Synthesis of Substituted Fluorene Derivatives and Related Natural Products from *para*-Quinone Methides

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Dedicated

To

My beloved parents

Aakka and Jija

And

Late Younger Brother

Mahesh

Declaration

The work presented in this thesis titled ***"Synthesis of Substituted Fluorene Derivatives and Related Natural Products from para-Quinone Methides"*** has been carried out by me under the supervision of **Prof. R. Vijaya Anand** in the Department of Chemical Sciences, Indian Institute of Science Education and Research (IISER) Mohali, Punjab.

This work hasn't been submitted to another university or organization in whole or in part for a degree, diploma, or fellowship.

When other people's contributions are involved, every attempt is undertaken to indicate this with appropriate acknowledgements of collaboration and exchanges properly. This thesis authenticates my original work, and the bibliography includes a complete description of all the sources used.

Pankhade Yogesh Ashok

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

Prof. R. Vijaya Anand

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Abstract

The main focus of this thesis work is on the inter- and intramolecular nucleophilic 1,6-conjugate addition reactions of suitably modified *p*-quinone methides (*p*-QMs) to access substituted-fluorenes and fluorene-based biologically significant natural products. The thesis is divided into three Chapters. Chapter 1 briefly introduces the reactivity of various p-QMs toward different nucleophiles and the annulation reactions of *p*-QMs leading to various carbocycles. Chapter 2 is sub-divided into two sections; namely, Part A and Part B. Part A describes the synthesis of 9-arylfluorenes by TfOH catalyzed intramolecular 1,6 annulation of 2-aryl phenyl *p*-QMs in a continuous flow microreactor. Part B deals with the synthesis of substituted 9,9-disubstituted fluorene & dihydrobenzo[*a*]fluorene derivatives through a silver catalyzed intramolecular 1,6-addition followed by cascade cyclization. Chapter 3 deals with the total synthesis of recently isolated fluorene-based natural products.

Chapter 1: General introduction to the chemistry of para-quinone methides (p-QMs)

A brief introduction to the unique reactivity and applications of substituted *p*-QMs in various carbocycles synthesis are discussed in this chapter (Figure 1).

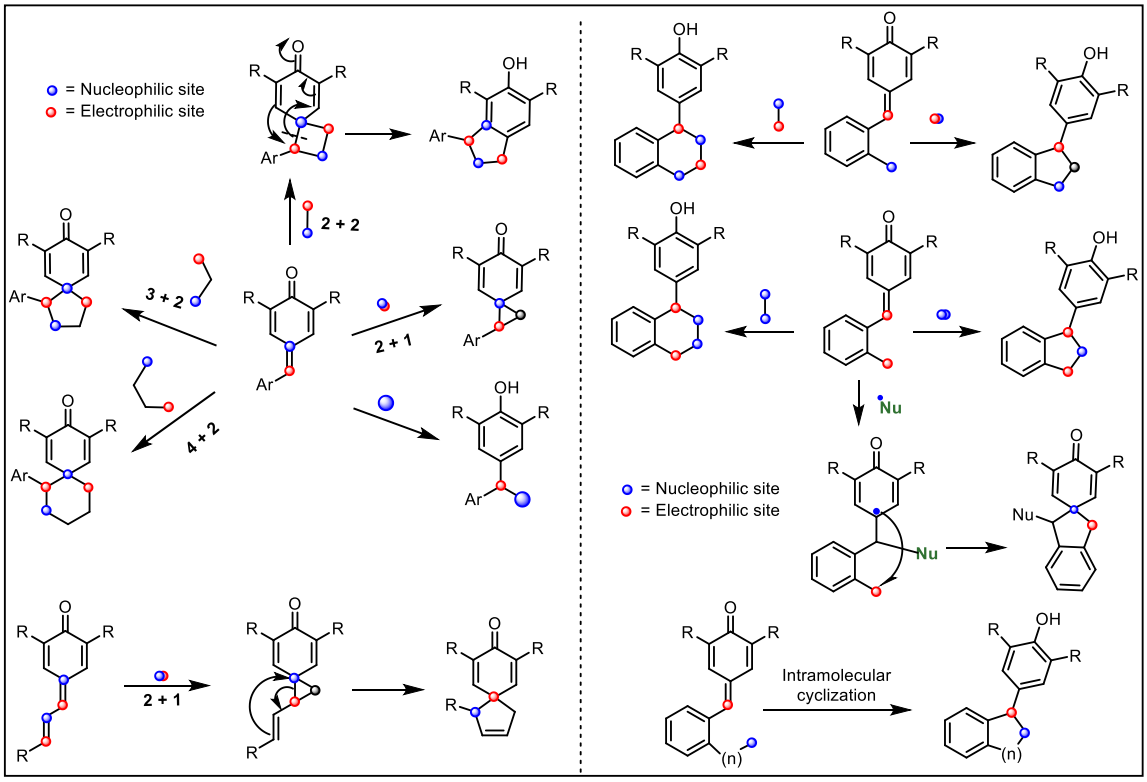


Figure 1. Annulation reactions of substituted *p*-QMs

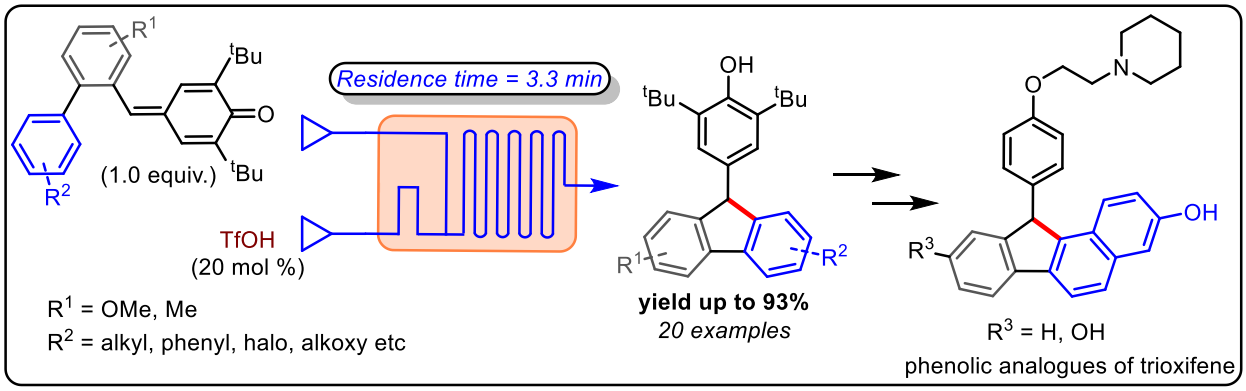
In recent years, the chemistry of *para* quinone methides (*p*-QMs) has been extensively explored in the synthesis of a wide range of basic to structurally complex organic molecules. Due to their distinctive reactivity with diverse nucleophiles, *p*-QMs are useful in the synthesis of a wide variety of compounds, such as diaryl/triarylmethanes, fused/spiro carbo and heterocycles, etc. Apart from serving as useful synthons, *p*-QMs are also found as intermediates in many biological pathways.

***Chapter 2:* Lewis acid/Bronsted acid-catalyzed synthesis of 9-substituted fluorenes and substituted dihydro-benzo[*a*]fluorenes**

Chapter 2 is subdivided into two parts

Part A: TfOH-catalyzed intramolecular annulation of 2-(Aryl)-phenyl-substituted p-quinone methides under continuous flow

Fluorene-based small molecules have been often employed in organic electronics over the past few decades due to their excellent optoelectronic properties. As a result, several recent reports have been published on the synthesis of 9-aryl fluorene.



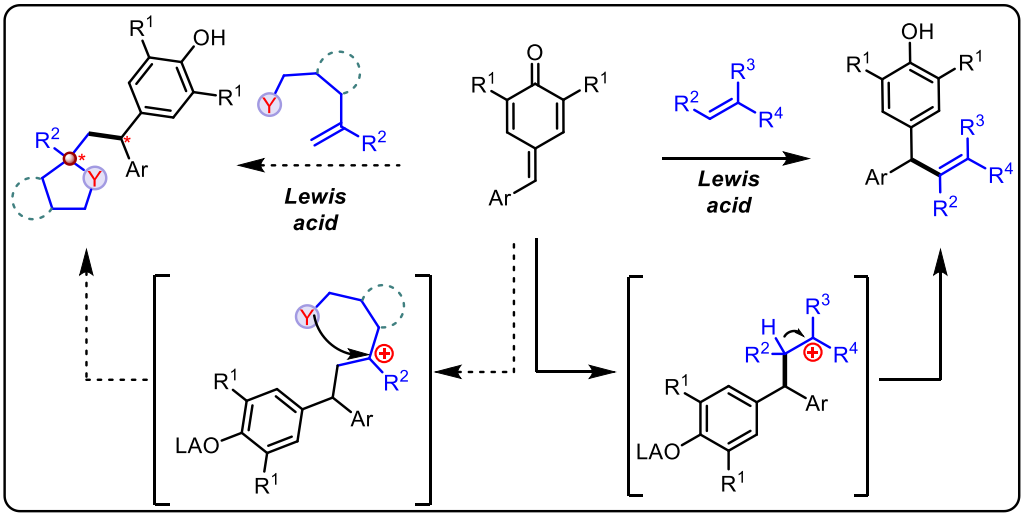
Scheme 1. Synthesis of 9-arylfluorenes under continuous-flow condition

This chapter shows the synthesis of 9-aryl fluorene derivatives through an intramolecular annulation of 2-(aryl)-phenyl-substituted *p*-QMs in a continuous-flow reactor using TfOH as a catalyst (Scheme 1).[2] In addition, this method was also elaborated for the formal synthesis of phenolic analogues of trioxifene, which are proven to possess antiestrogen properties.

Part B: Silver-catalyzed cascade approach to access 9,9-disubstituted fluorenes and dihydro-5H-benzo[a]fluorenes from p-quinone methides

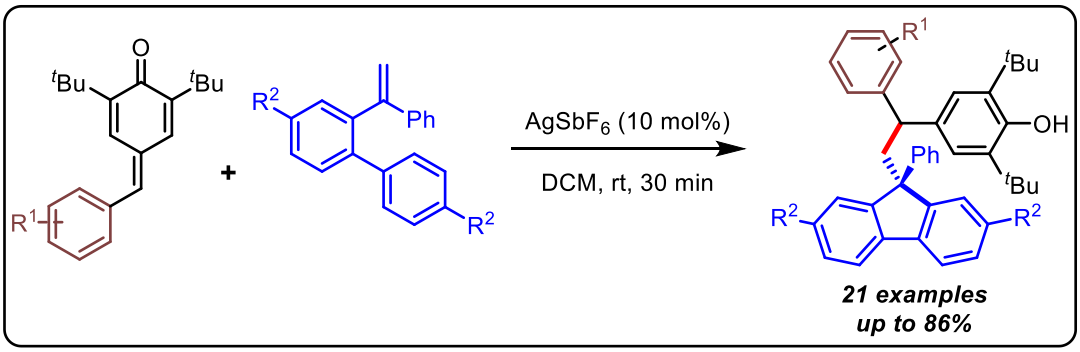
This chapter describes our efforts to explore *p*-QMs in synthesising 9,9-disubstituted fluorene derivatives and dihydro-*5H*-benzo[*a*]fluorene.[1]

In 2018 we described the Lewis acid-catalyzed hydroolifination of *para* quinone methides to access substituted vinyl diaryl methane derivatives via 1,6-conjugate addition followed by elimination. To the continuation of that work, we hypnotized that if we modify olefin in such a way that it contains an extra nucleophilic centre, then instead of elimination, that could be used for intramolecular cyclization (Scheme 2).



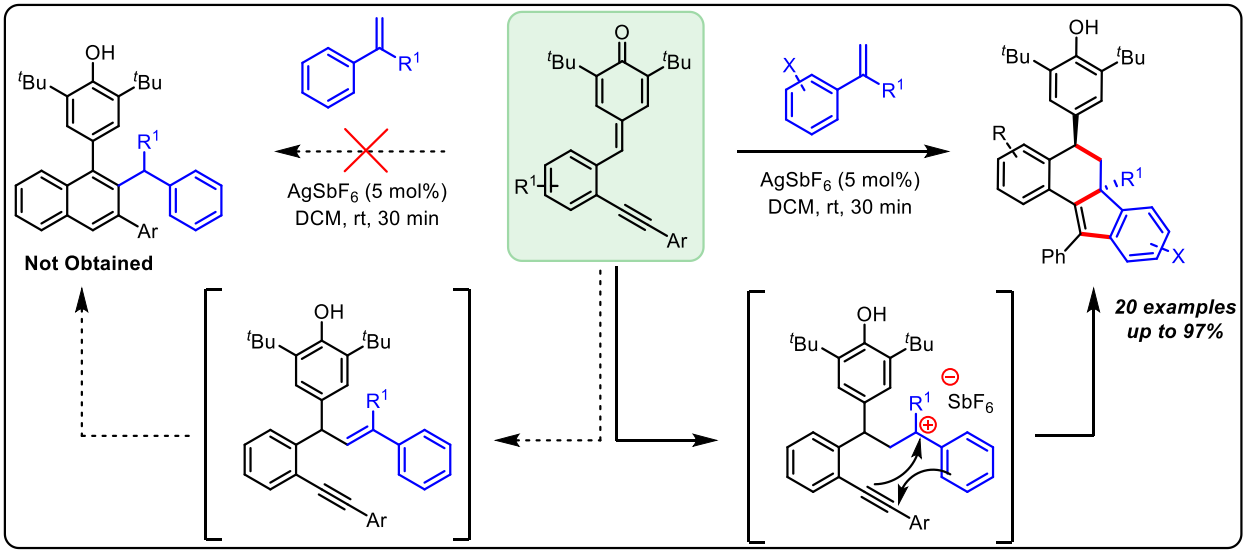
Scheme 2. Previous work and our hypothesis

So, for that, we have synthesized *o*-vinyl biaryl and treated it with *p*-QMs in the presence of a Lewis acid catalyst, leading to the formation of 9,9-disubstituted via electrophilic cascade cyclization (Scheme 3).



Scheme 3. Synthesis of 9,9-disubstituted fluorene derivatives

Next, we have elaborated this methodology to the synthesis of dihydrobenzo[*a*]fluorenes where diarylethene is treated with 2-alkynyl-phenyl-substituted *p*-QMs. We initially hypothesized that the reaction between 2-alkynyl-phenyl-substituted *p*-QM and diphenylethene in the presence of $AgSbF_6$ would lead to substituted-naphthalene derivative through a 1,6 conjugated addition followed by ene-yne cyclization.

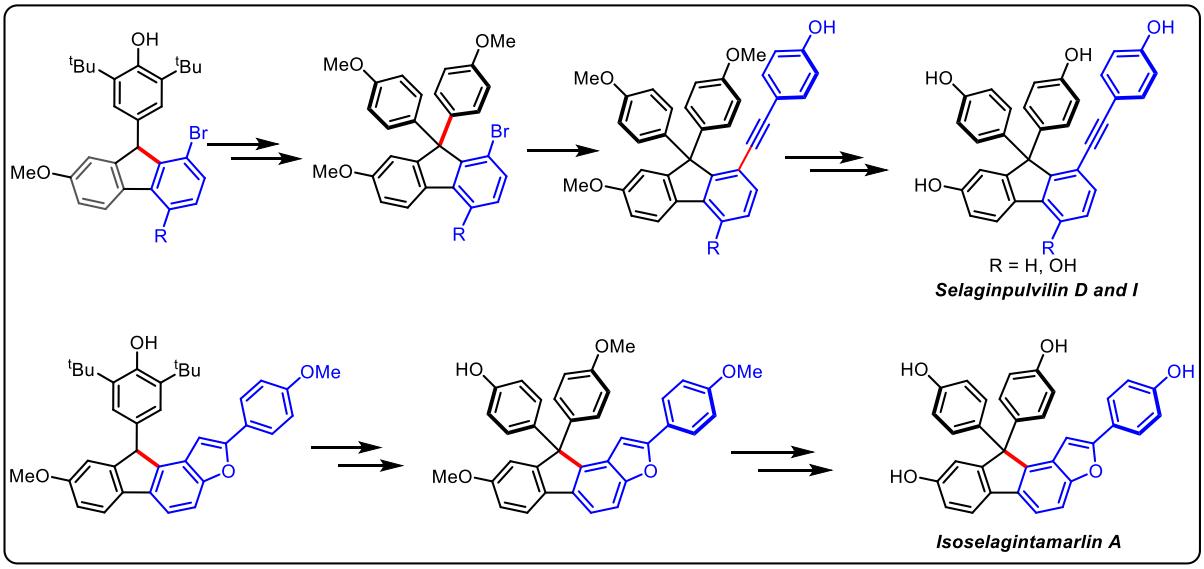


Scheme 4. Synthesis of dihydro-5*H*-benzo[*a*]fluorenes

However, surprisingly, this reaction led to dihydro-5*H*-benzo[*a*]fluorene as the sole product. Since only a very few reports are available in the literature for the synthesis of dihydro-5*H*-benzo[*a*]fluorenes, we took this project further and made a diverse range of dihydro-5*H*-benzo[*a*]fluorene derivatives under optimal conditions in good to excellent yields (Scheme 4). Since these transformations involve carbocation intermediates, and $AgSbF_6$ is known to stabilize the carbocation very well, other Lewis acids were found to be ineffective for this transformation.

Chapter 3: Total synthesis of isoselagintamarlin A and selaginpulvilin D and I

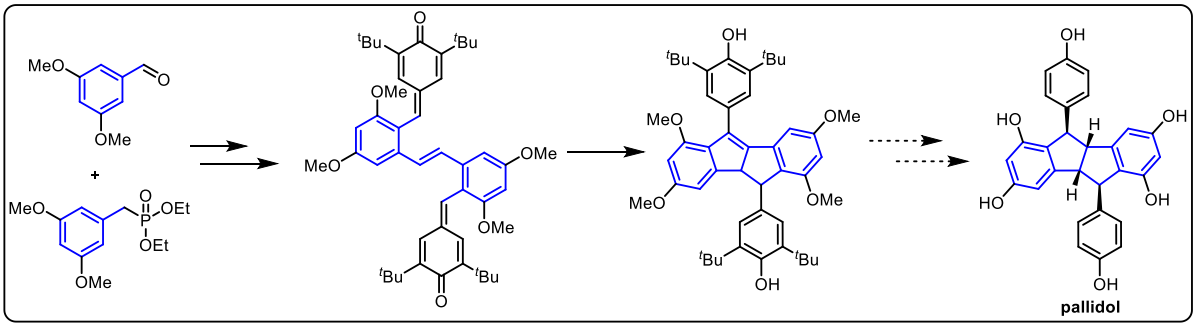
This chapter mainly focuses on the synthesis of some of the recently discovered fluorene-based natural products. Although fluorene core is rarely found in naturally occurring systems, it plays a crucial role in the development of synthetic bioactive compounds and has also found applications in material science. Selaginpuvilin A-D, a 9,9-diaryl fluorene-based natural products, were first isolated in 2014 by the Yin group. Since then, several others of the same family of natural products have been found, and some reports on their total syntheses have been published. However, alternative strategies are certainly required for the synthesis of these molecules as most of the hitherto known synthetic procedures involve multiple steps and, as a result, leading to low overall yields.



Scheme 5. First total synthesis of selaginpulvilin I and isoselagintamarlin A

After developing the methodology for synthesizing 9-aryl fluorene,[2] we envisioned that this synthetic protocol could be applied to synthesize some of the fluorene-based natural products. Therefore, in this chapter, we have described the first total synthesis of selaginpulvilin I and isoselagitamarlin A (Scheme 5), along with a brief description of the selaginellin natural products and a review of the literature on their syntheses.

We have also attempted the synthesis of pallidol, a resveratrol-based natural product. Even though the key step, intramolecular cyclization, was leading to the basic core of pallidol being achieved, the reduction of the alkene-part of the intermediate was not accomplished under several reduction conditions. (Scheme 6). Further optimization reactions to achieve this transformation are under progress.



Scheme 6. Attempted approach for the synthesis of pallidol

Abbreviations

ACN	Acetonitrile
Ac_2O	Acetic anhydride
acac	Acetylacetonate
a.t	Ambient temperature
Aq	Aqueous
AC	Adenylyl cyclase
BINAP	(2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl)
brs	Broad singlet
CCl_4	Carbon tetrachloride
clcd	Calculated
CSA	Camphorsulfonic acid
cm	Centimetre
δ	Chemical shift
$CHCl_3$	Chloroform
$CDCl_3$	Chloroform-D
J	Coupling constant
cy	Cyclohexyl
cod	1,5-cyclooctadiene
cAMP	Cyclic-Adinosine-3',5'-Monophosphate
CNS	Central nervous system
COPD	Chronic obstructive pulmonary disease
CysA	Cyclophilin A
°C	Degree celsius
dr	Diastereomeric ratio
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DCE	Dichloroethane
DCM	Dichloromethane
DMeO-BPY	4-4′-Dimethoxy-2-2′-bipyridine
DMA	Dimethylacetamide
DMSO	Dimethyl sulfoxide
d	Doublet

dd	Doublet of doublet
ddd	Doublet of doublet of doublet
dt	Doublet of triplets
dtbbpy	4,4′-Di-*tert*-butyl-2,2′-dipyridyl
DTBP	Di-*tert*-butyl peroxide
EWG	Electron withdrawing
E. C	Electrocyclic Reactions
ESI	Electrospray ionization
λ_{emi}	Emission maxima
ee	Enantiomeric excess
er	Enantiomeric ratio
EtOH	Ethanol
EtOAc	Ethylacetate
equiv	Equivalents
FT-IR	Fourier transform infrared spectroscopy
Hz	Hertz
HRMS	High-resolution Mass Spectrum
h	Hour(s)
i-Pr	*iso*-Propyl
LED	Light-emitting diode
m/z	Mass/Charge
MHz	Megahertz
m.p.	Melting point
Mes	Mesityl
MeOH	Methanol
MsOH	Methane Sulfonic Acid
*m*CPBA	*meta*-Chloroperoxybenzoic acid
mg	Milligram(s)
mL	Milliliter(s)
mmol	Millimole(s)
min	Minute(s)
µL	Microliter (s)
µm	Micrometre (s)
M.S.	Molecular sieves

m	Multiplet
DMF	*N*,*N*'-Dimethyl formamide
NMP	*N*-Methyl-2-pyrrolidone
NMR	Nuclear Magnetic Resonance
n-Pr	Propyl
P-TSA	*p*-Toluene sulfonic acid
PDE4	Phosphodiesterase-4
PAH	Polycyclic aromatic hydrocarbons
q	Quartet
R_f	Retention factor
rt	Room temperature
sept	Septet
s	Singlet
^{t}Bu	*tert*-Butyl
tert	Tertiary
TBAB	Tetrabutylammonium bromide
THF	Tetrahydrofuran
TMS	Tetramethylsilane
TFA	Trifluoroacetic acid
t	Triplet
td	Triplet of doublets
tt	Triplet of triplet
UV	Ultraviolet
Vis	Visible
XPhos	2-Dicyclohexylphoshino-2,4,6-triisopropylbipheny

Contents

Part B: **Silver-catalyzed cascade approach to access 9,9-disubstituted fluorenes and dihydro-5H-benzo[*a*]fluorenes from *p*-quinone methides**

Chapter 3: Total synthesis of isoselagintamarlin A and selaginpulvilin D and I

General introduction to applications of *p*-QMs and the synthesis of carbocycles from substituted *para*-quinone methides

1.1Introduction:

In recent years, the chemistry of *para* quinone methides (*p*-QMs) has been extensively explored and used to synthesize a variety of basic to complicated structural motifs. Basically, *p*-QM is an analogue of 1,4-benzoquinone, in which the methylene group replaces one of the carbonyl oxygens. Unlike standard 1,6-conjugated dienone systems, *p*-QMs are exceptionally reactive Michael acceptors with distinct reactivity and selectivity for nucleophiles due to a more stable zwitterionic form (Figure 1).[1]

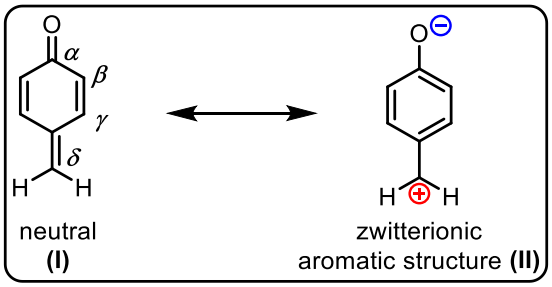


Figure 1. Zwitterionic form of *para*-quinone methide

In synthetic organic chemistry, *p*-QMs serve as great synthons and are also found as intermediates in many biological pathways[2] and in naturally occurring compounds (Figure 2).[3]

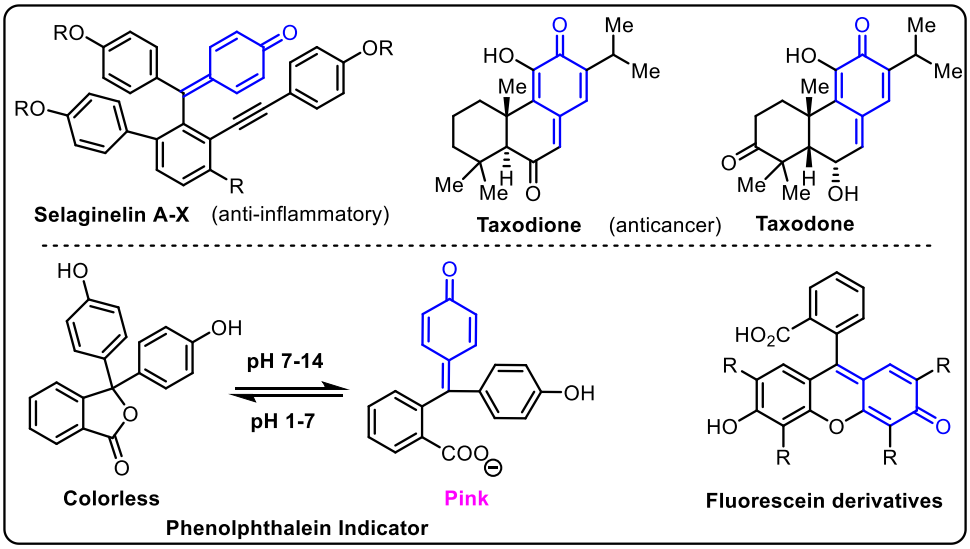


Figure 2:- *para*-Quinone methide-based natural products and applicable compounds

Additionally, self-immolative linkers containing *in situ* generated *p*-QMs unit are useful for molecular sensors, theranostic applications, and drug delivery[4]. Moreover, a commonly used phenolphthalein indicator in acid-base titrations are well known to show pink colour due to the formation of *p*-QM in an alkaline pH via ring opening. While in an acidic medium, ring closing gives the cyclic compound, and it results in the formation of a colourless solution. Furthermore, closed cyclic *p*-QMs such as fluorescein derivatives[5] have shown applications in dyes (Tokyo Green, Erythrosine, etc.) and photocatalysis (Eosin Y, Rose Bengal etc.).

Due to their distinctive reactivity with diverse nucleophiles, *p*-QMs are useful in the synthesis of a wide variety of compounds, such as diaryl/triarylmethanes, fused/spiro carbo and heterocycles, etc.[6] The unique reactivity of *p*-QM is due to the benzylic carbocation, which enables a highly regioselective nucleophilic attack at the 6-position. Moreover, the reactivity of *p*-QMs is also dependent on the type of nucleophile.

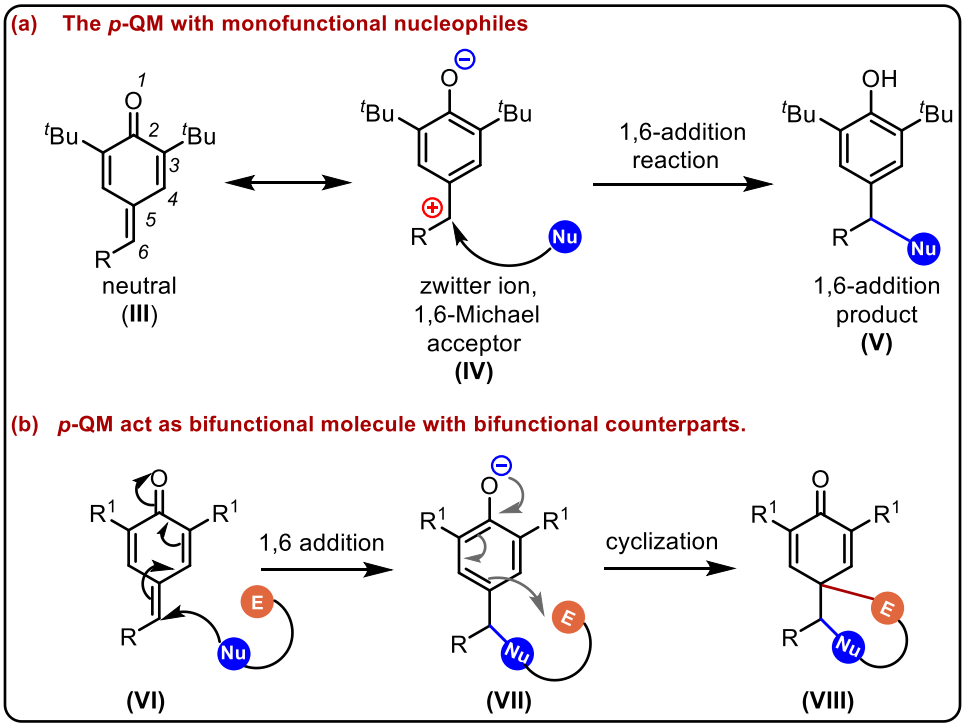


Figure 3. Reactivity of *p*-QMs

In the case of a monofunctional nucleophile, 1,6 conjugate addition results in diaryl/triaryl methanes **V** (Figure 3a). However, bifunctional molecules form spirocyclic rings **VIII** (Figure 3b). These results confirm that *p*-QM acts as a bifunctional molecule with bifunctional counterparts.

In order to synthesize different kinds of cyclic compounds, structural modification of *p*-QMs is necessary. Better reactivity with different kinds of bifunctional reagents is achieved

by functionalizing *p*-QMs with additional nucleophilic or electrophilic centres. For that, functionalized *p*-QMs were synthesized and used by various groups in the last few years to synthesize fused carbo/heterocyclic compounds.

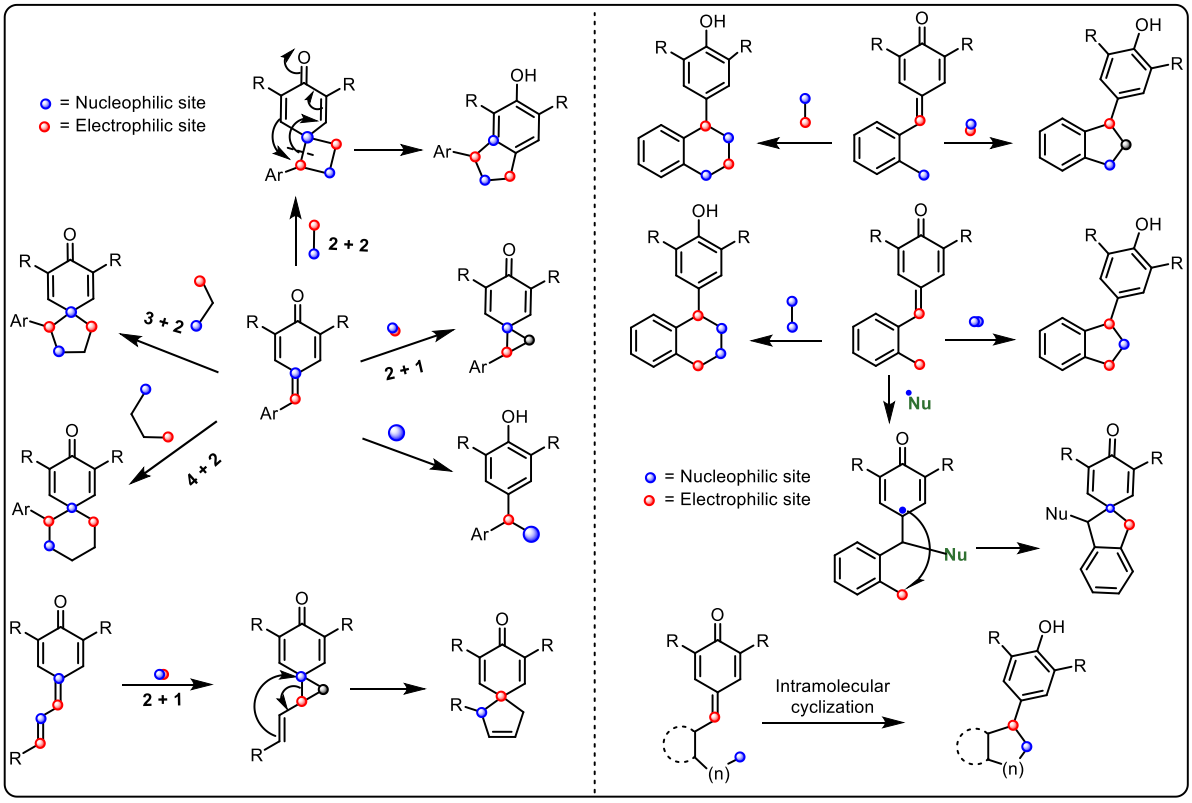


Figure 4. Annulations of *para*-quinone methides

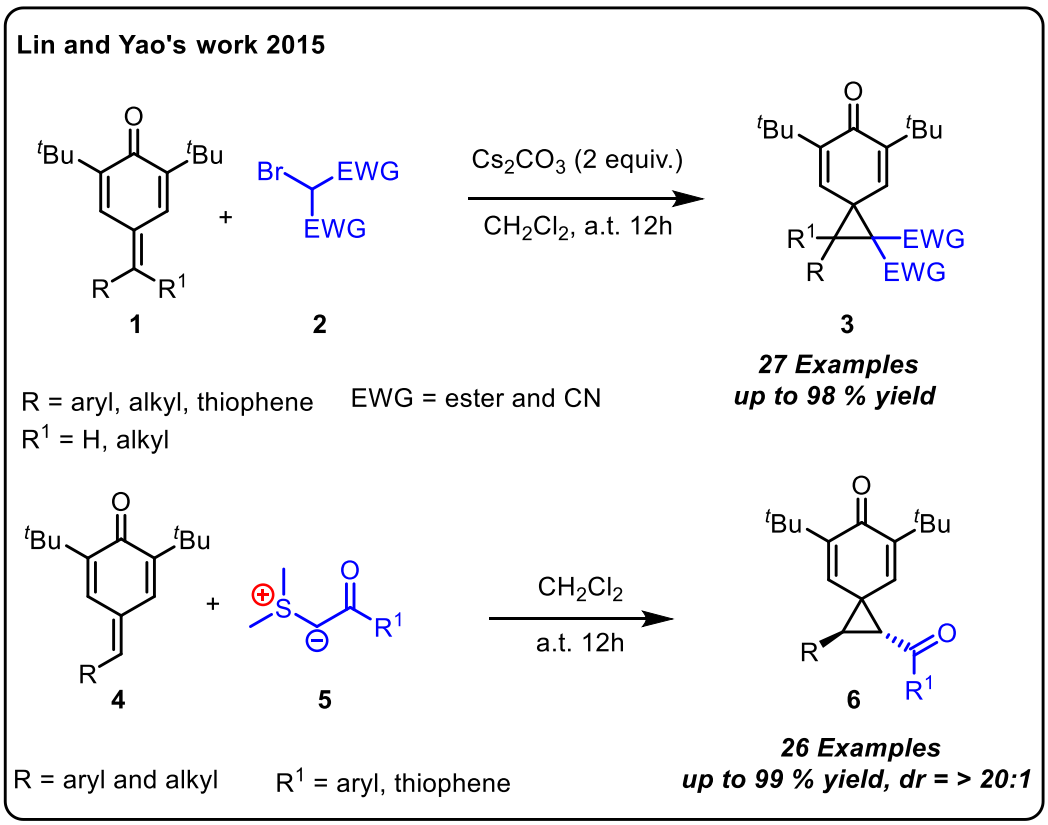
As shown in Figure 4, various cyclic compounds can be synthesized using *p*-QMs with appropriate nucleophiles. The [2+1], [3+2] and [4+2] annulation of *p*-QMs with bifunctional molecules furnish the spirocyclo *p*-dienones. Functionalized *p*-QMs were exploited predominantly for the synthesis of fused carbocycles and heterocycles. This chapter mainly focuses on the synthesis of carbocycles utilizing the substituted *para*-quinone methides (*p*-QMs).

1.2 Literature reports on the synthesis of spiro carbocycles

1.2.1 [2+1] annulation of *p*-QMs leading to spirocyclopropane *p*-dienones

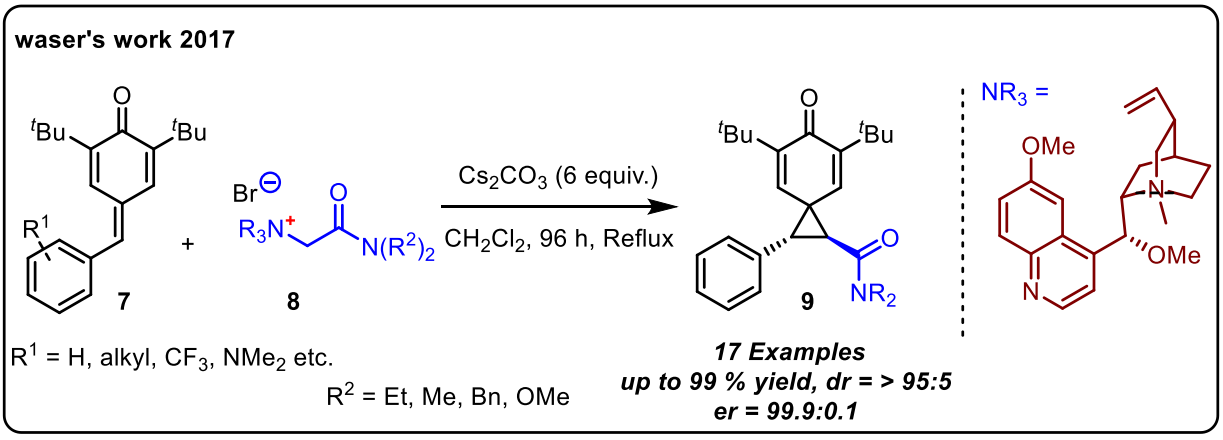
In 2015, Yao's and Lin's group described the synthesis of spiro[2.5]octa-4,7-dien-6-one **3** via a base-mediated 1,6 conjugate addition of dialkyl 2-bromomalonates (**2**) with **1** followed by dearomative annulation (Scheme 1).[7] Subsequently, in the same year, they published another report using sulfur ylides (**5**) and *p*-QMs (**4**) under catalyst free conditions. The domino type cyclization of sulfur ylide **5** with *p*-QMs **4** led to the formation of

spiro[2.5]octa-4,7-dien-6-one **6** with excellent yields and good diastereoselectivity (Scheme 1).



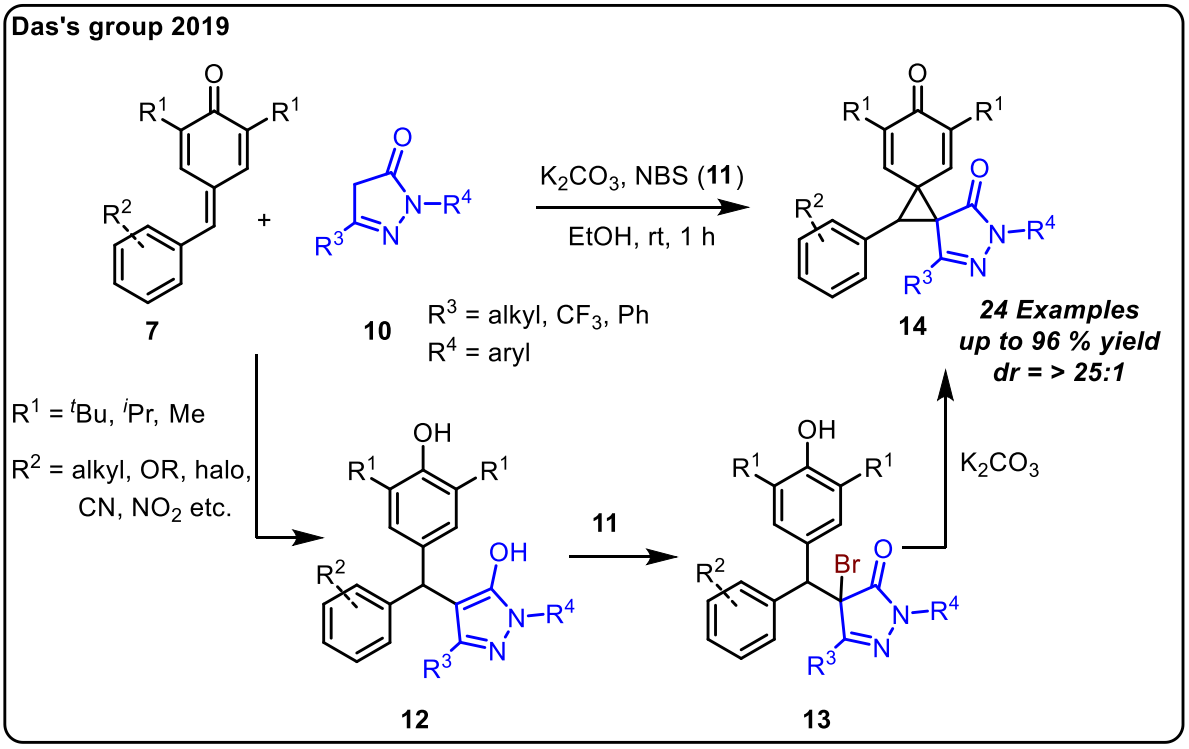
Scheme 1. The synthesis of spiro[2.5]octa-4,7-dien-6-one via [2+1] annulation

In 2017 Waser's group developed a highly enantioselective spirocyclopropanation of *p*-QMs with chiral cinchona alkaloid-based ammonium ylide **8** (Scheme 2).[8] As a result, the *trans* cyclopropane **9** was predominantly formed with a >99% *ee*.



Scheme 2. Enantioselective spirocyclopropanation of *p*-QMs

Annulation of pyrazolones (**10**) with *p*-QMs (7) in one pot, but in a stepwise manner, was disclosed recently by Das's group (Scheme 3).[9] The base mediated 1,6 conjugate addition of pyrazolone formed an adduct **12**, which on bromination with NBS **11,** gave an intermediate **13**. Then dearomative annulation of **13** in the presence of K_2CO_3 led to the corresponding bis-spiro[cyclohexadienone-cyclopropane-pyrazolone] **14**.



Scheme 3. The synthesis of bis-spiro[cyclohexadienone-cyclopropane-pyrazolone]

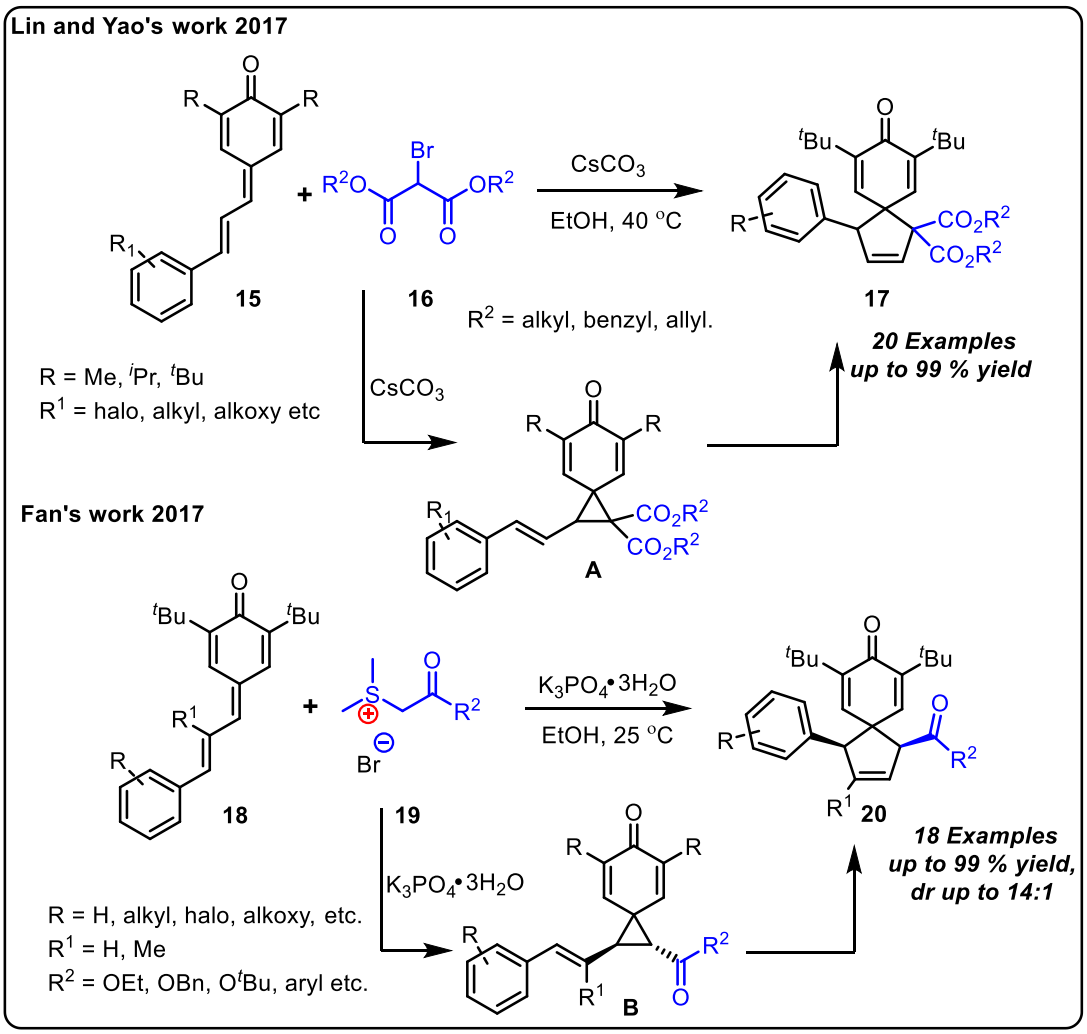
1.2.2 Cyclopropanation followed by vinyl cyclopropane rearrangement of vinyl *p*-QMs to access spyrocyclo-pentyl *p*-dienones

Lin and Yao performed a base mediated cyclopropanation reaction of vinyl *p*-QMs (**15**) with 2-bromomalonate derivatives (**16**) to form spiro[2.5]octa-4,7-dien-6-one derivatives **A**, which on vinyl cyclopropane rearrangement led to the desired spirocyclic products (**17**). Fan's group utilized sulphur ylides (**19**) with vinyl *p*-QMs (**18**) for the same type of transformation (Scheme 4).[10]

1.2.3 The synthesis of spirocyclopentyl *p*-dienones via [3+2] annulation of 1,3 bifunctional molecules with *p*-QMs

A novel strategy for an [3+2] annulation of vinyl cyclopropanes and *N*-tosyl vinyl aziridines (**21**) with *p*-QM (**7**) was developed by Lin and Yao's group for the synthesis of spirocyclopentyl *p*-dienones (**22**) under palladium and phosphine-thiourea cooperative

catalysis.[11a] The same group also developed another strategy for the synthesis of spirocyclopentyl *p*-dienones later in 2017.[11b]



Scheme 4. Synthesis of spirocyclopentyl *p*-dienones from vinyl *p*-QMs

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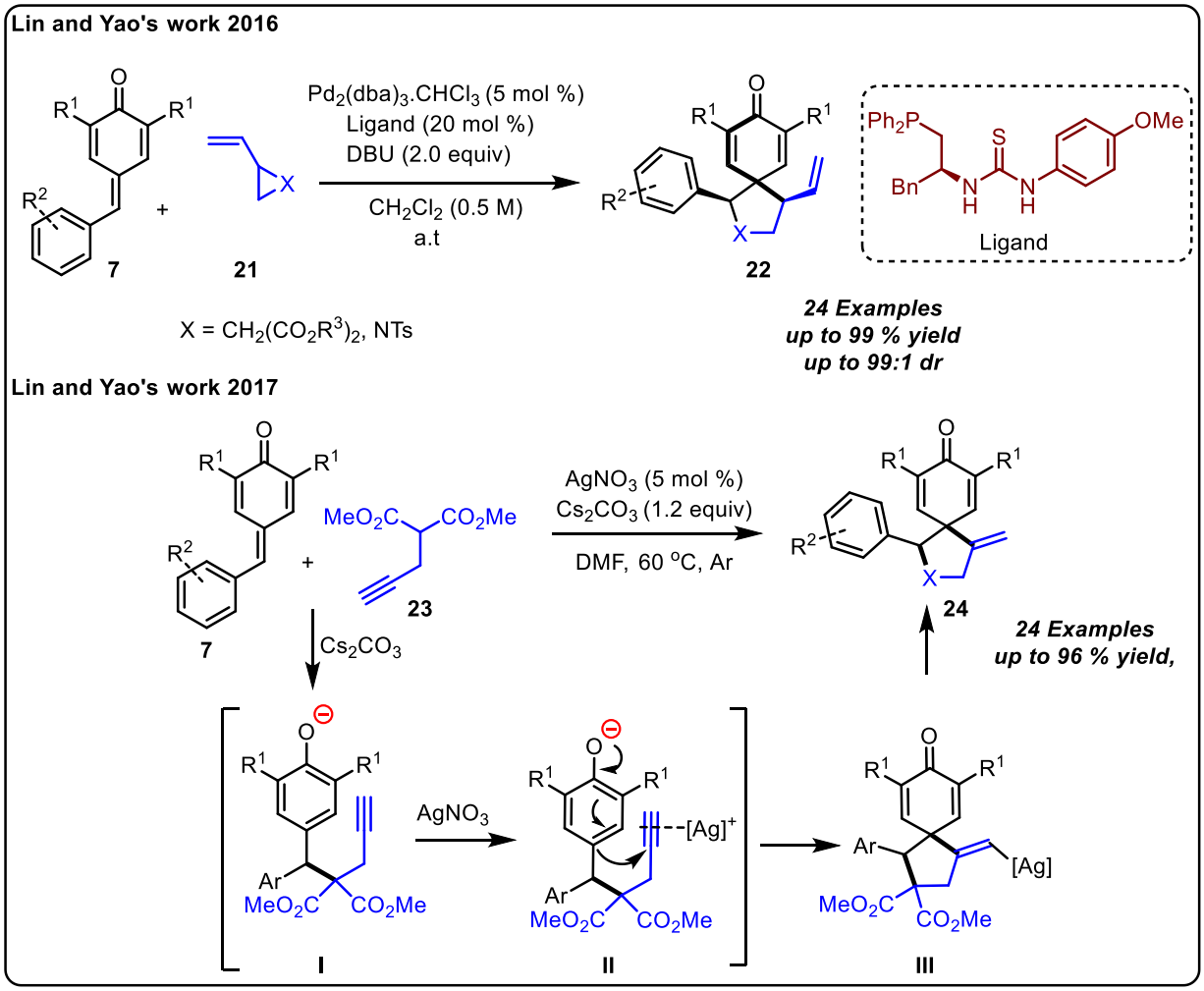
In this protocol, they used propargyl malonates (**23**) and *p*-QMs (**7**) with an equivalent amount of Cs_2CO_3 and a catalytic amount of $AgNO_3$. In this case, several *p*-QMs are treated with propargyl malonate to afford substituted spiro[4.5]deca-6, 9-dien-8-ones (**24**) (Scheme 5).

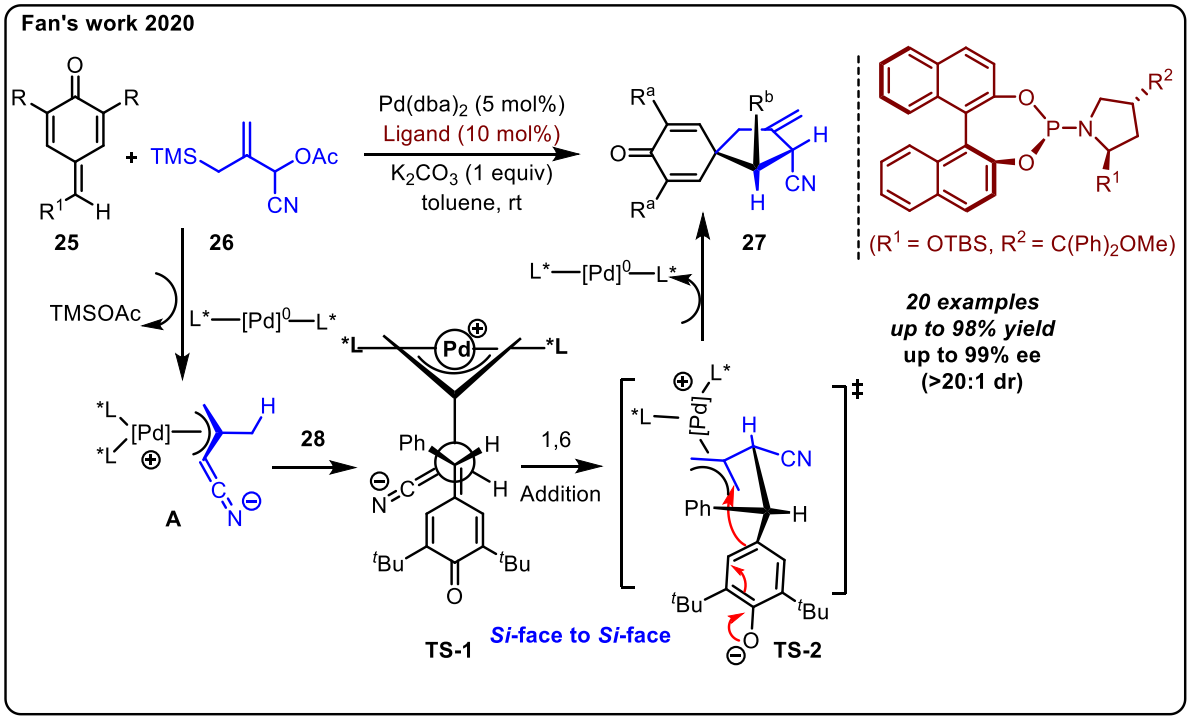
In 2020, Fan's group reported a highly regio- and stereoselective asymmetric [2+3] annulation of *p*-quinone methides (**25**) with CN-substituted trimethylenemethane (**26**). For this transformation, they used a palladium catalyst and chiral phosphoramidite L* with K_2CO_3 as a base to offer an enantioselective production of highly functionalized chiral spirocyclopentyl p-dienones (**27**). According to the Proposed mechanism, this reaction proceeds through a Pd-catalysed [2+3] annulation reaction of *p*-QM (**25**) with CN-TMM moiety (**26**) (Scheme 6).[12]



Scheme 5. The palladium-catalyzed [3+2] annulation of *p*-QMs

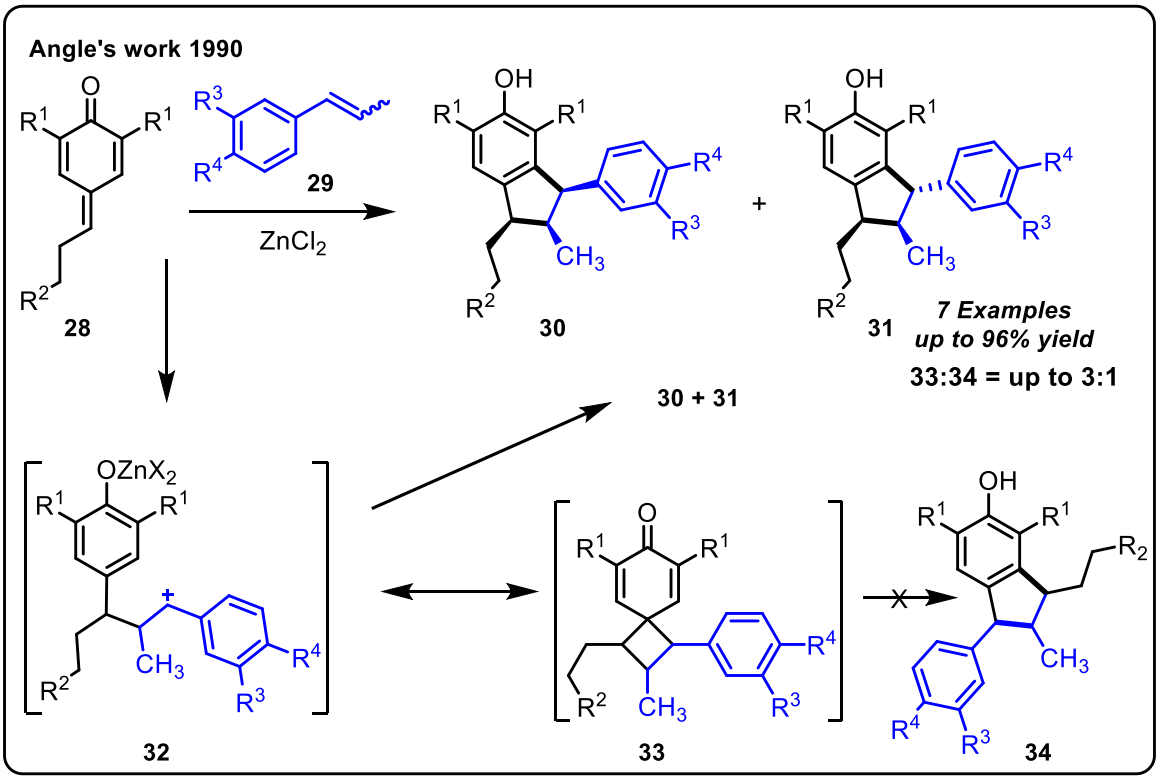
Initially, **26** is activated by the metal complex; $Pd(dba)_2$ and chiral phosphoramidite **L*,** generating a Pd-TMM moiety **A**. As proposed in **TS-1**, the *si* face is favoured for the nucleophilic addition of ketenimine moiety to the si face of *p*-QMs species (**28**) due to the small steric effect of the linear ketenimine group. The enantiotopic face of the *si* face of *p*-QMs **28** is controlled by steric hindrance minimization resulting from interaction with the chiral phosphoramidite **L*.** Accordingly, an asymmetric 1,6-addition of *p*-QM (**25**) from the *si* face to the *si* face of the ketenimine moiety affords a favourable transition state **TS-1**, Followed by intramolecular dearomatization through an S_N2' process in **TS-2**. Then, accordingly, the formation of desired spirocyclic product **30** with the regeneration of the active palladium catalyst takes place.

In 1992, Angel's group reported the synthesis of dihydro indenes **30** and **31** using $ZnCl_2$ as a catalyst. 1,6-Addition of styrenes (**29**) to alkyl *p*-QMs (**28**) followed by cyclization trough *m*-position of phenol to obtain dihydro indene (**30**) and (**31**) through a stepwise formal [3+2] cycloaddition processes (Scheme 7).[13]



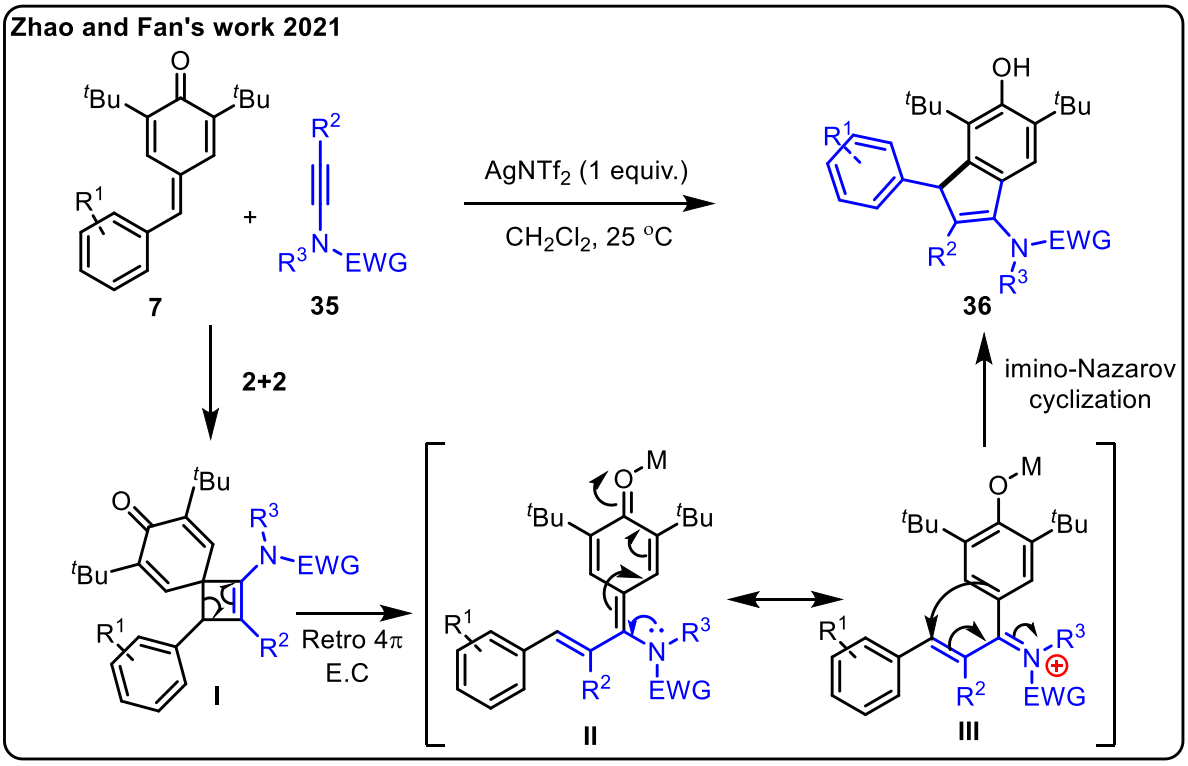
Scheme 6. Highly regio- and stereoselective asymmetric (2+3) annulation of *p*-QMs

1.2.4 The formal [3+2] and [2+2] annulation to access dihydroindene and aminoindene derivatives



Scheme 7. Synthesis of dihydro indenes by stepwise formal [3+2] cycloaddition of styrene

This transformation proceeds through the formation of a cationic intermediate **32**, which was directly captured by a newly formed aromatic ring through the *m*-position and gave the final product. The cyclization from the *p*-position afforded an unstable spiro[3.5]nona-5,8-dien-7-one **33**, which was eventually converted into **32** by ring opening; hence product **34** was not at all observed.

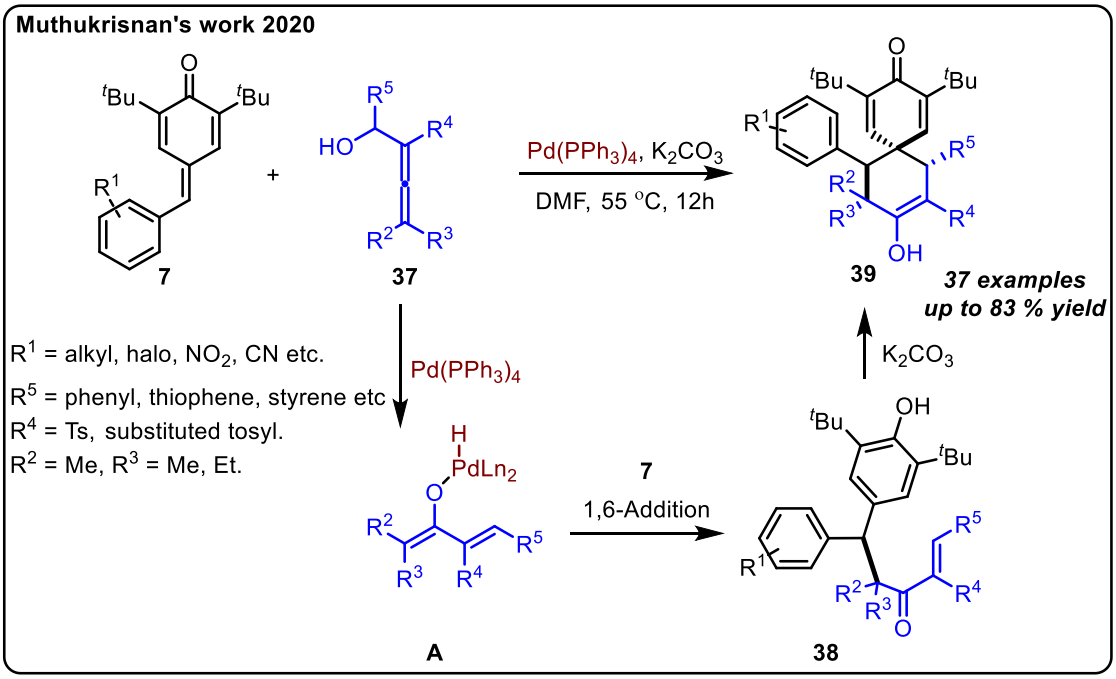


Scheme 8. The synthesis of amino-indene from *p*-QMs and ynamides

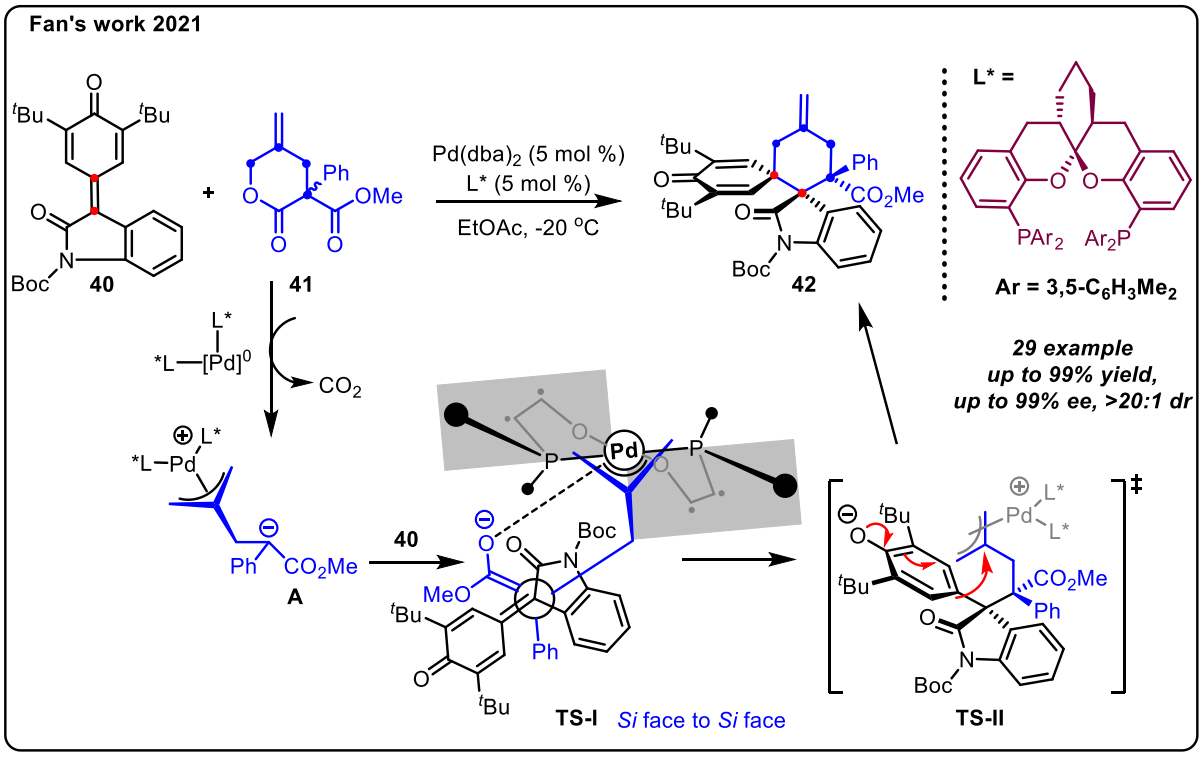
Very recently, Zhao and Fan's group described an annulation of ynamides (**35**) with *p*-QMs (**7**) using stoichiometric amounts of silver bis(trifluoromethanesulfonyl)imide (Scheme 8).[14] The tandem [2+2] addition of ynamides with *p*-QM leads to spirocyclobutene *p*-dienone (**I**). The retro 4π electrocyclization ring opening of **I** followed by isomerization led to conjugated imine **III**, which subsequently underwent imino-Nazarov cyclization and furnished the final product (**36**).

1.2.5 The [4+2] annulation of *p*-QMs to access spirocyclohexane *p*-dienone derivatives

The palladium catalyzed formal [4+2] annulation of sulfonyl allenols (**37**) with *p*-QMs to access spirocyclohexane *p*-dienones (**39**) was disclosed by Muthukrisnan's group in 2020 (Scheme 9).[15] The sulfonyl allenol **37** rearranges to the Pd-complex **A** by treatment of catalyst $Pd(PPh_3)_4$. The 1,6-conjugate addition of **A** to *p*-QM **7** generated an adduct **38**, which then underwent intramolecular cyclization to afford the product **39**.



Scheme 9. The synthesis of spirocyclohexane *p*-dienones using formal [4+2] annulation

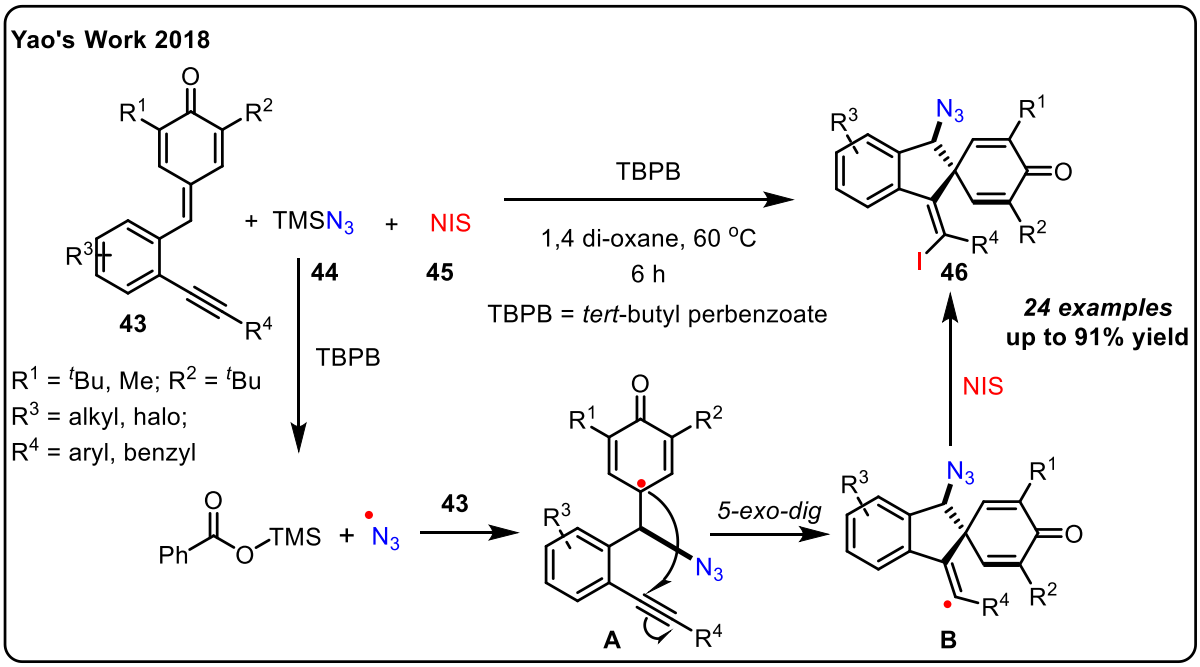


Scheme 10. Asymmetric [4+2] annulation of isatin-derived *p*-QMs

Very recently, Fan's group designed a new type of asymmetric catalytic [4+2] annulation reaction of aryl-substituted ϒ-methylidene-delta-valerolactones (GMDVs) [**41**] with isatin-derived *para*-quinone methides [**40**] for the synthesis of chiral cyclohexadienone-

fused cyclohexyl spirooxindoles with good to high yields (99%) and outstanding stereoselectivities (up to >20:1 *dr*, up to 95% *ee*) using a palladium catalyst and (S,S,S)-(-)-Xyl-SKP (Scheme 10).[16] In the initial step, decarboxylation of **41** took place, followed by oxidative addition of palladium catalyst to allyl cation. Due to the C_2-type symmetry of L*, an enantioselective 1,6-conjugate addition of the Si face of intermediate (**A**) to the Si face of the *p*-QM (**40**) took place to generate TS-I, followed by intramolecular dearomatization/Friedel-Crafts type cyclization and reductive elimination sequence to form the desired product **42**.

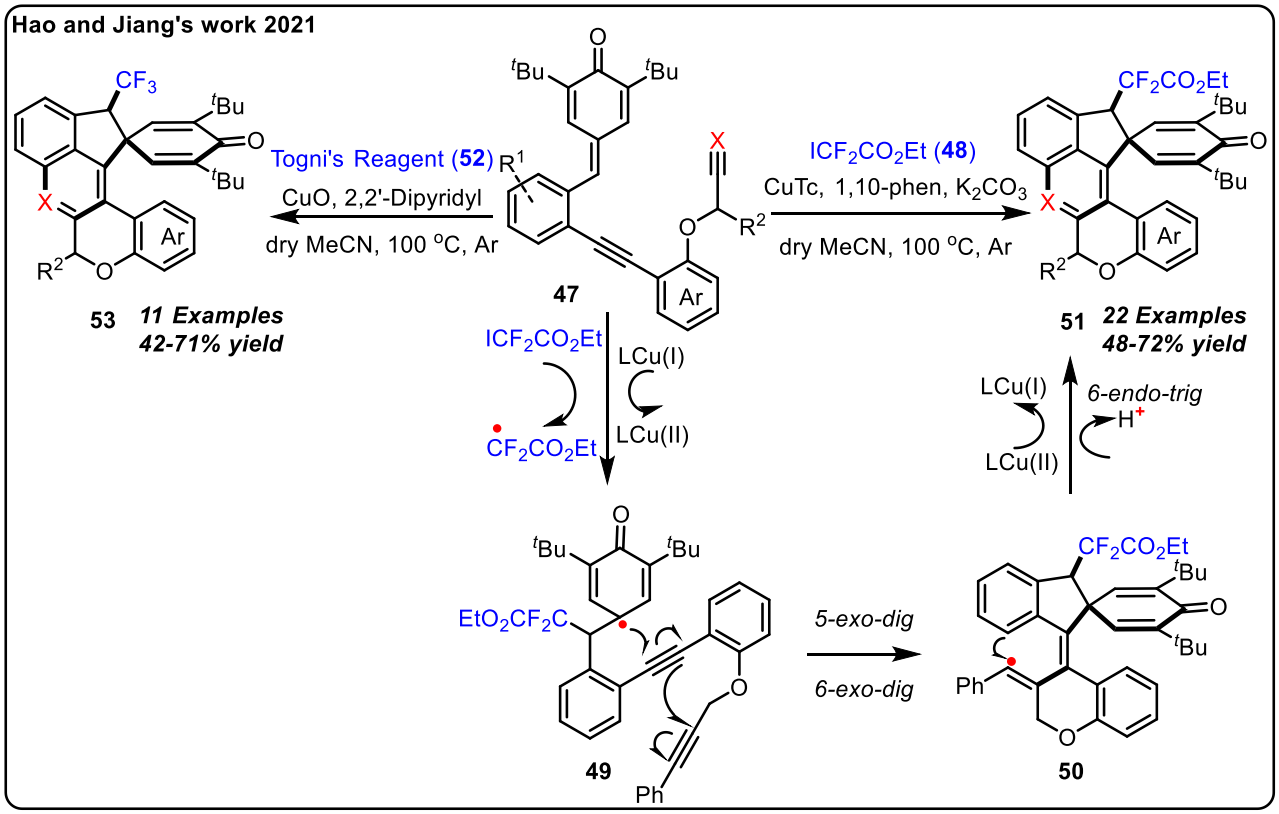
1.2.6 The cascade radical cyclization of 2-phenyl alkynylated *p*-QMs to access spiroindenes derivatives



Scheme 11. The synthesis of spiroindane derivatives

In 2018 Yao's group first used functionalized *p*-QM (**43**) to synthesize spirocyclic compounds through a cascade radical cyclization (Scheme 11).[17] Initially, TBPB breaks into radicals and generates azide radical from trimethylsilyl azide (**44**); then, 1,6-addition of azide radical to *p*-QM **43** generates another radical **A**. The intramolecular *5-exo-dig* cyclization of **A** generates another radical **B**, which further reacts with N-iodosuccinimide (**45**) to furnish spiroindane **46**.

Very recently, a Cu-catalyzed condition has been used by Guo, Hao and Jiang's group to synthesize pentacyclic spiroindenes [**51**] & [**53**] (Scheme 12).[18]



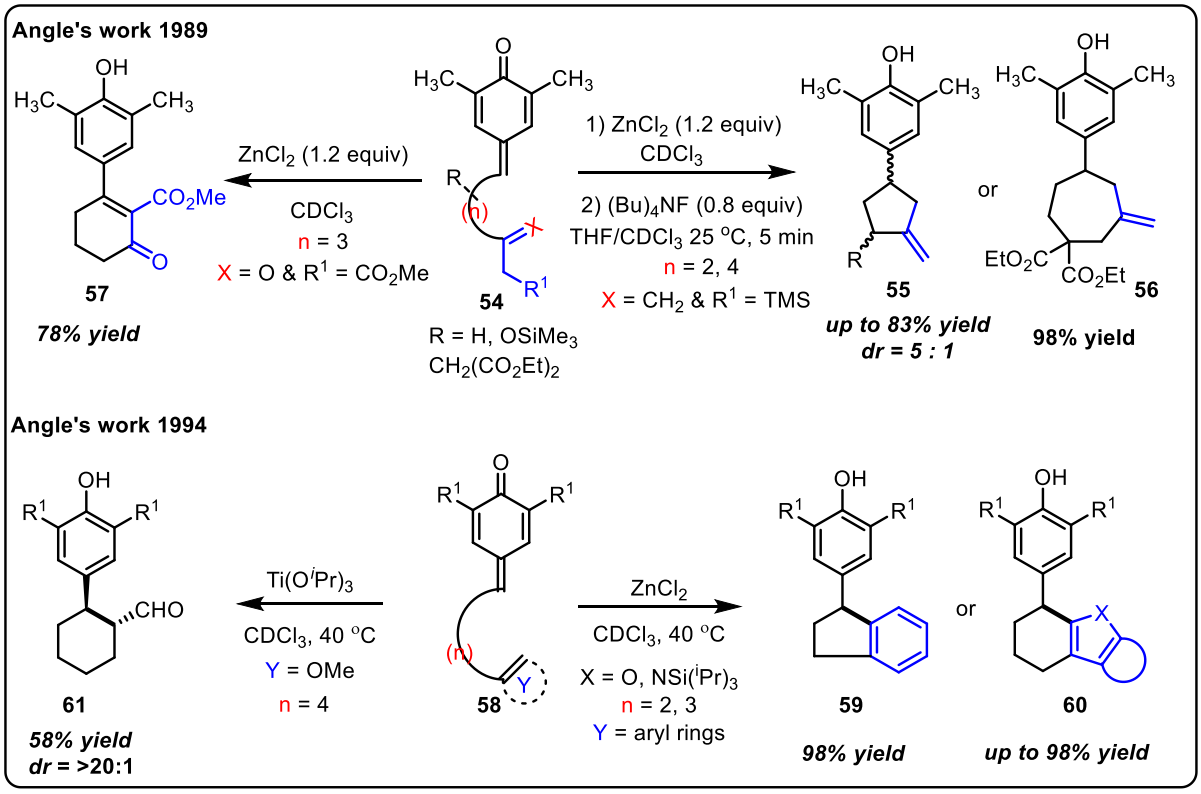
Scheme 12. The Cu catalyzed cascade radical cyclization to access pentacyclic spiroindenes

Fluoromethylation of enediyne and enyne-nitrile containing (*p*-QMs) with Togni's reagent **52** and ethyl iododifluoroacetate **48** afforded the corresponding products spiroindenes **51** and **53**, respectively, in moderate to good yields (42-72%). It was proposed that the reduction of ethyl iododifluoroacetate (**48**) affords a radical, which on 1,6-addition, formed another radical species **49**. The intramolecular sequential *5-exo-dig* and *6-exo-dig* afforded **50**, which again, on *6-endo-trig* cyclization, produced the desired product **51**.

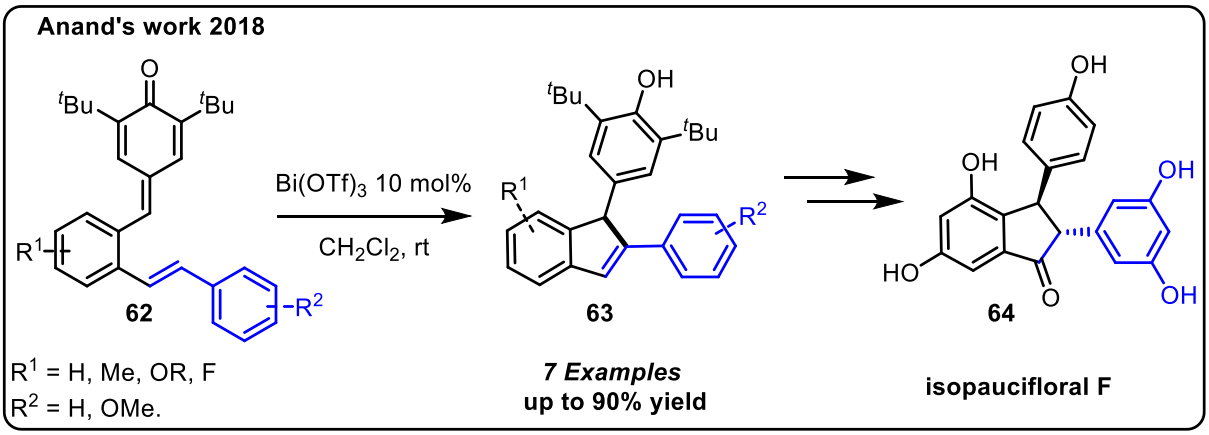
1.3 Literature reports on the synthesis of fused carbocycles

For the first time, in 1989, Angle and coworkers used *para*-quinone methides **54** to produce five-membered (**55**), six-membered (**57**), and seven-membered (**56**) carbocycles through intramolecular cyclization (Scheme 13).[19] Allyl-silanes and *β*-keto esters functionalized *p*-QMs were taken as starting materials, and $ZnCl_2$ was utilized as a catalyst. In order to build more complex fused rings, Lewis acids were employed with some other *p*-QMs (**58**) containing aryl and vinyl functionalities. Despite the fact that there have been numerous reports on the construction of spiro carbocycles in the recent past, there were not many attempts made in the fused carbocycles formation from *p*-QMs after Angel's work.

In 2018 Anand's group disclosed the synthesis of indene derivatives (**63**) by Bismuth-catalyzed intramolecular 1,6-conjugate hydroolifination of 2-alkenylated *p*-QMs (**62**) (Scheme 14).[20] This protocol was also elaborated to the total synthesis of isopaucifloral F (**64**).



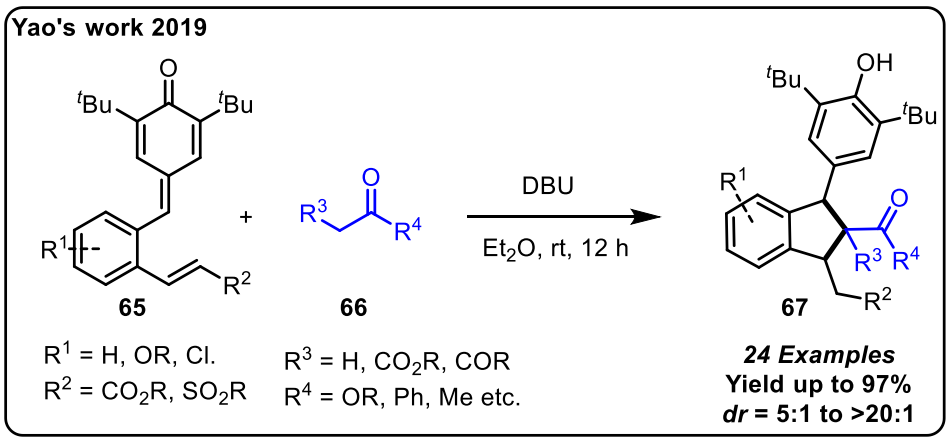
Scheme 13. Angel's approach for synthesis of various types of carbocycles



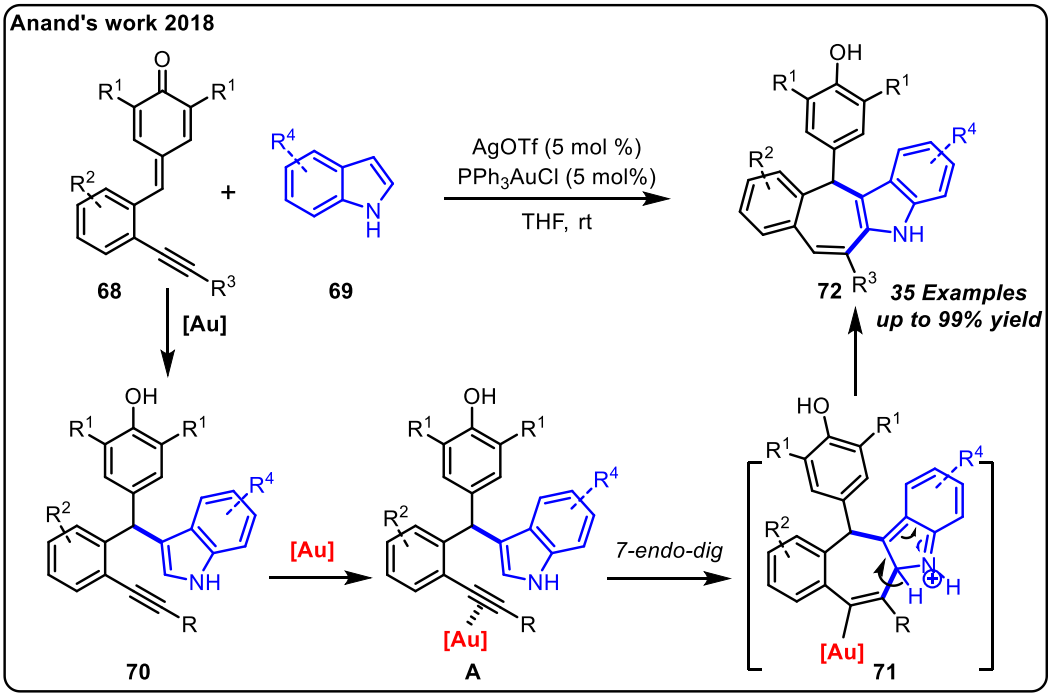
Scheme 14. The synthesis of indene and elaborated to synthesis of isopaucifloral F

Later on, in 2019, Yao's group developed a methodology for the synthesis of indane derivatives [**67**] (Scheme 15),[21] where they used functionalized biselectrophilic *p*-QMs (**65**) and 1,3 dicarbonyl molecules (**66**) with DBU as an organic base. In this transformation, the

1,3 dicarbonyl molecule **66** initially reacts with **65** in a 1,6-fashion followed by intramoleculat 1,4-addition with enone system to generate the indane derivatives (**67**).



Scheme 15. The synthesis of highly substituted indane derivatives



Scheme 16. The synthesis of cyclohepta[*b*]indoles from 2-phenyl alkynylated *p*-QMs

In 2018, Anand's group developed a methodology for the synthesis of cyclohepta[*b*]indoles (**72**) from 2-alkenylated *p*-QMs (**68)** and indoles (**69)** in the presence of PPh_3AuCl and AgOTf (Scheme 16).[22] The anion metathesis reaction between PPh_3AuCl and AgOTf generated a cationic [Au (I)] active species, which activates the carbonyl group of **68**. Then, the 1,6-conjugate addition takes place with indole to form the adduct **70**. Then [Au(I)] species activate alkyne forms **A**, which on intramolecular 7-endo-dig cyclization converted into intermediate **71**, which on deprotonation and reductive elimination generates the product **72**.

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Part A

TfOH-catalyzed intramolecular annulation of 2-(Aryl)-phenyl-substituted *p*-quinone methides under continuous-flow to access 9-aryl fluorenes

2.1.1 Introduction:

Though fluorenone-core is often found in many biologically significant natural products,[1] its counterpart, fluorene-core, is rarely found in naturally-occurring molecules. However, many unnatural fluorene derivatives are known, which possess remarkable biological activities.[2] The 9-aryl fluorene-core includes some interesting optical and electronic properties, which have been well explored in the area of materials science. For example, many 9-arylfluorene derivatives have applications as organic dyes[3], as principal ingredients in OLEDs,[4] photovoltaic cells, etc.[5] Besides, fluorene-based organic compounds have also been used in catalysis.[6] As a result, the 9-arylfluorene core has become an essential target in recent years, and many reports have appeared in the literature for synthesizing this core. In this part of the thesis, we have used 2-(aryl)-phenyl-substituted *p*-QMs in the presence of TfOH as a catalyst and gave an intramolecular 1-6 arylation to access 9-arylfluorene derivatives. For this transformation, we have used the continuous flow microreactor technique, which is an advanced engineering alternative for lab-scale synthesis over conventional organic synthetic chemistry.[7]

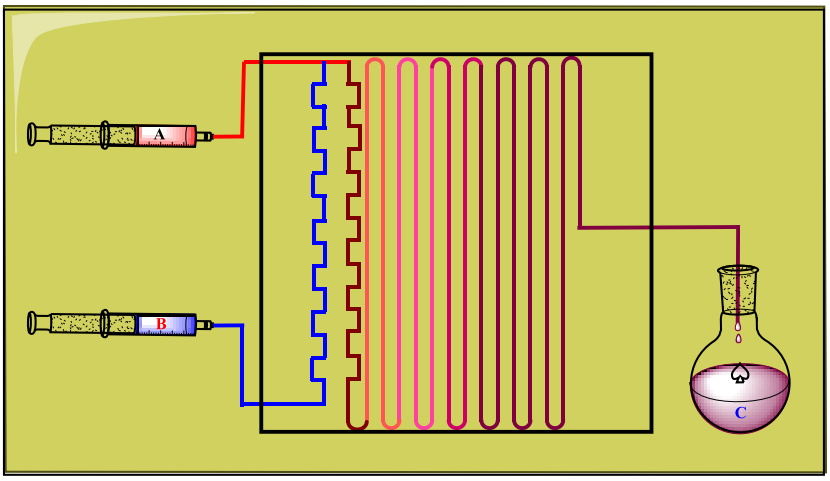


Figure 1. Continuous flow microreaction technology

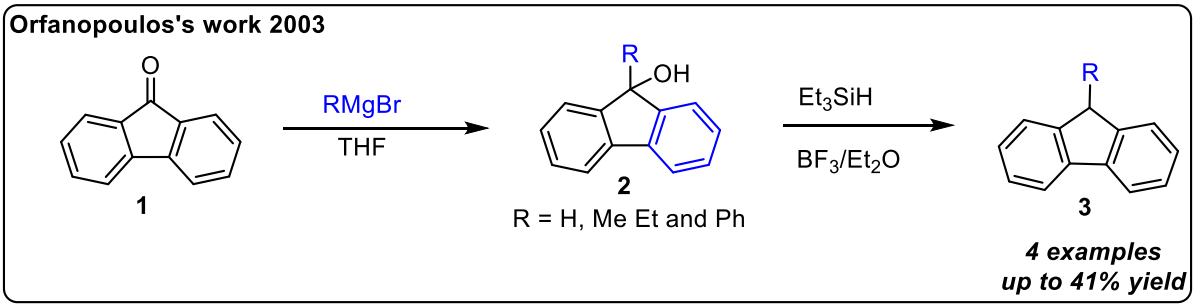
The continuous flow technique has been recently highly adopted in various industries for process development and manufacturing.[8] As one of the advantages of this technique, it is

so effective for scaling up the reaction; in batch reactors, this is the primary problem, especially when chemicals used are hazardous, toxic, explosive, or unstable intermediates formed during the reaction. For example, ozonolysis reaction is not often used in industries due to issues with handling ozone and unstable intermediates. In such cases, flow reactors are helpful as in these reactors, only a small amount of reagent is reacting at any given time. In this regard, there are few reports published for large-scale ozonolysis using a flow reactor.[9] Apart from industrial purposes, this technique is also used in academic research for developing synthetic methodologies using a microreactor. In this technique, reactions are carried out in structured micro channels with a diameter of less than 1000 µm. The reagents are continuously fed into the microreactor, and the products are continually collected from the reaction channels (Figure 1). Inert or non-reacting materials, including glass, silicon, stainless steel, ceramics, polymers, etc., are used to make microreactors. The overall heat/mass transfer in the reaction mixture rises in proportion to the smaller size of the microreactor, which improves the surface-to-volume ratio of the microchannels and facilitates adequate reagent mixing. Highly exothermic reactions and all those involving explosive or dangerous chemicals can be handled easily using this technique because only small amounts of the reaction mixture remain in the microchannels constantly.[10] Additionally, the formation of by-products in the reaction can also be controlled through this technology for the same reason. In addition, this technique has several other benefits over traditional flask chemistry, including reasonable safety control, rapid reaction times, reproducibility, etc.

2.1.2 Literature reports on the synthesis of 9-arylfluorene derivatives

Before moving to the actual thesis work, I would like to discuss some of the relevant literature on the synthesis of 9-arylfluorene derivatives.

2.1.2.1 Synthesis of 9-arylfluorenes through reduction of 9*H*-fluoren-9-ol

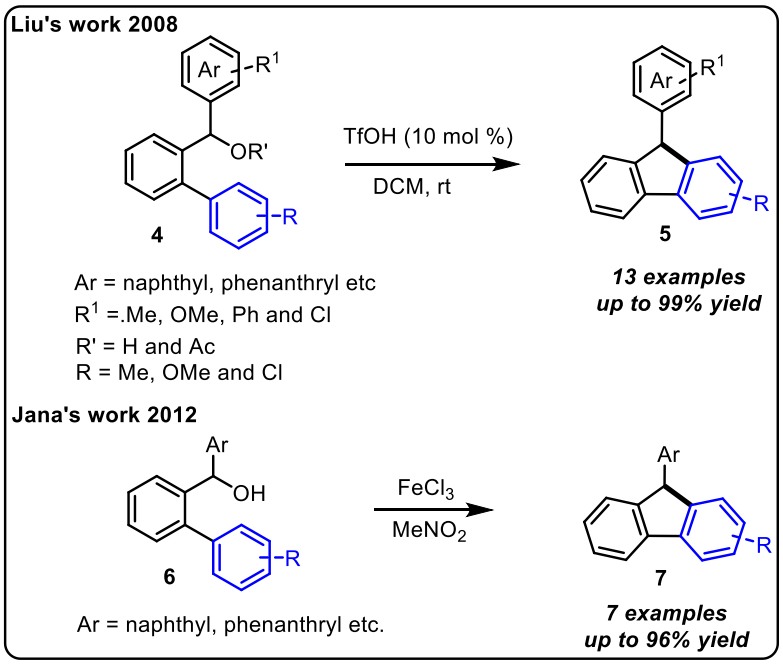


Scheme 1. Two step synthesis of 9-arylfluorenes from fluorenone

In 2003, Orfanopoulos and co-workers disclosed a two-step process for the syntheses of 9-substituted fluorenes from fluorenone (scheme 1).[11] The Grignard addition to fluorenone **1** leads to 9H-fluoren-9-ol derivatives (**2**), which could be reduced with Et_3SiH in the presence of catalytic amounts of BF_3/Et_2O, to give 9-substituted flurenes (**3**).

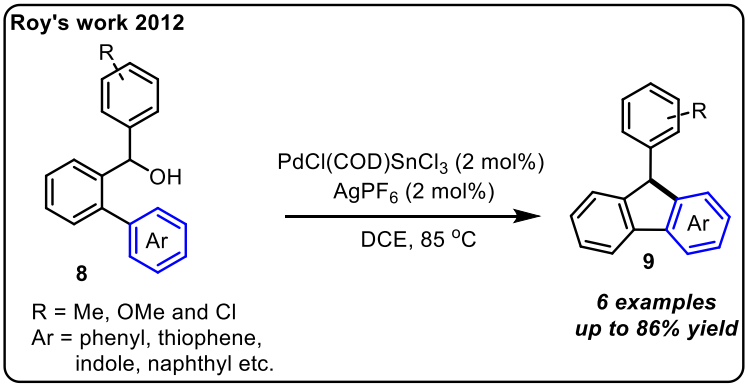
2.1.2.2 Ring-closing Friedel-Crafts reaction to access 9-arylfluorenes

In 2008, Liu's group disclosed an approach to the synthesis of 9-arylfluorene derivatives (**5**) using biaryl alcohols and acetates (**4**) in the presence of catalytic amounts of triflic acid (Scheme 2).[12a]



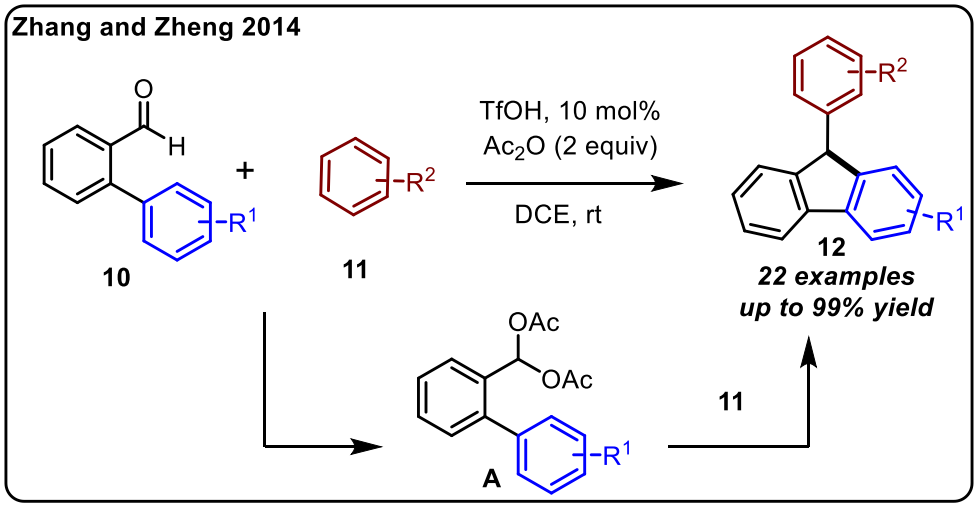
Scheme 2. Intramolecular Friedel-Craft reaction of biarylalcohols

Later, Jana's group used $FeCl_3$ as a catalyst for an intramolecular Friedel-Crafts reaction on **6** to get 9-arylfluorenes (**7**) in excellent yields (scheme 2).[12b]



Scheme 3. Pd-sn (bimetallic) catalysed intramolecular Friedel-Craft reaction

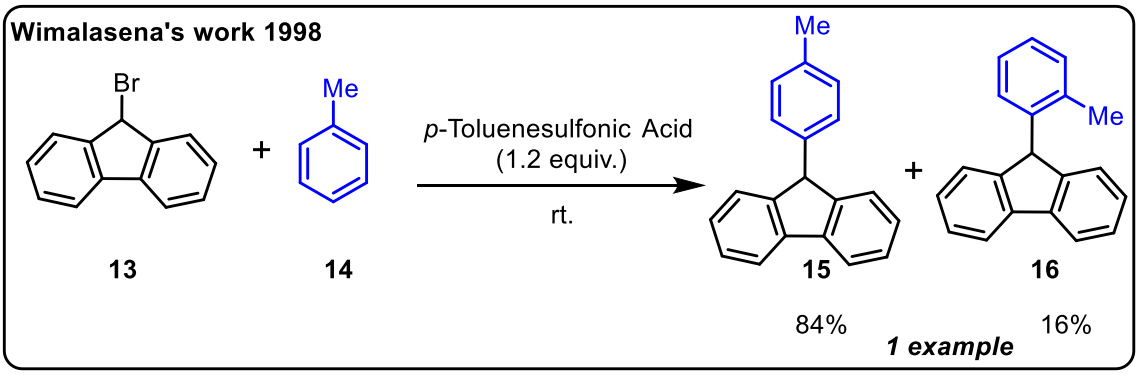
Similarly, Roy and co-workers used a combination of Pd-Sn (bimetalic) and silver catalysts for this transformation (Scheme 3).[13] Later, Zhang and Zheng described a triflic acid catalyzed Friedel-Craft reaction for the synthesis of 9-arylfluorenes [**12**] (Scheme 4). In this transformation, biaryl aldehyde **10** reacted with acetic anhydride to form a diacetate intermediate **A**, which subsequently underwent an intermolecular Friedel-Craft reaction followed by an intermolecular arylation with **11** to produce 9-arylfluorenes derivative **12**.[14]



Scheme 4. Double Friedel-Craft reaction of biaryl aldehyde using a strong acid

2.1.2.3 Synthesis of 9-arylfluorenes from 9-bromofluorenes

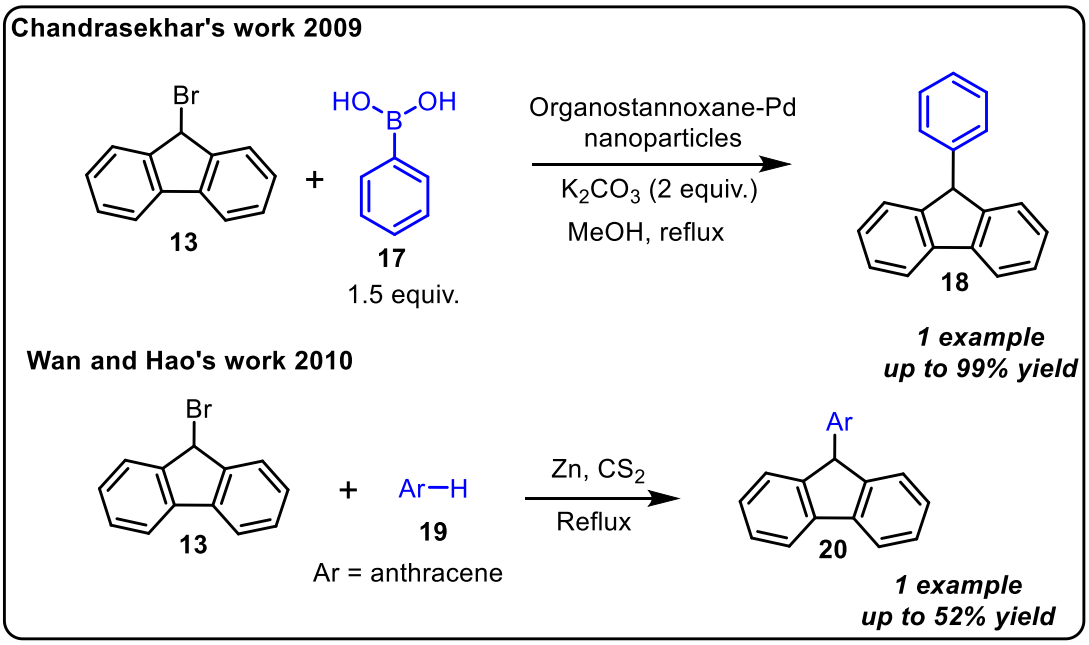
In 1998, Wimalasena's group reported a *p*-toluenesulfonic acid mediated Friedel-Crafts alkylation reaction of toluene with 9-bromofluorene **13** to obtain a mixture of *para* and *ortho* regioisomeric products **15** and **16** (scheme 5).[15]



Scheme 5. Friedel-Craft alkylation with 9-bromofluorene

Chandrashekar's group reported an organostannoxane-supported palladium nanoparticle catalyzed the Suzuki coupling reaction of 9-bromofluorene **13** with phenylboronic acid **17** to prepare 9-phenyl fluorene **18** in 99% yield.[16a] Later on, Wan and Hao also reported a zinc

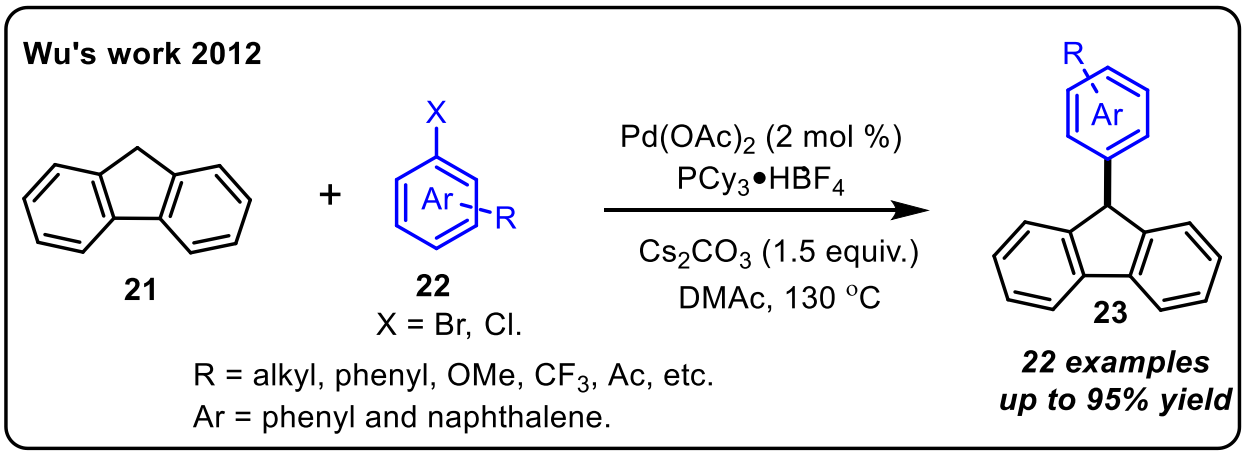
mediated radical coupling of anthracene **19** with 9-bromofluorene **13** to synthesize **20** (Scheme 6).[16b]



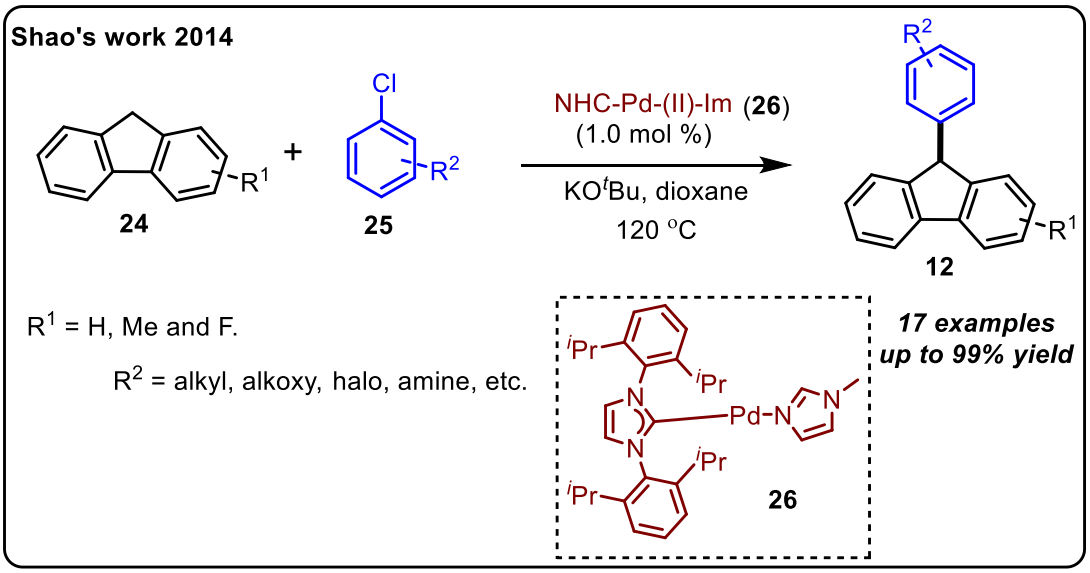
Scheme 6. Suzuki coupling and Friedel-Craft alkylation of 9-bromofluorene

2.1.2.4 Palladium-catalyzed direct C-H bond arylation of fluorene with haloarenes

In 2012, Wu's group reported a palladium-catalyzed direct C-H arylation of fluorene **21** with haloarenes (**22**) to access 9-arylfluorenes (**23**) (Scheme 7).[17] Subsequently, Shao's group reported C-H arylation of fluorenes (**24**) using NHC–palladium(II)–1-methylimidazole complex **26** as a catalyst for synthesizing 9-arylfluorene derivatives (**12**) (Scheme 8).[18]



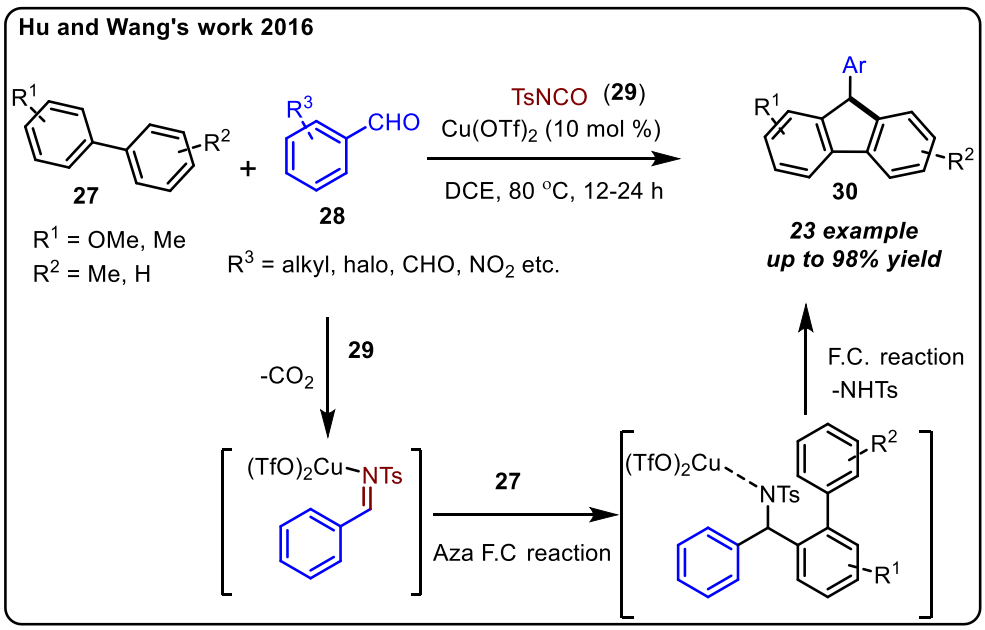
Scheme 7. Direct C-H arylation approach to the synthesis of 9-arylfluorenes



Scheme 8. Direct C-H arylation approach to the synthesis of 9-arylfluorenes

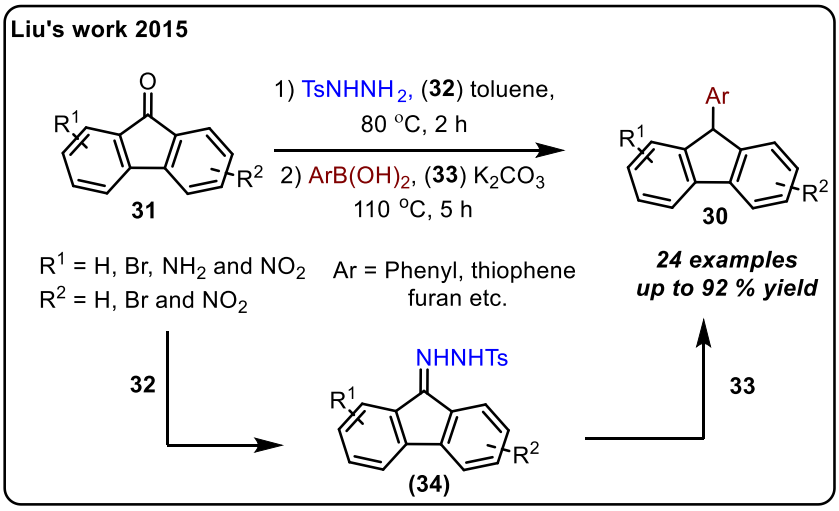
2.1.2.5. Miscellaneous reports on the synthesis of 9-arylfluorenes.

Hu and Wang reported a tosyl-isocyanate-mediated three-step tandem synthesis of 9-arylfluorene derivatives (**30**) using $Cu(OTf)_2$ as a catalyst. In this transformation, the reaction of tosyl isocyanate **29** and aryl aldehyde **28** led to tosyl imine through [2+2] addition followed by CO_2 liberation (Scheme 9).[19] Then, electron-rich biaryl **27** on aza-Friedel-Craft reaction with activated imine followed by intramolecular Friedel-Craft reaction finally led to 9-arylfluorenes (**30**).

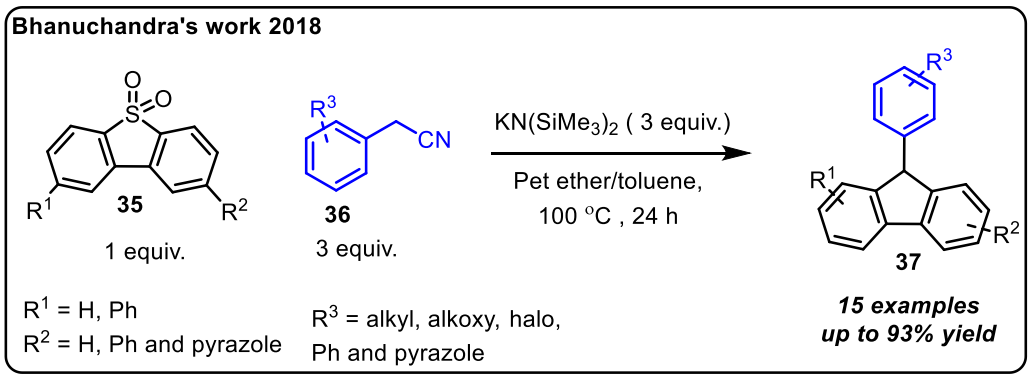


Scheme 9. Tosyl isocyanate-mediated three step tandom synthesis of 9-arylfluorene derivatives

Liu's group reported a metal-free approach to the synthesis of 9-aryl fluorenes (**30**) by reductive coupling of arylboronic acids (**33**) with *in situ* formed *N*-tosylhydrazones (**34**) from fluorenone (**31**) and tosylamine (**32**) (Scheme 10).[20] In 2018, Bhanuchandra's group disclosed an effective strategy for the synthesis of 9-arylfluorene derivatives (**38**) by KHMDS mediated S_NAr reaction between dibenzothiophene dioxides (**36**) and benzyl nitriles (**37**) [Scheme 11].[21]



Scheme 10. Metal-free approach for the synthesis of 9-arylfluorenes



Scheme 11. Metal free S_NAr reaction of benzyl nitrile and dibenzothiophene dioxide

2.1.3 Background:

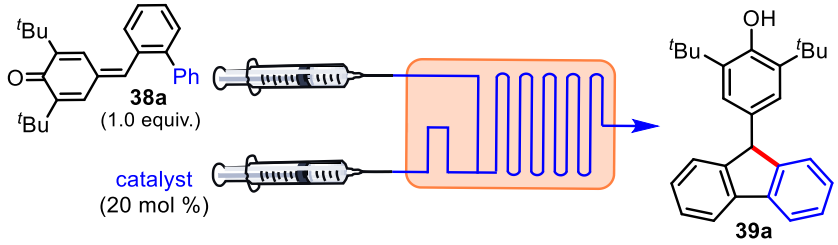
While exploring the *p*-quinone methides (*p*-QMs) as synthons to access a wide range of carbocycles, heterocycles and other triarylmethane derivatives,[22] we envisioned that 2-(aryl)-phenyl-substituted *p*-QMs could potentially serve as precursors for the construction of fluorene core. Herein, we report an acid-catalyzed intramolecular annulation of 2-(aryl)-phenyl-substituted *p*-QMs leading to a variety of 9-aryl-substituted fluorene derivatives. Since the microreaction technique has some inherent advantages over the conventional batch

processes, we have decided to develop this methodology under continues-flow conditions using a microreactor.

2.1.4 Results and discussion:

The optimization studies were carried out using a microreactor having a total volume of 100 µL, and the results are shown in Table 1.

Table1. Optimization Studies[a]



entry	catalyst	combined flow rate of **38a** & cat (µL/min)	solvent	Yield of **39a** [%][b]
1	CSA	40	CH_2Cl_2	NR
2	HCO_2H	40	CH_2Cl_2	NR
3	TFA	40	CH_2Cl_2	29
4	TfOH	40	CH_2Cl_2	75
5	**TfOH**	**30**	**CH_2Cl_2**	**83**
6	TfOH	20	CH_2Cl_2	84
7	TfOH	30	DCE	82
8	TfOH	30	PhMe	NR
9	TfOH	30	MeCN	trace
10	TfOH	30	DMF	trace
11[c]	TfOH	30	CH_2Cl_2	72
12[d]	TfOH	30	CH_2Cl_2	59
13	---	30	CH_2Cl_2	NR
14[e]	TfOH	30	CH_2Cl_2	82
15[f]	TfOH	30	CH_2Cl_2	74

[a]Reaction conditions: Reactions were carried out with 0.08 mmol of **38a** at 25 ˚C. [b] Yields reported are isolated yields. [c] 15 mol % of TfOH was used. [d] 10 mol % of TfOH was used. [e] The reaction was performed in 1.0 g (2.7 mmol) scale **38a** under continuous-flow method**.** [f] The reaction was performed in 1.0 g (2.7 mmol) scale of **38a** under batch process. (TfOH = Trifluoromethane sulphonic acid, TFA = Trifluoroacetic acid; CSA = Camphor sulfonic acid; 1,2-DCE = 1,2-Dichloroethane; DMF = Dimethylformamide; NR = No reaction).

In all the experiments, the chosen model substrate **38a** (0.081 mmol dissolved in 1 mL of solvent) and the acid catalyst (20 mol% in 1 mL of solvent) were taken in separate syringes, and these two solutions were injected into the microreactor at specified flow rates using syringe pumps. Initially, a couple of experiments were performed using **38a** (0.081 mmol dissolved in 1 mL of CH_2Cl_2) and acid catalyst (CSA or formic acid) [20 mol% in 1 mL of CH_2Cl_2]. These two solutions were injected at the combined flow rate of 40 µL/min (residence time = 2.5 min) through the microreactor maintained at 25 ^oC. However, the expected product **39a** was not observed (entries 1 & 2). When TFA was used as a catalyst, the required product **39a** was isolated in 29% yield (entry 3). The isolated product **39a** was comprehensively characterised by ^1H NMR, ^{13}C NMR, IR spectroscopy, and mass spectrometry. In ^1H NMR (see figure 2) presence of two singlets at δ 5.10 ppm and δ 5.00 ppm is due to the phenolic OH and C-9 proton respectively. In ^{13}C NMR (see figure 3), the presence of C-9 carbon peak is shown at δ 54.5 ppm and the absence of carbonyl peak from **38a** confirmed the formation of **39a**. The formation of OH in product **39a** was also confirmed by IR as peak at 3637 cm^{-1} was observed. Delightfully, when the same reaction was carried out in the presence of 20 mol% of triflic acid, the desired product **39a** was obtained in 75% yield (entry 4). Encouraged by this result, further optimization studies were carried out at different flow rates using triflic acid as a catalyst. When the flow rate was decreased to 30 µL/min (residence time = 3.3 min), **39a** was isolated in 83% yield (entry 5). However, there was only an incremental increase in the yield of **39a**, when the flow rate was further decreased to 20 µL/min [residence time = 5.0 min] (entry 6). Later, other solvents were also screened for this transformation. When the reaction was performed in 1,2-DCE, **39a** was isolated in 82% yield (entry 7). In the case of toluene, the reaction did not occur as the starting material was recovered unreacted (entry 8). Furthermore, MeCN and DMF were also screened; but in both cases, only traces of **39a** were observed (entries 9 &10). When the catalyst loading was decreased to 15 mol% or 10 mol%, **39a** was isolated in 72% and 59%, yields, respectively (entries 11 & 12). It was found that the reaction did not take place in the absence of the acid catalyst (entry 13); this observation clearly indicates that an acid catalyst is required for this transformation.

To compare the continuous-flow reaction with the batch process, a gram scale reaction was performed under both conditions, and product **39a** was isolated in 82 and 74% yield, respectively (entries 14 &15). These gram-scale experiments show that the continuous-

flow reaction is more advantageous than the batch process, as the product yield was much better, and no decomposition of **38a**/**39a** was observed.

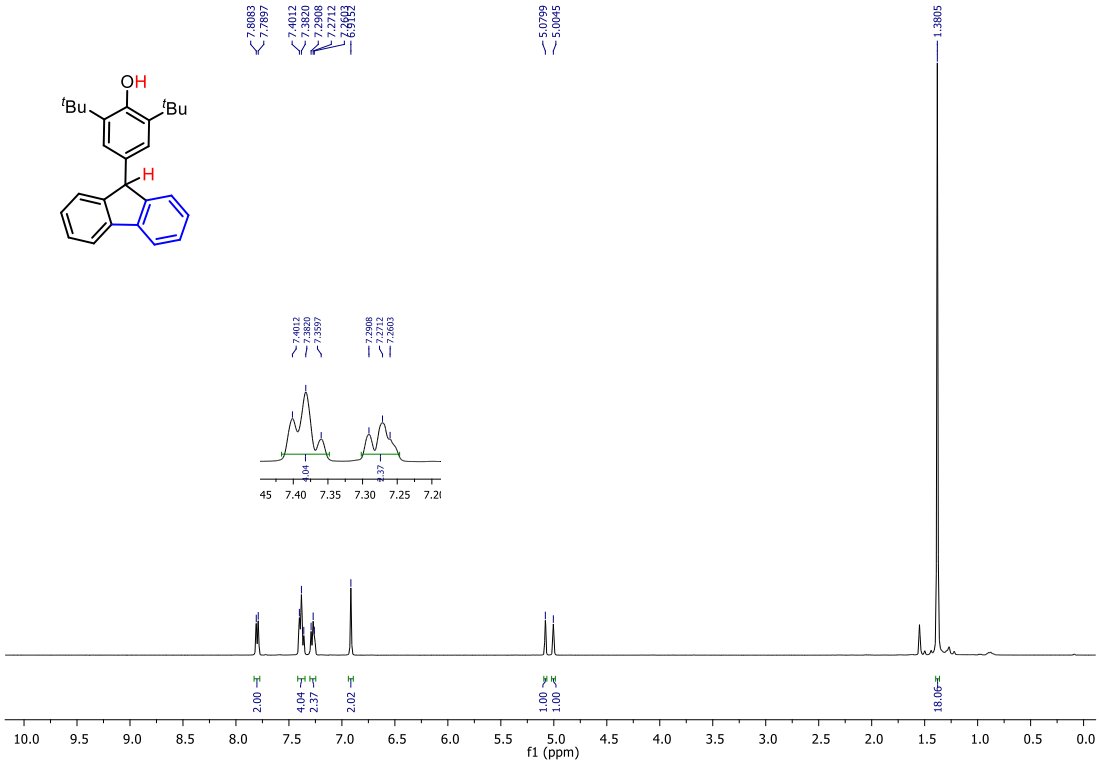


Figure 2. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **39a**

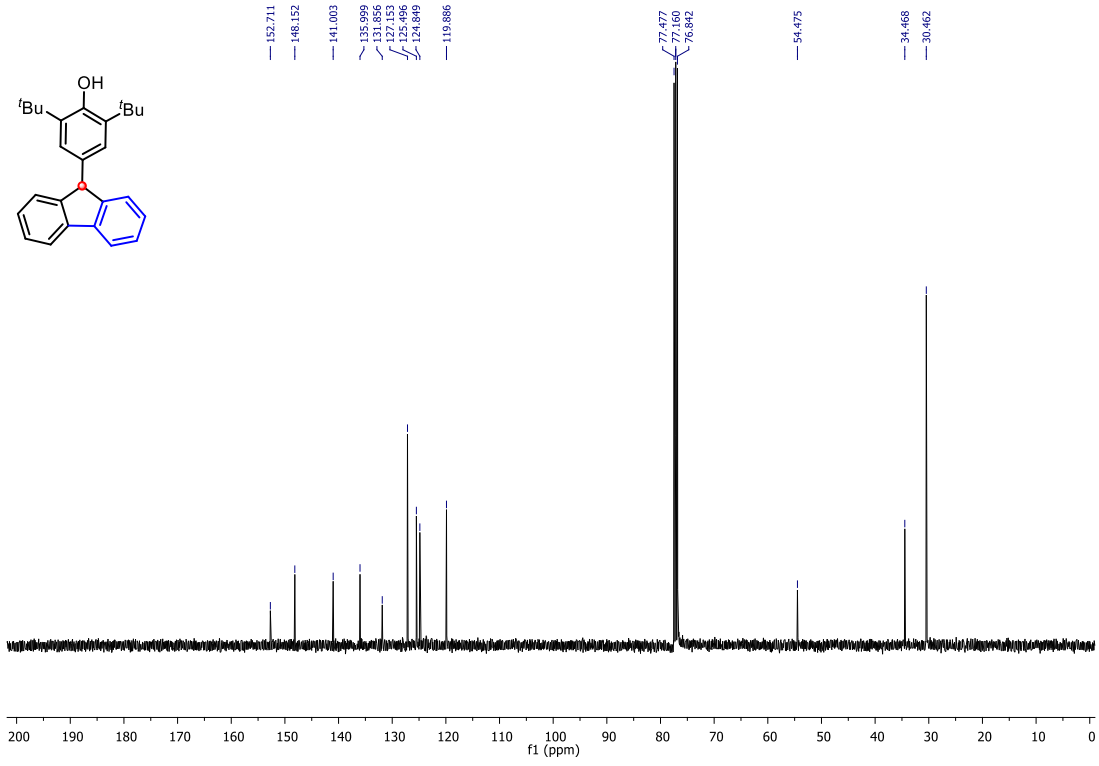
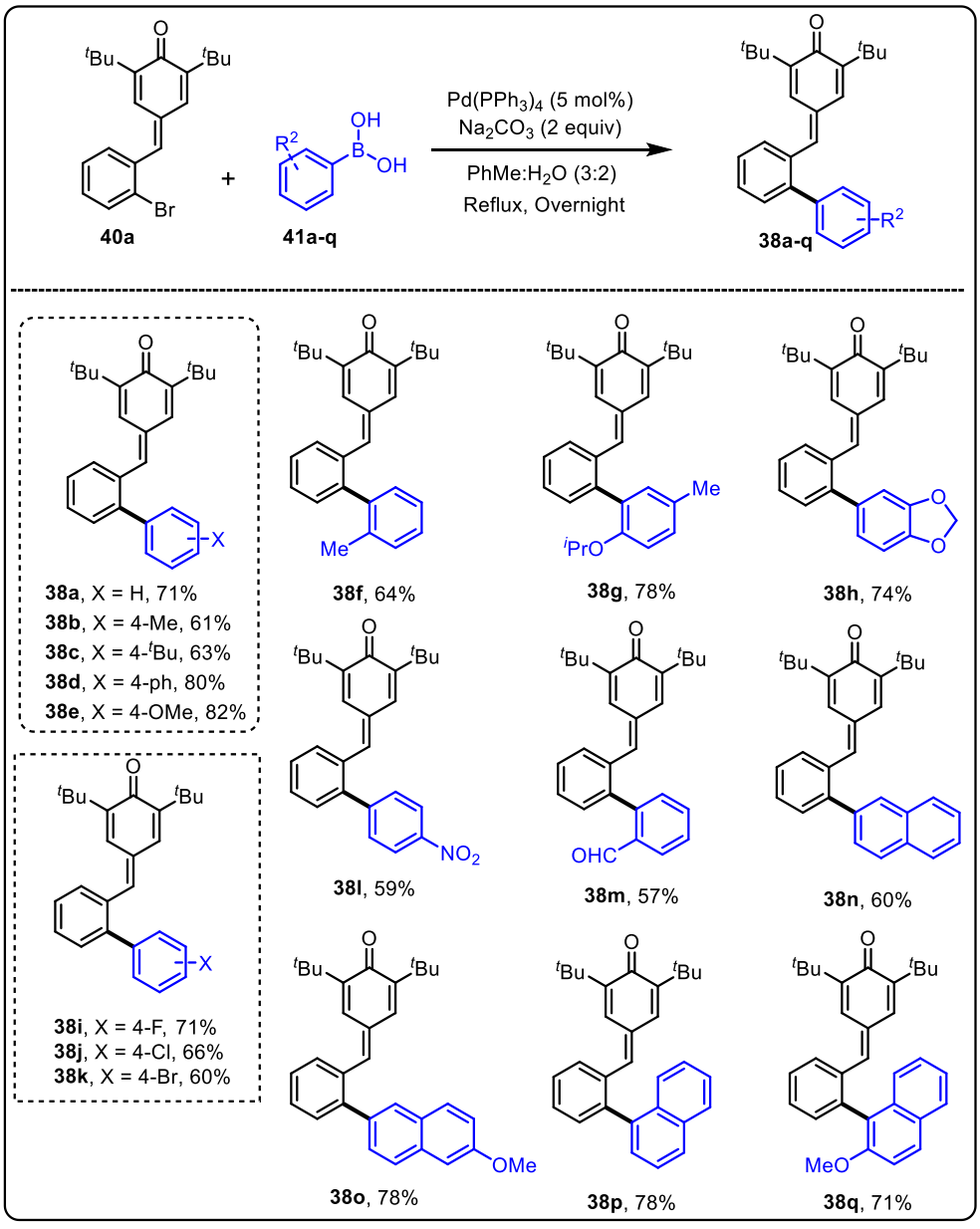


Figure 3. ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) spectrum of compound **39a**

In most optimization studies carried out under continuous-flow, only a small quantity of unreacted **39a** was observed along with product **39a** after the work-up. Since the continuous-flow reaction was cleaner and more effective when compared to the batch process, further elaborations and substrate scope studies have been carried out under continuous-flow conditions.

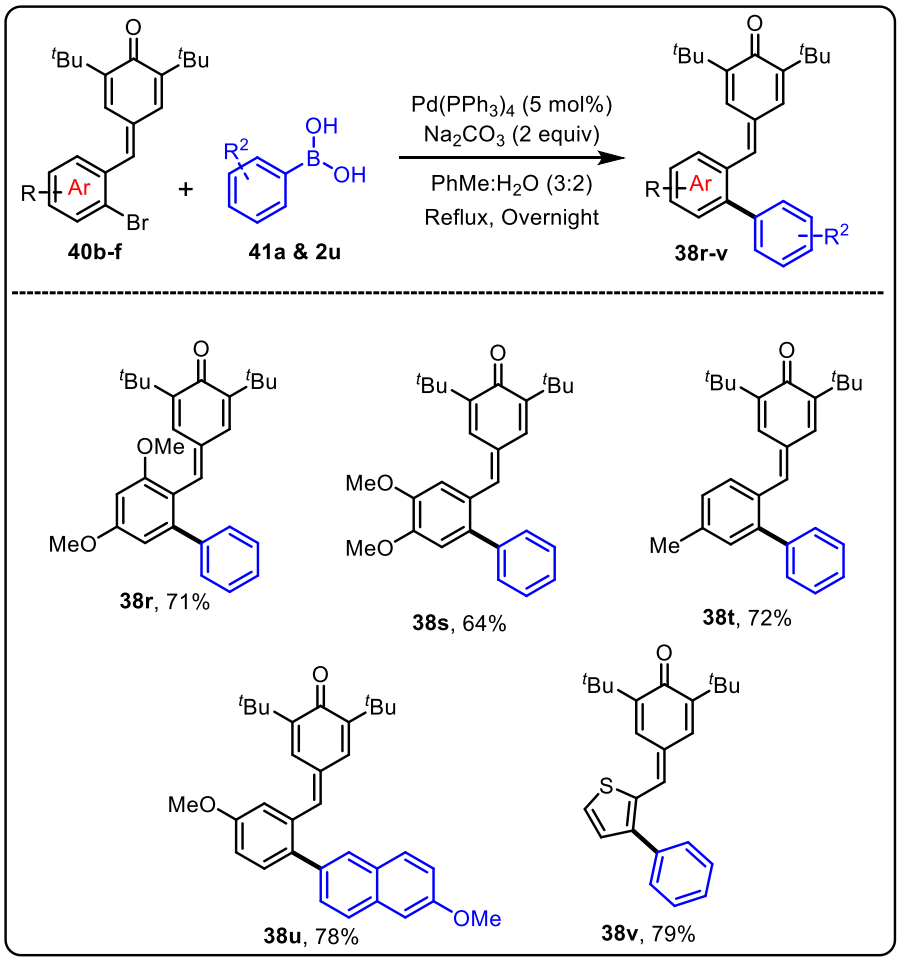
The 2-(aryl)-phenyl substituted *p*-QMs (**38a-v**) used in this study were prepared by the Suzuki coupling between a wide range of 2-bromo *p*-QMs (**40a-f**) and boronic acids (**41a-q**) as shown in Table 2 and 3.

Table 2. The synthesis of 2-(aryl)-phenyl substituted *p*-QMs



[a] Reactions were carried out in 0.80 mmol of **40a**. Yields reported are isolated yields.

Table 3. The synthesis of 2-(aryl)-phenyl substituted *p*-QMs

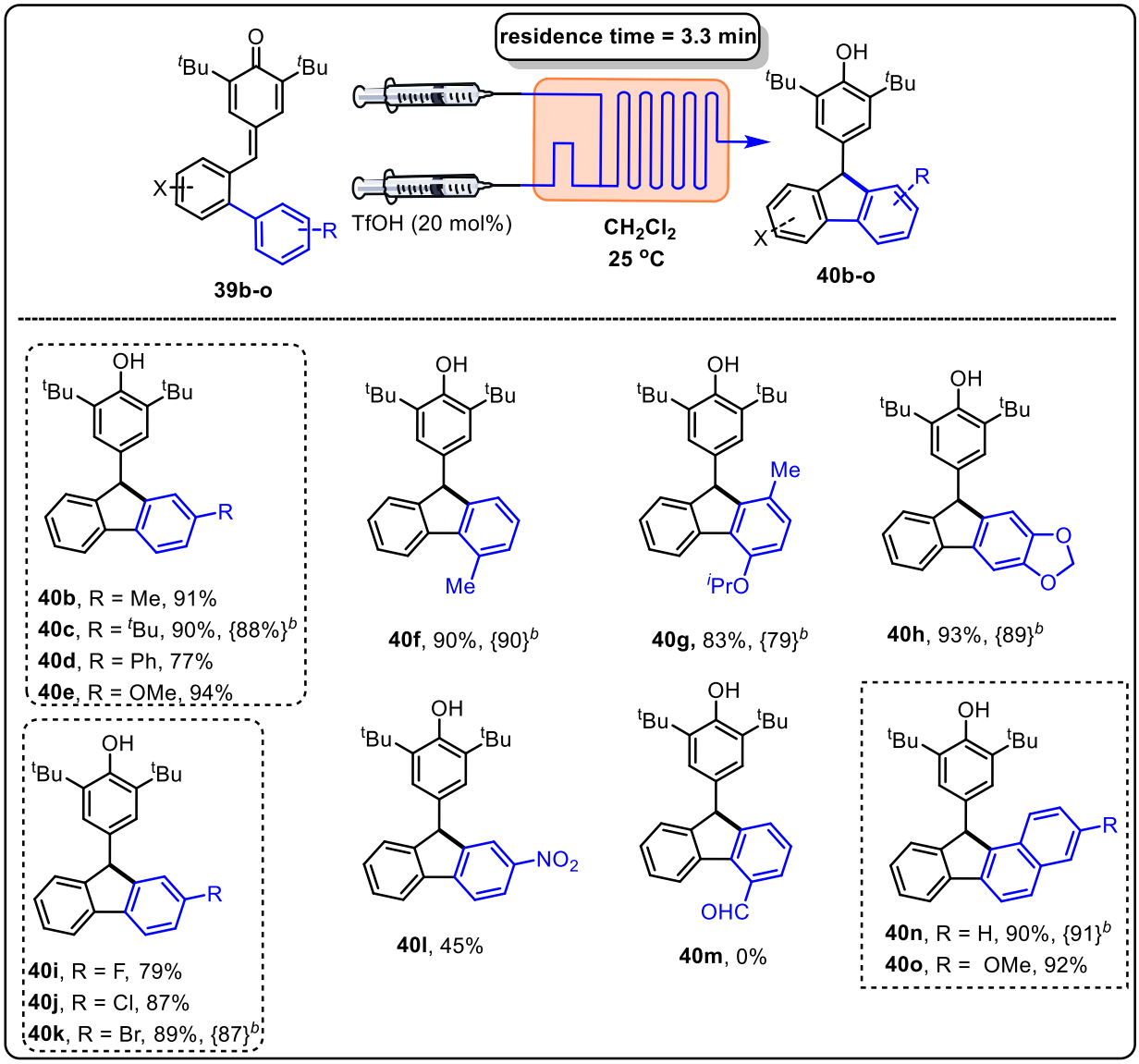


[a] Reactions were carried out in 0.69-0.79 mmol of **40b-f**. Yields reported are isolated yields.

With the optimal reaction conditions (Entry 5, Table 1) in hand, this methodology's substrate scope and limitations were examined (Chart 1 & Chart 2). It is evident from Chart 1 that this method worked very well for the 2-(aryl)-phenyl substituted *p*-QMs, especially in the cases of electron-rich aryl-substituted *p*-QMs (**38b-h**), and the expected products **39b-h** were isolated in the range of 77-93% yields. 2-(Halo-aryl)-phenyl-substituted *p*-QMs (**38i-k**) were also underwent cyclization under the standard conditions, and the corresponding products **39i-k** were obtained in the range of 79-89% of isolated yields. In the case of electron-poor nitro-phenyl-substituted precursor **38l**, the optimized condition was found to be unsuitable as the formation of product **39l** was not observed. Therefore, the reaction was carried out at 70 ^{o}C in 1,2-DCE as a solvent at a combine flow rate of 10 µL/min, and the product **39r** obtained in 45% yield. But in the case of **38m,** even at higher temperature no reaction

observed. Naphthyl-substituted *p*-QMs (**38n & 38o**) also gave the respective products **39n** & **39o** in 90% and 92% yields, respectively.

Chart 1. [a]Substrate Scope

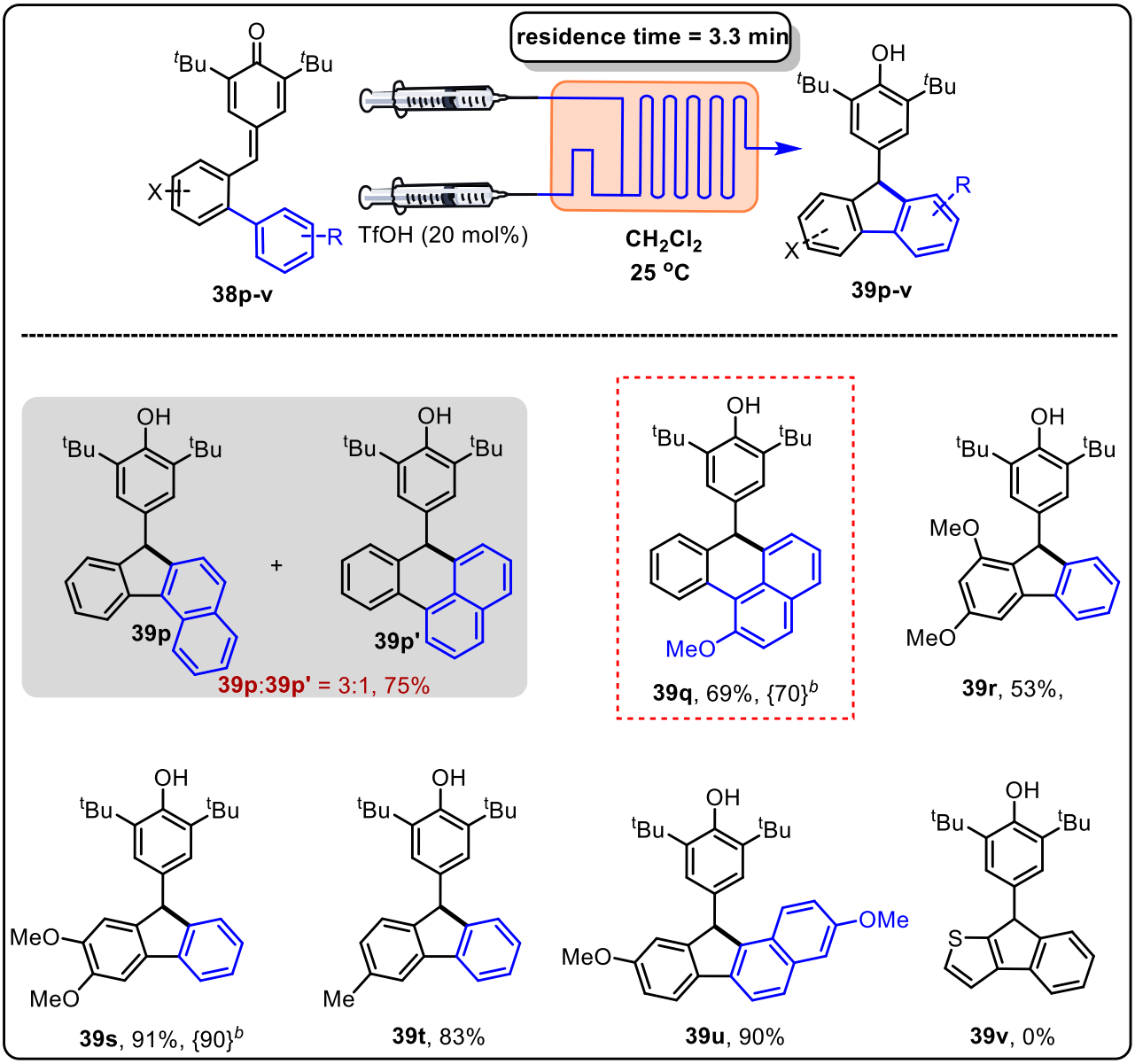


[a] Reactions were carried out in 0.067-0.078 mmol of **38b-o**. [b] Isolated yields of reaction performed under batch process. Yields reported are isolated yields.

However, in the case of **38p**, an inseparable mixture of products **39p** and **39p'** (regioisomers) was formed in a 3:1 ratio. In the case of **38q,** both *ortho* positions were blocked, giving benzo anthracene derivative **39q** in 69% yield. Other *p*-QMs, such as **38r-u,** provided the corresponding products **39s-v** in the range of 53-91% yields under the optimized conditions (Table 1, entry 5). Unfortunately, the *p*-QM **38v** [substituted with thiophene]

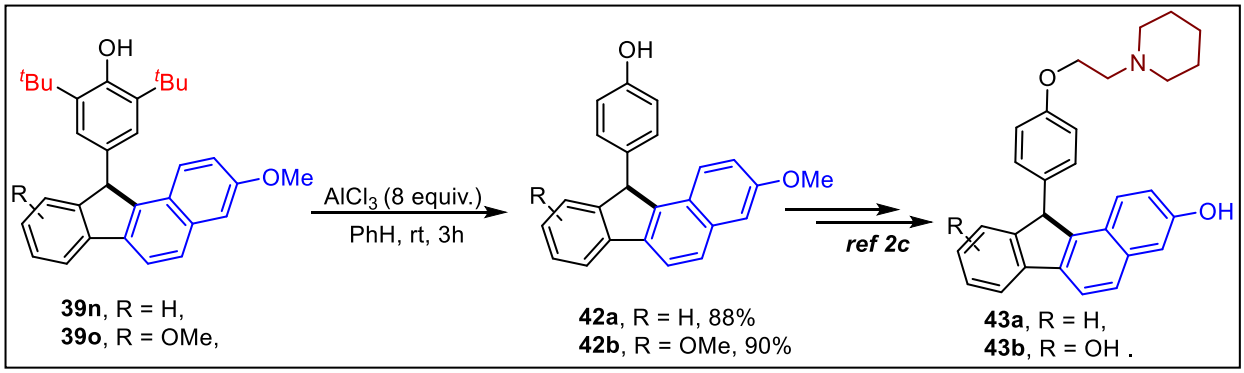
underwent decomposition during the reaction and, as a result, no product (**39v**) formation was observed in this case

Chart 2. Substrate Scope



[a] Reactions were carried out in 0.05-0.08 mmol of **38o-v**. [b] Isolated yields of reaction performed under batch process. The isomeric ratios of **39p/39p'** was calculated from the ^{1}H NMR analysis of crude mixture. Yields reported are isolated yields.

To show the synthetic utility, this protocol was further elaborated to the intermediates (**42a & 42b**) of phenolic analogues of trioxifene[2c] **43a** and **43b**, through de-*tert*-butylation of **39n** and **39o**, respectively, using excess $AlCl_3$ (Scheme 11).



Scheme 11. Synthetic Elaborations of Benzo-fused Fluorenes **39n** & **39o**

2.1.5 Conclusion:

In summary, we have established a convenient protocol for the synthesis of substituted 9-arylfluorenes in moderate to excellent yields through a TfOH-catalyzed 1,6-intramolecular annulation of 2-(aryl)-phenyl-substituted *p*-QMs. This methodology can also be used for synthesising benzo[*de*]anthracenes like **39**q using appropriate starting materials. Moreover, 11-aryl benzo[*a*]fluorene derivatives elaborate to the formal synthesis of phenolic analogues of trioxifene with better overall yield than the original paper with fewer steps.

2.1.6 Experimental Section:

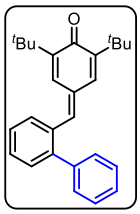
General Information. Continuous-flow reactions were performed using a FlowStart Evo B-340 instrument purchased from Future Chemistry Holding B.V. The microreactor was made up of borosilicate glass (channel width 600 μm; channel depth 500 μm), with an effective reaction volume of 100 μL. The microreactor setup has built-in syringe pumps, and all the reactions were carried out without a back pressure regulator. All other reactions were carried out under argon atmosphere employing flame-dried glassware. Most of the reagents and starting materials were purchased from commercial sources and used as such. 2-bromo *p*-quinone methide was prepared by following a literature procedure.[23] Melting points were recorded on the SMP20 melting point apparatus and are uncorrected. ^{1}H, ^{13}C and ^{19}F spectra were recorded in $CDCl_3$, DMSO-d_6 and acetone-d_6 (400, 100 and 376 MHz, respectively) on a Bruker FT-NMR spectrometer. Chemical shift (δ) values are reported in parts per million (ppm) relative to TMS, and the coupling constants (J) are reported in Hz. High resolution mass spectra were recorded on Waters Q-TOF Premier-HAB213 spectrometer. FT-IR spectra were recorded on a Perkin–Elmer FT-IR spectrometer. Thin layer chromatography was performed on Merck silica gel 60 F_{254} TLC plates. Column chromatography was carried out through silica gel (100-200 mesh) column using a mixture of EtOAc/hexane as eluent.

General procedure for the synthesis of 2-arylphenyl *p*-quinone methide derivatives (38a-v)

Procedure A (For the preparation of 38a-p, and 338r-v)

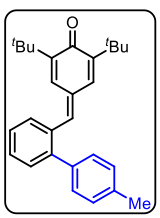
Nitrogen gas was purged through a mixture of aqueous solution of sodium carbonate (1.6 mmol, 2 equiv.) and toluene (2:3) [10 mL] for 15 min and then, to this mixture was added boronic acid [0.96 mmol, 1.2 equiv.], $Pd(PPh_3)_4$ [0.04 mmol, 5 mol%] and 4-(2-bromobenzylidene)-2,6-di-*tert*-butylcyclohexa-2,5-dienone [0.8 mmol, 1 equiv.] successively. The reaction mixture was stirred at 100 ^oC for 12 h. After completion of the reaction (monitored by TLC), the reaction mixture was diluted with ethyl acetate (30 mL) and water (10 mL). The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (20 mL × 2). The combined organic layer was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure. The residue was purified through neutral alumina column chromatography using hexane/EtOAc to obtain pure 2-arylphenyl *p*-quinone methide derivatives (**38a-p, & 38r-v**).

4-([1,1'-biphenyl]-2-ylmethylene)-2,6-di-*tert*-butylcyclohexa-2,5-dien-1-one (38a)



The reaction was performed at 0.80 mmol scale of corresponding 2-bromo phenyl substituted *p*-quinone methide**;** R_f = 0.5 (5% EtOAc in hexane); yellow solid (211 mg, 71% yield); m. p. = 152-154 ^oC; ^1H NMR (400 MHz, $CDCl_3$) δ 7.57 (s, 1H), 7.48–7.45 (m, 5H), 7.44 – 7.37 (m, 4H), 7.01 (s, 1H), 6.90 (s, 1H), 1.33 (s, 9H), 1.30 (s, 9H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 186.7, 149.4, 147.6, 143.2, 143.0, 140.4, 135.0, 134.1, 132.1, 131.8, 130.5, 130.1, 129.5, 128.5 (2C), 127.9, 127.4, 35.6, 35.2, 29.74, 29.65; FT-IR (neat): 2954, 1614, 1364, 1360, 749 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{27}H_{31}O$ $[M+H]^+$: 371.2375; found : 371.2361.

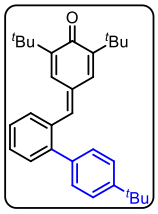
T**2,6-di-*tert*-butyl-4-((4'-methyl-[1,1'-biphenyl]-2-yl)methylene)cyclohexa-2,5-dien-1-one (38b)**



The reaction was performed at 0.80 mmol scale of corresponding 2-bromo phenyl substituted *p*-quinone methide; R_f = 0.4 (5% EtOAc in hexane); yellow solid (190 mg, 61% yield); m. p. = 137-139 ^oC; ^1H NMR (400 MHz, $CDCl_3$) δ 7.61 (s, 1H), 7.51 – 7.45 (m, 4H), 7.31 – 7.26 (m, 4H), 7.05 (s, 1H), 6.94 (s, 1H), 2.45 (s, 3H), 1.35 (s, 9H), 1.33 (s, 9H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 186.7, 149.3, 147.5, 143.5, 143.0, 137.7, 137.4, 135.1, 134.0, 132.1, 131.6, 130.5, 130.0, 129.5,

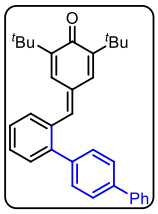
129.2, 128.6, 127.2, 35.6, 35.2, 29.7, 29.6, 21.4; FT-IR (neat): 2957, 2228, 1614, 1364, 1361, 821, 760 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{28}H_{33}O$ $[M+H]^+$: 385.2531; found : 385.2541.

2,6-di-*tert*-butyl-4-((4'-(*tert*-butyl)-[1,1'-biphenyl]-2-yl)methylene)cyclohexa-2,5-dien-1-one (38c)



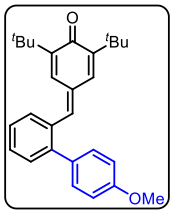
The reaction was performed at 0.80 mmol scale of corresponding 2-bromo phenyl substituted *p*-quinone methide**;** R_f = 0.4 (5% EtOAc in hexane); yellow solid (214 mg, 62% yield); m. p. = 128-130 ^oC; ^1H NMR (400 MHz, $CDCl_3$) δ 7.57 (s, 1H), 7.49 – 7.47 (m, 4H), 7.46 – 7.43 (m, 2H), 7.32 (d, *J* = 7.5 Hz, 2H), 7.08 (s, 1H), 6.94 (s, 1H), 1.38 (s, 9H), 1.33 (s, 9H), 1.32 (s, 9H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 186.7, 150.9, 149.3, 147.4, 143.7, 142.9, 137.3, 135.1, 134.0, 132.2, 131.7, 130.6, 129.8, 129.4, 128.6, 127.1, 125.4, 35.6, 35.2, 34.8, 31.5, 29.74, 29.66; FT-IR (neat): 2956, 1613, 1360, 1274, 764, 748 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{31}H_{39}O$ $[M+H]^+$: 427.3001; found : 427.2993.

4-([1,1':4',1''-terphenyl]-2-ylmethylene)-2,6-di-*tert*-butylcyclohexa-2,5-dien-1-one (38d)



The reaction was performed at 0.80 mmol scale of corresponding 2-bromo phenyl substituted *p*-quinone methide**;** R_f = 0.3 (5% EtOAc in hexane); yellow solid (287 mg, 80% yield); m. p. = 182-184 ^oC; ^1H NMR (400 MHz, $CDCl_3$) δ 7.71 – 7.68 (m, 4H), 7.62 (s, 1H), 7.56 – 7.52 (m, 3H), 7.49 – 7.47 (m, 5H), 7.41 – 7.38 (m, 1H), 7.09 (s, 1H), 7.00 (s, 1H), 1.36 (s, 9H), 1.33 (s, 9H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 186.7, 149.4, 147.6, 143.2 142.6, 140.6, 140.5, 139.3, 135.0, 134.0, 132.2, 131.8, 130.5, 130.46, 129.5 129.0, 128.5, 127.7, 127.4, 127.2, 127.1, 35.6, 35.2, 29.7, 29.65; IR (neat): 2961, 1613, 1275, 1265, 751 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{33}H_{35}O$ $[M+H]^+$: 447.2688; found : 447.2701.

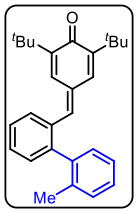
2,6-di-*tert*-butyl-4-((4'-methoxy-[1,1'-biphenyl]-2-yl)methylene)cyclohexa-2,5-dien-1-one (38e)



The reaction was performed at 0.80 mmol scale of corresponding 2-bromo phenyl substituted *p*-quinone methide**;** R_f = 0.5 (5% EtOAc in hexane); yellow solid (263 mg, 82% yield); m. p. = 183-185 ^oC; ^1H NMR (400 MHz, $CDCl_3$) δ 7.59 (s, 1H), 7.49 – 7.41 (m, 4H), 7.31 (d, *J* = 7.4 Hz, 2H), 7.02 (s, 1H), 8.00 (d, *J* = 7.5 Hz, 2H), 6.92 (s, 1H), 3.88 (s, 3H), 1.33 (s, 9H), 1.32 (s, 9H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 186.7, 159.5, 149.3, 147.5, 143.6, 142.7, 135.1 134.0, 132.7,

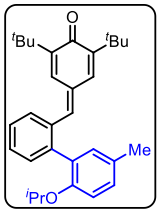
132.1, 131.6, 131.2, 130.4, 129.5, 128.6, 127.0, 113.9, 55.5, 35.6, 35.2, 29.7, 29.6; IR (neat): 2955, 1612, 1361, 1249, 763 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{28}H_{31}O_2$ $[M-H]^-$: 399.2324; found : 399.2338.

2,6-di-*tert*-butyl-4-((2'-methyl-[1,1'-biphenyl]-2-yl)methylene)cyclohexa-2,5-dien-1-one (38f)



The reaction was performed at 0.80 mmol scale of corresponding 2-bromo phenyl substituted *p*-quinone methide**;** R_f = 0.4 (5% EtOAc in hexane); yellow solid (199 mg, 64% yield); m. p. = 106-108 ^oC; ^1H NMR (400 MHz, $CDCl_3$) δ 7.52 – 7.49 (m, 2H), 7.48 – 7.45 (m, 2H), 7.35 – 7.24 (m, 4H), 7.14 (d, *J* = 7.4 Hz, 1H), 6.78 (d, *J* = 6.1 Hz, 2H), 2.07 (s, 3H),1.32 (s, 9H), 1.28 (s, 9H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 186.8, 149.4, 147.5, 143.1, 142.3, 140.1, 136.3, 135.0, 134.7, 131.9, 131.5, 130.6, 130.3, 130.1, 129.1, 128.3, 128.0, 127.3, 125.8, 35.6, 35.1, 29.7, 29.6, 20.3; FT-IR (neat): 2956, 1614, 1455, 1361, 757 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{28}H_{33}O$ $[M+H]^+$: 385.2531; found : 385.2545.

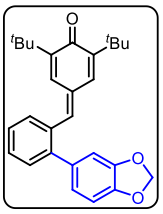
2,6-di-*tert*-butyl-4-((2'-isopropoxy-5'-methyl-[1,1'-biphenyl]-2-yl)methylene)cyclohexa-2,5-dien-1-one (38g)



The reaction was performed at 0.80 mmol scale of corresponding 2-bromo phenyl substituted *p*-quinone methide**;** R_f = 0.4 (5% EtOAc in hexane); gummy orange solid (277 mg, 78% yield); ^1H NMR (400 MHz, $CDCl_3$) δ 7.54 (s, 1H), 7.46 – 7.40 (m, 3H), 7.38 – 7.36 (m, 1H), 7.15 (d, *J* = 8.3 Hz, 1H), 7.04 (s, 1H), 7.00 (s, 1H), 6.85 (s, 1H), 6.83 (d, *J* = 8.4 Hz, 1H), 4.27 (sept, *J* = 6.0 Hz, 1H), 2.34 (s, 3H), 1.32 (s, 9H), 1.29 (s, 9H) 1.02 (d, *J* = 6.0 Hz, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 186.7, 153.1, 148.8, 147.3, 144.4, 140.6, 135.4, 135.2, 132.3, 131.3, 131.1, 130.9, 130.4, 129.7 (2C), 129.1, 128.9, 127.0, 114.1, 70.2, 35.5, 35.1, 29.7, 29.6, 22.3, 20.6; FT-IR (neat): 2957, 1614, 1497, 1360, 1258, 765 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{31}H_{39}O_2$ $[M+H]^+$: 443.2950; found : 443.2966.

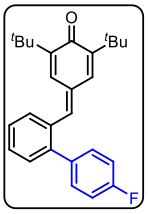
4-(2-(benzo[*d*][1,3]dioxol-5-yl)benzylidene)-2,6-di-*tert*-butylcyclohexa-2,5-dien-1-one (38h)

The reaction was performed at 0.80 mmol scale of corresponding 2-bromo phenyl substituted *p*-quinone methide**;** R_f= 0.2 (5% EtOAc in hexane); yellow solid (246 mg, 74% yield); m. p. = 200-202 ^oC; ^1H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, *J* = 1.6 Hz, 1H), 7.47 – 7.40 (m, 4H), 7.02 (s, 1H), 6.92 (d, *J* = 1.8 Hz, 1H), 6.89 – 6.86 (m, 2H), 6.81 (dd, *J* = 7.9, 0.92 Hz, 1H),



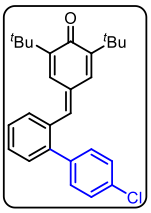
6.03 (s, 2H), 1.32 (s, 9H), 1.31 (s, 9H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 186.7, 149.4, 147.8, 147.6, 147.5, 143.1, 142.7, 135.0, 134.3, 134.1, 132.1, 131.7, 130.4, 129.4, 128.5, 127.2, 124.0, 110.3, 108.3, 101.4, 35.6, 35.2, 29.70, 29.65; FT-IR (neat): 2957, 2228, 1614, 1470, 1361, 842 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{28}H_{29}O_3$ $[M-H]^-$: 413.2117; found : 413.2134.

2,6-di-*tert*-butyl-4-((4'-fluoro-[1,1'-biphenyl]-2-yl)methylene)cyclohexa-2,5-dien-1-one (38i)



The reaction was performed at 0.80 mmol scale of corresponding 2-bromo phenyl substituted *p*-quinone methide**;** R_f = 0.4 (5% EtOAc in hexane); orange solid (223 mg, 71% yield); m. p. = 146-148 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (s, 1H), 7.48 – 7.46 (m, 4H), 7.36–7.33 (m, 2H), 7.16 – 7.12 (m, 2H), 7.00 (s, 1H), 6.90 (s, 1H), 1.33 (s, 9H), 1.32 (s, 9H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 186.7, 162.7 (d, J_{C-F} = 246.1 Hz), 149.5, 147.8, 142.7, 141.9, 136.3 (d, J_{C-F} = 3.2 Hz), 134.9, 134.1, 132.1 (d, J_{C-F} = 10.2 Hz), 131.6 (d, J_{C-F} = 8.1 Hz), 130., 129.5, 128.3, 127.5, 115.6, 115.4, 35.6, 35.2, 29.7, 29.6; ^{19}F NMR (376 MHz, $CDCl_3$) δ -114.3; IR (neat): 2956, 1613, 1551, 1470, 1254, 762 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{27}H_{30}FO$ $[M+H]^+$: 389.2281; found : 389.2299.

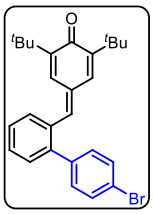
2,6-di-*tert*-butyl-4-((4'-chloro-[1,1'-biphenyl]-2-yl)methylene)cyclohexa-2,5-dien-1-one (38j)



The reaction was performed at 0.80 mmol scale of corresponding 2-bromo phenyl substituted *p*-quinone methide**;** R_f = 0.6 (5% EtOAc in hexane); yellow solid (215 mg, 66% yield); m. p. = 156-158 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (s, 1H), 7.50 – 7.46 (m, 4H), 7.42 (d, *J* = 8.3 Hz, 2H), 7.31 (d, *J* = 8.1 Hz, 2H), 7.00 (s, 1H), 6.90 (s, 1H), 1.33 (s, 9H), 1.32 (s, 9H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 186.7, 149.5, 147.8, 142.5, 141.7, 138.7, 134.8, 134.1, 134.0, 132.2, 132.1, 131.3, 130.3, 129.5, 128.7, 128.3, 127.7, 35.6, 35.2, 29.7, 29.6; IR (neat): 2956, 1550, 1468, 1383, 1090, 762 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{27}H_{30}ClO$ $[M+H]^+$: 405.1985; found : 405.1979.

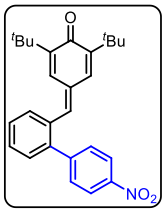
4-((4'-bromo-[1,1'-biphenyl]-2-yl)methylene)-2,6-di-*tert*-butylcyclohexa-2,5-dien-1-one (38k)

The reaction was performed at 0.80 mmol scale of corresponding 2-bromo phenyl substituted *p*-quinone methide**;** R_f = 0.6 (5% EtOAc in hexane); yellow solid (218 mg, 60% yield); m. p. = 149-151 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, *J* = 7.8 Hz, 2H), 7.54 (s, 1H), 7.50 –



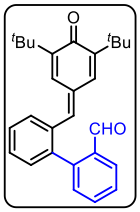
7.44 (m, 4H), 7.26 – 7.24 (m, 2H), 7.00 (s, 1H), 6.91 (s, 1H), 1.33 (s, 9H), 1.32 (s, 9H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 186.7, 149.6, 147.8, 142.4, 141.7, 139.2, 134.8, 133.9, 132.2, 132.1, 131.64, 131.6, 130.3, 129.5, 128.3, 127.8, 122.3, 35.6, 35.2, 29.7, 29.6; IR (neat): 2958, 1613, 1467, 1360, 1003, 758 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{27}H_{30}BrO$ $[M+H]^+$: 449.1480; found : 449.1464.

2,6-di-*tert*-butyl-4-((4'-nitro-[1,1'-biphenyl]-2-yl)methylene)cyclohexa-2,5-dien-1-one (38l)



The reaction was performed at 0.80 mmol scale of 2-bromo *p*-quinone methide; R_f = 0.2 (5% EtOAc in hexane); orange gummy solid (198 mg, 59% yield); m. p. = 207-209 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (d, *J* = 8.7 Hz, 2H), 7.56 (m, 1H), 7.54 – 7.52 (m, 4H), 7.49 – 6.47 (m, 2H), 6.88 (s, 1H), 6.87 (d, *J* = 2.2 Hz, 1H), 1.31 (s, 9H), 1.30 (s, 9H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 186.5, 149.8, 148.1, 147.3, 146.9, 141.0, 140.3, 134.4, 134.0, 132.6 132.2, 130.7, 130.2, 129.5, 128.6, 127.8, 123.6, 35.5, 35.1, 29.6, 29.5; FT-IR (neat): 2955, 2924, 2954, 1634, 1519, 1467, 1347, 1267, 749 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{27}H_{30}NO_3$ $[M+H]^+$: 416.2226; found : 416.2209.

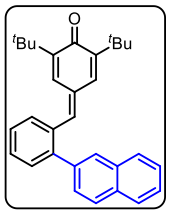
2'-((3,5-di-*tert*-butyl-4-oxocyclohexa-2,5-dien-1-ylidene)methyl)-[1,1'-biphenyl]-2-carbaldehyde (38m)



The reaction was performed at 0.80 mmol scale of 2-bromo *p*-quinone methide; R_f = 0.2 (5% EtOAc in hexane); orange gummy solid (183 mg, 57% yield); m. p. = 133-135 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.77 (s, 1H), 8.05 (d, *J* = 7.7 Hz, 1H), 7.68 – 7.65 (m, 1H), 7.57 (d, *J* = 7.6 Hz, 1H), 7.54 – 7.48 (m, 3H), 7.44 (d, *J* = 1.4 Hz, 1H), 7.37 (d, *J* = 7.2 Hz, 1H), 7.33 (d, *J* = 7.6 Hz, 1H), 6.73 (s, 2H), 1.30 (s, 9H), 1.26 (s, 9H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 191.5, 186.7, 149.9, 148.0, 143.9, 140.7, 138.7, 135.4, 134.6, 134.3 133.8, 132.8, 131.7, 131.6, 131.58, 129.1, 128.7, 128.4, 128.0, 127.8, 35.6, 35.1, 29.7, 29.6; FT-IR (neat): 2971, 2868, 1701, 1637, 1461, 1361, 1275, 750 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{28}H_{31}O_2$ $[M+H]^+$: 399.2324; found : 399.2322.

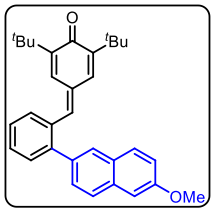
2,6-di-*tert*-butyl-4-(2-(naphthalen-2-yl)benzylidene)cyclohexa-2,5-dien-1-one (38n)

The reaction was performed at 0.80 mmol scale of corresponding 2-bromo phenyl substituted *p*-quinone methide**;** R_f = 0.5 (5% EtOAc in hexane); orange solid (204 mg, 60% yield); m. p. = 187-189 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 – 7.92 (m, 3H), 7.87 (s, 1H), 7.67 (s, 1H), 7.62 – 7.60 (m, 1H), 7.57 – 7.55 (m, 3H), 7.54 – 7.50 (m, 3H) 7.10 (s, 1H), 6.89 (s, 1H), 1.38



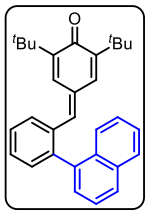
(s, 9H), 1.32 (s, 9H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 186.7, 149.4, 147.6, 143.04, 143.0, 137.9, 135.0, 134.3, 133.3, 132.7, 132.1, 131.9, 130.8, 129.5, 128.9, 128.5, 128.4, 128.2, 128.0, 127.8, 127.5, 126.7, 126.6, 35.6, 35.1, 29.7, 29.6; IR (neat): 2956, 1613, 1360, 1260, 750 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{31}H_{31}O$ $[M-H]^-$: 419.2375; found : 419.2393.

2,6-di-*tert*-butyl-4-(2-(6-methoxynaphthalen-2-yl)benzylidene)cyclohexa-2,5-dien-1-one (38o)



The reaction was performed at 0.80 mmol scale of corresponding 2-bromo phenyl substituted *p*-quinone methide**;** R_f = 0.4 (5% EtOAc in hexane); orange solid (282 mg, 78% yield); m. p. = 146-148 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 – 7.77 (m, 3H), 7.64 (s, 1H), 7.59 – 7.57 (m, 1H), 7.52 – 7.50 (m, 4H), 7.22 – 7.20 (m, 2H) 7.03 (s, 1H), 6.86 (s, 1H), 4.00 (s, 3H), 1.35 (s, 9H), 1.29 (s, 9H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 186.8, 158.3, 149.4, 147.6, 143.3, 143.2, 135.7, 135.0, 134.2, 134.0, 132.2, 131.8, 130.7, 129.9, 129.5, 128.8, 128.7(2C), 128.6, 127.3, 126.8, 119.6, 105.7, 55.6, 35.6, 35.2, 29.8, 29.6; IR (neat): 2961, 1611, 1274, 1258, 750 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{32}H_{33}O_2$ $[M-H]^-$: 449.2481; found : 449.2489.

2,6-di-*tert*-butyl-4-(2-(naphthalen-1-yl)benzylidene)cyclohexa-2,5-dien-1-one (39p)

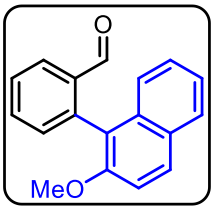


The reaction was performed at 0.80 mmol scale of corresponding 2-bromo phenyl substituted *p*-quinone methide; R_f = 0.4 (5% EtOAc in hexane); orange solid (264 mg, 78% yield); m. p. = 179-181 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 – 7.92 (m, 2H), 7.62 – 7.57 (m, 4H), 7.55 – 7.50 (m, 3H), 7.47 – 7.40 (m, 2H), 7.34 (d, *J* = 7.0 Hz, 1H), 6.77 (s, 1H), 6.64 (s, 1H), 1.35 (s, 9H), 1.22 (s, 9H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 186.7, 149.3, 147.4, 142.4, 141.6, 138.0, 135.5, 135.0, 133.8, 132.0, 131.9, 131.7, 131.69, 128.9, 128.5 (2C), 128.4, 128.3, 127.7, 126.6, 126.2, 126.1, 125.4, 35.6, 35.1, 29.8, 29.6; IR (neat): 2956, 1613, 1458, 1364, 1360, 821, 760 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{31}H_{31}O$ $[M-H]^-$: 419.2375; found : 419.2396.

2,6-di-tert-butyl-4-(2-(2-methoxynaphthalen-1-yl)benzylidene)cyclohexa-2,5-dien-1-one (38q)

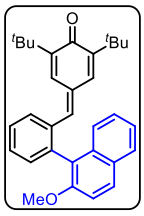
The title compound was prepared in two steps.

Synthesis of 2-(2-methoxynaphthalen-1-yl) benzaldehyde 2-(2-methoxynaphthalen-1-yl) benzaldehyde (I):



Nitrogen gas was purged through a mixture of an aqueous solution of sodium carbonate (445 mg, 4.2 mmol) and toluene (15 mL) for 15 min. Then, 2-formyl-phenylboronic acid [440.8 mg, 2.94 mmol], $Pd(PPh_3)_4$ (121 mg, 0.105 mmol) and 1-bromo-2-methoxynaphthalene [500 mg, 2.10 mmol] were successively added to this mixtute and the resulting mixture was refluxed at 100 ^oC for overnight. After completion of the reaction (monitored by TLC), the reaction mixture was diluted with ethyl acetate (30 mL) and water (10 mL). The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (30 mL × 2). The combined organic layer was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure. The residue was purified through neutral alumina column chromatography using hexane/EtOAc to obtain pure 2-(2-methoxynaphthalen-1-yl)benzaldehyde (**I**) (321mg, 58% yield) as orange solid. R_f = 0.1 (5% EtOAc in hexane); ^1H NMR (400 MHz, $CDCl_3$) δ 9.63 (d, *J* = 0.6 Hz, 1H), 8.13 (dd, *J* = 7.8, 1.0 Hz, 1H), 8.0 (d, *J* = 9.0 Hz, 1H), 7.89 – 7.85 (m, 1H), 7.73 (dt, *J* = 7.5, 1.4 Hz, 1H), 7.58 (t, *J* = 7.6, Hz, 1H), 7.39 – 7.35 (m, 4H), 7.34 – 7.31 (m, 1H), 3.83 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 192.8, 154.2 140.5, 135.1, 134.0, 132.5 (2C), 130.5, 129.0, 128.22, 128.15, 127.2, 127.1, 125.0, 124.0, 120.0, 112.8, 56.4; IR (neat): 3059, 2841, 2750, 1691, 1632, 1596, 1490, 1389, 1272, 1204, 1031 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{18}H_{14}NaO_2$ $[M+Na]^+$: 285.0891; found : 285.0882.

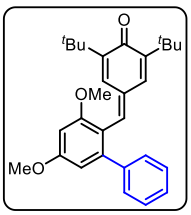
Synthesis of 38q:



The reaction was performed at 0.76 mmol scale of 2-(2-methoxynaphthalen-1-yl) benzaldehyde 2-(2-methoxynaphthalen-1-yl) benzaldehyde (**I**). R_f = 0.2 (5% EtOAc in hexane); orange gummy solid (256 mg, 71% yield); ^1H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, *J* = 9.0 Hz, 1H), 7.88 – 7.86 (m, 1H), 7.59 – 7.53 (m, 4H), 7.38 –7 .37 (m, 5H), 6.79 (s, 1H), 6.65 (s, 1H), 3.37 (s, 3H), 1.33 (s, 9H), 1.23 (s, 9H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 186.8, 154.2, 149.0, 147.3, 142.9, 137.7, 136.4, 135.0, 133.3, 132.1, 131.9, 131.3, 130.0, 129.2, 129.1, 128.6, 128.1, 127.6, 126.9, 125.0, 123.9, 122.9, 113.6, 56.6, 35.5, 35.0, 29.8, 29.6; IR (neat): 2956, 1611, 1489, 1255, 750 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{32}H_{35}O_2$ $[M+H]^+$: 451.2637; found : 451.2617.

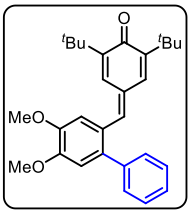
2,6-di-*tert*-butyl-4-((3,5-dimethoxy-[1,1'-biphenyl]-2-yl)methylene)cyclohexa-2,5-dien-1-one (38r)

The reaction was performed at 0.69 mmol scale of corresponding 2-bromo phenyl substituted *p*-quinone methide; R_f = 0.2 (5% EtOAc in hexane); orange gummy solid (212 mg, 71%



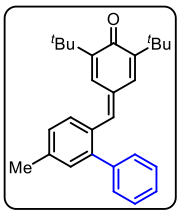
yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.32 (m, 4H), 7.29 – 7.26 (m, 1H), 6.90 – 6.88 (m, 3H), 6.60 (s, 1H), 6.54 (s, 1H), 3.89 (s, 3H), 3.85 (s, 3H), 1.27 (s, 9H), 1.17 (s, 9H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 186.8, 161.3, 158.7, 147.0, 146.6, 144.8, 140.7, 138.9, 134.9, 132.4, 130.0, 129.7, 128.3, 127.6, 116.2, 107.1, 97.6, 55.7, 55.65, 35.2, 35.0, 29.7, 29.6; FT-IR (neat): 2954, 1595, 1330, 1204, 749 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{29}H_{35}O_3$ $[M+H]^+$: 431.2586; found : 431.2604.

2,6-di-*tert*-butyl-4-((4,5-dimethoxy-[1,1'-biphenyl]-2-yl)methylene)cyclohexa-2,5-dien-1-one (38s)



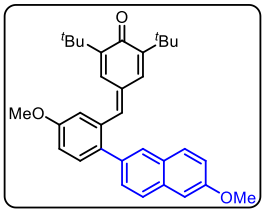
The reaction was performed at 0.69 mmol scale of corresponding 2-bromo phenyl substituted *p*-quinone methide; R_f = 0.1 (5% EtOAc in hexane); yellow solid (192 mg, 64% yield); m. p. = 167-169 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (s, 1H), 7.47 – 7.40 (m, 3H), 7.38 – 7.36 (m, 2H), 7.05 (s, 1H), 7.00 (s, 2H), 6.90 (s, 1H), 3.98 (s, 3H), 3.95 (s, 3H), 1.34 (s, 9H), 1.30 (s, 9H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 186.5, 150.1, 149.1, 148.1, 147.2, 143.4, 140.2, 137.0, 135.2, 130.7, 130.1, 128.5 (2C), 127.7, 126.4, 114.6, 113.2, 56.2, 56.17, 35.6, 35.1, 29.8, 29.6; FT-IR (neat): 2957, 1610, 1275, 1258, 750 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{29}H_{35}O_3$ $[M+H]^+$: 431.2586; found : 431.2602.

2,6-di-*tert*-butyl-4-((5-methyl-[1,1'-biphenyl]-2-yl)methylene)cyclohexa-2,5-dien-1-one (38t)



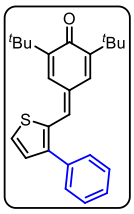
The reaction was performed at 0.77 mmol scale of corresponding 2-bromo phenyl substituted *p*-quinone methide; R_f = 0.4 (5% EtOAc in hexane); yellow gummy solid (215 mg, 72% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (s, 1H), 7.47 – 7.42 (m, 3H), 7.40 – 7.37 (m, 3H), 7.31 (s, 1H), 7.29 – 7.26 (m, 1H), 7.00 (s, 1H), 6.90 (s, 1H), 2.47 (s, 3H), 1.34 (s, 9H), 1.31 (s, 9H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 186.7, 149.1, 147.3, 143.5, 143.1, 140.4, 139.8, 135.1, 132.2, 131.34, 131.3, 131.28, 130.0, 128.6, 128.4, 128.3, 127.8, 35.6, 35.1, 29.7, 29.6, 21.6; FT-IR (neat): 2961, 1609, 1275, 1090, 766 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{28}H_{33}O$ $[M+H]^+$: 385.2531; found : 385.2541.

2,6-di-*tert*-butyl-4-(5-methoxy-2-(6-methoxynaphthalen-2-yl)benzylidene)cyclohexa-2,5-dien-1-one (38u)



The reaction was performed at 0.74 mmol scale of corresponding 2-bromo phenyl substituted *p*-quinone methide; R_f = 0.3 (5% EtOAc in hexane); orange solid (279 mg, 78% yield); m. p. = 176-178 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, *J* = 8.8 Hz, 2H), 7.73 – 7.70 (m, 2H), 7.49 (d, *J* = 9.0 Hz, 1H), 7.43 (d, *J* = 8.4 Hz, 1H), 7.21 – 7.19 (m, 2H), 7.08 – 7.07 (m, 2H), 7.02 (s, 1H), 6.87 (s, 1H), 4.00 (s, 3H), 3.90 (s, 3H),1.36 (s, 9H), 1.29 (s, 9H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 186.7, 158.7, 158.1, 149.4, 147.7, 143.2, 136.0, 135.3, 135.1, 135.0, 133.7, 131.9, 131.8, 129.8, 128.9, 128.8, 128.6, 128.4, 126.7, 119.5, 116.4, 116.1, 105.6, 55.7, 55.5, 35.7, 35.2, 29.8, 29.6; IR (neat): 2954, 1611, 1566, 1274, 749 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{33}H_{37}O_3$ $[M+H]^+$: 481.2743; found : 481.2722.

2,6-di-*tert*-butyl-4-((3-phenylthiophen-2-yl)methylene)cyclohexa-2,5-dien-1-one (38v)



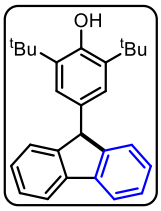
The reaction was performed at 0.79 mmol scale of 4-((3-bromothiophen-2-yl)methylene)-2,6-di-*tert*-butylcyclohexa-2,5-dien-1-one; R_f = 0.4 (5% EtOAc in hexane); gummy orange solid (236 mg, 79% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (s, 1H), 7.62 (d, *J* = 5.2 Hz, 1H), 7.55 – 7.51 (m, 2H), 7.47 – 7.46 (m, 3H), 7.25 (d, *J* = 5.2 Hz, 1H), 7.14 (s, 1H), 6.91 (s, 1H), 1.42 (s, 9H), 1.33 (s, 9H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 186.3, 149.5, 147.4, 147.3, 135.8, 135.4, 134.0, 133.7, 130.1, 130.0, 129.84, 129.8, 128.9, 128.3, 127.3, 35.9, 35.2, 29.8, 29.7; IR (neat): 2956, 1638, 1458, 1261, 1360, 821, 764 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{16}H_{29}SO$ $[M+H]^+$: 377.1939; found : 377.1951.

General procedures for the synthesis of 9-arylfluorenes (39a-u)

2-Arylphenyl *p*-quinone methides **38a-v** (0.08 mmol, 1 equiv.) dissolved in CH_2Cl_2 (1 mL) was taken in a syringe. Triflic acid (0.016 mmol, 20 mol %) dissolved in CH_2Cl_2 (1 mL) was taken in another syringe. These two solutions were injected simultaneously through the microreactor at flow rates of 15 $\mu L\,min^{-1}$ each. The temperature of the microreactor was maintained at 25 ^{o}C throughout the reaction. The reaction mixture collected at the outlet was concentrated under reduced pressure and directly loaded onto a silica-gel column and was purified using 5% EtOAc in hexane as an eluent to provide pure 9-arylfluorene derivatives **39a-u**.

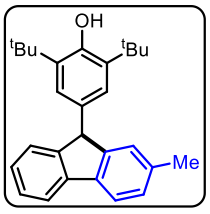
2,6-di-*tert*-butyl-4-(9*H*-fluoren-9-yl)phenol (39a)

The reaction was performed at 0.081 mmol scale of **38a**; R_f = 0.4 (5% EtOAc in hexane); pale yellow solid (25 mg, 83% yield); m. p. = 169-171 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ



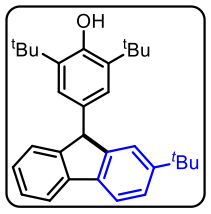
7.80 (d, *J* = 7.4 Hz, 2H), 7.40 – 7.36 (m, 4H), 7.29 – 7.26 (m, 2H), 6.92 (s, 2H), 5.08 (s, 1H), 5.01 (s, 1H), 1.38 (s, 18H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 152.7, 148.2, 141.0, 136.0, 131.9, 127.2(2C), 125.5, 124.9, 119.9, 54.5, 34.5, 30.5; FT-IR (neat): 3637, 2956, 1434, 1390, 1233, 1152, 740 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{27}H_{29}O$ $[M-H]^-$: 369.2218; found : 369.2235.

2,6-di-*tert*-butyl-4-(2-methyl-9*H*-fluoren-9-yl)phenol (39b)



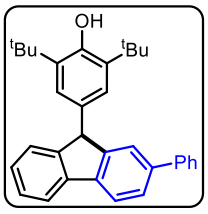
The reaction was performed at 0.078 mmol scale of **38b**; R_f = 0.4 (5% EtOAc in hexane); pale yellow solid (27.5 mg, 91% yield); m. p. = 176-178 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, *J* = 7.8 Hz, 1H), 7.67 (d, *J* = 7.6 Hz, 1H), 7.37 – 7.33 (m, 2H), 7.25 – 7.21 (m, 1H), 7.19 – 7.17 (m, 2H), 6.90 (s, 2H), 5.08 (s, 1H), 4.95 (s, 1H), 2.38 (s, 3H), 1.38 (s, 18H); ^{13}C $\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 152.7, 148.4, 148.1, 141.1, 138.4, 137.0, 135.9, 132.1, 128.0, 127.1, 126.7, 126.1, 125.4, 124.9, 119.6, 119.5, 54.3, 34.5, 30.5, 21.8; FT-IR (neat): 3643, 2956, 1435, 1275, 1267, 749 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{28}H_{31}O$ $[M-H]^-$: 383.2375; found : 383.2390.

2,6-di-*tert*-butyl-4-(2-(*tert*-butyl)-9*H*-fluoren-9-yl)phenol (39c)



The reaction was performed at 0.070 mmol scale of **38c**; R_f = 0.4 (5% EtOAc in hexane); pale yellow solid (27 mg, 90% yield); m. p. = 158-160 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 – 7.71 (m, 2H), 7.49 (s, 1H), 7.44 – 7.40 (m, 2H), 7.36 – 7.32 (m, 1H), 7.26 – 7.22 (m, 1H), 7.00 (s, 2H), 5.08 (s, 1H), 5.02 (s, 1H), 1.39 (s, 18H), 1.34 (s, 9H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 152.7, 150.4, 148.1, 147.4, 140.8, 138.7, 135.9, 131.9, 127.1, 126.7, 125.2, 124.8, 124.3, 122.8, 119.7, 119.4, 54.2, 35.1, 34.5, 31.7, 30.5; FT-IR (neat): 3640, 2957, 1663, 1361, 1275, 1267, 749 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{31}H_{37}O$ $[M-H]^-$: 425.2844; found : 425.2860.

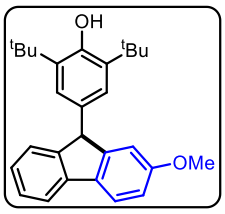
2,6-di-*tert*-butyl-4-(2-phenyl-9*H*-fluoren-9-yl)phenol (39d)



The reaction was performed at 0.067 mmol scale of **38d**; R_f = 0.4 (5% EtOAc in hexane); pale yellow solid (23.2 mg, 77% yield); m. p. = 173-175 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, *J* = 7.3 Hz, 1H), 7.84 (d, *J* = 7.4 Hz, 1H), 7.66 – 7.63 (m, 4H), 7.47 – 7.39 (m, 4H), 7.37 – 7.29 (m, 2H), 7.00 (s, 2H), 5.11 (s, 1H), 5.08 (s, 1H), 1.41 (s, 18H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 152.8, 148.8, 148.5, 141.6, 140.6, 140.4, 140.2, 136.1, 131.8, 128.9(2C), 127.3(2C), 127.2, 126.4, 125.5, 124.9, 124.2, 120.2, 120.0, 54.6, 34.5, 30.5; FT-IR (neat): 3634, 2956, 1452,

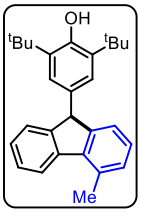
1275, 1152, 758 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{33}H_{33}O$ $[M-H]^-$: 445.2531; found : 445.2545.

2,6-di-*tert*-butyl-4-(2-methoxy-9*H*-fluoren-9-yl)phenol (39e)



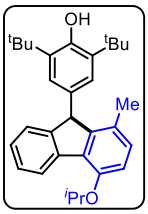
The reaction was performed at 0.075 mmol scale of **38e**; R_f = 0.3 (5% EtOAc in hexane); creamy white solid (28.3 mg, 94% yield); m. p. = 151-153 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (d, *J* = 8.3 Hz, 2H), 7.37 – 7.33 (m, 2H), 7.23 – 7.19 (m, 1H), 6.96 – 6.94 (m, 4H), 5.11 (s, 1H), 4.97 (s, 1H), 3.83 (s, 3H), 1.40 (s, 18H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 159.5, 152.7, 150.0, 147.7, 140.9, 136.0, 134.1, 131.9, 127.1, 126.0, 125.3, 124.9, 120.6, 119.1, 113.3, 111.1, 55.7, 54.5, 34.5, 30.5; FT-IR (neat): 3637, 2957, 1456, 1267, 1152, 749 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{28}H_{31}O_2$ $[M-H]^-$: 399.2324; found : 399.2339.

2,6-di-*tert*-butyl-4-(4-methyl-9*H*-fluoren-9-yl)phenol (39f)



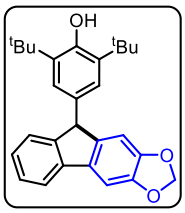
The reaction was performed at 0.078 mmol scale of **38f**; R_f = 0.4 (5% EtOAc in hexane); pale yellow solid (27.1 mg, 90% yield); m. p. = 175-177 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, *J* = 7.6 Hz, 1H), 7.42 – 7.38 (m, 2H), 7.33 – 7.24 (m, 2H), 7.20 – 7.15 (m, 2H), 6.92 (s, 2H), 5.10 (s, 1H), 4.98 (s, 1H), 2.79 (s, 3H), 1.39 (s, 18H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 152.7, 148.60, 148.57, 142.0, 139.0, 135.9, 132.9, 132.2, 129.4, 127.0, 126.8, 126.5, 125.4, 125.0, 123.1, 123.0, 54.5, 34.5, 30.5, 21.3; FT-IR (neat): 3636, 2956, 1452, 1361, 1267, 749 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{28}H_{31}O$ $[M-H]^-$: 383.2375; found : 383.2391.

2,6-di-*tert*-butyl-4-(4-*iso*-propoxy-1-methyl-9*H*-fluoren-9-yl)phenol (40g)



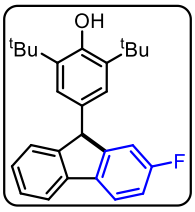
The reaction was performed at 0.067 mmol scale of **38g**; R_f = 0.4 (5% EtOAc in hexane); creamy solid (25.0 mg, 83% yield); m. p. = 143-145 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (d, *J* = 7.6 Hz, 1H), 7.33 – 7.29 (m, 2H), 7.20 – 7.16 (m, 1H), 7.00 (d, *J* = 8.2 Hz, 1H), 6.87 – 6.84 (m, 3H), 5.02 (s, 1H), 4.91 (s, 1H), 4.75 (sept, *J* = 5.9 Hz, 1H), 1.98 (s, 3H), 1.53 (d, *J* = 6.4 Hz, 3H), 1.47 (d, *J* = 5.9 Hz, 3H), 1.35 (s, 18H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 152.4, 152.3, 148.4, 147.5, 140.2, 135.9, 131.2, 130.4, 129.3, 127.2, 126.8, 126.1, 124.6, 124.5, 123.7, 112.3, 70.5, 54.5, 34.4, 30.5, 22.7, 22.4, 18.6; FT-IR (neat): 3640, 2963, 1500, 1434, 1274, 763 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{31}H_{37}O_2$ $[M-H]^-$: 441.2794; found : 441.2813.

2,6-di-*tert*-butyl-4-(9*H*-fluoreno[2,3-d][1,3]dioxol-9-yl)phenol (39h)



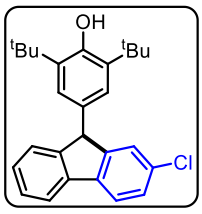
The reaction was performed at 0.073 mmol scale of **38h**; R_f = 0.3 (5% EtOAc in hexane); pale yellow solid (28.0 mg, 93% yield); m. p. = 155-157 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (d, J = 7.4 Hz, 1H), 7.35–7.31 (m, 2H), 7.23–7.17 (m, 2H), 6.88 (s, 2H), 6.83 (s, 1H), 5.99 (s, 2H), 5.08 (s, 1H), 4.85 (s, 1H), 1.39 (s, 18H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 152.7, 148.4, 147.5, 147.4, 142.4, 141.1, 136.1, 134.8, 131.8, 127.1, 126.0, 125.2, 124.7, 118.8, 106.2, 101.3, 100.5, 54.3, 34.5, 30.5; FT-IR (neat): 3640, 2940, 1474, 1433, 1267, 758 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{28}H_{29}O_3$ [M-H]$^-$: 413.2117; found : 413.2132.

2,6-di-*tert*-butyl-4-(2-fluoro-9*H*-fluoren-9-yl)phenol (39i)



The reaction was performed at 0.077 mmol scale of **38i**; R_f = 0.4 (5% EtOAc in hexane); pale yellow solid (23.8 mg, 79% yield); m. p. = 169-171 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 – 7.70 (m, 2H), 7.39 – 7.36 (m, 2H), 7.28 – 7.24 (m, 1H), 7.08 – 7.06 (m, 2H), 6.89 (s, 2H), 5.12 (s, 1H), 4.97 (s, 1H), 1.39 (s, 18H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 162.7 (d, $J_{C\text{-}F}$ = 243.2 Hz), 152.9, 150.5 (d, $J_{C\text{-}F}$ = 8 Hz), 148.1 (d, $J_{C\text{-}F}$ = 2.1 Hz), 140.2, 136.9 (d, $J_{C\text{-}F}$ = 2.2 Hz), 136.2, 131.3, 127.3, 126.9, 125.5, 124.8, 120.8(d, $J_{C\text{-}F}$ = 8.8 Hz), 119.6, 114.4(d, $J_{C\text{-}F}$ = 23 Hz), 112.7(d, $J_{C\text{-}F}$ = 22.7 Hz), 54.5(d, $J_{C\text{-}F}$ = 2.1 Hz), 34.5, 30.4; ^{19}F NMR (376 MHz, $CDCl_3$) δ -115.1; FT-IR (neat): 3637, 2956, 1469, 1433, 1260, 1122, 749 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{27}H_{28}FO$ [M-H]$^-$: 387.2124; found : 387.2140.

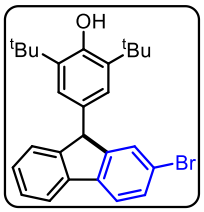
2,6-di-*tert*-butyl-4-(2-chloro-9*H*-fluoren-9-yl)phenol (39j)



The reaction was performed at 0.074 mmol scale of **38j**; R_f = 0.5 (5% EtOAc in hexane); almond white solid (26.2 mg, 87% yield); m. p. = 192-194 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, J = 7.5 Hz, 1H), 7.70 (d, J = 8.3 Hz, 1H), 7.40 – 7.37 (m, 1H), 7.35 – 7.34 (m, 3H), 7.29 (d, J = 7.4 Hz, 1H), 6.87 (s, 2H), 5.12 (s, 1H), 4.96 (s, 1H), 1.39 (s, 18H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 152.9, 150.0, 148.1, 140.0, 139.5, 136.2, 132.8, 131.1, 127.50, 127.48, 127.4, 125.8, 125.6, 124.8, 120.8, 119.9, 54.5, 34.5, 30.4; FT-IR (neat): 3637, 2957, 1466, 1434, 1274, 1267, 749 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{27}H_{28}ClO$ [M-H]$^-$: 403.1829; found : 403.1849.

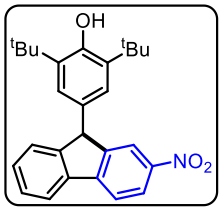
4-(2-bromo-9*H*-fluoren-9-yl)-2,6-di-*tert*-butylphenol (39k)

The reaction was performed at 0.067 mmol scale of **38k**; R_f = 0.5 (5% EtOAc in hexane); pale yellow solid (26.8 mg, 89% yield); m. p. = 159-161 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ



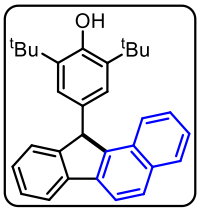
7.77 (d, *J* = 7.5 Hz, 1H), 7.65 (d, *J* = 8.4 Hz, 1H), 7.51 (s, 2H), 7.41 – 7.36 (m, 2H), 7.32 – 7.28 (m, 1H), 6.88 (s, 2H), 5.13 (s, 1H), 4.97 (s, 1H), 1.40 (s, 18H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 152.9, 150.3, 148.0, 139.97, 139.96, 136.2, 131.0, 130.3, 128.7, 127.6, 127.4, 125.6, 124.9, 121.2, 120.9, 120.0, 54.5, 34.5, 30.4; FT-IR (neat): 3634, 2956, 1436, 1404, 1275, 1261, 749 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{27}H_{28}BrO$ $[M-H]^-$: 447.1324; found : 447.1339.

2,6-di-*tert*-butyl-4-(2-nitro-9*H*-fluoren-9-yl)phenol (39l)



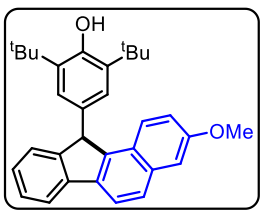
The reaction was performed at 0.072 mmol scale of **38l**; R_f = 0.2 (5% EtOAc in hexane); orange gummy solid (13.5 mg, 45% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32 – 8.28 (m, 1H), 8.21 (s, 1H), 7.88 (d, *J* = 8.3 Hz, 2H), 7.45 – 6.34 (m, 3H), 6.85 (s, 2H), 5.15 (s, 1H), 5.06 (s, 1H), 1.37 (s, 18H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 153.2, 150.0, 149.4, 147.4, 147.3, 138.7, 136.5, 130.0, 129.4, 127.8, 126.0, 124.8, 123.6, 121.3, 121.0, 120.0, 55.6, 34.5, 30.4; FT-IR (neat): 3435, 2958, 2854, 1522, 1434, 1338, 1275, 757 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{27}H_{30}NO_3$ $[M+H]^+$: 416.2226; found : 416.2209.

4-(11*H*-benzo[*a*]fluoren-11-yl)-2,6-di-*tert*-butylphenol (39n)



The reaction was performed at 0.071 mmol scale of **38n**; R_f = 0.3 (5% EtOAc in hexane); pale yellow solid (27 mg, 90% yield); m. p. = 217-219 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 – 7.90 (m, 3H), 7.82 (d, *J* = 7.5 Hz, 1H), 7.70 (d, *J* = 8.2 Hz, 1H), 7.44 – 7.38 (m, 3H), 7.36 – 7.32 (m, 1H), 7.28 – 7.24 (m, 1H), 6.90 (s, 2H), 5.28 (s, 1H), 5.10 (s, 1H), 1.32 (s, 18H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 152.6, 149.6, 142.9, 141.0, 139.2, 136.0, 133.5, 131.8, 130.8, 128.9, 128.7, 127.0, 126.9, 126.1, 125.2, 125.1, 125.0, 124.7, 119.6, 118.7, 54.2, 34.4, 30.4; FT-IR (neat): 3635, 2956, 1464, 1274, 1152, 749 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{31}H_{31}O$ $[M-H]^-$: 419.2375; found : 419.2393.

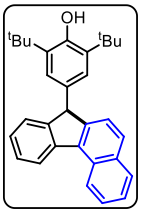
2,6-di-*tert*-butyl-4-(3-methoxy-11*H*-benzo[*a*]fluoren-11-yl)phenol (39o)



The reaction was performed at 0.067 mmol scale of **38o**; R_f = 0.2 (5% EtOAc in hexane); pale yellow solid (27.7 mg, 92% yield); m. p. = 180-182 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, *J* = 8.4 Hz, 1H), 7.83 – 7.78 (m, 2H), 7.59 (d, *J* = 9.2 Hz, 1H), 7.40 – 7.34 (m, 2H), 7.24 – 7.22 (m, 2H), 7.01 (d, *J* = 9.0 Hz, 1H), 6.89 (s, 2H), 5.23 (s, 1H), 5.04 (s, 1H), 3.92 (s, 3H), 1.32 (s, 18H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 157.1, 152.6, 149.2, 143.1, 141.2, 137.3, 136.1,

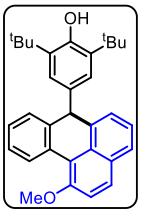
134.8, 131.9, 127.5, 127.0, 126.8, 126.4, 126.3, 124.9, 124.7, 119.3, 119.2, 118.7, 107.1, 55.4, 54.1, 34.4, 30.5; FT-IR (neat): 3640, 2940, 1593, 1459, 1434, 1267, 1154, 749 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{32}H_{33}O_2$ [M-H]$^-$: 449.2481; found : 449.2500.

4-(7*H*-benzo[*c*]fluoren-7-yl)-2,6-di-*tert*-butylphenol (39p)



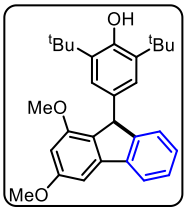
The reaction was performed at 0.071 mmol scale of **38p**; **39p** was obtained as a regioisomers in the ratio of 3:1; R_f = 0.4 (5% EtOAc in hexane); pale brown solid (22.8 mg, 75% yield for both isomer); m. p. = 97-99 ^oC; ^1H NMR (400 MHz, $CDCl_3$) (major isomer) δ 8.29 (d, *J* = 8.4 Hz, 1H), 7.87 (d, *J* = 7.8 Hz, 1H), 7.42 (d, *J* = 8.2 Hz, 1H), 7.26–7.22 (m, 1H), 7.16–7.12 (m, 1H), 7.02–6.98 (m, 1H), 6.96–6.92 (m, 2H), 6.81–6.75 (m, 2H), 6.39 (s, 2H), 4.56 (s, 1H), 4.51 (s, 1H), 0.84 (s, 18H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) (major isomer) δ 152.8, 149.5, 147.2, 142.0, 131.3, 129.6, 129.4, 128.1, 128.0, 127.9, 127.3, 126.6, 126.3, 125.4, 125.2, 125.1, 124.7, 124.1, 123.7, 122.9, 55.0, 34.5, 30.5; FT-IR (neat): 3632, 2957, 1433, 1361, 1275, 749 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{31}H_{31}O$ [M-H]$^-$: 419.2375; found : 419.2385.

2,6-di-*tert*-butyl-4-(1-methoxy-7*H*-benzo[*de*]anthracen-7-yl)phenol (39q)



The reaction was performed at 0.067 mmol scale of **38q**; R_f = 0.3 (5% EtOAc in hexane); purple solid (20.8 mg, 69% yield); m. p. = 166-168 ^oC; ^1H NMR (400 MHz, $CDCl_3$) δ 8.77 (d, *J* = 8.0 Hz, 1H), 7.76 (d, *J* = 9.0 Hz, 1H), 7.63 (d, *J* = 8.0 Hz, 1H), 7.41 – 7.38 (m, 2H), 7.37 – 7.33 (m, 2H), 7.30 – 7.28 (m, 1H), 7.26 – 7.22 (m, 1H), 6.88 (s, 2H), 5.42 (s, 1H), 4.92 (s, 1H), 4.07 (s, 3H), 1.26 (s, 18H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 155.1, 152.1 139.6, 137.9, 137.2, 135.5, 131.9, 130.1, 129.3, 129.2, 129.1, 128.4, 127.4, 126.5, 126.1, 125.8, 124.5, 124.0, 117.7, 116.3, 57.3, 51.9, 34.3, 30.3; FT-IR (neat): 3633, 2956, 1458, 1432, 1267, 769 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{32}H_{33}O_2$ [M-H]$^-$: 449.2481; found : 449.2495.

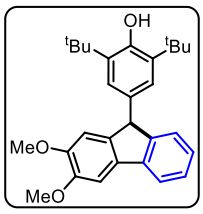
2,6-di-*tert*-butyl-4-(1,3-dimethoxy-9*H*-fluoren-9-yl)phenol (39r)



The reaction was performed at 0.068 mmol scale of **38r**; R_f = 0.2 (5% EtOAc in hexane); gummy solid (16 mg, 53% yield); ^1H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, *J* = 7.5 Hz, 1H), 7.39 (d, *J* = 7.4 Hz, 1H), 7.35 – 7.32 (m, 1H), 7.26 – 7.23 (m, 1H), 6.95 (s, 1H), 6.90 (s, 2H), 6.40 (s, 1H), 5.01 (s, 1H), 4.99 (s, 1H), 3.92 (s, 3H), 3.69 (s, 3H), 1.35 (s, 18H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 161.3, 157.5, 152.2, 149.4, 143.4, 140.8, 135.2, 131.2, 127.4, 127.3, 126.9, 125.4, 124.7, 119.8,

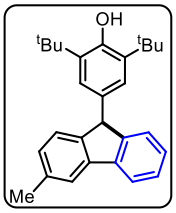
98.4, 96.5, 55.8, 55.6, 52.1, 34.4, 30.5; FT-IR (neat): 3633, 2955, 1589, 1494, 1433, 1267, 749 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{29}H_{35}O_3$ $[M+H]^+$: 431.2586; found : 431.2571.

2,6-di-*tert*-butyl-4-(2,3-dimethoxy-9*H*-fluoren-9-yl)phenol (39s)



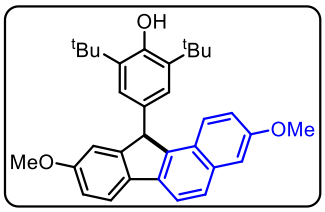
The reaction was performed at 0.068 mmol scale of **38s**; R_f = 0.1 (5% EtOAc in hexane); pale yellow solid (27.4 mg, 91% yield); m. p. = 153-155 ^oC; ^1H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, *J* = 7.6 Hz, 1H), 7.34 – 7.30 (m, 3H), 7.21 – 7.17 (m, 1H), 6.94 (bs, 3H), 5.09 (s, 1H), 4.92 (s, 1H), 4.02 (s, 3H), 3.88 (s, 3H), 1.39 (s, 18H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 152.7, 149.1, 149.0, 148.4, 141.1, 140.3, 136.0, 133.8, 131.9, 127.0, 125.9, 125.0, 124.7, 118.8, 108.7, 102.8, 56.3, 56.2, 54.2, 34.5, 30.5; FT-IR (neat): 3637, 2956, 1458, 1342, 1274, 749 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{29}H_{33}O_3$ $[M-H]^-$: 429.2430; found : 429.2412.

2,6-di-*tert*-butyl-4-(3-methyl-9*H*-fluoren-9-yl)phenol (39t)



The reaction was performed at 0.078 mmol scale of **38t**; R_f = 0.4 (5% EtOAc in hexane); pale yellow solid (25 mg, 83% yield); m. p. = 135-137 ^oC; ^1H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, *J* = 7.4 Hz, 1H), 7.61 (s, 1H), 7.39 – 7.35 (m, 2H), 7.28 – 7.24 (m, 2H), 7.09 (d, *J* = 7.6 Hz, 1H), 6.92 (s, 2H), 5.07 (s, 1H), 4.97 (s, 1H), 2.47 (s, 3H), 1.39 (s, 18H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 152.7, 148.6, 145.3, 141.13, 141.07, 136.7, 136.0, 132.1, 128.1, 127.1, 127.0, 125.5, 125.2, 124.8, 120.5, 119.7, 54.1, 34.5, 30.5, 21.7; FT-IR (neat): 3639, 2956, 1433, 1274, 1153, 749 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{28}H_{33}O$ $[M+H]^+$: 385.2531; found : 385.2522.

2,6-di-*tert*-butyl-4-(3,9-dimethoxy-11*H*-benzo[*a*]fluoren-11-yl)phenol (39u)

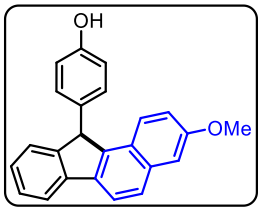


The reaction was performed at 0.063 mmol scale of **38o**; R_f = 0.1 (5% EtOAc in hexane); pale orange solid (27.1 mg, 90% yield); m. p. = 157-159 ^oC; ^1H NMR (400 MHz, $CDCl_3$) δ 7.86 – 7.78 (m, 2H), 7.67 (d, *J* = 8.3 Hz, 1H), 7.54 (d, *J* = 9.1 Hz, 1H), 7.20 (s, 1H), 7.00 (dd, *J* = 9.1, 1.0 Hz, 1H), 6.95 (s, 1H), 6.91 – 6.88 (m, 3H), 5.18 (s, 1H), 5.04 (s, 1H), 3.91 (s, 3H), 3.82 (s, 3H), 1.32 (s, 18H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 159.0, 156.7, 152.6, 151.1, 142.2, 137.2, 136.1, 134.3, 134.1, 132.0, 127.4, 126.5, 126.3, 124.6, 119.8, 118.9, 118.6, 112.2, 111.4, 107.0, 55.6, 55.3, 54.1, 34.4, 30.5; FT-IR (neat): 3640, 2956, 1485, 1267, 1165, 749 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{33}H_{35}O_3$ $[M-H]^-$: 479.2586; found : 479.2594.

Procedure for synthesis of 42a & 42b

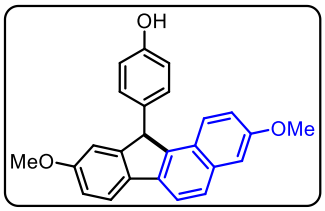
$AlCl_3$ (0.44 mmol 8 equiv.) was added to a solution of 9-aryl fluorene derivative **39n** (0.055 mmol 1 equiv.) in benzene (3 mL) at room temperature and the resultant mixture was stirred for 3 h. Then the mixture was transferred to a separating funnel containing 1:1 ice/1N HCl and extracted with ethyl acetate (3 × 10 mL). The combined organic layer was washed with saturated aq. $NaHCO_3$ and brine solutions successively, dried over anhydrous Na_2SO_4 and finally concentrated in vacuum. The crude material was purified through a silica gel column using ethyl acetate/hexane (20:80) mixture as an eluent to give pure products **42a & 42b**.

4-(3-methoxy-11*H*-benzo[*a*]fluoren-11-yl)phenol (42a)



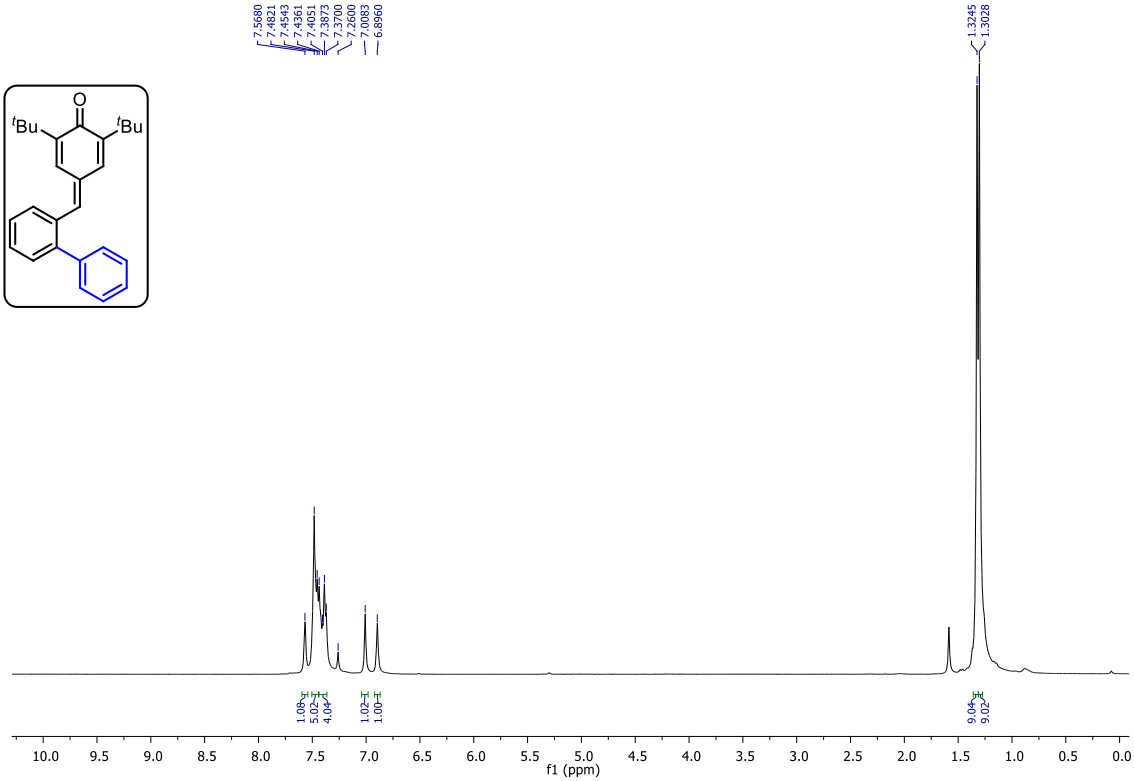
The reaction was performed at 0.055 mmol scale of **38n;** R_f = 0.1 (15% EtOAc in hexane); pale orange solid (16.5 mg, 88% yield); m. p. = 121-123 ^oC; ^1H NMR (400 MHz, DMSO-d_6) δ 9.27 (s, 1H), 8.06 (d, J = 8.3 Hz, 1H), 7.91 (d, J = 8.3 Hz, 2H), 7.57 (d, J = 9.0 Hz, 1H), 7.40 (s, 1H), 7.36 – 7.33 (m, 1H), 7.25 (d, J = 7.3 Hz, 1H), 7.22 – 7.18 (m, 1H), 7.05 (d, J = 9.1 Hz, 1H), 6.86 (d, J = 7.4 Hz, 2H), 6.64 (d, J = 7.5 Hz 2H), 5.39 (s, 1H), 3.85 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ 156.8, 156.0, 149.2, 143.1, 140.6, 136.5, 134.6, 131.7, 128.7, 127.5, 127.0, 126.5, 125.9, 125.2, 124.7, 119.5, 119.3, 118.8, 115.6, 107.4, 55.2, 52.3; FT-IR (neat): 3410, 1393, 1480, 1274, 1044, 749 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{24}H_{17}O_2$ $[M-H]^-$: 337.1229; found : 337.1216.

4-(3,9-dimethoxy-11*H*-benzo[*a*]fluoren-11-yl)phenol (42b)

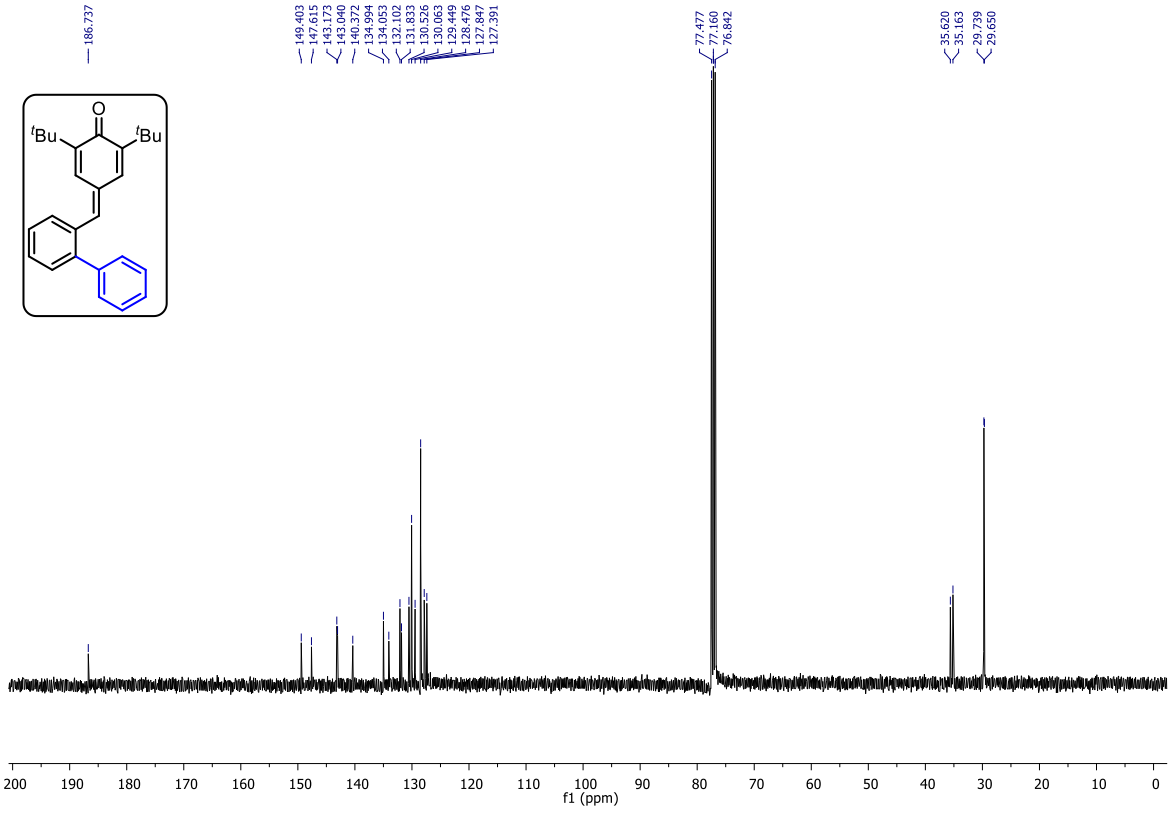


The reaction was performed at 0.052 mmol scale of **38o;** R_f = 0.1 (15% EtOAc in hexane); gummy orange solid (17.3 mg, 90% yield); ^1H NMR (400 MHz, DMSO-d_6) δ 9.28 (s, 1H), 8.00 (d, J = 8.3 Hz, 1H), 7.87 (d, J = 8.4 Hz, 1H), 7.80 (d, J = 8.3 Hz, 1H), 7.51 (d, J = 9.1 Hz, 1H), 7.37 (s, 1H), 7.0 (d, J = 9.1 Hz, 1H), 6.92 (d, J = 8.4 Hz, 1H), 6.87 (d, J = 7.8 Hz, 2H), 6.79 (s, 1H), 6.63 (d, J = 7.8 Hz 2H), 5.33 (s, 1H), 3.83 (s, 3H) 3.72 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO d_6) δ 158.8, 156.5, 156.0, 151.1, 142.2, 136.5, 133.9, 133.5, 131.9, 128.8, 127.4, 125.6, 125.3, 120.3, 119.0, 118.7, 115.7, 112.6, 110.7, 107.3, 55.3, 55.2, 52.3; FT-IR (neat): 3413, 1511, 1485, 1232, 1052, 749 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{25}H_{19}O_3$ $[M-H]^-$: 367.1334; found : 367.1349.

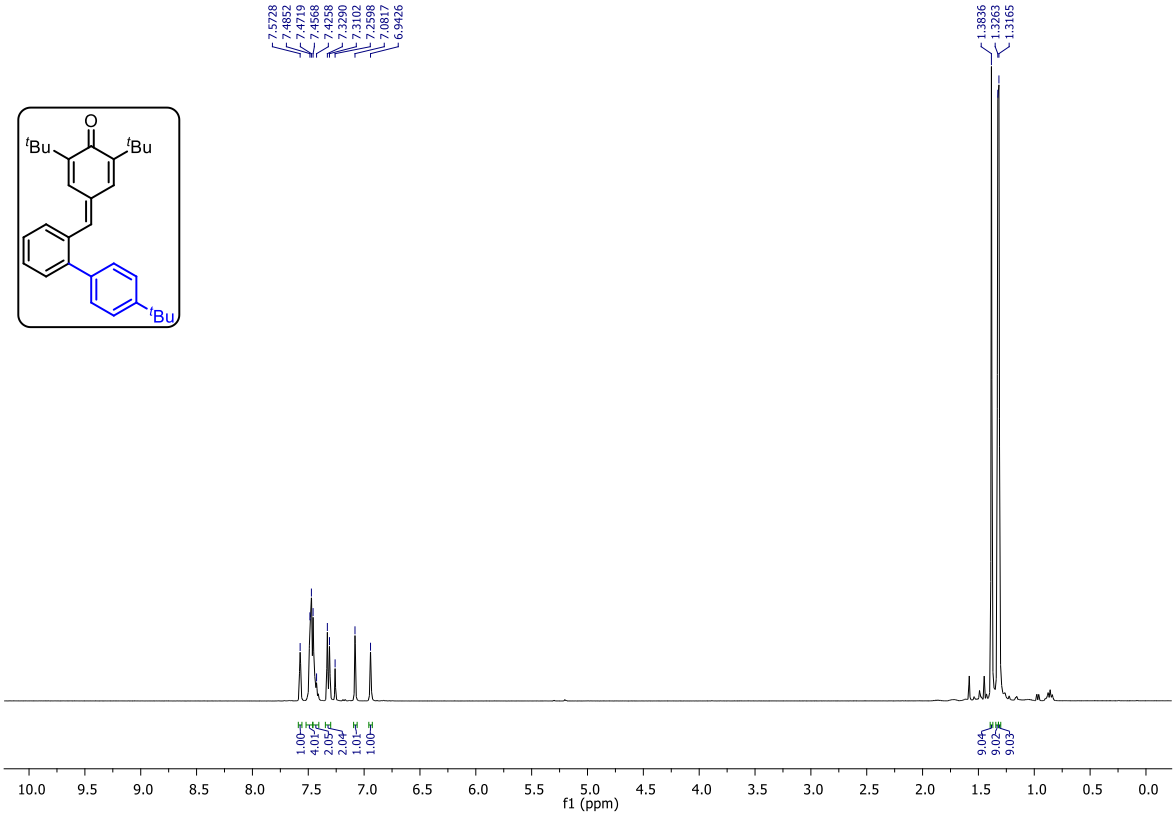
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **38a**



^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) spectrum of compound **38a**



^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **38c**



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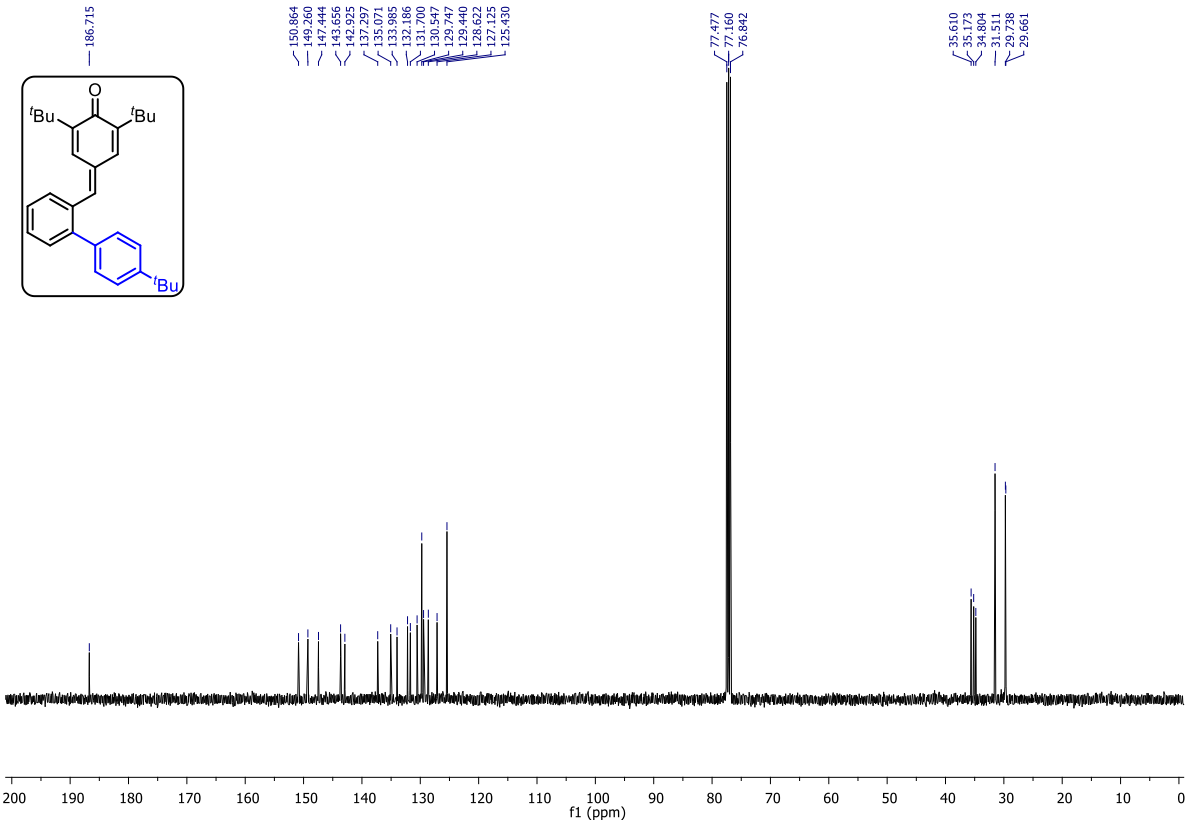
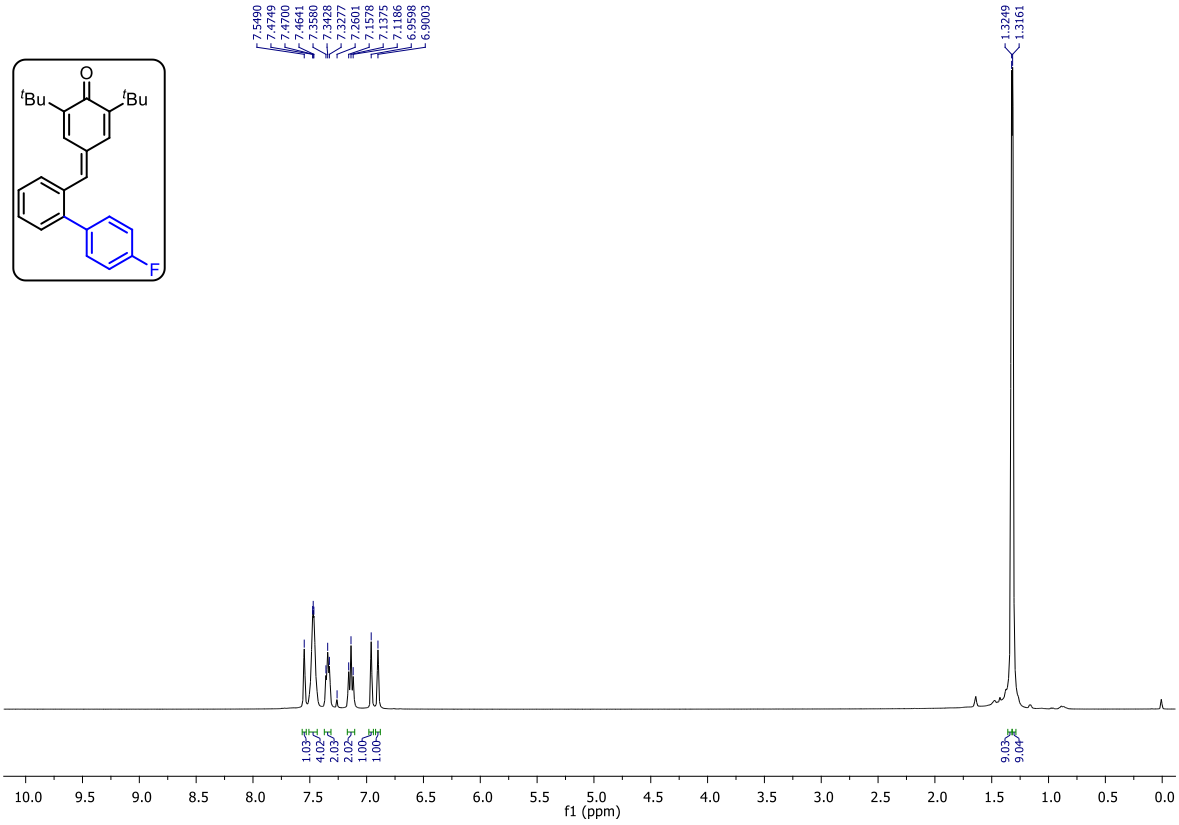
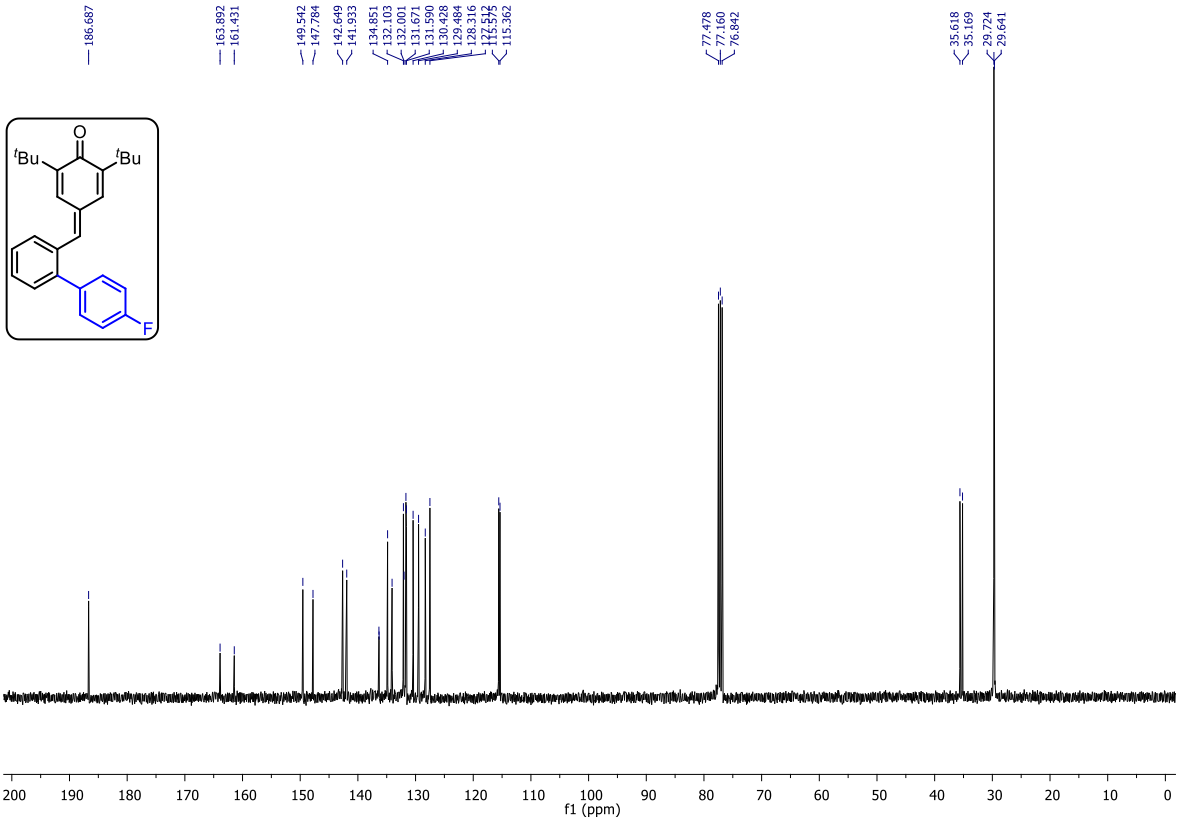


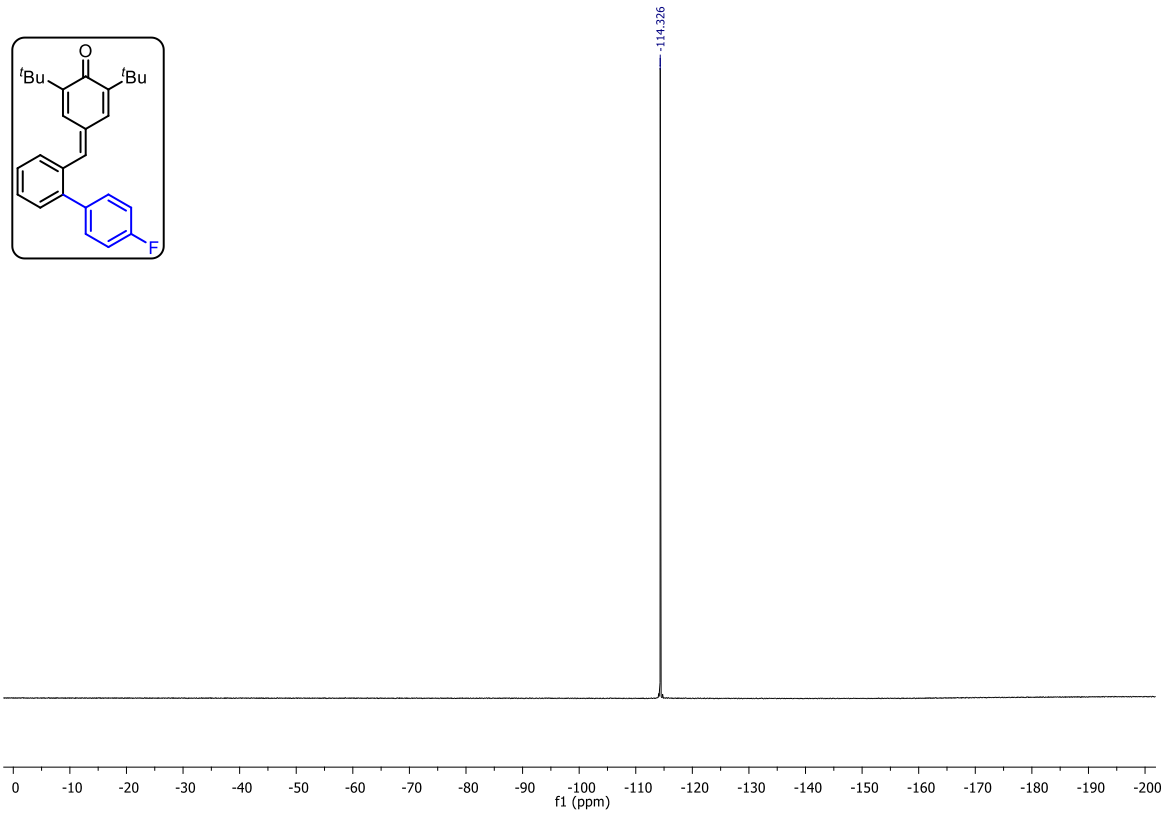
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **38i**



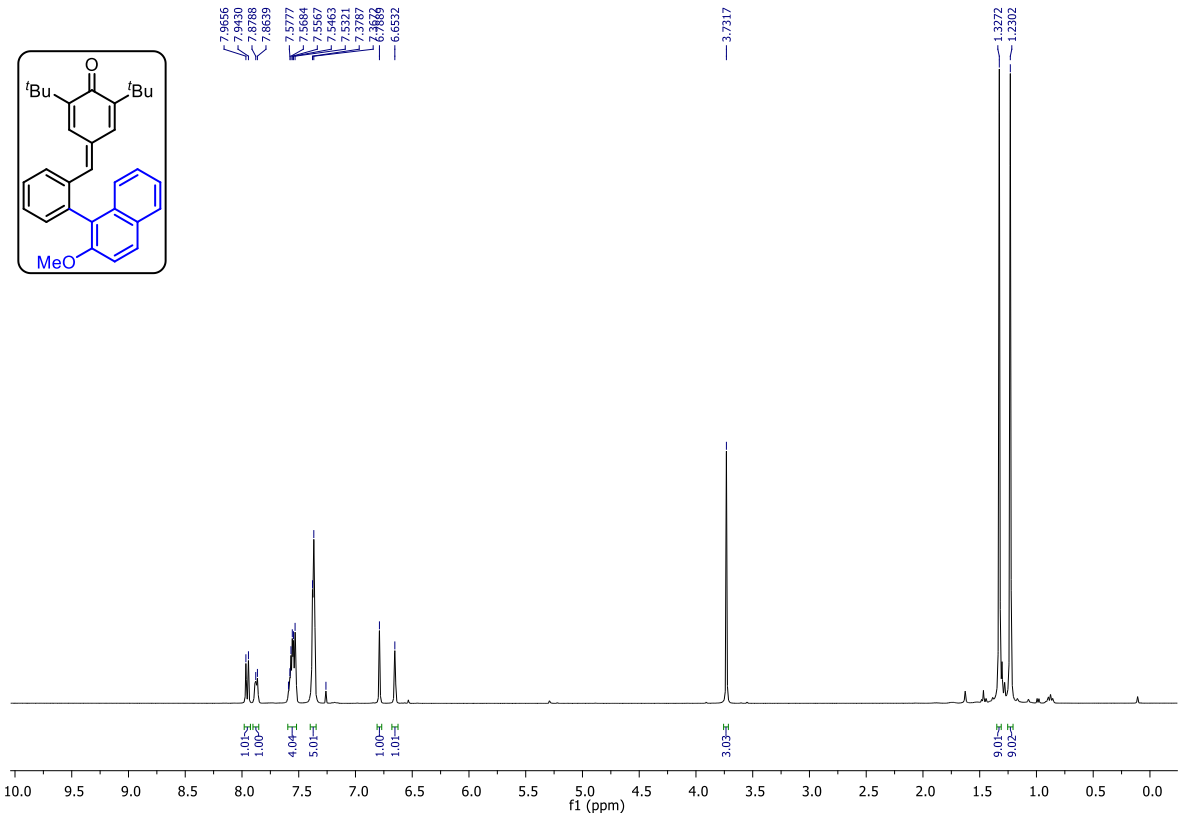
^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) spectrum of compound **38i**



^{19}F NMR (376 MHz, $CDCl_3$) spectrum of compound **38i**



^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **38q**



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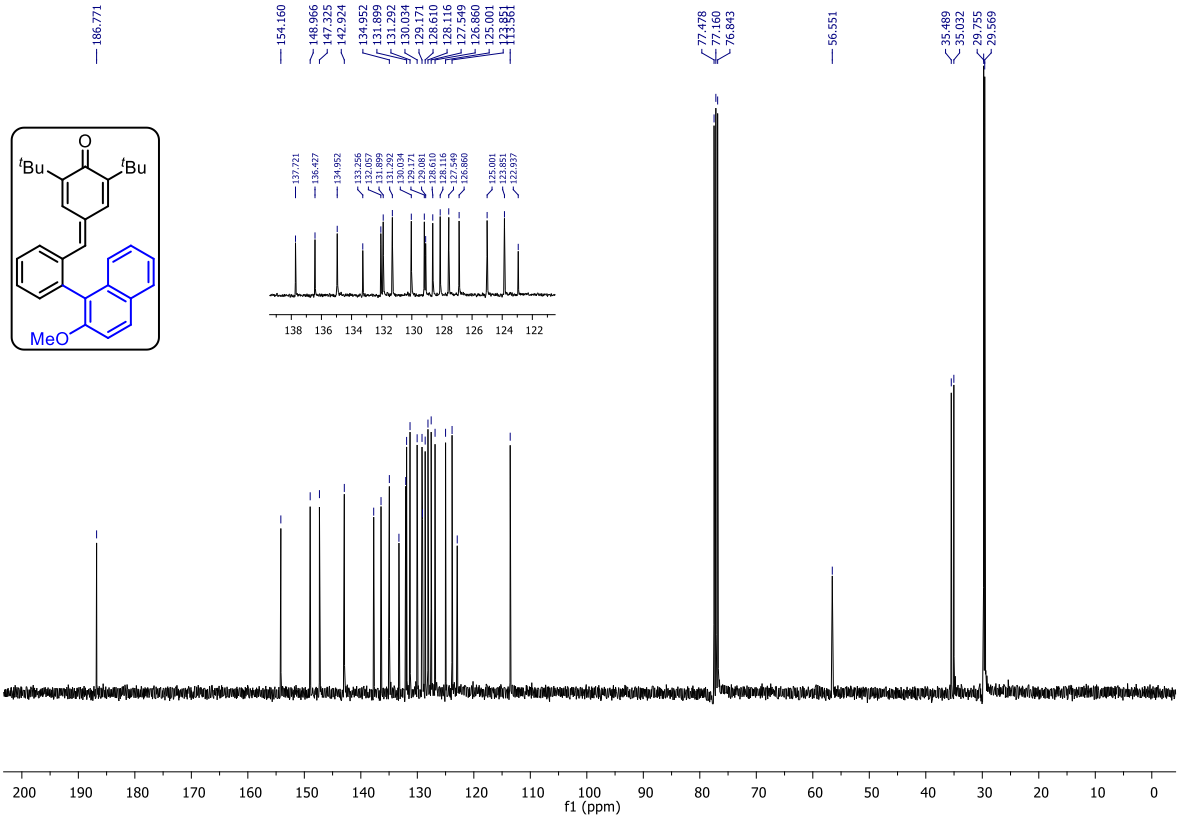
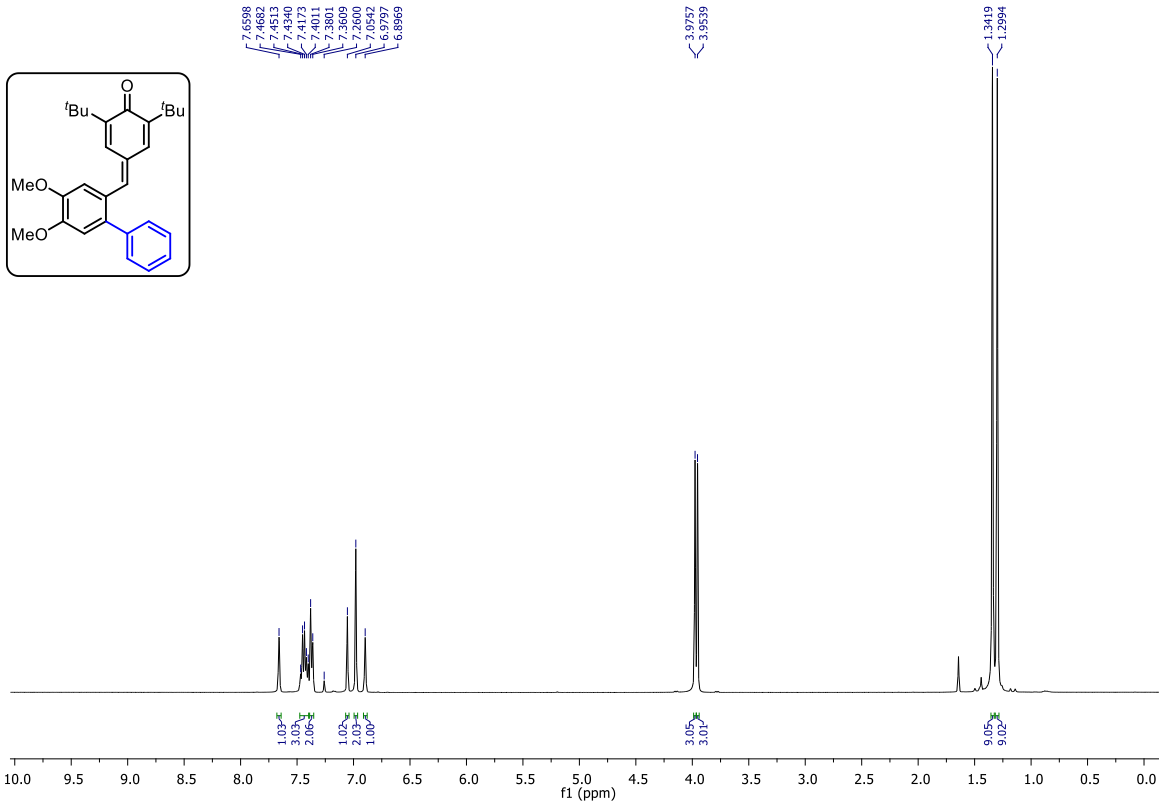


^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **38t**



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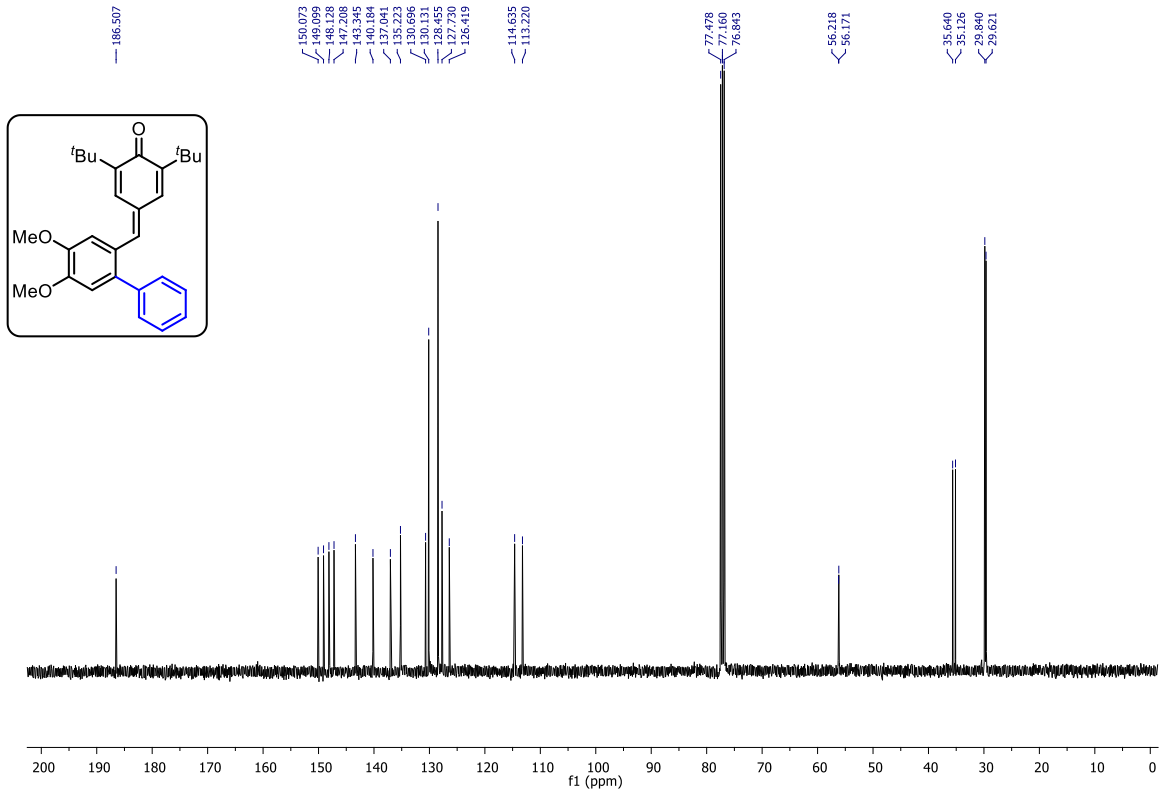
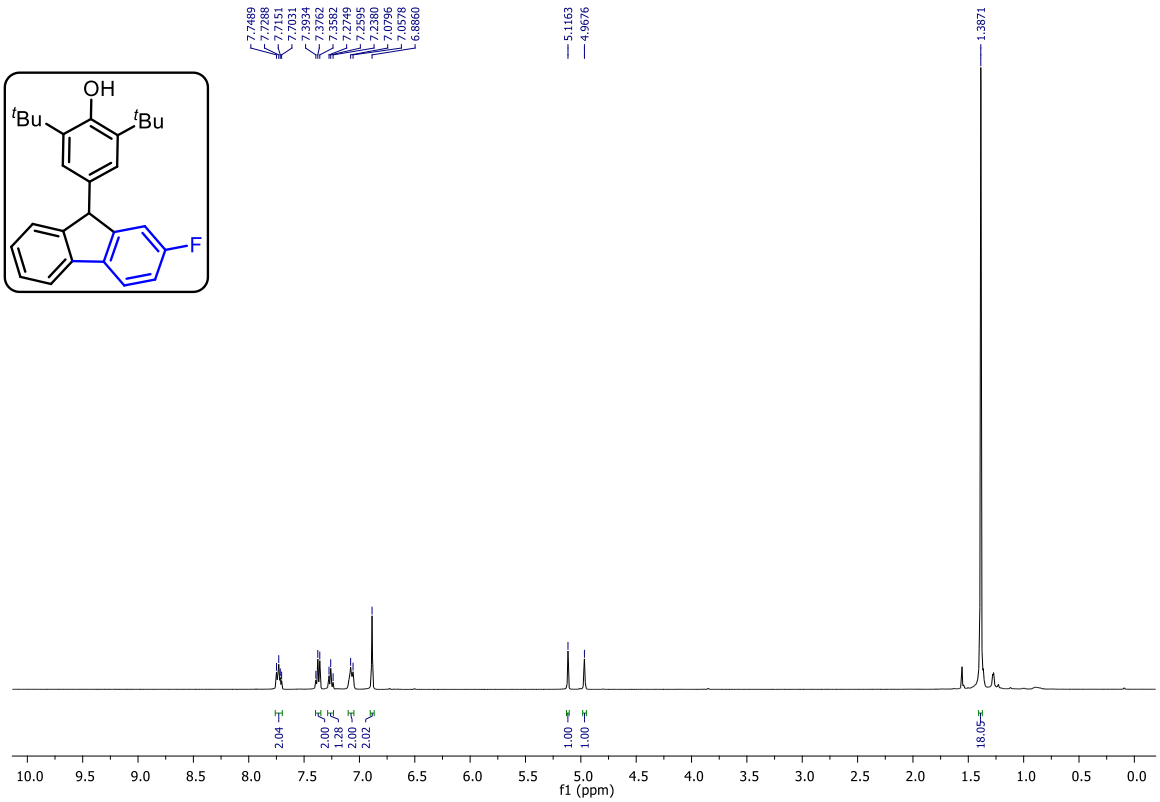


^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound 39i



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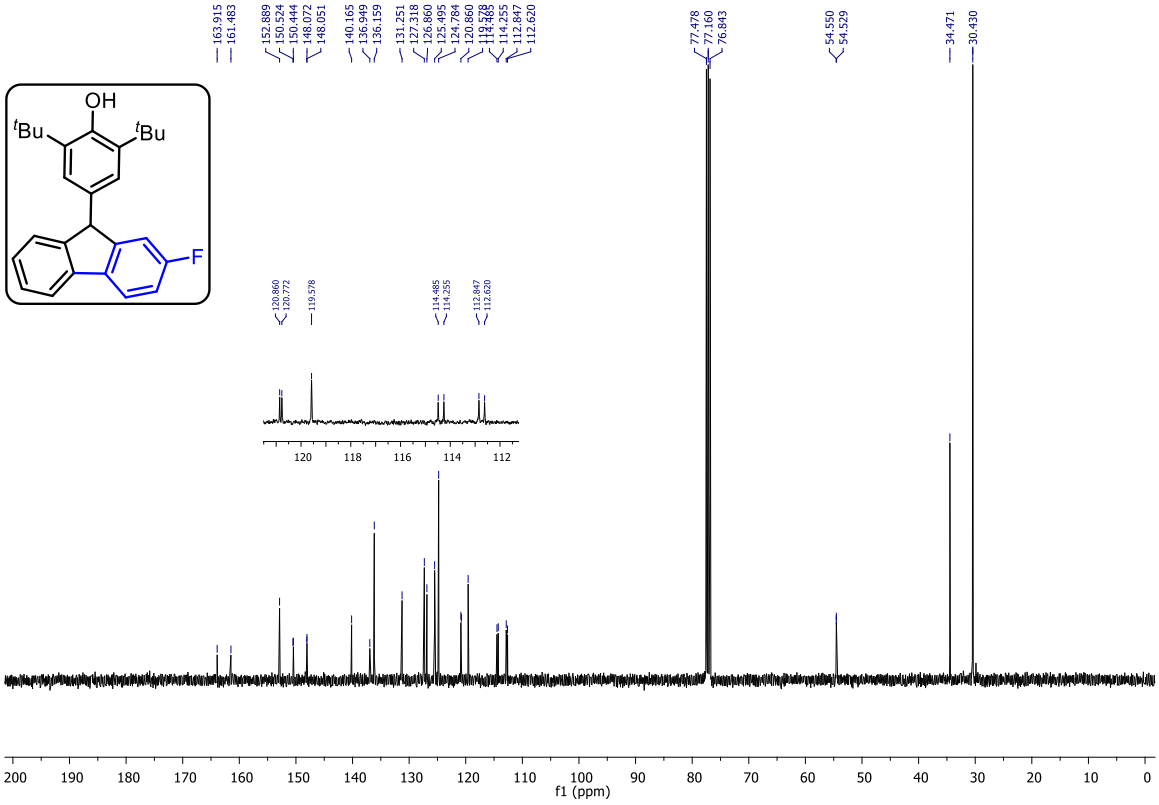
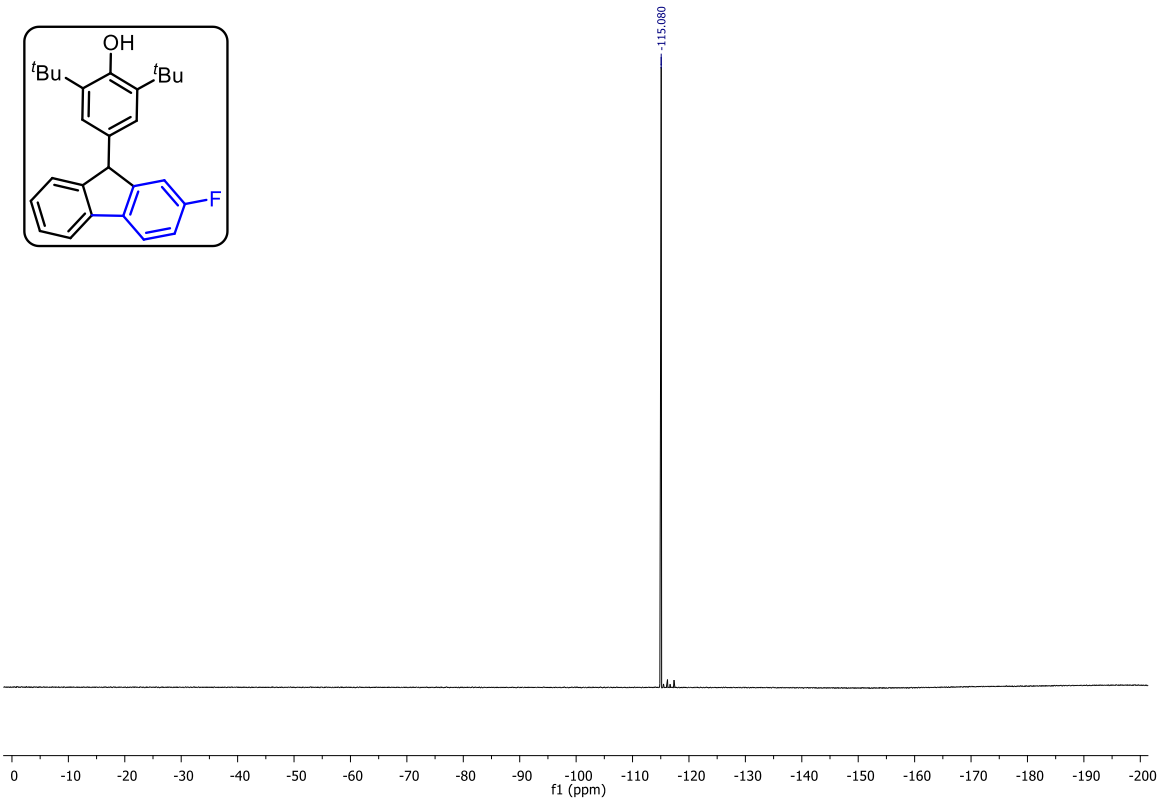
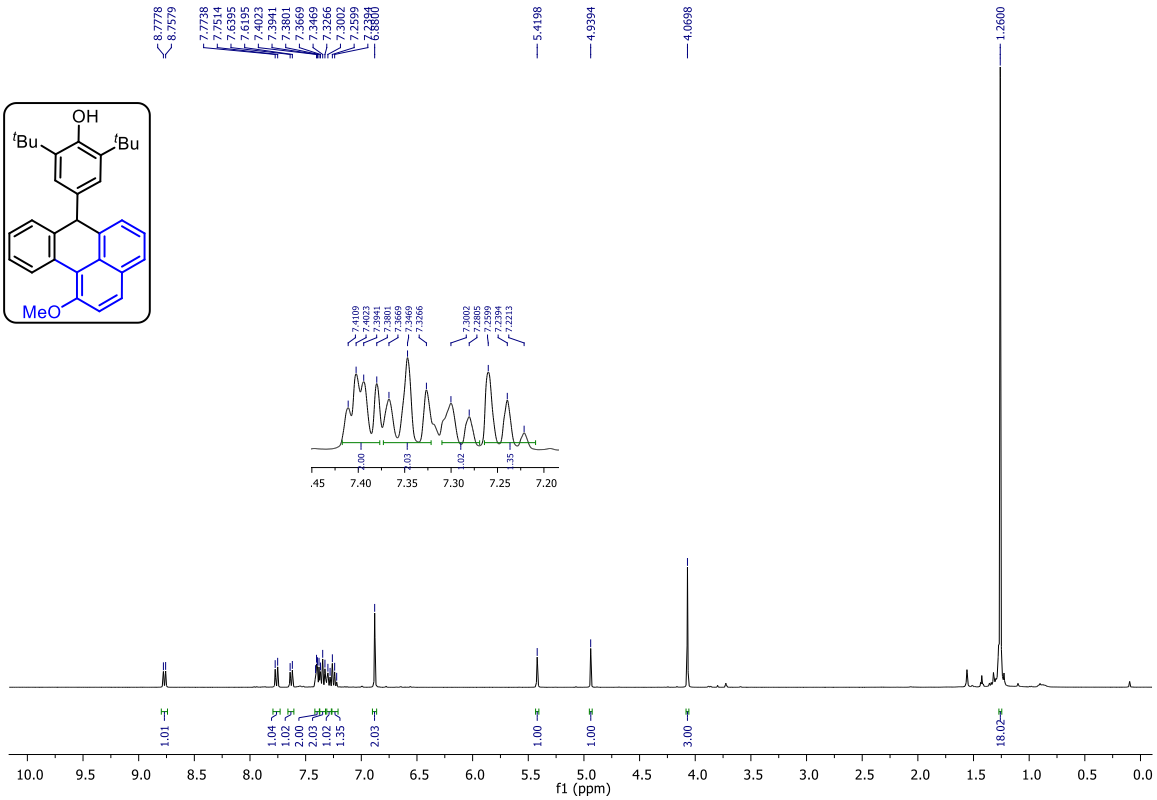


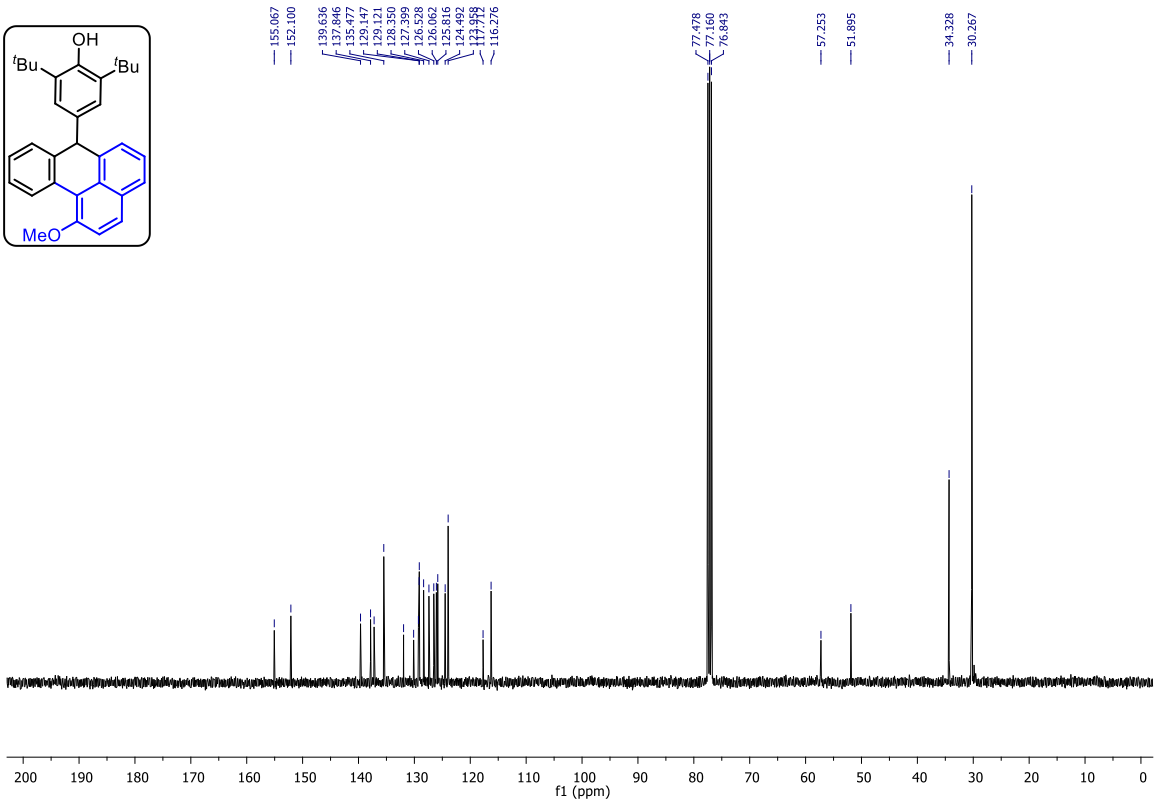
^{19}F NMR (376 MHz, $CDCl_3$) spectrum of compound **39i**



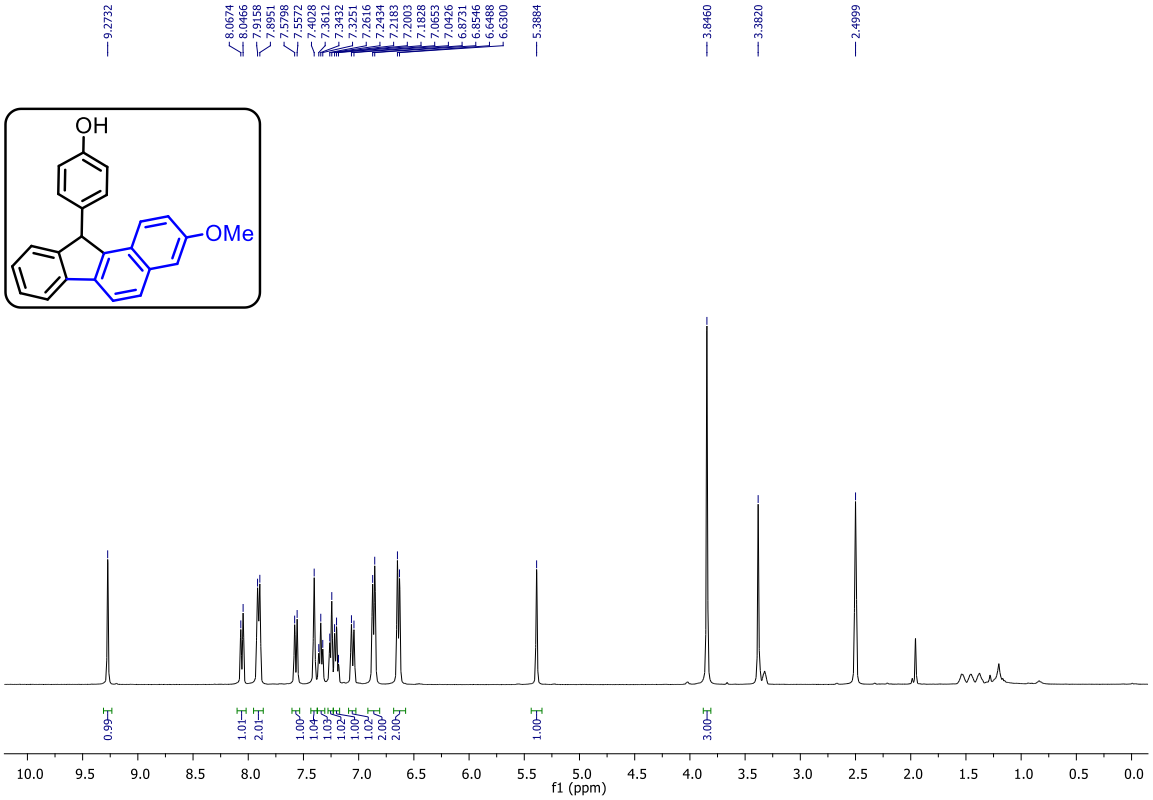
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **39q**



^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) spectrum of compound **39q**



^{1}H NMR (400 MHz, DMSOd_6) spectrum of compound **42a**



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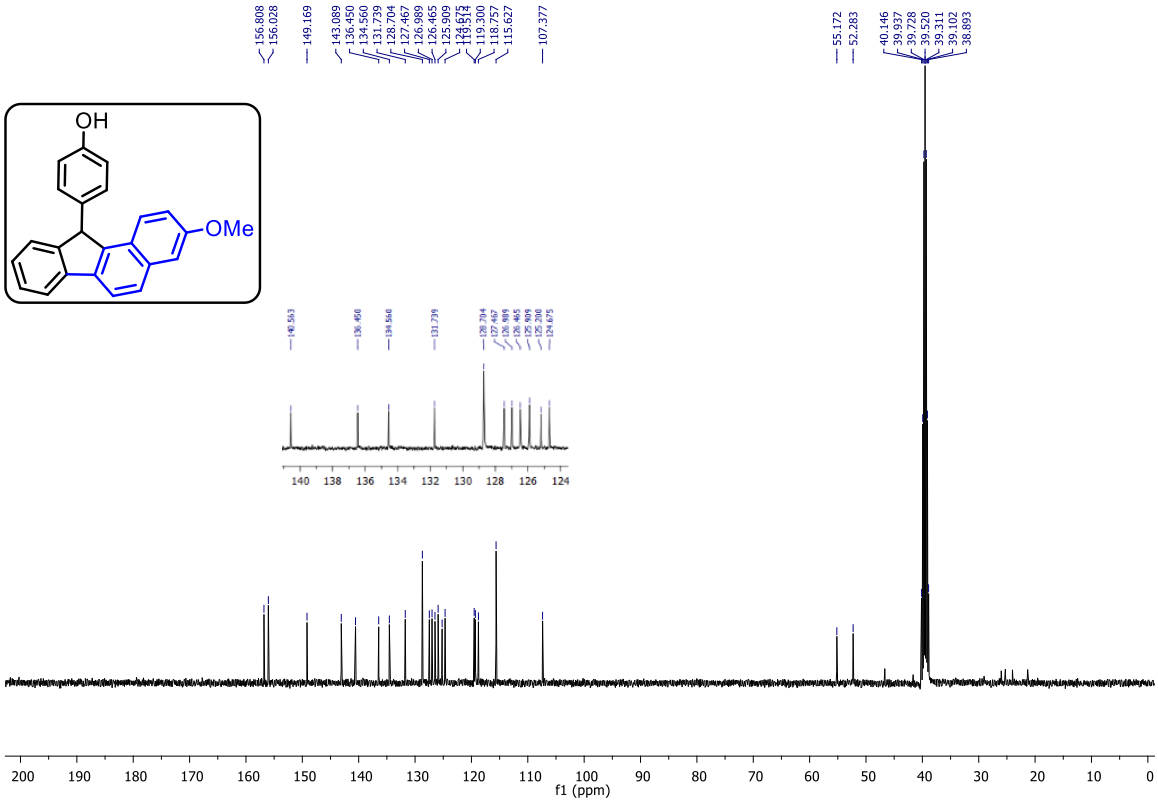
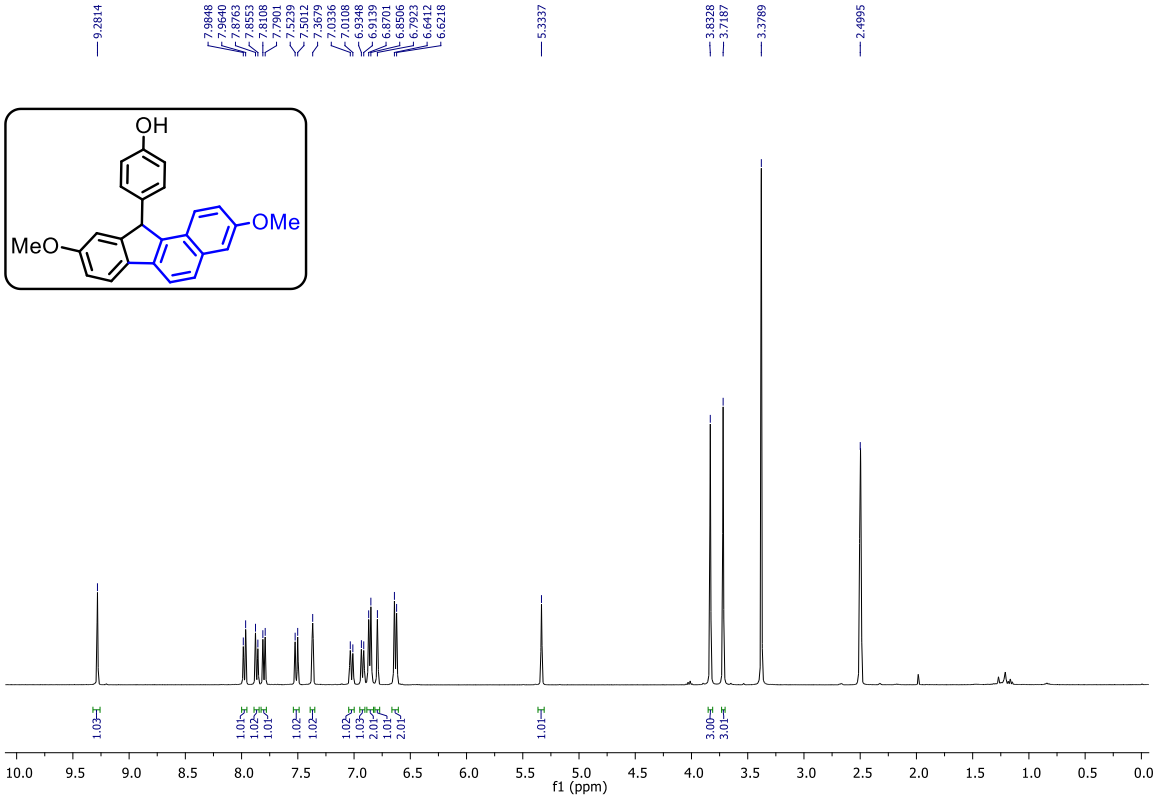


^{1}H NMR (400 MHz, DMSOd_6) spectrum of compound **42b**



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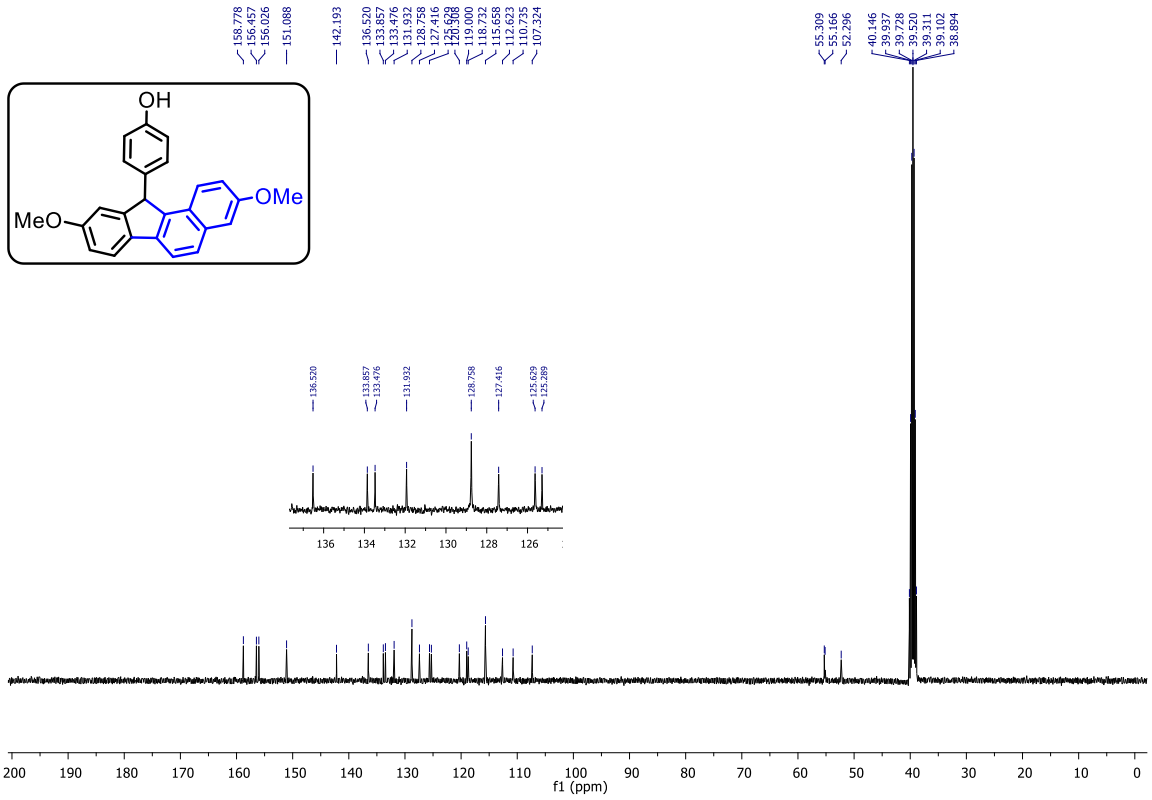

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Part B

Silver-catalyzed cascade approach to access 9,9-disubstituted fluorenes and dihydro-5H-benzo[*a*]fluorenes from *p*-quinone methides

2.2.1 Introduction:

Polycyclic aromatic hydrocarbons (PAH), such as tetracene, pentacene, hexacene, etc., have found fascinating applications in materials science. Due to their rigid and fused aromatic structures, they have shown electrochemical and photochemical properties.[1] Furthermore, other polycyclic aromatic compounds, such as fluorene analogues also found in various optoelectronic materials. The 9,9-disubstituted fluorene and benzofluorene are widely used in organic light-emitting diodes,[2] semiconductors,[3a] solar cells,[3b] and other devices.[4]

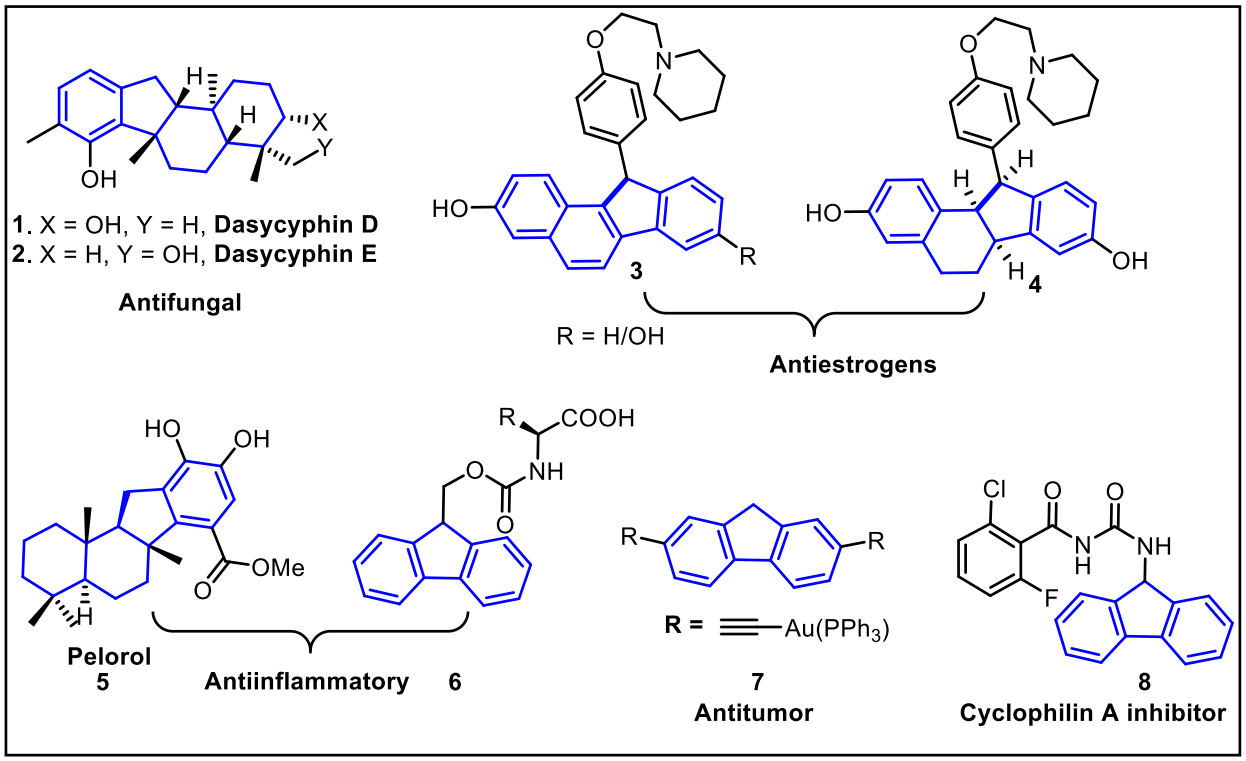


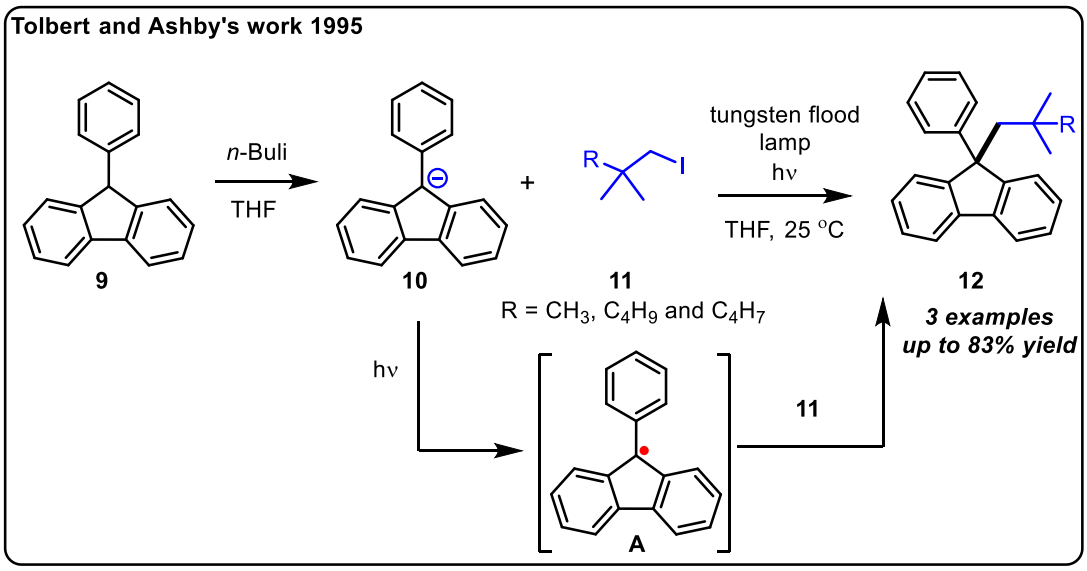
Figure 1. Biologically Significant fluorenes and benzo[*a*]fluorenes

Furthermore, introducing an aryl substitution at the C-9 position increased the morphological and thermal stability[5] of fluorene molecules; thus, the synthesis of 9-aryl or 9,9-diarylfluorene became one of the important transformations nowadays. These structural motifs can also act as ligands in organometallics and coordination chemistry.[6] In addition, there are natural or synthetic bioactive molecules possess these cores in aromatic or saturated forms. Such compounds show various therapeutic properties; for example, dasycyphin D & E (**1** & **2**) show antifungal activity;[7] benzo[*a*]fluorene[8a] **3**, and tetrahydrobenzo[*a*]fluorene[8b] **4**

act as antioestrogens (Figure 1). Whereas, palorol[9a] **5** and Fmoc-protected amino acids[9b] (**6**) have anti-inflammatory properties. In addition, 2,7-diethynylfluorene derivative of gold **7** acts as an antitumor agent,[10] and molecule **8**, synthesized by de novo drug approach, possess cyclophilin A (CysA) inhibitor activity.[11] Due to several applications of these molecules, many synthetic methodologies have been documented in the recent years; some are discussed here.

2.2.2 Literature reports on the synthesis of 9,9-disubstituted fluorene derivatives

In 1995, Tolbert and Ashby's group documented the alkylation of 9-phenylfluorene **9** with 1-iodo-2,2-dimethylalkanes (**11**) via a single electron transfer (SET) pathway. In this transformation, 9-phenylfluorene first reacts with *n*-butyllithium to generate 9-phenylfluorene anion (9PF$^-$), which was then irradiated to form radical intermediate **A** (Scheme 1).[12] Radical **A** then undergoes nucleophilic substitution reaction with iodoalkanes (**11**) to furnish 9,9-disubstituted fluorenes (**12**).

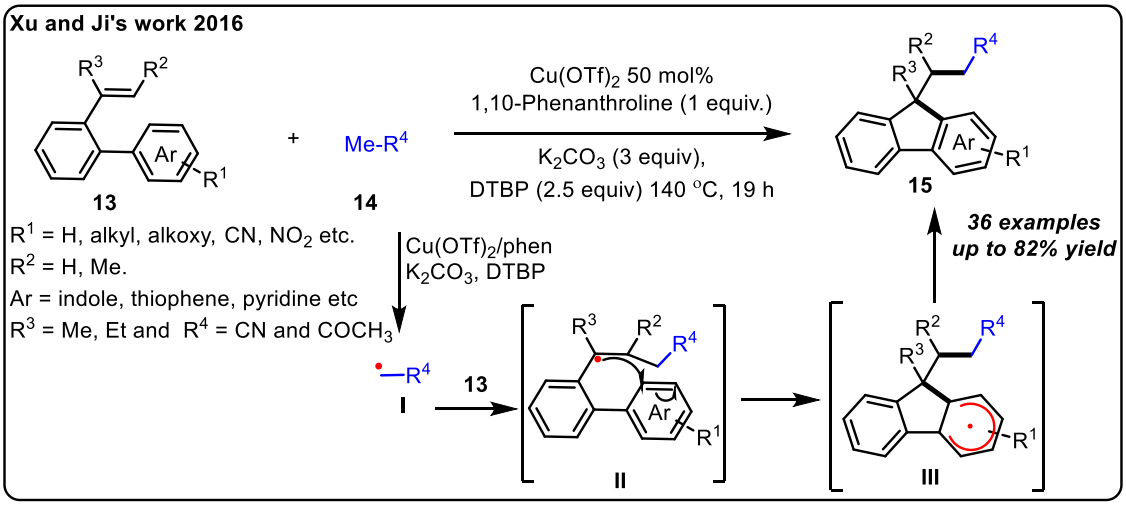


Scheme 1. Alkylation of 9-phenylfluorenes with 1-iodo-2,2-dimethylalkanes

The 9-phenylfluorene anion (9PF$^-$) did not directly react with 1-iodo-2,2-dimethylpropane, which indicates that this reaction went only through radical intermediate **A** after irradiation.

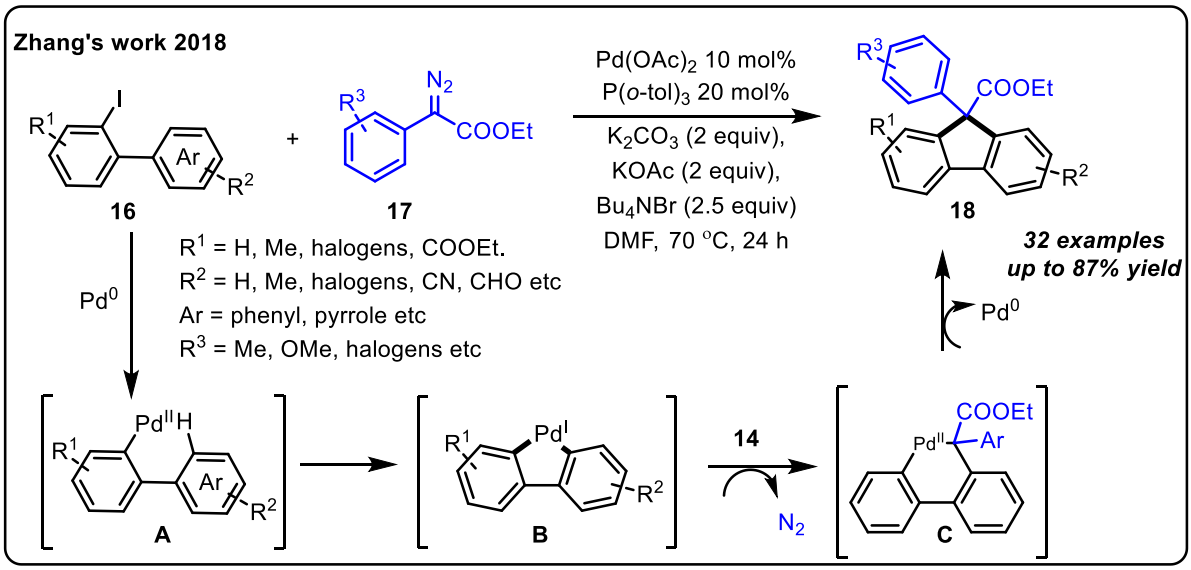
In 2016, Xu and Ji's group described a Cu-mediated domino oxidative coupling of biarylalkenes (**13**) with acetonitrile/acetone (**14**) followed by intramolecular cyclization to synthesized 9,9-disubstituted fluorenes [**15**] (Scheme 2).[13] Initially Cu oxidize acetonitrile/acetone and formed a radical intermediate **I**, which then reacted to alkene **13** to

generate another radical intermediate **II**. The intermediate **II** on intramolecular cyclization followed by oxidation and de-protonation obtained final product **15**.



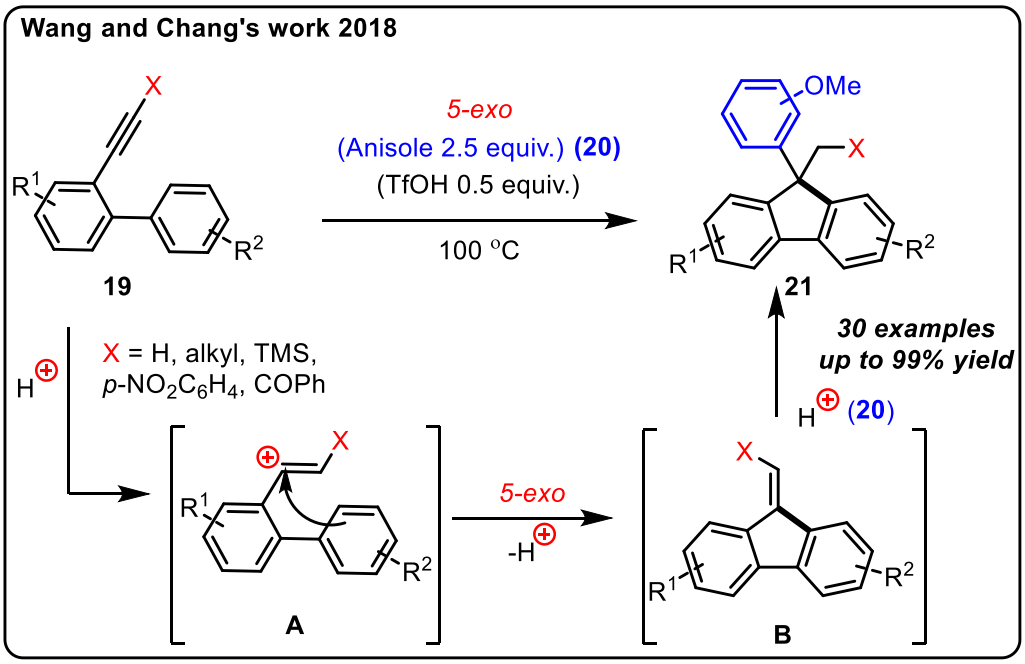
Scheme 2. Synthesis of 9,9-disubstituted fluorene derivatives

In 2018, Zhang's group disclosed a palladium-catalyzed C(sp^2)-H activation of 2-iodobiphenyls (**16**) followed by carbenoid insertion of α-diazoesters (**17**) to obtain 9,9-disubstituted fluorenes [**18**] (Scheme 3).[14] According to the proposed mechanism in the first step, oxidative insertion of [Pd] into 2-iodobiphenyl **16** takes place, leading to intermediate **A**. Subsequently, on intramolecular C-H activation, **A** produces the palladacycle **B**, which then undergoes insertion with α-diazoester **17** and generates another six-member palladacycle **C**. This compound C, after reductive elimination, delivers the product 9,9-disubstituted fluorene **18** with the regeneration of Pd-catalyst.



Scheme 3. Synthesis of 9,9-disubstituted fluorenes by C-H activation

Later on, in the same year, Wang and Chang's group documented a TfOH-catalyzed intramolecular cyclization of *o*-ethynylbiaryls (**19**) followed by Friedel-Craft reaction with anisole **20** to synthesize 9,9-disubstituted fluorene derivatives (**21**). In this transformation, initially, protonation of **19** leads to a carbocation **A,** which then undergoes an intramolecular *5-exo-dig* cyclization to form fluorene **B.** Subsequently, in the presence of TfOH, **B** undergoes addition with anisole to furnish the desired 9,9-disubstituted fluorenes **18** (Scheme 4).[15]

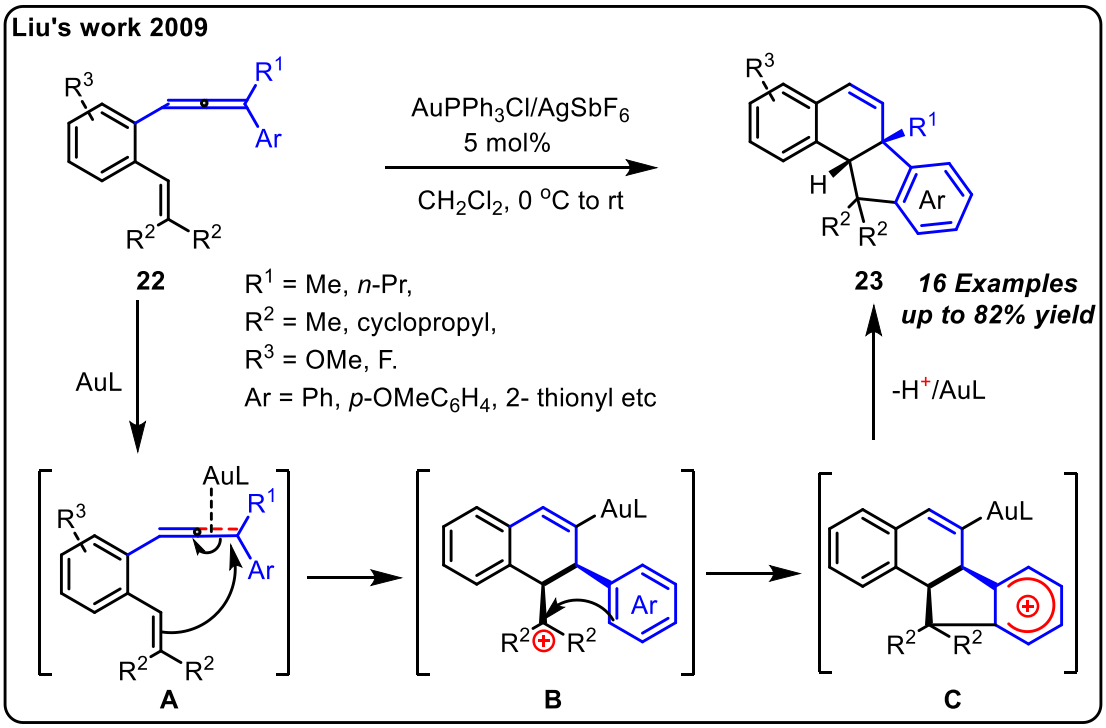


Scheme 4. Matal-free approach for synthesis of 9,9-disubstituted fluorenes

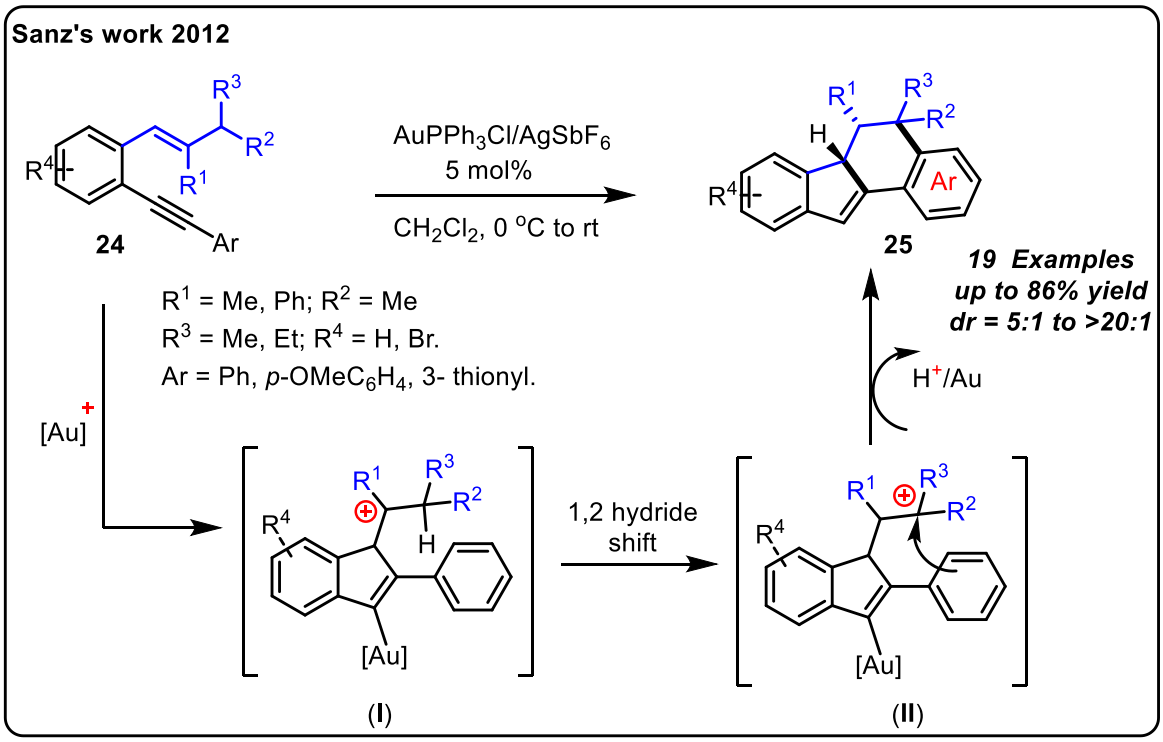
2.2.3 Literature reports on the synthesis of dihydrobenzo[*a*]fluorene derivatives

In 2009, Liu's group developed the synthesis of dihydrobenzo[*a*]fluorene (**23**) via [PPh_3AuCl]/$AgSbF_6$ catalyzed intramolecular [3+2] cycloaddition of 1-aryl-1-allen-6-enes (**22**). As per the proposed mechanism, in the initial step, coordination of Au with **22** followed by intramolecular cyclization led to the formation of cations **B**, which subsequently undergoes cyclization followed by aromatisation, leading to the product **23** (Scheme 5).[16]

In 2012 Sanz's group disclosed a gold-catalyzed formal [3+3] intramolecular cycloaddition of 2-alkynyl styrenes (**24**) to furnished dihydrobenzo[*a*]fluorene derivatives [**25**] (Scheme 6).[17] According to the proposed mechanism, the cationic gold(I) complex activates alkyne, which triggers intramolecular cyclization to generate an intermediate **I**. Subsequently, the intermediate **I** undergoes 1,2 hydride shift to form another carbocation **II**, which was trapped by the aromatic ring to form the desired product **25**.

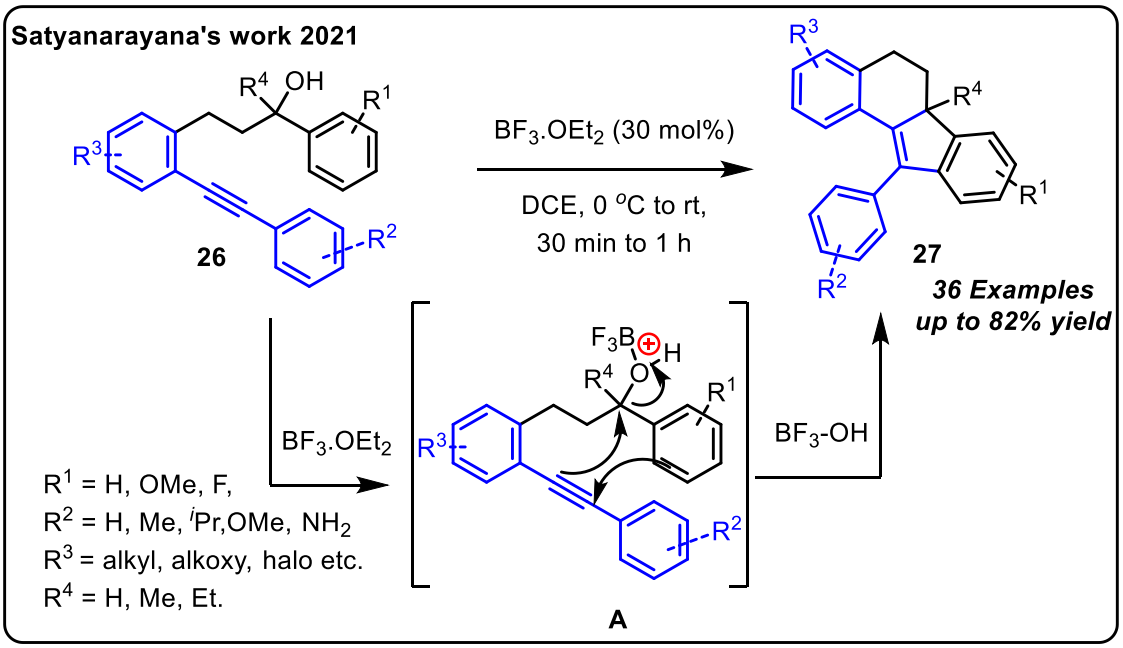


Scheme 5. Gold catalyzed [3+2] intramolecular cycloaddition of 1-aryl-1-allen-6-enes



Scheme 6. Gold catalyzed ene-enyne cyclization via carbocation rearrangement

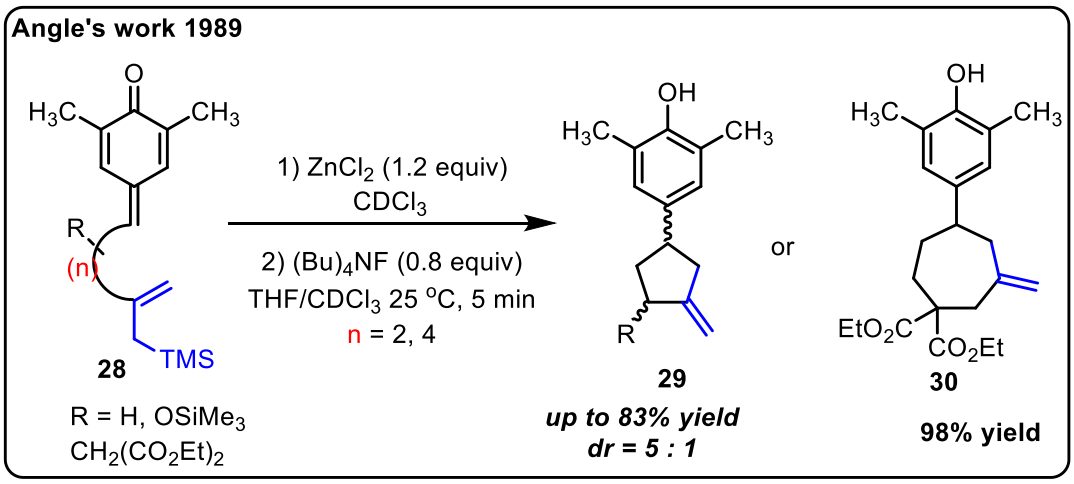
Very recently, Satyanarayana's group reported the regioselective synthesis of dihydrobenzo[*a*]fluorenes (**27**) from alkynols (**26**) using $BF_3.OEt_2$ as a Lewis acid catalyst. The tandem intramolecular cyclization was triggered by the Lewis acid through an intermediate **A** (Scheme 7).[18]



Scheme 7. Synthesis of dihydrobenzo[*a*]fluorenes from alkynols

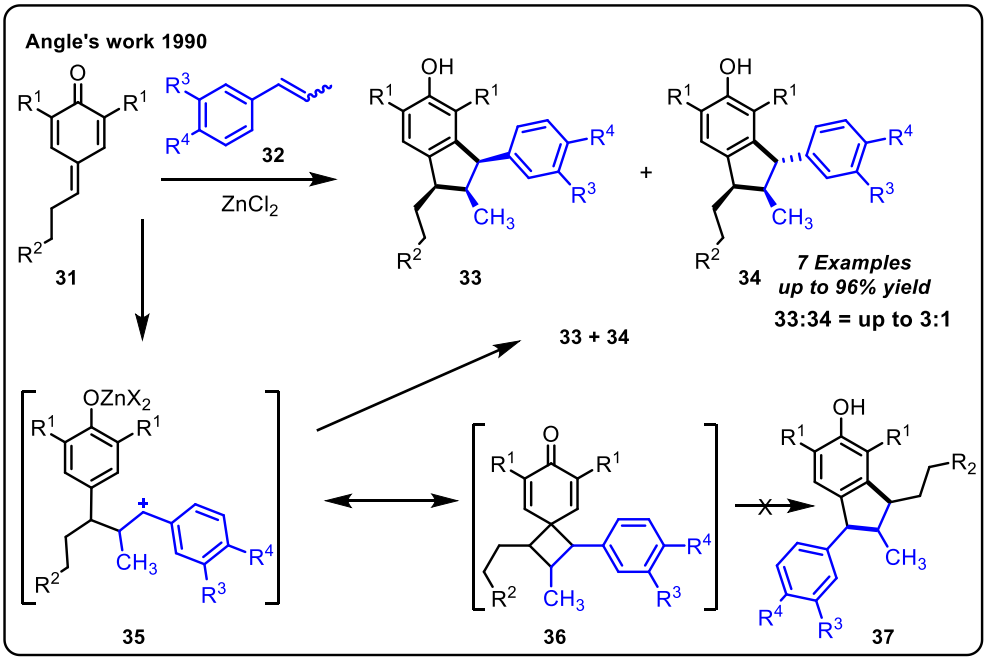
2.2.4 Literature reports on the 1,6 conjugate addition of alkenes

Alkenes have been used as nucleophiles in organic chemistry for many years. As alkenes act like bifunctional molecules, they are used in many cycloaddition reactions.[19] Additionally, these alkenes are also used in polymerization[20] and domino reactions.[21]



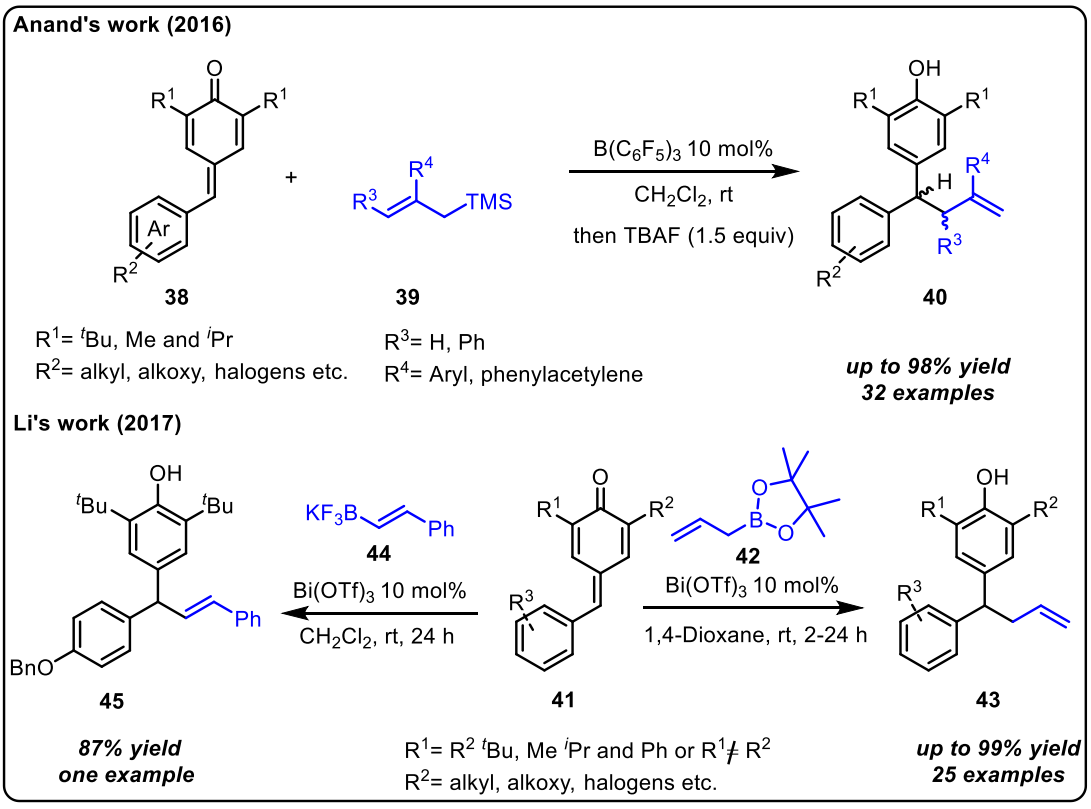
Scheme 8. Intramolecular 1,6-allylation of allyl silane functionalized *p*-QMs

The 1,6 conjugate addition of alkenes (activated) to *p*-QMs was first reported by Angel's group using allyl silane functionalized *p*-QMs (**28**) to prepare five (**29**), and seven-member (**30**) rings through intramolecular cyclization (Scheme 8).[22] Subsequently, one year later, the same group used unactivated alkene (styrenes) with alkyl *p*-QMs (**31**) for the synthesis of dihydro indenes **33** and **34** through stepwise formal [3+2] cycloaddition reactions (Scheme 9).[23] This transformation proceeds through the formation of a cationic intermediate **35**.



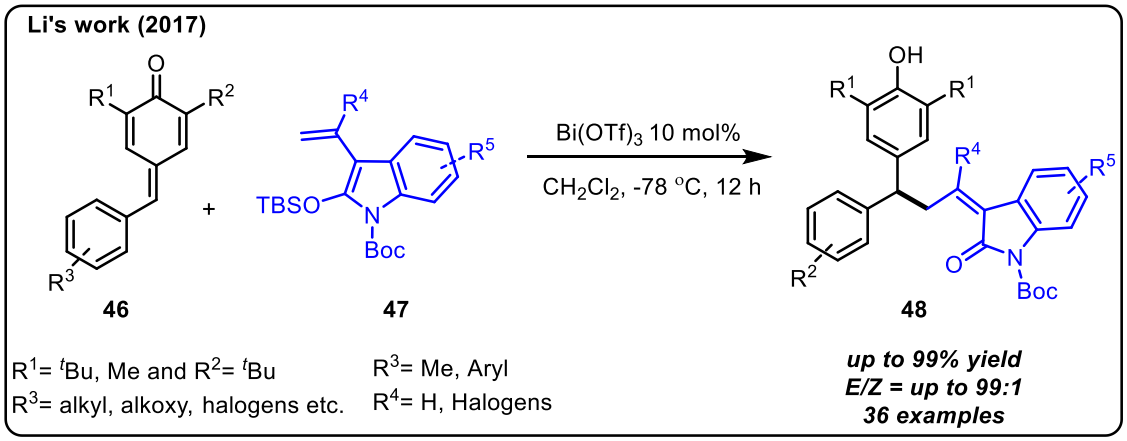
Scheme 9. Synthesis of dihydro indenes by stepwise formal [3+2] cycloaddition of styrene

This cation **35** could be directly captured by a newly formed aromatic ring through the *m*-position to produce the final product, or it could be cyclized from the *p*-position to afford spiro [3.5] nona-5,8-dien-7-one **36**. The unstable **36** was again converted into **35** by ring opening; hence product **37** was not at all observed.



Scheme 10. 1,6 allylation of *p*-QMs with allylic silane and boronic esters

In 2016 Anand's group described the allylation of *p*-QMs (**38**) with allyl trimethylsilane (**39**) using tris(pentafluorophenyl)borane as a catalyst to furnish allyl diarylmethanes [**40**] (Scheme 10).[24a] Similarly, in 2017, Li's group[24b] used allylic boronic acid pinacol ester (**42**) for 1,6 allylation in the presence of $Bi(OTf)_3$ as a catalyst. In this report, one example of hydrolefination of *p*-QM was also reported using styryltrifluoroboric acid potassium **43**.

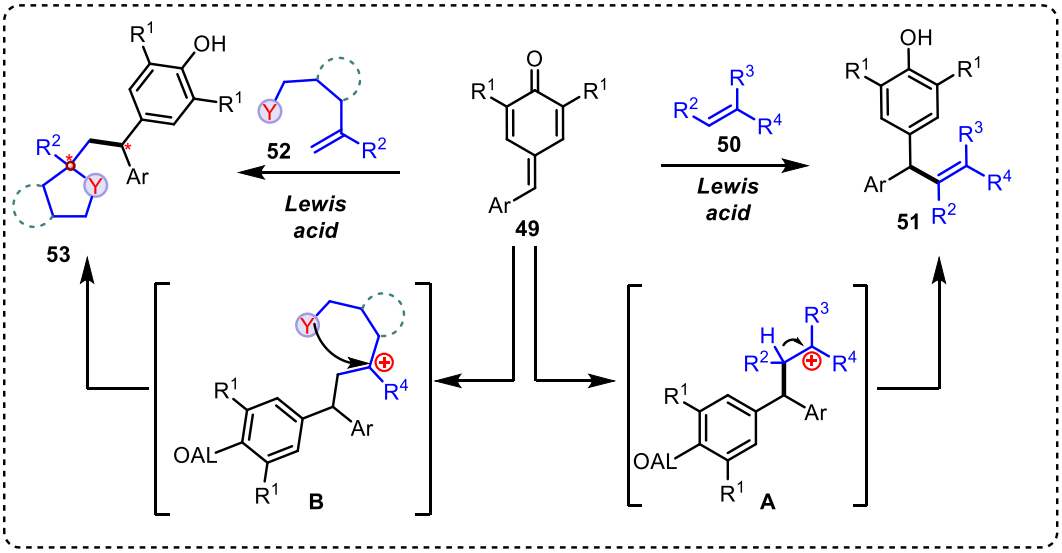


Scheme 11. 1,6-conjugate addition of 3-propenyl-2-silyloxyindoles to obtain functionalized oxindoles

Later on, the same group developed a highly diastereoselective addition of 3-propenyl-2-silyloxyindoles (**47**) to *p*-QMs (**46**). In this transformation, functionalized oxindoles (**48**) were formed as the final product in 99% yield and very good diastereoselectivities (up to Z/E > 99:1) (Scheme 11).[25]

2.2.5 Background:

In most of the reports discussed in the section **2.2**, only activated alkenes have been used for 1,6-conjugate addition reactions of *para* quinone methides. Recently, our group described an inter- and intramolecular hydroolefination of *p*-QMs for the synthesis of vinyl diaryl methane and indene derivatives from unactivated alkenes.[26] Furthermore, that methodology was elaborated to the total synthesis of (±) isopaucifloral F. In line with that, we have decided to elaborate it further for the synthesis of carbocycles. We envisioned that, in hydroolefination reactions, the carbocation intermediate generated during the reaction could be trapped if an additional C-nucleophilic site is present in the molecule, which could potentially lead to fused carbocycles. In this context, we have decided to synthesize the olefinic part with an additional nucleophilic site, which would give a 1,6-addition followed by intramolecular cyclization to produce carbocycles (Scheme 12).



Scheme 12. Hydroolefination followed by intramolecular cyclization

2.2.6 Results and discussion:

We began the optimization study using *p*-quinone methide **54a** and 2-(1-phenylvinyl)-1,1'-biaryl **55a** and the results are summarised in Table 1**.** Our initial effort using 10 mol% $Bi(OTf)_3$ did not yield any promising results as this reaction gave a complex mixture of products (entry 1). The reactions using 10 mol% of other metal triflates such as CuOTf.toluene complex, $Cu(OTf)_2$ and AgOTf also provided only complex mixtures (entries 2-4). Then, we reasoned that Lewis acids might not be suitable for this transformation, so we attempted Bronsted acid in place of Lewis acid, but regrettably, TfOH and H_2SO_4 were not also not found to be suitable as both delivered a complex mixture of products (entries 5 & 6). Fortunately, when $AgSbF_6$ was employed as a catalyst, the desired cyclized product **56a** was obtained in an 88% isolated yield in just 15 minutes (entry 7). The structure of **56a** deduced from ^{1}H NMR, ^{13}C NMR, IR spectroscopy and mass spectrometry. In ^{1}H NMR (see figure 2) the presence of singlet at δ 4.93 ppm due to phenolic OH, singlet at δ 1.35 ppm due to two symmetric *tert*-butyl groups and doublet of doublet at δ 3.32 ppm, triplet at δ 3.10 ppm for methylene and benzylic protons respectively; supported the formation of product **56a**. In ^{13}C NMR (see figure 3) disappearance of carbonyl peak at δ 186 ppm from **54a**, three aliphatic peak was observed at δ 59.1 ppm, δ 46.6 ppm and 45.9 ppm for quaternary C-9, methylene and benzylic carbons respectively also supported the formation of **56a**. Further in IR peak obsevered at 3631 cm^{-1} supported the formation of phenolic OH in product **56a**. Encouraged by this result, we performed a few more optimization experiments using $AgSbF_6$ as a catalyst in other solvents, including 1,2-dichloroethane, toluene, DMF, etc. (entries 8–12). However, none of them was found to be superior to CH_2Cl_2.

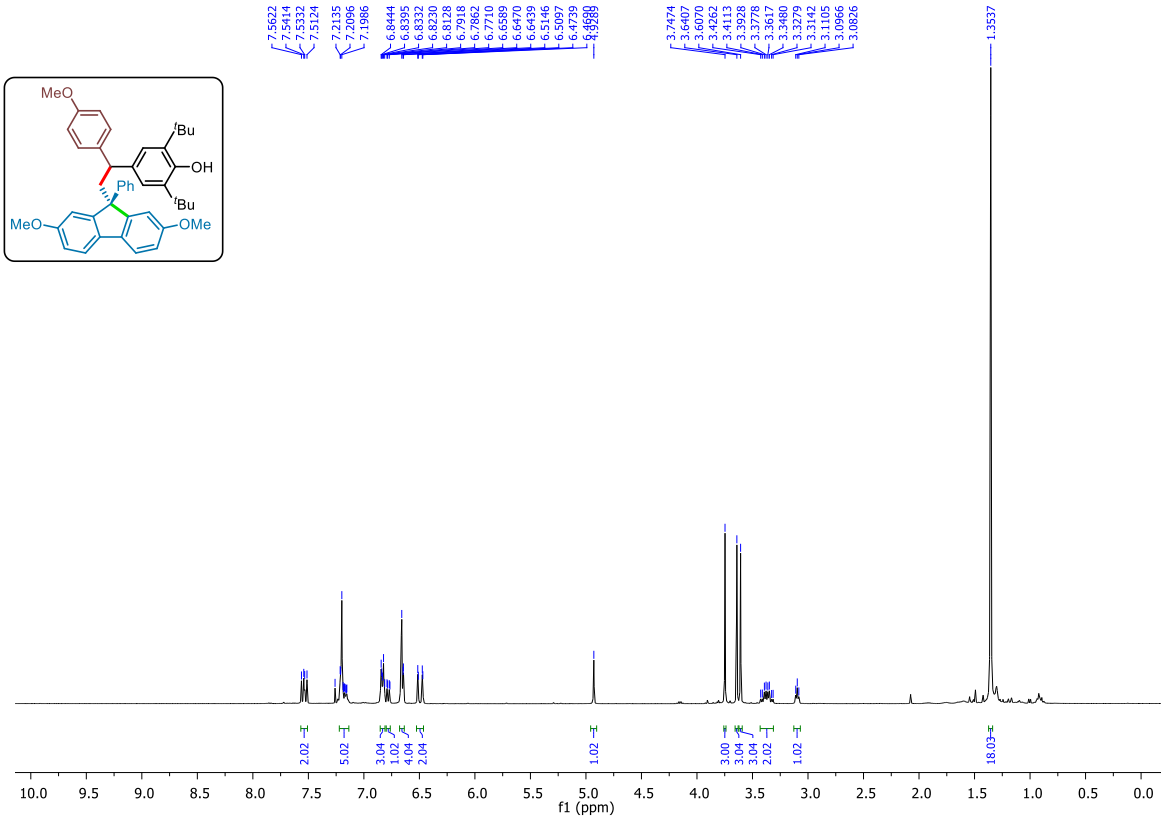


Figure 2. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **56a**

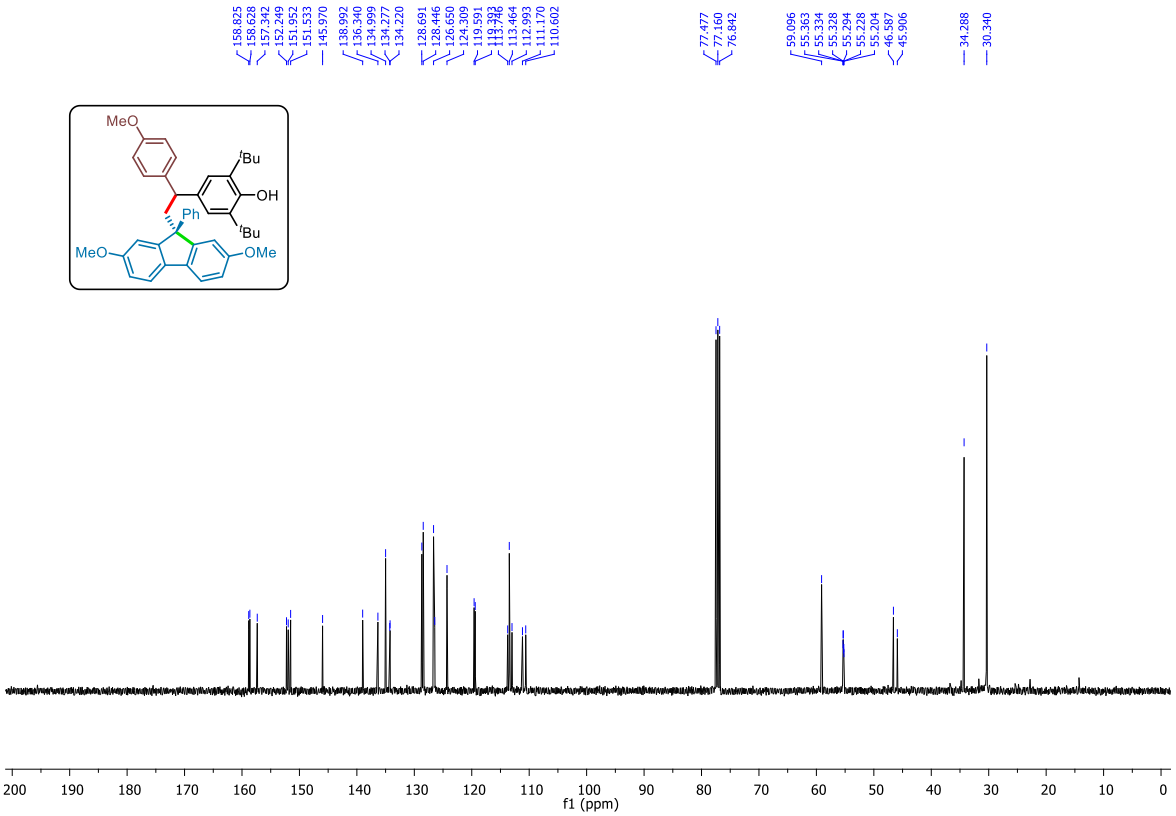
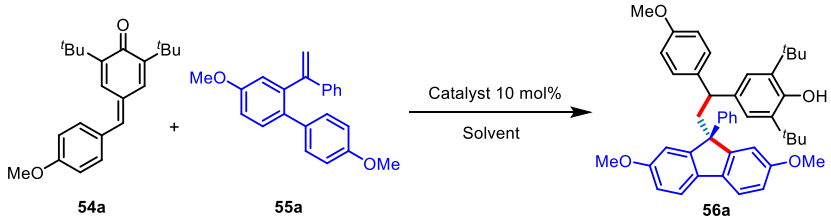


Figure 3. ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of compound **56a**

No reaction occurred in the absence of the catalyst, which clearly indicates the requirement of a Lewis acid catalyst for this transformation (entry 13).

Using a variety of substituted *p*-QMs and 2-(1-phenylvinyl)-1,1'-biaryls, the substrate scope was assessed under optimized condition (Table 1, entry 7); the outcomes are shown in Table 2. In the cases of *p*-QMs **54b-g**, it is apparent from Table 2 that this approach worked extremely well, regardless of the electronic nature of *p*-QMs, and the desired products **56b-g** were isolated in the range of 76-88% yields. In the case of *p*-QM **54h**, the expected product **56h** was isolated in 86% yield.

Table1. *Optimization Studies*[a]

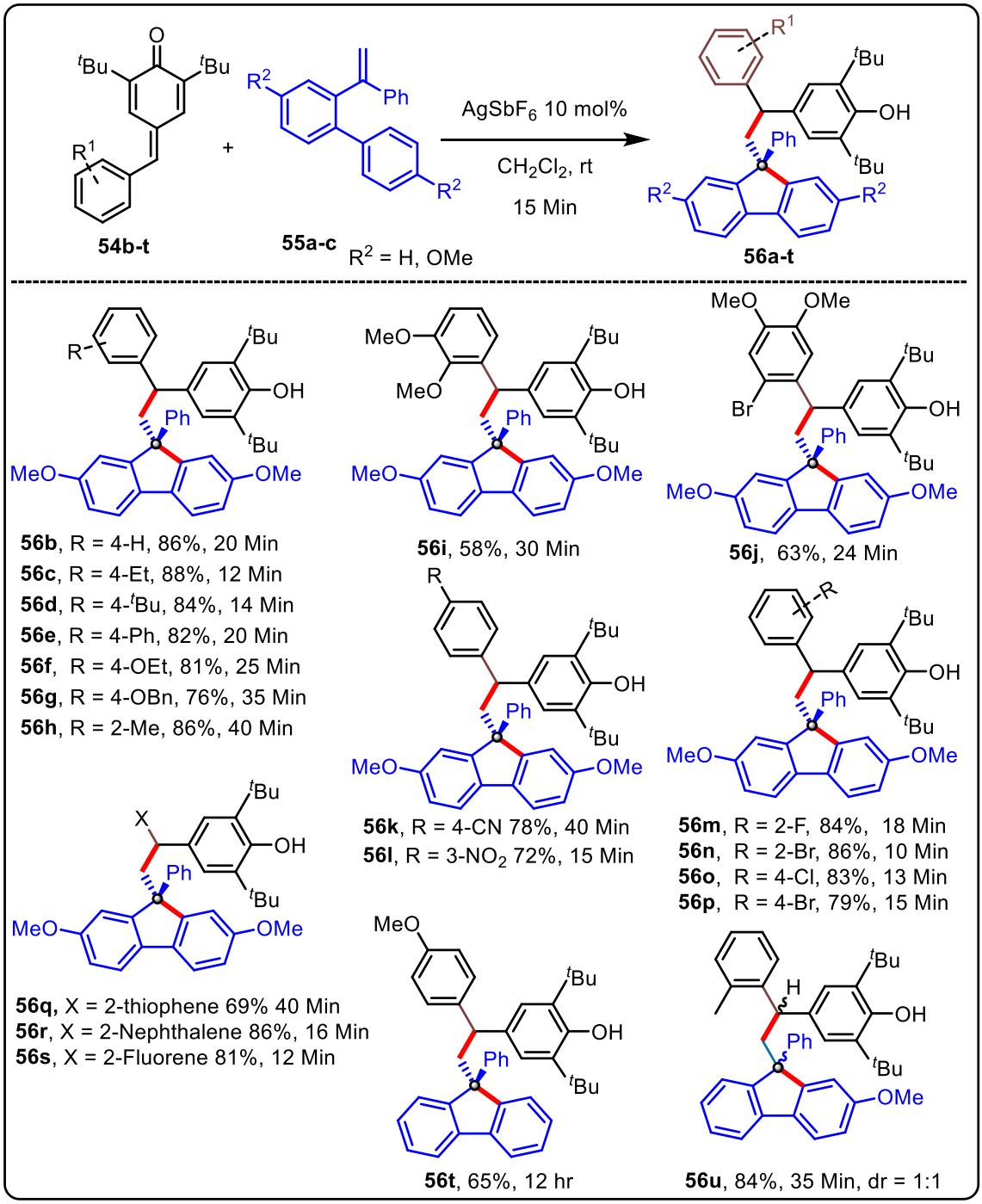


Entry	Catalyst	Solvent	Time [Min]	Yield [%] 56a
1	$Bi(OTf)_3$	DCM	30	CM
2	CuOTf.toulene	DCM	90	CM
3	$Cu(OTf)_2$	DCE	12	CM
4	AgOTf	DCM	120	CM
5	TfOH	DCM	15	CM
6	H_2SO_4	DCM	25	CM
7	**$AgSbF_6$**	**DCM**	**15**	**88**
8	$AgSbF_6$	DCE	20	86
9	$AgSbF_6$	MeCN	120	trace
10	$AgSbF_6$	THF	120	NR
11	$AgSbF_6$	PhMe	120	trace
12	$AgSbF_6$	DMF	120	NR
13	-	DCM	12(h)	NR

[a] Reaction conditions: All reactions were carried out with 0.123 mmol of **54a** and 0.135 mmol of **55a** in solvent (1.5 mL). CM = Complex Mixture. NR = no reaction. rt = room temperature.

Under the same conditions, methoxy substituted *p*-QMs **54i** & **54j** underwent smooth conversion and produced the desired products **56i** & **56j** in 58 and 63% of isolated yields, respectively. Interestingly, electron-poor aryl substituted *p*-QMs **54k** & **54l** also underwent cyclization and gave the respective products **56k** & **56l** in good yields (78% & 72%, respectively).

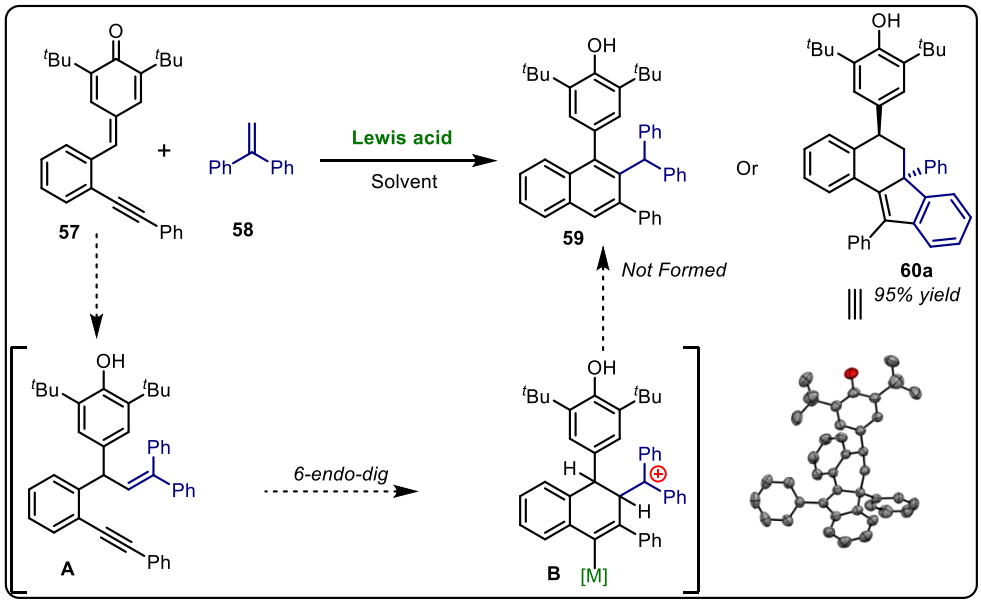
Table 2. Substrate Scope[a]



[a]Reactions were carried out in 0.05-0.08 mmol of **54b-t**. The diastereomeric ratios were calculated from the ^{1}H NMR analysis of the crude mixture. Yields reported are isolated yields.

Moreover, halogen substituted *p*-QMs **54m-p** provided the respective products **56m-p** in 79-86% yields under standard conditions. In addition, *p*-QMs **54q-s**, derived from different aryls, produced the fluorene derivatives **56q-s** in 69-86% isolated yields. The reaction with 2-(1-phenylvinyl)-1,1'-biphenyl **55b** was found to be sluggish; however, the product **56t** was formed in 65% yield. When the alkene **55c**, derived from an asymmetrical biaryl, was treated with **54a**, the product **56u** was obtained in 84% yield as a 1:1 mixture of diastereomers.

Next, we were interested in examining the reaction between 2-alkynylated *p*-quinone methides and styrenes. We envisioned that, in this case, it is possible to access substituted naphthalene derivatives (**59**) through the 1,6-conjugate addition of olefins (**58**) to 2-alkynylated *p*-quinone methides (**57**) followed by intramolecular electrophilic alkene-alkyne cyclization in a one-pot manner (Scheme 13).



Scheme 13. Cascade cyclization of **57a**

Our initial attempt using $Bi(OTf)_3$ as a catalyst did not give any fruitful results; unfortunately, only the decomposition of **57a** was observed (entry 1). Similarly, silver catalysts such as AgOTf, $AgNO_3$ and $Ag(CF_3COO)$ failed to effect this transformation (entries 2-4), as decomposition of **57a** was observed in these cases. However, when $AgSbF_6$ was used as a catalyst in CH_2Cl_2, **57a** was completely consumed within 15 min (entry 5). Interestingly, the expected naphthalene derivative **59** was not formed; instead, the dihydrobenzo[*a*]fluorene **60a** was obtained as a sole product in 95% yield [*dr* {anti: syn} = >20:1] (Scheme 13). The structure of **60a** was unambiguously confirmed by ^1H NMR, ^{13}C NMR, IR spectroscopy, and X-ray analysis. In ^1H NMR (see figure 4) singlet at δ 5.10 ppm for phenolic OH, singlet at δ

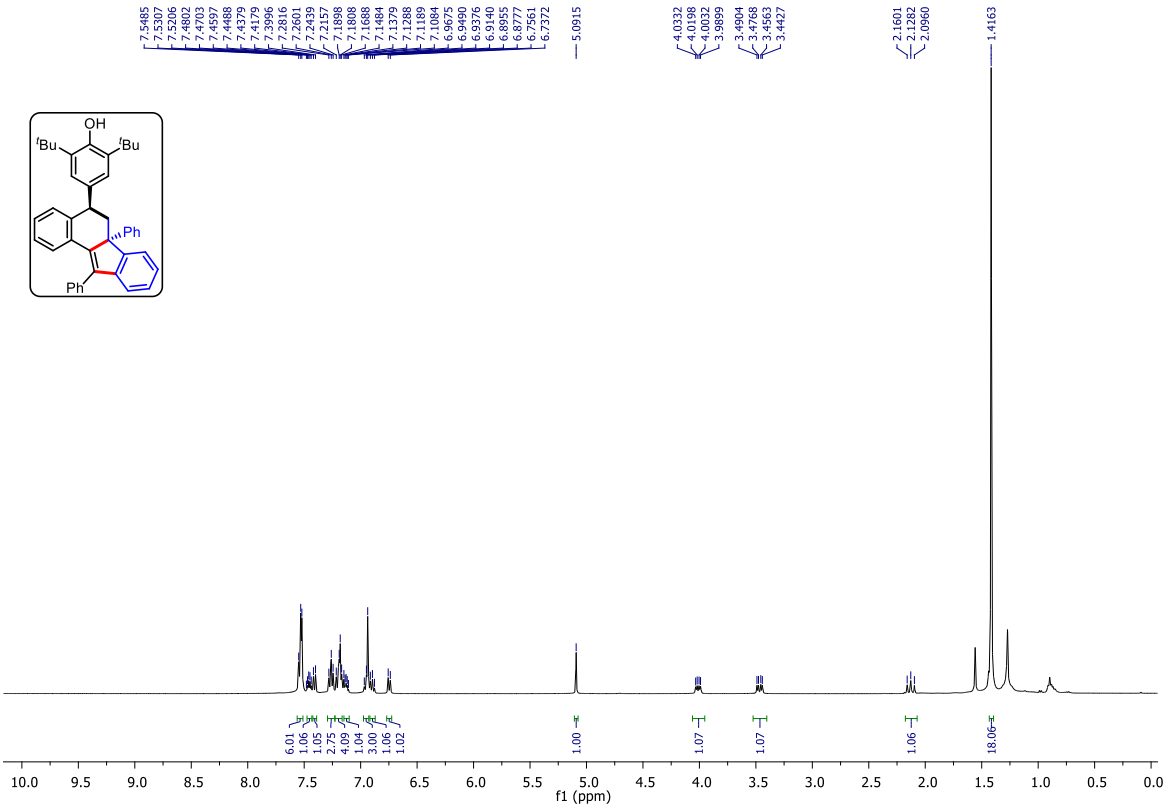


Figure 4. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **60a**

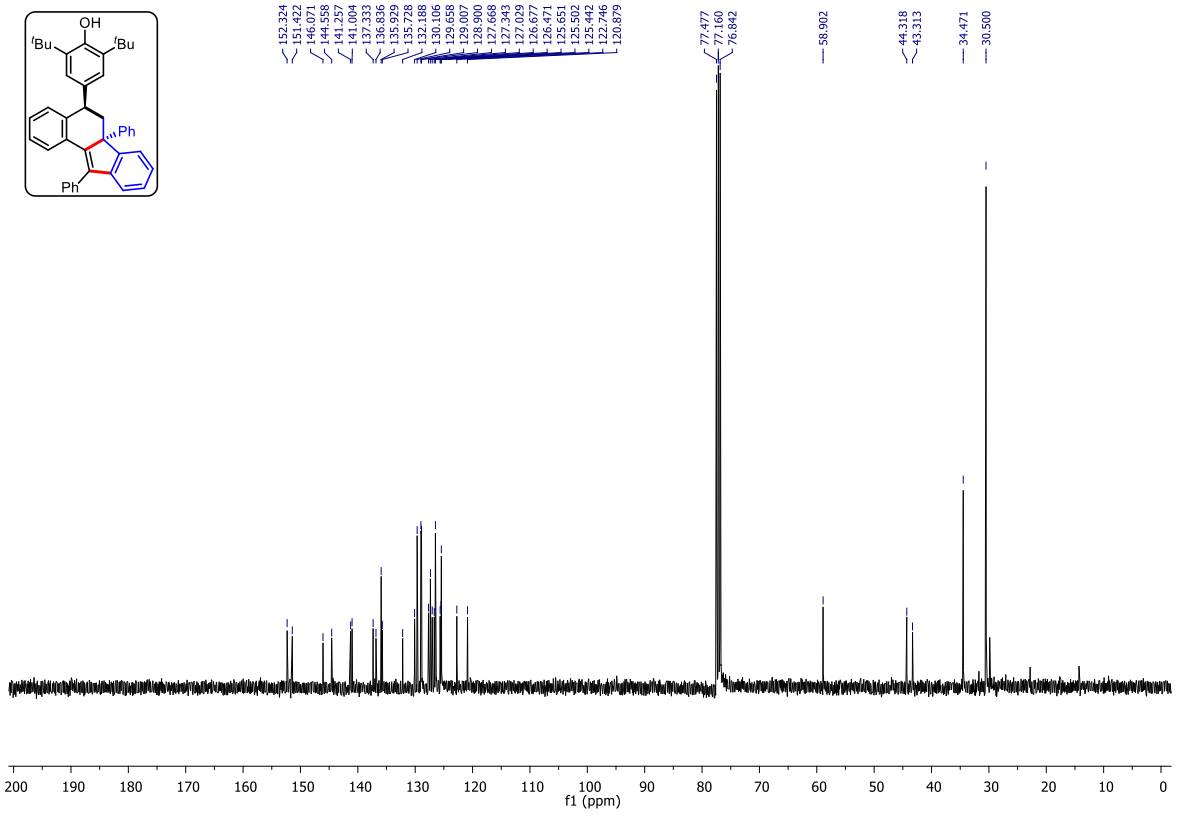
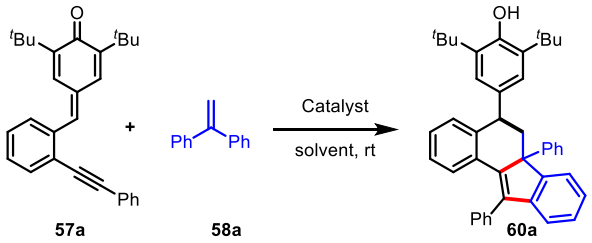


Figure 5. ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) spectrum of compound **60a**

1.42 ppm for two *tert*-butyl groups and two distereotropic protons from methylene obseved as doublet of doublet at δ 4.01 ppm, δ 3.46 ppm supported the formation of product **60a**. In ^{13}C NMR (see figure 5) alkyne peak, carbonyl peck from *p*-QM **57a** was missing and formation of new peaks at δ 58.9 ppm, δ 44.3 ppm, δ 43.3 ppm for quaternary C-6a, C-6 and C-5 supported the formation of **60a**. The formation of OH in product **60a** was also supported by IR peak observed at 3641 cm^{-1}. Further optimization was carried out using $AgSbF_6$ as a catalyst in other solvents such as toluene, MeCN, and THF. However, in all those cases, neither **60a** nor **59** was obtained, and in fact, the starting material **57a** remained as such (entries 10-12). Similarly, other Lewis acids such as $Cu(OTf)_2$, $PdCl_2$, and $Sc(OTf)_3$ failed to affect this transformation (entries 7-9).

After finding an optimal condition for this transformation (Table 3, entry 5), the substrate scope was investigated using a wide range of alkynylated *p*-QMs (**57b-k**) [Table 4] and (**57l-q**) [Table 5].

Table 3. *Optimization studies*[a]



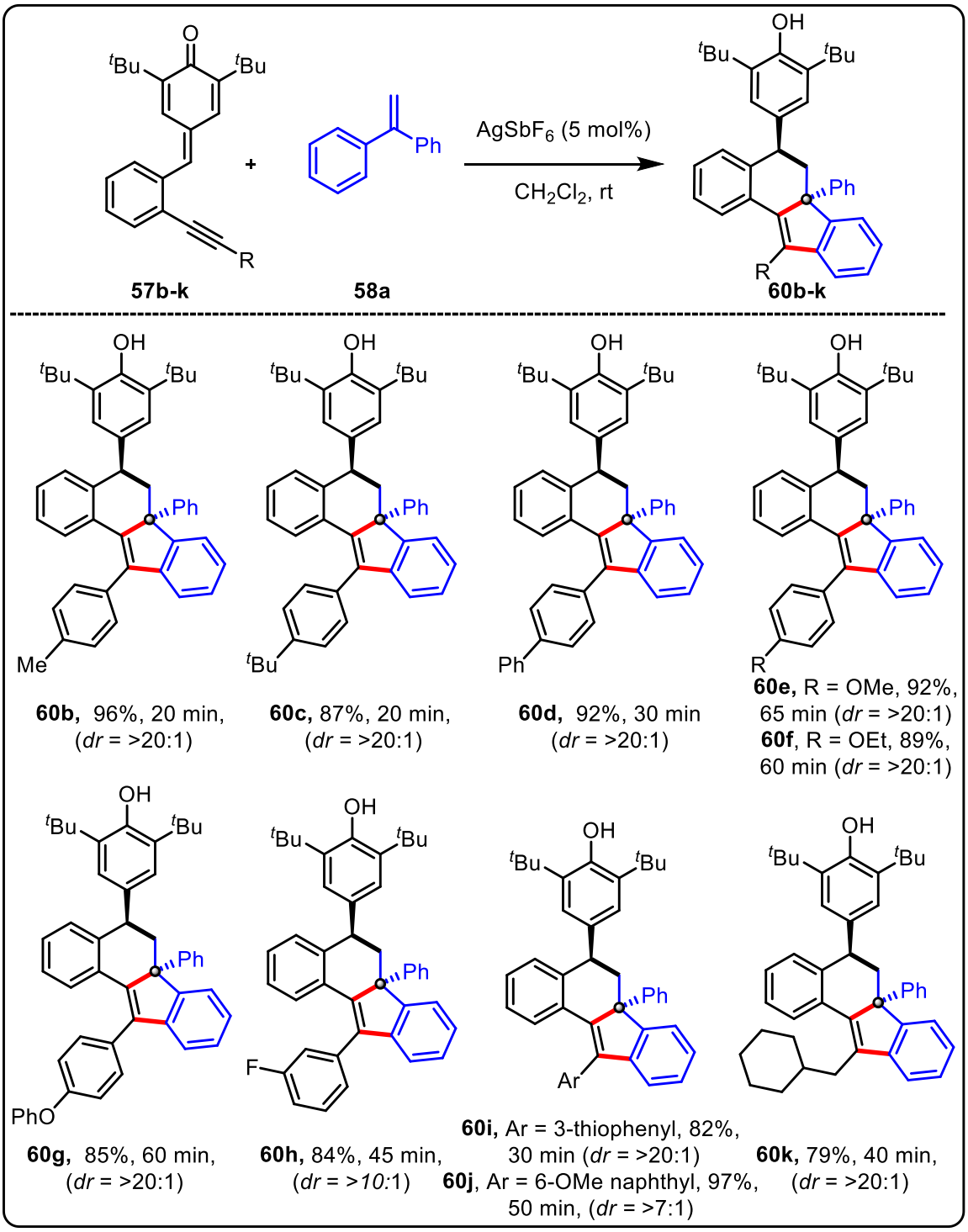
57a 58a 60a

entry	Catalyst	solvent	time [h]	isolated yield of 60a [%]
1	$Bi(OTf)_3$	DCM	1 h	CM
2	AgOTf	DCM	1 h	CM
3	$AgNO_3$	DCM	24 h	CM
4	$Ag(CF_3COO)$	DCM	24 h	CM
5	**$AgSbF_6$**	**DCM**	**15 min**	**95**
6	$Cu(OTf)_2$	DCM	24 h	NR
7	$PdCl_2$	DCM	24 h	NR
8	$Sc(OTf)_3$	DCM	24 h	NR
9	$AgSbF_6$	DCE	20 min	93
10	$AgSbF_6$	Toluene	24 h	Trace
11	$AgSbF_6$	ACN	24 h	NR
12	$AgSbF_6$	THF	24 h	NR

[a] *Reaction conditions:* All reactions were carried out with 0.062 mmol of **57a** and 0.074 mmol of **60a** in solvent (1.5 mL) at room temperature (30 - 33 °C). DCE = 1,2-dichloroethane. CM = Complex Mixture. NR = No reaction.

It is clear from table 4 that this method worked very well with *p*-QMs (**57b-g**), bearing electron-rich aryl substituents at the alkyne part, and the corresponding dihydrobenzo[*a*]fluorene derivatives **60b-g** were isolated in good to excellent yields and diastereoselectivity [*dr* {anti: syn} = 7:1 to >20:1] (Table 4).

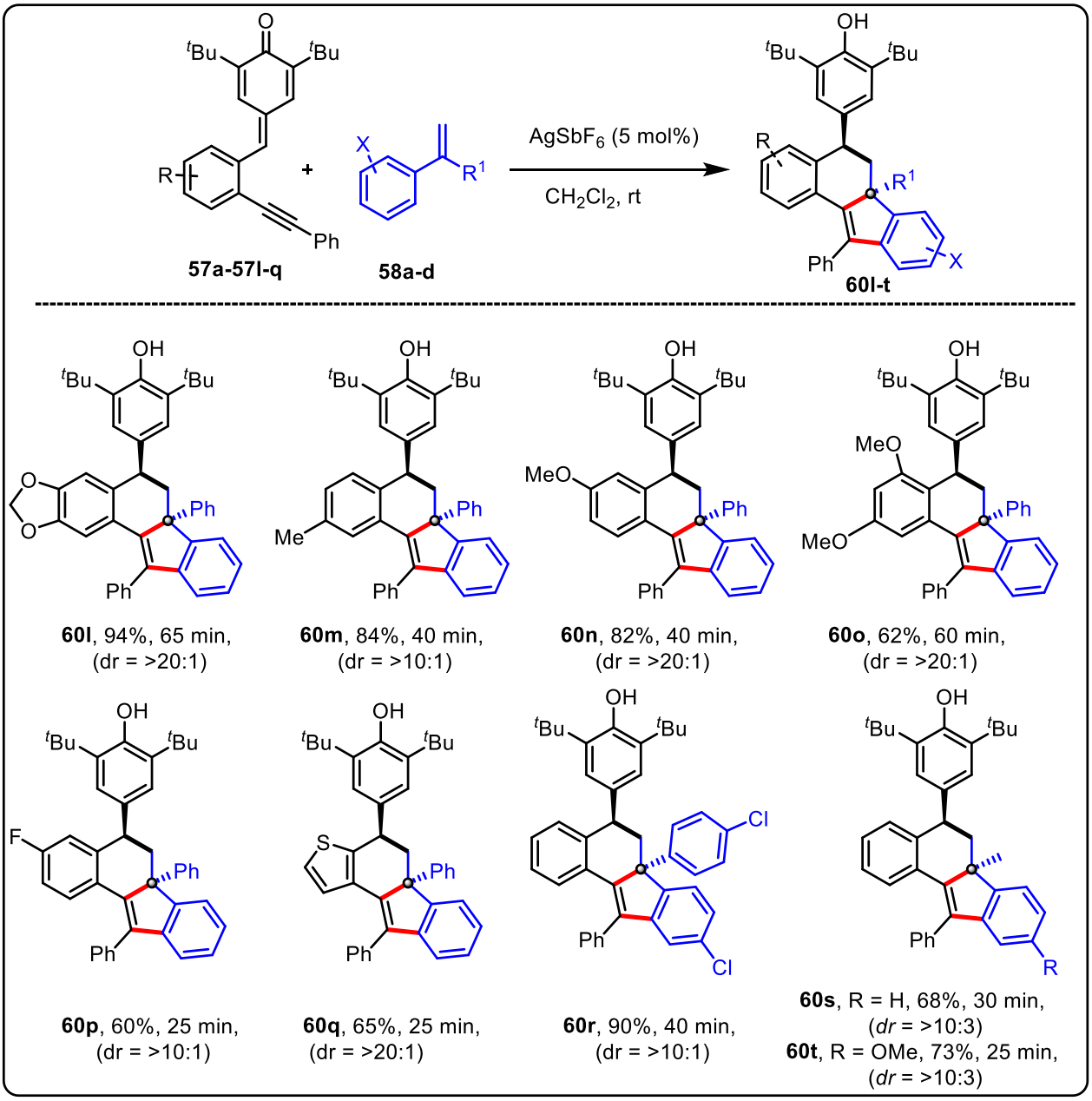
Table 4. Substrate scope with 2-alkynylated *p*-QMs having different substituted alkyne[a]



[a]Reactions were carried out in 0.06-0.25 mmol of **57b-t**. The diastereomeric ratios were calculated from the ^{1}H NMR analysis of the crude mixture. Yields reported are isolated yields.

In the case of 3-fluoro substituted *p*-QM **57h**, the respective product **60 h** was obtained in 84% yield. The *p*-QMs derived from thiophene (**57i**) and naphthalene acetylenes (**57j**) reacted under standard conditions and delivered the products **60i** and **60j** in 82% and 97% yields, respectively [*dr* {anti: syn} = 20:1 & 7:1, respectively].

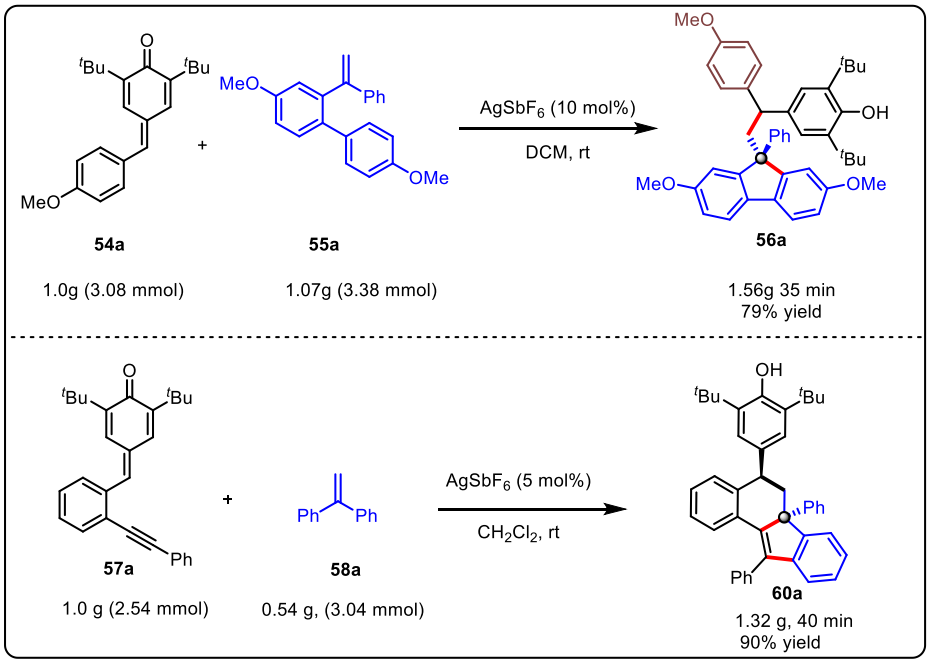
Table 5. Substrate scope with different 2-alkynylated *p*-QMs and substituted olefins[a]



[a]Reactions were carried out in 0.04-0.2 mmol of **57a-57l-q**. The diastereomeric ratios were calculated from the ^{1}H NMR analysis of the crude mixture. Yields reported are isolated yields.

In the case of *p*-QM **57k**, derived from alkyl acetylene, the respective product **60k** was produced in 79% yield (Table 4). Other *p*-QMs (**57l-o**), derived from substituted

benzaldehydes, also gave the respective dihydrobenzo[*a*]fluorenes **60l−o** in good yields and excellent diastereoselectivity [*dr* {anti: syn} = 10:1 to >20:1] (Table 5). The scope and limitations of this transformation were also examined by treating **57a** with substituted styrenes **58b-d** under the optimized reaction conditions, and the results are summarized in Table 5. In the case of alkene **58b**, derived from 4,4'-dichlorobenzophenone, the corresponding product **60r** was obtained in 90% yield with *dr* {anti: syn} =10:3. The alkenes derived from acetophenone derivatives **58c & 58d** gave the products **60s** and **60t** in 68 and 90% yields [*dr* {anti: syn} = 10:1].

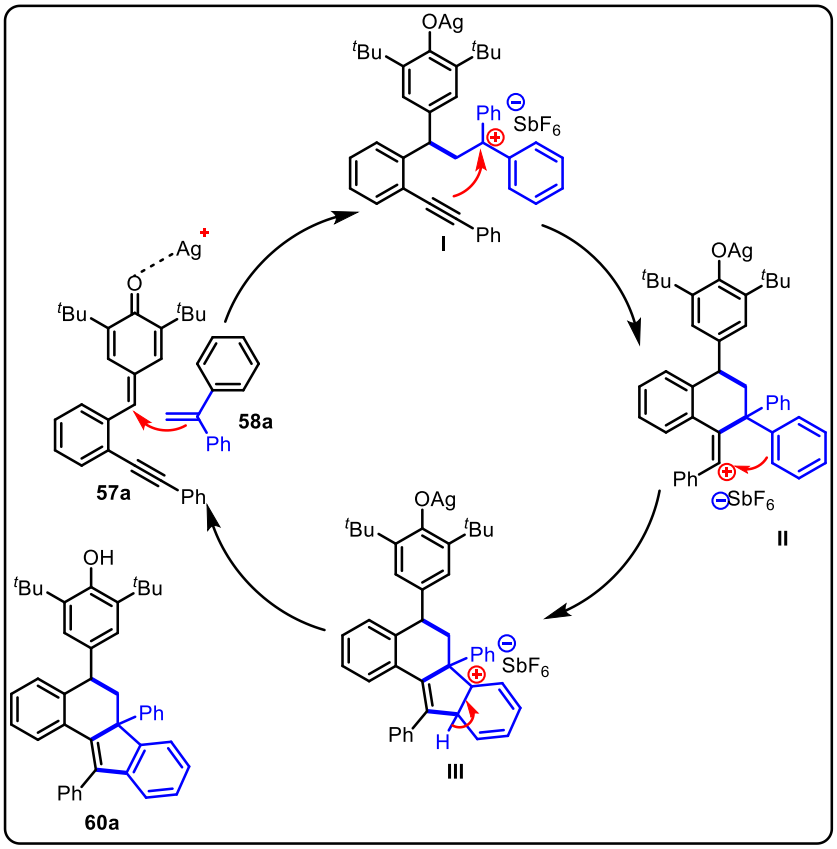


Scheme 14. Gram scale reactions

To demonstrate the scalability and robustness of the current methodology, reasonably large-scale reactions were carried out using both *para*-quinone methides **54a** and **57a** under standard conditions, and in both the cases, the respective products **56a** and **60a** in 79% and 86% yields, respectively. (Scheme 14).

A plausible mechanism for this reaction has been proposed (Scheme 15). We believe that, initially, the silver catalyst activates the carbonyl group of *p*-QM **57a,** and the subsequent 1,6-addition of olefin **58a** generates a reactive carbocation intermediate **I**, which gets trapped by the intramolecular attack of alkyne to generate another carbocation intermediate **II**. Then the carbocation intermediate **II** undergoes intramolecular Friedel−Crafts type cyclization to give yet another carbocation intermediate **III**, which further undergoes aromatization to generate the final product **60a** (Scheme 15). We believe that the SbF_6 anion plays a

significant role in stabilizing the carbocation intermediates wherever involved. This could be the reason why this particular transformation worked only with $AgSbF_6$, and those other Lewis acids, including other silver salts, failed to catalyze this transformation.



Scheme 15. a plausible mechanism for the formation of **60a**

2.2.7 Conclusion:

In conclusion, we have developed an efficient protocol for synthesizing 9,9-disubstituted fluorene and dihydrobenzo[*a*]fluorene derivatives through silver catalyzed electrophilic cascade cyclization. In this protocol, we first used 2-(1-phenyl vinyl)-1,1'-biaryl as a nucleophile to synthesise 9,9-disubstituted fluorene. Then the structurally modified 2-alkynyl-phenyl-substituted *p*-QM with simple 1,1-diaryl ethylene to access dihydroben[*a*]zofluorenes via 1,6 conjugate addition followed by intramolecular [3+2] cycloaddition. This methodology is notable for its short reaction time, good product yields, and 100% atom economy. Furthermore, this approach generates intermolecular and intramolecular carbon-carbon bonds and chiral quaternary centres. The heterocycles synthesis from this methodology is in progress.

2.2.8 Experimental Section:

General methods: All reactions were carried out under an argon atmosphere employing flame-dried glass wares. Most of the reagents and starting materials were purchased from commercial sources and used as such. *p*-Quinone methides (**54a-s** & **57a-q**) and **55b** were prepared by following a literature procedure.[27] (**55a** and **55c**) synthesise using known 2-aryl benzophenones.[28] Melting points were recorded on the SMP20 melting point apparatus and are uncorrected. ^{1}H, ^{13}C and ^{19}F spectra were recorded in $CDCl_3$ (400, 100 and 376 MHz, respectively) on Bruker FT-NMR spectrometer. Chemical shift (δ) values are reported in parts per million (ppm) relative to TMS, and the coupling constants (*J*) are reported in Hz. High-resolution mass spectra were recorded on Waters Q-TOF Premier-HAB213 spectrometer. FT-IR spectra were recorded on a Perkin–Elmer FT-IR spectrometer. UV-VIS studies were done on Agilent Technologies UV-Vis-NIR Spectrophotometer. Fluorescence emission studies were performed on Horiba Scientific Fluoromax spectro-fluorometer 4. Thin layer chromatography was performed on Merck silica gel 60 F_{254} TLC plates. Column chromatography was carried out through silica gel (100-200 mesh) using EtOAc/hexane as an eluent.

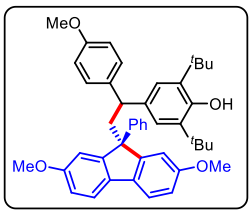
General Procedure for the Synthesis of 9,9-disubstituted fluorene Derivatives (56a−u)

Substituted alkene (1.1 equiv) was added to a solution of *p*-quinone methide (1 equiv) and $AgSbF_6$ (0.1 equiv) in CH_2Cl_2 (0.05 M), and the resultant mixture was stirred vigorously at room temperature until the *p*-quinone methide was completely consumed (monitored by TLC). After completion of the reaction, 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 9,9-disubstituted fluorene derivatives.

General Procedure for the Synthesis of Dihydrobenzo[*a*]-fluorene Derivatives (60a−q)

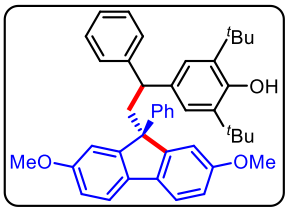
Substituted alkene (1.2 equiv) was added to a solution of 2-alkynylated *p*-quinone methide (1 equiv) and $AgSbF_6$ (0.05 equiv) in CH_2Cl_2 (0.05 M), and the resultant mixture was stirred vigorously at room temperature until the 2-alkynylated *p*-quinone methide was completely consumed (monitored by TLC). After completion of the reaction, 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 dihydrobenzo[*a*]fluorene derivatives.

2,6-di-*tert*-butyl-4-(2-(2,7-dimethoxy-9-phenyl-9H-fluoren-9-yl)-1-(4-methoxyphenyl)ethyl)phenol (56a)



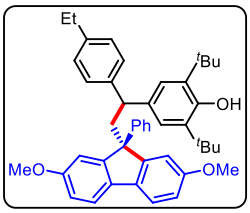
The reaction was performed at 0.123 mmol scale of **54a**; R_f = 0.1 (10% EtOAc in hexane); colorless gummy liquid (70 mg, 88% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 – 7.51 (m, 2H), 7.21 – 7.15 (m, 5H), 7.84 – 7.81 (m, 3H), 6.79 – 6.77 (m, 1H), 6.66 – 6.64 (m, 4H), 6.52 – 6.47 (m, 2H), 4.93 (s, 1H), 3.75 (s, 3H), 3.64 (s, 3H), 3.61 (s, 3H), 3.43 – 3.31 (m, 2H), 3.10 (t, *J* = 5.6 Hz, 1H), 1.35 (s, 18H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 158.8, 158.6, 157.3, 152.3, 152.0, 151.5, 146.0, 139.0, 136.3, 135.0, 134.3, 134.2, 128.7, 128.5, 126.7, 126.5, 124.5, 119.6, 119.4, 113.8, 113.5, 113.0, 111.2, 110.6, 59.1, 55.4, 55.3, 55.2, 46.6, 45.9, 34.3, 30.3; FT-IR (neat): 3631, 2923, 2854, 1609, 1467, 1302, 1272, 1237, 1180 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{44}H_{49}O_4$ [M+H]$^+$: 641.3631; found : 641.3617.

2,6-di-*tert*-butyl-4-(2-(2,7-dimethoxy-9-phenyl-9H-fluoren-9-yl)-1-phenylethyl)phenol (56b)



The reaction was performed at 0.136 mmol scale of **54b**; R_f = 0.2 (10% EtOAc in hexane); pale yellow gummy solid (72 mg, 86% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, *J* = 8.3 Hz, 1H), 7.52 (d, *J* = 8.3 Hz, 1H), 7.22 – 7.16 (m, 5H), 7.13 – 7.1 (m, 2H), 7.06 – 7.00 (m, 1H), 6.94 (d, *J* = 7.1 Hz, 2H), 6.83 (dd, *J* = 8.3, 2.3 Hz, 1H), 6.77 (dd, *J* = 8.3, 2.3 Hz, 1H), 6.65 (s, 2H), 6.49 (dd, *J* = 4.8, 2.3 Hz, 2H), 4.93 (s, 1H), 3.62 (s, 3H), 3.60 (s, 3H), 3.46 – 3.36 (m, 2H), 3.13 (t, *J* = 5.5 Hz, 1H), 1.35 (s, 18H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 158.8, 158.6, 152.2, 151.9, 151.6, 146.8, 145.9, 136.0, 135.0, 134.4, 134.2, 128.5, 128.1, 127.8, 126.7, 126.5, 125.4, 124.4, 119.6, 119.4, 113.9, 113.0, 111.2, 110.6, 59.1, 55.4, 55.2, 47.5, 45.7, 34.3, 30.3; FT-IR (neat): 3639, 2923, 2855, 1606, 1468, 1269, 1230, 1183 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{43}H_{47}O_3$ [M+H]$^+$: 611.3447; found : 611.3448.

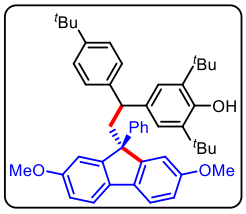
2,6-di-*tert*-butyl-4-(2-(2,7-dimethoxy-9-phenyl-9H-fluoren-9-yl)-1-(4-ethylphenyl)ethyl)phenol (56c)



The reaction was performed at 0.124 mmol scale of **54c**; R_f = 0.5 (10% EtOAc in hexane); colorless liquid (70 mg, 88% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (d, *J* = 8.3 Hz, 1H), 7.52 (d, *J* = 8.3 Hz, 1H), 7.24 – 7.20 (m, 4H), 7.18 – 7.15 (m, 1H), 7.00 (d, *J* = 7.4 Hz, 2H), 6.88 – 6.83 (m, 3H), 6.77 (dd, *J* = 8.3, 2.1 Hz, 1H), 6.66 (s, 2H), 6.54 – 6.53 (m, 1H), 6.48 (bs, 1H), 4.92 (s, 1H), 3.65 (s, 3H), 3.60 (s, 3H), 3.46 – 3.35 (m, 2H), 3.12 (t, *J* = 5.2 Hz, 1H), 2.57 (q, *J* = 7.6 Hz, 2H), 1.36 (s, 18H), 1.21 (t, J = 7.6 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ

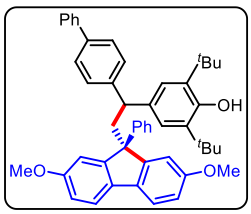
158.8, 158.6, 152.2, 152.0, 151.5, 146.0, 144.2, 141.1, 136.1, 134.9, 134.4, 134.2, 128.4, 127.7, 127.5, 126.7, 126.4, 124.4, 119.6, 119.4, 113.9, 113.0, 111.2, 110.5, 59.1, 55.4, 55.2, 47.2, 45.7, 34.3, 30.3, 28.4, 15.6; FT-IR (neat): 3632, 2954, 2923, 2854, 1608, 1467, 1374, 1272, 1230, 1155 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{45}H_{51}O_3$ $[M+H]^+$: 639.3838; found : 639.3810.

2,6-di-*tert*-butyl-4-(1-(4-(tert-butyl)phenyl)-2-(2,7-dimethoxy-9-phenyl-9H-fluoren-9-yl)ethyl)phenol (56d)



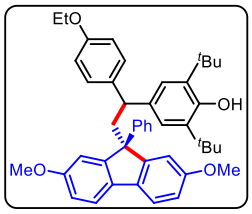
The reaction was performed at 0.114 mmol scale of **54d**; R_f = 0.3 (10% EtOAc in hexane); pale yellow liquid (64 mg, 84% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, *J* = 8.3 Hz, 1H), 7.51 (d, *J* = 8.3 Hz, 1H), 7.21 – 7.19 (m, 4H), 7.18 – 7.16 (m, 1H), 7.15 – 7.13 (m, 2H), 6.88 (d, *J* = 8.3 Hz, 2H), 6.84 (dd, *J* = 8.3, 2.3 Hz, 1H), 6.76 (dd, *J* = 8.3, 2.3 Hz, 1H), 6.66 (s, 2H), 6.57 (d, *J* = 2.3 Hz, 1H), 6.46 (d, *J* = 2.3 Hz, 1H), 4.91 (s, 1H), 3.66 (s, 3H), 3.59 (s, 3H), 3.45 – 3.35 (m, 2H), 3.13 (t, *J* = 5.4 Hz, 1H), 1.36 (s, 18H) 1.28 (s, 9H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 158.8, 158.6, 152.2, 152.1, 151.6, 148.0, 146.1, 143.8, 136.0, 134.9, 134.4, 134.2, 128.4, 127.4, 126.7, 126.4, 124.9, 124.5, 119.6, 119.4, 113.9, 113.1, 111.2, 110.4, 59.1, 55.5, 55.2, 47.1, 45.7, 34.33, 34.28, 31.5, 30.4; FT-IR (neat): 3642, 2953, 2922, 2854, 1607, 1467, 1363, 1270, 1229, 1154 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{45}H_{55}O_3$ $[M+H]^+$: 667.4151; found : 667.4130.

4-(1-([1,1'-biphenyl]-4-yl)-2-(2,7-dimethoxy-9-phenyl-9H-fluoren-9-yl)ethyl)-2,6-di-*tert*-butylphenol (56e)



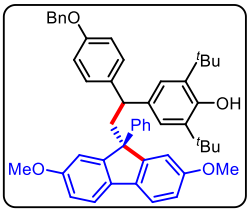
The reaction was performed at 0.108 mmol scale of **54e**; R_f = 0.4 (10% EtOAc in hexane); pale yellow liquid (61 mg, 82% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 – 7.57 (m, 4H), 7.45 (t, *J* = 7.6 Hz, 2H), 7.37 – 7.33 (m, 3H), 7.26 – 7.25 (m, 4H), 7.23 – 7.18 (m, 1H), 7.03 (d, *J* = 7.7 Hz, 2H), 6.86 – 6.84 (m, 2H), 6.76 (s, 2H), 6.60 (s, 1H), 6.52 (s, 1H), 5.00 (s, 1H), 3.66 (s, 3H), 3.57 (s, 3H), 3.48 (d, *J* = 4.9 Hz, 2H), 3.22 (m, 1H), 1.41 (s, 18H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 158.9, 158.7, 152.3, 151.9, 151.7, 145.9, 145.7, 141.3, 138.3, 136.1, 135.2, 134.3, 128.7, 128.5, 128.2, 127.1 (2C), 127.0, 126.8, 126.7, 126.5, 124.4, 119.6, 119.5, 113.7, 113.1, 111.2, 110.7, 59.1, 55.4, 55.2, 47.2, 45.8, 34.3, 30.4; FT-IR (neat): 3631, 2954, 2923, 2854, 1606, 1468, 1364, 1271, 1230, 1154 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{40}H_{50}NaO_3$ $[M+Na]^+$: 709; found : 559.2870.

2,6-di-*tert*-butyl-4-(2-(2,7-dimethoxy-9-phenyl-9H-fluoren-9-yl)-1-(4-ethoxyphenyl)ethyl)phenol (56f)



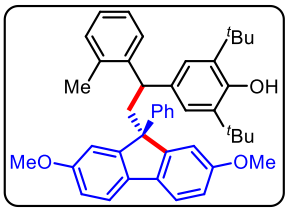
The reaction was performed at 0.118 mmol scale of **54**; R_f = 0.3 (10% EtOAc in hexane); pale yellow liquid (63 mg, 81% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, J = 8.3 Hz, 1H), 7.51 (d, J = 8.3 Hz, 1H), 7.22 – 7.17 (m, 4H), 7.16 – 7.12 (m, 1H), 6.83 – 6.79 (m, 3H), 6.76 (dd, J = 8.3, 5.9 Hz, 1H), 6.64 – 6.62 (m, 4H), 6.50 (d, J = 2.3 Hz, 1H), 6.46 (d, J = 2.3 Hz, 1H), 4.91 (s, 1H), 4.0 (q, J = 7.0 Hz, 2H), 3.63 (s, 3H), 3.59 (s, 3H), 3.41 – 3.30 (m, 2H), 3.07 (t, J = 5.6 Hz, 1H), 1.38 (t, J = 7.0 Hz, 3H), 1.34 (s, 18H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 158.8, 158.6, 156.7, 152.3, 152.0, 151.5, 146.0, 138.9, 136.4, 135.0, 134.3, 134.2, 128.7, 128.5, 126.7, 126.4, 124.3, 119.6, 119.4, 114.1, 113.8, 113.0, 111.2, 110.6, 63.4 59.1, 55.4, 55.2, 46.6, 45.9, 34.3, 30.4, 15.1; FT-IR (neat): 3633, 2923, 2854, 1609, 1467, 1376, 1272, 1236, 1180 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{45}H_{51}O_4$ [M+H]$^+$: 655.3787; found : 655.3770.

4-(1-(4-(benzyloxy)phenyl)-2-(2,7-dimethoxy-9-phenyl-9H-fluoren-9-yl)ethyl)-2,6-di-*tert*-butylphenol (56g)



The reaction was performed at 0.1 mmol scale of **54g**; R_f = 0.3 (10% EtOAc in hexane); pale yellow lquid (55 mg, 76% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 – 7.53 (m, 2H), 7.46 – 7.45 (m, 2H), 7.43 – 7.40 (m, 2H), 7.37 – 7.35 (m, 2H), 7.23 – 7.22 (m, 4H), 7.19 – 7.13 (m, 1H), 6.87 – 6.83 (m, 3H), 6.81 – 6.78 (m, 1H), 6.76 – 6.74 (m, 2H), 6.68 (s, 2H), 6.54 – 6.50 (m, 2H), 5.02 (s, 2H), 5.00 (s, 1H), 3.66 (s, 3H), 3.62 (s, 3H), 3.45 – 3.34 (m, 2H), 3.12 (t, J = 5.4 Hz, 1H), 1.38 (s, 18H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 158.8, 158.6, 156.7, 152.2, 152.0, 151.5, 146.0, 139.2, 137.4, 136.3, 135.0, 134.3, 134.2, 128.7, 128.6, 128.5, 128.0, 127.5, 126.7, 126.5, 124.3, 119.6, 119.4, 114.4, 113.8, 113.0, 111.2, 110.6, 70.1, 59.1, 55.4, 55.2, 46.6, 45.9, 34.3, 30.3; FT-IR (neat): 3632, 2953, 2925, 2855, 1608, 1468, 1434, 1267, 1233, 1179 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{50}H_{53}O_4$ [M+H]$^+$: 717.3944; found : 717.3941.

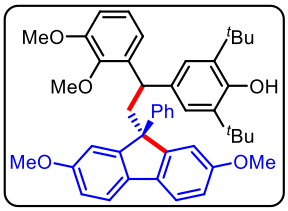
2,6-di-*tert*-butyl-4-(2-(2,7-dimethoxy-9-phenyl-9H-fluoren-9-yl)-1-(*o*-tolyl)ethyl)phenol (56h)



The reaction was performed at 0.130 mmol scale of **54h**; R_f = 0.4 (10% EtOAc in hexane); pale yellow liquid (70 mg, 86% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, J = 3.3 Hz, 1H), 7.53 – 7.51 (m,

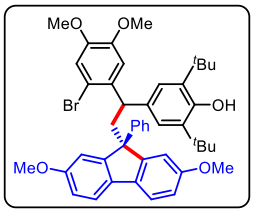
2H), 7.21 – 7.18 (m, 4H), 7.17 – 7.13 (m, 2H), 6.93 (t, *J* = 7.4 Hz, 1H), 6.84 – 6.77 (m, 3H), 6.63 (s, 2H), 6.51 (d, *J* = 2.3 Hz, 1H), 6.44 (d, *J* = 2.3 Hz, 1H), 4.87 (s, 1H), 3.59 (s, 3H), 3.57 (s, 3H), 3.43 (d, *J* = 5.6 Hz, 2H), 3.35 (t, *J* = 5.4 Hz, 1H), 1.68 (s, 3H), 1.32 (s, 18H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 158.8, 158.7, 152.4, 151.9, 151.5, 145.9, 145.1, 136.1, 135.6, 135.0, 134.3, 134.2, 130.1, 128.5, 126.9, 126.7, 126.5, 125.8, 125.3, 124.3, 119.5, 119.47, 114.0, 113.3, 111.1, 110.5, 59.3, 55.5, 55.2, 45.5, 42.0, 34.2, 30.3, 19.5; FT-IR FT-IR (neat): 3634, 2952, 2923, 2854, 1607, 1467, 1376, 1272, 1231, 1155 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{44}H_{49}O_3$ $[M+H]^+$: 625.3603; found : 625.3607.

2,6-di-*tert*-butyl-4-(2-(2,7-dimethoxy-9-phenyl-9H-fluoren-9-yl)-1-(2,3-dimethoxyphenyl)ethyl)phenol (56i)



The reaction was performed at 0.113 mmol scale of **54i**; R_f = 0.2 (10% EtOAc in hexane); pale yellow liquid (44 mg, 58% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, *J* = 8.3 Hz, 1H), 7.45 (d, *J* = 8.3 Hz, 1H), 7.21 – 7.20 (m, 4H), 7.17 – 7.13 (m, 1H), 7.02 (dd, *J* = 7.9, 1.2 Hz, 1H), 7.00 (t, *J* = 7.9 Hz, 1H), 6.83 (dd, *J* = 8.3, 2.3 Hz, 1H), 6.70 (dd, *J* = 8.3, 2.3 Hz, 1H), 6.65 – 6.63 (m, 4H), 6.41 (d, *J* = 2.3 Hz, 1H), 4.84 (s, 1H), 3.76 (s, 3H), 3.73 – 3.70 (m, 1H), 3.67 (s, 3H), 3.47 – 3.42 (m, 1H), 3.33 – 3.30 (m, 1H), 3.29 (s, 3H), 1.32 (s, 18H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 158.7, 158.4, 152.6, 152.24, 152.18, 151.4, 146.3, 146.1, 141.2, 135.5, 134.6, 134.5, 134.1, 128.4, 126.7, 126.4, 124.6, 123.6, 119.9, 119.6, 119.3, 113.4, 113.0, 111.1, 110.8, 109.6, 60.1 59.0, 55.6, 55.5, 55.1, 44.0, 40.0, 34.2, 30.3; FT-IR (neat): 3631, 2922, 2853, 1606, 1467, 1376, 1274, 1229, 1157, 1117 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{45}H_{51}O_5$ $[M+H]^+$: 671.3736; found : 671.3758.

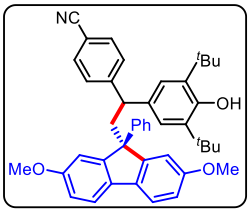
4-(1-(2-bromo-4,5-dimethoxyphenyl)-2-(2,7-dimethoxy-9-phenyl-9H-fluoren-9-yl)ethyl)-2,6-di-*tert*-butylphenol (56j)



The reaction was performed at 0.092 mmol scale of **54j**; R_f = 0.1 (10% EtOAc in hexane); pale yellow liquid (44 mg, 63% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, *J* = 8.3 Hz, 1H), 7.47 (d, *J* = 8.3 Hz, 1H), 7.21 – 7.19 (m, 4H), 7.17 – 7.14 (m, 1H), 6.89 (s, 1H), 6.79 (dd, *J* = 8.3, 2.3 Hz, 1H), 7.77 – 7.73 (m, 4H), 6.56 (dd, *J* = 6.0, 2.3 Hz, 2H), 4.91 (s, 1H), 3.88 (s, 3H), 3.77 (s, 3H), 3.75 (m, 1H), 3.67 (s, 3H), 3.64 (s, 3H), 3.40 – 3.30 (m, 2H), 1.34 (s, 18H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 158.8, 158.6, 152.1, 151.7, 151.6, 148.2, 147.3, 145.9, 137.2, 135.0, 134.8, 134.4, 134.36, 128.6, 126.6, 126.5, 124.2, 120.0, 119.7, 115.5, 114.5,

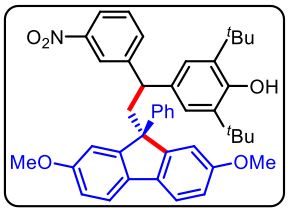
113.6, 113.0, 111.8, 111.0, 110.6, 58.9, 56.2, 56.1, 55.5, 55.3, 45.3, 44.6, 34.3, 30.3; FT-IR (neat): 3633, 2953, 2923, 2854, 1605, 1436, 1377, 1264, 1229, 1158 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{45}H_{49}NaBrO_5$ $[M+Na]^+$: 771.2661; found : 771.2675.

4-(1-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-2-(2,7-dimethoxy-9-phenyl-9H-fluoren-9-yl)ethyl)benzonitrile (56k)



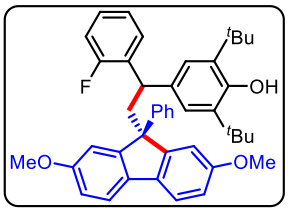
The reaction was performed at 0.125 mmol scale of **54k**; R_f = 0.2 (10% EtOAc in hexane); colorless liqid (62 mg, 78% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (d, *J* = 8.3 Hz, 1H), 7.50 (d, *J* = 8.3 Hz, 1H), 7.35 (d, *J* = 8.3 Hz, 2H), 7.25 – 7.21 (m, 2H), 7.19 – 7.15 (m, 3H), 7.00 (d, *J* = 8.3 Hz, 2H), 6.85 (dd, *J* = 8.3, 2.3 Hz, 1H), 6.77 (dd, *J* = 8.4, 2.4 Hz, 1H), 6.66 (s, 2H), 6.61 (d, *J* = 2.3 Hz, 1H), 6.33 (d, *J* = 2.3 Hz, 1H), 5.03 (s, 1H), 3.67 (s, 3H), 3.63 (s, 3H), 3.41 – 3.35 (m, 2H), 3.18 (t, *J* = 5.4 Hz, 1H), 1.36 (s, 18H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 158.9, 158.7, 152.0, 151.9, 151.5, 151.4, 145.3, 135.6, 134.9, 134.2, 134.1, 131.7, 128.6, 128.55, 126.7, 126.5, 124.1, 119.69, 119.67, 119.3, 113.3, 112.9, 111.4, 111.0, 109.0, 58.8, 55.4, 55.3, 47.6, 45.2, 34.4, 30.3; FT-IR (neat): 3631, 2923, 2854, 2226, 1606, 1467, 1364, 1273, 1229, 1183 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{44}H_{44}NO_3$ $[M-H]^-$: 634.3321; found : 634.3347.

2,6-di-*tert*-butyl-4-(2-(2,7-dimethoxy-9-phenyl-9H-fluoren-9-yl)-1-(3-nitrophenyl)ethyl)phenol (56l)



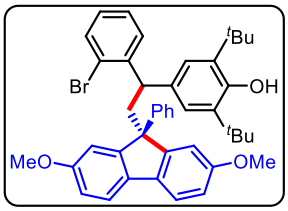
The reaction was performed at 0.118 mmol scale of **54l**; R_f = 0.3 (5% EtOAc in hexane); pale yellow gummy solid (56 mg, 72% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 – 7.81 (m, 1H), 7.62 (s, 1H), 7.59 (d, *J* = 8.3 Hz, 1H), 7.47 (d, *J* = 8.4 Hz, 1H), 7.24 – 7.19 (m, 5H), 7.18 – 7.14 (m, 2H), 6.88 (dd, *J* = 8.3, 2.4 Hz, 1H), 6.72 (s, 2H), 6.67 – 6.64 (m, 2H), 6.32 (d, *J* = 2.3 Hz, 1H), 5.03 (s, 1H), 3.69 (s, 3H), 3.57 (s, 3H), 3.44 – 3.33 (m, 2H), 3.26 – 3.23 (m, 1H), 1.36 (s, 18H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 159.0, 158.7, 152.1, 151.8, 151.5, 147.8, 147.7, 145.3, 135.7, 135.1, 134.3, 134.03, 134.0, 128.6 (2C), 126.7, 126.6, 124.1, 123.1, 120.6, 119.9, 119.8, 113.4, 113.1, 110.94, 110.86, 58.8, 55.4, 55.3, 47.2, 45.4, 34.4, 30.3; FT-IR FT-IR (neat): 3632, 2953, 2924, 2854, 1607, 1583, 1468, 1348, 1273, 1230, 1154 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{43}H_{44}NO_5$ $[M-H]^-$: 654.3219; found : 654.3223.

2,6-di-*tert*-butyl-4-(2-(2,7-dimethoxy-9-phenyl-9H-fluoren-9-yl)-1-(2-fluorophenyl)ethyl)phenol (56m)



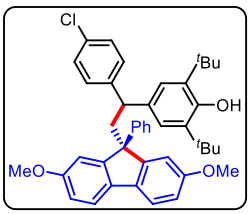
The reaction was performed at 0.128 mmol scale of **54m**; R_f = 0.4 (10% EtOAc in hexane); pale yellow gummy solid (68 mg, 84% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (t, J = 8.0 Hz, 2H), 7.24 – 7.19 (m, 4H), 7.18 – 7.14 (m, 1H), 7.02 – 7.00 (m, 2H), 7.90 – 7.86 (m, 1H), 6.82 – 6.75 (m, 3H), 6.73 (s, 2H), 6.61 (d, J = 2.2 Hz, 1H), 6.48 (d, J = 2.1 Hz, 1H), 5.00 (s, 1H), 3.67 (s, 3H), 3.61 (s, 3H), 3.51 – 3.46 (m, 2H), 3.36 (dd, J = 15.6, 7.8 Hz, 1H), 1.35 (s, 18H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 160.3 (d, $J_{C\text{-}F}$ = 243.7 Hz), 158.7, 158.6, 152.3, 151.8, 151.5, 145.9, 135.1, 134.9, 134.3, 134.2, 132.7 (d, $J_{C\text{-}F}$ = 13.9 Hz), 129.7 (d, $J_{C\text{-}F}$ = 4.9 Hz), 128.5, 127.1 (d, $J_{C\text{-}F}$ = 8.4 Hz), 126.7, 126.5, 124.5, 123.6 (d, $J_{C\text{-}F}$ = 3.2 Hz), 119.7, 119.6, 115.4 (d, $J_{C\text{-}F}$ = 22.9 Hz), 114.0, 112.9, 111.0, 110.2, 59.0, 55.4, 55.3, 43.9, 41.4, 34.3, 30.3; ^{19}F NMR (376 MHz, $CDCl_3$) δ -115.1; 3659, 2923, 2853, 1591, 1487, 1297, 1249, 1212, 1151 cm^{-1};HRMS (ESI): *m/z* calcd for $C_{43}H_{44}FO_3$ [M-H]$^-$: 627.3274; found : 627.3248.

4-(1-(2-bromophenyl)-2-(2,7-dimethoxy-9-phenyl-9H-fluoren-9-yl)ethyl)-2,6-di-*tert*-butylphenol (56n)



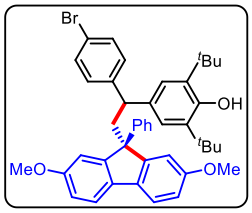
The reaction was performed at 0.107 mmol scale of **54n**; R_f = 0.4 (10% EtOAc in hexane); colorless gummy solid (64 mg, 86% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 – 7.49 (m, 3H), 7.26 – 7.23 (m, 1H), 7.21 – 7.18 (m, 5H), 7.17 – 7.14 (m, 1H), 6.85 (dt, J = 7.7, 1.5 Hz, 1H), 7.80 – 7.76 (m, 2H), 6.73 (s, 2H), 6.54 (d, J = 2.3 Hz, 1H), 6.47 (d, J = 2.3 Hz, 1H), 4.90 (s, 1H), 3.82 (t, J = 5.9 Hz, 1H), 3.63 (s, 3H), 3.62 (s, 3H), 3.44 – 3.35 (m, 2H), 1.33 (s, 18H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 158.7, 158.6, 152.2, 151.7, 151.5, 145.8, 145.4, 135.0, 134.9, 134.5, 134.4, 132.8, 128.7, 128.5, 127.1, 126.8, 126.7, 126.5, 125.0, 124.4, 120.1, 119.7, 113.8, 113.1, 110.9, 110.5, 59.0, 55.5, 55.3, 45.2, 44.9, 34.3, 30.3; FT-IR (neat): 3633, 2923, 2854, 1608, 1467, 1376, 1271, 1233, 1155 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{43}H_{46}BrO_3$ [M+H]$^+$: 689.2630; found : 689.2608.

2,6-di-*tert*-butyl-4-(1-(4-chlorophenyl)-2-(2,7-dimethoxy-9-phenyl-9H-fluoren-9-yl)ethyl)phenol (56o)



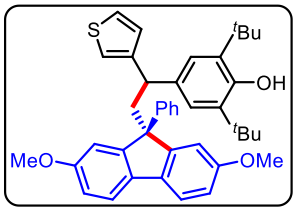
The reaction was performed at 0.122 mmol scale of **54o**; R_f = 0.2 (10% EtOAc in hexane); pale yellow liquid (66 mg, 83% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (t, J = 8.1 Hz, 2H), 7.24 – 7.16 (m, 5H), 7.04 (d, J = 8.5 Hz, 2H), 6.83 – 6.80 (m, 4H), 6.66 (s, 2H), 6.58 (d, J = 2.3 Hz, 1H), 6.39 (d, J = 2.3 Hz, 1H), 5.00 (s, 1H), 3.64 (s, 6H), 3.41 – 3.32 (m, 2H), 3.12 (t, J = 5.7 Hz, 1H), 1.36 (s, 18H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 158.83, 158.8, 152.1, 151.8, 151.7, 145.7, 144.8, 135.8, 135.3, 134.3, 134.2, 131.1, 129.2, 128.5, 128.0, 126.62, 126.56, 119.7, 119.5, 113.3, 113.1, 111.1, 111.0, 59.0, 55.4, 55.3, 46.8, 45.7, 34.3, 30.3; FT-IR (neat): 3634, 2953, 2923, 2854, 1607, 1467, 1375, 1271, 1229, 1154 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{43}H_{46}ClO_3$ [M+H]$^+$: 645.3135; found : 645.3158.

4-(1-(4-bromophenyl)-2-(2,7-dimethoxy-9-phenyl-9H-fluoren-9-yl)ethyl)-2,6-di-*tert*-butylphenol (56p)



The reaction was performed at 0.107 mmol scale of **54p**; R_f = 0.4 (10% EtOAc in hexane); pale yellow gummy solid (59 mg, 79% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (t, J = 8.5 Hz, 2H), 7.25 – 7.22 (m, 5H), 7.20 – 7.16 (m, 2H), 6.85 – 6.81 (m, 2H), 6.77 (d, J = 7.8 Hz, 2H), 6.68 (s, 2H), 6.59 (s, 1H), 6.40, (s, 1H), 5.0 (s, 1H), 3.66 (s, 3H), 3.65 (s, 3H), 3.41 – 3.35 (m, 2H), 3.11 (t, J = 5.6 Hz, 1H), 1.37 (s, 18H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 158.82, 158.79, 152.1, 151.9, 151.6, 145.6, 145.3, 135.7, 135.3, 134.3, 134.1, 130.5, 129.6, 128.5, 126.6, 126.57, 124.2, 119.7, 119.5, 119.2, 113.3, 113.1, 111.1, 111.0, 59.0, 55.4, 55.3, 46.9, 45.6, 34.3, 30.3; FT-IR (neat): 3638, 2923, 2854, 1607, 1467, 1364, 1271, 1231, 1155 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{43}H_{46}BrNaO_3$ [M+Na]$^+$: 711.2450; found : 711.2463.

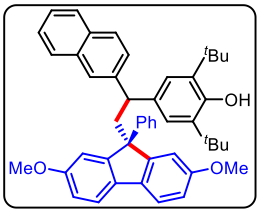
2,6-di-*tert*-butyl-4-(2-(2,7-dimethoxy-9-phenyl-9H-fluoren-9-yl)-1-(thiophen-3-yl)ethyl)phenol (56q)



The reaction was performed at 0.133 mmol scale of **54q**; R_f = 0.4 (10% EtOAc in hexane); pale purple liquid (57 mg, 69% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, J = 8.3 Hz, 1H), 7.51 (d, J = 8.3 Hz, 1H), 7.24 – 7.16 (m, 5H), 7.13 – 7.11 (m, 1H), 6.89 (dd, J = 8.3, 2.2 Hz, 1H), 7.79 – 7.75 (m, 2H), 6.66 (d, J = 2.1 Hz, 1H), 6.62 (s, 2H), 6.51 (d, J = 2.1 Hz, 1H), 6.43 (d, J = 2.2 Hz, 1H), 5.0 (s, 1H), 3.74 (s, 3H), 3.56 (s, 3H), 3.42 – 3.32 (m, 2H), 3.23 (t, J = 5.9 Hz, 1H), 1.37 (s, 18H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 158.9, 158.6, 152.1, 151.6, 147.9, 145.9, 135.7, 135.0, 134.4, 134.1, 128.5 (2C), 127.7, 126.6, 126.5, 124.9,

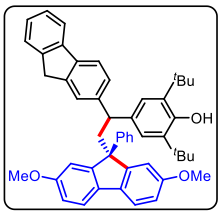
124.4, 120.1, 119.7, 119.4, 113.6, 113.3, 111.0, 110.5, 59.0, 55.6, 55.1, 45.9, 42.9, 34.3, 30.3; FT-IR (neat): 3632, 2922, 2854, 1607, 1467, 1364, 1303, 1230, 1184 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{41}H_{45}O_3S$ $[M+H]^+$: 617.3089; found : 617.3060.

2,6-di-*tert*-butyl-4-(2-(2,7-dimethoxy-9-phenyl-9H-fluoren-9-yl)-1-(naphthalen-2-yl)ethyl)phenol (56r)



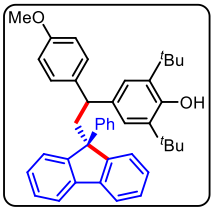
The reaction was performed at 0.116 mmol scale of **54r**; R_f = 0.4 (10% EtOAc in hexane); pale yellow liquid (66 mg, 86% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (d, *J* = 8.1 Hz, 1H), 7.59 (d, *J* = 8.1 Hz, 1H), 7.54 (d, *J* = 8.0 Hz, 2H), 7.49 (d, *J* = 8.6 Hz, 1H), 7.41 – 7.33 (m, 3H), 7.28 – 7.24 (m, 5H), 7.21 – 7.17 (m, 1H), 6.86 – 6.84 (m, 3H), 6.66 (s, 1H), 6.59 (d, *J* = 8.3 Hz, 1H), 6.32 (s, 1H), 4.93 (s, 1H), 4.13 (t, *J* = 5.0 Hz, 1H), 3.68 (s, 3H), 3.64 – 3.54 (m, 2H), 3.48 (s, 3H), 1.36 (s, 18H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 158.7, 158.4, 152.4, 151.64, 151.56, 145.8, 142.6, 135.7, 134.9, 134.4, 134.01, 133.98, 131.2, 128.48, 128.45, 126.7 (2C), 126.5, 126.3, 125.2, 125.0, 124.8, 124.5, 123.8, 119.6, 119.5, 113.7, 112.9, 111.4, 110.6, 59.3, 55.3, 55.2, 45.8, 41.3, 34.3, 30.3; FT-IR (neat): 3632, 2953, 2923, 2855, 1605, 1467, 1433, 1270, 1230, 1116 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{47}H_{47}O_3$ $[M-H]^-$: 659.3525; found : 659.3533.

2,6-di-*tert*-butyl-4-(2-(2,7-dimethoxy-9-phenyl-9H-fluoren-9-yl)-1-(9H-fluoren-2-yl)ethyl)phenol (56s)



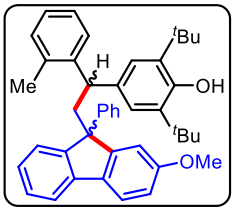
The reaction was performed at 0.105 mmol scale of **54s**; R_f = 0.2 (10% EtOAc in hexane); pale yellow gummy solid (60 mg, 81% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (dd, *J* = 7.2, 1.9 Hz, 1H), 7.62 – 7.53 (m, 4H), 7.39 – 7.36 (m, 1H), 7.31 – 7.23 (m, 5H), 7.21 – 7.10 (m, 2H), 7.00 (d, *J* = 2.4 Hz, 1H), 6.88 – 6.86 (m, 1H), 6.82 (d, *J* = 3.8 Hz, 2H), 6.74 – 6.71 (m, 1H), 6.66 – 6.65 (m, 1H), 6.46 – 6.45 (m, 1H), 5.00 (d, *J* = 3.1 Hz, 1H), 3.77 (s, 2H), 3.69 (d, *J* = 2.2 Hz, 3H), 3.50 (bs, 2H), 3.39 (d, *J* = 2.1 Hz, 3H), 3.27 – 3.26 (m, 1H), 1.41 (d, *J* = 3.4 Hz, 18H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 158.8, 158.6, 152.3, 151.8, 151.7, 145.9, 145.2, 143.3, 143.1, 141.9, 139.2, 136.4, 135.2 (2C), 134.4, 134.2, 128.5 (2C), 126.7 (2C), 126.5, 126.3, 126.2, 125.0, 124.4, 119.6, 119.5, 119.4, 119.3, 113.1, 111.1, 59.1, 55.3, 55.0, 47.6, 46.0, 36.9, 34.3, 30.4; FT-IR (neat): 3635, 2953, 2922, 2854, 1608, 1467, 1433, 1271, 1229, 1153 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{50}H_{49}O_3$ $[M+H]^+$: 699.3838; found : 699.3813.

2,6-di-*tert*-butyl-4-(1-(4-methoxyphenyl)-2-(9-phenyl-9H-fluoren-9-yl)ethyl)phenol (56t)



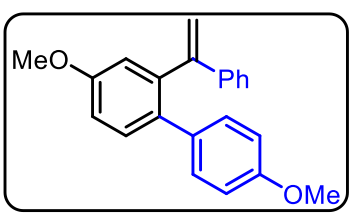
The reaction was performed at 0.123 mmol scale of 54a; R_f = 0.4 (10% EtOAc in hexane); colorless gummy solid (47 mg, 65% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, J = 7.7 Hz, 1H), 7.64 (d, J = 7.7 Hz, 1H), 7.32 – 7.28 (m, 1H), 7.20 – 7.16 (m, 5H), 7.15 – 7.12 (m, 1H), 7.09 – 7.04 (m, 2H), 7.00 – 7.96 (m, 2H), 6.84 – 6.82 (m, 2H), 6.64 (d, J = 8.6 Hz, 2H), 6.57 (s, 2H), 4.86 (s, 1H), 3.73 (s, 3H), 3.50 (dd, J = 13.6, 7.2 Hz, 1H), 3.36 (dd, J = 13.6, 5.1 Hz, 1H), 3.10 – 3.07 (m, 1H), 1.33 (s, 18H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 157.4, 151.5, 150.74, 150.72, 146.0, 141.3, 141.0, 139.0, 135.8, 134.9, 128.6, 128.4, 127.34, 127.25, 127.2, 127.1, 126.6, 126.4, 125.4, 125.3, 124.3, 119.7, 119.5, 113.6, 59.0, 55.4, 46.7, 45.4, 34.3, 30.4; FT-IR (neat): 3630, 3058, 2955, 22923, 1662, 1474, 1313, 1280, 1153, 1074 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{42}H_{45}O_2$ [M+H]$^+$: 581.3420; found : 581.3428.

2,6-di-*tert*-butyl-4-(2-(2-methoxy-9-phenyl-9H-fluoren-9-yl)-1-(*o*-tolyl)ethyl)phenol (56u)



The reaction was performed at 0.130 mmol scale of 54h; R_f = 0.4 (10% EtOAc in hexane); pale yellow gummy liquid (70 mg, 86% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (d, J = 7.6 Hz, 1H), 7.62 (dd, J = 8.3, 3.0 Hz, 3H), 7.56 (d, J = 7.8 Hz, 1H), 7.50 (d, J = 7.8 Hz, 1H), 7.31 – 7.28 (m, 1H), 7.27 – 7.19 (m, 10H), 7.17 – 7.13 (m, 5H), 7.08 (d, J = 7.4 Hz, 1H), 7.04 – 7.00 (m, 3H), 6.97 – 6.93 (m, 2H), 6.81 (s, 1H), 6.83 – 6.78 (m, 3H), 6.63 (s, 2H), 6.62 (s, 2H), 6.44 (d, J = 2.2 Hz, 2H), 4.88 (s, 1H), 4.87 (s, 1H), 3.58 (s, 3H), 3.55 (s, 3H), 3.52 – 3.49 (m, 2H), 3.48 – 3.42 (m, 2H), 3.40 – 3.37 (m, 1H), 3.34 – 3.31 (m, 1H), 1.69 (s, 3H), 1.67 (s, 3H), 1.33 (s, 36H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 159.5, 159.4, 152.5, 152.2, 151.6, 151.4, 150.7, 150.5, 145.91, 145.88, 145.8, 144.4, 141.3, 141.1, 135.94, 135.89, 135.8, 135.2, 134.9, 134.8, 134.2, 134.1, 130.2, 130.1, 128.4, 127.4, 127.3, 127.0, 126.7, 126.65, 126.6, 126.5, 126.3, 126.2, 126.1, 125.6, 125.3, 125.27, 125.1, 124.9, 124.3, 124.26, 120.5, 120.3, 118.9, 118.8, 114.3, 113.8, 111.0, 110.4, 59.3, 59.2, 55.5, 55.2, 45.4, 45.3, 42.1, 41.8, 34.3, 34.2, 30.4, 30.3, 19.6, 19.5; FT-IR (neat): 3633, 3053, 2926, 2869, 1610, 1458, 1362, 1308, 1263, 1209, 1154 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{44}H_{49}O_3$ [M+H]$^+$: 625.3603; found : 625.36011.

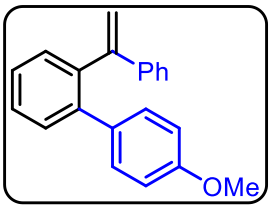
4,4'-dimethoxy-2-(1-phenylvinyl)-1,1'-biphenyl (55a)



In oven dry round bottom flask, methyl triphenylphosphonium bromide (2.35 g, 6.59 mmol) was taken; 15mL of anhydrous

Et_2O was added into it under an argon atmosphere, and the resultant mixture was stirred at room temperature for 10 min. Then the mixture was set at 0 °C temperature, and to this mixture, *n*-butyl lithium (4.11 mL) was added slowly and dropwise manner. After 45 min solution turned to dark orange then solution of (4,4'-dimethoxy-[1,1'-biphenyl]-2-yl)(phenyl)methanone[28a] (1.5 g, 4.71 mmol) in anhydrous THF (30 mL) was added dropwise, reaction then continued stirr at room temperature for 3 h. After completion, the reaction mixture was quenched with ice water (30 mL) and then extracted three times with ethyl acetate. Then the combined organic layer was dried over anhydrous sodium sulfate and filtered. The resulting residue was purified by silica gel column chromatography (ethyl acetate / hexane = 5:95) to provide pure (**57a**) as an white solid (1.26 g, 84%); R_f = 0.5 (10% EtOAc in hexane); mp = 83−85 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 – 7.25 (m, 1H), 7.14 (s, 5H), 7.12 – 7.11 (m, 2H), 6.96 (dd, *J* = 8.4, 2.8 Hz, 1H), 6.92 (d, *J* = 2.7 Hz, 1H), 6.72 – 6.68 (m, 2H), 5.61 (d, *J* = 1.1 Hz, 1H), 5.22 (d, *J* = 1.1 Hz, 1H), 3.86 (s, 3H) 3.75 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 158.5, 158.1, 149.7, 142.0, 141.1, 133.9, 133.8, 131.3, 130.3, 127.9, 127.3, 127.0, 116.4, 116.2, 113.4, 113.1, 55.5, 55.3; FT-IR (neat): 2998, 2956, 2899, 2835, 1605, 1486, 1324, 1292, 1247, 1179 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{22}H_{21}O_2$ $[M+H]^+$: 317.1542; found : 317.1544.

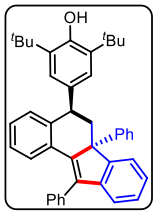
4'-methoxy-2-(1-phenylvinyl)-1,1'-biphenyl (55c)



In oven dry round bottom flask, methyl triphenylphosphonium bromide (1.38 g, 3.87 mmol) was taken; 15mL of anhydrous Et_2O was added into it under an argon atmosphere, and the resultant mixture was stirred at room temperature for 10 min. Then the mixture was set at 0 °C temperature, and to this mixture, *n*-butyl lithium (2.41 mL) was added slowly and dropwise manner. After 45 min solution turned to dark orange then solution of (4'-methoxy-[1,1'-biphenyl]-2-yl)(phenyl)methanone[28b] (0.8 g, 2.77 mmol) in anhydrous THF (30 mL) was added dropwise, reaction then continued stirr at room temperature for 3 h. After completion, the reaction mixture was quenched with ice water (30 mL) and then extracted three times with ethyl acetate. Then the combined organic layer was dried over anhydrous sodium sulfate and filtered. The resulting residue was purified by silica gel column chromatography (ethyl acetate / hexane = 5:95) to provide pure (**57c**) as an white solid (0.72 g, 90%); R_f = 0.6 (10% EtOAc in hexane); mp = 82−84 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 – 7.35 (m, 4H), 7.18 (d, *J* = 8.8 Hz, 3H), 7.14 (s, 4H), 6.73 (d, *J* = 8.7 Hz, 2H), 5.62 (d, *J* = 1.0 Hz, 1H), 5.22 (d, *J* = 1.0 Hz, 1H), 3.76 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ

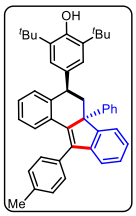
158.4, 149.8, 141.4, 141.0, 140.8, 134.2, 130.9, 130.3, 130.26, 127.9, 127.85, 127.3, 127.0, 126.9, 116.4, 113.2, 55.3; FT-IR (neat): 3055, 3024, 2956, 2835, 1611, 1478, 1296, 1243, 1178, 1037 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{21}H_{18}NaO$ $[M+Na]^+$: 309.1255; found : 309.1251.

2,6-Di-*tert*-butyl-4-(6a,11-diphenyl-6,6a-dihydro-5H-benzo[*a*]-fluoren-5-yl)phenol (60a)



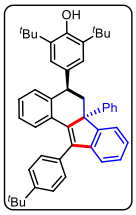
The reaction was performed on a 0.25mmol scale of 57a; R_f = 0.5 (5% EtOAc in hexane); white solid (137 mg, 95% yield, dr {anti:syn} = > 20:1); mp = 272−274 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55−7.52 (m, 6H), 7.48−7.44 (m, 1H), 7.41 (d, *J* = 7.3 Hz, 1H), 7.28−7.24 (m, 2H), 7.22−7.17 (m, 4H), 7.15−7.11 (m, 1H), 6.97−6.94 (m, 3H), 6.90 (t, *J* = 7.4 Hz, 1H), 6.75 (d, *J* = 7.6 Hz, 1H), 5.09 (s, 1H), 4.01 (dd, *J* = 12.0, 5.4 Hz, 1H), 3.47 (dd, *J* = 13.6, 5.4 Hz, 1H), 2.13 (t, *J* = 12.3 Hz, 1H), 1.42 (s, 18H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 152.3, 151.4, 146.1, 144.6, 141.3, 141.0, 137.3, 136.8, 135.9, 135.7, 132.2, 130.1, 129.7 (2C), 129.0, 128.9, 127.7, 127.3, 127.0, 126.7, 126.5, 125.7, 125.5, 125.4, 122.8, 120.9, 58.9, 44.3, 43.3, 34.5, 30.5; FT-IR (neat): 3641 cm^{-1}; HRMS (ESI): m/z calcd for $C_{43}H_{43}O$ $[M + H]^+$: 575.3314; found: 575.3291.

2,6-Di-*tert*-butyl-4-(6a-phenyl-11-(*p*-tolyl)-6,6a-dihydro-5Hbenzo[*a*]fluoren-5-yl)phenol (60b)



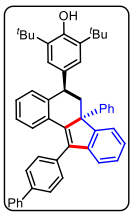
The reaction was performed on a 0.098 mmol scale of 57b; R_f = 0.5 (10% EtOAc in hexane); pale yellow solid (55 mg, 96% yield, dr {anti:syn} = >20:1); mp = 263−265 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58−7.56 (m, 2H), 7.45−7.42 (m, 3H), 7.39−7.33 (m, 2H), 7.30−7.26 (m, 3H), 7.23−7.18 (m, 3H), 7.17−7.09 (m, 2H), 6.98−6.95 (m, 3H), 6.78−6.76 (m, 1H), 5.12 (s, 1H), 4.04 (dd, *J* = 11.9, 5.4 Hz, 1H), 3.49 (dd, *J* = 12.6, 5.5 Hz, 1H), 2.51 (s, 3H), 2.15 (dd, *J* = 13.5, 12.6 Hz, 1H), 1.44 (s, 18H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 152.3, 151.4, 145.8, 144.7, 141.3, 140.9, 137.4, 137.3, 136.8, 135.9, 132.6, 132.4, 130.1, 129.7, 129.5, 128.9, 127.4, 127.3, 127.0, 126.6, 126.5, 125.6, 125.5, 125.4, 122.7, 120.9, 58.8, 44.3, 43.3, 34.5, 30.5, 21.6; FT-IR (neat): 3641 cm^{-1}; HRMS (ESI): m/z calcd for $C_{44}H_{43}O$ $[M - H]^-$: 587.3314; found: 587.3297.

2,6-Di-*tert*-butyl-4-(11-(4-(*tert*-butyl)phenyl)-6a-phenyl-6,6a-dihydro-5H-benzo[*a*]fluoren-5-yl)phenol (60c)



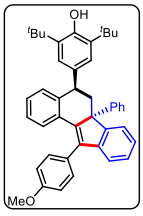
The reaction was performed on a 0.2 mmol scale of 57c; R_f = 0.5 (5% EtOAc in hexane); pale yellow solid (110.8 mg, 87% yield, dr {anti:syn} = >20:1); mp = 178−180 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55−7.53 (m, 4H), 7.46 (d, J = 8.0 Hz, 2H), 7.39 (d, J = 7.2 Hz, 1H), 7.28−7.23 (m, 4H), 7.19 (t, J = 7.9 Hz, 2H), 7.14−7.10 (m, 1H), 6.97−6.90 (m, 4H), 6.75 (d, J = 7.3 Hz, 1H), 5.09 (s, 1H), 4.02 (dd, J = 11.9, 5.4 Hz, 1H), 3.46 (dd, J = 13.6, 5.5 Hz, 1H), 2.14−2.08 (m, 1H), 1.43 (s, 9H), 1.42 (s, 18H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 152.3, 151.4, 150.5, 145.8, 144.7, 141.4, 140.9, 137.5, 136.8, 135.9, 132.5, 132.4, 130.1, 129.2, 128.9, 127.4, 127.2, 127.0, 126.6, 126.5, 125.8, 125.5, 125.4 (2C), 122.7, 121.1, 58.9, 44.3, 43.4, 34.9, 34.5, 31.6, 30.5; FT-IR (neat): 3644 cm^{-1}; HRMS (ESI): m/z calcd for $C_{47}H_{49}O$ [M − H]$^-$: 629.3783; found: 629.3804.

4-(11-([1,1'-biphenyl]-4-yl)-6a-phenyl-6,6a-dihydro-5H-benzo[*a*]fluoren-5-yl)-2,6-di-*tert*-butylphenol (60d)



The reaction was performed on a 0.2 mmol scale of 57d; R_f = 0.5 (5% EtOAc in hexane); pale yellow solid (120.1 mg, 92% yield, dr {anti:syn} = >20:1); mp = 272−274 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79−7.74 (m, 4H), 7.61 (d, J = 7.6 Hz, 2H), 7.57−7.50 (m, 4H), 7.43−7.39 (m, 2H), 7.32−7.26 (m, 4H), 7.23−7.13 (m, 3H), 6.99−6.91 (m, 4H), 6.77 (d, J = 7.4 Hz, 1H), 5.10 (s, 1H), 4.03 (dd, J = 11.8, 5.3 Hz, 1H), 3.49 (dd, J = 13.7, 5.4 Hz, 1H), 2.15 (t, J = 12.9 Hz, 1H), 1.43 (s, 18H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 152.3, 151.5, 146.3, 144.5, 141.3, 141.1, 140.9, 140.3, 137.4, 136.4, 136.0, 134.7, 132.2, 130.2, 130.1, 129.0, 128.9, 127.6, 127.5, 127.4, 127.2 (2C), 127.1, 126.7, 126.5, 125.7, 125.6, 125.5, 122.8, 120.9, 59.0, 44.3, 43.4, 34.5, 30.5; FT-IR (neat): 3635 cm^{-1}; HRMS (ESI): m/z calcd for $C_{49}H_{45}O$ [M − H]$^-$: 649.3470 found: 649.3475.

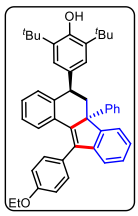
2,6-Di-*tert*-butyl-4-(11-(4-methoxyphenyl)-6a-phenyl-6,6a-dihydro-5H-benzo[*a*]fluoren-5-yl)phenol (60e)



The reaction was performed on a 0.070 mmol scale of 57e; R_f = 0.4 (5% EtOAc in hexane); white solid (39 mg, 92% yield, dr {anti:syn} = >20:1); mp = 261−263 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (d, J = 7.6 Hz, 2H), 7.45 (d, J = 8.1 Hz, 2H), 7.40 (d, J = 7.4 Hz, 1H), 7.28−7.24 (m, 3H), 7.21−7.11 (m, 4H), 7.07 (d, J = 8.5 Hz, 2H), 7.00−6.91 (m, 4H), 6.75 (d, J = 6.9 Hz, 1H), 5.09 (s, 1H), 4.00 (dd, J = 11.8, 5.2 Hz, 1H), 3.92 (s, 3H), 3.46 (dd, J = 13.6, 5.4 Hz, 1H), 2.11 (t, J = 12.9 Hz, 1H), 1.42 (s, 18H); ^{13}C{^{1}H}13C NMR (100 MHz, $CDCl_3$) δ 159.1 152.3, 151.4, 145.7, 144.8, 141.4, 141.0, 137.4, 136.4, 135.9, 132.4, 130.8, 130.1, 128.9, 127.8, 127.3, 127.2, 127.0,

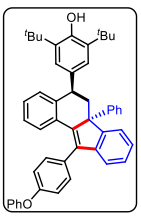
126.6, 126.5, 125.6, 125.5, 125.4, 122.7, 120.9, 114.5, 58.8, 55.4, 44.3, 43.3, 34.5, 30.5; FT-IR (neat): 3634 cm^{-1}; HRMS (ESI): m/z calcd for $C_{44}H_{43}O_2$ $[M - H]^-$: 603.3263; found: 603.3281.

2,6-di-*tert*-butyl-4-(11-(4-ethoxyphenyl)-6a-phenyl-6,6a-dihydro-5H-benzo[*a*]fluoren-5-yl)phenol (60f)



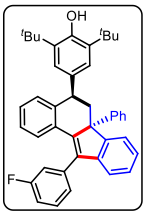
The reaction was performed on a 0.068 mmol scale of 57f; R_f = 0.4 (5% EtOAc in hexane); white solid (37.5 mg, 89% yield, dr {anti:syn} = >20:1); mp = 256−258 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (d, J = 7.6 Hz, 2H), 7.43 (d, J = 8.2 Hz, 2H), 7.40 (d, J = 7.3 Hz, 1H), 7.27−7.23 (m, 2H), 7.21−7.10 (m, 5H), 7.05 (d, J = 8.6 Hz, 2H), 7.00−6.89 (m, 4H), 6.74 (d, J = 7.0 Hz, 1H), 5.08 (s, 1H), (q, J = 7.0 Hz, 2H), 4.00 (dd, J = 11.8, 5.3 Hz, 1H), 3.45 (dd, J = 13.6, 5.4 Hz, 1H), 2.10 (t, J = 13.2 Hz, 1H), 1.50 (t, J = 7.0 Hz, 1H), 1.41 (s, 18H); ^{13}C{^{1}H} 13C NMR (100 MHz, $CDCl_3$) δ 158.5, 152.3, 151.4, 145.7, 144.8, 141.4, 140.9, 137.6, 137.4, 136.5, 135.9, 132.4, 130.8, 130.4, 130.1, 128.9, 127.6, 127.3, 127.2, 127.0, 126.6, 126.5, 125.6, 122.7, 120.9, 114.9, 63.6, 58.8, 53.6, 44.3, 34.5, 30.5, 15.1; FT-IR (neat): 3635 cm^{-1}; HRMS (ESI): m/z calcd for $C_{45}H_{45}O_2$ $[M - H]^-$: 617.3420; found: 617.3431.

2,6-Di-*tert*-butyl-4-(11-(4-phenoxyphenyl)-6a-phenyl-6,6a-dihydro-5H-benzo[*a*]fluoren-5-yl)phenol (60g)



The reaction was performed on a 0.2 mmol scale of 57g; R_f = 0.5 (5% EtOAc in hexane); orange gummy solid (114.9 mg, 85% yield, dr {anti:syn} = >20:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55−7.49 (m, 4H), 7.45−7.40 (m, 3H), 7.30−7.23 (m, 4H), 7.22−7.12 (m, 8H), 7.00−6.95 (m, 2H), 6.94 (s, 2H), 6.79−6.75 (m, 1H), 5.10 (s, 1H), 4.02 (dd, J = 11.9, 5.3 Hz, 1H), 3.47 (dd, J = 13.6, 5.5 Hz, 1H), 2.11 (dd, J = 13.6, 12.2 Hz, 1H), 1.41 (s, 18H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 157.2, 156.9, 152.3, 151.5, 146.2, 144.5, 141.2, 141.1, 137.3, 136.2, 136.0, 132.2, 131.1, 130.5, 130.2, 130.0, 128.9, 127.4, 127.3, 127.0, 126.7, 126.5, 125.7, 125.5, 125.4, 123.6, 122.8, 120.8, 119.3, 119.2, 58.9, 44.3, 43.4, 34.5, 30.5; FT-IR (neat): 3417 cm−1; HRMS (ESI): m/z calcd for $C_{49}H_{45}O_2$ $[M - H]^-$: 665.3420; found: 665.3444.

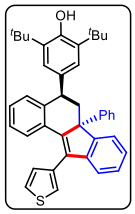
2,6-Di-*tert*-butyl-4-(11-(3-fluorophenyl)-6a-phenyl-6,6a-dihydro-5H-benzo[*a*]fluoren-5yl)phenol (60h)



The reaction was performed on a 0.072 mmol scale of 57h; R_f = 0.5 (5% EtOAc in hexane); pale yellow solid (36 mg, 84% yield, dr {anti:syn} = >10:1); mp = 264− 266 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54−7.48 (m, 3H), 7.42 (d, J = 7.3 Hz, 1H), 7.32−7.26 (m, 3H), 7.23−7.14 (m, 7H), 7.00−6.92 (m, 4H), 6.77 (d, J = 7.5 Hz, 1H), 5.11 (s, 1H), 4.03 (dd, J = 11.9, 5.3 Hz, 1H), 3.48 (dd, J = 13.7, 5.4 Hz, 1H), 2.15−2.07 (m, 1H), 1.43 (s, 18H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 163.3 (d, J_{C-F} = 244.9 Hz), 152.4, 151.4, 146.9, 144.0, 141.1, 141.0, 138.0 (d, J_{C-F} = 31.3 Hz), 137.2, 136.0, 135.5 (d, J_{C-F} = 2.0 Hz), 131.8, 130.6 (d, J_{C-F} = 33.4 Hz), 130.2, 128.9, 127.7, 127.3, 127.1, 126.8, 126.4, 125.9, 125.7, 125.5 (d, J_{C-F} = 2.8 Hz), 125.4, 122.9, 120.7, 116.3 (d, J_{C-F} = 21.2 Hz), 114.7 (d, J_{C-F} = 20.8 Hz), 59.0, 44.3, 43.4, 34.5, 30.5; ^{19}F NMR (376 MHz, $CDCl_3$) δ −112.54; FT-IR (neat): 3630 cm^{-1}; HRMS (ESI): m/z calcd for $C_{43}H_{40}FO$ $[M - H]^-$: 591.3063; found: 591.3083.

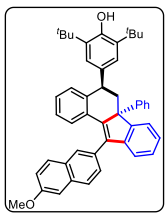
2,6-Di-*tert*-butyl-4-(6a-phenyl-11-(thiophen-3-yl)-6,6a-dihydro-5H-benzo[*a*]fluoren-5-yl)phenol (60i)

The reaction was performed on a 0.075 mmol scale of 57i; R_f = 0.5 (5% EtOAc in hexane); pale yellow solid (36 mg, 82% yield, dr {anti:syn} = >20:1); mp = 203−205 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53−7.48 (m, 4H), 7.40 (d, J = 7.3 Hz, 1H), 7.37−7.33 (m, 1H), 7.31 (d, J = 7.5 Hz, 1H), 7.28−7.24 (m, 2H), 7.22−7.10 (m, 4H), 7.00−6.96 (m, 2H), 6.93 (s, 2H),



6.78−6.74 (m, 1H), 5.09 (s, 1H), 4.01 (dd, J = 12.0, 5.4 Hz, 1H), 3.45 (dd, J = 13.6, 5.5 Hz, 1H), 2.10 (dd, J = 13.4, 12.2 Hz, 1H), 1.41 (s, 18H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 152.3, 151.3 146.8, 144.2, 141.2, 141.0, 137.3 135.9, 135.5, 132.3, 131.7, 130.1, 128.9, 128.8, 127.5, 127.2, 127.1, 126.7, 126.5, 126.0, 125.7, 125.6, 125.4, 124.0, 122.8, 120.9, 58.9, 44.3, 43.4, 34.5, 30.5; FT-IR (neat): 3637 cm^{-1}; HRMS (ESI): m/z calcd for $C_{41}H_{41}OS$ $[M + H]^+$: 581.2878; found: 581.2863.

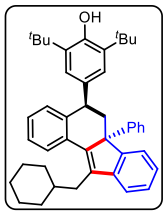
2,6-Di-*tert*-butyl-4-(11-(6-methoxynaphthalen-2-yl)-6a-phenyl-6,6a-dihydro-5H benzo[*a*]fluoren-5-yl)phenol (60j)



The reaction was performed on a 0.063 mmol scale of 57j; R_f = 0.4 (5% EtOAc in hexane); white solid (40 mg, 97% yield, dr {anti:syn} = >7:1); mp = 236−238 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (s, 1H), 7.89 (d, J = 8.4 Hz, 1H), 7.81 (d, J = 8.8 Hz, 1H), 7.59−7.56 (m, 3H), 7.44 (d, J = 7.1 Hz, 1H), 7.31−7.23 (m, 6H), 7.22−7.13 (m, 3H), 6.98−6.93 (m, 3H), 6.84 (t, J = 7.5 Hz, 1H), 6.77 (d, J = 7.8 Hz, 1H), 5.11 (s, 1H), 4.06 (dd, J = 11.9, 5.4 Hz, 1H), 4.00 (s, 3H), 3.51 (dd, J = 13.6,

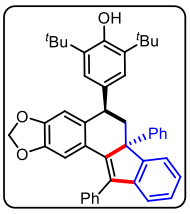
5.5 Hz, 1H), 2.18 (t, *J* = 13.2 Hz, 1H), 1.45 (s, 18H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 158.0, 152.3, 151.5, 146.2, 144.7, 141.3, 141.0, 137.4, 136.7, 135.9, 134.1, 132.3, 130.9, 130.1, 129.7, 129.4, 128.9, 128.4, 128.36, 127.5, 127.4, 127.3, 127.0, 126.7, 126.5, 125.7, 125.6, 125.5, 122.8, 120.9, 119.1, 106.0, 58.9, 55.5, 44.3, 43.3, 34.5, 30.5; FT-IR (neat): 3637 cm^{-1}; HRMS (ESI): m/z calcd for $C_{48}H_{45}O_2$ $[M - H]^-$: 653.3420; found: 653.3424.

2,6-Di-*tert*-butyl-4-(11-(cyclohexylmethyl)-6a-phenyl-6,6a-dihydro-5H-benzo[*a*]fluoren-5 yl)phenol (60k)



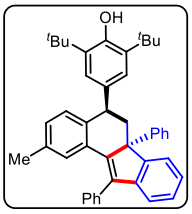
The reaction was performed on a 0.072 mmol scale of 57k; R_f = 0.5 (5% EtOAc in hexane); pale yellow solid (34 mg, 79% yield, dr {anti:syn} = >20:1); mp = 173−175 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (d, *J* = 7.8 Hz, 1H), 7.45 (d, *J* = 7.8 Hz, 2H), 7.41 (d, *J* = 7.6 Hz, 1H), 7.32 (d, *J* = 7.4 Hz, 1H), 7.25−7.21 (m, 4H), 7.15−7.08 (m, 2H), 7.03 (t, *J* = 7.6 Hz, 1H), 6.87 (s, 2H), 6.76 (d, *J* = 7.7 Hz, 1H), 5.06 (s, 1H), 3.95 (dd, *J* = 12.2, 5.2 Hz, 1H), 3.35 (dd, *J* = 13.6, 5.4 Hz, 1H), 2.98 (dd, *J* = 13.6, 8.5 Hz, 1H), 2.87 (dd, *J* = 13.7, 5.7 Hz, 1H), 1.98−1.87 (m, 3H), 1.79−1.77 (m, 2H), 1.66−1.65 (m, 2H), 1.37 (s, 18H), 1.21−1.16 (m, 3H), 1.08−0.94 (m, 2H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 152.3, 151.8, 145.6, 144.8, 141.6, 140.6, 137.3, 136.1, 135.9, 133.6, 130.2, 128.8, 126.9, 126.8, 126.7, 126.53, 126.5, 125.9, 125.5, 125.3, 122.6, 120.7, 59.0, 44.5, 44.1, 38.5, 34.5, 34.4, 33.8, 33.7, 30.5, 26.7, 26.6, 26.57; FT-IR (neat): 3641 cm^{-1}; HRMS (ESI): m/z calcd for $C_{44}H_{51}O$ $[M + H]^+$: 595.3940; found: 595.3967.

2,6-di-*tert*-butyl-4-(6a,11-diphenyl-6,6a-dihydro-5H-indeno[2',1':5,6]naphtho[2,3-d][1,3]dioxol-5-yl)phenol (60l)



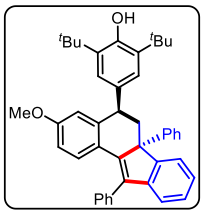
The reaction was performed on a 0.068 mmol scale of 57l; R_f = 0.3 (5% EtOAc in hexane); pale orange (40 mg, 94% yield, dr {anti:syn} = >20:1); mp = 230−232 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55−7.49 (m, 6H), 7.46−7.42 (m, 1H), 7.36 (d, *J* = 7.3 Hz, 1H), 7.29−7.25 (m, 2H), 7.19−7.13 (m, 3H), 7.10 (td, *J* = 7.2, 2 Hz, 1H), 6.90 (s, 2H), 6.63 (s, 1H), 6.20 (s, 1H), 5.81 (d, *J* = 1.3 Hz, 1H), 5.75 (d, *J* = 1.3 Hz, 1H), 5.08 (s, 1H), 3.87 (dd, *J* = 11.8, 5.4 Hz, 1H), 3.41 (dd, *J* = 13.6, 5.5 Hz, 1H), 2.06 (dd, *J* = 13.4, 12.1 Hz, 1H), 1.41 (s, 18H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 152.4, 150.9, 147.1, 145.9, 145.4, 144.7, 141.4, 137.2, 136.0, 135.64, 135.6, 129.7, 129.1, 128.9, 127.8, 127.0, 126.7, 126.5 (2C), 125.9, 125.5, 125.3, 122.7, 120.6, 110.0, 106.7, 100.8, 58.8, 44.6, 43.0, 34.5, 30.5; FT-IR (neat): 3634 cm^{-1}; HRMS (ESI): m/z calcd for $C_{44}H_{41}O_3$ $[M - H]^-$: 617.3056; found: 617.3051.

2,6-Di-*tert*-butyl-4-(2-methyl-6a,11-diphenyl-6,6a-dihydro-5Hbenzo[*a*]fluoren-5-yl)phenol (60m)



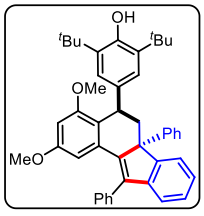
The reaction was performed on a 0.2 mmol scale of 57m; R_f = 0.5 (5% EtOAc in hexane); white solid (99 mg, 84% yield, dr {anti:syn} = >10:1); mp = 97−99 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58−7.52 (m, 6H), 7.50−7.46 (m, 1H), 7.43 (d, *J* = 7.3 Hz, 1H), 7.29 (t, *J* = 7.4 Hz, 2H), 7.23−7.13 (m, 4H), 7.02 (s, 1H), 6.97 (s, 2H), 6.79 (dd, *J* = 8.0, 1.4 Hz, 1H), 6.65 (d, *J* = 8.0 Hz, 1H), 5.11 (s, 1H), 3.99 (dd, *J* = 12.0, 5.2 Hz, 1H), 3.49 (dd, *J* = 13.6, 5.4 Hz, 1H), 2.15 (dd, *J* = 13.4, 12.3 Hz, 1H), 2.08 (s, 3H), 1.45 (s, 18H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 152.3, 151.5, 146.3, 144.6, 141.4, 138.0, 137.4, 136.7, 135.9, 135.8, 134.6, 131.9, 129.8, 129.7, 128.9, 128.4, 127.9, 127.6, 127.0, 126.6, 126.5, 125.6, 125.4, 122.7, 120.8, 58.9, 44.0, 43.4, 34.5, 30.5, 21.2; FT-IR (neat): 3638 cm^{-1}; HRMS (ESI): m/z calcd for $C_{44}H_{45}O$ [M + H]$^+$: 589.3470; found: 589.3447.

2,6-Di-*tert*-butyl-4-(3-methoxy-6a,11-diphenyl-6,6a-dihydro-5Hbenzo[*a*]fluoren-5-yl)phenol (60n)



The reaction was performed on a 0.2 mmol scale of 57n; R_f = 0.4 (5% EtOAc in hexane); Pale yellow (99.6 mg, 82% yield, dr {anti:syn} = >20:1); mp = 226−228 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55−7.53 (m, 6H), 7.47−7.43 (m, 1H), 7.40 (d, *J* = 7.4 Hz, 1H), 7.29−7.25 (m, 2H), 7.19−7.09 (m, 5H), 6.94 (s, 2H), 6.50 (dd, *J* = 8.6, 2.2 Hz, 1H), 6.28 (s, 1H), 5.09 (s, 1H), 3.96 (dd, *J* = 12.0, 5.1 Hz, 1H), 3.57 (s, 3H), 3.44 (dd, *J* = 13.6, 5.2 Hz, 1H), 2.16 (t, *J* = 12.9 Hz, 1H), 1.42 (s, 18H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 158.7, 152.4, 151.1, 145.9, 144.8, 142.8, 141.5, 136.8, 136.0, 135.96, 135.3, 129.7, 129.0, 128.9, 128.6, 127.6, 127.0, 126.6, 126.5, 125.4, 125.3, 125.29, 122.7, 120.5, 115.2, 111.6, 58.7, 55.0, 44.6, 42.8, 34.5, 30.5; FT-IR (neat): 3644 cm^{-1}; HRMS (ESI): m/z calcd for $C_{44}H_{45}O_2$ [M + H]$^+$: 605.3419; found: 605.3393.

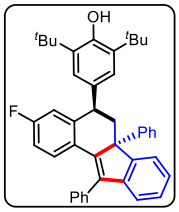
2,6-Di-*tert*-butyl-4-(2,4-dimethoxy-6a,11-diphenyl-6,6a-dihydro-5H-benzo[*a*]fluoren-5-yl)phenol (60o)



The reaction was performed on a 0.088 mmol scale of 57o; R_f = 0.3 (5% EtOAc in hexane); white solid (35 mg, 62% yield, dr {anti:syn} = >20:1); mp = 261−263 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, J = 7.3 Hz, 2H),

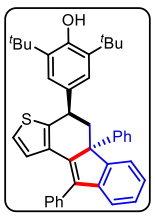
7.52 (t, J = 7.4 Hz, 2H), 7.46−7.42 (m, 3H), 7.32 (d, J = 7.3 Hz, 1H), 7.27−7.21 (m, 3H), 7.19−7.08 (m, 3H), 6.90 (s, 2H), 6.29 (d, J = 2.3 Hz, 1H), 6.12 (d, J = 2.3 Hz, 1H), 4.93 (s, 1H), 4.08 (dd, J = 10.7, 7.0 Hz, 1H), 3.56 (dd, J = 14.1, 6.9 Hz, 1H), 3.42 (s, 3H), 3.19 (s, 3H), 1.85 (dd, J = 14.1, 10.8 Hz, 1H), 1.40 (s, 18H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 158.9, 158.2, 152.0, 151.3, 147.3, 144.1, 140.8, 139.7, 136.7, 135.6, 135.3, 134.0, 129.8, 128.9, 128.7, 127.7, 126.9, 126.5 (2C), 125.7, 123.8, 123.1, 123.0, 120.9, 103.1, 100.2, 58.9, 55.5, 54.9, 43.1, 40.0, 34.4, 30.6; FT-IR (neat): 3634 cm^{-1}; HRMS (ESI): m/z calcd for $C_{45}H_{47}O_3$ $[M + H]^+$: 635.3525; found: 635.3552.

2,6-Di-*tert*-butyl-4-(3-fluoro-6a,11-diphenyl-6,6a-dihydro-5Hbenzo[*a*]fluoren-5-yl)phenol (60p)



The reaction was performed on a 0.048 mmol scale of 57p; R_f = 0.5 (5% EtOAc in hexane); colorless solid (17 mg, 60% yield, dr {anti:syn} = >10:1); mp = 190−192 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55−7.43 (m, 7H), 7.40 (d, J = 7.3 Hz, 1H), 7.29−7.25 (m, 2H), 7.21−7.11 (m, 5H), 6.91 (s, 2H), 6.61 (td, J = 8.4, 2.3 Hz, 1H), 6.46−6.42 (m, 1H), 5.12 (s, 1H), 3.96 (dd, J = 12.0, 5.4 Hz, 1H), 3.45 (dd, J = 13.7, 5.5 Hz, 1H), 2.11 (dd, J = 13.6, 12.1 Hz, 1H), 1.42 (s, 18H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 162.0 (d, J_{C-F} = 244.8 Hz), 152.6, 151.2, 145.0, 144.5, 143.7 (d, J_{C-F} = 7.0 Hz), 141.1, 136 (d, J_{C-F} = 1.3 Hz), 136.5, 136.2, 135.5, 129.6, 129.1, 129.0, 128.97, 128.4 (d, J_{C-F} = 2.9 Hz), 127.8, 127.1, 126.8, 126.4, 125.7, 125.3, 122.8, 120.9, 116.5 (d, J_{C-F} = 21.4 Hz), 113.2 (d, J_{C-F} = 21.7 Hz), 58.8, 44.6, 42.9, 34.5, 30.5; ^{19}F NMR (376 MHz, $CDCl_3$) δ −113.84; FT-IR (neat): 3639 cm^{-1}; HRMS(ESI): m/z calcd for $C_{43}H_{41}FNaO$ $[M + Na]^+$: 615.3039; found: 615.3014.

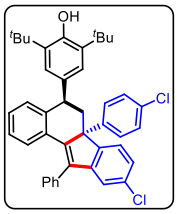
2,6-di-*tert*-butyl-4-(5a,10-diphenyl-5,5a-dihydro-4H-fluoreno[2,1-*b*]thiophen-4-yl)phenol (60q)



The reaction was performed on a 0.074 mmol scale of 57q; R_f = 0.4 (5% EtOAc in hexane); pale brown gummy solid (28 mg, 65% yield, dr {anti:syn} = >20:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63−7.61 (m, 4H), 7.58 (d, J = 7.4 Hz, 1H), 7.51 (d, J = 7.2 Hz, 1H), 7.35−7.29 (m, 3H), 7.26−7.22 (m, 2H), 7.20−7.13 (m, 3H), 7.04 (s, 2H), 7.00 (d, J = 5.3 Hz, 1H), 6.84 (d, J = 5.2 Hz, 1H), 5.18 (s, 1H), 4.01 (dd, J = 11.6, 4.3 Hz, 1H), 3.48 (dd, J = 13.1, 4.5 Hz, 1H), 2.29 (t, J = 12.4 Hz, 1H), 1.46 (s, 18H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 152.9, 150.0, 146.1, 144.7, 142.7, 142.3, 136.0, 135.5, 135.4, 135.2, 129.8, 128.9, 128.8(2C), 127.9, 127.2, 126.8, 126.2, 125.4, 124.8, 124.7, 123.8,

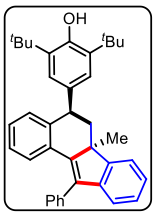
122.8, 120.5, 59.0, 43.1, 42.3, 34.5, 30.5; FT-IR (neat): 3639 cm^{-1}; HRMS(ESI): m/z calcd for $C_{41}H_{41}OS$ $[M + H]^+$: 581.2878; found: 581.2886.

2,6-Di-*tert*-butyl-4-(9-chloro-6a-(4-chlorophenyl)-11-phenyl-6,6a-dihydro-5H-benzo[*a*]fluoren-5-yl)phenol (60r)



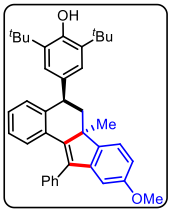
The reaction was performed on a 0.2 mmol scale of 57a; R_f = 0.1 (5% EtOAc in hexane); white solid (116.7 mg, 90% yield, dr {anti:syn} = >10:1); mp = 102−104 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57−7.53 (m, 2H), 7.51−7.48 (m, 3H), 7.44−7.42 (m, 2H), 7.27−7.23 (m, 3H), 7.19 (d, *J* = 7.6 Hz, 1H), 7.16 (d, J = 1.8 Hz, 1H), 7.11 (dd, *J* = 8.0, 1.9 Hz, 1H), 7.00 (td, *J* = 7.5, 1.3 Hz, 1H), 6.95−6.90 (m, 3H), 6.78 (d, *J* = 7.7 Hz, 1H), 5.13 (s, 1H), 3.98 (dd, *J* = 11.9, 5.4 Hz, 1H), 3.40 (dd, *J* = 13.8, 5.6 Hz, 1H), 2.10 (dd, *J* = 13.5, 12.4 Hz, 1H), 1.43 (s, 18H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 152.5, 149.2, 147.3, 146.3, 140.9, 139.3, 137.0, 136.1, 136.06, 134.8, 133.3, 132.7, 131.5, 130.2, 129.5, 129.24, 129.2, 128.1, 128.0, 127.8, 127.4, 125.8, 125.6, 125.4, 123.6, 121.2, 58.1, 44.2, 43.1, 34.5, 30.5; FT-IR (neat): 3637 cm^{-1}; HRMS (ESI): m/z calcd for $C_{43}H_{39}Cl_2O$ $[M - H]^-$: 641.2378; found: 641.2408.

2,6-Di-*tert*-butyl-4-(6a-methyl-11-phenyl-6,6a-dihydro-5Hbenzo[*a*]fluoren-5-yl)phenol (60s)



The reaction was performed on a 0.12 mmol scale of 57a; R_f = 0.4 (5% EtOAc in hexane); white solid (42 mg, 68% yield, dr {anti:syn} = >10:3); major isomer: mp = 87−89 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49−7.44 (m, 5H), 7.28−7.23 (m, 3H), 7.16−7.05 (m, 3H), 7.01−6.92 (m, 4H), 5.09 (s, 1H), 4.34 (dd, *J* = 11.8, 6.1 Hz, 1H), 2.72 (dd, *J* = 13.2, 6.1 Hz, 1H), 1.79−1.73 (m, 1H), 1.47 (s, 3H), 1.43 (s, 18H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 152.5, 152.2, 147.6, 145.0, 140.9, 137.8, 136.0, 135.9, 134.0, 131.6, 130.4, 129.7, 128.9, 127.5, 127.4, 127.3, 127.0, 125.5, 125.4, 125.2, 121.6, 120.7, 50.6, 44.1, 34.5 (2C), 30.5, 21.1; FT-IR (neat): 3638 cm^{-1}; HRMS (ESI): m/z calcd for $C_{38}H_{39}O$ $[M - H]^-$: 511.3000; found: 511.3022.

2,6-di-*tert*-butyl-4-(9-methoxy-6a-methyl-11-phenyl-6,6a-dihydro-5H-benzo[*a*]fluoren-5-yl)phenol (60t).



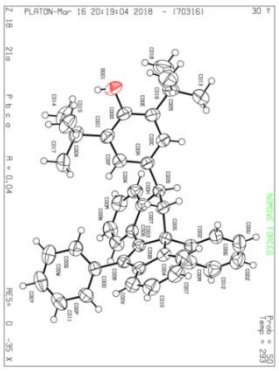
The reaction was performed on a 0.12 mmol scale of 57a; R_f = 0.3 (5% EtOAc in hexane); white solid (34.8 mg, 73% yield, dr {anti:syn} = >10:3); major isomer: mp = 93−95 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48−7.42 (m, 4H),

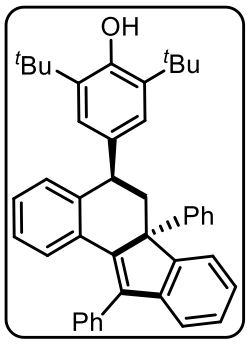
7.19−7.10 (m, 3H), 7.05−7.02 (m, 2H), 7.00−6.89 (m, 4H), 6.81 (dd, *J* = 8.3, 2.4 Hz, 1H), 5.07 (s, 1H), 4.30 (dd, *J* = 12.0, 6.3 Hz, 1H), 3.84 (s, 3H), 2.64 (dd, *J* = 13.1, 6.1 Hz, 1H), 1.75 (t, *J* = 12.6 Hz 1H), 1.42 (s, 18H), 1.40 (s, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 158.4, 154.4, 152.2, 145.7, 140.5, 138.1, 137.9, 136.2, 135.9, 133.7, 131.8, 130.4, 129.6, 128.9, 127.4, 127.2, 127.0, 125.5, 125.4, 121.2, 112.2, 108.2, 55.7, 50.5, 44.3, 44.2, 34.5, 30.5, 21.3; FT-IR (neat): 3635 cm^{-1}; HRMS (ESI): m/z calcd for $C_{39}H_{41}O_2$ $[M - H]^-$: 541.3107; found: 541.3115.

X-ray crystallographic analysis for compound 60a:

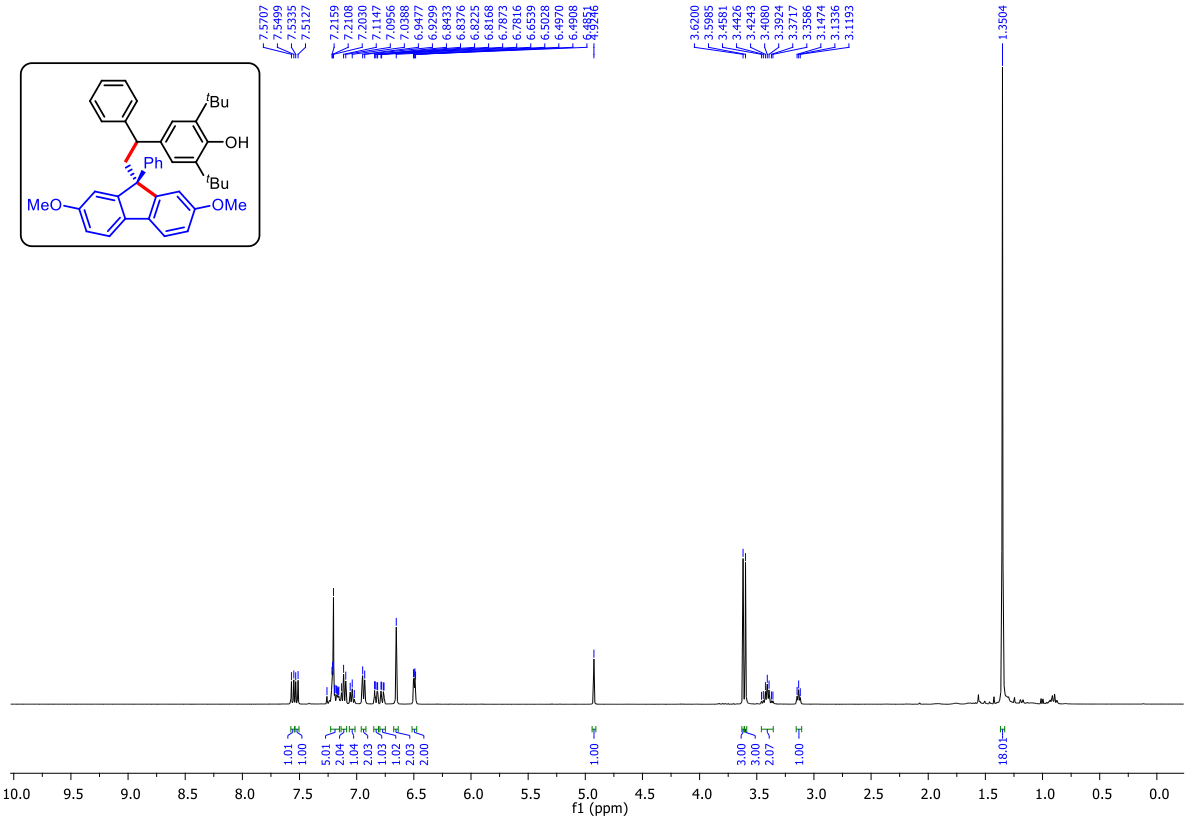
Table 1 Crystal data and structure refinement for compound 60a (CCDC 1830911)

Identification code	**60a**
Empirical formula	$C_{43}H_{42}O$
Formula weight	574.76
Temperature/K	293(2)
Crystal system	orthorhombic
Space group	Pbca
a/Å	14.3105(6)
b/Å	18.8797(8)
c/Å	24.8734(11)
α/°	90
β/°	90
γ/°	90
Volume/$Å^3$	6720.2(5)
Z	8
$\rho_{calc}g/cm^3$	1.136
μ/mm^{-1}	0.066
F(000)	2464.0
Crystal size/mm^3	0.2 × 0.2 × 0.15
Radiation	MoKα (λ = 0.71073)
2Θ range for data collection/°	5.418 to 49.998
Index ranges	$-17 \leq h \leq 16$, $-22 \leq k \leq 22$, $-18 \leq l \leq 29$
Reflections collected	33410
Independent reflections	5903 [R_{int} = 0.0290, R_{sigma} = 0.0182]
Data/restraints/parameters	5903/0/404
Goodness-of-fit on F^2	1.065
Final R indexes [I>=2σ (I)]	R_1 = 0.0445, wR_2 = 0.1128
Final R indexes [all data]	R_1 = 0.0575, wR_2 = 0.1299
Largest diff. peak/hole / e $Å^{-3}$	0.13/-0.19

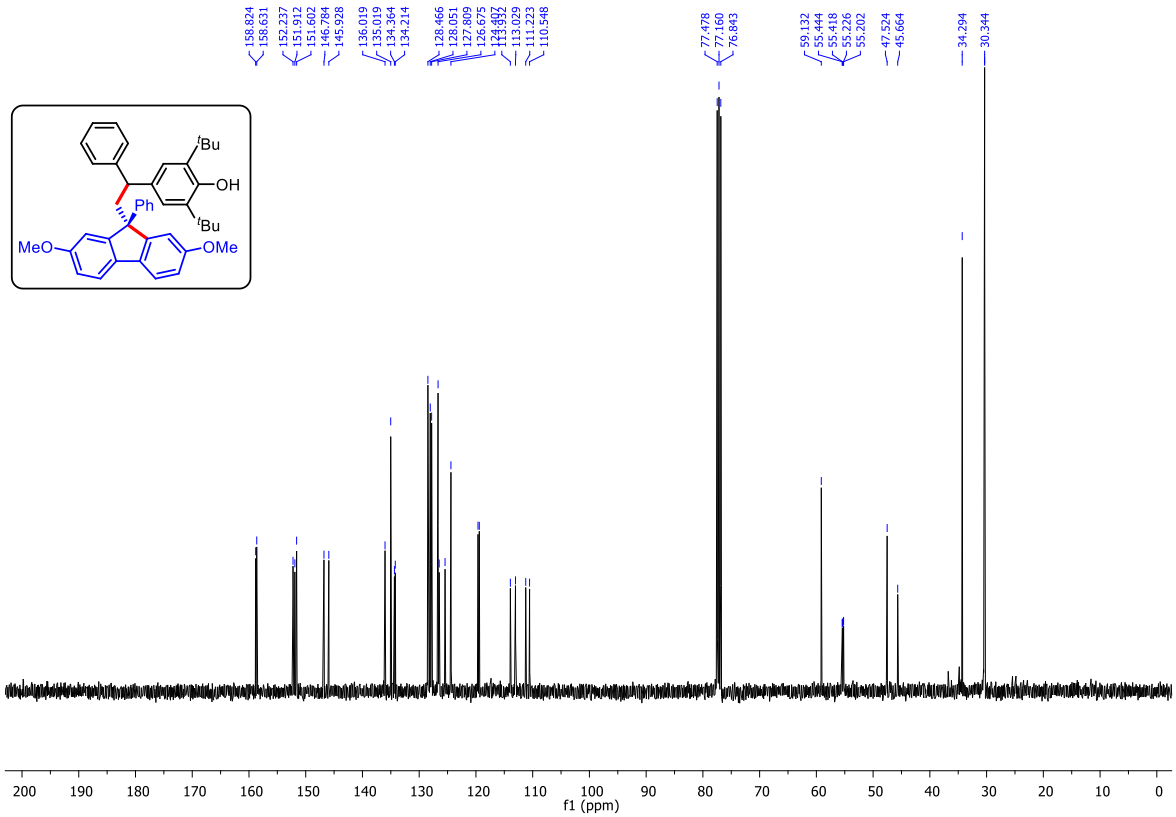




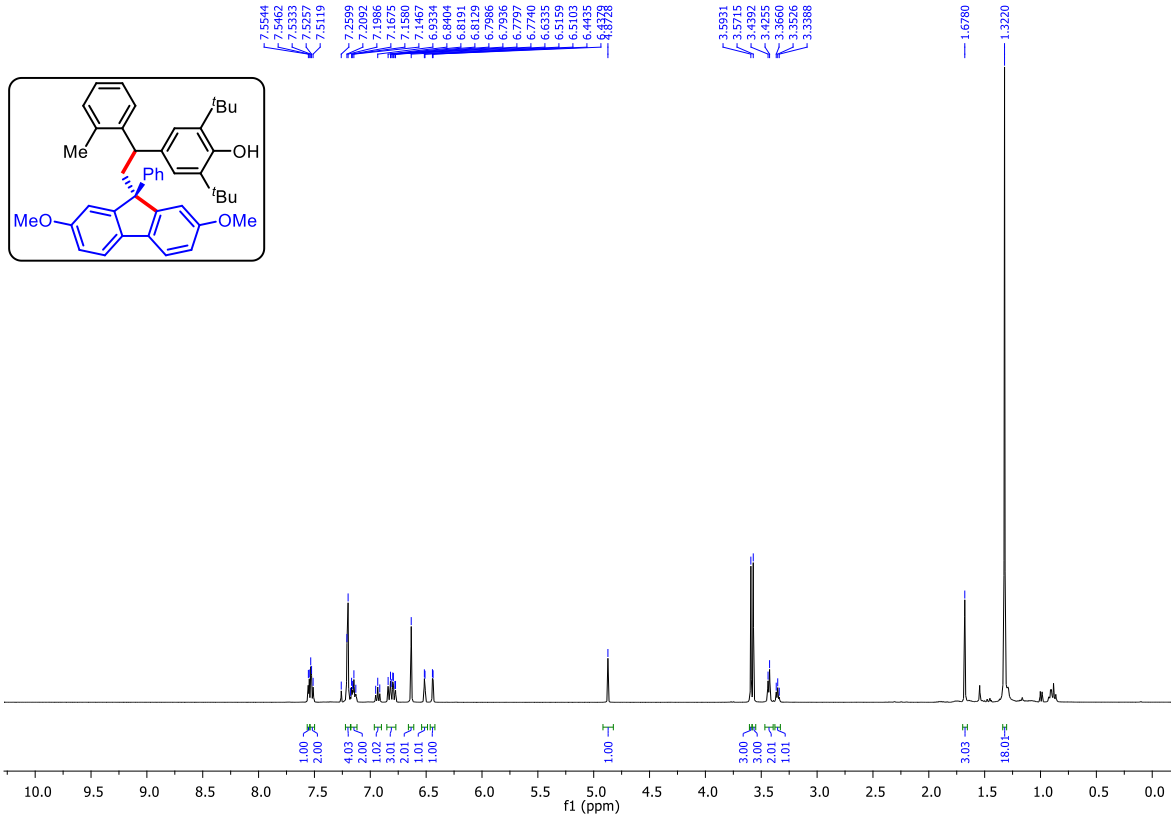
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **56b**



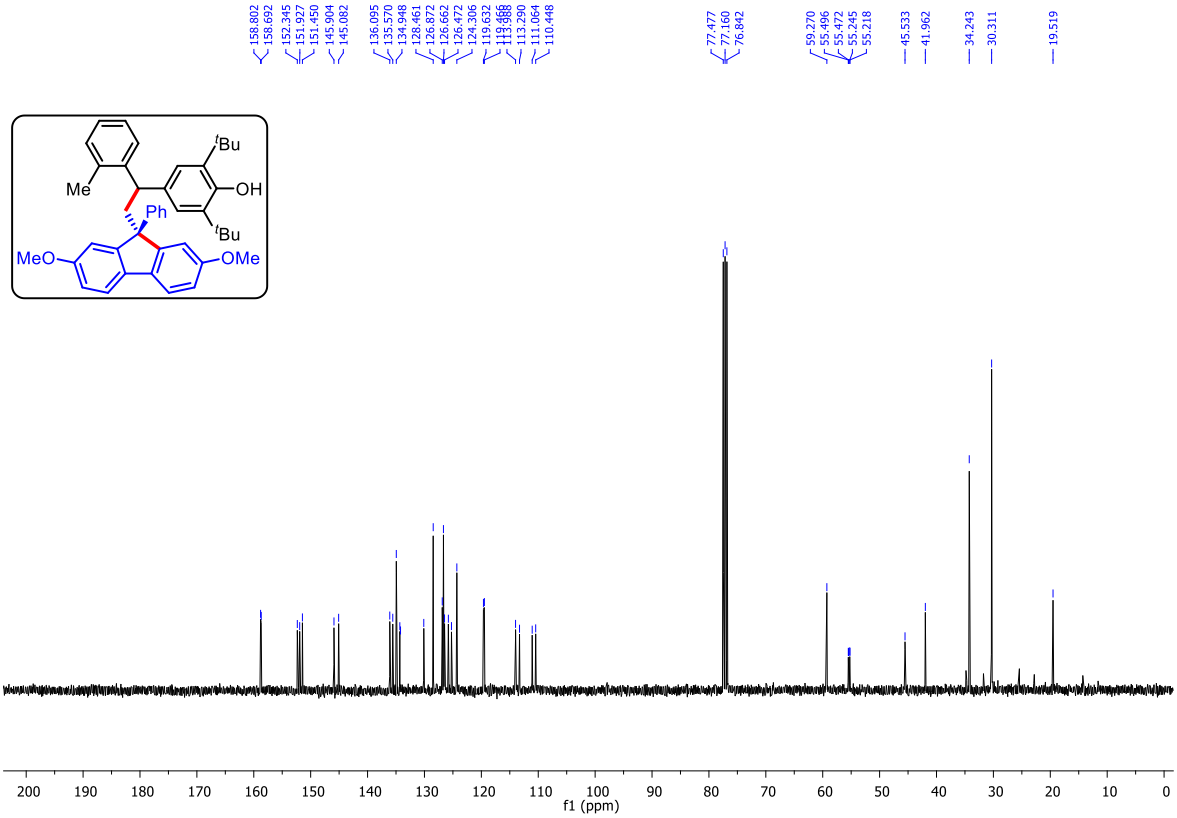
^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) spectrum of compound **56b**



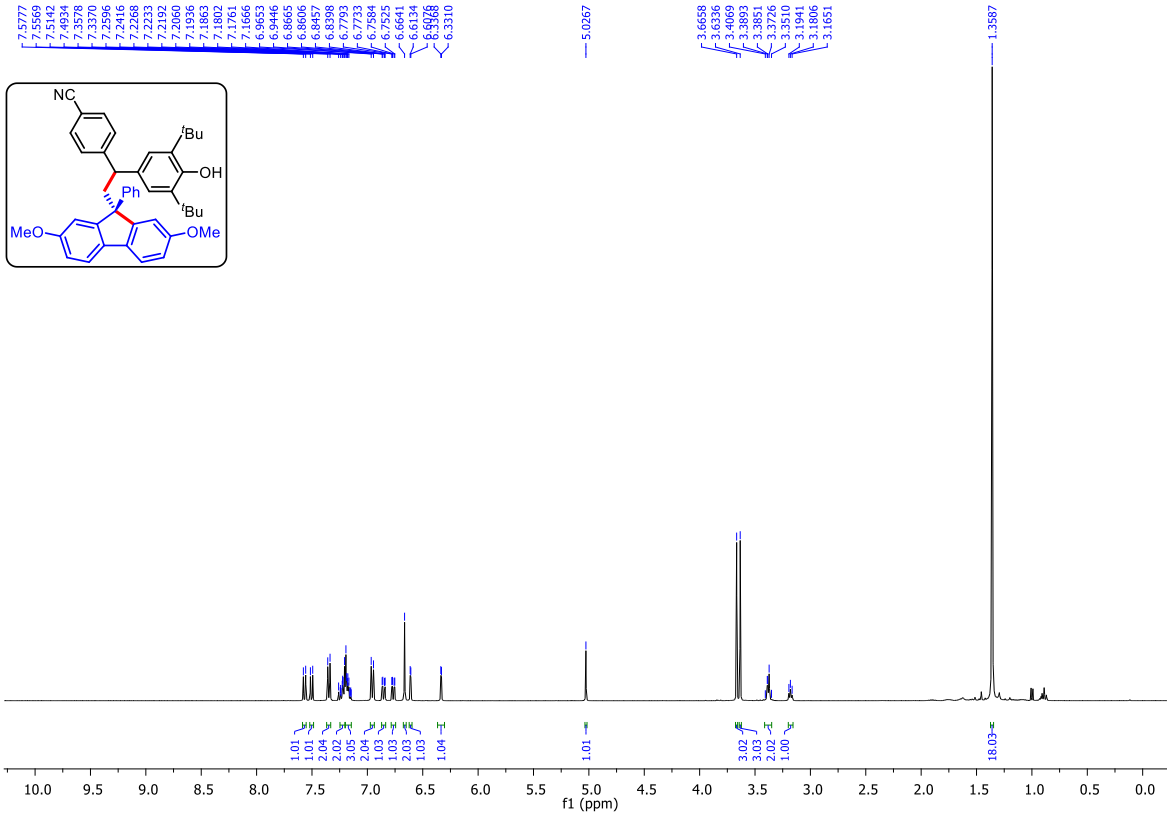
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **56h**



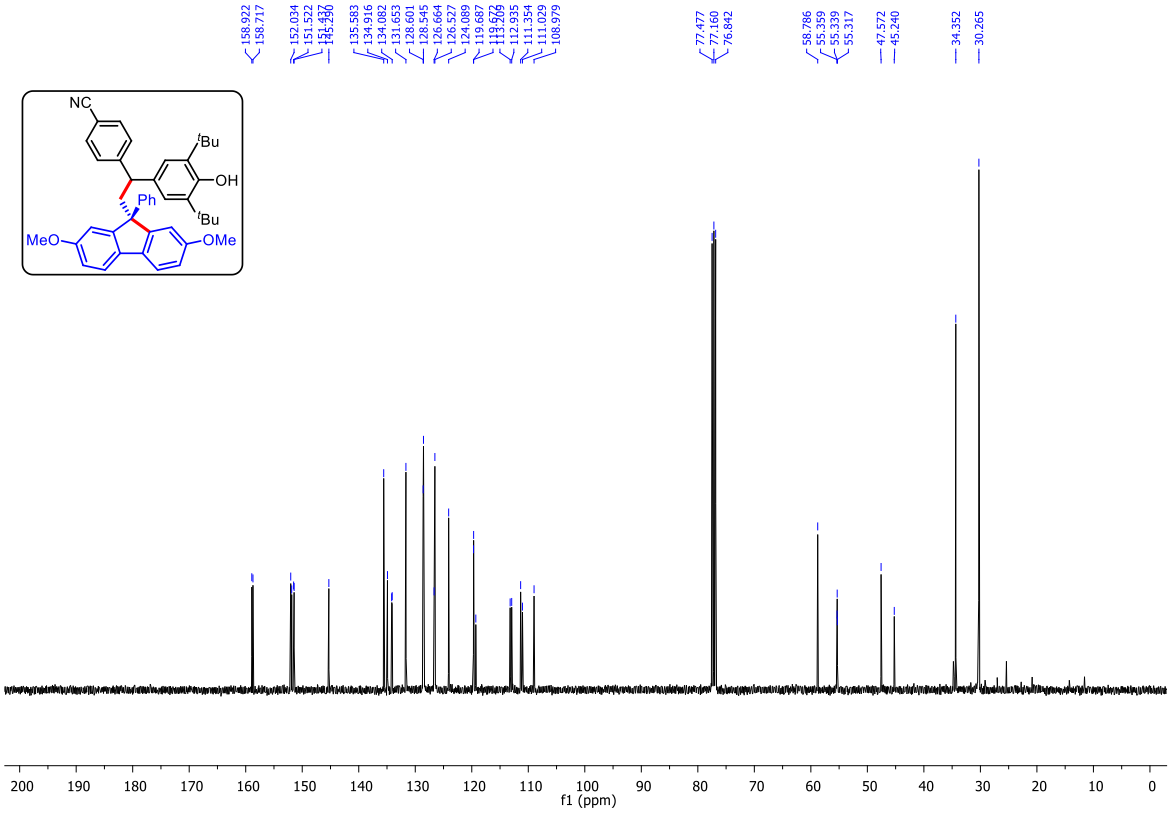
^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) spectrum of compound **56h**



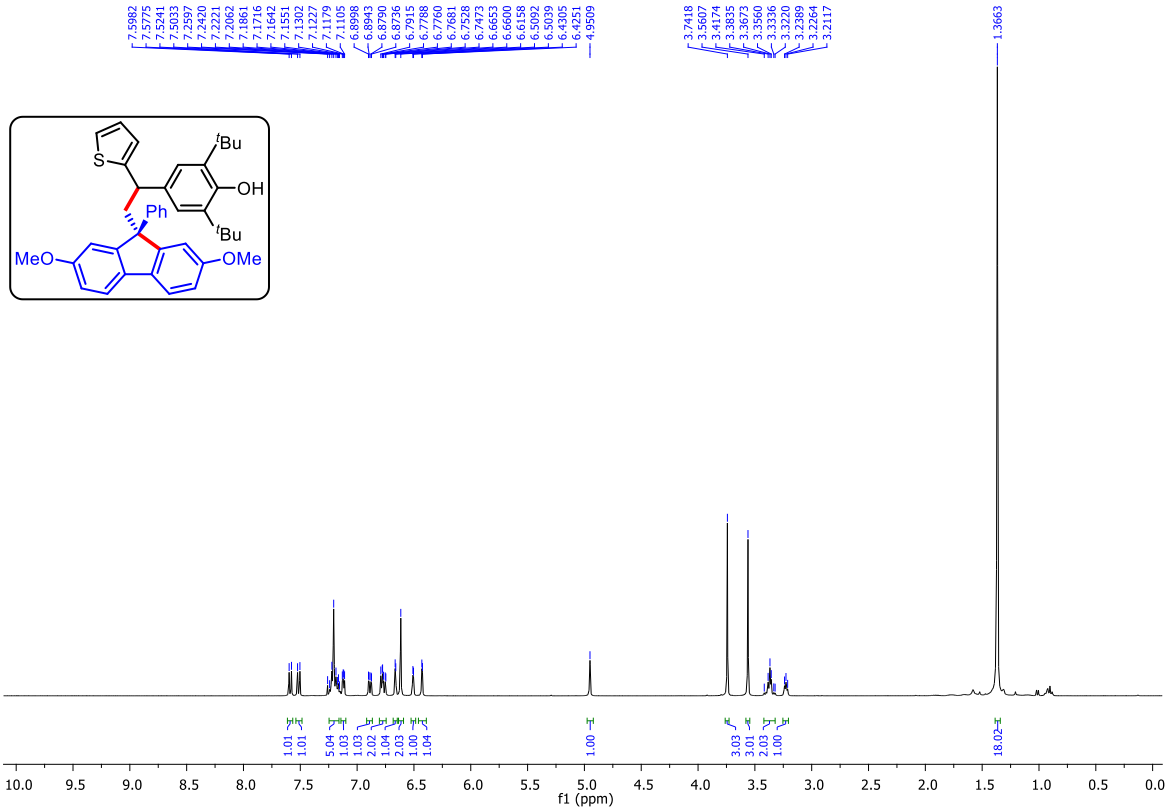
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **56k**



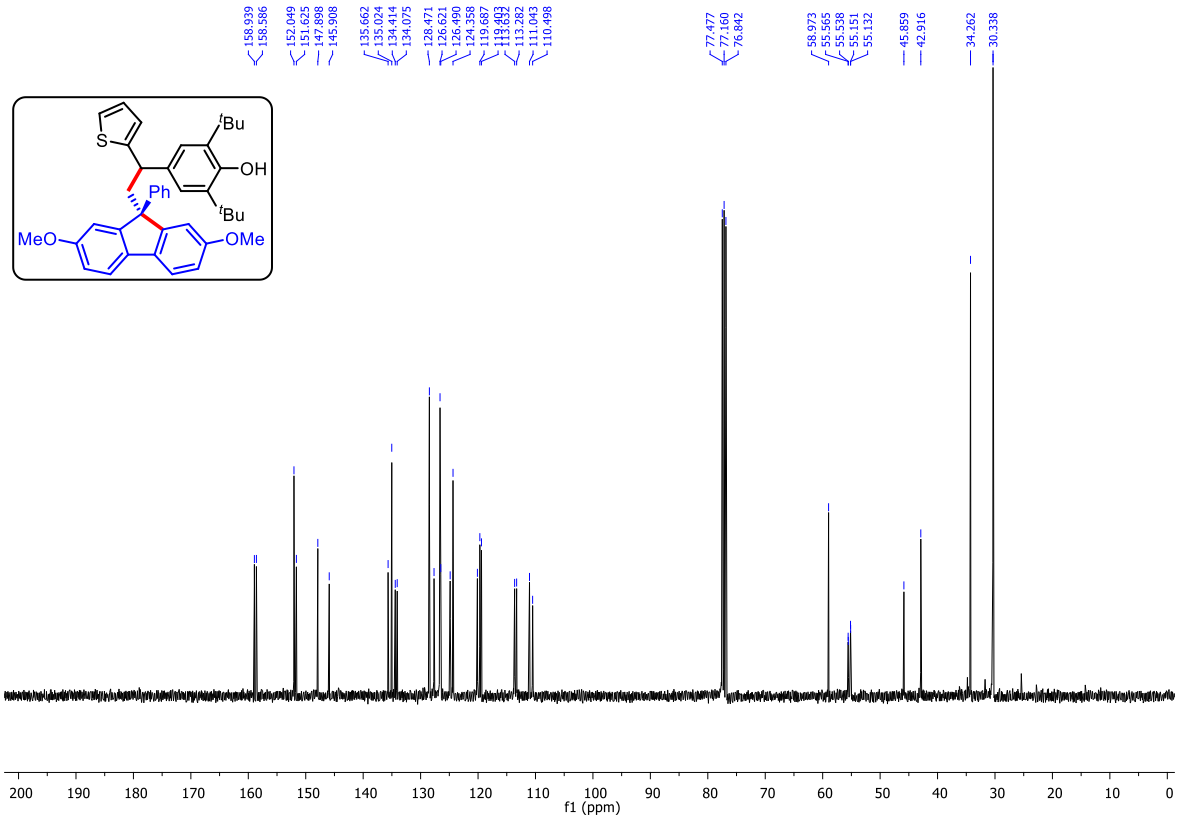
^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) spectrum of compound **56k**



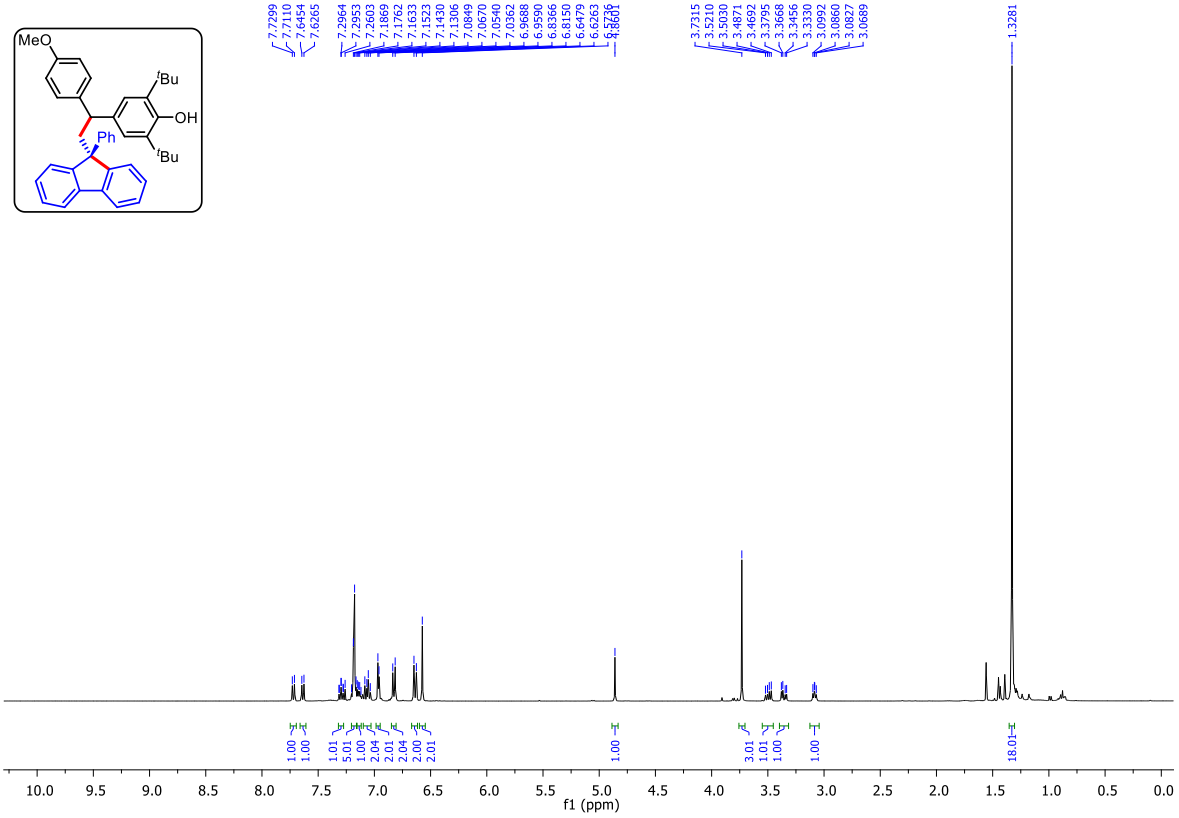
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **56q**



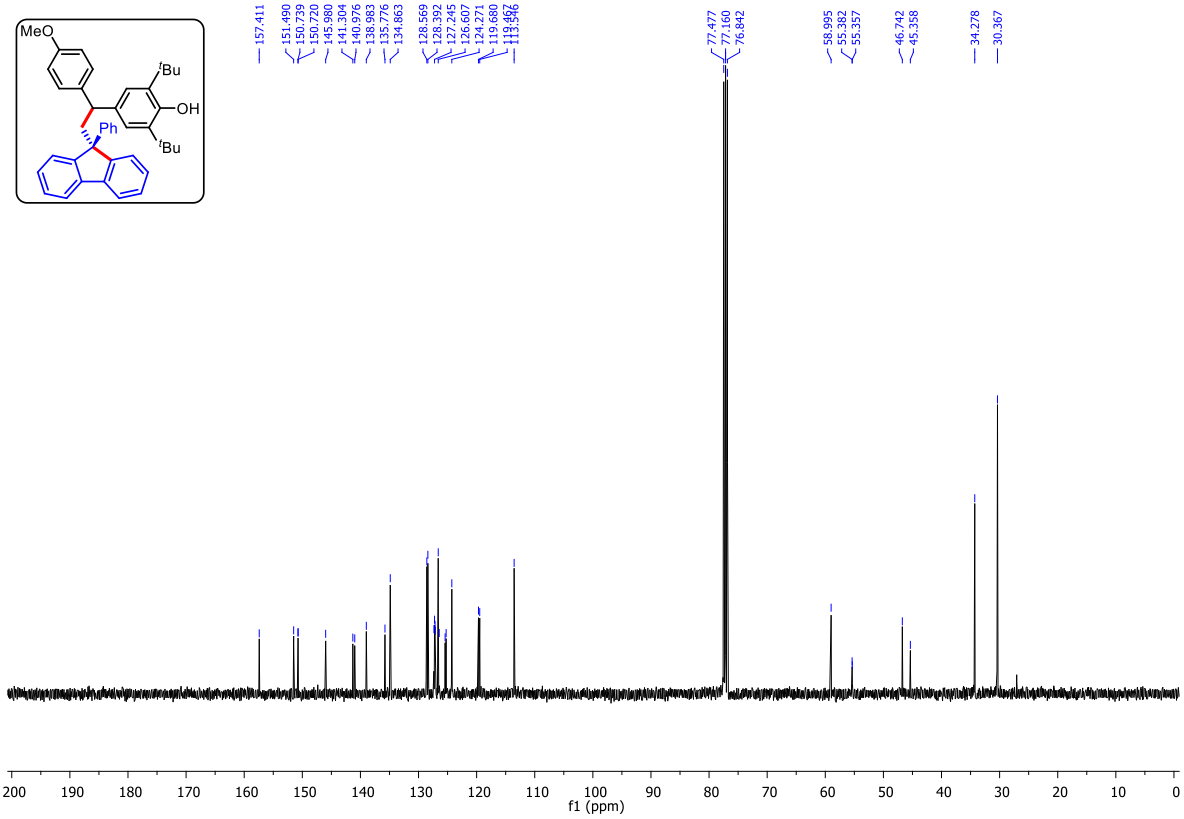
^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) spectrum of compound **56q**



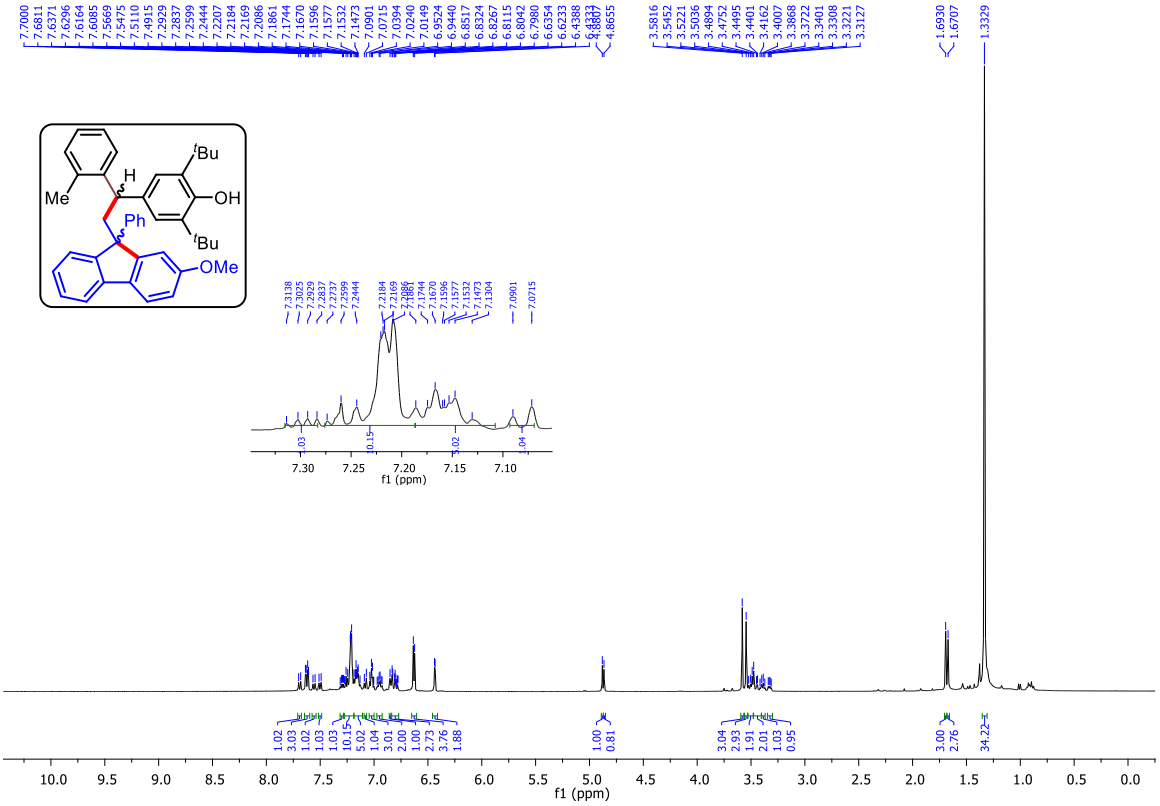
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **56t**



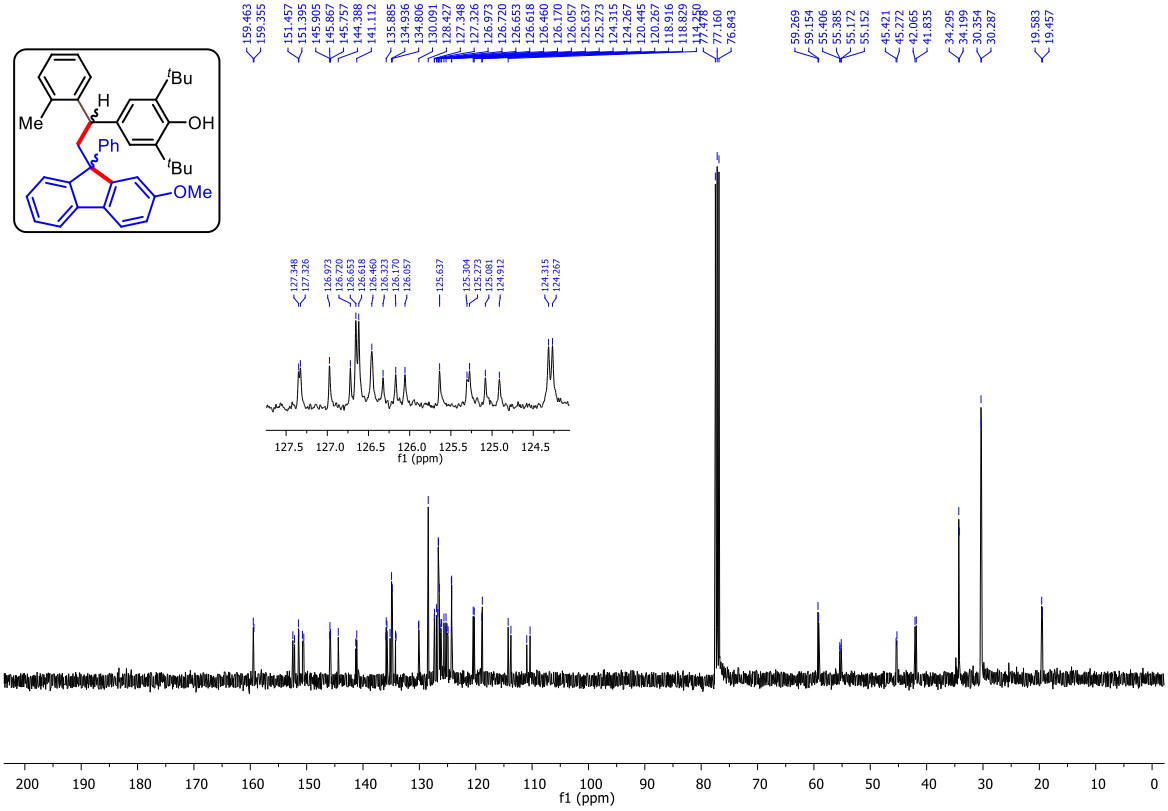
^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) spectrum of compound **56t**



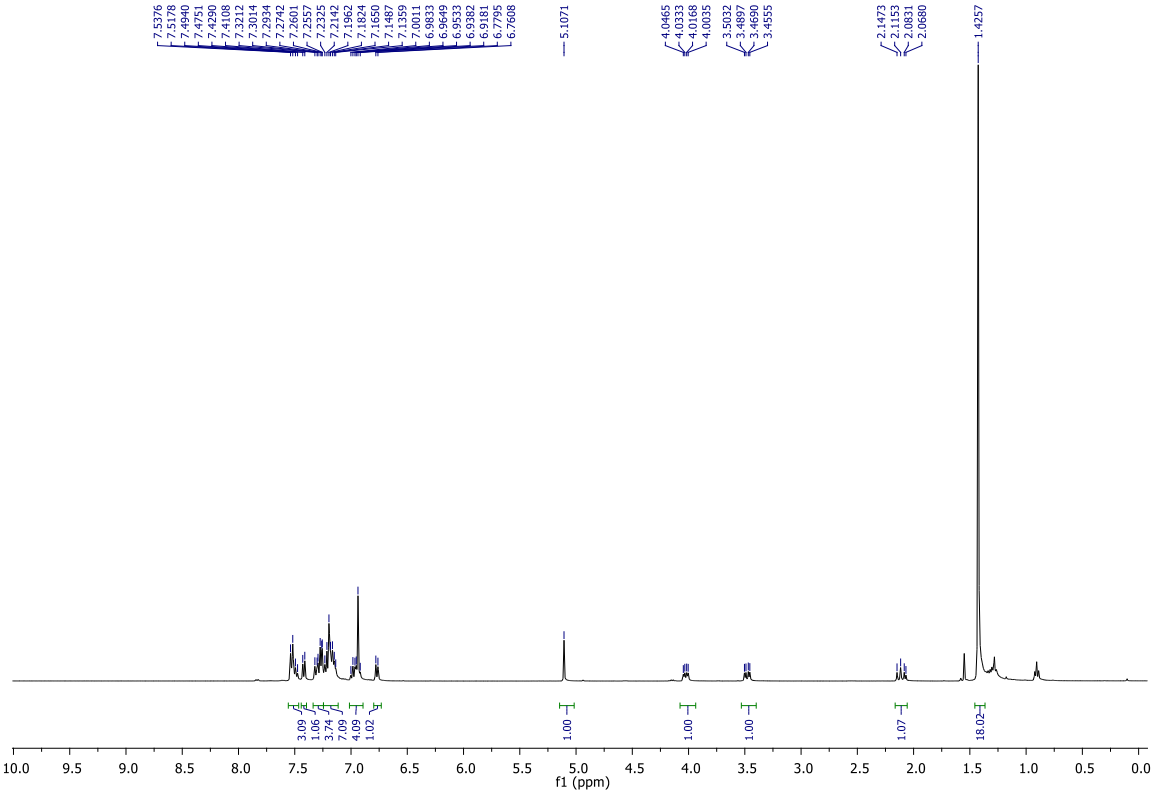
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **56u**



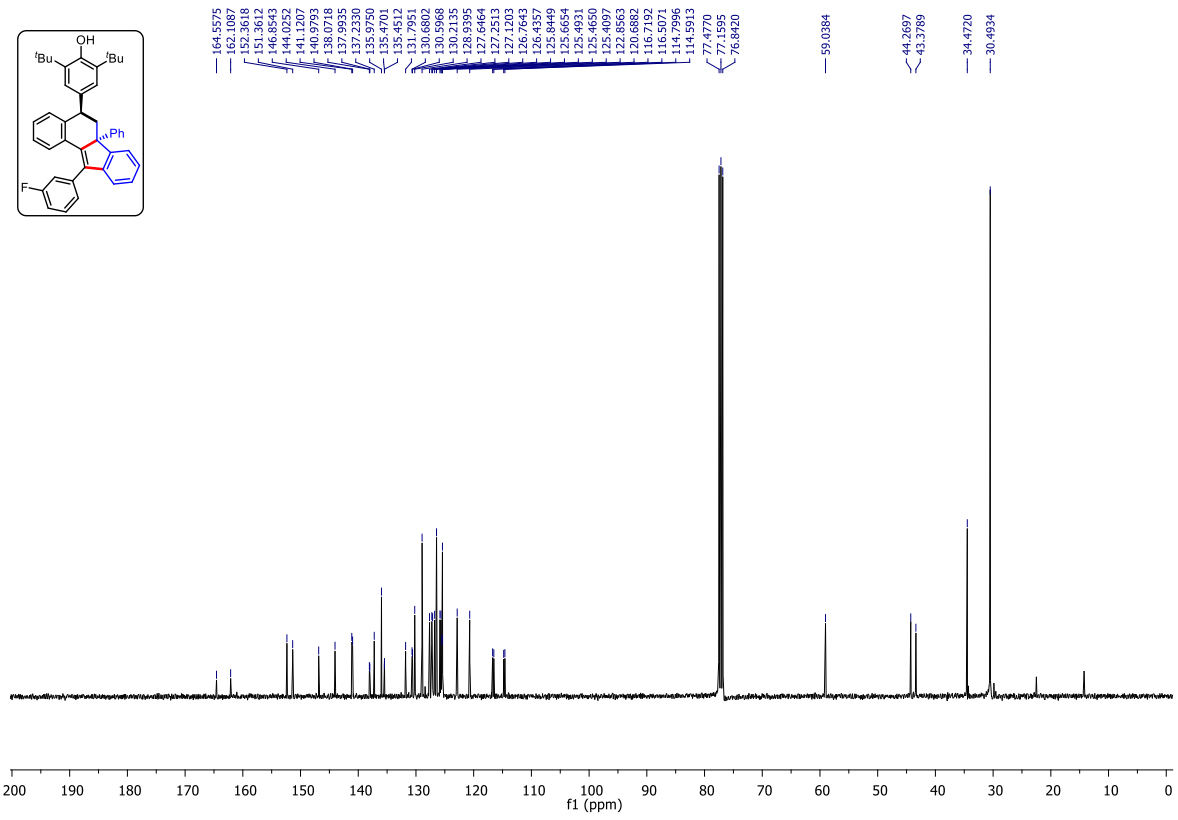
^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) spectrum of compound **56u**



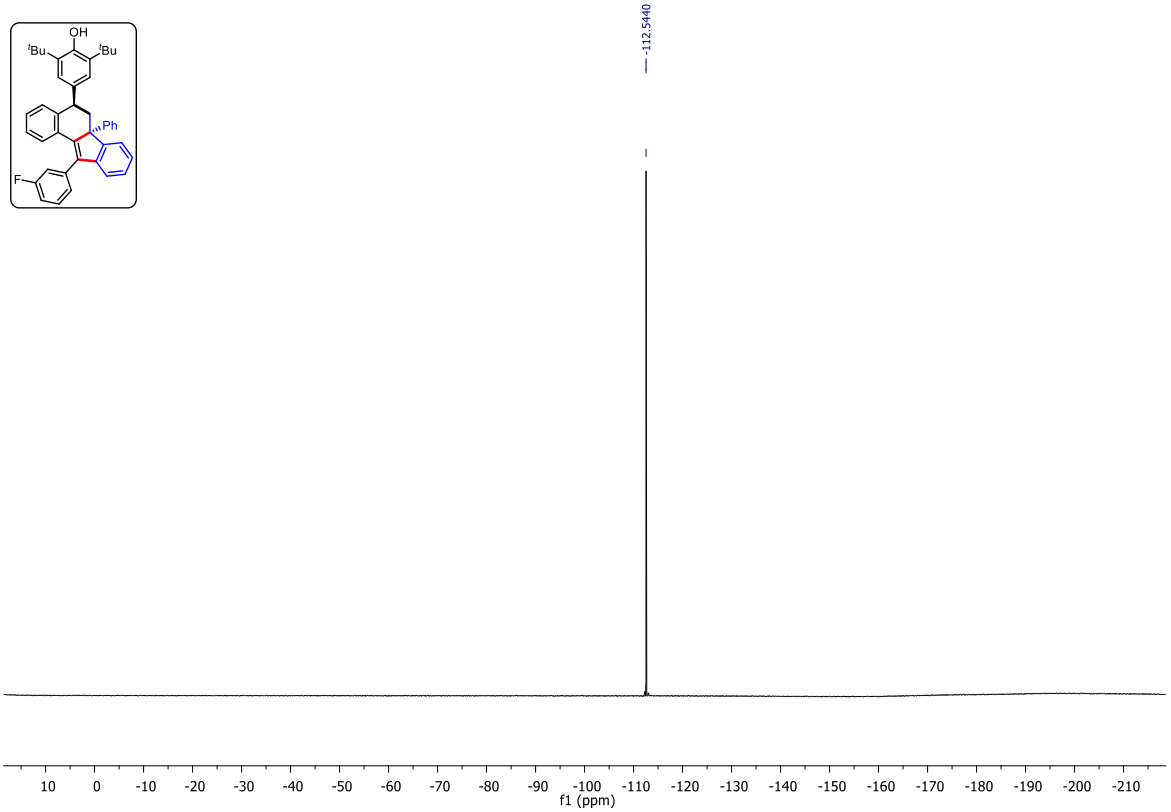
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **60h**



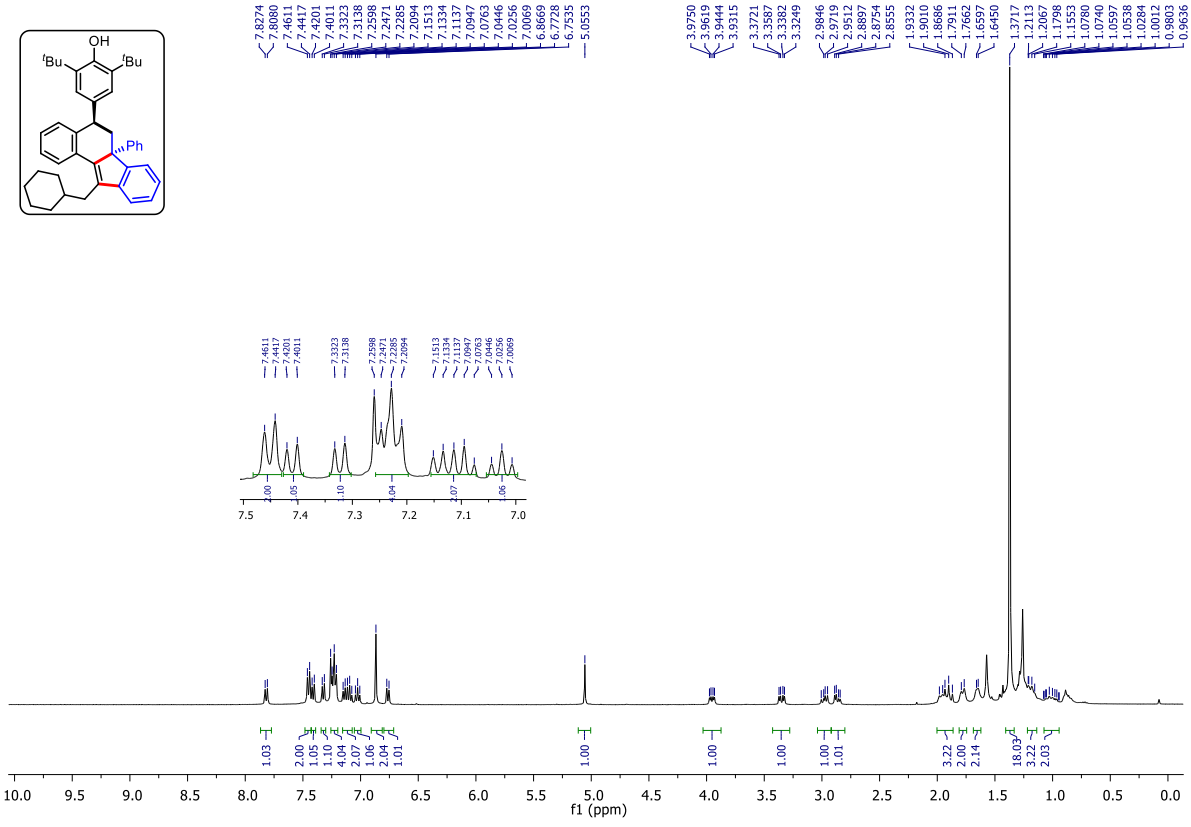
^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) spectrum of compound **60h**



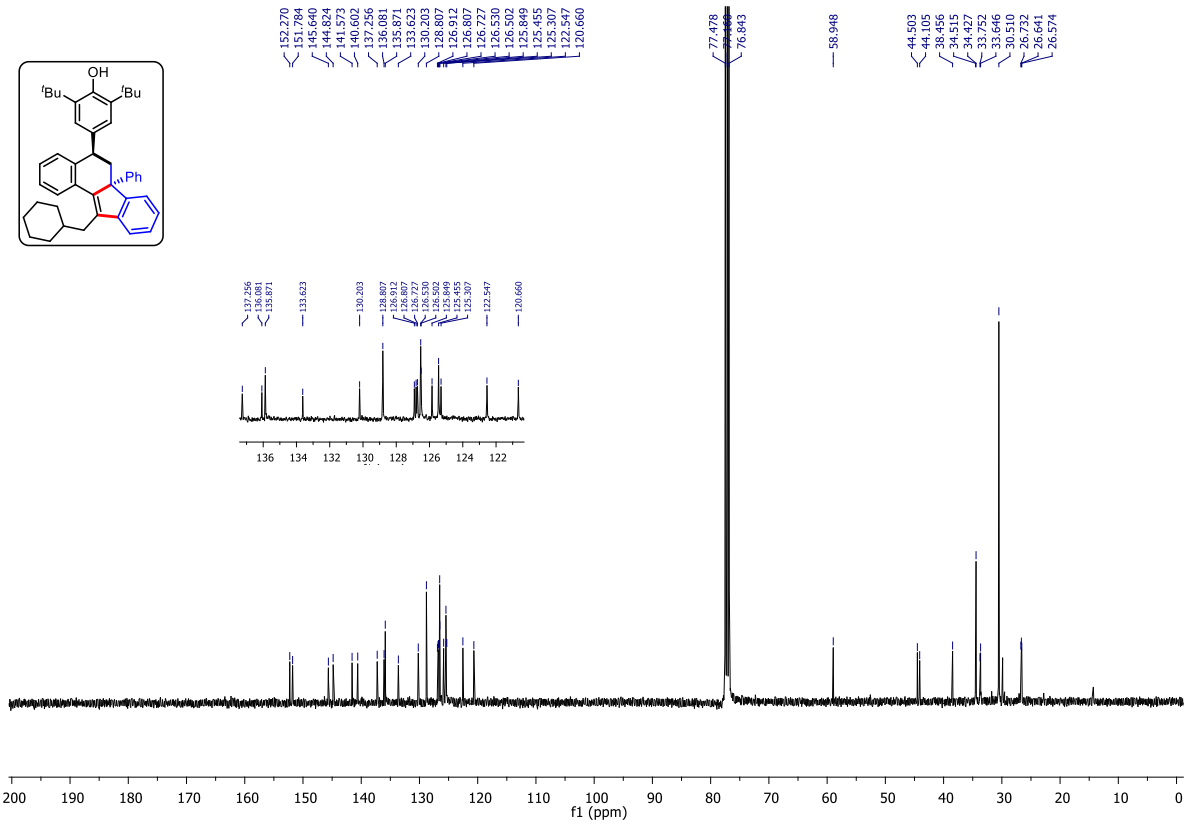
^{19}F NMR spectrum of compound **60h**



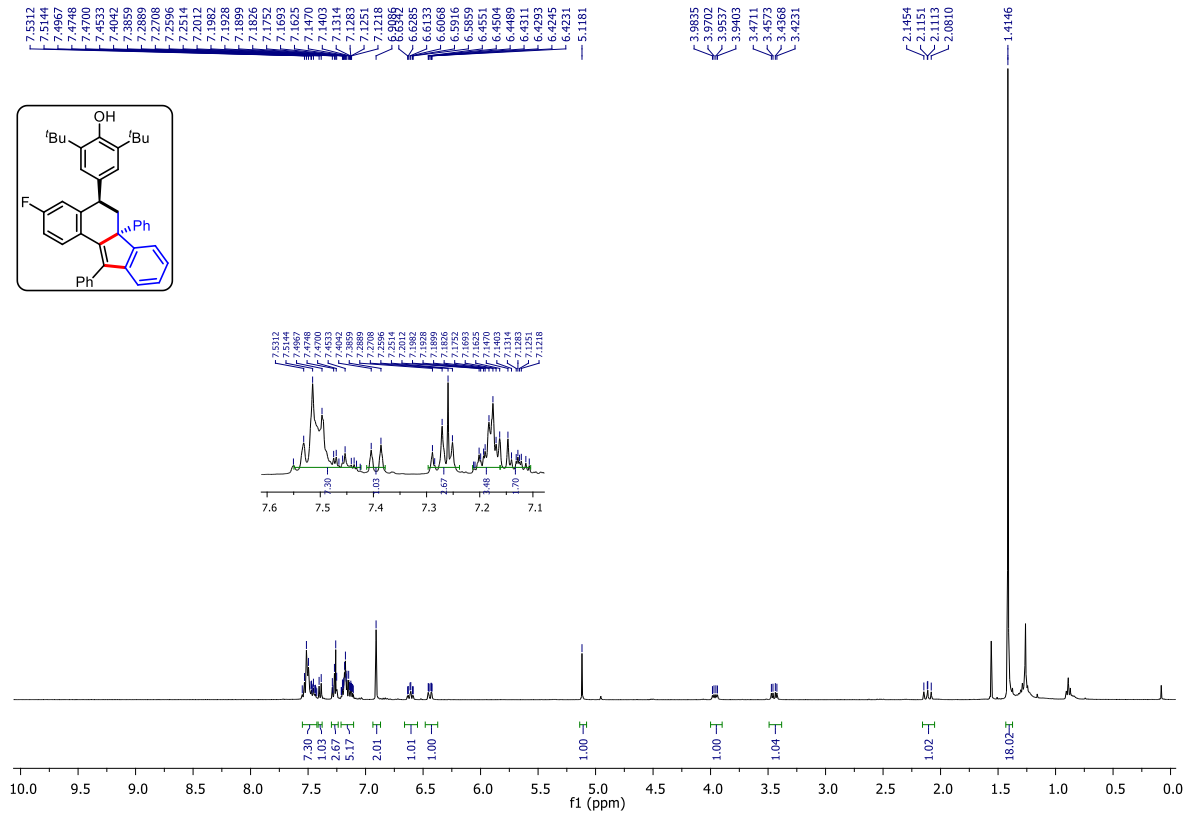
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **60k**



^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) spectrum of compound **60k**



^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **60p**



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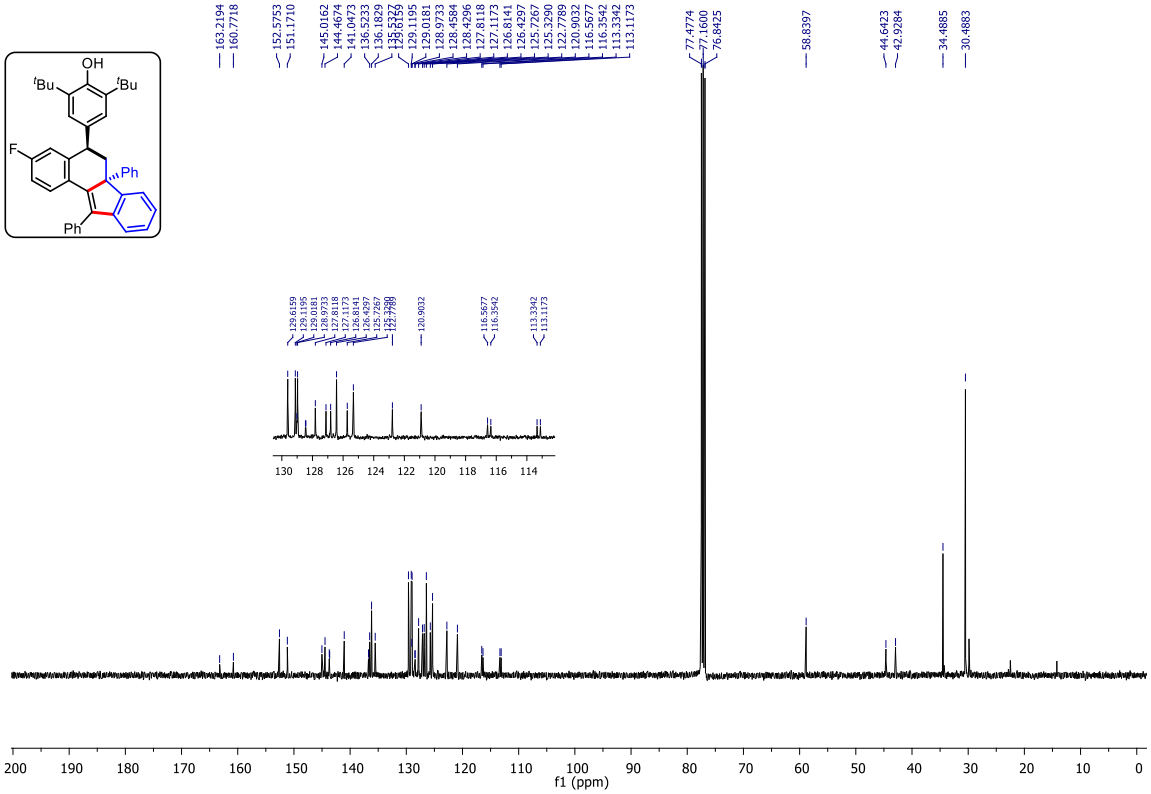
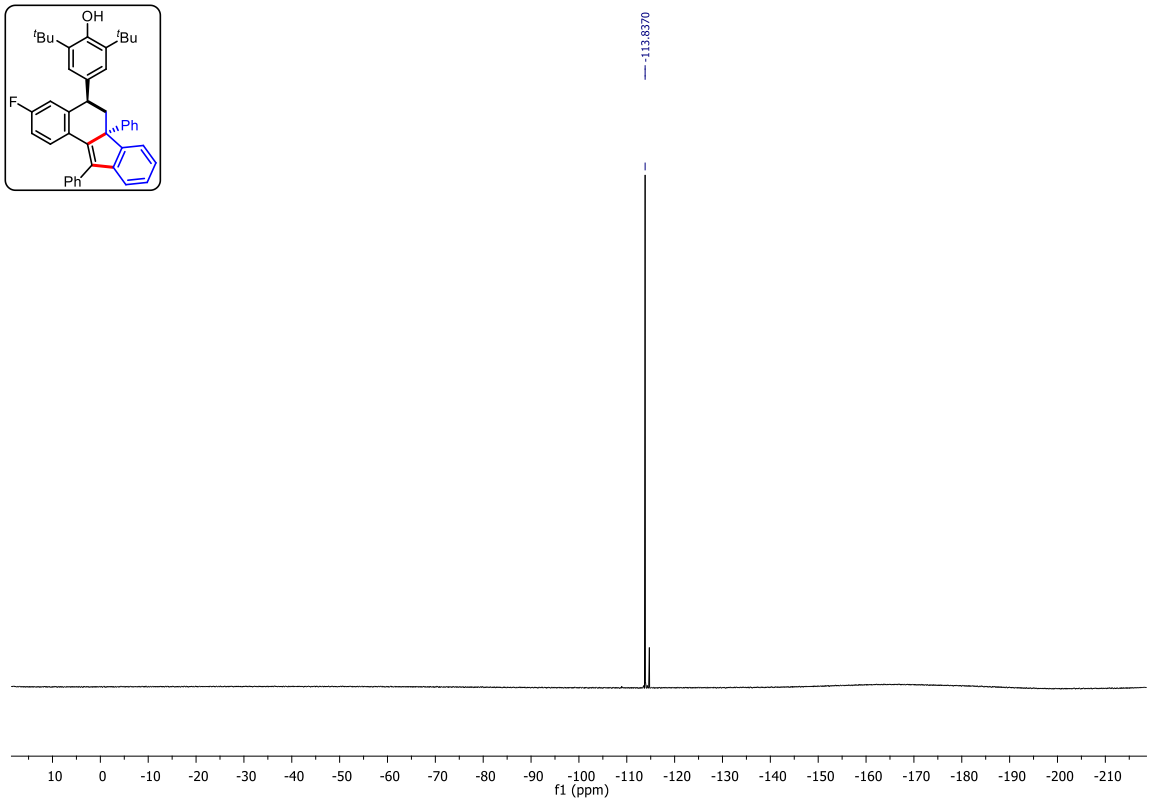
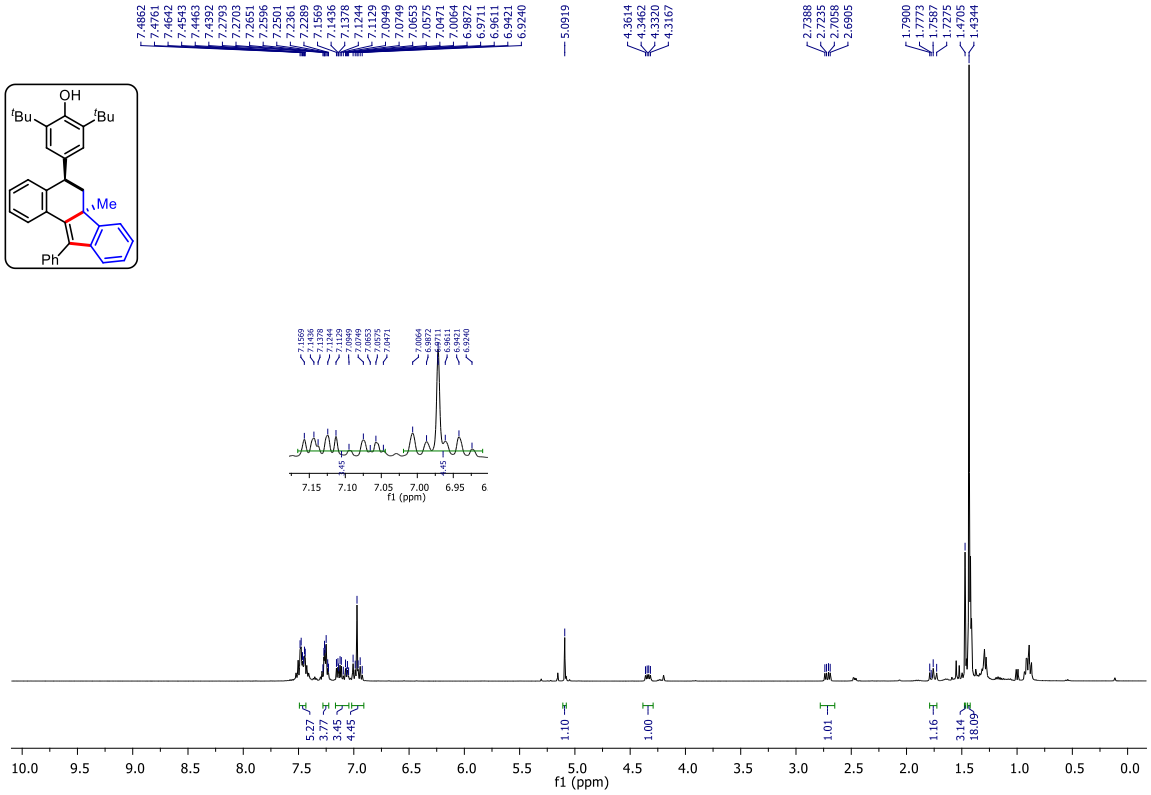


^{19}F NMR spectrum of compound **60p**



^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **60s**



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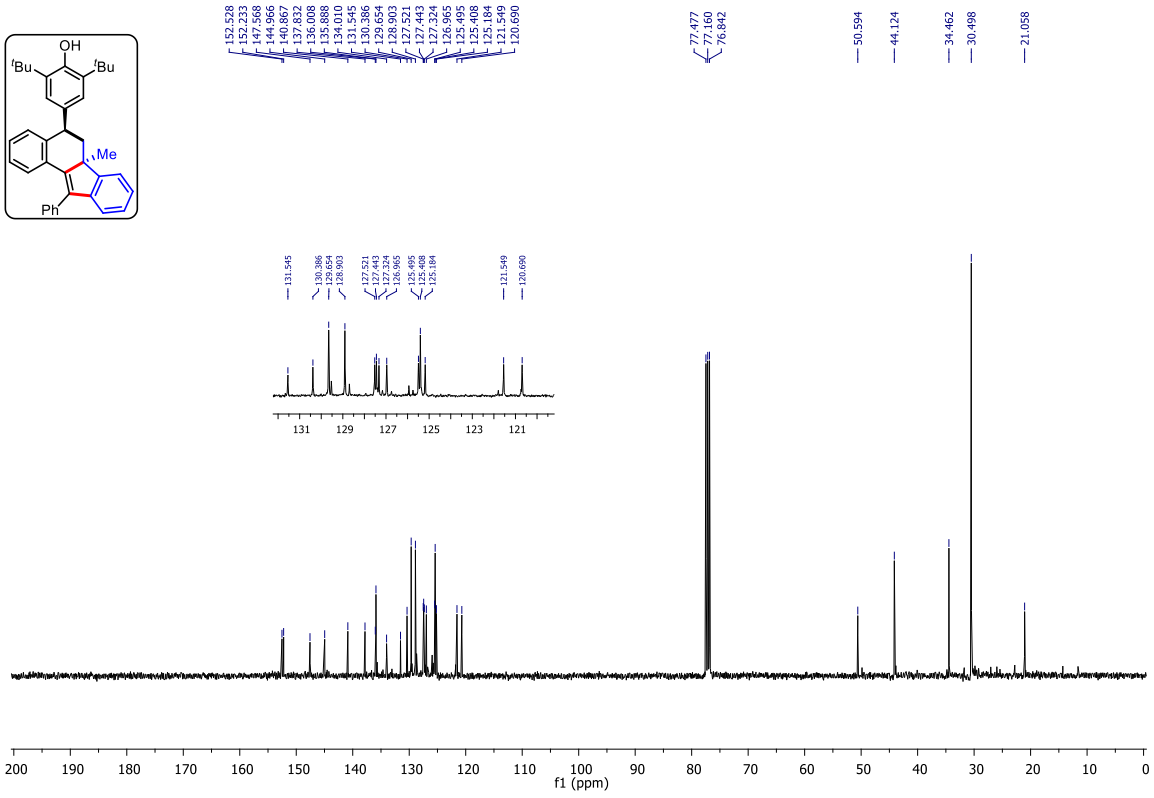

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Chapter 3

Total synthesis of isoselagintamarlin A and selaginpulvilin D and I

3.1 Introduction:

Cyclic-Adinosine-3',5'-Monophosphate (cAMP), acts as a secondary messenger in mammalian cells, which is crucial for cellular response and signal transduction.[1] A shortage of cAMP in cells causes a wide range of diseases, including CNS disorders,[2] metabolic disorders,[3] heart failure,[4] asthma,[5] inflammation,[6] and certain types of cancer.[7] Adenylyl cyclase (AC) and phosphodiesterase-4 (PDE4) are the enzymes responsible for the generation and breakdown of cAMP, respectively. It is necessary to use either phosphodiesterase-4 inhibitors or adenylyl cyclase activators to keep a consistent level of (cAMP) in cell. In the last two decades, natural and synthetic bioactive molecules have been used as potential drugs to activate (AC) and inhibit (PDE4). As a result, various naturally occurring compounds, like forskolin,[8] Ansellone A,[9] alotaketal A to E,[10] etc., which show activity as adenylyl cyclase activators, have been isolated and synthesised. The development of PDE4 inhibitors is greatly preferred over ACs activators because, generally, enzyme inhibition is preferred over enzyme activation in the drug discovery process. As a result, two PDE4 inhibitors, apremilast[11a] and roflumilast [11b] were just approved for the treatment of psoriatic arthritis and chronic obstructive pulmonary disease (COPD), respectively. Flavonoids, terpenes, and other natural compounds with outstanding therapeutic efficacy (IC50 0.960-1.81 μM) as (PDE4) inhibitors have been isolated and synthesised by several research groups.[12] To improve therapeutic efficacy, numerous highly desirable natural and synthetic compounds must be developed, demanding ongoing research in this field.

Selaginpulvilins A-D [1-4, Fig. 1] are a class of natural products with a 9,9-diaryl-fluorene skeleton that was isolated from *selaginella pulvinata* and other closely related plants in 2014.[13] Those plants have been used as herbs in China to treat the severe injury, asthma and dysmenorrhea. Later, a few additional selaginpulvilins E-J [5–10, Fig. 1] from *selaginella pulvinata* were isolated and thoroughly characterized.[14] Other selaginellin analogues, such as isoselagintamarlin A **11** and selagintamarlin A **12**, have also been recently isolated.[15-16] In fact, selagintamarlin A **12** significantly inhibits tubulin polymerization and has a remarkable inhibitory action against PDE4 (IC50 value 40 nM).[15] All of the selaginpulvilins (A-T) that have been isolated so far have excellent therapeutic activity as PDE4 inhibitors.[17,18]

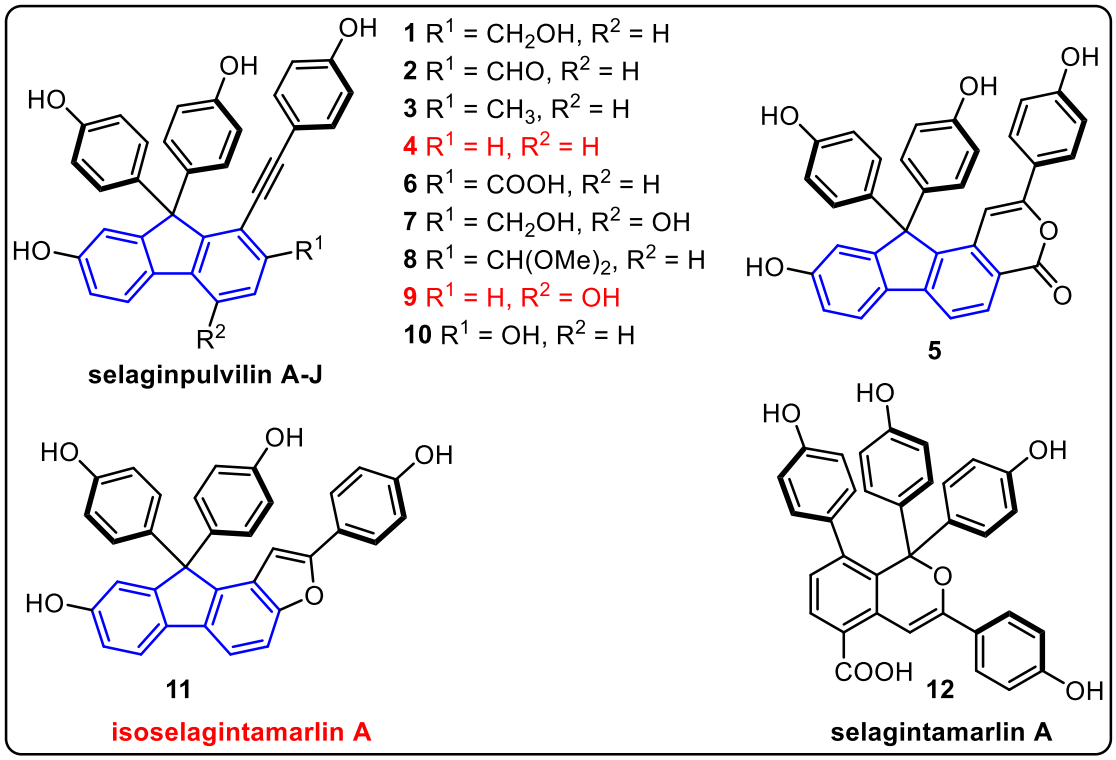
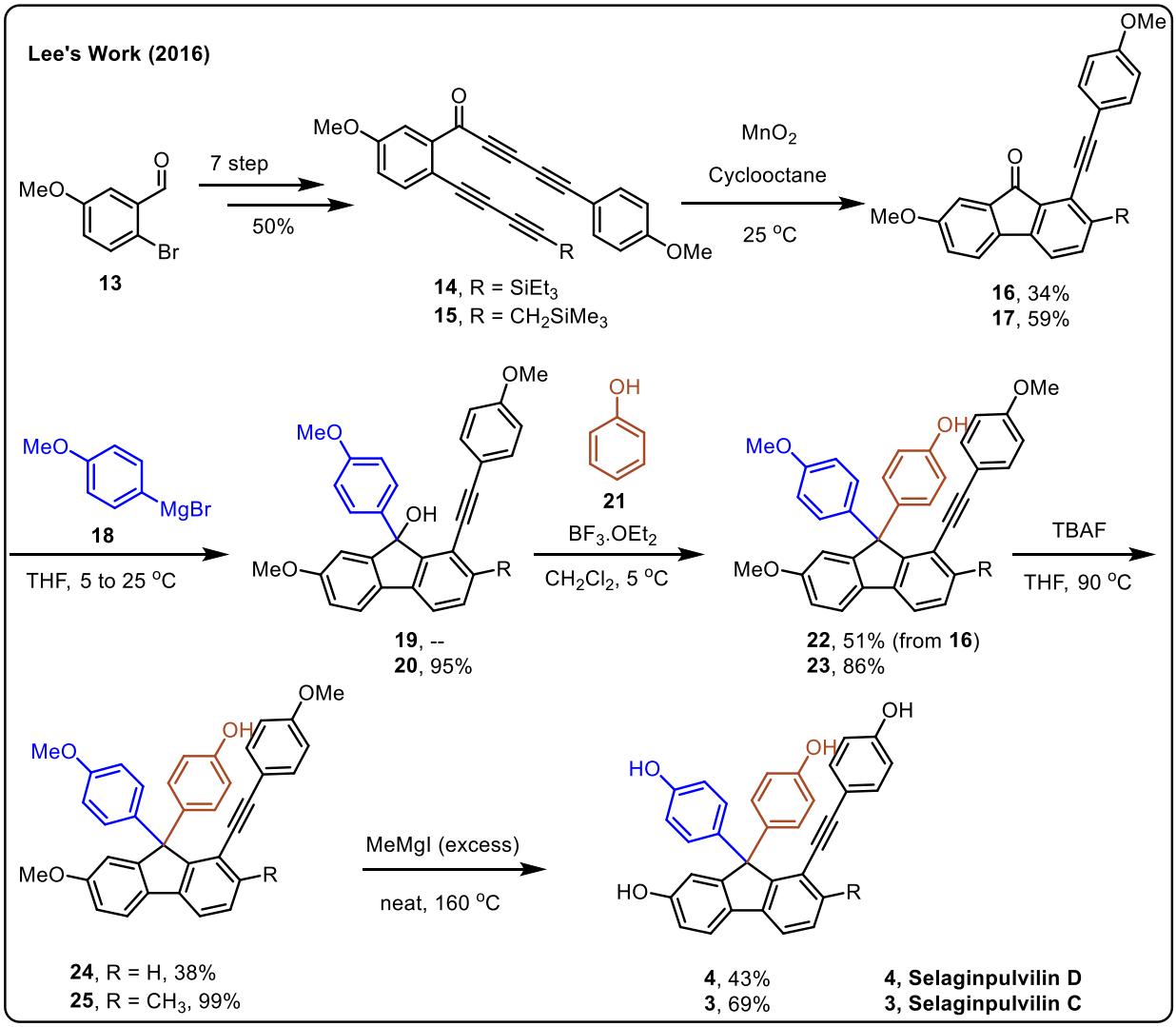


Figure 1. Structures of Selaginellin Analogues

Many research groups have been inspired to develop various synthetic approaches to access selaginpulvilins and their analogues because of the broad spectrum of biological activity and structural complexity. Several divergent approaches are reported for the synthesis of selaginpulvilin D **4** and related natural products from the same family. A few of these are discussed below.

3.2 Literature reports on the total synthesis of selaginpulvilins

Lee and co-workers reported a novel strategy for the first total synthesis of selaginpulvilin D and selaginpulvilin C in 2016. To make the basic core of these natural products, they started their synthesis from 2-bromo-5-methoxybenzaldehyde **13**. After seven conjugative steps, tetraynes **14** and **15** were obtained. Then, the hexadehydro Diels-Alder reaction[19] using MnO_2 with **14**/**15** led to the formation of 1-phenylethynyl fluorenone core **16**/**17**. Then, the introduction of two aryl groups on **16**/**17** through the addition of anisole-based Grignard reagent **18** followed by Friedel-Crafts reaction with phenol **21** using $BF_3.OEt_2$ generated 9,9 diaryl fluorenes (**22**/**23**) (Scheme 1).[20] Then, deprotection of the silyl and methoxy groups of **22**/**23** led to selaginpulvilin D **4** and selaginpulvilin C **3,** respectively**.**



Scheme 1. First total synthesis of Selaginpulvilin C & D using hexadehydro Diels-Alder reaction

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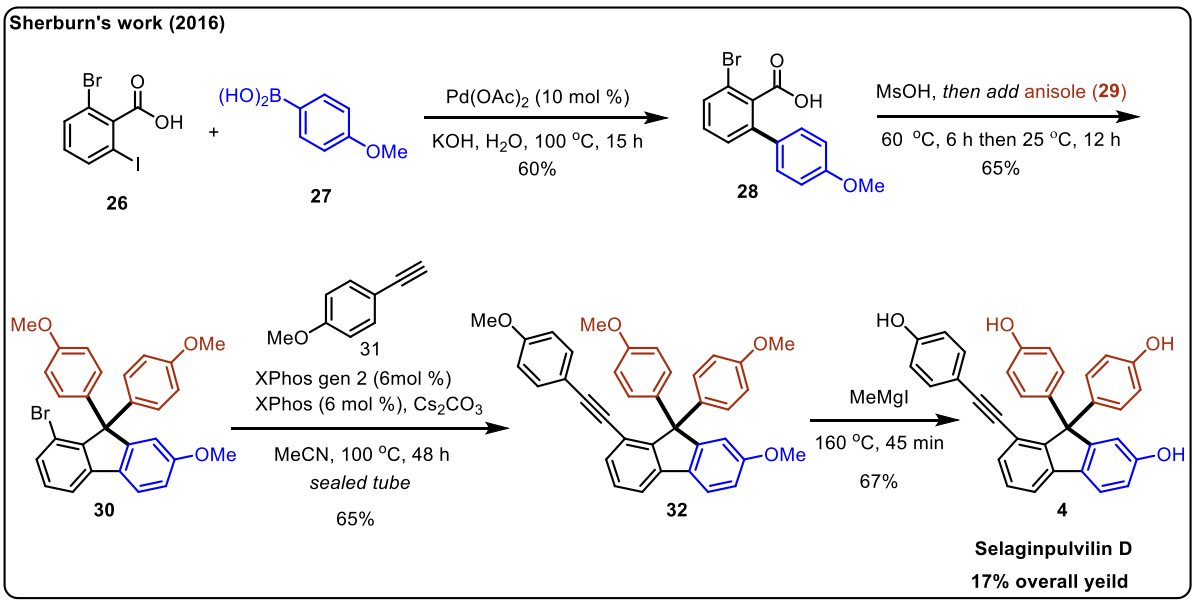
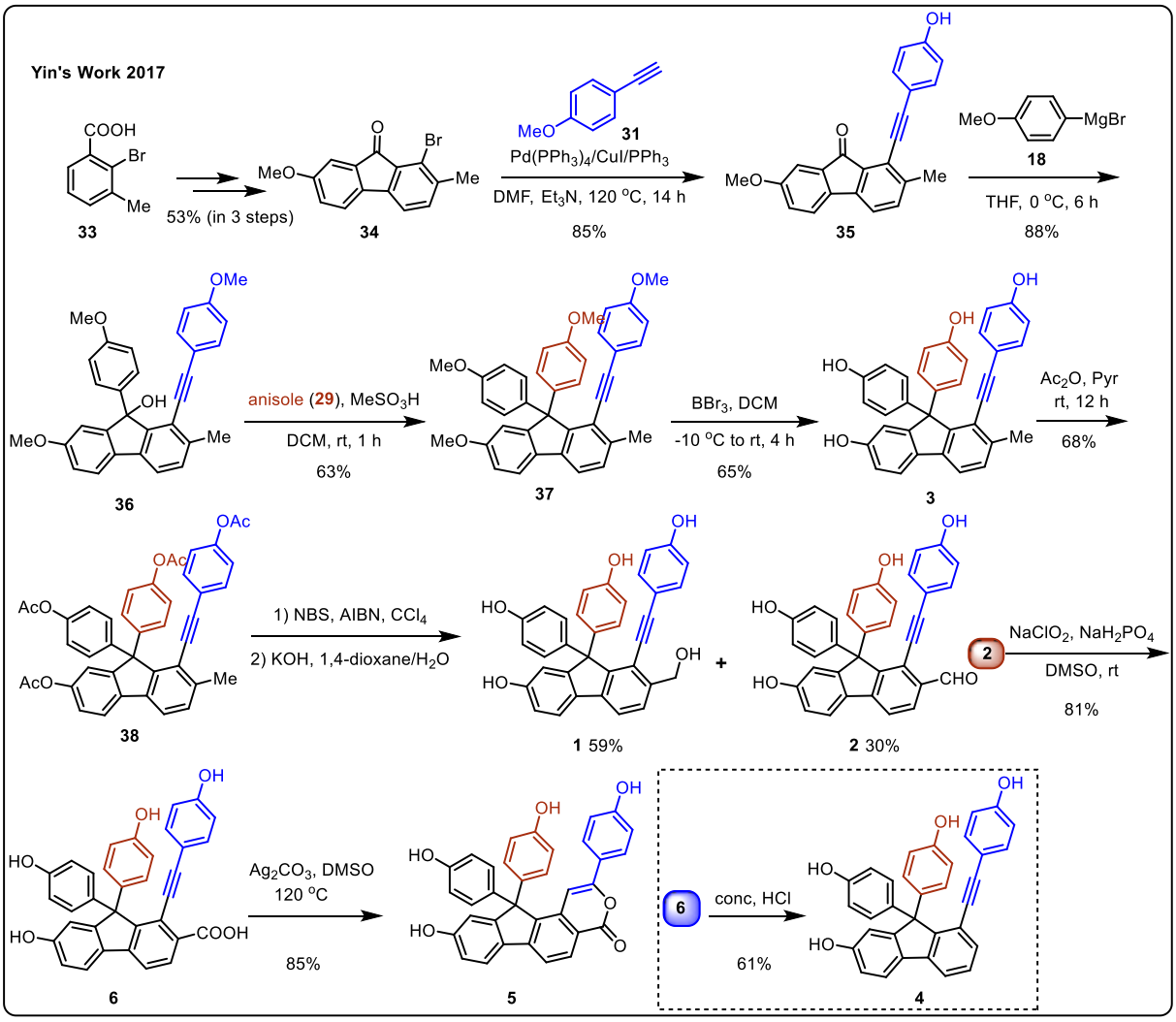
In the same year, Sherburn and co-workers came up with a different synthetic strategy for the synthesis of selaginpulvilin D **4** in only four steps. In the first step, 2-arylbenzoic acid **28** was synthesized from 2-bromo-6-iodobenzoic acid **26** and 4-methoxy boronic acid (**27**) through the Suzuki-Miyaura coupling reaction. The three-fold arylation of **28** with anisole **29** in the presence of a strong acid gave the required 9,9-diarylfluorene core **30** (Scheme 2).[21] The Sonogashira coupling between 4-(methoxyphenyl)-acetylene **31** and **30** afforded tetra methoxyselaginpulvilin D **32,** which on demethylation with MeMgI provided Selaginpulvilin D **4** in 17% overall yield.

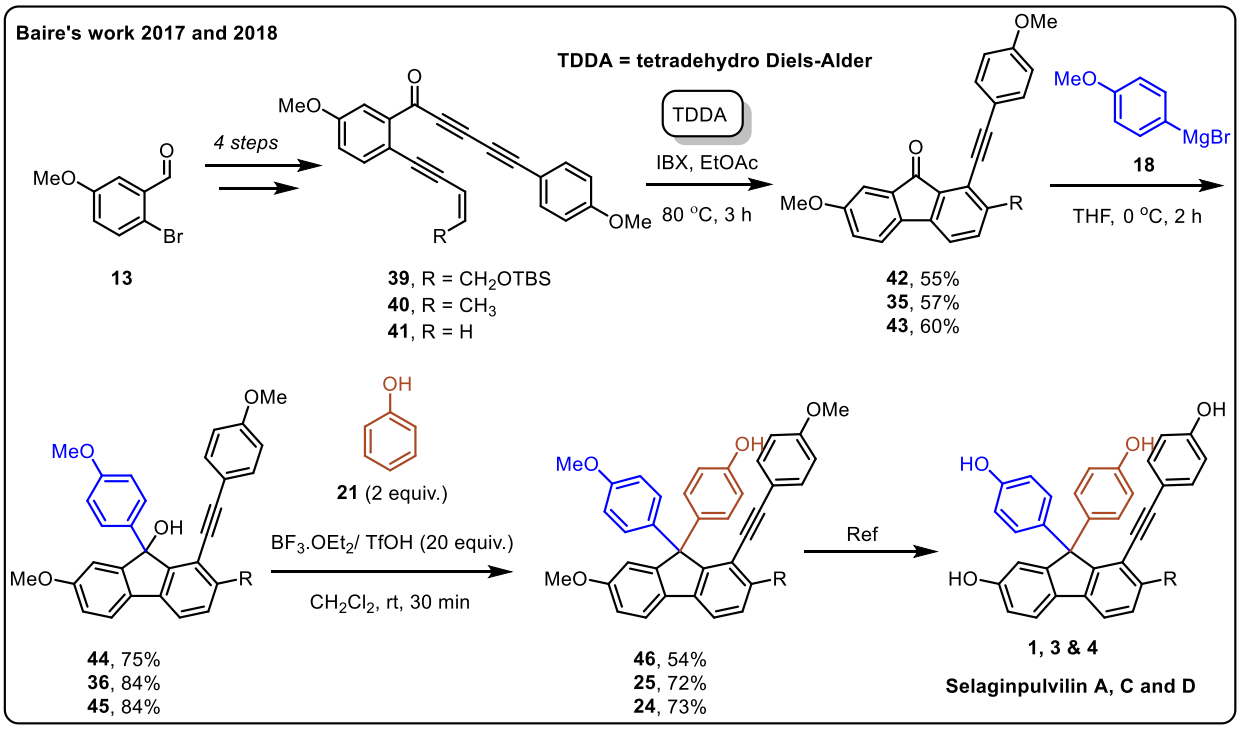


Scheme 2. Sherburn's approach for the synthesis of selaginpulvilin D



Scheme 3. Synthesis of selaginpulvilins A-F from selaginpulvilin C

In 2017 Yin's group again isolated some new selaginpulvilins E-J, and developed some approached for the synthesis of selaginpulvilin A-F. They have started their synthesis from 2-bromo-3-methylbenzoic acid **33;** after a couple of steps, they got the core molecule fluorenone **34.** The Sonogashira coupling of **34** with 4-methoxyphenyl-acetylene **31** afforded 1-phenylethynyl fluorenone **35**. Then, the addition of anisole-based Grignard reagent **18** to **35** followed by Friedel Craft reaction gave the methylated selaginpulvilin **C**, which on demethylation with BBr_3 generated selginpulvilin C **3**. Selaginpulvilin **C** (**3**) was further utilized to prepare other derivatives (scheme 3).[22] The benzylic bromination of selaginpulvilin C (**3**) with NBS followed by KOH treatment gave selaginpulvilins A (**1**) & B (**2**). The oxidation of selagipulvilin B (**2**) using $NaClO_2$ gave selaginpulvilin F (**6**). Intramolecular cyclization between an alkyne and carboxylic group of **6** in the presence of Ag_2CO_3 yielded selaginpulvilin E (**5**). Selaginpulvilin F **6** was treated with conc HCl to form selaginpulvilin D (**4**) via decarboxylation.

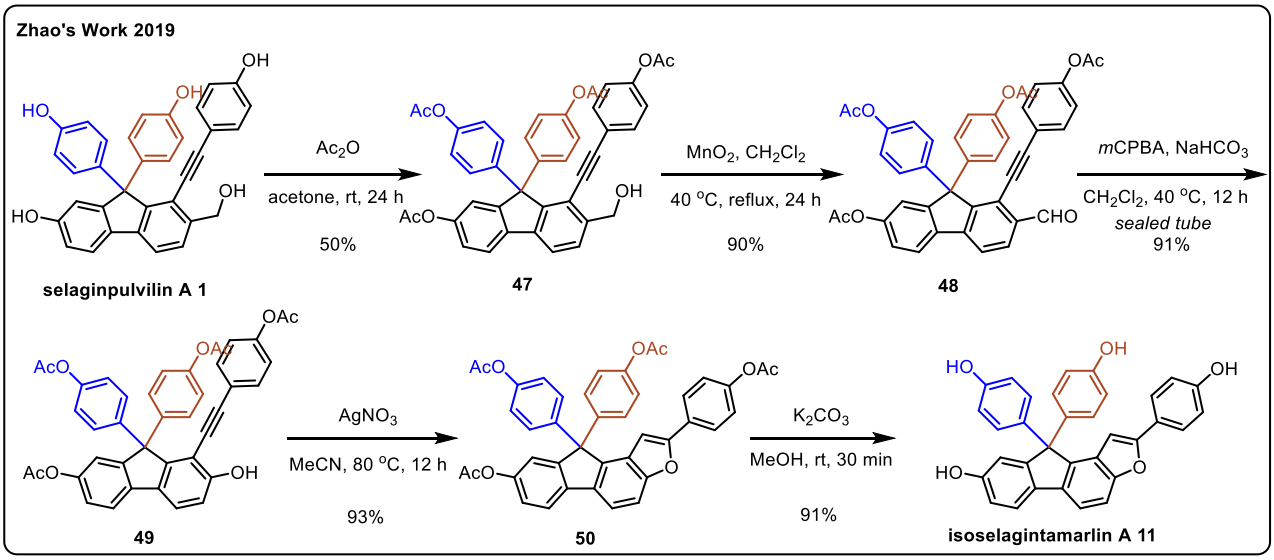


Scheme 4. Formal total synthesis of selaginpulvilin A, C, and D

Baire and co-workers reported the formal synthesis of selaginpulvilin D **4** in 2017 and selaginpulvilin A and C in 2018 (Scheme 4).[15] They have used tetradehydro Diels-Alder reaction to obtain the required fluorenone cores **42/35/43** from enyne-alkynes **39-41**. The addition of 4-methoxyphenyl Grignard reagent to fluorenones led to 9-aryl-9*H*-fluoren-9-ol derivatives **45/36/45** respectively. Then, the Friedel-Craft addition of phenol to **45/36/45** gave

the respective methylated selaginpulvilins **46/25/24** respectively. Then, the deprotection of the methoxy groups in **46/25/24** led to selaginpulvilin A, C, and D, respectively.[20]

In 2019 Zhao and co-workers isolated and characterized the benzofuran-based selaginellins analogue isoselagintamarlin A (**11**). In the same paper, they reported a bio-mimic synthesis of this natural product **11** (Scheme 5).[23] They started their synthetic approach with selaginpulvilin A; in the first step, selaginpulvilin A is acetylated at ambient temperature using Ac_2O to produce acylated product **47**. Then oxidation of primary alcohol to aldehyde with MnO_2 gave **48**, which on Dakin oxidation using *m*-CPBA gave the corresponding product **49**. Silver catalyzed benzofuran ring formation by intramolecular cyclization of **49** led to **50,** which on deprotection under basic condition gave isoselagintamalin A (**11**) in excellent yield.



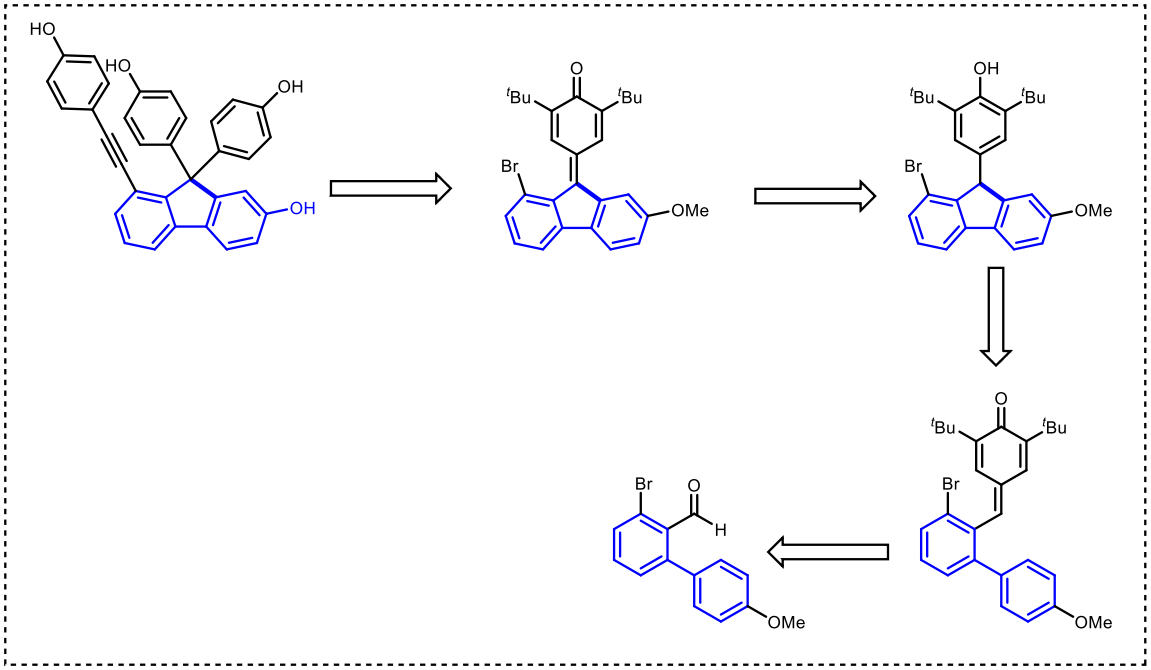
Scheme 5. Bio-mimetic synthesis of selagintamarlin A

3.3 Background:

While working on the synthesis of unsymmetrical diaryl- and triarylmethane derivatives via 1,6-conjugate addition of various nucleophiles to *p*-quinone methides, we envisioned that this chemistry could be utilized to synthesize fused carbocycles by introducing carbon nucleophilic site at *ortho* position which on intramolecular cyclization will give a cyclic framework. In this context, we developed a method to construct 9-arylfluorene rings using 2-arylphenyl *p*-QMs and then used that method to synthesize some natural products from Selaginellin family.

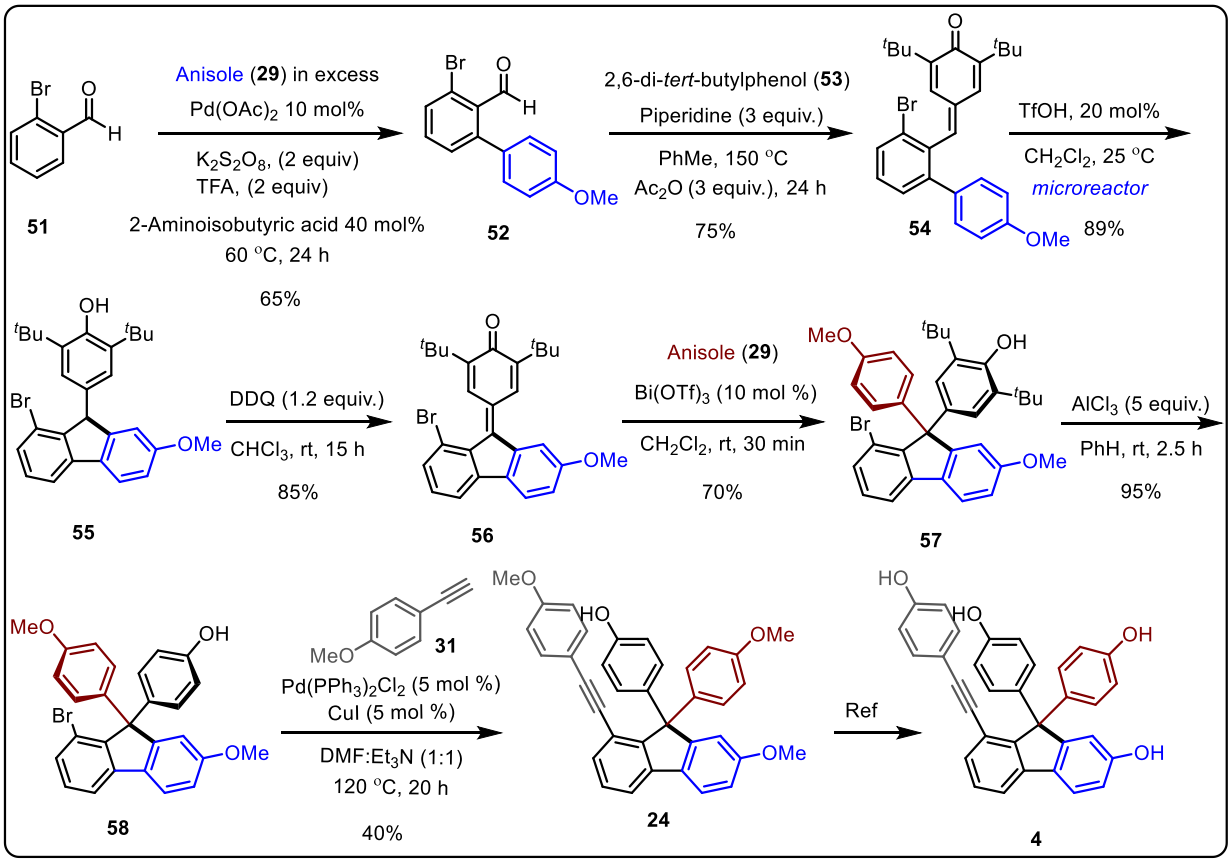
3.4 Our general approach towards the synthesis of selagnpulvilins D, I and isoselagintamarlin A

3.4.1 Formal synthesis of selaginpulvilin D



Scheme 6. Retrosynthetic analysis of selaginpulvilin D

A general retrosynthetic strategy for selaginpulvilin D is shown in Scheme 6. As shown in Scheme 6, these types of natural products could be constructed from readily available arylated bromo benzaldehydes. Therefore, we started the synthesis using commercially available 2-bromobenzaldehyde **51** (Scheme 7). The dehydrogenative arylation of 2-bromobenzaldehyde with anisole **29**[24] gives 3-bromo-4'-methoxy-[1,1'-biphenyl]-2-carbaldehyde **52** in 65% yield. Subsequently, **52** was treated with 2,6-di-*tert*-butylphenol **53** in the presence of piperidine and acetic anhydride to give 2-phenyl arylsubstituted *p*-QM **54**, which was then subjected to the cyclization reaction using a microreactor in the presence of TfOH as a catalyst to produce the fluorene derivative **55** in 89% yield. Becker's method[25] was utilized for the dearomative oxidation of **55** with 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ) to furnish the fuchsone derivative **56** in 85% yield. Then, a $Bi(OTf)_3$ catalyzed addition of anisole **29** to **56** generated the expected 9,9′-diarylated fluorene derivative **57**, which on subsequent de-*tert*-butylation reaction with an excess of $AlCl_3$ gave the corresponding product **58** in 95% yield. The bromoaryl fluorene derivative **58** was then subjected to a Sonogashira coupling reaction with 4-ethynylanisole **31** to form the methylated selaginpulvilin D **24**. The conversion of **24** to **4** via demethylation has already been reported in the literature.[20]

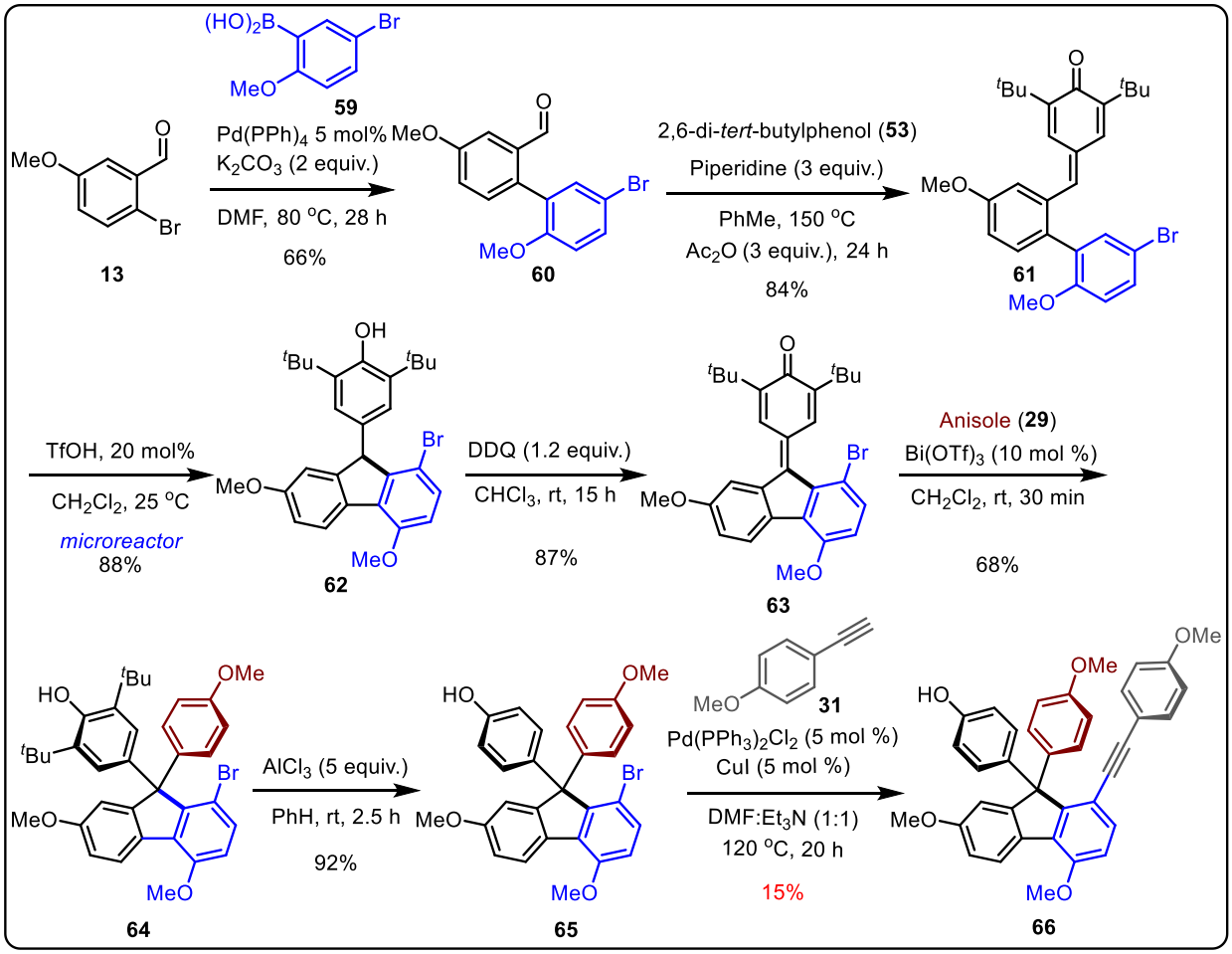


Scheme 7. Formal total synthesis of selaginpulvilin D

3.4.2 Total synthesis of selaginpulvilin I

After completion of the formal total synthesis of selaginpulvilin D **4**, we thought of employing similar strategy for the total the synthesis of selaginpulvilin I (**9**) from readily available 2-bromo-5-methoxybenzaldehyde **13** (Scheme 8). The Suzuki cross-coupling between **13** and 5-bromo-2-methoxyphenylboronic acid **59** gave 5′-bromo-2′,4-dimethoxy-[1,1′-biphenyl]-2-carbaldehyde **60** in 66% yield. Subsequently, **60** was treated with 2,6-di-*tert*- butylphenol **53** in the presence of piperidine and acetic anhydride to give 2-phenyl arylsubstituted *p*-QMs **61**, which was then subjected to cyclization in the microreactor to produce the fluorene derivative **62** in 88% yield. Becker's method was utilized for the dearomative oxidation of **62** with 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ) to furnish the fuchsone derivative **63** in 87% yield. Then, a Lewis acid catalyzed addition of anisole **29** to **63** generated the expected 9,9′-diarylated fluorene derivative **64**, which on subsequent de-*tert*-butylation reaction with an excess of $AlCl_3$ gave the corresponding product **65** in 92% yield. The bromoaryl fluorene derivative **65** was then subjected to a Sonogashira coupling reaction with 4-ethynylanisole **31**; however, unfortunately, the expected alkynylated product **66** was obtained only in 15% yield. At this point, we thought that the free phenolic −OH

group present in **65** could be the reason for getting a lesser yield of product **66** as unwanted side reactions are possible between the free phenol (in **65**) and alkyne (**31**). Therefore, we have decided to protect the phenolic −OH as methyl-ether and then carry out the Sonogashira coupling reaction. The methylation of **65** with dimethyl sulfate under basic conditions gave the methoxy derivative **67** in 89% yield (Scheme 9).



Scheme 8. Synthesis of methylated selaginpulvilin I

The Sonogashira coupling reaction between **67** and **31** was carried out, and under the best reaction condition, the alkynylated product **68** was obtained at the maximum of 51% yield. Unfortunately, we could not improve the yield of **68** any further, even though the coupling reaction was performed under various reaction conditions. The lower yield in the Sonogashira coupling reaction could be due to steric constraints as one of the ortho positions in the bromoarene moiety of **68** is heavily substituted. Finally, the universal demethylations of **68** with excess MeMgI provided the selaginpulvilin I (**9**) in 63% yield (overall yield of **9** = 7.5%). The selagipulvilin I (**9**) was characterised by ^{1}H NMR, ^{13}C NMR and IR spectroscopy; in ^{1}H NMR (see figure 2) only aromatic peaks are observed and missing OMe peaks from **68** supported the demethylation and formation of selaginpulvilin I (9).

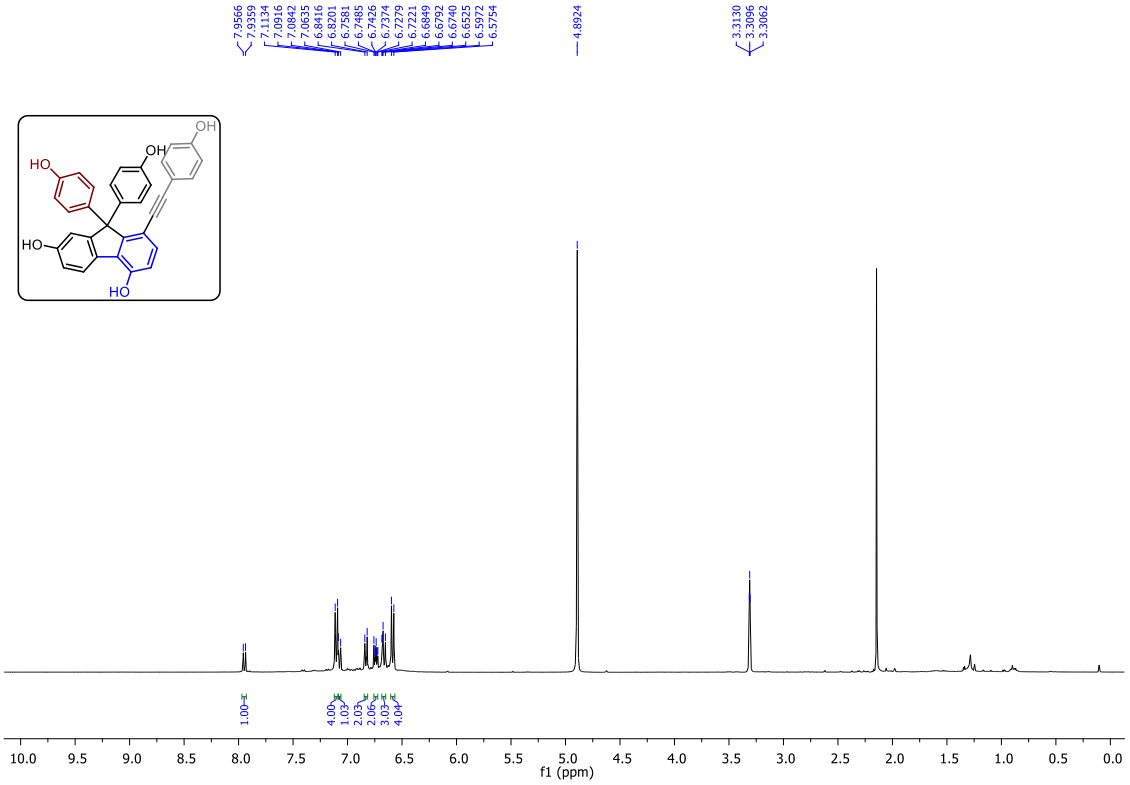


Figure 2. ^{1}H NMR (400 MHz, CD_3OD) spectrum of compound **9**

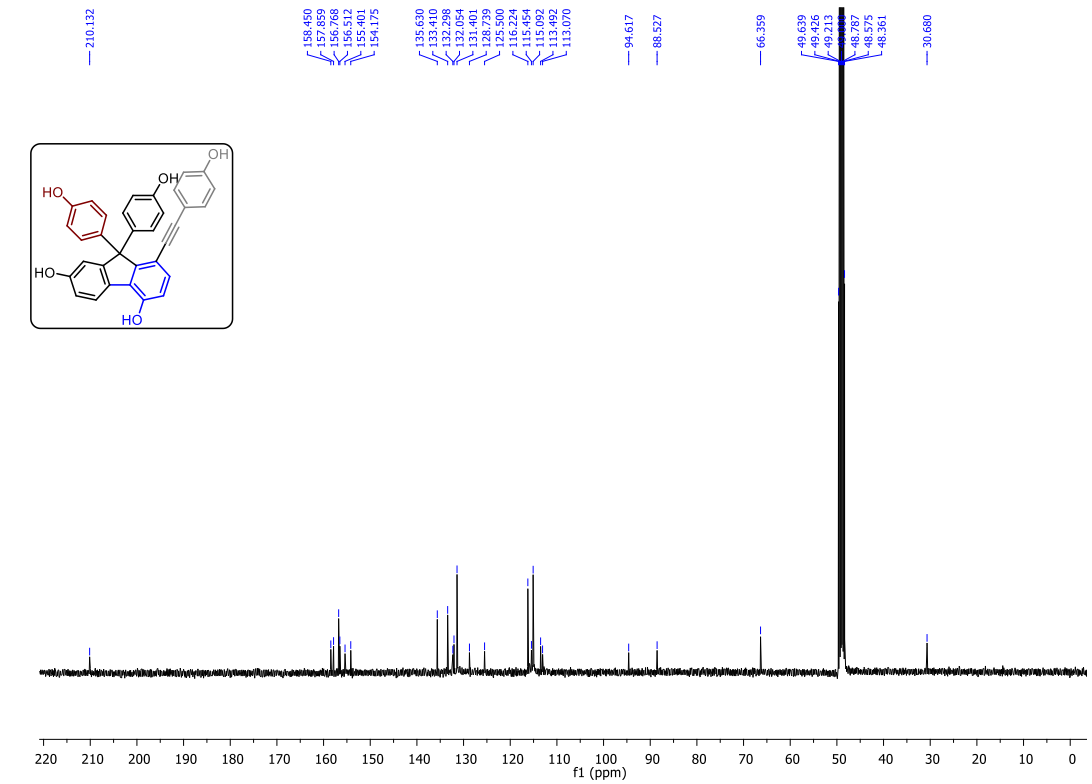
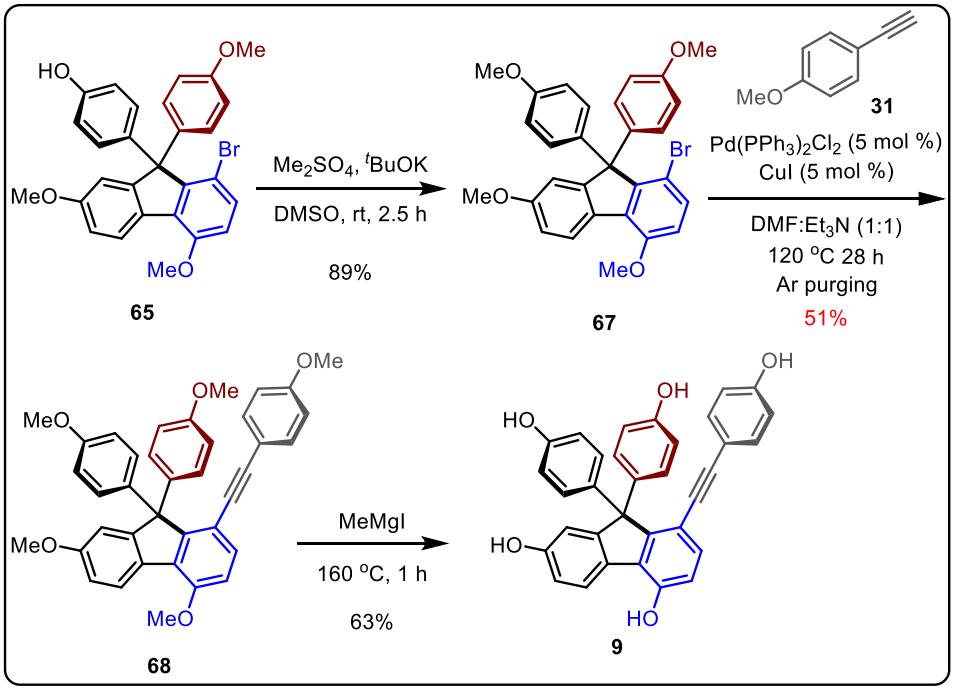


Figure 3. ^{13}C {^{1}H} NMR (100 MHz, CD_3OD) spectrum of compound **9**

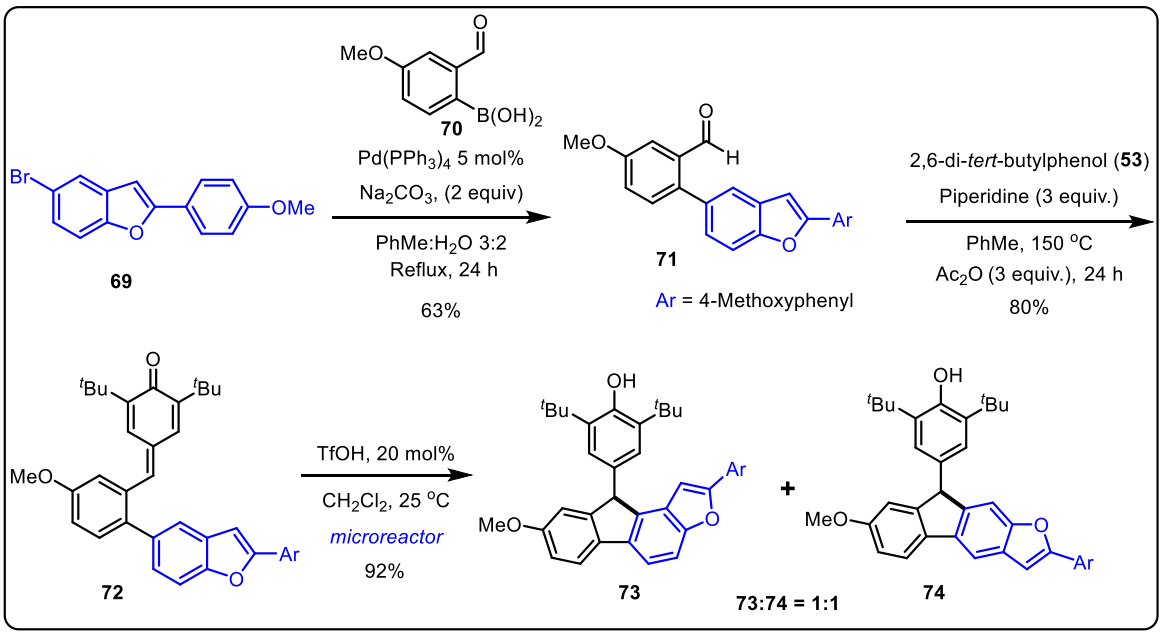


Scheme 9. Synthesis of selaginpulvilin I

In ^{13}C NMR (see figure 3) peaks for alkyne at δ 94.6 ppm and δ 88.5 ppm supported formation of **9**. Also the presence of OH was supported by IR peak at 3435 cm^{-1}. Morever ^{1}H and ^{13}C NMR was perfectly matched with the reported NMR in original paper.

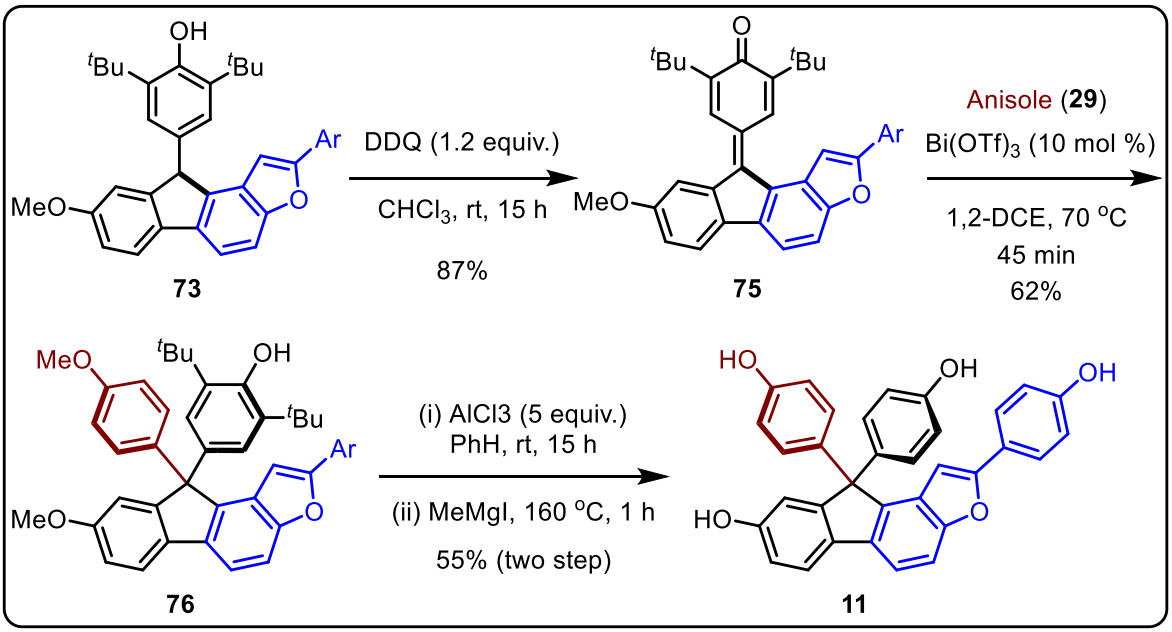
3.4.3 Total synthesis of isoselagintamarlin A

Similarly, for the total synthesis of isoselagintamarlin A (**11**), 5-bromo-2-(4-methoxy)-phenyl benzofuran **69**[26] was used as a starting material (Scheme 10).



Scheme 10. Synthesis of 9-aryl fluorene ring

The Suzuki coupling reaction between **69** and 2-formyl-4-methoxyphenylboronic acid **70** provided the aryl-substituted benzofuran derivative **71** (in 63% of isolated yield), which was subsequently converted to the *p*-QM **72** using the standard procedure. The *p*-QM **72** was then subjected to an intramolecular cyclization under continuous-flow conditions to give a mixture of regioisomers **73** and **74** in a 1:1 ratio in 92% combined yield. The oxidation of **73** with DDQ provided the respective



Scheme 11. Synthesis of isoselagintamarlin A

fuchsone derivative **75** in 87% yield, which was then subjected to a bismuth triflate-catalyzed 1,6-conjugate arylation with anisole (**29**) to give the 9,9′-diarylated fluorene derivative **76** in 62% yield (Scheme 11). De-*tert*-butylation of **76** with $AlCl_3$ followed by universal deprotection of methoxy groups using an excess of MeMgI gave the natural product, isoselagintamarlin A (**11**), in 55% yield (as shown in Scheme 8) (overall yield of **11** from **69** = 6.1%).

The isolelagintamarlin A (**11**) was characterised by ^{1}H NMR, ^{13}C NMR and IR spectroscopy; in ^{1}H NMR (see figure 4) only aromatic peaks and OH peaks was observed, there was peaks for *tert*-butyl and methoxy was missing from **76** supported the demethylation and *de-tert*-butylation of **76**. In ^{13}C NMR (see figure 5) peak at δ 65 ppm for quaternary C-9 carbon supported the formation of **11**. The formation of OH from demethylation was also supported by observed peak in IR at 3437 cm^{-1}.

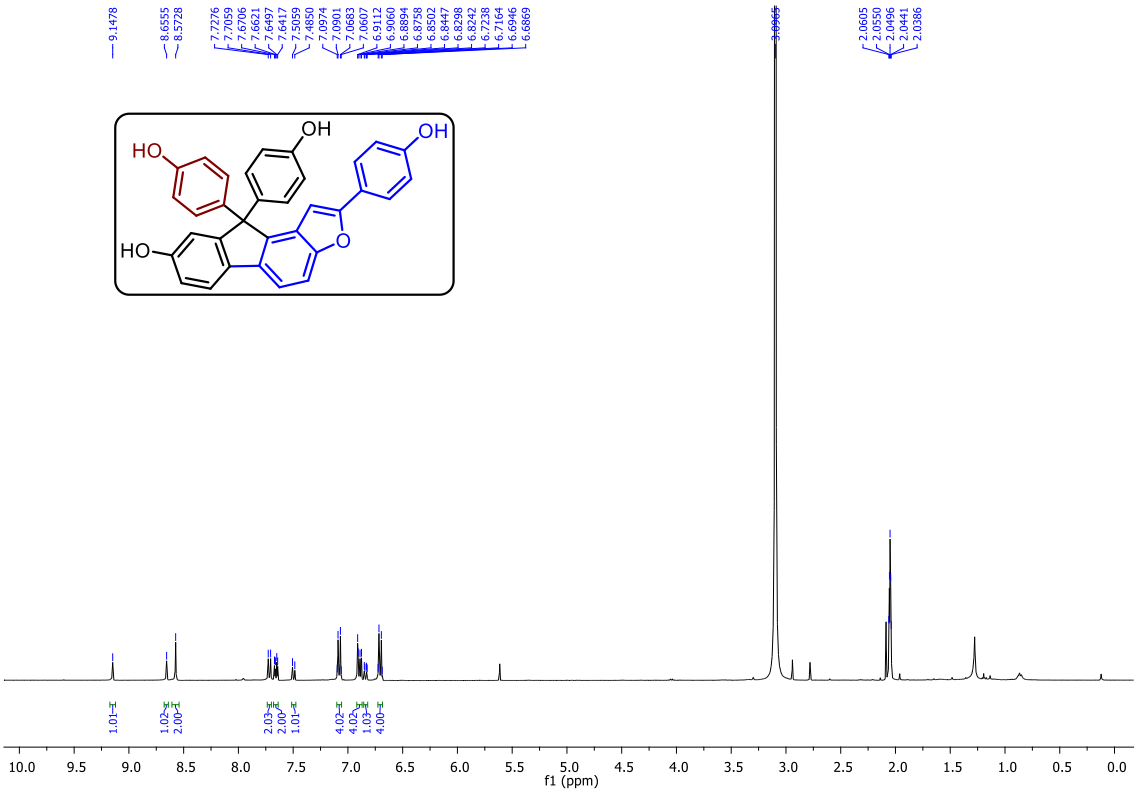


Figure 4. ^{1}H NMR (400 MHz, Acetone-d_6) spectrum of compound **11**

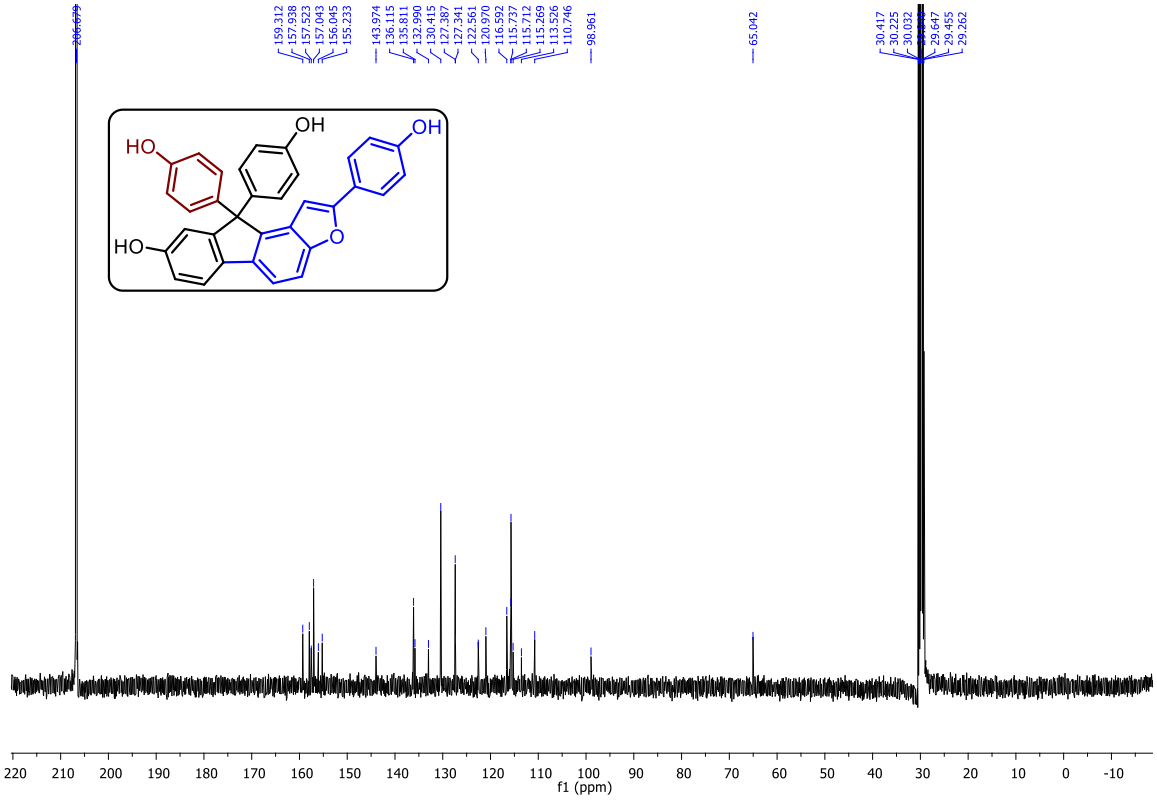
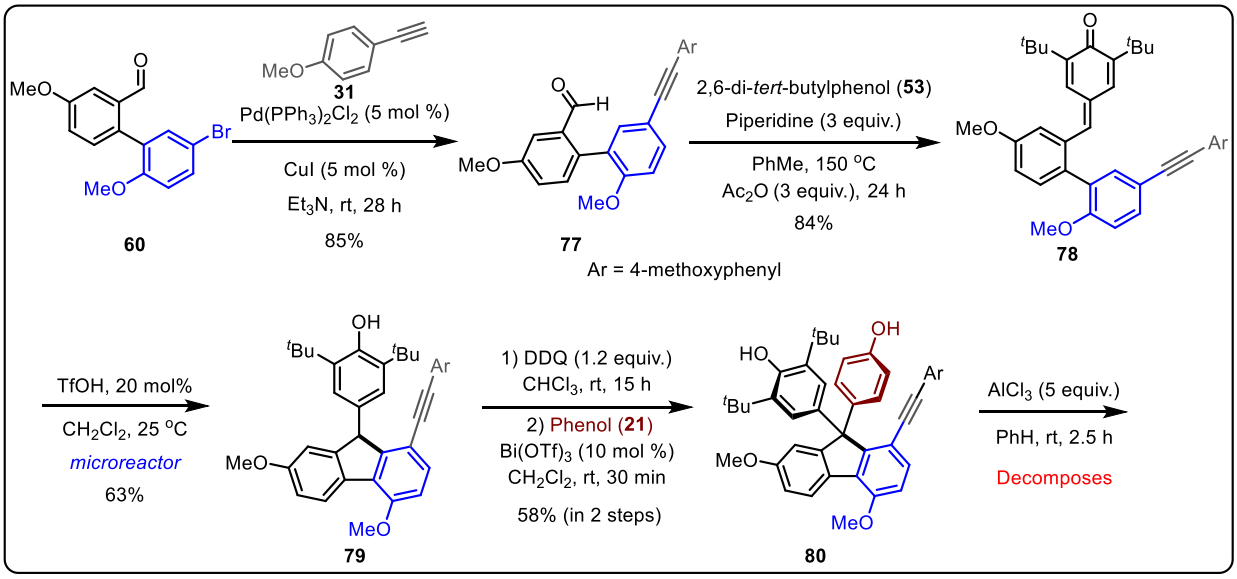


Figure 5. ^{13}C {^{1}H} NMR (100 MHz, Acetone-d_6) spectrum of compound **11**

3.4.4 Attempted total/formal synthesis of selaginpulvilin I

When we struggled with the Sonogashira coupling reaction in the synthesis of selaginpulvilin I, we decided to choose a different approach. In this approach, we have decided to preinstall the alkyne functionality before the cyclization step. Therefore, we performed the Sonogashira reaction on 5′-bromo-2′,4-dimethoxy-[1,1′-biphenyl]-2-carbaldehyde **60** with 4-ethynylanisole **31**, and in this case the desired alkynylated compound **77** was obtained in 85% yield (Scheme 12). Subsequently, **77** was treated with 2,6-di-*tert*-butylphenol **53** in the presence of piperidine and acetic anhydride to give 2-phenyl arylsubstituted *p*-QM **78**, which was then subjected to cyclization under continuous-flow conditions using a microreactor to produce the fluorene derivative **79** in 63% yield. The dearomative oxidation of **79** with DDQ followed by a Lewis acid catalyzed addition of phenol **21** generated the expected 9,9′-diarylated fluorene derivative **80** in 58% yield (2 steps).



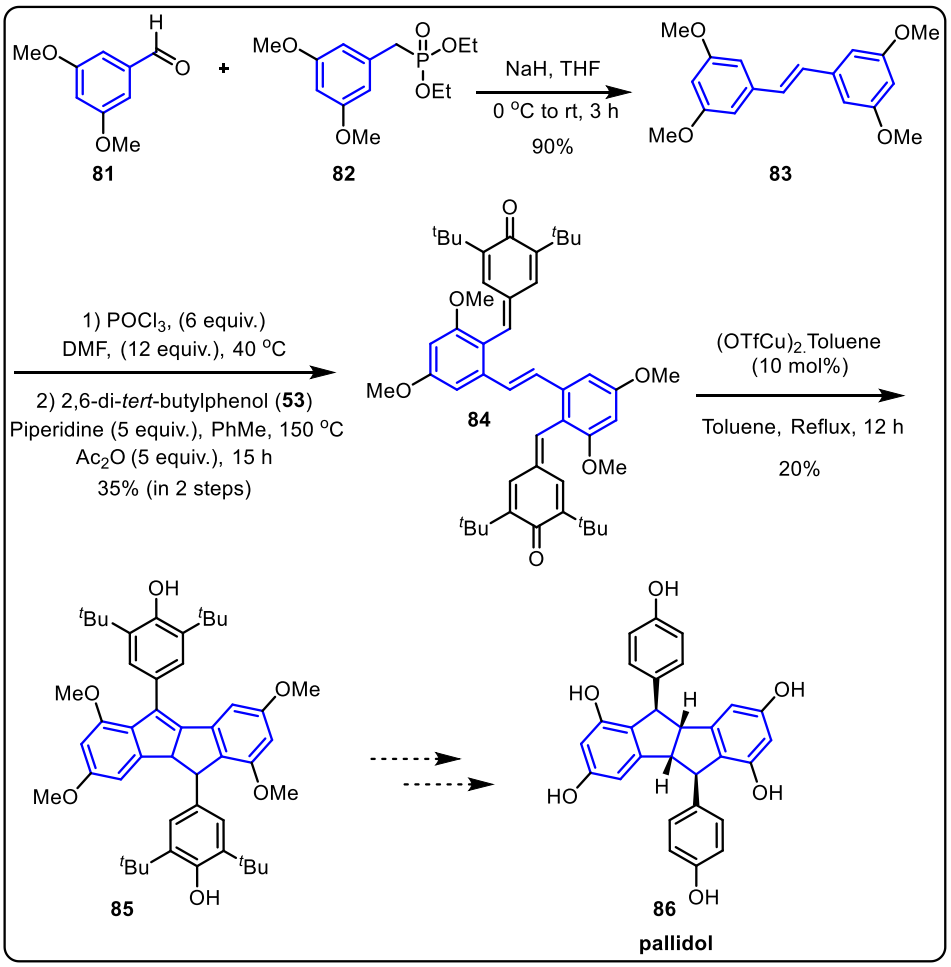
Scheme 12. Attempted approach for the synthesis of selaginpulvin I.

However, unfortunately, when **80** was subjected to de-*tert*-butylation reaction with an excess of $AlCl_3$ under various conditions gave only complex mixture of products. Therefore, we could not go further with this strategy.

3.4.5 Attempted total/formal synthesis of (±)-pallidol

Since some of the resveratrol based natural products resemble selaginpulvilins, we thought of elaborating a similar strategy to one of the resveratrol natural products (±)-pallidol **86**.[27] We have started the total/formal synthesis of **86** using a readily available 3,5-dimethoxybenzaldehyde **81**. The Witting reaction of **81** with **82** in the presence NaH

provided the stilbene derivative **83**. The Vilsmeier-Haack reaction of **83** gave the desired dialdehyde, which was then treated with 2,6-di-*tert*-butylphenol **53** in the presence of piperidine and acetic anhydride to give *p*-QM **84** in 35% yield (2 steps). Subsequently, **84** was treated with $(TfOCu)_2$.toluene complex under reflux condition generated the product **85**; however, only in only 20% yield. The cyclization step, i.e., the conversion of **84** to **85**, was attempted under various conditions using many protic and Lewis acids. However, we were unable to improve the yield of **85**. Further optimization experiments to improve the yields of **86** are currently under progress.



Scheme 13. Attempted approach for the synthesis of pallidol

3.5 Conclusion:

In summary, we have successfully used our methodology to synthesize three selagellin natural products with decent overall yield in 8 to 9 steps. Out of three natural products, selaginpulvilin I and isoselagintamarlin A are the first synthesis and have been isolated recently in 2017 and 2019, respectively. Due to the high therapeutic value of these natural products towards (PDE4) inhibition, new synthetic routs are highly required for the total

synthesis of segalinpulvilins. Moreover, we have also tried our previous methodology for the formal synthesis of resveratrol based natural product (pallidol).

3.6 Experimental Section:

General Information. Continuous-flow reactions were performed using a FlowStart Evo B-401 instrument purchased from Future Chemistry Holding B.V. The microreactor was made up of borosilicate glass (channel width 600 μm; channel depth 500 μm), with an effective reaction volume of 100 μL. The microreactor setup has in-built syringe pumps, and all the reactions were carried out without using a back pressure regulator. All other reactions were carried out under an argon atmosphere employing flame-dried glassware. Most of the reagents and starting materials were purchased from commercial sources and used as such. Melting points were recorded on the SMP20 melting point apparatus and were uncorrected. ^{1}H, ^{13}C and ^{19}F spectra were recorded in $CDCl_3$, DMSO-d_6 and acetone-d_6 (400, 100 and 376 MHz, respectively) on Bruker FT-NMR spectrometer. Chemical shift (δ) values are reported in parts per million (ppm) relative to TMS, and the coupling constants (J) are reported in Hz. High-resolution mass spectra were recorded on Waters Q-TOF Premier-HAB213 spectrometer. FT-IR spectra were recorded on a Perkin–Elmer FT-IR spectrometer. Thin layer chromatography was performed on Merck silica gel 60 F_{254} TLC plates. Column chromatography was carried out through a silica gel (100-200 mesh) column using a mixture of EtOAc/hexane as eluent.

General procedure For the preparation of (54, 61, 71 and 78)

In a Dean-Stark apparatus, a mixture of 2-arylated benzaldehyde (3.092 mmol, 1 equiv.) and 2,6-di-*tert*-butylphenol (3.40 mmol, 1.1 equiv.) in toluene (30 mL) was heated at 100 °C for 30 min. Piperidine (9.28 mmol, 3 equiv.) was then added to this reaction mixture at 100 °C in a drop-wise manner, and the resultant mixture was stirred at 150 ^{o}C for 24 h. The reaction mixture was then cooled to 100 ^{o}C, acetic anhydride (3 equiv.) was added, and the resulting solution was stirred for additional 1 h at the same temperature. The reaction mixture was then cooled to room temperature, poured into ice-cold water (50 mL), and extracted with dichloromethane (50 mL × 3). The combined organic layer was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by neutral alumina column chromatography using a mixture of ethyl acetate/hexane to obtain pure 2-aryl phenyl *p*-quinone methides **54, 61, 71** and **78**.

General procedures for the synthesis of 9-arylfluorenes (55, 62, 73, 74 and 79)

2-Arylphenyl *p*-quinone methide (1.252 mmol, 1 equiv.) dissolved in CH_2Cl_2 (5 mL) was taken in a syringe. Triflic acid (0.205 mmol, 20 mol %) dissolved in CH_2Cl_2 (5 mL) was taken in another syringe. These two solutions were injected simultaneously through the microreactor at flow rates of 15 $\mu L\,min^{-1}$ each. The temperature of the microreactor was maintained at 25 ^oC throughout the reaction. The reaction mixture collected at the outlet was concentrated under reduced pressure and directly loaded onto a silica-gel column and was purified using 5% EtOAc in hexane as an eluent to provide pure 9-arylfluorene derivatives **55, 62, 73, 74 and 79**.

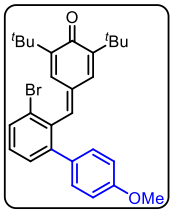
General procedures for the synthesis of fuchsones (56, 63 and 72)

A suspension of 9-arylfluorene derivative (2.5 mmol) and 2,3-dichloro-5,6-dicyanop-benzoquinone (3 mmol) in ethanol-free chloroform (15 ml, filtered through activated basic alumina) was shaken for 3 h under nitrogen. The precipitated hydroquinone was filtered off and washed with chloroform, and the solvent was evaporated in vacuo from the combined filtrates to give a red-coloured crystalline residue which was recrystallized by dissolving in hot chloroform and the addition of ether provided pure **56**, **63**, and **72**.

General procedures for the synthesis of 9,9-diarylfluorenes (57, 64, and 76)

Bismuth triflate (0.1 mmol) was added to a solution of 9,9-diarylfluorenes (1 mmol) and anisole (**29**) [15 mmol] in 10 mL of CH_2Cl_2. The resultant mixture was stirred for 30 min at room temperature. After completion of the reaction (monitored by TLC), the reaction mixture was diluted with ethyl acetate (5 mL) and washed with water (10 mL). The organic layer was dried over $MgSO_4$, and the solvent was evaporated under reduced pressure. The resulting residue was purified by silica gel column chromatography (ethyl acetate/hexane = 15:85) to provide pure **57**, **64**, and **76**.

4-((3-bromo-4'-methoxy-[1,1'-biphenyl]-2-yl)methylene)-2,6-di-tert-butylcyclohexa-2,5-dien-1-one (**54**)

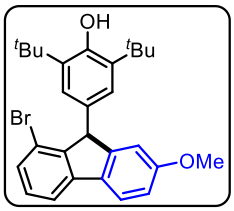


The reaction was performed at 3.092 mmol scale of 3-bromo-4'-methoxy-[1,1'-biphenyl]-2-carbaldehyde.[24] R_f = 0.3 (5% EtOAc in hexane); yellow solid (1130 mg, 76% yield); m. p. = 135-137 ^oC; ^1H NMR (400 MHz, $CDCl_3$) δ 7.64 (d, J = 7.9 Hz, 1H), 7.37 (d, J = 7.7 Hz, 1H), 7.30 – 7.26 (m, 1H), 7.18 (d, J = 7.9 Hz, 2H), 7.00 (s, 1H), 6.89 (s, 1H), 6.83 (d, J = 7.9 Hz, 2H), 6.66 (s, 1H), 3.77 (s, 3H), 1.28 (s, 9H), 1.18 (s, 9H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 186.6, 159.1, 148.3 148.0, 143.8, 140.5, 134.3, 133.8, 133.1, 132.6, 131.6, 131.0, 130.0, 129.5, 128.5, 125.0,

113.8, 55.4, 35.2, 35.1, 29.7, 29.4; IR (neat): 2956, 2923, 1615, 1565, 1515, 1360, 1275, 1041, cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{28}H_{32}BrO_2$ $[M+H]^+$: 479.1586; found : 479.1602.

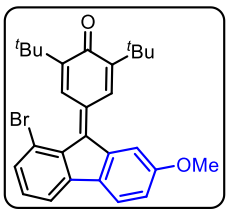
4-(1-bromo-7-methoxy-9H-fluoren-9-yl)-2,6-di-tert-butylphenol (55)

The reaction was performed at 1.25 mmol scale of **54**; R_f = 0.3 (5% EtOAc in hexane); white solid (550 mg, 91% yield); m. p. = 151-153 ^oC; ^1H NMR (400 MHz, $CDCl_3$) δ 7.64 (d, *J* = 7.2 Hz, 2H), 7.33 (d, *J* = 7.9 Hz, 1H), 7.24 – 7.21 (m, 1H), 6.90 – 6.88 (m, 2H), 6.83 (s, 2H), 5.04 (s, 1H), 4.95 (s, 1H), 3.80 (s, 3H), 1.35 (s, 18H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 160.0, 152.5, 150.5, 146.1, 143.9, 135.7, 132.7, 129.9, 129.8, 129.1, 125.0, 121.2, 121.0, 118.0, 113.2, 111.0, 56.0, 55.6, 34.4, 30.5; IR (neat): 3636, 2958, 1583, 1488, 1455, 1275, 1153, 630 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{28}H_{30}BrO_2$ $[M-H]^-$: 477.1429; found : 477.1446.



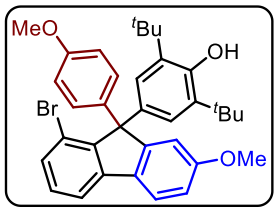
4-(1-bromo-7-methoxy-9H-fluoren-9-ylidene)-2,6-di-tert-butylcyclohexa-2,5-dien-1-one (56)

The reaction was performed at 2.5 mmol scale of **55**;. R_f = 0.4 (5% EtOAc in hexane); dark brown gummy solid (425 mg, 85% yield); ^1H NMR (400 MHz, $CDCl_3$) δ 7.92 (s, 1H), 7.53 (s, 1H), 7.47-7.44 (m, 2H), 6.39-6.36 (m, 2H), 7.17-7.14 (m, 1H), 6.85 (d, *J* = 8.3 Hz, 1H), 3.86 (s, 3H), 1.44 (s, 9H) 1.35 (s, 9H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 187.6, 160.0, 149.4, 147.3, 146.2, 144.9, 141.0, 137.1, 133.2, 133.0, 132.8, 132.5, 131.5, 128.5, 121.4, 121.9, 118.8, 115.4, 112.0, 55.7, 36.1, 35.9, 30.0, 29.9; IR (neat): 2956, 1598, 1549, 1453, 1362, 1275, 1233, 1024, 1031, cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{28}H_{30}BrO_2$ $[M+H]^+$: 477.1429; found : 477.1435.



4-(1-bromo-7-methoxy-9-(4-methoxyphenyl)-9H-fluoren-9-yl)-2,6-di-tert-butylphenol (57)

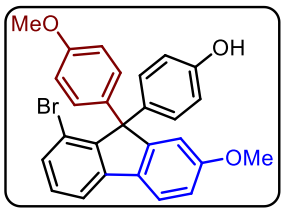
The reaction was performed at 1 mmol scale of **56**; R_f = 0.4 (15% EtOAc in hexane); pale orange solid (399 mg, 78% yield); m. p. = 196-198 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, *J* = 7.4 Hz, 1H), 7.61 (d, *J* = 8.1 Hz 1H), 7.34 (d, *J* = 7.9 Hz, 1H), 7.21-7.17 (m, 5H), 6.89-6.87 (m, 2H), 6.76 (d, *J* = 8.1 Hz, 2H), 5.12 (s, 1H), 3.78 (s, 3H), 3.75 (s, 3H), 1.36 (s, 18H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 160.5, 158.2, 156.6, 152.6, 149.1, 143.5, 134.6, 133.9, 131.6, 131.4, 130.8, 130.7, 129.2, 126.3, 122.0, 120.8, 118.5, 113.9, 112.9, 110.6,



66.5, 55.5, 55.2, 34.6, 30.5; IR (neat): 3286, 2956, 1956, 1706, 1509, 1437, 1263, 1042 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{35}H_{36}BrO_3$ $[M-H]^-$: 583.1848; found : 583.1821.

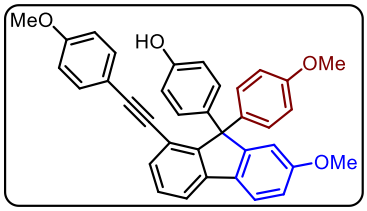
4-(1-bromo-7-methoxy-9-(4-methoxyphenyl)-9H-fluoren-9-yl)phenol (58)

To an oven-dried round bottom flask containing compound **57** (360 mg, 0.615 mmol) in 6 mL of benzene, $AlCl_3$ (410 mg, 3.075 mmol.) was added at room temperature, and the resultant mixture was stirred at room temperature for 2.5 h. After completion of the reaction,



it was transferred to a separatory funnel containing 1:1 ice/1N HCl and extracted with ethyl acetate (3 × 10 mL). The combined organic layer was washed with saturated aq. $NaHCO_3$ and then with brine solution, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography by using ethyl acetate/hexane (40:60) mixture as eluent to give pure (**58**) as pale yellow gummy solid (277 mg, 95% yield); R_f = 0.2 (30% EtOAc in hexane); ^1H NMR (400 MHz, $DMSOd_6$) δ 9.39 (s, 1H), 7.89 (d, *J* = 7.4 Hz, 1H), 7.82 (d, *J* = 8.4 Hz 1H), 7.37-7.35 (m, 1H), 7.31-7.27 (m, 1H), 7.12 (d, *J* = 8.0 Hz, 2H), 7.02 (d, *J* = 7.9 Hz, 2H), 6.94 (d, *J* = 8.4 Hz, 1H), 6.82-6.80 (m, 3H), 6.65 (d, *J* = 7.8 Hz, 2H), 3.69 (s, 3H), 3.68 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $DMSOd_6$) δ 160.2, 157.9, 156.1, 156.1, 148.4, 143.1, 132.5, 131.1, 130.7, 130.4, 130.1, 130.0, 129.9, 121.5, 121.2, 119.2, 114.6, 113.2, 113.2, 110.8, 65.3, 55.4, 55.0; IR (neat): 3397, 2962, 1494, 1449, 1413, 1290, 1176, 1040, cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{27}H_{21}BrO_3$ $[M-H]^-$: 471.0596; found : 471.0613.

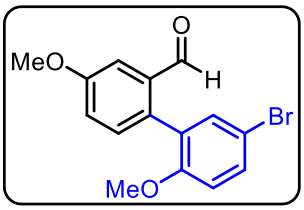
4-(7-methoxy-9-(4-methoxyphenyl)-1-((4-methoxyphenyl)ethynyl)-9H-fluoren-9-yl)phenol (24)



Argon gas was purged to a 1:1 mixture of DMF:Et_3N (10 mL) for 40 min., and to this mixture was added **58** (220 mg, 0.464 mmol), $PdCl_2(PPh_3)_2$ (16.28 mg, 0.0232 mmol) and CuI (4.42 mg, 0.0232 mmol) successively. The reaction mixture was stirred at room temperature for 10 minutes, and then, 4-ethynylanisole (**31**) [201 µL, 1.856 mmol] was added to it, and the resulting mixture was stirred vigorously at 120 ^oC for 20 h. After the completion of the reaction (monitored by TLC), triethylamine was removed under reduced pressure, and the residue was diluted with dichloromethane (30 mL) and water (10 mL). The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (20 mL x 2). The combined organic layer was dried

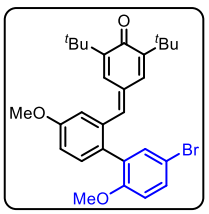
over anhydrous sodium sulphate, filtered and concentrated under reduced pressure. The residue was purified through silica gel column chromatography using hexane/EtOAc to get pure (**24**) as an orange gummy solid (98 mg, 40% yield). R_f = 0.1 (30% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66-7.63 (m, 2H), 7.32-7.31 (m, 2H), 7.23 (d, *J* = 8.6 Hz, 2H), 7.19 (d, *J* = 8.4 Hz 2H), 7.00 (d, *J* = 8.4 Hz, 2H), 7.89-6.87 (m, 1H), 6.84 (bs, 1H), 6.80 (d, *J* = 8.4 Hz, 2H), 6.72 (d, *J* = 8.6 Hz, 2H), 6.65 (d, *J* = 8.4 Hz, 2H), 4.69 (s, 1H), 3.81 (s, 3H), 3.75 (s, 3H), 3.73 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 160.3, 159.6, 158.3, 155.5, 154.2, 151.8, 140.8, 135.2, 135.0, 132.8, 132.2, 131.6, 130.5, 130.2, 127.7, 121.1, 120.8, 119.4, 115.6, 114.6, 114.1, 113.5, 113.1, 111.1, 96.0, 87.6, 65.0, 55.6 55.4, 55.3; IR (neat): 3288, 2924, 2356, 2030, 1605, 1510, 1463, 1260, 1031, cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{36}H_{27}O_4$ [M-H]$^-$: 523.1909; found : 523.1927.

5'-bromo-2',4-dimethoxy-[1,1'-biphenyl]-2-carbaldehyde (**60**)



To an oven-dried 50 mL round-bottomed flask, 2-bromo-5-methoxy benzaldehyde (**13**) [1.5g, 6.98 mmol] and 5-bromo-2-methoxyphenylboronic acid (**59**) [4.01 g, 17.45 mmol] were dissolved in 25 mL of DMF. To this mixture, K_2CO_3 (1.93 g, 13.96 mmol) and Pd $(PPh_3)_4$ (0.8 g, 0.698 mmol) were added, and the resulting suspension was stirred for 28 h at 80 ^{o}C. The reaction mixture was then quenched with NH_4Cl (30 mL) and extracted with ethyl acetate (3 × 30 mL). The organic phase was washed with water (3 × 30 mL), dried over $MgSO_4$, and concentrated under reduced pressure to yield the aldehyde (**60**) as an almond white solid (1497 mg, 66% yield); R_f = 0.2 (5% EtOAc in hexane); m. p. = 101-103 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.72 (s, 1H), 7.50 – 7.48 (m, 2H), 7.39 (s, 1H), 7.26 – 7.24 (m, 1H), 7.21 – 7.19 (m, 1H), 6.84 (d, *J* = 8.8 Hz, 1H), 3.89 (s, 3H), 3.72 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 192.0, 159.6, 155.9, 134.9, 134.1, 133.0, 132.42, 132.36, 128.8, 121.3, 113.3, 112.4, 109.8, 55.8, 55.7;IR (neat): 2933, 1691, 1603, 1502, 1483, 1386, 1235, 1026 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{15}H_{13}NaBrO3$ [M+Na]$^+$: 342.9946; found : 342.9961.

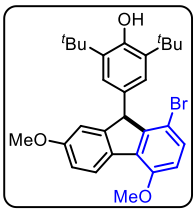
4-((5'-bromo-2',4-dimethoxy-[1,1'-biphenyl]-2-yl)methylene)-2,6-di-tert-butylcyclohexa-2,5-dien-1-one (61)



The reaction was performed at 4.36 mmol scale of the corresponding aldehyde **60**; R_f = 0.2 (5% EtOAc in hexane); yellow solid (1882 mg, 84% yield); m. p. = 133-135 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 – 7.43 (m,

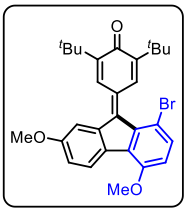
2H), 7.30 – 7.26 (m, 2H), 7.02 – 7.00 (m, 2H), 6.86 (s, 1H), 6.82 – 6.79 (m, 2H), 3.87 (s, 3H), 3.60 (s, 3H), 1.30 (s, 9H), 1.28 (s, 9H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 186.7, 159.0, 156.0, 149.3, 147.8, 142.5, 136.1, 134.9, 134.1, 132.0, 131.98, 131.9, 131.2, 130.6, 128.3, 115.8, 115.3, 112.9, 112.8, 55.7, 55.6 35.6, 35.1, 29.8, 29.7; IR (neat): 2956, 1612, 1479, 1387, 1360, 1258, 1026 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{29}H_{34}BrO_3$ $[M+H]^+$: 509.1691; found : 509.1666.

4-(1-bromo-4,7-dimethoxy-9H-fluoren-9-yl)-2,6-di-tert-butylphenol (62)



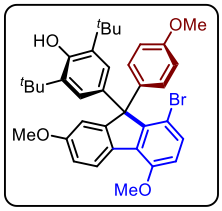
The reaction was performed at 1.571 mmol scale of **61**; R_f = 0.3 (5% EtOAc in hexane); pale yellow solid (708 mg, 88% yield); m. p. = 174-176 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, *J* = 8.1 Hz, 1H), 7.28 – 7.26 (m, 1H), 6.88 – 6.86 (m, 2H), 6.84 (s, 2H), 6.79 (d, *J* = 8.6 Hz, 1H), 5.03 (s, 1H), 4.93 (s, 1H), 4.01 (s, 3H), 3.80 (s, 3H), 1.36 (s, 18H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 159.2, 154.4, 152.5, 149.9, 147.3, 135.7, 132.1, 131.7, 130.3, 129.9, 125.0, 124.6, 112.7, 111.7, 111.5, 110.8, 56.4, 55.7, 55.6, 34.4, 30.5; IR (neat): 3629, 2956, 1511, 1488, 1433, 1302, 1277, 1042, 631 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{29}H_{34}BrO_3$ $[M+H]^+$: 509.1691; found : 509.1673.

4-(1-bromo-4,7-dimethoxy-9H-fluoren-9-ylidene)-2,6-di-tert-butylcyclohexa-2,5-dien-1-one (63)



The reaction was performed at 1.27 mmol scale of **62**; R_f = 0.3 (5% EtOAc in hexane); dark red solid (565 mg, 87% yield); m. p. = 247-151 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 – 7.90 (m, 2H), 7.51 (d, *J* = 2.4 Hz, 1H), 7.39 (d, *J* = 2.2 Hz, 1H), 7.31 (d, *J* = 8.8 Hz, 1H), 6.83 (dd, *J* = 8.5, 2.2 Hz, 1H), 6.79 (d, *J* = 8.8 Hz, 1H), 3.97 (s, 3H), 3.86 (s, 3H), 1.43 (s, 9H) 1.34 (s, 9H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 187.6, 159.1, 154.5, 149.3, 147.9, 146.1, 140.5, 138.4, 133.5, 133.4, 132.6 (2C), 131.9, 128.6, 125.5, 115.1, 115.0, 111.9, 111.6, 55.9, 55.6, 36.1, 35.8, 30.0, 29.9; IR (neat): 3287, 2944, 1588, 1556, 1462, 1360, 1274, 1078, 625 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{29}H_{32}BrO_3$ $[M+H]^+$: 507.1535; found : 507.1511.

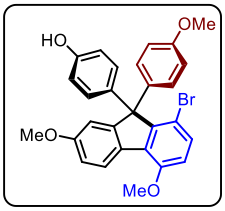
4-(1-bromo-4,7-dimethoxy-9-(4-methoxyphenyl)-9H-fluoren-9-yl)-2,6-di-tert-butylphenol (64)



The reaction was performed at 1.0 mmol scale of **63**; R_f = 0.3 (15% EtOAc in hexane); orange solid (422 mg, 68% yield); m. p. = 236-238 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, *J* = 8.0 Hz, 1H), 7.28 – 7.26

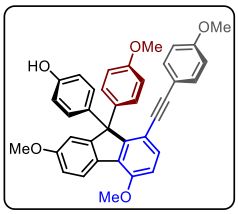
(m, 1H), 7.17 – 7.15 (m, 4H), 6.85 – 6.83 (m, 2H), 6.77 – 6.72 (m, 3H), 5.09 (s, 1H), 4.00 (s, 3H), 3.76 (s, 3H), 3.73 (s, 3H), 1.35 (s, 18H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 159.7, 158.1, 156.1, 154.8, 152.5, 150.3, 134.5, 134.0, 131.7, 131.3, 131.1, 130.8, 130.7, 126.4, 124.7, 113.3, 112.8, 112.4, 111.7, 110.4, 66.6, 55.7, 55.4, 55.2, 34.6, 30.5; IR (neat): 3288, 2955, 1508, 1490, 1463, 1267, 1260, 1041, 624 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{36}H_{38}BrO_4$ $[M-H]^-$: 613.1953; found : 613.1980.

4-(1-bromo-4,7-dimethoxy-9-(4-methoxyphenyl)-9H-fluoren-9-yl)phenol (65)



To an oven-dried round bottom flask containing compound **64** (350 mg, 0.568 mmol) in 6 mL of benzene, $AlCl_3$ (378.5 mg, 2.84 mmol.) was added at room temperature, and the resultant mixture was stirred at room temperature for 2.5 h. After completion of the reaction, it was transferred to a separatory funnel containing 1:1 ice/1N HCl and extracted with ethyl acetate (3 × 10 mL). The combined organic layer was washed with saturated aq. $NaHCO_3$ and then with brine solution, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography by using ethyl acetate/hexane (40:60) mixture as eluent to give pure (**65**) as pale yellow gummy solid (264 mg, 92% yield); R_f = 0.2 (30% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, *J* = 8.4 Hz, 1H), 7.28 – 7.23 (m, 3H), 7.18 (d, *J* = 8.3 Hz 2H), 6.84 (d, *J* = 8.6 Hz, 1H), 6.78 – 6.76 (m, 4H), 6.67 (d, *J* = 8.3 Hz, 2H), 5.03 (s, 1H), 4.00 (s, 3H), 3.76 (s, 3H), 3.73 (s, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 159.7, 158.3, 155.8, 154.8, 154.4, 149.9, 133.1, 133.0, 131.9, 131.2, 130.9, 130.8, 130.6, 124.9, 114.6, 113.2, 113.0, 112.2, 111.9, 110.7, 66.0, 55.7, 55.5, 55.3; IR (neat): 3403, 2935, 2836, 1608, 1464, 1436, 1251, 1044, 625 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{28}H_{22}BrO_4$ $[M-H]^-$: 501.0701; found : 501.0713.

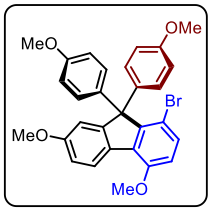
4-(4,7-dimethoxy-9-(4-methoxyphenyl)-1-((4-methoxyphenyl)ethynyl)-9H-fluoren-9-yl)phenol (**66**)



Argon gas was purged to a 1:1 mixture of DMF:Et_3N (10 mL) for 40 min., and to this mixture was added **65** (200 mg, 0.397 mmol), $PdCl_2(PPh_3)_2$ (13.87 mg, 0.0198 mmol) and CuI (3.76 mg, 0.0198 mmol) successively. The reaction mixture was stirred at room temperature for 10 minutes, and then, 4-ethynylanisole (**31**) [205 µL, 1.588 mmol] was added to it, and the resulting mixture was stirred vigorously at 120 ^{o}C for 20 h. After the completion of the reaction (monitored by TLC), triethylamine was removed under reduced pressure, and the

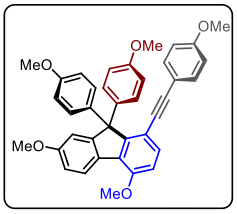
residue was diluted with dichloromethane (30 mL) and water (10 mL). The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (20 mL x 2). The combined organic layer was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure. The residue was purified through silica gel column chromatography using hexane/EtOAc to get pure (**66**) as an orange oil (34 mg, 15% yield). R_f = 0.1 (30% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (d, J = 8.4 Hz, 1H), 7.31 (d, J = 8.4 Hz, 1H), 7.26 – 7.23 (m, 2H), 7.19 (d, J = 8.4 Hz, 2H), 7.00 (d, J = 8.4 Hz, 2H), 6.87 – 6.85 (m, 2H), 6.83 (bs, 1H), 6.79 (d, J = 8.4 Hz, 2H), 6.72 (d, J = 8.6 Hz, 2H), 6.64 (d, J = 8.4 Hz, 2H), 4.93 (s, 1H), 4.02 (s, 3H), 3.79 (s, 3H), 3.75 (s, 3H), 3.73 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 159.5, 159.3, 158.2, 155.3, 155.1, 154.3, 153.6, 135.0, 134.9, 132.6, 132.4, 131.5, 130.5, 130.3, 128.6, 124.7, 116.0, 114.5, 114.0, 113.3, 113.1, 113.0, 110.9, 110.0, 94.1, 87.6, 65.3, 55.6, 55.5, 55.4, 55.3; IR (neat): 3430, 2927, 1633, 1512, 1267, 1175, 1033, cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{37}H_{29}O_5$ [M-H]$^-$: 553.2015; found : 553.2034.

1-bromo-4,7-dimethoxy-9,9-bis(4-methoxyphenyl)-9H-fluorene (**67**)



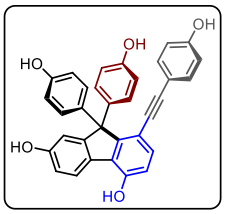
To a stirred solution of **65** (300 mg, 0.595 mmol) in anhydrous DMSO (8 mL), Potassium *tert*-butoxide (133.5 mg, 1.19 mmol) was added in a portion-wise manner at ambient temperature, and the resulting mixture was stirred for 30 min. Me_2SO_4 (112.7 µL, 1.19 mmol) was added to it, and the mixture was stirred for an additional 2.5 h. The reaction mixture was then poured into ice-cold water (20 mL) and extracted with ethyl acetate (25 mL × 3). The combined organic layer was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to obtain pure (**67**) as white gummy solid (274 mg, 89% yield). R_f = 0.3 (15% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (d, J = 8.4 Hz, 1H), 7.29 – 7.24 (m, 5H), 6.84 (d, J = 8.6 Hz, 1H), 6.79 – 6.76 (m, 6H), 4.00 (s, 3H), 3.76 (s, 6H), 3.73 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 159.8, 158.4, 155.8, 154.8, 150.0, 133.0, 131.9, 131.3, 130.9, 130.6, 124.9, 113.1, 113.0, 112.2, 111.9, 110.7, 66.0, 55.7, 55.5, 55.3(2C); IR (neat): 3425, 2957, 2835, 1608, 1508, 1463, 1251, 1179, 652 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{29}H_{26}BrO_4$ [M+H]$^+$: 517.1014; found : 517.1010.

4,7-dimethoxy-9,9-bis(4-methoxyphenyl)-1-((4-methoxyphenyl)ethynyl)-9H-fluorene (**68**)



Argon gas was purged to a mixture of 1:1 DMF:Et_3N (10 mL) for 40 min. and, to this mixture, was added **67** (200 mg, 0.386 mmol), $PdCl_2(PPh_3)_2$ (13.5 mg, 0.0193 mmol) and CuI (3.66 mg, 0.0193 mmol). The reaction mixture was stirred at room temperature for 10 min, and then 4-ethynylanisole (**31**) [200 µL, 1.54 mmol] was added to it. The resulting suspension was stirred vigorously at 120 ^oC for 20 h. After the reaction was complete (by TLC), triethylamine was removed under reduced pressure, and the residue was then diluted with dichloromethane (30 mL) and water (10 mL). Organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (20 mL x 2). The combined organic layer was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure. The residue was purified through silica gel column chromatography using hexane/EtOAc to get pure (**68**) as pale orange gummy solid (113 mg, 51% yield) R_f = 0.2 (30% EtOAc in hexane); ^1H NMR (400 MHz, $CDCl_3$) δ 8.04 (d, J = 8.4 Hz, 1H), 7.31 (d, J = 8.4 Hz, 1H), 7.27 – 7.23 (m, 4H), 6.99 – 6.96 (m, 2H), 6.88 – 6.85 (m, 2H), 6.83 (d, J = 2.3 Hz, 1H), 6.80–6.78 (m, 2H), 6.74 – 6.70 (m, 4H), 4.03 (s, 3H), 3.80 (s, 3H), 3.75 (s, 3H), 3.73 (s, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 159.5, 159.3, 158.3, 155.3, 155.1, 153.7, 135.0, 132.6, 132.4, 131.5, 130.3, 128.7, 124.7, 116.1, 114.0, 113.3, 113.1, 113.0, 110.9, 110.0, 94.1, 87.7, 65.3, 55.6, 55.5, 55.4, 55.33(2C); IR (neat): 3289, 2954, 2926, 1606, 1510, 1463, 1288, 1248, 1178, 1032, cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{38}H_{33}O_5$ $[M+H]^+$: 569.2328; found : 569.2335.

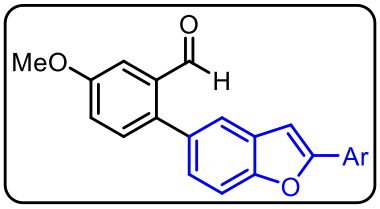
Synthesis of selaginpulvilin I (9)[15]



To an oven-dried Schlenk tube containing compound **73** (50 mg, 0.087 mmol) was added MeMgI (3M in diethyl ether) (725 µL, 2.17 mmol.). Then the solvent diethyl ether was removed under reduced pressure at rt to give a solid residue. The residue was then heated to 160 °C for 45 minutes. It was then cooled to room temperature and dissolved in 1:1 ethyl acetate: diethyl ether mixture (50 mL). To this mixture, water was then added in a drop-wise (Caution: initial vigorous gas evolution) manner (50 mL water was added in total), and the resulting suspension was extracted with ethyl acetate (3 x 100 mL). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was then purified through column chromatography (40% acetone in hexane) to get pure selaginpulvilin I (**9**) [27.4 mg, 63% yield] as pale purple oil. R_f = 0.2 (40% acetone in hexane); ^1H NMR (400 MHz, CD_3OD) δ 7.95 (d, J = 8.3 Hz, 1H), 7.10 (d, J = 8.7 Hz, 4H), 7.07 (d, J = 8.3 Hz, 1H), 6.83 (d, J = 8.2 Hz, 2H), 6.76 – 6.72 (m, 2H), 6.69 – 6.65 (m, 3H),

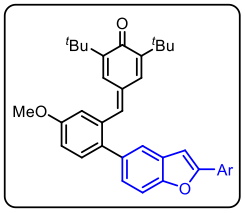
6.58 (d, *J* = 8.7 Hz, 4H), 6.44 (d, *J* = 8.6 Hz, 4H); $^{13}C\{^{1}H\}$ NMR (100 MHz, CD_3OD) δ 158.5, 157.9, 156.8, 156.5, 155.4, 154.2, 135.6, 133.4, 132.3, 132.1, 131.4, 128.7, 125.5, 116.2, 115.5, 115.1, 115.0, 113.5, 113.1, 113.0, 94.6, 88.5, 66.4; IR (neat): 3435, 2955, 1609, 1511, 1447, 1368, 1236, 1175, 819, cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{33}H_{23}O_5$ $[M+H]^+$: 499.1545; found : 499.1526.

5-methoxy-2-(2-(4-methoxyphenyl)benzofuran-5-yl)benzaldehyde (**71**)



Nitrogen gas was purged through a mixture of aqueous solution of sodium carbonate and toluene (15 mL) for 15 min and then, (2-formyl-4-methoxyphenyl)boronic acid (**70**) [445.2 mg, 2.47 mmol], $Pd(PPh_3)_4$ (95 mg, 0.082 mmol) and 5-bromo-2-(4-methoxyphenyl)benzofuran[26] (**69**) [500 mg, 1.649 mmol] were added to this mixture successively. The reaction mixture was refluxed at 100 ^{o}C for overnight. After completion of the reaction (monitored by TLC), the reaction mixture was diluted with ethyl acetate (30 mL) and water (10 mL). The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (30 mL × 2). The combined organic layer was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure. The residue was purified through neutral alumina column chromatography using hexane/EtOAc to obtain pure 5-methoxy-2-(2-(4-methoxyphenyl)benzofuran-5-yl)benzaldehyde (**71**) as white solid (376 mg, 63% yield); R_f = 0.2 (5% EtOAc in hexane); m. p. = 152-154 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.0 (s, 1H), 7.82 (d, *J* = 8.8 Hz, 2H), 7.55 (d, *J* = 8.3 Hz, 1H), 7.52 (d, *J* = 2.8 Hz, 1H), 7.49 (d, *J* = 1.4 Hz, 1H), 7.42 (d, *J* = 8.4 Hz, 1H), 7.23 – 7.19 (m, 2H), 7.00 (d, *J* = 8.8 Hz, 2H), 6.90 (s, 1H) 3.91 (s, 3H), 3.87 (s, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 192.8, 160.3, 159.1, 157.4, 154.5, 139.7, 134.8, 132.5, 132.4, 129.9, 126.7, 126.2, 123.1, 122.3, 121.5, 114.4, 110.9, 109.8, 99.6, 55.7, (d) 55.5 (d);IR (neat): 2924, 1682, 1505, 1273, 1254, 1038, 832 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{23}H_{19}O_4$ $[M+H]^+$: 359.1283; found : 359.1287.

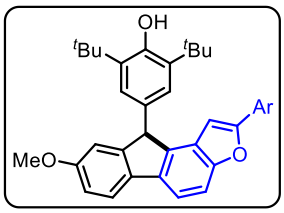
2,6-di-tert-butyl-4-(5-methoxy-2-(2-(4-methoxyphenyl)benzofuran-5-yl)benzylidene)-cyclohexa-2,5-dien-1-one (**72**)



The reaction was performed at 0.977 mmol scale of 5-methoxy-2-(2-(4-methoxyphenyl)benzofuran-5-yl)benzaldehyde (**71**); R_f = 0.2 (5% EtOAc in hexane); orange solid (428 mg, 80% yield); m. p. = 186-188 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (d, *J* = 8.8 Hz, 2H), 7.69 (d, *J* =

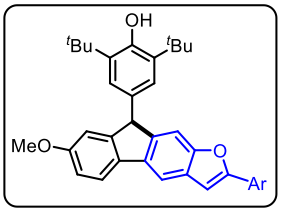
1.8 Hz, 1H), 7.53 (d, *J* = 8.4 Hz, 1H), 7.49 (d, *J* = 1.3 Hz, 1H) 7.46 – 7.43 (m, 1H), 7.20 (dd, *J* = 8.4, 1.7 Hz, 1H), 7.07 – 7.05 (m, 2H), 7.01 (s, 2H), 7.00 (s, 1H), 6.92 (s, 1H), 6.88 (d, *J* = 1.9 Hz, 1H), 3.89 (s, 3H), 3.87 (s, 3H), 1.36 (s, 9H), 1.29 (s, 9H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 186.7, 160.3, 158.6, 157.1, 154.3, 149.4, 147.6, 143.5, 136.4, 135.2, 135.04, 135.02, 131.9, 131.7, 129.8, 128.5, 126.6, 126.3, 123.2, 121.9, 116.4, 116.0, 114.4, 110.8, 99.8, 55.7, 55.5, 35.7, 35.2, 29.8, 29.6; IR (neat): 2956, 1611, 1507, 1461, 1275, 1254, cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{37}H_{39}O_4$ $[M+H]^+$: 547.2848; found : 547.2865.

2,6-di-tert-butyl-4-(8-methoxy-2-(4-methoxyphenyl)-10H-fluoreno[2,1-b]furan-10-yl)phenol (**73**)



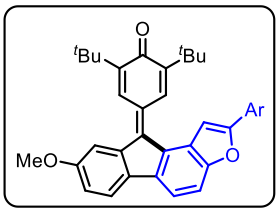
The reaction was performed at 0.713 mmol scale of **72,** and the products **78** and **79** were obtained in 92% yield (360 mg) as separable regioisomers; Data for **78**: R_f = 0.2 (5% EtOAc in hexane); pale yellow solid; m. p. = 214-216 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, *J* = 8.8 Hz, 2H), 7.67 (d, *J* = 8.3 Hz, 1H), 7.61 (d, *J* = 8.4 Hz, 1H), 7.50 (d, *J* = 8.3 Hz, 1H), 6.98 (s, 3H), 6.96 – 6.91 (m, 3H), 6.60 (s, 1H), 5.09 (s, 1H), 3.85 (s, 3H), 3.82 (s, 3H), 1.38 (s, 18H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 160.0, 158.9, 156.4, 154.6, 152.7, 150.0, 139.0, 136.0, 135.9, 134.6, 131.0, 126.8, 126.4, 125.0, 123.5, 119.9, 115.0, 114.3, 112.8, 111.1, 110.0, 98.3, 55.68, 55.47, 54.0, 34.5, 30.5; IR (neat): 3445, 2958, 1639, 1504, 1275, 1260, 1173, 1030 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{37}H_{39}O_4$ $[M+H]^+$: 547.2848; found : 547.2851.

2,6-di-tert-butyl-4-(7-methoxy-2-(4-methoxyphenyl)-9H-fluoreno[2,3-b]furan-9-yl)phenol (**74**)



R_f = 0.2 (5% EtOAc in hexane); orange solid; m. p. = 246-248 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 – 7.76 (m, 3H), 7.69 (d, *J* = 8.4 Hz, 1H), 7.41 (s, 1H), 6.97 (s, 1H), 6.95 – 6.92 (m, 5H), 6.90 (s, 1H), 5.10 (s, 1H), 5.02 (s, 1H), 3.85 (s, 3H), 3.82 (s, 3H), 1.39 (s, 18H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 159.9, 159.2, 156.2, 154.5, 152.8, 149.9, 145.2, 136.5, 136.1, 134.2, 132.5, 129.0, 126.3, 124.9, 123.7, 120.2, 114.3, 113.4, 111.1, 110.1, 108.3, 100.1, 55.70, 55.47, 54.4, 34.5, 30.5; IR (neat): 3424, 2956, 1611, 1506, 1436, 1251, 1176, 1036 cm^{-1};HRMS (ESI): *m/z* calcd for $C_{37}H_{39}O_4$ $[M+H]^+$: 547.2848; found : 547.2866.

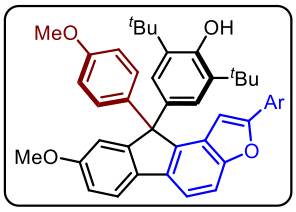
2,6-di-tert-butyl-4-(8-methoxy-2-(4-methoxyphenyl)-10H-fluoreno[2,1-b]furan-10-



ylidene)cyclohexa-2,5-dien-1-one (75)

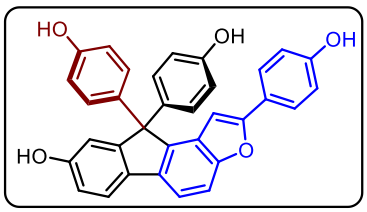
The reaction was performed at 0.292 mmol scale of (**73**); R_f = 0.2 (5% EtOAc in hexane); dark red solid (139 mg, 87% yield); m. p. = 249-251 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (d, *J* = 2.2 Hz, 1H), 7.84 (d, *J* = 2.3 Hz, 1H), 7.76 (d, *J* = 8.8 Hz, 2H), 7.42 (d, *J* = 8.3 Hz, 1H), 7.40 – 7.38 (m, 2H), 7.33 (d, *J* = 8.2 Hz, 1H), 7.06 (s, 1H), 7.00 (d, *J* = 8.8 Hz, 2H), 6.83 (dd, *J* = 8.3, 2.1 Hz, 1H), 3.87 (s, 6H), 1.48 (s, 9H) 1.39 (s, 9H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 187.0, 160.7, 159.2, 158.3, 155.7, 149.5, 149.0, 147.4, 139.9, 138.5, 135.3, 131.7, 131.6, 129.2, 128.8, 128.4, 126.6, 122.5, 120.5, 115.33, 115.26, 114.6, 113.4, 113.2, 101.1, 55.7, 55.5, 36.03, 36.02, 29.99, 29.98; IR (neat): 2925, 1634, 1462, 1275, 1261 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{37}H_{37}O_4$ [M+H]$^+$: 545.2692; found : 545.2697.

2,6-di-tert-butyl-4-(8-methoxy-2,10-bis(4-methoxyphenyl)-10H-fluoreno[2,1-b]furan-10-yl)phenol (76)



The reaction was performed at 0.22 mmol scale of (**75**); R_f = 0.2 (15% EtOAc in hexane); red solid (90 mg, 62% yield); m. p. = 236-238 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, *J* = 8.8 Hz, 2H), 7.65 (d, *J* = 8.3 Hz, 1H), 7.60 (d, *J* = 8.3 Hz, 1H), 7.49 (d, *J* = 8.3 Hz, 1H), 7.15 (s, 3H), 7.13 (s, 1H), 7.01 (d, *J* = 2.2 Hz, 1H), 6.95 – 6.93 (m, 2H), 6.92 – 6.90 (m, 1H), 6.75 (d, *J* = 8.8 Hz, 2H), 6.68 (s, 1H), 5.09 (s, 1H), 3.84 (s, 3H), 3.79 (s, 3H), 3.74 (s, 3H), 1.32 (s, 18H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 160.1, 159.2, 158.1, 156.3, 155.0, 154.8, 152.5, 143.5, 137.3, 135.1, 134.6, 134.3, 133.8, 129.7, 126.54, 126.50, 125.7, 123.5, 120.1, 115.4, 114.3, 113.5, 113.4, 111.3, 110.3, 98.9, 64.9, 55.6, 55.5, 55.2, 34.6, 30.5; IR (neat): 3626, 2956, 2926, 1611, 1505, 1463, 1248, 1176, 1112, 1030 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{44}H_{45}O_5$ [M+H]$^+$: 653.3267; found : 653.3268.

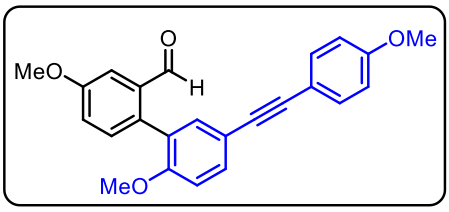
Isoselagintamarlin A (11)[16]



$AlCl_3$ (66.6 mg, 0.5 mmol) was added to a solution of compound **76** (65 mg, 0.1 mmol) in 3 mL of benzene, and the resultant mixture was stirred at rt for 15 h. It was then transferred to a separatory funnel containing 1:1 ice/1 N HCl solution and extracted with ethyl acetate (3 × 10 mL). The combined organic layer was washed with sat. aq. $NaHCO_3$ and brine solution successively dried over anhydrous Na_2SO_4 and concentrated under a vacuum. The crude material obtained was then dissolved in dry diethyl ether and transferred to a Schlenk tube, and, to this solution, MeMgI (3M in diethyl

ether) (700 µL, approx. 25 mol equiv.) was added. The solvent was removed under pressure at rt to give a solid residue, which was then heated to 160 ^{o}C for 45 minutes. It was cooled to room temperature and dissolved with 1:1 ethyl acetate: diethyl ether mixture (5 mL). Water was then added drop-wise (Caution: initial vigorous gas evolution) to the reaction mixture (5 mL water was added in total), and the resulting mixture was extracted with ethyl acetate (3 x 50 mL). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was then purified through column chromatography (40% acetone in hexane) to get pure Isoselagintamarlin A (**11**) as pale yellow oil (27.7 mg, 55% yield). R_f = 0.3 (70% EtOAc in hexane); ^{1}H NMR (400 MHz, acetone-d_6) δ 9.15 (s, 1H), 8.66 (s, 1H), 8.57 (s, 2H), 7.72 (d, J = 8.7 Hz, 2H), 7.66 (dd, J = 8.4, 3.4 Hz, 2H), 7.50 (d, J = 8.4 Hz, 1H), 7.10 – 1.06 (m, 4H) 6.91 – 6.88 (m, 4H), 6.84 (dd, J = 8.2, 2.2 Hz, 1H), 6.72 – 6.89 (m, 4H); ^{13}C{^{1}H} NMR (100 MHz, acetone-d_6) δ 159.3, 157.9, 157.5, 157.0, 156.0, 155.2, 144.0, 136.1, 135.8, 133.0, 130.4 (2C), 127.4, 127.3, 122.6, 121.0, 116.6, 115.74, 115.71 (2C), 115.3, 113.4, 110.7, 99.0, 65.0; IR (neat): 3437, 2958, 2926, 1613, 1507, 1423, 1376, 1260, 1247, 1173 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{32}H_{23}O_5$ $[M+H]^+$: 499.1545; found : 499.1554.

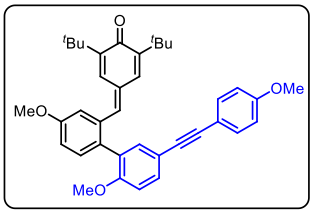
2',4-dimethoxy-5'-((4-methoxyphenyl)ethynyl)-[1,1'-biphenyl]-2-carbaldehyde (77)



4-Ethynylanisole [210 mg, 1.59 mmol] was added to a suspension of $PdCl_2(PPh_3)_2$ (33 mg, 0.047 mmol), CuI (9 mg, 0.047 mmol) and 5'-bromo-2',4-dimethoxy-[1,1'-biphenyl]-2-carbaldehyde (**60**) [300 mg, 0.94 mmol] in triethylamine (5 mL) at room temperature and the reaction mixture was heated to 80 ^{o}C and stirred vigorously under an inert atmosphere. After the reaction was complete (by TLC), triethylamine was removed under reduced pressure, and the residue was then diluted with dichloromethane (30 mL) and water (10 mL). Organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (20 mL x 2). The combined organic layer was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure. The residue was purified through silica gel column chromatography using hexane/EtOAc to get pure 2',4-dimethoxy-5'-((4-methoxyphenyl)ethynyl)-[1,1'-biphenyl]-2-carbaldehyde (**77**) (298 mg, 85% yield) as orange gummy solid. R_f = 0.1 (5% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.75 (s, 1H), 7.55 (dd, J = 8.5, 2.2 Hz, 1H), 7.50 (d, J = 2.8 Hz, 1H), 7.47 – 7.43 (m, 3H), 7.29 (d, J = 8.4 Hz, 1H), 7.21 (dd, J = 8.4, 2.8 Hz, 1H), 6.93 (d, J = 8.6 Hz, 1H), 6.89 – 6.85 (m, 2H), 3.90 (s, 3H), 3.82 (s, 3H), 3.75 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz,

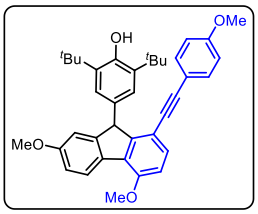
$CDCl_3$) δ 192.3, 159.6, 159.4, 156.6, 134.9, 134.7, 133.8, 133.0 (2C), 132.6, 127.0, 121.4, 116.3, 115.5, 114.1, 110.8, 109.6, 88.8, 87.5, 55.7 (2C), 55.4;IR (neat): 2944, 1690, 1603, 1511, 1488, 1290, 1267, 1046 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{24}H_{21}O_4$ $[M+H]^+$: 373.1440; found : 373.1431.

2,6-di-*tert*-butyl-4-((2',4-dimethoxy-5'-((4-methoxyphenyl)ethynyl)-[1,1'-biphenyl]-2-yl)methylene)cyclohexa-2,5-dien-1-one (78)



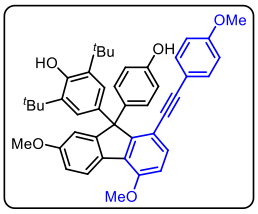
The reaction was carried out in 0.67 mmol of (**77**). R_f = 0.1 (5% EtOAc in hexane); orange gummy solid (305 mg, 81% yield); ^1H NMR (400 MHz, $CDCl_3$) δ 7.53 – 7.51 (m, 2H), 7.44 (d, *J* = 8.3 Hz, 2H), 7.37 (s, 1H), 7.30 (d, *J* = 9.1 Hz, 1H), 7.03 – 7.01 (m, 2H), 6.91 – 6.89 (m, 2H), 6.87 – 6.86 (m, 2H), 6.84 (s, 1H), 3.88 (s, 3H), 3.81 (s, 3H), 3.65 (s, 3H) 1.33 (s, 9H), 1.29 (s, 9H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 186.7, 159.6, 158.8, 156.7, 149.1, 147.6, 142.9, 136.1, 135.0, 134.7, 133.0, 132.6, 132.0, 131.9, 131.4, 129.4, 128.4, 115.9, 115.7, 115.6, 115.3, 114.1, 111.1, 88.6, 87.7, 55.6, 55.5, 55.4, 35.5, 35.1, 29.8, 29.6; FT-IR (neat): 2956, 2320, 1609, 1483, 1360, 1249 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{38}H_{41}O_4$ $[M+H]^+$: 561.3005; found : 561.2985.

2,6-di-tert-butyl-4-(4,7-dimethoxy-1-((4-methoxyphenyl)ethynyl)-9H-fluoren-9-yl)phenol (**79**)



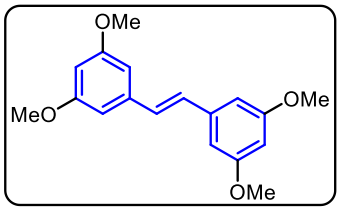
The reaction was performed at 0.054 mmol scale of **78**; R_f = 0.1 (5% EtOAc in hexane); pale orange solid (19 mg, 63% yield); m. p. = 172-174 ^oC; ^1H NMR (400 MHz, $CDCl_3$) δ 8.03 (d, *J* = 8.4 Hz, 1H), 7.37 (d, *J* = 8.4 Hz, 1H), 6.97 (s, 2H), 6.94 – 6.91 (m, 2H), 6.89 – 6.87 (m, 1H), 6.84 (d, *J* = 8.4 Hz, 2H), 6.71 (d, *J* = 8.4 Hz, 2H), 5.10 (s, 1H), 5.05 (s, 1H), 4.05 (s, 3H), 3.81 (s, 3H), 3.77 (s, 3H), 1.35 (s, 18H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 159.2, 159.0, 155.0, 152.5, 149.9, 149.6, 135.7, 132.9, 132.0, 130.6, 130.5, 130.1, 124.8, 124.4, 115.9, 113.7, 113.5, 112.1, 110.9, 109.8, 92.7, 86.7, 55.6, 55.5, 55.4, 55.1, 34.4, 30.5; FT-IR (neat): 3615, 2956, 1513, 1435, 1267, 1247, 1083 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{38}H_{39}O_4$ $[M-H]^-$: 559.2848; found : 559.2870.

2,6-di-tert-butyl-4-(9-(4-hydroxyphenyl)-4,7-dimethoxy-1-((4-methoxyphenyl)ethynyl)-9H-fluoren-9-yl)phenol (**80**)



A suspension of **79** (280 mg, 0.5 mmol) and 2,3-dichloro-5,6-dicyanop-benzoquinone (DDQ) [80 mg, 0.6 mmol] in ethanol-free chloroform (10 mL, filtered through activated basic alumina) was stirred for 15 h under nitrogen atmosphere. The precipitated hydroquinone was filtered off and washed with chloroform, and the filtrate was evaporated in a vacuum to give a red-coloured residue; the crude material obtained was then dissolved in CH_2Cl_2, then anisole (**29**) was added into it (approx 15 ml), and Bismuth triflate (65 mg, 0.1 mmol) was added to a solution. The resultant mixture was stirred for 30 min at room temperature. After the completion of the reaction (monitored by TLC), the reaction mixture was diluted with ethyl acetate (5 mL) and washed with water (10 mL). The organic layer was dried over $MgSO_4$, and the solvent was evaporated under reduced pressure. The resulting residue was purified by silica gel column chromatography (ethyl acetate / hexane = 15:85) to provide pure (**80**) as an brown gummy solid (190 mg, 58% yield); R_f = 0.1 (5% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (dd, J = 8.1, 0.6 Hz, 1H), 7.28 (d, J = 8.4 Hz, 1H), 7.21 (s, 2H), 7.05 – 7.02 (m, 2H), 6.87 – 6.86 (m, 2H), 6.84 (d, J = 8.5 Hz, 1H), 6.80 – 6.77 (m, 2H), 6.75 – 6.72 (m, 2H), 6.53 – 6.49 (m, 2H), 5.09 (s, 1H), 4.03 (s, 3H), 3.79 (s, 3H), 3.76 (s, 3H), 1.30 (s, 18H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 159.4, 159.2, 155.30, 155.29, 154.4, 153.9, 152.5, 136.3, 134.9, 132.7, 132.2, 131.81, 131.76, 130.8, 128.6, 126.1, 124.6, 116.2, 114.2, 113.8, 113.4, 113.0, 110.9, 109.8, 94.3, 88.2, 65.8, 55.6, 55.4, 55.36, 34.6, 30.5; FT-IR (neat): 3623, 2947, 1517, 1430, 1266, 1247, 1085 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{44}H_{43}O_5$ $[M-H]^-$: 651.3110; found : 651.3094.

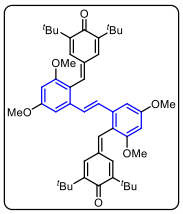
(E)-1,2-bis(3,5-dimethoxyphenyl)ethene (**83**)



Sodium hydride (0.649 g, 27.07 mmol) was added to a solution of diethyl 3,5-dimethoxybenzylphosphonate[28] **82** (7.282 g, 25.27 mmol) in anhydrous THF (15 mL) at 0 °C under an argon atmosphere, and then the mixture was stirred at room temperature for 10 min. To this mixture was slowly added dropwise a solution of 3,5-dimethoxy benzaldehyde **86** (3.0 g, 18.07 mmol) in anhydrous THF (30 mL) followed by continued stirring at room temperature for 3 h. After completion, the reaction mixture was quenched with ice water (30 mL) and then extracted three times with ethyl acetate. Then the combined organic layer was dried over anhydrous sodium sulfate and filtered. The resulting residue was purified by silica gel column chromatography (ethyl acetate / hexane = 15:85) to provide pure (**83**) as an white solid (4.87 g, 90%); R_f = 0.1 (10% EtOAc in hexane); ^{1}H NMR

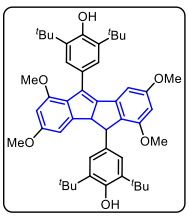
(400 MHz, $CDCl_3$) δ 7.02 (s, 2H), 6.68 (s, 4H), 6.41 (s, 2H), 3.84 (s, 12H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 161.1, 139.2, 129.3, 104.7, 100.2, 55.5; FT-IR (neat): 3623, 2947, 1517, 1430, 1266, 1247, 1085 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{18}H_{21}O_4$ $[M+H]^+$: 301.1440; found : 301.1452.

(E)-4,4'-((ethene-1,2-diylbis(4,6-dimethoxy-2,1-phenylene))bis(methanylylidene))bis(2,6-di-*tert*-butylcyclohexa-2,5-dien-1-one) (**84**)



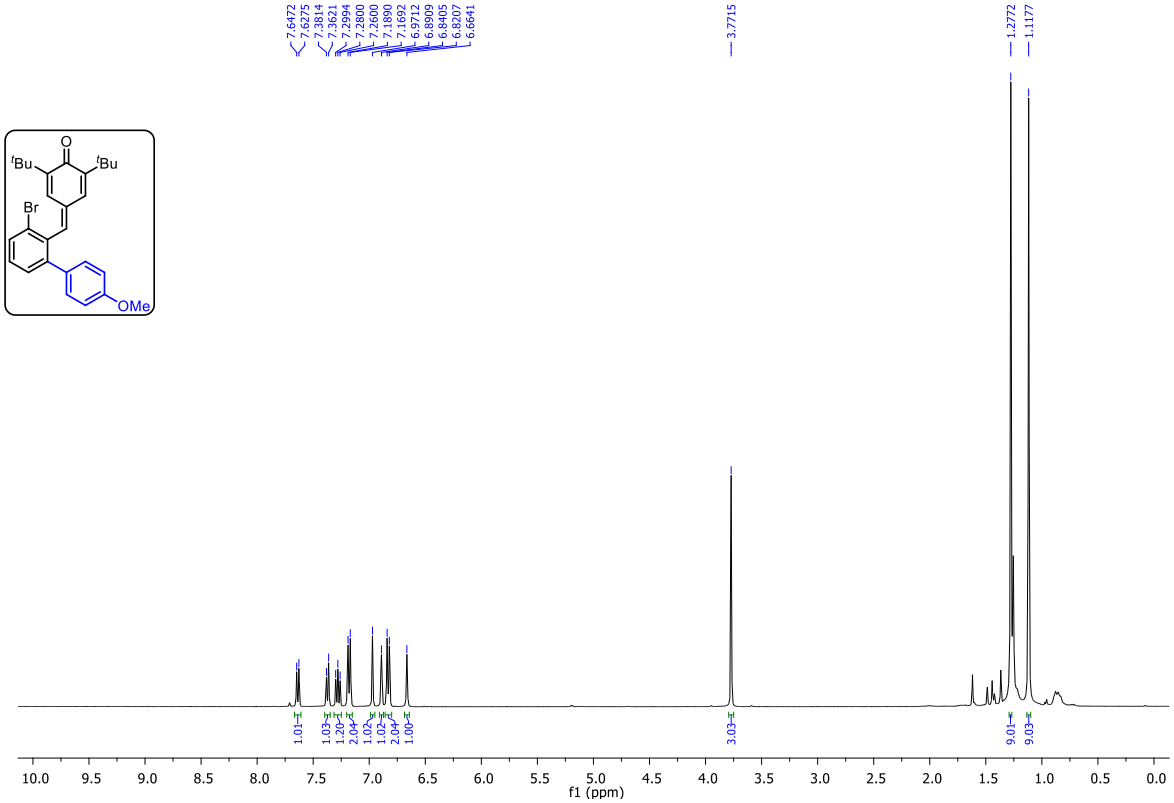
To an oven-dried round bottom flask containing compound **83** (4 g, 13.3 mmol) in (11.5 mL 159.6 mmol) of unhydrous DMF the resulting solution was cooled to 0 °C. $POCl_3$ (7.45 mL, 79.8 mmol.) was added dropwise and the now orange reaction contents were warmed to 40 °C and stirred for 6 h. After completion of the reaction, contents were poured into ice water (100 mL), quenched by the slow addition of solid KOH until a pH 14 was obtained, and allowed to stir for 12 h. Once achieved, the solid crude material was filtered and washed with ether. Then in a Dean-Stark apparatus, a crude mixture (10.1 mmol, 1 equiv.) and 2,6-di-*tert*-butylphenol (22.2 mmol, 2.2 equiv.) in toluene (50 mL) was heated at 100 °C for 30 min. Piperidine (50.5 mmol, 5 equiv.) was then added to this reaction mixture at 100 °C in a drop-wise manner, and the resultant mixture was stirred at 150 ^oC for 14 h. The reaction mixture was then cooled to 100 ^oC, acetic anhydride (50.5 mmol 5 equiv.) was added, and the resulting solution was stirred for additional 1 h at the same temperature. The reaction mixture was then cooled to room temperature, poured into ice-cold water (50 mL), and extracted with dichloromethane (50 mL × 3). The combined organic layer was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by neutral alumina column chromatography using a mixture of ethyl acetate/hexane to obtain pure (**84**) as a yellow solid (3.4 g, 35% yield); R_f = 0.2 (5% EtOAc in hexane); ^1H NMR (400 MHz, $CDCl_3$) δ 7.32 (s, 2H), 7.19 (d, *J* = 2.0 Hz, 2H), 6.91 (s, 4H), 6.42 (d, *J* = 1.9 Hz, 2H), 6.37 (d, *J* = 2.0 Hz, 2H), 3.82 (s, 6H), 3.61 (s, 6H), 1.33 (s, 18H), 1.02 (s, 18H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 186.8, 161.5, 159.6, 148.1, 147.1, 139.1, 138.5, 135.1, 133.4, 130.1, 129.2, 117.3, 100.6, 99.1, 55.8, 55.2, 34.3, 34.2, 29.6, 29.4; FT-IR (neat): 3623, 2947, 1517, 1430, 1266, 1247, 1085 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{48}H_{59}O_6$ $[M-H]^-$: 731.4312; found : 731.4326.

4,4'-(1,3,6,8-tetramethoxy-4b,5,9b,10-tetrahydroindeno[2,1-a]indene-5,10-diyl)bis(2,6-di-*tert*-butylphenol) (**85**)

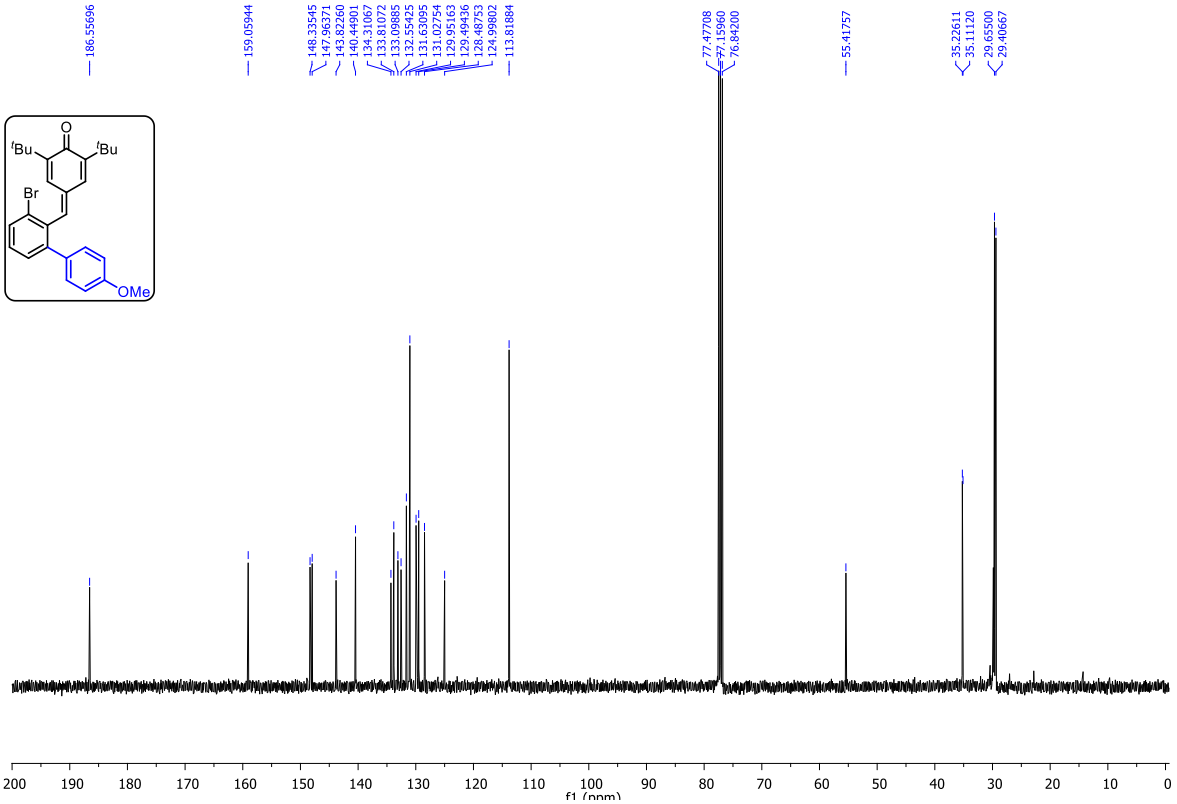


((OTfCu)$_2$.toluene) (10.3 mg, 0.02 mmol) was added to a solution of *p*-quinone methide **84** (150 mg, 0.20 mmol) in toluene at room temperature and the resultant mixture was stirred vigorously at 100 ^{o}C until the *p*-quinone methide was completely consumed (progress was monitored by TLC). After completion of the reaction, solvent was removed under reduced pressure and the residue was directly loaded on a silica gel column and eluted using 5 % EtOAc/hexane mixture to provide pure **85** as a pale yellow solid (30 mg, 20% yield); R_f = 0.1 (5% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (s, 2H), 7.19 (s, 2H), 6.47 (s, 1H), 6.41 (s, 1H), 6.33 (d, *J* = 1.8 Hz, 1H), 6.12 (d, *J* = 2.3 Hz, 2H), 5.22 (s, 1H), 5.08 (s, 1H), 4.18 (dd, *J* = 8.0, 2.0 Hz, 1H), 3.89 (d, *J* = 8.0 Hz, 1H), 3.83 (s, 3H), 3.75 (s, 6H), 3.57 (s, 3H), 1.48 (s, 36H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 158.9, 157.5, 156.0, 153.8, 153.1, 152.1, 152.08, 147.2, 139.1, 135.5, 135.0, 134.4, 131.4, 130.9, 127.6, 126.7, 124.2, 119.7, 116.7, 101.6, 97.7, 96.1, 69.5, 56.3, 55.73, 55.67, 53.6, 49.3, 34.62, 34.58, 30.8, 30.6; FT-IR (neat): 3623, 2947, 1517, 1430, 1266, 1247, 1085 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{48}H_{61}O_6$ $[M+H]^+$: 733.4468; found : 733.4475.

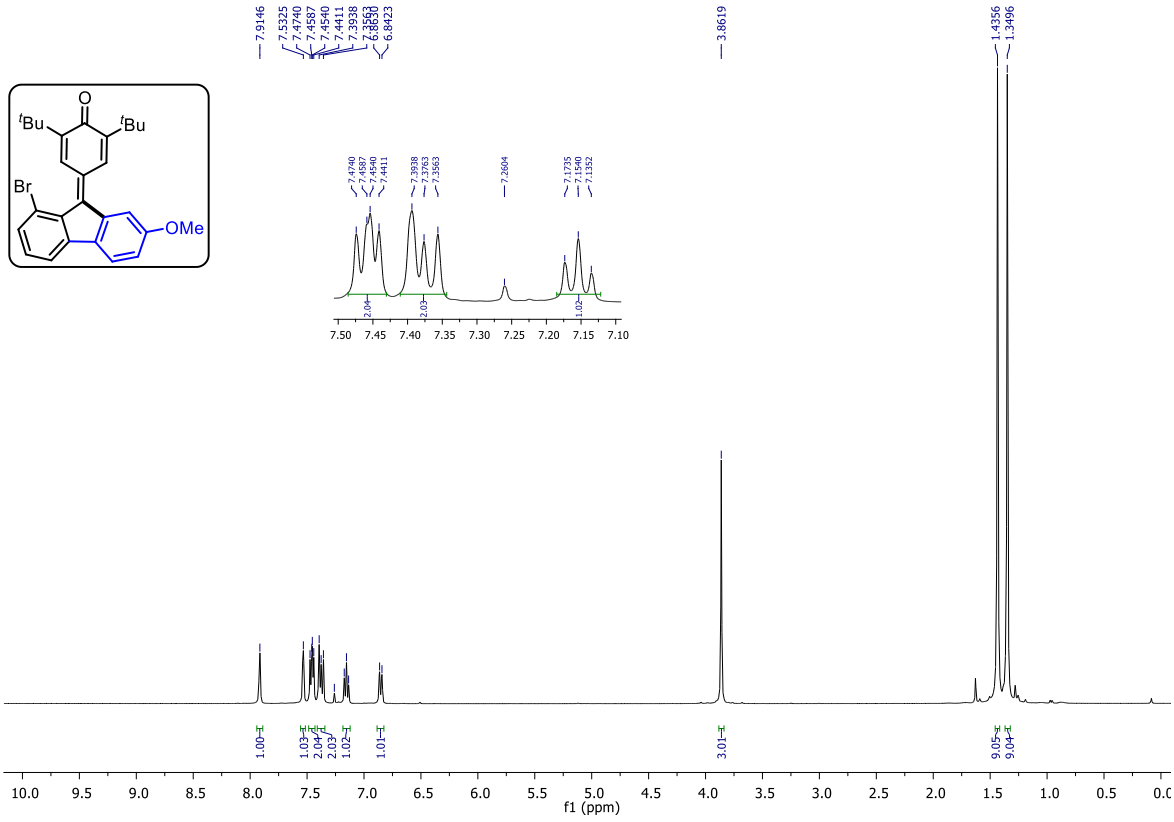
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **54**



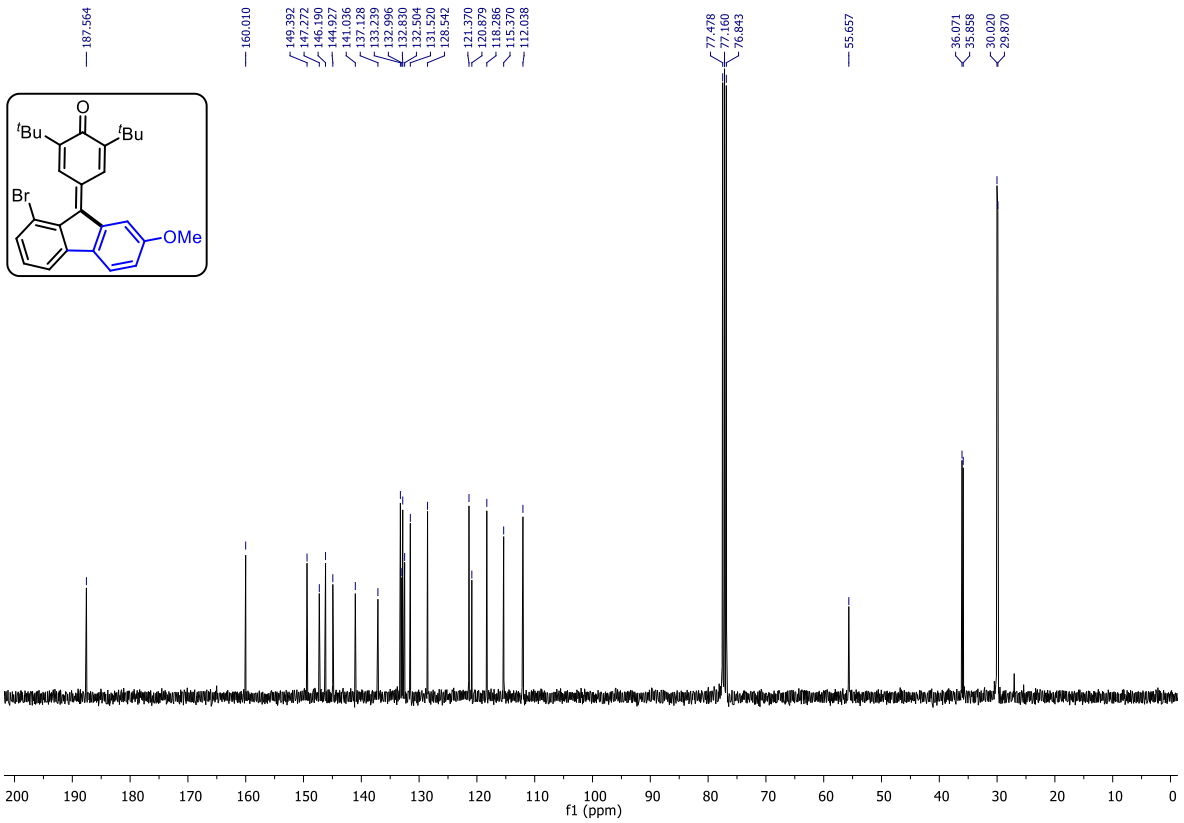
^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) spectrum of compound **54**



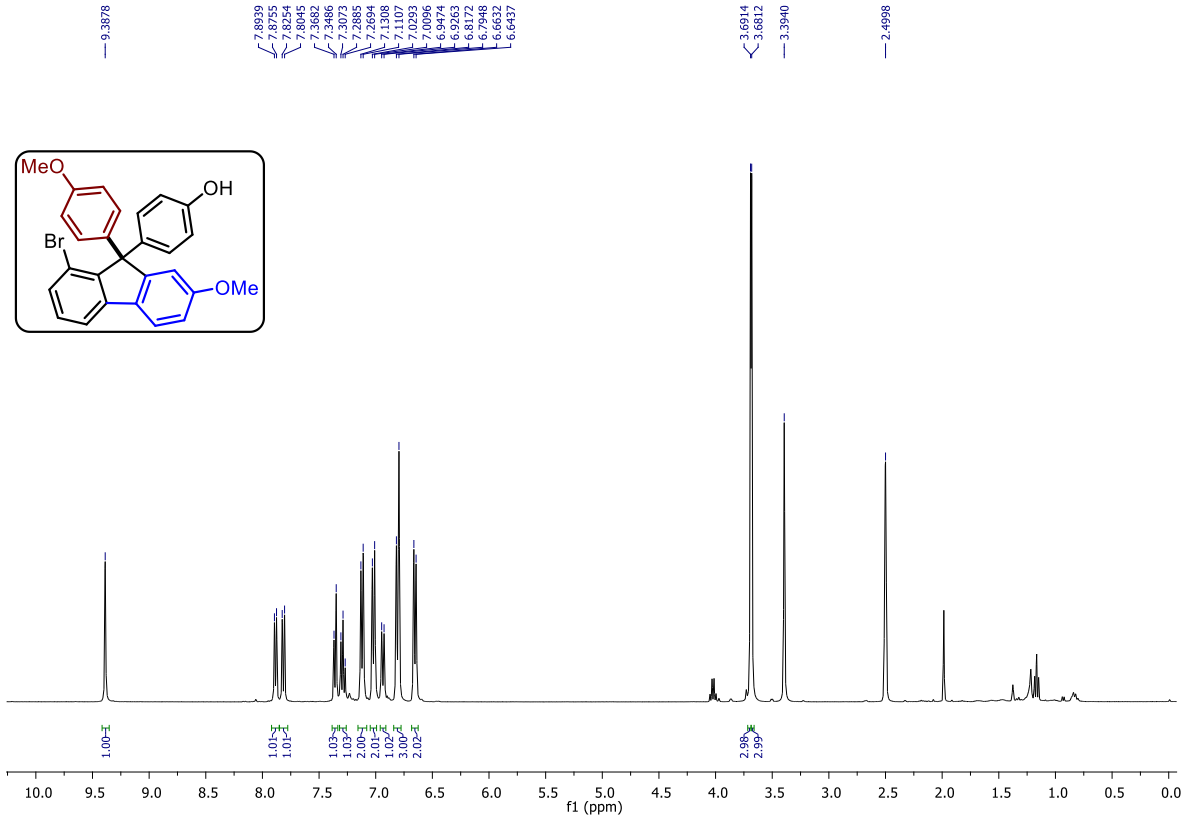
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **56**



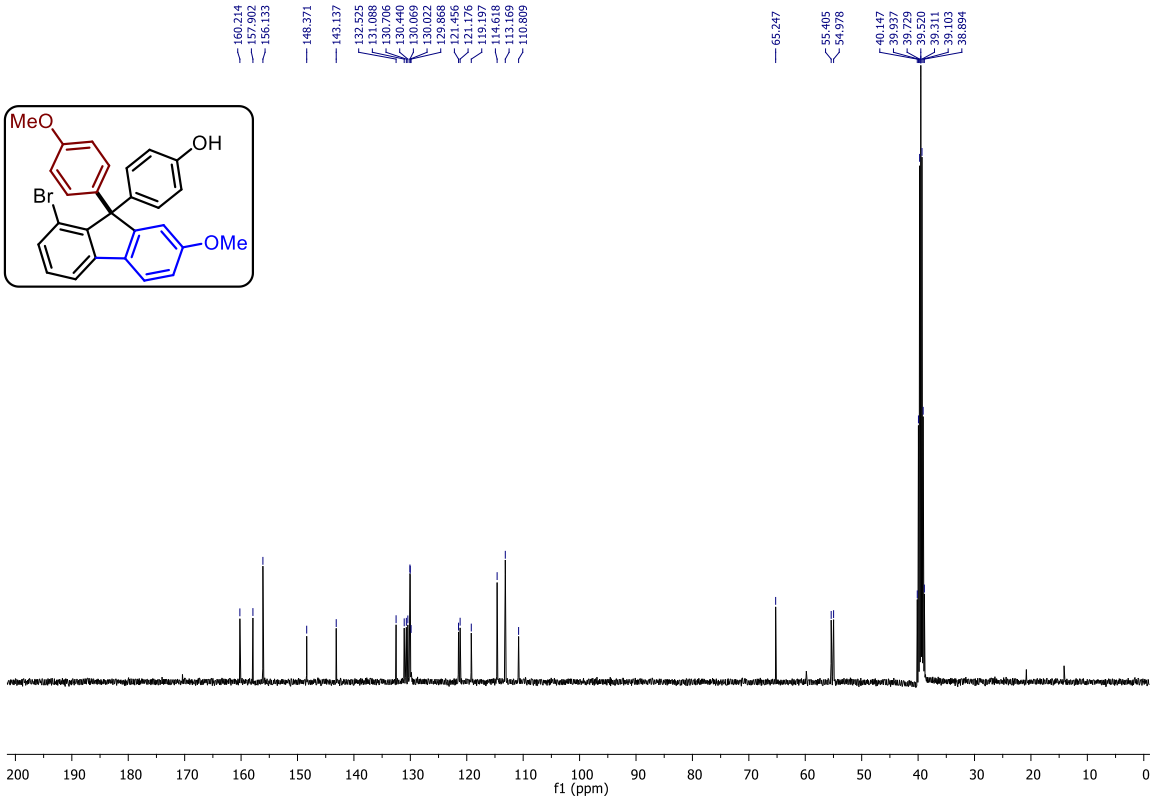
^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) spectrum of compound **56**



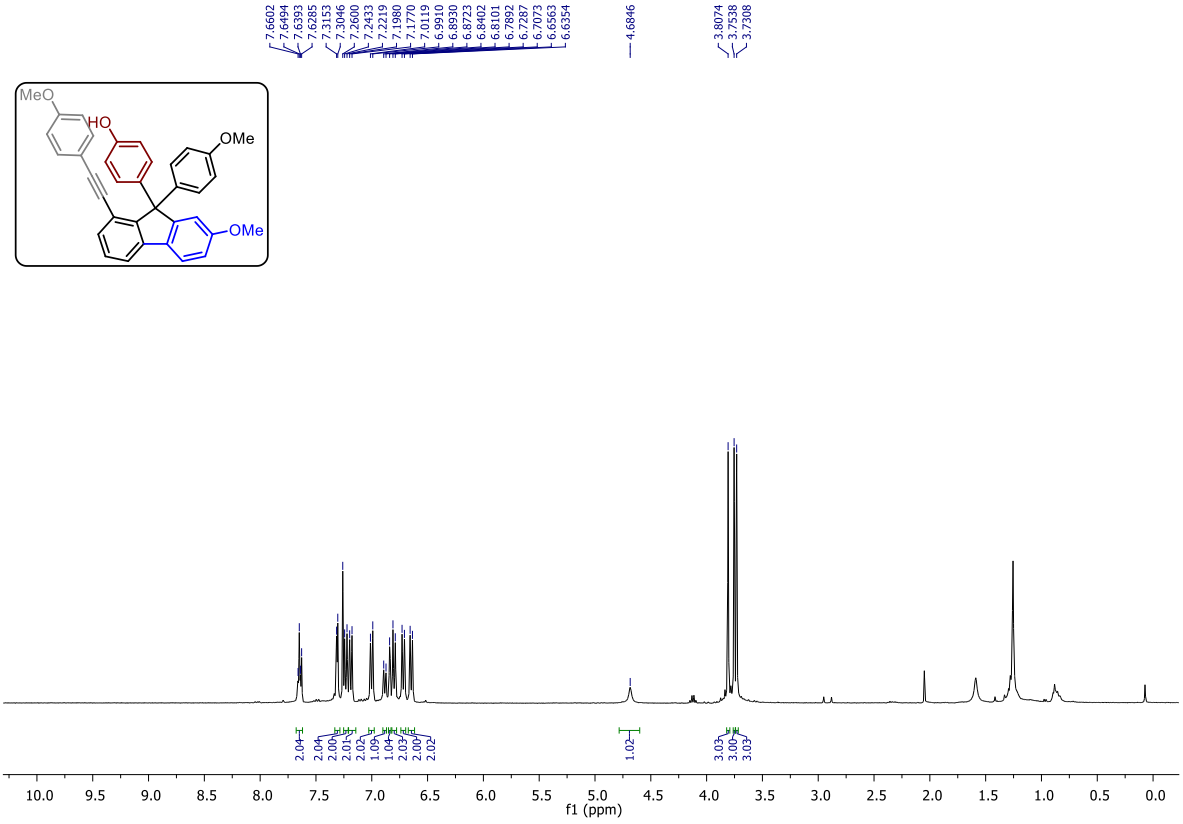
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **58**



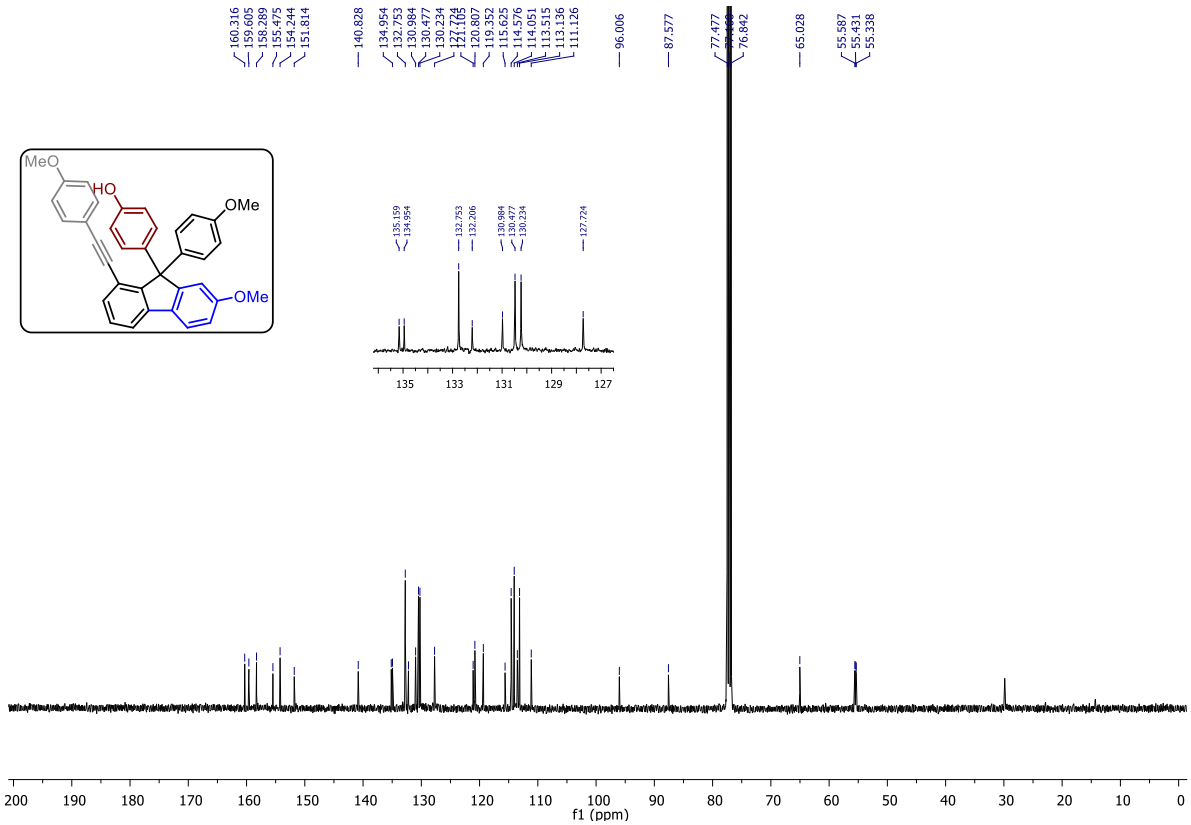
^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) spectrum of compound **58**



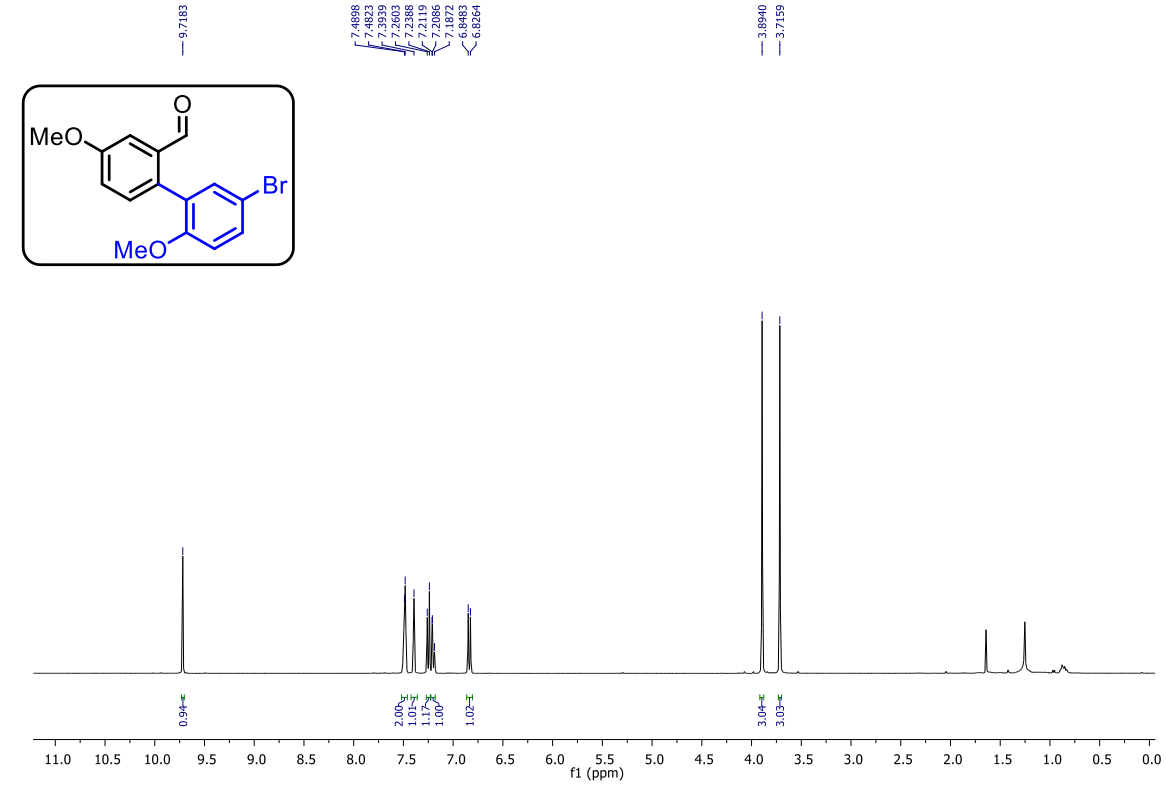
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **24**



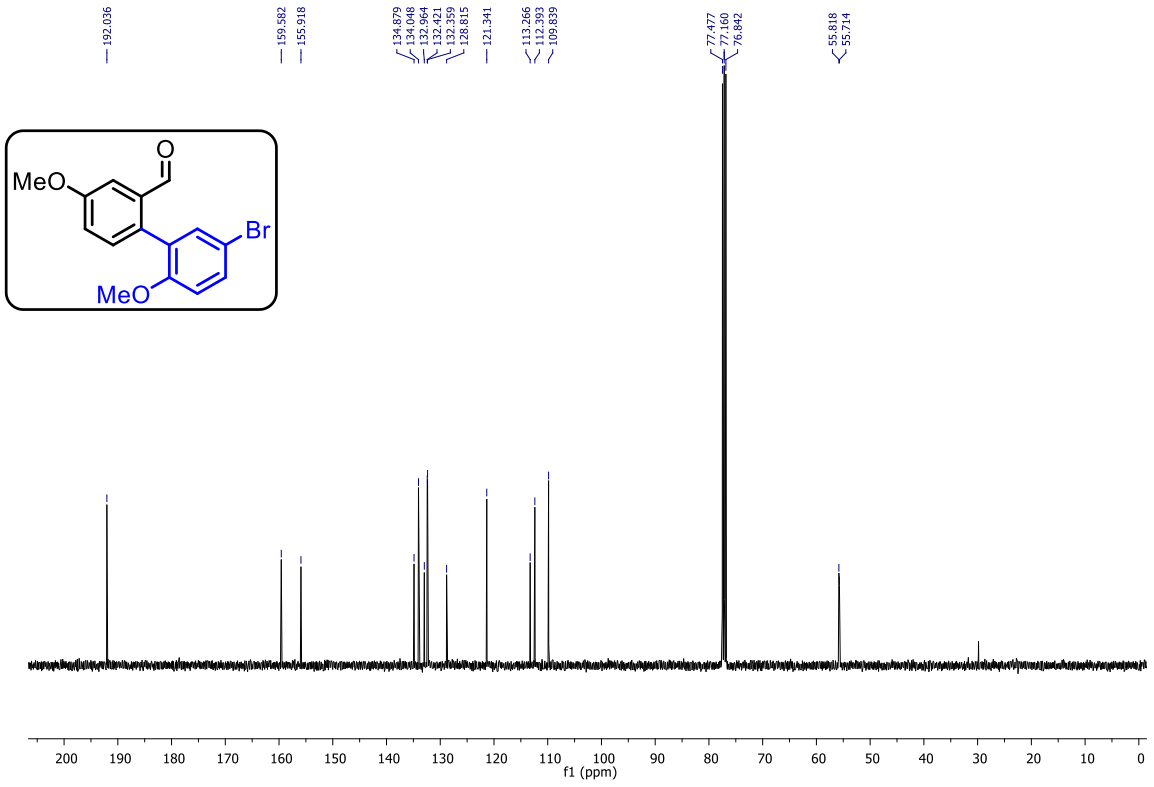
^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) spectrum of compound **24**



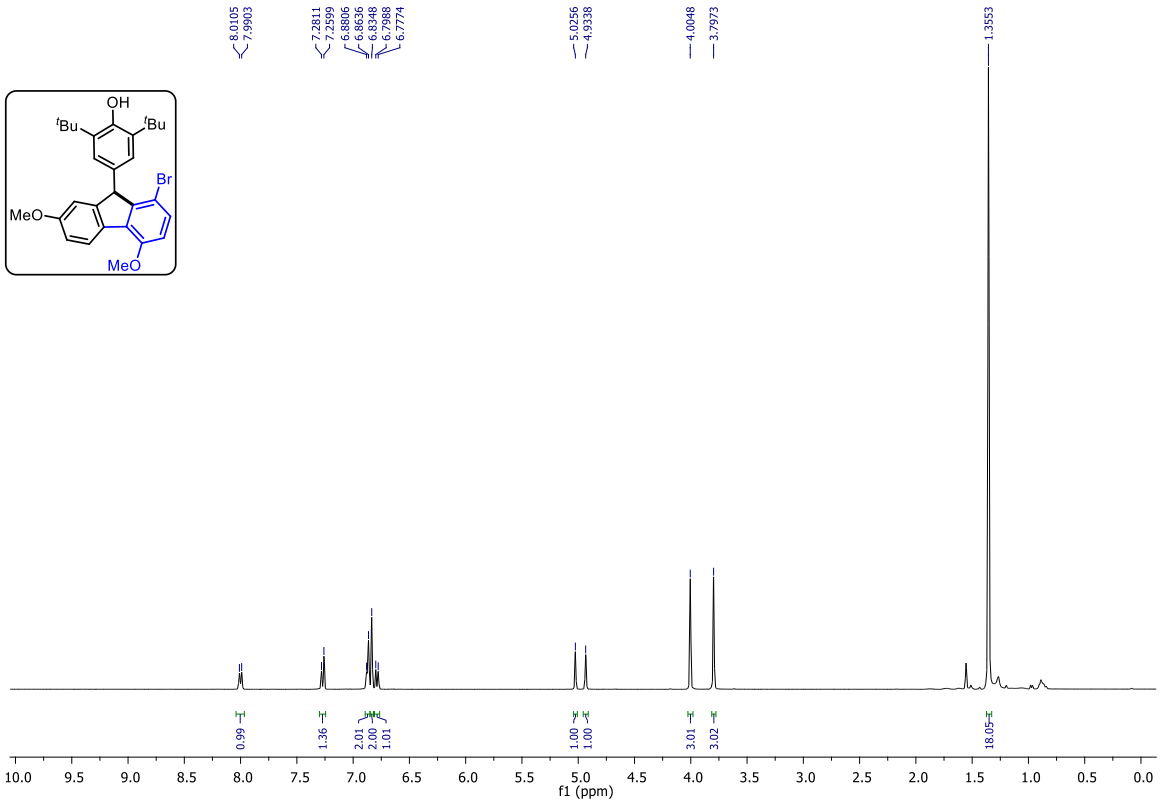
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **60**



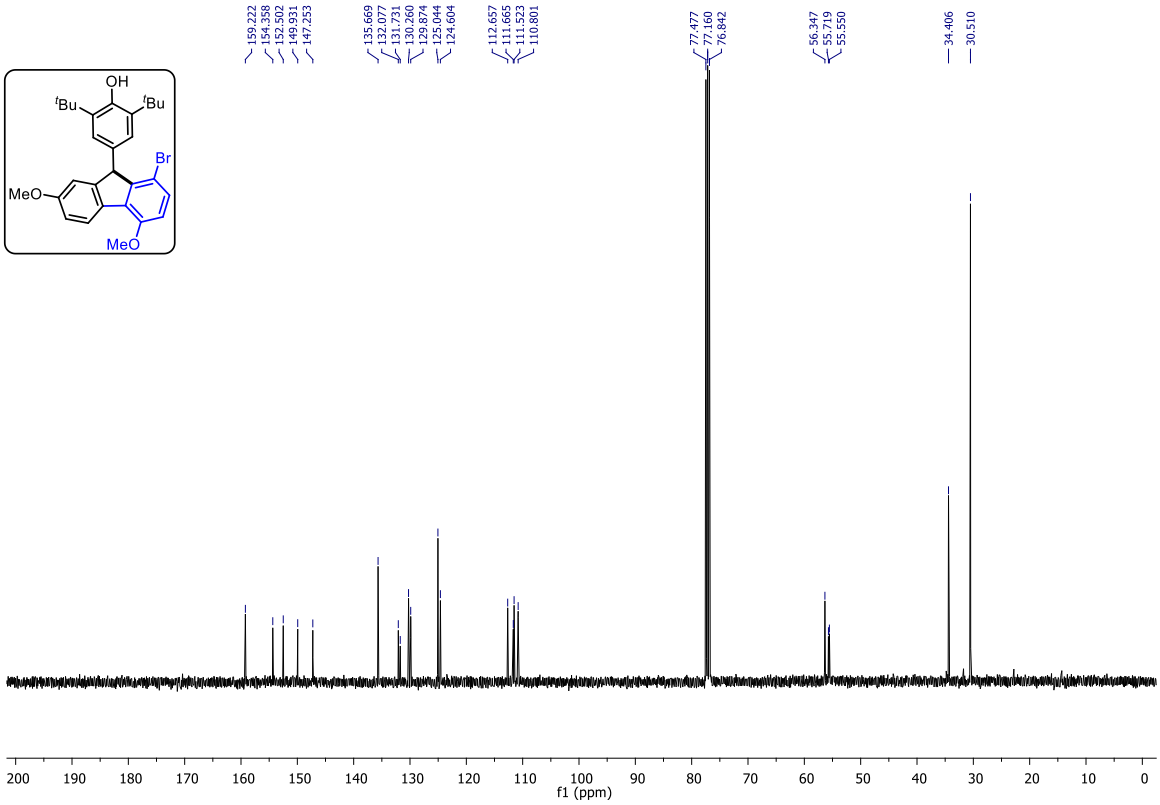
^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) spectrum of compound **60**



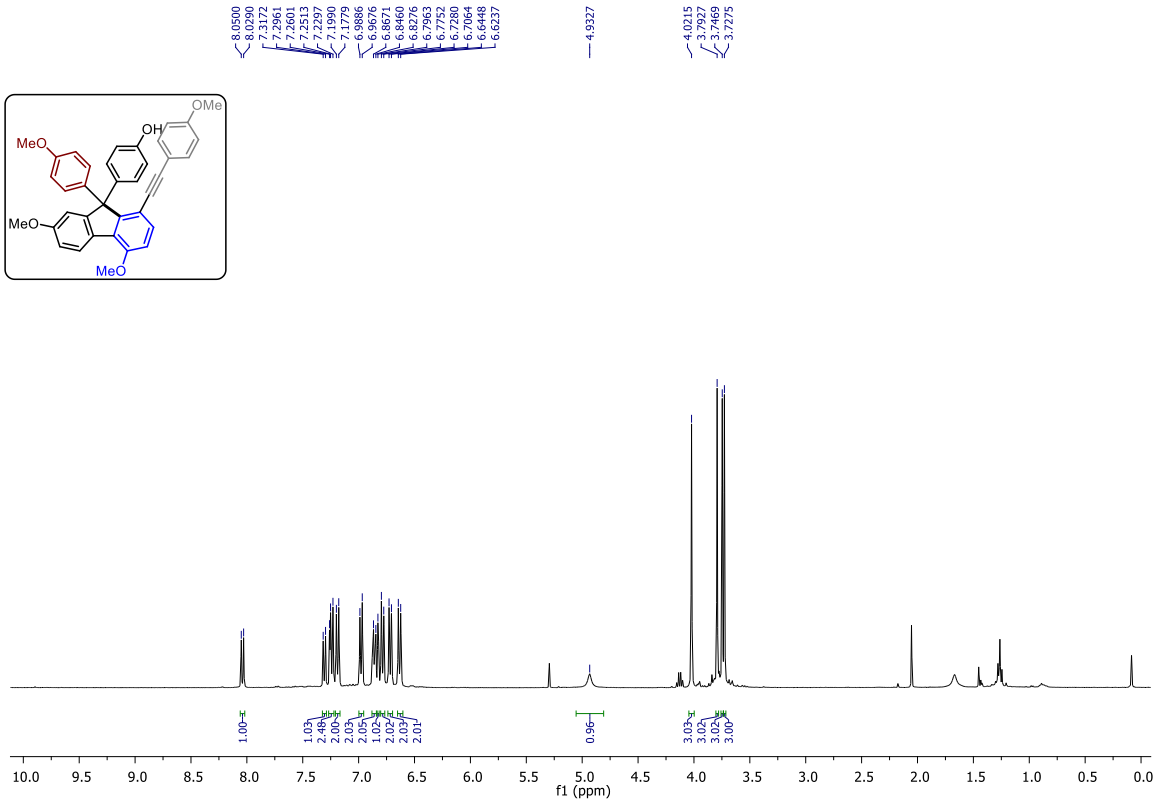
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **62**



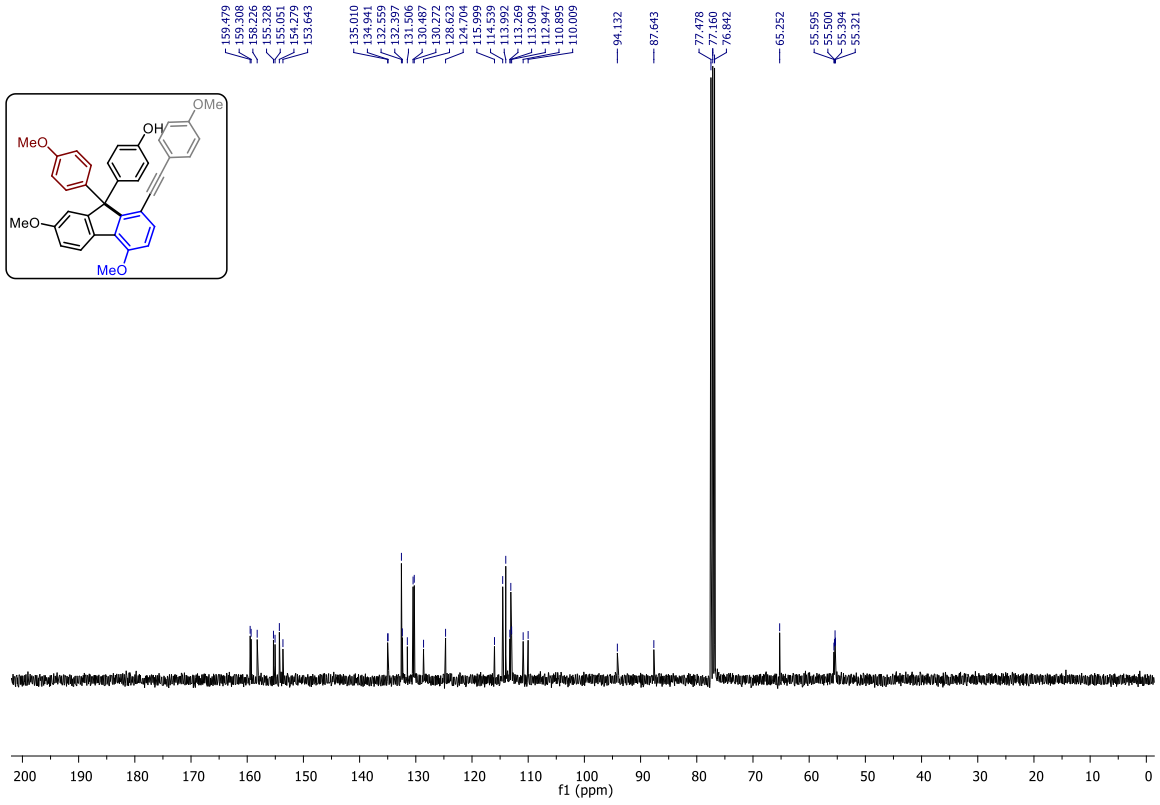
^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) spectrum of compound **62**



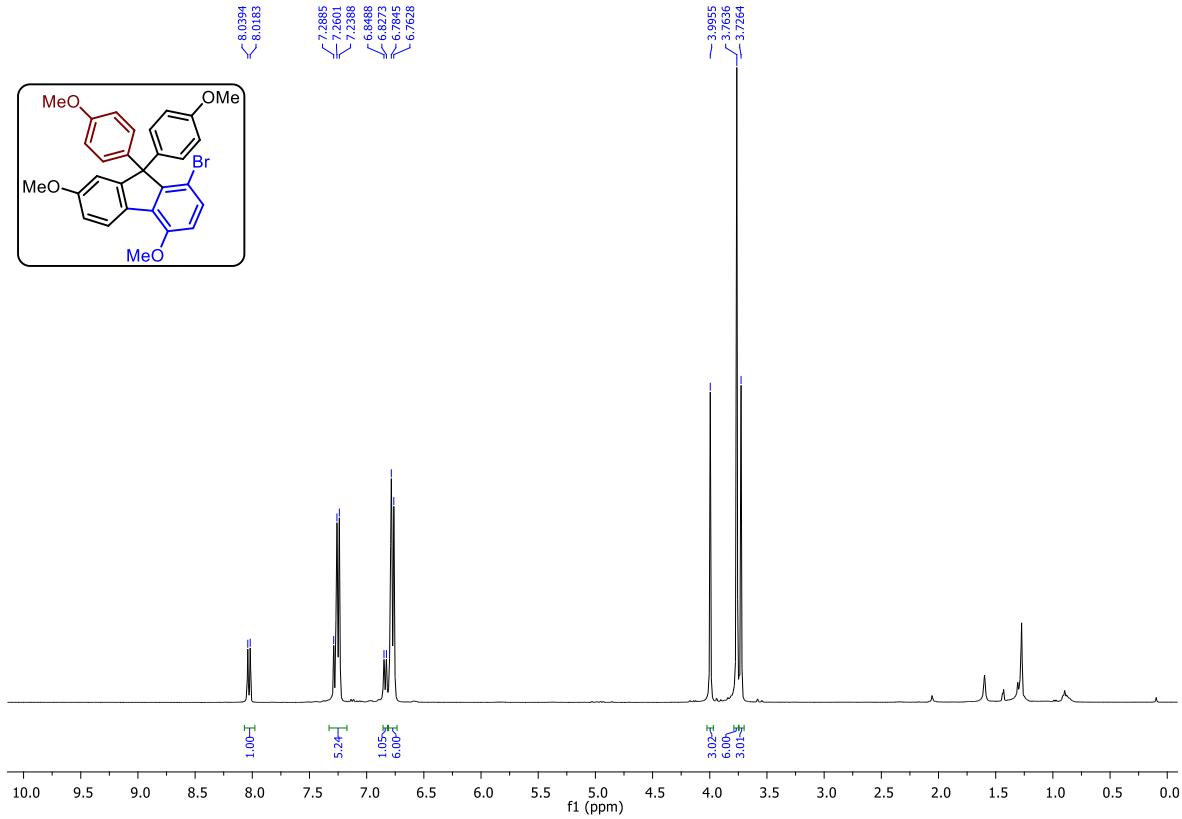
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **66**



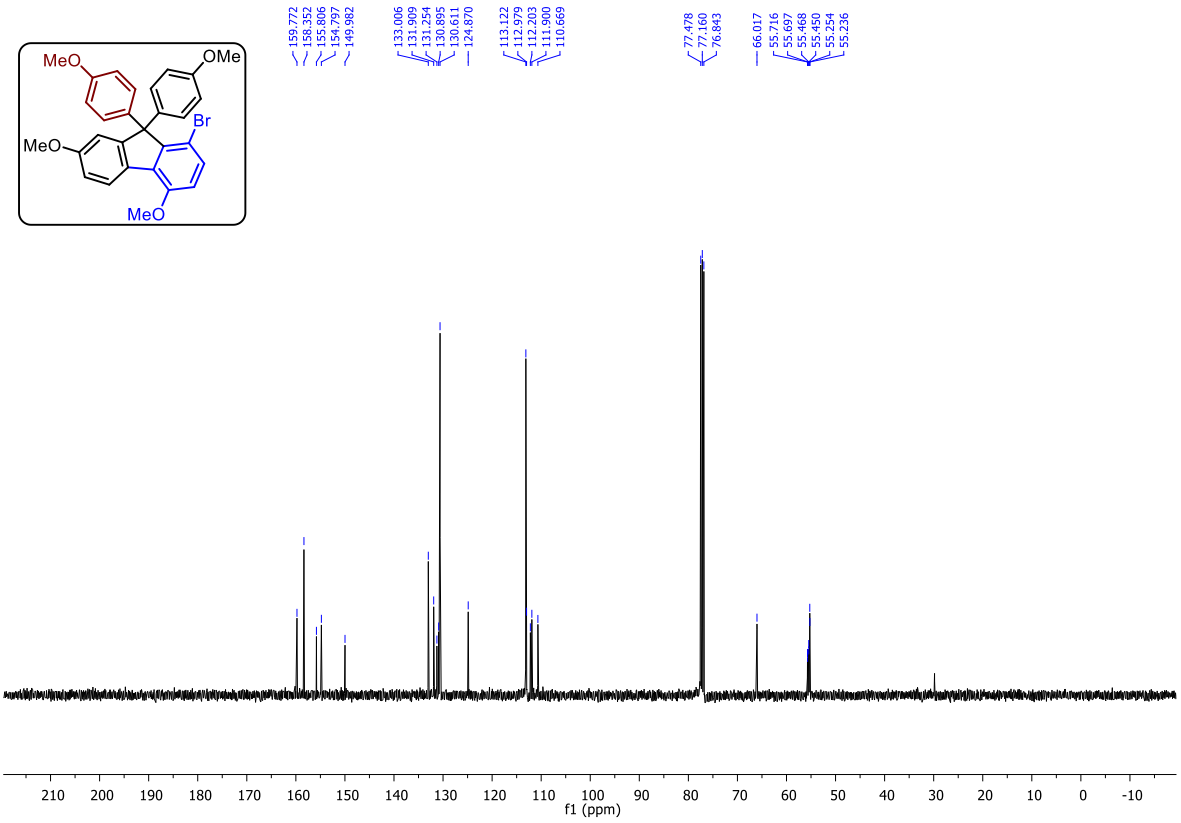
^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) spectrum of compound **66**



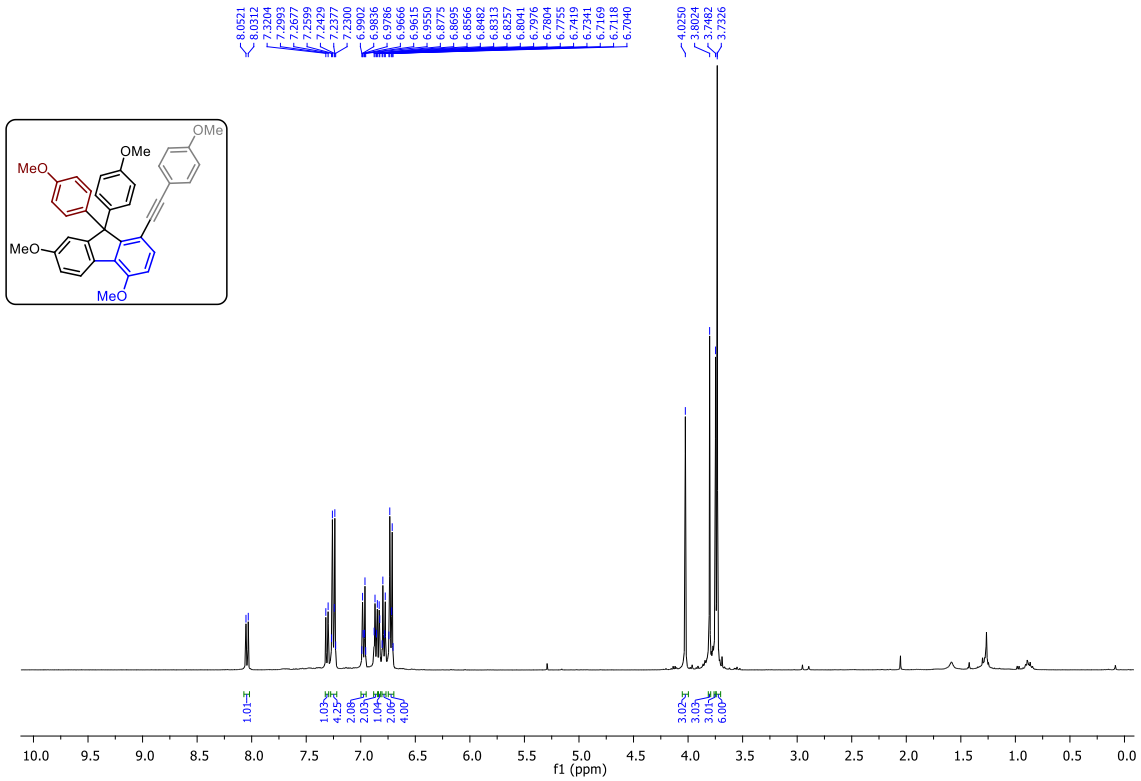
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **67**



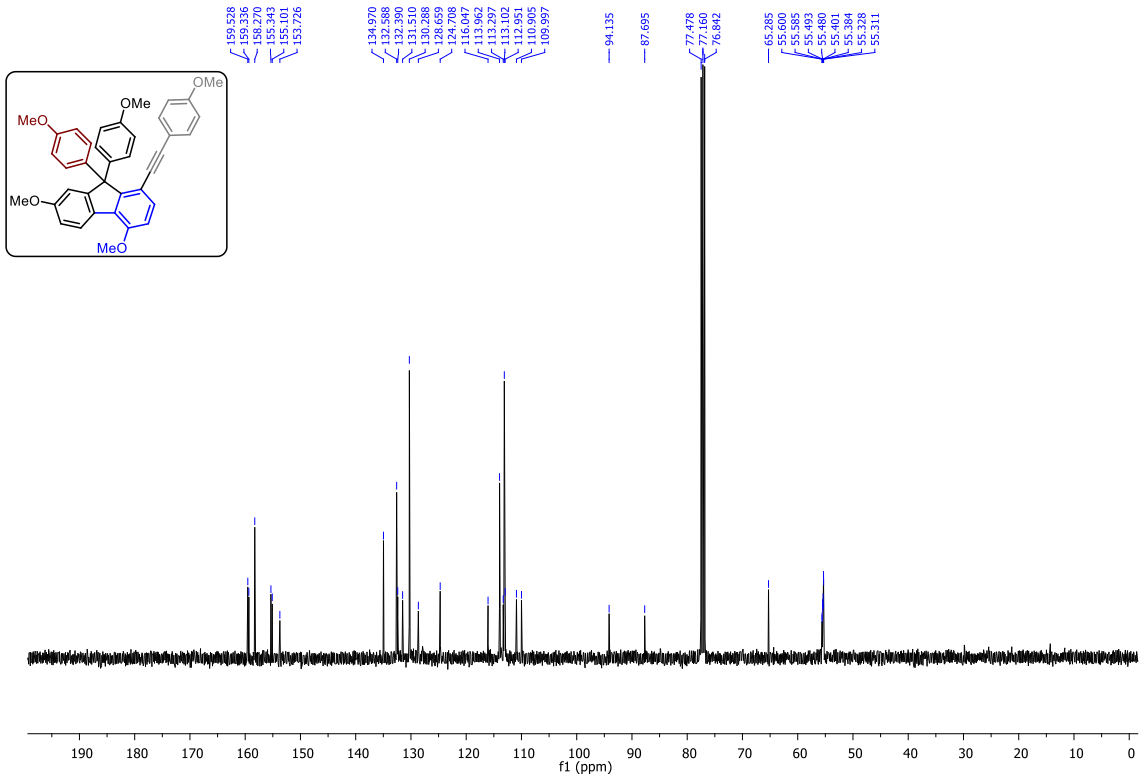
^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) spectrum of compound **67**



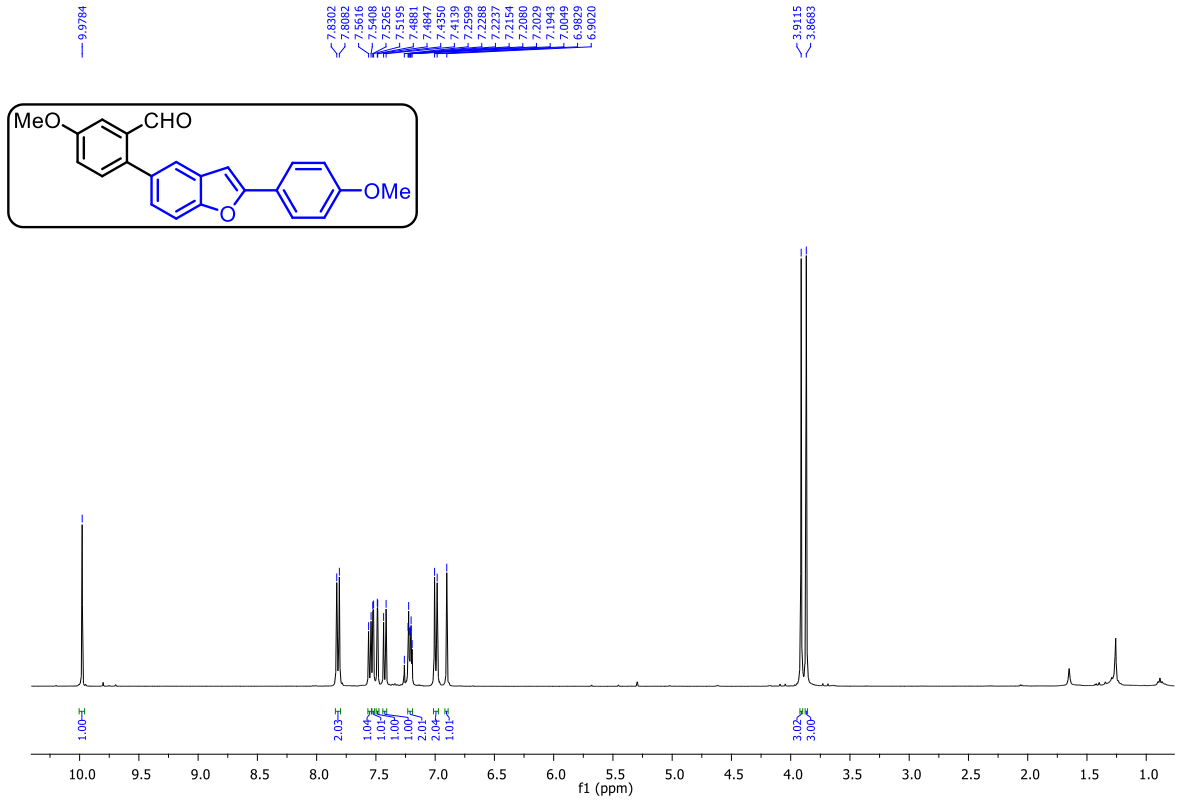
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **68**



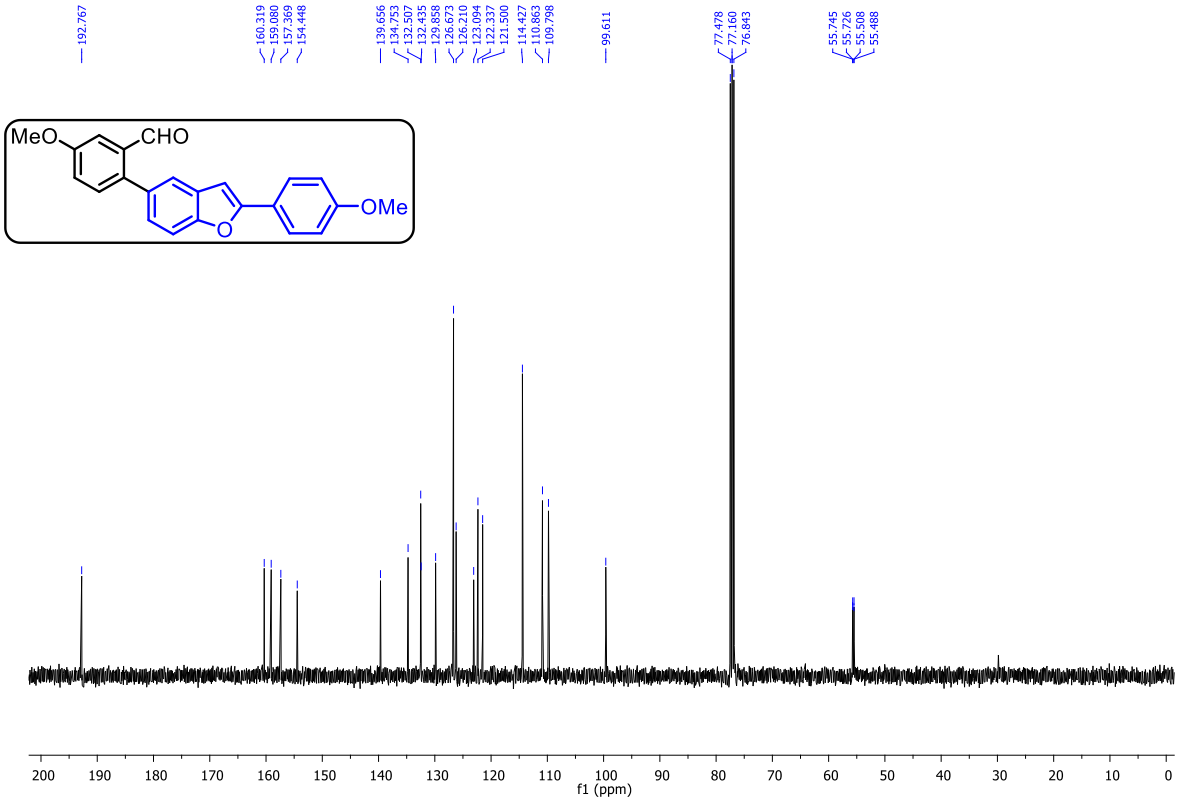
^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) spectrum of compound **68**



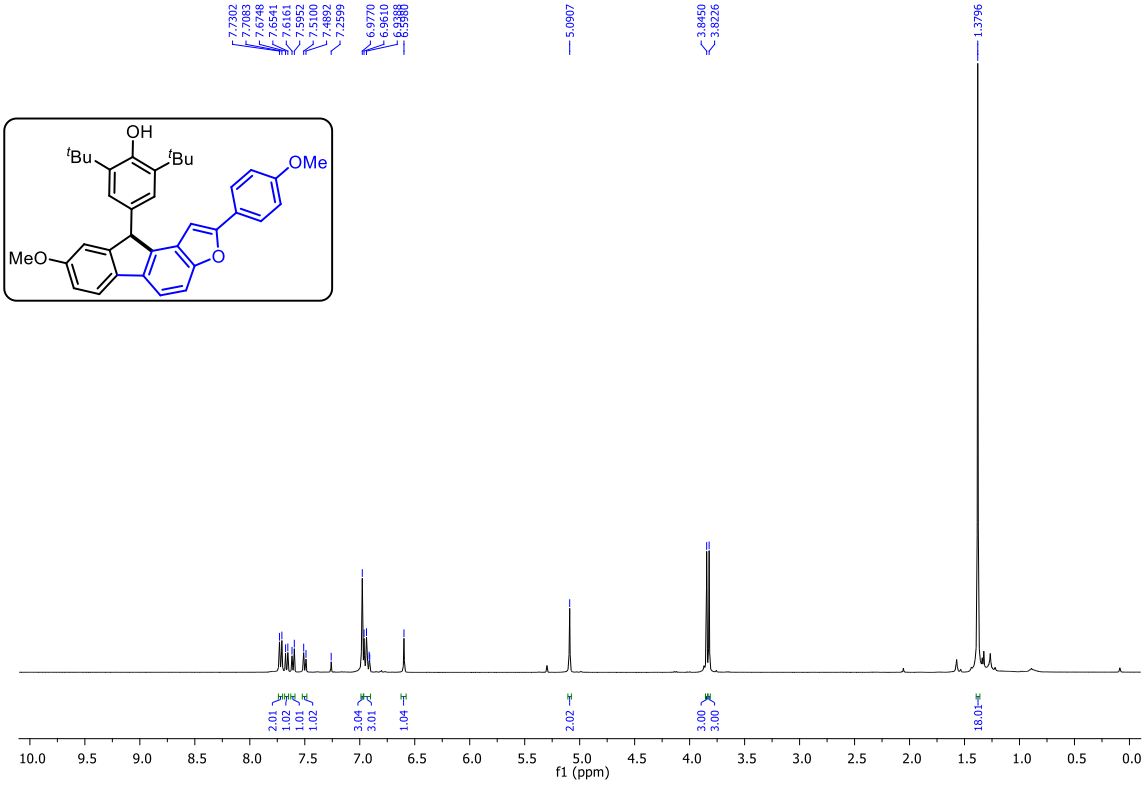
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **69**



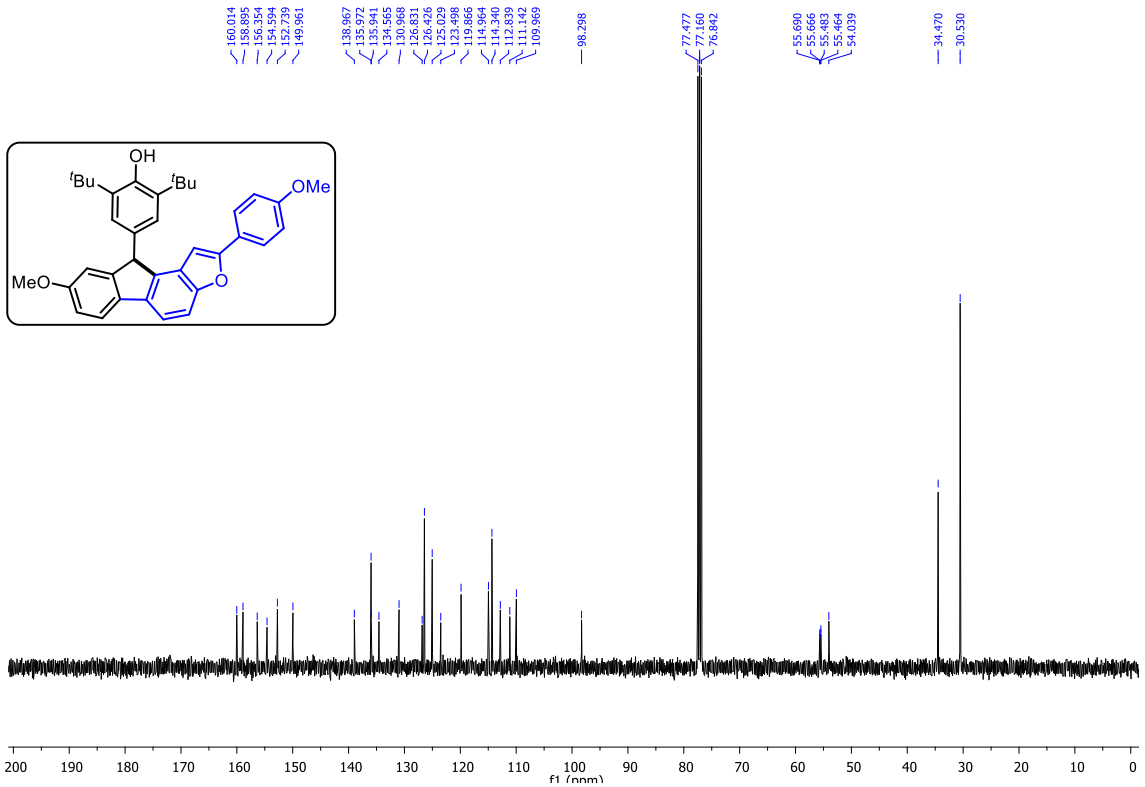
^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) spectrum of compound **69**



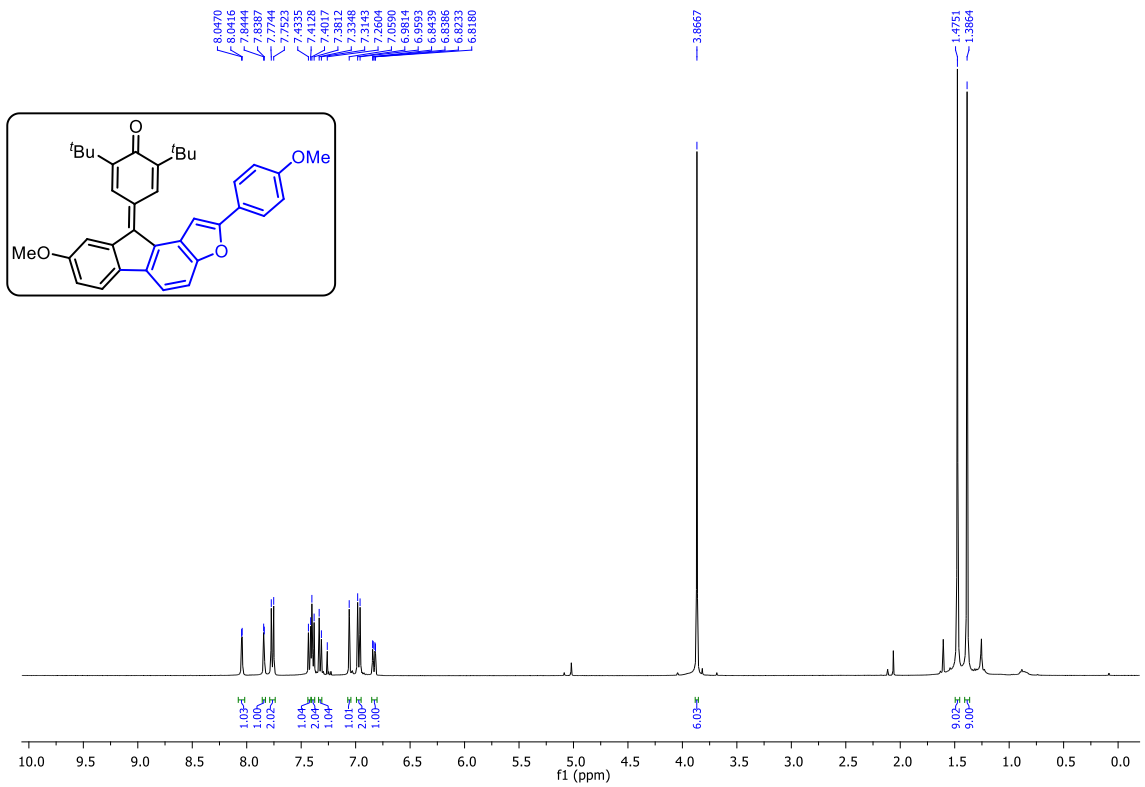
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **73**



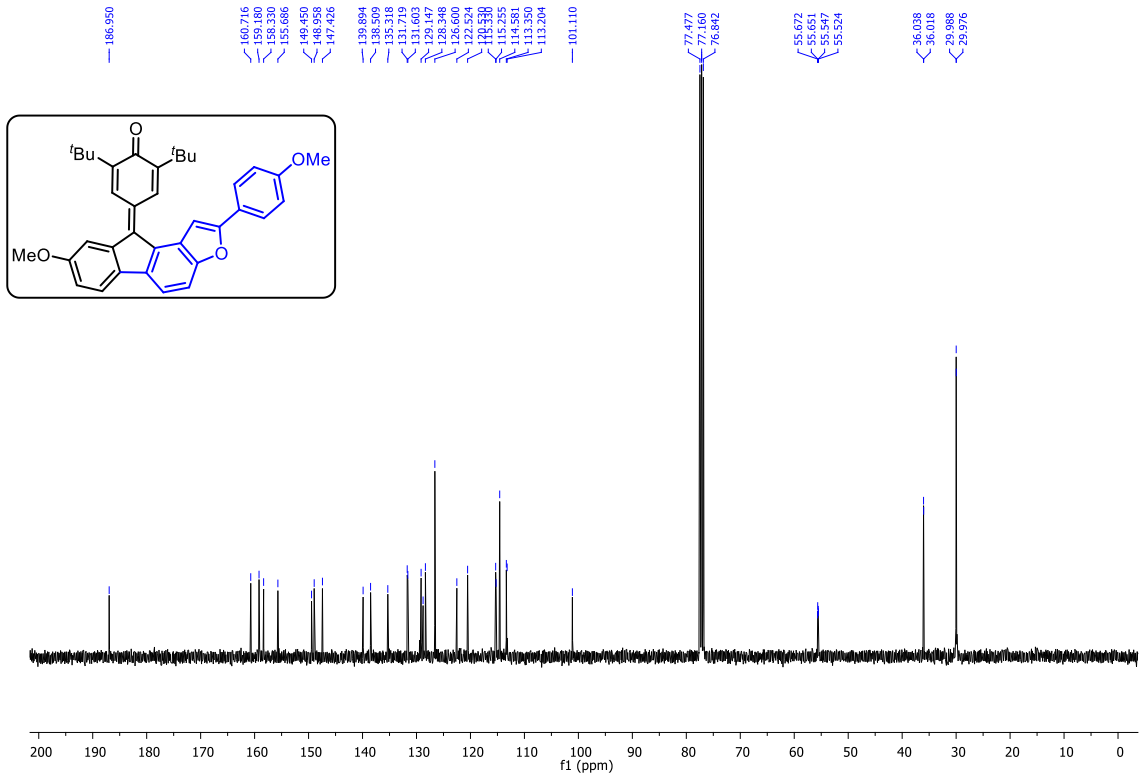
^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) spectrum of compound **73**



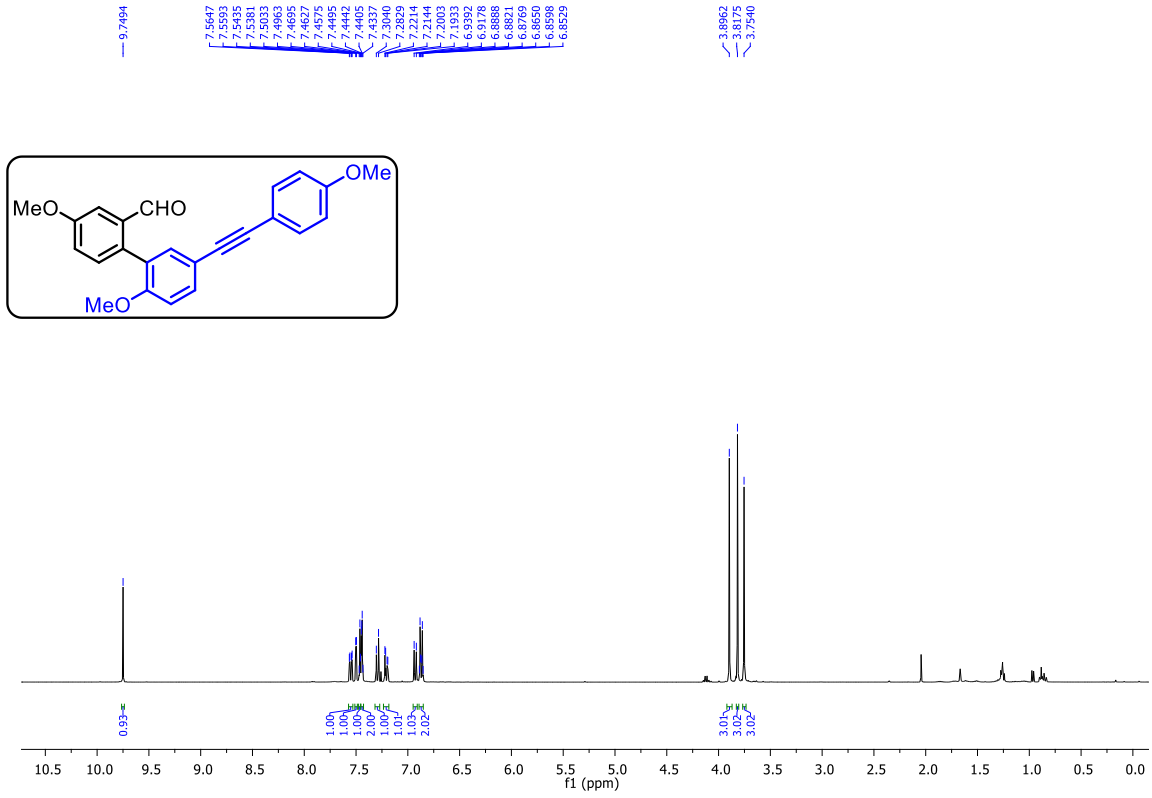
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **75**



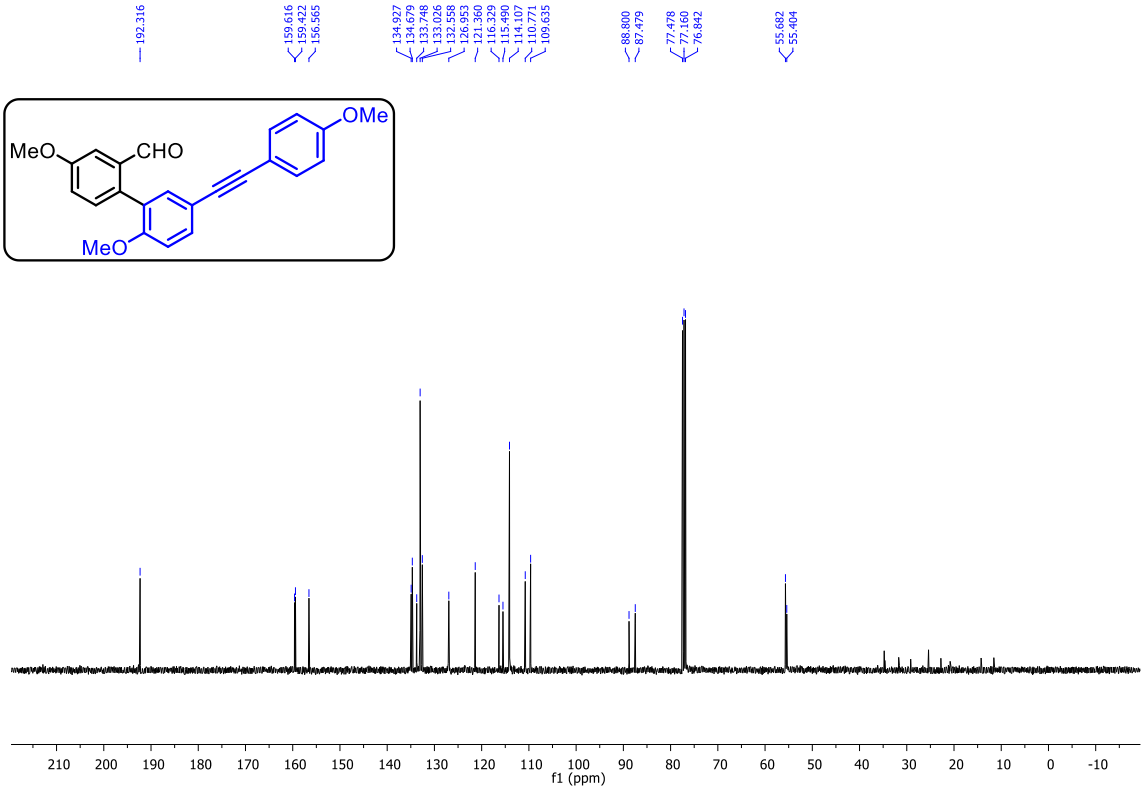
^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) spectrum of compound **75**



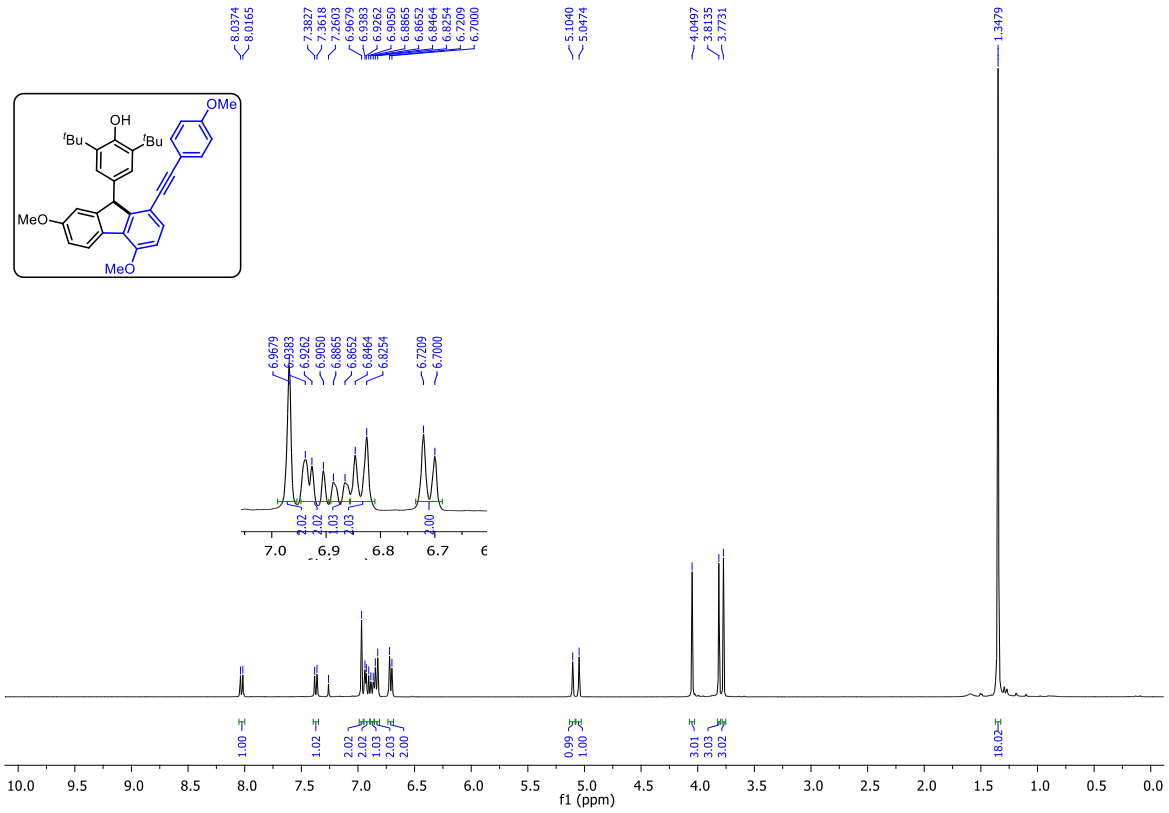
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **77**



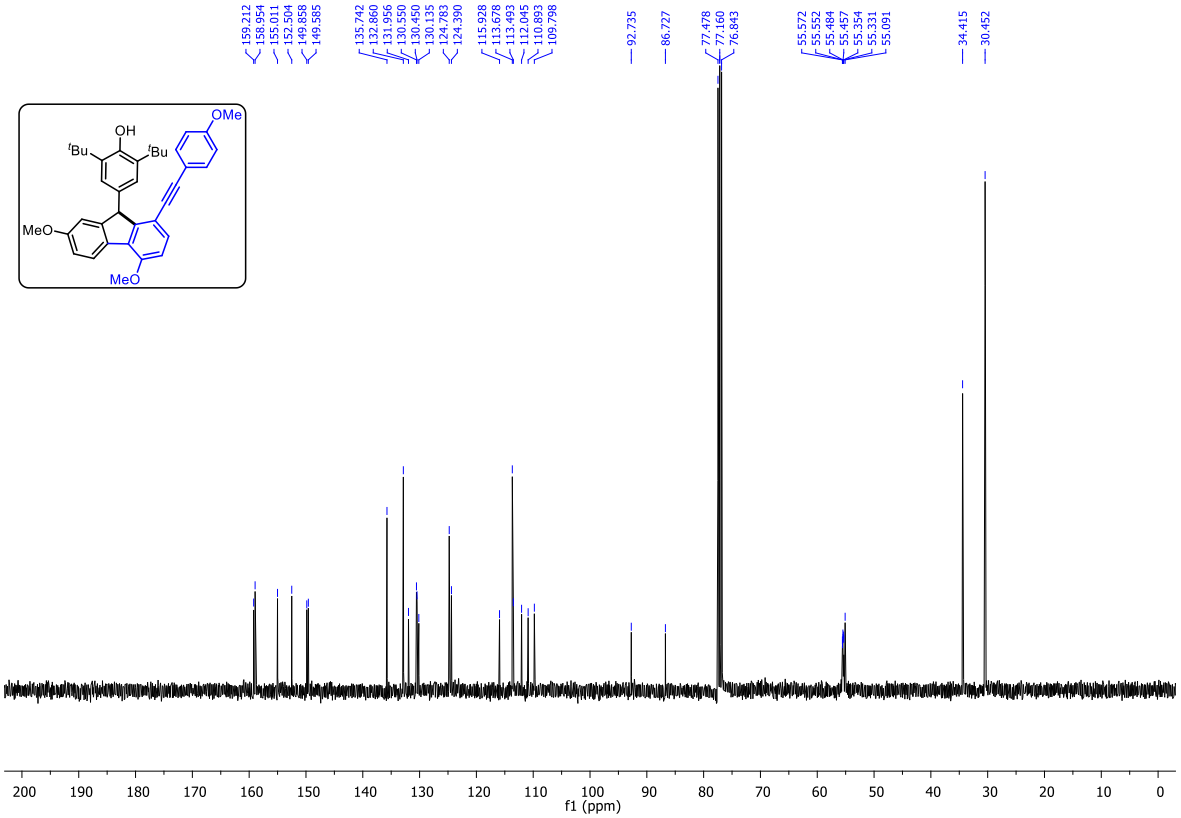
^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) spectrum of compound **77**



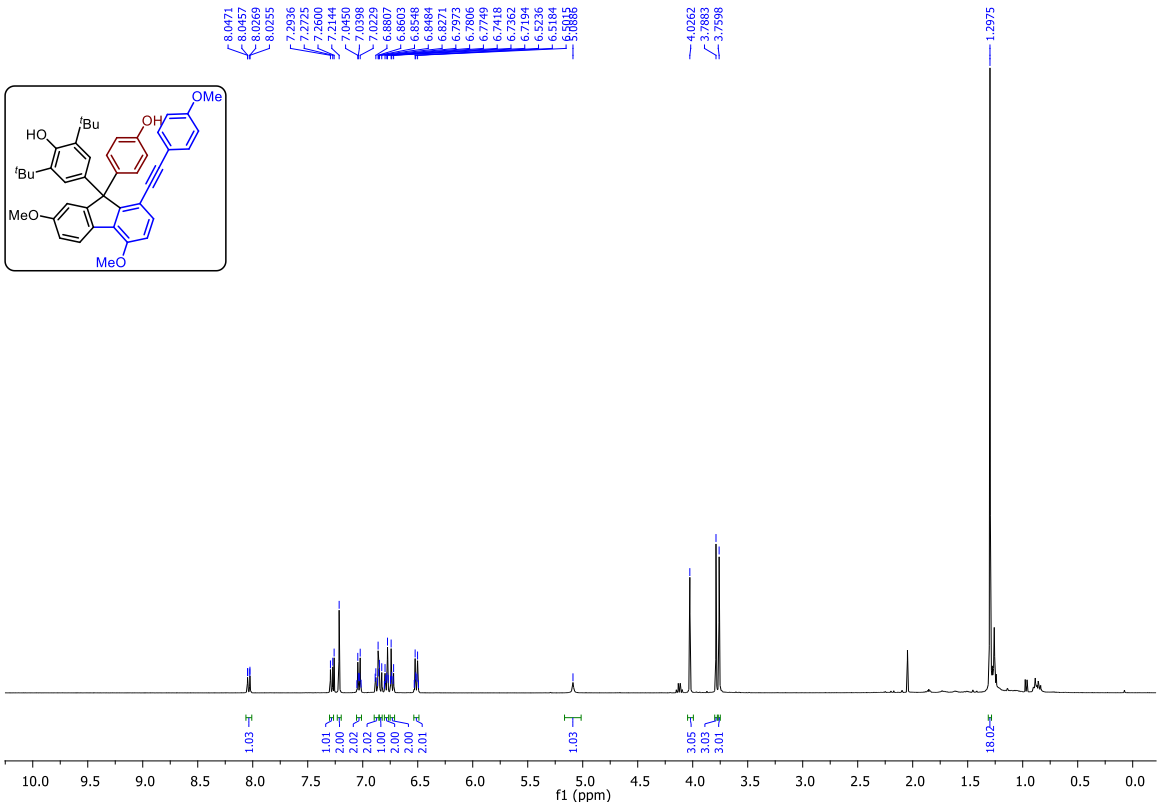
^{1}H {^{1}H} NMR (400 MHz, $CDCl_3$) spectrum of compound **79**



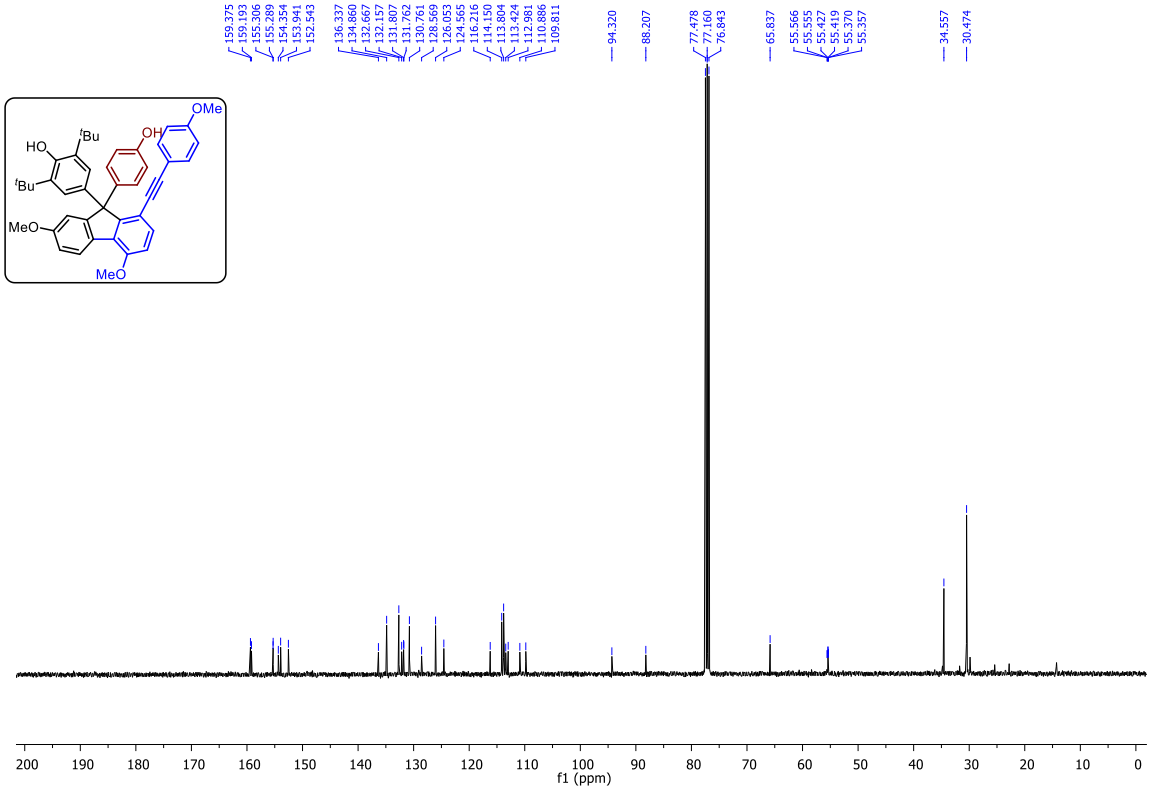
^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) spectrum of compound **79**



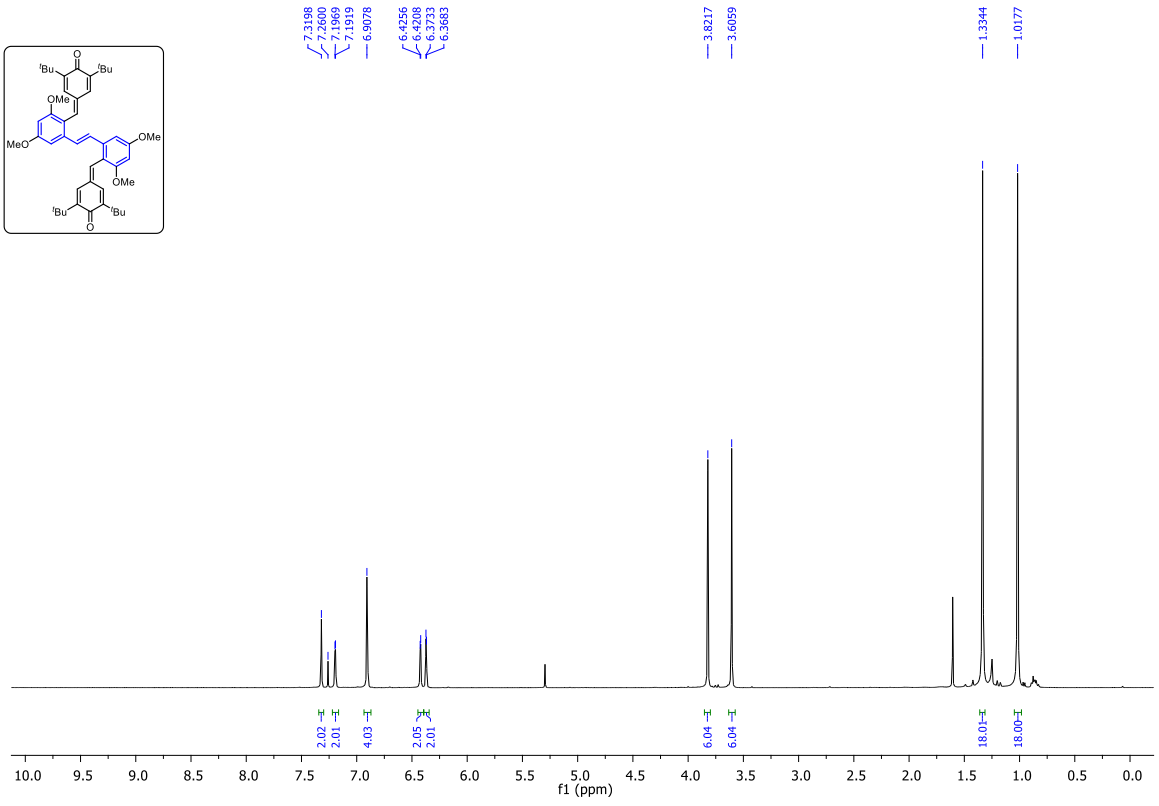
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **80**



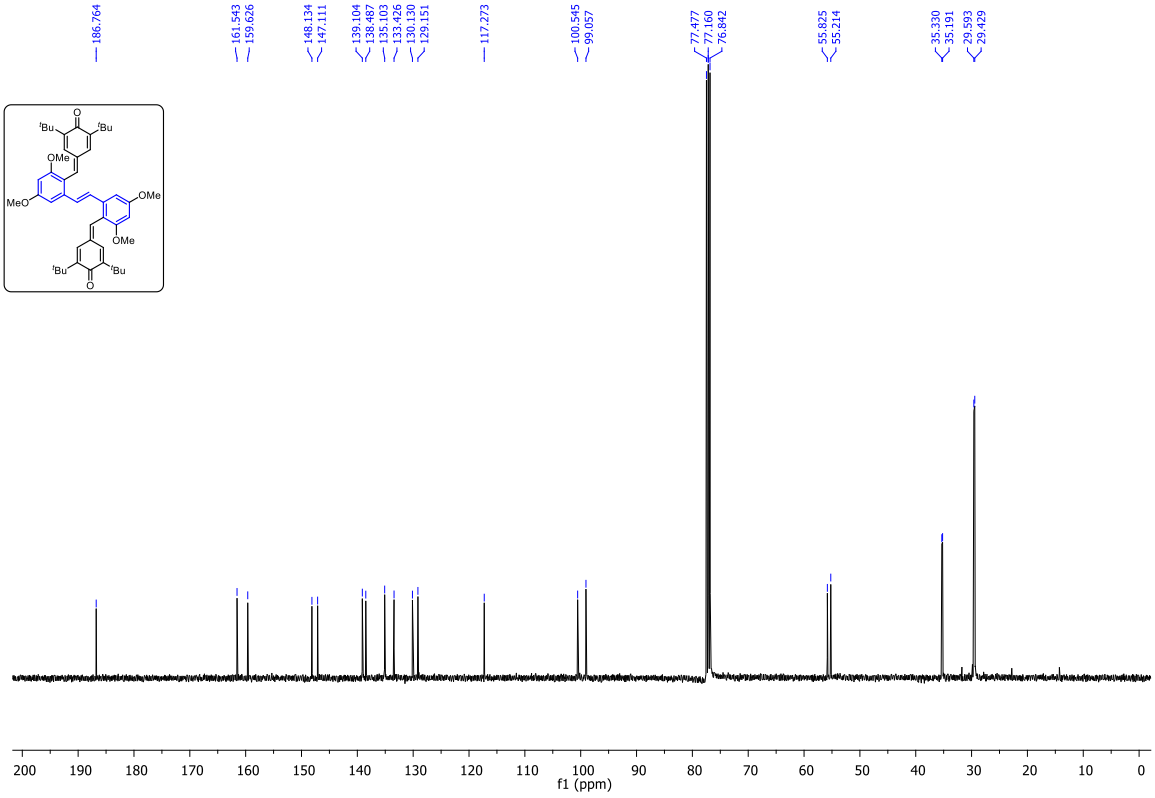
^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) spectrum of compound **80**



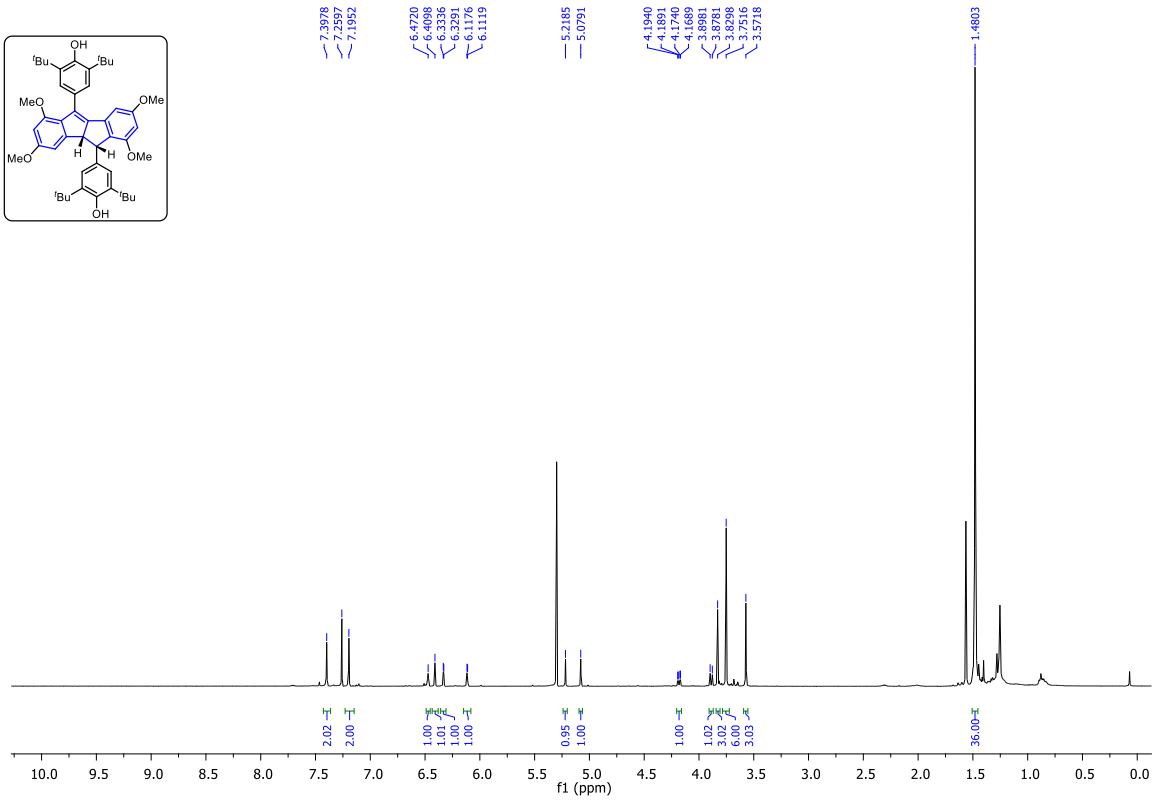
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **84**



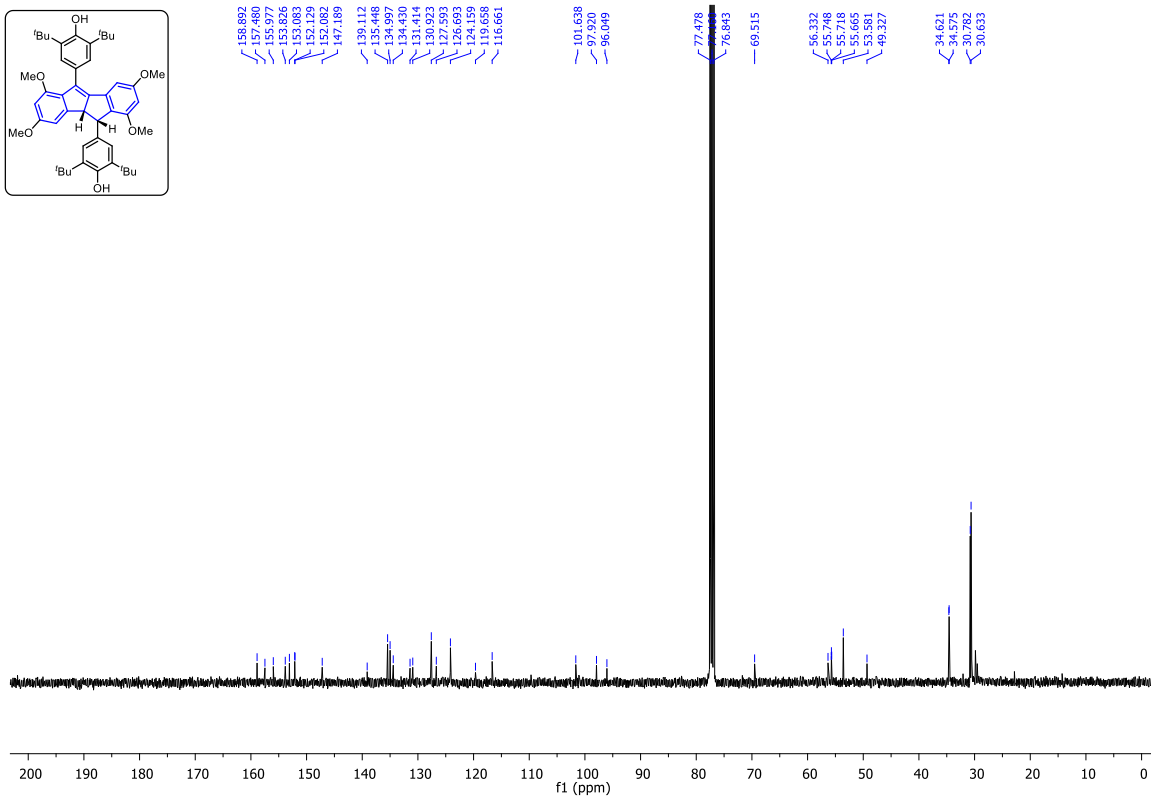
^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) spectrum of compound **84**



^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **85**



^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) spectrum of compound **85**



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CURRICULUM VITAE

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of Science Education and Research Mohali

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Experimental Organic Chemistry Skill:

- Firsthand experience in setting up a synthetic organic chemistry lab and designing projects.
- Good knowledge of organic, organometallic chemistry and organocatalysis (N-heterocyclic carbene and chiral phosphoric acid catalysis).
- Good knowledge and hands-on experience in a continuous-flow microreactor.
- Experience in the isolation, purification and characterization of a wide range of organic compounds by modern chromatographic and spectroscopic (IR, NMR, and HRMS) techniques. Proficiency in handling IR, 400 MHz NMR, and HPLC.
- Excellent practical skills in handling air/moisture sensitive reagents/reactions and milligram/gram scale reactions.
- Excellent knowledge of Windows family operating system with good command in Microsoft Word and PowerPoint, software packages including ChemDraw, expertise in E-notebook writing, Sci-Finder usage for searching literature/patents and handling NMR softwares (Top Spin, Mnova and spin works).
- Guided undergraduate students and research associated extensively and mentored them in formulating their projects.

Research Expertise: Natural product synthesis, Organometallic Chemistry, and Continuous flow chemistry.

Education and Research Training

- **2016 –: Ph. D. in Synthetic Organic Chemistry**, Department of Chemical Sciences, Indian Institute of Science Education and Research (IISER) Mohali, 140306, Punjab, India.

Thesis Title: *"Synthesis of Substituted Fluorene Derivatives and Related Natural Products from para-Quinone Methides"*

- **Ph.D. Thesis Supervisor:** Prof. R. Vijaya Anand

- **2013 – 2015: M.Sc. in Chemistry** (Dr. Babasaheb Ambedkar Marathwada University) Aurangabad, 431004, India, with CGPA **7.6**.
- **2011 – 2014: Bachelor of Science,** R. B. Attal. Arts, Science & Commerce College, Georai (B.A.M.U. Aurangabad), India, with **First Class (72.25%)**.

Awards/Scloarships and Grants

- Awarded **Senior Research Fellowship** and **Junior Research Fellowship** (MHRD Fellowship) from the Indian Institute of Science Education and Research (IISER) Mohali from August 2016 to July 2021.
- Qualified **CSIR-JRF** with all India 36th rank in **CSIR-UGC NET** (Council of Scientific and Industrial Research-University Grants Commission National Eligibility Test) examination held on December 2015.
- Qualified **CSIR-NET** with all India 88th rank in **CSIR-UGC NET** (Council of Scientific and Industrial Research-University Grants Commission National Eligibility Test) examination held on June 2016.
- Qualified State Eligibility Test (SET) for Assistant Professorship (Conducted by Savitribai Phule University, Maharashtra) held on May 2016.

List of Publications

1) "*1,6-Hydroolefination and Cascade Cyclization of p-Quinone Methides with Unactivated Olefins: Total Synthesis of (±)-Isopaucifloral F*." (‡These authors contributed equally to this work). **Pankhade, Y. A**.‡; Jadhav, A. S.‡; Hazra, R.; Anand, R. V. *J. Org. Chem.* **2018,** *83*, 10107.

2) "*TfOH-Catalyzed Intramolecular Annulation of 2-(Aryl)-Phenyl-Substituted p-Quinone Methides under Continuous Flow: Total Syntheses of Selaginpulvilin I and Isoselagintamarlin A*." **Pankhade, Y. A**.; Pandey, R.; Fatma, S.; Ahmad, F; Anand, R. V. *J. Org. Chem.* **2022,** *87*, 3363.

3) *"Construction of Oxygen- and Nitrogen-based Heterocycles from p-Quinone Methides"* **Pankhade, Y. A.**;[#] Singh, G.;[#] Pandey, R.;[#] Fatma, S.;[#] Anand, R. V. *Chem. Rec.* **2021**, *21*, 4150. [#]contributed equally.

4) *"Silver Catalyzed Electrophilic Cascade Cyclization Reaction of 2-Arylalkenes With p-QMs: Access to 9,9-disubstituted fluorenes"* **Pankhade, Y. A.**;[‡] Wadhave, A. K.;[‡] Ranga, P. K.; Anand, R. V. [‡]These authors contributed equally to this work (Manuscript under preparation).

5) "*A Tandem One-pot Approach to Access 1,2,3-Triazole-fused Isoindolines through Cu-Catalyzed 1,6-Conjugate Addition of Me_3SiN_3 to p-Quinone Methides followed by Intramolecular Click Cycloaddition*." Jadhav, A. S.; **Pankhade, Y. A.**; Anand, R. V. *J. Org. Chem.* **2018**, *83*,10107.

6) "*Exploring Gold Catalysis in 1,6-Conjugate Addition/Domino Electrophilic Cyclization Cascade: Synthesis of Cyclohepta[b]indoles*." Jadhav, A. S.; **Pankhade, Y. A.**; Anand, R. V. *J. Org. Chem.* **2018**, *83*, 8615.

7) "*Pd(II)-catalyzed annulation of terminal alkynes with 2-pyridinyl-substituted p-quinone methides: direct access to indolizines*." Ahmad, F.; Ranga, P. K.; **Pankhade, Y. A.**; Fatma, S.; Gouda, A.; Anand. R. V. *Chem. Commun.* **2022**, *58*, 13238.

Conferences/Symposia

- Presented a poster on "*Silver Catalyzed Elecrophilic Cascade Cyclization Reaction of o-Alkynylated p-QMs With Alkenes: Access to Dihydrobenzo[a]fluorenes*" **Pankhade, Y. A.**; Anand, R. V. in the *International Conference On Advancing Green Chemistry: Building A Sustainable Tomorrow* held at University of Delhi, India (3-4th October, 2017).
- Presented a poster on "*Silver Catalyzed Elecrophilic Cascade Cyclization Reaction of o-Alkynylated p-QMs With Alkenes : Access to Dihydrobenzo[a]fluorenes*" **Pankhade, Y. A.**; Anand, R. V. in the Inter IISER & NISER Chemistry Meet held at National Institute of Science Education and Research (NISER) Bhubaneswar, India (22-24th December, 2017).

- Delivered a talk entitled "1,6-Hydroolefination and Cascade Cyclization of *p*-Quinone Methides with Styrenes: Total Synthesis of (±)-Isopaucifloral F" **Pankhade, Y. A.**; Anand, R. V. in the *14th Junior National Organic Symposium (J-NOST)* held at CSIR-Indian Institute of Chemical Technology, Hyderabad, India (28-1st December, 2018).
- Participated in the *Recent Advances In Organic And Bioorganic Chemistry* (RAOBC) held at the Department of Chemical Sciences, Indian Institute of Science Education and Research (IISER) Mohali, S. A. S. Nagar, India (22-24th March, 2019).