Metal-free Transformations of *para*-Quinone Methides (*p*-QMs) to Oxygen-containing Heterocycles and Carbazoles

Gurdeep Singh

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Department of Chemical Sciences

Indian Institute of Science Education and Research (IISER) Mohali

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

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Dedicated

To

My beloved parents

Declaration

The work presented in this thesis has been carried out by me under the guidance of **Prof. R. Vijaya Anand** at the Indian Institute of Science Education and Research Mohali. This work has not been submitted in part or in full for a degree, diploma, or fellowship to any other university or institute. Whenever contributions of others are involved, every effort is made to indicate this clearly with due acknowledgment of collaborative research and discussions. This thesis is a bonafide record of original work done by me, and all sources listed within have been detailed in the bibliography.

Gurdeep Singh

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

Acknowledgment

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Abstract

The research work presented in this thesis primarily focuses on *metal-free transformations of para-quinone methides (p-QMs) to oxygen-containing heterocycles and carbazoles*. This thesis is divided into two sections, namely Chapter A and Chapter B. Chapter A describes the synthesis of oxygen-containing heterocycles from 2-hydroxyphenyl substituted *para*-quinone methides as a 1,6-conjugate acceptor and Chapter B involves the acid-mediated formation of heterocycles-substituted carbazoles from indole-based *p*-quinone methides and 2-indolyl methanols.

Chapter A: A metal-free approach to oxygen-containing heterocycles from 2-hydroxyphenyl substituted para-quinone methides

This chapter is subdivided into four parts.

Part 1: General introduction to the synthesis of oxygen-containing heterocycles from 2-hydroxyphenyl substituted para-quinone methides

A brief discussion on the synthetic applications of 2-hydroxyphenyl substituted *p*-quinone methides pertaining to oxygen-containing heterocycles has been included in this part.

Part 2: A one-pot approach to access 2,3-diarylbenzo[b]furans through an N-heterocyclic carbene catalyzed 1,6-conjugate addition followed by acid-mediated dehydrative cyclization

This part describes an *N*-heterocyclic carbene (NHC) catalyzed synthesis of 2,3-diarylbenzo[*b*]furan derivatives from 2-hydroxyphenyl substituted *p*-QMs. The benzo[*b*]furan scaffold is widely found in many natural products and biologically active molecules, and several of them display various impressive pharmacological activities such as anti-allergic, anti-HIV, cytotoxic, etc. (Figure 1). Although numerous synthetic techniques have been documented to access the 2,3-diarylbenzo[*b*]furan moiety, due to their fascinating and diverse

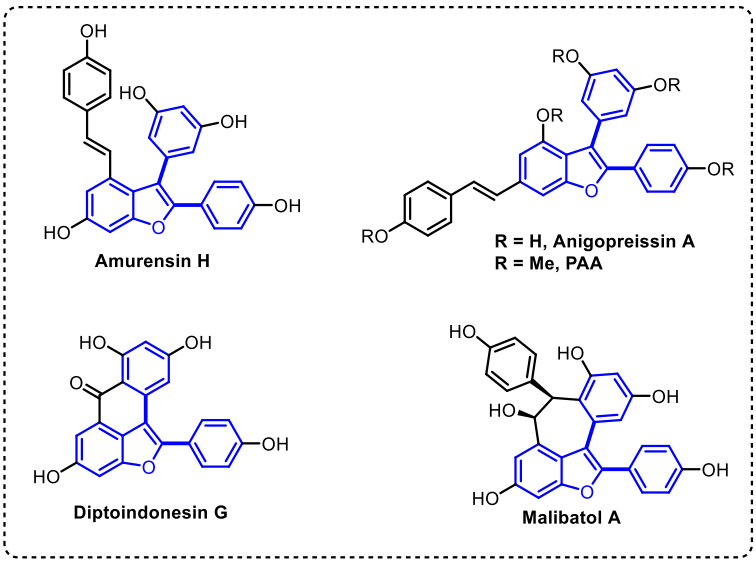
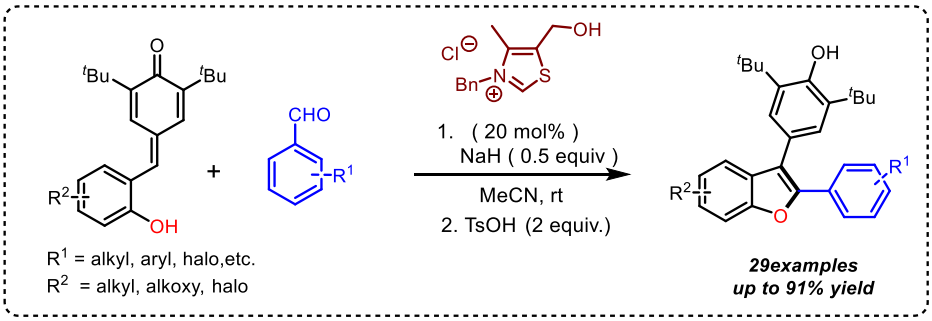


Figure 1. A few examples of biologically active 2,3-diarylbenzo[*b*]furan derivatives

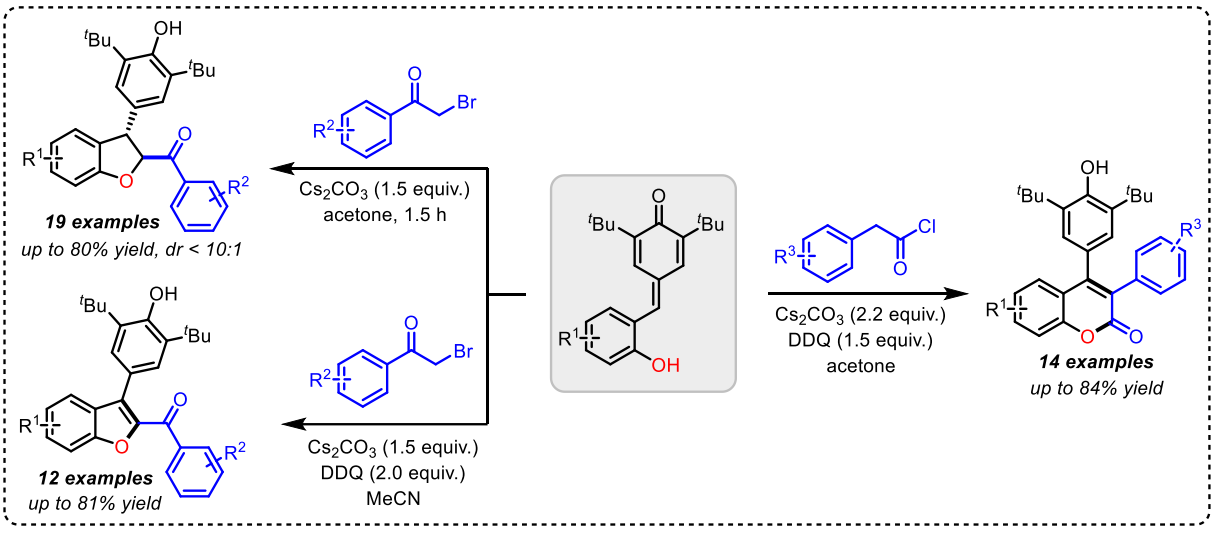
range of applications, most of which required pre-functionalization of starting material(s) and an expensive metal catalyst. Therefore, a practical, transition metal-free, or organocatalytic approach to 2,3-diarylbenzo[*b*]furans would be highly advantageous. While working in the area of *p*-QMs as 1,6- conjugate acceptors, we hypothesized that the 2,3-diarylbenzo[*b*]furans could be accessed in a one-pot manner from 2-hydroxyphenyl substituted *p*-QMs and aryl-aldehydes through an NHC catalyzed 1,6-conjugated addition of aldehydes to *p*-QMs followed by acid-mediated cyclization/dehydrative elimination sequence (Scheme 1). This protocol was found to be very general, and many 2,3-diarylbenzo[*b*]furan derivatives could be prepared in good to excellent yields under the optimized conditions.



Scheme 1. Synthesis of 2,3-diarylbenzo[*b*]furans from *p*-QMs and aromatic aldehydes

Part 3: A base-mediated one-pot approach to oxygen-based heterocycles from 2-hydroxyphenyl substituted para-quinone methides

This part of Chapter A describes the synthesis of 2,3-dihydrobezofurans, benzofurans, and coumarins from 2-hydroxyphenyl-substituted *p*-QMs. Initially, when *α*-bromo acetophenones were treated with *p*-QMs in the presence of stoichiometric amounts of Cs_2CO_3, 2,3-dihydrobenzofuran derivatives were obtained as diastereomers in moderate to good yields with good diastereomeric selectivity. This methodology was elaborated to the one-pot synthesis of 2,3-disubstituted benzo[*b*]furans from *α*-bromo acetophenones and *p*-QMs *via* dehydrogenative oxidation of 2,3-dihydrobenzofurans using DDQ as an oxidant. Furthermore, this concept was also successfully applied in the synthesis of 3,4-diaryl coumarin derivatives by treating aryl-acetyl chlorides with 2-hydroxyphenyl substituted *p*-QMs in the presence of Cs_2CO_3, followed by dehydrogenative oxidation with DDQ. Mechanistic investigation showed that the reaction proceeds through *O*-alkylation and *O*-acylation of *p*-QM with acetophenones and arylacetyl chloride, respectively, followed by intramolecular 1,6-conjugate addition.



Scheme 2. Base-mediated synthesis of various oxygen-containing heterocycles from *p*-QMs

Part 4: A one-pot approach to chromenes through formal [4+2]-annulation reaction of enaminones with 2-hydroxyphenyl substituted para-quinone methides

This part deals with the synthesis of chromene derivatives. Chromenes are an important class of oxygen-containing heterocycles found to show various pharmacological activities, such as anti-cancer, anti-oxidant, anti-fungal, etc. (Figure 2).

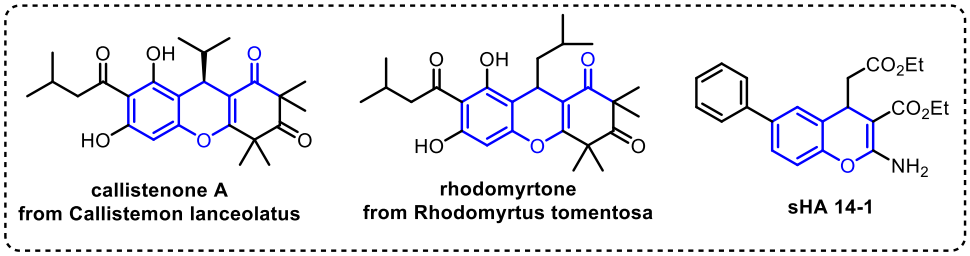


Figure 2. Naturally occurring and biologically active chromene derivatives

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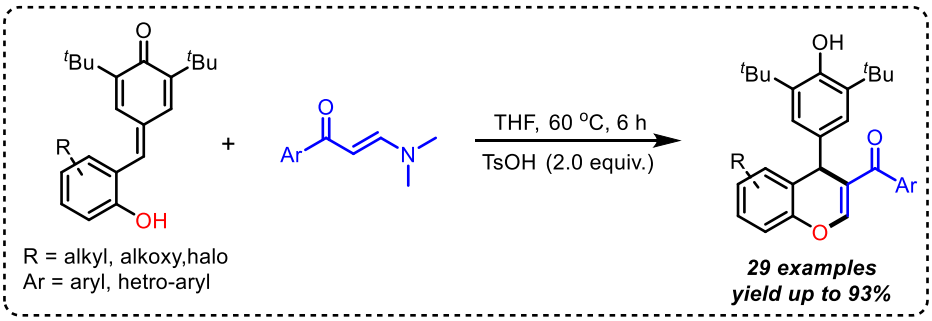
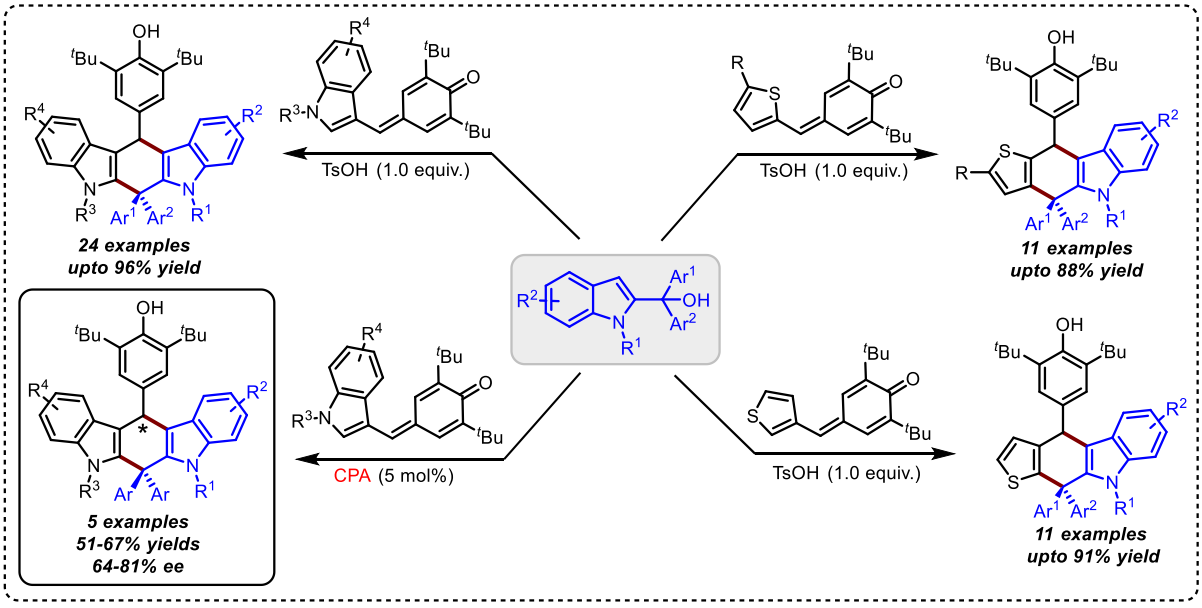
While working on the synthesis of oxygen-containing heterocycles, we envisioned that it could be possible to access chromene derivatives through a formal [4+2]-annulation of enaminones with 2-hydroxyphenyl substituted *p*-quinone methides. Based on this hypothesis, we have developed a metal-free protocol to access many chromene derivatives (Scheme 3). The reaction proceeds through the isomerization of *p*-QM to *o*-QM in the presence of TsOH, followed by conjugate addition of enaminone and other series of steps to produce chromene.



Scheme 3. Synthesis of chromenes from *p*-QMs and enaminones

Chapter B: A formal [3+3]-annulation approach to tetrahydroindolo[2,3-b]carbazoles from p-quinone methides and 2-indolylmethanol

This chapter provides a brief overview of tetrahydroindolo[2,3-*b*]carbazoles and also describes our approach to the synthesis of tetrahydroindolo[2,3-*b*]carbazoles. Basically, our protocol involves the 1,6-conjugate addition of 2-indolylmethanols to *p*-quinone methides (derived from indole-3-carboxaldehyde), followed by intramolecular cyclization and aromatization. An enantioselective version of this reaction was also developed using a chiral phosphoric acid. Further, this method was also elaborated to access tetrahydrothieno[2,3-*b*]carbazoles and tetrahydrothieno[3,2-*b*]carbazoles by employing *p*-QMs obtained from thiophene-3-carboxaldehyde and thiophene-2-carboxaldehyde, respectively.



Scheme 4. Synthesis of tetrahydroindolo[2,3-*b*]carbazoles, tetrahydrothieno[2,3-*b*]carbazoles and tetrahydrothieno[3,2-*b*]carbazoles from *p*-QMs

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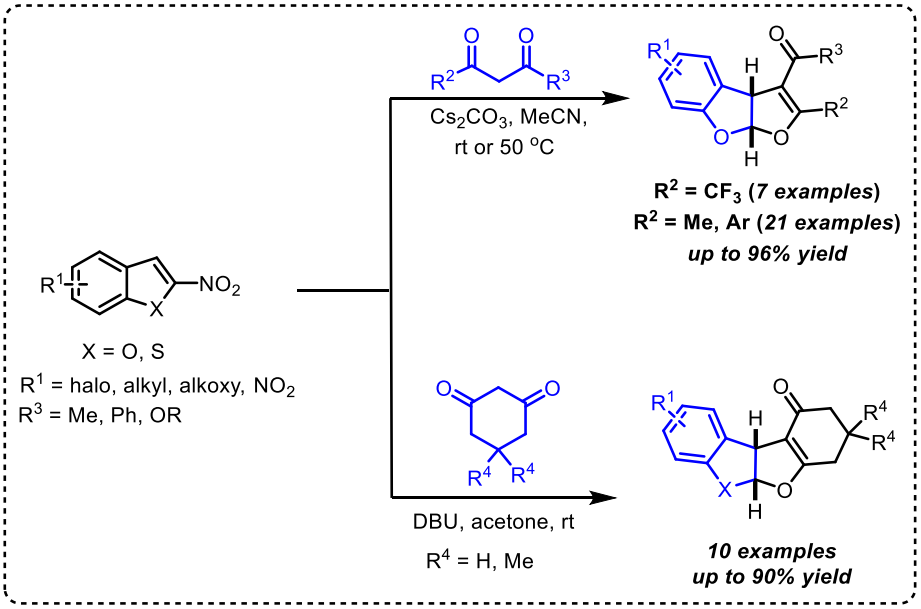
Appendix 1. A base-mediated approach towards dihydrofuro[2,3-b]benzofurans from 2-nitrobenzofurans and 1,3-dicarbonyls

A brief introduction to dihydrofuro[2,3-*b*]benzofurans and our protocol for the synthesis of such compounds are described. Dihydrofuro[2,3-*b*]benzofuran is an important class of oxygen-containing heterocycle that can be found in a variety of natural products and physiologically active compounds and have a variety of pharmacological properties. While investigating the synthesis of oxygen-containing heterocycles, we have developed a base-mediated Michael-addition of 1,3-dicarbonyl compounds to 2-nitrobenzofurans followed by intramolecular cyclization to produce dihydrofuro[2,3-*b*]benzofurans in moderate to good yields. Further, this methodology was extended to access $-CF_3$ containing dihydrofuro[2,3-*b*]benzofurans using trifluoroacetoacetate and 2-nitrobenzofurans.



Scheme 5. Synthesis of dihydrofuro[2,3-*b*]benzofurans from 2-nitrobenzofurans

Abbreviations

ACN	Acetonitrile
AcOH	Acetic acid
Ac_2O	Acetic anhydride
Aq	Aqueous
$B_2(pin)_2$	Bis(pinacolato)diboron
brs	Broad singlet
Bn	Benzyl
BAC	Bis(amino)cyclopropenylidene
BQ	1,4-Benzoquinone
$CHCl_3$	Chloroform
CCl_4	Carbon tetrachloride
CSA	Camphorsulfonic acid
clcd	Calculated
Cy `	Cyclohexyl
CO	Carbon monoxide
CsOAc	Caesium acetate
Cs_2CO_3	Cesium carbonate
cm	Centimetre
δ	Chemical shift
$CDCl_3$	Chloroform-D
J	Coupling constant
DCE	Dichloroethane
DCM	Dichloromethane
Et_2O	Diethyl ether
°C	Degree celsius
dr	Diastereomeric ratio
DMA	Dimethylacetamide
DMAP	4-Dimethylaminopyridine
DME	Dimethoxyethane
DMSO	Dimethyl sulfoxide
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DBN	1,5-Diazabicyclo[4.3.0]non-5-ene

d	Doublet
dd	Doublet of doublet
ddd	Doublet of doublet of doublet
dt	Doublet of triplets
EWG	Electron withdrawing
ESI	Electrospray ionization
ee	Enantiomeric excess
er	Enantiomeric ratio
EtOH	Ethanol
EtOAc	Ethylacetate
equiv	Equivalents
FT-IR	Fourier transform infrared spectroscopy
Hz	Hertz
HRMS	High-resolution Mass Spectrum
HPLC	High Performance Liquid Chromatography
h	Hour(s)
i-Pr	*iso*-Propyl
LED	Light-emitting diode
LHMDS	Lithium bis(trimethylsilyl)amide
LDA	Lithium diisopropylamide
^{t}BuOLi	Lithium-*tert*-butoxide
m/z	Mass/Charge
MHz	Megahertz
m.p.	Melting point
Mes	Mesityl
MeOH	Methanol
Mg	Milligram(s)
ml	Milliliter(s)
mmol	Millimole(s)
min	Minute(s)
µL	Microliter (s)
M.S.	Molecular sieves
m	Multiplet
DMF	*N*,*N*'-Dimethyl formamide

NHC	*N*-heterocyclic carbene
NMO	*N*-Methylmorpholine-*N*-oxide
NMR	Nuclear Magnetic Resonance
n-Pr	Propyl
^{t}BuOK	Potassium-*tert*-butoxide
$POCl_3$	Phosphoryl chloride
P-TSA	*p*-Toluene sulfonic acid
q	Quartet
R_f	Retention factor
rt	Room temperature
sept	Septet
s	Singlet
NaH	Sodium hydride
^{t}Bu	*tert*-Butyl
tert	Tertiary
Boc	*tert*-Butyloxycarbonyl
TBAB	Tetrabutylammonium bromide
TPAP	Tetrapropylammonium perruthenate
THF	Tetrahydrofuran
TMS	Tetramethylsilane
TBS	*tert*-Butyldimethylsilane
TFA	Trifluoroacetic acid
TFE	2,2,2-Trifluoroethanol
t	Triplet
td	Triplet of doublets
tt	Triplet of triplet
UV	Ultraviolet
Vis	Visible

Contents

Chapter A

Part 1

1. General introduction to the synthesis of oxygen-containing heterocycles from 2-hydroxyphenyl substituted *para*-quinone methides

1.1 Introduction

In recent years, *para*-quinone methides (*p*-QMs) chemistry has been widely explored for the synthesis of various organic structural moieties such as diaryl/triarylmethanes, carbocycles, heterocycles, *spiro*-cycles, etc.[1] In addition to the synthetic applications, *p*-QMs are usually found in nature and serve as intermediates in various biological and biosynthesis pathways.[2] These are structural analogs of 1,4-benzoquinone (**I**), in which one of the carbonyl group is replaced with a methylene group. In *p*-QM, different entities at both ends change dipole moment and polarizability compared to 1,4-benzoquinone, in which carbonyl groups at opposite ends counterbalance the polarizability effect.[3] Because of this, *p*-QM exists in a zwitterionic form (**III**).[4] The zwitterionic form stabilizes the cyclohexadiene ring *via* the aromatization reaction of *para* quinone methide and directs the nucleophile to attack the benzylic carbocation leading to the formation of more stable neutral aromatic compounds (Figure 1).

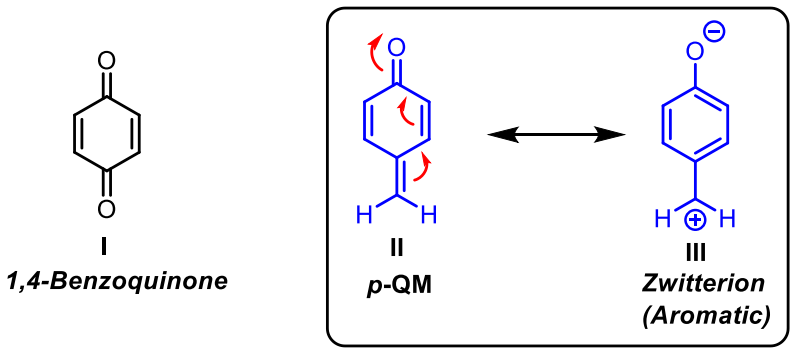


Figure 1. Zwitterionic form of *para*-quinone methide

The unsubstituted *p*-QMs were found to be highly reactive and unstable intermediates. It was reported in the literature that the presence of bulky alkyl substituent (*tert*-butyl) at the positions C2- and C6- increases the stability of *p*-QMs as well as hinders the attack of nucleophiles at the positions C1 (1,2-addition) and C3 (1,4-addition) (**IV**). Therefore, only *exo*-cyclic methylene carbon, which usually exists as a carbocation during the zwitterionic form, is

exposed to attack by the nucleophiles (**V**). Therefore, *p*-QMs are considered a suitable substrate for regiospecific 1,6-conjugate addition reactions by different nucleophiles (**VI**) [Figure 2].

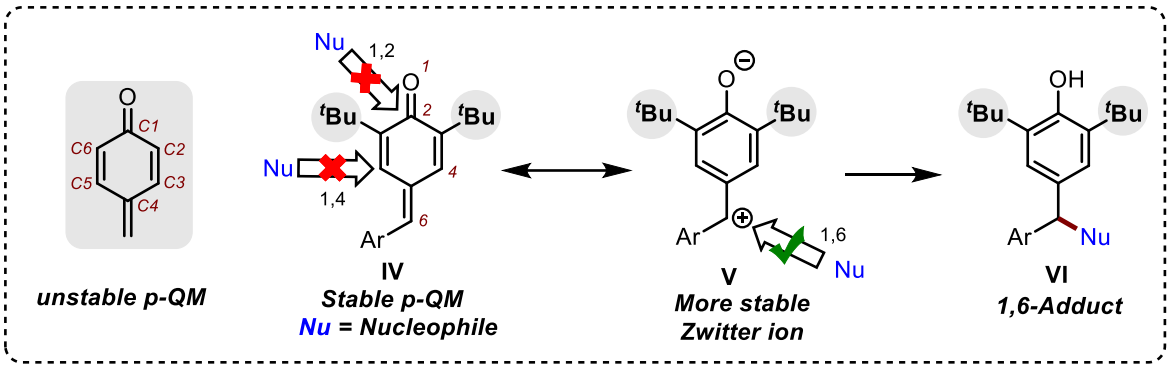


Figure 2. Reactivity of *p*-QM

Several reports have been documented in the literature for the applications of stable *p*-QM as a 1,6-acceptor to access structurally diverse diaryl and triarylmethane derivatives.[1]

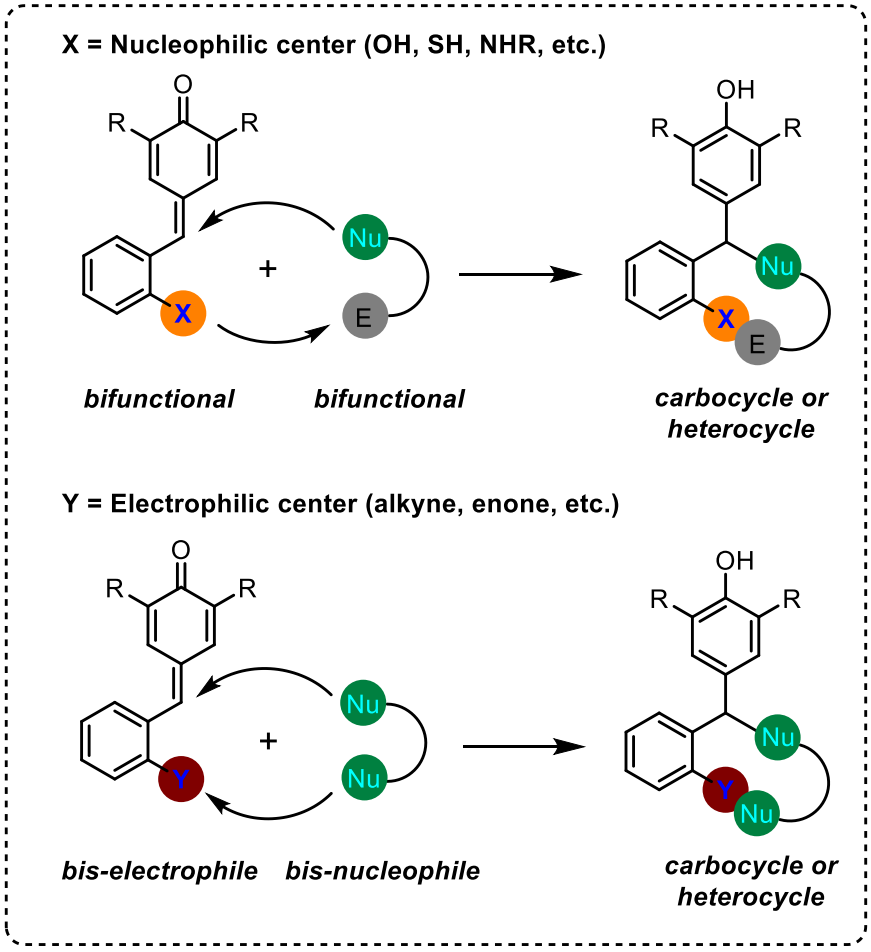


Figure 3. Hypothesis for the synthesis of carbocycles/heterocycles from *p*-QM

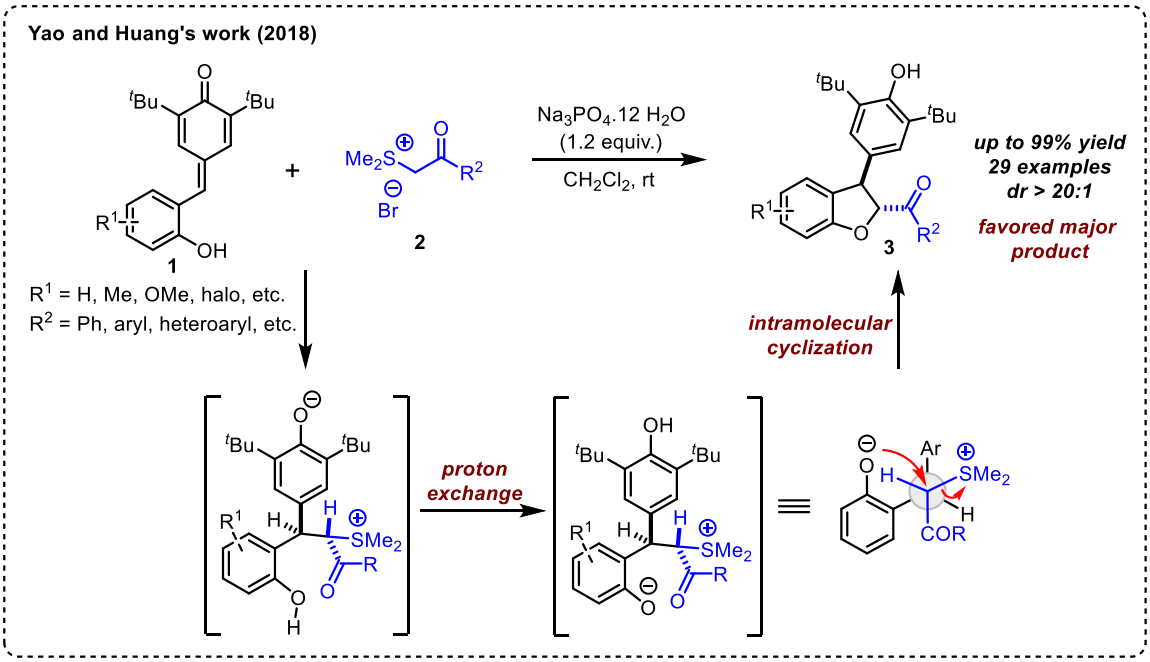
Recently, it was hypothesized that if some modifications (nucleophilic/electrophilic substituents) are introduced at the *ortho* position of the aryl group in the basic skeleton of *p*-QM, then it behaves like a bifunctional molecule. Depending on the substitution, it can react with another bifunctional molecule to produce fused carbocycles and heterocycles (Figure 3). After the Ender's group reported the synthesis of asymmetric chromanes from 2-hydroxyphenyl substituted *p*-QM and isatin-based enoates,[5] various groups have explored this substrate for the synthesis of structurally varied heterocycles and carbocycles.[6] This chapter focuses mainly on the syntheses of oxygen-containing heterocycles from 2-hydroxyphenyl substituted *para*-quinone methides.

1.2. Literature reports on the synthesis of five-membered oxygen-containing heterocycles

Recently, the synthesis of five-membered oxygen-containing heterocycles has been widely explored in the literature. A few examples are discussed here.

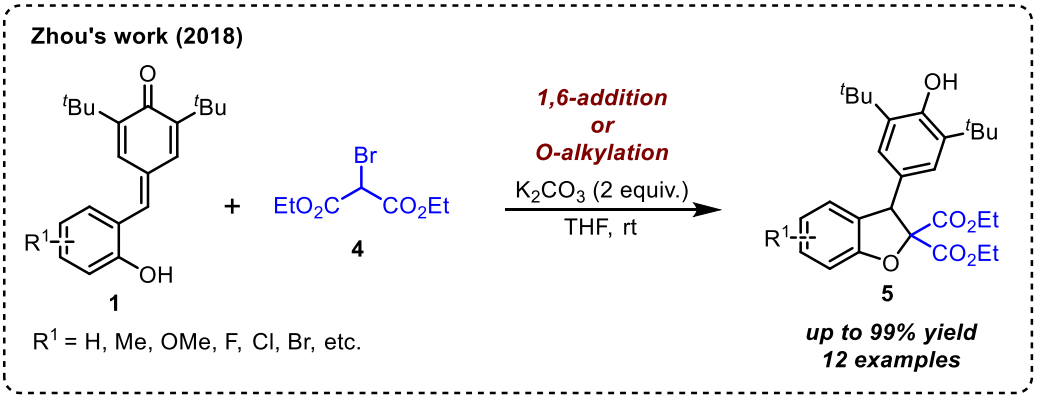
1.2.1 Synthesis of dihydrobenzofurans

In 2018, Yao and Huang established the [4+1] cycloaddition reaction of 2-hydroxyphenyl substituted *p*-QMs **1** and sulfonium salts **2** for the synthesis of 2,3-dihydrobenzofurans **3** in moderate to excellent diastereoselectivity. According to the proposed reaction mechanism, $Na_3PO_4.12H_2O$ abstracts the proton from the sulfonium salt, followed by



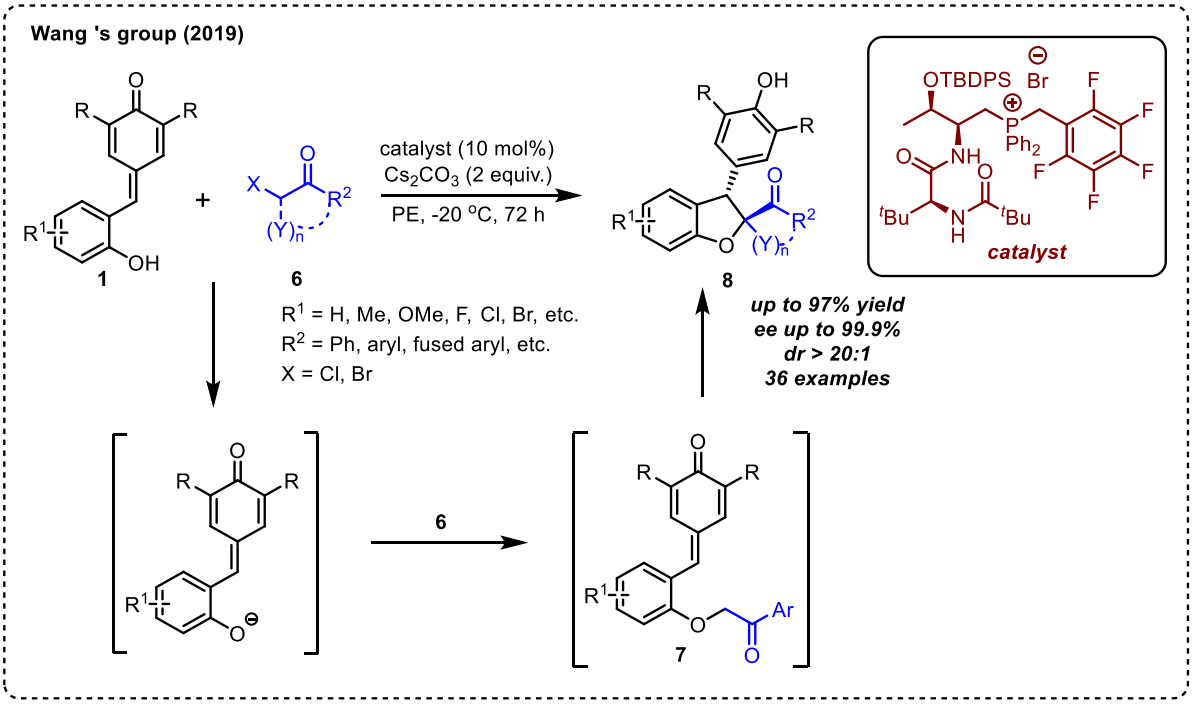
Scheme 1. Synthesis of 2,3-dihydrobenzofurans using sulfonium salts

1,6-conjugate addition to generate an intermediate, which subsequently undergoes proton exchange and an intramolecular nucleophilic substitution reaction to produce the final product (Scheme 1).[7] In the same year, the groups of Enders[8] and Yuan[9] independently reported the synthesis of 2,3-dihydrobenzofurans **3** from 2-hydroxyphenyl substituted *p*-QMs (**1**) and sulfonium salts or sulfur ylides under basic and catalyst-free reaction conditions, respectively.



Scheme 2. Synthesis of 2,3-dihydrobenzofurans using diethyl bromomalonate

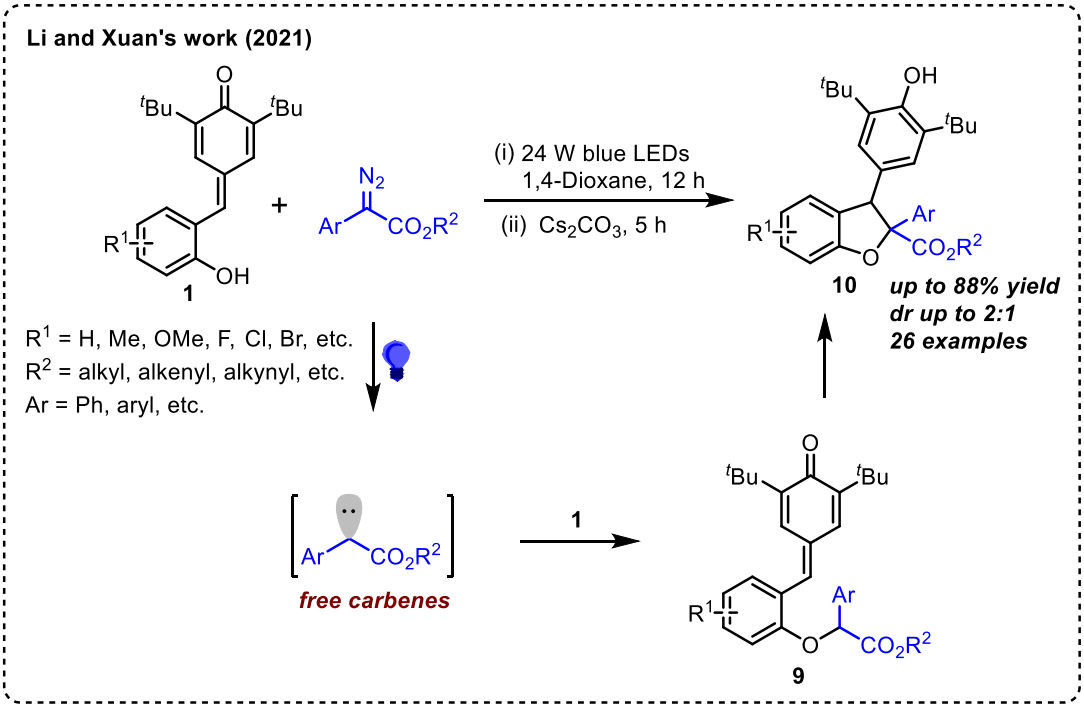
Later, Zhou's group developed a base-mediated synthesis of 3-aryl 2,3-dihydrobenzofurans (**5**) through 1,6-addition/*O*-alkylation of 2-hydroxyphenyl substituted *p*-QMs (**1**) and diethyl bromomalonate **4**. A variety of *p*-QMs (**1**) reacted efficiently with diethyl bromomalonate to obtain their respective products in excellent yields (Scheme 2).[10]



Scheme 3. Synthesis of 2,3-dihydrobenzofurans using α-halogenated ketones

In 2019, Wang and co-workers disclosed a chiral bifunctional phosphonium salt catalyzed stereoselective synthesis of 2,3-dihydrobenzofuran derivatives (**8**) through a [4+1] annulation of 2-hydroxyphenyl substituted *p*-QMs (**1**) and *α*-halogenated ketones (**6**). The mechanistic study revealed the generation of intermediate **7** through base-promoted alkylation of *p*-QM with **6**, followed by an enantioselective intramolecular 1,6-conjugate addition reaction to produce the product **8** (Scheme 3).[11]

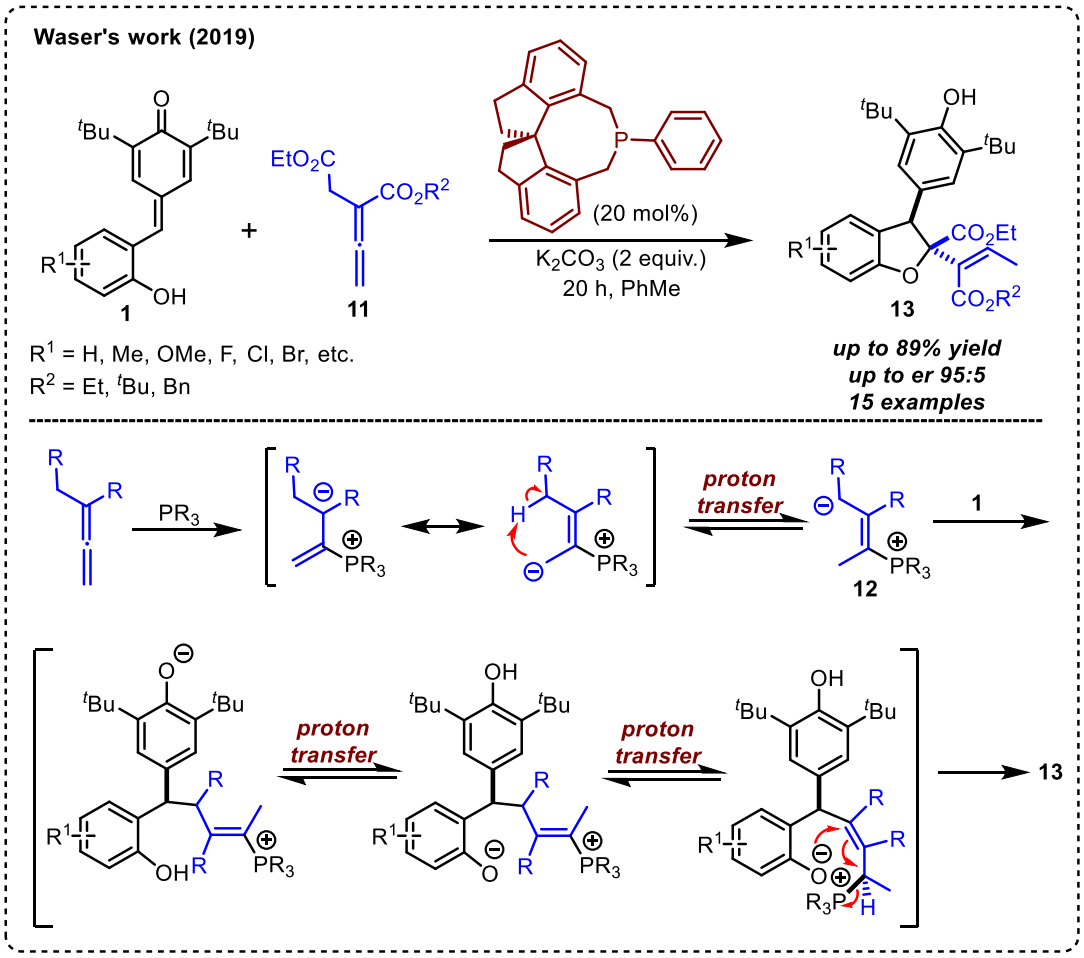
Recently, Li and Xuan reported a visible light and base-mediated synthesis of 2,3-dihydrobenzofurans (**10**) from 2-hydroxyphenyl substituted *p*-QMs (**1**) and aryl diazoacetates. Free carbene, which was generated from aryl diazoacetates by irradiation of blue LED, undergoes O-H bond insertion with the hydroxyl group of *p*-QM to generate an intermediate **9**. The intermediate **9** then undergoes an intramolecular 1,6-conjugate addition in the presence of Cs_2CO_3 to produce 2,3-dihydrobenzofuran derivatives **10** with moderate to good yields (Scheme 4).[12]



Scheme 4. Synthesis of 2,3-dihydrobenzofurans using aryl diazoacetates

The Waser group, in 2019, reported a chiral phosphine-catalyzed enantioselective synthesis of 2,3-dihydrobenzofuran derivatives (**13**) using allenoates (**11**) and 2-hydroxyphenyl substituted *p*-QMs (**1**). According to the proposed reaction mechanism, the phosphine catalyst activates the allenoate to generate a zwitterionic intermediate **12**, which then undergoes an enantioselective 1,6-conjugate addition to **1**, followed by a series of proton transfers and

intramolecular cyclization to furnish the product **13** in moderate yields with good enantioselectivity (Scheme 5).[13]

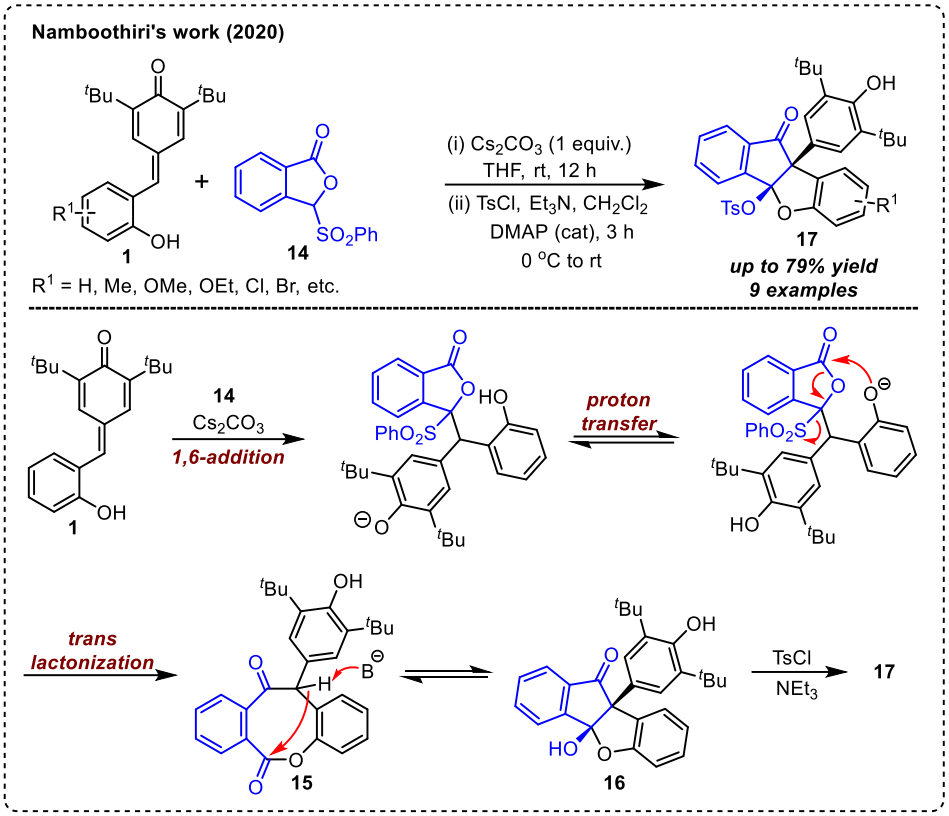


Scheme 5. Synthesis of 2,3-dihydrobenzofurans using allenoates

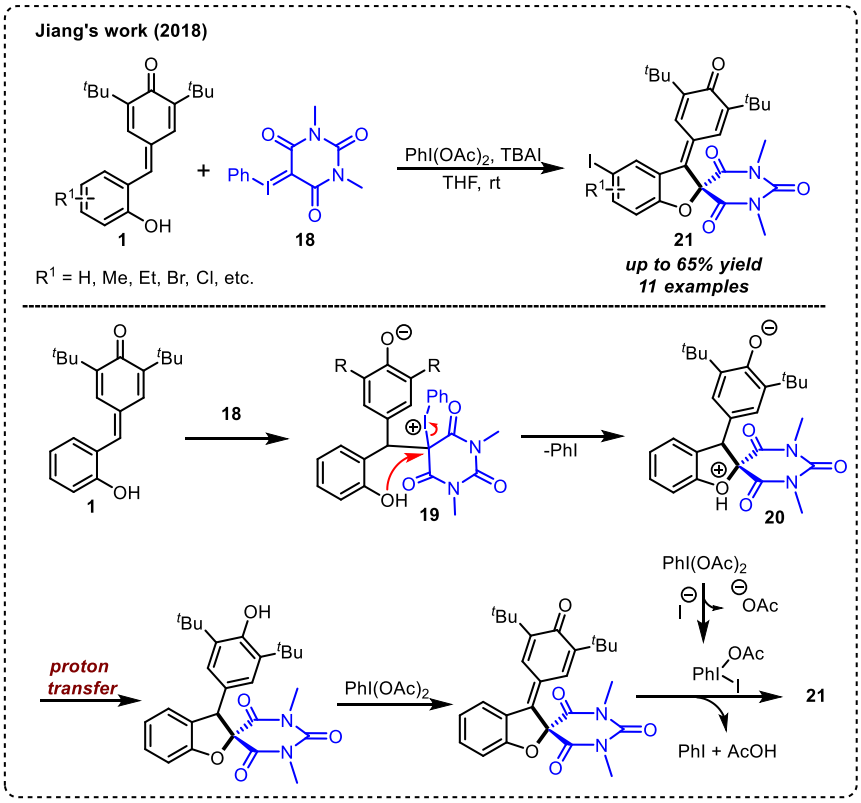
Another different approach was published by Namboothiri and co-workers, which involves a base-mediated Hauser–Kraus type annulation reaction of 2-hydroxyphenyl substituted *p*-QMs (**1**) to access indenofuran derivatives. The reaction proceeds through a base-mediated 1,6-conjugate addition of 3-sulfonylphthalide **14** to **1**, followed by proton transfer and *trans*-lactonization to generate an intermediate **15**. The intermediate **15** then undergoes a base-mediated cyclization/ring-opening/ring-closing sequence to form another intermediate **16**, which subsequently reacts with tosyl chloride to produce the final product **17** (Scheme 6).[14]

1.2.2 Synthesis of spirocyclic 2,3-dihydrobenzofurans

In 2018, Jiang and co-workers developed the synthesis of spirocyclic 2,3-dihydrobenzofurans (**21**) through a [4+1] annulation of phenyl iodonium ylides (**18**), and 2-hydroxyphenyl substituted *p*-QMs (**1**) under oxidative reaction conditions. The reaction



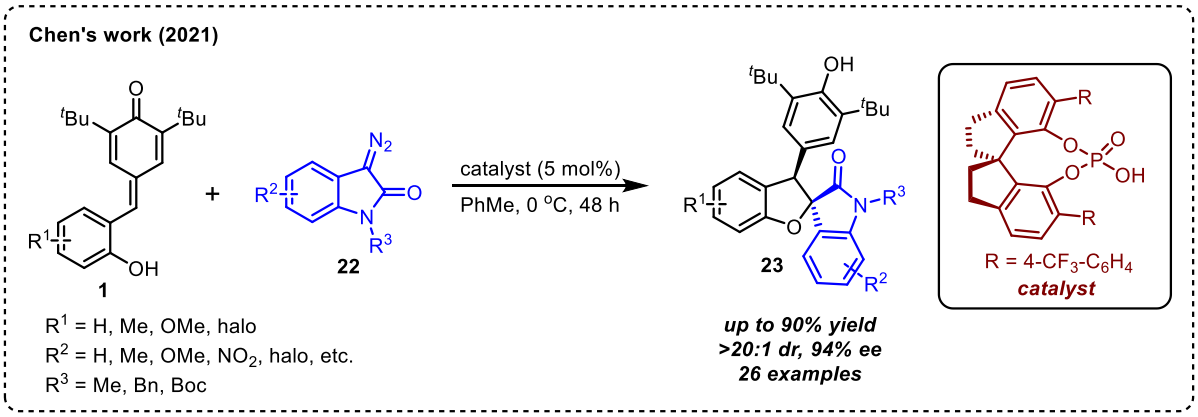
Scheme 6. Synthesis of indenofurans using 3-sulfonylphthalide



Scheme 7. Synthesis of spirocyclic 2,3-dihydrobenzofurans using phenyl iodonium ylides

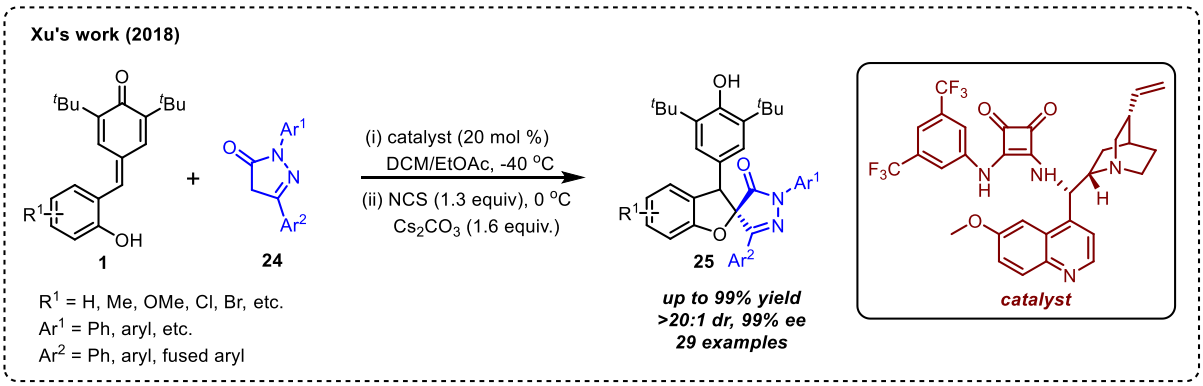
proceeds through the generation of an intermediate **19** by the 1,6-conjugate addition of iodonium ylides **18** to **1**, followed by intramolecular *oxo*-nucleophilic cyclization to generate another intermediate **20**. Furthermore, the intermediate **20** undergoes proton transfer/oxidative dearomatization and aromatic electrophilic iodination to produce the final product **21** (Scheme 7).[15]

Chen's and co-workers reported a chiral phosphoric acid catalyzed asymmetric synthesis of *spiro*-dihydrobenzofuran derivatives (**23**) through the reaction of 2-hydroxyphenyl substituted *p*-QMs (**1**) with 3-diazo oxindoles (**22**). According to the proposed reaction mechanism, initially, *p*-QM **1** is isomerized to *o*-QM, which is then immediately attacked by the 3-diazo oxindole followed by intramolecular nucleophilic substitution to furnish the product **23** with the release of nitrogen gas (Scheme 8).[16]



Scheme 8. Synthesis of *spiro*-dihydrobenzofurans using 3-diazooxindoles

Xu and co-workers have established the enantioselective synthesis of *spiro*-dihydrobenzofuran derivatives (**25**) from pyralozones (**24**) and 2-hydroxyphenyl-substituted *p*-QMs (**1**) under a squaramide-based bifunctional chiral catalyst. The reaction proceeds through

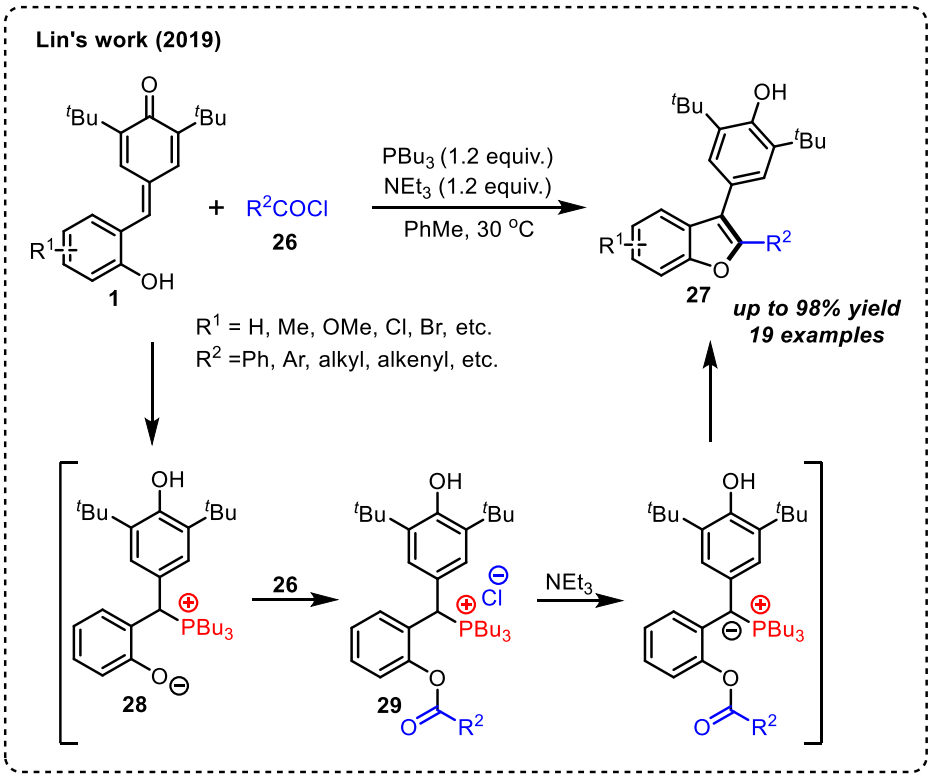


Scheme 9. Synthesis of *spiro*-dihydrobenzofurans using pyralozones

a 1,6-conjugate addition of **24** to activated 2-hydroxyphenyl-substituted *p*-QMs (**1**), followed by chlorination and intramolecular cyclization to produce the product **25** in moderate to good yield and excellent stereoselectivity (Scheme 9).[17]

1.2.3 Synthesis of benzo[*b*]furans

In 2019, Lin and co-workers described a phosphine-mediated synthesis of functionalized benzo[*b*]furans (**27**) from acyl chlorides (**26**) and 2-hydroxyphenyl-substituted *p*-QMs (**1**) under basic conditions. A variety of acyl chlorides were reacted efficiently with **1** under the standard reaction conditions to afford the products in moderate to good yields. The reaction proceeds through the generation of intermediate **28** by the reaction of **1** with PBu_3, followed by a reaction with **26** to form a phosphonium salt **29**. Then, the intermediate **29** undergoes deprotonation and, subsequently, an intramolecular Wittig reaction to produce the product **27** (Scheme 10).[18]



Scheme 10. Synthesis of benzo[*b*]furans using acyl chlorides

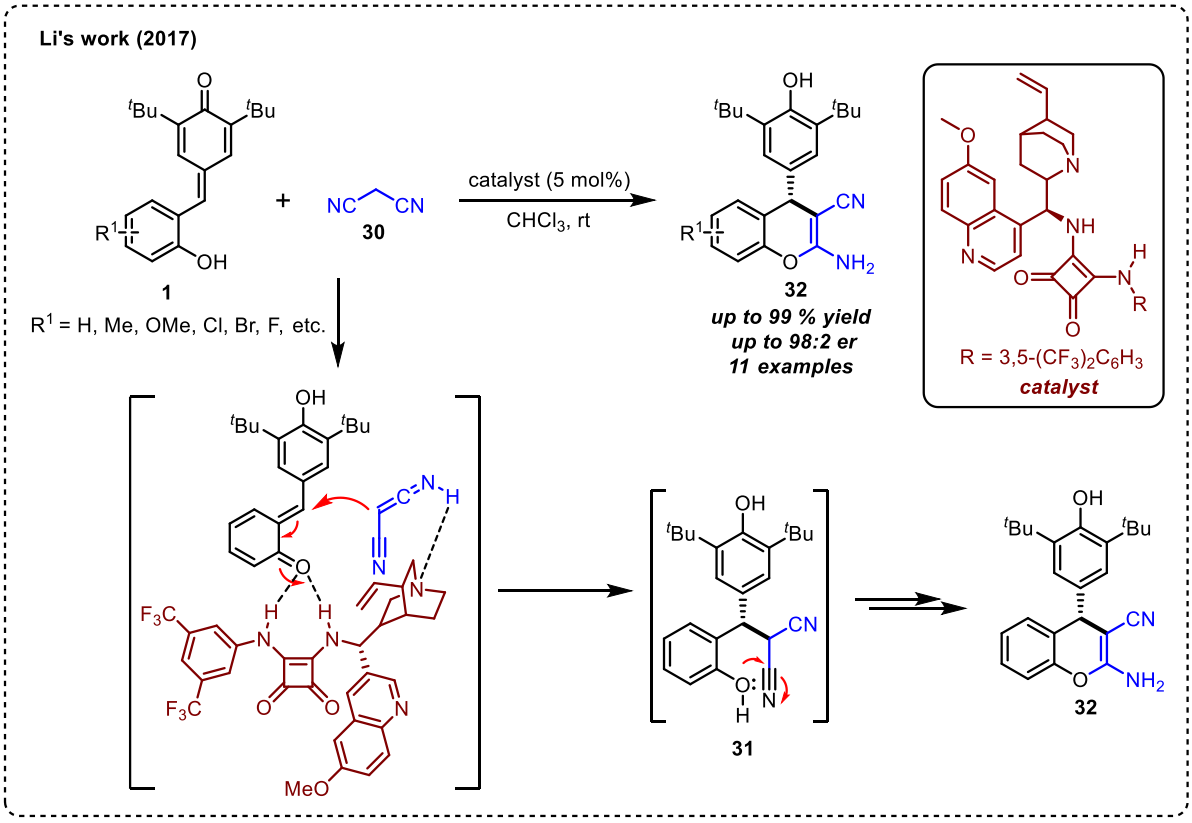
1.3 Literature reports on the synthesis of six-membered oxygen-containing heterocycles

For the synthesis of six-membered oxygen-containing heterocycles such as 4H-chromenes, xanthenes, chromanes, benzo-fused lactones, etc., several reports have been

documented in the literature. This section mainly focuses on the literature reports on the synthesis of 4H-chromenes and xanthenes derivatives.

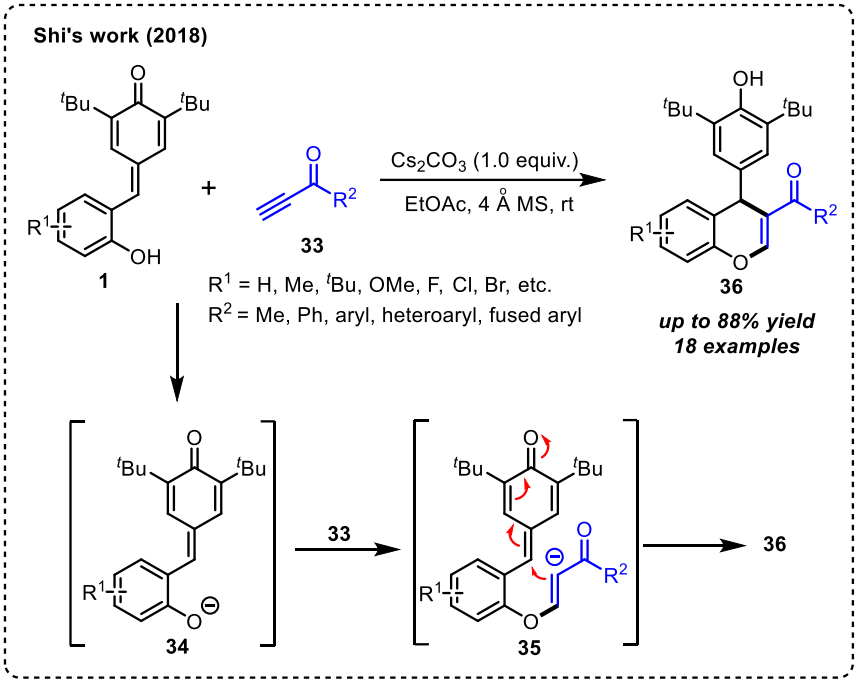
1.3.1 Synthesis of 4H-chromene derivatives

In 2017, Li and co-workers reported an enantioselective synthesis of 4H-chromene derivatives (**32**) by the reaction of 2-hydroxyphenyl substituted *p*-QMs (**1**) with malononitrile **30** in the presence of a chiral squaramide-based bifunctional catalyst. According to the proposed reaction mechanism, **1** isomerizes to *o*-QM in the presence of a catalyst. The bifunctional catalyst then activates the *o*-QM and malononitrile (**30**), which results in the formation of adduct **31**. The adduct subsequently **31** undergoes intramolecular cyclization and isomerization to furnish the chromene products **32** in moderate to good yields with excellent enantioselectivities. This methodology has also been elaborated with *β*-functionalized ketones to access chiral chromene derivatives (Scheme 11).[19] Later, Li and co-workers also demonstrated the synthesis of chiral 4H-chromene derivatives using a similar approach.[20]



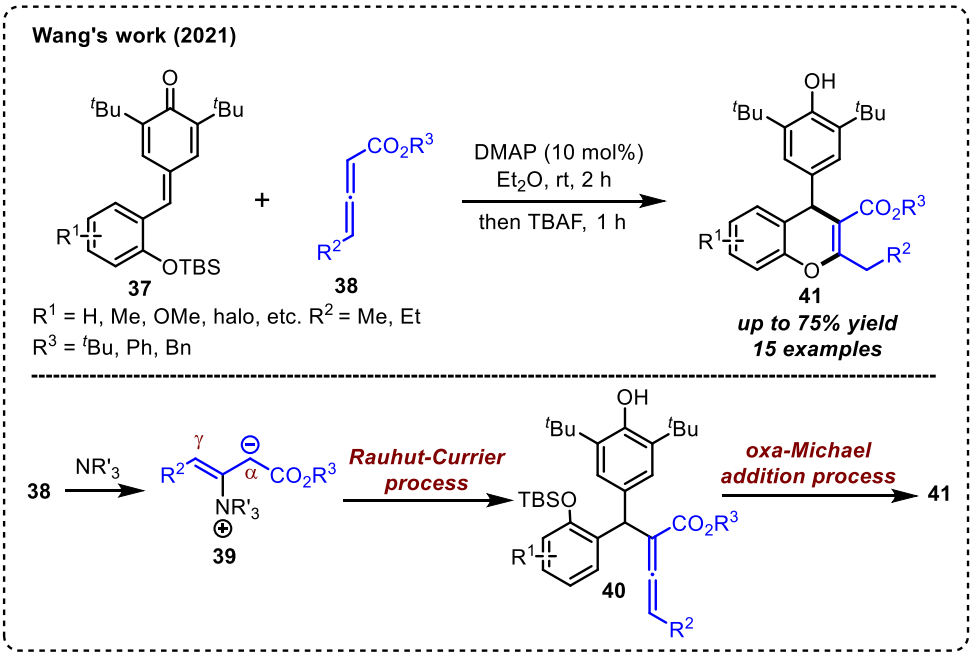
Scheme 11. Synthesis of 4H-chromenes using malononitriles

Shi and co-workers, in 2018, established a base-mediated [4+2] cycloaddition reaction of 2-hydroxyphenyl substituted *p*-QMs (**1**) and ynones (**33**) for the synthesis of chromene derivatives (**36**). A variety of 2-hydroxyphenyl substituted *p*-QMs (**1**) and ynones (**33**) were



Scheme 12. Synthesis of 4H-chromenes using ynones

reacted in the presence of Cs_2CO_3 to afford product **36** with moderate yield. The reaction proceeds through the generation of oxygen anion intermediate **34**, which reacts with ynone to generate another intermediate **35**. Then intermediate **35** undergoes intramolecular 1,6-conjugate addition to produce the product **36** (Scheme 12).[21]

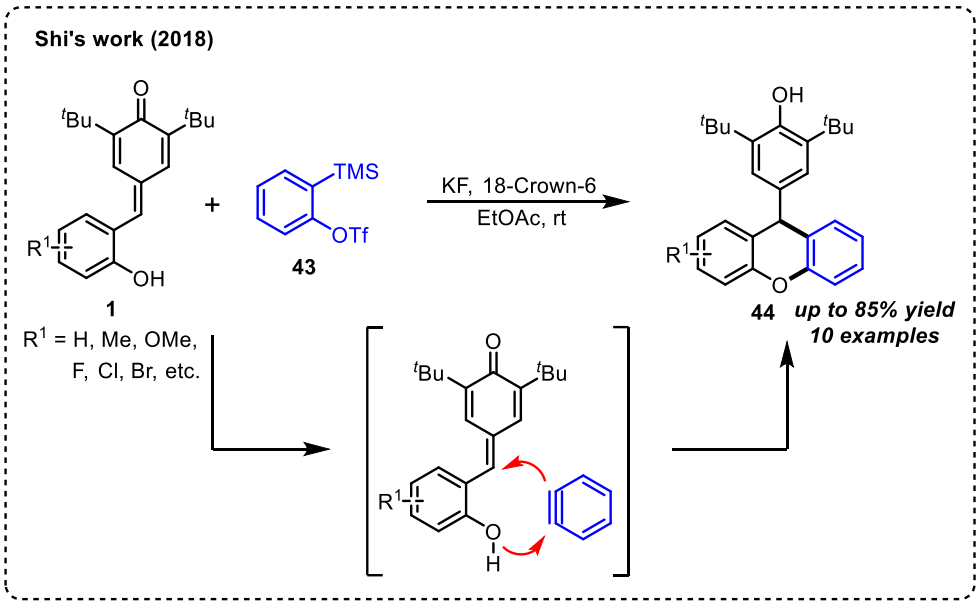


Scheme 13. Synthesis of 4H-chromenes using allenoates

Recently, Wang and co-workers described a DMAP-catalyzed Rauhut-Currier/*oxa*-Michael addition reaction of allenoates (**38**) with **37** to access chromene derivatives (**41**) in moderate to good yields. According to the proposed reaction mechanism, DMAP initially attacks the *β*-carbon of allenoate to generate an intermediate **39**, which then undergoes a 1,6-conjugate addition/proton transfer to form an allenoate adduct **40**. The adduct **40** undergoes deprotection and an intramolecular *oxa*-Michael reaction in the presence of TBAF to produce the product **41** (Scheme13).[22]

1.3.2 Synthesis of xanthene derivatives

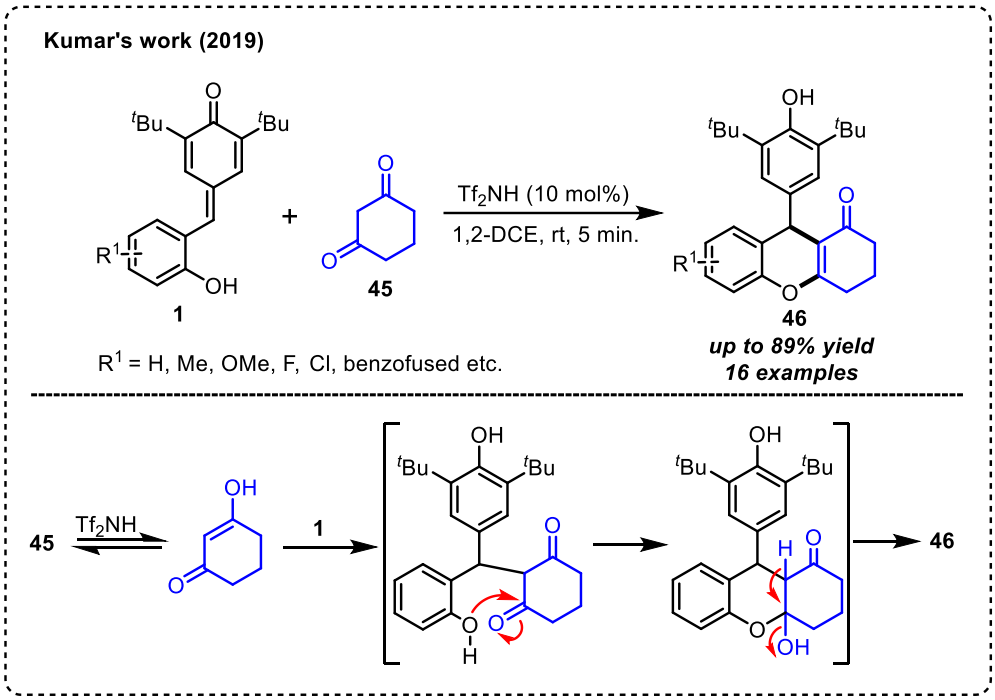
The research groups of Shi[21] and He[23] independently reported [4+2] annulation reactions of 2-hydroxyphenyl substituted *p*-QMs (**1**) and arynes for the synthesis of xanthene derivatives (**44**) in good to excellent yields. The reaction proceeds through the nucleophilic attack of a hydroxylic group on *in situ*-generated benzyne from their precursor **43**, to form an intermediate, which then undergoes intramolecular 1,6-conjugate addition to furnish the product **44** (Scheme 14).



Scheme 14. Synthesis of xanthenes using arynes

In 2019, Kumar and co-workers demonstrated a Brønsted acid-catalyzed synthesis of tetrahydro xanthenone derivatives (**46**) from 2-hydroxyphenyl substituted *p*-QMs (**1**) and cyclic 1,3-dicarbonyls (**45**) in moderate to good yields. A wide range of 2-hydroxyphenyl substituted *p*-QMs, and **45** underwent reaction in the presence of Tf_2NH to produce the product in moderate to good yields. The reaction proceeds through the 1,6-conjugate addition of **45** to activated *p*-QM, followed by intramolecular *oxa*-nucleophilic addition and dehydration to

obtain the desired product **46**. Under the same reaction conditions, the aliphatic 1,3-dicarbonyls produced 4H-chromenes (Scheme 15).[24]

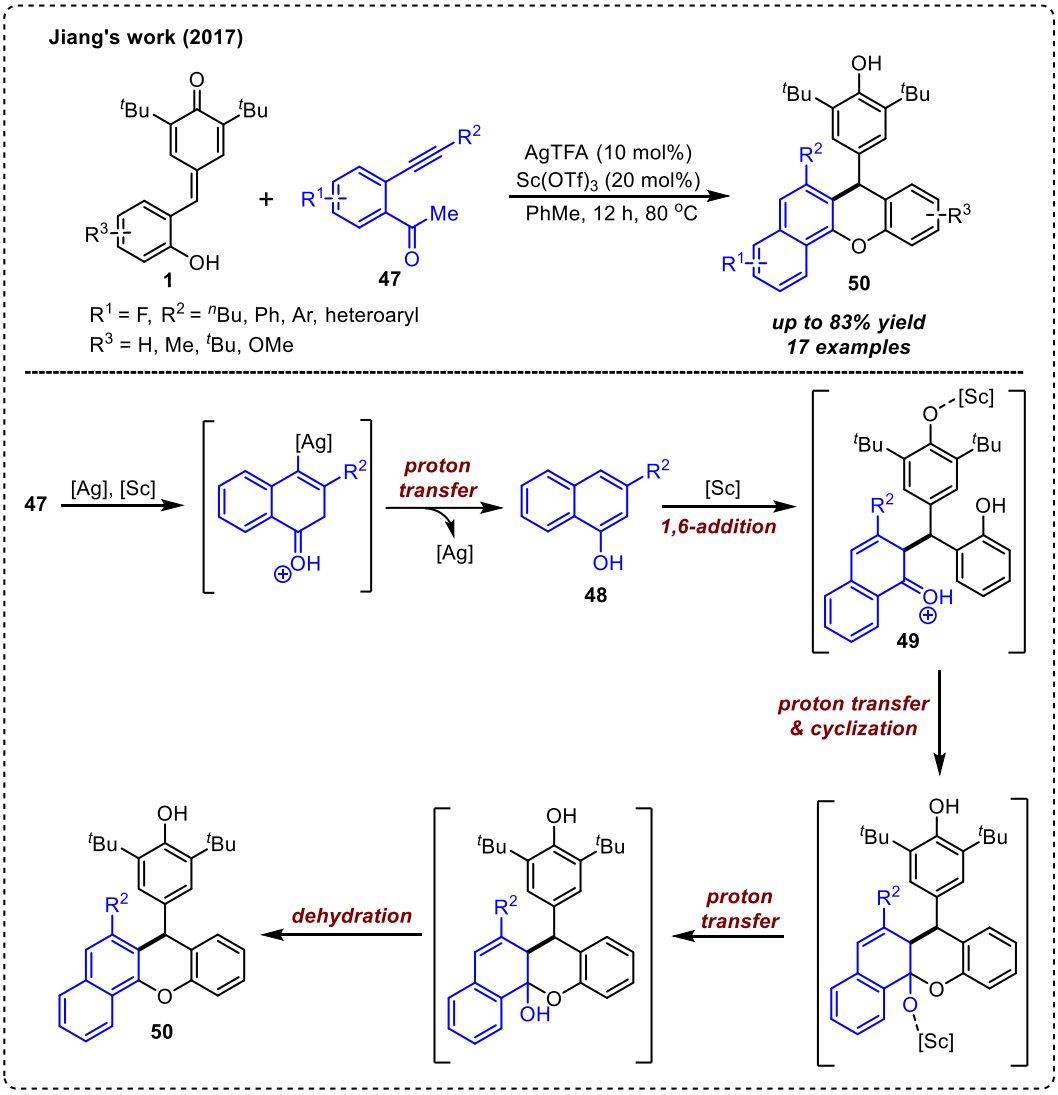


Scheme 15. Synthesis of tetrahydro xanthenones using 1,3-dicarbonyls

Jiang and co-workers reported the annulation reaction of *β*-alkynyl acetophenones (**47**) and 2-hydroxyphenyl-substituted *p*-QMs (**1**) in the presence of the combination of AgTFA and $Sc(OTf)_3$ for the synthesis of benzo[*c*]xanthene derivatives (**50**). According to the proposed reaction mechanism, **47** undergoes Ag/Sc catalyzed *6-endo-dig* cyclization followed by proton transfer to generate *α*-naphthol intermediate **48**, which attacks the activated *p*-QM (**1**) to yield an adduct **49**. Then, **49** undergoes proton transfer followed by an intramolecular cyclization and dehydration sequence to produce the product **50** (Scheme 16).[25]

1.3.3 Synthesis of chromane derivatives

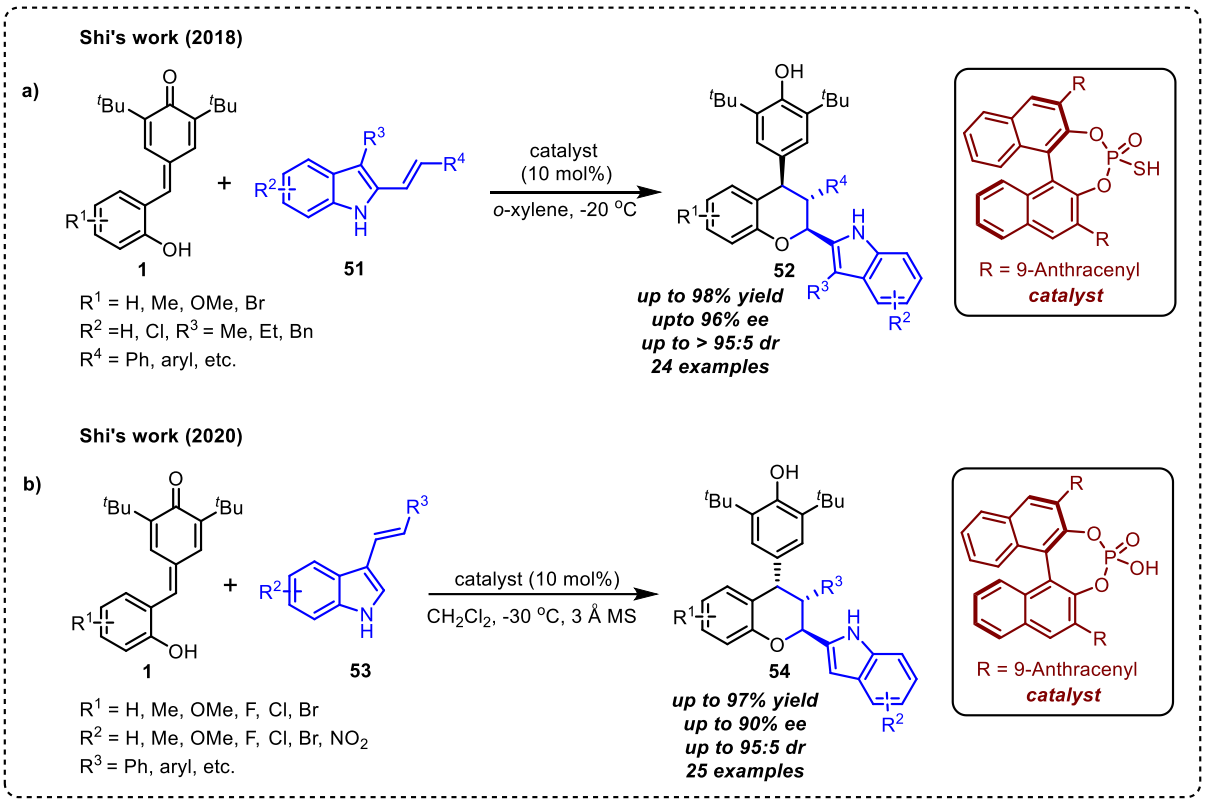
In 2018, Shi and co-workers reported a chiral BINOL-based phosphoric acid-catalyzed [4+2] cycloaddition reaction of 2-hydroxyphenyl substituted *p*-QMs (**1**) and 2-vinylindoles (**51**) for the synthesis of chiral chromane derivatives (**52**). The reaction proceeds through the enantioselective vinylogous conjugate addition of 2-vinylindoles (**51**) to **1** in the presence of chiral phosphoric acid, followed by an intramolecular cyclization to generate the product in good to excellent yield with high enantioselectivity (Scheme 17, **a**).[26] Later, Jiang[27] and Shi[28] groups independently described the synthesis of chromane derivatives (**54**) by using 2-hydroxyphenyl substituted *p*-QMs (**1**) and 3-vinylindoles (**53**) [Scheme 17, **b**].



Scheme 16. Synthesis of benzo[*c*]xanthene using *β*-alkynyl acetophenones

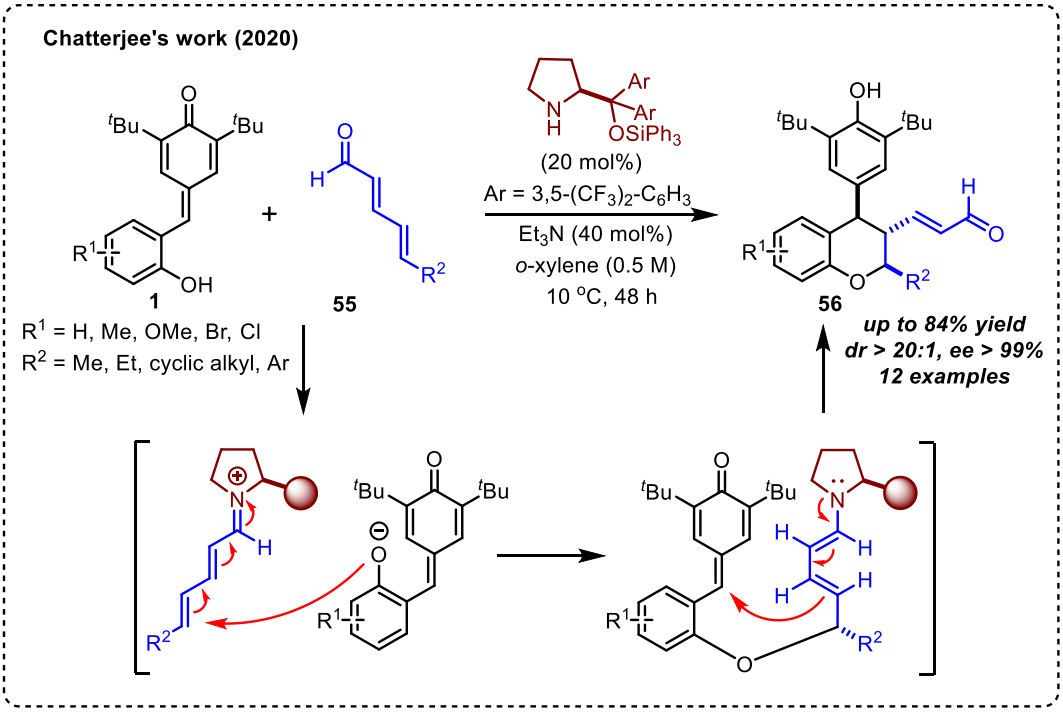
Recently, Chatterjee's group developed a chiral secondary amine-catalyzed synthesis of enantiomerically pure chromane derivatives (**56**) through an *oxa*-Michael/1,6-addition reaction of 2-hydroxyphenyl substituted *p*-QMs (**1**) and 2,4-dienal derivatives (**55**). A variety of 2,4-dienals and **1** were reacted under standard conditions to produce the product in good yields. According to the proposed reaction mechanism, an iminium ion-based intermediate was formed from a secondary amine catalyst and 2,4-dienal, followed by *oxa*-Michael addition to **1** and intramolecular vinylogous 1,6-conjugate addition to affording the desired product with high enantioselectivity (Scheme 18).[29]

For the first time, in 2016, Enders and co-workers, utilized 2-hydroxyphenyl substituted *p*-QMs (**1**) for the synthesis of enantiomerically pure *spiro*-cyclic chromane derivatives (**58**). A wide range of chiral *spiro*-cyclic chromanes have been synthesized with excellent yields and



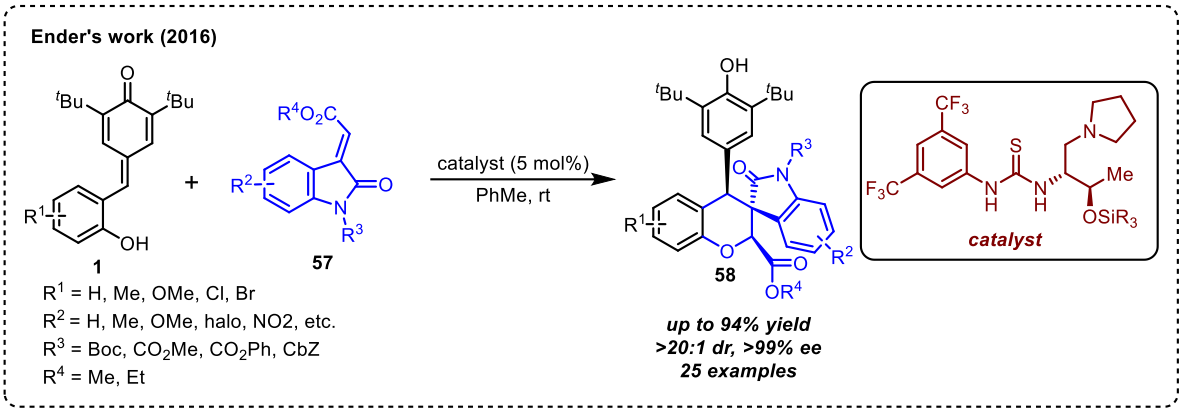
Scheme 17. Synthesis of chiral chromanes using vinyl indole derivatives

stereoselectivity by using **1** and isatin-derived enoates (**57**) in the presence of a chiral thiourea catalyst. According to the proposed reaction mechanism, the thiourea catalyst activates both **1**



Scheme 18. Synthesis of chiral chromanes using 2,4-dienals

and **57**, followed by an *oxa*-Michael/1,6-conjugate addition reaction to produce the product (Scheme 19).[5]

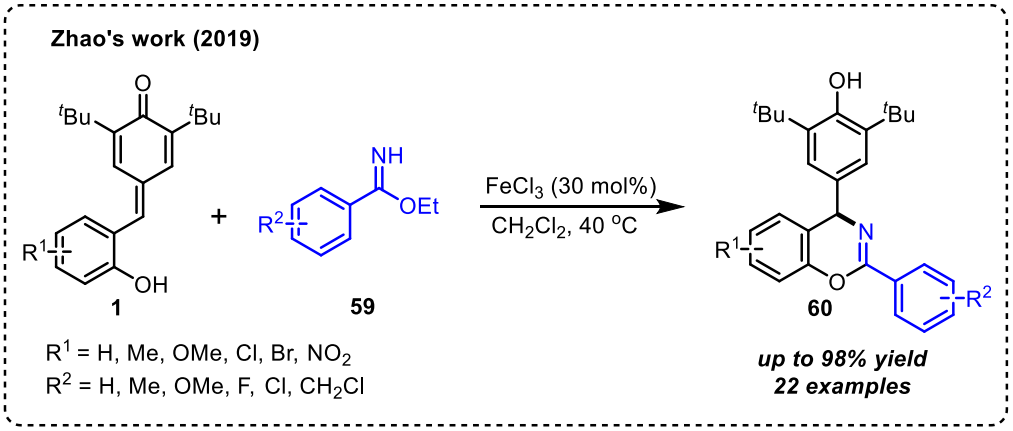


Scheme 19. Synthesis of chiral *spiro*-cyclic chromanes using isatin-derived enoates

1.4 Miscellaneous reports of 2-hydroxyphenyl substituted *p*-QMs

Various reports have been reported in the literature on the syntheses of other classes of oxygen-containing heterocycles. A few of them are discussed below.

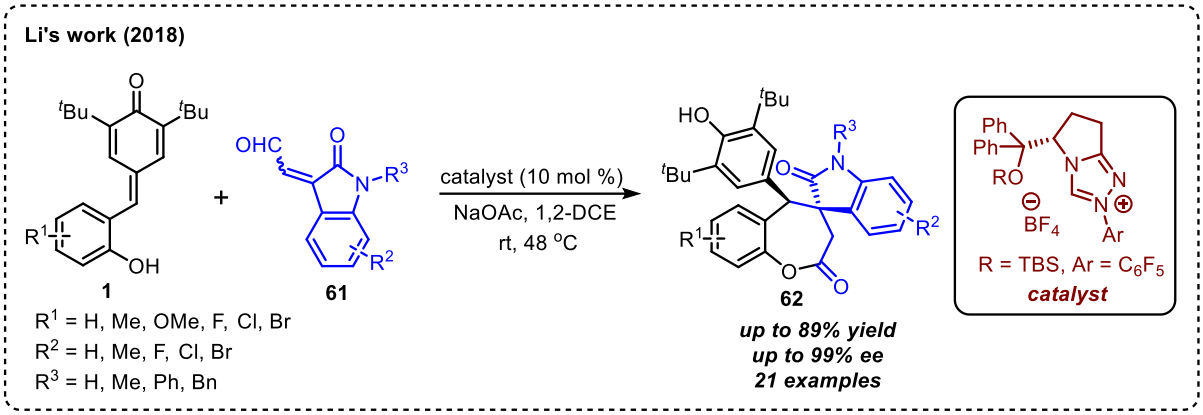
In 2019, Zhao and co-workers described the $FeCl_3$-catalyzed [4+2]-annulation reaction for the preparation of 2,4-diaryl-1,3-benzoxazine derivatives (**60**) from 2-hydroxyphenyl-substituted *p*-QMs (**1**) and imidates (**59**). According to the proposed reaction mechanism, initially, imidate undergoes 1,6-conjugate addition to activated *p*-QMs (**1**), followed by an intramolecular cyclization and elimination sequence to produce the product **60** (Scheme 20).[30]



Scheme 20. Synthesis of 1,3-benzoxazine derivatives using imidates

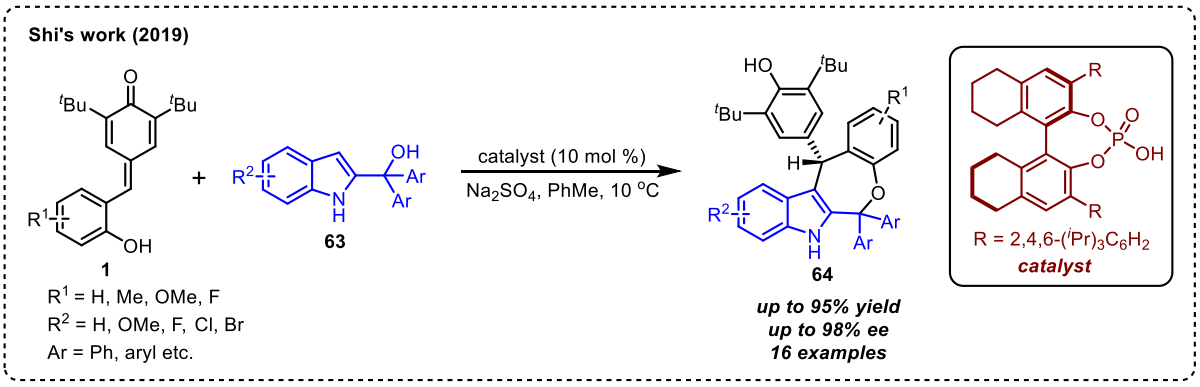
In 2018, Li's[31] and Ender's[32] groups independently developed a chiral *N*-heterocyclic carbene (NHC) catalyzed highly enantioselective synthesis of *spiro*-cyclic benzoxopinones (**62**) through a [4+3]-cycloaddition of 2-hydroxyphenyl-substituted *p*-QMs (**1**) with isatin-

derived enals (**61**). The reaction proceeds through the generation of a Breslow intermediate from NHC and **61**. Then the Breslow intermediate undergoes vinylogous conjugate addition to **1**, followed by intramolecular cyclization to yield the products (Scheme 21).



Scheme 21. Synthesis of *spiro*-cyclic benzoxopinones using isatin-derived enals

In 2019, Shi's group established the synthesis of enantioselective seven-membered oxygen-containing heterocycles (**64**) through an asymmetric [4+3]-annulation of 2-hydroxyphenyl substituted *p*-QMs (**1**) and 2-indolylmethanol (**63**) in the presence of a chiral phosphoric acid catalyst. A mechanistic study suggested the generation of *o*-QM from **1**, followed by enantioselective1,4-conjugate addition of **63** to activated *o*-QM and intramolecular cyclization to produce the product (Scheme 22).[33]



Scheme 22. Synthesis of seven-membered oxygen-containing heterocycles using 2-indolylmethanol

1.5 References

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Part 2

2. A one-pot approach to 2,3-diarylbenzo[*b*]furans through *N*-heterocyclic carbene catalyzed 1,6-conjugate addition followed by acid-mediated dehydrative cyclization

2.1 Introduction

The Benzo[*b*]furan scaffold is widely found in many natural products[1] and biologically active molecules (Figure 1).[2] Several of them show a variety of pharmacological activities. For example, Amurensin H is used to treat allergic airway inflammation.[2d] Anigopreissin A has been widely used as an inhibitor of HIV-1 reverse transcriptase,[2e] and the premethylated Anigopreissin A (PAA) exhibits inhibitory activity for human hepatoma cell proliferation.[2f,g] Diptoindonesin G has been found to show potent immunosuppressive[2h] and cytotoxic activity.[2i] Malibatol A is found to protect against brain injury.[2j] Apart from the therapeutic application, several benzo[*b*]furan-based molecules have found remarkable applications in different drug leads and also in materials chemistry as electroluminescence molecules.[3]

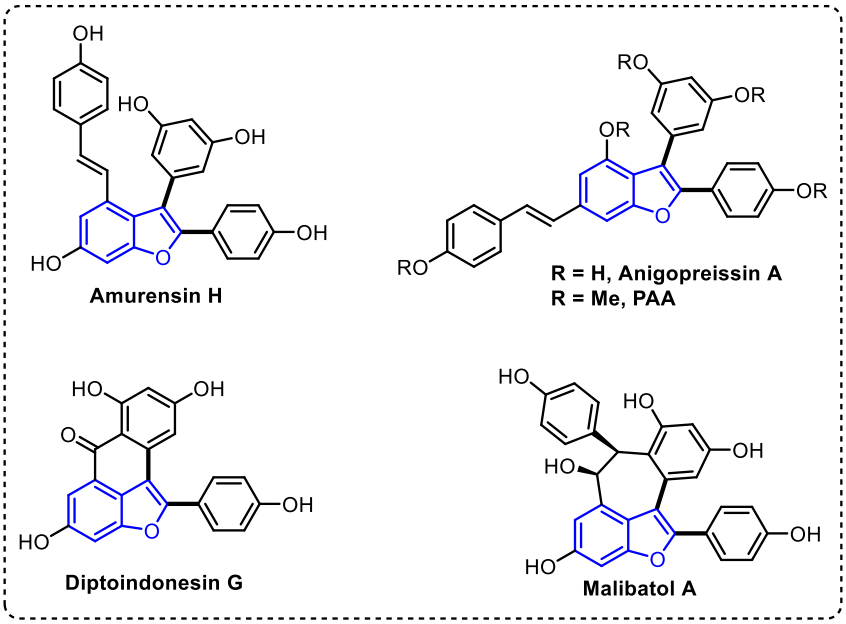


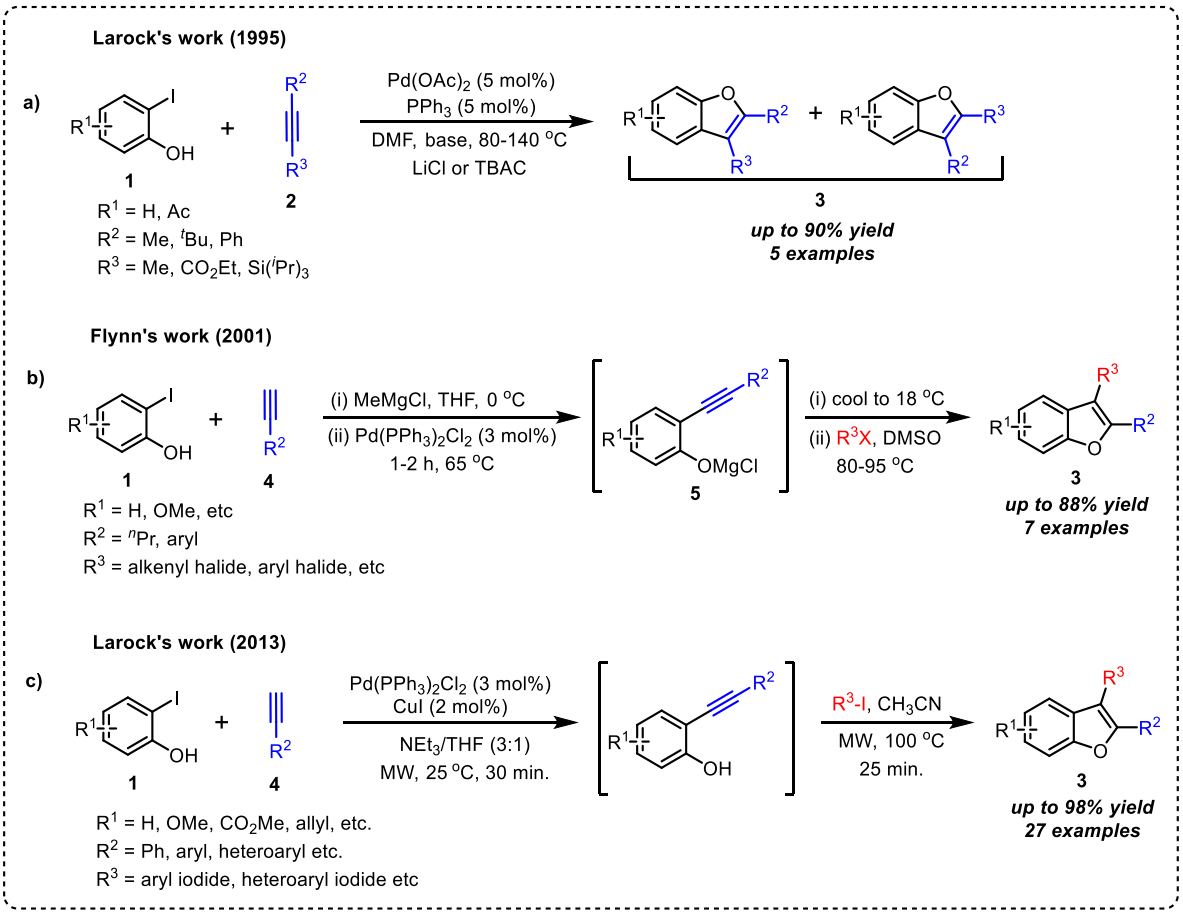
Figure 1. Biologically active 2,3-diarylbenzo[*b*]furan-based natural products

Due to their fascinating applications, numerous synthetic approaches have been reported to efficiently access the 2,3-diarylbenzo[*b*]furan moiety, and some of them are discussed below.[4]

2.2 Literature reports on the metal-catalyzed synthesis of benzofuran derivatives

2.2.1 Synthesis of 2,3-disubstituted benzofuran from *o*-iodophenols

In 1995, Larock and co-workers reported a palladium-catalyzed hetero-annulation reaction of *o*-iodophenol **1** with internal alkynes (**2**) for the synthesis of 2,3-disubstituted benzofurans (**3**). A variety of unsymmetrical internal alkynes were treated with *o*-iodophenol in the presence of $Pd(OAc)_2$ at higher temperatures. The regio-isomeric products (**3**) were isolated in moderate to good yields (Scheme 1, **a**).[5] Later, Flynn's group described the synthesis of **3** by the multi-component hetero-annulative coupling of *o*-iodophenol **1** with terminal alkynes (**4**) in the presence of palladium catalyst and MeMgCl. The reaction proceeds through the formation of intermediate *o*-alkynylphenoxy magnesium chloride **5** from the coupling of magnesium phenolate and magnesium acetylide. Furthermore, intermediate **5** undergoes an intramolecular cyclization in the presence of a suitable halide partner to give product **3** (Scheme 1, **b**).[6] Similarly, in 2013, Larock's group developed a microwave-assisted multicomponent

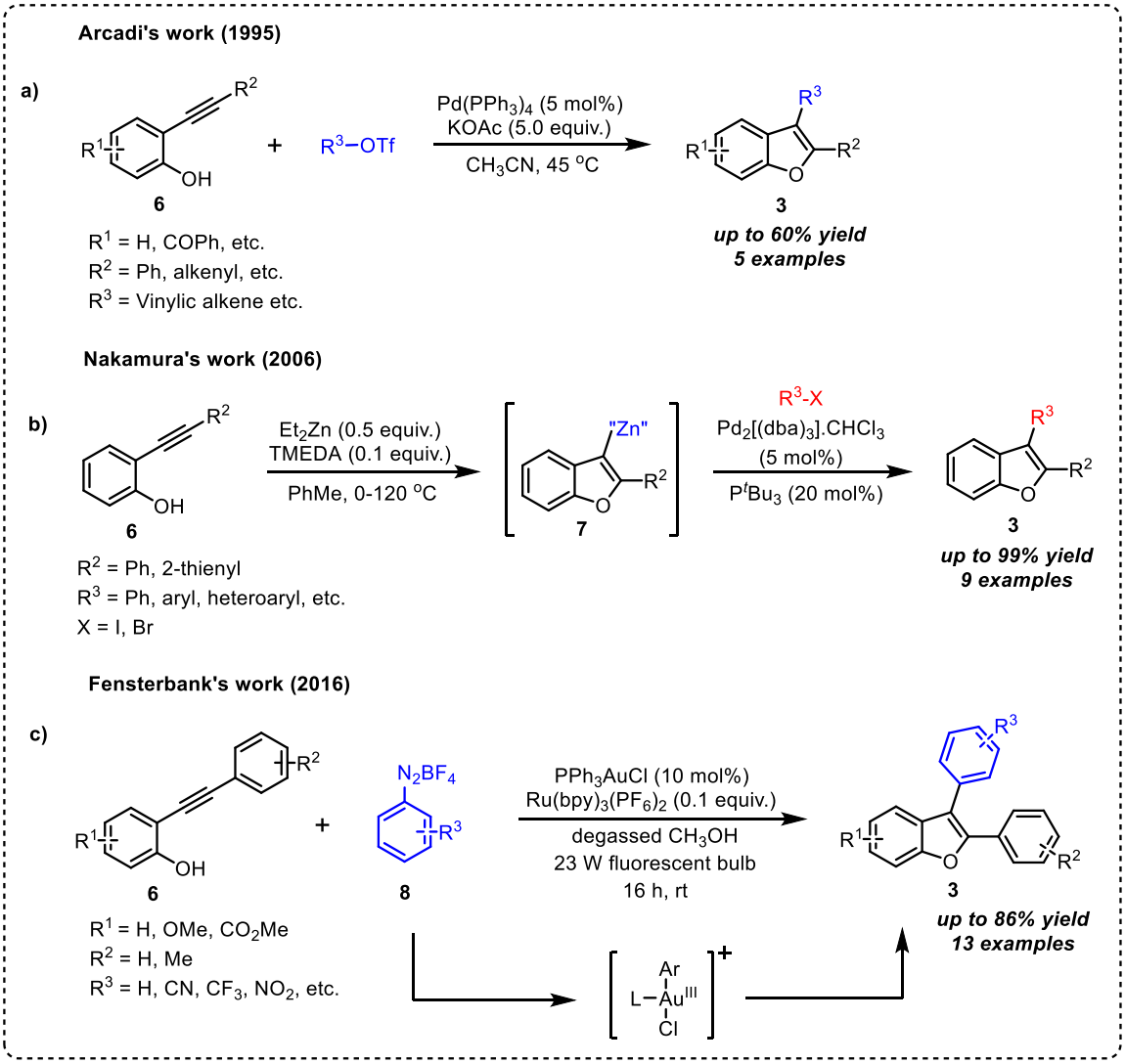


Scheme 1. Synthesis of 2,3-disubstituted benzo[*b*]furan derivatives from *o*-iodophenols

one-pot approach for preparing the 2,3-diarylbenzofuran derivatives using *o*-iodophenol (**1**), terminal alkynes (**4**), and aryl halides under Sonogashira reaction conditions. In this case, initially, Sonogashira coupling takes place between the terminal alkyne and **1**, followed by cyclization in the presence of aryl halide to form product **3** in moderate to good yields (Scheme 1, **c**).[7]

2.2.2 Synthesis of 2,3-disubstituted benzofurans from *o*-alkynyl phenols

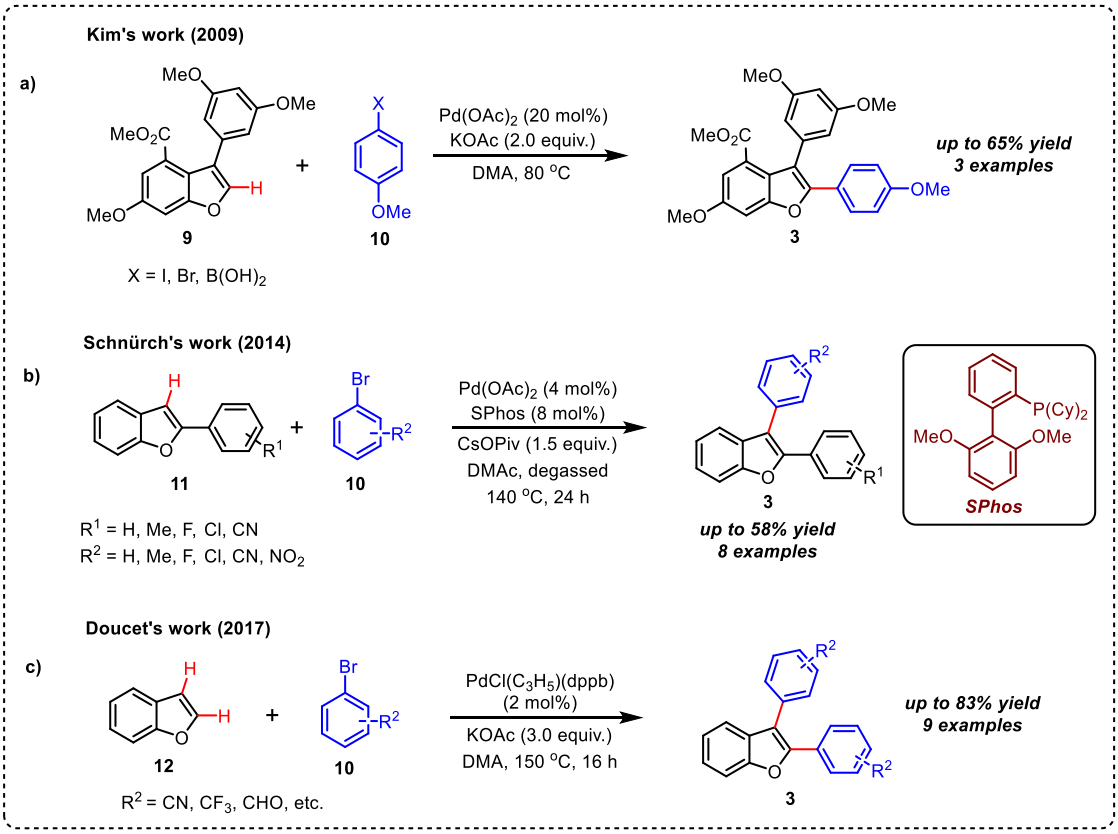
In 1995, Arcadi and co-workers reported the synthesis of substituted benzofuran derivatives from *o*-alkenyl or *o*-alkynyl phenols under different reaction conditions. 2,3-disubstituted benzofurans (**3**) were obtained from *o*-alkynyl phenols (**6**) and vinyl triflate in the presence of $Pd(PPh_3)_4$/KOAc in moderate yields. When the reaction was carried out in the presence of a CO balloon, 2-substituted-3-acyl benzofuran derivatives were produced



Scheme 2. Synthesis of 2,3-disubstituted benzo[*b*]furan derivatives from *o*-alkynyl phenols

(Scheme 2, **a**).[8] Similarly, Yang's group demonstrated the synthesis of 2,3-disubstituted benzofuran derivatives (**3**) through a palladium/bipyridine catalyzed hetero-annulation of aryl halides with *o*-alkynyl phenols (**6**) in moderate to good yield.[9] Later, Nakamura and co-workers developed a zinc-catalyzed cyclization of 2-alkynyl phenols (**6**) to 3-zinciobenzofuran intermediate **7** followed by a palladium-catalyzed coupling with suitable halide partners for the construction of 2,3-diarylbenzo[*b*]furan derivatives (**3**). In the presence of Et_2Zn, 2-alkynyl phenol undergoes deprotonation to generate zinc phenoxide, which was found to form oligomeric aggregates. Therefore, TMEDA (*N*,*N*,*N*',*N*'-tetramethylethylenediamine) was used to activate these aggregates for the reaction to proceed (Scheme 2, **b**).[10] Recently, Fensterbank developed the annulation of 2-alkynyl phenols (**6**) with aryl diazonium salts **8** by dual photoredox/gold catalysis for the synthesis of 2,3-diarylbenzo[*b*]furan derivatives **3**. The reaction proceeds through the generation of Au(III)-aryl complex from aryl diazonium salt and $Ru(bpy)_3(PF_6)_2$ upon irradiation with visible light. Then, the gold-complex activates the 2-alkynyl phenols, followed by *5-endo-dig* cyclization and subsequent reductive elimination, generating the desired product **3** (Scheme 2, **c**).[11]

2.2.3 Synthesis of 2,3-disubstituted benzofurans by direct arylation of benzofurans



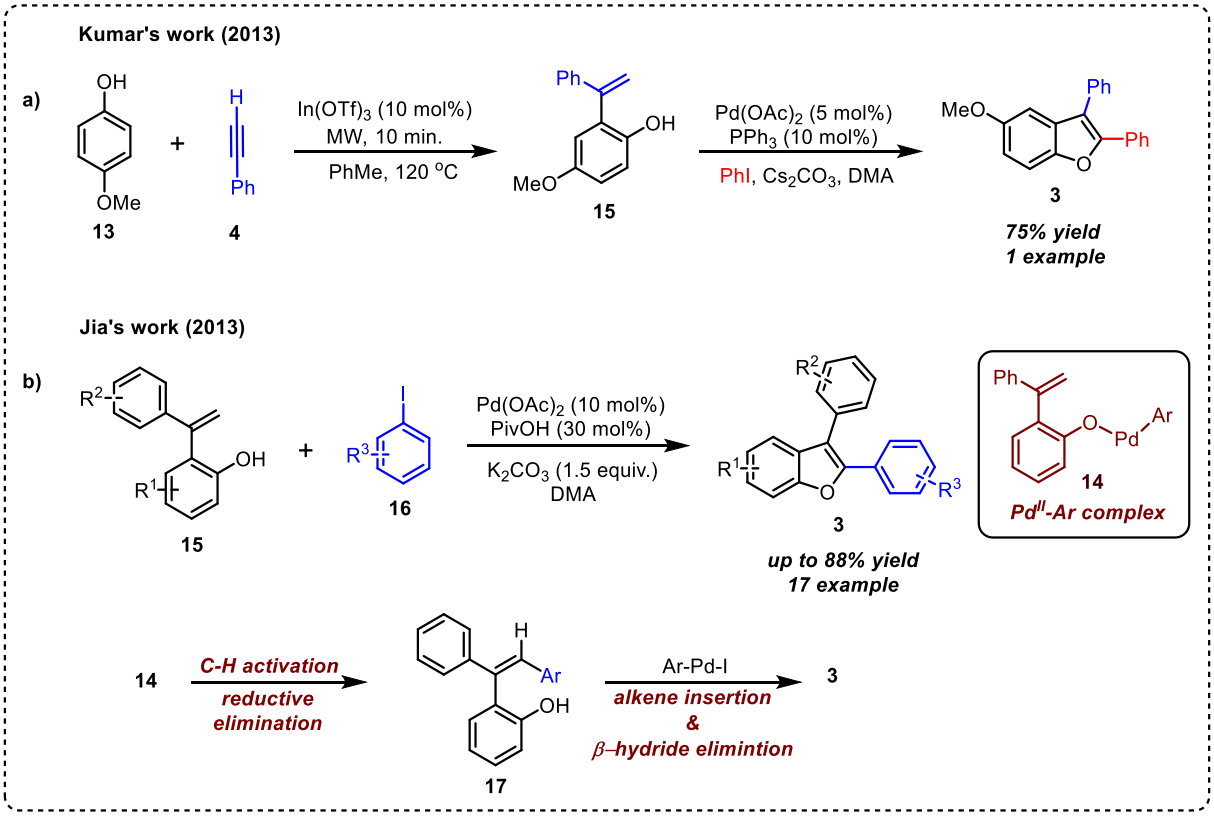
Scheme 3. Synthesis of 2,3-disubstituted benzo[*b*]furans by direct arylation of benzofurans

Several reports have also been developed to synthesize 2,3-diaryl benzo[*b*]furans through a metal-catalyzed direct arylation of benzo[*b*]furan with suitable aryl halides.[12-15] A few of them are discussed here.

In 2009, Kim and co-workers investigated a Palladium-catalyzed C–H activation of 3-aryl benzo[*b*]furan **9** followed by cross-coupling with an aryl halide **10** at C2-position to access 2,3-diaryl benzofuran derivatives (Scheme 3, **a**).[13] Similarly, Schnürch's group disclosed a palladium-catalyzed C3-arylation of 2-arylbenzofurans (**11**) for the synthesis of functionalized benzofuran derivatives **3** (Scheme 3, **b**).[14] Recently, Doucet and co-workers described a one-pot, direct C2, C3-diarylation of benzofuran **12** through a Pd-catalyzed coupling with aryl bromides **10** for the construction of 2,3-diaryl benzofurans in moderate to good yields (Scheme 3, **c**).

2.2.4 Synthesis of 2,3-disubstituted benzofuran derivatives from *α*–hydroxy styrenes

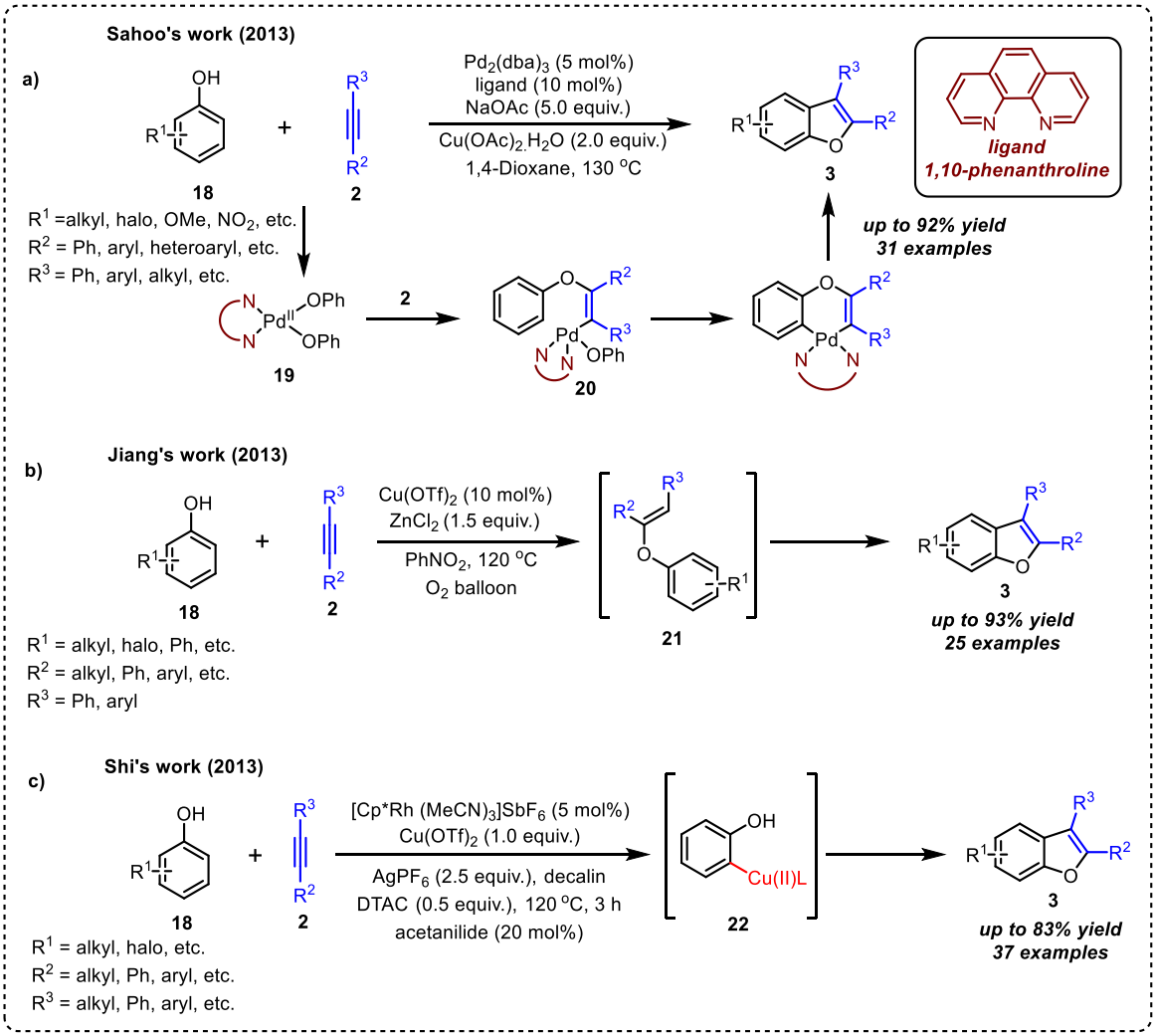
In 2013, Kumar and co-workers described the synthesis of 2,3-diphenylbenzo[*b*]furan **3** from 4-methoxy phenol **13** and phenylacetylene **4**. The reaction proceeds through the hydroarylation of **13** with alkynes in the presence of $In(OTf)_3$ under microwaves to generate *α*–hydroxy styrenes, which undergo Heck-oxyarylation followed by oxidation to produce the



Scheme 4. Synthesis of 2,3-disubstituted benzo[*b*]furan derivatives from *α*–hydroxy styrenes

product **3** in 75% yield. No product formation was observed with the *O*-protected phenol, which indicates the formation of oxygen-coordinated Pd(II)-aryl complex **14** (Scheme 4, **a**).[16] Similarly, Jia's group reported a palladium-catalyzed C–H activation/oxidation tandem reaction for the synthesis of **3** using 2-hydroxy styrenes (**15**) and iodobenzenes (**16**). A variety of 2-hydroxy styrenes and iodobenzenes reacted efficiently in the presence of $Pd(OAc)_2$/PivOH at 160 °C to afford the products in good yields. According to the proposed mechanism, complex **14** undergoes alkenyl C–H activation followed by a subsequent reductive elimination to generate an intermediate **17**. The intermediate **17** forms an oxygen-coordinated Pd(II)-aryl complex, which then undergoes an alkene insertion followed by *β*-hydride elimination to produce the product **3** (Scheme 4, **b**).[17]

2.2.5. Synthesis of 2,3-disubstituted benzofurans from phenols and internal alkynes



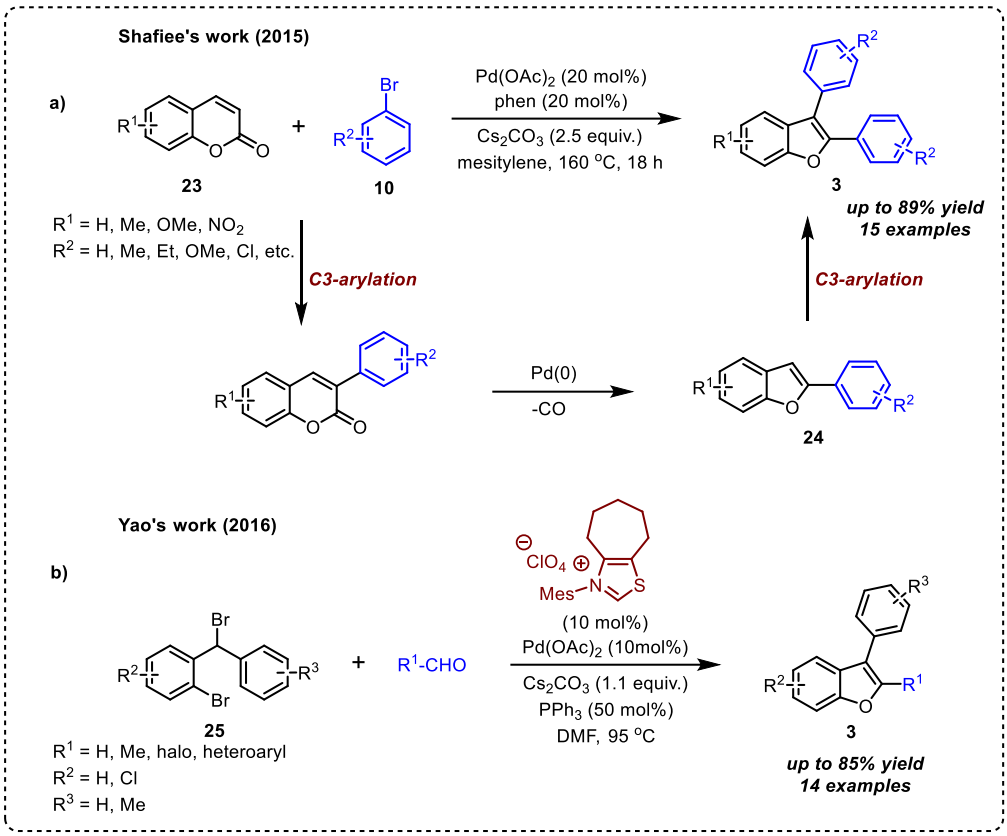
Scheme 5. Synthesis of 2,3-disubstituted benzo[*b*]furans from phenols and internal alkynes

In 2013, Sahoo and co-workers described an elegant protocol for the synthesis of 2,3-diarylbenzo[*b*]furan **3** through a palladium-catalyzed oxidative annulation of unactivated internal alkynes (**2**) and phenols (**18**). In the case of *meta*-substituted phenols, highly regioselective products (**3**) were obtained by the formation of a C–C bond at a less hindered site of phenol. The mechanistic study revealed that the reaction proceeds through the generation of Pd^{II}–phenoxide complex **19**, which undergoes *oxy*-palladation with an alkyne to generate an intermediate **20**, followed by *ortho* C–H insertion and reductive elimination to produce the product (Scheme 5, **a**).[18] In the same year, Jiang's[19] and Shi's[20] groups independently developed the copper-catalyzed one-pot approach for the synthesis of **3** using phenols (**18**) and internal alkynes (**2**). According to Jiang's proposal, phenol undergoes nucleophilic addition to alkyne **2**, activated by Cu(II) and Lewis acid, to generate an intermediate **21**, followed by C–H activation and oxidative cyclization in the presence of O_2 to give the product (Scheme 5, **b**). Shi's group proposed that the reaction proceeds through the reversible electrophilic carbo-cupration of phenol to produce an intermediate **22**, followed by alkyne insertion and intramolecular cyclization (Scheme 5, **c**). Recently, Satyanarayana and co-workers established the Lewis acid-mediated one-pot approach for the synthesis of **3** in moderate to good yields. A wide range of phenols (**18**) and internal alkynes (**2**) were reacted in the presence of $ZnCl_2$ to afford the products.[21]

2.2.6 Miscellaneous reports on the synthesis of 2,3-disubstituted benzofurans

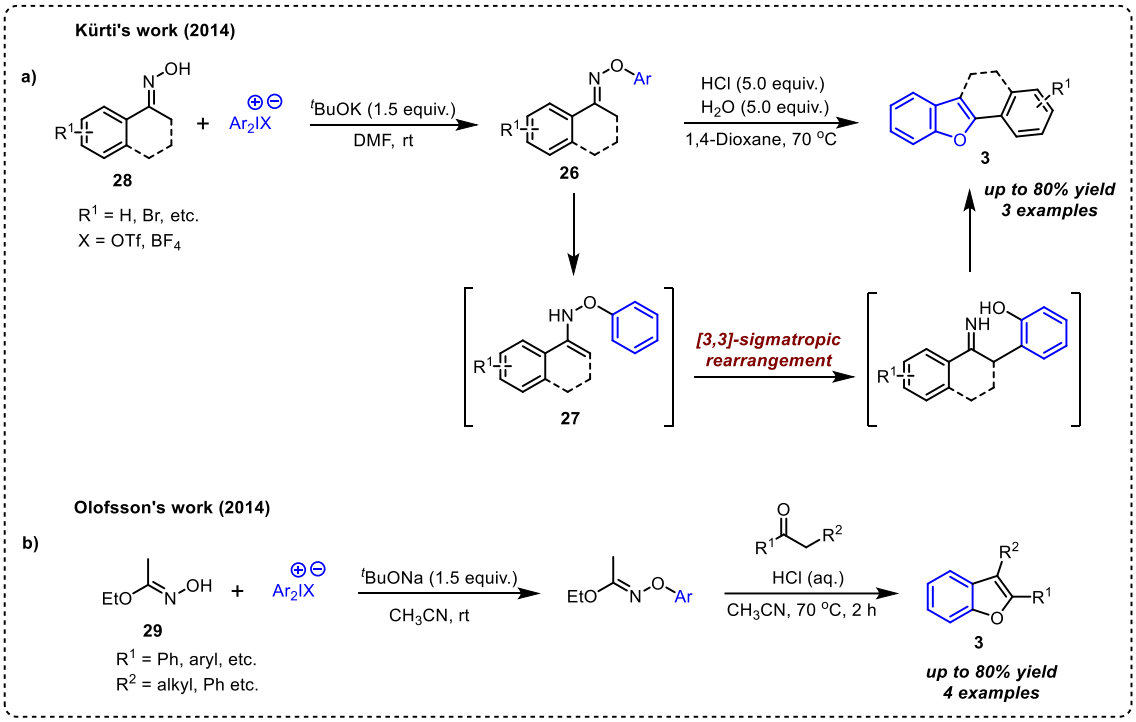
In 2015, Shafiee and co-workers reported a palladium-catalyzed decarbonylation of coumarins (**23**) to access 2,3-diarylbenzo[*b*]furan derivatives (**3**) in good yields. This protocol involves the activation of three types of C–C(H) bonds in one-pot. The reaction proceeds through the regioselective C3-arylation of **23** to generate 3-arylcoumarin, followed by decarbonylative reductive elimination to form 2-arylbenzofuran **24**. Further, compound **24** undergoes C3-arylation to give the product (Scheme 6, **a**).[22]

In 2016, Yao's group described the synthesis of **3** through nucleophilic substitution of 2'-bromodiphenyl bromomethanes (**25**) with Breslow intermediate (generated from NHC and aromatic aldehydes), followed by palladium-catalyzed intramolecular C–O bond formation. A variety of 2'-bromodiphenyl bromomethanes and aromatic aldehydes were reacted in thiazole-based NHC to afford the products in good yield (Scheme 6, **b**). [23]



Scheme 6. Synthesis of 2,3-disubstituted benzo[*b*]furans

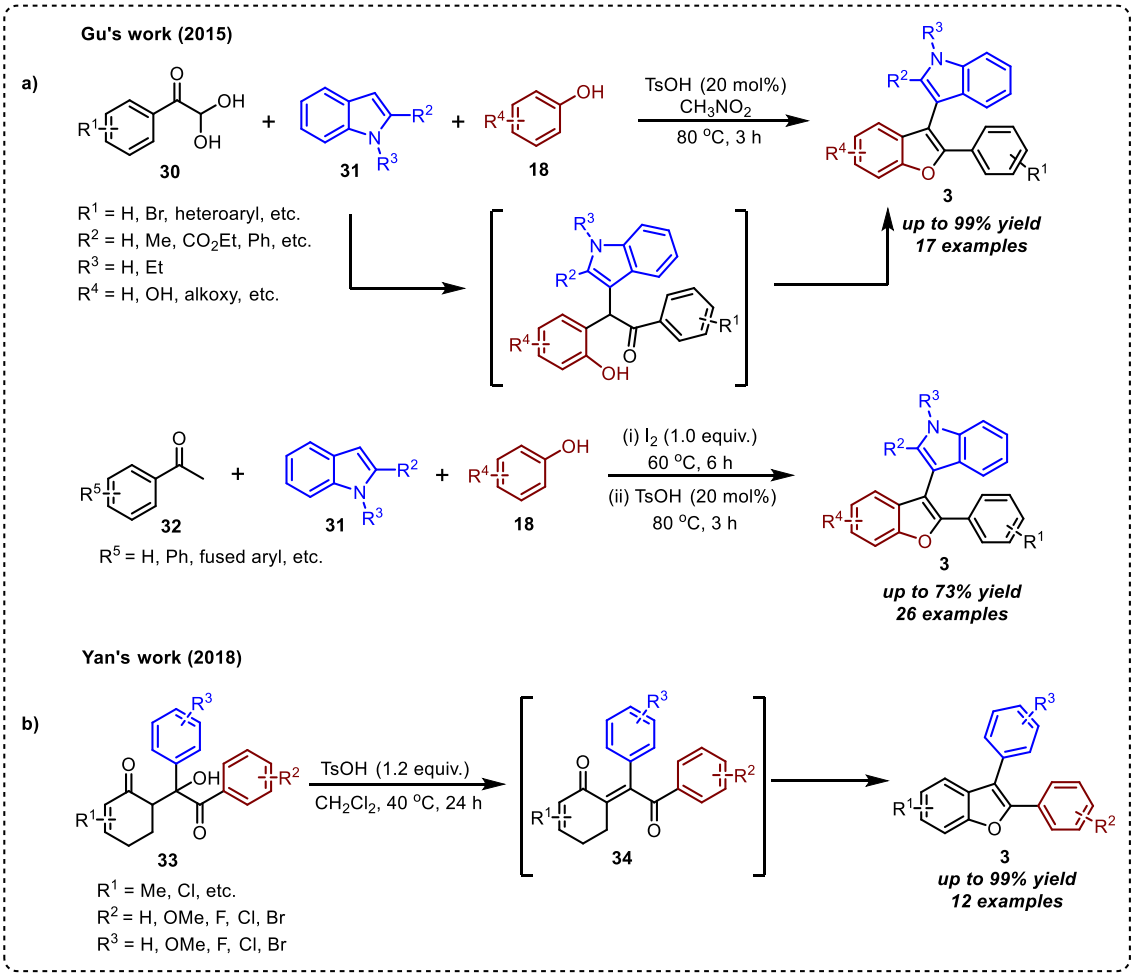
2.3 Literature reports on the synthesis of metal-free benzofuran derivatives



Scheme 7. Synthesis of 2,3-disubstituted benzo[*b*]furans from oxime derivatives

Apart from the metal-catalyzed reactions, a few metal-free approaches have also been established to synthesize 2,3-diarylbenzo[*b*]furans. A few of them are discussed in this section.

In 2014, Kürti and co-workers developed the synthesis of 2,3-disubstituted benzo[*b*]furans (**3**) from *O*-aryl ketoxime derivatives (**26**). The reaction proceeds through the acid-mediated generation of *O*-aryl-*N*-alkenyl hydroxylamine **27** from **26**, followed by [3,3]-sigmatropic rearrangement and intramolecular cyclization/elimination to produce the product. *O*-aryl ketoximes (**26**) can be obtained from the direct *O*-arylation of keto-oximes (**28**) with diaryliodonium salts in the presence of ^{t}BuOK at room temperature (Scheme 7, **a**).[24] Similarly, in the same year, Olofsson's group described a one-pot approach for the synthesis of 2,3-disubstituted benzo[*b*]furans (**3**) from ethyl acetohydroxamate (**29**) and diaryliodonium salts (Scheme 7, **b**).[25]

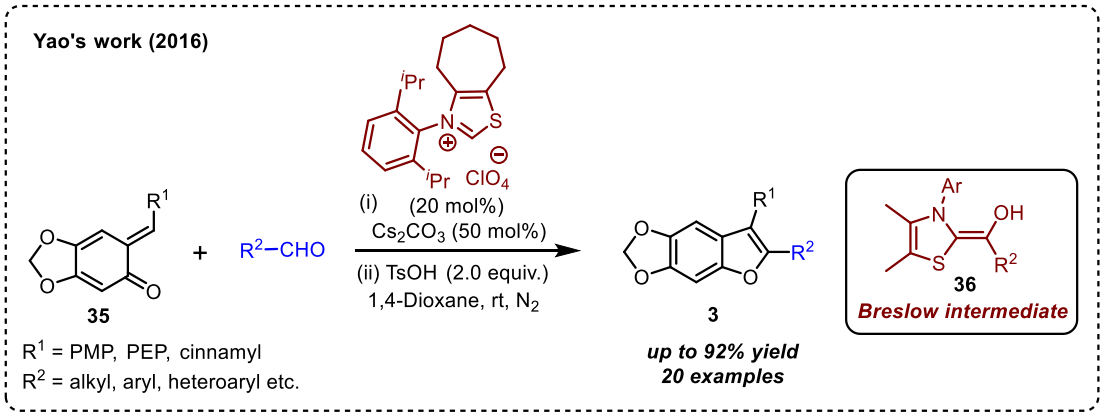


Scheme 8. Acid-mediated synthesis of 2,3-disubstituted benzo[*b*]furan derivatives

In 2015, Gu and co-workers demonstrated the acid-catalyzed multi-component reaction of alkylglyoxals (**30**), phenols (**18**), and indoles (**31**) to synthesize 2,3-disubstituted

benzo[*b*]furans (**3**) in moderate to good yields. They have also developed the sequential multi-component one-pot approach to access **3** by replacing alkylglyoxals with alkyl ketones (**32**) in I_2/DMSO system (Scheme 8, **a**).[26] Recently, Yan's group reported the acid-mediated one-pot protocol for synthesizing 2,3-disubstituted benzo[*b*]furans from **33**. The reaction proceeds through the formation **34** *via* acid-mediated dehydrative elimination, followed by furan annulation/dehydrative elimination and aromatization sequence to produce the product (Scheme 8, **c**).[27]

In 2016, Yao and co-workers described the *N*-heterocyclic carbene (NHC) catalyzed synthesis of 2,3-diarylbenzo[*b*]furan derivatives from *o*-quinone methides (**35**) and aromatic aldehydes. Initially, the Breslow intermediate **36** was generated from NHC and aromatic aldehyde. Then, this intermediate **36** attacks the *o*-quinone methide, followed by acid-mediated intramolecular cyclization and dehydrative elimination to produce product **3**. A variety of *o*-quinone methides (**35**) and aromatic benzaldehydes were reacted under the standard conditions to afford the products in moderate to good yield (Scheme 9).[28]



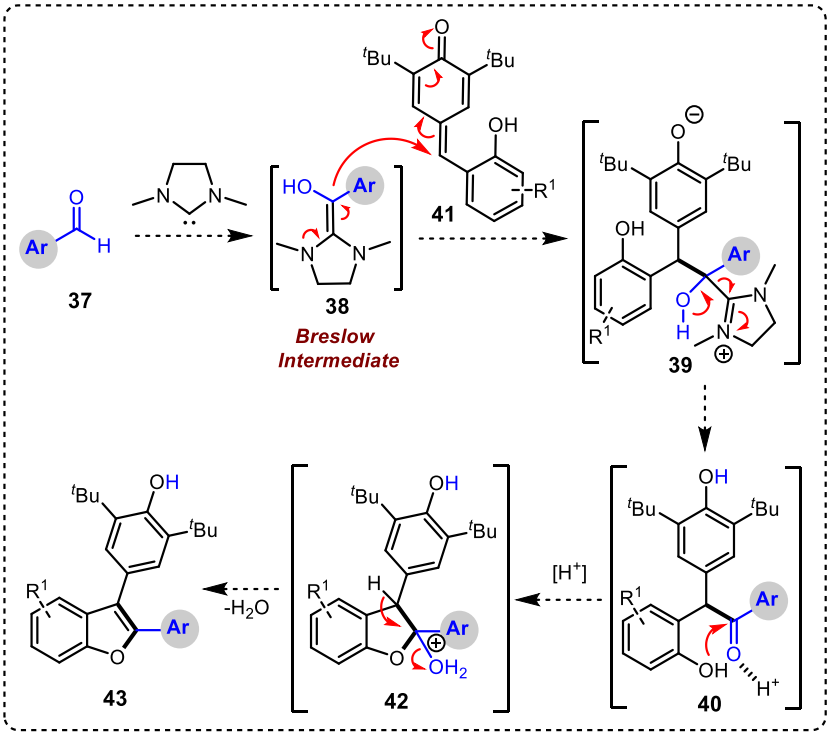
Scheme 9. NHC-catalyzed synthesis of 2,3-disubstituted benzo[*b*]furan derivatives

2.4 Background

Although all the above-mentioned approaches are elegant, most involve either the use of expensive metal catalysts or harsh reaction conditions, making those processes practically less attractive. Therefore, developing a practical method under organocatalytic conditions would be highly desirable.

Recently, our group developed a bis(amino)-cyclopropenylidene (BAC) catalyzed 1,6-conjugate addition of aromatic aldehydes to *p*-quinone methides (*p*-QMs) to access α,α'-diaryl acetophenone derivatives.[29a] Later, Zhang, Jiang, and co-workers reported the same methodology, where NHC was used as a catalyst.[29b] While working on this particular

transformation, we envisioned that if a hydroxyl group is introduced at the 2-position of the aryl group of *p*-QM **41**, then it is possible to elaborate the 1,6-adduct **40** to the corresponding 2,3-diarylbenzo[*b*]furan derivative **43** in a one-pot manner through acid-mediated dehydrative

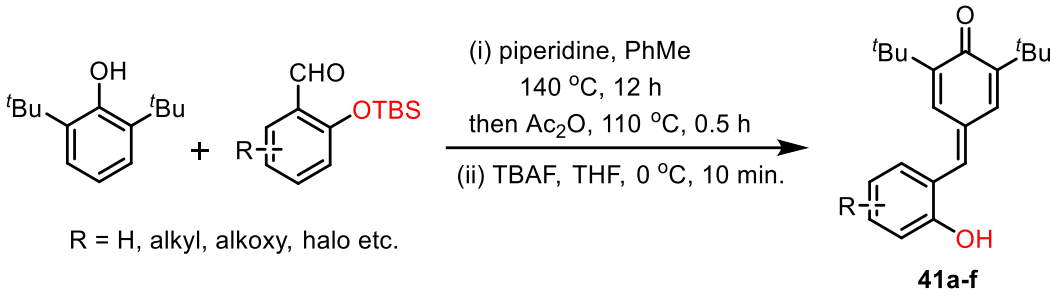


Scheme 10. Our hypothesis for the one-pot synthesis of 2,3-diarylbenzo[*b*]furans

annulation reaction (Scheme 10). Based on this concept, we have developed a one-pot approach to access 2,3-diarylbenzo[*b*]furan derivatives through *N*-heterocyclic carbene (NHC) catalyzed 1,6-conjugate addition of aromatic aldehydes to 2-hydroxyphenyl-substituted *p*-quinone methides followed by acid-mediated dehydrative annulation reaction, and the results are exemplified herein. Although 2-hydroxyphenyl-substituted *p*-quinone methides[30] have already been utilized as electrophiles in a few other synthetic transformations, to the best of our knowledge, these synthons have not been utilized in combination with NHC catalysis[31] for the synthesis of 2,3-diarylbenzo[*b*]furan derivatives so far. Thus, we have decided to explore this transformation in detail.

2.5 Result and discussion

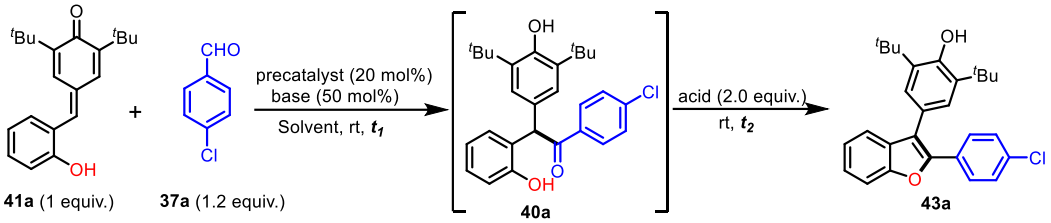
The 2-hydroxyphenyl-substituted *p*-QMs (**41a**–**f**) used in this study were prepared according to the literature procedure (Scheme 11).[30a]

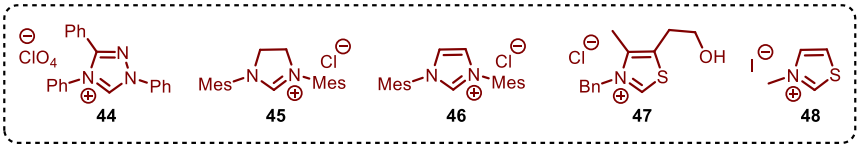


Scheme 11. Synthesis of 2-hydroxyphenyl-substituted *p*-QMs

To optimize the reaction conditions, a readily available 2-hydroxyphenyl-substituted *p*-QM **41a**[30a] was treated with 4-chloro benzaldehyde (**37a**) in the presence of a wide range of carbene precursors (**44**-**48**) under different conditions, and the results are summarized in Table 1. Our initial attempts were highly disappointing, as by using carbene precursors **44**-**46** and K_2CO_3 as a base in THF, the formation of intermediate **40a** did not take place under these reaction conditions (entries 1-3). However, delightfully, in the presence of thiazolium-based carbene precursor **47** and 50 mol% K_2CO_3, a complete conversion of **41a** to **40a** was observed within 12 h, and the expected diarylbenzo[*b*]furan **43a** was obtained in 50% yield within 12 h, after treating the reaction mixture with 2 equivalents of TsOH at rt (entry 4). When the reaction was carried out with another thiazolium precatalyst **48**, product **43a** was obtained only in a 10% yield (entry 5). Unfortunately, when Cs_2CO_3 was used as a base, the 1,6-addition reaction did not take place even after 24 h (entry 6). However, the reaction worked well when KO^{t}Bu was used as a base, and **43a** was obtained in 72% yield in that case (entry 7). Interestingly, when NaH was used as a base and **47** was used as a precatalyst in THF, the diarylbenzo[*b*]furan **43a** was obtained in a 78% isolated yield. Encouraged by this result, the optimization studies were elaborated with other solvents, such as CH_2Cl_2 and acetonitrile (entries 9 & 10). Although both the solvents were found to be very effective to drive this transformation with a considerable reduction in the reaction times, acetonitrile was found to be a bit superior to CH_2Cl_2 in driving the TsOH-mediated annulation step and, as a result, the product **43a** was obtained in 91% yield in that case (entry 10). Other acids, such as camphorsulfonic acid (CSA), methanesulfonic acid, and trifluoroacetic acid (TFA), were found to be less effective or ineffective for the annulation step (entries 11-13). When the amount of NaH was reduced to 20 mol%, the 1,6-conjugate addition step was found to be very slow, and, in fact, the reaction was not complete even after 24 h; so **43a** was obtained only in 65% yield (entry 14). Similarly, when one equivalent of TsOH was used instead of two equivalents, the annulation reaction was not complete even after 10 h, and the yield of **43a** was considerably reduced to 60% (entry 15).

Table 1. Catalyst screen and optimization[a]





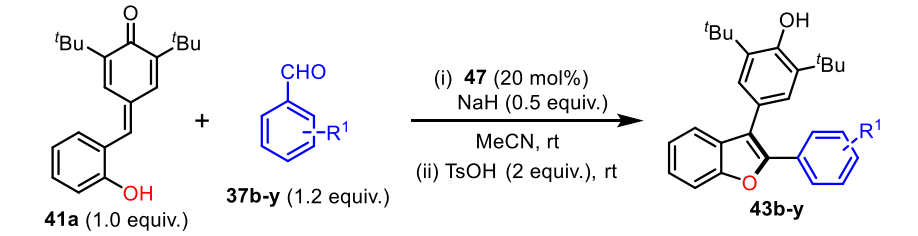
entry	precatalyst	base	acid	solvent	time (t_1+t_2) [h]	Yield of 43a [%]
1	**44**	K_2CO_3	-	THF	24+0	nr
2	**45**	K_2CO_3	-	THF	24+0	nr
3	**46**	K_2CO_3	-	THF	24+0	nr
4	**47**	K_2CO_3	TsOH	THF	12+12	50
5	**48**	K_2CO_3	TsOH	THF	12+12	10
6	**47**	Cs_2CO_3	TsOH	THF	24+0	nr
7	**47**	KO^{t}Bu	TsOH	THF	12+12	72
8	**47**	NaH	TsOH	THF	12+12	78
9	**47**	NaH	TsOH	CH_2Cl_2	4+2	85
10	**47**	**NaH**	**TsOH**	**MeCN**	**4+1**	**91**
11	**47**	NaH	CSA	MeCN	4+6	80
12	**47**	NaH	MsOH	MeCN	4+20	60
13	**47**	NaH	TFA	MeCN	4+20	nr
14[b]	**47**	NaH	TsOH	MeCN	24+1	65
15[c]	**47**	NaH	TsOH	MeCN	4+10	60
16[d]	**47**	NaH	TsOH	MeCN	6+1	86

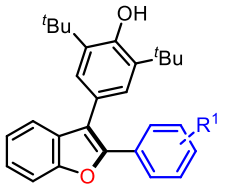
[a]All reactions were carried out with **41a** in 1.5 mL of solvent. [b]20 mol% of sodium hydride was used. [c]1.0 equiv. of TsOH was used. [d] Reaction was carried out with 3.22 mmol (1.0 g) of **41a** and 3.87 mmol of **37a**. nr = no reaction. Yields reported are isolated yields.

To show the practical applicability of this one-pot transformation, an experiment was carried out on a gram scale, in which 1.0 g (3.22 mmol) of **41a** was treated with **37a** (3.87 mmol) under the best conditions (entry 10), and in this case, **43a** was obtained in 1.20 g (86% yield) [entry 16].

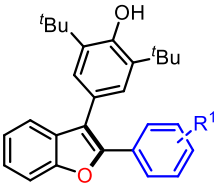
With the optimized conditions in hand, the scope and limitations of this transformation were examined (Scheme 12). This one-pot protocol worked well with electron-poor aromatic aldehydes (**37b-e**), and in those cases, the respective 2,3-diarylbenzo[*b*]furans **43b-e** were obtained in moderate to good yields (66-75%). This protocol was found to be very effective

Scheme 12. Substrate scope with different aromatic aldehydes[a]

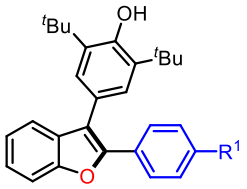




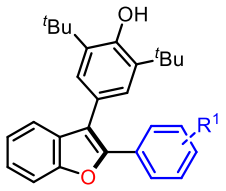
43b, R^1 = 4-CN, (4+1) h, 70%
43c, R^1 = 3-NO_2, (5+1) h, 75%
43d, R^1 = 4-CF_3, (6+1) h, 72%
43e, R^1 = 3-CF_3, (6+1) h, 66%



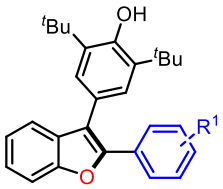
43f, R^1 = H, (5+1) h, 78%
43g, R^1 = 3,5-dimethoxy, (7+1) h, 75%
43h, R^1 = 4-OCF_3, (5+1) h, 84%



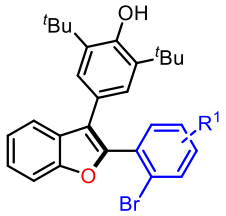
43i, R^1 = ^{t}Bu, (11+1) h, 28%
43j, R^1 = Et, (11+1) h, 23%
43k, R^1 = Me, (11+1) h, 25%



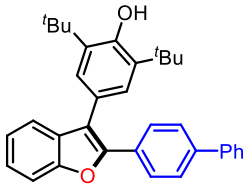
43l, R^1 = 4-Br, (7+1.5) h, 81%[b]
43m, R^1 = 2-Cl, (4+1) h, 81%
43n, R^1 = 2-Br, (4+1) h, 82%
43o, R^1 = 2-F, (4+1) h, 85%



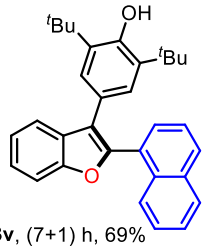
43p, R^1 = 2,4-dichloro, (4+1) h, 70%
43q, R^1 = 2,4-difluoro, (4+1) h, 78%



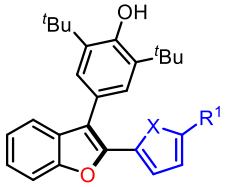
43r, R^1 = 5-F, (4+1) h, 58%
43s, R^1 = 5-OMe, (7+1) h, 51%
43t, R^1 = 4-Me, (11+1) h, 35%



43u, (7+1) h, 72%



43v, (7+1) h, 69%



43w, X = S, R^1 = H, (9+1) h, 72%
43x, X = S, R^1 = Br, (9+1) h, 75%
43y, X = O, R^1 = H, (9+1) h, 75%

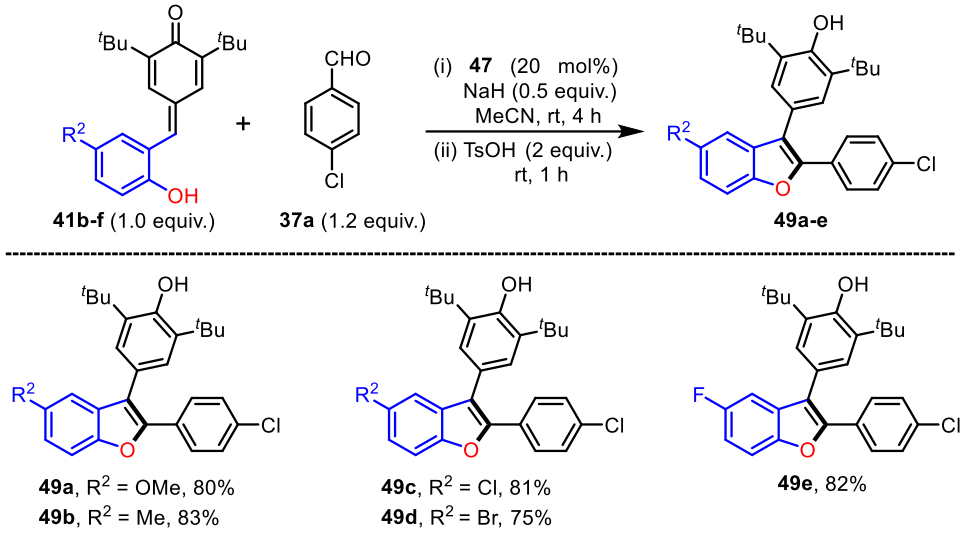
[a]All reactions were carried out in 30 mg (0.097 mmol) scale of **41a** in 1.5 mL of MeCN. Yields reported are isolated yields.

in the cases of benzaldehyde (**37f**) and methoxy- or trifluoromethoxy benzaldehydes (**37g** & **37h**) as the desired products (**43f-h**) were obtained in very good yields (75-84%). However, surprisingly in the cases of alkyl-substituted aldehydes (**37i-k**), the reaction was found to be very sluggish, and the respective products **43i-k** were isolated in poor yields (23-28%); because in those cases, the 1,6-conjugate addition step was found to be very slow, and also the complete conversion of **41a** to the respective 1,6-adducts was not realized even after stirring the reaction mixture for a prolonged period (24 h). The halo-substituted aromatic aldehydes (**37l-t**) reacted efficiently with **41a** to afford the desired annulated products **43l-t** in moderate to good yields

(35-85%). Sterically hindered aldehydes such as biphenyl-4-carboxaldehyde **37u** and 1-naphthaldehyde **37v** also underwent smooth conversion to the desired 2,3-diarylbenzo[*b*]furans (**43u-v**) in 72% and 69% yields, respectively. Under the standard conditions, hetero-aromatic aldehydes **37w-y** provided the corresponding 2,3-diarylbenzo[*b*]furans **43w-y** in good yields (72-75%).

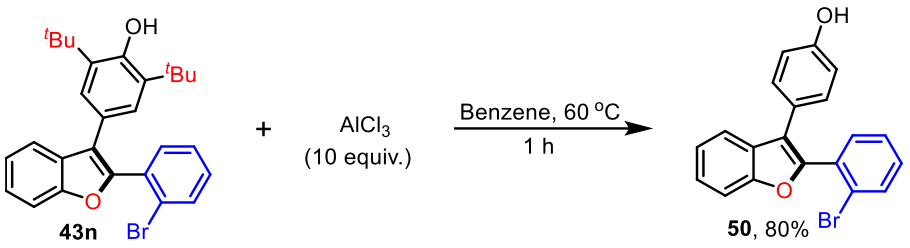
After exploring the substrate scope with different aromatic aldehydes, we investigated the generality of this protocol using different 2-hydroxyphenyl-substituted *para*-quinone methides (**41b-f**) and 4-chlorobenzaldehyde (**37a**) under optimized reaction conditions, and the results are summarized in Scheme 13. To our delight, this method worked very well with 2-hydroxy substituted *para*-quinone methides **41b** & **41c**, derived from electron-rich salicylaldehydes, and the desired products **49a** & **49b** were obtained in 80% and 83% isolated yields, respectively. Similarly, when **37a** was treated with halo-substituted 2-hydroxyphenyl-substituted *para*-quinone methides (**41d-f**), the desired 2,3-diarylbenzo[*b*]furans **49c-e** were obtained in the range of 75-82% yields.

Scheme 13. Substrate scope with different 2-hydroxy *para*-quinone methides[a]



[a]All reactions were carried out with 30 mg scale of **41b-f** in 1.5 mL of MeCN. Yields reported are isolated yields.

Toward the further expansion of the substrate scope, we attempted the de-*tert*-butylation reaction of one of the diarylbenzo[*b*]furans. In this context, **43n** was treated with an excess amount of $AlCl_3$ in benzene at 60 ^oC and, as expected, the corresponding de-*tert*-butylated 2,3-diarylbenzo[*b*]furan **50** was obtained in 80% yield within 1 h (Scheme 14).



Scheme 14. De-*tert*-butylation of **43n** using excess $AlCl_3$

2.6. Conclusion

We have successfully demonstrated a one-pot approach for the synthesis of 2,3-diarylbenzo[*b*]furans through *N*-heterocyclic carbene catalyzed 1,6-conjugate addition of aromatic aldehydes to 2-hydroxyphenyl-substituted *para*-quinone methides followed by TsOH mediated dehydrative aromatic annulation. This transformation occurs in mild conditions and is tolerant to a variety of functional groups. Moreover, this protocol provides easy and straight-forward access to a new set of 2,3-diarylbenzo[*b*]furans in moderate to good yields.

2.7. Experimental section

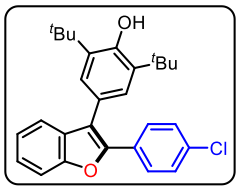
General information

All reactions were carried out under an argon atmosphere in an oven-dried round bottom flask. All the solvents were distilled before use and stored under an argon atmosphere. Most of the reagents and starting materials and NHC precursors (**45** to **48**) were purchased from commercial sources and used as such. All 2-hydroxyphenyl-substituted *p*-quinone methides were prepared by following a literature procedure.[30a] NHC precursor **44** was prepared according to the literature procedure.[32] 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 relatives to TMS, and the coupling constants (J) are reported in Hz. High-resolution mass spectra were recorded on Waters Q-TOF Premier–HAB213 spectrometer. FT-IR spectra were recorded on a Perkin-Elmer FTIR spectrometer. Thin-layer chromatography was performed on Merck silica gel 60 F_{254} TLC pellets and visualized by UV irradiation and $KMnO_4$ stain. Column chromatography was carried out through silica gel (100–200 mesh) using EtOAc/hexane as eluent.

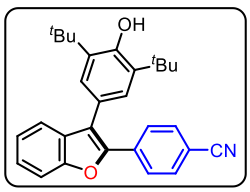
General procedure for the synthesis of 2,3-diarylbenzo[b]furans:

A mixture of 2-hydroxyphenyl-substituted *p*-quinone methide (0.097 mmol), 4-chlorobenzaldehyde (0.116 mmol), precatalyst **47** (0.0194 mmol), and NaH (0.0485 mmol) in anhydrous MeCN (1.5 mL) was stirred at room temperature under Ar atmosphere. After the reaction was complete (based on TLC analysis), TsOH (0.194 mmol) was added to the reaction mixture, and the resultant mixture was further stirred at room temperature until most of the intermediate (1,6-adduct) was completely consumed (based on TLC analysis). The reaction mixture was concentrated under reduced pressure, and the crude was directly loaded onto a silica gel column and purified using EtOAc/Hexane mixture as an eluent to get the pure product.

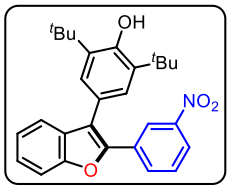
2,6-di-*tert*-butyl-4-(2-(4-chlorophenyl)benzofuran-3-yl)phenol (43a): The reaction was performed at 0.097 mmol scale of **41a**; R_f = 0.5 (5% EtOAc in hexane); white solid (37.7 mg, 91% yield); m. p. = 209–211 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, J = 8.6Hz, 2H), 7.59 (d, J = 7.6 Hz, 1H), 7.55 (d, J = 8.1 Hz, 1H), 7.36 (dd, J = 7.4, 1.2 Hz, 1H), 7.33 (s, 2H), 7.31 (d, J = 8.7 Hz, 2H), 7.27 – 7.25 (m, 1H), 5.34 (s, 1H), 1.46 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.1, 153.7, 148.9, 136.6, 133.9, 130.3, 129.7, 128.6, 128.2, 126.4, 124.9, 123.1, 123.05, 120.5, 118.9, 111.2, 34.6, 30.5; FT-IR (thin film, neat): 3633, 2659, 2876, 1449, 1261, 1153, 750 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{28}H_{28}ClO_2$ $[M–H]^–$: 431.1778; found : 431.1759.



4-(3-(3,5-di-*tert*-butyl-4-hydroxyphenyl)benzofuran-2-yl)benzonitrile (43b): The reaction was performed at 0.097 mmol scale of **41a**; R_f = 0.4 (5% EtOAc in hexane); white solid (28.7 mg, 70% yield); m. p. = 235–237 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (d, J = 8.4 Hz, 2H), 7.60 – 7.55 (m, 4H), 7.41 – 7.36 (m, 1H), 7.29 (s, 2H), 7.26 (s, 1H), 5.38 (s, 1H), 1.44 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.4, 154.1, 147.7, 136.8, 135.5, 132.1, 130.1, 127.1, 126.3, 125.8, 123.4, 122.6, 121.7, 121.0, 119.1, 111.4, 111.0, 34.7, 30.5; FT-IR (thin film, neat): 3615, 2960, 2856, 2220, 1602, 1452, 1263, 1159, 751 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{29}H_{28}NO_2$ $[M–H]^–$: 422.2120; found : 422.2105.

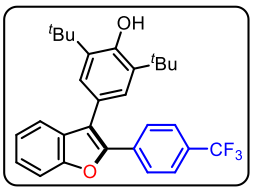


2,6-di-*tert*-butyl-4-(2-(3-nitrophenyl)benzofuran-3-yl)phenol (43c): The reaction was performed at 0.097 mmol scale of **41a**; R_f = 0.4 (5% EtOAc in hexane); pale yellow solid (32.2 mg, 75% yield); m. p. = 197–199 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.64 (t, J = 1.9 Hz, 1H), 8.14 (ddd, J = 3.2, 2.2, 0.9 Hz, 1H), 8.07 – 8.04 (m, 1H), 7.59 – 7.57 (m, 2H), 7.48 (t, J = 8.0 Hz, 1H), 7.41 – 7.37 (m, 1H), 7.32 (s, 2H), 7.31 – 7.27 (m, 1H), 5.39 (s, 1H),1.45 (s, 18H); ^{13}C NMR



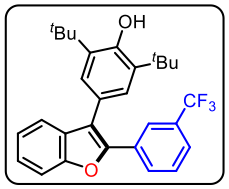
(100 MHz, $CDCl_3$) δ 154.3, 154.1, 148.5, 147.2, 136.9, 132.9, 132.2, 130.2, 129.3, 126.3, 125.7, 123.4, 122.5, 122.4, 121.4, 121.0, 120.9, 111.4, 34.6, 30.5; FT-IR (thin film, neat): 3630, 2961, 2852, 1531, 1450, 1265, 1153, 753 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{28}H_{28}O_4$ $[M–H]^-$: 442.2018; found : 442.2001.

2,6-di-*tert*-butyl-4-(2-(4-(trifluoromethyl)phenyl)benzofuran-3-yl)phenol (43d): The



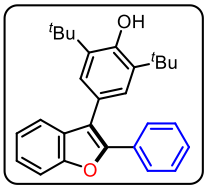
reaction was performed at 0.097 mmol scale of **41a**; R_f = 0.5 (5% EtOAc in hexane); white solid (32.5 mg, 72% yield); m. p. = 205–207 ºC; ^1H NMR (400 MHz, $CDCl_3$), δ 7.85 (d, J = 8.2 Hz, 2H), 7.57 (d, J = 8.2 Hz, 4H), 7.37 (t, J = 7.4 Hz, 1H), 7.31 (s, 2H), 7.29 (d, J = 7.8 Hz, 1H), 5.36 (s, 1H), 1.45 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.3, 153.9, 148.4, 136.7, 134.6 (apparent q, $J_{C\text{-}F}$ = 1.2 Hz), 130.3, 129.7 (q, $J_{C\text{-}F}$ = 32.4 Hz), 127.0, 126.4, 125.4, 125.3 (q, $J_{C\text{-}F}$ = 3.8 Hz), 124.2 (q, $J_{C\text{-}F}$ = 270.5 Hz), 123.2, 122.9, 120.8, 120.5, 111.4, 34.6, 30.5; ^{19}F NMR (376 MHz, $CDCl_3$) δ –62.65; FT-IR (thin film, neat): 3631, 2960, 2877, 1615, 1438, 1321, 1158, 1118, 1075, 843, 743 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{29}H_{28}F_3O_2$ $[M–H]^-$: 465.2041; found : 465.2029.

2,6-di-*tert*-butyl-4-(2-(3-(trifluoromethyl)phenyl)benzofuran-3-yl)phenol (43e): The



reaction was performed at 0.097 mmol scale of **41a**; R_f = 0.5 (5% EtOAc in hexane); white solid (29.8 mg, 66% yield); m. p. = 138–140 ºC; ^1H NMR (400 MHz, $CDCl_3$) δ 7.95 – 7.93 (m, 2H), 7.58 – 7.55 (m, 2H), 7.52 (d, J = 7.8 Hz, 1H), 7.44 (t, J = 7.8 Hz, 1H), 7.36 (t, J = 7.3 Hz, 1H), 7.30 (s, 2H), 7.26 (s, 1H), 5.34 (s, 1H), 1.44 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.2, 153.9, 148.3, 136.8, 132.0, 130.9 (q, $J_{C\text{-}F}$ = 32.0 Hz), 130.3, 129.8, 128.9, 126.3, 125.3, 124.6 (q, $J_{C\text{-}F}$ = 3.7 Hz), 124.1 (q, $J_{C\text{-}F}$ = 270.9 Hz), 123.6 (q, $J_{C\text{-}F}$ = 4.0 Hz), 123.2, 122.8, 120.8, 120.0, 111.3, 34.6, 30.4; ^{19}F NMR (376 MHz, $CDCl_3$) δ –62.85; FT-IR (thin film, neat): 3642, 2965, 2867, 1452, 1325, 1263, 1167, 1129, 751 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{29}H_{28}F_3O_2$ $[M–H]^-$: 465.2041; found : 465.2026.

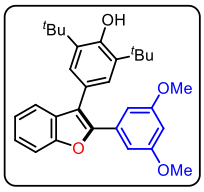
2,6-di-*tert*-butyl-4-(2-phenylbenzofuran-3-yl)phenol (43f): The reaction was performed at



0.097 mmol scale of **41a**; R_f = 0.5 (5% EtOAc in hexane); pale yellow solid (30.0 mg, 78% yield); m. p. = 151–153 ºC; ^1H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, J = 7.1 Hz, 2H), 7.59 (d, J = 7.6 Hz, 1H), 7.55 (d, J = 8.1 Hz, 1H), 7.33 (s, 3H), 7.31 – 7.25 (m, 4H), 5.29 (s, 1H), 1.43 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.2, 153.5, 150.2, 136.4, 131.2, 130.4, 128.33, 128.27, 127.2, 126.5, 124.6, 123.4, 122.9, 120.4, 118.4, 111.2, 34.6, 30.5; FT-IR (thin film, neat): 3642, 2966, 2857, 1440,

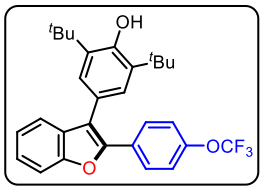
1368, 1217, 913, 762 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{28}H_{29}O_2$ $[M–H]^-$: 397.2168; found : 397.2152.

2,6-di-*tert*-butyl-4-(2-(3,5-dimethoxyphenyl)benzofuran-3-yl)phenol (43g): The reaction



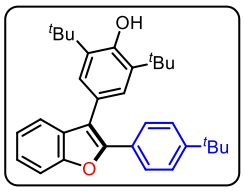
was performed at 0.097 mmol scale of **41a**; R_f = 0.3 (5% EtOAc in hexane); white solid (34.2 mg, 77% yield); m. p. = 174–176 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 – 7.53 (m, 2H), 7.36 – 7.34 (m, 1H), 7.32 (s, 2H), 7.27 – 7.24 (m, 1H), 6.88 (d, *J* = 2.3 Hz, 2H), 6.41 (t, *J* = 2.3 Hz, 1H), 5.31 (s, 1H), 3.69 (s, 6H), 1.45 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.6, 153.9, 153.5, 150.0, 136.5, 132.7, 130.7, 126.6, 124.8, 123.6, 122.9, 120.4, 119.0, 111.2, 104.7, 101.3, 55.3, 34.6, 30.5; FT-IR (thin film, neat): 3631, 2958, 2877, 1599, 1455, 1240, 1155, 1057, 749’ cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{30}H_{33}O_4$ $[M–H]^-$: 457.2379; found : 457.2391.

2,6-di-*tert*-butyl-4-(2-(4-(trifluoromethoxy)phenyl)benzofuran-3-yl)phenol (43h): The



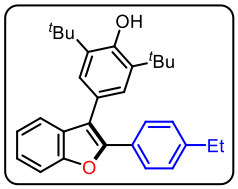
reaction was performed at 0.097 mmol scale of **41a**; R_f = 0.4 (5% EtOAc in hexane); white solid (38.8 mg, 83% yield); m. p. = 174–176 ºC; ^{1}H NMR (400 MHz, $CDCl_3$), δ 7.75 (d, *J* = 8.8 Hz, 2H), 7.60 (d, *J* = 7.7, Hz, 1H), 7.56 (d, *J* = 8.1 Hz, 1H), 7.37 – 7.33 (m, 1H), 7.31 (s, 2H), 7.29 (d, *J* = 7.5 Hz, 1H), 7.18 (d, *J* = 8.5 Hz, 2H), 5.34 (s, 1H), 1.44 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.2, 153.7, 148.9 (q, $J_{C\text{-}F}$ = 1.7 Hz), 148.8, 136.6, 130.2, 130.0, 128.6, 126.4, 125.0, 123.1, 123.0, 120.8, 120.59 (q, $J_{C\text{-}F}$ = 255.7 Hz), 120.57, 119.1, 111.3, 34.6, 30.5; ^{19}F NMR (376 MHz, $CDCl_3$) δ –57.80; FT-IR (thin film, neat): 3631, 2961, 2882, 1504, 1448, 1369, 1258, 1162, 846, 746 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{29}H_{28}F_3O_3$ $[M–H]^-$: 481.1991; found : 481.2009.

2,6-di-*tert*-butyl-4-(2-(4-(tert-butyl)phenyl)benzofuran-3-yl)phenol (43i): The reaction was

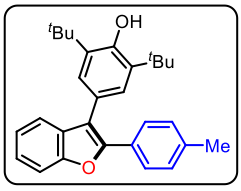


performed at 0.097 mmol scale of **41a**; R_f = 0.5 (5% EtOAc in hexane); white solid; (12.3 mg, 28% yield); m. p. = 178–180 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (d, *J* = 8.6 Hz, 2H), 7.58 – 7.56 (m, 1H), 7.54 (d, *J* = 8.1 Hz, 1H), 7.35 (d, *J* = 8.7 Hz, 2H), 7.31 (s, 2H), 7.30 – 7.29 (m, 1H), 7.26 – 7.23 (m, 1H), 5.28 (s, 1H), 1.43 (s, 18H), 1.32 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.1, 153.4, 151.4, 150.6, 136.2, 130.5, 128.3, 126.9, 126.5, 125.3, 124.4, 123.6, 122.8, 120.3, 117.8, 111.2, 34.8, 34.6, 31.4, 30.5; FT-IR (thin film, neat): 3636, 2959, 2877, 1450, 1369, 1234, 1157, 837, 748 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{32}H_{37}O_2$ $[M–H]^-$: 453.2794; found : 453.2813.

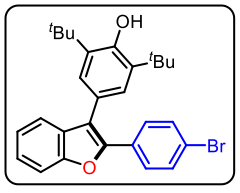
2,6-di-*tert*-butyl-4-(2-(4-ethylphenyl)benzofuran-3-yl)phenol (43j): The reaction was performed at 0.097 mmol scale of **41a**; R_f = 0.5 (5% EtOAc in hexane); pale yellow gummy solid; (9.5 mg, 23% yield); ^{1}H NMR (400 MHz, $CDCl_3$), δ 7.64 (d, J = 8.2 Hz, 2H), 7.57 (d, J = 7.5 Hz, 1H), 7.53 (d, J = 8.1 Hz, 1H), 7.32 (s, 2H), 7.30 (dd, J = 8.1, 1.1 Hz, 1H), 7.26 – 7.22 (m, 1H), 7.15 (d, J = 8.2 Hz, 2H), 5.28 (s, 1H), 2.65 (q, J = 7.6 Hz, 2H), 1.43 (s, 18H), 1.24 (t, J = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.1, 153.4, 150.5, 144.6, 136.3, 130.5, 128.6, 127.8, 127.1, 126.5, 124.4, 123.6, 122.8, 120.3, 117.7, 111.2, 34.6, 30.5, 28.9, 15.7; FT-IR (thin film, neat): 3637, 2960, 2872, 1450, 1370, 1233, 1154, 835, 748 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{30}H_{33}O_2$ $[M–H]^–$: 425.2481; found : 425.2477.



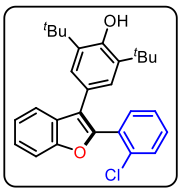
2,6-di-*tert*-butyl-4-(2-(p-tolyl)benzofuran-3-yl)phenol (43k): The reaction was performed at 0.082 mmol scale of **41a**; R_f = 0.5 (5% EtOAc in hexane); pale yellow solid (10.0 mg, 25% yield); m. p. = 182–184 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (d, J = 7.8 Hz, 2H), 7.56 (d, J = 7.7 Hz, 1H), 7.53 (d, J = 8.2 Hz, 1H), 7.32 (s, 2H), 7.30 (d, J = 7.8 Hz, 1H), 7.26 – 7.22 (m, 1H), 7.13 (d, J = 7.9 Hz, 2H), 5.28 (s, 1H), 2.36 (s, 3H), 1.44 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.1, 153.4, 150.4, 138.2, 136.3, 130.6, 129.0, 128.3, 127.0, 126.5, 124.4, 123.6, 122.8, 120.3, 117.7, 111.1, 34.6, 30.6, 21.5; FT-IR (thin film, neat): 3637, 2961, 2857, 1449, 1369, 1236 1154, 1075, 759 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{29}H_{31}ClO_2$ $[M–H]^–$: 411.2324; found : 411.2307.



4-(2-(4-bromophenyl)benzofuran-3-yl)-2,6-di-*tert*-butylphenol (43l): The reaction was performed at 0.097 mmol scale of **41a**; R_f = 0.5 (5% EtOAc in hexane); white solid (38.8 mg, 84% yield); m. p. = 229–231 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, J = 8.7 Hz, 2H), 7.58 – 7.53 (m, 2H) 7.45 (d, J = 8.7 Hz, 2H), 7.36 – 7.32 (m, 1H), 7.32 (s, 2H), 7.28 – 7.24 (m, 1H), 5.33 (s, 1H) 1.45 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.1, 153.7, 148.9, 136.6, 131.5, 130.4, 130.1, 128.4, 126.4, 125.0, 123.08, 123.06, 122.2, 120.5, 119.1, 111.2, 34.6, 30.5; FT IR (thin film, neat): 3632, 2965, 2856, 1446, 1263, 1156, 752 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{28}H_{28}BrO_2$ $[M–H]^–$: 475.1273; found : 475.1252.

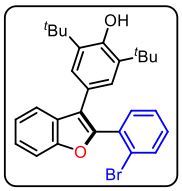


2,6-di-*tert*-butyl-4-(2-(2-chlorophenyl)benzofuran-3-yl)phenol (43m): The reaction was performed at 0.097 mmol scale of **41a**; R_f = 0.5 (5% EtOAc in hexane); white solid (33.9 mg, 81% yield); m. p. = 177–179 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 – 7.81 (m, 1H), 7.58 (d, J = 7.8 Hz, 1H), 7.49 (dd, J = 8.0, 1.2 Hz, 1H),

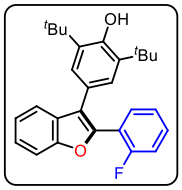


7.44 (dd, *J* = 7.6, 1.7 Hz, 1H), 7.40 – 7.38 (m, 1H), 7.36 – 7.32 (m, 2H), 7.31 – 7.28 (m, 1H), 7.22 (s, 2H), 5.20 (s, 1H), 1.35 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.9, 153.1, 148.6, 136.1, 135.0, 132.9, 131.0, 130.4, 130.1, 128.3, 126.7, 125.6, 124.7, 123.1, 123.0, 120.7, 120.4, 111.6, 34.5, 30.4; FT-IR (thin film, neat): 3633, 2958, 2867, 1447, 1266, 1155, 753 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{28}H_{28}ClO_2$ $[M–H]^-$: 431.1778; found : 431.1767.

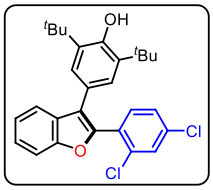
4-(2-(2-bromophenyl)benzofuran-3-yl)-2,6-di-*tert*-butylphenol (43n): The reaction was performed at 0.097 mmol scale of **41a**; R_f = 0.5 (5% EtOAc in hexane); pale yellow solid (37.9 mg, 82% yield); m. p. = 204–206 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 – 7.83 (m, 1H), 7.70 (dd, *J* = 7.7, 1.2 Hz, 1H), 7.60 – 7.57 (m, 1H), 7.44 – 7.41(m, 1H), 7.39 (dd, *J* = 7.3, 1.4 Hz, 1H), 7.36 (dd, *J* = 4.2, 1.6 Hz 1H), 7.34 – 7.31 (m, 1H), 7.309 – 7.27 (m, 1H), 7.23 (s, 2H); 5.20 (s, 1H) 1.36 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.8, 153.1, 150.0, 136.0, 133.2, 133.1, 130.7, 128.2, 127.3, 125.6 (2C), 124.9, 124.7, 123.05, 123.02, 120.8, 120.0, 111.7, 34.5, 30.4; FT-IR (thin film, neat): 3633, 2958, 2861, 1446, 1261, 1155, 752 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{28}H_{28}BrO_2$ $[M–H]^-$: 475.1273; found : 475.1251.



2,6-di-*tert*-butyl-4-(2-(2-fluorophenyl)benzofuran-3-yl)phenol (43o): The reaction was performed at 0.097 mmol scale of **41a**; R_f = 0.5 (5% EtOAc in hexane); white solid (33.8 mg, 84% yield); m. p. = 155–157 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 – 7.75 (m, 1H), 7.58 – 7.56 (m, 1H), 7.52 (td, *J* = 7.3, 1.7 Hz, 1H), 7.39 – 7.34 (m, 2H), 7.30 (td, *J* = 7.7, 1.2 Hz, 1H), 7.26 (s, 2H), 7.17 – 7.15 (m, 1H), 7.14 – 7.10 (m, 1H), 5.24 (s, 1H), 1.38 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.5, 159.0, 154.9, 153.3, 145.9 (d, $J_{C\text{-}F}$ = 1.5 Hz), 136.1, 131.7 (d, $J_{C\text{-}F}$ = 2.8 Hz), 130.7 (d, $J_{C\text{-}F}$ = 8.1 Hz), 128.8, 125.6, 124.8, 124.0 (d, $J_{C\text{-}F}$ = 3.6 Hz), 123.3 (d, $J_{C\text{-}F}$ = 0.7 Hz), 123.0, 120.6, 119.6 (d, $J_{C\text{-}F}$ = 13.9 Hz), 116.3 (d, $J_{C\text{-}F}$ = 21.4 Hz), 111.5, 34.5, 30.4; ^{19}F NMR (376 MHz, $CDCl_3$) δ – 111.04; FT-IR (thin film, neat): 3634, 2958, 2876, 1451, 1259, 1154, 753 cm^{-1} HRMS (ESI): *m/z* calcd for $C_{28}H_{28}FO_2$ $[M–H]^-$: 415.2073; found : 415.2054.

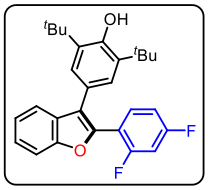


2,6-di-*tert*-butyl-4-(2-(2,4-dichlorophenyl)benzofuran-3-yl)phenol (43p): The reaction was performed at 0.097 mmol scale of **41a**; R_f = 0.5 (5% EtOAc in hexane); white solid (31.6 mg, 70% yield); m. p. = 147–149 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 – 7.79 (m, 1H), 7.57 (d, *J* = 7.9 Hz, 1H), 7.51 (d, *J* = 2.0 Hz, 1H), 7.40 – 7.38 (m, 2H), 7.34 (ddd, *J* = 8.8, 7.6, 1.5 Hz, 1H), 7.28 – 7.26 (m, 1H), 7.19 (s, 2H), 5.24 (s, 1H), 1.37 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.9, 153.3, 147.4, 136.2, 135.7, 135.6, 133.7, 130.0, 129.6, 128.3, 127.1, 125.6, 125.0, 123.1, 122.9, 121.0,

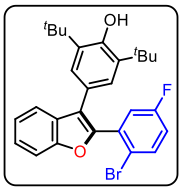


120.8, 111.6, 34.5, 30.4; FT-IR (thin film, neat): 3635, 2959, 2857, 1447, 1262, 1154, 750 cm^{-1} HRMS (ESI): *m/z* calcd for $C_{28}H_{27}Cl_2O_2$ $[M–H]^-$: 465.1388; found : 465.1374.

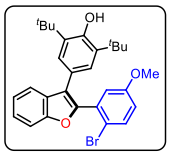
2,6-di-*tert*-butyl-4-(2-(2,4-difluorophenyl)benzofuran-3-yl)phenol (43q): The reaction was performed at 0.097 mmol scale of **41a**; R_f = 0.5 (5% EtOAc in hexane); white solid (33.2 mg, 79% yield); m. p. = 144–146 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 – 7.72 (m, 1H), 7.55 (d, J = 8.0 Hz, 1H), 7.52 – 7.46 (m, 1H), 7.35 (td, J = 7.3, 1.3 Hz, 1H), 7.29 (td, J = 7.7, 1.1 Hz, 1H), 7.23 (s, 2H), 6.92 – 6.89 (m, 1H), 6.88 – 6.85 (m, 1H), 5.24 (s, 1H), 1.38 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.6 (d, J_{C-F} = 254.2 Hz), 160.5 (d, J_{C-F} = 253.9 Hz), 154.9, 153.4, 145.0 (d, J_{C-F} = 1.7 Hz), 136.2, 132.7 (dd, J_{C-F} = 9.6, 4.3 Hz), 128.7, 125.6, 124.9, 123.1, 120.7, 120.6, 116.0 (dd, J_{C-F} = 141.0, 3.8 Hz), 111.53, 111.50 (dd, J_{C-F} = 21.2, 3.6 Hz), 104.7 (t, J_{C-F} = 25.4 Hz), 104.5, 34.5, 30.4; ^{19}F NMR (376 MHz, $CDCl_3$) δ –106.38 (d, J = 8.7 Hz), –108.24 (d, J = 8.8 Hz); FT-IR (thin film, neat): 3636, 2959, 2877, 1451, 1267, 1147, 753 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{28}H_{27}F_2O_2$ $[M–H]^-$: 433.1979; found : 433.1958.



4-(2-(2-bromo-5-fluorophenyl)benzofuran-3-yl)-2,6-di-*tert*-butylphenol (43r): The reaction was performed at 0.097 mmol scale of **41a**; R_f = 0.5 (5% EtOAc in hexane); white solid (28.3 mg, 59% yield); m. p. = 193–195 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 – 7.82 (m, 1H), 7.64 (dd, J = 8.8, 5.2 Hz, 1H), 7.59 (d, J = 8.0 Hz, 1H), 7.40 (td, J = 7.3, 1.3 Hz, 1H), 7.35 (td, J = 7.6, 1.2 Hz, 1H), 7.23 (s, 2H), 7.17 (dd, J = 8.8, 3.0 Hz, 1H), 7.03 (ddd, J = 8.8, 7.9, 3.1 Hz, 1H), 5.24(s, 1H), 1.38 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.6 (d, J_{C-F} = 246.7 Hz), 154.8, 153.4, 148.4 (d, J_{C-F} = 1.8 Hz), 136.2, 134.8 (d, J_{C-F} = 8.5 Hz), 134.6 (d, J_{C-F} = 8.1 Hz), 128.1, 125.6, 125.1, 123.2, 122.7, 120.9, 120.7, 120.1 (d, J_{C-F} = 23.0 Hz), 119.2 (d, J_{C-F} = 3.3 Hz), 117.9 (d, J_{C-F} = 22.3 Hz), 111.7, 34.5, 30.4; ^{19}F NMR (376 MHz, $CDCl_3$) δ –114.82; FT-IR (thin film, neat): 3635, 2957, 2861, 1448, 1262, 1156, 752 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{28}H_{27}BrFO_2$ $[M–H]^-$: 493.1178; found : 493.1159.

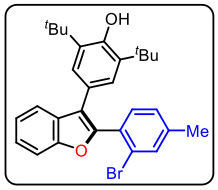


4-(2-(2-bromo-5-methoxyphenyl)benzofuran-3-yl)-2,6-di-*tert*-butylphenol (43s): The reaction was performed at 0.097 mmol scale of **41a**; R_f = 0.3 (5% EtOAc in hexane); pale yellow gummy solid (25.0 mg, 51% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (d, J = 7.6 Hz, 1H), 7.59 – 7.54 (m, 2H), 7.40 – 7.31 (m, 2H), 7.24 (s, 2H), 6.93 (d, J = 2.6 Hz, 1H), 6.85 (dd, J = 8.8, 2.8 Hz, 1H), 5.21 (s, 1H), 3.70 (s, 3H), 1.36 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.7, 154.7, 153.2, 149.8, 136.1, 133.9, 133.7, 128.3, 125.7, 124.8, 123.1, 123.0, 120.8, 120.1, 118.0, 117.1, 115.2, 111.7, 55.7, 34.5, 30.4;



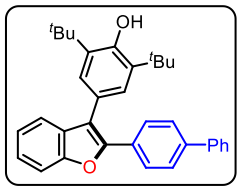
FT-IR (thin film, neat): 3642, 2970, 2862, 1452, 1266, 1157, 883, 753 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{29}H_{30}BrO_3$ $[M+Na]^+$: 505.1378; found : 505.1394.

4-(2-(2-bromo-4-methylphenyl)benzofuran-3-yl)-2,6-di-*tert*-butylphenol (43t): The



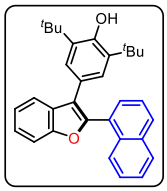
reaction was performed at 0.097 mmol scale of **41a**; R_f = 0.5 (10% EtOAc in hexane); pale solid (16.6mg, 35% yield); m. p. = 145–147 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 – 7.81 (m, 1H), 7.58 – 7.56 (m, 1H), 7.53 – 7.52 (m, 1H), 7.37 (td, *J* = 7.2, 1.4 Hz, 1H), 7.33 (dd, *J* = 7.6, 1.4 Hz, 1H), 7.29 (d, *J* = 7.8 Hz, 1H), 7.23 (s, 2H), 7.14 – 7.12 (m, 1H), 5.19 (s, 1H), 2.39 (s, 3H), 1.36 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.7, 153.0, 150.1, 141.1, 136.0, 133.6, 132.8, 130.1, 128.3, 128.1, 125.6, 124.7, 124.6, 123.2, 122.9, 120.7, 119.8, 111.6, 34.5, 30.4, 21.2; FT-IR (thin film, neat): 3633, 2958, 2877, 1447, 1242, 1154, 884, 818, 748, 3642, 2970, 2862, 1452, 1266, 1157, 883, 753 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{29}H_{30}BrO_2$ $[M–H]^–$: 489.1429; found : 489.1443.

4-(2-([1,1'-biphenyl]-4-yl)benzofuran-3-yl)-2,6-di-*tert*-butylphenol (43u): The reaction was



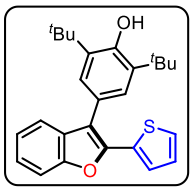
performed at 0.097 mmol scale of **41a**; R_f = 0.3 (5% EtOAc in hexane); pale yellow solid (33.0 mg, 72% yield); m. p. = 207–209 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, *J* = 8.1 Hz, 2H), 7.62 (d, *J* = 7.8 Hz, 2H), 7.59 – 7.55 (m, 4H), 7.45 (t, *J* = 7.6 Hz, 2H), 7.36 (s, 2H), 7.33 (d, *J* = 8.0 Hz 1H), 7.28 – 7.24 (m, 2H), 5.31 (s, 1H), 1.45 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.2, 153.6, 149.9, 140.8, 140.7, 136.5, 130.5, 130.2, 129.0, 127.6, 127.4, 127.1, 127.0, 126.5, 124.7, 123.5, 122.9, 120.4, 118.6, 111.2, 34.6, 30.6; FT-IR (thin film, neat): 3632, 2965, 2862, 1449, 1374, 1261, 1078, 912, 804, 744 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{34}H_{33}O_2$ $[M–H]^–$: 473.2481; found : 473.2461.

2,6-di-*tert*-butyl-4-(2-(naphthalen-1-yl)benzofuran-3-yl)phenol (43v): The reaction was

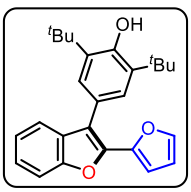


performed at 0.097 mmol scale of **41a**; R_f = 0.4 (20% EtOAc in hexane); pale yellow gummy solid (30.0 mg, 69 % yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, *J* = 8.2 Hz, 1H), 7.89 – 7.87 (m, 2H), 7.80 (d, *J* = 8.4 Hz, 1H), 7.68 (dd, *J* = 7.1, 1.0 Hz, 1H), 7.63 – 7.60 (m, 1H), 7.53 – 7.49 (m, 1H), 7.47 – 7.42 (m, 1H), 7.38 (td, *J* = 7.8, 1.5 Hz, 2H), 7.35 – 7.28 (m, 1H), 7.16 (s, 2H), 5.11 (s, 1H), 1.21 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.0, 152.9, 150.5, 136.0, 133.9, 131.8, 129.7, 129.4, 129.0, 128.7, 128.2, 126.4, 126.1, 125.7 (2C), 125.3, 124.5, 123.3, 123.0, 120.6, 120.1, 111.6, 34.3, 30.2; FT-IR (thin film, neat): 3633, 2957, 2924, 2874, 1448, 1365, 1259, 1155, 1044, 885, 750 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{32}H_{31}O_2$ $[M–H]^–$: 447.2324; found : 447.2311.

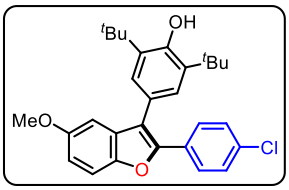
2,6-di-*tert*-butyl-4-(2-(thiophen-2-yl)benzofuran-3-yl)phenol (43w): The reaction was performed at 0.097 mmol scale of **41a**; R_f = 0.5 (5% EtOAc in hexane); pale yellow solid (28.2 mg, 72 % yield); m. p. = 188–190 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (t, J = 7.7 Hz, 2H), 7.44 – 7.43 (m, 1H), 7.37 (s, 2H), 7.31 (t, J = 7.9 Hz, 1H), 7.26 – 7.21 (m, 2H), 7.02 – 7.00 (m, 1H), 5.33 (s, 1H), 1.47 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.93, 153.87, 146.4, 136.4, 133.2, 130.5, 127.3, 126.7, 125.8, 125.5, 124.7, 123.1, 122.6, 120.3, 117.8, 111.1, 34.6, 30.5; FT-IR (thin film, neat): 3642, 2961, 2882, 1657, 1457, 1365, 1311, 1238, 1155, 879, 762 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{26}H_{37}O_2S$ $[M–H]^–$: 403.1732; found : 403.1746.



4-(2-(3-bromothiophen-2-yl)benzofuran-3-yl)-2,6-di-*tert*-butylphenol (43x): The reaction was performed at 0.097 mmol scale of **41a**; R_f = 0.5 (5% EtOAc in hexane); pale yellow solid (35.0 mg, 75 % yield); m. p. = 180–182 ºC; ^{1}H NMR (400 MHz, $CDCl_3$), δ 7.75 (d, J = 7.8 Hz, 1H), 7.56 (d, J = 8.1 Hz, 1H), 7.40 – 7.36 (m, 2H), 7.31 (d, J = 7.5 Hz, 1H), 7.28 (s, 2H), 7.04 (d, J = 5.3 Hz, 1H), 5.25 (s, 1H), 1.40 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.9, 154.9, 153.5, 136.2, 131.1, 128.6, 128.5, 128.1, 125.9, 125.3, 123.2, 122.8, 122.2, 120.8, 112.6, 111.6, 34.5, 30.4; FT-IR (thin film, neat): 3632, 2958, 2877, 1449, 1363, 1236, 1196, 1152, 865, 749 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{26}H_{26}BrO_2S$ $[M–H]^–$: 481.0837; found : 481.0827.



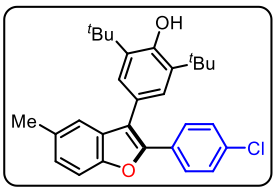
2,6-di-*tert*-butyl-4-(2-(furan-2-yl)benzofuran-3-yl)phenol (43y): The reaction was performed at 0.097 mmol scale of **41a**; R_f = 0.4 (5% EtOAc in hexane); pale yellow solid (27.8 mg, 74 % yield); m. p. = 165–167 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, J = 7.7 Hz, 1H), 7.54 (d, J = 8.1 Hz, 1H), 7.46 (d, J = 1.0 Hz, 1H), 7.45 (s, 2H), 7.35 –7.31 (m, 1H), 7.28 – 7.24 (m, 2H), 6.71 (d, J = 3.4 Hz, 1H), 5.33 (s, 1H), 1.49 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.2, 153.6, 146.4, 142.7, 142.4, 136.0, 129.7, 126.5, 124.9, 123.2, 122.4, 120.5, 118.0, 111.6, 111.3, 108.9, 34.6, 30.6; FT-IR (thin film, neat): 3628, 2961, 2852, 1449, 1363, 1217, 1155, 885, 739 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{26}H_{27}O_3$ $[M–H]^–$: 387.1960; found : 387.1977.



2,6-di-*tert*-butyl-4-(2-(4-chlorophenyl)-5-methoxybenzofuran-3-yl)phenol (49a): The reaction was performed at 0.088 mmol scale of **41b**; R_f = 0.3 (5% EtOAc in hexane); orange solid (32.6 mg, 80% yield); m. p. = 189–191 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (d, J = 8.7 Hz, 2H), 7.42 (d, J = 8.8 Hz, 1H), 7.30 (s, 2H), 7.27 (d, J = 8.7 Hz, 2H), 7.01 (d, J = 2.5 Hz, 1H), 6.94 (dd, J = 8.9, 2.6 Hz, 1H), 5.33 (s, 1H), 3.83 (s, 3H), 1.44 (s, 18H); ^{13}C NMR

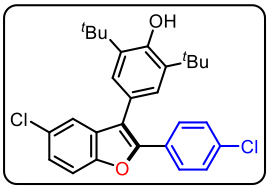
(100 MHz, $CDCl_3$) δ 156.3, 153.7, 149.8, 149.1, 136.6, 133.9, 130.8, 129.7, 128.5, 128.2, 126.3, 123.2, 119.1, 113.8, 111.7, 102.7, 56.0, 34.6, 30.6; FT-IR (thin film, neat): 3637, 2965, 2891, 1483, 1435, 1275, 754 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{29}H_{30}ClO_3$ $[M–H]^-$: 461.1883; found : 461.1866.

2,6-di-*tert*-butyl-4-(2-(4-chlorophenyl)-5-methylbenzofuran-3-yl)phenol (49b): The



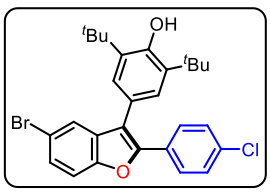
reaction was performed at 0.092 mmol scale of **41c**; R_f = 0.5 (5% EtOAc in hexane); white solid (34.3 mg, 83% yield); m. p. = 222–224 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, *J* = 8.8 Hz, 2H), 7.43 (d, *J* = 8.4 Hz, 1H), 7.36 – 7.35 (m, 1H) 7.32 (s, 2H), 7.29 (d, *J* = 8.8 Hz, 2H), 7.16 (dd, *J* = 8.4, 1.3 Hz, 1H), 5.34 (s, 1H), 2.46 (s, 3H), 1.47 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.6, 152.5, 149.1, 136.6, 133.8, 132.5, 130.4, 129.8, 128.5, 128.1, 126.4, 126.2, 123.3, 120.2, 118.8, 110.7, 34.6, 30.5, 21.6; FT-IR (thin film, neat): 3633, 2957, 2877, 1433, 1342, 1273, 1155, 832, 757 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{29}H_{30}ClO_2$ $[M–H]^-$: 445.1934; found : 445.1915.

2,6-di-*tert*-butyl-4-(5-chloro-2-(4-chlorophenyl)benzofuran-3-yl)phenol (49c): The



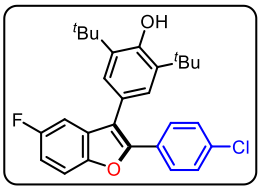
reaction was performed at 0.087 mmol scale of **41d**; R_f = 0.5 (5% EtOAc in hexane); white solid (33.0 mg, 81% yield); m. p. = 226–228 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (d, *J* = 8.8 Hz, 2H), 7.49 (d, *J* = 2.0 Hz, 1H), 7.44 (d, *J* = 8.7 Hz, 1H), 7.31 – 7.30 (m, 1H), 7.29 – 7.27 (m, 2H), 7.26 (s, 2H), 5.36 (s, 1H), 1.45 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.9, 152.5, 150.3, 136.8, 134.4, 131.8, 129.2, 128.7, 128.6, 128.2, 126.3, 125.1, 122.5, 120.1, 118.6, 112.2, 34.6, 30.5; FT-IR (thin film, neat): 3632, 2961, 2877, 1436, 1273, 1233, 1063, 828, 754 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{28}H_{27}Cl_2O_2$ $[M–H]^-$: 465.1388; found : 465.1378.

4-(5-bromo-2-(4-chlorophenyl)benzofuran-3-yl)-2,6-di-*tert*-butylphenol (49d): The



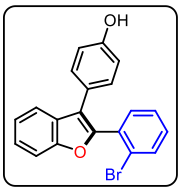
reaction was performed at 0.077 mmol scale of **41e**; R_f = 0.5 (5% EtOAc in hexane); orange solid (31.2 mg, 79% yield); m. p. = 211–213 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 – 7.63 (m, 2H), 7.62 – 7.61 (m, 1H), 7.41 – 7.40 (m, 2H), 7.29 (d, *J* = 8.8 Hz, 2H), 7.24 (s, 2H), 5.36 (s, 1H), 1.44 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.9, 152.8, 150.2, 136.8, 134.4, 132.5, 129.1, 128.7, 128.2, 127.8, 126.3, 123.2, 122.4, 118.5, 116.2, 112.7, 34.6, 30.5; FT-IR (thin film, neat): 3633, 2959, 2877, 1443, 1372, 1236, 1149, 831, 754 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{28}H_{27}BrClO_2$ $[M–H]^-$: 509.0883; found : 509.0905.

2,6-di-*tert*-butyl-4-(2-(4-chlorophenyl)-5-fluorobenzofuran-3-yl)phenol (49e): The



reaction was performed at 0.091 mmol scale of **41f**; R_f = 0.5 (5% EtOAc in hexane); white solid (33.6 mg, 82% yield); m. p. = 234–236 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (d, J = 8.5 Hz, 2H), 7.45 (dd, J = 8.8, 4.0 Hz, 1H), 7.29 (d, J = 8.6 Hz, 2H), 7.26 (s, 2H), 7.19 (dd, J = 8.6, 2.4 Hz, 1H), 7.04 (td, J = 9.0, 2.4 Hz, 1H), 5.34 (s, 1H) 1.44 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.6 (d, $J_{C\text{-}F}$ = 236.9 Hz), 153.8, 150.5 (d, $J_{C\text{-}F}$ = 37.8 Hz), 136.7, 134.3, 131.3 (d, $J_{C\text{-}F}$ = 10.3 Hz), 129.3, 128.6, 128.3, 126.2, 122.6, 119.2 (d, $J_{C\text{-}F}$ = 4.0 Hz), 112.6 (d, $J_{C\text{-}F}$ = 26.3 Hz), 111.9 (d, $J_{C\text{-}F}$ = 9.5 Hz) 106.1, 105.9, 34.6, 30.5; ^{19}F NMR (376 MHz, $CDCl_3$) δ –120.54; FT-IR (thin film, neat): 3637, 2956, 2867, 1467, 1371, 1243, 1148, 833, 795 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{28}H_{27}ClFO_2$ $[M–H]^-$: 449.1684; found : 449.1698.

General procedure for the de-tert-butylation of 43n



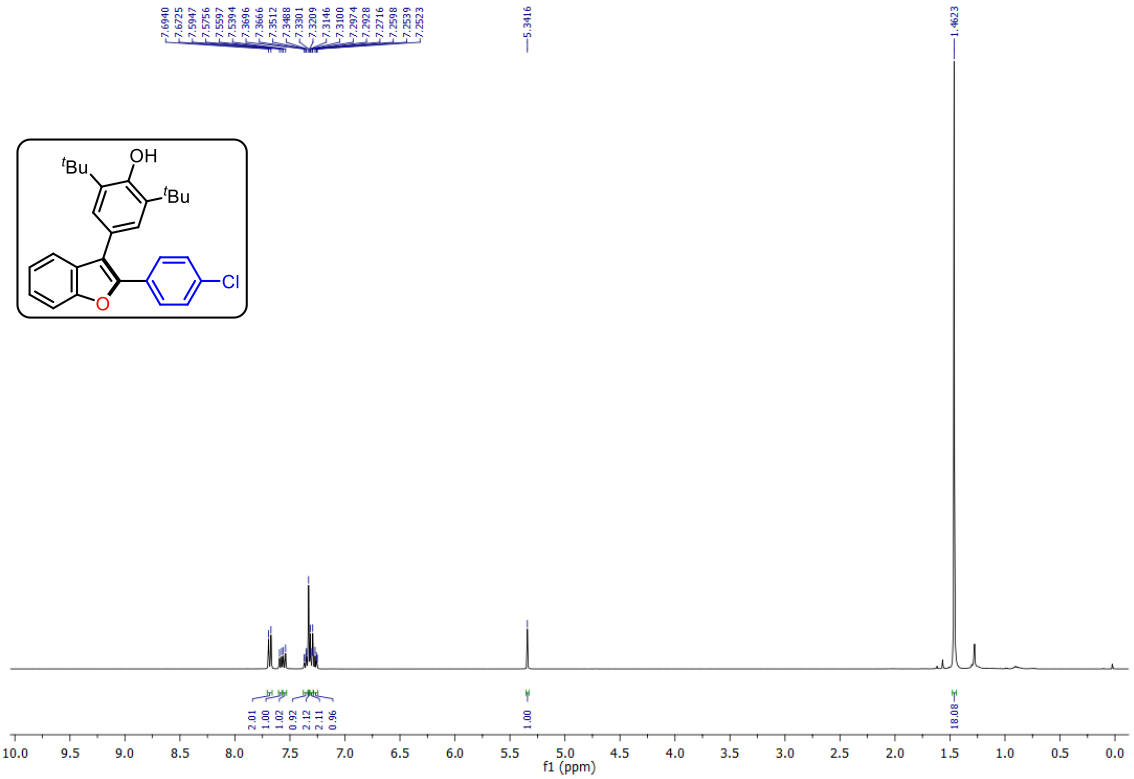
To a solution of **43n** (30 mg, 0.063 mmol) in dry benzene (3 mL), was added $AlCl_3$ (84 mg, 0.63 mmol) under argon atmosphere. The reaction mixture was stirred at 60 ºC for 1 h and then quenched with 10 mL of cold ice water. It was extracted with EtOAc (3 x 10 mL) and the combined organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was then purified through a silica gel column using EtOAc/Hexane mixture as an eluent to get the pure product **50** (18.4 mg, 80%) as pale yellow gummy solid; R_f = 0.3 (15% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (dd, J = 7.7, 0.5 Hz, 1H), 7.67 (dd, J = 7.7, 1.4 Hz, 1H), 7.58 (d, J = 8.2 Hz, 1H), 7.41 – 7.38 (m, 2H), 7.36 – 7.33 (m, 1H), 7.31 (s, 1H), 7.30 – 7.29 (m, 1H), 7.273 – 7.268 (m, 1H), 7.26 – 7.25 (m, 1H), 6.83 (d, J = 8.5 Hz, 2H), 4.94 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.9, 154.7, 150.1, 133.5, 133.0, 132.5, 130.8, 130.4, 128.5, 127.4, 124.93, 124.89, 124.3, 123.1, 120.5, 119.2, 115.8, 111.6; FT-IR (thin film, neat): 3394, 2923, 2854, 1515, 1451, 1266, 1085, 1031, 839, 753 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{20}H_{12}BrO_2$ $[M–H]^-$: 363.0021; found : 363.0039.

General procedure for the gram-scale synthesis of 43a

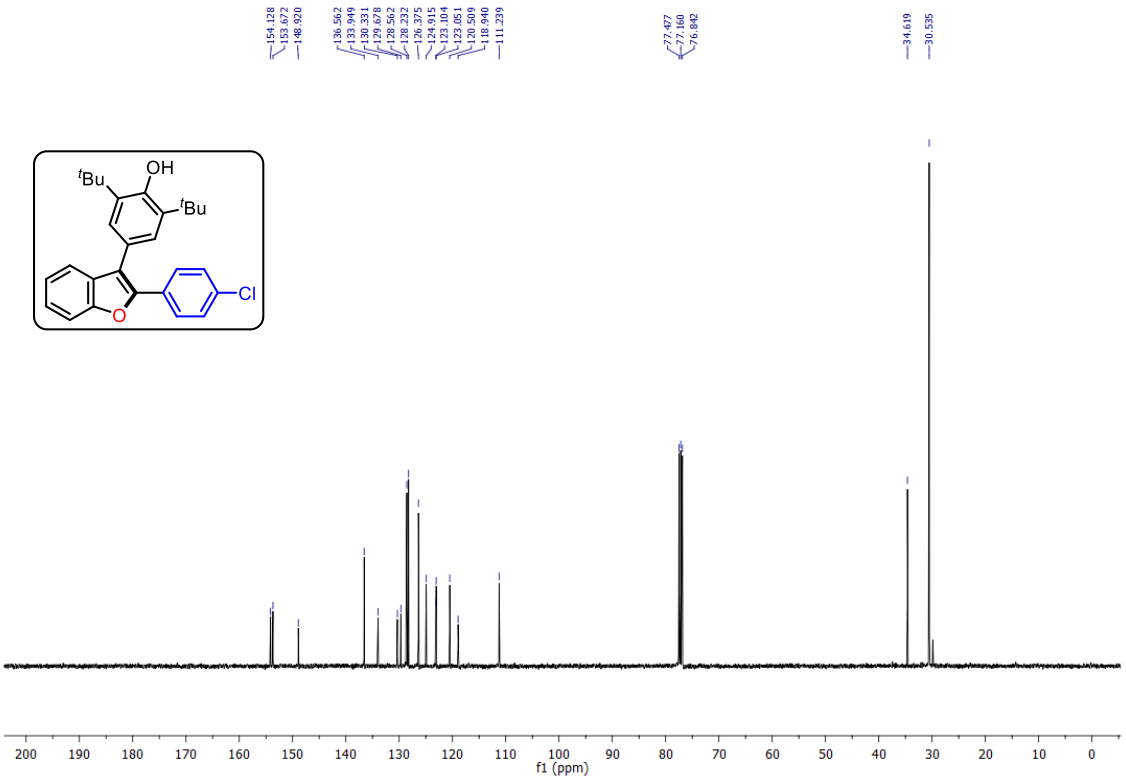
Anhydrous MeCN (40 mL) was added to a mixture of 2-hydroxy *p*-quinone methide **41a** (1.00 gm, 3.22 mmol), 4-Chlorobenzaldehyde **37a** (544 mg, 3.87 mmol), catalyst **47** (17.8 mg, 0.066 mmol) and NaH (64.4 mg, 1.61 mmol) under argon atmosphere and the resulting suspension was stirred at room temperature. After the reaction was complete (based on TLC analysis), TsOH (1109 mg, 6.44 mmol) was added to the reaction mixture and the resultant mixture was stirred at room temperature until the first addition product was completely consumed (based

on TLC analysis). The residue was then concentrated under reduced pressure and the residue was then purified through a silica gel column using EtOAc/Hexane mixture as an eluent to get the pure product **43a**.

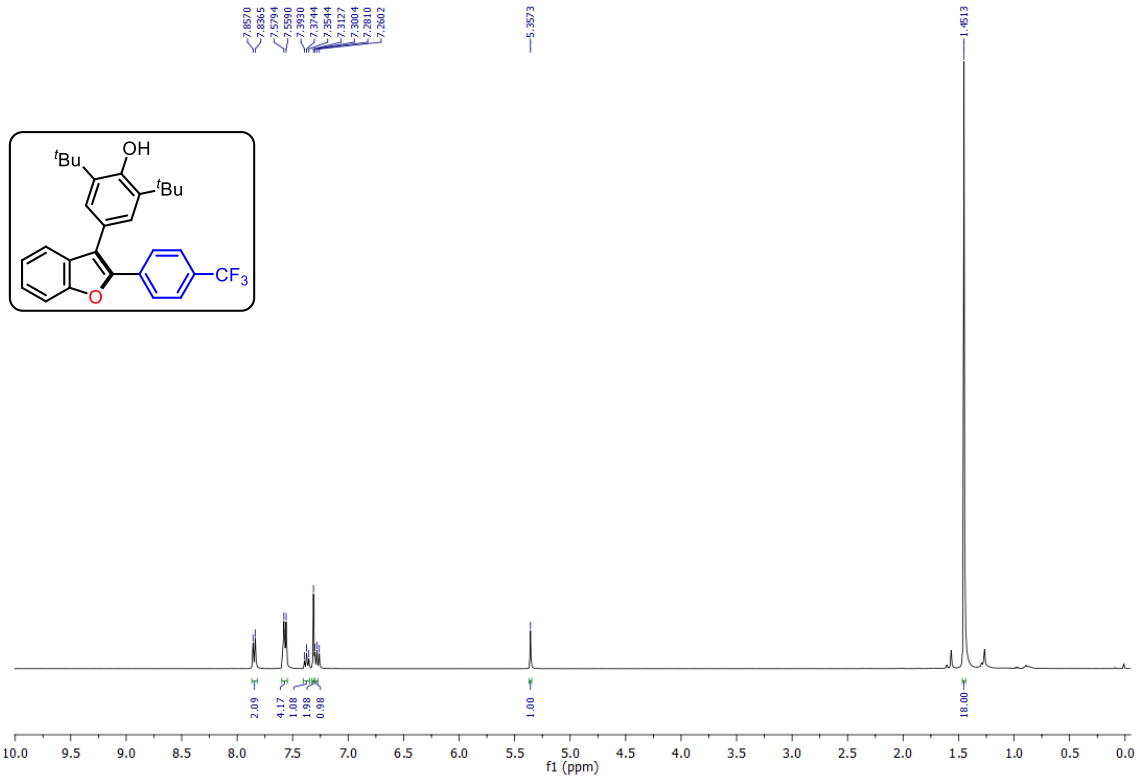
^{1}H NMR (400 MHz, $CDCl_3$) Spectrum of **43a**



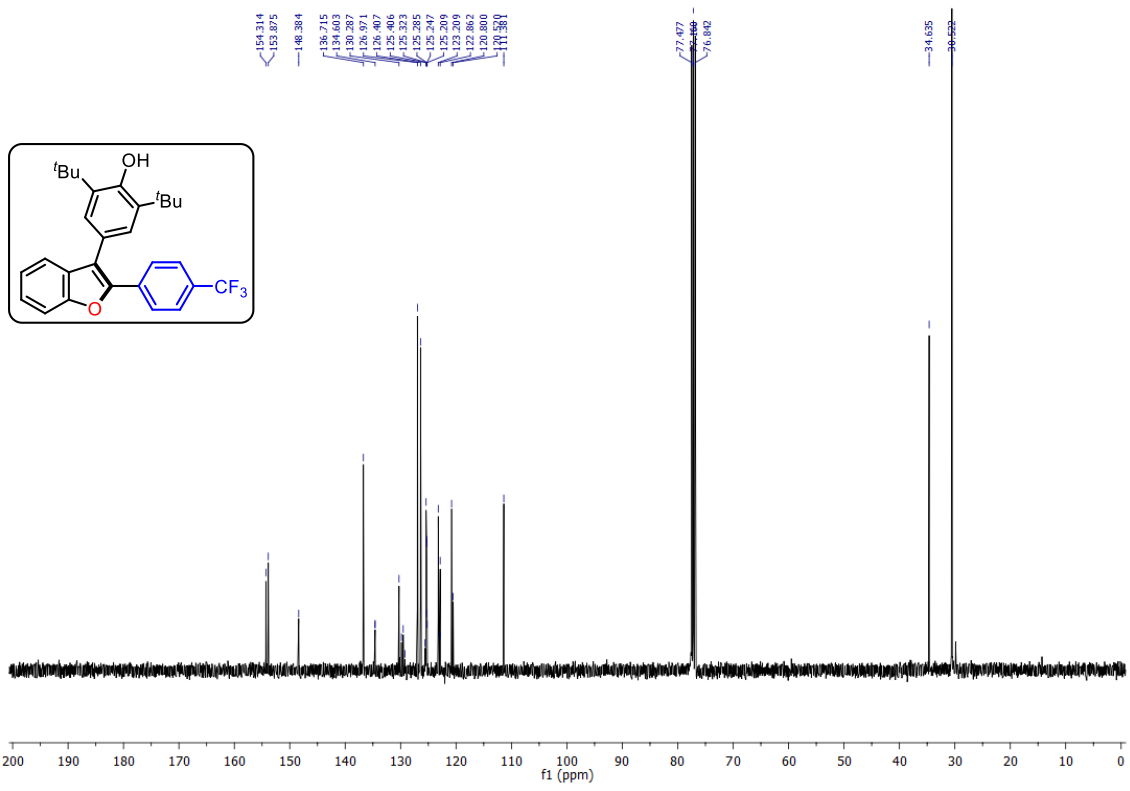
^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) Spectrum of **43a**



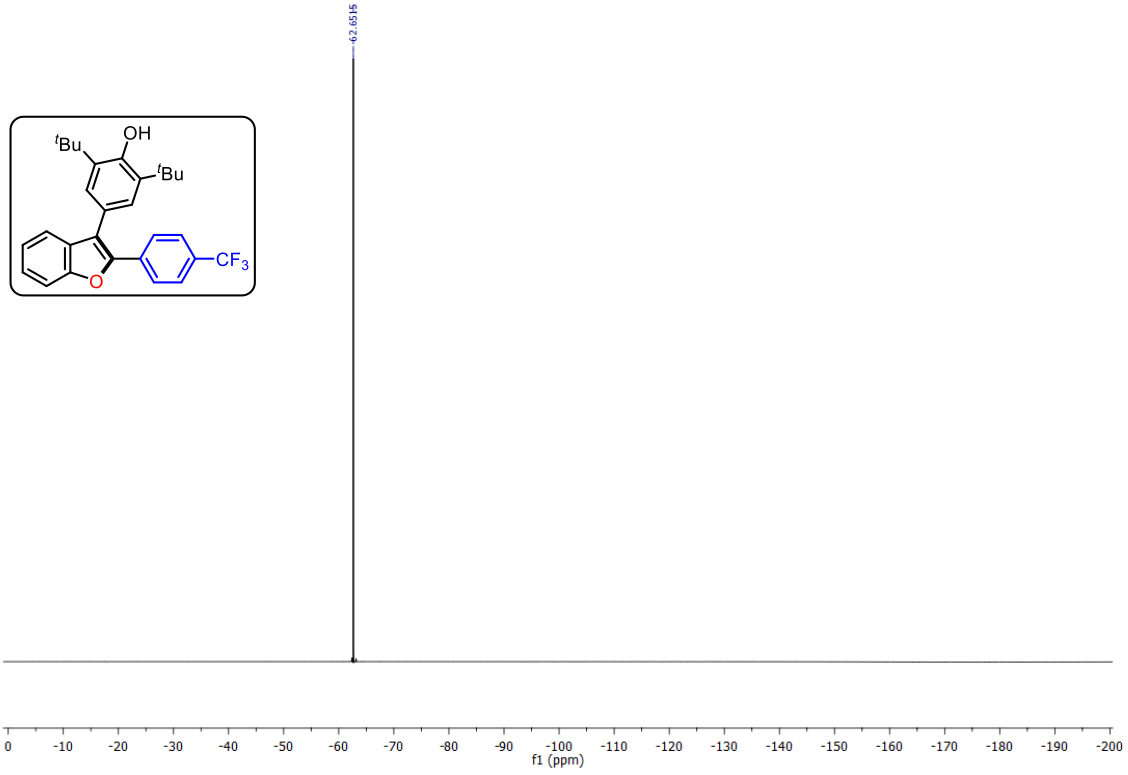
^{1}H NMR (400 MHz, $CDCl_3$) Spectrum of **43d**



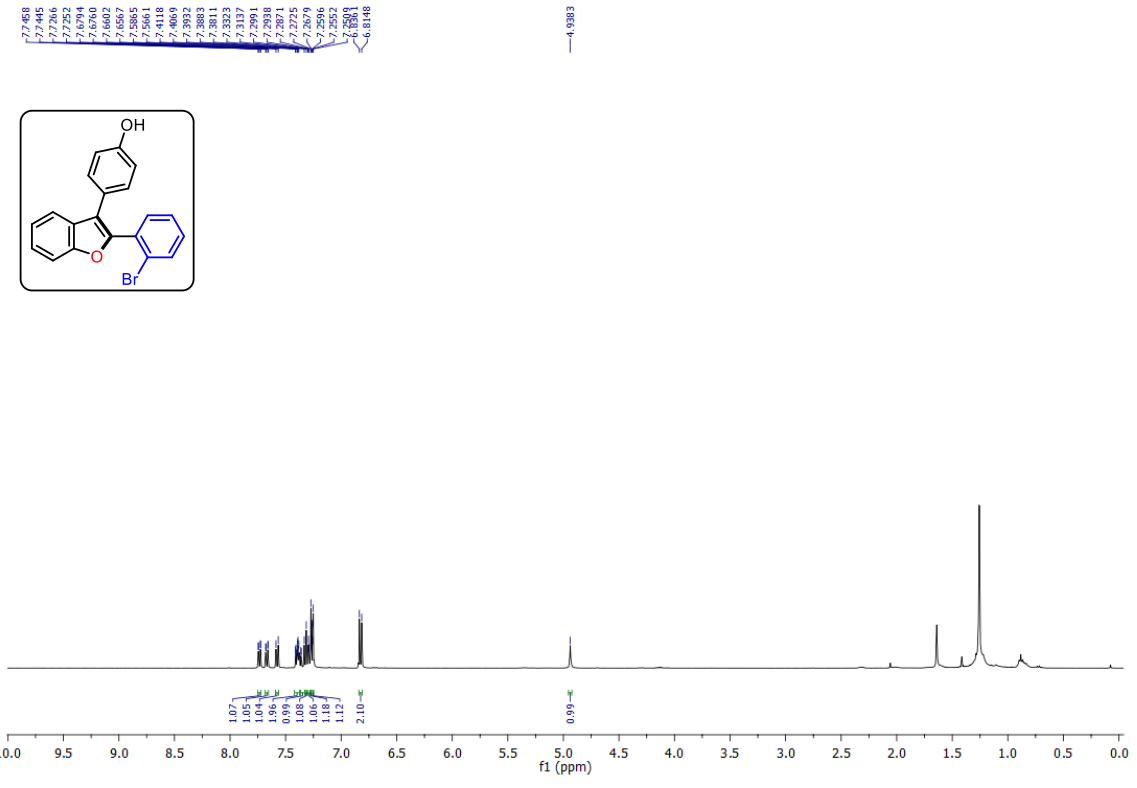
^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) Spectrum of **43d**



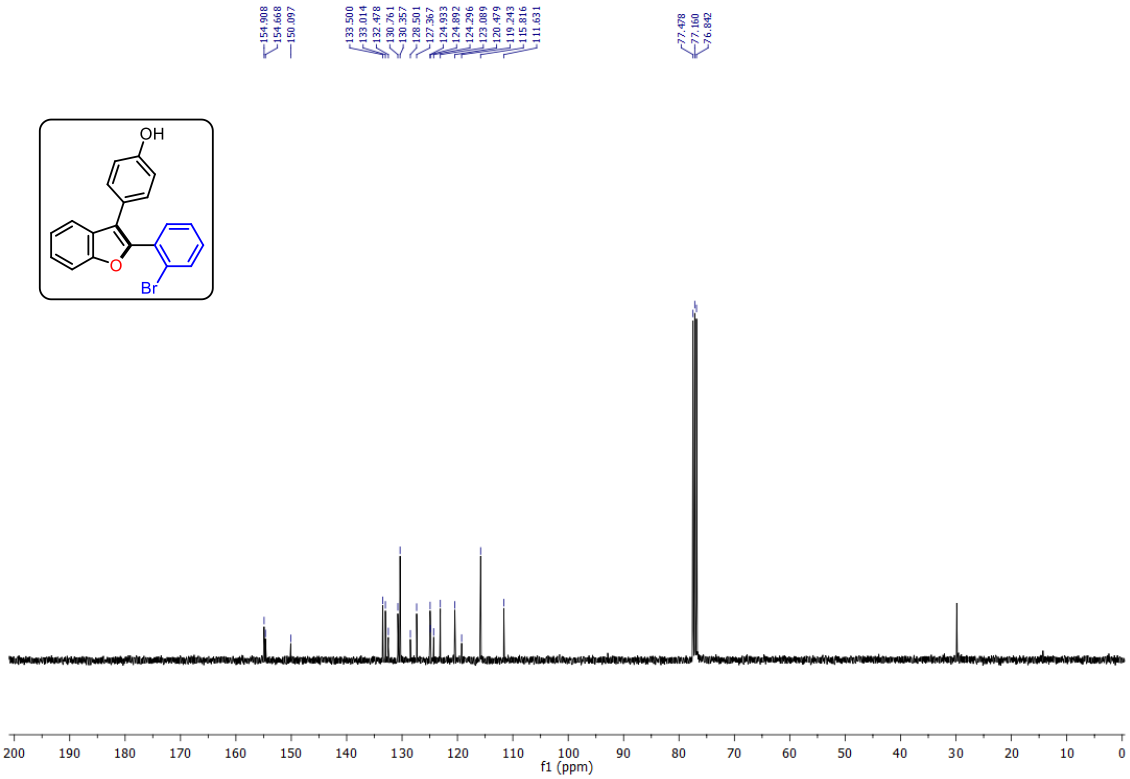
^{19}F {^{1}H} NMR (376 MHz, $CDCl_3$) Spectrum of **43d**



^{1}H NMR (400 MHz, $CDCl_3$) Spectrum of **50**



^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) Spectrum of **50**



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Part 3

3. Base-mediated one-pot synthesis of oxygen-based heterocycles from 2-hydroxyphenyl substituted *para*-quinone methides

3.1 Introduction

Oxygen-based heterocycles such as 2,3-dihydrobenzofurans, benzo[*b*]furans, and coumarins are privileged moieties found in various classes of natural products and other biologically active unnatural molecules (Fig. 1).[1] For example, pterocarpan derivatives, the second largest group of natural isoflavonoids, display unusual antiproliferative activities in various human cancer cell lines.[2a] One of the dihydrobenzofuran derivatives, (+)-obtusafuran, exhibits remarkable biological properties ranging from anti-carcinogenic to insect anti-feedant activities.[2b] The naturally occurring 2,3-diaryl-substituted benzo[*b*]furan, amurensin H, is used to treat allergic airway inflammation.[2c] Similarly, one of the resveratrol aneuploids, diptoindonesin G, shows potent immunosuppressive activity.[2d] Warfarin, a well-known coumarin derivative, is being used as a drug for the treatment of thromboembolic diseases.[2e]

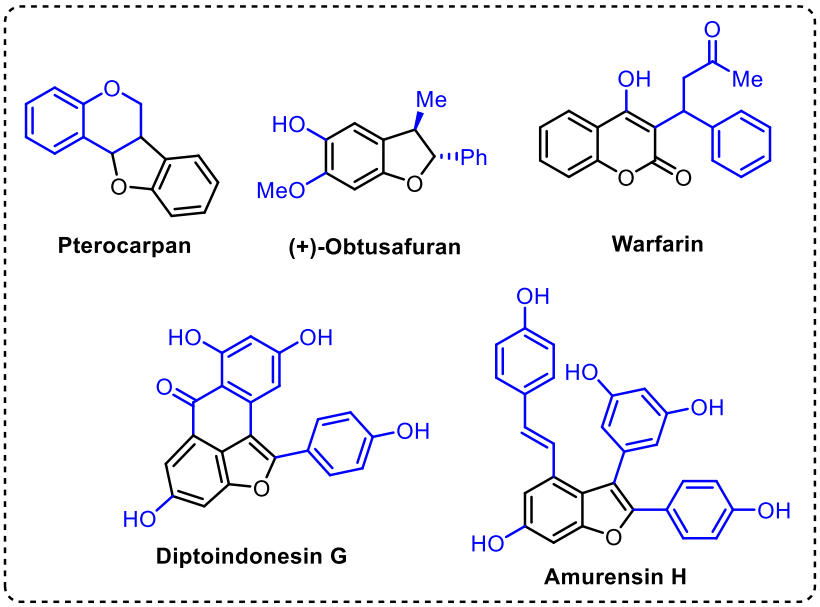


Figure 1. Oxygen-containing biologically significant heterocycles

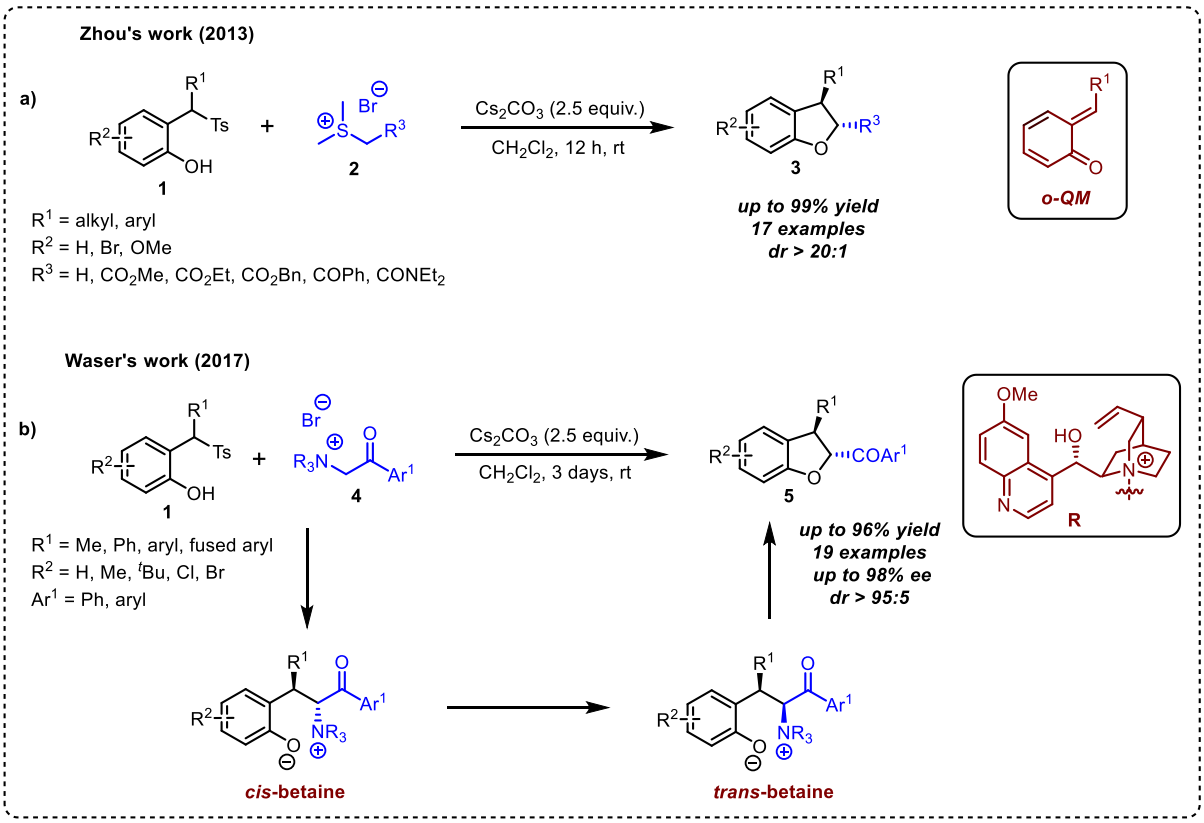
Owing to their wide range of pharmaceutical applications, the synthesis of oxygen-containing heterocycles[3] has gained interest over the last several years. In fact, the chemical syntheses of benzo[*b*]furan,[4a] 2,3-dihydrobenzofuran,[4b] and coumarin[1b,4c] based natural

products have been reviewed recently through various approaches. Some of the literature reports are discussed below.

3.2. Literature reports on the synthesis of dihydrobenzofuran

3.2.1 Synthesis of 2,3-dihydrobenzofurans from *o*-quinone methides (*o*-QMs)

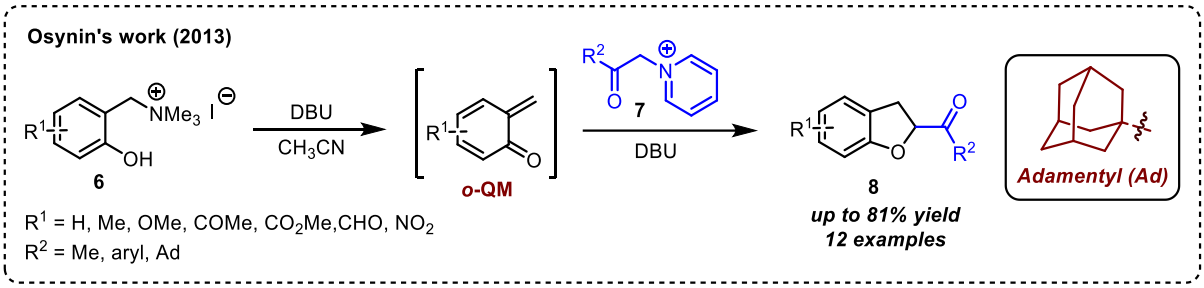
In 2013, Zhou and co-workers described the base-mediated [4+1] annulation reaction of *in situ* generated *o*-QMs (obtained from 2-tosylalkylphenols) and sulfur ylides (**2**) for the synthesis of *trans*-2,3-dihydrobenzofuran derivatives (**3**). The precursor, 2-tosylalkylphenols (**1**), could be synthesized by the reaction of salicylaldehyde and Grignard reagent, followed by an acid-mediated substitution reaction with the sodium salt of *p*-toluene sulfonic acid. A variety of 2-tosylalkylphenols (**1**) and sulfonium salts (**2**) were employed under the standard reaction condition, and the products were isolated in good yield with high diastereoselectivity (*dr* > *20:1*). They also carried out the reaction with camphor-derived chiral sulfur ylide, but the product was obtained in moderate enantioselectivity (37% *ee*) [Scheme 1, **a**].[5] Later, Waser's group developed the stereoselective synthesis of 2,3-dihydrobenzofurans (**5**) by the reaction of *in situ* generated *o*-QMs (obtained from 2-tosylalkylphenols) and cinchona alkaloid-based chiral ammonium ylides (**4**) in the presence of cesium carbonate as a base. The computational



Scheme 1. Synthesis of 2,3-dihydrobenzofuran from 2-tosylalkylphenols

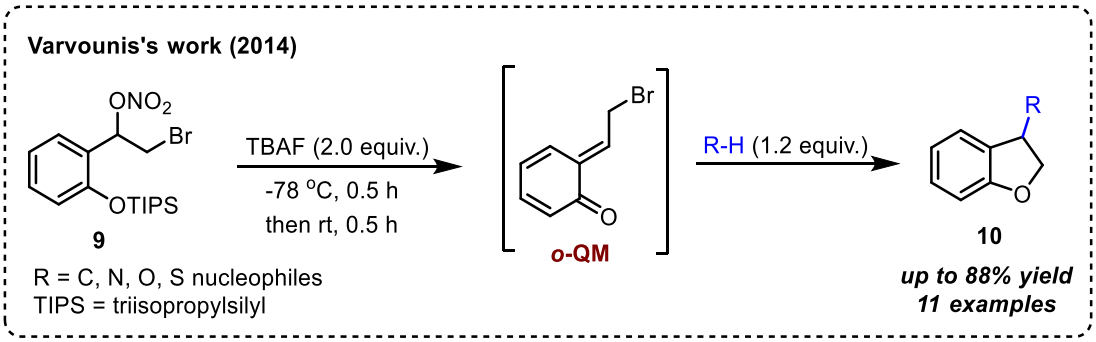
study revealed that the reaction goes through the formation of a *cis*-betaine intermediate, which immediately isomerizes to a *trans*-betaine intermediate, followed by intramolecular S_N2 type cyclization to afford the highly diastereoselective product **5** (Scheme 1, **b**).[6]

In 2013, Osyanin and co-workers disclosed a [4+1] cycloaddition reaction of phenolic Mannich bases (**6**) and pyridinium ylides (**7**) for the synthesis of 2-substituted 2,3-dihydrobenzofuran derivatives (**8**). According to the proposed reaction mechanism, the Mannich base gets converted to the *o*-quinone methide (*o*-QM) in the presence of DBU, then pyridinium ylide underwent 1,4-conjugate addition with the *o*-QM, followed by intramolecular substitution to produce the product **8**. This methodology has also been extended for the synthesis of dihydronaphtho[2,1-*b*]furan derivatives from the corresponding Mannich base (Scheme 2).[7]



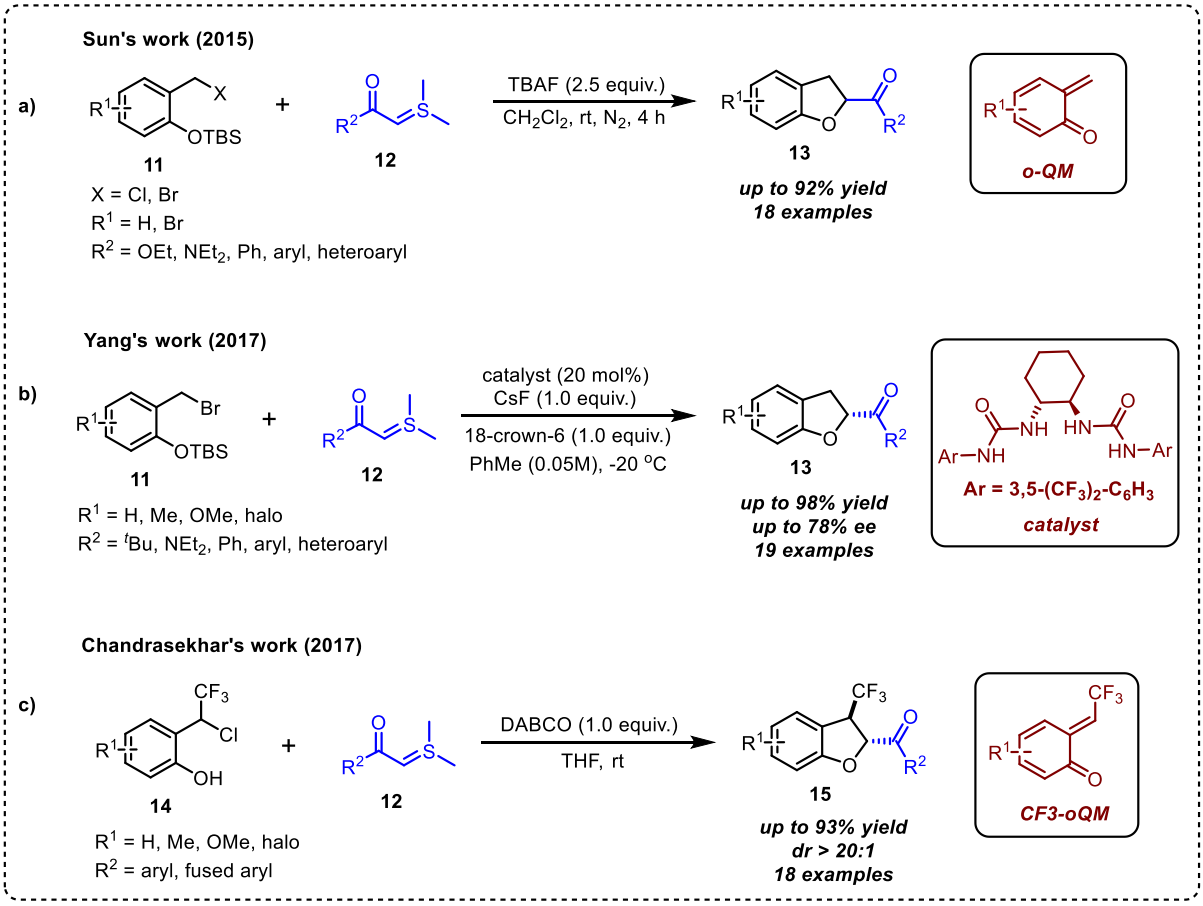
Scheme 2. Synthesis of 2,3-dihydrobenzofuran from Mannich base and pyridinium ylide

In 2014, Varvounis's group reported a one-pot synthesis of 3-substituted 2,3-dihydrobenzofuran derivatives (**10**) from 2-bromo-1-{2-[(triisopropylsilyl)oxy]phenyl}ethyl nitrate (**9**). Compound **9** undergoes a desilylation reaction in the presence of TBAF to produce an intermediate *o*-QM, which is then trapped by various C, N, O, and S nucleophiles, followed by an intramolecular nucleophilic substitution reaction to afford the product (Scheme 3).[8]



Scheme 3. TBAF-mediated synthesis of 3-substituted 2,3-dihydrobenzofurans

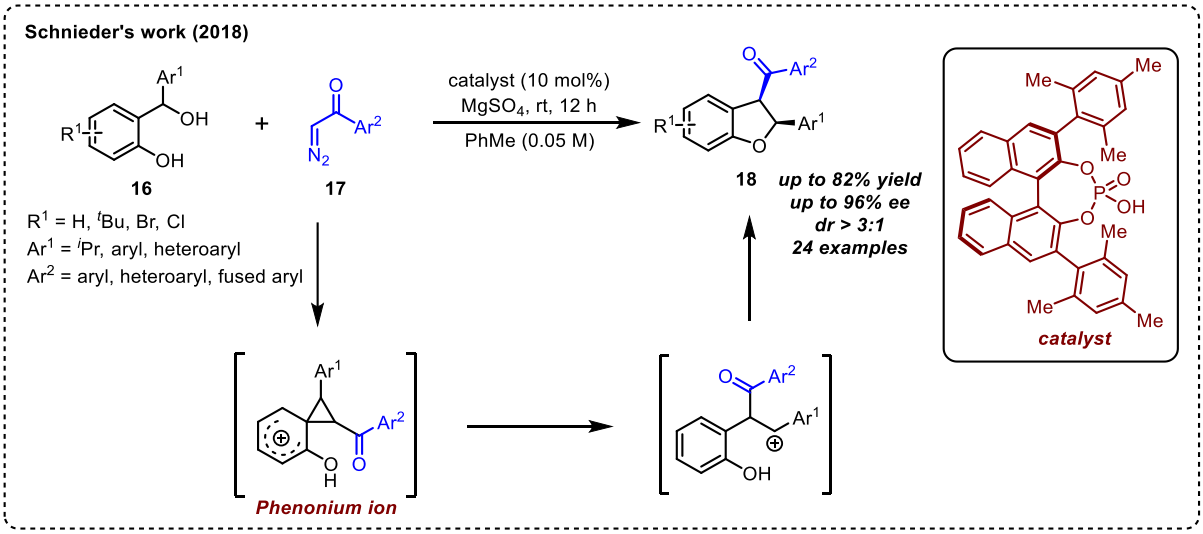
Later, Sun and co-workers developed the synthesis of 2-substituted 2,3-dihydrobenzofuran derivatives (**13**) through *in situ* generation of *o*-QMs (derived from *o*-silylated phenols **11**) and sulfur ylides (**12**) in the presence of TBAF. The reaction was also carried out with chiral camphor-based sulfonium salts, and the products were isolated with good yields and moderate enantioselectivity (up to 69% *ee*).[9] (Scheme 4, **a**) Similarly, Yang's group investigated the chiral urea catalyzed asymmetric [4+1] cycloaddition reaction of *in situ* generated *o*-QMs and sulfur ylides (**12**) for the synthesis of chiral 2,3-dihydrobenzofuran derivatives (**13**) in good yields with moderate enantioselectivity (up to 78% *ee*) [Scheme 4, **b**].[10] Recently, Chandrasekhar's group utilized the same concept for the synthesis of CF_3-containing dihydrobenzofurans (**15**) by *in situ* generations of CF_3-*o*-QM (obtained from *o*-hydroxy CF_3-benzyl chloride **14**) and sulfur ylides (**12**) in the presence of DABCO as a base (Scheme 4, **c**).[11]



Scheme 4. Synthesis of 2,3-dihydrobenzofurans from the reaction of sulfur ylides

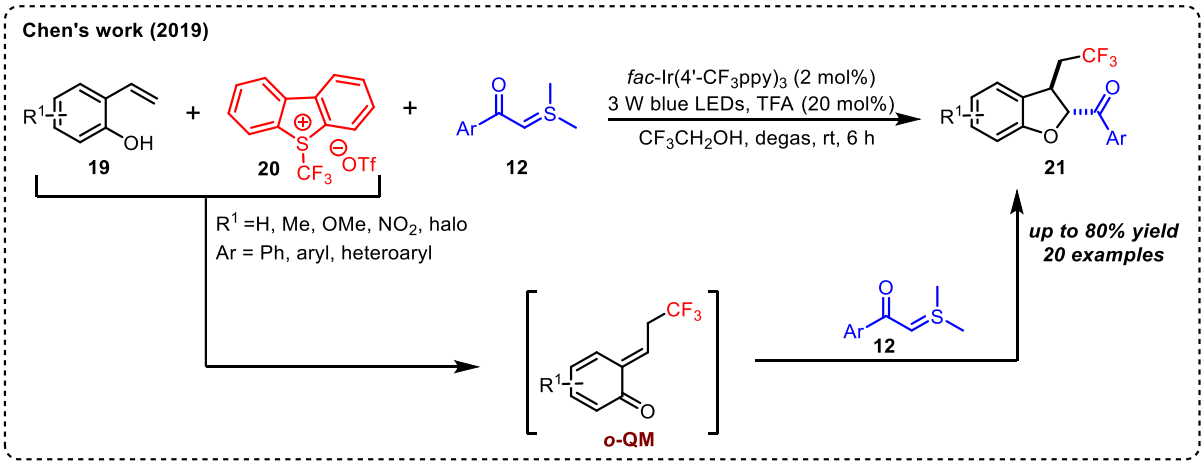
In 2018, Schneider and co-workers described a chiral Brønsted acid-catalyzed enantioselective synthesis of *cis*-2,3-dihydrobenzofuran derivatives (**18**) through the reaction of *in situ* generated *o*-QMs (derived from *o*-hydroxy benzhydryl alcohol (**16**) and *α*-

diazocarbonyl compounds (**17**). A variety of *o*-hydroxy benzhydryl alcohols and *α*-diazocarbonyl were reacted under the standard conditions to afford the product (**18**) with moderate yield and good enantioselectivity. The formation of unexpected products with inverted 2- and 3-substituents happens through the *spiro*-cyclic phenonium ion rearrangement (Scheme 5).[12]



Scheme 5. Synthesis of 2,3-dihydrobenzofurans from the reaction of *α*-diazocarbonyls

Recently, Chen and co-workers disclosed the photoredox-catalyzed *in situ* generations of *o*-QM from 2-vinyl phenol (**19**) and Umemoto's reagent (**20**) as a CF_3 radical source. Then *o*-QM undergoes an [4+1] annulation reaction with sulfur ylide (**12**) to give the CF_3-containing dihydrobenzofuran derivatives (**21**) in moderate yield. The reaction was also carried out with chiral (*R*)-BINOL-based sulfur ylide under the standard reaction conditions, and the product was obtained in low yield (18%) with poor enantioselectivity (25% *ee*). Instead of Umemoto's

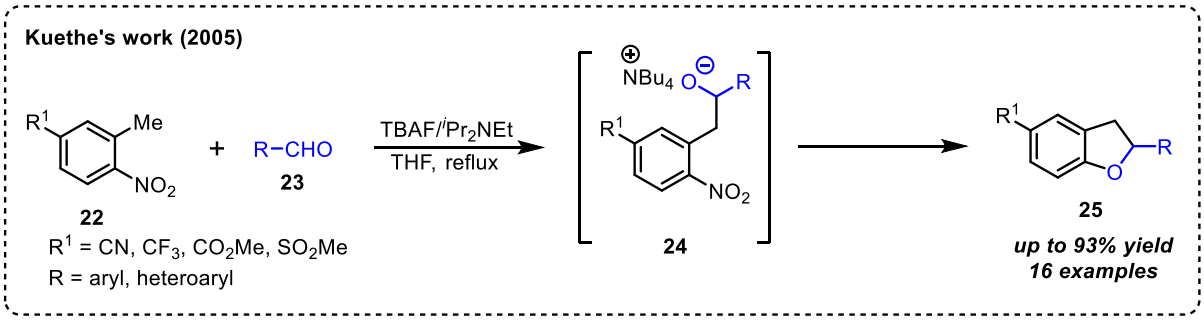


Scheme 6. Photoredox-catalyzed synthesis of 2,3-dihydrobenzofurans

reagent, iodoacetonitrile has also been used as a CN radical source, and the CN-containing dihydrobenzofuran was obtained in a 70% yield (Scheme 6).[13]

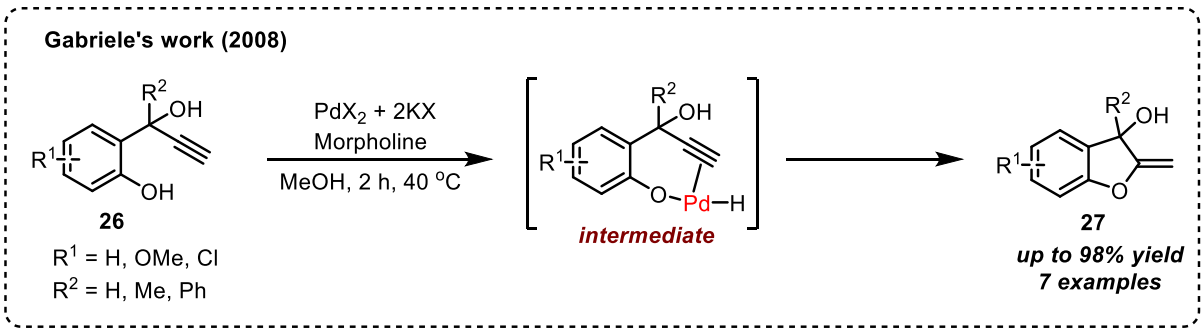
3.2.2 Miscellaneous reports on the synthesis of dihydrobenzofurans

In 2005, Kuethe and co-workers reported a one-pot approach for the synthesis of 2,3-dihydrobenzofuran (**25**) from *o*-nitrotoluenes (**22**) having electron-withdrawing groups and aromatic aldehydes (**23**). A variety of *o*-nitrotoluenes and aldehydes reacted efficiently in the presence of TBAF/$^{i}Pr_2NEt$ (Hünig's base) under refluxing THF to afford the expected products. The reaction proceeds through the formation of tetrabutylammonium alkoxide intermediate **24**, followed by an intramolecular nucleophilic aromatic substitution of the nitro group with alkoxide ion (Scheme 7).[14]



Scheme 7. Synthesis of 2,3-dihydrobenzofurans from *o*-nitrotoluenes

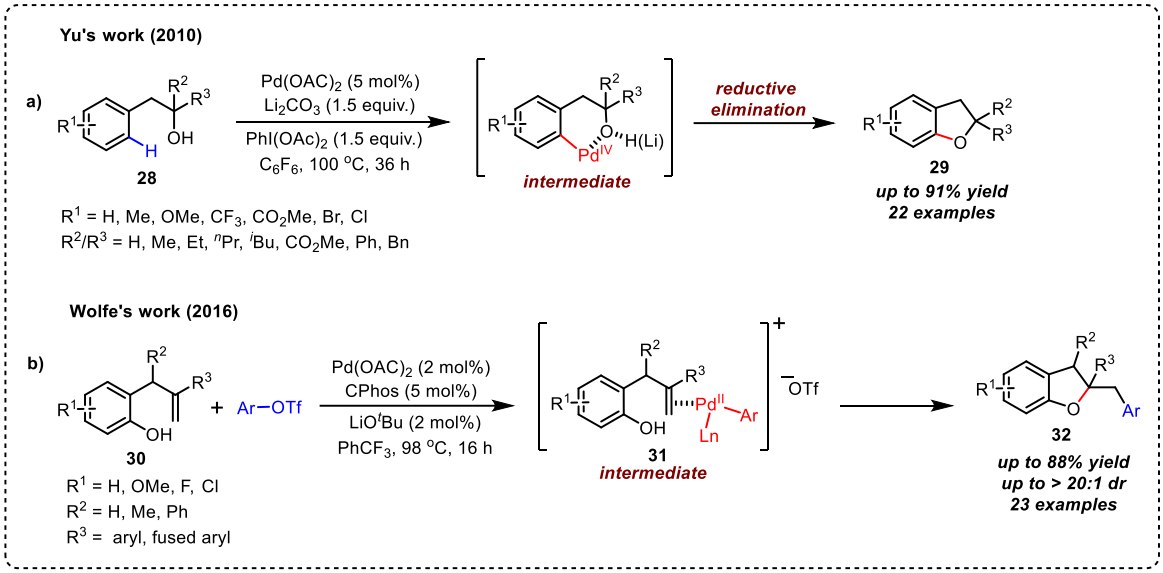
In 2008, Gabriele's group developed a palladium-catalyzed cycloisomerization of *o*-hydroxy propargylic alcohol (**26**) to synthesize dihydrobenzofurans having *exo*-cyclic alkenes. Initially, Pd (II) gets converted to Pd (0) in the presence of a base. Then, Pd (0) undergoes oxidative addition to the phenolic hydroxyl group, followed by alkyne insertion and reductive elimination to produce the product **27** (Scheme 8).[15]



Scheme 8. Synthesis of dihydrobenzofurans from *o*-hydroxy propargylic alcohol

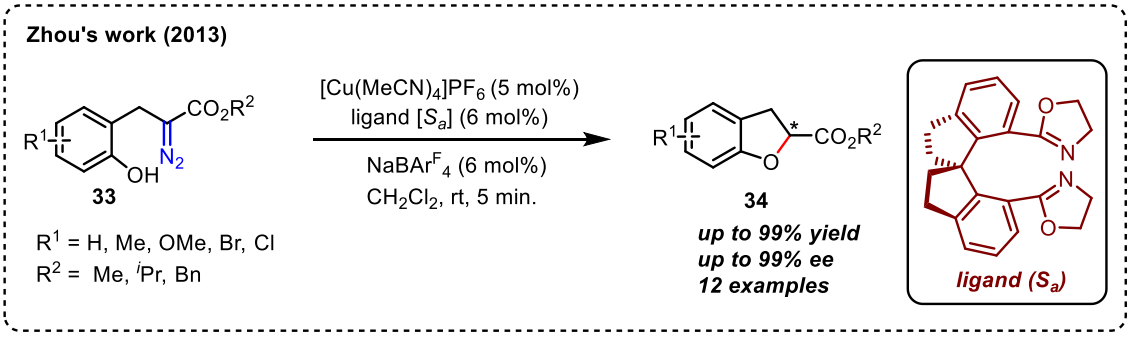
Later, Yu's group described a palladium-catalyzed synthesis of 2,2-disubstituted dihydrobenzofuran derivatives (**29**) from homo-benzylic alcohols (**28**). The reaction proceeds

through the hydroxyl group-directed C-H activation, followed by a C-O cyclization and reductive elimination sequence to produce the product (Scheme 9, **a**).[16] Later, Wolfe's group investigated the palladium-catalyzed construction of dihydrobenzofuran derivatives (**32**) through carboalkoxylation of 2-allyl phenols (**30**) and aryl triflates. A wide range of allyl phenols were treated with aryl triflates in the presence of Pd $(OAc)_2$/CPhos complex, and the related products were isolated in moderate yields. A mechanistic study revealed that the reaction proceeds through the oxidative addition of aryl triflate to the Pd/Cphos complex to generate a cationic palladium complex **31**, which then binds to the alkene, followed by an *anti*-oxypalladation/reductive elimination sequence to produce the product **32** (Scheme 9, **b**).[17]



Scheme 9. Palladium-catalyzed synthesis of dihydrobenzofurans

In 2013, Zhou and co-workers reported an enantioselective synthesis of dihydrobenzofuran derivatives (**34**) from *o*-hydroxy-2-diazopropanoates (**33**) through an intramolecular phenolic O-H bond insertion to carbenoid in the presence of *in situ* generated chiral copper catalyst. Various *o*-hydroxy-2-diazopropanoates (**33**) were reacted under



Scheme 10. Copper-catalyzed enantioselective synthesis of dihydrobenzofurans

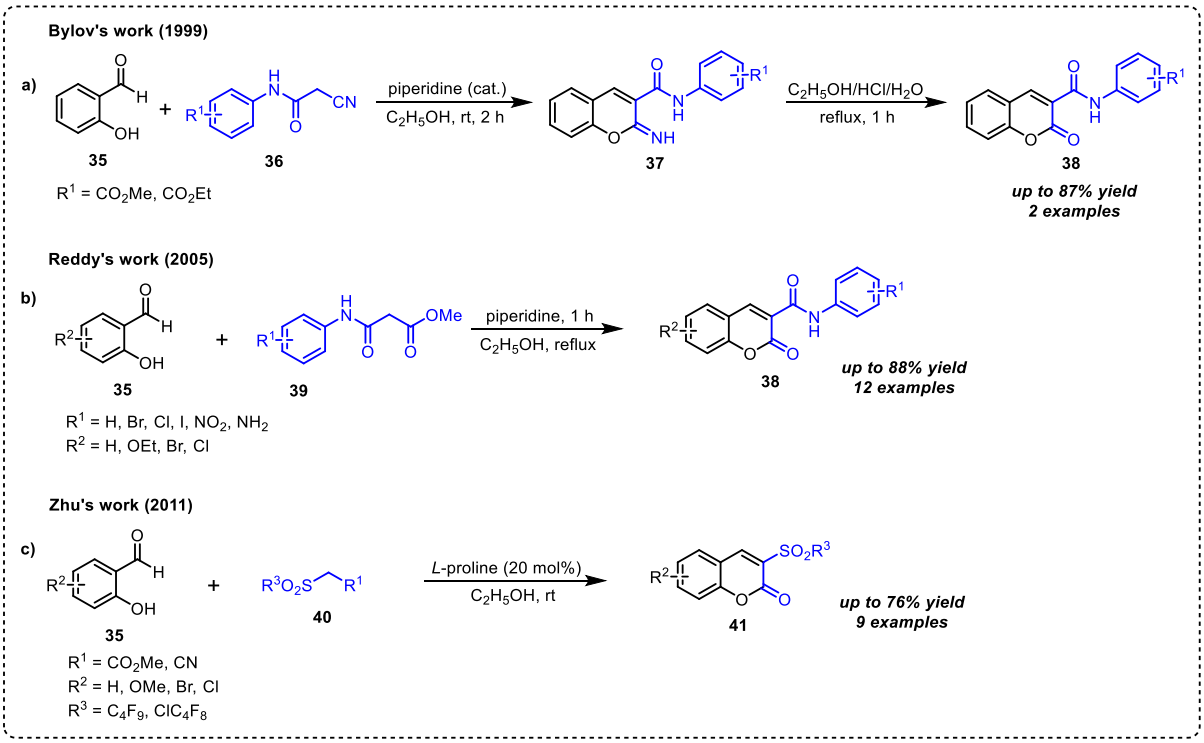
standard conditions to afford the products (**34**) in good yield with excellent enantioselectivity (up to 99% *ee*). This concept has been extended to synthesize an antihypertensive drug derivative (-)-nebivolol (Scheme 10).[18]

3.3 Literature reports on the synthesis of coumarin derivatives

The general approaches for synthesizing coumarin derivatives are Knoevenagal[19-22] and Pechmann[23-26] condensations, metal-catalyzed intramolecular cyclization of alkynoates,[27-31] carbonylative annulations, and carbonylative cyclizations of *o*-alkenyl phenols,[32-36] etc. and, few of them are discussed below in details.

3.3.1 Synthesis of coumarin derivatives through Knoevenagel condensation

Various reports have been known in the literature for synthesizing coumarin derivatives through condensation of 2-hydroxy aromatic benzaldehyde and active methylene compounds. In 1999, Bylov and co-workers developed the condensation of salicylaldehyde (**35**) and *N*-substituted cyano acetamides (**36**) in the presence of a catalytic amount of piperidine to produce imino analogs (**37**), which upon acid-mediated hydrolysis gave the 3-substituted coumarin derivatives (**38**). These derivatives are active anti-inflammatory agents (Scheme 11, **a**).[19] Similarly, Reddy's group described the condensation of methyl 3-anilino-3-oxopropionate (**39**) and salicylaldehyde (**35**) in the presence of piperidine under reflux conditions to access 3-

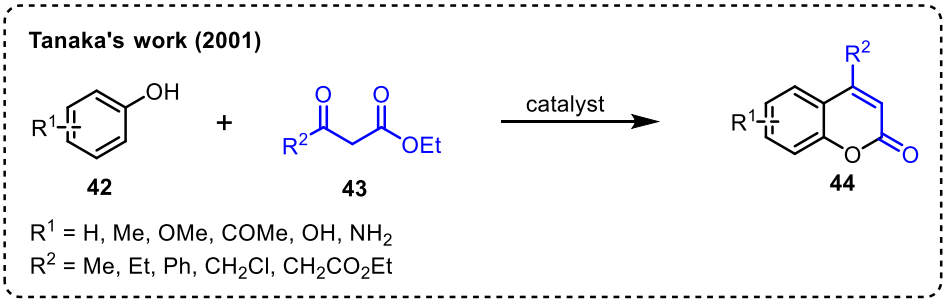


Scheme 11. Synthesis of 3-substituted coumarins through Knoevenagel condensation

substituted coumarin derivatives (**38**) [Scheme 11, **b**].[20] Later, Zhu and co-workers established the *L*-proline catalyzed condensation of salicylaldehyde (**35**) and (perfluoroalkanesulfonyl)-acetate (**40**) for the synthesis of 3-substituted coumarin derivatives (**41**). The reaction proceeds through enamine formation with **40**, which then undergoes 1,2-addition to salicylaldehyde, followed by intramolecular transesterification to produce the product **41** (Scheme 11, **c**).[21] Ionic liquids have also been explored to synthesize coumarin derivatives through Knoevenagel condensation of substituted salicylaldehyde and diethyl malonate.[22]

3.3.2 Synthesis of Coumarin derivatives through Pechmann Condensation

In the Pechmann condensation reaction, 4-substituted coumarin derivatives have been synthesized by the condensation reaction of phenols and *β*-keto acids or their equivalents in acidic conditions. Several reports have been documented in the literature on the synthesis of 4-aryl coumarin derivatives *via* Pechmann condensation. A few of them are summarized here.



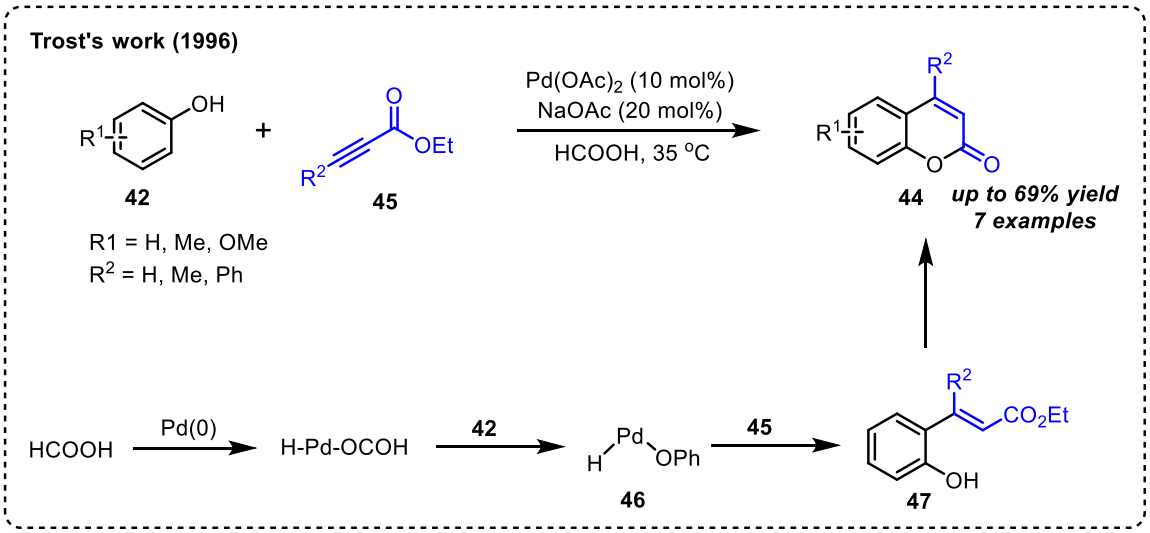
Scheme 12. A general method for the synthesis of coumarins through Pechmann condensation

In 2001, Tanaka and co-workers described the solvent-free synthesis of coumarin derivatives (**44**) by the Pechmann condensation reaction of phenols (**42**) and *β*-keto esters (**43**) in the presence of a catalytic amount of *p*-TsOH (5 mol%) at 60 ^{o}C.[23] Similarly, Bose's group reported the synthesis of **44** under microwave from phenols and *β*-keto esters.[24] Lewis acid[25] and ionic liquids[26] have also been reported as efficient catalysts for synthesizing 4-aryl coumarin derivatives *via* Pechmann condensation (Scheme 12).

3.3.3 Synthesis of coumarin derivatives from alkynoates

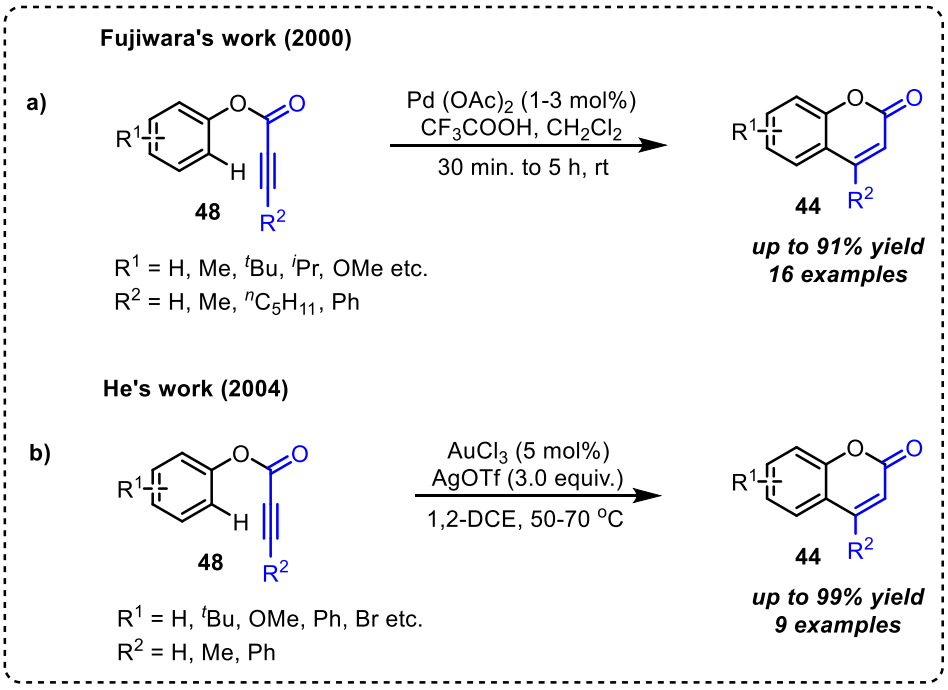
In 1996, Trost's group described the synthesis of coumarin derivatives from phenols (**42**) and alkynoates (**45**) in the presence of a palladium catalyst. According to the proposed reaction mechanism, initially, Pd (0) (obtained from Pd (II) and formic acid) and formic acid generate an active form of catalyst hydridopalladium carboxylate. Then palladium phenoxide **46** is generated from phenol and hydridopalladium carboxylate, followed by activation of

alkynes either *via* carbopalladation or hydridopalladation to generate cinnamate ester (**47**), which undergoes lactonization to produce coumarin derivatives (**44**) [Scheme 13].[27]



Scheme 13. Palladium-catalyzed synthesis of coumarin derivatives

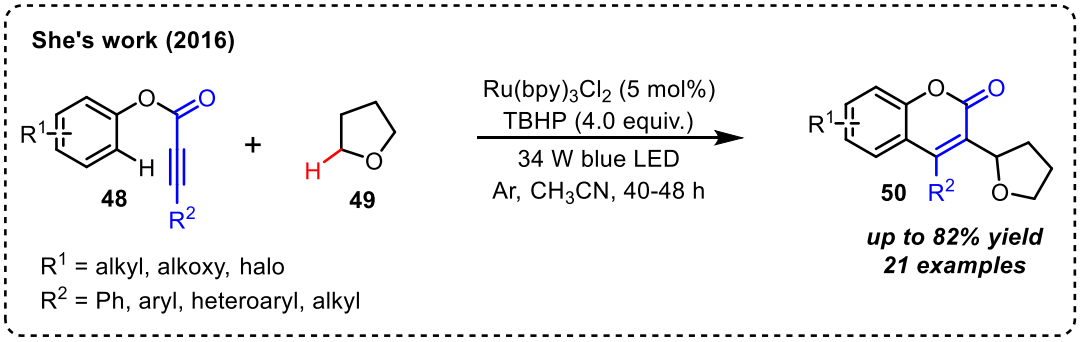
In 2000, Fujiwara and co-workers disclosed the synthesis of coumarin derivatives (**44**) by electrophilic metalation of aromatic C−H bond (**48**) in the presence of electrophilic cationic Pd (II) complex, leading to the formation of new C−C bond through intramolecular addition to alkynes. The cationic Pd (II) complex was generated *in situ* by the coordination of CF_3COO^- (from TFA) with the metal, which not only enhances the electrophilic metalation of aromatic



Scheme 14. Palladium-catalyzed synthesis of coumarins from alkynoates

C-H bond but also activates the C≡C bond for the formation of new C−C bond with arenes (Scheme 14, **a**).[28] They have also reported a one-pot intermolecular variation of this reaction for the synthesis of coumarin derivatives.[29] Similarly, He's group reported the intramolecular hydroarylation of C≡C bond in the presence of Au (III), which is pre-treated with 3.0 equivalents of AgOTf, for the synthesis of coumarin derivatives. It was assumed that AgOTf helps to generate a more electrophilic Au (III) complex (Scheme 14, **b**).[30]

In 2016, She's group developed the visible light-mediated photoredox-catalyzed synthesis of 3,4-disubstituted coumarins (**50**) from alkynoates *via* radical addition/cyclization cascade. A variety of electron-rich and halo-substituted alkynoates (**48**) and ethers (**49**) [cyclic & acylic] reacted efficiently under the standard reaction conditions to produce the product in good yield. The reaction proceeds through the addition of *α*-oxo radical to alkynoates, followed by intramolecular cyclization/oxidation and deprotonation to deliver the product (Scheme 15).[31]

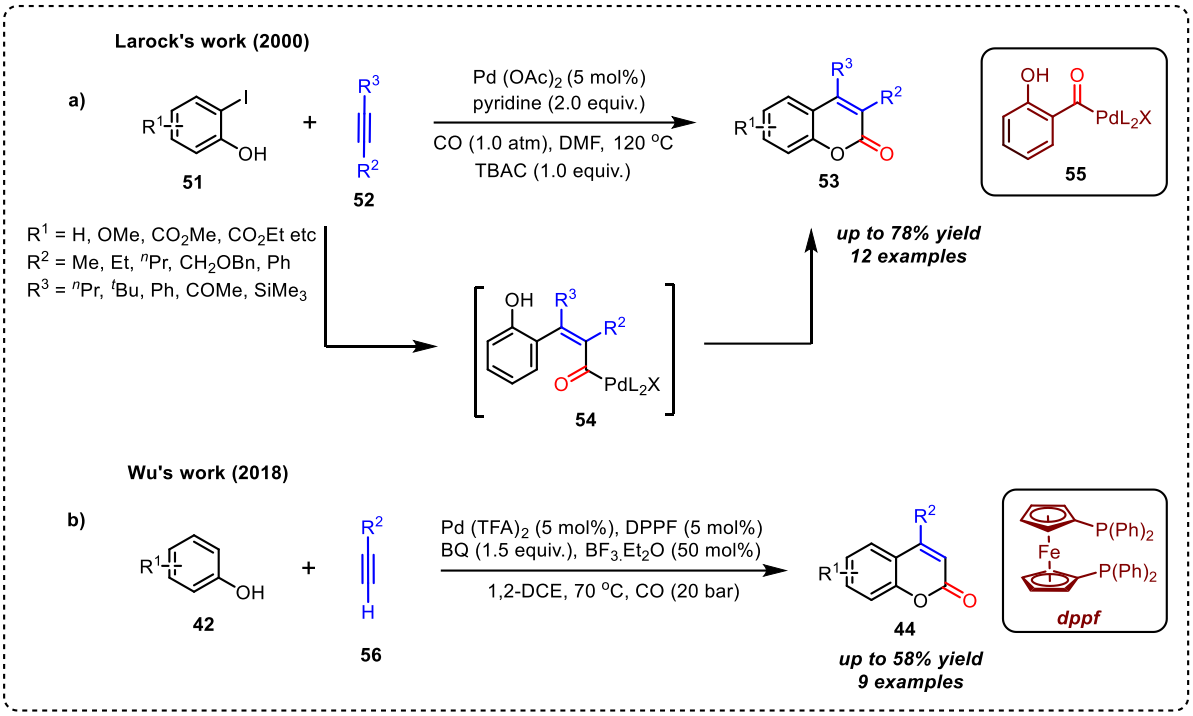


Scheme 15. Photoredox-catalyzed synthesis of coumarins from alkynoates

3.3.4 Synthesis of coumarin derivatives by carbonylative annulation reactions

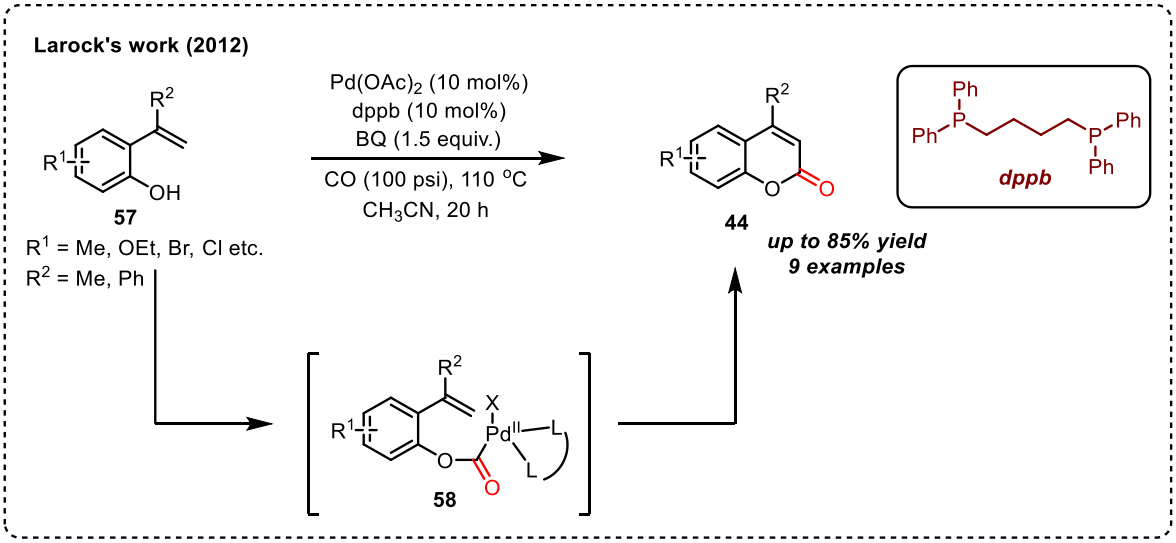
In 2000 Larock and co-workers described the palladium-catalyzed carbonylative coupling of internal alkynes (**52**) with 2-iodophenols (**51**) for the synthesis of 3,4-disubstituted coumarin derivatives (**53**). Unsymmetrical internal alkynes gave a mixture of regioisomers with moderate regioselectivity. According to the proposed reaction mechanism, initially, Pd (0) undergoes oxidation addition to aryl halide, followed by insertion of alkynes and then CO insertion to generate an acyl palladium intermediate **54**, which leads to the formation of the product after the attack of the phenolic hydroxyl group. The preference for insertion of alkynes in comparison to CO is not due to the inability of carbon monoxide but due to the low reactivity of acyl palladium complex **55** generated after the insertion of CO, as compared to faster decarbonylation under the standard reaction conditions (Scheme 16, **a**).[32] Recently, Wu's group

reported the palladium-catalyzed corbonylative coupling of phenols (**42**) with terminal alkynes (**56**) for the synthesis of coumarin derivatives (**44**) in moderate yield (Scheme 16, **b**).[33]



Scheme 16. Synthesis of coumarins by carbonylation reactions

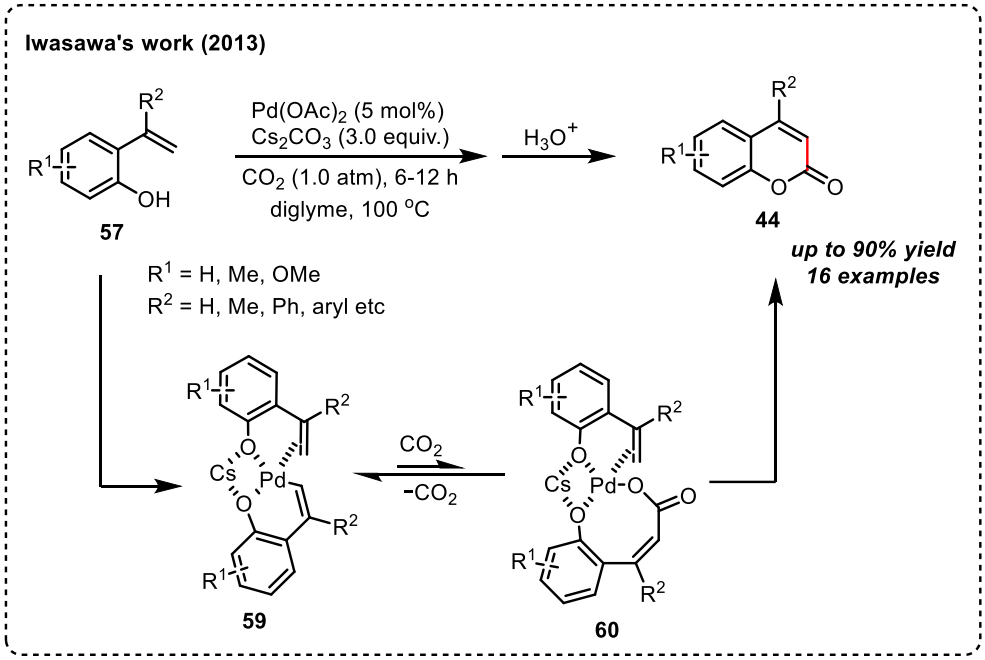
In 2012, Alper's group established the synthesis of coumarin derivatives (**44**) through palladium-catalyzed intramolecular oxidative cyclocarbonylation of 2-vinyl phenols (**57**). A variety of *o*-vinyl phenols reacted in the presence of Pd $(OAc)_2$, CO, and 1,4-benzoquinone as an oxidant to afford the products **44** in good yields. The reaction proceeds through the generation of palladium phenoxide after the ligand exchange, followed by CO insertion



Scheme 17. Synthesis of coumarins by carbonylative annulation reaction of *o*-vinyl phenols

to form an intermediate **58**. Further, intermediate **58** undergoes alkene insertion to produce alkyl palladium intermediate, which leads to product formation after *β*-hydride elimination (Scheme 17).[34] Similarly, Wang and co-workers disclosed a Cp*Co (III) catalyzed carbonylative annulation of 2-vinyl phenols (**57**) for the formation of coumarin derivatives (**44**).[35]

In 2013, Iwasawa and co-workers reported the palladium-catalyzed synthesis of coumarin derivatives (**44**) *via* carboxylation of the C−H bond of 2-vinyl phenols (**57**) with CO_2. According to the proposed mechanism, initially, two molecules of **57** in the presence of



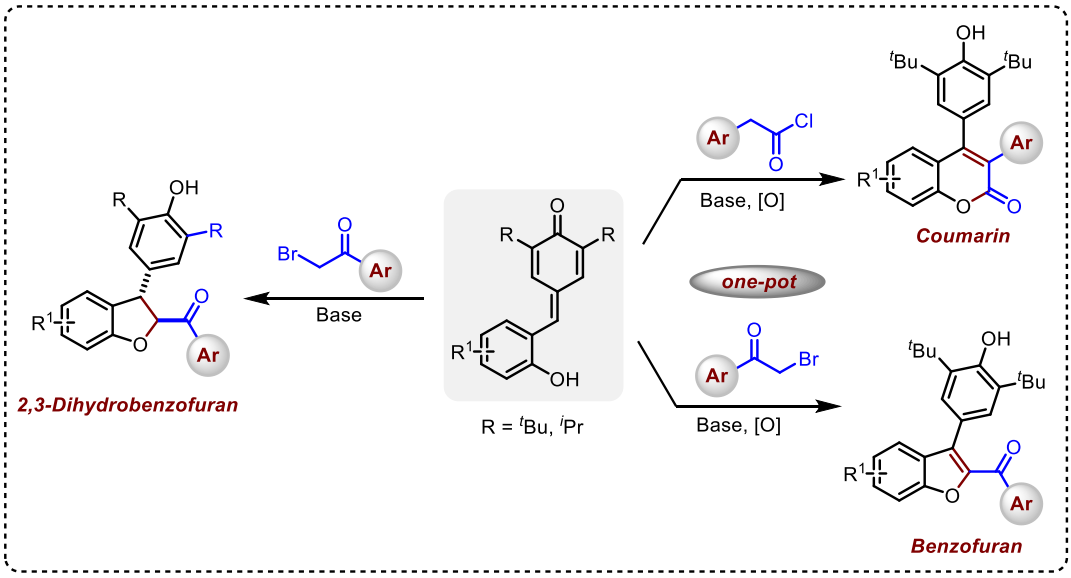
Scheme 18. Synthesis of coumarins by carboxylation reaction of *o*-vinyl phenols

$Pd(OAc)_2$ and Cs_2CO_3 generate an alkenyl palladium complex **59** through alkenyl C−H bond cleavage assisted by chelation, followed by reversible nucleophilic carboxylation with CO_2 to form an intermediate **60**. Then intermediate **60** then reacts with another molecule of **57** and base to produce the product **44** with the regeneration of **59** (Scheme 18).[36]

3.4 Background

Recently, the synthetic utility of 2-hydroxyphenyl-substituted *p*-quinone methides has been revealed in the preparation of many heterocycles[37] including 2,3-dihydrobenzofurans[38] and dihydrocoumarin derivatives.[39] In line with this, we have recently reported a one-pot protocol to access 2,3-diaryl-substituted benzo[*b*]furan derivatives through *N*-heterocyclic carbene (NHC) catalyzed 1,6-conjugate addition of aryl aldehydes to 2-hydroxyphenyl-

substituted *p*-quinone methides followed by acid-mediated dehydrative cyclization.[40] In continuation with our ongoing research in the area of *p*-QMs,[41] herein, we disclose an efficient one-pot method for the synthesis of 2,3-dihydrobenzofurans through a base-mediated *O*-alkylation of 2-hydroxyphenyl-substituted *p*-quinone methides with α-halo ketones followed by intramolecular 1,6-conjugate addition strategy (Scheme 19). This method was also elaborated for the synthesis of 2,3-disubstituted benzo[*b*]furan derivatives through the *in situ* oxidation of 2,3-dihydrobenzofurans. A similar protocol was also developed for the one-pot synthesis of 3,4-diaryl-substituted coumarin derivatives through *O*-acylation of 2-hydroxyphenyl-substituted *p*-quinone methides with arylacetyl halides followed by intramolecular 1,6-conjugate addition/oxidation strategy (Scheme 19). Although a few reports



Scheme 19. One-pot synthesis of 2,3-dihydrobenzofurans, benzo[*b*]furans and coumarins

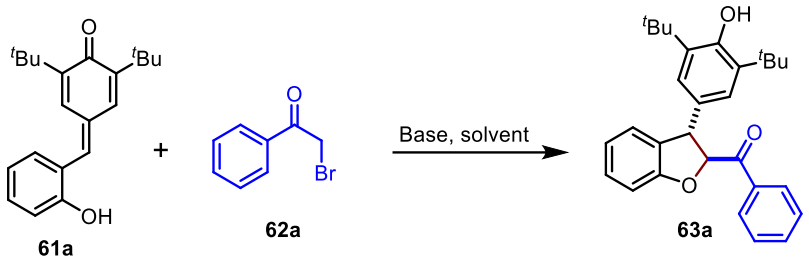
are available for the synthesis of 2,3-dihydrobenzofurans either through a formal [4+1]-annulation of 2-hydroxyphenyl-substituted *p*-QMs with sulfur ylides[38a-c] and allenoates[38d] or through the reaction of 2-hydroxyphenyl-substituted *p*-QMs with α-halo carbonyl compounds,[38e,f] the direct one-pot synthesis of 2,3-disubstituted benzo[*b*]furans and 3,4-diaryl-substituted coumarin derivatives from 2-hydroxyphenyl-substituted *p*-QMs through *O*-alkylation followed by cyclization and oxidation strategy (Scheme 19) has not been reported yet. Therefore, we have decided to explore these transformations.

3.5 Results and discussion

Since the proposed strategy to synthesize benzo[*b*]furans involves 2,3-dihydrobenzofurans as intermediates, we thought of identifying the best conditions for the

synthesis of 2,3-dihydrobenzofurans before exploring the one-pot synthesis of benzo[*b*]furans. In this regard, the optimization studies were initiated using a 2-hydroxyphenyl-substituted *p*-QM **61a** and 2-bromoacetophenone (phenacyl bromide) **62a** under various conditions (Table 1). Initially, the reaction between **61a** and **62a** was performed under basic conditions using 1.5 equivalents of K_2CO_3 in chlorinated solvents. However, the desired product **63a** was obtained only in trace quantities even after 24 h (entries 1 & 2). Interestingly, when the same reaction was performed in acetonitrile, the 2,3-dihydrobenzofuran **3a** was obtained as a diastereomeric pair [*dr* = 6:1 (*trans*:*cis*)] and the pure *trans*-**63**was isolated in 67% chemical yield (entry 3). It was found that the reaction worked well in acetone as the product *trans*-**63a** was obtained in 73% isolated yield (entry 4). When the reaction was carried out in acetonitrile, there was no change in the yield and diastereomeric ratio though the reaction time was reduced to 1.5 h (entry 5). Further optimization studies were carried out in acetone using other organic and inorganic bases. By using 1.5 equivalents of Cs_2CO_3 as a base, the 2,3-dihydrobenzofuran **63a** was obtained as a diastereomeric pair (*dr* = 10:1), and the pure *trans*-**63a** was isolated in the

Table1. Optimization study[a]

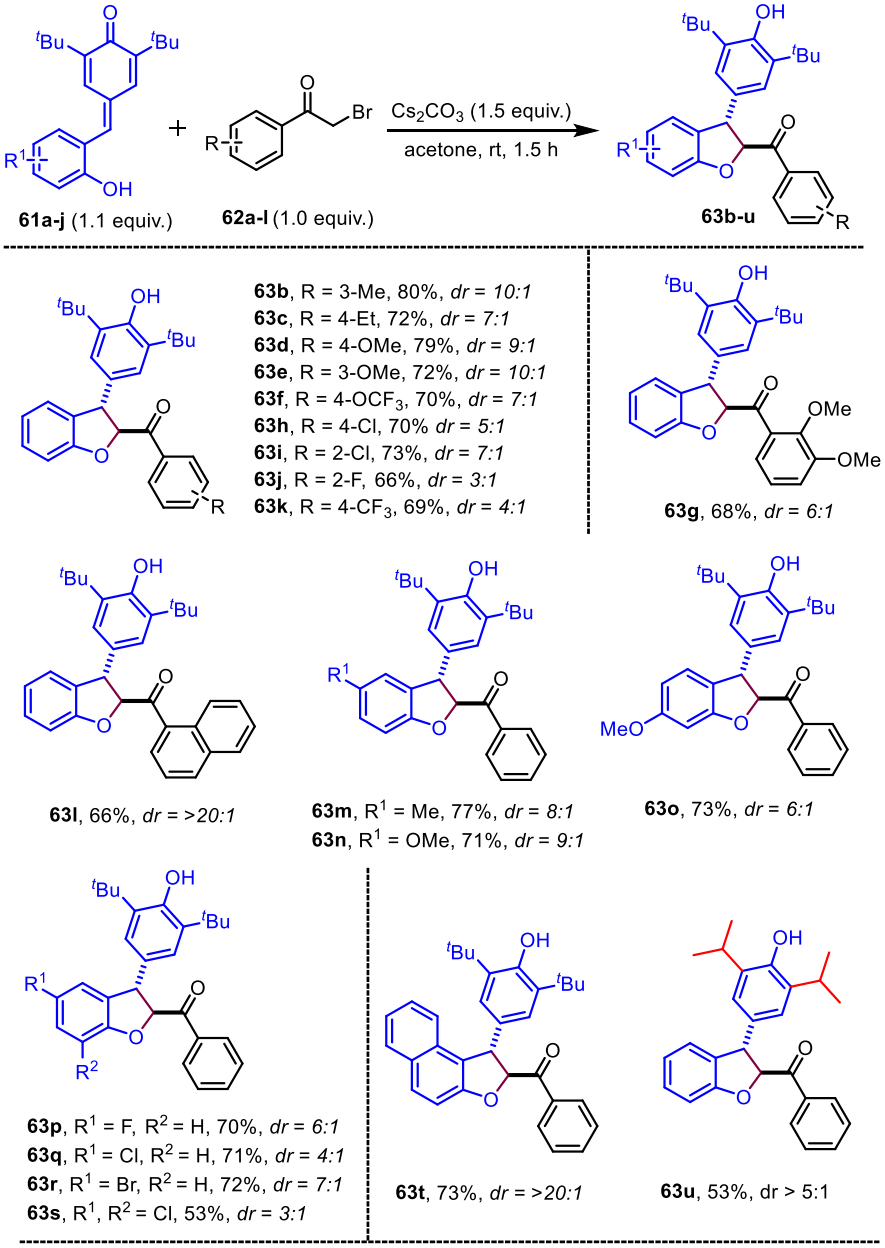


entry	base	solvent	time [h]	*dr* *(trans:cis)*[e]	isolated yield of *trans*-63a [%]
1	K_2CO_3	CH_2Cl_2	24	-	trace
2	K_2CO_3	$CHCl_3$	24	-	trace
3	K_2CO_3	CH_3CN	12	6:1	67
4	K_2CO_3	Acetone	8	9:1	73
5	Cs_2CO_3	CH_3CN	1.5	9:1	73
6	**Cs_2CO_3**	**Acetone**	**1.5**	**10:1**	**80**
7	NEt_3	Acetone	24	3:1	40
8	DBU	Acetone	24	7:1	46
9[b]	Cs_2CO_3	Acetone	24	9:1	71
10[c]	Cs_2CO_3	Acetone	1	9:1	80
11[d]	Cs_2CO_3	Acetone	24	9:1	30

[a] All reactions were carried out with **61a** (0.097 mmol), **62a** (0.088 mmol) and 1.5 equivalent of base in 1.5 mL of solvent. [b] 1.0 equivalent of base was used. [c] 2.0 equivalent of base was used. [d] Reaction was carried at 0 °C and 1.5 equivalent of base was used. [e] The diastereomeric ratio (*dr*) was calculated based on the ^{1}H NMR analysis of crude reaction mixture. The relative stereochemistry of the major isomer (*trans*-**63a**) was assigned by comparing the ^{1}H NMR data with the previous reports.[38]

maximum of 80% yield within 1.5 h (entry 6). Organic bases, such as triethylamine and DBU, were found to be less effective for this transformation (entries 7 & 8). The yield of **63a** was relatively low (71%) when the reaction was carried out with 1 equivalent of Cs_2CO_3 (entry 9), and there was no change in the yield and diastereoselectivity of **63a** when 2 equivalents of Cs_2CO_3 was used (entry 10). Since some decomposition was observed in most of the optimization experiments at room temperature, an experiment was conducted at a lower

Scheme 20. Substrate scope for the synthesis of *trans*-2,3-dihydrobenzofurans[a]



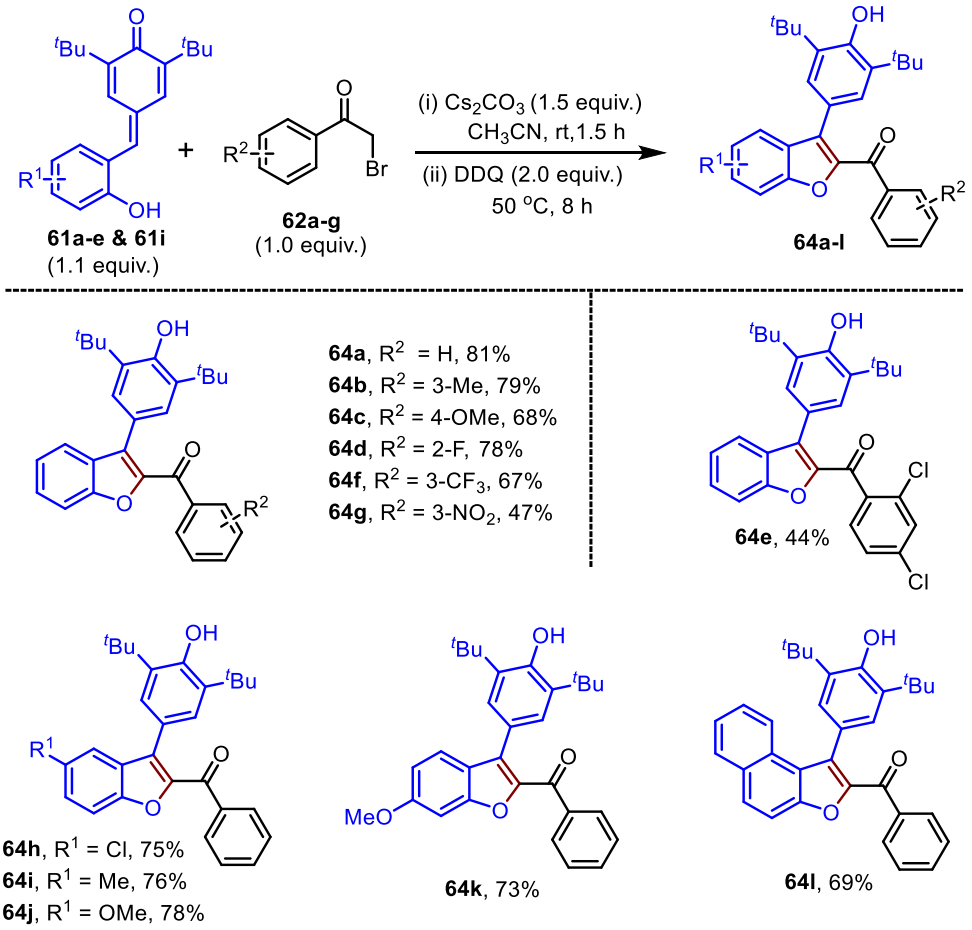
[a] All reactions were carried out in ~ 0.1 mmol scale of **61**(**a**-**j**) in 1.5 mL of acetone. Yields represented are isolated yields of the pure *trans*-isomer (major isomer). The diastereomeric ratios (*dr*) were calculated based on the ^{1}H NMR analysis of crude reaction mixtures.

temperature (0 ^{o}C) using 1.5 equivalents of Cs_2CO_3. However, in that case, although the reaction was found to be clean, the rate of the reaction was low, and product **63a** was obtained only in 30% isolated yield after 24 h (entry 11).

After finding the optimal reactions conditions (entry 6, Table 1), the substrate scope was investigated by employing a wide range of 2-hydroxyphenyl-substituted *p*-QMs (**61a**-**j**) and bromomethyl aryl ketones (**62a**-**l**), and the results are summarized in Scheme 20. In general, most of the bromomethyl aryl ketones (**62b**-**l**) reacted with **61a** and provided the respective *trans*-2,3-dihydrobenzofuran derivatives (**63b**-**l**) in moderate to good isolated yields. For example, the reaction of **61a** with bromomethyl aryl ketones **62a**-**k** (containing alkyl-, alkoxy- and halo-substitution at the aryl ring) provided the corresponding *trans*-2,3-dihydrobenzofuran derivatives **63a**-**k** in 66-80% isolated yields. In the case of bromomethyl 1-naphthyl ketone (**62l**), the product **63l** obtained in 66% yield. In the cases of reaction between **62a** and 2-hydroxyphenyl-substituted *p*-QMs **61b**-**h** (derived from the respective alkyl-, halo- and alkoxy- substituted salicylaldehydes), the *trans*-2,3-dihydrobenzofuran derivatives **63m**-**s** were obtained in the rage of 53-77% chemical yields. In the case of 2-hydroxyphenyl-substituted *p*-QM **61i** (derived from 2-hydroxy-1-naphthaldehyde), the respective product *trans*-**63t** was obtained in 73% yield. When the *p*-QM **61j** (derived from 2,6-diisopropylphenol), the product **63u** was isolated as a diastereomeric mixture in 53% yield.

To show the importance of this methodology, this concept was also elaborated to the one-pot synthesis of 2,3-disubstituted benzo[*b*]furans, directly from the 2-hydroxyphenyl-substituted *p*-QMs through the *in situ* dehydrogenative oxidation of 2,3-dihydrobenzofurans by DDQ, and the results are summarized in Scheme 21. It was found that the one-pot conversion of **61a** to the corresponding 2,3-disubstituted benzo[*b*]furan **64a** worked well using 2 equivalents of DDQ in acetonitrile and, in this case, **64a** was obtained in 81% yield. However, the same transformation in acetone provided the product **64a** only in 73% yield even after 24 h. Since acetonitrile was found to be a better solvent than acetone for this transformation, further elaboration of the substrate scope was performed in acetonitrile. As shown in Scheme 21, most of the reactions between **61a** and various bromomethyl aryl ketones (**62b**-**g**) worked well, and the respective products **64b**-**g** were obtained in the range of 44-79% yields. In the cases of reaction between **62a** and 2-hydroxyphenyl-substituted *p*-QMs **61b**-**e**, the benzo[*b*]furan derivatives **64h**-**k** were obtained in the rage of 73-78% yields. In the case of 2-hydroxyphenyl-substituted *p*-QM **61i**, the respective product **64l** was obtained in 69% yield.

Scheme 21. Substrate scope for the synthesis of benzo[*b*]furans[a]

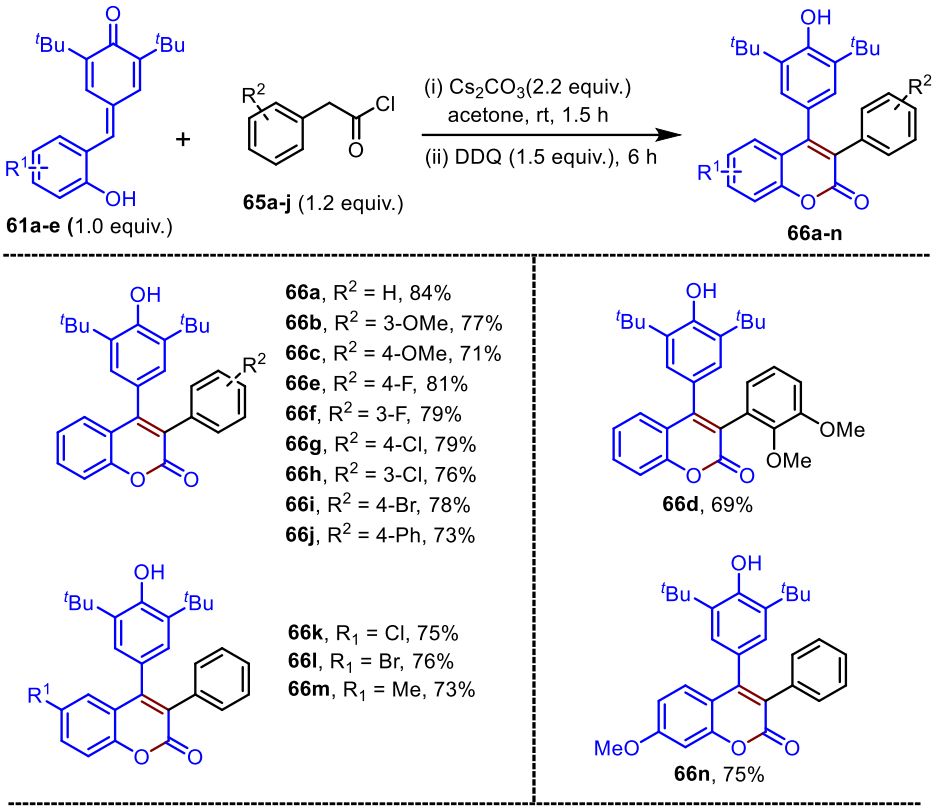


[a] All reactions were carried out in ~ 0.1 mmol scale of **61**(**a**-**e**) & **61i** in 1.5 mL of MeCN. Yields reported are isolated yields.

After exploring the application potential of this methodology in the synthesis of various 2,3-dihydrobenzofuran and benzo[*b*]furan derivatives, our attention was shifted to further elaborate this concept for the synthesis of other oxygen-based heterocycles. We envisioned that it could be possible to access 3,4-diaryl-substituted coumarin derivatives by treating 2-hydroxyphenyl-substituted *p*-QMs with arylacetyl halides followed by one-pot dehydrogenative oxidation with DDQ. In this regard, an initial experiment was carried out by treating **61a** with phenylacetyl chloride (**65a**) [1.2 equiv.] and Cs_2CO_3 (2.2 equiv.) in acetone for 1.5 h followed by the addition of DDQ (1.5 equiv.). As expected, in that case, the desired coumarin derivative **66a** was obtained in 84% isolated yield (Scheme 22). Encouraged by this result, the scope and limitations of this transformation were examined using various 2-hydroxyphenyl-substituted *p*-QMs (**61a**-**e**) and arylacetyl halides (**65a**-**j**), and the results are summarized in Scheme 22. Most of the arylacetyl halides (**65b**-**j**) reacted smoothly with **61a** and the respective products, after oxidation with DDQ, gave the corresponding diaryl-

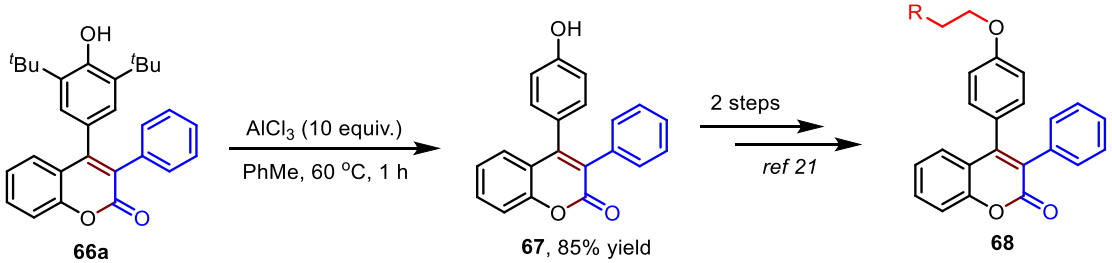
substituted coumarin derivatives **66b-j** in the range of 69-79% isolated yields. In addition, other 2-hydroxyphenyl-substituted *p*-QMs (**61b-e**) also reacted with phenylacetyl chloride (**65a**) and provided the desired products **66k-n** in good yields (73-76%).

Scheme 22. Substrate scope for the synthesis of coumarin derivatives[a]



[a] All reactions were carried out in ~ 0.1 mmol scale of **61**(**a-e**) in 1.5 mL of acetone. Yields reported are isolated yields.

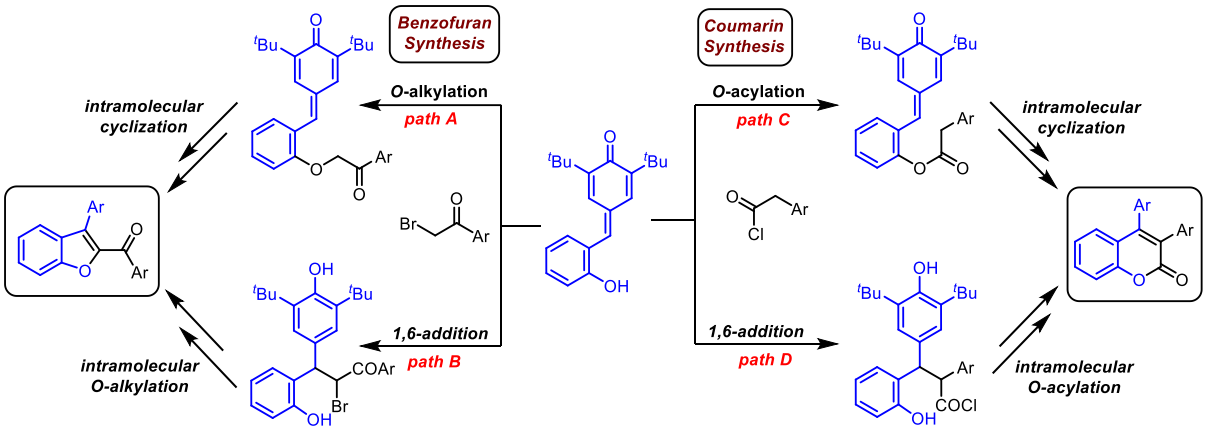
To show a practical application of this transformation, we thought of elaborating one of the coumarin derivatives to a biologically active 3,4-diaryl-substituted coumarin derivative **68**, which was found to act as an immunomodulating agent.[42] It has been reported that the coumarin derivative **68** could be easily accessed in a couple of steps from **67** through *O*-alkylation followed by amination with morpholine.[42] In fact, the coumarin derivative **67** could



Scheme 23. Formal synthesis of immunomodulating agent **68**

be prepared in one step from **66a** by removal of *t*-Bu groups. In this regard, the de-*tert*-butylation reaction of **66a** was carried out by treating it with an excess of $AlCl_3$ (10 equiv.) in toluene at 60 °C, and the expected product **67** was obtained in 85% yield (Scheme 23).

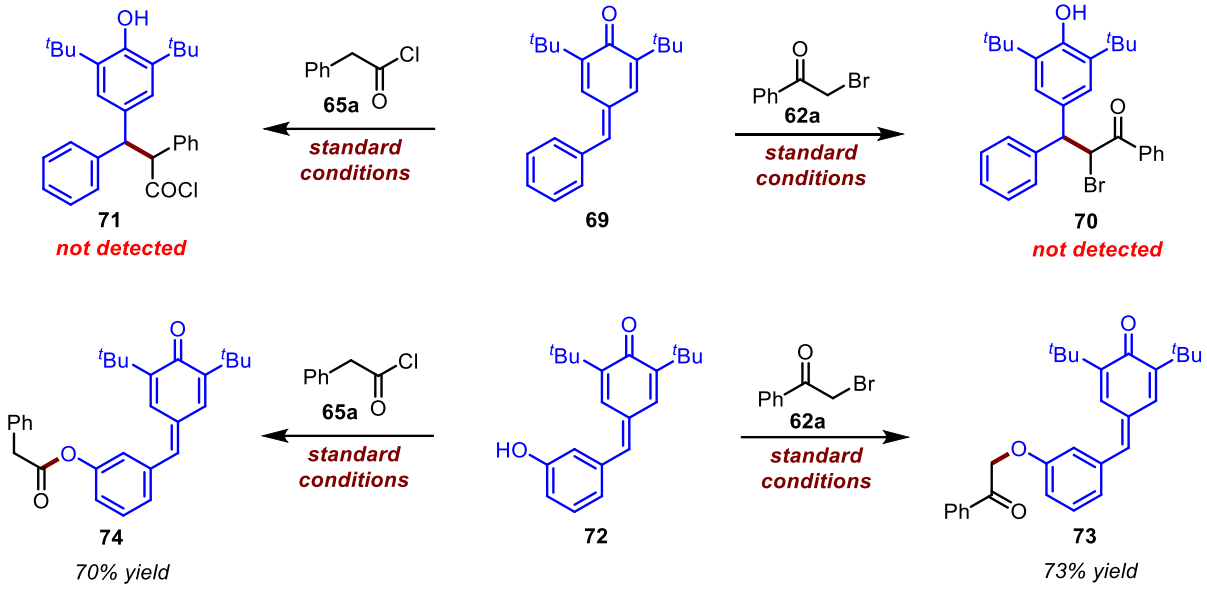
Later, we turned our attention to understand the mechanism of these transformations. There are two different pathways possible for both the transformations [benzofuran as well as coumarin formation] (Scheme 24); (i) *O*-alkylation followed by intramolecular cyclization



Scheme 24. Possible reaction pathways

(path A) or 1,6-conjugate addition followed by intramolecular *O*-alkylation (path B) in the case of 2,3-dihydrobenzofuran/benzo[*b*]furan formation and (ii) *O*-acylation followed by intramolecular cyclization (path C) or 1,6-conjugate addition followed by intramolecular *O*-acylation (path D) in the case of coumarin formation.

During the optimization studies, we thought of isolating the intermediate(s) in the reaction between 2-hydroxyphenyl-substituted *p*-QM (**61a**) and 2-bromoacetophenone (**62a**) [entry 6, Table 1]. However, we were not able to isolate any of the intermediates as we could not notice any other spot in the TLC except the starting materials (**61a** & **62a**) and the product (**63a**). Most probably, the transformation of the intermediate to product **63a** could be spontaneous. In fact, the ^{1}H NMR analysis of the crude reaction mixture before the completion of the reaction did not help much in identifying the intermediate(s). Therefore, to understand the actual reaction pathway(s), a few control experiments have been performed (Scheme 25). Initially, a couple of experiments had been carried out by treating phenyl-substituted *p*-QM **69** (instead of **61a**) with phenacyl bromide (**62a**) and phenylacetyl chloride (**65a**), individually under standard conditions. However, in both the cases, the corresponding 1,6-adducts **70** and **71** were not observed even after 24 h (Scheme 25). In fact, the starting material **69** was recovered unreacted in both the experiments.



Scheme 25. Control experiments

In another set of experiments, 3-hydroxyphenyl-substituted *p*-QM **72**[43] (instead of **61a**) was treated with **62a** and **65a**, individually under the standard conditions (Scheme 25). Interestingly, in those cases, the corresponding *O*-alkylated product **73** and *O*-acylated product **74** were obtained in 73% and 70% yields, respectively, within an hour. Moreover, the corresponding 1,6-adducts were not at all observed in both the cases. The above-mentioned control experiments clearly indicate that the reaction is proceeding through *O*-alkylation followed by intramolecular cyclization[38e] in the case of 2,3-dihydrobenzofuran/benzo[*b*]furan formation (path A, Scheme 24). Similarly, in the case of coumarin formation, one can conclude that the reaction is proceeding through *O*-acylation followed by intramolecular cyclization (path C, Scheme 24).

3.6 Conclusion

In conclusion, an effective one-pot protocol has been developed for the diastereoselective synthesis of *trans*-2,3-dihydrobenzofurans from 2-hydroxyaryl-substituted *p*-quinone methides through *O*-alkylation followed by 1,6-conjugate addition/cyclization strategy. This methodology has been elaborated for the one-pot synthesis of benzo[*b*]furans through the *in situ* dehydrogenative oxidation of the *trans*-2,3-dihydrobenzofuran intermediates. A similar methodology was also developed for the one-pot synthesis of 3,4-diaryl-substituted coumarin derivatives through the reaction between 2-hydroxyaryl-substituted *p*-quinone methides and arylacetyl chlorides followed by oxidation. Under the

optimal conditions, the above-mentioned oxygen-containing heterocycles could be accessed in moderate to good yields.

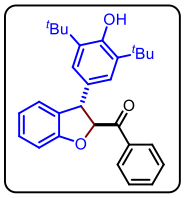
3.7. Experimental section

General information. All reactions were carried out under an argon atmosphere in an oven-dried round bottom flask. All the solvents were distilled before use and stored under an argon atmosphere. Most of the reagents and starting materials were purchased from commercial sources and used as such. The substituted 2-bromoacetophenones were prepared according to the literature procedure.[44] All 2-hydroxyphenyl-substituted *p*-quinone methides (**61a-j**)[37a] and 3-hydroxy phenyl-substituted *p*-quinone methide (**72**)[43] were prepared by following literature procedures. 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 relatives to TMS or $CDCl_3$ (7.26 ppm for ^{1}H and 77.16 ppm for ^{13}C NMR), and the coupling constants (*J*) are reported in Hz. High-resolution mass spectra were recorded on Waters Q–TOF Premier–HAB213 spectrometer. FT-IR spectra were recorded on a Perkin-Elmer FTIR spectrometer. Thin layer chromatography was performed on Merck silica gel 60 F_{254} TLC pellets and visualized by UV irradiation and $KMnO_4$ stain. Column chromatography was carried out through silica gel (100–200 mesh) using EtOAc/hexane as an eluent.

General procedure for the synthesis of 2,3-dihydrobenzofuran derivatives (63a-u):

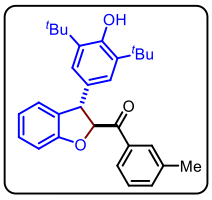
Bromomethyl aryl ketone [**62a-l**] (0.1 mmol, 1.0 equiv.) was added to a mixture of 2-hydroxyphenyl-subsituted *p*-QM [**61a-j**] (0.11 mmol, 1.1 equiv.) and Cs_2CO_3 (0.15 mmol, 1.5 equiv.) in acetone (1.5 mL, 0.06 M) and, the resulting suspension was stirred at room temperature until the bromomethyl aryl ketone was completely consumed (based on TLC analysis). The reaction mixture was concentrated under reduced pressure, and the residue [a mixture of *cis*- and *trans*-2,3-dihydrobenzofurans along with some amounts of the starting material(s)] was then purified through a silica gel column using EtOAc/Hexane mixture as an eluent to get the *trans*-2,3-dihydrobenzofuran derivatives (**63a-u**).

***trans*-[3-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-2,3-dihydrobenzofuran-2-yl](phenyl)methanone (63a):**[38b] The reaction was performed at 0.097 mmol scale of **61a**; white solid (31.0 mg, 80% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 – 7.93 (m, 2H), 7.60 (t, *J* = 7.4 Hz, 1H), 7.45 (t, *J* = 7.8 Hz, 2H), 7.22 (t, *J* = 7.9 Hz, 1H), 7.06 (d, *J* = 7.4 Hz, 1H), 7.00



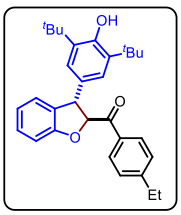
(d, *J* = 8.0 Hz, 1H), 6.96 (s, 2H), 6.91 (t, *J* = 7.4 Hz, 1H), 5.80 (d, *J* = 6.6 Hz, 1H), 5.20 (s, 1H), 4.86 (d, *J* = 6.6 Hz, 1H), 1.40 (s, 18H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 195.3, 159.3, 153.2, 136.3, 134.7, 133.8, 132.7, 129.5, 129.4, 128.8, 128.7, 125.6, 124.9, 121.6, 109.9, 90.9, 51.4, 34.5, 30.4; FT-IR (thin film, neat): 3636, 2959, 1694, 1261, 750 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{29}H_{31}O_3$ $[M–H]^-$: 427.2273; found : 427.2288.

***trans*-[3-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-2,3-dihydrobenzofuran-2-yl](*m*-tolyl)methanone (63b):**[38c] The reaction was performed at 0.097 mmol scale of **61a**; white solid



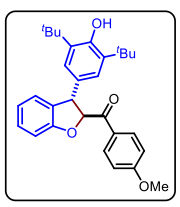
(31.6 mg, 80% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, *J* = 7.7 Hz, 1H), 7.66 (s, 1H), 7.40 (d, *J* = 7.5 Hz, 1H), 7.33 (t, *J* = 7.6 Hz, 1H), 7.21 (t, *J* = 7.7 Hz, 1H), 7.04 (d, *J* = 7.4 Hz, 1H), 6.99 (d, *J* = 8.1 Hz, 1H), 6.95 (s, 2H), 6.90 (t, *J* = 7.4 Hz, 1H), 5.80 (d, *J* = 6.8 Hz, 1H), 5.18 (s, 1H), 4.81 (d, *J* = 6.8 Hz, 1H), 2.36 (s, 3H), 1.38 (s, 18H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 195.5, 159.4, 153.2, 138.5, 136.4, 134.8, 134.6, 132.6, 129.9, 129.5, 128.8, 128.6, 126.6, 125.5, 124.9, 121.5, 110.0, 90.9, 51.7, 34.5, 30.4, 21.5; FT-IR (thin film, neat): 3636, 2958, 1695, 1479, 1267, 759 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{30}H_{33}O_3$ $[M–H]^-$: 441.2430; found : 441.2448.

***trans*-[3-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-2,3-dihydrobenzofuran-2-yl](4-ethylphenyl)-methanone (63c):** The reaction was performed at 0.097 mmol scale of **61a**;



white solid (29 mg, 72% yield); m. p. = 151–153 ºC; R_f = 0.2 (5% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, *J* = 7.4 Hz, 2H), 7.28 – 7.26 (m, 2H), 7.21 (t, *J* = 7.6 Hz, 1H), 7.05 (d, *J* = 7.5 Hz, 1H), 6.99 (d, *J* = 8.1 Hz, 1H), 6.95 (s, 2H), 6.90 (t, *J* = 7.5 Hz, 1H), 5.77 (d, *J* = 6.6 Hz, 1H), 5.18 (s, 1H), 4.84 (d, *J* = 6.6 Hz, 1H), 2.72 (q, *J* = 7.5 Hz, 2H) 1.38 (s, 18H), 1.27 (t, *J* = 7.5 Hz, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 195.0, 159.4, 153.1, 150.9, 136.3, 132.8, 132.4, 129.7, 129.5, 128.8, 128.3, 125.6, 124.9, 121.5, 109.9, 90.8, 51.5, 34.5, 30.4, 29.2, 15.3; FT-IR (thin film, neat): 3636, 2963, 1689, 1461, 1275, 750 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{31}H_{35}O_3$ $[M–H]^-$: 455.2586; found : 455.2599.

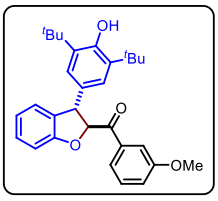
***trans*-[3-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-2,3-dihydrobenzofuran-2-yl](4-methoxyphenyl)-methanone (63d):**[38b] The reaction was performed at 0.097 mmol scale of



61a; white solid (31.6 mg, 79% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, *J* = 8.6 Hz, 2H), 7.20 (t, *J* = 7.7 Hz, 1H), 7.05 (d, *J* = 7.4 Hz, 1H), 6.98 – 6.96 (m, 3H), 6.92 – 6.88 (m, 3H), 5.74 (d, *J* = 6.8 Hz, 1H), 5.18 (s, 1H), 4.86 (d, *J* = 6.8 Hz, 1H), 3.87 (s, 3H), 1.38 (s, 18H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ

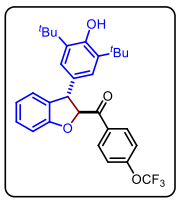
193.8, 164.0, 159.3, 153.1, 136.3, 132.7, 131.8, 129.6, 128.7, 127.7, 125.6, 125.0, 121.5, 113.9, 109.9, 90.8, 55.6, 51.5, 34.5, 30.4; FT-IR (thin film, neat): 3636, 2959, 1674, 1456, 1262, 750 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{30}H_{33}O_4$ $[M–H]^-$: 457.2379; found : 457.2397.

***trans*-[3-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-2,3-dihydrobenzofuran-2-yl](3-methoxyphenyl)-methanone (63e):**[38c] The reaction was performed at 0.097 mmol scale of



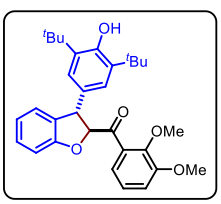
61n; white solid (28.8 mg, 72% yield); ^1H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, J = 7.6 Hz, 1H), 7.38 (s, 1H), 7.35 (t, J = 8.0 Hz, 1H), 7.21 (t, J = 7.7 Hz, 1H), 7.13 (d, J = 8.1 Hz, 1H), 7.03 (d, J = 7.4 Hz, 1H), 7.00 (d, J = 8.1 Hz, 1H), 6.94 (s, 2H), 6.90 (t, J = 7.4 Hz, 1H), 5.79 (d, J = 6.7 Hz, 1H), 5.19 (s, 1H), 4.79 (d, J = 6.7 Hz, 1H), 3.74 (s, 3H), 1.38 (s, 18H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 195.2, 159.8, 159.3, 153.2, 136.4, 135.9, 132.7, 129.7, 129.4, 128.8, 125.6, 124.9, 122.0, 121.6, 120.5, 113.4, 110.0, 90.9, 55.4, 51.8, 34.5, 30.3; FT-IR (thin film, neat): 3632, 2958, 1699, 1480, 1263, 750 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{30}H_{33}O_4$ $[M–H]^-$: 457.2379; found : 457.2399.

***trans*-[3-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-2,3-dihydrobenzofuran-2-yl](4-(trifluoromethoxy)-phenyl)methanone (63f):** The reaction was performed at 0.097 mmol



scale of **61a**; white solid (31.7 mg, 70% yield); m. p. = 127–129 ºC; R_f = 0.3 (5% EtOAc in hexane); ^1H NMR (400 MHz, $CDCl_3$) δ 8.01 (d, J = 8.4 Hz, 2H), 7.27 (d, J = 8.4 Hz, 2H), 7.21 (t, J = 7.7 Hz, 1H) 7.06 (d, J = 7.3 Hz, 1H), 6.98 – 6.96 (m, 3H), 6.91 (t, J = 7.4 Hz, 1H), 5.71 (d, J = 6.8 Hz, 1H), 5.20 (s, 1H), 4.90 (d, J = 6.8 Hz, 1H), 1.38 (s, 18H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 193.9, 159.0, 153.3, 153.1 (q, $J_{C\text{-}F}$ = 1.6 Hz), 136.5, 132.9, 132.4, 131.6, 129.3, 128.9, 125.7, 124.9, 121.8, 120.4, 120.39 (q, $J_{C\text{-}F}$ = 257.4 Hz), 110.0, 91.0, 51.1, 34.5, 30.4; $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$) δ –57.54; FT-IR (thin film, neat): 3639, 2960, 1696, 1479, 1268, 750 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{30}H_{30}F_3O_4$ $[M–H]^-$: 511.2096; found : 511.2119.

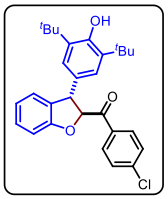
***trans*-[3-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-2,3-dihydrobenzofuran-2-yl](2,3-dimethoxyphenyl)-methanone (63g):** The reaction was performed at 0.097 mmol scale of



61a; white solid (29.5 mg, 68% yield); m. p. = 153–155 ºC; R_f = 0.1 (5% EtOAc in hexane); ^1H NMR (400 MHz, $CDCl_3$) δ 7.18 (d, J = 7.6 Hz, 1H), 7.11 – 7.07 (m, 2H), 7.06 – 7.04 (m, 1H), 7.02 (d, J = 7.4 Hz, 1H), 6.94 (d, J = 8.1 Hz, 1H), 6.87 (t, J = 7.4 Hz, 1H), 6.80 (s, 2H), 5.77 (d, J = 6.5 Hz, 1H), 5.10 (s, 1H), 4.70 (d, J = 6.4 Hz, 1H), 3.85 (s, 3H), 3.68 (s, 3H), 1.33 (s, 18H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 200.0, 159.5, 152.9, 152.8, 148.0, 136.0, 133.1, 131.9, 129.2, 128.7,

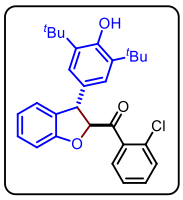
125.6, 124.7, 124.1, 121.3, 121.2, 116.1, 109.9, 93.3, 61.5, 56.0, 51.6, 34.4, 30.3; FT-IR (thin film, neat): 3627, 2956, 1699, 1478, 1267, 750 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{31}H_{35}O_5$ $[M–H]^-$: 487.2484; found : 487.2502.

***trans*-(4-chlorophenyl)[3-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-2,3-dihydrobenzofuran-2-yl]-methanone (63h):**[38b] The reaction was performed at 0.097 mmol scale of **61a**; white solid



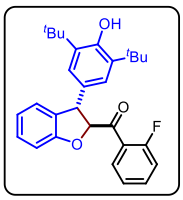
(29.2 mg, 70% yield); ^1H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, J = 8.4 Hz, 2H), 7.42 (d, J = 8.4 Hz, 2H), 7.21 (t, J = 7.7 Hz, 1H), 7.06 (d, J = 7.4 Hz, 1H), 6.98 – 6.96 (m, 3H), 6.92 (t, J = 7.4 Hz, 1H), 5.71 (d, J = 6.9 Hz, 1H), 5.20 (s, 1H), 4.89 (d, J = 6.9 Hz, 1H), 1.39 (s, 18H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 194.3, 159.1, 153.2, 140.3, 136.5, 133.1, 132.4, 130.9, 129.4, 129.0, 128.8, 125.6, 124.9, 121.7, 110.0, 91.0, 51.2, 34.5, 30.4; FT-IR (thin film, neat): 3636, 2959, 1695, 1479, 1261, 750 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{29}H_{30}ClO_3$ $[M–H]^-$: 461.1883; found : 461.1904.

***trans*-(2-chlorophenyl)[3-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-2,3-dihydrobenzofuran-2-yl]-methanone (63i):** The reaction was performed at 0.097 mmol scale of **61a**; white solid



(30.4 mg, 73% yield); m. p. = 133–135 ºC; R_f = 0.2 (5% EtOAc in hexane); ^1H NMR (400 MHz, $CDCl_3$) δ 7.42 – 7.37 (m, 3H), 7.30 – 7.28 (m, 1H), 7.18 (t, J = 7.6 Hz, 1H), 7.05 (d, J = 7.4 Hz, 1H), 6.91 – 6.90 (m, 2H), 6.84 (s, 2H), 5.69 (d, J = 6.5 Hz, 1H), 5.13 (s, 1H), 4.82 (d, J = 6.7 Hz, 1H), 1.34 (s, 18H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 200.1, 159.1, 153.1, 137.1, 136.2, 132.5, 132.2, 131.7, 130.5, 129.6, 129.0, 128.9, 126.8, 125.7, 124.6, 121.7, 110.0, 92.9, 51.5, 34.4, 30.3; FT-IR (thin film, neat): 3633, 2958, 1716, 1478, 1232, 751 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{29}H_{30}ClO_3$ $[M–H]^-$: 461.1883; found : 461.1894.

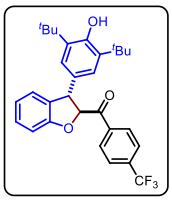
***trans*-[3-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-2,3-dihydrobenzofuran-2-yl](2-fluorophenyl)-methanone (63j):** The reaction was performed at 0.097 mmol scale of **61a**;



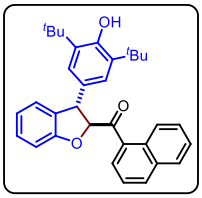
white solid (25.8 mg, 66% yield); m. p. = 129–131 ºC; R_f = 0.2 (5% EtOAc in hexane); ^1H NMR (400 MHz, $CDCl_3$) δ 7.77 (t, J = 7.4 Hz, 1H), 7.54 (q, J = 7.1, 1H), 7.26 – 7.23 (m, 1H), 7.18 (t, J = 7.7 Hz, 1H), 7.12 – 7.07 (m, 1H), 7.04 (d, J = 7.4 Hz. 1H), 6.94 (d, J = 8.1 Hz, 1H), 6.91 (s, 2H), 6.88 (d, J = 7.5 Hz, 1H), 5.73 (d, J = 6.1 Hz, 1H), 5.14 (s, 1H), 4.82 (d, J = 6.0 Hz, 1H), 1.37 (s, 18H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 195.5 (d, $J_{C\text{-}F}$ = 3.6 Hz), 161.4 (d, $J_{C\text{-}F}$ = 253.9 Hz), 159.2, 153.0, 136.1, 135.0 (d, $J_{C\text{-}F}$ = 8.9 Hz), 132.7, 131.3 (d, $J_{C\text{-}F}$ = 2.8 Hz), 129.3, 128.8, 125.6, 124.72, 124.68, 124.4 (d, $J_{C\text{-}F}$ = 13.5 Hz), 121.6, 116.6 (d, $J_{C\text{-}F}$ = 22.9 Hz), 109.9, 93.1 (d, $J_{C\text{-}F}$ = 5.8 Hz), 51.0, 34.5, 30.4; $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$) δ –108.95; FT-IR (thin film, neat):

3637, 2958, 1694, 1480, 1233, 751 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{29}H_{30}FO_3$ $[M–H]^-$: 445.2179; found : 445.2189.

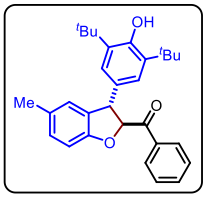
***trans*-[3-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-2,3-dihydrobenzofuran-2-yl]{4-(trifluoromethyl)-phenyl}methanone (63k):**[38c] The reaction was performed at 0.097 mmol scale of **61a**; pale yellow solid (30.8 mg, 69% yield); m. p. = 110–114 ºC; ^1H NMR (400 MHz, $CDCl_3$) δ 8.08 (d, J = 8.0 Hz, 2H), 7.74 (d, J = 8.1 Hz, 2H), 7.24 (t, J = 7.8 Hz, 1H), 7.09 (d, J = 7.4 Hz, 1H), 6.99 – 6.93 (m, 4H), 5.76 (d, J = 6.9 Hz, 1H), 5.23 (s, 1H), 4.94 (d, J = 6.9 Hz, 1H), 1.41 (s, 18H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 194.7, 159.0, 153.3, 137.6, 136.6, 135.0 (q, J_{C-F} = 32.5 Hz), 132.4, 129.9, 129.3, 128.9, 125.72 (q, J_{C-F} = 3.7 Hz), 125.67, 124.9, 123.6 (q, J_{C-F} = 271.2 Hz), 121.8, 110.0, 91.2, 51.1, 34.5, 30.4; $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$) δ –63.20; FT-IR (thin film, neat): 3639, 2960, 1699, 1479, 1325, 750 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{30}H_{30}F_3O_3$ $[M–H]^-$: 495.2147; found : 495.2161.



***trans*-[3-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-2,3-dihydrobenzofuran-2-yl](phenyl)methanone (63l):** The reaction was performed at 0.097 mmol scale of **61a**; white solid (27.9 mg, 66% yield); m. p. = 145–147 ºC; R_f = 0.2 (5% EtOAc in hexane); ^1H NMR (400 MHz, $CDCl_3$) δ 8.60 (d, J = 8.4 Hz, 1H), 8.00 (d, J = 8.2 Hz, 1H), 7.90 (d, J = 8.0 Hz, 1H), 7.75 (d, J = 7.2 Hz, 1H), 7.63 – 7.54 (m, 2H), 7.41 (t, J = 7.6 Hz, 1H), 7.22 (t, J = 7.6 Hz, 1H), 7.03 (d, J = 7.4 Hz, 1H), 7.00 (d, J = 8.0 Hz, 1H), 6.91 (t, J = 7.4 Hz, 1H), 6.76 (s, 2H), 5.88 (d, J = 7.0 Hz, 1H), 5.12 (s, 1H), 4.81 (d, J = 7.0 Hz, 1H), 1.30 (s, 18H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 199.2, 159.5, 153.0, 136.2, 134.0, 133.4, 133.1, 132.6, 130.9, 129.05, 129.01, 128.9, 128.7, 128.5, 126.8, 125.7 (2C), 124.7, 124.3, 121.6, 110.0, 92.4, 51.8, 34.4, 30.3; FT-IR (thin film, neat): 3627, 2958, 1683, 1479, 1261, 750 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{33}H_{33}CO_3$ $[M–H]^-$: 477.2430; found : 477.2450.

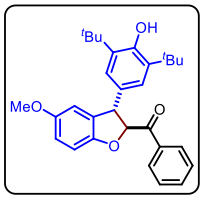


***trans*-[3-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-5-methyl-2,3-dihydrobenzofuran-2-yl](phenyl)-methanone (63m):**[38b] The reaction was performed at 0.092 mmol scale of **61b**; white solid (29.1 mg, 77% yield); ^1H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, J = 7.8 Hz, 2H), 7.59 (t, J = 7.6 Hz, 1H), 7.44 (t, J = 7.4 Hz, 2H), 7.00 (d, J = 8.2 Hz, 1H), 6.96 (s, 2H), 6.88 – 6.86 (m, 2H), 5.77 (d, J = 6.4 Hz, 1H), 5.19 (s, 1H), 4.80 (d, J = 6.4 Hz, 1H), 2.25 (s, 3H), 1.40 (s, 18H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 195.4, 157.3, 153.1, 136.3, 134.7, 133.7, 132.9, 130.9, 129.44, 129.40, 129.3, 128.7, 126.0, 124.9, 109.4, 91.1, 51.5, 34.5, 30.4, 20.9; FT-IR (thin film, neat): 3636, 2958,



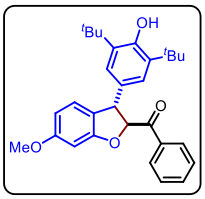
1699, 1489, 1275, 750 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{30}H_{33}O_3$ $[M–H]^-$: 441.2430; found : 441.2444.

***trans*-[3-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-5-methoxy-2,3-dihydrobenzofuran-2-yl](phenyl)-methanone (63n):**[38b] The reaction was performed at 0.088 mmol scale of **61c**;



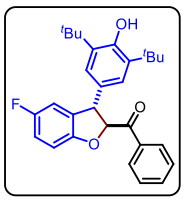
white solid (26.2 mg, 71% yield); ^1H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, *J*= 7.8 Hz, 2H), 7.59 (t, *J*= 7.4 Hz, 1H), 7.44 (t, *J* = 7.5 Hz, 2H), 6.98 (s, 2H), 6.89 (d, *J*= 8.7 Hz, 1H), 6.76 (d, *J*= 8.8 Hz, 1H), 6.62 (s, 1H), 5.76 (d, *J*= 6.6 Hz, 1H), 5.20 (s, 1H), 4.85 (d, *J* = 6.6 Hz, 1H), 3.71 (s, 3H), 1.40 (s, 18H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 195.4, 154.9, 153.4, 153.2, 136.4, 134.7, 133.8, 132.4, 130.3, 129.4, 128.7, 124.9, 114.4, 111.1, 110.0, 91.2, 56.2, 51.7, 34.5, 30.4; FT-IR (thin film, neat): 3627, 2957, 1695, 1486, 1234, 750 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{30}H_{33}O_4$ $[M–H]^-$: 457.2379; found : 457.2398.

***trans*-[3-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-6-methoxy-2,3-dihydrobenzofuran-2-yl](phenyl)-methanone (63o):**[38b] The reaction was performed at 0.088 mmol scale of **61d**;



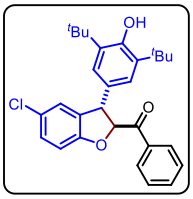
white solid (26.9 mg, 73% yield); ^1H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, *J* = 7.7 Hz, 2H), 7.60 (t, *J* = 7.5 Hz, 1H), 7.45 (t, *J* = 7.4 Hz, 2H), 6.94 – 6.91 (m, 3H), 6.59 (s, 1H), 6.46 (d, *J* = 8.2 Hz, 1H), 5.79 (d, *J* = 6.2 Hz, 1H), 5.18 (s, 1H), 4.75 (d, *J* = 6.2 Hz, 1H), 3.81 (s, 3H), 1.39 (s, 18H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 195.4, 160.9, 160.7, 153.1, 136.3, 134.6, 133.8, 133.0, 129.4, 128.7, 125.7, 124.8, 121.3, 107.7, 96.2, 91.8, 55.6, 51.0, 34.5, 30.4; FT-IR (thin film, neat): 3632, 2958, 1699, 1503, 1275, 750 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{30}H_{33}O_4$ $[M–H]^-$: 457.2379; found : 457.2397.

***trans*-[3-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-5-fluoro-2,3-dihydrobenzofuran-2-yl](phenyl)-methanone (63p):**[38b] The reaction was performed at 0.091 mmol scale of **61e**;



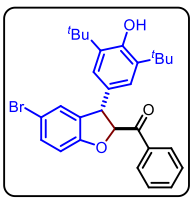
white solid (25.1 mg, 70% yield); ^1H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, *J* = 7.9 Hz, 2H), 7.60 (t, *J* = 7.2 Hz, 1H), 7.45 (t, *J* = 7.5 Hz, 2H), 6.94 (s, 2H), 6.89 (d, *J* = 6.3 Hz, 2H), 6.75 (d, *J* = 7.8 Hz, 1H), 5.81 (d, *J* = 6.6 Hz, 1H), 5.21 (s, 1H), 4.84 (d, *J* = 6.5 Hz, 1H), 1.39 (s, 18H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 195.0, 158.2 (d, $J_{C\text{-}F}$ = 236.5 Hz), 155.2 (d, $J_{C\text{-}F}$ = 1.3 Hz), 153.3, 136.5, 134.5, 133.9, 132.0, 131.0 (d, $J_{C\text{-}F}$ = 8.5 Hz), 129.5, 128.8, 124.8, 115.2 (d, $J_{C\text{-}F}$ = 24.3 Hz), 112.5 (d, $J_{C\text{-}F}$ = 24.7 Hz), 110.2 (d, $J_{C\text{-}F}$ = 8.4 Hz), 91.4, 51.4, 34.5, 30.4; $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$) δ –123.14; FT-IR (thin film, neat): 3636, 2959, 1699, 1483, 1233, 751 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{29}H_{30}FO_3$ $[M–H]^-$: 445.2179; found : 445.2201.

***trans*-[5-chloro-3-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-2,3-dihydrobenzofuran-2-yl](phenyl)-methanone (63q):**[38b] The reaction was performed at 0.087 mmol scale of **61f**;



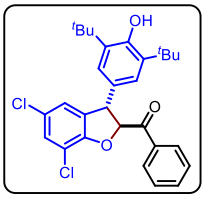
white solid (26.4 mg, 71% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, J = 8.0 Hz, 2H), 7.61 (t, J = 7.2 Hz, 1H), 7.45 (t, J = 7.5 Hz, 2H), 7.16 (d, J = 8.6 Hz, 1H), 7.01 (s, 1H), 6.94 (s, 2H), 6.91 (d, J = 8.6 Hz, 1H), 5.83 (d, J = 6.4 Hz, 1H), 5.22 (s, 1H), 4.81 (d, J = 6.4 Hz, 1H), 1.40 (s, 18H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 194.7, 157.9, 153.4, 136.6, 134.4, 134.0, 132.0, 131.6, 129.4, 128.81, 128.78, 126.3, 125.6, 124.8, 111.0, 91.4, 51.3, 34.5, 30.4; FT-IR (thin film, neat): 3633, 2959, 1699, 1475, 1261, 749 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{29}H_{30}ClO_3$ $[M–H]^–$: 461.1883; found : 461.1902.

***trans*-[5-bromo-3-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-2,3-dihydrobenzofuran-2-yl](phenyl)-methanone (63r):**[38b] The reaction was performed at 0.077 mmol scale of **61g**;



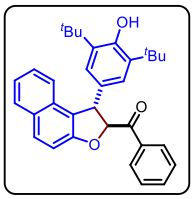
white solid (25.7 mg, 72% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, J = 7.6 Hz, 2H), 7.60 (t, J = 7.4 Hz, 1H), 7.45 (t, J = 7.6 Hz, 2H), 7.30 (d, J = 8.5 Hz, 1H), 7.15 (s, 1H), 6.94 (s, 2H), 6.87 (d, J = 8.5 Hz, 1H), 5.82 (d, J = 6.4 Hz, 1H), 5.23 (s, 1H), 4.81 (d, J = 6.4 Hz, 1H), 1.40 (s, 18H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 194.6, 158.4, 153.4, 136.6, 134.4, 134.0, 132.1, 132.0, 131.7, 129.4, 128.8, 128.5, 124.8, 113.4, 111.6, 91.3, 51.2, 34.5, 30.4; FT-IR (thin film, neat): 3633, 2958, 1699, 1471, 1262, 749 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{29}H_{30}BrO_3$ $[M–H]^–$: 505.1378; found : 505.1397.

***trans*-[5,7-dichloro-3-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-2,3-dihydrobenzofuran-2-yl](phenyl)methanone (63s) :** The reaction was performed at 0.079 mmol scale of **61h**; pale



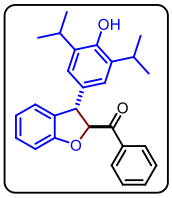
yellow gummy solid (21.0 mg, 53% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 – 7.93 (m, 2H), 7.63 – 7.59 (m, 1H), 7.48 – 7.44 (m, 2H), 7.22 (dd, J = 2.0, 0.7 Hz, 1H), 6.93 (s, 2H), 6.92 (dd, J = 2.0, 1.1 Hz, 1H), 5.88 (d, J = 6.8 Hz, 1H), 5.24 (s, 1H), 4.91 (d, J = 6.8 Hz, 1H), 1.40 (s, 18H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 193.9, 154.1, 153.6, 136.7, 134.3, 134.1, 132.8, 131.2, 129.5, 128.9 (2C), 126.7, 124.8, 124.1, 116.0, 91.5, 51.9, 34.5, 30.3; FT-IR (thin film, neat): 3638, 2959, 1699, 1456, 1238, 735 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{29}H_{29}Cl_2O_3$ $[M–H]^–$: 495.1494; found : 495.1475.

***trans*-[3-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-2,3-dihydronaphtho[2,3-*b*]furan-2-yl](phenyl)-methanone (63t):** The reaction was performed at 0.083 mmol scale of **61i**; pale yellow solid (26.3 mg, 73% yield); m. p. = 171–173 ºC; R_f = 0.2 (5% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (d, J = 7.8 Hz, 2H), 7.81 – 7.77 (m, 2H), 7.63 (t, J = 7.4 Hz,



1H), 7.49 (t, *J* = 7.4 Hz, 2H), 7.32 (d, *J* = 8.2 Hz, 2H), 7.29 – 7.23 (m, 2H), 7.00 (s, 2H), 5.94 (d, *J* = 5.1 Hz, 1H), 5.16 – 5.14 (m, 2H), 1.36 (s, 18H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 195.2, 157.2, 153.1, 136.4, 134.4, 133.9, 132.8, 130.6, 130.4, 130.2, 129.5, 128.8 (2C), 126.6, 124.6, 123.2, 123.1, 120.2, 112.2, 91.9, 51.2, 34.5, 30.4; FT-IR (thin film, neat): 3627, 2958, 1699, 1435, 1233, 750 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{33}H_{33}O_3$ $[M–H]^-$: 477.2430; found : 477.2451.

(3-(4-hydroxy-3,5-diisopropylphenyl)-2,3-dihydrobenzofuran-2-yl)(phenyl)methanone (63u): The reaction was performed at 0.11 mmol scale of **61j** and the product **63u** was obtained

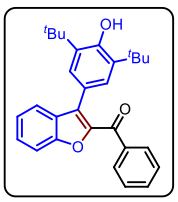


as an inseparable diastereomeric mixture; pale yellow gummy solid (22.6 mg, 53% yield); R_f = 0.1 (5% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$) [*major isomer*] δ 7.95 (t, *J* = 7.6 Hz, 4H), 7.63 – 7.58 (m, 2H), 7.51 – 7.43 (m, 4H), 7.25 – 7.21 (m, 1H), 7.04 – 6.99 (m, 2H), 6.93 (s, 2H), 5.79 (d, *J* = 6.8 Hz, 1H), 5.09 (s, 1H), 4.91 (d, *J* = 6.8 Hz, 1H), 3.33 – 3.23 (m, 2H), 1.20 (d, *J* = 6.6 Hz, 6H), 1.12 (d, *J* = 6.8 Hz, 6H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) [*diastereomers*] δ 195.1, 193.9, 159.3, 152.5, 142.3, 138.6, 134.7, 134.6, 133.9, 129.4, 129.2, 129.0, 128.8, 128.0, 125.5, 124.2, 121.7, 110.1, 90.7, 51.3, 26.8, 24.2, 24.1; FT-IR (thin film, neat): 3505, 2961, 1694, 1471, 1226, 750 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{27}H_{27}O_3$ $[M–H]^-$: 399.1960; found : 399.1942.

General procedure for the synthesis of Benzofuran derivatives (64a-l)

Bromomethyl aryl ketone [**62a-g**] (1.0 equiv.) was added to the suspension of 2-hydroxyphenyl-subsituted *p*-QM [**61a-e** & **61i**] (1.1 equiv.), and Cs_2CO_3 (1.5 equiv.) in acetonitrile (0.06 M) and the resulting suspension was stirred at room temperature. After the reaction was complete (based on TLC analysis), DDQ (2.0 equiv.) was added, and the reaction mixture was stirred at 50 °C until the former reaction product was completely consumed (based on TLC analysis). The residue was filtered through a pad of celite, and the filtrate was then concentrated under reduced pressure. The residue was purified through a silica gel column, using EtOAc/Hexane mixture as an eluent, to get the pure product (**64a-l**).

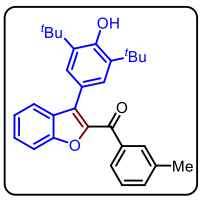
[3-(3,5-di-*tert*-butyl-4-hydroxyphenyl)benzofuran-2-yl](phenyl)methanone (64a):[38b] The



reaction was performed at 0.097 mmol scale of **61a**; white solid (31.2 mg, 81% yield); ^{1}H NMR (400 MHz, $CDCl_3$), δ 7.75 (d, *J* = 7.9 Hz, 1H), 7.67 (t, *J* = 7.7 Hz, 3H), 7.55 – 7.51 (m, 1H), 7.39 -7.34 (m, 2H) 7.20 – 7.17 (m, 4H), 5.25 (s, 1H), 1.35 (s, 18H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 186.7, 155.0, 154.1, 146.8, 137.4, 136.1, 132.4, 130.8, 129.9, 128.3 (2C), 127.9, 127.3, 123.9, 122.8, 121.9, 112.6,

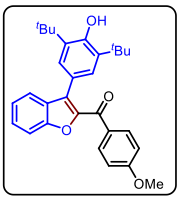
34.4, 30.3; FT-IR (thin film, neat): 3631, 2958, 1649, 1448, 1161, 728 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{29}H_{31}O_3$ $[M+H]^-$: 427.2273; found : 427.2257.

[3-(3,5-di-*tert*-butyl-4-hydroxyphenyl)benzofuran-2-yl](*m*-tolyl)methanone (64b): The



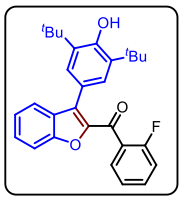
reaction was performed at 0.097 mmol scale of **61a**; white solid (31 mg, 79% yield); m. p. = 180–182 ºC; R_f = 0.6 (5% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$), δ 7.75 (d, J = 7.9 Hz, 1H), 7.67 (d, J = 8.4 Hz, 1H), 7.54 – 7.51 (m, 2H), 7.42 (s, 1H), 7.36 (t, J = 7.6 Hz, 1H), 7.16 (d, J = 7.6 Hz, 1H), 7.14 (s, 2H), 7.09 (t, J = 7.6 Hz, 1H), 5.25 (s, 1H), 2.16 (s, 3H), 1.34 (s, 18H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 186.9, 155.1, 154.1, 146.8, 137.5, 137.3, 136.0, 133.2, 130.7, 130.6, 128.31, 128.28, 127.9, 127.2, 127.0, 123.8, 122.8, 122.1, 112.6, 34.3, 30.2, 21.2; FT-IR (thin film, neat): 3627, 2958, 1645, 1436, 1238, 1144, 744 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{30}H_{33}O_3$ $[M+H]^+$: 441.2430; found : 441.2415.

[3-(3,5-di-*tert*-butyl-4-hydroxyphenyl)benzofuran-2-yl](4-methoxyphenyl)methanone (64c): The reaction was performed at 0.097 mmol scale of **61a**; white solid (27.1 mg, 68%



yield); m. p. = 182–184 ºC; R_f = 0.4 (5% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$), δ 7.75 (d, J = 7.9 Hz, 1H), 7.70 – 7.65 (m, 3H), 7.51 (t, J = 7.8 Hz, 1H), 7.35 (t, J = 7.6 Hz, 1H), 7.17 (s, 2H), 6.66 (d, J = 8.6 Hz, 2H), 5.26 (s, 1H), 3.76 (s, 3H), 1.36 (s, 18H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 185.3, 163.1, 154.9, 154.0, 147.1, 136.1, 132.3, 130.0, 129.8, 128.3, 128.0, 127.3, 123.8, 122.6, 122.1, 113.1, 112.5, 55.4, 34.4, 30.3; FT-IR (thin film, neat): 3627, 2958, 1639, 1435, 1258, 1160, 750 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{30}H_{33}O_4$ $[M+H]^+$: 457.2379; found : 457.2399.

[3-(3,5-di-*tert*-butyl-4-hydroxyphenyl)benzofuran-2-yl](2-fluorophenyl)methanone (64d): The reaction was performed at 0.097 mmol scale of **61a**; white solid (30.3 mg, 78%



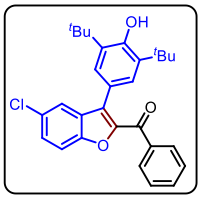
yield); m. p. = 166–168 ºC; R_f = 0.6 (5% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$), δ 7.68 – 7.63 (m, 2H), 7.55 – 7.46 (m, 2H), 7.33 (t, J = 7.5 Hz, 1H), 7.30 – 7.26 (m, 1H), 7.17 (s, 2H), 7.02 (t, J = 7.5 Hz, 1H), 6.79 (t, J = 9.1 Hz, 1H), 5.26 (s, 1H), 1.37 (s, 18H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 182.9, 160.1 (d, $J_{C\text{-}F}$ = 252.0 Hz), 155.1, 154.1, 147.1, 135.7, 133.2 (d, $J_{C\text{-}F}$ = 8.4 Hz), 132.2 (d, $J_{C\text{-}F}$ = 0.9 Hz), 130.8 (d, $J_{C\text{-}F}$ = 2.4 Hz), 128.9, 128.8, 127.4 (d, $J_{C\text{-}F}$ = 13.8 Hz), 127.1, 123.94 (d, $J_{C\text{-}F}$ = 3.6 Hz), 123.90, 123.1, 121.4, 115.9 (d, $J_{C\text{-}F}$ = 21.6 Hz), 112.6, 34.3, 30.3; ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ –111.80; FT-IR (thin film, neat): 3632, 2959, 1652, 1454, 1153, 750 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{29}H_{30}FO_3$ $[M+H]^+$: 445.2165; found : 445.2179.

[3-(3,5-di-*tert*-butyl-4-hydroxyphenyl)benzofuran-2-yl](2,4-dichlorophenyl)methanone (64e): The reaction was performed at 0.097 mmol scale of **61a**; white solid (19.5 mg, 44% yield); m. p. = 167–169 ºC; R_f = 0.6 (5% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 – 7.60 (m, 2H), 7.54 (t, J = 7.3 Hz, 1H), 7.33 (t, J = 7.4 Hz, 1H), 7.21 (d, J = 8.2 Hz, 1H), 7.18 (s, 1H), 7.10 (s, 2H), 7.01 (d, J = 8.2 Hz, 1H), 5.30 (s, 1H), 1.40 (s, 18H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 183.7, 155.3, 154.3, 146.6, 136.7, 136.5, 135.8, 133.3, 132.9, 131.0, 129.8, 129.3, 129.0, 126.73, 126.71, 124.1, 123.3, 121.2, 112.7, 34.4, 30.3; FT-IR (thin film, neat): 3632, 2959, 1652, 1434, 1238, 1144, 967 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{29}H_{29}Cl_2O_3$ $[M+H]^+$: 495.1494; found : 495.1516.

[3-(3,5-di-*tert*-butyl-4-hydroxyphenyl)benzofuran-2-yl](3-(trifluoromethyl)phenyl)methanone (64f): The reaction was performed at 0.097 mmol scale of **61a**; white solid (28.5 mg, 67% yield); m. p. = 155–157 ºC; R_f = 0.7 (5% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$), δ 7.78 – 7.73 (m, 3H), 7.67 (d, J = 8.4 Hz, 1H), 7.56 (t, J = 7.4 Hz, 1H), 7.45 (d, J = 8.0 Hz, 2H), 7.38 (t, J = 7.6 Hz, 1H), 7.15 (s, 2H), 5.29 (s, 1H), 1.35 (s, 18H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 185.4, 155.2, 154.5, 146.4, 140.6 (q, $J_{C\text{-}F}$ = 0.9 Hz), 136.3, 133.6, 133.3, 132.1, 130.0 (2C), 128.9, 128.2, 127.2, 124.8 (q, $J_{C\text{-}F}$ = 3.6 Hz), 124.1, 123.6 (q, $J_{C\text{-}F}$ = 270.9 Hz), 123.0, 121.6, 112.7, 34.4, 30.2; ^{19}F NMR (376 MHz, $CDCl_3$) δ –63.17; FT-IR (thin film, neat): 3632, 2959, 1651, 1436, 1168, 762 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{30}H_{30}F_3O_3$ $[M+H]^+$: 495.2147; found : 495.2125.

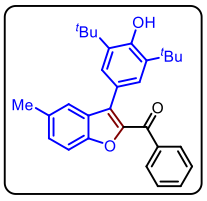
[3-(3,5-di-*tert*-butyl-4-hydroxyphenyl)benzofuran-2-yl](3-nitrophenyl)methanone (64g): The reaction was performed at 0.097 mmol scale of **61a**; pale yellow solid (19.1 mg, 47% yield); m. p. = 189–191 ºC; R_f = 0.4 (5% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36 (s, 1H), 8.20 (d, J = 8.0 Hz, 1H), 8.13 (d, J = 7.6 Hz, 1H), 7.74 (d, J = 8.2 Hz, 1H), 7.69 (d, J = 8.4 Hz, 1H) 7.58 (t, J = 7.5 Hz, 1H), 7.50 (t, J = 7.9 Hz, 1H), 7.39 (t, J = 7.5 Hz, 1H), 7.12 (s, 2H), 5.29 (s, 1H), 1.32 (s, 18H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 184.0, 155.4, 154.4, 147.3, 145.9, 138.8, 136.4, 135.0, 132.6, 129.3, 129.2, 128.2, 127.3, 126.5, 125.4, 124.3, 123.1, 121.4, 112.7, 34.3, 30.1; FT-IR (thin film, neat): 3626, 2959, 1652, 1435, 1275, 750 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{29}H_{30}NO_5$ $[M+H]^+$: 472.2124; found : 472.2144.

[5-chloro-3-(3,5-di-*tert*-butyl-4-hydroxyphenyl)benzofuran-2-yl](phenyl)methanone (64h): The reaction was performed at 0.087 mmol scale of **61f**; pale yellow gummy solid (27.8 mg, 75% yield); R_f = 0.5 (5% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 – 7.66 (m, 3H), 7.59 (d, J = 8.8 Hz, 1H), 7.47 (d, J = 8.8 Hz, 1H), 7.38 (t, J = 7.4 Hz, 1H), 7.19 (t, J

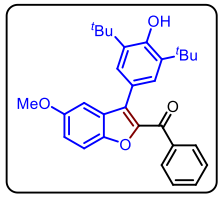


= 7.5 Hz, 2H), 7.12 (s, 2H), 5.28 (s, 1H), 1.35 (s, 18H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 186.4, 154.3, 153.3, 147.8, 137.1, 136.3, 132.6, 130.0, 129.9, 129.7, 129.6, 128.6, 127.9, 127.1, 122.2, 121.3, 113.7, 34.4, 30.3; FT-IR (thin film, neat): 3632, 2958, 1645, 1430, 1160, 733 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{29}H_{30}ClO_3$ $[M+H]^+$: 461.1883; found : 461.1868.

[3-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-5-methylbenzofuran-2-yl](phenyl)methanone (64i): The reaction was performed at 0.092 mmol scale of **61b**; white solid (28.6 mg, 76% yield); m. p. = 142–144 ºC; R_f = 0.5 (5% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, *J* = 7.7 Hz, 2H), 7.54 (d, *J* = 8.5 Hz, 1H), 7.51 (s, 1H), 7.38 – 7.33 (m, 2H), 7.19 (d, *J* = 7.5 Hz, 2H), 7.15 (s, 2H), 5.25 (s, 1H), 2.47 (s, 3H), 1.35 (s, 18H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 186.6, 154.1, 153.5, 147.0, 137.5, 136.0, 133.5, 132.3, 130.6, 129.92, 129.88, 128.4, 127.8, 127.2, 122.2, 122.1, 112.1, 34.3, 30.3, 21.6; FT-IR (thin film, neat): 3627, 2958, 1645, 1431, 1239, 749 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{30}H_{33}O_3$ $[M+H]^+$: 441.2430; found : 441.2408.

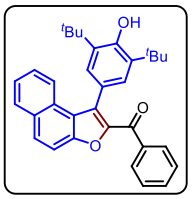


[3-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-6-methoxybenzofuran-2-yl](phenyl)methanone (64j): The reaction was performed at 0.088 mmol scale of **61d**; white solid (28.6 mg, 78% yield); m. p. = 181–183 ºC; R_f = 0.4 (5% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, *J* = 7.8 Hz, 2H), 7.59 (d, *J* = 8.7 Hz, 1H), 7.34 (t, *J* = 7.3 Hz, 1H), 7.18 – 7.13 (m, 5H), 6.98 (d, *J* = 8.7 Hz, 1H), 5.25 (s, 1H), 3.91 (s, 3H), 1.34 (s, 18H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 186.1, 161.3, 156.5, 154.1, 146.5, 137.8, 136.0, 132.1, 131.6, 129.8, 127.8, 127.2, 123.3, 122.1, 121.7, 114.3, 95.6, 55.9, 34.3, 30.3; FT-IR (thin film, neat): 3627, 2959, 1634, 1267, 1156, 750 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{30}H_{33}O_4$ $[M+H]^+$: 457.2379; found : 457.2361.



[3-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-5-methoxybenzofuran-2-yl](phenyl)methanone (64k): The reaction was performed at 0.088 mmol scale of **61c**; pale yellow gummy solid (26.8 mg, 73% yield); R_f = 0.3 (5% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, *J* = 7.7 Hz, 2H), 7.56 – 7.54 (m, 1H), 7.37 (t, *J* = 7.3 Hz, 1H), 7.21 – 7.18 (m, 4H), 7.15 – 7.13 (m, 2H), 5.26 (s, 1H), 3.84 (s, 3H), 1.36 (s, 18H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 186.5, 156.7, 154.1, 150.2, 147.6, 137.5, 136.1, 132.4, 130.7, 129.9, 128.7, 127.9, 127.2, 122.0, 118.4, 113.3, 103.5, 56.0, 34.4, 30.3; FT-IR (thin film, neat): 3627, 2957, 1645, 1481, 1275, 750 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{30}H_{33}O_4$ $[M+H]^+$: 457.2379; found : 457.2365.

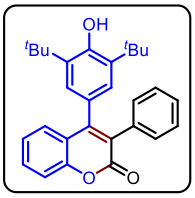
[3-(3,5-di-*tert*-butyl-4-hydroxyphenyl)naphtho[2,3-*b*]furan-2-yl](phenyl)methanone (64l): The reaction was performed at 0.083 mmol scale of **61i**; yellow gummy solid (24.8 mg, 69% yield); R_f = 0.2 (5% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 – 7.93 (m, 3H), 7.79 (d, J = 9.0 Hz, 1H), 7.60 (d, J = 7.9 Hz, 2H), 7.48 (t, J = 7.2 Hz, 1H), 7.39 – 7.31 (m, 2H), 7.16 – 7.13 (m, 4H), 5.24 (s, 1H), 1.35 (s, 18H); ^{13}C{^{1}H}C NMR (100 MHz, $CDCl_3$) δ 186.4, 154.0, 153.7, 147.7, 137.8, 135.9, 132.7, 131.9, 131.2, 130.5, 129.51, 129.46, 129.3, 127.71, 127.68, 126.8, 125.2, 123.4, 122.9, 121.8, 113.1, 34.4, 30.4; FT-IR (thin film, neat): 3618, 2924, 1644, 1433, 1233, 709 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{33}H_{33}O_3$ $[M+H]^+$: 477.2430; found : 477.2412.



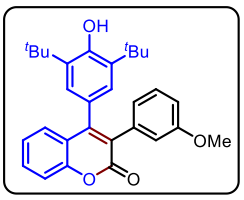
General procedure for the synthesis of coumarin derivatives

Arylacetyl halide [**65a-j**] (1.2 equiv.) was added to a mixture of 2-hydroxyphenyl-subsituted *p*-QM [**61a-e**] (1.0 equiv.) and Cs_2CO_3 (2.2 equiv.) in acetone (0.06 M) and, the resulting suspension was stirred at room temperature for 1.5 h. Then DDQ (1.5 equiv.) was added to the reaction mixture, and the resultant mixture was stirred at room temperature for additional 6 h. The reaction mixture was filtered through a pad celite, and the filtrate was concentrated under reduced pressure. The crude was purified through a silica gel column using EtOAc/Hexane mixture as an eluent to get the pure coumarin derivative (**66a-n**).

4-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-3-phenyl-2H-chromen-2-one (66a): The reaction was performed at 0.097 mmol scale of **61a**; white solid (34.6 mg, 84% yield); m. p. = 197–199 ºC; R_f = 0.3 (10% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 – 7.52 (m, 2H), 7.44 (d, J = 8.3 Hz, 1H), 7.26 – 7.22 (m, 1H), 7.20 – 7.14 (m, 3H), 7.05 (d, J = 7.6 Hz, 2H), 6.87 (s, 2H), 5.28 (s, 1H), 1.29 (s, 18H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 161.6, 154.0, 153.6, 152.8, 135.8, 134.9, 131.3, 130.7, 128.2, 127.8, 127.3, 127.2, 126.6, 125.0, 124.1, 120.7, 117.0, 34.3, 30.3; FT-IR (thin film, neat): 3633, 2957, 1717, 1451, 763 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{29}H_{31}O_3$ $[M+H]^+$: 427.2273; found : 427.2260.

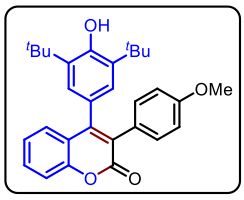


4-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-3-(3-methoxyphenyl)-2H-chromen-2-one (66b): The reaction was performed at 0.097 mmol scale of **61a**; white solid (34 mg, 77% yield); m. p. = 197–199 ºC; R_f = 0.2 (10% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 – 7.53 (m, 2H), 7.43 (d, J = 8.5 Hz, 1H), 7.26 – 7.22 (m, 1H), 7.15 (t, J = 7.9 Hz, 1H), 6.89 (s, 2H), 6.82 (d, J = 7.5 Hz, 1H), 6.72 (d, J = 8.3 Hz, 1H), 6.42 (s, 1H), 5.30 (s, 1H), 3.52 (s, 3H), 1.29 (s, 18H);



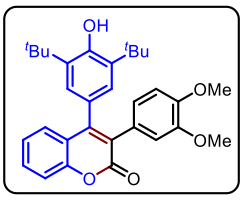
$^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 161.5, 159.1, 154.0, 153.6, 152.7, 136.0, 135.9, 131.4, 128.9, 128.1, 127.1, 126.4, 125.1, 124.1, 123.3, 120.6, 117.0, 115.4, 114.3, 55.1, 34.4, 30.2; FT-IR (thin film, neat): 3625, 2957, 1716, 1601, 758 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{30}H_{33}O_4$ $[M+H]^+$: 457.2379; found : 457.2360.

4-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-3-(4-methoxyphenyl)-2H-chromen-2-one (66c):

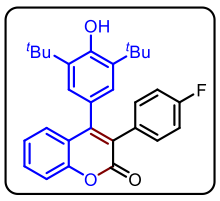


The reaction was performed at 0.097 mmol scale of **61a**; white solid (31.3 mg, 71% yield); m. p. = 224–226 ºC; R_f = 0.2 (10% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 – 7.51 (m, 2H), 7.42 (d, *J* = 8.5 Hz, 1H), 7.23 (t, *J* = 7.6 Hz, 1H), 6.97 (d, *J* = 8.4 Hz, 2H), 6.87 (s, 2H), 6.72 (d, *J* = 8.4 Hz, 2H), 5.28 (s, 1H), 3.74 (s, 3H), 1.30 (s, 18H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 158.8, 153.9, 153.7, 153.5, 152.3, 135.8, 131.9, 131.2, 128.1, 127.2, 127.1, 126.2, 125.2, 124.1, 116.9, 113.4, 110.9, 55.4, 34.4, 30.3; FT-IR (thin film, neat): 3604, 2923, 1717, 1608, 763 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{30}H_{33}O_4$ $[M+H]^+$: 457.2379; found : 457.2374.

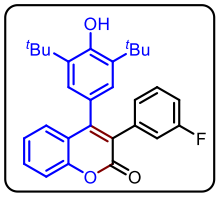
4-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-3-(3,4-dimethoxyphenyl)-2H-chromen-2-one (66d): The reaction was performed at 0.097 mmol scale of **61a**; white solid (32.4 mg, 69% yield); m. p. = 256–258 ºC; R_f = 0.2 (20% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 – 7.51 (m, 2H), 7.43 (d, *J* = 8.5 Hz, 1H), 7.26 – 7.22 (m, 1H), 6.90 – 6.88 (m, 3H), 6.79 (d, *J* = 8.3 Hz, 1H), 6.33 (s, 1H), 5.32 (s, 1H), 3.83 (s, 3H), 3.50 (s, 3H), 1.30 (s, 18H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 161.7, 153.9, 153.4, 152.1, 148.3, 148.2, 136.0, 131.2, 128.0, 127.2, 127.1, 126.0, 125.4, 124.1, 123.6, 120.6, 116.9, 114.2, 110.6, 56.1, 55.6, 34.4, 30.3; FT-IR (thin film, neat): 3632, 2957, 1716, 1603, 1251, 764 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{31}H_{35}O_5$ $[M+H]^+$: 487.2484; found : 487.2466.



4-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-3-(4-fluorophenyl)-2H-chromen-2-one (66e): The reaction was performed at 0.097 mmol scale of **61a**; white solid (34.8 mg, 81% yield); m. p. = 204–206 ºC; R_f = 0.3 (10% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 – 7.50 (m, 2H), 7.43 (d, *J* = 8.2 Hz, 1H), 7.26 – 7.22 (m, 1H), 7.05 – 7.02 (m, 2H), 6.90 – 6.86 (m, 4H), 5.32 (s, 1H), 1.30 (s, 18H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 162.0 (d, $J_{C\text{-}F}$ = 245.6 Hz), 161.6, 154.1, 153.5, 153.1, 136.0, 132.5 (d, $J_{C\text{-}F}$ = 8.0 Hz), 131.5, 130.9 (d, $J_{C\text{-}F}$ = 3.5 Hz), 128.2, 127.1, 125.5, 124.8, 124.2, 120.5, 117.0, 114.8 (d, $J_{C\text{-}F}$ = 21.5 Hz), 34.4, 30.3; $^{19}F\{^{1}H\}$ NMR (376 MHz, $CDCl_3$) δ –114.7; FT-IR (thin film, neat): 3611, 2960, 1713, 1450, 803 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{29}H_{30}FO_3$ $[M+H]^+$: 445.2179; found : 445.2163.

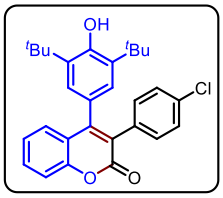


4-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-3-(3-fluorophenyl)-2H-chromen-2-one (66f): The



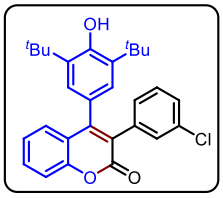
reaction was performed at 0.097 mmol scale of **61a**; white solid (33.9 mg, 79% yield); m. p. = 229–231 ºC; R_f = 0.3 (10% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 – 7.52 (m, 2H), 7.44 (d, J = 8.2 Hz, 1H), 7.28 – 7.24 (m, 1H), 7.20 – 7.14 (m, 1H), 6.90 – 6.86 (m, 2H), 6. 88 (s, 2H), 6.77 – 6.74 (m, 1H), 5.33 (s, 1H), 1.31 (s, 18H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 162.4 (d, $J_{C\text{-}F}$ = 244.1 Hz), 161.2, 154.2, 153.6, 153.5, 137.1(d, $J_{C\text{-}F}$ = 8.3 Hz), 136.0, 131.7, 129.2 (d, $J_{C\text{-}F}$ = 8.2 Hz), 128.3, 127.0, 126.6 (d, $J_{C\text{-}F}$ = 2.9 Hz), 125.3 (d, $J_{C\text{-}F}$ = 7.6 Hz), 124.6, 124.3, 120.4, 117.8 (d, $J_{C\text{-}F}$ = 22.3 Hz), 117.0, 114.2 (d, $J_{C\text{-}F}$ = 20.8 Hz), 34.4, 30.2; ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ –114.3; FT-IR (thin film, neat): 3632, 2959, 1716, 1484, 758 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{29}H_{30}FO_3$ $[M+H]^+$: 445.2179; found : 445.2165.

3-(4-chlorophenyl)-4-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-2H-chromen-2-one (66g): The



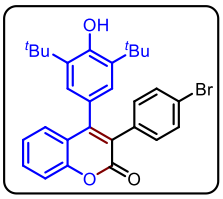
reaction was performed at 0.097 mmol scale of **61a**; white solid (35.2 mg, 79% yield); m. p. = 207–209 ºC; R_f = 0.3 (10% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (dd, J = 14.2, 8.1 Hz, 2H), 7.44 (d, J = 8.2 Hz, 1H), 7.27 – 7.23 (m, 1H), 7.17 (d, J = 8.1 Hz, 2H), 7.00 (d, J = 8.1 Hz, 2H), 6.85 (s, 2H), 5.34 (s, 1H), 1.31 (s, 18H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 161.4, 154.2, 153.6, 153.3, 136.0, 133.5, 133.3, 132.1, 131.6, 128.2, 127.9, 127.1, 125.3, 124.7, 124.3, 120.4, 117.0, 34.4, 30.2; FT-IR (thin film, neat): 3611, 2957, 1713, 1602, 758 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{29}H_{30}ClO_3$ $[M+H]^+$: 461.1883; found : 461.1858.

3-(3-chlorophenyl)-4-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-2H-chromen-2-one (66h): The



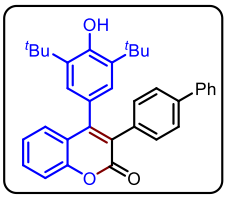
reaction was performed at 0.097 mmol scale of **61a**; white solid (33.9 mg, 76% yield); m. p. = 259–261 ºC; R_f = 0.3 (10% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 – 7.53 (m, 2H), 7.44 (d, J = 8.2 Hz, 1H), 7.28 – 7.24 (m, 1H), 7.18 – 7.13 (m, 2H), 7.08 – 7.04 (m, 1H), 6.94 (s, 1H), 6.86 (s, 2H), 5.34 (s, 1H), 1.31 (s, 18H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 161.2, 154.3, 153.7, 153.6, 136.7, 136.1, 133.6, 131.8, 131.0, 129.0, 128.9, 128.3, 127.4, 127.0, 125.2, 124.6, 124.3, 120.4, 117.0, 34.4, 30.2; FT-IR (thin film, neat): 3637, 2960, 1717, 1438, 759 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{29}H_{30}ClO_3$ $[M+H]^+$: 461.1883; found : 461.1900.

3-(4-bromophenyl)-4-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-2H-chromen-2-one (66i): The reaction was performed at 0.097 mmol scale of **61a**; white solid (38.1 mg, 78% yield); m. p. = 271–273 ºC; R_f = 0.3 (10% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 – 7.52 (m, 2H), 7.44 (d, J = 8.2 Hz, 1H), 7.32 (d, J = 8.1 Hz, 2H), 7.27 – 7.23 (m, 1H), 6.93 (d, J = 8.1



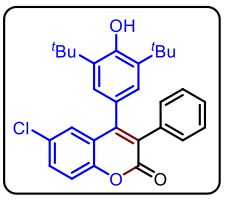
Hz, 2H), 6.84 (s, 2H), 5.33 (s, 1H), 1.31 (s, 18H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 161.3, 154.2, 153.6, 153.2, 136.0, 134.0, 132.4, 131.7, 130.9, 128.2, 127.2, 125.3, 124.7, 124.3, 121.6, 120.4, 117.0, 34.4, 30.3; FT-IR (thin film, neat): 3608, 2957, 1723, 1438, 758 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{29}H_{30}BrO_3$ $[M+H]^+$: 505.1378; found : 505.1362.

3-([1,1'-biphenyl]-4-yl)-4-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-2H-chromen-2-one (66j):



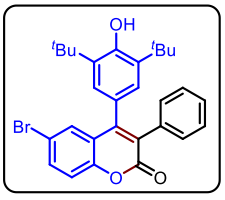
The reaction was performed at 0.097 mmol scale of **61a**; white solid (35.5 mg, 73% yield); m. p. = 239–241 ºC; R_f = 0.3 (10% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 – 7.54 (m, 2H), 7.50 (d, *J* = 7.8 Hz, 2H), 7.47 – 7.40 (m, 5H), 7.35 – 7.31 (m, 1H), 7.28 – 7.24 (m, 1H), 7.13 (d, *J* = 7.9 Hz, 2H), 6.91 (s, 2H), 5.30 (s, 1H), 1.29 (s, 18H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 161.7, 154.1, 153.6, 152.8, 141.2, 140.3, 135.9, 134.01, 133.99, 131.4, 131.1, 128.8, 128.2, 127.3, 127.2, 126.6, 126.1, 124.9, 124.2, 120.6, 117.0, 34.4, 30.3; FT-IR (thin film, neat): 3625, 2958, 1716, 1486, 765 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{35}H_{35}O_3$ $[M+H]^+$: 503.2586; found : 503.2599.

6-chloro-4-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-3-phenyl-2H-chromen-2-one (66k): The



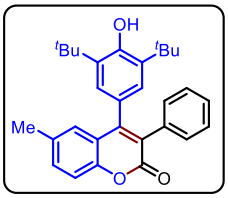
reaction was performed at 0.087 mmol scale of **61f**; white solid (30.1 mg, 75% yield); m. p. = 228–230 ºC; R_f = 0.3 (10% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (d, *J* = 2.0 Hz, 1H), 7.49 (dd, *J* = 8.8, 2.0 Hz, 1H), 7.37 (d, *J* = 8.7 Hz, 1H), 7.21 – 7.18 (m, 3H), 7.05 – 7.03 (m, 2H), 6.84 (s, 2H), 5.32 (s, 1H), 1.29 (s, 18H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 161.1, 154.2, 151.9, 151.6, 136.0, 134.5, 131.3, 130.6, 129.5, 128.7, 127.9, 127.5, 127.4, 127.2, 124.3, 121.9, 118.4, 34.4, 30.2; FT-IR (thin film, neat): 3606, 2965, 1732, 1439, 759 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{29}H_{30}ClO_3$ $[M+H]^+$: 461.1883; found : 461.1863.

6-bromo-4-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-3-phenyl-2H-chromen-2-one (66l): The



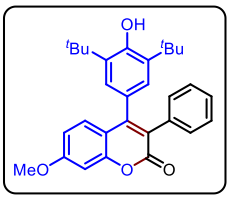
reaction was performed at 0.077 mmol scale of **61g**; white solid (29.6 mg, 76% yield); m. p. = 246–248 ºC; R_f = 0.3 (10% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (s, 1H), 7.62 (d, *J* = 8.8 Hz, 1H), 7.31 (d, *J* = 8.7 Hz ,1H), 7.22 – 7.18 (m, 3H), 7.05 – 7.03 (m, 2H), 6.84 (s, 2H), 5.32 (s, 1H), 1.29 (s, 18H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 161.1, 154.3, 152.4, 151.5, 136.0, 134.5, 134.1, 130.62, 130.58, 127.9, 127.6, 127.4, 127.2, 124.2, 122.3, 118.7, 116.9, 34.4, 30.2; FT-IR (thin film, neat): 3606, 2968, 1732, 1439, 759 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{29}H_{30}BrO_3$ $[M+H]^+$: 505.1378; found : 505.1361.

4-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-6-methyl-3-phenyl-2H-chromen-2-one (66m): The



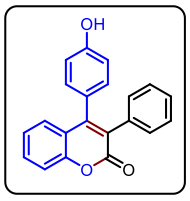
reaction was performed at 0.092 mmol scale of **61b**; white solid (29.7 mg, 73% yield); m. p. = 217–219 ºC; R_f = 0.3 (10% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 – 7.31 (m, 3H), 7.18 – 7.15 (m, 3H), 7.04 (d, *J* = 7.3 Hz, 2H), 6.86 (s, 2H), 5.28 (s, 1H), 2.35 (s, 3H), 1.29 (s, 18H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 161.9, 153.9, 152.7, 151.7, 135.7, 135.1, 133.7, 132.3, 130.7, 127.9, 127.8, 127.3, 127.2, 126.5, 125.1, 120.3, 116.7, 34.4, 30.3, 21.2; FT-IR (thin film, neat): 3611, 2962, 1717, 1440, 764 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{30}H_{33}O_3$ $[M+H]^+$: 441.2430; found : 441.2413.

4-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-7-methoxy-3-phenyl-2H-chromen-2-one (66n): The



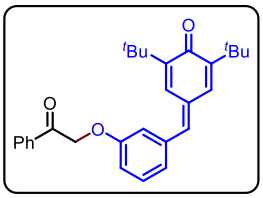
reaction was performed at 0.088 mmol scale of **61d**; white solid (30.2 mg, 75% yield); m. p. = 195–197 ºC; R_f = 0.2 (10% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (d, *J* = 9.0 Hz, 1H), 7.18 – 7.13 (m, 3H), 7.03 (d, *J* = 7.3 Hz, 2H), 6.93 (d, *J* = 1.6 Hz, 1H), 6.84 (s, 2H), 6.82 – 6.80 (m, 1H), 5.26 (s, 1H), 3.90 (s, 3H), 1.28 (s, 18H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 162.5, 155.3, 153.9, 153.0, 150.4, 135.7, 135.1, 130.8, 129.2, 127.8, 127.2, 127.1, 125.3, 123.4, 114.1, 112.3, 100.8, 55.9, 34.3, 30.3; FT-IR (thin film, neat): 3631, 2958, 1708, 1438, 764 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{30}H_{33}O_4$ $[M+H]^+$: 457.2379; found : 457.2393.

Procedure for de-tert-butylation of 66a



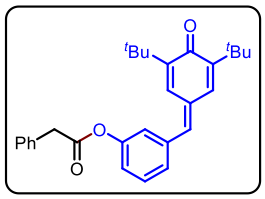
$AlCl_3$ (109 mg, 0.82 mmol, 10 equiv.) was added to a solution of **66a** (35 mg, 0.082 mmol, 1 equiv.) in dry toluene (2 mL) under an argon atmosphere. The resulting reaction mixture was stirred at 60 ºC for 1 h and then quenched with 5 mL of ice-cold water. It was extracted with EtOAc (3 x 10 mL), and the combined organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was then purified through a silica gel column using EtOAc/Hexane mixture as an eluent to get the pure product **67**[42] (21.9 mg, 85%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.67 (s, 1H), 7.63 (t, *J* = 7.8 Hz, 1H), 7.49 (d, *J* = 8.2 Hz, 1H), 7.29 (t, *J* = 7.8 Hz, 1H), 7.22 – 7.17 (m, 4H), 7.13 (d, *J* = 7.3 Hz, 2H), 6.97 (d, *J* = 8.2 Hz, 2H), 6.70 (d, *J* = 8.2 Hz, 2H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 160.4, 157.3, 152.6, 151.4, 134.6, 131.7, 130.7, 130.6, 127.6, 127.5, 127.2, 126.4, 124.5, 124.4, 120.5, 116.4, 115.1; FT-IR (thin film, neat): 3218, 2923, 1674, 1441, 1295, 765 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{21}H_{15}O_3$ $[M+H]^+$: 315.1021; found : 315.1010.

Procedure for synthesis of 73



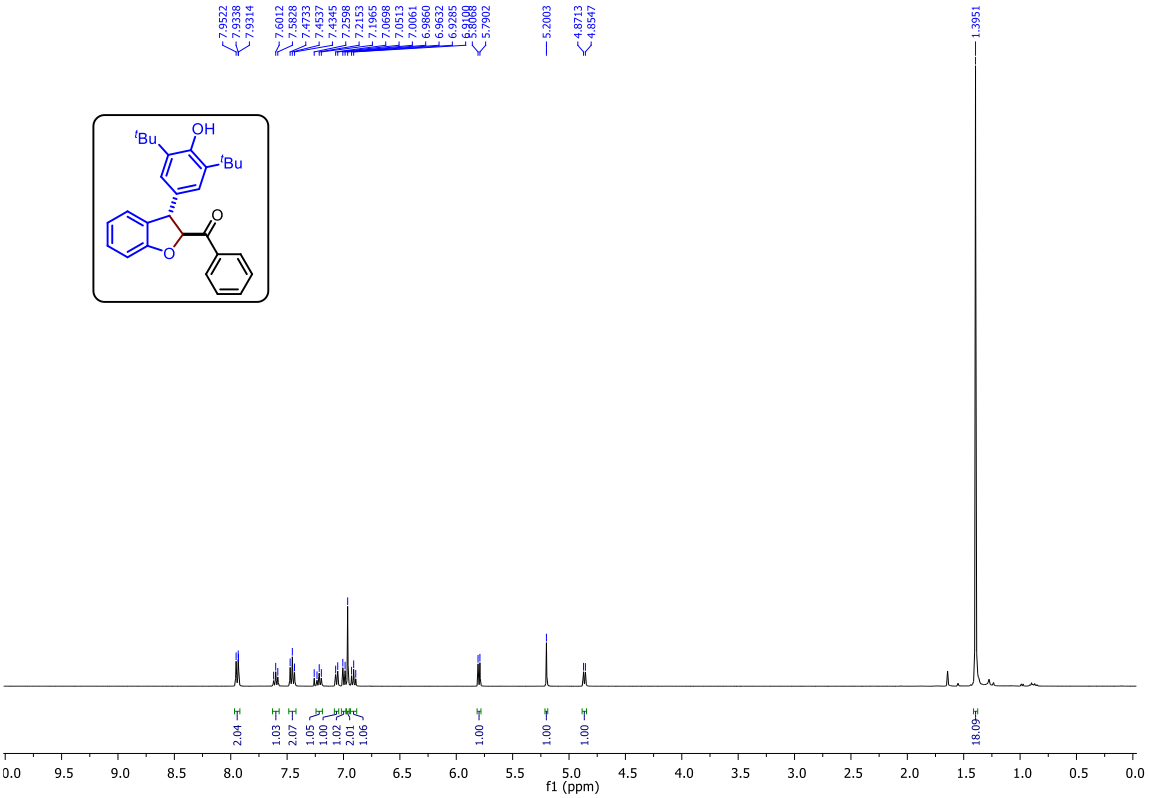
2-Bromoacetophenone [**62a**] (17.5 mg, 0.088 mmol, 1.0 equiv.) was added to a mixture of 3-hydroxyphenyl-substituted *p*-QM [**72**][43] (30 mg, 0.097 mmol, 1.1 equiv.) and Cs_2CO_3 (43 mg, 0.132 mmol, 1.5 equiv.) in acetone (1.5 mL) and, the resulting suspension was stirred at room temperature until the 2-bromoacetophenone was completely consumed (based on TLC analysis). The reaction mixture was concentrated under reduced pressure, and the residue was then purified through a silica gel column using EtOAc/Hexane mixture as an eluent to get the pure compound **73**. Yellow gummy solid (30.3 mg, 73% yield); R_f = 0.2 (10% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 – 7.99 (m, 2H), 7.63 (t, *J* = 7.4 Hz, 1H), 7.53 – 7.49 (m, 3H), 7.39 – 7.34 (m, 1H), 7.13 (s, 1H), 7.09 (d, *J* = 7.5 Hz, 1H), 7.00 – 6.97 (m, 3H), 5.34 (s, 2H), 1.32 (s, 9H), 1.27 (s, 9H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 194.1, 186.7, 158.4, 149.6, 148.0, 142.1, 137.4, 135.2, 134.4, 134.2, 132.4, 130.1, 129.0, 128.2, 127.8, 123.9, 116.3, 115.9, 70.9, 35.6, 35.1, 29.7, 29.6; FT-IR (thin film, neat): 2957, 1705, 1438, 1614, 1557, 754 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{29}H_{33}O_3$ $[M+H]^+$: 429.2430; found : 429.2439.

Procedure for synthesis of 74

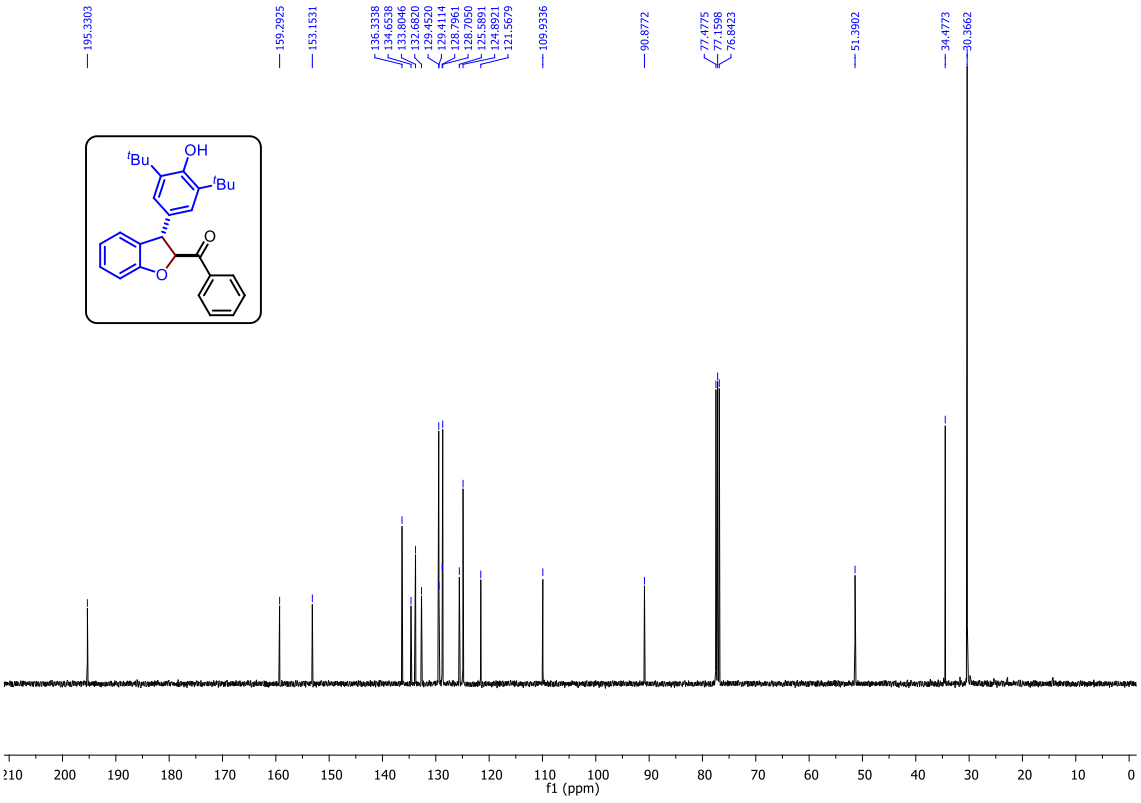


Phenyl acetylchloride [**65a**] (25.5 µL, 0.193 mmol, 1.2 equiv.) was added to a mixture of 3-hydroxyphenyl-substituted *p*-QM [**72**][43] (50.0 mg, 0.161 mmol, 1.0 equiv.) and Cs_2CO_3 (115.4 mg, 0.354 mmol, 2.2 equiv.) in acetone (2.0 mL) and, the resulting suspension was stirred at room temperature until the phenyl acetylchloride was completely consumed (based on TLC analysis). The reaction mixture was concentrated under reduced pressure, and the residue was then purified through a silica gel column using EtOAc/Hexane mixture as an eluent to get the pure compound **74**. Yellow gummy solid (40.0 mg, 70% yield); R_f = 0.2 (10% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (d, *J* = 2.3 Hz, 1H), 7.44 – 7.41 (m, 1H), 7.40 – 7.36 (m, 4H), 7.34 – 7.32 (m, 1H), 7.31 – 7.29 (m, 1H), 7.14 – 7.09 (m, 3H), 6.98 (d, *J* = 2.3 Hz, 1H), 3.88 (s, 2H), 1.33 (s, 9H), 1.28 (s, 9H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 186.7, 170.0, 151.0, 149.8, 148.2, 140.9, 137.4, 135.0, 133.4, 132.7, 129.9, 129.3(2C), 128.9, 127.9, 127.6, 123.4, 122.1, 41.6, 35.6, 35.2, 29.64, 29.62; FT-IR (thin film, neat): 2957, 1760, 1614, 1362, 754 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{29}H_{33}O_3$ $[M+H]^+$: 429.2430; found : 429.2432.

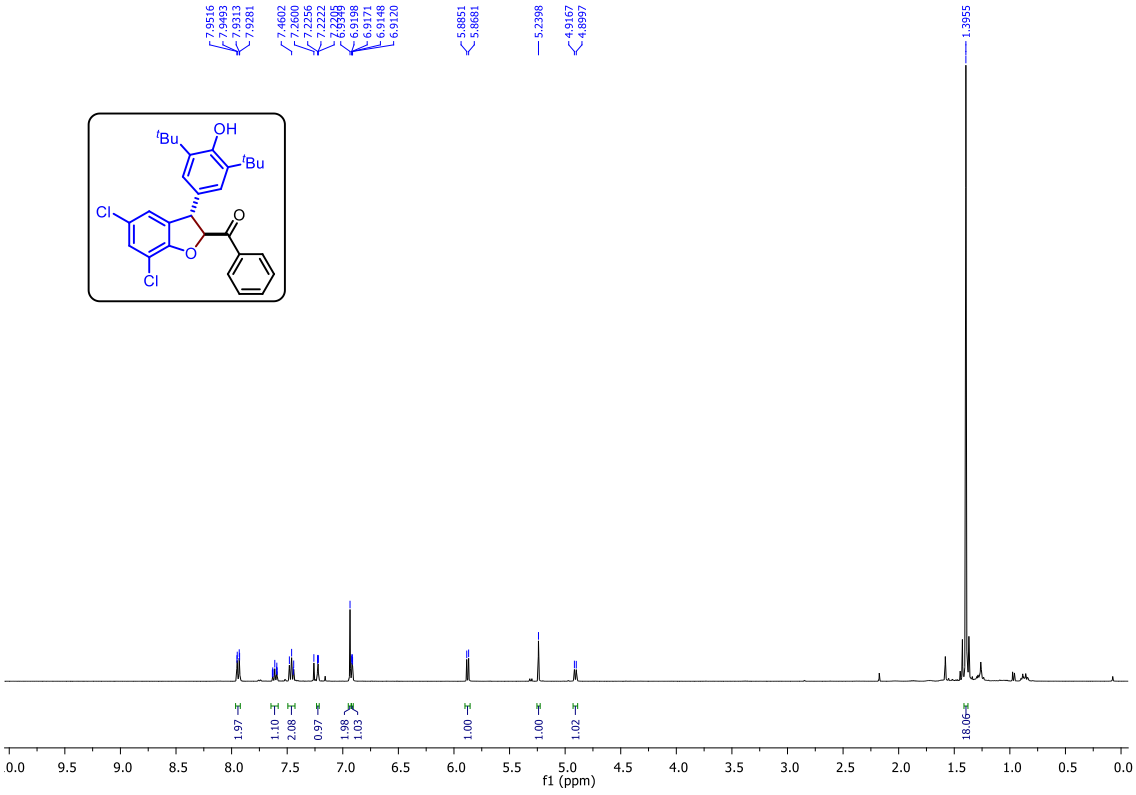
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **63a**



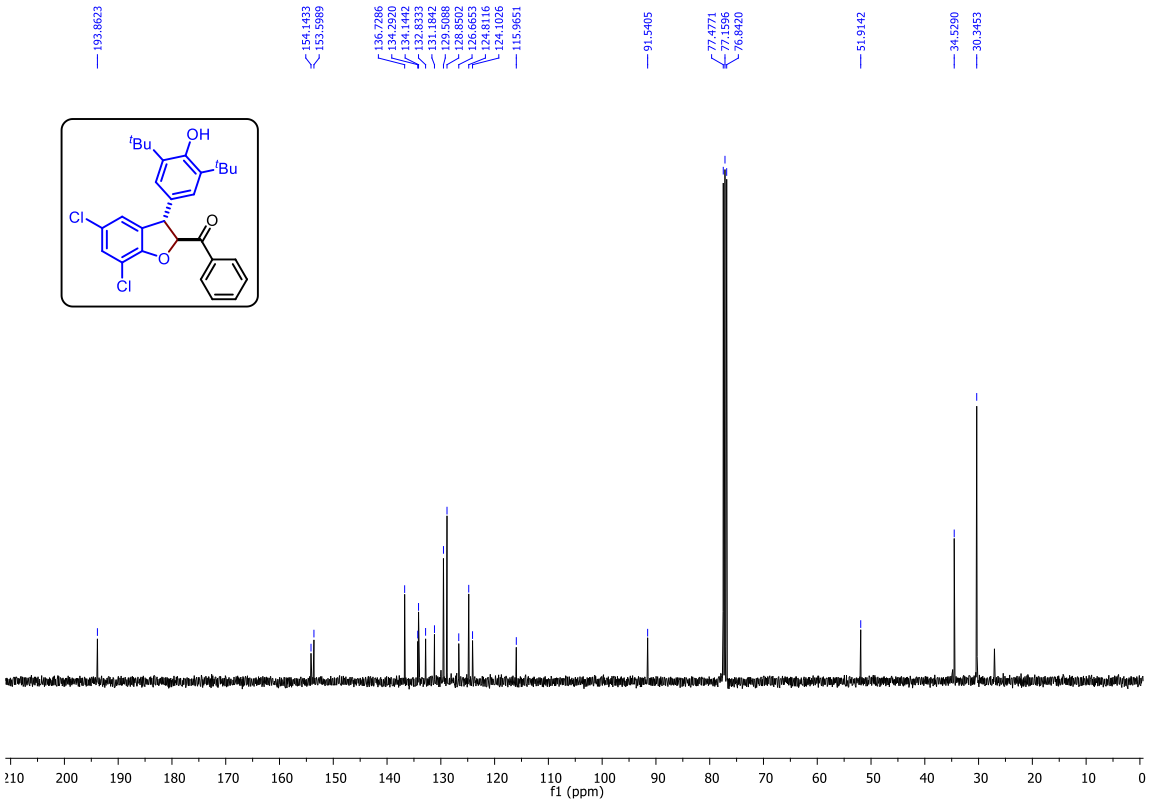
^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) Spectrum of **63a**



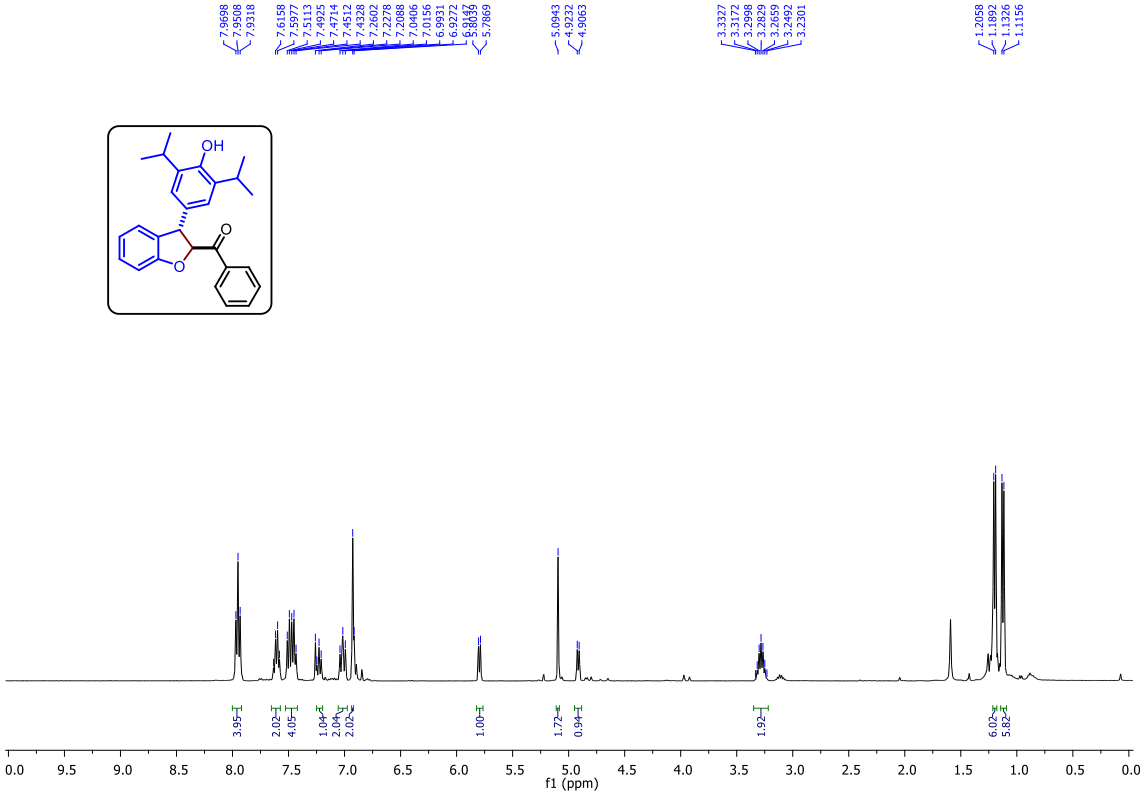
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **63s**



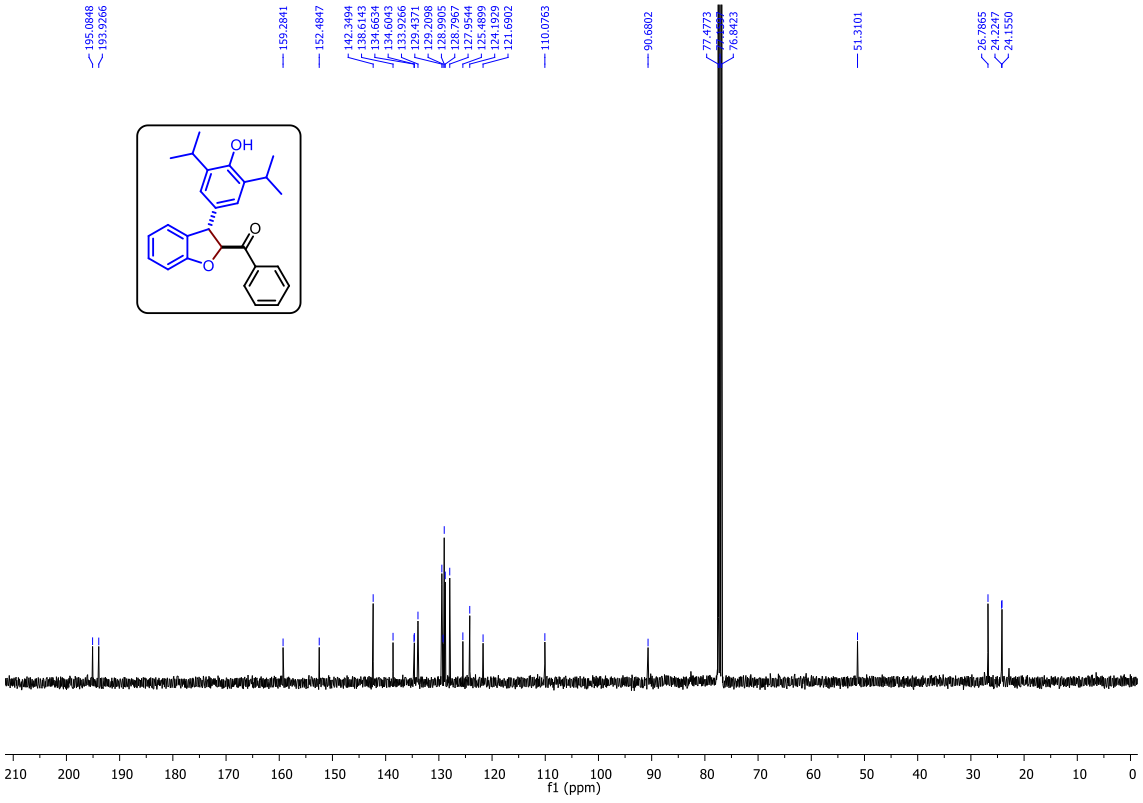
^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) spectrum of **63s**



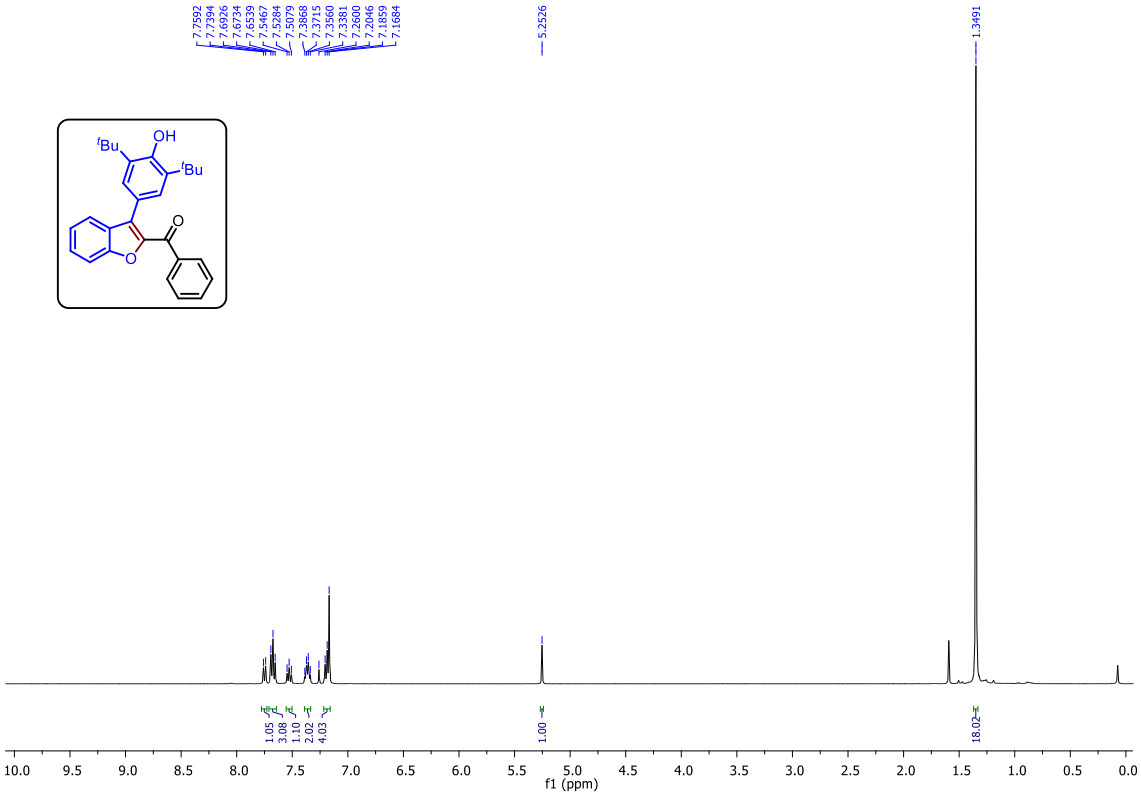
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **63u**



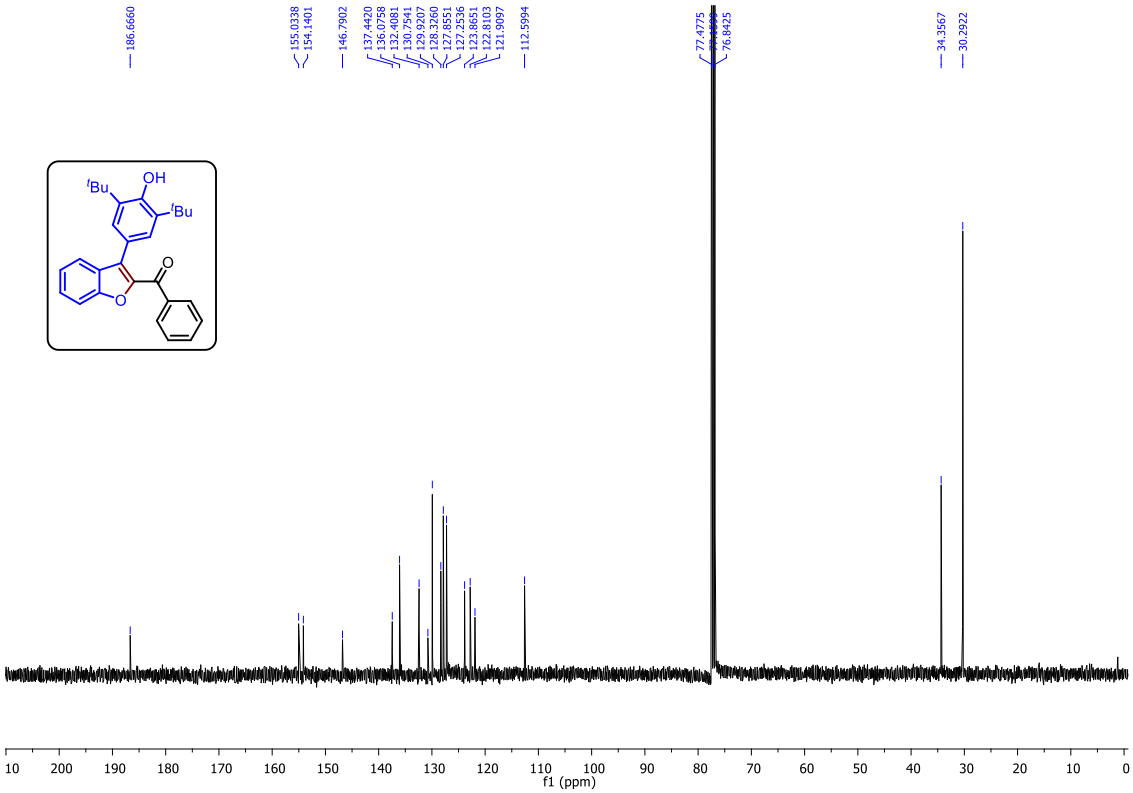
^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) spectrum of **63u**



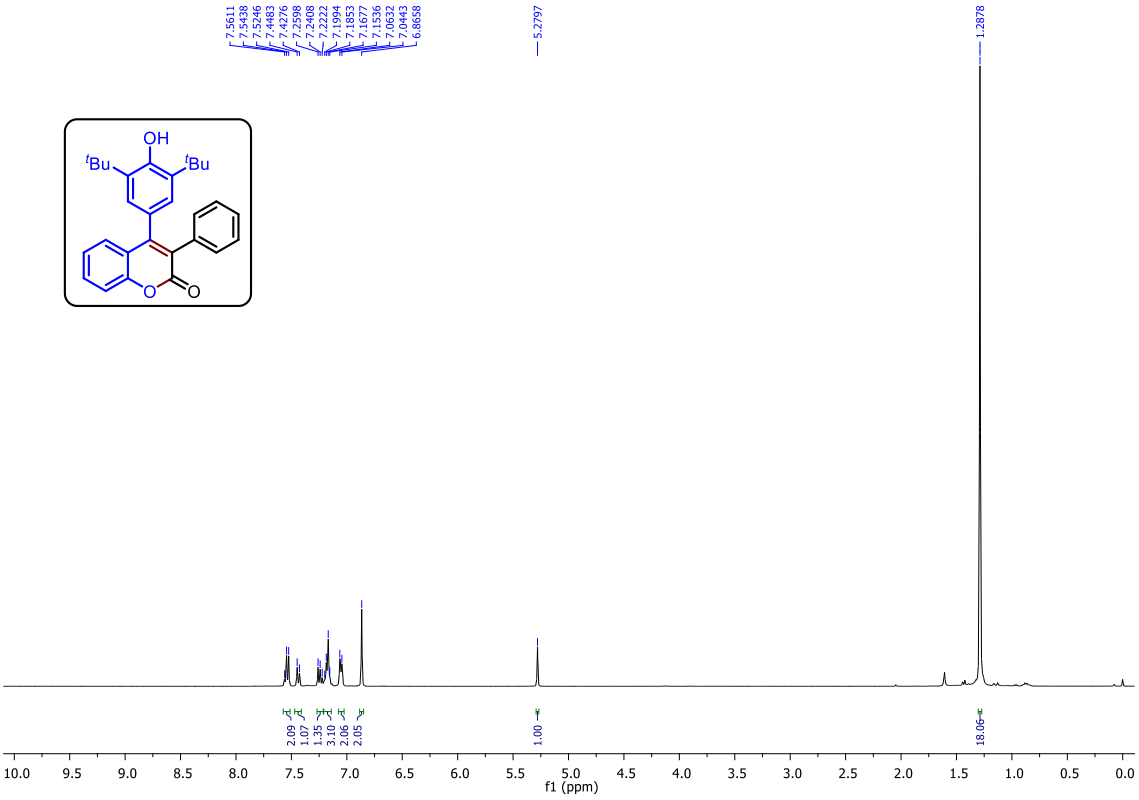
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **64a**



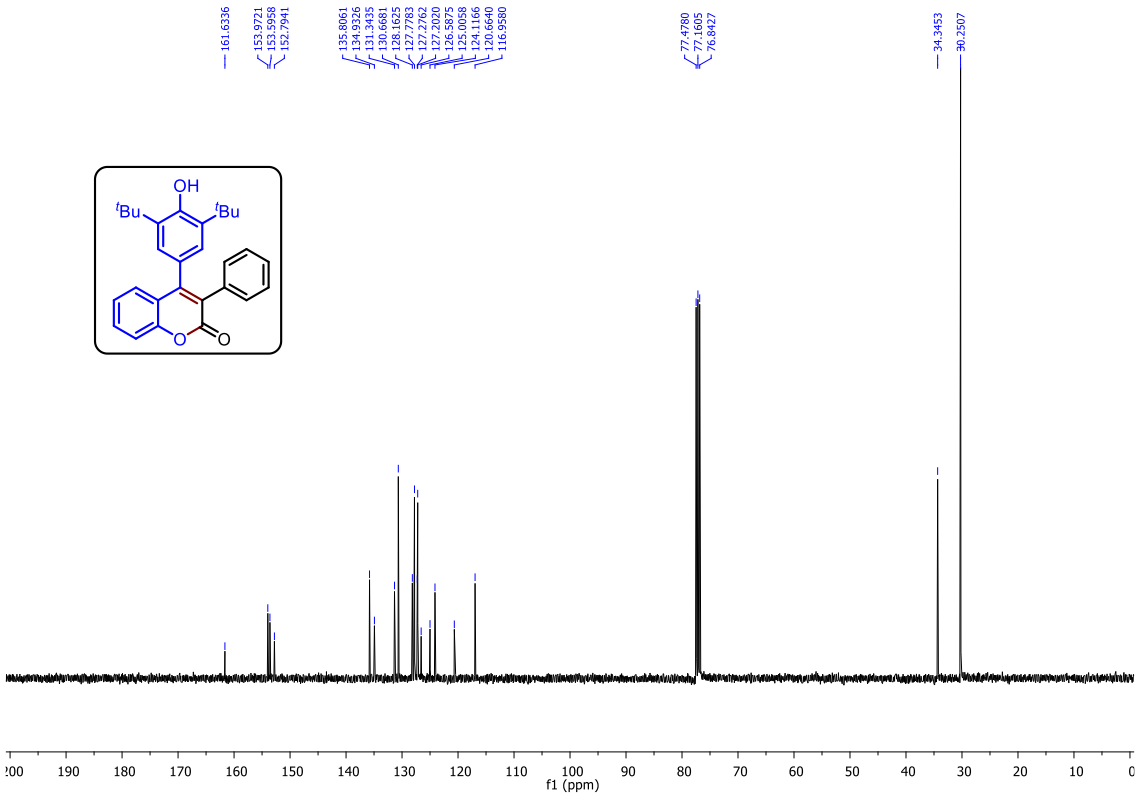
^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) spectrum of **64a**



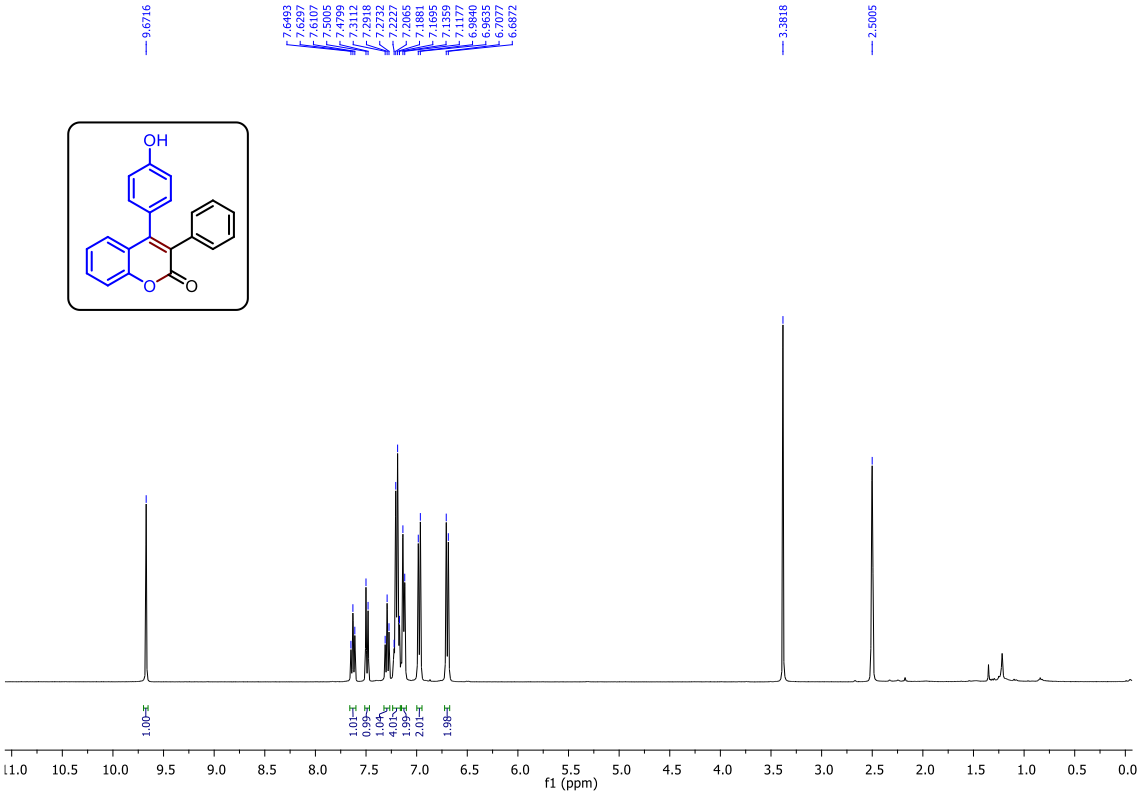
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **66a**



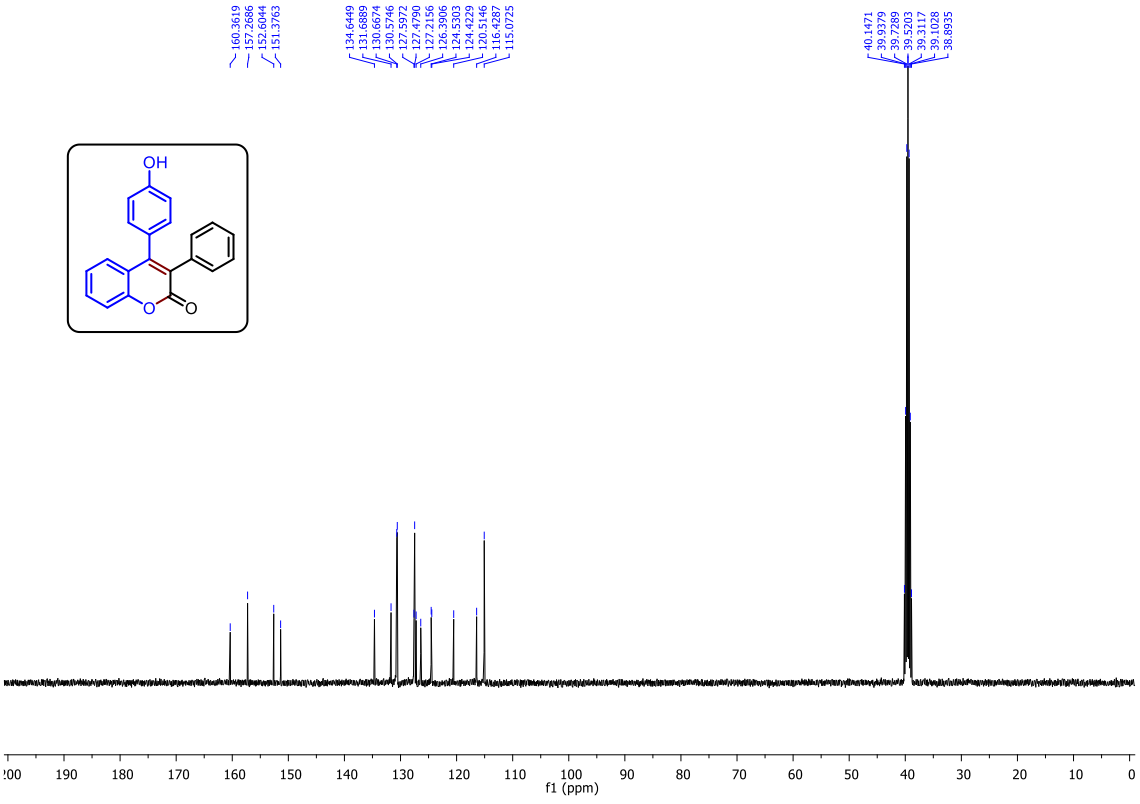
^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) spectrum of **66a**



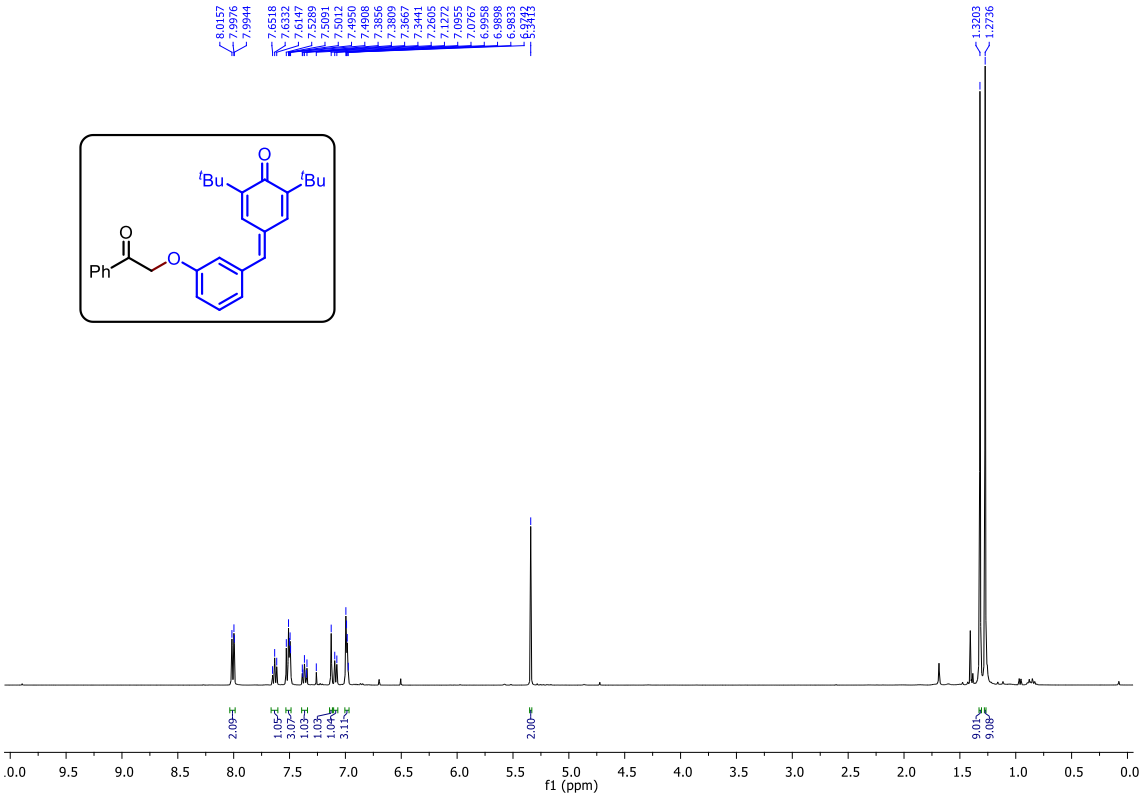
^{1}H NMR (400 MHz, DMSO- d_6) spectrum of **67**



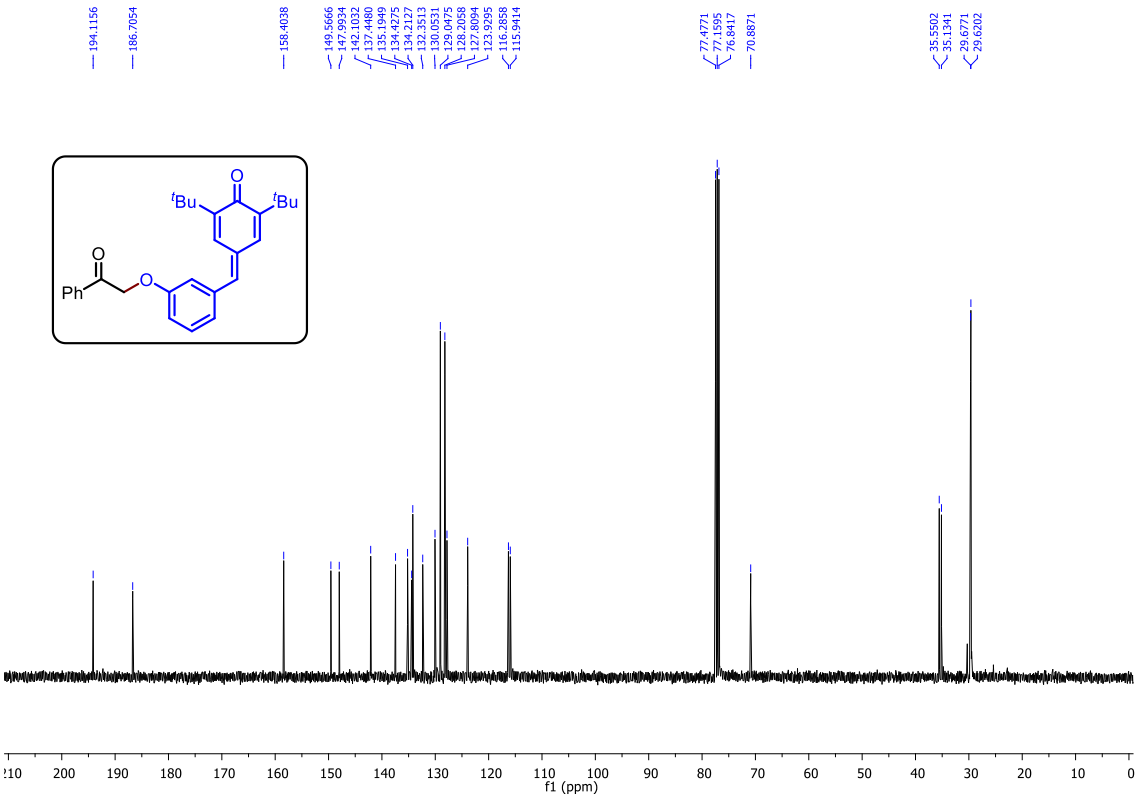
^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) spectrum of **67**



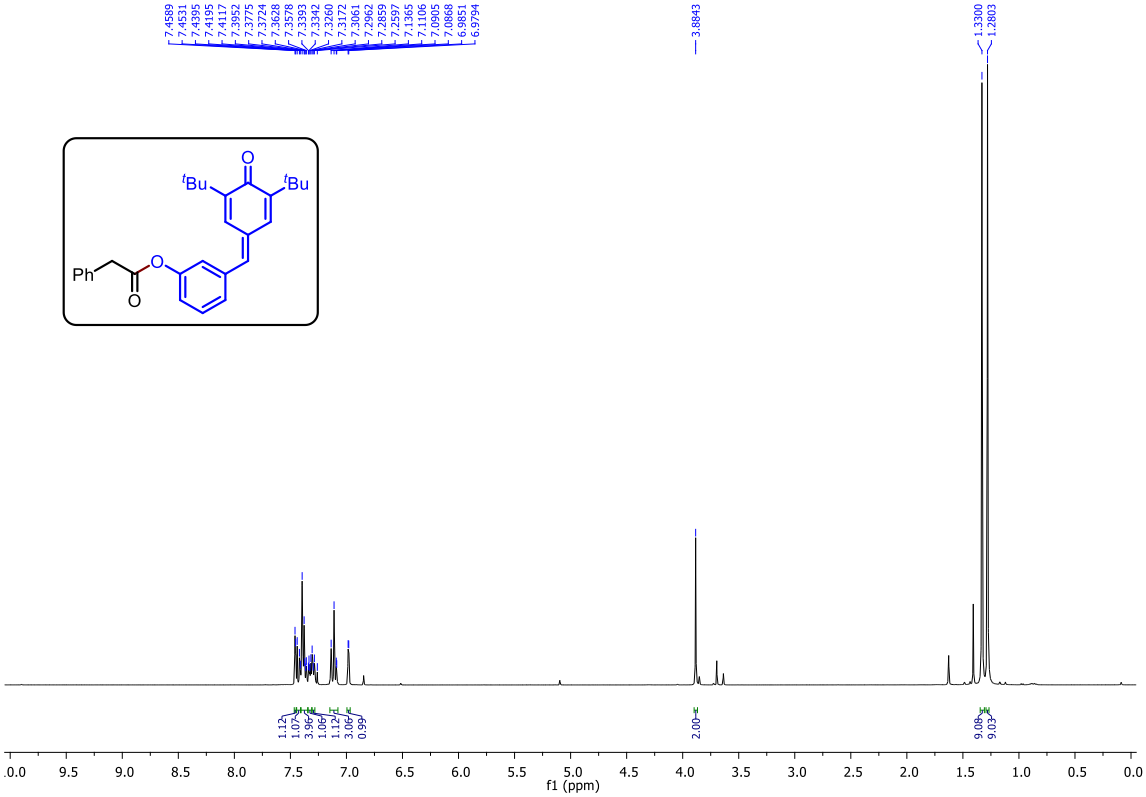
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **73**



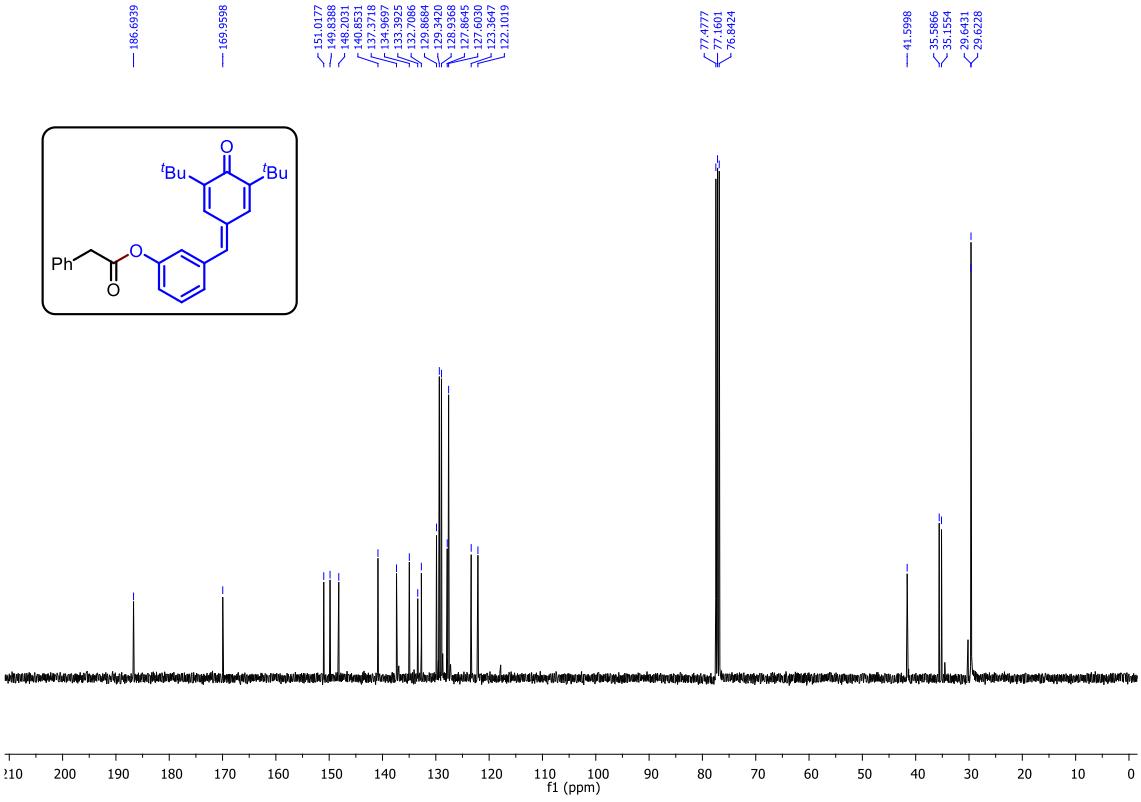
^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) spectrum of **73**



^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **74**



^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) spectrum of **74**



3.8. Reference

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Part 4

4. One-pot approach for the synthesis of chromenes through formal [4+2]-annulation reaction of enaminones and 2-hydroxyphenyl substituted *para*-quinone methides

4.1. Introduction

4H-chromenes or 4H-1-benzopyran is a privileged class of oxygen-containing heterocycles,[1] and many natural and unnatural derivatives of this heterocycle possess pharmacological activities such as anti-cancer, anti-oxidant, anti-inflammatory, anti-hypertensive, anti-fungal, and anti-convulsant amongst others (Fig. 1).[2]

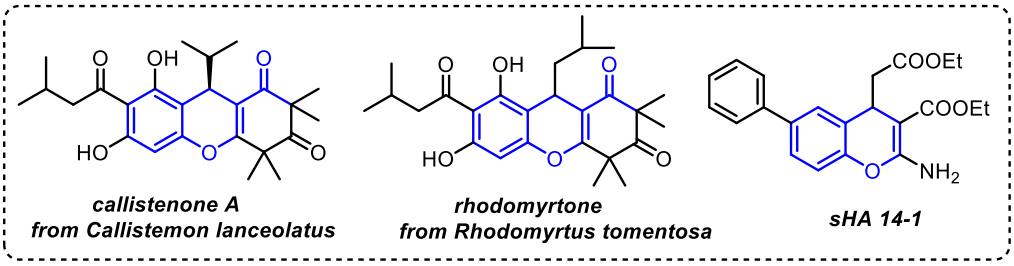


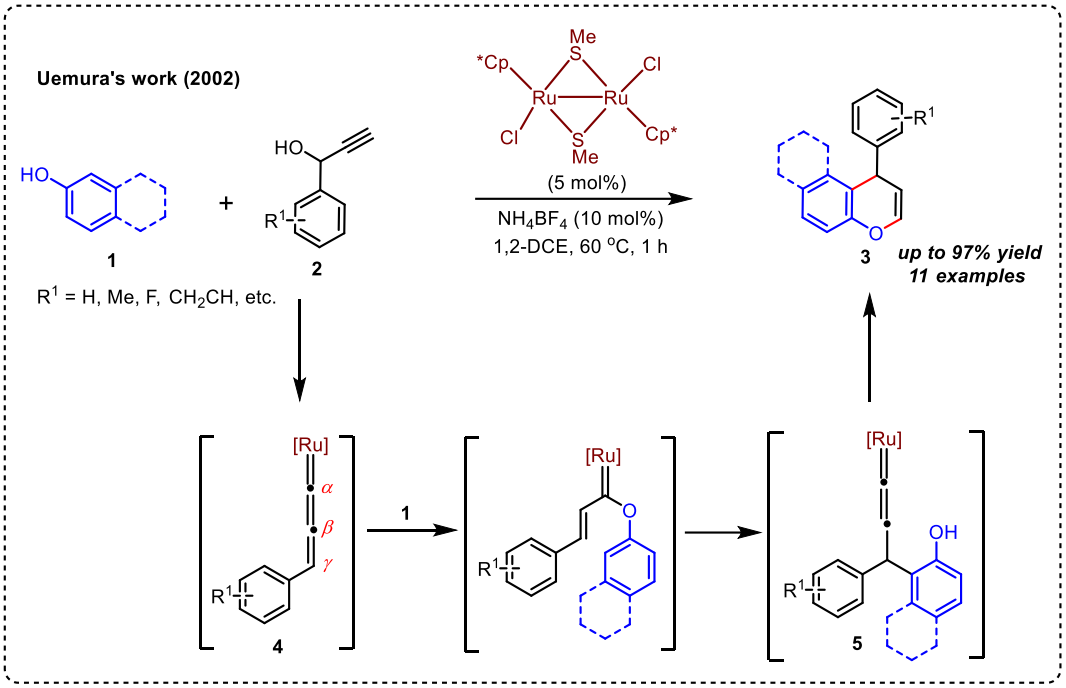
Figure 1. Natural products and biologically active molecules.

Many synthetic approaches have been developed for the construction of 4H-chromene derivatives under metal-catalyzed and metal-free conditions,[3] few of them are discussed below.

4.2. Literature reports on the synthesis of 4H-chromene derivatives

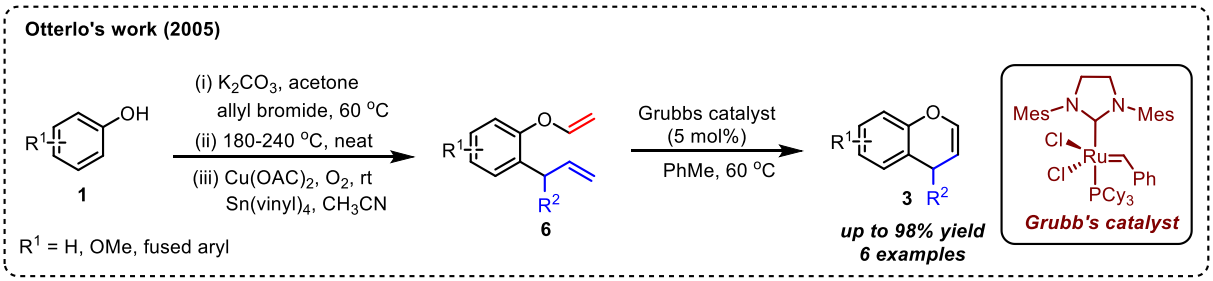
4.2.1. Metal-catalyzed synthesis of 4H-chromenes

In 2002, Uemura and co-workers described the ruthenium-catalyzed annulation reaction of phenols/*β*-naphthols (**1**) and propargylic alcohols (**2**) for the synthesis of pyran derivatives (**3**) *via* allenylidene complex (**4**). The reaction proceeds through the generation of the allenylidene complex **4** by the reaction of **2** and ruthenium catalyst in the presence of NH_4BF_4. Then *β*-naphthol oxygen attacks at the C_α atom of **4**, followed by Claisen rearrangement to generate another intermediate **5**. Then, the hydroxyl group of **5** attacks the C_α atom to produce product **3**. Another possibility for the generation of **5** is the attack of *β*-naphthol carbon at the C_γ of **4** may not be excluded (Scheme 1).[4]



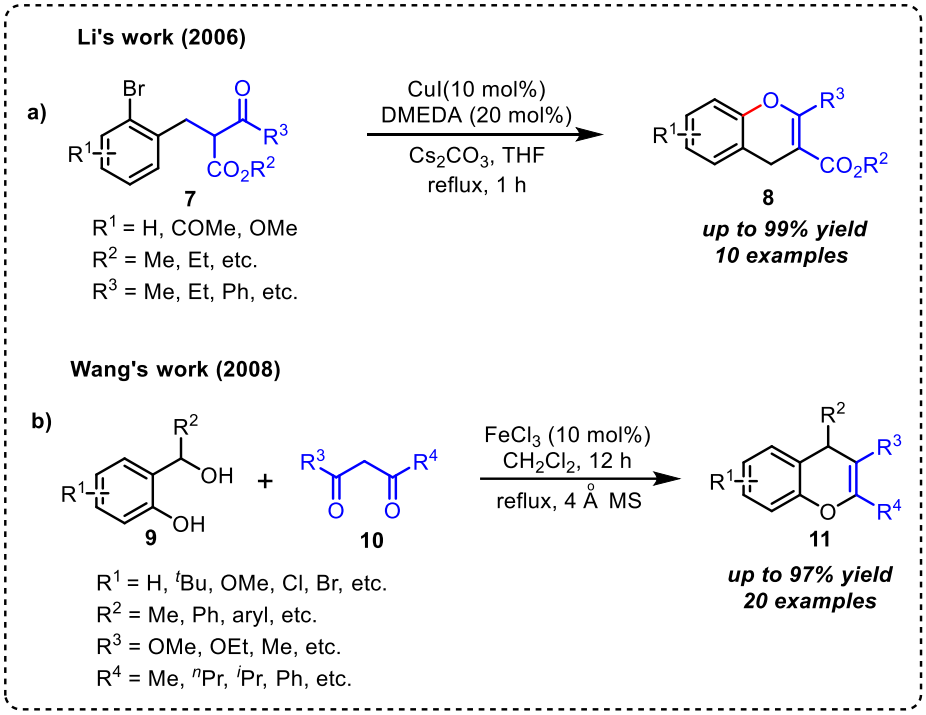
Scheme 1. Ruthenium-catalyzed synthesis of pyran derivatives

In 2005, Otterlo's group developed the synthesis of 4H-chromene derivatives *via* ring-closing metathesis (RCM) of *O*-vinyl aryl allyl compound (**6**) with 2nd generation Grubb's catalyst. Compounds **6** were obtained by reacting phenols with allyl bromide to generate an aryl allyl ether, followed by the Claisen rearrangement to form *o*-allyl phenol derivatives. Further, these *O*-vinyl aryl allyl derivatives undergo a copper-mediated *O*-vinylation in the presence of tertavinyltin complex to form **6** (Scheme 2).[5]



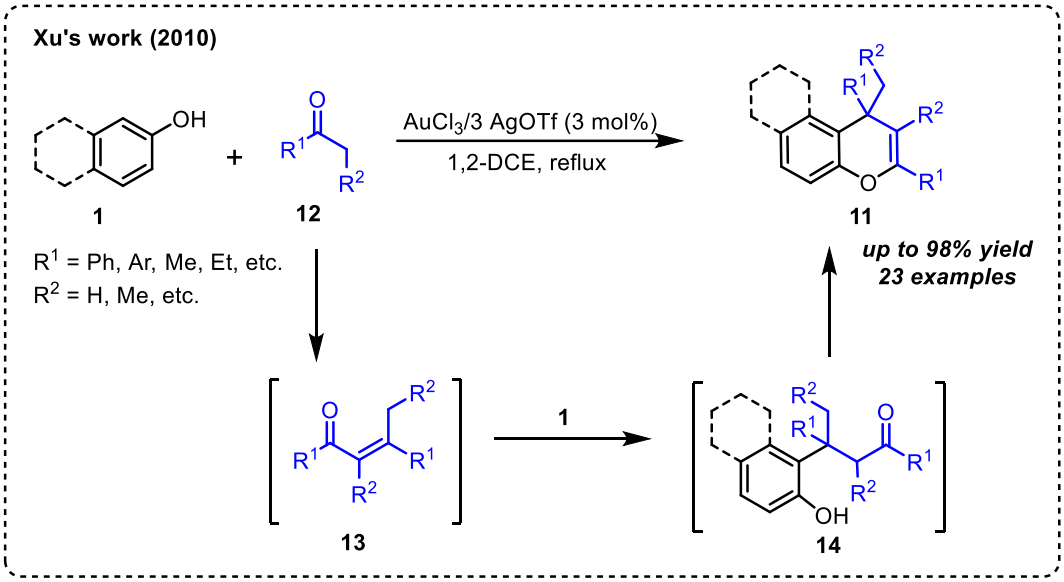
Scheme 2. Synthesis of 4H-chromenes *via* ring-closing metathesis with Grubb's catalyst

Later, Li and co-workers reported the copper-catalyzed synthesis of 4H-chromene derivatives (**8**) from *α*-(2-bromobenzyl)-*β*-keto esters (**7**). The reaction proceeds through an intramolecular coupling of aryl bromides with 1,3-dicarbonyls *via* *O*-arylation, leading to a six-membered heterocyclic ring. A variety of substituted *α*-(2-bromobenzyl)-*β*-keto esters worked efficiently in CuI/DMEDA under refluxing THF conditions to furnish the products in moderate to good yields (Scheme 3, **a**).[6] In 2008, Wang's group established a $FeCl_3$-catalyzed synthesis



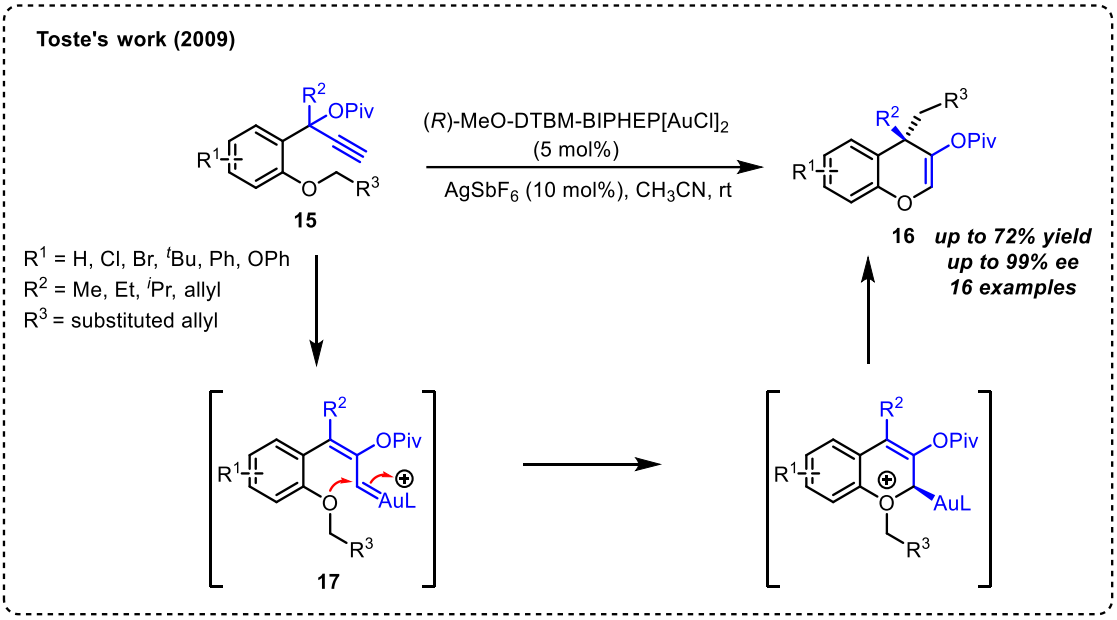
Scheme 3. (a) Copper-catalyzed synthesis of 4H-chromene derivatives (b) $FeCl_3$-catalyzed synthesis of 4H-chromene derivatives

of 4H-chromene derivatives by the annulation reaction of 1,3-dicarbonyls (**10**) and substituted 2-(hydroxymethyl)phenols (**9**). It was assumed that the reaction proceeds through the *in situ* generations of *o*-quinone methide followed by the attack of 1,3-dicarbonyl and subsequent intramolecular cyclization/elimination sequence to produce the product (Scheme 3, **b**).[7]



Scheme 4. Gold (III)-catalyzed synthesis of 4H-chromene derivatives

Xu's group, in 2010, established the gold(III)-catalyzed annulation reaction of phenols/*β*-naphthols (**1**) with ketones (**12**) for the synthesis of 4H-chromene derivatives (**11**) in moderate to good yield. According to the proposed reaction mechanism, initially, ketone undergoes a self-condensation reaction in the presence of gold(III) to generate *α*, *β*-unsaturated carbonyl compound **13**, followed by 1,4-conjugate addition of phenols/*β*-naphthols to **13**, to produce an intermediate **14**. Then, the intermediate **14** undergoes an intramolecular cyclization/elimination to give the product **16** (Scheme 4).[8]



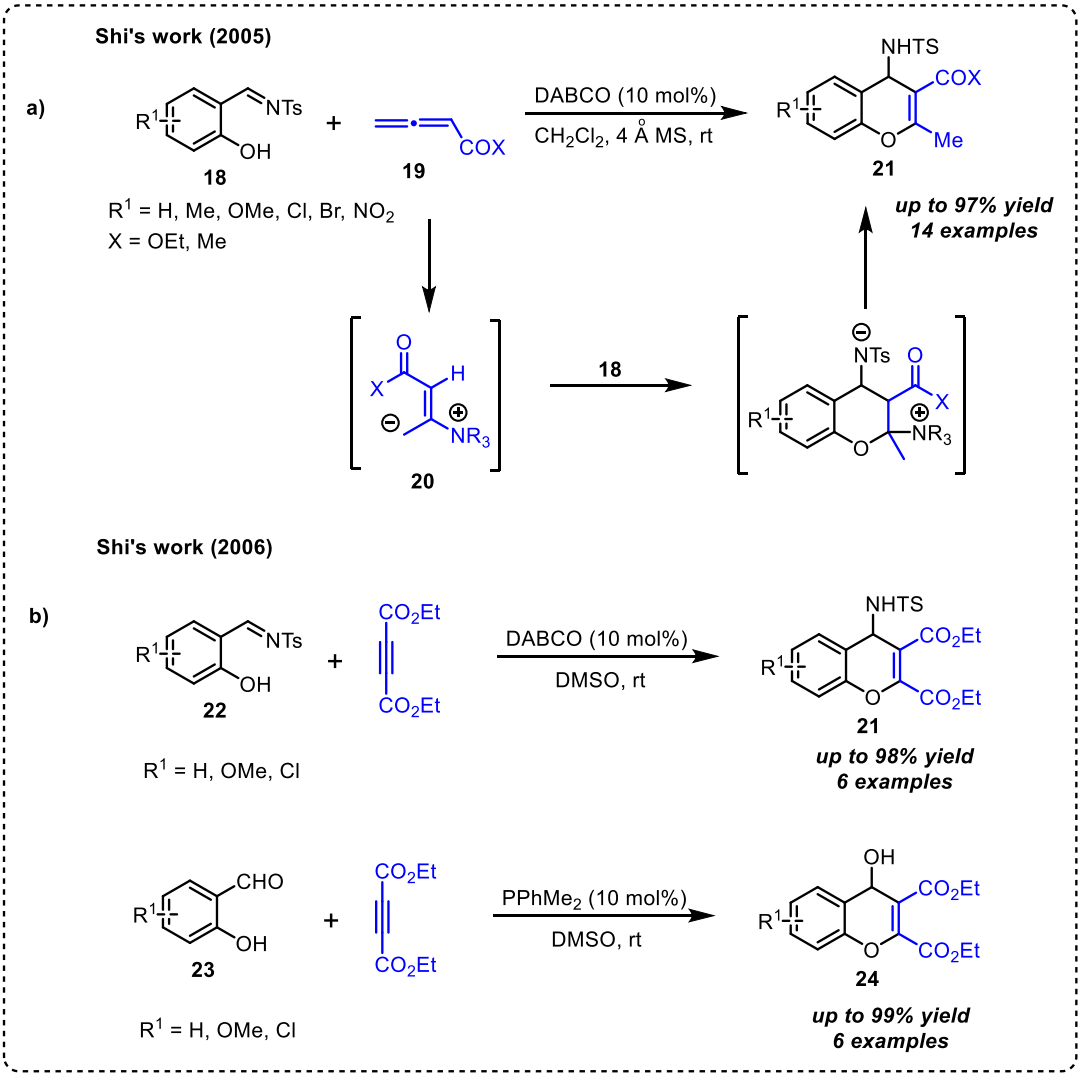
Scheme 5. Gold (I)-catalyzed synthesis of 4H-chromene derivatives

Toste and co-workers reported the enantioselective synthesis of 4H-chromene derivatives (**16**) through gold(I)-catalyzed carboalkoxylation of propargylic esters (**15**). Various propargylic esters reacted well under standard conditions to afford the products in good yield and high enantioselectivity. The reaction proceeds through the formation of gold(I)-carbenoid (**17**) from the gold-catalyzed rearrangement of **15**, followed by an intramolecular attack by the ether oxygen and subsequent rearrangement to produce the product (Scheme 5).[9]

4.2.2. Metal-free synthesis of 4H-chromenes

In 2005, Shi and co-workers reported the DABCO-catalyzed [4+2] cycloaddition of allenic ester/ketones (**19**) with salicyl-*N*-tosylamine (**18**) for the synthesis of substituted chromene derivatives. The reaction is believed to proceed through the formation of a zwitterionic intermediate (**20**) by the reaction of salicyl-*N*-tosylamine with **19** in the presence of a base, which abstracts the proton from phenol, followed by Michael addition/Mannich reaction and elimination to give the chromene **21** as a product. When the reaction was carried

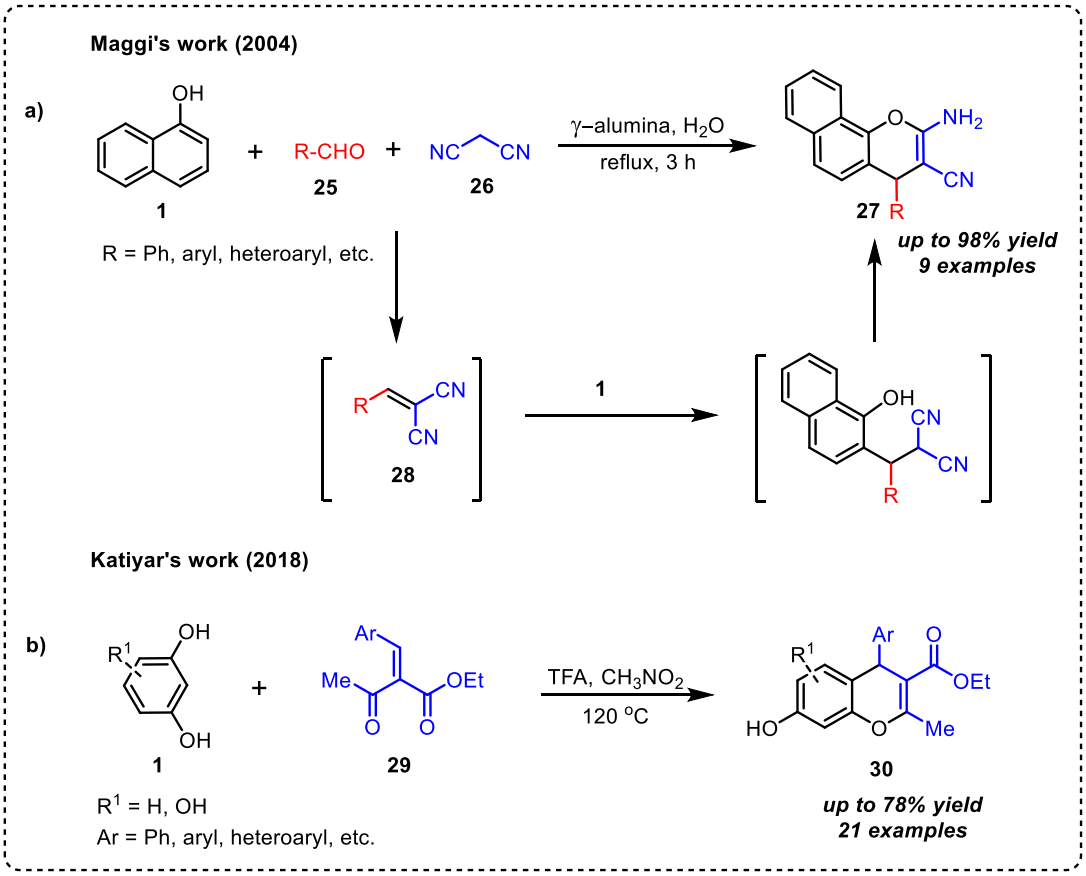
out with salicylaldehyde under similar conditions, Michael addition products were observed rather than the chromene derivatives (Scheme 6, **a**).[10] Later, the same group developed the annulation reaction of salicyl-*N*-tosylamine **22** or salicylaldehyde **23** with diethyl acetylenedicarboxylate in the presence of DABCO and $PPhMe_2$, respectively, for the construction of substituted chromene derivatives **21** & **24** in good to excellent yields (Scheme, **b**).[11]



Scheme 6. Synthesis of chromene derivatives from salicyl-*N*-tosylamine and salicylaldehydes

The general way to synthesize chromene derivatives is the multi-component annulation reaction of phenols, aromatic aldehydes, and active methylene compounds. For the synthesis of chromene derivatives, various reports have been known in the literature using different types of catalysts. In 2004, Maggi and co-workers described the basic alumina-catalyzed synthesis of chromenes (**27**) by the annulation of α-naphthol **1**, aldehyde **25**, and malononitrile **26** in the presence of water. According to the proposed reaction mechanism, benzylidene malononitrile

28 was generated by the Knoevenagel condensation of aldehyde and malononitrile. Then *α*-naphthol undergoes a reaction with **28**, followed by an intramolecular nucleophilic attack by the hydroxy group on CN, which leads to the formation of the product **27** (Scheme 7, **a**).[12] Later, Lee,[13a] Abrouki,[13b] Ramesh,[13c] etc. groups have independently reported the synthesis of chromenes by using the phenols, aldehydes, and malononitriles. Recently, Katiyar's group demonstrated the TFA-catalyzed preparation of substituted chromenes (**30**) by the Michael–addition of resorcinol **1** to benzylidene oxobutanoates (**29**), followed by intramolecular cyclization. The benzylidene oxobutanoates (**29**) were obtained by the *L*-proline-catalyzed Knoevenagel condensation reaction of aldehydes and ethyl acetoacetate. (Scheme 7, **b**).[14]



Scheme 7. Synthesis of substituted chromenes by the condensation reaction of phenols, aldehydes, and active methylene compounds

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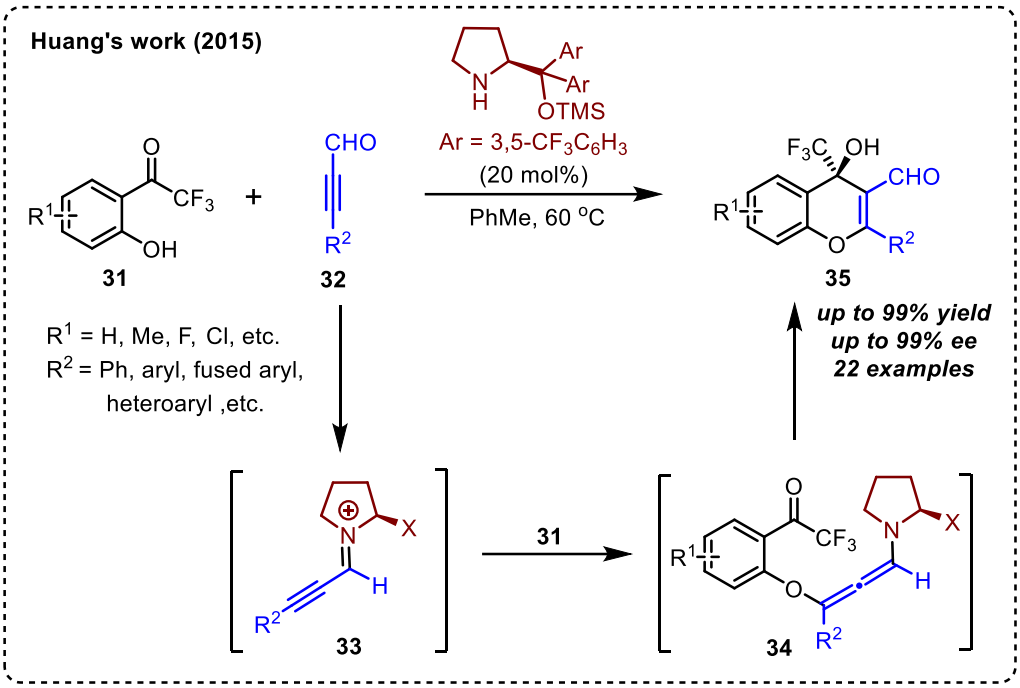
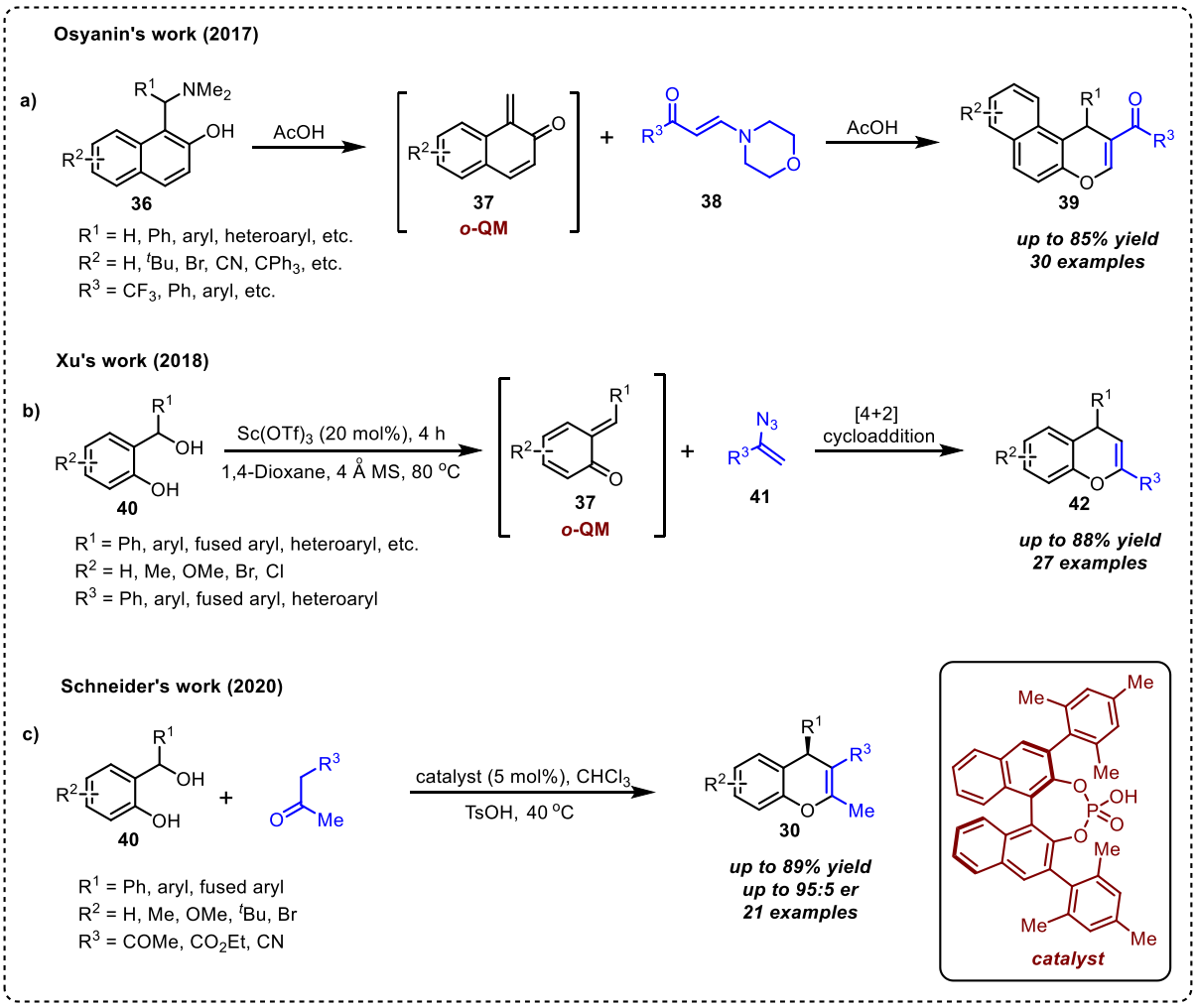
In 2015, Huang's group disclosed a chiral secondary amine-catalyzed enantioselective synthesis of CF_3-substituted 4H-chromene derivatives (**35**) by the reaction of 2-trifluoroacetylphenols (**31**) and alkynals (**32**) *via* an iminium-allenamine intermediate. According to the proposed reaction mechanism, initially, the iminium ion **33** is formed by the reaction of alkynal and chiral secondary amine, followed by *oxa*-Michael addition with **31** to

generate alleneamine intermediate **34**, which subsequently undergoes intramolecular cyclization to form the product (Scheme 8).[15]



Scheme 8. Chiral secondary amine-catalyzed enantioselective synthesis of 4H-chromenes

Various literature reports have been recently developed for the synthesis of 4H-chromenes derivatives through *in situ* generations of *ortho*-quinone methides (*o*-QMs). Osyanin's group, in 2017, established the synthesis of 4H-chromene products (**39**) *via* [4+2] cycloaddition reaction of *in situ* generated *o*-QMs (**37**) with enaminones (**38**). A wide range of *o*-QM precursors (**36**) and enaminones (**38**) was employed in the presence of acetic acid as a solvent under reflux conditions to afford the products **39** in moderate to good yields (Scheme 9, **a**).[16] Similarly, Xu's group disclosed a Lewis acid-catalyzed annulation reaction of *in situ* generated *o*-QMs (**37**) from *o*-hydroxybenzhydryl alcohols (**40**) with vinyl azides (**41**) for the synthesis of chromenes (**42**). According to the reaction mechanism, initially, *o*-QMs were generated, followed by an attack of vinyl azides to *o*-QMs, and then intramolecular cyclization/elimination of hydrazoic acid to give the product **42** (Scheme 9, **b**).[17] In 2022, Schneider's group reported an enantioselective synthesis of 4H-chromenes (**30**) by using *o*-hydroxybenzhydryl alcohols (**40**). The reaction proceeds through the chiral phosphoric acid-catalyzed generation of *o*-QMs, followed by a cycloaddition with *β*-dicarbonyls or *β*-keto nitriles, or *β*-keto esters and subsequent intramolecular cyclization and elimination to produce the product **30** (Scheme 9, **c**).[18]



Scheme 9. Synthesis of 4H-chromene derivatives from *o*-QMs

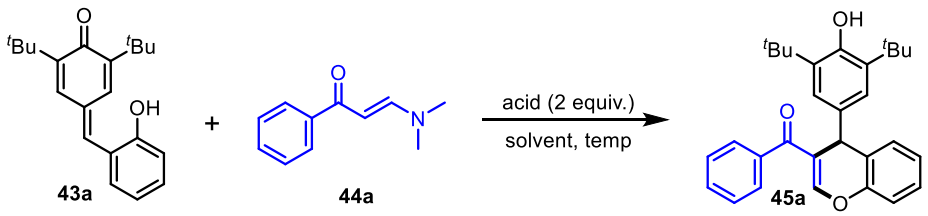
4.3 Background

In recent years, significant developments in the synthetic elaboration of *p*-quinone methides (*p*-QMs) have been realized.[19] Our research group also contributed in this area, mainly on the synthetic applications of *p*-QMs to access triaryl-/diarylmethane-based heterocycles,[20] and carbocycles[21] through vinylogous conjugate addition reactions of *p*-QMs with various nucleophiles. While exploring *p*-QMs as synthons in the synthesis of oxygen-containing heterocycles,[22] we have realized that it is possible to access 4H-chromenes through an acid-mediated reaction between enaminones[23] and *p*-QMs. Although a few methods have been established for synthesizing 4H-chromene derivatives using *p*-QMs as precursors,[24] to the best of our knowledge, the reaction between *p*-QMs and enaminones leads to 4H-chromenes has not been reported so far, and this prompted us to work on this specific transformation.

4.4. Result and discussion

To find out the optimal reaction conditions for the synthesis of 4H-chromenones, the reaction between 2-hydroxyphenyl-substituted *p*-QM (**43a**, 1.0 equiv.) and *N*,*N*-dimethyl enaminone (**44a**, 1.3 equiv) was examined under different acidic conditions, and the results are summarized in Table 1. In our initial attempts, we employed TsOH (2 equiv.) as an acid promotor in the CH_3CN medium, and within an hour, some conversion was observed, and the desired 4H-chromene **45a** was isolated in 18% yield at room temperature (entry 1). When the same reaction was conducted at 60 ^oC, significant improvement in the conversion of **43a** was observed, and the product **45a** was obtained in 50% isolated yield (entry 2). Increasing the reaction time to 5 h by maintaining the reaction at 60 ^oC resulted in improving the yields of

Table 1. Optimization study[a]



entry	acid	solvent	time	temp (^oC)	yield (%)
1	TsOH	CH_3CN	1	25	18
2	TsOH	CH_3CN	1	60	50
3	TsOH	CH_3CN	5	60	65
4	TsOH	PhMe	5	60	62
5	TsOH	PhMe	5	90	60
6	TsOH	1,4-Dioxane	5	60	71
7	TsOH	THF	5	60	77
8[b]	**TsOH**	**THF**	**5**	**60**	**84**
9[b]	CSA	THF	5	60	72
10[b]	TFA	THF	5	60	63
11	-	THF	24	60	nr

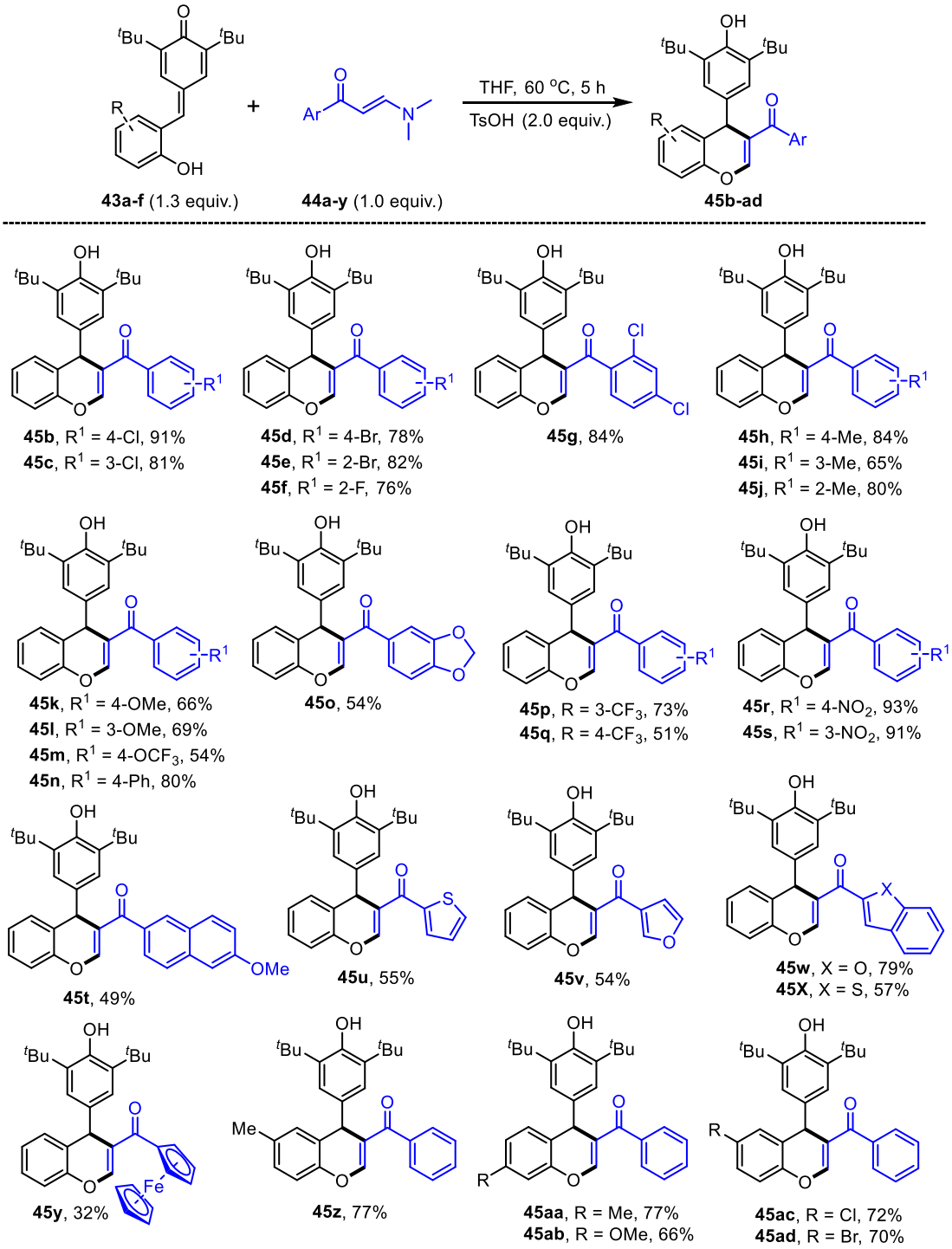
[a] All reactions were carried out with **43a** (0.097 mmol), **44a** (0.126 mmol), and TsOH (2.0 equiv.) in 1.5 mL of solvent. [b] Reaction was carried out with **43a** (0.097 mmol), **44a** (0.075), and acid (2.0 equiv.) in 1.5 mL solvent. nr = No reaction. Yields reported are isolated yields.

45a to 65% (entry 3). Toluene was found to be a less effective solvent for this transformation, even at elevated temperatures (entries 4 & 5). Further improvement in the yield of **45a** (71%) was achieved when the reaction was performed in 1,4-dioxane at 60 ^{o}C (entry 6). The reaction worked relatively well in THF at 60 ^{o}C, and in that case, **45a** was isolated in 77% yield (entry 7). Interestingly, when we changed the stoichiometry of **43a** (1.1 equiv.) and **44a** (1.0 equiv.), the conversion took place smoothly, and the product **45a** formed in 84% yield (entry 8). Other Brønsted acids, such as 10-camphorsulfonic acid and trifluoroacetic acid, were found to be a bit less effective for this transformation (entries 9 & 10). No product formation was observed when the reaction was carried out without an acid promotor, which clearly shows that an acidic environment is required to drive this transformation (entry 11).

While evaluating the scope and limitation of this transformation, the optimal condition (entry 8, Table 1) was employed for the reaction between various 2- hydroxyphenyl-substituted *p*-QMs **43a**-**f** and *N*,*N*-dimethyl enaminones **44a**-**y**, and the results are summarized in Scheme 10. The standard condition was found to be suitable for the reaction between **43a** and halo-substituted *N*,*N*-dimethyl enaminones (**44b**-**g**), and in all those cases, the respective 4H-chromenes (**45b**-**g**) were obtained in the range of 76-91% yields. The *N*,*N*-dimethyl enaminones **44h**-**t** [derived from methyl-, methoxy-, aryl-, trifluoromethyl- and nitro-substituted acetophenones and acetyl naphthalene] underwent annulation reaction with **43a** and gave the respective 4H-chromenes **45h-t** in moderate to good yields (49-93%). However, enaminones **44u** & **44v**, prepared from 2-acetyl thiophene and 3-acetyl furan, furnished the expected products **45u** & **45v** in relatively lower yields (55 and 54%, respectively). When the reactions were carried out between heteroaryl-based enaminones **44w**-**y** and **43a**, the expected products **45w**-**y** were isolated in moderate yields (32-79%). The applicability of the protocol was also tested with 2- hydroxyphenyl-substituted *p*-quinone methides **43b**-**f** and, in those cases, the expected 4H-chromenes **45z** and **45aa**-**ad** were isolated in good yields (66-77%).

During the optimization studies for the synthesis of 4H-chromene **45a**, we observed that the reaction between **43a** and **34a** at room temperature gave the product **45a** only in 18% yield (entry 1, Table 1). While analyzing the reaction mixture by TLC, along with the spot that corresponds to product **45a**, another prominent spot (possibly, an intermediate) was also observed. We realized that if we identify the structure of this compound, it would provide some insights into understanding the reaction mechanism. However, unfortunately, we were unable to isolate this compound in pure form. But, the ^{1}H NMR analysis of the crude reaction mixture

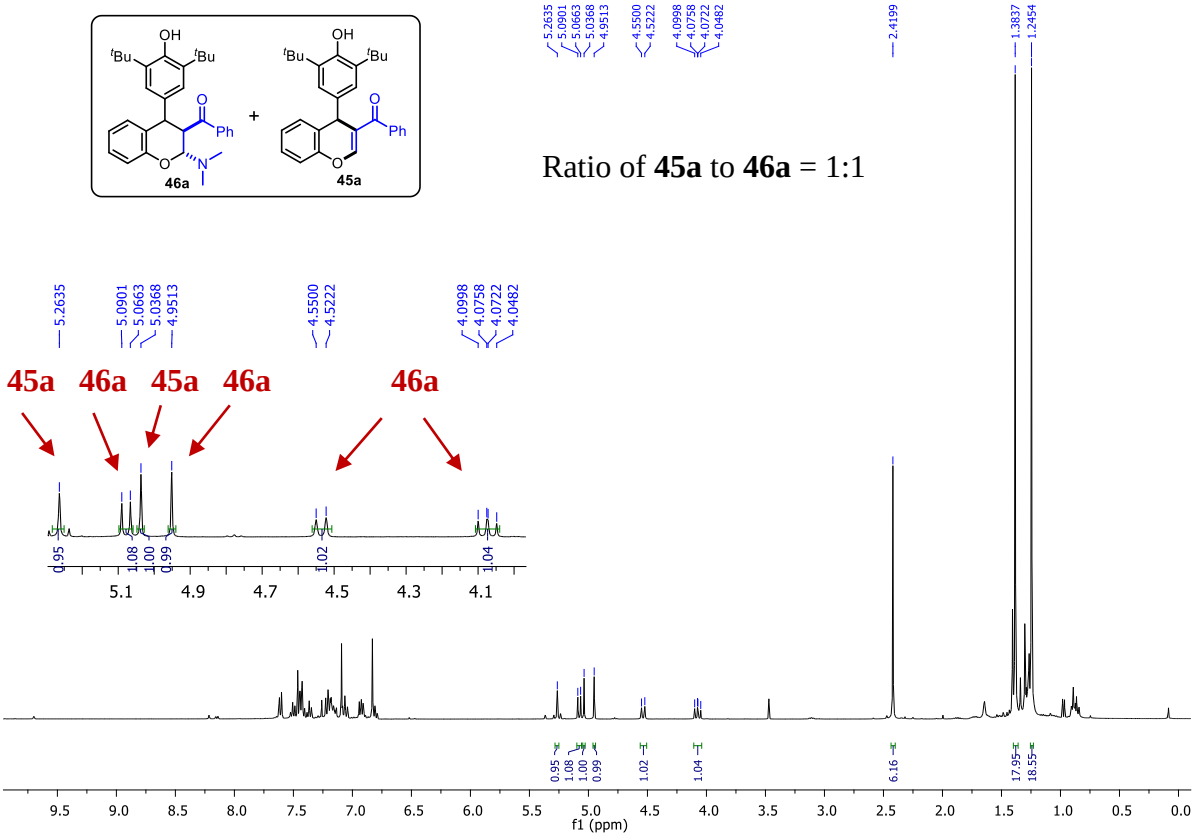
Scheme 10. Substrate scope with various enaminones and *p*-QMs.[a]



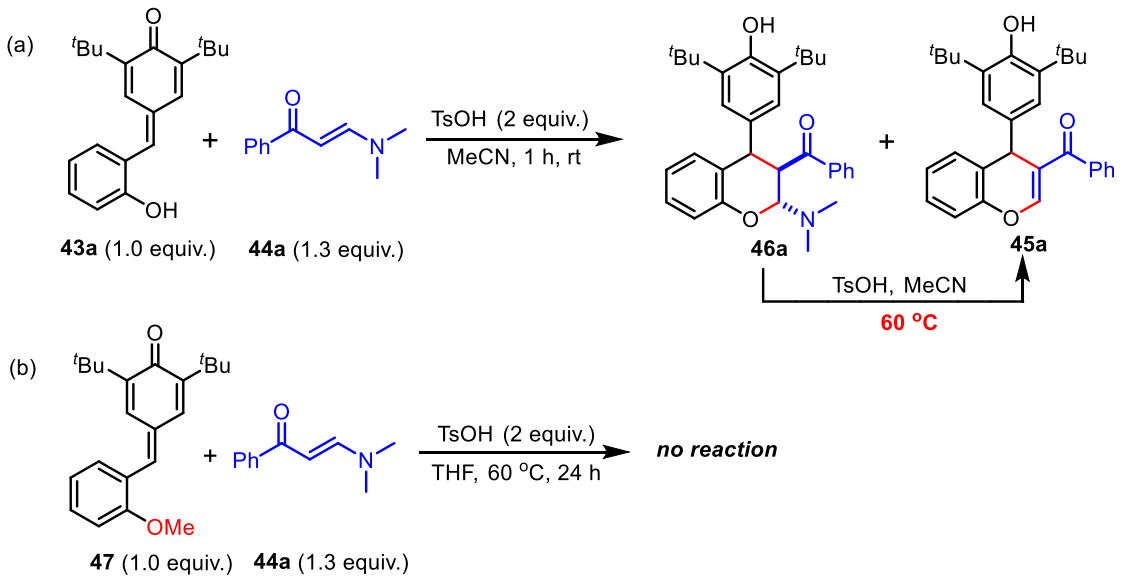
[a]All reactions were carried out with 30 mg scale of **43a-f** in 1.5 mL of THF. Yields reported are isolated yields.

revealed that the compound was actually a chromane derivative **46a**, in which the -acyl and -NMe_2 groups were *trans* to each other (please see crude ^{1}H NMR spectrum below). When the mixture (**46a** and **45a**) was treated with TsOH at room temperature in MeCN, no conversion

^{1}H crude NMR (400 MHz, $CDCl_3$) Spectrum of **45a + 46a**



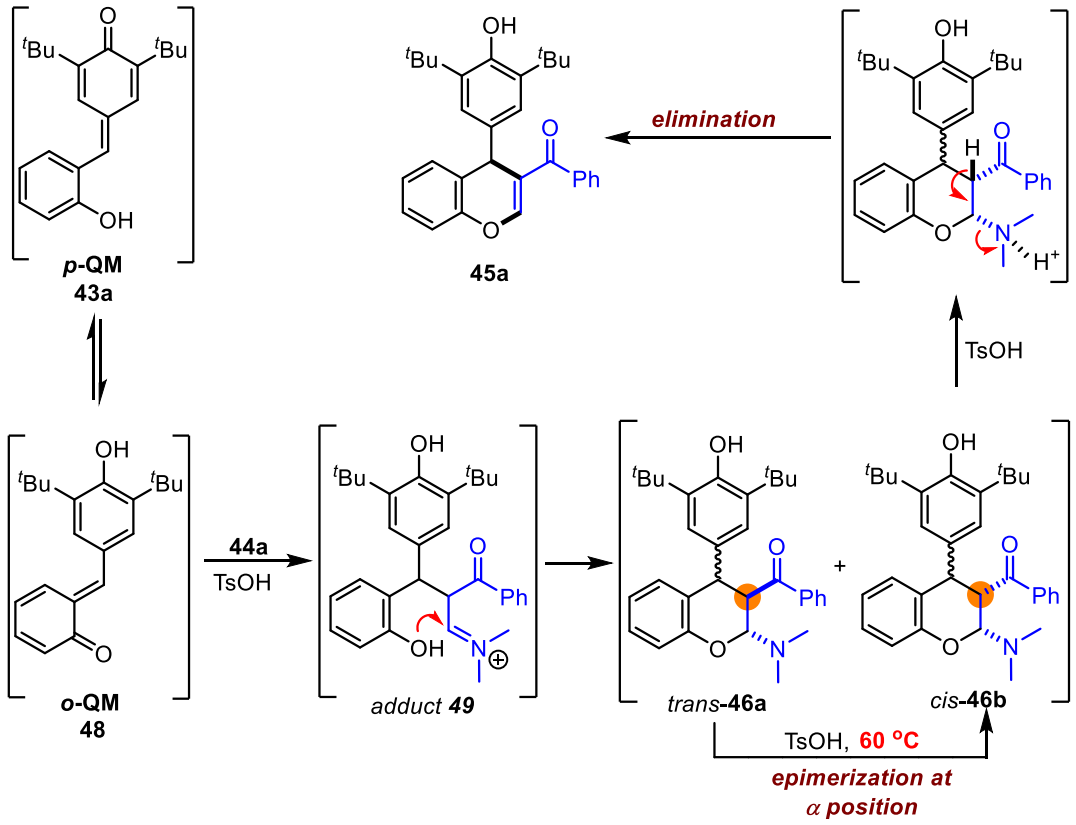
of **46a** to **45a** was observed. However, interestingly, when the reaction temperature was increased to 60 °C, **46a** was completely converted to **45a** within 5 h in THF (Scheme 11, **a**). In another experiment, 2-methoxyphenyl-substituted *p*-QM **47** was treated with **44a**, under the standard reaction conditions. However, interestingly, no reaction was observed even after 24 h



Scheme 11. Control experiments for mechanistic investigation

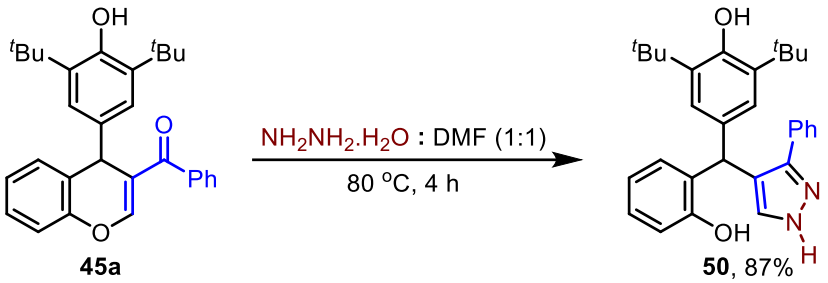
and the starting material remained as such (Scheme 11, **b**). This experiment clearly shows that reaction is probably going *via in situ* generations of *o*-quinone methide from **43a**.

Based on the above-mentioned observations and control experiments, a plausible mechanism for the formation of 4H-chromene **45a** has been proposed (Scheme 12). Initially, *p*-QM **43a** undergoes isomerization to *o*-QM **48**, which then undergoes 1,4-conjugate addition with enaminone **44a** to generate an adduct **49**. Then adduct **49** undergoes an intramolecular cyclization to give both *trans*- and *cis*-isomers of chromene (**46a** & **46b**). The *cis*-isomer **46b**, in which the α-hydrogen is suitably positioned (*anti*-periplanar to -NMe_2 group), once formed, immediately undergoes an acid-mediated elimination to generate the product **45a**. However, the *trans*-isomer **46a** doesn't undergo elimination as the α-hydrogen in **46a** is *syn*-periplanar to the -NMe_2 group. When the reaction temperature is raised to 60 ^{o}C, we believe that acid-mediated epimerization takes place at the α-position and, as a result, **46a** gets slowly converted into **46b**, which subsequently undergoes elimination to give the product **45a** (Scheme 12).



Scheme 12. Proposed mechanism of formation of 4H-chromene **45a**

Next, to show the practical applications of this transformation, one of the 4H-chromene derivatives, **45a** was treated with hydrazine hydrate at 80 ^{o}C to give a pyrazole derivative **50** in 87% yield (Scheme 13).



Scheme 13. Synthetic elaboration of **45a**

4.5 Conclusions

In conclusion, we have successfully demonstrated a Brønsted acid-mediated approach for the synthesis of 4H-chromenes through a 1,6-conjugate addition of *N*,*N*-dimethyl enaminones to *p*-QMs followed by intramolecular cyclization/elimination sequence. Since 4H-chromenes are considered as one of the privileged class of compounds in drug discovery, we believe the developed methodology would definitely be useful for the synthesis of those drugs and related natural products.

4.6 Experimental section

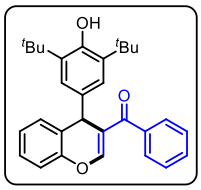
General information. All reactions were carried out under an argon atmosphere in an oven-dried round bottom flask. All the solvents were distilled before use and stored under an argon atmosphere. Most of the reagents and starting materials were purchased from commercial sources and used as such. *N*,*N*-dimethyl enaminones were prepared according to the literature procedure.[23] 2-hydroxyphenyl-substituted *p*-quinone methides were prepared by following a literature procedure.[19] Melting points were recorded on the SMP20 melting point apparatus and are uncorrected. ^{1}H, ^{13}C, and ^{19}F spectra were recorded in $CDCl_3$ and DMSO (400, 100, and 376 MHz, respectively) on Bruker FT–NMR spectrometer. Chemical shift (δ) values are reported in parts per million relatives to TMS, and the coupling constants (*J*) are reported in Hz. High-resolution mass spectra were recorded on Waters Q-TOF Premier–HAB213 spectrometer. FT-IR spectra were recorded on a Perkin-Elmer FTIR spectrometer. Thin-layer chromatography was performed on Merck silica gel 60 F_{254} TLC pellets and visualized by UV irradiation and $KMnO_4$ stain. Column chromatography was carried out through silica gel (100–200 mesh) using EtOAc/hexane as eluent.

General procedure for the synthesis of 4H-Chromenes :

Anhydrous THF (2.0 mL) was added to a mixture of 2-hydroxyphenyl-substituted *p*-QM (30 mg, 1.3 equiv.), *N, N*-Dimethyl enaminone (1.0 equiv.) and TsOH (2.0 equiv.) under argon

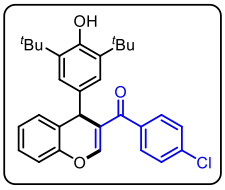
atmosphere, and the resulting suspension was stirred at 60 °C for 5 hours. After the reaction was complete (based on TLC analysis), the residue was then concentrated under reduced pressure and then purified through a silica gel column using EtOAc/Hexane mixture as an eluent to get the pure product.

(4-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-4H-chromen-3-yl)(phenyl)methanone (45a): The



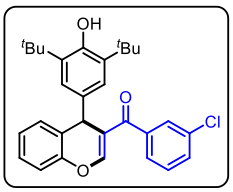
reaction was performed at 0.097 mmol scale of **43a**; white solid (27.8 mg, 85% yield); R_f = 0.4 (10% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 – 7.60 (m, 2H), 7.52 – 7.48 (m, 1H), 7.46 (s, 1H), 7.44 – 7.41 (m, 2H), 7.20 – 7.15 (m, 2H), 7.09 (s, 2H), 7.08 – 7.04 (m, 2H), 5.27 (s, 1H), 5.04 (s, 1H), 1.39 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.9, 153.4, 152.5, 149.3, 138.9, 136.4, 135.8, 131.7, 130.4, 128.9, 128.4, 127.6, 125.2, 125.1, 124.6, 120.0, 116.5, 39.0, 34.4, 30.4; FT-IR (thin film, neat): 3636, 2958, 1633, 1224, 700 cm^{-1}; HRMS (APCI): *m/z* calcd for $C_{30}H_{32}NaO_3$ $[M+Na]^+$: 463.2249; found : 463.2246.

(4-chlorophenyl)(4-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-4H-chromen-3-yl)methanone (45b): The reaction was performed at 0.097 mmol scale of **43a**; white solid (33.0 mg, 91%



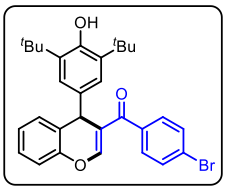
yield); R_f = 0.4 (10% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 – 7.53 (m, 2H), 7.42 (s, 1H), 7.41 – 7.39 (m, 2H), 7.20 – 7.16 (m, 2H), 7.09 – 7.04 (m, 4H), 5.23 (s, 1H), 5.04 (s, 1H), 1.37 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.7, 153.2, 152.6, 149.3, 138.0, 137.2, 136.3, 135.8, 130.4, 130.3, 128.8, 127.7, 125.3, 124.9, 124.6, 119.9, 116.6, 39.0, 34.4, 30.4; FT-IR (thin film, neat): 3635, 2957, 1630, 1223, 729 cm^{-1}; HRMS (APCI): *m/z* calcd for $C_{30}H_{31}ClNaO_3$ $[M+Na]^+$: 497.1859; found : 497.1855.

(3-chlorophenyl)(4-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-4H-chromen-3-yl)methanone (45c): The reaction was performed at 0.097 mmol scale of **43a**; white solid (28.8 mg, 81%

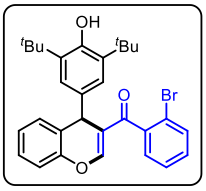


yield); R_f = 0.4 (10% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 – 7.55 (m, 1H), 7.48 – 7.46 (m, 2H), 7.44 (s, 1H), 7.38 – 7.34 (m, 1H), 7.20 – 7.16 (m, 2H), 7.09 – 7.05 (m, 4H), 5.22 (s, 1H), 5.05 (s, 1H), 1.38 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.4, 153.5, 152.6, 149.2, 140.6, 136.2, 135.9, 134.6, 131.6, 130.4, 129.8, 128.9, 127.7, 126.9, 125.4, 124.9, 124.6, 119.9, 116.6, 39.0, 38.9, 34.4, 30.4; FT-IR (thin film, neat): 3635, 2959, 1652, 1223, 715 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{30}H_{31}ClNaO_3$ $[M+Na]^+$: 497.1859; found : 497.1850.

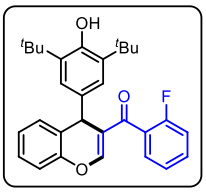
(4-bromophenyl)(4-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-4H-chromen-3-yl)methanone (45d): The reaction was performed at 0.097 mmol scale of **43a**; white solid (30.0 mg, 78% yield); R_f = 0.4 (10% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 – 7.55 (m, 2H), 7.49 – 7.46 (m, 2H), 7.43 (s, 1H), 7.20 – 7.16 (m, 2H), 7.09 – 7.04 (m, 4H), 5.23 (s, 1H), 5.05 (s, 1H), 1.38 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.8, 153.2, 152.6, 149.2, 137.6, 136.2, 135.8, 131.7, 130.43, 130.40, 126.7, 126.5, 125.3, 124.9, 124.6, 119.9, 116.6, 39.0, 38.9, 34.4, 30.4; FT-IR (thin film, neat): 3635, 2958, 1632, 1224, 688 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{30}H_{31}BrNaO_3$ $[M+Na]^+$: 541.1354; found : 541.1342.



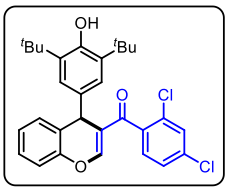
(2-bromophenyl)(4-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-4H-chromen-3-yl)methanone (45e): The reaction was performed at 0.097 mmol scale of **43a**; white solid (31.8 mg, 82% yield); R_f = 0.4 (10% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, *J* = 7.9 Hz, 1H), 7.32 (t, *J* = 7.3 Hz, 1H), 7.28 – 7.24 (m, 2H), 7.21 – 7.18 (m, 2H), 7.16 – 7.13 (m, 1H), 7.09 (d, *J* = 7.4 Hz, 1H), 7.06 – 7.05 (m, 3H), 5.18 (s, 1H), 5.05 (s, 1H), 1.38 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.8, 155.6, 152.5, 149.4, 140.5, 136.0, 135.6, 133.3, 130.8, 130.5, 128.6, 127.7, 127.2, 125.6, 125.0, 124.8, 120.7, 119.6, 116.6, 38.5, 34.4, 30.4; FT-IR (thin film, neat): 3637, 2959, 1657, 1223, 750 cm^{-1}; HRMS (APCI): *m/z* calcd for $C_{30}H_{31}BrNaO_3$ $[M+Na]^+$: 541.1354; found : 541.1371.



(4-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-4H-chromen-3-yl)(2-fluorophenyl)methanone (45f): The reaction was performed at 0.097 mmol scale of **43a**; white solid (26.1 mg, 76% yield); R_f = 0.4 (10% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (d, *J* = 2.0 Hz, 1H), 7.45 – 7.40 (m, 1H), 7.32 (td, *J* = 7.5, 1.8 Hz, 1H), 7.21 – 7.18 (m, 2H), 7.16 – 7.13 (m, 1H), 7.10 – 7.03 (m, 5H), 5.19 (s, 1H), 5.04 (s, 1H), 1.39 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.0, 159.5 (d, $J_{C\text{-}F}$ = 249.0 Hz), 155.1 (d, $J_{C\text{-}F}$ = 2.1 Hz), 152.6, 149.2, 136.2, 135.7, 132.3 (d, $J_{C\text{-}F}$ = 8.0 Hz), 130.4, 130.1 (d, $J_{C\text{-}F}$ = 3.2 Hz), 127.6, 127.4 (d, $J_{C\text{-}F}$ = 15.8 Hz), 125.4, 125.1, 124.6, 124.4 (d, $J_{C\text{-}F}$ = 3.5 Hz), 121.0 (d, $J_{C\text{-}F}$ = 0.8 Hz), 116.7, 116.3 (d, $J_{C\text{-}F}$ = 21.7 Hz), 38.6 (d, *J* = 1.2 Hz), 34.4, 30.4; ^{19}F NMR (376 MHz, $CDCl_3$) δ –113.76; FT-IR (thin film, neat): 3636, 2957, 1633, 1226, 807 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{30}H_{31}FNaO_3$ $[M+Na]^+$: 481.2155; found : 481.2161.

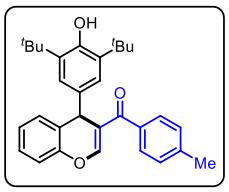


(4-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-4H-chromen-3-yl)(2,4-dichlorophenyl)methanone (45g)*:* The reaction was performed at 0.097 mmol scale of **43a**; white solid (32.0 mg, 84% yield); R_f = 0.4 (10% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (d, *J* = 1.8 Hz,



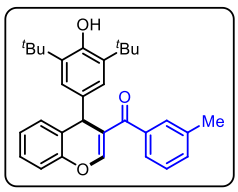
1H), 7.31 (s, 1H), 7.28 – 7.26 (m, 1H), 7.20 – 7.16 (m, 2H), 7.12 – 7.08 (m, 2H), 7.07 – 7.05 (m, 1H), 7.03 (s, 2H), 5.15 (s, 1H), 5.06 (s, 1H), 1.38 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.1, 155.4, 152.6, 149.3, 136.9, 136.2, 136.0, 135.7, 132.2, 130.5, 130.0, 129.6, 127.8, 127.1, 125.6, 124.9, 124.7, 120.8, 116.7, 38.5, 34.4, 30.4; FT-IR (thin film, neat): 3638 2956, 1661, 1224, 786 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{30}H_{30}Cl_2NaO_3$ $[M+H]^+$: 531.1470; found : 531.1475.

(4-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-4H-chromen-3-yl)(*p*-tolyl)methanone (45h)*:* The



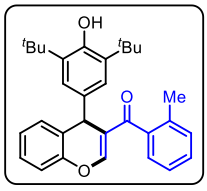
reaction was performed at 0.097 mmol scale of **43a**; white solid (23.8 mg, 71% yield); R_f = 0.4 (10% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54(d, *J* = 8.1 Hz, 2H), 7.45 (s, 1H), 7.23 (d, *J* = 7.8 Hz, 2H), 7.19 – 7.14 (m, 2H), 7.09 (s, 2H), 7.08 – 7.03 (m, 2H), 5.26 (s, 1H), 5.02 (s, 1H), 2.40 (s, 3H), 1.38 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.7, 152.7, 152.5, 149.3, 142.3, 136.4, 136.1, 135.7, 130.4, 129.12, 129.11, 127.5, 125.1, 125.09, 124.6, 119.9, 116.5, 39.1, 39.05, 34.4, 30.4, 21.7, 21.6; FT-IR (thin film, neat): 3636, 2958, 1634, 1223 cm^{-1}; HRMS (APCI): *m/z* calcd for $C_{31}H_{34}NaO_3$ $[M+Na]^+$: 477.2406; found : 477.2417.

(4-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-4H-chromen-3-yl)(*m*-tolyl)methanone (45i)*:* The



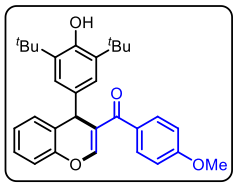
reaction was performed at 0.097 mmol scale of **43a**; white solid (22.2 mg, 65% yield); R_f = 0.4 (10% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (s, 1H), 7.42 – 7.38 (m, 2H), 7.31 – 7.28 (m, 2H), 7.20 – 7.15 (m, 2H), 7.09 (s, 2H), 7.08 – 7.04 (m, 2H), 5.26 (s, 1H), 5.03 (s, 1H), 2.39 (s, 3H), 1.39 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.1, 153.1, 152.5, 149.3, 139.0, 138.3, 136.4, 135.8, 132.4, 130.4, 129.5, 128.3, 127.6, 126.1, 125.15, 125.1, 124.6, 120.0, 116.5, 39.0, 34.4, 30.4, 21.5; FT-IR (thin film, neat): 3635, 2959, 1647, 1224, 751 cm^{-1}; HRMS (APCI): *m/z* calcd for $C_{31}H_{34}NaO_3$ $[M+Na]^+$: 477.2406; found : 477.2410.

(4-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-4H-chromen-3-yl)(*o*-tolyl)methanone (45j)*:* The

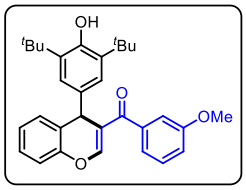


reaction was performed at 0.097 mmol scale of **43a**; white solid (26.8 mg, 80% yield); R_f = 0.4 (10% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 – 7.28 (m, 2H), 7.21 (d, *J* = 7.5 Hz, 2H), 7.18 – 7.15 (m, 3H), 7.09 (dd, *J* = 7.4, 1.1 Hz, 1H), 7.06 – 7.04 (m, 3H), 5.21 (s, 1H), 5.06 (s, 1H), 2.09 (s, 3H), 1.39 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.9, 154.7, 152.5, 149.5, 139.0, 136.4, 135.9, 135.7, 130.8, 130.5, 129.6, 127.7, 127.3, 125.4, 125.3, 125.0, 124.7, 121.6, 116.6, 38.5, 34.4, 30.4, 19.1; FT-IR (thin film, neat): 3626, 2958, 1694, 1225, 755 cm^{-1}; HRMS (APCI): *m/z* calcd for $C_{31}H_{34}NaO_3$ $[M+Na]^+$: 477.2406; found : 477.2417.

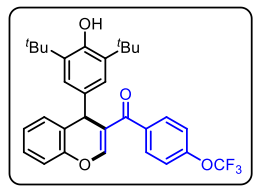
(4-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-4H-chromen-3-yl)(4-methoxyphenyl)methanone (45k)*:* The reaction was performed at 0.097 mmol scale of **43a**; white solid (23.0 mg, 66% yield); R_f = 0.3 (10% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, J = 8.8 Hz, 2H), 7.43 (s, 1H), 7.18 – 7.14 (m, 2H), 7.08 (s, 2H), 7.07 – 7.03 (m, 2H), 6.92 (d, J = 8.8 Hz, 2H), 5.27 (s, 1H), 5.02 (s, 1H), 3.85 (s, 3H), 1.37 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.8, 162.7, 152.5, 151.9, 149.3, 136.4, 135.8, 131.4, 131.2, 130.4, 127.5, 125.1, 125.0, 124.6, 119.7, 116.5, 113.7, 55.6, 55.5, 39.2, 34.4, 30.4; FT-IR (thin film, neat): 3632, 2957, 1633, 1223, 711 cm^{-1}; HRMS (APCI): *m/z* calcd for $C_{31}H_{34}NaO_3$ $[M+Na]^+$: 493.2355; found : 493.2358.



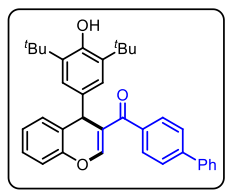
(4-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-4H-chromen-3-yl)(3-methoxyphenyl)methanone (45l)*:* The reaction was performed at 0.097 mmol scale of **43a**; white solid (24.0 mg, 69% yield); R_f = 0.3 (10% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (s, 1H), 7.33 (t, J = 7.8 Hz, 1H), 7.20 – 7.15 (m, 3H), 7.14 – 7.13 (m, 1H), 7.09 (s, 2H), 7.08 – 7.03 (m, 3H), 5.26 (s, 1H), 5.05 (s, 1H), 3.82 (s, 3H), 1.39 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.6, 159.7, 153.4, 152.5, 149.3, 140.2, 136.4, 135.8, 130.4, 129.4, 127.6, 125.2, 125.1, 124.6, 121.3, 119.9, 117.9, 116.5, 113.5, 55.51, 55.5, 39.0, 38.98, 34.4, 30.4; FT-IR (thin film, neat): 3634, 2958, 1633, 1225, 781 cm^{-1}; HRMS (APCI): *m/z* calcd for $C_{31}H_{34}NaO_3$ $[M+Na]^+$: 493.2355; found : 493.2354.



(4-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-4H-chromen-3-yl)(4-(trifluoromethoxy)phenyl)methanone (45m): The reaction was performed at 0.097 mmol scale of **43a**; white solid (21.0 mg, 54% yield); R_f = 0.4 (10% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, J = 8.7 Hz, 2H), 7.44 (s, 1H), 7.28 – 7.26 (m, 2H), 7.20 – 7.17 (m, 2H), 7.09 – 7.05 (m, 4H), 5.24 (s, 1H), 5.04 (s, 1H), 1.38 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.4, 153.4, 152.6, 151.6 (q, $J_{C\text{-}F}$ = 1.9 Hz), 149.3, 137.3, 136.3, 135.9, 130.7, 130.4, 127.7, 125.3, 124.9, 124.6, 120.6, 120.4 (q, $J_{C\text{-}F}$ = 256.9 Hz), 120.0, 116.6, 39.0, 38.9, 34.4, 30.4; ^{19}F NMR (376 MHz, $CDCl_3$) δ –57.67; FT-IR (thin film, neat): 3629, 2922, 1629, 1376, 1259, 740 cm^{-1} HRMS (ESI): *m/z* calcd for $C_{31}H_{30}F_3O_4$ $[M–H]^–$: 523.2096; found : 523.2091.

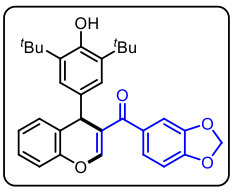


[1,1'-biphenyl]-4-yl(4-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-4H-chromen-3-yl)methanone (45n)*:* The reaction was performed at 0.097 mmol scale of **43a**; white solid (31.0 mg, 80% yield); R_f = 0.3 (10% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 – 7.62 (m, 6H), 7.54 (s, 1H), 7.50 – 7.46 (m, 2H), 7.42



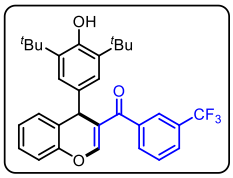
– 7.38 (m, 1H), 7.22 – 7.17 (m, 2H), 7.12 (s, 2H), 7.10 – 7.06 (m, 2H), 5.31 (s, 1H), 5.05 (s, 1H), 1.40 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.5, 153.0, 152.5, 149.3, 144.6, 140.2, 137.6, 136.4, 135.8, 130.4, 129.6, 129.1, 128.2, 127.6, 127.4, 127.2, 125.2, 125.1, 124.6, 120.0, 116.6, 39.1, 34.4, 30.5; FT-IR (thin film, neat): 3636, 2960, 1651, 1223, 750 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{36}H_{36}NaO_3$ $[M+Na]^+$: 539.2562; found : 539.2574.

benzo[*d*][1,3]dioxol-5-yl(4-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-4H-chromen-3-yl)methanone (45o): The reaction was performed at 0.097 mmol scale of **43a**; white solid



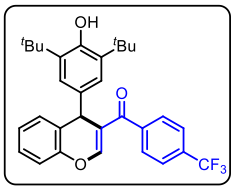
(19.4 mg, 54% yield); R_f = 0.2 (10% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (s, 1H), 7.22 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.18 – 7.14 (m, 3H), 7.07 – 7.03 (m, 4H), 6.82 (d, *J* = 8.0 Hz, 1H), 6.02 (d, *J* = 2.6 Hz, 1H), 5.24 (s, 1H), 5.02 (s, 1H), 1.37 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.3, 152.5, 151.9, 150.9, 149.3, 148.0, 136.3, 135.8, 133.1, 130.4, 127.6, 125.1, 125.0, 124.8, 124.6, 119.7, 116.5, 109.3, 107.9, 101.8, 39.3, 39.2, 34.4, 30.4; FT-IR (thin film, neat): 3633, 2921, 1628, 1262, 740 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{31}H_{31}O_5$ $[M–H]^–$: 483.2171; found : 483.2160.

(4-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-4H-chromen-3-yl)(3-(trifluoromethyl)phenyl)methanone (45p): The reaction was performed at 0.097 mmol scale



of **43a**; white solid (27.8 mg, 73% yield); R_f = 0.4 (10% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (s, 1H), 7.79 – 7.74 (m, 2H), 7.57 (t, *J* = 7.8 Hz, 1H), 7.42 (s, 1H), 7.20 – 7.17 (m, 2H), 7.10 – 7.05 (m, 4H), 5.24 (s, 1H), 5.06 (s, 1H), 1.38 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.5, 153.5, 152.7, 149.2, 139.6, 136.2, 136.0, 132.0, 131.0 (q, J_{C-F} = 32.6 Hz), 130.4, 129.2, 128.2 (q, J_{C-F} = 3.5 Hz), 127.8, 125.7 (q, J_{C-F} = 3.8 Hz), 125.4, 124.8, 124.6, 123.8 (q, J_{C-F} = 270.9 Hz), 120.0, 116.6, 39.0 (d, *J* = 1.3 Hz), 34.4, 30.4; ^{19}F NMR (376 MHz, $CDCl_3$) δ –62.74; FT-IR (thin film, neat): 3638, 2959, 1638, 1227, 756 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{31}H_{31}F_3NaO_3$ $[M+Na]^+$: 531.2123; found : 531.2112.

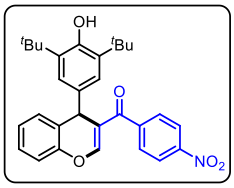
(4-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-4H-chromen-3-yl)(4-(trifluoromethyl)phenyl)methanone (45q): The reaction was performed at 0.097 mmol scale



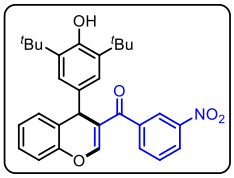
of **43a**; white solid (19.3 mg, 51% yield); R_f = 0.4 (10% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 – 7.66 (m, 4H), 7.43 (s, 1H), 7.20 – 7.17 (m, 2H), 7.10 – 7.06 (m, 4H), 5.23 (s, 1H), 5.06 (s, 1H), 1.38 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.7, 154.0, 152.6, 149.2, 142.1, 136.2, 135.9, 133.1 (q, J_{C-F} = 32.4 Hz), 130.4, 129.0, 127.8, 125.5 (q, J_{C-F} = 3.7 Hz), 124.9, 124.6,

123.8 (q, $J_{C\text{-}F}$ = 270.9 Hz), 120.1, 116.6, 38.9, 38.8, 34.4, 30.4; ^{19}F NMR (376 MHz, $CDCl_3$) δ –62.93; FT-IR (thin film, neat): 3637, 2922, 1634, 1318, 1227, 760 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{31}H_{30}F_3O_3$ $[M–H]^-$: 507.2147; found : 507.2168.

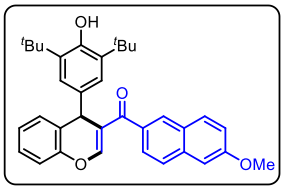
(4-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-4H-chromen-3-yl)(4-nitrophenyl)methanone (45r): The reaction was performed at 0.097 mmol scale of **43a**; white solid (33.8 mg, 93% yield); R_f = 0.2 (10% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (d, *J* = 8.8 Hz, 2H), 7.71 (d, *J* = 8.8 Hz, 2H), 7.42 (s, 1H), 7.22 – 7.18 (m, 2H), 7.11 – 7.07 (m, 2H), 7.06 (s, 2H), 5.22 (s, 1H), 5.08 (s, 1H), 1.39 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.9, 154.4, 152.7, 149.4, 149.2, 144.3, 136.1, 136.0, 130.4, 129.6, 127.9, 125.6, 124.7, 124.6, 123.8, 120.2, 116.6, 38.8, 34.4, 30.4; FT-IR (thin film, neat): 3636, 2959, 1694, 1261, 750 cm^{-1}; HRMS (APCI): *m/z* calcd for $C_{30}H_{31}NNaO_5$ $[M+Na]^+$: 508.2100; found : 508.2089.



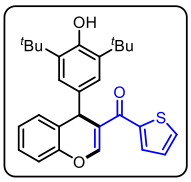
(4-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-4H-chromen-3-yl)(3-nitrophenyl)methanone (45s): The reaction was performed at 0.097 mmol scale of **43a**; white solid (33.1 mg, 91% yield); R_f = 0.2 (10% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41 – 8.40 (m, 1H), 8.37 – 8.34 (m, 1H), 7.91 (d, *J* = 7.7 Hz, 1H), 7.63 (t, *J* = 7.9 Hz, 1H), 7.43 (s, 1H), 7.22 – 7.17 (m, 2H), 7.11 – 7.07 (m, 4H), 5.23 (s, 1H), 5.07 (s, 1H), 1.39 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.4, 153.7, 152.7, 149.1, 148.1, 140.4, 136.05, 136.0, 134.4, 130.4, 129.8, 127.8, 126.1, 125.6, 124.7, 124.6, 123.7, 120.0, 116.7, 39.0, 38.9, 34.4, 30.4; FT-IR (thin film, neat): 3618, 2963, 1630, 1226, 719 cm^{-1}; HRMS (APCI): *m/z* calcd for $C_{30}H_{31}NNaO_5$ $[M+Na]^+$: 508.2100; found : 508.2088.



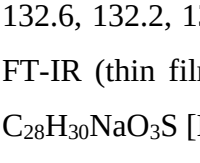
(4-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-4H-chromen-3-yl)(6-methoxynaphthalen-2-yl)methanone (45t): The reaction was performed at 0.097 mmol scale of **43a**; white solid (18.9 mg, 49% yield); R_f = 0.3 (10% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (s, 1H), 7.80 – 7.76 (m, 2H), 7.73 – 7.71 (m, 1H), 7.51 (s, 1H), 7.22 – 7.19 (m, 2H), 7.18 – 7.15 (m, 2H), 7.14 (s, 2H), 7.09 – 7.05 (m, 2H), 5.33 (s, 1H), 5.03 (s, 1H), 3.94 (s, 3H), 1.39 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.7, 159.4, 152.5, 152.4, 149.4, 136.6, 136.4, 135.8, 134.0, 130.7, 130.4, 130.0, 127.8, 127.6, 127.2, 126.1, 125.1 (2C), 124.7, 119.9, 119.8, 116.5, 105.8, 55.6, 55.5, 39.3, 39.2, 34.4, 30.5; FT-IR (thin film, neat): 3634, 2958, 1628, 1223, 739 cm^{-1} HRMS (ESI): *m/z* calcd for $C_{35}H_{35}O_4$ $[M–H]^-$: 519.2535; found : 519.2548.



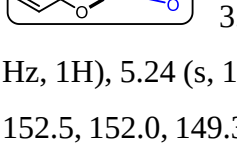
(4-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-4H-chromen-3-yl)(thiophen-2-yl)methanone (40u)*:* The reaction was performed at 0.097 mmol scale of **38a**; white solid (18.2 mg, 55% yield); R_f = 0.3 (10% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74(s, 1H), 7.61 – 7.59 (m, 2H), 7.18 – 7.15 (m, 2H), 7.10 (dd, *J* = 4.8, 3.8 Hz, 1H), 7.07 (s, 2H), 7.06 – 7.04 (m, 2H), 5.25 (s, 1H), 5.02 (s, 1H), 1.36 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 185.8, 152.6, 150.9, 149.2, 143.7, 136.1, 135.8, 132.6, 132.2, 130.3, 127.7, 127.6, 125.1, 125.0, 124.6, 120.0, 116.5, 39.4, 39.37, 34.4, 30.4; FT-IR (thin film, neat): 3631, 2961, 1625, 1242, 750 cm^{-1}; HRMS (APCI): *m/z* calcd for $C_{28}H_{30}NaO_3S$ $[M+Na]^+$: 469.1813; found : 469.1816.



(4-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-4H-chromen-3-yl)(furan-3-yl)methanone (45v): The reaction was performed at 0.097 mmol scale of **43a**; gummy solid (17.3 mg, 54% yield); R_f = 0.3 (10% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (s, 1H), 7.57 – 7.56 (m, 1H), 7.19 – 7.15 (m, 2H), 7.13 (d, *J* = 3.5 Hz, 1H), 7.08 – 7.07 (m, 1H), 7.06 – 7.04 (m, 3H), 6.51 (dd, *J* = 3.5, 1.7 Hz, 1H), 5.24 (s, 1H), 5.02 (s, 1H), 1.36 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.1, 152.8, 152.5, 152.0, 149.3, 145.8, 136.3, 135.7, 130.2, 127.5, 125.2, 125.1, 124.6, 119.4, 117.8, 116.5, 112.0, 38.79, 38.77, 34.4, 30.4; FT-IR (thin film, neat): 3640, 2921, 1634, 1225, 756 cm^{-1}; ; HRMS (ESI): *m/z* calcd for $C_{28}H_{29}O_4$ $[M–H]^–$: 429.2066; found : 429.2052.



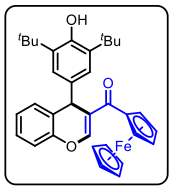
benzofuran-2-yl(4-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-4H-chromen-3-yl)methanone (45w): The reaction was performed at 0.097 mmol scale of **43a**; white solid (28.3 mg, 79% yield); R_f = 0.4 (10% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (s, 1H), 7.69 (d, *J* = 7.8 Hz, 1H), 7.58 (dd, *J* = 8.4, 0.8 Hz, 1H), 7.47 – 7.43 (m, 2H), 7.32 – 7.28 (m, 1H), 7.22 – 7.18 (m, 2H), 7.12 – 7.06 (m, 4H), 5.29 (s, 1H), 5.02 (s, 1H), 1.36 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 181.5, 155.5, 153.0, 152.9, 152.5, 149.3, 136.3, 135.7, 130.3, 127.8, 127.6, 127.0, 125.3, 125.2, 124.7, 124.0, 123.1, 119.9, 116.5, 113.7, 112.4, 38.84, 38.82, 34.4, 30.4; FT-IR (thin film, neat): 3634, 2959, 1628, 1297, 1222, 738 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{32}H_{31}O_4$ $[M–H]^–$: 479.2222; found : 479.2232.



benzo[b]thiophen-2-yl(4-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-4H-chromen-3-yl)methanone (45x): The reaction was performed at 0.097 mmol scale of **43a**; white solid (21.0 mg, 57% yield); R_f = 0.4 (10% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 – 7.85 (m, 2H), 7.83 (s, 1H), 7.82 (s, 1H), 7.45 – 7.39 (m, 2H), 7.21 – 7.17 (m, 2H), 7.10 (s, 2H), 7.09 – 7.06

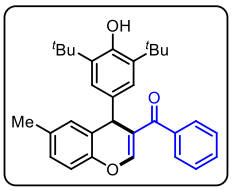
(m, 2H), 5.28 (s, 1H), 5.03 (s, 1H), 1.37 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 187.0, 152.6, 151.5, 149.2, 143.1, 142.0, 138.9, 136.1, 135.8, 130.3, 129.2, 127.7, 127.1, 125.7, 125.2, 125.1, 124.9, 124.6, 122.9, 120.1, 116.6, 39.4, 39.3, 34.4, 30.4; FT-IR (thin film, neat): 3633, 2957, 1627, 1225, 746 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{32}H_{31}O_3S$ $[M–H]^-$: 495.1994; found : 495.2008.

(4-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-4H-chromen-3-yl)(ferrocenyl)methanone (45y):

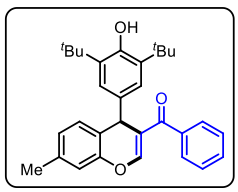


The reaction was performed at 0.097 mmol scale of **43a**; brown gummy solid (13.0 mg, 32% yield); R_f = 0.2 (10% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (s, 1H), 7.17 – 7.10 (m, 4H), 7.05 – 7.00 (m, 2H), 5.25 (s, 1H), 5.03 (s, 1H), 4.98 – 4.97 (m, 1H), 4.57 – 4.56 (m, 1H), 4.47 – 4.46 (m, 1H), 4.38 – 4.37 (m, 1H), 3.76 (s, 5H), 1.40 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.6, 152.7, 149.4, 147.7, 137.0, 135.9, 130.7, 127.4, 125.3 (2C), 124.8, 121.3, 116.4, 79.3, 72.5, 72.1, 71.3, 70.1, 69.0, 39.5, 39.4, 34.4, 30.6; FT-IR (thin film, neat): 3649, 2920, 1637, 1458, 1230, 745 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{34}H_{35}FeO_3$ $[M–H]^-$: 547.1936; found : 547.1943.

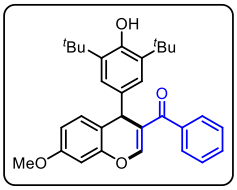
(4-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-6-methyl-4H-chromen-3-yl)(phenyl)methanone (45z)*:* The reaction was performed at 0.092 mmol scale of **43b**; white solid (24.8 mg, 77% yield); R_f = 0.4 (10% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 – 7.58 (m, 2H), 7.50 (t, *J* = 7.4 Hz, 1H), 7.46 (s, 1H), 7.44 – 7.40 (m, 2H), 7.11 (s, 2H), 6.99 – 6.94 (m, 3H), 5.22 (s, 1H), 5.05 (s, 1H), 2.27 (s, 3H), 1.40 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.0, 153.6, 152.5, 147.4, 139.0, 136.5, 135.7, 134.7, 131.6, 130.5, 128.9 (2C), 128.4, 128.3, 124.6, 120.0, 116.3, 39.04, 39.0, 34.4, 30.5, 21.0; FT-IR (thin film, neat): 3638, 2958, 1633, 1211, 749 cm^{-1}; HRMS (APCI): *m/z* calcd for $C_{31}H_{34}NaO_3$ $[M+Na]^+$: 477.2406; found : 477.2412.



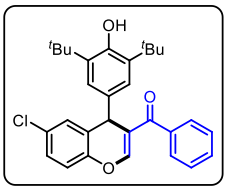
(4-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-7-methyl-4H-chromen-3-yl)(phenyl)methanone (45aa): The reaction was performed at 0.092 mmol scale of **43c**; white solid (24.8.1 mg, 77% yield); R_f = 0.4 (10% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, *J* = 7.4 Hz, 2H), 7.50 (t, *J* = 7.3 Hz, 1H), 7.45 (s, 1H), 7.44 – 7.40 (m, 2H), 7.09 (s, 2H), 7.06 (d, *J* = 7.7 Hz, 1H), 6.89 – 6.86 (m, 2H), 5.21 (s, 1H), 5.02 (s, 1H), 2.31 (s, 3H), 1.38 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.0, 153.5, 152.5, 149.1, 139.0, 137.6, 136.5, 135.7, 131.6, 130.0, 128.9, 128.4, 126.1, 124.5, 122.1, 120.0, 116.8, 38.71, 38.7, 34.4, 30.5, 21.1; FT-IR (thin film, neat): 3632, 2959, 1654, 1223, 749 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{31}H_{34}NaO_3$ $[M+Na]^+$: 477.2406; found : 477.2420.



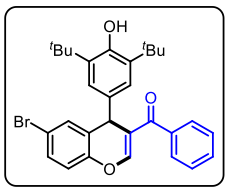
(4-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-7-methyl-4H-chromen-3-yl)(phenyl)methanone (40ab)*:* The reaction was performed at 0.088 mmol scale of **38d**; white solid (21.1 mg, 66% yield); R_f = 0.3 (10% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 – 7.59 (m, 2H), 7.50 (t, *J* = 7.4 Hz, 1H), 7.44 – 7.40 (m, 3H), 7.07 – 7.05 (m, 3H), 6.65 (dd, *J* = 8.5, 2.6 Hz, 1H), 6.58 (d, *J* = 2.5 Hz, 1H), 5.19 (s, 1H), 5.02 (s, 1H), 3.78 (s, 3H), 1.38 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.0, 159.0, 153.1, 152.4, 149.8, 138.9, 136.6, 135.7, 131.7, 131.0, 128.9, 128.4, 124.6, 120.3, 117.2, 111.8, 101.4, 55.6, 55.5, 38.5, 38.4, 34.4, 30.5; FT-IR (thin film, neat): 3635, 2958, 1635, 1205, 735 cm^{-1}; HRMS (APCI): *m/z* calcd for $C_{31}H_{34}NaO_4$ $[M+Na]^+$: 493.2355; found : 493.2356.



(6-chloro-4-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-4H-chromen-3-yl)(phenyl)methanone (45ac)*:* The reaction was performed at 0.087 mmol scale of **43e**; white solid (23.0 mg, 72% yield); R_f = 0.4 (10% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 – 7.58 (m, 2H), 7.51 (t, *J* = 7.4 Hz, 1H), 7.44 – 7.40 (m, 3H), 7.14 – 7.11 (m, 2H), 7.07 (s, 2H), 7.00 (d, *J* = 8.6 Hz, 1H), 5.20 (s, 1H), 5.08 (s, 1H), 1.39 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.6, 152.8, 152.7, 147.9, 138.7, 136.0, 135.7, 131.8, 130.1, 129.9, 128.9, 128.5, 127.8, 126.8, 124.6, 119.6, 118.0, 39.11, 39.1, 34.4, 30.4; FT-IR (thin film, neat): 3635, 2958, 1636, 1226, 739 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{30}H_{31}ClNaO_3$ $[M+Na]^+$: 497.1859; found : 497.1847.

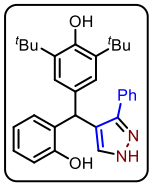


(6-bromo-4-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-4H-chromen-3-yl)(phenyl)methanone (45ad)*:* The reaction was performed at 0.077 mmol scale of **43f**; white solid (21.4 mg, 70% yield); R_f = 0.4 (10% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, *J* = 7.1 Hz, 2H), 7.51 (t, *J* = 7.4 Hz, 1H), 7.44 – 7.40 (m, 3H), 7.28 – 7.26 (m, 2H), 7.05 (s, 2H), 6.94 (d, *J* = 8.9 Hz, 1H), 5.19 (s, 1H), 5.08 (s, 1H), 1.39 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.5, 152.8, 152.7, 148.4, 138.7, 136.0, 135.7 133.0, 131.9, 130.7, 128.5, 128.9, 127.2, 124.6, 119.8, 118.4, 117.5, 39.0, 34.4, 30.4; FT-IR (thin film, neat): 3633, 2958, 1636, 1223, 747 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{30}H_{31}BrNaO_3$ $[M+Na]^+$: 541.1354; found : 541.1339.



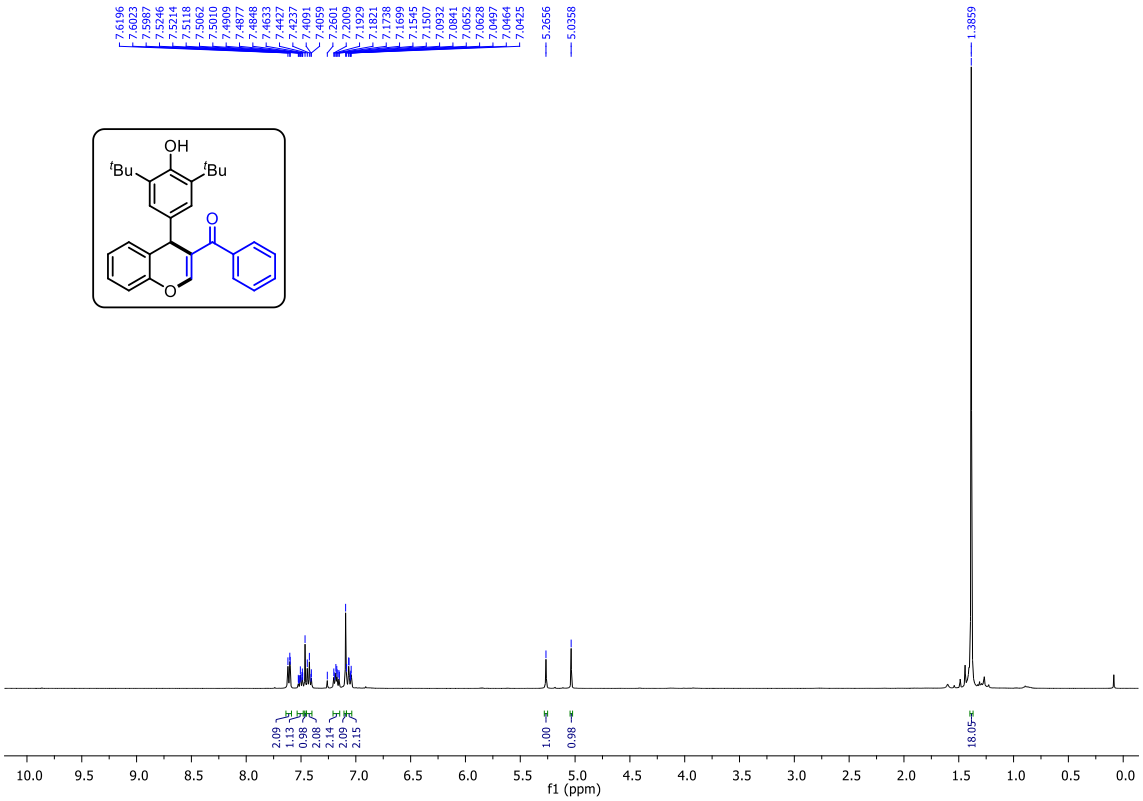
Procedure for the synthesis of hydrazine derivative 50:

To a solution of **45a** (40 mg, 0.091 mmoL) and $NH_2.NH_2.H_2O$ (1 mL), DMF (1 mL) was added, and the reaction mixture was stirred at 80 ^{o}C. After the reaction was complete (based on TLC analysis), H_2O was added to the reaction mixture, the organic layer was extracted with EtOAc (3 x 10 mL) and the combined organic layer was dried over anhydrous sodium sulfate and concentrated under reduced

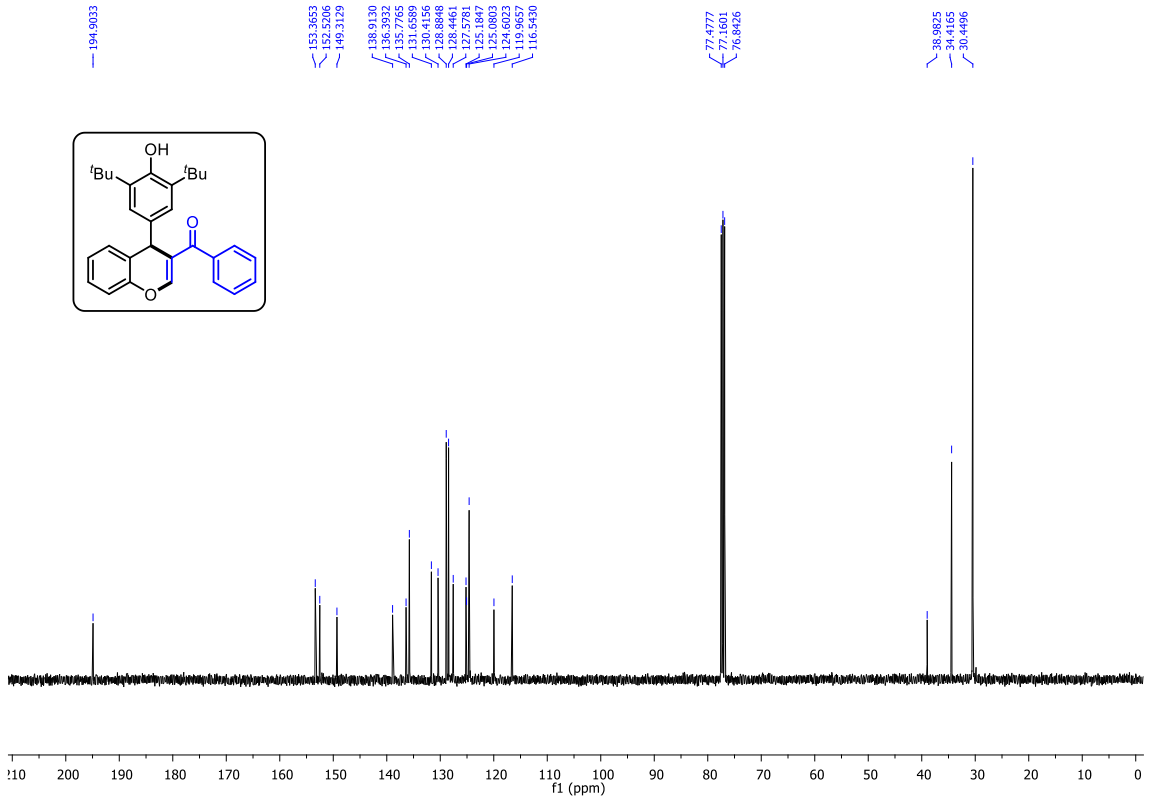


pressure. The residue was then purified through a silica gel column using EtOAc/Hexane mixture as an eluent to get the pure product **50**. (35.9 mg, 87% yield); R_f = 0.2 (50% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 – 7.33 (m, 2H), 7.23 – 7.18 (m, 3H), 7.12 – 7.09 (m, 2H), 6.98 (d, *J* = 7.8 Hz, 1H), 6.96 (s, 2H), 6.84 (d, *J* = 7.5 Hz, 1H), 6.80 (d, *J* = 8.2 Hz, 1H), 5.58 (s, 1H), 1.34 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.6, 152.5, 145.0, 136.1, 135.8, 133.1, 131.5, 131.2, 129.8, 128.6, 128.1, 127.95, 127.9, 125.5, 121.0, 120.7, 116.4, 41.3, 34.5, 30.4; FT-IR (thin film, neat): 3640, 2958, 1610, 1250, 1040 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{30}H_{35}N_2O_2$ $[M+H]^+$: 455.2699; found : 455.2704.

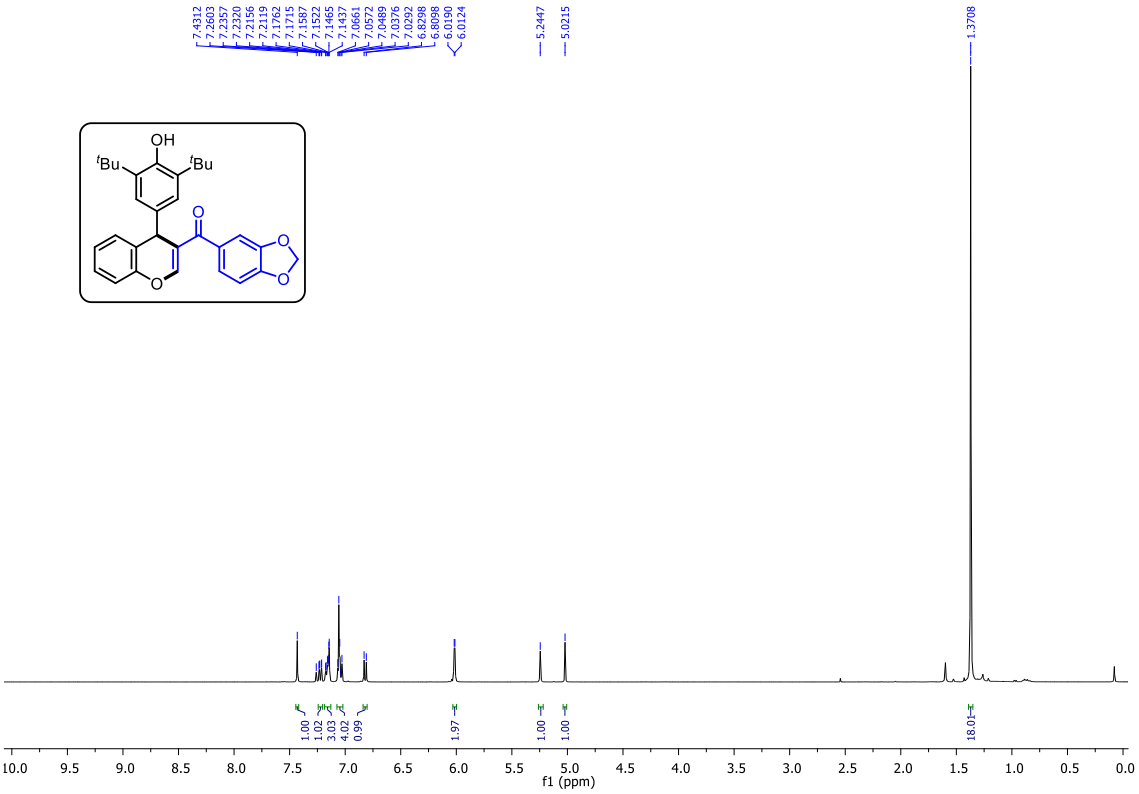
^{1}H NMR (400 MHz, $CDCl_3$) Spectrum of **45a**



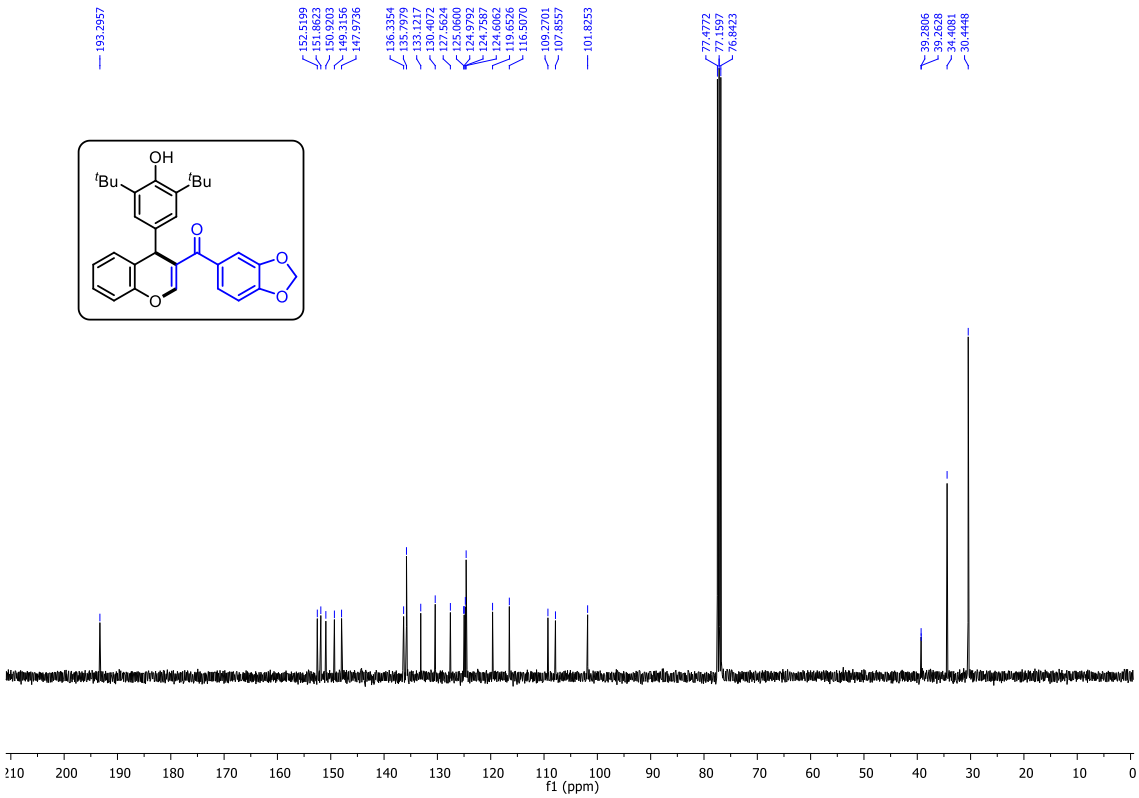
^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) Spectrum of **45a**



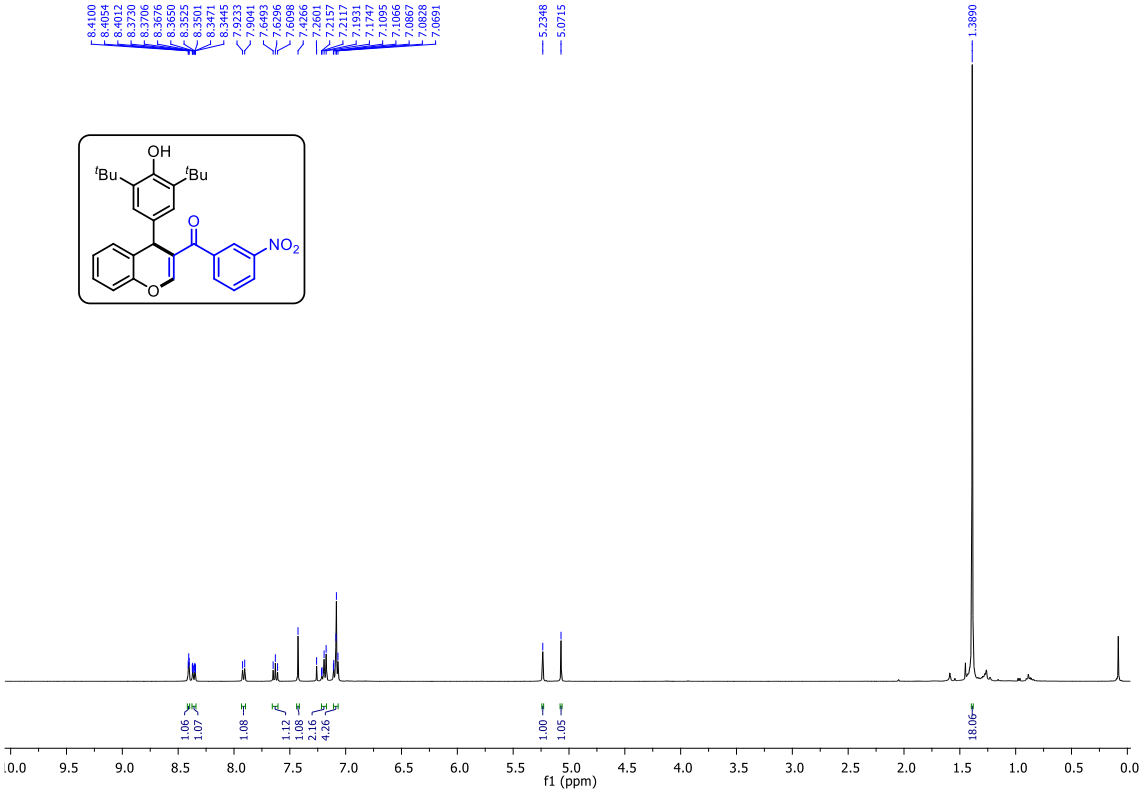
^{1}H NMR (400 MHz, $CDCl_3$) Spectrum of **45o**



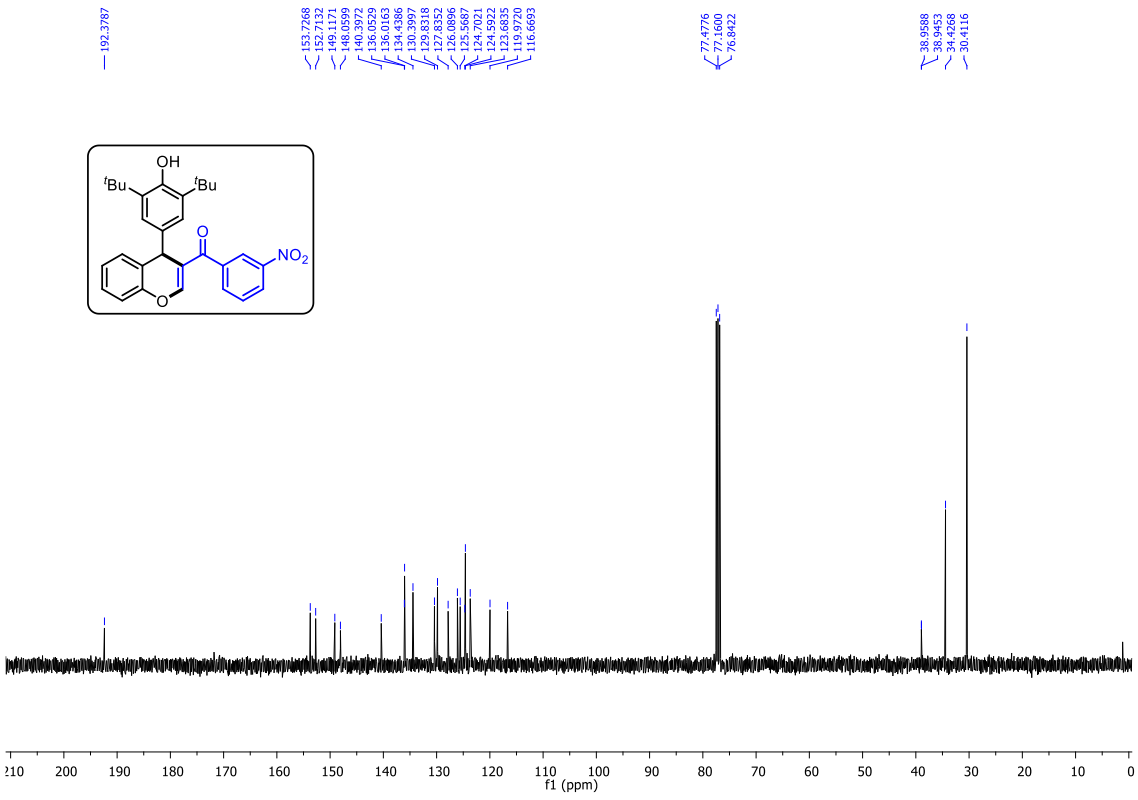
^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) Spectrum of **45o**



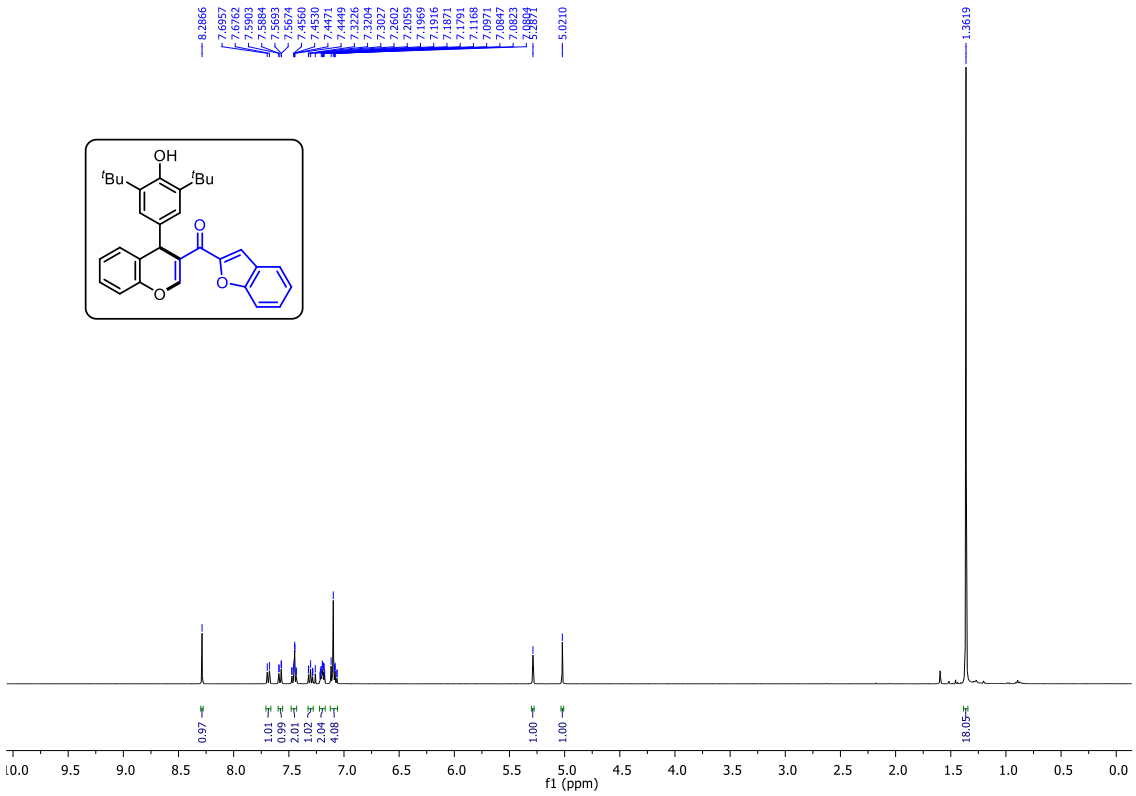
^{1}H NMR (400 MHz, $CDCl_3$) Spectrum of **45s**



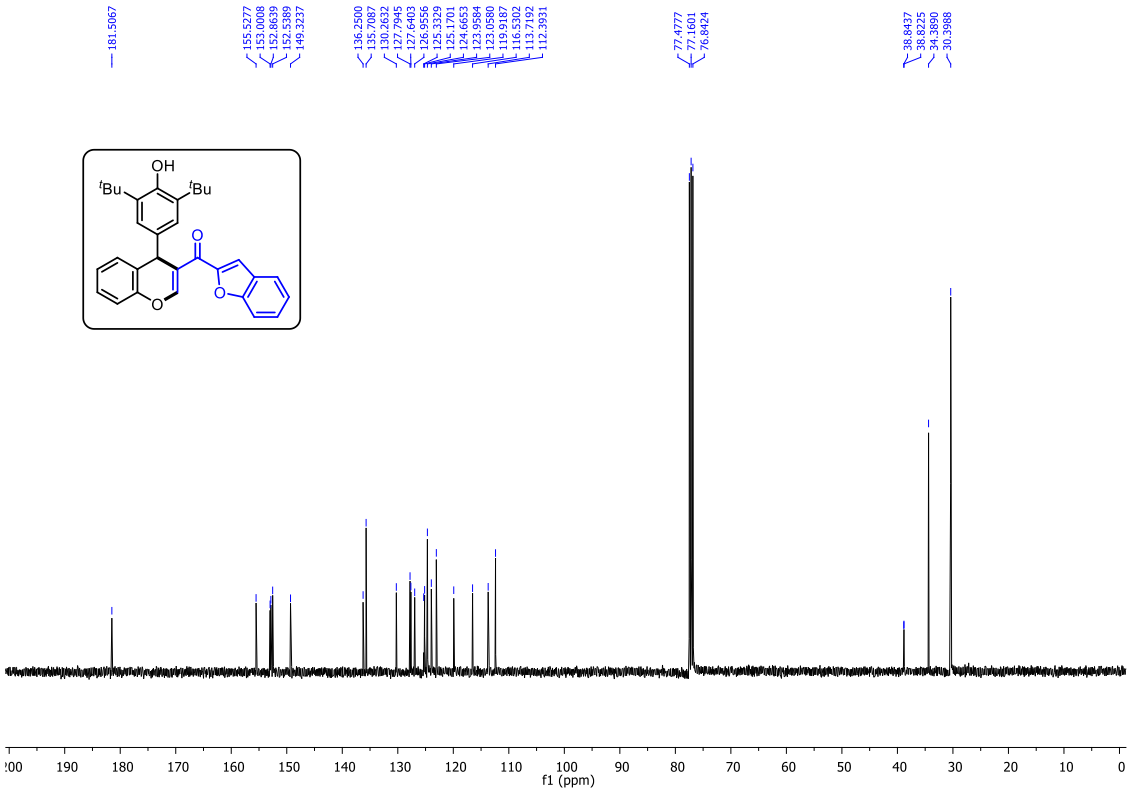
^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) Spectrum of **45s**



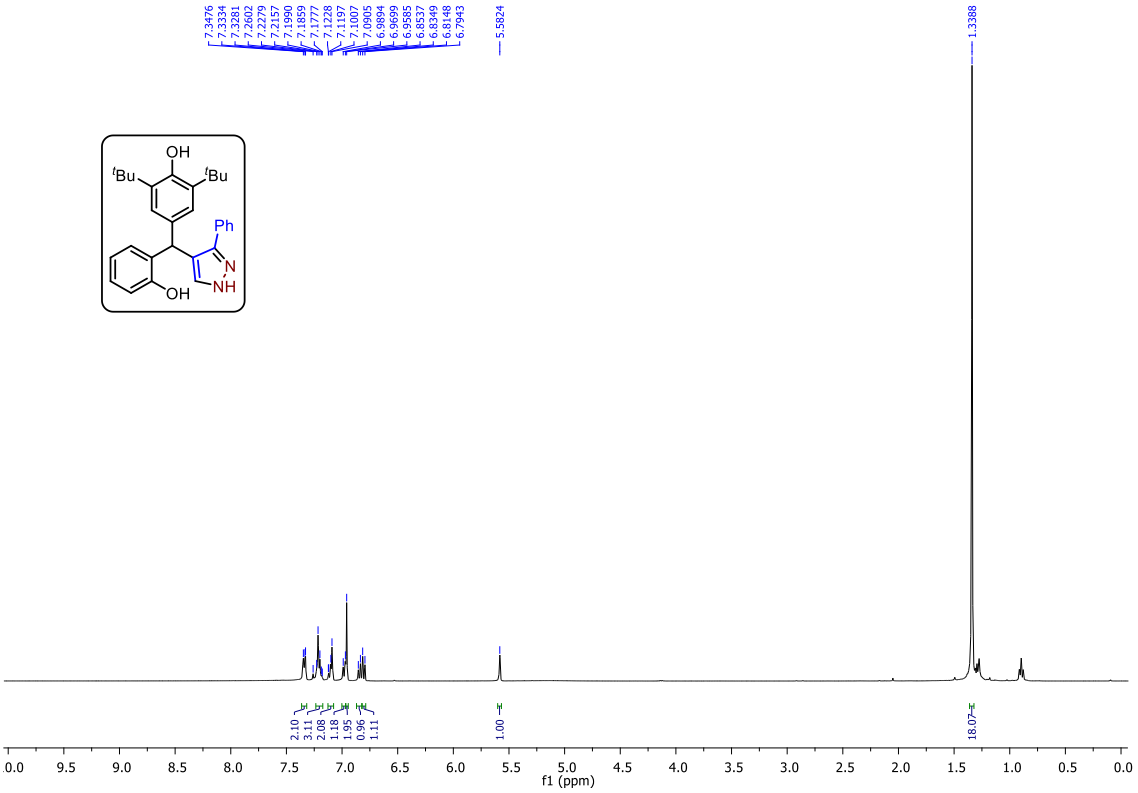
^{1}H NMR (400 MHz, $CDCl_3$) Spectrum of **45w**



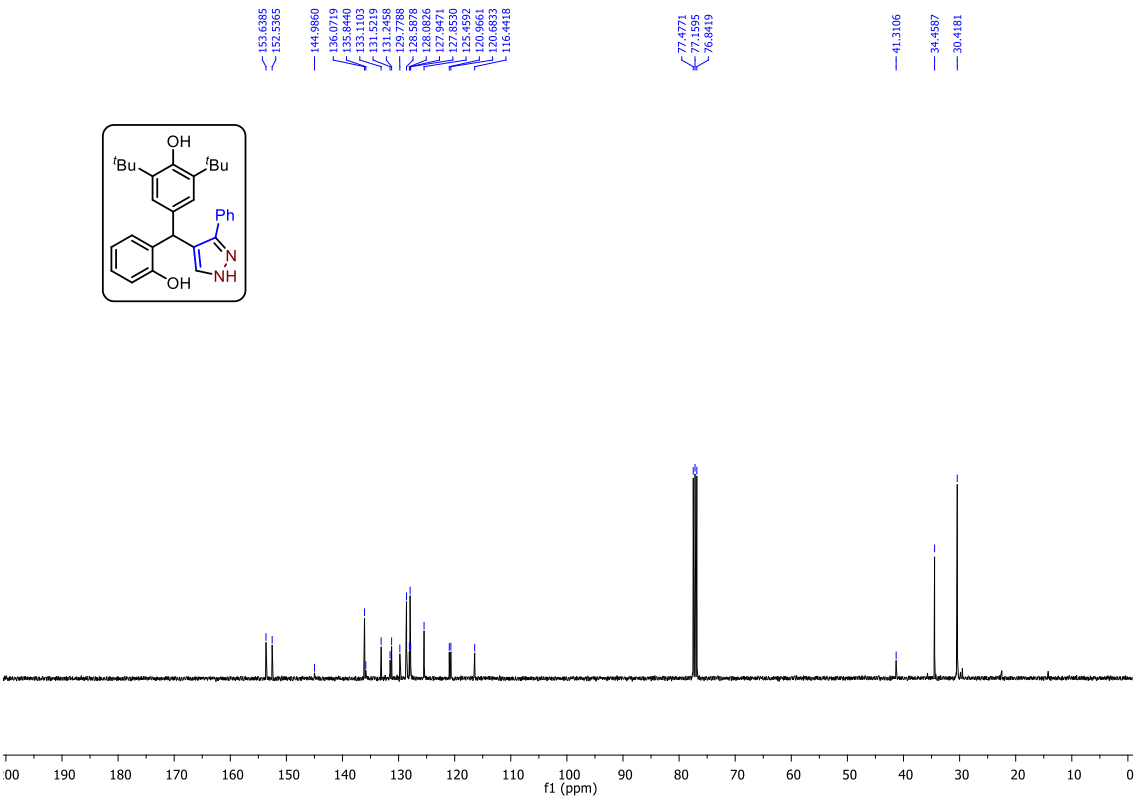
^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) Spectrum of **45w**



^{1}H NMR (400 MHz, $CDCl_3$) Spectrum of **50**



^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) Spectrum of **50**



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Chapter B

1. A formal [3+3]-annulation approach to tetrahydroindolo[2,3-*b*]carbazoles from *para*-quinone methides and 2-indolylmethanol

1.1 Introduction

The dihydroindolocarbazoles, generally known as indolocarbazoles (ICZs), are an interesting class of bis-indole-based heterocycles consisting of a carbazole unit fused with an indole moiety. Depending on the position and orientation of the indole component fused to the benzene ring of the carbazole unit, these compounds are classified into five isomers (Figure 1).[1] The indolocarbazole core is often found as a basic unit in a variety of natural products and biologically active molecules.[2] The structural rigidity and co-planarity make ICZs suitable semiconductor material for OFET (organic field-effect transistors) and OLEDs (organic light-emitting diodes).[3] Moreover, since many ICZs possess high light extinction coefficient, they are used as dyes in DSSCs (dye-sensitized solar cells) and OPVs (organic photovoltaics).[4] These remarkable and widespread applications of ICZs made these compounds attractive in terms of synthetic perspective, and many protocols have been developed to access them in the

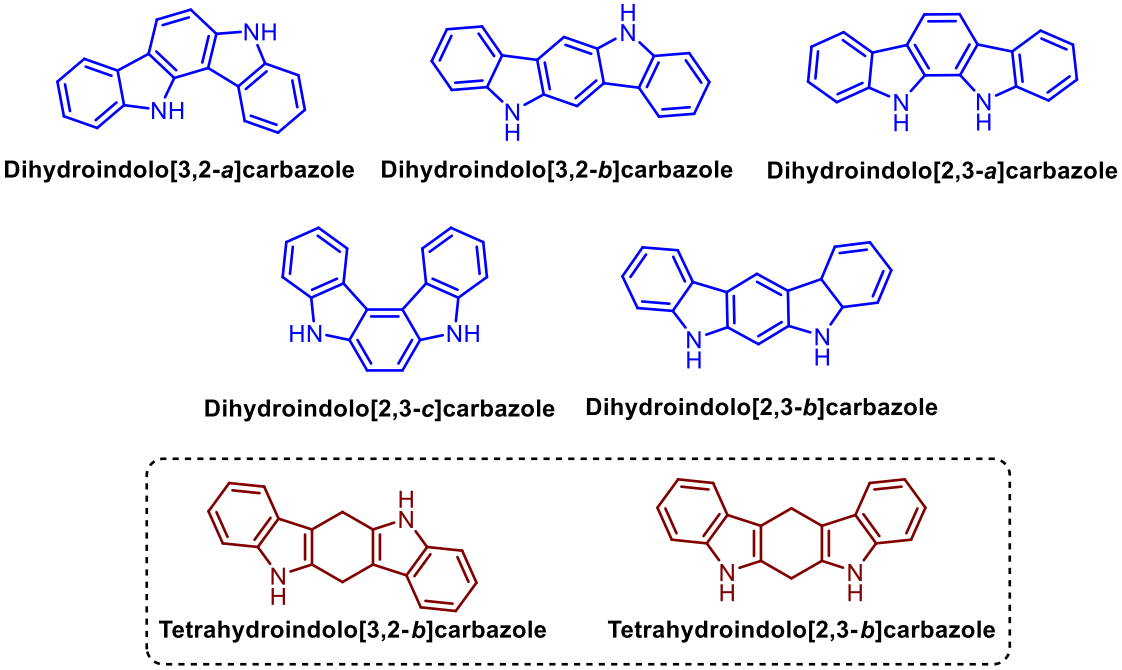


Figure 1. Isomers of dihydro- and tetrahydro-indolocarbazoles

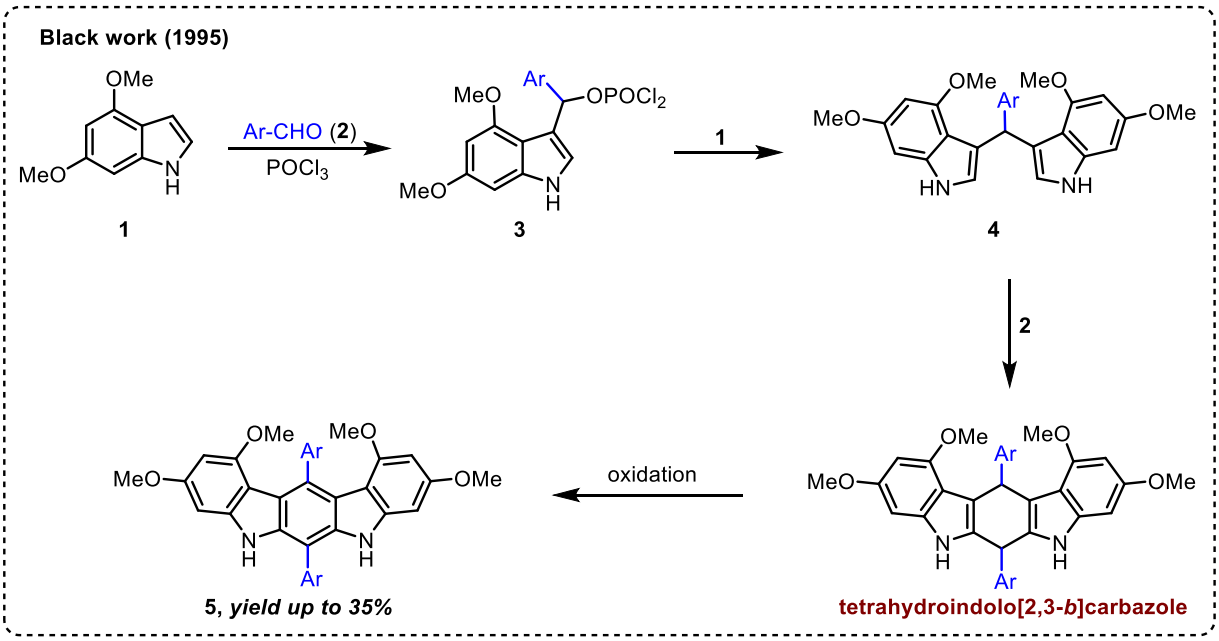
past few decades.[5] Similar to other ICZ isomers, the dihydroindolo[2,3-*b*]carbazoles also possess noteworthy medicinal values[6] and material properties.[7] Therefore, many metal-mediated/catalyzed as well as metal-free general synthetic approaches have been established to access dihydroindolo[2,3-*b*]carbazole core. A few of them are discussed below in more detail.

In 1961, Bearse and co-workers reported the synthesis of indolo[2,3-*b*]carbazole by catalytic dehydrogenation of *N*,*N*-diphenyl-*m*-phenylenediamine in the vapor phase at 500 ^{o}C, and the product was obtained in less than 5% yield.[8]

1.2 Literature reports on the synthesis of indolo[2,3-*b*]carbazole derivatives

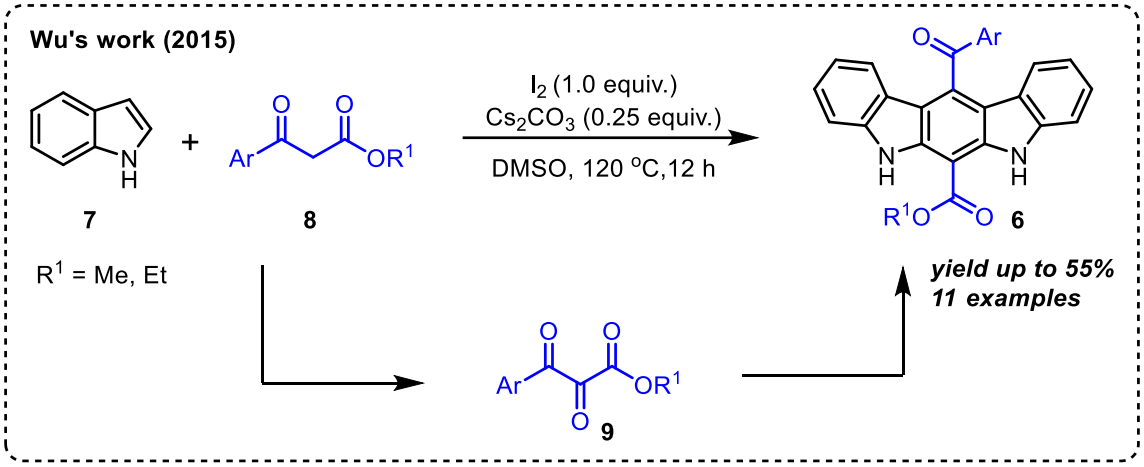
1.2.1 Synthesis of indolo[2,3-*b*]carbazoles with indole and carbonyl compounds

Black and co-workers described the synthesis of dihydroindolo[2,3-*b*]carbazole derivatives (**5**) by the reaction of 4,6-dimethoxyindole **1** and aromatic aldehydes (**2**) in the presence of phosphoryl chloride under refluxing conditions. When indole **1** was reacted with **2**, an intermediate **3** was produced, which further reacted with **1** to generate 3,3'-diindolylmethane **4**. Then, 3,3'-diindolylmethane **4** reacted with aromatic aldehyde **2**, followed by oxidation, gave the dihydroindolo[2,3-*b*]carbazole derivatives (**5**) as the final product (Scheme 1).[9]



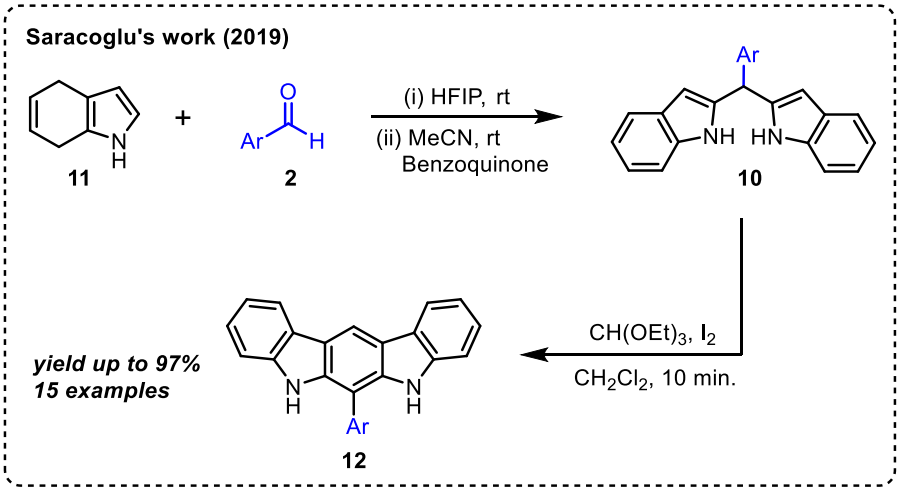
Scheme 1. Synthesis of dihydroindolo[2,3-*b*]carbazole derivatives

Bhuyan and co-workers reported the I_2-catalyzed synthesis of 6,12-disubstituted 5,7-dihydroindolo[2,3-*b*]carbazole derivatives from indole and aldehydes through the 3,3'-bis(indolyl)methanes (BIMs) intermediate.[10] The same group also described the I_2-catalyzed isomerization of 3,3'-bis(indolyl)methane to form indolo[3,2-*b*]carbazoles in refluxing acetonitrile.[11] Later investigation by Dehean and co-workers claimed that the Bhuyan approach does not produce dihydroindolo[2,3-*b*]carbazoles, but indolo[3,2-*b*]carbazoles are produced.[12]



Scheme 2. Iodine-mediated synthesis of indolo[2,3-*b*]carbazole derivatives

In 2015, Wu and co-workers developed the iodine-mediated synthesis of indolo[2,3-*b*]carbazole (**6**) derivatives *via* [2+2+1+1] cyclization of indole (**7**) and *β*-keto esters(**8**). The reaction proceeds through an iodination/Kornblum oxidation of *β*-keto ester to generate an intermediate (**9**) followed by the addition of indole, then hydrolyzation and decarboxylation to generate 3,3'-bis(indolyl)methane which, on further reaction with **9** followed by deacylation, yielded **6** (Scheme 2).[13]

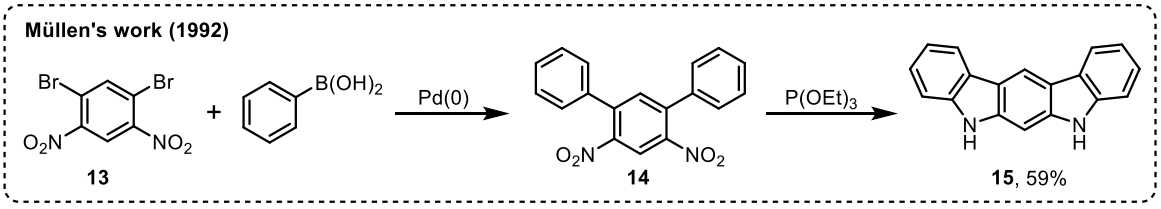


Scheme 3. Synthesis of 5,7-dihydroindolo[2,3-*b*]carbazole derivatives

Recently, Saracoglu and co-workers demonstrated the synthesis of 2,2′-bis(indolyl)arylmethanes (**10**) from 4,7-dihydroindole **11** and aromatic aldehydes (**2**), which on further reaction with triethyl orthoformate in the presence of a catalytic amount of iodine to produce 5,7-dihydroindolo[2,3-*b*]carbazole derivatives (**12**) in good to excellent yields (Scheme 3).[14]

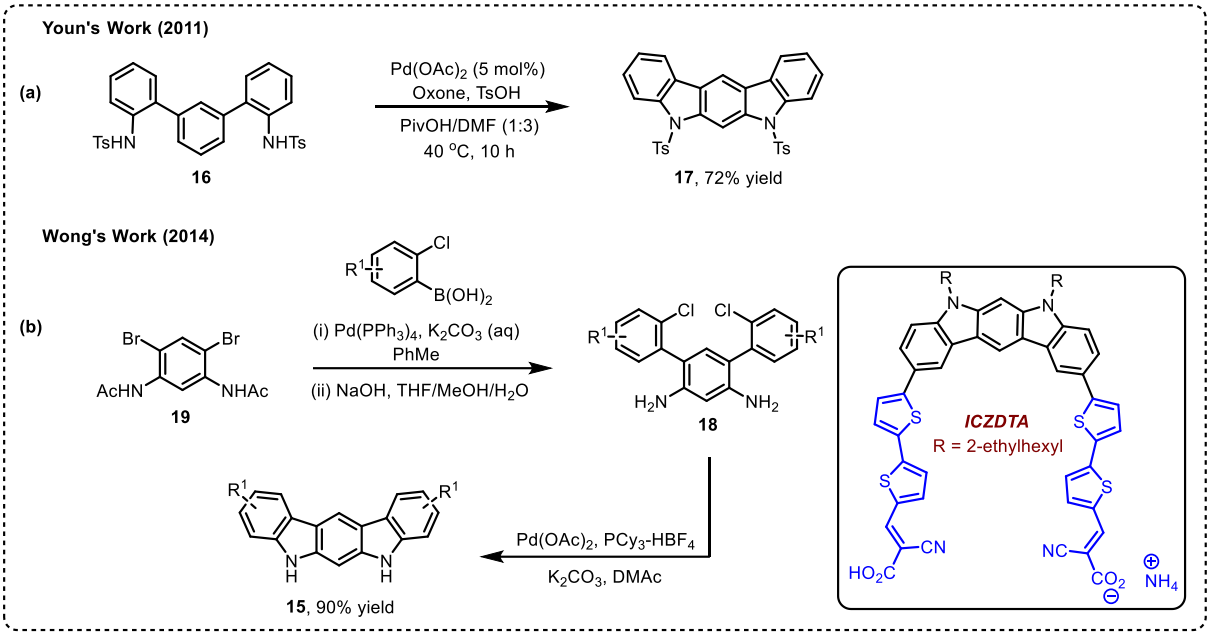
1.2.2 Metal-catalyzed synthesis of indolo[2,3-*b*]carbazole derivatives

In 1992, Müllen and co-workers used the Cadogan carbazole approach to synthesize 5,7-dihydroindolo[2,3-*b*]carbazole derivatives (**15**). In this protocol, dinitrophenyl benzene **14** underwent a double reductive ring-closing reaction with triethyl phosphite to access **15** in 59% yield. The precursor **14** was prepared by Suzuki coupling of phenylboronic acid with 1,3-dibromo-4,6-dinitrobenzene (**13**) in the presence of a Pd(0) catalyst (Scheme 4).[15] Later, Lu[16] and Wu[17] independently reported the synthesis of benzo-fused 5,7-dihydroindolo[2,3-*b*]carbazole derivatives using the Cadogan carbazole approach and found that these compounds have been used extensively in material chemistry as fluorescent sensors to detect vapors of explosives.

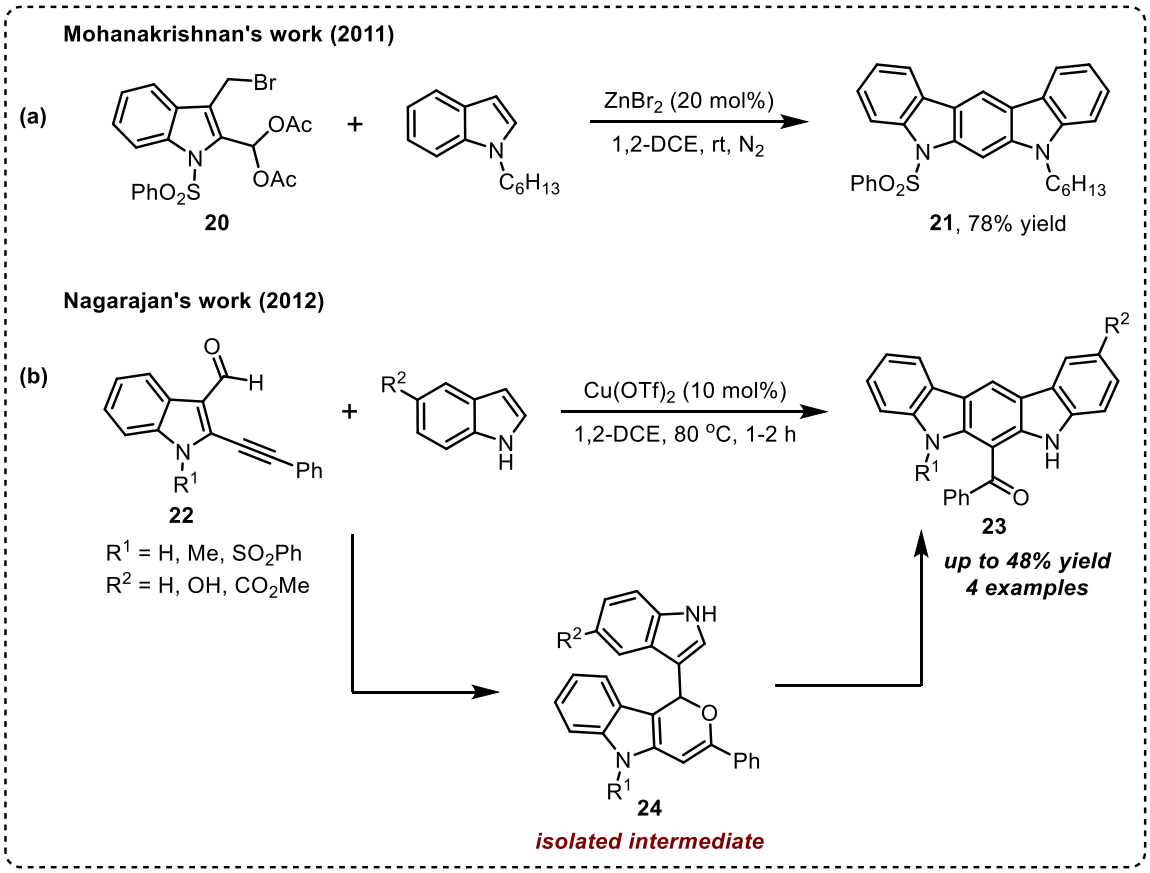


Scheme 4. Cadogan-cyclization for the synthesis of 5,7-dihydroindolo[2,3-*b*]carbazoles

In 2011, Youn and co-workers reported one example of the synthesis of 5,7-dihydroindolo[2,3-*b*]carbazole **17** through an intramolecular Pd-catalyzed double C−H amination reaction of *N*,*N*'-bistosyl-2,2''-diamino-[1,1';3',1'']terphenyl **16** in 72% yield (Scheme 5, **a**).[18] Similarly, the Wong group described a double-intramolecular Buchwald-Hartwig coupling of **18**, which was obtained from a Suzuki coupling of 4,6-dibromo-1,3-phenylenediacetamide (**19**) with 2-(chlorophenyl)boronic acid followed by hydrolysis. This reaction yielded 5,7-dihydroindolo[2,3-*b*]carbazoles (**15**) in a 90% yield. This methodology was extended to develop a new dye (ICZDTA) having two bithiophene groups as the bidentate anchor (Scheme 5, **b**).[19]



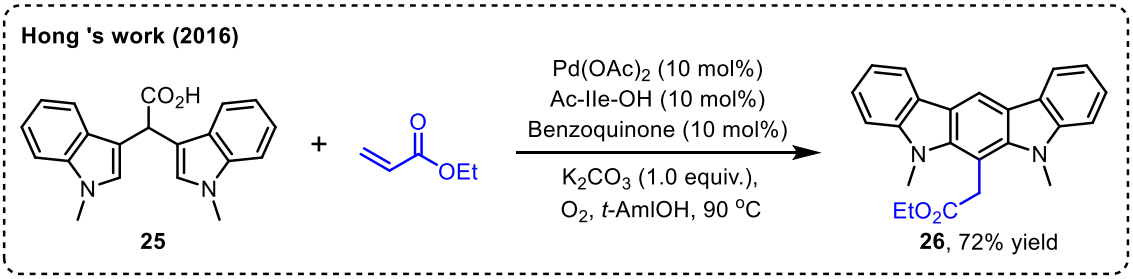
Scheme 5. Buchwald-Hartwig approach for the synthesis of dihydroindolo[2,3-*b*]carbazoles



Scheme 6. Zinc and copper-catalyzed synthesis of dihydroindolo[2,3-*b*]carbazoles

Mohanakrishnan and co-workers reported a $ZnBr_2$-catalyzed reaction of *N*-hexylindole and **20** to access indolo[2,3-*b*]carbazoles (**21**) in a 78% yield. The starting material **20** was obtained from 1-(phenylsulfonyl)-3-methylindole-2-carbaldehyde by acetylation followed by a bromination sequence (Scheme 6, **a**).[20] In line with this, Nagarajan and co-workers established a copper (II) triflate catalyzed hetero-annulation of 2-alkynylcarbazole-3-carboxaldehyde **22** and indole to construct indolo[2,3-*b*]carbazole derivatives (**23**) in moderate yields. A mechanistic study revealed the generation of intermediate **24**, by the reaction of **22** and indole, which then underwent electrocyclization/aromatization to form the desired product (Scheme 6, **b**).[21] Recently, Maiti's group reported the copper (II) catalyzed multi-component reaction of indole, phenyl glyoxal, and 1,3-dicarbonyl compound or their equivalents to construct 5,7-dihydroindolo[2,3-*b*]carbazoles in moderate yields. According to the proposed mechanism, the reaction goes through an intermediate 3,3'-bis(indolyl)methane followed by oxidative cyclization in the presence of DABCO.[22]

In 2016, Hong and co-workers reported one example of the synthesis of 5,7-dihydroindolo[2,3-*b*]carbazole **26** through a Palladium (II) catalyzed annulation of 3,3'-bis(indolyl)methane-based carboxylic acid **25** with ethyl acrylate. The reaction proceeds through a carboxylic acid-directed C-H alkenylation/C-H activation followed by intramolecular C-C bond formation and decarboxylative aromatization sequence (Scheme 7).[23]

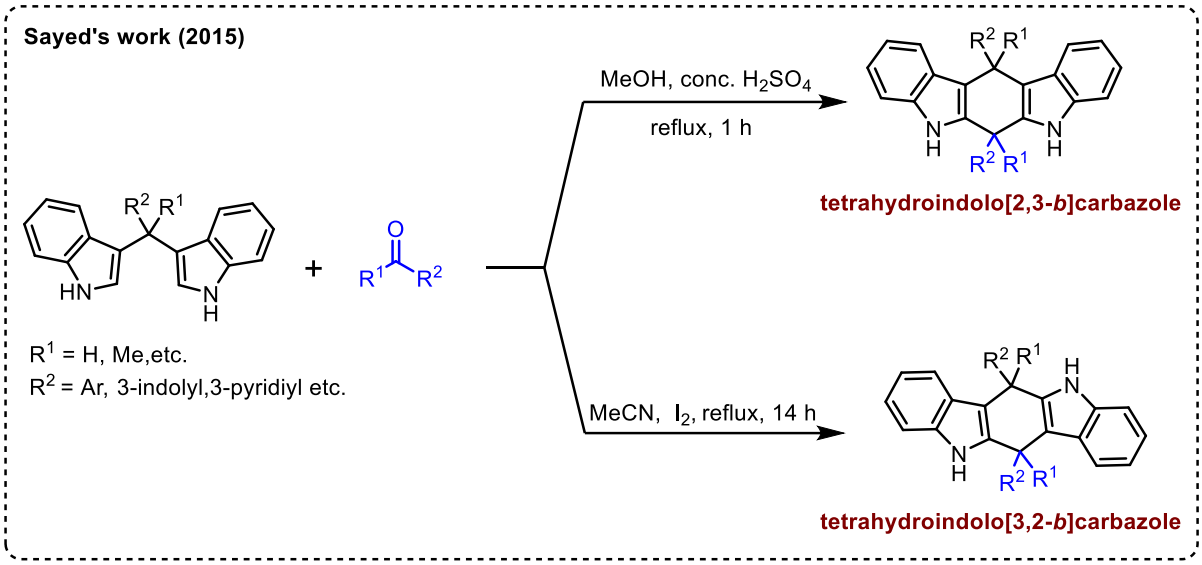


Scheme 7. Palladium-catalyzed synthesis of 5,7-dihydroindolo[2,3-*b*]carbazoles

1.3 Background

Like ICZs, the tetrahydroindolocarbazoles (THICZs) also exist in isomeric forms, and among those, the tetrahydroindolo[3,2-*b*]carbazoles and tetrahydroindolo[2,3-*b*]carbazoles (Figure 1) have been relatively more explored, while considering the pharmaceutical applications of these compounds.[24] In tetrahydroindolocarbazole, the indole unit is fused to tetrahydrocarbazole moiety. Surprisingly, although there are a few methods described for the

synthesis of tetrahydroindolo[3,2-*b*]carbazoles,[25] only one general synthetic procedure (from aldehydes and indoles) is available in the literature for the synthesis of symmetrical tetrahydroindolo[2,3-*b*]carbazoles.[26] Sayed and co-workers synthesized tetrahydroindolo[2,3-*b*]carbazole derivatives by cyclizative condensation of BIMs with carbonyl compounds (aldehydes and ketones) in the presence of H_2SO_4 in MeOH under refluxing conditions.[26] It was observed that a short reaction time was crucial to affording the *cis*-isomer of tetrahydroindolo[2,3-*b*]carbazole derivatives. Under prolonged reaction time in iodine, BIMs undergo Planchar rearrangement, leading to the *trans*-isomer of tetrahydroindolo[3,2-*b*]carbazoles (Scheme 8).



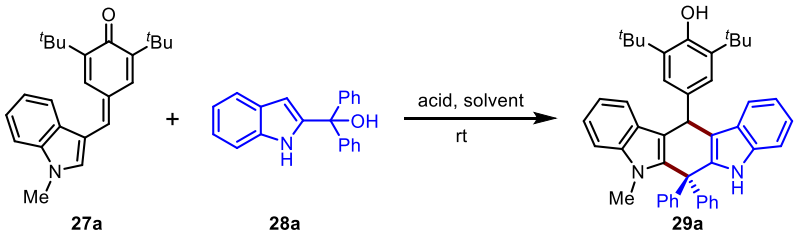
Scheme 8. Synthesis of tetrahydroindolocarbazole derivatives

To the best of our knowledge, no reports have been available for the synthesis of unsymmetrical tetrahydroindolo[2,3-*b*]carbazoles till now. This incited us to think about devising a convenient route to access these compounds. Since our expertise lies in the area of *p*-quinone methide (*p*-QM) chemistry,[27] we thought of utilizing this chemistry for this purpose. Herein, we describe an acid-mediated direct annulation reaction between 3-indolyl-*p*-quinone methides and 2-indolylmethanols[28] leading to a wide range of unsymmetrical tetrahydroindolo[2,3-*b*]carbazoles. This general protocol was elaborated to the synthesis of other heterocyclo-fused tetrahydrocarbazoles and also to the synthesis of enantiomerically-enriched tetrahydroindolo[2,3-*b*]carbazoles using a chiral phosphoric acid as a catalyst.

1.4 Result and discussion

To optimize the reaction conditions, many reactions were carried out with 3-indolyl-substituted *p*-QM **27a** and 2-indolylmethanol **28a** under acidic conditions using various Brønsted acids, and the results are shown in Table 1. In our initial attempt itself, when a catalytic amount of TsOH (20 mol%) was used in the reaction, the desired product **29a** was obtained in a 55% isolated yield within 5 hours at room temperature (entry 1). Increasing the loading of TsOH helped to some extent in improving the yield of **29a** to 64% within an hour (entry 2). Encouraged by this observation, various solvents were screened with 50 mol% of TsOH (entries 3-8); and it was observed that the reaction worked relatively better in acetone as the product **29a** was isolated in 75% yield in that case (entry 8). However, we found that 50 mol% of TsOH was not enough to drive the reaction to completion, as there was no improvement in the yield of **29a** even if the reaction mixture was left to react for a prolonged

Table 1. Optimization studies[a]

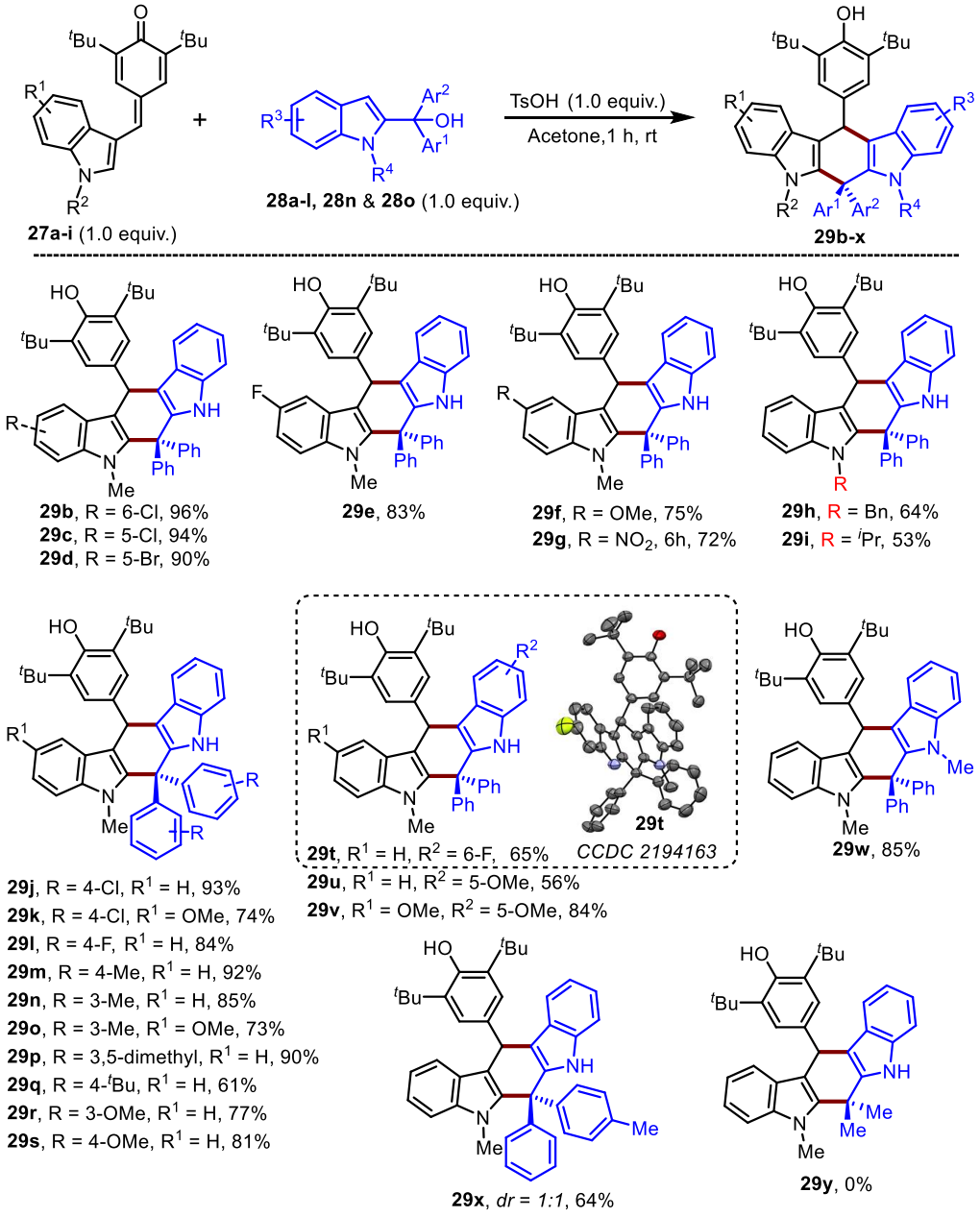


entry	acid	solvent	time [h]	yield (%)
1[b]	TsOH	CH_2Cl_2	5	55
2	TsOH	CH_2Cl_2	1	64
3	TsOH	CH_3CN	1	58
4	TsOH	PhMe	12	50
5	TsOH	THF	12	44
6	TsOH	CCl_4	1	66
7	TsOH	1,2-DCE	1	60
8	TsOH	acetone	1	75
9	TsOH	acetone	12	75
10[c]	**TsOH**	**acetone**	**1**	**90**
11[c]	CSA	acetone	1	72
12[c]	TFA	acetone	1	60
13	-	acetone	24	n.r.

[a]Reaction conditions: All reactions were carried out with **27a** (0.058 mmol), **28a** (0.058 mmol), and 50 mol% of TsOH in 1.5 mL of solvent. [b]20 mol% of TsOH was used. [c]1 equiv. of TsOH was used. The yields reported are isolated yields.

time (entry 9). We realized that an equivalent amount of TsOH with respect to **27a** would help in improving the yield of **29a**, and as expected, the reaction using an equivalent amount of TsOH provided **29a** in a 90% yield within an hour (entry 10). We found other Brønsted acids, such as CSA and TFA, were inferior in driving this transformation when compared to TsOH (entries 11 & 12). No product formation was observed without an acid promotor, which verifies the requirement of an acidic environment for this transformation (entry 13).

Scheme 9. Substrate scope for the synthesis of tetrahydroindolo[2,3-*b*]carbazole derivatives[a]

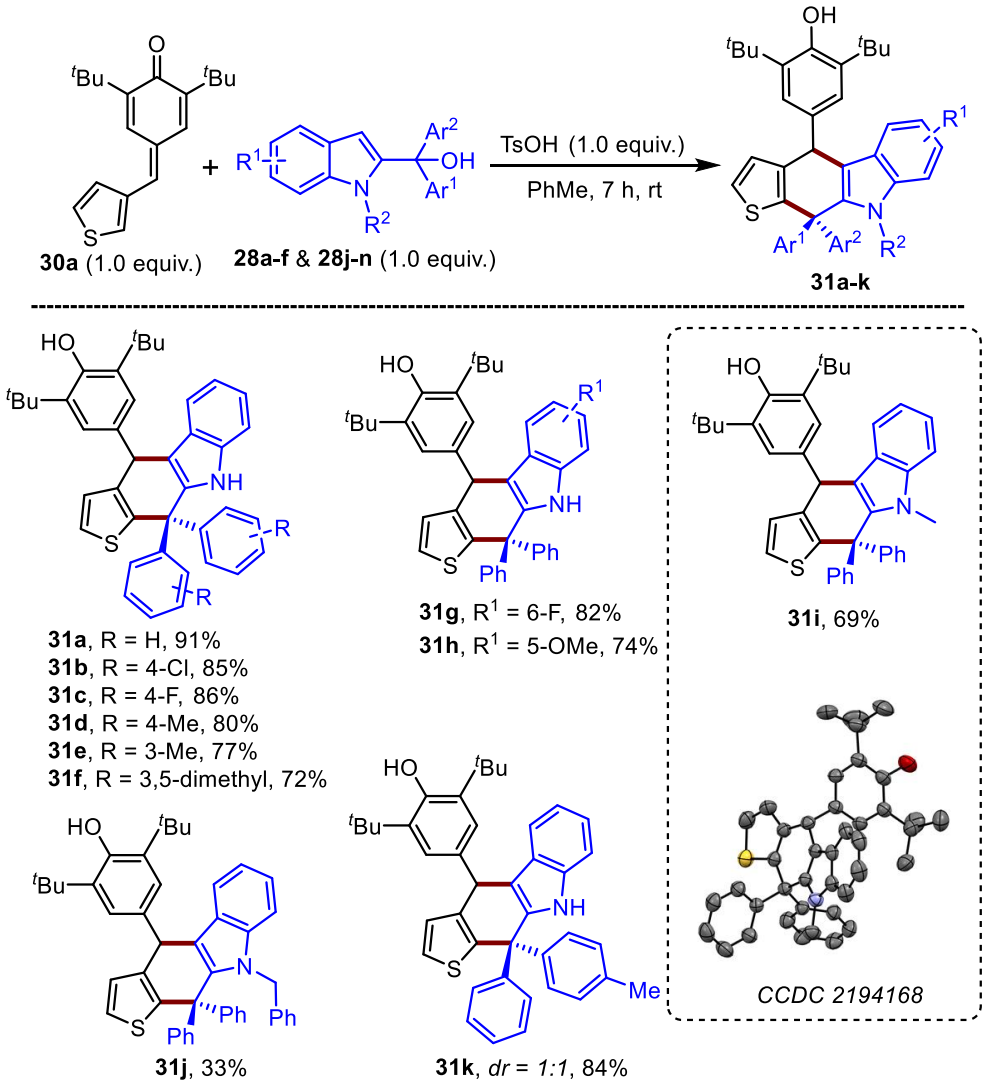


[a]Reaction conditions: All reactions were carried out with 30 mg of (**27a-i)** in acetone (1.5 mL). The yields reported are isolated yields. The diastereomeric ratio (*dr*) was calculated based on the ^{1}H NMR analysis of crude reaction mixture.

Having the optimized reaction conditions in hand (entry 10, Table 1), the substrate scope and boundaries were assessed using a wide range of 3-indolyl-substituted *p*-quinone methides **27a**-**i** and 2-indolylmethanols (**28a**-**l**, **28n** & **28o**) and the results are summarized in Scheme 9. In general, the synthons **27a**-**e**, derived from halogenated *N*-methyl indole-3-carboxaldehyde, reacted efficiently with **28a** to give their corresponding products **29a**-**e** in high yields (83-96%). Interestingly, the 5-methoxyindole-substituted *p*-QM **27f** and 5-nitroindole-substituted *p*-QM **27g** reacted with **28a** and provided the respective products **29f** and **29g** in almost the same yields (75 and 72%, respectively). However, the reaction of **27g** with **28a** took a longer time (6 h) to complete for obvious reasons. The reactions also progressed well with other *N*-alkylated 3-indolyl-substituted *p*-QMs **27h** & **27i** and gave the products **29h** and **29i** in 64 and 53% yields, respectively. To increase the substrate scope further, many substituted 2-indolylmethanols (**28b**-**k**) were employed and, in those cases, the desired tetrahydroindolo[2,3-*b*]carbalzoles **29j**-**v** were obtained in moderate to excellent isolated yields (56-93%). In the case of reaction between **27a** and *N*-methyl-2-indolylmethanol **28l**, the symmetrical tetrahydroindolo[2,3-*b*]carbazole **29w** was obtained in an 85% yield. When the reaction was carried out with 2-indolylmethanol **28n**, bearing different aryl groups, the corresponding product **29x** was obtained as a 1:1 diastereomeric mixture in 64% yield. Interestingly, no product (**29y**) formation was observed when the reaction was performed with **27a** and 2-indolylmethanol **28o**, having methyl groups instead of aryl groups.

This protocol was then extended to the synthesis of tetrahydrothieno[2,3-*b*]carbazole derivatives by treating the *p*-QM **30a** (prepared from 3-thiophene carboxaldehyde and 2,6-di-*t*-butylphenol) and 2-indolylmethanols (Scheme 10). A short optimization studies between **30a** and **28a** under different reaction conditions revealed the reaction worked well with equivalent amounts of TsOH in toluene as, in this case, the expected product **31a** was obtained in 91% yield within 7 hours. Similarly, other substituted 2-indolylmethanols **28b**-**f** & **28j**-**m** were subjected to react with **30a** in toluene and, in those cases, the respective tetrahydrothieno[2,3-*b*]carbazole derivatives **31b**-**j** were obtained in the range of 33-86% isolated yields (Scheme 10). Further, the reaction was carried out with 2-indolylmetahnol **28n** under the standard conditions with **30a**, and the expected product **31k** was obtained as a 1:1 diastereomeric mixture in 84% yield. The structure of one of the tetrahydrothieno[2,3-*b*]carbazole derivatives **31i** has been confirmed by single-crystal X-ray analysis.

Scheme 10. Substrate scope for the synthesis of tetrahydrothieno[2,3-*b*]carbazole derivatives[a]

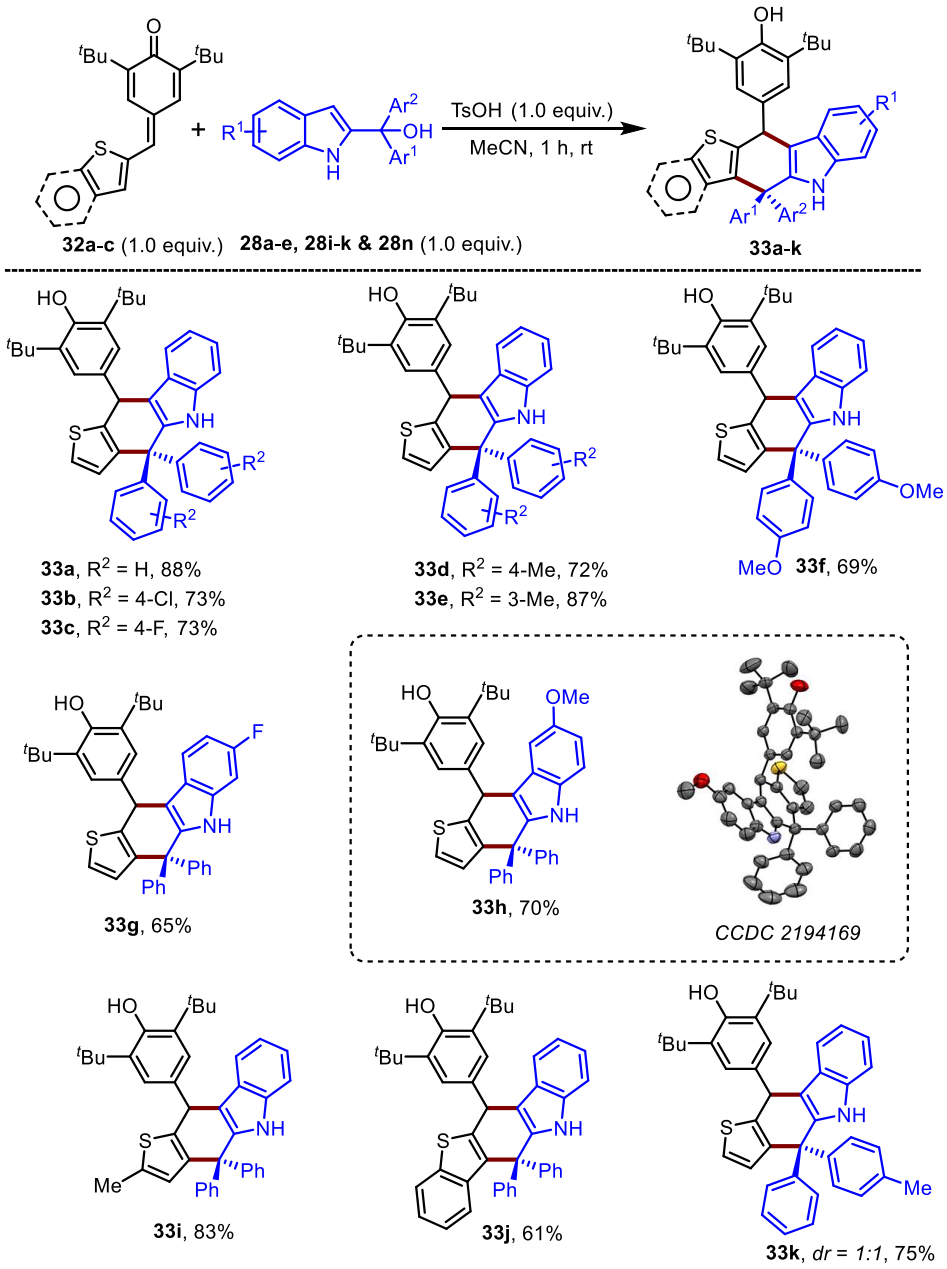


[a]Reaction conditions: All reactions were carried out with 30 mg of **30a** in toluene (1.5 mL). The yields reported are isolated yields. The diastereomeric ratio (*dr*) was calculated based on the ^{1}H NMR analysis of crude reaction mixture.

Next, we thought if 2-thiophenyl-substituted *p*-QM is used in place of 3-thiophenyl-substituted *p*-QM (**30a**), it is possible to access tetrahydrothieno[3,2-*b*]carbazole derivatives. In line with this, a few optimization experiments were performed using 2-thiophenyl-substituted *p*-QM **32a** and **28a** under various conditions using TsOH as a promotor. It was found that the reaction in MeCN provided the expected product **33a** in better yield (88%). Therefore, further substrate-scope studies have been carried out in MeCN using various 2-thiophenyl-substituted *p*-QMs and 2-indolylmethanol derivatives (Scheme 11). Most of the reactions between **32a** and 2-indolylmethanols (**28a**-**e** & **28i**-**k**) worked reasonably well, and

the respective tetrahydrothieno[3,2-*b*]carbazoles **33b-h** were obtained in the range of 65-87% yields. Other *p*-QMs **32b** & **32c** (derived from 5-methyl thiophene-2-carboxaldehyde and benzothiophene-2-carboxaldehyde, respectively) also reacted with **28a** to give the products **33i** and **33j** in 83 and 61% yields, respectively. In the case of a reaction between **32a** and 2-indolylmethanol **28n**, having both aryl substituents different, the corresponding product **33k** was obtained in 75% yield as a 1:1 diastereomeric mixture.

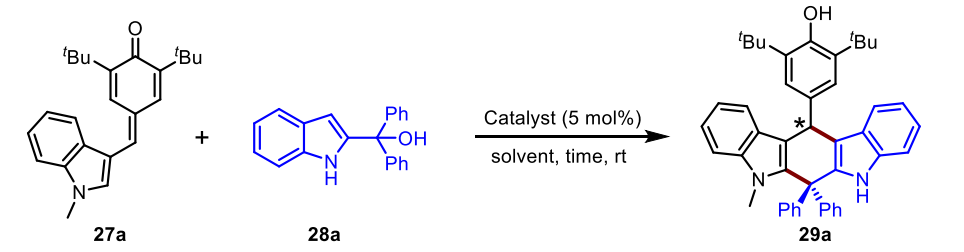
Scheme 11. Substrate scope for the synthesis of tetrahydrothieno[3,2-*b*]carbazole derivatives[a]



[a]Reaction conditions: All reactions were carried out with 30 mg of **32a-c** in acetonitrile (1.5 mL). The yields reported are isolated yields. The diastereomeric ratio (*dr*) was calculated based on the ^{1}H NMR analysis of crude reaction mixture.

Since this transformation proceeds under acidic conditions, we felt enantiomerically pure acid promotors, such as chiral phosphoric acids, would possibly drive the reaction between 2-indolylmethanols and 3-indolyl-substituted *p*-QMs in an enantioselective manner, which would potentially lead to enantiomerically enriched tetrahydroindolo[2,3-*b*]carbazoles. In this regard, a few optimization experiments have been conducted between **27a** and **28a** under

Table 2. Optimization studies for the enantioselective synthesis of tetrahydroindolo[2,3-*b*]carbazoles[a]

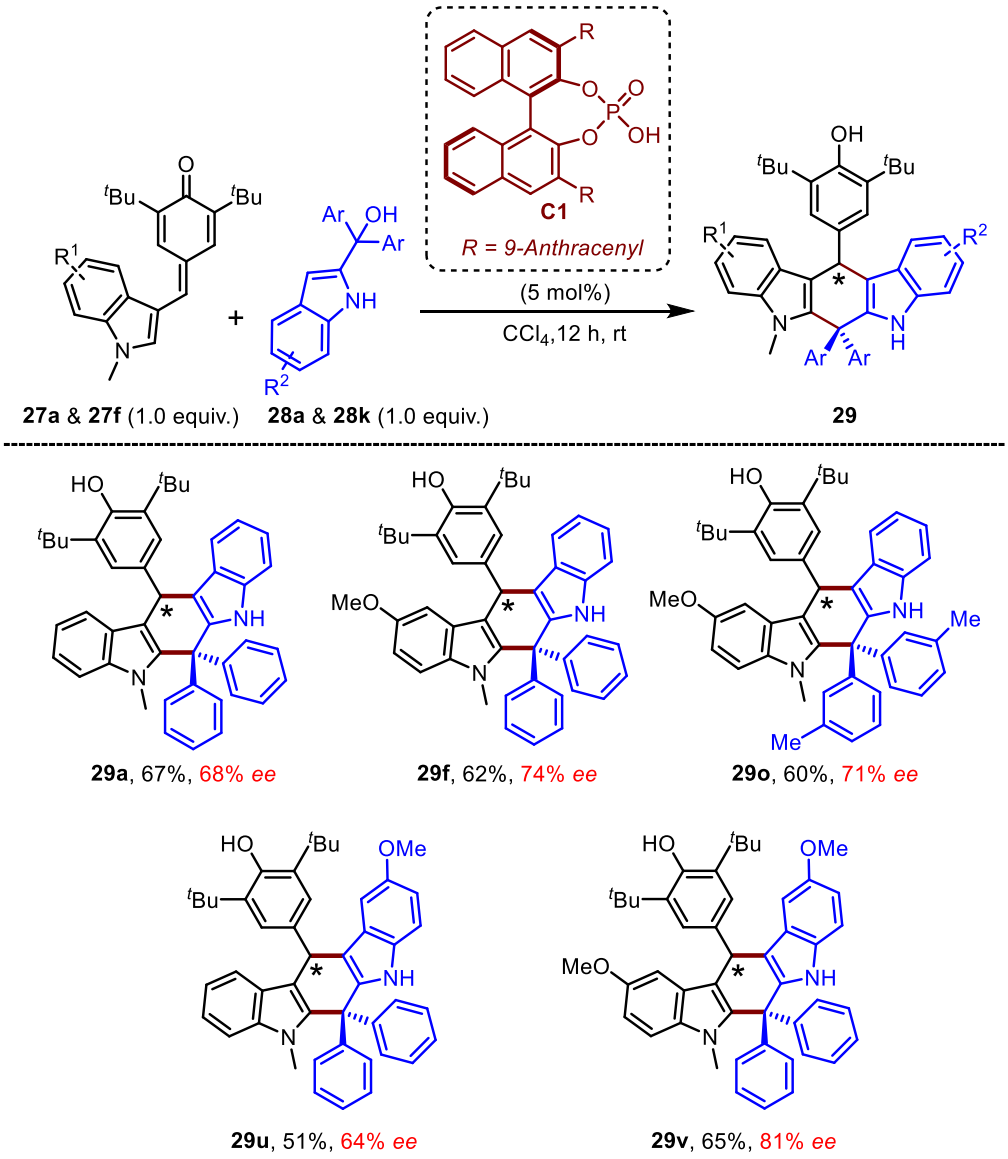


entry	catalyst	solvent	additive	time (h)	yield (%)	*ee* (%)
1	**C1**	PhMe	-	12	49	44
2	**C1**	CH_2Cl_2	-	12	45	40
3	**C1**	CH_3Cl	-	12	45	32
4	**C1**	**CCl_4**	**-**	**12**	**67**	**68**
5	**C2**	CCl_4	-	24	40	30
6	**C3**	CCl_4	-	24	35	50
7	**C4**	CCl_4	-	24	28	12
8	**C5**	CCl_4	-	12	43	20
9	**C1**	CCl_4	HFIP	12	53	46
10	**C1**	CCl_4	H_2O	12	51	58
11	**C1**	CCl_4	Neutral Al_2O_3	24	n.r.	-
12	**C1**	CCl_4	3Å MS	24	40	58
13	**C1**	CCl_4	4Å MS	24	42	56
14	**C1**	CCl_4	5Å MS	24	38	60
15	**C1**	CCl_4	0 °C	48	40	50

[a]Reaction conditions: All reactions were carried out with **27a** (0.058 mmol), **28a** (0.058 mmol), 5 mol% of catalyst and 100 mg of additive in 2.0 mL of solvent.

various conditions using BINOL-derived chiral phosphoric acids, and the results are shown in Table 2. Initially, the reaction was carried out in the presence of **C1** as a chiral catalyst and toluene as a solvent. Delightfully, we were able to isolate the desired product with 44% enantiomeric excess (*ee*) and 49% yield (entry 1). Encouraged by this result, the reaction was performed with different solvents (entries 2-4), and it was observed that CCl_4 was found to be the best solvent for this transformation, and product **29a** was obtained in 67% yield with 68% *ee*. Further, various chiral phosphoric acids were screened and found to be less superior than the **C1** catalyst (entries 5-8). The enantiomeric excess of the product was not improved with

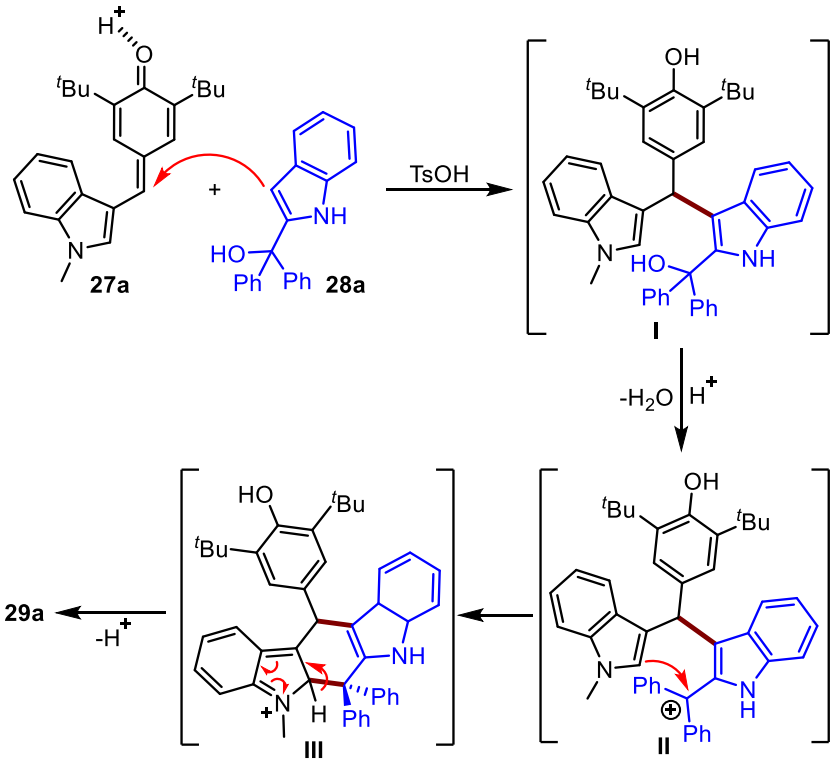
Scheme 12. Substrate scope for enantioselective synthesis of tetrahydroindolo[2,3-*b*]carbazole derivatives[a]



[a]Reaction conditions: All reactions were carried out with 30 mg of **27a** & **27f** with **28a** & **28k** (1.0 equiv.) in CCl_4 (2.0 mL). The yields reported are isolated yields.

the use of different types of additives (entries 9-14). At low temperatures, the reaction was found to be very sluggish, and the product was produced in 40% yield and 50% *ee* (entry 15). Therefore, further elaborations, in terms of substrate scope, have been carried out using **C1** as a catalyst, and the enantiomerically-enriched products **29f**, **29o**, **29u,** and **29v** were obtained in moderate yields and enantiomeric excess (64-81% *ee*). The maximum enantioselectivity (81% *ee*) was obtained in the case of tetrahydroindolo[2,3-*b*]carbazole **29v**, where both the indole units are substituted with methoxy groups (Scheme 12).

Based on the outcome of the reaction, a plausible mechanism was proposed (Scheme 13). Initially, the acid promotor activates the 3-indolyl-substituted *p*-QM **27a**, and subsequently, 2-indolylmethanol **28a** adds to **27a** in a 1,6-fashion to generate the 1,6-adduct **I**. The acid-mediated dehydration of **I** leads to a carbocation intermediate **II**, which then undergoes an intramolecular cyclization followed by proton elimination to generate product **29a** (Scheme 13).



Scheme 13. Plausible mechanism

1.5 Conclusion

In conclusion, we have described a simple, acid-mediated approach to the synthesis of a wide range of heterocyclo-fused tetrahydrocarbazole derivatives through a formal [3+3]-

annulation of 2-indolylmethanols with *p*-QMs, derived from heterocycles such as indole and thiophene. Initially, the developed protocol was employed to access various substituted tetrahydroindolo[2,3-*b*]carbazole derivatives in moderate to excellent yields. Later, it was extended to the synthesis of many tetrahydrothieno[2,3-*b*]carbazoles and tetrahydrothieno[3,2-*b*]carbazoles. In addition, an enantioselective version for the synthesis of enantiomerically-enriched tetrahydroindolo[2,3-*b*]carbazoles has also been attempted using a chiral phosphoric acid as a catalyst. In the enantioselective version, a maximum of 81% *ee* was achieved at this point in time. Notably, to the best of our knowledge, these are the first examples of enantiomerically-pure tetrahydroindolo[2,3-*b*]carbazole derivatives.

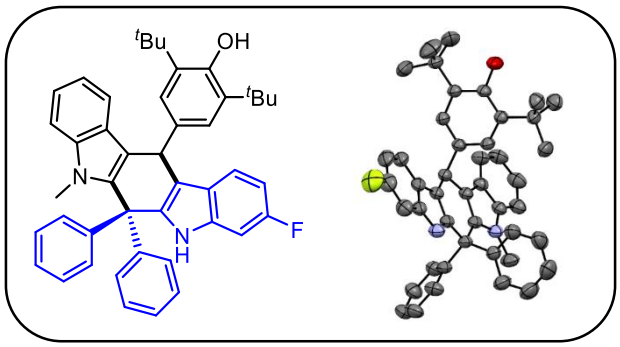
1.6 Experimental section

General information. All reactions were carried out under an argon atmosphere in an oven-dried round bottom flask. All the solvents were distilled before use and stored under an argon atmosphere. Most of the reagents and starting materials were purchased from commercial sources and used as such. 2-indolylmethanols were prepared according to the literature procedure.[28] *p*-quinone methides were prepared by following a literature procedure.[29] Melting points were recorded on the SMP20 melting point apparatus and are uncorrected. ^{1}H, ^{13}C, and ^{19}F spectra were recorded in $CDCl_3$ and DMSO (400, 100, and 376 MHz, respectively) on Bruker FT–NMR spectrometer. Chemical shift (δ) values are reported in parts per million relatives to TMS, and the coupling constants (J) are reported in Hz. High-resolution mass spectra were recorded on Waters Q-TOF Premier–HAB213 spectrometer. FT-IR spectra were recorded on a Perkin-Elmer FTIR spectrometer. Thin-layer chromatography was performed on Merck silica gel 60 F_{254} TLC pellets and visualized by UV irradiation and $KMnO_4$ stain. Column chromatography was carried out through silica gel (100–200 mesh) using EtOAc/hexane as eluent.

X-ray crystallographic analysis for compound 29t:

Table 3: Crystal data and structure refinement for compound **29t** (CCDC 2194163)

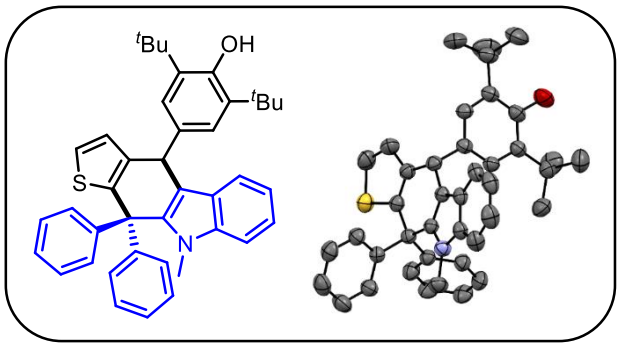
Identification code	XX-GS-40-RT
Empirical formula	$C_{45}H_{43}FN_2O$
Formula weight	646.81
Temperature/K	298.01(1)
Crystal system	triclinic
Space group	P-1
a/Å	10.7970(5)
b/Å	11.7144(5)
c/Å	17.2757(7)
α/°	109.155(4)
β/°	106.362(4)
γ/°	90.359(4)
Volume/Å^3	1968.69(16)
Z	2
ρ_{calc}g/cm^3	1.091
μ/mm^{-1}	0.068
F(000)	688.0
Crystal size/mm^3	0.1 × 0.1 × 0.1
Radiation	Mo Kα (λ = 0.71073)
2Θ range for data collection/°	5.116 to 65.482
Index ranges	-15 ≤ h ≤ 15, -17 ≤ k ≤ 16, -25 ≤ l ≤ 26
Reflections collected	29730
Independent reflections	13262 [R_{int} = 0.0326, R_{sigma} = 0.0555]
Data/restraints/parameters	13262/0/449
Goodness-of-fit on F^2	1.042
Final R indexes [I>=2σ (I)]	R_1 = 0.0804, wR_2 = 0.2270
Final R indexes [all data]	R_1 = 0.1393, wR_2 = 0.2817
Largest diff. peak/hole / e Å^{-3}	0.65/-0.24



X-ray crystallographic analysis for compound 31i:

Table 4: Crystal data and structure refinement for compound **31i** (CCDC2194168)

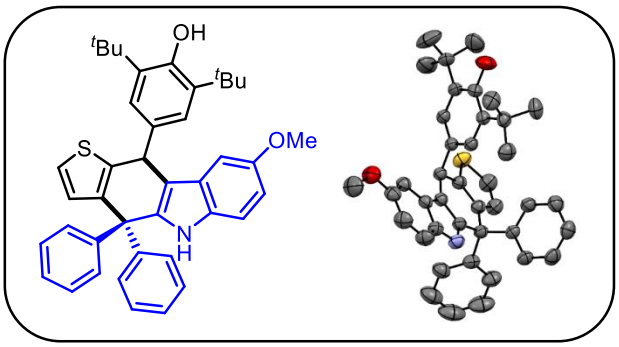
Identification code	XX GS-78_RT
Empirical formula	$C_{42}H_{43}Cl_2NOS$
Formula weight	680.73
Temperature/K	298.0(1)
Crystal system	triclinic
Space group	P-1
a/Å	9.2987(4)
b/Å	12.1896(5)
c/Å	17.6436(8)
α/°	109.223(4)
β/°	90.262(4)
γ/°	104.830(4)
Volume/Å^3	1816.78(15)
Z	2
ρ_{calc}g/cm^3	1.244
μ/mm^{-1}	0.270
F(000)	720.0
Crystal size/mm^3	0.1 × 0.1 × 0.1
Radiation	Mo Kα (λ = 0.71073)
2Θ range for data collection/°	4.914 to 50.108
Index ranges	-11 ≤ h ≤ 11, -14 ≤ k ≤ 14, -21 ≤ l ≤ 21
Reflections collected	25964
Independent reflections	6428 [R_{int} = 0.0417, R_{sigma} = 0.0327]
Data/restraints/parameters	6428/0/404
Goodness-of-fit on F^2	1.064
Final R indexes [I>=2σ (I)]	R_1 = 0.0575, wR_2 = 0.1586
Final R indexes [all data]	R_1 = 0.0754, wR_2 = 0.1808
Largest diff. peak/hole / e Å^{-3}	0.45/-0.22



X-ray crystallographic analysis for compound 33h:

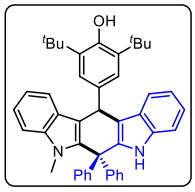
Table 5: Crystal data and structure refinement for compound **33h** (CCDC 2194169)

Identification code	XX-GS-61
Empirical formula	$C_{41}H_{40}NO_2S$
Formula weight	610.80
Temperature/K	298.01(1)
Crystal system	monoclinic
Space group	P21/c
a/Å	10.9175(3)
b/Å	10.7799(3)
c/Å	29.2158(10)
α/°	90
β/°	91.629(3)
γ/°	90
Volume/Å^3	3437.00(18)
Z	4
ρ_{calc}g/cm^3	1.180
μ/mm^{-1}	0.130
F(000)	1300.0
Crystal size/mm^3	0.1 × 0.1 × 0.1
Radiation	Mo Kα (λ = 0.71073)
2Θ range for data collection/°	5.312 to 65.554
Index ranges	-16 ≤ h ≤ 16, -16 ≤ k ≤ 16, -44 ≤ l ≤ 43
Reflections collected	50310
Independent reflections	12028 [R_{int} = 0.0444, R_{sigma} = 0.0366]
Data/restraints/parameters	12028/0/413
Goodness-of-fit on F^2	1.026
Final R indexes [I>=2σ (I)]	R_1 = 0.0656, wR_2 = 0.1800
Final R indexes [all data]	R_1 = 0.1093, wR_2 = 0.2239
Largest diff. peak/hole / e Å^{-3}	0.61/-0.22

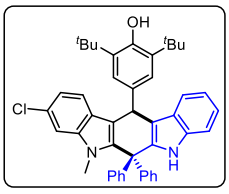


General procedure for the synthesis of tetrahydroindolo[2,3-b]carbazole derivatives (29a-x): TsOH (1.0 equiv.) was added to a solution of *p*-QM [**27a-i**] (30 mg, 1.0 equiv.) and 2-indolylmethanol [**28a-l**, **28o** & **28n**] (1.0 equiv.) in acetone (1.5 mL), and the resulting suspension were stirred at room temperature for 1 hour. After the reaction was complete (based on TLC analysis), the residue was then concentrated under reduced pressure, and the residue was then purified through a silica gel column using EtOAc/Hexane mixture as an eluent to get the pure products [**29a-x**].

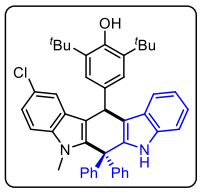
2,6-di-*tert*-butyl-4-(5-methyl-6,6-diphenyl-5,6,7,12-tetrahydroindolo[2,3-*b*]carbazol-12-yl)phenol (29a): The reaction was performed at 0.086 mmol scale of **27a**; white solid (48.9 mg, 90% yield); m. p. =269–271 ºC; R_f = 0.3 (15% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 – 7.64 (m, 3H), 7.60 (d, *J* = 7.9 Hz, 1H), 7.51 (d, *J* = 7.8 Hz, 1H), 7.44 – 7.37 (m, 5H), 7.35 – 7.32 (m, 2H), 7.30 – 7.29 (m, 1H), 7.28 – 7.23 (m, 3H), 7.21 (s, 2H), 7.14 – 7.08 (m, 2H), 7.05 – 7.01 (m, 1H), 5.75 (s, 1H), 4.97 (s, 1H), 3.30 (s, 3H), 1.35 (s, 18H); ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 152.0, 143.1, 142.4, 138.7, 138.4, 137.3, 137.1, 135.4, 135.3, 129.8, 129.3 (2C), 128.8, 128.5, 127.2, 126.6, 126.1, 125.3, 121.8, 121.5, 120.3, 120.1, 119.4, 119.0, 115.5, 114.7, 110.9, 108.8, 52.6, 39.62, 39.6, 34.3, 32.2, 30.5; FT-IR (thin film, neat): 3635, 3434, 2957, 1598, 737 cm^{-1}; HRMS (APCI): *m/z* calcd for $C_{45}H_{45}N_2O$ $[M+H]^+$: 629.3532; found : 629.3540.



2,6-di-*tert*-butyl-4-(3-chloro-5-methyl-6,6-diphenyl-5,6,7,12-tetrahydroindolo[2,3-*b*]carbazol-12-yl)phenol (29b): The reaction was performed at 0.079 mmol scale of **27b**; white solid (50.0 mg, 96% yield); m. p. = 276–278 ºC; R_f = 0.3 (15% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (s, 1H), 7.59 (d, *J* = 8.0 Hz, 2H), 7.46 (d, *J* = 7.8 Hz, 1H), 7.41 – 7.36 (m, 5H), 7.34 – 7.24 (m, 4H), 7.22 – 7.20 (m, 2H), 7.15 (s, 2H), 7.11 – 7.07 (m, 1H), 7.01 – 6.97 (m, 2H), 5.66 (s, 1H), 4.96 (s, 1H), 3.24 (s, 3H), 1.32 (s, 18H); ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 152.1, 142.8, 142.1, 138.9, 138.4, 137.8, 137.3, 135.6, 135.0, 129.7, 129.2 (2C), 128.9, 128.6, 127.7, 127.3, 126.5, 125.3, 124.6, 121.9, 121.0, 120.1, 119.7, 119.4, 115.7, 114.3, 110.9, 109.0, 52.6, 39.52, 39.5, 34.4, 32.4, 30.5; FT-IR (thin film, neat): 3633, 3458, 2957, 1603, 733 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{45}H_{44}ClN_2O$ $[M+H]^+$: 663.3142; found : 663.3146.

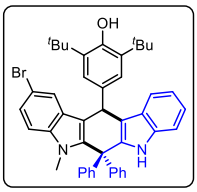


2,6-di-*tert*-butyl-4-(2-chloro-5-methyl-6,6-diphenyl-5,6,7,12-tetrahydroindolo[2,3-*b*]carbazol-12-yl)phenol (29c): The reaction was performed at 0.079 mmol scale of **27c**; white solid (49.0 mg, 94% yield); m. p. = 265–267 ºC; R_f = 0.3 (15% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (s, 1H), 7.60 – 7.58 (m, 2H), 7.55 – 7.54 (m, 1H), 7.46 – 7.39 (m,



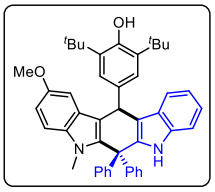
4H), 7.37 – 7.26 (m, 5H), 7.23 (d, J = 8.0 Hz, 1H), 7.17 – 7.16 (m, 2H), 7.13 – 7.09 (m, 3H), 7.03 – 6.99 (m, 1H), 5.67 (s, 1H), 5.00 (s, 1H), 3.26 (s, 3H), 1.34 (s, 18H); ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 152.2, 142.8, 142.1, 138.5, 138.3, 137.3, 136.8, 135.6, 134.8, 129.8, 129.2 (2C), 128.9, 128.6, 127.3, 127.0, 126.5, 125.3, 124.7, 121.9, 121.7, 120.1, 119.8, 119.5, 115.3, 114.3, 110.9, 109.9, 52.6, 39.5, 39.4, 34.4, 32.4, 30.5; FT-IR (thin film, neat): 3636, 3457, 2957, 1468, 732 cm^{-1}; HRMS (APCI): *m/z* calcd for $C_{45}H_{44}ClN_2O$ $[M+H]^+$: 663.3142; found : 663.3166.

4-(2-bromo-5-methyl-6,6-diphenyl-5,6,7,12-tetrahydroindolo[2,3-*b*]carbazol-12-yl)-2,6-di-*tert*-butylphenol (29d): The reaction was performed at 0.070 mmol scale of **27d**; white solid (44.8 mg, 90% yield); m. p. = 267–269 ºC; R_f = 0.3 (15% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (s, 1H), 7.67 (s, 1H), 7.60 – 7.58 (m, 2H), 7.43 – 7.32 (m, 11H), 7.17 – 7.16 (m, 2H), 7.13 – 7.08 (m, 2H), 7.03 – 7.00 (m, 1H), 5.67 (s, 1H), 5.00 (s, 1H), 3.25 (s, 3H), 1.35 (s, 18H); ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 152.2, 142.7, 142.0, 138.6, 138.1, 137.3, 137.1, 135.6, 134.8, 129.8, 129.2 (2C), 128.9, 128.6, 127.7, 127.3, 126.5, 125.3, 124.2, 122.9, 121.9, 120.1, 119.5, 115.3, 114.2, 112.3, 110.9, 110.4, 52.6, 39.45, 39.4, 34.4, 32.3, 30.5; FT-IR (thin film, neat): 3634, 3432, 2957, 1466, 1229, 737 cm^{-1}; HRMS (APCI): *m/z* calcd for $C_{45}H_{44}BrN_2O$ $[M+H]^+$: 707.2637; found : 707.2658.



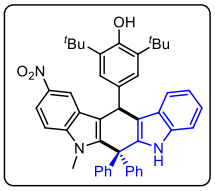
2,6-di-*tert*-butyl-4-(2-fluoro-5-methyl-6,6-diphenyl-5,6,7,12-tetrahydroindolo[2,3-*b*]carbazol-12-yl)phenol (29e): The reaction was performed at 0.082 mmol scale of **27e**; white solid (44.1 mg, 83% yield); m. p. = 277–279 ºC; R_f = 0.3 (15% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (s, 1H), 7.60 – 7.57 (m, 2H), 7.45 (d, J = 7.8 Hz, 1H), 7.41 – 7.35 (m, 4H), 7.34 – 7.26 (m, 4H), 7.20 (d, J = 8.0 Hz, 1H), 7.15 (s, 2H), 7.14 – 7.12 (m, 1H), 7.11 – 7.07 (m, 2H), 7.01 – 6.97 (m, 1H), 6.94 – 6.89 (m, 1H), 5.63 (s, 1H), 4.96 (s, 1H), 3.26 (s, 3H), 1.32 (s, 18H); ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 157.5 (d, $J_{C\text{-}F}$ = 232.4 Hz), 152.2, 142.9, 142.2, 138.7, 138.4, 137.3, 135.6, 135.0, 134.9, 129.7, 129.2 (2C), 128.9, 128.6, 127.3, 126.5, 126.3 (d, $J_{C\text{-}F}$ = 9.9 Hz), 125.3, 121.9, 120.1, 119.4, 115.4 (d, $J_{C\text{-}F}$ = 4.7 Hz), 114.4, 110.9, 109.6 (d, $J_{C\text{-}F}$ = 26.2 Hz), 109.4 (d, $J_{C\text{-}F}$ = 9.8 Hz), 105.1 (d, $J_{C\text{-}F}$ = 23.5 Hz), 52.7, 39.6, 39.5, 34.4, 32.5, 30.5; ^{19}F {^{1}H} NMR (376 MHz, $CDCl_3$) δ –125.1; FT-IR (thin film, neat): 3636, 2956, 1484, 1149, 737 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{45}H_{44}FN_2O$ $[M+H]^+$: 647.3438; found : 647.3463.

2,6-di-*tert*-butyl-4-(2-methoxy-5-methyl-6,6-diphenyl-5,6,7,12-tetrahydroindolo[2,3-*b*]carbazol-12-yl)phenol (29f): The reaction was performed at 0.079 mmol scale of **27f**; white



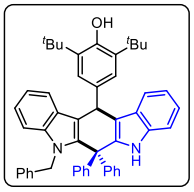
solid (39.3 mg, 75% yield); m. p. = 159–161 ºC; R_f = 0.2 (15% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (s, 1H), 7.60 (d, J = 7.5 Hz, 2H), 7.40 – 7.37 (m, 5H), 7.33 – 7.25 (m, 4H), 7.22 – 7.20 (m, 1H), 7.19 (s, 2H), 7.12 – 7.07 (m, 2H), 7.00 – 6.95 (m, 2H), 6.83 (dd, J = 8.8, 2.4 Hz, 1H), 5.64 (s, 1H), 4.95 (s, 1H), 3.77 (s, 3H), 3.24 (s, 3H), 1.32 (s, 18H); ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 153.5, 152.0, 143.0, 142.5, 138.7, 137.5, 137.3, 135.5, 135.4, 133.6, 129.8, 129.3, 128.8, 128.5, 127.2, 127.1, 126.6, 126.3, 125.4, 121.8, 120.1, 119.3, 115.1, 114.5, 111.8, 110.9, 109.6, 101.7, 55.8, 55.7, 52.7, 39.7, 34.3, 32.3, 30.5; FT-IR (thin film, neat): 3634, 2956, 1486, 1228, 736 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{46}H_{47}N_2O_2$ $[M+H]^+$: 659.3638; found : 659.3655.

2,6-di-*tert*-butyl-4-(5-methyl-2-nitro-6,6-diphenyl-5,6,7,12-tetrahydroindolo[2,3-*b*]carbazol-12-yl)phenol (29g): The reaction was performed at 0.076 mmol scale of **27g**; white



solid (37.0 mg, 72% yield); m. p. = 278–280 ºC; R_f = 0.2 (15% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.53 (d, J = 2.2 Hz, 1H), 8.05 (dd, J = 9.0, 2.2 Hz, 1H), 7.70 (s, 1H), 7.59 – 7.57 (m, 2H), 7.43 – 7.25 (m, 9H), 7.22 (d, J = 8.0 Hz, 1H), 7.20 – 7.18 (m, 3H), 7.12 – 7.08 (m, 1H), 7.01 – 6.97 (m, 1H), 5.72 (s, 1H), 5.01 (s, 1H), 3.31 (s, 3H), 1.32 (s, 18H); ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 152.5, 142.1, 141.6, 141.3, 141.2, 140.1, 138.2, 137.4, 136.0, 134.4, 129.7, 129.12 (2C), 129.1, 128.8, 127.6, 126.3, 125.3, 125.2, 122.2, 120.1, 119.6, 118.2, 117.6, 117.3, 113.7, 111.0, 108.8, 52.7, 39.4, 34.4, 32.8, 30.5; FT-IR (thin film, neat): 3631, 3428, 2957, 1483, 735 cm^{-1}; HRMS (APCI): *m/z* calcd for $C_{45}H_{44}N_3O_3$ $[M+H]^+$: 674.3383; found : 674.3416.

4-(5-benzyl-6,6-diphenyl-5,6,7,12-tetrahydroindolo[2,3-*b*]carbazol-12-yl)-2,6-di-*tert*-butylphenol (29h): The reaction was performed at 0.071 mmol scale of **27h**; white solid (31.9



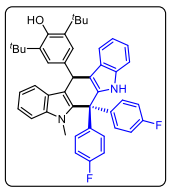
mg, 64% yield); gummy solid; R_f = 0.3 (15% EtOAc in hexane); ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.56 (s, 1H), 7.61 (d, J = 7.6 Hz, 2H), 7.42 (d, J = 8.1 Hz, 1H), 7.29 – 7.15 (m, 9H), 7.10 (t, J = 7.5 Hz, 2H), 7.04 – 6.98 (m, 1H), 6.95 – 6.91 (m, 2H), 6.88 – 6.81 (m, 5H), 6.78 – 6.76 (m, 1H), 6.64 (s, 1H), 6.19 (d, J = 7.6 Hz, 2H), 5.72 (s, 1H), 5.14 – 5.03 (m, 2H), 1.24 (s, 18H); ^{13}C {^{1}H} NMR (100 MHz, DMSO-d_6) δ 151.7, 142.5, 141.7, 138.9, 138.7, 137.5, 137.4, 137.1, 136.4, 129.4, 128.3, 128.2, 127.5, 126.7, 126.5, 126.48, 126.13, 126.1, 125.7, 125.3, 125.1, 124.7, 121.5, 121.1, 119.7, 119.2, 119.0, 118.3, 114.3, 112.0, 111.2, 110.4, 52.2, 48.4, 48.36, 38.5, 34.6, 30.6; FT-IR (thin film, neat): 3634, 3295, 2953, 1459, 735 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{51}H_{49}N_2O$ $[M+H]^+$: 705.3845; found : 705.3869.

2,6-di-*tert*-butyl-4-(5-isopropyl-6,6-diphenyl-5,6,7,12-tetrahydroindolo[2,3-*b*]carbazol-12-yl)phenol (29i): The reaction was performed at 0.080 mmol scale of **27i**; white solid (27.8 mg, 53% yield); gummy solid; R_f = 0.3 (15% EtOAc in hexane); ^{1}H NMR (400 MHz, DMSO-d$_6$) δ 10.56 (s, 1H), 7.73 (d, *J* = 7.8 Hz, 2H), 7.44 – 7.33 (m, 5H), 7.30 – 7.24 (m, 5H), 7.18 – 7.12 (m, 2H), 7.08 (s, 2H), 6.99 – 6.94 (m, 1H), 6.90 – 6.84 (m, 2H), 6.78 – 6.74 (m, 1H), 6.57 (s, 1H), 5.61 – 5.60 (m, 1H), 4.20 (sept, *J* = 6.2 Hz, 1H), 1.21 – 1.17 (m, 24H); ^{13}C {^{1}H} NMR (100 MHz, DMSO-d$_6$) δ 151.7, 143.2, 141.4, 139.5, 138.9, 137.5, 137.0, 136.5, 135.0, 129.6, 129.4, 128.3, 128.2, 127.0, 126.7, 126.5, 125.2, 124.6, 121.04, 121.0, 119.8, 119.1, 118.3, 118.2, 113.6, 112.4, 111.6, 111.2, 52.4, 47.8, 38.4, 34.5, 30.6; 19.9, 19.3; FT-IR (thin film, neat): 3647, 3465, 2922, 1460, 740 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{47}H_{49}N_2O$ [M+H]$^+$: 657.3845; found : 657.3859.

4-(6,6-bis(4-chlorophenyl)-5-methyl-5,6,7,12-tetrahydroindolo[2,3-*b*]carbazol-12-yl)-2,6-di-*tert*-butylphenol (29j): The reaction was performed at 0.086 mmol scale of **27a**; white solid (56.0 mg,93% yield); m. p. = 195–197 ºC; R_f = 0.3 (15% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 – 7.57 (m, 2H), 7.53 – 7.51 (m, 2H), 7.47 (d, *J* = 7.8 Hz, 1H), 7.38 – 7.36 (m, 2H), 7.31 – 7.21 (m, 7H), 7.15 – 7.08 (m, 4H), 7.05 – 7.01 (m, 1H), 5.69 (s, 1H), 4.96 (s, 1H), 3.27 (s, 3H), 1.31 (s, 18H); ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 152.1, 141.5, 140.8, 138.4, 137.7, 137.4, 136.0, 135.5, 134.8, 133.4, 131.0, 130.5 (2C), 129.1, 128.8, 126.5, 126.0, 125.2, 122.2, 121.9, 120.4, 120.2, 119.7, 119.3, 116.1, 115.2, 111.0, 109.0, 51.8, 39.5, 34.3, 32.3, 30.4; FT-IR (thin film, neat): 3636, 3456, 2956, 1488, 735 cm^{-1}; HRMS (APCI): *m/z* calcd for $C_{45}H_{43}Cl_2N_2O$ [M+H]$^+$: 697.2752; found : 697.2740.

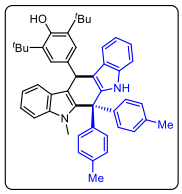
4-(6,6-bis(4-chlorophenyl)-2-methoxy-5-methyl-5,6,7,12-tetrahydroindolo[2,3-*b*]carbazol-12-yl)-2,6-di-*tert*-butylphenol (29k): The reaction was performed at 0.079 mmol scale of **27f**; white solid (42.8 mg, 74% yield); gummy solid; R_f = 0.3 (15% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (s, 1H), 7.50 – 7.47 (m, 2H), 7.37 (d, *J* = 8.1 Hz, 1H), 7.35 – 7.32 (m, 2H), 7.26 – 7.21 (m, 5H), 7.13 – 7.08 (m, 4H), 7.00 – 6.96 (m, 1H), 6.95 (d, *J* = 2.4 Hz, 1H), 6.84 (dd, *J* = 8.8, 2.4 Hz, 1H), 5.59 (s, 1H), 4.95 (s, 1H), 3.76 (s, 3H), 3.22 (s, 3H), 1.29 (s, 18H); ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 153.7, 152.1, 141.4, 140.9, 137.7, 137.4, 136.4, 135.6, 134.9, 133.6, 133.43, 133.4, 131.0, 130.5, 129.1, 128.8, 126.5, 126.2, 125.2, 122.2, 120.2, 119.7, 115.6, 115.1, 112.2, 111.0, 109.8, 101.7, 55.8, 51.9, 39.64, 39.6, 34.3, 32.4, 30.5; FT-IR (thin film, neat): 3636, 2953, 1486, 1229, 739 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{46}H_{43}Cl_2N_2O_2$ [M–H]$^-$: 725.2702; found : 725.2720.

4-(6,6-bis(4-fluorophenyl)-5-methyl-5,6,7,12-tetrahydroindolo[2,3-*b*]carbazol-12-yl)-2,6-di-*tert*-butylphenol (29l): The reaction was performed at 0.086 mmol scale of **27a**; white solid



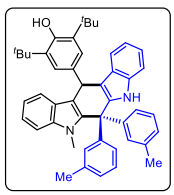
(48.2 mg, 84% yield); m. p. = 172–174 ºC; R_f = 0.3 (15% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 – 7.55 (m, 4H), 7.46 (d, J = 7.8 Hz, 1H), 7.32 – 7.28 (m, 2H), 7.27 – 7.20 (m, 3H), 7.14 – 7.10 (m, 4H), 7.08 – 7.06 (m, 2H), 7.04 – 6.98 (m, 3H), 5.68 (s, 1H), 4.95 (s, 1H), 3.26 (s, 3H), 1.30 (s, 18H); ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 161.82 (d, $J_{C\text{-}F}$ = 246.2 Hz), 161.8 (d, $J_{C\text{-}F}$ = 246.4 Hz), 152.1, 138.9 (d, $J_{C\text{-}F}$ = 3.3 Hz), 138.4, 138.3, 138.2 (d, $J_{C\text{-}F}$ = 3.0 Hz), 137.4, 136.6, 135.5, 135.0, 131.4 (d, $J_{C\text{-}F}$ = 7.9 Hz), 130.8 (d, $J_{C\text{-}F}$ = 7.8 Hz), 126.6, 126.0, 125.2, 122.1, 121.8, 120.3, 120.2, 119.6, 119.3, 115.8 (d, $J_{C\text{-}F}$ = 21.2 Hz), 115.7 (d, $J_{C\text{-}F}$ = 19.3 Hz), 115.4, 114.9, 110.9, 108.9, 51.6, 39.5, 34.3, 32.2, 30.5; ^{19}F {^{1}H} NMR (376 MHz, $CDCl_3$) δ –114.8, –115.2; FT-IR (thin film, neat): 3636, 3457, 2958, 1504, 735 cm^{-1}; HRMS (APCI): *m/z* calcd for $C_{45}H_{43}F_2N_2O$ $[M+H]^+$: 665.3343; found : 665.3365.

2,6-di-*tert*-butyl-4-(5-methyl-6,6-di-*p*-tolyl-5,6,7,12-tetrahydroindolo[2,3-*b*]carbazol-12-yl)phenol (29m): The reaction was performed at 0.086 mmol scale of **27a**; white solid (52.2



mg, 92% yield); m. p. = 267–269 ºC; R_f = 0.3 (15% EtOAc in hexane); ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.51 (s, 1H), 7.42 (d, J = 8.2 Hz, 2H), 7.32 (d, J = 7.8 Hz, 1H), 7.24 (d, J = 7.8 Hz, 1H), 7.20 (d, J = 8.2 Hz, 1H), 7.14 – 7.10 (m, 3H), 7.09 – 7.03 (m, 6H), 7.00 – 6.96 (m, 1H), 6.89 – 6.84 (m, 2H), 6.74 (t, J = 7.4 Hz, 1H), 6.53 (s, 1H), 5.59 (s, 1H), 3.04 (s, 3H), 2.21 (s, 3H), 2.17 (s, 3H), 1.14 (s, 18H); ^{13}C {^{1}H} NMR (100 MHz, DMSO-d_6) δ 151.7, 140.4, 139.4, 139.1, 138.8, 137.9, 137.5, 137.3, 136.5, 136.0, 135.9, 129.4, 129.1, 128.8, 125.3, 124.6, 121.24, 121.2, 120.9, 119.3, 119.0, 118.99, 118.7, 118.3, 114.3, 112.0, 111.2, 109.3, 51.5, 38.6, 34.5, 31.8, 30.6, 20.6 (2C); FT-IR (thin film, neat): 3635, 3459, 2957, 1509, 734 cm^{-1}; HRMS (APCI): *m/z* calcd for $C_{47}H_{49}N_2O$ $[M+H]^+$: 657.3845; found : 657.3873.

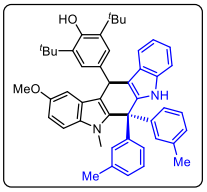
2**,6-di-*tert*-butyl-4-(5-methyl-6,6-di-*m*-tolyl-5,6,7,12-tetrahydroindolo[2,3-*b*]carbazol-12-yl)phenol (29n):** The reaction was performed at 0.086mmol scale of **27a**; white solid (48.2



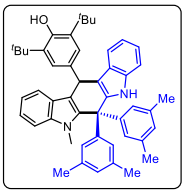
mg, 85% yield); m. p. = 247–249 ºC; R_f = 0.3 (15% EtOAc in hexane); ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.60 (s, 1H), 7.45 (s, 1H), 7.33 (d, J = 7.8 Hz, 2H), 7.28 – 7.21 (m, 3H), 7.19 –7.13 (m, 2H), 7.11 – 7.09 (m, 3H), 7.04 – 6.99 (m, 4H), 6.93 – 6.87 (m, 2H), 6.80 – 6.76 (m, 1H), 6.58 (s, 1H), 5.61 (s, 1H), 3.08 (s, 3H), 2.25 (s, 3H), 2.14 (s, 3H), 1.18 (s, 18H); ^{13}C {^{1}H} NMR (100 MHz, DMSO-d_6) δ 151.7, 143.4, 141.9, 139.0, 138.9, 137.9, 137.4, 137.36, 137.3, 137.1, 136.4, 129.9, 129.7, 128.3, 128.1, 127.6, 127.4, 126.8, 126.4, 125.3, 125.2, 124.6, 121.2, 120.9, 119.4, 119.0, 118.7, 118.2,

114.2, 112.1, 111.3, 109.4, 52.0, 38.6, 34.5, 31.8, 30.6, 21.52, 21.5, 21.35, 21.3; FT-IR (thin film, neat): 3643, 3432, 2953, 1460, 738 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{47}H_{49}N_2O$ $[M+H]^+$: 657.3845; found : 657.3862.

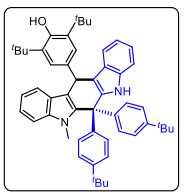
2,6-di-*tert*-butyl-4-(2-methoxy-5-methyl-6,6-di-*m*-tolyl-5,6,7,12-tetrahydroindolo[2,3-*b*]carbazol-12-yl)phenol (29o): The reaction was performed at 0.079 mmol scale of **27f**; white solid (39.8 mg, 73% yield); gummy solid; R_f = 0.3 (15% EtOAc in hexane); ^1H NMR (400 MHz, $CDCl_3$) δ 7.67 (s, 1H), 7.38 – 7.34 (m, 3H), 7.27 – 7.25 (m, 1H), 7.23 – 7.21 (m, 1H), 7.18 – 7.15 (m, 4H), 7.13 (s, 1H), 7.11 – 7.04 (m, 4H), 6.99 – 6.95 (m, 2H), 6.83 (dd, *J* = 8.8, 2.5 Hz, 1H), 5.62 (s, 1H), 4.94 (s, 1H), 3.77 (s, 3H), 3.23 (s, 3H), 2.34 (s, 3H), 2.24 (s, 3H), 1.30 (s, 18H); ^{13}C $\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 153.5, 152.0, 143.2, 142.6, 138.9, 138.21, 138.2, 137.8, 137.3, 135.5, 135.4, 133.6, 130.5, 129.8, 128.7, 128.2, 128.0, 127.9, 126.8, 126.7, 126.5, 126.4, 125.4, 121.6, 120.0, 119.2, 115.1, 114.5, 111.6, 110.9, 109.6, 101.6, 55.8, 55.76, 52.6, 39.81, 39.8, 34.3, 32.4, 30.5, 22.0, 21.8; FT-IR (thin film, neat): 3633, 3452, 2922, 1485, 1229, 738 cm^{-1}; HRMS (APCI): *m/z* calcd for $C_{48}H_{51}N_2O_2$ $[M+H]^+$: 687.3951; found : 687.3978.



4-(6,6-bis(3,5-dimethylphenyl)-5-methyl-5,6,7,12-tetrahydroindolo[2,3-*b*]carbazol-12-yl)-2,6-di-*tert*-butylphenol (29p): The reaction was performed at 0.086 mmol scale of **27a**; white solid (53.2 mg, 90% yield); m. p. = 276–278 ºC; R_f = 0.3 (15% EtOAc in hexane); ^1H NMR (400 MHz, $CDCl_3$) δ 7.75 (s, 1H), 7.58 (d, *J* = 7.8 Hz, 1H), 7.43 (d, *J* = 7.8 Hz, 1H), 7.27 – 7.24 (m, 2H), 7.22 –7.18 (m, 3H), 7.14 (s, 2H), 7.11 – 7.05 (m, 2H), 6.99 (t, *J* = 7.4 Hz, 1H), 6.96 (s, 1H), 6.90 – 6.87 (m, 3H), 5.68 (s, 1H), 4.93 (s, 1H), 3.28 (s, 3H), 2.30 (s, 6H), 2.22 (s, 6H), 1.29 (s, 18H); ^{13}C $\{^1H\}$NMR (100 MHz, $CDCl_3$) δ 151.9, 143.6, 142.6, 139.2, 138.3, 138.0, 137.8, 137.7, 137.2, 135.4, 135.3, 128.9, 128.8, 127.6, 127.0, 126.8, 126.3, 125.3, 121.4, 121.1, 120.1, 120.0, 119.1, 118.8, 115.4, 114.4, 110.9, 108.9, 52.4, 39.7, 39.67, 34.2, 32.4, 30.5, 21.9, 21.89, 21.67, 21.66; FT-IR (thin film, neat): 3643, 3461, 2956, 1467, 738 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{49}H_{51}N_2O$ $[M–H]^–$: 683.4001; found : 683.4017.

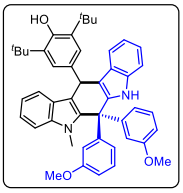


4-(6,6-bis(4-(tert-butyl)phenyl)-5-methyl-5,6,7,12-tetrahydroindolo[2,3-*b*]carbazol-12-yl)-2,6-di-*tert*-butylphenol (29q): The reaction was performed at 0.086 mmol scale of **27a**; white solid (39.0 mg, 61% yield); m. p. = 227–229 ºC; R_f = 0.4 (15% EtOAc in hexane); ^1H NMR (400 MHz, DMSO-d_6) δ 10.66 (s, 1H), 7.56 – 7.54 (m, 2H), 7.42 – 7.37 (m, 3H), 7.34 – 7.30 (m, 3H), 7.26 (d, *J* = 8.3 Hz, 1H), 7.21 – 7.19 (m, 3H), 7.09 –7.03 (m, 3H), 6.94 – 6.90 (m, 2H), 6.82 – 6.79 (m, 1H),



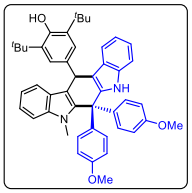
6.59 (s, 1H), 5.64 (s, 1H), 3.07 (s, 3H), 1.26 (s, 9H), 1.22 (s, 9H), 1.20 (s, 18H); ^{13}C {^{1}H} NMR (100 MHz, DMSO-d_6) δ 151.6, 148.9, 148.86, 140.3, 139.3, 138.9, 138.86, 138.8, 137.8, 137.4, 137.2, 136.5, 129.2, 128.8, 125.2, 124.9, 124.5, 121.2, 120.9, 119.3, 119.0, 118.7, 118.2, 114.2, 111.8, 111.2, 111.18, 109.2, 51.4, 38.5, 34.5, 34.2, 34.1, 31.7, 31.12, 31.1, 30.6; FT-IR (thin film, neat): 3644, 3409, 2958, 1462, 734 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{53}H_{59}N_2O$ $[M–H]^–$: 739.4627; found : 739.4635.

4-(6,6-bis(3-methoxyphenyl)-5-methyl-5,6,7,12-tetrahydroindolo[2,3-*b*]carbazol-12-yl)-2,6-di-*tert*-butylphenol (29r): The reaction was performed at 0.086 mmol scale of **27a**; white



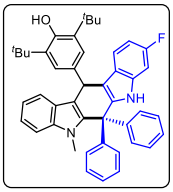
solid (45.8 mg, 77% yield); m. p. = 253–255 ºC; R_f = 0.2 (15% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (s, 1H), 7.54 (d, *J* = 7.8 Hz, 1H), 7.45 (d, *J* = 7.8 Hz, 1H), 7.29 – 7.19 (m, 5H), 7.16 – 7.14 (m, 2H), 7.12 (s, 2H), 7.10 – 7.03 (m, 2H), 6.98 (t, *J* = 7.4 Hz, 1H), 6.93 – 6.92 (m, 1H), 6.89 (d, *J* = 7.8 Hz, 1H), 6.83 – 6.80 (m, 1H), 6.77 (dd, *J* = 8.1, 2.2 Hz, 1H), 5.66 (s, 1H), 4.91 (s, 1H), 3.74 (s, 3H), 3.69 (s, 3H), 3.30 (s, 3H), 1.28 (s, 18H); ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 159.8, 159.7, 152.2, 145.0 144.1, 138.45, 138.4, 137.2, 137.1, 135.4, 135.3, 129.7, 129.5, 126.7, 126.2, 125.3, 122.4, 121.8, 121.7, 121.5, 120.2, 120.1 119.3, 119.0, 116.6, 116.5, 115.7, 114.8, 111.5, 111.0, 110.9, 108.9, 55.4, 55.3, 52.5, 39.6, 34.3, 32.3, 30.5; FT-IR (thin film, neat): 3624, 3434, 2955, 1483, 736 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{47}H_{49}N_2O_3$ $[M+H]^+$: 689.3743; found : 689.3773.

4-(6,6-bis(4-methoxyphenyl)-5-methyl-5,6,7,12-tetrahydroindolo[2,3-*b*]carbazol-12-yl)-2,6-di-*tert*-butylphenol (29s): The reaction was performed at 0.086 mmol scale of **27a**; white



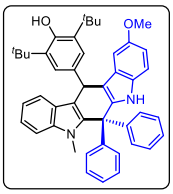
solid (48.2 mg, 81% yield); m. p. = 263–265 ºC; R_f = 0.2 (15% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (s, 1H), 7.57 (d, *J* = 7.8 Hz, 1H), 7.50 (d, *J* = 8.9 Hz, 2H), 7.46 (d, *J* = 7.8 Hz, 1H), 7.28 – 7.18 (m, 5H), 7.15 (s, 2H), 7.11 – 7.05 (m, 2H), 7.01 – 6.98 (m, 1H), 6.90 (d, *J* = 8.9 Hz, 2H), 6.82 (d, *J* = 8.9 Hz, 2H), 5.68 (s, 1H), 4.93 (s, 1H), 3.82 (s, 3H), 3.78 (s, 3H), 3.29 (s, 3H), 1.31 (s, 18H); ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 158.5, 158.46, 152.0, 139.4 138.3, 137.6, 137.3, 135.44, 135.4, 135.36, 134.8, 131.0, 130.3, 126.7, 126.2, 125.3, 121.6, 121.4, 120.2, 120.0, 119.3, 119.0, 115.4, 114.3, 114.1, 113.7, 110.8, 108.8, 55.44, 55.4, 51.2, 39.6, 34.3, 32.1, 30.5; FT-IR (thin film, neat): 3624, 3391, 2956, 1507, 735 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{47}H_{49}N_2O_3$ $[M+H]^+$: 689.3743; found : 689.3766.

2,6-di-*tert*-butyl-4-(3-fluoro-7-methyl-6,6-diphenyl-5,6,7,12-tetrahydroindolo[2,3-*b*]carbazol-12-yl)phenol (29t): The reaction was performed at 0.086 mmol scale of **27a**; white



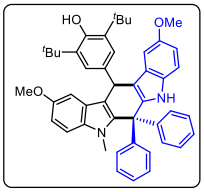
solid (36.3 mg, 65% yield); m. p. = 175–177 ºC; R_f = 0.3 (15% EtOAc in hexane); ^{1}H NMR (400 MHz, DMSO-d$_6$) δ 10.76 (s, 1H), 7.59 (d, J = 7.7 Hz, 2H), 7.40 – 7.36 (m, 3H), 7.32 – 7.30 (m, 2H), 7.28 – 7.20 (m, 6H), 7.09 (s, 2H), 7.06 – 7.02 (m, 1H), 6.94 – 6.90 (m, 2H), 6.71 – 6.66 (m, 1H), 6.61 (s, 1H), 5.64 (s, 1H), 3.07 (s, 3H), 1.19 (s, 18H); ^{13}C {^{1}H} NMR (100 MHz, DMSO-d$_6$) δ 158.7 (d, $J_{C\text{-}F}$ = 232.2 Hz), 151.8, 142.9, 141.7, 139.5 (d, $J_{C\text{-}F}$ = 3.4 Hz), 138.9, 137.9, 137.3, 137.2, 137.0, 136.1, 129.4, 129.1, 128.5, 128.2, 127.0, 126.8, 125.2, 124.5, 119.9 (d, $J_{C\text{-}F}$ = 10.3 Hz), 119.4, 118.8, 114.2, 112.3, 109.3, 106.7 (d, $J_{C\text{-}F}$ = 25.4 Hz), 97.4, 97.2, 52.1, 38.41, 38.4, 34.5, 31.7, 30.6; ^{19}F {^{1}H} NMR (376 MHz, CDCl$_3$) δ –121.6; FT-IR (thin film, neat): 3541, 3241, 2922, 1459, 738 cm^{-1}; HRMS (APCI): *m/z* calcd for $C_{45}H_{44}FN_2O$ $[M+H]^+$: 647.3438; found : 647.3453.

2,6-di-*tert*-butyl-4-(2-methoxy-7-methyl-6,6-diphenyl-5,6,7,12-tetrahydroindolo[2,3-*b*]carbazol-12-yl)phenol (29u): The reaction was performed at 0.086 mmol scale of **27a**; white



solid (31.9 mg, 56% yield); m. p. = 248–250 ºC; R_f = 0.3 (15% EtOAc in hexane); ^{1}H NMR (400 MHz, DMSO-d$_6$) δ 10.46 (s, 1H), 7.63 (d, J = 7.6 Hz, 2H), 7.40 – 7.36 (m, 2H), 7.32 – 7.30 (m, 2H), 7.28 – 7.20 (m, 6H), 7.15 (s, 2H), 7.08 – 7.02 (m, 2H), 6.92 – 6.88 (m, 1H), 6.81 (d, J = 2.3 Hz, 1H), 6.62 (s, 1H), 6.58 (dd, J = 8.7, 2.4 Hz, 1H), 5.59 (s, 1H), 3.62 (s, 3H), 3.10 (s, 3H), 1.22 (s, 18H); ^{13}C {^{1}H} NMR (100 MHz, DMSO-d$_6$) δ 152.7, 151.7, 143.2, 142.0, 139.4, 139.0, 137.9, 137.3, 136.4, 132.4, 129.4, 129.1, 128.4, 128.2, 126.9, 126.7, 125.5, 125.3, 124.6, 121.3, 119.3, 118.8 114.2, 112.1, 111.9, 110.9, 109.3, 101.0, 55.1, 55.07, 52.2, 38.7, 34.5, 31.7, 30.6; FT-IR (thin film, neat): 3642, 3433, 2954, 1482, 736 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{46}H_{47}N_2O_2$ $[M+H]^+$: 659.3638; found : 659.3659.

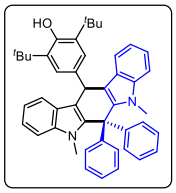
2,6-di-*tert*-butyl-4-(2,10-dimethoxy-5-methyl-6,6-diphenyl-5,6,7,12-tetrahydroindolo[2,3-*b*]carbazol-12-yl)phenol (29v): The reaction was performed at 0.086



mmol scale of **27a**; white solid (45.9 mg, 84% yield); m. p. = 271–273 ºC; R_f = 0.2 (15% EtOAc in hexane); ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.59 – 7.56 (m, 2H), 7.51 (s, 1H), 7.38 – 7.35 (m, 4H), 7.31 – 7.23 (m, 4H), 7.20 (s, 2H), 7.11 – 7.06 (m, 2H), 6.86 (d, J = 2.4 Hz, 1H), 6.82 – 6.79 (m, 2H), 6.71 (dd, J = 8.7, 2.5 Hz, 1H), 5.57 (s, 1H), 4.96 (s, 1H), 3.72 (s, 3H), 3.70 (s, 3H), 3.23 (s, 3H), 1.31 (s, 18H); ^{13}C {^{1}H} NMR (100 MHz, CDCl$_3$) δ 153.6, 153.5, 152.0, 142.9, 142.6, 139.3, 137.5, 135.7, 135.4, 133.6, 132.3, 129.7, 129.3 (2C), 128.8, 128.5, 127.2, 127.1, 127.0, 126.3, 125.5,

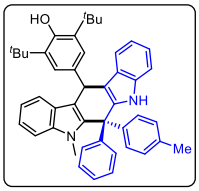
114.9, 114.4, 111.8, 111.6, 109.6, 101.7, 101.6, 55.7, 55.6, 52.7, 39.9, 39.8, 34.3, 32.3, 30.6; FT-IR (thin film, neat): 3632, 3367, 2924, 1485, 737 cm^{-1}; HRMS (APCI): *m/z* calcd for $C_{47}H_{49}N_2O_3$ $[M+H]^+$: 689.3743; found : 689.3766.

2,6-di-*tert*-butyl-4-(5,7-dimethyl-6,6-diphenyl-5,6,7,12-tetrahydroindolo[2,3-*b*]carbazol-12-yl)phenol (29w): The reaction was performed at 0.086 mmol scale of **27a**; white solid (47.2



mg, 85% yield); m. p. = 195–197 ºC; R_f = 0.3 (15% EtOAc in hexane); ^1H NMR (400 MHz, DMSO-d_6) δ 7.55 – 7.53 (m, 2H), 7.44 – 7.39 (m, 4H), 7.36 – 7.23 (m, 8H), 7.07 – 7.03 (m, 4H), 6.94 – 6.90 (m, 2H), 6.60 (s, 1H), 5.68 (s, 1H), 3.14 (s, 6H), 1.16 (s, 18H); ^{13}C {^1H} NMR (100 MHz, DMSO-d_6) δ 151.7, 142.9, 141.9, 138.92, 138.9, 138.3, 136.0, 129.2, 129.0, 128.8, 128.7, 127.2, 127.17, 125.0, 124.7, 121.4, 119.2, 118.9, 113.9, 109.5, 52.9, 38.8, 34.4, 32.4, 30.5; FT-IR (thin film, neat): 3635, 2956, 1469, 735 cm^{-1}; HRMS (APCI): *m/z* calcd for $C_{46}H_{47}N_2O$ $[M+H]^+$: 643.3688; found : 643.3699.

2,6-di-*tert*-butyl-4-(5-methyl-6-phenyl-6-(*p*-tolyl)-5,6,7,12-tetrahydroindolo[2,3-*b*]carbazol-12-yl)phenol (29x): The reaction was performed at 0.086 mmol scale of **1a** and



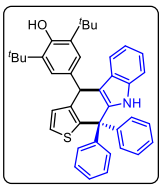
the product was obtained as an inseparable mixture of diastereomers in the ratio of 1:1; pale yellow gummy liquid (35.5 mg, 64% yield); R_f = 0.2 (10% EtOAc in hexane); ^1H NMR (400 MHz, $CDCl_3$) δ 7.65 – 7.54 (m, 3H), 7.49 – 7.44 (m, 2H), 7.40 – 7.29 (m, 3H), 7.27 – 7.15 (m, 8H), 7.11 – 7.07 (m, 2H), 7.07 – 6.97 (m, 2H), 5.69 (s, 1H), 4.93 (s, 1H), 3.28 – 3.26 (m, 3H), 2.38 – 2.34 (m, 3H), 1.31 – 1.30 (m, 18H); ^{13}C {^1H} NMR (100 MHz, $CDCl_3$) δ 152.0, 143.3, 142.6, 140.1, 139.4, 139.0, 138.8, 138.4, 138.3, 137.32, 137.31, 137.3, 137.2, 136.9, 136.85, 135.4, 135.3, 129.8, 129.7, 129.5, 129.3, 129.2, 129.17, 128.8, 128.5, 127.13, 127.12, 126.65, 126.63, 126.2, 125.3, 121.7, 121.4, 120.2, 120.1, 120.0, 119.3, 119.0, 115.5, 115.4, 114.53, 114.51, 114.4, 110.8, 108.8, 52.29, 52.27, 39.6, 34.34, 34.32, 32.22, 32.2, 30.54, 30.5, 21.1, 21.07; FT-IR (thin film, neat): 3634, 3432, 2954, 1594, 735 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{46}H_{47}N_2O$ $[M+H]^+$: 643.3688; found : 643.3716.

General procedure for the synthesis of tetrahydrothieno[2,3-b]carbazole derivatives (31a-k):

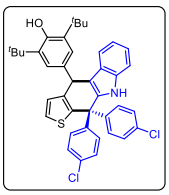
To a solution of *para*-quinone methide [**30a**] (30 mg, 1.0 equiv.) and 2-indolylmethanols [**28a-f** & **28j-n**] (1.0 equiv.) in toluene (1.5 mL), TsOH (1.0 equiv.) was added. The resulting reaction mixture was stirred at room temperature for 7 hours. After the reaction was complete (based on TLC analysis), the residue was then concentrated under reduced pressure and the

residue was then purified through a silica gel column using EtOAc/Hexane mixture as an eluent to get the pure product [**31a-k**].

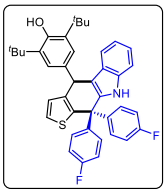
2,6-di-*tert*-butyl-4-(10,10-diphenyl-9,10-dihydro-4H-thieno[2,3-*b*]carbazol-4-yl)phenol (31a): The reaction was performed at 0.10 mmol scale of **30a**; white solid (53.0 mg, 91% yield); m. p. = 178–180 ºC; R_f = 0.6 (10% EtOAc in hexane); ^{1}H NMR (400 MHz, DMSO-d$_6$) δ 10.66 (s, 1H), 7.35 – 7.33 (m, 2H), 7.30 (d, J = 5.2 Hz, 1H), 7.27 – 7.21 (m, 5H), 7.19 – 7.15 (m, 2H), 7.11 – 7.09 (m, 3H), 6.96 (s, 2H), 6.94 – 6.90 (m, 1H), 6.78 – 6.75 (m, 1H), 6.70 (d, J = 5.2 Hz, 1H), 6.67 (s, 1H), 5.37 (s, 1H), 1.21 (s, 18H); ^{13}C {^{1}H} NMR (100 MHz, DMSO-d$_6$) δ 152.1, 147.2, 146.7, 142.0, 139.8, 139.0, 137.4, 136.6, 135.7, 128.8, 128.7, 128.1, 128.0, 126.8, 126.7, 126.6, 126.1, 125.3, 124.5, 121.2, 119.1, 118.3, 112.0, 111.4, 53.6, 41.32, 41.31, 34.5, 30.5; FT-IR (thin film, neat): 3631, 3226, 2940, 1490, 735 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{40}H_{40}NOS$ $[M+H]^+$: 582.2831; found : 582.2828.



4-(10,10-bis(4-chlorophenyl)-9,10-dihydro-4H-thieno[2,3-*b*]carbazol-4-yl)-2,6-di-*tert*-butylphenol (31b): The reaction was performed at 0.10 mmol scale of **30a**; white solid (55.3 mg, 85% yield); m. p. = 246–248 ºC; R_f = 0.6 (10% EtOAc in hexane); ^{1}H NMR (400 MHz, DMSO-d$_6$) δ 10.76 (s, 1H), 7.38 – 7.35 (m, 5H), 7.32 – 7.29 (m, 2H), 7.23 – 7.21 (m, 1H), 7.14 – 7.06 (m, 3H), 6.98 – 6.94 (m, 1H), 6.89 – 6.88 (m, 2H), 6.82 – 6.79 (m, 1H), 6.76 (d, J = 5.2 Hz, 1H), 6.684 – 6.68 (m, 1H), 5.40 – 5.39 (m, 1H), 1.19 – 1.18 (s, 18H); ^{13}C {^{1}H} NMR (100 MHz, DMSO-d$_6$) δ 152.1, 145.6, 145.0, 141.0, 140.4, 139.0, 137.4, 135.9, 135.3, 131.73, 131.7, 130.44, 130.42, 128.2, 128.1, 127.1, 126.5, 125.2, 124.3, 121.5, 119.2, 118.5, 112.5, 111.4, 52.7, 41.2, 34.5, 30.4; FT-IR (thin film, neat): 3633, 3443, 2923, 1487, 742 cm^{-1}; HRMS (APCI): *m/z* calcd for $C_{40}H_{38}Cl_2NOS$ $[M+H]^+$: 650.2051; found : 650.2074.

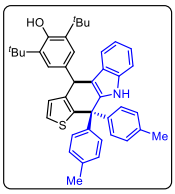


4-(10,10-bis(4-fluorophenyl)-9,10-dihydro-4H-thieno[2,3-*b*]carbazol-4-yl)-2,6-di-*tert*-butylphenol (31c): The reaction was performed at 0.10 mmol scale of **30a**; white solid (53.1 mg, 86% yield); gummy solid; R_f = 0.6 (10% EtOAc in hexane); ^{1}H NMR (400 MHz, DMSO-d$_6$) δ 10.74 (s, 1H), 7.38 – 7.31 (m, 3H), 7.21 (d, J = 8.0 Hz, 1H), 7.15 – 7.08 (m, 7H), 6.95 (t, J = 7.4 Hz, 1H), 6.90 – 6.87 (m, 2H), 6.81 – 6.78 (m, 1H), 6.76 – 6.72 (m, 1H), 6.68 – 6.65 (m, 1H), 5.38 (s, 1H), 1.19 (s, 18H); ^{13}C {^{1}H} NMR (100 MHz, DMSO-d$_6$) δ 161.0 (d, J_{C-F} = 242.8 Hz), 160.9 (d, J_{C-F} = 242.4 Hz), 152.1, 143.2 (d, J_{C-F} = 3.2 Hz), 142.6 (d, J_{C-F} = 2.9 Hz), 141.8, 140.1, 139.0, 137.4, 136.5, 135.4, 130.6, 130.5, 127.0, 126.4, 125.2, 124.3, 121.4, 119.2, 118.5, 114.92 (d, J_{C-F} = 21.2 Hz),

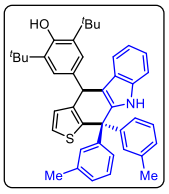


114.87 (d, $J_{C\text{-}F}$ = 21.1 Hz), 112.2, 111.4, 52.5, 41.2, 34.5, 30.4; $^{19}F\{^{1}H\}$ NMR (376 MHz, $CDCl_3$) δ –116.03, –116.16; FT-IR (thin film, neat): 3643, 3463, 2922, 1504, 740 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{40}H_{36}F_2NOS$ $[M–H]^-$: 616.2486; found : 616.2504.

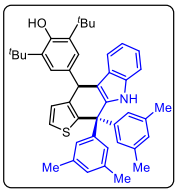
2,6-di-*tert*-butyl-4-(10,10-di-*p*-tolyl-9,10-dihydro-4H-thieno[2,3-*b*]carbazol-4-yl)phenol (31d): The reaction was performed at 0.10 mmol scale of **30a**; white solid (48.8 mg, 80% yield); m. p. = 195–197 ºC; R_f = 0.6 (10% EtOAc in hexane); ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.58 (s, 1H), 7.29 (d, J = 5.2 Hz, 1H), 7.22 – 7.18 (m, 3H), 7.10 – 7.05 (m, 5H), 6.99 – 6.97 (m, 2H), 6.95 – 6.90 (m, 3H), 6.78 – 6.75 (m, 1H), 6.69 (d, J = 5.2 Hz, 1H), 6.66 (s, 1H), 5.35 (s, 1H), 2.22 (s, 3H), 2.21 (s, 3H), 1.21 (s, 18H); ^{13}C $\{^{1}H\}$ NMR (100 MHz, DMSO-d_6) δ 152.0, 144.4, 143.9, 142.5, 139.6, 138.9, 137.3, 137.1, 135.73, 135.7, 135.66, 128.7, 128.6, 128.56, 128.5, 126.8, 125.8, 125.3, 124.4, 121.1, 119.0, 118.2, 111.7, 111.3, 52.9, 41.31, 41.3, 34.5, 30.5, 20.6, 20.5; FT-IR (thin film, neat): 3644, 3462, 2923, 1457, 738 cm^{-1}; HRMS (APCI): *m/z* calcd for $C_{42}H_{44}NOS$ $[M+H]^+$: 610.3144; found : 610.3147.



2,6-di-*tert*-butyl-4-(10,10-di-*m*-tolyl-9,10-dihydro-4H-thieno[2,3-*b*]carbazol-4-yl)phenol (31e): The reaction was performed at 0.10 mmol scale of **30a**; white solid (47.0 mg, 77% yield); m. p. = 205–207 ºC; R_f = 0.6 (10% EtOAc in hexane); ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.62 (s, 1H), 7.28 (d, J = 5.2 Hz, 1H), 7.19 (d, J = 8.0 Hz, 1H), 7.15 – 7.10 (m, 4H), 7.09 – 6.98 (m, 3H), 6.96 (m, 2H), 6.93 – 6.89 (m, 3H), 6.75 (t, J = 7.3 Hz, 1H), 6.67 – 6.66 (m, 2H), 5.34 (s, 1H), 2.17 (s, 3H), 2.14 (s, 3H), 1.21 (s, 18H); ^{13}C $\{^{1}H\}$ NMR (100 MHz, DMSO-d_6) δ 152.0, 147.4, 146.8, 142.1, 139.7, 139.0 (2C), 137.4, 137.0, 136.9, 136.7, 135.8, 129.33, 129.3, 129.2, 127.9, 127.3, 126.8, 126.1, 125.9, 125.3, 124.5, 121.1, 119.15, 119.1, 118.3, 111.8, 111.4, 53.5, 41.34, 41.33, 34.5, 30.5, 21.45, 21.43, 21.36, 21.34; FT-IR (thin film, neat): 3643, 3459, 2923, 1484, 738 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{42}H_{44}NOS$ $[M+H]^+$: 610.3144; found : 610.3138.

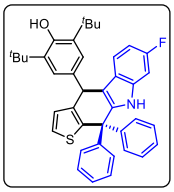


4-(10,10-bis(3,5-dimethylphenyl)-9,10-dihydro-4H-thieno[2,3-*b*]carbazol-4-yl)-2,6-di-*tert*-butylphenol (31f): The reaction was performed at 0.10 mmol scale of **30a**; white solid (45.9 mg, 72% yield); gummy solid; R_f = 0.6 (10% EtOAc in hexane); ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.57 (s, 1H), 7.31 (d, J = 5.2 Hz, 1H), 7.20 (d, J = 8.0 Hz, 1H), 7.01 (d, J = 8.0 Hz, 1H), 6.97 (s, 2H), 6.94 – 6.91 (m, 3H), 6.86 (s, 1H), 6.80 (s, 1H), 6.77 – 6.74 (m, 1H), 6.69 – 6.68 (m, 3H), 6.66 (d, J = 5.2 Hz, 1H), 5.32 (s, 1H), 2.15 (s, 6H), 2.12 (s, 6H), 1.21 (s, 18H); ^{13}C $\{^{1}H\}$ NMR (100 MHz, DMSO-d_6) δ 152.0, 147.6, 147.0, 142.1, 139.6, 139.0, 137.3, 136.8, 136.71, 136.69, 135.8,

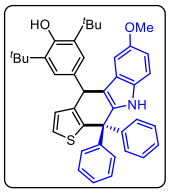


128.1, 128.0, 126.7, 126.51, 126.46, 125.8, 125.3, 124.5, 121.1, 119.1, 118.2, 111.6, 111.4, 53.3, 41.3, 34.5, 30.5, 21.34, 21.32, 21.25, 21.23; FT-IR (thin film, neat): 3646, 3433, 2922, 1458, 740 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{44}H_{48}NOS$ $[M+H]^+$: 638.3457; found : 638.3468.

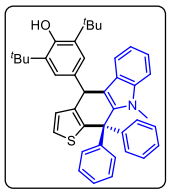
2,6-di-*tert*-butyl-4-(7-fluoro-10,10-diphenyl-9,10-dihydro-4H-thieno[2,3-*b*]carbazol-4-yl)phenol (31g): The reaction was performed at 0.10 mmol scale of **30a**; white solid (49.2 mg, 82% yield); m. p. = 115–117 ºC; R_f = 0.6 (10% EtOAc in hexane); ^1H NMR (400 MHz, DMSO-d_6) δ 10.81 (s, 1H), 7.37 (d, J = 5.2 Hz, 1H), 7.35 – 7.29 (m, 6H), 7.27 – 7.21 (m, 2H), 7.13 – 7.11 (m, 2H), 7.06 – 7.03 (m, 1H), 6.97 – 6.93 (m, 3H), 6.74 (d, J = 5.2 Hz, 1H), 6.72 – 6.66 (m, 2H), 5.39 (s, 1H), 1.23 (s, 18H); ^{13}C {^1H} NMR (100 MHz, DMSO-d_6) δ 158.8 (d, $J_{C\text{-}F}$ = 233.1 Hz), 152.1, 147.0, 146.5, 141.8, 139.7, 139.1, 137.4, 137.3 (d, $J_{C\text{-}F}$ = 3.7 Hz), 135.4, 128.7, 128.6, 128.13, 128.1, 126.8, 126.7, 126.2, 124.4, 122.1, 120.0 (d, $J_{C\text{-}F}$ = 10.1 Hz), 112.1, 106.7 (d, $J_{C\text{-}F}$ = 24.3 Hz), 97.5, 97.3, 53.5, 41.1, 41.0, 34.5, 30.5; $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$) δ –121.4; FT-IR (thin film, neat): 3643, 3463, 2922, 1460, 730 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{40}H_{37}FNOS$ $[M–H]^–$: 598.2580; found : 598.2604.



2,6-di-*tert*-butyl-4-(6-methoxy-10,10-diphenyl-9,10-dihydro-4H-thieno[2,3-*b*]carbazol-4-yl)phenol (31h): The reaction was performed at 0.10 mmol scale of **30a**; white solid (45.2 mg, 74% yield); gummy solid; R_f = 0.5 (10% EtOAc in hexane); ^1H NMR (400 MHz, DMSO-d_6) δ 10.50 (s, 1H), 7.37 – 7.34 (m, 3H), 7.32 – 7.30 (m, 2H), 7.28 – 7.24 (m, 3H), 7.22 – 7.18 (m, 1H), 7.12 – 7.09 (m, 3H), 7.02 (s, 2H), 6.71 (s, 1H), 6.66 (d, J = 5.2 Hz, 1H), 6.62 – 6.60 (m, 2H), 5.33 (s, 1H), 3.57 (s, 3H), 1.25 (s, 18H); ^{13}C {^1H} NMR (100 MHz, DMSO-d_6) δ 152.7, 152.0, 147.3, 146.8, 142.2, 139.9, 139.0, 136.9, 135.7, 132.4, 128.8, 128.6, 128.03, 128.0, 126.9, 126.6, 126.1, 125.6, 124.6, 112.1, 112.01, 112.0, 111.0, 101.2, 55.1, 55.0, 53.6, 41.5, 34.5, 30.5; FT-IR (thin film, neat): 3674, 3445, 2924, 1485, 737 cm^{-1}; HRMS (APCI): *m/z* calcd for $C_{41}H_{42}NO_2S$ $[M+H]^+$: 612.2936; found : 612.2931.

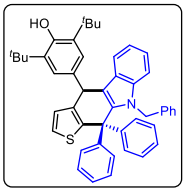


2,6-di-*tert*-butyl-4-(9-methyl-10,10-diphenyl-9,10-dihydro-4H-thieno[2,3-*b*]carbazol-4-yl)phenol (31i): The reaction was performed at 0.10 mmol scale of **30a**; white solid (41.1 mg, 69% yield); m. p. = 253–255 ºC; R_f = 0.6 (10% EtOAc in hexane); ^1H NMR (400 MHz, $CDCl_3$) δ 7.59 – 7.57 (m, 2H), 7.41 – 7.38 (m, 3H), 7.36 – 7.32 (m, 2H), 7.30 – 7.26 (m, 3H), 7.24 – 7.15 (m, 3H), 7.09 (d, J = 5.2 Hz, 1H), 7.04 – 7.00 (m, 3H), 6.72 (d, J = 5.2 Hz, 1H), 5.47 (s, 1H), 4.97 (s, 1H), 3.15 (s, 3H), 1.30 (s, 18H); ^{13}C {^1H} NMR (100 MHz, $CDCl_3$) δ 152.2, 145.7, 145.3, 143.7, 138.8, 138.4, 137.9, 135.6, 135.2, 129.9, 129.8, 128.3, 128.1, 126.93, 126.9, 126.5, 125.8, 125.2, 125.0,

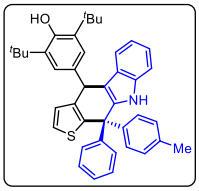


121.6, 120.2, 119.0, 113.9, 108.9, 54.2, 42.32, 42.3, 34.4, 32.1, 30.5; FT-IR (thin film, neat): 3635, 2923, 1469, 738 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{41}H_{42}NOS$ $[M+H]^+$: 596.2987; found : 596.2976.

4-(9-benzyl-10,10-diphenyl-9,10-dihydro-4H-thieno[2,3-*b*]carbazol-4-yl)-2,6-di-*tert*-butylphenol (31j): The reaction was performed at 0.10 mmol scale of **30a**; white solid (22.2 mg, 33% yield); m. p. = 215–217 ºC; R_f = 0.5 (10% EtOAc in hexane); ^1H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, *J* = 7.2 Hz, 2H), 7.39 – 7.35 (m, 3H), 7.20 – 7.13 (m, 3H), 7.11 – 7.08 (m, 5H), 7.05 – 6.97 (m, 4H), 6.91 – 6.88 (m, 3H), 6.77 (d, *J* = 5.3 Hz, 1H), 6.25 (d, *J* = 7.4 Hz, 2H), 5.56 (s, 1H), 5.16 – 5.04 (m, 2H), 5.03 (s, 1H), 1.36 (s, 18H); ^{13}C {^1H} NMR (100 MHz, $CDCl_3$) δ 152.3, 145.8, 144.5, 143.7, 138.4, 138.2, 138.1, 137.1, 135.7, 135.3, 129.9, 129.7, 128.2, 128.1, 127.8, 126.8, 126.7, 126.3, 126.2, 126.1, 125.4, 125.3, 125.2, 122.0, 120.3, 119.4, 113.7, 110.4, 54.3, 49.1, 42.15, 42.13, 34.4, 30.5; FT-IR (thin film, neat): 3634, 2957, 1465, 732 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{47}H_{46}NOS$ $[M+H]^+$: 672.3300; found : 672.3315.



2,6-di-*tert*-butyl-4-(10-phenyl-10-(*p*-tolyl)-9,10-dihydro-4H-thieno[2,3-*b*]carbazol-4-yl)phenol (31k): The reaction was performed at 0.10 mmol scale of **4a** and the product was obtained as an inseparable mixture of diastereomers in the ratio of 1:1; pale yellow gummy liquid (50.0 mg, 84% yield); R_f = 0.6 (10% EtOAc in hexane); ^1H NMR (400 MHz, DMSO-d_6) δ 10.62 (s, 1H), 7.33 – 7.31 (m, 2H), 7.27 – 7.17 (m, 5H), 7.10 – 7.05 (m, 4H), 6.98 – 6.90 (m, 4H), 6.78 – 6.75 (m, 1H), 6.70 – 6.68 (m, 1H), 6.67 (s, 1H), 5.36 – 5.35 (m, 1H), 2.22– 2.21 (m, 3H), 1.20 (s, 18H); ^{13}C {^1H} NMR (100 MHz, DMSO-d_6) δ 152.0, 147.3, 146.8, 144.4, 143.7, 142.28, 142.26, 139.77, 139.73, 139.0, 138.97, 137.4, 136.91, 136.9, 135.83, 135.8, 135.7, 128.8, 128.7, 128.63, 128.61, 128.6, 128.05, 128.0, 126.83, 126.81, 126.7, 126.6, 126.0, 125.3, 124.4, 121.1, 119.1, 118.3, 111.9, 111.3, 53.2, 41.3, 41.27, 34.5, 30.5, 20.6; FT-IR (thin film, neat): 3633, 3224, 2942, 1493, 737 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{41}H_{42}NOS$ $[M+H]^+$: 596.2987; found : 596.2985.

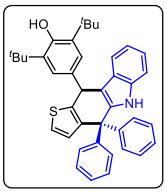


General procedure for the synthesis of tetrahydrothieno[3,2-b]carbazole derivatives (33a-k):

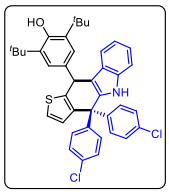
Para-quinone methide [**32a-c**] (30 mg, 1.0 equiv.) and 2-indolylmethanols [**28a-e**, **28i-k** & **28n**] (1.0 equiv.) were dissolved in acetonitrile (1.5 mL) and, then TsOH (1.0 equiv.) was added. The resulting reaction mixture was stirred at room temperature for 1 hour. After the reaction was complete (based on TLC analysis), the residue was then concentrated under

reduced pressure and the residue was then purified through a silica gel column using EtOAc/Hexane mixture as an eluent to get the pure products [**33a-k**].

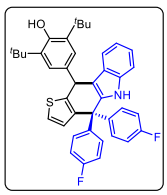
2,6-di-*tert*-butyl-4-(4,4-diphenyl-5,10-dihydro-4H-thieno[3,2-*b*]carbazol-10-yl)phenol (33a): The reaction was performed at 0.10 mmol scale of **32a**; white solid (51.2 mg, 88% yield); gummy solid; R_f = 0.6 (10% EtOAc in hexane); ^{1}H NMR (400 MHz, DMSO-d$_6$) δ 10.64 (s, 1H), 7.34 – 7.26 (m, 7H), 7.25 – 7.18 (m, 3H), 7.16 – 7.11 (m, 3H), 7.02 (s, 2H), 6.96 (t, J = 7.5 Hz, 1H), 6.81 (t, J = 7.5 Hz, 1H), 6.75 (s, 1H), 6.68 (d, J = 5.3 Hz, 1H), 5.61 (s, 1H), 1.24 (s, 18H); ^{13}C {^{1}H} NMR (100 MHz, DMSO-d$_6$) δ 152.3, 146.3, 146.0, 141.3, 139.3, 139.0 (2C), 137.4, 137.3, 136.4, 128.8 (2C), 128.1 (2C), 127.3, 126.4, 125.0, 124.9, 124.2, 121.1, 119.1, 118.3, 111.4, 111.3, 53.4, 40.9, 40.88, 34.5, 30.5; FT-IR (thin film, neat): 3637, 3457, 2923, 1488, 738 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{40}H_{40}NOS$ $[M+H]^+$: 582.2831; found : 582.2820.



4-(4,4-bis(4-chlorophenyl)-5,10-dihydro-4H-thieno[3,2-*b*]carbazol-10-yl)-2,6-di-*tert*-butylphenol (33b): The reaction was performed at 0.10 mmol scale of **32a**; white solid (47.5 mg, 73% yield); m. p. = 236–238 ºC; R_f = 0.6 (10% EtOAc in hexane); ^{1}H NMR (400 MHz, DMSO-d$_6$) δ 10.72 (s, 1H), 7.39 – 7.36 (m, 5H), 7.31 – 7.28 (m, 2H), 7.24 (d, J = 8.1 Hz, 1H), 7.18 (d, J = 7.9 Hz, 1H), 7.08 (d, J = 8.6 Hz, 2H), 7.01 – 6.97 (m, 1H), 6.94 (s, 2H), 6.84 (t, J = 7.4 Hz, 1H), 6.75 (s, 1H), 6.69 (d, J = 5.3 Hz, 1H), 5.62 (s, 1H), 1.22 (s, 18H); ^{13}C {^{1}H} NMR (100 MHz, DMSO-d$_6$) δ 152.3, 144.9, 144.4, 141.9, 139.0, 138.6, 137.4, 136.6, 136.1, 131.5, 131.4, 130.6, 130.5, 128.2, 128.1, 126.9, 125.3, 125.0, 124.1, 121.4, 119.1, 118.5, 111.8, 111.4, 52.6, 40.75, 40.73, 34.5, 30.4; FT-IR (thin film, neat): 3638, 3457, 2923, 1489, 739 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{40}H_{36}Cl_2NOS$ $[M–H]^–$: 648.1895; found : 648.1915.

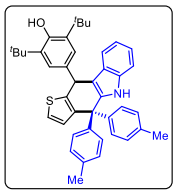


4-(4,4-bis(4-fluorophenyl)-5,10-dihydro-4H-thieno[3,2-*b*]carbazol-10-yl)-2,6-di-*tert*-butylphenol (33c): The reaction was performed at 0.10 mmol scale of **32a**; white solid (47.0 mg, 73% yield); gummy solid; R_f = 0.6 (10% EtOAc in hexane); ^{1}H NMR (400 MHz, DMSO-d$_6$) δ 10.70 (s, 1H), 7.34 – 7.30 (m, 3H), 7.24 (d, J = 8.1 Hz, 1H), 7.17 – 7.14 (m, 2H), 7.13 – 7.07 (m, 5H), 6.98 (d, J = 7.4 Hz, 1H), 6.96 (s, 2H), 6.83 (t, J = 7.5 Hz, 1H), 6.75 (s, 1H), 6.68 (d, J = 5.3 Hz, 1H), 5.60 (s, 1H), 1.22 (s, 18H); ^{13}C {^{1}H} NMR (100 MHz, DMSO-d$_6$) δ 160.8 (d, $J_{C\text{-}F}$ = 242.2 Hz), 152.3, 142.4 (d, $J_{C\text{-}F}$ = 3.0 Hz), 142.0 (d, $J_{C\text{-}F}$ = 3.0 Hz), 141.6, 139.2, 139.0, 137.4, 137.2, 136.2, 130.73, 130.7, 130.6, 127.0, 125.2, 125.0, 124.1, 121.3, 119.1, 118.5, 114.9 (d, $J_{C\text{-}F}$ = 21.0 Hz), 114.8 (d, $J_{C\text{-}F}$ = 21.2 Hz), 111.5, 114.4, 52.3, 40.8, 40.78, 34.5, 30.4; ^{19}F {^{1}H} NMR (376 MHz, $CDCl_3$) δ –

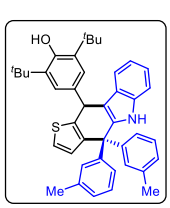


116.44, –116.48; FT-IR (thin film, neat): 3649, 3458, 2921, 1459, 741 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{40}H_{38}F_2NOS$ $[M+H]^+$: 618.2642; found : 618.2635.

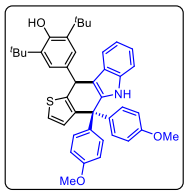
2,6-di-*tert*-butyl-4-(4,4-di-p-tolyl-5,10-dihydro-4H-thieno[3,2-*b*]carbazol-10-yl)phenol (33d): The reaction was performed at 0.10 mmol scale of **32a**; white solid (43.9 mg, 72% yield); m. p. = 197–199 ºC; R_f = 0.6 (10% EtOAc in hexane); ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.56 (s, 1H), 7.27 (d, *J* = 5.3 Hz, 1H), 7.23 – 7.20 (m, 2H), 7.18 (s, 1H), 7.13 (d, *J* = 7.9 Hz, 1H), 7.07 (d, *J* = 7.9 Hz, 4H), 7.00 – 6.93 (m, 5H), 6.80 (t, *J* = 7.5 Hz, 1H), 6.73 (s, 1H), 6.64 (d, *J* = 5.3 Hz, 1H), 5.57 (s, 1H), 2.24 (s, 3H), 2.23 (s, 3H), 1.23 (s, 18H); ^{13}C {^{1}H} NMR (100 MHz, DMSO-d_6) δ 152.2, 143.5, 143.2, 141.1, 139.8, 139.0, 137.9, 137.3, 136.4, 135.5, 135.4, 128.75, 128.7, 128.6, 127.3, 125.1, 124.6, 124.2, 121.0, 119.0, 118.2, 111.3 (2C), 111.1, 52.7, 40.9, 40.88, 34.5, 30.4, 20.52, 20.51; FT-IR (thin film, neat): 3640, 3457, 2922, 1457, 738 cm^{-1}; HRMS (APCI): *m/z* calcd for $C_{42}H_{44}NOS$ $[M+H]^+$: 610.3144; found : 610.3157.



2,6-di-*tert*-butyl-4-(4,4-di-*m*-tolyl-5,10-dihydro-4H-thieno[3,2-*b*]carbazol-10-yl)phenol (33e): The reaction was performed at 0.10 mmol scale of **32a**; white solid (53.0 mg, 87% yield); m. p. = 205–207 ºC; R_f = 0.6 (10% EtOAc in hexane); ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.61 (s, 1H), 7.28 (d, *J* = 5.3 Hz, 1H), 7.23 (d, *J* = 8.1 Hz, 1H), 7.19 – 7.13 (m, 3H), 7.12 – 7.10 (m, 2H), 7.05 – 7.03 (m, 3H), 7.01 (d, *J* = 7.6 Hz, 1H), 6.95 (t, *J* = 7.4 Hz, 1H), 6.92 – 6.90 (m, 2H), 6.80 (t, *J* = 7.5 Hz, 1H), 6.75 (s, 1H), 6.69 (d, *J* = 5.3 Hz, 1H), 5.58 (s, 1H), 2.21 (s, 3H), 2.18 (s, 3H), 1.25 (s, 18H); ^{13}C {^{1}H} NMR (100 MHz, DMSO-d_6) δ 152.3, 146.5, 146.1, 141.3, 139.3, 139.0, 137.5, 137.3, 136.9 (2C), 136.4, 129.4, 129.3, 127.9, 127.4, 127.12, 127.1, 126.13, 126.1, 125.0, 124.7, 124.6, 124.2, 121.1, 119.1, 118.2, 111.4, 111.1, 53.3, 40.95, 40.93, 34.5, 30.5, 21.41, 21.4, 21.33, 21.31; FT-IR (thin film, neat): 3638, 3458, 2922, 1457, 739 cm^{-1}; HRMS (APCI): *m/z* calcd for $C_{42}H_{44}NOS$ $[M+H]^+$: 610.3144; found : 610.3148.

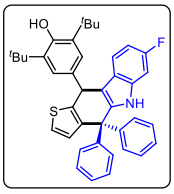


4-(4,4-bis(3-methoxyphenyl)-5,10-dihydro-4H-thieno[3,2-*b*]carbazol-10-yl)-2,6-di-*tert*-butylphenol (33f): The reaction was performed at 0.10 mmol scale of **32a**; white solid (44.3 mg, 69% yield); gummy solid; R_f = 0.4 (10% EtOAc in hexane); ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.58 (s, 1H), 7.29 (d, *J* = 5.3 Hz, 1H), 7.23 – 7.20 (m, 3H), 7.14 (d, *J* = 8.0 Hz, 1H), 7.02 – 6.99 (m, 4H), 6.95 (t, *J* = 7.7 Hz, 1H), 6.85 – 6.82 (m, 4H), 6.80 (d, *J* = 7.2 Hz, 1H), 6.73 (s, 1H), 6.64 (d, *J* = 5.3 Hz, 1H), 5.56 (s, 1H), 3.694 (s, 3H), 3.691 (s, 3H), 1.23 (s, 18H); ^{13}C {^{1}H} NMR (100 MHz, DMSO-d_6) δ 157.7, 157.6, 152.2, 140.8, 140.2, 139.0, 138.6, 138.3, 138.2, 137.3, 136.4, 129.9, 129.8, 127.3, 125.1, 124.65, 124.6, 124.2, 121.0, 119.0, 118.2, 113.4, 111.3, 110.9, 55.1, 55.07,

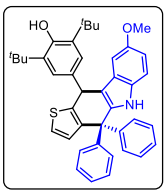


52.0, 40.89, 40.87, 34.5, 30.4; FT-IR (thin film, neat): 3626, 3455, 2922, 1458, 738 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{42}H_{44}NO_3S$ $[M+H]^+$: 642.3042; found : 642.3058.

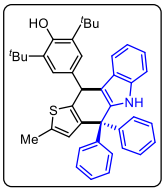
2,6-di-*tert*-butyl-4-(7-fluoro-4,4-diphenyl-5,10-dihydro-4H-thieno[3,2-*b*]carbazol-10-yl)phenol (33g): The reaction was performed at 0.10 mmol scale of **32a**; white solid (39.0 mg, 65% yield); gummy solid; R_f = 0.6 (10% EtOAc in hexane); ^1H NMR (400 MHz, DMSO-d_6) δ 10.76 (s, 1H), 7.30 – 7.29 (m, 6H), 7.26 (s, 1H), 7.25 – 7.19 (m, 2H), 7.11 (d, J = 7.6 Hz, 2H), 7.09 – 7.05 (m, 1H), 7.00 (s, 2H), 6.98 – 6.95 (m, 1H), 6.76 (s, 1H), 6.72 – 6.66 (m, 2H), 5.60 (s, 1H), 1.24 (s, 18H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ 158.7 (d, $J_{C\text{-}F}$ = 232.8 Hz), 152.3, 146.1, 145.8, 141.2, 139.12, 139.1, 138.1 (d, $J_{C\text{-}F}$ = 3.4 Hz), 137.3 (d, $J_{C\text{-}F}$ = 12.7 Hz), 136.1, 128.8, 128.77, 128.1, 127.2, 126.5, 124.9, 124.2, 121.9, 119.9, 111.4, 106.7 (d, $J_{C\text{-}F}$ = 24.4 Hz), 106.7 (d, $J_{C\text{-}F}$ = 24.5 Hz), 97.6 (d, $J_{C\text{-}F}$ = 1.6 Hz), 97.3 (d, $J_{C\text{-}F}$ = 1.5 Hz), 53.4, 40.7, 40.68, 34.5, 30.5; $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$) δ –121.47; FT-IR (thin film, neat): 3615, 3458, 2923, 1488, 736 cm^{-1}; HRMS (APCI): *m/z* calcd for $C_{40}H_{39}FNOS$ $[M+H]^+$: 600.2736; found : 600.2725.



2,6-di-*tert*-butyl-4-(8-methoxy-4,4-diphenyl-5,10-dihydro-4H-thieno[3,2-*b*]carbazol-10-yl)phenol (33h): The reaction was performed at 0.10 mmol scale of **32a**; white solid (42.8 mg, 70% yield); m. p. = 246–248 ºC; R_f = 0.5 (10% EtOAc in hexane); ^1H NMR (400 MHz, $CDCl_3$) δ 10.46 (s, 1H), 7.35 – 7.30 (m, 5H), 7.28 – 7.24 (m, 3H), 7.23 – 7.19 (m, 1H), 7.12 – 7.10 (m, 3H), 7.05 (s, 2H), 6.76 (s, 1H), 6.69 (d, J = 5.3 Hz, 1H), 6.65 – 6.64 (m, 1H), 6.63 – 6.60 (m, 1H), 5.54 (s, 1H), 3.59 (s, 3H), 1.26 (s, 18H); ^{13}C $\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 152.7, 152.3, 146.4, 146.1, 141.3, 139.6, 139.0, 137.7, 136.4, 132.4, 128.82, 128.8, 128.06, 128.04, 127.2, 126.43, 126.4, 125.3, 124.9, 124.4, 112.0, 111.5, 110.9, 101.1, 55.12, 55.1, 53.5, 41.08, 41.04, 34.5, 30.5; FT-IR (thin film, neat): 3627, 3456, 2922, 1483, 736 cm^{-1}; HRMS (APCI): *m/z* calcd for $C_{41}H_{42}NO_2S$ $[M+H]^+$: 612.2936; found : 612.2917.

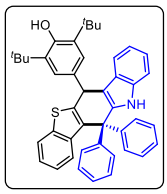


2,6-di-*tert*-butyl-4-(2-methyl-4,4-diphenyl-5,10-dihydro-4H-thieno[3,2-*b*]carbazol-10-yl)phenol (33i): The reaction was performed at 0.095 mmol scale of **32b**; white solid (47.1 mg, 83% yield); m. p. = 273–275 ºC; R_f = 0.6 (10% EtOAc in hexane); ^1H NMR (400 MHz, $CDCl_3$) δ 7.64 (s, 1H), 7.40 – 7.38 (m, 2H), 7.34 – 7.26 (m, 8H), 7.24 – 7.21 (m, 2H), 7.10 (t, J = 7.2 Hz, 1H), 7.07 (s, 2H), 6.98 (t, J = 7.4 Hz, 1H), 6.47 (s, 1H), 5.53 (s, 1H), 5.05 (s, 1H), 2.35 (s, 3H), 1.36 (s, 18H); ^{13}C $\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 152.5, 146.2, 146.1, 140.2, 138.6, 138.4, 137.5, 137.0, 135.6, 135.5, 129.12, 129.1, 128.43, 128.4, 126.8, 126.7, 126.3, 124.9, 124.8, 121.8, 120.1, 119.3, 113.2,

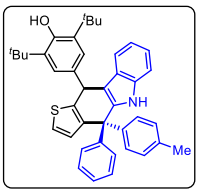


110.9, 53.8, 41.87, 41.85, 34.4, 30.5, 15.91, 15.9; FT-IR (thin film, neat): 3620, 3450, 2956, 1434, 732 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{41}H_{42}NOS$ $[M+H]^+$: 596.2987; found : 596.2992.

2,6-di-*tert*-butyl-4-(12,12-diphenyl-11,12-dihydro-6H-benzo[4,5]thieno[3,2-*b*]carbazol-6-yl)phenol (33j): The reaction was performed at 0.086 mmol scale of **32c**; white solid (33.0 mg, 61% yield); gummy solid; R_f = 0.5 (10% EtOAc in hexane); ^1H NMR (400 MHz, $CDCl_3$) δ 7.71 – 7.69 (m, 1H), 7.61 (s, 1H), 7.53 – 7.50 (m, 2H), 7.33 – 7.29 (m, 4H), 7.28 – 7.22 (m, 6H), 7.18 – 7.09 (m, 3H), 7.07 – 7.04 (m, 3H), 7.02 – 6.97 (m, 1H), 5.67 (s, 1H), 5.05 (s, 1H), 1.30 (s, 18H); ^{13}C {^1H} NMR (100 MHz, $CDCl_3$) δ 152.8, 145.9, 143.8, 143.5, 140.3, 139.6, 138.0, 137.0, 135.9, 134.4, 132.6, 129.5, 129.4 (2C), 128.6, 128.5, 127.1, 126.2, 125.2, 124.9, 123.4, 123.3, 122.5, 121.9, 120.0, 119.6, 112.4, 111.1, 54.1, 43.2, 43.1, 34.4, 30.4; FT-IR (thin film, neat): 3632, 3456, 2922, 1457, 739 cm^{-1}; HRMS (APCI): *m/z* calcd for $C_{44}H_{42}NOS$ $[M+H]^+$: 632.2987; found : 632.2999.



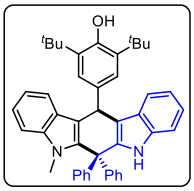
2,6-di-*tert*-butyl-4-(4-phenyl-4-(*p*-tolyl)-5,10-dihydro-4H-thieno[3,2-*b*]carbazol-10-yl)phenol (33k): The reaction was performed at 0.10 mmol scale of **6a** and the product was obtained as an inseparable mixture of diastereomers in the ratio of 1:1; pale yellow gummy solid (44.6 mg, 75% yield); R_f = 0.6 (10% EtOAc in hexane); ^1H NMR (400 MHz, DMSO-d_6) δ 10.57 (s, 1H), 7.29 – 7.22 (m, 4H), 7.20 – 7.15 (m, 3H), 7.12 – 7.04 (m, 4H), 6.97 – 6.90 (m, 4H), 6.79 – 6.75 (m, 1H), 6.72 (s, 1H), 6.64 – 6.61 (m, 1H), 5.56 – 5.55 (m, 1H), 2.21 – 2.20 (m, 3H), 1.20 (s, 18H); ^{13}C {^1H} NMR (100 MHz, DMSO-d_6) δ 152.3, 146.4, 146.1, 143.4, 143.1, 141.2, 141.19, 139.6, 139.03, 139.02, 137.7, 137.6, 137.3, 136.4, 135.6, 135.5, 128.8, 128.77, 128.65, 128.1, 127.3, 126.4, 125.1, 124.8, 124.3, 121.12, 121.10, 119.1, 118.3, 111.4, 111.21, 111.2, 53.1, 40.90, 40.89, 34.5, 30.5, 20.6, 20.5; FT-IR (thin film, neat): 3635, 3454, 2920, 1484, 735 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{41}H_{42}NOS$ $[M+H]^+$: 596.2987; found : 596.2994.



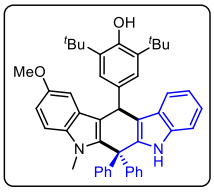
General procedure for the enantioselective synthesis of tetrahydroindolo[2,3-b]carbazole derivatives (29):

To a solution of *p*-QM [**27a** or **27f**] (30 mg, 1.0 equiv.) and 2-indolylmethanol [**28a** or **28k**] (1.0 equiv.) in CCl_4 (2.0 mL), chiral phosphoric acid [**C1**] (0.5 mol%) was added, and the resulting suspension was stirred at room temperature for 12 hours. After the reaction was complete (based on TLC analysis), the residue was then concentrated under reduced pressure, and the residue was then purified through a silica gel column using EtOAc/Hexane mixture as an eluent to get the pure product.

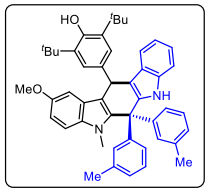
2,6-di-*tert*-butyl-4-(5-methyl-6,6-diphenyl-5,6,7,12-tetrahydroindolo[2,3-*b*]carbazol-12-yl)phenol (29a): The reaction was performed at 0.086 mmol scale of **27a**; white solid (36.4 mg, 67% yield); Optical rotation: $[\alpha]_D^{25}$ +12.31 (*c* 0.13, $CHCl_3$) for a sample with 68% *ee*. The enantiomeric excess was determined by HPLC analysis using Daicel Chiralpak OD-H Column (99:1 *n*-Hexane/2-Propanol, 0.8 mL/min, 254 nm, τ_{major} = 17.59 min, τ_{minor} = 26.08 min).



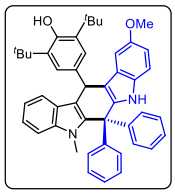
2,6-di-*tert*-butyl-4-(2-methoxy-5-methyl-6,6-diphenyl-5,6,7,12-tetrahydroindolo[2,3-*b*]carbazol-12-yl)phenol (29f): The reaction was performed at 0.079 mmol scale of **27f**; white solid (32.5 mg, 62% yield); Optical rotation: $[\alpha]_D^{25}$ +10.67 (*c* 0.15, $CHCl_3$) for a sample with 74% *ee*. The enantiomeric excess was determined by HPLC analysis using Daicel Chiralpak OD-H Column (98.5:1.5 *n*-Hexane/2-Propanol, 1.0 mL/min, 254 nm, τ_{major} = 14.42 min, τ_{minor} = 22.02 min).



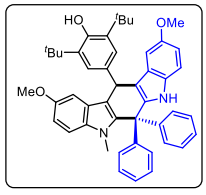
2,6-di-*tert*-butyl-4-(2-methoxy-5-methyl-6,6-di-*m*-tolyl-5,6,7,12-tetrahydroindolo[2,3-*b*]carbazol-12-yl)phenol (29o): The reaction was performed at 0.079 mmol scale of **27f**; white solid (32.7 mg, 60% yield); Optical rotation: $[\alpha]_D^{25}$ +15.00 (*c* 0.1, $CHCl_3$) for a sample with 75% *ee*. The enantiomeric excess was determined by HPLC analysis using Daicel Chiralpak OD-H Column (98.8:1.2 *n*-Hexane/2-Propanol, 1.0 mL/min, 254 nm, τ_{major} = 13.07 min, τ_{minor} = 27.97 min).



2,6-di-*tert*-butyl-4-(2-methoxy-7-methyl-6,6-diphenyl-5,6,7,12-tetrahydroindolo[2,3-*b*]carbazol-12-yl)phenol (29u): The reaction was performed at 0.079 mmol scale of **27a**; white solid (26.7 mg, 51% yield); Optical rotation: $[\alpha]_D^{25}$ +7.00 (*c* 0.1, $CHCl_3$) for a sample with 64% *ee*. The enantiomeric excess was determined by HPLC analysis using Daicel Chiralpak OD-H Column (98.5:1.5 *n*-Hexane/2-Propanol, 1.0 mL/min, 254 nm, τ_{major} = 19.46 min, τ_{minor} = 29.31 min).



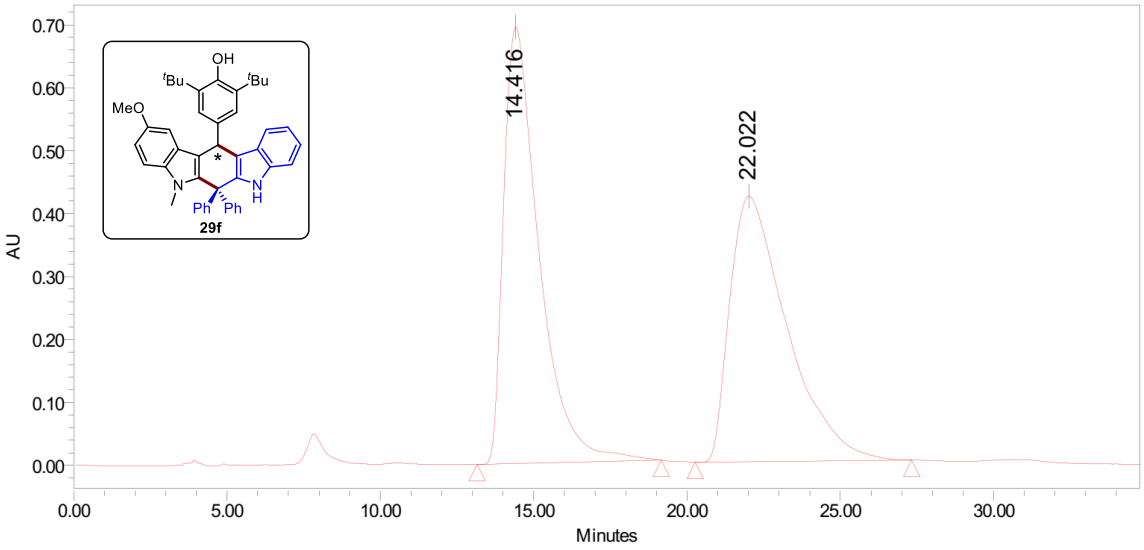
2,6-di-*tert*-butyl-4-(2,10-dimethoxy-5-methyl-6,6-diphenyl-5,6,7,12-tetrahydroindolo[2,3-*b*]carbazol-12-yl)phenol (29v): The reaction was performed at 0.079 mmol scale of **27f**; white solid (35.5 mg, 65% yield); Optical rotation: $[\alpha]_D^{25}$ +12.22 (*c* 0.9, $CHCl_3$) for a sample with 81% *ee*. The enantiomeric excess was determined by HPLC analysis using Daicel Chiralpak OD-H Column (98.3:1.7 *n*-Hexane/2-Propanol, 1.0 mL/min, 254 nm, τ_{major} = 18.54 min, τ_{minor} = 28.85 min).



HPLC Chromatogram

SAMPLE INFORMATION			
Sample Name:	xx-gs-82,1 re	Acquired By:	System
Sample Type:	Unknown	Sample Set Name	
Vial:	1	Acq. Method Set:	2 %
Injection #:	2	Processing Method	xx gs 821
Injection Volume:	20.00 ul	Channel Name:	254.0nm
Run Time:	60.0 Minutes	Proc. Chnl. Descr.:	PDA 254.0 nm
Date Acquired:	01-03-2022 12:16:03 IST		
Date Processed:	02-07-2022 02:43:30 IST		

Auto-Scaled Chromatogram



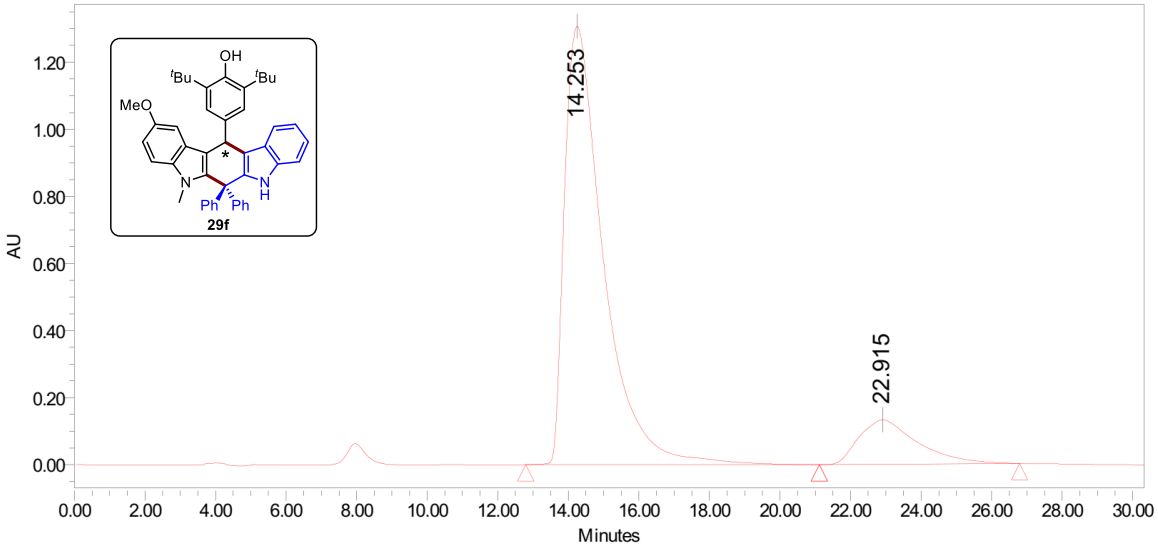
Peak Results

	RT	Area	Height	% Area
1	14.416	55701047	693831	50.47
2	22.022	54656803	421890	49.53

SAMPLE INFORMATION

Sample Name:	xx-gs-82,2 chiral	Acquired By:	System
Sample Type:	Unknown	Sample Set Name	
Vial:	1	Acq. Method Set:	2 %
Injection #:	3	Processing Method	gs82chiral
Injection Volume:	20.00 ul	Channel Name:	254.0nm
Run Time:	60.0 Minutes	Proc. Chnl. Descr.:	PDA 254.0 nm
Date Acquired:	01-03-2022 12:51:54 IST		
Date Processed:	02-07-2022 03:23:14 IST		

Auto-Scaled Chromatogram



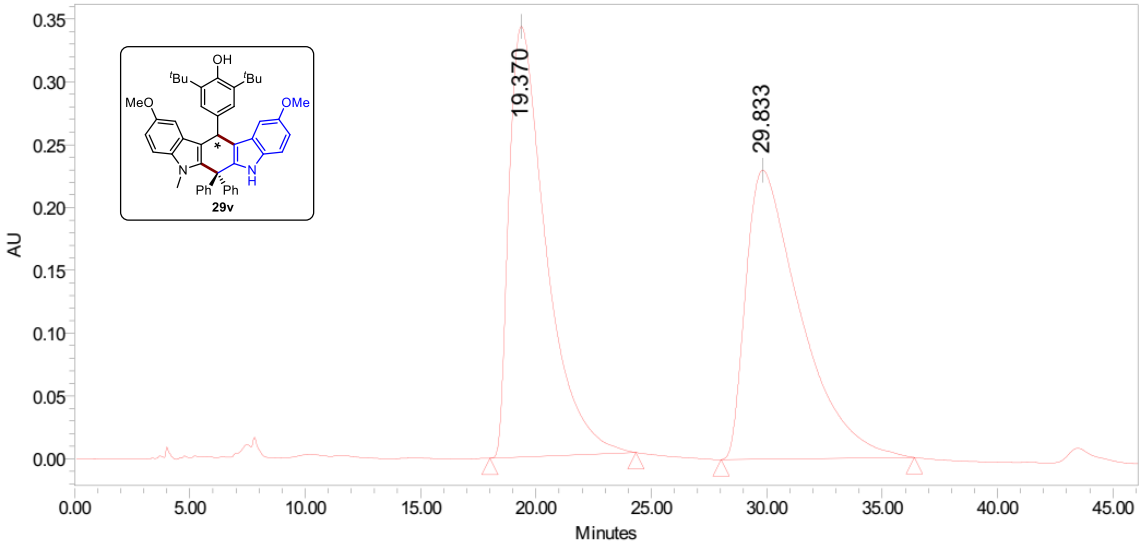
Peak Results

	RT	Area	Height	% Area
1	14.253	100310496	1307090	86.76
2	22.915	15310400	132753	13.24

SAMPLE INFORMATION

Sample Name:	XX-GS-85,1	Acquired By:	System
Sample Type:	Unknown	Sample Set Name	
Vial:	1	Acq. Method Set:	2 %
Injection #:	1	Processing Method	xxgs851rac
Injection Volume:	20.00 ul	Channel Name:	254.0nm
Run Time:	60.0 Minutes	Proc. Chnl. Descr.:	PDA 254.0 nm
Date Acquired:	03-03-2022 10:31:49 IST		
Date Processed:	02-07-2022 04:25:09 IST		

Auto-Scaled Chromatogram



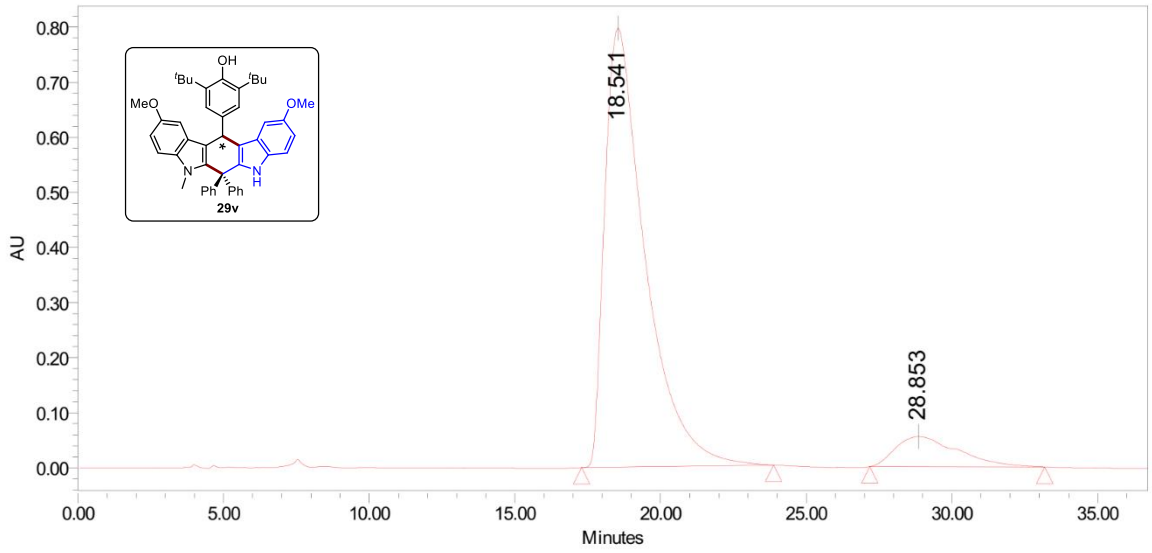
Peak Results

	RT	Area	Height	% Area
1	19.370	38154251	342738	50.13
2	29.833	37954529	229970	49.87

SAMPLE INFORMATION

Sample Name:	XX-GS-85,2 chiral	Acquired By:	System
Sample Type:	Unknown	Sample Set Name	
Vial:	1	Acq. Method Set:	2 %
Injection #:	2	Processing Method	xxgs852chiral
Injection Volume:	20.00 ul	Channel Name:	254.0nm
Run Time:	60.0 Minutes	Proc. Chnl. Descr.:	PDA 254.0 nm
Date Acquired:	03-03-2022 11:18:37 IST		
Date Processed:	02-07-2022 04:30:21 IST		

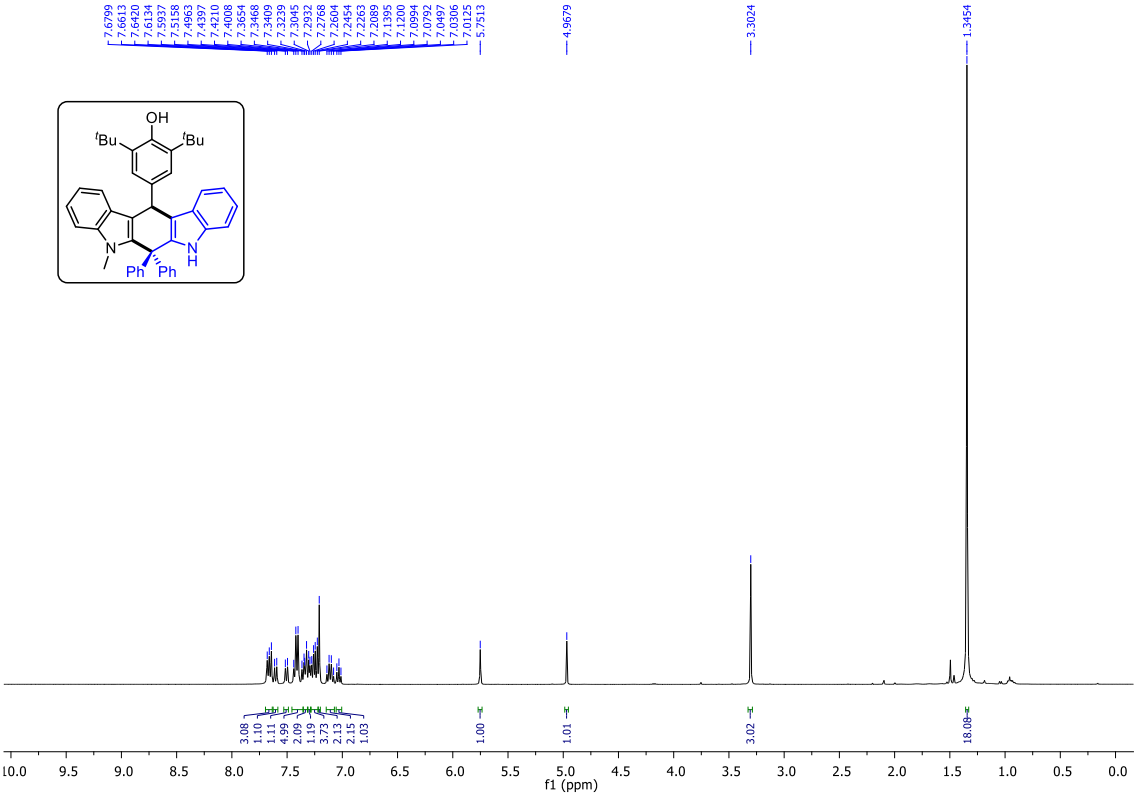
Auto-Scaled Chromatogram



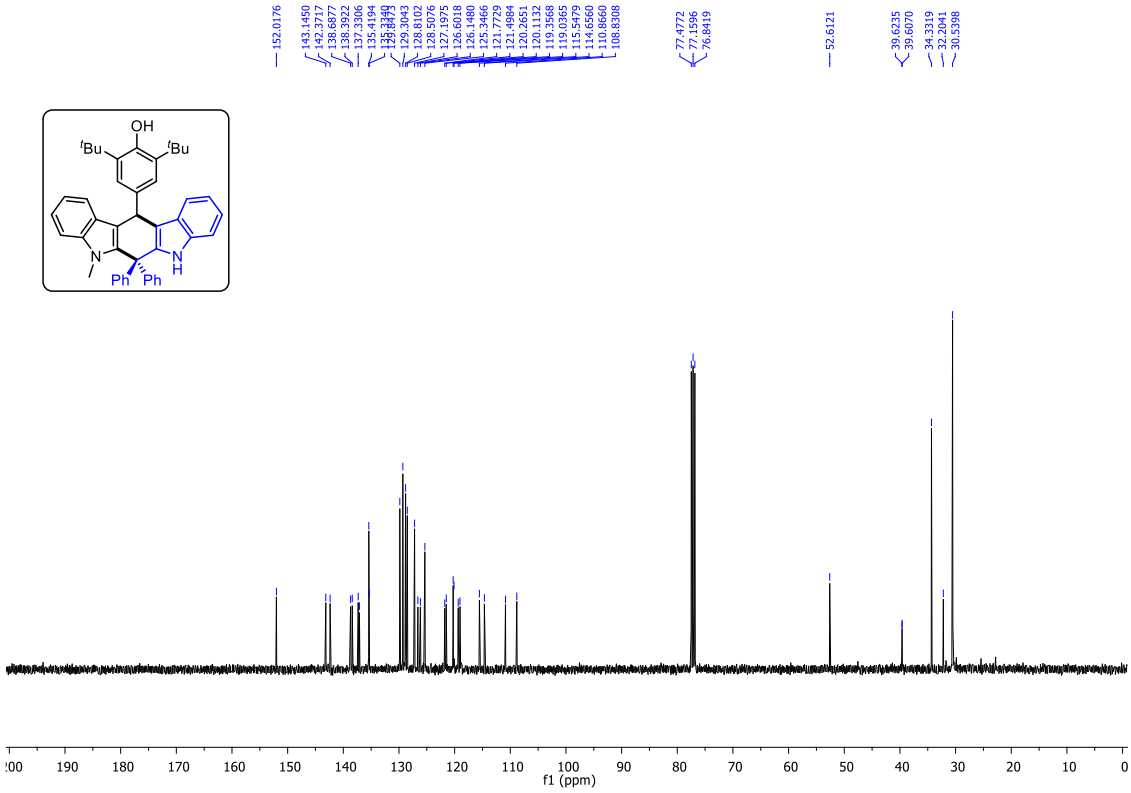
Peak Results

	RT	Area	Height	% Area
1	18.541	76819983	796750	90.40
2	28.853	8157908	54724	9.60

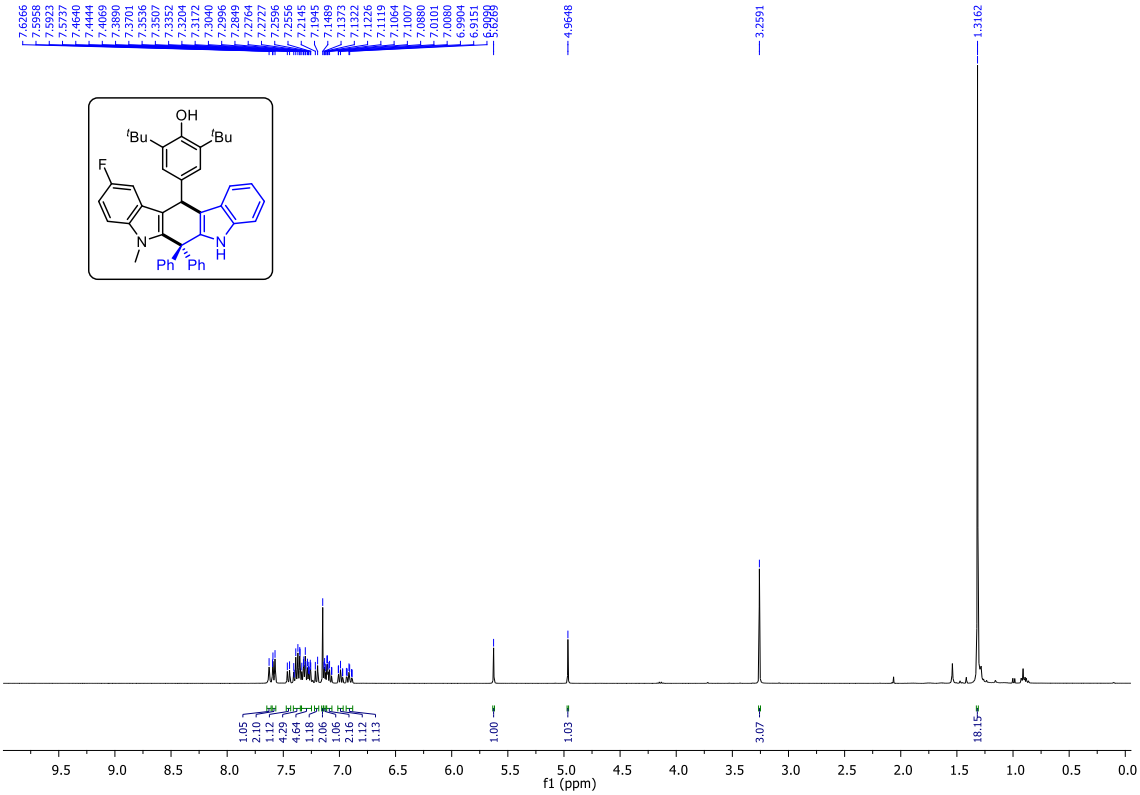
^{1}H NMR (400 MHz, $CDCl_3$) Spectrum of **29a**



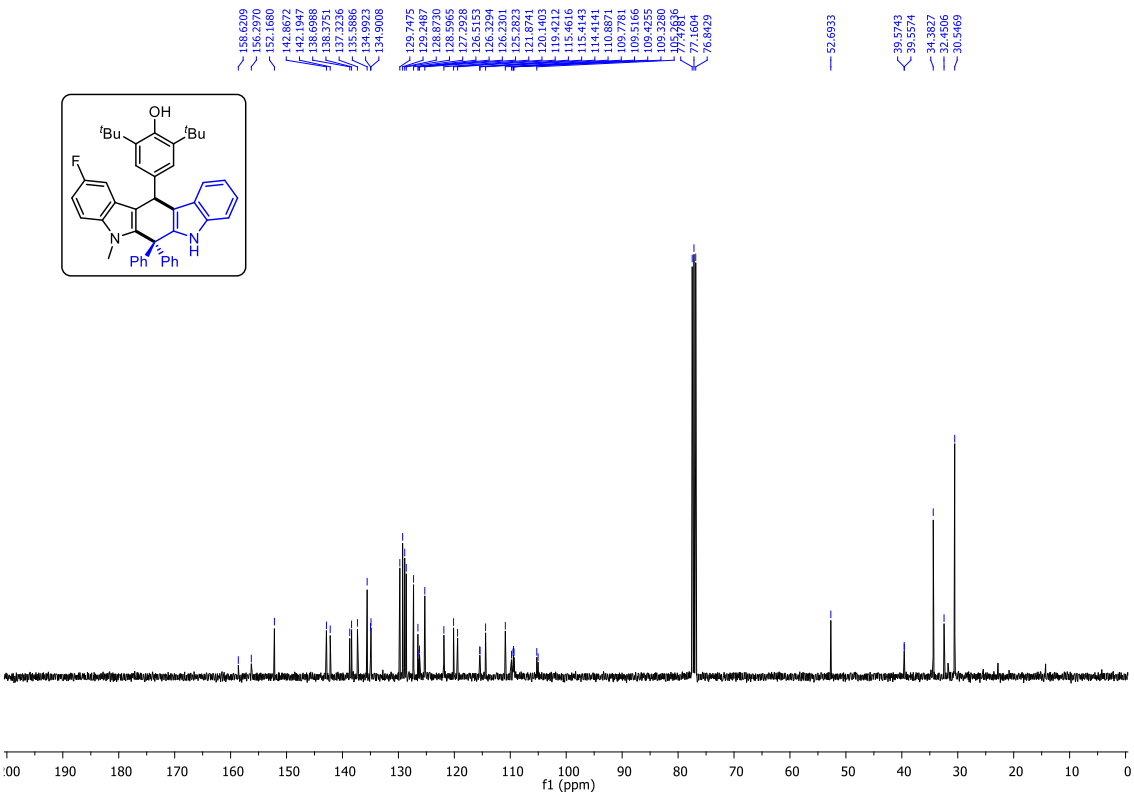
^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) Spectrum of **29a**



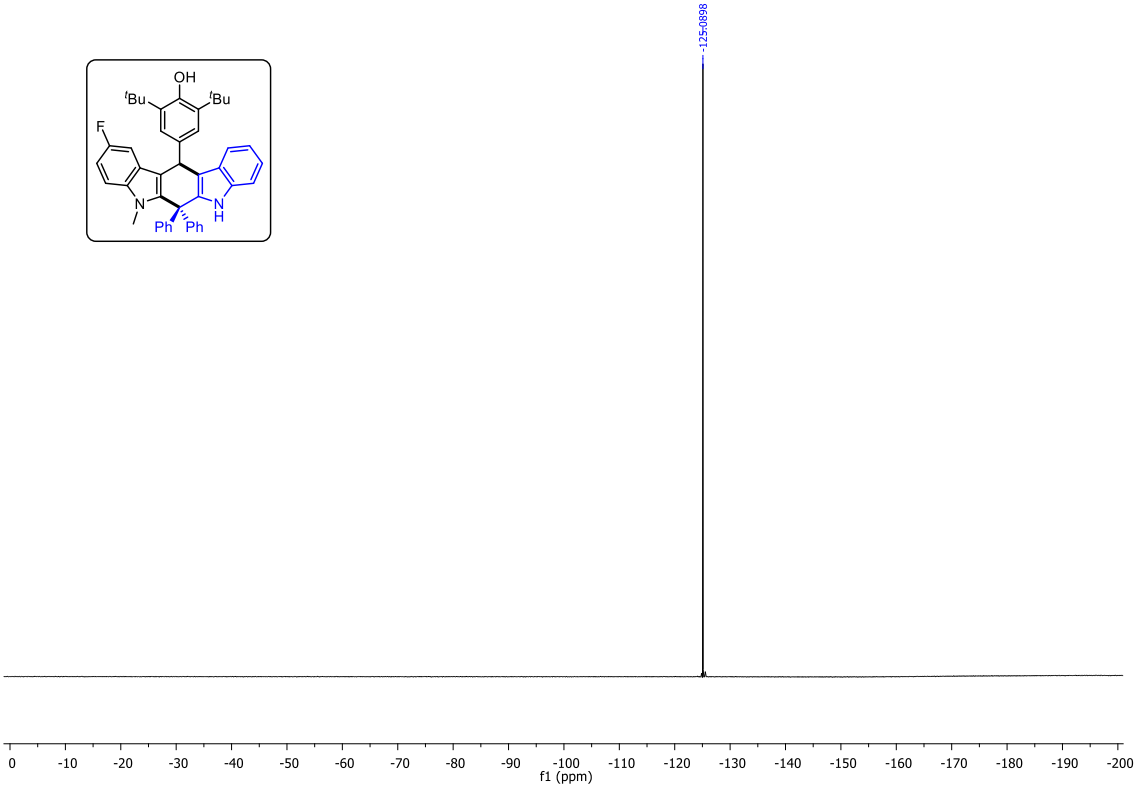
^{1}H NMR (400 MHz, $CDCl_3$) Spectrum of **29e**



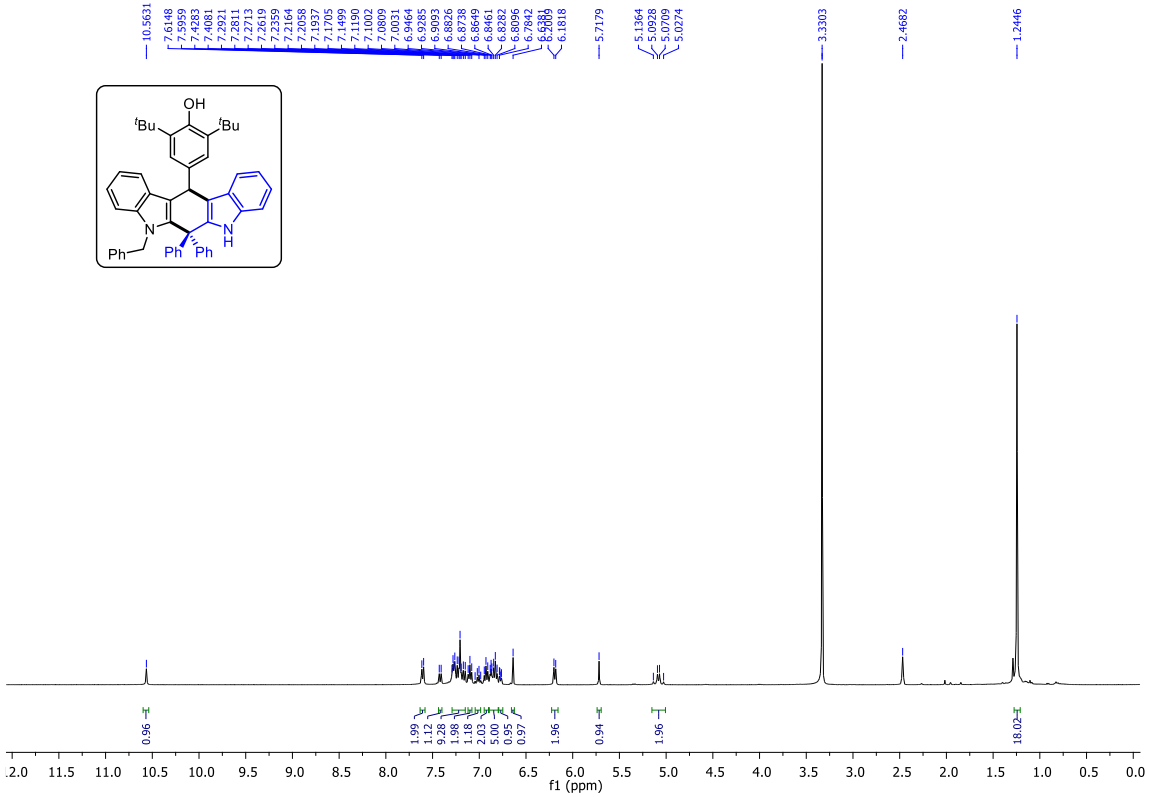
^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) Spectrum of **29e**



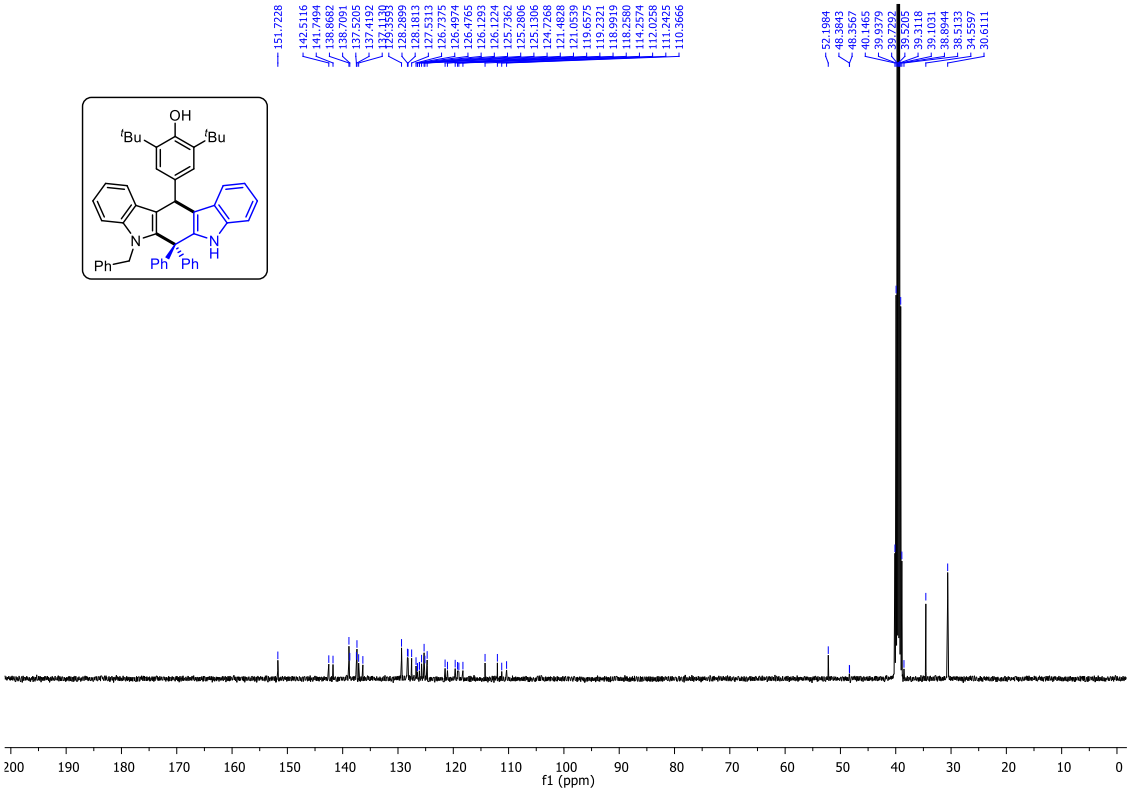
^{19}F {^{1}H} NMR (376 MHz, $CDCl_3$) Spectrum of **29e**



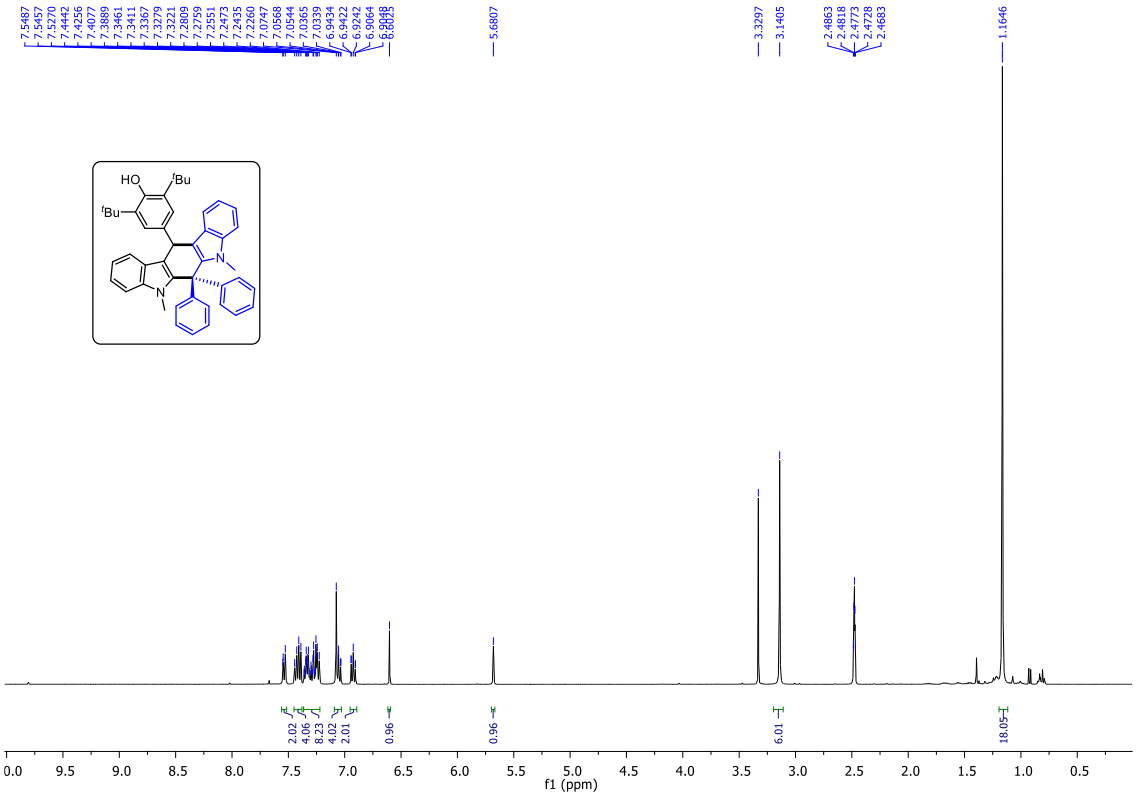
^{1}H NMR (400 MHz, DMSO-d_6) Spectrum of **29j**



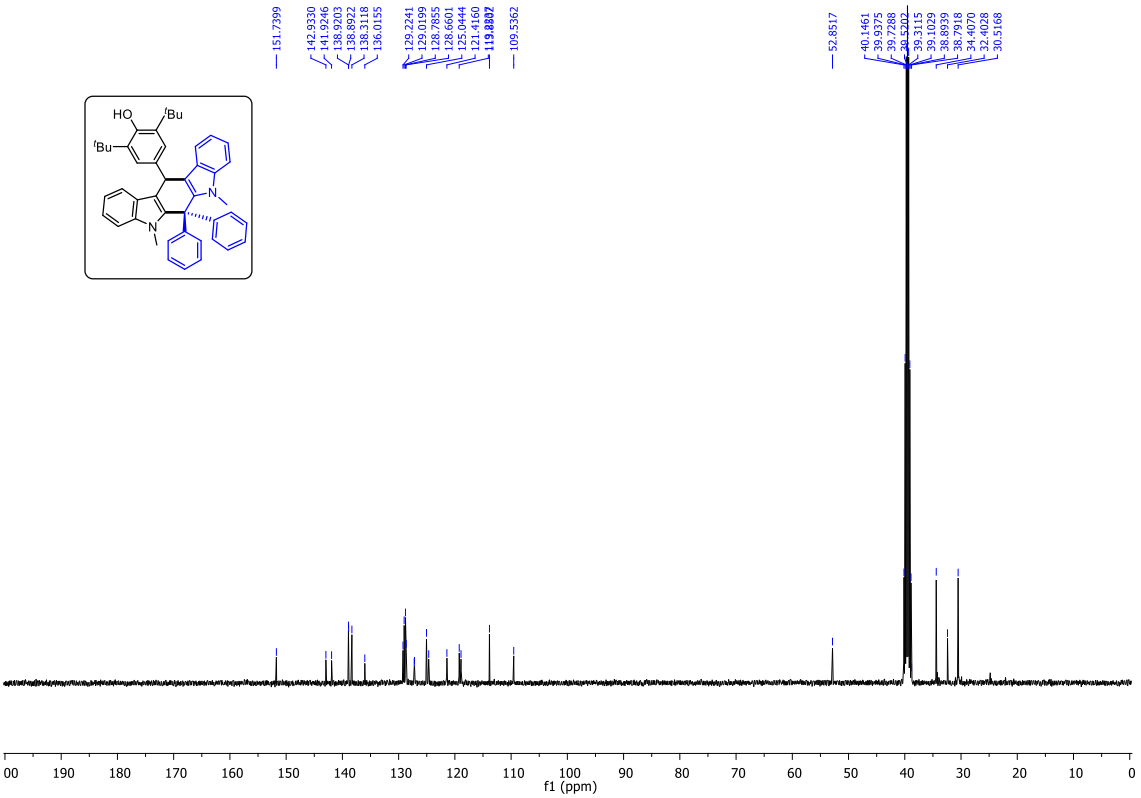
^{13}C {^{1}H} NMR (100 MHz, DMSO-d_6) Spectrum of **29j**



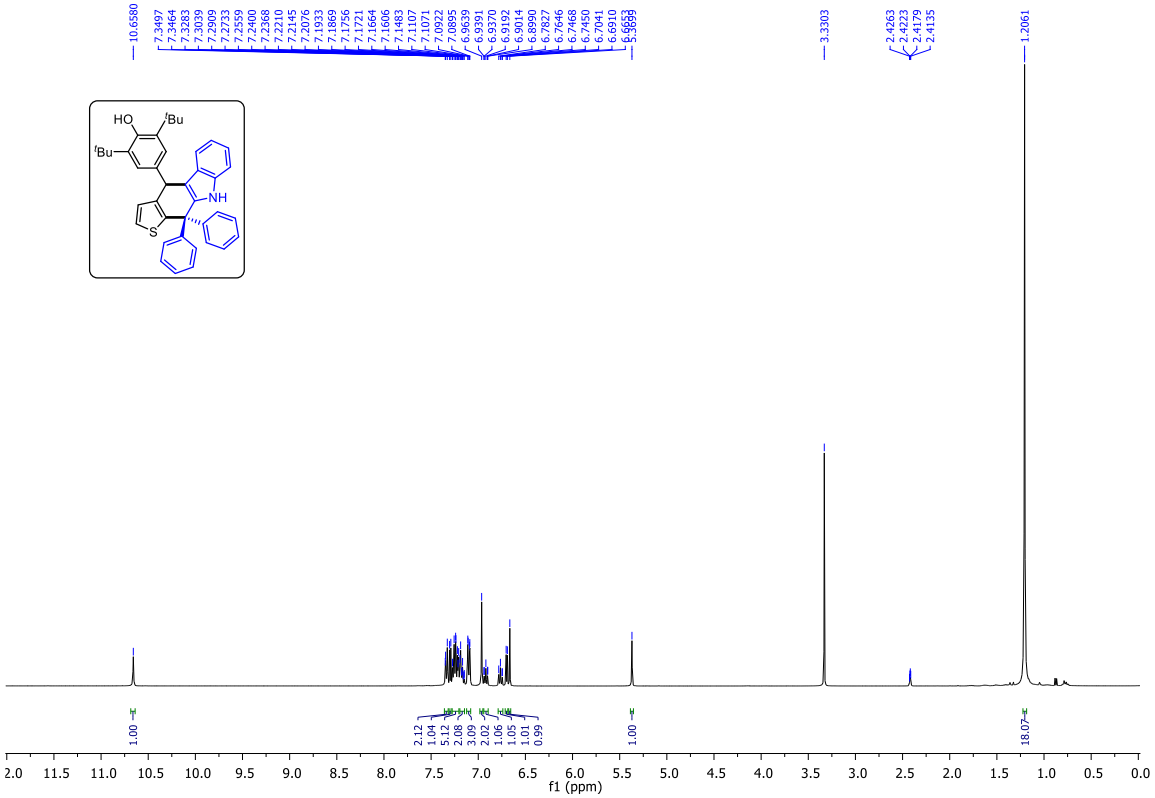
^{1}H NMR (400 MHz, $CDCl_3$) Spectrum of **29w**



^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) Spectrum of **29w**



^{1}H NMR (400 MHz, DMSO-d_6) Spectrum of **31a**



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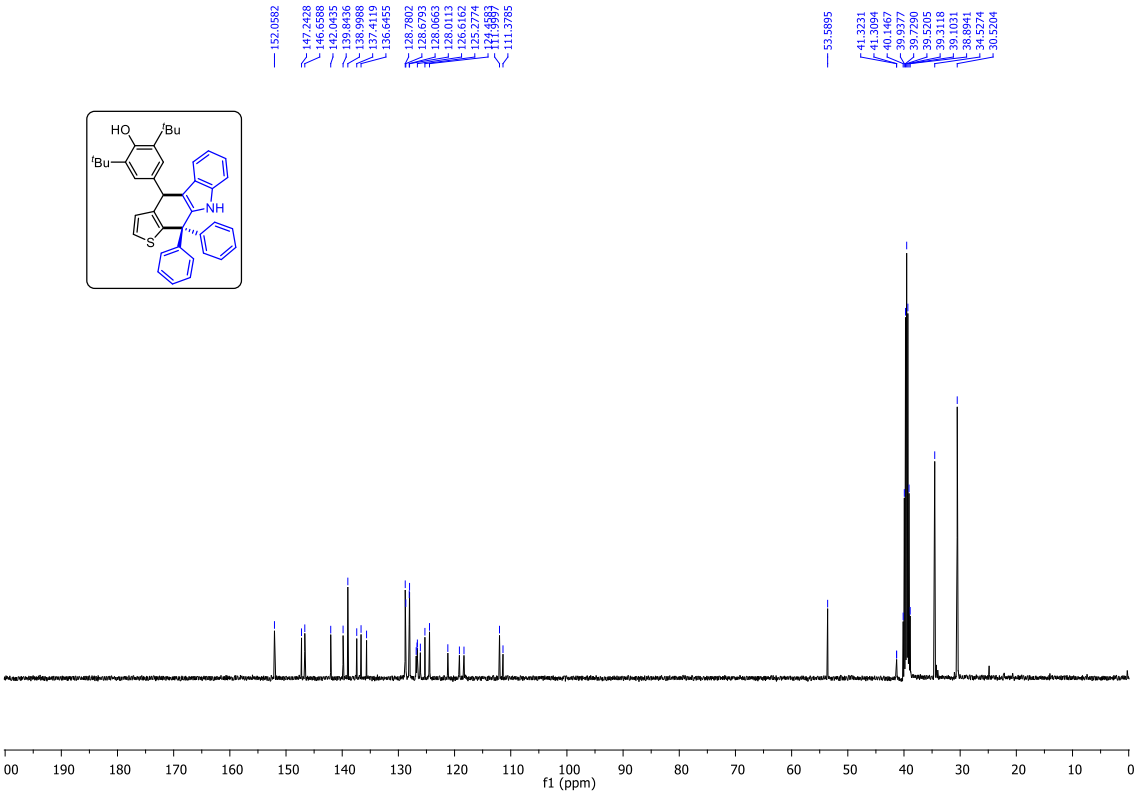

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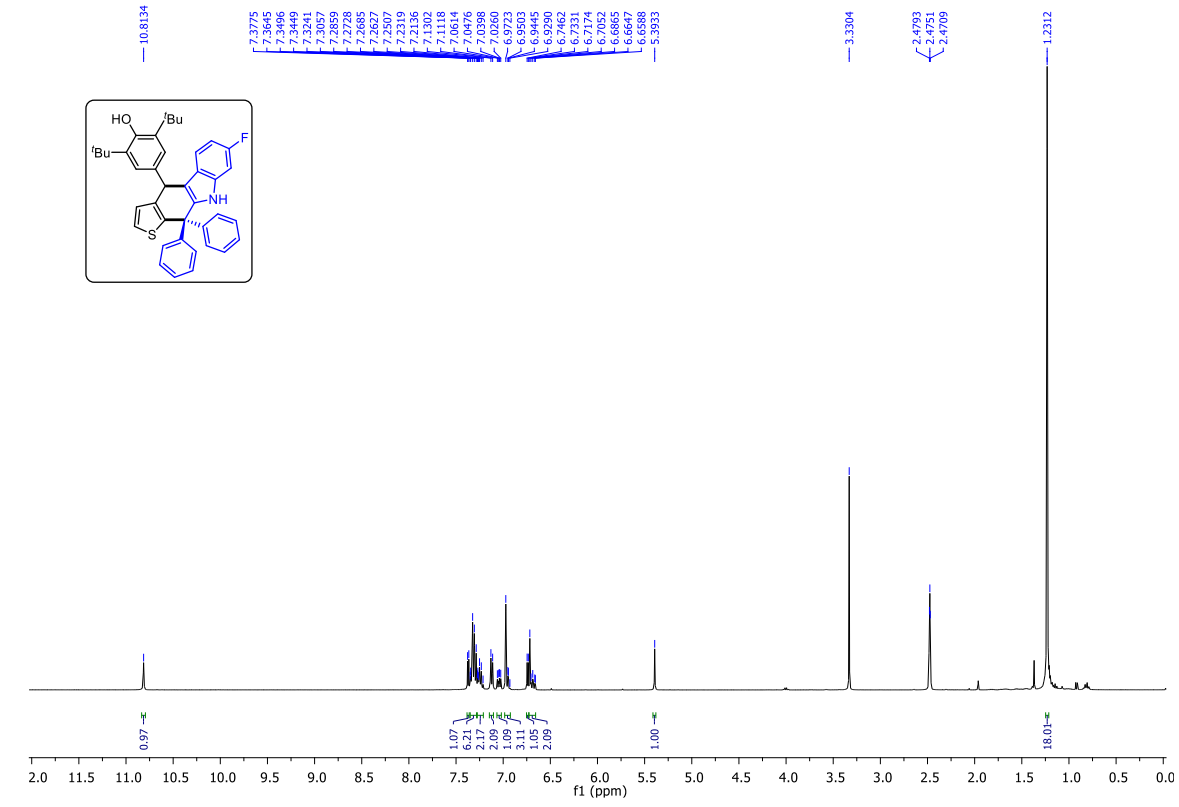

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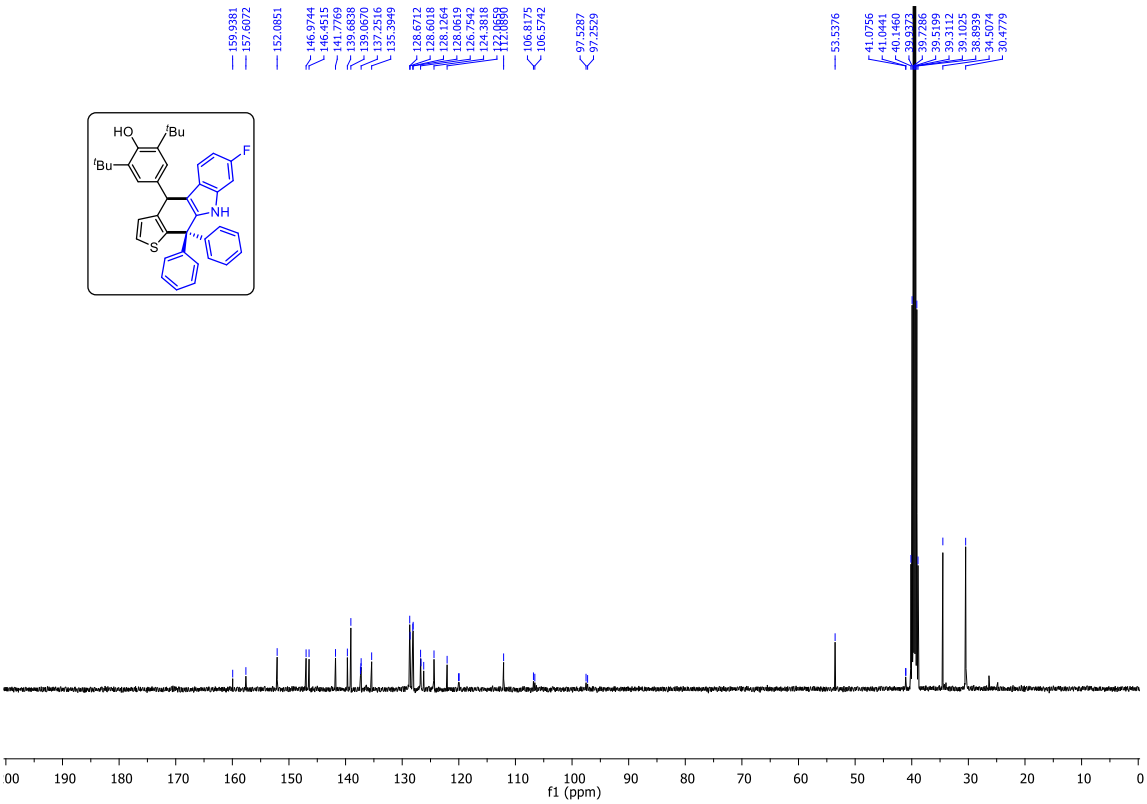

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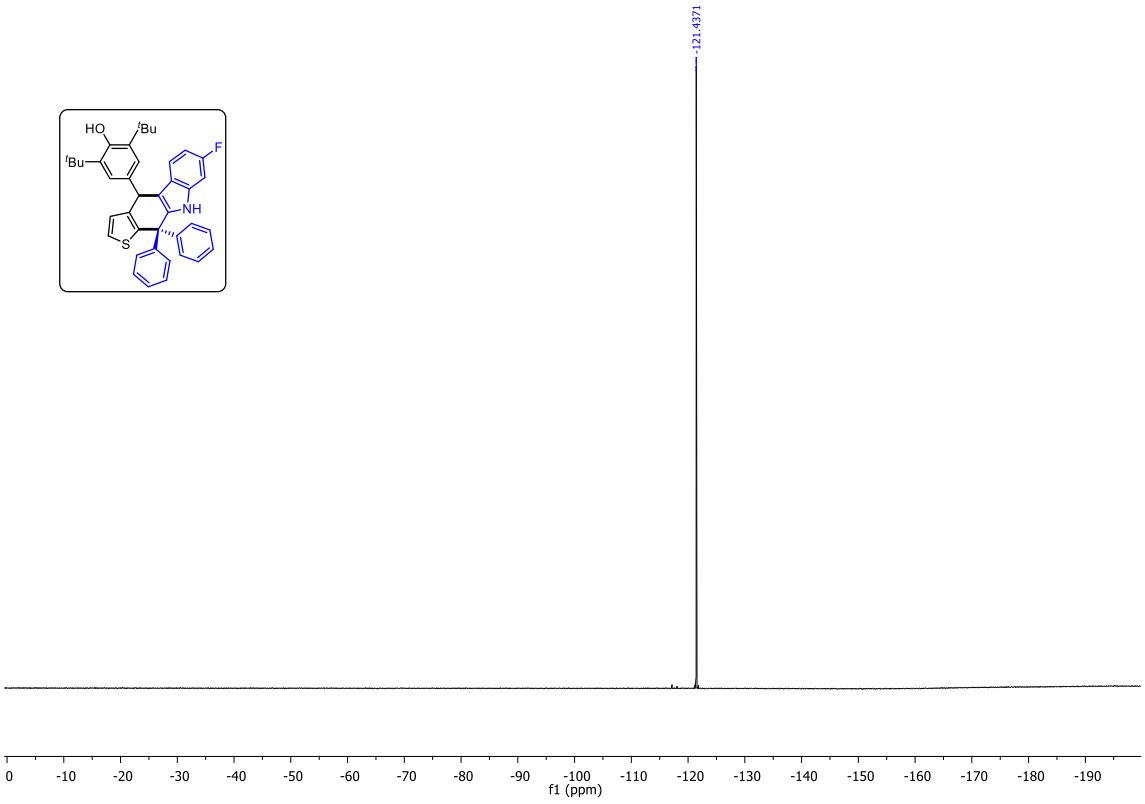

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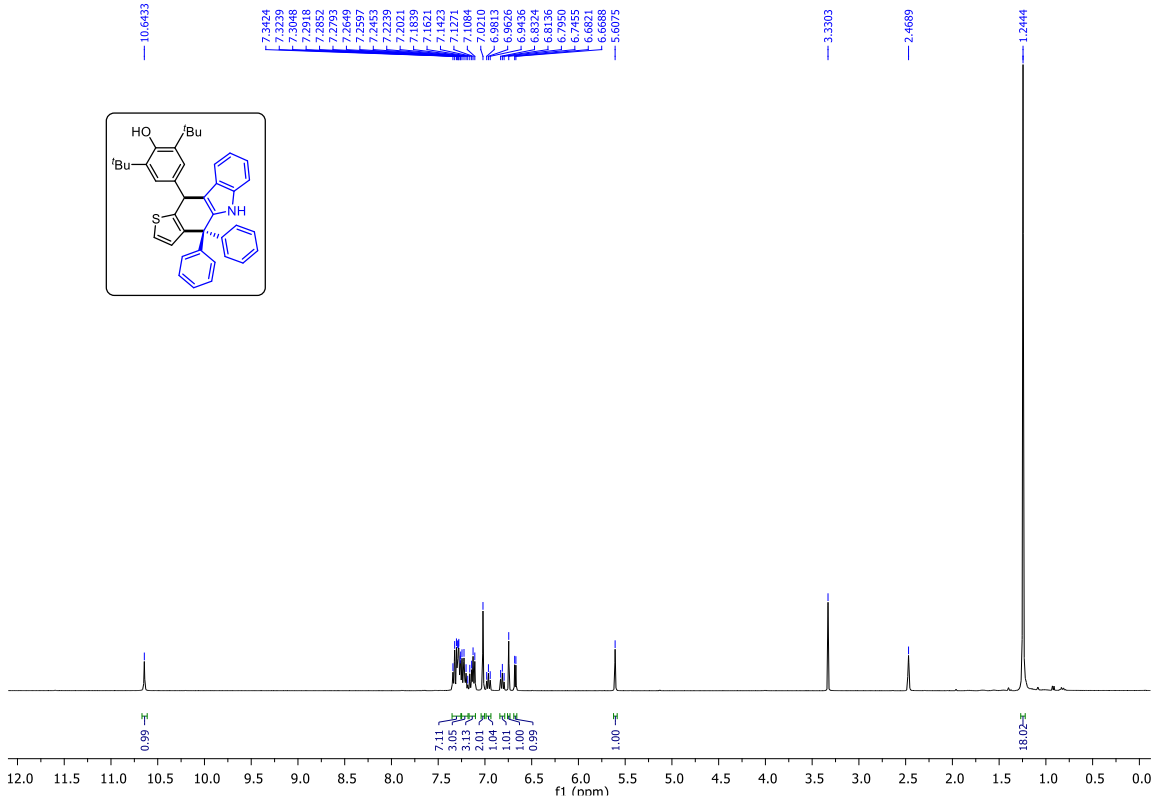

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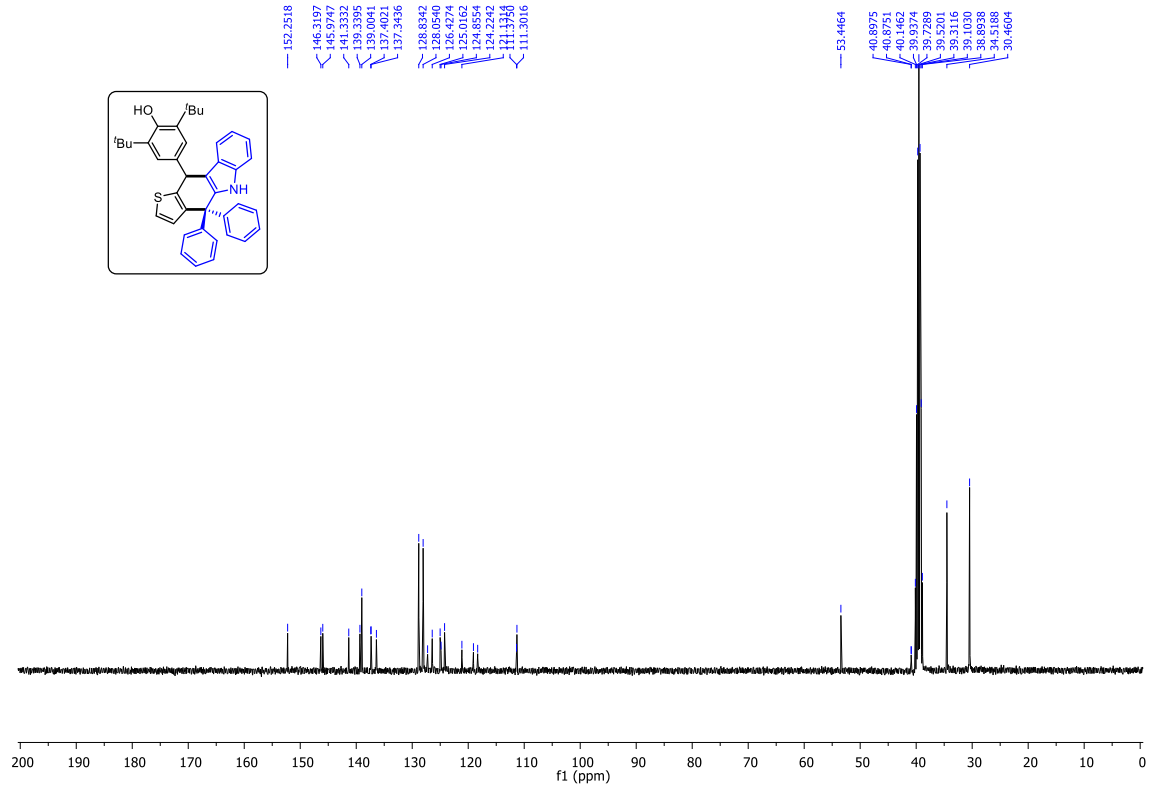

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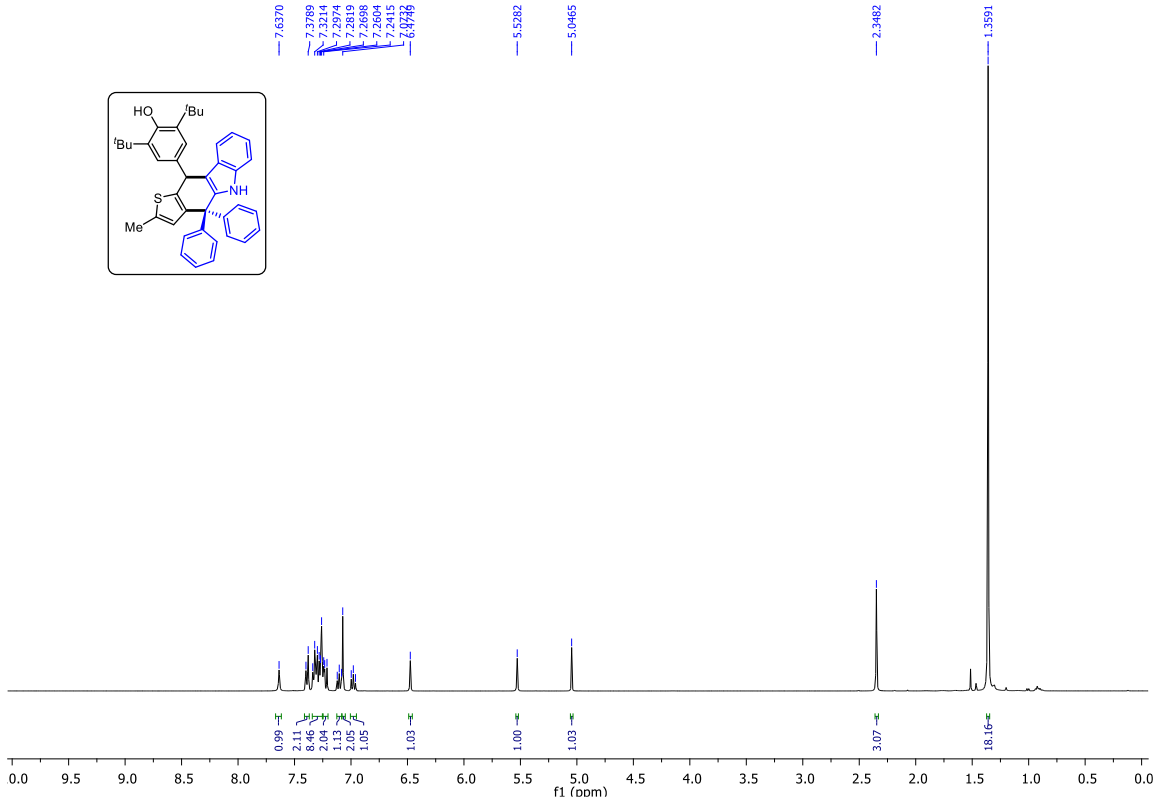

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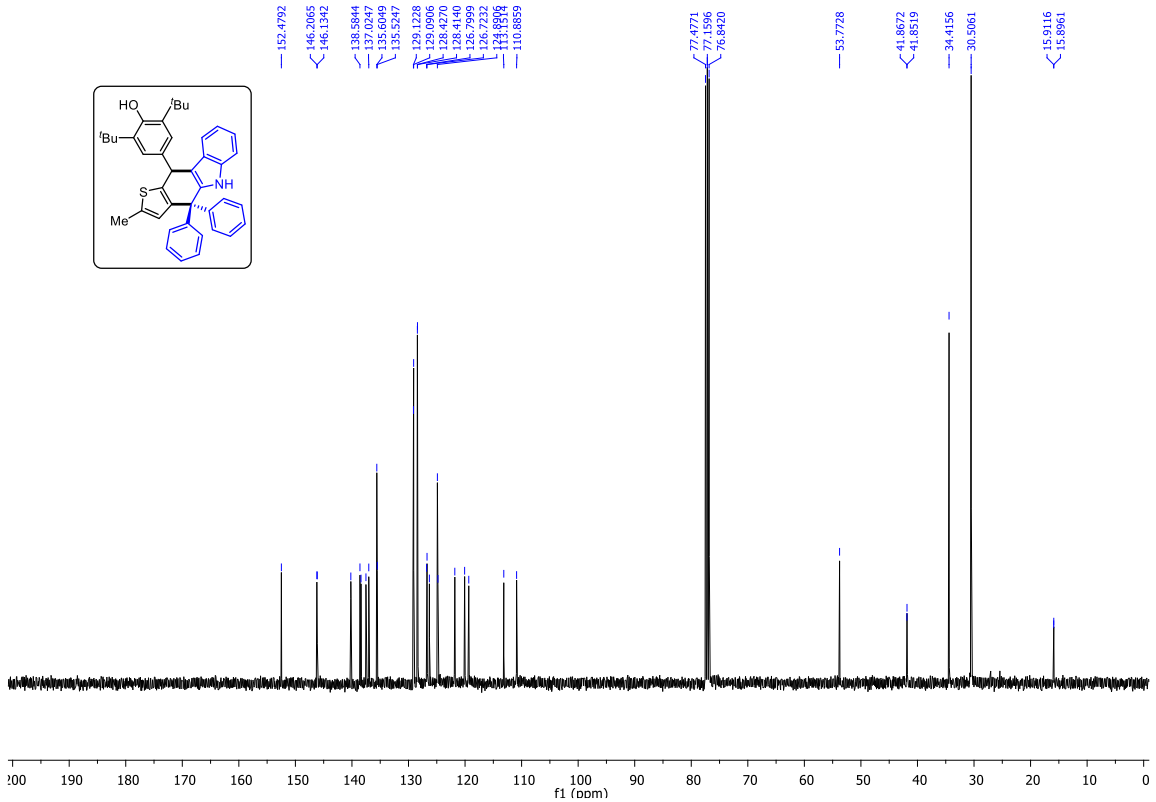

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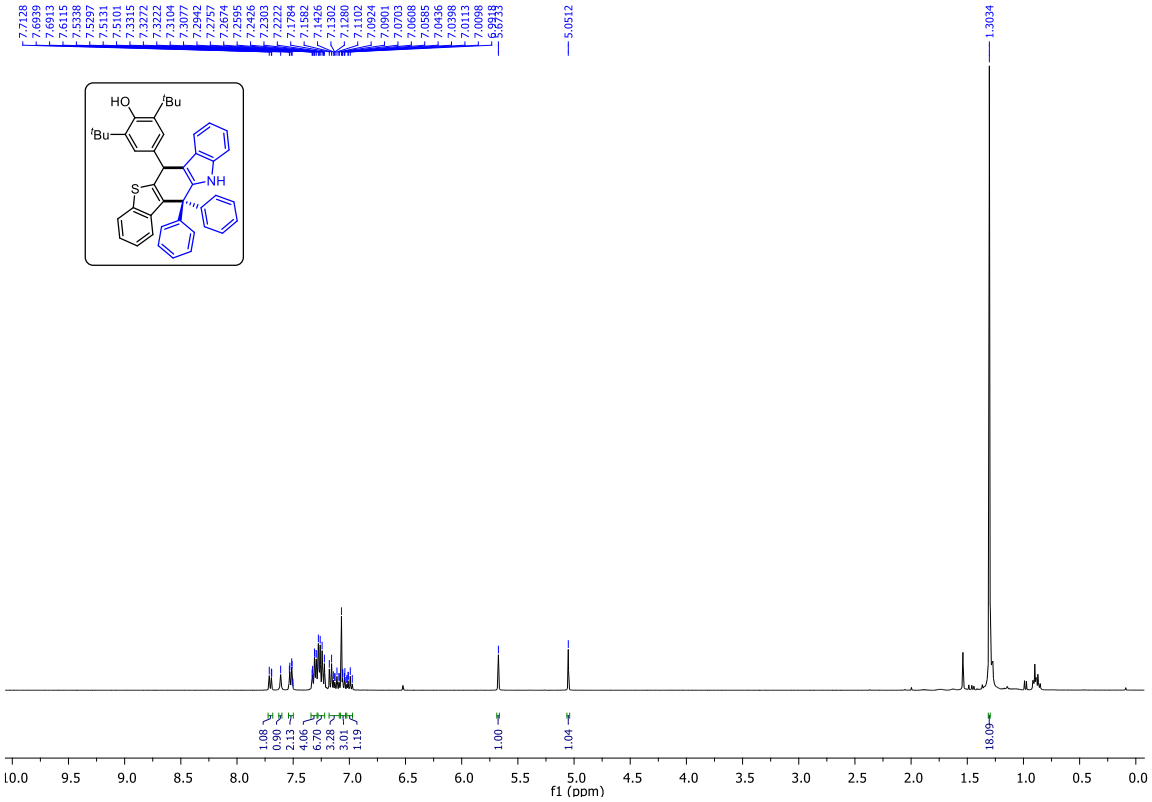

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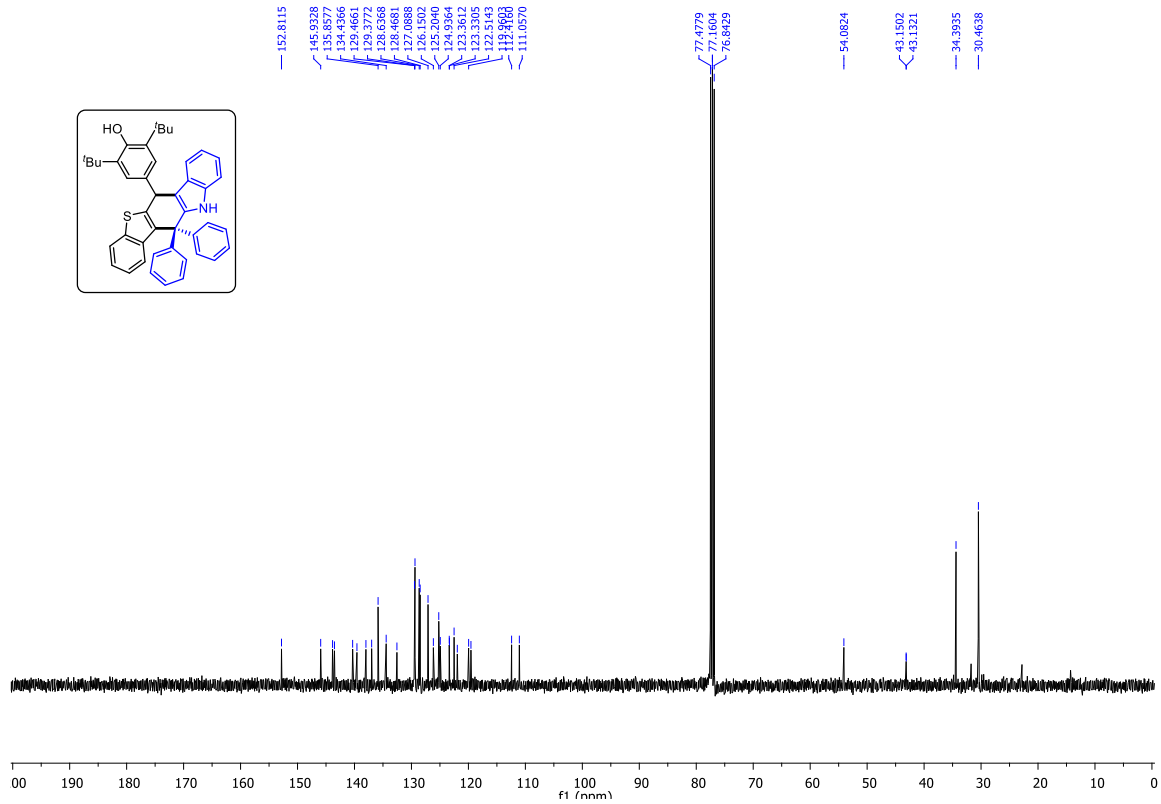

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Appendix 1

1. A base-mediated approach towards dihydrofuro[2,3-*b*]benzofurans from 2-nitrobenzofurans and 1,3-dicarbonyls

1.1 Introduction

Furo[2,3-*b*]benzofuran and dihydrofuro[2,3-*b*]benzofuran are a class of privileged scaffolds and are found, as an integral part, of various natural products and biologically active molecules (Figure 1**)**.[1] For example, watsonianone B, isolated from the plant *Corymbia watsonia*, showed remarkable anti-malarial activity through the inhibition of the growth of chloroquine (3D7).[1a] Rhodomyrtosones, derived from the plant *Rhodomyrtus tomentosa*, are found to be potent anti-biotics against Gram-positive bacteria.[1b] Aflatoxins, a class of mycotoxins, are among the most carcinogens known to humans, produced by the fungi *Aspergillus* and *Penicillium* species.[1c] Apart from these therapeutic applications, some of the benzofurofuran-based diphosphines have been used as ligands in transition-metal catalysis.[2] In addition, a few furo[2,3-*b*] benzofuran-related compounds have shown remarkable value in the area of polymer as well as materials chemistry.[3]

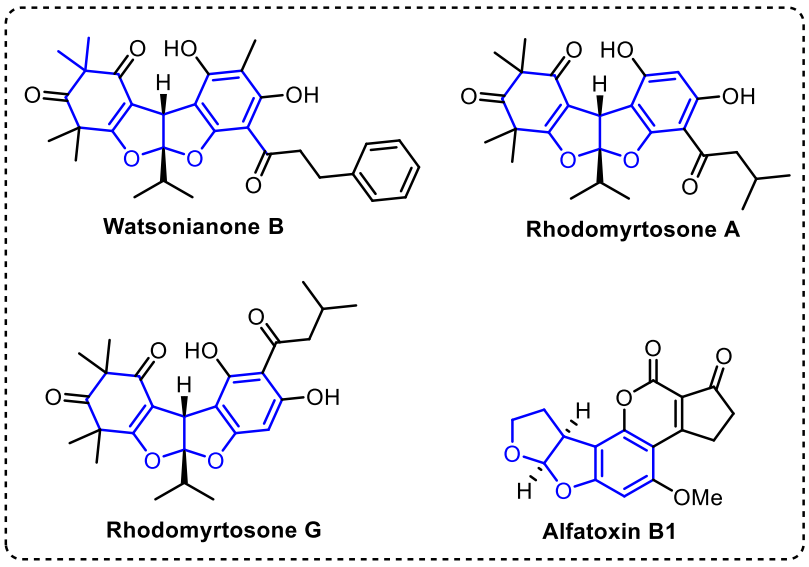


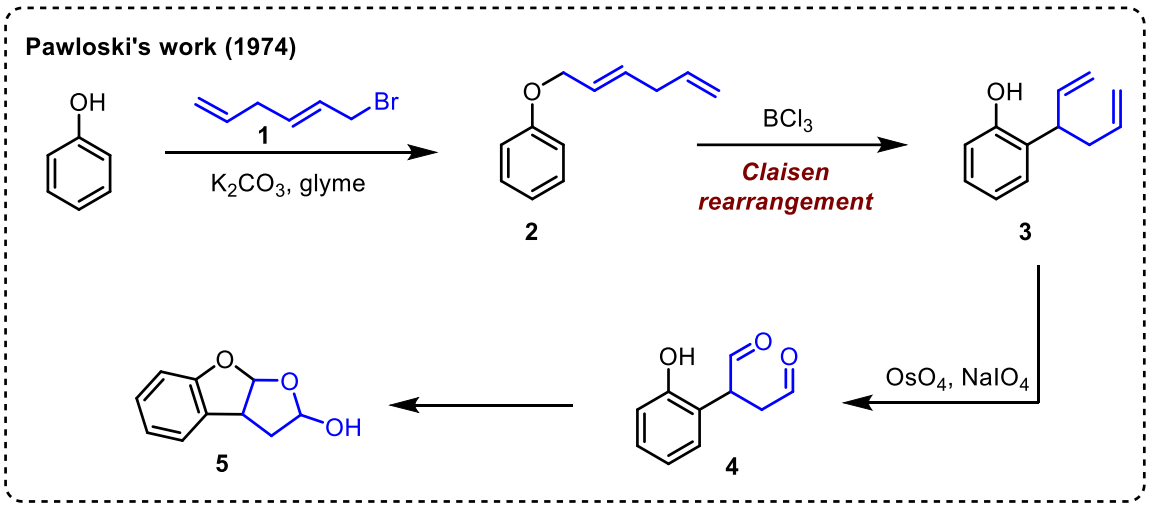
Figure 1. Representative biologically active molecules and natural products

Due to their fascinating applications, numerous synthetic approaches have been developed to access the dihydrofuro[2,3-*b*]benzofuran derivatives. A few of them are discussed below.

1.2 Literature reports on the synthesis of dihydrofurofurans/dihydrofurobenzofurans

1.2.1 Synthesis of dihydrofuro[2,3-*b*]benzofuran/dihydrofuro[2,3-*b*]furan derivatives through Claisen rearrangement

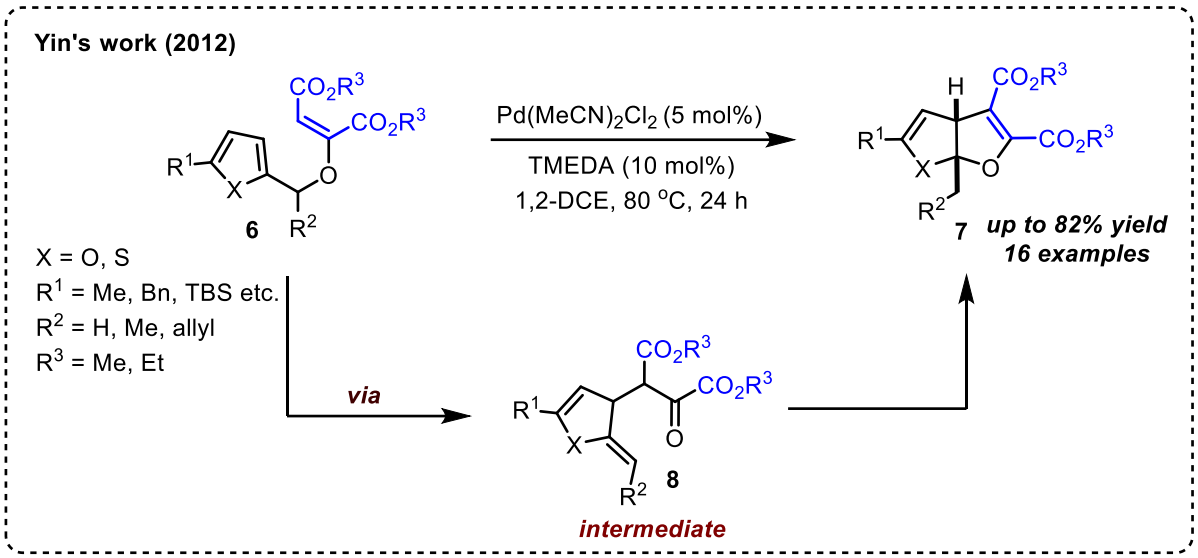
In 1974, Pawlowski and co-workers described the synthesis of 3a,8a-dihydrofuro[2,3-*b*]benzofuran **5** from phenol and 1-bromo-2,5-hexadienes (**1**) through an *O*-alkylation of phenol (to generate an ether **2**), followed by BCl_3-catalyzed Claisen rearrangement to form 2-(hexa-1,5-dien-3-yl)phenol **3**. Further, oxidative cleavage of **3** with OsO_4/$NaIO_4$ directly yields 3a,8a-dihydrofuro[2,3-*b*]benzofuran **5** through a dialdehyde intermediate **4** as shown in Scheme 1.[4] Similarly, Cava and co-workers reported the synthesis of dihydrofurofuran by using the same concept starting from 1,3-dihydroxyanthraquinone. This methodology has also been extended for the synthesis of 6,8-dideoxyversicolorin A.[5]



Scheme 1. Synthesis of 3a,8a-dihydrofuro[2,3-*b*]benzofuran through Claisen rearrangement

Yin's group demonstrated the synthesis of 3a,8a-dihydrofuro[2,3-*b*]furan derivatives (**7**) from furylcarbinols (**6**). The reaction proceeds through a palladium-catalyzed Claisen rearrangement of furylcarbinols (**6**) to generate an intermediate **8**, followed by a ring closure to produce **7**. This transformation worked efficiently with electron-rich furylcarbinol derivatives; however, no product formation was observed with electron-poor furylcarbinol derivatives (formyl and methoxycarbonyl). These observations led to the conclusion that

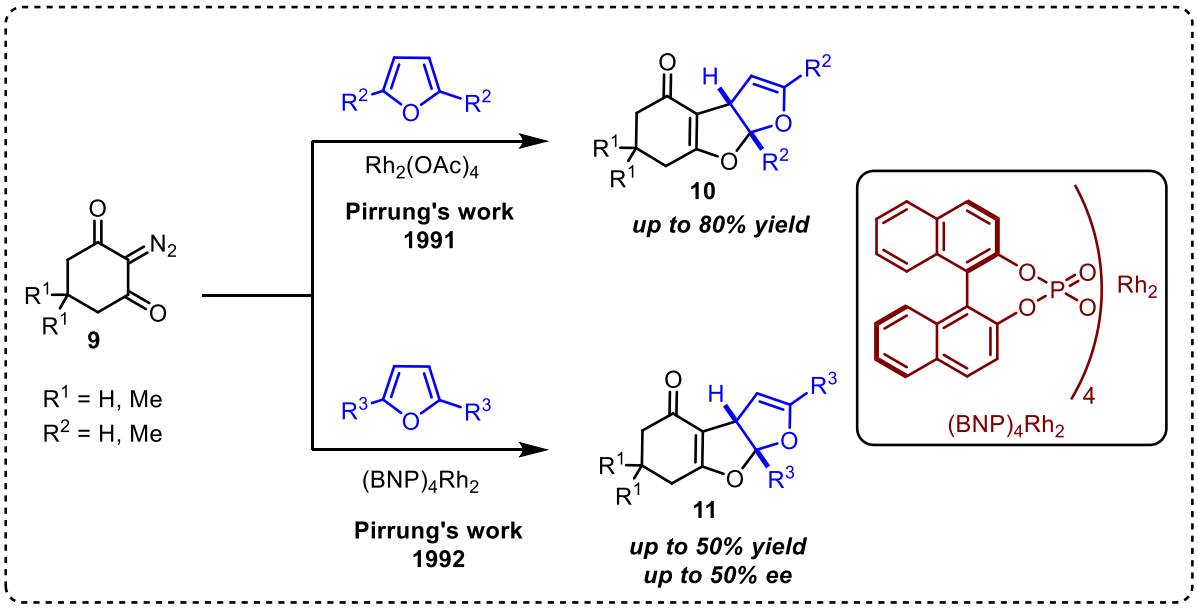
electron-rich substituents facilitate the cleavage of the C-O bond, which is essential for this transformation (Scheme 2).[6]



Scheme 2. Palladium-catalyzed synthesis of 3a,8a-dihydrofuro[2,3-*b*]furans

1.2.2 Rhodium-catalyzed synthesis of dihydrofuro[2,3-*b*]furans

Pirrung's group reported a rhodium-catalyzed synthesis of 3a,8a-dihydrofuro[2,3-*b*]furans (**10**) from 2-diazo-1,3-cyclohexadione **9** and furan derivatives in moderate yields. The yield of the product was found to be more with 2,5-dimethyl furan (80%). In this reaction, carbenoid was thought to be generated from **9** in the presence of $Rh_2(OAc)_4$ catalyst, which undergoes cyclopropanation with furan.[7] Later, the same group developed an enantioselective

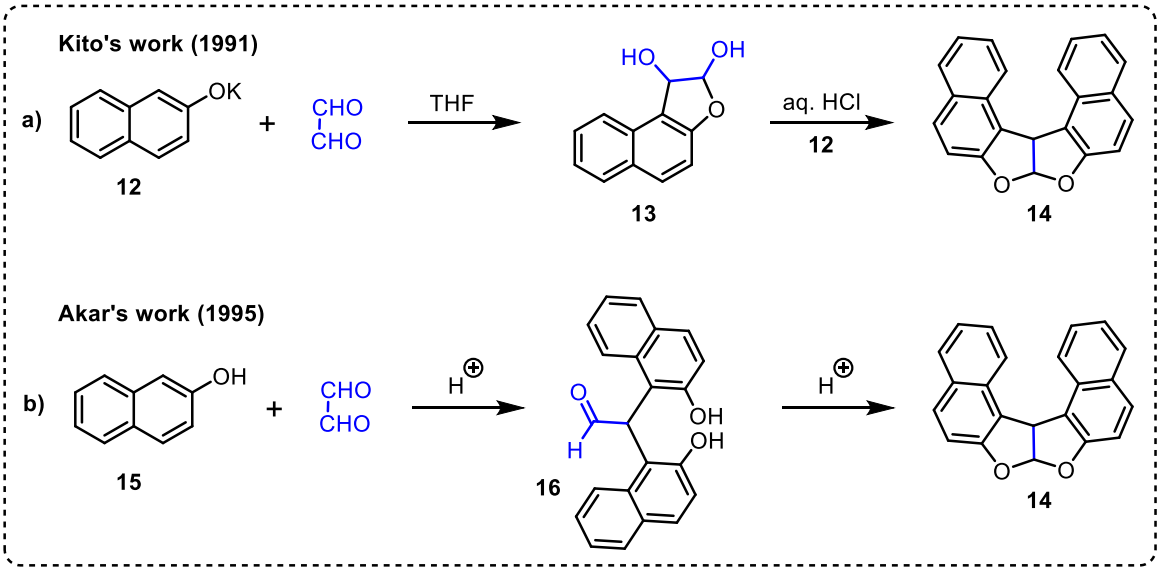


Scheme 3. Rhodium-catalyzed synthesis of 3a,8a-dihydrofuro[2,3-*b*]furans

synthesis of **11** by using a chiral rhodium-based catalyst $(BNP)_4Rh_2$. The yield and enantiomeric excess (*ee*) of the product obtained in this transformation were up to 50 and 50%, respectively (Scheme 3).[8]

1.2.3 Synthesis through condensation of phenols and glyoxals

In 1991, Kito and co-workers described the reaction of potassium 2-naphthyl oxide **12** and 40% aqueous glyoxal in THF to produce l,2-dihydronaphtho[2,l-*b*]furan-l,2-diol **13**, which, on acidification with aqueous HCl, gave the dihydronaphtho[2,l-*b*]naphthofurofuran **14** in 92% yield within 3 hours (Scheme 4, **a**).[9] Similarly, Akar's group reported the condensation reaction of 2-naphthol **15** with glyoxal in the presence of a mild acid to produce **14**. Initially, 2 moles of **15** undergo a condensation reaction with glyoxal to generate an intermediate **16**, which then undergoes an intramolecular acetalization reaction to give **14** (Scheme 4, **b**).[10]



Scheme 4. Condensation reaction for the synthesis of naphthofurofurans

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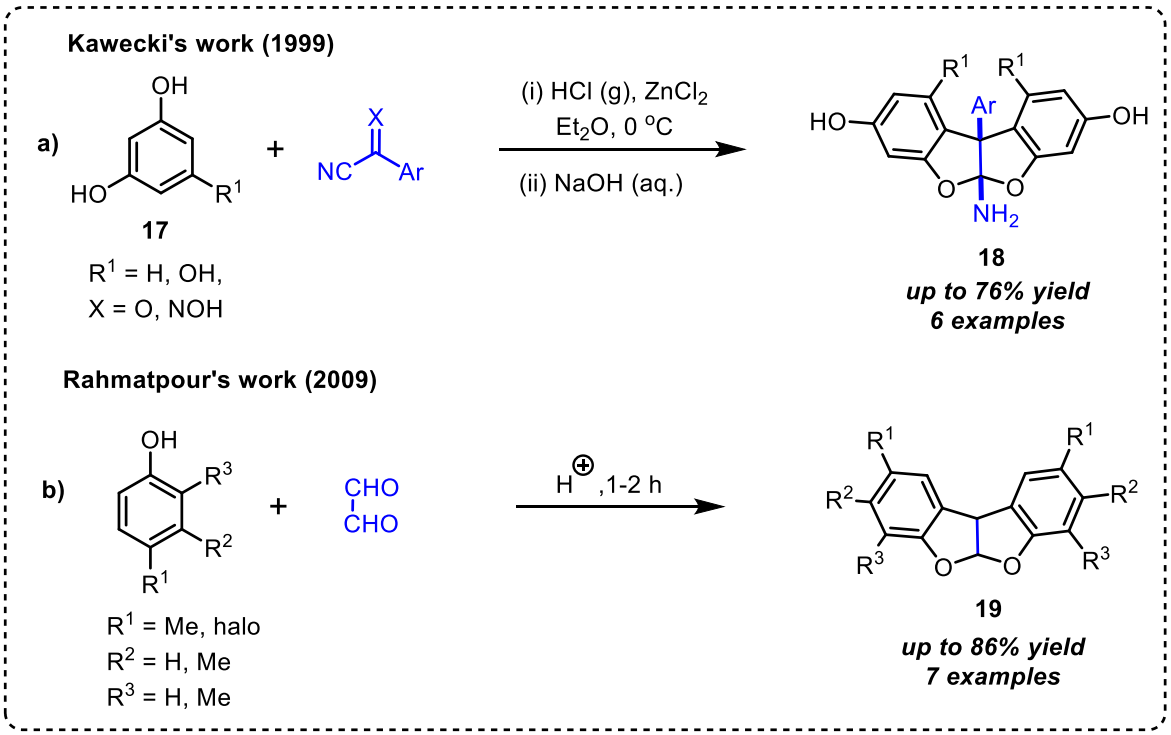
Kawęcki's group, in 1999, disclosed the synthesis of dihydrobenzofuro[2,3-*b*]benzofuranol derivatives (**18**) under Hoesch reaction conditions. A variety of aromatic *α*-hydroxyiminonitriles or *α*-oxonitriles (**17**) underwent a condensation reaction with phenols in the presence of $ZnCl_2$, followed by treatment with aqueous NaOH to produce the desired product **18** in moderate yield. This reaction worked only for the aromatic nitriles, and diketone products were obtained in the case of aliphatic nitrile (Scheme 5, **a**).[11] Similarly, Rahmatpour and co-workers demonstrated the condensation reaction of *para*-substituted phenols with glyoxal in the presence of acidic conditions to synthesize dihydrobenzofuro[2,3-*b*]benzofurans (**19**), followed by an oxidation reaction with $KMnO_4$ to give dicarboxylic acid-based benzofuro[2,3-*b*]benzofuran derivatives which have been used as a monomer unit in polymer

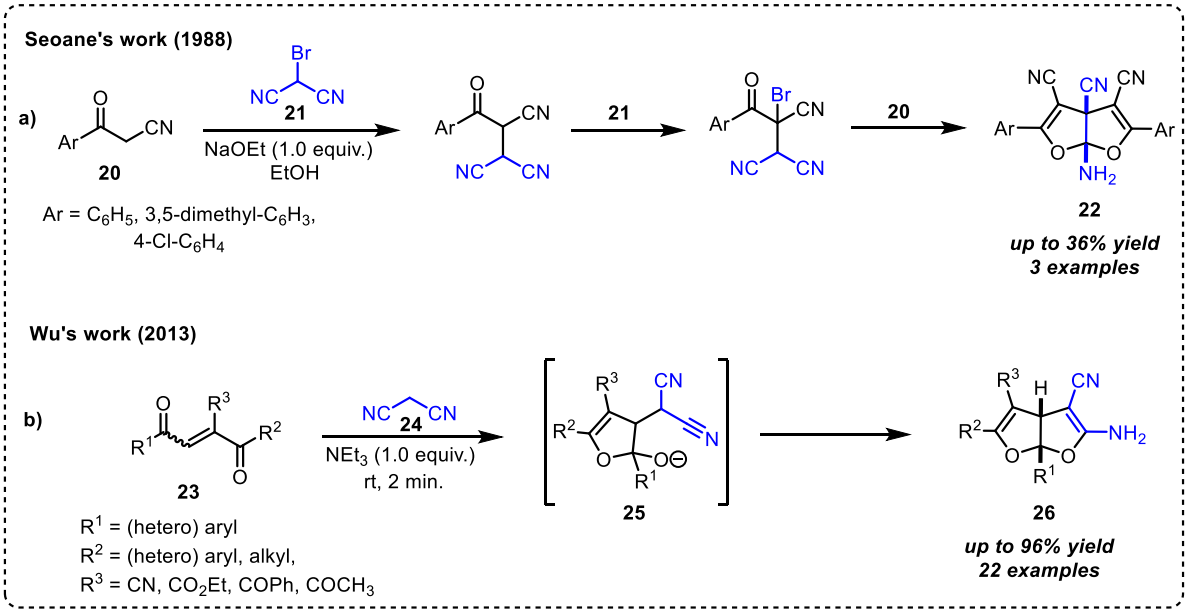
chemistry. When thiophenol/aniline was used instead of phenol, the expected product was not observed under similar reaction conditions (Scheme 5, **b**).[12]



Scheme 5. Condensation reactions for the synthesis of dihydrobenzofuro[2,3-*b*]benzofurans

1.2.4 Metal-free synthesis of dihydrofuro[2,3-*b*]furans

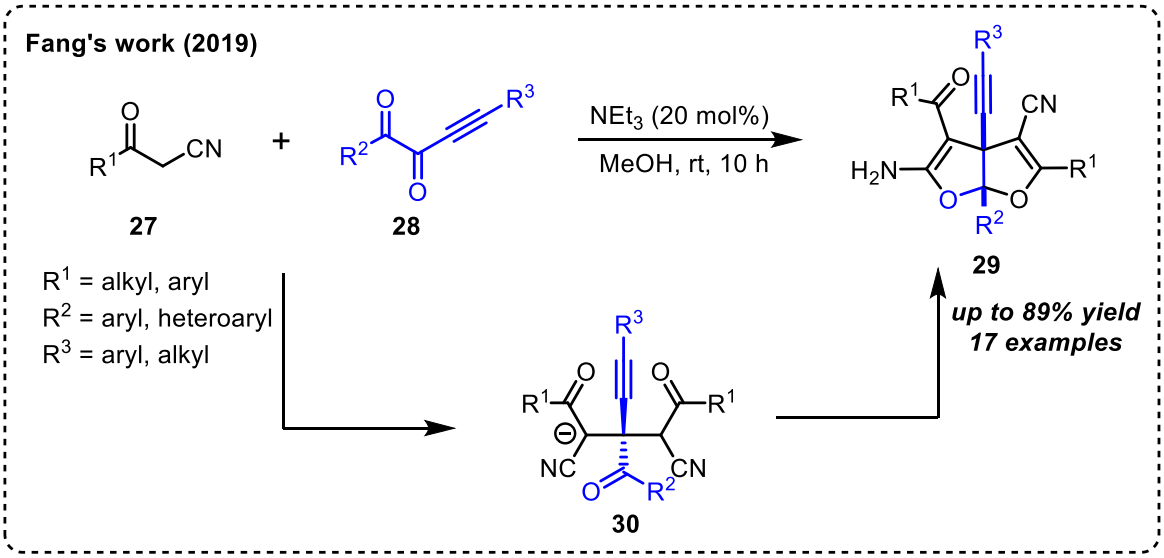
In 1988, Seoane and co-workers reported the reaction between *α*-cyanoacetophenone **20** and bromomalononitrile **21** in the presence of sodium ethoxide to synthesize



Scheme 6. Metal-free synthesis of dihydrofuro[2,3-*b*]furans

dihydrofuro[2,3-*b*]furan derivatives (**22**). It was found that an equivalent amount of compound **21** is required for this transformation as half equivalent of **21** is used as a brominating agent and another half equivalent for substitution reaction (Scheme 6, **a**).[13] Similarly, Wu's group discussed the synthesis of dihydrofuro[2,3-*b*]furans (**26**) by the bicyclization reaction of unsymmetrical 1,4-enediones (**23**) with malononitrile (**24**). The reaction proceeds through the 1,4-Michael-addition of malononitrile to **23** in the presence of a base to generate an intermediate 2,3-dihydrofuran **25**, followed by intramolecular cyclization/isomerization sequence to produce the product **26**. This methodology was also extended to a one-pot synthesis of **26** directly from methyl ketones (Scheme 6, **b**).[14]

Recently, Fang and co-workers disclosed the synthesis of dihydrofuro[2,3-*b*]furan (**29**) derivatives through a base-catalyzed annulation reaction of *α*-cyanoketones (**27**) with alkynyl ***α***-diketones (**28**). A variety of *α*-cyanoketones were reacted with alkynyl *α*-diketones in the presence of 20 mol% of NEt_3 in methanol to provide the respective dihydrofurofurans in moderate to excellent yields. The reaction proceeds through the condensation reaction of **27** and **28** to generate an intermediate **30**. The intermediate **30** underwent an intramolecular cyclization/isomerization to give the expected product **29**. It is worth mentioning that, under different reaction conditions, other heterocyclic compounds were obtained from the same starting material (Scheme 7).[15]



Scheme 7. NEt_3-catalyzed the synthesis of dihydrofuro[2,3-*b*]furans

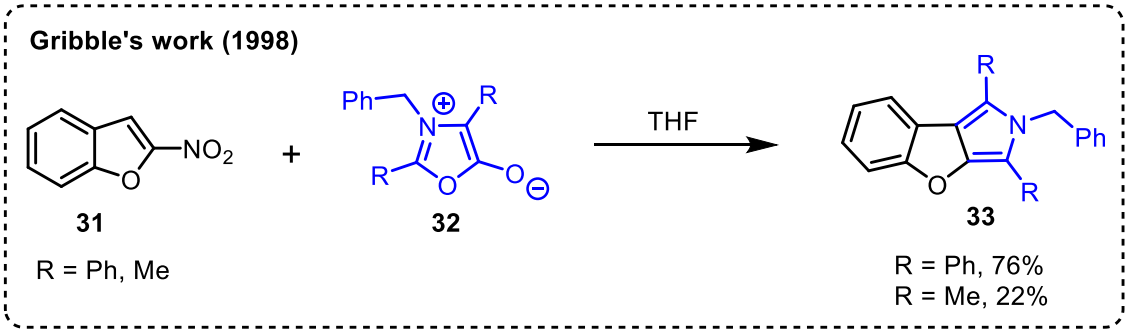
1.3 Literature reports on the reactivity of 2-nitrobenzo[*b*]furans

Benzo[*b*]furans are very reactive towards electrophilic substitution reactions; usually, the reaction takes place at the C-2 position. However, when a nitro-group is introduced at the

C-2 position of the benzo[*b*]furan ring, it behaves very differently for obvious reasons. The nitro substitution makes the furan ring electron-deficient and the C-3 position susceptible to nucleophilic attack. This concept has been realized in synthesizing a wide range of oxygen-containing heterocycles. A few of them are discussed below.

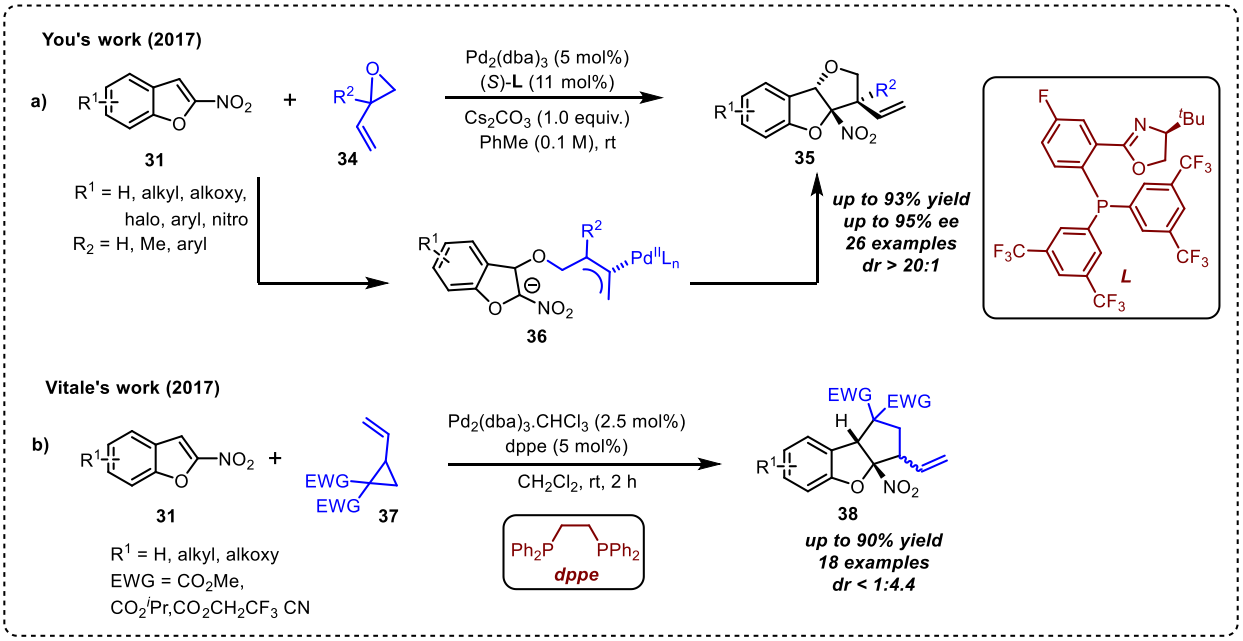
1.3.1 1,3-dipolar cycloaddition reactions of 2-nitrobenzo[*b*]furans

1n 1998, Gribble and co-workers described the 1,3-dipolar cycloaddition reactions of Münchnones (mesoionic 1,3-oxazolium-5-olates) [**32**] and 2-nitrobenzo[*b*]furans (**31**) for the synthesis of benzo[*b*]furo[2,3-*c*]pyrrole (**33**) derivatives. The starting material Münchnones was obtained by the cyclodehydration reaction of amino acids and *N*,*N*-diisopropylcarbodiimide (DIPC) [Scheme 8].[16]



Scheme 8. 1,3-dipolar cycloaddition reaction

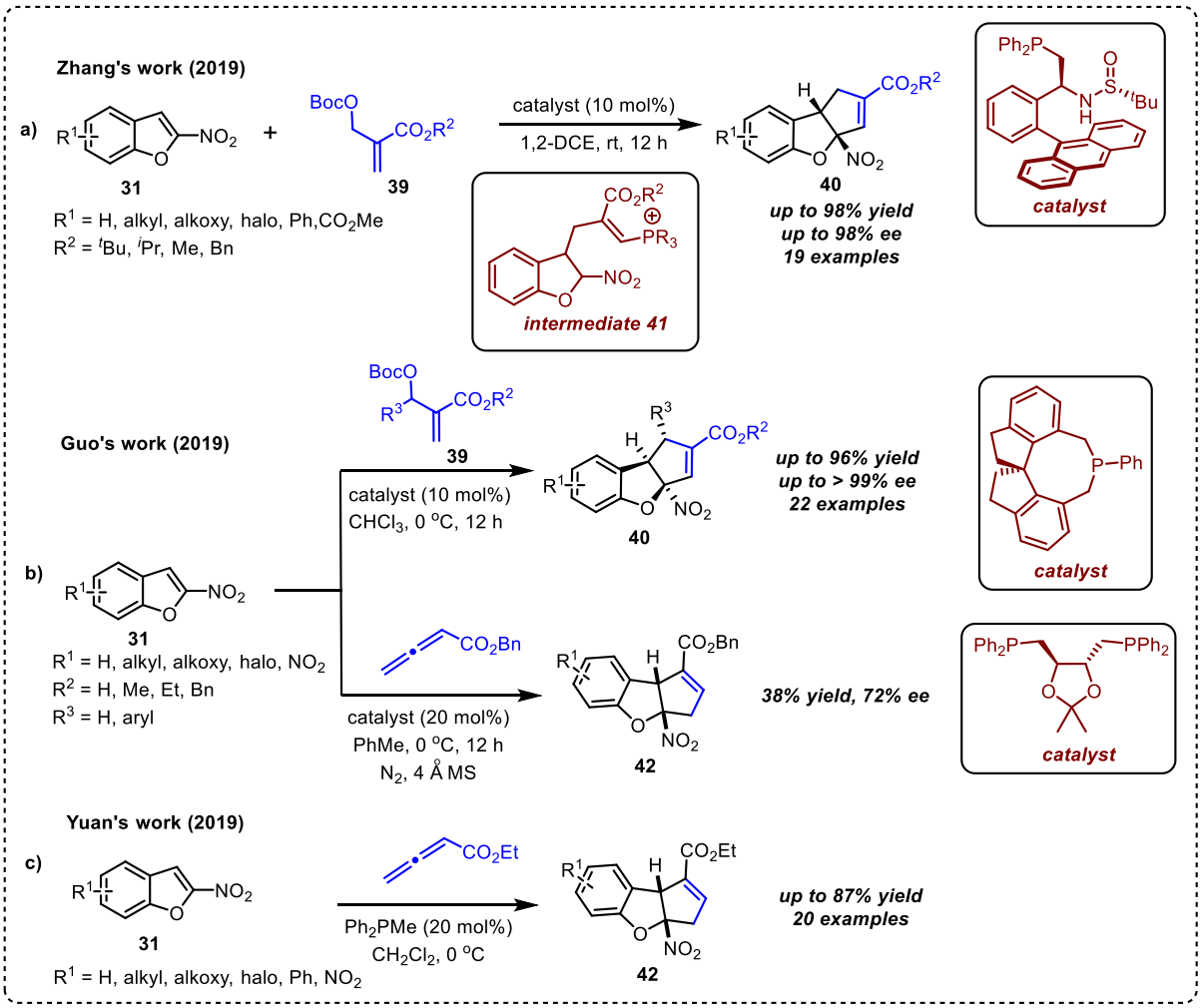
1.3.2 Palladium-catalyzed [3+2] cycloaddition reaction of 2-nitrobenzo[*b*]furans



Scheme 9. Palladium-catalyzed [3+2] cycloaddition reaction

You's group, in 2017, reported a highly stereoselective synthesis of tetrahydrofurofurans (**35**) *via* palladium-catalyzed dearomative [3+2] cycloaddition reaction of 2-nitrobenzo[*b*]furans (**31**) and epoxybutenes (**34**) in the presence of chiral PHOX ligand. A wide range of 2-nitrobenzo[*b*]furans (**31**) and epoxybutene (**34**) were reacted under standard conditions, leading to the formation of products **35** with vicinal quaternary stereogenic carbon centers. The reaction proceeds through the palladium-catalyzed ring-opening of epoxybutene, followed by 1,4-addition to **31**, to generate an intermediate **36**, which further underwent intramolecular cyclization to produce product **35** (Scheme 9, **a**).[17] Similarly, Vitale's group demonstrated the palladium-catalyzed dearomative [3+2] cycloaddition reaction of 2-nitrobenzo[*b*]furans (**31**) and vinyl cyclopropanes (**37**) for the synthesis of cyclopenta[*b*]benzofuran derivatives (**38**) in moderate to good yield (Scheme 9, **b**).[18]

1.3.3. Phosphine-catalyzed [3+2] cycloaddition reaction of 2-nitrobenzo[*b*]furans

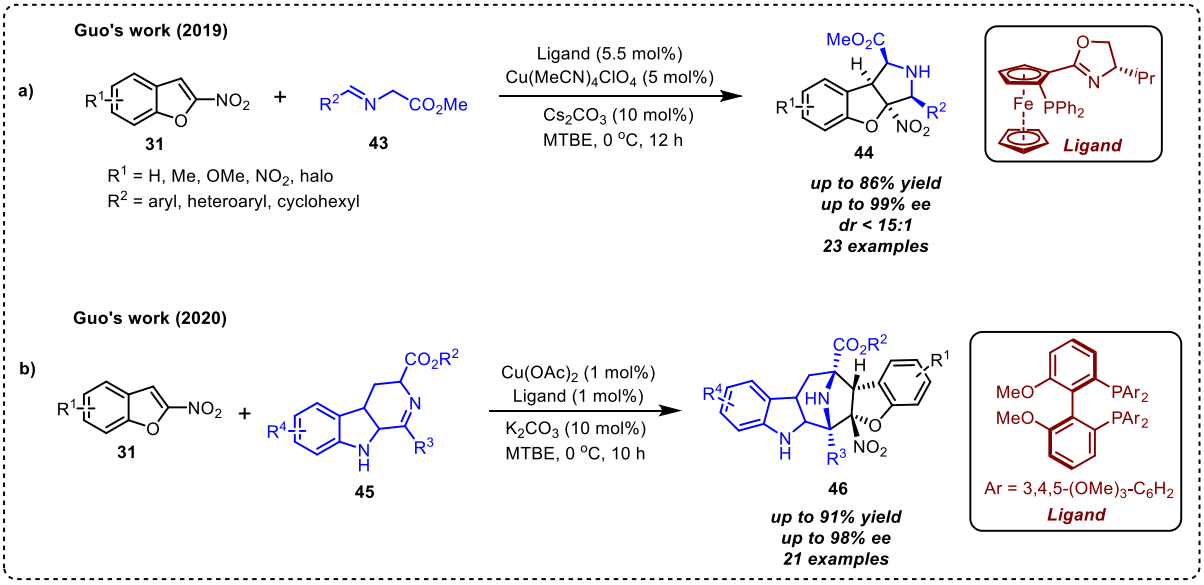


Scheme 10. Phosphine-catalyzed dearomative [3+2] cycloaddition reactions

In 2019, Zhang's[19] and Guo's[20] group independently reported the enantioselective synthesis of dihydrobenzofurans (**40**) *via* phosphine-catalyzed asymmetric dearomative [3+2] cycloaddition reaction of 2-nitrobenzo[*b*]furans (**31**) and MBH carbonates (**39**). In both the cases, the reaction worked efficiently with various 2-nitrobenzo[*b*]furans (**31**) and Morita–Baylis–Hillman (MBH) carbonates (**39**) in the presence of phosphine catalyst to afford the products in high stereoselectivity. According to the proposed reaction mechanism, a phosphonium ylide was generated from **39**, which underwent conjugate addition to 2-nitrobenzo[*b*]furans to form an intermediate **41**. Then intermediate **41** followed the intramolecular cyclization to produce product **40** (Scheme 10, **a** & **b**). In addition to this, Guo's group also investigated the phosphine-catalyzed asymmetric dearomative [3+2] cycloaddition reaction of 2-nitrobenzo[*b*]furans (**31**) and allenoates (Scheme 10, **b**).[20] Similarly, in the same year, Yuan and co-workers demonstrated the synthesis of cyclopenta[*b*]benzofuran derivatives (**42**) from the reaction of 2-nitrobenzo[*b*]furans (**31**) and allenoates under phosphine-catalyzed reaction conditions. They have extended this methodology for the synthesis of cyclopenta[*b*]benzothiophene derivatives with 3-nitrobenzo[*b*]thiophenes and allenoates (Scheme 10, **c**).[21]

1.3.4 Copper-catalyzed reactions of 2-nitrobenzo[*b*]furans

Guo's and co-workers disclosed highly stereoselective synthesis of [2,3]-fused hydrobenzofurans (**44**) in good to excellent yields through an asymmetric dearomative 1,3-dipolar cycloaddition reaction of 2-nitrobenzo[*b*]furans (**31**) with azomethine ylides (**43**). A variety of 2-nitrobenzo[*b*]furans (**31**) were reacted with **43** in the presence of chiral Cu(I)/^{i}Pr-

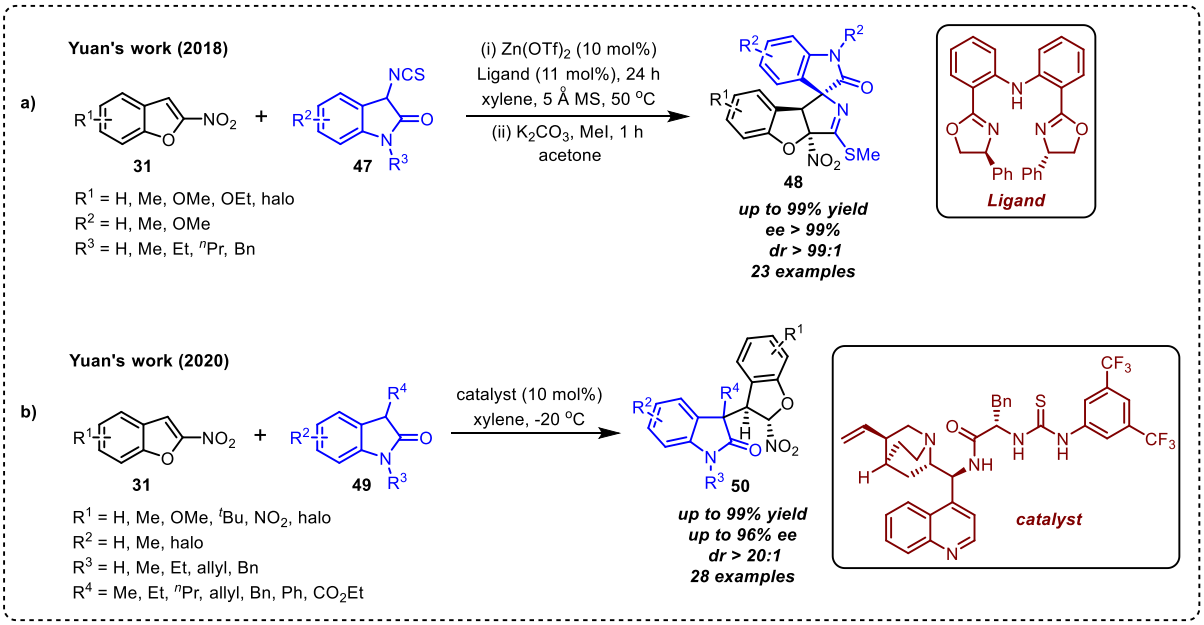


Scheme 11. Copper (I)-catalyzed 1,3-dipolar cycloaddition reaction

phosferrox complex to produce product **44** with four vicinal stereogenic centers (Scheme 11, **a**).[22] Recently, the same group also developed a chiral copper complex catalyzed asymmetric dearoamative [3+2] cycloaddition reaction of 2-nitrobenzo[*b*]furans (**31**) with cyclic azomethine ylides (**45**) to afford the fused polycyclic tropane derivatives (**46**) in good yields (Scheme 11, **b**).[23]

1.3.5 Reactions of 2-nitrobenzo[*b*]furans with 3-substituted oxindoles

In 2018, Yuan and co-workers described an asymmetric dearomative [3+2] cycloaddition reaction of 2-nitrobenzo[*b*]furans (**31**) and 3-isothiocyanato oxindoles (**47**) for the synthesis of *spiro*-oxindoles-based 2,3-dihydrobenzofuran derivatives (**48**) in the presence of chiral bis(oxazoline)/$Zn(OTf)_2$ catalyst (Scheme 12, **a**).[24] No product formation was observed when the reaction was carried out with 3-methyl-2-nitrobenzo[*b*]furans under standard reaction conditions. Recently, the same group developed an organo-catalyzed enantioselective synthesis of 3,3'-disubstituted oxindole derivatives (**50**) through asymmetric dearomative conjugate addition of 3-pyrrolyl-oxindoles (**49**) to 2-nitrobenzo[*b*]furans (**31**). The reaction worked smoothly with a variety of 3-substituted oxindoles and 2-nitrobenzo[*b*]furans (**31**) in the presence of chiral thiourea catalyst, and the products (**50**) were obtained in moderate to good yield (Scheme 12, **b**).[25]



Scheme 12. Reactions of 3-substituted oxindoles with 2-nitrobenzo[*b*]furans

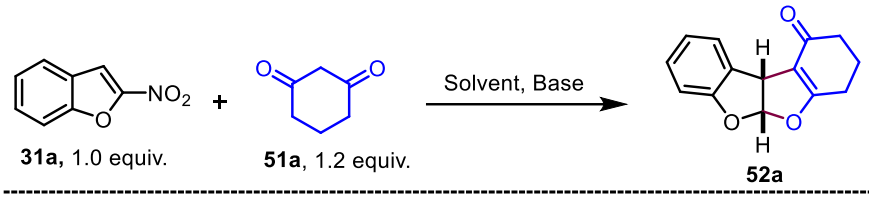
1.4 Background

Although most of the protocols mentioned above suffer from downsides such as expensive transition metal catalysts, harsh reaction conditions, low regioselectivity, and poor substrate scope, and therefore, developing a simple and practical approach for the synthesis of dihydrofuro[2,3-*b*]benzofuran derivatives from readily available precursors under relatively milder reaction conditions is highly desirable considering the synthetic applications as well as the structural complexity of these compounds. However, to the best of our knowledge, 2-nitrobenzofurans have not been utilized yet for the synthesis of dihydrofuro[2,3-*b*]benzofuran derivatives. While working on synthesizing oxygen- and nitrogen-containing heterocycles from *p*-quinone methides,[26] we envisioned that 2-nitrobenzofuran could be an alternative precursor to access functional and structurally complex dihydrobenzofuran derivatives. Herein, we report a simple and unprecedented protocol for the synthesis of dihydrofuro[2,3-*b*]benzofurans involving a base-mediated annulation reaction of 2-nitrobenzofurans with 1,3-dicarbonyls under very mild conditions.

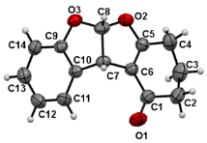
1.4 Results and discussion

To optimize the reaction conditions, we initiated our investigation by treating readily available 2-nitrobenzo[*b*]furan[17] **31a** with 1,3-cyclohexanedione **51a** under basic conditions utilizing a wide range of organic and inorganic bases, and the results are summarized in Table 1. To our delight, in our initial attempt itself, with Cs_2CO_3 as a base and CH_3CN as a medium, gave the desired product **52a** (*cis*- isomer) in 75% isolated yield within 1.5 h (entry 1). The structure of **52a** (CCDC 2057423) was unambiguously confirmed by X-ray analysis. Further screening was carried out with different inorganic bases (entries 2-4), however, the yield of **52a** was found to be much less under those conditions when compared to entry 1. Surprisingly, when DBU was used as a base, the yield of **52a** was improved up to 82%, and the reaction reached completion within 1 h (entry 5). However, other organic bases, such as Hünig's base and triethylamine, were found to be less effective for this transformation when compared to DBU (entries 6 & 7). Later, to identify the best solvent for this reaction, a few experiments have been carried out in different solvents using DBU as a base (entries 8-13). Among the solvents screened, acetone was found to be the best, and, in this case, the expected product **52a** was isolated in 86% yield within 1.5 h (entry 11). Lowering the amount of DBU to 1.5 equivalent decreased the yield of **52a** considerably (entry 14). Product **52a** was not formed when the reaction was carried out without a base, which clearly indicates that a base is required to promote this transformation (entry 15).

Table 1. Optimization study[a]



31a, 1.0 equiv. **51a**, 1.2 equiv. **52a**



CCDC2057423

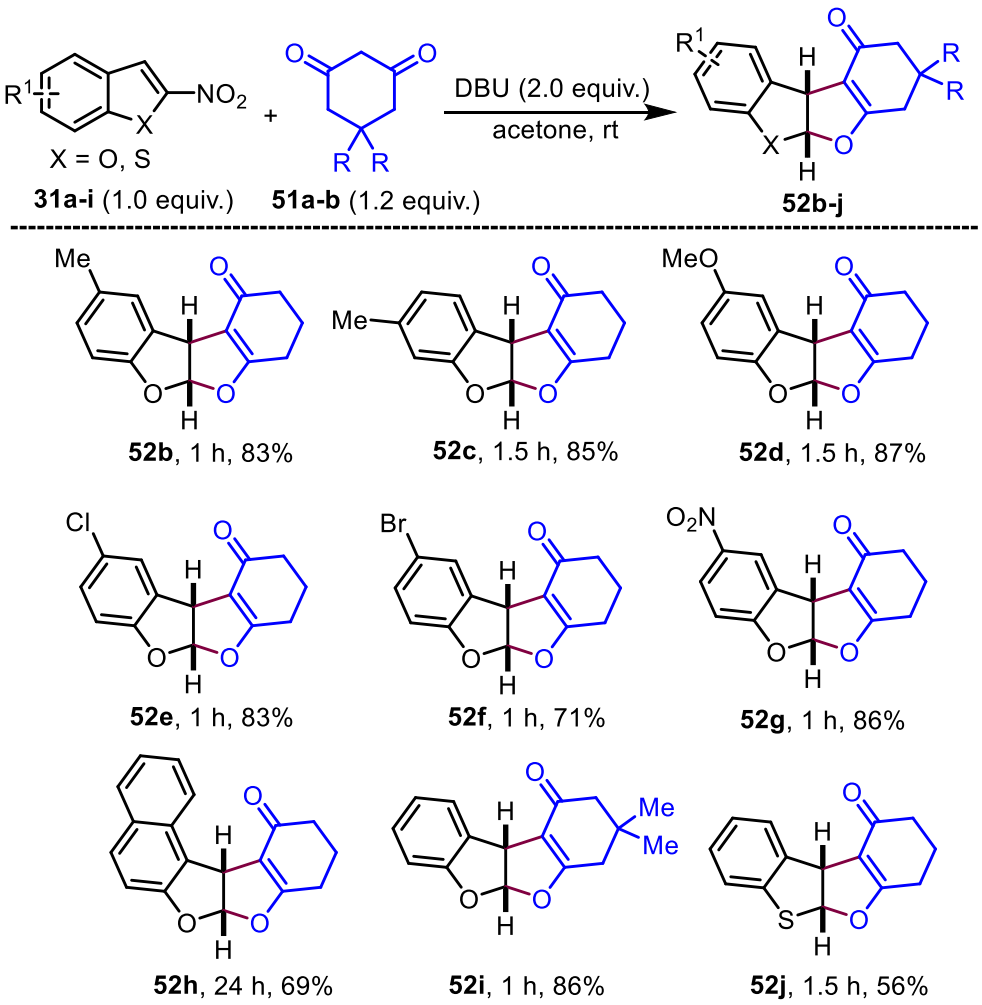
entry	base	solvent	time [h]	yield [%]
1	Cs_2CO_3	CH_3CN	1.5	75
2	K_2CO_3	CH_3CN	24	39
3	KO^{t}Bu	CH_3CN	1.5	46
4	NaH	CH_3CN	24	28
5	DBU	CH_3CN	1	82
6	$^i Pr_2NEt$	CH_3CN	24	39
7	NEt_3	CH_3CN	24	39
8	DBN	CH_3CN	1.5	46
9	DBU	THF	1.5	54
10	DBU	CH_2Cl_2	24	82
11	**DBU**	**acetone**	**1.5**	**86**
12	DBU	PhMe	24	43
13	DBU	DMF	1	82
14[b]	DBU	acetone	24	71
15	--	acetone	24	0

[a]All reactions were carried out with 30.0 mg scale of **31a** and 2.0 equiv. of base in 1.5 mL of solvent. [b]1.5 equiv. of base was used. The relative stereochemistry of **52a** (*cis*-) has been confirmed by ^{1}H NMR and X-ray analysis. Yields reported are isolated yields.

After finding the optimal conditions, we examined the scope and limitation(s) of this transformation using a wide range of substituted 2-nitrobenzo[*b*]furans (**31a-h**) and 1,3-cyclohexanedions (**51a** & **51b**), and the results are summarized in Scheme 13. It is evident from Scheme 13 that the reaction worked well with all the substrates, irrespective of the electronic nature of the aryl group present in 2-nitrobenzo[*b*]furans. For example, electron-rich 2-nitrobenzo[*b*]furans (**31b-d**) underwent smooth conversion to give the respective dihydrofuro[2,3-*b*]benzofurans (**52b-d**) in very good yields (83-87%). This protocol also worked well for halogen-substituted 2-nitrobenzo[*b*]furans (**31e** & **31f**), and the desired products (**52e** & **52f**) were isolated in good yields (71 and 83%, respectively). 2-Nitrobenzo[*b*]furan (**31g**), substituted with an electron-withdrawing functional group (-NO_2) in the aromatic ring, also gave the expected product **52g** in a very good yield (86%). Sterically hindered 2-nitrobenzo[*b*]furan (**31h**) was also found to be suitable for this transformation, and, in that case, the desired product **52h** was obtained in moderate yield (69%). When the reaction was carried out with dimedone (**51b**) and **31a** under the optimized reaction conditions, the

respective product **52i** obtained in 86% yield. In addition, 2-nitrobenzothiophene (**31i**) also underwent reaction with **51a** under the standard reaction conditions giving the expected product **52j** in 56% isolated yield.

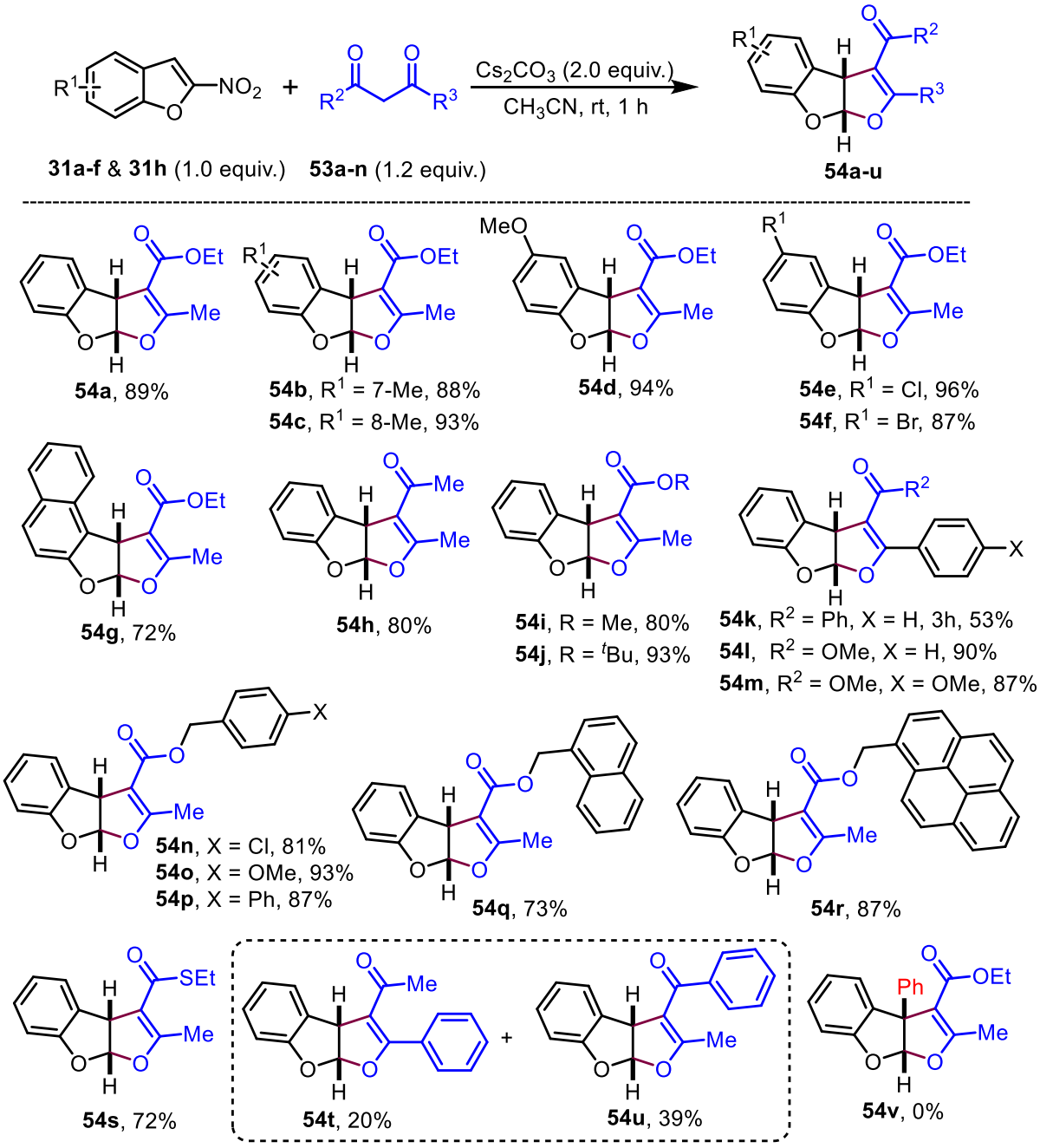
Scheme 13. Substrate scope of various 2-nitrobenzo[*b*]furans and cyclic 1,3-dicarbonyls[a]



[a]All reactions were carried out with 30 mg scale of (**31a-i)** in 1.5 mL of acetone. Yields reported are isolated yields.

After exploring the cyclic 1,3-diketone derivatives, we were interested to elaborate this protocol for acyclic 1,3-diketone derivatives as well. However, when a reaction between acetoacetic ester (**53a**) and 2-nitrobenzo[*b*]furan (**31a**) was carried out under the optimized conditions for cyclic 1,3-dicarbonyls (entry 11, Table 1), the expected dihydrofuro[2,3-*b*]benzofuran **54a** was obtained only in 67% yield. Moreover, the reaction took a bit longer time to attain completion. Therefore, we decided to perform a few optimization experiments to find out the best condition for the acyclic 1,3-dicarbonyls. Interestingly, when a reaction between **53a** and **31a** was carried out using 2 equivalents of Cs_2CO_3 in acetonitrile, the

Scheme 14. Substrate scope of various 2-nitro benzo[*b*]furans and aliphatic 1,3-dicarbonyls[a]



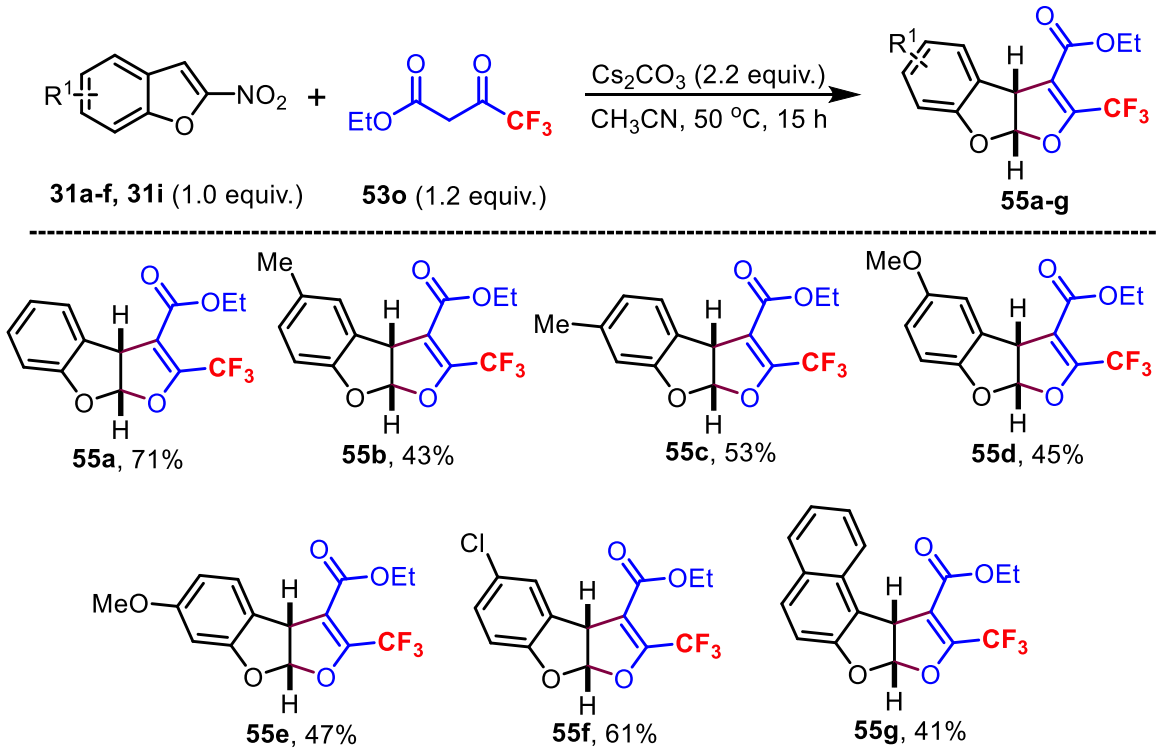
[a]All reactions were carried out with 30 mg scale of (**31a-f & 31h)** in 1.5 mL of MeCN. Yields reported are isolated yields.

expected product **54a** was obtained in 89% yield within 1 h (Scheme 14). These conditions were employed for other acyclic 1,3-dicarbonyls, and, in most cases, the expected dihydrofuro[2,3-*b*]benzofurans (**54b-r**) were isolated in moderate to good yields (Table 3). In addition, *S*-ethyl acetothioacetate (**53k**) also underwent a smooth reaction with **31a** and produced **54s** in 72% yield. When the reaction was carried out with an unsymmetrical diketone (benzoylacetone) a mixture of regioisomers **54t** & **54u** were obtained in 75% combined yield

with a ratio of 1:1.5. These regioisomers (**54t** & **54u**) could be separated by column chromatography and were isolated in yields, respectively. Unfortunately, 2-nitro-3-phenylbenzofuran failed to react with **53a** under the standard reaction conditions (**54v**).

To further elaborate the substrate scope, we thought of using ethyl 4,4,4-trifluoroacetoacetate (**53o**) to access trifluoromethylated dihydrofuro[2,3-*b*]benzofurans. There are several reports available on the importance of CF_3-containing heterocycles and other derivatives in pharmaceutical science.[27] Motivated by the significance of this functional group, we started evaluating the scope of this transformation using ethyl 4,4,4-trifluoroacetoacetate (**53o**) and a wide range of 2-nitrobenzo[*b*]furans (**31a-f** & **31h**), and the results are shown in Scheme 15. In most cases, the reaction proceeded smoothly and resulted in the formation of the respective trifluoromethylated dihydrofuro[2,3-*b*]benzofurans (**55a-g**) in the range of 41-71% yields (Scheme 15). However, unlike other acyclic 1,3-dicarbonyls, the reactions involving ethyl 4,4,4-trifluoroacetoacetate (**53o**) took place at a relatively higher temperature of 50 °C and produced the respective products (**55a-g**) in relatively lower yields.

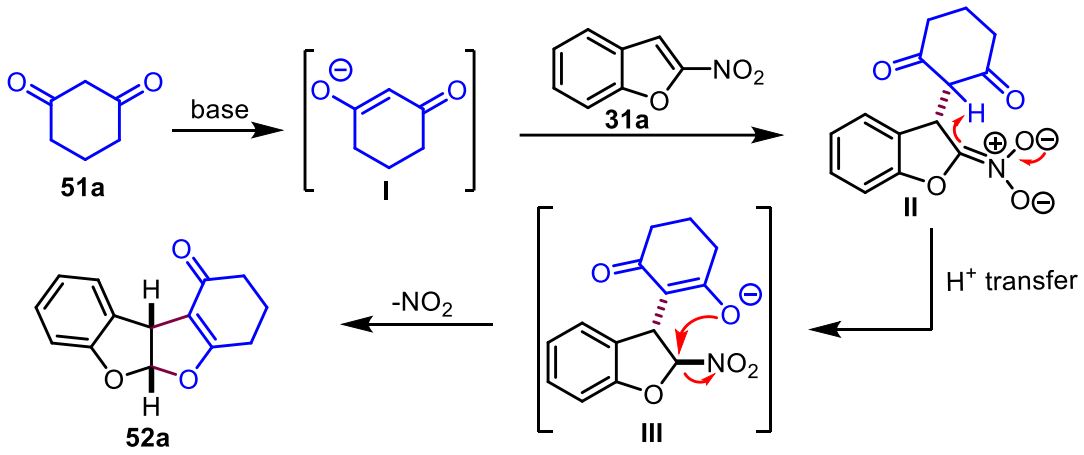
Scheme 15. Substrate scope of various 2-nitro benzo[*b*]furans and ethyl trifluoroacetoacetate[a]



[a]All reactions were carried out with 30 mg scale of (**31a-f**, **31h)** in 1.5 mL of MeCN. Yields reported are isolated yields.

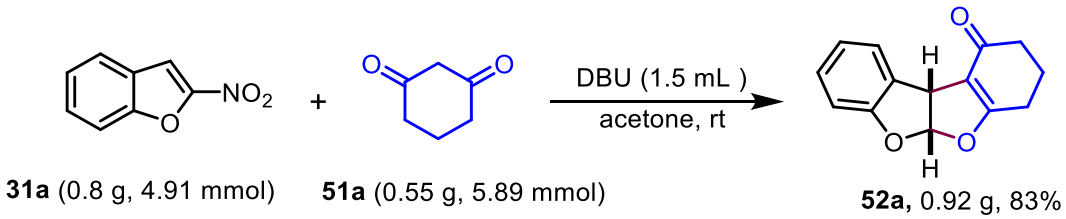
Based on the outcome of the reaction, a plausible reaction mechanism for this transformation has been proposed (Scheme16). Initially, the base abstracts the acidic proton

from 1,3- dicarbonyl (**51a**) to generate the enolate **I**, which immediately attacks the C-3 position of **31a** to form intermediate **II**. The intermediate **II** undergoes intramolecular proton transfer to generate another enolate **III**, which then undergoes intramolecular cyclization to generate product **31a** with the elimination of nitrite anion.



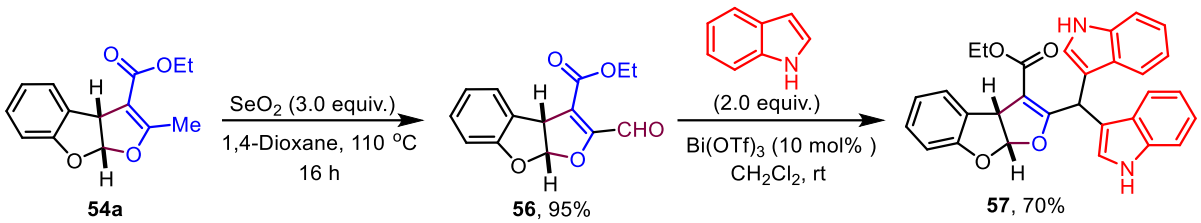
Scheme 16. Plausible reaction mechanism

To show the practicality of this methodology, an experiment was performed on relatively larger scale of **31a** (0.8 g scale) under standard conditions, and in that case, the product **52a** was obtained in 83% yield (Scheme 17).



Scheme 17. A relatively large-scale reaction of **31a**

Further, to show the synthetic significance of this transformation, one of the dihydrofuro[2,3-*b*]benzofurans **54a** was subjected to oxidation with SeO_2 to access the corresponding fused-dihydrobenzofuran aldehyde **56** in 95% yield (Scheme 18). Since indole-containing diaryl- and triarylmethanes derivatives possess various biological properties,[28] we thought of converting **56** to a diindolylmethane analogue. Therefore, subsequently, the aldehyde **56** was treated with 2 equivalents of indole under Lewis acidic conditions to provide the bis-indolyl tri-substituted methane **57** in 70% yield (Scheme 18).



54a **56**, 95% **57**, 70%

Scheme 18. Synthetic elaboration

1.6 Conclusion

In conclusion, we have demonstrated a simple base-mediated approach for the synthesis of dihydrofuro-[2,3-*b*]-benzofuran derivatives from 2-nitrobenzofurans under mild conditions. A wide range of cyclic as well as acyclic 1,3-dicarbonyls reacted with 2-nitrobenzofurans, and the respective dihydrofuro-[2,3-*b*]-benzofuran derivatives have been obtained in moderate to excellent yields. This protocol has also been extended to the synthesis of many trifluoromethylated dihydrofuro-[2,3-*b*]-benzofuran derivatives in good yields. Since many furo[2,3-*b*]benzofuran and dihydrofuro[2,3-*b*]benzofuran possess remarkable pharmaceutical properties, we believe, this methodology would be definitely useful in making some of those biologically important compounds in the near future.

1.7 Experimental section

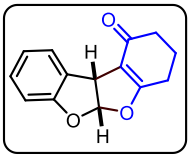
General information

All reactions were carried out in an oven-dried round bottom flask. All the solvents were distilled before use and stored under an argon atmosphere. Most of the reagents and starting materials were purchased from commercial sources and used as such. All 2-Nitrobenzo[*b*]furans were prepared according to the literature procedure.[17] 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 relatives to TMS, and the coupling constants (J) are reported in Hz. High-resolution mass spectra were recorded on Waters Q-TOF Premier–HAB213 spectrometer. FT-IR spectra were recorded on a Perkin-Elmer FTIR spectrometer. Single crystal X-ray data was collected using an XtaLabmini X-ray diffractometer. Thin-layer chromatography was performed on Merck silica gel 60 F_{254} TLC pellets and visualized by UV irradiation and $KMnO_4$ stain. Column chromatography was carried out through silica gel (100–200 mesh) using EtOAc/hexane as eluent.

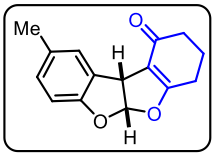
General procedure for the synthesis of dihydrofuro[2,3-b]benzofurans (52a-j):

DBU (0.368 mmol, 2.0 equiv.) was added to a solution of 2-nitrobenzo[*b*]furan (0.184 mmol, 1.0 equiv.) and cyclic 1,3-dicarbonyl compound (0.221 mmol, 1.2 equiv.) in acetone (1.5 mL), and the resulting reaction mixture was stirred at room temperature. After the reaction was complete (based on TLC analysis), the residue was then concentrated under reduced pressure and then purified through a silica gel column using EtOAc/Hexane mixture as an eluent to get the pure product.

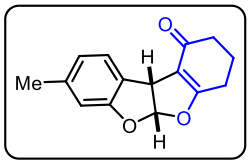
3,4,5a,10b-tetrahydrobenzofuro[2,3-*b*]benzofuran-1(2H)-one (**52a**)**:**[8b] The reaction was performed at 0.184 mmol scale of **31a**; white solid (36.1 mg, 86% yield); m. p. = 84–86 ºC; R_f = 0.2 (20% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, *J* = 7.4 Hz, 1H), 7.16 (t, *J* = 7.8 Hz, 1H), 6.95 – 6.89 (m, 2H), 6.77 (d, *J* = 7.2 Hz, 1H), 4.82 (d, *J* = 7.1 Hz, 1H), 2.55 – 2.43 (m, 2H), 2.40 – 2.26 (m, 2H), 2.07 – 1.96 (m, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 194.7, 176.1, 157.2, 128.7, 126.6, 126.3, 122.4, 115.7, 113.3, 110.0, 48.0, 36.6, 23.6, 21.5; FT-IR (thin film, neat): 2948, 1644, 1476, 1182, 755 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{14}H_{13}O_3$ $[M+H]^+$: 229.0865; found : 229.0855.



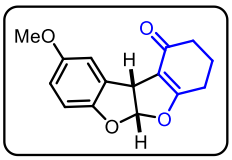
9-methyl-3,4,5a,10b-tetrahydrobenzofuro[2,3-*b*]benzofuran-1(2H)-one (52b): The reaction was performed at 0.169 mmol scale of **31b**; white solid (34.0 mg, 83% yield); m. p. = 121–123 ºC; R_f = 0.2 (20% EtOAc in hexane);^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (s, 1H), 6.96 (d, *J* = 8.1 Hz, 1H), 6.79 (d, *J* = 8.2 Hz, 1H), 6.76 (d, *J* = 7.2 Hz, 1H), 4.79 (d, *J* = 7.1 Hz, 1H), 2.54 – 2.45 (m, 2H), 2.40 – 2.31 (m, 2H), 2.27 (s, 3H), 2.06 – 1.99 (m, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 194.8, 176.2, 155.2, 132.0, 129.2, 126.69, 126.67, 115.9, 113.6, 109.6, 48.0, 36.7, 23.7, 21.5, 20.9; FT-IR (thin film, neat): 2948, 1645, 1487, 1177, 951 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{15}H_{15}O_3$ $[M+H]^+$: 243.1021; found : 243.1009.



8-methyl-3,4,5a,10b-tetrahydrobenzofuro[2,3-*b*]benzofuran-1(2H)-one (52c): The reaction was performed at 0.169 mmol scale of **31c**; pale yellow solid (34.8 mg, 85% yield); m. p. = 123–125 ºC; R_f = 0.2 (20% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (d, *J* = 7.5 Hz, 1H), 6.78 – 6.73 (m, 3H), 4.79 (d, *J* = 7.0 Hz, 1H), 2.55 – 2.45 (m, 2H), 2.42 – 2.31 (m, 5H), 2.07 – 1.96 (m, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 194.8, 176.1, 157.5, 139.2, 125.8, 123.8, 123.1, 116.0, 113.6, 110.7, 47.8, 36.7, 23.6, 21.6, 21.5; FT-IR (thin film, neat): 2952, 1645, 1495, 1179, 944 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{15}H_{15}O_3$ $[M+H]^+$: 243.1021; found : 243.1014.

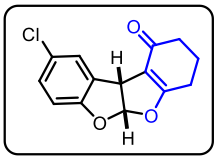


9-methoxy-3,4,5a,10b-tetrahydrobenzofuro[2,3-*b*]benzofuran-1(2H)-one (52d): The



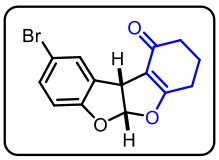
reaction was performed at 0.155 mmol scale of **31d**; pale yellow solid (34.9 mg, 87% yield); m. p. = 97–99 ºC; R_f = 0.1 (20% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16 (s, 1H), 6.83 (d, J = 8.7 Hz, 1H), 6.78 (d, J = 7.1 Hz, 1H), 6.72 (d, J = 8.7 Hz, 1H), 4.83 (d, J = 7.1 Hz, 1H), 3.77 (s, 3H), 2.56 – 2.46 (m, 2H), 2.43 – 2.30 (m, 2H), 2.08 – 2.01 (m, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 194.8, 176.4, 155.4, 151.1, 127.5, 115.6, 114.8, 113.9, 111.1, 110.2, 56.1, 48.5, 36.7, 23.7, 21.5; FT-IR (thin film, neat): 2941, 1644, 1486, 1216, 953 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{15}H_{15}O_4$ $[M+H]^+$: 259.0970; found : 259.0957.

9-chloro-3,4,5a,10b-tetrahydrobenzofuro[2,3-*b*]benzofuran-1(2H)-one (52e): The reaction



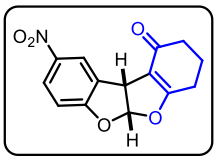
was performed at 0.152 mmol scale of **31e**; white solid (33.2 mg, 83% yield); m. p. = 82–84 ºC; R_f = 0.2 (20% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (d, J = 1.7 Hz, 1H), 7.10 (dd, J = 8.5, 2.2 Hz, 1H), 6.80 (d, J = 8.6 Hz, 1H), 6.77 (d, J = 7.2 Hz, 1H), 4.80 (d, J = 7.1 Hz, 1H), 2.53 – 2.46 (m, 2H), 2.37 – 2.29 (m, 2H), 2.06 – 1.99 (m, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 194.5, 176.2, 155.8, 128.7, 128.5, 127.2, 126.3, 115.2, 113.6, 110.9, 48.0, 36.6, 23.6, 21.5; FT-IR (thin film, neat): 2952, 1645, 1471, 1182, 949 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{14}H_{12}ClO_3$ $[M+H]^+$: 263.0475; found : 263.0462.

9-bromo-3,4,5a,10b-tetrahydrobenzofuro[2,3-*b*]benzofuran-1(2H)-one (52f): The reaction



was performed at 0.124 mmol scale of **31f**; white solid (27.0 mg, 71% yield); m. p. = 148–150 ºC; R_f = 0.2 (20% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (s, 1H), 7.26 – 7.24 (m, 1H), 6.78 – 6.76 (m, 2H), 4.80 (d, J = 6.6 Hz, 1H), 2.51 – 2.49 (m, 2H), 2.37 – 2.32 (m, 2H), 2.06 – 1.99 (m, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 194.5, 176.2, 156.4, 131.7, 129.2, 129.0, 115.3, 114.4, 113.5, 111.6, 48.0, 36.6, 23.6, 21.5; FT-IR (thin film, neat): 2952, 1645, 1470, 1181, 947 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{14}H_{12}BrO_3$ $[M+H]^+$: 306.9970; found : 306.9955.

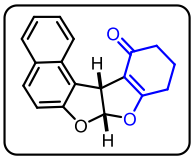
9-nitro-3,4,5a,10b-tetrahydrobenzofuro[2,3-*b*]benzofuran-1(2H)-one (52g): The reaction



was performed at 0.144 mmol scale of **31g**; white solid (33.8 mg, 86% yield); m. p. = 110–112 ºC; R_f = 0.1 (20% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.44 (s, 1H), 8.13 (d, J = 8.8 Hz, 1H), 6.96 (d, J = 8.8 Hz, 1H), 6.90 (d, J = 7.2 Hz, 1H), 4.90 (d, J = 7.1 Hz, 1H), 2.60 – 2.48 (m, 2H), 2.43 – 2.28 (m, 2H), 2.11 – 1.99 (m, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 194.4, 176.1, 162.2, 143.4, 128.3, 126.0, 122.6, 114.8, 114.1, 110.0, 47.6, 36.6, 23.6, 21.5; FT-IR (thin film, neat): 2952,

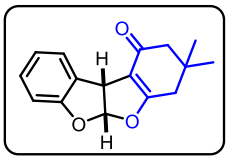
1646, 1472, 1217, 957 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{14}H_{12}NO_5$ $[M+H]^+$: 274.0715; found : 274.0707.

9,10,11,12b-tetrahydronaphtho[1',2':4,5]furo[2,3-*b*]benzofuran-12(7aH)-one (52h): The



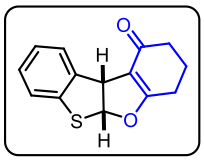
reaction was performed at 0.141 mmol scale of **31h**; pale yellow solid (27.0 mg, 69% yield); m. p. = 74–76 ºC; R_f = 0.2 (20% EtOAc in hexane); ^1H NMR (400 MHz, $CDCl_3$) δ 8.71 (d, *J* = 8.4 Hz, 1H), 7.80 – 7.74 (m, 2H), 7.57 (t, *J* = 7.6 Hz, 1H), 7.36 (t, *J* = 7.5 Hz, 1H), 7.20 (d, *J* = 8.7 Hz, 1H), 6.96 (d, *J* = 7.1 Hz, 1H), 5.17 (d, *J* = 7.1 Hz, 1H), 2.54 – 2.51 (m, 2H), 2.44 – 2.30 (m, 2H), 2.08 – 1.89 (m, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 194.4, 177.7, 155.3, 130.7, 130.4, 130.3, 128.4, 127.3, 125.6, 124.1, 119.3, 116.1, 114.7, 111.8, 47.9, 36.9, 24.1, 21.0; FT-IR (thin film, neat): 2970, 1634, 1464, 1217, 976 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{18}H_{15}O_3$ $[M+H]^+$: 279.1021; found : 279.1011.

3,3-dimethyl-3,4,5a,10b-tetrahydrobenzofuro[2,3-*b*]benzofuran-1(2H)-one (52i): The



reaction was performed at 0.184 mmol scale of **31a**; colorless gummy liquid (42.4 mg, 90% yield); R_f = 0.3 (20% EtOAc in hexane); ^1H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, *J* = 7.4 Hz, 1H), 7.15 (t, *J* = 7.7 Hz, 1H), 6.94 – 6.88 (m, 2H), 6.80 (d, *J* = 7.1 Hz, 1H), 4.84 (d, *J* = 7.0 Hz, 1H), 2.34 (s, 2H), 2.25 – 2.16 (m, 2H), 1.10 (s, 3H); 0.99 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 194.1, 175.0, 157.1, 128.7, 126.6, 126.2, 122.4, 114.4, 113.6, 110.0, 51.1, 47.9, 37.5, 34.3, 29.0, 28.4; FT-IR (thin film, neat): 2959, 1644, 1477, 1204, 953 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{16}H_{17}O_3$ $[M+H]^+$: 257.1178; found : 257.1167.

3,4,5a,10b-Tetrahydrobenzo[4,5]thieno[2,3-*b*]benzofuran-1(2H)-one (3j):[8b] The reaction



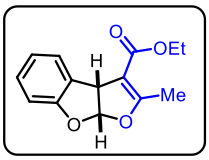
was performed at 0.167 mmol scale of **31i**; white solid (22.8 mg, 56% yield); R_f=0.3 (15% EtOAc in hexane); ^1H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, *J*=7.7 Hz, 1H), 7.20-7.16 (m, 2H), 7.11-7.05 (m, 1H), 6.69 (d, *J*=8.7 Hz, 1H), 5.19 (d, *J*=8.6 Hz, 1H), 2.48-2.44 (m, 2H), 2.38-2.35 (m, 2H), 2.09-1.93 (m, 2H); 0.99 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 194.7, 177.3, 139.8, 137.2, 128.4, 126.9, 125.5, 121.5, 115.9, 96.1, 54.6, 36.9, 24.0, 21.4.

***General procedure for the synthesis of dihydrofuro[2,3-b]benzofurans (54a-q) from acyclic 1,3-dicarbonyls*:**

Cs_2CO_3 (0.368 mmol, 2.0 equiv.) was added to a solution of 2-nitrobenzo[*b*]furan (0.184 mmol, 1 equiv.) and acyclic 1,3-dicarbonyl compound (0.221 mmol, 1.2 equiv.) in CH_3CN (1.5 mL), and the resulting suspension was stirred at room temperature for 1 h. The reaction mixture was

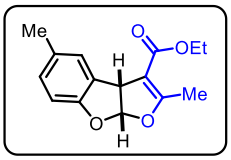
concentrated under reduced pressure and the residue was then purified through a silica gel column using EtOAc/Hexane mixture as an eluent to get the pure product.

Ethyl 2-methyl-3a,8a-dihydrofuro[2,3-*b*]benzofuran-3-carboxylate (54a): The reaction



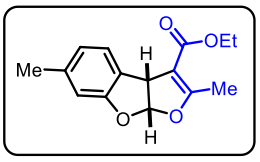
was performed at 0.183 mmol scale of **31a**; pale yellow gummy liquid (26.9 mg, 89% yield); R_f = 0.3 (5% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (d, J = 7.4 Hz, 1H), 7.18 (t, J = 7.7 Hz, 1H) 7.95 – 6.90 (m, 2H), 6.67 (d, J = 7.4 Hz, 1H), 4.83 (d, J = 7.4 Hz, 1H), 4.33 – 4.20 (m, 2H), 2.25 (s, 3H), 1.37 (t, J = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 167.5, 165.1, 157.6, 128.9, 127.3, 125.9, 121.9, 111.0, 110.1, 105.9, 60.1, 50.6, 14.6, 14.2; FT-IR (thin film, neat): 2977, 1652, 1476, 1204, 957 cm^{-1}; HRMS (APCI): *m/z* calcd for $C_{14}H_{14}O_4$ $[M]^+$: 246.0892; found : 246.0900.

Ethyl 2,5-dimethyl-3a,8a-dihydrofuro[2,3-*b*]benzofuran-3-carboxylate (54b): The



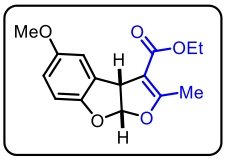
reaction was performed at 0.169 mmol scale of **31b**; white solid (38.8 mg, 88% yield); m. p. = 75–77 ºC; R_f = 0.3 (5% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (s, 1H), 6.97 (d, J = 8.1 Hz, 1H), 6.80 (d, J = 8.1 Hz, 1H), 6.64 (d, J = 7.4 Hz, 1H), 4.79 (d, J = 7.3 Hz, 1H), 4.36 – 4.20 (m, 2H), 2.29 (s, 3H), 2.24 (s, 3H), 1.38 (t, J = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 167.5, 165.1, 155.5, 131.3, 129.2, 127.3, 126.4, 111.2, 109.6, 105.9, 60.1, 50.6, 21.0, 14.6, 14.2; FT-IR (thin film, neat): 2974, 1699, 1487, 1211, 958 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{15}H_{16}O_4$ $[M+H]^+$: 260.1049; found : 260.1059.

Ethyl 2,6-dimethyl-3a,8a-dihydrofuro[2,3-*b*]benzofuran-3-carboxylate (54c): The reaction



was performed at 0.169 mmol scale of **31c**; pale yellow solid (40.9 mg, 93% yield); m. p. = 66–68 ºC; R_f = 0.3 (5% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (d, J = 7.4 Hz, 1H), 6.76 – 6.74 (m, 2H), 6.65 (d, J = 7.4 Hz, 1H), 4.79 (d, J = 7.2 Hz, 1H), 4.33 – 4.20 (m, 2H), 2.32 (s, 3H), 2.24 (d, J = 1.4 Hz, 3H), 1.37 (t, J = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 167.4, 165.1, 157.8, 139.2, 125.4, 124.4, 122.6, 111.2, 110.7, 106.1, 60.0, 50.4, 21.6, 14.6, 14.2; FT-IR (thin film, neat): 2984, 1699, 1495, 1204, 974 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{15}H_{16}O_4$ $[M+H]^+$: 260.1049; found : 260.1038.

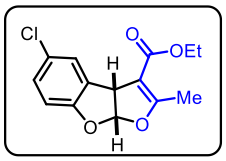
Ethyl 5-methoxy-2-methyl-3a,8a-dihydrofuro[2,3-*b*]benzofuran-3-carboxylate (54d): The



reaction was performed at 0.155 mmol scale of **31d**; white solid (40.3 mg, 94% yield); m. p. = 79–81 ºC; R_f = 0.2 (5% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.11 (d, J = 2.6 Hz, 1H), 6.81 (d, J = 8.7 Hz, 1H), 6.71

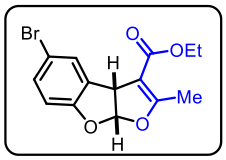
(dd, *J* = 8.7, 2.6 Hz, 1H), 6.64 (d, *J* = 7.4 Hz, 1H), 4.79 (d, *J* = 7.4 Hz, 1H), 4.34 – 4.19 (m, 2H), 3.75 (s, 3H), 2.24 (d, *J* = 1.4 Hz, 3H), 1.37 (t, *J* = 7.2 Hz, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 167.8, 165.0, 155.1, 151.5, 128.2, 114.1, 111.6, 111.4, 110.1, 105.6, 60.1, 56.0, 51.0, 14.6, 14.2; FT-IR (thin film, neat): 2977, 1705, 1486, 1212, 958 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{15}H_{17}O_5$ $[M+H]^+$: 277.1076; found : 277.1067.

Ethyl 5-chloro-2-methyl-3a,8a-dihydrofuro[2,3-*b*]benzofuran-3-carboxylate (54e): The



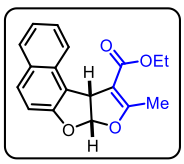
reaction was performed at 0.152 mmol scale of **31e**; pale yellow solid (41.0 mg, 96% yield); m. p. = 74–76 ºC; R_f = 0.3 (5% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (s, 1H), 7.12 (d, *J* = 8.4 Hz, 1H), 6.81 (d, *J* = 8.5 Hz, 1H), 6.65 (d, *J* = 7.4 Hz, 1H), 4.79 (d, *J* = 7.4 Hz, 1H), 4.36 – 4.20 (m, 2H), 2.24 (s, 3H), 1.37 (t, *J* = 7.1 Hz, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 167.8, 164.8, 156.2, 129.1, 128.7, 126.7, 126.2, 111.3, 111.0, 105.4, 60.3, 50.6, 14.6, 14.2; FT-IR (thin film, neat): 2984, 1705, 1471, 1202, 977 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{14}H_{14}ClO_4$ $[M+H]^+$: 281.0581; found : 281.0576.

Ethyl 5-bromo-2-methyl-3a,8a-dihydrofuro[2,3-*b*]benzofuran-3-carboxylate (54f): The



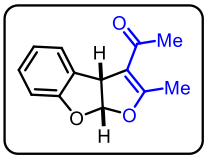
reaction was performed at 0.124 mmol scale of **31f**; pale yellow solid (35.1 mg, 87% yield); m. p. = 83–85 ºC; R_f = 0.3 (5% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (s, 1H), 7.28 – 7.26 (m, 1H), 6.78 (d, *J* = 8.2 Hz, 1H), 6.65 (d, *J* = 6.9 Hz, 1H), 4.80 (d, *J* = 7.0 Hz, 1H), 4.37 – 4.20 (m, 2H), 2.25 (s, 3H), 1.38 (t, *J* = 6.7 Hz, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 167.8, 164.8, 156.8, 131.7, 129.7, 129.1, 113.9, 111.6, 111.2, 105.5, 60.3, 50.6, 14.6, 14.2; FT-IR (thin film, neat): 2970, 1712, 1469, 1202, 976 cm^{-1}; HRMS (APCI): *m/z* calcd for $C_{14}H_{13}BrO_4$ $[M]^+$: 323.9997; found : 323.9986.

Ethyl 9-methyl-7a,10a-dihydrofuro[2,3-*b*]naphtho[1,2-*d*]furan-10-carboxylate (54g): The



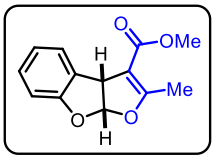
reaction was performed at 0.141 mmol scale of **31h**; pale yellow solid (25.0 mg, 72% yield); m. p. = 67–69 ºC; R_f = 0.2 (5% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41 (d, *J* = 8.5 Hz, 1H), 7.80 (d, *J* = 8.2 Hz, 1H), 7.74 (d, *J* = 8.8 Hz, 1H), 7.49 (t, *J* = 7.5 Hz, 1H), 7.34 (t, *J* = 7.6 Hz, 1H), 7.19 (d, *J* = 8.8 Hz, 1H), 6.84 (d, *J* = 7.3 Hz, 1H), 5.26 (d, *J* = 7.2 Hz, 1H), 4.26 (q, *J* = 7.0 Hz, 2H), 2.25 (s, 3H), 1.34 (t, *J* = 7.1 Hz, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 167.9, 165.4, 155.6, 130.6 (2C), 130.2, 128.7, 126.8, 124.9, 123.6, 119.6, 112.3, 112.0, 106.3, 60.4, 50.8, 14.6, 14.5; FT-IR (thin film, neat): 2981, 1699, 1380, 1210, 981 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{18}H_{16}O_4$ $[M+H]^+$: 296.1049; found : 296.1062.

1-(2-methyl-3a,8a-dihydrofuro[2,3-*b*]benzofuran-3-yl)ethan-1-one (54h): The reaction



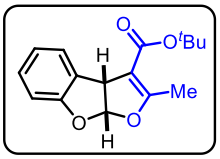
was performed at 0.184 mmol scale of **31a**; pale yellow solid (29.0 mg, 73% yield); m. p. = 116–118 ºC; R_f = 0.3 (5% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, J = 7.4 Hz, 1H), 7.16 (t, J = 7.7 Hz, 1H), 6.93 – 6.89 (m, 2H), 6.62 (d, J = 7.4 Hz, 1H), 4.93 (d, J = 7.4 Hz, 1H), 2.34 (s, 3H), 2.27 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 192.9, 166.0, 157.4, 128.7, 127.5, 126.4, 122.1, 117.7, 110.5, 109.9, 51.2, 29.6, 15.4; FT-IR (thin film, neat): 2992, 1626, 1475, 1202, 974 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{13}H_{13}O_3$ $[M+H]^+$: 217.0865; found : 217.0854.

Methyl 2-methyl-3a,8a-dihydrofuro[2,3-*b*]benzofuran-3-carboxylate (54i): The reaction



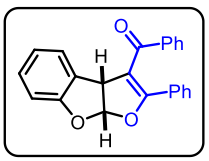
was performed at 0.184 mmol scale of **31a**; white solid (34.2 mg, 80% yield); m. p. = 78–80 ºC; R_f = 0.2 (5% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, J = 7.4 Hz, 1H), 7.18 (t, J = 7.7 Hz, 1H), 6.93 (dd, J = 11.1, 8.0 Hz, 2H), 6.67 (d, J = 7.4 Hz, 1H), 4.83 (d, J = 7.4 Hz, 1H), 3.81 (s, 3H), 2.24 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 167.8, 165.4, 157.6, 128.9, 127.2, 125.9, 122.0, 111.0, 110.1, 105.7, 51.3, 50.6, 14.2; FT-IR (thin film, neat): 2959, 1699, 1478, 1219, 980 cm^{-1}; HRMS (APCI): *m/z* calcd for $C_{13}H_{12}O_4$ $[M]^+$: 232.0736; found : 232.0729.

tert-butyl 2-methyl-3a,8a-dihydrofuro[2,3-*b*]benzofuran-3-carboxylate (54j): The



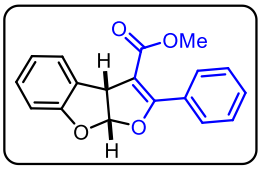
reaction was performed at 0.184 mmol scale of **31a**; pale yellow gummy liquid (46.9 mg, 93% yield); R_f = 0.3 (5% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, J = 7.4 Hz, 1H), 7.18 (t, J = 7.7 Hz, 1H), 6.95 – 6.90 (m, 2H), 6.63 (d, J = 7.4 Hz, 1H), 4.80 (d, J = 7.3 Hz, 1H), 2.20 (s, 3H), 1.55 (s, 9H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 166.3, 164.4, 157.5, 128.7, 127.5, 125.7, 121.8, 110.6, 110.0, 107.1, 80.6, 50.7, 28.5, 14.1; FT-IR (thin film, neat): 2981, 1694, 1476, 1222, 976 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{16}H_{19}O_4$ $[M+H]^+$: 275.1283; found : 275.1275.

Phenyl(2-phenyl-3a,8a-dihydrofuro[2,3-*b*]benzofuran-3-yl)methanone (5k): The reaction



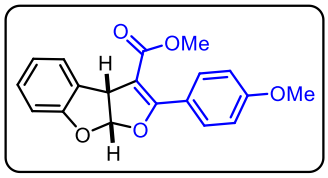
was performed at 0.184 mmol scale of **31a**; pale yellow solid (33.2 mg, 53% yield); m. p. = 94–96 ºC; R_f = 0.3 (10% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 – 7.55 (m, 1H), 7.38 – 7.37 (m, 2H), 7.27 – 7.20 (m, 5H), 7.05 – 6.87 (m, 7H), 5.34 (dd, J = 6.4, 3.9 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 192.8, 164.2, 157.5, 138.6, 131.6, 130.4 (2C), 129.4 (2C), 128.9 (2C), 128.8, 127.8, 127.7, 126.9, 126.0, 122.1, 114.4, 110.6, 109.9, 53.4; FT-IR (thin film, neat): 3060, 1622, 1475, 1221, 994 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{23}H_{17}O_3$ $[M+H]^+$: 341.1178; found : 341.1162.

methyl-2-phenyl-3a,8a-dihydrofuro[2,3-*b*]benzofuran-3-carboxylate (54l): The reaction



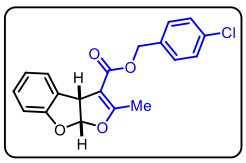
was performed at 0.183 mmol scale of **31a**; yellow gummy solid (42.2 mg, 90% yield); R_f = 0.2 (5% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 – 7.78 (m, 2H), 7.54 (d, *J*=7.4 Hz, 1H), 7.46 – 7.37 (m, 3H), 7.24 – 7.20 (m, 1H), 6.99 – 6.95 (m, 2H), 6.81 (d, *J*=7.5 Hz, 1H), 5.07 (d, *J*=7.5 Hz, 1H), 3.79 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, CDCl3) δ 164.8, 164.7, 157.8, 131.0, 129.6, 129.1, 128.8, 127.8, 127.1, 125.9, 122.0, 110.4, 110.2, 105.4, 52.2, 51.4; FT-IR (thin film, neat): 2958, 1710, 1694, 1224, 1092, 761 cm^{-1}; HRMS (ESI): m/z calcd for $C_{18}H_{15}O_4$ $[M+H]^+$: 295.0964; found: 295.0970.

Methyl 2-(4-methoxyphenyl)-3a,8a-dihydrofuro[2,3-*b*]benzofuran-3-carboxylate (54m):



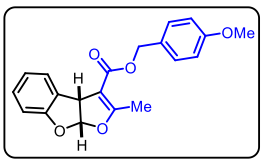
The reaction was performed at 0.183 mmol scale of **31a**; white solid (51.8 mg, 87% yield); m. p.=112°C; R_f = 0.1 (5% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, *J*=9.0 Hz, 2H), 7.53 (d, *J*=7.4 Hz, 1H), 7.21 (t, *J*=7.3 Hz, 1H), 6.99 – 6.93 (m, 2H), 6.90 (d, *J*=9.0 Hz, 2H), 6.77 (d, *J*=7.4 Hz, 1H), 5.04 (d, *J*=7.4 Hz, 1H), 3.83 (s, 3H), 3.82 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, CDCl3) δ 164.9, 164.7, 161.7, 157.7, 131.5, 129.0, 127.4, 125.8, 122.0, 121.0, 113.1, 110.1, 110.0, 103.8, 55.4, 52.1, 51.3; FT-IR (thin film, neat): 2958, 1714, 1606, 1263, 1084 cm^{-1}; HRMS (ESI): m/z calcd for $C_{19}H_{17}O_5$ $[M+H]^+$: 325.1076; found: 325.1064.

4-Chlorobenzyl 2-methyl-3a,8a-dihydrofuro[2,3-*b*]benzofuran-3-carboxylate (54n): The



reaction was performed at 0.184 mmol scale of **31a**; pale yellow solid (51.0 mg, 81% yield); m. p. = 109–111 ºC; R_f = 0.3 (5% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.36 (m, 5H), 7.17 (t, *J* = 7.6 Hz, 1H), 6.92 – 6.85 (m, 2H), 6.67 (d, *J* = 7.4 Hz, 1H), 5.22 (ABq, *J* = 12.4 Hz, 2H), 4.84 (d, *J* = 7.0 Hz, 1H), 2.25 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 168.3, 164.6, 157.4, 134.6, 134.2, 129.8, 128.9 (2C), 127.0, 125.8, 121.9, 111.0, 110.0, 105.5, 65.1, 50.5, 14.3; FT-IR (thin film, neat): 2930, 1699, 1476, 1204, 976 cm^{-1}; HRMS (APCI): *m/z* calcd for $C_{19}H_{15}ClO_4$ $[M]^+$: 342.0659; found : 342.0647.

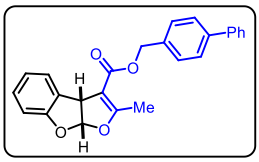
4-Methoxybenzyl 2-methyl-3a,8a-dihydrofuro[2,3-*b*]benzofuran-3-carboxylate (54o):



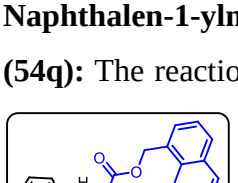
The reaction was performed at 0.184 mmol scale of **31a**; pale yellow gummy liquid (57.9 mg, 93% yield); R_f = 0.2 (5% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.36 (m, 3H), 7.16 (t, *J* = 7.4 Hz, 1H), 6.93 – 6.84 (m, 4H), 6.65 (d, *J* = 7.1 Hz, 1H), 5.20 (ABq, *J* = 11.8 Hz, 2H), 4.82 (d, *J* = 6.7

Hz, 1H), 3.83 (s, 3H), 2.24 (s, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 167.9, 164.8, 159.7, 157.5, 130.3, 128.8, 128.3, 127.2, 126.0, 121.9, 114.1, 111.0, 110.0, 105.7, 65.8, 53.4, 50.6, 14.3; FT-IR (thin film, neat): 2955, 1699, 1476, 1247, 975 cm^{-1}; HRMS (APCI): *m/z* calcd for $C_{20}H_{18}O_5$ $[M]^+$: 338.1154; found : 338.1170.

[1,1'-biphenyl]-4-ylmethyl 2-methyl-3a,8a-dihydrofuro[2,3-*b*]benzofuran-3-carboxylate (54p): The reaction was performed at 0.184 mmol scale of **31a**; pale yellow solid (61.5 mg, 87% yield); m. p. = 80–82 ºC; R_f = 0.3 (5% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 – 7.61 (m, 4H), 7.52 – 7.45 (m, 5H), 7.40 – 7.36 (m, 1H), 7.18 (t, *J* = 7.7 Hz, 1H), 6.92 (d, *J* = 8.0 Hz, 1H), 6.88 (t, *J* = 7.5 Hz, 1H), 6.68 (d, *J* = 7.4 Hz, 1H), 5.32 (ABq, *J* = 12.3 Hz, 2H), 4.88 (d, *J* = 7.4 Hz, 1H), 2.28 (s, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 168.2, 164.8, 157.5, 141.3, 140.7, 135.2, 128.95, 128.92, 128.89, 127.6, 127.5, 127.2, 127.1, 126.0, 121.9, 111.0, 110.0, 105.7, 65.7, 50.6, 14.3; FT-IR (thin film, neat): 2923, 1699, 1476, 1221, 975 cm^{-1}; HRMS (APCI): *m/z* calcd for $C_{25}H_{20}O_4$ $[M]^+$: 384.1362; found : 384.1371.



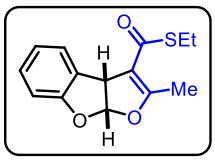
Naphthalen-1-ylmethyl 2-methyl-3a,8a-dihydrofuro[2,3-*b*]benzofuran-3-carboxylate (54q): The reaction was performed at 0.184 mmol scale of **31a**; pale yellow solid (48.1 mg, 73% yield); m. p. = 101–103 ºC; R_f = 0.3 (5% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (d, *J* = 7.9 Hz, 1H), 7.94 – 7.89 (m, 2H), 7.63 (d, *J* = 6.8 Hz, 1H), 7.61 – 7.53 (m, 2H), 7.50 (dd, *J* = 8.1, 7.2 Hz, 1H), 7.29 (d, *J* = 7.5 Hz, 1H), 7.16 – 7.12 (m, 1H), 6.89 (d, *J* = 8.0 Hz, 1H), 6.73 (td, *J* = 7.5, 0.8 Hz, 1H), 6.62 (d, *J* = 7.4 Hz, 1H), 5.73 (ABq, *J* = 12.4 Hz, 2H), 4.79 (d, *J* = 7.4 Hz, 1H), 2.22 (d, *J* = 1.3 Hz, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 168.3, 164.9, 157.5, 133.9, 131.8, 131.7, 129.5, 128.9, 128.8, 128.0, 127.0, 126.7, 126.1, 126.0, 125.4, 123.8, 121.9, 111.0, 109.9, 105.7, 64.3, 50.5, 14.3; FT-IR (thin film, neat): 2923, 1699, 1475, 1203, 974 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{23}H_{19}O_4$ $[M+H]^+$: 359.1283; found : 359.1273.



Pyren-1-ylmethyl 2-methyl-3a,8a-dihydrofuro[2,3-*b*]benzofuran-3-carboxylate (54r): The reaction was performed at 0.184 mmol scale of **31a**; white solid (69.2 mg, 87% yield); m. p. = 172–174 ºC; R_f = 0.3 (5% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.34 (d, *J* = 9.2 Hz, 1H), 8.24 – 8.22 (m, 2H), 8.20 – 8.17 (m, 2H), 8.12 – 8.03 (m, 4H), 7.30 (d, *J* = 7.5 Hz, 1H), 7.09 (t, *J* = 7.7 Hz, 1H), 6.86 (d, *J* = 8.0 Hz, 1H), 6.65 (t, *J* = 7.4 Hz, 1H), 6.61 (d, *J* = 7.4 Hz, 1H), 5.96 (ABq, *J* = 12.3 Hz, 2H), 4.80 (d, *J* = 7.4 Hz, 1H), 2.20 (s, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 168.4, 165.0, 157.5, 132.0, 131.3, 130.8, 129.8, 129.0, 128.8, 128.4, 128.2, 128.0, 127.5, 127.1, 126.3, 126.0, 125.7, 125.6, 125.1, 124.82, 124.76, 123.1, 121.9, 111.0, 110.0,

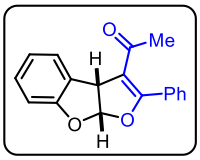
105.7, 64.6, 50.6, 14.4; FT-IR (thin film, neat): 2923, 1683, 1475, 1202, 844 cm^{-1}; HRMS (APCI): *m/z* calcd for $C_{29}H_{20}O_4$ $[M]^+$: 432.1362; found : 432.1377.

S-ethyl 2-methyl-3a,8a-dihydrofuro[2,3-*b*]benzofuran-3-carbothioate (54s): The reaction



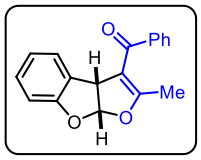
was performed at 0.184 mmol scale of **31a**; brown gummy liquid (15.4 mg, 32% yield); R_f = 0.4 (5% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (d, *J* = 7.5 Hz, 1H), 7.21 – 7.17 (m, 1H), 6.96 – 6.92 (m, 2H), 6.68 (d, *J* = 7.4 Hz, 1H), 4.95 (d, *J* = 7.4 Hz, 1H), 3.09 – 2.96 (m, 2H), 2.30 (d, *J* = 1.2 Hz, 3H), 1.33 (t, *J* = 7.4 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 185.7, 166.0, 157.5, 129.0, 127.0, 126.2, 122.1, 114.6, 111.2, 110.2, 50.9, 23.4, 15.3, 15.1; FT-IR (thin film, neat): 2970, 1615, 1476, 1231, 979 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{14}H_{15}O_3S$ $[M+H]^+$: 263.0742; found : 263.0730.

1-(2-Phenyl-3a,8a-dihydrofuro[2,3-*b*]benzofuran-3-yl)ethan-1-one (54t): The reaction was



performed at 0.183 mmol scale of **31a**; obtained as a regioisomers in the ratio of 1:1.5; (*Minor isomer*) yellow gummy solid (10.2 mg, 20% yield); R_f = 0.2 (5% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, *J*=7.4 Hz, 1H), 7.50 – 7.42 (m, 5H), 7.20 (t, *J*=7.7 Hz, 1H), 6.97 – 6.93 (m, 2H), 6.78 (d, *J*=7.4 Hz, 1H), 5.12 (d, *J*=7.4 Hz, 1H), 1.93 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, CDCl3) δ 194.2, 165.7, 157.6, 131.1, 130.0, 129.4, 128.8, 128.6, 127.3, 126.7, 122.2, 118.3, 110.8, 110.0, 52.2, 29.1; FT-IR (thin film, neat): 2922, 1634, 1212, 1040, 753 cm^{-1}; HRMS (APCI): m/z calcd for $C_{18}H_{15}O_3$ $[M+H]^+$: 279.1021; found: 279.1010.

(2-Methyl-3a,8a-dihydrofuro[2,3-*b*]benzofuran-3-yl)(phenyl)methanone (54u): The

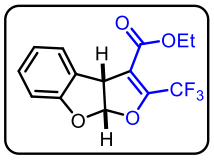


reaction was performed at 0.183 mmol scale of **31a**; obtained as a regioisomers in the ratio of 1:1.5; (*Major isomer*) yellow gummy solid (20.0 mg, 39% yield); R_f = 0.2 (5% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51-7.48 (m, 3H), 7.43 – 7.46 (m, 3H), 7.19 – 7.15 (m, 1H), 6.93 (d, *J*=8.0 Hz, 1H), 6.88 (dt, *J*=7.5, 0.6 Hz, 1H), 6.72 (d, *J*=7.4 Hz, 1H), 5.2 (d, *J*=7.3 Hz, 1H), 1.77 (d, *J*=1.2 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, CDCl3) δ 192.7, 167.0, 157.4, 140.5, 131.6, 128.9, 128.6, 128.1, 127.3, 125.9, 122.2, 116.2, 110.8, 110.0, 51.9, 15.5; FT-IR (thin film, neat): 2926, 1618, 1208, 1044, 984 cm^{-1}; HRMS (ESI): m/z calcd for $C_{18}H_{15}O_3$ $[M+H]^+$: 279.1021; found: 279.1012.

General procedure for the synthesis of trifluoromethylated dihydrofuro[2,3-b]benzofurans (55a-g):

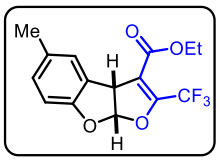
Cs_2CO_3 (0.405 mmol, 2.2 equiv.) was added to a solution of 2-nitrobenzo[*b*]furan (0.184 mmol, 1 equiv.) and ethyl 4,4,4-trifluoroacetoacetate (0.276 mmol, 1.5 equiv.) in CH_3CN (1.5 mL), and the resulting suspension was stirred at 50 ºC for 15 h. The reaction mixture was concentrated under reduced pressure, and the residue was then purified through a silica gel column using EtOAc/Hexane mixture as an eluent to get the pure product.

Ethyl 2-(trifluoromethyl)-3a,8a-dihydrofuro[2,3-*b*]benzofuran-3-carboxylate (55a): The



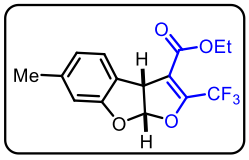
reaction was performed at 0.184 mmol scale of **31a**; pale yellow gummy liquid (39.2 mg, 71% yield); R_f = 0.3 (5% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (d, J = 7.5 Hz, 1H), 7.26 – 7.22 (m, 1H), 7.00 – 6.96 (m, 2H), 6.80 (d, J = 7.5 Hz, 1H), 5.03 (dd, J = 7.4, 1.6 Hz, 1H), 4.37 – 4.24 (m, 2H), 1.34 (t, J = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 161.5, 157.4, 151.0 (q, $^2J_{C\text{-}F}$ = 40.5 Hz), 129.6, 125.9, 124.6, 122.5, 118.0 (q, $^1J_{C\text{-}F}$ = 271.8 Hz), 111.9 (q, $^3J_{C\text{-}F}$ = 2.5 Hz), 111.3, 110.5, 61.5, 52.0, 14.0; ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ –64.4; FT-IR (thin film, neat): 2990, 1720, 1503, 1223 cm^{-1}; HRMS (APCI): *m/z* calcd for $C_{14}H_{11}F_3O_4$ $[M]^+$: 300.0609; found : 300.0618.

Ethyl 5-methyl-2-(trifluoromethyl)-3a,8a-dihydrofuro[2,3-*b*]benzofuran-3-carboxylate (55b): The reaction was performed at 0.169 mmol scale of **31b**; pale yellow solid (22.9 mg,



43% yield); m. p. = 99–101 ºC; R_f = 0.3 (5% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (s, 1H), 7.04 (dd, J = 8.2, 1.1 Hz, 1H), 6.85 (d, J = 8.2 Hz, 1H), 6.78 (d, J = 7.5 Hz, 1H), 5.00 – 4.97 (m, 1H), 4.39 – 4.24 (m, 2H), 2.30 (s, 3H), 1.35 (t, J = 7.2 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 161.7, 155.4, 151.1 (q, $^2J_{C\text{-}F}$ = 40.1 Hz), 132.2, 130.1, 126.4, 124.7, 118.1 (q, $^1J_{C\text{-}F}$ = 271.9 Hz), 112.0 (q, $^3J_{C\text{-}F}$ = 2.5 Hz), 111.7, 110.1, 61.6, 52.1, 21.0, 14.1; ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ –64.4; FT-IR (thin film, neat): 2988, 1716, 1489, 1213, 1001 cm^{-1}; HRMS (APCI): *m/z* calcd for $C_{15}H_{13}F_3O_4$ $[M]^+$: 314.0766; found : 314.0773.

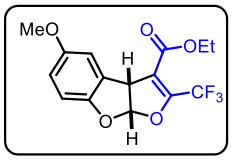
Ethyl 6-methyl-2-(trifluoromethyl)-3a,8a-dihydrofuro[2,3-*b*]benzofuran-3-carboxylate (55c): The reaction was performed at 0.169 mmol scale of **31c**; white solid (28.2 mg, 53%



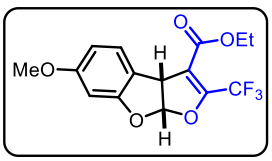
yield); m. p. = 69–71 ºC; R_f = 0.3 (5% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (d, J = 8.0 Hz, 1H), 6.80 – 6.77 (m, 3H), 4.99 (dd, J = 7.4, 1.5 Hz, 1H), 4.37 – 4.24 (m, 2H), 2.34 (s, 3H), 1.34 (t, J = 7.2 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 161.5, 157.6, 150.8 (q, $^2J_{C\text{-}F}$ = 40.1 Hz), 140.1, 125.4, 123.2, 121.7, 118.0 (q, $^1J_{C\text{-}F}$ = 271.9 Hz), 112.1 (q, $^3J_{C\text{-}F}$ = 2.5 Hz), 111.5, 111.1, 61.4, 51.7, 21.5, 14.0; ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ –64.4; FT-IR (thin film, neat): 2992, 1716,

1497, 1235, 1000 cm^{-1}; HRMS (APCI): *m/z* calcd for $C_{15}H_{13}F_3O_4$ $[M]^+$: 314.0766; found : 314.0752.

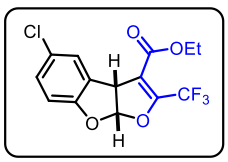
Ethyl 5-methoxy-2-(trifluoromethyl)-3a,8a-dihydrofuro[2,3-*b*]benzofuran-3-carboxylate (55d): The reaction was performed at 0.155 mmol scale of **31d**; pale yellow solid (23.1 mg, 45% yield); m. p. = 105–107 ºC; R_f = 0.2 (5% EtOAc in hexane); ^1H NMR (400 MHz, $CDCl_3$) δ 7.09 (s, 1H), 6.87 (d, J = 8.6 Hz, 1H), 6.79 – 6.77 (m, 2H), 4.99 (d, J = 6.8 Hz, 1H), 4.38 – 4.24 (m, 2H), 3.76 (s, 3H), 1.35 (t, J = 6.9 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 161.7, 155.5, 151.43, 151.4 (q, $^2J_{C\text{-}F}$ = 40.0 Hz), 125.7, 118.1 (q, $^1J_{C\text{-}F}$ = 271.8 Hz), 115.1, 112.0, 111.8 (q, $^3J_{C\text{-}F}$ = 2.4 Hz), 111.5, 110.7, 61.6, 56.1, 52.4, 14.1; $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$) δ –64.4; FT-IR (thin film, neat): 2995, 1705, 1491, 1217, 1007 cm^{-1}; HRMS (APCI): *m/z* calcd for $C_{15}H_{13}F_3O_5$ $[M]^+$: 330.0715; found : 330.0727.



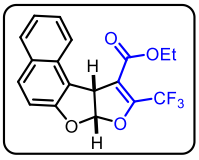
Ethyl 6-methoxy-2-(trifluoromethyl)-3a,8a-dihydrofuro[2,3-*b*]benzofuran-3-carboxylate (55e): The reaction was performed at 0.155 mmol scale of **31i**; white solid (24.1 mg, 47% yield); m. p. = 97–99 ºC; R_f = 0.2 (5% EtOAc in hexane); ^1H NMR (400 MHz, $CDCl_3$) δ 7.37 (d, J = 8.1 Hz, 1H), 6.79 (d, J = 7.4 Hz, 1H), 6.53 – 6.51 (m, 2H), 4.97 (d, J = 7.2 Hz, 1H), 4.36 – 4.23 (m, 2H), 3.78 (s, 3H), 1.34 (t, J = 7.0 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 161.7, 161.5, 158.9, 150.8 (q, $^2J_{C\text{-}F}$ = 40.0 Hz), 126.1, 118.1 (q, $^1J_{C\text{-}F}$ = 271.7 Hz), 116.7, 112.4 (q, $^3J_{C\text{-}F}$ = 2.8 Hz), 112.1, 108.4, 97.0, 61.6, 55.8, 51.6, 14.1; $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$) δ –64.4; FT-IR (thin film, neat): 2923, 1716, 1498, 1307, 996 cm^{-1}; HRMS (APCI): *m/z* calcd for $C_{15}H_{13}F_3O_5$ $[M]^+$: 330.0715; found : 330.0719.



Ethyl 5-chloro-2-(trifluoromethyl)-3a,8a-dihydrofuro[2,3-*b*]benzofuran-3-carboxylate (55f): The reaction was performed at 0.152 mmol scale of **31e**; pale yellow solid (31.0 mg, 61% yield); m. p. = 68–70 ºC; R_f = 0.3 (5% EtOAc in hexane); ^1H NMR (400 MHz, $CDCl_3$) δ 7.51 (s, 1H), 7.20 (d, J = 8.6 Hz, 1H), 6.89 (d, J = 8.5 Hz, 1H), 6.80 (d, J = 7.5 Hz, 1 H), 5.01 (d. J = 7.3 Hz, 1H), 4.40 – 4.25 (m, 2H), 1.36 (t, J = 7.2 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 161.4, 156.2, 151.4 (q, $^2J_{C\text{-}F}$ = 40.3 Hz), 129.7, 127.5, 126.6, 126.2, 118.0 (q, $^1J_{C\text{-}F}$ = 271.9 Hz), 111.7, 111.6 (t, $^3J_{C\text{-}F}$ = 2.8 Hz), 111.5, 61.8, 52.0, 14.1; $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$) δ –64.4; FT-IR (thin film, neat): 2927, 1717, 1472, 1308, 999 cm^{-1}; HRMS (APCI): *m/z* calcd for $C_{14}H_{10}ClF_3O_4$ $[M]^+$: 334.0220; found : 334.0214.



Ethyl 9-(trifluoromethyl)-7a,10a-dihydrofuro[2,3-*b*]naphtho[1,2-*d*]furan-10-carboxylate (55g): The reaction was performed at 0.140 mmol scale of **31h**; pale yellow gummy liquid

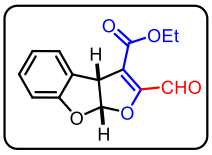


(20.0 mg, 41% yield); R_f = 0.2 (5% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, J = 8.4, 1H), 7.83 (d, J = 8.3 Hz, 1H), 7.80 (d, J = 8.8 Hz, 1H), 7.50 (t, J = 7.4 Hz, 1H), 7.36 (t, J = 7.5 Hz, 1H), 7.23 (d, J = 8.8 Hz, 1H), 6.98 (d, J = 7.4 Hz, 1H), 5.53 – 5.50 (m, 1H), 4.33 – 4.16 (m, 2H), 1.24 (t, J = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 162.7, 155.8, 149.4 (q, $^2J_{C\text{-}F}$ = 40.0 Hz), 131.5, 130.4, 130.2, 129.0, 127.5, 124.1, 123.7, 118.3 (q, $^1J_{C\text{-}F}$ = 271.3 Hz), 116.8, 112.6 (t, $^3J_{C\text{-}F}$ = 2.1 Hz), 112.6, 112.1, 62.1, 52.7, 13.8; ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ –65.0; FT-IR (thin film, neat): 2925, 1717, 1464, 1303, 995 cm^{-1}; HRMS (APCI): *m/z* calcd for $C_{18}H_{13}F_3O_4$ $[M]^+$: 350.0766; found : 350.0751.

General procedure for the large-scale reaction:

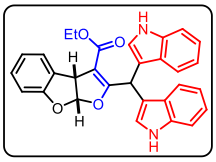
DBU (1.47 mL, 9.82 mmol) was added to a solution of 2-nitrobenzo[*b*]furan **31a** (0.8 g, 4.91 mmol) and cyclic 1,3-dicarbonyl compound **51a** (0.55 g, 5.89 mmol) in acetone (30 mL), and the resulting reaction mixture was stirred at room temperature. After the reaction was complete (based on TLC analysis), the residue was then concentrated under reduced pressure and the residue was then purified through a silica gel column using EtOAc/Hexane mixture as an eluent to get the pure product **52a** in 83% yield (0.92 g).

General procedure for the preparation of 56:



SeO_2 (41.0 mg, 0.366 mmol) was added to a solution of **54a** (30 mg, 0.122 mmol) in 1,4-Dioxane (2 mL), and the resulting suspension was stirred at 110 ^{o}C for 16 h. Then the mixture was filtered through a celite pad and washed with EtOAc (10 mL x 2). The combined filtrate was concentrated under reduced pressure. The residue was then purified through a silica gel column using EtOAc/Hexane mixture as an eluent to get the pure product **56**; pale yellow gummy liquid (32.1 mg, 95% yield); R_f = 0.2 (15% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.26 (s, 1H), 7.51 (d, J = 7.5 Hz, 1H), 7.22 (t, J = 7.7 Hz, 1H), 6.98 – 6.93 (m, 2H), 6.79 (d, J = 7.3 Hz, 1H), 5.04 (d, J = 7.4 Hz, 1H), 4.45 – 4.33 (m, 2H), 1.42 (t, J = 7.0 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 182.63 (d, J = 2.2 Hz), 162.5, 157.7, 157.2, 129.7, 125.8, 124.6, 122.4, 119.9, 111.1, 110.6, 61.9, 51.6, 14.4; FT-IR (thin film, neat): 2988, 1694, 1626, 1476, 1121, 967 cm^{-1}; HRMS (APCI): *m/z* calcd for $C_{14}H_{12}O_5$ $[M]^+$: 260.0685; found : 260.0694.

General procedure for the synthesis of 57:

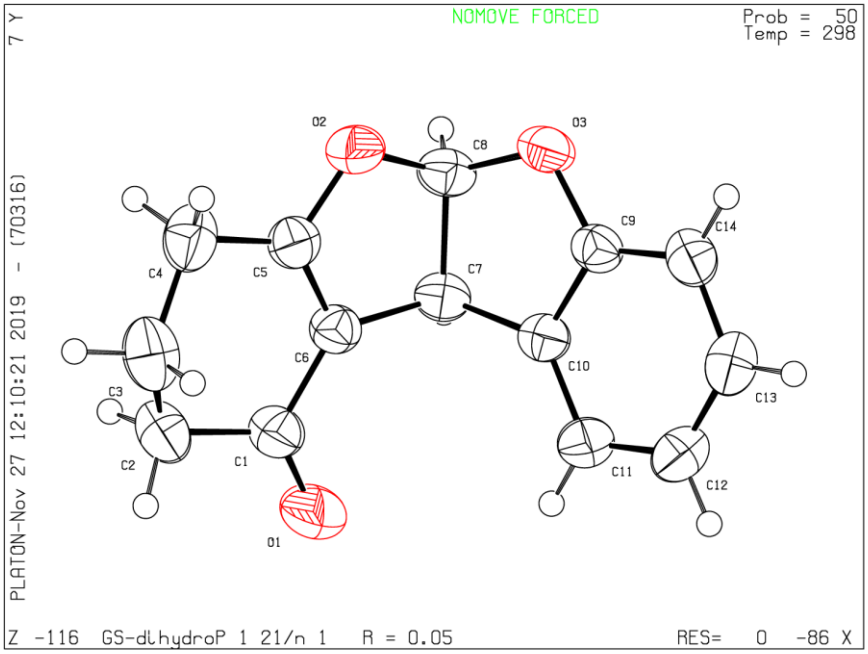


To a solution of **56** (25 mg, 0.096 mmol), indole (22.5 mg, 0.192 mmol) in CH_2Cl_2 (1.5 mL) was added $Bi(OTf)_3$ (6.3 mg, 0.0096 mmol), and the resulting mixture was stirred at room temperature for 4 h. Then reaction mixture was concentrated under reduced pressure, and the residue was purified through a silica gel column using EtOAc/Hexane mixture as an eluent to get the pure product **57**; pale yellow solid (32.0 mg, 70% yield); m. p. = 180–182 ºC; R_f = 0.1 (20% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (s, 1H), 7.86 (s, 1H), 7.80 (d, *J* = 7.9 Hz, 1H), 7.57 (d, *J* = 7.5 Hz, 1H), 7.34 (d, *J* = 8.0 Hz, 2H), 7.27 – 7.24 (m, 1H), 7.21 (dd, *J* = 8.2, 1.0 Hz, 1H), 7.18 – 7.08 (m, 4H), 6.96 – 6.88 (m, 4H), 6.78 (s, 1H), 6.61 (d, *J* = 7.3 Hz, 1H), 4.86 (d, *J* = 7.3 Hz, 1H), 4.46 – 4.30 (m, 2H), 1.44 (t, *J* = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 169.8, 164.9, 157.6, 136.3, 136.1, 128.9, 127.2, 126.9, 126.8, 126.2, 124.3, 123.0, 122.2, 122.0, 121.9, 119.7, 119.6, 119.5, 119.4, 114.9, 114.2, 111.4, 111.2, 111.1, 109.9, 105.2, 60.5, 50.7, 31.9, 14.7; FT-IR (thin film, neat): 3412, 2957, 1683, 1459, 1201, 748 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{30}H_{24}N_2NaO_4$ $[M+Na]^+$: 499.1634; found : 499.1642.

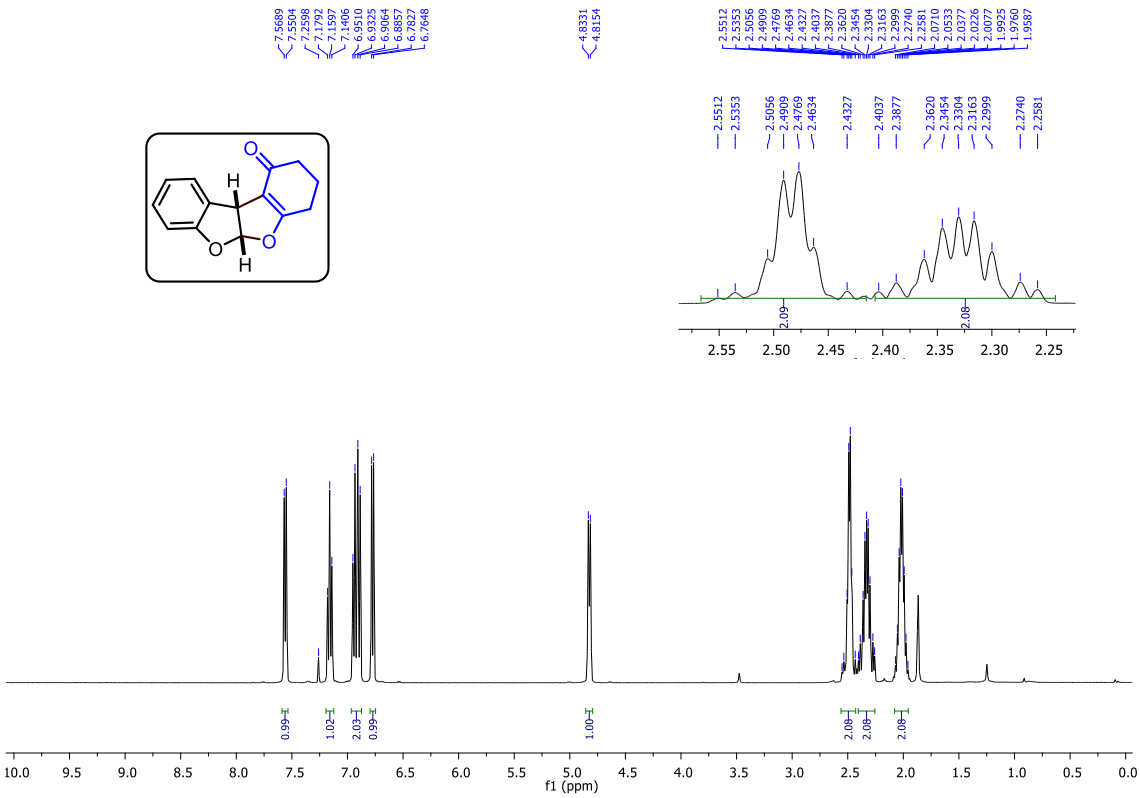
1. X-ray crystallographic analysis for compound 52a:

Table S1: Crystal data and structure refinement for compound **52a** (CCDC 2057423)

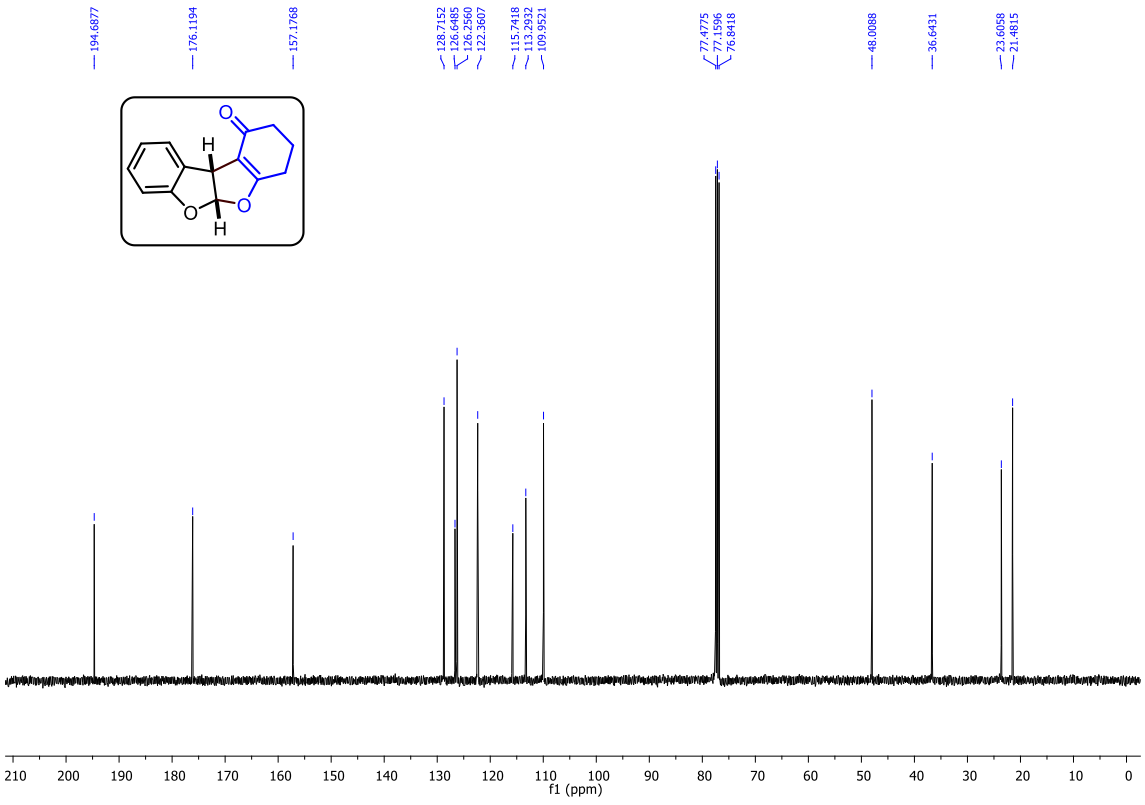
Identification code	GS-dihydrofurofuran
Empirical formula	$C_{14}H_{12}O_3$
Formula weight	228.25
Temperature/K	298.00
Crystal system	monoclinic
Space group	P 1 21/n 1
a/Å	7.6093(4)
b/Å	8.4738(4)
c/Å	17.6745(9)
α/°	90
β/°	97.913(4)
γ/°	90
Volume/Å3	1128.79(10)
Z	4
ρcalcg/cm3	1.3430
μ/mm-1	0.094
F(000)	480.2789
Crystal size/mm3	0.2 × 0.2 × 0.2
Radiation	Mo Kα (λ = 0.71073)
2Θ range for data collection/°	5.34 to 65.4
Index ranges	$-10 \leq h \leq 8$, $-8 \leq k \leq 12$, $-23 \leq l \leq 26$
Reflections collected	5373
Independent reflections	3540 [Rint = 0.0156, Rsigma = 0.0279]
Data/restraints/parameters	3540/0/154
Goodness-of-fit on F2	1.0434
Final R indexes [I>=2σ (I)]	R1 = 0.0502, wR2 = 0.1411
Final R indexes [all data]	R1 = 0.0690, wR2 = 0.1625
Largest diff. peak/hole / e Å-3	0.2999/-0.2312


NOMOVE FORCED
Prob = 50
Temp = 298
7 Y
PLATON-Nov 27 12:10:21 2019 - (70316)
O2
O3
C8
C9
C14
C4
C5
C7
C6
C10
C13
C3
C2
C1
C11
C12
O1
Z -116 GS-dihydroP 1 21/n 1 R = 0.05
RES= 0 -86 X

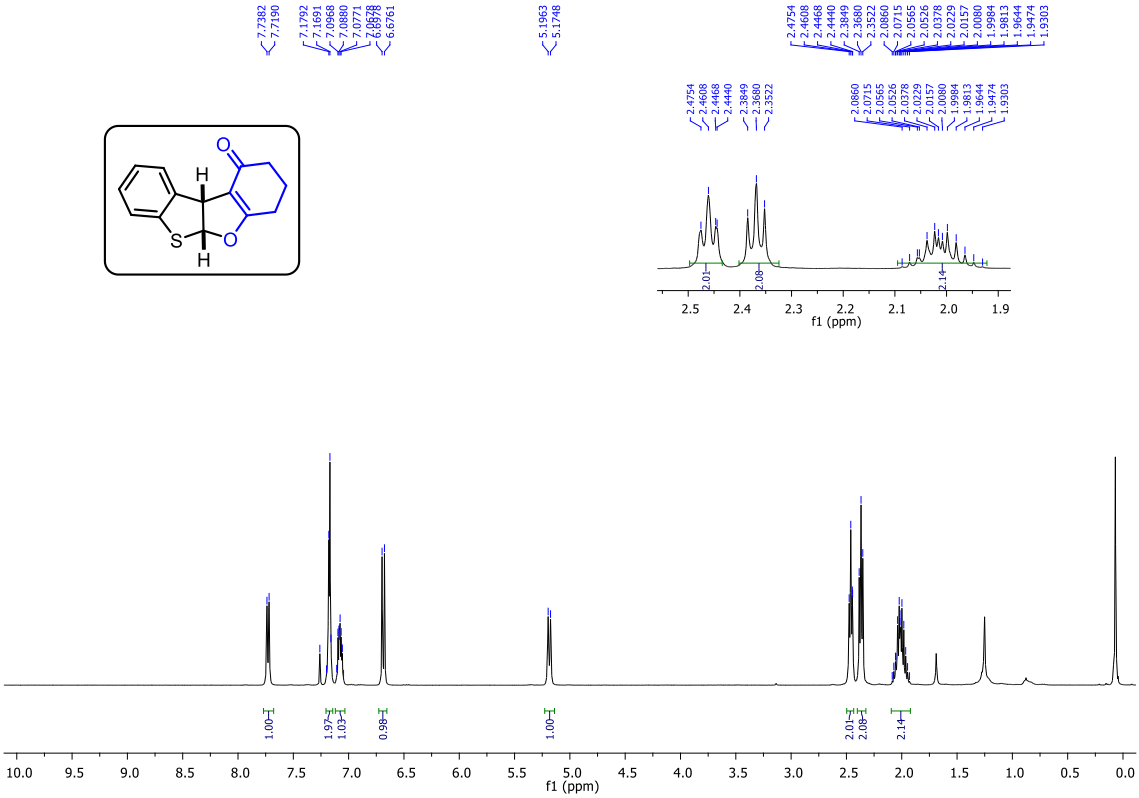
^{1}H NMR (400 MHz, $CDCl_3$) Spectrum of **52a**



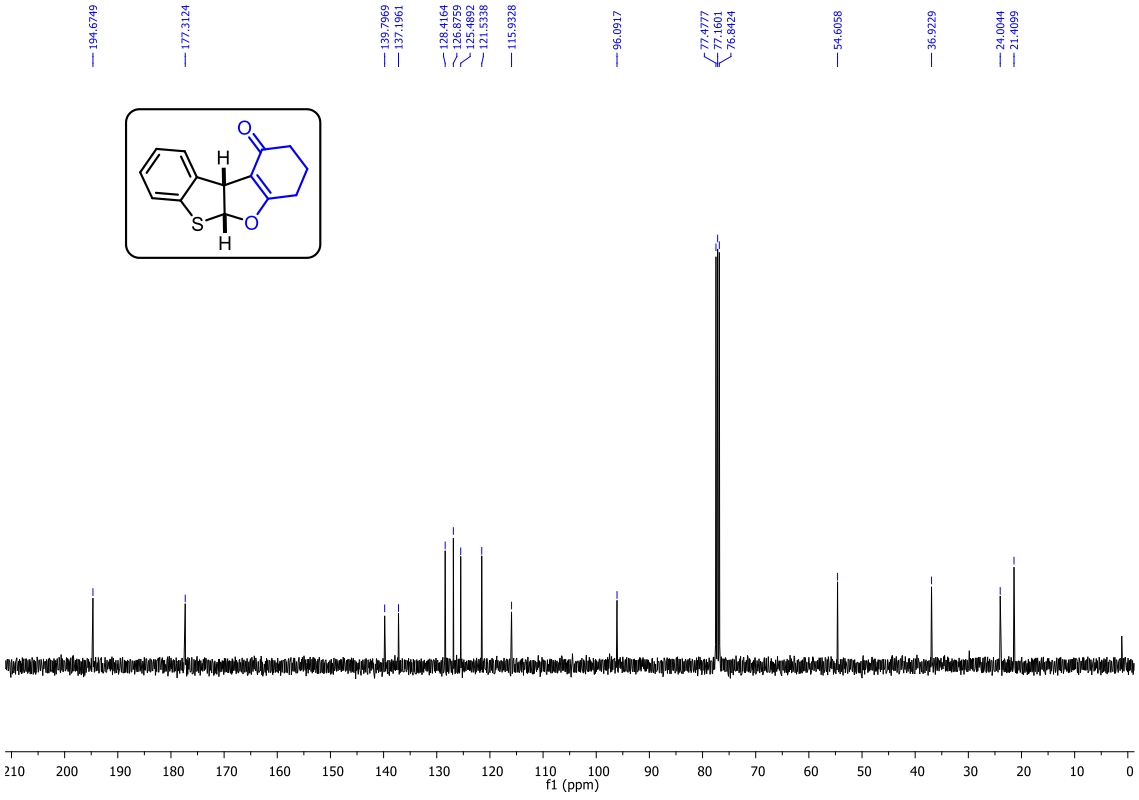
^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) Spectrum of **52a**



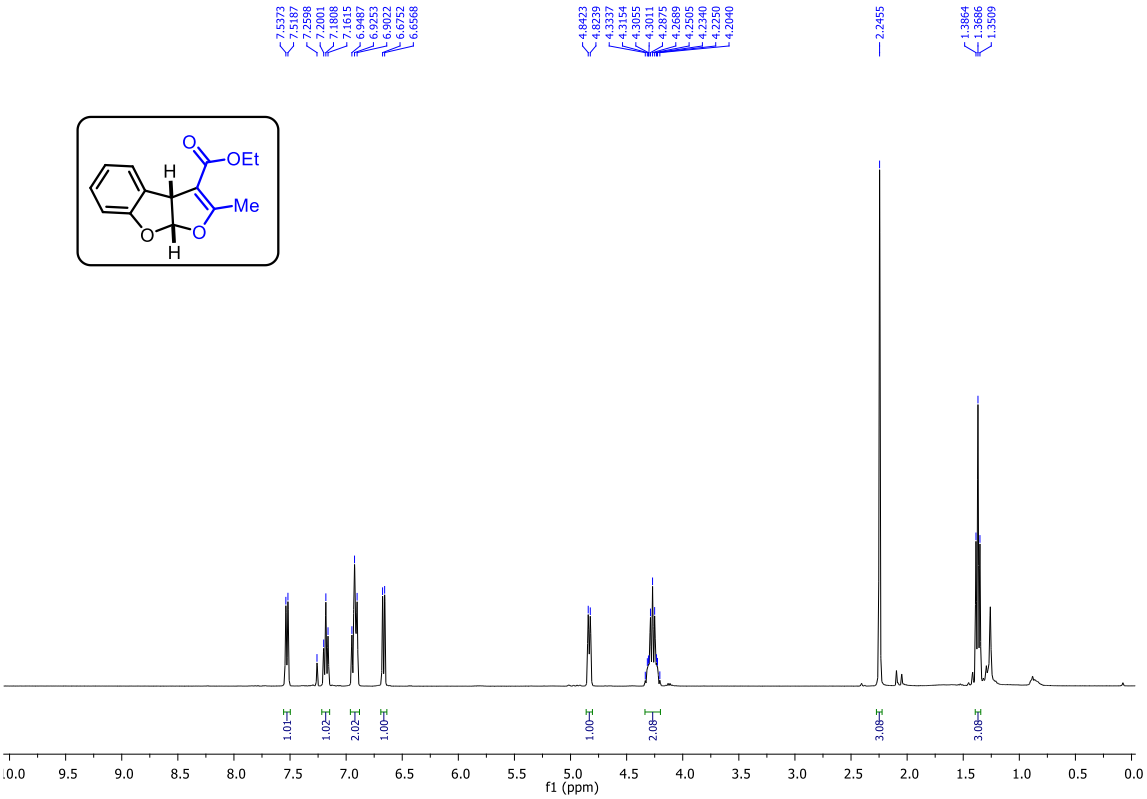
^{1}H NMR (400 MHz, $CDCl_3$) Spectrum of **52j**



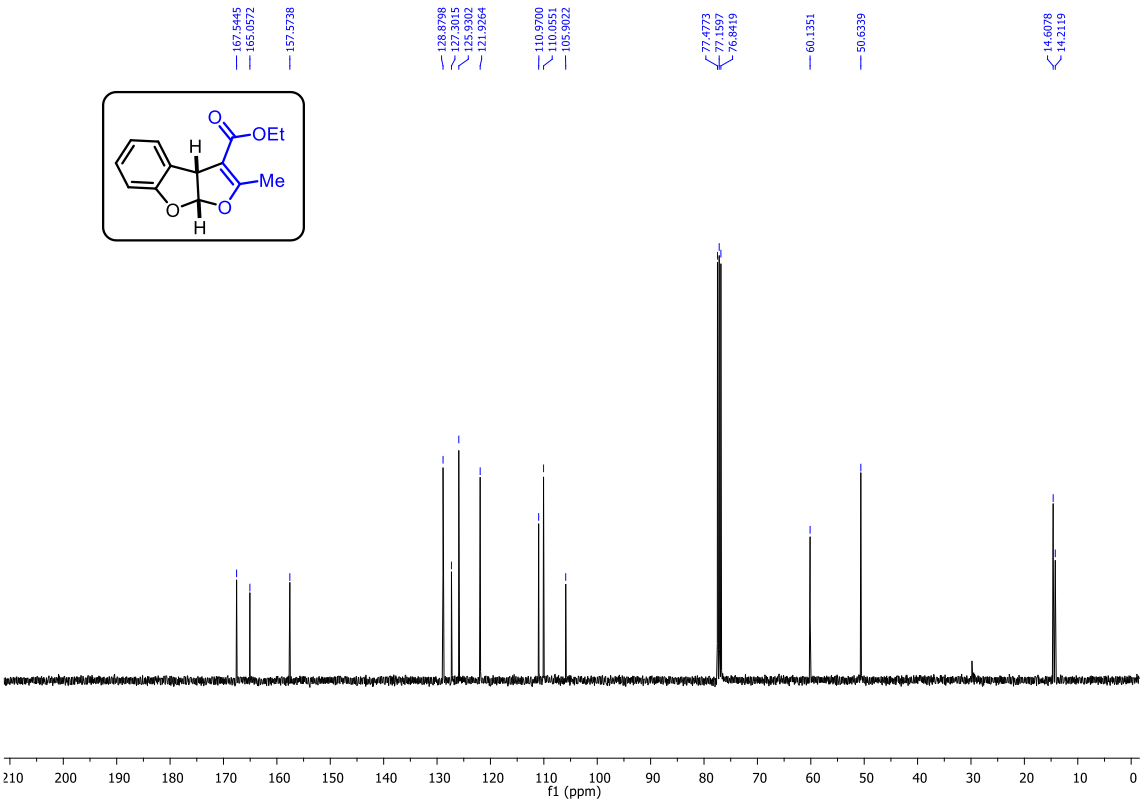
^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) Spectrum of **52j**



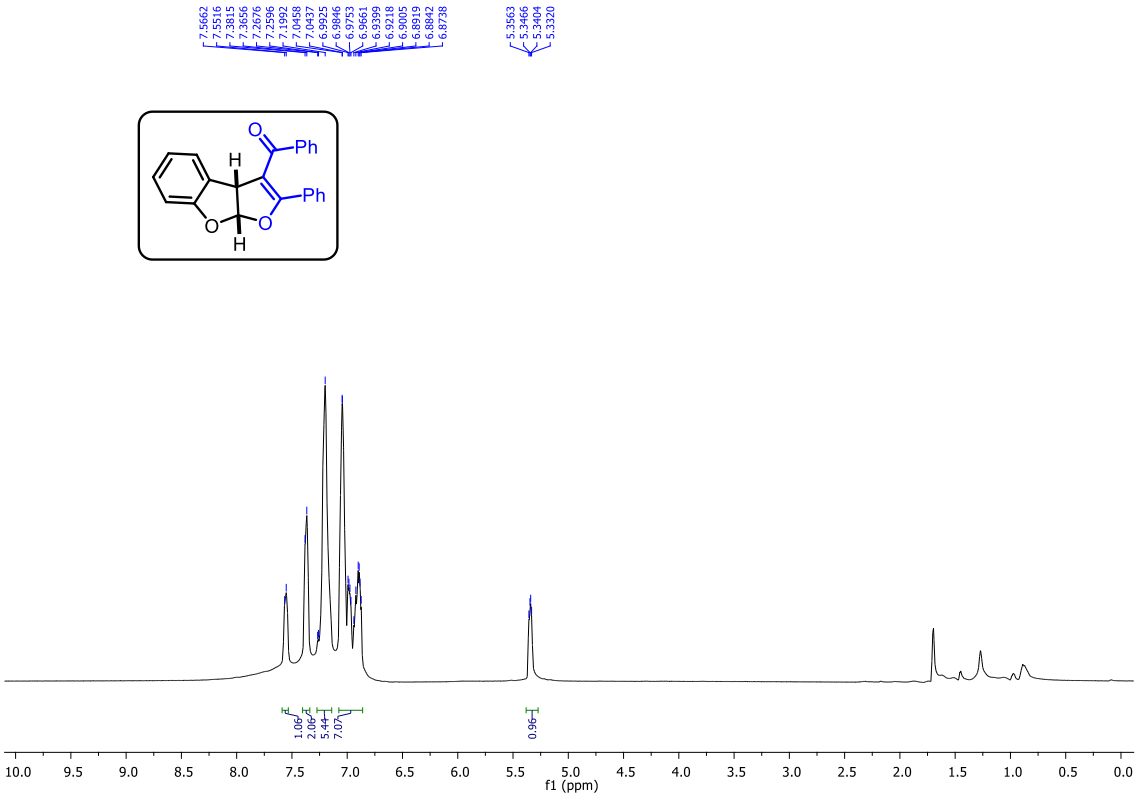
^{1}H NMR (400 MHz, $CDCl_3$) Spectrum of **54a**



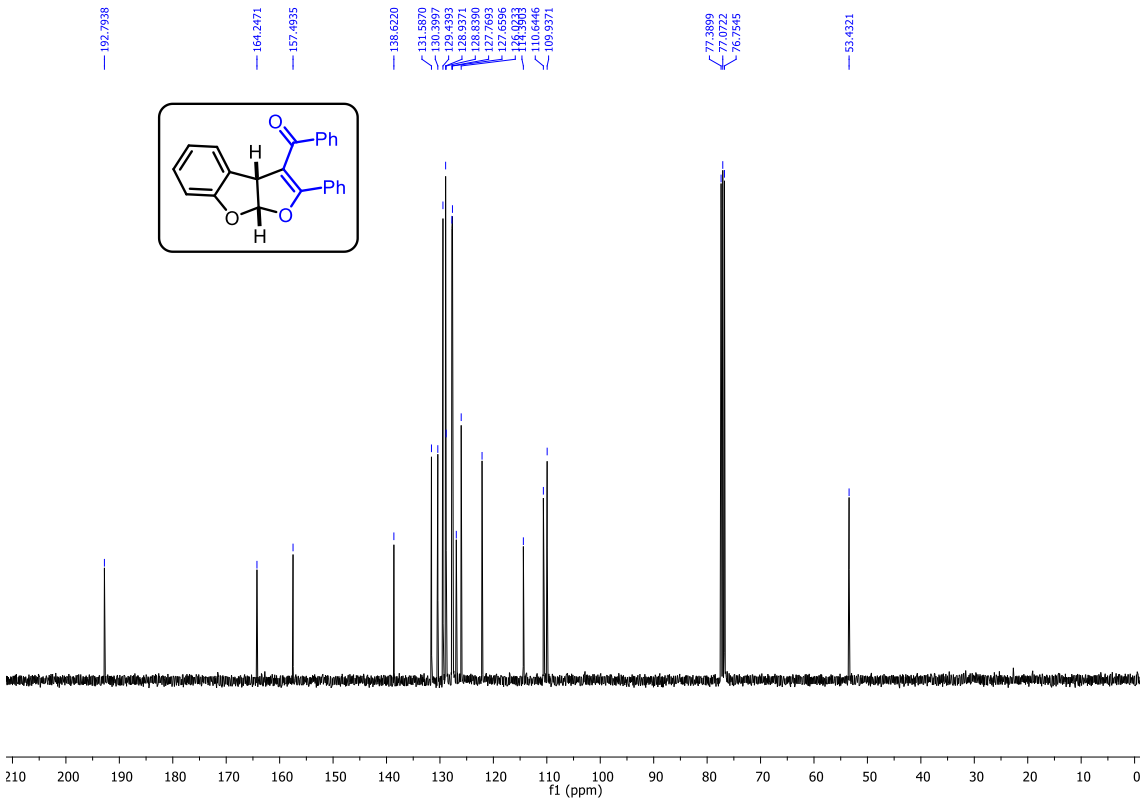
^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) Spectrum of **54a**



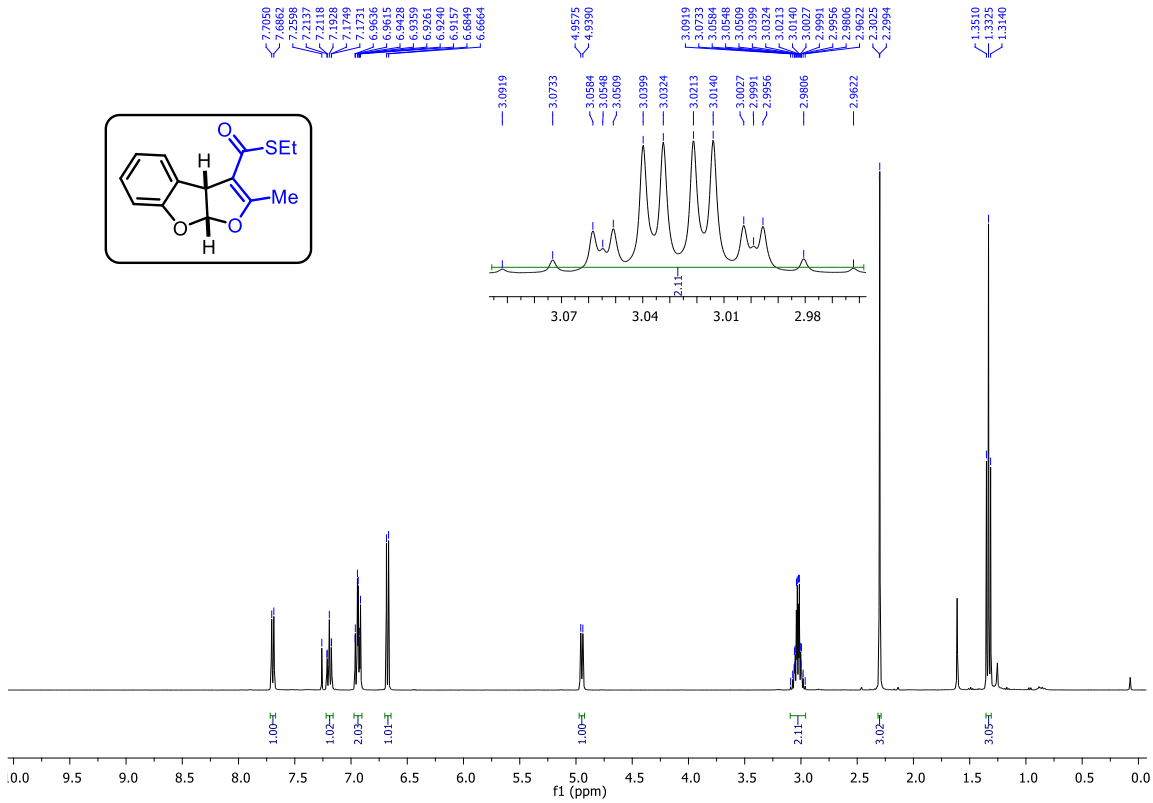
^{1}H NMR (400 MHz, $CDCl_3$) Spectrum of **54k**



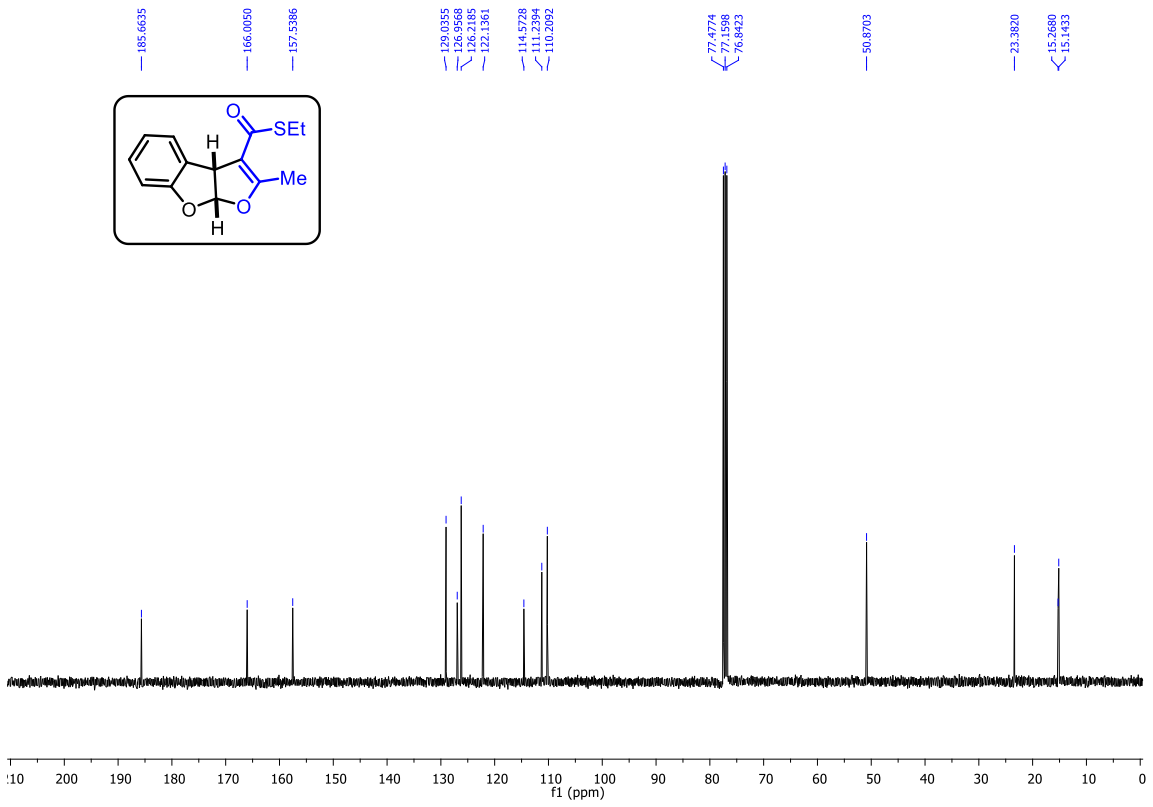
^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) Spectrum of **54k**



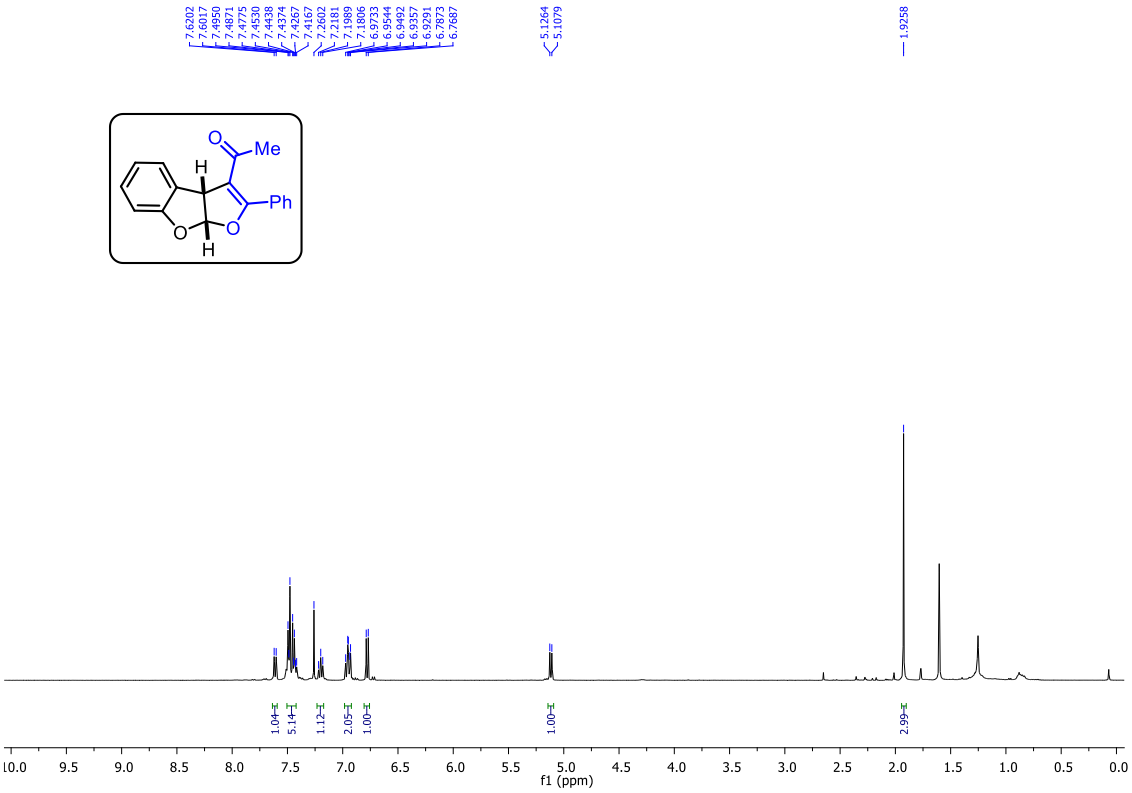
^{1}H NMR (400 MHz, $CDCl_3$) Spectrum of **54s**



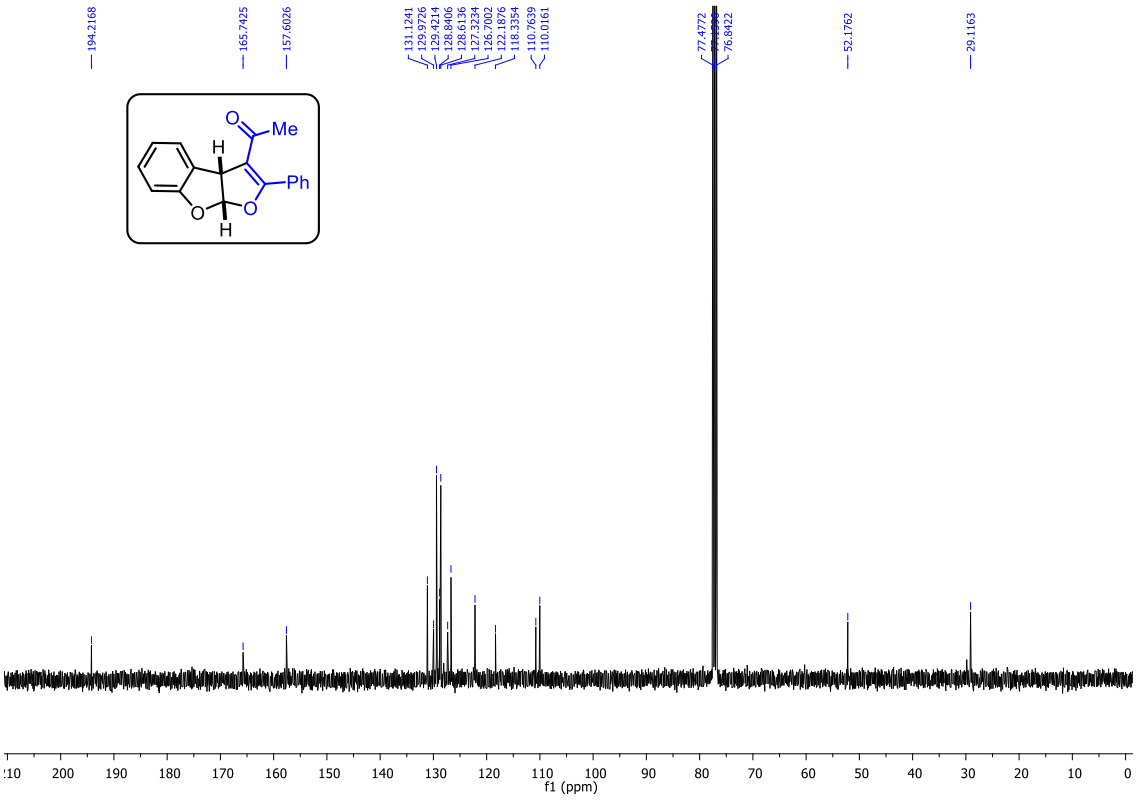
^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) Spectrum of **54s**



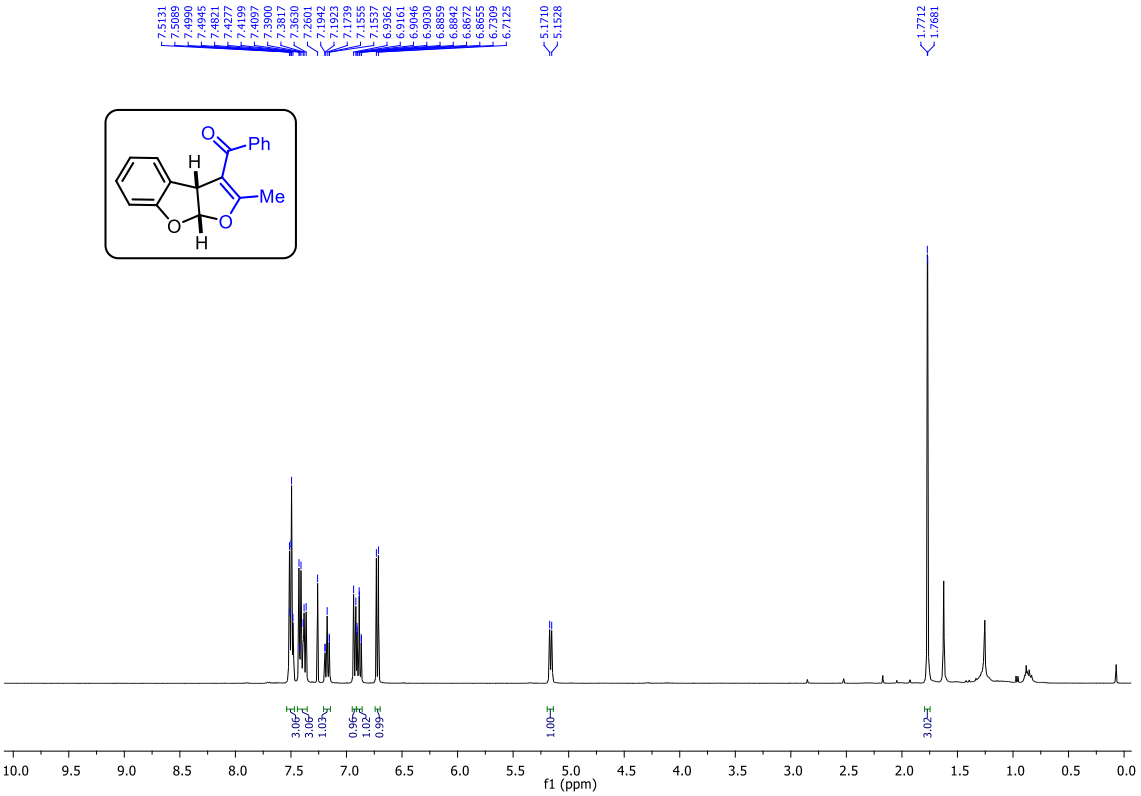
^{1}H NMR (400 MHz, $CDCl_3$) Spectrum of **54t**



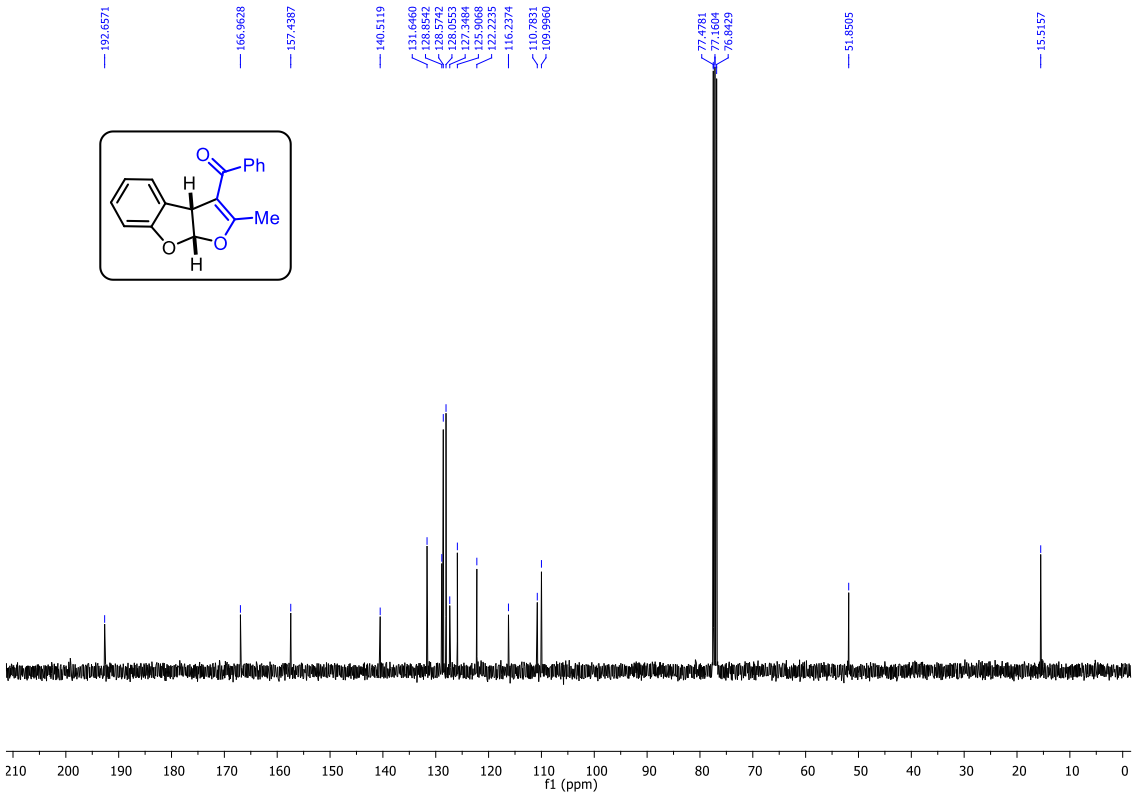
^{13}C NMR (100 MHz, $CDCl_3$) Spectrum of **54t**



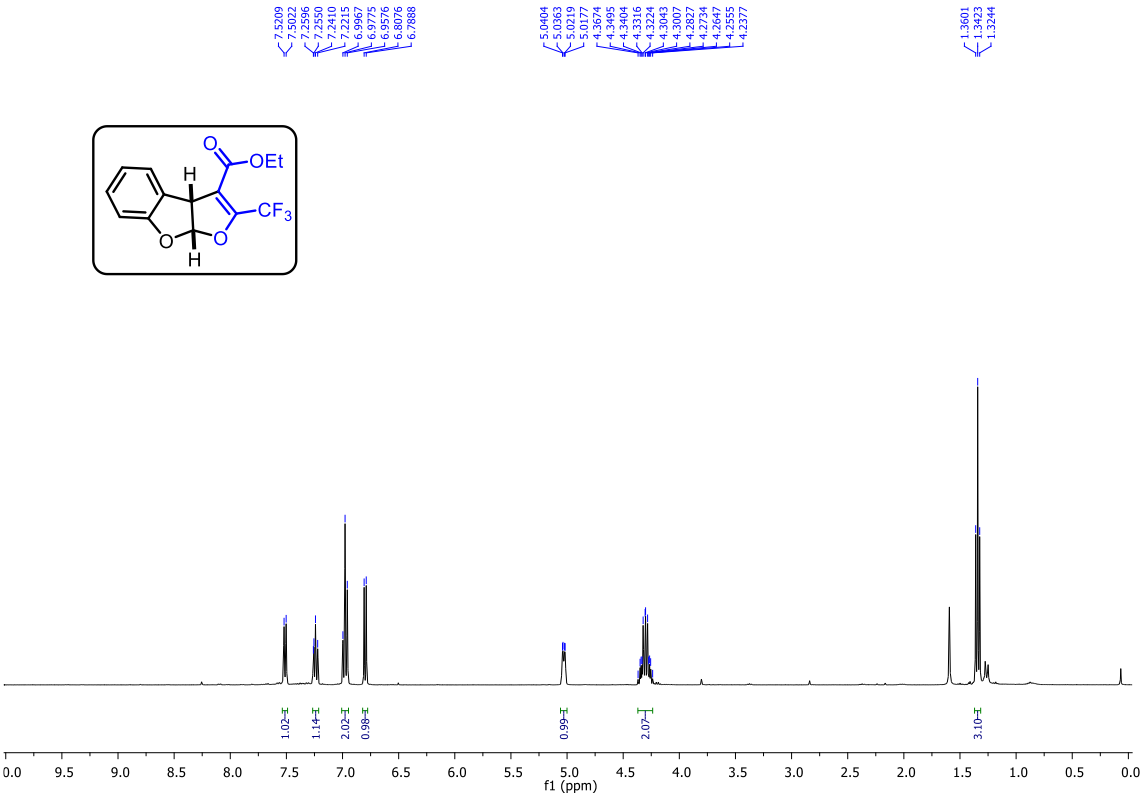
^{1}H NMR (400 MHz, $CDCl_3$) Spectrum of **54u**



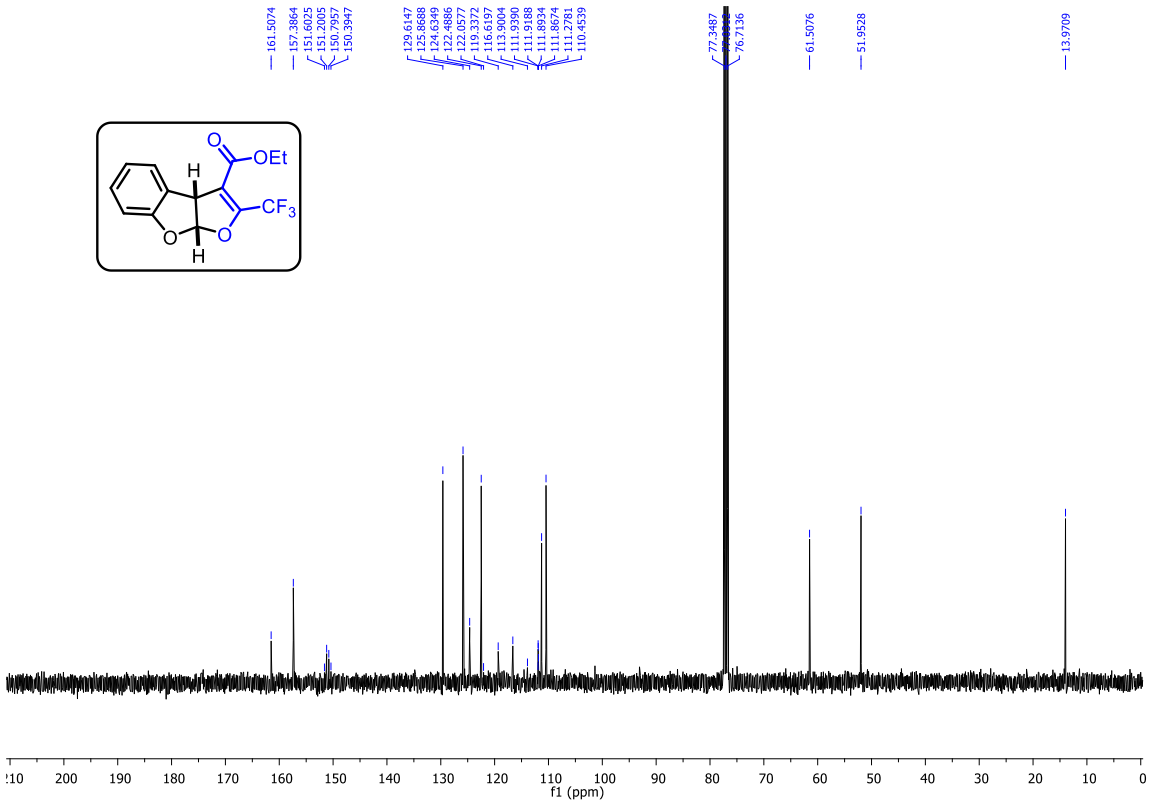
^{13}C NMR (100 MHz, $CDCl_3$) Spectrum of **54u**



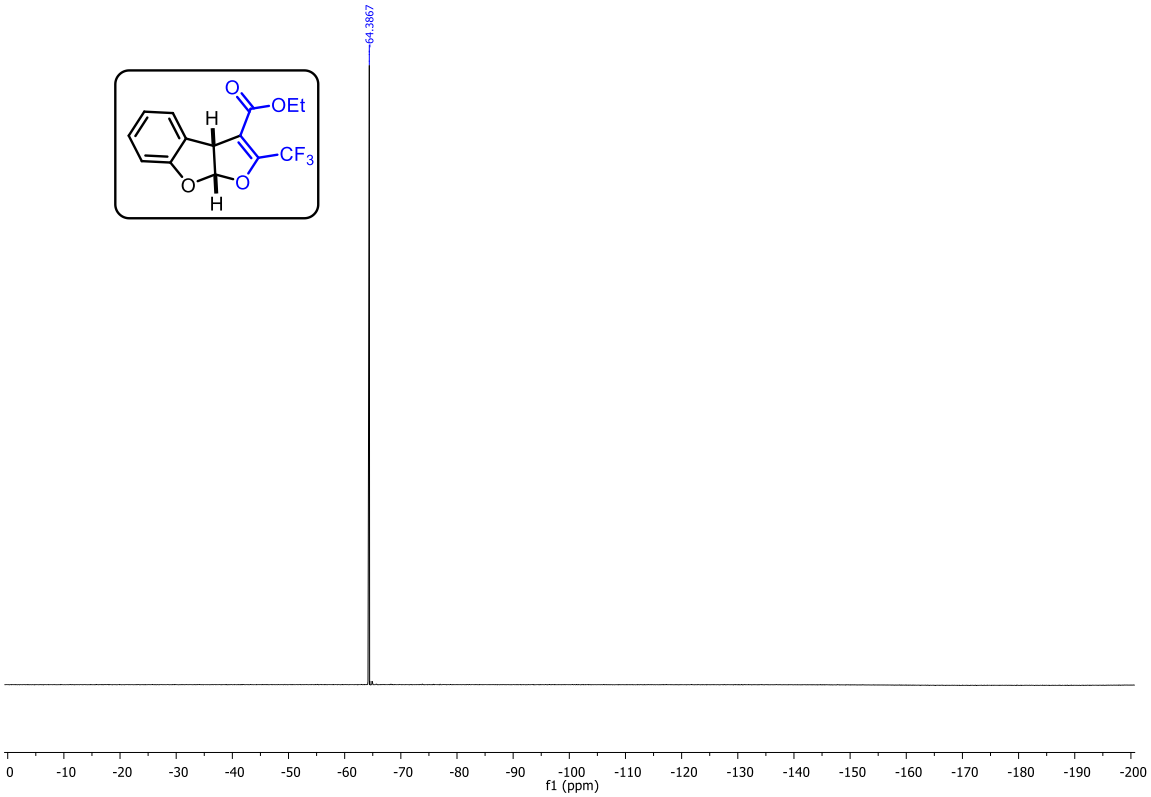
^{1}H NMR (400 MHz, $CDCl_3$) Spectrum of **55a**



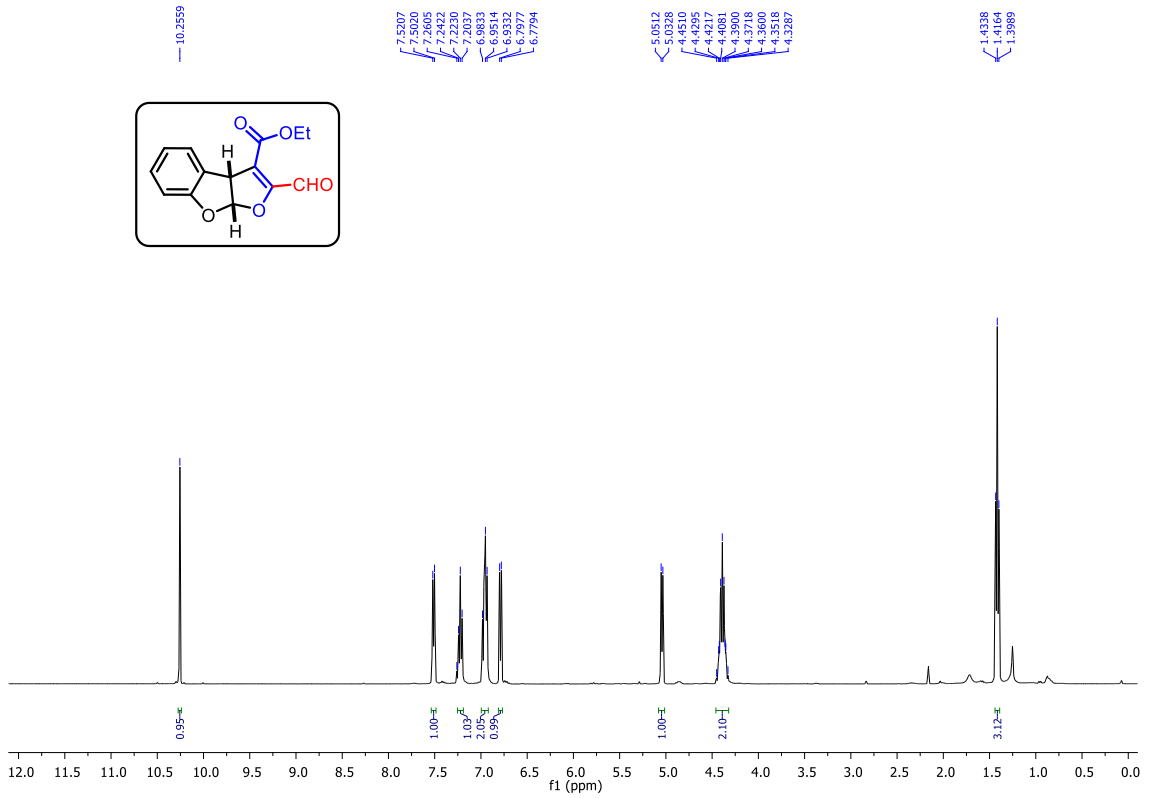
^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) Spectrum of **55a**



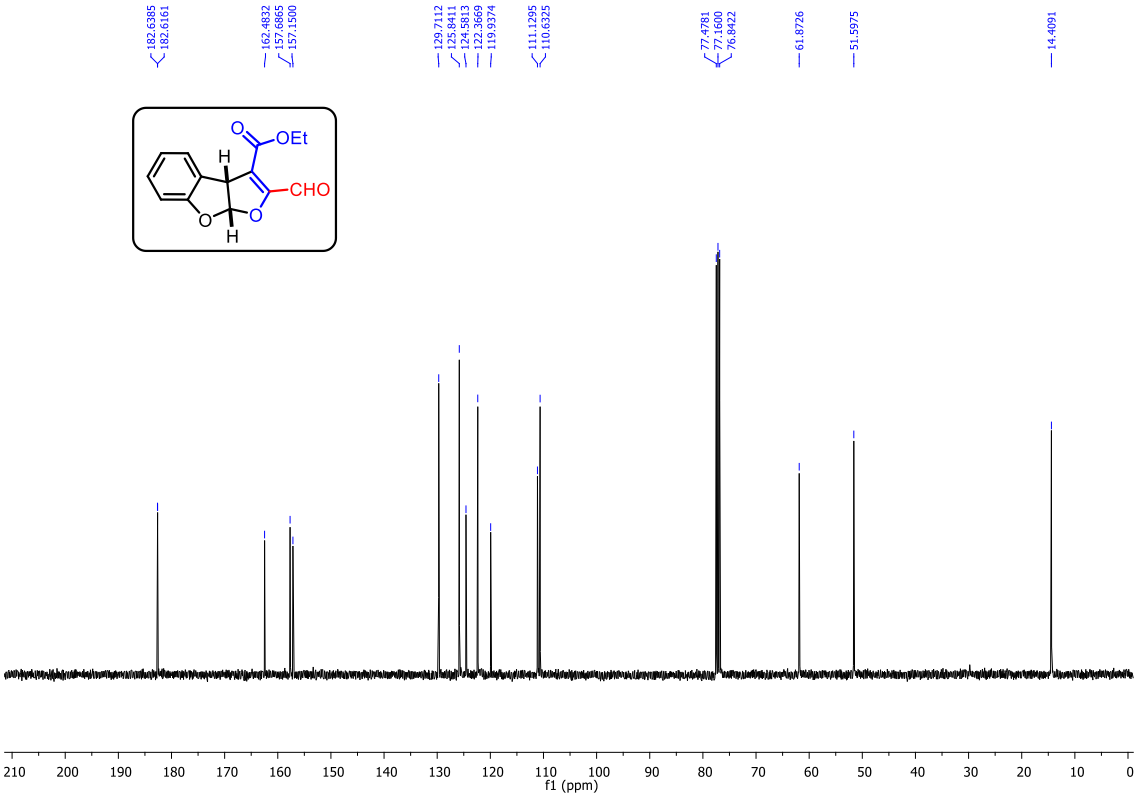
^{19}F {^{1}H} NMR (376 MHz, $CDCl_3$) Spectrum of **55a**



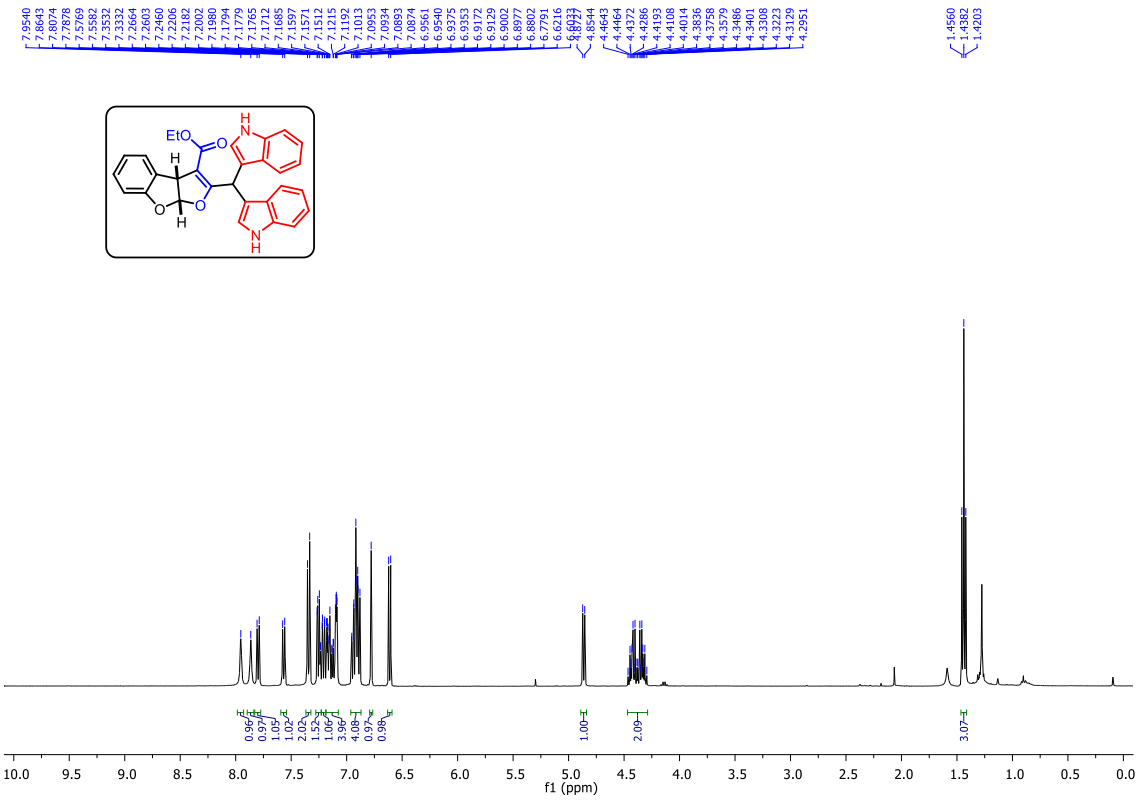
^{1}H NMR (400 MHz, $CDCl_3$) Spectrum of **56**



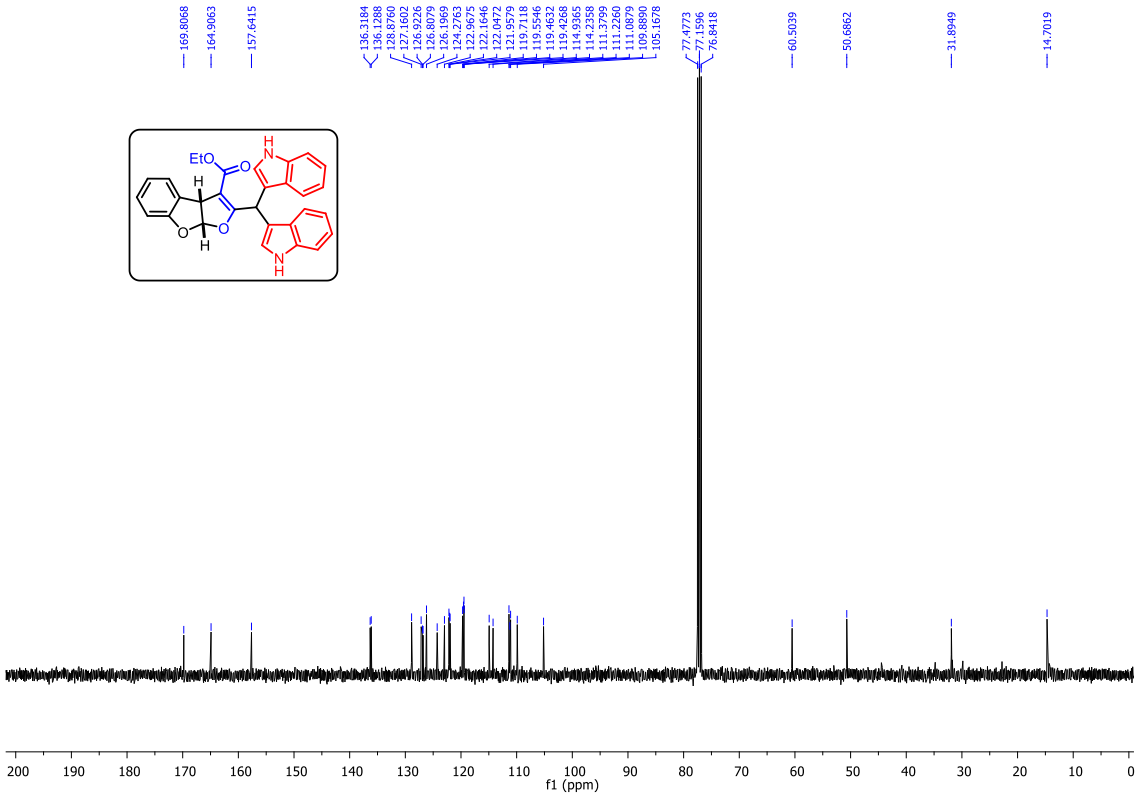
^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) Spectrum of **56**



^{1}H NMR (400 MHz, $CDCl_3$) Spectrum of **57**



^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) Spectrum of **57**



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CURRICULUM VITAE

Mr. Gurdeep Singh

Department of Chemical Science, Indian Institute
of Science Education and Research Mohali

E-mail: *gurdep92@gmail.com*

Mob: *+91-9464170142*

Experimental Organic Chemistry Skill: First hand experience in setting up a synthetic organic chemistry lab and designing projects. Excellent knowledge in the synthesis of *N*-heterocyclic carbene (NHC) and Bis-(amino)cyclopropenylidene (BAC) precursors and their applications in organocatalysis. Good knowledge of organic and organometallic chemistry, performing reactions in a continuous-flow microreactor, microwave reactor, and Schlenk line. Excellent practical skills in handling air/moisture sensitive reagents/reactions and gram/milligram scale reactions. Good knowledge of multi-step synthesis. Experience in modern chromatographic and spectroscopic (IR, UV, NMR, and HRMS) techniques. Proficiency in handling HPLC and Biotage-Isolera One flash column chromatography.

Research Expertise: Synthetic Organic Chemistry, Organocatalysis.

Education and Research Training

- **2017 –: Ph. D. in Synthetic Organic Chemistry**, Department of Chemical Sciences, Indian Institute of Science Education and Research (IISER) Mohali, 140306,Punjab, India.
  - **Thesis Title:** *"Metal-free Transformations of para-Quinone Methides (p-QMs) to Oxygen-containing Heterocycles and Carbazoles"*
  - **Ph.D. Thesis Supervisor:** Prof. R. Vijaya Anand
- **2014 – 2017: MS in Chemistry**, Department of Chemical Sciences, Indian Institute of Science Education and Research (IISER) Mohali, 140306, Punjab, India, with CPI **8.3**.
  - **M.S. Thesis Title:** "Bis-(dialkylamino)-cyclopropenylidene (BAC) Catalyzed Conjugate Addition of Nucleophiles to *para*-Quinone Methides and Chalcones"
  - **M.S. Thesis Supervisor:** Prof. R. Vijaya Anand

- **2011 – 2014: Bachelor of Science,** Post Graduate Govt. College Sector 11, Chandigarh (Affiliated with Panjab University Chandigarh), with **First Class (80.10%)**.
    - *College Topper*

Awards/Scloarships and Grants

- Received the **Best Poster Award** from the organizers of the *" International Symposium on Recent Advances in Self-assembled Materials a Supramolecular Chemistry"* held at Guru Nanak Dev University (GNDU) Amritsar held on 19th March 2022.
- Awarded **Senior Research Fellowship** and **Junior Research Fellowship** (MHRD Fellowship) from the Indian Institute of Science Education and Research (IISER) Mohali from August 2017 to July 2022.
- Awarded **Fellowship** (MHRD Fellowship) from the Indian Institute of Science Education and Research (IISER) Mohali from August 2014 to May 2017.
- Awarded **INSPIRE Fellowship** from the Department of Science and Technology (DST), Government of India, from 2011 to 2014.
- Qualified **CSIR-JRF** with all India 82nd rank in **CSIR-UGC NET** (Council of Scientific and Industrial Research-University Grants Commission National Eligibility Test) examination held on December 2016.
- Qualified **CSIR-NET** with all India 34th rank in **CSIR-UGC NET** (Council of Scientific and Industrial Research-University Grants Commission National Eligibility Test) examination held on December 2015.
  Qualified Graduate Aptitude Test in Engineering (GATE) held in February 2017.

List of Publications

1) *"Reactions of Enaminones with p-Quinone Methides: Access to Chromenone and Chromene Derivatives"* **Singh, G.**;# Sharma, S.;# Rekha, Pandey, R.; Singh, R.; Kumar, T.; Anand, R. V. *Eur. J. Org. Chem,* **2022**, *doi. org/10.1002/ejoc.202200792*
# contributed equally.

2) *"A Base-Mediated Approach Towards Dihydrofuro[2,3-b]Benzofurans from 2-*

Nitrobenzofurans and 1,3-Dicarbonyls" **Singh, G.**; Pandey, R.; Kurup, A. S.; Anand, R. V. *Chem. Asian J.* **2021**, *16*, 127.

3) *"Base Mediated One-pot Synthesis of Oxygen Based Heterocycles from 2-Hydroxyphenyl-substituted para-Quinone Methides"* **Singh, G.**; Kumar, S.; Chowdhury, A; Anand, R. V. *J. Org. Chem.* **2019**, *84*, 15978.

4) *"A One-pot Approach to 2,3-Diarylbenzo[b]furans Through N-Heterocyclic Carbene Catalyzed 1,6-Conjugate Addition Followed by Acid Mediated Dehydrative Cyclization"* **Singh, G.**; Goswami, P.; Sharma, S.; Anand, R. V. *J. Org. Chem.* **2018**, *83*, 10546.

5) *"Exploring bis-(amino)cyclopropenylidene as a Non-covalent Bronsted base Catalyst in Conjugate Addition Reactions"* **Singh, G.**; Goswami, P.; Anand, R. V. *Org. Biomol. Chem.* **2018**, *16*, 384.

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

7) *"Recent Advances in the Organocatalytic Applications of Cyclopropene- and Cyclopropenium-based Small Molecules"* **Singh, G.**;[#] Ranga, P. K.;[#] Ahmad, F.;[#] Tyagi, A.;[#] Anand, R. V. *Org. Biomol. Chem.* **2021**, *19*, 9541. [#]contributed equally

8) *"A Formal [3+3] Annulation Approach to Tetrahydroindolo[2,3-b]carbazoles from p-Quinone Methides and 2-indolylmethanol"* **Singh, G.**;[#] Sharma, S.;[#] Pandey, Anand R. V. [#]contributed equally (Manuscript submitted).

9) *"Organocatalytic O-acylation of phenols/alcohols and N-acylation of Indoles with Cyclopropenones"* **Singh, G.**; [#] Goswami, P.; [#] Kumar, S.; Anand, R. V. [#]contributed equally (Manuscript under preparation).

10) *"Tropylium Salt-promoted Vinylogous Aza-Michael Addition of Carbamates to para-Quinone Methides: Elaboration to Diastereomerically Pure α,α'-Diarylmethyl Carbamates"* Rekha, Sharma, S.; **Singh, G**, Anand, R. V. *ACS Org. Inorg. Au* **2022**, *2*, 186.

11) *"Base-mediated Sequential One-pot Approach for the Synthesis of 2,3-*

Disubstituted Indoles from 2-(Tosylamino)aryl-substituted para-Quinone Methides" Pandey, R.; **Singh, G.**; Gour, V.; Anand, R. V. *Tetrahedron* **2021**, *82*, 131950.

12) *"Bis(amino)cyclopropenylidene Catalyzed Rauhut-Currier Reaction between α,β-unsaturated Carbonyl Compounds and para-Quinone Methides"* Goswami, P.; Sharma, S.; **Singh, G.**; Anand, R. V. *J. Org. Chem.* **2018**, *83*, 4213.

13) *"N-Heterocyclic Carbene Catalyzed 1,6-conjugate Addition of Me_3Si-CN to para-Quinone Methides and Fuchsones: Access to α-arylated Nitriles"* Goswami, P.; **Singh, G.**; Anand, R. V. *Org. Lett.* **2017**, *19*, 1982.

Conferences/Symposia

- Presented a poster on "Bis-(amino)cyclopropenylidene catalyzed diversity-oriented synthesis of diaryl- and triarylmethanes"**Singh G.**; 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).
- Participated in the 24th *National Conference on Liquid Crystals* held at the Department of Chemical Sciences, Indian Institute of Science Education and Research (IISER) Mohali, S. A. S. Nagar, India (11-13th October, 2017).
- Presented a poster on "A one-pot approach to 2,3-diarylbenzo[*b*]furans through *N*-heterocyclic carbene catalyzed 1,6-conjugate addition followed by acid-mediated dehydrative cyclization" **Singh G.**; 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).
- Presented a poster on "A one-pot approach to 2,3-diarylbenzo[*b*]furans through *N*-heterocyclic carbene catalyzed 1,6-conjugate addition followed by acid-mediated dehydrative cyclization" **Singh G.**; Anand, R. V. in the *Symposium On Recent Advances In Bioorganic and Medicinal Chemistry* held at NIPER, S.A.S. Nagar, India on 30th August 2019.

- Delivered a talk entitled "A one-pot approach for the synthesis of oxygen-containing heterocycles" **Singh G.**; Anand, R. V. in the *15th Junior National Organic Symposium (J-NOST)* held at Department of Chemistry, University of Delhi, India (18-21st October, 2019).
- Participated in the *1st Crikc Chemistry Symposium* (CCS 2019) held at the Department of Chemical Sciences, Indian Institute of Science Education and Research (IISER) Mohali, S. A. S. Nagar, India (2nd & 3rd November, 2019).
- Presented a poster on "A one-pot approach for the synthesis of oxygen-containing heterocycles" **Singh G.**; Anand, R. V. in the *Symposium On Recent Advances In Self-Assembled Materials and Supramolecular Chemistry* held at Department of Chemistry, Guru Nanak Dev University, Amritsar, India on 19th March 2022.