Improved Synthetic Transformations to Access Indole and Naphthol Appended Conjugates

by

VALMIKI PRAVEEN KUMAR

10CC16A39007

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Under the supervision of
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Sector 19, Kamla Nehru Nagar,
Ghaziabad, U. P. – 201 002, India

2023

.....To my Parents and Brothers

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August 7, 2023

CERTIFICATE

This is to certify that the work incorporated in this Ph.D. thesis entitled, *"Improved Synthetic Transformations to Access Indole and Naphthol Appended Conjugates"*, submitted by ***Mr. Valmiki Praveen Kumar*** to the Academy of Scientific and Innovative Research (AcSIR) in fulfilment of the requirements for the award of the Degree of ***Doctor of Philosophy in Science***, embodies original research work carried out by the student. We further certify that this work has not been submitted to any other University or Institution in part or full for the award of any degree or diploma. Research materials obtained from other sources and used in this research work have been duly acknowledged in the thesis. Images, illustrations, figures, tables, etc., used in the thesis from other sources have also been duly cited and acknowledged.

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Valmiki Praveen Kumar
7/8/23

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(Thesis Supervisor)

7/8/2023
Dr. Priya S.

(Thesis Co-Supervisor)

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Valmiki Praveen Kumar

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LIST OF ABBREVIATIONS

Å	:	Angstrom
Ar	:	Argon
Ar-	:	Aryl
Ac	:	Acetyl
AcOH	:	Acetic acid
atm	:	Atmosphere
BINAP	:	2,2′-Bis(diphenylphosphino)-1,1′-binaphthyl
Bn	:	Benzyl
t-Bu	:	Tertiary butyl
BoC	:	*tert*-Butyloxycarbonyl
BHT		Butylated hydroxytoluene
Calcd	:	Calculated
CCDC	:	Cambridge crystallographic data centre
CAN	:	Ceric ammonium nitrate
CNTs	:	Carbon nanotubes
DABCO	:	1,4-Diazabicyclo[2.2.2]octane
DBN	:	1,5-Diazabicyclo[4.3.0]non-5-ene
DBU	:	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCB	:	Dichlorobenzene
DCE	:	Dichloroethane
DCM	:	Dichloromethane
d	:	Doublet

dd	:	Doublet of doublets
DDQ	:	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DCDMH	:	1,3-dichloro-5,5-dimethyl hydantoin
DIPEA	:	*N*,*N*-Diisopropylethylamine
DMA	:	*N*,*N*-Dimethylacetamide
DMAP	:	*N*,*N*-Dimethylpyridine-4-amine
DMF	:	*N*,*N*-Dimethylformamide
DMS	:	Dimethyl sulfide
DMSO	:	Dimethyl sulfoxide
dr	:	Diastereomeric ratio
dt	:	Doublet of triplets
EBHP	:	Ethyl
ee	:	Enantiomeric excess
Equiv.	:	Equivalent
er	:	Enantiomeric ratio
ESI	:	Electron spray ionization
Et	:	Ethylbenzene hydroperoxide
Et_3N	:	Triethylamine
EtOAc	:	Ethyl acetate
EtOH	:	Ethanol
FT-IR	:	Fourier transform infrared spectroscopy
h	:	Hour

IPA	:	Isopropyl alcohol
HAT		Hydrogen atom transfer
HI	:	Hydroiodic acid
HRMS	:	High resolution mass spectrometry
Hz	:	Hertz
J	:	Coupling constant
m	:	Multiplet
m	:	Meta
MCR	:	Multicomponent reaction
Me	:	Methyl
Mes	:	2,4,6-trimethylphenyl
$MesAcr^{+}BF_4^{-}$		9-Mesityl-10-methylacridinium tetrafluoroborate
MeOH	:	Methanol
mg	:	Milligram
MHz	:	Mega hertz
min	:	Minutes
mL	:	Millilitre
mmol	:	Millimolar
mol%	:	Mole percent
mp	:	Melting point
MS	:	Molecular sieves
MW	:	Microwave

ND	:	Not detected
NHC	:	*N*-heterocyclic carbene
NIS	:	*N*-iodosuccinimide
NBS	:	*N*-bromosuccinimide
NMM	:	*N*-methyl morpholine
NMR	:	Nuclear magnetic resonance
NOESY		Nuclear Overhauser Effect Spectroscopy
o	:	Ortho
p	:	Para
PC	:	photocatalyst
PET	:	Photoinduced electron transfer
Ph	:	Phenyl
i-Pr	:	Isopropyl
PIDA	:	Phenyliodine(III)diacetate
PNBA	:	*p*-Nitrobenzoic acid
PTSA	:	*p*-Toluenesulfonic acid
q	:	Quartet
rt	:	Room temperature
s	:	Singlet
SET	:	Single electron transfer
t	:	Triplet
TBAI	:	Tetra-n-butylammonium iodide

TBHP	:	*tert*- Butyl hyrdoperoxide
TBA][Gly] IL	:	: Tetrabutylammonium glycinate [TBA][Gly] ionic liquid
TCCA	:	trichloro-1,3,5-triazinane-2,4,6-trione
tert	:	Tertiary
TEMPO	:	2,2,6,6-Tetramethylpiperidine 1-oxyl, 2,2,6,6-Tetramethyl-1-piperidinyloxy, free radical
TfOH	:	Trifluoromethanesulfonic acid
TFA	:	Trifluoroacetic acid
THF	:	Tetrahydrofuran
TLC	:	Thin layer chromatography
TMG	:	Tetramethylguanidine
TMEDA	:	*N*,*N*,*N*′,*N*′-Tetramethylethylenediamine
TMS	:	Tetramethylsilane
T(*p*-F)PPT	:	2,4,6-tris(4-fluorophenyl)pyrylium tetrafluoroborate
T(*p*-Br)PPT	:	2,4,6-tris(4-bromophenyl)pyrylium tetrafluoroborate
T(*p*-Me)PPT	:	2,4,6-tris(4-methylphenyl)pyrylium tetrafluoroborate
T(*p*-OMe)PPT	:	2,4,6-tris(4-methoxyphenyl)pyrylium tetrafluoroborate
Tol	:	Tolyl
Ts	:	Tosyl
δ	:	NMR chemical shift in parts per million

PREFACE

Conjugates are the compounds formed from the attachment of a moiety to another molecule entity, substituent, or functional group. Introducing various substituents onto these scaffolds can modulate their physicochemical and biological properties, making them valuable tools in drug discovery and materials science. The beauty of heterocyclic appended organic molecules lies in their ability to bestow new characteristics upon the parent compound, rendering it more versatile and adaptable. By skillfully incorporating various appendages, researchers can fine-tune properties like solubility, reactivity, stability, and biological activity, among others. Such modifications enable researchers to craft molecules with tailored functionalities that are indispensable in various scientific fields.

Among the various heterocycles, aryl/cycloalkyl appended indole and naphthol frameworks are privileged substructures owing to their prevalence in natural products and pharmaceutically active compounds. These moieties make up the pharmacophores of numerous biologically active compounds, including analgesic, anti-inflammatory, anti-cancer, antituberculosis, antioxidant, anticonvulsant, anti-bacterial & anti-fungal substances. Direct functionalization of indoles and naphthol provides a powerful tool for the synthesis of functionalized indoles and naphthols.

Introduction of an aryl, cycloalkyl moiety or heteroatom to indole and naphthol derivatives is typically achieved by transition-metal catalyzed C-H functionalization *viz.* cross-coupling reactions, Friedel-Craft alkylation, multicomponent coupling reaction. These protocols require harsh reaction conditions, expensive catalysts, additives and tedious purification procedures. To overcome these pitfalls, improved organic synthetic methods can provide a better alternative, these protocols can be faster, more efficient, more economical, reduce waste, and minimize the use of hazardous materials. They can enable the synthesis of more complex and diverse molecules, as well as make existing synthetic pathways more efficient and precise. This thesis will focus on the development of improved organic synthetic methods. The goal is to develop simplified synthetic methods that are efficient and compatible with a range of substrates, using either single-step or multi-step processes.

In this regard, it is interesting for us to explore the synthesis and applications of indole and naphthol appended conjugates. such attractive indole and naphthol appended conjugates using easily accessible substrates under mild sustainable reaction conditions. Therefore, we discussed the diverse synthetic strategies which could utilize easily accessible substrates, and environmentally friendly and mild reaction conditions for the stereoselective synthesis of indole and naphthol appended conjugates. The results of these studies are embodied in the

thesis entitled ***"Improved Synthetic Transformations to Access Indole and Naphthol Appended Conjugates"***

The thesis is divided into four chapters. **Chapter 1** briefly explains the classical methods for synthesizing indole and naphthol appended conjugates, followed by the modern approaches that have emerged in recent years such as visible light-induced and electrochemical approaches are also envisaged. Further, the functionalization strategies and various applications of indole and naphthol conjugates in diverse fields are also covered.

In **Chapter 2** we synthesized a range of functionalized indole appended dihydronaphthalenone hybrid analogues *via* $Sc(OTf)_3$ catalysed Michael addition of indoles to the arylidene and hetero arylidene tetralones at room temperature. And the synthesized compounds were screened for antibacterial and antitubercular activities. We successfully identified a novel structural class, which inhibits the set of organisms with very low minimum inhibition concentrations. Among the novel compounds, **38o** and **38p** are the most active with a minimum inhibition concentration of 3.12 μg/ml. against *E. coli* and *S. aureus.* And **38o** and **38p** also found more potent analogues in inhibiting the *M. tuberculosis* with a minimum inhibition concentration of 6.25 μg/ml. Our studies complement new and exciting findings, which strongly suggest that the indolyl naphthalenones have real potential in finding suitable "Leads" for developing antitubercular therapeutics.

A literature survey has revealed that ethylbenzene hydroperoxide (EBHP) is less explored as an oxidizing agent for the epoxidation reactions**.** Nonhazardous and easily accessible EBHP is utilized as an oxidizing agent for the epoxidation of oxindole chalcones in **Chapter 3.** The reaction condition applicable to electron-deficient, electron-rich arylideneindolin-2-ones, heteroarylideneindolin-2-ones and alkylideneindolin-2-ones to yield the diastereoselective aryl/heteroaryl and alkyl spiro oxiranes. This procedure enables access to diastereoselective *trans*-spiro-epoxy oxindoles in a very short reaction time.

Chapter 4. describes the synthesis of 2-vinyl phenols through visible light-promoted hydroarylation of phenyl acetylenes with naphthols and phenols. This approach provides an efficient and convergent route for accessing a wide range of ortho-allyl phenols with high functional group tolerance. In addition, this strategy occurs under mild and metal-free conditions upon irradiation with simple household LEDs and averting the use of external ligands and additives. Hence formed products serve as the versatile building blocks for subsequent synthetic transformations.

Chapter 1

Indole and Naphthol Conjugates: Recent Advances in Biological Applications and Synthetic Strategies

1.1. Abstract

In the vast and intricate world of organic chemistry, the manipulation and modification of molecules play a pivotal role in shaping the foundation of scientific advancements. The molecular assemblies formed by combining two or more distinct organic moieties through covalent linkages give rise to a plethora of unique properties and functionalities. These compounds have emerged as a powerful tool in designing novel materials, pharmaceuticals, and functionalized structures with tailored properties and applications.

1.2. Introduction

Conjugates are the compounds formed from the attachment of a moiety to another molecule entity, substituent, or functional group. Introducing various substituents onto these scaffolds can modulate their physicochemical[1,2] and biological properties,[3,4] making them valuable tools in drug discovery and materials science.[5–7] The beauty of appended organic molecules lies in their ability to bestow new characteristics upon the parent compound, rendering it more versatile and adaptable.[8,9] By skillfully incorporating various appendages, researchers can fine-tune properties like solubility, reactivity, stability,[10,11]and biological activity,[2,12] among others. Such modifications enable researchers to craft molecules with tailored functionalities that are indispensable in various scientific fields.[13,14]

In this journey through the realm of appended organic molecules, we will explore the methodologies employed to achieve these modifications, the unique properties they confer upon the resulting compounds, and the groundbreaking applications they have found in fields such as drug development, materials science, and nanotechnology.

1.2.1. Importance of indole-appended conjugates

Indole is a bicyclic aromatic heterocyclic compound containing a benzene ring fused pyrrole ring. Indole conjugates are a fascinating class of organic compounds that have garnered significant attention from researchers in the fields of chemistry, biochemistry and pharmacology.[15–17] Indole is found in various natural products and pharmaceuticals and possesses a unique scaffold that lends itself to functionalization and subsequent conjugation with other molecules.[18–21] The synthesis of indole conjugates has emerged as a powerful strategy in organic chemistry, enabling the construction of diverse molecular architectures with a wide range of applications.

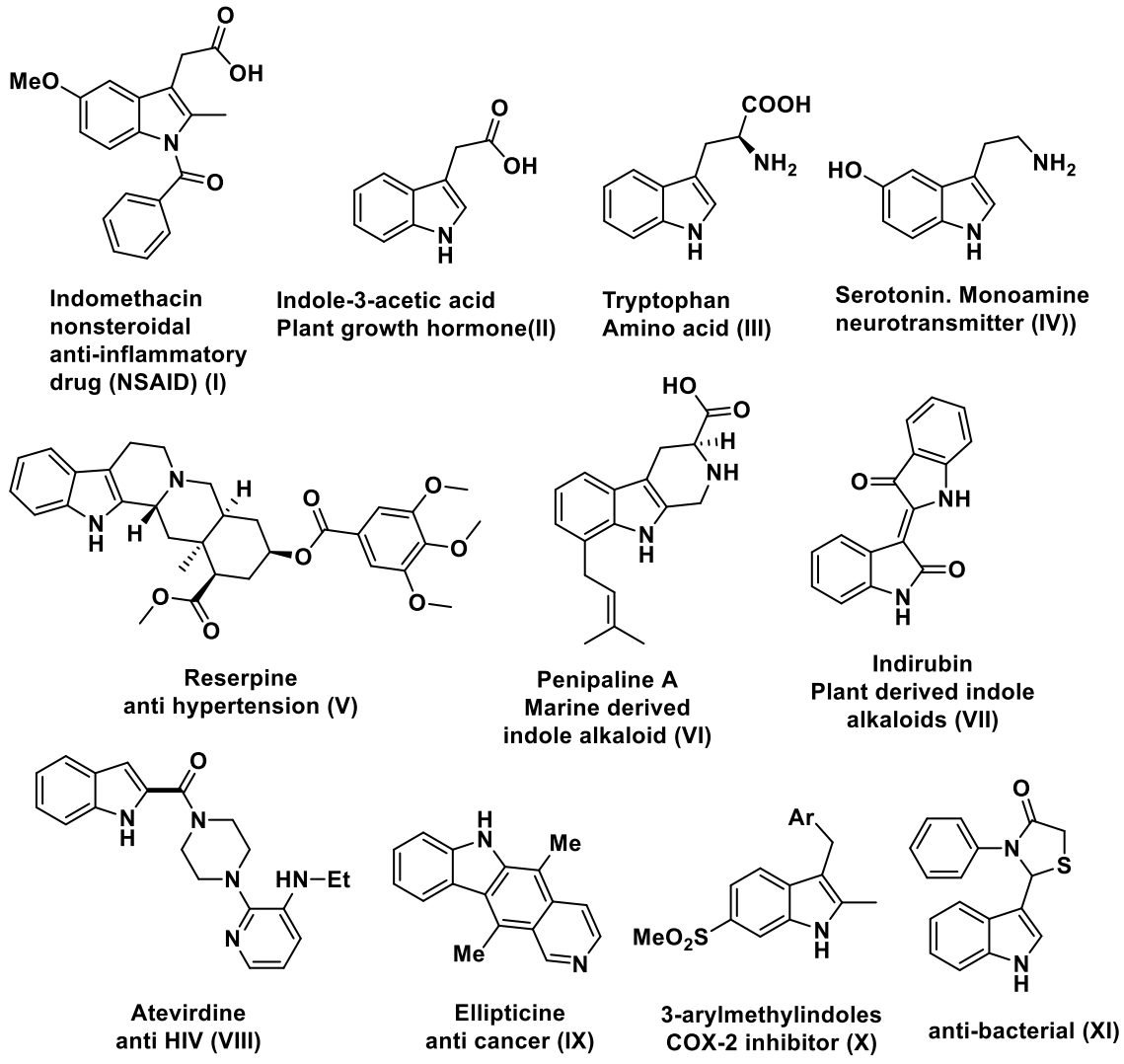


Figure 1.1. Selected bioactive indole appended conjugates

The indole with a diverse functional group, offers a remarkable platform for the synthesis of a wide range of derivatives and conjugates. Indole conjugates exhibit a significant range of biological activities and are vital for numerous biological processes.[22,23] They have been found within a wide variety of natural products, such as alkaloids,[24,25] and secondary metabolites of plants.[26] In addition, they also exhibit various bioactivities *viz.* anti-inflammatory,[27–30] antimicrobial,[31,32] antiviral,[33,34] antitumor,[35–37] and neuroprotective activities, etc. **(Figure 1.1).** The structural adaptability of indole also enables the synthesis of novel conjugates with other molecules, resulting in very effective pharmacological agents, agrochemicals,[38–40] and materials with a variety of applications.[41–44] Moreover, their involvement in modulating crucial signaling pathways and molecular targets has prompted interest in developing novel drug candidates with enhanced efficacy and minimal adverse effects.

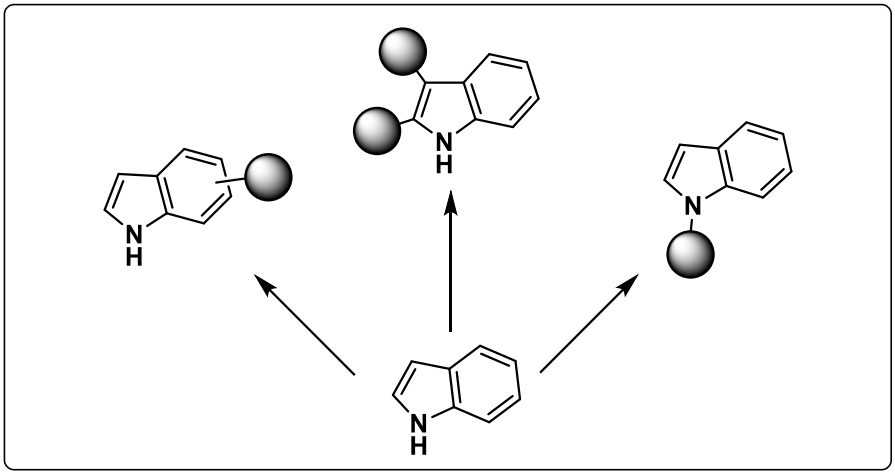


Figure 1.2. Indole functionalization.

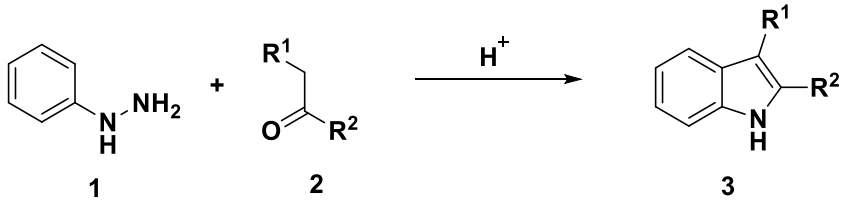
1.3. Synthetic strategies for indole appended conjugates

The synthesis of indole conjugates involves the attachment of an indole moiety to another molecule or functional group. This can be achieved through various synthetic strategies such as condensation reactions, nucleophilic substitutions, or transition metal-catalyzed

reactions.[45–49] Herein, we are discussing a few important methodologies developed for accessing indole-appended conjugates.

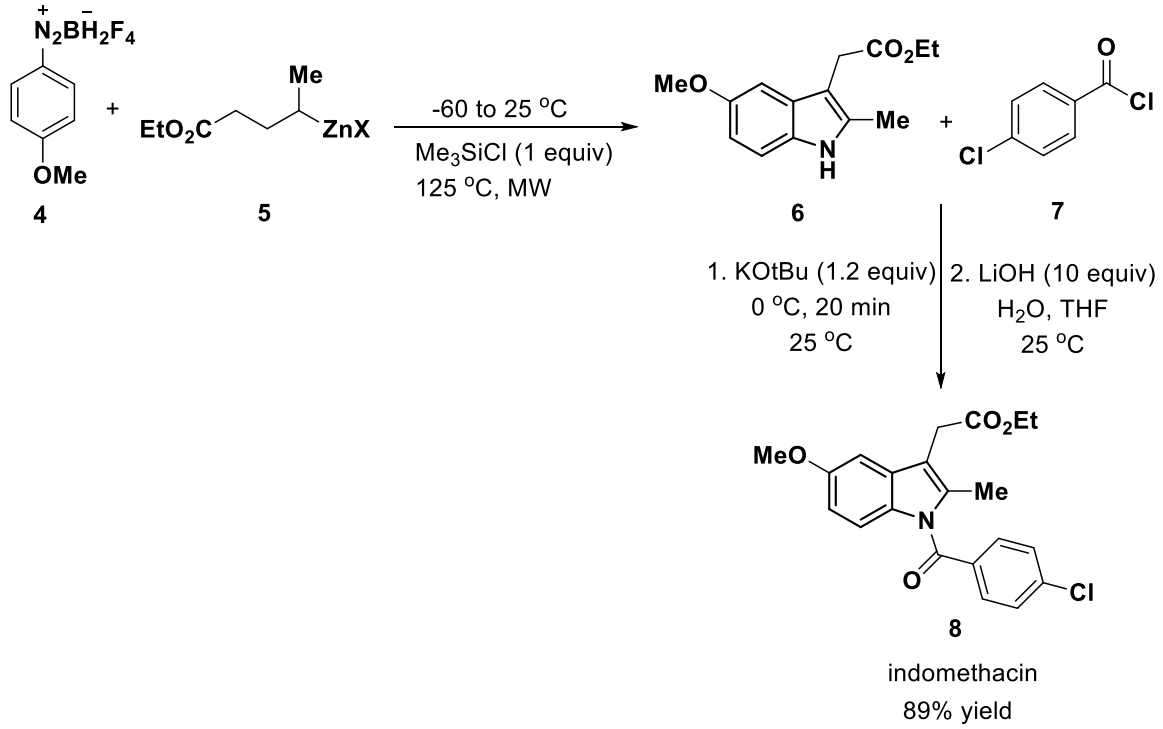
1.3.1. Condensation reaction

The Fischer indole synthesis is one of the earliest and most well-known methods for indole synthesis. It involves the condensation of phenyl hydrazine **1** with a carbonyl compound **2**, followed by acid-catalyzed cyclization to give indoles **3**.[50] This classic method offers moderate yields, but it suffers from limited substrate scope and sensitivity to reaction conditions (**Scheme 1.1)**.

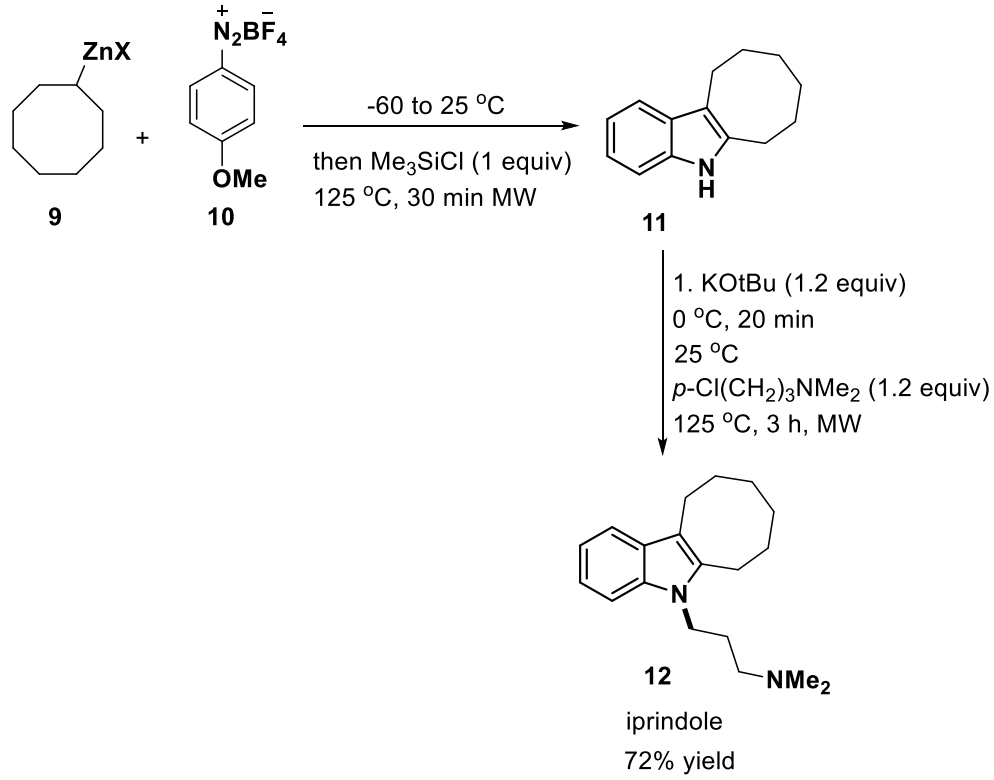


Scheme 1.1. Fischer indole synthesis

Knochel *et al*. applied the organometallic variation of the Fischer indole synthesis to access indomethacin **8** an anti-inflammatory drug and iprindole an antidepressant.[51] The reaction of the organozinc reagent **5** with the aryldiazonium salt **4** under standard conditions furnishes the indole **6**, which is then converted to indomethacin **8** in two steps (**Scheme 1.2**)**.** Similarly, cyclooctylzinc bromide **9** adds to PhN_2BF_4 **10** under microwave irradiation and forms indole **11** followed by N-alkylation of **11** leads to iprindole **12** (**Scheme 1.3**).



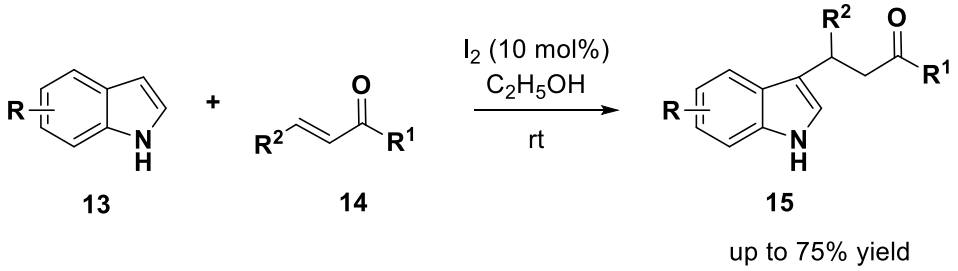
Scheme 1.2. Fischer indole synthesis to access **i**ndomethacin



Scheme 1.3. Fischer indole synthesis to access iprindole

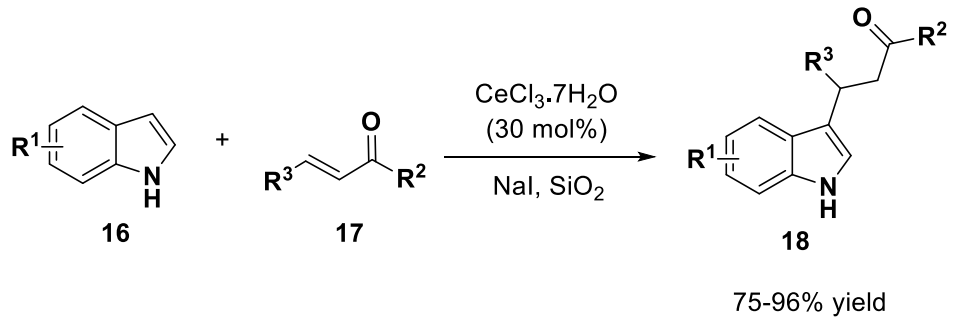
1.3.2. Michael addition

Michael addition provides an easy method to construct indole appended frameworks through conjugate addition of indole to the unsaturated ketones. Wang and coworkers demonstrated conjugate addition of indole **13** to the *α,β*-unsaturated ketones **14** resulting in the alkylation of indole in the presence of a catalytic amount of molecular I_2 at room temperature.[52] The reaction afforded the corresponding adduct excellent yields up to 96% **(Scheme 1.4)**.



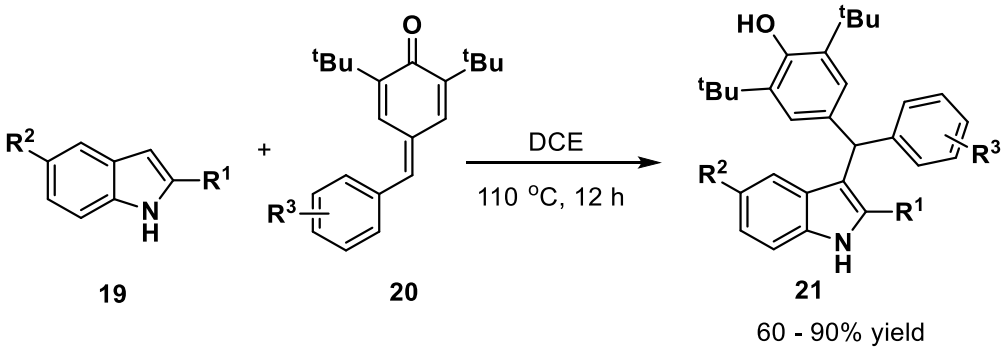
Scheme 1.4. Iodine catalyzed Michael addition of indole

Bartoli *et al.* showcased a silica gel-supported alkylation of indoles using the Michael addition. They have shown a conjugated addition of various substituted indoles **16** to cyclic and acyclic *α,β*-unsaturated ketones **17** using silica gel supported $CeCl_3,7H_2O$-NaI as catalyst **(Scheme 1.5)**.[53]



Scheme 1.5. Silica gel-supported Michael addition

Kumaran *et al*. in 2020 reported a catalyst-free Michael addition of indole **19** to the *para*-quinone methides **20** to obtain indole appended unsymmetrical triarylmethanes **21**. The reaction proceeds at 110 ^oC in DCE (**Scheme 1.6)**.

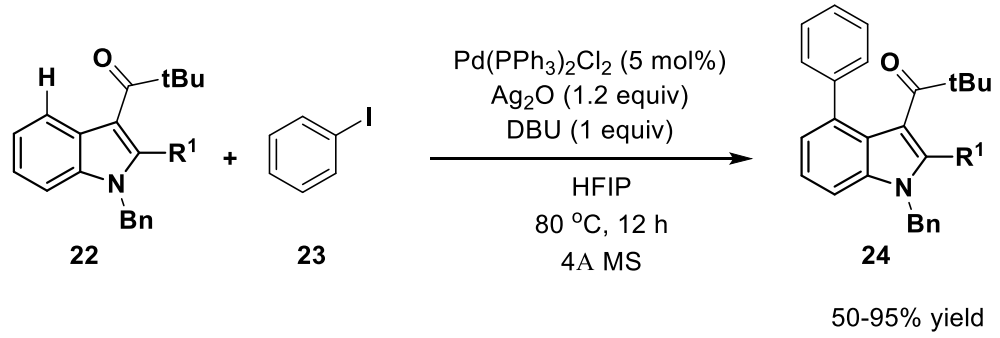


19 20 21

Scheme 1.6. Catalyst-free 1,6-conjugate addition of indoles

1.3.3. Metal-catalyzed reactions

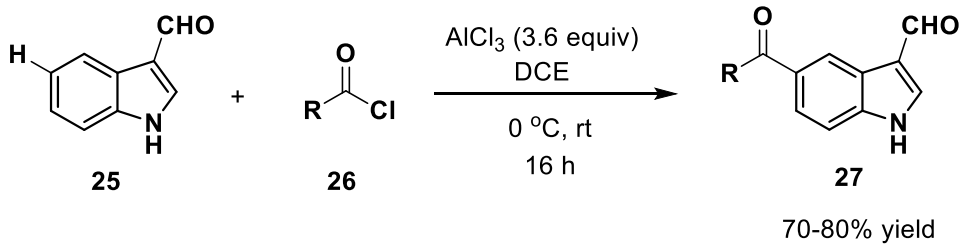
In 2017, exploiting the directing group influence, Shi and colleagues reported the C4-selective C-H arylation of indole **22** compounds using aryl iodide **23** as coupling partners. In this work, the large pivaloyl directing group preferably cyclopalladiates at the C4-position, and consecutive oxidative addition of the aryl iodide and subsequent reductive elimination forms the C4-arylated indole **24** (**Scheme 1.7**).



22 23 24

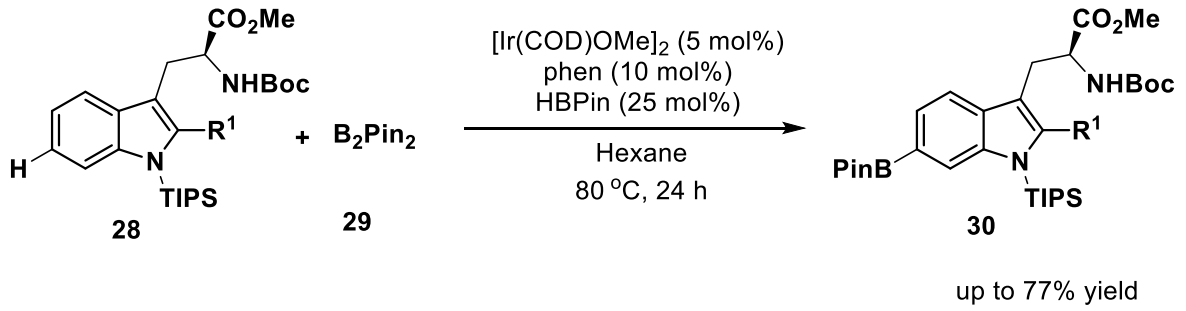
Scheme 1.7. Palladium-catalyzed C4-selective C-H arylation indole

Demopoulos *et al*. successfully demonstrated the $AlCl_3$ catalyzed Friedel- Crafts-type acylation of the free indole **25** using acyl chlorides **26**. This reaction gives a mixture of C5- and C6-substituted indoles in a ~ 3:1 ratio favouring the formation of C5-substituted indole **27** as the major product (**Scheme 1.8**).



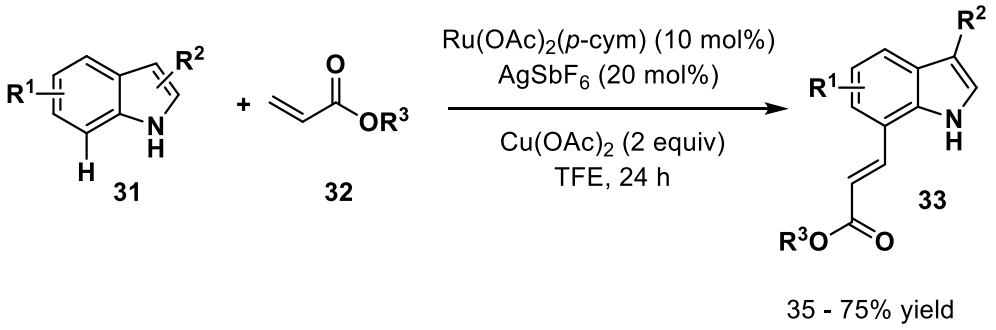
Scheme 1.8. Lewis acid catalyzed Friedel crafts type acylation of indole.

Baran *et al.* in 2015 reported the remote C6-selective C-H borylation of tryptophan derivatives **28** utilizing an iridium catalyst. The bulkier ligand group controls the selectivity of the reaction from the less hindered C-H bonds **(Scheme 1.9**). In addition, this protocol forms a crucial step in the total synthesis of the natural products fumitremorgin A and verruculogen.



Scheme 1.9. C6-selective C-H borylation of tryptophan derivatives.

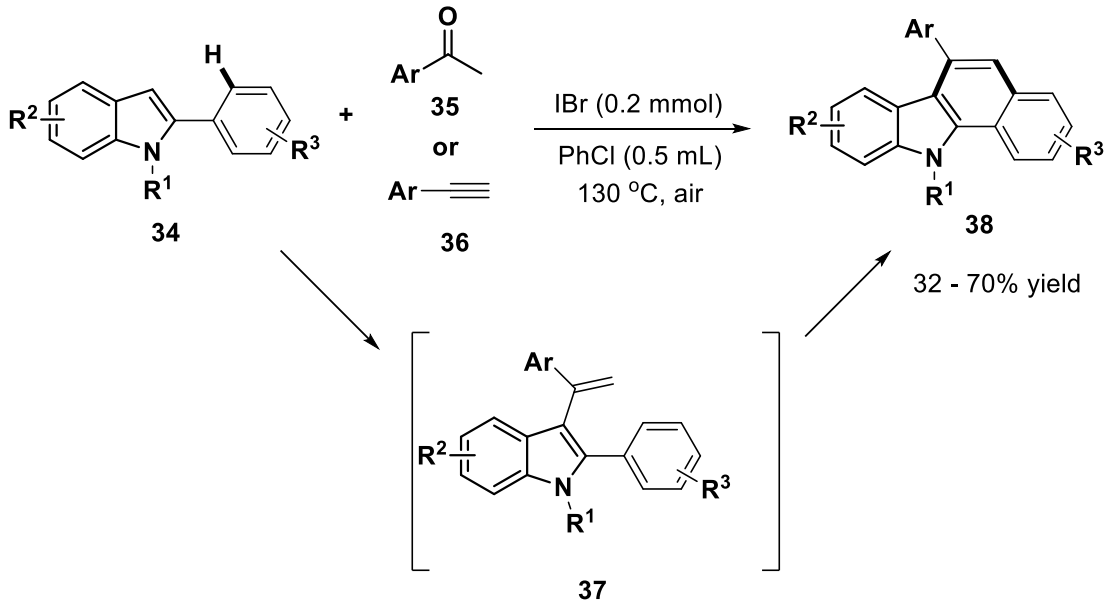
Ackermann *et al.* in **2020** Demonstrated Ruthenium catalyzed C-7 selective olefination of Indoles **31** with acrylates **32** as a coupling partner under mild conditions.[49] This protocol employs expensive ruthenium metal catalysts (**Scheme 1.10**). The reaction offers exclusive site selectivity towards C-7 and further, the procedure is also extended for the construction of C-N bonds at C-7.



Scheme 1.10. Ruthenium catalyzed C-7 selective olefination of Indoles

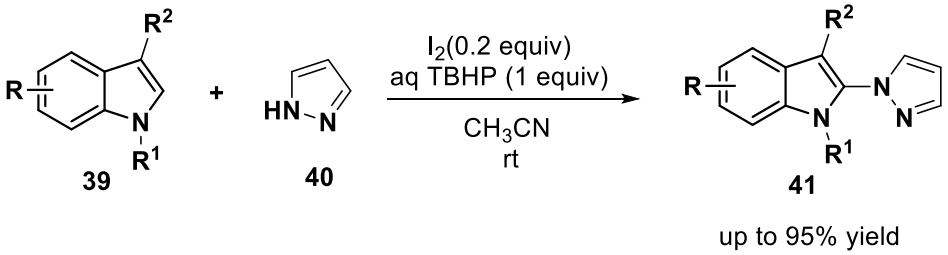
1.3.4. Metal-free strategies for indole-appended conjugates

Tan *et al.* developed a metal-free versatile strategy for the construction of benzo[*a*]carbazoles **38** from readily accessible starting materials *via* double Csp^2-H bond functionalization.[55] In this reaction 2-aryl indoles **34** and aryl ketones **35** undergo dehydrative condensation to give 2-aryl-3-vinyl-indoles **37** as key intermediates, these key intermediates undergo direct cyclisation between two Csp^2-H bonds to give corresponding benzo[*a*]carbazoles **38**. Furthermore, they successfully extended this protocol for employing terminal aromatic alkynes **36** as the condensation partners **(**Scheme **1.11**).



Scheme 1.11. Metal-free double Csp^2-H bond functionalization of indole.

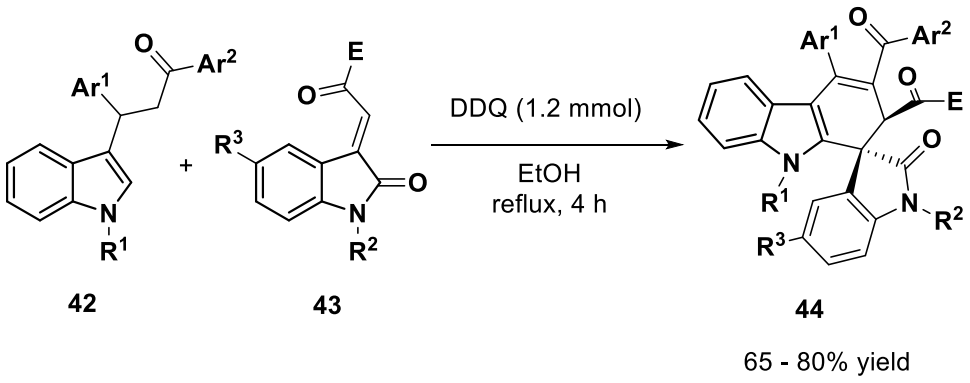
Beukeaw *et al.* reported an expedient metal-free catalytic method for regio- and chemoselective cross-coupling reaction between indole **39** C-H bond and azole **40** N-H bond.[56] This iodine-catalyzed oxidative coupling protocol offers mild reactions as it can be carried out at room temperature, utilizing an inexpensive and ubiquitous catalytic combination. This protocol provides an easy and convenient route to construct a library of N-linked 2-(azole-1-yl)indole **41** derivatives with potential medicinal applications (**Scheme 1.12**).



Scheme 1.12. Iodine catalyzed oxidative cross-coupling of indoles and azoles.

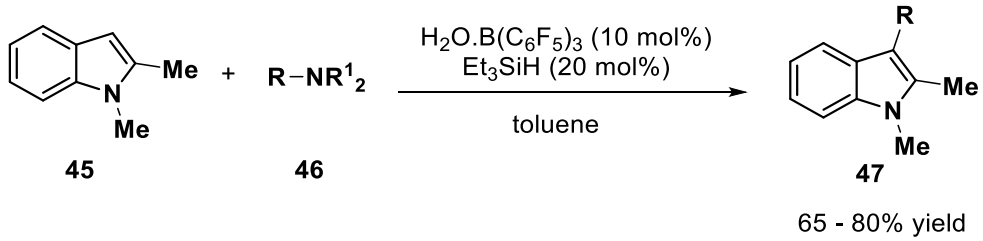
In 2021 Zhan *et al*. disclosed an efficient strategy for the synthesis of complex spiro-carbazole-oxindole **44** frameworks. This strategy involves DDQ-catalyzed oxidative dehydrogenative Diels–Alder reaction between 3-(indol-3-yl)-1,3-diphenyl propane-1ones **42** and 3-phenacylidene oxindoles **43**.[57] The reaction offers the corresponding products in

refluxing ethanol. The advantage of this methodology lies in the high diastereoselective product formation. The reaction exhibits broad functional group tolerance and encourages employing readily accessible starting materials. Further, the authors also confirmed the involvement of a normal electron-demanding Diels–Alder reaction mechanism using DFT calculations (**Scheme 1.13**).



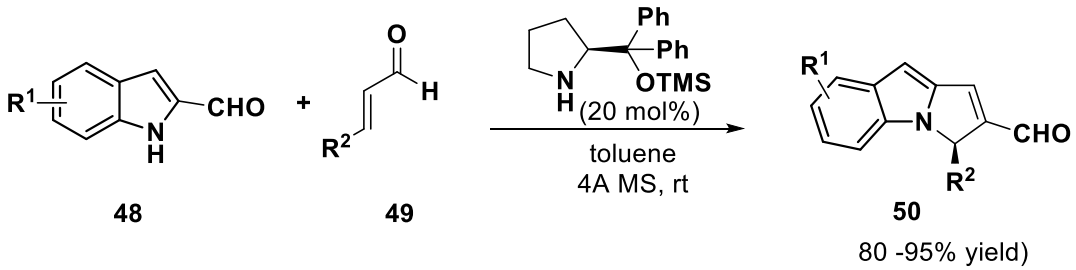
Scheme 1.13. DDQ catalyzed dehydrogenative Diels–Alder reaction to synthesize spiro[carbazole-1,3′-indolines]

Basak *et al.* developed a new protocol for direct C3 alkylation of indoles **44** with amine-derived alkylating agents **45** using $B(C_6F_5)_3$ catalyst.[58] The reaction displays a broad scope and exceptional chemo selectivity, avoiding the N-methylation and formation of 3,3′-diindolylmethane in indole substrates (**Scheme 1.14**). This $B(C_6F_5)_3$ catalyzed strategy encompasses several classes of indole, including 1-, 2-, and 1,2-substituted indoles for direct methylations. The reaction displays a broad scope with exceptional chemoselectivity, avoiding the N-methylation and formation of 3,3′-diindolylmethane. In addition, this strategy also worked well for oxindoles to offer chemo selectively C3- alkylation of diverse oxindoles avoiding the dialkylation in oxindoles



Scheme 1.14. $B(C_6F_5)_3$-Catalyzed Direct C3 Alkylation of Indoles

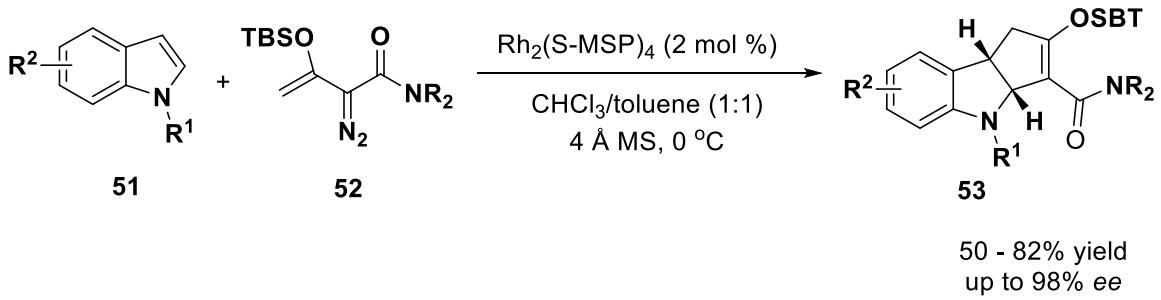
Wang and co-workers reported a one-pot protocol for the synthesis of chiral pyrrolo[1,2-*a*]indole-2-carbaldehydes[59] **(Scheme 1.15**). This reaction proceeds *via* an asymmetric organocatalytic cascade aza-Michael/aldol reaction between indole-2carbaldehydes **48** and *α,β*-unsaturated aldehydes **49** to give pyrrolo[1,2-*a*]indole-2-carbaldehydes **50**. The distinctive feature of this procedure is that it enables to access optically active pyrrolo[1,2-*a*]indole tricyclic rings in one step. Thus, formed products contain an aldehyde functionality that can be further transformed.



Scheme 1.15. Asymmetric organocatalytic N-alkylation of indole-2-carbaldehydes with *α,β*-unsaturated aldehydes

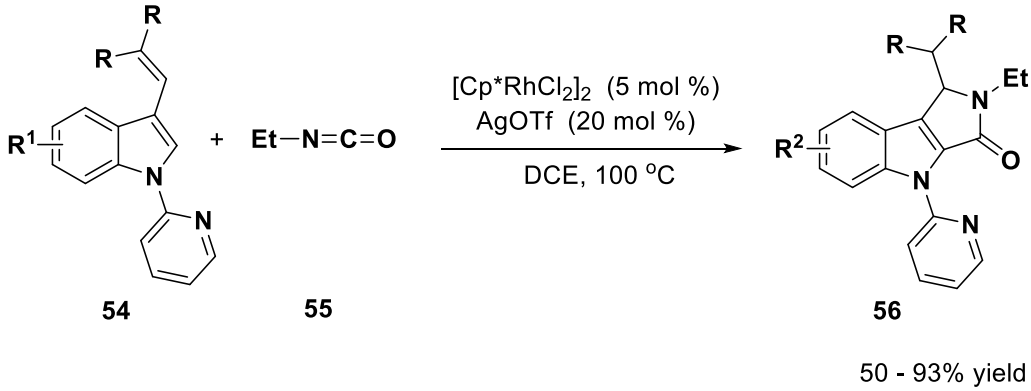
1.3.5. Synthesis of indole appended conjugates *via* cycloaddition

Jing *et al.* in 2016 synthesized chiral cyclopentane-fused indolines *via* formal [3+2]-annulation reactions of indoles with electrophilic enol carbenes.[60] This annulation reaction occurs in high regio- and enantio-controlled manner. High enantioselectivity and exclusive regiocontrol are achieved when enol diazoacetamides **52** reacts with the N-substituted indoles **51** without substituents at the 2- or 3-positions *via* a selective vinylogous addition process. presence of less sterically encumbered prolinate-ligated dirhodium(II) catalyst controls the regio and enantioselectivity of the product formation **(Scheme 1.16**).



Scheme 1.16. [3+2]-annulation of indoles with electrophilic enol carbene intermediates.

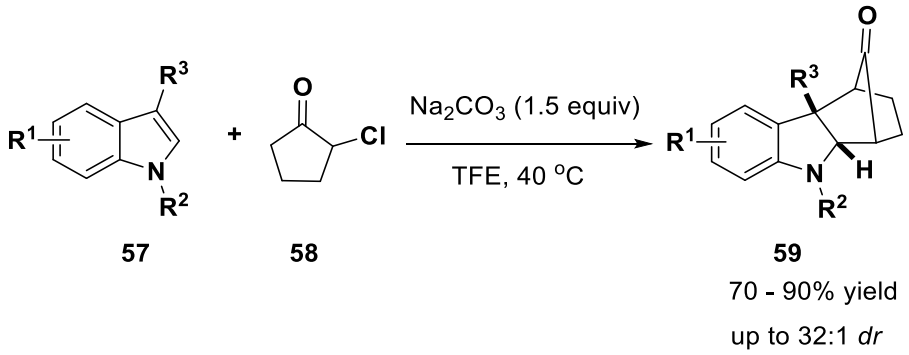
Xing and coworkers envisaged a methodology for synthesizing 1,2-dihydropyrrolo[3,4-b]indol-3-one frameworks through a formal [3+2] cycloaddition between indoles with electron-deficient alkenes **54** and isocyanates **55**.[61] (**Scheme 1.17**) This reaction involves the sequential coupling reaction initiated by the C-H activation and followed by aza-Michael addition, a series of 1,2- dihydropyrrolo[3,4-b]indol-3-ones **56** with diverse substitution are constructed in moderate to good yields by forming new C-C bond and one C-N bond.



Scheme 1.17. Synthesis of 1,2-dihydropyrrolo[3,4-*b*]indol-3-ones *via* a formal [3+2] cycloaddition.

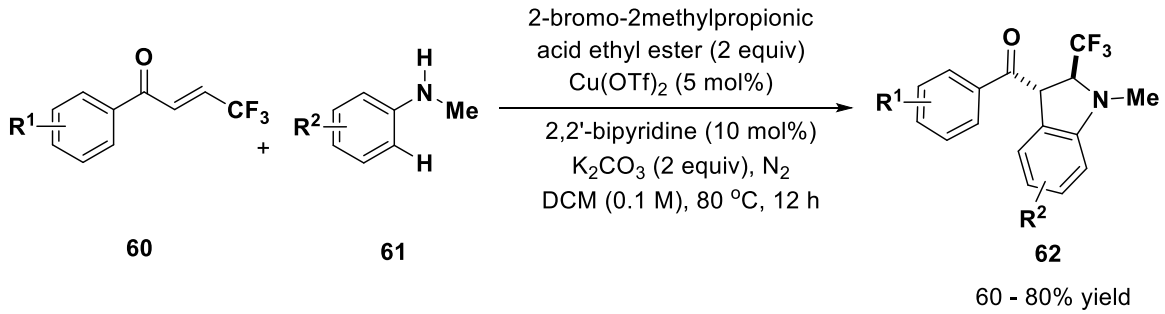
Hughes *et al.* disclosed a diastereoselective (3+2) dearomative annulation of 3-substituted indoles **57** with *α*-halo ketones **58** to construct highly functionalized cyclopenta fused indoline compounds **59**.[62] The reaction proceeds to offer the aspired products in high efficiency, and high diastereoselectivity is observed in the product formation. Further, this

methodology was successfully extended to synthesize cyclohexane-fused indoline compounds in a significant regiochemical controlled way (**Scheme 1.18**).



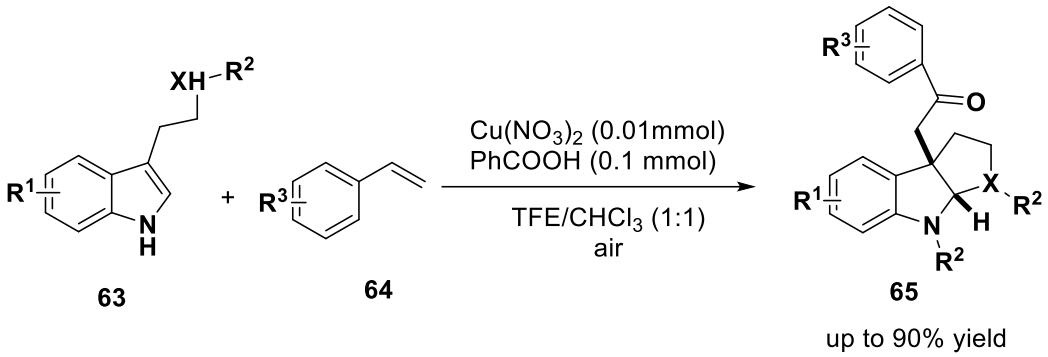
Scheme 1.18. Dearomative indole (3 + 2) cycloaddition reactions

Ji *et al.* successfully demonstrated the construction of C-2 trifluoromethylation indolinylketone frameworks **62** through a copper-catalyzed cyclization between N-alkyl aniline **61** and *β*-(trifluoromethyl)-*α,β*-unsaturated enones **60.**[63] Mechanistic studies revealed that the reaction proceeds in a radical pathway by a single-electron transfer process. This protocol shows a high functional group tolerance and high diastereoselectivity (*dr*, up to >20: 1) under mild reaction conditions. Further, the product formation in gram scale synthesis proved the advantage and efficiency of this protocol (**Scheme 1.19**).



Scheme 1.19. Copper-catalyzed synthesis of trifluoromethylated indolinyl ketones.

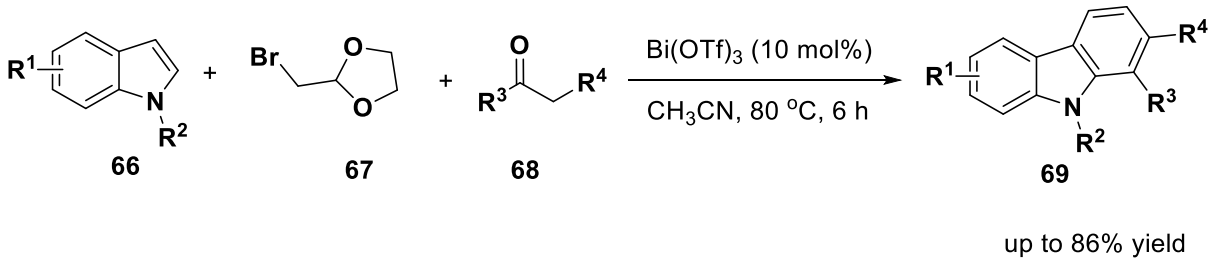
Copper-catalyzed protocol for the rapid construction of 3*α*-benzoylmethyl pyrrolidino[2,3-*b*]- indolines **65** through the oxidative annulation between tryptamine derivatives **63** and aryl ethylene **64** was reported by Chen *et al.*[64] In this procedure copper salts are oxidized by air rendering this procedure highly eco-friendly process (**Scheme 1.20**).



Scheme 1.20. Copper-catalyzed synthesis of 3*α*-Benzoylmethyl Pyrrolidino[2,3-*b*] indolines.

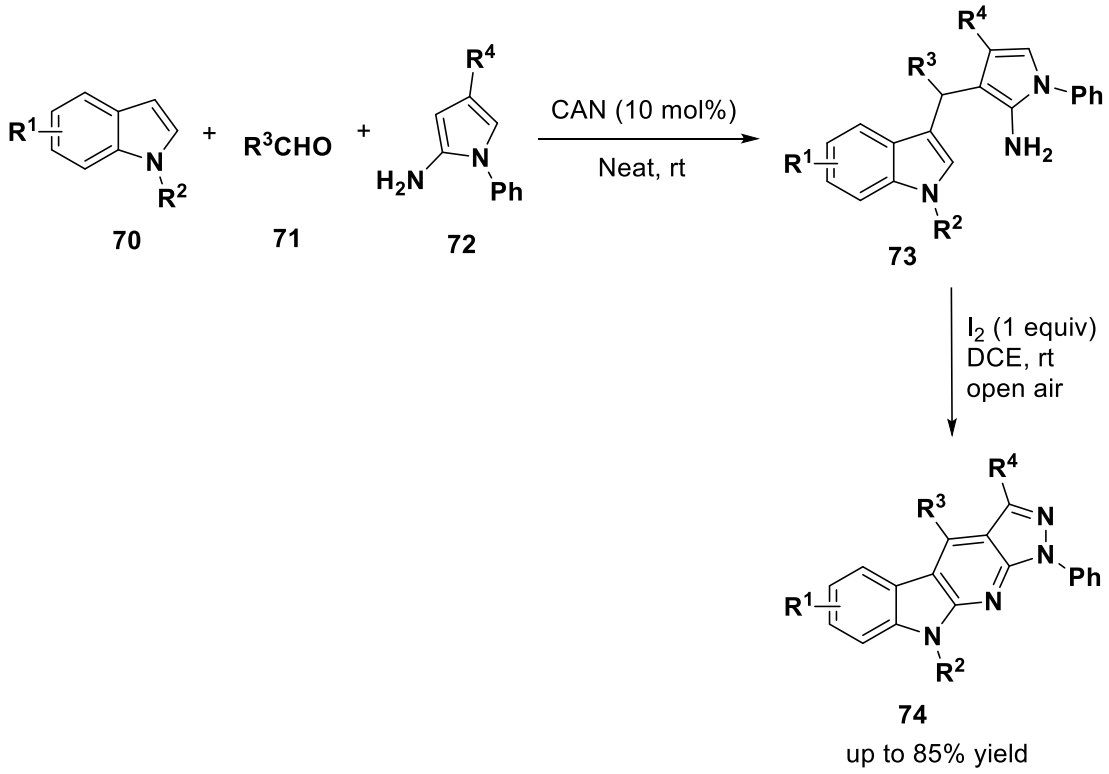
1.3.6. Multicomponent reactions

Gu *et al.* Gu *et al.* reported bismuth(III) triflate-catalyzed carbazole synthesis using the three-component reaction of indoles **66**, *α*-bromoacetaldehyde acetals **67** and ketones **68**.[65] This tandem reaction provides a straightforward approach for synthesizing carbazole derivatives **69** (**Scheme 1.21**).



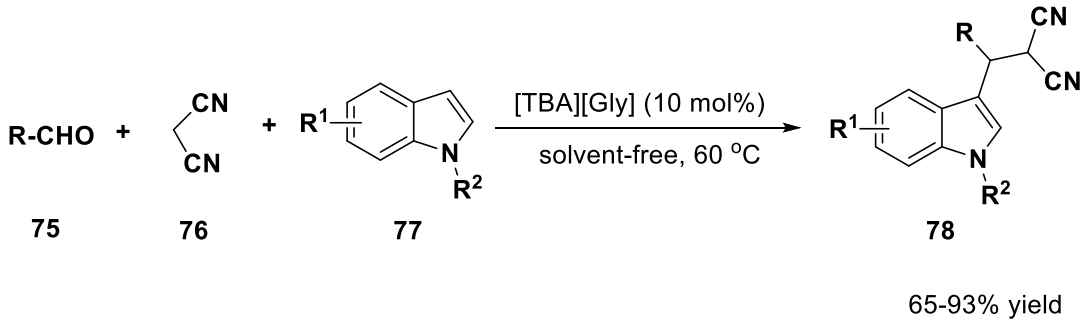
Scheme 1.21. Bismuth(III) triflate catalyzed indole to-carbazole transformation.

Deka and coworkers uncovered an efficient strategy to synthesize *α*-carboline derivatives, involving ceric ammonium nitrate(CAN) catalyzed condensation of indoles **70**, aldehydes **71** and pyrazol-5-amine **73** to give 3-substituted indoles **74** which undergo subsequent I_2-promoted intramolecular C2 amination and aromatisation forms *α*-carbolines[66] (**Scheme 1.22**).



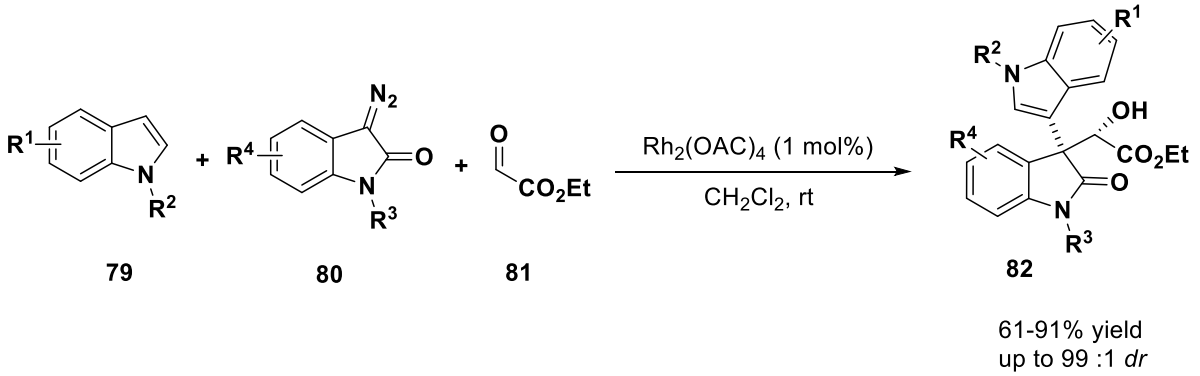
Scheme 1.22. Multi-component synthesis of 3-substituted indoles.

Rawat and co-workers employed Tetrabutylammonium glycinate [TBA][Gly] ionic liquid as an organocatalyst for the construction of 3-substituted indoles.[67] Substituted aromatic/aliphatic aldehydes **75**, malononitrile **76** and indoles **77** in the presence of [TBA][Gly] ionic liquid at 60 ^{o}C under neat condition afford 3-substituted indoles **78** in excellent yields. The main advantage of this approach is the [TBA][Gly] ionic liquid's ability to be recycled six times without losing catalytic activity (**Scheme 1.23).**



Scheme 1.23. Multi-component synthesis of 3-substituted indoles.

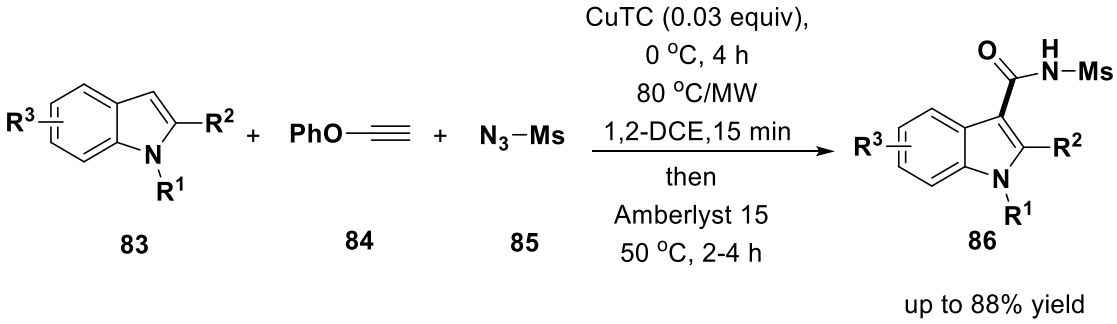
A highly effective three-component reaction of 3-diazo oxindoles **80** with indoles 79 and ethyl glyoxylate **81** was developed by Xing *et al*. using the Rh_2-$(OAc)_4$ catalyst[68]. This reaction enables the step-efficient production of mixed, *α,β*-bisindole **82** with quaternary carbon centres in high yields and superior diastereoselectivities. (**Scheme 1.24).**



79 80 81 82

Scheme 1.24. Rh_2-$(OAc)_4$ catalyzed a three-component reaction for synthesizing *α,β*-bisindoles

Davies *et al*. have showcased an effective process for the aminoacylation of indoles through 4-alkoxy N-sulfonyltriazole intermediates.[69] In this multicomponent one-pot cascade reaction, the product oxo-tryptamine **86** can be synthesized. Herein, the alkoxy-substituted triazoles **85** undergo nitrogen extrusion at relatively mild circumstances without the need for a dirhodium catalyst (**Scheme 1.25**).

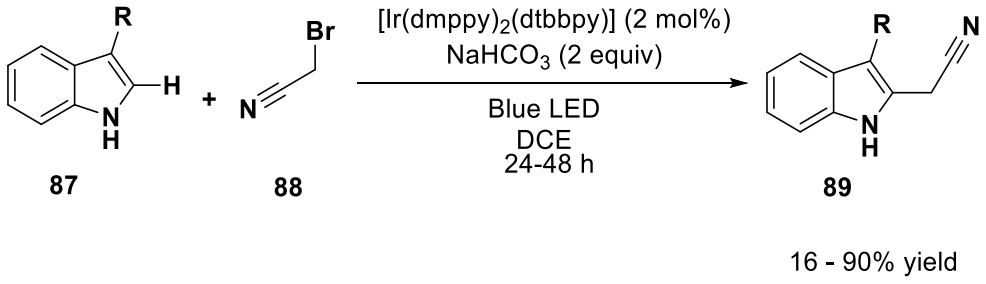


83 84 85 86

Scheme 1.25. One pot aminoacylation of indoles

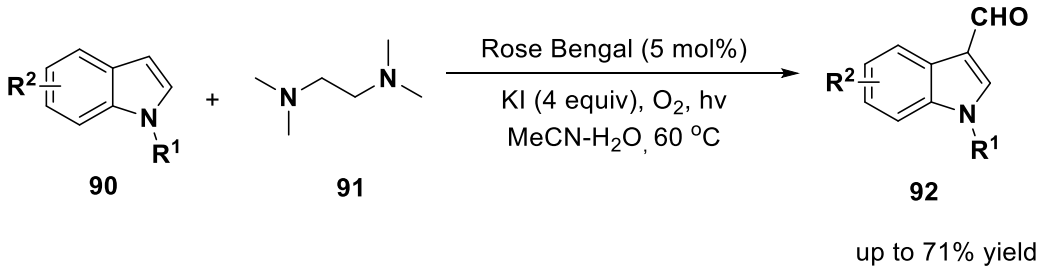
1.3.7. Photo-induced indole functionalization

Conrad *et al*. achieved photoredox cyanomethylation of indoles at the 2- or 3-position, using the Iridium complex as a photocatalyst under blue LED irradiation.[70] The reaction offers synthetically useful cyanomethyl indoles **89** in one step in 16-90% yield. The reaction proceeds through the radical mechanism the nitrile synthon is generated as a radical from bromoacetonitrile **88** under standard reaction conditions and then combines with the indole **87** to offer the desired product (**Scheme 1.26**).



Scheme 1.26. Photoredox cyanomethylation of indoles.

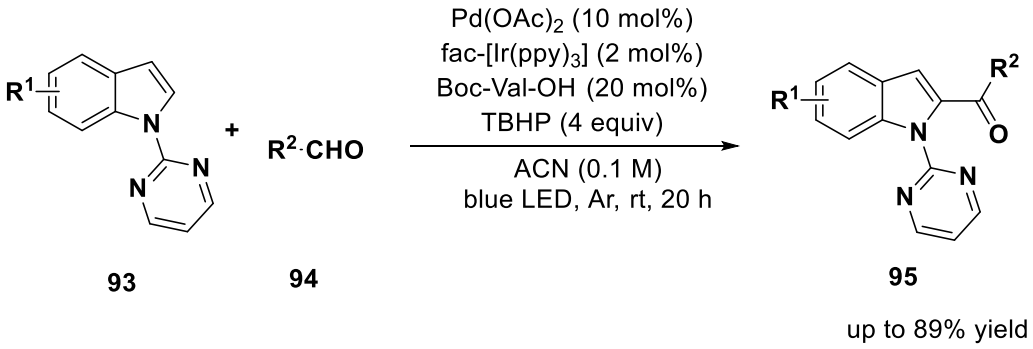
A Rose Bengal-catalyzed aerobic visible-light-induced indole **90** C-3 formylation process was reported by Li *et al*. In this transition-metal-free process, TMEDA **91** serves as the one carbon atom source through the cleavage of the C-N bond and molecular oxygen serves as the terminal oxidant to give 3-formyl indole **92** (**Scheme 1.27**).[71]



Scheme 1.27. Photo-induced acylation of indoles

Eycken *et al*. developed an efficient and versatile methodology to achieve C2-acylation of indole derivatives with aldehydes **94** through batch and flow-based dual photoredox/transition metal catalysis.[72] selectively C-2 position of N-pyrimidylindoles **93**

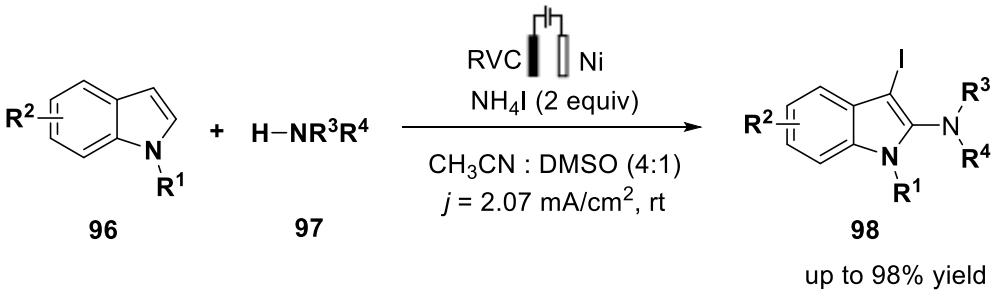
underwent C-H bond functionalization. This acylation reaction occurs at mild reaction conditions and shows a wide functional group tolerance (**Scheme 1.28**).



Scheme 1.28. C2-acylation of indole *via* dual catalysis

1.3.8. Electrochemical indole functionalization.

Zheng *et al.* developed an eco-friendly electrochemical approach for the iodoamination of various indole derivatives.[73] This strategy enables the iodoamiantion of diverse indoles **96** with unactivated amines, benzotriazoles and amino acid derivatives **97**. Further, this protocol was successfully extended for the late-stage iodoamination of natural products and pharmaceuticals (**Scheme 1.29**).



Scheme 1.29. Electrochemical iodoamination of indoles

1.4. Importance of naphthol appended conjugates

Naphthol is a hydroxyl group-bearing compound derived from naphthalene. These derivatives have been found to exhibit various biological activities and have potential applications in the field of medicine and drug discovery. As a result of their ability to interact with biological systems and exhibit specific properties the naphthol appended frameworks possess various biological applications such as anti-bacterial,[74] anti-cancer,[75] anti-diabetic, anti-viral,[75] anti-fungal,[76,77] anti-depression,[78,79] anti-malarial properties[80] (**Figure 1.3**). β-naphthol serves as a synthon in various organic syntheses.[81,82] The α-position of the β-naphthol is highly active and can participate in various chemical reactions.[83] As a result, the α-position has fascinated organic chemists towards the intriguing functionalization of β-naphthols. The α-position of β-naphthol can undergo various chemical transformations, such as alkylation, arylation, cyclization, amination and halogenation, etc., these chemical reactions can be used to construct naphthol-appended conjugates for diverse applications.[84,85]

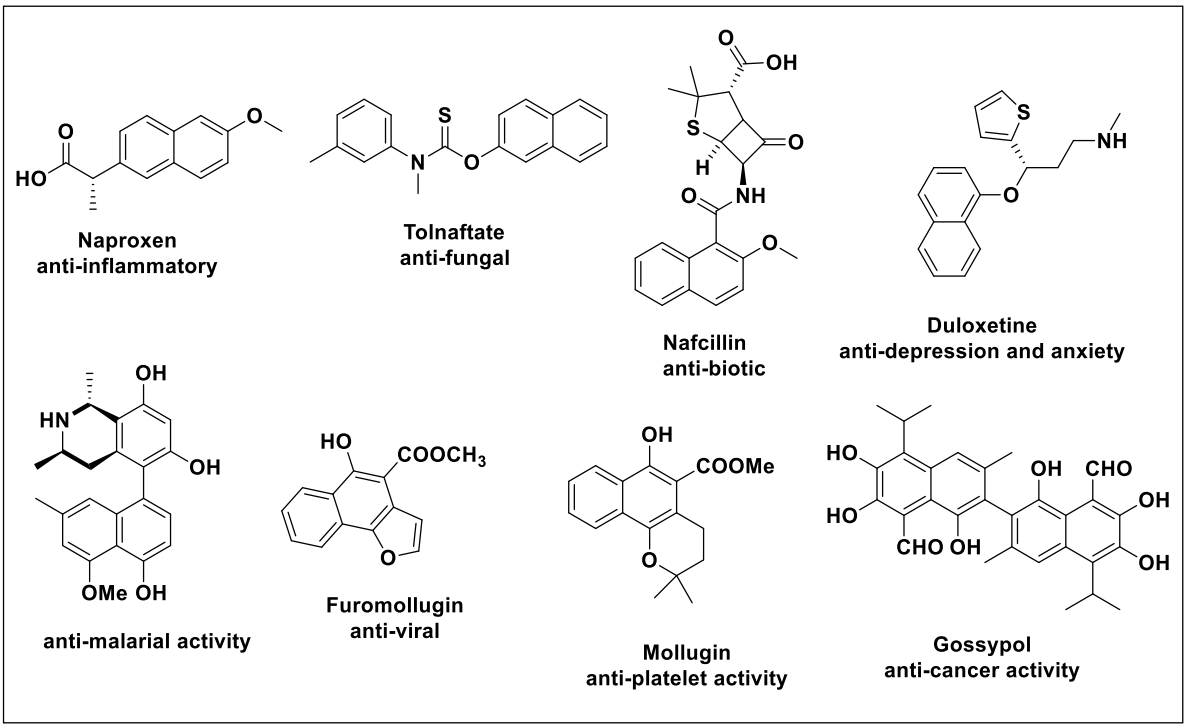


Figure 1.3. Selected bio-actives containing naphthol derivatives

The alkyl naphthol exhibits antibacterial and antihypertensive effects,[86] naphthopyran or naphthofuran forms an important skeleton of various active substances.[87,88] binaphthol is

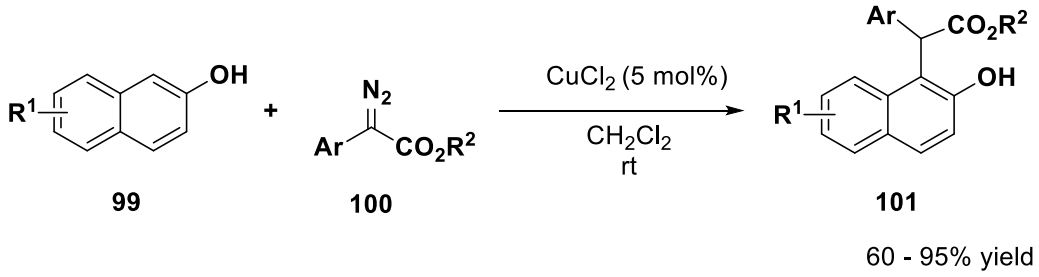
used as a Chiral ligand.[89] aryl sulfides.[90] arylamines.[91] and fluorinated naphthols. are used in various applications.[92,93] Owing to this broad range of applications, the modification and synthesis of naphthol-appended conjugates have always been one of the most interesting topics.

1.4.1 Synthetic strategies for naphthol appended conjugates

In the early organic synthesis methods, the structural modification of the *β*-naphthol usually employs transition metal-catalyzed coupling reactions to access important naphthol-appended molecular frameworks.[85] In recent years, due to growing concerns towards environmental benignity there are several improved protocols such as Metal-free synthesis, one-pot multicomponent reactions, and visible light-induced approaches have been developed to synthesize naphthol conjugates in an eco-friendly manner.[85] Herein, we are discussing some of the recently improved strategies for the synthesis of naphthol-appended conjugates.

1.4.2. Metal-catalyzed functionalisation

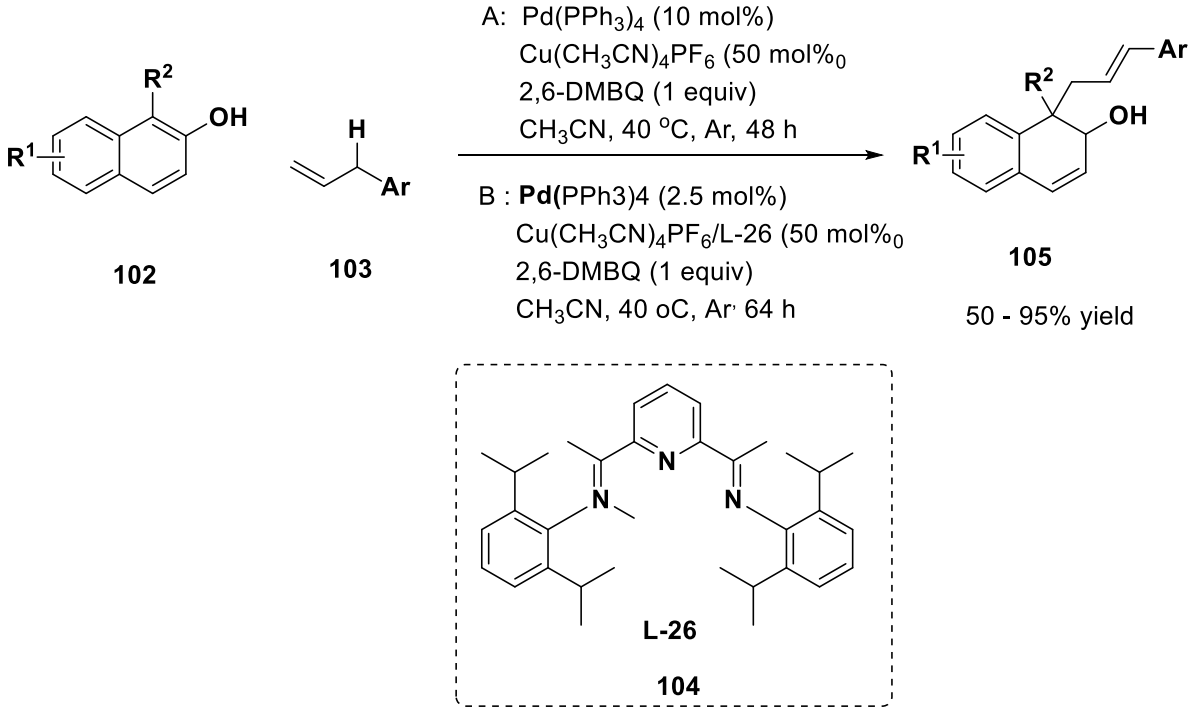
Liu *et al*. in 2020 demonstrated the ortho-selective C–H bond functionalization of phenols and naphthols **99** using a copper catalyst.[94] They have employed *α*-aryl-*α*-diazoesters **100** as coupling partners for this transformation. In this reaction, $CuCl_2$ effectively encourages the extremely chemo- and site-selective functionalization of C-H bonds under benign reaction conditions (**Scheme 1.30**).



Scheme 1.30. Copper-catalyzed C-H functionalization of naphthols.

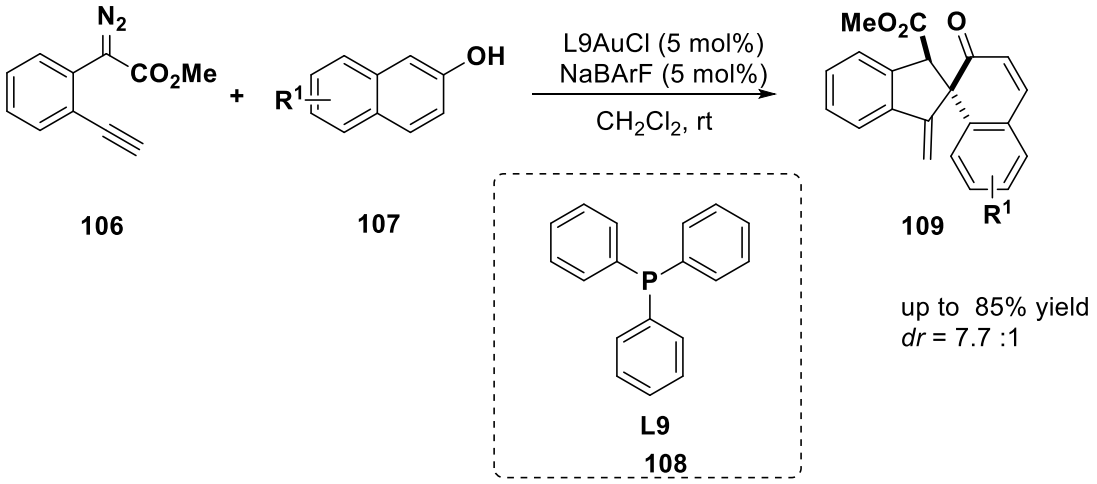
Yang *et al.* revealed a direct oxidative allylic C-H dearomatization of 2-naphthols **102** through cooperative palladium/copper catalysis.[95] Co-operative combination of

$Pd(PPh_3)_4/Cu(MeCN)_4PF_6$ in this protocol enables to achieve excellent chemoselectivities in the construction of cyclohexadienones **105** with quaternary carbon centres. These base-free reaction conditions are well tolerated by peptides during their late-stage functionalization (**Scheme 1.31**).



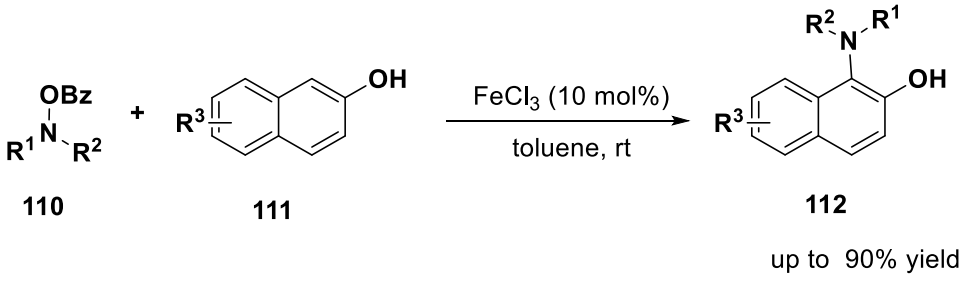
Scheme 1.31. Direct oxidative allylic C-H dearomatization of 2-naphthols

Liu *et al*. reported a protocol for the C–H bond functionalization/dearomatization of naphthols **107** utilizing *ortho*-alkynylaryl-*α*-diazoesters **106**.[96] In the presence of gold complex, phenols and naphthols undergo extremely site- and chemo-selective C-H bond functionalization with *ortho*-alkynylaryl-*α*-diazoesters **106**, producing alkynyl naphthol derivatives **109** that can proceed through subsequent carbocyclization dearomatization reaction (**Scheme 1.32**).



Scheme 1.32. C–H bond functionalization of naphthols with *ortho*-alkynyl aryl-*α*-diazo esters

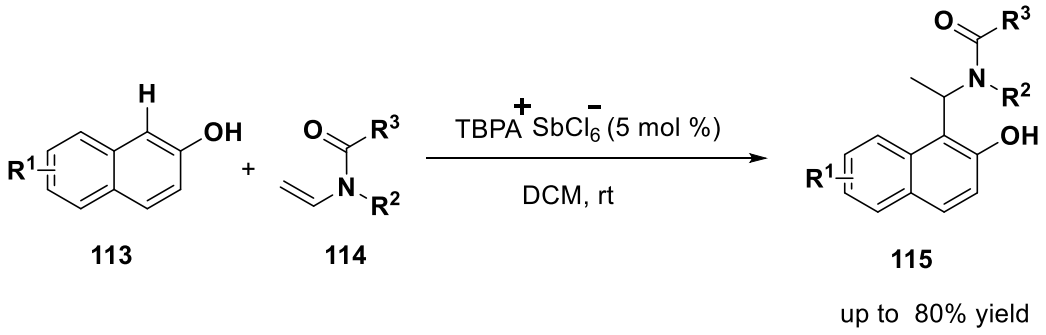
In 2016 novel and efficient protocol for the direct alkyl amination of phenols using Fe catalyst was reported by Luo's research group.[97] The salient feature of this strategy is the direct formation of N-alkyl-substituted aminophenols **112** by a radical process through an interaction between naphthols **111** and O-benzoyl-N-alkylhydroxylamines **110** in the presence of iron-catalyst. This reaction proceeds without the aid of ligands or other additives, smoothly offering N-alkyl-substituted aminophenols **112** at room temperature in moderate to good yields (**Scheme 1.33**). Further, mechanistic studies revealed that the $FeCl_3$ acts as an initiator and a Lewis acid as well as promotes this transformation.



Scheme 1.33. $FeCl_3$ catalyzed the synthesis of N-alkyl-substituted aminophenols

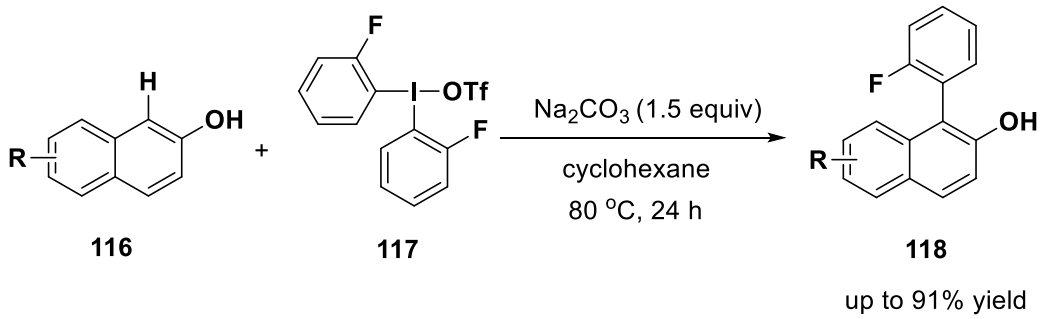
1.4.3. Metal-free catalyzed functionalisation

Electron-rich alkenes serve as effective alkylating agents. A metal-free radical cation 3-(4-bromophenyl)-ammonium hexachloride $SbCl_6$) was utilized as a catalyst by Huo *et al.* for the innovative, regioselective Friedel-Crafts alkylation of *β*-naphthols **113** with enamines or enethers.[98] Acyclic enamides or *E* nitrogen heterocycles **114** react smoothly with naphthol to give *α*-alkylated products **115** without forming O-alkylated by-products. In this protocol catalytic amount of triarylaminium salt generates radicals from electron-rich enamides or enethers for the alkylation. This cost-effective, environmentally friendly process creates a novel Friedel crafts alkylation between 2-naphthols and electron-rich alkenes by using a nonmetallic catalyst with modest loadings (**Scheme 1.34**).



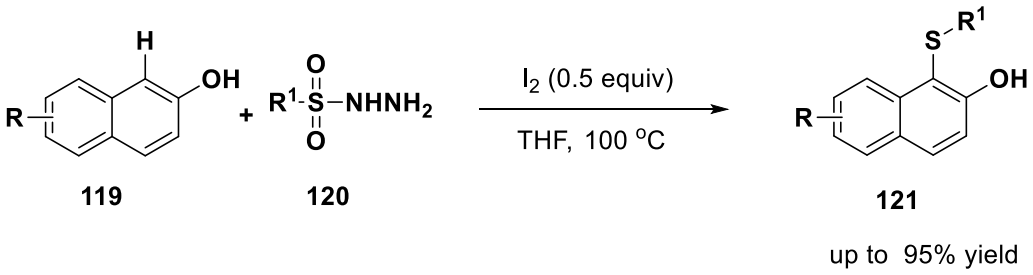
Scheme 1.34. Friedel-Crafts alkylation of *β*- naphthols with enamines.

Kalek *et al.* developed a base-catalyzed metal-free regioselective C-H arylation of 2-naphthols **116** using diaryliodonium salts **117**.[99] Under mild experimental conditions, the reaction continues and produces various arylated naphthols **118** with different substitution patterns. This strategy permits the inclusion of electron-deficient aryls, unlike other metal-free aryl-aryl cross-couplings of phenols that had hitherto only been possible with the insertion of electron-rich aryl moieties very well.



Scheme 1.35. Metal-free arylation of 2-naphthol

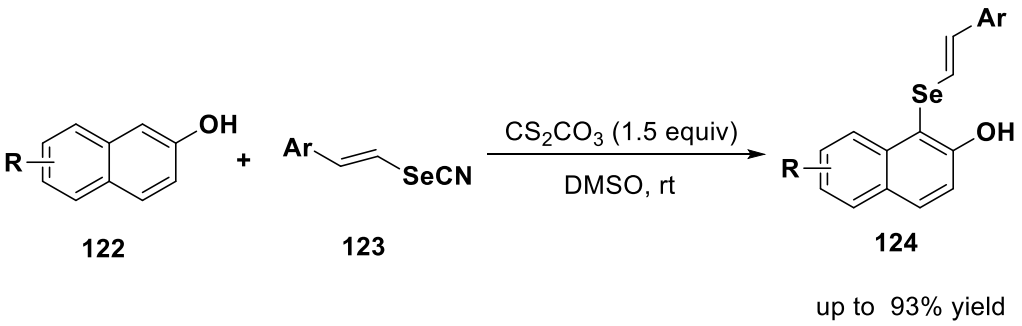
Huang *et al*. reported iodine-mediated thiolation of naphthol to rapidly access synthetically useful thioethers from commonly available substrates, such as substituted naphthol **119** and sulfonyl hydrazides **120**.[100] The C-H bond functionalization of naphthols with sulfonyl hydrazides undergoes through C-S bond formation and S-N/S-O bonds cleavage between Sulfonyl hydrazides and naphthols. In this procedure, various substituents, such as alkyl, methoxyl, chloro, bromo, and fluoro groups are tolerated and reacted smoothly to afford thiolated naphthols **121** in moderate to good yields (**Scheme 1.36**). Further, the authors also showcased the application of this protocol towards the thiolation of naphthylamines in good yields.



Scheme 1.36. Iodine-mediated thiolation of naphthol

Bicyclic aromatic hydrocarbon selenium compounds have received a considerable amount of attention as lead compounds because of their diverse spectrum of biological activity and their use in medicinal applications. In 2018, Ranu's research team successfully performed the selenization reaction of the C-H bond at the α-position of β-naphthol **122** using selenocyanate **123** and diaryl diselenide as selenization reagents.[101] Styryl selenocyanate or diaryl diselenide substituted with electron-withdrawing or electron-donating groups can easily

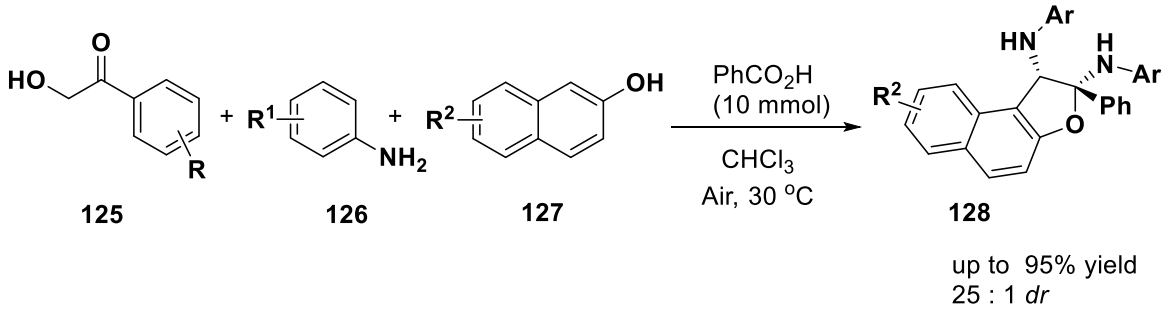
react with *β*-naphthol resulting in the equivalent selenium compounds **124**. High yield, ambient reaction condition, broad substrate scope, and use of no metal or oxidant are the appealing characteristics of this procedure (**Scheme 1.37**).



Scheme 1.37. Metal-free selenization of *β*-naphthol

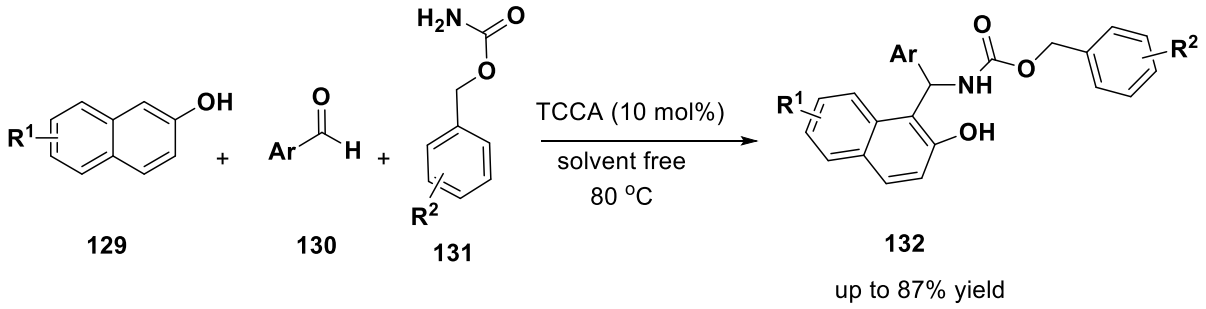
1.4.4. Multi-component reactions

Polysubstituted 1,2-dihydronaphthofurans **128** were successfully synthesized in high yields and with good diastereoselectivities by Li *et al* in 2022. through a tandem C–H annulation of *α*-hydroxyl ketone **125** and aniline **126** with 2-naphthol **127**.[102] The reaction is efficiently achieved by several tandem processes, including Heyns rearrangement, oxidation, Friedel-Crafts reaction, and cyclization. The activation of the imine by an intramolecular hydrogen bond is theorized to be the cause for the reaction's remarkable stereoselectivity (**Scheme 1.38**). Since air is employed directly as the oxidation medium, the reaction is secure and simple to carry out.



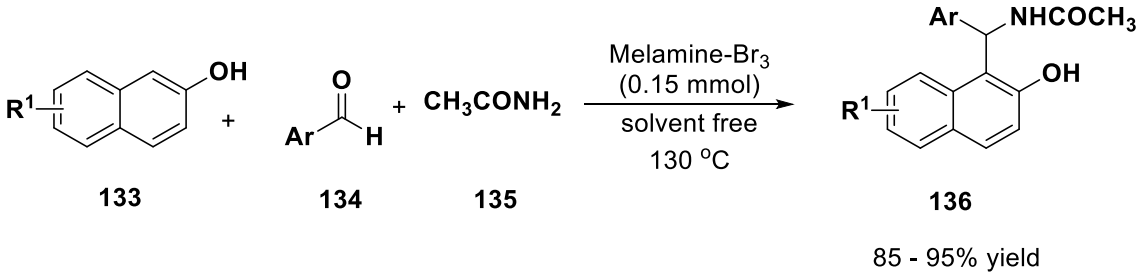
Scheme 1.38. Organo-catalyzed synthesis of polysubstituted 1,2-dihydronaphthofurans

The research team of Khazaei used inexpensive, non-toxic trichloro-1,3,5-triazinane-2,4,6-trione (TCCA) and 1,3-dichloro-5,5-dimethyl hydantoin (DCDMH) as a catalyst for the three-component reaction of *β*-naphthol **129**, aromatic aldehyde **130**, and substituted amide **131** to give 1-carbamato-alkyl-2-naphthol derivatives **132** under solvent-free reaction condition[103] (**Scheme 1.39**). Aromatic aldehydes bearing both electron-donating and electron-withdrawing functional groups react smoothly under this solvent-free condition However, the aldehydes bearing electron-withdrawing groups afforded the lower yields.



Scheme 1.39. Three-component one-pot synthesis of 1-carbamato-alkyl-2-naphthol derivatives

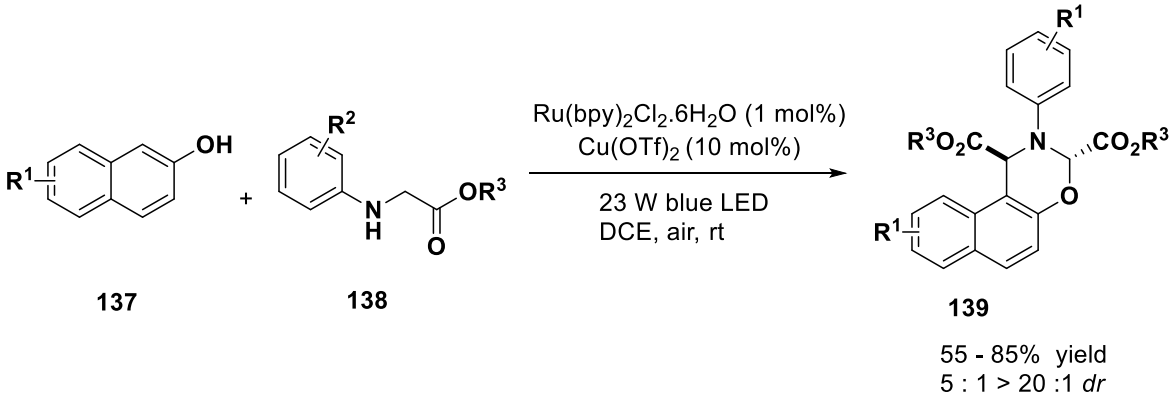
Choghamaran *et al.* disclosed a new catalytic method by utilizing the melamine-Br_3 as an effective catalyst for accessing 1-amidoalkyl-2-naphthol derivatives **136** *via* the one-pot multi-component condensation of 2-naphthol **133** with aromatic aldehydes **134** and acetamide/thioacetamide **135** under solvent-free conditions (**Scheme 1.40**).[104] This process has several benefits over currently used approaches, it offers high yield and a quick reaction time. Additionally, the catalytic system is simple to prepare, very effective, and environmentally benign.



Scheme 1.40. Melamine-Br_3 catalyzed amido alkylation of *β*-naphthol

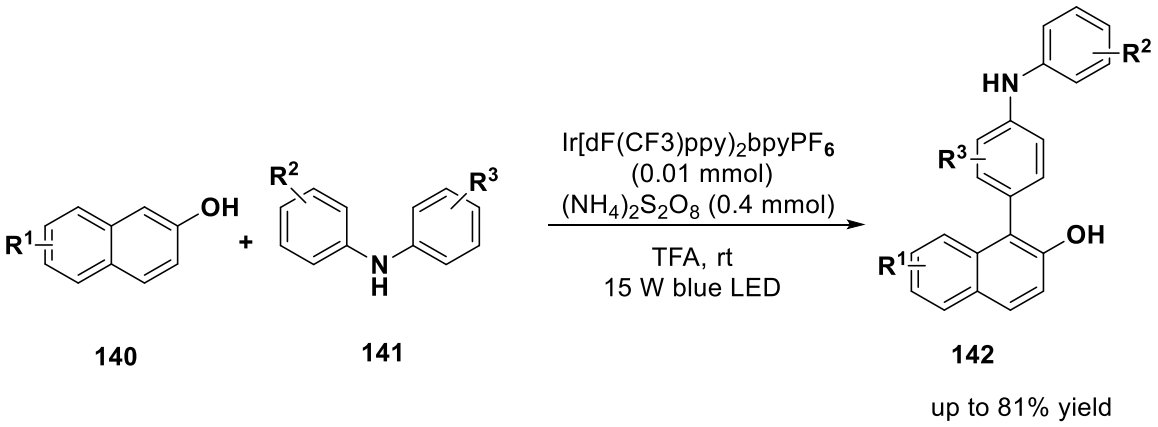
1.4.5. Visible light-induced reactions

Li *et al.* reported a novel strategy for the synthesis of 1,3-benzoxazines **139** through the CDC of glycine esters **138** with *β*-naphthols **137**, through the synergistic fusion of photoredox and Lewis acid catalysis (**Scheme 1.41**).[105] Under benign reaction conditions, several 1,3-benzoxazines **139** were produced in good yields and with good diastereoselectivities Moreover, the reaction demonstrates excellent functional group tolerance and scalability. Further, this protocol expands the synthetic toolbox for accessing 1,3-benzoxazines.



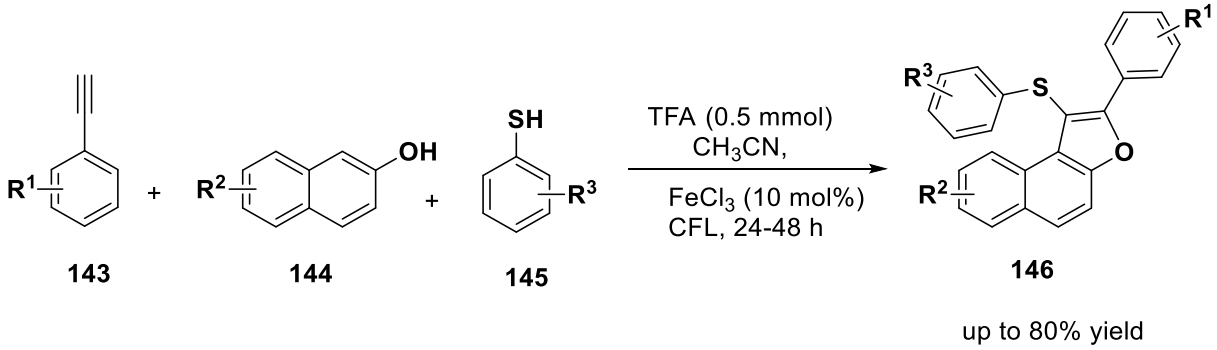
Scheme 1.41. Photoredox synthesis of 1,3-benzoxazines.

Xia *et al*. with the aid of a photocatalyst and blue LED irradiation developed the direct cross-dehydrogenative coupling reaction between 2-naphthol derivatives **140** and aniline **141** /phenol derivatives.[106] Non-symmetrical atropisomers biaryl compounds **142**, especially those of the BINOL type, can be easily accessed using this strategy (**Scheme 1.42**). Further, this procedure provides an efficient and easy route to synthesize nonsymmetrical atropisomeric biaryls, which are frequently present in natural products and materials science applications.



Scheme 1.42. Visible light induced cross-dehydrogenative coupling of 2-naphthol.

Shah *et al.* developed a visible-light-mediated approach for the construction of diverse naphthofurans **146** *via* oxidative annulation of naphthols **144** with alkynes **143** and thiols **145** (**Scheme 1.43**).[107] The reaction depends on the *in situ* generation of an electron donor-acceptor pair between thiophenol and phenylacetylene, which acts as the light-absorbing system. The approach makes it simpler to convert 1,4-naphthoquinone, 1,4-naphthol, and 1-naphthol into a range of highly functionalized naphthofurans.



Scheme 1.43. Visible-light-mediated synthesis of naphthofurans.

1.5 Summary and Outline of the Thesis

The exploration of organic conjugates has unveiled a rich and vast array of opportunities in chemistry, enabling advancements across various disciplines. Improved organic synthesis techniques for these conjugates offer numerous benefits over traditional approaches in terms of efficiency, selectivity, and sustainability, with increased reaction rates, easier purification

processes, and the ability to access diverse chemical entities for the discovery of new therapeutic agents and the development of advanced materials.

Indole and naphthol frameworks are the privileged substructures owing to their prevalence in natural products and pharmaceutically active compounds. The direct functionalization of indoles and naphthol derivatives provides a powerful tool for the synthesis of functionalized indoles and naphthols with diverse biological activities and other potential applications in various fields. In this context, we have explored the synthesis, functionalization, and applications of indole and naphthol-appended conjugates. The classical methods for synthesizing indole and naphthol appended conjugates are discussed, followed by an overview of modern approaches that have emerged in recent years. The functionalization strategies and various applications of indole and naphthol conjugates in diverse fields are also presented.

We synthesized a range of functionalized indole-appended dihydronaphthalenone hybrid analogues screened for antibacterial and antitubercular activities. We successfully identified a novel structural class that inhibits a set of organisms with very low minimum inhibition concentrations The details of the synthesis and application are the subject matter of the second chapter. The utilization of Ethylbenzene hydroperoxide (EBHP) as an oxidizing agent for the epoxidation of oxindole chalcones to access the synthesis of spiro-epoxy oxindoles is demonstrated in the third chapter. The fourth chapter uncovers the visible-light-induced radical hydroarylation of terminal alkynes with naphthols and phenols using pyrylium salt as a photocatalyst.

1.6. References

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$Sc(OTf)_3$ Catalyzed Michael Addition of Indoles to Access Dihydronaphthalenone Indole Hybrids

2.1 Abstract

A new series of indole-appended dihydronaphthalenone analogues **(38a-n)** have been synthesized through the Lewis acid-catalyzed Michael addition of indoles to the arylidene/ hetero arylidene ketones. The synthesized compounds were subjected to antibacterial and antitubercular screening. Among the synthesized compounds, the minimum inhibition concentration of **38l** (against *E.coli*) and **38o** (against *E.coli* & *S.aureus*) was found to be as low as 3.12 µg mL^{-1} as compared to the standard antibacterial drug Ciprofloxacin 2 µg mL^{-1}. In anti-tubercular activity, compounds **38o** and **38p** with minimum inhibition concentration 6.25 µg mL^{-1} were found to be more potent analogues when compared with the drugs pyrazinamide 4 µg mL^{-1} and streptomycin 6 µg ml^{-1}. Compounds **38i**, **38j**, **38m** and **38n** also showed promising activity against the group of organisms tested. These indole-appended dihydronaphthalenone scaffolds represent a promising template for medicinal chemistry research. Its unique structure, ease of synthesis, and diverse pharmacological activities make it an attractive platform for the design and development of novel drug candidates.

2.2 Introduction

In recent decades, heterocyclic structures have become prominent structural units in the realm of drug discovery.[1] As they constitute to be key building blocks in medicinal chemistry. Currently, more than 90% of the approved drugs in the market are from heterocyclic derivatives.[2] Among the various heterocyclic structures, indole scaffolds are ubiquitous features of natural and synthetic origin drugs. Continued attention has been focused on heterocyclic compounds owing to their major roles in biological processes and pharmaceuticals.[2–5] Among the important heterocycles, novel scaffolds containing

naphthalenone have been identified as one of the privileged structures in drug discovery.[6,7] Due to their significant roles in biological processes and medications, heterocyclic compounds have received attention and ongoing research in recent years. And the novel scaffolds incorporating naphthalenone have been found as one of the preferred structures in drug discovery. Perrone *et al*. established Napamezole as an α_2-adrenergic receptor antagonist and a selective inhibitor of 5-hydroxytryptamine re-uptake of both *invitro* and *invivo.*[8, 9] Alex and coworkers designed naphthalenyl-dihydroimidazoles with the inspiration of Napamezole based hybrid library which suggested that the potential antidepressants can display combined α_2-adrenoceptor antagonist and monoamine uptake inhibitor properties.[10, 11] Mephtetramine represents yet another generation of new psychoactive substances.[12] Liu *et al.* discovered a series of novel naphthalenyl pyrimidinones as potent HIV-1 inhibitors.[13] **(Figure 2.1).** On the other hand, structurally diverse indole appended analogues are widely distributed in nature and serve as a core component in numerous bioactive molecules.[14] And claimed to exhibit a vital role in various biological activities, including antimicrobial, antiviral, anti-inflammatory, analgesic, and CNS depressant properties etc.[15, 16]

We presumed that the fusion of the indole and dihydronaphthlenone moieties creates a novel chemical scaffold with enhanced biological potential.[17, 18] Indole-appended dihydronaphthlenones offer a wide range of opportunities for the development of new drug candidates, as they combine the desirable properties of both parent compounds.[19, 20] This structural modification can lead to improved drug-like properties, increased potency, and expanded pharmacological profiles.[21, 22] Additionally, indole-appended tetralones can find applications in material science and catalysis.[23, 24] The unique electronic and structural features of these compounds make them potential candidates for designing organic materials with tailored properties, such as optoelectronic materials or catalysts for various chemical transformations.[25, 26] The functional groups present on the indole and tetralone frameworks can be further modified to introduce specific functionalities, enabling fine-tuning of the desired material characteristics.[27, 28]

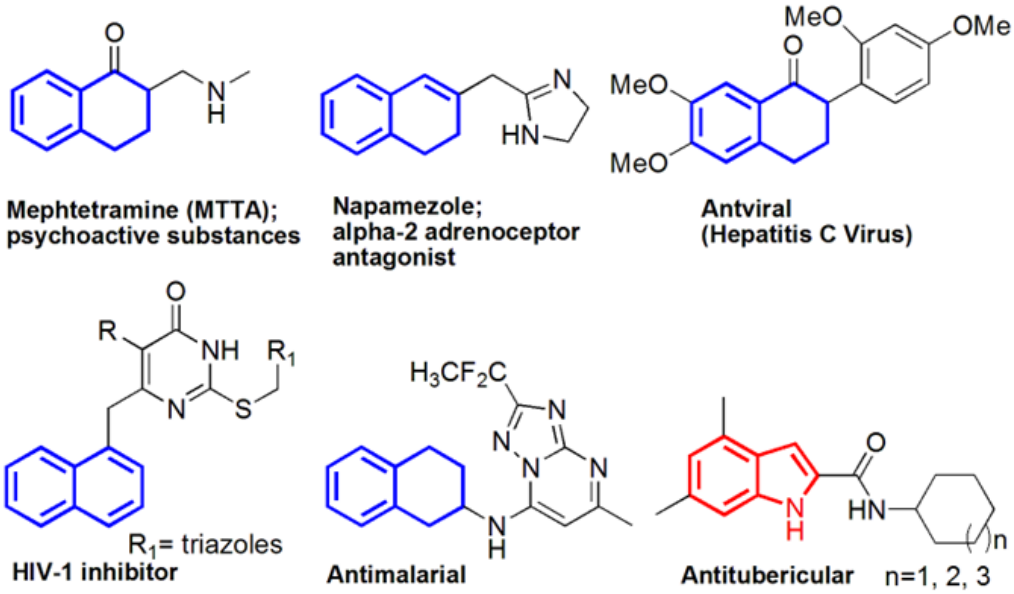


Figure 2.1: Selected pharmaceutically important naphthalenone-derived bio-actives.

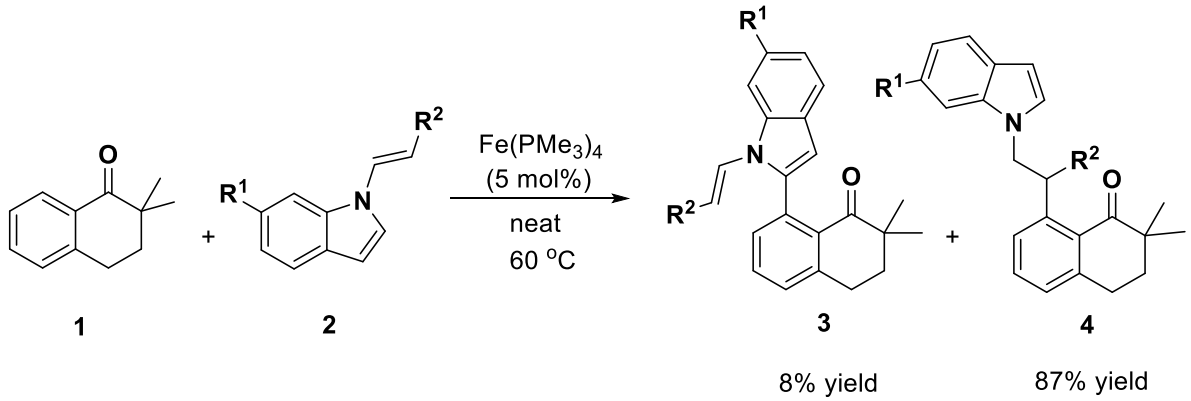
Noteworthily, previous research in our laboratory led to the discovery of a series of novel indole analogues possessing excellent antimicrobial, antioxidant and anticancer activities.[29,30] Most interestingly, a more recent literature survey has revealed that the incorporation of a thiophene moiety can significantly enhance the antimicrobial activity of candidate compounds.[31–33]

Prompted by the above consideration, and as a part of our ongoing research on developing novel scaffolds with more effective antimicrobial activity, we assumed that incorporating indole scaffold into arylidene and hetero arylidene naphthalenones through the molecular hybridization approach might be an effective strategy for discovering novel hybrid nucleus with potential bioactivity. Therefore, in the present work, we described a facile and convenient synthesis and antimicrobial, anti-tubercular activities of indole appended dihydro naphthalenone bearing various substituted aryl and thiophene rings, which, to the best of our knowledge, have not yet been reported.

2.2.1. Synthetic approaches towards indole appended naphthalenones

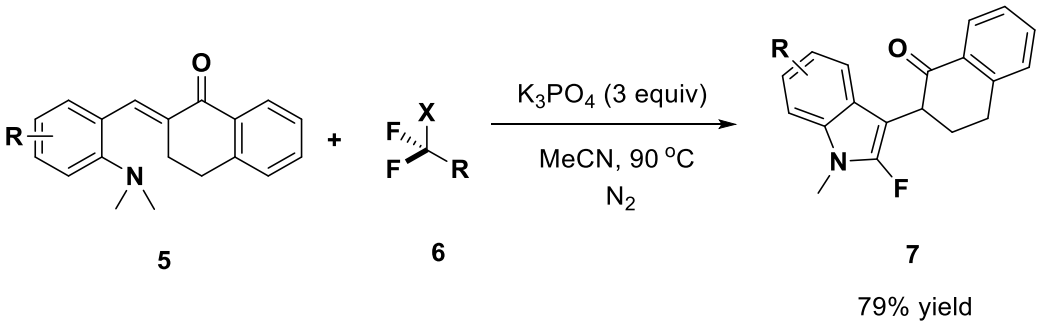
$Fe(PMe_3)_4$ catalyzed *ortho*-selective C-H alkylation of aromatic ketones with *N-alkenyl indoles* is developed by Kimura *et al*. In this enviable work, they successfully demonstrated the C-H alkylation of 2,2-dimethyl-1-tetralone **1** with substituted *N-vinyl indoles* **2**.

Furthermore, this reaction also produced an indolylation product **3** as a minor product, which is considered to be formed *via* 1,4-iron migration from the iron alkyl intermediate. The enticing feature of this technique is that it produces the aspired products in good yield under neat conditions. **(Scheme 2.1)**.[34]



Scheme 2.1. Fe- catalyzed *ortho*-selective C-H alkylation of aromatic ketones

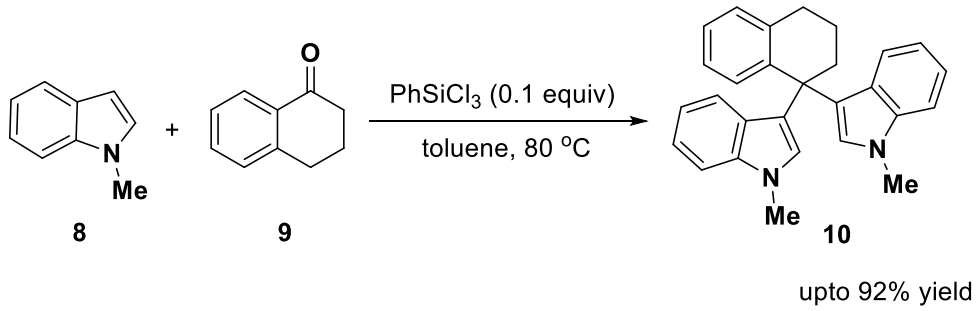
Su *et al*. developed a straightforward synthetic approach to access 2-fluoro indoles **7** from ortho-vinyl anilines **5.** This strategy enables the construction of indole scaffolds alongside the incorporation of fluorine atoms on the C2 position in a formal [4+1] cyclization from easily accessible *ortho*-vinyl anilines **5** and difluorocarbene **6**. Additionally, this reaction occurs under mild conditions without any transition metals or oxidants **(Scheme 3.2)**.[35]



Scheme 2.2. Base-catalyzed synthesis of 2-fluoroindole

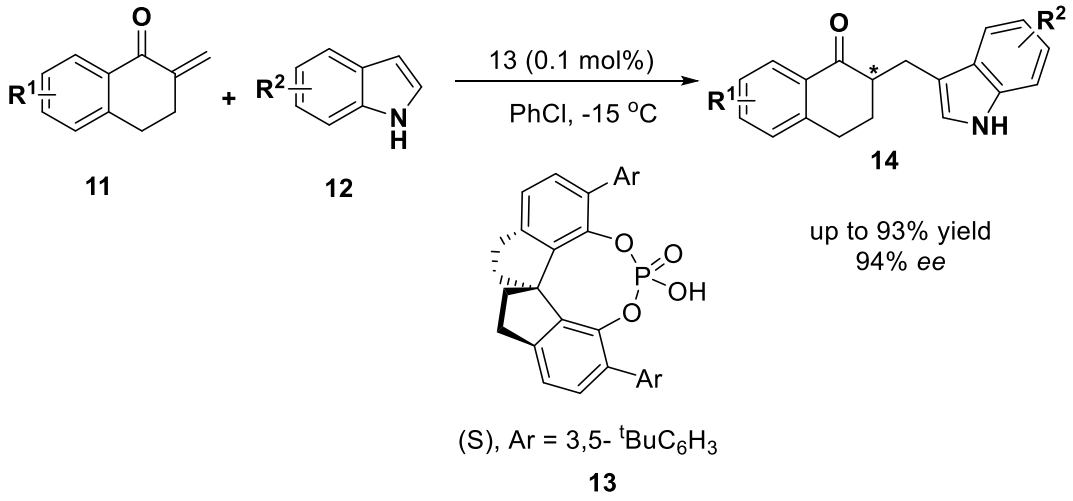
Bis(indolyl)methanes bearing an all-carbon quaternary centre are prevalent in a broad range of natural products and biologically active compounds. To create bis(indolyl)methanes **10** containing all-carbon quaternary centres, Lee *et al*. established a Lewis acid-catalyzed strategy involving the two-fold addition of indoles **8** to ketones **9**. In addition, they also

demonstrated the scope of this reaction for the various ketones ranging from dialkyl ketones to diaryl ketones. This process advances by the formation of tertiary alcohol as an intermediate and followed by the release of water. In addition, they also showed the utilization of the obtained bis(indolyl)methanes for constructing various indole-fused aromatic polycycles and bis(indolyl)alkenes**(Scheme 2.3)**.[36]



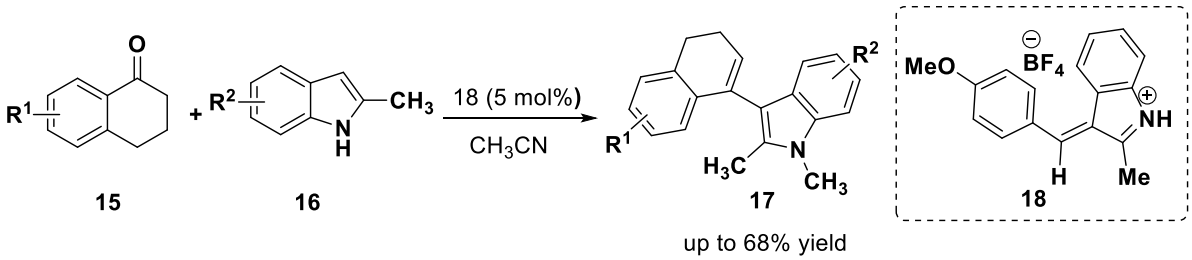
Scheme 2.3. PhsiCl$_3$ catalyzed synthesis of bis(indolyl)methanes

Li *et al.* reported a chiral spiro phosphoric acid **13** catalyzed Friedel-Crafts conjugate addition of indoles **12** to exocyclic enones **11**. This protocol is highly enantioselective (up to 98% *ee*) and facilitates to furnish of indole-containing cyclic ketones with an α-chiral centre **14**. In addition to this, the protocol is extended to various other exocyclic enones and substituted pyrroles to offer the corresponding products in good yields with similar enantioselectivity. **(Scheme 2.4)**.[37]



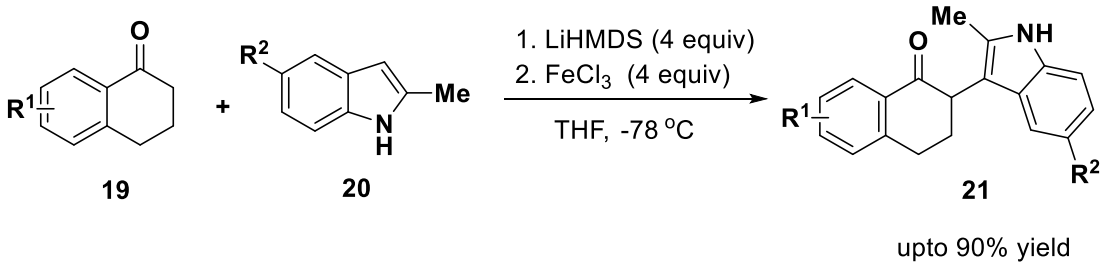
Scheme 2.4. Chiral spiro phosphoric acid catalyzed conjugate addition of indoles

Barbero's group reported an intriguing protocol for synthesizing 3-vinyl indoles **17** through a clean dehydrative coupling reaction between ketones **15** and indoles **16.** Herein, highly stable and non-nucleophilic aryl(2- methyl indol-3-yl)methylium salts **18** are utilized as efficient Lewis acid catalysts for this transformation. (**Scheme 2.5)**.[38]



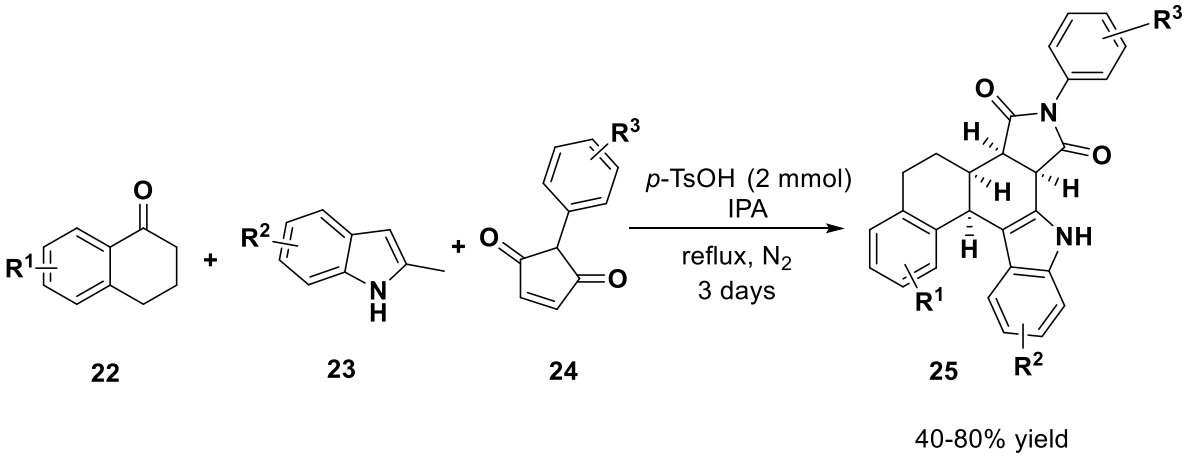
Scheme 2.5. Organic salt catalyzed synthesizing 3-vinyl indoles

Lu *et al.* presented an approach for iron-catalyzed direct oxidative coupling of C2-substituted indoles **20** and tetralones **19** to obtain indole-appended dihydronaphthalenone motifs **21**. This reaction worked well for a wide range of substrates in affording the corresponding products in moderate to good yield. Thus, formed compounds exhibited promising anticancer properties in various cell lines and can able to overcome multidrug resistance in KB/VCR cells in preliminary biological evaluation **(Scheme 2.6)**[39]



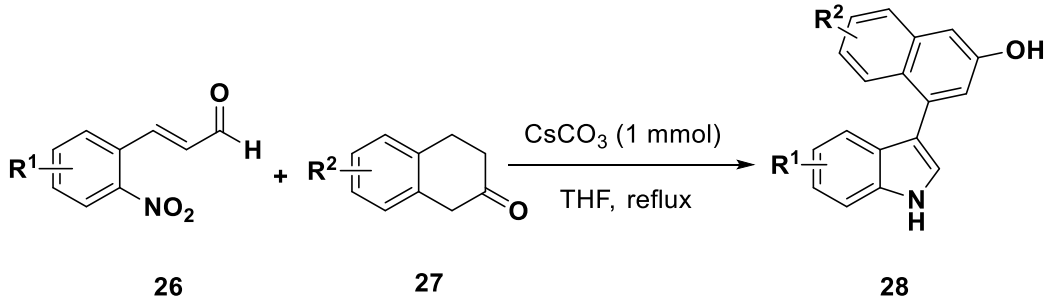
Scheme 2.6. Fe catalyzed synthesis of indole-appended dihydronaphthalenone.

Noland *et al*. reported an astounding one-pot protocol for synthesizing tetrahydrocarbazoles. Herein, vinyl indole obtained from the acid-catalyzed condensation of indole **23** with 1-tetralones **22** undergoes subsequent cyclisation with dienophile *N-phenyl maleimides* **24** in isopropyl alcohol to yield annulated tetrahydro carbazoles **24**. This sequence of condensation and Diels-Alder reactions were performed at reflux conditions in isopropyl alcohol in the presence of *p*-TsOH (**Scheme 2.7**).[40]



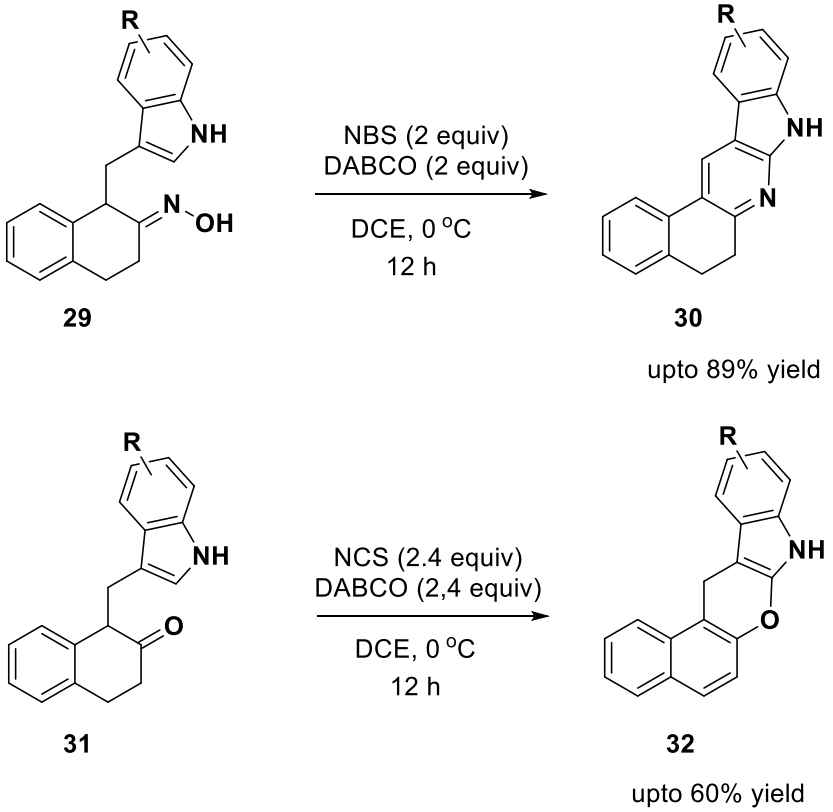
Scheme 2.7. PTSA catalyzed the synthesis of tetrahydrocarbazoles.

To synthesize polysubstituted 3-naphthyl indole **28,** Poudel *et al*. demonstrated a transition metal-free reaction of readily accessible 2-nitrocinnamaldehydes **26** with *β*-tetralones **27**. They additionally expanded this approach to build 3-naphthylbenzo[*g*]indole fluorophores. This oxidative cross-coupling reaction occurs with a mild base at reflux condition in THF solvent **(Scheme 2.8)**.[41]



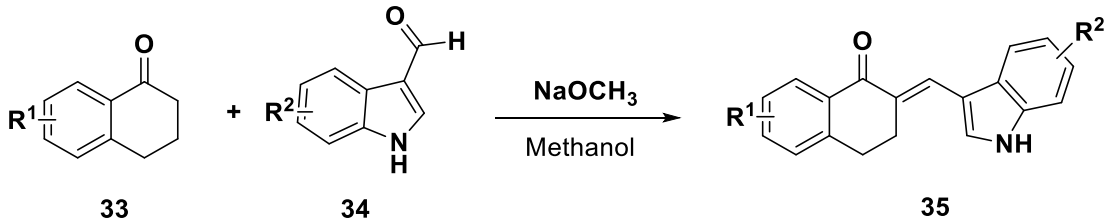
Scheme 2.8. $CsCO_3$ catalyzed synthesize polysubstituted 3-naphthylindole.

By utilising NBS to catalyze the intramolecular oxidative cyclization/aromatization of *β*-tetralone oximes **29**, Jiang *et al*. successfully synthesized fused polycyclic molecules *α*-Carbolines containing (pyrido[2,3-*b*]indole) **30**. additionally, When NCS is employed as a catalyst, it facilitated the cyclization and aromatization of *α* -((indol-3-yl)methyl)-tetralone **31** to produce benzo[5,6]chromeno[2,3-b]indoles **32**. This reaction features mild reaction conditions **(Scheme 2.9)**.[42]



Scheme 2.9. NBS catalyzed the synthesis of indole-fused polycyclic compounds.

Wang *et al*. synthesized a novel class of indole appended tetralone chalcones by Claisen-Schmidt condensation reaction of tetralones **33** with indole carboxaldehyde **34**. Their findings offered credence to the investigation of indolyl-tetralone chalcones **35** as a novel structural template for the development of anticancer therapeutics for cancers harbouring KRAS mutations, such as A549 lung cancer cells (**Scheme 2.10)**.[43]



Scheme 2.10. Synthesis of indole appended tetralone chalcones.

2.3. Background to the present work

The construction of indole-appended tetralones provides a simplified approach to accessing valuable natural product scaffolds.[10,44] We assumed that incorporating indole scaffold into arylidene and hetero arylidene naphthalenones through the molecular hybridization approach might be an effective strategy for discovering novel hybrid nuclei with potential bioactivity.

We focus on the indole-appended tetralone scaffold and explore its potential as a valuable template for the design and synthesis of novel drug candidates. Therefore, in the present work, we described a facile and convenient synthesis and antimicrobial, anti-tubercular activities of indole appended dihydro naphthalenone bearing various substituted aryl and thiophene rings which, to our knowledge, have not yet been reported.

2.4. Results and Discussion

2.4.1 Chemistry

In our initial design, we postulated that *α,β*-unsaturated arylidene and hetero arylidene tetralones can undergo Lewis acid catalyzed Michael addition with indoles **(36a-i)** at room temperature to yield the indole appended dihydro naphthalene hybrid analogues. We started our investigation by stirring a mixture of 0.1982 mmol of (*E*)-2-(4-fluoro benzylidene)-3,4-dihydronaphthalen-1(2*H*)-one **(36e)** with 1equivalence of 5-methoxy-1*H* indole **(37g)** in presence of 5 mol% of Sc(OTf)$_3$ under Argon atmosphere. After 14 hours we obtained the product 2-((4-fluorophenyl)(5-methoxy-1*H*-indol-3-yl)methyl)-3,4-dihydronaphthalen-1(2*H*) in 20% yield. The resulting product was characterized by various spectroscopic analyses such as ^{1}H NMR, ^{13}C NMR, and HRMS spectroscopy. In the ^{1}H NMR one proton singlet at δ 8.00 indicates the presence of the NH group from the indole moiety and a three proton singlet at δ 3.77 confirmed the presence of the methoxy group from the indole moiety. Further, two proton multiplet at δ 2.96 corresponds to the two benzylic protons from tetralone moiety (**Figure 2.2**). It is further confirmed by the ^{13}C NMR spectrum, a signal appeared at δ 198.2 in ^{13}C NMR corresponds to the carbonyl carbon from the tetralone. Further, a signal at δ 55.3 corresponds to carbon from the methoxy functional group. (**Figure 2.3**). Additionally, the mass spectrometric data was also in good agreement with the exact mass of the product. Further, the

single crystal X-ray structure unambiguously confirmed the product as 2-((4-fluorophenyl)(5-methoxy-1*H*-indol-3-yl)methyl)-3,4-dihydronaphthalen-1(2*H*) (**Figure 2.4**).

To develop a convenient method for better yield of the products, we tried to optimized-optimize the reaction by considering different Lewis acids, various solvents and temperature parameters etc. Then we experimented with DCM solvent by loading 5 mol% $Sc(OTf)_3$ and failed to obtain the aspired product even in traces(**Table 2.1 entry 2**). Further attempts made by employing $Cu(OTf)_2$, $Zn(OTf)_3$ and $Zr(CpCl_3)$ in DCM solvent at room temperature also failed to form the aspired product (entry 1,3,4). Then again, we switched the solvent system to CH_3CN and performed the reaction in the presence of 10 mol% of $Sc(OTf)_3$ at room temperature after 14 hours delightfully the anticipated product was formed in 66% yield (entry **6**). Further investigation was done in the presence of 10 mol%. $Zr(CpCl_3)$, $Zn(OTf)_3$, and $Cu(OTf)_2$ in CH_3CN and in all these trials only 10 mol%. $Zn(OTf)_3$ in CH_3CN offered the product in 30% yield along with some complex byproducts (entry 8). Additionally, the attempts made at an elevated temperature 60 ^oC also failed to enhance the product formation (entries 10-14).

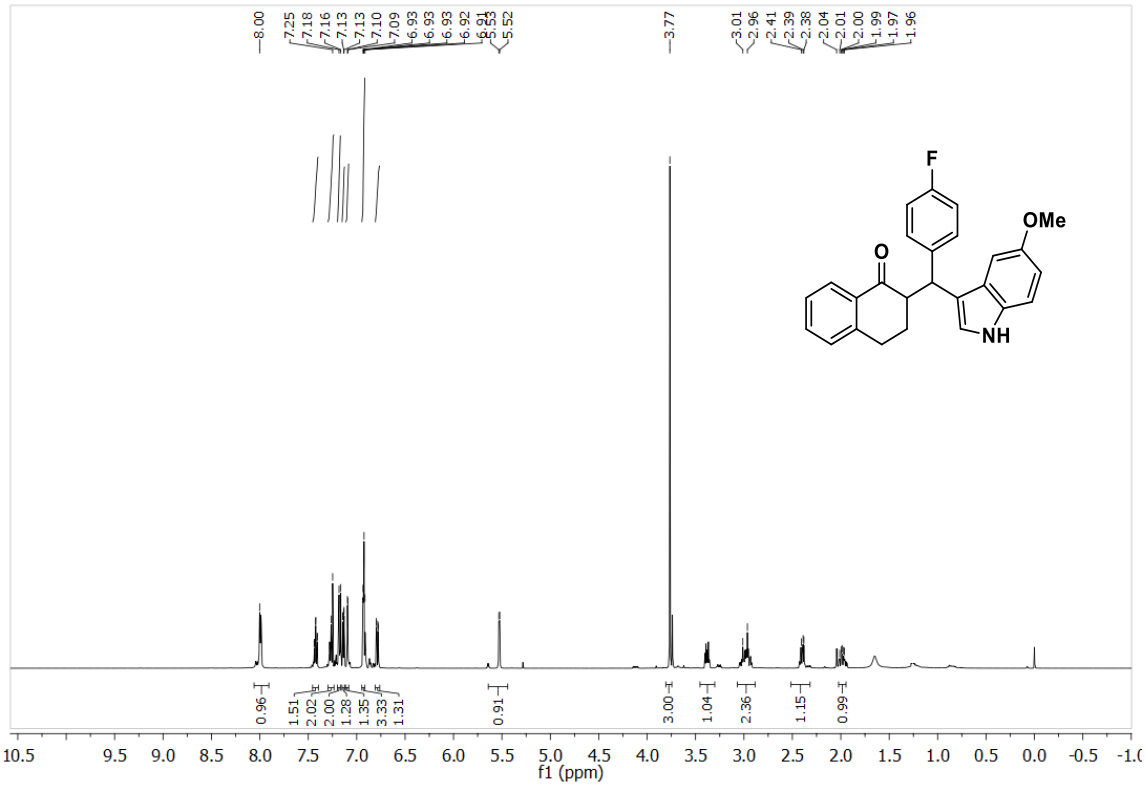


Figure 2.2. ^{1}H NMR of 38r in $CDCl_3$

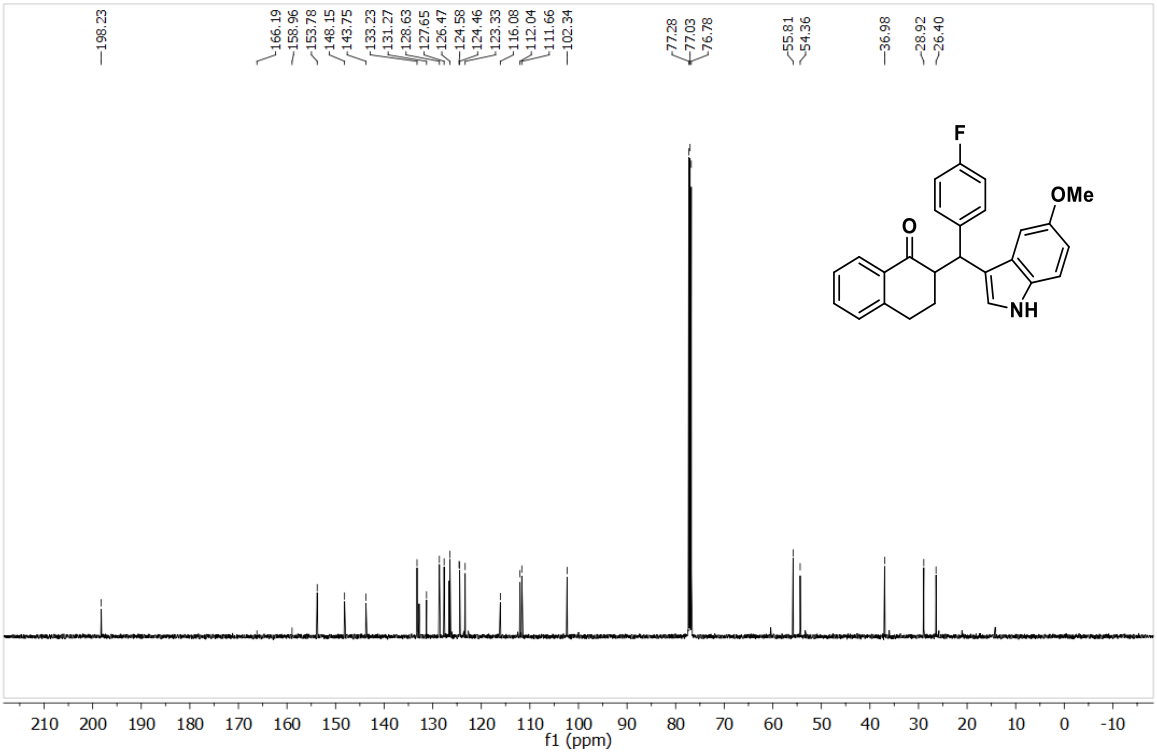


Figure 2.3. ^{13}C NMR of 38r in $CDCl_3$

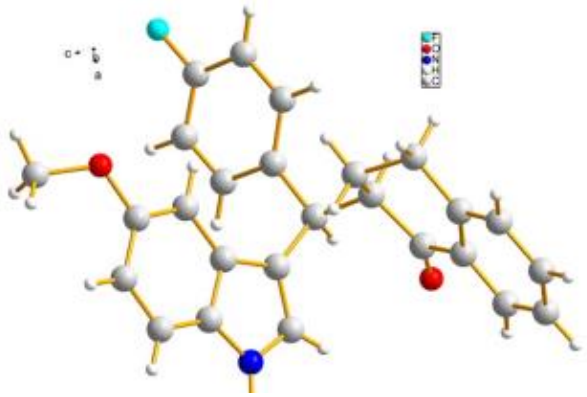
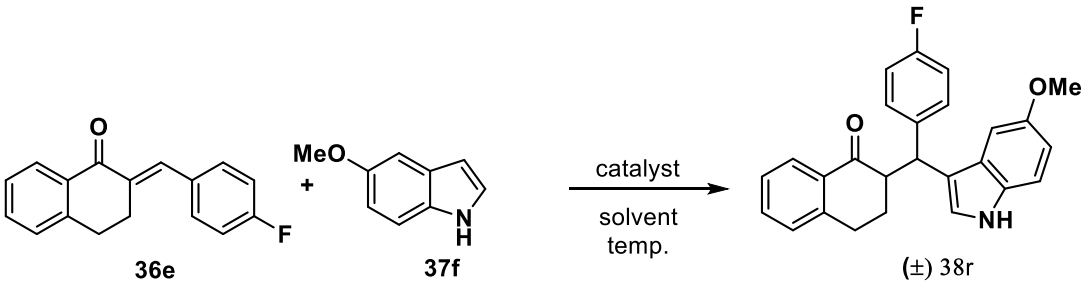


Figure 2.4. X-ray crystal structure of 38r (**CCDC 152120**)

From the optimization table, using an equimolar combination of tetralone chalcone and substituted indole in the presence of 10 mol% $Sc(OTf)_3$ in CH_3CN as standard optimized reaction condition (entry 6). We successfully synthesized a library of indole-appended dihydronaphthalenone bearing various substitutions on both indoles and dihydronaphthalenones. Arylidene tetralones bearing different functional groups such as -F, -Cl, -Br, $-CH_3$, $-OCH_3$ reacted smoothly with the various indoles with diverse substitutions to give indole appended dihydronapthalenones in moderate to good yield. Further, we also extended the scope of this protocol for the hetero arylidene tetralone chalcones bearing thiophene and furan rings. These heteroarylidene-substituted dihydronaphthalenones also reacted smoothly to afford the corresponding products in good yield.

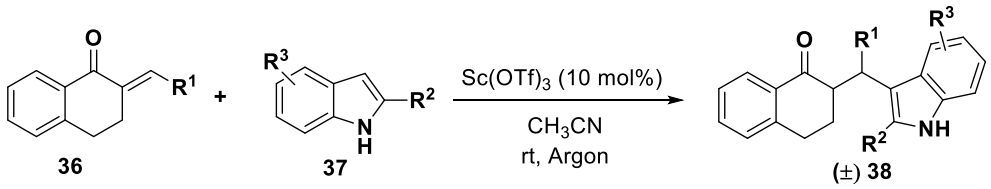
Table 2.1. Optimization of reaction conditions [a]



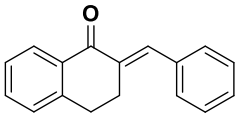
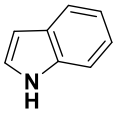
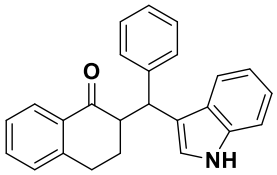
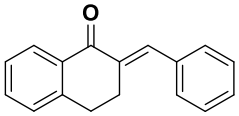
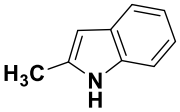
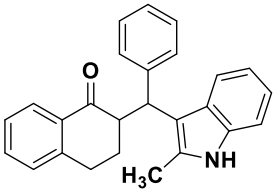
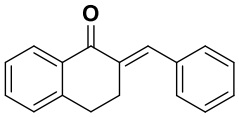
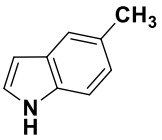
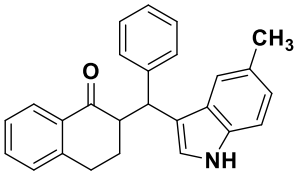
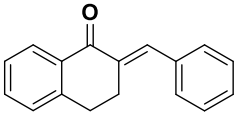
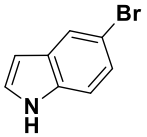
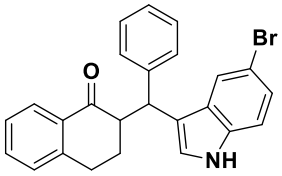
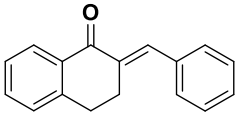
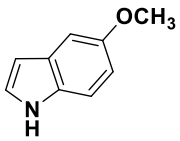
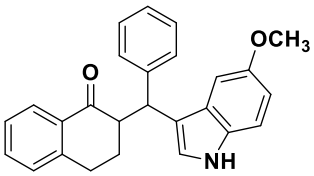
Entry	Catalyst	Solvent	Temperature (^{o}C)	Time (h)	Yield(%)[c]
1	$Cu(OTf)_2$	DCM	rt	14	no reaction[b]
2	$Sc(OTf)_3$	DCM	rt	14	no reaction[b]
3	$Zn(OTf)_2$	DCM	rt	14	no reaction[b]
4	$Zr(CpCl_3)$	DCM	rt	14	no reaction[b]
5	$Cu(OTf)_2$	CH_3CN	rt	14	no reaction
6	$Sc(OTf)_3$	CH_3CN	rt	14	66
7	$Sc(OTf)_3$	CH_3CN	rt	14	20[b]
8	$Zn(OTf)_2$	CH_3CN	rt	14	30
9	$Zr(CpCl_3)$	CH_3CN	rt	14	no reaction
10	$Cu(OTf)_2$	CH_3CN	60	14	trace
11	$Sc(OTf)_3$	CH_3CN	60	14	trace
12	$Zn(OTf)_2$	CH_3CN	60	14	trace
13	$Zr(CpCl_3)$	CH_3CN	60	14	trace

Standard reaction conditions: *conditions* unless otherwise mentioned (*E*)-2-benzylidene-3,4-dihydronaphthalen-1(2*H*)-one (**3a**) (0.1280 mmol), 1*H*-indole(**4a**), (0.1280 mmol), catalyst (10 mol%), solvent (3mL), were stirred in a Schlenk tube for 14 hours under argon atmosphere. [b]5mol% catalyst is used *isolated* yield.

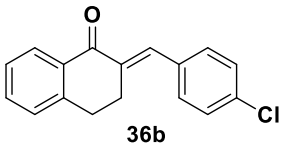
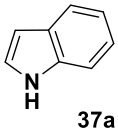
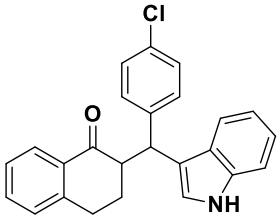
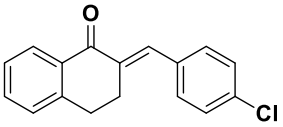
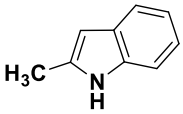
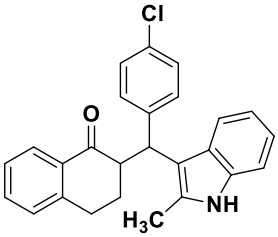
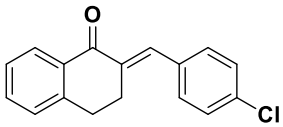
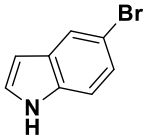
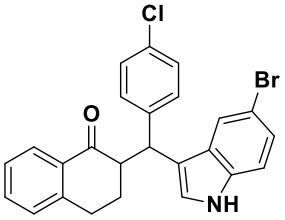
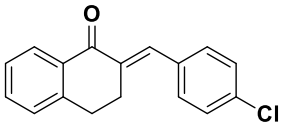
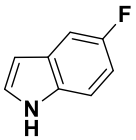
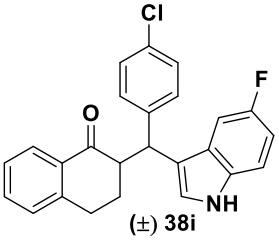
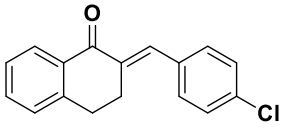
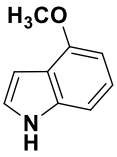
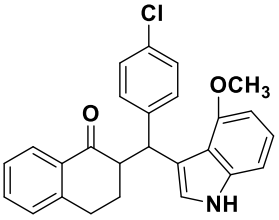
Table 2.2. Scope of the reaction



36 37 (±) 38

Entry	Arylidenetetralone	Indole	Product	Yield [%]
1	 36a	 37a	 (±) 38a	66
2	 36a	 37b	 (±) 38b	59
3	 36a	 37c	 (±) 38c	65
4	 36a	 37d	 (±) 38d	65
5	 36a	 37e	 (±) 38e	72

……...continued **Table 2.2.**

Entry	Arylidenetetralone	Indole	Product	Yield [%]
6	 36b	 37a	 (±) 38f	70
7	 36b	 37b	 (±) 38g	72
8	 36b	 37c	 (±) 38h	61
9	 36b	 37d	 (±) 38i	62
10	 36b	 37e	 (±) 38j	76

……...continued **Table 2.2.**

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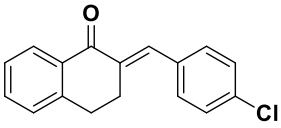
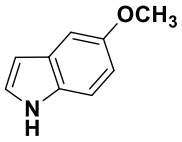
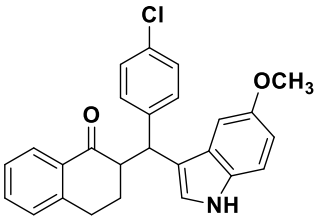
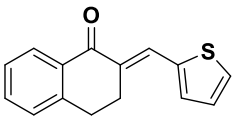
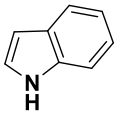
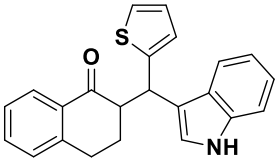
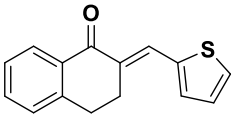
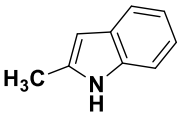
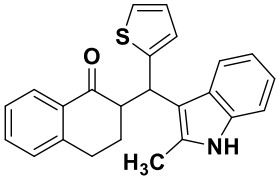
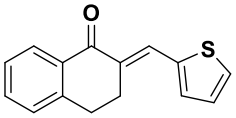
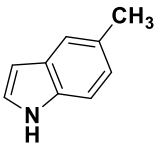
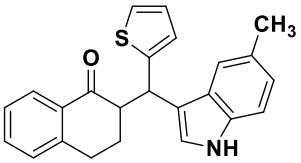
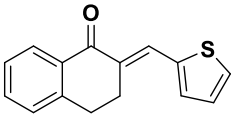
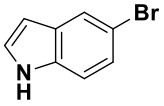
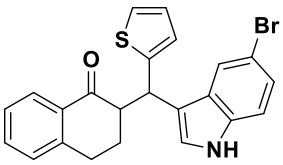
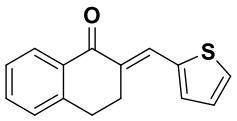
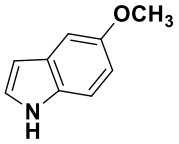
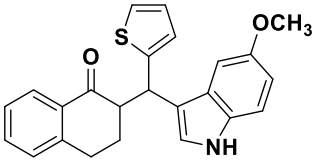
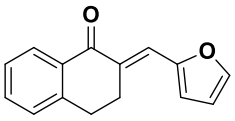
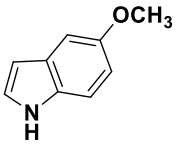
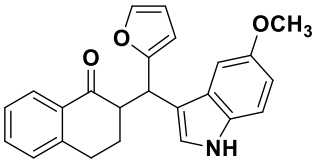
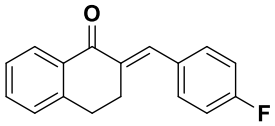
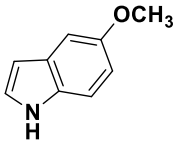
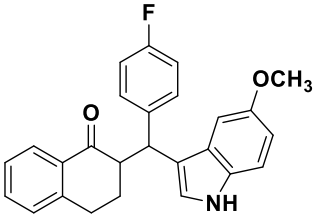
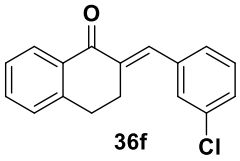
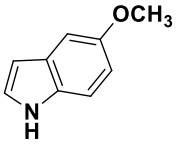
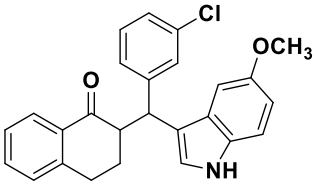
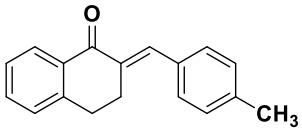
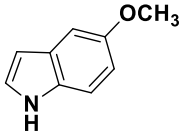
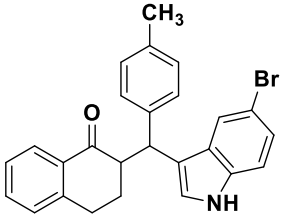
11	 36b	 37f	 (±) 38k	52
12	 36c	 37a	 (±) 38l	63
13	 36c	 37b	 (±) 38m	69
14	 36c	 37c	 (±) 38n	69
15	 35c	 36d	 (±) 38o	

……...continued **Table 2.2.**

Entry	Arylidenetetralone	Indole	Product	Yield [%]
16	 **36c**	 **37f**	 **(±) 38p**	54
17	 **36d**	 **37f**	 **(±) 38q**	51
18	 **36e**	 **37f**	 **(±) 38r**	67
19	 **36f**	 **37f**	 **(±) 38s**	70
20	 **36g**	 **37f**	 **(±) 38t**	43

2.4.2 Biological evaluation

All the synthesized compounds have been evaluated for antibacterial and antitubercular activity. The antibacterial activity was performed against two Gram-positive (*Staphylococcus aureus-MTCC 902* and *Staphylococcus epidermidis-MTCC 435*) and three Gram-negative (*E. coli-MTCC 2622*, *Salmonella typhi-MTCC 3216*, and *Klebsiella pneumoniae-MTCC 109*) bacteria using Ciprofloxacin as standard.

Table 2.3: Antibacterial and Antitubercular Evaluation

Compound	MIC in µg mL^{-1}					
	E. coli	***S. typhi***	***S. aureus***	***K. pneumonia***	***S. epidermis***	***M. tuberculosis***
38a	100	> 100	50	> 100	> 100	> 100
38b	> 100	> 100	> 100	> 100	> 100	> 100
38c	> 100	> 100	> 100	> 100	> 100	> 100
38d	50	100	50	> 100	> 100	> 100
38e	50	50	25	> 100	> 100	50
38f	50	50	25	> 100	> 100	> 100
38g	50	100	50	> 100	> 100	> 100
38h	50	100	25	> 100	> 100	100
38i	12.5	50	25	> 100	100	50
38j	12.5	25	12.5	> 100	100	12.5
38k	25	50	50	> 100	> 100	25
38l	3.12	6.25	12.5	50	12.5	25
38m	12.5	25	12.5	100	50	12.5
38n	12.5	25	12.5	100	50	12.5
38o	3.12	12.5	3.12	50	12.5	6.25
38p	3.12	25	3.12	100	100	6.25
38q	12.5	25	12.5	> 100	> 100	25
38r	12.5	25	> 100	> 100	> 100	25
38s	50	50	25	> 100	> 100	> 100
38t	50	100	100	> 100	> 100	> 100
Ciprofloxacin	2.5	2.5	2.5	2.5	2.5	5
Pyrazinamide	-	-	-	-	-	5
Streptomycin	-	-	-	-	-	5

Among the tested compounds **38i–38r** showed better activity against *E. coli*, *S. typhi*, and *S. aureus* and **38l -38o** also showed better activity against *S. epidermidis* selectively with very low MIC range (12.5–50 μg/mL). In contrast, against *K. pneumonia*, none of the compounds has shown inhibition potency. Compounds **38a-38h** exhibited very poor inhibition properties against all five organisms, especially *K. pneumoniae* and *S. epidermidis*. In comparison with the substituted aryl ring, thiophene derivatives showed the highest activity. Among the various substitutions on the indole ring (2nd, 4th, and 5th), 5-F and 4-OMe showed more inhibition and other derivatives showed moderate to less activity. To enhance the minimum inhibition concentration, 5-OMe substituted indole derivatives (**38k**, **38p - 38s**) were synthesized and evaluated. To our delight, we found that compounds **38p**, **38q**, and **38r** are worth exploring for further studies. Among the novel compounds, **38l**, **38o**, and **38p** are found to be most active with a minimum inhibition concentration of 3.12 μg/mL against *E. coli* and *S. aureus.* It is worth noting that most of the compounds exhibited moderate to good inhibition but no clear trend could be summarized.

In antitubercular activity, Pyrazinamide and Streptomycin were used as standard drugs for comparison, compounds **38i-38k** and **38n-38r** have shown promising results with a MIC range of 6.25– 50 μg/mL. In particular, with the least MIC (6.25 μg/mL), compounds **38o** and **38p** are the most potent derivatives of all. Compounds **38j** and **38n** also showed some better tendency of *M. tuberculosis* inhibition. In contrast, compounds **38a–38h**, **38l–38m**, and **38s–38t** showed poor inhibition activity. As in the case of antibacterial results suggested, thiophene appended derivatives **38n-38p** are the compounds to be looked into for further developments whereas **38o** and **38p** are proved to be more potent analogues in inhibiting the *M. tuberculosis*.

2.5. Conclusion

In summary, we have designed and synthesized indole-appended dihydro-naphthalenones by Lewis acid catalyzed facile and convenient process. We successfully identified a novel structural class, which inhibits the set of organisms with very low minimum inhibition concentrations. Among the novel compounds, **38l**, **38o**, and **38p** are the most active with a minimum inhibition concentration of 3.12 μg/mL against *E. coli* and *S. aureus*. While **38o** and **38p** are the more potent analogues in inhibiting *M. tuberculosis*.

Our studies complement new and exciting findings which strongly suggest that the indolylnaphthalenones have real potential in finding suitable "Leads" for the development of antitubercular therapeutics. Further exploration of these scaffolds, including the synthesis of analogues and the evaluation of their pharmacological properties, is expected to uncover valuable insights into the structure-activity relationship and enable the development of potent and selective compounds.

2.6. General experimental methods

2.6.1 Chemistry

All the reactions are performed with commercially available best-grade chemicals without further purification. All the solvents used were reagent grade, column chromatography was performed using 100-200 mesh silica gel and mixtures of hexane-ethyl acetate were used for elution of the products. Melting points were determined on a Buchi melting point apparatus and are uncorrected. Proton nuclear magnetic resonance spectra (^{1}H NMR) were recorded on a Bruker AMX 500 spectrophotometer ($CDCl_3$ as solvent). Chemical shifts for ^{1}H NMR spectra are reported as δ in units of parts per million (ppm) downfield from $SiMe_4$ (δ 0.0) and relative to the signal of chloroform-d. Coupling constants are reported as *J* value in Hz. Carbon nuclear magnetic resonance spectra (^{13}C NMR) are reported as δ in units of parts per million (ppm) downfield from $SiMe_4$ (δ 0.0) and relative to the signal of chloroform-d. Mass spectra were recorded under EI/HRMS at 60,000 resolutions using a Thermo Scientific Exactive mass spectrometer. IR spectra were recorded on Bruker FT-IR spectrometer.

2.7 Experimental procedures

2.7.1 General procedure for the synthesis of 2-arylidene / heteroarylidene-3,4-dihydronaphthalen-1(2*H*)-one (37a-37g)

To a solution of aryl aldehyde or hetero aryl aldehydes (3.5 mmol) in 10 mL of EtOH at 0 ^{0}C was added slowly aqueous NaOH solution (0.5g in 5mL) followed by the slow addition of the 3,4-dihydronaphthalen-1(2*H*)-one (3.5 mmol). The reaction mixture was stirred at 0^0 C and allowed to warm at room temperature with monitoring TLC. The reaction was usually completed in 4 hrs, after diluting the reaction mixture with water, the precipitate was washed with water and then with a minimal amount of diethyl ether to afford a pure product **37.**

2.7.2 General procedure for the Lewis acid catalyzed Michael addition of indoles to the arylidene / hetero arylidene ketones (38a-38t).

Arylidene/hetero arylidene tetralones (**36**), Indole **(37),** and Sc(OTf)$_3$ (10 mol%) are sequentially introduced to an oven-dried Schlenk tube with a magnetic stir bar and a rubber septum is fitted to Schlenk tube and sealed tightly. Then the mixture is degassed using a vacuum pump. This is followed by the addition of 2 mL of dry acetonitrile and argon purge. It was tightly sealed afterwards, and it was left at room temperature overnight to stir. Once the reaction is completed (TLC), remove the solvent under reduced pressure. Product **38** is separated by column chromatography using silica gel with a mesh size of 100–200. Using a 15% combination of hexane and EtOAc as the eluent.

2.7.3. Antibacterial activity

The antimicrobial activities of compounds **(38a-38t)** were determined by the disc diffusion method (CLSI 2012) against bacteria. The test cultures maintained in nutrient agar slant at 4 °C were sub-cultured in nutrient broth to obtain the working cultures approximately containing 1×10^6 CFU/mL. The compounds with various concentrations were incorporated in a 6 mm sterile disc. Mueller Hinton (MH) agar plates were swabbed with each bacterial strain and the test disks were placed along with the control disks. Ciprofloxacin was used as a positive control. Plates were incubated overnight at 37 °C. A clear, distinct zone of inhibition was visualized surrounding the discs. The minimum inhibitory concentration (MIC) of antimicrobial activity of the test agents was determined by measuring the zone of inhibition expressed in mm.

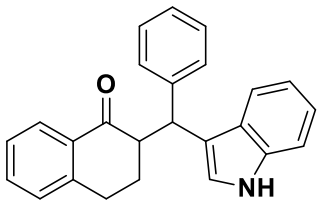
2.7.4. Antitubercular activity

The antitubercular activity of compounds **38a-38t** was assessed against *M. tuberculosis* (ATTC-27294) using the agar microdilution method, where twofold dilutions of each test compound were carried out. Pyrazinamide and Streptomycin were used as standard drugs for comparison. Growth of bacilli was observed after 30 days of incubation at 37 ^oC and minimum inhibitory concentration (MIC) was recorded. Compounds **38j-38o** exhibited promising activity with MIC 6.12 µg mL^{-1}. And the rest of the compounds exhibited moderate to poor activity with MIC 50, 100 and > 100 µg mL^{-1}.

2.8. Characterization data of compounds

Synthesis of 2-((1*H*-indol-3-yl)(phenyl)methyl)-3,4-dihydronaphthalen-1(2*H*)-one (38a)

(*E*)-2-benzylidene-3,4-dihydronaphthalen-1(2*H*)-one, 1*H*-indole and $Sc(OTf)_3$ (10 mol%) are sequentially introduced to an oven-dried Schlenk tube with a magnetic stir bar and a rubber septum is fitted to Schlenk tube and sealed tightly. Then the mixture is degassed using a vacuum pump. This is followed by the addition of 2 mL of dry acetonitrile and argon purge. It was tightly sealed afterwards, and it was left at room temperature overnight to stir. Once the reaction is completed (TLC) remove the solvent under reduced pressure. The product **38a** is separated from column chromatography using silica gel with a mesh size of 100–200. Using a 15% combination of hexane and EtOAc as the eluent in 66% yield.

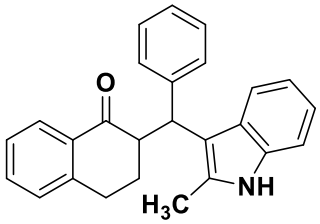


Yield: 66%; IR (KBr, cm^{-1}): 3413, 3050, 3027, 2928, 1670, 1599, 1454, 1337, 1289, 1101, 1024, 921; **^{1}H NMR (500 MHz, $CDCl_3$)**: δ (ppm): 1.96 - 2.04 (m, 1H), 2.38 – 2.41 (m, 1H), 2.96 - 3.01 (m, 2H), 3.37 – 3.39 (m, 1H), 5.53 (d, *J* = 5.0 Hz, 1H), 6.96 (d, *J* = 2.0 Hz, 1H), 7.14 - 7.30 (m, 9H), 7.32 -7.33 (m, 2H), 7.44 - 7.46 (m, 2H), 8.09 (s, D_2O exchangeable NH); **^{13}C NMR (125 MHz, $CDCl_3$):** δ (ppm): 26.3, 28.4, 41.0, 52.8, 112.5, 116.3, 121.8, 122.3, 122.5, 123.7, 124.8, 126.6, 127.6, 127.9, 128.6, 129.0, 130.9, 134.7, 135.9, 136.9, 139.8, 143.4, 199.2; **HRMS** (m/z): $[M+Na]^+$ calculated for ($C_{25}H_{21}NO$) is 374.1521 and found 374.1512.

2-((2-methyl-1*H*-indol-3-yl)(phenyl)methyl)-3,4-dihydronaphthalen-1(2*H*)-one (38b)

(*E*)-2-benzylidene-3,4-dihydronaphthalen-1(2*H*)-one, 2-methyl-1*H*-indole and $Sc(OTf)_3$ (10 mol%) are sequentially introduced to an oven-dried Schlenk tube with a magnetic stir bar and a rubber septum is fitted to Schlenk tube and sealed tightly. Then the mixture is

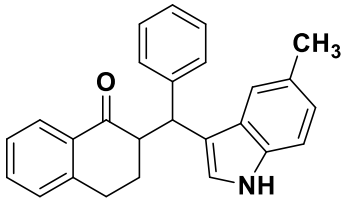
degassed using a vacuum pump. This is followed by the addition of 2 mL of dry acetonitrile and argon purge. It was tightly sealed afterwards, and it was left at room temperature overnight to stir. Once the reaction is completed (TLC) remove the solvent under reduced pressure. The product **38b** is separated from column chromatography using silica gel with a mesh size of 100–200. Using a 15% combination of hexane and EtOAc as the eluent in 59% yield.



Yield: 59%; **IR (KBr, cm^{-1}):** 3390, 3056, 2925, 2754, 1679, 1527, 1457, 1333, 1222, 1156, 1012, 966, 913; **^{1}H NMR (500 MHz, CDCl$_3$):** δ (ppm): 1.92 - 2.01 (m, 1H), 2.38 – 2.40 (m, 1H), 2.30 (s, 3H), 2.96 - 3.01 (m, 2H), 3.37 – 3.39 (m, 1H), 5.52 (d, *J* = 5.0 Hz, 1H), 6.91 -6.93 (m, 3H), 6.98 - 7.07 (m, 3H), 7.20-7.23 (m, 4H), 7.28 - 7.34 (m, 4H), 7.43 - 7.47 (m, 2H), 8.00 (s, D_2O exchangeable NH), **^{13}C NMR (125 MHz, CDCl$_3$):** δ (ppm): 21.1, 26.2, 28.1, 42.2, 52.4, 54.6, 112.3, 114.1, 119.5, 120.3, 121.7, 123.6, 126.6, 127.6, 128.4, 128.8, 129.2, 132.8, 133.3, 134.7, 135.9, 136.7, 142.7, 198.1; **HRMS** (m/z): $[M+Na]^+$ calculated for ($C_{26}H_{23}$ NO) is 388.1677 and found 388.1672.

2-((5-methyl-1*H*-indol-3-yl)(phenyl)methyl)-3,4-dihydronaphthalen-1(2*H*)-one (38c)

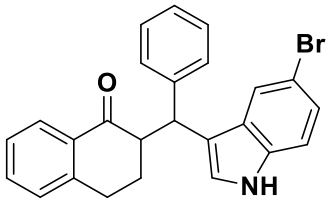
(*E*)-2-(4-chlorobenzylidene)-3,4-dihydronaphthalen-1(2*H*)-one, 5-methyl-1*H*-indole and Sc(OTf)$_3$ (10 mol%) are sequentially introduced to an oven-dried Schlenk tube with a magnetic stir bar and a rubber septum is fitted to Schlenk tube and sealed tightly. Then the mixture is degassed using a vacuum pump. This is followed by the addition of 2 mL of dry acetonitrile and argon purge. It was tightly sealed afterwards, and it was left at room temperature overnight to stir. Once the reaction is completed (TLC) remove the solvent under reduced pressure. The product **38c** is separated from column chromatography using silica gel with a mesh size of 100–200. Using a 15% combination of hexane and EtOAc as the eluent in 65% yield.



Yield: 65%; **IR (KBr, cm^{-1}):** 3406, 3065, 2854, 1679, 1595, 1432, 1221, 1112, 1015, 966, 915; **^{1}H NMR(500 MHz, $CDCl_3$):** δ (ppm): δ1.91 - 2.00 (m, 1H), 2.38 – 2.40 (m, 1H), 2.30 (s, 3H), 2.96 - 3.01 (m, 2H), 3.37 – 3.39 (m, 1H), 5.52 (d, *J* = 5.0 Hz, 1H), 6.86 (d, *J* = 1.5 Hz, 1H), 6.90 - 7.00 (m, 3H), 7.13 - 7.34 (m, 6H), 7.42 - 7.45 (m, 2H), 8.01 (s, D_2O exchangeable NH), **^{13} C NMR (125 MHz, $CDCl_3$)**:δ (ppm): 21.3, 26.2, 28.2, 42.3, 52.4, 112.4, 116.2, 120.1, 121.7, 123.7, 124.8, 125.2, 126.7, 127.7, 127.9, 128.5, 128.8, 132.9, 133.3, 134.8, 135.9, 136.8, 142.81, 198.2; **HRMS** (m/z): $[M+Na]^+$ calculated for($C_{26}H_{23}$ NO) is 388.1677 and found 388.1672.

2-((5-bromo-1*H*-indol-3-yl)(phenyl)methyl)-3,4-dihydronaphthalen-1(2*H*)-one (38d)

(*E*)-2-benzylidene-3,4-dihydronaphthalen-1(2*H*)-one, 5-bromo-1*H*-indole and $Sc(OTf)_3$ (10 mol%) are sequentially introduced to an oven-dried Schlenk tube with a magnetic stir bar and a rubber septum is fitted to Schlenk tube and sealed tightly. Then the mixture is degassed using a vacuum pump. This is followed by the addition of 2 mL of dry acetonitrile and argon purge. It was tightly sealed afterwards, and it was left at room temperature overnight to stir. Once the reaction is completed (TLC) remove the solvent under reduced pressure. The product **38d** is separated from column chromatography using silica gel with a mesh size of 100–200 using a 15% combination of hexane and EtOAc as the eluent in 65% yield.

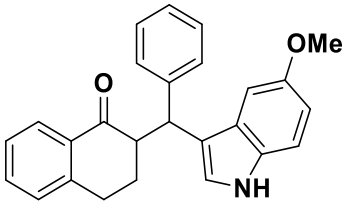


Yield: 65%; **IR (KBr, cm^{-1}):** 3334, 3058, 3027, 2920, 2851, 1707, 1678, 1599, 1492, 1455, 1358, 1265, 1220; **^{1}H NMR (500 MHz, $CDCl_3$):** δ (ppm): 1.91 - 2.01 (m, 1H), 2.38 – 2.40 (m, 1H), 2.96 - 3.01 (m, 2H), 3.37 – 3.39 (m, 1H), 5.52 (d, *J* = 5.0 Hz, 1H), 6.84 (m, 1H), 6.92 - 7.00 (m, 5H), 7.19 - 7.23 (m, 4H), 7.39 - 7.42 (m, 2H), 7.94 - 7.95 (d, *J* = 6.5 Hz, 1H), 8.01 (s, D_2O exchangeable NH); **^{13}C NMR (125 MHz, $CDCl_3$):** δ (ppm): 26.3, 28.4, 41.32, 52.2, 112.4,

113.5, 116.5, 121.9, 122.4, 123.9, 124.8, 126.5, 127.6, 127.8, 128.4, 128.9, 129.2, 132.7, 133.2, 134.8, 136.24, 143.5, 198.9; **HRMS** (m/z): $[M+Na]^+$ calculated for ($C_{25}H_{20}BrNO$) is 452.0626 and found 452.1126.

2-((4-methoxy-1*H*-indol-3-yl)(phenyl)methyl)-3,4-dihydronaphthalen-1(2*H*)-one (38e)

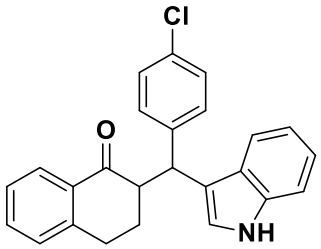
(*E*)-2-benzylidene-3,4-dihydronaphthalen-1(2*H*)-one, 4-methoxy-1*H*-indole and Sc(OTf)$_3$ (10 mol%) are sequentially introduced to an oven-dried Schlenk tube with a magnetic stir bar and a rubber septum is fitted to Schlenk tube and sealed tightly. Then the mixture is degassed using a vacuum pump. This is followed by the addition of 2 mL of dry acetonitrile and argon purge. It was tightly sealed afterwards, and it was left at room temperature overnight to stir. Once the reaction is completed (TLC) remove the solvent under reduced pressure. Product **38e** is separated from column chromatography using silica gel with a mesh size of 100–200. Using a 15% combination of hexane and EtOAc as the eluent in 72% yield.



Yield: 72%; **IR (KBr, cm^{-1}):** 3397, 3059, 3026, 2924, 2853, 1679, 1599, 1454, 1361, 1271, 1016, 966, 913; **^{1}H NMR (500 MHz, CDCl$_3$):** δ (ppm): 1.93 - 2.02 (m, 1H), 2.38 – 2.41 (m, 1H), 2.95 - 3.00 (m, 2H), 3.37 – 3.39 (m, 1H), 3.77 (s, 3H), 5.51 (d, *J* = 5.0 Hz, 1H), 6.91 -6.93 (m, 3H), 6.71 (m, 1H) 6.92 - 6.96 (m, 2H), 7.04 - 7.28 (m, 6H), 7.38 - 7.46 (m, 3H), 8.01 (s, D_2O exchangeable NH); **^{13}C NMR (125MHz, CDCl$_3$):** δ (ppm): 26.2, 28.3, 42.0, 52.7, 54.6, 112.4, 116.2, 120.7, 122.4, 123.7, 124.3, 125.4, 126.6, 127.6, 127.9, 128.5, 128.8, 132.9, 133.3, 136.97, 139.9, 143.4, 153.2, 199.1; **HRMS** (m/z): $[M+Na]^+$ calculated for ($C_{26}H_{23}NO_2$) is 404.1626 and found 404.1621.

2-((4-chlorophenyl)(1*H*-indol-3-yl)methyl)-3,4-dihydronaphthalen-1(2*H*)-one (38f)

(*E*)-2-(4-chlorobenzylidene)-3,4-dihydronaphthalen-1(2*H*)-one, 1*H*-indole and $Sc(OTf)_3$ (10 mol%) are sequentially introduced to an oven-dried Schlenk tube with a magnetic stir bar and a rubber septum is fitted to Schlenk tube and sealed tightly. Then the mixture is degassed using a vacuum pump. This is followed by the addition of 2 mL of dry acetonitrile and argon purge. It was tightly sealed afterwards, and it was left at room temperature overnight to stir. Once the reaction is completed (TLC) remove the solvent under reduced pressure. The product **38f** is separated from column chromatography using silica gel with a mesh size of 100–200. Using a 15% combination of hexane and EtOAc as the eluent in 70% yield.

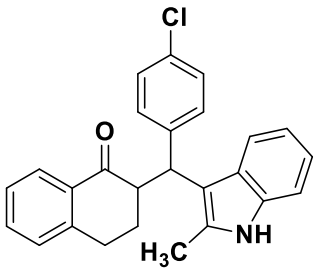


Yield: 70%; **IR (KBr, cm^{-1}):** 3354, 3061, 2922, 1679, 1595, 1488, 1350, 1227, 1069, 965, 919; **^{1}H NMR(500 MHz, $CDCl_3$)**:δ (ppm): 1.94 - 2.03 (m, 1H), 2.39 – 2.41 (m, 1H), 2.96 - 3.01 (m, 2H), 3.37 – 3.39 (m, 1H), 5.53 (d, *J* = 5.0 Hz, 1H), 6.91 -6.93 (m, 3H), 6.90 (d, *J* = 1.5 Hz, 1H), 7.10 - 7.13 (m, 3H), 7.20 - 7.35 (m, 6H), 7.41 - 7.46 (m, 1H),), 8.01 (s, D_2O exchangeable NH); **^{13}C NMR (125MHz, $CDCl_3$):** δ (ppm): 26.4, 28.3, 41.02, 52.4, 101.9, 102.2, 111.6, 116.2, 118.2, 123.5, 126.6, 126.7, 127.5, 127.9, 128.1, 128.3, 128.6, 128.8, 129.4, 130.4, 133.8, 139.7, 141.6, 142.4, 198.5; **HRMS** (m/z): $[M+Na]^+$ calculated for($C_{25}H_{20}ClNO$) is 408.1131 and found 408.1148.

2-((4-chlorophenyl)(2-methyl-1*H*-indol-3-yl)(methyl)-3,4-dihydronaphthalene-1(2*H*)-one (38g)

(*E*)-2-(4-chlorobenzylidene)-3,4-dihydronaphthalen-1(2*H*)-one, 2-methyl-1*H*-indole and $Sc(OTf)_3$ (10 mol%) are sequentially introduced to an oven-dried Schlenk tube with a magnetic stir bar and a rubber septum is fitted to Schlenk tube and sealed tightly. Then the mixture is degassed using a vacuum pump. This is followed by the addition of 2 mL of dry acetonitrile and argon purge. It was tightly sealed afterwards, and it was left at room

temperature overnight to stir. Once the reaction is completed (TLC) remove the solvent under reduced pressure. The product **38g** is separated from column chromatography using silica gel with a mesh size of 100–200. Using a 15% combination of hexane and EtOAc as the eluent in 72% yield.

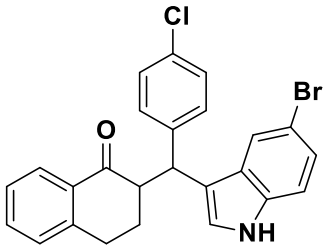


Yield: 72%; **IR (KBr, cm^{-1}):** 3392, 3056, 2924, 2754, 1680, 1599, 1527, 1489, 1458, 1302, 1221, 1156, 1091, 1013, 965; **^{1}H NMR (500 MHz, CDCl$_3$)**:δ (ppm): 1.94 - 2.03 (m, 1H), 2.31 (s, 1H), 2.39 – 2.41 (m, 1H), 2.96 - 3.01 (m, 2H), 3.37 – 3.39 (m, 1H), 5.54 (d, *J* = 5.0 Hz, 1H), 6.91 -6.93 (m, 3H), 7.06 - 7.08 (m, 2H), 7.18 - 7.20(m, 4H), 7.24 - 7.30 (m, 3H), 7.43 - 7.46 (m, 2H), 8.06 (s, D_2O exchangeable NH); **^{13}C NMR (125MHz, CDCl$_3$):** δ (ppm): 21.4, 25.8, 28.6, 41.3, 52.5, 111.0, 112.2, 120.2, 121.3, 122.0, 124.1, 124 6, 125.7, 126.1, 127.1, 128.3, 128.6, 130.6, 131.3, 132.7, 133.1, 142.0, 143.4, 198.6; **HRMS** (m/z): $[M+Na]^+$ calculated for ($C_{26}H_{22}ClNO$) is 422.1288 and found 422.1280.

2-((5-bromo-1*H*-indol-3-yl)(4-chlorophenyl)methyl)-3,4-dihydronaphthalene-1(2*H*)-one (38h)

(*E*)-2-(4-chlorobenzylidene)-3,4-dihydronaphthalen-1(2*H*)-one, 5-bromo-1*H*-indole and Sc(OTf)$_3$ (10 mol%) are sequentially introduced to an oven-dried Schlenk tube with a magnetic stir bar and a rubber septum is fitted to Schlenk tube and sealed tightly. Then the mixture is degassed using a vacuum pump. This is followed by the addition of 2 mL of dry acetonitrile and argon purge. It was tightly sealed afterwards, and it was left at room temperature overnight to stir. Once the reaction is completed (TLC) remove the solvent under reduced pressure. The product **38h** is separated from column chromatography using silica gel with a mesh size of 100–200. Using a 15% combination of hexane and EtOAc as the eluent in 61% yield.

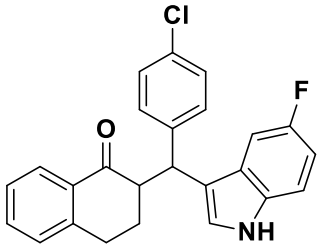
Yield: 61%; **IR (KBr, cm^{-1})**: 3354, 3061, 2922, 1679, 1595, 1488, 1350, 1227, 1069, 965, 919; **^{1}H NMR (500 MHz,**



$CDCl_3$): δ (ppm): 1.93 - 2.03 (m, 1H), 2.39 – 2.41 (m, 1H), 2.97 - 3.02 (m, 2H), 3.3 – 3.39 (m, 1H), 5.54 (d, *J* = 5.0 Hz, 1H), 6.96 (d, *J* = 1.5 Hz, 1H), 7.13 - 7.20 (m, 4H), 7.22 - 7.30 (m, 5H), 7.41 - 7.43 (m, 2H), 8.01 (s, D_2O exchangeable NH); **^{13}C NMR (125MHz, $CDCl_3$):** δ (ppm): 26.4, 28.5, 42.1, 52.4, 113.9, 116.2, 117.4, 121.3, 122.1, 124.3, 124 8, 125.7, 126.2, 127.5, 128.7, 129.7, 130.2, 131.4, 132.8, 133.1, 142.1, 143.5, 199.0; **HRMS** (m/z): $[M+Na]^+$ calculated for ($C_{25}H_{19}BrClNO$) is 486.0236 and found 486.0230.

2-((4-chlorophenyl)(5-fluoro-1*H*-indol-3-yl)(methyl)-3,4-dihydronaphthalene-1(2*H*)-one (38i)

(*E*)-2-(4-chlorobenzylidene)-3,4-dihydronaphthalen-1(2*H*)-one, 5-fluoro-1*H*-indole and $Sc(OTf)_3$ (10 mol%) are sequentially introduced to an oven-dried Schlenk tube with a magnetic stir bar and a rubber septum is fitted to Schlenk tube and sealed tightly. Then the mixture is degassed using a vacuum pump. This is followed by the addition of 2 mL of dry acetonitrile and argon purge. It was tightly sealed afterwards, and it was left at room temperature overnight to stir. Once the reaction is completed (TLC) remove the solvent under reduced pressure. The product **38i** is separated from column chromatography using silica gel with a mesh size of 100–200. Using a 15% combination of hexane and EtOAc as the eluent in 62% yield.

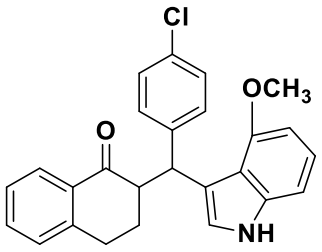


Yield: 62%; **IR (KBr, cm^{-1}):** 3352, 3062, 2928, 1675, 1595, 1486, 1353, 1237, 1222, 1063, 963, 915; **^{1}H NMR (500 MHz, $CDCl_3$):** δ (ppm): δ 1.93 - 2.01 (m, 1H), 2.38 – 2.40 (m, 1H), 2.97 - 3.02 (m, 2H), 3.37 – 3.39 (m, 1H), 5.54 (d, *J* = 5.0 Hz, 1H), 6.94 (d, *J* = 1.5 Hz, 1H), 7.25 (m, 6H), 7.29 - 7.32 (m, 3H), 7.45 - 7.49 (m, 2H), 8.01 (s, D_2O exchangeable NH); **^{13}C NMR (125MHz, $CDCl_3$):** δ (ppm): 26.4, 28.5, 42.2, 51.4, 112.4, 115.2, 116.4, 121.4, 122.2,

124.3, 124. 9, 125.7, 126.3, 127.2, 128.4, 128.7, 130.7, 131.5, 132.8, 134.3, 142.0, 148.5, 199.0; **HRMS** (m/z): $[M+Na]^+$ calculated for ($C_{25}H_{19}ClFNO$) is 426.1037 and found 426.1029.

2-((4-chlorophenyl)(4-methoxy-1*H*-indol-3-yl)methyl)-3,4-dihydronaphthalene-1(2*H*)-one (38j)

(*E*)-2-(4-chlorobenzylidene)-3,4-dihydronaphthalen-1(2*H*)-one, 4-methoxy1*H*-indole and Sc(OTf)$_3$ (10 mol%) are sequentially introduced to an oven-dried Schlenk tube with a magnetic stir bar and a rubber septum is fitted to Schlenk tube and sealed tightly. Then the mixture is degassed using a vacuum pump. This is followed by the addition of 2 mL of dry acetonitrile and argon purge. It was tightly sealed afterwards, and it was left at room temperature overnight to stir. Once the reaction is completed (TLC) remove the solvent under reduced pressure. The product **3j** is separated from column chromatography using silica gel with a mesh size of 100–200. Using a 15% combination of hexane and EtOAc as the eluent in 76% yield.

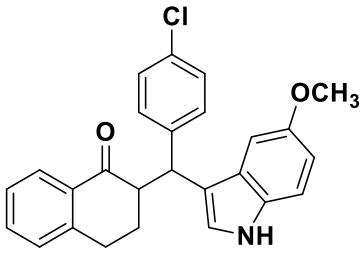


Yield: 76.%; **IR (KBr, cm^{-1}):** 3398, 3062, 2925, 2854, 1743, 1679, 1614, 1598, 1436, 1361, 1219, 1014, 916; **^{1}H NMR (500 MHz, CDCl$_3$):** δ (ppm): 1.94 - 2.03 (m, 1H), 2.39 – 2.41 (m, 1H), 2.96 - 3.01 (m, 2H), 3.37 – 3.39 (m, 1H), 3.37 (s, 3H), 5.52 (d, *J* = 5.0 Hz, 1H), 6.95 (d, *J* = 1.5 Hz, 1H), 7.04 - 7.07 (m, 2H), 7.16 - 7.18 (m, 3H), 7.22 - 7.30 (m, 3H), 7.45 - 7.48 (m, 2H), 8.06 (s, D_2O exchangeable NH); **^{13}C NMR (125MHz, CDCl$_3$):** δ (ppm): 26.4, 28.6, 42.1, 51.4. 55.6, 101.56, 116.1, 118.4, 119.2, 122.1, 126.5, 127.61, 128.1, 128.3, 128.6, 129.4, 130.5, 131.3, 132.8, 133.3, 142.1, 143.8, 153.6, 199.0; **HRMS** (m/z): $[M+Na]^+$

calculated for ($C_{26}H_{22}ClNO_2$) is 438.1237 and found 438.1228.

2-((4-chlorophenyl)(5-methoxy-1*H*-indol-3-yl)methyl)-3,4-dihydronaphthalen-1(2*H*)-one (38k)

(*E*)-2-(4-chlorobenzylidene)-3,4-dihydronaphthalen-1(2*H*)-one, 5-methoxy-1*H*-indole and $Sc(OTf)_3$ (10 mol%) are sequentially introduced to an oven-dried Schlenk tube with a magnetic stir bar and a rubber septum is fitted to Schlenk tube and sealed tightly. Then the mixture is degassed using a vacuum pump. This is followed by the addition of 2 mL of dry acetonitrile and argon purge. It was tightly sealed afterwards, and it was left at room temperature overnight to stir. Once the reaction is completed (TLC) remove the solvent under reduced pressure. The product **38k** is separated from column chromatography using silica gel with a mesh size of 100–200. Using a 15% combination of hexane and EtOAc as the eluent in 52% yield.

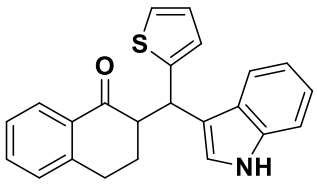


Yield: 52 %; **IR (KBr, cm^{-1}):** 3350, 3150, 2920, 1670, 1614, 1506, 1455, 1355, 1238, 1221, 1156, 1061, 963, 916; **^{1}H NMR (500 MHz, $CDCl_3$):** δ (ppm): 1.94 - 2.03 (m, 1H), 2.39 – 2.41 (m, 1H), 2.96 - 3.01 (m, 2H), 3.37 – 3.39 (m, 1H), 3.39 (s, 3H), 5.52 (d, *J* = 5.0 Hz, 1H), 6.94 (m,2H), 7.14 - 7.19 (m, 4H), 7.23 -7.26 (m, 4H), 7.43 - 7.46 (m, 2H), 8.01 (s, D_2O exchangeable NH); **^{13}C NMR (125MHz, $CDCl_3$):** δ (ppm): 26.4, 28.3, 41.0, 52.6, 55.8, 101.7, 112.0, 112.2, 116.1, 122.2, 126.7, 127.6, 128.1, 128.3, 128.7, 129.5, 130.62, 131.4, 132.8, 133.3, 142.1, 143.5, 153.5, 199.0; **HRMS** (m/z): $[M+Na]^+$ calculated for ($C_{26}H_{22}ClNO_2$) is 438.1237 and found 438.1241.

2-((1*H*-indol-3-yl)(thiophen-2-yl)methyl)-3,4-dihydronaphthalen-1(2*H*)-one (38l)

(*E*)-2-(thiophen-2-ylmethylene)-3,4-dihydronaphthalen-1(2*H*)-one, 1*H*-indole and $Sc(OTf)_3$ (10 mol%) are sequentially introduced to an oven-dried Schlenk tube with a

magnetic stir bar and a rubber septum is fitted to Schlenk tube and sealed tightly. Then the mixture is degassed using a vacuum pump. This is followed by the addition of 2 mL of dry acetonitrile and argon purge. It was tightly sealed afterwards, and it was left at room temperature overnight to stir. Once the reaction is completed (TLC) remove the solvent under reduced pressure. The product **38l** is separated from column chromatography using silica gel with a mesh size of 100–200. Using a 15% combination of hexane and EtOAc as the eluent in 63% yield.

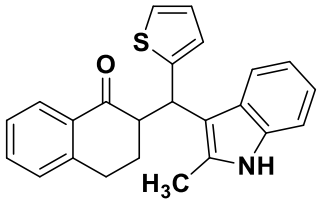


Yield: 63%; **IR (KBr, cm^{-1}):** 3348, 3061, 2916, 1668, 1582, 1483, 1452, 1356, 1236, 1221, 1152, 1060, 960, 915: **^{1}H NMR(500 MHz, CDCl$_3$):** δ (ppm): 1.96 - 2.04 (m, 1H), 2.40 – 2.42 (m, 1H), 2.96 - 3.01 (m, 2H), 3.38 – 3.40 (m, 1H), 5.53 (d, *J* = 5.0 Hz, 1H), 6.83 - 6.84 (d, *J* = 2.0 Hz, 1H), 6.89 -6.93 (m, 2H), 7.08 - 7.21 (m, 5H), 7.25 - 7.31 (m, 3H), 7.41- 7.43 (m, 1H), 8.05 (s, D_2O exchangeable NH); **^{13}C NMR(125MHz, CDCl$_3$):** δ (ppm): 26.1, 23.3, 38.5, 52.0, 112.0, 116.0, 119.2, 120.2, 123.1, 124.2, 124.6, 126.3, 126.6, 127.5, 127.8, 128.5, 131.2, 132.7, 133.2, 143.79, 148.1, 149.5, 198.1; **HRMS** (m/z): $[M+Na]^+$ calculated for ($C_{23}H_{19}NOS$) is 380.1085 and found 380.1079.

2(-(2-methyl-1*H*-indol-3-yl)(thiophene-2-yl)methyl)-3,4-dihydronaphthalene-1(2*H*)-one (38m)

(*E*)-2-(thiophen-2-ylmethylene)-3,4-dihydronaphthalen-1(2*H*)-one, 2-methyl-1*H*-indole and Sc(OTf)$_3$ (10 mol%) are sequentially introduced to an oven-dried Schlenk tube with a magnetic stir bar and a rubber septum is fitted to Schlenk tube and sealed tightly. Then the mixture is degassed using a vacuum pump. This is followed by the addition of 2 mL of dry acetonitrile and argon purge. It was tightly sealed afterwards, and it was left at room temperature overnight to stir. Once the reaction is completed (TLC) remove the solvent under reduced pressure. The product **38m** is separated from column chromatography using

silica gel with a mesh size of 100–200. Using a 15% combination of hexane and EtOAc as the eluent in 69% yield.

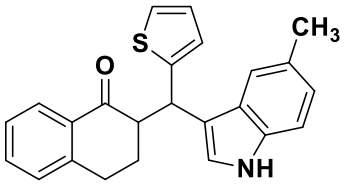


Yield: 69%; **IR (KBr, cm^{-1}):** 3407, 3103, 3066, 2924, 2855, 1678, 1598, 1482, 1433,1331, 1290, 1115, 1061, 964, 913; **^{1}H NMR(500 MHz, CDCl$_3$)**: δ (ppm): 1.95 - 2.04 (m, 1H), 2.40 – 2.42 (m, 1H), 2.96 - 3.01 (m, 2H), 3.38 – 3.40 (m, 1H), 5.54 (d, *J* = 5.0 Hz, 1H), 7.00 - 7.34 (m, 9H), 7.43 - 7.46 (m, 2H), 8.01 (s, D_2O exchangeable NH) **^{13}C NMR (125MHz, CDCl$_3$):** δ (ppm): 21.2, 26.5, 29.2, 37.0, 54.3, 102.2, 111.5, 112.0, 116.3, 123.2, 124.4, 124.8, 126.4, 126.5, 127.3, 127.5, 128.6, 131,4, 133.1, 143.7, 148.1, 154.0, 185.3, 198.2; **HRMS** (m/z): $[M+Na]^+$ calculated for ($C_{24}H_{21}NOS$) is 394.1242 and found 394.1239.

2-((5-methyl-1*H*-indol-3-yl)(thiophen-2-yl)methyl)-3,4-dihydronaphthalen-1(2*H*)-one (38n)

(*E*)-2-(thiophen-2-ylmethylene)-3,4-dihydronaphthalen-1(2*H*)-one, 5-methyl-1*H*-indole and $Sc(OTf)_3$ (10 mol%) are sequentially introduced to an oven-dried Schlenk tube with a magnetic stir bar and a rubber septum is fitted to Schlenk tube and sealed tightly. Then the mixture is degassed using a vacuum pump. This is followed by the addition of 2 mL of dry acetonitrile and argon purge. It was tightly sealed afterwards, and it was left at room temperature overnight to stir. Once the reaction is completed (TLC) remove the solvent under reduced pressure. The product **38n** is separated from column chromatography using silica gel with a mesh size of 100–200. Using a 15% combination of hexane and EtOAc as the eluent in 69% yield.

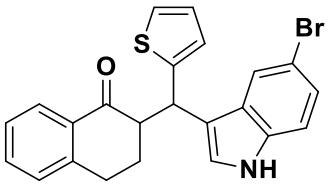
Yield: 69%; **IR (KBr, cm^{-1}):** 3407, 3103, 3066, 2924, 2855, 1678, 1598, 1482, 1433, 1331, 1290, 1115, 1061, 964, 913; **^{1}H NMR (500 MHz, CDCl$_3$):**δ (ppm): 1.96 - 2.04 (m, 1H), 2.40 – 2.42 (m, 1H), 2.96 - 3.01 (m, 2H), 3.38 – 3.40 (m, 1H), 5.53 (d, *J* = 5.0 Hz, 1H), 6.85 (d, *J* = 1.5 Hz, 1H), 6.90



- 7.09 (m, 5H,), 7.12- 7.16 (m,2H), 7.43 - 7.46 (m, 2H), 7.95 (s, D_2O exchangeable NH); **^{13}C NMR (125MHz, $CDCl_3$):** δ (ppm): 21.3, 26.3, 28.8, 36.8, 54.2, 111.49, 112.6, 118.0, 123.4, 124.4, 124.6, 126.4, 126.5, 127.5, 127.6, 128.5, 130.2, 131.1, 132.6, 133.1, 143.5, 148.1, 152.7, 198.3; **HRMS** (m/z): $[M+Na]^+$ calculated for ($C_{24}H_{21}$ NOS) is 394.2442 and found 394.1239.

2-((5-bromo-1*H*-indol-3-yl)(thiophen-2-yl)methyl)-3,4-dihydronaphthalen-1(2*H*)-one (38o)

(*E*)-2-(thiophen-2-ylmethylene)-3,4-dihydronaphthalen-1(2*H*)-one, 5-bromo-1*H*-indole and Sc(OTf)$_3$ (10 mol%) are sequentially introduced to an oven-dried Schlenk tube with a magnetic stir bar and a rubber septum is fitted to Schlenk tube and sealed tightly. Then the mixture is degassed using a vacuum pump. This is followed by the addition of 2 mL of dry acetonitrile and argon purge. It was tightly sealed afterwards, and it was left at room temperature overnight to stir. Once the reaction is completed (TLC) remove the solvent under reduced pressure. The product **38o** is separated from column chromatography using silica gel with a mesh size of 100–200. Using a 15% combination of hexane and EtOAc as the eluent in 62% yield.

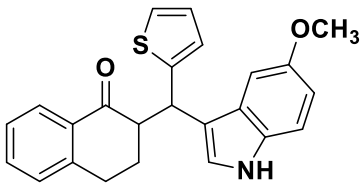


Yield: 62%; **IR (KBr, cm^{-1}):** 3350, 3064, 2920, 1670, 1588, 1485, 1455, 1355, 1238, 1221, 1156, 1061, 963, 916; **^{1}H NMR (500 MHz, $CDCl_3$):** δ (ppm): 1.95 - 2.02 (m, 1H), 2.39 – 2.41 (m, 1H), 2.96 - 3.01 (m, 2H), 3.38 – 3.40 (m, 1H), 5.53 (d, *J* = 5.0 Hz, 1H), 6.87 (s, 1H), 6.91 -6.94 (m, 2H), 7.06 (m, 1H), 7.15 - 7.35 (m, 3H), 7.41 - 7.45 (m,2H), 8.05(s, D_2O exchangeable NH); **^{13}C NMR (125MHz, $CDCl_3$)**:δ (ppm): 26.5, 29.2, 37.0, 54.3, 113.6, 116.1, 118.5, 120.2, 123.3, 124.3, 124.6, 125.3, 126.6, 127.3, 127.8, 128.6, 131.2, 132.8, 133.2, 143.8, 148.2, 150.1, 199.2;

HRMS (m/z): $[M+Na]^+$ calculated for ($C_{23}H_{18}BrNOS$) is 458.0190 and found 458.0175.

2-((5-methoxy-1*H*-indol-3-yl)(thiophen-2-yl)methyl)-3,4-dihydronaphthalen-1(2*H*)-one (38p)

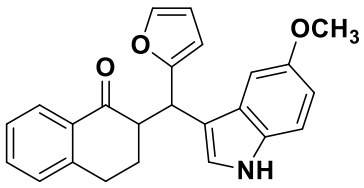
(*E*)-2-(thiophen-2-ylmethylene)-3,4-dihydronaphthalen-1(2*H*)-one, 5-methoxy-1*H*-indole and $Sc(OTf)_3$ (10 mol%) are sequentially introduced to an oven-dried Schlenk tube with a magnetic stir bar and a rubber septum is fitted to Schlenk tube and sealed tightly. Then the mixture is degassed using a vacuum pump. This is followed by the addition of 2 mL of dry acetonitrile and argon purge. It was tightly sealed afterwards, and it was left at room temperature overnight to stir. Once the reaction is completed (TLC) remove the solvent under reduced pressure. The product **38p** is separated from column chromatography using silica gel with a mesh size of 100–200. Using a 15% combination of hexane and EtOAc as the eluent in 54% yield.



Yield: 54%; **IR (KBr, cm^{-1}):** 3350, 3064, 2920, 1670, 1588, 1485, 1455, 1355, 1238, 1221, 1156, 1061, 963, 916; **^{1}H NMR (500 MHz, $CDCl_3$):** δ (ppm): 1.95 - 2.03 (m, 1H), 2.38 – 2.41 (m, 1H), 2.96 - 3.01 (m, 2H), 3.33 – 3.37 (m, 1H), 3.39 (s,3H), 5.52 (d, *J* = 5.0 Hz, 1H), 6.79 (d, *J* = 2.5 Hz, 1H), 6.90 - 7.17 (m, 7H), 7.21 - 7.27 (m, 1H), 7.40 - 7.43 (m, 2H), 8.04 (s, D_2O exchangeable NH); **^{13}C NMR (125MHz, $CDCl_3$):** δ (ppm): 26.3, 28.9, 36.9, 54.3, 55.8, 111.66, 112.0 112.2, 116.0, 123.3, 124.4, 124.7, 126.4, 126.6, 127.5, 127.7, 128.6, 131.2, 132.80, 133.2, 143.8, 148.1, 153.7, 198.2; **HRMS** (m/z): $[M+Na]^+$ calculated for ($C_{24}H_{21}NO_2S$) is 410.1191 and found 410.1200.

2-(furan-2-yl(5-methoxy-1*H*-indol-3-yl)methyl)-3,4-dihydronaphthalen-1(2*H*)-one (38q)

(*E*)-2-(furan-2-ylmethylene)-3,4-dihydronaphthalen-1(2*H*)-one, 5-methoxy-1*H*-indole and Sc(OTf)$_3$ (10 mol%) are sequentially introduced to an oven-dried Schlenk tube with a magnetic stir bar and a rubber septum is fitted to Schlenk tube and sealed tightly. Then the mixture is degassed using a vacuum pump. This is followed by the addition of 2 mL of dry acetonitrile and argon purge. It was tightly sealed afterwards, and it was left at room temperature overnight to stir. Once the reaction is completed (TLC) remove the solvent under reduced pressure. The product **38q** is separated from column chromatography using silica gel with a mesh size of 100–200. Using a 15% combination of hexane and EtOAc as the eluent in 51% yield.

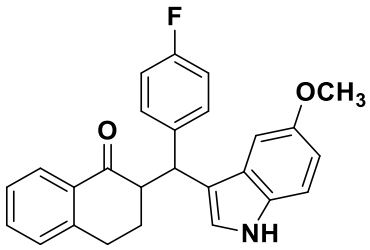


Yield: 51%; **IR (KBr, cm^{-1}):** 3348, 3061, 2918, 1680, 1585, 1480, 1455, 1350, 1238, 1221, 1156, 1065, 963, 916; **^{1}H NMR (500 MHz, CDCl$_3$):** δ (ppm): 2.28 - 2.35 (m, 2H), 2.98 - 3.18 (m, 2H), 3.36 - 3.38 (m, 1H), 3.80 (s, 3H), 5.34 - 5.35 (d, *J* = 5.0 Hz, 1H), 6.15 - 6.18 (m, 2H), 6.77 (d, *J* = 1.5 Hz, 1H), 6.85 - 6.96 (m, 1H), 7.11 – 7.14 (m, 3H), 7.24 -7. 26 (m, 2H), 7.41 -7.43 (m, 2H), 8.02 (s, D$_2$O exchangeable NH),; **^{13}C NMR (125MHz, CDCl$_3$):** δ (ppm): 26.2, 29.2, 37.0, 54.2, 55.6, 101.9, 112.9, 124.2, 124.4, 126.3, 126.5, 127.1, 127.43, 128.6, 131.3, 131.7, 132.5,141.5, 146.2, 152.1, 185.5, 198.1; **HRMS** (m/z): [M+Na]$^+$ calculated for ($C_{24}H_{21}NO_3$) is 394.1419 and found 394.1432.

2-((4-fluorophenyl)(5-methoxy-1*H*-indol-3-yl)methyl)-3,4-dihydronaphthalen-1(2*H*)-one (38r)

(*E*)-2-(4-fluorobenzylidene)-3,4-dihydronaphthalen-1(2*H*)-one, 5-methoxy-1*H* indole and Sc(OTf)$_3$ (10 mol%) are sequentially introduced to an oven-dried Schlenk tube with a magnetic stir bar and a rubber septum is fitted to Schlenk tube and sealed tightly. Then the

mixture is degassed using a vacuum pump. This is followed by the addition of 2 mL of dry acetonitrile and argon purge. It was tightly sealed afterwards, and it was left at room temperature overnight to stir. Once the reaction is completed (TLC) remove the solvent under reduced pressure. The product **38r** is separated from column chromatography using silica gel with a mesh size of 100–200. Using a 15% combination of hexane and EtOAc as the eluent in 67% yield.

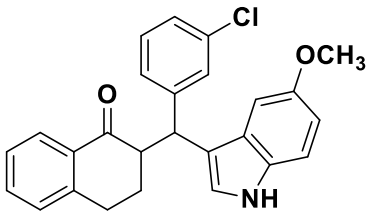


Yield: 67%; **IR (KBr, cm^{-1}):** 3351, 3152, 2920, 1670, 1612, 1506, 1455, 1355, 1238, 1220, 1156, 1061, 965, 916; **^{1}H NMR(500 MHz, $CDCl_3$): δ** (ppm): 1.96 - 2.04 (m, 1H), 2.38 – 2.41 (m, 1H), 2.96 - 3.01 (m, 2H), 3.37 – 3.39 (m, 1H), 3.77 (s, 3H), 5.52 (d, *J* = 5.0 Hz, 1H), 6.91 -6.93 (m, 3H), 7.09 -7.10 (m, 1H), 7.13 – 7.14 (m, 1H), 7.16 - 7. 18 (m, 2H), 7.25 - 7.26 (m, 2H), 7.41 – 7.44 (m, 2H), 8.00 (s, D_2O exchangeable NH); 13**C NMR (125MHz, $CDCl_3$): δ** 198.2, 166.1, 158.9, 153.7, 148.1, 143.7, 133.2, 131.2, 128.6, 127.6, 126.4, 124.4, 123.3, 116.0, 112.0, 102.3, 55.8,54.3, 36.9, 28.9, 26.4, **HRMS**(m/z): $[M+Na]^+$ calculated for ($C_{26}H_{22}FNO_2$) is 422.1532 and found 422.1538.

2-((3-chlorophenyl)(5-methoxy-1*H*-indol-3-yl)methyl)-3,4-dihydronaphthalen-1(2*H*)-one (38s)

(*E*)-2-(3-chlorobenzylidene)-3,4-dihydronaphthalen-1(2*H*)-one, 5-methoxy-1*H*-indole and $Sc(OTf)_3$ (10 mol%) are sequentially introduced to an oven-dried Schlenk tube with a magnetic stir bar and a rubber septum is fitted to Schlenk tube and sealed tightly. Then the mixture is degassed using a vacuum pump. This is followed by the addition of 2 mL of dry acetonitrile and argon purge. It was tightly sealed afterwards, and it was left at room temperature overnight to stir. Once the reaction is completed (TLC) remove the solvent under reduced pressure. The product **38s** is separated from column chromatography using

silica gel with a mesh size of 100–200. Using a 15% combination of hexane and EtOAc as the eluent in 70% yield.



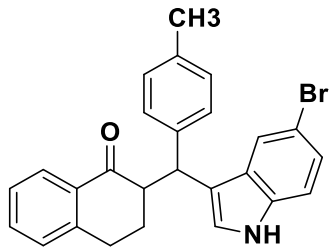
Yield: 70%; **IR (KBr, cm^{-1}):** 3350, 3150, 2920, 1670, 1614, 1506, 1455, 1355, 1238, 1221, 1156, 1061, 963, 916; **^{1}H NMR(500 MHz, CDCl$_3$):** δ (ppm): 1.94 - 2.00 (m, 1H), 2.41 – 2.42 (m, 1H), 2.96 - 3.01 (m, 2H), 3.38 – 3.40 (m, 1H), 5.54 (d, *J* = 5.0 Hz, 1H), 6.66 (d, *J* = 2.5 Hz, 1H), 6.77 - 6.85 (m, 2H), 6.97 -6.99 (m,2H), 7.16 - 7.23 (m, 4H), 7.43 - 7.46 (m, 1H), 8.01 (s, D_2O exchangeable NH); **^{13}C NMR (125MHz, CDCl$_3$):** δ (ppm): 26.4, 28.5, 40.3, 52.2, 55.78, 102.3, 116.9, 122.2, 126.3, 126.5, 126.6, 127.8, 128.2, 128.6, 129.1, 129.3, 129.4, 132.7, 133.2, 134.06, 143.4, 143.5, 144.3, 153.8, 199.4;

HRMS (m/z): $[M+Na]^+$ calculated for ($C_{26}H_{22}ClNO_2$) is 438.1237 and found 438.1245.

2-((5-bromo-1*H*-indol-3-yl)(p-tolyl)methyl)-3,4-dihydronaphthalen-1(2*H*)-one (38t)

(*E*)-2-(4-methylbenzylidene)-3,4-dihydronaphthalen-1(2*H*)-one, 5-bromo-1*H*-indole and Sc(OTf)$_3$ (10 mol%) are sequentially introduced to an oven-dried Schlenk tube with a magnetic stir bar and a rubber septum is fitted to Schlenk tube and sealed tightly. Then the mixture is degassed using a vacuum pump. This is followed by the addition of 2 mL of dry acetonitrile and argon purge. It was tightly sealed afterwards, and it was left at room temperature overnight to stir. Once the reaction is completed (TLC) remove the solvent under reduced pressure. The product **38t** is separated from column chromatography using silica gel with a mesh size of 100–200. Using a 15% combination of hexane and EtOAc as the eluent in 43% yield.

Yield: 43%; **IR (KBr, cm^{-1}):**3349, 3061, 2925, 1680, 1584, 1480, 1455, 1350, 1238, 1221, 1086, 1065; **^{1}H NMR(500 MHz, CDCl$_3$):** δ (ppm): 1.96 - 2.04 (m, 1H), 2.40 – 2.42



(m, 1H), 2.28 (s, 3H), 2.96 - 3.01 (m, 2H), 3.38 – 3.40 (m, 1H), 5.53 (d, *J* = 5.0 Hz, 1H), 7.03 (m, 2H), 7.03 - 7.33 (m, 9H), 7.41 - 7.42 (m, 1H), 8.10 (s, D_2O exchangeable NH); **^{13}C NMR (125MHz, $CDCl_3$):** δ(ppm): 21.0, 26.4, 28.2, 41.0, 52.8, 112.4, 112.7, 116.6, 121.8, 122.3, 123.8, 124.8, 126.6, 127.6, 127.9, 128.6, 129.0, 133.2, 134.8, 135.7, 138.9, 139.8, 143.5, 199.1; **HRMS** (m/z): $[M+Na]^+$ calculated for ($C_{26}H_{22}BrNO$) is 466.0782 and found 466.0788.

2.9. References

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Ethylbenzene Hydroperoxide: An Efficient Oxidizing Agent for Diastereoselective Synthesis of Spiro-epoxy Oxindoles

3.1. Abstract

Ethylbenzene hydroperoxide (EBHP) has been studied for the epoxidation of oxindole chalcones with various inorganic bases and different solvent systems. 10 M solution of NaOH with EBHP in hexane furnished a high yield of spiro epoxy oxindoles in a short reaction time at room temperature. The reaction condition applicable to electron-deficient, electron-rich arylidene-indolin-2-ones, hetero-arylidene indolin-2-ones and alkylidene-indolin-2-ones to yield the diastereoselective aryl/heteroaryl and alkyl spiro-oxiranes. Comparative studies amid peroxide reagents showed EBHP is the best in terms of diastereoselectivity, yield and reaction time. The Isotope labelling experiment showed the participation of water molecules in this oxidation mechanism.

3.2. Introduction

Epoxides or oxiranes are important structural components possessing a unique spirocyclic structure, consisting of an oxindole core and an epoxy group fused, which confers them with remarkable chemical and biological properties and is found in natural products and synthetic pharmacological active molecules.[1–5] Moreover, spiro-epoxy oxindoles have become indispensable tools in the synthesis of complex natural products. The intricate molecular architectures found in natural products, such as alkaloids and terpenes, can be efficiently constructed using spiro epoxy-oxindoles as key building blocks.[6–13] This synthetic versatility not only facilitates the efficient production of natural products but also affords the exploration of their potential therapeutic activities and biological applications. Oxindole molecule with its functional group diversity expressed a wide range of medicinal applications. Among the various oxindole derivatives, spiro-epoxy oxindoles are privileged scaffolds, found in many pharmacologically active synthetic and natural products which exhibit significant biological activities (**Figure 3.1**).[14–17]

Moreover, spiro-epoxy oxindoles have become indispensable tools in the synthesis of complex natural products. The synthetic transformations of spiro-epoxy oxindoles *via* Friedel-Crafts arylation and nucleophilic ring-opening processes of the spiro-epoxy oxindoles, ring opening followed by cycloaddition reactions which produce 3,3-disubstituted oxindoles and spiro-oxindoles, have received the major attention and provide an easy route to access many enviable molecular scaffolds with diverse biological properties.[18–22] As a result, the synthesis of spiro-epoxy oxindoles is a fascinating area of interest for organic and medicinal chemists. Further research findings may explore their potential and unravel their mechanisms of action, a discovery that could ultimately result in the development of novel therapeutics, and innovative functional materials.[23]

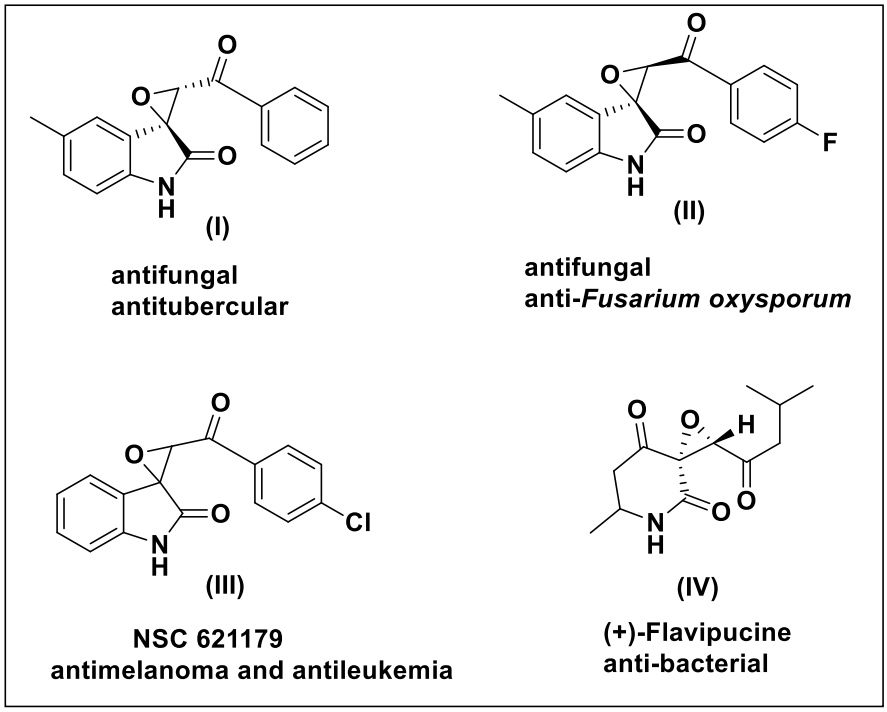


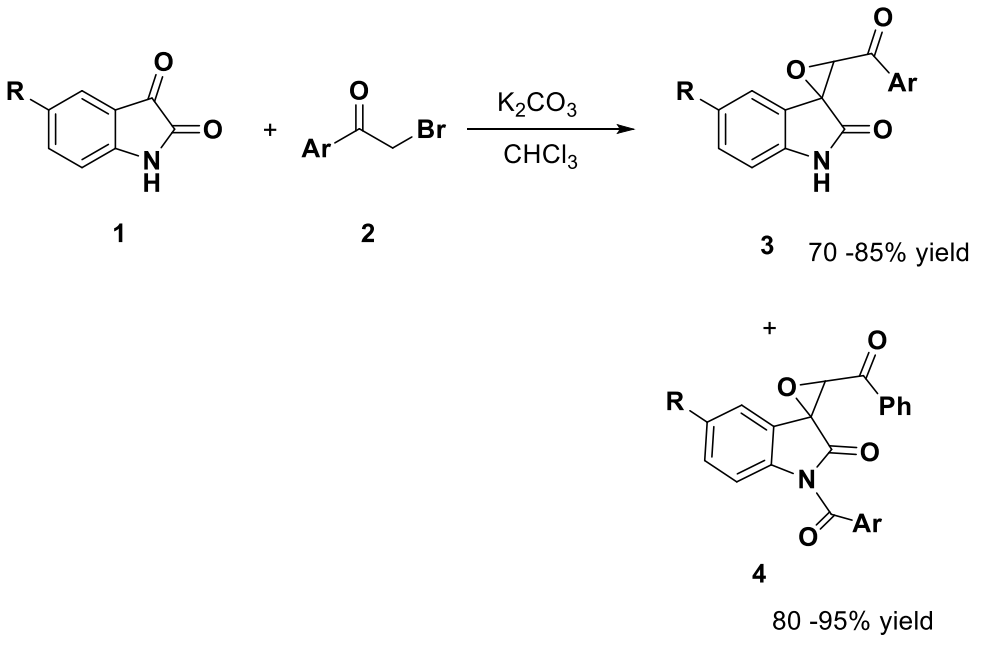
Figure. 3.1. Selected bioactive spiro-epoxides

3.2.1. Synthetic approaches towards spiro-epoxy oxindole

The last two decades have seen a wide range of initiatives, particularly in the area of finding novel ways to synthesize spiro-epoxy oxindoles and modify this scaffold.[24] Predominantly the spiro-epoxy oxindole skeleton can be achieved by Darzens reaction or Corey-Chaykovsky epoxidation[25] and from 3-alkenyl oxindole with exocyclic double bond serve as a viable precursor for the spiro-epoxide construction in presence of suitable oxygen source and a base.

3.2.1.1. From isatins

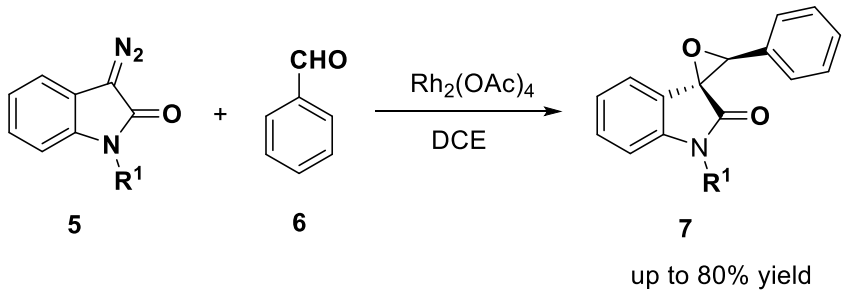
Owing to its biological and synthetic importance spiro-epoxy oxindole skeletons are accomplished *via* diverse approaches. In 2013 Fu *et al.* reported Darzens type reaction between isatins **1** and phenacyl bromides **2** to accomplish spiro-epoxy oxindole **3.** When one equivalence of phenacyl bromide is used only compound **3** is formed and upon using 2.2 equivalents of phenacyl bromide N-alkylated spiro-epoxy oxindoles **4** were obtained in good yields **(Scheme 3.1)** [26].



Scheme 3.1. Base catalyzed synthesis of spiro-epoxy oxindole

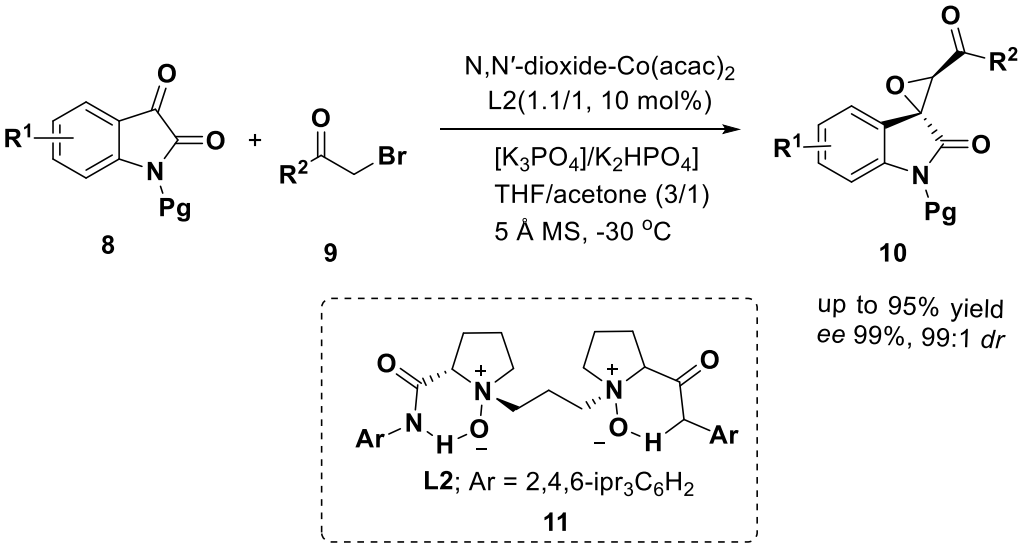
In 2014 Muthusamy *et al.* reported $Rh_2(OAc)_4$ catalyzed reaction of cyclic diazo amides **5** with aryl aldehydes **6** to furnish *cis* aryl substituted epoxy oxindoles **7**. The reaction proceeds

in an intermolecular stereoselective manner to form an epoxide ring. In addition, authors have also demonstrated the formation of *Bis*-spiro-indolo-oxiranes, when dialdehydes react with cyclic diazoamides in the presence of *in-situ* generated cyclic rhodium carbenoids. **(Scheme 3.2)**[27].



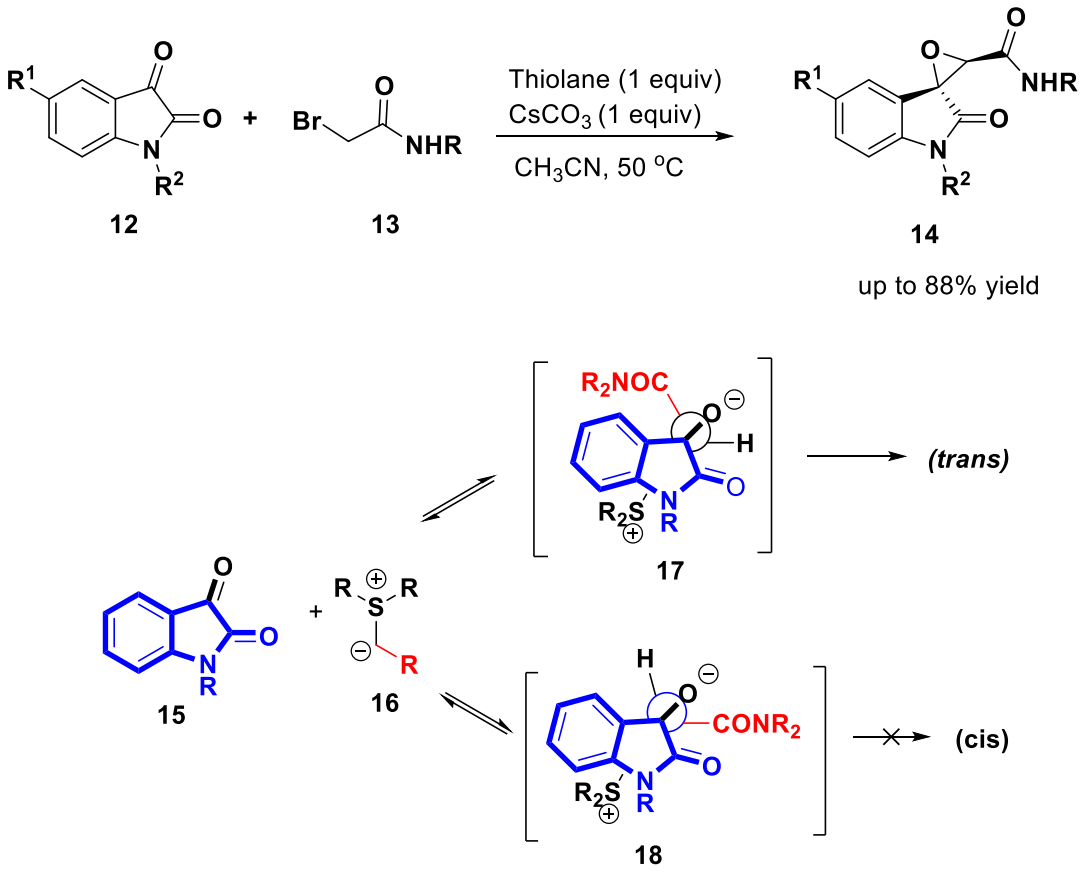
Scheme 3.2. Rhodium acetate catalyzed the synthesis of spiro-epoxy oxindoles

In the same year (2014) Feng's research group demonstrated the asymmetric synthesis of benzoyl-substituted *trans*-spiro-oxirane-oxindoles **11** using *N, N′*-dioxide-Co(acac)$_2$ as the catalyst. This reaction involves a Darzens reaction between phenacyl bromides **9** and N-protected isatins **8**. The reaction is carried out in a 3:1 mixture of THF/acetone at -30 ^{C}. The addition of an enolate (*Z* or *E*) generated from phenacyl bromide attacks the *Re*-face of isatin with its *Si*-face forming bromohydrin. After cyclization, the desired spiro-epoxy oxindole **11** is formed. **(Scheme 3.3)**[28].



Scheme 3.3. Enantioselective synthesis of spiro-epoxy oxindoles

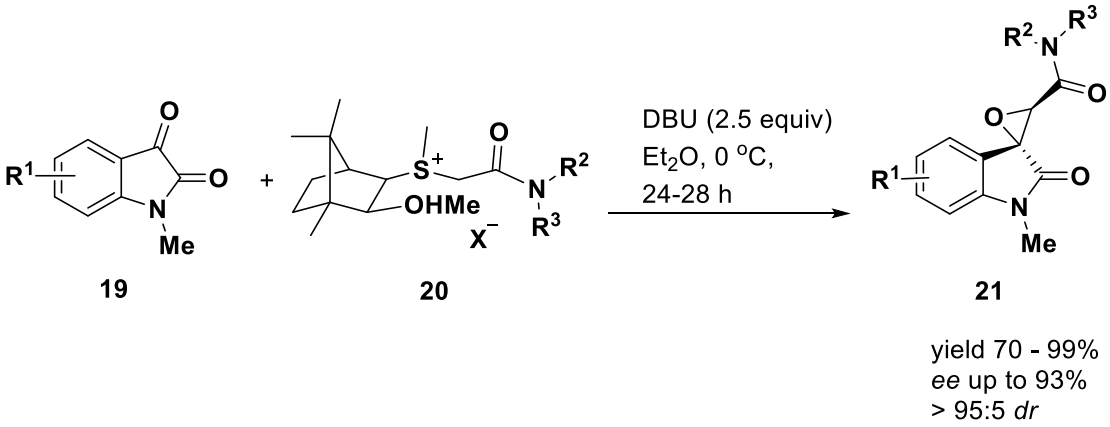
In 2007, Briere et *al.* first attempted a stereoselective Darzen's reaction between isatin **12** and *α*-halo amides **13** using a stoichiometric C_2 symmetric chiral sulfide and obtained exclusively new stable *trans*-oxiranes **14** after column chromatography, from products highly diastereo-enriched crude products. This expeditious methodology avoids any protection-deprotection sequence from the readily available isatins **12**. The reaction proceeds *via* a quasi [2+2] addition of the ylide reagent forming *cisoid* betains **17**, then C-C a bond rotation offers *transoid* betaines **18** after the ring closure process offers the *trans* oxiranes **14 (Scheme 3.4)**.[29]



Scheme 3.4. Synthesis of spiro-epoxy oxindole using thiolanes

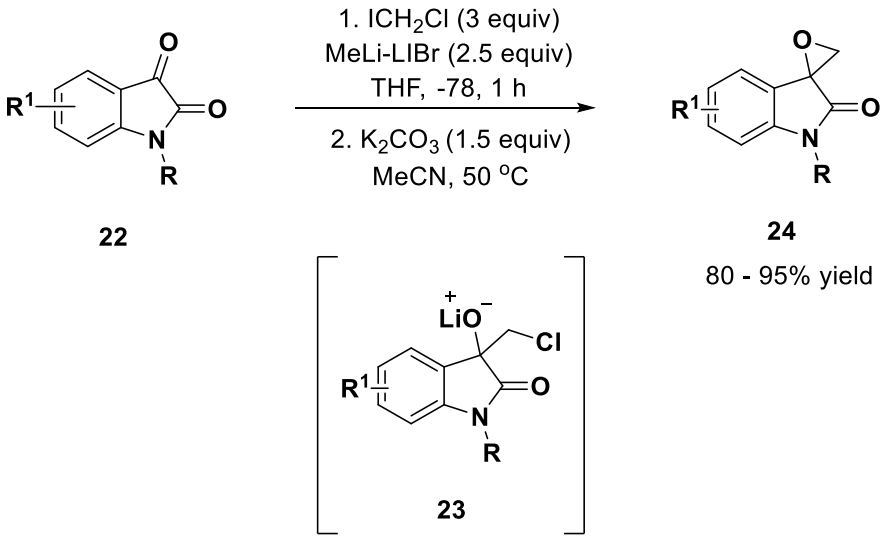
Later in 2014, Xiao et *al.* revealed the asymmetric synthesis of diethylacetamide substituted epoxy oxindoles **21** by employing stoichiometric *in-situ* generated sulphur ylides from derived camphor-derived sulfonium salts **20**. It involves the stereo-controlled attack of the amide-stabilized sulfonium ylide generated *in-situ* from **20** in the presence of DBU onto

the carbonyl of the isatin and followed by the subsequent cyclisation offers the desired epoxy oxindoles. **(Scheme 3.5)**[30].



Scheme 3.5. Synthesis of spiro-epoxides using camphor-derived chiral sulfur ylides

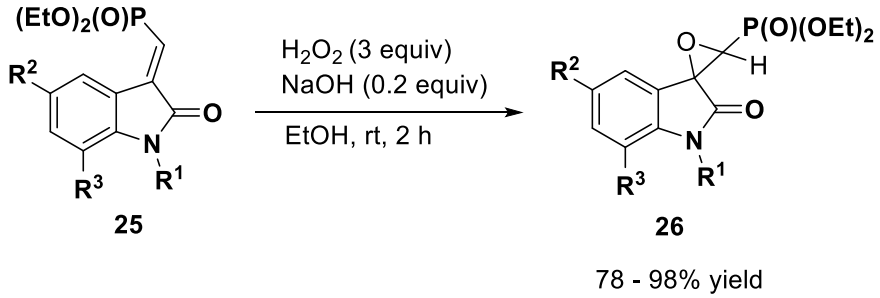
Lithium halocarbenoids were utilised by Pace and colleagues to create spiro-epoxy oxindoles **24** from isatin **22.** MeLi-LiBr and chloroiodomethane were used to synthesize the chloromethyl lithium carbenoid, which instantly interacts with isatin **22** to create a halohydrin intermediate **23**. Additionally, utilising potassium carbonate in the ring closure process led to the production of the required spiro-epoxides **24**. The unique chemoselectivity of $LiCH_2Cl$ towards isatin carbonyl rather than Weinreb amide was this method's intrinsic advantage, even when utilising an excess of $LiCH_2Cl$, **(Scheme 3.6)**[31].



Scheme 3.6. Synthesis of spiro-epoxy oxindole from lithium halocarbenoids

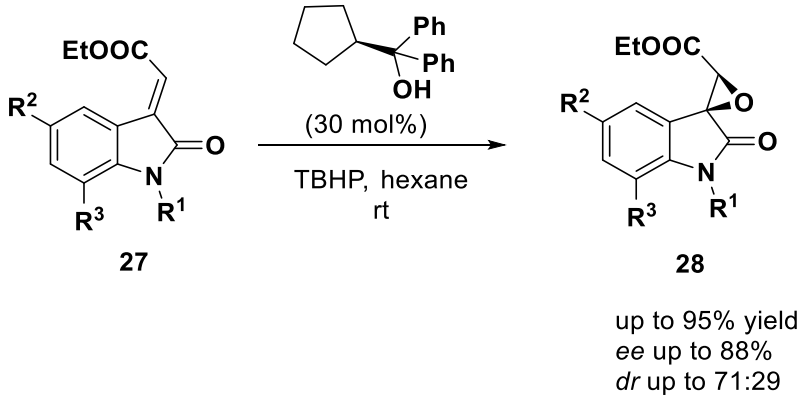
3.2.1.2. From 3-alkenyl oxindole

The exocyclic double bond on the 3-alkenyl oxindole makes it a good precursor for spiro-epoxide synthesis. This epoxidation reaction requires an appropriate base and a sufficient oxidant as an oxygen source. to access spiro-epoxy oxindole phosphonates **26**, Gasperi and colleagues revealed 3-(phosphoryl methylene) oxindole **25** epoxidation with H_2O_2/NaOH as the catalyst and obtained *trans* isomer as the predominant product **(Scheme 3.7)**[32].



Scheme 3.7. Epoxidation of 3-(phosphorylmethylene)oxindoles

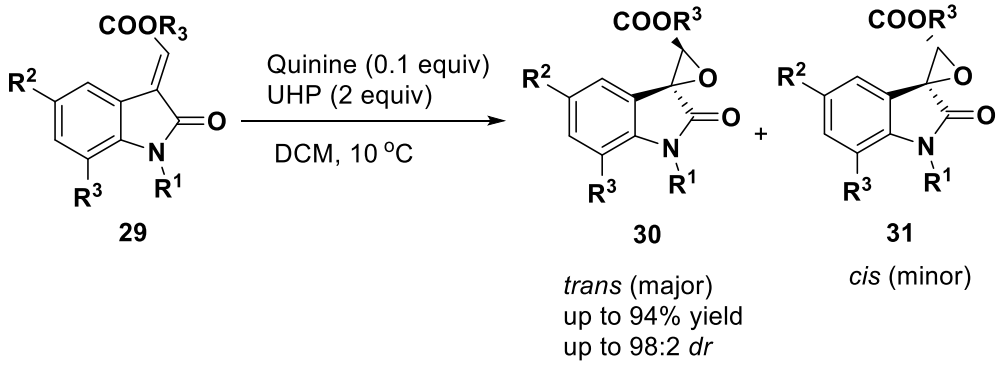
An organocatalytic asymmetric epoxidation of *α*-ylideneoxindole esters **27** to offer spiro-oxiranes with two new contiguous stereocenters **28** is reported by Gasperi's research group in 2011. Herein, they successfully demonstrated (*S*)-*α*,*α*-diphenylprolinol as an organocatalyst for the asymmetric epoxidation reaction **(Scheme 3.8)**[33].



Scheme 3.8. Enantioselective epoxidation of 3-alkenyl oxindoles

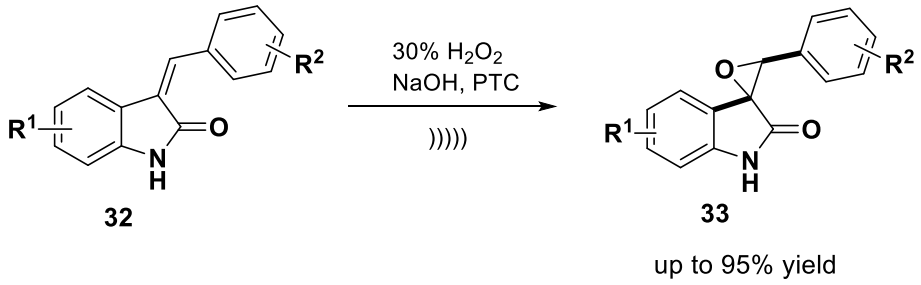
In 2013, Chouhan's group developed diastereoselective epoxidation of (*E*)-3-ylidene-indolin-2-ones **29** using natural product quinine and urea-hydrogen peroxide. protocol affords epoxides **30** in excellent yields with exclusively *trans* diastereoselectivity. Further, authors

have demonstrated the regioselective aminolysis of the synthesized *trans* epoxides using aniline derivatives in water, under sonication. the reaction proceeds to afford the product by opening the oxirane ring from the less hindered end **(Scheme 3.9)**[34].



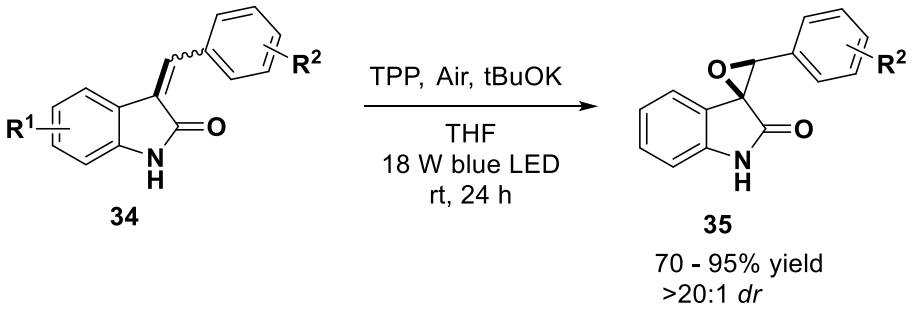
Scheme 3.9. Quinine catalyzed diastereoselective synthesis of spiro-epoxy oxindoles

The use of ultrasound irradiation as an energy source for the synthesis of spiro-epoxy oxindole **33** from arylidene-indolin-2-ones with hydrogen peroxide was successfully demonstrated by Dandia et *al*. employing cetyl trimethylcetyl trimethyl ammonium bromide as a phase transfer catalyst under ultrasound irradiation **(Scheme 3.10)**[35].



Scheme 3.10. Ultrasound-mediated spiro-epoxy oxindole synthesis

Luo *et al*. envisaged visible-light-induced aerobic epoxidation of arylidene-indolin-2-ones **34** for the efficient synthesis of spiro-epoxy oxindole derivatives **35**. The reaction is catalyzed by meso tetraphenyl porphyrin (TPP) in cyclic ether. Under visible light irradiation molecular oxygen is activated from the triplet state ($^3O_2$) to the singlet state ($^1O_2$) by TPP through energy transfer to generate in situ peroxide of THF (THF-OOH). Thus, generated peroxide acts as an oxygen source for the epoxidation reaction under standard reaction conditions. **(Scheme 3.11)**[36]



Scheme 3.11. Visible light-mediated spiro-epoxy oxindole synthesis

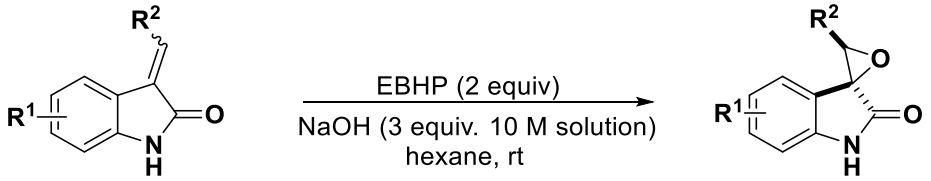
3.3. Background to the present work

Spiro-epoxy oxindoles, which have an epoxide ring fused to their C-3 position, are regarded as versatile building blocks. Many synthetic and medicinal chemists have been drawn in by the privileged frameworks' potential applications in organic synthesis and drug discovery. Spiroepoxy oxindoles can be achieved by the Darzens reaction or Corey-Chaykovsky epoxidation reaction. Further, the innate ring strain of these compounds can be exploited in ring-opening/expansion reactions.

Although the aforementioned methods are well known, they have some limitations, including a narrow substrate range, functional group incompatibility, and competitive reactions that result in the formation of side products. Organic hydroperoxides are widely employed in oxidation chemistry as reagents and also are found as valuable intermediates or building blocks in several chemical processes such as polymerizations, radical chemistry etc.[16] Even though peroxides are the primary oxidising agents, the use of photosensitizers in commercial applications is discouraged due to their longer reaction times, low diastereoselectivity, and need for additives such as phase transfer catalysts. Ethylbenzene hydroperoxide (EBHP) is a valuable reagent used as an oxygen carrier in the epoxidation reaction of propene.[17] Moreover, it can be easily prepared by oxidation of 1- phenylethanol using H_2O_2 at the laboratory scale, unlike other peroxides[18].

Inspired by the discussed approaches and as a part of our enduring interest in developing efficient synthetic protocols to synthesize spiro-heterocycles,[37,38] and functionalised heterocycles,[39] herein, we report a straightforward method for diastereoselective

epoxidation of chalcones to spiro-epoxy oxindoles at room temperature, in a short reaction time (**Scheme 3.12**).



Scheme 3.12.

3.4. Results and Discussion

In our initial approach, stirring the 3-benzylideneindolin-2-one (**36a**) in xylene (mixture of isomers) in the presence of 1 equivalence of solid NaOH at room temperature after 24 hours serendipitously *trans*- spiro oxindole-epoxide (**37a**) is formed in 62% yield (**Table 3.1,** entry 1). The structure of the product was confirmed through various spectroscopic analyses such as ^{1}H NMR, ^{13}C NMR and mass spectrometry. In the ^{1}H NMR one proton singlet at δ 4.86 indicates the presence of methyl protons from the oxirane ring, further presence of one proton singlet at δ 9.43 confirmed the presence of NH group from the oxindole moiety (**Figure 3.2**). It is further confirmed by the ^{13}C NMR spectrum. Moreover, the signal that appeared at δ 174.6 in ^{13}C NMR corresponds to the carbonyl carbon of the amide group present in the oxindole (**Figure 3.3**). Further two signals at δ 65.5 and 62.1 correspond to the two carbons from the oxirane ring (**Figure 3.3**). Additionally, the mass spectrometric data was also in good agreement with the exact mass of the product. Further, the single crystal X-ray structure unambiguously confirmed the product as a *trans*-isomer (**Figure 3.4.**).

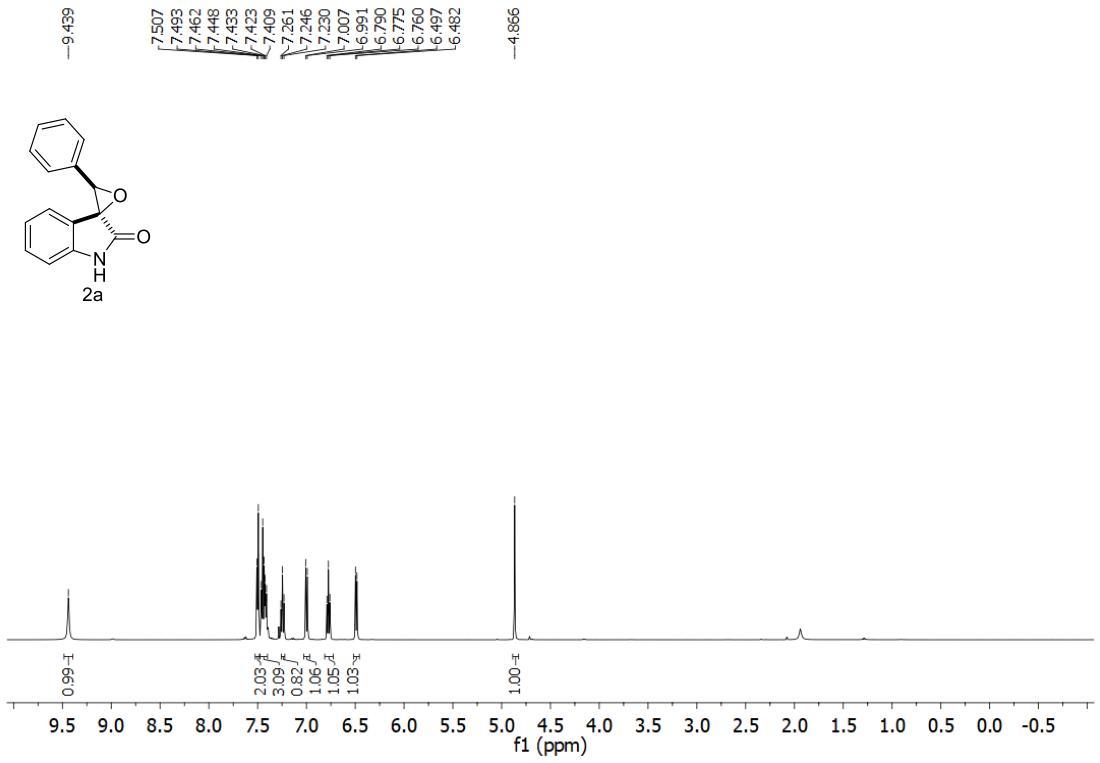


Figure 3.2. ^{1}H NMR of **37a** in $CDCl_3$

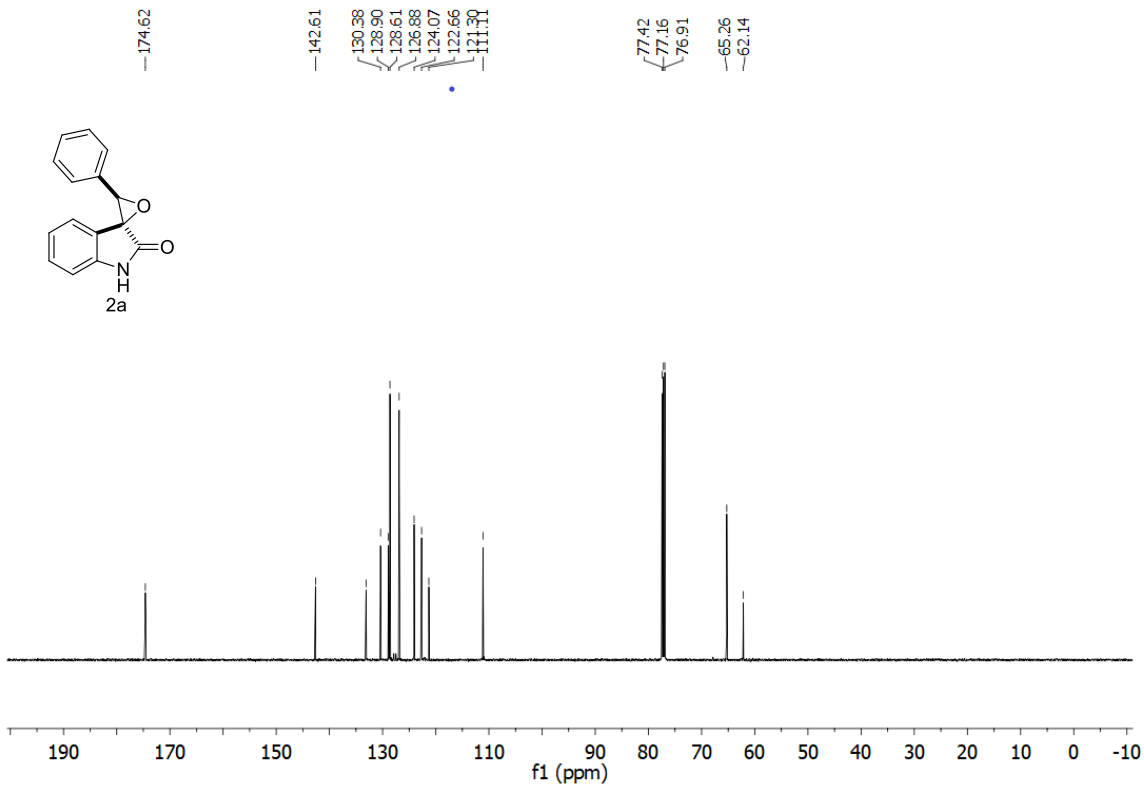


Figure 3.3. ^{13}C NMR of **37a** in $CDCl_3$

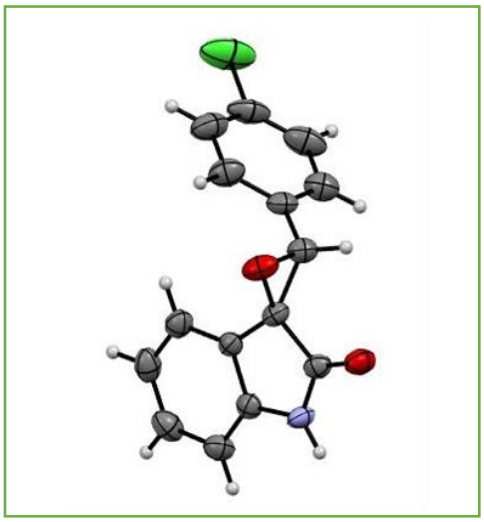
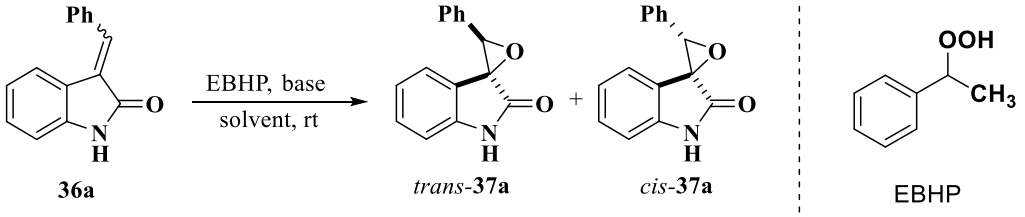


Figure 3.4. Single crystal X-ray structure of **37o** (**CCDC 1937798**)

After confirming the structure of the product, we were delighted by this result of epoxidation without any external oxidant, then added a 3-molar solution of NaOH to the mixture of 3-benzylideneindolin-2-one (**36a**) in xylene and obtained the **37a** in 93% yield keeping *trans: cis* ratio 7:1 (entry 2). The molar solution of NaOH in water enhanced the product formation, indicating that the water may be acting as an oxygen source for this enviable reaction. However, it is highly impossible to split the water to give oxygen at room temperature in the absence of metal complexes and light irradiation.

Table 3.1. Optimization of reaction conditions [a]



36a *trans*-**37a** *cis*-**37a** EBHP

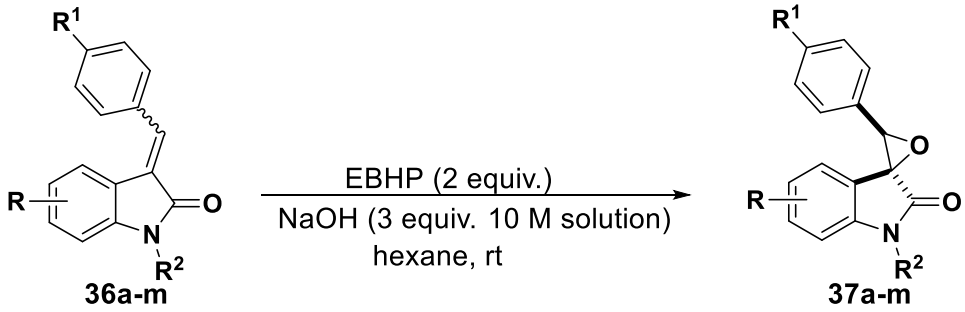
entry	solvent	base	base strength (M)	oxidant	time	yield (%)[b] (dr)[c]
1	xylene (old)	NaOH	1 equiv	-	24 h	62[c]
2	xylene (old)	NaOH	3	-	4.5h	93(7:1)
3	xylene	NaOH	3	-	24 h	no reaction
4	xylene	NaOH	3	EBHP	4.5 h	91(7:1)
5	xylene	NaOH	6	EBHP	1 h	93(7:1)
6	xylene	NaOH	10	EBHP	30 min	95(14:1)
7	xylene	NaOH	14	EBHP	30 min	81
8	xylene	NaOH	10	TBHP	2.5 h	84(8:1)
9	xylene	NaOH	10	H_2O_2	24 h	06
10	xylene	LiOH	10	EBHP	1 h	56
11	xylene	KOH	10	EBHP	1 h	74
12	DCM	NaOH	10	EBHP	1 h	97(7:1)
13	*o*-xylene	NaOH	10	EBHP	30 min	97(10:1)
14	*p*-xylene	NaOH	10	EBHP	30 min	93(29:1)
15	methanol	NaOH	10	EBHP	1 h	93(32:1)
16	**hexane**	**NaOH**	**10**	**EBHP**	**15 min**	**97**
17	hexane	NaOH	10	EBHP	30 min	97
18	hexane	NaOH	-	EBHP	24 h	trace[d]

[conditions] unless otherwise mentioned, **1a** (0.13 mmol), EBHP (2 equiv), molar solution of base (3 equiv) in 2 mL of solvent used at room temperature. [b Isolated yields]. determined by isolation and referring to the ratio of *trans*-**2a** to cis-**2a**. [c] 1 equiv. of solid NaOH added. [d] reaction was carried out under dry conditions.

when we performed the same reaction by adding solvent from a brand-new xylene bottle the reaction does not afford the product even in traces (entry 3). This suggested that there may be an impurity present in the previously used xylene solvent bottle which is acting as an oxidant for this epoxidation reaction. To confirm our postulation, we successfully isolated and characterised the impurity from the previously used old xylene solvent as Ethyl benzene

hydroperoxide (EBHP). Further when we performed a reaction by adding 2 equivalences of isolated EBHP to the reaction mixture containing xylene from a brand-new bottle and obtained the corresponding spiro epoxy oxindole in a similar yield (entry 4). After confirming the oxidising agent, we screened various reaction parameters to obtain optimized reaction conditions. Further, by Increasing the concentration of base from 3 M to 6 M, the reaction time was gradually reduced from 4.5 h to 1 h without altering the yield of the product (entry 5). The diastereoselectivity and product formation was further improved by increasing the concentration of base to 10 M with 95% yield and retaining a *trans: cis* ratio of 14:1 within 30 minutes of reaction time. However, a further increment in base strength to 14 M declined the percentage of yield to 81% (entries 6-7). Replacing the EBHP with TBHP showed a decrement in product formation to 84% (entry 8). When H_2O_2 is employed as an oxidizing agent, yield declines drastically and there was no effect on continuing the reaction even after 24 h (entry 9). Comparing the attempts made by replacing NaOH with the other hydroxy bases such as $LiOH.H_2O$, KOH was found less effective in transforming the chalcones into the spiro oxiranes (entries 10-11).

Table 3.2. Scope of arylidene oxindole



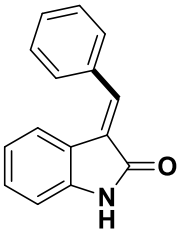
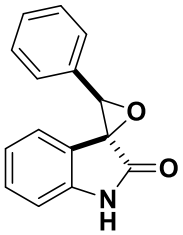
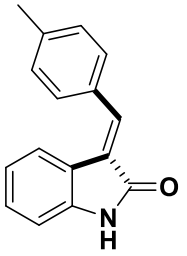
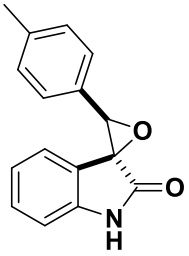
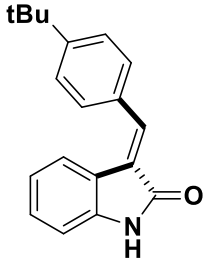
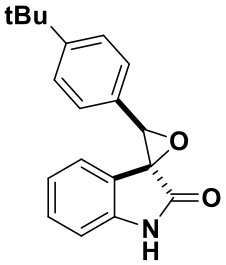
Entry	Oxindole chalcone	Product	Yield(%)
1	 36a	 (±) 37a	97%
2	 36b	 (±) 37b,	79%
3	 36c	 (±) 37c	92%

Table 3.2 continues…….

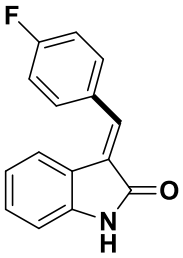
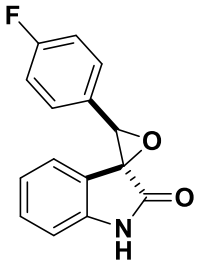
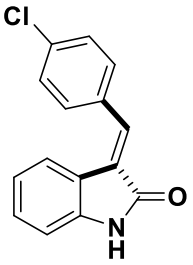
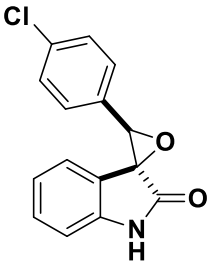
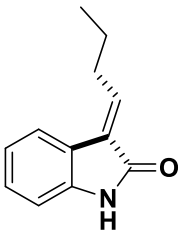
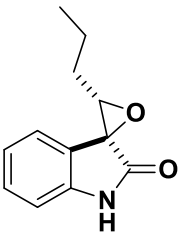
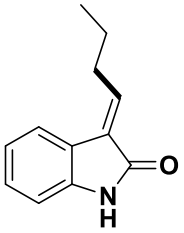
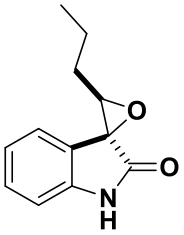
Entry	Oxindole chalcone	Product	Yield(%)
4	 36d	 (±) 37d	94%
5	 36e	 (±) 37e	88%
6	 36f	 (±) 37f	50%
7	 36g	 (±) 37g	60%

Table 3.2 continues…….

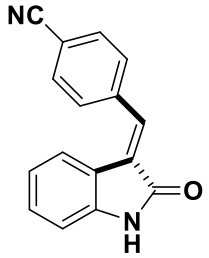
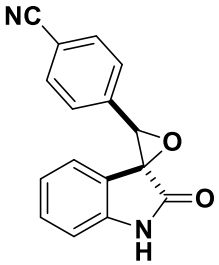
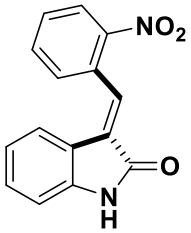
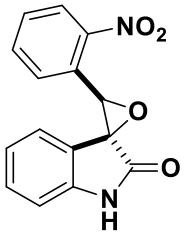
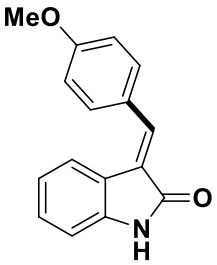
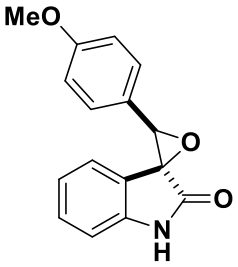
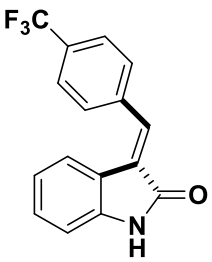
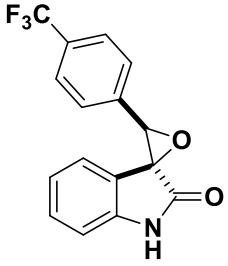
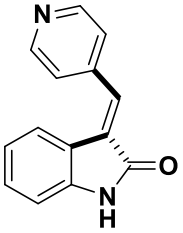
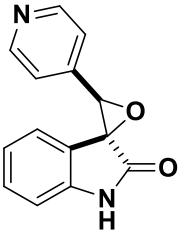
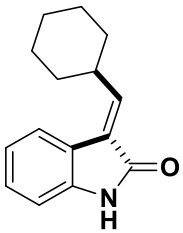
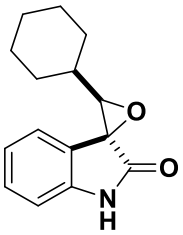
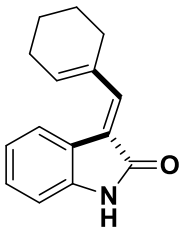
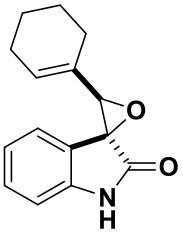
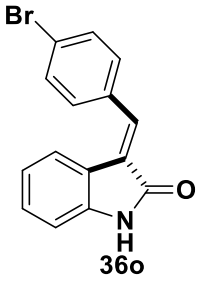
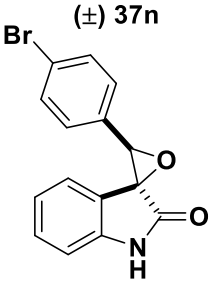
Entry	Oxindole chalcone	Product	Yield(%)
8	 36h	 (±) 37h	97%
9	 36i	 (±) 37i	98%
10	 36j	 (±) 37j	98%
11	 36k	 (±) 37k	79%

Table 3.2 continues…….

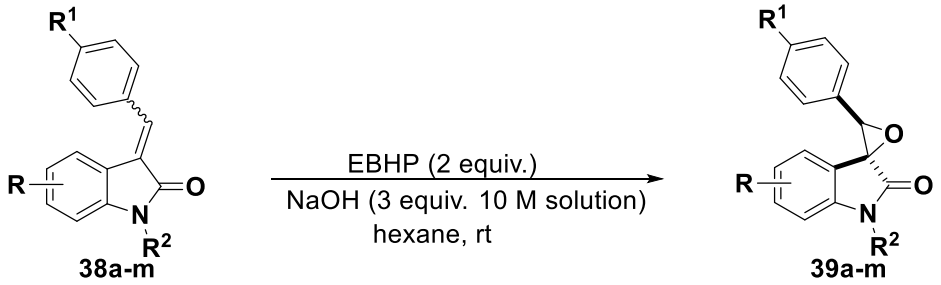
Entry	Oxindole chalcone	Product	Yield(%)
12	 36l,	 (±) 37l	70%
13	 36m	 (±) 37m	57%
14	 36n	 (±) 37n	69%
15	 36o	 (±) 37o	92%

Upon solvent screening, in dichloromethane, we could achieve the highest yield of 97%, but poor diastereoselectivity was observed (entry 12). Reaction performed with single isomer solvents of xylene *viz*. *o*-xylene and *p*-xylene, the latter one showed satisfactory trans: cis ratio 29:1 (entries 13-14). The polar solvent methanol was also found as a feasible medium for the successful formation of the product with the highest selectivity of 32:1 ratio (entry 15). Finally, hexane was found to be the best solvent system with the highest percentage of yield

97% and a single *trans*-isomer with the shortest reaction time of 15 minutes (entry 16). No further impact on either selectivity or yield upon extending the reaction time to 30 minutes (entry 17). A trace amount of product was observed when the reaction was carried out under dry conditions (entry 18).

With the optimized reaction condition in hand, we sought to investigate the scope and generality of this protocol for various substituted 3-benzylideneindolin-2-ones. Epoxidation was achieved successfully in good yields for the electron-rich CH_3, OCH_3 functional groups. Further, the oxindole chalcones bearing diverse electron withdrawing functionalities viz. F, Cl, Br, CF_3. NO_2, CN also reacted smoothly to form the aspired spiro epoxides in good yields. In addition to this the n-butyraldehyde derived oxindole chalcones **36f, 36g (Table 3.2.)** were also formed the corresponding products in good yields**.** Compounds **38l, 38m (Table 3.3**) and cyclic oxindole chalcones successfully offered the expected products in better yields **37m, 37n (Table 3.2.).** Further, the reaction conditions also favoured pyridine-derived oxindole **36l** chalcone in perusing the intended spiro oxirane **37l.** The reaction also proceeded smoothly with the N-methyl substituted oxindole chalcone **38k** to give the product **39k (Table 3.3)** without the significant influence of the substitution on the product formation. From the above-discussed scope of the reaction, it is evident that the product formation proceeds in good yields irrespective of the substitutions on both aryl and oxindole moieties of the oxindole chalcones.

Table 3.3. Scope for the substitution on the oxindole ring



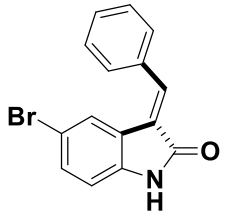
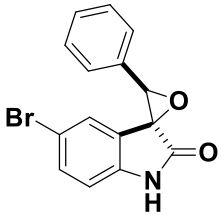
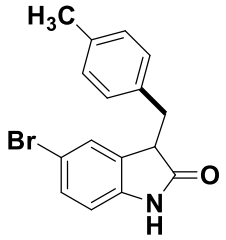
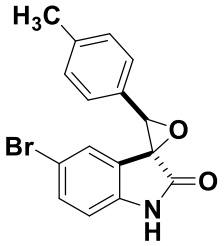
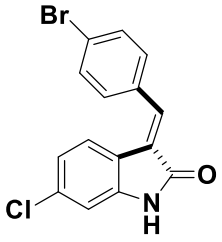
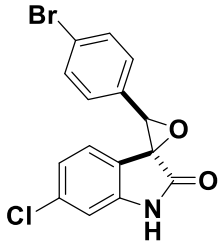
Entry	Oxindole chalcone	Product	Yield(%)
1	 38a	 (±) 39a	86%
2	 38b	 (±) 39b	95%
3	 38c	 (±) 39c	86%

Table 3.3 continues…….

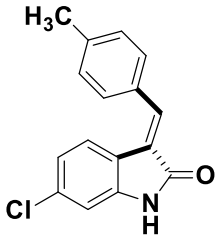
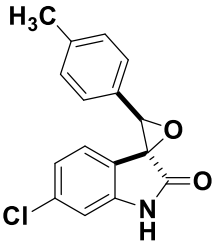
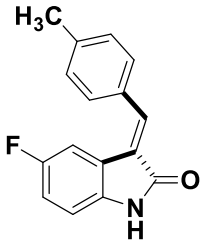
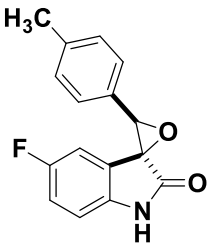
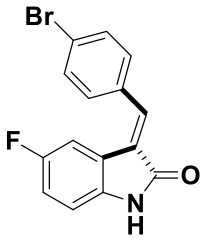
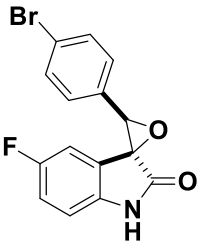
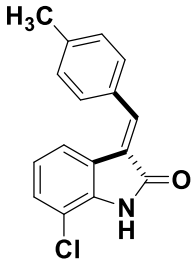
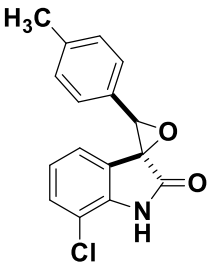
Entry	Oxindole chalcone	Product	Yield(%)
4	 38d	 (±) 39d	86%
5	 38e	 (±) 39e	77%
6	 38f	 (±) 39f	92%
7	 38g	 (±) 39f	76%

Table 3.3 continues…….

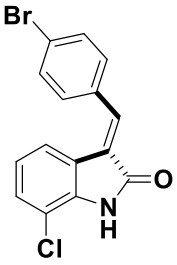
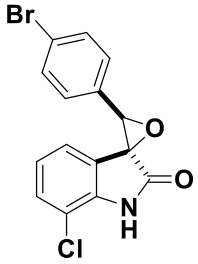
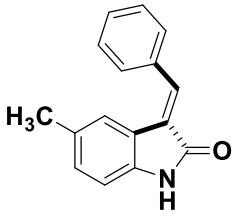
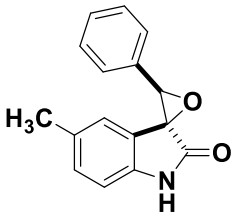
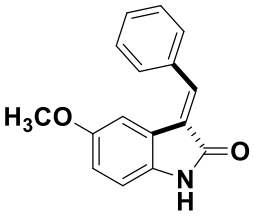
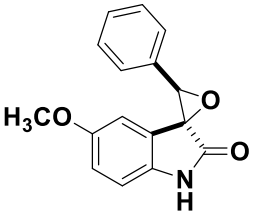
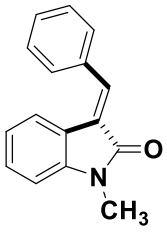
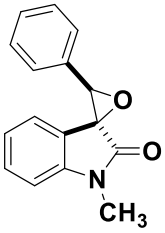
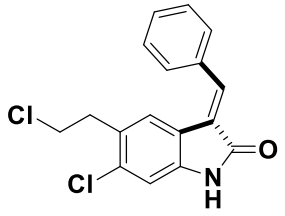
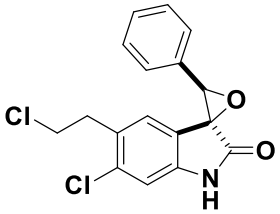
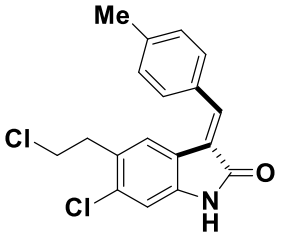
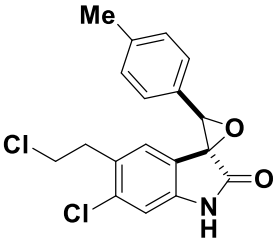
Entry	Oxindole chalcone	Product	Yield(%)
8	 38h		77%
9	 38i	 (±) 39i	90%
10	 38j	 (±) 39j	86%
11	 38k	 (±) 39k	76%

Table 3.3 continues…….

Entry	Oxindole chalcone	Product	Yield(%)
12	 38l	 (±) 39l	90%
13	 38m	 (±) 39m	92%

From the spectroscopic and single crystal X-ray structure it is evident that the reaction is highly diastereoselective and forms selectively the *trans-spiro-epoxy* oxindoles. However, when the reaction is carried out with the *Z* and *E* isomers of 3-butylideneindolin-2-one (**36f** & **36g**), diastereomerically *cis* and *trans* of 3'-prop-ylspiro[indoline-3,2'-oxiran]-2-one are formed respectively **37f** and **37g (Table. 3.2).** The *trans* and *cis* configuration for the spiro-epoxy oxiranes **37f** and **37g** were unequivocally assigned by comparing the NOESY spectroscopic data.

In the NOESY spectrum of **37f (Figure 3.5**) cross-peaks were found between the epoxide proton [δ 3.63 (s, 1H, OCH)], and aromatic 4-H proton [δ 7.08-7.10 (m, 2H, CH)] are due to the spatial interaction, and this interaction is due to the spatial proximity of these nuclei, further cross-peaks are generated by the spatial interaction between the H atom of the N-H [δ 8.97 (s, 1H, NH)] group and 7-H atom on the aromatic ring [δ 6.97 (d, *J* = 7.5Hz, 1H)]. These correlations prove that the diastereomer **37f** is a *cis*-isomer.

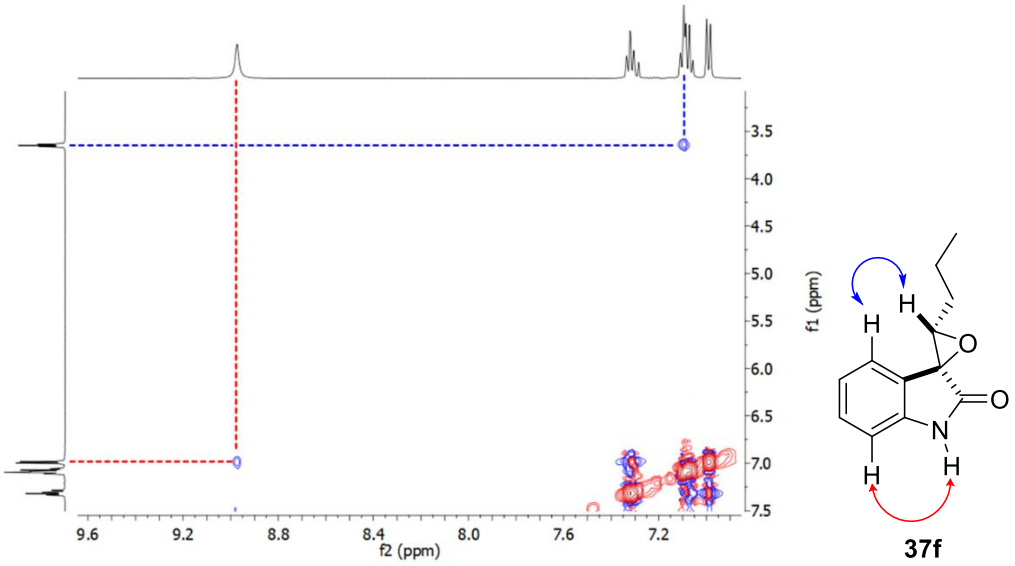


Figure 3.5. NOESY spectrum of compound 37f

Conversely, no correlations were observed between the epoxide proton and aromatic proton in the **37g** isomer **(Figure 3.6)** although, the through-space connectivity between the N-H group [δ 9.83 (s, 1H, NH)] and the aromatic 7-H atom [δ 7.04 (m, 2H, CH)] is still present. This data unequivocally confirms that epoxide **37g** is a *trans*-isomer.

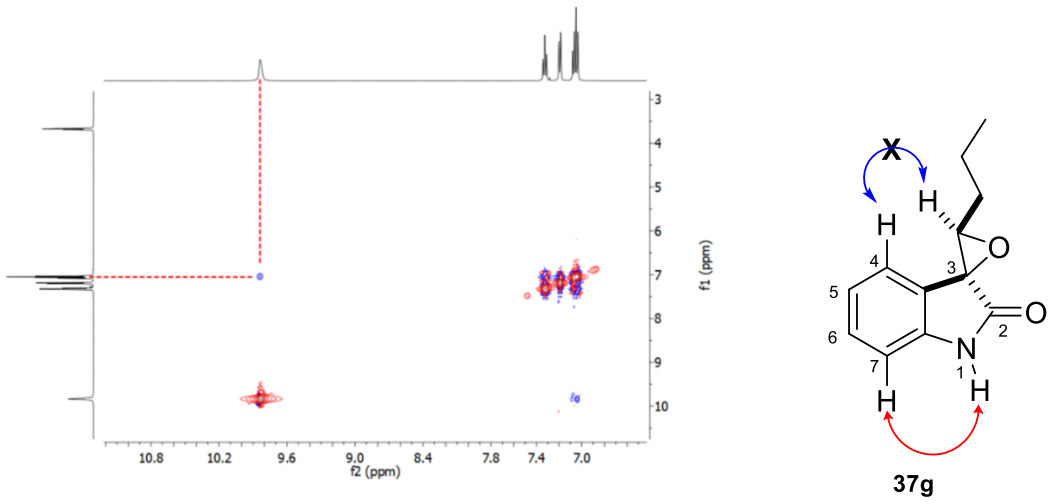
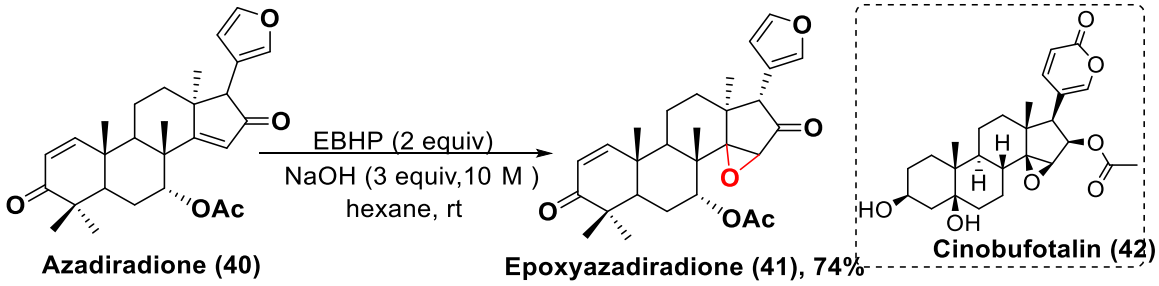


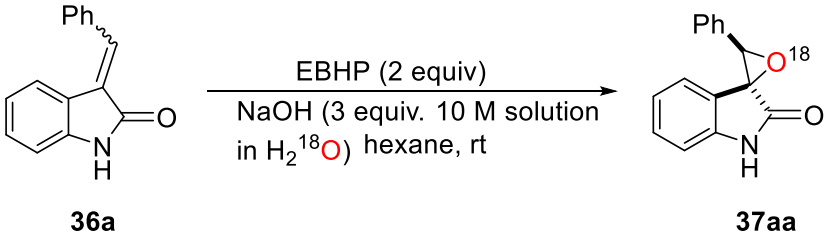
Figure 3.6. NOESY spectrum of compound 37g

Encouraged by the results obtained from the epoxidation of diversified oxindole systems, we speculated to extend this protocol in transforming some natural products. Intrigued by the rumination on extension of this protocol we successfully demonstrated our protocol in transforming the azadiradione into the epoxy azadiradione (**Scheme 3.13)**. Azadiradione and epoxy azadiradione. These phytochemicals are known to exhibit broad-spectrum medicinal properties.[40] This application accentuates the perspective of the protocol in the late-stage diversification of phytochemicals and complex structures viz. Cinobufotalin, Gedunin etc.



Scheme 3.13. Late-stage epoxidation on Azadiradione

Herein, we successfully demonstrated an epoxidation protocol that utilizes a minimum quantity of water as compared to usual oxidation processes. The quantity of water ultimately decides the strength of the basic solution. There is a clear indication of the role of water/strength of the sodium hydroxide solution during the optimization of reaction conditions (**Table 3.1**).



Scheme 3.14. Isotope labelling experiment using $H_2{}^{18}O$

To confirm further, a reaction was performed using a 10 M NaOH solution enriched with $H_2{}^{18}O$. The reaction proceeded smoothly, product 3**7aa** was obtained with 80% yield

(**Scheme 3.14**). Surprisingly, we observed a corresponding mass peak of product 3**7aa** with ^{18}O isotope at 16% intensity concerning the base peak (**Figure 3.7)**

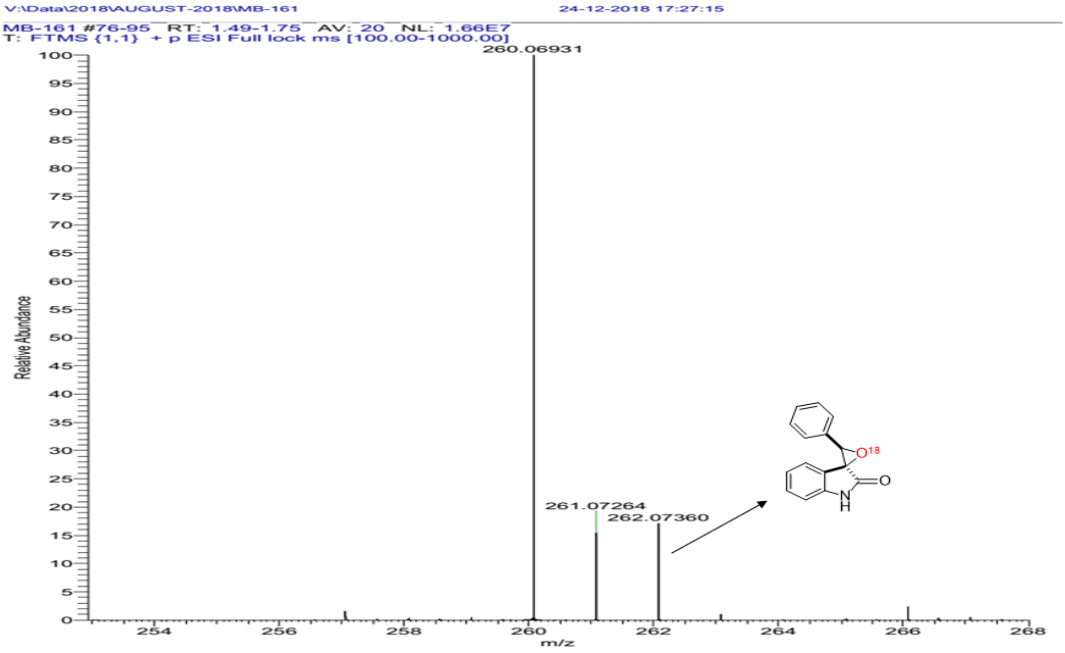
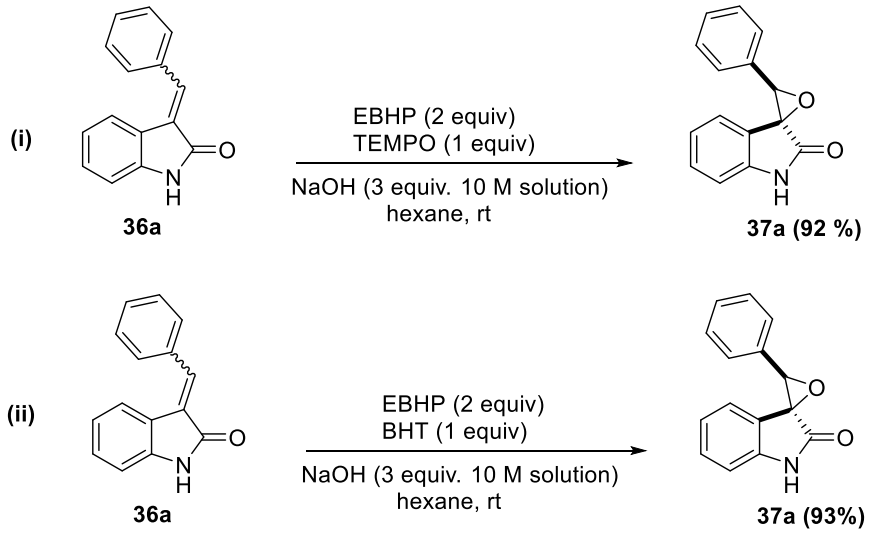


Figure 3.7. HRMS spectra of $H_2{}^{18}O$ enriched 37aa

When we looked into the literature there are a few reports which discussed oxygen exchange between peroxide and water molecules. Anbar and Guttmann reported hydroxide ion catalyzed exchange of oxygen between water and H_2O_2 in 1M NaOH solution with a rate constant of $1.1x10^{-7}$ at 25 °C and the authors also studied induced isotopic exchange on the interaction of H_2O_2 with OCl^-, IO_4^-, MnO_4^-, Fe^{+2}, Fe^{+3}, Ce^{+4}, NO_2 and NO_2.[41,42]They suggested the formation of peroxy-complexes of the type XOOH which facilitates the isotopic exchange with water.[43] Hence, we emphasize that there may be an exchange of oxygen between water and peroxide. The base is the most important component in the epoxidation reactions, which plays a pivotal role in the activation of peroxides. Inorganic bases like NaOH, and KOH are very often utilized in the form of an aqueous solution.[44,45] The reactivity of hydroxide ions depends on the concentration of the base in aqueous media. A progressive increase in the concentration of OH^- diminishes its hydration number 'n' up to a value of 3.5 at the highest concentration of base (50% aqueous NaOH).[46] In low-polarity solvent, the largely dehydrated

OH^- ion is an extremely powerful base and it allows for the generation of anions even from very weak organic acids (up to pKa = 38).[47]



Scheme 3.15. Radical trapping experiments; (i) TEMPO as a radical scavenger, (ii) BHT as a radical scavenger

It is well known that the stereochemistry of the starting alkene is not necessarily retained in the epoxide. For example, the epoxidations of both *E*- and *Z*-3-methyl-3-penten-2-one with basic H_2O_2 in methanol afford predominantly the *E* epoxide product.[48] To our surprise (*Z*) isomers of 3-butylideneindolin-2-one (**36f**) produced *cis*- 3'-propylspiro(indoline-3,2'-oxiran)-2-one (**37f**) exclusively. To gain some insights into the reaction mechanism we carried out some controlled experiments using radical scavengers such as 2,2,6,6-tetramethylpiperidin-1-yl) oxidant (TEMPO, 1 equiv.) and 3,5-di-*tert*-4-butylhydroxytoluene (BHT, 1 equiv.) (**Scheme 3.15**). The yield did not lower upon adding a radical scavenger to the reaction mixture; thus, a radical process is probably unlikely to be involved. The above-mentioned literature reports and our experimental results suggest that there is a need for a re-examination of the mechanism of epoxidation reaction involving peroxide and base. Further, an investigation of the mechanism and synthetic utility of demonstrated protocol is in progress at our lab.

3.5 Conclusion

In conclusion, we have designed and developed a simple and straightforward methodology for transforming oxindole chalcones to the corresponding spiro-epoxides by utilising EBHP as an oxidising agent at room temperature. The reaction afforded the spiro epoxy oxindoles excellent yields. Various electron-deficient, electron-rich functionalised arylidene-indolin-2-ones are well tolerated. Further, this protocol is successfully extended to the diverse hetero arylidene-indolin-2-ones and alkylidene-indolin-2-ones. With this method, diastereoselective trans-spiro-epoxy oxindoles can be accessed in an extremely quick reaction time.

3.6 General experimental methods

All the reactions are performed with commercially available best-grade chemicals without further purification. All of the solvents used are reagent-grade and commercially available. Column chromatography was performed using 100−200 mesh silica gel, and mixtures of hexane−ethyl acetate were used for the elution of the products. Proton nuclear magnetic resonance spectra (^{1}H NMR) were recorded on a Bruker AMX 500 spectrometer. Chemical shifts for ^{1}H NMR spectra are reported as δ in units of parts per million (ppm) downfield from $Si(CH_3)_4$ (δ 0.0) and relative to the signal of chloroform-d (δ 7.26, singlet), DMSO-d_6 (2.50 quintate), Acetone-d_6 (2.05 quintate). Multiplicities are given as s (singlet); d (doublet); t (triplet); q (quartet); dd (doublet of doublet); dt (doublet of triplet); m (multiplet). Coupling constants are reported as *J* values in Hz (Hertz). Carbon nuclear magnetic resonance spectra (^{13}C NMR) are reported as δ in units of parts per million (ppm) downfield from $Si(CH_3)_4$ (δ 0.0) and relative to the signal of chloroform-d (δ 77.16, triplet), DMSO-d_6 (39.52 quintate), Acetone-d_6 (206.26 singlet and 29.84 septate). The mass spectra were recorded under EI/HRMS at 60,000 resolutions using a Thermo Scientific Exactive mass spectrometer. IR spectra were recorded on a Bruker FT-IR spectrometer.

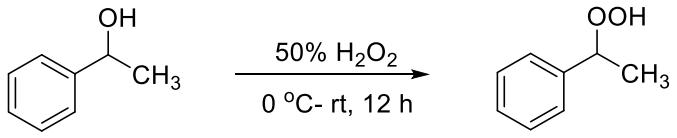
3.7. Experimental procedures

3.7.1. General procedure for the synthesis of (*E*)-3-benzylideneindolin-2-one

Aryldehyde (16.8 mL, 165 mmol) and piperidine (2.97 mL, 300 mmol) were added to a suspension of oxindole (20.0 g, 150 mmol) in ethanol (132 mL). The solution was heated at 80 °C for 1.5 h. The reaction was allowed to cool to room temperature. The precipitate was

filtered, washed with ethanol and dried to afford the product as a yellow solid (26.5 g, 80% yield).

3.7.2. General procedure for the synthesis of ethylbenzene hydroperoxides (EBHP)



43 **44**

At 0°C 5 g of $MgSO_4$ was added to 8 mL of 50% H_2O_2 for 30 min. To this mixture, 1-Phenylethanol **43** (8 mmol) was added dropwise and stirred at 0 °C for 2 h. The solution was then stirred at room temperature for a further 12 h and then quenched with $NaHCO_3$. The crude product was extracted with diethyl ether (3x15 mL) and the combined organic extracts were dried over $MgSO_4$. The solvent was removed in *vacuo* and the product **44** purified by column chromatography.

3.7.3. General procedure for the diastereoselective synthesis of spiro-epoxy oxindole from oxindole chalcones.

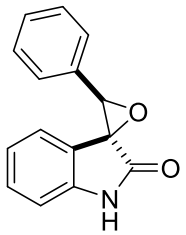
10 M aqueous solution of NaOH (3 equiv.) was added dropwise to the stirring solution of (*E*)-3-benzylideneindolin-2-one (30 mg, 0.13 mmol) and EBHP (2 equiv.) in 2 mL of hexane at room temperature. After 15 minutes 4 mL water was added and the product was extracted with ethyl acetate, evaporated in *vacuo* and the residue on silica gel (100-200 mesh) column chromatography with mixtures of ethyl acetate in hexane yielded the products.

3.8. Characterization data of spiro-epoxy oxindole

3'-Phenylspiro[indoline-3,2'-oxiran]-2-one (37a)

10 M aqueous solution of NaOH (3 equiv.) was added dropwise to the stirring solution of **(*E*)-3-benzylideneindolin-2-one** (30 mg, 0.13 mmol) and EBHP (2 equiv.) in 2 mL of hexane at room temperature. After 15 minutes 4 mL water was added and the product was

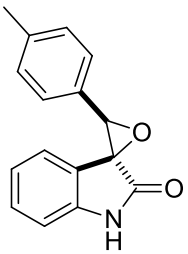
extracted with ethyl acetate, evaporated in *vacuo* and the residue on silica gel (100-200 mesh) column chromatography with mixtures of ethyl acetate in hexane yielded the product **37a.**



White solid (31 mg, 97%, m.p = 162-163.5 ^{o}C); R_f = 0.25 (hexane/ethyl acetate = 70/30); **IR (neat, cm^{-1}):** 3208, 2981, 1716, 1625, 1607, 1516,1468, 1345, 1245, 1222, 1016, 926, 839, 786; **^{1}H NMR (500 MHz, CDCl$_3$): δ** 9.43 (br, 1H), 7.49 (d, *J* =7.0 Hz, 2H), 7.40-7.46 (m, 3H), 7.23 (d, *J* = 8.0 Hz, 1H), 6.99 (d, *J* = 8.0 Hz, 1H), 6.76 (t, *J* = 7.5 Hz, 1H), 6.48 (d, *J* = 7.5 Hz, 1H), 4.86 (s, 1H); **^{13}C NMR (125 MHz, CDCl$_3$):** δ 174.6, 142.6, 130.3, 128.9, 128.6, 126.8, 124.0, 122.6, 121.3, 111.1, 65.2, 62.1; **HRMS (ESI) *m/z*:** calcd. for $C_{15}H_{12}NO_2$ ([*M*+H]$^+$): 238.0868, found 238.0870.

3'-(*p*-Tolyl)spiro[indoline-3,2'-oxiran]-2-one (37b)

10 M aqueous solution of NaOH (3 equiv.) was added dropwise to the stirring solution of (*E*)-3-(4-methylbenzylidene) indolin-2-one (30 mg, 0.13 mmol) and EBHP (2 equiv.) in 2 mL of hexane at room temperature. After 15 minutes 4 mL water was added and the product was extracted with ethyl acetate, evaporated in *vacuo* and the residue on silica gel (100-200 mesh) column chromatography with mixtures of ethyl acetate in hexane yielded the product **37b.**

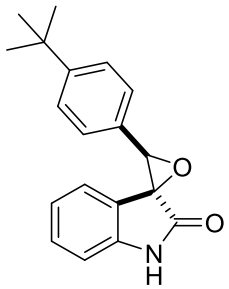


White solid (25 mg, 79%, m.p = 164-166 ^{o}C); R_f = 0.25 (hexane/ethyl acetate = 70/30); **IR (neat, cm^{-1}):** 3209, 2987, 1719, 1625, 1607, 1516,1469, 1342, 1246, 1229, 1015, 926, 832, 780; **^{1}H NMR (500 MHz, CDCl$_3$):** δ 9.02 (br, 1H), 7.36 (d, *J* =8.0 Hz, 2H), 7.22 - 7.20 (m, 3H), 6.95 (d, *J* = 7.5 Hz, 1H), 6.76 (t, *J* = 7.5 Hz, 1H), 6.51 (d, *J* = 7.5 Hz, 1H), 4.79 (s, 1H), 2.38 (s, 3H); **^{13}C NMR (125 MHz, CDCl$_3$):** δ 174.4, 142.4, 138.7, 130.2, 130.0, 129.3, 126.7, 124.1, 122.6, 121.4, 110.9, 65.4, 62.0, 21.4; **HRMS**

(ESI) *m/z*: calcd. for $C_{16}H_{14}NO_2$ ([*M*+H]$^+$): 252.1025, found 252.1026.

3'-(4-(*tert*-Butyl)phenyl)spiro[indoline-3,2'-oxiran]-2-one (37c)

10 M aqueous solution of NaOH (3 equiv.) was added dropwise to the stirring solution of (*E*)-3-(4-(tert-butyl) benzylidene)indolin-2-one (30 mg, 0.13 mmol) and EBHP (2 equiv.) in 2 mL of hexane at room temperature. After 15 minutes 4 mL water was added and the product was extracted with ethyl acetate, evaporated in *vacuo* and the residue on silica gel (100-200 mesh) column chromatography with mixtures of ethyl acetate in hexane yielded the product **37c**.

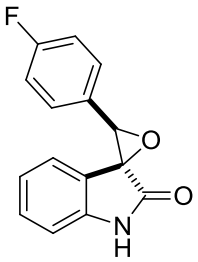


White solid (29 mg, 92%, m.p = 168-171 ^oC); R_f = 0.28 (hexane/ethyl acetate = 70/30); **IR (neat, cm^{-1})**: 3212, 2980, 1719, 1628, 1607, 1513,1472, 1348, 1246, 1230, 1019, 929, 838, 790; **^{1}H NMR (500 MHz, $CDCl_3$):** δ 8.52 (br, 1H), 7.38 - 7.44 (m, 4H), 7.22 (t, *J* = 7.5 Hz, 1H), 6.93 (d, *J* = 8.0 Hz, 1H), 6.77 (t, *J* = 7.5 Hz, 1H), 6.54 (d, *J* = 7.5 Hz, 1H), 4.79 (s, 1H), 1.33 (s, 9H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ 174.0, 152.0, 142.3, 130.2, 130.0, 126.6, 125.5, 124.2, 122.6, 121.5, 110.7, 65.4, 62.0, 34.8, 31.4; **HRMS (ESI) *m/z***: calcd. for $C_{19}H_{20}NO_2$ ([*M*+H]$^+$): 294.1494, found 294.1495.

3'-(4-Fluorophenyl)spiro[indoline-3,2'-oxiran]-2-one (37d)

10 M aqueous solution of NaOH (3 equiv.) was added dropwise to the stirring solution of (*E*)-3-(4-fluorobenzylidene) indolin-2-one(30 mg, 0.13 mmol) and EBHP (2 equiv.) in 2 mL of hexane at room temperature. After 15 minutes 4 mL water was added and the product was extracted with ethyl acetate, evaporated in *vacuo* and the residue on silica gel (100-200 mesh) column chromatography with mixtures of ethyl acetate in hexane yielded the product **37d**

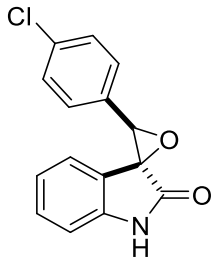
White solid (30 mg, 94%, m.p = 203-205 ^oC); R_f = 0.28 (hexane/ethyl acetate = 70/30); **IR (neat, cm^{-1}):** 3206,



2982, 1718, 1622, 1607, 1513,1468, 1340, 1245, 1225, 1017, 921, 836, 785; **^{1}H NMR (500 MHz, $CDCl_3$):** δ 8.96 (br, 1H), 7.43 - 7.46 (m, 2H), 7.22 – 7.26 (m, 1H), 7.11 (t, *J* = 8.5 Hz, 2H), 6.96 (d, *J* = 8.0 Hz, 1H), 6.78 (t, *J* = 7.5 Hz, 1H), 6.43 (d, *J* = 7.5 Hz, 1H), 4.78 (s, 1H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ 174.0, 163.9, 162.0, 142.5, 130.5, 128.7, 128.7, 124.0, 122.7, 121.1, 115.8, 115.7, 111.0, 64.6, 62.0; **HRMS (ESI) *m/z*:** calcd. for $C_{15}H_{11}FNO_2$ ([*M*+H]$^+$): 256.0774 found: 256.0777.

3'-(4-Chlorophenyl)spiro[indoline-3,2'-oxiran]-2-one (37e)

10 M aqueous solution of NaOH (3 equiv.) was added dropwise to the stirring solution of (*E*)-3-(4-chlorobenzylidene) indolin-2-one (30 mg, 0.13 mmol) and EBHP (2 equiv.) in 2 mL of hexane at room temperature. After 15 minutes 4 mL water was added and the product was extracted with ethyl acetate, evaporated in *vacuo* and the residue on silica gel (100-200 mesh) column chromatography with mixtures of ethyl acetate in hexane yielded the product **37e**

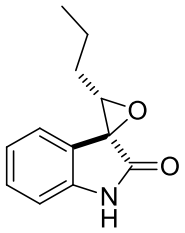


Pale yellow solid (28 mg, 88%, m.p = 246-249 ^{o}C); R_f = 0.28 (hexane/ethyl acetate = 70/30); **IR (neat, cm^{-1}):** 3202, 3095, 3067, 1719, 1624, 1493, 1468, 1430, 1342, 1223, 1205, 1089, 920, 816, 741; **^{1}H NMR (500 MHz, $CDCl_3$): δ** 8.01 (br, 1H), 7.40 (s, 4H), 7.24 (d, *J* = 8.0 Hz, 1H), 6.92 (d, *J* = 8.0 Hz, 1H), 6.79 (t, *J* = 7.5 Hz, 1H), 6.45 (d, *J* = 8.0 Hz, 1H), 4.76 (s, 1H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ 173.1, 142.3, 134.8, 131.6, 130.5, 128.9, 128.3, 124.1, 122.8, 120.9, 110.8, 64.6, 61.8; **HRMS (ESI) *m/z***: calcd. for $C_{15}H_{11}ClNO_2$ ([*M*+H]$^+$): 272.0478, found 272.0482.

***cis*-3'-Propylspiro[indoline-3,2'-oxiran]-2-one (37f)**

10 M aqueous solution of NaOH (3 equiv.) was added dropwise to the stirring solution of (*Z*)-3-butylideneindolin-2-one (30 mg, 0.13 mmol) and EBHP (2 equiv.) in 2 mL of

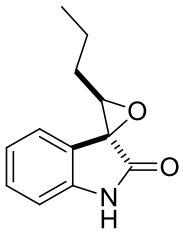
hexane at room temperature. After 15 minutes 4 mL water was added and the product was extracted with ethyl acetate, evaporated in *vacuo* and the residue on silica gel (100-200 mesh) column chromatography with mixtures of ethyl acetate in hexane yielded the product **37f**



White solid (16 mg, 50%, m.p = 160-162.5 ^{o}C); R_f = 0.28 (hexane/ethyl acetate = 70/30); IR (neat, cm^{-1}): 3157, 3094, 3037, 2959,2870, 1718, 1624, 1472, 1351, 1297, 1135, 1090, 1017, 948, 806, 754; **^{1}H NMR (500 MHz, $CDCl_3$):** δ 8.51 (br, 1H), 7.28 – 7.31 (m, 1H), 7.03 – 7.08 (m, 2H), 6.95 (d, J = 7.5 Hz, 1H), 3.62 (t, J = 6.0 Hz, 1H), 2.14 – 2.21 (m, 1H), 1.95-2.02 (m, 1H), 1.58 – 1.65 (m, 1H), 1.48 – 1.54 (m, 1H), 0.99 (t, J = 7.0 Hz, 3H); **^{13}C NMR (125 MHz, $CDCl_3$): δ** 174.1, 141.5, 130.0, 124.7, 122.8, 122.0, 110.6, 67.7, 60.00, 28.1, 19.8, 13.8; **HRMS (ESI) m/z:** calcd. for $C_{12}H_{14}NO_2$ ($[M+H]^+$): 204.1025, found 204.1028.

***trans*-3'-Propylspiro[indoline-3,2'-oxiran]-2-one (37g)**

10 M aqueous solution of NaOH (3 equiv.) was added dropwise to the stirring solution of (*E*)-3-butylideneindolin-2-one (30 mg, 0.13 mmol) and EBHP (2 equiv.) in 2 mL of hexane at room temperature. After 15 minutes 4 mL water was added and the product was extracted with ethyl acetate, evaporated in *vacuo* and the residue on silica gel (100-200 mesh) column chromatography with mixtures of ethyl acetate in hexane yielded the product **37g**

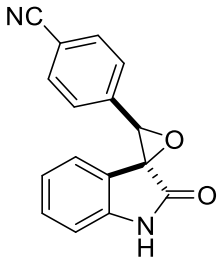


Transparent liquid (19 mg, 60%, R_f = 0.28 (hexane/ethyl acetate = 70/30); **IR (neat, cm^{-1}):** 3234, 3063, 2962, 2931, 2873, 1715, 1621, 1467, 1308, 1291, 1257, 1157, 1067, 1022,904, 747; **^{1}H NMR (500 MHz, $CDCl_3$):** δ 9.80 (br, 1H), 7.29 (t, *J* = 7.5 Hz, 1H), 7.15 – 7.16 (d, *J* = 7.5 Hz, 1H), 7.00 – 7.04 (m, 2H), 3.64 (t, *J* = 5.5 Hz, 1H), 1.86 – 1.91 (m, 1H), 1.75 – 1.79 (m, 1H), 1.57 – 1.61 (m, 1H), 1.46 – 1.51 (m, 1H), 0.96 (t, *J* = 7.5 Hz, 3H); **^{13}C NMR**

(125 MHz, $CDCl_3$): δ 175.6, 142.6, 130.1, 124.3, 122.7, 122.3, 111.2, 65.7, 60.82, 30.0, 19.7, 13.8; **HRMS** (ESI) *m*/*z*: calcd. for $C_{12}H_{14}NO_2$ ([*M*+H]$^+$): 204.1025, found: 204.1030.

2-Oxospiro[indoline-3,2'-oxiran]-3'-yl)benzonitrile (37h)

10 M aqueous solution of NaOH (3 equiv.) was added dropwise to the stirring solution of (*E)*-4-((2-oxoindolin-3-ylidene) methyl) benzonitrile (30 mg, 0.13 mmol) and EBHP (2 equiv.) in 2 mL of hexane at room temperature. After 15 minutes 4 mL water was added and the product was extracted with ethyl acetate, evaporated in *vacuo* and the residue on silica gel (100-200 mesh) column chromatography with mixtures of ethyl acetate in hexane yielded the product **37h**

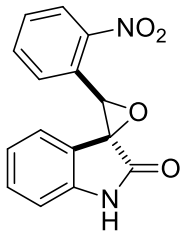


White solid (31 mg, 97%, m.p = 172-175 ^oC); R_f = 0.28 (hexane/ethyl acetate = 70/30); **IR (neat, cm^{-1}):** 3196, 3154,3075, 2225, 1715, 1623, 1508, 1467, 1416, 1223, 1103, 922, 855, 826, 741; **^{1}H NMR (500 MHz, Acetone-d_6):** δ 9.67 (br, 1H), 7.76 (d, *J* = 8.0 Hz, 2H), 7.67 (d, *J* = 8.0 Hz, 2H), 7.12 (td, *J* = 8.0 Hz, *J* = 1.0 Hz, 1H), 6.86 (d, *J* = 7.5 Hz, 1H), 6.61 (t, *J* = 7.5 Hz, 1H), 6.32 (d, *J* = 7.5 Hz, 1H), 4.67 (s, 1H); **^{13}C NMR (125 MHz, Acetone-d_6):** δ 171.4, 144.0, 139.1, 132.2, 130.5, 127.8, 123.3, 121.7, 120.6, 118.2, 112.2, 110.6, 110.6, 64.0, 61.8; **HRMS (ESI) *m*/*z*:** calcd. for $C_{16}H_{10}N_2O_2$ ([*M*+Na]$^+$): 263.0821, found 263.0826.

3'-(2-Nitrophenyl)spiro[indoline-3,2'-oxiran]-2-one (37i)

10 M aqueous solution of NaOH (3 equiv.) was added dropwise to the stirring solution of (*E*)-3-(2-nitrobenzylidene) indolin-2-one30 mg, 0.13 mmol) and EBHP (2 equiv.) in 2 mL of hexane at room temperature. After 15 minutes 4 mL water was added and the product was extracted with ethyl acetate, evaporated in *vacuo* and the residue on silica gel (100-

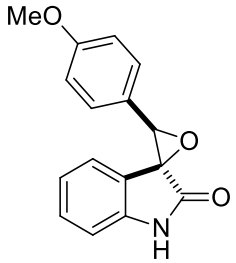
200 mesh) column chromatography with mixtures of ethyl acetate in hexane yielded the product **37i**



Pale yellow solid (31 mg, 98%, m.p = 174 – 176 ^{o}C); R_f = 0.28 (hexane/ethyl acetate = 70/30); **IR (neat, cm^{-1}):** 3232, 3098, 2925, 2856, 1729, 1622, 1577, 1523, 1468, 1411, 1342, 1217, 1202, 1161, 1081, 914, 855, 791; **^{1}H NMR (500 MHz, Acetone-d$_6$):** δ 9.69 (br, 1H), 8.10 (d, *J* = 8.5 Hz, 1H), 7.86 – 7.89 (m, 2H), 7.64 (d, *J* = 6.5 Hz, 1H), 7.08 (t, *J* = 7.5 Hz, 1H), 6.85 (d, *J* = 7.5 Hz, 1H), 6.53 (t, *J* = 7.5 Hz, 1H), 5.96 (d, *J* = 7.5 Hz, 1H), 4.95 (s, 1H); **^{13}C NMR (125 MHz, Acetone-d$_6$):** δ 171.5, 147.2, 143.9, 134.6, 130.7, 130.5, 130.0, 129.4, 124.7, 122.5, 121.6, 120.6, 110.7, 110.6, 64.0, 61.7; **HRMS (ESI) *m/z***: calcd. For $C_{15}H_{10}N_2O_4$ ([*M*+Na]$^{+}$): 305.0538, found 305.0543.

3'-(4-Methoxyphenyl)spiro[indoline-3,2'-oxiran]-2-one (37j)

10 M aqueous solution of NaOH (3 equiv.) was added dropwise to the stirring solution of €-3-(4-methoxy benzylidene)indolin-2-one (30 mg, 0.13 mmol) and EBHP (2 equiv.) in 2 mL of hexane at room temperature. After 15 minutes 4 mL water was added and the product was extracted with ethyl acetate, evaporated in *vacuo* and the residue on silica gel (100-200 mesh) column chromatography with mixtures of ethyl acetate in hexane yielded the product **37j.**

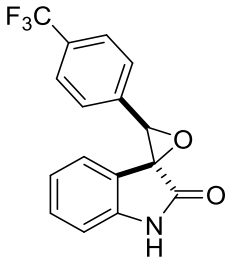


White solid (31 mg, 98%, m.p = 179 – 182 ^{o}C); R_f = 0.28 (hexane/ethyl acetate = 70/30); **IR (neat, cm^{-1}):** 3142, 3075, 3023, 2957, 2834, 1723, 1614, 1514, 1464, 1394, 1304, 1219, 1033, 894, 792; **^{1}H NMR (500 MHz, CDCl$_3$):** **δ** 8.91 (br, 1H), 7.39 (d, *J* = 8.5 Hz, 2H), 7.22 (t, *J* = 7.5 Hz, 1H), 6.95 (d, *J* = 8.5 Hz, 3H), 6.77 (t, *J* = 7.5 Hz, 1H), 6.50 (d, *J* = 7.5 Hz, 1H), 4.77 (s, 1H), 3.83 (s, 3H); **^{13}C NMR (125 MHz, CDCl$_3$):** δ 174.3, 160.0, 142.4, 130.2, 128.2, 125.1, 124.2, 122.6, 121.5, 114.0, 110.8, 65.2, 62.1,

55.4; **HRMS (ESI) *m/z***: calcd. For $C_{16}H_{14}NO_3$ ([*M*+H]$^+$): 268.0974, found: 268.0978.

3'-(4-(Trifluoromethyl)phenyl)spiro[indoline-3,2'-oxiran]-2-one (37k)

10 M aqueous solution of NaOH (3 equiv.) was added dropwise to the stirring solution of €-3-(4-(trifluoromethyl)benzylidene)indolin-2-one (30 mg, 0.13 mmol) and EBHP (2 equiv.) in 2 mL of hexane at room temperature. After 15 minutes 4 mL water was added and the product was extracted with ethyl acetate, evaporated in *vacuo* and the residue on silica gel (100-200 mesh) column chromatography with mixtures of ethyl acetate in hexane yielded the product **37k**

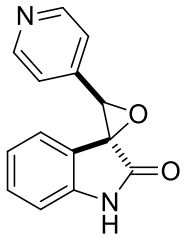


White solid (25 mg, 79%, m.p = 202 -205 ^{o}C); R_f = 0.19 (hexane/ethyl acetate = 70/30); **IR (neat, cm^{-1}):** 3214, 2989, 1719, 1623, 1610, 1516,1469, 1343, 1246, 1229, 1015, 924, 837, 786; **^{1}H NMR (500 MHz, Acetone-d$_6$):** δ 9.85 (br, 1H), 7.83 (s, 4H), 7.24 – 7.26 (m, 1H), 7.00 (d, *J* = 8.0 Hz, 1H), 6.73 – 6.76 (m, 1H), 6.47 (d, *J* = 8.0 Hz, 1H), 4.83 (s, 1H); **^{13}C NMR (125 MHz, Acetone-d$_6$):** δ 171.67, 144.0, 138.3, 130.4, 127.6, 125.4, 125.3, 125.3, 123.3, 121.7, 120.8, 110.6, 64.0, 61.8; **HRMS (ESI) *m/z*** calcd. for $C_{16}H_{10}F_3NO_2$ ([*M*+Na]$^+$): 328.0561, found 328.0570.

3'-(Pyridin-4-yl)spiro[indoline-3,2'-oxiran]-2-one (37l)

10 M aqueous solution of NaOH (3 equiv.) was added dropwise to the stirring solution of (*E*)-3-(pyridin-4-ylmethylene)indolin-2-one (30 mg, 0.13 mmol) and EBHP (2 equiv.) in 2 mL of hexane at room temperature. After 15 minutes 4 mL water was added and the product was extracted with ethyl acetate, evaporated in *vacuo* and the residue on silica gel (100-200 mesh) column chromatography with mixtures of ethyl acetate in hexane yielded the product **37l**

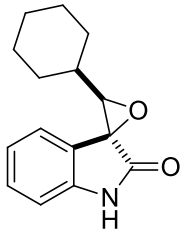
White solid (22 mg, 70%, m.p = 154 -156 ^{o}C); R_f = 0.28 (hexane/ethyl acetate = 70/30); **IR (neat, cm^{-1}):** 3069, 2999, 2874, 2813, 2683, 1738, 1626, 1604, 1554, 1470,



1414, 1329, 1292, 1263, 1155, 1104, 1069, 936, 895, 746; **^{1}H NMR (500 MHz, DMSO-d$_6$):** δ 10.94 (br, 1H), 8.64 (d, *J* = 6.0 Hz, 2H), 7.53 (d, *J* = 6.0 Hz, 2H), 7.25 (t, *J* = 7.5 Hz, 1H), 6.93 (d, *J* = 7.5 Hz, 1H), 6.74 (t, *J* = 7.5 Hz, 1H), 6.40 (d, *J* = 8.0 Hz, 1H), 4.75 (s, 1H); **^{13}C NMR (125 MHz, DMSO-d$_6$):** δ 172.1, 150.1, 144.4, 142.4, 131.1, 123.4, 122.2, 122.0, 120.6, 111.2, 63.5, 62.0; **HRMS (ESI)** *m*/*z* : [calcd. for $C_{14}H_{11}N_2O_2$ ([*M*+H]$^+$): 239.0821, found: 239.0823.

3'-Cyclohexylspiro[indoline-3,2'-oxiran]-2-one (37m)

10 M aqueous solution of NaOH (3 equiv.) was added dropwise to the stirring solution of (*E*)-3-(cyclohexylmethylene)indolin-2-one (30 mg, 0.13 mmol) and EBHP (2 equiv.) in 2 mL of hexane at room temperature. After 15 minutes 4 mL water was added and the product was extracted with ethyl acetate, evaporated in *vacuo* and the residue on silica gel (100-200 mesh) column chromatography with mixtures of ethyl acetate in hexane yielded the product **37m**

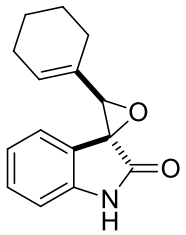


Transparent liquid (18 mg, 57%; R_f = 0.28 (hexane/ethyl acetate = 70/30); **IR (neat, cm^{-1}):** 3230, 3064, 2961, 2876, 1717, 1621, 1469, 1306, 1290, 1251, 1156, 1065, 1021,903, 741; **^{1}H NMR (500 MHz, Acetone-d$_6$):** δ 9.53 (br, 1H), 7.20 (t, *J* = 7.5 Hz, 1H), 7.16 (d, *J* = 7.5 Hz, 1H), 6.89 - 6.93 (m, 2H), 3.13 (d, *J* = 9.0 Hz, 1H), 1.62 – 1.67 (m, 2H), 1.51 – 1.53 (m, 2H), 1.10 - 1.27 (m, 7H); **^{13}C NMR (125 MHz, Acetone-d$_6$):** δ 173.1, 143.7, 129.8, 123.8, 122.3, 121.9, 110.5, 68.9, 59.9, 36.7, 30.2, 28.1, 25.8, 25.1, 25.0; **HRMS (ESI) *m*/*z***: calcd. for $C_{15}H_{17}NO_2$ ([*M*+Na]$^+$): 266.1157, found 266.1163.

3'-(Cyclohex-1-en-1-yl)spiro[indoline-3,2'-oxiran]-2-one (37n)

10 M aqueous solution of NaOH (3 equiv.) was added dropwise to the stirring solution of (*E*)-3-(cyclohex-1-en-1-ylmethylene) indolin-2-one (30 mg, 0.13 mmol) and EBHP (2 equiv.) in 2 mL of hexane at room temperature. After 15 minutes 4 mL water was added

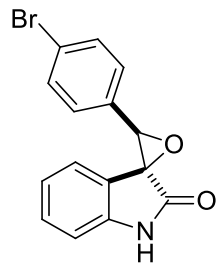
and the product was extracted with ethyl acetate, evaporated in *vacuo* and the residue on silica gel (100-200 mesh) column chromatography with mixtures of ethyl acetate in hexane yielded the product **37n**



Pale yellow liquid (22 mg, 69%,) R_f = 0.28 (hexane/ethyl acetate = 70/**30); IR (neat, cm^{-1}):** 3234, 3061, 2962, 2870, 1715, 1621, 1470, 1303, 1292, 1254, 1153, 1066, 1022, 903, 745; **^{1}H NMR (500 MHz, Acetone-d$_6$):** δ 9.52 (br, 1H), 7.18 (t, *J* = 7.5 Hz, 1H), 7.01 (d, *J* = 7.5 Hz, 1H), 6.81 – 6.87 (m, 2H), 5.88 (s, 1H), 3.78 (s, 1H), 2.04 – 2.05 (m, 2H), 1.45 – 1.49 (m, 6H); **^{13}C NMR (125 MHz, Acetone-d$_6$): δ** 172.4, 143.6, 130.5, 129.9, 125.0, 123.5, 121.6, 110.3, 65.5, 60.2, 25.1, 24.2, 22.1, 21.9. **HRMS (ESI) *m*/*z***: calcd. for $C_{15}H_{15}NO_2$ ([*M*+Na]$^+$): 264.1000, found, 264.1006.

3'-(4-Bromophenyl)spiro[indoline-3,2'-oxiran]-2-one (37o)

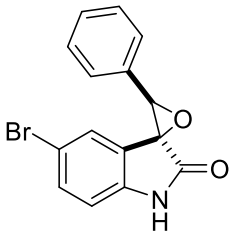
10 M aqueous solution of NaOH (3 equiv.) was added dropwise to the stirring solution of (*E*)-3-(4-bromobenzylidene)indolin-2-one (30 mg, 0.13 mmol) and EBHP (2 equiv.) in 2 mL of hexane at room temperature. After 15 minutes 4 mL water was added and the product was extracted with ethyl acetate, evaporated in *vacuo* and the residue on silica gel (100-200 mesh) column chromatography with mixtures of ethyl acetate in hexane yielded the product **37o**



White solid (29 mg, 92%, m.p = 184 -186 ^{o}C); R_f = 0.28 (hexane/ethyl acetate = 70/30); **IR (neat, cm^{-1}):** 3211, 2990, 1718, 1623, 1610, 1516, 1468, 1416, 1342, 1241, 1228, 1019, 920, 834, 789; **^{1}H NMR (500 MHz, DMSO-d$_6$):** δ 10.88 (br, 1H), 7.65 (d, *J* = 8.5 Hz, 2H), 7.47 (d, *J* = 8.5 Hz, 2H), 7.25 (t, *J* = 7.5 Hz, 1H), 6.92 (d, *J* = 8.0 Hz, 1H), 6.76 (t, *J* = 7.5 Hz, 1H), 6.38 (d, *J* = 7.5 Hz, 1H), 4.69 (s, 1H); **^{13}C NMR (125 MHz, DMSO-d$_6$):** δ 172.3, 144.3, 133.1, 131.8, 130.9, 129.4, 123.5, 122.2, 122.0, 120.9, 111.1, 64.2, 62.1; **HRMS (ESI) *m*/*z***: calcd. for $C_{15}H_{11}{}^{79}BrNO_2$ ([*M*+H]$^+$): 315.9973, found 315.9980.

5-Bromo-3'-phenylspiro[indoline-3,2'-oxiran]-2-one (39a)

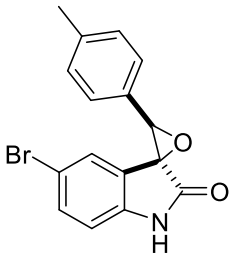
10 M aqueous solution of NaOH (3 equiv.) was added dropwise to the stirring solution of (*E*)-3-benzylidene-5-bromoindolin-2-one (30 mg, 0.13 mmol) and EBHP (2 equiv.) in 2 mL of hexane at room temperature. After 15 minutes 4 mL water was added and the product was extracted with ethyl acetate, evaporated in *vacuo* and the residue on silica gel (100-200 mesh) column chromatography with mixtures of ethyl acetate in hexane yielded the product **39a**.



White solid (27 mg, 86%, m.p = 181- 184 ^{o}C); R_f = 0.22 (hexane/ethyl acetate = 70/30); **IR (neat, cm^{-1})**: 3199, 3088, 2922, 2848, 1621, 1472, 1410, 1311, 1254, 1206, 1119, 1020, 919, 816; **^{1}H NMR (500 MHz, CDCl$_3$):** δ 8.91 (br, 1H), 7.37 (s, 5H), 7.28 (d, *J* = 8.0 Hz, 1H), 6.77 (d, 8.0 Hz, 1H), 6.48 (s, 1H), 4.75 (s, 1H), **^{13}C NMR (125 MHz, CDCl$_3$):** δ 173.6, 141.4, 133.1, 132.5, 129.3, 128.8, 127.3, 126.8, 123.4, 115.3, 65.5, 61.6; **HRMS (ESI) *m*/*z***: calcd. for $C_{15}H_{10}{}^{79}BrNO_2$ ([*M*+Na]$^+$): 337.9793, and found 337.9793.

5-Bromo-3'-(*m*-tolyl)spiro[indoline-3,2'-oxiran]-2-one (39b)

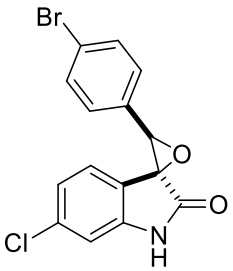
10 M aqueous solution of NaOH (3 equiv.) was added dropwise to the stirring solution of (*E*)-5-bromo-3-(4-methylbenzylidene)indolin-2-one (30 mg, 0.13 mmol) and EBHP (2 equiv.) in 2 mL of hexane at room temperature. After 15 minutes 4 mL water was added and the product was extracted with ethyl acetate, evaporated in *vacuo* and the residue on silica gel (100-200 mesh) column chromatography with mixtures of ethyl acetate in hexane yielded the product **39b**.



White solid (30 mg, 95%, m.p = 203.6 – 205.8 ^{o}C); R_f = 0.25 (hexane/ethyl acetate = 70/30); **IR (neat, cm^{-1}):** 3204, 3089, 2983, 2926, 2846, 1624, 1513,1469, 1436, 1311, 1258, 1225, 1206, 1070, 921, 816; **^{1}H NMR (500 MHz, $CDCl_3$):** δ 9.00 (br, 1H), 7.32-7.35 (m, 3H), 7.23 (m, 2H), 6.83 (d, *J* = 8.5 Hz, 1H), 6.61 (s, 1H), 4.78 (s, 1H), 2.39 (s, 3H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ 173.8, 141.4, 139.2, 133.0, 129.4, 127.3, 126.7, 123.6, 115.3, 112.2, 65.7, 61.8, 21.4; **HRMS (ESI)** ***m/z***: calcd. for $C_{16}H_{12}{}^{79}BrNO_2$ ([*M*+Na]$^{+}$): 351.9949, found 351.9951.

3'-(4-Bromophenyl)-6-chlorospiro[indoline-3,2'-oxiran]-2-one (39c)

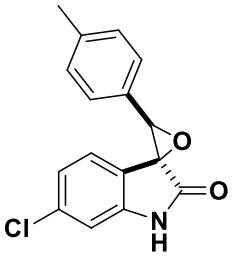
10 M aqueous solution of NaOH (3 equiv.) was added dropwise to the stirring solution of (*E*)-3-(4-bromobenzylidene)-6-chloroindolin-2-one (30 mg, 0.13 mmol) and EBHP (2 equiv.) in 2 mL of hexane at room temperature. After 15 minutes 4 mL water was added and the product was extracted with ethyl acetate, evaporated in *vacuo* and the residue on silica gel (100-200 mesh) column chromatography with mixtures of ethyl acetate in hexane yielded the product 3**9c**.



White solid (27 mg, 86%, m.p = 201.4 - 203 ^{o}C); R_f = 0.22 (hexane/ethyl acetate = 70/30); **IR (neat, cm^{-1}):** 3019, 3004, 2916, 2848, 1727, 1619, 1488, 1413, 1340, 1280, 1243, 1226, 1165, 1103, 1067, 927, 913, 852, 744; **^{1}H NMR (500 MHz, CDCl$_3$):** δ 8.03 (br, 1H), 7.59 (d, *J* = 8.0 Hz, 2H), 7.35 (d, *J* = 8.0 Hz, 2H), 6.95 (s, 1H), 6.80 (d, *J* = 8.0 Hz, 1H), 6.37 (d, *J* = 8.0 Hz, 1H), 4.76 (s, 1H); **^{13}C NMR (125 MHz, CDCl$_3$)** δ 172.1, 139.8, 131.9, 131.8, 130.4, 128.8, 128.5, 126.6, 123.6, 122.2, 116.0, 64.9, 62.2; **HRMS (ESI) *m/z*:** calcd. for $C_{15}H_9{}^{79}BrClNO_2$ ([*M*+Na]$^{+}$) : 371.9403; found 371.9407.

6-Chloro-3'-(*p*-Tolyl)spiro[indoline-3,2'-oxiran]-2-one (39d)

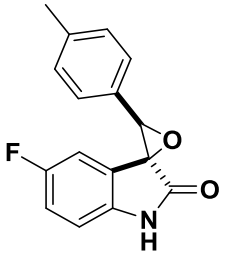
10 M aqueous solution of NaOH (3 equiv.) was added dropwise to the stirring solution of (*E*)-6-chloro-3-(4-methylbenzylidene)indolin-2-one (30 mg, 0.13 mmol) and EBHP (2 equiv.) in 2 mL of hexane at room temperature. After 15 minutes 4 mL water was added and the product was extracted with ethyl acetate, evaporated in *vacuo* and the residue on silica gel (100-200 mesh) column chromatography with mixtures of ethyl acetate in hexane yielded the product **39d**



White solid (27 mg, 86%, m.p = 175- 178.5 ^{o}C); R_f = 0.31 (hexane/ethyl acetate = 70/30); **IR (neat, cm^{-1})**: 3214, 3138, 2916, 2848, 1723, 1615, 1485, 1447, 1328, 1219, 1116, 1075, 921, 894, 728; **^{1}H NMR (500 MHz, CDCl$_3$):** δ 9.08 (br, 1H), 7.33(d, *J* = 8.0 Hz, 2H), 7.22 (d, *J* = 8.0 Hz, 2H), 6.96 (s, 1H), 6.74 (d, *J* = 8.0 Hz, 1H), 6.39 (d, *J* = 8.0 Hz, 1H), 4.78 (s, 1H), 2.38 (s, 3H), **^{13}C NMR (125 MHz, CDCl$_3$):** δ 174.2, 143.4, 139.0, 136., 129.7, 129.4, 126.7, 125.0, 122.8, 119.9, 111.6, 65.5, 61.7, 21.4; **HRMS (ESI) *m/z*:** calcd. for $C_{16}H_{12}ClNO_2$ ([*M*+Na]$^{+}$): 308.0454, found 308.0458.

5-Fluoro-3'-(*p*-Tolyl)spiro[indoline-3,2'-oxiran]-2-one (39e)

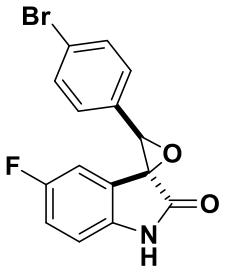
10 M aqueous solution of NaOH (3 equiv.) was added dropwise to the stirring solution of (*E*)-5-fluoro-3-(4-methylbenzylidene)indolin-2-one (30 mg, 0.13 mmol) and EBHP (2 equiv.) in 2 mL of hexane at room temperature. After 15 minutes 4 mL water was added and the product was extracted with ethyl acetate, evaporated in *vacuo* and the residue on silica gel (100-200 mesh) column chromatography with mixtures of ethyl acetate in hexane yielded the product **39e**



White solid (24 mg, 77%, m.p = 193- 196.5 ^{o}C); R_f = 0.22 (hexane/ethyl acetate = 70/30); **IR (neat, cm^{-1}):** 3210, 3191,2916, 1719, 1631, 1612, 1518, 1482, 1468, 1301, 1255, 1180, 1151, 899, 857, 745; **^{1}H NMR (500 MHz, $CDCl_3$):** δ 8.78 (s, 1H), 7.36 (d, 7.5 Hz, 2H), 7.25 - 7.28 (m, 2H), 6.93 – 6.96 (m, 1H), 6.88 - 6.90 (m, 1H), 6.28 (d, *J* = 8.5 Hz, 1H), 4.81 (s, 1H), 2.41 (s, 3H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ 174.2, 159.7, 157.7, 139.1, 138.3, 129.5, 126.6, 123.2, 116.8, 112.2, 111.4, 65.6, 62.0, 21.4; **HRMS (ESI) *m*/*z***: calcd. for $C_{16}H_{12}FNO_2$ ([*M*+Na]$^{+}$): 292.0750, found 292.0755.

3'-(4-Bromophenyl)-5-fluorospiro[indoline-3,2'-oxiran]-2-one (39f)

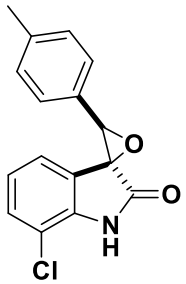
10 M aqueous solution of NaOH (3 equiv.) was added dropwise to the stirring solution of (*E*)-3-(4-bromobenzylidene)-5-fluoroindolin-2-one (30 mg, 0.13 mmol) and EBHP (2 equiv.) in 2 mL of hexane at room temperature. After 15 minutes 4 mL water was added and the product was extracted with ethyl acetate, evaporated in *vacuo* and the residue on silica gel (100-200 mesh) column chromatography with mixtures of ethyl acetate in hexane yielded the product **39f**



White solid (29 mg, 92%, m.p = 203 - 205 ^{o}C); R_f = 0.28 (hexane/ethyl acetate = 70/30); **IR (neat, cm^{-1}):** 3214, 3193,2918, 1716, 1634, 1616, 1513, 1487, 1465, 1308, 1256, 1182, 1151, 892, 856, 743; **^{1}H NMR (500 MHz, $CDCl_3$):** δ 8.36 (br, 1H), 7.61 (d, *J* = 8.0 Hz, 2H), 7.36 (d, *J* = 8.0 Hz, 2H), 6.96-6.99 (m, 1H), 6.87-6.89 (m, 1H), 6.23 (d, *J* = 7.5 Hz, 1H), 4.77 (s, 1H); **^{13}C NMR (125 MHz, $CDCl_3$) δ** 173.0, 138.3, 132.1, 128.4, 123.4, 117.1, 117.0, 112.2, 112.0, 111.4, 111.4, 64.9, 61.8; **HRMS (ESI) *m/z***: calcd. for $C_{15}H_9{}^{79}BrFNO_2$ ([*M*+Na]$^{+}$): 355.9698, found 355.9706.

7-Chloro-3'-(*p*-tolyl)spiro[indoline-3,2'-oxiran]-2-one (39g)

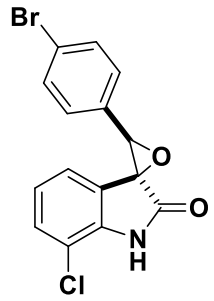
10 M aqueous solution of NaOH (3 equiv.) was added dropwise to the stirring solution of (*E*)-7-chloro-3-(4-methylbenzylidene)indolin-2-one (30 mg, 0.13 mmol) and EBHP (2 equiv.) in 2 mL of hexane at room temperature. After 15 minutes 4 mL water was added and the product was extracted with ethyl acetate, evaporated in *vacuo* and the residue on silica gel (100-200 mesh) column chromatography with mixtures of ethyl acetate in hexane yielded the product **39g**



White solid (24 mg, 76%, m.p = 201 - 203 ^{o}C); R_f = 0.38 (hexane/ethyl acetate = 70/30); IR (neat, cm^{-1}): 3216, 3195,2914, 1720, 1635, 1615, 1517, 1483, 1464, 1302, 1259, 1182, 1156, 894, 856, 749; **^{1}H NMR (500 MHz, $CDCl_3$):** δ 8.33 (br, 1H), 7.34 (d, *J* = 7.5 Hz, 2H), 7.22-7.24 (m, 3H), 6.72 – 6.74 (m, 1H), 6.43 (d, *J* = 8.0 Hz, 1H), 4.82 (s, 1H), 2.40 (s, 3H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ 172.7, 139.8, 138.9, 130.0, 129.7, 129.3, 126.7, 123.4, 123.2, 122.4, 115.8, 65.7, 62.3, 21.4; **HRMS (ESI) *m/z***: calcd. for $C_{16}H_{12}ClNO_2$ ([*M*+Na]$^{+}$): 308.0454, found 308.0454.

3'-(4-Bromophenyl)-7-chlorospiro[indoline-3,2'-oxiran]-2-one (39h)

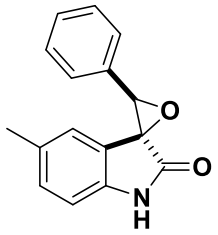
10 M aqueous solution of NaOH (3 equiv.) was added dropwise to the stirring solution of (*E*)-3-(4-bromobenzylidene)-7-chloroindolin-2-one (30 mg, 0.13 mmol) and EBHP (2 equiv.) in 2 mL of hexane at room temperature. After 15 minutes 4 mL water was added and the product was extracted with ethyl acetate, evaporated in *vacuo* and the residue on silica gel (100-200 mesh) column chromatography with mixtures of ethyl acetate in hexane yielded the product **39h**



White solid (24 mg, 77%, m.p = 208 - 210 ^{o}C); R_f = 0.36 (hexane/ethyl acetate = 70/30); **IR (neat, cm^{-1}):** 3213, 3196,2917, 1720, 1635, 1618, 1519, 1484, 1470, 1305, 1256, 1182, 1154, 899, 858, 742; **^{1}H NMR (500 MHz, $CDCl_3$):** δ 7.94 (br, 1H), 7.59 (d, *J* = 7.5 Hz, 2H), 7.36 (d, *J* = 8.0 Hz, 2H), 7.25 – 7.28 (m, 1H), 6.77 (t, *J* = 8.0 Hz, 1H), 6.37 (d, *J* = 7.5 Hz, 1H), 4.77 (s, 1H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ 171.8, 139.8, 131.9, 131.8, 130.4, 128.5, 123.6, 123.2, 122.6, 122.3, 116.0, 64.9, 62.2; **HRMS (ESI) *m/z***: ([*M*+H]$^{+}$) calcd. for $C_{15}H_9{}^{79}BrClNO_2$: 349.9583, found, 349.9586.

5-Methyl-3'-phenylspiro[indoline-3,2'-oxiran]-2-one (39i)

10 M aqueous solution of NaOH (3 equiv.) was added dropwise to the stirring solution of (*E*)-3-benzylidene-5-methylindolin-2-one (30 mg, 0.13 mmol) and EBHP (2 equiv.) in 2 mL of hexane at room temperature. After 15 minutes 4 mL water was added and the product was extracted with ethyl acetate, evaporated in *vacuo* and the residue on silica gel (100-200 mesh) column chromatography with mixtures of ethyl acetate in hexane yielded the product **39i**

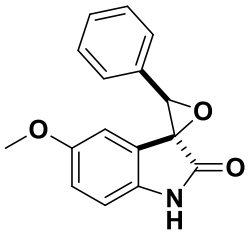


White solid (29 mg, 90%), m.p = 161- 163 ^{o}C; R_f = 0.22 (hexane/ethyl acetate = 70/30); **IR (neat, cm^{-1}):** 3072, 2992, 2876, 2810, 2683, 1738, 1626, 1604, 1554, 1471, 1416, 1328, 1290, 1261, 1156, 1102, 1071, 938, 896, 748; **^{1}H NMR (500 MHz, $CDCl_3$):** δ 8.41 (br, 1H), 7.47-7.38 (m, 5H), 7.01 (d, *J* = 8.0 Hz,

1H), 6.80 (d, *J* = 8.0 Hz, 1H), 6.25 (s, 1H), 4.80 (s, 1H), 2.05 (s, 3H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ 173.9, 139.9, 133.2, 132.2, 130.6, 128.8, 128.5, 126.9, 124.9, 121.3, 110.4, 65.2, 62.0, 21.0; **HRMS (ESI)** *m*/*z* : [calcd. for $C_{16}H_{13}NNaO_2$ ([*M*+Na]$^+$): 274.0844, found: 274.0843.

5-Methoxy-3'-phenylspiro[indoline-3,2'-oxiran]-2-one (39j)

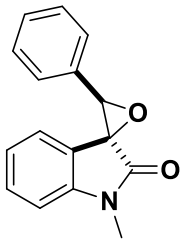
10 M aqueous solution of NaOH (3 equiv.) was added dropwise to the stirring solution of (*E*)-3-benzylidene-5-methoxyindolin-2-one (30 mg, 0.13 mmol) and EBHP (2 equiv.) in 2 mL of hexane at room temperature. After 15 minutes 4 mL water was added and the product was extracted with ethyl acetate, evaporated in *vacuo* and the residue on silica gel (100-200 mesh) column chromatography with mixtures of ethyl acetate in hexane yielded the product **39j**



White solid (27 mg, 86%, m.p = 165 - 168 ^{o}C); R_f = 0.12 (hexane/ethyl acetate = 70/30); **IR (neat, cm^{-1}):** 3142, 3076, 3024, 2957, 2834, 1723, 1614, 1514, 1466, 1392, 1306, 1219, 1033, 894, 792; **^{1}H NMR (500 MHz, $CDCl_3$):** δ 8.42 (br, 1H), 7.47-7.38 (m, 5H), 6.82 (d, *J* = 8.5 Hz, 1H), 6.75 (dd, *J* = 8.5, 2.5 Hz, 1H), 6.01 (d, *J* = 2.0 Hz, 1H), 4.82 (s, 1H), 3.46 (s, 3H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ 173.8, 155.5, 135.6, 133.1, 128.9, 128.6, 126.9, 122.4, 115.8, 111.2, 110.4, 65.1, 62.0, 55.5; **HRMS (ESI)** *m*/*z* : [calcd. for $C_{16}H_{13}NNaO_3$ ([*M*+Na]$^+$): 290.0793, found: 290.0793

1-Methyl-3'-phenylspiro[indoline-3,2'-oxiran]-2-one (39k)

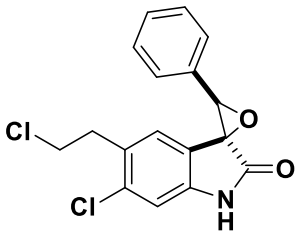
10 M aqueous solution of NaOH (3 equiv.) was added dropwise to the stirring solution of (*E*)-3-benzylidene-1-methylindolin-2-one (30 mg, 0.13 mmol) and EBHP (2 equiv.) in 2 mL of hexane at room temperature. After 15 minutes 4 mL water was added and the product was extracted with ethyl acetate, evaporated in *vacuo* and the residue on silica gel (100-200 mesh) column chromatography with mixtures of ethyl acetate in hexane yielded the product **39k.**



White solid (24 mg, 76%, m.p = 178- 180.5 ^{o}C); R_f = 0.37 (hexane/ethyl acetate = 70/30); **IR (neat, cm^{-1}):** 2996, 2872, 2810, 2679, 1738, 1626, 1600, 1554, 1470, 1414, 1329, 1292, 1263, 1155, 1104, 1066, 936, 895, 745; **^{1}H NMR (500 MHz, $CDCl_3$):** δ 7.38-7.29 (m, 5H), 7.19 (d, *J* = 7.5 Hz, 1H), 6.79 (d, *J* = 7.5 Hz, 1H), 6.69 (t, *J* = 7.5 Hz, 1H), 6.39 (d, *J* = 7.5 Hz, 1H), 4.75 (s, 1H), 3.22 (s, 3H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ 171.8, 145.3, 133.3, 130.2, 128.8, 128.5, 126.8, 123.7, 122.6, 121.0, 108.7, 65.1, 61.7, 26.7; **HRMS (ESI)** *m*/*z* : [calcd. for $C_{16}H_{13}NNaO_2$ ([*M*+Na]$^{+}$): 274.0844, found: 274.0853.

6-Chloro-5-(2-chloroethyl)-3'-phenylspiro[indoline-3,2'-oxiran]-2-one (39l)

10 M aqueous solution of NaOH (3 equiv.) was added dropwise to the stirring solution of (*E*)-3-benzylidene-6-chloro-5-(2-chloroethyl)indolin-2-one (30 mg, 0.13 mmol) and EBHP (2 equiv.) in 2 mL of hexane at room temperature. After 15 minutes 4 mL water was added and the product was extracted with ethyl acetate, evaporated in *vacuo* and the residue on silica gel (100-200 mesh) column chromatography with mixtures of ethyl acetate in hexane yielded the product **39l.**

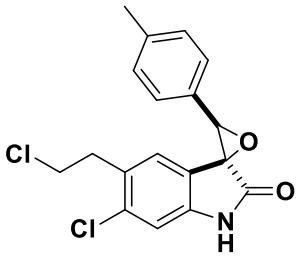


White solid (28 mg, 90%, m.p = 186- 188 ^{o}C); R_f = 0.30 (hexane/ethyl acetate = 70/30); **IR (neat, cm^{-1}):** 3209, 3185, 2958, 1722, 1615, 1516, 1485, 1424, 1394, 1326, 1241, 1178, 1075, 921, 894, 729; **^{1}H NMR (500 MHz, $CDCl_3$): δ** 8.75 (s, 1H), 7.32-7.37 (m, 5H), 6.91 (s, 1H), 6,29 (s, 1H), 4.75 (s, 1H), 3.30-3.39 (m, 2H), 2.83-2.89 (m, 1H), 2.70-2.76 (m, 1H); **^{13}C NMR (125 MHz, $CDCl_3$): δ** 173.8, 142.0, 135.8, 132.7, 129.6, 129.1, 128.7, 126.8, 126.6, 120.1, 112.1, 65.3, 61.5, 43.0, 36.2, 29.8; **HRMS (ESI) *m*/*z***: calcd.

for $C_{17}H_{13}Cl_2NO_2$ ([*M*+Na]$^+$): 356.0221, found: 356.0226.

6-Chloro-5-(2-chloroethyl)-3'-(*p*-tolyl)spiro[indoline-3,2'-oxiran]-2-one (39m)

10 M aqueous solution of NaOH (3 equiv.) was added dropwise to the stirring solution of (*E*)-6-chloro-5-(2-chloroethyl)-3-(4-methyl benzylidene)indolin-2-one (30 mg, 0.13 mmol) and EBHP (2 equiv.) in 2 mL of hexane at room temperature. After 15 minutes 4 mL water was added and the product was extracted with ethyl acetate, evaporated in *vacuo* and the residue on silica gel (100-200 mesh) column chromatography with mixtures of ethyl acetate in hexane yielded the product **39m.**

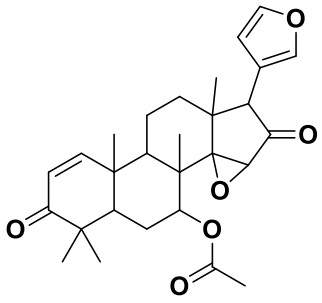


White solid (29mg, 92%, m.p = 179- 181 ^oC); R_f = 0.26 (hexane/ethyl acetate = 70/30); **IR (neat, cm^{-1}):** 3208, 3087, 2958, 2923, 1724, 1627, 1592, 1627, 1478, 1420, 1389, 1310, 1292, 1230, 1178, 1080, 963, 913, 854, 738; **^{1}H NMR (500 MHz, $CDCl_3$):** δ 8.9 (br, 1H), 7.25 (d, *J* = 7.5 Hz, 2H), 7.16 (d, *J* = 7.5 Hz, 2H), 6.91 (s, 1H), 6.25 (s, 1H), 4.72 (s, 1H), 3.32-3.41 (m, 2H), 2.87-2.90 (m, 1H), 2.72-2.74 (m, 1H), 2.21 (s, 3H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ 174.1, 142.1, 139.1, 135.7, 129.7, 129.6, 129.3, 126.7, 126.7, 120.3, 112.19, 65.5, 61.6, 43.0, 36.2, 21.4; **HRMS (ESI) *m/z*:** calcd. for $C_{18}H_{15}Cl_2NO_2$ ([M+Na]$^+$): 370.0378, found: 370.0381.

Epoxyazadiradione-1-(furan-3-yl)-3b,6,6,9a,11a-pentamethyl-2,7-dioxo 1,2,2a,3b,4,5,5a,6,7,9a,9b,10,11,11a-tetradecahydronaphtho[1',2':6,7]indeno[1,7a-b]oxiren-4-yl acetate (41)

10 M aqueous solution of NaOH (3 equiv.) was added dropwise to the stirring solution of **azadiradione (40)** (30 mg, 0.13 mmol) and EBHP (2 equiv.) in 2 mL of hexane at room temperature. After 15 minutes 4 mL water was added and the product was extracted with

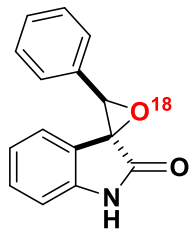
ethyl acetate, evaporated in *vacuo* and the residue on silica gel (100-200 mesh) column chromatography with mixtures of ethyl acetate in hexane yielded the product 41**.**



White solid (36mg 74%, m.p = 188 – 189.5 ^{o}C), **IR (neat, cm^{-1}):** 2964, 1746, 1729, 1667, 1238, 1029, 826. (**^{1}H NMR (500 MHz, CDCl$_3$);** δ(ppm): 7.57 (s, 1H), 7.41 (s, 1H), 7.19 (d, *J* =10.0 Hz, 1H), 6.25 (s, 1H), 5.90 (d, *J* =10.0 Hz, 1H), 4.74 (s, 1H), 3.90 (s, 1H), 3.42 (s, 1H), 2.63-2.65 (m, 1H), 2.17-2.21 (m, 2H), 2.04 (s, 3H), 1.23 (s, 3H), 1.22 (s, 3H), 1.09 (s, 3H), 1.08 (s, 3H), 1.04 (s,3H).**^{13}C NMR (125 MHz, CDCl$_3$);** δ 208.5, 204.3, 169.8, 157.6, 142.5, 141.6, 125.9, 116.6, 111.0, 73.7, 72.6, 57.3, 51.1, 46.8, 44.3, 43.2, 42.6, 39.8, 39.8, 29.2, 27.1, 24.9, 24.3, 21.4, 21.14, 19.9, 19.5, 16.2; **HRMS (ESI**) ***m/z***: calcd. for $C_{28}H_{34}O_6$ ([*M*+Na]$^{+}$): 489.2253, found: 489.2275.

^{18}O incorporated 3'-Phenylspiro[indoline-3,2'-oxiran]-2-one (37aa)

10 M aqueous solution of NaOH (3 equiv.) was added dropwise to the stirring solution of (*E*)-3-benzylideneindolin-2-one (30 mg, 0.13 mmol) and EBHP (2 equiv.) in 2 mL of hexane at room temperature. After 15 minutes 4 mL ^{18}O enriched water was added and the product was extracted with ethyl acetate, evaporated in *vacuo* and the residue on silica gel (100-200 mesh) column chromatography with mixtures of ethyl acetate in hexane yielded the product **37aa.**



White solid (26 mg, 80%); R_f = 0.25 (hexane/ethyl acetate = 70/30); IR (neat, cm^{-1}): 3208, 2981, 1716, 1625, 1607, 1516,1468, 1345, 1245, 1222, 1016, 926, 839, 786; **^{1}H NMR (500 MHz, CDCl$_3$): δ** 8.77 (br, 1H), 7.39 (d, *J* =7Hz, 2H), 7.30-7.36 (m, 3H), 7.13 (d, *J* = 7.5 Hz, 1H), 6.86 (d, *J* = 8 Hz, 1H), 6.67 (t, *J* = 7.5 Hz, 1H), 6.38 (d, *J* = 7.5 Hz, 1H), 4.75 (s, 1H); **^{13}C NMR (125 MHz, CDCl$_3$): δ** 174.0, 142.3, 133.0,

130.2. 128.7, 128.5, 126.7, 124.0, 122.5, 121.2, 111.0, 65.1, 61.9; **HRMS (ESI) *m*/*z***: calcd. for $C_{15}H_{12}NO_2$ ($[M+Na]^+$): 262.0729, found: 262.0736.

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Photoinduced Radical Hydroarylation of Terminal Alkynes with Naphthols and Phenols

4.1. Abstract

Visible light-promoted hydroarylation of phenyl acetylenes with naphthols and phenols is achieved using 2,4,6-tris(4-fluorophenyl)pyrylium tetrafluoroborate (T(*p*-F)PPT) as photocatalyst at room temperature without the need of any external ligand or additive. Apart from its excellent functional group tolerance, the protocol described herein represents an appealing alternative strategy to the classical transition-metal catalyzed hydroarylation reactions. Mechanistic investigations revealed that the reaction involves the radical pathway. Herein, we are reporting the first intermolecular radical hydroarylation of alkynes.

4.2. Introduction

Synthesis of substituted Styrenes *via* one-step C-H hydroarylation of alkynes has proven to be a straightforward and atom-economical approach.[1–3] The 2-vinyl phenol moiety constitutes the backbone of many bioactive compounds **(Figure 4.1)**. For example, Oxyresveratrol **(I)** is a natural compound found in grapes, peanuts, and mulberries. It is a derivative of resveratrol and has gained attention for antioxidant, anti-inflammatory, and anti-cancer properties.[4] Doxepin **(II)** is a medication primarily used as an antidepressant. It belongs to a class of drugs known as tricyclic antidepressants (TCAs). Doxepin increases the levels of serotonin and norepinephrine, which helps to improve mood and relieves symptoms of depression.[5] Azoxystrobin **(III)**, a highly effective fungicide, is an example of the strobilurin chemical family. It is frequently employed in agriculture to prevent the crop from fungal infections. Azoxystrobin prevents fungi from growing and reproducing by inhibiting their ability to respiration process.[6] Oxyresveratrol 2-O-*β*-D-glucopyranoside **(IV)** is a glucoside derivative of oxyresveratrol, it is found in various plant sources, including the roots of Morus alba (white mulberry). It is a stilbenoid compound that exhibits antioxidant and anti-inflammatory

properties.[7] Pinoxepin **(V)** is used as an antipsychotic and antidepressant.[8] Apart from the bioactive applications, these hydroxy styrene derivatives serve as versatile synthetic precursors for various organic transformations as well as building blocks in material science.[9,10]

In recent years photocatalysis has emerged as a powerful tool in synthetic chemistry, offering sustainable and efficient routes for the construction of complex organic molecules.[11] Among the diverse transformations enabled by photocatalysis, hydroarylation has gained considerable attention due to its ability to forge carbon-carbon bonds between unsaturated substrates and aromatic compounds. The development of photocatalysts and reaction conditions for the intermolecular hydroarylation of styrene has made substantial strides in recent years.[11] Various organic dyes, transition metal complexes, and semiconductor-based photocatalysts are employed to harness visible light energy and ease the reaction.[12] Despite these substantial developments in the radical hydroarylation of styrenes, the photocatalyzed hydroarylation of alkynes remained untapped.

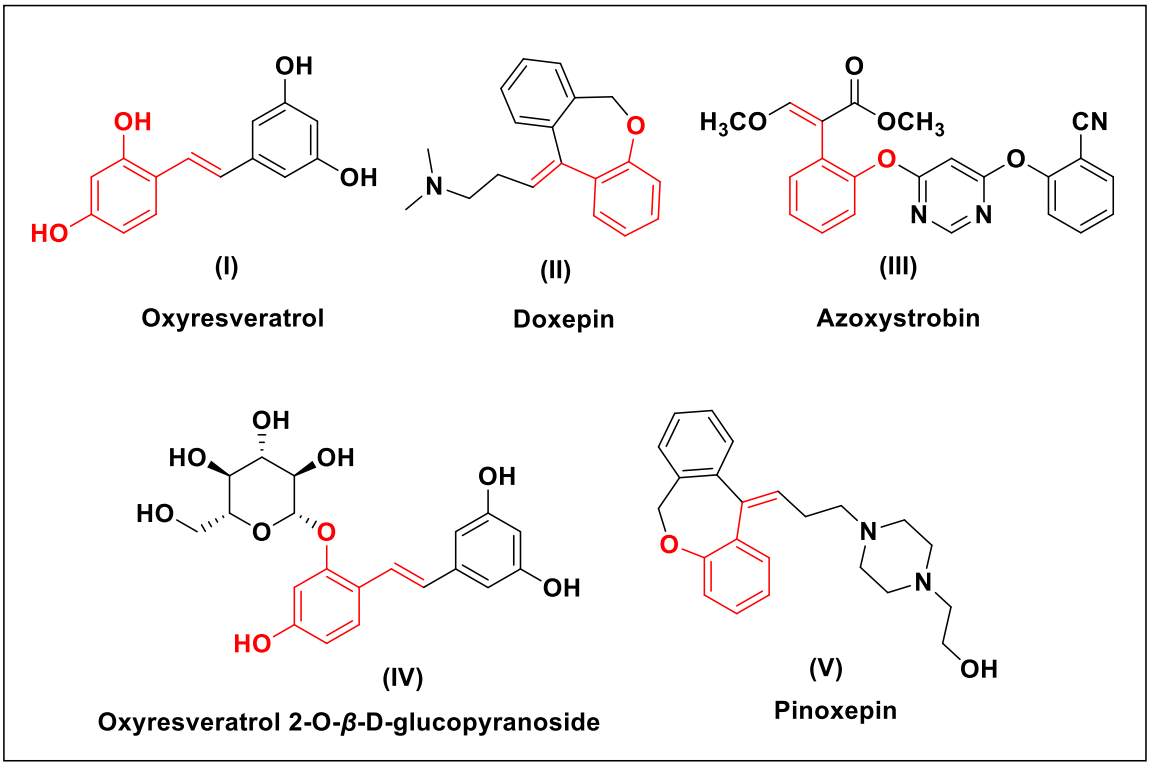
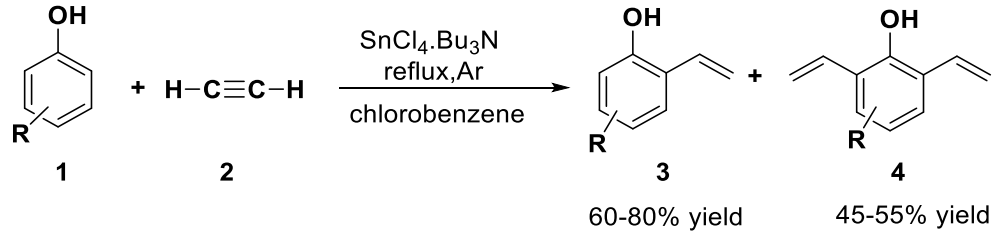


Figure 4.1. Selected bioactive molecules bearing 2-vinyl phenol scaffold

4.2.1. Synthetic approaches towards 2-hydroxy styrenes

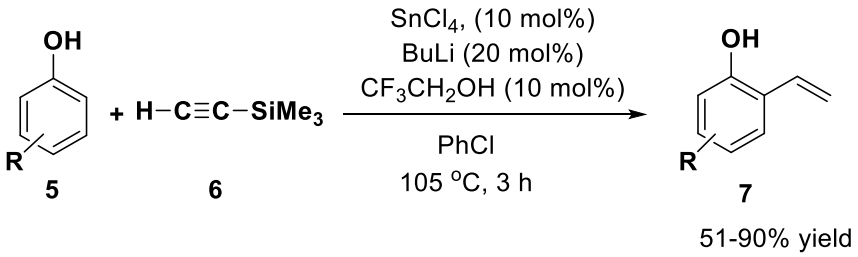
Due to their significance, numerous seminal publications on the synthesis of *ortho*-allyl phenols have been reported during the past decades, and these important developments in the hydroarylation of alkynes have been made possible by two predominant strategies: a) Metal-catalyzed C-H activation of terminal alkynes relying upon the radius of the metal catalyst,[13–17] b) Bronsted or Lewis acid catalyzed Friedel-Crafts type hydroarylation of alkynes with electron-rich aromatic compounds.[18–21]

In this vein, Yamaguchi *et al*. reported pioneering work on the alkenylation of various functionalized phenols with ethyne. The vinyl phenols were obtained by refluxing phenols **1** with ethyne **2** in chlorobenzene, using $SnCl_4$-Bu_3N as a catalyst. The reaction offers better yields under an argon atmosphere. They have also extended this protocol for *bis*-vinylated phenols **4** with ethyne by varying the reaction conditions. A reaction temperature of 100 °C was necessary for *bis*-vinylation to occur and a lower temperature for *mono*-vinylation (**Scheme 4.4).**[22]



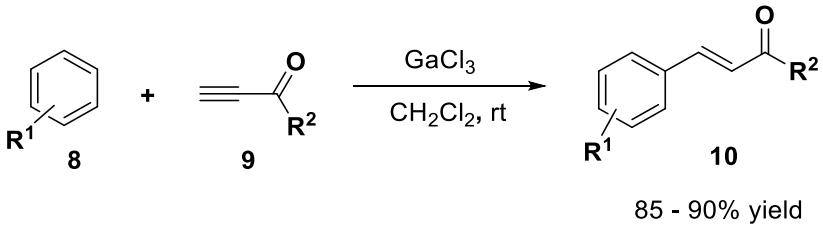
Scheme 4.1. Vinylation of phenols from ethyne using $SnCl_4$ catalyst

Ethenylation to the *o*-position to the hydroxy group of the phenols is demonstrated by Yamaguchi *et al*. in 2000. This ethenylation reaction of phenol **5** with silyl ethyne **6** is catalyzed by the $SnCl_4$-BuLi reagent. The corresponding *ortho*-vinyl phenols were produced by sequentially adding butyllithium (20 mol%), $SnCl_4$ (10 mol%), and silyl ethyne to the phenol in chlorobenzene and heating at 105 °C for 3 hours to obtain the product **7**. Additionally, it was shown that the turnover number (TON) based on $SnCl_4$ for o-substituted phenols is 8 to 9 while that for m- or *p*-substituted phenols is 3 to 4 **(Scheme 4.2**).[23]



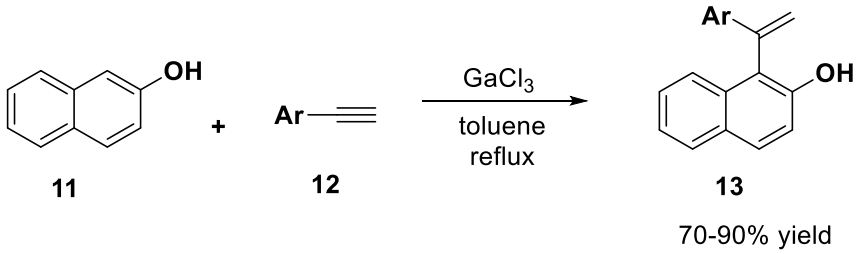
Scheme 4.2. $SnCl_4$ catalyzed **e**thenylation of phenols

In 2007, Yadav *et al*. emphasized the Gallium (III) chloride as an effective Lewis acid to activate alkynes or alkenes. Their group developed a highly stereoselective method for synthesising *E*-configured *α,β*-unsaturated ketones **10**. Herein arenes **8** and ynones **9** react in presence of Gallium (III) chloride at room temperature to form corresponding *E*-configured *α, β*-unsaturated ketones **10**. Lewis acid $GaCl_3$ activates alkynes under mild conditions, and then the arene moiety reacts with the activated alkyne to offer the final product **(Scheme 4.3**).[24]



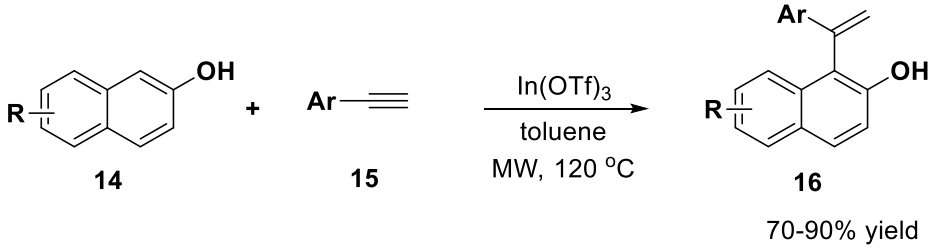
Scheme 4.3. Gallium catalyzed hydroarylation of ynones

Again in 2009, Yadav *et al.* reported the Gallium (III) Chloride catalyzed hydroarylation of aryl acetylenes **12** with naphthols and phenols **11**. In this protocol cross-coupling of aryl alkynes with naphthols occurs in the presence of 10 mol% gallium (III) chloride in refluxing toluene to form hydroxy vinyl arenes. Further, the scope of this methodology was found amenable in activating the styrenes to furnish cross-coupled products with naphthol (**Scheme 4.4**).[25]



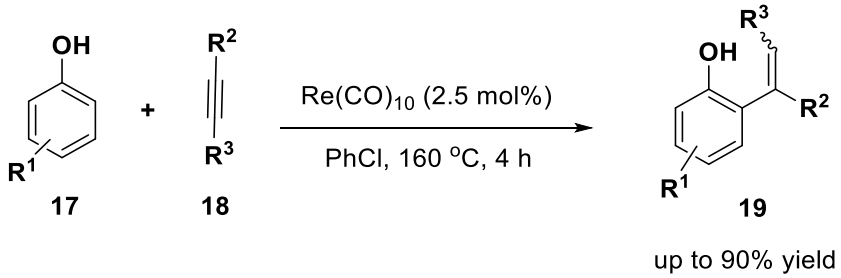
Scheme 4.4. Gallium catalyzed hydroarylation of aryl alkynes

Anil Kumar *et al.* devised a methodology for the hydroarylation of naphthols **14** and alkynes **15** in the presence of $In(OTf)_3$ under microwave irradiation. Additionally, they demonstrated the synthetic exploitation of α-hydroxy styrenes **16** for the construction of 2,3 diaryl naphthofurans *via* one-pot Heck-oxyarylation between the produced α-hydroxy styrenes and aryl halides **(Scheme 4.5**).[26]



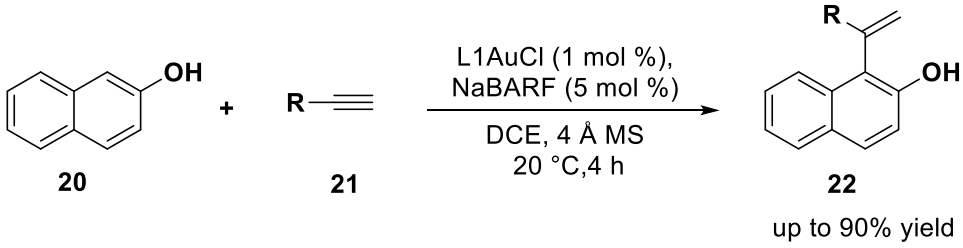
Scheme 4.5. Gallium catalyzed synthesis of 2-vinyl naphthols

The research team of Murai disclosed direct rhenium-catalyzed *ortho*-alkenylation (C-alkenylation) of unprotected phenols **17** with internal alkynes **18** in 2019. 2-Alkenylphenol **19** was obtained by reacting phenols with 3 equivalents of phenylacetylene in chlorobenzene at 160 °C for 48 hours in the presence of 5 mol% $Re_2(CO)_{10}$ catalyst. Additionally, they have showcased the synthetic utility of 2-Alkenylphenol to access 2H-chromenes *via* [3 + 2 + 1] cycloaddition of phenols and two alkynes (**Scheme 4.6**).[27]



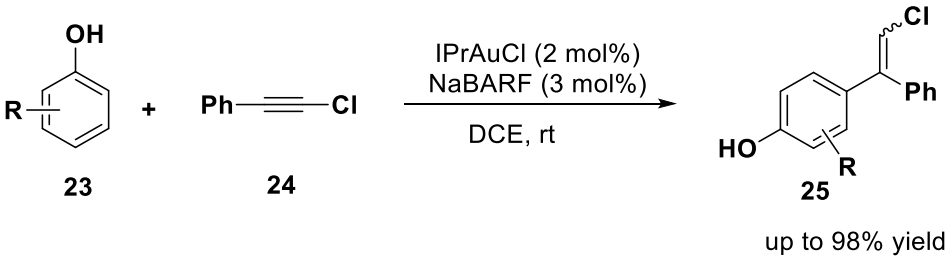
Scheme 4.6. Rhenium catalyzed *ortho*-alkenylation of phenols

In 2020, Ting Li *et al*. presented an effective gold-catalyzed intermolecular hydroarylation of alkynes **21** from naphthols **20** to form 2-vinyl naphthols **22** in soft reaction conditions. This transformation features moderate to outstanding efficiency due to its wide substrate scope **(Scheme 4.7**)[28].



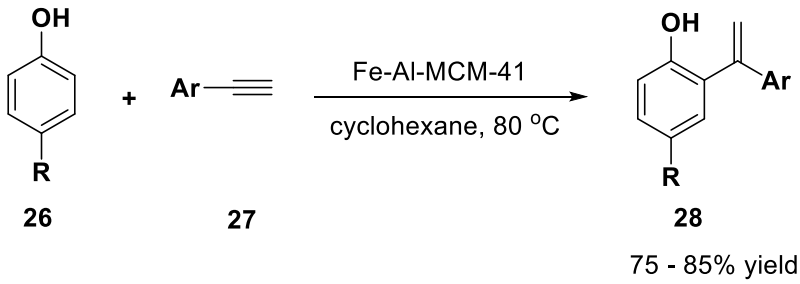
Scheme 4.7. Gold-catalyzed intermolecular hydroarylation of alkynes

The research conducted by Hashmi *et al*. demonstrates the gold-catalyzed chemo- and stereoselective addition of unprotected phenols **23** to haloalkynes **24** to give hydroarylated product **25.** The key finding is that the choice of catalyst influences the stereo-selectivity of the reaction, highlighting the importance of the catalyst and ligand. The significance of this work lies in its favourable substrate scope, mild reaction conditions, and the utilization of readily available starting materials. It demonstrates the potential to modify bioactive molecules, even at a late stage, which is valuable in drug discovery and development **(Scheme 4.8**)[29].



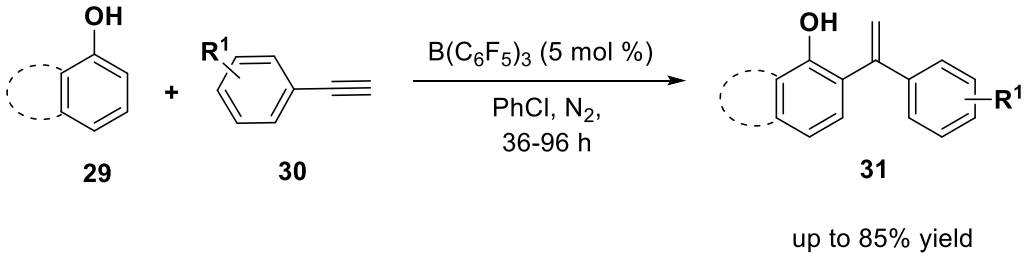
Scheme 4.8. Gold-catalyzed chemo- and stereoselective addition

Koner and Haldarand discovered the Iron-containing mesoporous aluminosilicate (Fe-Al-MCM-4) catalyzed oxidative coupling of aryl alkynes **27** with phenols **26** to form 1,1-diaryl alkenes **28**. The reaction proceeds well in cyclohexane as solvent at 80 ^{o}C. The significance of this procedure lies in the straightforward recovery of the catalyst from the reaction mixture. Simple centrifugation is sufficient to separate the catalyst from the mixture, eliminating the need for complex procedures or treatments. Additionally, the catalyst can be reused multiple times without requiring any special treatment apart from washing, further simplifying the process **(Scheme 4.9)**[30].



Scheme 4.9. Iron-catalyzed oxidative coupling of aryl alkynes with phenols

Huang's research group showcased an efficient and practical method for the synthesis of 2-*gem*-vinyl phenols **31** from phenols **29** and phenyl acetylenes **30** using $B(C_6F_5)_3$ catalyst. These transformations exhibited a diverse substrate scope under mild reaction conditions. The efficient one-step conversion of the resulting product **31** into a variety of functional molecules such as coumarin derivative, diaryl ether, and benzofuran with acceptable yields depicted the synthetic significance of the 2-*gem*-vinyl phenol moiety. Further, mechanistic investigations revealed that these transformations proceed through phenol activation by $B(C_6F_5)_3$ followed by a subsequent protonation of alkyne/Friedel-Crafts-type reaction (**Scheme 5**).[31]



Scheme 4.10. Boron catalyzed the synthesis of 2-*gem*-vinyl phenol

4.3. Background to the present work

In 2016, Guo *et al*. reported the intramolecular hydroarylation of alkynes under UV irradiation.[32] Inspired by this pivotal work, and in the persistence of our interest in the development of new and innovative synthetic routes for accessing complex heterocycles and valuable building blocks. We speculated that we could achieve the intermolecular photoinduced C-H hydroarylation of phenyl acetylenes with naphthols and phenols under mild reaction conditions.

4.4. Results and Discussion

In our initial design and approach, we chose naphthalene-2-ol (**32a**, 0.35 mmol) and 4-ethynyl-toluene (**33a**, 1.2 equiv.) as substrates in DCM solvent and 5 mol% 2,4,6-tris(4-fluorophenyl)pyrylium tetrafluoroborate (T(*p*-F)PPT) as photocatalyst. Under the white LED irradiation, this protocol was found to be quite successful and afforded the corresponding hydro-arylated product 1-(1-(*p*-tolyl)vinyl) naphthalene-2-ol (**34a)** in 40% yield **(Table 4.1, entry 1)**. The structure of the product was confirmed through various spectroscopic analyses such as ^{1}H NMR, ^{13}C NMR and mass spectrometry. Three proton singlet at δ 2.23 indicates the presence of methyl protons from the tolyl group and two singlets integrating one proton at δ 6.19 and δ 5.36 corresponds to the alkene geminal protons. Further, one proton singlet at δ 5.55 indicates the presence of OH group from the 2-naphthol moiety. In addition, the deuterium exchange experiment confirmed the presence of OH proton at δ 5.55 (**Figure 4.2**). Further, the presence of the tolyl methyl group is confirmed by the signal at δ 21.2 and two carbon signals at δ 117.9 and δ 117.3 depicts the two alkene carbons of the vinyl group (**Figure 4.3**). Additionally, the mass spectrometric data was also in good agreement with the exact mass of the product.

Encouraged by the formation of the anticipated product, we next focused on optimizing the reaction conditions to obtain better yields. On scrutinizing a range of solvents **(Table 4.1, entries 2-6)**, DCM proved to be a suitable solvent for this enviable transformation. After an extensive screening of various photocatalysts, *viz*. $MesAcr^{+}BF_4^{-}$, Eosin Y, Rose Bengal and different derivatives of pyrylium salts like TPPT, T(*p*-Cl)PPT, T(*p*-Br)PPT, T(*p*-Me)PPT, T(*p*-OMe)PPT were found to be inefficacious in improving the yield. Further attempts made in the presence of co-oxidants such as $K_2S_2O_8$, $(NH_4)_2S_2O_8$ and $Na_2S_2O_8$ also failed to improve the yield **(Table 4.1, entry 21-23).** When we performed the reaction in presence of a catalyst (T(*p*-F)PPT) and without the light irradiation product was not formed **(Table 4.1, entry 25)**. In addition, when the reaction mixture is irradiated with white LED without the catalyst (T(*p*-F)PPT) also did not offer the product **(Table 4.1, entry 24)**.

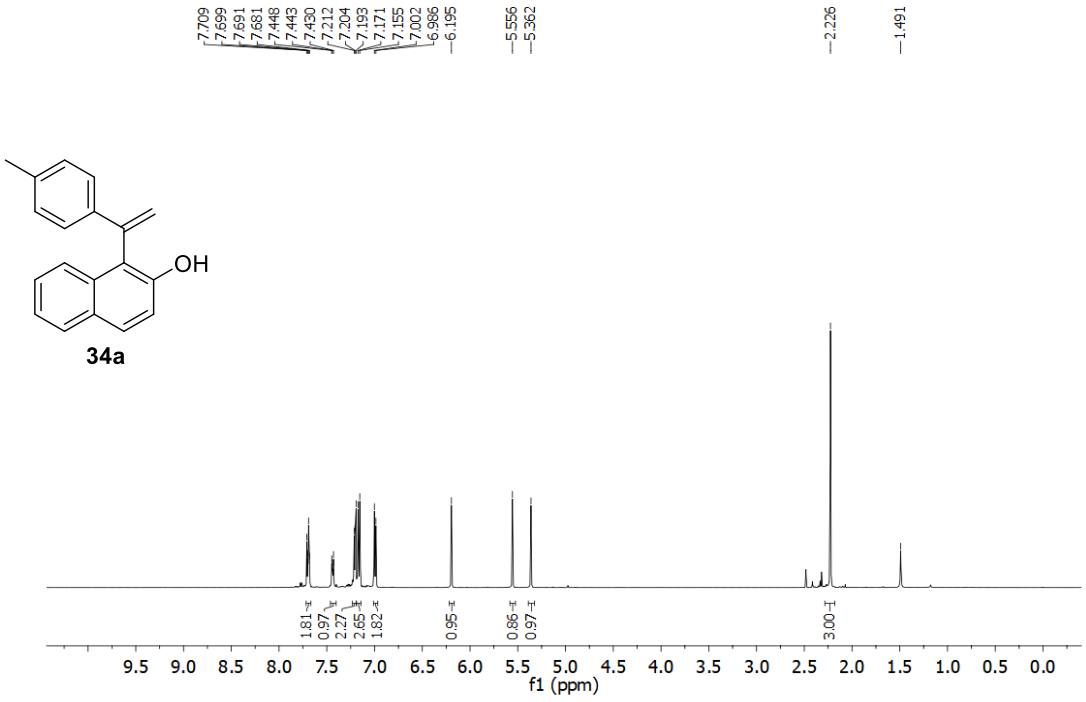


Figure 4.2. ^{1}H NMR of 34a in $CDCl_3$

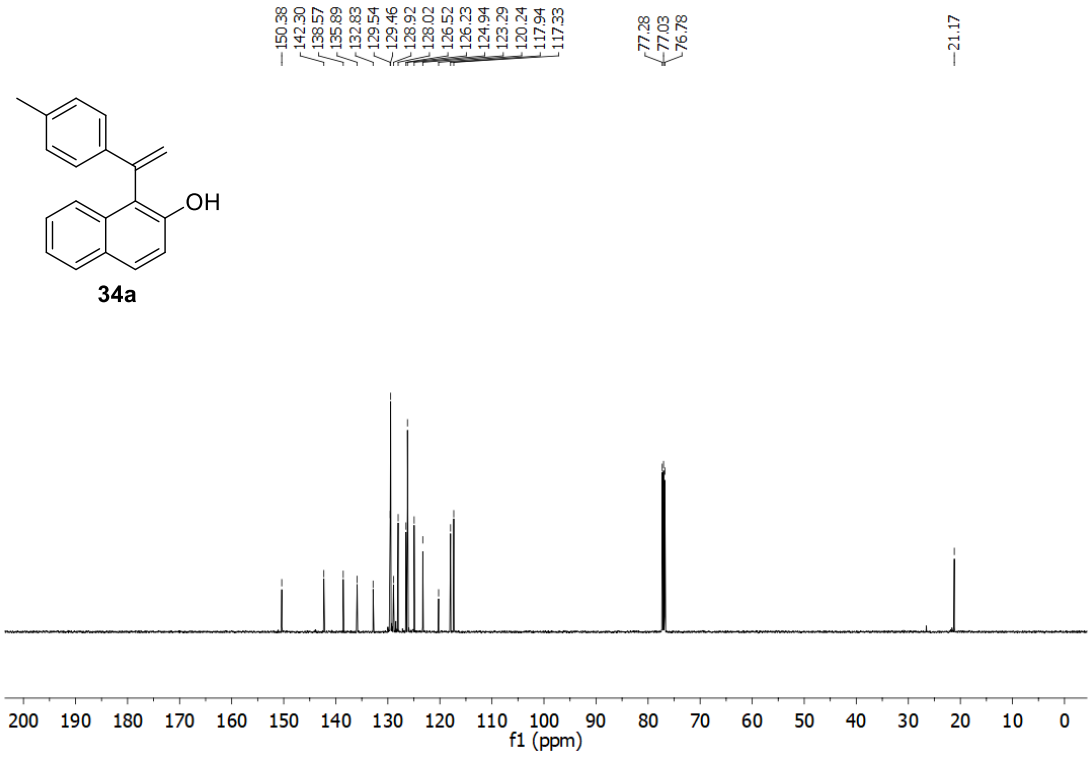
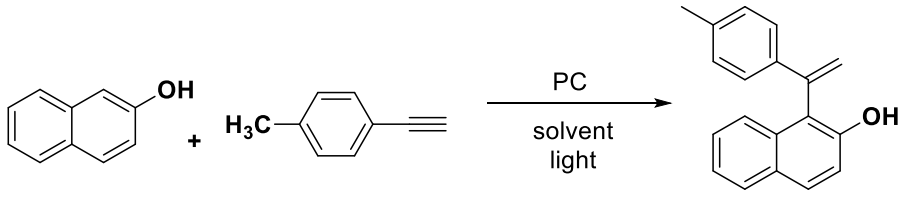


Figure 4.3. $^{13}C\{^{1}H\}$ NMR of 34a in $CDCl_3$

Table 4.1: Optimisation of reaction conditions[a]



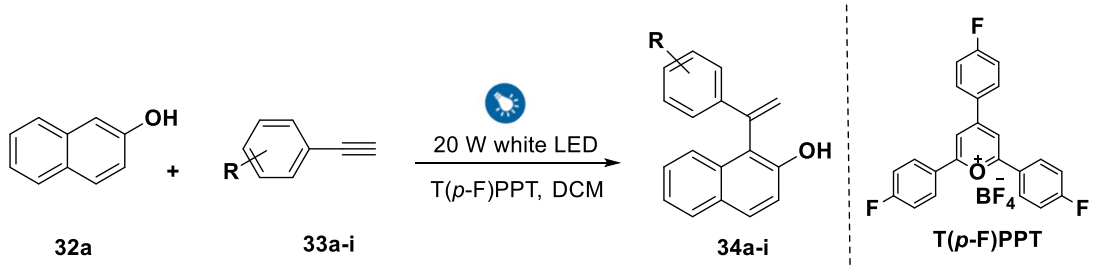
32a 33a 34a

entry	1a (equiv.)	2a (equiv.)	photocatalyst	additive (oxidant)	solvent	light source	yield (%)
1	1	1.2	T(*p*-F)PPT	-	DCM	White LED	40
2	1	2	T(*p*-F)PPT	-	DCE	White LED	15
3	1	2	T(*p*-F)PPT	-	CH_3CN	White LED	N.D
4	1	2	T(*p*-F)PPT	-	MeOH	White LED	N.D
5	1	2	T(*p*-F)PPT	-	HFIP	White LED	N.D
6	1	2	T(*p*-F)PPT	-	TFE	White LED	N.D
7	**1**	**2**	**T(*p*-F)PPT**	**-**	**DCM**	**White LED**	**89**
8	1	2.5	T(*p*-F)PPT	-	DCM	White LED	70
9	1	3	T(*p*-F)PPT	-	DCM	White LED	69
10	1	2	$MesAcr^+BF_4^-$,	-	DCM	White LED	N.D
11	1	2	Eosin Y	-	DCM	White LED	N.D
12	1	2	Rose bengal	-	DCM	White LED	N.D
13	1	2	TPPT	-	DCM	White LED	N.D
14	1	2	T(*p*-Cl)PPT	-	DCM	White LED	15
15	1	2	T(*p*-Me)PPT	-	DCM	White LED	N.D
16	1	2	T(*p*-OMe)PPT	-	DCM	White LED	trace
17	1	2	T(*p*-F)PPT	-	TFE	White LED	18
18	1	2	T(*p*-Br)PPT	-	DCM	White LED	5
19	1	2	T(*p*-F)PPT	-	DCM	White LED	80[b]
20	1	2	T(*p*-F)PPT	-	DCM	White LED	78[c]
21	1	2	T(*p*-F)PPT	$K_2S_2O_8$	DCM	White LED	ND
22	1	2	T(*p*-F)PPT	$(NH_4)_2S_2O_8$	DCM	White LED	trace
23	1	2	T(*p*-F)PPT	$Na_2S_2O_8$	DCM	White LED	trace
24	1	2	No catalyst	-	DCM	White LED	ND
25	1	2	T(*p*-F)PPT	-	DCM	No light	ND

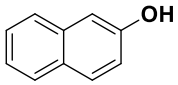
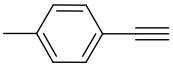
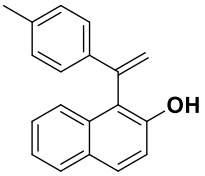
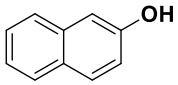
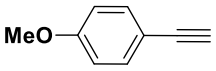
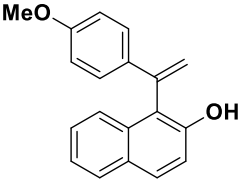
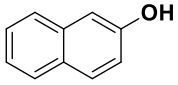
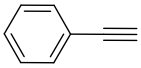
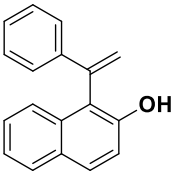
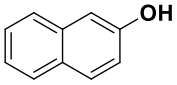
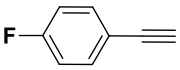
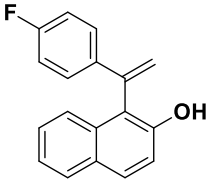
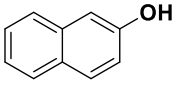
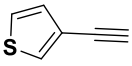
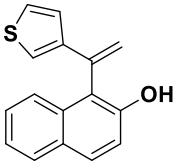
[a]unless otherwise mentioned 1a (0.3468) mmol, 2a (2equv.) and 5 mol% catalyst in 1 mL of solvent. [b]10 mol% catalyst added. [c]15 mol% catalyst added. ND- Not detected

Controlled experiments revealed that the photocatalyst and light irradiation is a must for this important transformation, in the absence of either of them, the reaction failed to form the anticipated product even in traces **(Table 4.1, entry 24-25)**. Considering T(*p*-F)PPT, white LED as the suitable photocatalyst and light source respectively, and with 2 equivalence of phenylacetylene at room temperature in DCM (**Table 4.1, entry 7)** as the optimised reaction parameters. We successfully explored the scope for the various substituted phenyl acetylenes

Table 4.2. Scope of phenylacetylene



32a 33a-i 34a-i T(*p*-F)PPT

Sl. no.	Naphthol	Phenylacetylene	Product	Yield [%]
1	 32a	 33a	 34a	89
2	 32a	 33b	 34b	90
3	 32a	 33c	 34c	83
4	 32a	 33d	 34d	76
5	 32a	 33e	 34e	75

……..continued **Table 4.2**

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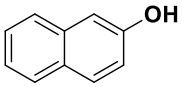
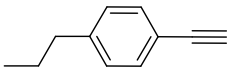
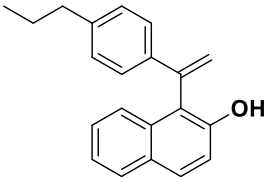
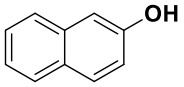
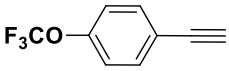
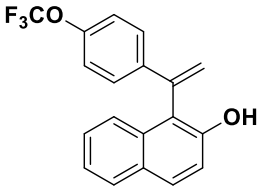
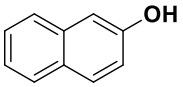
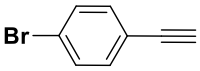
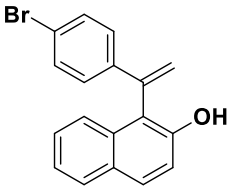
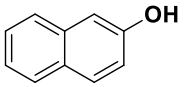
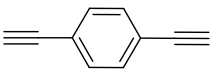
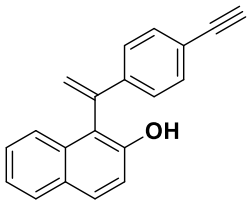
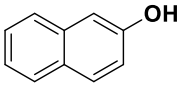
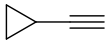
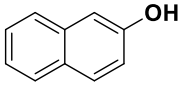
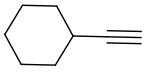
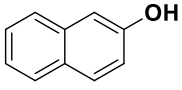
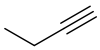
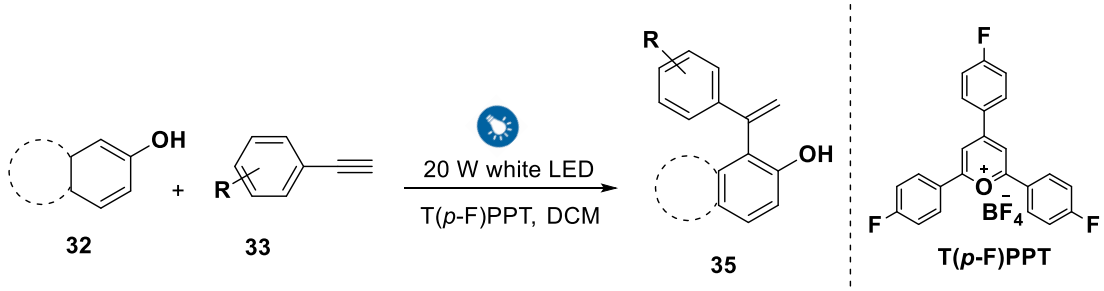
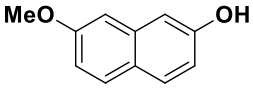
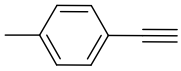
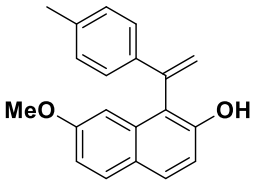
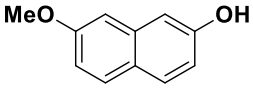
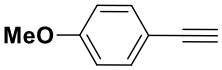
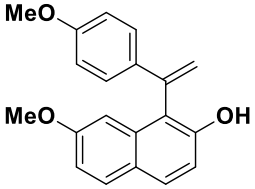
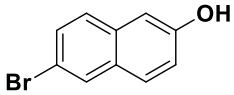
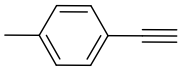
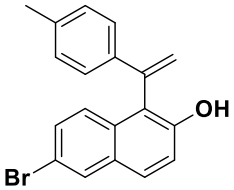
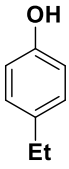
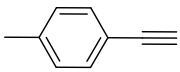
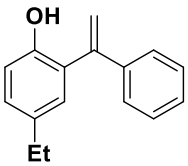
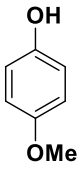
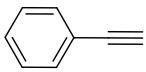
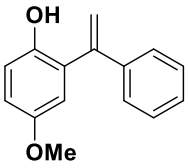
6	 32a	 33f	 34f	95
7	 32a	 33g	 34g	70
8	 32a	 33h	 34h	74
9	 32a	 33i	 34i	65
10	 32a	 33j	No reaction	
11	 32a	 33k	No reaction	
12	 32a	 33l	No reaction	

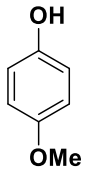
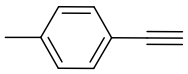
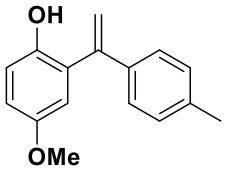
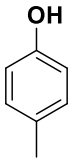
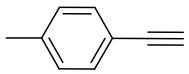
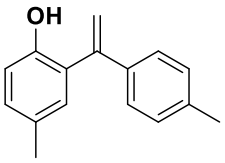
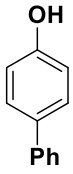
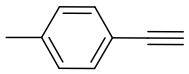
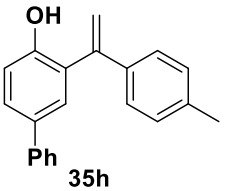
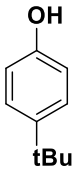
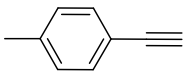
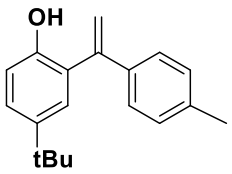
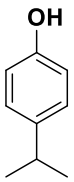
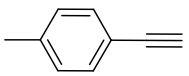
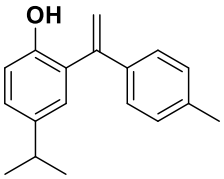
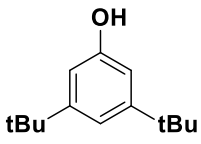
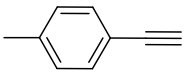
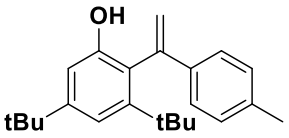
Table 4.3. Scope of phenols



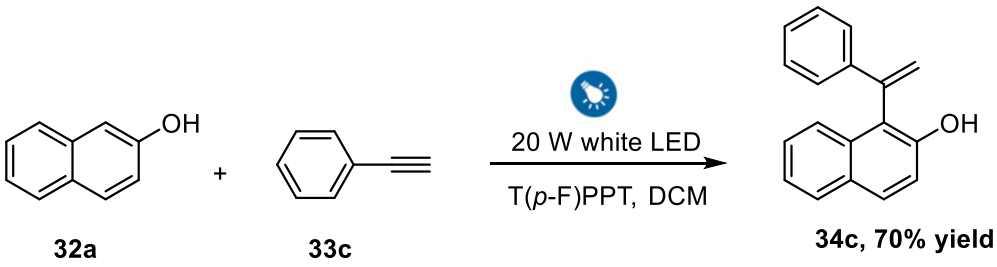
32 + 33 → 35; T(*p*-F)PPT

Sl. no.	Phenol	Phenylacetylene	Product	Yield [%]
1	 32b	 33a	 35a	88
2	 32b	 33b	 35b	95
3	 32c	 33a	 35c	85
4	 32d	 33a	 35d	58
5	 32e	 33c	 35e	50

…….. **Table 4.3**

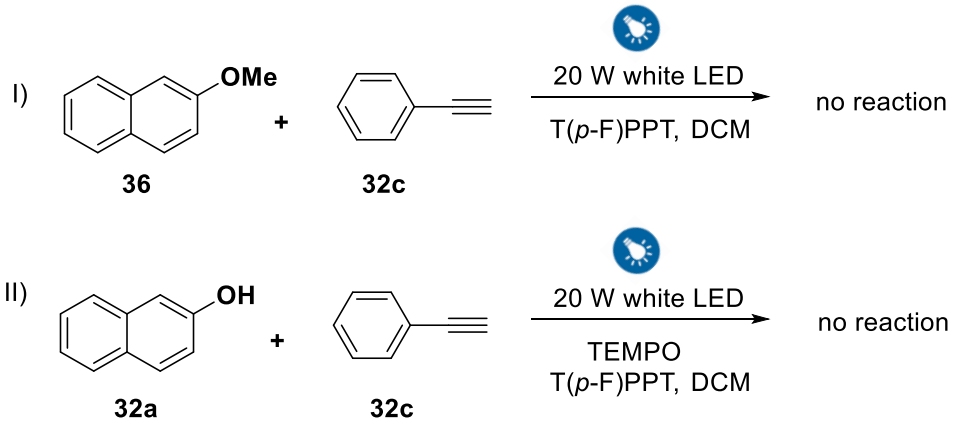
Sl.No.	Phenol	Phenyl acetylene	Product	Yield [%]
6	 32e	 33a	 35f	55
7	 32f	 33a	 35g	51
8	 32g	 33a	 35h	49
9	 32h	 33a	 35i	52
10	 32i	 33a	 35j	55
11	 32k	 33a	 35k	60

bearing different electron-donating and withdrawing substitutions. It is vital to highlight that, groups such as methoxy, fluoride, bromide, and trifluoromethoxy were well tolerated and furnished the corresponding products with nearly equal efficiencies, substantiating that the efficiency of the approach is not significantly altered by the substitutions on the aryl ring **(table 4.2)**. Along with this, it is noteworthy that the 1,4 diethynylbenzene gave exclusively *mono*-hydroarylation product **34i** in 65% yield**.** Besides, the protocol worked well for heterocyclic acetylene thiophene-3-acetylene to obtain desired product **34e** in 75% yield.



Scheme 4.11. Gram scale synthesis

However, under standard conditions aliphatic, cyclic substituted terminal alkynes and internal alkynes remained unreactive (**Table 4.2. 33j, 33k, 33l**). This may be due to the greater redox potential of these alkynes. Further, to demonstrate the synthetic utility of this protocol we utilised different substituted naphthols with **32a** and were delighted to obtain the *ortho*-substituted product in good yield (**Table 4.3**).



Scheme 4.12. Controlled experiments

These delightful results encouraged us to demonstrate the diversification of this methodology by extending this protocol to a series of phenols. Phenols bearing various functional groups were compatible in resulting *ortho*-alkenylated products with good yields. Functional groups like, -OMe, -Br, -Et **(Table 4.3)** were also well tolerated. Furthermore, the reaction conditions were also amenable for the disubstituted phenols to furnish the aspired products **(Table 4.3)** in good yields. In addition, this reaction is also compliant with gram scale synthesis and offered the product **34c** in 70% yield (**Scheme 4.11)**. However, when the reaction was performed using 2-methoxy naphthalene **36** failed to furnish the hydroarylated product, confirming that the presence of the -OH group is necessary for this reaction **(Scheme 4.12(II))**. In addition, we have demonstrated the synthetic utility of hydroarylated product, 2-*gem*-vinyl phenol scaffolds by performing a couple of useful synthetic transformations to access enviable compounds. Compound **34c** is converted to vinyl iodide **39 (Scheme 4.13)**, which can be utilized as a useful synthon for further transformation through transition-metal-catalyzed cross-coupling reactions etc. Additionally, we also demonstrated the one-pot ring annulation of 2-*gem*-vinyl phenol scaffolds into naphthofuran derivatives in good yields **(Scheme 4.13)**.

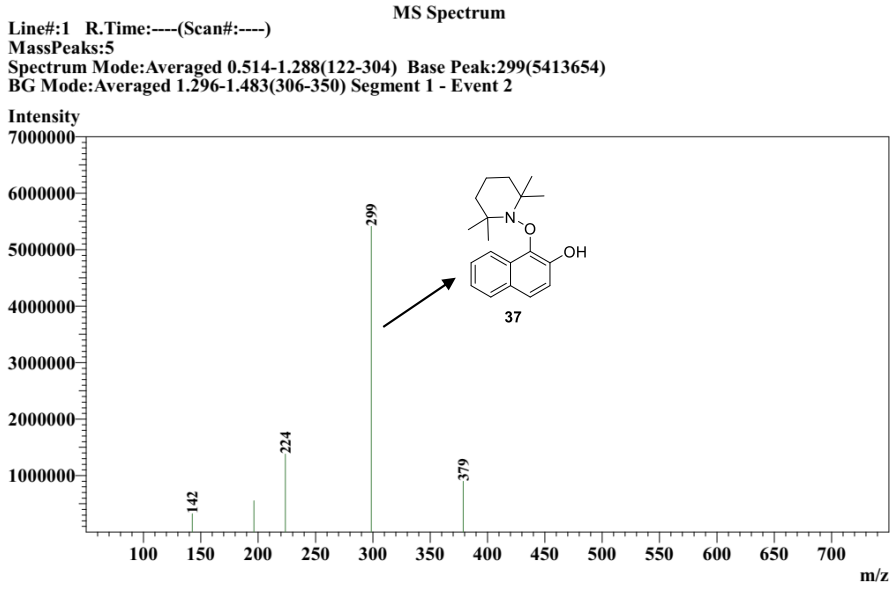
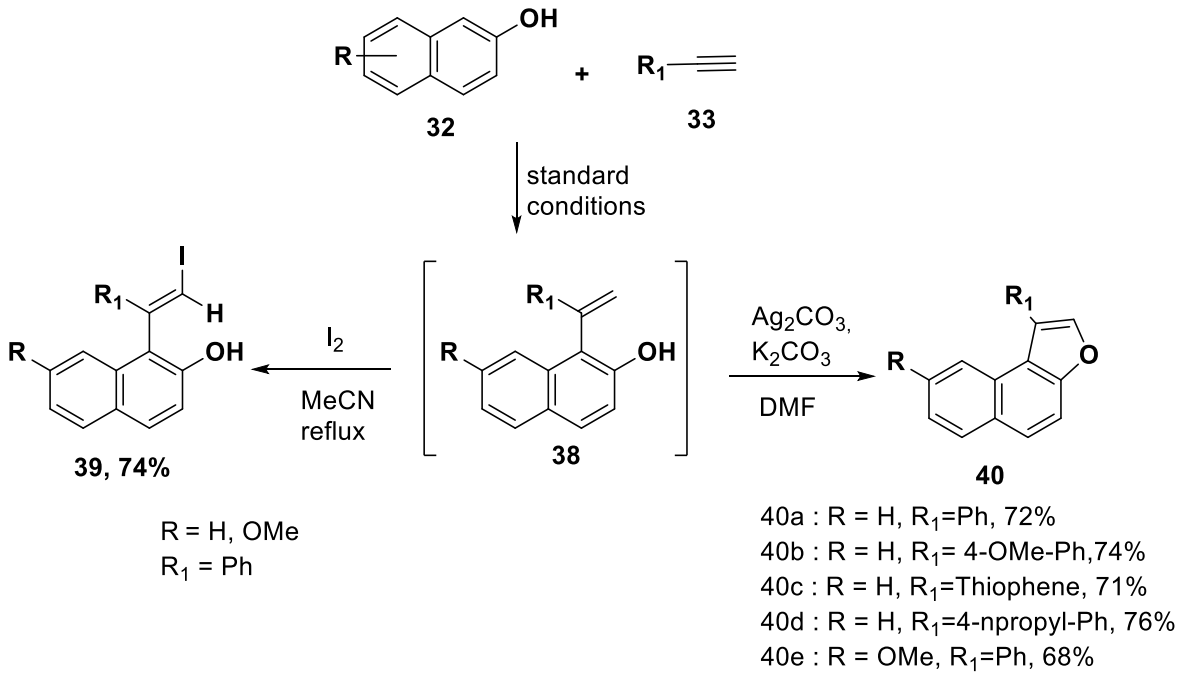


Figure 4.4. TEMPO adduct of 32a

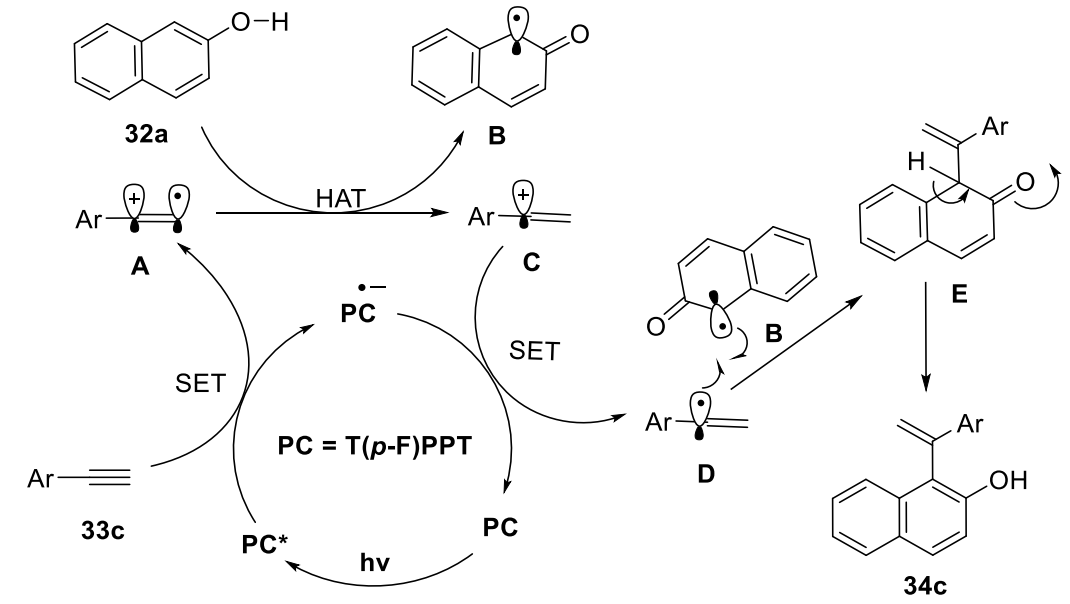


Scheme 4.13. One-pot demonstration of the synthetic utility of hydroarylated products

To gain some insight into the reaction mechanism, the radical inhibitor 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) was added into the reaction system under standard reaction conditions, but product **34c** was not detected **(Scheme 4.12 (II))**. However, through LCMS analysis we confirmed the formation of TEMPO adduct **37** of 2 -naphthol **(Figure 4.4)**, in the reaction mixture. which indicates that a radical pathway might be involved in this transformation.

4.5. Plausible mechanism

Based on the above-mentioned mechanistic investigations, a plausible mechanism for this photoinduced hydroarylation was proposed as depicted in **Scheme 4.14**. Single electron oxidation of alkyne **33c** to form a radical cation **A** in the presence of excited photocatalyst **PC***[33] (T(*p*-F)PPT = +2.29V vs SCE in MeCN) and under the photoredox condition intermediate **A** reacts with the naphthol **32a** forming the intermediates **B** and **C** *via* hydrogen atom transfer (HAT). Next, the acetylene cation **C** oxidises the **PC**$^{\bullet-}$ to form ground state photocatalyst **PC** *via* SET. Thus, completing the photo redox cycle of the PC and availing the photocatalyst (PC) for the next cycle.



Scheme 4.14. Plausible mechanism

On the other hand, intermediate **D** reacts with **B** to form a new bond resulting the intermediate **E** which upon subsequent aromatisation offers the hydroarylated product **34c**. It is noteworthy to mention here that, this reaction does not require any co-oxidant to complete the catalytic cycle of the **PC**.

4.6. Conclusion

In summary, we have developed a visible light-promoted strategy for the alkenylation of naphthols and phenols using T(*p*-F)PPT as a photocatalyst. This approach provides an efficient and convergent route for accessing a wide range of *ortho*-allyl phenols with high functional group tolerance. In addition, this strategy occurs under mild and metal-free conditions upon irradiation with simple household LEDs and averting the use of extra ligands and additives. Hence formed products serve as the versatile building blocks for subsequent synthetic transformations.

4.7. General experimental methods.

All the reactions are performed with commercially available best-grade chemicals without further purification. All of the solvents used are reagent-grade and commercially available. Column chromatography was performed using 100−200 mesh silica gel, and mixtures of hexane−ethyl acetate were used for the elution of the products. Proton nuclear magnetic resonance spectra (^{1}H NMR) were recorded on a Bruker AMX 500 spectrometer ($CDCl_3$ as solvent). Chemical shifts for ^{1}H NMR spectra are reported as δ in units of parts per million (ppm) downfield from $SiMe_4$ (δ 0.0) and relative to the signal of chloroform-d (δ 7.25, singlet) Multiplicities are given as s (singlet); d (doublet); t (triplet); q (quartet); dd (doublet of doublet); dt (doublet of triplet); m (multiplet). Coupling constants are reported as *J* values in Hz. Carbon nuclear magnetic resonance spectra $^{13}C\{^1H\}$ NMR are reported as δ in units of parts per million (ppm) downfield from $SiMe_4$ (δ 0.0) and relative to the signal of chloroform-d (δ 77.03, triplet). The mass spectra were recorded under EI/HRMS at 60,000 resolutions using a Thermo Scientific Exactive mass spectrometer.

4.8. General procedure for preparation of 2-hydroxy styrenes

To a 5 dram glass vial equipped with a magnetic stir bar naphthalene-2-ol or phenols (0.3468 mmol), Phenyl acetylene **2** (0.6936 mmol), 1 mL of DCM solvent and photocatalyst T(*p*-F)PPT (5 mol%) were sequentially added. The solution was stirred at a distance of ~3 cm from 20 W white LED at room temperature. After completion of the reaction monitored by TLC, the solvent was removed in *vacuo* and extracted with ethyl acetate (3x10 mL), organic layers were dried over Na_2SO_4 and evaporated in *vacuo* and purified by column chromatography using 100–200 mesh silica gel with ethyl acetate/hexane (1:9) as the eluent to afford the corresponding hydroarylated compounds as a product.

4.9. Control experiments

To a 5-dram glass vial equipped with a magnetic stir bar naphthalene-2-ol (0.3468 mmol), Phenyl acetylene (0.6936 mmol), 1 mL of DCM solvent and photocatalyst T(*p*-F)PPT (5 mol%) and TEMPO were sequentially added. The solution was stirred at a distance of ~3 cm from 20 W white LED at room temperature. After completion of the reaction monitored by

TLC, the solvent was removed in *vacuo* and extracted with ethyl acetate (3x10 ml), organic layers were dried over Na_2SO_4 and evaporated in *vacuo* and purified by column chromatography using 100–200 mesh silica gel with ethyl acetate/hexane (1:9) as the eluent to afford the corresponding hydroarylated compounds as products.

4.10. Product transformations:

4.10.1. General procedure for one-pot synthesis of vinyl iodide

To a round bottom flask equipped with a magnetic stir bar naphthalene-2-ol (0.3468 mmol), phenylacetylene (0.6936 mmol), 2 mL of DCM solvent and photocatalyst T(*p*-F)PPT (5 mol%) were sequentially added. The solution was stirred at a distance of ~3 cm from 20 W white LED at room temperature. After completion of the reaction monitored by TLC, the solvent was removed in *vacuo* then to this crude I_2 (128.8 mg, 2.5 mmol), and MeCN (2mL) was added. The reaction mixture was refluxed for 4 h. Allow the reaction to cool at room temperature and quenched with $Na_2S_2O_3$ solution, then extracted with Ethyl acetate (2 x 10mL). The combined organic layer was dried over anhydrous Na_2SO_4 and then concentrated under reduced pressure to afford the crude product. The residue was purified by column chromatography using 100–200 mesh silica gel with hexane /ethyl acetate (9: 1, v/v) to afford the product **39** (96 mg, 74% yield).

4.10.2. General procedure for one-pot synthesis of naphthofuran derivatives

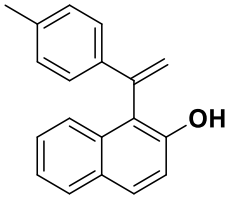
To a round bottom flask equipped with a magnetic stir bar naphthalen-2-ol (0.3468 mmol), Phenyl acetylene (0.6936 mmol), 2 mL of DCM solvent and photocatalyst T(*p*-F)PPT (5 mol%) were sequentially added. The solution was stirred at a distance of ~3cm from 20 W white LED at room temperature. After completion of the reaction monitored by TLC, the solvent was removed in *vacuo*, then to this crude K_2CO_3 (67.8mg, 0.4912 mmol) and $AgCO_3$ (90.3mg, 0.3274 mmol) DMF (2 mL), were added under Argon atmosphere, and stirred at 120 °C for 20 h. Allow the reaction mixture to cool down and add 5 mL of water into the reaction mixture and then extracted it with ethyl acetate (EA) (3x15 mL). The combined organic layer was dried over anhydrous Na_2SO_4. After concentration, the residue was purified by column

chromatography using 100–200 mesh silica gel with hexane /ethyl acetate (10: 1, v/v) to afford the product **40.**

4.11. Characterisation data of synthesized compounds

1-(1-(*p*-tolyl)vinyl)naphthalen-2-ol (34a)

To a 5 dram glass vial equipped with a magnetic stir bar naphthalene-2-ol (0.3468 mmol), 1-ethynyl-4-methylbenzene (0.6936 mmol), 1 mL of DCM solvent and photocatalyst T(*p*-F)PPT (5 mol%) were sequentially added. The solution was stirred at a distance of ~3 cm from 20 W white LED at room temperature. After completion of the reaction monitored by TLC, the solvent was removed in *vacuo* and extracted with ethyl acetate (3x10 mL), organic layers were dried over Na_2SO_4 and evaporated in *vacuo* and purified by column chromatography using 100–200 mesh silica gel with ethyl acetate/hexane (1:9) as the eluent to afford the corresponding hydroarylated compound **34a** as a product.



Pale yellow liquid (80.34mg, 89% Yield); **^{1}H NMR (500 MHz, $CDCl_3$) δ** 7.69 -7.70 (m, 2H), 7.40 -7.44 (m, 3H), 7.19 – 7.21 (m, 2H), 7.15 (d, *J* = 8.0 Hz, 3H), 6.99 (d, *J* = 10.0 Hz, 2H), 6.19 (s, 1H), 5.55 (s, 1H), 5.36 (s, 1H), 2.23 (s, 3H).

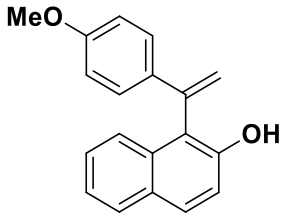
^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 150.4, 142.3, 138.6, 135.92, 132.8, 129.5, 129.4, 128.9, 128.0, 126.5, 126.2, 124.9, 123.3, 120.2, 117.9, 117.3, 21.2.

HRMS (ESI-Orbitrap) m/z: Calcd. For $C_{19}H_{16}O([M+H]^+)$ 261.1279; found 261.1275

1-(1-(4-methoxyphenyl) vinyl)naphthalen-2-ol (34b)

To a 5-dram glass vial equipped with a magnetic stir bar naphthalene-2-ol (0.3468 mmol), 1-ethynyl-4-methoxybenzene (0.6936 mmol), 1 mL of DCM solvent and photocatalyst T(*p*-F)PPT (5 mol%) were sequentially added. The solution was stirred at a distance of ~3 cm from 20 W white LED at room temperature. After completion of the reaction monitored by TLC, the solvent was removed in *vacuo* and extracted with ethyl acetate (3x10 mL), organic layers were dried over Na_2SO_4 and evaporated in *vacuo* and purified by column

chromatography using 100–200 mesh silica gel with ethyl acetate/hexane (1:9) as the eluent to afford the corresponding hydroarylated compound **34b** as a product.



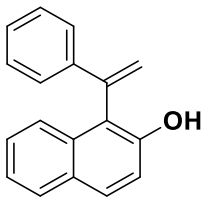
White solid (86.30 mg, 90% Yield); Mp: 82-84 ^{o}C; **^{1}H NMR (500 MHz, CDCl$_3$) δ** 7.63-7.67 (m, 2H), 7.41 – 7.42 (m, 1H), 7.14 – 7.19 (m, 5H), 6.66 (d, *J* = 8.5 Hz, 2H), 6.08 (s, 1H), 5.58 (s, 1H), 5.26 (s, 1H), 3.62 (s, 3H).

^{13}C{^{1}H} NMR (125 MHz, CDCl$_3$) δ 159.9, 150.4, 141.8, 132.87, 131.2, 129.5, 128.9, 128.0, 127.7, 126.5, 125.0, 123.3, 120.3, 117.3, 116.7, 114.1, 55.3.

HRMS (ESI-Orbitrap) m/z: Calcd. for $C_{19}H_{16}O_2$ ($[M+H]^+$) 277.1228; found 277.1228

1-(1-phenylvinyl) naphthalen-2-ol (34c)

To a 5 dram glass vial equipped with a magnetic stir bar naphthalene-2-ol (0.3468 mmol), ethynylbenzene (0.6936 mmol), 1 mL of DCM solvent and photocatalyst T(*p*-F)PPT (5 mol%) were sequentially added. The solution was stirred at a distance of ~3 cm from 20 W white LED at room temperature. After completion of the reaction monitored by TLC, the solvent was removed in *vacuo* and extracted with ethyl acetate (3x10 mL), organic layers were dried over Na_2SO_4 and evaporated in *vacuo* and purified by column chromatography using 100–200 mesh silica gel with ethyl acetate/hexane (1:9) as the eluent to afford the corresponding hydroarylated compound **34c** as a product.



Pale yellow solid (71mg, 83% Yield); Mp: 112-113 ^{o}C

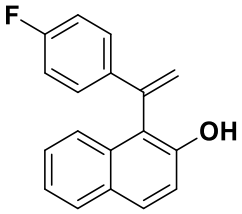
^{1}H NMR (500 MHz, CDCl$_3$) δ 7.70 -7.73 (m,2H), 7.43 – 7.45 (m, 1H), 7.28 – 7.30 (m, 2H), 7.18 - 7.23 (m, 6H), 6.26 (s, 1H), 5.55 (s, 1H), 5.44 (s, 1H).

^{13}C{^{1}H} NMR (125 MHz, CDCl$_3$) δ 150.4, 142.5, 138.7, 132.79, 129.6, 128.9, 128.7, 128.5, 128.0, 126.5, 126.3, 124.9, 123.3, 120.0, 118.9, 117.3, 77.2, 77.0, 76.7.

HRMS (ESI-Orbitrap) m/z: Calcd for $C_{18}H_{14}O$($[M+H]^+$) 247.1122; found 247.1122

1-(1-(4-fluorophenyl)vinyl) naphthalen-2-ol (34d)

To a 5 dram glass vial equipped with a magnetic stir bar naphthalene-2-ol (0.3468 mmol), 1-ethynyl-4-fluorobenzene (0.6936 mmol), 1 mL of DCM solvent and photocatalyst T(*p*-F)PPT (5 mol%) were sequentially added. The solution was stirred at a distance of ~3 cm from 20 W white LED at room temperature. After completion of the reaction monitored by TLC, the solvent was removed in *vacuo* and extracted with ethyl acetate (3x10 mL), organic layers were dried over Na_2SO_4 and evaporated in *vacuo* and purified by column chromatography using 100–200 mesh silica gel with ethyl acetate/hexane (1:9) as the eluent to afford the corresponding hydroarylated compound **34d** as a product.



Yellow viscous liquid (70mg, 76% Yield); **^{1}H NMR (500 MHz, $CDCl_3$) δ** 7.70 – 7.73 (m, 2H), 7.39 7.40 (m, 1H), 7.18 – 7.25 (m, 5H), 6.88(t, *J* = 8.0 Hz, 2H), 6.19 (s, 1H), 5.50 (s, 1H), 5.41 (s, 1H).

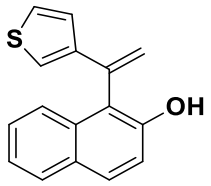
^{13}C{^{1}H} NMR (125MHz, $CDCl_3$) δ 163.9, 161.9, 150.4, 141.57, 134.9, 134.8, 132.6, 129.8, 128.9, 128.1, 128.1, 128.0, 126.6, 124.7, 123.4, 119.7, 118.5, 117.3, 115.7, 115.5,

HRMS (ESI) m/z: Calcd. For $C_{18}H_{13}FO([M+H]^+)$ 265.1028; found 265.1039

1-(1-(thiophen-3-yl)vinyl)naphthalen-2-ol (34e)

To a 5-dram glass vial equipped with a magnetic stir bar naphthalene-2-ol (0.3468 mmol), 3-ethynyl thiophene (0.6936 mmol), 1 mL of DCM solvent and photocatalyst T(*p*-F)PPT (5 mol%) were sequentially added. The solution was stirred at a distance of ~3 cm from 20 W white LED at room temperature. After completion of the reaction monitored by TLC, the solvent was removed in *vacuo* and extracted with ethyl acetate (3x10 mL), organic layers were dried over Na_2SO_4 and evaporated in *vacuo* and purified by column chromatography using 100–200 mesh silica gel with ethyl acetate/hexane (1:9) as the eluent to afford the corresponding hydroarylated compound **34e** as a product.

Pale yellow liquid (61mg, 75% Yield); **^{1}H NMR (500 MHz, $CDCl_3$) δ** 7.70 (d, *J* = 8.5 Hz, 2H), 7.50 (d, *J* = 8.5



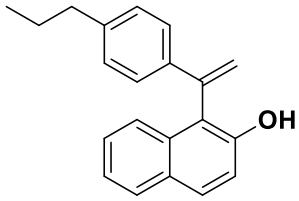
Hz, 1H), 7.22 – 7.28 (m, 4H), 7.17 (d, *J* = 8.0 Hz, 1H), 6.74 (s, 1H), 6.16 (s, 1H), 5.48 (s, 1H), 5.35 (s, 1H).

$^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 150.0, 140.9, 137.3, 132.71, 129.6, 128.8, 128.0, 126.5, 125.1, 124.8, 124.2, 123.3, 120.2, 117.7, 117.3.

HRMS (ESI-Orbitrap) m/z: Calcd. for $C_{16}H_{12}OS([M+H]^+)$ 253.0687; found 253.0695

1-(1-(4-propylphenyl) vinyl)naphthalen-2-ol (34f)

To a 5 dram glass vial equipped with a magnetic stir bar naphthalen-2-ol (0.3468 mmol), 1-ethynyl-4-propylbenzene (06936 mmol), 1 mL of DCM solvent and photocatalyst T(*p*-F)PPT (5 mol%) were sequentially added. The solution was stirred at a distance of ~3 cm from 20 W white LED at room temperature. After completion of the reaction monitored by TLC, the solvent was removed in *vacuo* and extracted with ethyl acetate (3x10 ml), organic layers were dried over Na_2SO_4 and evaporated in *vacuo* and purified by column chromatography using 100–200 mesh silica gel with ethyl acetate/hexane (1:9) as the eluent to afford the corresponding hydroarylated compound **34f** as a product.



yellow liquid (95mg,95% Yield); **^1H NMR (500 MHz, $CDCl_3$)** δ 7.70 – 7.72 (m, 2H), 7.45 – 7.46 (m, 1H), 7.17 - 7.23 (m, 5H), 7.00 (d, *J* = 8.0 Hz, 2H), 6.22 (s, 1H), 5.54 (s, 1H), 5.38 (s, 1H), 2.47 (t, J = 7.5 Hz, 2H), 2.05 (sext, 2H), 0.84 (t, *J* = 7.5 Hz, 3H).

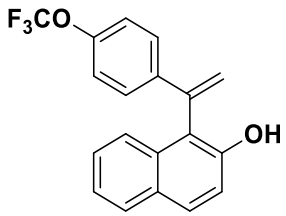
$^{13}C\{^1H\}$ NMR (125 MHz,) δ 150.3, 143.4, 142.3, 136.0, 132.85, 129.5, 128.9, 128.8, 128.0, 126.5, 126.2, 124.9, 123.2, 120.2, 118.0, 117.3, 37.7, 24.4, 13.8.

HRMS (ESI-Orbitrap) m/z: Calcd. for $C_{21}H_{20}O([M+H]^{+})$ 289.1592; found 289.1593

1-(1-(4-(trifluoromethoxy) phenyl)vinyl)naphthalen-2-ol (34g)

To a 5 dram glass vial equipped with a magnetic stir bar naphthalene-2-ol (0.3468 mmol), 1-ethynyl-4-(trifluoromethoxy)benzene (06936 mmol), 1 mL of DCM solvent and photocatalyst T(*p*-F)PPT (5 mol%) were sequentially added. The solution was stirred at a distance of ~3 cm from 20 W white LED at room temperature. After completion of the

reaction monitored by TLC, the solvent was removed in *vacuo* and extracted with ethyl acetate (3x10 ml), organic layers were dried over Na_2SO_4 and evaporated in *vacuo* and purified by column chromatography using 100–200 mesh silica gel with ethyl acetate/hexane (1:9) as the eluent to afford the corresponding hydroarylated compound **34g** as a product.



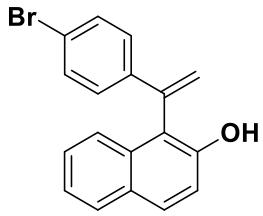
Yellow viscous liquid (80.30mg, 70% Yield); 1**H NMR (500 MHz, $CDCl_3$) δ** 7.71 – 7.74 (m, 2H), 7.38 – 7.40 (m, 1H), 7.29 (d, *J* = 8.5 Hz, 2H), 7.23 – 7.25 (m, 2H), 7.18 – 7.21 (m, 1H), 7.03 - 7.05 (d, *J* = 8.5 Hz, 2H), 6.25 (s, 1H), 5.48 – 5.50 (d, *J* = 9.5 Hz, 2H).

$^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 150.4, 149.3, 141.3, 137.38, 132.5, 129.9, 128.9, 128.1, 127.7, 126.7, 124.6, 123.4, 121.0, 119.6, 119.4, 117.3.

HRMS (ESI-Orbitrap) m/z: Calcd. for $C_{19}H_{13}F_3O_2([M+H]^+)$ 331.0945, found 331.0948.

1-(1-(4-bromophenyl)vinyl) naphthalen-2-ol (34h)

To a 5 dram glass vial equipped with a magnetic stir bar naphthalene-2-ol (0.3468 mmol), 1-bromo-4-ethynylbenzene (06936 mmol), 1 mL of DCM solvent and photocatalyst T(*p*-F)PPT (5 mol%) were sequentially added. The solution was stirred at a distance of ~3 cm from 20 W white LED at room temperature. After completion of the reaction monitored by TLC, the solvent was removed in *vacuo* and extracted with ethyl acetate (3x10 ml), organic layers were dried over Na_2SO_4 and evaporated in *vacuo* and purified by column chromatography using 100–200 mesh silica gel with ethyl acetate/hexane (1:9) as the eluent to afford the corresponding hydroarylated compound **34h** as a product.



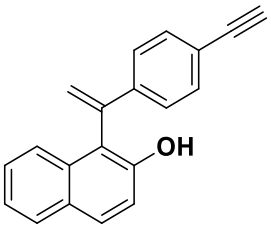
Pale yellow oil (82mg, 74% Yield); **^1H NMR (500 MHz, $CDCl_3$) δ** 7.69 - 7.72 (m, 2H), 7.35 - 7.37 (m, 1H), 7.30 (d, *J* = 8.5 Hz, 2H), 7.16 -7.24 (m,3H), 7.12 (d, *J* = 8.5 Hz, 2H), 6.23 (s, 1H), 5.51 (s, 1H), 5.45 (s, 1H).

$^{13}C\{^1H\}$ NMR (125MHz, $CDCl_3$) δ 150.4, 141.6, 137.7, 132.63, 131.8, 129.9, 128.9, 128.1, 127.9, 126.7, 124.7, 123.4, 122.7, 119.4, 119.3, 117.3,

HRMS (ESI-Orbitrap) m/z: Calcd. for $C_{18}H_{13}BrO([M+H]^+)$ 325.0228; found 327.0173.

1-(1-(4-ethynylphenyl) vinyl)naphthalen-2-ol (34i)

To a 5 dram glass vial equipped with a magnetic stir bar naphthalene-2-ol (0.3468 mmol), 1,4-diethynylbenzene (06936 mmol), 1 mL of DCM solvent and photocatalyst T(*p*-F)PPT (5 mol%) were sequentially added. The solution was stirred at a distance of ~3 cm from 20 W white LED at room temperature. After completion of the reaction monitored by TLC, the solvent was removed in *vacuo* and extracted with ethyl acetate (3x10 ml), organic layers were dried over Na_2SO_4 and evaporated in *vacuo* and purified by column chromatography using 100–200 mesh silica gel with ethyl acetate/hexane (1:9) as the eluent to afford the corresponding hydroarylated compound **34i** as a product.



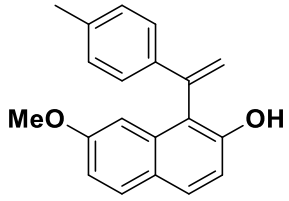
Yellow oil (76mg, 80% Yield); **^{1}H NMR (500 MHz, $CDCl_3$) δ** 7.72 – 7.74 (m, 2H), 7.36 – 7.38 (m, 1H), 7.32 – 7.33 (d, *J* = 8.5 Hz, 2H), 7.22 – 7.24 (m, 4H), 7.18 (d, *J* = 2.5 Hz, 1H), 6.28 (s, 1H), 5.49 - 5.50 (d, *J* = 6.5 Hz, 2H), 3.02 (s, 2H).

^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 150.4, 141.9, 139.1, 132.6, 132.5, 129.8, 128.9, 128.1, 126.6, 126.2, 124.7, 123.4, 122.2, 119.8, 119.4, 117.3, 83.3, 78.2.

HRMS (ESI-Orbitrap) m/z: Calcd. for $C_{20}H_{14}O([M+Na]^+)$ 293.0942 ; found 292.0861.

7-methoxy-1-(1-(*p*-tolyl)vinyl)naphthalen-2-ol (35a)

To a 5-dram glass vial equipped with a magnetic stir bar 7-methoxynaphthalen-2-ol (0.3468 mmol), 1-ethynyl-4-methylbenzene (06936 mmol), 1 mL of DCM solvent and photocatalyst T(*p*-F)PPT (5 mol%) were sequentially added. The solution was stirred at a distance of ~3 cm from 20 W white LED at room temperature. After completion of the reaction monitored by TLC, the solvent was removed in *vacuo* and extracted with ethyl acetate (3x10 ml), organic layers were dried over Na_2SO_4 and evaporated in *vacuo* and purified by column chromatography using 100–200 mesh silica gel with ethyl acetate/hexane (1:9) as the eluent to afford the corresponding hydroarylated compound **35a** as a product.

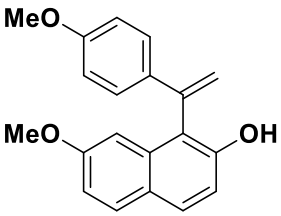


Dark brown liquid (73mg, 88% yield); **^{1}H NMR (500 MHz, $CDCl_3$) δ** 7.60 (dd, *J* = 18.0 Hz, 9.0 Hz, 4H), 7.18 (d, *J* = 8.0 Hz, 2H), 7.04 (s, 1H), 6.99 -7.02 (m, 2H), 6.86 (dd, *J* = 9.0 Hz, 2.5 Hz, 1H), 6.73 (d, *J* = 2.0 Hz, 1H), 6.17 (s, 1H), 5.56 (s, 1H), .5.39 (s, 1H), 3.57 (s, 1H), 2.24 (s, 3H). **^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ** 158.1, 151.0, 142.7, 138.53, 136.0, 134.0, 129.5, 129.4, 129.2, 126.3, 124.3, 119.5, 117.9, 115.5, 114.7, 104.0, 55.0, 21.1.

HRMS (ESI-Orbitrap) m/z: Calcd. For $C_{20}H_{18}O_2([M+H]^+)$ 291.1385; found 291.1380.

7-methoxy-1-(1-(4-methoxyphenyl)vinyl)naphthalen-2-ol (35b)

To a 5 dram glass vial equipped with a magnetic stir bar 7-methoxynaphthalen-2-ol (0.3468 mmol), 1-ethynyl-4-methoxybenzene (06936 mmol), 1 mL of DCM solvent and photocatalyst T(*p*-F)PPT (5 mol%) were sequentially added. The solution was stirred at a distance of ~3 cm from 20 W white LED at room temperature. After completion of the reaction monitored by TLC, the solvent was removed in *vacuo* and extracted with ethyl acetate (3x10 ml), organic layers were dried over Na_2SO_4 and evaporated in *vacuo* and purified by column chromatography using 100–200 mesh silica gel with ethyl acetate/hexane (1:9) as the eluent to afford the corresponding hydroarylated compound **35b** as a product.



White solid (84mg, 95% yield); Mp: 119-120 ^{o}C;

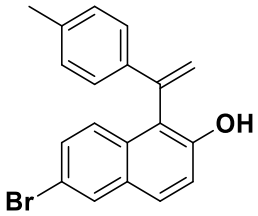
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.60 (dd, *J* = 16.0, 9.0 Hz, 2H), 7.22 (d, *J* = 9.0 Hz, 2H), 7.03 (d, *J* = 9.0 Hz, 1H), 6.86 (dd, *J* = 9.0 Hz, 2.5 Hz, 1H), 6.70 (d, *J* = 9.0 Hz, 3H), 6.10 (s, 1H), 5.62 (s, 1H), 5.32 (s, 1H), 3.68 (s, 3H), 3.57 (s, 3H).

^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 159.9, 158.1, 151.0, 142.19, 134.0, 131.3, 129.5, 129.2, 127.7, 124.2, 119.5, 116.7, 115.5, 114.7, 114.0, 104.0, 55.3, 55.0.

HRMS (ESI-Orbitrap) m/z: Calcd. for $C_{20}H_{18}O_3([M+H]^+)$307.1334; found 307.1338

6-bromo-1-(1-(*p*-tolyl)vinyl)naphthalen-2-ol (35c)

To a 5-dram glass vial equipped with a magnetic stir bar 6-bromonaphthalen-2-ol (0.3468 mmol), 1-ethynyl-4-methylbenzene (06936 mmol), 1 mL of DCM solvent and photocatalyst T(*p*-F)PPT (5 mol%) were sequentially added. The solution was stirred at a distance of ~3 cm from 20 W white LED at room temperature. After completion of the reaction monitored by TLC, the solvent was removed in *vacuo* and extracted with ethyl acetate (3x10 ml), organic layers were dried over Na_2SO_4 and evaporated in *vacuo* and purified by column chromatography using 100–200 mesh silica gel with ethyl acetate/hexane (1:9) as the eluent to afford the corresponding hydroarylated compound **35c** as a product.



Yellow oil (64 mg, 85% yield);

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.84 (s, 1H), 7.60 – 7.61 (d, *J* = 9.0 Hz, 1H), 7.25 -7.31 (m, 2H), 7.19 – 7.21 (d, *J* = 9.0 Hz, 1H), 7.12 - 7.13 (d, *J* = 8.5 Hz, 2H), 6.99 - 7.01 (d, *J* = 8.0 Hz, 2H), 6.20 (s, 1H), 5.58 (s, 1H), 5.36 (s, 1H), 2.23 (s, 3H).

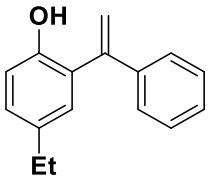
^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 150.7, 141.8, 138.8, 135.60, 131.3, 130.0, 129.9, 129.7, 129.5, 128.6, 126.8, 126.1, 120.4, 118.5, 118.2, 117.1, 21.2.

HRMS (ESI-Orbitrap) m/z: Calcd. for $C_{19}H_{15}BrO([M+Na]^+)$ 361.0204 ; found 362.1155

4-ethyl-2-(1-phenylvinyl)phenol (35d)

To a 5-dram glass vial equipped with a magnetic stir bar 4-ethylphenol (0.3468 mmol), ethylbenzene (06936 mmol), 1 mL of DCM solvent and photocatalyst T(*p*-F)PPT (5 mol%) were sequentially added. The solution was stirred at a distance of ~3 cm from 20 W white LED at room temperature. After completion of the reaction monitored by TLC, the solvent was removed in *vacuo* and extracted with ethyl acetate (3x10 ml), organic layers were dried over Na_2SO_4 and evaporated in *vacuo* and purified by column chromatography using 100–200 mesh silica gel with ethyl acetate/hexane (1:9) as the eluent to afford the corresponding hydroarylated compound **35d** as a product.

Colourless liquid (55 mg, 51% yield); **^{1}H NMR (500 MHz, $CDCl_3$) δ** 7.18 - 7.20 (m, 2H), 7.06 - 7.08 (d, *J* = 8.0 Hz,



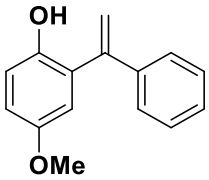
2H), 6.99 -7.01 (d, *J* = 8.5 Hz, 2H), 6.88 (s, 1H), 6.78 - 6.79 (d, *J* = 8.0 Hz, 1H), 5.73 (s, 1H), 5.27 (s, 1H), 4.93 (s, 1H), 2.47 - 2.51 (q, 2H), 2.27 (s, 3H), 1.11 - 1.14 (t, *J* = 7.5 Hz, 3H)

^{13}C NMR (1265MHz, $CDCl_3$) δ 151.04, 145.29, 138.60, 136.59, 136.12, 129.57, 129.42, 128.73, 127.41, 127.00, 115.70, 115.58, 77.28, 77.03, 76.78, 27.96, 21.21, 15.85.

HRMS (ESI-Orbitrap) m/z: Calcd. for $C_{16}H_{16}O([M+Na]^+)$ 225.1279 ; found 225.1283.

4-methoxy-2-(1-phenylvinyl)phenol (35e)

To a 5-dram glass vial equipped with a magnetic stir bar 4-methoxy phenol **(**0.3468 mmol), ethylbenzene (06936 mmol), 1 mL of DCM solvent and photocatalyst T(*p*-F)PPT (5 mol%) were sequentially 2added. The solution was stirred at a distance of ~3 cm from 20 W white LED at room temperature. After completion of the reaction monitored by TLC, the solvent was removed in *vacuo* and extracted with ethyl acetate (3x10 ml), organic layers were dried over Na_2SO_4 and evaporated in *vacuo* and purified by column chromatography using 100–200 mesh silica gel with ethyl acetate/hexane (1:9) as the eluent to afford the corresponding hydroarylated compound **35e** as a product.



Viscous liquid (46 mg, 50% yield); 1**H NMR (500 MHz, $CDCl_3$) δ** 7.33 – 7.38 (m, 5H), 6.87 (d, *J* = 9.0Hz 1H), 6.81-6.84 (m, 1H), 6.639(d, *J* = 2.5 Hz, 1H), 5.86 (s, 1H), 5.42 (s, 1H), 4.78 (s, 1H), 3.74 (s, 3H).

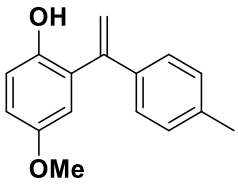
^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 153.3, 147.1, 145.3, 139.1, 128.7, 128.6, 128.1, 127.0, 116.7, 116.5, 115.3, 115.1, 55.7.

HRMS (ESI-Orbitrap) m/z: Calcd. for $C_{15}H_{14}O_2([M+H]^+)$ 227.1072; found 227.1068.

4-methoxy-2-(1-(*p*-tolyl)vinyl)phenol (35f)

To a 5 dram glass vial equipped with a magnetic stir bar 4-methoxy phenol **(**0.3468 mmol), 1-ethynyl-4-methylbenzene **(**06936 mmol), 1 mL of DCM solvent and photocatalyst T(*p*-F)PPT (5 mol%) were sequentially added. The solution was stirred at a distance of ~3 cm

from 20 W white LED at room temperature. After completion of the reaction monitored by TLC, the solvent was removed in *vacuo* and extracted with ethyl acetate (3x10 ml), organic layers were dried over Na_2SO_4 and evaporated in *vacuo* and purified by column chromatography using 100–200 mesh silica gel with ethyl acetate/hexane (1:9) as the eluent to afford the corresponding hydroarylated compound **35f** as a product.



Viscous liquid (53mg, 55% yield); **^{1}H NMR (500 MHz, $CDCl_3$) δ** 7.17 – 7.20 (d, *J* = 3.0 Hz, 2H), 7.06 - 7.07 (d, *J* = 8.0 Hz, 2H), 6.78 – 6.80 (d, *J* = 4.0 Hz, 2H), 6.73 – 6.75 (dd, *J* = 7.0, 3.0 Hz, 1H), 6.25 – 6.31 (d, J = 3.0 Hz, 1H) 5.73 (s, 1H), 5.28 (s, 1H), 4.73 (s, 1H), 3.69 (s, 3H), 2.27 (s, 3H).

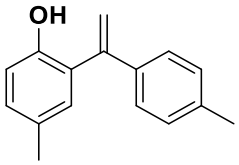
^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 153.3, 147.1, 145.1, 138.69, 136.2, 129.4, 128.2, 126.9, 116.5, 115.9, 115.2, 115.0, 55.7, 21.2.

HRMS (ESI-Orbitrap) m/z: Calcd. For $C_{16}H_{16}O_2([M+H]^+)$ 241.1229; found 241.1228.

4-methyl-2-(1-(*p*-tolyl)vinyl)phenol (35g)

To a 5-dram glass vial equipped with a magnetic stir bar *p*-cresol **(**0.3468 mmol), 1-ethynyl-4-methylbenzene (06936 mmol), 1 mL of DCM solvent and photocatalyst T(*p*-F)PPT (5 mol%) were sequentially added. The solution was stirred at a distance of ~3 cm from 20 W white LED at room temperature. After completion of the reaction monitored by TLC, the solvent was removed in *vacuo* and extracted with ethyl acetate (3x10 ml), organic layers were dried over Na_2SO_4 and evaporated in *vacuo* and purified by column chromatography using 100–200 mesh silica gel with ethyl acetate/hexane (1:9) as the eluent to afford the corresponding hydroarylated compound **35g** as a product.

Colourless liquid (53 mg, 51% yield); **^{1}H NMR (500 MHz, $CDCl_3$) δ** 7.18 – 7.20 (d, *J* = 7.5 Hz, 2H), 7.06 – 7.08 (d, *J* = 8.0 Hz, 2H), 6.96 - 6.98 (dd, *J* = 8.5 Hz, 3 Hz, 1H), 6.87 (s, 1H), 6.76 - 6.77 (d, *J* = 8.0 Hz, 1H), 5.72 (s, 1H), 5.27 (s, 1H), 4.93 (s, 1H), 2.28 (s, 3H), 2.20 (s, 3H).

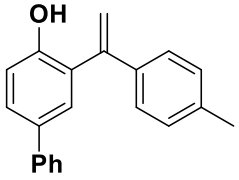


$^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$) δ 150.8, 145.2, 138.5, 136.61, 130.6, 129.9, 129.5, 129.4, 127.4, 126.99, 115.7, 115.5, 21.1, 20.4.

HRMS (ESI-Orbitrap) m/z: Calcd. for $C_{16}H_{16}O([M+H]^+)$ 225.1279 ; found 225.1279.

4-methyl-2-(1-(*p*-tolyl)vinyl)phenol (35h)

To a 5-dram glass vial equipped with a magnetic stir bar *p*-cresol **(**0.3468 mmol), 1-ethynyl-4-methylbenzene (06936 mmol), 1 mL of DCM solvent and photocatalyst T(*p*-F)PPT (5 mol%) were sequentially added. The solution was stirred at a distance of ~3 cm from 20 W white LED at room temperature. After completion of the reaction monitored by TLC, the solvent was removed in *vacuo* and extracted with ethyl acetate (3x10 ml), organic layers were dried over Na_2SO_4 and evaporated in *vacuo* and purified by column chromatography using 100–200 mesh silica gel with ethyl acetate/hexane (1:9) as the eluent to afford the corresponding hydroarylated compound **35h** as a product.



Colourless liquid (59 mg, 50% yield); **^{1}H NMR (500 MHz, $CDCl_3$) δ** 7.46 - 7.48 (d, *J* = 7.5 Hz, 2H), 7.42 - 7.43 (d, *J* = 8.5 Hz, 1H), 7.30 - 7.33 (m, 3H), 7.21 - 7.24 (m, 2H), 7.18 (s, 1H), 7.08 -7.09 (d, *J* = 7.5 Hz), 6.94 - 6.95 (d, *J* = 8.0 Hz, 1H), 5.79 (s, 1H), 5.35 (s, 1H), 5.13(s, 1H), 2.28 (s, 3H);

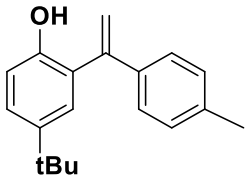
^{13}C NMR (125 MHz, DMSO) δ 152.76, 145.03, 140.60, 138.79, 136.31, 133.61, 129.51, 129.00, 128.72, 128.08, 127.02, 126.74, 116.23, 116.08, 77.28, 77.03, 76.78, 21.21.

HRMS (ESI-Orbitrap) m/z: Calcd. for $C_{21}H_{18}O([M+H]^+)$ 287.1436 ; found 287.1441.

4-(tert-butyl)-2-(1-(*p*-tolyl)vinyl)phenol (35i)

To a 5-dram glass vial equipped with a magnetic stir bar 4-(*tert*-butyl)phenol (0.3468 mmol), 1-ethynyl-4-methylbenzene (06936 mmol), 1 mL of DCM solvent and photocatalyst T(*p*-F)PPT (5 mol%) were sequentially added. The solution was stirred at a distance of ~3 cm from 20 W white LED at room temperature. After completion of the reaction monitored by TLC, the solvent was removed in *vacuo* and extracted with ethyl acetate (3x10 ml), organic

layers were dried over Na_2SO_4 and evaporated in *vacuo* and purified by column chromatography using 100–200 mesh silica gel with ethyl acetate/hexane (1:9) as the eluent to afford the corresponding hydroarylated compound **35i** as a product.



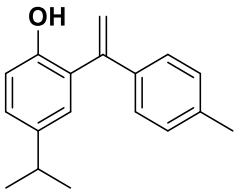
Pale yellow liquid (46 mg, 52% yield); **^{1}H NMR (500 MHz, $CDCl_3$) δ** 7.17 – 7.21 (m, 3H), 7.06 – 7.08 (m, 3H), 6.78 - 6.80 (d, *J* = 8.5 Hz, 1H), 5.74 (s, 1H), 5.28 (s, 1H), 4.93 (s, 1H), 2.28 (s, 3H), 1.21 (s, 9H).

^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 150.78, 145.49, 143.11, 138.59, 136.49, 129.42, 127.22, 126.96, 126.30, 115.64, 115.18, 34.10, 31.55, 21.21.

HRMS (ESI-Orbitrap) m/z: Calcd. for $C_{19}H_{22}O([M+H]^+)$ 267.1748; found 267.1753

4-isopropyl-2-(1-(*p*-tolyl)vinyl)phenol (35j)

To a 5 dram glass vial equipped with a magnetic stir bar 4-isopropylphenol (0.3468 mmol), 1-ethynyl-4-methylbenzene (06936 mmol), 1 mL of DCM solvent and photocatalyst T(*p*-F)PPT (5 mol%) were sequentially added. The solution was stirred at a distance of ~3 cm from 20 W white LED at room temperature. After completion of the reaction monitored by TLC, the solvent was removed in *vacuo* and extracted with ethyl acetate (3x10 ml), organic layers were dried over Na_2SO_4 and evaporated in *vacuo* and purified by column chromatography using 100–200 mesh silica gel with ethyl acetate/hexane (1:9) as the eluent to afford the corresponding hydroarylated compound **35j** as a product.



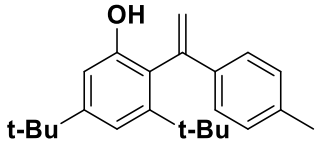
Colourless liquid (51 mg, 55% yield); **^{1}H NMR (500 MHz, $CDCl_3$) δ** 7.18 – 7.20 (m, 2H), 7.06 - 7.08 (d, *J* = 8.0 Hz, 2H), 7.03 – 7.04 (dd, *J* = 8.5, 2.5 Hz, 1H), 6.91 (d, *J* = 2.0 Hz, 1H), 6.79 - 6.80 (d, *J* = 8.0 Hz, 1H), 5.74 (s, 1H), 5.28 (s, 1H), 4.93 (s, 1H), 2.72 - 2.80 (sept, 1H), 2.29 (s, 3H), 1.15 (s, 3H), 1.13 (s, 3H).

$^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$) δ 151.0, 145.3, 140.7, 138.59, 136.5, 129.4, 128.2, 127.3, 127.2, 126.9, 115.6, 115.5, 33.2, 24.2, 21.2.

HRMS (ESI-Orbitrap) m/z: Calcd. for $C_{18}H_{20}OH([M+H]^+)$ 253.1592**;** found 253.1588

3,5-di-tert-butyl-2-(1-(*p*-tolyl)vinyl)phenol (35k)

To a 5-dram glass vial equipped with a magnetic stir bar 3,5-di-*tert*-butylphenol (0.3468 mmol), 1-ethynyl-4-methylbenzene (06936 mmol), 1 mL of DCM solvent and photocatalyst T(*p*-F)PPT (5 mol%) were sequentially added. The solution was stirred at a distance of ~3 cm from 20 W white LED at room temperature. After completion of the reaction monitored by TLC, the solvent was removed in *vacuo* and extracted with ethyl acetate (3x10 ml), organic layers were dried over Na_2SO_4 and evaporated in *vacuo* and purified by column chromatography using 100–200 mesh silica gel with ethyl acetate/hexane (1:9) as the eluent to afford the corresponding hydroarylated compound **35k** as a product.



35k

Viscous liquid (46 mg, 60% yield); **^{1}H NMR (500 MHz, $CDCl_3$) δ** 7.21 - 7.22 (d, *J* = 8.0 Hz, 2H), 7.09 - 7.12 (m, 3H), 6.92 (d, *J* = 2.0 Hz, 1H), 6.21 (s, 1H), 5.38 – 5.39 (d, *J* = 4.5 Hz, 1H), 2.32 (s, 3H), 1.34 (s, 9H), 1.32 (s, 9H).

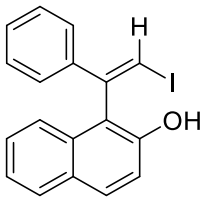
$^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$) δ 152.6, 151.4, 148.1, 145.18, 138.2, 136.5, 129.3, 126.1, 123.2, 118.1, 116.3, 109.8, 77.2, 77.0, 76.7, 37.1, 34.8, 32.3, 31.3, 21.1.

HRMS (ESI-Orbitrap) m/z: Calcd. for $C_{23}H_{30}OH([M+H]^+)$ 323.2374; found 323.2374

(*E*)-1-(2-iodo-1-phenylvinyl)naphthalen-2-ol (39)

To a round bottom flask equipped with a magnetic stir bar naphthalen-2-ol (0.3468 mmol), Phenyl acetylene (0.6936 mmol), 2 mL of DCM solvent and photocatalyst T(*p*-F)PPT (5 mol%) were sequentially added. The solution was stirred at a distance of ~3 cm from 20 W white LED at room temperature. After completion of the reaction monitored by TLC, the solvent was removed in *vacuo* then to this crude I_2 (128.8 mg, 2.5 mmol), and MeCN (2mL) was added. The reaction mixture was refluxed for 4 h. allow the reaction to cool at room temperature and quenched with $Na_2S_2O_3$ solution, then extracted with Ethyl acetate (2 x

10mL). The combined organic layer was dried over anhydrous Na_2SO_4 and then concentrated under reduced pressure to afford the crude product. The residue was purified by column chromatography using 100–200 mesh silica gel with hexane /ethyl acetate (10: 2, v/v) to afford the product **39** (96 mg, 74% yield).



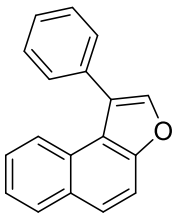
Viscous liquid (96 mg, 74% yield); **^{1}H NMR (500 MHz, CDCl3) δ** 7.29-7.78 (m, 2H), 7.36 (s, 1H), 7.40 (d, *J* = 8.5 Hz, 1H), 7.5-7.28(m, 7H), 5.18 (s, 1H).

^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 149.4, 146.8, 138.6, 131.5, 130.4, 129.1, 128.9, 128.8, 128.2, 127.0, 126.4, 124.0, 123.7, 121.1, 117.6, 86.0.

HRMS (ESI-Orbitrap) m/z: Calcd. for $C_{18}H_{13}IO([M+H]^+)$ 373.0089; found 373.0091

1-phenylnaphtho[2,1-*b*]furan (40a)

To a round bottom flask equipped with a magnetic stir bar naphthalen-2-ol (0.3468 mmol), Phenyl acetylene (0.6936 mmol), 2 mL of DCM solvent and photocatalyst T(*p*-F)PPT (5 mol%) were sequentially added. The solution was stirred at a distance of ~3cm from 20 W white LED at room temperature. After completion of the reaction monitored by TLC, the solvent was removed in *vacuo* then to this crude K_2CO_3 (67.8mg, 0.4912 mmol) and $AgCO_3$ (90.3mg, 0.3274 mmol) DMF (2 mL), was added under Ar atmosphere, and stirred at 120 ℃ for 20 h. allow the reaction mixture to cool down and add 5mL of water into the reaction mixture and then extracted with ethyl acetate (EA) (3x15mL). The combined organic layer was dried over anhydrous Na_2SO_4. After concentration, the residue was purified by column chromatography using 100–200 mesh silica gel with hexane /ethyl acetate (10: 1, v/v) to afford the product **40a.**



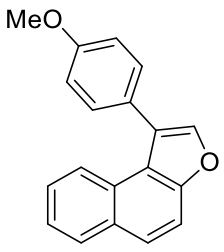
Colourless liquid (55 mg, 65% yield); **^{1}H NMR (500 MHz, CDCl3) δ** 8.08 (d, *J* = 8.5 Hz, 1H), 7.99 (d, *J* = 9.0 Hz, 1H), 7.82 (d, *J* = 9.0 Hz, 1H), 7.33 -7.76 (m, 2H), 7.67 (d, *J* =7.5 Hz, 2H), 7.52-7.58 (m, 3H), 7.47 7.50 (m, 1H), 7.40 (t, *J* = 7.5 Hz, 1H)

$^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$) δ 153.1, 141.7, 133.1, 130.8, 129.8, 128.9, 128.6, 128.3, 127.8, 125.9, 125.9, 124.4, 124.3, 123.3, 120.7, 112.6.

HRMS ((ESI-Orbitrap) m/z: Calcd. for $C_{18}H_{12}O([M+H]^+)$ 245.0966; found 245.0968

methoxyphenyl)naphtho[2,1-*b*]furan (40b)

To a round bottom flask equipped with a magnetic stir bar naphthalen-2-ol (0.3468 mmol), Phenyl acetylene (0.6936 mmol), 2 mL of DCM solvent and photocatalyst T(*p*-F)PPT (5 mol%) were sequentially added. The solution was stirred at a distance of ~3cm from 20 W white LED at room temperature. After completion of the reaction monitored by TLC, the solvent was removed in *vacuo* then to this crude K_2CO_3 (67.8mg, 0.4912 mmol) and $AgCO_3$ (90.3mg, 0.3274 mmol) DMF (2 mL), was added under Argon atmosphere, and stirred at 120 ℃ for 20 h. allow the reaction mixture to cool down and add 5mL of water into the reaction mixture and then extracted with ethyl acetate (EA) (3x15mL). The combined organic layer was dried over anhydrous Na_2SO_4. After concentration, the residue was purified by column chromatography using 100–200 mesh silica gel with hexane /ethyl acetate (10: 1, v/v) to afford the product **40b.**



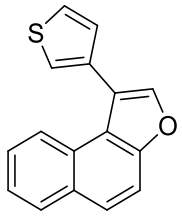
Yellow liquid (65 mg, 68% yield); **^{1}HNMR (500 MHz, CDCl3) δ** 7.91 (d, *J* **=** 8.0 Hz, 1H), 7.81 (d *J* = 8.5 Hz, 1H), 7.63 (d, *J* = 9.0 Hz, 1H), 7.57 (d, *J* = 9.0 Hz, 1H), 7.52 (s, 1H), 7.39 (d, *J* = 7.5 Hz), 7.30 (t, *J* = 7.5 Hz, 1H), 7.24 (t, *J* = 7.5 Hz, 1H), 6.92 (d, *J* = 7.5 Hz, 1H), 3.75 (s, 3H**).**

$^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$) δ 159.3, 153.0, 141.5, 133.5, 130.9, 130.7, 128.8, 128.3, 125.9, 125.8, 125.1, 124.2, 123.9, 123.3, 120.9, 114.0, 112.6, 55.3. **HRMS (ESI-Orbitrap) m/z**: Calcd. for $C_{19}H_{14}O_2([M+H]^+)$ 275.1072; found 272.1072

1-(thiophen-3-yl)naphtho[2,1-*b*]furan(40c)

To a round bottom flask equipped with a magnetic stir bar naphthalene-2-ol (0.3468 mmol), 3-ethynyl thiophene (0.6936 mmol), 2 mL of DCM solvent and photocatalyst T(*p*-F)PPT (5

mol%) were sequentially added. The solution was stirred at a distance of ~3cm from 20 W white LED at room temperature. After completion of the reaction monitored by TLC, the solvent was removed in *vacuo* then to this crude K_2CO_3 (67.8mg, 0.4912 mmol) and $AgCO_3$ (90.3mg, 0.3274 mmol) DMF (2 mL), was added under Argon atmosphere, and stirred at 120 ℃ for 20 h. Allow the reaction mixture to cool down and add 5mL of water into the reaction mixture and then extracted with ethyl acetate (EA) (3x15mL). The combined organic layer was dried over anhydrous Na_2SO_4. After concentration, the residue was purified by column chromatography using 100–200 mesh silica gel with hexane /ethyl acetate (10: 1, v/v) to afford the product **40c.**



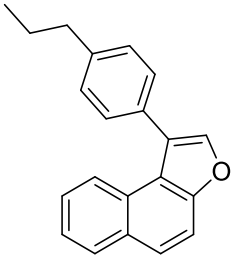
Pale yellow liquid (54 mg, 62% yield); **1H NMR (500 MHz, CDCl3) δ** 8.10 (d, *J* = 8.0 Hz), 7.97 (d, *J* = 8.0 Hz, 1H0, 7.79 (d, *J* = 9.0 Hz, 1H), 7.70 – 7.73 (m, 2H), 7.42 – 7.54 (m, 4H), 7.37 (d, *J* = 5.0 Hz, 1H).

$^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 153.0, 141.8, 132.7, 130.7, 129.3, 128.8, 128.3, 126.1, 126.0, 125.9, 124.4, 123.8, 123.3, 120.9, 119.0, 112.6.

HRMS (ESI-Orbitrap) m/z: Calcd. for $C_{18}H_{10}OS([M+H]^+)$ 251.0530; found 251.0525

1-(4-propylphenyl)naphtho[2,1-*b*]furan (40d)

To a round bottom flask equipped with a magnetic stir bar naphthalene-2-ol (0.3468 mmol), 1-ethynyl-4-propylbenzene (06936 mmol), 2 mL of DCM solvent and photocatalyst T(*p*-F)PPT (5 mol%) were sequentially added. The solution was stirred at a distance of ~3cm from 20 W white LED at room temperature. After completion of the reaction monitored by TLC, the solvent was removed in *vacuo* then to this crude K_2CO_3 (67.8mg, 0.4912 mmol) and $AgCO_3$ (90.3mg, 0.3274 mmol) DMF (2 mL), was added under Argon atmosphere, and stirred at 120 ℃ for 20 h. allow the reaction mixture to cool down and add 5mL of water into the reaction mixture and then extracted with ethyl acetate (EA) (3x15mL). The combined organic layer was dried over anhydrous Na_2SO_4. After concentration, the residue was purified by column chromatography using 100–200 mesh silica gel with hexane /ethyl acetate (10: 1, v/v) to afford the product **40d.**



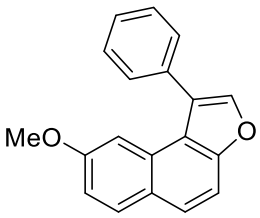
Colourless liquid (68 mg, 68% yield); **1H NMR (500 MHz, CDCl3) δ** 8.09 (d, *J* = Hz,1H), 9.97 (d, *J* = 8.0 Hz), 7.95 (d, *J* = 9.0 Hz), 7.69 -7.73 (m, 2H), 7.56 (d, *J* = 8.0 Hz, 1H), 7.44 -7.47 (m, 1H), 7.39 (t, *J* = 7.5 Hz, 2H), 2.74 (t, *J* = 7.5 Hz, 2H), 1.75 -1.82 (sext, 2H), 1.06 (t, *J* = 7.5 Hz, 3H).

$^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$) δ 153.1, 142.4, 141.6, 130.8, 130.2, 129.7, 128.8, 128.6, 128.4, 125.9, 125.8, 124.4, 124.3, 123.4, 120.8, 112.6, 37.9, 24.5, 13.9.

HRMS (ESI-Orbitrap) m/z: Calcd. for $C_{21}H_{18}O([M+H]^+)$ 287.1435; found 287.1444.

1-(4-propylphenyl)naphtho[2,1-*b*]furan (40e)

To a round bottom flask equipped with a magnetic stir bar 7-methoxynaphthalen-2-ol (0.3468 mmol), ethylbenzene (0.6936 mmol), 2 mL of DCM solvent and photocatalyst T(*p*-F)PPT (5 mol%) were sequentially added. The solution was stirred at a distance of ~3cm from 20 W white LED at room temperature. After completion of the reaction monitored by TLC, the solvent was removed in *vacuo* then to this crude K_2CO_3 (67.8mg, 0.4912 mmol) and $AgCO_3$ (90.3mg, 0.3274 mmol) DMF (2 mL), was added under Argon atmosphere, and stirred at 120 ℃ for 20 h. allow the reaction mixture to cool down and add 5mL of water into the reaction mixture and then extracted with ethyl acetate (EA) (3x15mL) The combined organic layer was dried over anhydrous Na_2SO_4. After concentration, the residue was purified by column chromatography using 100–200 mesh silica gel with hexane /ethyl acetate (10: 1, v/v) to afford the product **40e.**



Yellow liquid (59 mg, 62% yield); **1H NMR (500 MHz, CDCl3) δ** 7.84(d, *J* = 10 Hz, 1H), 7.71 (d, *J* = 10 Hz, 2H), 7.64(d, *J* = 5 Hz, 2H), 7.51 – 7.57 (m,3H), 7.45 – 7.48 (m, 1H), 7.30 (s, 1H), 7.08 (d, *J* = 10 Hz, 1H), 3.57 (s, 3H).

$^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$) δ 157.74, 153.62, 141.13, 133.13, 130.26, 130.09, 129.46, 128.41, 127.88, 125.70, 125.66, 124.22, 120.11, 116.35, 110.12, 102.87, 54.86.

HRMS (ESI-Orbitrap) m/z: Calcd. For $C_{19}H_{14}O_2$([M+H]$^+$) 275.1072; found 275.1075

4.12. References

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ABSTRACT

Name of the Student**:** **Valmiki Praveen Kumar**
Registration No**.: 10CC16A39007**
Faculty of Study**:** Chemical Sciences Year of Submission**: 2023**
AcSIR academic centre/CSIR Lab**:** CSIR-National Institute for Interdisciplinary Science and Technology (CSIR-NIIST)
Name of the Supervisor: **Dr. Sasidhar B.S.**
Name of the Co-Supervisor: **Dr. Priya S.**
Title of the thesis: **Improved Synthetic Transformations to Access Indole and Naphthol Appended Conjugates**

Conjugates are the compounds formed from the attachment of a moiety to another molecule entity, substituent, or functional group. Introducing various substituents onto these scaffolds can modulate their physicochemical and biological properties, making them valuable tools in drug discovery and materials science. The beauty of appended organic molecules lies in their ability to bestow new characteristics upon the parent compound, rendering it more versatile and adaptable. By skillfully incorporating various appendages, researchers can fine-tune properties. Such modifications enable researchers to craft molecules with tailored functionalities that are indispensable in various scientific fields. Among the various heterocycles, aryl/cycloalkyl appended indole and naphthol frameworks are privileged substructures owing to their prevalence in natural products and pharmaceutically active compounds. Thus, in **Chapter 1,** we discussed the classical methods for synthesising indole and naphthol appended conjugates, followed by the modern approaches that have emerged in recent years such as visible light-induced and electrochemical approaches are also envisaged. Further, various applications of indole and naphthol conjugate in diverse fields are also covered.

Chapter 2. We synthesized a range of functionalized indole-appended dihydronaphthalenone hybrid analogs screened for antibacterial and antitubercular activities. We successfully identified a novel structural class, which inhibits the set of organisms with very low minimum inhibition concentrations. Among the novel compounds, **38o** and **38p** are the most active with a minimum inhibition concentration of 3.12 μg/ml. against *E. coli* and *S. aureus.* And **38o** and **38p** also found more potent analogues in inhibiting the *M. tuberculosis* with minimum inhibition concentration of 6.25 μg/ml. These exciting findings suggest that the indolyl naphthalenones have real potential in finding suitable "Leads" for developing antitubercular therapeutics.

A literature survey has revealed that ethylbenzene hydroperoxide (EBHP) is less explored as an oxidizing agent for epoxidation reactions**.** Nonhazardous and easily accessible EBHP is utilized as an oxidizing agent for the epoxidation of oxindole chalcones in **Chapter 3.** The reaction condition applicable to electron-deficient, electron-rich arylideneindolin-2-ones, heteroarylideneindolin-2-ones and alkylideneindolin-2-ones to yield the diastereoselective aryl/heteroaryl and alkyl spiro oxiranes. This procedure enables access of diastereoselective *trans*-spiro-epoxy oxindoles in a very short reaction time.

Chapter 4. describes the synthesis of 2-vinyl phenols through visible light-promoted hydroarylation of phenyl acetylenes with naphthols and phenols. This approach provides an efficient and convergent route for accessing a wide range of ortho-allyl phenols with high functional group tolerance. In addition, this strategy occurs under mild and metal-free conditions upon irradiation with simple household LEDs and averting the use of external ligands and additives. Hence formed products serve as the versatile building blocks for subsequent synthetic transformations.

List of Publications Emanating from the Thesis

1. **Kumar, V. P,** Renjitha, J. Salfeena, C. T. F. Ashitha, K. T. Keri, R. S. Varughese, S. Sasidhar, B. S, Antibacterial and Antitubercular Evaluation of Dihydronaphthalenone-Indole Hybrid Analogs. *Chem Biol Drug Des*., **2017,** 90, 703–708.
2. **Valmiki, P. K**.; Banyangala, M.; Varughese, S.; Somappa, S. B. Ethylbenzene Hydroperoxide: An Efficient Oxidizing Agent for Diastereoselective Synthesis of Spiroepoxy Oxindoles. *Tetrahedron Lett.* **2022**, *108*, 154126.
3. **V. Praveen Kumar**, C. S Athira, B. Mohan, S. Priya, and B. S. Sasidhar. Photoinduced Radical Hydroarylation of Terminal Alkynes with Naphthols and Phenols (Manuscript to be submitted)

List of Publications not Related to Thesis Work

1. Ashitha, K. T.; **Praveen Kumar, V**.; Fathimath Salfeena, C. T.; Sasidhar, B. S. $BF_3{\cdot}OEt_2$- Mediated tandem annulation: A strategy to construct functionalized chromeno- and pyrano-fused pyridines. *J. Org. Chem*. **2018**, 83, 113–124.

2. Renjitha Jalaja, Shyni G. Leela, **Praveen K. Valmiki**, Chettiyan Thodi F. Salfeena, Kizhakkan T. Ashitha, Venkata Rao D. Krishna Rao, Mangalam S. Nair, Raghu K. Gopalan, and Sasidhar B. Somappa. *ACS Med. Chem. Lett.*, **2018**, *9* (7), 662–666

3. Fathimath Salfeena, C. T.; Basavaraja.; Ashitha, K. T.; **Kumar, V. P**.; Varughese, S.; Suresh, C. H.; Sasidhar, B. S. Synthesis of symmetrical and unsymmetrical triaryl pyrylium ions: via an inverse electron demand Diels-Alder reaction. *Chem. Commun*. **2018**, 54, 12463–12466.

4. Athira, C. S.; Basavaraja, D.; **Praveen K. V.;** Shridevi D.; Sasidhar B. S. $Cu(OAc)_2$ Catalyzed Aerobic Oxidative 2-Aryl-3-acylquinoline Synthesis via Aza-Michael Addition and Aldol Condensation of *α, β*-Unsaturated ketones and 2-Aminobenzyl alcohols. *Tetrahedron Letters,* **2022,** 104, 154043.

5. Athira C. Santhoshkumar, Basavaraja Durugappa, Siddalingeshwar V. Doddamani, Aiswarya Siby, Praveen K. Valmiki, Sasidhar B. Somappa, Diastereoselective Synthesis of Fused Tricyclic Pyridopyrimidines via Tandem Cyclization of Allenoates

and Cyclic Amidines. *Organic Letters* **2023**, 25, 42, 7711-7715

PATENT -NOT RELATED TO THESIS

(1) **Praveen, K. V**.; Basavaraja, D.; Sasidhar, B. S. An Improved Process for the Preparation of Nitazoxanide and Intermediates Thereof. [Patent filed- **PCT application no: PCT/IN2022/050843, 21-Sep-22**].

Contribution to Academic Conferences

1. **Praveen Kumar. V.** at the *30th Kerala Science Congress held at Govt. Brennen College, Thalassery, Kannur. during* 28-30 January 2018. [**Participated**]

2. Molecular Hybrids of Dihydronaphthalenone and Indole as Potential Antibacterial and Anti-Tubercular Agetns. **Praveen Kumar. V,** Basavaraja, Sasidhar. B. S. **Poster presentation** at *8th Annual meeting of Indian Academy of Biomedical Sciences and Conference on Translation of Basic Scientific Insights into Affordable Health Products* held at CSIR-NIIST, Thiruvananthapuram, India, 25-27 February, 2019.

   Background: Antibiotics and other antimicrobial drugs have saved millions of lives and relieved patients suffering from various diseases. Over the time the problem is further increased by the increase in antibiotic-resistance in bacteria. Heterocyclic compounds constitute wide variety of drugs. Naphthalenone and indole appended scaffolds have also been featured in many drugs and bioactives. Therefore herein, a new series of indole appended dihydro naphthalenone hybrid analogues have been synthesized through the Lewis acid catalyzed Michael addition of indoles to the arylidene/hetero arylidene ketones, and screened for antibacterial and anti-tubercular activities.

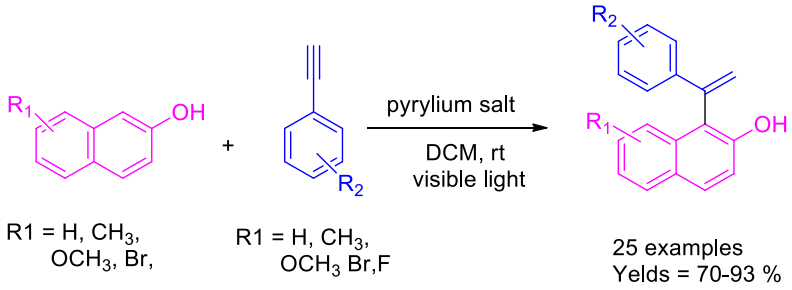
   Method: A dry Schlenk tube is charged with indole (1eq), arylidene/hetero arylidene ketones (1eq) and $Sc(OTf)_3$ (10 mol %) under argon atmosphere. 2 ml of dry acetonitrile is added and after closing it tightly stirred for an overnight at room temperature. After the completion of reaction (TLC), the solvent was removed under reduced pressure. The product is separated using column chromatography on silica gel of 100-200 mesh. All the purified novel compounds have been subjected for antibacterial evaluations according to the standard procedure.

   Results: All the synthesized Dihydro naphthalenone-indole hybrid analogues have been evaluated for antibacterial and antitubercular activity. The minimum inhibition concentration against *E.coli* and *S.aureus* was found to be as low as 3.12 μg ml^{-1} as compared to the standard antibacterial drug Ciprofloxacin 2 μg ml^{-1}. In anti-tubercular activity, the minimum inhibition concentration 6.25 μg ml^{-1} was found to be more

potent analogues when compared with that of the drugs pyrazinamide 4 µg ml^{-1} and streptomycin 6 µg ml^{-1}.

3. Photoinduced Hydroarylation of Terminal Alkynes with Naphthols and Phenols. **Praveen Kumar. V**, Sasidhar. B. S. **Poster presentation** at the *International Conference on Chemistry and Applications of Soft Materials* (CASM-2022) held at CSIR-NIIST, Thiruvananthapuram, India, 25-27 July, 2022.

   Over the past years, significant renaissance of visible light-mediated catalysis has enabled the researchers to achieve various novel and challenging unconventional synthetic transformations in organic chemistry.[1,2,3] Among various photocatalysts, Triarylpyrylium salts have gained special interest because of their outstanding photophysical and chemical properties. They exhibit strong absorption within the visible spectrum (λ_{max} = 410 to 450 nm) and are strongly oxidizing in both the singlet and triplet excited states.[4] These properties make them particularly appealing for PET applications.[4] Herein, by exploiting the PET properties of Triarylpyrylium salts, we envisioned the pyrylium catalysed photoinduced hydroarylation of alkynes with phenols and naphthols using household LED bulb as a light source. Further, this transformation features a broad substrate scope with functional group tolerance on both phenols and alkynes offering good yields (**Scheme 1**).



Scheme 1. Photoinduced hydroarylation

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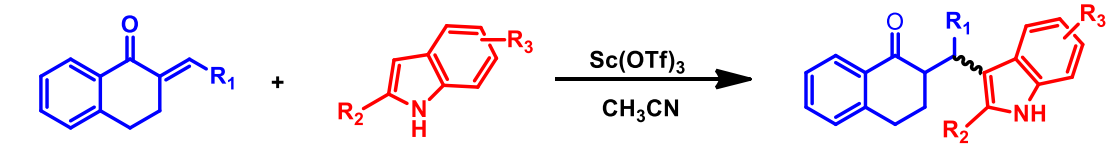
4. Miranda MA, García H. *Chem Rev*. **1994**; 94: 1063–1089.

4. Dihydronaphthalenone-Indole Analogs as Promising Antibacterial and Antitubercular Agents. **Valmiki Praveen Kumar** and Sasidhar B. Somappa. **poster presentation** at National Seminar on Recent Trends in Disease Prevention and Health Management held at CSIR-National Institute for Interdisciplinary Science and Technology, Thiruvananthapuram, Kerala. 14 & 15 December 2022.

   Antibiotics and other antimicrobial drugs have saved millions of lives and relieved patients suffering from various diseases. Over the time the problem is further increased by the increase in antibiotic-resistance in bacteria. Heterocyclic compounds constitute wide variety of drugs. Recently, Naphthalenone and indole appended scaffolds have also been featured in many drugs and bioactives. Therefore we assumed that incorporating indole scaffold into arylidene and hetero arylidene naphthalenones through the molecular hybridization approach might be an effective strategy for discovering novel hybrid nucleus with potential bioactivity. And herein, a new series of indole appended dihydro naphthalenone hybrid analogues have been synthesized through the Lewis acid catalyzed Michael addition of indoles to the arylidene/hetero arylidene ketones, and screened for antibacterial and anti-tubercular activities.



R_1 = Ph, 4-Cl-Ph, 4-F-Ph, 3-Cl-Ph,4-Me-Ph 2-Thiophene, 2-Furan

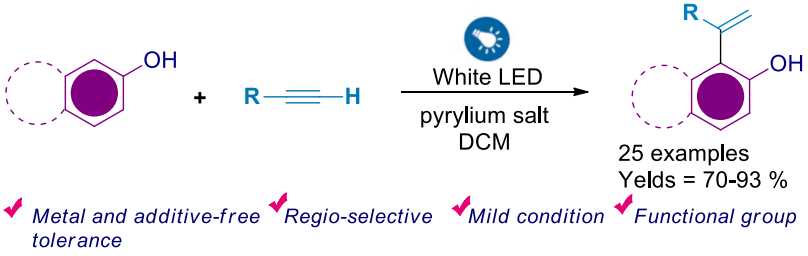
R_2 = H,Me
R_3 = 5-H, 4-OMe, 5-Br, 5-F, 5-Me, 5-OMe

20 Examples
Yield = 60 - 75%

Key Words: Naphthalenones, Indole, Antimicrobial, Antitubericular, Michael addition, Antibiotics.

5. Visible Light Driven C-H Activation to Access 2hydroxy Styrenes. **Valmiki praveen Kumar** and Sasidhar B. Somappa. **Oral presentation** at the International Conference of International Academy of Physical Science (CONIAPS XXVII) on Innovations in Computational and Physical Sciences for Sustainable Development (ICPSSD-2022) held at Vijayanagara Sri Krishnadevaraya University, Ballari, India, 21-23 December, 2022.

C-H hydroarylation of alkynes provides a straightforward and atom-economical method for the synthesis of substituted styrenes.[1-3] In recent years, visible-light-initiated organic reactions have gained copious attention and often provided better alternatives compared to the similar conventional counterpart protocols in terms of cost effectiveness, operational simplicity, reusability and environmental benefits. Among various photocatalysts, Triarylpyrylium salts have gained special interest because of their outstanding photophysical and chemical properties. They exhibit strong absorption within the visible spectrum (λ_{max} = 410 to 450 nm) and are strongly oxidizing in both the singlet and triplet excited states.[4] These properties make them particularly appealing for PET applications.[4] Herein, by exploiting the PET properties of Triarylpyrylium salts, we envisioned the pyrylium catalysed photoinduced hydroarylation of alkynes with phenols and naphthols using household LED bulb as a light source. Further, this transformation features a broad substrate scope with functional group tolerance on both phenols and alkynes offering good yields (Scheme 1).



Scheme 2. Photoinduced hydroarylation

References

1 Boyarskiy, V. P.; Ryabukhin, D. S.; Bokach, N. A.; Vasilyev, A. V. *Chem. Rev.* **2016**, *116* (10), 5894–5986.

2 Jia, C.; Lu, W.; Oyamada, J.; Kitamura, T.; Matsuda, K.; Irie, M.; Fujiwara, Y. *J. Am. Chem. Soc.* **2000**, *122* (30), 7252–7263.

3 Gao, R.; Yi, C. S. *J. Org. Chem.* **2010**, *75* (9), 3144–3146.

4. Miranda MA, García H. *Chem Rev*. **1994**; 94: 1063–1089.

DOI: 10.1111/cbdd.14286

CORRECTION

Correction to "Antibacterial and antitubercular evaluation of dihydronaphthalenone-indole hybrid analogs"

Valmiki PK, Jalaja R, Chettiyan Thodi FS, et al. Antibacterial and antitubercular evaluation of dihydronaphthalenone-indole hybrid analogs. *Chem Biol Drug Des*. 2017;90:703–708. https://doi.org/10.1111/cbdd.12990

The first affiliation was incorrectly published as Academy of Scientific and Innovative Research (AcSIR), New Delhi, India.

The correct affiliation is:

Academy of Scientific and Innovative Research (AcSIR), Ghaziabad, 201002, India

We apologize for this error.

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RESEARCH ARTICLE

WILEY

Antibacterial and antitubercular evaluation of dihydronaphthalenone-indole hybrid analogs

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A new series of indole appended dihydronaphthalenone hybrid analogs (**5a–t**) have been synthesized through the Lewis acid catalyzed Michael addition of indoles to the arylidene/hetero arylidene ketones. All the synthesized derivatives are well characterized through the ^{1}H-NMR, ^{13}C-NMR, HRMS spectroscopic techniques, compound **5r** was further confirmed through single crystal X-ray analysis and screened for antibacterial and antitubercular activities. Among the synthesized compounds, the minimum inhibition concentration of **5l** (against *Escherichia coli*) and **5o** & **5p** (against *E. coli* & *Staphylococcus aureus*) was found to be as low as 3.12 μg/ml as compared to the standard antibacterial drug ciprofloxacin 2.5 μg/ml. In antitubercular activity, compounds **5o** and **5p** with minimum inhibition concentration 6.25 μg/ml were found to be comparable with that of the drugs Pyrazinamide 5 μg/ml and Streptomycin 5 μg/ml. Compounds **5i**, **5j**, **5m**, **5n**, **5q**, and **5r** also showed promising activity against group of organisms tested.

KEYWORDS
antibiotics, antimicrobial, antitubericular, indole, Michael addition, Naphthalenones

1 | INTRODUCTION

Antibiotics and other antimicrobial drugs have saved millions of lives and relieved patients suffering from various diseases. Over the time, bacteria have developed resistance to existing drugs, and antibiotic resistance continues to spread like wildfire.[1] Especially in India, the situation is quite alarming. Crude infectious disease mortality rate in India today is 416.75 per 100,000 persons and is twice the rate prevailing in the United States when antibiotics were introduced.[2,3] In the past one and half decades, tuberculosis (TB) has been recurred as one of the foremost causes of human death worldwide (nearly 3 million deaths per year). Over 33% of the world's population is infected with this deadly disease.[4] Astonishingly, almost 0.23 million cases of multidrug resistant (MDR-TB) reports found only in India per year.[5] Alongside, there are many other deadly diseases such as cancer; Alzheimer's and central nervous system (CNS) related disorder with very high mortality rate and increased incidence ratio. The above statistics illustrate the alarming situation the world is facing in search of life saving drugs.

In the recent decades, continued attention has been focused on the heterocyclic compounds owing to their major roles in biological processes and pharmaceuticals.[6–9] Benzimidazole-oxadiazole hybrids have showed promising MIC against both Gram-positive, Gram-negative bacteria and also against *Mycobacterium tuberculosis*.[10] Cappoen et al.,[11] synthesized diazene derivatives with 90% growth inhibition against the clinically relevant mycobacterial species such as *Mycobacterium bovis*, *Mycobacterium avium*, and *Mycobacterium ulcerans*. Quinoline-based heterocycles also showed significant activity against the growth of *M. tuberculosis* with MIC 0.02 μg/ml, which is proved to be more potent than the clinically used standard drugs.[12] Among the important heterocycles, novel scaffolds containing naphthalenone have been identified as one of the privileged

structures in drug discovery.[6,13,14] Perrone et al.,[15,16] established napamezole as a α_2-adrenergic receptor antagonist and a selective inhibitor of 5-hydroxytryptamine reuptake both in vitro and in vivo. Alex and coworkers designed naphthalenyl dihydroimidazoles with the inspiration of napamezole-based hybrid library, which suggested that the potential antidepressants can display combined α_2-adrenoceptor antagonist and monoamine uptake inhibitor properties.[17] Mephtetramine represent yet another generation of new psychoactive substance.[18] Liu et al.,[19] discovered a series of novel naphthalenyl pyrimidinones as potent HIV-1 inhibitors (Figure 1).

On other hand, structurally diverse indole appended analogs have been claimed to exhibit various biological activities, including antimicrobial, antiviral, anti-inflammatory, analgesic, and CNS depressant properties.[20–22] Noteworthily, previous research in our laboratory led to the discovery of a series of novel indole analogs possessing excellent antimicrobial, antioxidant, and anticancer activities.[23–26] Most interestingly, more recent literature survey has revealed that the incorporation of a thiophene moiety can significantly enhance the antimicrobial activity of candidate compounds.[27–29]

Prompted by the above consideration and as a part of our ongoing research on developing novel molecular templates[30] with enhanced antimicrobial activity, we assumed that incorporating indole scaffold into arylidene and hetero arylidene naphthalenones through the molecular hybridization approach might be an effective strategy for discovering novel hybrid nucleus with potential bioactivity. Therefore, in this work, we described a facile and convenient synthesis and antimicrobial, anti-tubercular activities of indole appended dihydro-naphthalenone bearing various substituted aryl, thiophene, and furan rings (**5a–t**), which have, to our knowledge, not been reported so far.

2 | MATERIALS AND METHODS

2.1 | Chemistry

All the reactions are performed with commercially available analytical grade chemicals without further purification. Column chromatography was performed using 100–200 mesh silica gel and mixtures of *n*-hexane-ethyl acetate (3:1) as eluting solvent. Proton nuclear magnetic resonance spectra (^{1}H NMR) were recorded on a Bruker AMX 500 spectrophotometer ($CDCl_3$ as solvent). Chemical shifts for ^{1}H NMR spectra are reported as δ in units of parts per million (ppm) downfield from $SiMe_4$ (δ 0.0) and relative to the signal of chloroform-*d*. Coupling constants are reported as *J* value in Hz. Carbon nuclear magnetic resonance spectra (^{13}C NMR) are reported as δ in units of parts per million (ppm) downfield from $SiMe_4$ (δ 0.0) and relative to the signal of chloroform-*d*. Mass spectra were recorded under EI/HRMS at 60,000 resolution using Thermo Scientific Exactive mass spectrometer. IR spectra were recorded on Bruker FT-IR spectrometer.

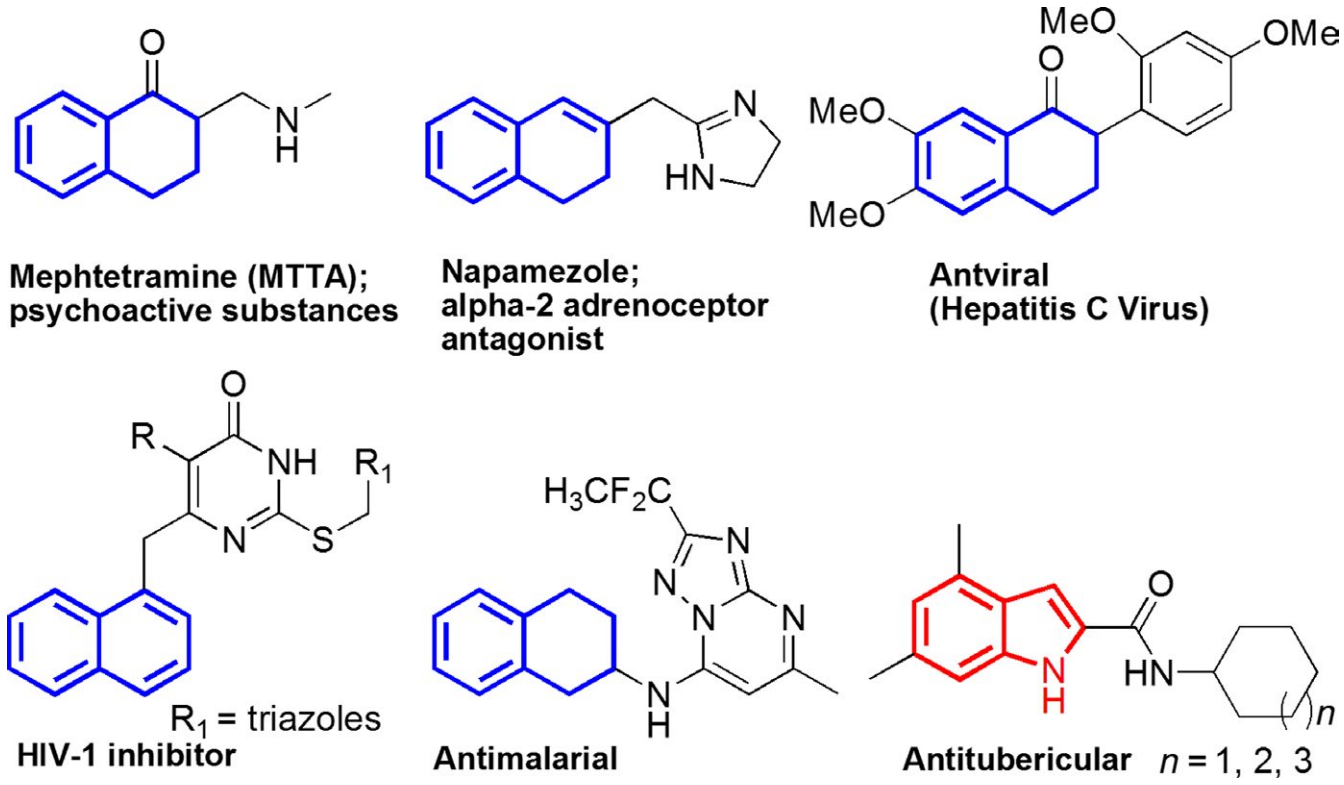


FIGURE 1 Representative pharmaceutically important bioactives on which the design of target molecules are adapted [Colour figure can be viewed at wileyonlinelibrary.com]

2.2 | General procedure for the synthesis of 2-arylidene/heteroarylidene-3, 4-dihydronaphthalen-1(2*H*)-one (3a–g)

One equivalent of arylaldehyde or hetero arylaldehydes (**2**) (3.5 mmol) are added to the solution of one equivalent of 3,4-dihydronaphthalen-1(2*H*)-one (**1**) (3.5 mmol) in 10 ml ethanol. To the reaction mixture, aqueous solution of NaOH (0.5 g in 5 ml) was added drop wise for about 20 min at 0°C. The reaction mixture was further stirred at room temperature (4 hrs), after the completion of the reaction (TLC), the reaction mixture was then filtered, washed with cold methanol, and dried to yield 60%–90% solid compound (**3**). Products are confirmed from ^{1}H NMR and HRMS.[31]

2.3 | General procedure for the $Sc(OTf)_3$ catalyzed Michael addition of indoles to the arylidene/hetero arylidene ketones (5a–t)

A dry Schlenk tube is charged with indole (**4**) (1 eq), arylidene/hetero arylidene ketones (**3**) (1 eq) and $Sc(OTf)_3$ (10 mol %). It is fitted with a rubber septum and degassed the mixture for a while. Two millilitre of dry acetonitrile is added to it and purged with argon. After closing it tightly stirred for an overnight at room temperature. After the completion of reaction (TLC), remove the solvent under reduced pressure. The product is separated using column chromatography on silica gel of 100–200 mesh.

2.4 | Antibacterial activity

The antimicrobial activities of compounds (**5a–t**) were determined by the disk diffusion method (CLSI 2012) against bacteria. The test cultures maintained in nutrient agar slant at 4°C were subcultured in nutrient broth to obtain the working cultures approximately containing 1×10^6 CFU/ml. The compounds with various concentrations were incorporated in a 6-mm sterile disk. Mueller Hinton (MH) agar plates were swabbed with each bacterial strain, and the test disks were placed along with the control disks. Ciprofloxacin was used as positive control. Plates were incubated overnight at 37°C. Clear, distinct zone of inhibition was visualized surrounding the disks. The minimum inhibitory concentration (MIC) of antimicrobial activity of the test agents was determined by measuring the zone of inhibition expressed in mm.[1]

2.5 | Antitubercular activity

The antitubercular activity of compounds (**5a–t**) was assessed against *M. tuberculosis* (ATTC-27294) using the agar microdilution method, where twofold dilutions of each test compound was carried out.[32] Pyrazinamide and Streptomycin were used as a standard drug for comparison. Growth of bacilli was observed after 3 days of incubation at 37°C, and MIC was recorded. Compounds **5o** and **5p** exhibited promising activity with MIC 6.25 μg/ml, and the rest of the compounds exhibited moderate to poor activity with MIC 12.5, 25, 50, 100, and >100 μg/ml.

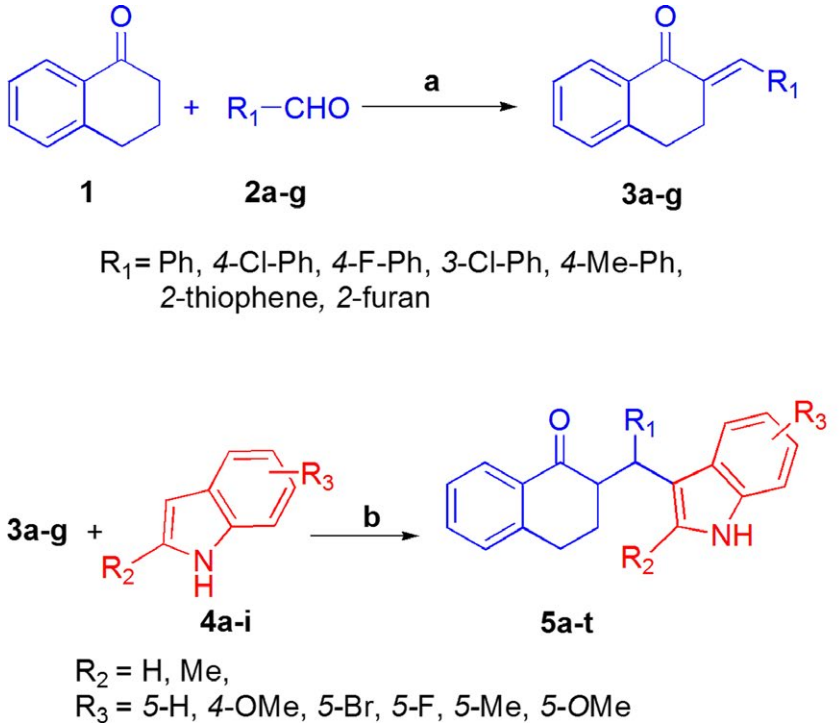
3 | RESULTS

The synthetic route for targeted compounds (**5a–t**) is shown in Scheme 1. The key intermediates (**3a–g**) were obtained through the base catalyzed Knoevenagel condensation of tetralone (**1**) with various aryl and hetero aryl aldehydes (**2a–g**). The readily available arylidene and hetero arylidene derivatives (**3a–g**) undergo Lewis acid catalyzed Michael addition with indoles (**4a–i**) at room temperature to yield the indole appended dihydronaphthalenone hybrid analogs. To develop a convenient method for better yield of the products, we optimized the reaction by considering different Lewis acids, various solvents and temperature parameter. When we started our investigation with Michael addition of 1H-indole (**4a**) to the (E)-2-benzylidene-3,4-dihydronaphthalen-1(2*H*)-one (**3a**), $Zr(CpCl_3)$ as the Lewis acid in DCM at room temperature, we did not get any new spot in TLC. We carried out same reaction by changing the various Lewis acids, such as $Zn(OTf)_3$, $Sc(OTf)_3$, and $Cu(OTf)_2$ to notice, the reaction did not undergo. Also, we screened the reaction with range of solvents with various Lewis acids at room temperature. When the reaction carried out with $Sc(OTf)_3$ as Lewis acid and acetonitrile as solvent we got a clear spot in TLC and was confirmed as the target compound. Also, we tried the reaction at 60°C in acetonitrile with various Lewis acids such as $Zr(CpCl_3)$, $Sc(OTf)_3$, $Zn(OTf)_3$, and $Cu(OTf)_2$. Among various Lewis acids screened at 60°C, $Zr(CpCl_3)$ gave better yield, which is less than that of the $Sc(OTf)_3$ at room temperature. Whereas, $Zn(OTf)_3$ gave by-products along with the starting materials. Therefore, at room temperature in acetonitrile, $Sc(OTf)_3$ as the Lewis acid is considered as the optimized condition for further exploration of the reaction. The screening for the optimization of the reaction has been tabulated in Table S1.

Structure of the resulting compound was characterized from the spectral analysis of ^{1}H NMR, ^{13}C NMR, HRMS, and IR. The structure was finally unambiguously confirmed through the single crystal X-ray analysis (Figure 2). All the synthesized compounds have been evaluated for antibacterial and antitubercular activity (Table 1).

4 | DISCUSSION

The antibacterial activity was performed against two Gram-positive (*Staphylococcus aureus-MTCC 902* and



Comp	R_1	R_2	R_3
5a	Ph	H	H
5b	Ph	2-Me	H
5c	Ph	H	5-Me
5d	Ph	H	5-Br
5e	Ph	H	4-OMe
5f	4-Cl-Ph	H	H
5g	4-Cl-Ph	2-Me	H
5h	4-Cl-Ph	H	5-Br
5i	4-Cl-Ph	H	5-F
5j	4-Cl-Ph	H	4-OMe
5k	4-Cl-Ph	H	5-OMe
5l	2-thiophene	H	H
5m	2-thiophene	2-Me	H
5n	2-thiophene	H	5-Me
5o	2-thiophene	H	5-Br
5p	2-thiophene	H	5-OMe
5q	2-furan	H	5-OMe
5r	4-F-Ph	H	5-OMe
5s	3-Cl-Ph	H	5-OMe
5t	4-Me-Ph	H	5-Br

SCHEME 1 Michael addition of indoles to the arylidene/hetero arylidene ketones; Reagents and conditions: (a) NaOH, EtOH, 0°C (20 min), rt (4 hr); (b) $Sc(OTf)_3$ (10 mol%), CH_3CN, rt (12–14 hr) [Colour figure can be viewed at wileyonlinelibrary.com]

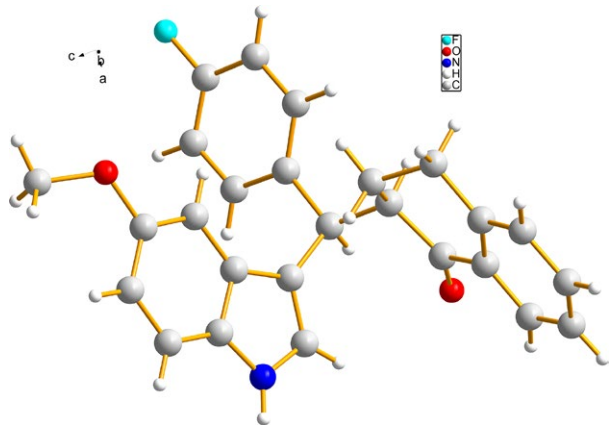


FIGURE 2 Single crystal X-ray structure for **5r** (CCDC 1521201; structural illustrations have been drawn with DIAMOND) [Colour figure can be viewed at wileyonlinelibrary.com]

Staphylococcus epidermidis-MTCC 435) and three Gram-negative (*E. coli-MTCC 2622*, *Salmonella typhi-MTCC 3216*, and *Klebsiella pneumoniae-MTCC 109*) bacteria. Among the tested compounds **5i–r** have showed better activity against *E. coli*, *S. typhi*, and *S. aureus* and **5l–o** also showed better activity against *S. epidermidis* selectively with very low MIC range (12.5–50 μg/ml). In contrast, against *K. pneumoniae*, none of the compounds has showed inhibition potency. Compounds **5a–h** exhibited very poor inhibition property against all the five organisms, especially *K. pneumoniae* and *S. epidermidis*. In comparison with substituted aryl ring, thiophene derivatives showed highest activity. Among the various substitutions on indole ring (2nd, 4th, and 5th), 5-F and 4-OMe showed more inhibition, and other derivatives showed moderate to less activity. To enhance the minimum inhibition concentration, 5-OMe substituted indole derivatives (**5k**, **5p–s**) were synthesized and evaluated. To our delight we found that, compounds **5p**, **5q**, and **5r** are worth exploring for further studies. It is worth noting that most of the compounds exhibited moderate to good inhibition but no clear trend could be summarized.

In antitubercular activity, compounds **5i–k** and **5n–r** have showed promising results with MIC range 6.25–50 μg/ml. In particular, with the least MIC (6.25 μg/ml), compound **5o** and **5p** are the most potent derivatives of all. Compounds **5j** and **5n** also showed some better tendency of *M. tuberculosis* inhibition. In contrast, compounds **5a–h**, **5l–m**, and **5s–t** showed poor inhibition activity. As in the case of antibacterial results suggested, thiophene appended derivatives **5n–p** are the compounds to be looked in for further developments.

5 | CONCLUSION

In summary, we have designed and synthesized indole appended dihydro-naphthalenones by Lewis acid catalyzed facile and convenient process. We successfully identified a

TABLE 1 Antibacterial and antitubercular evaluation

	MIC in µg/ml					
Compd	***E. coli***	***S. typhi***	***S. aureus***	***K. pneumoniae***	***S. epidermidis***	***M. tuberculosis***
5a	100	>100	50	>100	>100	>100
5b	>100	>100	>100	>100	>100	>100
5c	>100	>100	>100	>100	>100	>100
5d	50	100	50	>100	>100	>100
5e	50	50	25	>100	>100	>100
5f	50	50	25	>100	>100	>100
5g	50	100	50	>100	>100	>100
5h	50	100	25	>100	>100	100
5i	12.5	50	25	>100	100	50
5j	12.5	25	12.5	>100	100	12.5
5k	25	50	50	>100	>100	25
5l	3.12	6.25	12.5	50	12.5	>100
5m	12.5	25	12.5	100	50	>100
5n	12.5	25	12.5	100	50	12.5
5o	3.12	12.5	3.12	50	50	6.25
5p	3.12	25	3.12	100	100	6.25
5q	12.5	25	12.5	>100	>100	25
5r	12.5	25	>100	>100	>100	25
5s	50	50	25	>100	>100	>100
5t	50	100	100	>100	>100	>100
Ciprofloxacin	2.5	2.5	2.5	2.5	2.5	5
Pyrazinamide	—	—	—	—	—	5
Streptomycin	—	—	—	—	—	5

novel structural class, which inhibits the set of organisms with very low minimum inhibition concentrations. Among the novel compounds, **5l**, **5o**, and **5p**, are the most active with minimum inhibition concentration of 3.12 µg/ml against *E. coli* and *S. aureus*. While, **5o** and **5p** are the more potent analogs in inhibiting the *M. tuberculosis*. Our studies complement new and exciting findings, which strongly suggest that the indolyl naphthalenones have real potential in finding suitable "Leads" for development of antitubercular therapeutics.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interests.

END NOTE

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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Ethylbenzene Hydroperoxide: An efficient oxidizing agent for diastereoselective synthesis of Spiroepoxy oxindoles

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ABSTRACT

Ethylbenzene hydroperoxide (EBHP) has been studied for the epoxidation of oxindole chalcones with various inorganic bases and different solvent systems. 10 M solution of NaOH with EBHP in hexane furnished a high yield of spiro epoxy oxindoles in a short reaction time at room temperature. The reaction condition applicable to electron-deficient, electron-rich arylideneindolin-2-ones, heteroarylideneindolin-2-ones and alkylideneindolin-2-ones to yield the diastereoselective aryl/heteroaryl and alkyl spirooxiranes. Comparative studies amid peroxide reagents showed EBHP is the best in terms of diastereoselectivity, yield and reaction time. Isotope labelling experiment showed the participation of water molecules in this oxidation mechanism.

Introduction

Epoxides or oxiranes are important structural components found in natural products and synthetic pharmacological active molecules[1]. The subsequent transformation of epoxides is highly advantageous to build structurally diverse molecules for the utility of various applications[2]. Oxindole molecule with its functional group diversity expressed a wide range of medicinal applications [3]. Among the various oxindole derivatives, spiroepoxyoxindoles are privileged scaffolds, found in many pharmacologically active synthetic and natural products which exhibit significant biological activities (Figure 1)[3,4]. The synthetic transformations of spiroepoxyoxindoles provide an easy route to access many enviable molecular scaffolds with diverse biological properties[5]. As a result, the synthesis of spiroepoxyoxindoles is a fascinating area of interest for organic and medicinal chemists.

Spiroepoxyoxindole skeletons are accomplished via diverse approaches such as the Darzen's type reaction between isatins and phenacyl bromides [6], epoxidations of isatin with the *in situ* generated sulfur ylides [7], $Rh_2(OAc)_4$ catalysed reaction of 3-diazo oxindoles with aromatic aldehydes.[8] Despite these developments, chemists have given more attention to synthesize chiral spiroepoxy oxindoles with high *enantio* and diastereoselectivities. In 2007, Briere et *al.* first attempted a stereoselective Darzens reaction using a stoichiometric amount of a chiral sulphide[9]. In 2011, Gasperi's group reported (S)-α,α-di-phenylprolinol catalysed asymmetric epoxidation of α-ylideneoxindole esters to offer spirooxirane [10]. Later in 2014, Xiao et *al.* successfully demonstrated the asymmetric synthesis of diethylacetamide substituted epoxyoxindoles by employing stoichiometric *in situ* generated sulphur ylides from camphor derived sulfonium salts [11]. In the same year Feng's research group has shown the asymmetric synthesis of benzyl substituted *trans*-spiro oxiraneoxindoles using *N, N′*-dioxide-$Co(acac)_2$ as the catalyst (Scheme 1)[4].

The most frequently used oxidizing agents for the epoxidation of electron-deficient alkenes are organic or inorganic peroxides in combination with metal salts/complexes and bases [12]. Luo et *al.* reported epoxidation of arylideneindolin-2-ones by *in situ* generated peroxide of THF [13]. In 2013 Chouhan's group developed diastereoselective epoxidation of (*E*)-3-ylidene-indolin-2-ones using natural product quinine and urea-hydrogen peroxide [14]. Use of ultrasound irradiation as an energy source for the synthesis of spiroepoxyoxindole with hydrogen peroxide was successfully demonstrated by Dandia et *al* [15]. Although, the aforementioned protocols are well established, possess certain drawbacks such as lack of substrate scope, functional group incompatibility and competitive reactions leading to the formation of side products. Even

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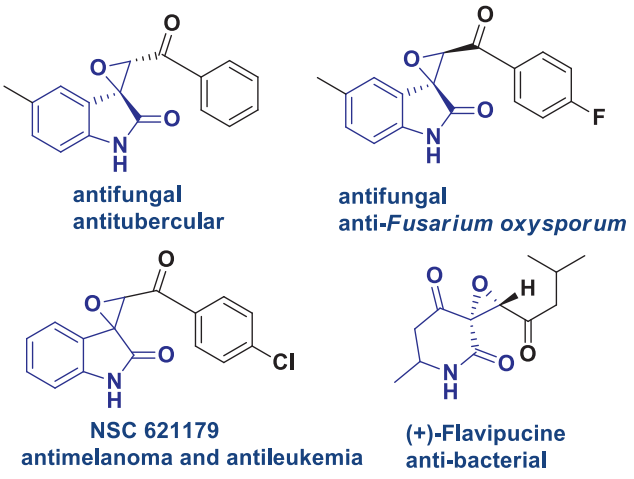


Fig 1. Selected bioactive spiroepoxyoxindoles.

though, the peroxides are the front-line oxidizing agents, with prolonged reaction time, poor diastereoselectivity and use of additives like phase transfer catalyst, the photosensitizer is not encouraged for industrial application.

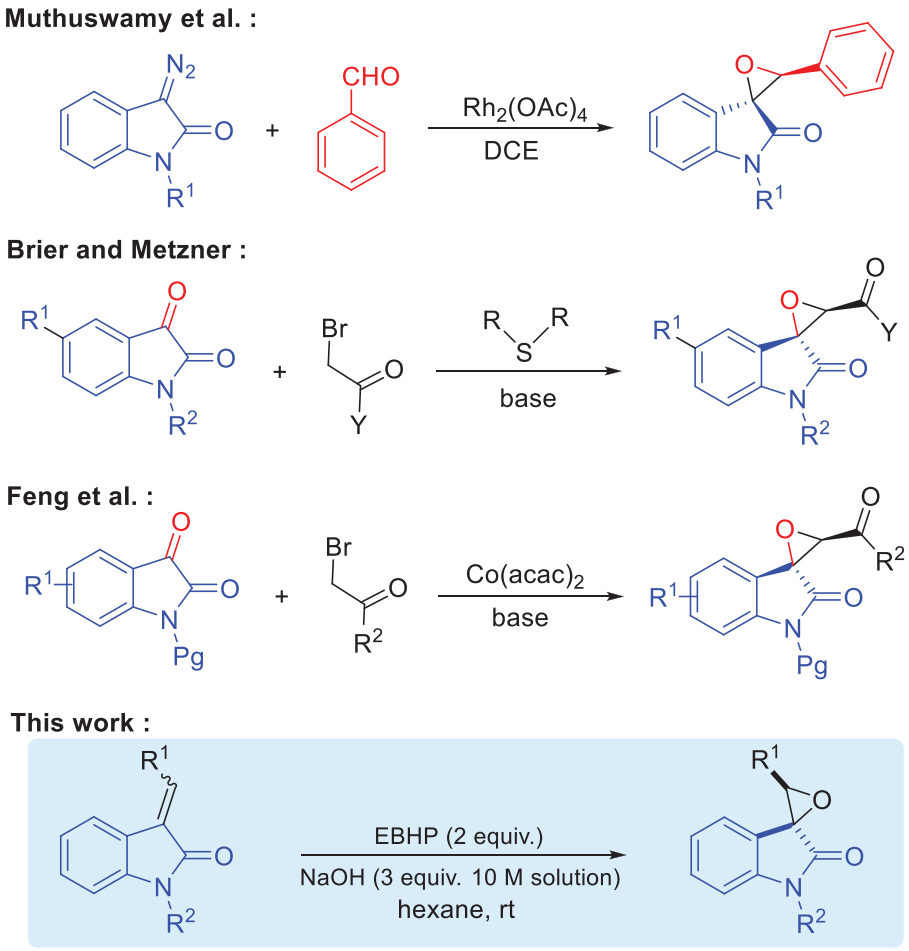
Organic hydroperoxides are widely employed in oxidation chemistry as reagents, and also are found as valuable intermediates or building blocks in several chemical processes such as polymerizations, radical chemistry etc [16]. Ethylbenzene hydroperoxide (EBHP) is a valuable reagent used as an oxygen carrier in epoxidation reaction of propene [17] and moreover it can be easily prepared by oxidation of 1- phenylethanol using H_2O_2 at laboratory scale unlike other peroxides [18].

The base is the most important component in the epoxidation reactions, which plays a pivotal role in the activation of peroxides. Inorganic bases like NaOH, KOH are very often utilized in the form of an aqueous solution [19]. The reactivity of hydroxide ions depends on the concentration of the base in aqueous media. A progressive increase in the concentration of OH^- diminishes its hydration number 'n' up to a value of 3.5 at the highest concentration of base (50 % aqueous NaOH) [20]. In low-polarity solvent, the largely dehydrated OH^- ion is an extremely powerful base and it allows for the generation of anions even from very weak organic acids (up to pKa = 38) [21].

Inspired by the discussed approaches and as a part of our enduring interest in developing efficient synthetic protocols to synthesise spiroheterocycles[22] and functionalised heterocycles [23]. Herein, we report a straightforward method for diastereoselective epoxidation of chalcones to spiroepoxyoxindoles at room temperature, in a short reaction time.

Results and discussion

In our initial approach, the addition of 1 equivalence of solid NaOH to the solution of 3-benzylideneindolin-2-one (**1a**) and 2

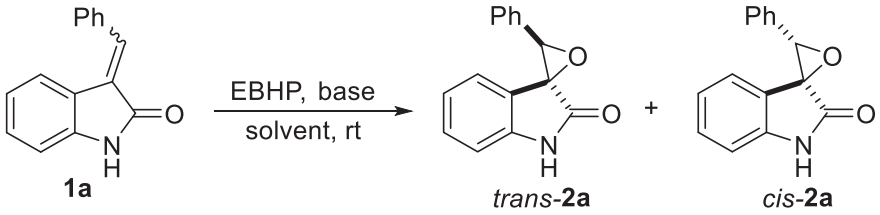


Scheme 1. Different approaches of spiroepoxyoxindoles synthesis.

equiv. of EBHP in xylene (mixture of isomers) at room temperature after 24 h of stirring resulted in the formation of *trans*- spirooxindole-epoxide (**2a**) in 62 % of yield (Table 1**, entry 1**).

Upon increasing the addition of base from 2 to 3 equivalences, elevation in the product yield was observed (**entries 2–3**). The addition of 3 M solution of NaOH (3 equivalence) in water showed better conversion of starting material to product furnishing 93 % yield keeping *trans:cis* ratio 7:1 (**entry 4**). Increasing the concentraion of base from 3 M to 6 M, the reaction time was gradually reduced from 4.5 h to 1 h without affecting the yield of the product (**entry 5**). The yield and diastereoselectivity of the product were further improved upon increasing the concentration of base to 10 M with 95 % yield and retaining *trans:cis* ratio of 14:1 within 30 min of reaction time. However, further increment in base strength to 14 M declined the percentage of yield to 81(**entries 6–7**). Replacement of EBHP by TBHP showed a decrement in the product yield to 84 % (**entry 8**). When H_2O_2 was used as an oxidizing agent, yield declined drastically and there was no effect on continuing the reaction even after 24 h (**entry 9**). The other bases like LiOH·H_2O, KOH afforded moderate yield compared to NaOH (**entries 10–11**). Upon solvent screening, in dichloromethane, we could achieve the highest yield of 97 %, but poor diastereoselectivity was observed (**entry 12**). Reaction performed with single isomer solvents of xylene *viz. o*-xylene and *p*-xylene, the latter one showed satisfactory *trans:cis* ratio 29:1 (**entries 13–14**). The polar solvent methanol was also found as a feasible medium for the successful formation of the product with the highest selectivity of 32:1 ratio (**entry 15**). Finally, hexane was found to be the best solvent system with the highest percentage of yield 97 % and a single *trans*-isomer with the shortest reaction time of 15 min (**entry 16**). Adverse impact on either selectivity or yield was not found upon extending the reaction time to 30 min (**entry 17**). A trace amount

Table 1
Optimization of reaction condition.[a]



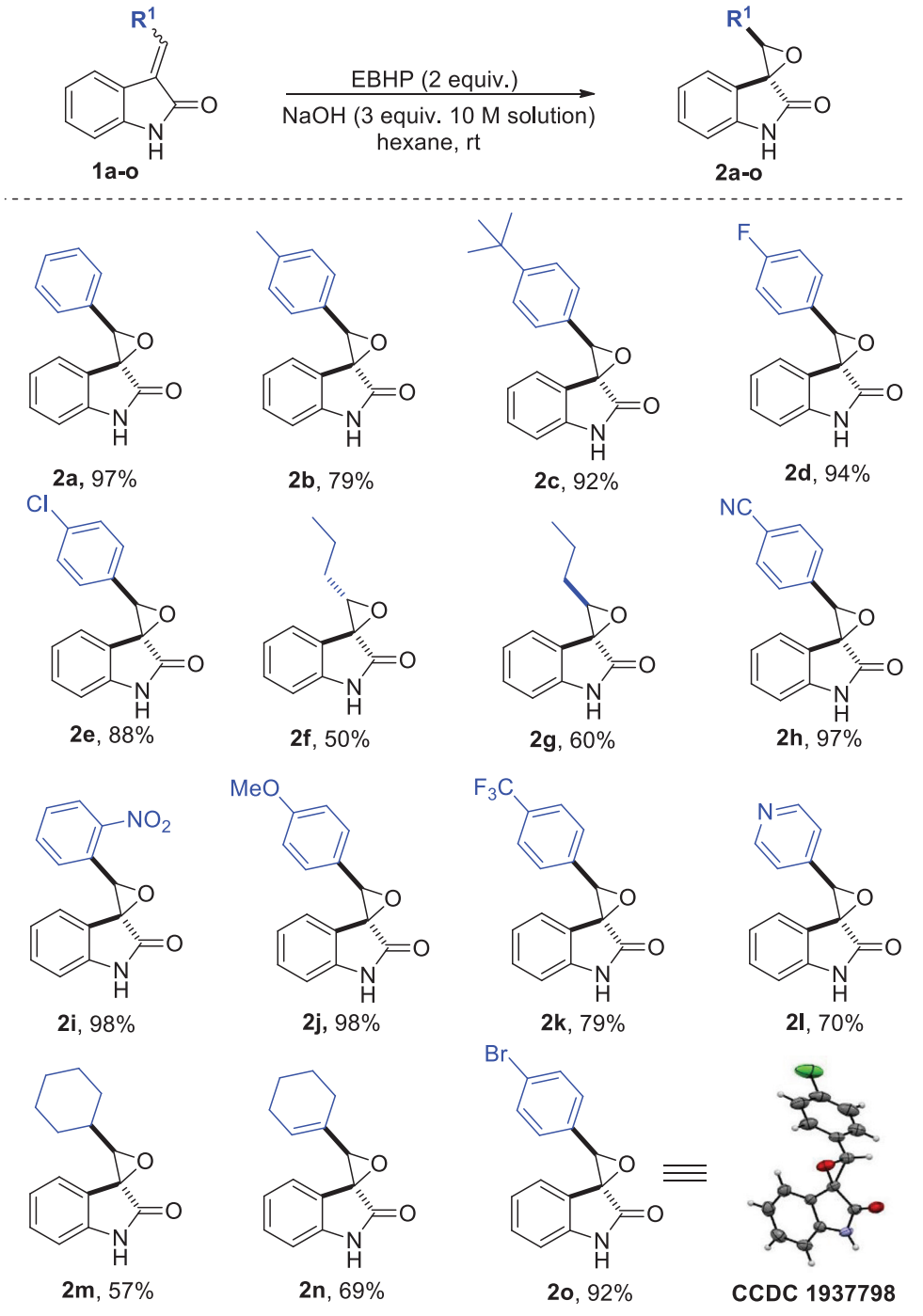
entry	solvent	base	base strength (M)	time	yield (%)[b] (dr)[c]
1	xylene	NaOH	-	24 h	62[d]
2	xylene	NaOH	-	24 h	68[e]
3	xylene	NaOH	-	24 h	75[f]
4	xylene	NaOH	3	4.5 h	93(7:1)
5	xylene	NaOH	6	1 h	93(7:1)
6	xylene	NaOH	10	30 min	95(14:1)
7	xylene	NaOH	14	30 min	81
8	xylene	NaOH	10	2.5 h	84(8:1)[g]
9	xylene	NaOH	10	24 h	06[h]
10	xylene	LiOH	10	1 h	56
11	xylene	KOH	10	1 h	74
12	DCM	NaOH	10	1 h	97(7:1)
13	*o*-xylene	NaOH	10	30 min	97(10:1)
14	*p*-xylene	NaOH	10	30 min	93(29:1)
15	methanol	NaOH	10	1 h	93(32:1)
16	hexane	NaOH	10	15 min	97
17	hexane	NaOH	10	30 min	97
18	hexane	NaOH	-	24 h	trace[i]

[a] Reaction conditions unless otherwise mentioned, **1a** (0.13 mmol), EBHP (2 equiv.), base (3 equiv.) in 2 mL of solvent used at room temperature. [b]Isolated yields. [c]Determined by isolation and referring to the ratio of *trans*-**2a** to *cis*-**2a**. [d]1 equiv. of solid NaOH added. [e]2 equiv. of solid NaOH added. [f]3 equiv. of solid NaOH added. [g]70% TBHP (2 equiv.) was added. [h]30% H_2O_2 (2 equiv.) was added. [i]Reaction was carried out under dry condition.

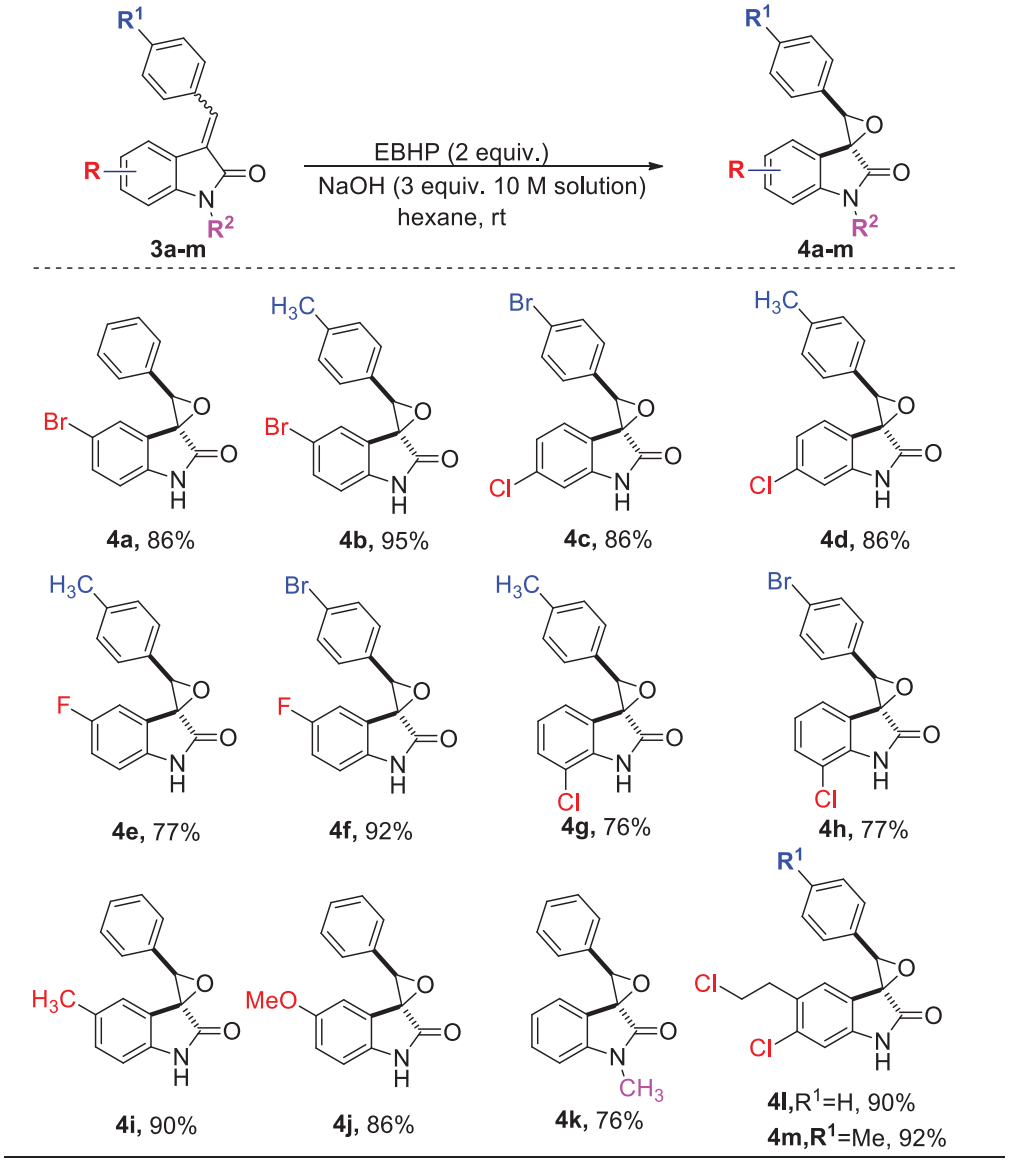
of product was observed when the reaction was carried out under dry conditions (**entry 18**).

With the optimized reaction condition in hand, we sought to investigate the scope and generality of this protocol for various substituted 3-benzylideneindolin-2-ones. Epoxidation was achieved successfully in good yields for all the electron-donating and withdrawing substitutions on oxindole chalcones. And the reaction also progressed well with aliphatic and cyclic oxindole chalcones without the significant impact of the substitution (Scheme 2 and 3). After confirming the structure through various spectroscopic techniques *viz.* ^{1}H NMR, ^{13}C NMR, and NOESY experiment (**Supporting information** (**SI**)), we found that *trans*-isomer was the major compound formed and further it was unambiguously confirmed by the single-crystal X-ray analysis (**Figure S4; SI**). It is evident that the reaction is highly diastereoselective and forms selectively the *trans*-spiroepoxy oxindoles. However, when the reaction is carried out with the *Z* and *E* isomers of 3-butylideneindolin-2-one (**1f** & **1 g**), diastereomerically *cis* and *trans* of 3′- prop-ylspiro[*indoline*-3,2′-*oxiran*]-2-one are formed respectively (**2f** & **2 g**; Scheme 2).

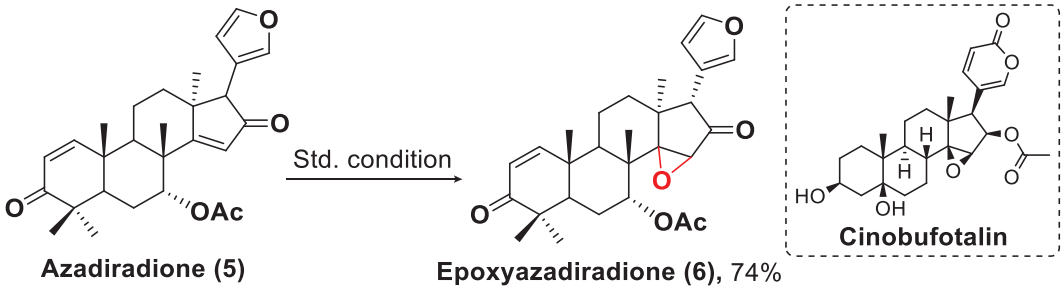
Along with the epoxidation of diversified oxindole systems, we successfully demonstrated our protocol in the epoxidation of



Scheme 2. Scope of the chalcones with unsubstituted oxindoles.



Scheme 3. Substrate scope for the chalcones with various substituted oxindoles.



Scheme 4. Late-stage epoxidation on Azadiradione.

azadiradione to epoxy azadiradione (Scheme 4). Azadiradione[24] and epoxy azadiradione are phytochemicals known to exhibit broad-spectrum medicinal properties [25]. This emphasizes the perspective of the protocol in the late-stage diversification of phytochemicals and complex structures *viz.* Cinobufotalin, Gedunin etc.

Herein, the successfully demonstrated epoxidation protocol utilizes a minimum quantity of water as compared to usual oxidation processes. The quantity of water ultimately decides the strength of the basic solution. There is a clear indication of the role of water/strength of the sodium hydroxide solution during the optimization of reaction conditions (Table 1). In order to confirm further, a reac-

tion was performed using a 10 M NaOH solution enriched with $H_2^{18}O$. The reaction proceeded smoothly, product **7** was obtained in 80 % yield (Scheme 5). Surprisingly, we observed a corresponding mass peak of product **7** with ^{18}O isotope at 16 % intensity with respect to base peak (**Figure S1; SI**).

When we looked into the literature there are a few reports which discussed oxygen exchange between peroxide and water molecules [26]. Anbar and Guttmann reported hydroxide ion catalyzed exchange of oxygen between water and H_2O_2 in 1 M NaOH solution with a rate constant of $1.1x10^{-7}$ at 25 °C and the authors also studied induced isotopic exchange on the interaction of H_2O_2 with OCl^-, IO_4^-, MnO_4^-, Fe^{+2}, Fe^{+3}, Ce^{+4}, NO_2 and NO_2^- [26]. They suggested the formation of peroxy-complexes of the type XOOH which facilitates the isotopic exchange with water [26]. Hence, we emphasize that there may be an exchange of oxygen between water and peroxide.

It is well known that the stereochemistry of the starting alkene is not necessarily retained in the epoxide [27]. For example, the epoxidations of both *E*- and *Z*-3-methyl-3-penten-2-one with basic H_2O_2 in methanol afford predominantly the *E* epoxide product [27]. To our surprise (*Z*) isomers of 3-butylideneindolin-2-one (**1f**) produced *cis*- 3′-propylspiro(indoline-3,2′-oxiran)-2-one (**2f**) exclusively. To gain some insights into the reaction mechanism we carried out some control experiments using radical scavengers such as 2,2,6,6-tetramethylpiperidin-1-yl)oxidanyl (TEMPO, 1 equiv.) and 3,5-di-*tert*-4 butylhydroxytoluene (BHT, 1 equiv.) (Scheme 6). The yield did not decrease when a radical scavenger was added to the reaction; thus, a radical process is probably unlikely to be involved. The above-mentioned literature reports and our experimental results suggest that there is a need for re-examination of the mechanism of epoxidation reaction involving peroxide and base. Further, investigation of the mechanism and synthetic utility of demonstrated protocol is in progress at our lab.

Conclusion

In conclusion, we have developed a simple and efficient process for transforming oxindole chalcones to the corresponding epoxides by using EBHP at room temperature in excellent yields. The protocol proceeds well with a variety of electron-deficient, electron-rich arylideneindolin-2-ones, heteroarylideneindolin-2-ones and alkylideneindolin-2-ones. This procedure enables access of diastereoselective *trans*-spiroepoxy oxindoles in a very short reaction time.

Data availability

Data will be made available on request.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

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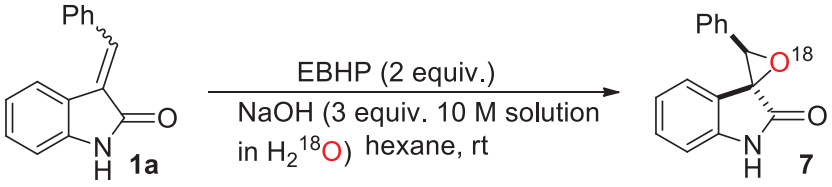
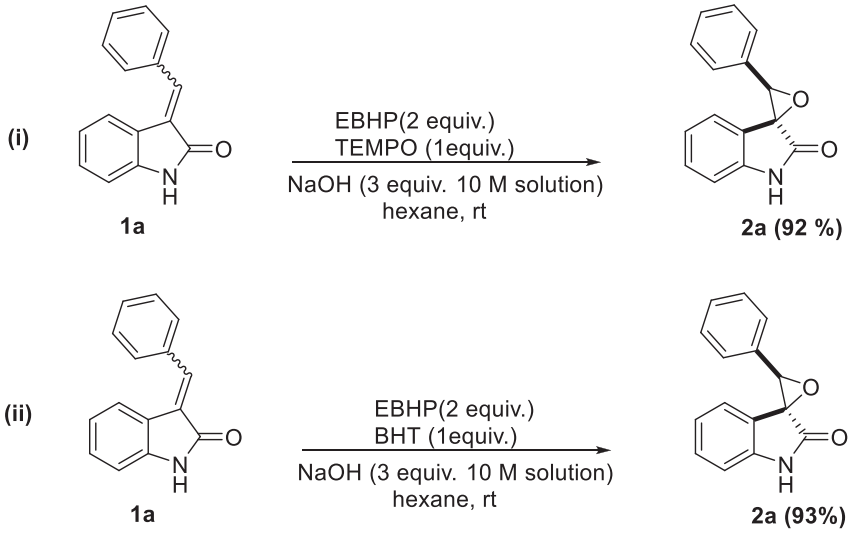


Scheme 5. Isotope labelling experiment using $H_2^{18}O$.



Scheme 6. Radical trapping experiments.

Viji S., of CSIR-NIIST for recording NMR and mass spectra respectively.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2022.154126.

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