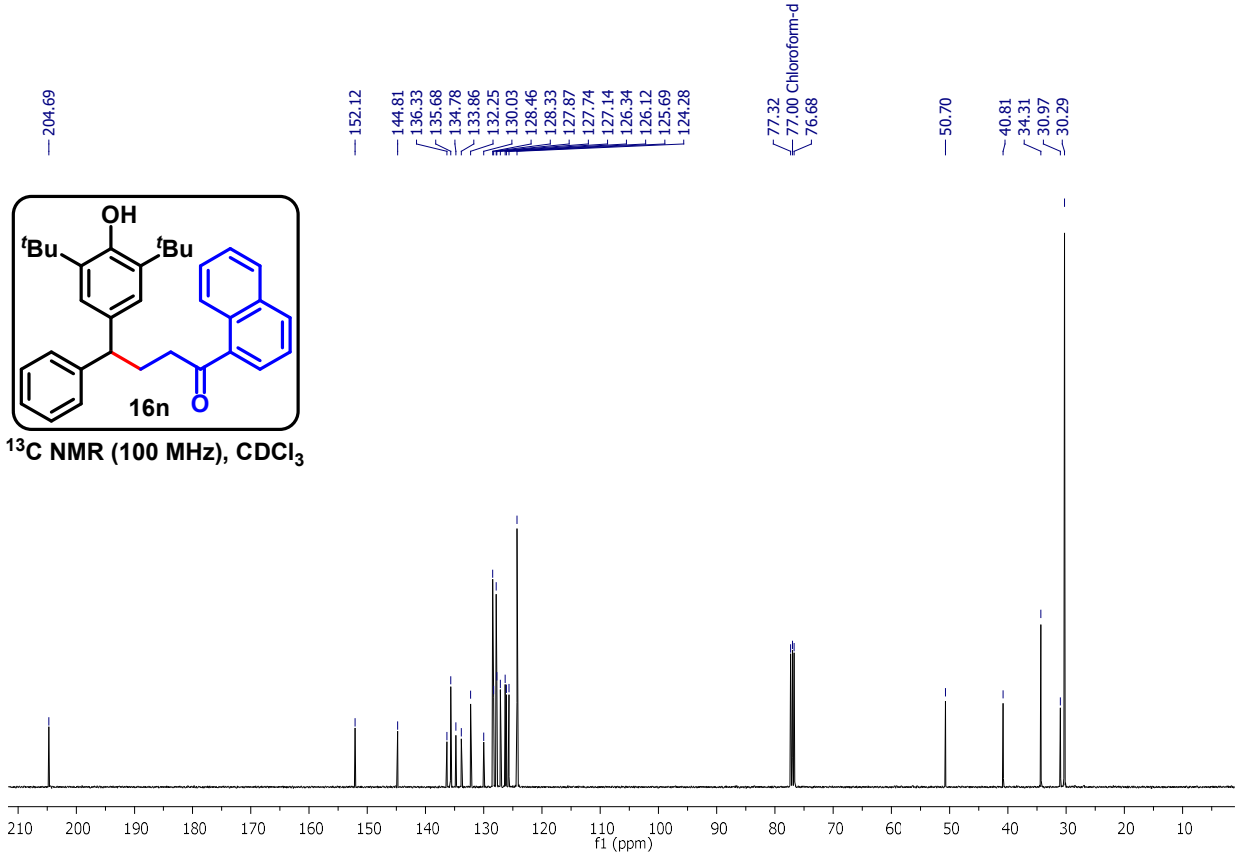
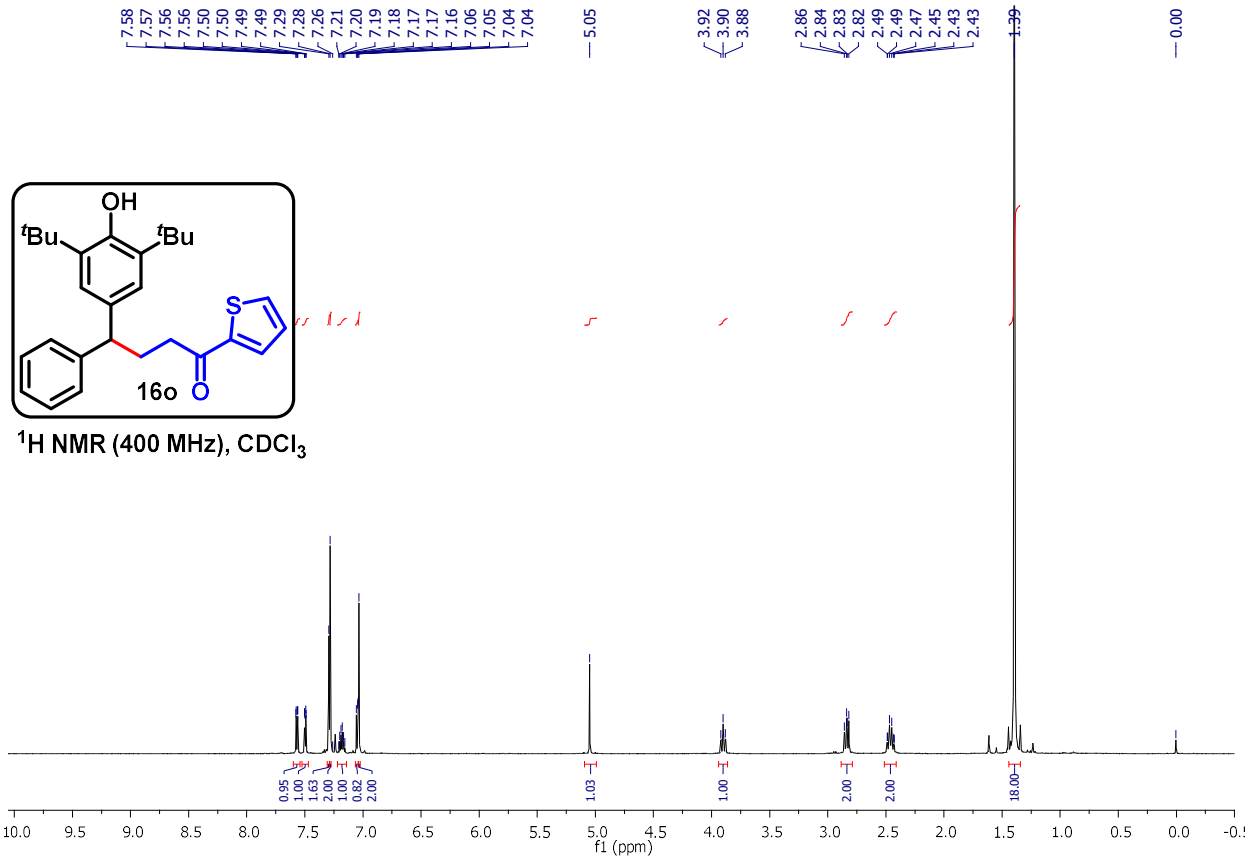
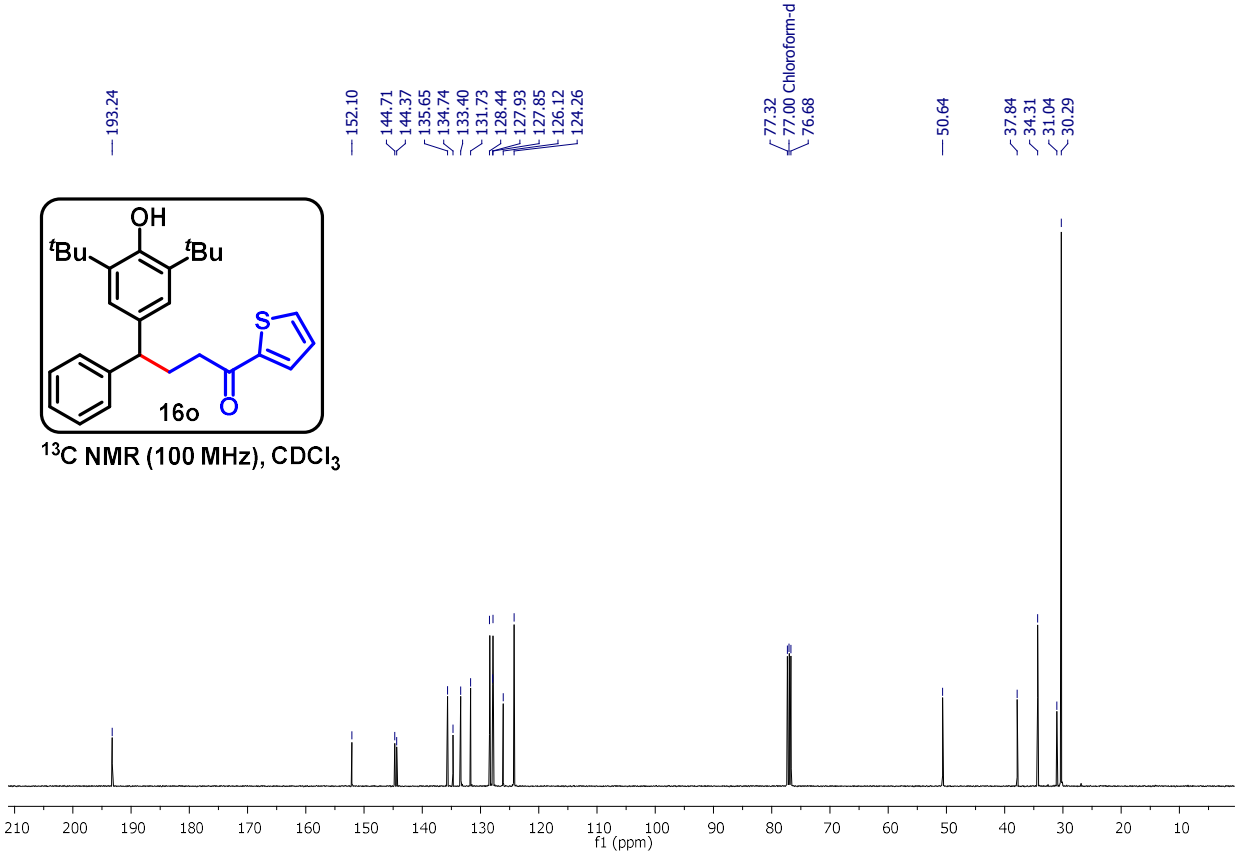


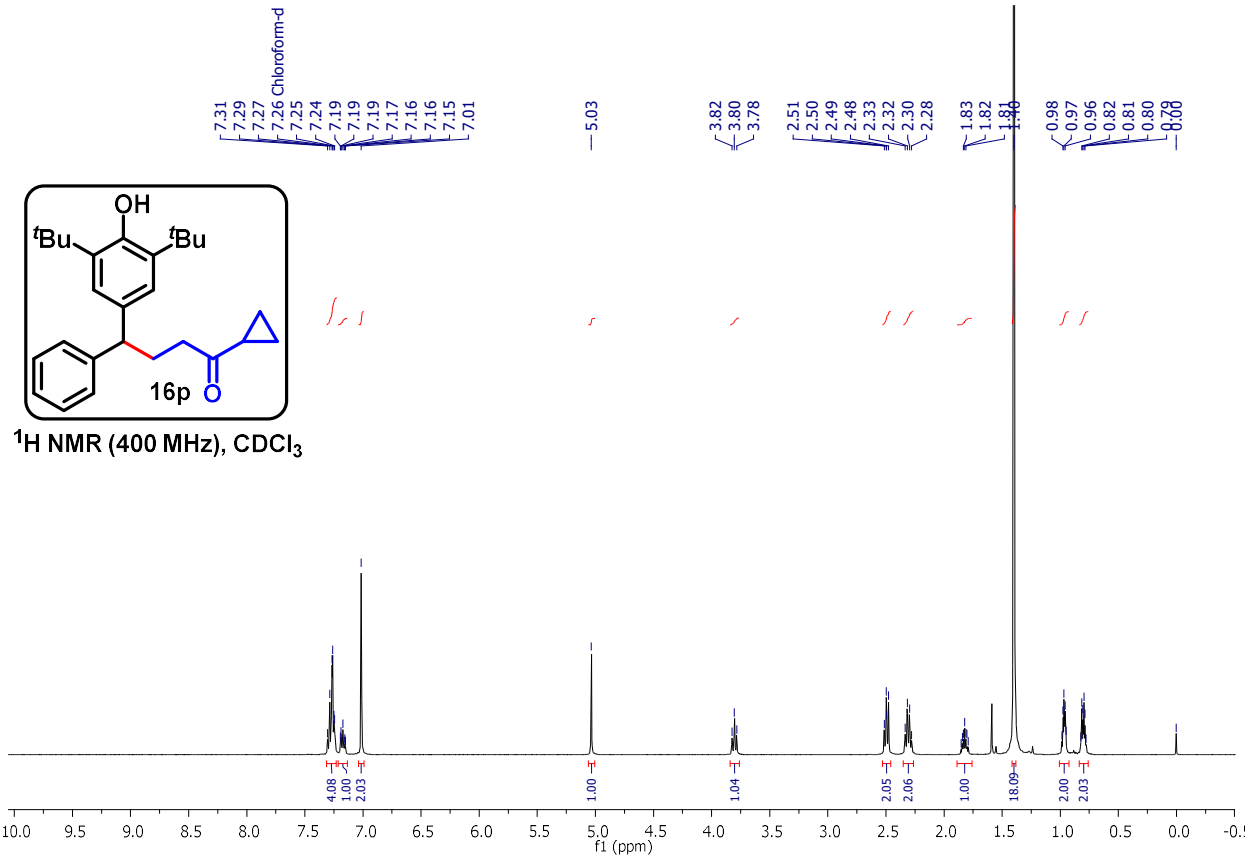
^{13}C NMR (100 MHz), $CDCl_3$



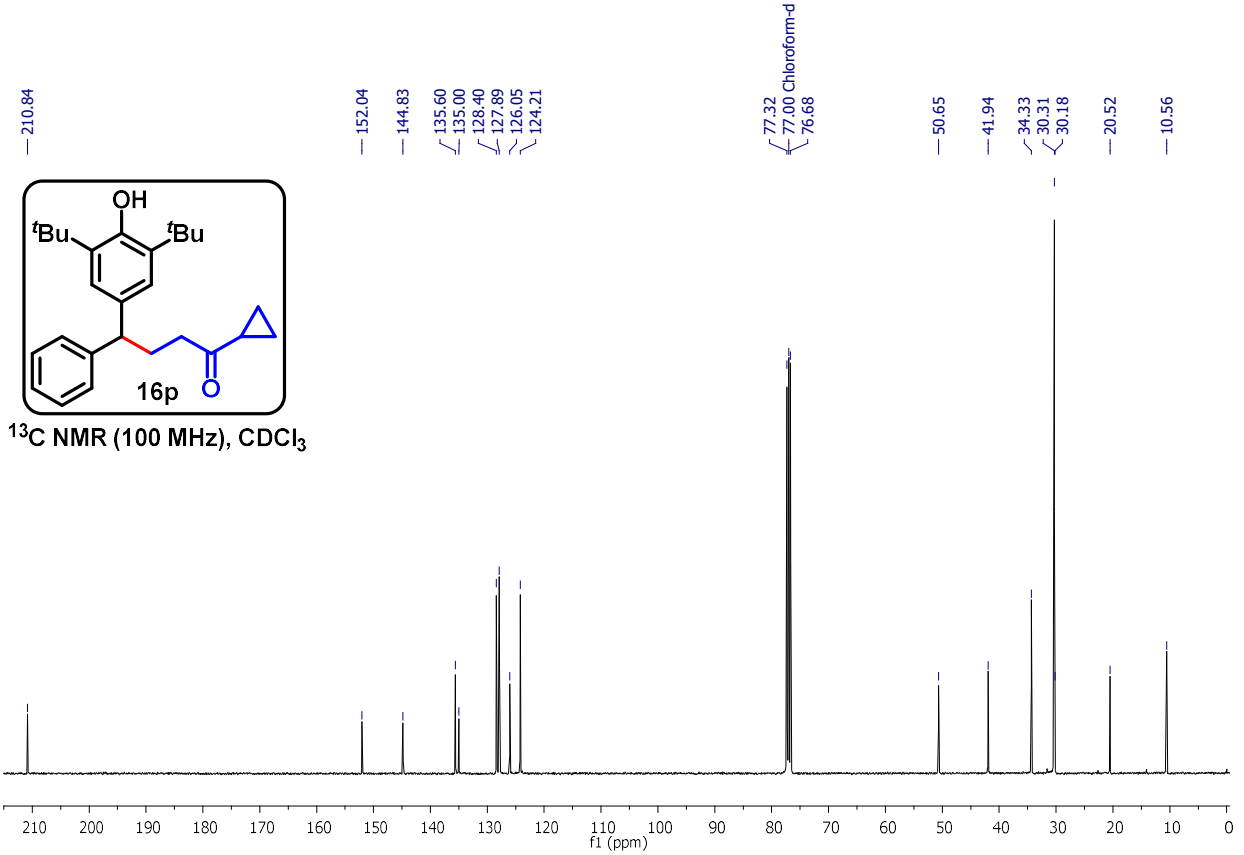
^{1}H NMR (400 MHz), $CDCl_3$



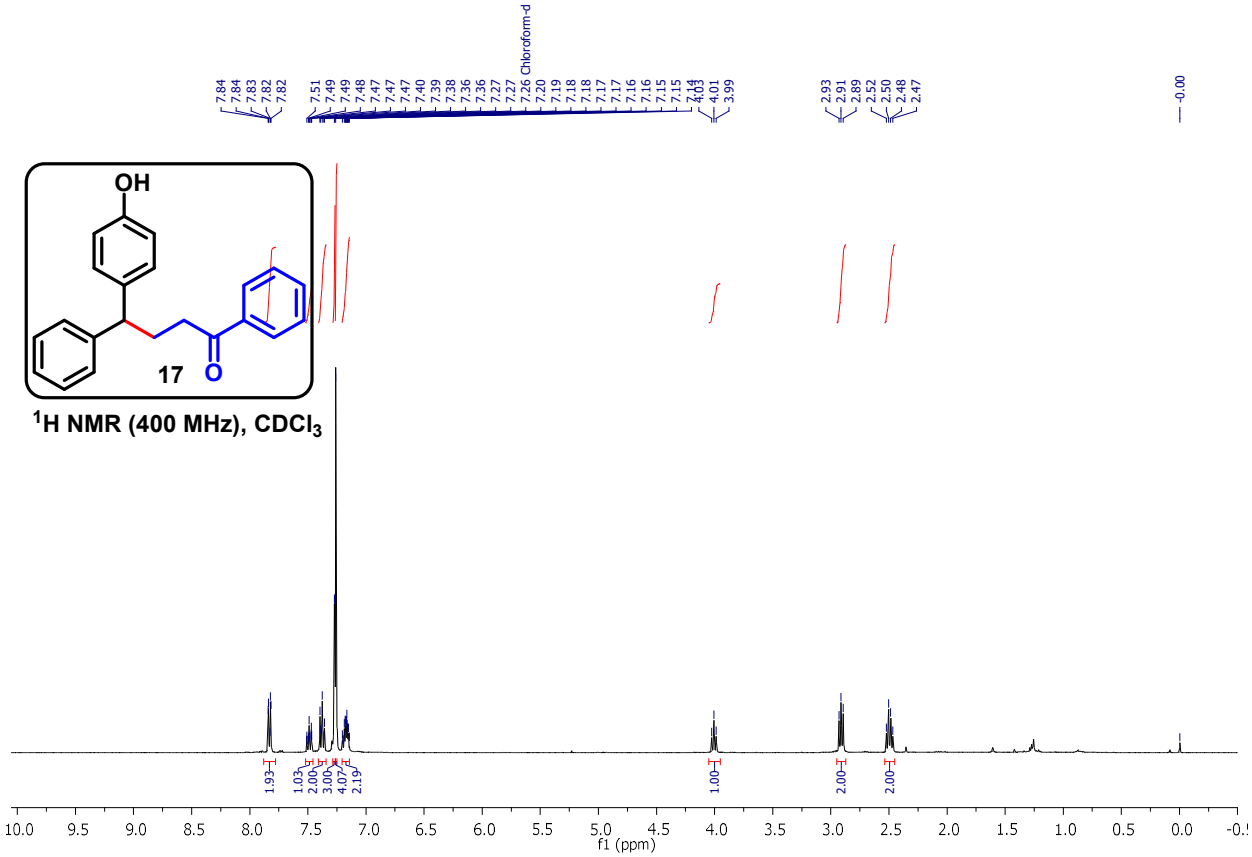
^{13}C NMR (100 MHz), $CDCl_3$



^{1}H NMR (400 MHz), $CDCl_3$



^{13}C NMR (100 MHz), $CDCl_3$


OH
17
O
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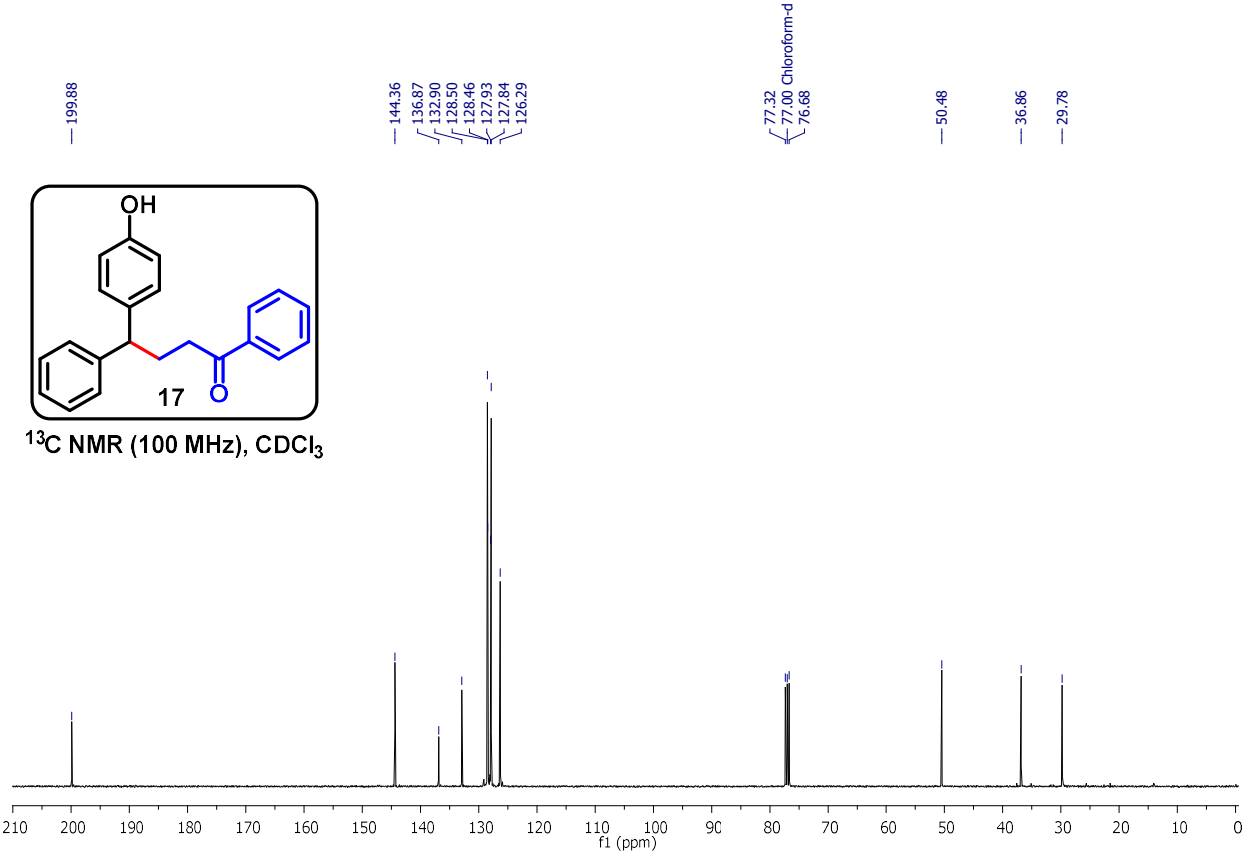
f1 (ppm)


OH
17
O
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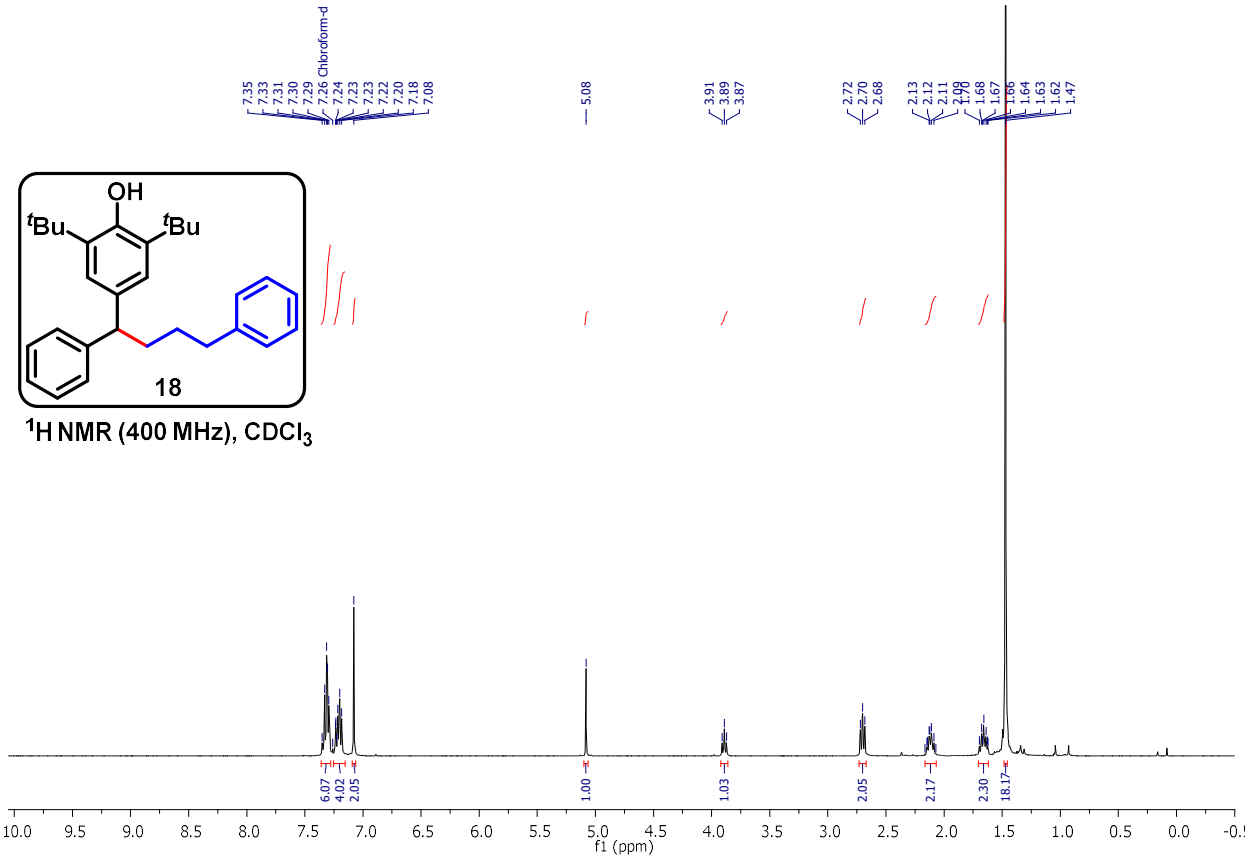
f1 (ppm)



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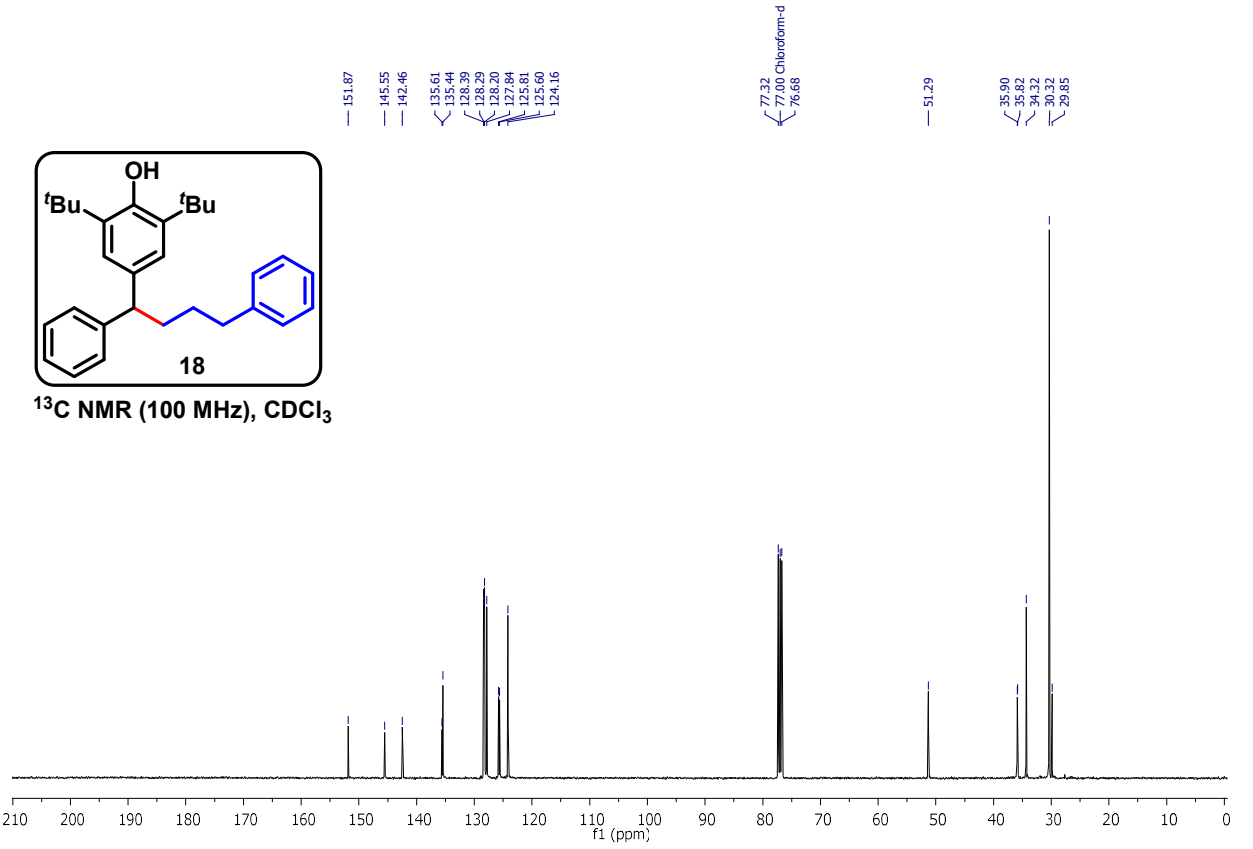

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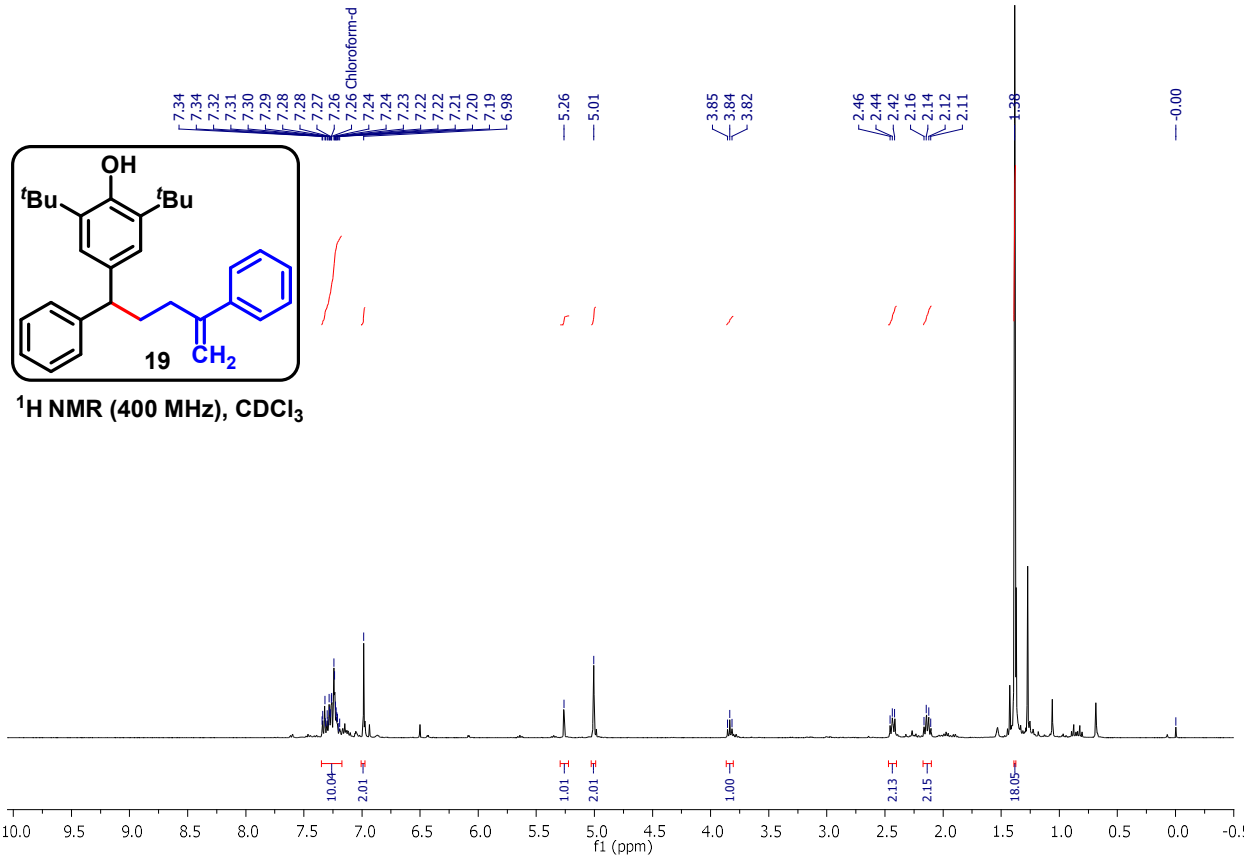

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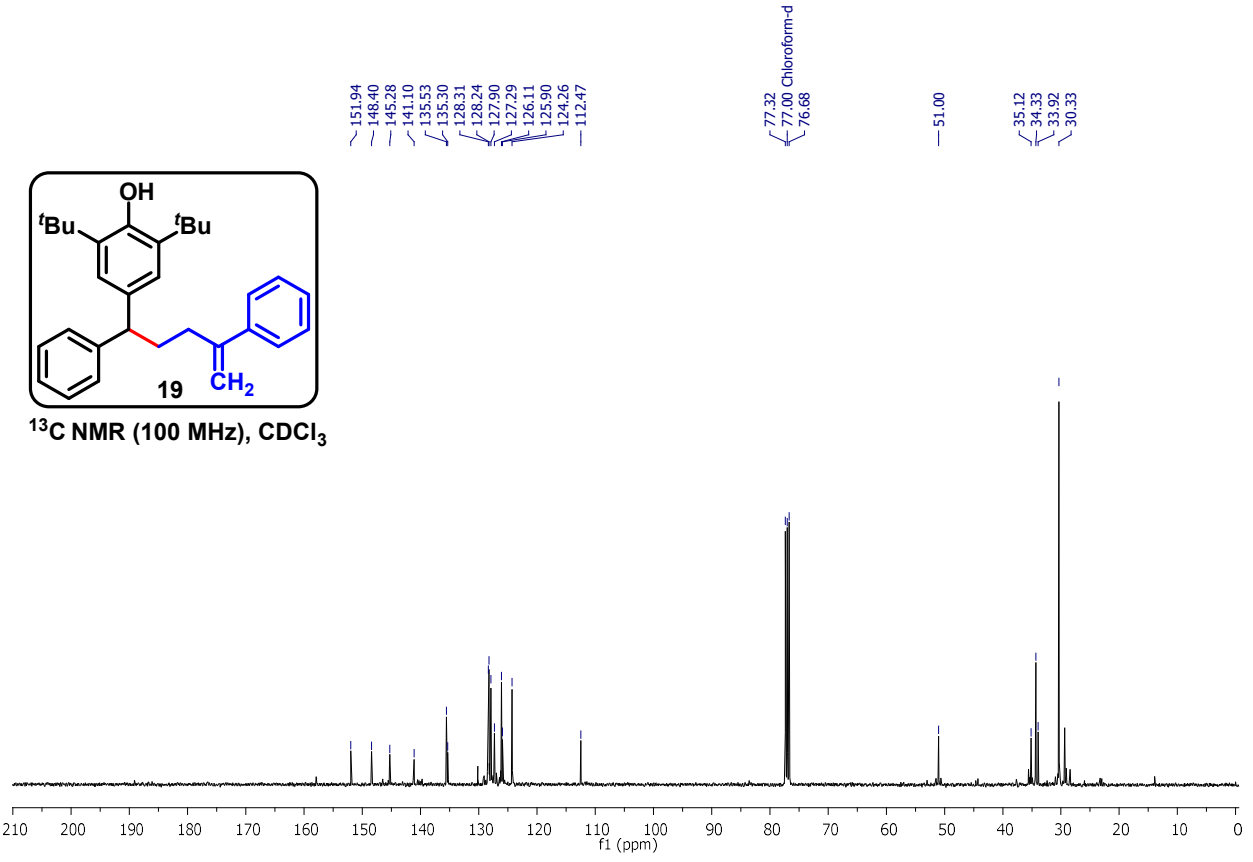

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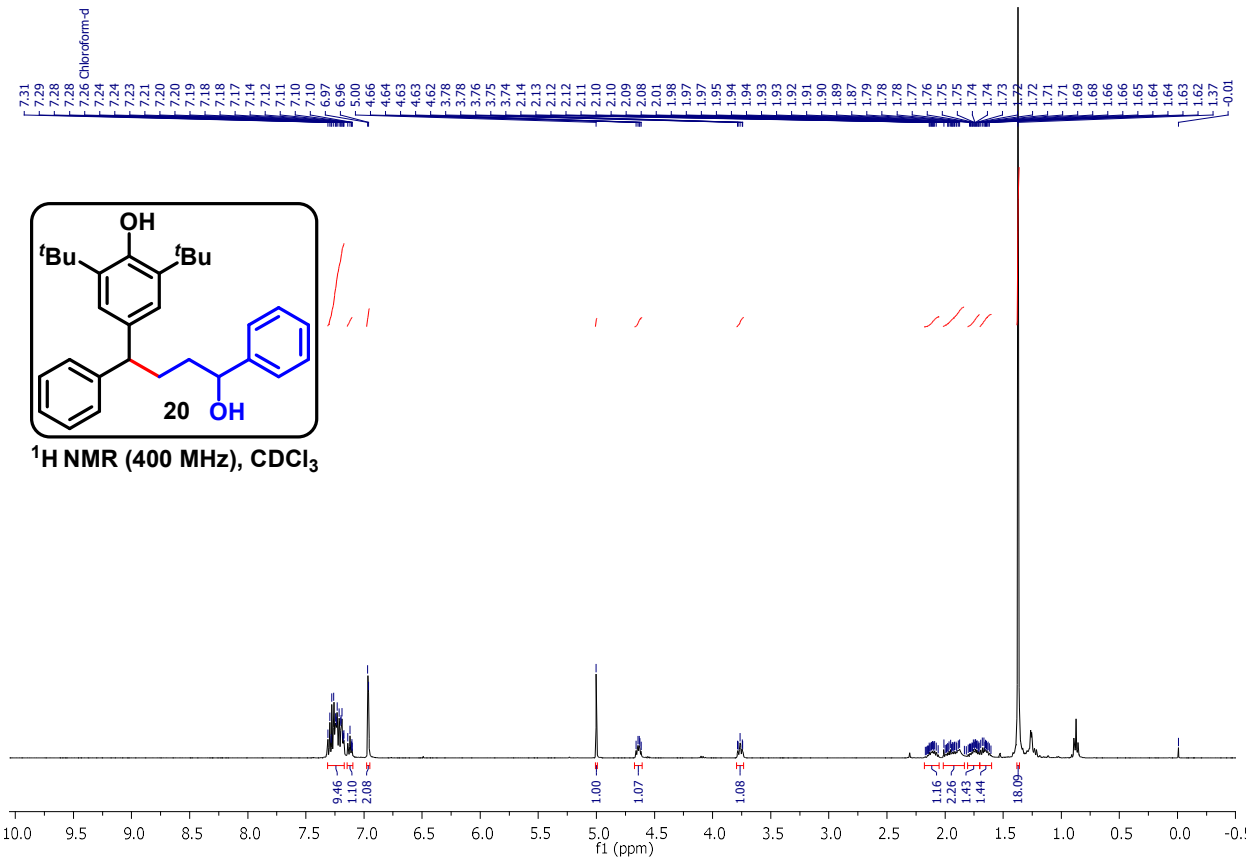

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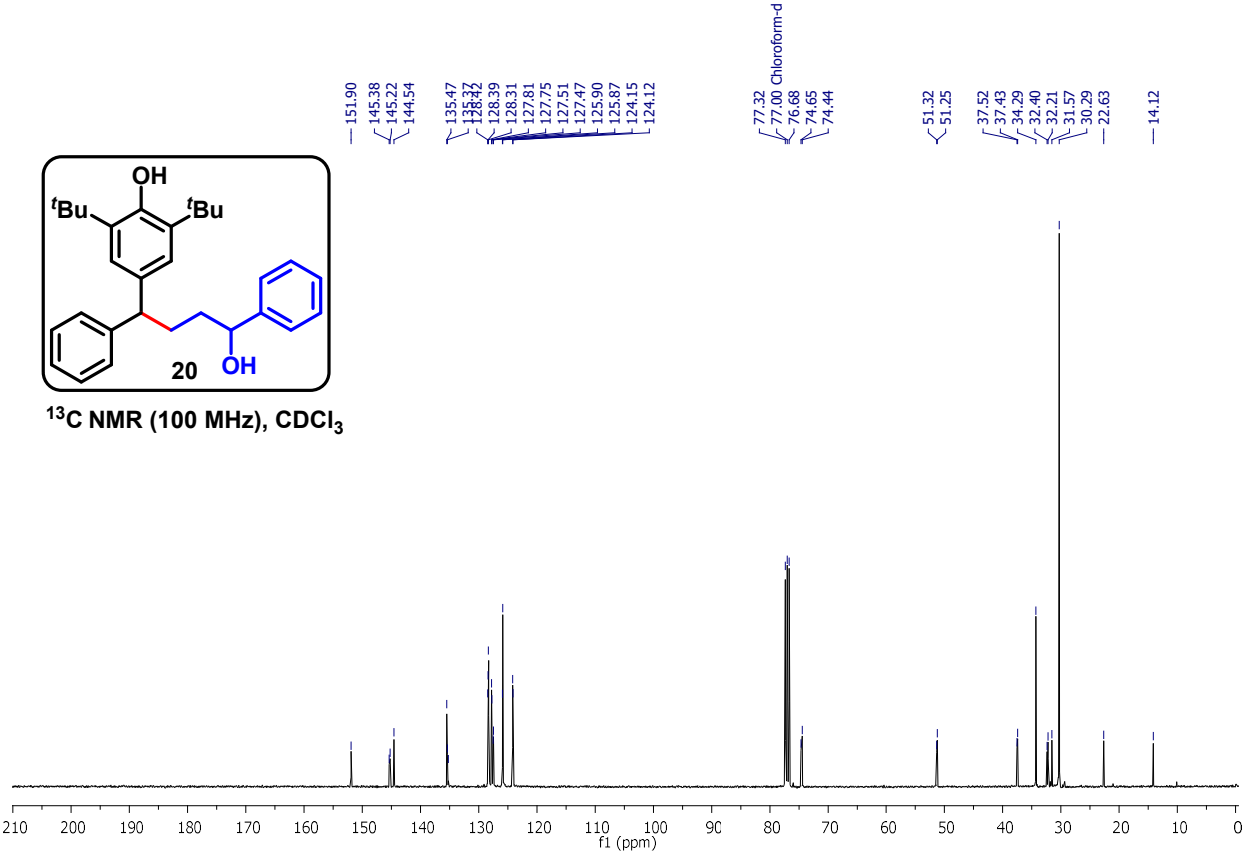

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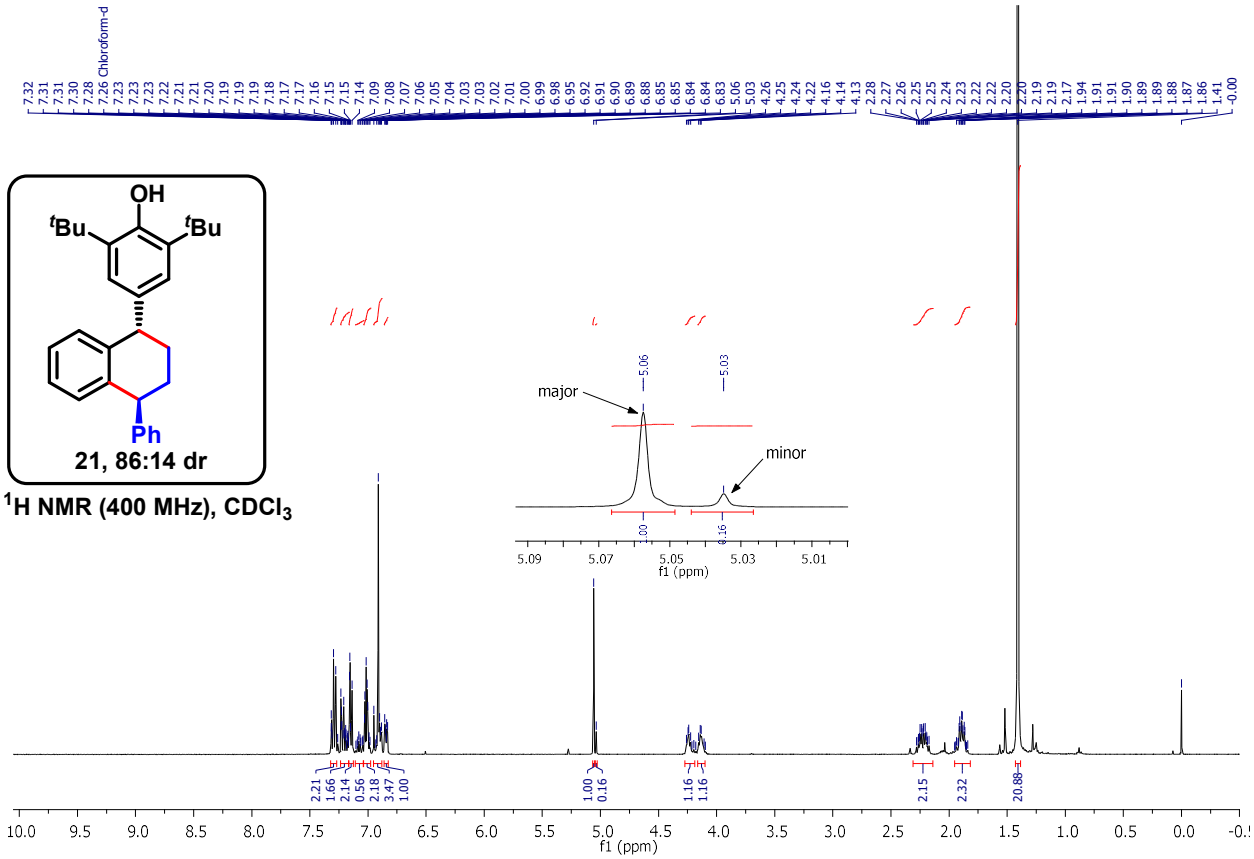

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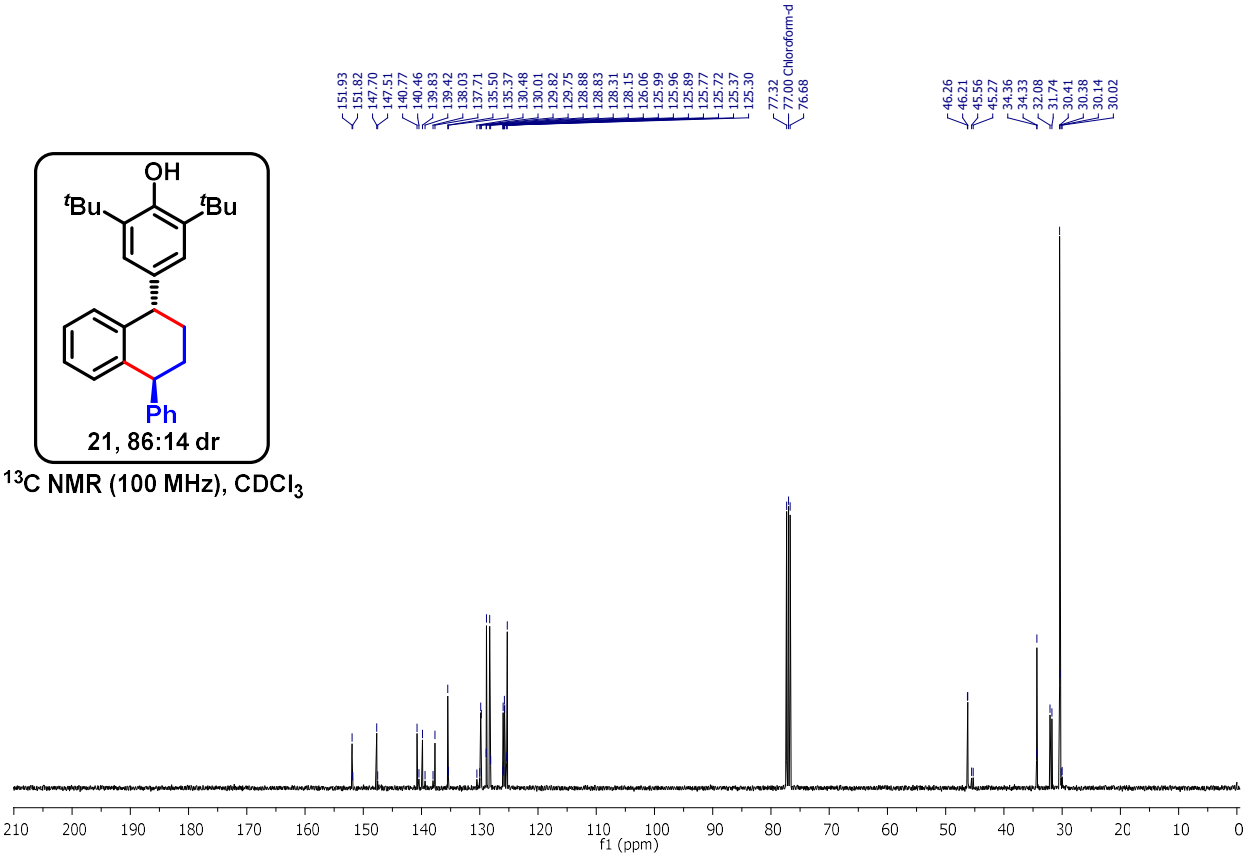

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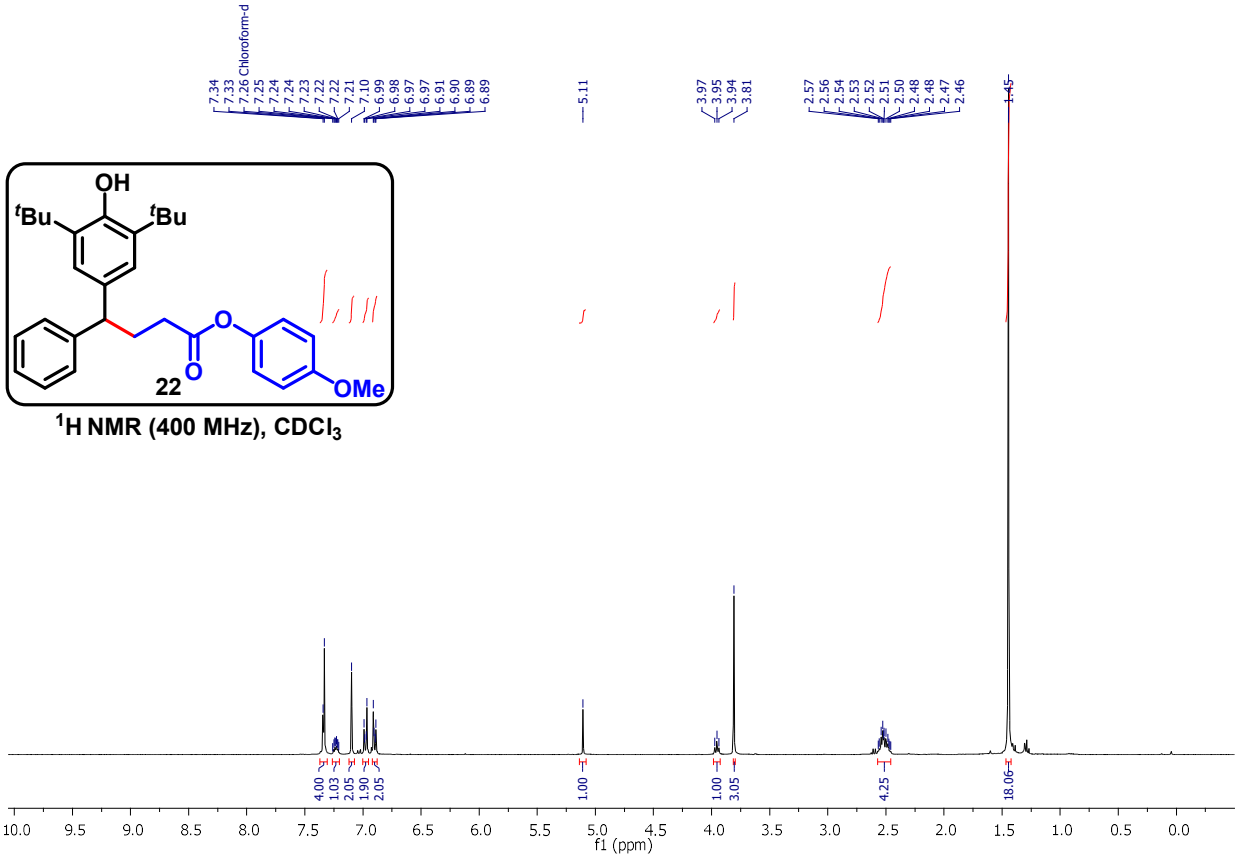

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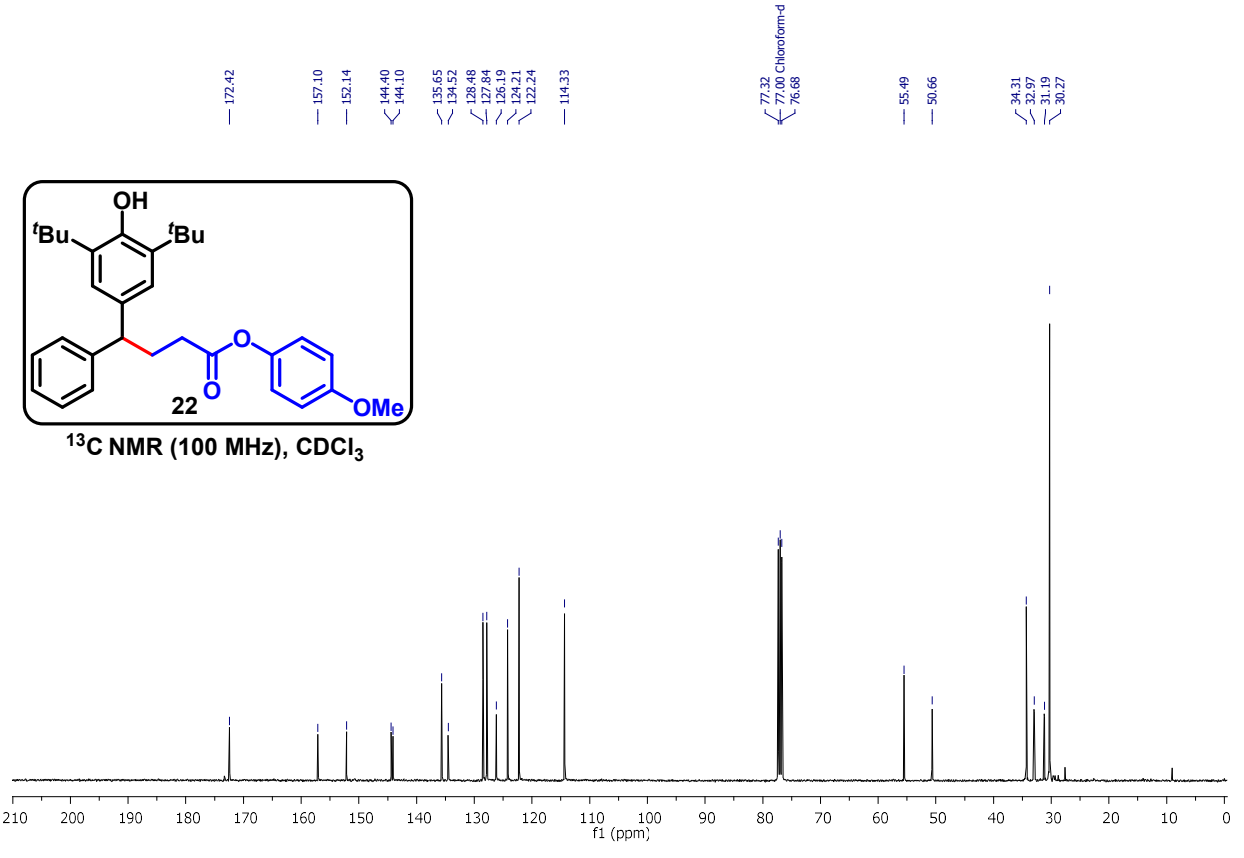

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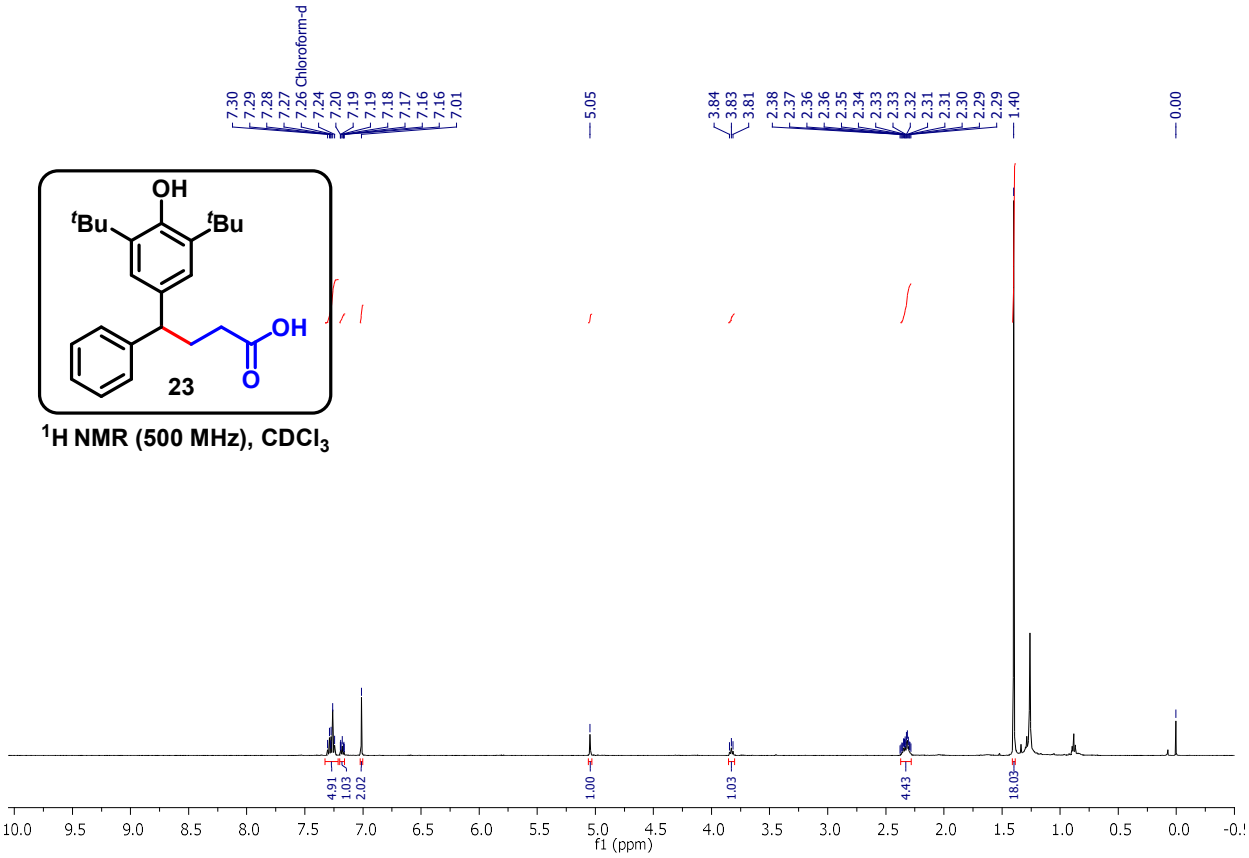

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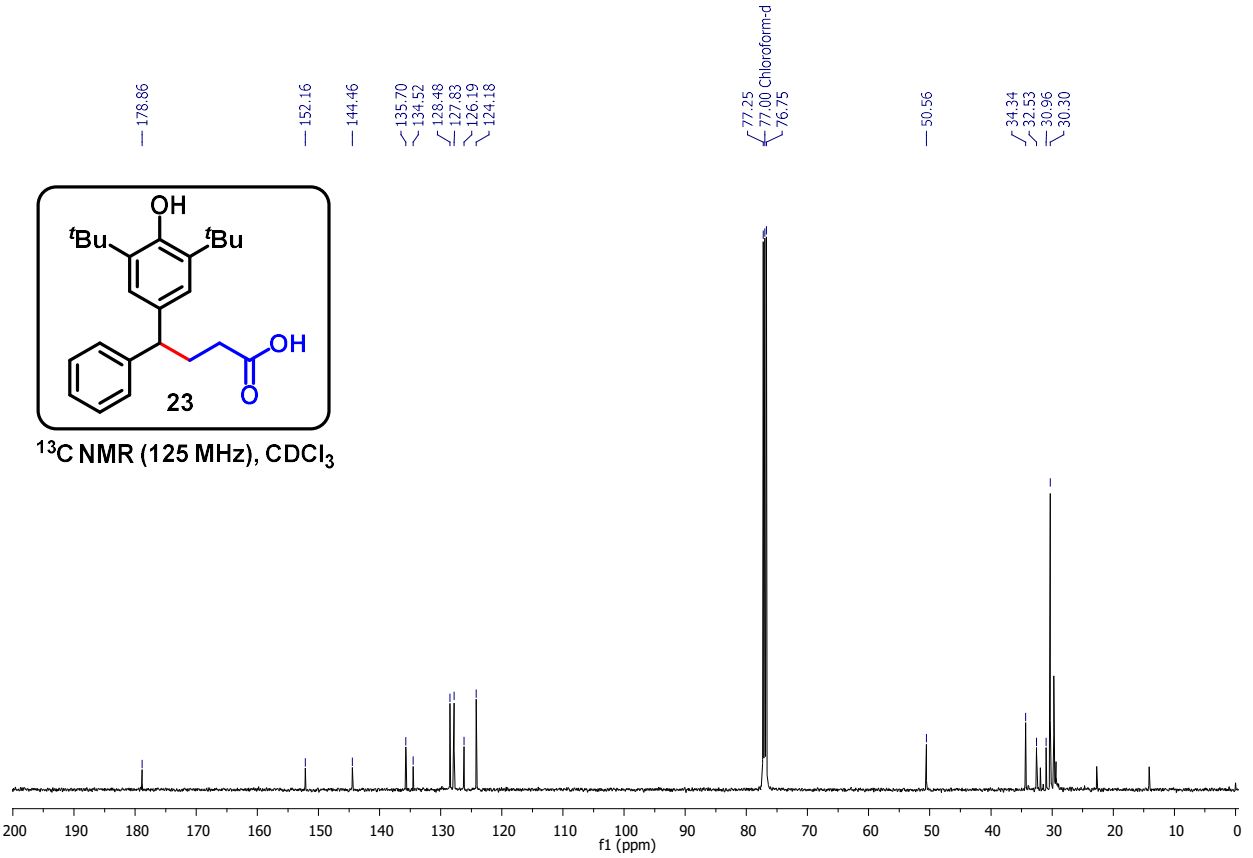

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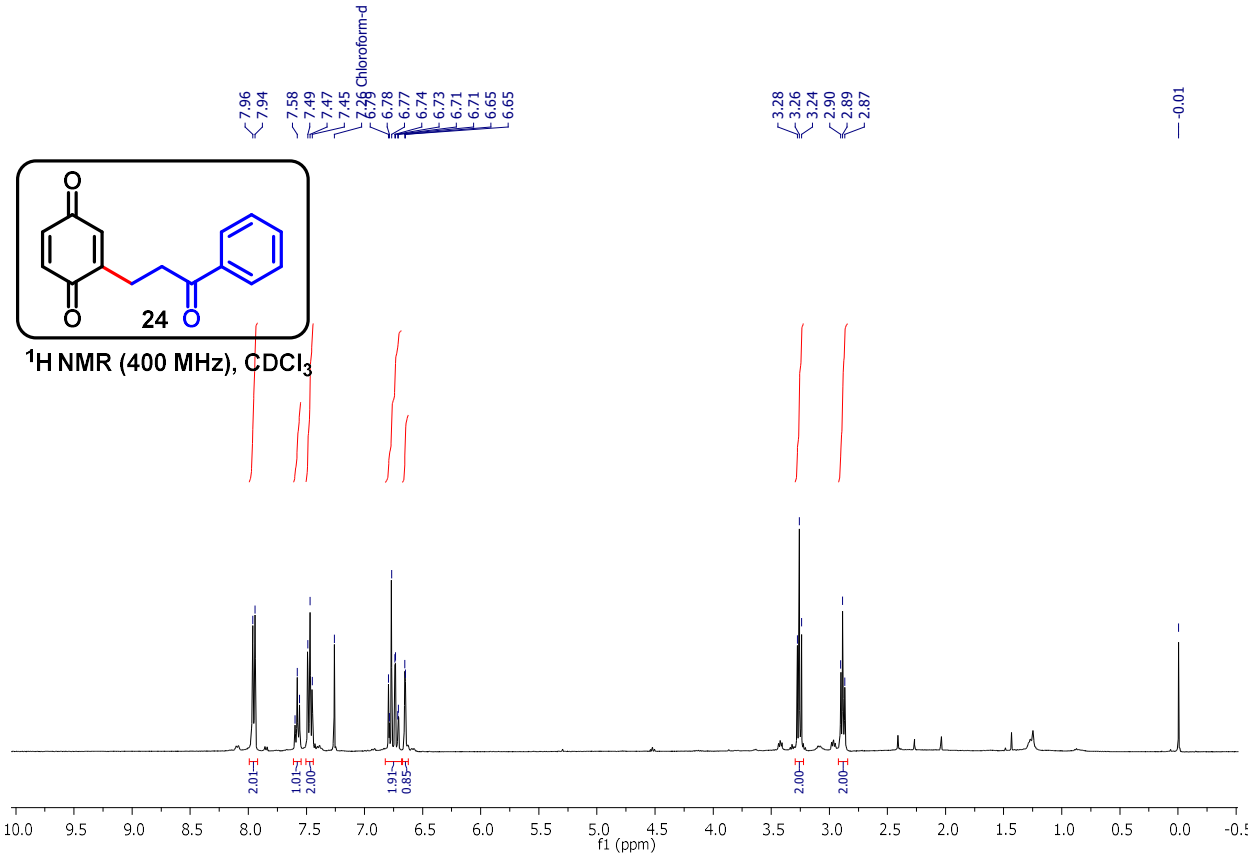

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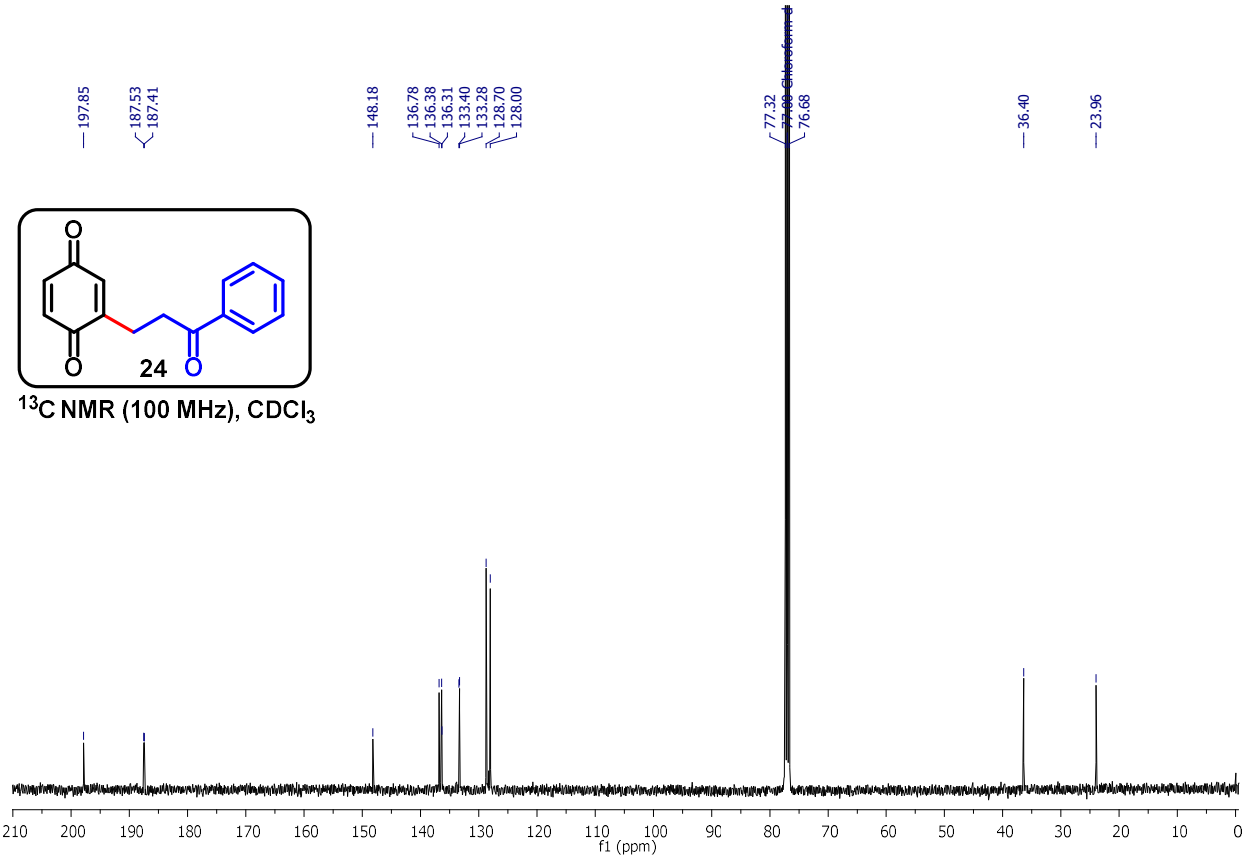

^{13}C NMR (100 MHz), $CDCl_3$

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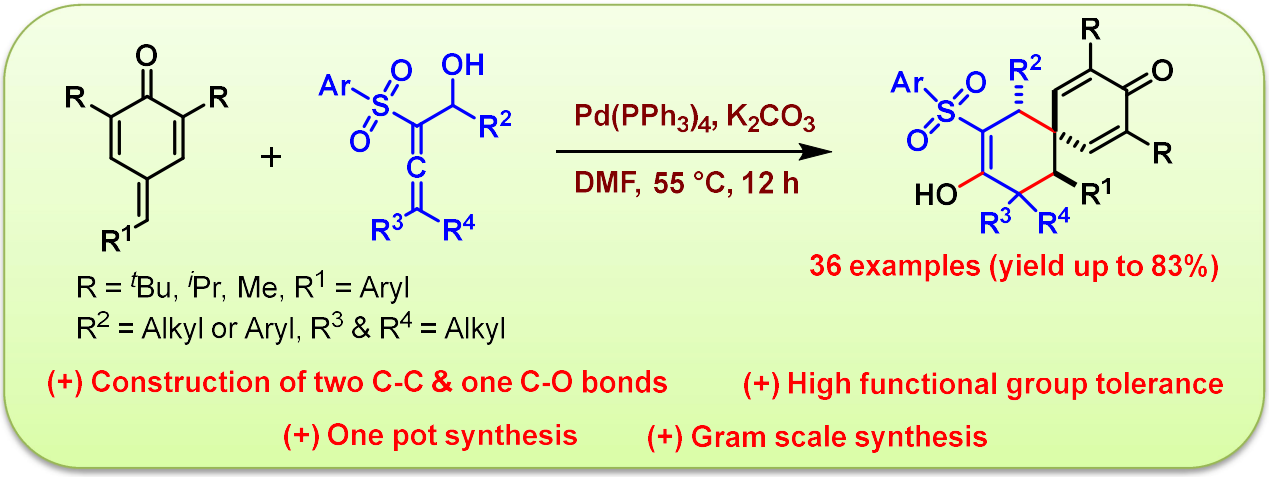
CHAPTER-4

1,6-Conjugate Addition Initiated Formal [4+2] Annulation of *p*-Quinone Methides with Sulfonyl Allenols: An Unique Access to Spiro[5.5]undeca-1,4-dien-3-one Scaffolds.

1,6-Conjugate Addition Initiated Formal [4+2] Annulation of *p*-Quinone Methides with Sulfonyl Allenols: An Unique Access to Spiro[5.5]undeca-1,4-dien-3-one Scaffolds

This chapter includes an expedient one-pot synthesis of carbocyclic spiro[5.5]undeca-1,4-dien-3-ones *via* 1,6-conjugate addition initiated formal [4+2] annulation sequences employing *p*-quinone methides and sulfonyl allenols, is presented. Further, this synthetic protocol tolerates a wide variety of *p*-quinone methides and sulfonyl allenols and affords the corresponding structurally unique spiro[5.5]undeca-1,4-dien-3-ones in good to excellent yields under mild reaction conditions.



Chem. Commun., **2020**,*56*, 5022-5025.

4.1 Introduction

The ubiquity of spirocyclohexadienone framework in a plethora of natural products and pharmaceuticals constitutes the efficient construction of this core of significant interest.[1,2] Spiro[5.5]undeca- 1,4-dien-3-ones, an important subclass of spirocyclohexadienones is regarded as a privileged structural scaffold that are abundantly present in natural products such as tatanan B-C, laurencenone B-C and other similar bioactive molecules (Figure. 4.1).[3,4] Indeed, these scaffolds exhibit various biological activities such as anti-biofouling activity, antiproliferative activity, cytotoxicity against HeLa and Hep-2 human carcinoma cell lines and antifungal activities.[4] Besides, they are valuable intermediates in the synthesis of several natural products.[4b] There are several strategies exists in the literature for the efficient construction of spirocyclohexadienone

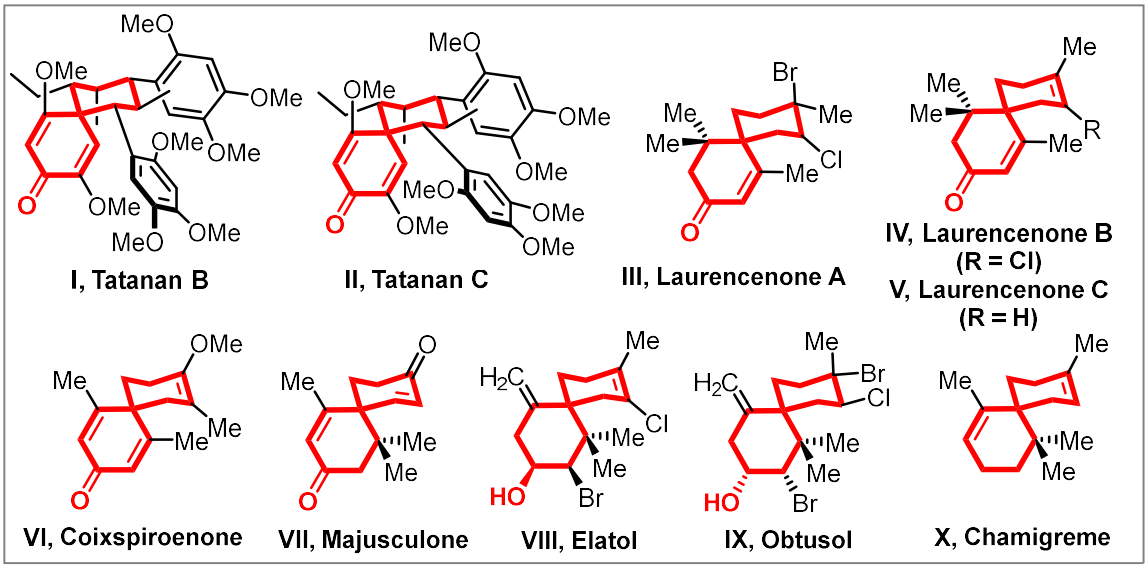


Fig. 4.1. Representative spiro[5.5]undeca-1,4-dien-3-one based natural products.

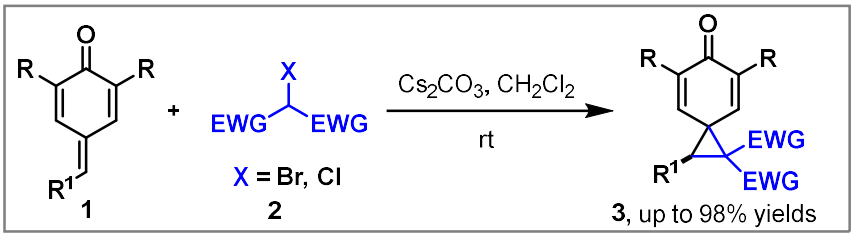
core. However, the methods available for the preparation of spiro[5.5]undeca-1,4-dien-3-one core remains elusive.[5] Therefore, the development of a new streamlined strategy to access this class of structurally interesting and synthetically challenging spirocycles is highly desirable. As discussed in chapter 1, *p*-quinone methides (*p*-QMs) have been employed in many 1,6- addition reactions to generate complex molecular architecture.[6,7] In contrast to simple 1,6-nucleophilic addition reactions, cycloaddition reactions that result in spiro-cyclization of *p*-QMs have received less attention because dearomatization of the reaction intermediate is required. In recent years, intermolecular [2 + n] cycloaddition reactions for the synthesis of spirocarbocycles by employing *p*-QM as a synthon and prefunctionalized nucleophiles containing additional functional sites have made significant progress.[8-11] Few selected reports on [2 + n] cycloaddition

reactions to synthesize spirocarbocycles have been described as follows.

4.2 Literature Precedence on [2 + n] Annulation Reactions for the Synthesis of Spirocarbocycles:

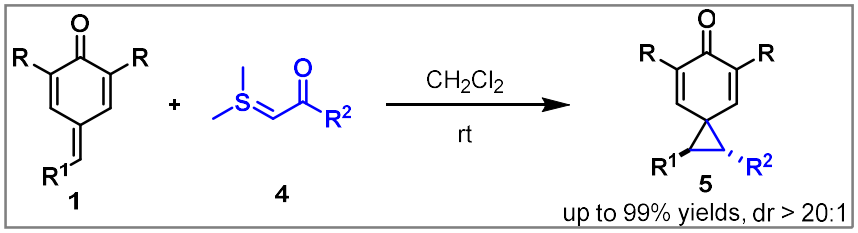
[2 + 1] Annulation Reaction:

The reaction of *p*-QMs **1** with *α*-bromo malonates, sulfonium salts, sulfur ylides and ammonium ylides are successfully employed in [2 + 1] annulation reaction to produce different spiro-cyclopropane derivatives.[8] In 2015, Lin and co-workers reported a 1,6-addition induced dearomatization strategy of *p*-QMs **1** with *α*-halo malonates **2** for the efficient construction of carbocyclic spiro[2.5]octa-4,7-dien-6- ones **3**. The method obviated the need for metal catalysis and proceeded well under mild conditions. The final spiro-products contained two or three consecutive quaternary centres (Scheme 4.1).[8a]



Scheme 4.1. [2 + 1] Annulation reaction of *p*-QM with *α*-halo malonates.

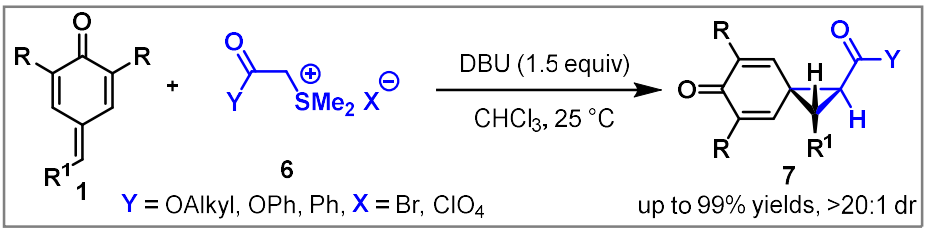
The same group in 2015 demonstrated 1,6-conjugate addition mediated [2+1] annulation of *p*-QMs **1** with sulfur ylides **4** to access various carbocyclic spiro[2.5]octa-4,7-dien-6-one derivatives **5**. The reaction exhibited high diastereoselectivity, good functional group tolerance and scalability, and avoiding metals and bases (Scheme 4.2).[8b]



Scheme 4.2. [2 + 1] Annulation reaction of *p*-QM with sulfur ylides.

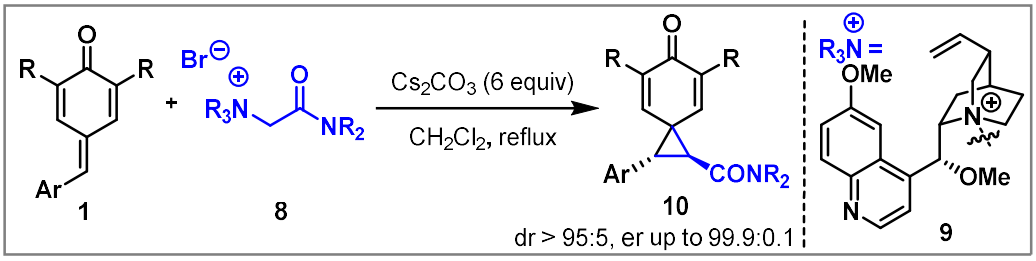
In 2016, Fan *et al*. reported DBU-mediated stereoselective [2 + 1]-carbo-spirocyclopropanation of *p*-QMs **1** with sulfonium salts **6** *via* 1,6-addition induced intramolecular dearomatizing cyclization cascade. This reaction provides a mild and effective method for assembling synthetically and structurally attractive spirocyclopropanyl *para*-dienones **7**. Usage of axially chiral sulfonium salt has enabled the enantioselective access to such functionalized

para-dienones (Scheme 4.3).[8c]



Scheme 4.3. [2 + 1] Annulation reaction of *p*-QM with sulfonium salts.

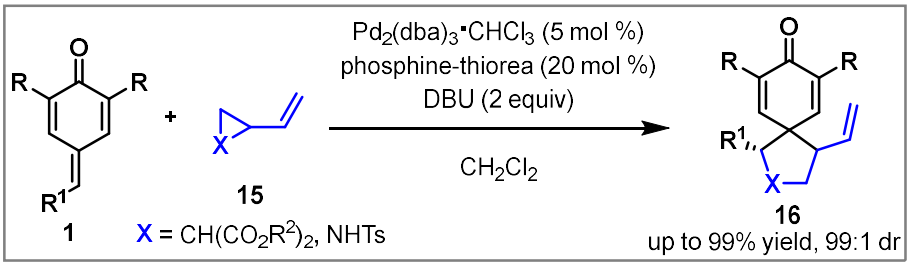
In 2017, Waser and co-workers reported enantioselective spirocyclopropanation employing cinchona alkaloid-based chiral ammonium ylides **8** with *p*-quinone methides **1**. This method offers a straightforward protocol for the construction of chiral spiro[2.5]octa-4,7-dien-6-one skeleton **10**, a frequently found structural motif in important biologically active molecules (Scheme 4.4).[8d]



Scheme 4.4. Enantioselective [2 + 1] annulation reaction of *p*-QM with ammonium ylides.

[3 + 2] Annulation Reaction:

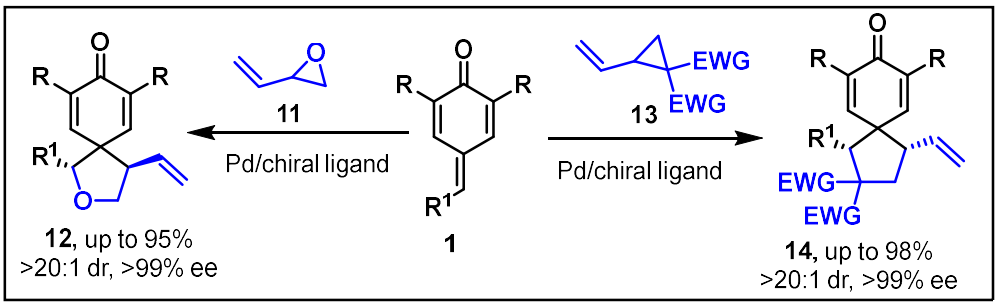
In 2016, Lin and co-workers developed intermolecular [3 + 2] annulation between *p*-QMs **1** and vinyl cyclopropanes **15** for the synthesis of spiro[4.5]deca-6,9-diene-8-ones **16**. The palladium and phosphine-thiourea cooperative catalysis simultaneously activate *p*-QM and vinyl cyclopropane, providing the spiro-products with high yields and diastereoselectivities. The reaction exhibited good functional group compatibility and scalability (Scheme 4.5).[9a]



Scheme 4.5. [3 + 1] Annulation reaction of *p*-QM with vinyl cyclopropanes.

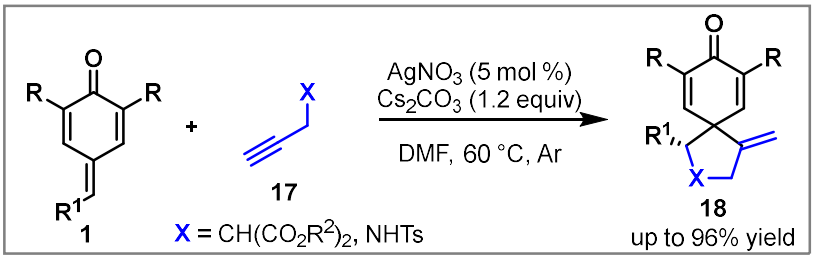
On a similar line, in the same year, Zhao *et al*. reported stereoselective Pd-catalyzed 1,6-conjugate addition induced formal [3 + 2] annulation of *p*-quinone methides **1** with vinyl epox

ides/cyclopropanes **11/13**. This protocol efficiently provides various carbocyclic spiro[4.5]decane derivatives **14** with excellent stereocontrol at ambient temperature from easily accessible starting materials and catalysts (Scheme 4.6).[9b]



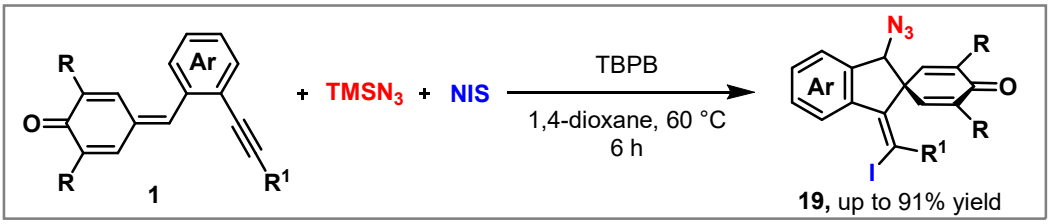
Scheme 4.6. [3 + 1] Annulation reaction of *p*-QM with vinyl epoxides/cyclopropanes.

In 2017, Lin *et al.* documented the silver-catalyzed cascade 1,6-addition/5-exo-dig cyclization reaction of *p*-quinone methides **1** with propargyl malonates **17**. This strategy provides efficient access to spiro[4.5]deca-6,9-diene-8-ones in high yields with good functional group tolerance and high atom economy (Scheme 4.7).[9c]



Scheme 4.7. [3 + 1] Annulation reaction of *p*-QM with propargyl malonates.

In 2018, the same group developed the three component cascade radical iodoazidation of *p*-QMs **1** with $TMSN_3$ and NIS to construct carbocyclic spiro[4.5]deca-6,9-dien-8-ones **19**. This chemoselective and efficient 1,6-addition of azide radical triggered a regioselective 5-exo-dig cyclization/radical coupling process, allowing C–N, C–C, and C–I bonds in a one-pot (Scheme 4.8).[10]



Scheme 4.8. [3 + 1] annulation *via* radical cascade between *p*-QMs, $TMSN_3$ and NIS.

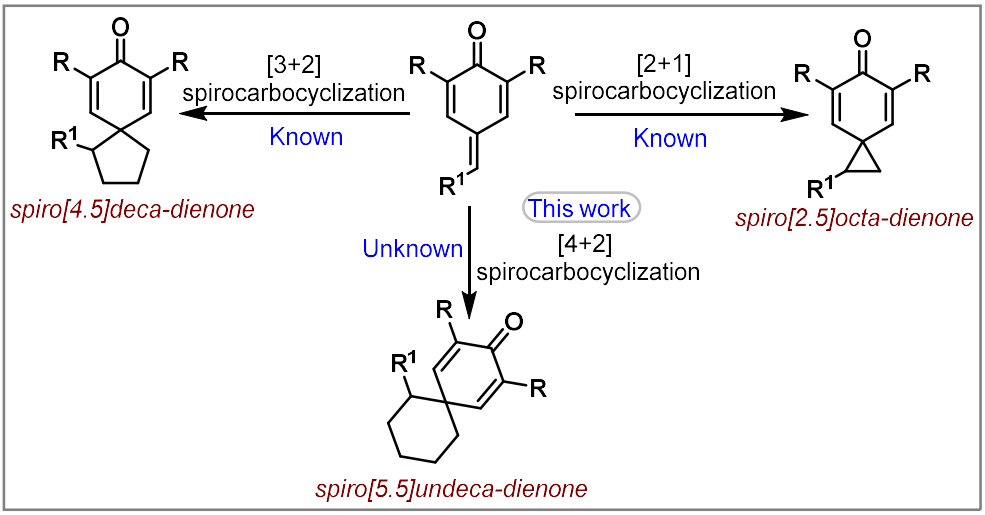
The spirocyclization of vinyl *p*-Quinone methides (*p*-VQMs) with bromomalonates or sulfur

ylides *via* 1,6-Addition/VCP rearrangement reactions has also been discovered to achieve spiro[4.5]deca-6,9-dien 8- ones.[11]

4.3. Present Work

4.3.1. Statement of the Problem

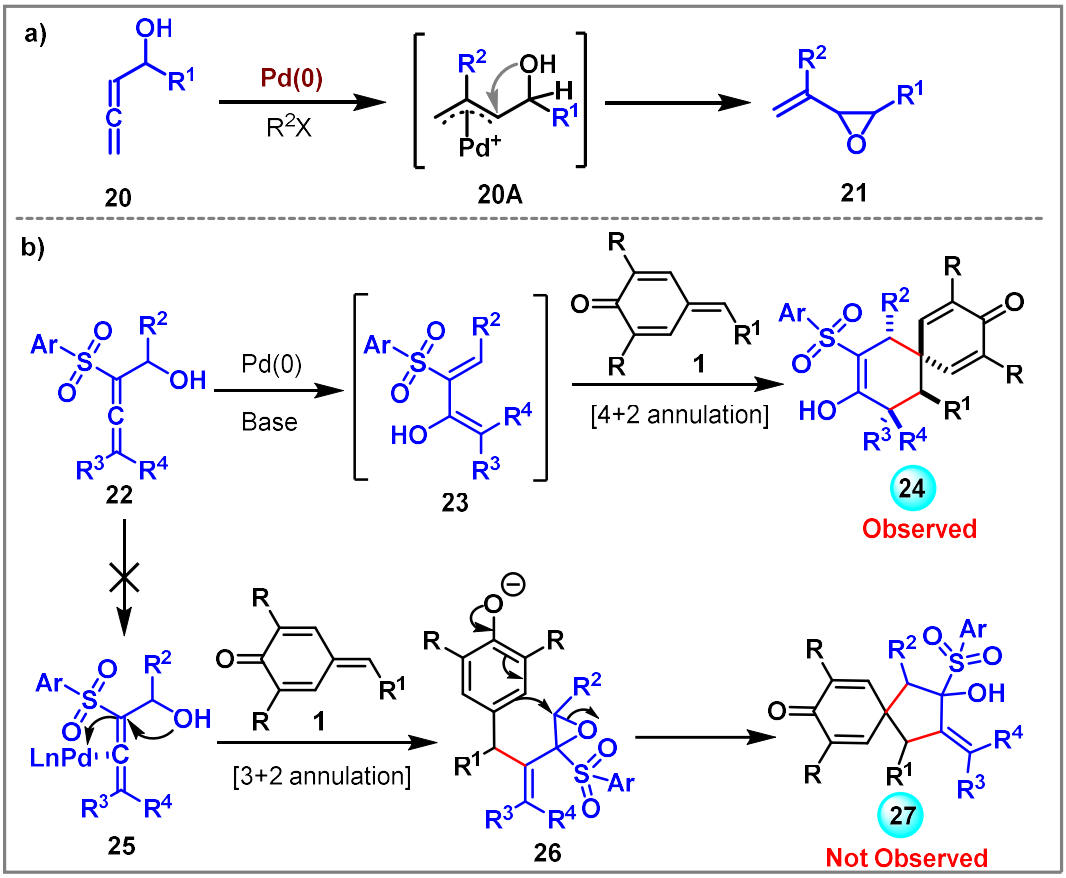
As discussed above, the [2+1] and [3+2]-carbocyclic dearomative spirocyclization reactions with *p*-QMs have been well studied. Both the [2+1] and [3+2] carbocyclization reactions gave spiro[2.5]octa-4,7-dien-6-one and spiro[4.5]deca-6,9-diene-8-ones core respectively. However, to the best of our knowledge, there is no report on the construction of carbocyclic spiro[5.5]undeca-7,10-dien-9-ones employing *p*-QM (Scheme 4.9).



Scheme 4.9. Previous work: *p*-QM induced [2+n] spirocarbocyclization.

On the other hand, in the last few decades, allene derivatives have received considerable attention mainly due to their unique reactivity and ability to form important molecules with diverse functionalities.[12] Among these, sulfonyl allenols are unique as electron-withdrawing sulfone moiety adjacent to the π-system helps to control its chemistry; however, its potential synthetic utility remains underexplored.[13] Transition metal-catalyzed, especially palladium-mediated reactions of allene derivatives, are quite intriguing and possess wide synthetic utility.[14] Significant contributions from the group of Ma[15] and Harmata[13] have led to many pioneering advances in this area. In 1999, Ma and co-workers demonstrated the Pd-catalyzed insertion and subsequent cyclization reaction of 2,3-allenols with aryl or alkenyl halides. This reaction produces highly optically active *trans*-2,3-disubstituted vinylic oxiranes in a diastereoselective manner (Scheme 4.10a). Intrigued by the chemistry of allenols and the recent developments in [2+n]-annulation reactions employing *p*-quinone methides, we reasoned that sulfonyl allenol

could undergo cycloetherification reaction followed by 1,6-conjugate addition/dearomatization with *p*-QM under palladium catalysis would form spiro[4.5]deca-6,9-dien-8-one core **27** (Scheme 4.10b). Surprisingly, instead of spiro[4.5]deca-6,9-dien-8-one core **27,** we observed the formation of spiro[5.5]undeca-1,4-dien-3-one derivative **24**. In this chapter, we describe an unprecedented, palladium-catalyzed, 1,6-conjugate addition initiated formal [4+2] annulation reaction between sulfonyl allenols and *p*-QM that enables highly regio and diastereoselective access to carbocyclic spiro[5.5]undeca-1,4-dien-3-one derivatives in one-pot.



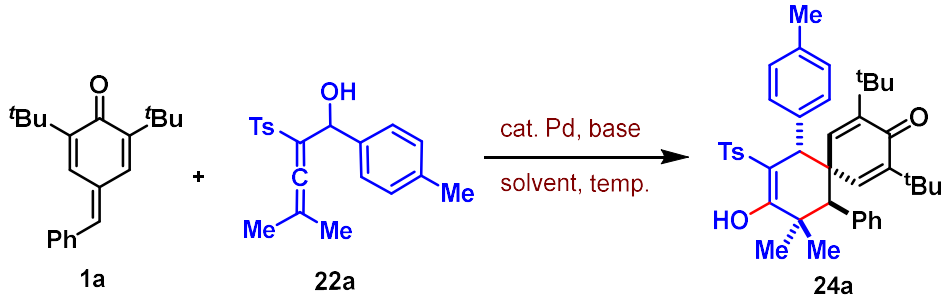
Scheme 4.10. Hypothesis on spirocarbocyclization sulfonyl allenol with *p*-QMs.

4.4 Results and Discussion

4.4.1 Optimization of Reaction Conditions

To test our hypothesis, the present studies were initiated by treating *p*-QM **1a** with sulfonyl allenol **22a** in the presence of $Pd(PPh_3)_4$ (5 mol %) using K_2CO_3 (1.5 equiv) as a base in DMF at room temperature (Table 4.1). To our surprise, under these conditions, spiro[5.5]undeca-1,4-dien-3-one derivative **24a** was isolated, albeit in 10% yield (Table 4.1, entry 1). The structure of **24a** was characterised with the help of NMR spectroscopy and HRMS

Table 4.1. Optimization of Reaction Conditions[a]



Entry	Catalyst	Base	Solvents	Temp	Yield[b] (%)
1	$Pd(PPh_3)_4$	K_2CO_3	DMF	rt	10
2	$Pd(PPh_3)_4$	K_2CO_3	DMF	rt	22[c]
3	$Pd(PPh_3)_4$	K_2CO_3	DMF	55 °C	60
4	$Pd(PPh_3)_4$	Na_2CO_3	DMF	55 °C	NR
5	$Pd(PPh_3)_4$	K_3PO_4	DMF	55 °C	18
6	$Pd(PPh_3)_4$	Cs_2CO_3	DMF	55 °C	NR
7	$Pd(PPh_3)_4$	K_2CO_3	THF	55 °C	10
8	$Pd(PPh_3)_4$	K_2CO_3	DMSO	55 °C	NR
9	$Pd(PPh_3)_4$	K_2CO_3	CH_3CN	55 °C	NR
10	$Pd(PPh_3)_2Cl_2$	K_2CO_3	DMF	55 °C	NR
11	$Pd_2(dba)_3$	K_2CO_3	DMF	55 °C	NR
12	$Pd(OAc)_2$	K_2CO_3	DMF	55 °C	NR
13	$Pd(OAc)_2$	K_2CO_3	DMF	55 °C	NR[d]
14	$Pd(PPh_3)_4$	K_2CO_3	DMF	70 °C	46
15	$Pd(PPh_3)_4$	K_2CO_3	DMF	55 °C	82[e]
16	$Pd(PPh_3)_4$	K_2CO_3	DMF	55 °C	83[f]
17	--	K_2CO_3	DMF	55 °C	NR

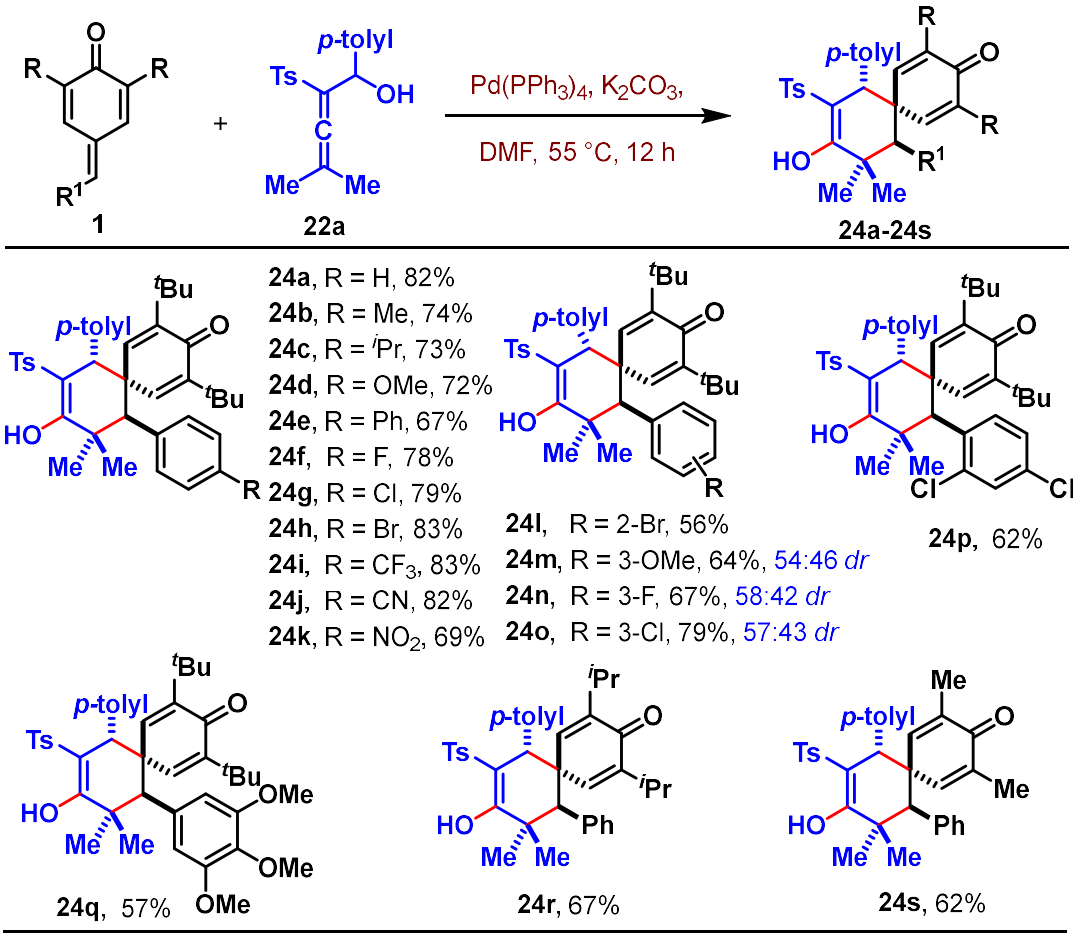
[a]All reactions were performed using with 0.33 mmol **1a**, 0.51 mmol **22a**, 0.51 mmol base, 5 mol % $Pd(PPh_3)_4$, dry DMF (2.0 mL), 12 h; [b]Isolated yields; [c]3.0 equiv. of K_2CO_3 was employed; [d]20 mole % PPh_3 ligand was employed; [e]10 mol % $Pd(PPh_3)_4$ catalyst was employed; [f]15 mol% $Pd(PPh_3)_4$ catalyst was employed.

analysis. In the ^{1}H NMR spectrum of **24a**, the *tert*-butyl groups of *p*-QM at 2,6-position appeared as two separate singlets at δ 1.13(s, 9H) and 0.66 (s, 9H), whereas the two characteristic CH-methine protons appeared as a singlet at δ 3.23 (s, 1 H) and 3.40 (s, 1 H). In the ^{13}C NMR spectrum, the singlet at δ 185.7 corre sponds to *para*-dienone carbonyl, and the characteristic spiro-carbon appeared at δ 44.5 (s). The HRMS peak at 637.3344 (calculated for $C_{41}H_{49}O_4S$ 637.3346) further supported the constitution of compound **24a.** With this structure confirmation and inspired by our initial result, we studied various parameters to optimize the reaction conditions. While increasing the amount of K_2CO_3 to 3.0 equiv, the yield of the desired product **24a** increased to 22% (Table 4.1, entry 2). Notably, when the reaction was performed at 55 °C, the yield of **24a** was enhanced to 60% (Table 4.1, entry 3). Subsequently, the effect of bases were examined (Table 4.1, entries 4−6), and found that K_2CO_3 was an efficient base for this transformation. DMF exhibited the best results after screening solvents such as THF, DMSO, and CH_3CN (Table 4.1, entries 7−9). Different palladium catalysts ($Pd(PPh_3)_2Cl_2$, $Pd_2(dba)_3$, $Pd(OAc)_2$ and $Pd(OAc)_2/PPh_3$ were evaluated and found that $Pd(PPh_3)_4$ is the appropriate catalyst of choice (Table 4.1, entries 10-13). Further, we noted that the higher reaction temperature affects the formation of desired product **24a** (Table 4.1, entry 14, 46%). (Table 4.1, entry 15). Further, increasing the catalyst loading did not help to improve the yield (Table 4.1, entry 16). Finally, in the absence of $Pd(PPh_3)_4$ catalyst, we did not observe the formation of the desired product **24a** (Table 4.1, entry 17).

4.4.2 Substrate Scope of *p*-Quinone Methides

With the optimized conditions in hand, we investigated the scope of various *p*-QMs **(1)** with sulfonyl allenol (**22a**), and the results are summarized in Table 4.2. It was found that a series of *para*-, *meta* and *ortho*- substituted *p*-QMs (**1b**–**1o**) underwent smooth [4+2] annulation with **22a** to deliver the corresponding spiro[5.5]undeca-1,4-dien-3-one products (**24b**–**24o**) in good yields (56–83%) with high tolerance of functional groups, including halides (–F, –Cl, –Br), strong electron donating (-Me, -*i*-Pr, –OMe, –Ph) and withdrawing groups (–CF_3, –CN, –NO_2). In the case of meta substituted *p*-QMs, the desired products are obtained as a diastereomeric mixture. Interestingly, the di- and tri-substituted *p*-QMs were also readily engaged under the optimized condition to give the corresponding products **24p** and **24q** in 62% and 57% yields, respectively. Notably, while replacing the di-*tert*-butyl groups of *p*-QMs with di-*iso*-propyl and dimethyl groups, the respective products **24r** and **24s** were obtained in 67% and 62% yields.

Table 4.2. Substrate scope of *p*-quinone methides **1**[a,b,c]



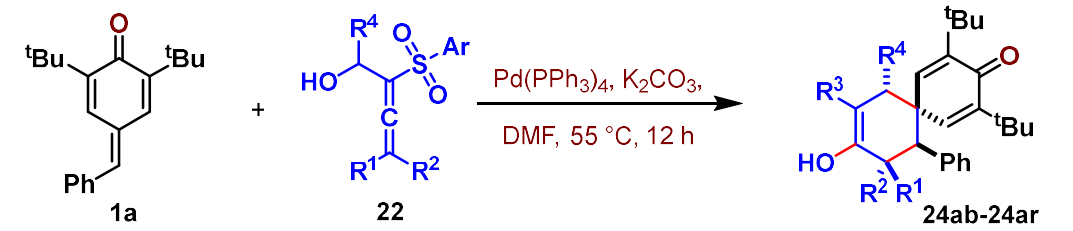
[a]All reactions were performed using with 0.33 mmol **1**, 0.51 mmol **22a**, 1.0 mmol K_2CO_3, 10 mol % $Pd(PPh_3)_4$, dry DMF (2.0 mL), 55 °C 12 h; [b]Isolated yields are given; [c]dr ratio determined by ^1H NMR analysis.

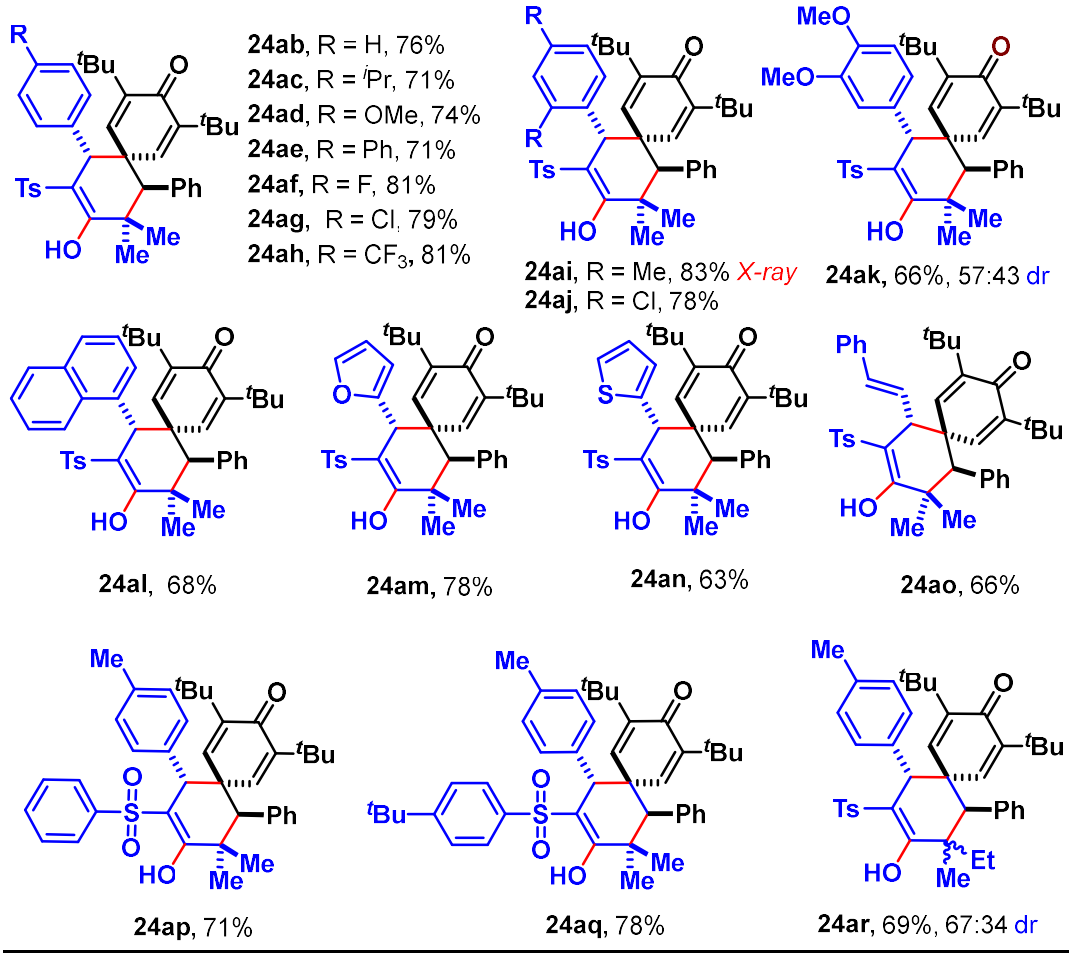
4.4.3 Substrate Scope of Sulfonyl Allenols

Subsequently, we explored the reactivity of various sulfonyl allenols **2** with **1a**. As shown in Table 4.3, a wide range of sulfonyl allenols (**22b**–**22h**) with mono-substituted aromatic rings efficiently participated in the [4+2] annulation with **1a** to exclusively furnish the desired spirocyclic products (**24ab**–**24ah**) in good yields (71–81%). Disubstitution on the aryl ring of sulfonyl allenols (**22i** & **22j**) also performed well to afford the desired products **24ai** and **24aj** in 83% and 78%, respectively. It is worth noting that the structure of **24ai** was unambiguously determined by single crystal X-ray diffraction analysis. Besides, 3,4 dimethoxy substitution on aryl ring of sulfonyl allenol **22k was** also well-tolerated to afford the desired product **24ak** in 66% yield with 57:43 dr. Additionally, sulfonyl allenol with bulky naphthyl group could also produce **24al** in 68% yield. Sulfonyl allenols derived from heterocyclic rings such as

2-furanyl and 2- thienyl reacted smoothly with **1a** to give the corresponding products **24am** and **24an** in 78% and 63% yields, respectively. Notably, the trans-cinnamyl group bearing sulfonyl allenol **22o** proved equally effective in this transformation. Further, variation of substitution in the sulfone part of the sulfonyl allenols was also well-tolerated, affording the corresponding products **24ap**–**24aq** in good yields (71–78%). Similarly, sulfonyl allenols bearing unsymmetrical terminal quaternary carbon **22r** also produce **24ar** in 69 % yield with 67:34 dr.

Table 4.3. Substrate scope of sulfonyl allenols[a,b,c]





[a]All reactions were performed using with 0.33 mmol **1a**, 0.51 mmol **22**, 1.0 mmol K_2CO_3, 10 mol % $Pd(PPh_3)_4$, dry DMF (2.0 mL), 55 °C 12 h; [b]Isolated yields are given, [c]dr ratio determined by ^1H NMR analysis.

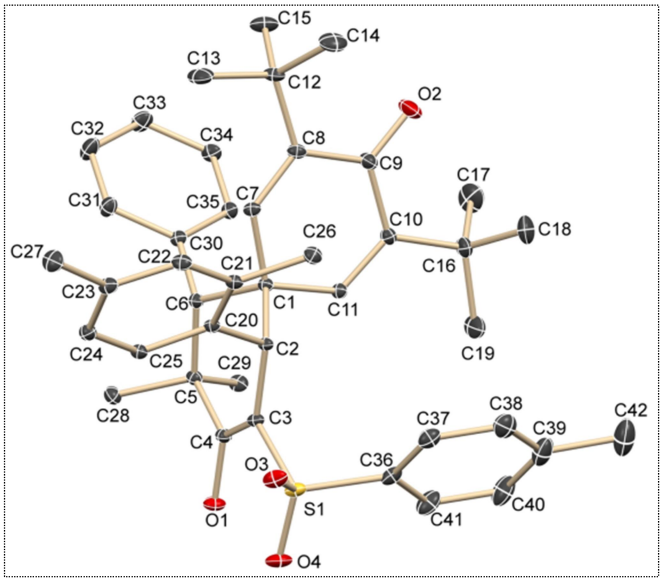
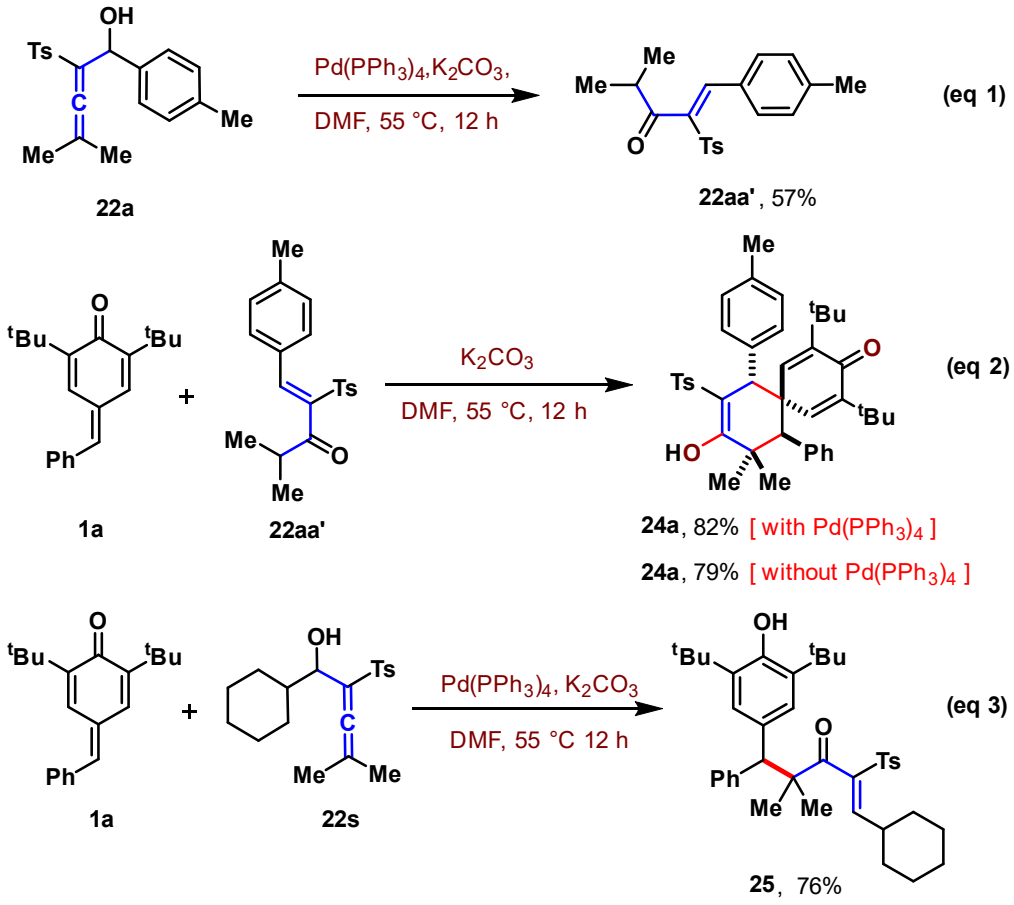


Fig. 4.2.ORTEP drawing of **24ai** (**CCDC1950350**)

4.4.4 Control Experiments

To gain some insights into the mechanistic pathway of this transformation, a few control reactions were carried out. As shown in scheme 4.11, in the absence of *p*-QM, sulfonyl allenol

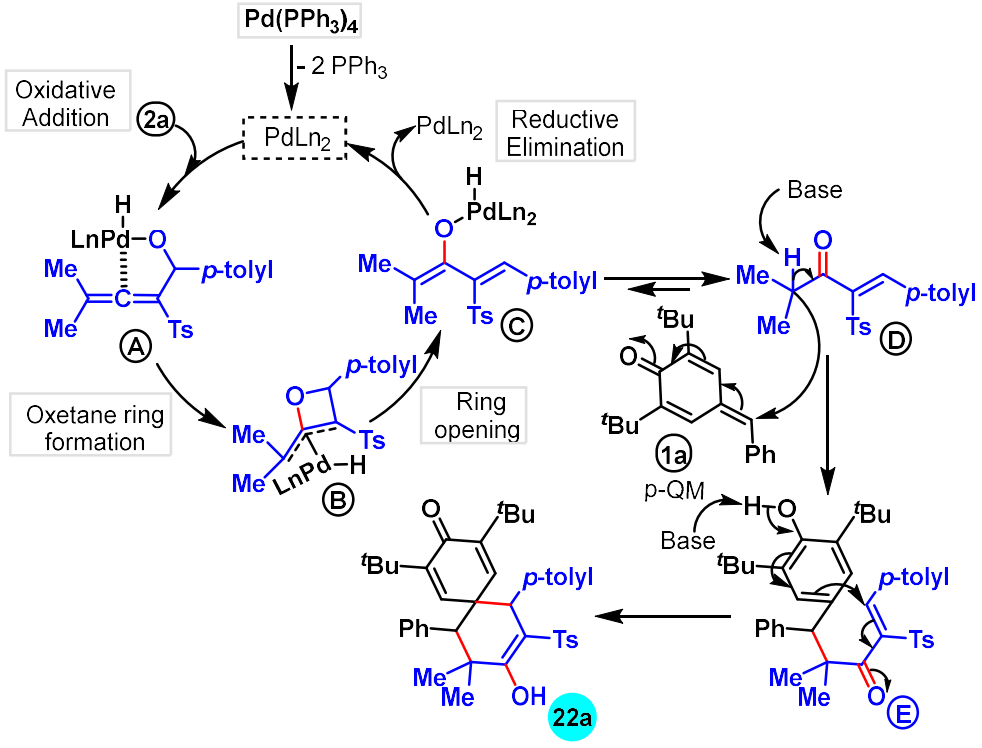


Scheme 4.11. Control experiments

2a alone under optimized conditions provided *α,β*-unsaturated ketone **2aa'** in 57% yield. Further, the intermediate **2aa'** was allowed to react with **1a**, with standard reaction conditions afforded **24a** in 82% yield. Interestingly, the same reaction proceeded well in the absence of $Pd(PPh_3)_4$, the results indicate that palladium is essential only for the formation of *α,β*-unsaturated ketone intermediate from sulfonyl allenols. In addition, under optimized condition, cyclohexyl-derived sulfonyl allenol **2s** with **1a** ceased at conjugated addition product **4**, which imply that the reaction proceeds *via* 1,6-conjugate addition first followed by dearomative spirocyclization.

4.4.5 Reaction Mechanism

Based on the above control experiments and previous reports [16] a tentative reaction mechanism for the [4+2] annulation reaction is depicted in Scheme 3 (Compound **24a** as an example).

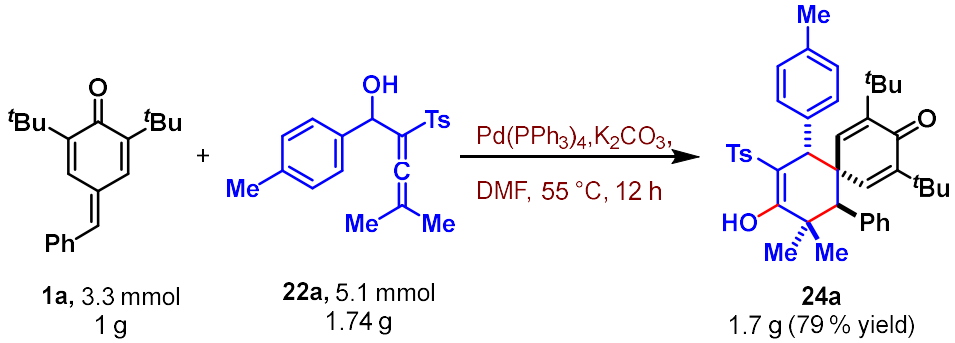


Scheme 4.12. Tentative mechanism of the reaction.

At first, the reaction is initiated by Pd-alkoxide **A** formation through oxidative addition of sulfonyl allenol **22a** to Pd (0). Further, **A** undergoes 4-exodig metala-oxycyclization, giving rise to the π-allyl oxetene intermediate **B**. The ring opening of intermediate **B** generates reactive diene Pd-complex **C**. Next, the intermediate **C** tautomerizes to intermediate **D,** which on deprotonation under basic condition undergoes 1,6-conjugate addition with *p*-QM **1a** gave intermediate **E,** which on subsequent ring closure dearomatization generates the desired spirocyclic framework.

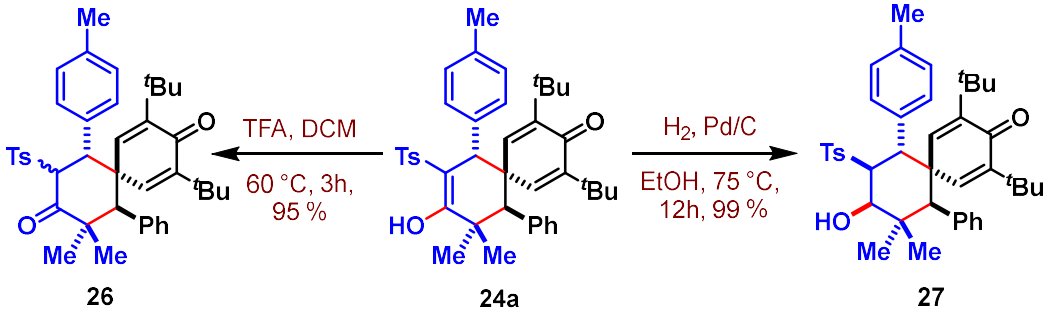
4.4.6 Gram Scale and Synthetic Utility

To confirm the scalability of this protocol, a scale-up reaction was carried out. Under optimal conditions, the reaction of *p*-QM **1a** with sulfonyl allenol **22a,** the corresponding spiro-dienone product **24a,** was obtained in a 79 % yield (Scheme 4.13).



Scheme 4.13. Gram scale synthesis.

Subsequently, synthetic transformations of the spiro-dienone product **24a** were conducted. As shown in scheme 4.14, Pd/C-catalyzed hydrogenation of **24a** in ethanol readily afforded hydrogenated product **27** in 99% yield. Moreover, tautomerization of **24a** with TFA led to the corresponding diketone **26** in a 95 % yield.



Scheme 4.14. Synthetic utility

4.5 Conclusion

In conclusion, we have developed a facile one pot strategy to prepare carbocyclic spiro[5.5]undeca-1,4-dien-3-ones *via* conjugate addition induced formal [4+2] annulation of sulfonyl allenols with *p*-QMs for the first time. The reaction features a broad substrate scope and good functional group tolerance, allowing efficient access to a wide variety of highly substituted spiro[5.5]undeca-1,4- dien-3-ones in good yields. Importantly, the present strategy provides straightforward access to spiro[5.5]undeca-1,4-dien-3-one skeleton that is prevalent in several biologically relevant natural products.

4.6 Experimental Section

4.6.1 Preparation of Sulfonyl Allenols:

All the *p*-QMs were prepared as per the procedure described in the section 1.2.5.1 (chapter 1). and all the sulfonyl allenols were prepared following the literature procedures.[13a-b,13c-d]

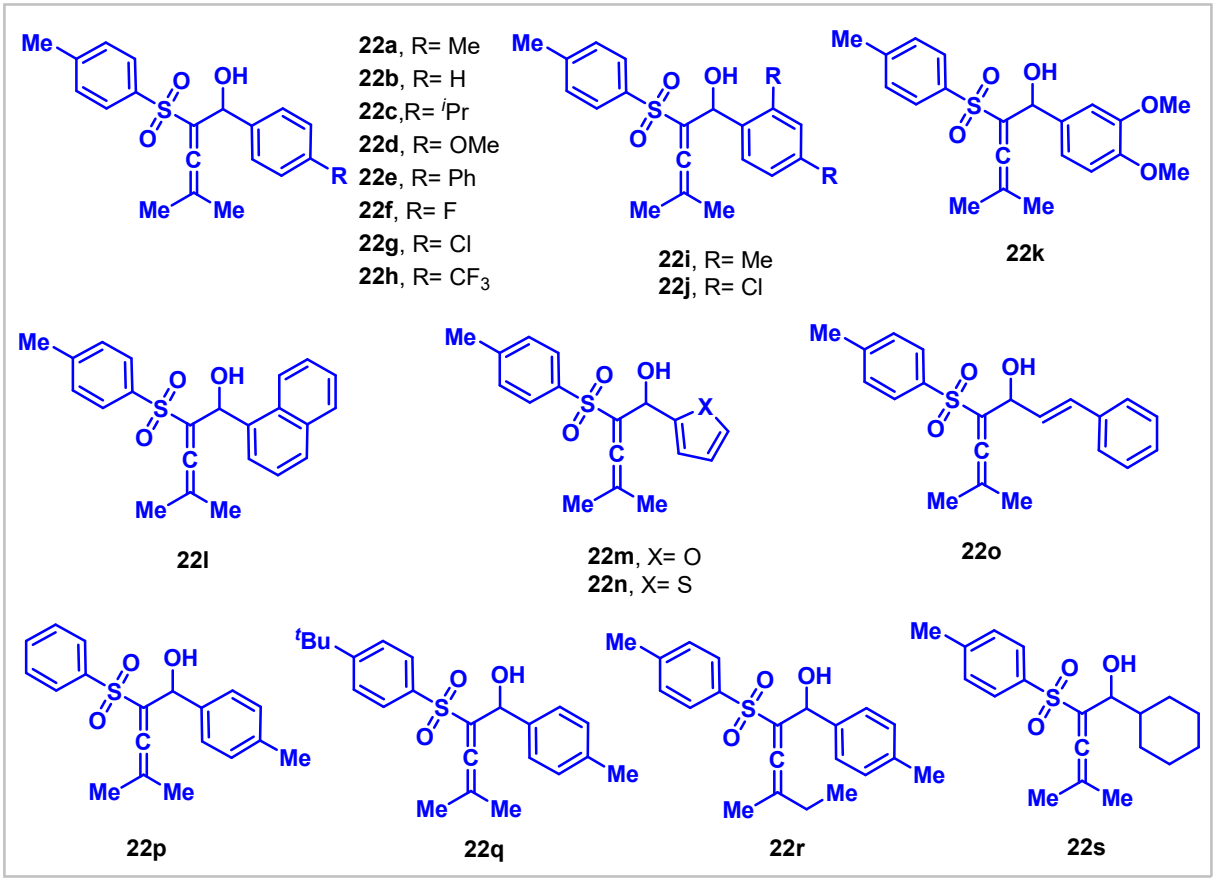
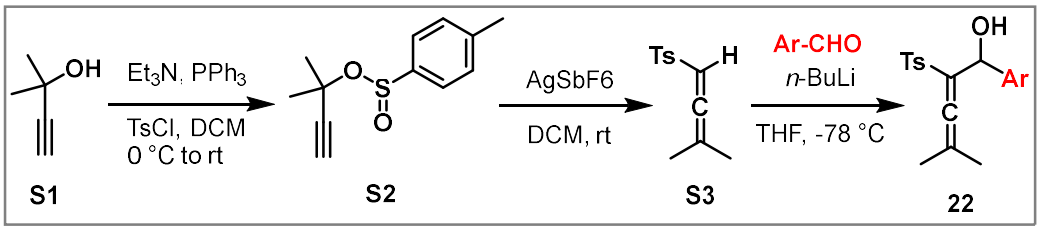


Fig. 4.2 Structures of sulfonyl allenols used in this study.



Scheme 4.15. Preparation of sulfonyl allenols

Step-1: In a flame-dried round bottom flask under argon atmosphere, the *p*-toluenesulfonyl chloride (1.0 eq) was dissolved in CH_2Cl_2 and triethylamine (1.1 eq) was added. A solution of 2-methyl-3-butyn-2-ol **S1** (1.0 eq) and triphenylphosphine (1.0 eq) in CH_2Cl_2 was added drop-wise to the reaction solution at 0 °C over 1 hour. The reaction was stirred at room temperature and monitored by TLC until consumption of sulfonyl chloride. The reaction was quenched with

water and extracted with CH_2Cl_2. The organic extracts were concentrated on the rotary evaporator. The crude product was purified by column chromatography to afford the sulfinate ester **S2**.

*Step-2***:** To a solution of the sulfinate ester **S2** in CH_2Cl_2 (0.1 M) under an argon atmosphere was added silver hexafluoroantimonate (2 mol %). The reaction was stirred at room temperature and monitored by TLC until complete conversion of starting material. The reaction mixture was filtered through Celite in a sintered glass funnel, rinsing with CH_2Cl_2, and the filtrate was concentrated *in vacuo* to yield the pure allenic sulfone **S3**.

Step-3: An allenic sulfone **S3** (1 equiv) was dissolved in dry THF under an argon atmosphere and cooled to -78 °C. A solution of *n*-BuLi (1.74 M in hexanes, 1.2 equiv) was added dropwise at -78 °C. The reaction was stirred for 20 min at -78 °C. Then a solution of aldehyde (1.1 equiv) in THF was added slowly to the reaction mixture at -78 °C. The reaction was stirred at -78 °C for 2 h, then quenched with saturated NH_4Cl (50 mL) and extracted with dichloromethane (3 x 20 mL). The combined organic layers were dried over Na_2SO_4, concentrated by rotary evaporation, and purified by flash column chromatography over silica gel to yield the product **22**.

4.6.2. General Procedure for Preparation Spiro[5.5]undeca-1,4-dien-3-one from *p*-QMs (24):

To a 5 mL screw-cap vial containing a stir bar were added *p*-QMs **1** (0.33 mmol, 1.0 equiv), sulfonyl allenol **22** (0.51 mmol, 1.5 equiv), $Pd(PPh_3)_4$ (10 mol%), K_2CO_3 (3.0 equiv) and dry DMF (4 mL). The reaction vial was fitted with a cap, evacuated, filled with nitrogen and heated at 55 °C for 12 h. The reaction mixture was allowed to warm to ambient temperature. The reaction mixture was diluted with EtOAc, and the organic layer was washed with ice cold water (3 X 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure to afford a crude mixture which was purified by column chromatography (silica gel, petroleum ether/EtOAc) to afford the corresponding spiro[5.5]undeca-1,4-dien-3-one **24** product.

4.6.3. Procedure for the Preparation of Intermediate 22aa':

To a 5 mL screw-cap vial containing a stir bar were added 4-methyl-1-(*p*-tolyl)-2-tosylpenta-2,3-dien-1-ol **22a** (0.29 mmol, 1 equiv), $Pd(PPh_3)_4$ (10 mol%), K_2CO_3 (3.0 equiv) and dry DMF (4 mL). The reaction vial was fitted with a cap, evacuated, and filled with nitrogen and heated at 55 °C for 12 h. The reaction mixture was allowed to warm to ambient temperature. The reaction mixture was diluted with EtOAc and the organic layer was washed with ice

cold water (3 X 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, and the solvent was removed under reduced pressure to afford a crude mixture which was purified by column chromatography (silica gel, petroleum ether/EtOAc) to afford the corresponding intermediate **2aa'**as 57 % yield.

4.6.4 Control Experiment:

To a seal tube containing a stir bar were added *p*-QM **1a** (33 mmol, 1.0 equiv), 4-methyl-1-(*p*-tolyl)-2-tosylpent-1-en-3-one **22aa**' (0.51 mmol, 1.5 equiv), K_2CO_3 (3.0 equiv,) and dry DMF (3 mL). The reaction vial was fitted with a cap, evacuated, and filled with nitrogen and heated at 55 °C for 12 h. The reaction mixture was allowed to warm to ambient temperature. The reaction mixture was diluted with EtOAc and work up with cold H_2O (3 X 10 mL). After completion of the work up, EtOAc was evaporated on rotary evaporator and purified by flash silica gel column using a gradient of ethyl acetate / petroleum ether to afford corresponding 2,4-Di-tert-butyl-9-hydroxy-10,10-dimethyl-11-phenyl-7-(*p*-tolyl)-8-tosylspiro[5.5]undeca-1,4,8-trien-3-one **24a** in 79 %.

4.6.5 Procedure for the Preparation 1-Cyclohexyl-5-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-4,4- dimethyl-5-phenyl-2-tosylpent-1-en-3-one (25):

To a 5 mL screw-cap vial containing a stir bar were added *p*-QM **1a** (0.33 mmol, 1.0 equiv), 1-Cyclohexyl-4-methyl-2-tosylpenta-2,3-dien-1-ol **22s** (0.51 mmol, 1.5 equiv), $Pd(PPh_3)_4$ (10 mol%), K_2CO_3 (3.0 equiv) and dry DMF (4 mL). The reaction vial was fitted with a cap, evacuated, and filled with nitrogen and heated at 55 °C for 12 h. The reaction mixture was allowed to warm to ambient temperature. The reaction mixture was diluted with EtOAc, and the organic layer was washed with ice cold water (3 X 10 mL). After completion of the work up, EtOAc was evaporated on the rotary evaporator and purified by flash silica gel column using a gradient ethyl acetate / petroleum ether to afford corresponding **25** as 76 % yield.

4.6.6 Procedure for Gram Scale Synthesis:

To a seal tube containing a stir bar were added *p*-QM **1a** (3.3 mmol, 1.0 equiv), 4-methyl-1-(p-tolyl)-2-tosylpenta-2,3-dien-1-ol **22a** (5.1 mmol, 1.5 equiv), $Pd(PPh_3)_4$ (10 mol%), K_2CO_3 (3.0 equiv,) and dry DMF (30 mL). The reaction vial was fitted with a cap, evacuated, and filled with nitrogen and heated at 55 °C for 12 h. The reaction mixture was allowed to warm to ambient temperature. The reaction mixture was diluted with EtOAc and work up with cold H_2O (3 X 25 mL). After completion of the work up, EtOAc was evaporated on rotary evaporator and pu-

rified by flash silica gel column using a gradient of ethyl acetate / petroleum ether to afford corresponding product **24a** in 79 % yield.

4.6.7 Procedure for Product Transformations.

a) Procedure for the synthesis of 26:

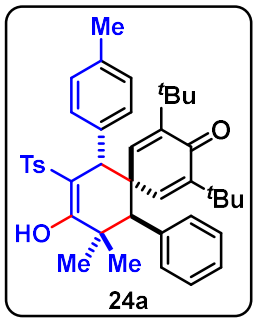
To a 5 mL screw-cap vial containing a stir bar were added 2,4-Di-tert-butyl-9-hydroxy-10,10-dimethyl-11-phenyl-7-(p-tolyl)-8-tosylspiro[5.5]undeca-1,4,8-trien-3-one **24a** (0.33 mmol, 1 equiv.) and DCM (2.0 mL) Trifluoroacetic acid (0.5 ml) The reaction vial was fitted with a cap, evacuated, and filled with nitrogen and heated at 60 °C for 3 h. The reaction mixture was allowed to warm to ambient temperature. The reaction mixture was diluted with DCM and work up with ice cold H_2O (3 X 10 mL). After completion of the work-up, DCM was evaporated on rotary evaporator and purified by flash silica gel column using a gradient of ethyl acetate / petroleum ether to afford the corresponding 2,4-di-*tert*-butyl-8,8-dimethyl-7-phenyl-11-(*p*-tolyl)-10-tosylspiro[5.5]undeca-1,4-diene-3,9-dione **26** in 95% yield.

b) Procedure for Synthesis of 27:

To the solution of **24a** (0.15 mmol, 1 equiv.) in EtOH (5 mL) was added palladium on carbon (10 mg, 10 wt %) in hydrogenation reactor, and the reaction mixture was stirred under hydrogen (300 psi) with 75 °C for 12 h. After the completion of the reaction (indicated by TLC), the catalyst was filtered over a plug of Celite bed (EtOAc eluent), and the solvent was evaporated under reduced pressure to afford the corresponding product 2,4-di-*tert*-butyl-9-hydroxy-8,8-dimethyl-7-phenyl-11-(*p*-tolyl)-10-tosylspiro[5.5]undeca-1,4-dien-3-one **27** in 99% yield.

4.6.8 Characterization of 24a-24z, 24ab-24ar and 25-27, 22aa':

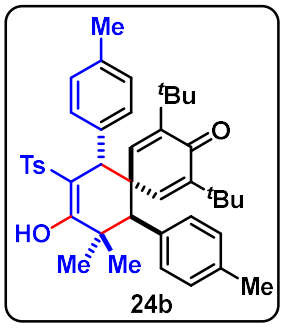
2,4-Di-*tert*-butyl-9-hydroxy-10,10-dimethyl-11-phenyl-7-(*p*-tolyl)-8-tosylspiro[5.5]undeca-1,4,8-trien-3-one (24a):



White Solid, 178 mg, 82 % yield; mp = 180-182 °C; R_f = 0.6 (Pet. ether/Ethyl acetate- 90:10); **^{1}H NMR (500 MHz, $CDCl_3$) δ** = 11.25 (s, 1 H), 7.64 - 7.58 (d, *J* = 8.0 Hz, 2 H), 7.25 - 7.20 (d, *J* = 8.0 Hz, 2 H), 7.14 - 7.02 (m, 5 H), 6.98 (s, 1 H), 6.95 (s, 1 H), 6.91 (d, *J* = 2.7 Hz, 1 H), 6.76 (d, *J* = 7.6 Hz, 2 H), 5.25 (d, *J* = 2.7 Hz, 1 H), 3.40 (s, 1 H), 3.23 (s, 1 H), 2.40 (s, 3 H), 2.34 (s, 3 H), 1.41 (s, 3 H), 1.28 (s, 3 H), 1.13 (s, 9 H), 0.66 (s, 9 H); **^{13}C NMR (125 MHz, $CDCl_3$) δ** =185.7, 169.5, 147.6, 145.6, 145.4, 144.5, 141.4, 137.4, 137.0, 136.9, 135.7, 131.9, 131.5, 129.9, 128.7, 128.6, 128.5, 128.4, 127.6, 127.4, 127.1,

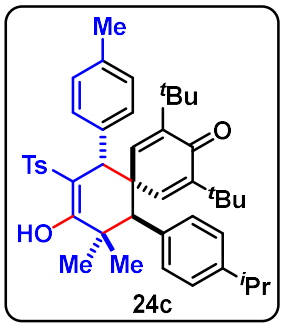
127.0, 105.1, 53.5, 50.6, 44.5, 40.5, 35.0, 34.3, 29.0, 28.6, 28.3, 22.7, 21.5, 21.0; **HRMS (ESI-TOF)** m/z: $[M+H]^+$ calcd for $C_{41}H_{49}O_4S$ 637.3346, found 637.3344.

2,4-Di-*tert*-butyl-9-hydroxy-10,10-dimethyl-7,11-di-*p*-tolyl-8-tosylspiro[5.5]undeca-1,4,8-trien-3-one (24b):



Yellow Solid, 156 mg, 74 % yield; mp = 206-207 °C; R_f = 0.6 (Pet. ether/Ethyl acetate- 90:10); **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 11.24 (s, 1 H), 7.64 - 7.58 (d, *J* = 8.4 Hz, 2 H), 7.25 - 7.20 (d, *J* = 7.6 Hz, 2 H), 7.14 - 7.01 (d, 3 H), 6.87 (d, *J* = 3.1 Hz, 2 H), 6.84 - 6.72 (m, 3 H), 6.62 (s, 1 H), 5.25 (d, *J* = 3.1 Hz, 1 H), 3.38 (s, 1 H), 3.17 (s, 1 H), 2.40 (s, 3 H), 2.34 (s, 3 H), 2.18 (s, 3 H), 1.40 (s, 3 H), 1.27 (s, 3 H), 1.12 (s, 9 H), 0.66 (s, 9 H); **^{13}C NMR (100 MHz, $CDCl_3$) δ** = 185.8, 169.6, 147.5, 145.8, 145.2, 144.5, 141.5, 137.4, 137.0, 136.8, 135.8, 133.7, 131.8, 131.5, 129.9, 128.7, 128.6, 128.3, 128.0, 127.74, 127.70, 127.3, 105.1, 53.1, 50.5, 44.5, 40.5, 34.9, 34.4, 29.0, 28.6, 28.3, 22.7, 21.5, 21.1, 20.8; **HRMS (ESI-TOF)** m/z: $[M+H]^+$calcd for $C_{42}H_{51}O_4S$ 651.3503, found 651.3502.

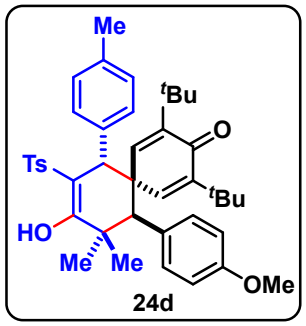
2,4-Di-*tert*-butyl-9-hydroxy-11-(4-*iso*propylphenyl)-10,10-dimethyl-7-(*p*-tolyl)-8-tosylspiro[5.5]undeca-1,4,8-trien-3-one (24c):



White Solid, 146 mg, 73 % yield; mp = 193-194 °C; R_f = 0.7 (Pet. ether/Ethyl acetate- 90:10); **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 11.24 (s, 1 H), 7.66 - 7.56 (m, *J* = 8.2 Hz, 2 H), 7.25 - 7.19 (m, *J* = 7.8 Hz, 2 H), 7.15 - 7.09 (m, 1 H), 7.09 - 7.00 (m, 2 H), 6.94 - 6.87 (m, 1 H), 6.87 (d, *J* = 2.7 Hz, 1 H), 6.83 (br. s., 2 H), 6.76 (d, *J* = 7.3 Hz, 1 H), 6.63 (d, *J* = 6.4 Hz, 1 H), 5.23 (d, *J* = 3.2 Hz, 1 H), 3.38 (s, 1 H), 3.18 (s, 1 H), 2.73 (spt, *J* = 6.9 Hz, 1 H), 2.40 (s, 3 H), 2.34 (s, 3 H), 1.41 (s, 3 H), 1.28 (s, 3 H), 1.12 (s, 9 H), 1.09 (d, *J* = 6.9 Hz, 6 H), 0.64 (s, 9 H); **^{13}C NMR (100 MHz, $CDCl_3$) δ** = 185.8, 169.7, 147.8, 147.5, 145.7, 145.2, 144.5, 141.5, 137.4, 136.9, 135.8, 134.0, 131.9, 131.5, 129.9, 128.7, 128.6, 128.5 128.4, 127.4, 125.4, 125.1, 105.0, 53.2, 50.4, 44.5, 40.5, 34.9, 34.3, 33.6, 29.0, 28.6, 28.3, 23.9, 22.7, 21.5, 21.1; **HRMS (ESI-TOF)** m/z: $[M+H]^+$ calcd for $C_{44}H_{55}O_4S$ 679.3816, found 679.3820.

2,4-Di-*tert*-butyl-9-hydroxy-11-(4-methoxyphenyl)-10,10-dimethyl-7-(*p*-tolyl)-8-tosylspiro [5.5]undeca-1,4,8-trien-3-one (24d):

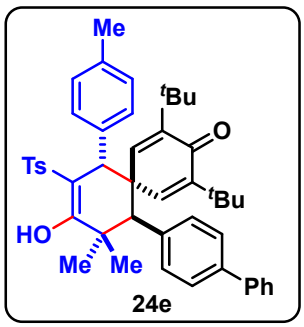
White Solid, 147 mg, 72 % yield; mp = 164-165 °C; R_f = 0.6 (Pet. ether/Ethyl acetate- 90:10); **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 11.24 (s, 1 H), 7.63 - 7.58 (m, 2 H), 7.25 - 7.20 (m, *J* = 8.2



24d

Hz, 2 H), 7.13 - 7.02 (m, 3 H), 6.87 (d, *J* = 3.2 Hz, 1 H), 6.84 (br. s., 1 H), 6.76 (d, *J* = 7.3 Hz, 1 H), 6.71 - 6.63 (m, 1 H), 6.63 - 6.57 (m, 1 H), 6.57 - 6.48 (m, 1 H), 5.26 (d, *J* = 2.7 Hz, 1 H), 3.67 (s, 3 H), 3.38 (s, 1 H), 3.17 (s, 1 H), 2.40 (s, 3 H), 2.34 (s, 3 H), 1.39 (s, 3 H), 1.25 (s, 3 H), 1.12 (s, 9 H), 0.69 (s, 9 H); **^{13}C NMR (100 MHz, $CDCl_3$) δ** = 185.8, 169.6, 158.7, 147.6, 145.9, 145.3, 144.5, 141.5, 137.4, 137.0, 135.8, 133.0, 131.5, 129.9, 129.4, 129.3, 129.0, 128.7, 128.6, 128.4, 127.4, 125.3, 105.1, 55.2, 52.6, 50.6, 44.6, 40.6, 35.0, 34.4, 29.0, 28.7, 28.3, 22.6, 21.5, 21.1; **HRMS (ESI-TOF)** m/z: $[M+H]^+$ calcd for $C_{42}H_{51}O_5S$ 667.3452, found 667.3445.

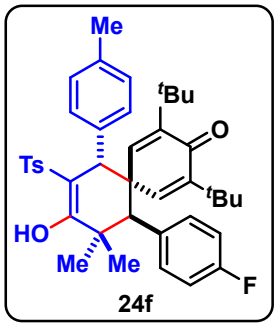
11-([1,1'-biphenyl]-4-yl)-2,4-Di-*tert*-butyl-9-hydroxy-10,10-dimethyl-7-(*p*-tolyl)-8-tosylspiro [5.5]undeca-1,4,8-trien-3-one (24e):



24e

White Solid, 128 mg, 67 % yield; mp = 160-162 °C; R_f = 0.5 (Pet. ether/Ethyl acetate- 90:10); **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 11.27 (s, 1 H), 7.63 (d, *J* = 8.2 Hz, 2 H), 7.46 - 7.41 (m, 2 H), 7.40 - 7.35 (m, 2 H), 7.33 - 7.27 (m, 2 H), 7.26 - 7.20 (m, 3 H), 7.16 - 7.12 (m, 1 H), 7.11 - 7.05 (m, 2 H), 7.01 (d, *J* = 7.3 Hz, 1 H), 6.91 (d, *J* = 3.2 Hz, 1 H), 6.86 - 6.74 (m, 2 H), 5.29 (d, *J* = 2.7 Hz, 1 H), 3.42 (s, 1 H), 3.27 (s, 1 H), 2.41 (s, 3 H), 2.35 (s, 3 H), 1.46 (s, 3 H), 1.33 (s, 3 H), 1.15 (s, 10 H), 0.66 (s, 9 H); **^{13}C NMR (100 MHz, $CDCl_3$) δ** = 185.7, 169.4, 147.7, 145.5, 145.4, 144.5, 141.4, 140.6, 140.2, 137.3, 137.0, 136.0, 135.7, 132.4, 131.5, 129.9, 128.8, 128.8, 128.7, 128.4, 127.4, 127.2, 126.9, 126.2, 125.8, 105.1, 53.3, 50.5, 44.5, 40.5, 35.0, 34.4, 29.0, 28.6, 28.38 22.7, 21.5, 21.1; **HRMS (ESI-TOF)** m/z: $[M+H]^+$ calcd for $C_{47}H_{53}O_4S$ 713.3659, found 713.3657.

2,4-Di-*tert*-butyl-11-(4-fluorophenyl)-9-hydroxy-10,10-dimethyl-7-(*p*-tolyl)-8-tosylspiro[5.5] undeca-1,4,8-trien-3-one (24f):

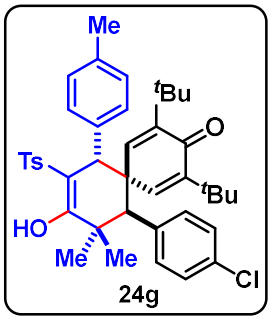


24f

White solid, 163 mg, 78 % yield; mp = 186-188 °C; R_f = 0.7 (Pet. ether/Ethyl acetate- 90:10); **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 11.25 (s, 1 H), 7.64 - 7.55 (d, *J* = 8.4 Hz, 2 H), 7.25 - 7.18 (d, *J* = 8.4 Hz, 2 H), 7.11 - 7.02 (m, 3 H), 6.91 (s, 1 H), 6.88 (d, *J* = 3.1 Hz, 1 H), 6.73 (s, 2 H), 6.77 (s, 2 H), 5.24 (d, *J* = 3.1 Hz, 1 H), 3.39 (s, 1 H), 3.22 (s, 1 H), 2.40 (s, 3 H), 2.34 (s, 3 H), 1.39 (s, 3 H), 1.24 (s, 3 H), 1.12 (s, 9 H), 0.69 (s, 9 H); **^{13}C NMR (100 MHz, $CDCl_3$) δ** = 185.5, 169.2, 163.2, 160.8, 147.9, 145.5, 144.6, 141.1, 137.2, 135.6, 133.3, 132.7, 131.5, 129.9, 128.7, 128.3, 127.4, 114.2, 105.2, 52.7, 50.6,

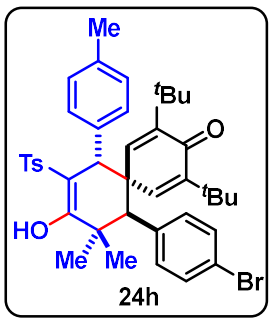
44.4, 40.4, 35.0, 34.4, 29.0, 28.7, 28.3, 22.5, 21.5, 21.1; **^{19}F NMR (376 MHz, $CDCl_3$) δ** = -115.3; **HRMS (ESI-TOF)** m/z: $[M+H]^+$ calcd for $C_{41}H_{48}O_4FS$ 655.3252, found 655.3251.

2,4-Di-*tert*-butyl-11-(4-chlorophenyl)-9-hydroxy-10,10-dimethyl-7-(*p*-tolyl)-8-tosylspiro [5.5]undeca-1,4,8-trien-3-one (24g):



White solid, 161 mg, 79 % yield; mp = 226-227 °C; R_f = 0.7 (Pet. ether/Ethyl acetate- 90:10); **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 11.25 (s, 1 H), 7.63 - 7.56 (m, *J* = 8.3 Hz, 2 H), 7.24 - 7.19 (m, *J* = 8.1 Hz, 2 H), 7.11 - 7.03 (m, 4 H), 7.03 - 6.95 (m, 1 H), 6.95 - 6.84 (m, 2 H), 6.76 (d, *J* = 7.3 Hz, 1 H), 6.73 - 6.61 (m, 1 H), 5.23 (d, *J* = 3.2 Hz, 1 H), 3.40 (s, 1 H), 3.20 (s, 1 H), 2.40 (s, 3 H), 2.34 (s, 3 H), 1.39 (s, 3 H), 1.24 (s, 3 H), 1.12 (s, 9 H), 0.70 (s, 9 H); **^{13}C NMR (100 MHz, $CDCl_3$) δ** = 185.5, 169.0, 147.9, 145.7, 145.2, 144.6, 141.0, 137.3, 137.1, 135.5, 135.5, 133.2, 131.5, 129.9, 129.6, 128.7, 128.7, 128.3, 127.6, 127.4,127.3, 127.2, 105.2, 52.9, 50.5, 44.4, 40.4, 35.0, 34.5, 29.0, 28.6, 28.3, 22.6, 21.5, 21.0; **HRMS (ESI-TOF)** m/z: $[M+H]^+$ calcd for $C_{41}H_{48}O_4ClS$ 671.2956, found 671.2946.

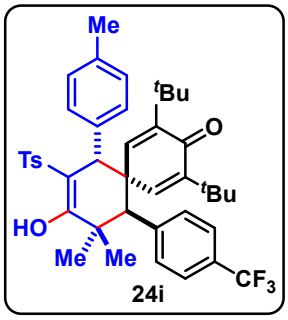
11-(4-bromophenyl)-2,4-Di-*tert*-butyl-9-hydroxy-10,10-dimethyl-7-(*p*-tolyl)-8-tosylspiro [5.5]undeca-1,4,8-trien-3-one (24h):



Yellow Solid, 159 mg, 83 % yield; mp = 228-230 °C; R_f = 0.7 (Pet. ether/Ethyl acetate- 90:10); **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 11.25 (s, 1 H), 7.60 (d, *J* = 7.6 Hz, 2 H), 7.22 (d, *J* = 8.4 Hz, 3 H), 7.14 (d, *J* = 7.6 Hz, 1 H), 7.10 - 7.02 (m, 3 H), 6.86 (d, *J* = 3.1 Hz, 1 H), 6.83 (d, J = 7.6 Hz, 1 H), 6.76 (d, *J* = 7.6 Hz, 1 H), 6.68 - 6.57 (d, 1 H), 5.23 (d, *J* = 3.1 Hz, 1 H), 3.40 (s, 1 H), 3.18 (s, 1 H), 2.40 (s, 3 H), 2.34 (s, 3 H), 1.39 (s, 3 H), 1.24 (s, 3 H), 1.12 (s, 9 H), 0.70 (s, 9 H); **^{13}C NMR (100 MHz, $CDCl_3$) δ** = 185.5, 169.0, 148.0, 145.7, 145.2, 144.6, 141.0, 137.2, 137.1, 136.0, 135.5, 133.5, 131.5, 130.7, 130.6, 130.2, 129.9, 128.8, 128.7, 128.2, 127.4, 121.3, 105.2, 53.0, 50.5, 44.3, 40.3, 35.0, 34.5, 29.0, 28.6, 28.3, 22.5, 21.5, 21.1; **HRMS (ESI-TOF)** m/z: $[M+Na]^+$ calcd for $C_{41}H_{47}O_4{}^{81}BrNaS$ 739.2250, found 739.2253.

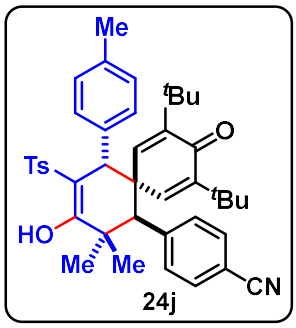
2,4-Di-*tert*-butyl-9-hydroxy-10,10-dimethyl-7-(*p*-tolyl)-8-tosyl-11-(4-(trifluoromethyl) phen-yl)spiro[5.5]undeca-1,4,8-trien-3-one (24i):

White solid, 145 mg, 83 % yield; mp = 215-216 °C; R_f = 0.8 (Pet. ether/Ethyl acetate- 90:10); **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 11.27 (s, 1 H), 7.60 (d, *J* = 8.3 Hz, 2 H), 7.41 - 7.32 (m, 1 H), 7.25 (br. s., 1 H), 7.23 (s, 2 H), 7.14 - 7.01 (m, 4 H), 6.95 - 6.84 (m, 2 H), 6.76 (d, *J* = 8.1 Hz, 1



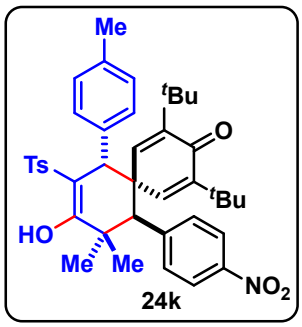
H), 5.22 (d, *J* = 2.9 Hz, 1 H), 3.43 (s, 1 H), 3.30 (s, 1 H), 2.40 (s, 3 H), 2.35 (s, 3 H), 1.41 (s, 3 H), 1.27 (s, 3 H), 1.14 (s, 9 H), 0.64 (s, 9 H); **^{13}C NMR (100 MHz, $CDCl_3$) δ** = 185.4, 168.8, 148.1, 146.5, 146.0, 144.8, 144.6, 141.2, 140.9, 137.2, 135.4, 132.1, 132.0, 131.5, 131.5, 129.9, 129.8, 129.4, 128.8, 128.8, 128.7, 128.3, 127.4, 105.3, 53.5, 50.5, 44.3, 40.4, 35.1, 34.4, 29.0, 28.6, 28.3 22.6, 21.5, 21.1; **^{19}F NMR (376 MHz, $CDCl_3$) δ** = -62.7; **HRMS (ESI-TOF)** m/z: $[M+H]^+$ calcd for $C_{42}H_{48}O_4F_3S$ 705.3220, found 705.3210.

4-(8,10-Di-*tert*-butyl-3-hydroxy-2,2-dimethyl-9-oxo-5-(*p*-tolyl)-4-tosylspiro[5.5]undeca-3,7,10-trien-1-yl)benzonitrile (24j):



White solid, 169 mg, 82 % yield; mp = 219-220 °C; R_f = 0.5 (Pet. ether/Ethyl acetate- 90:10); **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 11.27 (s, 1 H), 7.68 - 7.53 (d, *J* = 7.9 Hz, 2 H), 7.40 - 7.31 (d, 2 H), 7.25 - 7.15 (d, *J* = 7.9 Hz, 2 H), 7.06 (m, 4 H), 6.89 (d, *J* = 2.4 Hz, 2 H), 6.76 (d, *J* = 7.3 Hz, 1 H), 5.20 (d, *J* = 2.4 Hz, 1 H), 3.43 (s, 1 H), 3.29 (s, 1 H), 2.39 (s, 3 H), 2.34 (s, 3 H), 1.40 (s, 3 H), 1.24 (s, 3 H), 1.13 (s, 9 H), 0.67 (s, 9 H); **^{13}C NMR (100 MHz, $CDCl_3$) δ** = 185.2, 168.5, 148.3, 146.3, 144.7, 144.5, 142.7, 140.7, 137.3, 137.2, 135.2, 132.5, 131.5,130.7, 130.6, 129.9, 129.2, 128.8, 128.7, 128.2, 127.4, 118.3, 111.2, 105.4, 53.7, 50.6, 44.2, 40.4, 35.1, 34.5, 29.0, 28.6, 28.3, 22.6, 21.5, 21.0; **HRMS (ESI-TOF)** m/z: $[M+H]^+$ calcd for $C_{42}H_{48}O_4NS$ 662.3299, found 662.3295.

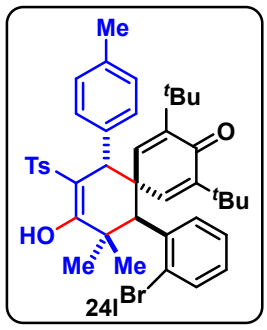
2,4-Di-*tert*-butyl-9-hydroxy-10,10-dimethyl-11-(4-nitrophenyl)-7-(*p*-tolyl)-8-tosylspiro[5.5]undeca-1,4,8-trien-3-one (24k):



White solid, 138 mg, 69 % yield; mp = 206-207 °C; R_f = 0.5 (Pet. ether/Ethyl acetate- 90:10); **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 11.28 (s, 1 H), 7.97 (d, *J* = 7.3 Hz, 1 H), 7.88 (d, *J* = 8.2 Hz, 1 H), 7.62 - 7.57 (m, *J* = 8.2 Hz, 2 H), 7.24 - 7.20 (m, *J* = 7.8 Hz, 2 H), 7.15 (d, *J* = 7.8 Hz, 1 H), 7.09 - 7.04 (m, 3 H), 6.97 (d, *J* = 7.8 Hz, 1 H), 6.91 (d, *J* = 2.7 Hz, 1 H), 6.76 (d, *J* = 7.8 Hz, 1 H), 5.22 (d, *J* = 3.2 Hz, 1 H), 3.44 (s, 1 H), 3.37 (s, 1 H), 2.40 (s, 3 H), 2.34 (s, 3 H), 1.41 (s, 3 H), 1.25 (s, 3 H), 1.14 (s, 9 H), 0.65 (s, 9 H); **^{13}C NMR (100 MHz, $CDCl_3$) δ** = 185.2, 168.4, 148.5, 147.0, 146.3, 144.9, 144.7, 144.4, 140.6, 137.4, 137.1, 135.1, 132.7, 131.5, 129.9, 129.1, 128.9, 128.8, 128.2, 127.4, 122.8, 122.1, 105.4, 53.4, 50.6, 44.2, 40.3, 35.1, 34.5, 29.0, 28.6, 28.4, 22.6, 21.5, 21.1; **HRMS (ESI-**

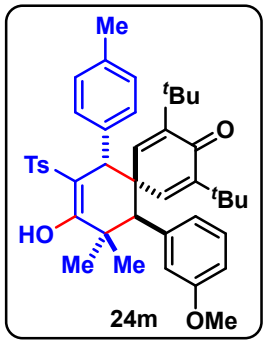
TOF) m/z: $[M+H]^+$ calcd for $C_{41}H_{48}O_6NS$ 682.3197, found 682.3187.

11-(2-bromophenyl)-2,4-Di-*tert*-butyl-9-hydroxy-10,10-dimethyl-7-(*p*-tolyl)-8-tosylspiro [5.5]undeca-1,4,8-trien-3-one (24l):



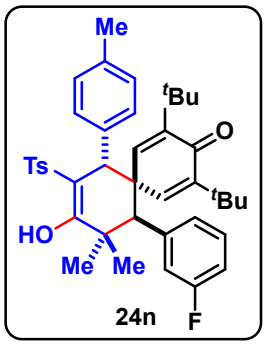
White solid, 107 mg, 56 % yield; mp = 188-189 °C; R_f = 0.5 (Pet. ether/Ethyl acetate- 90:10); **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 11.26 (s, 1 H), 7.59 (d, *J* = 8.5 Hz, 2 H), 7.46 - 7.38 (m, 1 H), 7.24 - 7.14 (m, 3 H), 7.08 - 6.99 (m, 3 H), 6.98 - 6.90 (m, 2 H), 6.86 (d, *J* = 3.1 Hz, 1 H), 6.75 (d, *J* = 7.3 Hz, 1 H), 5.37 (d, *J* = 3.1 Hz, 1 H), 4.24 (s, 1 H), 3.44 (s, 1 H), 2.40 (s, 3 H), 2.33 (s, 3 H), 1.42 (s, 3 H), 1.35 (s, 3 H), 1.13 (s, 9 H), 0.65 (s, 9 H); **^{13}C NMR (100 MHz, $CDCl_3$) δ** = 185.5, 169.0, 148.1, 146.0, 144.5, 144.3, 140.8, 137.5, 137.0, 136.2, 135.4, 132.9, 131.4, 130.8, 129.8, 128.8, 128.7, 128.5, 127.5, 127.4, 125.8, 105.4, 50.4, 49.4, 45.8, 41.5, 35.0, 34.4, 29.1, 28.7, 28.0 23.3, 22.6, 21.5; **HRMS (ESI-TOF)** m/z: $[M+Na]^+$ calcd for $C_{41}H_{47}O_4{}^{81}BrNaS$ 739.2250, found 739.2248.

2,4-Di-*tert*-butyl-9-hydroxy-11-(3-methoxyphenyl)-10,10-dimethyl-7-(*p*-tolyl)-8-tosylspiro [5.5]undeca-1,4,8-trien-3-one (24m):



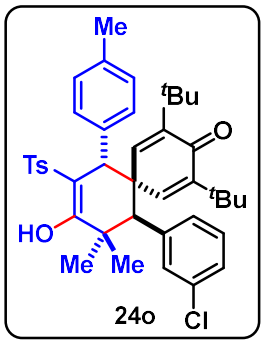
White solid, 131 mg, 64 % yield; dr = 54:46 mp = 116-117 °C; R_f = 0.6 (Pet. ether/Ethyl acetate- 90:10); **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 11.25 (s, 1.90 H), 7.59 (d, *J* = 7.6 Hz, 3.87 H), 7.21 (d, *J* = 7.6 Hz, 3.96 H), 7.05 (t, *J* = 7.8 Hz, 5.97 H), 7.01 - 6.92 (m, 2.44 H), 6.90 (d, *J* = 9.0 Hz, 1.55 H), 6.76 (d, *J* = 6.8 Hz, 1.87 H), 6.70 - 6.61 (m, 1.94 H), 6.52 (d, *J* = 7.6 Hz, 0.85 H), 6.48 (s, 1 H), 6.35 (d, *J* = 7.6 Hz, 1 H), 6.31 (s, 0.78 H), 5.27 (d, *J* = 2.9 Hz, 1.91H), 3.68 (s, 2.72 H), 3.56 (s, 3 H), 3.40 (s, 1.92 H), 3.26 (s, 1 H), 3.15 (s, 0.84 H), 2.39 (s, 5.79 H), 2.34 (s, 5.90 H), 1.42 (s, 5.81 H), 1.28 (br. s., 6.24 H), 1.13 (s, 17.53 H), 0.69 (s, 17.45 H); **^{13}C NMR (100 MHz, $CDCl_3$) δ** = 185.8, 185.7, 169.6, 169.4, 158.9, 158.7, 147.6, 147.5, 145.6, 145.4, 145.3, 144.5, 141.9, 141.3, 138.4, 137.3, 137.0, 135.5, 131.4, 129.8, 129.7, 129.2, 129.0, 128.6, 128.5, 128.4, 128.3, 128.2, 128.0, 127.3, 124.4, 121.2, 119.0, 114.5, 113.1, 110.7, 105.1, 55.4, 55.2, 53.6, 53.0, 50.9, 50.6, 44.4, 41.7, 40.5, 34.9, 34.4, 29.1, 29.0, 28.6, 28.3, 22.7, 22.4, 21.6, 21.5, 21.0; **HRMS (ESI-TOF)** m/z: $[M+H]^+$ calcd for $C_{42}H_{51}O_5S$ 667.3452, found 667.3444.

2,4-Di-*tert*-butyl-11-(3-fluorophenyl)-9-hydroxy-10,10-dimethyl-7-(*p*-tolyl)-8-tosylspiro[5.5] undeca-1,4,8-trien-3-one (24n):



White solid, 141 mg, 67 % yield; dr = 58:42; mp = 223-224 °C; R_f = 0.6 (Pet. ether/Ethyl acetate- 90:10); **^{1}H NMR (400 MHz, CDCl$_3$) δ** = 11.26 (s, 1.76 H), 7.60 (d, *J* = 7.6 Hz, 3.59 H), 7.22 (d, *J* = 7.6 Hz, 3.58 H), 7.13 - 7.01- 6.97 (m, 7.30 H), 6.87 (m, 1.89 H), 6.85 - 6.81 (m, 1.55 H), 6.81 - 6.73 (m, 2.49 H), 6.68 (d, *J* = 10.5 Hz, 1.34 H), 6.61 - 6.53 (m, 1 H), 6.53 - 6.41 (m, 0.70 H), 5.25 (br. s., 1.79 H), 3.39 (br. s., 1.77 H), 3.25 (s, 1 H), 3.18 (s, 0.73 H), 2.40 (s, 5.42 H), 2.34 (s, 5.38 H), 1.42 (s, 5.43 H), 1.27 (s, 5.50 H), 1.13 (s, 16.18 H), 0.69 (s, 16.14 H); **^{13}C NMR (100 MHz, CDCl$_3$) δ** = 185.5, 169.1, 145.8, 145.7, 145.1, 144.6, 144.6, 140.8, 139.5, 139.4, 137.3, 137.2, 135.5, 135.4, 131.5, 131.5, 131.5, 129.9, 128.8, 128.7, 128.2, 127.4, 105.2, 50.6, 44.4, 40.4, 35.0, 34.4, 29.0, 28.7, 28.4, 22.7, 21.5, 21.1; **^{19}F NMR (376 MHz, CDCl$_3$) δ** = -113.6, -114.3; **HRMS (ESI-TOF)** m/z: $[M+H]^+$ calcd for $C_{41}H_{48}O_4FS$ 655.3252, found 655.3249.

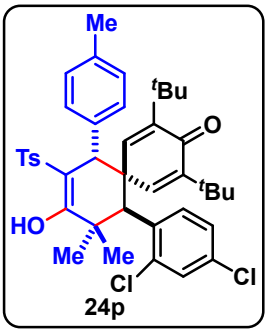
2,4-Di-*tert*-butyl-11-(3-chlorophenyl)-9-hydroxy-10,10-dimethyl-7-(*p*-tolyl)-8-tosylspiro [5.5]undeca-1,4,8-trien-3-one (24o):



White solid, 161 mg, 79 % yield; dr = 57:43; mp = 190-191 °C; R_f = 0.6 (Pet. ether/Ethyl acetate- 90:10); **^{1}H NMR (400 MHz, CDCl$_3$) δ** = 11.26 (s, 1.70 H), 7.60 (m, 3.51 H), 7.23 (m, *J* = 7.3 Hz, 3.55 H), 7.14 - 7.01 (m, 7.83 H), 7.01 - 6.91 (m, 2.20 H), 6.87 (m, 2.70 H), 6.76 (d, *J* = 6.9 Hz, 2.48 H), 6.65 (d, *J* = 7.3 Hz, 1 H), 5.25 (br. s., 0.73 H), 5.21 (br. s., 1 H), 3.41 (s, 0.75 H), 3.39 (s, 1 H), 3.21 (s, 1 H), 3.16 (s, 0.76 H), 2.40 (s, 5.18 H), 2.34 (s, 5.19 H), 1.42 (s, 5.40 H), 1.26 (s, 5.54 H), 1.19 - 1.09 (m, 15.78 H), 0.69 (s, 15.71 H); **^{13}C NMR (100 MHz, CDCl$_3$) δ** = 185.5, 169.0, 148.2, 147.9, 145.8, 145.1, 145.0, 144.6, 141.0, 140.8, 139.0, 137.2, 135.5, 135.4, 133.5, 133.3, 131.5, 129.9, 128.7, 128.7, 128.6, 128.2, 127.4, 127.2, 126.7, 105.1, 53.4, 53.0, 50.5, 44.3, 40.3, 35.0, 34.4, 29.0, 28.7, 28.4, 22.6, 22.4, 21.5, 21.1; **HRMS (ESI-TOF)** m/z: $[M+Na]^+$ calcd for $C_{41}H_{47}O_4ClNaS$ 693.2776, found 693.2780.

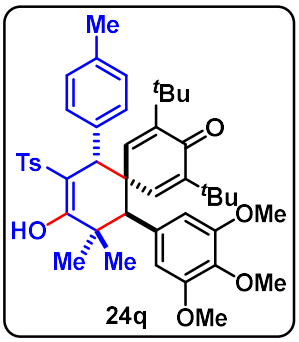
2,4-Di-*tert*-butyl-11-(2,4-dichlorophenyl)-9-hydroxy-10,10-dimethyl-7-(*p*-tolyl)-8-tosylspiro [5.5]undeca-1,4,8-trien-3-one (24p):

White solid, 121 mg, 62 % yield; mp = 115-117 °C; R_f = 0.6 (Pet. ether/Ethyl acetate- 90:10); **^{1}H NMR (400 MHz, CDCl$_3$) δ** = 11.26 (s, 1 H), 7.61 - 7.55 (m, *J* = 8.3 Hz, 2 H), 7.25 (d, *J* = 2.2 Hz, 1 H), 7.22 - 7.17 (m, *J* = 7.8 Hz, 2 H), 7.12 (d, *J* = 6.8 Hz, 1 H), 7.04 (d, *J* = 8.1 Hz, 2 H), 6.95 (d, *J* = 8.8 Hz, 1 H), 6.90 (dd, *J* = 2.2, 8.8 Hz, 1 H), 6.84 (d, *J* = 2.9 Hz, 1 H), 6.75 (d, *J*



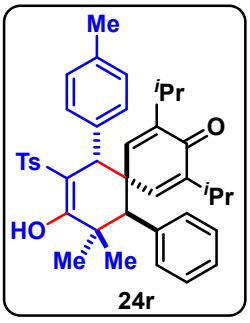
= 7.1 Hz, 1 H), 5.29 (d, *J* = 2.9 Hz, 1 H), 4.22 (s, 1 H), 3.45 (s, 1 H), 2.40 (s, 3 H), 2.33 (s, 3 H), 1.38 (s, 3 H), 1.32 (s, 3 H), 1.13 (s, 9 H), 0.68 (s, 9 H); **^{13}C NMR (100 MHz, CDCl$_3$) δ** = 185.3, 168.7, 148.3, 146.4, 144.5, 143.8, 140.6, 137.4, 137.2, 136.4, 135.2, 133.6, 133.3, 131.4, 131.2, 129.8, 129.0, 128.8, 128.6, 128.4, 127.3, 125.5, 105.4, 50.3, 46.0, 45.4, 41.2, 35.0, 34.4, 34.1, 29.1, 28.6, 28.1 23.1, 21.5, 21.1; **HRMS (ESI-TOF)** m/z: $[M+Na]^+$ calcd for $C_{41}H_{46}O_4Cl_2NaS$ 727.2386, found 727.2385.

2,4-Di-*tert*-butyl-9-hydroxy-10,10-dimethyl-7-(*p*-tolyl)-8-tosyl-11-(3,4,5-trimethoxyphenyl) spiro[5.5]undeca-1,4,8-trien-3-one(24q):



White solid, 107 mg, 57 % yield; mp = 192-194 °C; R_f = 0.3 (Pet. ether/Ethyl acetate- 90:10); **^{1}H NMR (400 MHz, CDCl$_3$) δ** = 11.27 (s, 1 H), 7.59 - 7.53 (m, *J* = 8.2 Hz, 2 H), 7.20 - 7.16 (m, *J* = 8.2 Hz, 2 H), 7.07 - 7.01 (m, 3 H), 7.00 (d, *J* = 3.2 Hz, 1 H), 6.76 (d, *J* = 8.2 Hz, 1 H), 6.14 (d, *J* = 1.8 Hz, 1 H), 5.94 (d, *J* = 1.8 Hz, 1 H), 5.32 (d, *J* = 2.7 Hz, 1 H), 3.73 (s, 3 H), 3.70 (s, 3 H), 3.55 (s, 3 H), 3.42 (s, 1 H), 3.17 (s, 1 H), 2.38 (s, 3 H), 2.34 (s, 3 H), 1.43 (s, 3 H), 1.27 (s, 3 H), 1.12 (s, 9 H), 0.74 (s, 9 H); **^{13}C NMR (100 MHz, CDCl$_3$) δ** = 186.0, 169.6, 152.5, 152.0, 147.6, 145.7, 145.5, 144.5, 142.5, 137.8, 137.3, 137.0, 135.4, 132.7, 131.5, 129.8, 128.7, 128.6, 128.5, 127.4, 110.0, 106.5, 105.3, 60.8, 56.6, 56.5, 53.4, 51.3, 44.5, 40.7, 35.0, 34.5, 29.3, 28.7, 28.4, 22.3, 21.5, 21.1; **HRMS (ESI-TOF)** m/z: $[M+H]^+$ calcd for $C_{44}H_{55}O_7S$ 727.3663, found 727.3657.

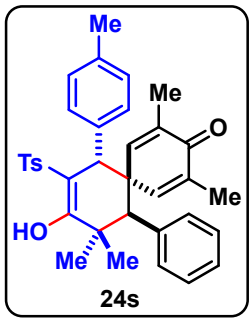
9-Hydroxy-2,4-diisopropyl-10,10-dimethyl-11-phenyl-7-(*p*-tolyl)-8-tosylspiro[5.5]undeca-1,4,8-trien-3-one (24r):



White solid, 153 mg, 67 % yield; mp = 166-168 °C; R_f = 0.4 (Pet. ether/Ethyl acetate- 95:05); **^{1}H NMR (400 MHz, CDCl$_3$) δ** = 11.28 (s, 1 H), 7.60 - 7.55 (m, *J* = 8.2 Hz, 2 H), 7.21 - 7.16 (m, *J* = 8.2 Hz, 2 H), 7.12 - 6.99 (m, 5 H), 6.99 - 6.86 (m, 3 H), 6.75 (d, *J* = 7.3 Hz, 2 H), 5.28 (d, *J* = 2.3 Hz, 1 H), 3.43 (s, 1 H), 3.28 (s, 1 H), 3.01 (spt, *J* = 6.8 Hz, 1 H), 2.63 (spt, *J* = 6.8 Hz, 1 H), 2.39 (s, 3 H), 2.34 (s, 3 H), 1.40 (s, 3 H), 1.27 (s, 3 H), 1.08 (d, *J* = 6.9 Hz, 3 H), 0.85 (d, *J* = 6.9 Hz, 3 H), 0.63 (d, *J* = 6.9 Hz, 3 H), 0.09 (d, *J* = 6.9 Hz, 3 H); **^{13}C NMR (100 MHz, CDCl$_3$) δ** = 184.5, 169.5, 145.8, 145.7, 144.5, 144.0, 141.9, 137.3, 137.0, 136.8, 135.5, 131.9, 131.6, 129.8, 128.6, 128.4, 127.6, 127.4, 127.2, 105.1, 53.3, 50.4, 44.6, 40.6, 28.1, 26.6, 25.4, 22.6, 21.6, 21.5, 21.5, 21.3, 21.0, 20.7; **HRMS (ESI-TOF)**

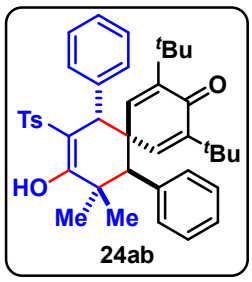
m/z: $[M+H]^+$ calcd for $C_{39}H_{45}O_4S$ 609.3033, found 609.3024.

9-Hydroxy-2,4,10,10-tetramethyl-11-phenyl-7-(*p*-tolyl)-8-tosylspiro[5.5]undeca-1,4,8-trien-3-one (24s):



White solid, 162 mg, 62 % yield; mp = 164-166 °C; R_f = 0.3 (Pet. ether/Ethyl acetate- 95:05); **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 11.21 (s, 1 H), 7.76 (dd, *J* = 1.4, 8.2 Hz, 1 H), 7.54 - 7.50 (m, 3 H), 7.18 (d, *J* = 8.2 Hz, 2 H), 7.13 - 7.05 (m, 2 H), 7.05 - 6.98 (m, 4 H), 6.93 (m, 1 H), 6.76 (m, 1 H), 5.43 (dd, *J* = 1.4, 3.2 Hz, 1 H), 3.45 (s, 1 H), 3.23 (s, 1 H), 2.40 (s, 3 H), 2.32 (s, 3 H), 2.29 (s, 3 H), 1.81 (s, 3 H), 1.40 (s, 3 H), 1.20 (s, 3 H); **^{13}C NMR (100 MHz, $CDCl_3$) δ** = 186.5, 169.3, 156.5, 149.5, 146.1, 144.4, 138.4, 137.2, 137.0, 136.7, 136.1, 135.3, 134.4, 131.7, 131.5, 129.7, 129.5, 128.7, 128.1, 127.5, 127.2, 122.8, 105.2, 52.9, 51.0, 45.5, 40.6, 28.0, 22.7, 21.5, 21.0, 16.7, 15.9, 15.4; **HRMS (ESI-TOF)** m/z: $[M+H]^+$ calcd for $C_{35}H_{37}O_4S$ 553.2412, found 553.2412.

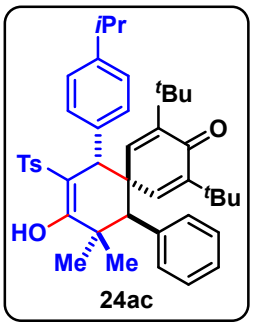
2,4-Di-*tert*-butyl-9-hydroxy-10,10-dimethyl-7,11-diphenyl-8-tosylspiro[5.5]undeca-1,4,8-trien-3-one (24ab) :



White solid, 160 mg, 76 % yield; mp = 217-218 °C; R_f = 0.8 (Pet. ether/Ethyl acetate- 90:10); **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 11.27 (s, 1 H), 7.65 - 7.57 (m, 2 H), 7.29 - 7.20 (m, 6 H), 7.12 - 7.04 (m, 2 H), 7.02 - 6.92 (m, 2 H), 6.91 (d, *J* = 3.2 Hz, 1 H), 6.90 - 6.86 (m, 1 H), 6.77 - 6.68 (m, 1 H), 5.19 (d, *J* = 3.2 Hz, 1 H), 3.44 (s, 1 H), 3.22 (s, 1 H), 2.39 (s, 3 H), 1.42 (s, 3 H), 1.29 (s, 3 H), 1.14 (s, 9 H), 0.64 (s, 9 H); **^{13}C NMR (100 MHz, $CDCl_3$) δ** = 185.7, 169.6, 147.6, 145.4, 144.6, 141.3, 138.8, 137.2, 136.7, 131.9, 131.7, 129.9, 128.5, 128.4, 128.0, 127.8, 127.6, 127.4, 127.2, 127.0, 104.9, 53.5, 50.9, 44.4, 40.5, 35.0, 34.3, 29.0, 28.6, 28.3, 22.7, 21.5; **HRMS (ESI-TOF)** m/z: $[M+H]^+$ calcd for $C_{40}H_{47}O_4S$ 623.3190, found 623.3186.

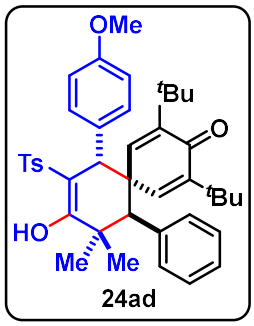
2,4-Di-*tert*-butyl-9-hydroxy-7-(4-isopropylphenyl)-10,10-dimethyl-11-phenyl-8-tosylspiro [5.5]undeca-1,4,8-trien-3-one (24ac):

White solid, 159 mg, 71 % yield; mp = 207-209 °C; R_f = 0.6 (Pet. ether/Ethyl acetate- 90:10); **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 11.24 (s, 1 H), 7.58 - 7.53 (m, 2 H), 7.19 - 7.14 (m, 2 H), 7.13 - 7.07 (m, 2 H), 7.05 (s, 3 H), 6.98 (d, *J* = 3.2 Hz, 3 H), 6.78 (d, *J* = 8.1 Hz, 2 H), 5.19 (d, *J* = 2.9 Hz, 1 H), 3.49 (s, 1 H), 3.23 (s, 1 H), 2.87 (spt, *J* = 6.9 Hz, 1 H), 2.37 (s, 3 H), 1.41 (s, 3 H), 1.29 (s, 3 H), 1.25 (d, *J* = 2.7 Hz, 3 H), 1.23 (d, *J* = 2.4 Hz, 3 H), 1.18 (s, 9 H), 0.64 (s, 9 H);



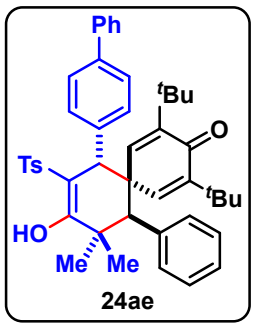
^{13}C NMR (100 MHz, $CDCl_3$) δ = 185.7, 169.4, 147.9, 147.6, 145.6, 145.3, 144.2, 141.5, 137.6, 136.9, 135.9, 131.9, 131.6, 129.7, 128.6, 128.1, 127.3, 127.1, 127.0, 125.9, 125.8, 105.2, 53.5, 50.6, 44.5, 40.5, 35.0, 34.3, 33.6, , 29.1, 28.5, 28.3, 24.1, 23.8, 22.8, 21.5; **HRMS (ESI-TOF)** m/z: $[M+H]^+$ calcd for $C_{43}H_{53}O_4S$ 665.3659, found 665.3660.

2,4-Di-*tert*-butyl-9-hydroxy-7-(4-methoxyphenyl)-10,10-dimethyl-11-phenyl-8-tosylspiro [5.5]undeca-1,4,8-trien-3-one (24ad):



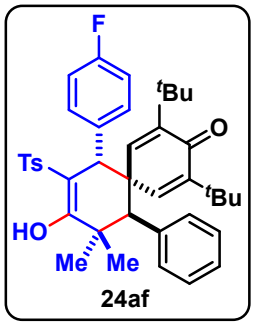
White solid, 164 mg, 74 % yield; mp = 170-172 °C; R_f = 0.6 (Pet. ether/Ethyl acetate- 90:10); **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 11.24 (s, 1 H), 7.66 - 7.57 (d, *J* = 8.4 Hz, 2 H), 7.26 - 7.19 (d, *J* = 8.4 Hz, 2 H), 7.13 (d, *J* = 7.6 Hz, 1 H), 7.11 - 7.04 (m, 2 H), 7.01 - 6.88 (m, 3 H), 6.83 - 6.71 (m, 4 H), 5.26 (d, *J* = 3.1 Hz, 1 H), 3.81 (s, 3 H), 3.40 (s, 1 H), 3.20 (s, 1 H), 2.40 (s, 3 H), 1.40 (s, 3 H), 1.28 (s, 3 H), 1.13 (s, 9 H), 0.66 (s, 9 H); **^{13}C NMR (100 MHz, $CDCl_3$) δ** = 185.7, 169.4, 158.8, 147.6, 145.6, 145.4, 144.5, 141.4, 137.4, 136.8, 132.5, 131.9, 130.7, 129.9, 129.5, 128.5, 127.6, 127.3, 127.1, 127.0, 113.5, 113.0, 105.2, 55.2, 53.5, 50.2, 44.6, 40.5, 35.0, 34.3, 29.0, 28.6, 28.3, 22.6, 21.5; **HRMS (ESI-TOF)** m/z: $[M+Na]^+$ calcd for $C_{41}H_{48}O_5NaS$ 675.3115, found 675.3109.

7-([1,1'-biphenyl]-4-yl)-2,4-Di-*tert*-butyl-9-hydroxy-10,10-dimethyl-11-phenyl-8-tosylspiro [5.5]undeca-1,4,8-trien-3-one (24ae):



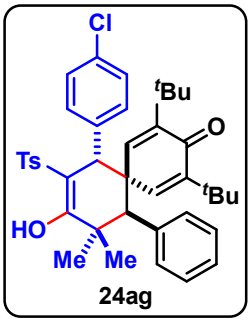
White solid, 168 mg, 71 % yield; mp = 227-228 °C; R_f = 0.5 (Pet. ether/Ethyl acetate- 90:10); **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 11.30 (s, 1 H), 7.64 - 7.58 (m, 4 H), 7.50 - 7.45 (m, 4 H), 7.40 - 7.35 (m, 1 H), 7.26 (m, 1 H), 7.21 (d, *J* = 7.8 Hz, 2 H), 7.13 - 7.05 (m, 2 H), 7.04 - 6.91 (m, 4 H), 6.77 (s, 1 H), 5.29 (d, *J* = 2.7 Hz, 1 H), 3.53 (s, 1 H), 3.26 (s, 1 H), 2.34 (s, 3 H), 1.45 (s, 3 H), 1.31 (s, 3 H), 1.17 (s, 9 H), 0.67 (s, 9 H); **^{13}C NMR (100 MHz, $CDCl_3$) δ** = 185.7, 169.7, 147.7, 145.6, 145.3, 144.6, 141.3, 140.4, 140.1, 137.8, 137.4, 136.7, 132.1, 131.9, 130.3, 129.9, 129.0, 128.9, 128.8, 128.5, 127.7, 127.4, 127.2, 127.0, 126.6, 126.4, 105.0, 53.7, 50.7, 44.5, 40.6, 35.0, 34.4, 29.1, 28.6, 28.3, 22.7, 21.5; **HRMS (ESI-TOF)** m/z: $[M+H]^+$ calcd for $C_{46}H_{51}O_4S$ 699.3503, found 699.3502.

2,4-Di-*tert*-butyl-7-(4-fluorophenyl)-9-hydroxy-10,10-dimethyl-11-phenyl-8-tosylspiro[5.5] undeca-1,4,8-trien-3-one (24af):



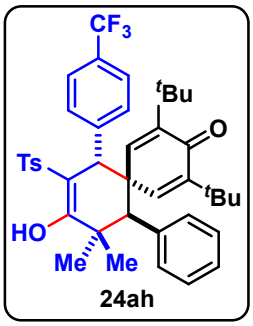
White solid, 176 mg, 81 % yield; mp = 209-211 °C; R_f = 0.6 (Pet. ether/Ethyl acetate- 90:10); **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 11.27 (s, 1 H), 7.61 (d, *J* = 8.1 Hz, 2 H), 7.24 (dd, *J* = 0.7, 8.6 Hz, 2 H), 7.19 (br. s., 1 H), 7.13 - 7.06 (m, 2 H), 7.04 - 6.91 (m, 4 H), 6.90 (d, *J* = 3.2 Hz, 1 H), 6.89 - 6.81 (m, 1 H), 6.73 (m, 1 H), 5.19 (d, *J* = 3.2 Hz, 1 H), 3.43 (s, 1 H), 3.15 (s, 1 H), 2.41 (s, 3 H), 1.41 (s, 3 H), 1.29 (s, 3 H), 1.14 (s, 9 H), 0.65 (s, 9 H); **^{13}C NMR (100 MHz, $CDCl_3$) δ** = 185.6, 169.8, 163.2, 160.8, 147.8, 145.8, 144.8, 141.1, 137.2, 136.6, 134.7, 133.1, 133.0, 131.9, 130.0, 128.4, 127.7, 127.3, 127.0, 114.9, 114.7, 105.0, 53.6, 50.3, 44.4, 44.3, 40.5, 35.0, 34.4, 29.0, 28.6, 28.4, 22.7, 21.5; **^{19}F NMR (376 MHz, $CDCl_3$) δ** = -114.9; **HRMS (ESI-TOF)** m/z: $[M+Na]^+$ calcd for $C_{40}H_{45}O_4FNaS$ 663.2915, found 663.2899.

2,4-Di-*tert*-butyl-7-(4-chlorophenyl)-9-hydroxy-10,10-dimethyl-11-phenyl-8-tosylspiro[5.5] undeca-1,4,8-trien-3-one (24ag):



White solid, 176 mg, 79 % yield; mp = 201-202 °C; R_f = 0.6 (Pet. ether/Ethyl acetate- 90:10); **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 11.28 (s, 1 H), 7.62 - 7.55 (m, 2 H), 7.23 (dd, *J* = 5.3, 7.6 Hz, 4 H), 7.17 - 7.05 (m, 3 H), 6.99 (m, 1 H), 6.94 (m, 1 H), 6.91 (d, *J* = 2.7 Hz, 1 H), 6.83 (d, *J* = 7.3 Hz, 1 H), 6.78 - 6.67 (m, 1 H), 5.19 (d, *J* = 2.7 Hz, 1 H), 3.42 (s, 1 H), 3.12 (s, 1 H), 2.42 (s, 3 H), 1.40 (s, 3 H), 1.28 (s, 3 H), 1.14 (s, 9 H), 0.66 (s, 9 H); **^{13}C NMR (100 MHz, $CDCl_3$) δ** = 185.5, 169.9, 147.9, 145.9, 144.9, 144.8, 141.0, 137.5, 137.1, 136.5, 133.3, 132.8, 131.9, 130.0, 129.8, 128.4, 128.2, 127.9, 127.7, 127.3, 127.1, 104.8, 53.7, 50.4, 44.3, 40.6, 35.0, 34.4, 29.0, 28.6, 28.4, 22.7, 21.5; **HRMS (ESI-TOF)** m/z: $[M+Na]^+$ calcd for $C_{40}H_{45}O_4ClNaS$ 679.2619, found 679.2613.

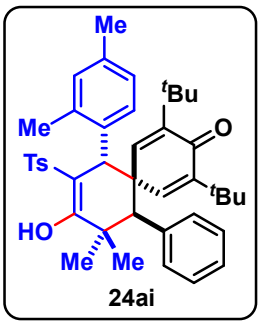
2,4-Di-*tert*-butyl-9-hydroxy-10,10-dimethyl-11-phenyl-8-tosyl-7-(4(trifluoromethyl)phenyl) spiro[5.5]undeca-1,4,8-trien-3-one (24ah):



White solid, 190 mg, 81 % yield; mp = 258-260 °C; R_f = 0.8 (Pet. ether/Ethyl acetate- 90:10); **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 11.32 (s, 1 H), 7.54 (d, *J* = 8.3 Hz, 2 H), 7.47 (d, *J* = 6.8 Hz, 2 H), 7.31 - 7.23 (m, 1 H), 7.21 - 7.16 (m, 2 H), 7.11 (d, *J* = 6.6 Hz, 2 H), 7.06 - 6.90 (m, 4 H), 6.81 - 6.66 (m, 1 H), 5.12 (d, *J* = 3.2 Hz, 1 H), 3.57 (s, 1 H), 3.12 (s, 1 H), 2.38 (s, 3 H), 1.42 (s, 3 H), 1.31 (s, 3 H), 1.18 (s, 9 H), 0.64 (s, 9 H); **^{13}C NMR (100 MHz, $CDCl_3$) δ** = 185.5, 170.2, 148.0, 146.2, 144.9, 144.3, 143.1, 140.8, 137.1,

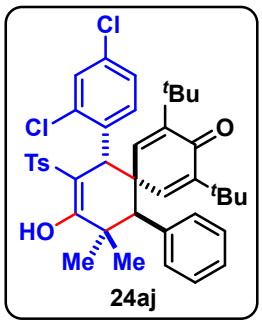
136.3, 132.1, 129.9, 129.4, 128.8, 128.4, 127.8, 127.4, 127.3, 127.1, 125.3, 124.9, 124.5, 122.6, 104.6, 53.8, 50.8, 44.2, 40.7, 35.1, 34.4, 29.1, 28.6, 28.4, 22.8, 21.4; **^{19}F NMR (376 MHz, $CDCl_3$) δ** = -62.4; **HRMS (ESI-TOF)** m/z: $[M+H]^+$ calcd for $C_{41}H_{46}O_4F_3S$ 691.3063, found 691.3058.

2,4-Di-*tert*-butyl-7-(2,4-dimethylphenyl)-9-hydroxy-10,10-dimethyl-11-phenyl-8-tosylspiro [5.5]undeca-1,4,8-trien-3-one (24ai):



White solid, 183 mg, 83 % yield; mp = 215-217 °C; R_f = 0.7 (Pet. ether/Ethyl acetate- 90:10); **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 11.17 (s, 1 H), 7.59 - 7.51 (d, *J* = 8.4 Hz, 2 H), 7.22 - 7.17 (d, *J* = 7.6 Hz, 2 H), 7.08 (d, *J* = 3.8 Hz, 2 H), 7.03 - 6.96 (m, 2 H), 6.96 - 6.91 (m, 1 H), 6.91 - 6.85 (m, 3 H), 6.79 - 6.70 (m, 1 H), 5.28 (d, *J* = 2.3 Hz, 1 H), 3.82 (s, 1 H), 3.40 (s, 1 H), 2.40 (s, 3 H), 2.29 (s, 3 H), 2.05 (s, 3 H), 1.40 (s, 3 H), 1.30 (s, 3 H), 1.16 (s, 9 H), 0.57 (s, 9 H); **^{13}C NMR (100 MHz, $CDCl_3$) δ** = 185.4, 169.2, 147.4, 145.9, 144.4, 144.2, 141.3, 137.7, 136.7, 136.5, 134.1, 132.1, 131.5, 129.7, 128.7, 128.5, 127.7, 127.1, 127.0, 126.5, 105.8, 53.3, 44.5, 44.2, 40.3, 35.0, 34.1, 29.1, 28.3, 28.1, 22.8, 21.5, 20.9, 20.6; **HRMS (ESI-TOF)** m/z: $[M+H]^+$ calcd for $C_{42}H_{51}O_4S$ 651.3503, found 651.3497.

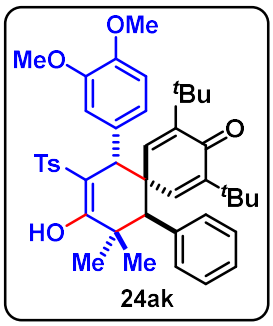
2,4-Di-*tert*-butyl-7-(2,4-dimethylphenyl)-9-hydroxy-10,10-dimethyl-11-phenyl-8-tosylspiro [5.5]undeca-1,4,8-trien-3-one (24aj):



White solid, 183 mg, 78 % yield; mp = 239-241 °C; R_f = 0.8 (Pet. ether/Ethyl acetate- 90:10); **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 11.30 (s, 1 H), 7.75 - 7.69 (m, 2 H), 7.38 (d, *J* = 1.8 Hz, 1 H), 7.34 - 7.27 (m, 4 H), 7.15 - 7.08 (m, 2 H), 7.03 - 6.95 (m, 1 H), 6.91 (d, *J* = 8.2 Hz, 1 H), 6.76 (br. s., 1 H), 6.70 (d, *J* = 3.2 Hz, 1 H), 5.18 (d, *J* = 3.2 Hz, 1 H), 4.05 (s, 1 H), 3.19 (s, 1 H), 2.43 (s, 3 H), 1.41 (s, 3 H), 1.29 (s, 3 H), 1.08 (s, 9 H), 0.61 (s, 9 H); **^{13}C NMR (100 MHz, $CDCl_3$) δ** = 185.1, 170.1, 148.0, 146.6, 145.1, 142.4, 139.7, 136.6, 136.2, 136.0, 135.6, 133.8, 132.0, 131.1, 130.1, 129.6, 128.4, 127.8, 127.6, 127.4, 127.1, 127.0, 104.5, 53.7, 44.6, 44.0, 40.4, 34.9, 34.2, 28.9, 28.4, 28.2, 22.7, 21.5; **HRMS (ESI-TOF)** m/z: $[M+H]^+$ calcd for $C_{40}H_{45}O_4Cl_2S$ 691.2410, found 691.2402.

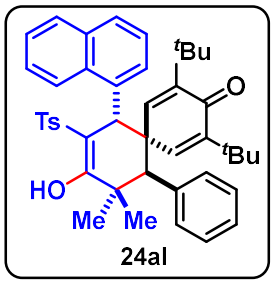
2,4-Di-*tert*-butyl-7-(3,4-dimethoxyphenyl)-9-hydroxy-10,10-dimethyl-11-phenyl-8-tosyl spiro[5.5]undeca-1,4,8-trien-3-one (24ak):

White solid, 153 mg, 66 % yield; dr = 57:43; mp = 199-201 °C; R_f = 0.4 (Pet. ether/Ethyl acetate- 90:10); **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 11.24 (s, 0.72 H), 11.20 (s, 1 H), 7.59 (d, *J* = 7.8



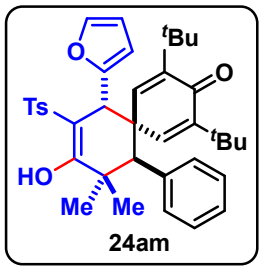
Hz, 2 H), 7.54 (d, *J* = 7.8 Hz, 1.46 H), 7.22 (d, *J* = 7.8 Hz, 2 H), 7.18 (d, *J* = 7.8 Hz, 1.60 H), 7.14 - 7.05 (m, 3.53 H), 7.03 - 6.89 (m, 5.32 H), 6.75 (d, *J* = 8.2 Hz, 1.70 H), 6.72 (s, 2.81 H), 6.59 (s, 0.75 H), 6.48 (d, *J* = 7.3 Hz, 0.75 H), 6.35 (s, 1 H), 5.31 (d, *J* = 2.7 Hz, 1 H), 5.24 (d, *J* = 2.7 Hz, 0.70 H), 3.89 (s, 5.37 H), 3.82 (d, *J* = 4.6 Hz, 5.38 H), 3.53 (s, 0.75 H), 3.38 (s, 1 H), 3.27 (s, 1.76 H), 2.39 (s, 5.31 H), 1.40 (s, 5.37 H), 1.29 (d, *J* = 4.6 Hz, 5.73 H), 1.18 (d, *J* = 7.3 Hz, 16 H), 0.65 (s, 16 H); **^{13}C NMR (100 MHz, $CDCl_3$) δ** = 185.8, 185.7, 169.4, 148.3, 148.2, 148.1, 147.7, 145.5, 145.4, 144.4, 141.6, 141.3, 137.6, 136.8, 136.7, 131.9, 131.1, 129.8, 129.7, 128.5, 127.7, 127.3, 127.2, 127.0, 123.9, 121.2, 114.0, 111.7, 110.5, 110.2, 105.7, 105.5, 55.7, 55.7, 55.6, 53.8, 53.7, 50.5, 44.7, 40.5, 40.5, 35.0, 34.3, 29.1, 28.7, 28.7, 28.3, 22.7, 22.6, 21.5; **HRMS (ESI-TOF)** m/z: $[M+H]^+$ calcd for $C_{42}H_{51}O_6S$ 683.3401, found 683.3408.

2,4-Di-*tert*-butyl-9-hydroxy-10,10-dimethyl-7-(naphthalen-1-yl)-11-phenyl-8-tosylspiro [5.5]undeca-1,4,8-trien-3-one (24al):



White solid, 155 mg, 68 % yield; mp = 258-260 °C; R_f = 0.7 (Pet. ether/Ethyl acetate- 90:10); **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 11.32 (s, 1 H), 7.84 - 7.80 (m, 1 H), 7.74 (d, *J* = 7.8 Hz, 1 H), 7.52 - 7.36 (m, 7 H), 7.05 (dd, *J* = 2.3, 5.5 Hz, 4 H), 7.03 - 6.91 (m, 3 H), 6.67 (d, *J* = 7.3 Hz, 1 H), 4.85 (d, *J* = 3.2 Hz, 1 H), 4.47 (s, 1 H), 3.42 (s, 1 H), 2.32 (s, 3 H), 1.47 (s, 3 H), 1.35 (s, 3 H), 1.24 (s, 9 H), 0.19 (s, 9 H); **^{13}C NMR (100 MHz, $CDCl_3$) δ** = 185.4, 169.6, 148.0, 145.1, 145.0, 144.5, 141.1, 136.7, 136.6, 134.8, 133.7, 132.1, 131.9, 129.6, 128.8, 128.4, 128.1, 127.6, 127.53, 127.5, 127.1, 127.0, 126.3, 125.6, 124.6, 123.9, 105.4, 53.6, 44.8, 43.6, 40.5, 35.1, 33.8, 29.2, 28.1, 27.6, 22.9, 21.4; **HRMS (ESI-TOF)** m/z: $[M+H]^+$ calcd for $C_{44}H_{49}O_4S$ 673.3346, found 673.3328.

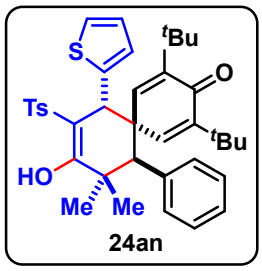
2,4-Di-*tert*-butyl-7-(furan-2-yl)-9-hydroxy-10,10-dimethyl-11-phenyl-8-tosylspiro[5.5] undeca-1,4,8-trien-3-one (24am):



White solid, 162 mg, 78 % yield; mp = 183-184 °C; R_f = 0.7 (Pet. ether/Ethyl acetate- 90:10); **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 11.15 (s, 1 H), 7.70 - 7.66 (m, 2 H), 7.29 (dd, *J* = 1.0, 1.7 Hz, 2 H), 7.27 (d, *J* = 0.7 Hz, 1 H), 7.12 (s, 2 H), 7.00 (s, 1 H), 6.93 (s, 1 H), 6.84 (s, 1 H), 6.79 (d, *J* = 3.2 Hz, 1 H), 6.32 - 6.28 (m, 1 H), 6.09 (dd, *J* = 0.6, 2.6 Hz, 1 H), 5.37 (d, *J* = 3.2 Hz, 1 H), 3.49 (s, 1 H), 3.39 (s, 1 H), 2.41 (s, 3 H), 1.37 (s, 3 H), 1.25 (s, 3 H),

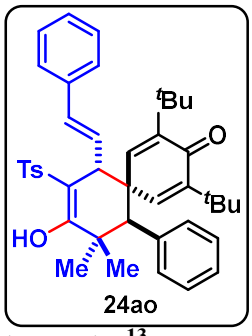
1.11 (s, 9 H), 0.70 (s, 9 H); **^{13}C NMR (100 MHz, $CDCl_3$) δ** = 185.6, 169.9, 152.8, 148.4, 146.2, 144.6, 144.4, 141.8, 139.7, 137.3, 136.9, 130.0, 127.2, 110.7, 109.9, 103.6, 54.9, 44.8, 44.2, 40.5, 35.0, 34.2, 29.0, 28.6, 28.4, 22.5, 21.5; **HRMS (ESI-TOF)** m/z: $[M+H]^+$ calcd for $C_{38}H_{45}O_5S$ 613.2982, found 613.2976.

2,4-Di-*tert*-butyl-9-hydroxy-10,10-dimethyl-11-phenyl-7-(thiophen-2-yl)-8-tosylspiro[5.5] undeca-1,4,8-trien-3-one (24an):



White solid, 134 mg, 63 % yield; mp = 213-215 °C; R_f = 0.8 (Pet. ether/Ethyl acetate- 90:10); **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 11.17 (s, 1 H), 7.64 (d, *J* = 8.2 Hz, 2 H), 7.25 (d, *J* = 7.8 Hz, 2 H), 7.20 (dd, *J* = 0.9, 5.0 Hz, 1 H), 7.12 (d, 2 H), 7.01 (m, 1 H), 6.96 (m, 1 H), 6.91 (dd, *J* = 3.7, 5.0 Hz, 1 H), 6.87 (d, *J* = 3.2 Hz, 1 H), 6.84 (m, 1 H), 6.73 (d, *J* = 3.2 Hz, 1 H), 5.51 (d, *J* = 3.2 Hz, 1 H), 3.70 (s, 1 H), 3.52 (s, 1 H), 2.41 (s, 3 H), 1.41 (s, 3 H), 1.27 (s, 3 H), 1.13 (s, 9 H), 0.69 (s, 9 H); **^{13}C NMR (100 MHz, $CDCl_3$) δ** = 185.6, 169.5, 148.2, 145.9, 145.0, 144.6, 143.6, 140.4, 137.4, 136.8, 131.9, 129.9, 128.4, 127.8, 127.7, 127.2, 127.1, 126.7, 125.3, 106.6, 54.1, 46.0, 44.5, 40.5, 35.0, 34.4, 29.0, 28.6, 28.3, 22.7, 21.5; **HRMS (ESI-TOF)** m/z: $[M+H]^+$ calcd for $C_{38}H_{45}O_4S_2$ 629.2754, found 629.2749.

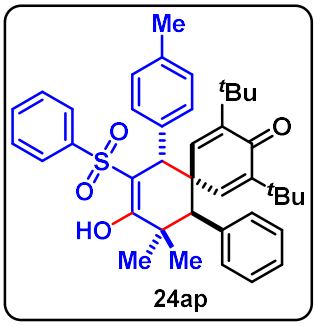
(*E*)-2,4-Di-*tert*-butyl-9-hydroxy-10,10-dimethyl-11-phenyl-7-styryl-8-tosylspiro[5.5]undeca-1,4,8-trien-3-one (24ao):



White solid, 146 mg, 66 % yield; mp = 247-249 °C; R_f = 0.6 (Pet. ether/Ethyl acetate- 90:10); **^{1}H NMR (500 MHz, $CDCl_3$) δ** = 11.21 (s, 1 H), 7.77 (d, *J* = 8.4 Hz, 2 H), 7.33 (d, *J* = 7.2 Hz, 2 H), 7.30 - 7.21 (m, 5 H), 7.15 (m, 2 H), 7.03 (m, 1 H), 6.94 (m, 2 H), 6.90 (d, *J* = 3.1 Hz, 1 H), 6.32 (d, *J* = 15.6 Hz, 1 H), 6.09 - 5.98 (m, 2 H), 3.26 (s, 1 H), 3.03 (d, *J* = 7.6 Hz, 1 H), 2.30 (s, 3 H), 1.36 (s, 3 H), 1.25 (s, 3 H), 1.16 (s, 9 H), 0.79 (s, 9 H); **^{13}C NMR (125 MHz, $CDCl_3$) δ** = 185.6, 169.5, 148.0, 146.4, 144.8, 140.8, 137.7, 137.0, 136.4, 135.0, 131.9, 131.4, 130.1, 129.1, 128.6, 128.5, 128.3, 127.8, 127.5, 127.3, 127.1, 126.4, 104.9, 55.2, 47.9, 45.1, 40.7, 35.0, 34.5, 29.0, 28.9, 28.7, 22.6, 21.4; **HRMS (ESI-TOF)** m/z: $[M+Na]^+$ calcd for $C_{42}H_{48}O_4SNa$ 671.3448, found 671.3448.

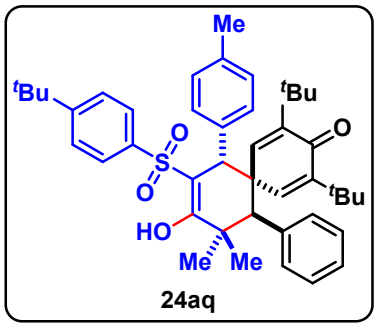
2,4-Di-*tert*-butyl-9-hydroxy-10,10-dimethyl-11-phenyl-8-(phenylsulfonyl)-7-(p-tolyl)spiro [5.5]undeca-1,4,8-trien-3-one (24ap):

White solid, 150 mg, 71 % yield; mp = 192-194 °C; R_f = 0.7 (Pet. ether/Ethyl acetate- 90:10); **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 11.25 (s, 1 H), 7.75 - 7.68 (m, 2 H), 7.58 - 7.51 (m, 1 H),



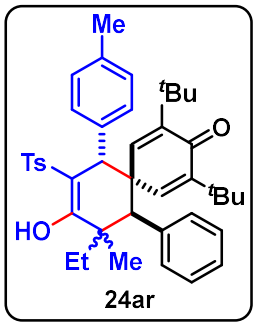
7.45 - 7.38 (m, 2 H), 7.14 - 6.98 (m, 6 H), 6.96 (d, *J* = 3.2 Hz, 2 H), 6.82 - 6.68 (m, 2 H), 5.25 (d, *J* = 3.2 Hz, 1 H), 3.47 (s, 1 H), 3.23 (s, 1 H), 2.32 (s, 3 H), 1.41 (s, 3 H), 1.30 (s, 3 H), 1.15 (s, 9 H), 0.66 (s, 9 H); **^{13}C NMR (100 MHz, CDCl$_3$) δ** = 185.7, 170.1, 147.7, 145.5, 145.4, 141.4, 140.5, 137.0, 136.8, 135.5, 133.3, 131.6, 129.2, 128.6, 128.5, 128.3, 127.3, 127.2, 105.0, 53.5, 50.6, 44.5, 40.6, 35.0, 34.4, 29.2, 28.6, 28.3, 22.7, 21.0; **HRMS (ESI-TOF)** m/z: $[M+Na]^+$ calcd for $C_{40}H_{46}O_4SNa$ 645.3439, found 645.3439.

2,4-Di-*tert*-butyl-8-((4-(tert-butyl)phenyl)sulfonyl)-9-hydroxy-10,10-dimethyl-11-phenyl-7-(p-tolyl)spiro[5.5]undeca-1,4,8-trien-3-one (24aq):



White solid, 180 mg, 78 % yield; mp = 192-194 °C; R_f = 0.7 (Pet. ether/Ethyl acetate- 90:10); **^{1}H NMR (400 MHz, CDCl$_3$) δ** = 11.25 (s, 1 H), 7.64 - 7.60 (m, 2 H), 7.43 - 7.38 (m, 2 H), 7.12 - 7.06 (m, 2 H), 7.06 - 7.00 (m, 3 H), 7.00 - 6.92 (m, 3 H), 6.79 (d, *J* = 7.3 Hz, 1 H), 6.74 (s, 1 H), 5.25 (d, *J* = 3.2 Hz, 1 H), 3.51 (s, 1 H), 3.22 (s, 1 H), 2.31 (s, 3 H), 1.41 (s, 3 H), 1.32 (s, 9 H), 1.29 (s, 3 H), 1.15 (s, 9 H), 0.65 (s, 9 H); **^{13}C NMR (100 MHz, CDCl$_3$) δ** = 185.7, 169.7, 157.3, 147.5, 145.6, 145.5, 145.5, 141.6, 137.5, 136.9, 136.8, 135.7, 132.0, 131.9, 131.6, 128.6, 128.5, 128.3, 127.6, 127.2, 127.1, 126.2, 105.2, 53.5, 50.6, 44.5, 40.5, 35.2, 35.1, 34.4, 31.0, 29.3, 28.6, 28.3, 22.7, 21.1; **HRMS (ESI-TOF)** m/z: $[M+Na]^+$ calcd for $C_{44}H_{54}O_4SNa$ 701.8619, found 701.8619.

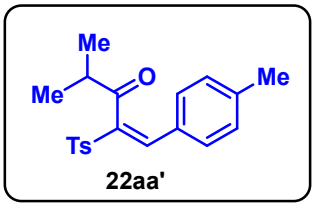
2,4-Di-*tert*-butyl-10-ethyl-9-hydroxy-10-methyl-11-phenyl-7-(p-tolyl)-8-tosylspiro[5.5]undeca-1,4,8-trien-3-one (24ar):



White solid, 152 mg, 69 % yield; dr = 67:34; mp = 185-186 °C; R_f = 0.7 (Pet. ether/Ethyl acetate- 90:10); **^{1}H NMR (400 MHz, CDCl$_3$) δ** = 11.34 (s, 0.97 H), 11.28 (s, 0.51 H), 7.64 - 7.56 (m, 3.13 H), 7.26 - 7.20 (m, 3.36 H), 7.18 - 7.13 (m, 0.92 H), 7.09 - 7.05 (m, 3 H), 7.04 - 7.02 (m, 3.38 H), 7.00 - 6.94 (m, 1.64 H), 6.94 - 6.86 (m, 2.98 H), 6.76 (d, *J* = 6.1 Hz, 2.25 H), 5.25 (d, *J* = 2.9 Hz, 1 H), 5.20 (d, *J* = 2.9 Hz, 0.51 H), 3.45 (s, 1 H), 3.38 (s, 1 H), 3.37 (s, 0.50 H), 3.24 (s, 0.51 H), 2.41 (s, 4.76 H), 2.36 - 2.31 (m, 4.71 H), 2.07 - 1.97 (m, 0.53 H), 1.93 - 1.83 (m, 1 H), 1.64 (qd, *J* = 7.4, 14.6 Hz, 0.68 H), 1.45 (s, 1.62 H), 1.39 - 1.34 (m, 1.17 H), 1.32 (s, 3.30 H), 1.25 - 1.19 (m, 3.30 H), 1.14 (s, 9.40 H), 1.12 (s, 4.72 H),

0.77 (t, *J* = 7.5 Hz, 1.93 H), 0.66 (s, 4.80 H), 0.63 (s, 9.50 H); **^{13}C NMR (100 MHz, $CDCl_3$) δ** = 185.8, 170.4, 169.0, 147.0, 146.8, 146.1, 146.0, 145.3, 145.0, 144.5, 144.5, 142.3, 142.0, 137.7, 137.6, 137.3, 137.1, 137.0, 136.9, 136.0, 135.8, 129.9, 129.8, 128.5, 127.7, 127.3, 127.2, 127.1, 106.8, 105.4, 76.7, 54.3, 51.1, 50.2, 48.9, 44.5, 44.2, 44.2, 42.9, 35.0, 34.9, 34.4, 34.3, 32.7, 29.0, 29.0, 28.6, 28.6, 27.8, 24.5, 23.2, 21.5, 21.5, 21.1, 21.0, 10.8, 10.4; **HRMS (ESI-TOF)** m/z: $[M+H]^+$ calcd for $C_{42}H_{51}O_4S$ 651.3499, found 651.3499.

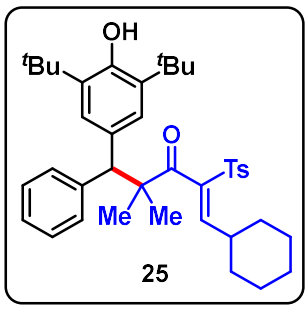
4-Methyl-1-(*p*-tolyl)-2-tosylpent-1-en-3-one (22aa'):



22aa'

Brown liquid, 57 mg, 57 % yield; R_f = 0.3 (Pet. ether/Ethyl acetate- 80:20); **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 7.97 (s, 1 H), 7.79 (d, *J* = 8.7 Hz, 2 H), 7.33 (d, *J* = 8.2 Hz, 2 H), 7.18 (s, 4 H), 2.69 (spt, *J* = 6.9 Hz, 1 H), 2.43 (s, 3 H), 2.37 (s, 3 H), 1.06 (d, *J* = 6.9 Hz, 6 H); **^{13}C NMR (100 MHz, $CDCl_3$) δ** = 206.0, 144.5, 141.9, 141.8, 141.0, 137.5, 129.8, 129.7, 129.5, 129.2, 128.5, 41.7, 21.6, 21.4, 18.0; **HRMS (ESI-TOF)** m/z: $[M+H]^+$ calcd for $C_{20}H_{23}O_3S$ 343.1362, found 343.1359.

1-Cyclohexyl-5-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-4,4-dimethyl-5-phenyl-2-tosylpent-1-en-3-one (25):

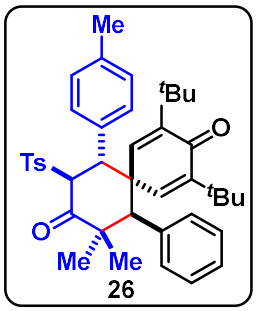


25

Brown liquid, 0.162 mg, 76 % yield; R_f = 0.6 (Pet. ether/Ethyl acetate- 80:20); **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 7.53 (d, *J* = 8.2 Hz, 2 H), 7.41 (d, *J* = 7.8 Hz, 2 H), 7.27 (s, 1 H), 7.25 - 7.18 (m, 5 H), 7.17 - 7.11 (m, 1 H), 6.58 (d, *J* = 10.1 Hz, 1 H), 5.04 (s, 1 H), 4.55 (s, 1 H), 2.41 (s, 3 H), 1.52 (s, 3 H), 1.45 (d, *J* = 12.4 Hz, 3 H), 1.39 (s, 18 H), 1.25 (s, 3 H), 1.19 (d, *J* = 8.7 Hz, 1 H), 1.16 - 0.99 (m, 2 H), 0.97 - 0.70 (m, 5 H); **^{13}C NMR (100 MHz, $CDCl_3$) δ** = 207.6, 152.4, 149.4, 144.3, 142.5, 140.5, 136.8, 135.1, 131.8, 130.7, 129.6, 128.3, 128.1, 127.0, 126.4, 57.4, 53.8, 37.2, 34.3, 31.0, 30.9, 30.4, 26.4, 25.2, 23.9, 23.7, 21.7; **HRMS (ESI-TOF)** m/z: $[M+Na]^+$ calcd for $C_{40}H_{52}O_4NaS$ 651.3479, found 651.3474.

2,4-Di-*tert*-butyl-8,8-dimethyl-7-phenyl-11-(*p*-tolyl)-10-tosylspiro[5.5]undeca-1,4-diene-3,9-dione (26):

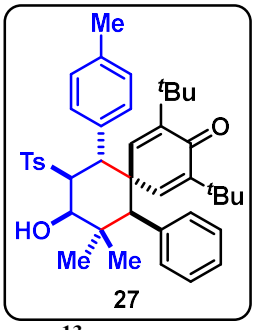
White solid, 71 mg, 71 % yield; mp = 107-109 °C; R_f = 0.5 (Pet. ether/Ethyl acetate- 90:10); **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 7.59 (d, *J* = 8.2 Hz, 2 H), 7.29 - 7.24 (m, 1 H), 7.21 (d, *J* = 8.2 Hz, 2 H), 7.19 - 7.14 (m, 2 H), 7.03 (t, *J* = 7.3 Hz, 1 H), 6.90 (d, *J* = 7.8 Hz, 1 H), 6.85 - 6.78 (m, *J* = 7.8 Hz, 2 H), 6.71 - 6.63 (m, *J* = 8.2 Hz, 2 H), 6.55 (d, *J* = 3.2 Hz, 1 H), 6.12 (s, 1 H),



26

4.62 (d, *J* = 9.2 Hz, 1 H), 4.24 (d, *J* = 8.7 Hz, 1 H), 3.84 (s, 1 H), 2.38 (s, 3 H), 2.18 (s, 3 H), 1.48 (s, 3 H), 1.17 (s, 9 H), 1.17 (s, 3 H), 0.67 (s, 9 H); **^{13}C NMR (100 MHz, $CDCl_3$) δ** = 206.7, 185.1, 149.8, 147.3, 145.3, 144.8, 137.3, 137.0, 136.6, 134.6, 134.6, 131.3, 129.7, 129.6, 128.8, 128.5, 128.4, 128.1, 127.9, 127.8, 127.4, 127.3, 76.5, 60.3, 52.8, 48.3, 47.9, 35.4, 34.1, 28.8, 28.5, 28.4, 24.6, 21.6, 20.9; **HRMS (ESI-TOF)** m/z: $[M+H]^+$ calcd for $C_{41}H_{49}O_4S$ 637.3346, found 637.3345.

2,4-Di-*tert*-butyl-9-hydroxy-8,8-dimethyl-7-phenyl-11-(p-tolyl)-10-tosylspiro[5.5]undeca-1,4-dien-3-one (27):



27

White solid, 99 mg, 99 % yield; mp = 173-175 °C; R_f = 0.3 (Pet. ether/Ethyl acetate- 90:10); **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 7.17 - 7.06 (m, 5 H), 7.00 (d, *J* = 9.2 Hz, 5 H), 6.76- 6.69 (d, *J* = 7.3 Hz, 2 H), 6.36 - 6.20 (m, 3 H), 5.30 (s, 1 H), 4.73 - 4.60 (d, 1 H), 4.28 (d, *J* = 12.2 Hz, 1 H), 3.87 (d, *J* = 12.2 Hz, 1 H), 3.50 (s, 1 H), 3.30 (d, *J* = 4.3 Hz, 1 H), 2.38 (s, 3 H), 2.13 (s, 3 H), 1.44 (s, 3 H), 1.12 (s, 9 H), 0.92 (s, 3 H), 0.70 (s, 9 H); **^{13}C NMR (100 MHz, $CDCl_3$) δ** = 185.0, 148.4, 146.9, 146.7, 143.6, 138.1, 137.6, 137.4, 136.5, 132.6, 131.6, 131.4, 129.0, 128.8, 128.5, 127.9, 127.6, 127.1, 126.8, 126.6, 126.2, 74.6, 65.6, 55.5, 53.4, 50.7, 47.8, 40.1, 35.2, 34.0, 28.6, 28.5, 23.5, 21.5, 20.9; **HRMS (ESI-TOF)** m/z: $[M+H]^+$ calcd for $C_{41}H_{51}O_4S$ 639.3506, found 639.3506.

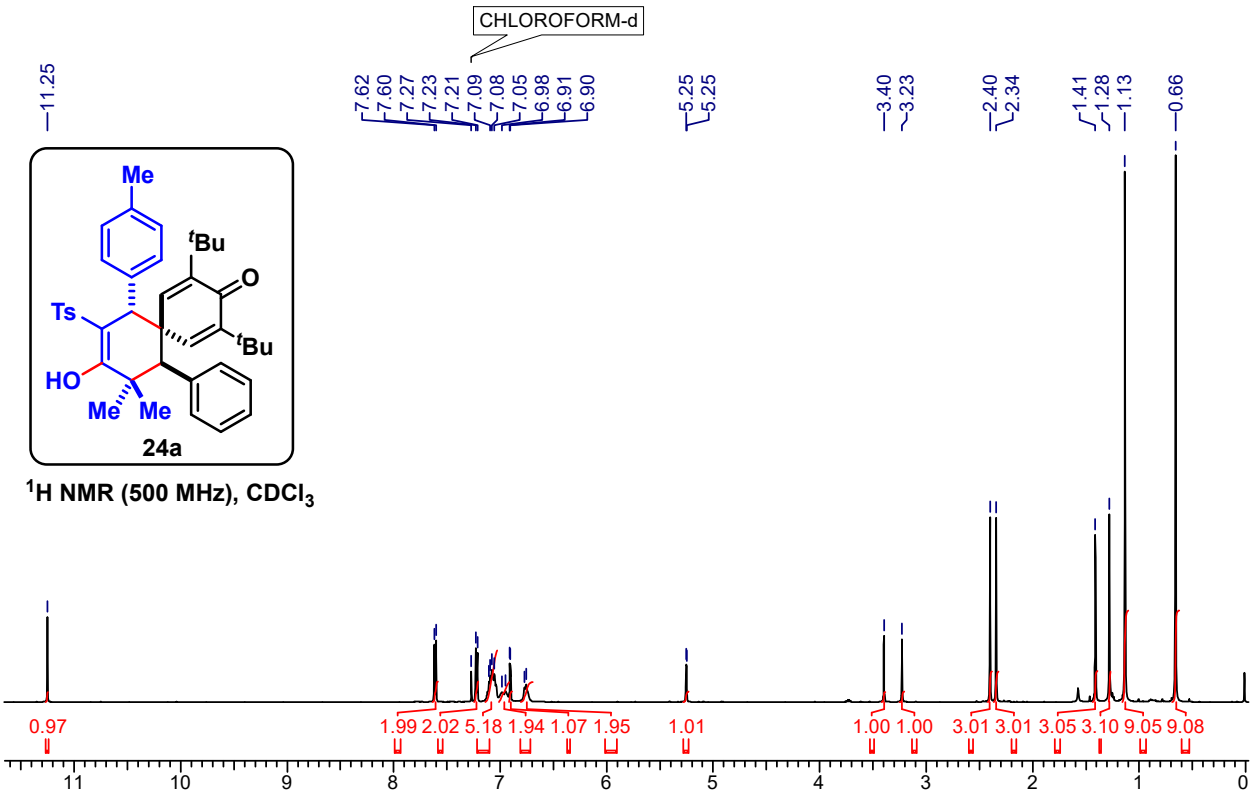
4.6.9 Single Crystal Analysis Data

An X-ray intensity data measurement of compound **24ai** was carried out on a Bruker D8 VENTURE Kappa Duo PHOTON II CPAD diffractometer equipped with Incoatech multilayer mirror optics. The intensity measurements were carried out at 100(2) K temperature with Mo micro-focus sealed tube diffraction source (MoK_α= 0.71073 Å). The X-ray generator was operated at 50 kV and 1.4. A preliminary set of cell constants and an orientation matrix were calculated from three sets of 36 frames. Data were collected with ω scan width of 0.5° at different settings of φ and 2θ with a frame time of 15 secs keeping the sample-to-detector distance fixed at 5.00 cm. The X-ray data collection was monitored by APEX3 program (Bruker, 2016).[17] All the data were corrected for Lorentzian, polarization and absorption effects using SAINT and SADABS programs (Bruker, 2016).[17] Using APEX3 (Bruker) program suite, the structure was solved with the ShelXS-97 (Sheldrick, 2008)[18] structure solution program, using direct methods. The model was refined with a version of ShelXL-2013 (Sheldrick, 2015)[19] using Least Squares minimisa-

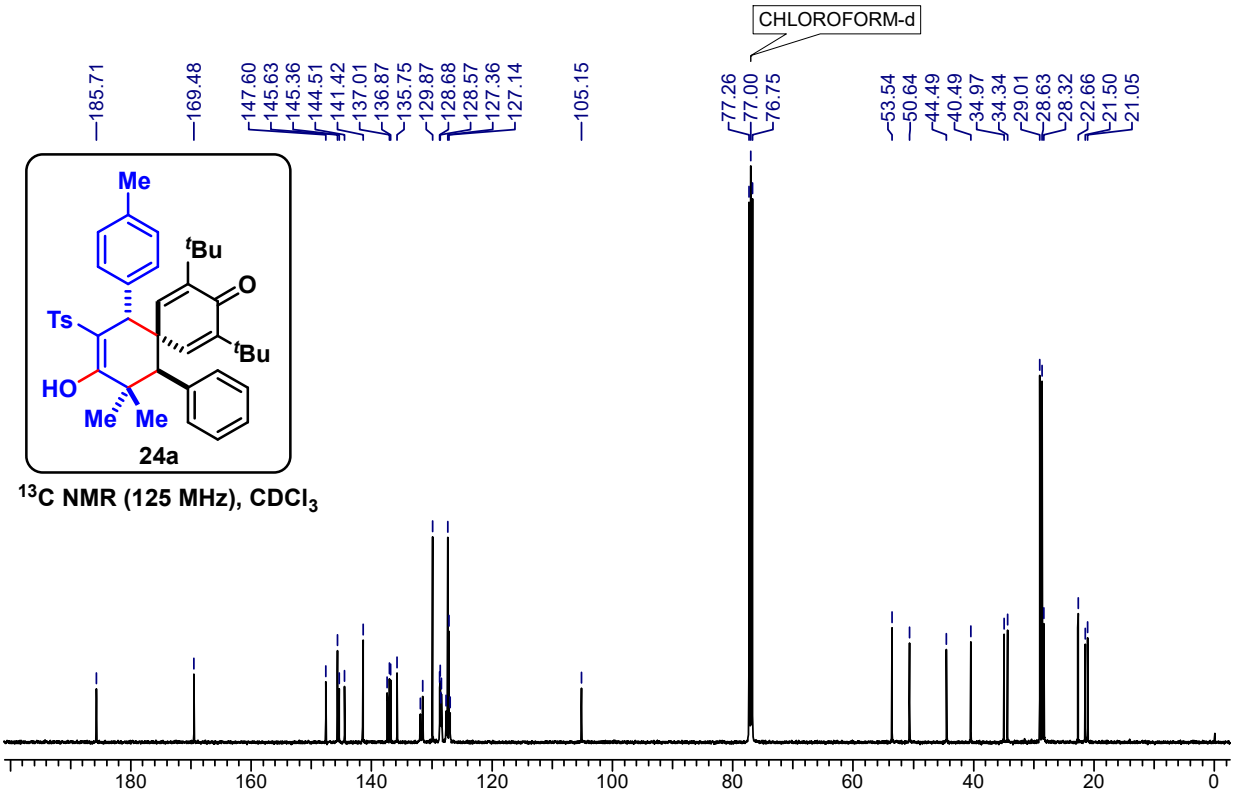
tion. All the hydrogen atoms were placed in a geometrically idealized position and constrained to ride on its parent atoms. An *ORTEP* III[20] view of compounds was drawn with 30% probability displacement ellipsoids, and H atoms are omitted for clarity.

Crystal data of **24ai:** $C_{42}H_{50}O_4S$, M = 650.88, colorless block, 0.48 x 0. 23 x 0.14 mm^3, monoclinic, space group $P2_1/c$, a = 17.0878(7) Å, b = 10.7963(4) Å, c = 21.0437(9) Å, β = 109.074(2)°, V = 3669.1(3) $Å^3$, Z = 4, T = 100(2) K, $2\theta_{max}$= 61.052°, D_{calc} (g cm^{-3}) = 1.178, $F(000)$ = 1400, μ (mm^{-1}) = 0.128, 130989 reflections collected, 11176 unique reflections (R_{int} = 0.0458, R_{sig} = 0.0219), 9223 observed ($I > 2\sigma(I)$) reflections, multi-scan absorption correction, T_{min} = 0.941, T_{max} = 0.982, 436 refined parameters, Good of Fit = S = 1.069, $R1$ = 0.0391, $wR2$ = 0.0968 (all data R = 0.0530, $wR2$ = 0.1089), maximum and minimum residual electron densities; $\Delta\rho_{max}$ = 0.392, $\Delta\rho_{min}$= -0.386 (e $Å^{-3}$), **CCDC No. 1950350** .

4.7. Spectral Data

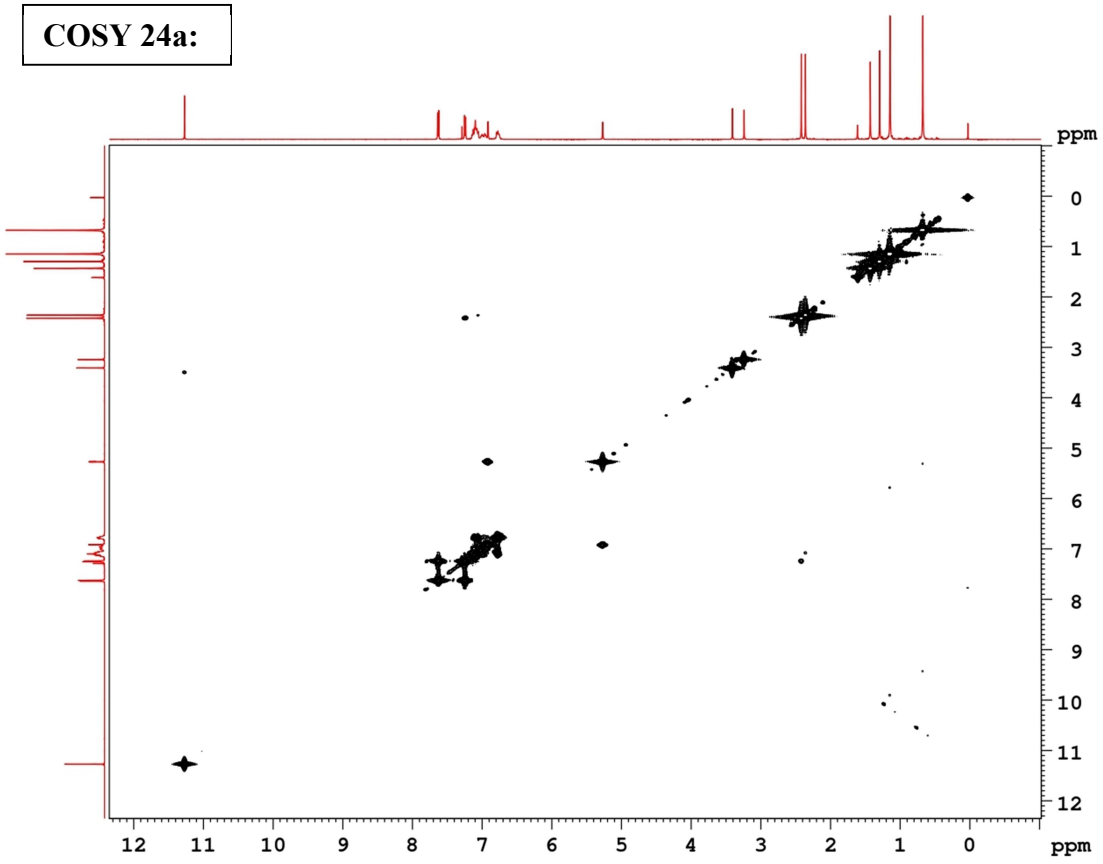


^{1}H NMR (500 MHz), $CDCl_3$

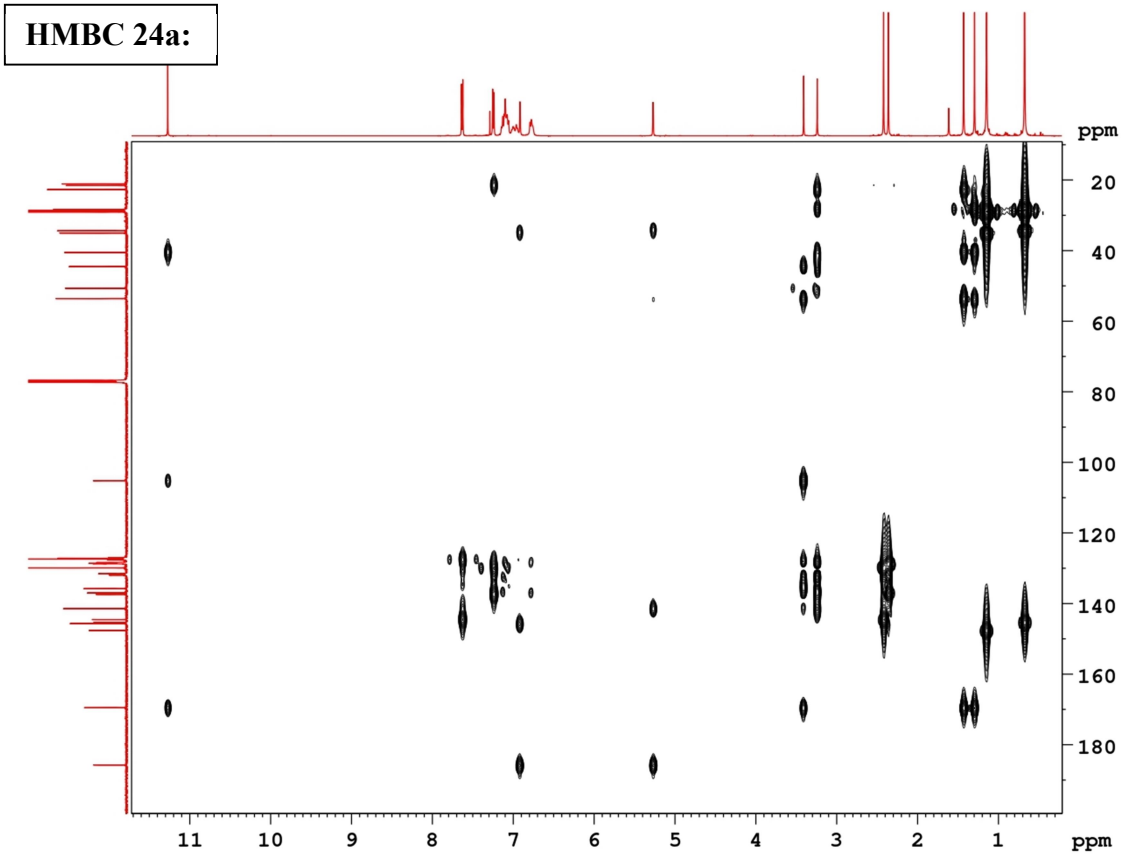


^{13}C NMR (125 MHz), $CDCl_3$

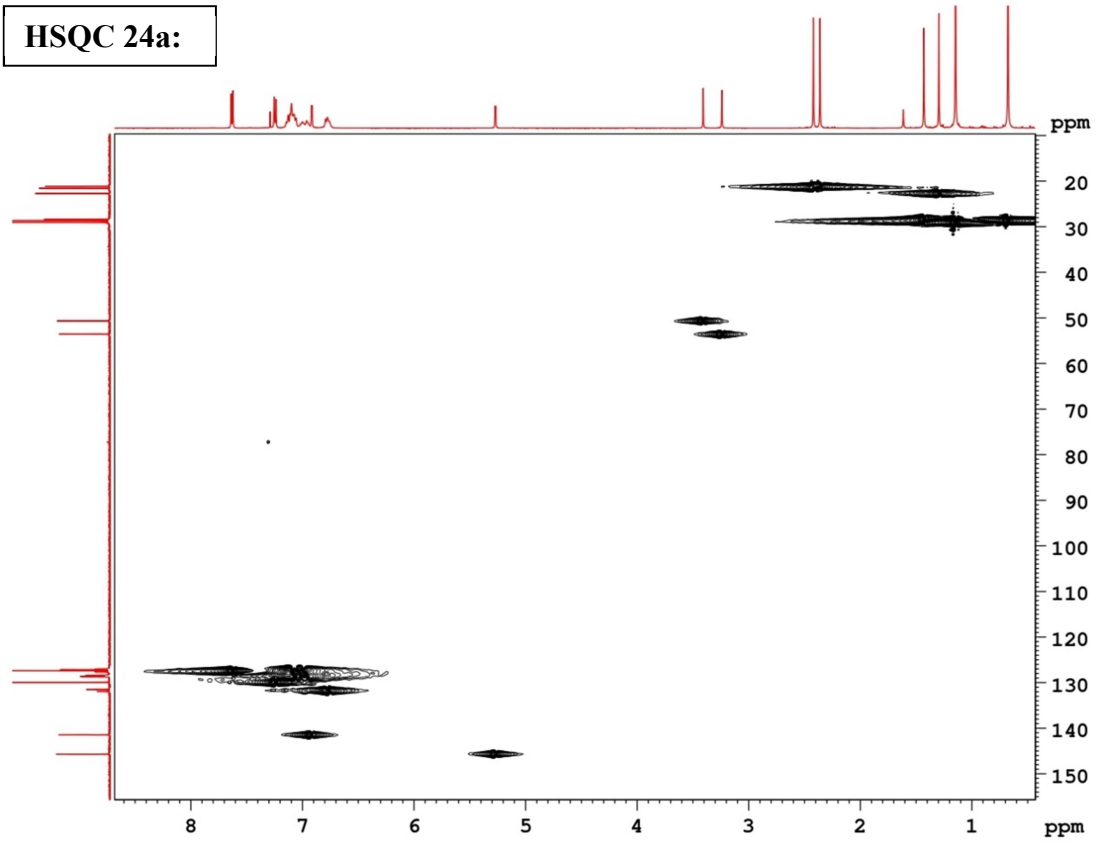
COSY 24a:



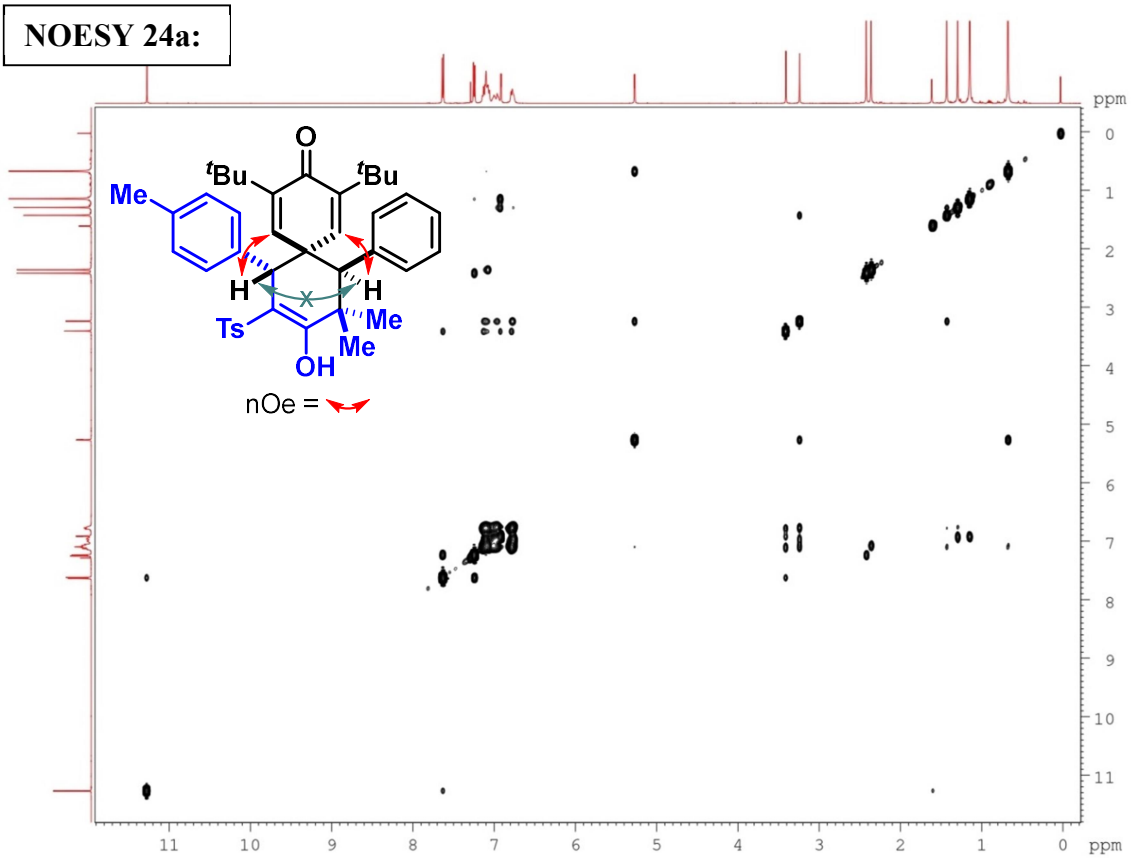
HMBC 24a:

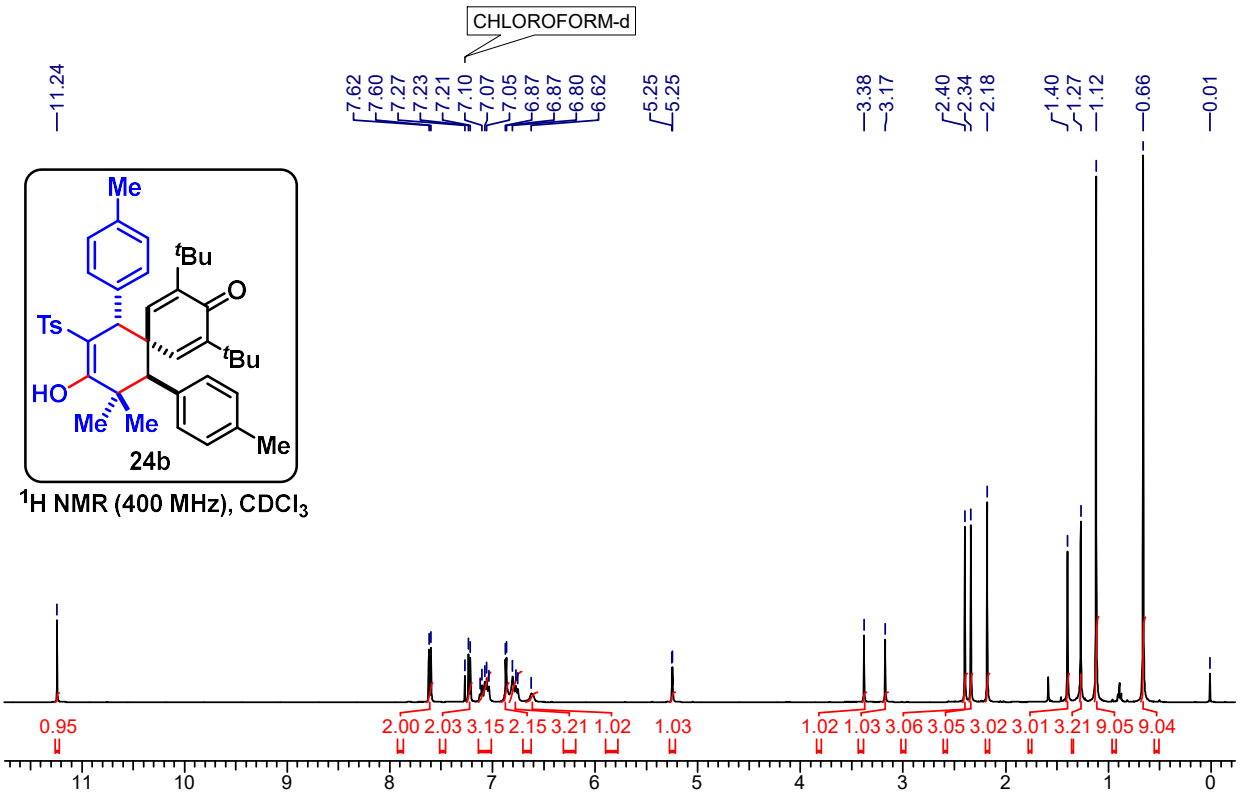


HSQC 24a:

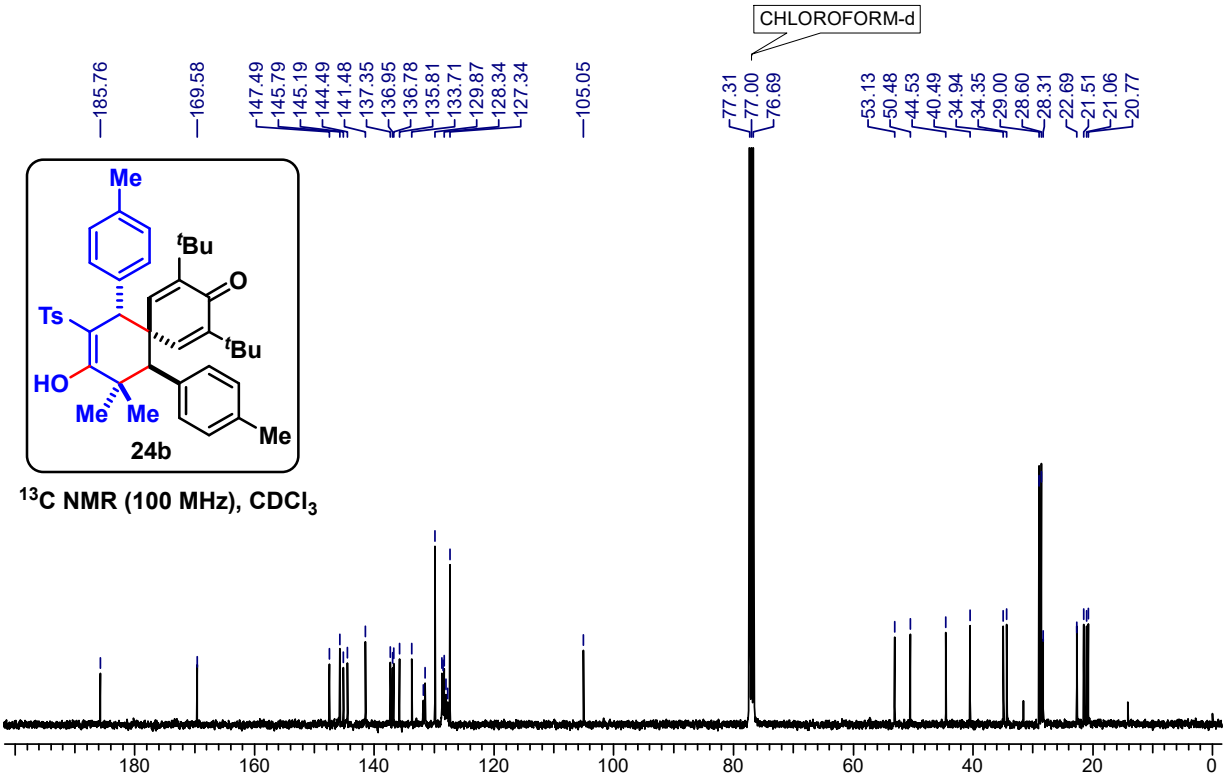


NOESY 24a:

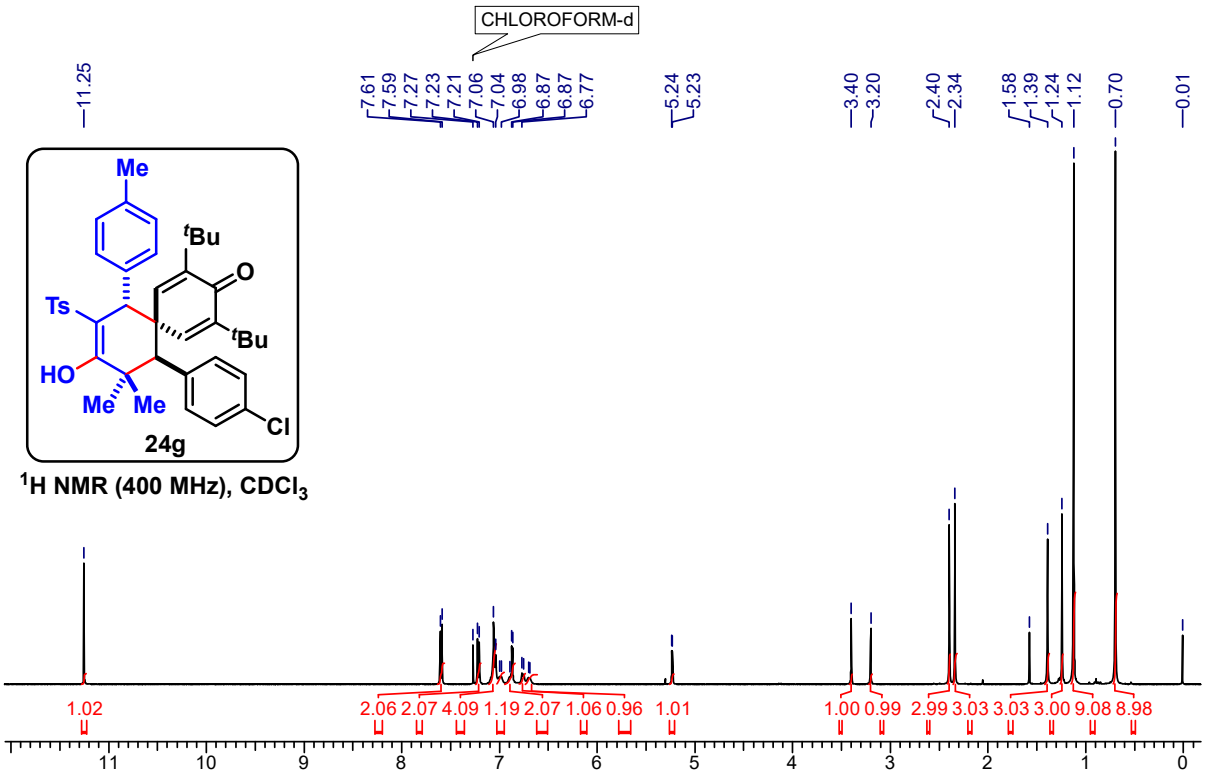




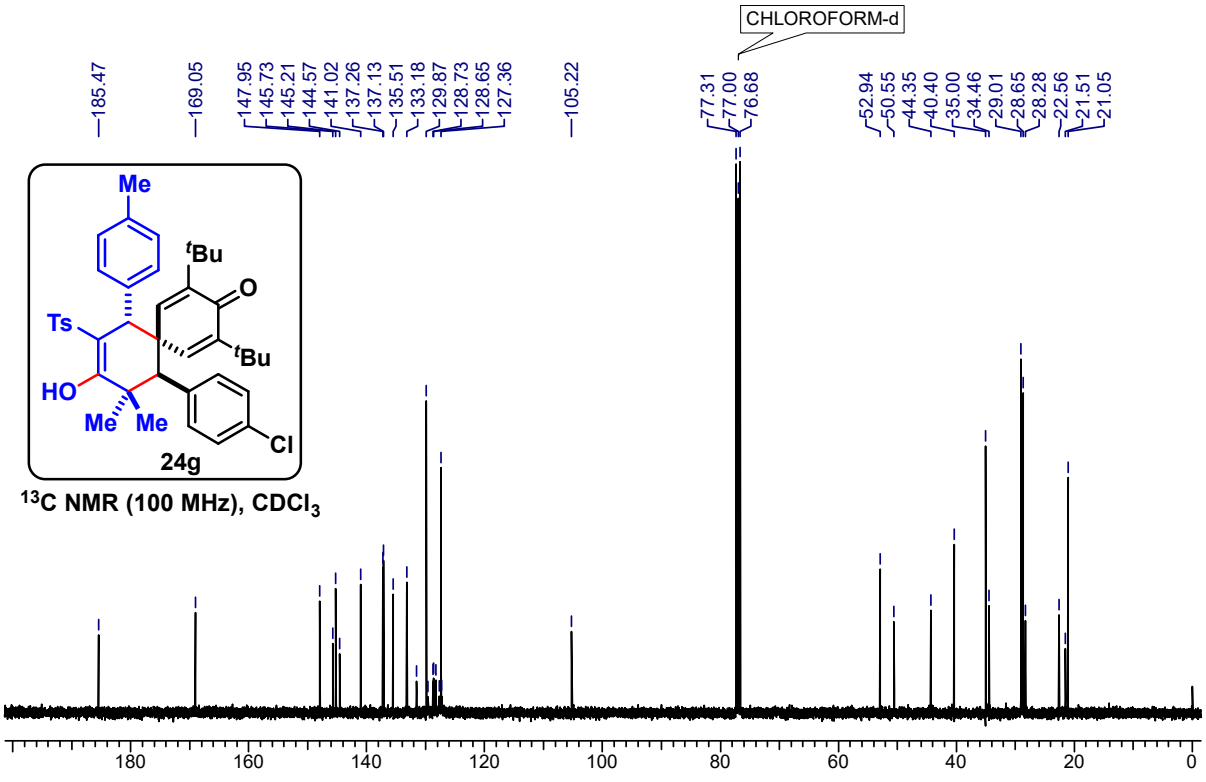
^{1}H NMR (400 MHz), $CDCl_3$



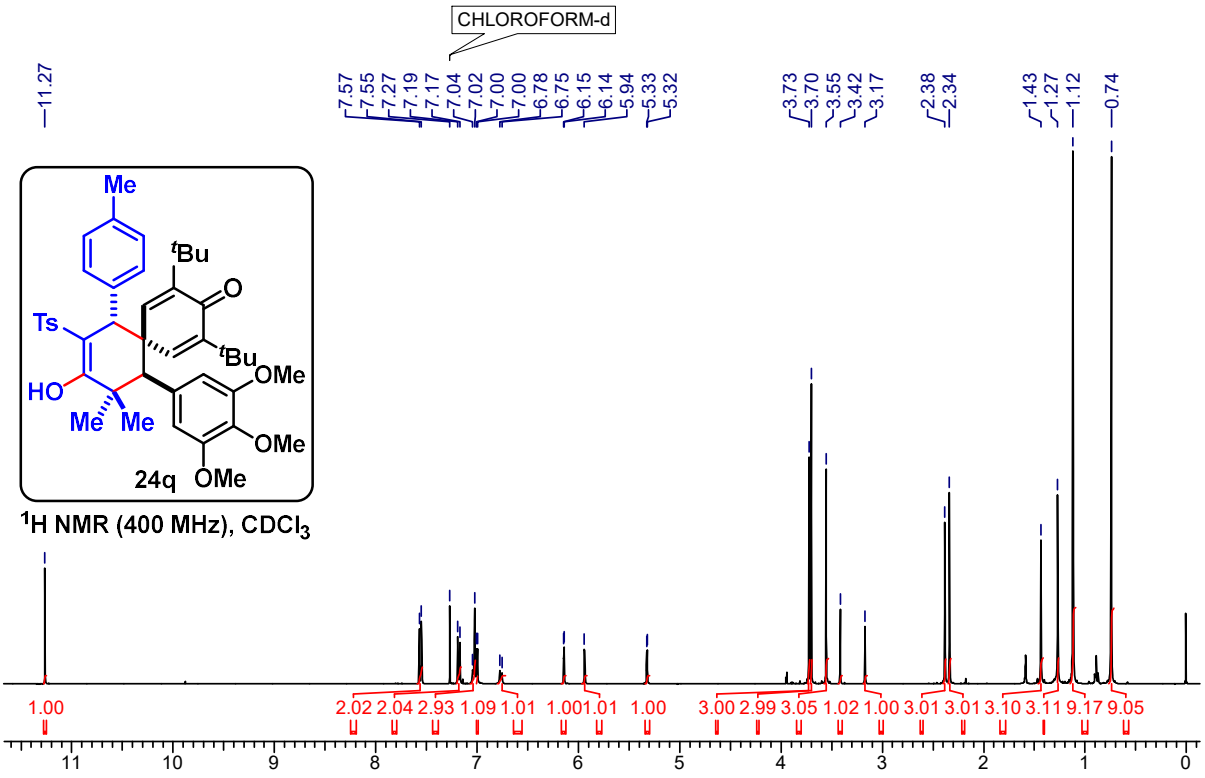
^{13}C NMR (100 MHz), $CDCl_3$



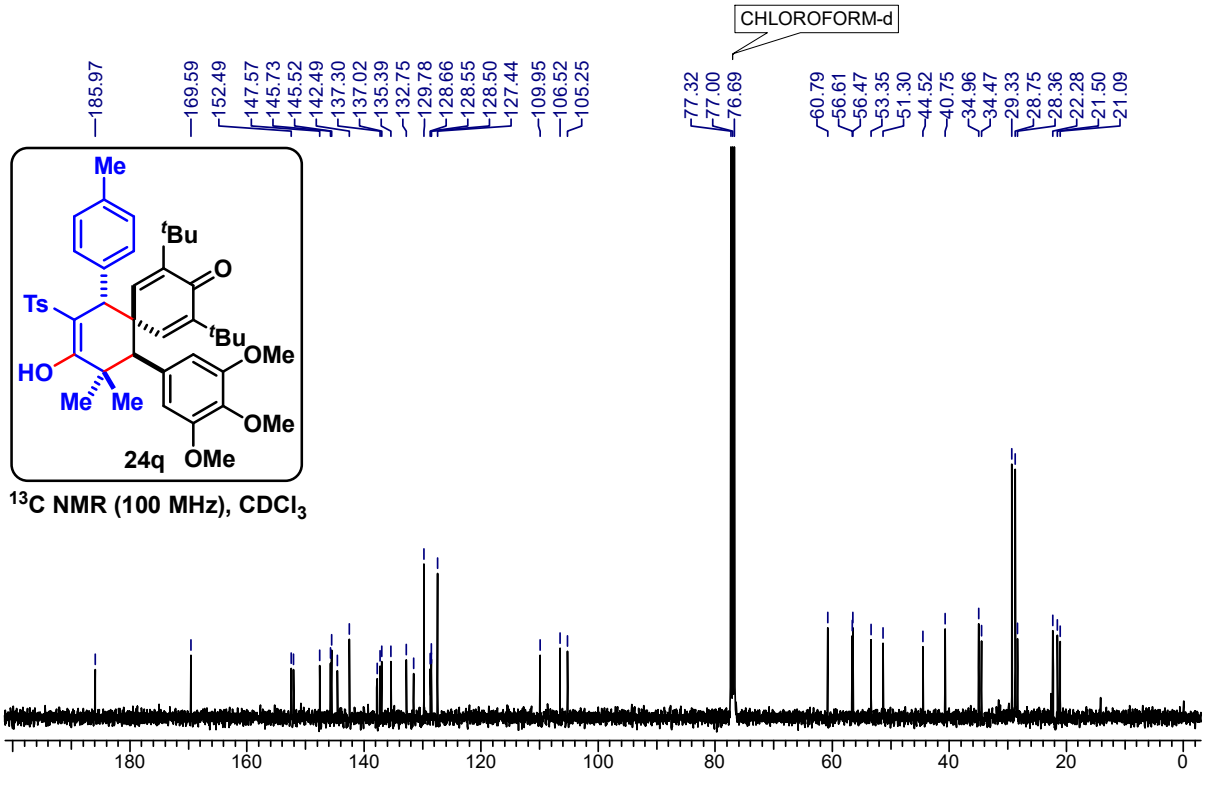
^{1}H NMR (400 MHz), $CDCl_3$



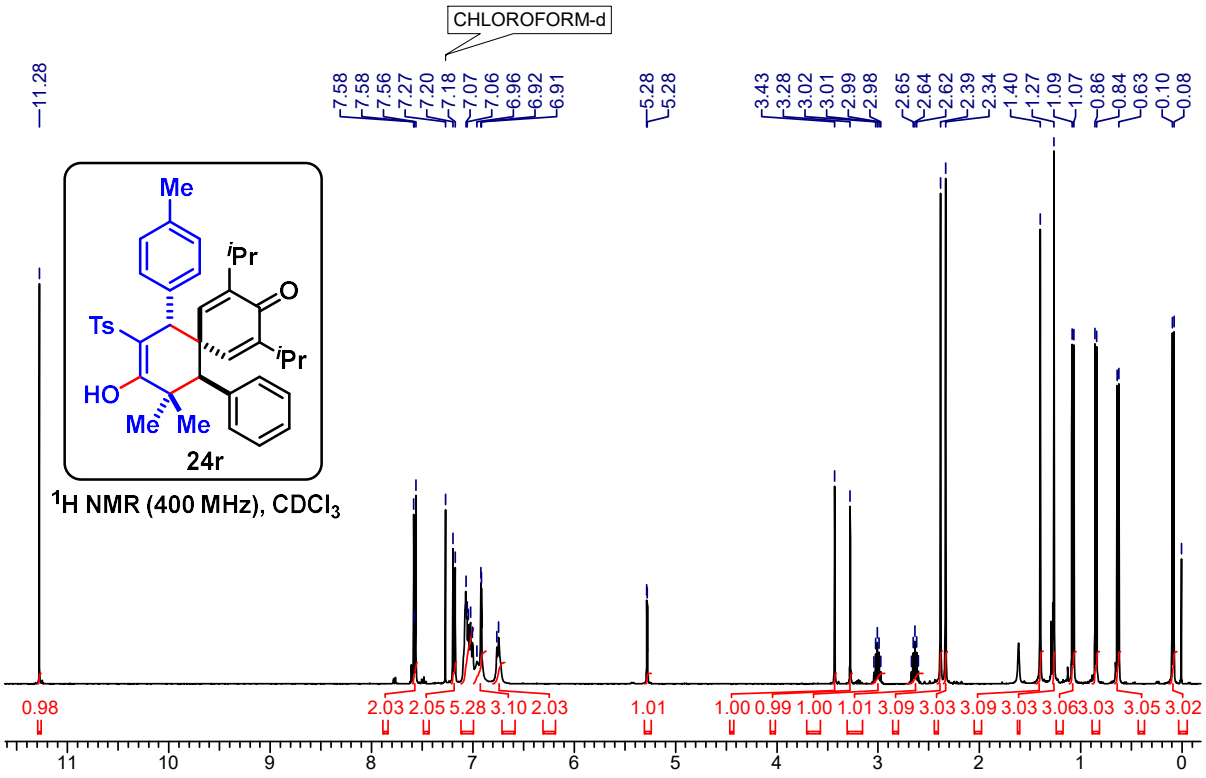
^{13}C NMR (100 MHz), $CDCl_3$



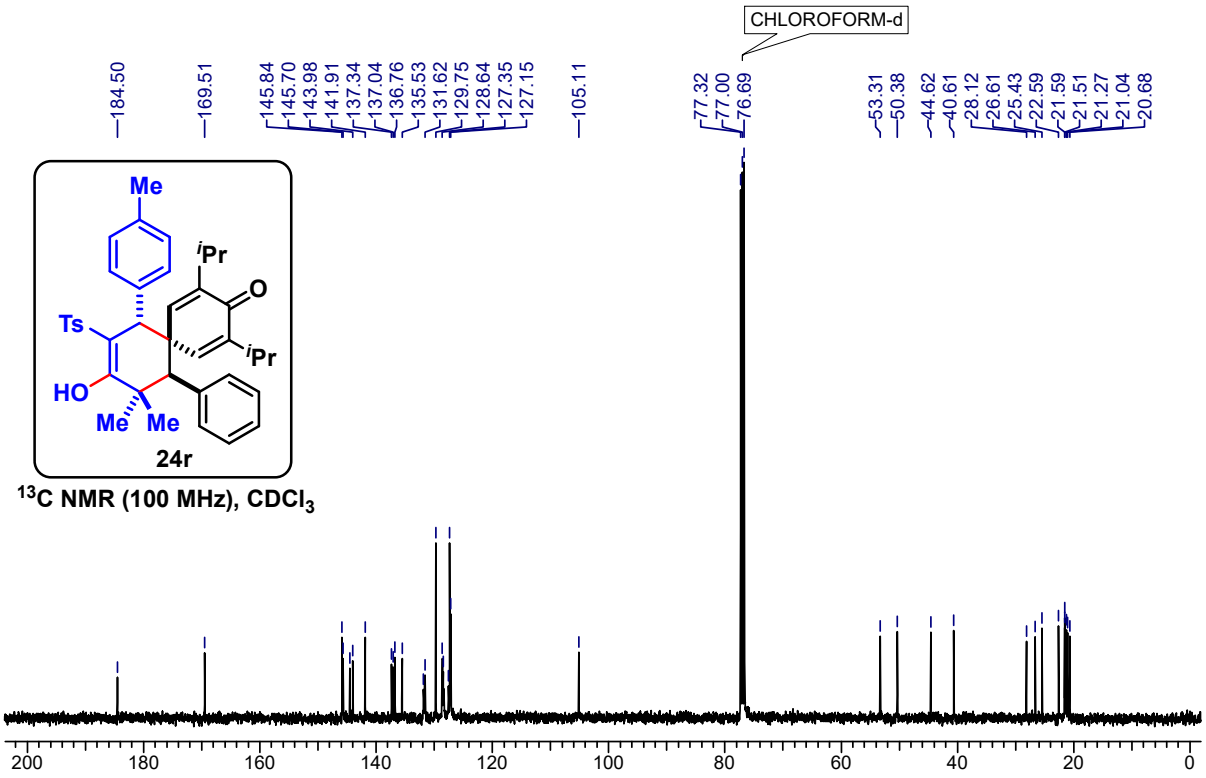
^{1}H NMR (400 MHz), $CDCl_3$



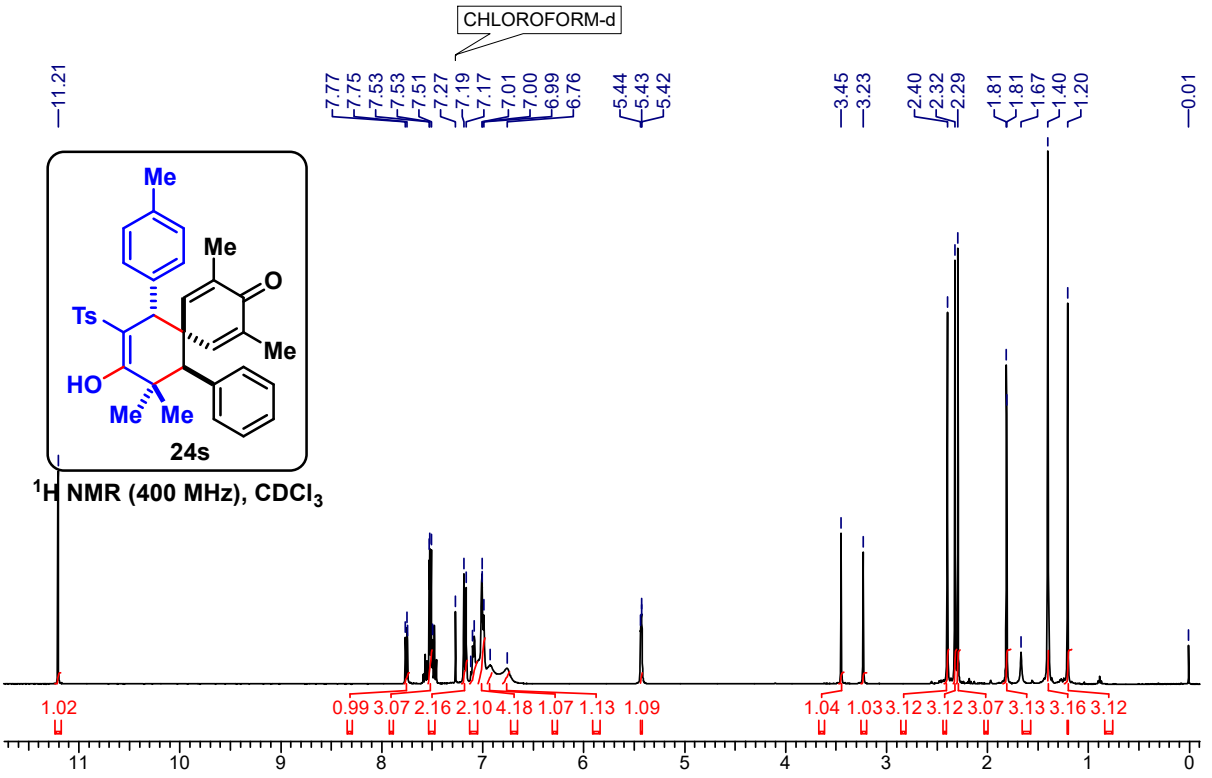
^{13}C NMR (100 MHz), $CDCl_3$



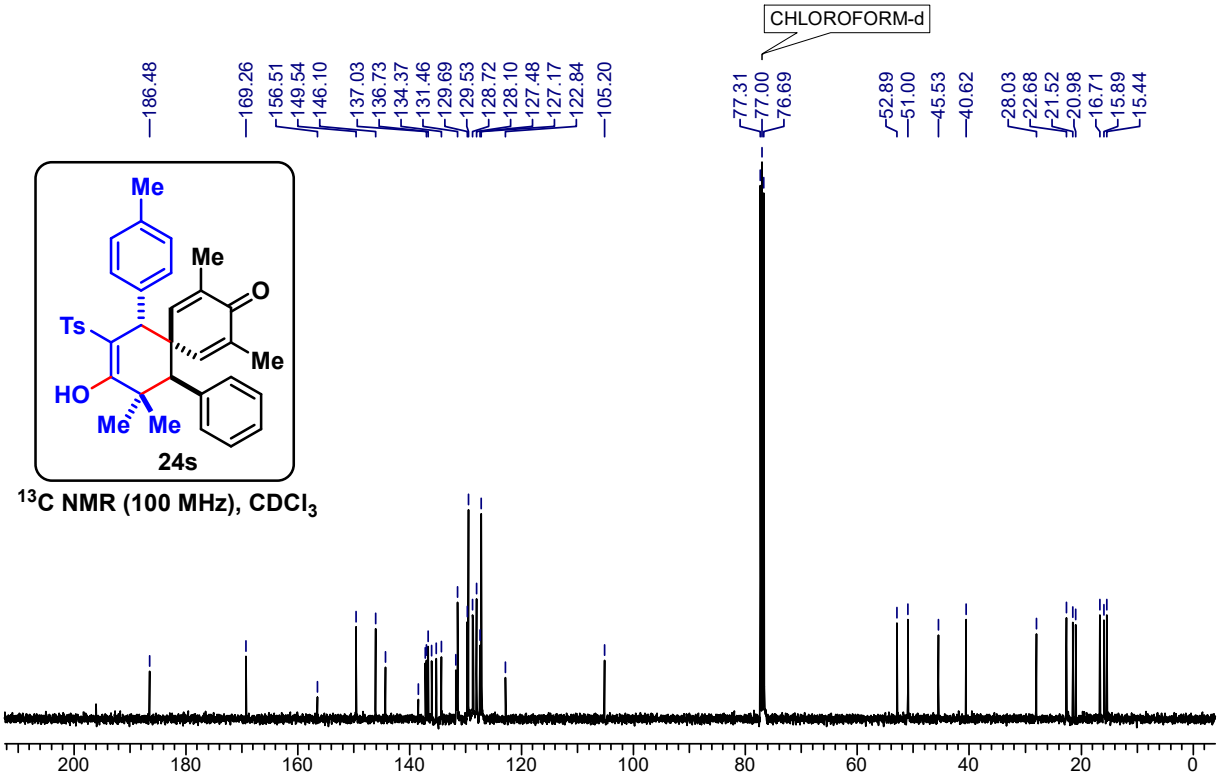
^{1}H NMR (400 MHz), $CDCl_3$



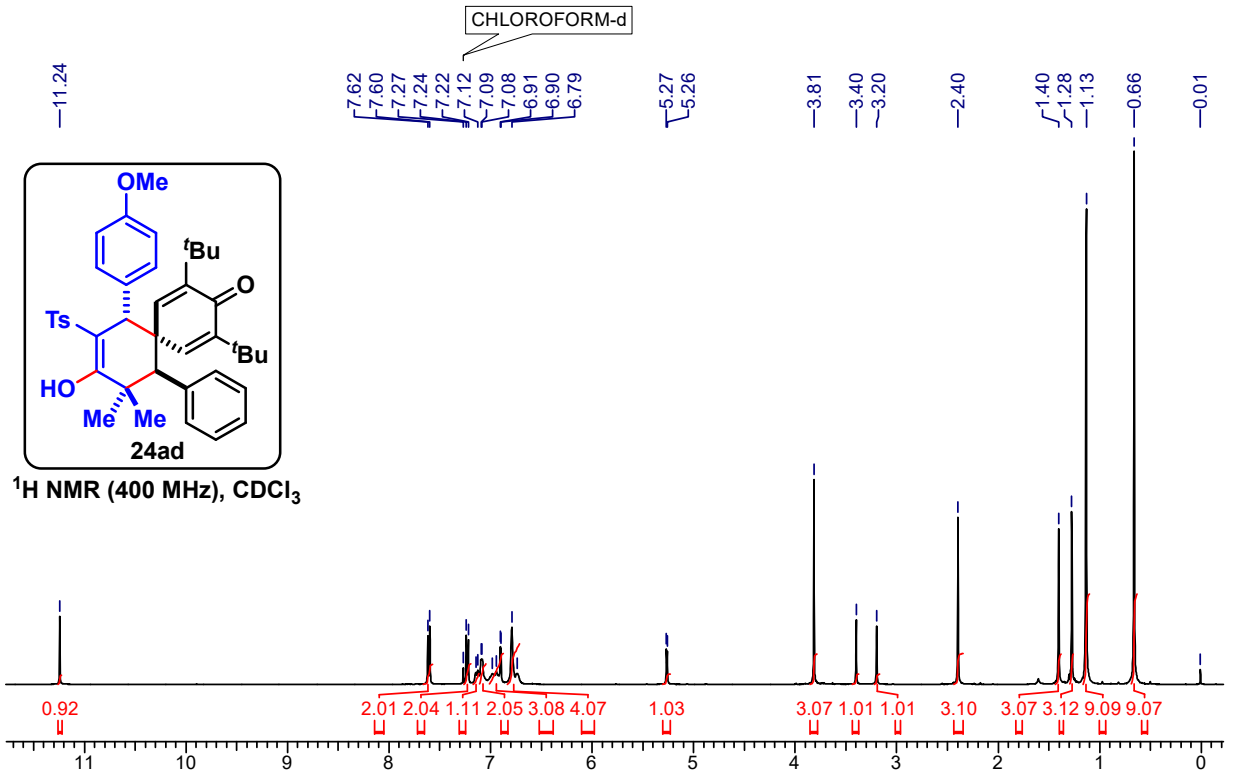
^{13}C NMR (100 MHz), $CDCl_3$



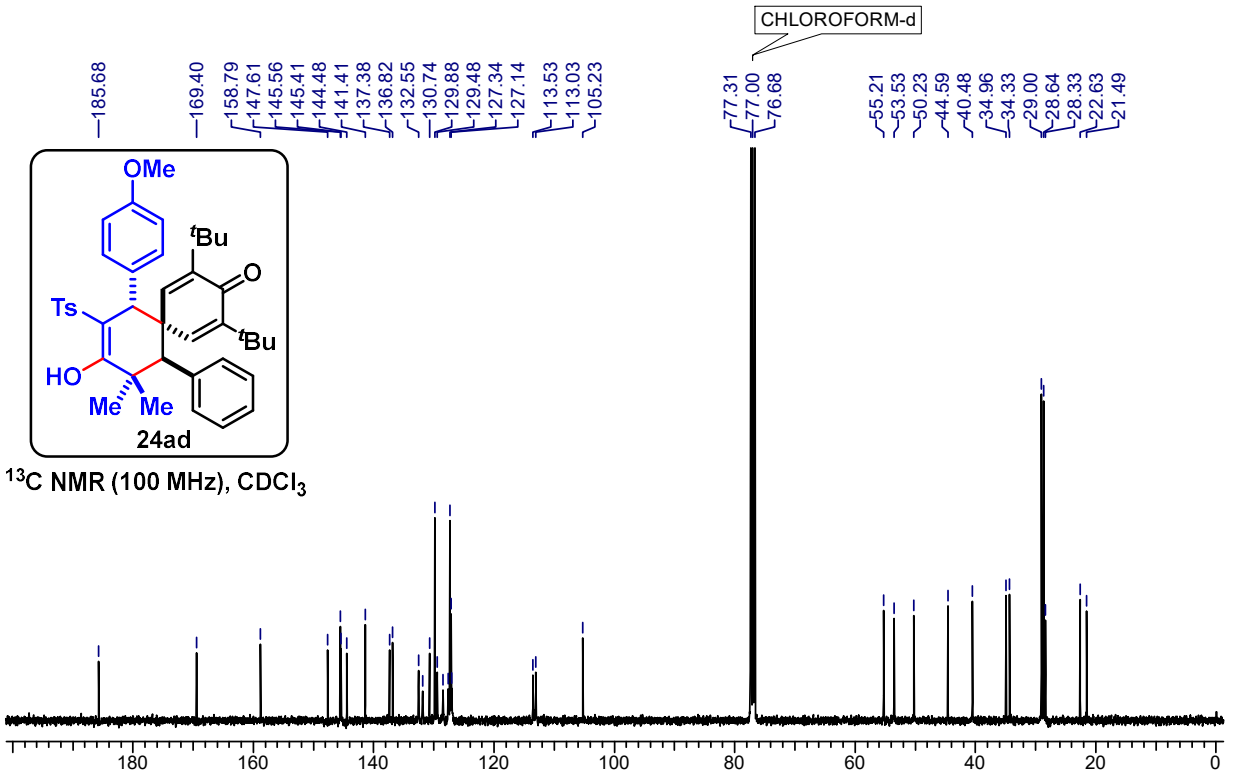
^{1}H NMR (400 MHz), $CDCl_3$



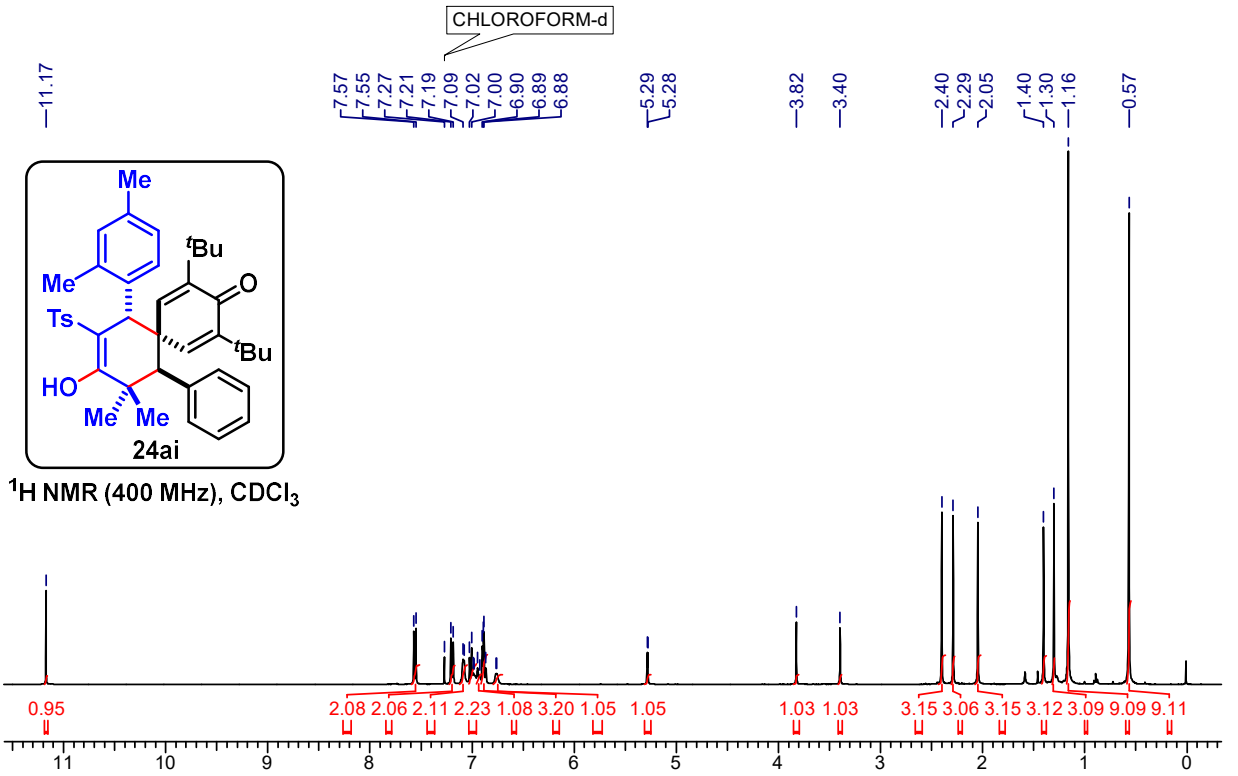
^{13}C NMR (100 MHz), $CDCl_3$



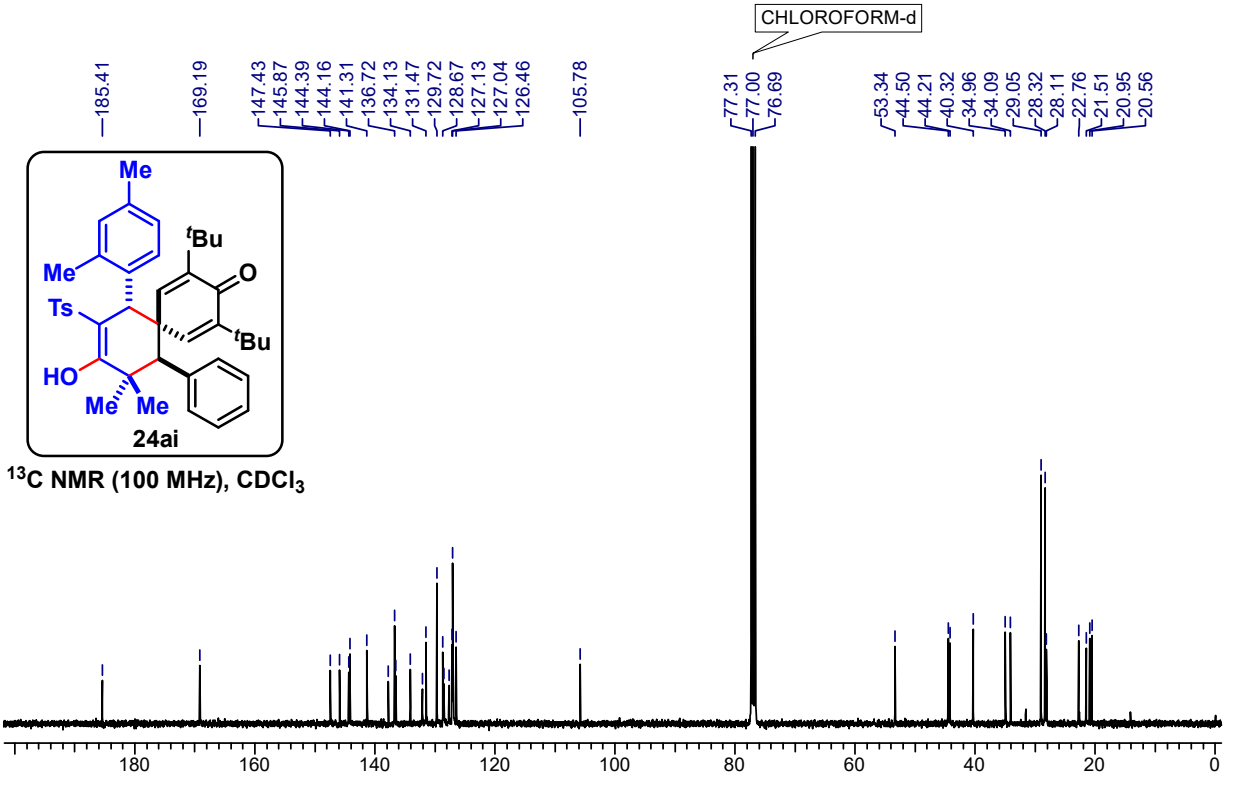
^{1}H NMR (400 MHz), $CDCl_3$



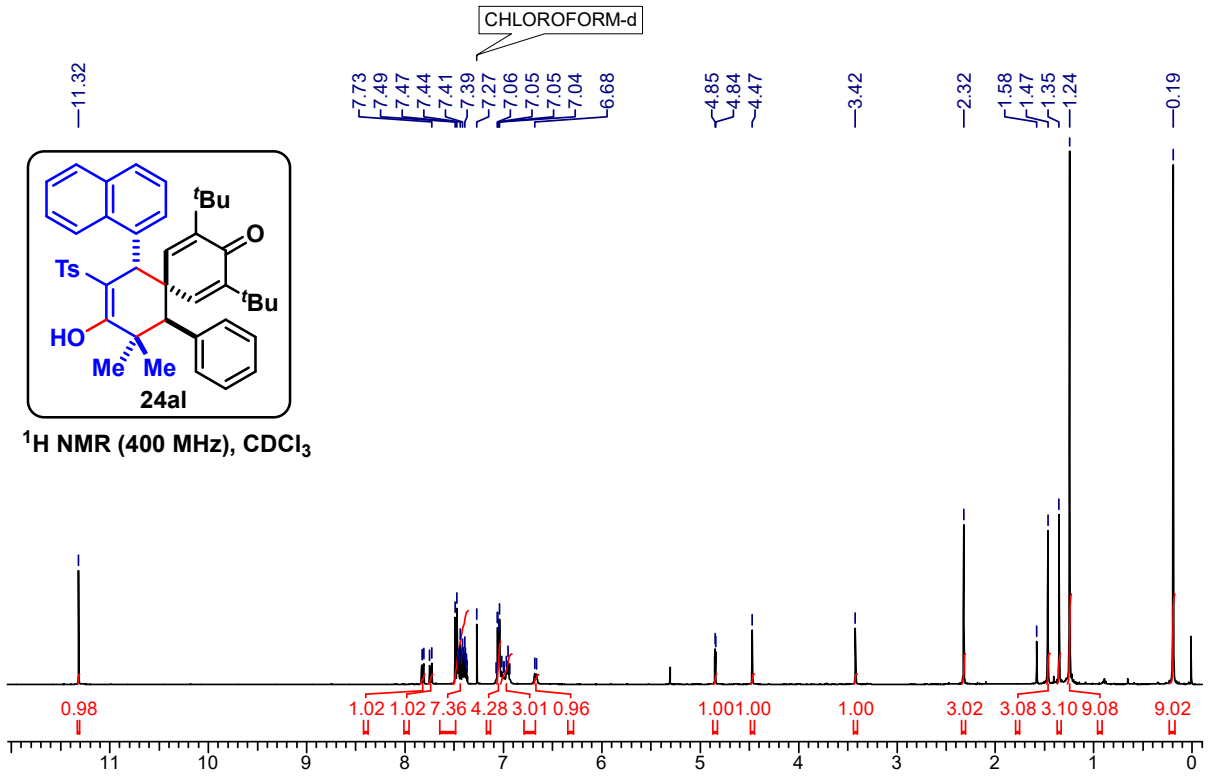
^{13}C NMR (100 MHz), $CDCl_3$



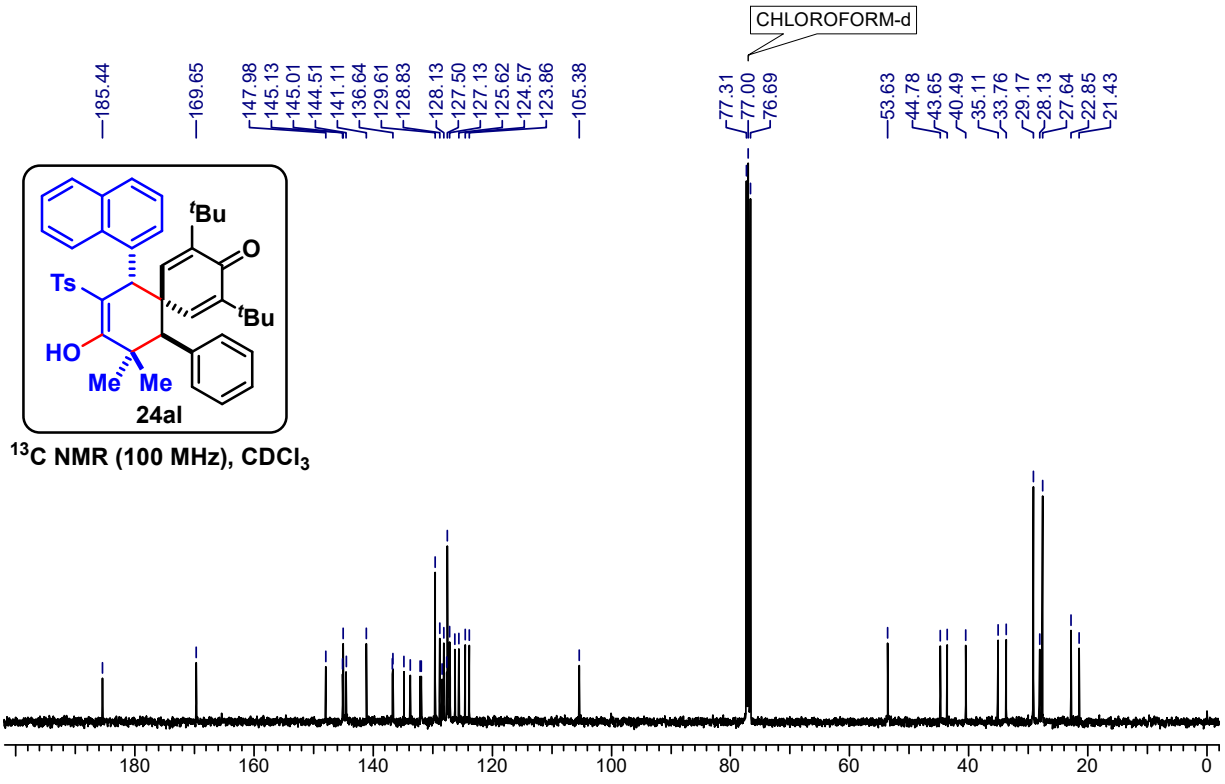
^{1}H NMR (400 MHz), $CDCl_3$



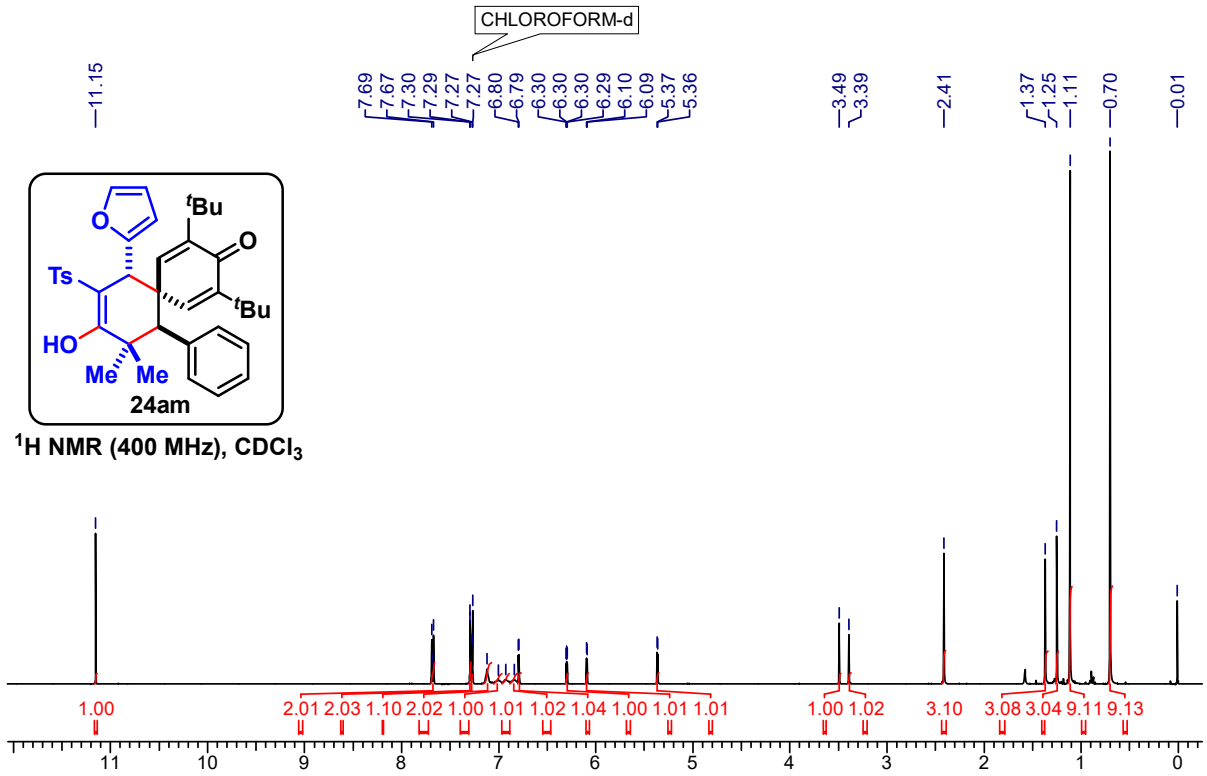
^{13}C NMR (100 MHz), $CDCl_3$



^{1}H NMR (400 MHz), $CDCl_3$



^{13}C NMR (100 MHz), $CDCl_3$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7.67
7.30
7.29
7.27
7.27
6.80
6.79
6.30
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6.30
6.29
6.10
6.09
5.37
5.36
3.49
3.39
2.41
1.37
1.25
1.11
0.70
0.01
tBu
O
Ts
tBu
HO
Me
Me
24am
1H NMR (400 MHz), CDCl3
1.00
2.01 2.03 1.10 2.02 1.00 1.01 1.02 1.04 1.00 1.01 1.01
1.00 1.02
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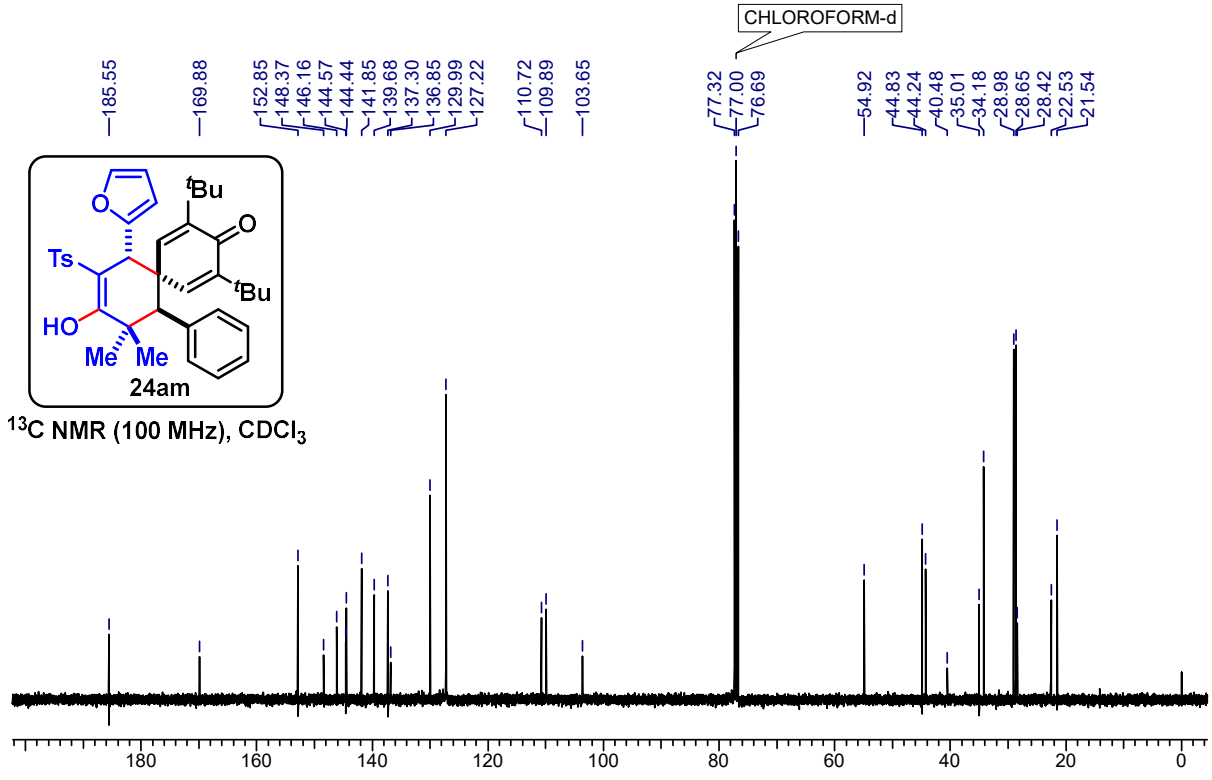
9
8
7
6
5
4
3
2
1
0


CHLOROFORM-d
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152.85
148.37
146.16
144.57
144.44
141.85
139.68
137.30
136.85
129.99
127.22
110.72
109.89
103.65
77.32
77.00
76.69
54.92
44.83
44.24
40.48
35.01
34.18
28.98
28.65
28.42
22.53
21.54
tBu
O
Ts
tBu
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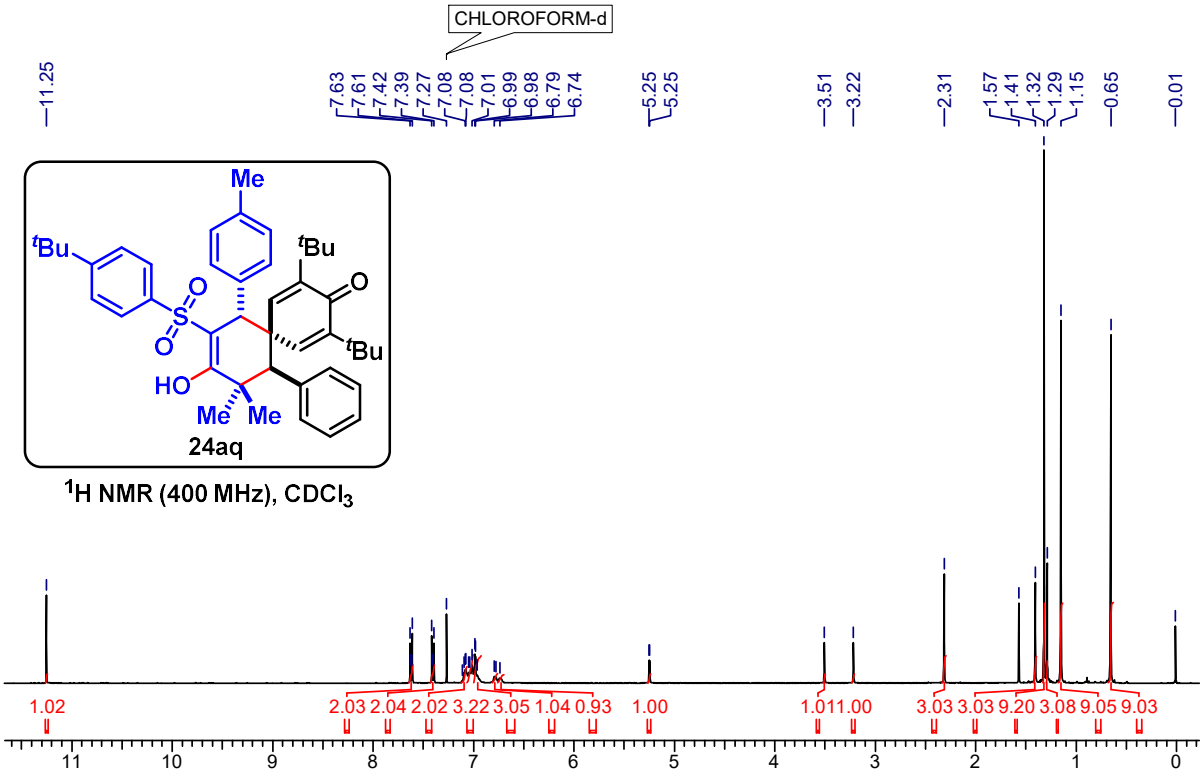
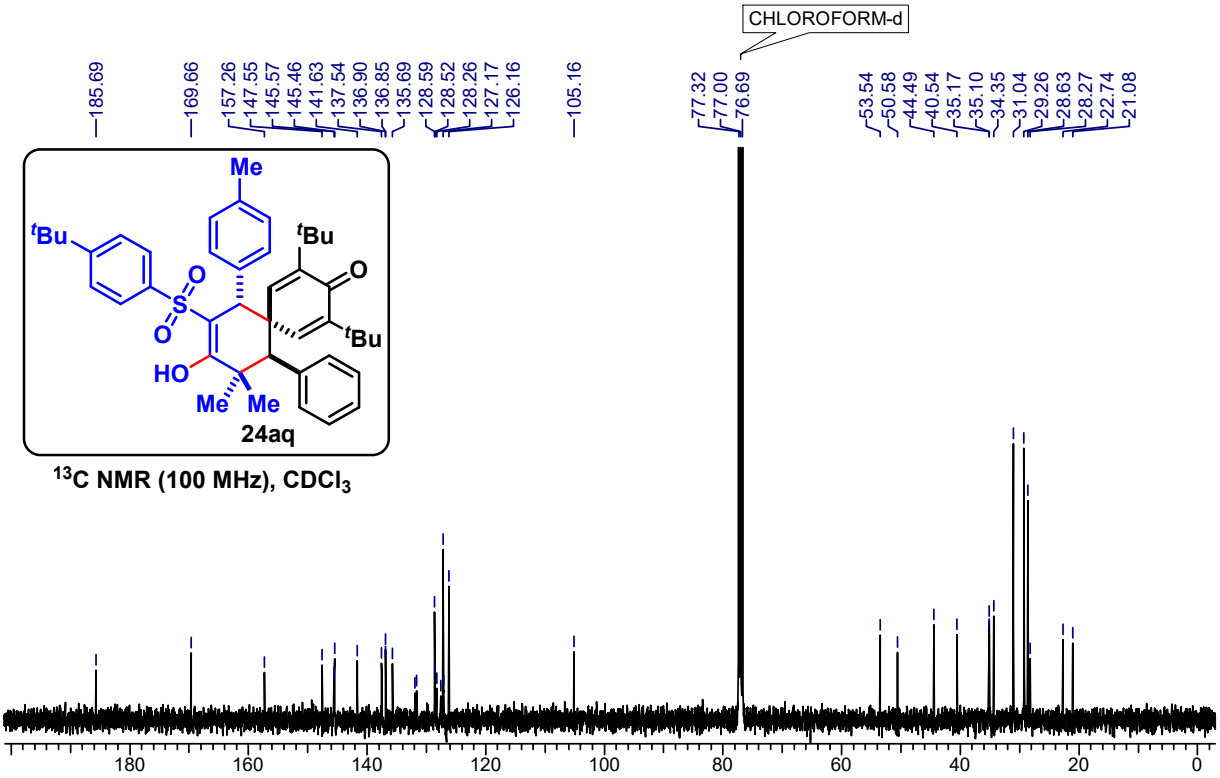
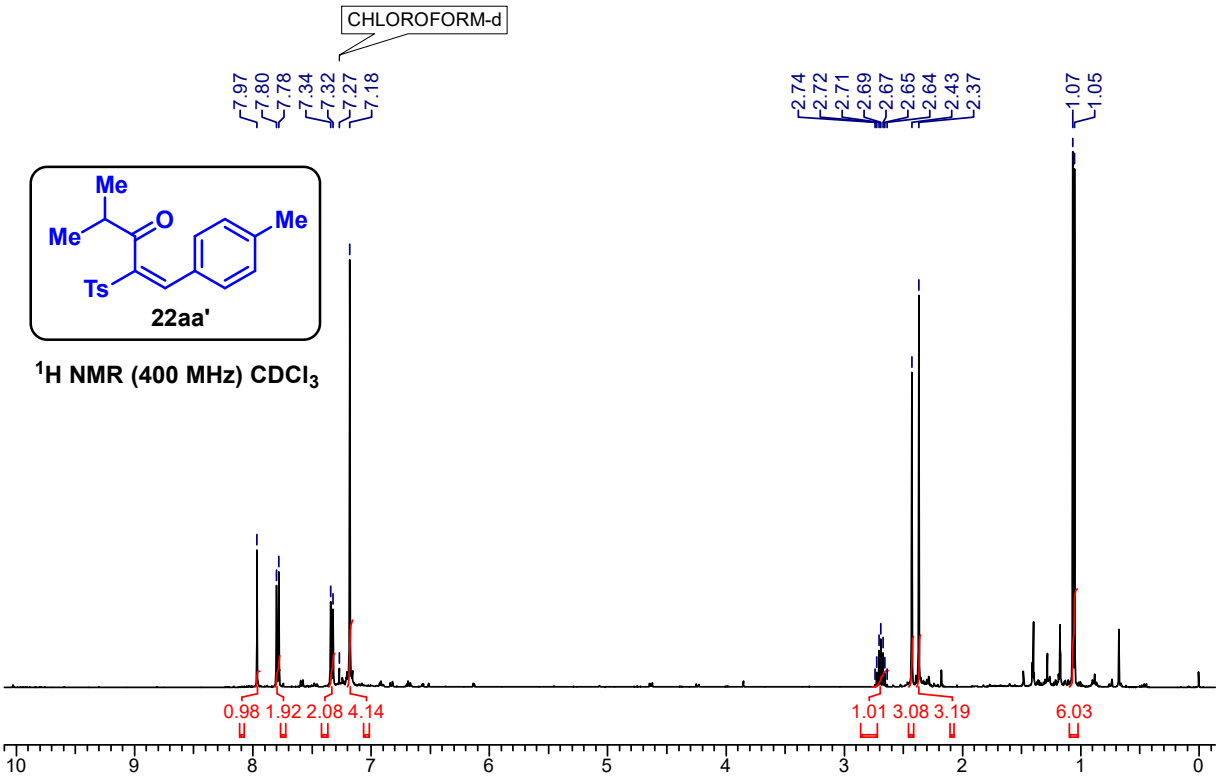
Me
Me
24am
13C NMR (100 MHz), CDCl3
180
160
140
120
100
80
60
40
20
0



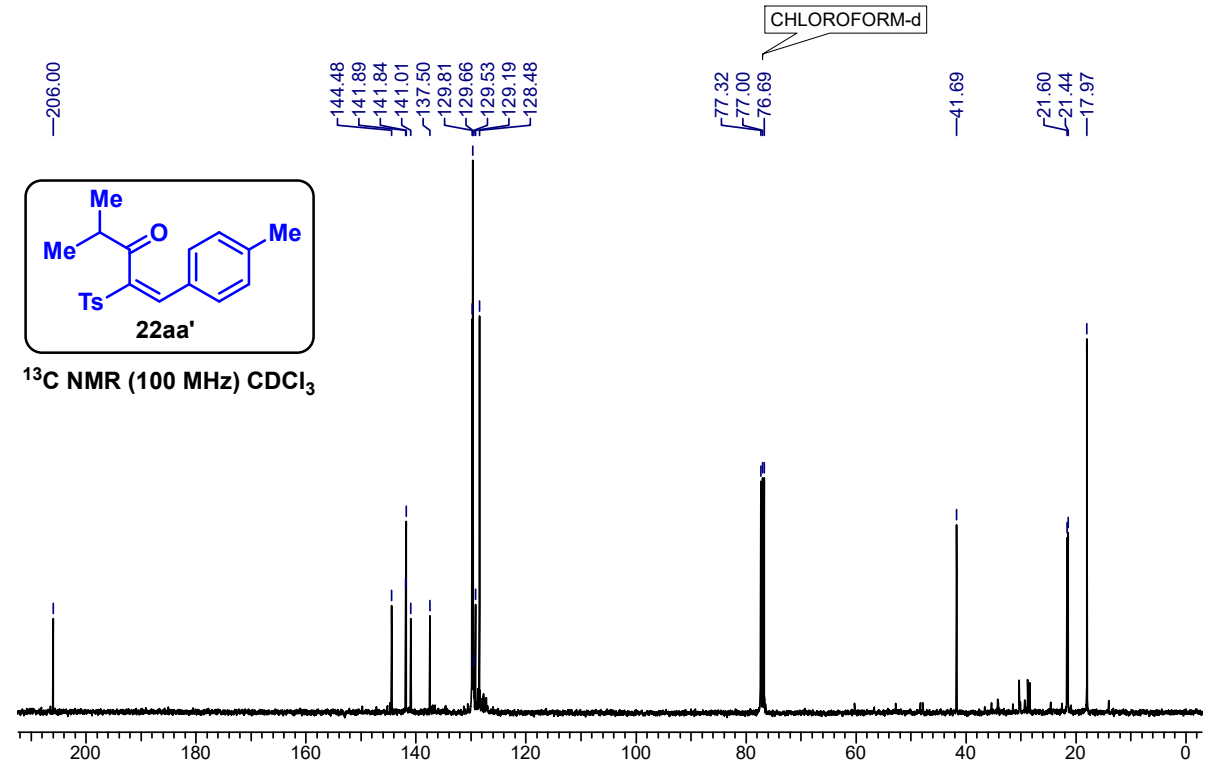
^{1}H NMR (400 MHz), $CDCl_3$



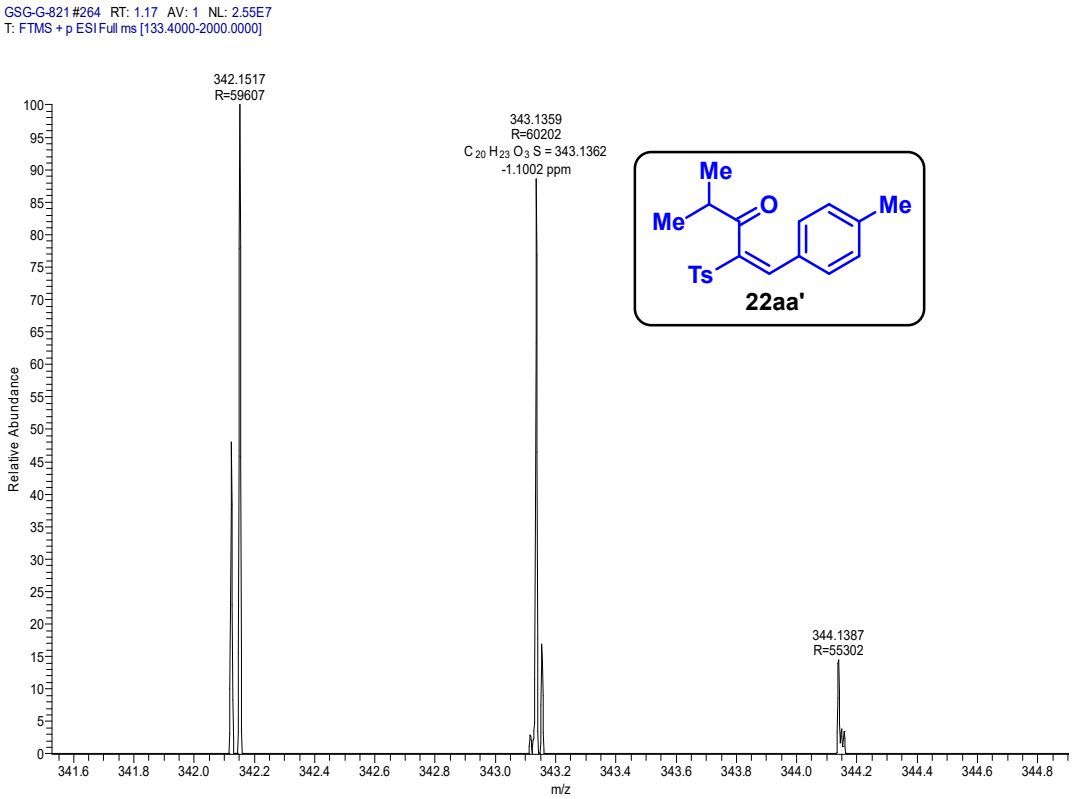
^{13}C NMR (100 MHz), $CDCl_3$

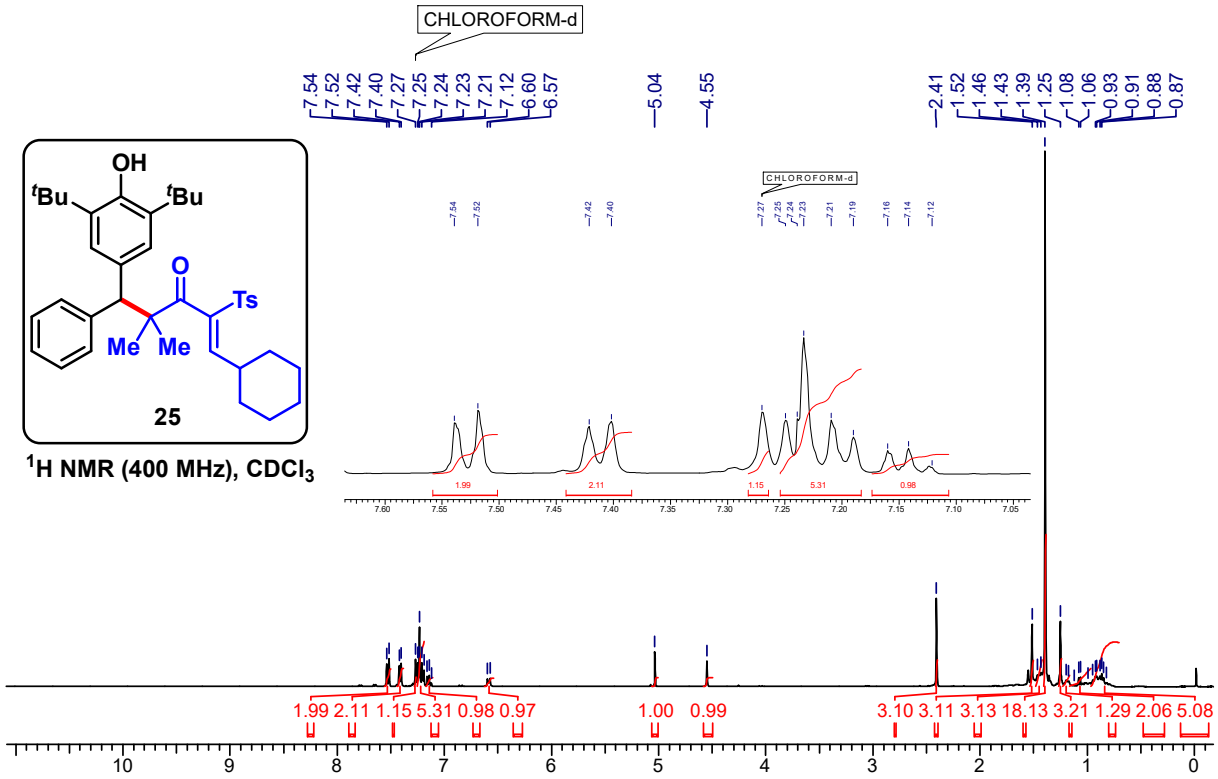


^{1}H NMR (400 MHz) $CDCl_3$



^{13}C NMR (100 MHz) $CDCl_3$


GSG-G-821 #264 RT: 1.17 AV: 1 NL: 2.55E7
T: FTMS + p ESI Full ms [133.4000-2000.0000]
342.1517
R=59607
343.1359
R=60202
C 20 H 23 O 3 S = 343.1362
-1.1002 ppm
344.1387
R=55302
Relative Abundance
m/z
Me
Me
O
Me
Ts
22aa'


CHLOROFORM-d
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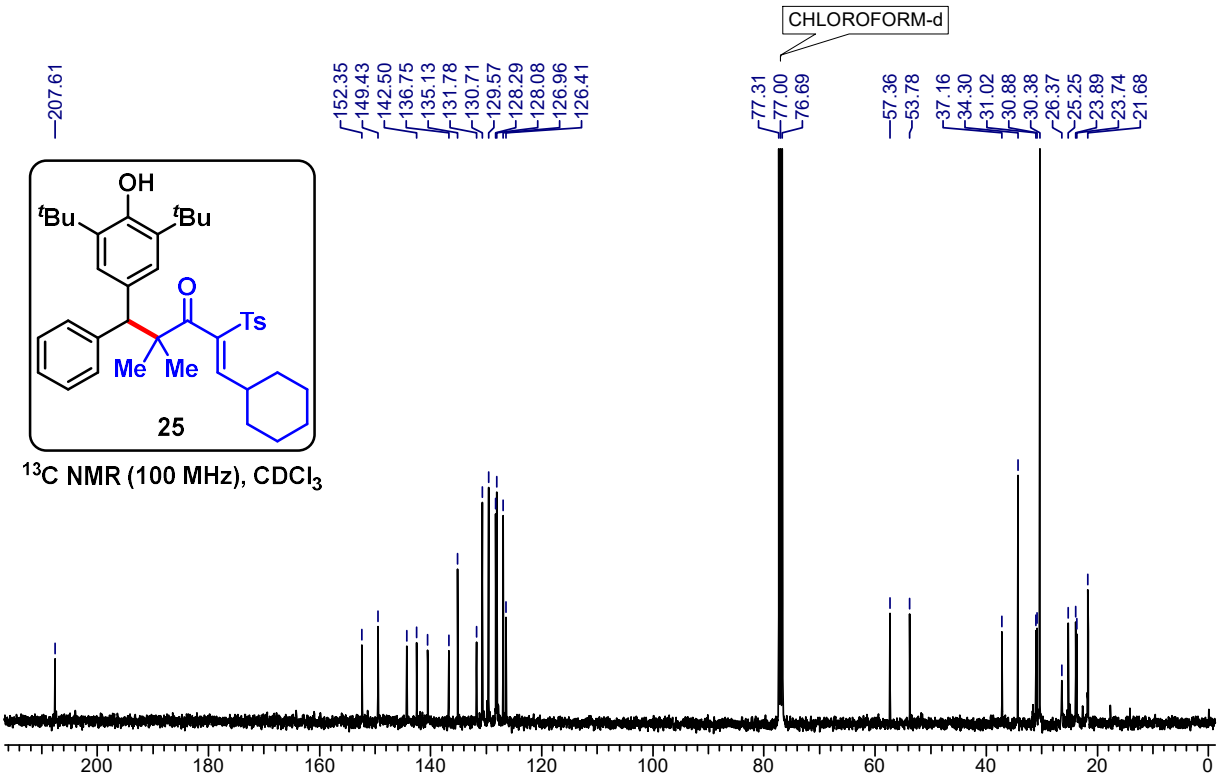
5.04
4.55
2.41 1.52 1.46 1.43 1.39 1.25 1.08 1.06 0.93 0.91 0.88 0.87
OH
tBu
tBu
O
Ts
Me Me
25
1H NMR (400 MHz), CDCl3
1.99 2.11 1.15 5.31 0.98 0.97
1.00 0.99
3.10 3.11 3.13 18.13 3.21 1.29 2.06 5.08



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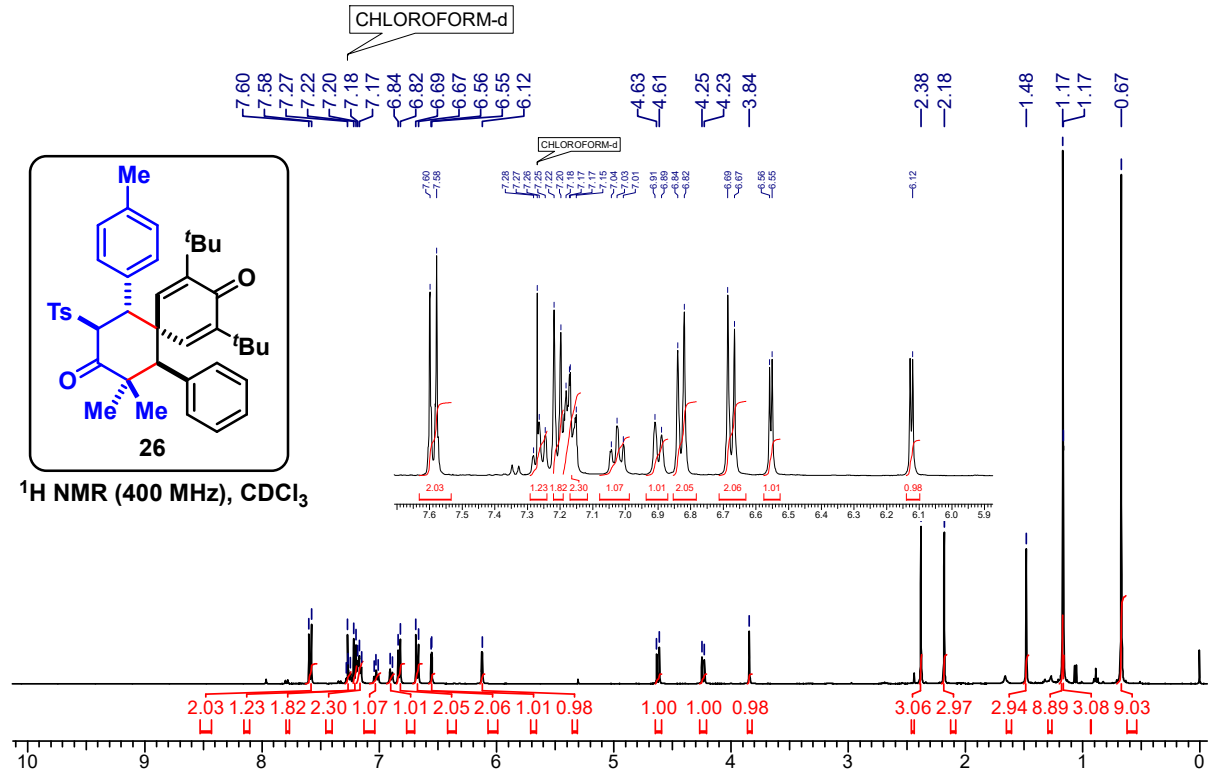

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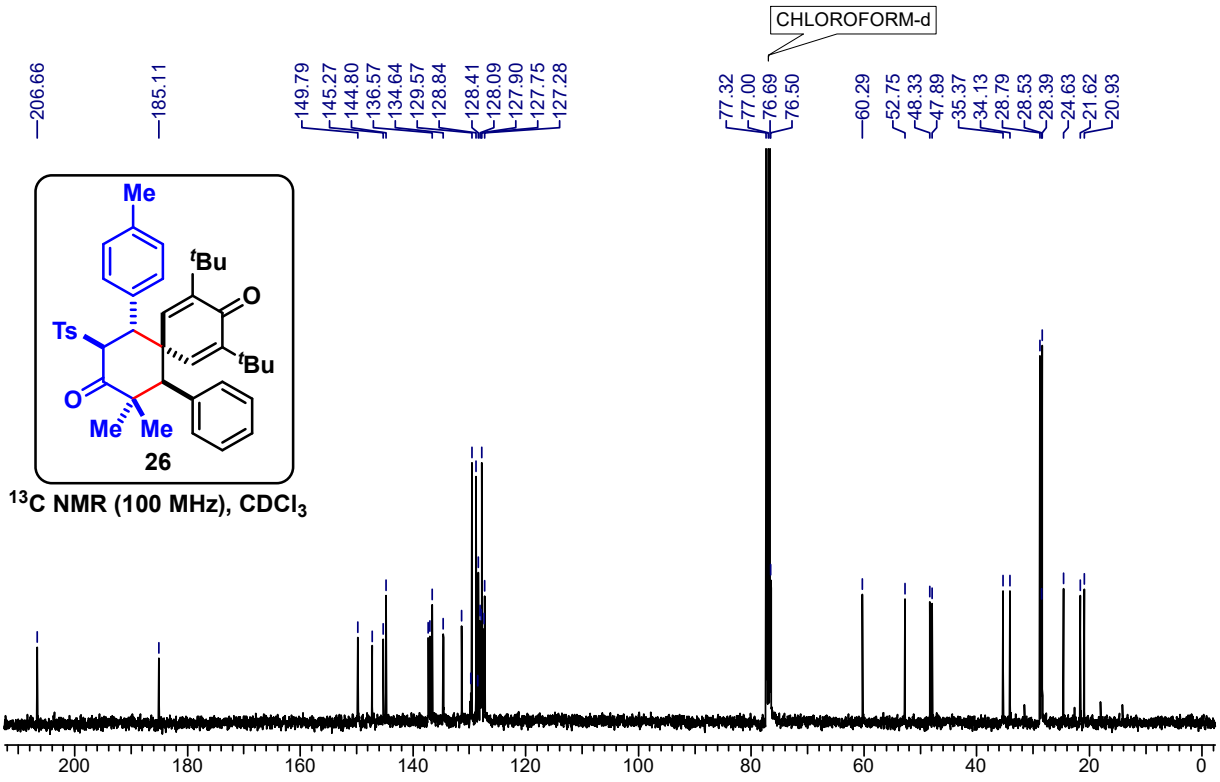

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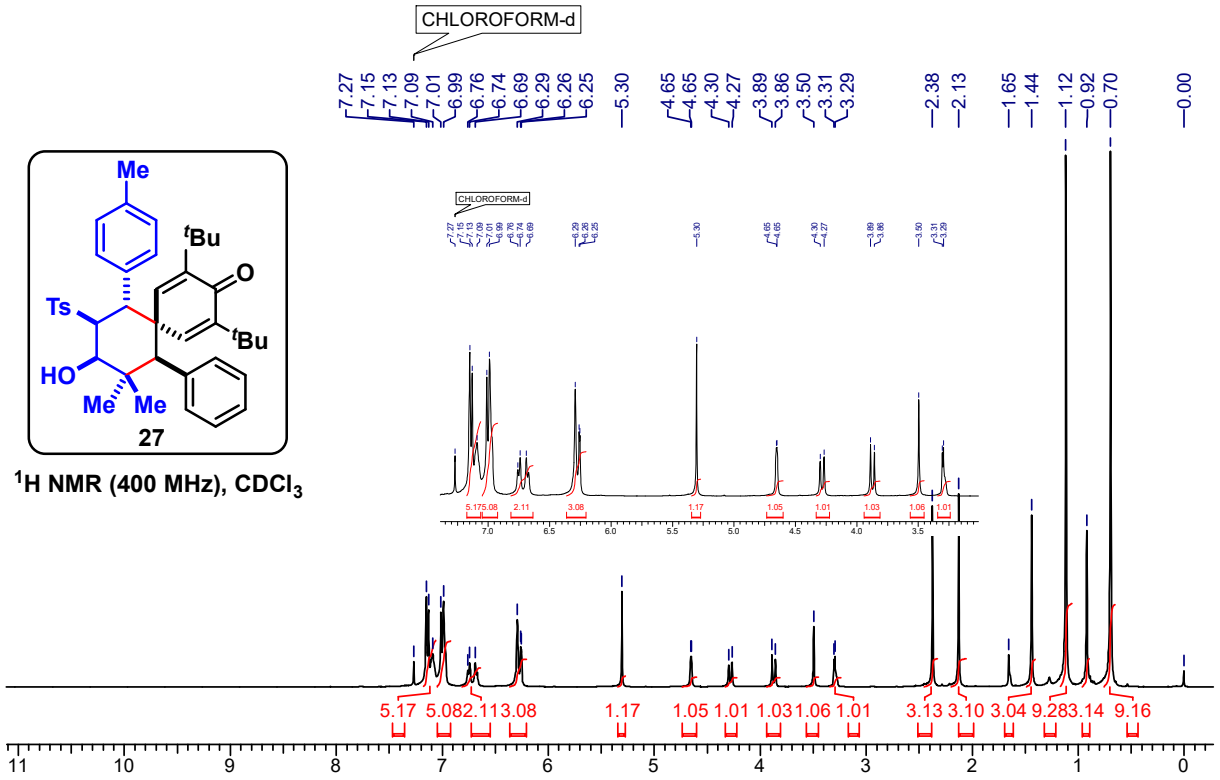

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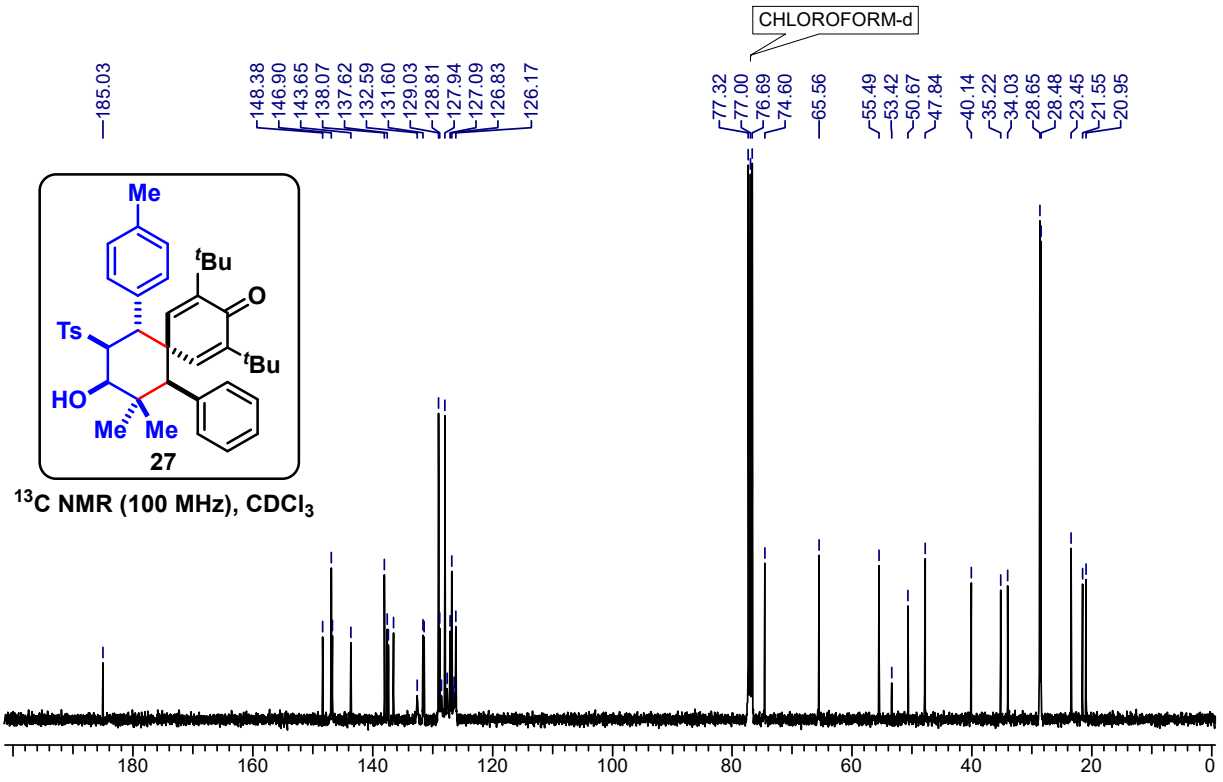

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ABSTRACT

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Faculty of Study: Chemical Science **Year of Submission:** 2022

AcSIR academic centre/CSIR Lab: **Name of the Supervisor:** Dr. M. Muthukrishnan

CSIR-National Chemical Laboratory, Pune.

Title of the thesis: Exploring New Synthetic Transformations Employing *p*-Quinone Methides as Versatile Acceptors in 1,6-Addition Reactions.

Quinone methides (QMs), particularly, *p*-quinone methides (*p*-QMs) are important structural moieties widely featured in many potential bioactive molecules. Due to their unique reactivity, they have been widely explored in many 1,6-addition or other reactions to generate diverse complex organic molecules. Despite the great progress achieved in this chemistry, still there is hope for new investigation on radical addition, dearomative spirocyclization and development of new transformations to access biologically relevant molecules. In the present thesis, we developed Lewis acid mediated 1,6-addition reaction, radical addition and 1,6-addition/annulation reaction with *p*-QMs for the synthesis of various biologically relevant and structurally diverse molecules.

Chapter 1 describes *p*-quinone methides (*p*-QMs): a versatile acceptor for the synthesis of structurally diverse molecules. This chapter includes two sections, **Section-I** describes an brief introduction to *p*-quinone methide chemistry and **Section-II** focus on the synthesis of diverse 3-diarylmethine substituted dihydropyrroles that comprises of silver-catalyzed cascade cyclization/1,6-conjugate addition of homopropargyl sulfonamides to *p*-quinone methides. **Chapter 2** covers, Lewis acid catalyzed 1,6-conjugate addition of isocyanides to *p*-quinone methides for accessing *α*-arylated nitriles and amides. This chapter includes two sections, **Section-I** deals with the synthesis of *α*-arylated nitriles *via* $BF_3 \cdot OEt_2$ catalyzed cyanation of *p*-QMs using *tert*-butyl isocyanide as a cyanide source. **Section-II** of this chapter describes the synthesis of *α*-arylated acetamides that comprise aminocarbonylation of *p*-quinone methides with isocyanides under metal free condition. C**hapter-3,** deals with the synthesis of *γ*, *γ*-diaryl ketones through iron mediated tandem ring opening/1,6-conjugate addition of cyclopropanols with *p*-quinone methides. **Chapter 4**, describes the synthesis of carbocyclic spiro[5.5]undeca-1,4-dien-3-one scaffolds *via* 1,6-conjugate addition initiated formal [4+2] annulation of *p*- quinone methides with sulfonyl allenols.

List of Publications Emanating from the Thesis work

1. **Shirsath, S. R.**; Shinde, G. H.; Shaikh, A. C.; Muthukrishnan, M. Accessing *α*-Arylated Nitriles via $BF_3 \cdot OEt_2$ Catalyzed Cyanation of *para*-Quinone Methides Using *tert*-Butyl Isocyanide as a Cyanide Source. *J. Org. Chem.* **2018**, *83*, 12305-12314.
2. Ghotekar, G. S.; **Shirsath, S. R.**; Shaikh, A. C.; Muthukrishnan, M. 1, 6-Conjugate Addition Initiated Formal [4+ 2] Annulation of *p*-Quinone Methides with Sulfonyl Allenols: A Unique Access to Spiro [5.5] undeca-1, 4-dien-3-one Scaffolds. *Chem. Commun.* **2020,** *56*, 5022-5025.
3. **Shirsath, S. R.**; Ghotekar, G. S.; Bahadur, V.; Gonnade, R. G.; Muthukrishnan, M. Silver-Catalyzed Cascade Cyclization/1,6-Conjugate Addition of Homopropargyl Sulfonamides to *p*-Quinone Methides: An Approach to Diverse 3-Diarylmethine Substituted Dihydropyrroles. *J. Org. Chem.,* **2020,** *85*, 15038-15050.
4. **Shirsath, S. R**.; Chandgude. S. M., Muthukrishnan, M. Iron Catalyzed Tandem Ring Opening/1,6-Conjugate Addition of Cyclopropanols with *p*-Quinone Methides: New Access to *γ*, *γ*-Diaryl Ketones. *Chem. Commun.* **2021,** *57*, 13582–13585.
5. **Shirsath, S. R**.; More, D. A.; Muthukrishnan, M. Metal-Free Aminocarbonylation of *p*-Quinone Methides with Isocyanides: Synthesis of Sterically Hindered *α*-Arylated Acetamides. *Chem. Asian J.* **2022**, *17*, e202200642 (https://doi.org/10.1002/asia.202200642).

List of Publications Non-Emanating from the Thesis Work

1. More, D. A.; **Shirsath, S. R**.; Muthukrishnan, M. Visible Light-Promoted C−H aminoalkylation of Quinoxalin-2(1H)-ones with Alkyl Anilines *via* Electron Donor-Acceptor Complexes (*Manuscript under Preparation*).
2. Shinde, R. A.; **Shirsath, S. R**.; Muthukrishnan, M. Iron Mediated Oxidative Ring Opening-Homocoupling of Cyclopropanols: Facile Access to 1,6-Diketones (*Manuscript under Preparation*).
3. Vara. V.; **Shirsath, S. R**.; Ghotekar, G. S.; Muthukrishnan, M. Synthesis of *β,β*-Diarylated Isoxazoline Derivatives via Mn(III)-Catalyzed Cascade Cyclization of *β*, *γ* – Unsaturated Oximes/1,6-Addition with *p*-Quinone Methides (*Manuscript under Preparation*).

4. Shinde, R. A.; **Shirsath, S. R**.; Muthukrishnan, M. Synthesis of Coumarin Derivatives *via* Silver Mediated Radical Cyclization of Alkynoates with Cyclopropanols (*Manuscript under Preparation*).
5. More, D. A.; **Shirsath, S. R**.; Vinoth, M. K.; Muthukrishnan. M. Bronsted Acid-Catalyzed Metal-Free Synthesis of Substituted Quinoline-Fused Lactones and Lactams from *N*-Aryl Glycine Derivatives (*Manuscript under Preparation*).

Patents- Nil

List of Posters Presented with Details

1. National Science Day Poster Session at CSIR-National Chemical Laboratory, Pune (February 25-27, **2019**)

Title: Accessing *α*-arylated Nitriles *via* $BF_3.OEt_2$ Catalyzed Cyanation of *para*-Quinone Methides using *tert*-Butyl Isocyanide as a Cyanide Source**.**

Abstract: $BF_3.OEt_2$ catalyzed 1,6-conjugate addition of *tert*-butyl isocyanide to *para*-quinone methides and fuchsones for the synthesis of *α*-diaryl- and *α*-triaryl nitriles has been developed. This protocol allows to access *α*-diaryl- and *α*-triaryl nitriles in good to excellent yields and with a broad substrate scope, which could be further functionalized to give a versatile set of products. This is the first example wherein *tert*-butyl isocyanide has been used as a cyanide source for 1,6-conjugate addition.

2. National Science Day Poster Session at CSIR-National Chemical Laboratory, Pune (February 25-27, **2020**) (***Received Best Poster Award***)

and

First Virtual JNOST Conference organized by IISC-Bangalore on 31st Oct-1st Nov 2020.

Title: 1,6-Conjugate Addition Initiated Formal [4+2] Annulation of *p*-Quinone Methides with Sulfonyl allenols: An Expedient Access to Spi-ro[5.5]undeca-1,4-dien-3-one Scaffolds

Abstract: An expedient one pot synthesis of carbocyclic spiro[5.5]undeca-1,4-dien-3-ones *via* 1,6-conjugate addition initiated formal [4+2] annulation sequences employing *p*-quinone methides and sulfonyl allenols, is presented. Further, this synthetic protocol tolerates a wide variety of *p*-quinone methides and sulfonyl allenols and affords the corresponding structurally unique spiro[5.5]undeca-1,4-dien-3-ones in good to excellent yields under mild reaction condition.

3. National Science Day Poster Session at CSIR-National Chemical Laboratory, Pune (February 25-27, **2021**)

Title: Silver-Catalyzed Cascade Cyclization/1,6-Conjugate Addition of Homopropargyl Sulfonamides to *p*-Quinone Methides: An Approach to Diverse 3-Diarylmethine Substituted Dihydropyrroles

Abstract: A silver-catalyzed cycloisomerization/1,6-conjugate addition of homopropargyl sulfonamides to *p*-quinone methides to access diverse diarylmethine substituted dihydropyrroles has been disclosed. The reaction pathway involves an intramolecular cascade cyclization of homopropargyl sulfonamides to generate a highly reactive dihydropyrrole intermediate in situ followed by conjugate addition with *p*-quinone methides. This method provides an efficient and scalable route for the synthesis of 3- diarylmethine substituted dihydropyrroles, in one pot.

List of Conference Attended with Details

1. Nov 2019- NCL-Research Foundation Annual Students Conference-NCL Pune.
2. January 2020- Advances Organic Synthesis (AOS)- IISER/NCL Pune.
3. First Virtual JNOST Conference organized by IISC-Bangalore on 31st Oct-1st Nov 2020.

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Accessing α-Arylated Nitriles via BF_3·OEt_2 Catalyzed Cyanation of *para*-Quinone Methides Using *tert*-Butyl Isocyanide as a Cyanide Source

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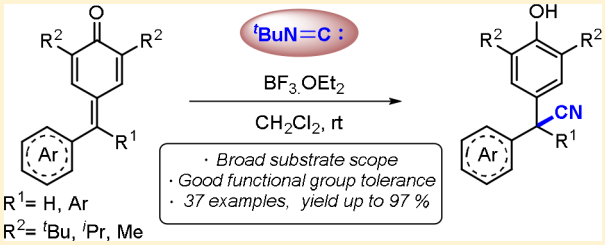
Supporting Information

ABSTRACT: BF_3·OEt_2 catalyzed 1,6-conjugate addition of *tert*-butyl isocyanide to *para*-quinone methides and fuchsones for the synthesis of α-diaryl and α-triaryl nitriles has been reported. This protocol allows α-diaryl- and α-triaryl nitriles to be accessed in good to excellent yields and with a broad substrate scope, which could be further functionalized to give a versatile set of products. This is the first example wherein *tert*-butyl isocyanide has been used as a cyanide source for the 1,6-conjugate addition.



The synthesis of nitrile-containing organic frameworks, in particular α-arylated nitrile compounds, is of great importance, as these structures exist in several natural products, a vast range of functional molecules relevant to pharmaceuticals, agrochemicals, and functional materials (Figure 1).[1] For instance, more than 30 nitrile-containing

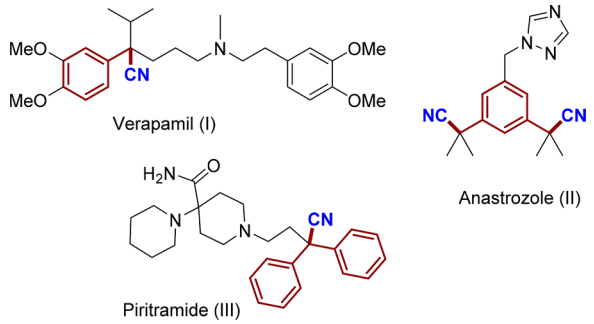


Figure 1. Representative biologically important α-arylated nitriles.

drugs have been approved for the treatment of depression, breast cancer, and Parkinson's disease, while 20 more are in clinical trials.[2] On the other hand, they are valuable precursors in organic synthesis for the preparation of carboxylic acids, amides, aldehydes, ketones, amidines, amines, *N*-containing heterocycles, etc.[3] or as directing groups for remote C−H activation through weak coordination.[4] Consequently, several synthetic approaches toward the synthesis of α-arylated nitriles have been explored and that mainly involves nucleophilic substitution of a benzylic halide,[5] dehydration of aldoximes/amides,[6] addition of cyanide to diarylcarbinols,[7] coupling reactions of nitriles with aryl halides,[8] and others.[9] However, most of these methods suffer from drawbacks such as harsh reaction conditions, expensive catalysts, usage of notorious toxic cyanide sources, etc. Therefore, the development of a robust strategy for the synthesis of diverse functional-group-rich α-aryl nitriles is highly desirable.

In recent years, the *p*-quinone methides (*p*-QMs) have attracted a great deal of attention among the synthetic community due to its unique reactivity and its ability to make complex architectures that are found in several pharmaceuticals and natural products.[10] The *p*-QMs have the ability to undergo several reaction modes that involve mainly 1,6-conjugate additions,[11] [4 + 2]-annulations,[12] [3 + 2]-annulations,[13] and [2 + 1]-annulations.[14] Very recently, *p*-QMs have been successfully utilized for the synthesis of α-diaryl and α-triaryl nitriles wherein the reaction relied upon the usage of TMSCN as a cyanide source and the NHC-catalyst for the activation of TMSCN.[15] As part of our continuing interest in the synthesis of natural products like small molecules for various biological applications,[16] we encountered a need for an efficient methodology for the synthesis of α-arylated nitriles. With regard to practicality, we chose to explore *tert*-butyl isocyanide as an alternate cyanide source, avoiding the use of toxic cyanides for the 1,6-conjugate addition reaction of *p*-QM.[17] Importantly, in recent years *tert*-butyl isocyanide has been efficiently utilized as an alternative "CN" source.[18] Hence, in the present manuscript we describe the amenability of *tert*-butyl isocyanide as a source of cyanide for the successful preparation of α-diaryl and α-triaryl nitriles from *p*-QMs. To the best of our knowledge, this is the first example where *tert*-butyl isocyanide has been used as a cyanide source for the 1,6-conjugate addition.

We began our optimization studies with *p*-quinone methide **1a**, which contains removable *t*-Bu groups at the ortho

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1,6-Conjugate addition initiated formal [4+2] annulation of *p*-quinone methides with sulfonyl allenols: a unique access to spiro[5.5]undeca-1,4-dien-3-one scaffolds†

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An expedient one-pot synthesis of carbocyclic spiro[5.5]undeca-1,4-dien-3-ones *via* 1,6-conjugate addition initiated formal [4+2] annulation sequences by employing *p*-quinone methides and sulfonyl allenols is presented. Furthermore, this synthetic protocol tolerates a wide variety of *p*-quinone methides and sulfonyl allenols and affords the corresponding structurally unique spiro[5.5]undeca-1,4-dien-3-ones in good yield under mild reaction conditions.

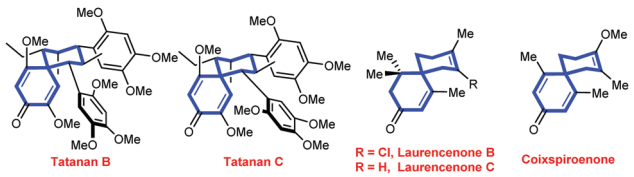

Fig. 1 Representative spiro[5.5]undeca-1,4-dien-3-one based natural products.

The ubiquity of the spirocyclohexadienone framework in a plethora of natural products and pharmaceuticals demands the efficient construction of this core which is of significant interest.[1,2] Spiro[5.5]undeca-1,4-dien-3-ones, an important subclass of spirocyclohexadienones, are regarded as privileged structural scaffolds that are abundantly present in natural products such as tatanan B–C, laurencenone B–C and other similar bioactive molecules (Fig. 1).[3,4] Indeed, these scaffolds exhibit various biological activities, such as anti-biofouling activity, antiproliferative activity, cytotoxicity against HeLa and Hep-2 human carcinoma cell lines and antifungal activities.[4] Besides, they are useful intermediates in the synthesis of several natural products.[4b] Several strategies exist in the literature for the efficient construction of spirocyclohexadienone core; however, methods available for the preparation of the spiro[5.5]undeca-1,4-dien-3-one core remain elusive.[5] Therefore, the development of a new streamlined strategy to access this class of structurally interesting and synthetically challenging spirocycles is highly desirable. In recent years, *p*-quinone methides (*p*-QMs) have been extensively explored as Michael acceptors to undergo 1,6-conjugate addition reactions with a variety of nucleophiles to generate complex molecular architecture.[6,7] Particularly, intermolecular [2+*n*] cycloaddition reactions for the synthesis of spirocarbocycles by employing *p*-QMs as synthons have made significant progress.[8–11] For example, α-bromo malonates, sulfonium salts, sulfur ylides and ammonium ylides are successfully employed in the [2+1] annulation reaction with *p*-QMs to achieve spiro[2.5]octa-4,7-dien-6-ones.[8] Furthermore, spiro[4.5]deca-6,9-dien-8-ones have been effectively synthesized using Pd- and Ag-catalyzed [3+2] annulation of *p*-QMs with vinylcyclopropanes and propargylmalonates, respectively.[9] 1,6-Addition/VCP rearrangement reactions of vinyl *p*-quinone methides (*p*-VQMs) with bromomalonates or sulfur ylides have also been discovered to achieve spiro[4.5]deca-6,9-dien-8-ones.[10] Recently, the cascade radical iodoazidation of *p*-QMs emerged as an alternate way to construct spiro[4.5]deca-6,9-dien-8-ones *via* the 1,6-addition/cyclization strategy.[11] However, to the best of our knowledge, there is no report on the construction of carbocyclic spiro[5.5]undeca-7,10-dien-9-ones by employing *p*-QMs.

In the last decade, allene derivatives have received considerable attention mainly due to their unique reactivity along with their ability to form important molecules with diverse functionalities.[12] Among these, sulfonyl allenols are special ones as the presence of electron-withdrawing sulfone moiety adjacent to the π-system helps to control their chemistry; however, their potential synthetic utility remains underexplored.[13] Transition metal catalyzed, especially palladium mediated, reactions of allene derivatives are quite intriguing and possess wide synthetic utility.[14] Significant contributions from the group of Ma[15] and Harmata[13] have led to many pioneering advances in this area. As part of our ongoing interest across the reactivity of *p*-QMs,[16] herein we describe an unprecedented 1,6-conjugate addition initiated formal [4+2] annulation reaction between sulfonyl allenols and *p*-QMs to access carbocyclic spiro[5.5]-undeca-1,4-dien-3-one derivatives in one-pot (Scheme 1).

The present study was initiated by treating *p*-QM **1a** with sulfonyl allenol **2a** in the presence of $Pd(PPh_3)_4$ (5 mol%) using

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Silver-Catalyzed Cascade Cyclization/1,6-Conjugate Addition of Homopropargyl Sulfonamides to *p*-Quinone Methides: An Approach to Diverse 3-Diarylmethine Substituted Dihydropyrroles

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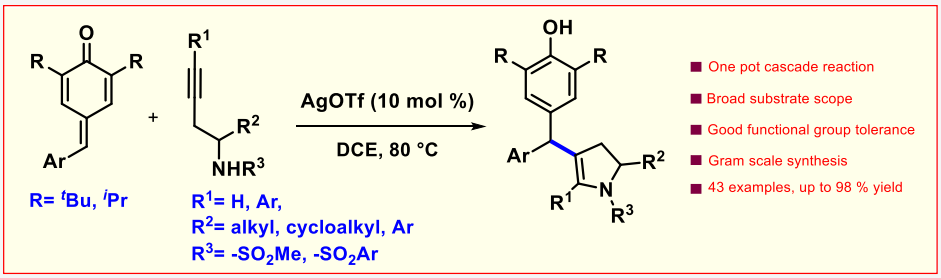

ABSTRACT: A silver-catalyzed cycloisomerization/1,6-conjugate addition of homopropargyl sulfonamides to *p*-quinone methides to access diverse diarylmethine substituted dihydropyrroles has been disclosed. The reaction pathway involves an intramolecular cascade cyclization of homopropargyl sulfonamides to generate a highly reactive dihydropyrrole intermediate in situ followed by conjugate addition with *p*-quinone methides. This method provides an efficient and scalable route for the synthesis of 3-diarylmethine substituted dihydropyrroles, in one pot.

INTRODUCTION

Substituted dihydropyrroles are an important framework present in a plethora of natural products and pharmaceutical agents, and further they serve as versatile building blocks in the synthesis of complex organic molecules.[1,2] Of particular importance are the diarylmethine substituted dihydropyrroles that are present in several bioactive agents used to treat several disorders such as overactive bladder (Darifenacin), epilepsy, inflammation, etc. (Figure 1).[3] Therefore, the development of a rapid, catalytic, and one-pot strategy to access these kinds of pyrrole derivatives is of high value. In recent years, the metal-catalyzed electrophilic cyclization of heteroatomic nucleophiles with alkynes has emerged as a general and efficient protocol for the construction of a wide variety of heterocycles. Notably, for the construction of substituted dihydropyrroles, catalytic cascade cyclization of alkynamine followed by trapping with suitable electrophiles would be an ideal and extremely useful strategy.[4−7] For example, Feng,[7a] Rodriguez,[7b,c] Xu,[7d] and co-workers elegantly developed a dual catalytic approach for cascade cyclization/inverse-electron-demand hetero-Diels−Alder reactions for the synthesis of structurally complex polyheterocyclic products. Anand[7e] and Chang's group[7f] reported a metal-catalyzed protocol to construct unsymmetrical diarylindolylmethanes through a domino electrophilic cyclization-extended conjugate addition approach. Very recently, Shi[7g] and Xu[7h] disclosed gold catalyzed oxa-[4 + 2] cyclizations of quinone methides with alkynyl benzyl alcohols for the construction of fused and spiroacetal skeletons. Despite the merit of these elegant approaches, still most of the methods require a dual catalytic system for substrate activation, prolonged reaction duration, and limited substrate scope.

In recent years, the chemistry of *p*-quinone methides (p-QMs) has been well recognized and widely used in organic synthesis due to their unique 1,6-reactivity toward a variety of nucleophiles.[8−10] In view of our interest in the chemistry of *p*-QMs,[11] we envisioned that intramolecular cyclization of an appropriately substituted homopropargylic amine activated by suitable π-acid would generate reactive dihydropyrrole intermediates in situ. Subsequently, conjugate addition of this dihydropyrrole intermediate from the β-position to *p*-QM could result in a straightforward access to diarylmethine substituted dihydropyrroles, in one pot. We herein disclose the successful realization of this strategy, and to the best of our knowledge, Lewis acid catalyzed cycloisomerization/1,6-conjugate addition of homopropargyl sulfonamides to *p*-quinone methides to access diarylmethine substituted dihydropyrroles has not yet been reported.

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Iron catalyzed tandem ring opening/1,6-conjugate addition of cyclopropanols with *p*-quinone methides: new access to γ,γ-diaryl ketones†

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An iron(III) catalyzed tandem ring opening/1,6-conjugate addition of cyclopropanols to *p*-quinone methides leading to γ,γ-diaryl ketones has been described. This catalytic protocol provides a novel and efficient method to access γ,γ-diaryl ketone derivatives in good to excellent yields with high functional group tolerance. Importantly, γ,γ-diaryl ketone can be further functionalized to give a versatile set of useful products.

γ,γ-Diarylketones and their derivatives are frequently encountered in numerous bioactive molecules and natural products.[1] Furthermore, compounds possessing the γ,γ-diaryl ketone motif are known integrin receptor inhibitors, and nitric oxide donors and serve as a precursor for the antidepressant drug Zoloft (Fig. 1).[2] Despite this significance, in contrast to their structural analogues such as α,α- and β,β-diaryl ketones that can be easily prepared through several methods, surprisingly synthetic strategies to access γ,γ-diaryl ketones are rare and considered challenging.[3d]

Intriguingly, a few new approaches to address their synthesis were reported recently. Dixneuf *et al.*[3a] disclosed a strategy to prepare γ,γ-diaryl ketones employing the silver catalyzed hydroarylation of β,γ-unsaturated allylic ketones prepared from terminal alkynes *via* ruthenium catalysis (Scheme 1a). May[3b] and Moran's group[3c] independently described a strategy of synthesising γ,γ-diaryl ketones *via* the Brønsted acid-catalyzed arylative ring opening of donor–acceptor cyclopropanes (Scheme 1b). In 2019 Shu *et al.*[3d] reported a photocatalytic γ-arylation of carbonyl compounds *via* the radical relay alkylarylation of α-bromocarbonyl precursors with boronic acids and alkenes to access γ,γ-diarylketones. Very recently, Giri *et al.*[3e] disclosed the synthesis of γ,γ-diarylcarbonyl derivatives employing the nickel catalyzed α-carbonylalkylarylation of vinylarenes with α-halocarbonylcompounds and arylzinc reagents (Scheme 1c).

Despite their merits, however, there are certain disadvantages associated with these methods such as the requirement for expensive and sensitive catalysts, harsh reaction conditions, and limited substrate scopes, *etc.* Therefore developing a simple and efficient strategy to access these γ,γ-diarylketones from easily accessible starting materials is ideal and highly desirable.

In recent years, the radical ring opening of strained cycloalkanols, especially cyclopropanols has been established as a versatile strategy in the synthesis of a wide range of highly functionalized organic compounds.[4–6] On the other hand, the rapid emergence of *p*-quinone methide (*p*-QMs) chemistry and their important utility as reactive electrophiles in 1,6-conjugate additions have been well harnessed in synthetic chemistry.[7] In contrast to the studies on the nucleophilic 1,6-addition of *p*-QMs, the quest for the radical addition of *p*-QMs remains scarce.[8] Furthermore, *p*-QMs have been efficiently utilized for the synthesis of α,α- and β,β-diaryl carbonyl derivaties.[9,10] However, to the best of our knowledge, reactions employing *p*-QMs that give direct access to γ,γ-diarylketones is not yet explored. With our ongoing interest in exploring *p*-QM chemistry for useful synthetic transformations,[11] we envisioned that the radical ring opening of cyclopropanols and the subsequent 1,6-conjugate addition with *p*-QMs would provide a new opportunity to access structurally important γ,γ-diarylketones. Herein, we describe a successful realization of this strategy;

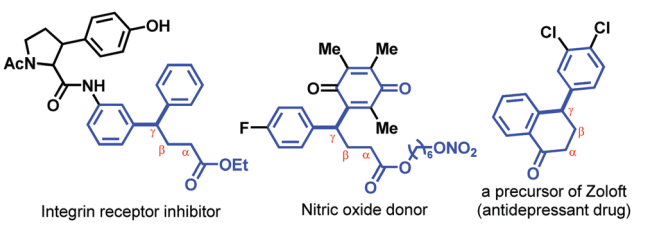

Fig. 1 Representative bioactive compounds possessing the γ,γ-diarylketone moiety.

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† Electronic supplementary information (ESI) available. CCDC 2103437. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/d1cc05997a

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Metal-Free Aminocarbonylation of *p*-Quinone Methides with Isocyanides: Synthesis of Sterically Hindered α-Arylated Acetamides

Sachin R. Shirsath,[a, b] Devidas A. More,[a, b] and M. Muthukrishnan*[a, b]

Abstract: The synthesis of sterically hindered α-arylated acetamides generally requires a multistep reaction sequence and is also difficult to access due to steric constraints. This protocol allows the synthesis of sterically hindered α-arylated acetamides in moderate to high yields *via* 1,6-addition of isocyanides to *p*-quinone methides in the presence of $BF_3.OEt_2$. The present transformation features transition metal-free conditions, avoiding the use of toxic carbon monoxide, broad substrate scope, mild reaction conditions, and operational simplicity.

Introduction

α-Arylated acetamides are prevalent in numerous natural products, leading pharmaceuticals and crop protection chemicals (Figure 1).[1,2] Therefore, the development of novel methods for the synthesis of α-arylated acetamides have attracted the attention of researchers. The conventional way of making aryl acetamides based on the coupling reaction of activated acids with amines in the presence of coupling agents produces enormous waste and increases the cost of industrial production. In a pioneering study, Heck and co-workers reported the palladium catalyzed aminocarbonylation of aryl halides with amines and carbon monoxide to prepare arylated amides.[3] Subsequently, several research groups contributed significantly to this approach to make α-arylated acetamides *via* palladium-catalyzed aminocarbonylation protocols employing electrophiles such as benzyl halides or benzyl pseudohalides with amines or nitroarenes, and CO or $Mo(CO)_6$ as a C1 building block (Scheme 1a).[4] Alternatively, palladium-catalyzed aminocarbonylation of styrene with CO insertion also studied (Scheme 1b).[5] Palladium-catalyzed oxidative carbonylation of benzylic C(sp^3)–H bonds with a stoichiometric amount of oxidants also developed as a new route for the synthesis of α-arylated acetamides (Scheme 1c).[6] Recently, Chen and co-workers reported the nickel-catalyzed aminocarbonylation of secondary benzyl chlorides with isocyanides to access α-arylated acetamide derivatives (Scheme 1d).[7] Despite these achievements, most of the methods described above provide only mono α-aryl-substituted acetamides and requires the use of transition metal catalysts, toxic carbon monoxide, harsh

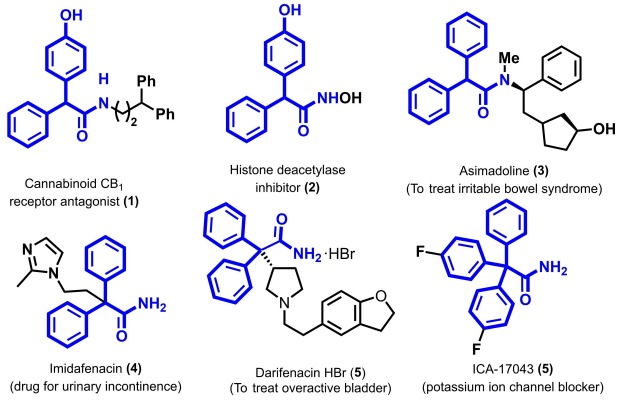
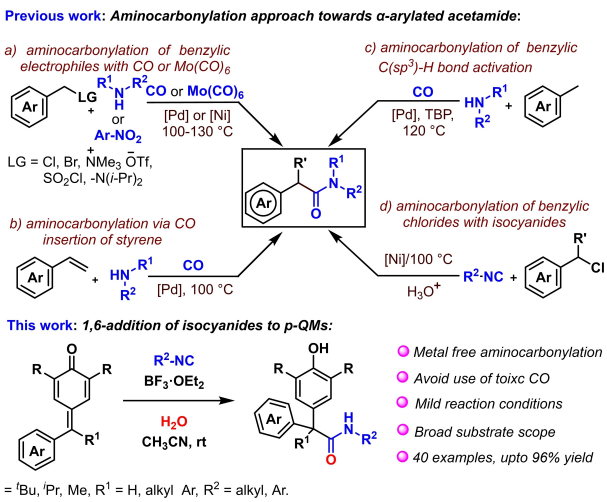


Figure 1. Selected bioactive compounds and drugs containing α-arylated acetamides moiety.



Scheme 1. Background and present work.

reaction conditions, etc. However, in contrast with the synthesis of simple mono α-arylated acetamides, methods for the preparation of α-arylated acetamides with restricted steric hindrance such as α-di/triaryl acetamides are rare and considered to be challenging.[7] Therefore, the development of simple,

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