# Metal-free Approaches Toward *N*-Heterocycles and Diarylmethanes under Batch as well as Continuous-flow Conditions

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*A thesis submitted for the partial fulfillment of*

*the degree of Doctor of Philosophy*

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*Dedicated to my family*

*for their love and affection*

# Declaration

The work presented in this thesis titled "*Metal-free Approaches Toward N-Heterocycles and Diarylmethanes under Batch as well as Continuous-flow Conditions*" 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.

**Rajat Pandey**

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

**Prof. R. Vijaya Anand**

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# Abstract

This thesis work is divided into two parts Part A & Part B. Part A includes the synthesis of nitrogen-containing heterocycles from 2-(tosylamino)aryl-substituted *p*-QMs and *ortho*-aminobenzyl alcohols under batch process and, Part B involves the synthesis of diarylmethanes under continuous-flow conditions using microreaction technology.

**Part A: Synthesis of Nitrogen-containing Heterocycles from 2-(Tosylamino)aryl-substituted *para*-Quinone Methides & *ortho*-Aminobenzyl alcohols**

Part A is sub-divided into two chapters.

***Chapter 1:* A One-pot Approach to the Synthesis of 2,3-Disubstituted Indoles from 2-(Tosylamino)aryl-substituted *para*-Quinone Methides**

This chapter discusses the reactivity profile of *p*-QMs and 2-(tosylamino)aryl-substituted *para*-quinone methides, and their application in the synthesis of nitrogen-containing heterocycles. 2,3-Disubstituted indoles are important heterocyclic scaffolds and, are often found as an integral part of many natural and unnatural molecules that possess remarkable therapeutic properties (Figure 1). While exploring the synthesis of heterocyclic compounds, we envisioned that it could be possible to synthesize 2,3-disubstituted indole derivatives from 2-(tosylamino)aryl-substituted *p*-QMs. A combination of inorganic and organic base is found to be effective for the desired transformation. This is a multi-step transformation and proceeds through inorganic base mediated *N*-alkylation of 2-(tosylamino)aryl-substituted *p*-QM with bromomethyl aryl ketone followed by 1,6 intramolecular cyclization and eliminative isomerization/aromatization to provide a variety of 2,3-substituted indoles in moderate to good yields (Scheme 1).

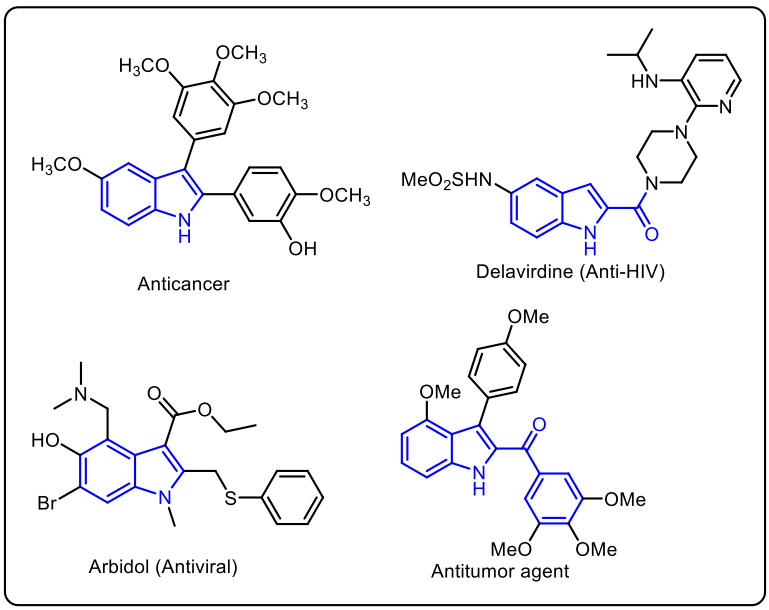
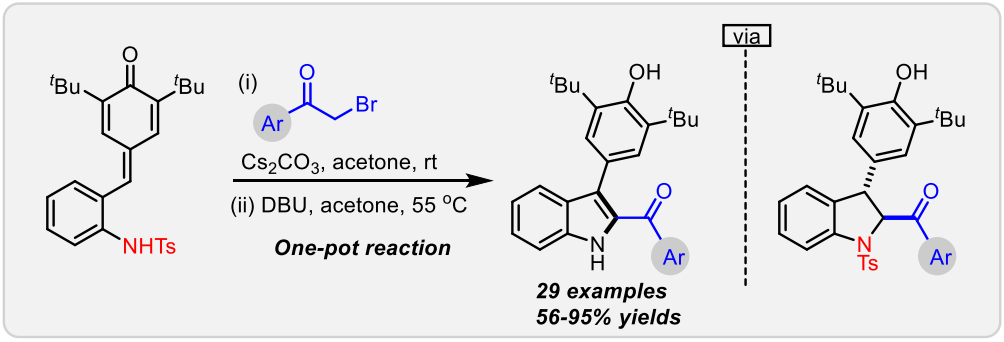



**Figure 1.** Indole-based biologically active compounds.




**Scheme 1.** Synthesis of 2,3-disubstituted indoles from *p*-QMs and 2-bromoacetophenone

***Chapter 2:*** **Brønsted Acid Mediated Approach Towards Tetrahydroacridinone and Diydroquinoline Derivatives from *in-situ* Generated Aza-*o*-Quinone Methides.**

This chapter describes the synthesis of acridine and quinoline derivatives from *ortho*-aminobenzyl alcohols with different nucleophiles under acidic conditions. Tetrahydroacridinone & dihydroquinoline derivatives are an interesting and important class of nitrogen-containing heterocycles and, are present in various active pharmaceutical ingredients (APIs) and bioactive moieties. Apart from therapeutic properties, quinoline derivatives are also being used as pigment and dyes. In addition, acridine derivatives and

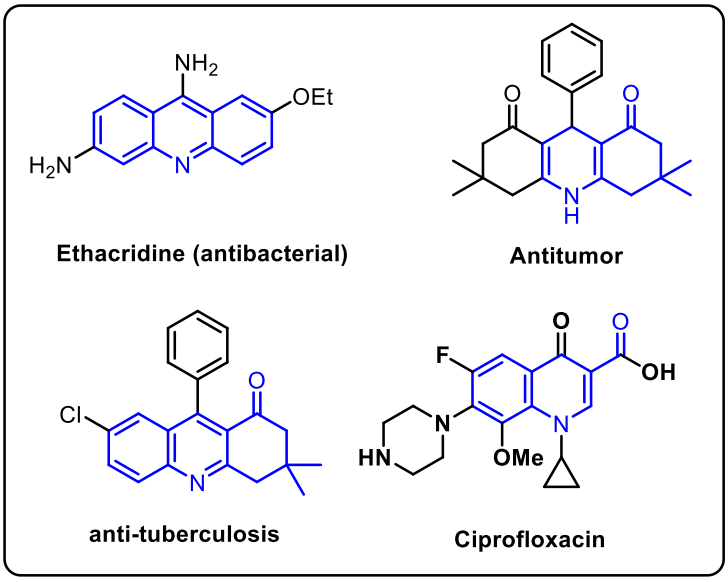



**Figure 2.** Nitrogen-containing biologically active compounds.

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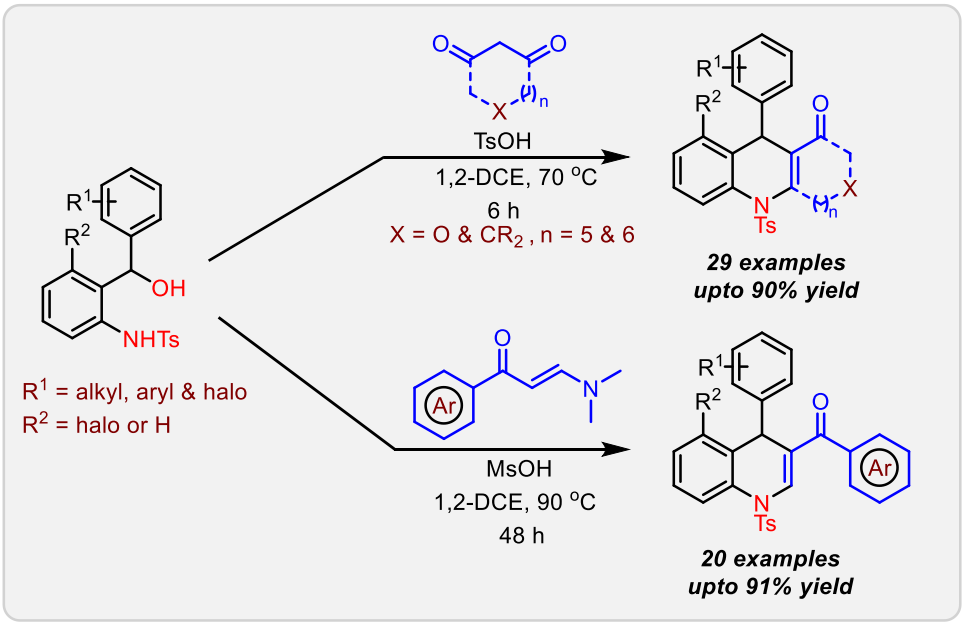


**Scheme 2.** Synthesis of tetrahydroacridinone and diydroquinoline derivatives.

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their salts are used as an organo-photocatalyst in various transformations. So, while exploring the synthesis of nitrogen-containing heterocyclic compounds, we have developed a one-pot approach for the synthesis of tetrahydroacridinone and diydroquinoline derivatives by the reaction of *ortho*-aminobenzyl alcohol with cyclic 1,3-dicarbonyl compounds and enaminones, respectively. In both the transformations, the reaction proceeds through a

common intermediate, i.e., aza-*o*-quinone methide, which is generated during the reaction under acidic conditions. In the case of tetrahydroacridinone formation, the reaction proceeds through a Michael addition of 1,3-dicarbonyls to aza-*o*-quinone methide followed by intramolecular cyclization-elimination sequence. The formation of dihydroquinoline proceeds through a formal [4+2]-annulation of enaminones with aza-*o*-quinone methide followed by acid-mediated elimination.

**Part B: Synthesis of Diarylmethanes from *p*-Quinone Methides under Continuous-flow Conditions**

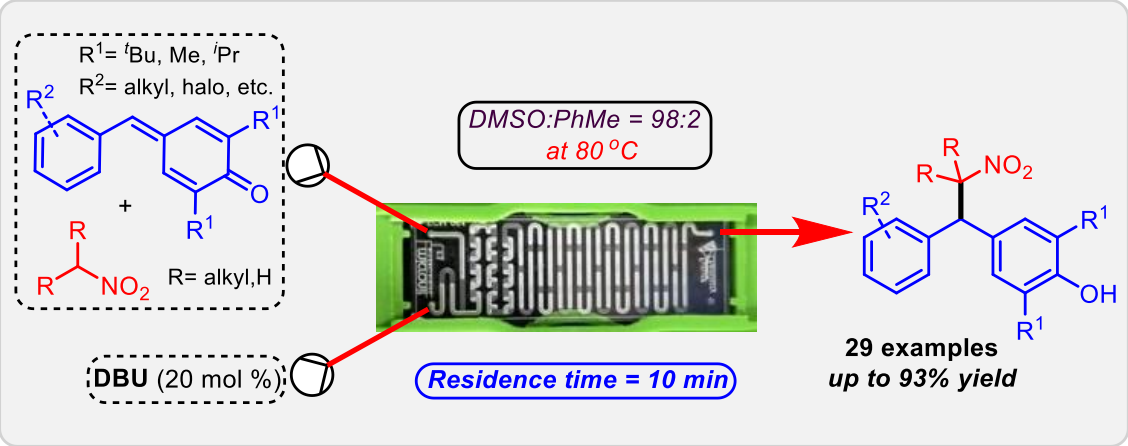
Part B is subdivided into two chapters.

***Chapter 1:*** **General Introduction to Continuous-flow Chemistry**

This chapter provides insights into microreaction technology and its application in organic synthesis, especially in method development, natural product synthesis and enantioselective transformations.

***Chapter 2:*** **Base Catalyzed 1,6-Conjugate Addition of Nitroalkanes to *p*-Quinone Methides under Continuous-flow**

This chapter describes a base catalyzed 1,6-conjugate addition of nitroalkanes to *p*-QMs under continuous-flow conditions. Although the 1,4-Micheal addition of nitroalkanes to various moieties are well explored, there are only a few reports available for the vinylogous 1,6-conjugate addition of nitroalkanes to dienone systems. We have developed an efficient base-catalyzed addition of nitroalkane to *p*-QMs to access a variety of nitro-containing diarlymethanes in moderate to good yields. Further, we have also demonstrated the advantage of a continuous-flow reactor over the batch process.




**Scheme 3.** Synthesis of nitro-containing diarylmethanes.

# Abbreviations

| | |
|---|---|
| ABZ | azidobenziodazolone |
| ACN | Acetonitrile |
| AcOH | Acetic acid |
| $Ac_2O$ | Acetic anhydride |
| Aq | Aqueous |
| $B_2(pin)_2$ | Bis(pinacolato)diboron |
| BIOAc | acetoxybenziodoxolone |
| brs | Broad singlet |
| Bn | Benzyl |
| 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 |
| $\delta$ | 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

# Part A: Synthesis of *N*-heterocycles from *p*-QMs & aza-*o*-QMs

## *Chapter 1*

## A One-pot Approach for the Synthesis of 2,3-Disubstituted Indoles from 2-(Tosylamino)aryl-substituted *para*-Quinone Methides

### 1.1 General introduction to *para*-quinone methides (*p*-QMs)

*para*-quinone methides (*p*-QMs), due to their unique reactivity profiles, have proved to be effective synthons for the synthesis of various organic molecules. They are involved as intermediates in the synthesis of natural products as well as in several chemical processes.[1] Structurally, *p*-QMs (**II**) are analogues of benzoquinone moiety (**I**), in which a methylene group is present instead of one of the carbonyl groups, which makes *p*-QMs more polarizable due to the presence of different functionality on the opposite side, thus they exist in their more stable canonical form **III** (Figure 1).[2]

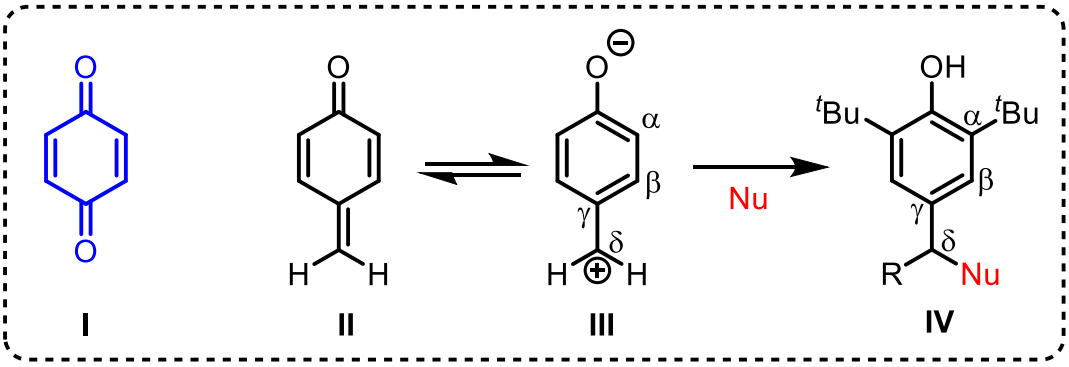
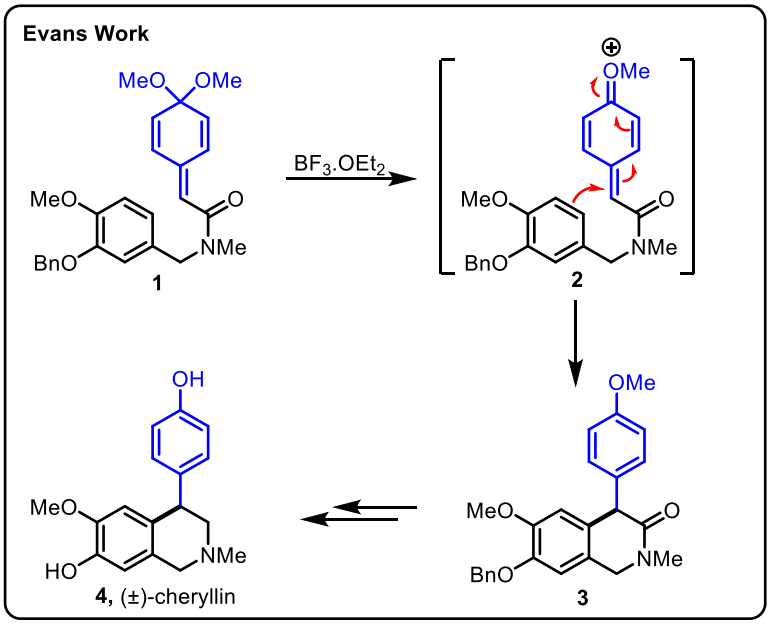



**Figure 1**. Canonical forms of *p*-QMs

Unsubstituted *p*-QMs are highly unstable intermediates; however introduction of bulky substituents at α and δ positions provide stability to *p*-QMs. This also allows the nucleophile to attack at the δ position in a regioselective manner by blocking α and β position, thus avoiding the competing reactions such as 1,2-addition and 1,4-conjugate addition.[3] Evan's group in 1978, for the first time, reported the total synthesis of (±)-cheryllin, a tetrahydroisoquinoline-based natural product through a Lewis acid catalyzed reaction of masked *p*-QMs (Scheme 1).[4] Later, various strategies have been demonstrated for the 1,6-conjugate addition of *p*-QMs with various nucleophiles.[5]

In the last few decades, to expose their wider synthetic applications, the core structure of *p*-QMs was modified by introducing another functionality such as alkyne, alkene, OH, NHTs, etc. at the *ortho* position of the aryl ring, which makes the *p*-QM a bifunctional synthon. Thus, one can access various heterocycles and carbocycles by treating these *p*-QMs with appropriate coupling partners (Figure 2). As a result, many synthetic protocols have been established, under this concept, for the synthesis of various nitrogen and oxygen-containing heterocycles.[6]




**Scheme 1**. Total synthesis of (±)-cheryllin by Evans group

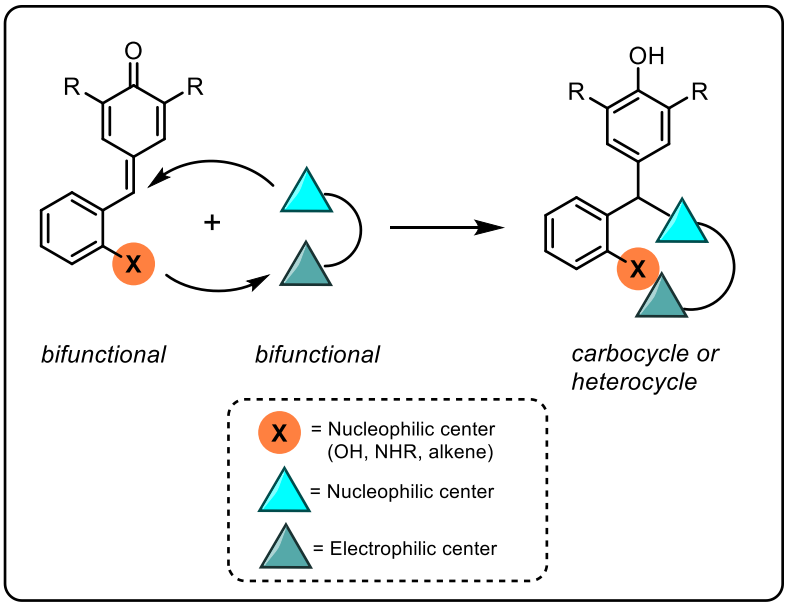
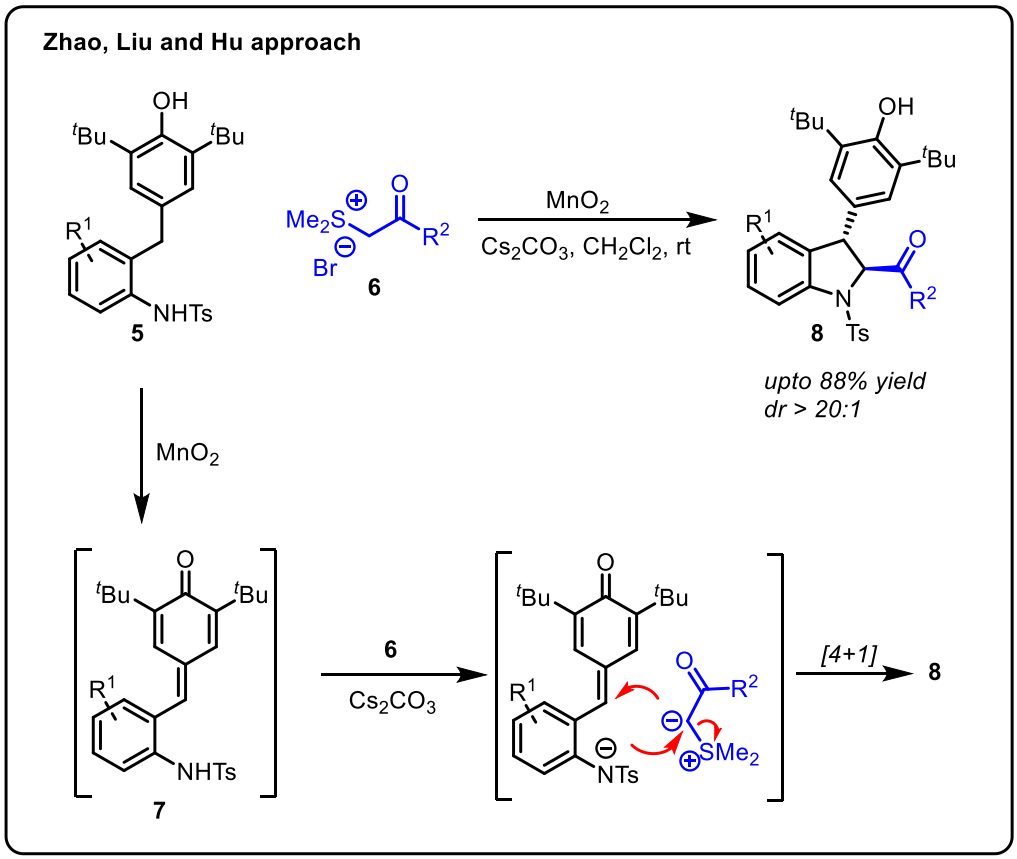



**Figure 2**. Reactivity profile of modified *p*-QMs

## 1.2 Literature reports on the synthesis of nitrogen-containing heterocycles from *p*-QMs

### 1.2.1 Synthesis of dihydroindoles, isoindolines and pyrazolines

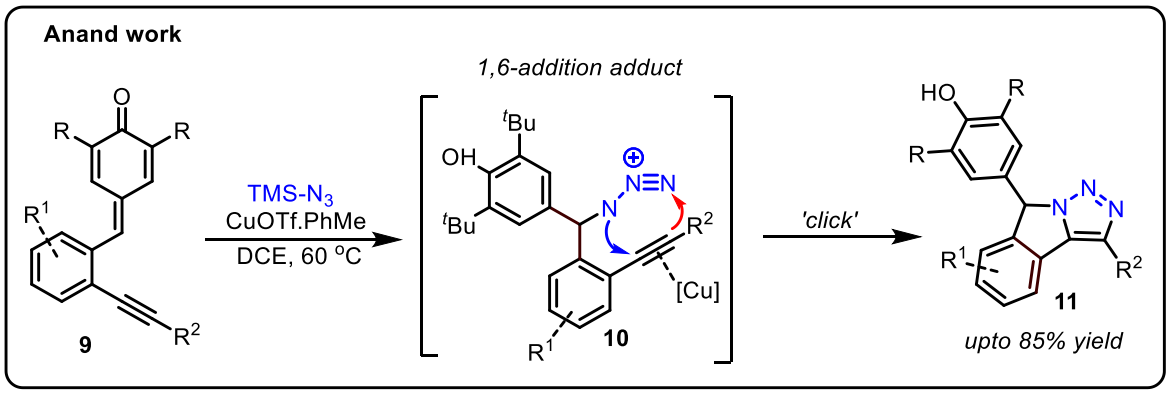
Zhao, Liu, and Hu reported the synthesis of substituted dihydroindole derivatives (**8**) through the reaction of *in-situ* generated 2-(tosylamino)aryl-substituted *p*-QMs (**7**) with sulfonium ylides (**6**). Initially, oxidation of **5** generates an intermediate **7**, which then undergoes [4+1] annulation reaction with sulfonium ylide **6** to give **8** in high diastereoselectivities (Scheme 2).[7a] Later in 2020, the same group reported the synthesis of indole derivatives through the reaction of phenacyl bromide with **7**, under basic conditions followed by DDQ meditative oxidation.[7b]




**Scheme 2**. Synthesis of dihydroindoles from sulfonium ylide

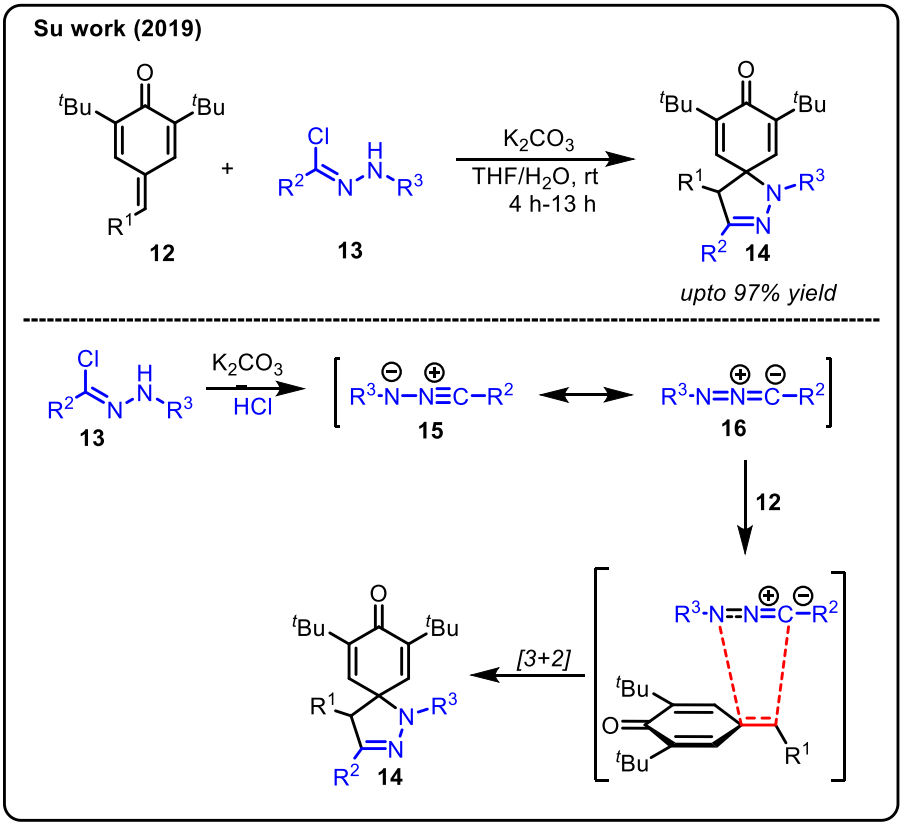
Anand and co-workers have established a one-pot approach for the synthesis of isoindoline derivatives from 2-(alkynyl)phenyl-substituted *p*-QMs (**9**) along with trimethylsilyl azide (Scheme 3). The reaction proceeds through the 1,6-conjugate addition of trimethylsilyl azide to **9** in the presence of a Cu-catalyst resulting in an intermediate **10**,

which then undergoes intramolecular click cyclization to afford triazole-fused isoindoline derivatives **11** in excellent yields.[8]




**Scheme 3**. Anand's approach for the synthesis of isoindoline derivatives

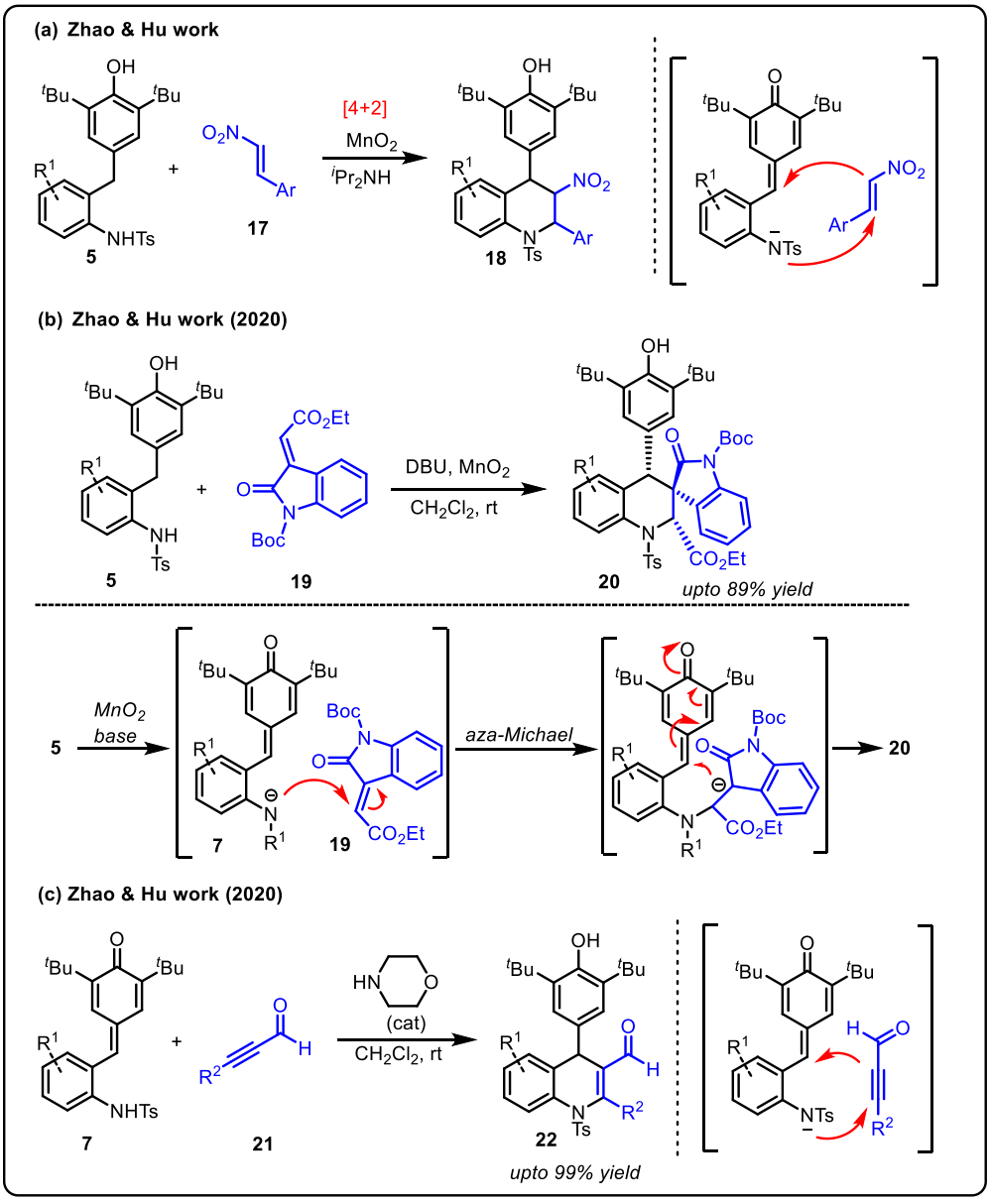
Recently, Su and co-workers reported the synthesis of pyrazoline-based spirocycles (**14**) from *p*-QM **12** and *in-situ* generated nitrile imines under metal-free conditions (Scheme 4). Hydrazonyl chloride **13** in the presence of potassium carbonate produces nitrile imine, which has two canonical forms, **15** & **16**, out of which, **16** undergoes a [3+2] cyclization to give **14** in moderate to good yields (as shown in Scheme 4).[9]




**Scheme 4**. Synthesis of pyrazoline from *p*-QMs

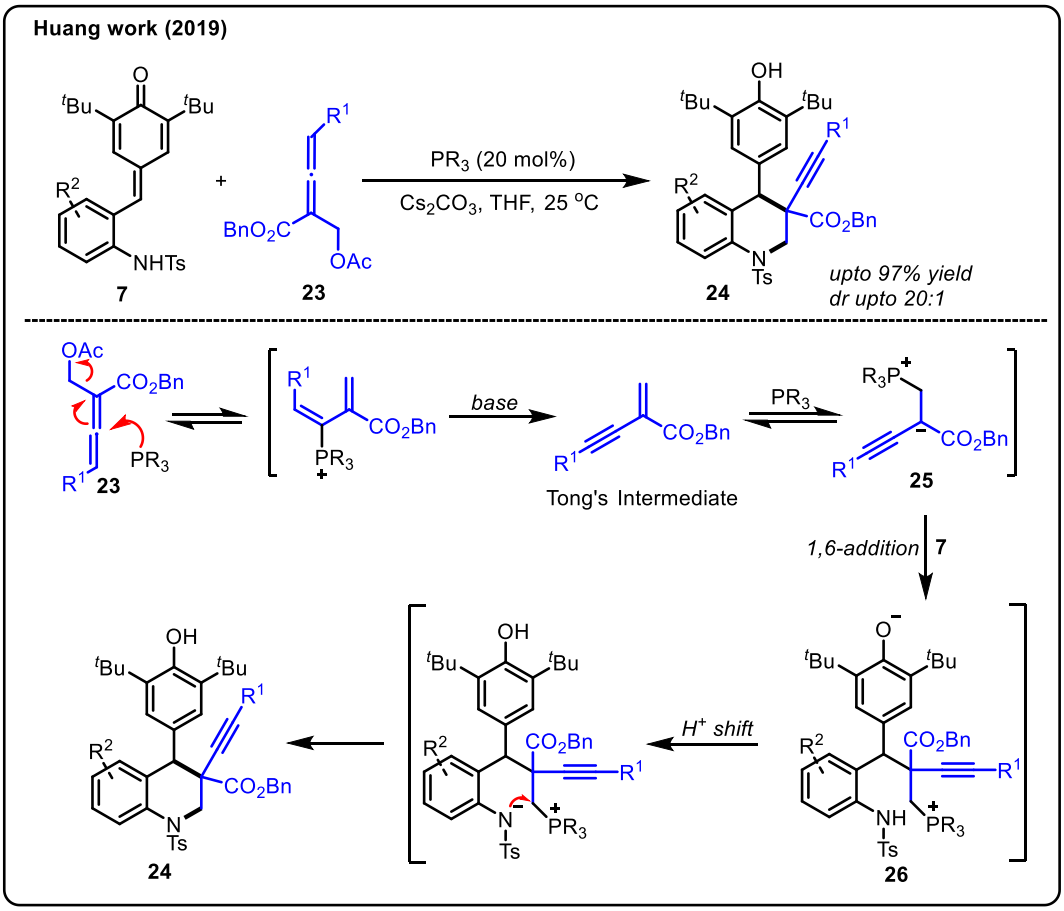
## 1.2.2 Synthesis of dihydro-/tetrahydroquinolines from modified *p*-QMs

In 2018, Zhao and Hu reported the synthesis of tetrahydroquinoline derivatives (**18**) from *in-situ* generated 2-(tosylamino)aryl-substituted *p*-QMs (**7**) and nitroalkenes (**17**) [Scheme 5, **a**]. The reaction proceeds through an aza-Micahel addition of **7** to **17,** followed by an intramolecular cyclization sequence to furnish **18** in good yields.[10a] Later same group established the synthesis of spirocyclic tetrahydroquinoline derivatives (**20**) from *in-situ* generated *p*-QMs (**7**). In this case, **7** undergoes a [4+2] type cyclization with isatin derivative **19** to give oxindole bearing tetrahydroisoquinoline derivatives (**20**) in good yields.[10b] Zhao and Hu also reported an organocatalytic approach for the synthesis of dihydroquinoline



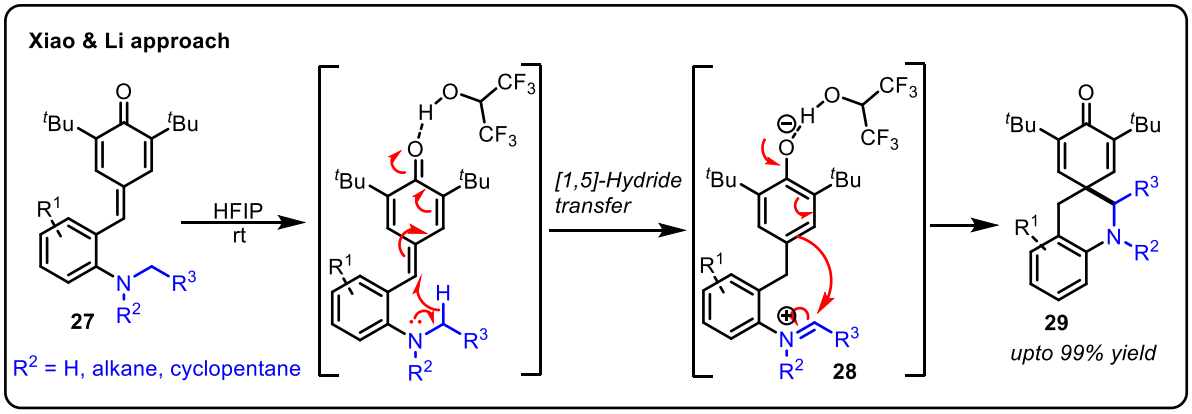

**Scheme 5**. Zhao and Hu approach for the synthesis of quinoline derivatives

derivatives (**22**) from **7** and ynals (**21**) [Scheme 5, **c**]. According to the proposed mechanism, morpholine deprotonates the NH proton of **7,** which then undergoes aza-Michael reaction with ynal **21** followed by intramolecular cyclization to give **22** in excellent yields (Scheme 5).[10c] In line with this, Huang and co-workers in 2019 reported a phosphine-based domino reaction for the synthesis of tetrahydroquinoline derivatives (**24**) [Scheme 6]. In a control experiment, it was observed that allenoate **23**, upon reaction with phosphine, generated Tong's intermediate, which then gave the respective 1,3 bipolar intermediate **25**. Addition of **25** to **7** provided another intermediate **26,** which upon proton transfer and intramolecular cyclization afforded **24** in good yields and excellent diastereoselectivity (Scheme 6).[11]




**Scheme 6**. Synthesis of tetrahydroquinoline from allenoate and *p*-QMs

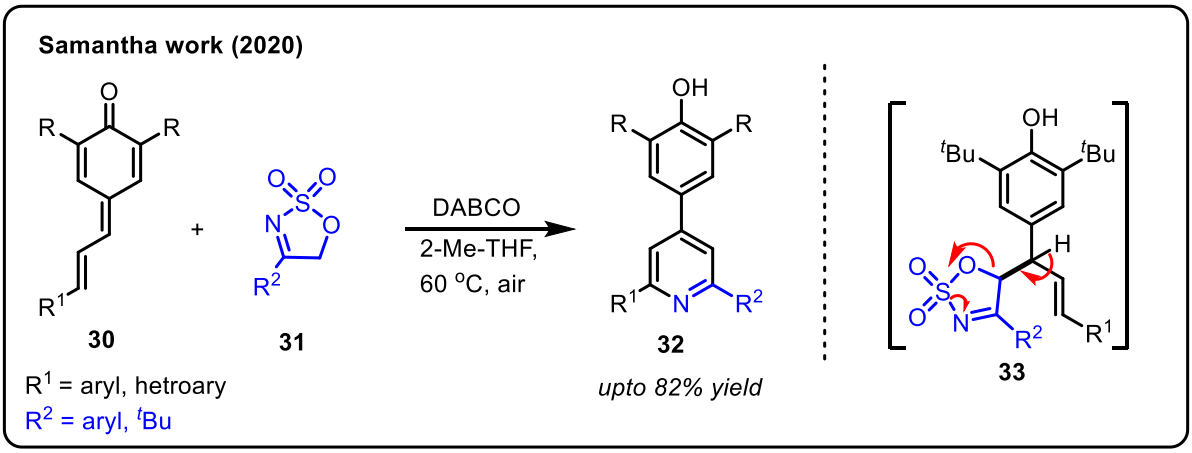
In 2019, Xiao and Li demonstrated a fascinating approach for the synthesis of spirocyclic tetrahydroquinoline derivatives (**29**) using hexafluoroisopropanol (HFIP) as a solvent and promoter under catalyst-free conditions. HFIP, through hydrogen bonding, activates the *p*-QM and generate an imine intermediate **28** through 1,5-hydride transfer. This intermediate **28** then undergoes dearomative cyclization to produce **29** in excellent yields (Scheme 7).[12]




**Scheme 7**. Xiao and Li approach for the synthesis of spirocyclic tetrahydroquinoline derivatives

## 1.2.3 Synthesis of hydroquinolinones, pyridines & benzodiazepines

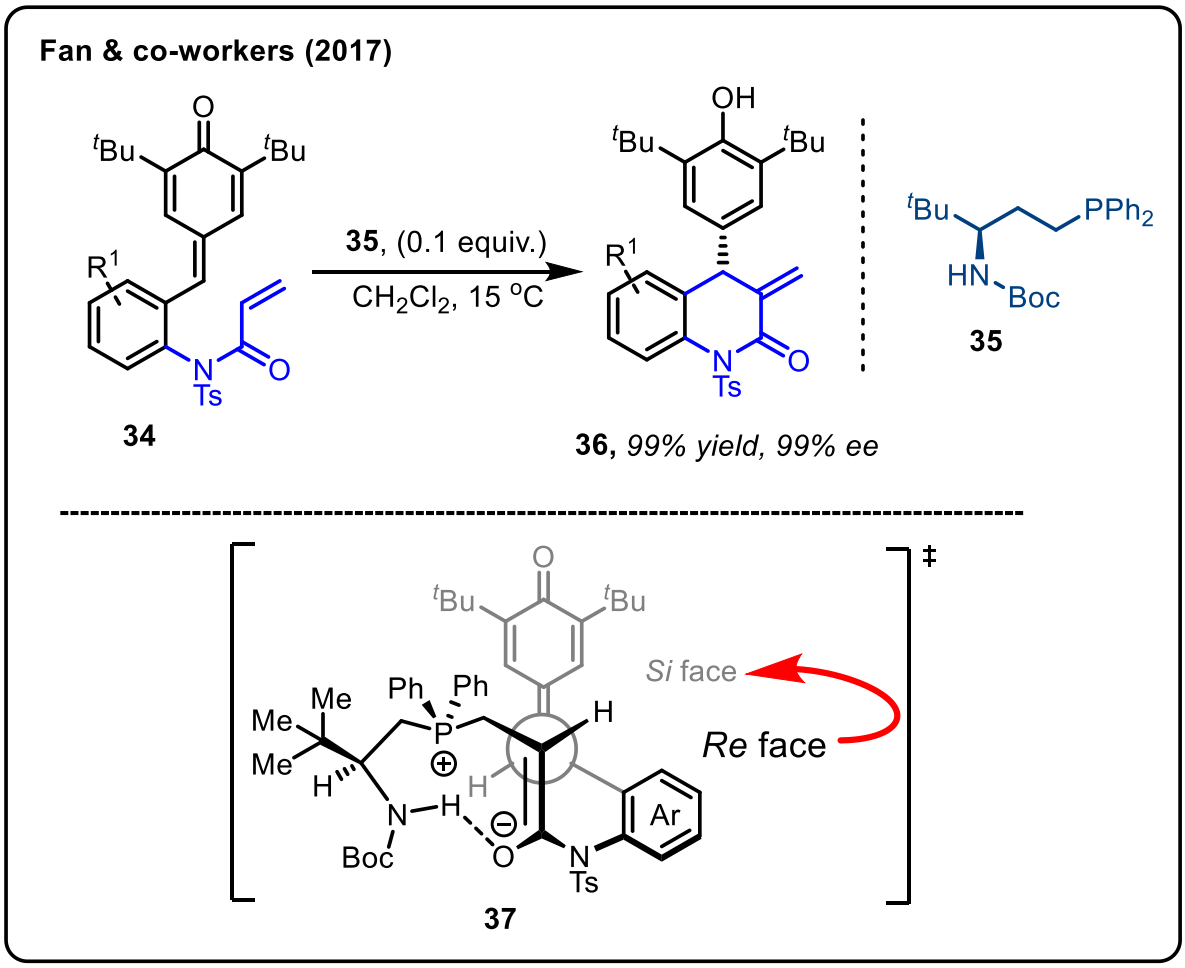
Apart from the above-mentioned reports, *p*-QMs have been explored as synthons for the synthesis of pyridine and other seven-membered nitrogen-containing heterocyclic compounds. For example, Samantha and co-workers have developed an efficient synthesis of pyridine derivatives (**32**) through the reaction of **30** with cyclic sulfamidates **31** (Scheme 8). The sulfamidate **31**, under basic conditions, attack vinyl *p*-QMs **30** to generate an intermediate **33**, which upon $SO_3$ elimination and series of rearrangement provides the corresponding pyridine derivatives (**32**) in good yields.[13]




**Scheme 8**. Synthesis of pyridine from cyclic sulfamidate

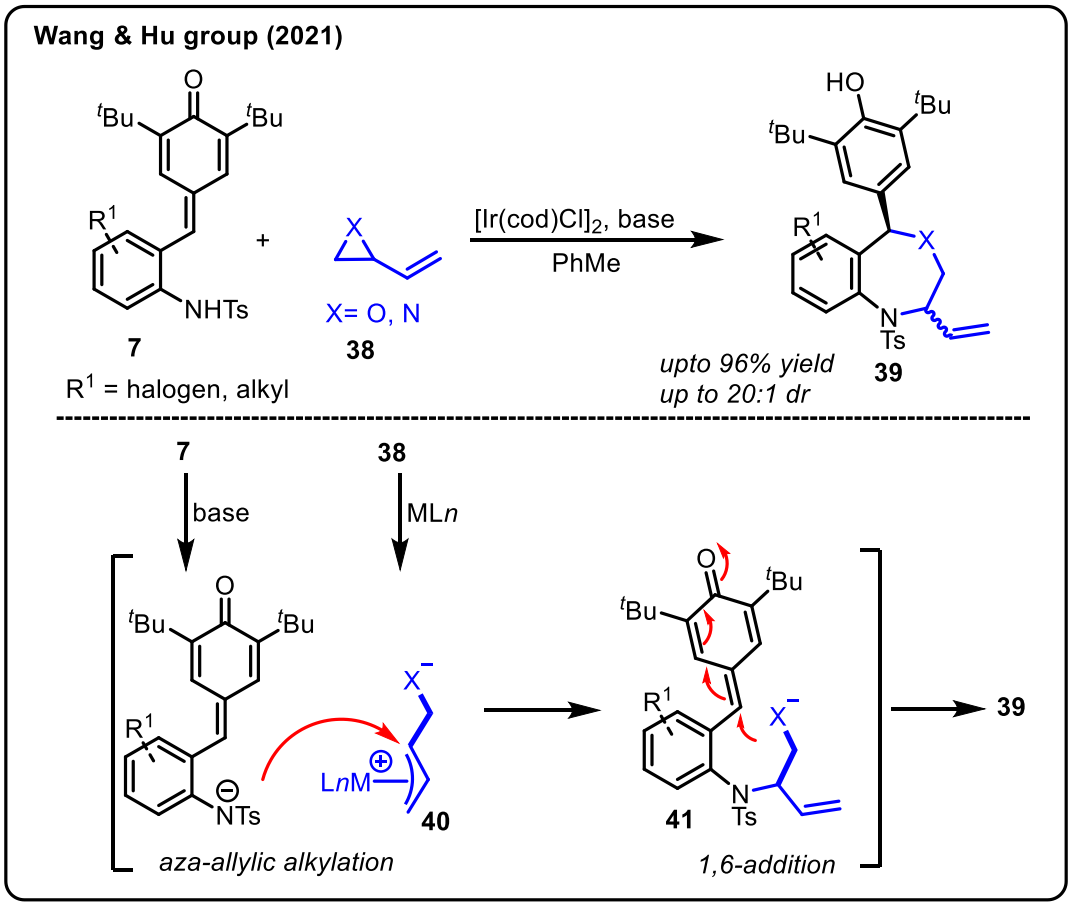
A few years ago, Fan and co-workers reported an elegant synthesis of chiral hydroquinolinones derivatives (**36**) through an intramolecular Rauhut–Currier reaction of ester-derived *p*-QMs (**34**) in the presence of phosphine-based ligand **35**. In the mechanistic

study, the authors proposed that the reaction proceeds through an intermediate **37**, which undergoes 1,6 addition from the less hindered side (*Re* face) to afford enantiomerically pure **36** in excellent yields (Scheme 9).[14]




**Scheme 9**. Enantioselective synthesis of hydroquinolinones derivatives

Recently, Wang and Hu reported the synthesis of tetrahydro-benzodiazepine and tetrahydro-benzooxazepine derivatives in the presence of an iridium-based metal complex (Scheme 10). Vinylic oxiranes or aziridines (**38**) upon reaction with a metal complex forms a π-allyl complex **40**, which then reacts with the deprotonated **7** to form an intermediate **41**, which subsequently undergoes 1,6-addition to generates the corresponding products **39** in good chemical yields and diastereoselectivity (*dr* upto 20:1).[15]




**Scheme 10**. Synthesis of seven-member nitrogen-containing heterocycles

## 1.3 Literature reports for the synthesis of indole derivatives

2,3-Disubstituted indoles, which contribute as one of the essential heterocyclic scaffolds, are found as an integral part of many natural and unnatural molecules that possess remarkable therapeutic properties (Figure 1).[16] Due to their biological importance and structural diversity, the 2,3-disubstituted indole core is still considered an attractive target for many synthetic and medicinal chemists. As a result, in the last several decades, many different synthetic strategies have been designed and demonstrated for the construction of this particular heterocyclic core. Apart from the classical Fischer and Bischler indole synthesis in the late 19th century,[17] many protocols,[18] including the atom-economical intramolecular hydroamination-based approaches, have been developed under transition-metal catalysis.[19,20] A few of the synthetic strategies are discussed in this section; Refvik and co-workers reported the synthesis of 2,3-disubstituted indoles (**44**) from *ortho* iodoanilines (**42**) and internal alkynes (**43**) [Scheme 11]. The heteroannulation process occurs through an oxidative addition of **42** to Pd (0) complex, followed by *syn* insertion of **43** into the aryl palladium bond. Further reductive elimination process affords the product **44** in good yields.[19b] Similarly, Pang and

co-workers, in 2013, developed an elegant approach for substituted indole derivatives (**46**) from **42** and **43** using an NHC-palladium complex as a catalyst **45** (Scheme 11).[19c]

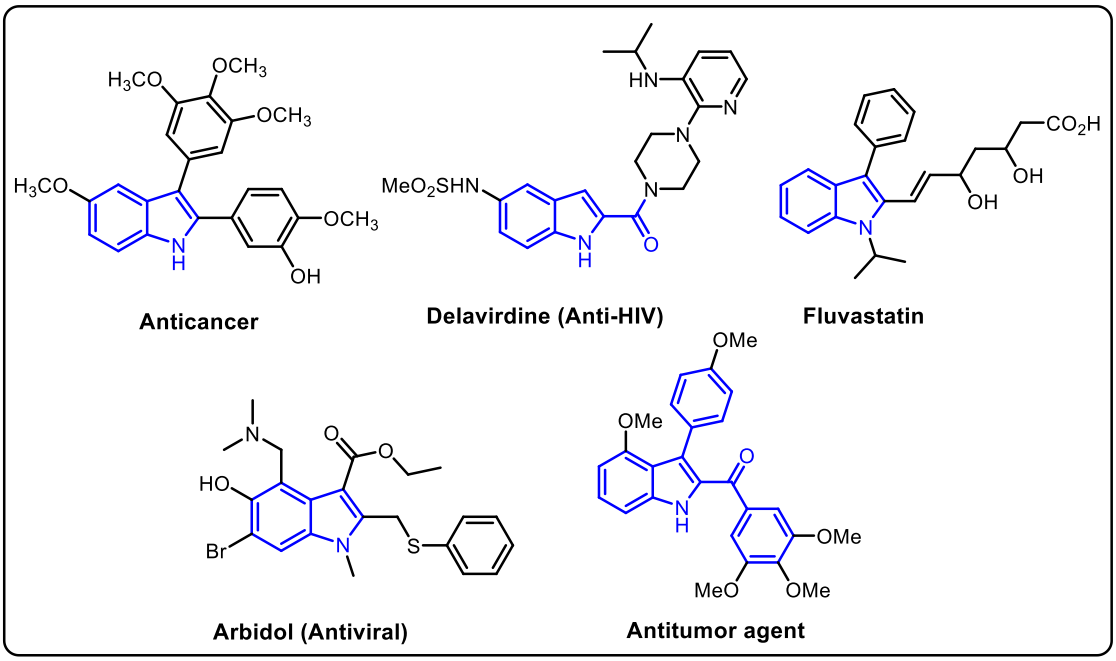
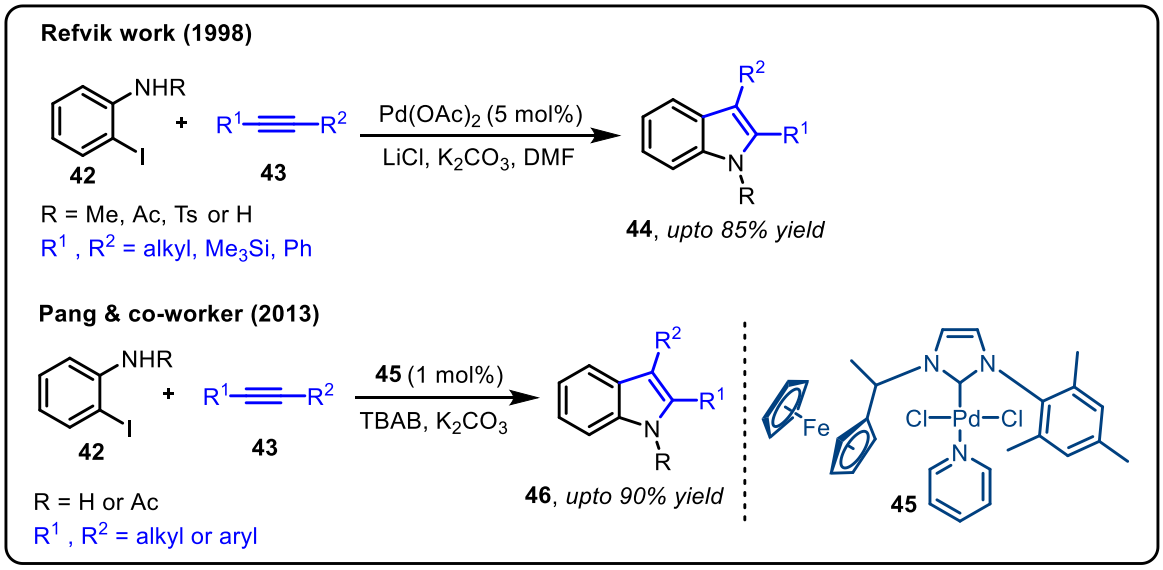
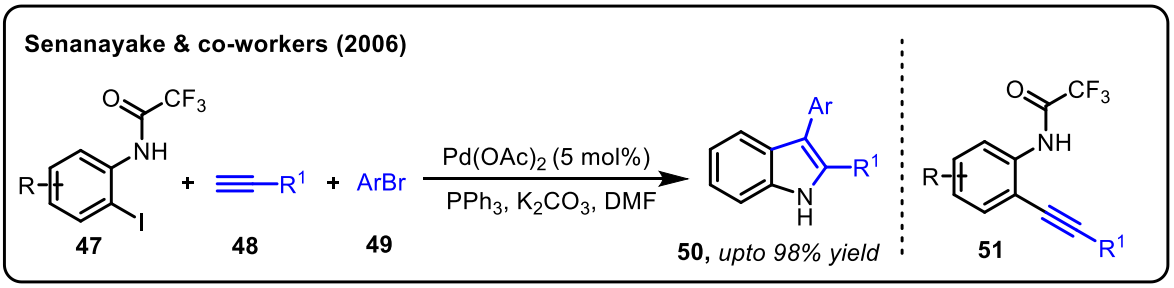



**Figure 3**. Biologically active substituted Indoles.



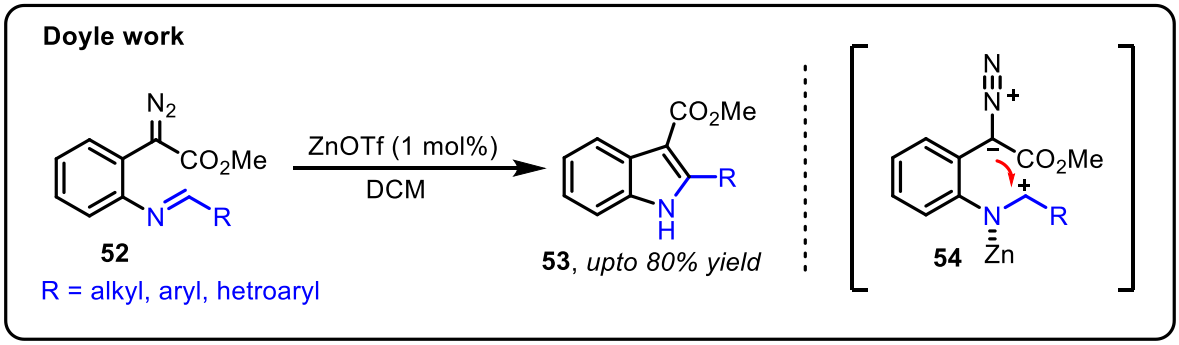

**Scheme 11**. Palladium-catalyzed synthesis of 2,3-disubstituted indoles

In 2006, Senanayake and co-workers established a three-component approach towards the synthesis of substituted indole derivatives (**50**) [Scheme 12]. Initially, the *ortho*-substituted iodoaniline **47** undergoes the Sonogashira coupling with terminal alkyne **48** to generate intermediate **51**, which upon aminopalladation process with arylbromide **49** generates **50** in good yields and excellent regioselectivity (Scheme 12).[20i]



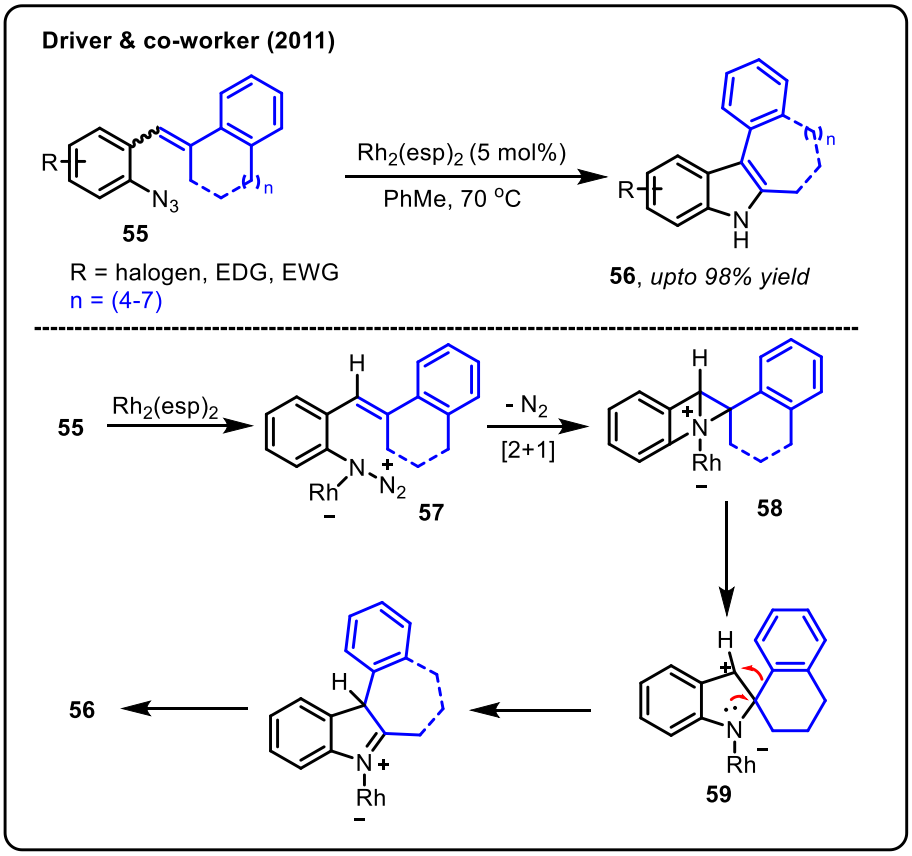

**Scheme 12**. Multicomponent synthesis of 2,3-disubstituted indoles

A few other metal-catalyzed intramolecular C-C bond formation approaches have been disclosed for the synthesis of 2,3-disubstituted indole derivatives.[21] For example, Doyle and co-workers have demonstrated a Lewis acid mediated approach for the synthesis of indole derivative (**53**) [Scheme 13]. As proposed in the mechanism, the *ortho* azo substituted imine derivative **52** in the presence of a Lewis acid generates an intermediate **54**, which upon intramolecular cyclization followed by elimination of nitrogen molecule affords **53** in excellent yields (Scheme 13).[20j]



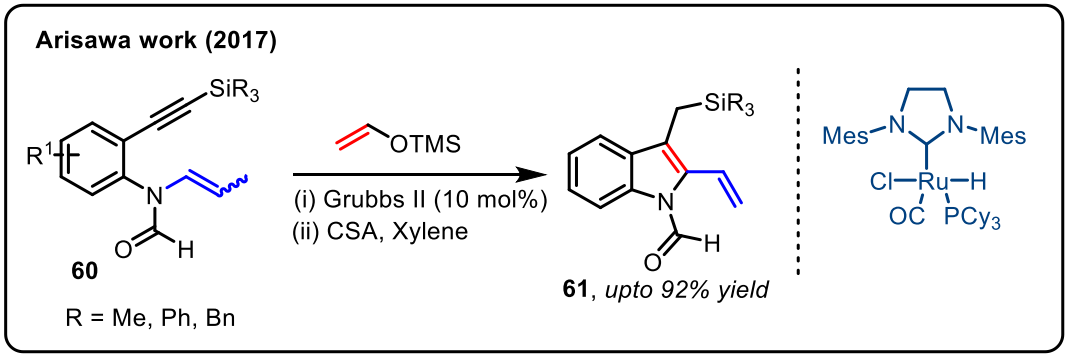

**Scheme 13**. Doyle's approach for the synthesis of 2,3-disubstituted indoles

Driver's group developed an efficient protocol for the synthesis of fused-indoles (**56**) from substituted styryl azides (**55**) in the presence of a Rh-catalyst. Rhodium carboxylate, on reaction with **55,** generates an intermediate **57**, which then undergoes a [2+1] cycloaddition to furnish **58**. This intermediate **58** upon electrocyclization provides a nitrene intermediate **59**, which then undergoes a series of rearrangements to afford 2,3-disubstituted indoles **56** in good yields (Scheme 14).[21d]




**Scheme 14**. Rhodium catalyzed synthesis of fused indole derivatives

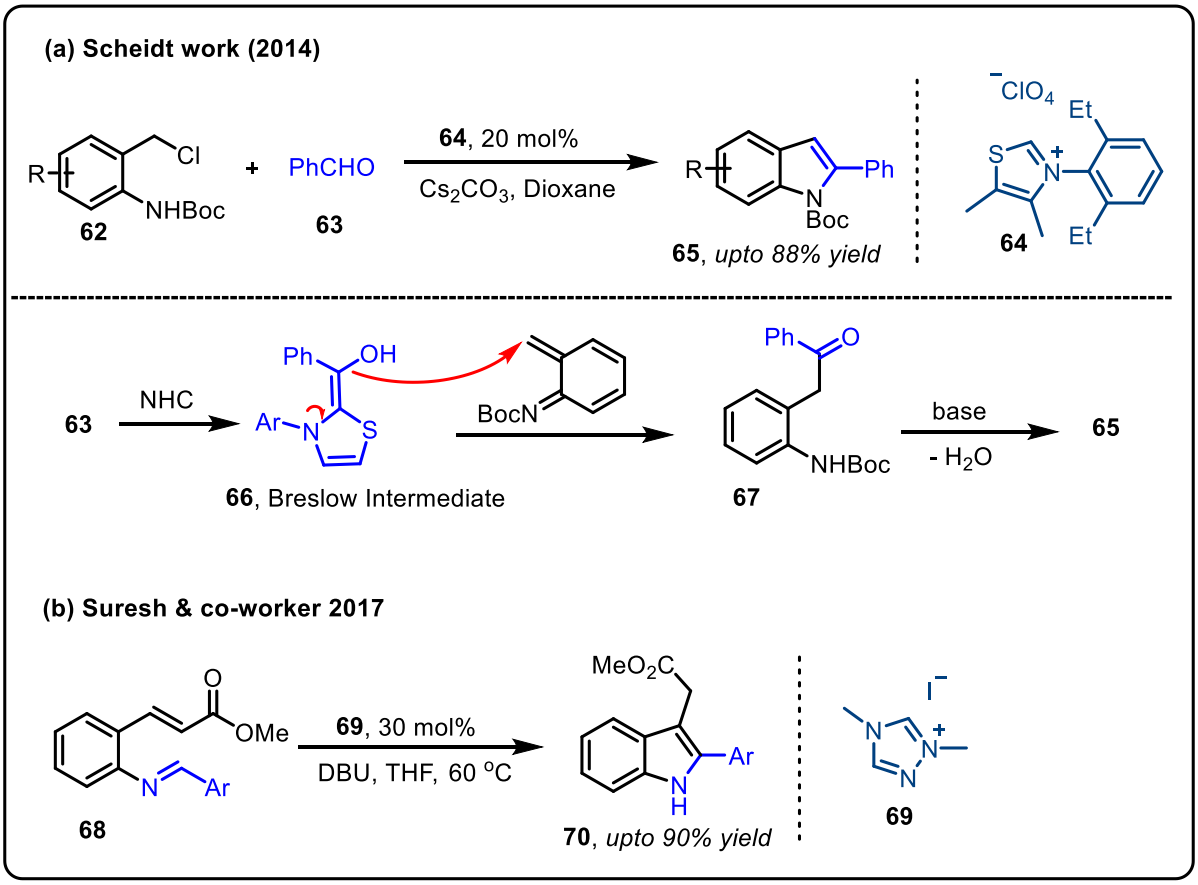
Recently, in 2017, Arisawa and co-workers reported the synthesis of 2,3-disubstituted indole derivatives (**61**) through an intramolecular reaction between enamide and silylalkynes through a ruthenium hydride-mediated metathesis reaction followed by acid-mediated aromatization sequence (Scheme 15).[21b]




**Scheme 15**. Synthesis of indole derivatives using Grubbs catalyst

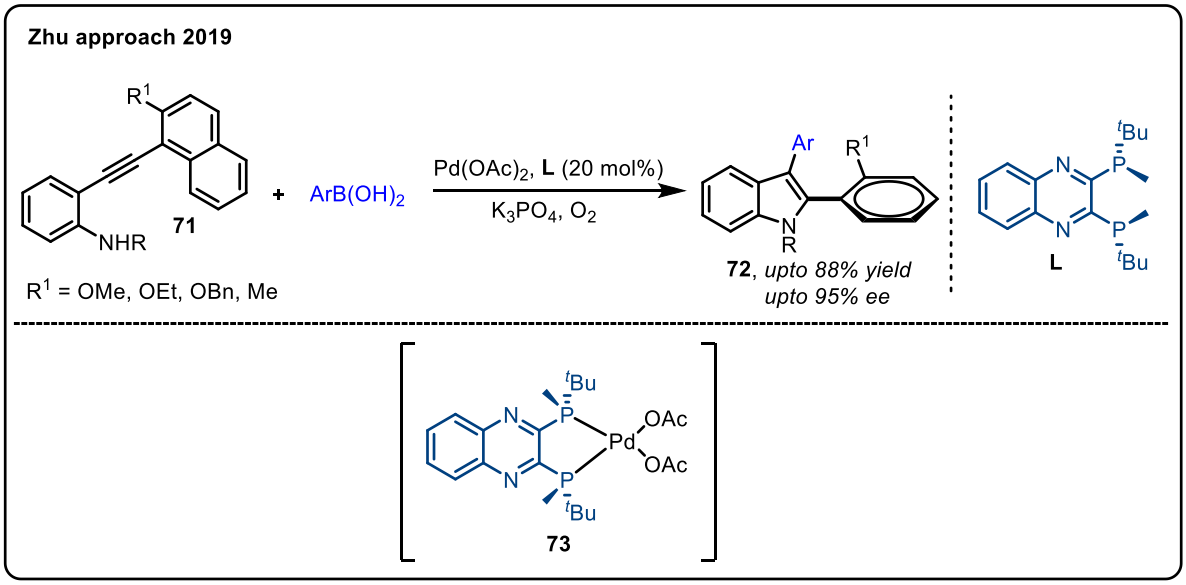
Apart from metal-catalyzed reactions, a few organocatalytic methods, mostly based on *N*-heterocyclic carbene catalysis, have also been divulged for the synthesis of 2,3-disubstituted indoles.[22] Scheidt's group developed the synthesis of 2-aryl indole derivatives

(**65**) from *o*-amino-substituted benzyl halides (**62**) and aldehydes (**63**) using a thiazolium-based NHC **64** as a catalyst (Scheme 16). As proposed by the authors, aldehyde **63**, on reaction with NHC **64** forms a Breslow intermediate **66**, which then reacts with *in-situ* generated *aza-ortho* quinone methide to generate another intermediate **67**. This intermediate **67** subsequently undergoes an intramolecular cyclization and elimination sequence to give **65** in good yields.[22b] Similarly, Suresh and co-workers have demonstrated the synthesis of 2,3-disubstituted indole derivatives (**70**) in the presence of a triazole-based NHC as a catalyst (Scheme 16).[22c]



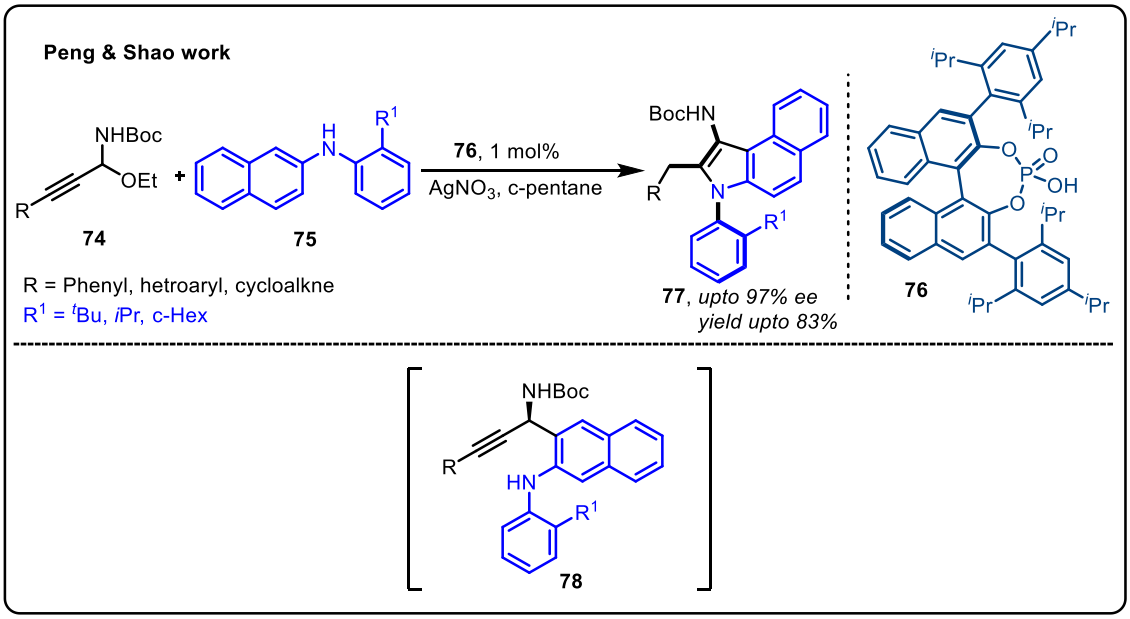

**Scheme 16**. NHC catalyzed synthesis of substituted indole

A few years ago, Zhu's group has developed an enantioselective approach for the synthesis of substituted indoles (**72**) using Cacchi's protocol. Palladium acetate initially forms an active ligand complex **73**, which initiates the coupling reaction between 2-alkynylanilines derivative (**71**) and aryl boronic acid to give **72** in excellent enantioselectivity (Scheme 17).[22d]




**Scheme 17**. Enantioselective synthesis of 2,3-disubstituted indoles

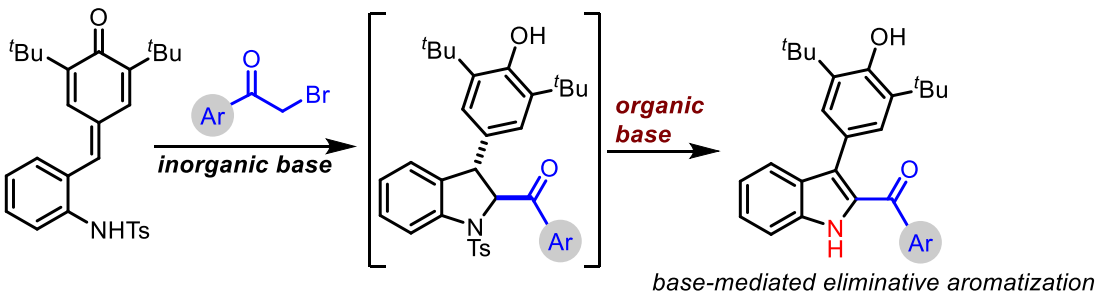
Recently, Peng and Shao developed a novel method for the synthesis of axially chiral indole derivatives (**77**) under organocatalytic conditions. A chiral phosphoric acid **76** in combination with silver nitrate was used as a catalyst. The authors explained that initially, in the presence of **76,** naphthylamine derivative **75** adds to **74** to give an intermediate **78**, which then undergoes 5-*exo* selective cyclization followed by a series of rearrangements to give substituted indole derivatives (**77**) in moderate to good yields and excellent enantiomeric purity (Scheme 18).[22e]




**Scheme 18**. Peng and Shao approach for the synthesis of chiral indoles

## 1.4 Background

Owing to the inimitable reactivity profile, *para*-Quinone Methides (*p*-QMs) have been serving as valued synthons for the construction of various carbocycles, heterocycles and, also for the synthesis of many other arylated organic molecules.[23] Especially, the 2-hydroxyphenyl-substituted *p*-QMs have been utilized as precursors for the synthesis of a wide range of oxygen-containing heterocycles.[24] In line with this, we envisioned that it could be possible to synthesize 2,3-disubstituted indole derivatives from 2-(tosylamino)aryl-substituted *p*-QMs, which are not explored much in the synthesis of amine-based heterocycles.[25] Herein, we report a practical one-pot approach for the synthesis of 2,3-disubstituted indoles through a base-mediated *N*-alkylation of 2-(tosylamino)aryl-substituted *p*-QMs with halomethylaryl ketones followed by intramolecular cyclization and then base-mediated tosyl group elimination sequence (Scheme 19).

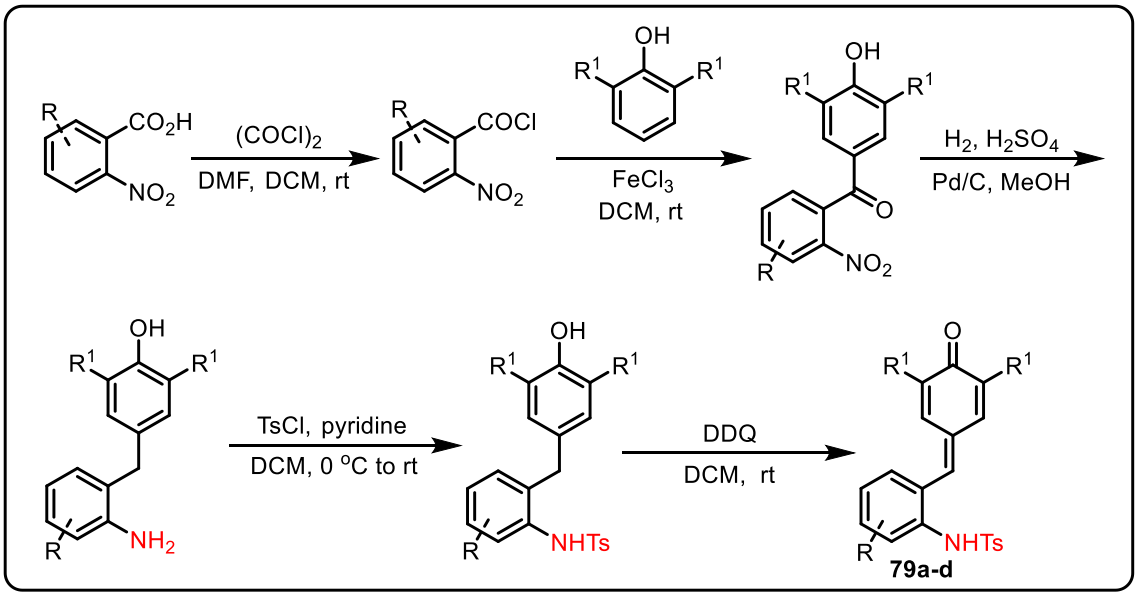



**Scheme 19**. Our approach towards 2,3-disubstituted indoles

## 1.5 Result and discussion

The 2-(tosylamino)aryl-substituted *p*-QMs **79a**–**d** used in this study were prepared according to the literature procedure (Scheme 20).[25a] The optimization studies have been carried out using the 2-(tosylamino)aryl-substituted *p*-QM **79a** and phenacyl bromide **80a** as model substrates. The reaction between **79a** and **80a** has been performed under different conditions and the results are summarised in Table 1. Initially, when the reaction was carried out with 1.2 equiv. of DBU in acetone, at room temperature for 1 h and at 55 $^{o}$C for 6 h, **82a** was not observed, instead, the intermediate dihydroindole derivative **81** was obtained as a mixture of diastereomers (*dr* = 2:1) in 67% yield (entry 1). Since our interest was to prepare the indole derivative **82a** (through the elimination of Ts-group in **81**), we have decided to increase the equivalents of the base. When the reaction was performed with 3 equivalents of DBU, **82a** was obtained in 43 % yield (entry 2). Encouraged by this result further optimization reactions have been carried out with 3 equivalents of DBU in different solvents

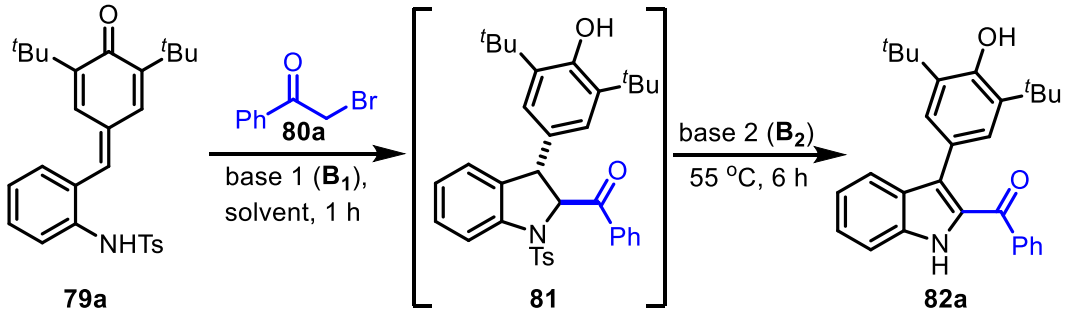
(Entries 3-5). The reaction did not proceed in DMF (entry 3) and, the product **82a** was obtained in 21 and 44% yields in toluene and acetonitrile, respectively (entries 4 & 5). However, when other base such as triethylamine was used, **81** was obtained as a sole product (entry 6). DABCO was found to be ineffective for this transformation as even **81** was not obtained in this case (entry 7). Other inorganic bases such as cesium carbonate and potassium carbonate promoted only the *N*-alkylation and cyclization steps and, in both the cases, only **81** was obtained in 84 and 71% yields, respectively (entries 8 & 9).




**Scheme 20**. Synthesis of 2-(tosylamino)aryl-substituted *p*-QMs

Interestingly, when a combination of inorganic base ($Cs_2CO_3$ as $\mathbf{B_1}$) and organic base (DBU as $\mathbf{B_2}$) was used in the reaction, the expected indole derivative **82a** was obtained in 80% isolated yield along with trace quantities of **81** in acetone (entry 10). This combination also promoted the formation of **82a** in acetonitrile, but the yield of **82a** was a bit inferior when compared to the reaction in acetone (entry 11). It is clear from these experiments that the inorganic base promotes the *N*-alkylation and cyclization steps at room temperature, and the organic base is responsible for the elimination of the tosyl group that leads to the formation of unprotected indole **82a**. The combination of $K_2CO_3$ + DBU was also found to be effective (entry 12), but provided the product **82a** only in 70% yield. Unfortunately, the combination of $Cs_2CO_3$ + $Et_3N$ was found to be ineffective for the formation of **82a** as $Et_3N$ failed to convert **81** to **82a** (entry 13).

**Table 1.** Optimization Study[a]

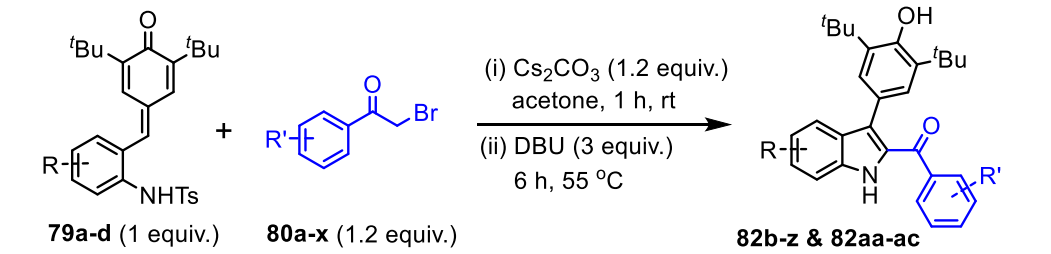



| entry | $\mathbf{B_1}$ + $\mathbf{B_2}$ | solvent | yield of **81** [%] | yield of **82a** [%] |
|---|---|---|---|---|
| 1[b] | DBU | acetone | 67 (*dr* = 2:1)[e] | - |
| 2[c] | DBU | acetone | trace | 43 |
| 3[c] | DBU | DMF | - | - |
| 4[c] | DBU | PhMe | trace | 21 |
| 5[c] | DBU | MeCN | trace | 44 |
| 6[c] | $NEt_3$ | acetone | 80 (*dr* = 3:1)[e] | - |
| 7[c] | DABCO | acetone | - | - |
| 8[c] | $Cs_2CO_3$ | acetone | 84 (*dr* = 4:1)[e] | - |
| 9[c] | $K_2CO_3$ | acetone | 71(*dr* = 3:1)[e] | - |
| **10[d]** | **$Cs_2CO_3$ + DBU** | **acetone** | **trace** | **80** |
| 11[d] | $Cs_2CO_3$ + DBU | MeCN | trace | 73 |
| 12[d] | $K_2CO_3$ + DBU | acetone | trace | 70 |
| 13[d] | $Cs_2CO_3$ + $NEt_3$ | acetone | 73 (*dr* = 4:1)[e] | trace |

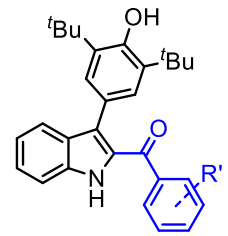
[a]Reaction Conditions: All reactions were carried at 0.086 mmol scale of **79a** with 1.2 equiv. of **80a** and 3-4.2 equiv. of the base(s) with respect to **79a** at room temperature for an hour followed by 55 °C for 6 h. [b]1.2 equiv. of DBU was used. [c]3.0 equiv. of base was used. [d]1.2 equiv. of inorganic base ($\mathbf{B_1}$) and 3.0 equiv. of organic base ($\mathbf{B_2}$) were used. [e]The diastereomeric ratios were calculated based on the crude $^1$H NMR analysis.

After having the optimal conditions in hand (entry 10, Table 1), the substrate scope and limitations of this transformation were evaluated using different bromomethylaryl ketones (**80b-x**) and 2-(tosylamino)aryl-substituted *p*-QMs (**79a-d**) and, the results are summarized in Chart 1. As shown in the table, most of the halomethylaryl ketones (**80b-i**), substituted with electron-rich arenes, reacted with **79a** smoothly under the standard conditions and furnished the respective 2,3-disubstituted indoles (**82b-i**) in the range of 56-76% yields. Similarly, other bromomethylaryl ketones such as **80j** (naphthyl-substituted), **80k-u** (haloaryl-substituted) and **80v-x** (substituted with electron-poor arenes) were subjected to react with **79a** and the corresponding indole derivatives (**82j-x**) had been isolated in moderate to good yields (71-95%). The substrate scope was elaborated to other 2-(tosylamino)aryl-substituted *p*-QMs (**79b-d**) and, the respective products **82y-z** & **82aa-ac** were obtained in the range of 73-89% yields.

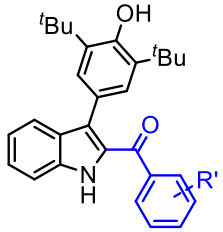
**Chart 1.** Substrate scope[a]



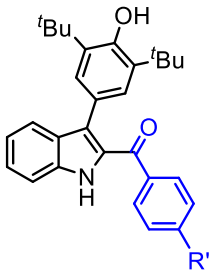

**79a-d** (1 equiv.) **80a-x** (1.2 equiv.) **82b-z & 82aa-ac**



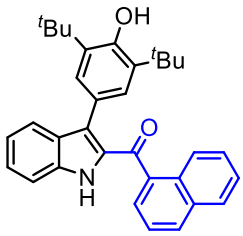
**82b** R' = 3-Me, 60%
**82c** R' = 4-Me, 65%
**82d** R' = 4-Et, 56%



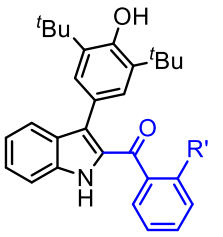
**82e** R' = 3-OMe, 62%
**82f** R' = 2,3-OMe, 60%
**82g** R' = 4-OMe, 76%



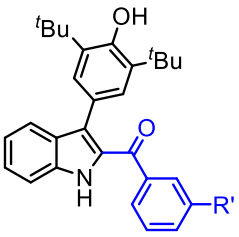
**82h** R' = SMe, 69%
**82i** R' = Ph, 62%



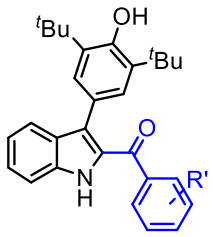
**82j,** 86%



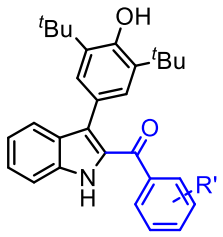
**82k** R' = Cl, 76%
**82l** R' = Br, 86%



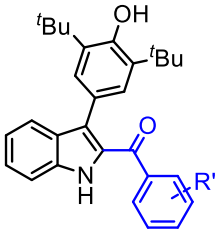
**82m** R' = Cl, 85%
**82n** R' = Br, 71%



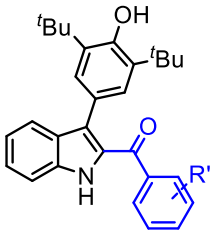
**82o** R' = 4-Cl, 84%
**82p** R' = 4-Br, 81%
**82q** R' = 2,4-Cl, 78%



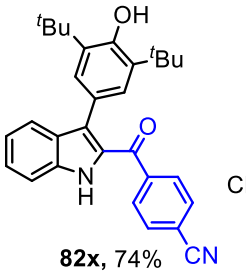
**82r** R' = 2-F, 81%
**82s** R' = 2-Br, 5-F, 82%



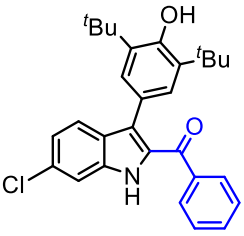
**82t** R' = 3-$CF_3$, 91%
**82u** R' = 4-$CF_3$, 95%



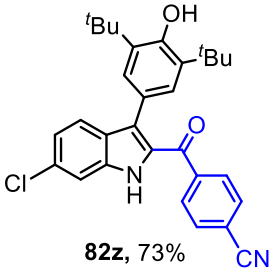
**82v** R' = 3-$NO_2$, 77%
**82w** R' = 4-$NO_2$, 86%



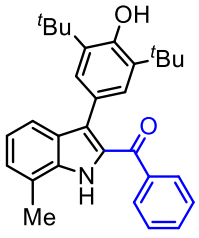
**82x,** 74%



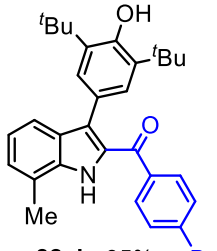
**82y,** 89%



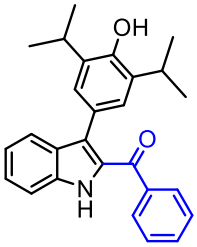
**82z,** 73%



**82aa,** 77%



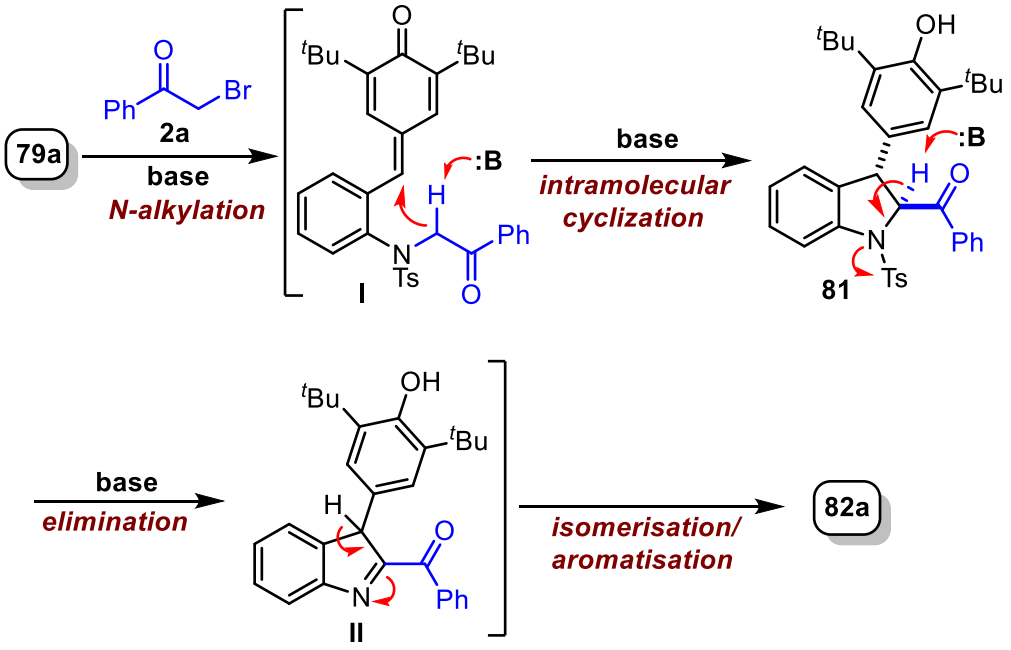
**82ab,** 85%



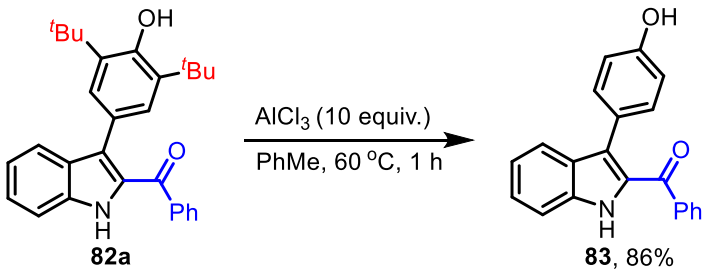
**82ac,** 75%

[a]Reaction conditions: All reactions were performed in 40 mg scale (0.09-0.08 mmol) of **79a-d** and with 1.2 equiv. of **80a-x** in 1.5 mL of acetone. Yields reported are isolated yields.

Based on the outcome of the reaction and also the similar types of previous reports, a plausible mechanism has been proposed for this transformation (Scheme 21). The inorganic base ($Cs_2CO_3$) mediates the *N*-alkylation of **79a** with **80a** that results in the formation of intermediate **I**, which undergoes intramolecular cyclization under basic conditions to provide the dihydroindole derivative **81**. The organic base (DBU) is responsible for the elimination of tosyl group and, that leads to the formation of intermediate **II**, which than undergoes isomerization/aromatization to provide the 2,3-disubstituted indole **82a**.



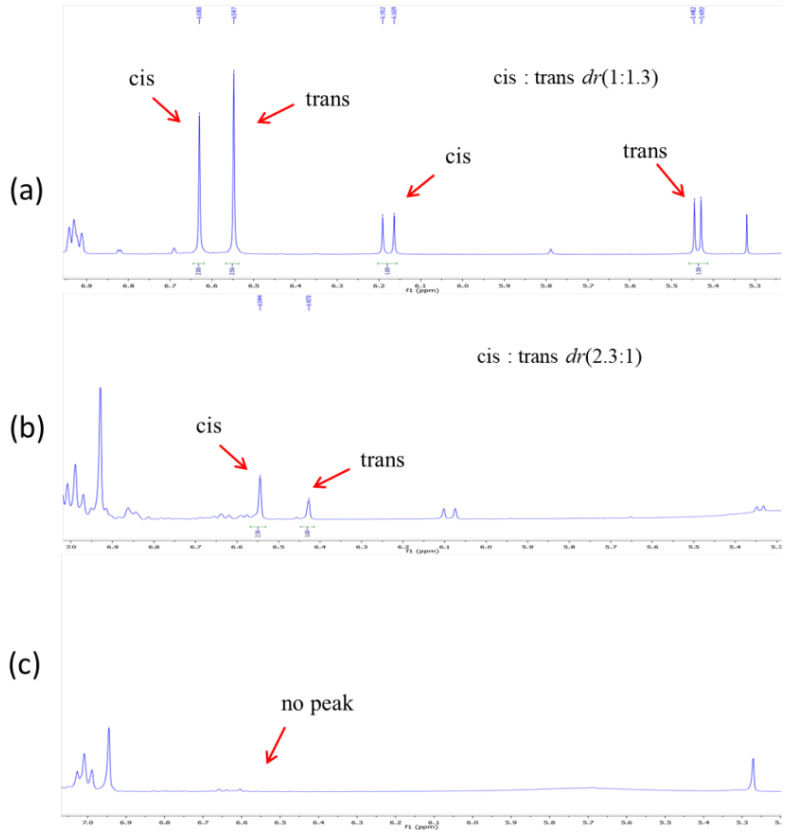

**Scheme 21.** Plausible mechanism




**Scheme 22.** De-*tert*-butylation of **82a**

Further to investigate the rate of elimination step for intermediate **81**, to afford product **82a** NMR controlled experiments were performed and it was found that rate of conversion for *trans* isomer is more when compare to *cis* isomer (as shown in Figure 4). To further extend the scope of this transformation, one of the 2,3-disubstituted indoles (**82a**) was

subjected to de-*tert*-butylation with excess of $AlCl_3$ and, as expected, the corresponding product **83** was obtained in 86% yield (Scheme 22).




(a) Isolated intermediate (**81**) (b) Crude reaction mixture after 3 h (c) Crude reaction mixture after 6 h

**Figure 4**. NMR controlled experiments

## 1.6 Conclusion

In conclusion, we have developed a base-mediated one-pot sequential approach for the synthesis of densely functionalized 2,3-disubstituted indoles from 2-(tosylamino)aryl-substituted *p*-QMs and bromomethyl aryl ketones. A combination of the inorganic and organic base was used to effect this transformation. Many 2,3-disubstituted indoles could be accessed in moderate to excellent yields under the standardized reaction conditions. This is a multi-step transformation and proceeds through inorganic base-mediated *N*-alkylation of 2-(tosylamino)aryl-substituted *p*-QM with bromomethyl aryl ketone followed by 1,6 intramolecular cyclization and then eliminative isomerization/aromatization to provide the 2,3-substituted indoles.

## 1.7 Experimental section

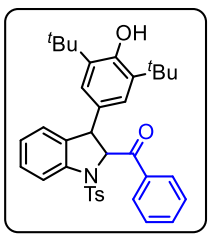
### General Information

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 argon atmosphere. Most of the reagents, and starting materials were purchased from commercial sources and used as such. All 2-(tosylamino)aryl-substituted *p*-QMs were prepared by following a literature procedure.[25d] Bromomethyl aryl ketones were prepared according to the known literature procedure.[26] Melting points were recorded on SMP20 melting point apparatus and are uncorrected. $^{1}H$, $^{13}C$ and $^{19}F$ spectra were recorded in $CDCl_3$ (500/400, 125/100 and 376 MHz, respectively) on Bruker FT–NMR spectrometer. Chemical shift (d) 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 $F_{254}$ precoated TLC plates and visualized by UV irradiation and/or $KMnO_4$ 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-disubstituted indoles (82a-z & 82aa-ac)

Acetone (1.5 mL) was added to a mixture of 2-(tosylamino)phenyl p-quinone methide (79**a-d**, 0.086 mmol, 1 equiv.), bromomethyl aryl ketone (**80a-x**, 0.103 mmol, 1.2 equiv.) followed by the addition of $Cs_2CO_3$ (0.103 mmol, 1.2 equiv.). The resulting suspension was stirred at room temperature for an hour. DBU (0.258 mmol, 3 equiv.) was added to the reaction mixture and the reaction mixture was further allowed to stir at 55 °C for 6 hours. 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 (**82a-z & 82aa-ac**).

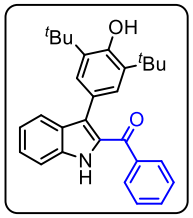
**{3-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-1-tosylindolin-2-yl}(phenyl)methanone (81)**. The




reaction was performed at 0.086 mmol scale of **79a** (Entry 8, Table 1). White solid (42 mg, 84% yield); Diastereomeric ratio = 4:1; Major diastereomer (*trans*); $^{1}H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.86 – 7.82 (m, 4H), 7.64 – 7.56 (m, 2H), 7.48 – 7.39 (m, 3H), 7.30 – 7.25 (m, 4H), 6.98 (t, *J* = 7.4 Hz, 1H), 6.92 – 6.89 (m, 1H), 6.53 (s, 2H), 5.42 (d, *J* = 6.4 Hz, 1H), 5.15 (s, 1H), 4.33 (d, *J* = 6.3 Hz, 1H), 2.40 (s, 3H), 1.24 (s, 18H); $^{13}C$ NMR (100 MHz,

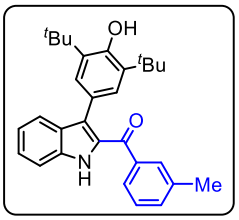
$CDCl_3$) $\delta$ 195.7, 153.3, 144.4, 142.0, 136.3, 135.0, 133.7, 132.5, 132.4, 130.0, 129.9, 129.3, 128.8, 127.9, 127.6, 126.1, 124.8, 124.0, 114.0, 74.2, 52.2, 34.3, 30.2, 22.6.

**{3-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-*1H*-indol-2-yl}(phenyl)methanone (82a).** The



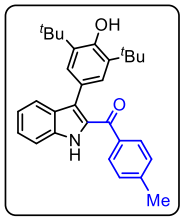

reaction was performed at 0.086 mmol scale of **79a**; $R_f$ = 0.3 (15% EtOAc in hexane); Yellow solid (29.2 mg, 80% yield); m. p. = 178–180 °C; $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 9.32 (s, 1H), 7.76 (dd, *J* = 8.2, 1.0 Hz, 1H), 7.54 – 7.52 (m, 2H), 7.51 – 7.49 (m, 1H), 7.42 – 7.39 (m, 1H), 7.28 – 7.24 (m, 1H), 7.20 – 7.17 (m, 1H), 7.07 – 7.03 (m, 2H), 6.92 (s, 2H), 5.01 (s, 1H), 1.30 (s, 18H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 189.6, 153.1, 137.8, 136.7, 135.9, 131.7, 130.9, 129.9, 128.0, 127.9, 127.5, 126.9, 126.7, 124.8, 122.6, 121.0, 112.1, 34.2, 30.3; FT-IR (thin film, neat): 3668, 3413, 2992, 1615, 749 cm$^{-1}$; HRMS (ESI): *m/z* calcd for $C_{29}H_{32}NO_2$ $[M+H]^+$ : 426.2433; found : 426.2451.

**{3-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-*1H*-indol-2-yl}(m-tolyl)methanone (82b).** The



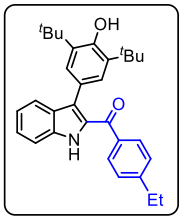

reaction was performed at 0.086 mmol scale of **79a**; $R_f$ = 0.3 (15% EtOAc in hexane); Yellow solid (22.7 mg, 60% yield); m. p. = 223–225 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 9.28 (s, 1H), 7.77 (d, *J* = 8.2 Hz, 1H), 7.49 (d, *J* = 8.3 Hz, 1H), 7.42 – 7.38 (m, 2H), 7.30 (s, 1H), 7.18 (t, *J* = 7.6 Hz, 1H), 7.08 (d, *J* = 7.5 Hz, 1H), 7.03 (d, *J* = 7.6 Hz, 1H), 7.00 (s, 2H), 5.10 (s, 1H), 2.07 (s, 3H), 1.30 (s, 18H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 189.7, 153.0, 137.6, 137.2, 136.6, 135.7, 132.6, 131.0, 130.8, 128.0, 127.9, 127.7, 126.8, 126.7, 126.6, 125.0, 122.6, 121.0, 112.0, 34.2, 30.2, 21.1; FT-IR (thin film, neat): 3628, 3325, 2955, 1614, 746 cm$^{-1}$; HRMS (ESI): *m/z* calcd for $C_{30}H_{34}NO_2$ $[M+H]^+$ : 440.2590; found : 440.2608.

**{3-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-*1H*-indol-2-yl}(p-tolyl)methanone (82c).** The



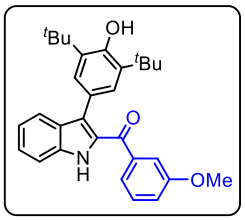

reaction was performed at 0.086 mmol scale of **79a**; $R_f$ = 0.3 (15% EtOAc in hexane); Yellow solid (24.6 mg, 65% yield); m. p. = 200–202 °C; $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 9.28 (s, 1H), 7.77 (dd, *J* = 8.2 , 1.0 Hz, 1H), 7.49 (td, *J* = 8.3 , 0.9 Hz, 1H), 7.43 – 7.41 (m, 2H), 7.40 – 7.38 (m, 1H), 7.18 (td, *J* = 6.9 , 1.0 Hz, 1H), 6.99 (s, 2H), 6.85 – 6.83 (m, 2H), 5.01 (s, 1H), 2.26 (s, 3H), 1.30 (s, 18H), $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 189.4, 153.1, 142.3, 136.5, 135.8, 135.1, 131.0, 130.0, 128.2, 127.94, 127.87, 126.52, 126.50, 124.9, 122.5, 121.0, 112.0, 34.2, 30.3, 21.6; FT-IR (thin film, neat): 3635, 3320, 2956, 1603, 743 cm$^{-1}$; HRMS (ESI): *m/z* calcd for $C_{30}H_{34}NO_2$ $[M+H]^+$ : 440.2590; found : 440.2608.

**{3-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-*1H*-indol-2-yl}(4-ethylphenyl)methanone (82d).**



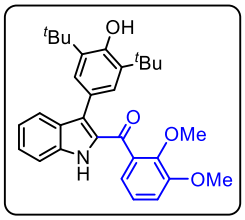

The reaction was performed at 0.086 mmol scale of **79a**; $R_f$ = 0.3 (15% EtOAc in hexane); Yellow solid (21.9 mg, 56% yield); m. p. = 208–210 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 9.22 (s, 1H), 7.77 (d, $J$ = 8.2 Hz, 1H), 7.49 (d, $J$ = 8.2 Hz, 1H), 7.45 (d, $J$ = 7.6 Hz, 2H), 7.40 (t, $J$ = 7.4 Hz, 1H), 7.18 (t, $J$ = 7.5 Hz, 1H), 7.00 (s, 2H), 6.87 (d, $J$ = 7.6 Hz, 2H), 5.07 (s, 1H), 2.52 (q, $J$ = 7.6 Hz, 2H), 1.30 (s, 18H), 1.13 (t, $J$ = 7.5 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 189.5, 153.0, 148.4, 136.5, 135.8, 135.3, 131.1, 130.1, 127.9, 127.86, 127.0, 126.5, 126.45, 125.0, 122.5, 121.0, 112.0, 34.2, 30.3, 28.8, 14.9; FT-IR (thin film, neat): 3635, 3316, 2957, 1602, 749 cm$^{-1}$; HRMS (ESI): *m/z* calcd for $C_{31}H_{36}NO_2$ $[M+H]^+$ : 454.2746; found : 454.2767.

**{3-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-*1H*-indol-2-yl}(3-methoxyphenyl)methanone**



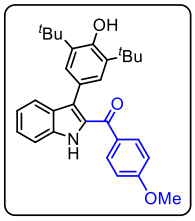

**(82e).** The reaction was performed at 0.086 mmol scale of **79a**; $R_f$ = 0.3 (15% EtOAc in hexane); Yellow solid (24.3 mg, 62% yield); m. p. = 173–175 °C; $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 9.22 (s, 1H), 7.79 – 7.77 (m, 1H), 7.49 (dt, $J$ = 8.4, 0.9 Hz, 1H), 7.42 – 7.39 (m, 1H), 7.21 – 7.17 (m, 2H), 7.04 – 7.01 (m, 4H), 6.84 – 6.81 (m, 1H), 5.10 (s, 1H), 3.56 (s, 3H), 1.31 (s, 18H), $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 189.4, 158.9, 153.1, 139.1, 136.7, 135.9, 130.7, 128.8, 128.0, 127.9, 126.7 (2C), 124.9, 122.7, 122.3, 121.1, 118.8, 114.2, 112.0, 55.3, 34.2, 30.3; FT-IR (thin film, neat): 3635, 3330, 2956, 1614, 768 cm$^{-1}$; HRMS (ESI): *m/z* calcd for $C_{30}H_{34}NO_3$ $[M+H]^+$ : 456.2539; found : 456.2555.

**{3-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-*1H*-indol-2-yl}(2,3-dimethoxyphenyl)methanone**



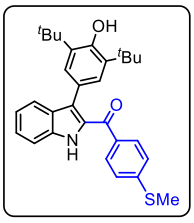

**(82f).** The reaction was performed at 0.086 mmol scale of **79a**; $R_f$ = 0.3 (15% EtOAc in hexane);Yellow solid (25.0 mg, 60% yield); m. p. = 163–165 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 9.26 (s, 1H), 7.60 (d, $J$ = 8.1 Hz, 1H), 7.46 (d, $J$ = 8.4 Hz, 1H), 7.38 (t, $J$ = 7.3 Hz, 1H), 7.12 (t, $J$ = 7.6 Hz, 1H), 6.95 (s, 2H), 6.72 (d, $J$ = 7.3 Hz, 1H), 6.62 – 6.56 (m, 2H), 5.06 (s, 1H), 3.87 (s, 3H), 3.75 (s, 3H), 1.33 (s, 18H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 188.0, 152.9, 152.4, 147.2, 136.6, 135.2, 134.1, 131.5, 128.7, 128.1, 127.4, 126.9, 124.4, 122.89, 122.86, 121.6, 120.8, 114.0, 112.0, 62.2, 55.7, 34.2, 30.3; FT-IR (thin film, neat): 3635, 3322, 2955, 1615, 758 cm$^{-1}$; HRMS (ESI): *m/z* calcd for $C_{31}H_{36}NO_4$ $[M+H]^+$ : 486.2644; found : 486.2667.

**{3-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-*1H*-indol-2-yl}(4-methoxyphenyl)methanone**



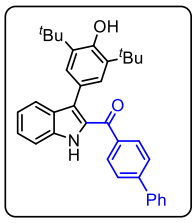
**(82g).** The reaction was performed at 0.086 mmol scale of **79a**; $R_f$ = 0.3 (15% EtOAc in hexane); Yellow solid (29.8 mg, 76% yield); m. p. = 180–182 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 9.32 (s, 1H), 7.78 (d, $J$ = 8.1 Hz, 1H), 7.51 (t, $J$ = 8.8 Hz, 3H), 7.39 (t, $J$ = 7.2 Hz, 1H), 7.18 (t, $J$ = 7.5 Hz, 1H), 7.00 (s, 2H), 6.52 (d, $J$ = 8.6 Hz, 2H), 5.12 (s, 1H), 3.71 (s, 3H), 1.31 (s, 18H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 188.4, 162.6, 152.9, 136.5, 135.9, 132.1, 131.1, 130.3, 127.90, 127.86, 126.4, 126.1, 125.1, 122.4, 120.9, 112.8, 112.0, 55.3, 34.2, 30.3; FT-IR (thin film, neat): 3639, 3326, 2957, 1612, 758 cm$^{-1}$; HRMS (ESI): *m/z* calcd for $C_{30}H_{34}NO_3$ $[M+H]^+$ : 456.2539; found : 456.2527.

**{3-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-*1H*-indol-2-yl}(4-(methylthio)phenyl)methanone**



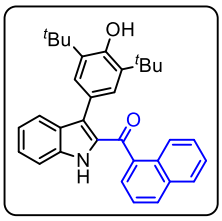
**(82h).** The reaction was performed at 0.086 mmol scale of **79a**; $R_f$ = 0.3 (15% EtOAc in hexane); Orange solid (28.0 mg, 69% yield); m. p. = 226–228 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 9.25 (s, 1H), 7.77 (d, $J$ = 8.2 Hz, 1H), 7.49 (d, $J$ = 8.3 Hz, 1H), 7.44 – 7.38 (m, 3H), 7.18 (t, $J$ = 7.6 Hz, 1H), 6.99 (s, 2H), 6.84 (d, $J$ = 8.3 Hz, 2H), 5.13 (s, 1H), 2.36 (s, 3H), 1.31 (s, 18H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 188.6, 153.1, 144.2, 136.6, 136.0, 133.8, 131.0, 130.3, 127.89, 127.87, 126.59, 126.57, 124.9, 124.1, 122.5, 121.0, 112.0, 34.3, 30.3, 14.8; FT-IR (thin film, neat): 3627, 3309, 2955, 1615, 747 cm$^{-1}$; HRMS (ESI): *m/z* calcd for $C_{30}H_{34}NO_2S$ $[M+H]^+$ : 472.2310; found : 472.2328.

**[1,1'-Biphenyl]-4-yl(3-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-*1H*-indol-2-yl)methanone**



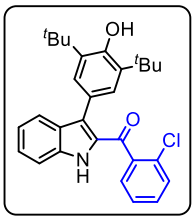
**(82i).** The reaction was performed at 0.086 mmol scale of **79a**; $R_f$ = 0.3 (15% EtOAc in hexane); Yellow solid (26.7 mg, 62% yield); m. p. = 210–214 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 9.28 (s, 1H), 7.79 (d, $J$ = 8.1 Hz, 1H), 7.60 (d, $J$ = 8.3 Hz, 2H), 7.51 (d, $J$ = 8.3 Hz, 1H), 7.45 – 7.38 (m, 5H), 7.37 – 7.33 (m, 1H), 7.26 – 7.24 (m, 2H), 7.19 (t, $J$ = 7.9 Hz, 1H), 7.04 (s, 2H), 5.10 (s, 1H), 1.28 (s, 18H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 189.1, 153.2, 144.6, 140.4, 136.6, 136.5, 135.9, 131.0, 130.4, 128.9, 127.98, 127.94, 127.90, 127.3, 126.9, 126.7, 126.3, 124.9, 122.6, 121.1, 112.1, 34.3, 30.3; FT-IR (thin film, neat): 3634, 3320, 2957, 1601, 746 cm$^{-1}$; HRMS (ESI): *m/z* calcd for $C_{35}H_{35}NaO_2$ $[M+Na]^+$ : 524.2565; found : 524.2575.

**{3-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-*1H*-indol-2-yl}(naphthalen-1-yl)methanone (82j).**



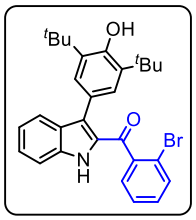
The reaction was performed at 0.086 mmol scale of **79a**; $R_f$ = 0.3 (15% EtOAc in hexane); Yellow solid (35.3 mg, 86% yield); m. p. = 142–144 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 9.63 (s, 1H), 8.28 (d, $J$ = 8.0 Hz, 1H), 7.74 (d, $J$ = 7.6 Hz, 1H), 7.65 (t, $J$ = 9.4 Hz, 2H), 7.55 – 7.46 (m, 3H),7.44 – 7.38 (m, 2H), 7.16 (t, $J$ = 7.5 Hz, 1H), 6.98 (t, $J$ = 7.6 Hz, 1H), 6.75 (s, 2H), 4.93 (s, 1H), 1.10 (s, 18H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 190.1, 152.7, 136.8, 135.7, 135.2, 133.5, 132.1, 130.9 (2C), 128.9, 128.6, 128.4, 128.36, 127.2, 127.0 (2C), 126.3, 125.4, 124.6, 124.1, 122.9, 121.0, 112.1, 33.9, 30.0; FT-IR (thin film, neat): 3628, 3331, 2951, 1615, 758 cm$^{-1}$; HRMS (ESI): *m/z* calcd for $C_{33}H_{33}NNaO_2$ $[M+Na]^+$ : 498.2409; found : 498.2386.

**(2-Chlorophenyl){3-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-*1H*-indol-2-yl}methanone (82k).**



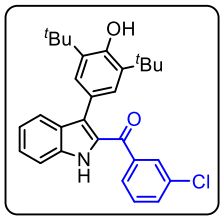
The reaction was performed at 0.086 mmol scale of **79a**; $R_f$ = 0.3 (15% EtOAc in hexane); Yellow solid (30.0 mg, 76% yield); m. p. = 170–172 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 9.40 (s, 1H), 7.56 (d, $J$ = 8.2 Hz, 1H), 7.50 (d, $J$ = 8.3 Hz, 1H), 7.41 (t, $J$ = 7.2 Hz, 1H), 7.16 – 7.11 (m, 3H), 7.08 (t, $J$ = 7.3 Hz, 1H), 6.92 (s, 2H), 6.87 (t, $J$ = 7.4 Hz, 1H), 5.07 (s, 1H), 1.34 (s, 18H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 187.2, 153.0, 138.1, 136.9, 135.2, 131.6, 131.0, 130.8, 130.2, 129.8, 129.1, 128.9, 127.4, 127.3, 125.9, 124.0, 123.0, 121.0, 112.1, 34.2, 30.3; FT-IR (thin film, neat): 3639, 3326, 2957, 1617, 758 cm$^{-1}$; HRMS (ESI): *m/z* calcd for $C_{29}H_{31}ClNO_2$ $[M+H]^+$ : 460.2043; found : 460.2030.

**(2-Bromophenyl){3-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-*1H*-indol-2-yl}methanone (82l).**



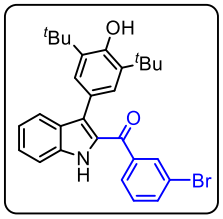
The reaction was performed at 0.086 mmol scale of **79a**; $R_f$ = 0.3 (15% EtOAc in hexane); Yellow solid (37.1 mg, 86% yield); m. p. = 186–188 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 9.47 (s, 1H), 7.55 (d, $J$ = 8.2 Hz, 1H), 7.51 (d, $J$ = 8.3 Hz, 1H), 7.41 (t, $J$ = 7.2 Hz, 1H), 7.32 (d, $J$ = 8.0 Hz, 1H), 7.15 – 7.10 (m, 2H), 7.00 (t, $J$ = 7.6 Hz, 1H), 6.93 – 6.89 (m, 3H), 5.08 (s, 1H), 1.35 (s, 18H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 187.9, 153.0, 139.9, 137.0, 135.2, 133.0, 130.9, 130.7, 130.3, 129.1, 129.0, 127.4, 127.3, 126.4, 124.0, 123.0, 121.0, 120.3, 112.1, 34.2, 30.3; FT-IR (thin film, neat): 3635, 3325, 2956, 1615, 747 cm$^{-1}$; HRMS (ESI): *m/z* calcd for $C_{29}H_{31}BrNO_2$ $[M+H]^+$ : 504.1538; found : 504.1555.

**(3-Chlorophenyl){3-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-*1H*-indol-2-yl}methanone**



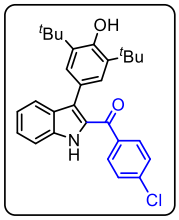
**(82m).** The reaction was performed at 0.086 mmol scale of **79a**; $R_f$ = 0.3 (15% EtOAc in hexane); Yellow solid (33.6 mg, 85% yield); m. p. = 201–203 °C; $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 9.37 (s, 1H), 7.76 (dd, $J$ = 8.2, 0.9 Hz, 1H), 7.51 – 7.46 (m, 3H), 7.44 – 7.40 (m, 1H), ), 7.23 (ddd, $J$ = 8.0, 2.2, 1.1 Hz, 1H), 7.21 – 7.18 (m, 1H), 7.06 (t, $J$ = 7.8 Hz, 1H), 7.00 (s, 2H), 5.16 (s, 1H), 1.33 (s, 18H), $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 188.1, 153.4, 139.6, 136.9, 136.1, 133.8, 131.6, 130.4, 130.2, 129.0, 128.0, 127.8, 127.59, 127.58, 127.0, 124.6, 122.7, 121.2, 112.1, 34.3, 30.3; FT-IR (thin film, neat): 3639, 3338, 2957, 1615, 758 cm$^{-1}$; HRMS (ESI): *m/z* calcd for $C_{29}H_{31}ClNO_2$ $[M+H]^+$ : 460.2043; found : 460.2030.

**(3-Bromophenyl){3-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-*1H*-indol-2-yl}methanone (82n).**



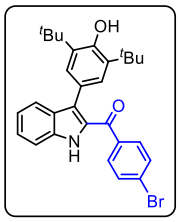
The reaction was performed at 0.086 mmol scale of **79a**; $R_f$ = 0.3 (15% EtOAc in hexane); Yellow solid (30.9 mg, 71% yield); m. p. = 187–189 °C; $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 9.34 (s, 1H), 7.76 (dd, $J$ = 8.2, 1.1 Hz, 1H), 7.63 (t, $J$ = 1.8 Hz, 1H), 7.54 – 7.52 (m, 1H), 7.51 – 7.49 (m, 1H), 7.44 – 7.40 (m, 1H), 7.40 – 7.38 (m, 1H), 7.21 – 7.18 (m, 1H), 7.01 – 6.98 (m, 3H), 5.16 (s, 1H), 1.33 (s, 18H), $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 188.0, 153.4, 139.8, 136.9, 136.1, 134.5, 133.1, 130.3, 129.2, 128.1, 128.0, 127.8, 127.5, 127.0, 124.5, 122.7, 121.8, 121.2, 112.1, 34.3, 30.3; FT-IR (thin film, neat): 3639, 3338, 2957, 1615, 763 cm$^{-1}$; HRMS (ESI): *m/z* calcd for $C_{29}H_{31}BrNO_2$ $[M+H]^+$ : 504.1538; found : 504.1563.

**(4-Chlorophenyl){3-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-*1H*-indol-2-yl}methanone (82o).**



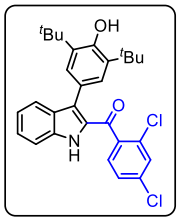
The reaction was performed at 0.086 mmol scale of **79a**; $R_f$ = 0.3 (15% EtOAc in hexane); Yellow solid (33.1 mg, 84% yield); m. p. = 203–205 °C; $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 9.38 (s, 1H), 7.76 (dd, $J$ = 8.2, 1.0 Hz, 1H), 7.50 (td, $J$ = 8.4, 0.9 Hz, 1H), 7.47 – 7.45 (m, 2H), 7.43 – 7.40 (m, 1H), 7.21 – 7.18 (m, 1H), 7.03 – 7.00 (m, 2H), 6.98 (s, 2H), 5.17 (s, 1H), 1.33 (s, 18H), $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 188.2, 153.4, 138.0, 136.8, 136.19, 136.14, 131.2, 130.6, 128.0, 127.9, 127.8, 127.2, 126.9, 124.6, 122.7, 121.2, 112.1, 34.3, 30.3; FT-IR (thin film, neat): 3623, 3346, 2923, 1615, 747 cm$^{-1}$; HRMS (ESI): *m/z* calcd for $C_{29}H_{31}ClNO_2$ $[M+H]^+$ : 460.2043; found : 460.2034.

**(4-Bromophenyl){3-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-*1H*-indol-2-yl}methanone (82p).**



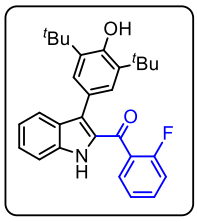
The reaction was performed at 0.086 mmol scale of **79a**; $R_f$ = 0.3 (15% EtOAc in hexane); Yellow solid (35.1 mg, 81% yield); m. p. = 201–203 °C; $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 9.39 (s, 1H), 7.76 (dd, $J$ = 8.1, 1.0 Hz, 1H), 7.50 (td, $J$ = 8.3 0.9 Hz, 1H), 7.43 – 7.40 (m, 1H), 7.39 – 7.37 (m, 2H), 7.21 – 7.19 (m, 1H), 7.19 – 7.17 (m, 2H) 6.97 (s, 2H), 5.18 (s, 1H), 1.33 (s, 18H), $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 188.4, 153.4, 136.8, 136.6, 136.1, 131.3, 130.7, 130.6, 127.92, 127.85, 127.3, 127.0, 126.6, 124.6, 122.7, 121.2, 112.1, 34.3, 30.3; FT-IR (thin film, neat): 3635, 3330, 2963, 1615, 763 cm$^{-1}$; HRMS (ESI): *m/z* calcd for $C_{29}H_{31}BrNO_2$ $[M+H]^+$ : 504.1538; found : 504.1513.

**{3-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-*1H*-indol-2-yl}(2,4-dichlorophenyl)methanone**

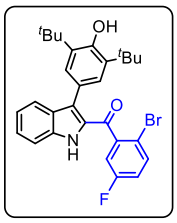


**(82q).** The reaction was performed at 0.086 mmol scale of **79a**; $R_f$ = 0.2 (15% EtOAc in hexane); Yellow solid (33.3 mg, 78% yield); m. p. = 205–209 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 9.41 (s, 1H), 7.56 (dd, $J$ = 8.2, 0.7 Hz, 1H), 7.50 (d, $J$ = 8.4 Hz, 1H), 7.44 – 7.40 (m, 1H), 7.16 – 7.13 (m, 2H), 7.05 (d, $J$ = 8.3 Hz, 1H), 6.91 (s, 2H), 6.82 (dd, $J$ = 8.3, 1.9 Hz, 1H), 5.15 (s, 1H), 1.37 (s, 18H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 189.7, 153.0, 137.6, 137.2, 136.6, 135.7, 132.6, 131.0, 130.8, 128.0, 127.9, 127.7, 126.8, 126.7, 126.6, 125.0, 122.6, 121.0, 112.0, 34.2, 30.2, 21.1; FT-IR (thin film, neat): 3632, 3319, 2956, 1616, 749 cm$^{-1}$; HRMS (ESI): *m/z* calcd for $C_{29}H_{29}Cl_2NO_2$ $[M+Na]^+$ : 516.1473; found : 516.1492.

**{3-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-*1H*-indol-2-yl}(2-fluorophenyl)methanone (82r).**

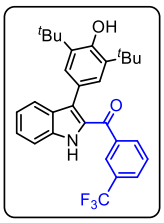


The reaction was performed at 0.086 mmol scale of **79a**; $R_f$ = 0.3 (15% EtOAc in hexane); Yellow solid (30.9 mg, 81% yield); m. p. = 200–202 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 9.35 (s, 1H), 7.64 (d, $J$ = 8.1 Hz, 1H), 7.49 (d, $J$ = 8.3 Hz, 1H), 7.41 (t, $J$ = 7.4 Hz, 1H), 7.30 (t, $J$ = 7.2 Hz, 1H), 7.20 – 7.13 (m, 2H), 6.97 (s, 2H), 6.84 (t, $J$ = 7.5 Hz, 1H), 6.72 (t, $J$ = 9.1 Hz, 1H), 5.09 (s, 1H), 1.33 (s, 18H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 185.4, 159.9 (d, $J_{C\text{-}F}$ = 251.3 Hz), 153.1, 136.8, 135.4, 132.4 (d, $J_{C\text{-}F}$ = 8.3 Hz), 131.4, 130.8 (d, $J_{C\text{-}F}$ = 2.5 Hz), 128.6, 128.5, 127.5 (2C) , 127.2, 124.1, 123.5 (d, $J_{C\text{-}F}$ = 3.4 Hz), 122.8, 121.0, 115.7 (d, $J_{C\text{-}F}$ = 21.5 Hz), 112.1, 34.2, 30.3; $^{19}$F NMR (376 MHz, $CDCl_3$) $\delta$ –112.70; FT-IR (thin film, neat): 3643, 3322, 2955, 1615, 746 cm$^{-1}$; HRMS (ESI): *m/z* calcd for $C_{29}H_{31}FNO_2$ $[M+H]^+$ : 444.2339; found : 444.2361.

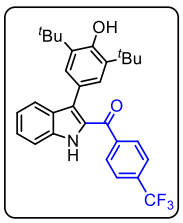
**(2-Bromo-5-fluorophenyl){3-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-*1H*-indol-2-yl}methanone (82s).** 

The reaction was performed at 0.086 mmol scale of **79a**; $R_f$ = 0.2 (15% EtOAc in hexane); Yellow solid (37 mg, 82% yield); m. p. = 170–173 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 9.45 (s, 1H), 7.55 (d, $J$ = 8.2 Hz, 1H), 7.51 (d, $J$ = 8.4 Hz, 1H), 7.43 (t, $J$ = 7.2 Hz, 1H), 7.29 – 7.26 (m, 1H), 7.15 (t, $J$ = 7.5 Hz, 1H), 6.94 (s, 2H), 6.82 (dd, $J$ = 8.3, 2.9 Hz, 1H), 6.72 (td, $J$ = 8.2, 2.9 Hz, 1H), 5.14 (s, 1H), 1.36 (s, 18H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 186.4 (d, $J_{C\text{-}F}$ = 1.6 Hz), 160.8 (d, $J_{C\text{-}F}$ = 247.1 Hz), 153.2, 141.4 (d, $J_{C\text{-}F}$ = 6.7 Hz), 137.1, 135.4, 134.4 (d, $J_{C\text{-}F}$ = 7.6 Hz), 130.3, 129.7, 128.9, 127.5, 127.1, 123.9, 123.1, 121.2, 118.1 (d, $J_{C\text{-}F}$ = 22.2 Hz), 117.6 (d, $J_{C\text{-}F}$ = 24.3 Hz), 114.6 (d, $J_{C\text{-}F}$ = 3.3 Hz), 112.2, 34.2, 30.2; $^{19}$F NMR (376 MHz, $CDCl_3$) $\delta$ –114.59; FT-IR (thin film, neat): 3636, 3329, 2957, 1619, 746 cm$^{-1}$.

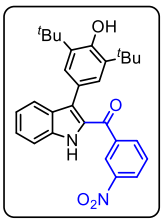
**{3-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-*1H*-indol-2-yl}(3-(trifluoromethyl)phenyl)methanone (82t).** The reaction was performed at 0.086 mmol scale of **79a**; $R_f$ = 0.2 (15% EtOAc in hexane); Yellow solid (38.6 mg, 91% yield); m. p. = 190–193 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 9.36 (s, 1H), 7.84 (d, $J$ = 7.8 Hz, 1H), 7.78 – 7.76 (m, 2H), 7.54 – 7.50 (m, 2H), 7.45 – 7.43 (m, 1H), 7.30 (t, $J$ = 7.8 Hz, 1H), 7.22 – 7.18 (m, 1H), 7.00 (s, 2H), 5.15 (s, 1H), 1.29 (s, 18H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 187.9, 153.4, 138.5, 137.0, 136.1, 132.8, 130.1 (q, $J_{C\text{-}F}$ = 32.5 Hz), 130.0, 128.4, 128.3(q, $J_{C\text{-}F}$ = 3.4 Hz), 127.94, 127.90, 127.5, 127.2, 126.98 (q, $J_{C\text{-}F}$ = 4.0 Hz), 124.1, 123.6 (q, $J_{C\text{-}F}$ = 271.1 Hz), 122.8, 121.3, 112.1, 34.2, 30.2; $^{19}$F NMR (376 MHz, $CDCl_3$) $\delta$ –62.61; FT-IR (thin film, neat): 3647, 3333, 2960, 1620, 746 cm$^{-1}$; HRMS (ESI): *m/z* calcd for $C_{30}H_{30}F_3NO_2$ $[M+Na]^+$ : 516.2126; found : 516.2147.




**{3-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-*1H*-indol-2-yl}(4-(trifluoromethyl)phenyl)methanone (82u).** The reaction was performed at 0.086 mmol scale of **79a**; $R_f$ = 0.2 (15% EtOAc in hexane); Yellow solid (40.8 mg, 95% yield); m. p. = 220–222 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 9.45 (s, 1H), 7.75 (d, $J$ = 8.2 Hz, 1H), 7.61 (d, $J$ = 8.0 Hz, 2H), 7.52 (d, $J$ = 8.3 Hz, 1H), 7.44 (t, $J$ = 7.2 Hz, 1H), 7.31 (d, $J$ = 8.0 Hz, 2H), 7.20 (t, $J$ = 7.7 Hz, 1H), 6.96 (s, 2H), 5.14 (s, 1H), 1.30 (s, 18H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 188.4, 153.4, 141.1, 136.9, 136.1, 133.0, 132.7, 130.6, 129.9, 128.0, 127.9, 127.8, 127.2, 124.5 (q, $J_{C\text{-}F}$ = 3.8 Hz), 123.7 (q, $J_{C\text{-}F}$ = 270.9 Hz), 122.7, 121.3, 112.2, 34.2, 30.3; $^{19}$F NMR (376 MHz, $CDCl_3$) $\delta$ –63.14; FT-IR (thin film, neat): 3643, 3342, 2963, 1615, 758 cm$^{-1}$; HRMS (ESI): *m/z* calcd for $C_{30}H_{31}F_3NO_2$ $[M+H]^+$ : 494.2307; found : 494.2321.

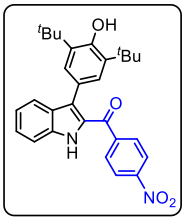


**(3-{3,5-Di-*tert*-butyl-4-hydroxyphenyl}-*1H*-indol-2-yl)(3-nitrophenyl)methanone (82v).**



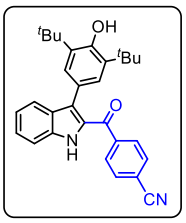
The reaction was performed at 0.086 mmol scale of **79a**; $R_f$ = 0.2 (15% EtOAc in hexane); Yellow solid (31.1 mg, 77% yield); m. p. = 190–192 °C; $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 9.36 (s, 1H), 8.24 (t, *J* = 8.2 Hz, 1H), 8.10 (ddd, *J* = 8.3, 2.3, 1.2 Hz, 1H), 8.00 (dt, *J* = 7.7, 1.4 Hz, 1H), 7.73 (dd, *J* = 8.2, 1.0 Hz, 1H), 7.52 (dt, *J* = 8.4, 0.9 Hz, 1H), 7.46 – 7.43 (m, 1H), 7.40 (t, *J* = 6.5 Hz, 1H), 7.22 – 7.19 (m, 1H), 6.97 (s, 2H), 5.14 (s, 1H), 1.27 (s, 18H), $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 186.9, 153.4, 147.1, 139.3, 137.1, 136.2, 134.7, 130.0, 129.0, 128.3, 127.97, 127.92, 127.5, 125.9, 125.6, 124.2, 122.8, 121.5, 112.2, 34.2, 30.1; FT-IR (thin film, neat): 3615, 3342, 2959, 1610, 758 cm$^{-1}$; HRMS (ESI): *m/z* calcd for $C_{29}H_{31}N_2O_4$ $[M+H]^+$ : 471.2284; found : 471.2296.

**{3-(3,5-Di-*tert*-butyl-4-hydroxyphenyl}-*1H*-indol-2-yl)(4-nitrophenyl)methanone (82w).**



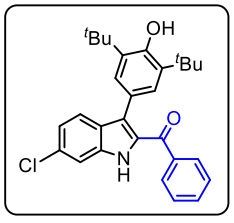
The reaction was performed at 0.086 mmol scale of **79a**; $R_f$ = 0.1 (15% EtOAc in hexane); Yellow solid (35 mg, 86% yield); m. p. = 235–237 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 9.34 (s, 1H), 7.89 – 7.86 (m, 2H), 7.72 (d, *J* = 8.1 Hz, 1H), 7.62 – 7.60 (m, 2H), 7.51 (d, *J* = 8.3 Hz, 1H), 7.47 – 7.43 (m, 1H), 7.22 – 7.19 (m, 1H) 6.93 (s, 2H), 5.15 (s, 1H), 1.29 (s, 18H), $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 187.4, 153.6, 149.0, 143.4, 137.1, 136.2, 130.43, 130.40, 128.5, 127.9, 127.8, 127.6, 124.3, 122.8, 122.5, 121.5, 112.2, 34.2, 30.3; FT-IR (thin film, neat): 3635, 3328, 2957, 1619, 746 cm$^{-1}$; HRMS (ESI): m/z calcd for $C_{29}H_{31}N_2O_4$ $[M+H]^+$ : 471.2284; found : 471.2276.

**4-{3-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-*1H*-indole-2-carbonyl}benzonitrile (82x).** The



reaction was performed at 0.086 mmol scale of **79a**; $R_f$ = 0.2 (15% EtOAc in hexane); Yellow solid (28.8 mg, 74% yield); m. p. = 242–244 °C; $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 9.37 (s, 1H), 7.74 – 7.72 (m, 1H), 7.59 – 7.57 (m, 2H), 7.50 (dt, *J* = 8.4, 1.0 Hz, 1H), 7.46 – 7.42 (m, 1H), 7.35 – 7.32 (m, 2H), 7.22 – 7.19 (m, 1H), 6.95 (s, 2H), 5.20 (s, 1H), 1.32 (s, 18H), $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 187.6, 153.6, 141.8, 137.1, 136.3, 131.2, 130.3, 130.1, 128.1, 127.9, 127.85, 127.5, 124.3, 122.8, 121.4, 118.1, 114.7, 112.2, 34.3, 30.3; FT-IR (thin film, neat): 3635, 3334, 2959, 2234, 1615, 749 cm$^{-1}$; HRMS (ESI): *m/z* calcd for $C_{30}H_{31}N_2O_4$ $[M+H]^+$ : 451.2386; found : 451.2402.

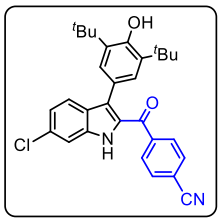
**{6-Chloro-3-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-*1H*-indol-2-yl}(phenyl)methanone**



**(82y).** The reaction was performed at 0.080 mmol scale of **79b**; $R_f$ = 0.3 (15% EtOAc in hexane); Yellow solid (34.1 mg, 89% yield); m. p. =

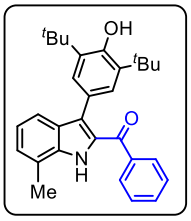
206–208 °C; $^{1}$H NMR (400 MHz, $CDCl_3$) $\delta$ 9.50 (s, 1H), 7.66 (d, $J$ = 8.6 Hz, 1H), 7.53 – 7.50 (m, 3H), 7.29 – 7.26 (m, 1H), 7.14 (d, $J$ = 8.6 Hz, 1H), 7.06 (t, $J$ = 7.5 Hz, 2H), 6.95 (s,2H), 5.12 (s, 1H), 1.30 (s, 18H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 189.5, 153.3, 137.5, 136.9, 136.0, 132.6, 131.9, 131.3, 129.8, 127.7, 127.6, 126.9, 126.6, 124.3, 123.6, 122.1, 111.8, 34.2, 30.3; FT-IR (thin film, neat): 3629, 3334, 2957, 1609, 749 cm$^{-1}$; HRMS (ESI): *m/z* calcd for $C_{29}H_{30}ClNaNO_2$ $[M+Na]^+$ : 482.1863; found : 482.1844.

**4-{6-Chloro-3-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-*1H*-indole-2-carbonyl}benzonitrile**



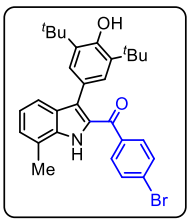

**(82z).** The reaction was performed at 0.080 mmol scale of **79b**; $R_f$ = 0.3 (15% EtOAc in hexane); Yellow solid (29.3 mg, 73% yield); m. p. = 240–242 °C; $^{1}$H NMR (400 MHz, $CDCl_3$) $\delta$ 9.27 (s, 1H), 7.63 (d, $J$ = 8.7 Hz, 1H), 7.55 (d, $J$ = 7.4 Hz, 2H), 7.49 (s, 1H), 7.33 (d, $J$ = 7.7 Hz, 2H), 7.16 (d, $J$ = 8.9 Hz, 1H), 6.90 (s, 2H), 5.21 (s, 1H), 1.30 (s, 18H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 187.3, 153.8, 141.4, 137.2, 136.4, 133.5, 131.2, 130.7, 130.1, 128.0, 127.7, 126.5, 123.9, 123.7, 122.6, 118.0, 114.8, 111.9, 34.3, 30.3; FT-IR (thin film, neat): 3635, 3338, 2992, 2238, 1615, 758 cm$^{-1}$; HRMS (ESI): *m/z* calcd for $C_{30}H_{30}ClN_2O_2$ $[M+H]^+$ : 485.1996; found : 485.1978.

**{3-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-7-methyl-*1H*-indol-2-yl}(phenyl)methanone**



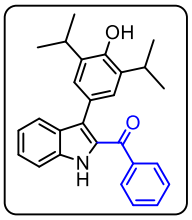

**(82aa).** The reaction was performed at 0.083 mmol scale of **79c**; $R_f$ = 0.3 (15% EtOAc in hexane); Yellow gummy solid (27.9 mg, 77% yield); $^{1}$H NMR (400 MHz, $CDCl_3$) $\delta$ 9.34 (s, 1H), 7.61 (d, $J$ = 8.1 Hz, 1H), 7.53 (d, $J$ = 7.6 Hz, 2H), 7.28 – 7.24 (m, 1H), 7.21 (d, $J$ = 6.9 Hz, 1H), 7.11 (t, $J$ = 7.4 Hz, 1H), 7.05 (t, $J$ = 7.6 Hz, 2H), 6.98 (s, 2H), 5.01 (s, 1H), 2.60 (s, 3H), 1.30 (s, 18H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 189.8, 153.1, 137.9, 136.5, 135.8, 131.7, 130.7, 129.9, 127.8, 127.54, 127.52, 127.47, 126.8, 125.0, 121.5, 121.3, 120.2, 34.2, 30.3, 16.9; FT-IR (thin film, neat): 3640, 2960, 1615, 757 cm$^{-1}$; HRMS (ESI): *m/z* calcd for $C_{30}H_{34}NO_2$ $[M+H]^+$ : 440.2590; found : 440.2571.

**(4-Bromophenyl){3-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-7-methyl-*1H*-indol-2-yl}methanone (82ab).** The reaction was performed at 0.083 mmol scale of **79c**; $R_f$ = 0.3 (15% EtOAc in hexane); Yellow solid (36.6 mg, 85% yield); m. p. = 205–207 °C; $^{1}$H NMR (400 MHz, $CDCl_3$) $\delta$ 9.37 (s, 1H), 7.60 (d, $J$ = 8.1 Hz, 1H), 7.38 (d, $J$ = 8.3 Hz, 2H), 7.21 (d, $J$ = 7.0 Hz, 1H), 7.17 (d, $J$ = 8.3 Hz, 2H), 7.12 (t, $J$ = 7.4 Hz, 1H), 6.96 (s, 2H), 5.17 (s, 1H), 2.59 (s, 3H), 1.33 (s, 18H);



$^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 188.5, 153.3, 136.64, 136.61, 136.0, 131.3, 130.7, 130.5, 127.89, 127.83, 127.5, 127.1, 126.6, 124.8, 121.5, 121.5, 120.2, 34.3, 30.3, 16.9; FT-IR (thin film, neat): 3627, 3334, 2955, 1615, 756 cm$^{-1}$; HRMS (ESI): *m/z* calcd for $C_{30}H_{33}BrNO_2$ $[M+H]^+$ : 518.1695; found : 518.1678.

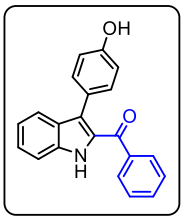
**{3-(4-Hydroxy-3,5-diisopropylphenyl)-*1H*-indol-2-yl}(phenyl)methanone (82ac).** The




reaction was performed at 0.091 mmol scale of **79d**; $R_f$ = 0.2 (15% EtOAc in hexane); Yellow gummy solid (27.1 mg, 75% yield); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 9.20 (s, 1H), 7.72 (d, *J* = 7.5 Hz, 1H), 7.55 (dd, *J* = 8.4, 1.3 Hz, 2H), 7.50 (d, *J* = 8.3 Hz, 1H), 7.43 – 7.39 (m, 1H), 7.25 – 7.22 (m, 1H), 7.20 – 7.16 (m, 1H), 7.05 (t, *J* = 8.0 Hz, 2H), 6.89 (s, 2H), 4.71 (s, 1H), 3.02 (sept, *J* = 6.9 Hz, 2H), 1.10 (d, *J* = 6.8 Hz, 12H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 189.6, 149.1, 137.6, 136.5, 133.7, 131.8, 130.8, 130.0, 128.1, 127.6, 126.6, 126.4, 126.3, 126.1, 122.5, 121.1, 112.0, 27.1, 22.9; FT-IR (thin film, neat): 3662, 3330, 2964, 1609, 754 cm$^{-1}$; HRMS (ESI): *m/z* calcd for $C_{27}H_{27}NNaO_2$ $[M+Na]^+$ : 420.1939; found : 420.1922.

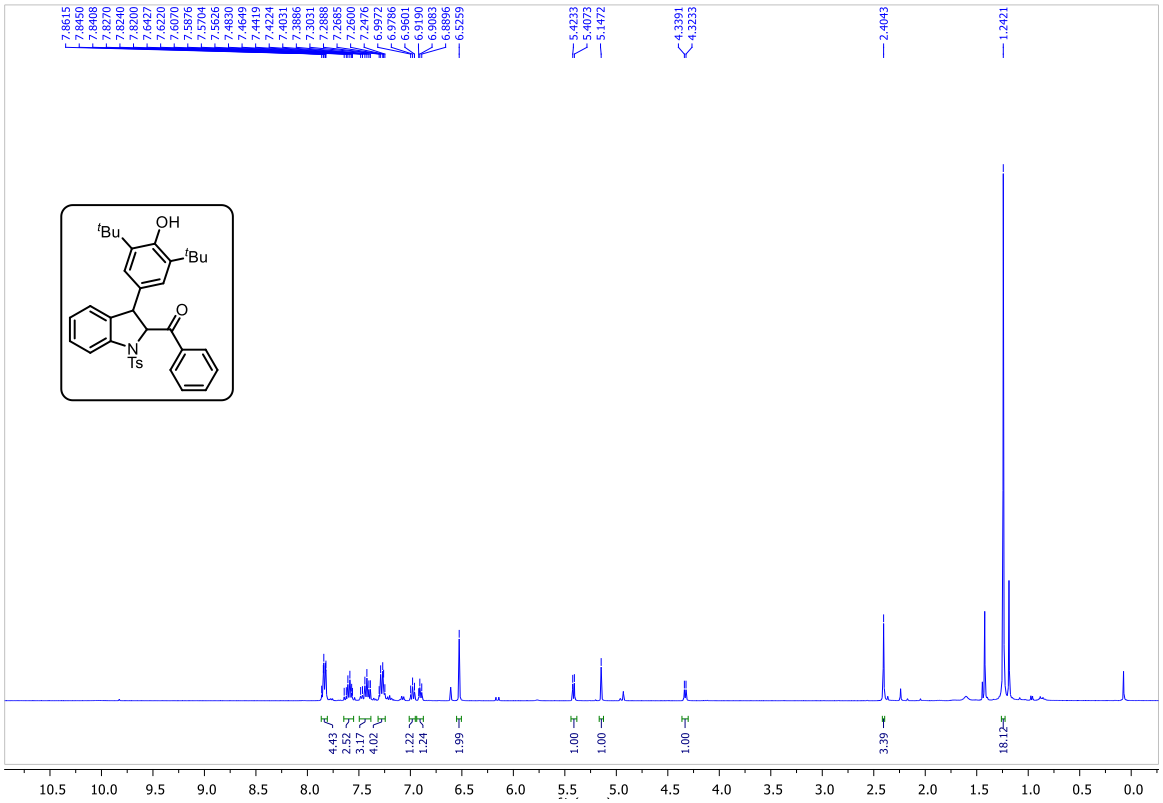
**Procedure for de-*tert*-butylation of 82a**

To a solution of **82a** (40 mg, 0.094 mmol) in dry toulene (2.0 mL) was added $AlCl_3$ (125 mg, 0.94 mmol) under an argon atmosphere. The reaction mixture was stirred at 60 °C for 1 h and then quenched with 5 mL of ice-cold water. It was extracted with EtOAc (3 × 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 an EtOAc/hexane mixture as an eluent to get the pure product **83**. $R_f$ = 0.2 (20% EtOAc in

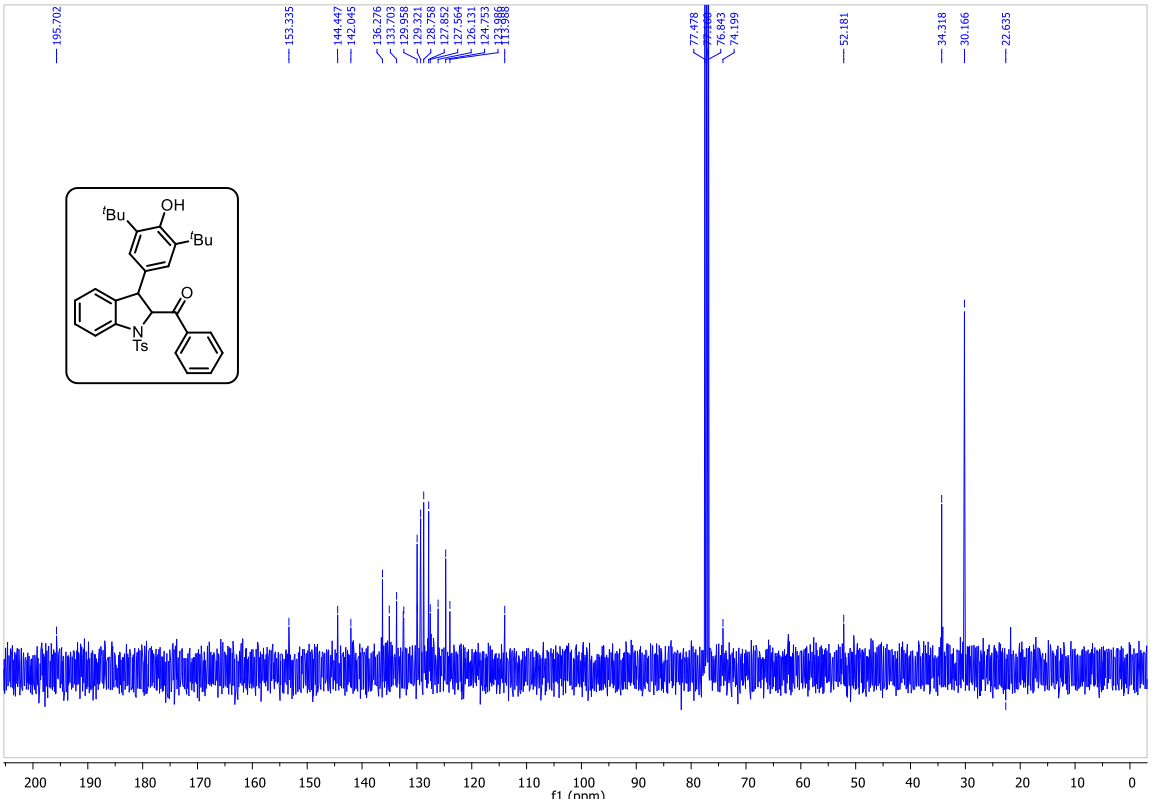



hexane); yellow gummy solid (25.3 mg, 86% yield); $^1$H NMR (400 MHz, DMSO) $\delta$ 11.69 (s, 1H), 9.20 (s, 1H), 7.49 (d, *J* = 7.7 Hz, 1H), 7.42 – 7.37 (m, 3H), 7.33 – 7.27 (m, 3H), 7.16 (t, *J* = 7.6 Hz, 2H), 6.84 (d, *J* = 8.2 Hz, 2H), 6.42 (d, *J* = 8.1 Hz, 2H); $^{13}$C NMR (100 MHz, DMSO) $\delta$ 185.4, 155.8, 138.9, 137.1, 130.9, 130.3, 129.3, 129.0, 127.6, 127.3, 126.4, 125.4, 123.7, 120.7, 118.3, 116.7, 114.5; FT-IR (thin film, neat): 3566, 3272, 2923, 1615, 758 cm$^{-1}$; HRMS (ESI): *m/z* calcd for $C_{21}H_{16}NO_2$ $[M+H]^+$ : 314.1181; found : 314.1174.

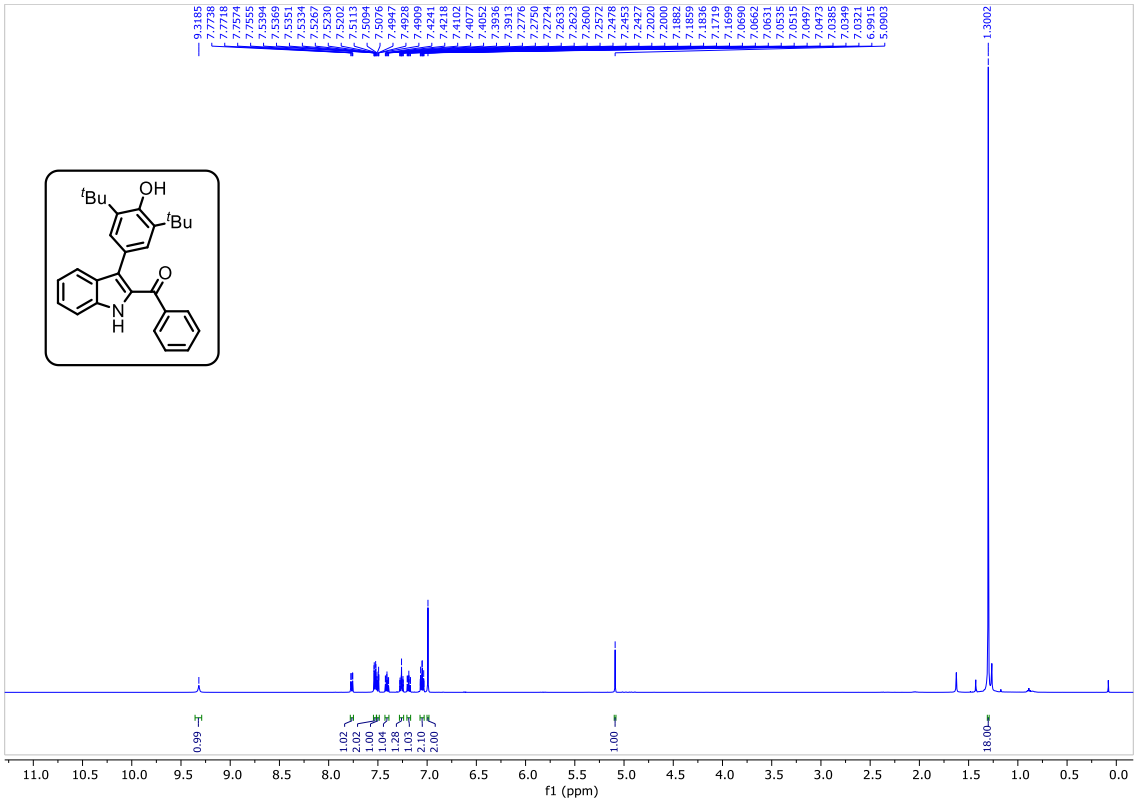
$^{1}$H NMR Spectra of **81**



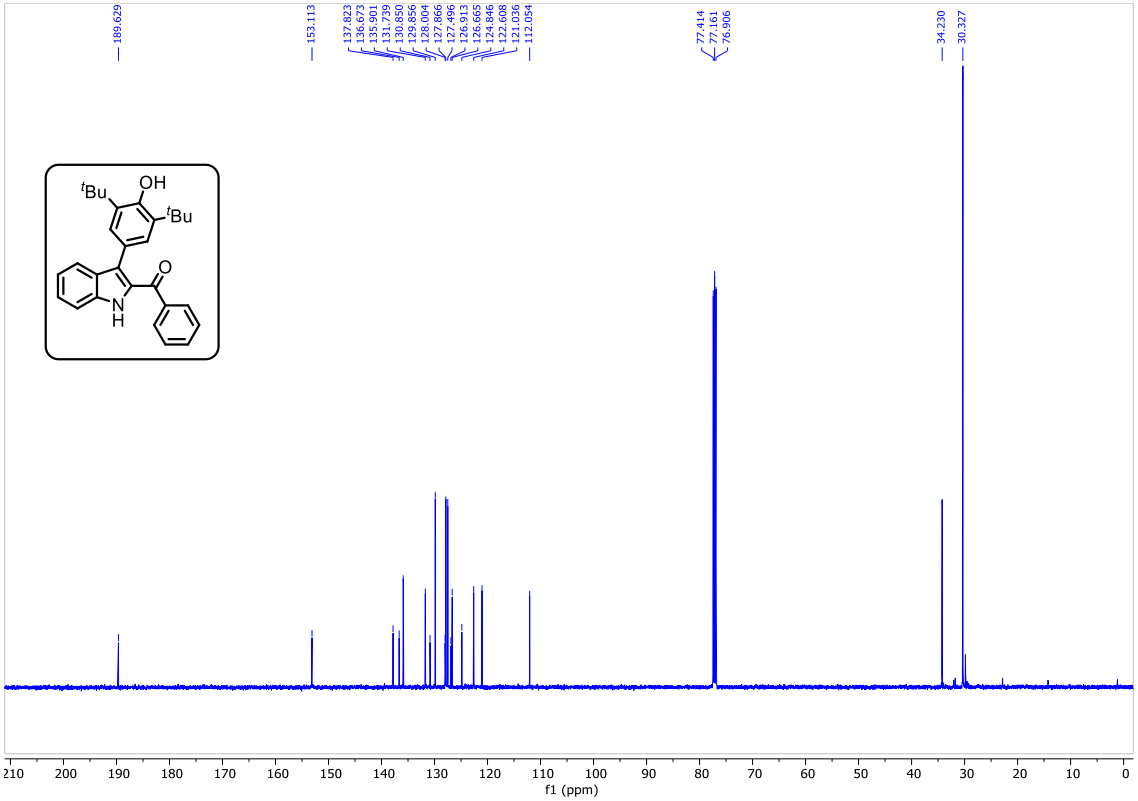

$^{13}$C NMR Spectra of **81**



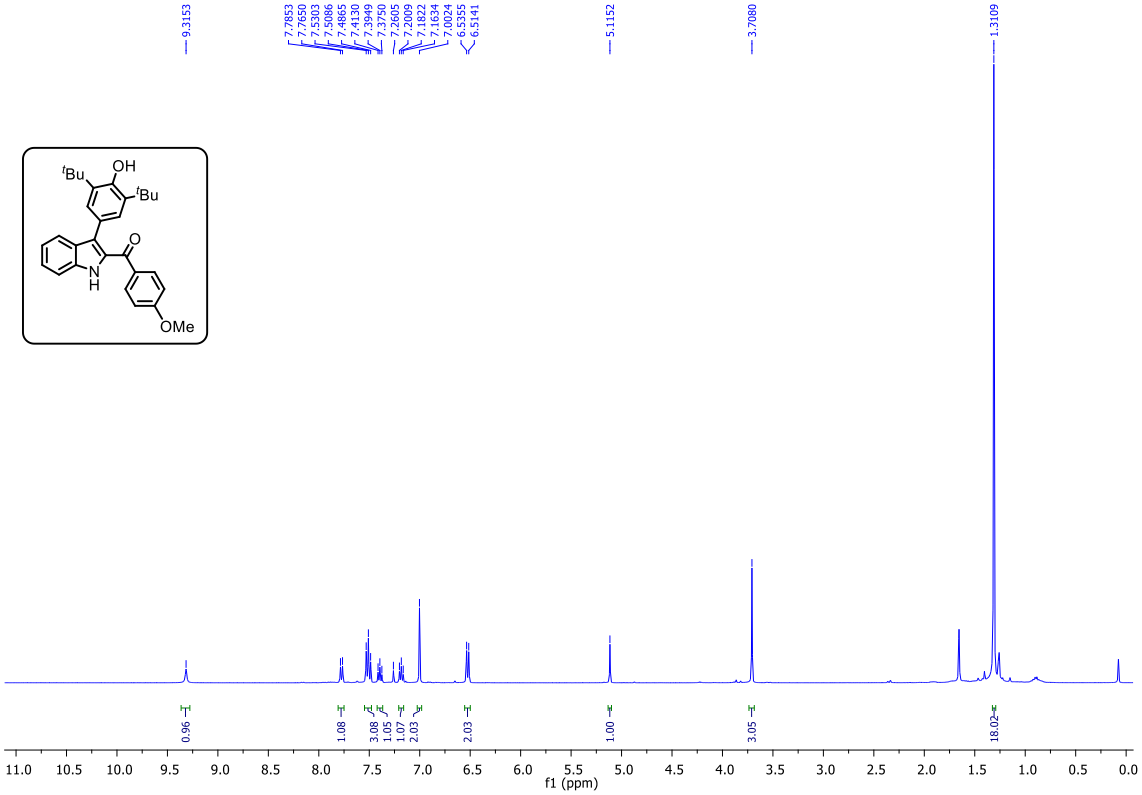
$^{1}$H NMR Spectra of **82a**



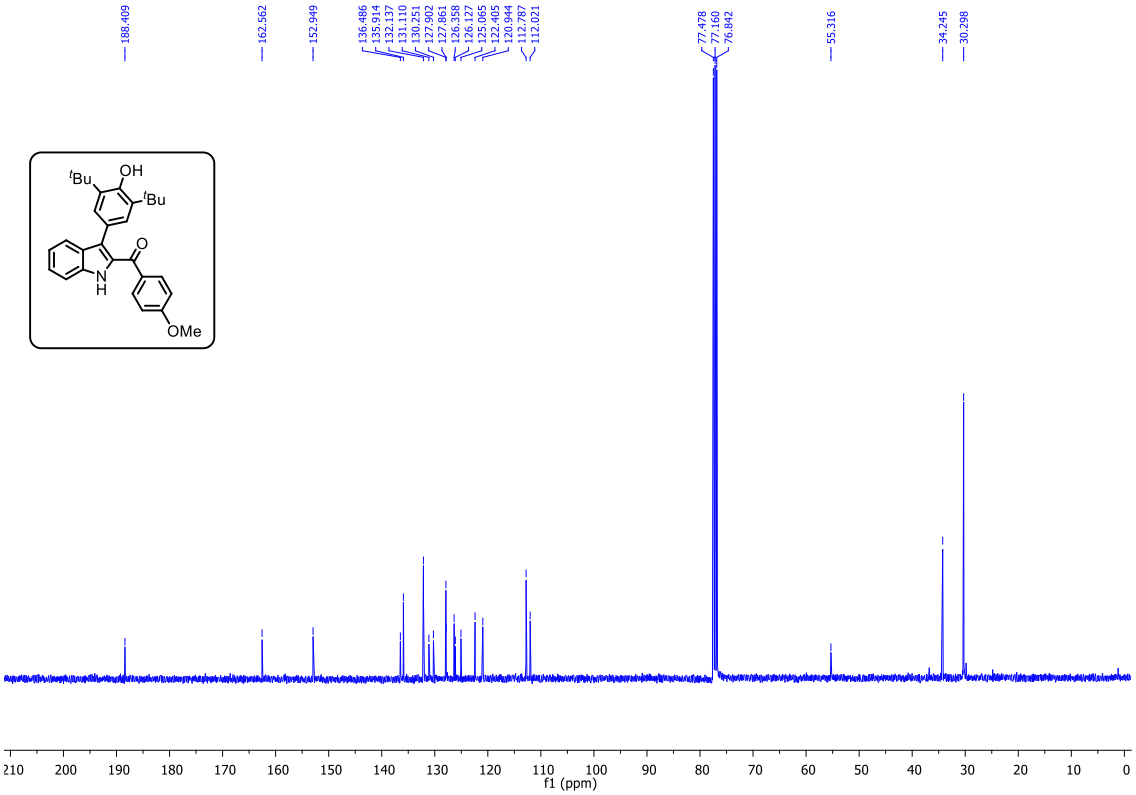

$^{13}$C NMR Spectra of **82a**



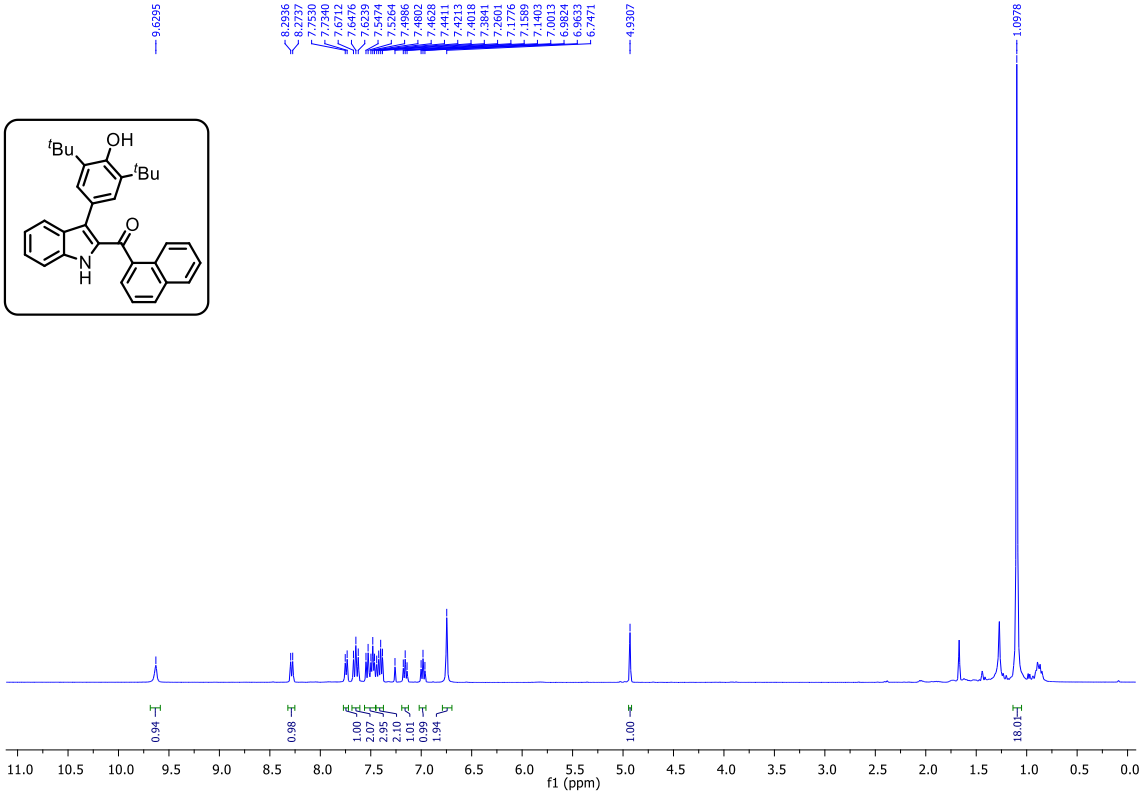
## $^{1}$H NMR Spectra of **82g**



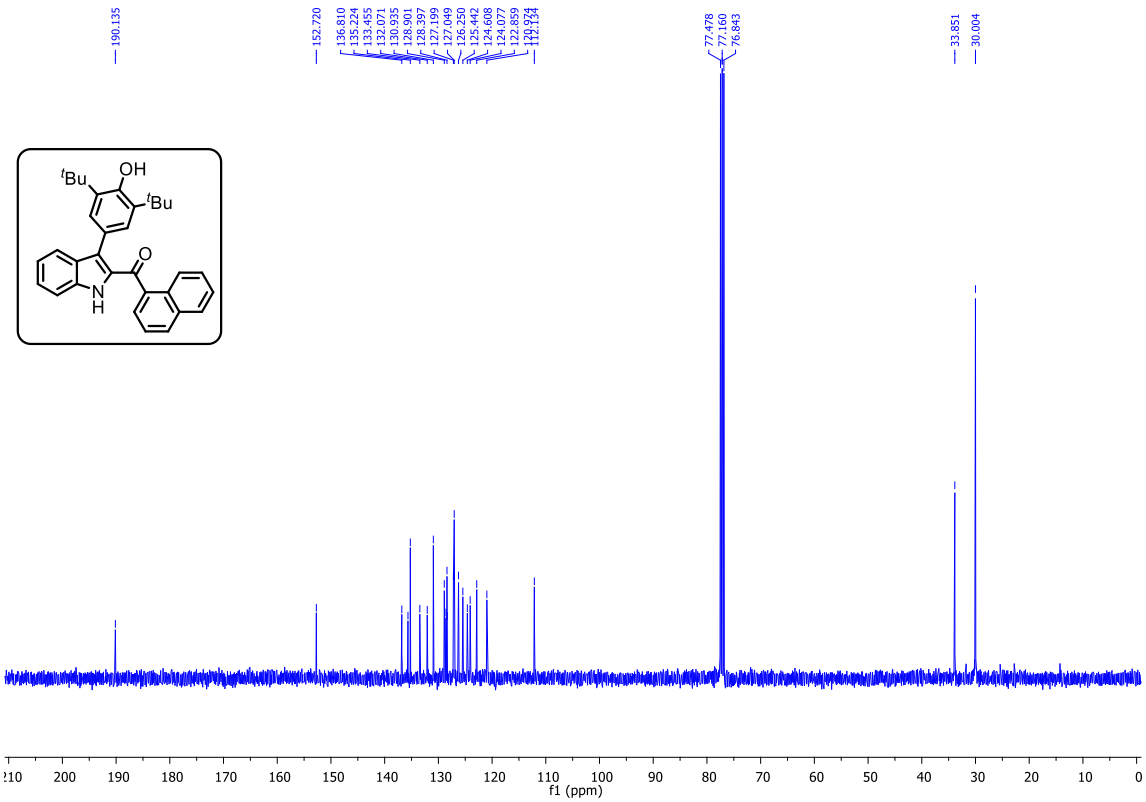

## $^{13}$C NMR Spectra of **82g**



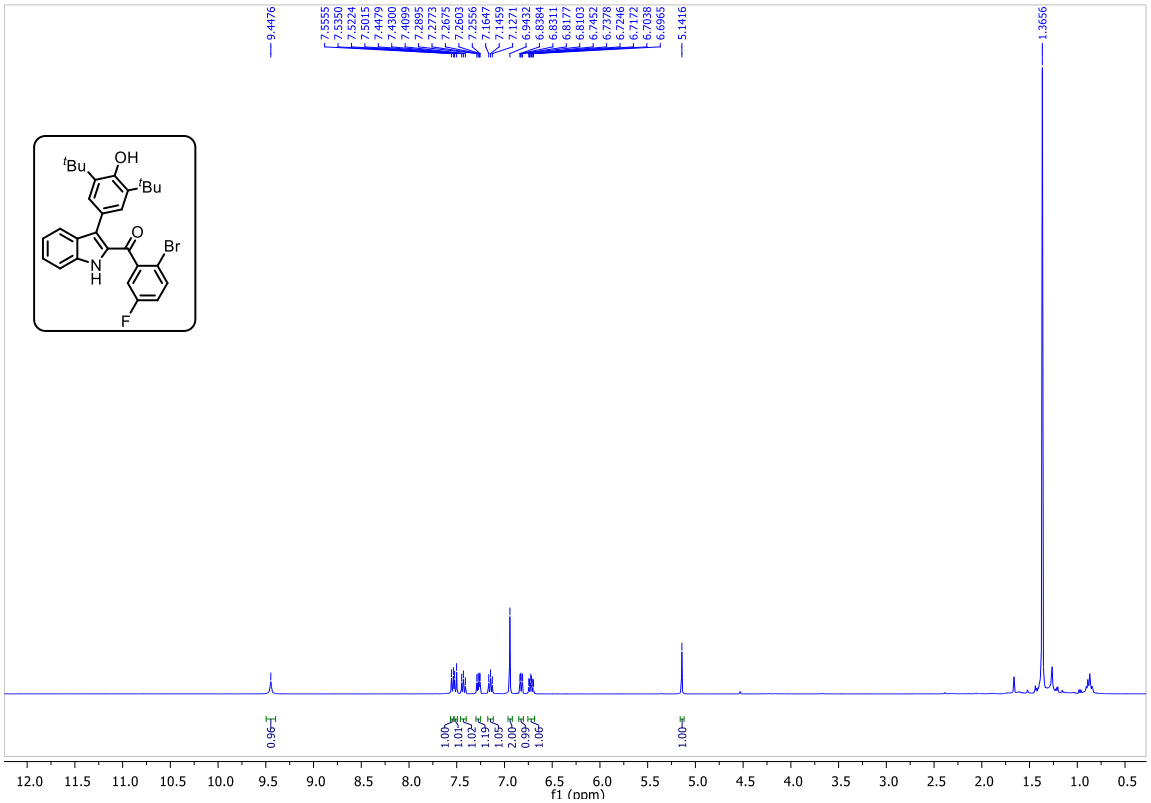
## $^{1}$H NMR Spectra of **82j**



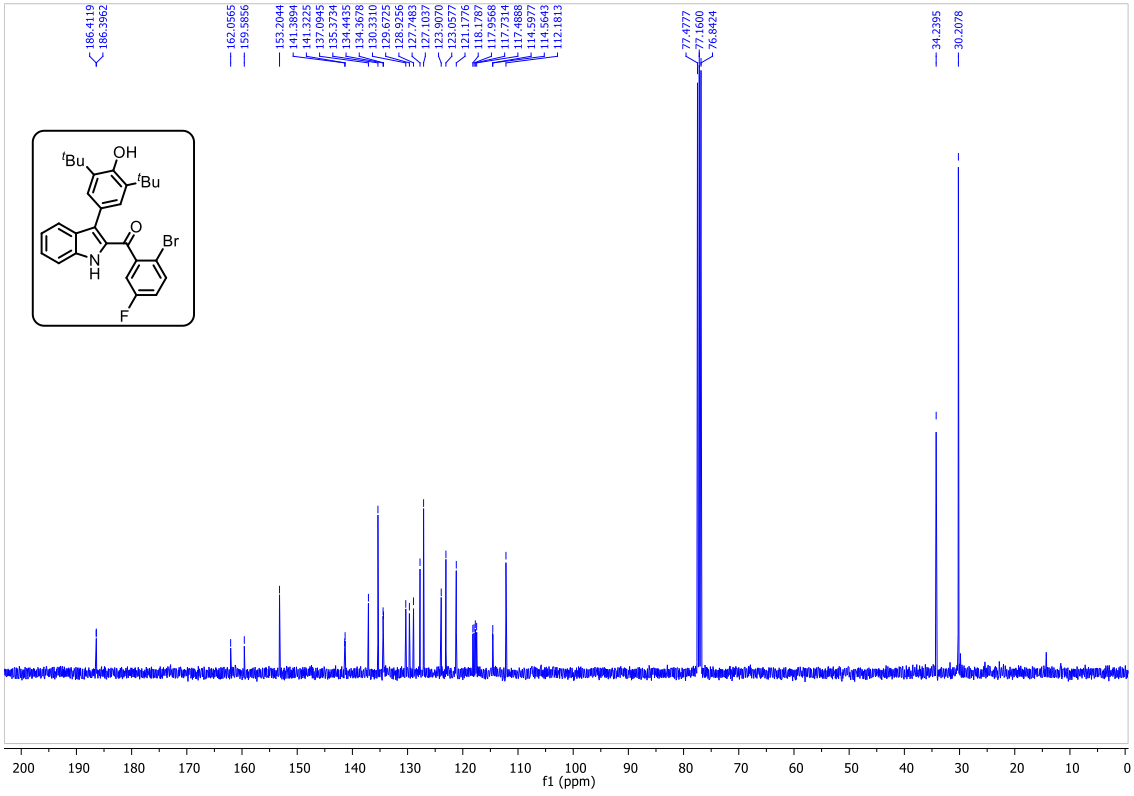

## $^{13}$C NMR Spectra of **82j**



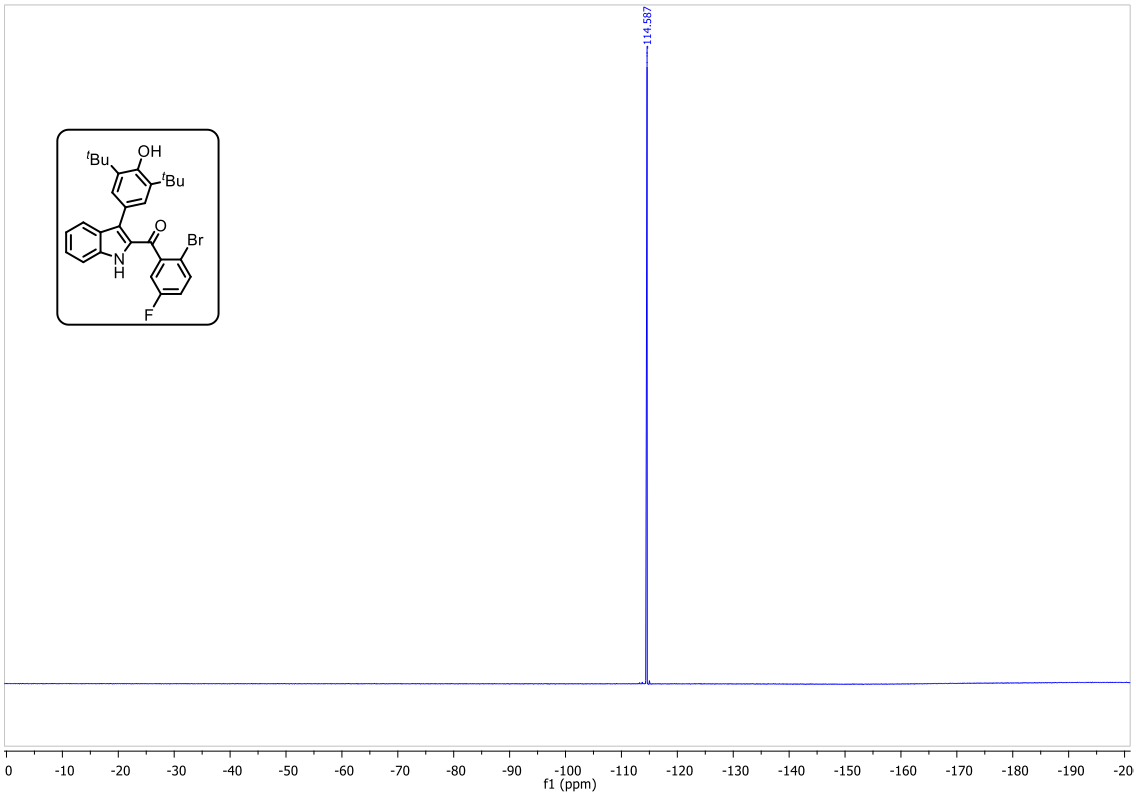
## $^{1}$H NMR Spectra of **82s**



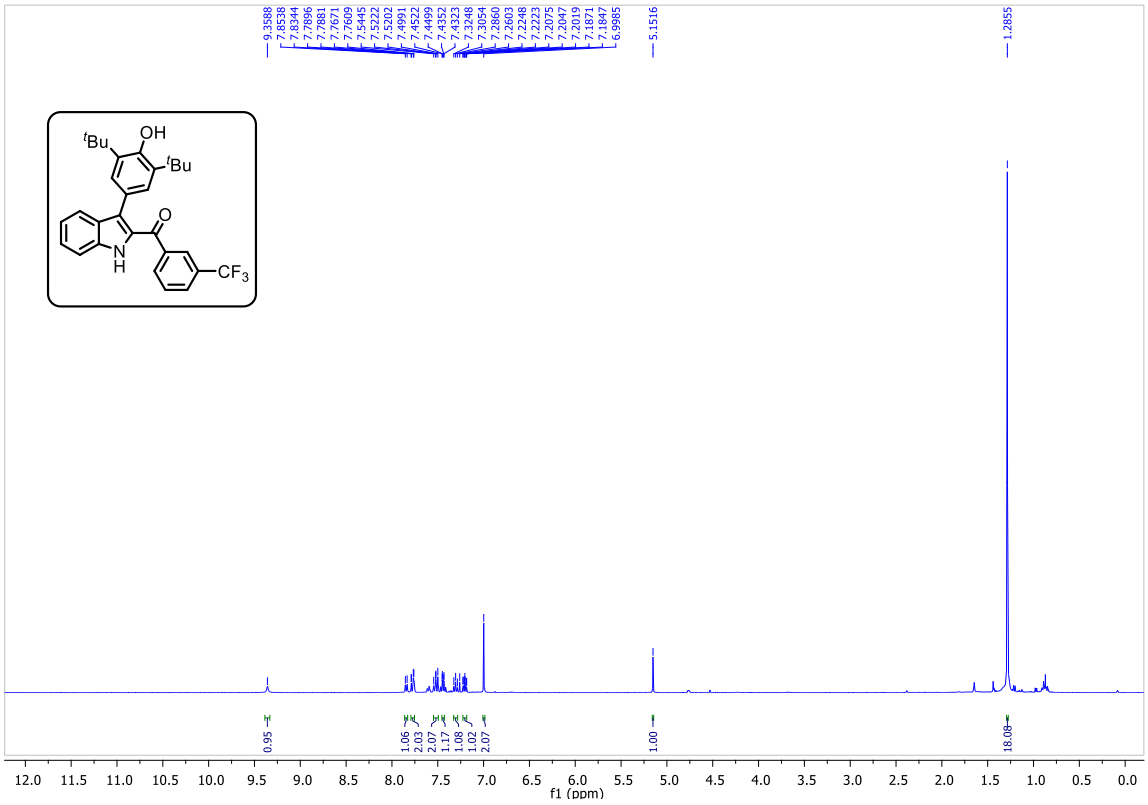

## $^{13}$C NMR Spectra of **82s**



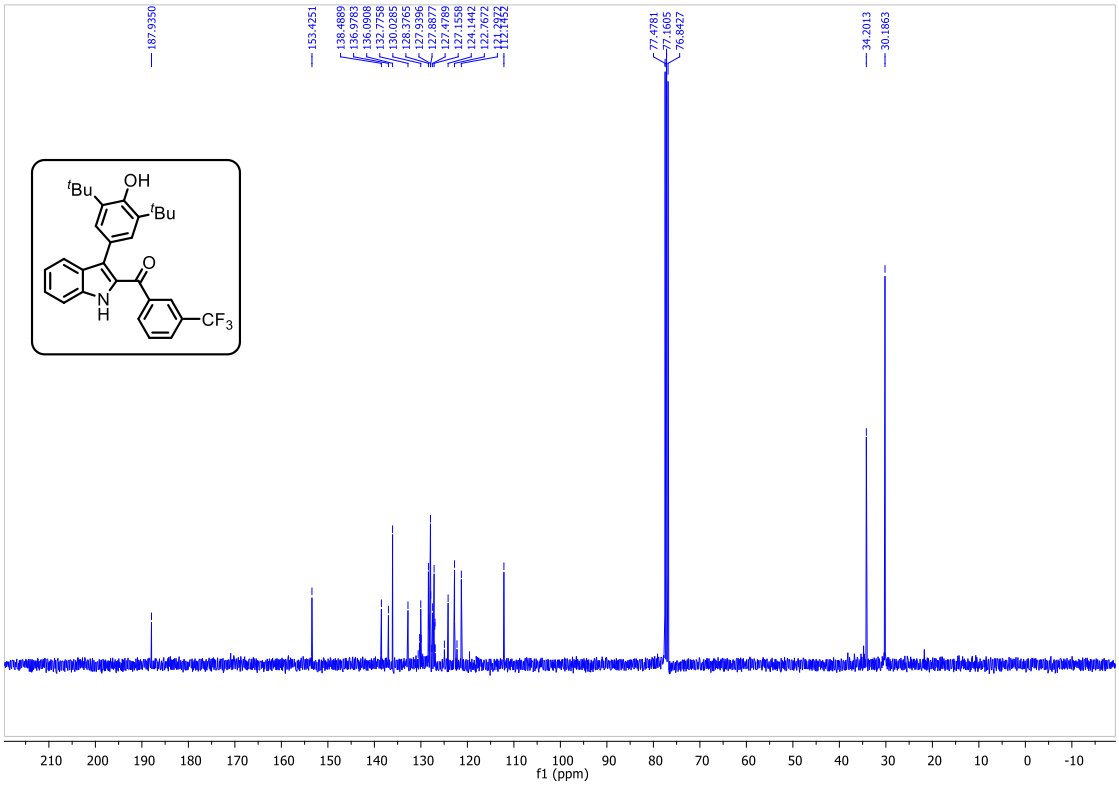
## $^{19}$F NMR Spectra of **82s**



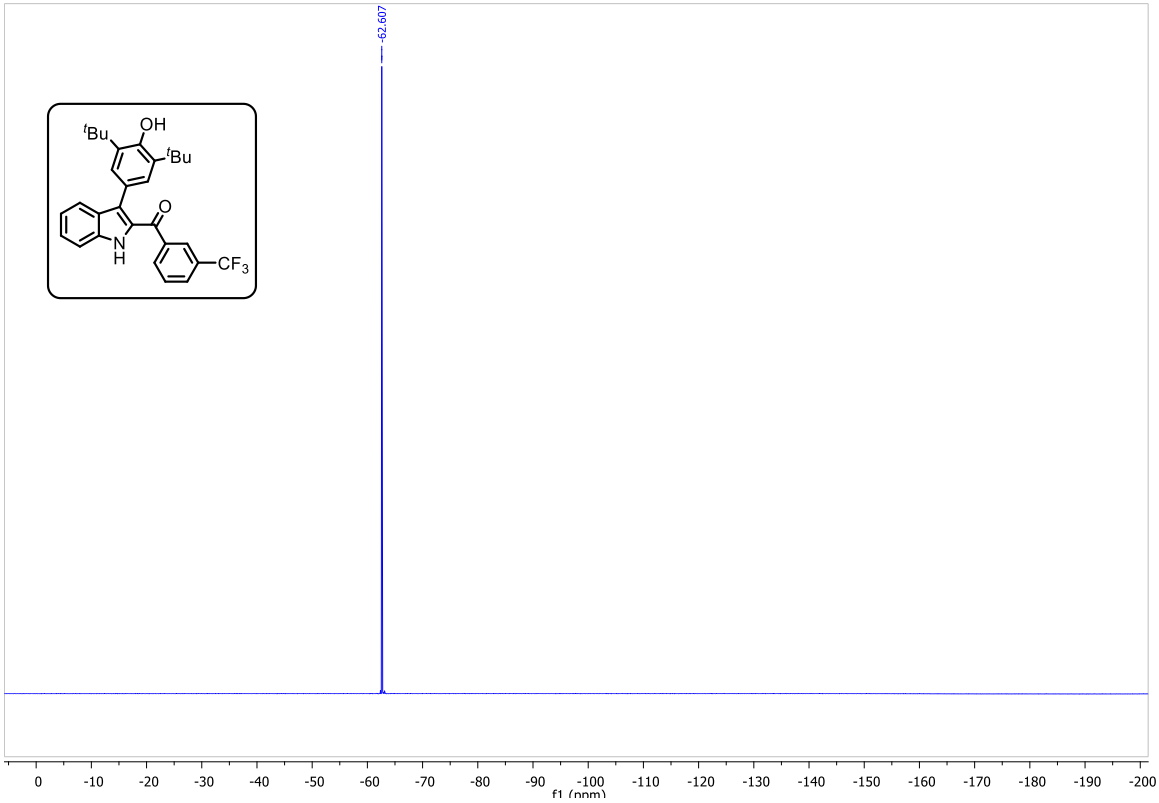

## $^{1}$H NMR Spectra of **82t**



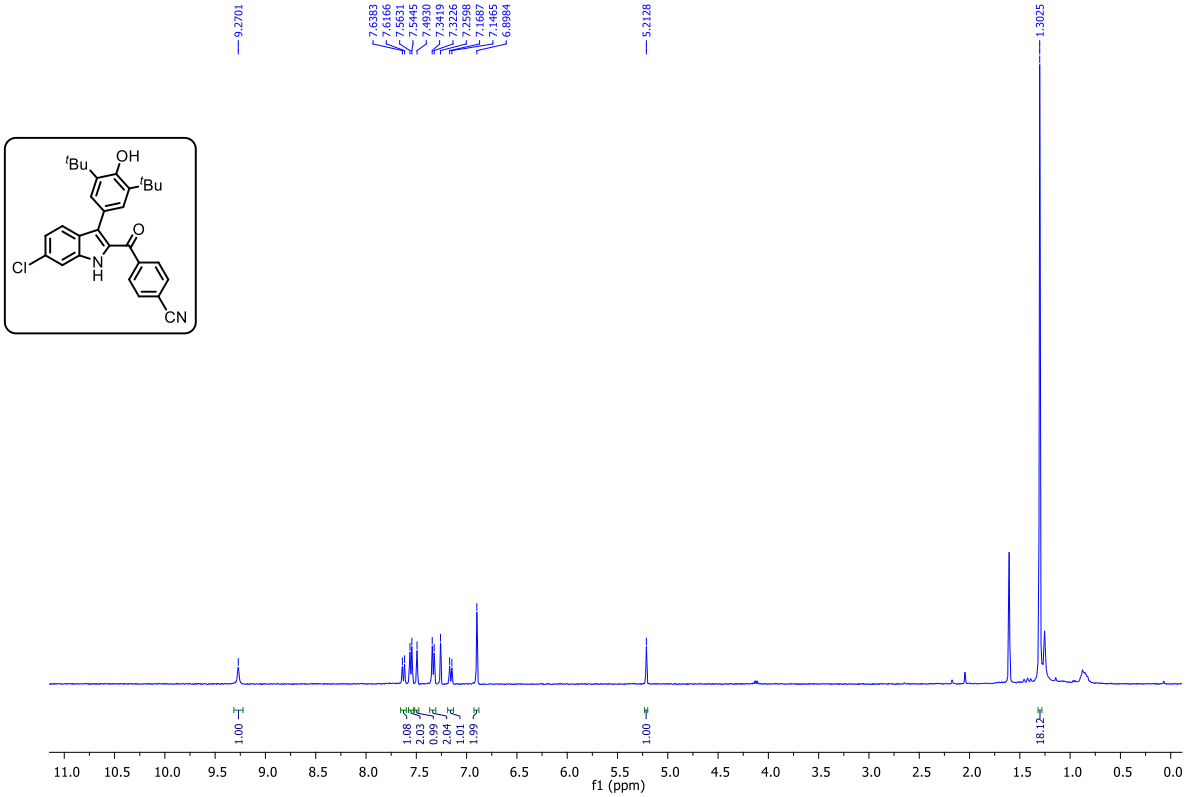
$^{13}$C NMR Spectra of **82t**



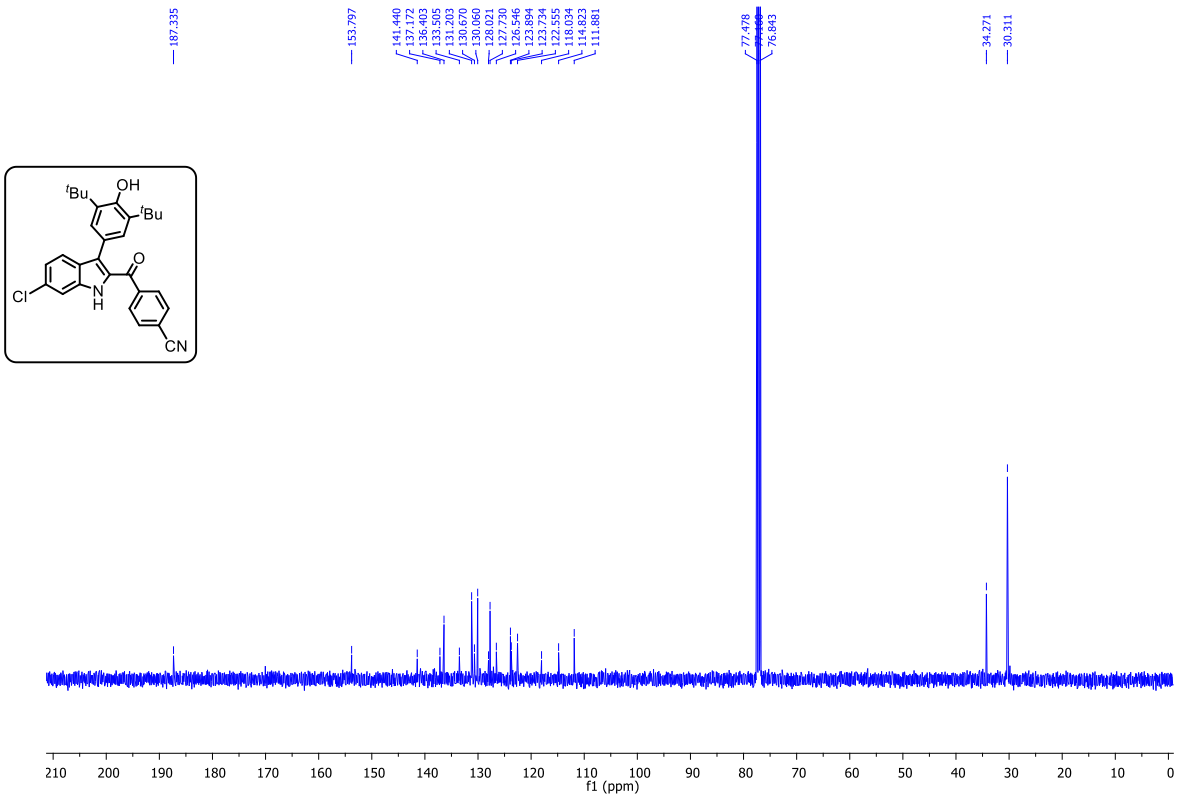

$^{19}$F NMR Spectra of **82t**



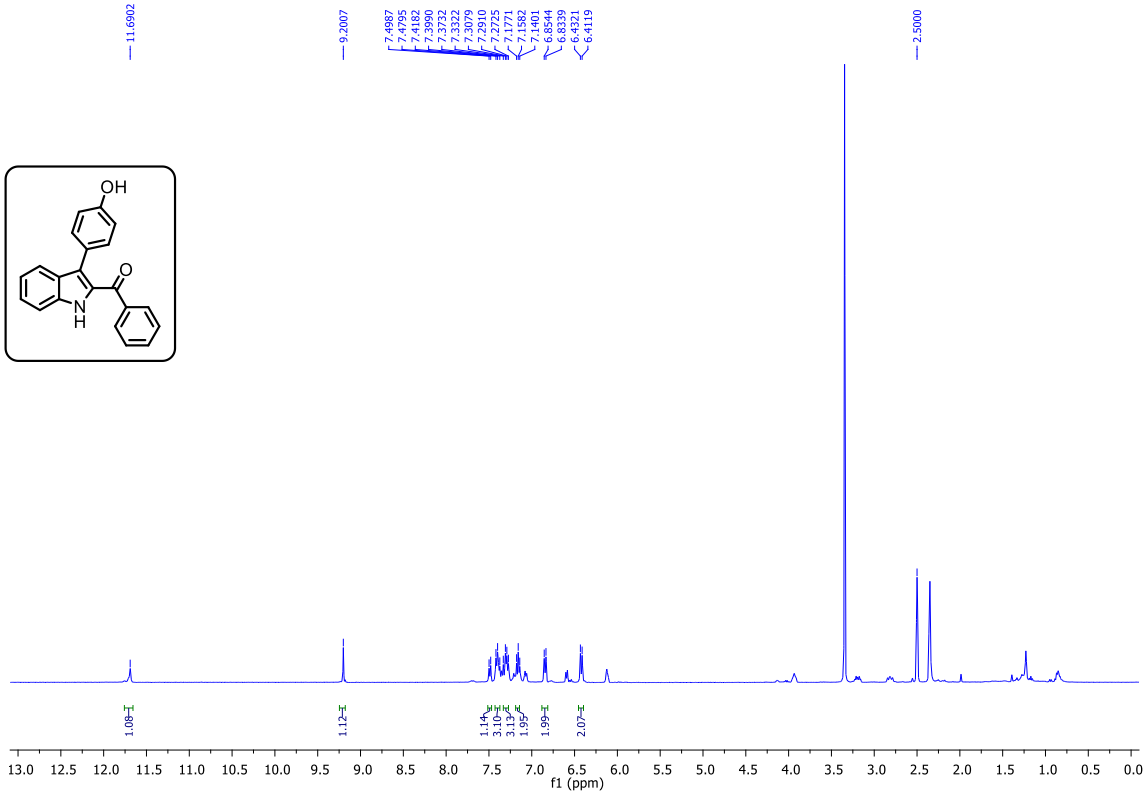
## $^{1}$H NMR Spectra of **82z**



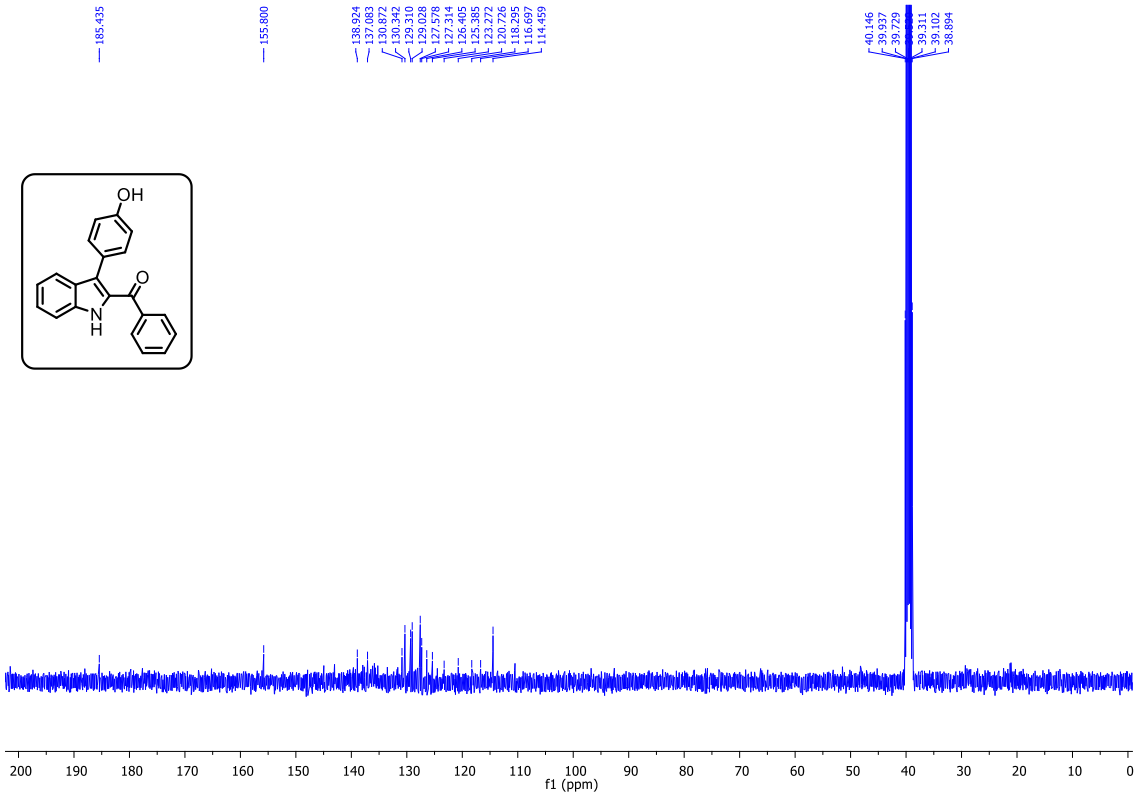

## $^{13}$C NMR Spectra of **82z**



$^{1}$H NMR Spectra of **83**




$^{13}$C NMR Spectra of **83**



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# *Chapter 2*

## Brønsted Acid Mediated Approach Towards Tetrahydroacridinone and Diydroquinoline Derivatives from *in-situ* Generated Aza-*o*-Quinone Methides

### 2.1 Introduction

Nitrogen-containing heterocycles, especially acridine and quinoline derivatives, are prevalent in nature and, due to their distinct functionality, they are found in various natural and unnatural molecules and possess various bioactive properties such as anti-bacterial, anti-malarial, anti-cancer, anti-microbial, etc. (Figure 1).[1] In fact, compound **I** has proved to be effective against microorganisms such as *Bacillus cereus* and *E. coli*, and compound **V** has $IC_{90}$ value more than 100 µM, and shows activity against *M. tuberculosis* H37Rv. Apart from therapeutic properties, acridine derivatives were used as pigment, dyes and are also used as a fluorescent material for biomolecule visualization.[2] In addition, acridine derivatives and their salts are used as organo-photocatalysts in various organic transformations.[3] Due to their versatility, many methods have been demonstrated for the synthesis of acridine and quinoline derivatives. A few of them are discussed below.

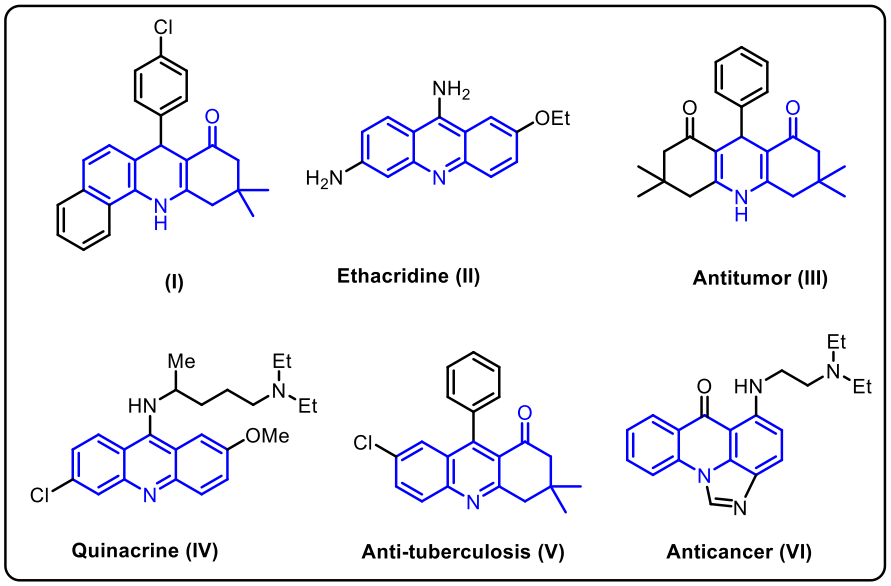
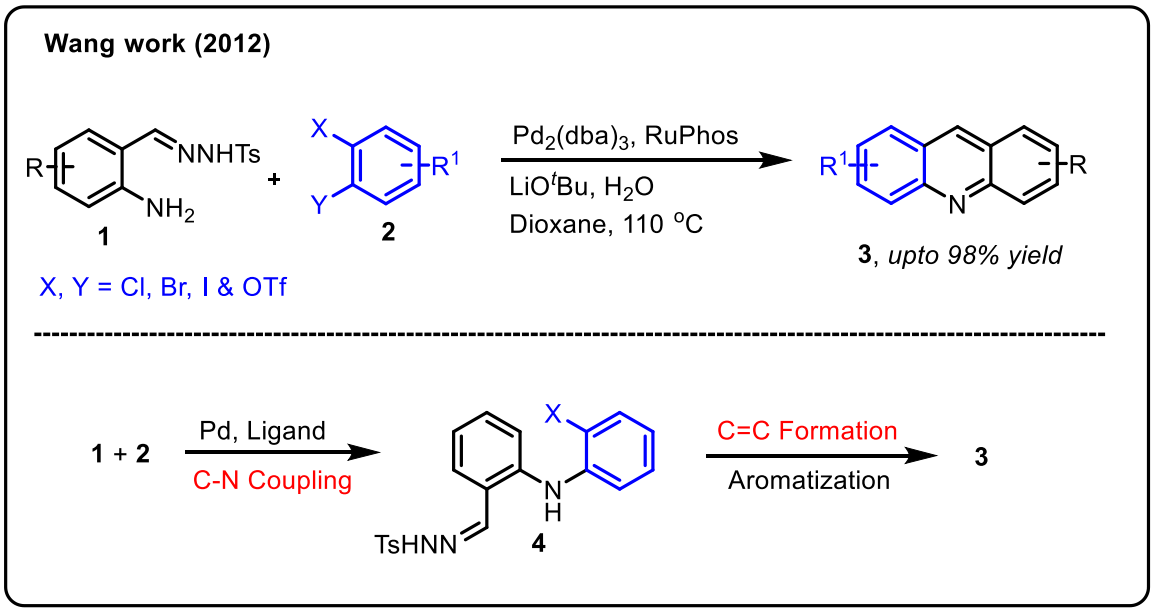



**Figure 1.** Biologically active compounds

## 2.2 Literature reports on the synthesis of acridine and quinoline derivatives

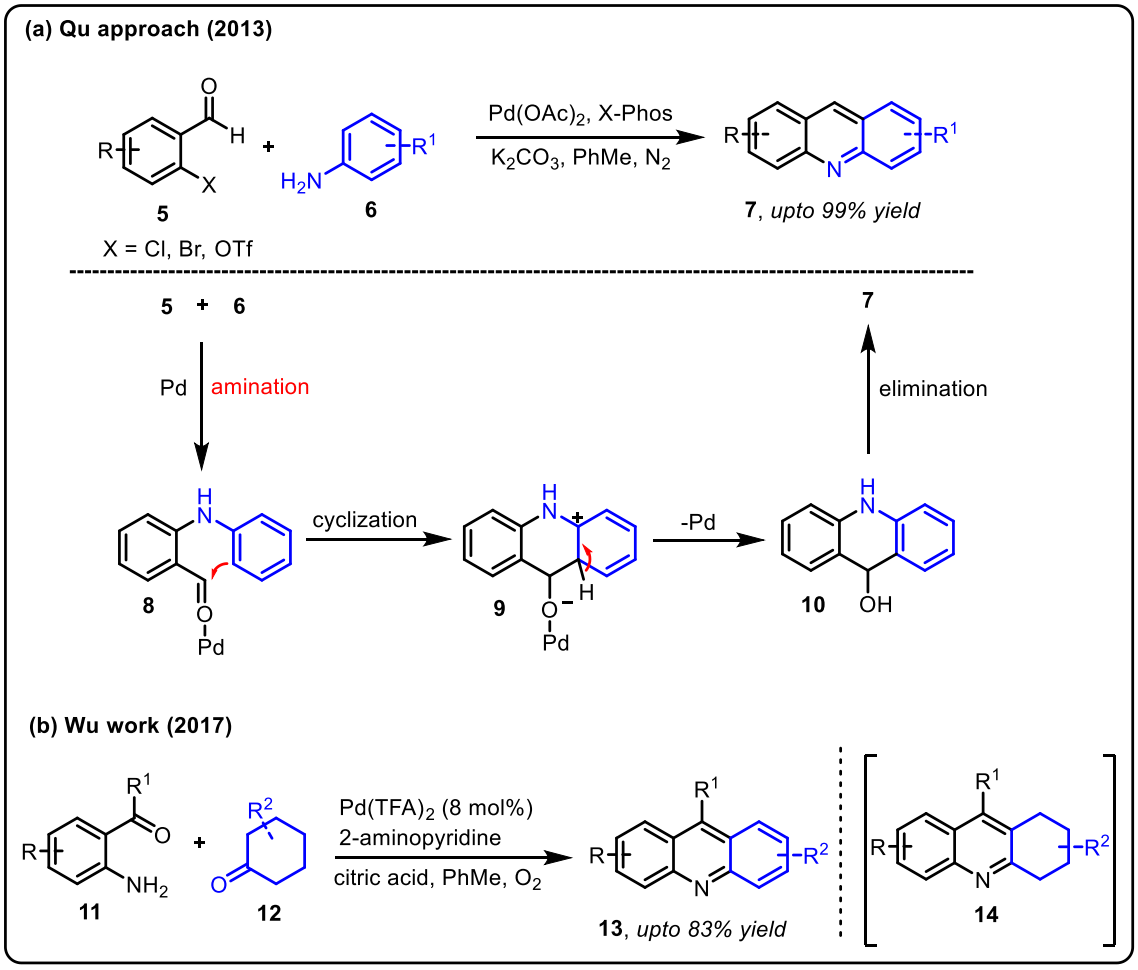
Various synthetic strategies have been developed for the synthesis of acridine and quinoline derivatives. A way back in 1878, for the first time, Brenthsen reported the synthesis of 5-substituted acridine derivatives by heating diarylamines with organic acids or anhydrides in the presence of zinc chloride.[4] After this seminal work, a series of methods employing metals, especially palladium,[5] and other transition metals[6] have been explored for the synthesis of the acridine-based heterocyclic core. For example, Wang and co-workers in 2012 reported the synthesis of acridine derivatives (**3**) using tosylhyrdrazones (**1**) and *ortho*-substituted halo benzenes (**2**) [Scheme 1]. During the mechanistic investigation, two possible pathways were proposed and, in pathway a, **1** & **2,** in the presence of palladium complex, undergo C-N cross-coupling reaction to give intermediate **4,** which upon subsequent C=C bond formation and aromatization gives **3** in excellent yields. In path b, initially, the formation of C=C bond takes places followed by intramolecular C-N cross-coupling, which results in the formation of acridine derivatives (Scheme 1).[5b]




**Scheme 1**. Synthesis of acridine derivatives from tosylhyrdrazones

In line with this, Qu and co-workers have developed an efficient one-pot protocol for the synthesis of acridine derivatives (**7**) from *o*-substituted benzaldehydes (**5**) and substituted anilines (**6**) [Scheme 2, **a**]. A variety of anilines and halo-substituted benzaldehyde were employed under optimal conditions for this transformation, and the respective products **7** were obtained in good to excellent yields. Initially, **5** and **6** undergo an amination reaction in the presence of palladium acetate to give an intermediate **8**, which upon intramolecular

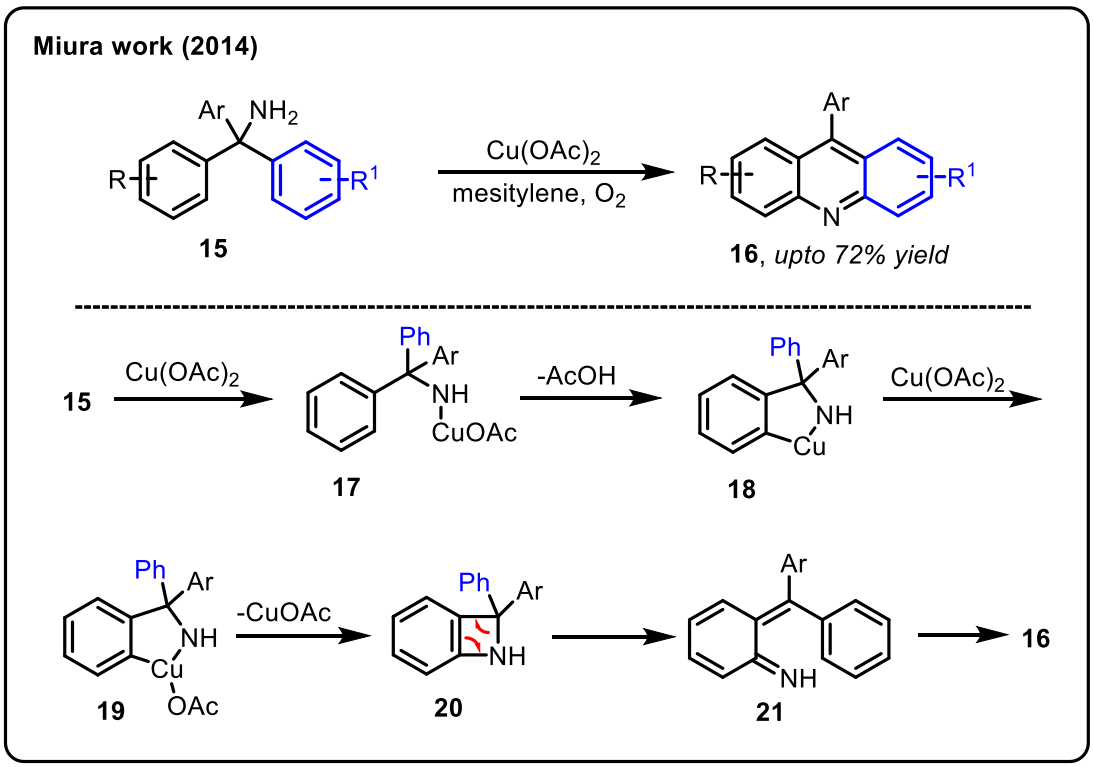
cyclization generates another intermediate **9**. The intermediate **9** then undergoes a series of rearrangements followed by the elimination of water to give **7** in good yield.[5c] Wu's group demonstrated the synthesis of acridine derivatives (**13**) through an annulation reaction between *o*-aminophenyl ketones (**11**) and cyclohexanone derivatives (**12**). In this method, citric acid initially catalyzes the annulation reaction between **11** and **12** to give an intermediate **14**, which upon isomerization and β-hydride elimination cycle under oxygen atmosphere give **13** in moderate to good yields (Scheme 2, **b**).[5e]




**Scheme 2**. Palladium-catalyzed synthesis of acridine derivatives

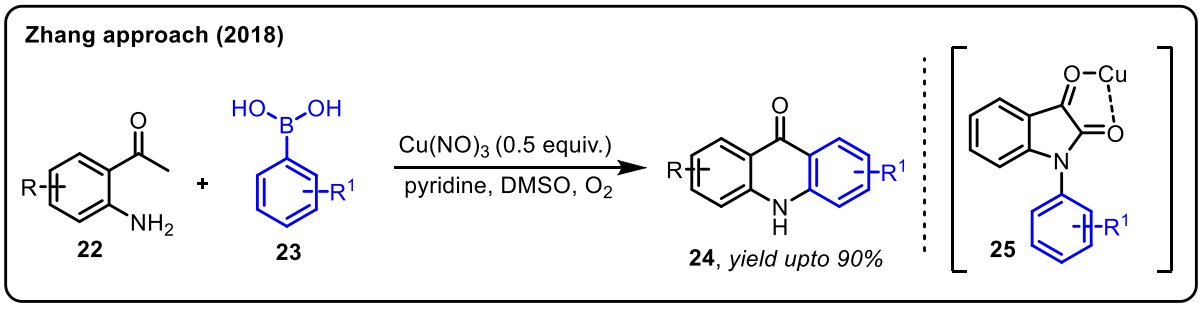
Besides palladium, various other transition metals have also been employed as a catalyst for the synthesis of acridine derivatives. In 2014, Miura and co-workers reported an elegant approach for the synthesis of 9-aryl acridine derivatives (**16**) from tritylamines (**15**) using copper acetate as a catalyst (Scheme 3). Amine functionality of **15** upon coordination with copper catalyst followed by cyclometalation forms an intermediate **18**, which then undergoes a series of rearrangements to give another intermediate **21**. Finally, the

intermediate **21** upon subsequent [4+2] cyclization and dehydrogenation steps gives **16** in good yields (as shown in Scheme 3).[6d]



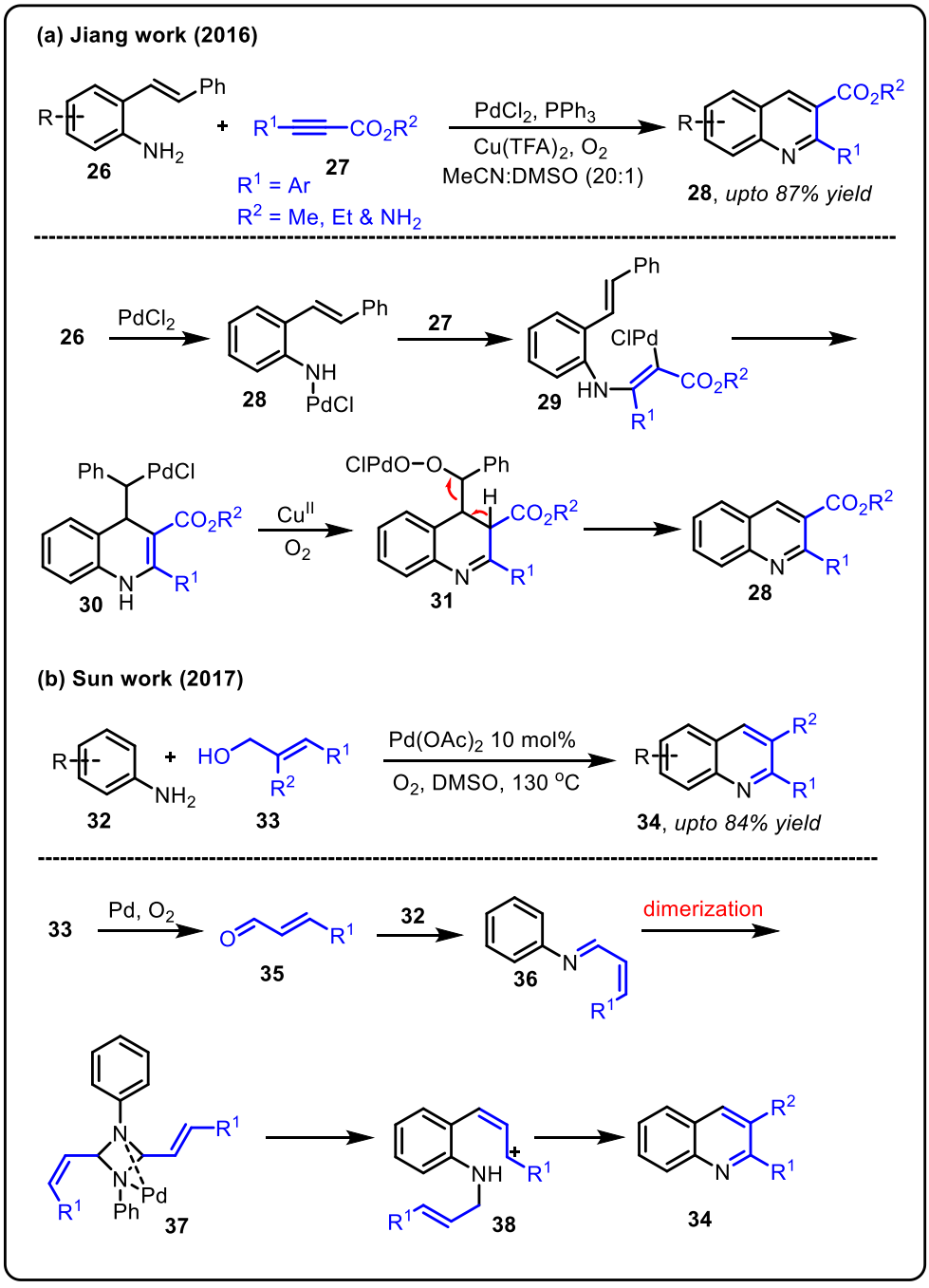

**Scheme 3**. Synthesis of acridine derivatives from tritylamines

Recently Zhang's group has reported a method for the synthesis of acridones derivatives (**24**) from 2-amino acetophenones (**22**) and boronic acids (**23**) under an oxygen atmosphere (Scheme 4). Under basic conditions, **22** and **23** undergo a cross-coupling reaction in the presence of copper nitrate followed by intramolecular cyclization/oxidation sequence generates an isatin-based intermediate **25**. This intermediate **25** upon C-H activation and carbon monoxide extrusion generates the product **24** in excellent yields (Scheme 4).[6e]



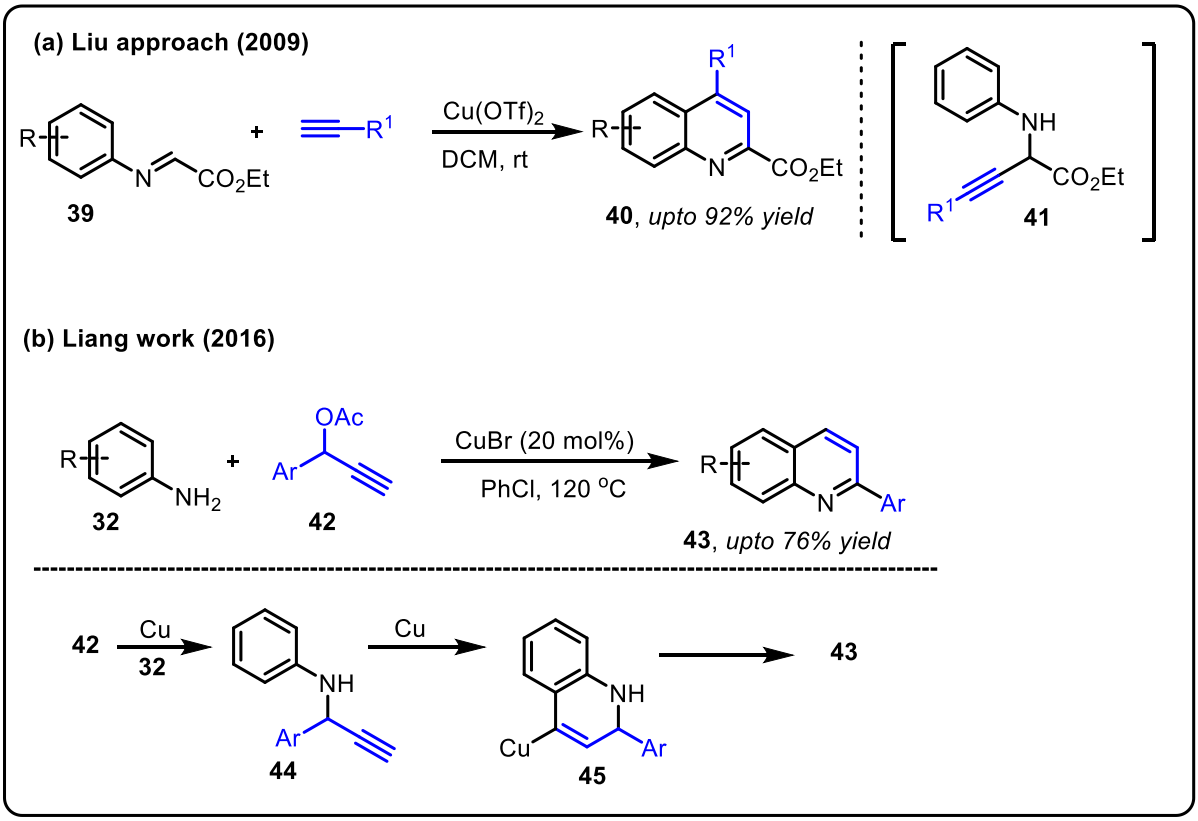

**Scheme 4**. Zhang's approach for the synthesis of acridones derivatives employing transition metal

Similarly, for the synthesis of quinoline derivatives, various methods employing transition metals as catalyst are reported. Jiang and co-workers in 2016 demonstrated a palladium and copper-mediated oxidative annulation of the internal alkynes (**27**) and *o*-substituted anilines (**26**) in the presence of molecular oxygen (Scheme 5, **a**). The authors proposed that initially palladium catalyst interacts with the amine group of **26,** which then react with **27** to give an intermediate **29**. This intermediate **29** upon migratory insertion gives another intermediate **30**, which, in the presence of copper and molecular oxygen gets




**Scheme 5**. Palladium-catalyzed synthesis of quinoline derivatives

rearranged to 2,3- disubstituted quinolone derivatives (**28**) in good yields.[7c] In line with this, Sun's group developed the synthesis of substituted quinolone derivatives (**34**) from anilines (**32**) and allyl alcohols (**33**). A variety of substituted anilines and allyl alcohol were tolerated under optimized conditions, and corresponding products **34** were obtained in moderate to good yields. According to the proposed mechanism by the authors, allyl alcohol, in the presence of palladium, gets oxidized to its corresponding aldehyde **35**, which then reacts with **32** to form an imine intermediate **36**. The imine **36** then undergoes self-dimerization to give diazetidine **37**, which upon irreversible cyclization in the presence of palladium gives a carbocation **38**. This intermediate **38** upon intramolecular cyclization and loss of imine moiety gives the final product **34** (Scheme 5, **b**).[7d]

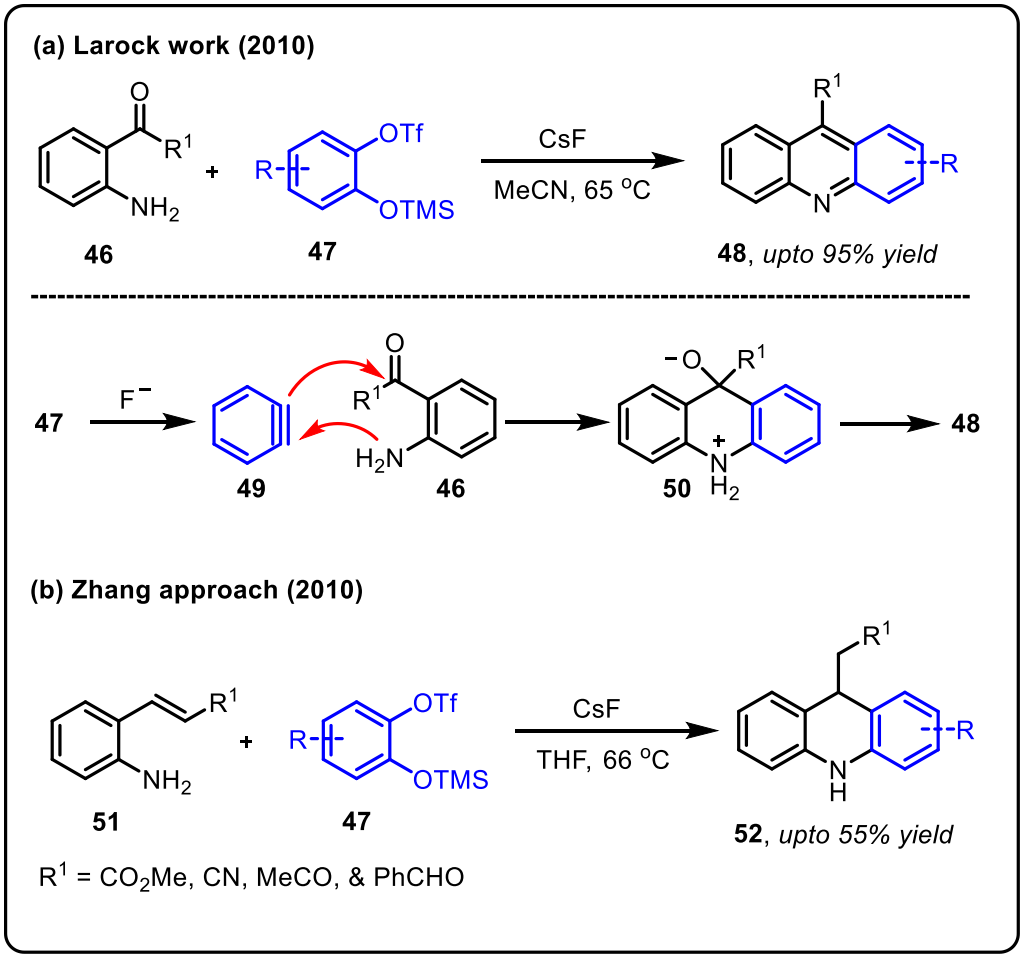



**Scheme 6**. Copper salt mediated approach for the synthesis of quinoline derivatives

Liu's group established an efficient protocol to access substituted quinolines (**40**) from substituted imines (**39**) and terminal alkynes in the presence of copper triflate as a catalyst (Scheme 6, **a**). The reaction proceeds through alkyne addition on **39** followed by oxidative cyclization to produce the product **40**.[7a] Liang and co-workers have also reported a copper-mediated synthesis of 2-aryl quinoline derivatives (**43**) from anilines and acetylene esters (**42**). Initially, in the presence of copper catalyst, amine adds to **42** to give an intermediate **44**,

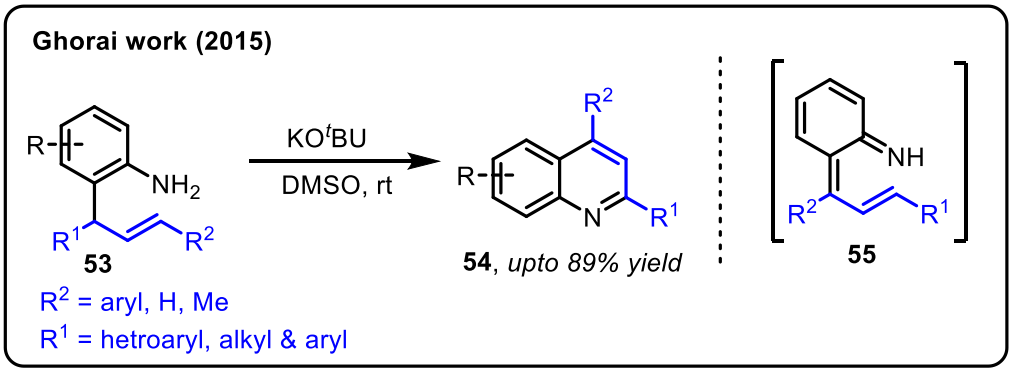
which upon subsequent cyclization followed by an oxidation process generates **43** in good yields (Scheme 6, **b**).[7b]

The syntheses of acridine and quinoline derivatives have also been well explored under metal-free conditions, and in most of those methods, the *in-situ* generated aryne is found to be a key intermediate.[8] For example, Larock and co-workers established an elegant approach for the synthesis of acridine derivatives (**48**) using 2-aminoaryl ketones (**46**) and *in-situ* generated benzyne derivatives, derived from **47**. Initially, *o*-(trimethylsilyl)phenyl triflate **47**, in the presence of a fluoride source, gets converted to benzyne **49**, which upon [4+2] cyclization with **46** generates an intermediate **50**, which the undergoes proton transfer followed by dehydration to afford **48** in excellent yields (Scheme 7, **a**).[8b] Similarly, Zhang's group has also reported the synthesis of dihydroacridine derivatives (**52**) from 2-aminophenyl acrylate derivatives (**51**) and **47** employing the same strategy. A wide variety of benzyne precursors and acrylate derivatives were employed under the optimal reaction condition, and corresponding products (**52**) were obtained in moderate to good yields (Scheme 7, **b**).[8a]



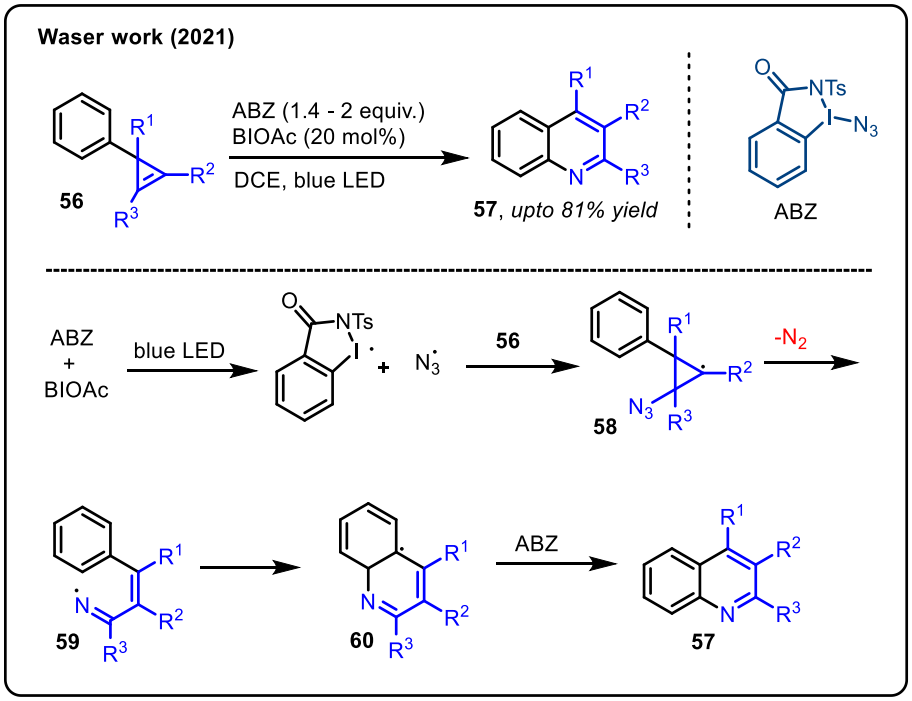

**Scheme 7**. Synthesis of acridine derivatives from *in-situ* generated aryne intermediate

In 2015, Ghorai's group developed a base-mediated approach to the synthesis of quinoline derivatives (**54**) from 2-cinnamylaniline derivatives (**53**). The reaction proceeds through an intermediate **55** (Scheme 8).[9a]




**Scheme 8**. Metal-free approach for the synthesis of quinoline derivatives

Recently, Waser and co-workers have demonstrated a photochemical approach for the synthesis of quinoline derivatives (**57**) from aryl-substituted cyclopropenes (**56**). Upon irradiation of blue LED, BIOAc (acetoxybenziodoxolone) and ABZ generate iodanyl and azidyl radicals, respectively. Iodanyl radical then reacts with **56** to generate a radical intermediate **58**, which upon rearrangement and loss of nitrogen molecule, gives intermediate **59**. The intermediate **59** upon cyclization followed by oxidation-deprotonation step gives the final product **57** in good yields (Scheme 9).[9d]

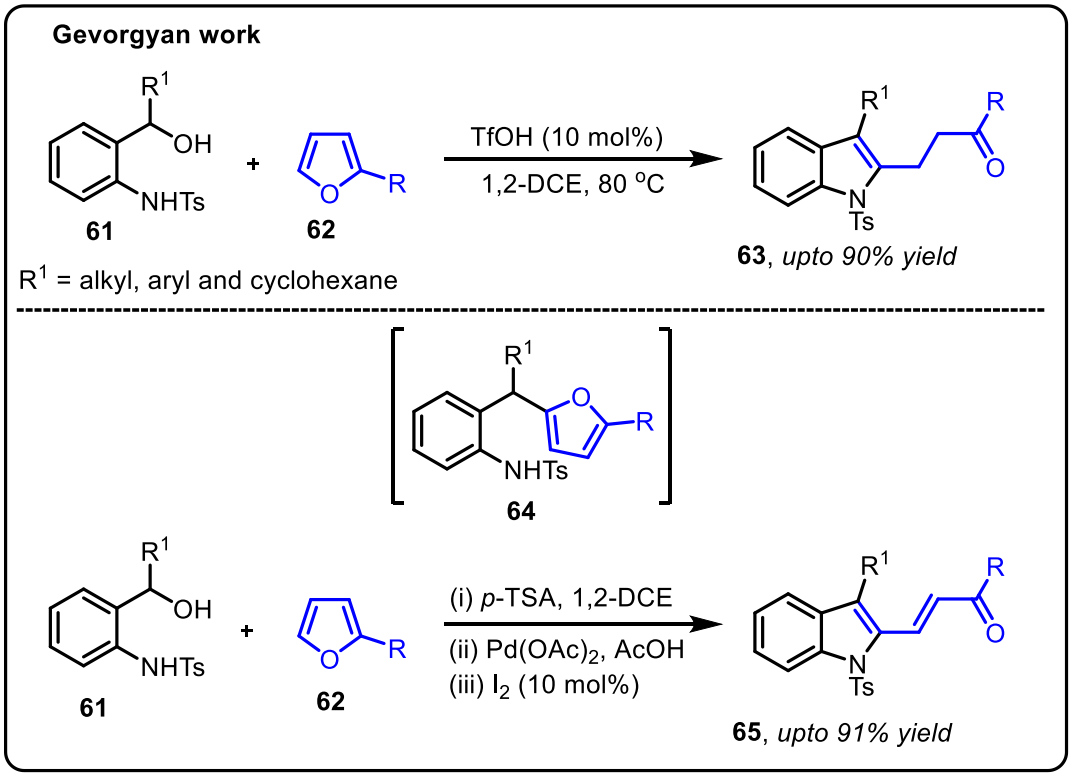



**Scheme 9**. Photochemical approach for the synthesis of substituted quinoline derivatives

## 2.3 Literature reports on the reactivity of 2-aminobenzyl alcohol

2-aminobenzyl alcohol has proved to be an effective substrate for constructing nitrogen-containing heterocyclic compounds.[10-12] In the presence of a Brønsted acid or in the presence of heat and light, 2-aminobenzyl alcohol gets isomerized to aza *ortho*-quinone methides, thus making it a more reactive species.[10g] Various research groups have explored 2-aminobenzyl alcohol for the synthesis of diaryl and triarylmethanes as well as nitrogen-containing heterocyclic compounds. A few of them are discussed below.

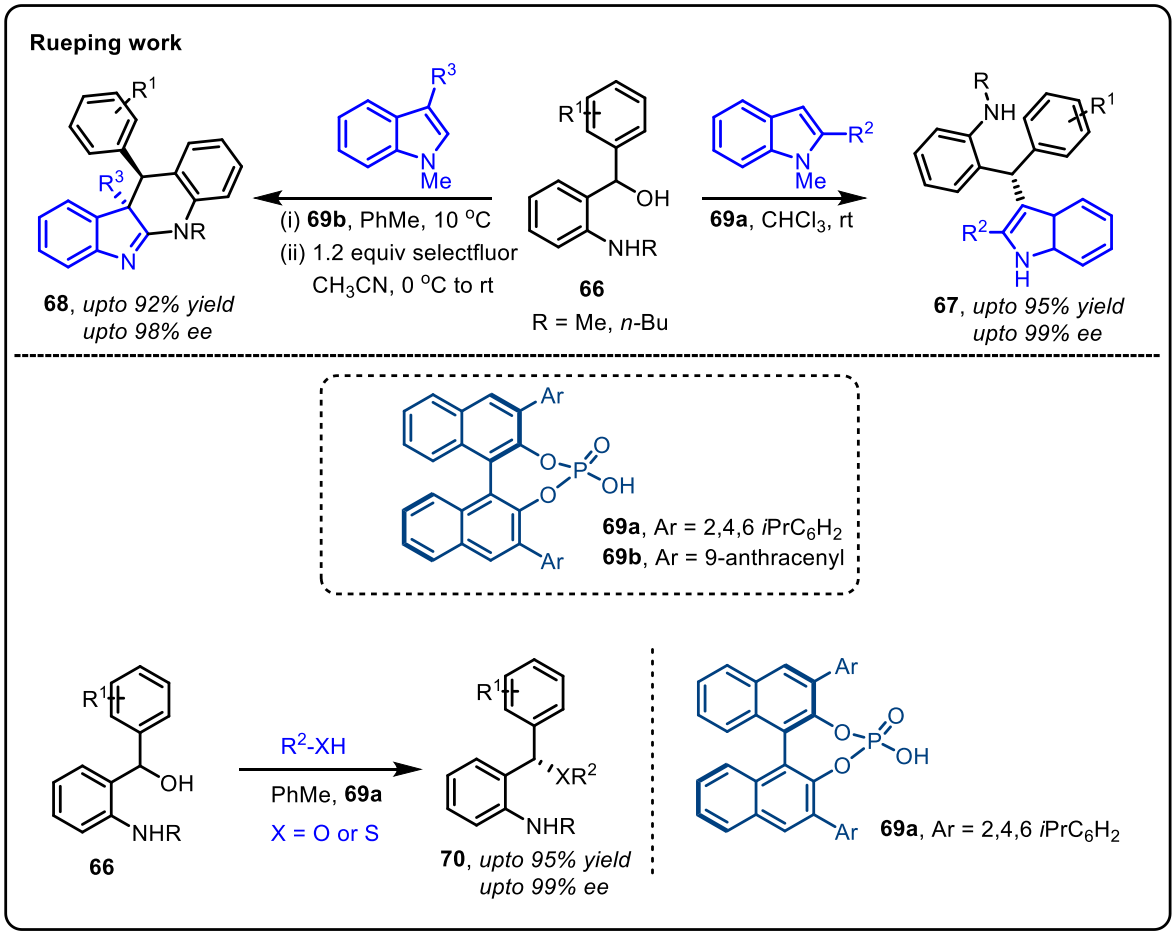
In 2013, Gevorgyan and co-workers reported the synthesis of indole derivatives from 2-aminobenzyl alcohols (**61**) and furans (**62**) under Brønsted acid conditions (Scheme 10). Initially, in the presence of triflic acid, an intermediate **64** is formed and the furan ring in intermediate **64** upon ring opening and intramolecular cyclization gives **63** in good yield. Later, in 2018, the same group reported the synthesis of functionalized indole derivatives (**65**) using a similar strategy. A wide range of 2-aminobenzyl alcohols (**61**) and furan derivatives (**62**) were screened under optimized conditions, and related products (**65**) were obtained in good to excellent yields (Scheme 10).[10a,f]




**Scheme 10**. Gevorgyan approach for the synthesis of indole derivatives

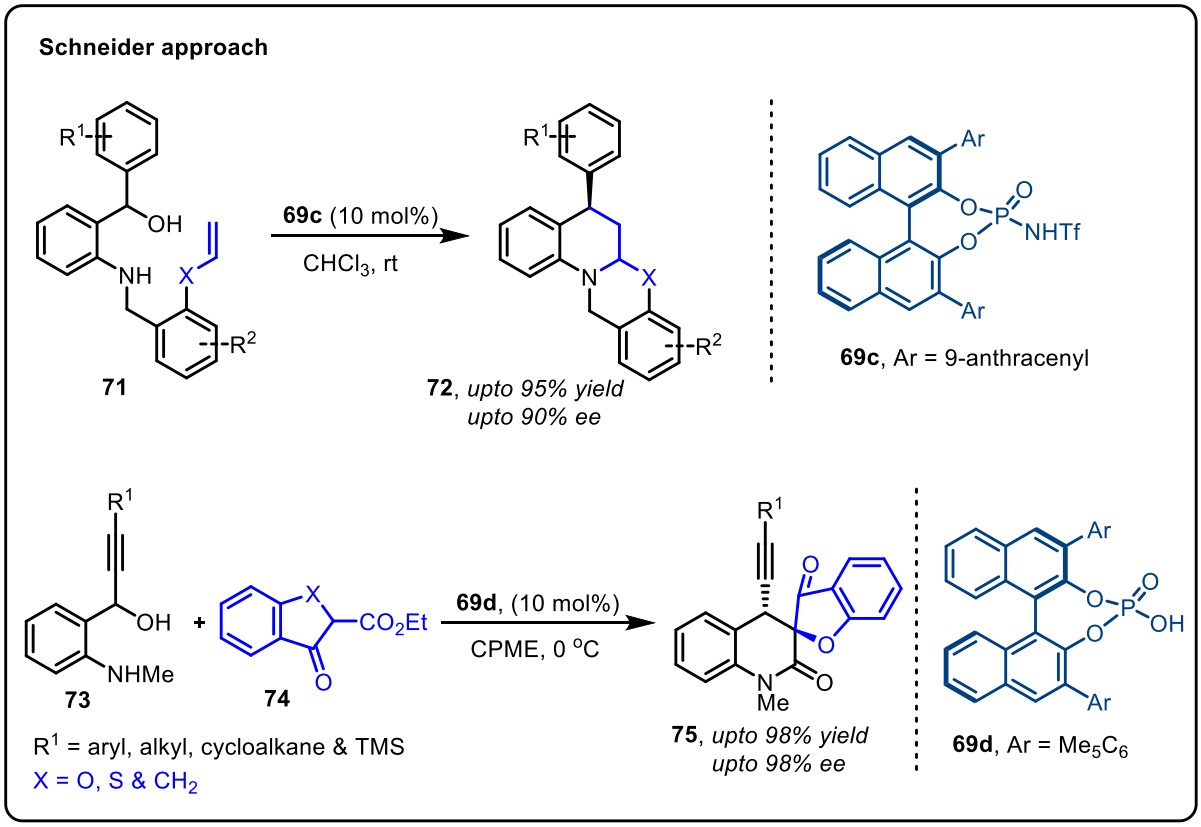
Rueping and co-workers reported the synthesis of indole-containing triarylmethanes (**67**) as well as fused nitrogen-containing communesin derivatives (**68**) from 2-aminobenzyl

alcohols (**66**) and substituted indoles (Scheme 11). A chiral phosphoric acid was used as an organocatalyst, which acts as a dual catalyst as it activates the nucleophilic partner as well as **66,** and corresponding products **67** and **68** were obtained in good yield and excellent enantioselectivity. Later, the same group developed an asymmetric synthesis of thioethers and ethers, by the enantioselective addition of thiol or alcohol to **66**, in the presence of BINOL-based chiral phosphoric acid **69a** (Scheme 11).[11a-b]



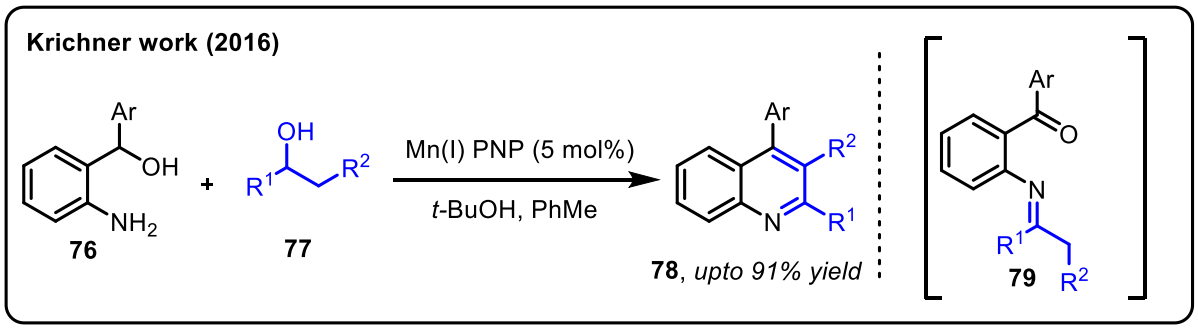

**Scheme 11**. Phosphoric acid-catalyzed reaction of 2-aminobenzyl alcohol

Schneider and co-workers have demonstrated an elegant approach for the synthesis of quinolizidines derivatives (**72**) from 2-aminobenzyl alcohols (**71**) [Scheme 12]. In this case, *N*-triflyl phosphoric acid amide **69c** was used as a catalyst. The reaction proceeds through an enantioselective [4+2] cyclization. Later, the same group reported the synthesis of spirocyclic dihydroquinolones derivatives (75) [Scheme 12]. A variety of β-substituted cyclic esters (**74**) and alkyne-substituted *o*-aminobenzyl alcohols (**73**) were employed in the presence of Brønsted acid condition, and the corresponding compounds (**75**) were obtained in moderate to good yield and excellent enantioselectivity (Scheme 12).[12a,c]




**Scheme 12**. Schneider's approach for the synthesis of nitrogen-containing heterocycles from 2-aminobenzyl alcohol

In 2016, Krichner and co-workers reported the synthesis of quinoline derivatives (**78**) using a Manganese pincer complex (Scheme 13). As per the proposed mechanism, in the presence of Mn(I) catalyst, both 2-aminobenzyl alcohol **76** and the secondary alcohol **77** get oxidized to their respective ketones, which then undergo an annulation to give the corresponding quinoline derivatives (**78**) in good yields.[12f]

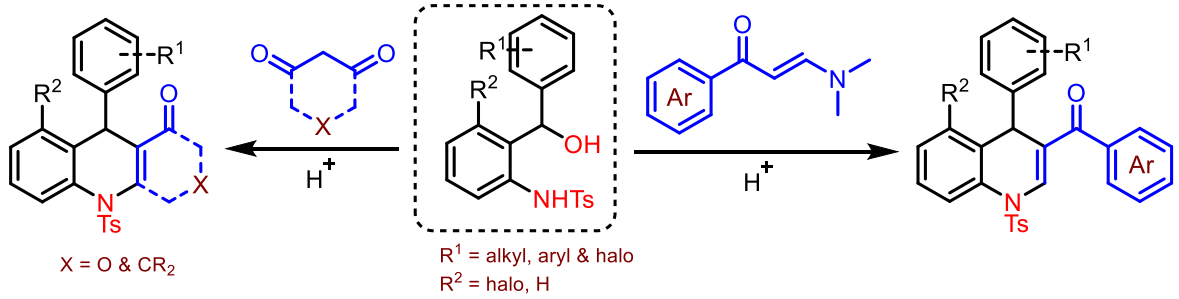



**Scheme 13**. Manganese (I) catalyzed reaction of 2-aminobenzyl alcohol

## 2.4 Background

While working on the synthesis of carbocycles and heterocycles from *para*-quinone methides (*p*-QMs) as a synthons,[14] we realized that if *ortho*-aminobenzyl alcohol is treated

with cyclic 1,3-dicarbonyl compounds and enaminones, we may end up in getting tetrahydroacridinone and dihydroquinoline derivatives, respectively under acidic conditions (Scheme 14).




**Scheme 14.** Our approach for the synthesis of tetrahydroacridinone and dihydroquinoline derivatives.

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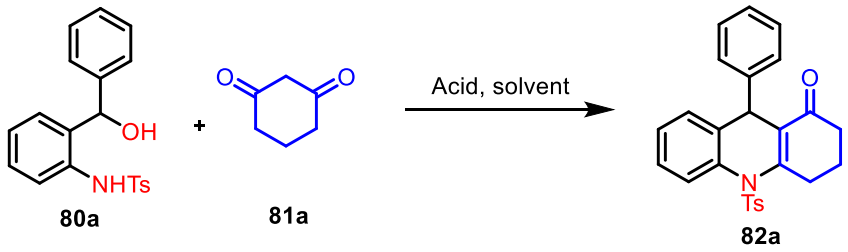
## 2.5 Result and discussion

Initially, the reaction between *ortho*-aminobenzyl alcohol **80a** and 1,3-cyclohexanedione **81a** was considered, as this reaction would potentially lead to tetrahydroacridinones derivative **82a** under acidic conditions. Therefore, the reaction between **80a** and **81a** has been carried out using different acid catalysts under different conditions, and the results are portrayed in Table 1. At first, when catalytic as well as an equivalent amount of TsOH is used in $CH_2Cl_2$ as a solvent, desired product **82a** was not obtained at room temperature conditions (entries 1 & 2). However, interestingly, the same reaction, when conducted in toluene at 70 $^oC$, desired product **82a** was obtained in 42% of the isolated yield in 12 hours (entry 3). Based on the above result, we realized that the reaction requires an elevated temperature as many steps are involved in this transformation. Then, the optimization studies were extended using different protic as well as aprotic solvents at 70 $^oC$ (entries 4-7). Although the reaction did not proceed in non-chlorinated solvents such as DMSO and MeCN (entries 4 & 5), it worked well in chloroform and 1,2-dichloroethane and, in those cases, **82a** was obtained in 62 and 78% yields, respectively (entries 6 & 7). Other organic acids such as camphorsulfonic acid (CSA), triflic acid, and trifluoroacetic acid (TFA) were also used and found to be inferior to TsOH acid (entries 8-10). To prove that an acid catalyst is required at elevated temperature, an experiment was performed without a catalyst in 1,2- DCE solvent at 70 $^oC$, and as expected, the desired product **82a** was not obtained even after 24h. This experiment indicates that an acid catalyst is required for the above transformation.

**Table 1**. Optimization study[a]

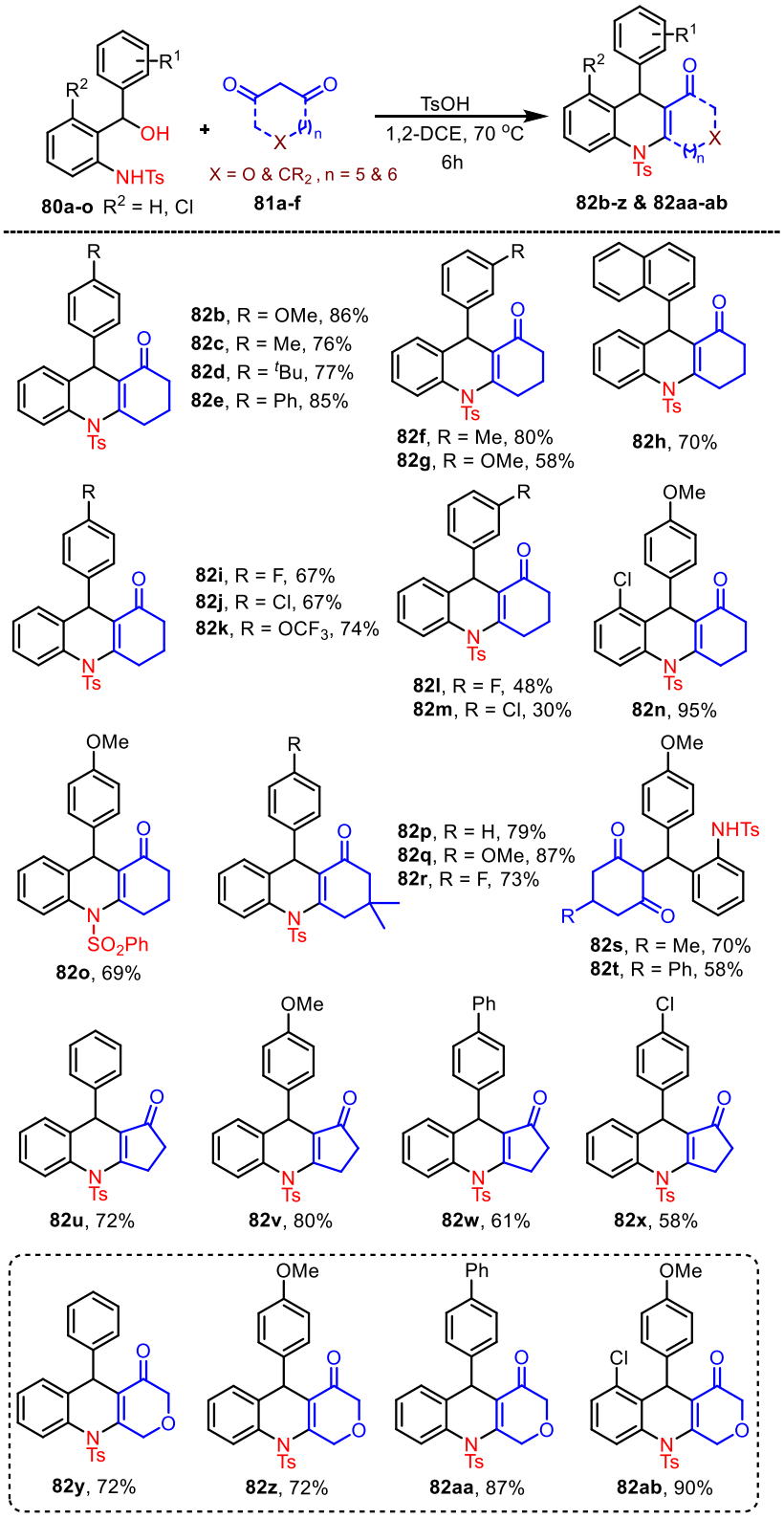



| entry | acid | solvent | time (h) | yield of **82a** [%] |
|---|---|---|---|---|
| 1[b,c] | TsOH | $CH_2Cl_2$ | 24 | nr |
| 2[b] | TsOH | $CH_2Cl_2$ | 24 | nr |
| 3 | TsOH | PhMe | 12 | 42 |
| 4 | TsOH | DMSO | 24 | nr |
| 5 | TsOH | MeCN | 24 | trace |
| 6 | TsOH | $CHCl_3$ | 6 | 62 |
| **7** | **TsOH** | **1,2- DCE** | **6** | **78** |
| 8 | CSA | 1,2- DCE | 6 | 46 |
| 9 | TfOH | 1,2- DCE | 6 | 35 |
| 10 | TFA | 1,2- DCE | 24 | trace |
| 11[d] | - | 1,2- DCE | 24 | nr |

[a]Reaction Conditions: All reactions were carried at 0.084 mmol scale of **80a** with 1.3 equiv. of **81a** and 1.3 equiv. of the acid with respect to **80a** at 70 $^oC$. [b]reaction was performed at rt. [c] reaction was performed in 20 mol % of TsOH. [d]reaction was performed without catalyst. Yields reported are isolated yields.

With optimal reaction conditions (entry 7, Table 1) in hand, the scope and limitations of this transformation were evaluated. In general, most of the *ortho*-aminobenzyl alcohols **80b-o** reacted with cyclic 1,3 dicarbonyls **81a-f**, and the results are summarized in Table 2. For example, the reaction of **81a** with a variety of *ortho*-aminobenzyl alcohol-bearing electron donating groups on *para*- and *meta*-position provided the corresponding products **82b-h** in good to excellent yields (58–86%). In the case of halo- and $CF_3$-containing *ortho*-aminobenzyl alcohols (**80i-n**), the tetrahydroacridinone derivatives **82i-n** were obtained in the range of 30–95% of isolated yields. The *para*-trifluoromethoxy substituted *ortho*-aminobenzyl alcohol **80k** reacted at a slower rate, and, therefore, the reaction took a bit longer time (10 h) to complete.

**Table 2**. Substrate Scope[a]



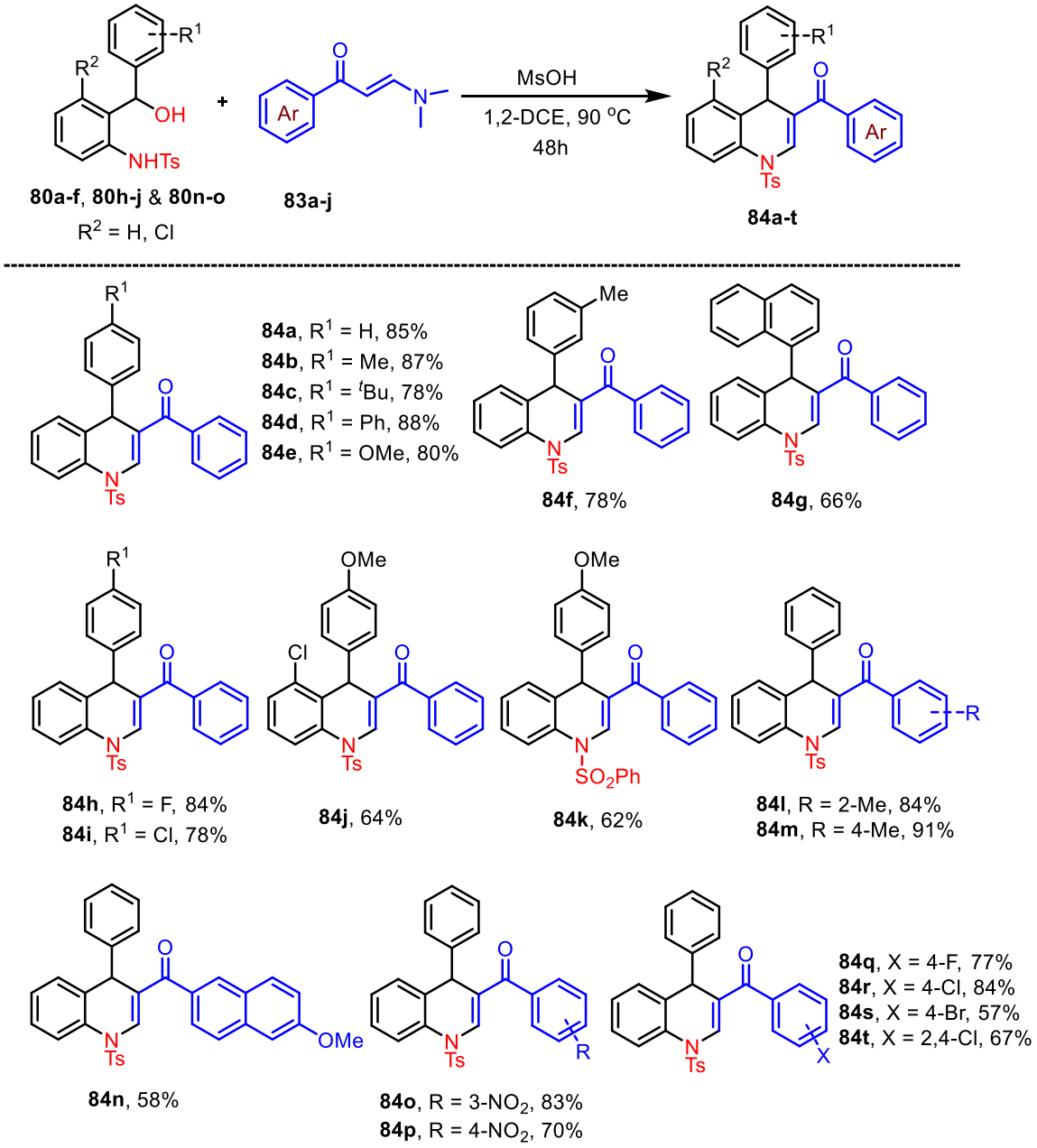

[a] Reaction conditions: All reactions were carried out with a 30 mg (0.85-0.70 mmol) scale of (**80a-o**) and with 1.3 equiv. of **81a-f** in 1.5 mL of 1,2-DCE. Yields reported are isolated yields.

Other substitutions either at the nitrogen atom of *ortho*-aminobenzyl alcohol (**80o**) or in 1,3-dicarbonyl (**81b**) did not affect the reaction rate or the yield of a product as these substrates also underwent smooth conversion to their respective products **82o-r** in good yields (69-87%) under optimal conditions. However, when methyl and phenyl substituted *β*-dicarbonyl compounds (**81c-d**) were subjected to the optimal conditions, only addition products **82s** and **82t** were obtained in 70 and 58% of yields, respectively. Other cyclic dicarbonyl compounds such as 1,3-cyclopentanedione **81e** and 3,5-pyrandione **81f** also reacted smoothly with different *ortho*-aminobenzyl alcohols and the corresponding products **82u-z** and **82aa-ab** were obtained in the range of 72–90% of isolated yields as shown in Table 2.

Later, we realized that a similar protocol shall be applied for the synthesis of dihydroquinoline derivatives using enaminones in place of 1,3-dicarbonyls. In this regard, a few optimization experiments were conducted using *N*,*N*-dimethyl enaminone **83a**, and *ortho*-aminobenzyl alcohol **80a**, and it was found that when **80a** (1.5 equiv.) was treated with **83a** (1.0 equiv.) in the presence of methanesulphonic acid (3.0 equiv) for 48 h, the corresponding dihydroquinoline derivative **84a** was obtained in 85% of isolated yield. By considering this reaction condition as the standard one, the scope and limitations of this protocol were examined, and the results are summarized in Table 3. Electron-rich, as well as halo-containing *ortho*-aminobenzyl alcohols **80b-j** furnished the corresponding dihydroquinolines **84b-j** in 64–88% of isolated yields. The benzenesulfonyl protected *ortho*-aminobenzyl alcohol gave the corresponding product **84k** in 62% of isolated yield. Other *N*,*N*-dimethyl enaminones **83b-k** having different substitution patterns and electronic properties were also screened under standard conditions, and in those cases, corresponding products **84l-t** were obtained in the range of 58–91% of isolated yields.

Based on the outcome of the reactions and reaction conditions, plausible mechanisms have been proposed for the formation of tetrahydroacridinone (Route A) and dihydroquinoline (Route B) [Scheme 15]. Initially, in the presence of an acid, **80a** isomerizes to the respective aza *ortho*-quinone methide **I**, which subsequently reacts with **81a** to give an intermediate **II** (Route A). This intermediate **II** then undergoes an intramolecular cyclization in the presence of acid to generate another intermediate **III**, which gets converted to tetrahydroacridinone **82a** with the elimination of water. Similarly, the aza-*o*-QM **I** undergoes a formal [4+2]-annulation with **83a** to generate an intermediate **IV**, which on subsequent elimination under acidic conditions, generates dihydroquinoline **84a** along with dimethylamine (Route B, Scheme 15).

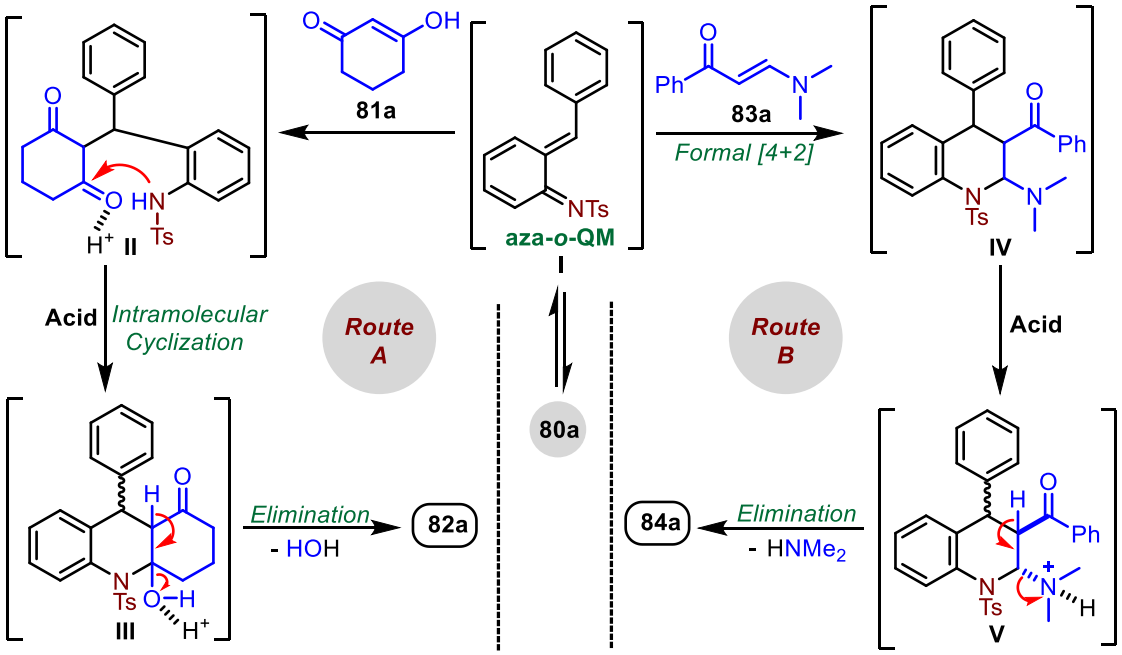
**Table 3** Substrate Scope[a]




[a] Reaction conditions: All reactions were carried out with a 30 mg (0.85-0.70 mmol) scale of (**80a-f**, **80h-j**, **& 80n-o**) and with 1.0 equiv of **83a-j** in 1.5 mL of 1,2-DCE. Yields reported are isolated yields.

Further, to show the synthetic applications of the transformation, one of the tetrahydroacridinone derivate **82b** was treated with an excess of DBU at 80 °C in acetonitrile, and the detosylated product dihydroacridinone **85** was obtained in 84% of isolated yield. Also, dihydroquinoline derivative **84a** was converted into quinolone derivative **86** in 72% of isolated yield under the basic condition at 80 °C in toluene. To show the scalability of this transformation, a relatively larger scale reaction was performed using **80b,** and in this case,

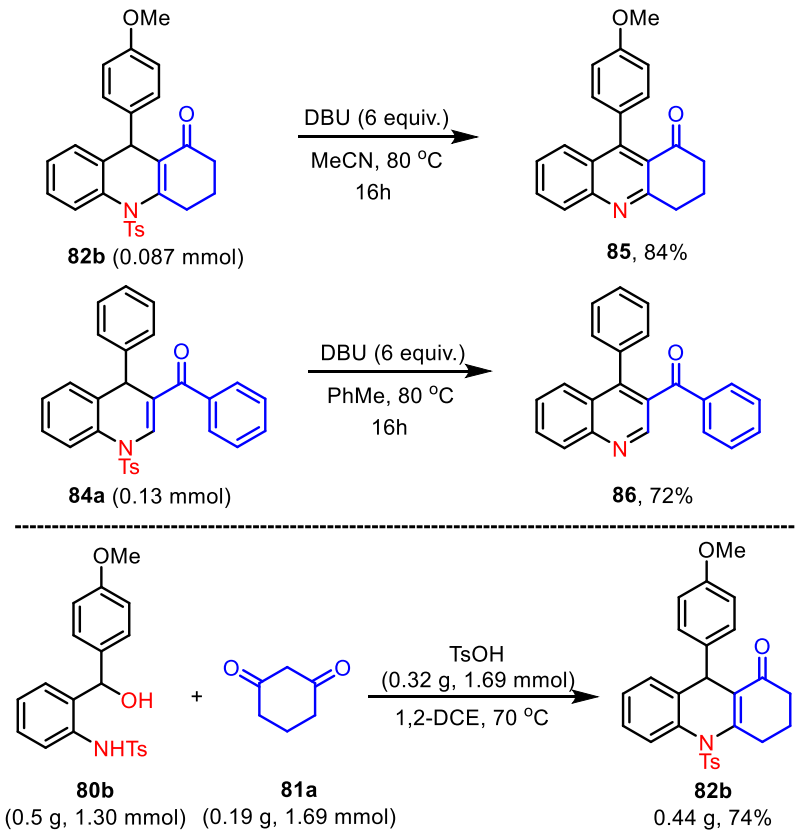
the desired terahydroacridinone derivative **82b** was obtained in 74% yield (as shown in Scheme 16).




**Scheme 15**. Plausible Mechanism for the formation of Tetrahydroacridinone and Dihydroquinoline

## 2.6 Conclusion

In summary, we have demonstrated simple and straight-forward Brønsted acid-mediated approaches to the synthesis of tetrahydroacridinone and dihydroquinoline derivatives through a reaction of *ortho*-aminobenzyl alcohol with cyclic 1,3-dicarbonyls & *N*,*N*-dimethyl enaminones, respectively. Both transformations proceed through aza-*o*-quinone methide, which is formed through acid-mediated dehydration of *ortho*-aminobenzyl alcohol. Considering the operational simplicity of these transformations and also the applications of both classes of products (tetrahydroacridinone and dihydroquinoline derivatives), we believe that these protocols will definitely find interest to synthetic as well as medicinal chemists.



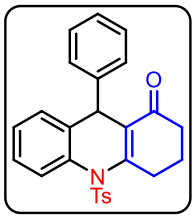

**Scheme 16.** Synthetic elaboration and scale-up reaction.

## 2.7 Experimental section

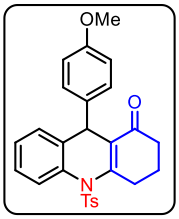
**General Information.** All reactions were carried out in an oven-dried round bottom flask. All the solvents were distilled before use and stored under an argon atmosphere. Most of the reagents and starting materials were purchased from commercial sources and used as such. All 2-aminobenzyl alcohol was prepared according to the literature procedure.[10a,f] 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 ($\delta$) 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) and neutral alumina using EtOAc/hexane as an eluent.

**General procedure for the synthesis of tetrahydroacridinone derivatives (82a-z) & (82aa-ab):** TsOH (0.109 mmol, 1.3 equiv.) was added to a solution of *ortho*-aminobenzyl alcohol (0.084 mmol, 1 equiv.) and cyclic 1,3-dicarbonyl compound (0.109 mmol, 1.3 equiv.) in 1,2-DCE (1.5 mL), and the resulting reaction mixture was stirred at 70 $^{o}$C. After the reaction was complete (based on TLC analysis), the solvent was removed 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 tetrahydroacridinone derivative.

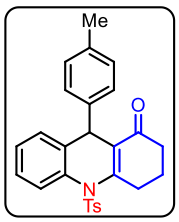
**9-Phenyl-10-tosyl-3,4,9,10-tetrahydroacridin-1(2H)-one (82a):** The reaction was performed at 0.085 mmol scale of **80a**; white solid (28.5 mg, 78% yield); m. p. = 182–184 ºC; $R_f$ = 0.3 (20% EtOAc in hexane); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.72 – 7.70 (m, 1H), 7.28 – 7.21 (m, 5H), 7.14 – 7.08 (m, 3H), 6.92 (d, *J* = 8.2 Hz, 2H), 6.89 (d, *J* = 7.0 Hz, 2H), 5.26 (s, 1H), 3.45 – 3.38 (m, 1H), 2.76 – 2.69 (m, 1H), 2.66 – 2.60 (m, 1H), 2.49 – 2.42 (m, 1H), 2.30 (s, 3H), 2.11 – 2.03 (m, 2H); $^{13}$C{$^1$H} NMR (100 MHz, $CDCl_3$) $\delta$ 197.5, 155.9, 144.5, 142.4, 136.9, 136.0, 133.1, 129.9, 129.6, 128.5, 127.6, 127.5, 127.2, 126.8, 126.4, 126.1, 122.6, 39.13, 39.12, 37.4, 30.7, 22.8, 21.69, 21.67; FT-IR (thin film, neat): 3060, 2956, 1663, 1174, 788 cm$^{-1}$; HRMS (ESI): *m/z* calcd for $C_{26}H_{24}NO_3S$ $[M+H]^+$ : 430.1477; found : 430.1468.




**9-(4-Methoxyphenyl)-10-tosyl-3,4,9,10-tetrahydroacridin-1(2H)-one (82b):** The reaction was performed at 0.078 mmol scale of **80b** white solid (31.0 mg, 86% yield); m. p. = 145–147 ºC; $R_f$ = 0.3 (20% EtOAc in hexane); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.92 (d, *J* = 8.1 Hz, 1H), 7.30 (d, *J* = 8.3 Hz, 2H), 7.28 – 7.21 (m, 3H), 6.96 (d, *J* = 8.2 Hz, 2H), 6.80 (d, *J* = 8.6 Hz, 2H), 6.64 (d, *J* = 8.7 Hz, 2H), 5.18 (s, 1H), 3.76 (s, 3H), 3.44 – 3.37 (m, 1H), 2.75 – 2.67 (m, 1H), 2.65 – 2.58 (m, 1H), 2.48 – 2.42 (m, 1H), 2.32 (s, 3H), 2.13 – 2.01 (m, 2H); $^{13}$C{$^1$H} NMR (100 MHz, $CDCl_3$) $\delta$ 197.5, 158.1, 155.7, 144.5, 136.8, 136.2, 134.7, 133.5, 129.7, 129.6, 128.3, 127.9, 127.6, 126.7, 126.4, 122.7, 113.8, 55.33, 55.3, 38.44, 38.43, 37.4, 30.7, 22.8, 21.66, 21.65; FT-IR (thin film, neat): 3061, 2953, 1660, 1174, 780 cm$^{-1}$; HRMS (ESI): *m/z* calcd for $C_{27}H_{26}NO_4S$ $[M+H]^+$ : 460.1583; found : 460.1566.

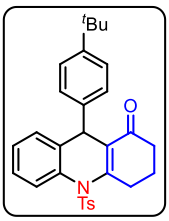



**9-(*p*-Tolyl)-10-tosyl-3,4,9,10-tetrahydroacridin-1(2H)-one (82c):** The reaction was performed at 0.082 mmol scale of **80c**; white solid (27.4 mg, 76% yield); m. p. = 173–175 ºC; $R_f$ = 0.3 (20% EtOAc in hexane); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.71 – 7.69 (m, 1H), 7.30 (d, *J* = 8.4 Hz, 2H), 7.28 – 7.20 (m, 3H),



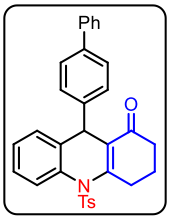
6.94 – 6.90 (m, 4H), 6.77 (d, *J* = 8.0 Hz, 2H), 5.21 (s, 1H), 3.44 – 3.37 (m, 1H), 2.74 – 2.67 (m, 1H), 2.66 – 2.58 (m, 1H), 2.48 – 2.41 (m, 1H), 2.32 (s, 3H), 2.29 (s, 3H), 2.13 – 2.02 (m, 2H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) $\delta$ 197.4, 155.7, 144.4, 139.4, 136.8, 136.3, 135.6, 133.4, 129.8, 129.5, 129.1, 127.7, 127.6, 127.1, 126.7, 126.4, 122.6, 38.84, 38.83, 37.4, 30.7, 22.8, 21.70, 21.69, 21.12, 21.11; FT-IR (thin film, neat): 3058, 2924, 1661, 1172, 779 $cm^{-1}$; HRMS (ESI): *m/z* calcd for $C_{27}H_{26}NO_3S$ $[M+H]^+$ : 444.1633; found : 444.1619.

**9-(4-(*Tert*-butyl)phenyl)-10-tosyl-3,4,9,10-tetrahydroacridin-1(2H)-one (82d):** The



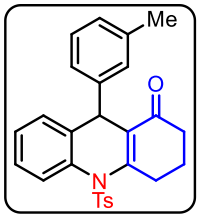

reaction was performed at 0.073 mmol scale of **80d**; white solid (27.2 mg, 77% yield); m. p. = 101–103 ºC; $R_f$ = 0.4 (20% EtOAc in hexane); $^{1}H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.65 – 7.62 (m, 1H), 7.33 (d, *J* = 8.4 Hz, 2H), 7.28 – 7.24 (m, 1H), 7.23 – 7.18 (m, 4H), 6.98 (d, *J* = 8.2 Hz, 2H), 6.91 (d, *J* = 8.3 Hz, 2H), 5.25 (s, 1H), 3.41 – 3.34 (m, 1H), 2.75 – 2.67 (m, 1H), 2.65 – 2.57 (m, 1H), 2.48 – 2.40 (m, 1H), 2.32 (s, 3H), 2.09 – 2.02 (m, 2H), 1.30 (s, 9H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) $\delta$ 197.3, 155.6, 149.1, 144.5, 139.1, 136.8, 136.2, 133.1, 129.7, 129.6, 127.9, 127.0, 126.9, 126.6, 126.3, 125.4, 122.0, 38.92, 38.91, 37.4, 34.5, 31.6, 30.5, 22.7, 21.75, 21.74; FT-IR (thin film, neat): 2960, 1663, 1174, 785 $cm^{-1}$; HRMS (ESI): *m/z* calcd for $C_{30}H_{32}NO_3S$ $[M+H]^+$ : 486.2103; found : 486.2101.

**9-([1,1'-Biphenyl]-4-yl)-10-tosyl-3,4,9,10-tetrahydroacridin-1(2H)-one (82e) :** The




reaction was performed at 0.070 mmol scale of **80e**; white solid (30.0 mg, 85% yield); m. p. = 189–191 ºC; $R_f$ = 0.3 (20% EtOAc in hexane); $^{1}H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.77 – 7.75 (m, 1H), 7.57 – 7.55 (m, 2H), 7.45 – 7.42 (m, 2H), 7.35 – 7.33 (m, 3H), 7.32 – 7.25 (m, 5H), 6.95 (d, *J* = 8.2 Hz, 2H), 6.88 (d, *J* = 8.2 Hz, 2H), 5.29 (s, 1H), 3.49 – 3.42 (m, 1H), 2.79 – 2.72 (m, 1H), 2.70 – 2.62 (m, 1H), 2.52 – 2.45 (m, 1H), 2.15 (s, 3H), 2.13 – 2.04 (m, 2H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) $\delta$ 197.5, 156.1, 144.6, 141.6, 140.8, 139.0, 136.9, 136.1, 133.1, 129.9, 129.5, 128.9, 127.7, 127.6, 127.5, 127.3, 127.1, 126.9 (2C), 126.5, 122.8, 38.91, 38.90, 37.4, 30.8, 22.8, 21.56, 21.54; FT-IR (thin film, neat): 3031, 2953, 1663, 1174, 762 $cm^{-1}$; HRMS (ESI): *m/z* calcd for $C_{32}H_{28}NO_3S$ $[M+H]^+$ : 506.1790; found : 506.1778.

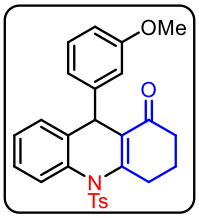
**9-(*m*-Tolyl)-10-tosyl-3,4,9,10-tetrahydroacridin-1(2H)-one (82f):** The reaction was




performed at 0.082 mmol scale of **80f**; white solid (29.0 mg, 80% yield); m. p. = 162–164 ºC; $R_f$ = 0.3 (20% EtOAc in hexane); $^{1}H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.70 – 7.67 (m, 1H), 7.30 – 7.21 (m, 5H), 7.02 – 6.98 (m, 1H),

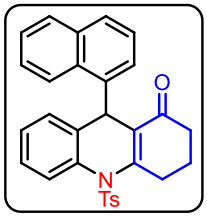
6.95 – 6.93 (m, 3H), 6.74 (s, 1H), 6.68 (d, *J* = 7.6 Hz, 1H), 5.22 (s, 1H), 3.45 – 3.37 (m, 1H), 2.75 – 2.67 (m, 1H), 2.66 – 2.60 (m, 1H), 2.48 – 2.41 (m, 1H), 2.31 (s, 3H), 2.21 (s, 3H), 2.12 – 2.02 (m, 2H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) $\delta$ 197.4, 155.8, 144.4, 142.4, 137.9, 136.9, 136.3, 133.4, 129.9, 129.6, 128.4, 128.0, 127.7, 127.6, 127.0, 126.7, 126.4, 124.3, 122.6, 39.13, 39.11, 37.4, 30.6, 22.8, 21.69, 21.67; FT-IR (thin film, neat): 3043, 2924, 1662, 1172, 779 $cm^{-1}$; HRMS (ESI): *m/z* calcd for $C_{27}H_{26}NO_3S$ $[M+H]^+$ : 444.1633; found : 444.1620.

**9-(3-Methoxyphenyl)-10-tosyl-3,4,9,10-tetrahydroacridin-1(2H)-one (82g):** The reaction



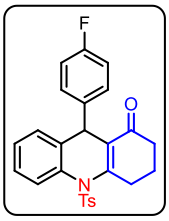

was performed at 0.078 mmol scale of **80g**; white solid (20.6 mg, 58% yield); m. p. = 143–145 ºC; $R_f$ = 0.3 (20% EtOAc in hexane); $^{1}H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.71 – 7.68 (m, 1H), 7.31 (d, *J* = 8.3 Hz, 2H), 7.28 – 7.21 (m, 3H), 7.04 (t, *J* = 8.0 Hz, 1H), 6.95 (d, *J* = 8.2 Hz, 2H), 6.68 (dd, *J* = 8.1, 2.3 Hz, 1H), 6.53 (d, *J* = 7.7 Hz, 1H), 6.40 (s, 1H), 5.23 (s, 1H), 3.66 (s, 3H), 3.46 – 3.38 (m, 1H), 2.74 – 2.67 (m, 1H), 2.65 – 2.59 (m, 1H), 2.49 – 2.41 (m, 1H), 2.31 (s, 3H), 2.10 – 2.04 (m, 2H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) $\delta$ 197.4, 159.6, 155.9, 144.5, 144.1, 136.9, 136.2, 133.1, 129.8, 129.6, 129.4, 127.6, 127.5, 126.8, 126.4, 122.6, 119.8, 112.7, 112.1, 55.14, 55.12, 39.20, 39.18, 37.4, 30.7, 22.8, 21.68, 21.65; FT-IR (thin film, neat): 2924, 1662, 1152, 779 $cm^{-1}$; HRMS (ESI): *m/z* calcd for $C_{27}H_{26}NO_4S$ $[M+H]^+$ : 460.1583; found : 460.1584.

**9-(Naphthalen-1-yl)-10-tosyl-3,4,9,10-tetrahydroacridin-1(2H)-one (82h):** The reaction




was performed at 0.074 mmol scale of **80h**; white solid (25.0 mg, 70% yield); m. p. = 195–197 ºC; $R_f$ = 0.3 (20% EtOAc in hexane); $^{1}H$ NMR (400 MHz, $CDCl_3$) $\delta$ 8.35 (bs, 1H), 7.82 (d, *J* = 7.6 Hz, 1H), 7.68 (d, *J* = 7.4 Hz, 3H), 7.57 – 7.51 (m, 2H), 7.45 (t, *J* = 7.2 Hz, 1H), 7.34 – 7.30 (m, 3H), 7.22 – 7.16 (m, 2H), 7.04 – 7.01 (m, 2H), 5.40 (bs, 1H), 3.29 – 3.21 (m, 1H), 2.85 – 2.79 (m, 1H), 2.48 (s, 3H), 2.45 – 2.39 (m, 1H), 2.36 – 2.28 (m, 1H), 2.07 – 2.01 (m, 2H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) $\delta$ 196.5, 154.5, 145.0, 138.9, 137.0, 135.9, 135.2, 134.3, 131.5, 130.1, 129.0, 128.8, 127.6, 127.5, 126.8, 126.7, 126.2, 125.94, 125.91, 125.7, 125.5, 124.1, 123.5, 37.4, 36.7, 30.9, 22.3, 21.79, 21.76; FT-IR (thin film, neat): 3066, 2925, 1665, 1172, 773 $cm^{-1}$; HRMS (ESI): *m/z* calcd for $C_{30}H_{26}NO_4S$ $[M+H]^+$ : 480.1633; found : 480.1623.

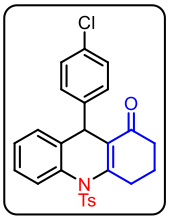
**9-(4-Fluorophenyl)-10-tosyl-3,4,9,10-tetrahydroacridin-1(2H)-one (82i):** The reaction was




performed at 0.081 mmol scale of **80i**; white solid (24.2 mg, 67% yield); m. p. = 206–208 ºC; $R_f$ = 0.4 (20% EtOAc in hexane); $^{1}H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.76 (d, *J* = 7.6 Hz, 1H), 7.32 – 7.28 (m, 3H), 7.26 – 7.23 (m, 2H), 6.97 (d, *J*

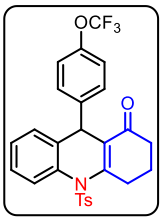
= 8.0 Hz, 2H), 6.81 – 6.76 (m, 2H), 6.74 – 6.71 (m, 2H), 5.19 (s, 1H), 3.47 – 3.39 (m, 1H), 2.76 – 2.68 (m, 1H), 2.67 – 2.59 (m, 1H), 2.50 – 2.42 (m, 1H), 2.33 (s, 3H), 2.15 – 2.02 (m, 2H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) $\delta$ 197.6, 161.4 (d, $J_{C\text{-}F}$ = 243.1 Hz), 156.2, 144.7, 138.4 (d, $J_{C\text{-}F}$ = 3.0 Hz), 136.9, 136.3, 133.1, 129.8, 129.6, 128.7 (d, $J_{C\text{-}F}$ = 7.9 Hz), 127.9, 127.5, 127.0, 126.6, 123.0, 115.1 (d, $J_{C\text{-}F}$ = 21.1 Hz), 38.49, 38.48, 37.4, 30.8, 22.8, 21.63, 21.62; $^{19}F\{^{1}H\}$ NMR (376 MHz, $CDCl_3$) δ –117.1; FT-IR (thin film, neat): 2957, 1658, 1174, 784 $cm^{-1}$; HRMS (ESI): *m/z* calcd for $C_{26}H_{23}FNO_3S$ $[M+H]^+$ : 448.1383; found : 448.1372.

**9-(4-Chlorophenyl)-10-tosyl-3,4,9,10-tetrahydroacridin-1(2H)-one (82j):** The reaction



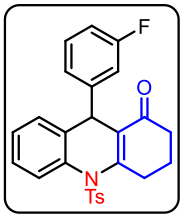

was performed at 0.077 mmol scale of **80j**; white solid (20.7 mg, 67% yield); m. p. = 201–203 ºC; $R_f$ = 0.5 (20% EtOAc in hexane); $^{1}H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.82 – 7.79 (m, 1H), 7.32 (td, *J* =7.0, 2.0 Hz, 1H), 7.29 – 7.22 (m, 4H), 7.02 – 6.98 (m, 2H), 6.94 (d, *J* = 8.1 Hz, 2H), 6.71 (d, *J* = 8.0 Hz, 2H), 5.17 (s, 1H), 3.50 – 3.42 (m, 1H), 2.77 – 2.70 (m, 1H), 2.67 – 2.60 (m, 1H), 2.50 – 2.42 (m, 1H), 2.34 (s, 3H), 2.16 – 2.04 (m, 2H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) $\delta$ 197.6, 156.4, 144.8, 141.2, 136.9, 136.0, 132.8, 132.0, 129.9, 129.5, 128.5, 128.4, 127.8, 127.4, 127.1, 126.7, 123.2, 38.54, 38.53, 37.4, 31.0, 22.9, 21.71, 21.69; FT-IR (thin film, neat): 2955, 1662, 1174, 782 $cm^{-1}$; HRMS (ESI): *m/z* calcd for $C_{26}H_{23}ClNO_3S$ $[M+H]^+$ : 464.1087; found : 464.1091.

**10-Tosyl-9-(4-(trifluoromethoxy)phenyl)-3,4,9,10-tetrahydroacridin-1(2H)-one (82k):**




The reaction was performed at 0.069 mmol scale of **80k**; white solid (26.0 mg, 74% yield); m. p. = 96–98 ºC; $R_f$ = 0.5 (20% EtOAc in hexane); $^{1}H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.75 (d, *J* = 7.8 Hz, 1H), 7.33 (d, *J* = 8.8 Hz, 2H), 7.31 – 7.28 (m, 1H), 7.26 – 7.23 (m, 2H), 6.98 (d, *J* = 8.3 Hz, 2H), 6.95 – 6.88 (m, 4H), 5.24 (s, 1H), 3.46 – 3.39 (m, 1H), 2.76 – 2.69 (m, 1H), 2.66 – 2.59 (m, 1H), 2.50 – 2.43 (m, 1H), 2.33 (s, 3H), 2.15 – 2.02 (m, 2H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) $\delta$ 197.5, 156.3, 147.7 (q, *J* = 1.4 Hz), 144.9, 141.2, 136.9 136.3, 132.6, 129.8, 129.6, 128.7, 127.6, 127.3, 127.2, 126.7, 122.9, 120.7, 120.6 (q, *J* = 255 Hz), 38.71, 38.69, 37.4, 30.8, 22.8, 21.60, 21.58; $^{19}F\{^{1}H\}$ NMR (376 MHz, $CDCl_3$) δ –57.7; FT-IR (thin film, neat): 3066, 2926, 1662, 1154, 783 $cm^{-1}$; HRMS (ESI): *m/z* calcd for $C_{27}H_{23}F_3NO_4S$ $[M+H]^+$ : 514.1300; found : 514.1297.

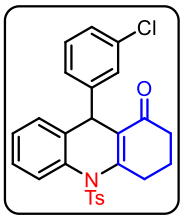
**9-(3-Fluorophenyl)-10-tosyl-3,4,9,10-tetrahydroacridin-1(2H)-one (82l):** The reaction




was performed at 0.081 mmol scale of **82l**; white solid (17.1 mg, 48% yield); m. p. = 202–204 ºC; $R_f$ = 0.4 (20% EtOAc in hexane); $^{1}H$ NMR (400 MHz,

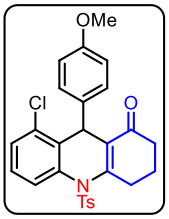
$CDCl_3$) $\delta$ 7.81 (d, $J$ = 7.9 Hz, 1H), 7.34 – 7.24 (m, 5H), 7.09 – 7.04 (m, 1H), 6.91 (d, $J$ = 8.2 Hz, 2H), 6.80 (td, $J$ = 8.2, 2.1 Hz, 1H), 6.68 (d, $J$ = 7.8 Hz, 1H), 6.35 (d, $J$ = 10.5 Hz, 1H), 5.21 (s, 1H), 3.52 – 3.44 (m, 1H), 2.79 – 2.72 (m, 1H), 2.69 – 2.62 (m, 1H), 2.52 – 2.44 (m, 1H), 2.30 (s, 3H), 2.16 – 2.04 (m, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) $\delta$ 197.6, 162.8 (d, $J$ = 243.8 Hz), 156.6, 145.4 (d, $J$ = 6.6 Hz), 144.7, 136.9, 135.7, 132.6, 130.0, 129.8 (d, $J$ = 8.0 Hz), 129.6, 127.5, 127.4, 127.2, 126.7, 123.2, 122.9 (d, $J$ = 2.9 Hz), 114.2 (d, $J$ = 22.2 Hz), 113.0 (d, $J$ = 21.1 Hz), 38.8, 37.4, 31.0, 22.9, 21.66, 21.63; $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$) δ –112.5; FT-IR (thin film, neat): 2924, 1663, 1174, 779 $cm^{-1}$; HRMS (ESI): *m/z* calcd for $C_{14}H_{13}O_3$ $[M+H]^+$ : 229.0865; found : 229.0855.

**9-(3-Chlorophenyl)-10-tosyl-3,4,9,10-tetrahydroacridin-1(2H)-one (82m):** The reaction



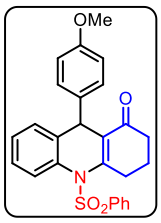

was performed at 0.077 mmol scale of **80m**; white solid (10.6 mg, 30% yield); m. p. = 203–205 ºC; $R_f$ = 0.5 (20% EtOAc in hexane); $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.79 (d, $J$ = 7.7 Hz, 1H), 7.33 – 7.24 (m, 5H), 7.09 (d, $J$ = 8.0 Hz, 1H), 7.03 (t, $J$ = 7.8 Hz, 1H), 6.93 (d, $J$ = 8.2 Hz, 2H), 6.76 (d, $J$ = 7.8 Hz, 1H), 6.71 (s, 1H), 5.19 (s, 1H), 3.52 – 3.44 (m, 1H), 2.79 – 2.72 (m, 1H), 2.70 – 2.62 (m, 1H), 2.51 – 2.44 (m, 1H), 2.30 (s, 3H), 2.17 – 2.06 (m, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) $\delta$ 197.5, 156.6, 144.8, 144.7, 136.9, 135.7, 134.3, 132.5, 129.9, 129.7, 129.6, 127.5, 127.4, 127.3, 127.2, 126.7, 126.4, 125.4, 123.2, 38.78, 38.77, 37.3, 30.9, 22.9, 21.75, 21.74; FT-IR (thin film, neat): 2924, 1663, 1174, 774 $cm^{-1}$; HRMS (ESI): *m/z* calcd for $C_{26}H_{23}ClNO_3S$ $[M+H]^+$ : 464.1087; found : 464.1078.

**8-Chloro-9-(4-methoxyphenyl)-10-tosyl-3,4,9,10-tetrahydroacridin-1(2H)-one (82n):** The



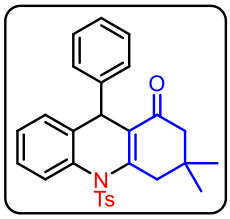

reaction was performed at 0.072 mmol scale of **80n**; white solid (33.8 mg, 95% yield); m. p. = 184–186 ºC; $R_f$ = 0.3 (20% EtOAc in hexane); $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.65 – 7.63 (m, 1H), 7.29 (d, $J$ = 8.4 Hz, 2H), 7.23 – 7.20 (m, 2H), 6.97 (d, $J$ = 8.2 Hz, 2H), 6.77 (d, $J$ = 8.6 Hz, 2H), 6.66 – 6.63 (m, 2H), 5.12 (s, 1H), 3.76 (s, 3H), 3.43 – 3.35 (m, 1H), 2.74 – 2.67 (m, 1H), 2.65 – 2.57 (m, 1H), 2.49 – 2.41 (m, 1H), 2.33 (s, 3H), 2.11 – 2.02 (m, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) $\delta$ 197.2, 158.3, 155.6, 144.8, 135.9, 135.4, 135.3, 133.9, 132.0, 129.7, 129.4, 128.2, 127.6, 127.4, 126.9, 124.0, 113.9, 55.35, 55.33, 38.4, 37.3, 30.7, 22.8, 21.68, 21.67; FT-IR (thin film, neat): 2959, 1663, 1172, 764 $cm^{-1}$; HRMS (ESI): *m/z* calcd for $C_{27}H_{25}ClNO_4S$ $[M+H]^+$ : 494.1193; found : 494.1198.

**9-(4-Methoxyphenyl)-10-(phenylsulfonyl)-3,4,9,10-tetrahydroacridin-1(2H)-one (82o):**



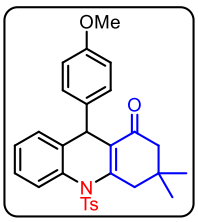

The reaction was performed at 0.081 mmol scale of **80o**; pale yellow gummy solid (25.0 mg, 69% yield); $R_f$ = 0.3 (20% EtOAc in hexane); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.69 – 7.66 (m, 1H), 7.47 – 7.41 (m, 3H), 7.28 – 7.19 (m, 5H), 6.82 (d, *J* = 8.7 Hz, 2H), 6.66 (d, *J* = 8.7 Hz, 2H), 5.20 (s, 1H), 3.76 (s, 3H), 3.42 – 3.35 (m, 1H), 2.74 – 2.67 (m, 1H), 2.66 – 2.58 (m, 1H), 2.49 – 2.41 (m, 1H), 2.10 – 2.03 (m, 2H); $^{13}$C{$^1$H} NMR (100 MHz, $CDCl_3$) $\delta$ 197.4, 158.1, 155.5, 139.4, 136.8, 134.6, 133.6, 133.5, 129.8, 129.0, 128.3, 128.0, 127.6, 126.8, 126.5, 122.5, 114.0, 55.38, 55.35, 38.51, 38.49, 37.4, 30.6, 22.8; FT-IR (thin film, neat): 29424, 1661, 1178, 784 cm$^{-1}$; HRMS (ESI): *m/z* calcd for $C_{26}H_{24}NO_4S$ $[M+H]^+$ : 446.1426; found : 446.1436.

**3,3-Dimethyl-9-phenyl-10-tosyl-3,4,9,10-tetrahydroacridin-1(2H)-one (82p):** The reaction



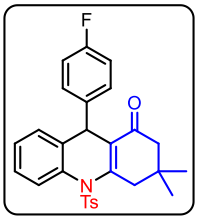

was performed at 0.085 mmol scale of **80a**; white solid (30.8 mg, 79% yield); m. p. = 208–210 ºC; $R_f$ = 0.4 (20% EtOAc in hexane); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.76 – 7.74 (m, 1H), 7.30 – 7.24 (m, 3H), 7.21 (d, *J* = 8.3 Hz, 2H), 7.15 – 7.07 (m, 3H), 6.88 (d, *J* = 8.1 Hz, 2H), 6.85 – 6.83 (m, 2H), 5.26 (s, 1H), 3.28 (d, *J* = 17.6 Hz, 1H), 2.61 (d, *J* = 17.6 Hz, 1H), 2.48 (d, *J* = 16.3 Hz, 1H), 2.35 – 2.29 (m, 4H), 1.06 (s, 3H), 1.01 (m, 3H); $^{13}$C{$^1$H} NMR (100 MHz, $CDCl_3$) $\delta$ 197.6, 153.9, 144.5, 142.6, 136.8, 135.9, 132.9, 130.0, 129.6, 128.5, 127.7, 127.2, 126.8, 126.5, 126.4, 126.1, 122.8, 51.0, 44.2, 39.01, 39.0, 34.2, 28.15, 28.05, 21.70, 21.69; FT-IR (thin film, neat): 2924, 1662, 1171, 761 cm$^{-1}$; HRMS (ESI): *m/z* calcd for $C_{28}H_{28}NO_3S$ $[M+H]^+$ : 458.1790; found : 458.1779.

**9-(4-Methoxyphenyl)-3,3-dimethyl-10-tosyl-3,4,9,10-tetrahydroacridin-1(2H)-one (82q):**



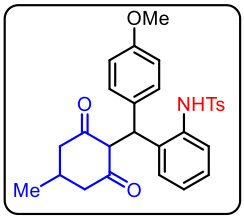

The reaction was performed at 0.078 mmol scale of **80b**; white solid (33.3 mg, 87% yield); m. p. = 169–171 ºC; $R_f$ = 0.3 (20% EtOAc in hexane); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.73 (d, *J* = 7.5 Hz, 1H), 7.29 – 7.23 (m, 5H), 6.92 (d, *J* = 8.1 Hz, 2H), 6.75 (d, *J* = 8.3 Hz, 2H), 6.65 – 6.61 (m, 2H), 5.18 (s, 1H), 3.76 (s, 3H), 3.28 (d, *J* = 17.6 Hz, 1H), 2.60 (d, *J* = 17.6 Hz, 1H), 2.47 (d, *J* = 16.5 Hz, 1H), 2.32 – 2.29 (m, 4H), 1.06 (s, 3H), 1.01 (s, 3H); $^{13}$C{$^1$H} NMR (100 MHz, $CDCl_3$) $\delta$ 197.6, 158.0, 153.7, 144.5, 136.8, 136.1, 134.9, 133.3, 129.9, 129.5, 128.2, 127.7, 126.9, 126.7, 126.4, 122.8, 113.8, 55.35, 55.32, 51.0, 44.2, 38.32, 38.31, 34.1, 28.2, 28.1, 21.67, 21.65; FT-IR (thin film, neat): 2925, 1661, 1172, 785 cm$^{-1}$; HRMS (ESI): *m/z* calcd for $C_{29}H_{30}NO_4S$ $[M+H]^+$ : 488.1896; found : 488.1881.

**9-(4-Fluorophenyl)-3,3-dimethyl-10-tosyl-3,4,9,10-tetrahydroacridin-1(2H)-one (82r):**



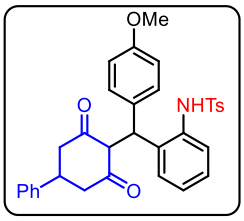

The reaction was performed at 0.081 mmol scale of **80i**; white solid (28.0 mg, 73% yield); m. p. = 176–178 ºC; $R_f$ = 0.4 (20% EtOAc in hexane); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.79 (d, $J$ = 7.6 Hz, 1H), 7.33 – 7.22 (m, 5H), 6.94 (d, $J$ = 8.1 Hz, 2H), 6.77 – 6.75 (m, 2H), 6.74 – 6.71 (m, 2H), 5.20 (s, 1H), 3.32 (d, $J$ = 19.6 Hz, 1H), 2.61 (d, $J$ = 17.6 Hz, 1H), 2.48 (d, $J$ = 16.3 Hz, 1H), 2.34 – 2.30 (m, 4H), 1.10 (s, 3H), 1.01 (s, 3H); $^{13}$C{$^1$H} NMR (100 MHz, $CDCl_3$) $\delta$ 197.7, 161.4 (d, $J$ = 243.0 Hz) , 154.2, 144.7, 138.6 (d, $J$ = 3.0 Hz), 136.9, 136.2, 132.9, 129.9, 129.6, 128.7 (d, $J$ = 8.0 Hz), 127.5, 127.1, 126.9, 126.6, 123.2, 115.1 (d, $J$ = 21.1 Hz), 51.0, 44.4, 38.39, 38.37, 34.2, 28.3, 28.0, 21.63, 21.61; $^{19}$F{$^1$H} NMR (376 MHz, $CDCl_3$) δ –117.1; FT-IR (thin film, neat): 2955, 1662, 1176, 785 cm$^{-1}$; HRMS (ESI): *m/z* calcd for $C_{28}H_{27}FNO_3S$ $[M+H]^+$ : 476.1696; found : 476.1685.

**N-(2-((4-methoxyphenyl)(4-methyl-2,6-dioxocyclohexyl)methyl)phenyl)-4-**



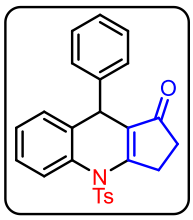

**methylbenzenesulfonamide (82s):** The reaction was performed at 0.078 mmol scale of **80b** white solid (27 mg, 70% yield); m. p. = 162–164 ºC; $R_f$ = 0.3 (20% EtOAc in hexane); The product was obtained as 1.6:1 diasteromeric mixture; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.79 (d, $J$ = 7.7 Hz, 1H), 7.64 – 7.62 (m, 1H), 7.31 – 7.29 (m, 3H), 7.27 – 7.21 (m, 10H), 6.97 (d, $J$ = 8.2 Hz, 2H), 6.91 (d, $J$ = 8.2 Hz, 2H), 6.83 (d, $J$ = 8.6 Hz, 2H), 6.70 (d, $J$ = 8.6 Hz, 2H), 6.66 (d, $J$ = 8.7 Hz, 2H), 6.59 (d, $J$ = 8.8 Hz, 2H), 5.17 (s, 1H), 5.16 (s, 1H), 3.76 (s, 3H), 3.75 (s, 3H), 3.60 – 3.52 (m, 1H), 3.05 – 2.98 (m, 1H), 2.92 – 2.87 (m, 1H), 2.67 – 2.62 (m, 1H), 2.61 – 2.57 (m, 1H), 2.38 – 2.35 (m, 1H), 2.33(s, 3H), 2.30 (s, 3H), 2.12 – 2.05 (m, 1H), 1.12 (d, $J$ = 6.2 Hz, 3H), 1.09 (d, $J$ = 6.0 Hz, 3H); $^{13}$C{$^1$H} NMR (100 MHz, $CDCl_3$) $\delta$ 197.7, 197.5, 158.1, 158.0, 155.4, 154.8, 144.53, 144.47, 136.9, 136.7, 136.4, 135.8, 134.7, 134.6, 133.8, 133.1, 129.82, 129.80, 129.6, 129.5, 128.3, 128.2, 128.1, 127.8, 127.5, 126.9, 126.8, 126.7, 126.5, 126.3, 123.1, 122.3, 113.8, 133.7, 55.36, 55.35, 55.32, 55.30, 45.6, 45.5, 39.7, 38.48, 38.47, 38.40, 38.38, 37.8, 32.4, 28.5, 21.69, 21.67, 21.4, 20.8; FT-IR (thin film, neat): 2924, 1661, 1176, 787 cm$^{-1}$; HRMS (ESI): *m/z* calcd for $C_{28}H_{30}NO_5S$ $[M+H]^+$ : 492.1845; found : 492.1869.

**N-(2-((2,6-dioxo-4-phenylcyclohexyl)(4-methoxyphenyl)methyl)phenyl)-4-**



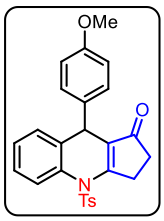

**methylbenzenesulfonamide (82t):** The reaction was performed at 0.078 mmol scale of **80b** white solid (23.8 mg, 57% yield); m. p. = 188–190 ºC; $R_f$ = 0.3 (20% EtOAc in hexane); The product was obtained as 1.3:1 diasteromeric mixture; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.83 (d, $J$ = 7.5 Hz, 1H), 7.61 – 7.59 (m, 1H), 7.39 – 7.33 (m, 8H), 7.31 – 7.29 (m, 6H), 7.27 – 7.22 (m, 11H), 6.99 (d, $J$ = 8.2 Hz, 1H), 6.93 – 6.88 (m, 4H), 6.73 – 6.71 (m, 4H), 6.61 – 6.59 (m, 2H), 5.24 (s, 1H), 5.21 (s, 1H), 3.79 (s, 3H), 3.71 (s, 3H), 3.57 – 3.50 (m, 1H), 3.46 – 3.33 (m, 2H), 3.17 – 3.12 (m, 1H), 2.95 – 2.85 (m, 2H), 2.82 – 2.75 (m, 2H), 2.66 – 2.58 (m, 1H), 2.34 (s, 3H), 2.29 (s, 3H); $^{13}$C{$^1$H} NMR (100 MHz, $CDCl_3$) $\delta$ 196.8, 196.6, 158.3, 158.1, 155.1, 154.5, 144.60, 144.59, 142.6, 142.4, 137.0, 136.7, 136.5, 136.0, 134.64, 134.61, 133.8, 133.0, 129.9, 129.8, 129.7, 129.5, 129.0, 128.9, 128.5, 128.4, 128.2, 127.9, 127.6, 127.33, 127.30, 127.1, 126.9, 126.8, 126.7, 126.5, 123.1, 122.3, 113.9, 113.8, 55.42, 55.40, 55.37, 55.34, 44.3, 44.2, 42.9, 39.3, 38.7, 38.61, 38.59, 38.50, 38.48, 37.2, 21.72, 21.70, 21.68, 21.66; FT-IR (thin film, neat): 2924, 1663, 1175, 788 cm$^{-1}$; HRMS (ESI): *m/z* calcd for $C_{33}H_{31}NNaO_5S$ $[M+Na]^+$ : 576.1821; found : 576.1831.

**9-Phenyl-4-tosyl-2,3,4,9-tetrahydro-1*H*-cyclopenta[*b*]quinolin-1-one (82u):** The reaction




was performed at 0.085 mmol scale of **80a**; white solid (25.0 mg, 72% yield); m. p. = 163–165 ºC; $R_f$ = 0.3 (20% EtOAc in hexane); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.15 (d, $J$ = 8.0 Hz, 1H), 7.47 (d, $J$ = 8.3 Hz, 2H), 7.35 – 7.30 (m, 1H), 7.22 (td, $J$ = 7.6, 1.0 Hz, 1H), 7.10 (dd, $J$ = 7.6, 1.2 Hz, 1H), 7.08 – 7.04 (m, 3H), 6.96 (t, $J$ = 7.8 Hz, 2H), 6.63 (d, $J$ = 7.6 Hz, 2H), 4.92 (s, 1H), 3.55 – 3.48 (m, 1H), 3.01 – 2.95 (m, 1H), 2.59 (qdd, $J$ = 18.5, 7.2, 2.2 Hz, 2H), 2.37 (s, 3H); $^{13}$C{$^1$H} NMR (100 MHz, $CDCl_3$) $\delta$ 204.1, 165.8, 145.1, 142.8, 136.5, 135.2, 131.1, 131.0, 130.3, 130.0, 128.3, 127.6, 127.4, 127.3, 127.0, 126.1, 123.0, 39.8, 35.4, 29.8, 21.79, 21.78; FT-IR (thin film, neat): 3059, 2924, 1694, 1171, 772 cm$^{-1}$; HRMS (ESI): *m/z* calcd for $C_{25}H_{22}NO_3S$ $[M+H]^+$ : 416.1320; found : 416.1325.

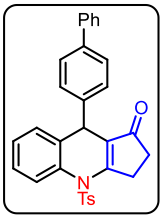
**9-(4-Methoxyphenyl)-4-tosyl-2,3,4,9-tetrahydro-1*H*-cyclopenta[*b*]quinolin-1-one (82v):**




The reaction was performed at 0.078 mmol scale of **80b**; white solid (28.0 mg, 80% yield); m. p. = 149–151 ºC; $R_f$ = 0.3 (20% EtOAc in hexane); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.13 (d, $J$ = 7.9 Hz, 1H), 7.49 (d, $J$ = 8.3 Hz, 2H), 7.33 – 7.29 (m, 1H), 7.21 (td, $J$ = 7.5, 1.0 Hz, 1H), 7.11 – 7.08 (m, 3H), 6.55 – 6.49 (m, 4H), 4.85 (s, 1H), 3.73 (s, 3H), 3.54 – 3.47 (m, 1H), 3.00 – 2.94 (m, 1H), 2.58 (qdd,

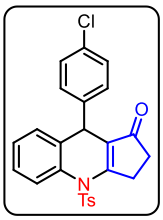
*J* = 18.5, 7.1, 2.2 Hz, 2H), 2.39 (s, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) $\delta$ 204.2, 165.5, 158.0, 145.2, 136.4, 135.3, 135.2, 131.5, 130.9, 130.5, 130.0, 128.4, 127.6, 127.4, 127.0, 123.0, 113.7, 55.29, 55.27, 39.1, 35.4, 29.8, 21.77, 21.75; FT-IR (thin film, neat): 2925, 1696, 1175, 765 $cm^{-1}$; HRMS (ESI): *m/z* calcd for $C_{26}H_{24}NO_4S$ $[M+H]^+$ : 446.1426; found : 444.1430.

**9-([1,1'-Biphenyl]-4-yl)-4-tosyl-2,3,4,9-tetrahydro-1*H*-cyclopenta[*b*]quinolin-1-one**



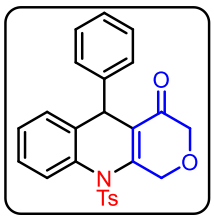

**(82w):** The reaction was performed at 0.070 mmol scale of **80e**; white solid (20.8 mg, 61% yield); m. p. = 188–190 ºC; $R_f$ = 0.3 (20% EtOAc in hexane); $^{1}H$ NMR (400 MHz, $CDCl_3$) $\delta$ 8.17 (d, *J* = 8.3 Hz, 1H), 7.51 – 7.48 (m, 4H), 7.42 (t, *J* = 7.4 Hz, 2H), 7.37 – 7.31 (m, 2H), 7.26 – 7.23 (m, 1H), 7.20 (d, *J* = 8.2 Hz, 2H), 7.15 (dd *J* = 7.6, 1.2 Hz, 1H), 7.07 (d, *J* = 8.2 Hz, 2H), 6.71 (d, *J* = 8.2 Hz, 2H), 4.97 (s, 1H), 3.57 – 3.50 (m, 1H), 3.03 – 2.97 (m, 1H), 2.62 (qdd, *J* = 18.6, 7.2, 2.2 Hz, 2H), 2.24 (s, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) $\delta$ 204.1, 165.9, 145.3, 142.0, 140.8, 139.1, 136.6, 135.3, 131.1, 131.0, 130.2, 130.0, 128.9, 127.8, 127.6, 127.5, 127.4, 127.1, 127.0, 126.9, 123.0, 39.6, 35.5, 29.9, 21.69, 21.68; FT-IR (thin film, neat): 2923, 1694, 1172, 753 $cm^{-1}$; HRMS (ESI): *m/z* calcd for $C_{31}H_{26}NO_3S$ $[M+H]^+$ : 492.1633; found : 492.1630.

**9-(4-Chlorophenyl)-4-tosyl-2,3,4,9-tetrahydro-1*H*-cyclopenta[*b*]quinolin-1-one (82x):**




The reaction was performed at 0.077 mmol scale of **80j**; white solid (20.0 mg, 58% yield); m. p. = 154–156 ºC; $R_f$ = 0.3 (20% EtOAc in hexane); $^{1}H$ NMR (400 MHz, $CDCl_3$) $\delta$ 8.17 (d, *J* = 8.4 Hz, 1H), 7.41 (d, *J* = 8.3 Hz, 2H), 7.38 – 7.34 (m, 1H), 7.26 – 7.23 (m, 1H), 7.09 – 7.04 (m, 3H), 6.89 (d, *J* = 8.4 Hz, 2H), 6.54 (d, *J* = 8.4 Hz, 2H), 4.88 (s, 1H), 3.56 – 3.49 (m, 1H), 3.02 – 2.95 (m, 1H), 2.61 (qdd, *J* = 18.6, 7.2, 2.2 Hz, 2H), 2.39 (s, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) $\delta$ 204.2, 166.3, 145.5, 141.6, 136.6, 135.2, 132.0, 130.9, 130.7, 130.5, 130.0, 128.6, 128.4, 127.8, 127.4, 127.2, 123.4, 39.1, 35.5, 29.9, 21.79, 21.77; FT-IR (thin film, neat): 2924, 1696, 1173, 767 $cm^{-1}$; HRMS (ESI): *m/z* calcd for $C_{25}H_{21}ClNO_3S$ $[M+H]^+$ : 450.0931; found : 450.0934.

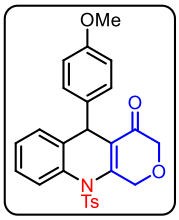
**5-Phenyl-10-tosyl-5,10-dihydro-1*H*-pyrano[3,4-*b*]quinolin-4(3H)-one (82y):** The reaction




was performed at 0.085 mmol scale of **80a**; white solid (26.0 mg, 72% yield); m. p. = 162–164 ºC; $R_f$ = 0.4 (20% EtOAc in hexane); $^{1}H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.92 (d, *J* = 7.7 Hz, 1H), 7.34 (td, *J* = 7.5, 1.6 Hz, 1H), 7.30 – 7.21 (m, 4H), 7.09 (t, *J* = 7.3 Hz, 1H), 7.00 (t, *J* = 7.8 Hz, 2H), 6.88 (d, *J* = 8.3 Hz, 2H), 6.72 (d, *J* = 7.8 Hz, 2H), 5.37 (d, *J* = 16.4 Hz, 1H), 5.14 (s, 1H), 4.63 (d, *J* = 16.5 Hz, 1H), 4.36 (d, *J* = 16.3 Hz, 1H), 4.18 (dd, *J* = 16.3, 1.2 Hz, 1H), 2.28 (s,

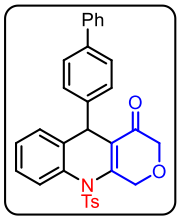
3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) $\delta$ 193.4, 153.5, 145.0, 142.3, 136.1, 134.7, 132.3, 130.4, 129.7, 128.5, 127.6, 127.3, 127.1, 127.0, 126.0, 125.3, 123.3, 72.1, 68.0, 38.3, 21.75, 21.74; FT-IR (thin film, neat): 3061, 2924, 1676, 1164, 780 $cm^{-1}$; HRMS (ESI): *m/z* calcd for $C_{25}H_{22}NO_4S$ $[M+H]^+$ : 432.1270; found : 432.1268.

**5-(4-Methoxyphenyl)-10-tosyl-5,10-dihydro-1*H*-pyrano[3,4-*b*]quinolin-4(3H)-one (82z):**



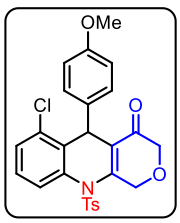

The reaction was performed at 0.078 mmol scale of **80b**; white solid (26.0 mg, 72% yield); m. p. = 159–161 ºC; $R_f$ = 0.3 (20% EtOAc in hexane); $^{1}H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.91 (d, *J* = 8.0 Hz, 1H), 7.35 – 7.25 (m, 4H), 7.20 (dd, *J* = 7.5, 1.3 Hz, 1H), 6.92 (d, *J* = 8.2 Hz, 2H), 6.62 (d, *J* = 8.6 Hz, 2H), 6.54 (d, *J* = 8.8 Hz, 2H), 5.35 (d, *J* = 16.4 Hz, 1H), 5.06 (s, 1H), 4.63 (d, *J* = 16.4 Hz, 1H), 4.34 (d, *J* = 16.2 Hz, 1H), 4.17 (dd, *J* = 16.3, 1.0 Hz, 1H), 3.75 (s, 3H), 2.31 (s, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) $\delta$ 193.5, 158.0, 153.3, 145.0, 136.0, 134.9, 134.6, 132.7, 130.2, 129.7, 128.2, 127.6, 127.2, 127.0, 125.6, 123.2, 113.8, 72.1, 68.0, 55.32, 55.30, 37.6, 21.68, 21.67; FT-IR (thin film, neat): 2926, 1675, 1163, 782 $cm^{-1}$; HRMS (ESI): *m/z* calcd for $C_{26}H_{24}NO_5S$ $[M+H]^+$ : 462.1370; found : 462.1375.

**5-([1,1'-Biphenyl]-4-yl)-10-tosyl-5,10-dihydro-1*H*-pyrano[3,4-*b*]quinolin-4(3H)-one**




**(82aa):** The reaction was performed at 0.070 mmol scale of **80e**; white solid (30.6 mg, 87% yield); m. p. = 171–173 ºC; $R_f$ = 04 (20% EtOAc in hexane); $^{1}H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.96 (dd, *J* = 8.2, 1.1 Hz, 1H), 7.55 – 7.53 (m, 2H), 7.46 – 7.42 (m, 2H) , 7.39 – 7.33 (m, 3H), 7.31 – 7.23 (m, 5H), 6.85 (d, *J* = 8.0 Hz, 2H), 6.79 (d, *J* = 8.0 Hz, 2H), 5.40 (d, *J* = 16.5 Hz, 1H), 5.19 (s, 1H), 4.66 (d, *J* = 16.5 Hz, 1H), 4.39 (d, *J* = 16.3 Hz, 1H), 4.21 (dd, *J* = 16.3, 1.3 Hz, 1H), 2.07 (s, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) $\delta$ 193.5, 153.7, 145.2, 141.5, 140.6, 138.9, 136.1, 134.9, 132.3, 130.3, 129.6, 129.0, 127.6, 127.54, 127.45, 127.4, 127.1, 127.0, 126.9, 125.3, 123.3, 72.1, 68.1, 38.1, 21.52, 21.51; FT-IR (thin film, neat): 2922, 1677, 1166, 758 $cm^{-1}$; HRMS (ESI): *m/z* calcd for $C_{31}H_{26}NO_4S$ $[M+H]^+$ : 508.1583; found : 508.1562.

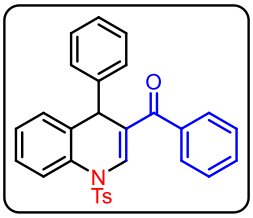
**6-Chloro-5-(4-methoxyphenyl)-10-tosyl-5,10-dihydro-1*H*-pyrano[3,4-*b*]quinolin-4(3H)-one (82ab):** The reaction was performed at 0.072 mmol scale of **80n**; white solid (32.0 mg, 90% yield); m. p. = 140–142 ºC; $R_f$ = 0.3 (20% EtOAc in hexane); $^{1}H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.86 (d, *J* = 8.9 Hz, 1H), 7.30 – 7.27 (m, 3H), 7.17 (d, *J* = 2.4 Hz, 1H), 6.95 (d, *J* = 8.1 Hz, 2H), 6.61 – 6.53 (m, 4H), 5.33 (d, *J* = 16.5 Hz, 1H), 4.99 (s, 1H), 4.63 (d, *J* = 16.5 Hz, 1H), 4.33 (dd, *J* = 16.4, 0.8 Hz, 1H), 4.17 (dd, *J* = 16.4, 1.3 Hz, 1H), 3.76 (s, 3H), 2.33 (s, 3H); $^{13}C\{^{1}H\}$ NMR (100



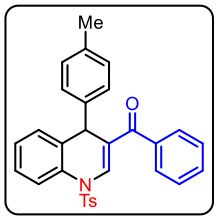
MHz, $CDCl_3$) $\delta$ 193.2, 158.2, 153.1, 145.4, 134.6, 134.5, 133.9, 132.7, 129.9, 129.8, 128.1, 127.6 (2C), 127.4, 125.2, 124.6, 113.9, 72.0, 68.0, 55.34, 55.31, 37.6, 21.71, 21.69; FT-IR (thin film, neat): 2924, 1678, 1166, 738 $cm^{-1}$; HRMS (ESI): *m/z* calcd for $C_{26}H_{23}ClNO_5S$ $[M+H]^+$ : 496.0985; found : 496.0974.

**General procedure for the synthesis of dihydroquinoline derivatives (84a-t):** MsOH (0.168 mmol, 3.0 equiv.) was added to a solution of *ortho*-aminobenzyl alcohol (0.084 mmol, 1.5 equiv.) and *N*,*N*-dimethyl enaminone (0.056 mmol, 1.0 equiv.) in 1,2-DCE (1.5 mL), and the resulting reaction mixture was stirred at 90 $^oC$. After the reaction was complete (based on TLC analysis), the solvent was removed under reduced pressure and the residue was then purified through a neutral alumina or silica gel column using EtOAc/Hexane mixture as an eluent to get the pure product.

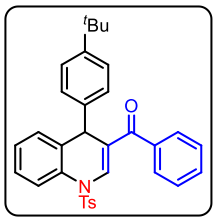
**Phenyl(4-phenyl-1-tosyl-1,4-dihydroquinolin-3-yl)methanone (84a):** The reaction was performed at 0.085 mmol scale of **80a**; white solid (22.1 mg, 85% yield); m. p. = 134–136 $^oC$; $R_f$ = 0.4 (15% EtOAc in hexane); $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 8.08 (d, *J* = 8.2 Hz, 1H), 7.95 (s, 1H), 7.70 (d, *J* = 8.3 Hz, 2H), 7.60 – 7.59 (m, 2H), 7.56 – 7.52 (m, 1H), 7.48 – 7.44 (m, 2H), 7.28 (d, *J* = 8.2 Hz, 2H), 7.25 – 7.20 (m, 1H), 7.15 – 7.13 (m, 2H), 7.09 – 7.05 (m, 1H), 7.04 – 7.00 (m, 2H), 6.82 – 6.80 (m, 2H), 5.38 (s, 1H), 2.44 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) $\delta$ 194.8, 145.5, 144.6, 138.4, 138.2, 134.8, 133.3, 132.0, 131.0, 130.3, 129.6, 129.0, 128.6, 128.5, 127.7, 127.64, 127.5, 126.7, 126.5, 122.9, 119.2, 42.14, 42.12, 21.85, 21.83; FT-IR (thin film, neat): 3065, 2924, 1636, 1172, 761 $cm^{-1}$; HRMS (ESI): *m/z* calcd for $C_{29}H_{24}NO_4S$ $[M+H]^+$ : 466.1477; found : 466.1472.




**Phenyl(4-(*p*-tolyl)-1-tosyl-1,4-dihydroquinolin-3-yl)methanone (84b):** The reaction was performed at 0.082 mmol scale of **80c**; white solid (22.8 mg, 87% yield); m. p. = 148–150 $^oC$; $R_f$ = 0.4 (15% EtOAc in hexane); $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 8.06 (d, *J* = 8.4 Hz, 1H), 7.94 (s, 1H), 7.71 (d, *J* = 8.3 Hz, 2H), 7.61 – 7.59 (m, 2H), 7.56 – 7.52 (m, 1H), 7.48 – 7.44 (m, 2H), 7.30 (d, *J* = 8.2 Hz, 2H), 7.23 – 7.19 (m, 1H), 7.14 – 7.10 (m, 2H), 6.83 (d, *J* = 8.0 Hz, 2H), 6.71 (d, *J* = 8.0 Hz, 2H), 5.34 (s, 1H), 2.45 (s, 3H), 2.22 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) $\delta$ 194.7, 145.3, 141.7, 138.3, 137.9, 135.9, 134.7, 133.1, 131.8, 130.8, 130.1, 129.7, 129.1, 128.9, 128.5, 127.5, 127.4, 127.3, 126.6, 122.9, 119.0, 41.67, 41.64, 21.72, 21.7, 21.02, 21.0; FT-IR (thin film, neat): 3029, 2924, 1636, 1172, 760 $cm^{-1}$; HRMS (ESI): *m/z* calcd for $C_{30}H_{26}NO_3S$ $[M+H]^+$ : 480.1633; found : 480.1628.

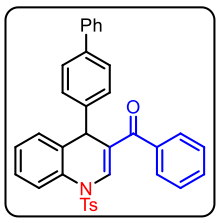


**(4-(4-(*Tert*-butyl)phenyl)-1-tosyl-1,4-dihydroquinolin-3-yl)(phenyl)methanone (84c):** The



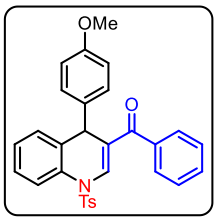

reaction was performed at 0.073 mmol scale of **80d**; white solid (20.0 mg, 78% yield); m. p. = 152–154 ºC; $R_f$ = 0.4 (15% EtOAc in hexane); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.06 (d, $J$ = 8.4 Hz, 1H), 7.94 (s, 1H), 7.72 (d, $J$ = 8.4 Hz, 2H), 7.61 – 7.59 (m, 2H), 7.56 – 7.52 (m, 1H), 7.48 – 7.44 (m, 2H), 7.31 (d, $J$ = 8.2 Hz, 2H), 7.23 – 7.19 (m, 1H), 7.16 – 7.10 (m, 2H), 7.02 (d, $J$ = 8.4 Hz, 2H), 6.70 (d, $J$ = 8.4 Hz, 2H), 5.34 (s, 1H), 2.46 (s, 3H), 1.22 (s, 9H); $^{13}$C{$^1$H} NMR (100 MHz, $CDCl_3$) $\delta$ 194.8, 149.1, 145.4, 141.4, 138.4, 138.2, 134.9, 133.2, 131.9, 130.9, 130.3, 129.9, 129.0, 128.6, 127.7, 127.4, 127.2, 126.7, 125.4, 122.9, 119.1, 41.7, 41.68, 34.4, 31.4, 21.89, 21.87; FT-IR (thin film, neat): 2960, 1637, 1174, 760 cm$^{-1}$; HRMS (ESI): *m/z* calcd for $C_{33}H_{32}NO_3S$ $[M+H]^+$ : 522.2103; found : 522.2101.

**(4-([1,1'-Biphenyl]-4-yl)-1-tosyl-1,4-dihydroquinolin-3-yl)(phenyl)methanone (84d):** The



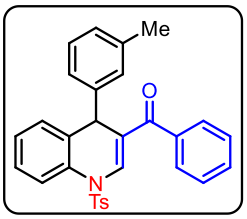

reaction was performed at 0.070 mmol scale of **80e**; white solid (22.2 mg, 88% yield); m. p. = 208–210 ºC; $R_f$ = 0.4 (15% EtOAc in hexane); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.10 (d, $J$ = 8.4 Hz, 1H), 7.98 (s, 1H), 7.71 (d, $J$ = 8.3 Hz, 2H), 7.63 – 7.61 (m, 2H), 7.57 – 7.53 (m, 1H), 7.49 – 7.45 (m, 4H), 7.40 (t, $J$ = 7.3 Hz, 2H), 7.33 – 7.30 (m, 2H), 7.28 – 7.23 (m, 4H), 7.20 – 7.14 (m, 2H), 6.87 (d, $J$ = 8.2 Hz, 2H), 5.42 (s, 1H), 2.39 (s, 3H); $^{13}$C{$^1$H} NMR (100 MHz, $CDCl_3$) $\delta$ 194.8, 145.6, 143.7, 140.8, 139.3, 138.43, 138.38, 134.9, 133.4, 132.0, 130.9, 130.3, 129.6, 129.0, 128.9, 128.6, 128.0, 127.64, 127.61, 127.3, 127.2, 127.0, 126.8, 122.8, 119.2, 41.82, 41.80, 21.8; FT-IR (thin film, neat): 3031, 2924, 1635, 1173, 763 cm$^{-1}$; HRMS (ESI): *m/z* calcd for $C_{35}H_{28}NO_3S$ $[M+H]^+$ : 542.1790; found : 542.1792.

**(4-(4-Methoxyphenyl)-1-tosyl-1,4-dihydroquinolin-3-yl)(phenyl)methanone (84e):** The

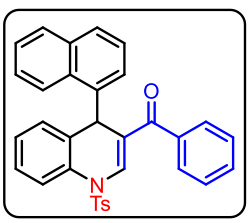



reaction was performed at 0.078 mmol scale of **80b**; white solid (20.6 mg, 80% yield); m. p. = 148–150 ºC; $R_f$ = 0.4 (15% EtOAc in hexane); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.07 (d, $J$ = 8.4 Hz, 1H), 7.91 (s, 1H), 7.70 (d, $J$ = 8.3 Hz, 2H), 7.60 – 7.58 (m, 2H), 7.56 – 7.52 (m, 1H), 7.48 – 7.44 (m, 2H), 7.30 (d, $J$ = 8.2 Hz, 2H), 7.24 – 7.19 (m, 1H), 7.12 (d, $J$ = 4.3 Hz, 2H), 6.71 (d, $J$ = 8.6 Hz, 2H), 6.57 – 6.53 (m, 2H), 5.32 (s, 1H), 3.71 (s, 3H), 2.45 (s, 3H); $^{13}$C{$^1$H} NMR (100 MHz, $CDCl_3$) $\delta$ 194.9, 158.1, 145.5, 138.4, 137.9, 137.1, 134.8, 133.2, 131.9, 130.9, 130.2, 129.9, 129.0, 128.7, 128.6, 127.6, 127.4, 126.7, 123.1, 119.2, 113.8, 55.25, 55.22, 41.33, 41.30, 21.84, 21.82; FT-IR (thin film, neat): 2924, 1637, 1175, 761 cm$^{-1}$; HRMS (ESI): *m/z* calcd for $C_{30}H_{26}NO_4S$ $[M+H]^+$ : 496.1583; found : 496.1575.

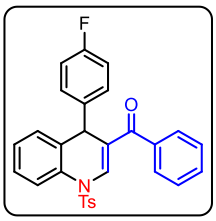
**Phenyl(4-(*m*-tolyl)-1-tosyl-1,4-dihydroquinolin-3-yl)methanone (84f):** The reaction was performed at 0.082 mmol scale of **80f**; white solid (20.3 mg, 78% yield); m. p. = 178–180 ºC; $R_f$ = 0.4 (15% EtOAc in hexane); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.03 (d, *J* = 8.4 Hz, 1H), 7.97 (s, 1H), 7.71 (d, *J* = 7.8 Hz, 2H), 7.61 (d, *J* = 7.6 Hz, 2H), 7.56 – 7.52 (m, 1H), 7.48 – 7.44 (m, 2H), 7.29 (d, *J* = 7.9 Hz, 2H), 7.20 (t, *J* = 7.8 Hz, 1H), 7.16 – 7.10 (m, 2H), 6.89 – 6.86 (m, 3H), 6.47 (s, 1H), 5.34 (s, 1H), 2.43 (s, 3H), 2.20 (s, 3H); $^{13}$C{$^1$H} NMR (100 MHz, $CDCl_3$) $\delta$ 194.8, 145.5, 144.7, 138.4, 138.1, 138.0, 134.9, 133.1, 131.9, 131.0, 130.2, 129.5, 129.0, 128.6, 128.4, 127.6 (2C), 127.42, 127.4, 126.6, 124.6, 122.6, 118.9, 42.08, 42.06, 21.84, 21.82, 21.61, 21.59; FT-IR (thin film, neat): 3059, 2924, 1633, 1173, 759 cm$^{-1}$; HRMS (ESI): *m/z* calcd for $C_{30}H_{26}NO_3S$ $[M+H]^+$ : 480.1633; found : 480.1620.




**(4-(Naphthalen-1-yl)-1-tosyl-1,4-dihydroquinolin-3-yl)(phenyl)methanone (84g):** The reaction was performed at 0.074 mmol scale of **80h**; white solid (17.0 mg, 66% yield); m. p. = 165–167 ºC; $R_f$ = 0.4 (15% EtOAc in hexane); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.62 (d, *J* = 8.6 Hz, 1H), 8.05 – 8.03 (m, 2H), 7.81 (d, *J* = 8.4 Hz, 2H), 7.77 (d, *J* = 8.3 Hz, 1H), 7.61 – 7.57 (m, 4H), 7.52 – 7.48 (m, 1H), 7.47 – 7.45 (m, 1H), 7.43 – 7.38 (m, 4H), 7.16 – 7.12 (m, 1H), 7.07 – 7.04 (m, 2H), 6.97 – 6.93 (m, 1H), 6.73 (d, *J* = 7.0 Hz, 1H), 6.21 (s, 1H), 2.49 (s, 3H); $^{13}$C{$^1$H} NMR (100 MHz, $CDCl_3$) $\delta$ 194.7, 145.6, 142.0, 138.0, 137.3, 134.9, 134.0, 132.5, 132.1, 131.1, 130.4 (2C), 130.3, 129.1, 128.8, 128.5, 127.7, 127.41, 127.4, 126.9, 126.7, 126.5, 125.8, 125.4, 123.9, 123.0, 119.1, 37.1, 21.91, 21.9; FT-IR (thin film, neat): 3063, 2925, 1636, 1174, 760 cm$^{-1}$; HRMS (ESI): *m/z* calcd for $C_{33}H_{26}NO_3S$ $[M+H]^+$ : 516.1633; found : 516.1636.

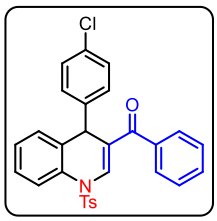



**(4-(4-Fluorophenyl)-1-tosyl-1,4-dihydroquinolin-3-yl)(phenyl)methanone (84h):** The reaction was performed at 0.081 mmol scale of **80i**; white solid (22.0 mg, 84% yield); m. p. = 158–160 ºC; $R_f$ = 0.5 (15% EtOAc in hexane); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.09 (d, *J* = 8.4 Hz, 1H), 7.94 (s, 1H), 7.67 (d, *J* = 8.3 Hz, 2H), 7.60 – 7.58 (m, 2H), 7.56 – 7.54 (m, 1H), 7.49 – 7.45 (m, 2H), 7.28 (d, *J* = 8.4 Hz, 2H), 7.26 – 7.23 (m, 1H), 7.17 – 7.14 (m, 1H), 7.12 – 7.10 (m, 1H), 6.77 – 6.72 (m, 2H), 6.71 – 6.65 (m, 2H), 5.35 (s, 1H), 2.44 (s, 3H); $^{13}$C{$^1$H} NMR (100 MHz, $CDCl_3$) $\delta$ 194.7, 161.4 (d, *J* = 243.5 Hz), 145.6, 140.6 (d, *J* = 3.1 Hz), 138.5, 138.3, 134.8, 133.3, 132.1, 130.9, 130.2, 129.4, 129.2 (d, *J* = 8.0 Hz), 128.9, 128.7, 127.7, 127.6, 126.8, 122.9, 119.3, 115.2 (d, *J* = 21.2 Hz), 41.32, 41.3, 21.81, 21.8; $^{19}$F{$^1$H} NMR (376



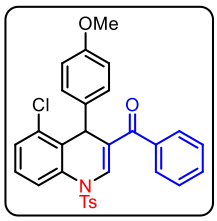
MHz, $CDCl_3$) δ –116.3; FT-IR (thin film, neat): 3069, 2925, 1634, 1173, 760 $cm^{-1}$; HRMS (ESI): *m/z* calcd for $C_{29}H_{23}FNO_3S$ $[M+H]^+$ : 484.1383; found : 484.1367.

**(4-(4-Chlorophenyl)-1-tosyl-1,4-dihydroquinolin-3-yl)(phenyl)methanone (84i):** The



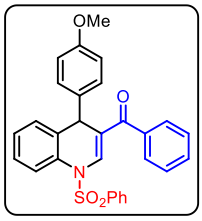

reaction was performed at 0.077 mmol scale of **80j**; white solid (20.1 mg, 78% yield); m. p. = 127–129 ºC; $R_f$ = 0.5 (15% EtOAc in hexane); $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 8.10 (d, *J* = 8.2 Hz, 1H), 7.95 (s, 1H), 7.66 (d, *J* = 8.4 Hz, 2H), 7.60 – 7.58 (m, 2H), 7.56 – 7.54 (m, 1H), 7.49 – 7.45 (m, 2H), 7.28 – 7.24 (m, 3H), 7.16 (td, *J* = 7.6, 1.0 Hz, 1H), 7.11 (dd, *J* = 7.6, 1.6 Hz, 1H), 6.97 – 6.94 (m, 2H), 6.72 – 6.69 (m, 2H), 5.34 (s, 1H), 2.45 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) $\delta$ 194.7, 145.7, 143.2, 138.8, 138.2, 134.8, 133.4, 132.3, 132.1, 130.8, 130.2, 129.1, 128.95, 128.93, 128.7, 128.6, 127.8, 127.5, 126.9, 122.7, 119.4, 41.42, 41.4, 21.84, 21.82; FT-IR (thin film, neat): 2925, 1633, 1174, 761 $cm^{-1}$; HRMS (ESI): *m/z* calcd for $C_{29}H_{23}ClNO_3S$ $[M+H]^+$ : 500.1087; found : 500.1084.

**(5-Chloro-4-(4-methoxyphenyl)-1-tosyl-1,4-dihydroquinolin-3-yl)(phenyl)methanone**




**(84j):** The reaction was performed at 0.072 mmol scale of **80n**; white solid (16.2 mg, 64% yield); m. p. = 184–186 ºC; $R_f$ = 0.4 (15% EtOAc in hexane); $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 8.04 (d, *J* = 9.0 Hz, 1H), 7.87 (s, 1H), 7.69 (d, *J* = 8.2 Hz, 2H), 7.57 (d, *J* = 7.6 Hz, 2H), 7.54 (d, *J* = 7.0 Hz, 1H), 7.48 – 7.44 (m, 2H), 7.32 (d, *J* = 8.2 Hz, 2H), 7.17 (dd, *J* = 9.0, 2.4 Hz, 1H), 7.08 (d, *J* = 2.3 Hz, 1H), 6.66 (d, *J* = 8.6 Hz, 2H), 6.55 (d, *J* = 8.6 Hz, 2H), 5.25 (s, 1H), 3.71 (s, 3H), 2.47 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) $\delta$ 194.6, 158.3, 145.8, 138.2, 137.4, 136.4, 134.5, 132.1, 132.09, 131.83, 131.76, 130.6, 130.4, 128.9, 128.7, 128.6, 127.64, 127.6, 122.9, 120.7, 114.0, 55.29, 55.26, 41.37, 41.35, 21.87, 21.86; FT-IR (thin film, neat): 2924, 1635, 1174, 730 $cm^{-1}$; HRMS (ESI): *m/z* calcd for $C_{30}H_{25}ClNO_4S$ $[M+H]^+$ : 530.1193; found : 530.1187.

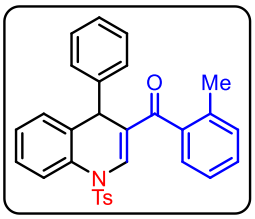
**(4-(4-Methoxyphenyl)-1-(phenylsulfonyl)-1,4-dihydroquinolin-3-yl)(phenyl)methanone**



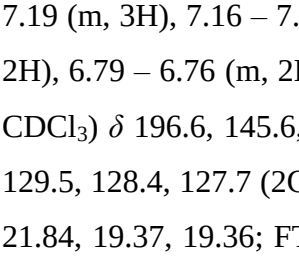

**(84k):** The reaction was performed at 0.081 mmol scale of **80o**; white solid (16.1 mg, 62% yield); m. p. = 182–184 ºC; $R_f$ = 0.4 (15% EtOAc in hexane); $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 8.06 (d, *J* = 8.5 Hz, 1H), 7.90 (s, 1H), 7.82 (d, *J* = 7.9 Hz, 2H), 7.66 (t, *J* = 7.4 Hz, 1H), 7.59 (d, *J* = 7.6 Hz, 2H), 7.56 – 7.50 (m, 3H), 7.48 – 7.44 (m, 2H), 7.24 – 7.20 (m, 1H), 7.15 – 7.12 (m, 2H), 6.69 (d, *J* = 8.5 Hz, 2H), 6.55 (d, *J* = 8.5 Hz, 2H), 5.31 (s, 1H), 3.70 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) $\delta$ 194.9, 158.1, 138.4, 137.9, 137.7, 136.9, 134.3, 133.2, 132.0, 131.0, 129.9,

129.7, 129.0, 128.7, 128.6, 127.6, 127.5, 126.8, 123.4, 119.1, 113.9, 55.29, 55.27, 41.35, 41.33; FT-IR (thin film, neat): 2924, 1638, 1178, 759 $cm^{-1}$; HRMS (ESI): *m/z* calcd for $C_{29}H_{24}NO_4S$ $[M+H]^+$ : 482.1426; found : 482.1405.

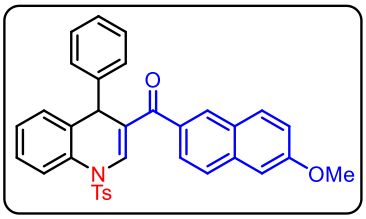
**(4-Phenyl-1-tosyl-1,4-dihydroquinolin-3-yl)(*o*-tolyl)methanone (84l):** The reaction was performed at 0.085 mmol scale of **80a**; white solid (22.0 mg, 84% yield); m. p. = 166–168 ºC; $R_f$ = 0.4 (15% EtOAc in hexane); $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 8.08 (d, *J* = 8.4 Hz, 1H), 7.72 (s, 1H), 7.66 – 7.64 (m, 2H), 7.35 (td, *J* = 7.5, 1.3 Hz, 1H), 7.29 (d, *J* = 8.0 Hz, 2H), 7.25 – 7.19 (m, 3H), 7.16 – 7.13 (m, 2H), 7.12 – 7.09 (m, 1H), 7.09 – 7.05 (m, 1H), 7.03 – 6.99 (m, 2H), 6.79 – 6.76 (m, 2H), 5.38 (s, 1H), 2.45 (s, 3H), 2.16 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) $\delta$ 196.6, 145.6, 144.6, 139.4, 138.4, 136.0, 134.7, 133.3, 131.1, 131.0, 130.2, 130.1, 129.5, 128.4, 127.7 (2C), 127.6, 127.4, 126.8, 126.5, 125.4, 124.3 119.3, 41.44, 41.43, 21.85, 21.84, 19.37, 19.36; FT-IR (thin film, neat): 2924, 1631, 1173, 739 $cm^{-1}$; HRMS (ESI): *m/z* calcd for $C_{30}H_{26}NO_3S$ $[M+H]^+$ : 480.1633; found : 480.1645.




**(4-Phenyl-1-tosyl-1,4-dihydroquinolin-3-yl)(p-tolyl)methanone (84m):** The reaction was performed at 0.085 mmol scale of **80a**; white solid (23.8 mg, 91% yield); m. p. = 141–143 ºC; $R_f$ = 0.4 (15% EtOAc in hexane); $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 8.09 (d, *J* = 8.4 Hz, 1H), 7.95 (s, 1H), 7.72 (d, *J* = 8.0 Hz, 2H), 7.54 (d, *J* = 9.8 Hz, 2H), 7.31 – 7.27 (m, 4H), 7.25 – 7.22 (m, 1H), 7.15 – 7.14 (m, 2H), 7.09 – 7.05 (m, 2H), 7.03 – 7.01 (m, 1H), 6.81 (d, *J* = 7.4 Hz, 2H), 5.39 (s, 1H), 2.46 (s, 3H), 2.44 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) $\delta$ 194.6, 145.4, 144.7, 142.7, 137.6, 135.6, 134.9, 133.3, 131.0, 130.2, 129.6, 129.3, 129.2, 128.5, 127.7, 127.6, 127.5, 126.7, 126.4, 123.0 119.2, 42.27, 42.24, 21.85, 21.82, 21.73, 21.70; FT-IR (thin film, neat): 3029, 2924, 1633, 1173, 752 $cm^{-1}$; HRMS (ESI): *m/z* calcd for $C_{30}H_{26}NO_3S$ $[M+H]^+$ : 480.1633; found : 480.1651.

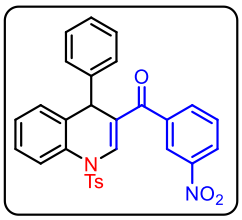



**(6-Methoxynaphthalen-2-yl)(4-phenyl-1-tosyl-1,4-dihydroquinolin-3-yl)methanone (84n):** The reaction was performed at 0.085 mmol scale of **80a**; white solid (18.0 mg, 58% yield); m. p. = 141–143 ºC; $R_f$ = 0.4 (15% EtOAc in hexane); $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 8.08 (d, *J* = 8.4 Hz, 1H), 8.04 (s, 1H), 8.00 (s, 1H), 7.83 – 7.79 (m, 2H), 7.72 – 7.68 (m, 3H), 7.30 (d, *J* = 8.2 Hz, 2H), 7.25 – 7.20 (m, 2H), 7.17 – 7.14 (m, 3H), 7.09 – 7.01 (m, 3H), 6.85 – 6.83 (m, 2H), 5.41 (s, 1H), 3.96 (s, 3H), 2.45 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) $\delta$ 194.5, 145.4, 144.7, 137.6, 136.8, 134.9, 133.44, 133.4, 131.0,



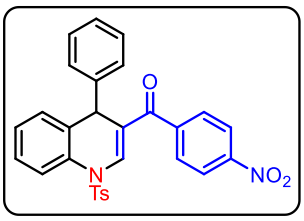
130.8, 130.3, 130.1, 129.7, 128.5, 127.9, 127.7, 127.6 (2C), 127.5, 127.3, 126.7, 126.5, 126.1, 123.1, 119.9, 119.2, 105.9, 55.59, 55.55, 42.47, 42.44, 21.86, 21.83; FT-IR (thin film, neat): 3031, 2925, 1636, 1173, 759 $cm^{-1}$; HRMS (ESI): *m/z* calcd for $C_{34}H_{28}NO_4S$ $[M+H]^+$ : 546.1739; found : 546.1750.

**(3-Nitrophenyl)(4-phenyl-1-tosyl-1,4-dihydroquinolin-3-yl)methanone (84o):** The



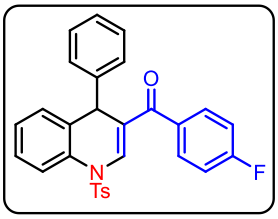

reaction was performed at 0.085 mmol scale of **80a**; white solid (24.0 mg, 83% yield); m. p. = 145–147 ºC; $R_f$ = 0.4 (15% EtOAc in hexane); $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 8.42 – 8.39 (m, 1H), 8.38 – 8.37 (m, 1H), 8.14 (d, *J* = 8.4 Hz, 1H), 7.95 (d, *J* = 7.7 Hz, 1H), 7.90 (s, 1H), 7.78 (d, *J* = 8.3 Hz, 2H), 7.68 (t, *J* = 7.9 Hz, 1H), 7.38 (d, *J* = 8.2 Hz, 2H), 7.27 – 7.23 (m, 1H), 7.17 – 7.11 (m, 2H), 7.10 – 7.06 (m, 1H), 7.04 – 7.00 (m, 2H), 6.75 – 6.74 (m, 2H), 5.34 (s, 1H), 2.48 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) $\delta$ 192.2, 148.0, 145.9, 144.3, 139.8, 138.8, 134.7, 134.5, 132.9, 131.0, 130.5, 130.1, 129.2, 128.6, 127.8, 127.64, 127.61, 127.0, 126.8, 126.4, 123.7, 122.3, 119.3, 42.16, 42.13, 21.89, 21.87; FT-IR (thin film, neat): 3078, 2924, 1635, 1173, 763 $cm^{-1}$; HRMS (ESI): *m/z* calcd for $C_{29}H_{23}N_2O_5S$ $[M+H]^+$ : 511.1328; found : 511.1339.

**(4-Nitrophenyl)(4-phenyl-1-tosyl-1,4-dihydroquinolin-3-yl)methanone (84p):** The




reaction was performed at 0.085 mmol scale of **80a**; white solid (20.1 mg, 70% yield); m. p. = 165–167 ºC; $R_f$ = 0.4 (15% EtOAc in hexane); $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 8.34 – 8.30 (m, 2H), 8.05 (d, *J* = 8.4 Hz, 1H), 7.92 (s, 1H), 7.72 – 7.69 (m, 4H), 7.31 (d, *J* = 8.0 Hz, 2H), 7.25 – 7.20 (m, 1H), 7.17 – 7.14 (m, 2H), 7.12 – 7.07 (m, 1H), 7.07 – 7.02 (m, 2H), 6.84 – 6.81 (m, 2H), 5.34 (s, 1H), 2.45 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) $\delta$ 192.7, 149.6, 145.9, 144.4, 144.0, 139.5, 134.5, 133.0, 131.0, 130.4, 129.7, 129.1, 128.6, 127.8, 127.7, 127.6, 127.0, 126.8, 123.9, 122.2, 118.9, 41.93, 41.91, 21.90, 21.87; FT-IR (thin film, neat): 2924, 1631, 1173, 760 $cm^{-1}$; HRMS (ESI): *m/z* calcd for $C_{29}H_{23}N_2O_5S$ $[M+H]^+$ : 511.1328; found : 511.1351.

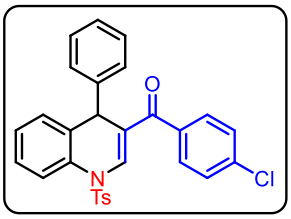
**(4-Fluorophenyl)(4-phenyl-1-tosyl-1,4-dihydroquinolin-3-yl)methanone (84q):** The




reaction was performed at 0.085 mmol scale of **80a**; white solid (20.1 mg, 77% yield); m. p. = 149–151 ºC; $R_f$ = 0.5 (15% EtOAc in hexane); $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 8.05 (d, *J* = 8.4 Hz, 1H), 7.91 (s, 1H), 7.70 (d, *J* = 8.3 Hz, 2H), 7.64 – 7.60 (m, 2H), 7.29 (d, *J* = 8.2

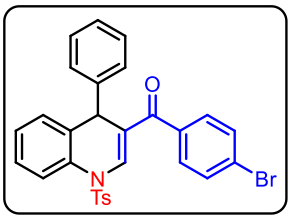
Hz, 2H), 7.24 – 7.20 (m, 1H), 7.17 – 7.12 (m, 4H), 7.09 – 7.00 (m, 3H), 6.80 (d, *J* = 6.9 Hz, 2H), 5.35 (s, 1H), 2.44 (s, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) $\delta$ 193.4, 165.1 (d, *J* = 251.5 Hz), 145.6, 144.6, 139.1, 137.8, 134.7, 134.5 (d, *J* = 3.1 Hz), 133.2, 131.5, 131.4, 130.9, 130.3, 129.4, 128.5, 127.62, 127.58, 126.7 (d, *J* = 17.3 Hz), 122.6, 119.1, 115.8 (d, *J* = 21.7 Hz), 42.25, 42.24, 21.86, 21.84; $^{19}F\{^{1}H\}$ NMR (376 MHz, $CDCl_3$) δ –107.0; FT-IR (thin film, neat): 2924, 1635, 1173, 760 $cm^{-1}$; HRMS (ESI): *m/z* calcd for $C_{29}H_{23}FNO_3S$ $[M+H]^+$ : 484.1383; found : 484.1386.

**(4-Chlorophenyl)(4-phenyl-1-tosyl-1,4-dihydroquinolin-3-yl)methanone (84r):** The



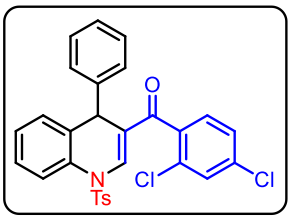

reaction was performed at 0.085 mmol scale of **80a**; white solid (21.6 mg, 84% yield); m. p. = 149–151 ºC; $R_f$ = 0.5 (15% EtOAc in hexane); $^{1}H$ NMR (400 MHz, $CDCl_3$) $\delta$ 8.06 (d, *J* = 8.4 Hz, 1H), 7.92 (s, 1H), 7.70 (d, *J* = 8.3 Hz, 2H), 7.54 (d, *J* = 8.4 Hz, 2H), 7.44 (d, *J* = 8.4 Hz, 2H), 7.29 (d, *J* = 8.3 Hz, 2H), 7.24 – 7.19 (m, 1H), 7.13 (d, *J* = 4.2 Hz, 2H), 7.09 – 7.05 (m, 1H), 7.04 – 7.00 (m, 2H), 6.81 – 6.79 (m, 2H), 5.34 (s, 1H), 2.44 (s, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) $\delta$ 193.5, 145.6, 144.6, 138.3, 138.1, 136.7, 134.7, 133.2, 130.9, 130.4, 130.3, 129.4, 128.9, 128.5, 127.63 (2C), 127.6, 126.8, 126.6, 122.5, 119.1, 42.17, 42.15, 21.86, 21.84; FT-IR (thin film, neat): 2924, 1633, 1173, 757 $cm^{-1}$; HRMS (ESI): *m/z* calcd for $C_{29}H_{23}ClNO_3S$ $[M+H]^+$ : 500.1087; found : 500.1092.

**(4-Bromophenyl)(4-phenyl-1-tosyl-1,4-dihydroquinolin-3-yl)methanone (84s):** The




reaction was performed at 0.085 mmol scale of **80a**; white solid (17.7 mg, 57% yield); m. p. = 133–135 ºC; $R_f$ = 0.5 (15% EtOAc in hexane); $^{1}H$ NMR (400 MHz, $CDCl_3$) $\delta$ 8.10 (d, *J* = 8.4 Hz, 1H), 7.90 (s, 1H), 7.73 (d, *J* = 8.4 Hz, 2H), 7.68 – 7.65 (m, 2H), 7.51 (d, *J* = 7.7 Hz, 1H), 7.37 – 7.34 (m, 2H), 7.32 – 7.29 (m, 1H), 7.25 – 7.20 (m, 1H), 7.15 – 7.12 (m, 2H), 7.09 – 7.05 (m, 1H), 7.03 – 6.99 (m, 2H), 6.75 (d, *J* = 7.2 Hz, 2H), 5.32 (s, 1H), 2.46 (s, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) $\delta$ 193.1, 145.7, 144.4, 140.3, 138.5, 134.8, 134.7, 133.2, 131.8, 131.0, 130.4, 130.3, 129.4, 128.6, 127.6, 127.4, 126.9, 126.6, 122.8, 122.7, 119.3, 42.14, 42.12, 21.88, 21.86; FT-IR (thin film, neat): 2924, 1630, 1173, 745 $cm^{-1}$; HRMS (ESI): *m/z* calcd for $C_{29}H_{23}BrNO_3S$ $[M+H]^+$ : 544.0582; found : 544.0594.

**(2,4-Dichlorophenyl)(4-phenyl-1-tosyl-1,4-dihydroquinolin-3-yl)methanone (84t):** The

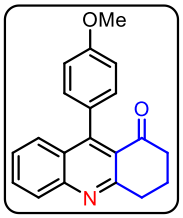



reaction was performed at 0.085 mmol scale of **80a**; white solid (20.1 mg, 67% yield); m. p. = 174–176 ºC; $R_f$ = 0.5 (20% EtOAc in

hexane); $^{1}$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.09 (d, $J$ = 8.4 Hz, 1H), 7.74 (s, 1H), 7.70 – 7.67 (m, 2H), 7.46 (d, $J$ = 1.9 Hz, 1H), 7.33 (dd, $J$ = 8.2, 1.9 Hz, 1H), 7.28 (d, $J$ = 8.0 Hz, 2H), 7.25 – 7.19 (m, 1H), 7.16 – 7.13 (m, 3H), 7.09 – 7.05 (m, 1H), 7.02 – 6.98 (m, 2H), 6.78 – 6.75 (m, 2H), 5.32 (s, 1H), 2.44 (s, 3H); $^{13}$C{$^{1}$H} NMR (100 MHz, $CDCl_3$) $\delta$ 192.0, 145.7, 144.2, 140.3, 136.53, 136.50, 134.5, 133.1, 132.1, 131.0, 130.3, 130.2, 129.8, 129.3, 128.4, 127.78, 127.75, 127.7, 127.4, 127.0, 126.6, 123.1, 119.1, 41.35, 41.33, 21.86, 21.83; FT-IR (thin film, neat): 2924, 1630, 1174, 757 cm$^{-1}$; HRMS (ESI): *m/z* calcd for $C_{29}H_{22}Cl_2NO_3S$ $[M+H]^+$ : 534.0697; found : 534.0714.

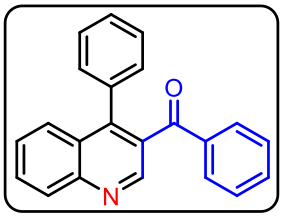
**Procedure for the synthesis of dihydroacridinone derivative (85):** DBU (78 µl, 0.522 mmol) was added to a solution of **82b** (40 mg, 0.087 mmol) in 1.5 ml of acetonitrile, the reaction mixture was then stirred at 80 $^{o}$C. After the reaction was complete (based on TLC analysis), the residue was 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.

**9-(4-Methoxyphenyl)-3,4-dihydroacridin-1(2H)-one (85):** Yellow solid (22.2 mg, 84% yield); m. p. = 187–189 ºC; $R_f$ = 0.2 (30% EtOAc in hexane); $^{1}$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.05 (d, $J$ = 8.4 Hz, 1H), 7.78 – 7.74 (m, 1H), 7.54 (d, $J$ = 8.0 Hz, 1H), 7.41 (t, $J$ = 7.3 Hz, 1H), 7.11 (d, $J$ = 8.6 Hz, 2H), 7.04 (d, $J$ = 8.6 Hz, 2H), 3.90 (s, 3H), 3.36 (t, $J$ = 6.2 Hz, 2H), 2.71 (t, $J$ = 6.5 Hz, 2H), 2.25 (quint, $J$ = 6.7 Hz, 2H); $^{13}$C{$^{1}$H} NMR (100 MHz, $CDCl_3$) $\delta$ 198.4, 162.4, 159.2, 151.5, 148.8, 131.8, 129.63, 129.58, 128.6, 128.4, 128.0, 126.5, 124.4, 113.8, 55.4, 40.9, 34.8, 21.5; FT-IR (thin film, neat): 2925, 1692, 1178, 768 cm$^{-1}$; HRMS (ESI): *m/z* calcd for $C_{20}H_{18}NO_2$ $[M+H]^+$ : 304.1338; found : 304.1346.




**Procedure for the synthesis of quinoline derivative (86):** DBU (115 µl, 0.773 mmol) was added to a solution of **84a** (60 mg, 0.129 mmol) in 1.5 ml of toluene, and the reaction mixture was then stirred at 80 $^{o}$C. 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 neutral alumina gel column using EtOAc/Hexane mixture as an eluent to get the pure product.

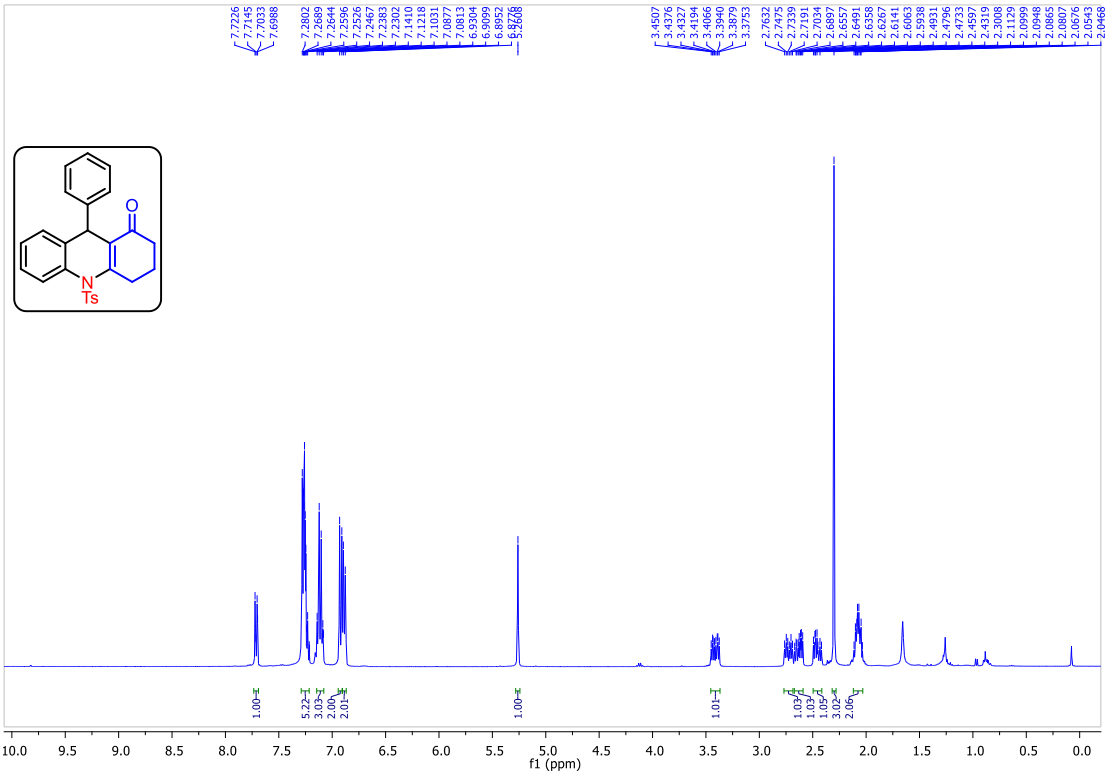
**Phenyl(4-phenylquinolin-3-yl)methanone (86):** Buff white gummy solid (29 mg, 72% yield); $R_f$ = 0.4 (15% EtOAc in hexane); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 9.00 (s, 1H), 8.24 (d, $J$ = 8.4 Hz, 1H), 7.84 – 7.78 (m, 2H), 7.62 – 7.60 (m, 2H), 7.58 – 7.53 (m, 1H), 7.44 (t, $J$ = 7.4 Hz, 1H), 7.30 – 7.27 (m, 7H); $^{13}$C{$^1$H} NMR (100 MHz, $CDCl_3$) $\delta$ 197.0, 148.9, 148.7, 147.2, 137.4, 135.0, 133.4, 131.9, 130.7, 130.2, 129.91, 129.87, 128.7, 128.37, 128.35, 127.7, 126.9, 126.6; FT-IR (thin film, neat): 3028, 2929, 1684, 1180, 765 cm$^{-1}$; HRMS (ESI): *m/z* calcd for $C_{22}H_{16}NO$ $[M+H]^+$ : 310.1232; found : 310.1247.



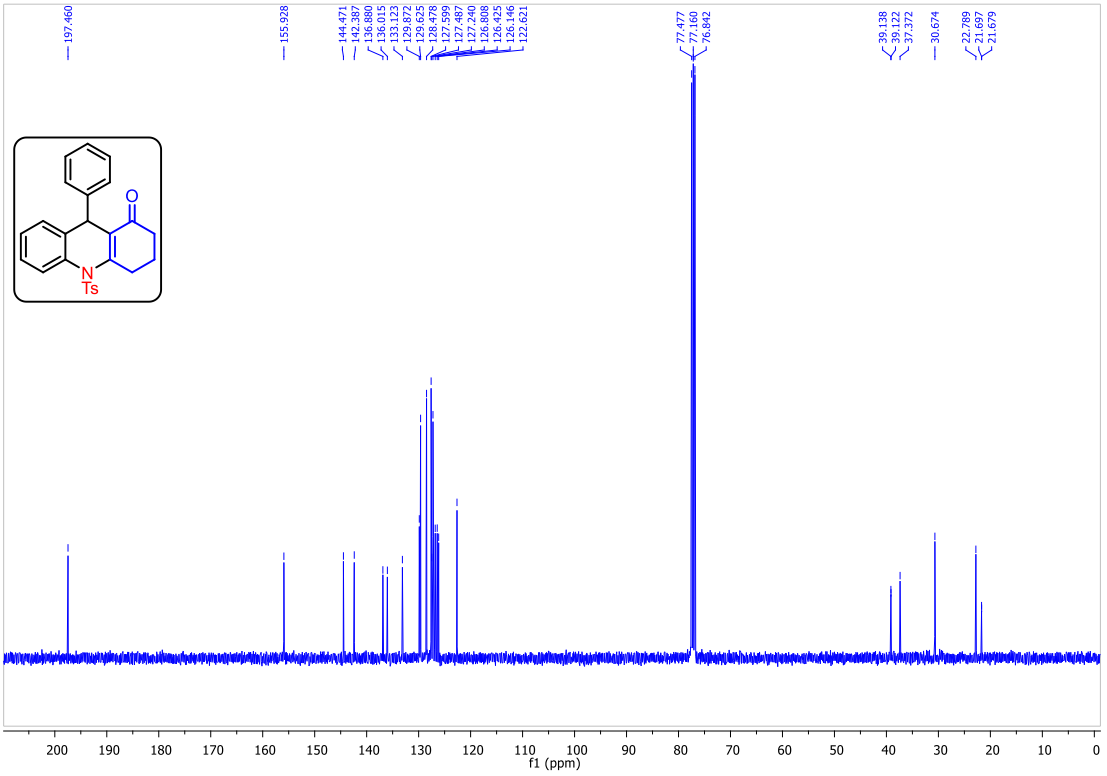

**Procedure for gram-scale synthesis of 82b.**

In a 50 mL oven-dried round bottom flask, *ortho*-aminobenzyl alcohol **80b** (0.5 g, 1.30 mmol), 1,3-cyclohexanedione **81a** (0.19 g, 1.69 mmol), and TsOH (0.32 g, 1.69 mmol) were dissolved in 15 mL of 1,2-DCE. The resulting reaction mixture was stirred at 70 $^o$C; after the completion of the reaction, the organic layer was concentrated under reduced pressure. The residue was then purified through silica gel chromatography using EtOAc/Hexane mixture as an eluent to get the pure **82b** in 74% isolated yield.

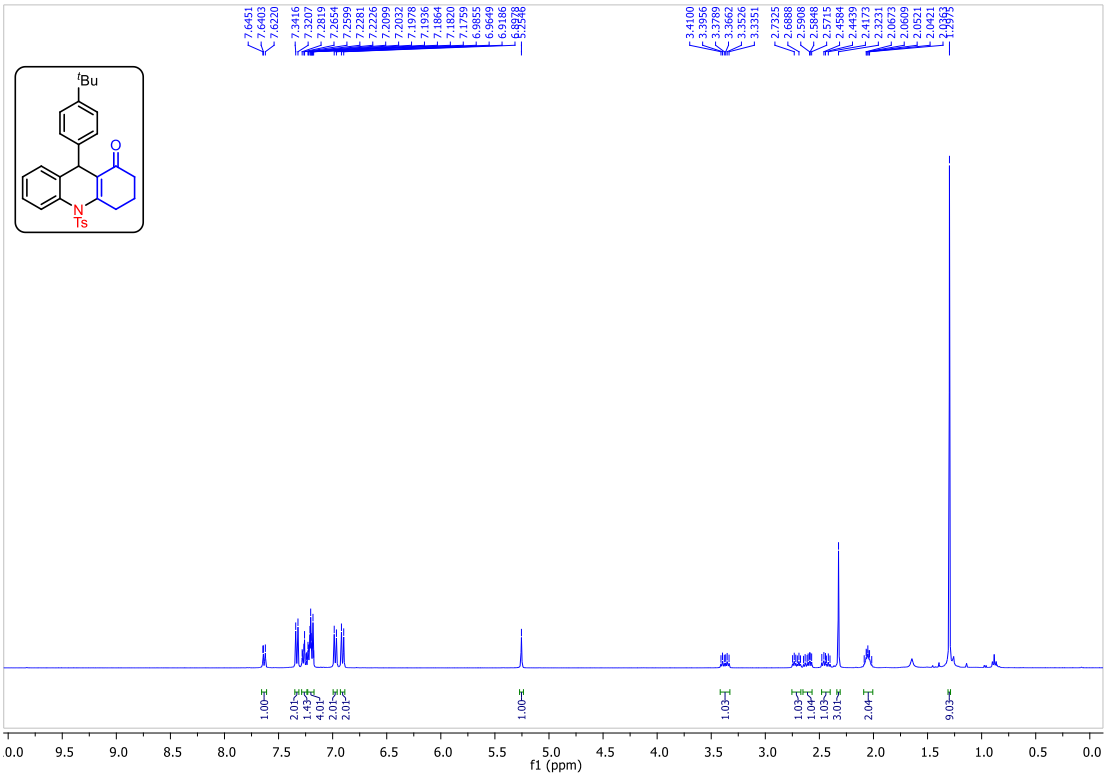
## $^{1}$H Spectra of **82a**



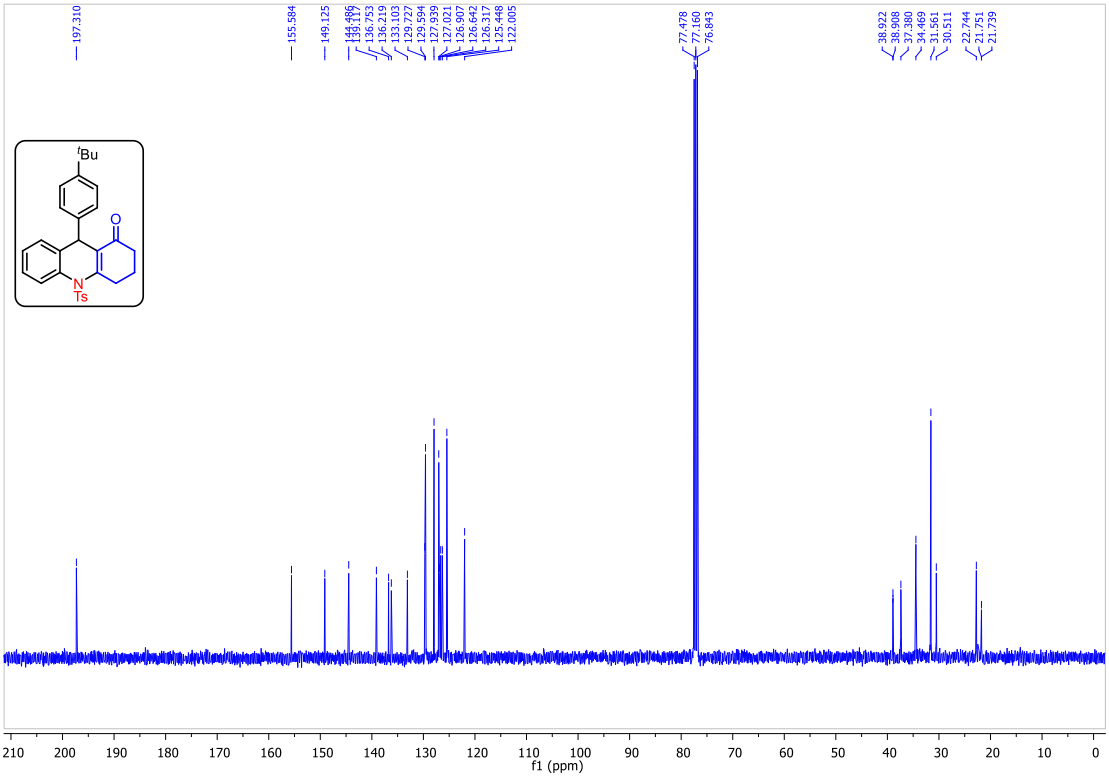

## $^{13}$C Spectra of **82a**



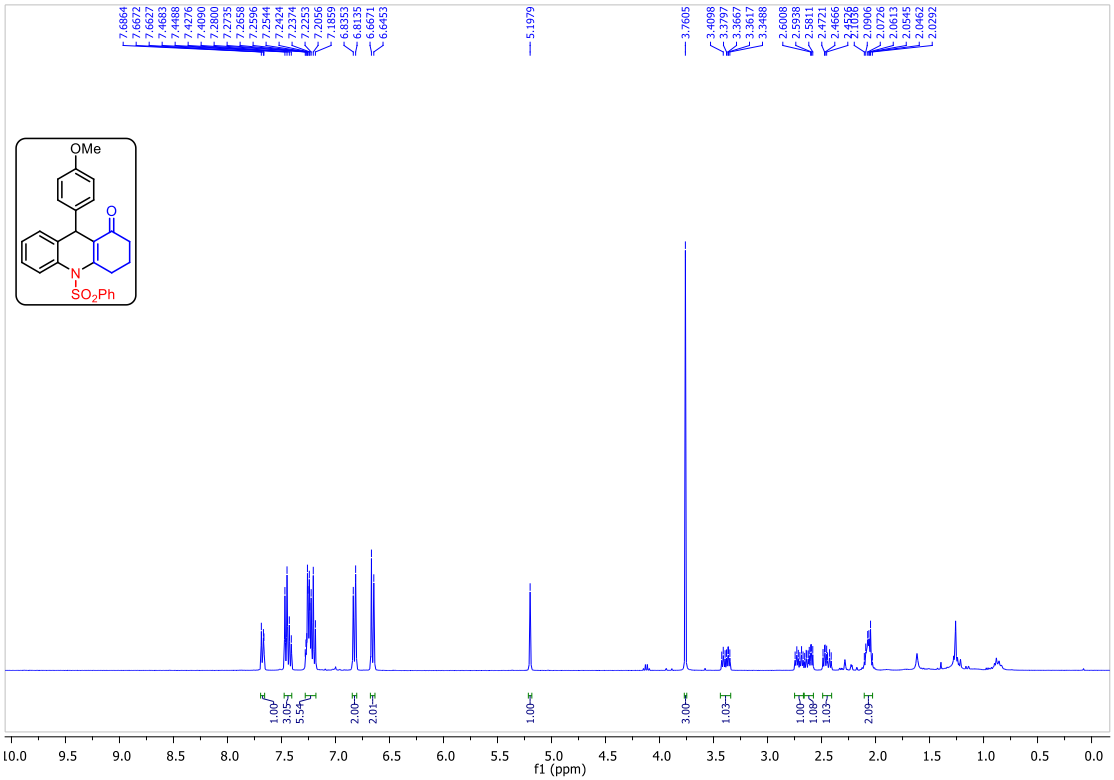
## $^{1}$H Spectra of **82d**



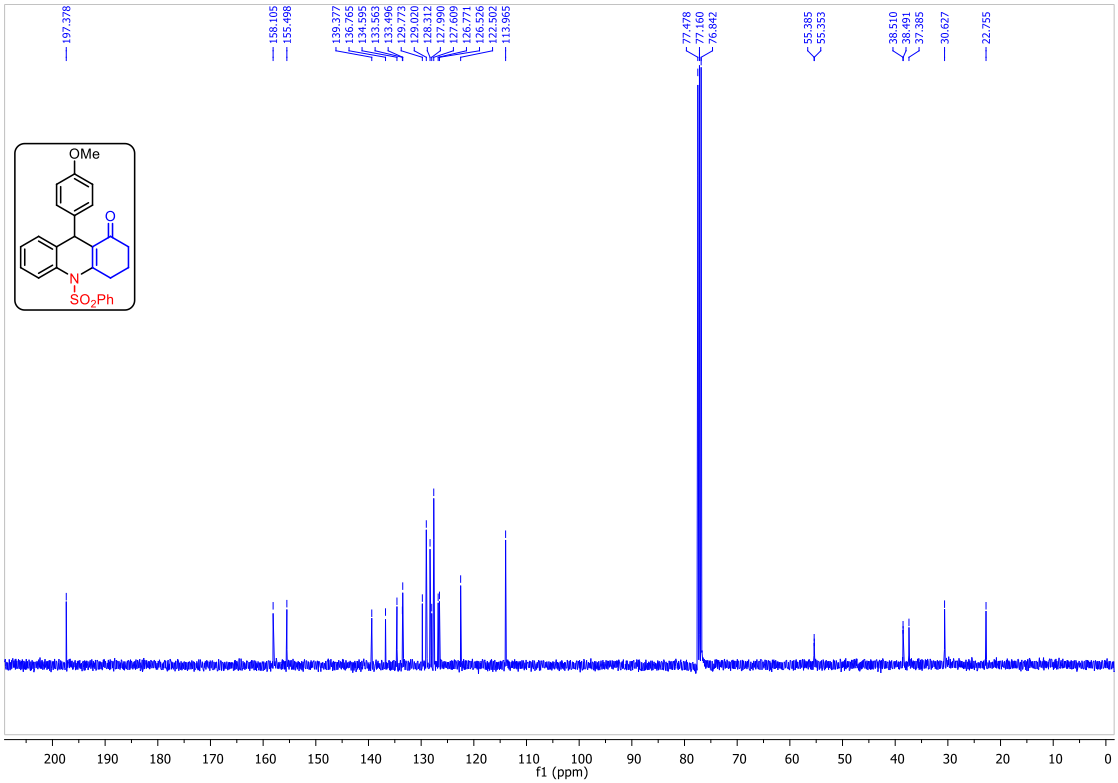

## $^{13}$C Spectra of **82d**



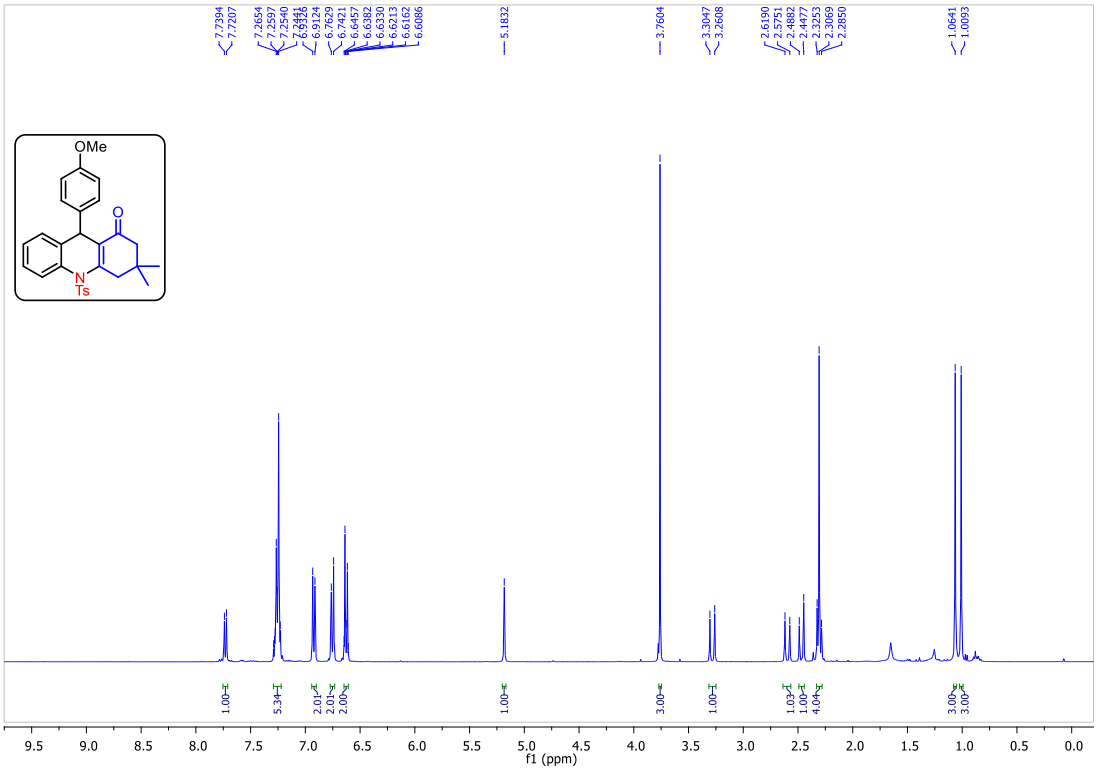
## $^{1}$H NMR Spectra of **82o**




## $^{13}$C Spectra of **82o**



## $^{1}$H Spectra of **82q**

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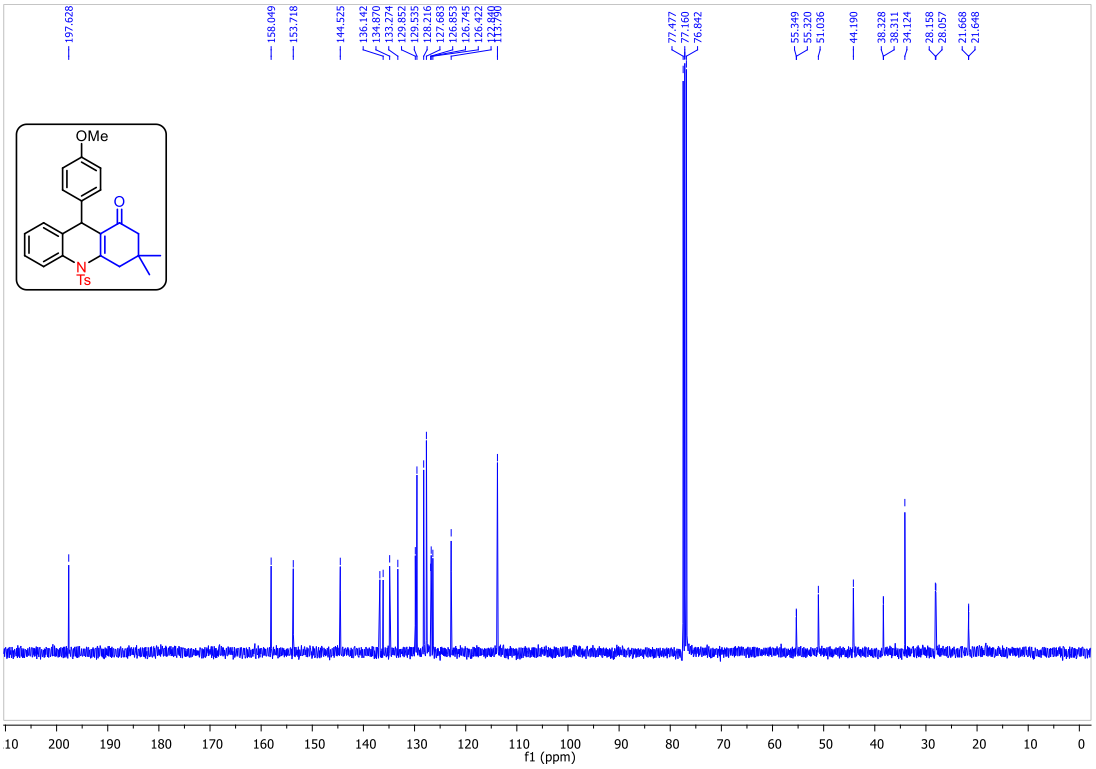

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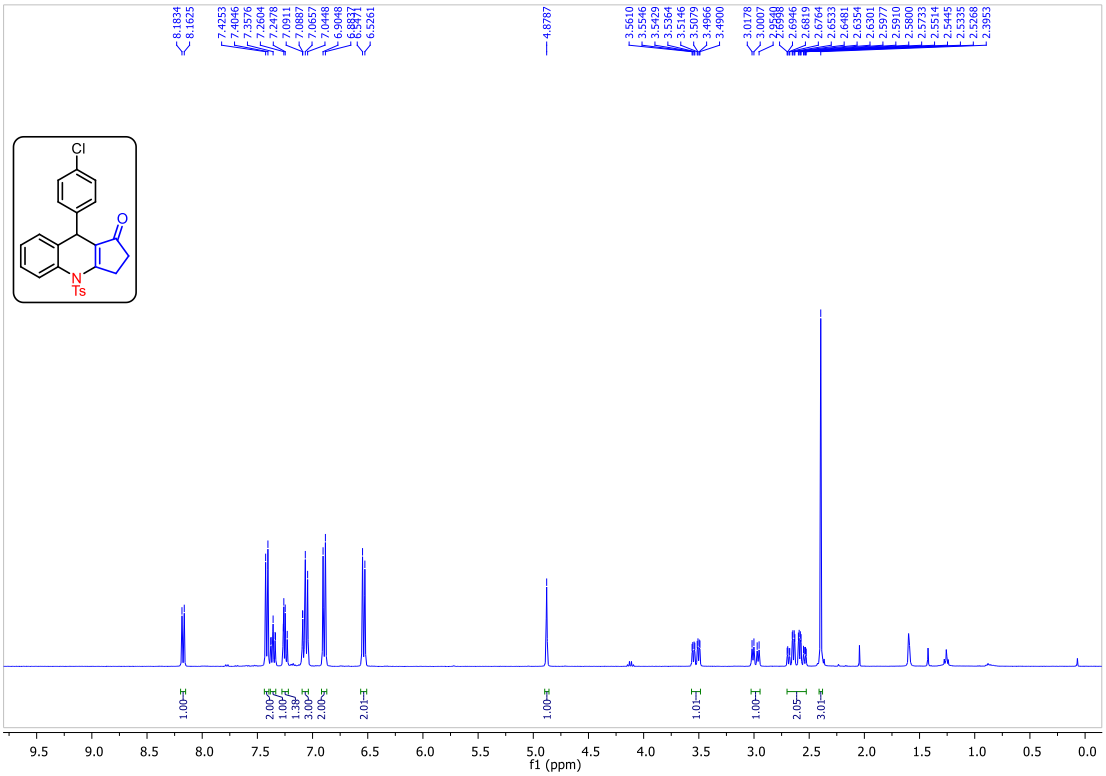


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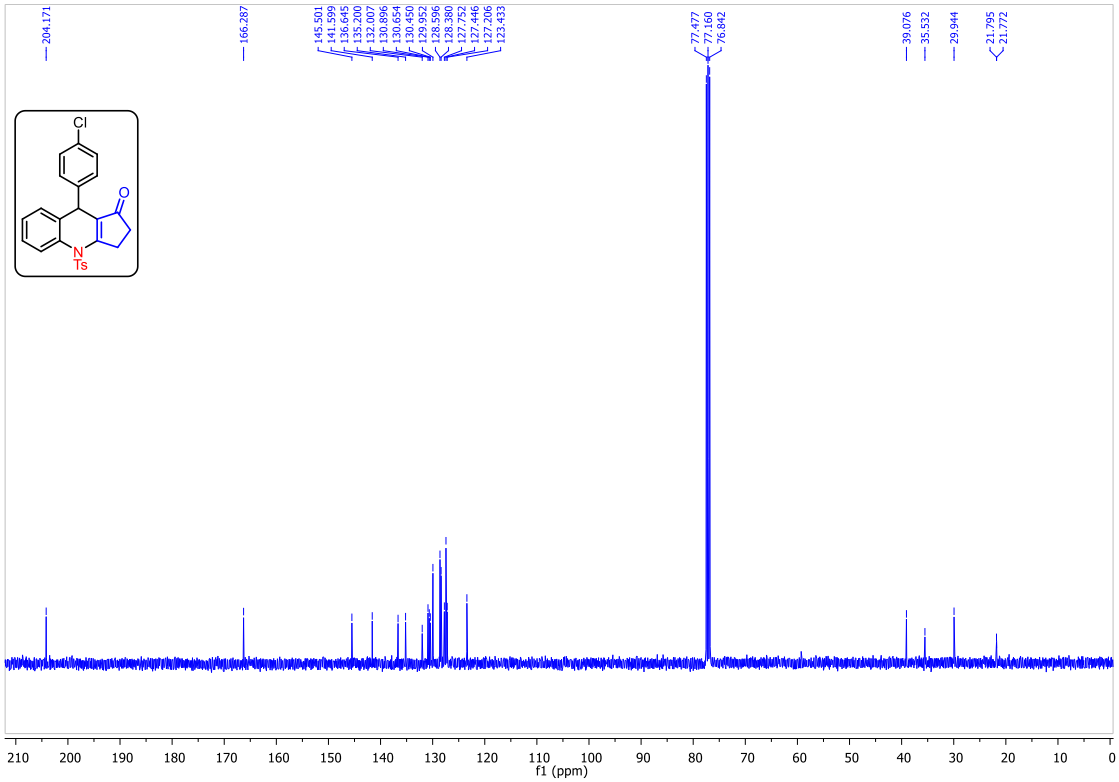

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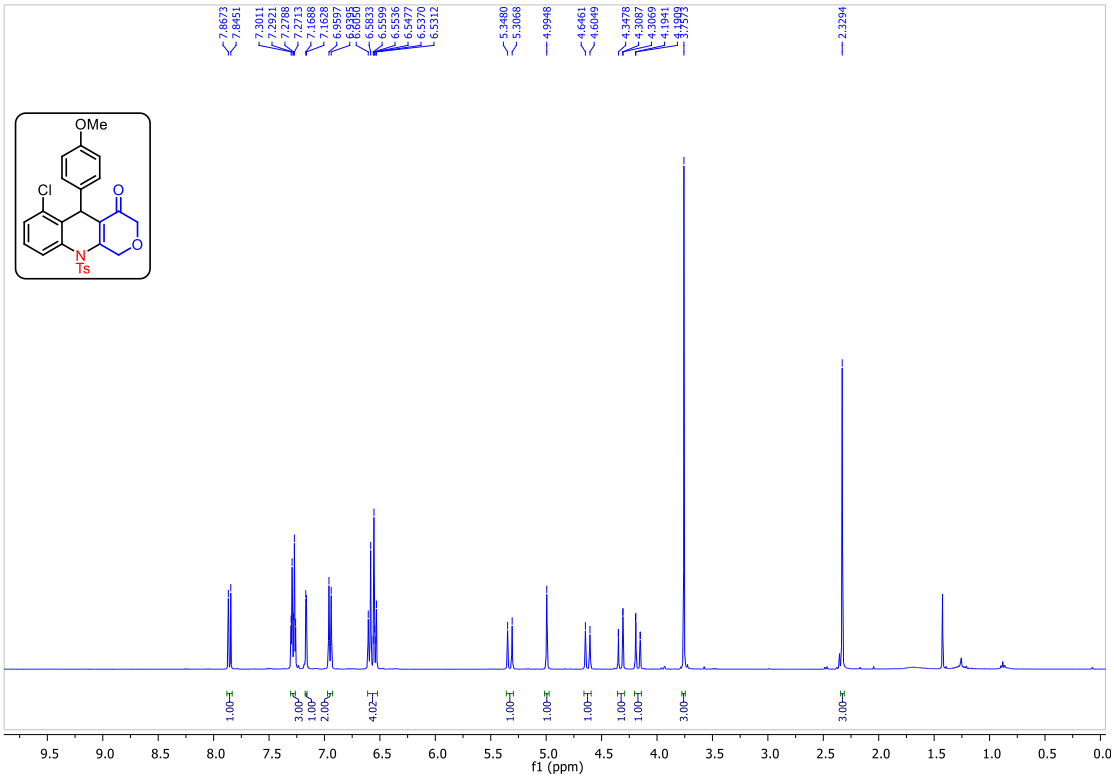


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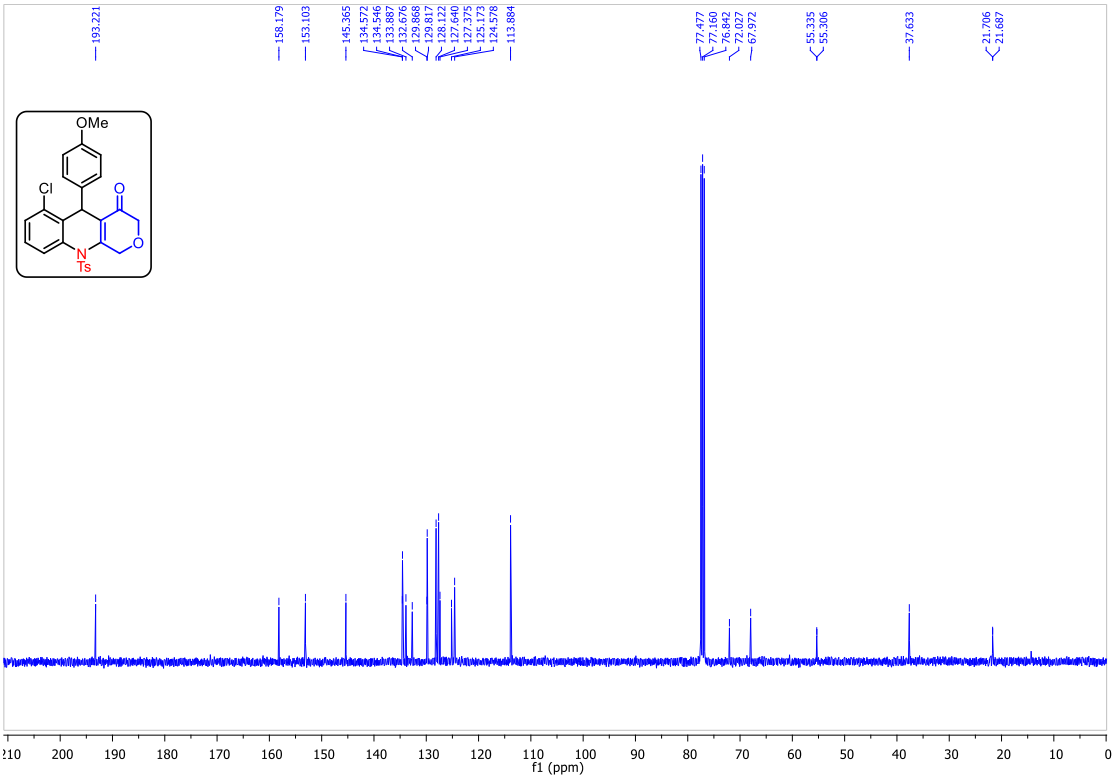

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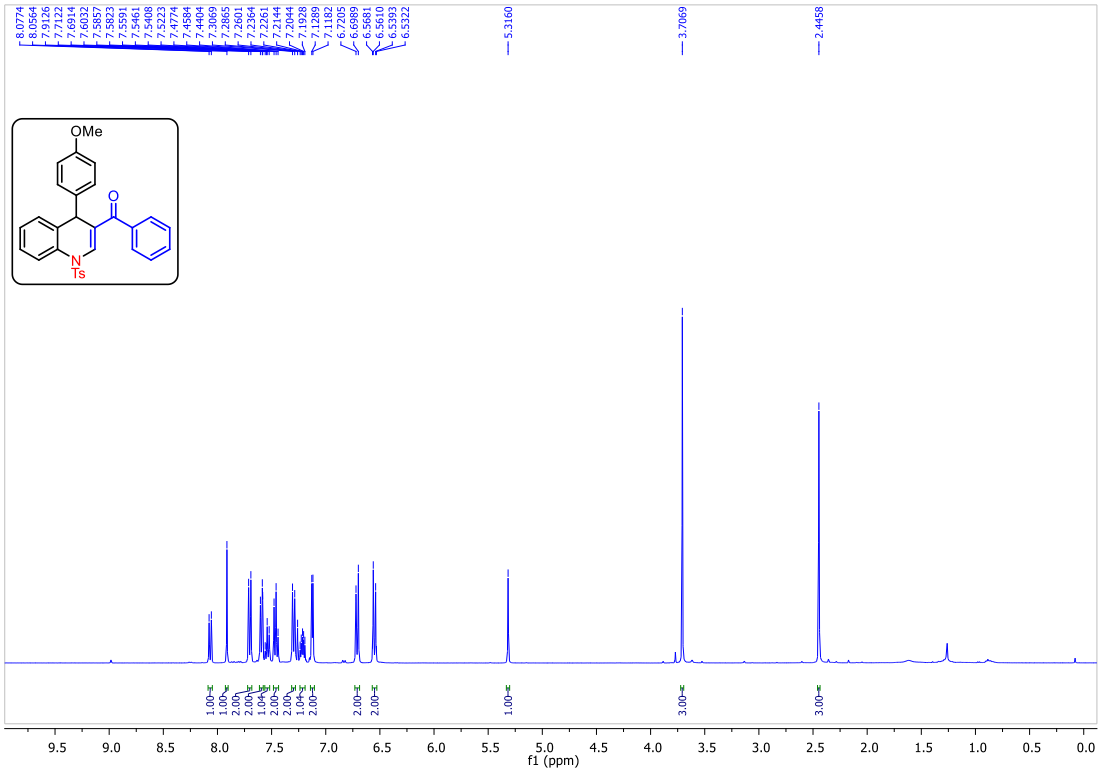
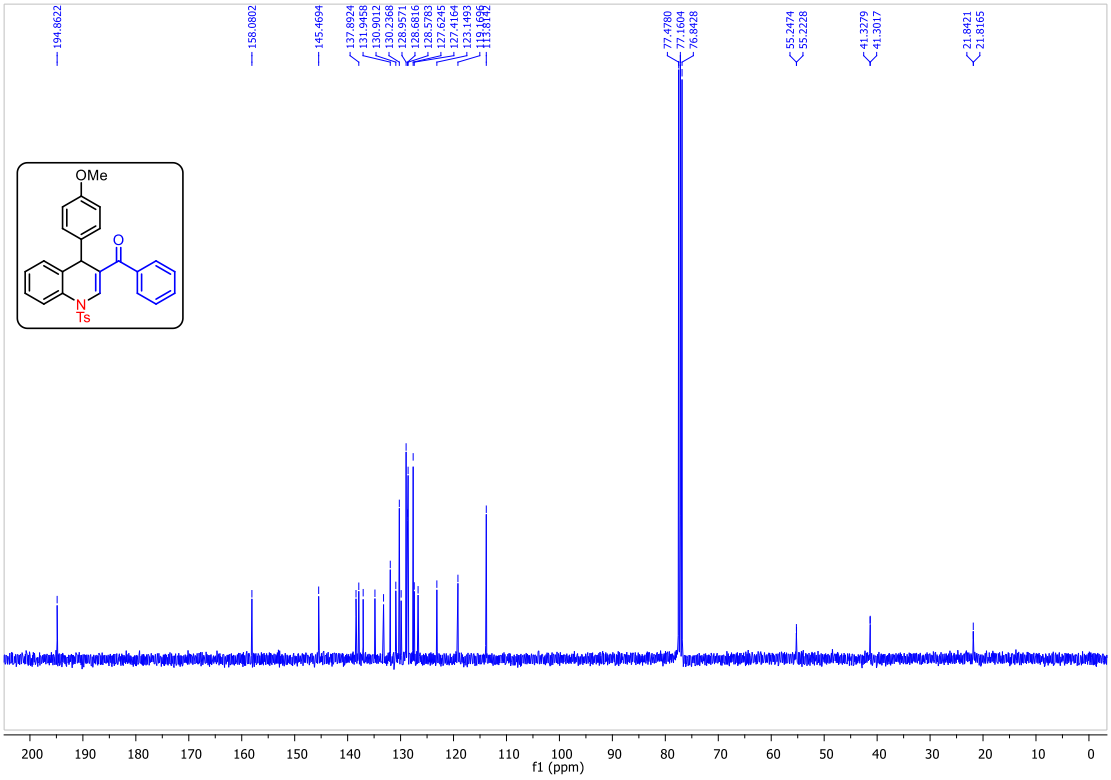



## $^{13}$C Spectra of 84**e**



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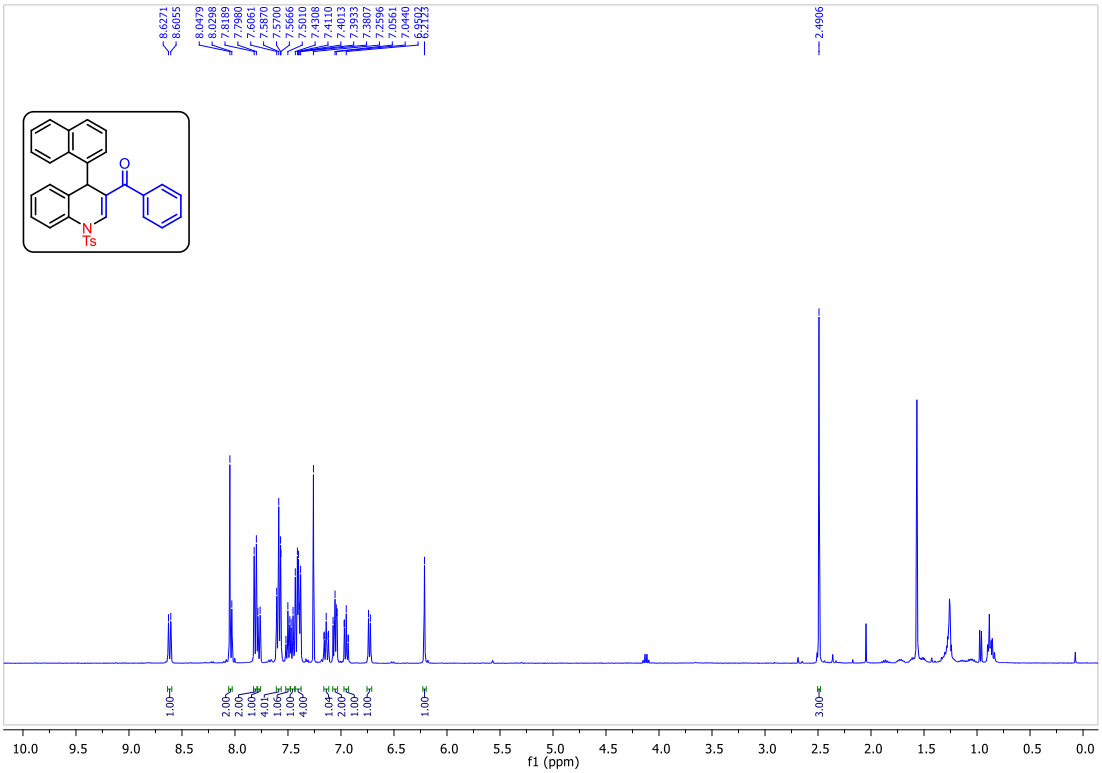


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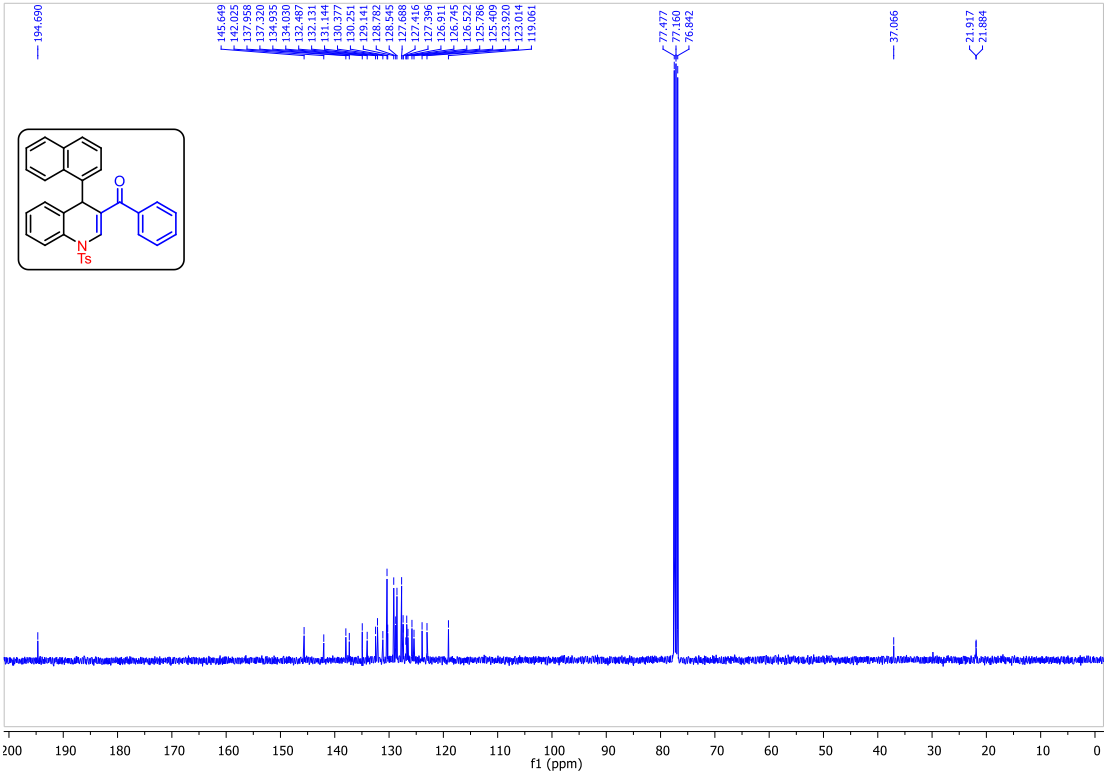

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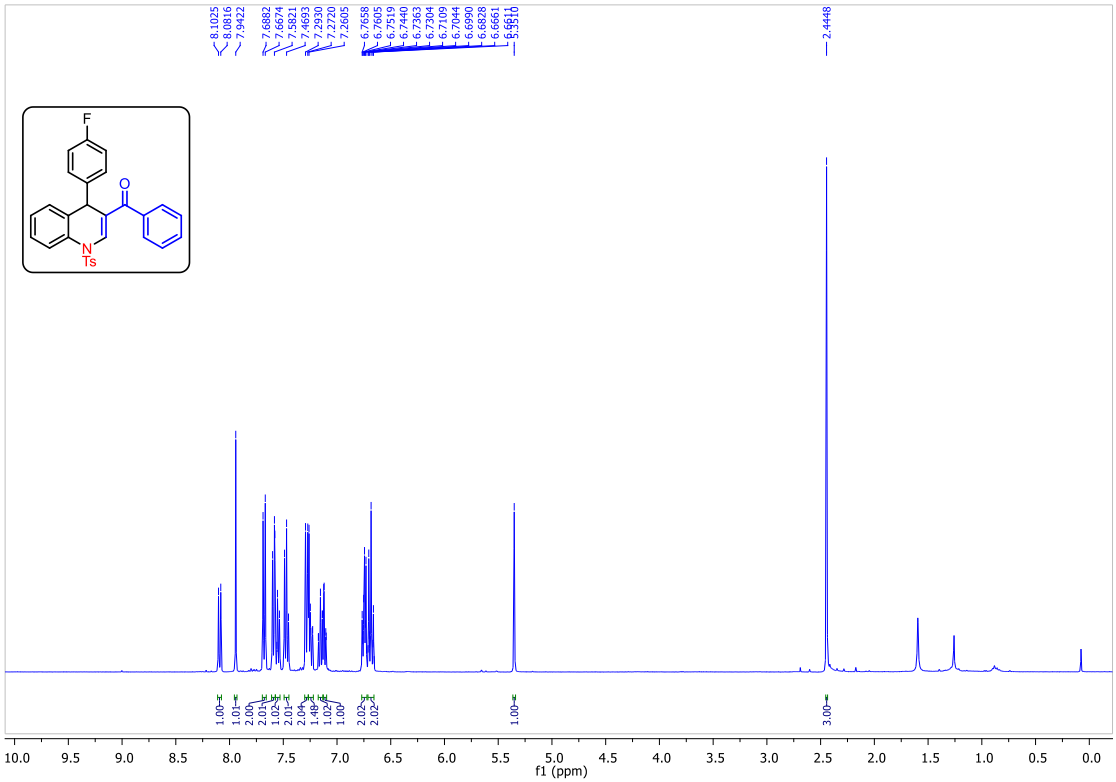


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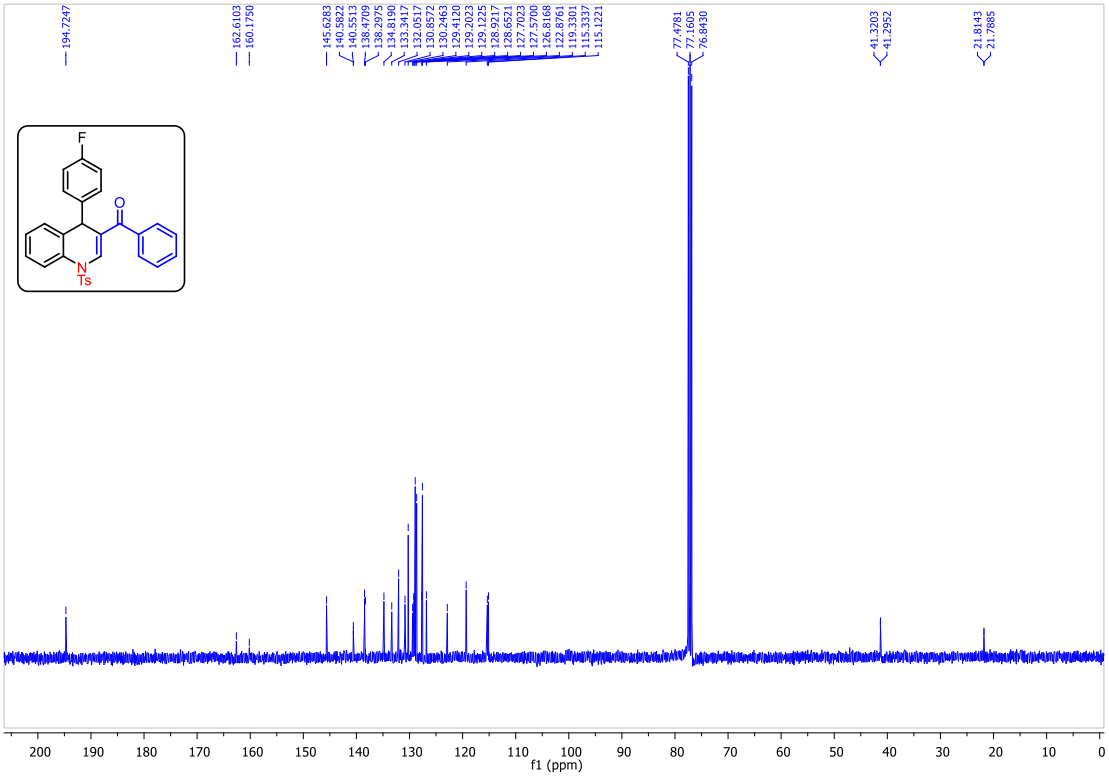
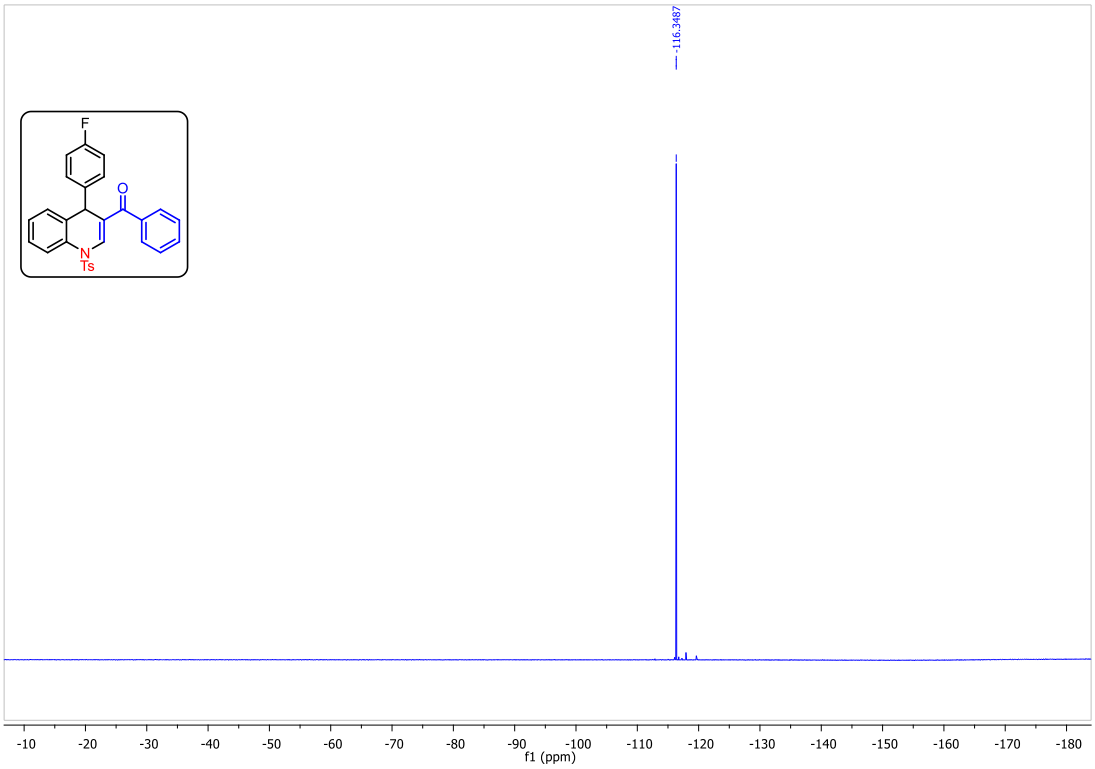


## $^{19}$F NMR Spectra of **84h**

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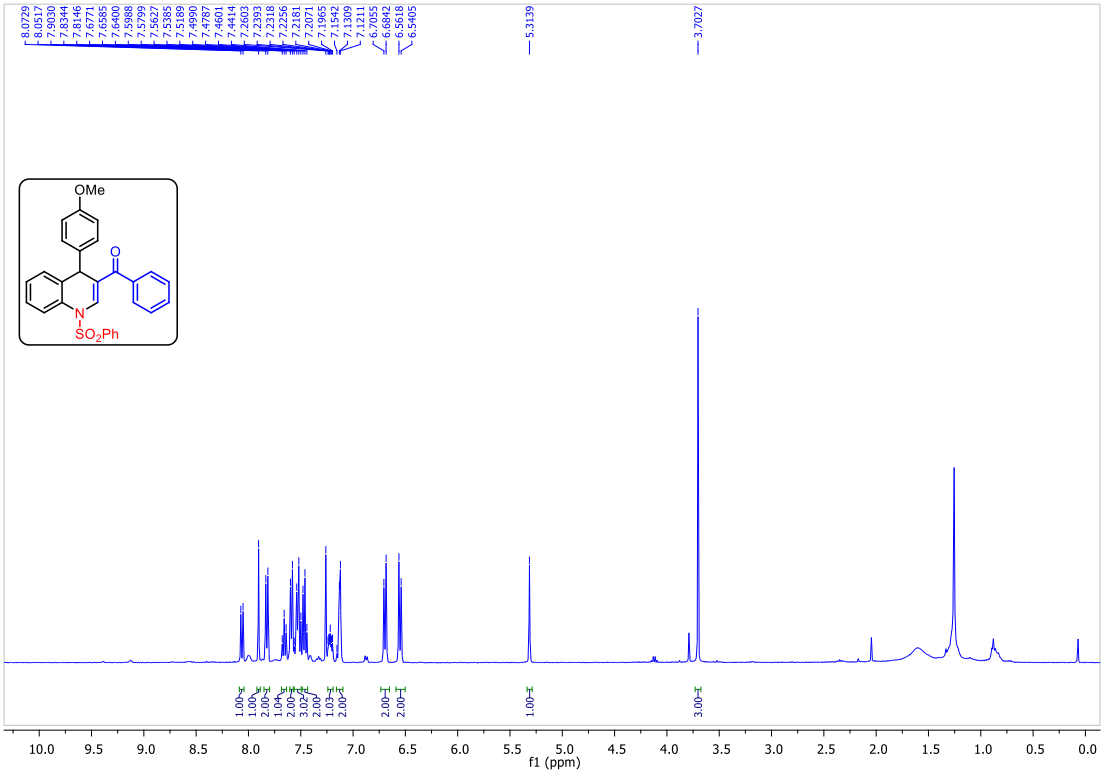

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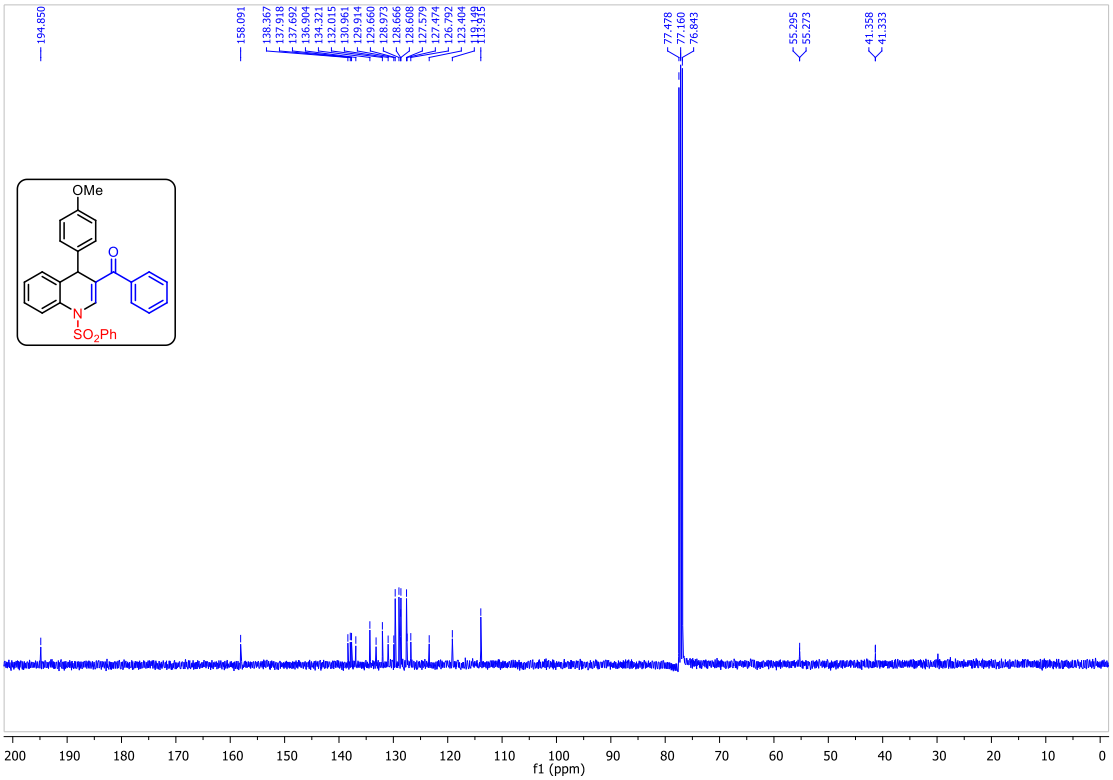


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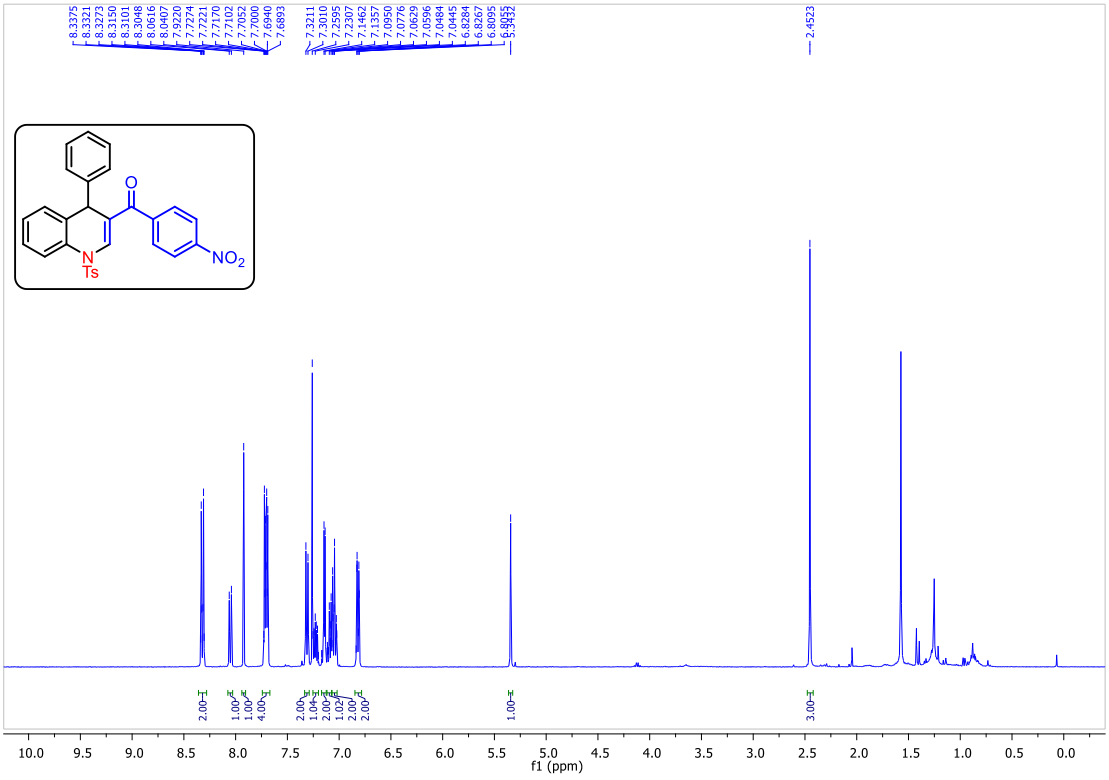

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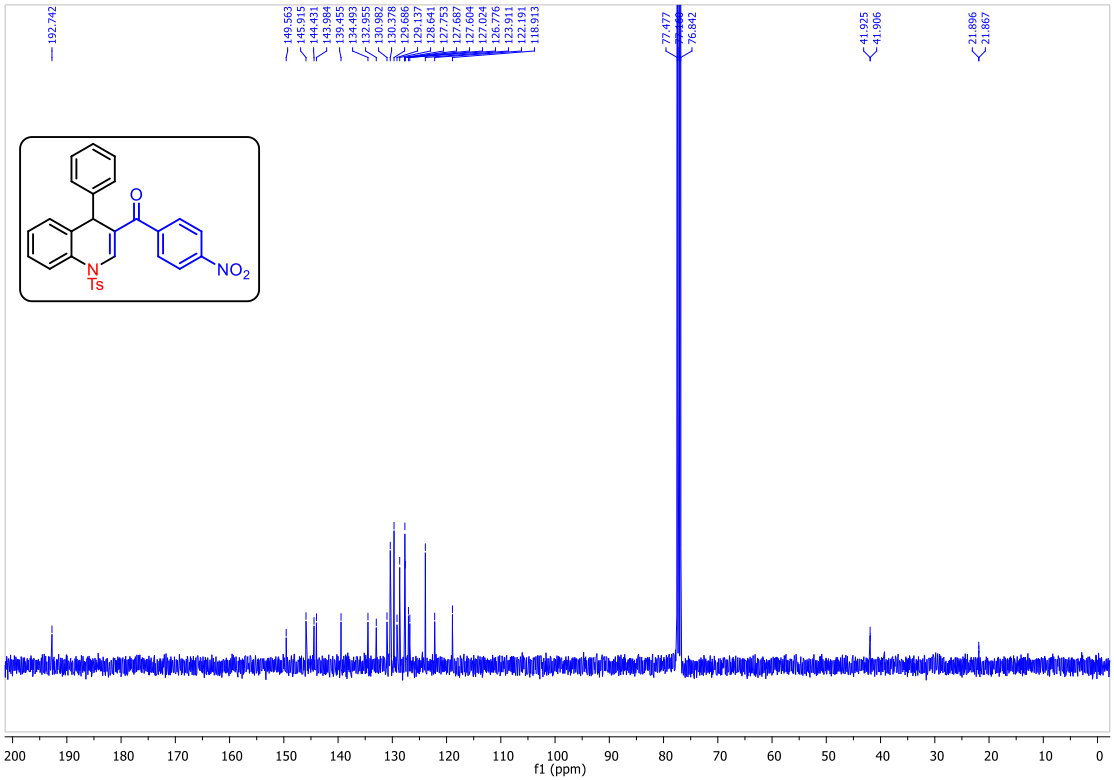
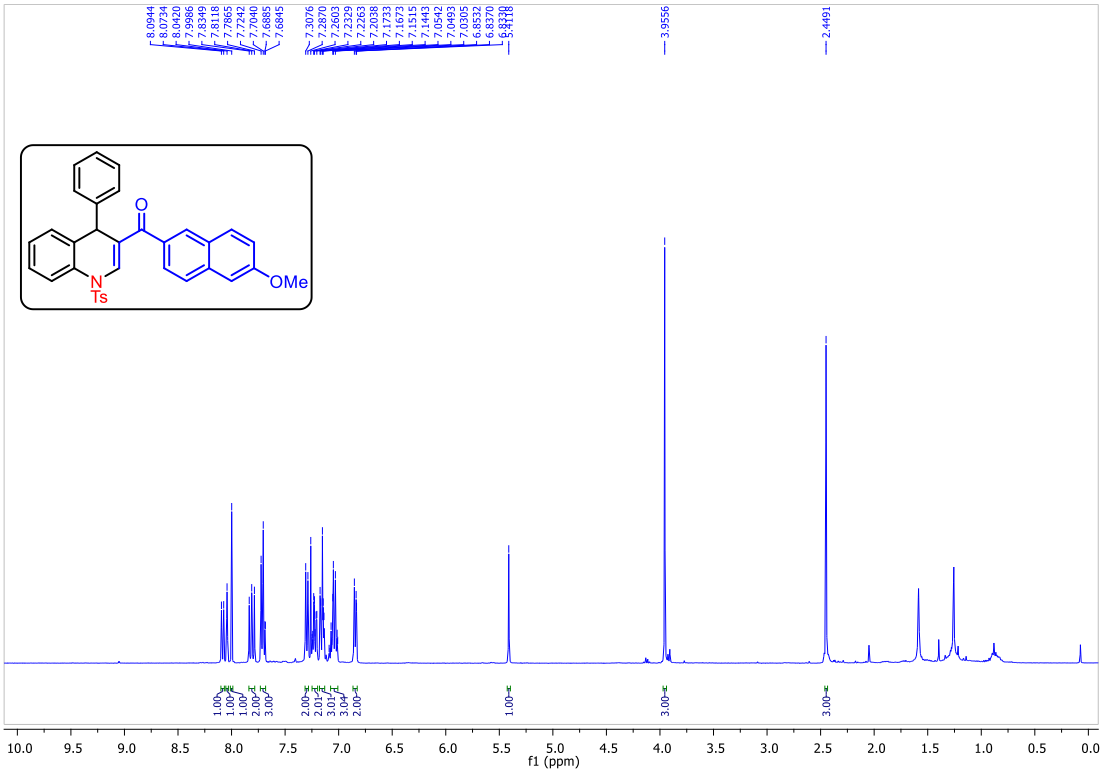



$^{1}$H NMR Spectra of **84n**



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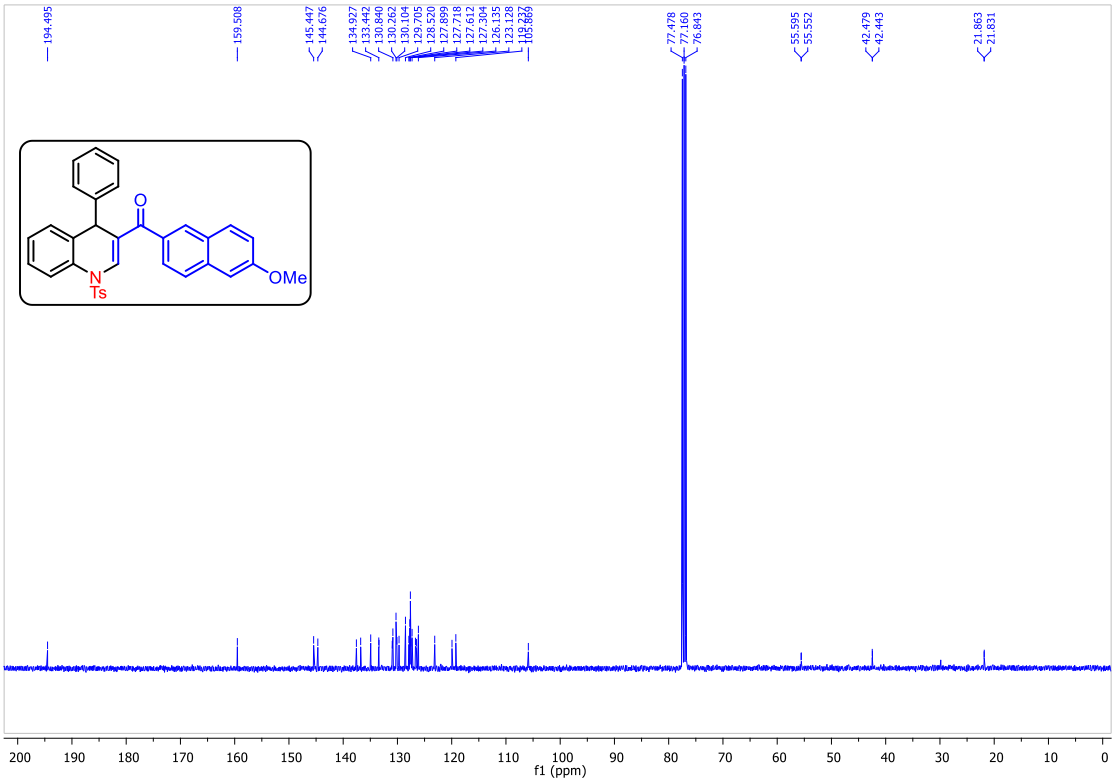


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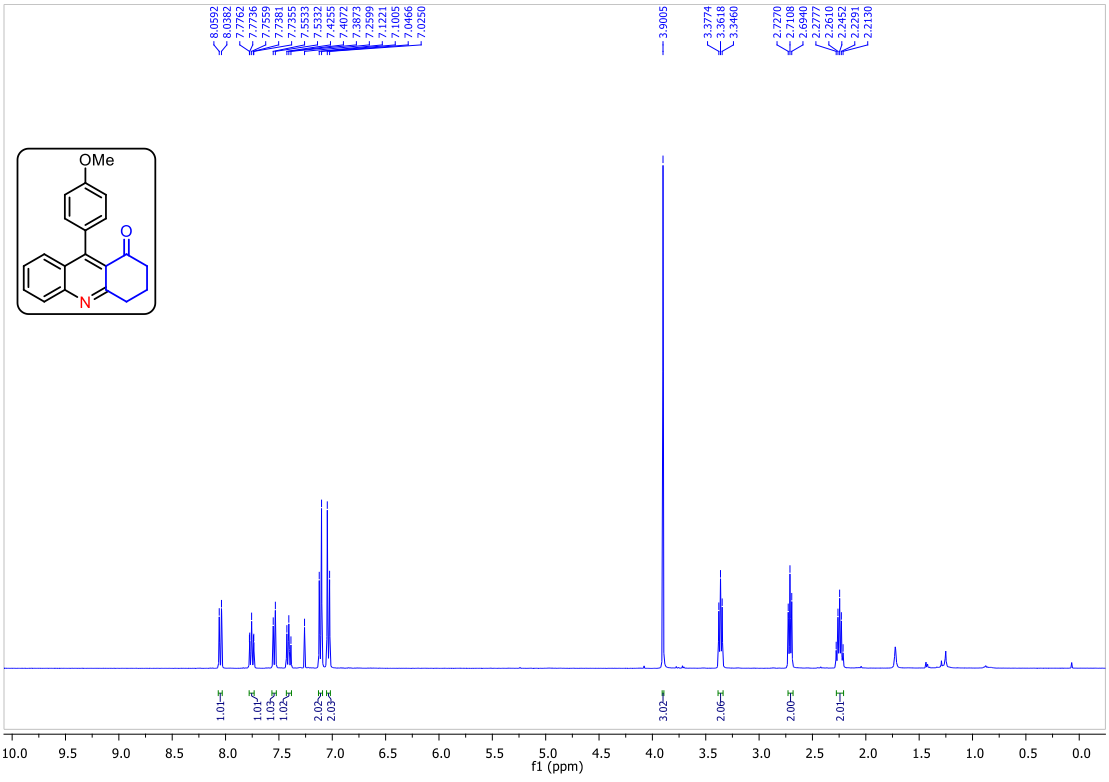

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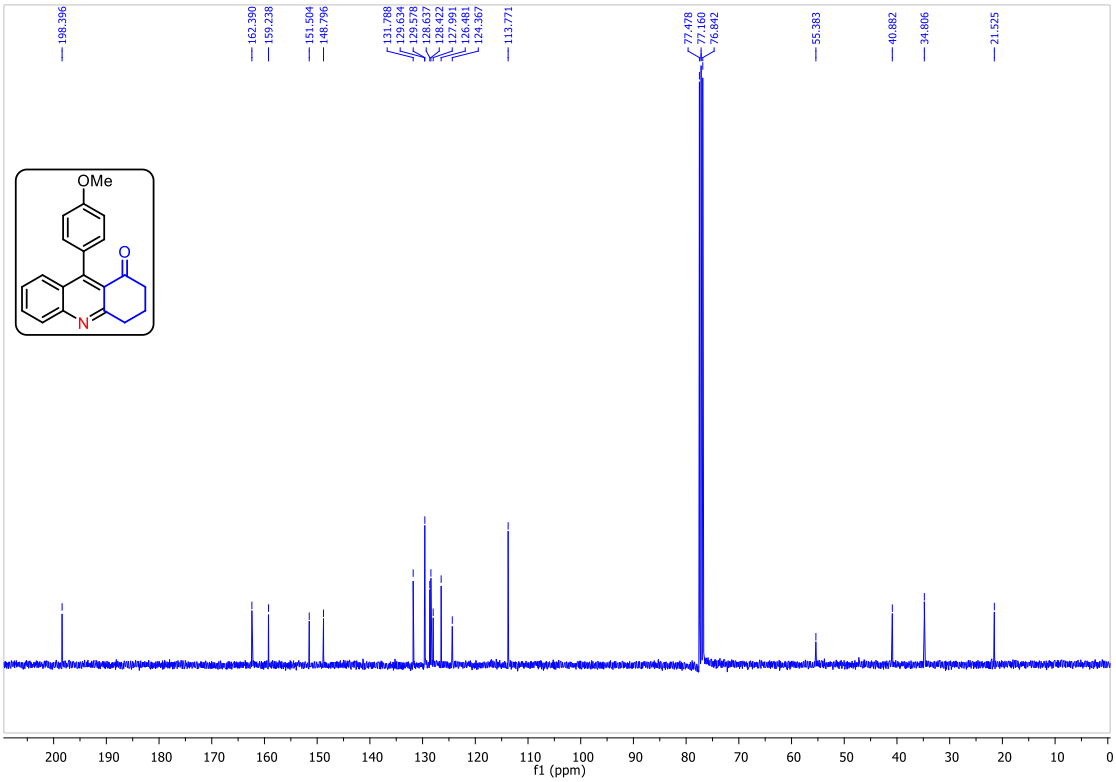


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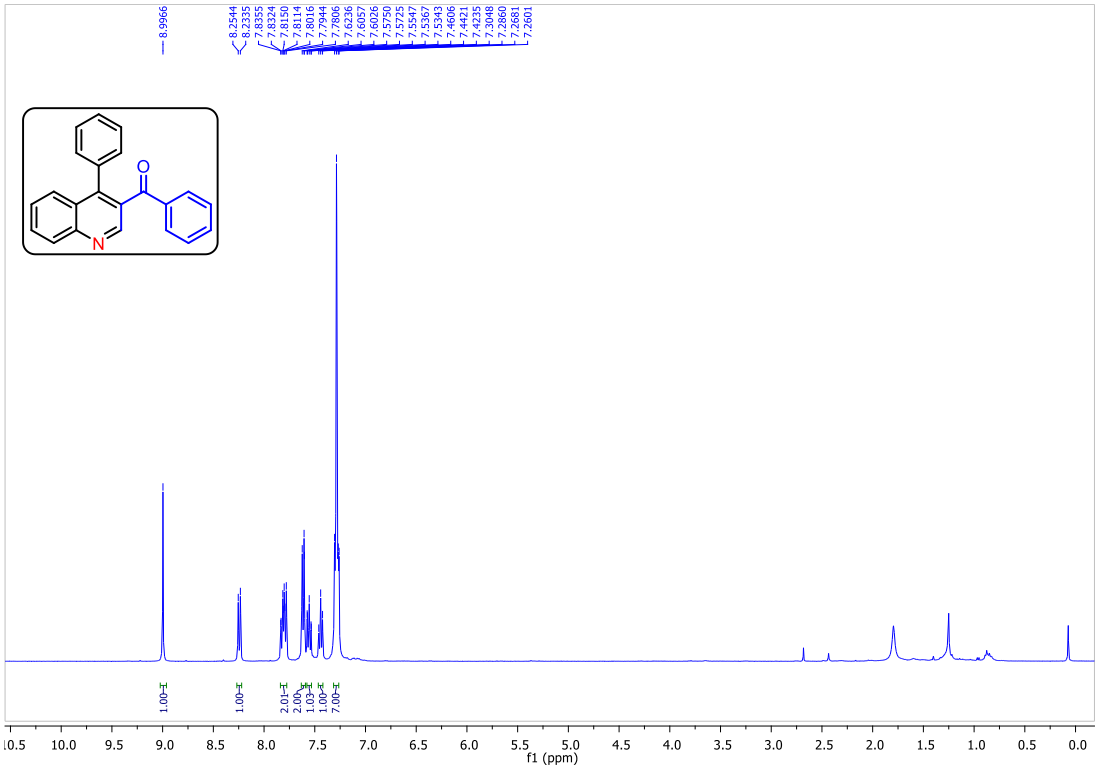

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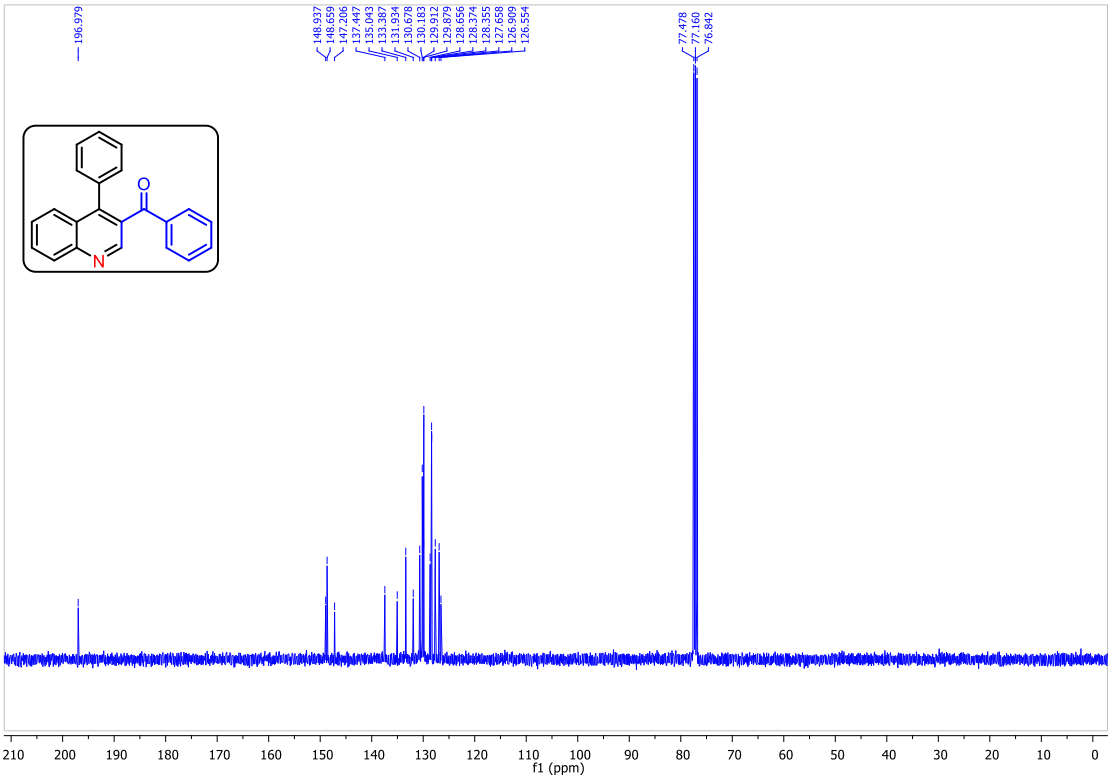


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# Part B: Synthesis of Diarylmethanes from *p*-QMs under Continuous-flow Conditions

## *Chapter 1*

## 1. General introduction to continuous-flow technology

### 1.1 Introduction

Continuous-flow technology, often referred to as a modern-day tool for the organic chemist, has gained a lot of interest over the last few decades in synthetic organic synthesis, especially in methods development, synthesis of APIs and natural products, as well as in enantioselective transformations.[1-4] Continuous-flow reactors are of three types: chip-based reactors (Microreactors), coil-based reactors, and packed bed reactors (often used in heterogeneous catalysis). Microreactors are miniaturized devices and are made up of non-reacting or inert materials such as glass, polymers, inactive metals, silicon, etc. In microreaction technology, the reaction occurs in microchips with dimensions in the sub-micrometer range to the sub-millimeter scale, in which reactants are continuously flushed into the channels, and the product is constantly eluted out from the outlet (Figure 1).

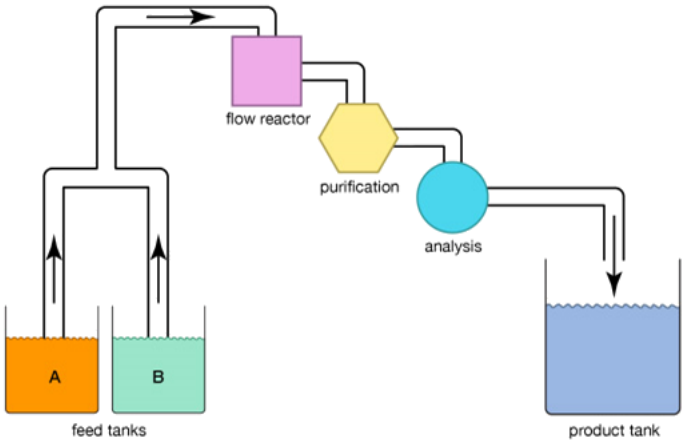



**Figure 1**. Continuous-flow technology

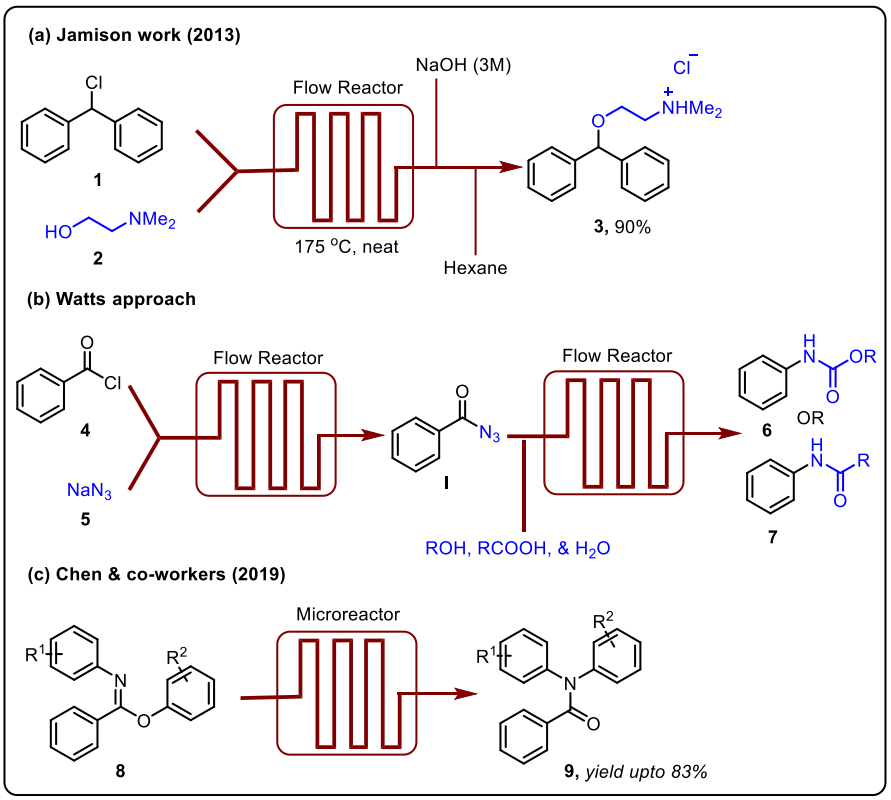
As reaction in flow reactors occurs in microchannels, which results in a high surface-to-volume ratio; thus, heat/mass transfer of reaction mixture is more efficient when compared to the batch process. In the continuous-flow method, reactant as well as the product are continuously eluted out thus, only a small amount of reactant is present in microchannels, making this technology more feasible for highly exothermic reactions and reactions involving

reactive intermediates and hazardous chemicals.[3] Apart from these, it also avoids by-product formation and provides precise control over temperature and pressure, short reaction time, and provides more safety when compared to the batch process.

Owing to the above-mentioned advantage, microreaction technology has been widely used in synthetic organic chemistry, some of which are discussed below.

## 1.2 Conventional and multi-component reactions under continuous-flow

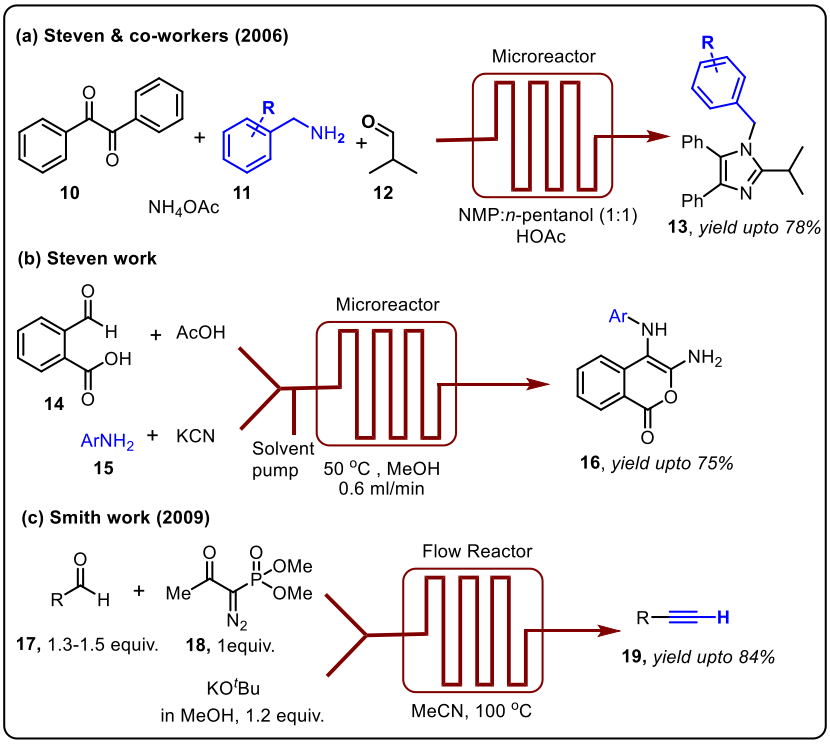
Microreaction technology, due to its operational efficiency, has been utilized for MCR and conventional reactions.[4] In 2013, Jamison and co-workers reported the synthesis of diphenhydramine hydrochloride **3** from chlorodiphenylmethane **1** and dimethylethanolamine **2** at elevated temperatures. After completion of the reaction, it was quenched with NaOH. In the same line, it was then extracted with hexane, and upon treatment with hydrochloric acid, **3** was obtained in 90% isolated yield.[4e] Later, Watts and co-workers demonstrated that sodium azide **5**, which is difficult to handle in the batch process, can be employed as a reagent in microreactor. They have reported the synthesis of carbamates **6**, amides **7**, and amines through *in-situ* generated acyl azide **I**, which upon heating gets converted to phenyl




**Scheme 1**. Conventional reactions under continuous-flow reactors

isocyanate, it then upon reaction with alcohol, acid and water generates **6**, **7**, and amines respectively.[4f] In 2019, Chen and co-workers reported the Chapman rearrangement of imino ethers **8**. In this rearrangement, several imino ethers **8** were converted into *N*,*N*-diphenylbenzamide derivatives (**9**) at elevated temperatures in moderate to good yields (as shown in Scheme 1).[4g]

It is possible to carry out multi-component reactions under flow conditions. Stevens and co-workers reported the synthesis of tetra-substituted imidazole **13** using microreaction technology. Benzil **10**, isobutyraldehyde **12**, and substituted benzylamine **11**, along with ammonium acetate, were flushed into the microreactor channels in the presence of acetic acid at 120 $^{o}$C and the substituted imidazole derivatives (**13**) were obtained in moderate to good yields.[4h] Later, the same group reported the synthesis of 3,4-diamino-1*H*-isochromen-1-ones (**16**) through *in situ* generation of hydrogen cyanide. 2-Formylbenzoic acid **14** along with acetic acid were injected into the reactor. Parallelly, a solution of amine **15** and potassium cyanide in MeOH was also injected to the microreactor. As the products **16** are crystalline in nature, to avoid clogging in the microchannel, an inert perfluorinated solvent, Fluorinert FC-70 was introduced to reaction flow (as shown in Scheme 2).[4i] Smith and co-worker in 2009 reported the synthesis of the terminal alkynes **19** using Bestmann–Ohira reagent **18** with an appropriate aldehyde (**17**). Further, they have also elaborated this approach for the synthesis

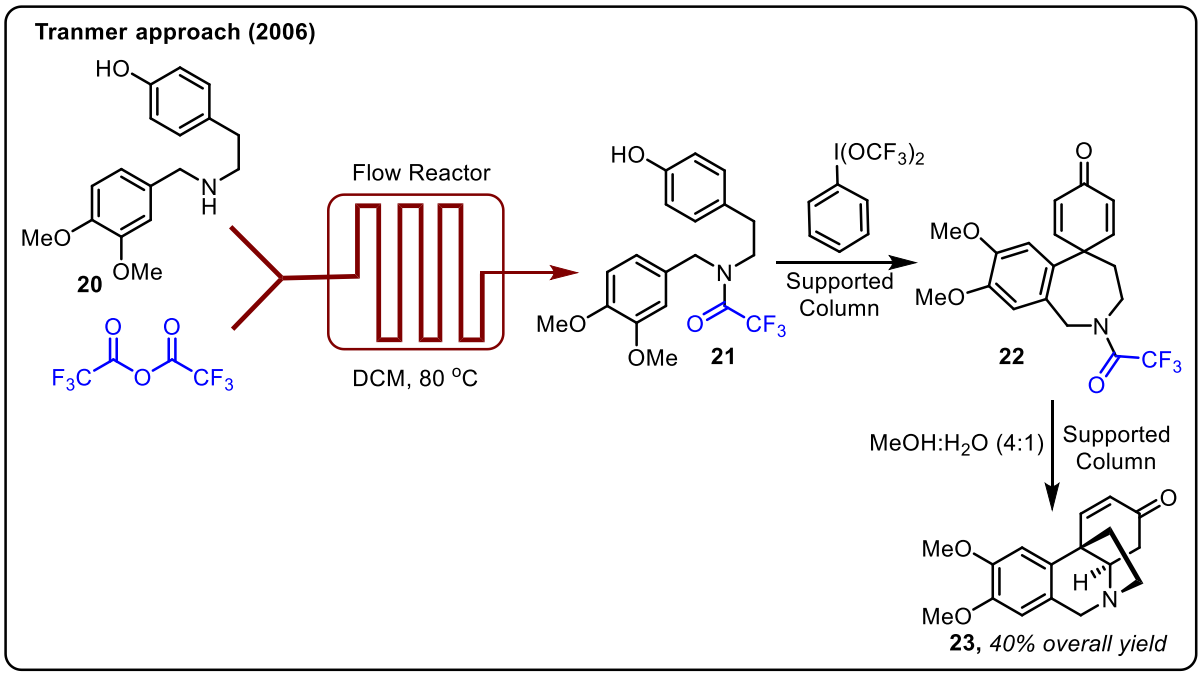



**Scheme 2**. Multi-component reactions under continuous-flow reactors

of triazole derivatives by *in-situ* treatment of azide moieties with terminal alkyne under microreaction technology (Scheme 2, **c**).[4j]

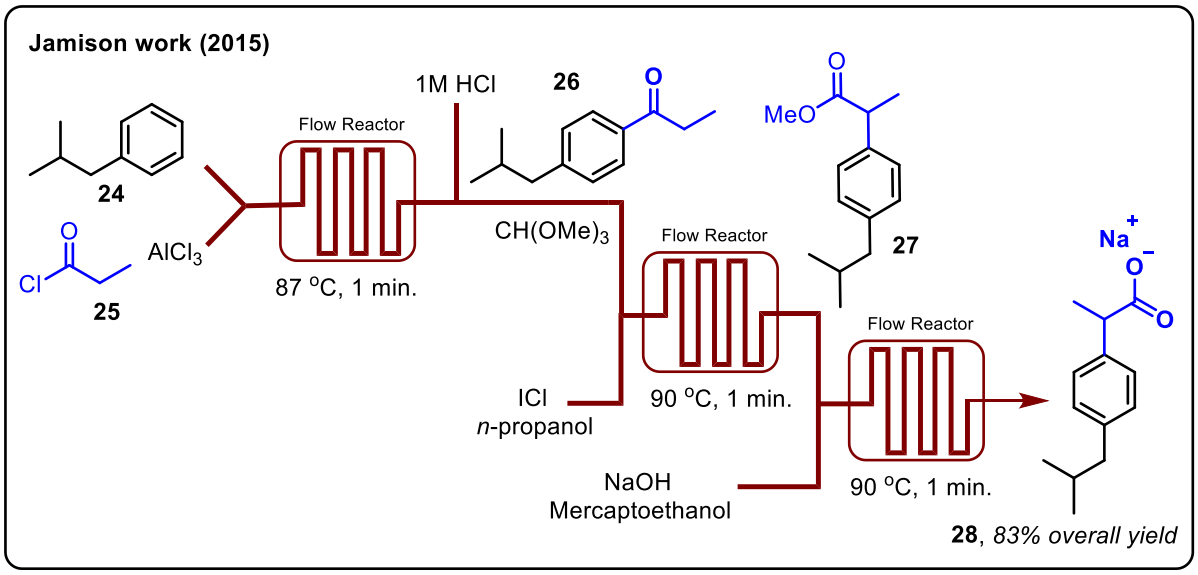
## 1.3 Synthesis of APIs and Natural products

Synthesis of APIs and natural products in high yields involving minimum number of steps has always be the primary interest of synthetic chemists. Microreaction technology has been proven to be one of the most effective ways to achieve such a paradigm.[5,6] Tranmer and co-workers have reported the synthesis of oxomaritidine **23** by employing flow chemistry. For this purpose, amine derivative **20**, which was also synthesized under continuous-flow technology, and trifluoroacetic anhydride (TFAA) were subjected to react in microchannels to provide the corresponding amide **21**, which was then passed on to a polymer-based column containing supported (ditrifluoroacetoxyiodo)benzene to give a seven-membered intermediate **22**. This intermediate **22** was then passed through a polymer-supported basic column in a mixture of solvent to give natural product **23** with 90% of purity (as shown in Scheme 3).[5d] A significant advantage of this method was that it doesn't require purification in any steps, and only one side product was obtained, which could easily be separated by preparative HPLC. Ibuprofen is one of the essential active pharmaceutical molecules, and it is one of the major components present in various anti-inflammatory drugs. Jamison and co-workers have reported the synthesis of Ibuprofen **28** by employing microreaction




**Scheme 3**. Total synthesis of (±)-oxomaritidine **23** employing flow chemistry

technology. Initially, $AlCl_3$ along with propionyl chloride **25**, promotes the Friedel–Craft reaction with **24**. The reaction mixture was then treated with hydrogen chloride (1.0 M) solution to give aryl ketone intermediate **26**, which upon treatment with ICl at 90 $^oC$ gave the corresponding ester **27**. This ester **27** was then treated with mercaptoethanol followed by saponification under a microreactor generated **28** in 83% yield (Scheme 4). The significant advantage of this reaction is that one can obtain 8.1g of **28** in an hour, which is much greater when compared to the classical batch approach.[6e]

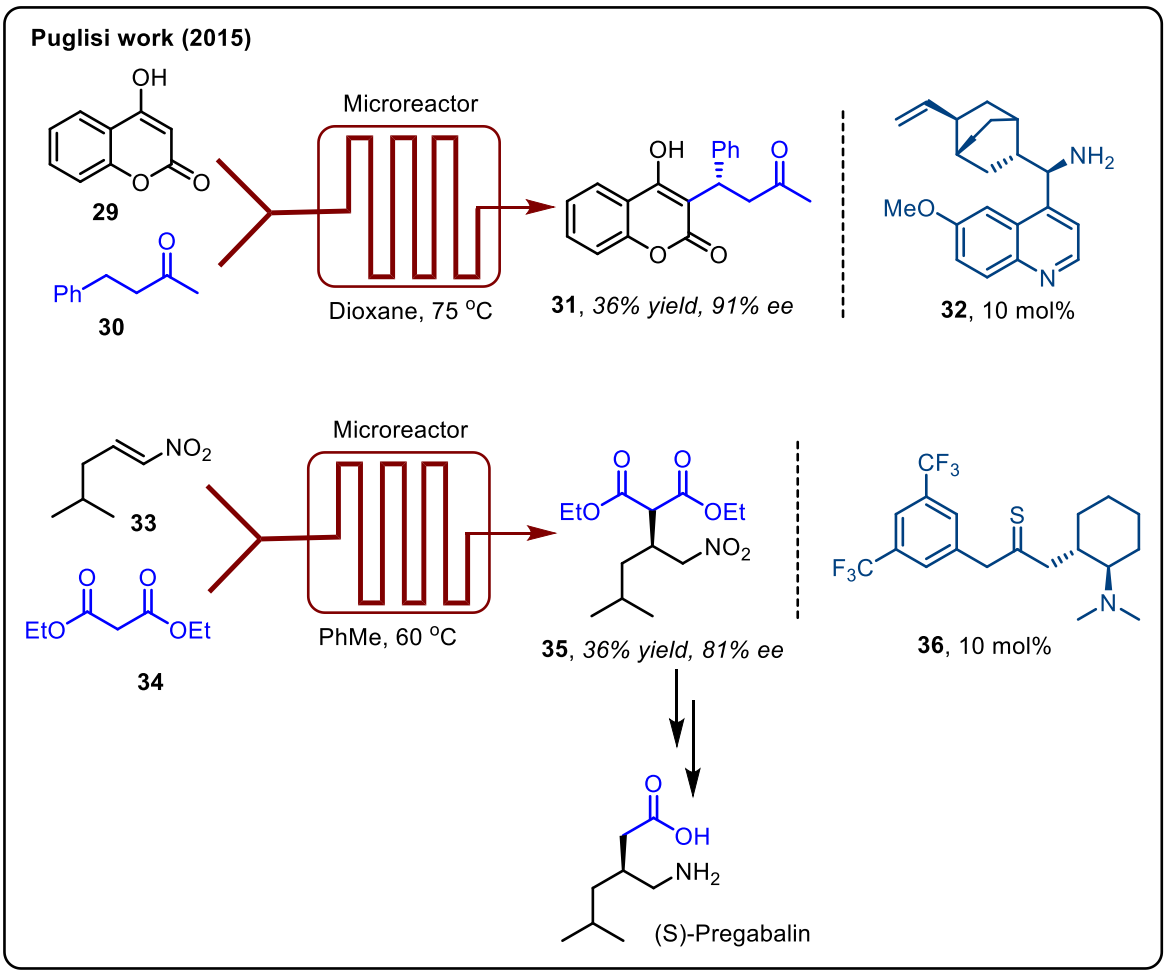



**Scheme 4.** Synthesis of Ibuprofen **28**

## 1.4 Homogenous reactions

Organocatalysis under continuous-flow technology in homogenous conditions is challenging to achieve, as the reactant and catalyst are continuously eluted out from the microchips of the reactor. There is significantly less time for interaction among reagents and catalyst; despite this, various enantioselective transformations have been reported.[7,8] Puglisi and co-workers reported the asymmetric synthesis of (*S*)-warfarin and (*S*)-pregabalin precursor, for the first time, using a homogenous catalyst. Synthesis of (*S*)-warfarin **31** was achieved using a cinchona-based catalyst **32**. Coumarin **29** was taken in the syringe and injected to the microreactor; parallelly **30** along with **32** in dioxane was also injected into microchannels at the same time. The product **31** was obtained in excellent enantioselectivity and moderate yield. Similarly, nitroalkene **33** was flushed into microchannels along with a combination of diethylmalonate **34** and thiourea-based catalyst **36** dissolved in toluene to get

**35** in moderate yield and good enantioselectivity. Further, this protocol was elaborated to the synthesis of (*S*)-pregabalin (as shown in Scheme 5).[7f]




**Scheme 5**. Synthesis of chiral compounds under homogenous conditions

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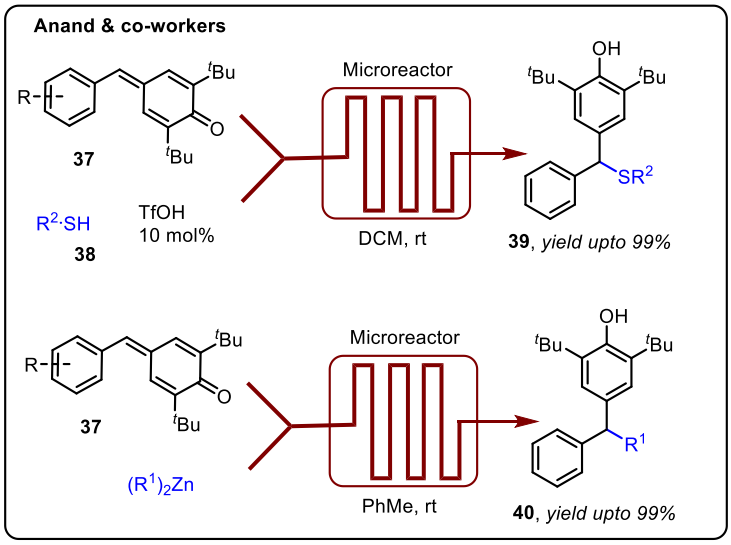
Anand and co-workers have reported the synthesis of thioether derivatives and diarylmethanes using a microreactor. Authors have explored the reactivity of *para*-quinone methides (*p*-QMs) [**37**] for 1,6-conjugate addition with thiols (**38**) to afford thioether derivatives (**39**) in excellent yields. Further, they had also demonstrated the chemo-selectivity of the protocol by reacting *p*-QM with 2-mercaptoethanol. Similarly, they have also reported the synthesis of diarlymethane derivative **40** through the reaction of *p*-QMs with dialkylzinc compounds under catalyst-free conditions (as shown in Scheme 6).[8]



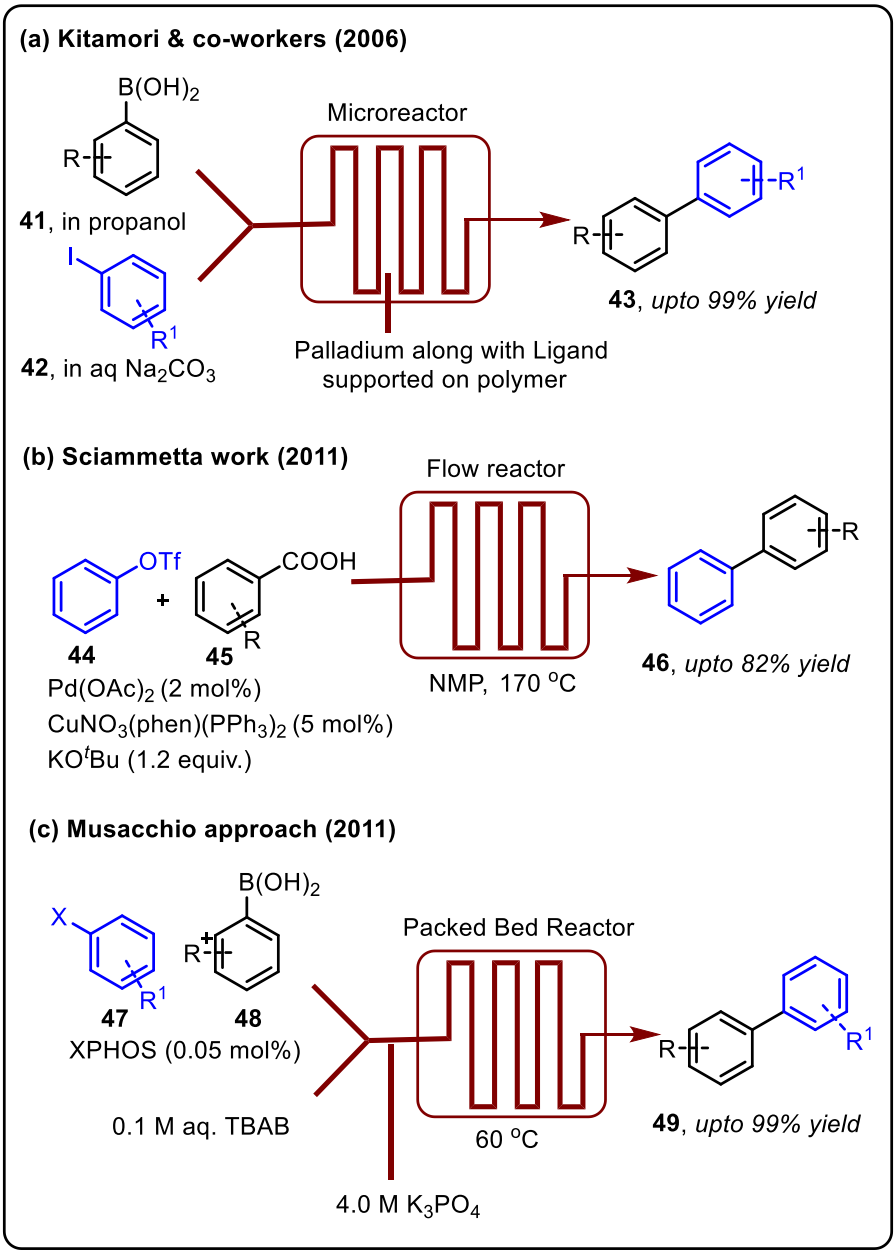

**Scheme 6**. Anand's approach for synthesis of diarylmethanes

## 1.5 Heterogeneous reactions

Heterogeneous reactions under flow reactors are generally carried out in packed bed reactors or channels with pre-coating of catalyst. It is another fascinating area of research under flow conditions and is well-explored for coupling reactions, bio-enzymatic reactions, organocatalysis, and many more.[9,10]

Kitamori and co-workers reported the Suzuki−Miyaura Coupling in a microreactor having an embedded membrane of palladium with a ligand that is supported on a polymer. In fact, this membrane was made by injecting an aqueous solution of $(NH_4)_2PdCl_4$ and polymer-supported triarylphosphine ligand in ethyl acetate in the opposite direction, and the polymer membrane was embedded on microchannels, which was then utilized for the synthesis of biaryl derivatives (**43**) from boronic acid (**41**) and aryl iodide (**42**).[10a] Later on, Sciammetta and co-workers also reported the synthesis of biaryl compounds by the cross-coupling of aryl triflate (**44**) and benzoic acid derivatives (**45**). NMP was the choice of solvent as it dissolved all the components, including palladium acetate, KO$^t$Bu, and copper precursor. All the reactants dissolved in NMP was flushed through a stainless steel reactor, and the biaryl products (**46**) were obtained in good yields (Scheme 7).[10b] The authors have also highlighted that when the same reaction was performed in the batch process, less than 10% yield of **46** was obtained making this methodology superior under flow conditions. Musacchio and co-workers have demonstrated an efficient Suzuki Miyaura coupling reaction between hetero-aryl boronic acid **48** and aryl halide **47** to generate **49** using XPHOS as a pre-catalyst. The reaction was performed in a packed bed reactor with very low catalyst loading. Compounds

**47** and **48** along with XPHOS in NMP were injected to the packed bed reaction through a syringe and, at the same time, an aqueous solution of TBAB and potassium phosphate was also injected to the reactor through another syringe, to give **49** in excellent yield.[10c]




**Scheme 7**. Synthesis of biaryl compounds using heterogeneous catalysis

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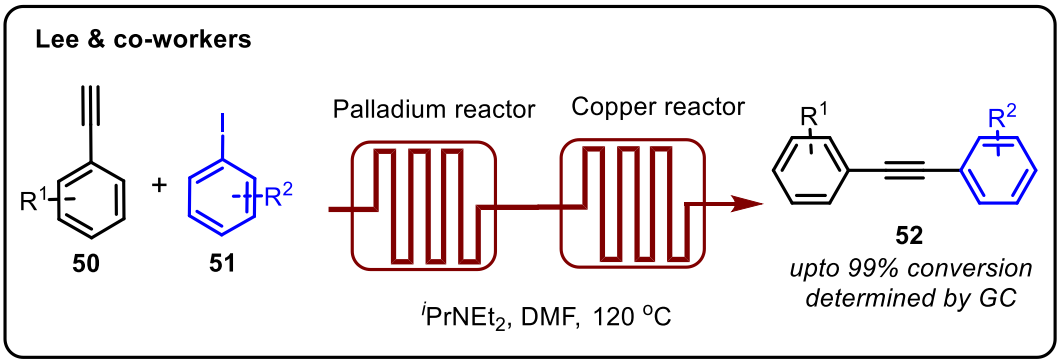
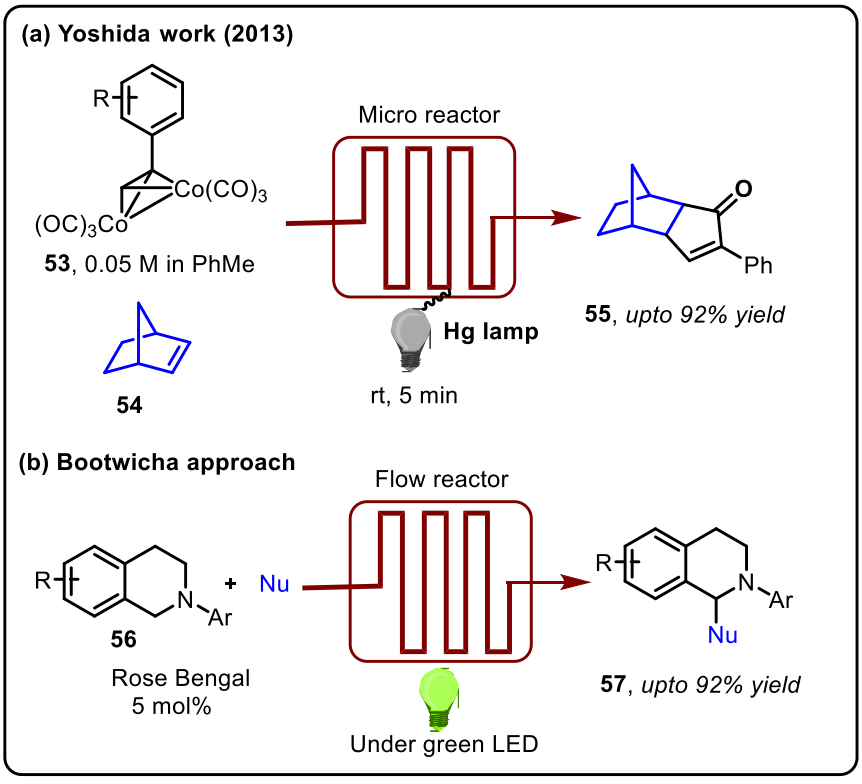
Lee and co-worker have reported the synthesis of the internal alkynes (**52**) through Sonogashira coupling reaction between **50** and **51** (Scheme 8).[10d] Apart from this, various hydrogenation reactions involving metal in combination with hydrogen were also explored in continuous flow technology.




**Scheme 8.** Synthesis of internal alkyne through coupling reaction

## 1.6 Miscellaneous reactions

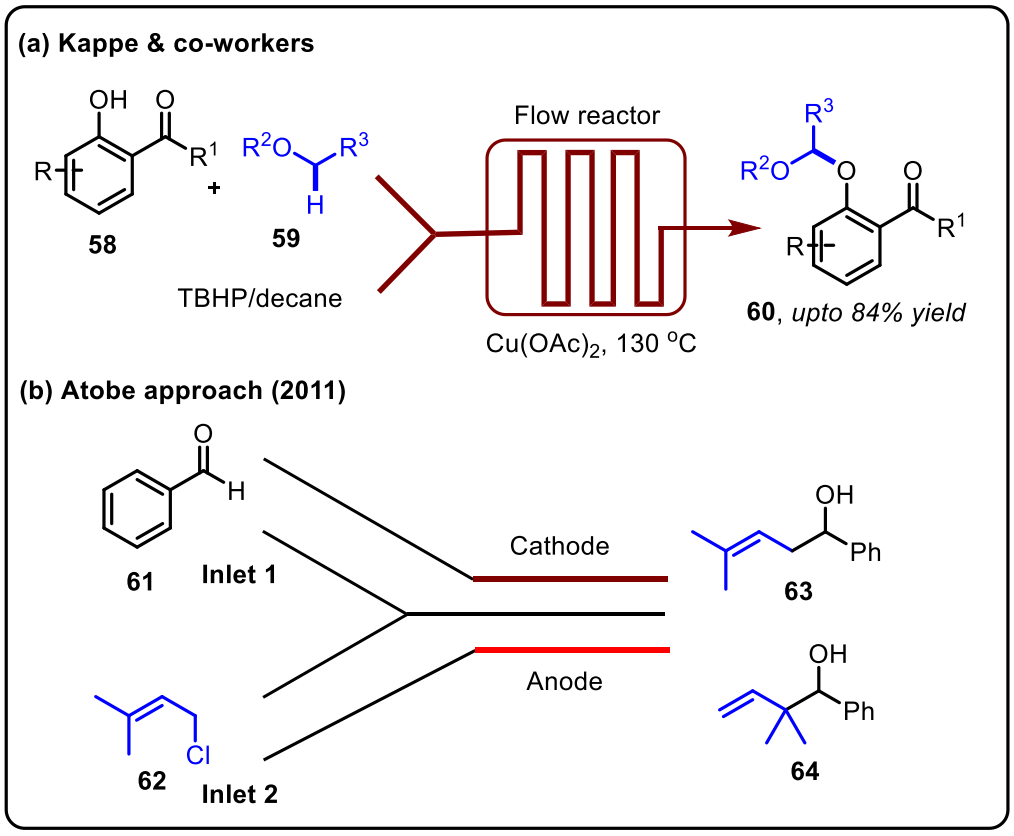
Apart from the above-mentioned applications, flow reactors were also utilized in photochemical reactions, C-H bond activation, electrochemical reaction, and oxidation/reduction processes.[11] Yoshida and co-workers reported the synthesis of cyclopentenone derivatives **55** using photochemical flow microreactors. Norbornene **54**, along with cobalt complex **53**, was injected into the microreactor in the presence of a mercury lamp (Scheme 9). The reaction mixture underwent Pauson–Khand type reaction to afford **55** in good yields. Further, they have also demonstrated an intramolecular version of this




**Scheme 9**. Photochemical reaction under Flow reactor.

reaction.[11a] Bootwicha and co-workers reported the synthesis of tetrahydroisoquinoline derivatives (**52**) using cross-dehydrogenative coupling reactions. Rose Bengal was used as an organophotocatalyst, and several nucleophiles such as nitromethane, TMSCN, diethylmalonate, etc. were used as a coupling partner to provide corresponding products **57** in good yield (Scheme 9).[11b]

In 2012, Kappe and co-workers established a C-H bond activation strategy to prepare unsymmetrical acetals **60** under flow conditions using a copper catalyst (Scheme 10). In this reaction, substituted ethers (**59**) were subjected to react with **58** in the presence of TBHP and copper catalyst to provide unsymmetrical acetals **60** in good yields. The reaction proceeds through an activation of C-H bond in ether, which leads to the formation of new C-O bond.[11c]

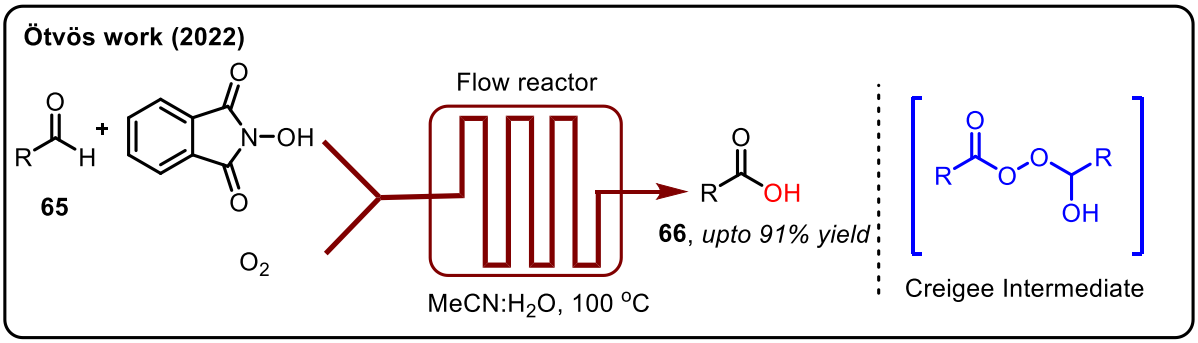



**Scheme 10**. Electrochemical and C-H bond activation reaction under the flow process

Atobe and co-workers in 2011 reported a carbonyl allylation reaction under a fabricated electrochemical microreactor. Benzaldehyde **61** and allylic chloride **62** were injected into the cathode and anode unit, respectively, and the α adduct **63** was obtained as a major product. Interestingly when **62** was injected in cathode unit and **61** was injected to anode unit, the ϒ adduct **64** was obtained as major product (Scheme 10, **b**).[11d] It was believed that the

regioselectivity of these products was mainly related to the reduction potentials difference between the starting substrates.

Recently, in 2022 Ötvös and co-workers reported an aerobic oxidation of aldehydes (**65**) under continuous flow conditions to get the corresponding acids (**66**). *N*-Hydroxyphthalimide was used in combination with molecular oxygen to promote the transformation. The reaction proceeds through the formation of Creigee intermediate and, the respective acid derivatives (**66**) were obtained in excellent yields (Scheme 11).[11e] Along with **66**, peracid was also formed in the reaction mixture, which could be easily be eliminated through an aqueous workup.




**Scheme 11**. Oxidation reaction in Flow Reactors

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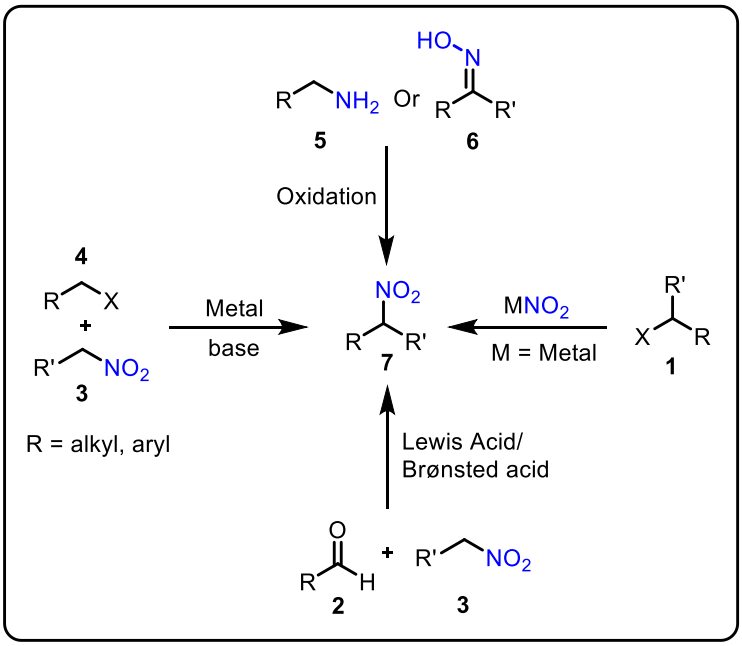
# *Chapter 2*

## Base Catalyzed 1,6-Conjugate Addition of Nitroalkanes to *p*-Quinone Methides under Continuous-flow

### 2.1 Introduction

Over the past several decades, the chemistry of nitroalkanes has been recognized as one of the crucial research areas in synthetic chemistry.[1] Nitroalkanes serve as a valuable synthon in the synthesis of natural products,[2] biologically active unnatural active pharmaceutical ingredients (APIs)[3] and other useful compounds such as carbonyl compounds, carbohydrates, heterocycles, peptides, etc.[4] Although there are several different methods available for the synthesis of nitroalkanes, the most popular one is the introduction of nitro group through the displacement reaction between the alkyl halides and a suitable inorganic or organic nitrite sources.[5] Subsequently, other substituted nitroalkanes could be easily accessed from simple nitroalkanes through Henry or nitro-aldol reactions,[6] alkylation/arylation reactions, etc. (Scheme 1).[7]




**Scheme 1**. Approach towards the synthesis of nitro compounds.

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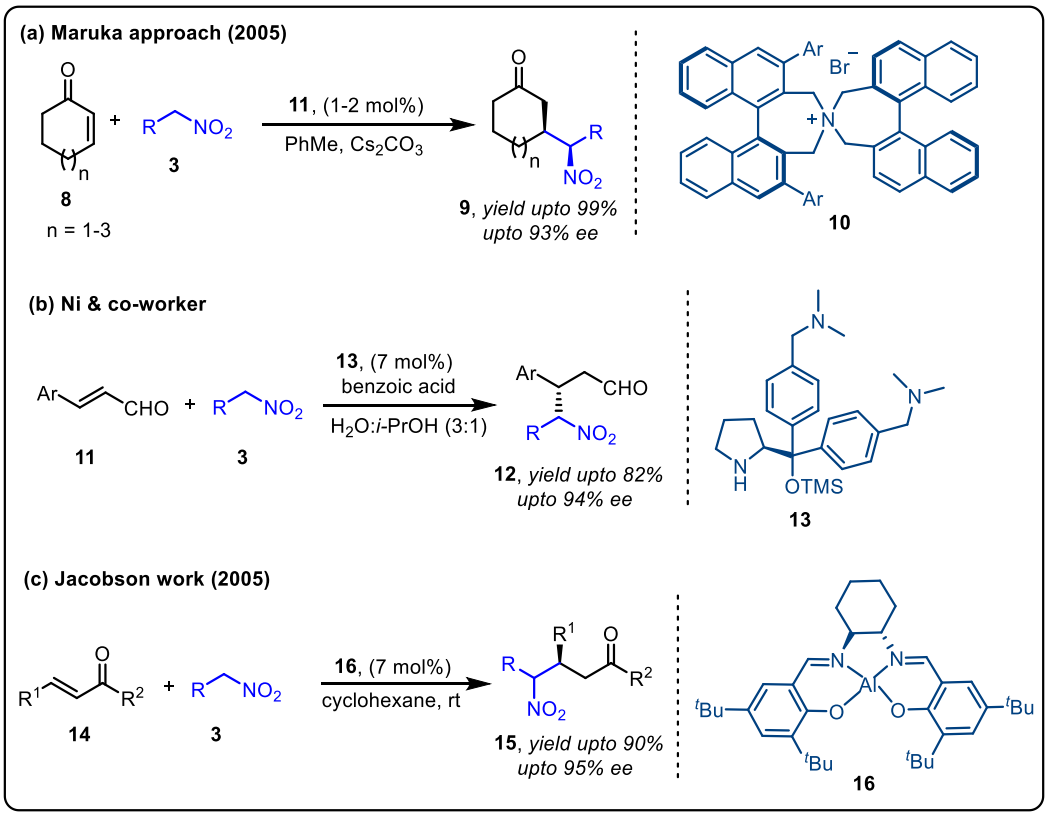
The 1,4-conjugate addition of nitroalkanes to enones,[8] especially the enantioselective version, to access other functionalized nitroalkanes in enantiomerically pure form, has been well explored using either chiral organocatalysts[9] or transition metal catalysts.[10] Maruka and

co-workers in 2005 reported an enantioselective addition of nitroalkanes (**3**) to cyclic unsaturated ketones (**8**), using a chiral ammonium salt as a phase transfer catalyst (Scheme 2, **a**).[9d] Later, Ni and co-workers have utilized a prolinol-based organocatalyst **13** in combination with a Brønsted acid for the addition of **3** to α,β-unsaturated aldehydes (**11**) to prepare the corresponding adducts (**12**) in good yields and high enantioselectivities.[9e] Jacobson and co-workers have also demonstrated an enantioselective addition of **3** to α,β-unsaturated ketones (**14**) using a metal salen complex **16** to get the corresponding conjugate addition products (**15**) with high enantiomeric purity (Scheme 2, **c**).[10c]




**Scheme 2**. Enantioselective addition of nitro alkanes

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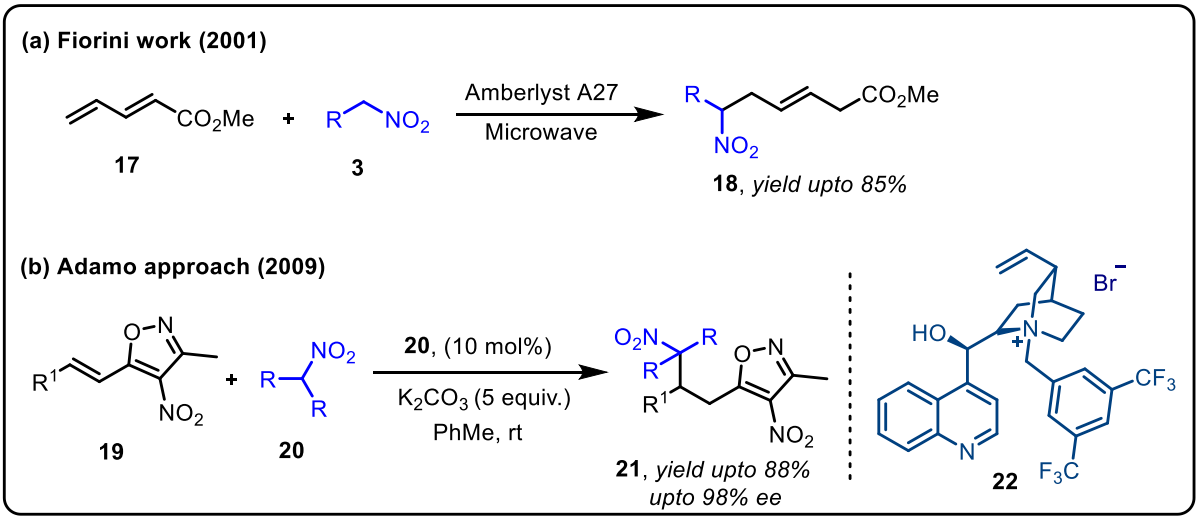
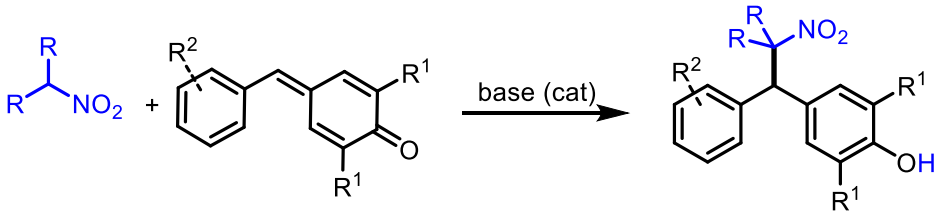
The 1,6-conjugate addition of nitroalkanes to the linear dienone system has also been investigated using appropriate catalytic systems.[11] Fiorini and co-workers reported a 1,6-conjugate addition of **3** to electron-deficient dienes (**17**) under microwave conditions using Amberlyst A27 as a catalyst to prepare the addition products (**18**) [Scheme 3, **a**].[11a] Adamo and co-workers have demonstrated an enantioselective 1,6-conjugate addition of substituted nitroalkanes (**20**) and 4-nitro-5-styrylisoxazoles (**19**) using a cinchona-based phase transfer catalyst **22** to synthesize highly functionalized nitro alkanes **21** (Scheme 3, **b**).[11b]




**Scheme 3**. 1,6-conjuate addition of nitro-alkanes

## 2.2 Background

Till now, only a handful of reports are available in the literature for the 1,6-conjugate addition of nitroalkanes to *p*-QMs, although several reports,[12] including ours,[13] are available for the vinylogous Michael addition of other active methylene compounds to *p*-QMs. Consequently, while working on the nucleophilic addition reactions of *p*-QMs,[14] we have developed a base-catalyzed method for the synthesis of highly substituted nitroalkane derivatives through 1,6-conjugate addition of nitroalkanes to *p*-quinone methides (Scheme 1).




**Scheme 4**. 1,6-Conjugate addition of nitroalkanes to *p*-QMs

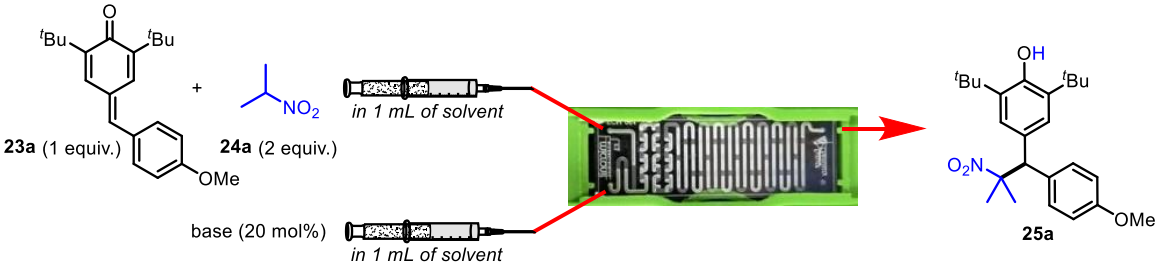
Since the microreaction technique is emerging as a better alternative to the batch reaction technique due to its operational simplicity and higher efficiency,[15] we have decided to develop this methodology under continuous-flow using a microreactor. This particular technique has found many applications in synthetic organic chemistry, especially in methods development,[16] synthesis of natural products and APIs,[17] and asymmetric synthesis.[18] In the recent past, we have also utilized this technique to access diarylalkanes and diarylmethyl

thioethers through 1,6-conjugate addition of dialkylzinc reagents and thiols, respectively to *p*-QMs under continuous-flow.[19]

## 2.3 Results and Discussions

The optimization experiments were performed with *p*-QM **23a** and 2-nitropropane **24a** under continuous-flow conditions using a commercial glass microreactor having a total volume of 100 μL. In all the experiments, a mixture of **23a** and **24a** was dissolved in 1 mL of solvent and injected into the microreactor through a syringe. Parallelly, a solution of a base in 1 mL of solvent was introduced to the microreactor through another syringe.

**Table 1.** Optimization Studies[a]



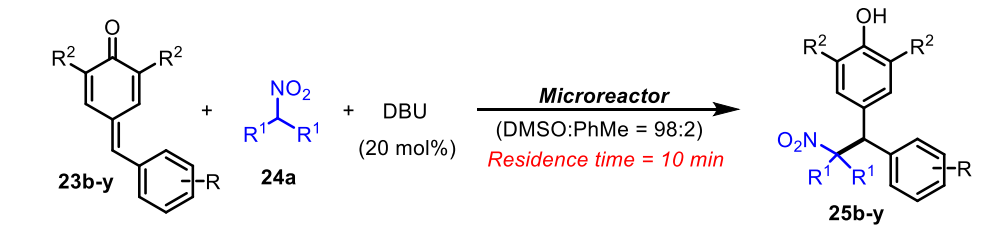

| entry | base | solvent | flow rate **23a** & **24a** + base in solvent [μL $min^{-1}$] | residence time [min] | temp [°C] | yield of **25a** [%] |
|---|---|---|---|---|---|---|
| 1 | DBU | PhMe | 20+20 | 2.5 | rt | nd |
| 2 | DBU | PhMe | 20+20 | 2.5 | 80 | nd |
| 3 | DBU | DMSO | 20+20 | 2.5 | rt | 58 |
| 4 | DBU | DMSO:PhMe (98:2) | 20+20 | 2.5 | rt | 74 |
| 5 | DBU | DMSO:PhMe (98:2) | 20+20 | 2.5 | 80 | 78 |
| 6 | **DBU** | **DMSO:PhMe (98:2)** | **5+5** | **10** | **80** | **91** |
| 7 | 4-DMAP | DMSO:PhMe (98:2) | 5+5 | 10 | 80 | nd |
| 8 | DABCO | DMSO:PhMe (98:2) | 5+5 | 10 | 80 | trace |
| 9 | DBN | DMSO:PhMe (98:2) | 5+5 | 10 | 80 | 60 |
| 10 | DBU | MeCN | 5+5 | 10 | 60 | 67 |
| 11 | DBU | 1,4-dioxane | 5+5 | 10 | 80 | trace |
| 12 | DBU | DMF | 5+5 | 10 | 80 | 65 |
| 13 | DBU | THF | 5+5 | 10 | 60 | nd |
| 14[b] | DBU | DMSO:PhMe (98:2) | 5+5 | 10 | 80 | 45 |
| 15[c] | DBU | DMSO:PhMe (98:2) | 5+5 | 10 | 80 | 53 |
| 16[d] | DBU | DMSO:PhMe (98:2) | 5+5 | 10 | 80 | 71 |
| 17 | - | DMSO:PhMe (98:2) | 5+5 | 10 | 80 | nd |

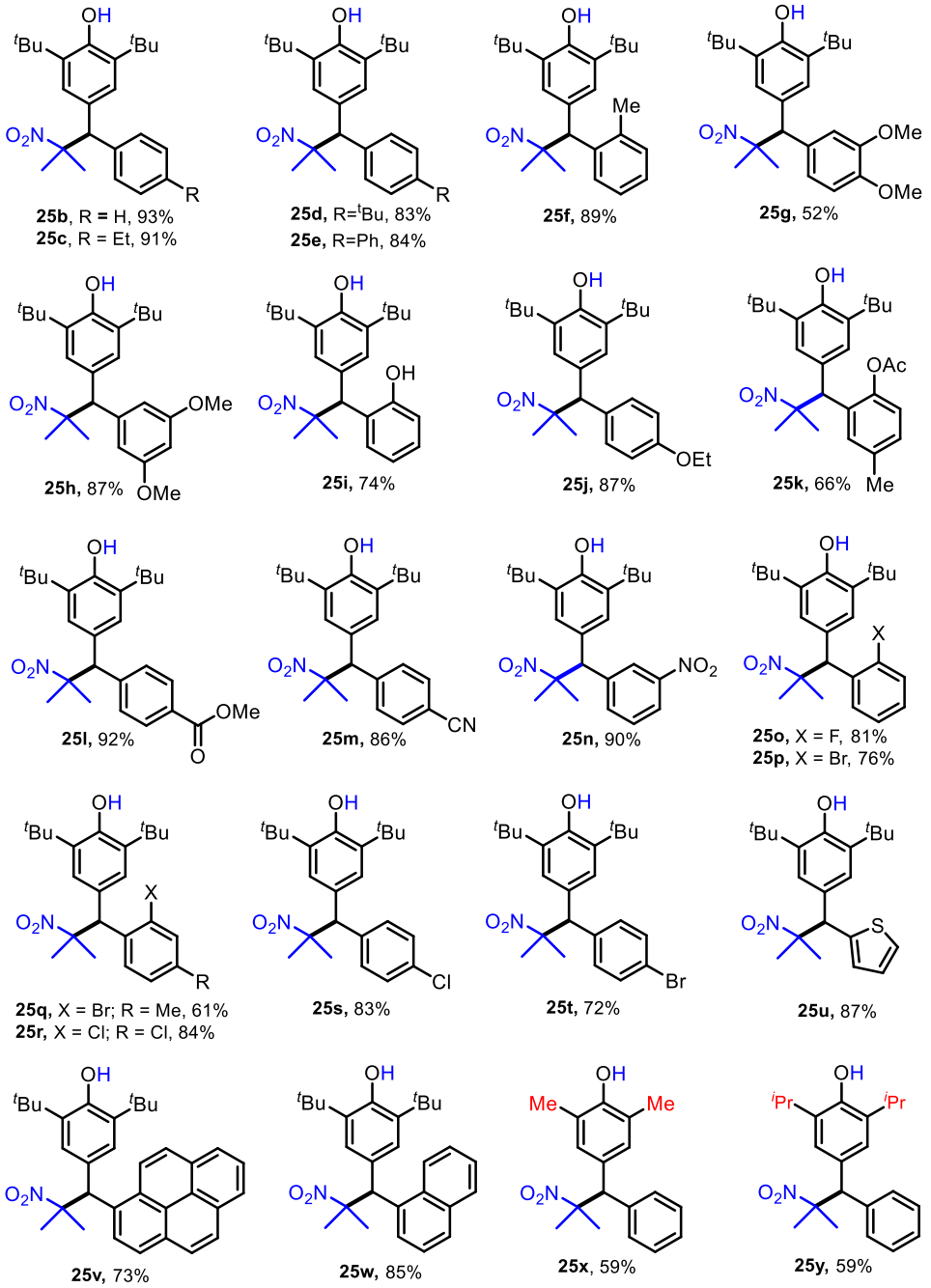
[a] Reaction conditions: All the experiments were carried out with 0.12 mmol of **23a**, 0.24 mmol of **24a** and 0.024 mmol of DBU in solvent. [b] 5 mol % of DBU was used. [c] 10 mol % of DBU was used. [d] 15 mol % of DBU was used. DBU = 1,8-Diazabicyclo-[5.4.0]undec-7-ene. DABCO = 1,4-diazabicyclo-[2.2.2]octane. DBN = 1,5-Diazabicyclo-[4.3.0]non-5-ene. nd = Not detected.

The results of the optimization studies are summarized in Table 1. Initially, a couple of experiments were carried out using toluene as a solvent at rt and at 80 $^{o}$C (residence time = 2.5 min). However, in both the experiments, the required product **25a** was not observed (entries 1 & 2). To our delight, when the reaction was performed in DMSO with the residence time of 2.5 min, **25a** was isolated in 58% yield (entry 3). However, in this case, we observed that **23a** was slowly crystallizing in the syringe over a period of time, and due to this, some blockage was observed in the microchannels. So, we have decided to explore a combination of a polar and a non-polar solvent for further studies. Subsequently, when the reaction was carried in DMSO:toluene (98:2) mixture, the yield of **25a** was increased to 74% at rt (entry 4). The yield of **25a** was further improved to 78% by increasing the temperature to 80 $^{o}$C under the flow rate 40 μL/min (entry 5). At this point, we believed that the yield of **25a** would be improved to a great extent if the residence time of the reaction mixture in the microchannels is increased. Accordingly, we conducted another experiment by increasing the residence time to 10 min, and as expected, **25a** was obtained in 91% yield (entry 6). Unfortunately, other bases such as, 4-DMAP and DABCO failed to catalyze the reaction (entries 7 & 8). DBN was found to be effective for this transformation, but the product **25a** was obtained only in 60% yield (entry 9). Next, to find the best solvent system for this transformation, a few optimization experiments were performed in other solvents (entries 10-13). In the case of MeCN and DMF, **25a** was isolated in 67 and 65% yield, respectively (entries 10 & 12), but the reaction did not proceed in other solvents such as, 1,4-dioxane and THF (entries 11 & 13). Lowering the catalyst loading (5-15 mol%) affected the yield of **3a** considerably (entries 14-16). Another experiment was carried out without the base catalyst and, in this case, no reaction was observed (entry 17). This experiment obviously signifies that a base catalyst is required for this transformation.

After finding the best reaction condition (entry 6, Table 1), the general applicability of this protocol was evaluated using a wide range of *p*-quinone methides and nitroalkanes (Table 2 and Table 3). Most of the *p*-QMs **23b-k** (substituted with electron-rich arenes) underwent the 1,6-addition reaction with **24a** and provided the corresponding 1,6-adducts **25b-k** in the range of 66-93% yields. Other *p*-QMs **23l-n** (substituted with electron-poor arenes) also reacted with **24a** efficiently and gave the respective products **25l-n** in excellent yields (86-92%). The substrate scope was extended to haloarene-substituted (**23o-t**) and heteroaryl-substituted (**23u**) *p*-QMs and, in those cases, the 1,6-addition products **25o-u** were obtained in the range of 61-84% yields.

**Table 2**. Substrate Scope[a]

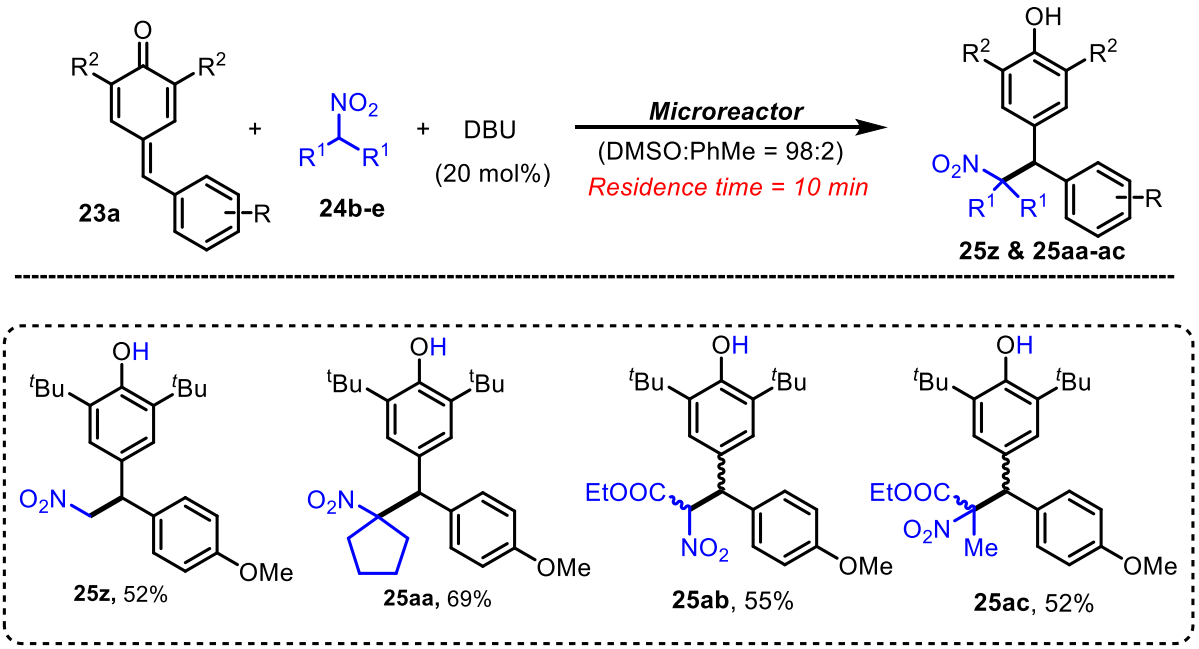



[a] Reaction conditions: All the experiments were carried out in 40 mg (0.19-0.10 mmol) scale of **23(b-y)** and with 2.0 equiv. of **24a**. Yields reported are isolated yields.

In the cases of *p*-QMs **23v** & **23w** (derived from fused aromatic aldehydes), the products **25v** and **25w** were isolated in 73 and 85% yields, respectively. Delightfully, the present protocol worked moderately well in the cases of other *p*-QMs **23x** & **23y** (derived from 2,6-dimethylphenol and propofol, respectively), and the products **25x** & **25y** were obtained in 59% yields. Other nitroalkanes such as, nitromethane (**24b**) and 1-nitro-cyclopentane (**24c**) also reacted with **23a** under standard conditions and gave the respective products **25z** and **25aa** in 52 and 69% yields, respectively. When ethyl nitroacetate was used as a nucleophile, the respective product **25ab** was obtained in 55% yield as a mixture of diastereomers (*dr* = 1:1). Similarly, ethyl 2-nitropropionate provided the corresponding product **25ac** in 52% yield and 1.3:1 diastereomeric ratio. The actual photograph of the reaction set-up is shown in Figure 1.

**Table 3**. Substrate Scope[a]




[a] Reaction conditions: All the experiments were carried out in 40 mg (0.12 mmol) scale of **23a** and with 2.0 equiv. of **24b-e**. Yields reported are isolated yields.

After evaluating the scope and limitations of this transformation using several *p*-QMs and nitroalkanes (Table 2 & Table 3), we wanted to compare the efficiency of the continuous-flow process against the batch process on a large scale. In this regard, a gram-scale reaction was performed using **23a** and **24a** under continuous-flow as well as batch processes (Scheme 5). As expected, in the case of continuous-flow reaction, the product **25a** was obtained in

80% yield. When the same reaction was carried out at room temperature under batch conditions, **25a** was obtained in 69% yield after 24 h and, in that case, complete consumption

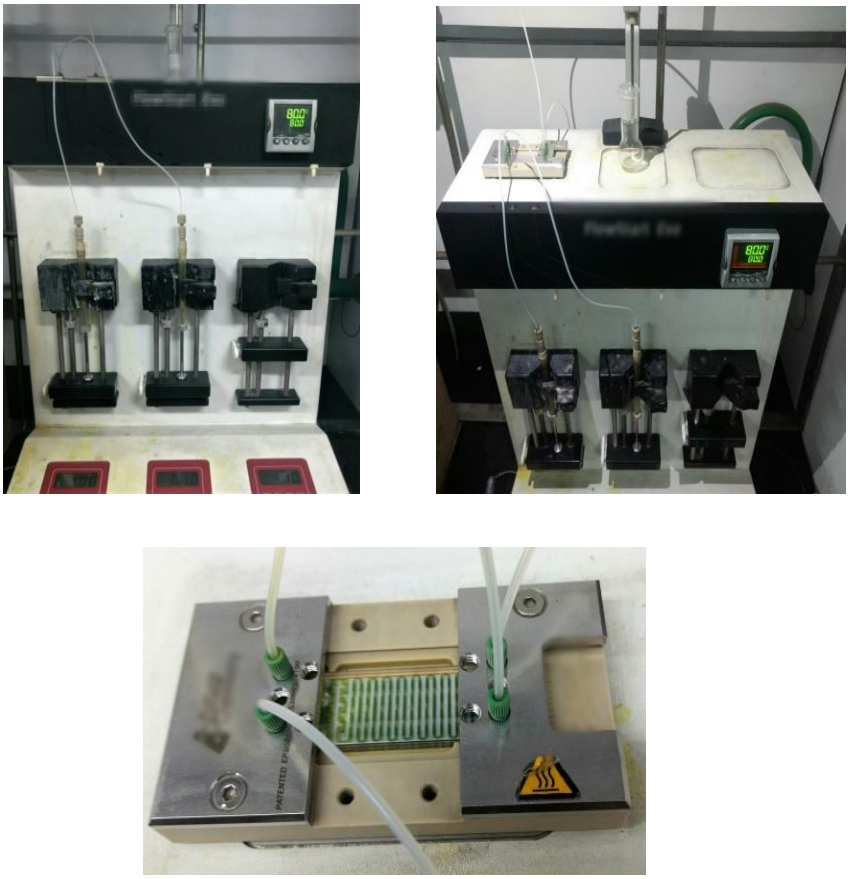
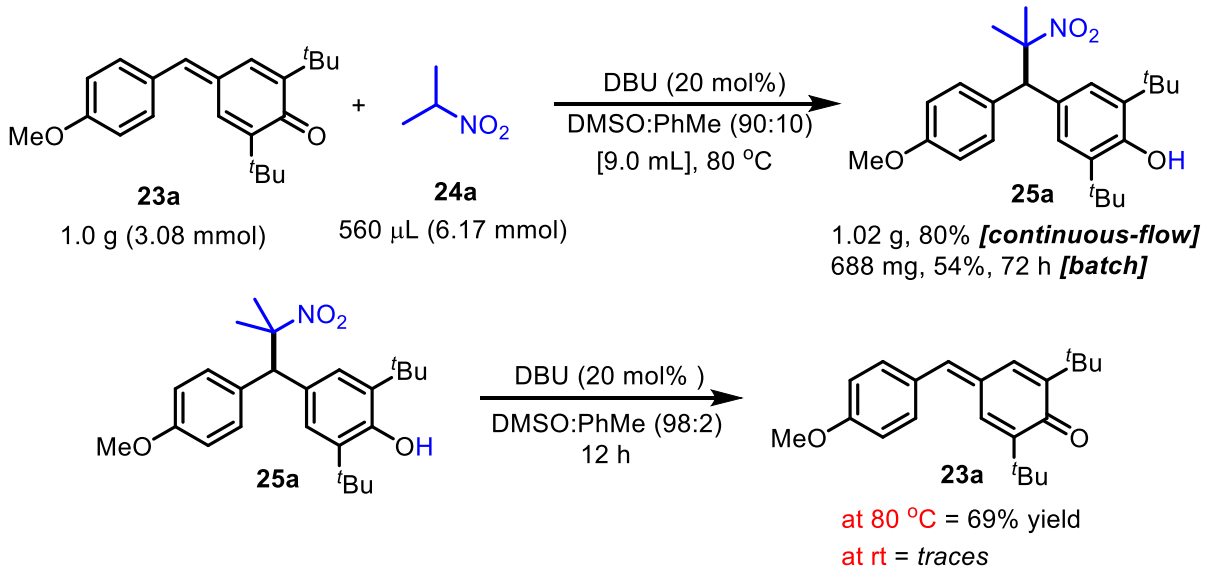


**Figure 1**. Actual photograph of reaction set-up.

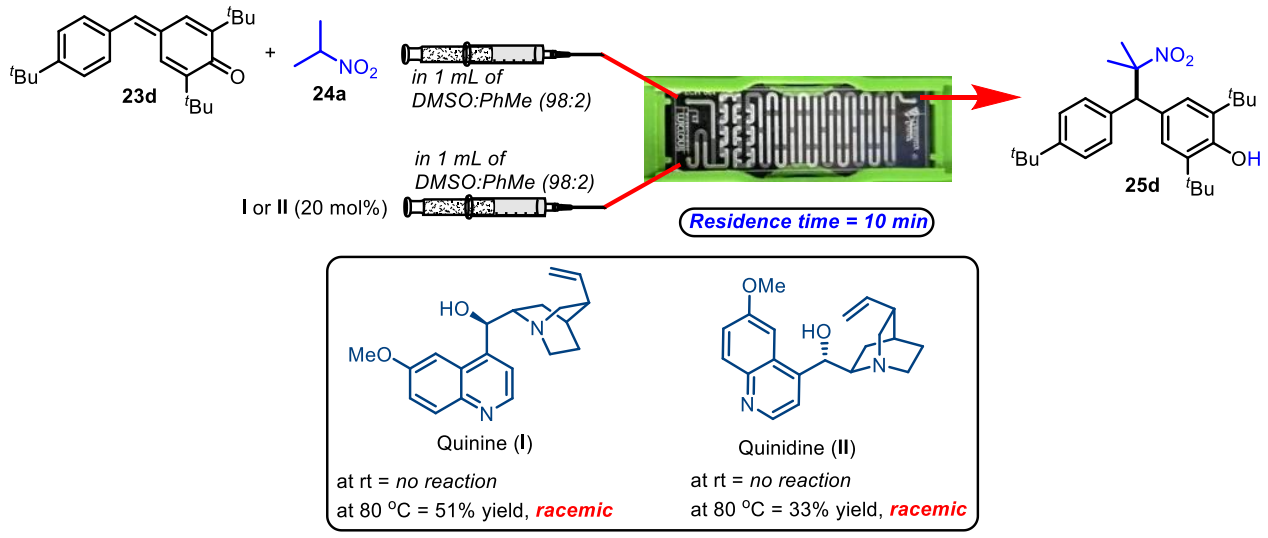
of **23a** was not observed. However, when the batch reaction was carried out at 80 $^{o}$C (standard conditions), **25a** was obtained only in 54% yield. Since the yield of **25a** was substantially low at 80 $^{o}$C, and also the complete conversion of **23a** was not observed even after 3 days, we suspected that the retro-vinylogous Michael-type reaction was taking place in the case of a batch process. We believe that this could be the main reason for the lower yield of the product in the batch method. To confirm this, a batch reaction was carried out, in which, the 1,6-adduct **25a** was treated with 20 mol% DBU in DMSO-toluene mixture at 80 $^{o}$C and, as expected, the *p*-QM **23a** was obtained in 69% yield (Scheme 5). Interestingly, when the same batch reaction was carried out at room temperature, **23a** was observed only in trace amounts. The above-mentioned experiments led to the following conclusions. The 1,6-addition reaction between **23a** and **24a** is reversible only at higher temperature (in this case, 80 $^{o}$C). So, one can conclude that, in the batch process, since the product **25a** stays in the

reaction flask for a longer period, the extent of the retro-1,6-addition reaction is high. On the other hand, in the continuous-flow method, though the reaction channels are kept at 80 °C, the reaction mixture does not stay in the microchannels for a long time. In fact, it is continuously removed from the microchannels through the outlet and collected in a flask that is kept at room temperature. This means the reaction mixture gets cooled to room temperature immediately after coming out of the microchannels. This clearly signifies that the retro-1,6-addition reaction is not possible in this case as this reaction does not take place at room temperature (Scheme 5). This is the primary reason for getting the higher yield of **25a** in continuous-flow method when compared to the batch process. From this observation, one can also conclude that the continuous-flow method is more advantageous than the batch process for this particular transformation.




**Scheme 5**. Batch vs continuous-flow processes and control experiments

The enantioselective version of this transformation was attempted using a couple of chiral amine catalysts. A few reactions were carried out in the microreactor with **23d** and **24a** using 20 mol% of quinine (**I**) or quinidine (**II**) under different conditions, and the results are summarized in Scheme 6. When the reaction was carried out at room temperature using **I** or **II**, the product **25d** was not formed in either case. However, when another reaction was performed with **I** or **II** at 80 °C, **3d** was obtained in 51 and 33% yields, respectively. Unfortunately, in both the cases, the adduct **25d** was obtained as a racemic mixture (Scheme 6).




**Scheme 6**: Attempted enantioselective reactions with chiral bases under continuous-flow

## 2.4 Conclusion

In conclusion, an effective method for the synthesis of highly substituted nitroalkane derivatives has been developed under continuous-flow conditions using the microreaction technology. This reaction proceeds through a base-catalyzed 1,6-conjugate addition of nitroalkanes to *p*-quinone methides, and the respective 1,6-adducts were obtained in good yields. The comparison between the continuous-flow method and the batch process through control experiments revealed that the former approach is more advantageous when compared to the later process as the retro-1,6-reaction was arrested in the former case and, as a result, the 1,6-adducts were obtained in good to excellent yields.

## 2.5 Experimental Section

### General methods

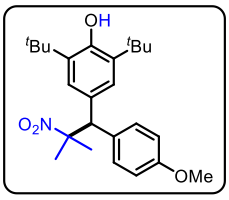
Continuous-flow reactions were performed using FlowStart Evo B-401 instrument purchased from Future Chemistry Holding B.V. The microreactor was made up of borosilicate glass (channel width 600 µm, channel depth 500 µm) with effective reaction volume of 100 µL. The microreactor set up has in-built syringe pumps and all the reactions were carried out without using back pressure regulator. Most of the reagents and starting materials were purchased from commercial sources and used without further purification. All *p*-quinone

methides were prepared by following a literature procedure.[12a] Melting points were recorded on SMP20 melting point apparatus and are uncorrected. $^{1}H$, $^{13}C$ and $^{19}F$ spectra were recorded in $CDCl_3$ (400, 100 and 376 MHz respectively) on Bruker FT-NMR spectrometer. Chemical shift (δ) values are reported in parts per million relative to TMS and the coupling constants (*J*) are reported in Hz. High resolution mass spectra were recorded on Waters Q-TOF Premier-HAB213 spectrometer. FT-IR spectra were recorded on a Perkin–Elmer FTIR spectrometer. Thin layer chromatography was performed on Merck silica gel 60 $F_{254}$ TLC pellets. Column chromatography was carried out through silica gel (100-200 mesh) using EtOAc/hexane as an eluent.

**General procedure for the 1,6-conjugate reaction of nitroalkanes to *p*-quinone methides under continuous-flow:**

*p*-Quinone methide (0.12 mmol, 1 equiv.) and 2-nitroalkane (0.24 mmol, 2 equiv.) were dissolved in 1 mL of DMSO:toluene (98:2) mixture and taken in a syringe. DBU (0.024 mmol, 20 mol%) was dissolved in 1 mL of DMSO:toluene (98:2) mixture and taken in another syringe. These two solutions were injected simultaneously through the microchannels at the flow rates of 5 µL/min each (residence time = 10 min). The temperature of microchannels was maintained at 80 °C throughout the reaction. The reaction mixture collected at the outlet and was quenched with water. It was extracted with diethyl ether (10 mL x 2). The organic layer was concentrated under reduced pressure and the crude was then loaded on a silica gel column and purified using hexane/EtOAc mixture as an eluent to provide the pure 1,6-adduct.

**2,6-Di-*tert*-butyl-4-(1-(4-methoxyphenyl)-2-methyl-2-nitropropyl)phenol** (**25a**): The




reaction was performed at 40 mg scale (0.123 mmol) of **23a**; $R_f$ = 0.3 (5% EtOAc in hexane); pale yellow solid (46.3 mg, 91% yield); m.p. = 143–145 $^{o}C$; $^{1}H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.29 (d, $J$ = 8.3 Hz, 2H), 7.12 (s, 2H), 6.83 (d, $J$ = 8.4 Hz, 2H), 5.12 (s, 1H), 4.62 (s, 1H), 3.77 (s, 3H), 1.64 (s, 3H), 1.63 (s, 3H), 1.41 (s, 18H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 158.8, 153.0, 135.7, 131.5, 130.7, 129.5, 126.2, 114.0, 92.9, 60.0, 55.3, 34.5, 30.4, 25.4, 25.0; FT-IR (thin film, neat): 3421, 2958, 1263, 753 $cm^{-1}$; HRMS (ESI): *m/z* calcd for $C_{25}H_{35}NO_4$ $[M-H]^-$ : 412.2488; found : 412.2470.

**2,6-Di-*tert*-butyl-4-(2-methyl-2-nitro-1-phenylpropyl) phenol (25b):** The reaction was performed at 40 mg scale (0.135 mmol) of **23b**; $R_f$ = 0.4 (5% EtOAc in hexane); yellow solid (48.4 mg, 93% yield); m.p. = 98–100 $^oC$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.38 (d, $J$ = 7.7 Hz, 2H), 7.30 (t, $J$ = 7.5 Hz, 2H), 7.26 - 7.22 (m, 1H), 7.14 (s, 2H), 5.14 (s, 1H), 4.67 (s, 1H), 1.66 (s, 6H), 1.42 (s, 18H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 153.1, 139.5, 135.7, 129.7, 129.1, 128.6, 127.4, 126.3, 92.8, 60.7, 34.5, 30.4, 25.4, 25.2; FT-IR (thin film, neat): 3634, 2959, 1264, 750 $cm^{-1}$; HRMS (ESI): *m/z* calcd for $C_{24}H_{33}NO_3$ $[M-H]^-$ : 382.2382; found : 382.2365.

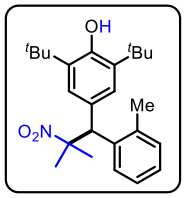
**2,6-Di-*tert*-butyl-4-(1-(4-ethylphenyl)-2-methyl-2-nitropropyl) phenol (25c):** The reaction was performed at 40 mg scale (0.124 mmol) of **23c**; $R_f$ = 0.4 (5% EtOAc in hexane); pale yellow gummy solid (46.5 mg, 91% yield); $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.30 (d, $J$ = 8.0 Hz, 2H), 7.15 - 7.12 (m, 4H), 5.12 (s, 1H), 4.63 (s, 1H), 2.61 (q, $J$ = 7.6 Hz, 2H), 1.65 (s, 3H), 1.64 (s, 3H), 1.41 (s, 18H), 1.20 (t, $J$ = 7.6 Hz, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 153.1, 143.3, 136.6, 135.6, 129.6, 129.3, 128.1, 126.3, 92.9, 60.5, 34.5, 30.4, 28.4, 25.4, 25.1, 15.5; FT-IR (thin film, neat): 3437, 2963, 1261, 752 $cm^{-1}$; HRMS (ESI): *m/z* calcd for $C_{26}H_{37}NO_3$ $[M-H]^-$ : 410.2695; found : 410.2677.

**2,6-Di-*tert*-butyl-4-(1-(4-(tert-butyl) phenyl)-2-methyl-2-nitropropyl) phenol (25d):** The reaction was performed at 40 mg scale (0.113 mmol) of **23d**; $R_f$ = 0.4 (5% EtOAc in hexane); pale yellow solid (41.3 mg, 83% yield); m.p. = 134–136 $^oC$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.31 (s, 4H), 7.17 (s, 2H), 5.13 (s, 1H), 4.63 (s, 1H), 1.65 (s, 3H), 1.64(s, 3H), 1.42 (s, 18H), 1.28 (s, 9H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 153.1, 150.1, 136.2, 135.6, 129.3, 126.4, 125.5, 93.0, 60.5, 34.52, 34.50, 31.4, 30.4 (2C), 25.3, 25.1; FT-IR (thin film, neat): 3636, 2960, 1266, 752 $cm^{-1}$; HRMS (ESI): *m/z* calcd for $C_{28}H_{41}NO_3$ $[M-H]^-$: 438.3008; found : 438.3026.

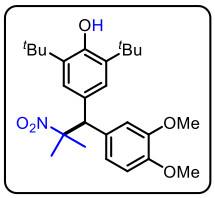
**4-(1-([1,1'-Biphenyl]-4-yl)-2-methyl-2-nitropropyl)-2,6-di-*tert*-butylphenol (25e):** The reaction was performed at 40 mg scale (0.107 mmol) of **23e**; $R_f$ = 0.5 (5% EtOAc in hexane); pale yellow solid (41.4 mg, 84% yield); m.p. = 148–150 $^oC$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.58 - 7.52 (m, 4H), 7.46 - 7.40 (m, 4H), 7.35 - 7.31 (m, 1H), 5.15 (s, 1H), 4.72 (s, 1H), 1.70 (s, 3H), 1.68 (s, 3H), 1.42 (s, 18H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 153.2, 140.6, 140.1, 138.5, 135.8, 130.1, 129.1, 128.9, 127.5, 127.3, 127.1, 126.3, 92.8, 60.5, 34.5, 30.4, 25.5, 25.1; FT-IR (thin film, neat):

3426, 2987, 1266, 751 $cm^{-1}$; HRMS (ESI): *m/z* calcd for $C_{30}H_{34}NO_3$ $[M-Na]^-$ : 458.2695; found : 458.2676.

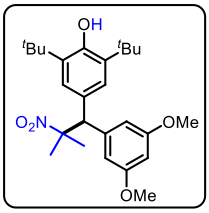
**2,6-Di-*tert*-butyl-4-(2-methyl-2-nitro-1-(o-tolyl) propyl) phenol** (**25f**): The reaction was performed at 40 mg scale (0.129 mmol) of **23f**; $R_f$ = 0.4 (5% EtOAc in hexane); pale yellow gummy solid (45.9 mg, 89% yield); m.p. = 136–138$^oC$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.54 (d, *J* = 7.8 Hz, 1H), 7.20 (td, *J* =6.4, 2.6 Hz, 1H), 7.16 - 7.10 (m, 2H), 7.04 (s, 2H), 5.11 (s, 1H), 5.03 (s, 1H), 2.38 (s, 3H), 1.73 (s, 3H), 1.66 (s, 3H), 1.38 (s, 18H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 153.0, 138.4, 137.4, 135.5, 131.4, 128.5, 127.1, 127.0, 126.7, 126.0, 93.1, 54.4, 34.4, 30.4, 26.0, 25.6, 21.0; FT-IR (thin film, neat): 3632, 2961, 1267, 754 $cm^{-1}$; HRMS (ESI): *m/z* calcd for $C_{25}H_{35}NO_3$ $[M-H]^-$ : 396.2539; found : 396.2556.



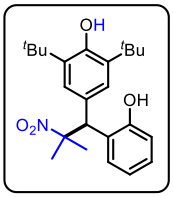

**2,6-Di-*tert*-butyl-4-(1-(3, 4-dimethoxyphenyl)-2-methyl-2-nitropropyl) phenol** (**25g**)**:** The reaction was performed at 40 mg scale (0.112 mmol) of **23g**; $R_f$ = 0.1 (5% EtOAc in hexane); yellow gummy solid (25.6 mg, 52% yield); $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.15 (s, 2H), 6.94 - 6.89 (m, 2H), 6.80 (d, *J* = 8.3 Hz, 1H), 5.14 (s, 1H), 4.60 (s, 1H), 3.87 (s, 3H), 3.85 (s, 3H), 1.65 (s, 3H), 1.63 (s, 3H), 1.41 (s, 18H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 153.1, 148.6, 148.3, 135.7, 131.8, 129.2, 126.2, 121.9, 113.1, 111.1, 93.0, 60.3, 55.94, 55.92, 34.5, 30.4, 25.5, 25.0; FT-IR (thin film, neat): 3435, 2959, 1266, 751 $cm^{-1}$; HRMS (ESI): *m/z* calcd for $C_{26}H_{37}NO_3$ $[M-H]^-$ : 442.2593; found : 442.2573.




**2,6-Di-*tert*-butyl-4-(1-(3, 5-dimethoxyphenyl)-2-methyl-2-nitropropyl) phenol** (**25h**): The reaction was performed at 40 mg scale (0.112 mmol) of **23h**; $R_f$ = 0.3 (5% EtOAc in hexane); pale yellow solid (43.5 mg, 87% yield); m.p. = 134–136 $^oC$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.14 (s, 2H), 6.54 (d, *J* = 2.1 Hz, 2H), 6.35 (t, *J* = 2.0 Hz, 1H), 5.15 (s, 1H), 4.60 (s, 1H), 3.77 (s, 6H), 1.67 (s, 3H), 1.65 (s, 3H), 1.41 (s, 18H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 160.7, 153.2, 141.5, 135.6, 128.8, 126.3, 108.1, 99.0, 92.8, 60.8, 55.4, 34.5, 30.4, 25.35, 25.30; FT-IR (thin film, neat): 3626, 2958, 1265, 750 $cm^{-1}$; HRMS (ESI): *m/z* calcd for $C_{26}H_{37}NO_3$ $[M-H]^-$: 442.2593; found : 442.2573.

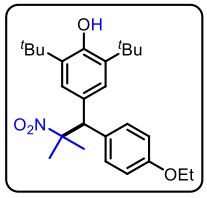


**2,6-Di-*tert*-butyl-4-(1-(2-hydroxyphenyl)-2-methyl-2-nitropropyl)phenol** (**25i**): The



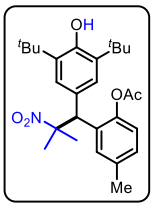

reaction was performed at 40 mg scale (0.128 mmol) of **23i**; $R_f$ = 0.1 (5% EtOAc in hexane); pale yellow gummy solid (39.2 mg, 76% yield); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.46 (dd, $J$ = 7.8, 1.4 Hz, 1H), 7.12 - 7.09 (m, 3H), 6.94 - 6.90 (m, 1H), 6.74 (dd, $J$ = 8.0, 0.92 Hz, 1H), 5.27 (s, 1H), 5.14 (s, 1H), 5.01 (brs, 1H), 1.71 (s, 3H), 1.68 (s, 3H), 1.39 (s, 18H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 153.7, 153.1, 135.7, 129.5, 129.0, 128.3, 126.6, 126.5, 120.9, 116.5, 92.5, 51.0, 34.5, 30.4, 25.9, 25.4; FT-IR (KBr): 3632, 3448, 2959, 1266, 752 cm$^{-1}$; HRMS (ESI): *m/z* calcd for $C_{24}H_{33}NO_4$ $[M-H]^-$ : 398.2331; found : 398.2343.

**2,6-Di-*tert*-butyl-4-(1-(4-ethoxyphenyl)-2-methyl-2-nitropropyl) phenol** (**25j**)**:** The



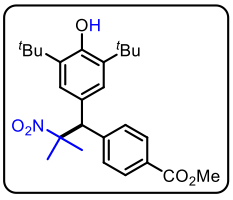

reaction was performed at 40 mg scale (0.118 mmol) of **23j**; $R_f$ = 0.5 (5% EtOAc in hexane); pale yellow solid (44.1 mg, 87% yield); m.p. = 122–124 $^o$C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.27 (d, $J$ = 8.9 Hz, 2H), 7.12 (s, 2H), 6.82 (d, $J$ = 8.5 Hz, 2H), 5.12 (s, 1H), 4.61 (s, 1H), 4.01 (q, $J$ = 7.0 Hz, 2H), 1.62 (s, 6H), 1.40 (s, 18H), 1.38 (t, $J$ = 6.8 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 158.2, 153.0, 135.6, 131.3, 130.7, 129.5, 126.2, 114.5, 93.0, 63.5, 60.0, 34.5, 30.4, 25.3, 25.1, 15.0; FT-IR (KBr): 3444, 2958, 1260, 753 cm$^{-1}$; HRMS (ESI): *m/z* calcd for $C_{26}H_{37}NO_4$ $[M+Na]^+$: 450.2620; found : 450.2604.

**2-(1-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-2-methyl-2-nitropropyl)-4-methylphenyl acetate** (25**k**)**:** The reaction was performed at 40 mg scale (0.109 mmol) of **23k**; $R_f$ = 0.2 (5%




EtOAc in hexane); pale yellow solid (32.7mg, 66% yield); m.p. = 128–130 $^o$C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.29 (d, $J$ = 1.5 Hz, 1H), 7.07 (dd, $J$ = 8.2, 1.5 Hz, 2H), 6.97 (s, 2H), 6.94 (d, $J$ = 8.2 Hz, 1H), 5.11 (s, 1H), 4.99 (s, 1H), 2.34 (s, 3H), 2.27 (s, 3H), 1.72 (s, 3H), 1.61 (s, 3H), 1.37 (s, 18H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 169.3, 153.0, 147.0, 135.5, 135.4, 131.6, 129.9, 128.8, 128.7, 126.2, 123.0, 92.2, 51.5, 34.4, 30.3, 26.5, 24.8, 21.5, 21.1; FT-IR (thin film, neat): 3632, 2966, 1764, 1268, 754 cm$^{-1}$; HRMS (ESI): *m/z* calcd for $C_{27}H_{37}NO_5$ $[M-H]^-$ : 454.2593; found : 454.2571.

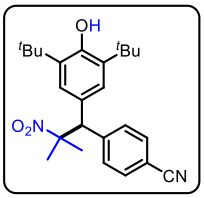
**Methyl 4-(1-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-2-methyl-2-nitropropyl) benzoate** (**25l**):




The reaction was performed at 40 mg scale (0.113 mmol) of **23l**; $R_f$ = 0.2 (5% EtOAc in hexane); pale yellow solid (46.4 mg, 92% yield); m.p. = 145–147 $^o$C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.97 (d, $J$ = 8.1 Hz, 2H),

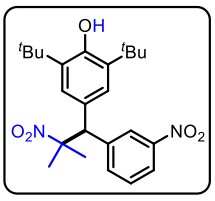
7.44 (d, $J$ = 8.2 Hz, 2H), 7.10 (s, 2H), 5.18 (s, 1H), 4.75 (s, 1H), 3.90 (s, 3H), 1.66 (s, 6H), 1.40 (s, 18H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 166.9, 153.3, 144.7, 135.9, 129.9, 129.7, 129.2, 128.4, 126.3, 92.4, 60.5, 52.3, 34.5, 30.4, 25.8, 24.9; FT-IR (thin film, neat): 3633, 2957, 1723,1281, 755 cm$^{-1}$; HRMS (ESI): *m/z* calcd for $C_{26}H_{35}NO_5$ [M-H]$^-$: 440.2437; found : 440.2427.

**4-(1-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-2-methyl-2-nitropropyl) benzonitrile**



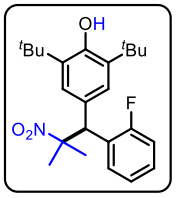

(**25m**):The reaction was performed at 40 mg scale (0.125 mmol) of **23m**; $R_f$ = 0.1 (5% EtOAc in hexane); pale yellow solid (44.1 mg, 86% yield); m.p. = 140–142 $^o$C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.59 (d, $J$ = 8.1 Hz, 2H), 7.45 (d, $J$ = 8.2 Hz, 2H), 7.06 (s, 2H), 5.22 (s, 1H), 4.72 (s, 1H), 1.67 (s, 3H), 1.64 (s, 3H), 1.41 (s, 18H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 153.5, 145.0, 136.2, 132.4, 130.3, 127.9, 126.3, 118.7, 111.3, 92.1, 60.5, 34.5, 30.4, 26.4, 24.4; FT-IR (KBr): 3630, 2959, 2230, 1264, 752 cm$^{-1}$; HRMS (ESI): *m/z* calcd for $C_{25}H_{32}N_2O_3$ [M-H]$^-$ : 407.2335; found : 407.2326.

**2,6-Di-*tert*-butyl-4-(2-methyl-2-nitro-1-(3-nitrophenyl) propyl) phenol** (**25n**): The




reaction was performed at 40 mg scale (0.117 mmol) of **23n**; $R_f$ = 0.2 (5% EtOAc in hexane); pale yellow solid (45.2 mg, 90% yield); m.p. = 130–132 $^o$C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.33 (t, $J$ = 2.0Hz, 1H), 8.14 - 8.11 (m, 1H), 7.68 (d, $J$ = 7.8 Hz, 1H), 7.49 (t, $J$ = 8.0 Hz, 1H), 7.14 (s, 2H), 5.23 (s, 1H), 4.77 (s, 1H), 1.71 (s, 3H), 1.66 (s, 3H), 1.42 (s, 18H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 153.6, 148.3, 141.5, 136.2, 135.7, 129.6, 127.7, 126.3, 124.4 122.5, 92.2, 60.1, 34.5, 30.4, 26.4, 24.2; FT-IR (thin film, neat): 3629, 2958, 1240, 736 cm$^{-1}$; HRMS (ESI): *m/z* calcd for $C_{24}H_{32}N_2O_5$ [M-H]$^-$: 427.2233; found : 427.2214.

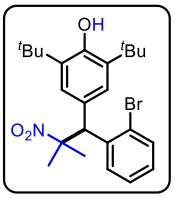
**2,6-Di-*tert*-butyl-4-(1-(2-fluorophenyl)-2-methyl-2-nitropropyl) phenol** (**25o**): The




reaction was performed at 40 mg scale (0.128 mmol) of **23o**; $R_f$ = 0.4 (5% EtOAc in hexane); yellow solid (41.7 mg, 81% yield); m.p. = 103–105 $^o$C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.52 (td, $J$ = 7.7, 1.4 Hz, 1H), 7.24 - 7.20 (m, 1H), 7.12 (d, $J$ = 7.8 Hz, 1H), 7.11 (s, 2H), 7.05 (t, $J$ = 10.2 Hz, 1H), 5.15 (s, 1H), 5.11 (s, 1H), 1.70 (s, 3H), 1.65 (s, 3H), 1.40 (s, 18H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 161.0 (d, $J_{C-F}$ = 244.5 Hz), 153.2, 135.7, 130.1 (d, $J_{C-F}$ = 2.9 Hz), 129.0 (d, $J_{C-F}$ = 8.7 Hz), 128.4, 127.0 (d, $J_{C-F}$ = 13.3 Hz), 126.4, 124.1 (d, $J_{C-F}$ = 3.6 Hz), 116.0 (d, $J_{C-F}$ = 24 Hz), 92.1, 51.2 (d, $J_{C-F}$ = 3.7 Hz), 34.5, 30.4, 26.1, 25.1; $^{19}$F NMR (376 MHz, $CDCl_3$) $\delta$ –114.50; FT-IR

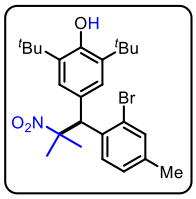
(KBr): 3436, 2963, 1264, 751 $cm^{-1}$; HRMS (ESI): *m/z* calcd for $C_{24}H_{32}FNO_3$ $[M-H]^-$ : 400.2288; found : 400.2270.

**4-(1-(2-Bromophenyl)-2-methyl-2-nitropropyl)-2,6-di-*tert*-butylphenol** (**25p**): The



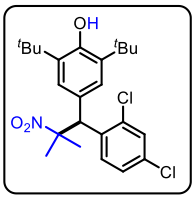

reaction was performed at 40 mg scale (0.107 mmol) of **23p**; $R_f$ = 0.4 (5% EtOAc in hexane); pale yellow solid (37.8 mg, 76% yield); m.p. = 156–158 $^oC$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.62 - 7.58 (m, 2H), 7.30 (t, *J* = 7.6 Hz, 1H), 7.11 - 7.09 (m, 1H), 7.07 (s, 2H), 5.41 (s, 1H), 5.14 (s, 1H), 1.74 (s, 3H), 1.67 (s, 3H), 1.39 (s, 18H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 153.2, 139.3, 135.6, 133.8, 129.1, 128.7, 128.1, 127.5, 127.0, 126.6, 92.3, 57.4, 34.5, 30.4, 26.2, 25.4; FT-IR (KBr): 3633, 2957, 1240, 754 $cm^{-1}$; HRMS (ESI): *m/z* calcd for $C_{24}H_{32}BrNO_3$ $[M-H]^-$ : 460.1487; found : 460.1465.

**4-(1-(2-Bromo-4-methylphenyl)-2-methyl-2-nitropropyl)-2,6-di-*tert*-butylphenol** (**25q**):



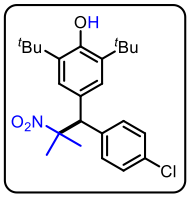

The reaction was performed at 40 mg scale (0.103 mmol) of **23q**; $R_f$ = 0.5 (5% EtOAc in hexane); pale yellow solid (29.8 mg, 61% yield); m.p. = 141–143 $^oC$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.48 (d, *J* = 8.1 Hz, 1H), 7.42 (d, *J* = 1.0 Hz, 1H), 7.10 (dd, *J* = 8.2, 1.2 Hz, 1H), 7.07 (s, 2H), 5.34 (s, 1H), 5.13 (s, 1H), 2.28 (s, 3H), 1.73 (s, 3H), 1.66 (s, 3H), 1.39 (s, 18H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 153.1, 138.8, 136.1, 135.5, 134.2, 128.8, 128.4, 128.3, 126.8, 126.5, 92.3, 57.1, 34.5, 30.4, 26.2, 25.3, 20.7; FT-IR (thin film, neat): 3425, 2958, 1266, 751 $cm^{-1}$; HRMS (ESI): *m/z* calcd for $C_{25}H_{34}BrNO_3$ $[M-H]^-$: 474.1644; found : 474.1624.

**2,6-Di-*tert*-butyl-4-(1-(2,4-dichlorophenyl)-2-methyl-2-nitropropyl) phenol** (**25r**): The



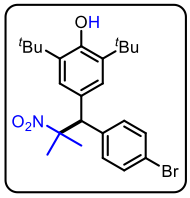

reaction was performed at 40 mg scale (0.110 mmol) of **23r**; $R_f$ = 0.4 (5% EtOAc in hexane); pale yellow gummy solid (42.1 mg, 84% yield); $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.53 (d, *J* = 8.6 Hz, 1H), 7.41 (d, *J* = 2.2 Hz, 1H), 7.24 (dd, *J* = 8.6, 2.3 Hz, 1H), 7.02 (s, 2H), 5.32 (s, 1H), 5.17 (s, 1H), 1.72 (s, 3H), 1.66 (s, 3H), 1.39 (s, 18H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 153.3, 136.4, 136.2, 135.8, 133.5, 130.1, 129.9, 127.7, 127.2, 126.4, 91.8, 54.2, 34.5, 30.4, 26.0, 25.8; FT-IR (thin film, neat): 3632, 2961, 1266, 739 $cm^{-1}$; HRMS (ESI): *m/z* calcd for $C_{24}H_{31}ClNO_3$ $[M-H]^-$ : 450.1603; found : 450.1584.

**2,6-Di-*tert*-butyl-4-(1-(4-chlorophenyl)-2-methyl-2-nitropropyl) phenol** (**25s**): The



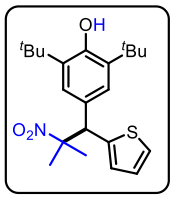

reaction was performed at 40 mg scale (0.121 mmol) of **23s**; $R_f$ = 0.5 (5% EtOAc in hexane); pale yellow solid (42.1 mg, 83% yield); m.p. = 134–136 $^{o}$C; $^{1}$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.31 - 7.28 (m, 4H), 7.10 (s, 2H), 5.17 (s, 1H), 4.65 (s, 1H), 1.65 (s, 3H), 1.63 (s, 3H), 1.41 (s, 18H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 153.2, 138.0, 135.9, 133.3, 130.9, 128.8, 128.7, 126.2, 92.5, 60.0, 34.5, 30.4, 25.8, 24.8; FT-IR (KBr): 3425, 2992, 1266, 752 cm$^{-1}$; HRMS (ESI): *m/z* calcd for $C_{24}H_{32}ClNO_3$ $[M-H]^-$ : 416.1992; found : 416.1973.

**4-(1-(4-Bromophenyl)-2-methyl-2-nitropropyl)-2,6-di-*tert*-butylphenol** (**25t**): The reaction



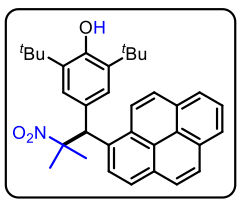

was performed at 40 mg scale (0.107 mmol) of **23t**; $R_f$ = 0.5 (5% EtOAc in hexane); pale yellow solid (35.6 mg, 72% yield); m.p. = 132–134 $^{o}$C;$^{1}$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.42 (d, $J$ = 8.3 Hz, 2H), 7.23 (d, $J$ = 8.3 Hz, 2H), 7.08 (s, 2H), 5.17 (s, 1H), 4.64 (s, 1H), 1.65 (s, 3H), 1.63(s, 3H), 1.41 (s, 18H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 153.3, 138.6, 135.9, 131.7, 131.3, 128.6, 126.2, 121.5, 92.4, 60.1, 34.5, 30.4, 25.8, 24.8; FT-IR (thin film, neat): 3629, 2961, 1266, 753 cm$^{-1}$; HRMS (ESI): *m/z* calcd for $C_{24}H_{32}BrNO_3$ $[M-H]^-$ : 460.1487; found : 460.1466.

**2,6-Di-*tert*-butyl-4-(2-methyl-2-nitro-1-(thiophen-2-yl)propyl)phenol** (**25u**): The reaction




was performed at 40 mg scale (0.133 mmol) of **23u**; $R_f$ = 0.4 (5% EtOAc in hexane); pale yellow solid (45.3 mg, 87% yield); m.p. = 135–137 $^{o}$C; $^{1}$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.23 (s, 2H), 7.21 (d, $J$ = 0.8 Hz, 1H), 6.98 (dd, $J$ = 3.5, 0.8 Hz, 1H), 6.94 (dd, $J$ = 5.1, 3.5 Hz, 1H), 5.19 (s, 1H), 5.05 (s, 1H), 1.68 (s, 3H), 1.60 (s, 3H), 1.44 (s, 18H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 153.4, 141.1, 135.7, 128.1, 127.9, 126.6, 126.5, 125.2, 93.0, 56.3, 34.5, 30.4, 25.0, 23.9; FT-IR (thin film, neat): 3631, 2960, 1262, 753 cm$^{-1}$; HRMS (ESI): *m/z* calcd for $C_{22}H_{31}NO_3S$ $[M-H]^-$ : 388.1946; found : 388.1929.

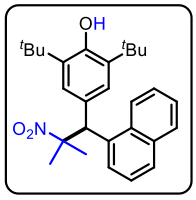
**2,6-Di-*tert*-butyl-4-(2-methyl-2-nitro-1-(pyren-1-yl)propyl)phenol** (**25v**): The reaction was




performed at 40 mg scale (0.096 mmol) of **23v**; $R_f$ = 0.4 (5% EtOAc in hexane); orange solid (35.3 mg, 73% yield); m.p. = 218–220 $^{o}$C; $^{1}$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.60 (d, $J$ = 9.5 Hz, 1H), 8.22 - 8.16 (m, 5H), 8.08 - 7.99 (m, 3H), 7.20 (s, 2H), 6.12 (s, 1H), 5.11 (s, 1H), 1.93 (s, 3H), 1.69 (s, 3H), 1.37 (s, 18H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 152.9, 135.7, 133.8, 131.5, 130.7, 130.4, 130.1, 129.9, 128.3, 127.7, 127.5, 126.3, 126.2, 126.1, 125.6, 125.5, 125.2, 125.0,

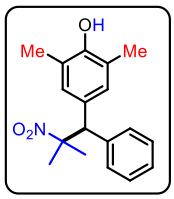
124.6, 123.0, 93.3, 53.3, 34.5, 30.4, 27.2, 25.1; FT-IR (thin film, neat): 3433, 2963, 1266, 752 $cm^{-1}$; HRMS (ESI): *m/z* calcd for $C_{34}H_{37}NO_3$ $[M-H]^-$: 506.2695; found : 506.2679.

**2,6-Di-*tert*-butyl-4-(2-methyl-1-(naphthalen-1-yl)-2-nitropropyl) phenol (25w):** The



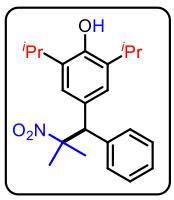

reaction was performed at 40 mg scale (0.116 mmol) of **23w**; $R_f$ = 0.4 (5% EtOAc in hexane); pale yellow solid (42.7 mg, 85% yield); m.p. = 148–150 $^oC$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 8.29 (d, *J* = 8.6 Hz, 1H), 7.84 (dd, *J* = 7.9, 0.7 Hz, 1H), 7.77 (d, *J* = 8.3 Hz, 1H), 7.72 (d, *J* = 7.3 Hz, 1H), 7.56 - 7.51 (m, 1H), 7.47 (t, *J* = 7.9 Hz, 2H), 7.13 (s, 2H), 5.77 (s, 1H), 5.10 (s, 1H), 1.83 (s, 3H), 1.68 (s, 3H), 1.37 (s, 18H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 153.0, 136.0, 135.6, 134.4, 132.7, 129.2, 129.1, 128.1, 126.6, 126.4, 125.7, 125.2, 125.0, 123.5, 93.1, 53.1, 34.5, 30.4, 26.3, 25.9; FT-IR (thin film, neat): 3631, 2959, 1238, 752 $cm^{-1}$; HRMS (ESI): *m/z* calcd for $C_{28}H_{35}NO_3$ $[M-H]^-$ : 432.2539; found : 432.2521.

**2,6-Dimethyl-4-(2-methyl-2-nitro-1-phenylpropyl) phenol (25x):** The reaction was



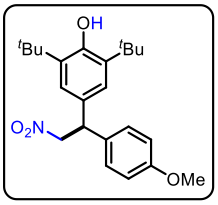

performed at 40 mg scale (0.190 mmol) of **23x**; $R_f$ = 0.1 (5% EtOAc in hexane); pale yellow solid (33.6 mg, 59% yield); m.p. = 93–95 $^oC$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.36 - 7.34 (m, 2H), 7.32 - 7.28 (m, 2H), 7.26 - 7.21 (m, 1H), 6.96 (s, 2H), 4.65 (s, 1H), 4.57 (s, 1H), 2.21 (s, 6H), 1.68 (s, 3H), 1.67 (s, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 151.7, 139.4, 130.4, 129.9, 129.5, 128.7, 127.4, 123.1, 92.5, 60.0, 25.4, 25.3, 16.2; FT-IR (thin film, neat): 3469, 2968, 1268, 754 $cm^{-1}$; HRMS (ESI): *m/z* calcd for $C_{18}H_{21}NO_3$ $[M-H]^-$ : 298.1443; found : 298.1456.

**2,6-Diisopropyl-4-(2-methyl-2-nitro-1-phenylpropyl) phenol (25y):** The reaction was

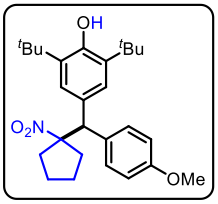



performed at 40 mg scale (0.150 mmol) of **23y**; $R_f$ = 0.2 (5% EtOAc in hexane); yellow gummy solid (31.4 mg, 59% yield); $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.38 - 7.36 (m, 2H), 7.32 - 7.29 (m, 2H), 7.25 - 7.22 (m, 1H), 7.03 (s, 2H), 4.77 (s, 1H), 4.70 (s, 1H), 3.11 (sept, *J* = 6.8 Hz, 2H), 1.67 (s, 3H), 1.65 (s, 3H), 1.24 (d, *J* = 6.8 Hz, 6H), 1.23 (d, *J* = 6.8 Hz, 6H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 149.4, 139.3, 133.6, 130.5, 129.6, 128.6, 127.4, 124.9, 92.7, 60.5, 27.3, 25.5, 25.1, 22.87, 22.85; FT-IR (KBr): 3434, 2974, 1269, 754 $cm^{-1}$; HRMS (ESI): *m/z* calcd for $C_{22}H_{29}NO_3$ $[M-H]^-$ : 354.2069; found : 354.2054.

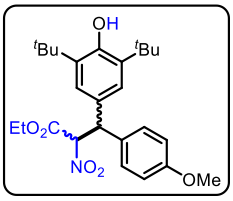
**2,6-Di-*tert*-butyl-4-(1-(4-methoxyphenyl)-2-nitroethyl) phenol (25z):** The reaction was performed at 40 mg scale (0.123 mmol) of **23a**; $R_f$ = 0.4 (5% EtOAc in hexane); yellow gummy solid (24.8 mg, 52% yield); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.18 (d, $J$ = 8.7 Hz, 2H), 7.0 (s, 2H), 6.86 (d, $J$ = 8.7 Hz, 2H), 5.15 (s, 1H), 4.95 – 4.85 (m, 2H), 4.76 (dd, $J$ = 9.3, 7.2 Hz, 1H), 3.78 (s, 3H), 1.40 (s, 18H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 158.9, 153.1, 136.3, 131.8, 130.1, 128.8, 124.3, 114.4, 80.2, 55.4, 48.6, 34.5, 30.3; FT-IR (thin film, neat): 3628, 2959, 1259, 754 cm$^{-1}$; HRMS (ESI): *m/z* calcd for $C_{23}H_{31}NO_4$ $[M-H]^-$ : 384.2175; found : 384.2158.



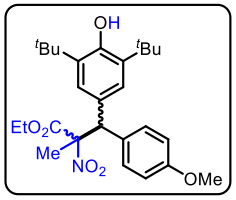

**2,6-Di-*tert*-butyl-4-((4-methoxyphenyl) (1-nitrocyclopentyl) methyl) phenol (25aa):** The reaction was performed at 40 mg scale (0.123 mmol) of **23a**; $R_f$ = 0.3 (5% EtOAc in hexane); pale yellow solid (37.1 mg, 69% yield); m.p. = 132–134 $^o$C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.26 (d, $J$ = 8.7 Hz, 2H), 7.10 (s, 2H), 6.82 (d, $J$ = 8.7 Hz, 2H), 5.11 (s, 1H), 4.83 (s, 1H), 3.77 (s, 3H), 2.74 - 2.70 (m, 2H), 2.11 - 2.04 (m, 2H), 1.64 - 1.58 (m, 2H), 1.53 - 1.50 (m, 2H), 1.40 (s, 18H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 158.6, 152.9, 135.6, 132.1, 130.8, 130.0, 126.2, 113.9, 105.0, 57.5, 55.3, 35.19, 35.18, 34.5, 30.4, 23.4, 23.3; FT-IR (thin film, neat): 3630, 2960, 1259, 753 cm$^{-1}$; HRMS (ESI): *m/z* calcd for $C_{25}H_{35}NO_4$ $[M-H]^-$ : 438.2644; found : 438.2664.




**Ethyl 3-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-3-(4-methoxyphenyl)-2-nitropropanoate (25ab)**: The reaction was performed at 0.123 mmol scale of **23a**; $R_f$ = 0.1 (5% EtOAc in hexane); pale yellow gummy solid (30.6 mg, 55% yield); The product was obtained as 1:1 diasteromeric mixture. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.26 (d, $J$ = 8.7 Hz, 2H), 7.21 (d, $J$ = 8.7 Hz, 2H), 7.07 (s, 2H), 7.03 (s, 2H), 6.85 (d, $J$ = 6.9 Hz, 2H), 6.83 (d, $J$ = 6.9 Hz, 2H), 5.86 (d, $J$ = 10.3 Hz, 1H), 5.83 (d, $J$ = 10.3 Hz, 1H), 5.15 (s, 1H), 5.13 (s, 1H), 4.89 (d, $J$ = 4.1 Hz, 1H), 4.86 (d, $J$ = 4.1 Hz, 1H), 4.08 - 4.02 (m, 2H), 4.01 – 3.94 (m, 2H), 1.39 (s, 18H), 1.38 (s, 18H), 1.04 (t, $J$ = 5.4 Hz, 3H), 0.94 (t, $J$ = 5.4 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 163.7, 163.6, 159.1, 159.0, 153.4, 153.3, 136.3, 136.27, 129.4, 129.1, 128.5, 128.2, 124.9, 124.0, 114.5, 114.3, 91.98, 91.95, 63.0, 62.8, 55.37, 55.35, 52.0, 51.9, 34.49, 34.47, 30.33, 30.32, 13.8, 13.6; FT-IR (thin film, neat): 3627, 2960, 1748, 1565, 753 cm$^{-1}$; HRMS (ESI): *m/z* calcd for $C_{25}H_{35}NO_4$ $[M+Na]^+$ : 480.2362; found : 480.2341.



**Ethyl 3-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-3-(4-methoxyphenyl)-2-methyl-2-nitropropanoate** (**25ac**): The reaction was performed at 0.123 mmol scale of **23a**; $R_f$ = 0.1 (5% EtOAc in hexane); pale yellow gummy solid (30.2 mg, 52% yield); The product was obtained as 1.3:1 diasteromeric mixture. *Major diastereoisomer*: $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.32 (d, $J$ = 2.1 Hz, 2H), 7.13 (s, 2H), 6.83 (d, $J$ = 1.6 Hz, 2H), 5.25 (s, 1H), 5.14 (s, 1H), 4.03 – 3.98 (m, 2H), 3.76 (s, 3H), 1.93 (s, 3H), 1.40 (s, 18H), 0.99 (t, $J$ = 7.1 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 166.6, 158.7, 153.07, 135.72, 131.1, 130.79, 126.4, 113.76, 97.6, 62.75, 55.32, 55.31, 34.5, 30.4, 20.8, 13.6; *Minor diastereoisomer*: $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.30 (d, $J$ = 2.1 Hz, 2H), 7.14 (s, 2H), 6.80 (d, $J$ = 1.7 Hz, 2H), 5.20 (s, 1H), 5.13 (s, 1H), 4.05 (q, $J$ = 7.1 Hz, 2H), 3.77 (s, 3H), 1.94 (s, 3H), 1.39 (s, 18H), 1.07 (t, $J$ = 7.2 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 166.7, 158.8, 153.09, 135.68, 131.0, 130.76, 126.7, 113.8, 97.5, 62.8, 55.36, 55.29, 34.5, 30.4, 21.0, 13.7; FT-IR (thin film, neat): 3620, 2965, 1740, 1561, 758 cm$^{-1}$; HRMS (ESI): *m/z* calcd for $C_{27}H_{37}NO_6$ $[M+Na]^+$ : 472.2699; found : 494.2519.




**Procedure for the gram-scale reaction of 23a with 24a under continuous-flow conditions:**

*p*-Quinone methide **23a** (1.0 g, 3.1 mmol) and 2-nitropropane **24a** (0.56 mL, 6.2 mmol) were dissolved in 9 mL of DMSO:toluene (98:2) mixture and taken in a syringe. DBU (91 µL, 0.62 mmol) was dissolved in 9 mL of DMSO:toluene (90:10) mixture and taken in another syringe. These two solutions were injected simultaneously through the microchannels at the flow rates of 5 µL/min each (residence time = 10 min). The temperature of microchannels was maintained at 80 °C throughout the reaction. The reaction mixture collected at the outlet and was quenched with water. It was extracted with diethyl ether (50 mL x 3). The organic layer was concentrated under reduced pressure and the crude was then loaded on a silica gel column and purified using hexane/EtOAc mixture as an eluent to provide the pure 1,6-adduct **25a**. Yield 1.02 g (80%).

**Procedure for the gram-scale reaction of 23a with 24a under conventional batch process:**

In a 100 mL round-bottomed flask, *p*-quinone methide 23**a** (1.0 g, 3.1 mmol), 2-nitropropane **2a** (0.56 mL, 6.2 mmol) and DBU (90 µL, 0.61 mmol) were dissolved in 20 mL of DMSO:toluene (90:10) mixture and the resulting mixture was stirred at 80 °C for 72 h.

The mixture was cooled to room temperature and diluted with water. It was extracted with diethyl ether (50 mL x 3). The organic layer was concentrated under reduced pressure and the crude was then loaded on a silica gel column and purified using hexane/EtOAc mixture as an eluent to provide the pure 1,6-adduct **25a**. Yield 0.69 g (54%).

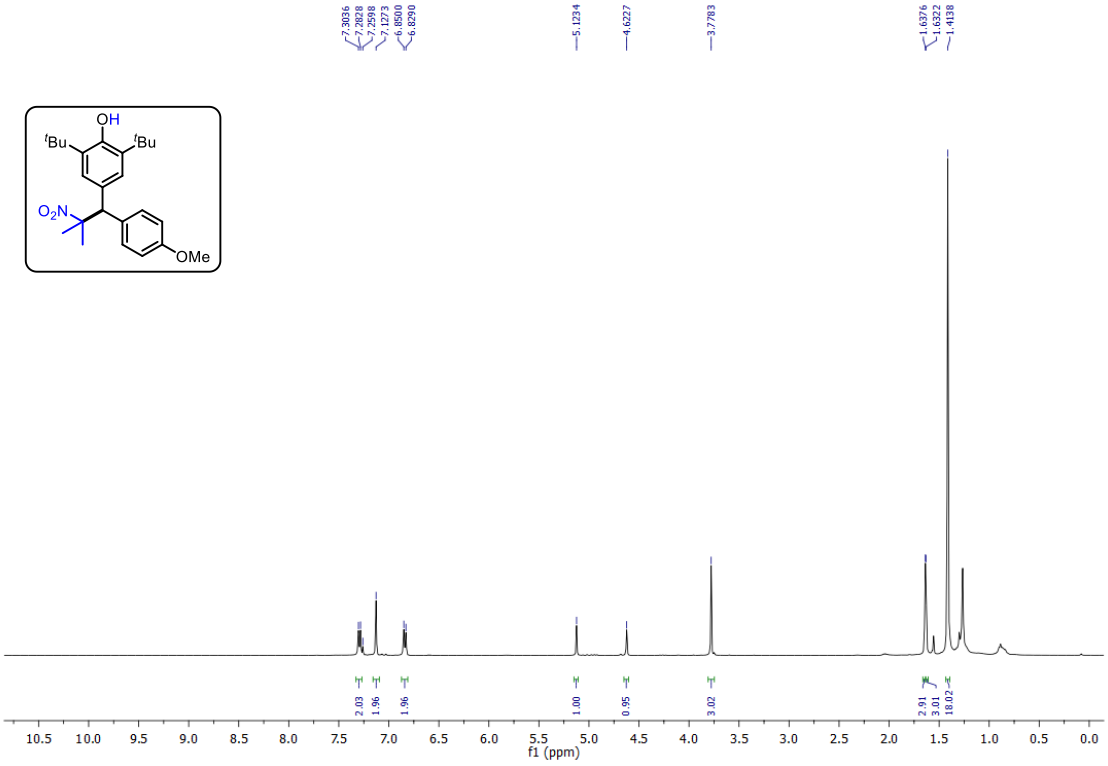
**Procedure for the retro-1,6-conjugate addition reaction of 25a with DBU under batch process**:

In a 10 mL round-bottomed flask, a mixture of 1,6-adduct **25a** (40 mg, 0.096 mmol) and DBU (3 μL [stock solution], 0.019 mmol) was dissolved in 2 mL of DMSO:toluene (98:2) mixture and the resulting mixture was stirred at 80 $^{o}$C for 12 h. The mixture was cooled to room temperature and diluted with water. It was extracted with diethyl ether (10 mL x 3). The organic layer was concentrated under reduced pressure and the crude was then loaded on a silica gel column and purified using hexane/EtOAc mixture as an eluent to provide the pure 1,6-adduct **1a**. Yield 20.4 mg (65%).

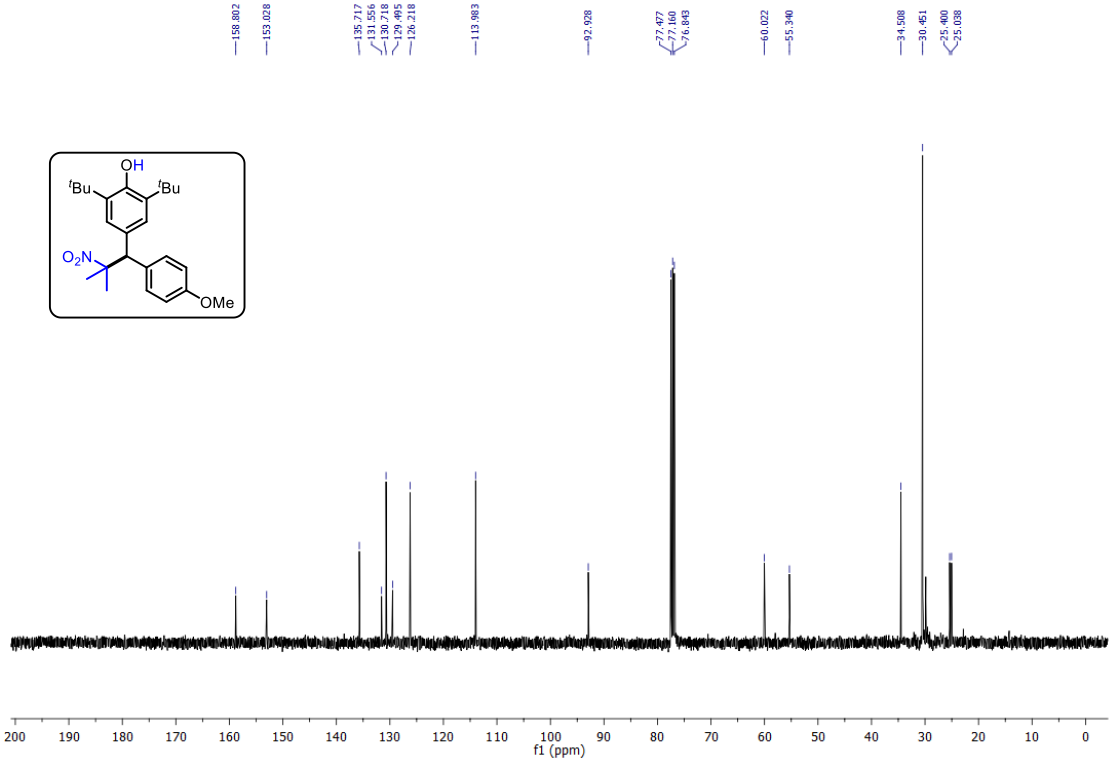
**Attempted enantioselective synthesis of 3d using chiral base**

*p*-Quinone methide **1d** (40 mg, 0.113 mmol) and 2-nitropropane (21μL, 0.23 mmol) were dissolved in 1 mL of DMSO:toluene (98:2) mixture and taken in a syringe. Chiral base **I** or **II** (8 mg, 0.023 mmol) was dissolved in 1 mL of DMSO:toluene (98:2) mixture and taken in another syringe. These two solutions were injected simultaneously through the microchannels at the flow rates of 5 μL/min each (residence time = 10 min). The temperature of microchannels was maintained either at room temperature or at 80 °C throughout the reaction. The reaction mixture collected at the outlet and was quenched with water. It was extracted with diethylether (10 mL x 2). The organic layer was concentrated under reduced pressure and the crude was then loaded on a silica gel column and purified using hexane/EtOAc mixture as an eluent to provide the pure 1,6-adduct **3d**. HPLC analysis was performed using Diacel Chiralpak OD-H column (*n*-Hexane, 0.8 ml/min, 254nm).

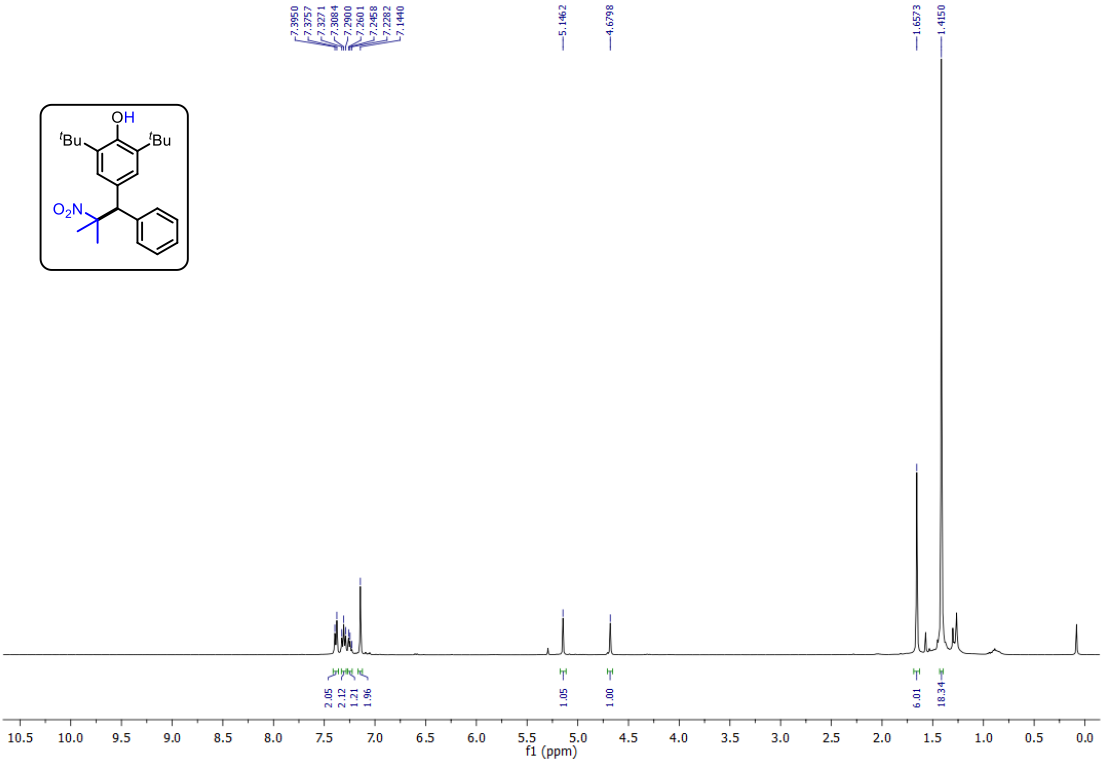
$^{1}$H NMR spectrum of **25a**



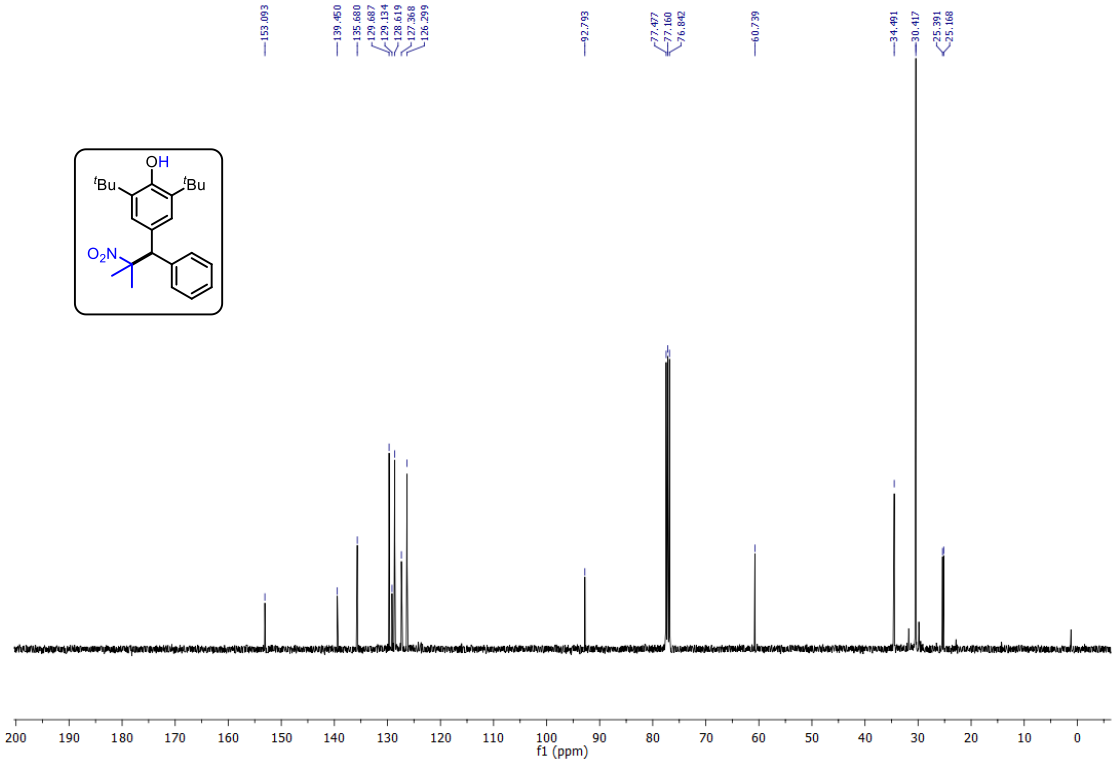

$^{13}$C NMR spectrum of **25a**



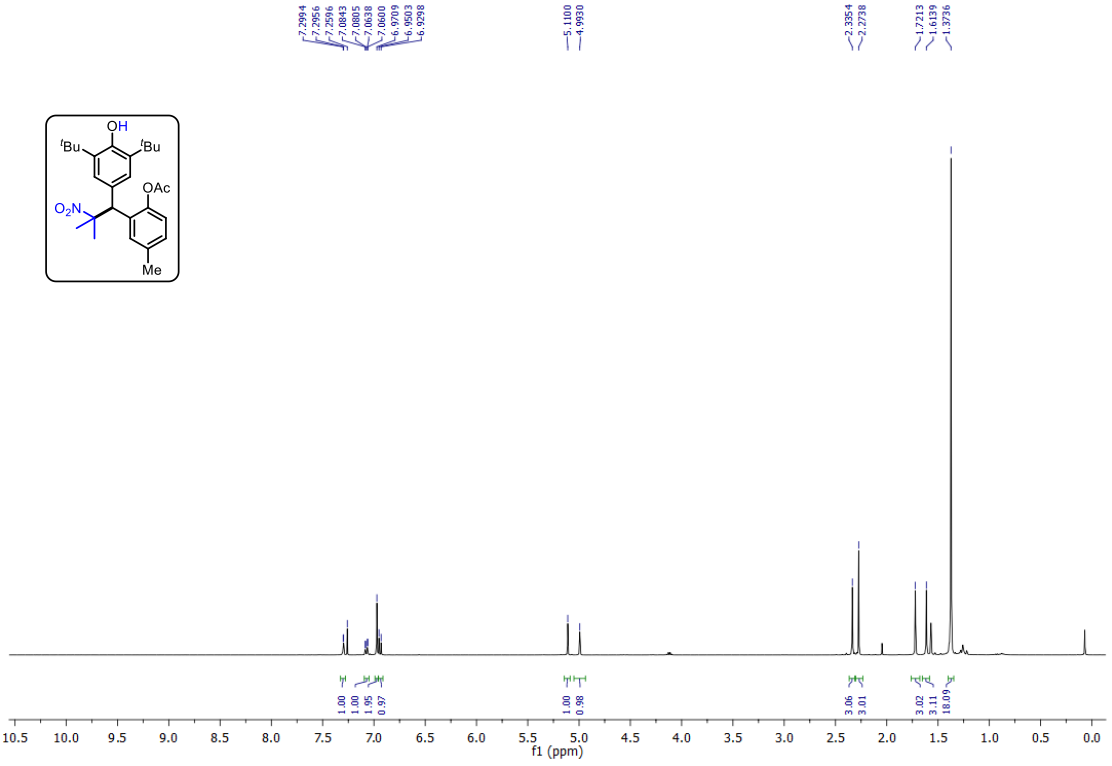
$^{1}$H NMR spectrum of 25b



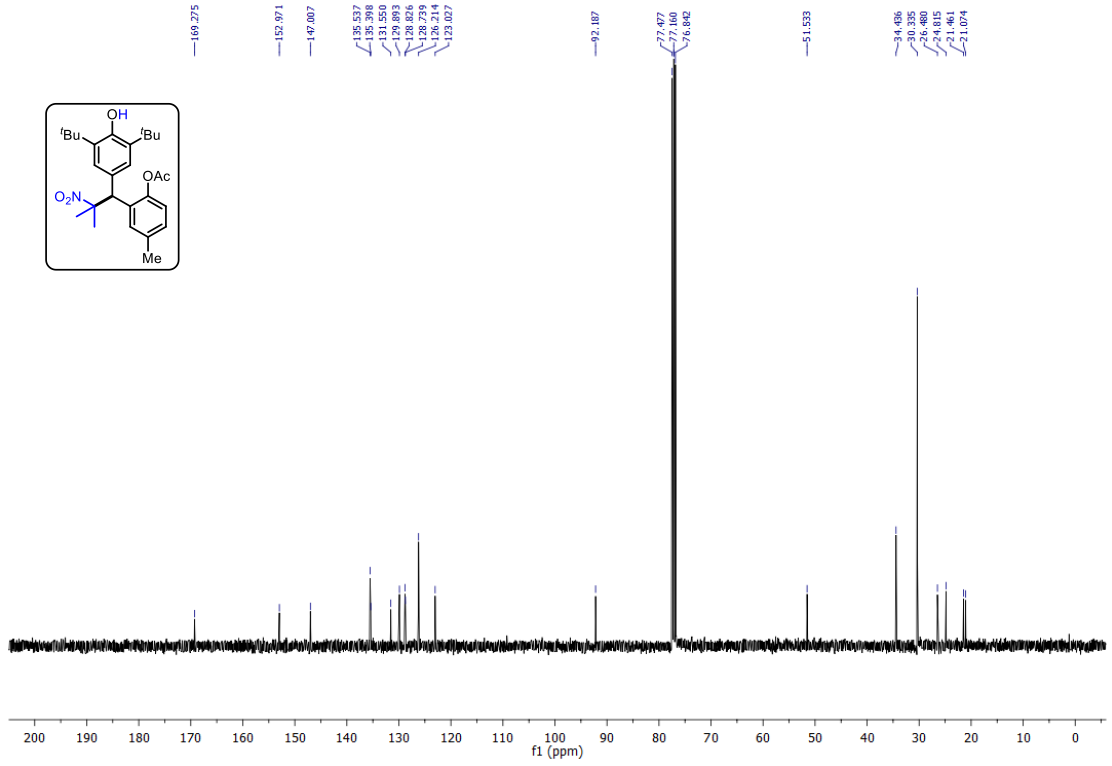

$^{13}$C NMR spectrum of **25b**



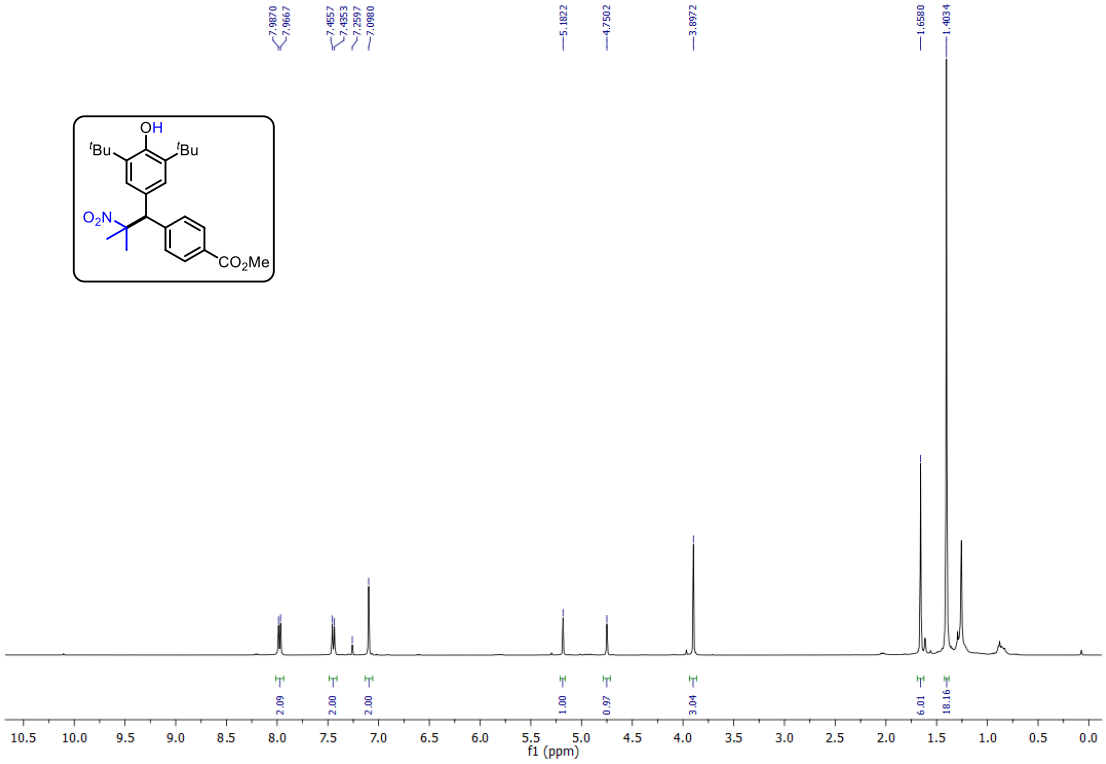
$^{1}$H NMR spectrum of **25k**



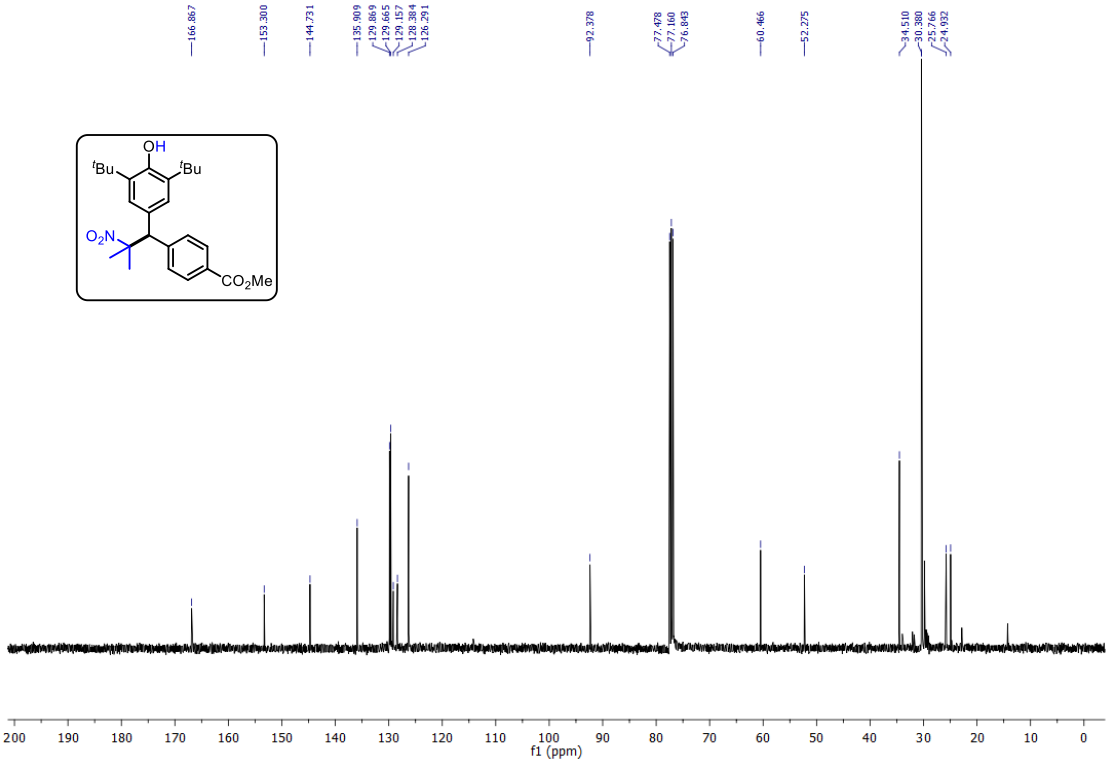

$^{13}$C NMR spectrum of **25k**



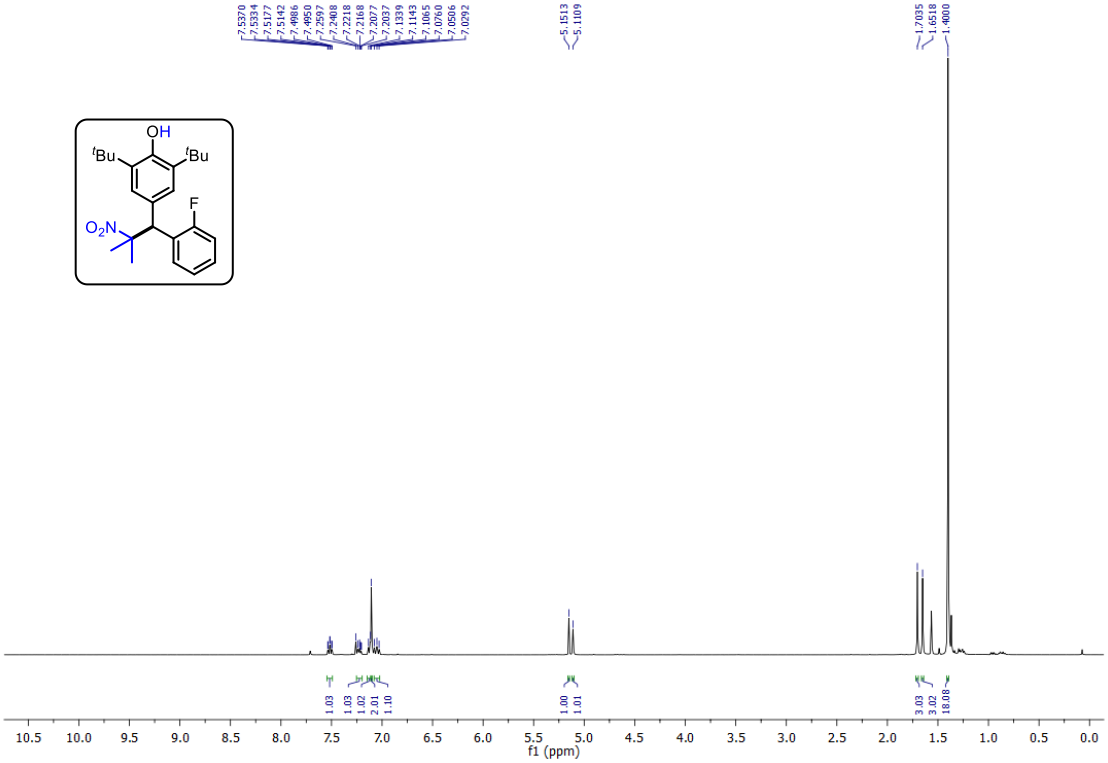
$^{1}$H NMR spectrum of **25l**



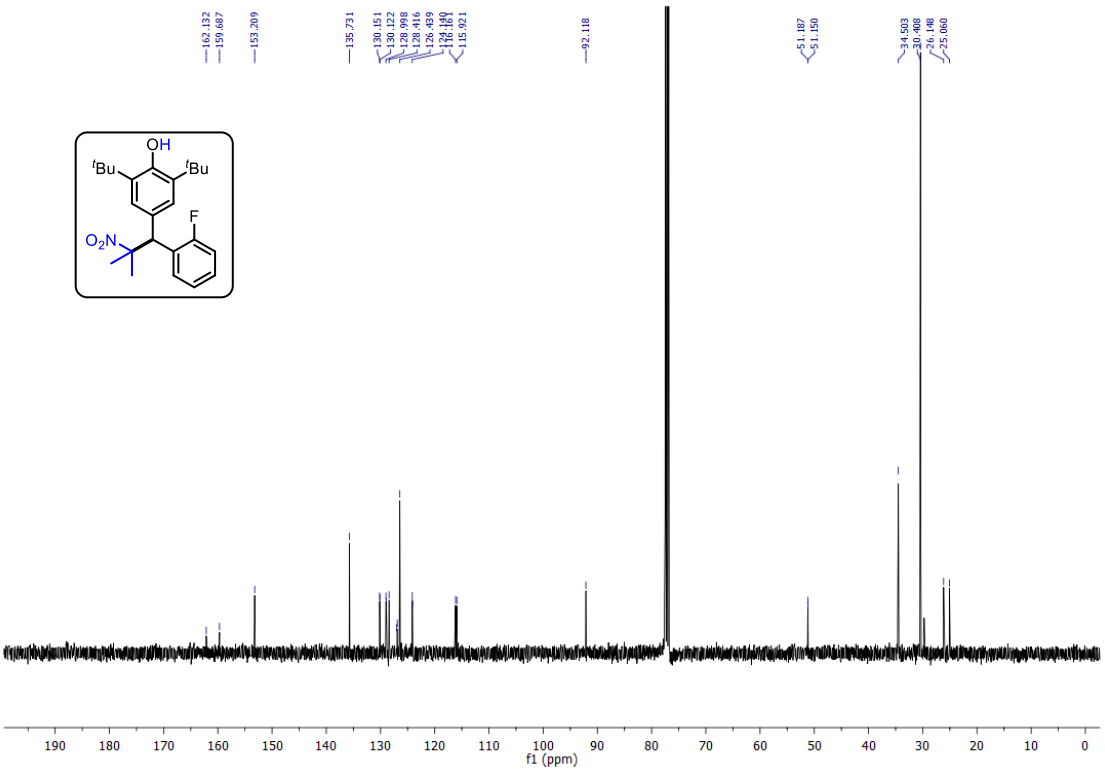

$^{13}$C NMR spectrum of **25l**



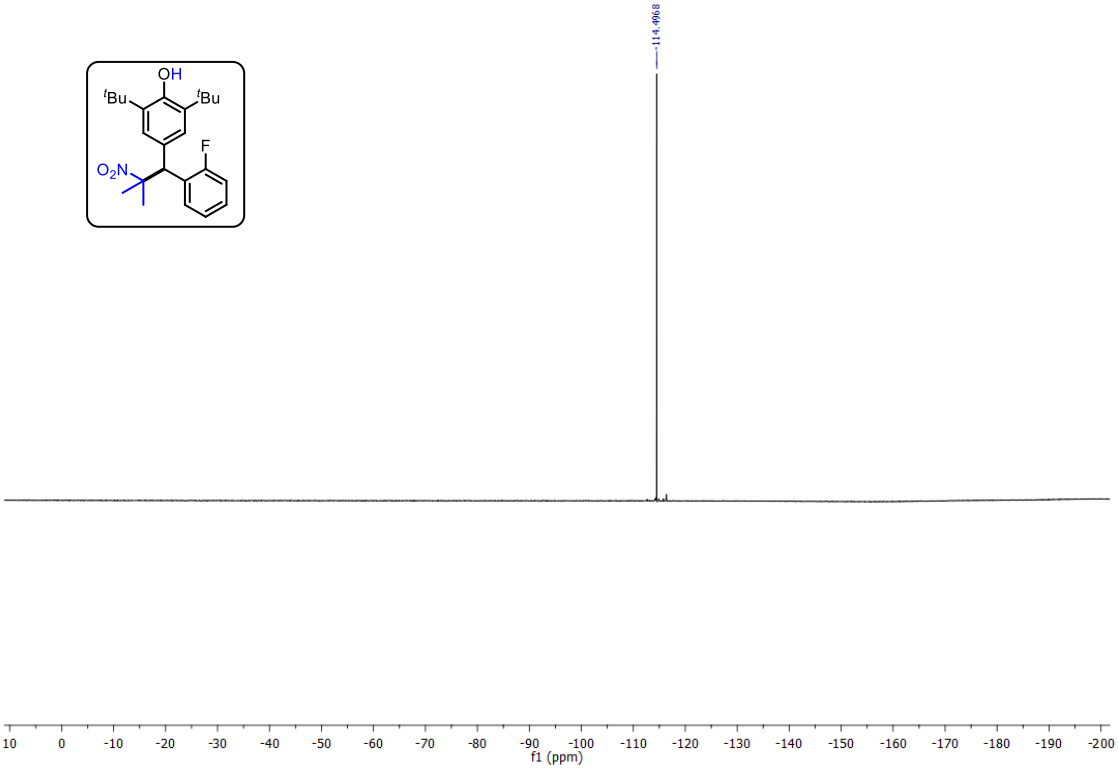
$^{1}$H NMR spectrum of **25o**



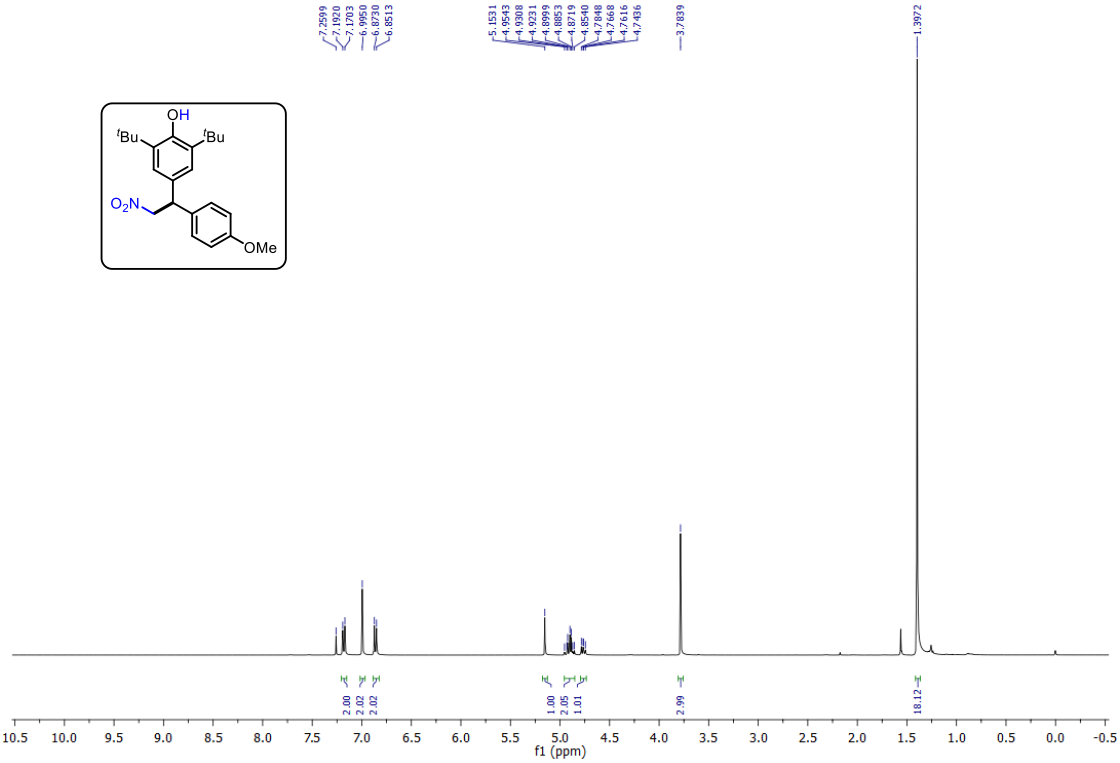

$^{13}$C NMR spectrum of **25o**



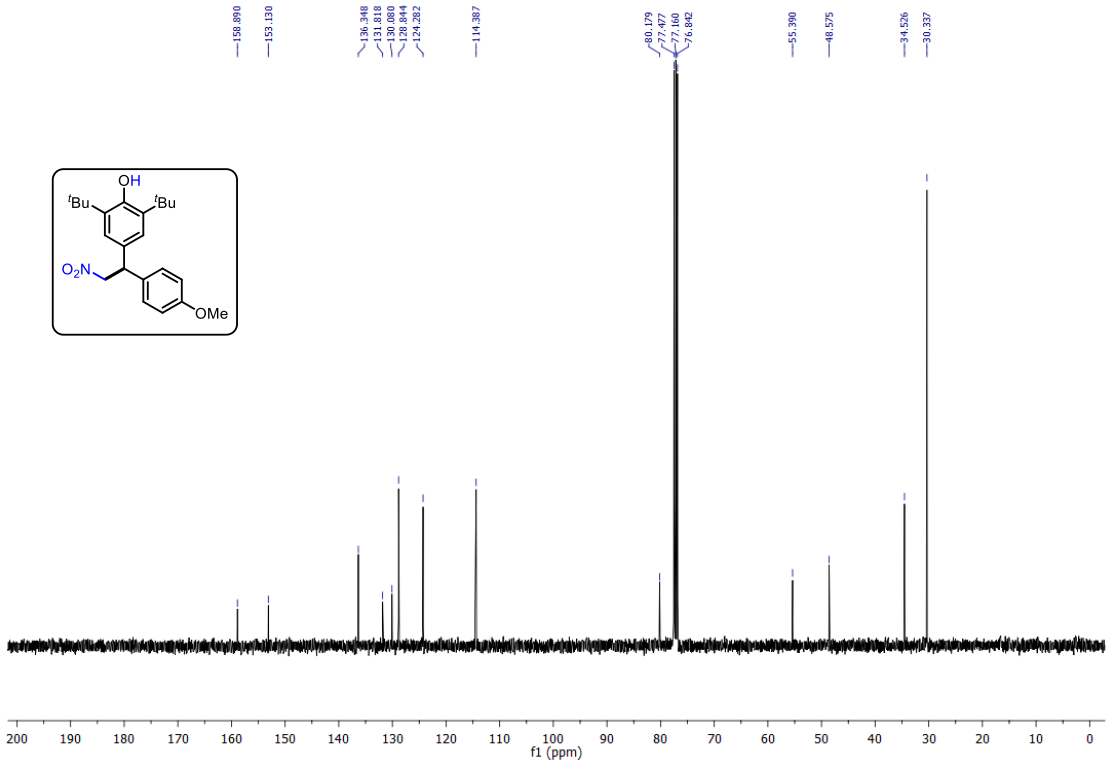
$^{19}$F NMR spectrum of **25o**



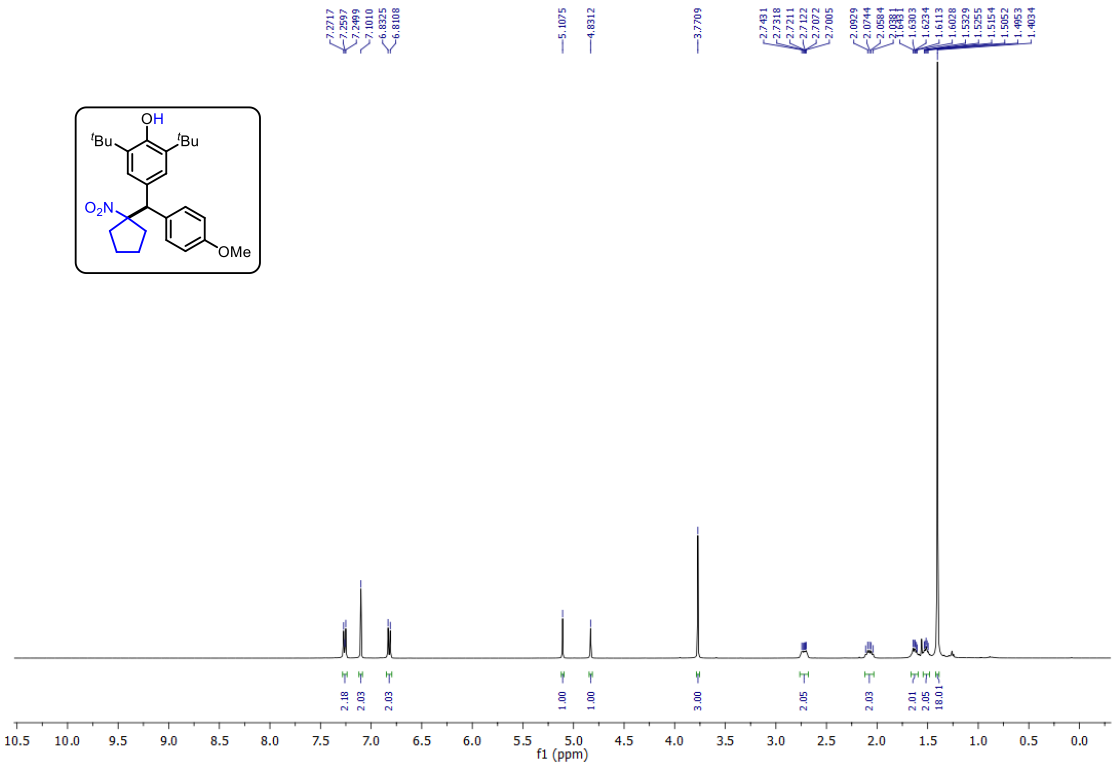

$^{1}$H NMR spectrum of **25z**



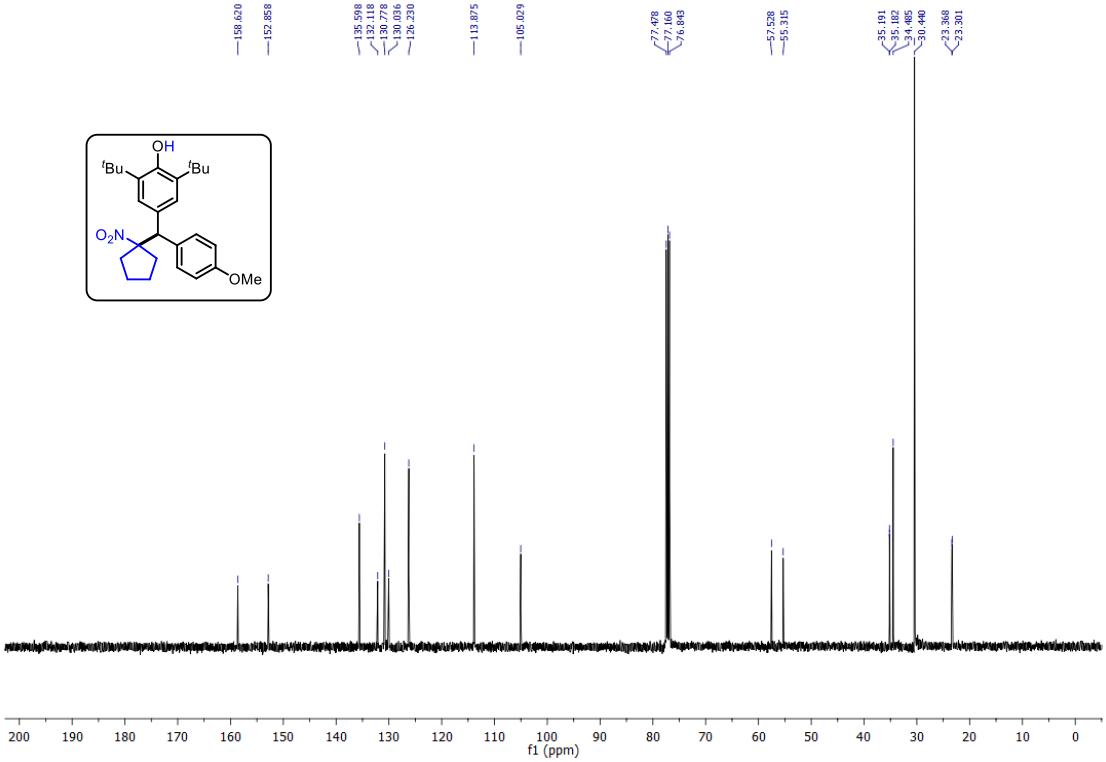
$^{13}$C NMR spectrum of **25z**



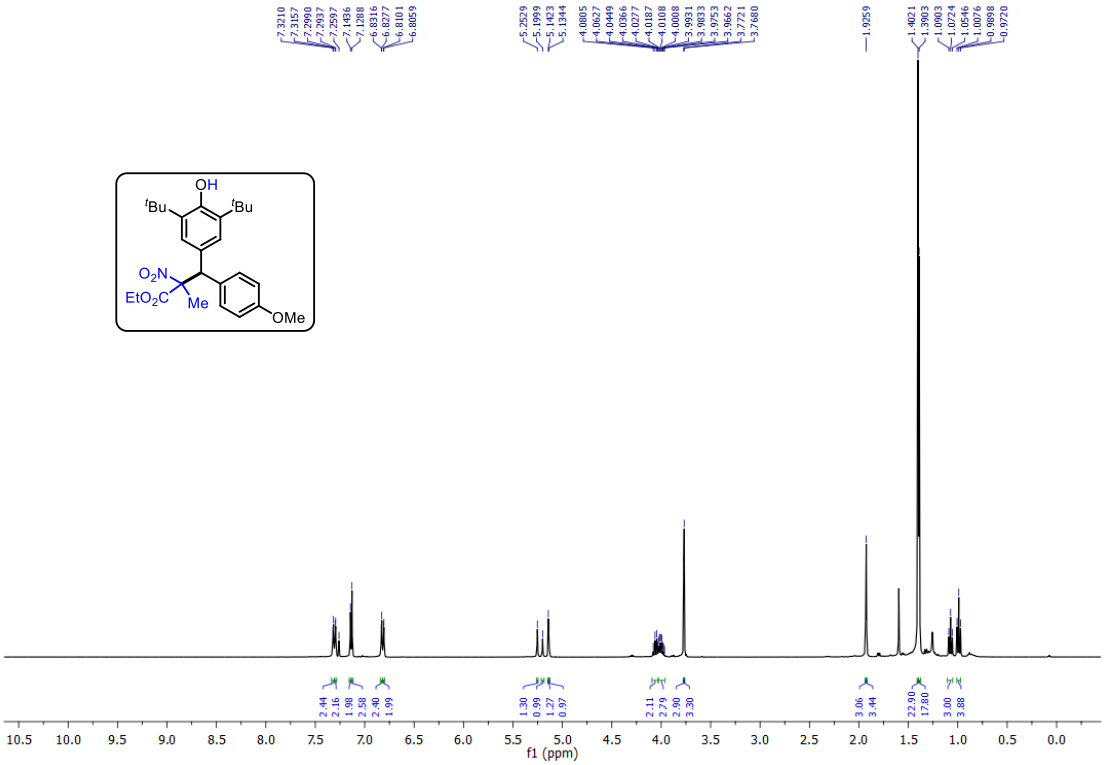

$^{1}$H NMR spectrum of **25aa**



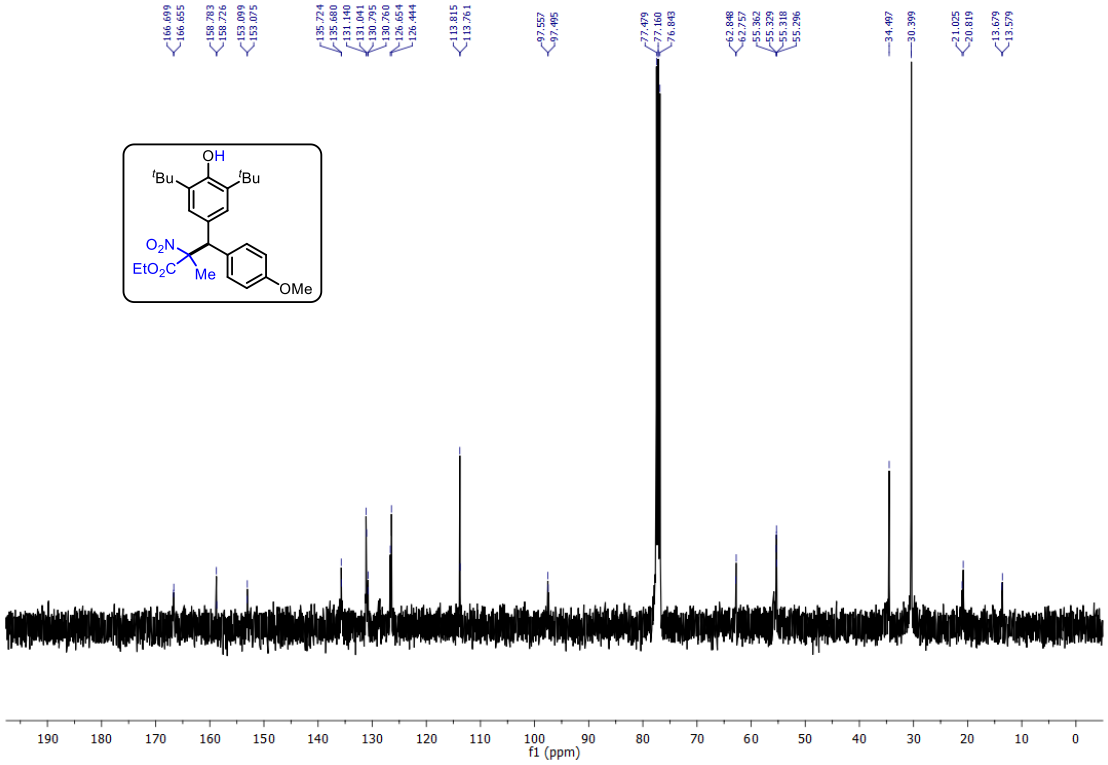
$^{13}$C NMR spectrum of **25aa**




$^{1}$H NMR spectrum of **25ac**



$^{13}$C NMR spectrum of **25ac**



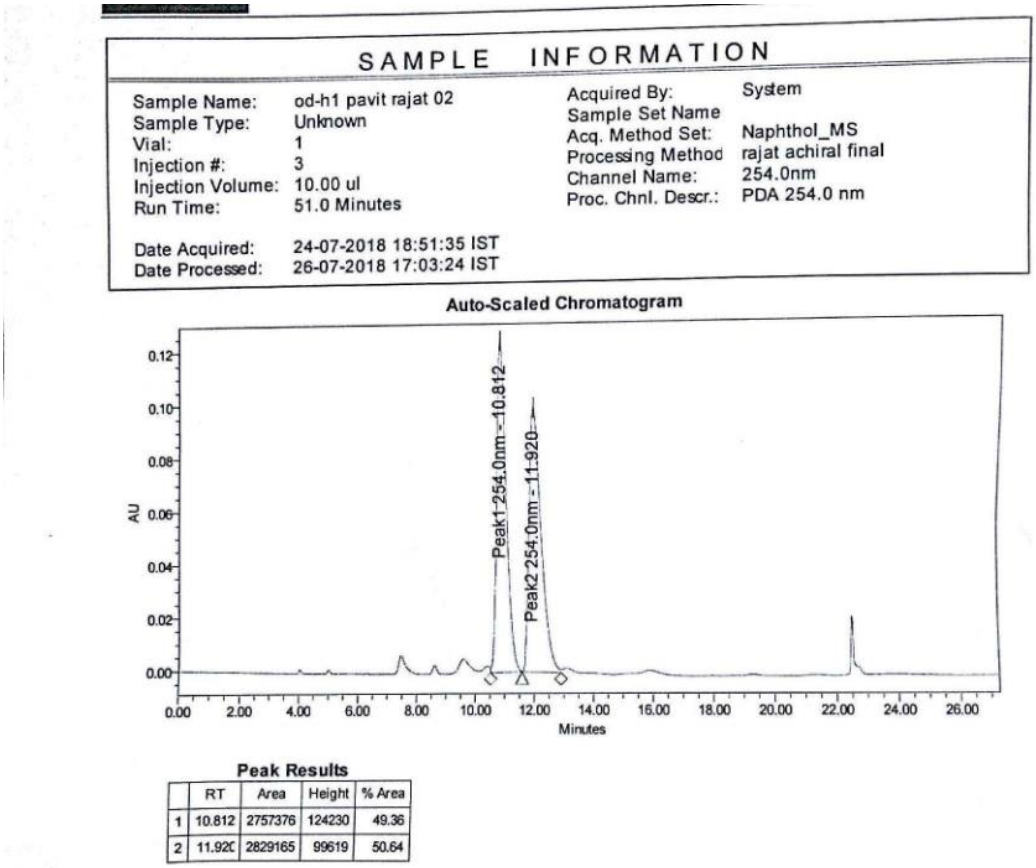



**Figure 2** HPLC data for compound **25d** (racemic).

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HPLC analysis was performed using Diacel Chiralpak OD-H column (*n*-Hexane, 0.8 mL/min, 254 nm).

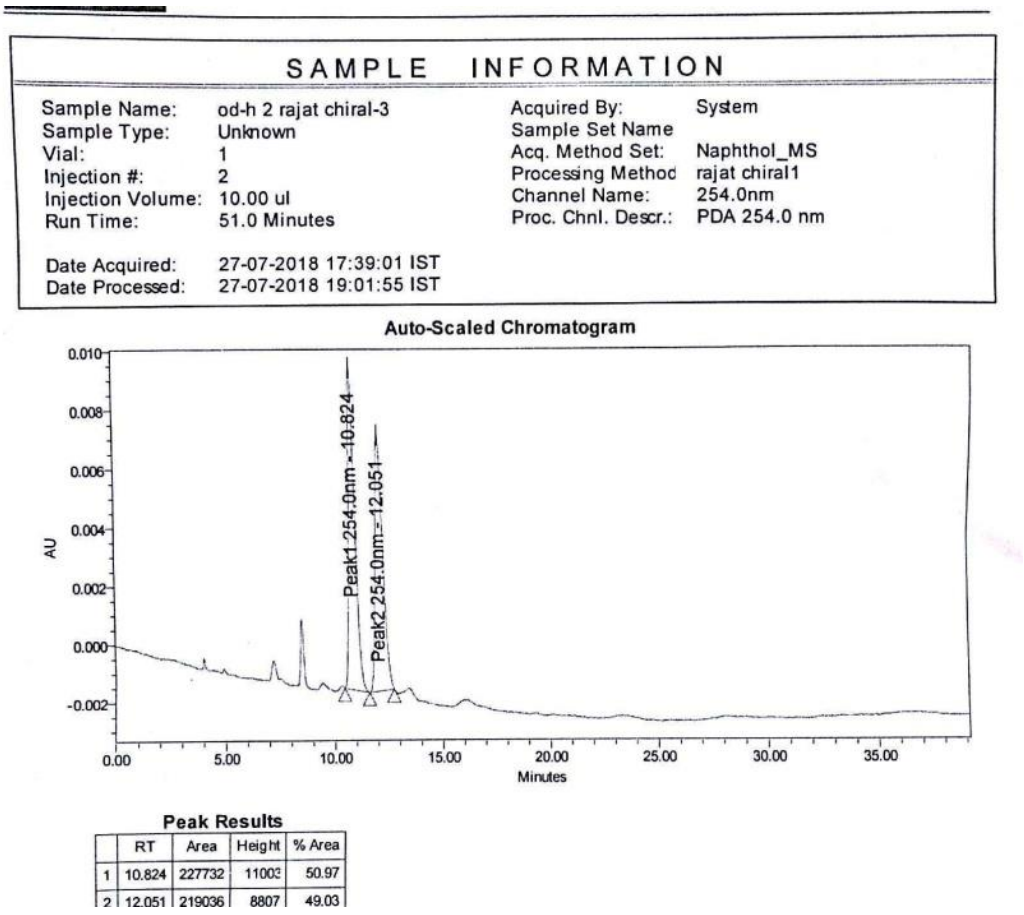


**Figure 3.** HPLC data for compound **25d** (through enantioselective reaction)

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HPLC analysis was performed using Diacel Chiralpak OD-H column (*n*-Hexane, 0.8 mL/min, 254 nm)

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19. (a) Jadhav, A. S.; Anand, R. V. *Org. Biomol. Chem*. **2017**, *15*, 56. (b) Jadhav, A. S.; Anand, R. V. *Eur. J. Org. Chem*. **2017**, *2017*, 3716.

# Curriculum Vitae

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## Education & Research Experience

- 2017 to present - 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 Approaches Toward N-Heterocycles and Diarylmethanes under Batch as well as Continuous-flow Conditions*"
    - Ph.D. Thesis Supervisor: Prof. R. Vijaya Anand
- Master of Science from Visvesvaraya National Institute Of Technology VNIT, Nagpur, India in the year 2017 with 9.2 CGPA (Institute Topper)
    - Thesis Title "*Baker's Yeast Catalyzed One-pot four Component Synthesis of Pyranopyrazole*"
- Bachelors in Chemistry (Honors) from Kirorimal College affiliated to Delhi University with 78.8 percent in the year 2015.
- Senior Secondary from CBSE Board in the year 2012 with 91.60 percent
- Higher Secondary School from CBSE Board in the year 2010 with 91.25 percent

## Awards & Achievements

- Awarded INSPIRE Fellowship from the Department of Science and Technology (DST), Government of India, from 2017 to 2022.
- Gold medallist VNIT, Nagpur (2017).
- Qualified Graduate Aptitude Test in Engineering (GATE) in the year 2017 with all India rank 1476.
- Aspirant of CSSS Scholarship from CBSE (2012-2017).

- SRFP Fellow in Jawaharlal Nehru Centre For Advanced Scientific Research (JNCASR) under Prof. Subi Jacob George (2016).
- Qualified IIT-JAM in the year 2015 with AIR-338.
- Successfully completed course Principles of Bio-Chemistry through edX, course being affiliated to Harvard University.

## Conferences

- Volunteered and presented a poster entitiled “A Base-mediated Sequential One-pot Approach to 2,3-Disubstituted Indoles from 2-(Tosylamino)arylsubstituted *para*-Quinone Methides” in "*29th CRSI-National Symposium in Chemistry*" held at IISER Mohali-2022.
- Delivered a talk entitled "A Base-mediated Sequential One-pot Approach to 2,3-Disubstituted Indoles from 2-(Tosylamino)arylsubstituted *para*-Quinone Methides" in *XVII Junior National Organic Symposium* (J-NOST) Conference held at University of Hyderabad-2022.
- Participated in the *1st Crikc Chemistry Symposium* (CCS 2019) held at the Department of Chemical Sciences, IISER Mohali-2019.
- Attended and volunteered in *Recent Advances in Organic and Bioorganic Chemistry* “RAOBC Conference” held at IISER Mohali-2019.
- Presented a poster entitled “Base Catalyzed 1,6-Conjugate Addition of Nitroalkanes to *p*-Quinone Methides under Continuous-flow” in *Frontiers in Chemical Sciences* (FICS) Conference held at IIT- Guwahati-2018.
- Attended and volunteered in *National Conference of Liquid Crystal* (NCLC) held at IISER Mohali-2017.
- Presented a poster entitled “Biocatlysed synthesis of Pyranopyrazole” in *Pre-ICOS Conference* held at IISER-Bhopal-2017.

## List of Publications

1. **Pandey, R**; Anand, R. V. "Base Catalyzed 1,6-Conjugate Addition of Nitroalkanes to *p*-Quinone Methides under Continuous-Flow" *ACS Omega* **2018**, *3*, 13967. [Link]

2. **Pandey, R.**; Singh, G.; Gour, V.; Anand, R. V. "Base-mediated Sequential One-pot Approach for the Synthesis of 2,3-Disubstituted Indoles from 2-(Tosylamino)aryl-substituted *para*-Quinone Methides" *Tetrahedron* **2021**, *82*, 131950. [Link]

3. Singh, G.; **Pandey, R.**; Kurup, A. S.; Anand, R. V. "A Base-Mediated Approach Towards Dihydrofuro[2,3 b]Benzofurans from 2-Nitrobenzofurans and 1,3-Dicarbonyls" *Chem. Asian J.* **2021**, *16*, 1271. [Link]

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

5. Pankhade, Y. A.; **Pandey, R.**; Fatma, S.; Ahmad, F.; Anand, R. V. "TfOH-catalyzed Intramolecular Annulation of 2-(Aryl)-phenyl-substituted *p*-Quinone Methides Under Continuous-flow: Total Syntheses of Selaginpulvilin I and Isoselagintamarlin A″ *J. Org. Chem*. **2022**, *87*, 3363. [Link]

6. Singh, G.; Sharma, S.; Rekha.; **Pandey, R.**; Singh, R.; Kumar, T.; Anand, R. V. "Reactions of Enaminones with *p*-Quinone Methides: Access to 4H-Chromene and 4H-Chromen-4-one Derivatives" *Eur. J. Org. Chem*. **2022**, 10.1002/ejoc.202200792. [Link]

7. **Pandey, R.**; Singh, G.; Hinge, S.; Anand, R. V. "Brønsted Acid-mediated Approaches Toward Tetrahydroacridinones and Dihydroquinolines from *ortho*-Amino-benzyl Alcohols" Manuscript Under Preparation.