

**Transition-Metal-Catalyzed Auxiliary Assisted Site-Selective C-H
Functionalization: Access to Functionalized N-Heterocycles**

A Thesis Submitted

in Partial Fulfilment of the Requirements

for the Degree of

DOCTOR OF PHILOSOPHY

by

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January 2025**



***Dedicated To
My Parents***



INDIAN INSTITUTE OF TECHNOLOGY GUWAHATI
Department of Chemistry

STATEMENT

I hereby declare that the matter embodied in this thesis is the result of investigations carried out by me in the Department of Chemistry, Indian Institute of Technology Guwahati, Guwahati, India under the supervision of Prof. Tharmalingam Punniyamurthy.

In keeping with the general practice of reporting scientific observations, due acknowledgement has been made wherever the work described is based on the findings of other investigators.

Guwahati
January 2025

Shubhajit Basak



INDIAN INSTITUTE OF TECHNOLOGY GUWAHATI

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CERTIFICATE

This is to certify that Mr. Shubhajit Basak has been working under my supervision since March 2019. I am forwarding his thesis entitled “*Transition-Metal-Catalyzed Auxiliary Assisted Site-Selective C-H Functionalization: Access to Functionalized N-Heterocycles*” being submitted for the Ph.D. degree of this institute. I certify that he has fulfilled all the requirements according to the rules of this institute, and regarding the investigations embodied in his thesis and this work has not been submitted elsewhere for a degree.

Guwahati
January 2025

Prof. Tharmalingam Punniyamurthy
Supervisor

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May God bless you all!

Shubhajit Basak

List of Abbreviations

Ar	aryl
Ac	acetyl
acac	acetylacetone
Ad	adamantane
Å	angstrom (10^{-8} cm)
BHT	butylated hydroxytoluene
Bn	benzyl
Boc	<i>tert</i> -butoxycarbonyl
BQ	benzoquinone
Bz	benzoyl
Cp*	1,2,3,4,5-pentamethylcyclopentadiene
CCDC	Cambridge crystallographic data center
Cy	cyclohexyl
<i>p</i> -cymene	4-isopropyltoluene
DG	directing group
DMSO	dimethylsulfoxide
dppf	1,1'-bis(diphenylphosphino)ferrocene
DIPEA	<i>N,N</i> -diisopropylethylamine
EDG	electron donating group
equiv	equivalent
ee	enantiomeric excess
Et	ethyl
ESI	electrospray ionization
EWG	electron withdrawing group
FT-IR	Fourier transform infrared spectroscopy
FG	functional group
HFIP	hexafluoroisopropanol
Het	heterocyclic
HRMS	high-resolution mass spectrometry

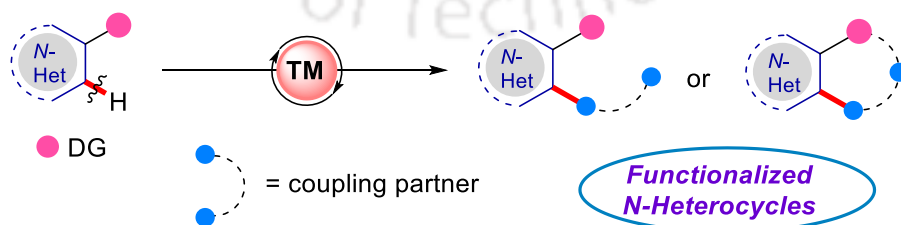
Hz	hertz
ⁱ Pr	isopropyl
LG	leaving group
m/z	mass to charge ratio
mp	melting point
Mes	mesityl
MHz	megahertz
nm	nanometer
NMR	nuclear magnetic resonance
NHPI	<i>N</i> -hydroxyphthalimide
Me	methyl
ORTEP	oak ridge thermal ellipsoid plot
R _f	retardation factor
rt	room temperature
Piv	pivaloyl
py	pyridyl
pym	pyrimidyl
PIDA	Phenyliodine(III) diacetate
PG	protecting group
TFE	2,2,2-trifluoroethanol
TCE	2,2,2-trichloroethanol
TIPS	triisopropylsilyl
TFA	trifluoroacetic acid
TMEDA	tetramethylethylenediamine
TEMPO	2,2,6,6-tetramethylpiperidin-1-oxyl
TLC	thin layer chromatography
TMS	trimethylsilyl
TM	transition metal
VCP	vinylcyclopropane
μL	Microliter

Abstract

The thesis is comprised of four chapters. The first chapter describes a general introduction of the auxiliary assisted regioselective C-H functionalization of *N*-heterocycles under transition-metal (TM) catalysis. The second chapter demonstrates a Pd-catalyzed C4-H arylation of indoles utilizing simple arenes *via* 2-fold C-H activation/C-C coupling. The third chapter deals with merging C-H/C-C activation for the C4-H allylation of indoles with vinylcyclopropanes under redox-neutral Ru-catalysis. The fourth chapter illustrates a cascade C-H functionalization/2-fold annulation of 2-aryloxazolines with 1,2,3-triazoles to afford heteroaryl-tethered oxazoloisoquinolinones under Rh-catalysis.

Chapter I. Auxiliary Assisted Regioselective C-H Functionalization of *N*-Heterocycles

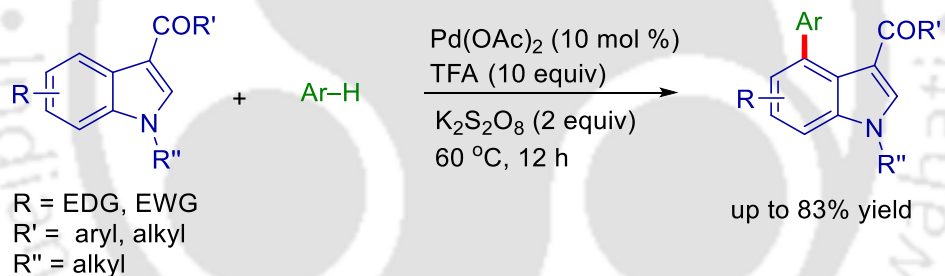
Nitrogen-containing heterocyclic scaffolds are the building block of a wide array of bioactive compounds, natural products, drugs and organic materials. In addition, they can serve as useful ligands, catalyst and protecting groups in synthetic organic chemistry. In view of the multifarious application of *N*-Heterocycles, the rational development of synthetic methodology for their functionalization or construction has attracted remarkable attention over the years. Consequently, transition-metal catalyzed C-H functionalization has evolved as a powerful tool which provides a straightforward route to access functionalized *N*-heterocycles. In addition, DG assistance offers an advanced regiocontrol in C-H functionalization reactions. This chapter focuses methodologies based on the TM-catalyzed DG-assisted C-H activation for the synthesis of functionalized *N*-heterocycles, which are reported in literatures.



Scheme 1. Auxiliary-Assisted C-H Activation/Functionalization utilizing TM-catalysis

Chapter II. Palladium-Catalyzed C4-H Arylation of Indoles with Arenes

The heteroaromatic indoles are the versatile structural scaffolds present in a plentiful biologically active molecules, natural products and drugs. Thus, the directing group (DG) assisted C-H functionalization of indole utilizing TM-catalysis has emerged as a research hotspot in synthetic organic chemistry. Due to the presence of intrinsically reactive pyrrole core in indole scaffold, the C2- and C3-functionalization is extensively explored, whereas the benzenoid (C4-C7) C-H functionalization is less studied. In addition, the distal C4-H functionalization in presence of free C2-H bond of indole is a challenging task when a DG is positioned at C3-site. Herein, we have described a weak benzoyl-assisted C4-H arylation of indoles employing arenes as aryl source utilizing Pd-catalysis *via* a 2-fold C-H activation pathway. The salient features include exclusive site selectivity, functional group tolerance and late-stage modifications of the target product.



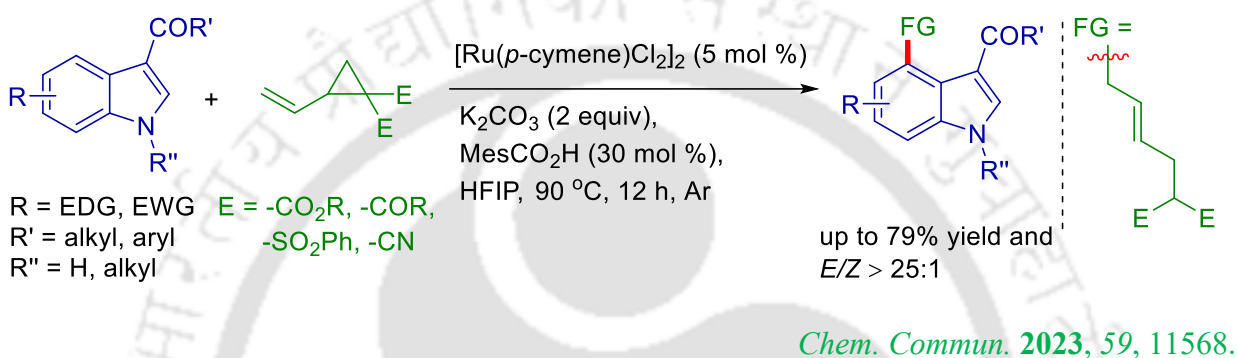
Org. Lett. **2022**, *24*, 554.

Scheme 2. Pd(II)-Catalyzed C4-H Arylation of Indoles using Arenes

Chapter III. Ruthenium-Catalyzed C4-H Allylation of Indoles with Vinylcyclopropanes

The privileged indole frameworks have turned into one of the most investigated organic scaffolds due to their high natural abundance and bioavailability. In addition, the significant pharmacological properties of indole alkaloids render them as a key component in medicinal science and drug discovery. Tremendous efforts have thus been made on the site-selective C-H

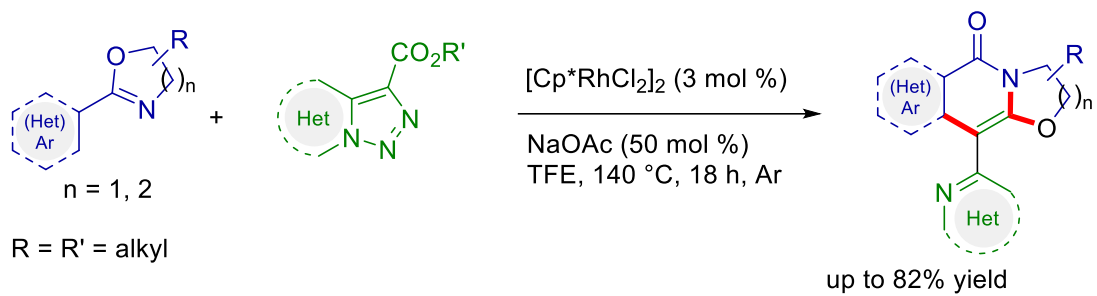
functionalization of indole utilizing DG assistance and TM-catalysis. In this realm, the pyrrolic C-H (C2 and C3) functionalization are well-established in light of inherent reactivity, while the less reactive remote C4-H functionalization is less explored. Moreover, the C-H functionalization with challenging C-C activation has attracted a great attention in contemporary synthetic research. This chapter demonstrates a merging C-H/C-C activation strategy for the acyl DG-guided C4-H allylation of indoles with vinylcyclopropanes under redox-neutral Ru-catalysis.



Scheme 3. Ru(II)-Catalyzed C4-H Allylation of Indoles Exploiting VCPs

Chapter IV. Rhodium-Catalyzed Cascade C-H Activation and Annulation of (Hetero)arenes with Pyridotriazoles

The TM-catalyzed DG-assisted C-H functionalization and annulation in a unified tandem process has come up a transformative tool to construct complex molecular scaffolds in a predictable and practical way. Utilizing this concept, the quest for the development of synthetic methodology for the expeditious construction of cyclic isoquinolinones has gained a prime focus in recent years. Among them, the synthesis of polycyclic oxazolo- and oxazino-isoquinolinone scaffolds is important due to their captivating biological and medicinal properties. Thus, the development of an efficient method for their construction would be advantageous. Herein, we have developed a Rh-catalyzed cascade C-H activation/ two-fold annulation of (hetero)aryl-oxazolines and pyridotriazoles for the rapid access of heteroaryl-tethered oxazoloisoquinolinones. This step-economic transformation involves the consecutive annulation sequence, broad substrate scope and production of green by-products *viz.* N_2 , alcohol, H_2O as the practical features.



Chem. Commun. **2025**, *61*, 1693.

Scheme 4. Rh(III)-Catalyzed Cascade C-H Activation/2-Fold Annulation with Pyridotriazoles



Contents

Statement	i
Certificate	ii
Acknowledgement	iii
List of abbreviations	v
Abstract	vii
Contents	xi
Chapter I. Auxiliary Assisted Regioselective C-H Functionalization of <i>N</i>-Heterocycles	
1.1 State-of-art for the C-H Functionalization of <i>N</i> -Heterocycles	4
1.2 Auxiliary Assisted C-H Functionalization of <i>N</i> -heterocycles	
1.2.1 Functionalization of Indoles	5
1.2.2 Functionalization of Isoquinolinones	6
1.2.3 Functionalization of Carbazoles	8
1.2.4 Functionalization of 2-Pyridones	9
1.2.5 Functionalization of Pyrroles	11
1.2.6 Functionalization of Quinolines	12
1.3 C-H Activation/Annulation to Access Functionalized <i>N</i> -Heterocycles	13
1.4 Objective of the Thesis	16
1.5 References	16
Chapter II. Palladium-Catalyzed C4-H Arylation of Indoles with Arenes	
2.1 C4-H Functionalization of Indoles	22
2.2 C-H Arylation of (Hetero)arenes	
2.2.1 Using Prefunctionalized Arenes	24
2.2.2 Using Simple Arenes	25
2.3 Present Study	25
2.4 Experimental Section	33
2.5 Characterization Data	36
2.6 References	58

2.7 Selected NMR Spectra	60
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Chapter III. Ruthenium-Catalyzed C4-H Allylation of Indoles with Vinylcyclopropanes

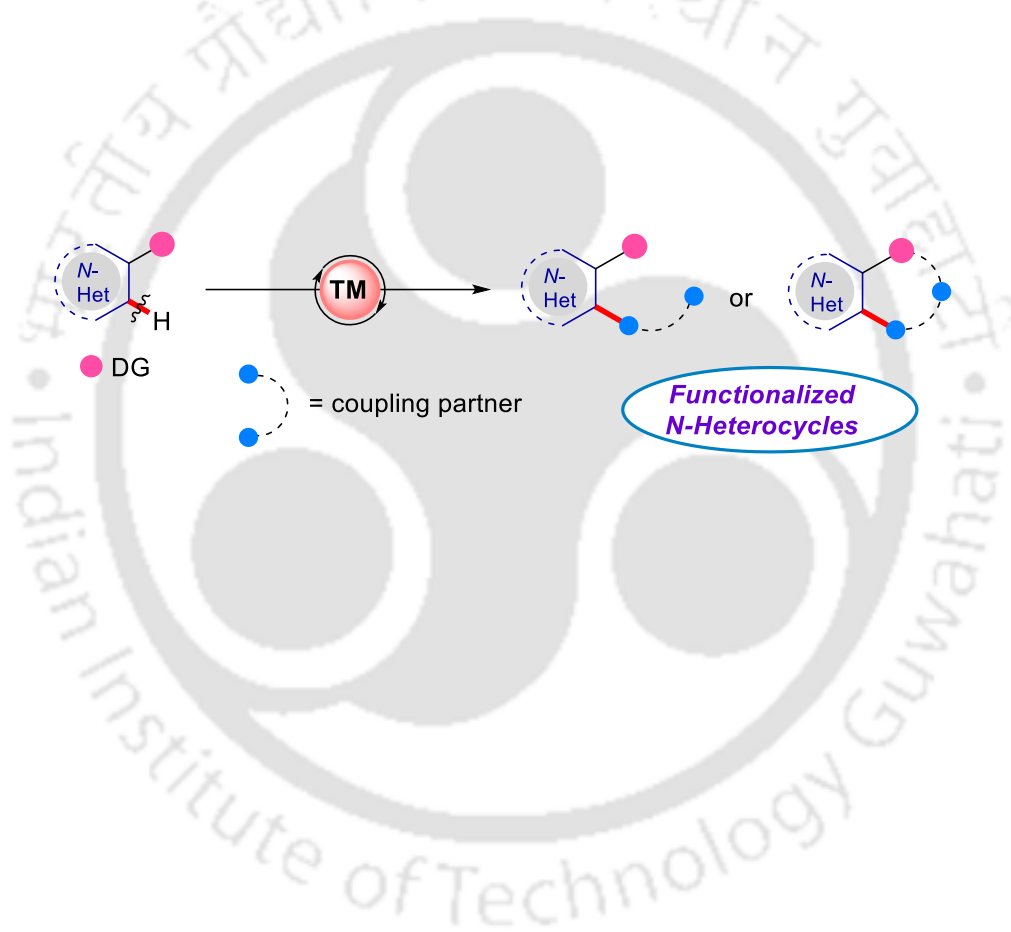
3.1 C-H Allylation of (Hetero)arenes	
3.1.1 Using Morita-Baylis-Hillaman (MBH) Adducts	66
3.1.2 Using Allyl Acetate	67
3.1.3 Using Allyl Carbonate	68
3.1.4 Using Dioxolanone	68
3.1.5 Using Vinylcyclopropanes	69
3.2 Present Study	69
3.3 Experimental Section	78
3.4 Characterization Data	81
3.5 References	100
3.6 Selected NMR Spectra	102

Chapter IV. Rhodium-Catalyzed Cascade C-H Activation and Annulation of (Hetero)arenes with Pyridotriazoles

4.1 C-H Functionalization of 2-Aryloxazolines	108
4.2 Ring-Opening Annulation of 2-Aryloxazolines	108
4.3 Reactivity of Pyridotriazoles	109
4.4 Present Study	111
4.5 Experimental Section	119
4.6 Characterization Data	124
4.7 References	144
4.8 HPLC Chromatograms	146
4.9 Selected NMR Spectra	148
Thesis Overview	151
Summary	153
List of Publications	155

Chapter I

Auxiliary Assisted Regioselective C-H Functionalization of N-Heterocycles





Auxiliary Assisted Regioselective C-H Functionalization of *N*-Heterocycles

Nitrogen-based heterocycles are considered as the privileged molecules due to their abundance in natural products, agrochemicals and organic materials.¹ Moreover, they constitute the structural backbone in a myriad of bio-relevant compounds, nucleic acids, vitamins, antibiotics and clinical drugs (Figure 1).² In addition, the incorporation of specific functionalities into an *N*-heterocyclic scaffold can tune their physicochemical properties *viz.* chemical reactivity and biological activity. Thus, suitable functionalization of *N*-heterocyclic framework has attracted a great deal of attention over the past decades, unlocking their vast potential as therapeutic agents and the key components. Moreover, polycyclic *N*-heterocycles exhibit varied physiochemical properties such as photochromic properties, bio-chemiluminescence, electrical and thermal conductivity, which renders them useful in material sciences for the development of sensors, dyes, organic conductors and light-emitting diodes.³

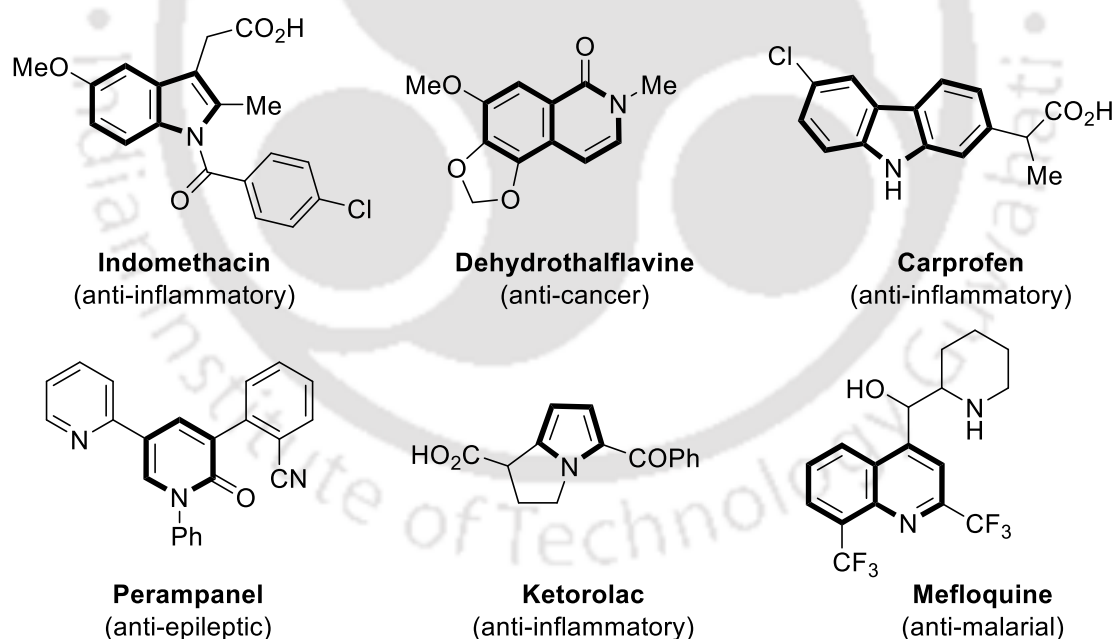


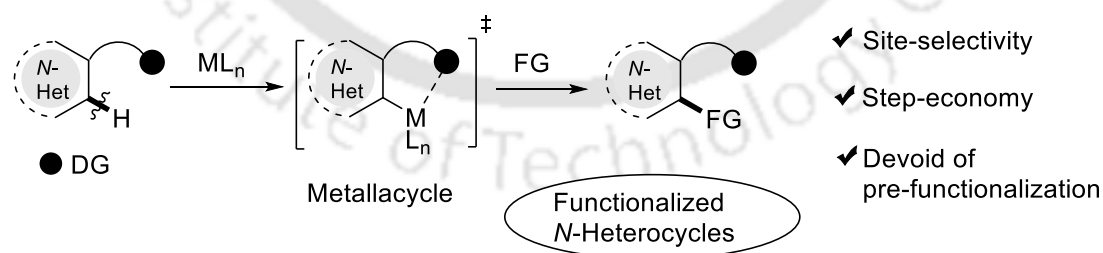
Figure 1. Representative Examples of Bioactive *N*-Heterocycles

Considering the profound significance, the development of efficient and sustainable synthetic strategies for the rapid access of the functionalized *N*-heterocycles has come up a highly sought after research goal in synthetic organic chemistry. The objective can be realized by the functionalization of naturally and synthetically accessible *N*-heterocyclic scaffold or rational

design of heterocyclic core with pre-installed functionalities. In this endeavour, transition-metal-catalyzed C-H functionalization has emerged as a powerful synthetic tool as it offers step- and atom-economical routes to the structural modification of molecular scaffolds.⁴ Further, exploiting directing group (DG) assistance provides a unique solution to the rapid synthesis of complex molecules in a convenient and predictable manner.⁵ As congeners of *N*-heterocycles, indoles, isoquinolinones, carbazoles, 2-pyridones, pyrroles and quinolines are ubiquitous in a plethora of bioactive scaffolds and pharmaceuticals with a broad spectrum of therapeutic applications. In this section, the methods for the DG-assisted site-selective C-H functionalization as well as synthesis of the aforementioned heterocycles are presented.

1.1 State-of-art for the C-H Functionalization of *N*-Heterocycles

The C-H functionalization of nitrogen-containing heterocyclic scaffolds has been a great interest of research as they are largely woven into natural products and biologically active compounds. In this realm, transition-metal-catalyzed C-H activation has evolved as a powerful synthetic tool to construct C-C and C-heteroatom bonds with step- and atom-economic fashion. In addition, it avoids the use of pre-functionalized substrate precursors, offering a straightforward route to access intricate molecular frameworks. Moreover, due to the subtle reactivity difference of multiple C-H bonds in these heterocyclic scaffolds, the selective C-H bond editing is a formidable challenge. To resolve the selectivity issue, the C-H functionalization utilizing DG assistance has gained a significant attention in recent years. The DG in association with the C-H substrate and metal catalyst can form a metallacycle intermediate, which can lead to target functionalization (Scheme 1).⁵



Scheme 1. Outline of DG-Assisted C-H Activation/Functionalization

1.2 Auxiliary Assisted C-H Functionalization of *N*-Heterocycles

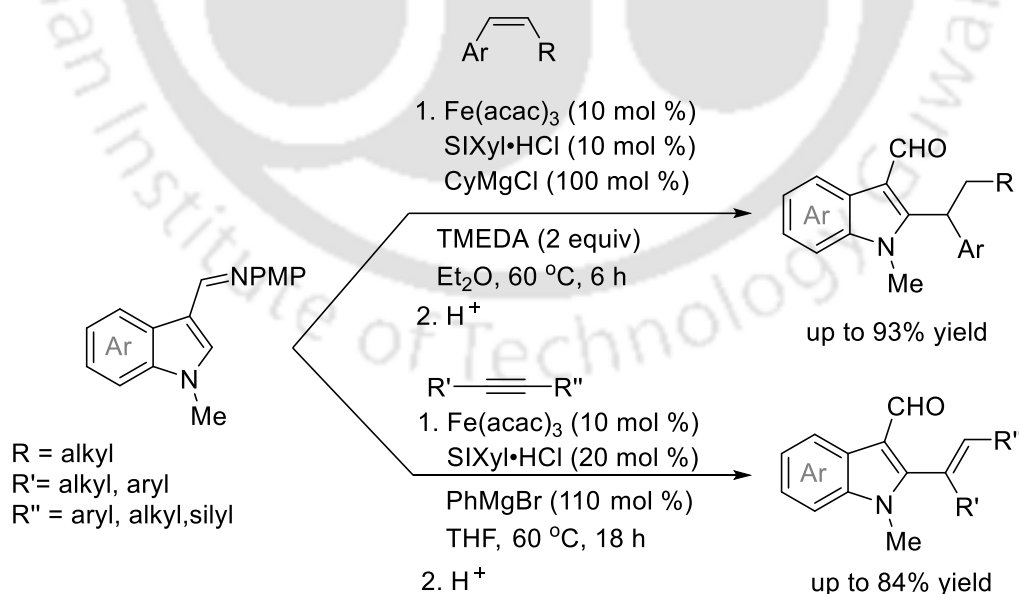
The site-selective C-H functionalization of prevailing *N*-heterocyclic scaffolds such as indoles, isoquinolinones, carbazoles, 2-pyridones, pyrroles and quinolines has become a fascinating area

of contemporary synthetic research. Tireless efforts have been put into the chelation-assisted C-H functionalization of mentioned heterocycles to fabricate molecular complexity.

1.2.1 Functionalization of Indoles

Indoles are the important structural motifs ubiquitously present in a vast array naturally occurring and medicinal compounds.⁶ This prominent scaffold is the building block of numerous commercially available pharmaceuticals and is regarded as fourth most prevalent heteroaromatic subunit.^{2a} In addition, they are the integral part of a cell growth hormone auxin, an essential amino acid tryptophan and animal hormone serotonin. Owing to their remarkable applications, the development of synthetic methods for the regioselective C-H functionalization of indoles has surfaced as the frontline research objective in the domain of organic synthesis.

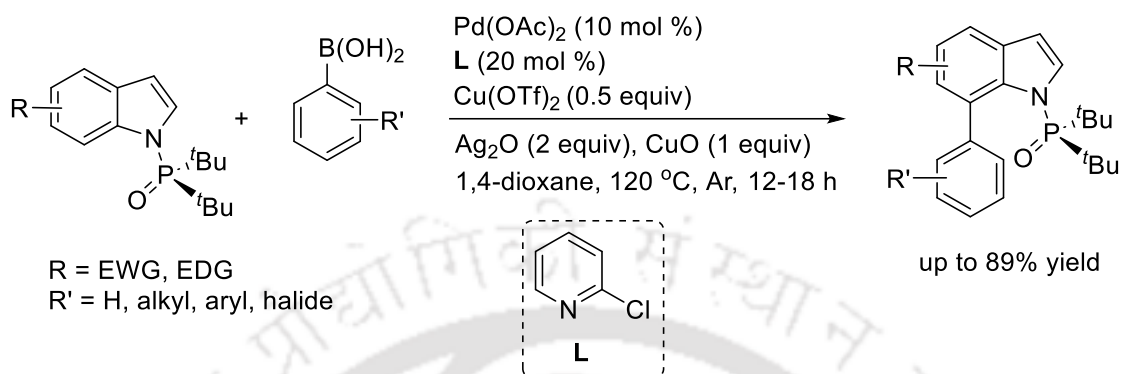
Yoshikai and co-workers accomplished imine directed iron-*N*-heterocyclic carbene (NHC) catalyzed C2-alkylation and alkenylation of indole using vinylarenes and internal alkyne, respectively (Scheme 2).⁷ The reaction showcased the generation of iron-NHC catalyst from a Fe(III) salt, an imidazolium salt, and Grignard reagent. Further, the protocol provides 1,1-diaryllalkane derivative with excellent regioselectivity.



Scheme 2. Fe-Catalyzed C2-Alkylation and Alkenylation of Indole

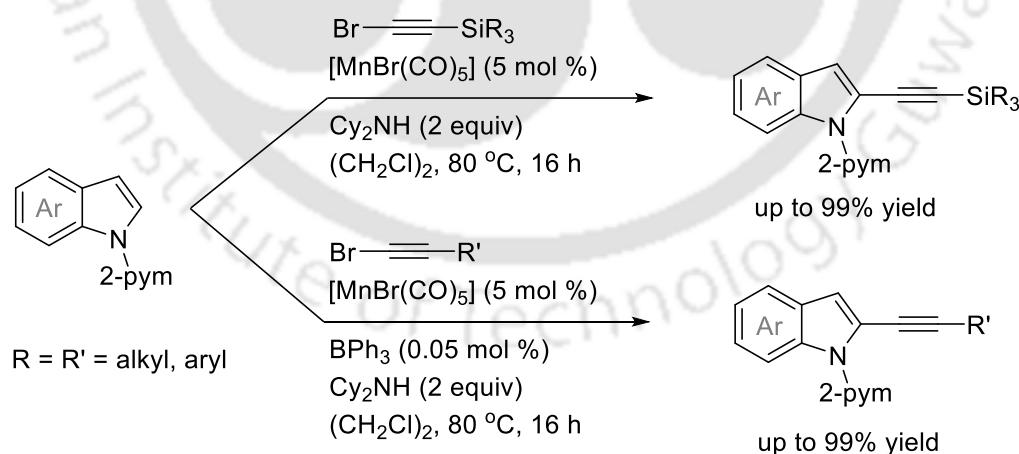
Shi and co-workers developed the Pd(II)-catalyzed C7-H arylation of indole with arylboronic acids (Scheme 3).⁸ The exclusive regioselectivity was attributed to the choice of a sterically

bulky and removable phosphinoyl DG and pyridine-type ligand. The protocol was suited for wide range of indoles and boronic acids to afford the arylated products.



Scheme 3. Pd-Catalyzed C7-H Arylation of Indole

Ackermann and co-worker reported the Mn-catalyzed alkynylation of indole at C2 position using organic halides (Scheme 4).⁹ The catalytic approach demonstrated broad applicability to silyl alkynes, as well as the more interesting aryl, alkenyl, and alkyl alkynes. Further, the potent synthetic ability of the protocol was exemplified by the late-stage modification of cyclic and acyclic peptides.



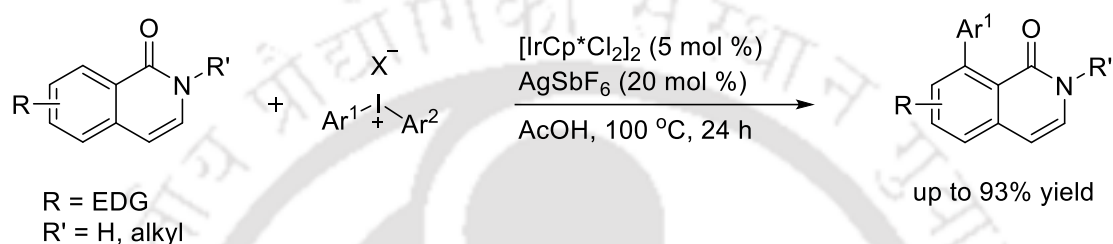
Scheme 4. Mn(I)-Catalyzed C2- Alkynylation of Indole

1.2.2 Functionalization of Isoquinolinones

Functionalized isoquinolinones, one of the intriguing *N*-heterocyclic scaffolds, are found in varied natural products with significant biological activities and pharmaceutical importance.¹⁰

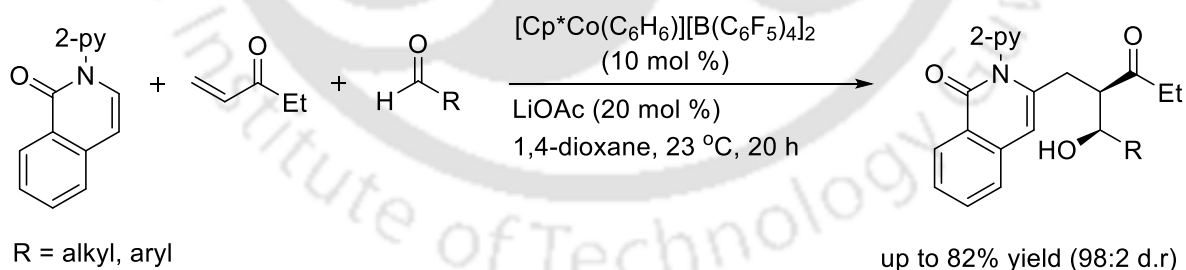
Thus, the rational design of synthetic strategies for their structure elaboration has attracted a considerable interest.

The Ir(III)-catalyzed C8-selective arylation of isoquinolinones was reported using coordinating amide as DG (Scheme 5).¹¹ An array of functionalized diaryliodonium salts were employed as the arylating source. In addition, the use of AcOH as the solvent was essential to achieve a higher conversion.



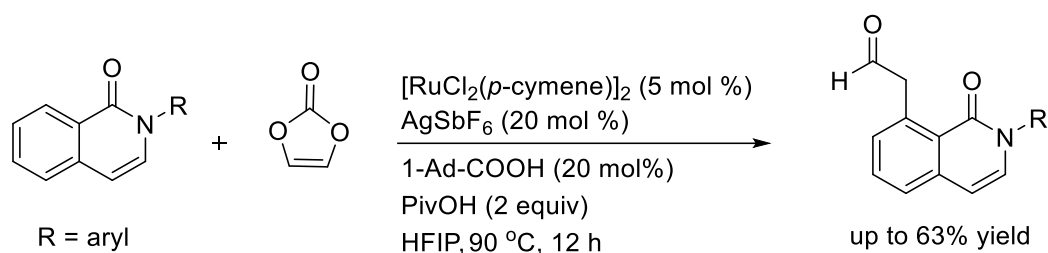
Scheme 5. Ir-Catalyzed C8-Arylation of Isoquinolinone

Ellman and co-workers disclosed the 2-pyridyl DG assisted C-H functionalization of isoquinolinones via three-component addition of enone and aldehyde utilizing an unprecedented Co-catalysis (Scheme 6).¹² The reaction proceeded at ambient temperature with diastereoselectivity.



Scheme 6. Co-Catalyzed Three-Component Coupling of Isoquinolinone

The Ru(II)-catalyzed C8-formylmethylation of isoquinolinones with vinylene carbonate was developed utilizing amide carbonyl DG (Scheme 7).¹³ The procedure was highlighted with the scalability and good functional group compatibility.

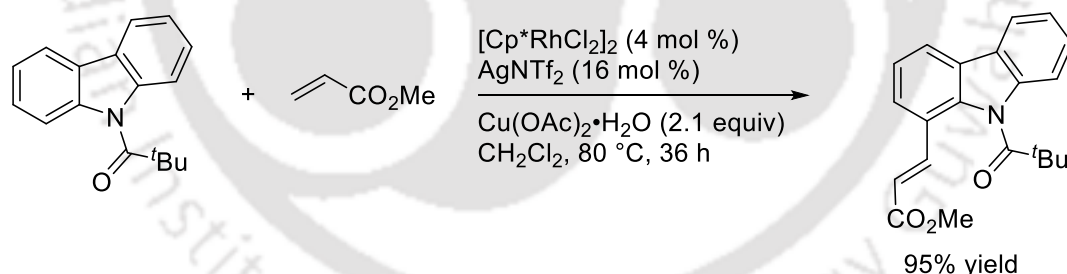


Scheme 7. Ru-Catalyzed C-8 Formylmethylation of Isoquinolinone

1.2.3 Functionalization of Carbazoles

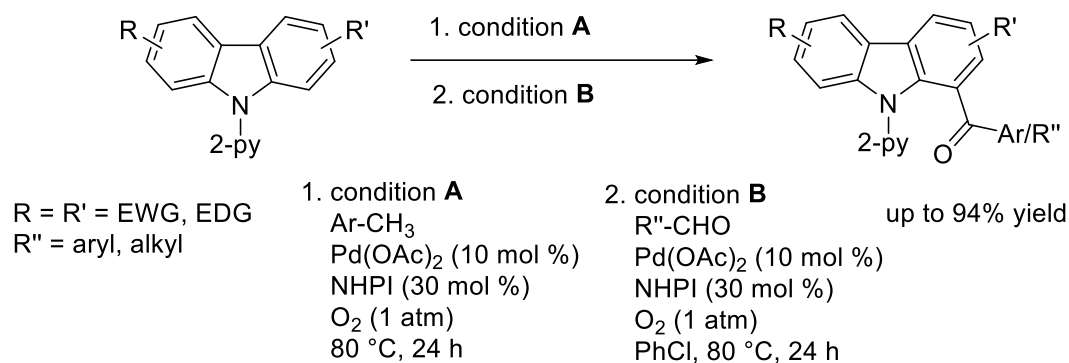
Given the importance on the widespread applications in medicinal and material sciences,¹⁴ the site-selective C-H functionalization of carbazole motif has been a primary focus to the synthetic fronts. The installation of a suitable DG at the *N*-atom of carbazole enables the desired functionalization at the C1- and C8-position utilizing TM-catalysis.

Ma and co-authors demonstrated a Rh-catalyzed site-selective alkenylation of carbazoles utilizing weak coordinating and easily removable pivaloyl DG (Scheme 8).¹⁵ The use of Rh-catalyst and pivaloyl DG was crucial to furnish the alkenylation in high yield and regioselectivity.



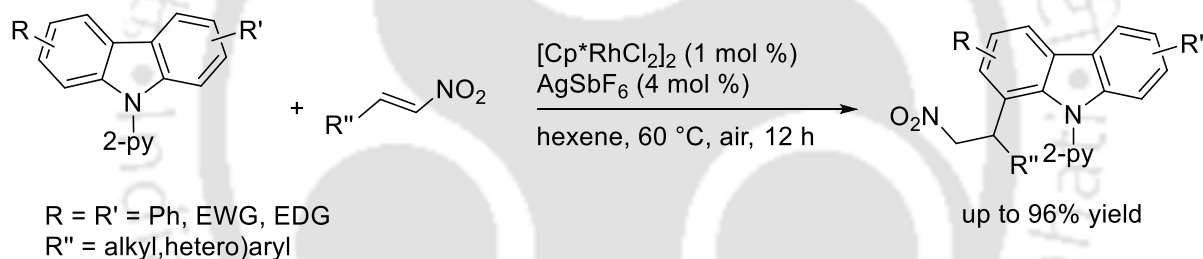
Scheme 8. Rh-Catalyzed Regioselective CH-Alkenylation of Carbazole

The Pd-catalyzed site-selective acylation of carbazole was developed using toluene derivative as solvent as well as acylating agent (Scheme 9).¹⁶ The use of NHPI as co-catalyst and oxygen as sole oxidant render the method environmentally benign. The strategy was extended to aldehyde as acyl source.



Scheme 9. Pd-Catalyzed Site-selective Acylation of Carbazole

Liu and Zhou groups reported the Rh(III)-catalyzed *ortho*-alkylation of carbazole using nitroalkene as an alkylating agent (Scheme 10).¹⁷ Among the various DGs (pyrimidyl, benzothiazolyl and quinolinyl), pyridyl serves an efficient DG. Both aromatic and aliphatic nitroalkenes amenable to give the product in good yield.

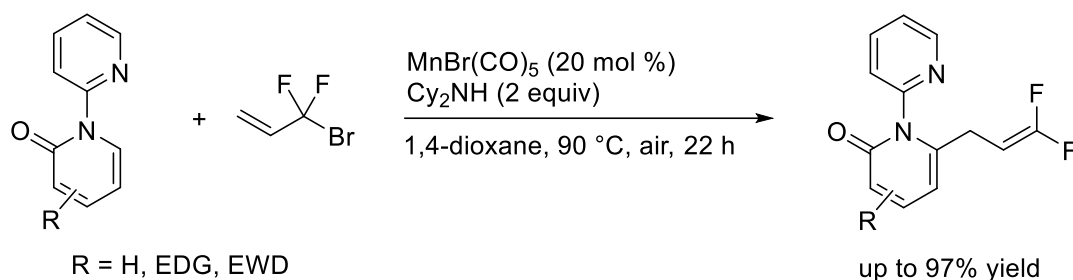


Scheme 10. Rh-Catalyzed *ortho*-Alkylation of Carbazole with Nitroalkene

1.2.4 Functionalization of 2-Pyridones

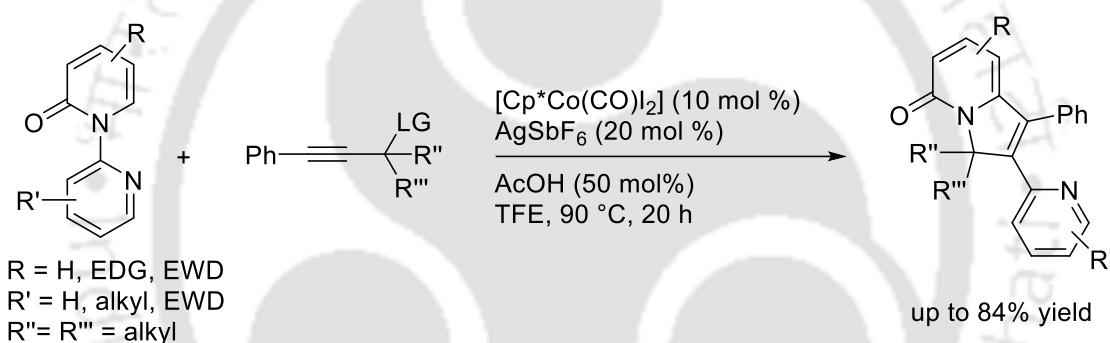
The congeners of 2-pyridones have been widely distributed in naturally occurring bioactive compounds, advanced organic materials and drug molecules.¹⁸ Moreover, their derivatives serve as a useful ligand in DG-guided remote C-H functionalization.^{18b} In this vein, the synthetic decoration of 2-pyridone scaffolds continues to be a cutting-edge area of research in recent years.

Zhang group described the Mn(I)-catalyzed C-H activation strategy for direct 3,3-difluoroallylation of 2-pyridones utilizing 3-bromo-3,3-difluoropropene as the difluoroallylation agent (Scheme 11).¹⁹ A broad range of substrates were amenable to afford the allylated product with good functional group compatibility.



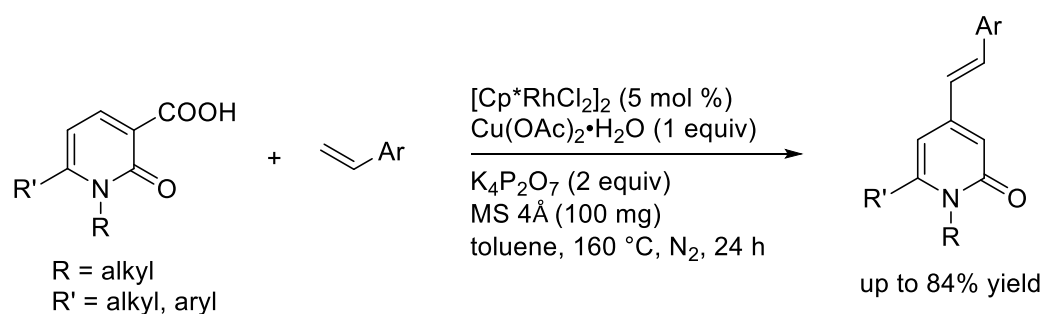
Scheme 11. Mn-Catalyzed 3,3-Difluoroallylation of 2-Pyridone

Ackermann and co-workers accomplished the Co-catalyzed domino reaction that enables the one-step synthesis of various bioactive indolizinone alkaloid derivatives (Scheme 12).²⁰ The reaction proceeds *via* cascade of C-H activation, C-N cleavage, pyridyl DG migration and alkyne annulation. The authors have conducted the mechanistic experiments and DFT calculations to elucidate the reaction pathway.



Scheme 12. Co-Catalyzed Domino C-H Activation/Annulation

Recently, Miura group established the Rh-catalyzed C4-H alkenylation of 3-carboxy-2-pyridones with styrenes (Scheme 13).²¹ The carboxylic group at the C3 position of 2-pyridone acts as a traceless DG, delivering the exclusive C4-alkenylated product with subsequent decarboxylation. The strategy paves the way for the construction of diversely substituted 2-pyridones through sequential C-H activation.

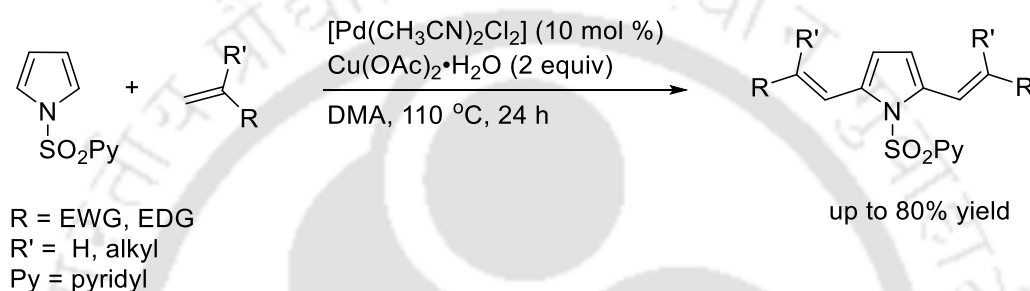


Scheme 13. Rh-Catalyzed C4-H Alkenylation of 2-Pyridone

1.2.5 Functionalization of Pyrroles

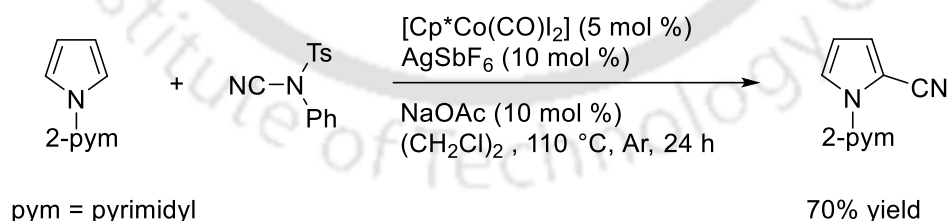
Pyrroles are the important class of *N*-heterocyclic scaffolds having broad bioavailability and medicinal importance. The selective C-H functionalization at the α -position of pyrroles can be achieved with the aid of DG, installed at the *N*-atom in presence of TM-catalyst.

Carretero group developed the Pd(II)-catalyzed *N*-(2-pyridyl)sulfonyl assisted double alkenylation at the C2 and C5 position of pyrrole (Scheme 14).²² The activating *N*-(2-pyridyl)sulfonyl group can be easily removed after the transformation. The procedure was well-tolerated with varied substituted alkenes.



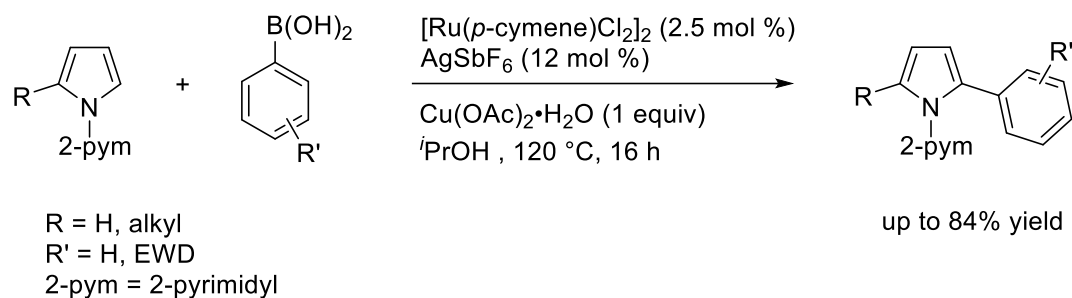
Scheme 14. Pd-Catalyzed Alkenylation of Pyrrole

Glorius and co-workers accomplished the Co(III)-catalyzed C2-selective cyanation of pyrrole exploiting 2-pyrimidyl assistance under ambient temperature (Scheme 15).²³ The procedure featured with the use of stable and less toxic *N*-cyano-*N*-phenyl-*p*-toluenesulfonamide (NCTS) as cyanating source and bench-stable Co-catalyst.



Scheme 15. Co-Catalyzed C2-Cyanation of Pyrrole

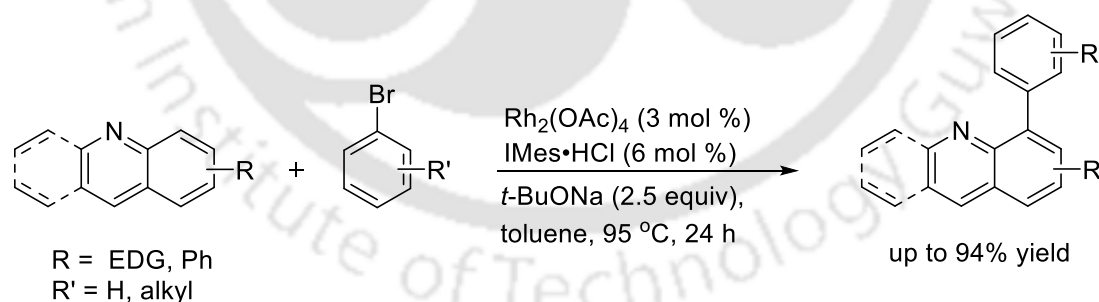
The Ru-catalyzed 2-pyrimidyl assisted oxidative C2-H arylation of pyrroles with boronic acid as an aryl source was detailed by Pilarski group (Scheme 16).²⁴ The mono-arylated pyrroles was obtained when the other *ortho*-position was blocked. Boronic acids of both electron-deficient and electron-rich were well-tolerated.

**Scheme 16.** Ru-Catalyzed Oxidative C2-H Arylation of Pyrrole

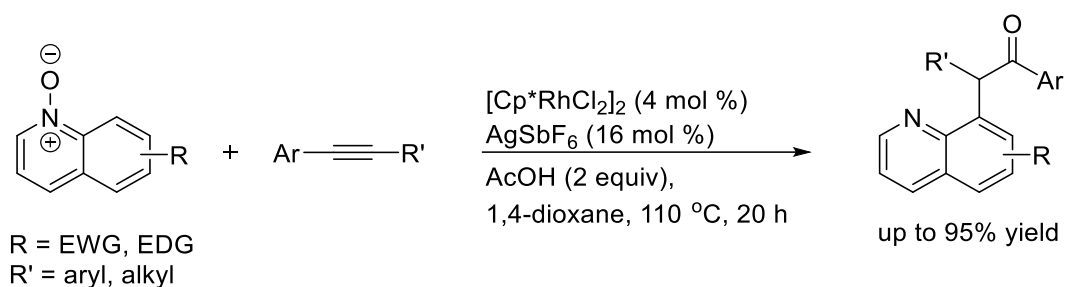
1.2.6 Functionalization of Quinolines

The aza-heterocyclic quinoline scaffolds are present in numerous drug molecules and biologically relevant entities. In addition, they are the cardinal constituents of the chimanine class of alkaloids having antifungal, antibacterial and antitumor activities.²⁵ Hence, significant progress has been witnessed on the DG-assisted site-selective C-H functionalization of quinolines.

Chang and co-workers reported an efficient regioselective direct C8-H arylation of quinolines with aryl bromide under Rh(NHC)-catalytic system (Scheme 17).²⁶ The appropriate choice of NHC ligand and Rh-catalyst was found to be crucial to access a diverse range 8-arylquinolines in high yields and selectivity.

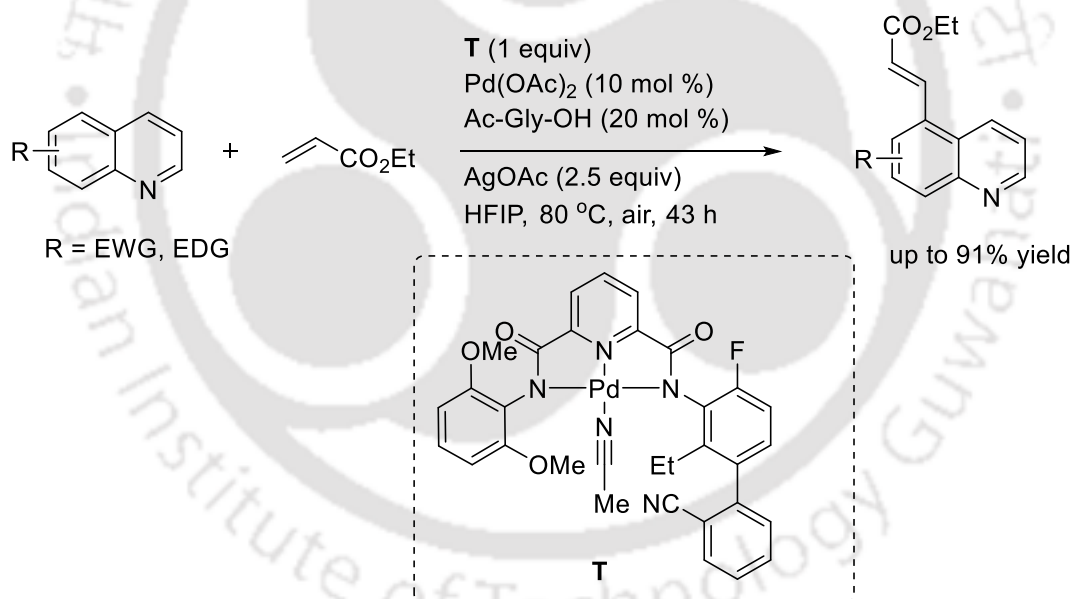
**Scheme 17.** Rh(NHC)-Catalyzed C8-Arylation of Quinoline

The Rh(III)-catalyzed redox-neutral coupling of quinoline *N*-oxide with internal alkynes was realized for synthesis of α -(8-quinolyl)acetophenones (Scheme 18).²⁷ The procedure involves a C-H activation followed by *O*-atom transfer (OAT) pathway. Further, the N–O group serves as the directing auxiliary as well as *O*-atom donor.



Scheme 18. Rh-Catalyzed Coupling of Quinoline and Alkynes

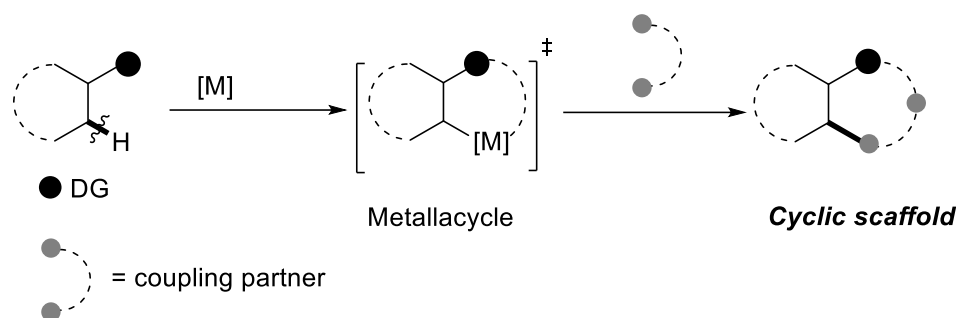
Yu group reported the Pd-catalyzed remote site-selective olefination of quinoline utilizing bifunctional nitrile template, which can bind with the heterocyclic substrate through reversible coordination (Scheme 19).²⁸ Diverse array of quinolines having electronically varied substituents gave the desired olefination products. In addition, the method proved its potential applicability by the late-stage modification of an antileukaemic and antitumour alkaloid.



Scheme 19. Pd-Catalyzed Remote C–H Olefination of Quinoline

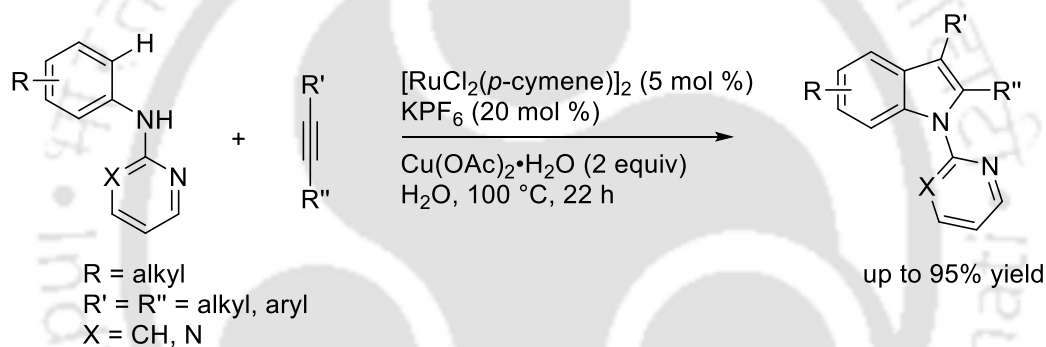
1.3 C–H Activation/Annulation to Access Functionalized *N*-Heterocycles

The DG-assisted tandem C–H functionalization and annulation reaction utilizing TM-catalysis offers a straightforward approach for the synthesis functionalized *N*-heterocycles in atom- and step-economical manner.²⁹ In recent years, much efforts have thus been made on this domain by the synthetic chemists.



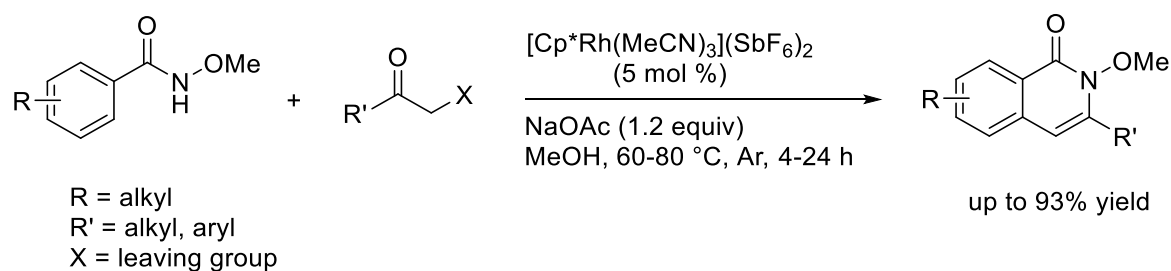
Scheme 20. DG-Assisted C-H Activation/Annulation Pathway

Ackermann and co-workers accomplished the Ru-catalyzed oxidative annulation of removable DG tethered anilines and alkynes to afford functionalized indoles with broad scope (Scheme 21).³⁰ The method was highlighted for the use of water as sustainable solvent and DG removal after the transformation.



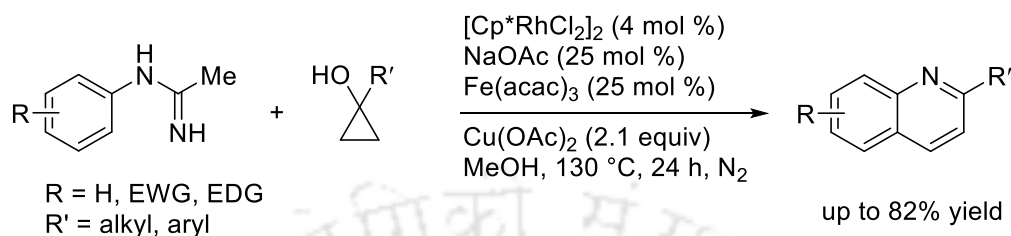
Scheme 21. Synthesis of Indole utilizing Ru-Catalysis.

Glorius group developed an efficient approach for the synthesis of isoquinolinones utilizing a redox-neutral Rh(III)-catalysis under mild reaction conditions (Scheme 22).³¹ A variety of amides were annulated with α -halo and pseudohalo ketones as oxidized alkyne equivalent to furnish *N*-heterocyclic scaffolds with good functional group tolerance.



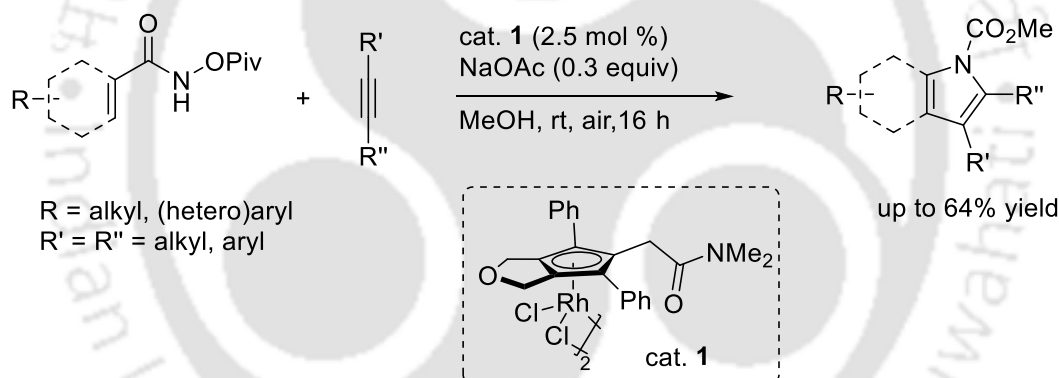
Scheme 22. Synthesis of Isoquinolinones under redox-neutral Rh(III)-Catalysis.

Li and co-workers reported the Rh-catalyzed sequential C-H/C-C activation of imidamide and cyclopropanol to access C2-substituted quinolines with broad substrate diversity (Scheme 23).³² The C-C and C-N bond formation, use of bifunctional imidamide DG and cyclopropanol as the versatile C3-synthon are the salient features.



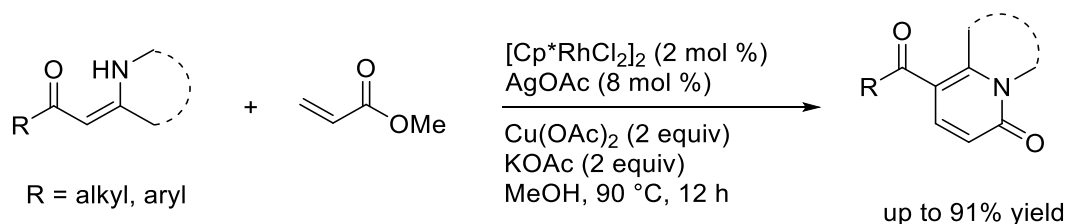
Scheme 23. Sequential C-H/C-C activation for the Synthesis of Quinolines

The Rh-catalyzed formal Lossen rearrangement/[3+2]-annulative coupling of acrylamides with alkynes was reported for the rapid construction of substituted pyrroles (Scheme 24).³³ The reaction pathway involves the C-H bond cleavage, alkyne insertion and Lossen rearrangement.



Scheme 24. Synthesis of Functionalized Pyrroles under Rh-Catalysis.

Loh and co-workers achieved a formal [3+3]-annulation of enamines and acrylates for the synthesis of a diverse *N*-substituted 2-pyridones under Rh-catalysis (Scheme 25).³⁴ Deuterium exchange and control experiments provided insight into the reaction pathway. The mechanism involving C-H functionalization and subsequent aminolysis cyclization was proposed.



Scheme 25. Expedient Synthesis of 2-Pyridones.

1.4 Objective of the Thesis

Transition-metal-catalyzed auxiliary-assisted site-selective C-H functionalization of *N*-heterocyclic scaffolds are the burgeoning field of research. A handful of synthetic methodologies is discussed in the light of varied DGs and metal catalysts with synthetically convenient yields and good functional group compatibility. However, there is still several synthetic void that can pave the way of further research in this emerging area.

- The DG-guided C-H functionalization at the C2- and C7-positions of indoles are extensively studied, while the distal C4-H functionalization is a formidable challenge in catalytic synthetic transformation, which can be explored.
- In several aforementioned studies, the DG removal upon functionalization gives rise to a major hurdle. Thus, the use of removable DG can be introduced to ease the synthetic effort.
- The C-H functionalization with concomitant C-C activation is attracted great interest of research in terms of atom- and step-economy. In this view, small strained ring systems can be exploited to achieve the goal.
- A number of previously discussed methodologies requires the pre-functionalized or activated coupling partners for the desired functionalization. The cross-dehydrogenative coupling strategy can be followed to address the issue.
- The C-H functionalization and annulation cascade reactions with electronically rich coupling agents such as alkenes and alkynes are well-established, whereas electron deficient carbene precursors can be utilized for this purpose.
- The annulative coupling furnishes the cyclic structural frameworks, however, the sequential multifold annulation can produce valuable polycyclic scaffolds, which can be investigated.
- The use of silver oxidant often limits novelty of the methodology from the sustainability viewpoint. In this context, the utilization of less-toxic oxidant or oxidant-free approach would fertile this area.

1.5 References

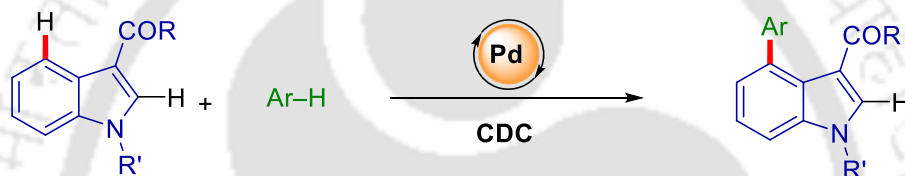
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Chapter II

Palladium-Catalyzed C4-H Arylation of Indoles with Arenes



- C4-selectivity
- weak chelation
- arene as aryl source

Org. Lett. **2022**, *24*, 554.



Palladium-Catalyzed C4-H Arylation of Indoles with Arenes

Indoles and their derivatives are the pivotal structural frameworks found in a plethora of biologically active compounds and natural products.¹ Owing to the inherent reactivity of the pyrrole ring of indole C2 and C3 functionalizations have been well studied, while the selective functionalization at the indole benzenoid segment (C4-C7) remains elusive.^{2,3} In particular, intrinsically inert C4-H functionalization of indoles has garnered substantial attention due to their abundance in bio-relevant compounds and potent pharmacophores (Figure 1).⁴ The implementation of a DG at C3-site to target C4-position as close proximity poses a significant challenge, which arises from the competing formation of five-membered metallacycle at C2 over a six-membered metallacycle at C4 (Scheme 1). To surmount this propensity and achieve the exclusive C4-selectivity, a tailor-made removable DG at C3-site is desirable. In this context, DG-guided C4-H functionalizations such as amidation,⁵ trifluoroalkylation,⁶ acylation,⁷ borylation,⁸ allylation,⁹ alkenylation¹⁰ and alkylation,¹¹ are realized under metal-catalysis. Due to the widespread applications of the C4-arylated indoles in biological and medicinal sciences, their construction has become a prominent research goal to the synthetic front. In this vein, the exquisite research by the groups of Yu,¹² Shi¹³ and Yang¹⁴ revealed the Pd-catalyzed C4-H arylation of indole with aryl iodide as the arylating agent employing a series of carbonyl based DGs *viz.* formyl, pivaloyl and acetyl groups. Moreover, the arylation employing arenes *via* cross-dehydrogenative coupling (CDC) strategy is an inexplicable task in synthetic organic chemistry, especially with the proper control of regio-, chemo- and stereo-selectivity.¹⁵ In this realm, the development of a suitable protocol to achieve C4-arylation of indoles with arenes would be valuable. Herein, we present a Pd-catalyzed 2-fold C-H activation for the C4-H arylation of indoles with arenes as the aryl source using benzoyl DG.

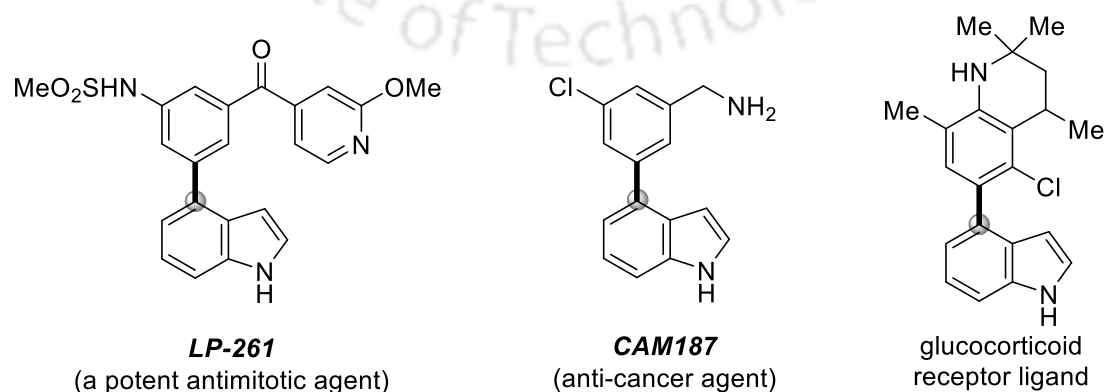
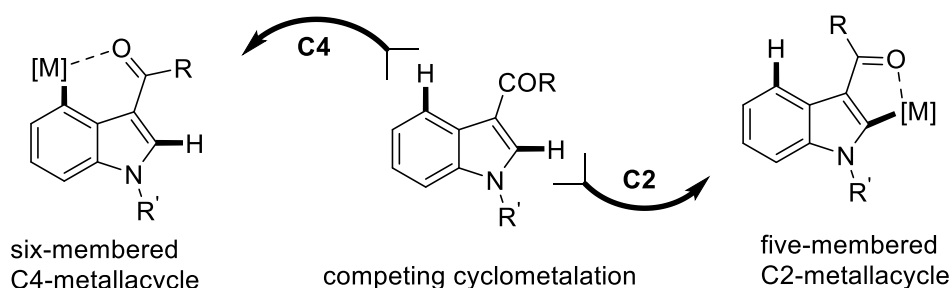


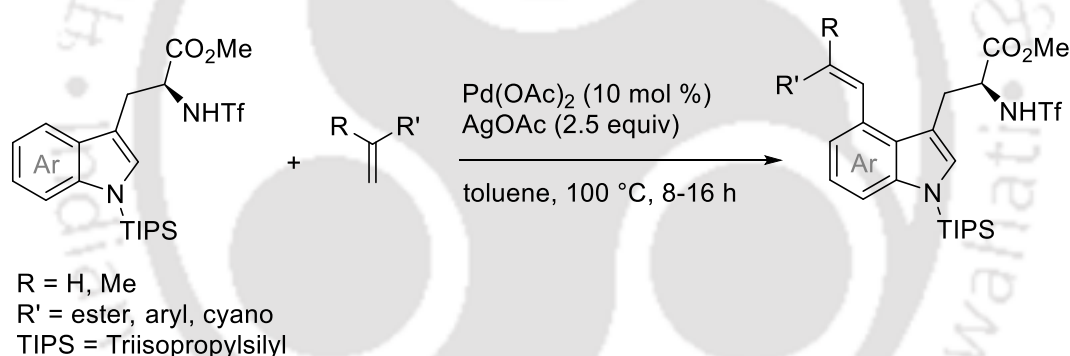
Figure 1. Examples of Biologically Important C4-Substituted Indoles.



Scheme 1. Challenges of C4-H Activation of Indoles

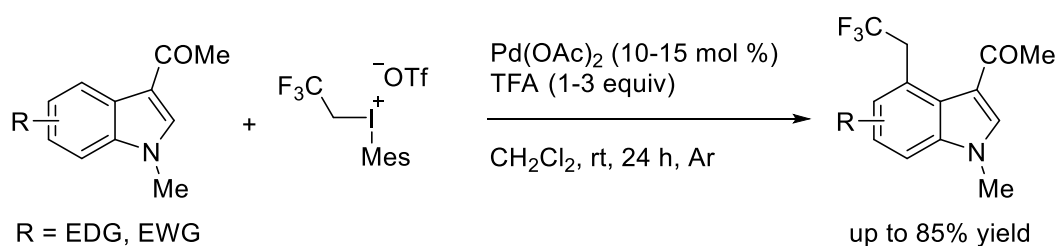
2.1 C4-H Functionalization of Indole

Jia and co-workers demonstrated an unprecedented Pd-catalyzed C4-olefination of tryptophan with terminal olefins to access 4-substituted tryptophans (Scheme 2).¹⁶ Further, the biomimetic total synthesis of (+)-*cis*- and (-)-*trans*-clavicipitic acid utilizing this method highlights the synthetic potential of the strategy.



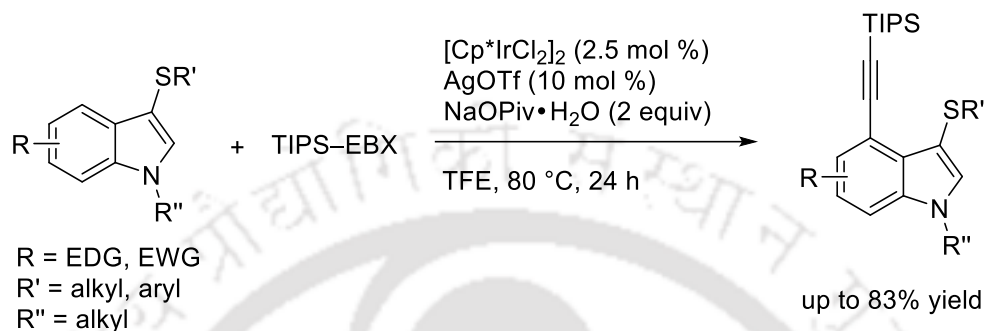
Scheme 2. Pd-Catalyzed C4-Olefination of Tryptophan

Shi group reported the Pd-catalyzed C4-trifluoroalkylation of indoles with the assistance of removable acetyl DG under mild conditions (Scheme 3).⁶ Highly reactive (1*H*, 1*H*-perfluoroalkyl)mesityliodonium triflate has been used as coupling partner. The exclusive site-selectivity, substrate scope and functional group tolerance are the significant features.



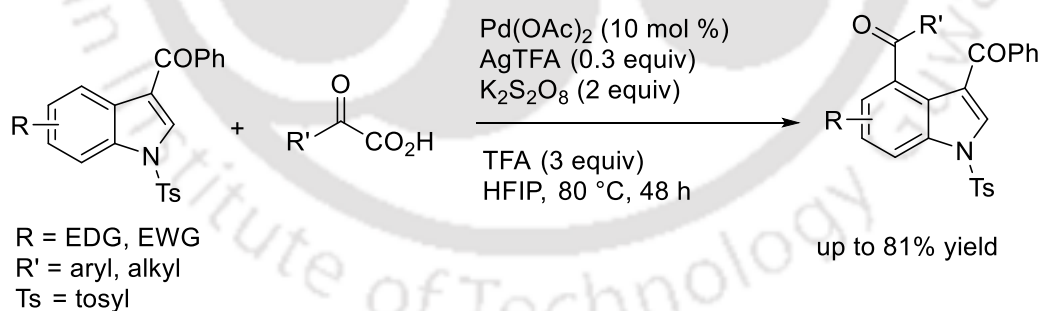
Scheme 3. Pd-Catalyzed C4-Trifluoroalkylation of Indoles

Alkynylation at the C4 position of indole with TIPS-EBX was described utilizing Ir-catalysis (Scheme 4).¹⁷ The removable and modifiable thioether functionality was used as auxiliary assistance. A wide range of indole substrates were found to be compatible, providing the alkynylated products in synthetically convenient yields.



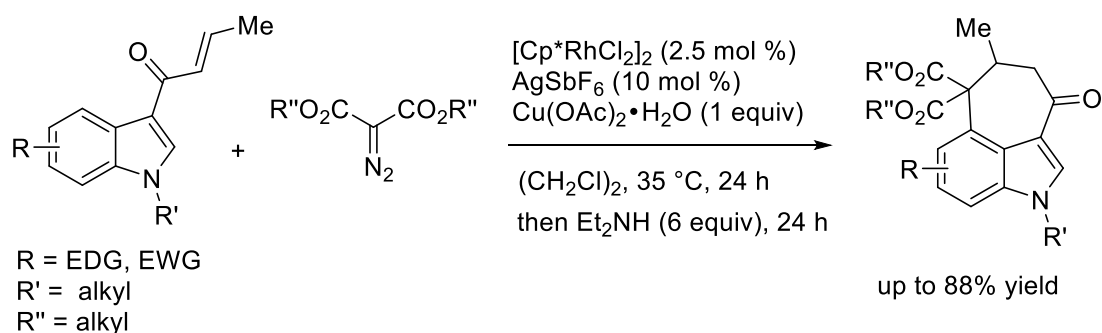
Scheme 4. Ir-Catalyzed C4-Alkynylation of Indoles

The Pd-catalyzed ketone-directed C4-selective acylation of indoles was developed utilizing α -oxocarboxylic acids (Scheme 5).⁷ Control experiments suggest the involvement of a Pd(II)/Pd(IV) species and acyl radicals formed through $\text{K}_2\text{S}_2\text{O}_8$ promoted decarboxylation of α -oxocarboxylic acids.



Scheme 5. Pd-Catalyzed C4-Acylation of Indoles

Harada and Nemoto groups accomplished the Rh-catalyzed direct synthesis of 3,4-fused tricyclic indoles employing α -diazomalonates with the aid of enone DG (Scheme 6).¹⁸ Detailed experimental and theoretical mechanistic studies revealed that the C-H activation was reversible and the site-selective C-H functionalization was governed by the Rh-carbene formation.

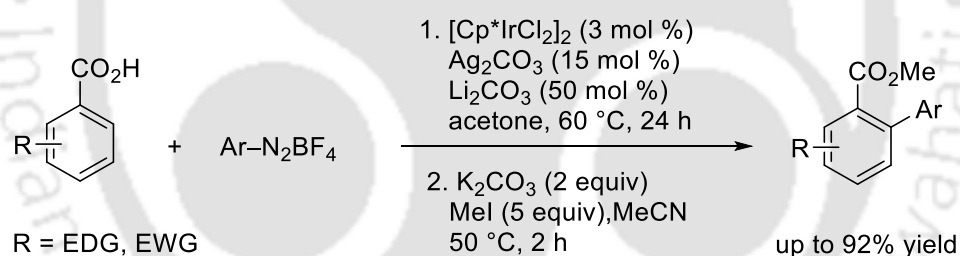


Scheme 6. Rh-Catalyzed One-pot 3,4-Fused Tricyclic Indole Synthesis

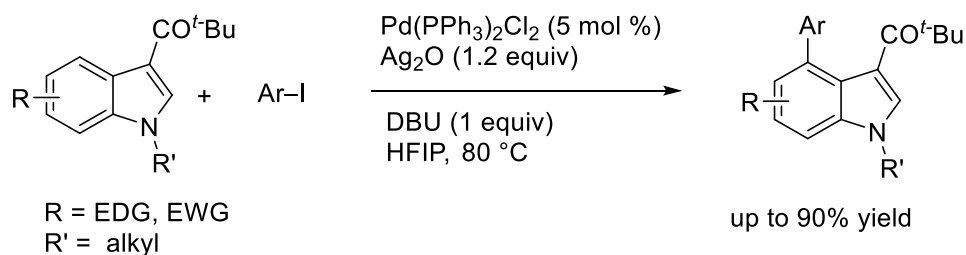
2.2 C-H Arylation of (Hetero)arenes

2.2.1 Using Prefunctionalized Arenes

Gooßen group reported the Ir(III)-catalyzed carboxylate directed *ortho*-arylation of benzoic acids with arenediazonium salts (Scheme 7).¹⁹ Electronically varied substrates were well tolerated under the mild reaction conditions. The carboxylate DG can be tracelessly removed or transformed into other functional groups, showcasing the prospective advantages.

Scheme 7. Ir-Catalyzed *ortho*-Arylation of Benzoic Acids

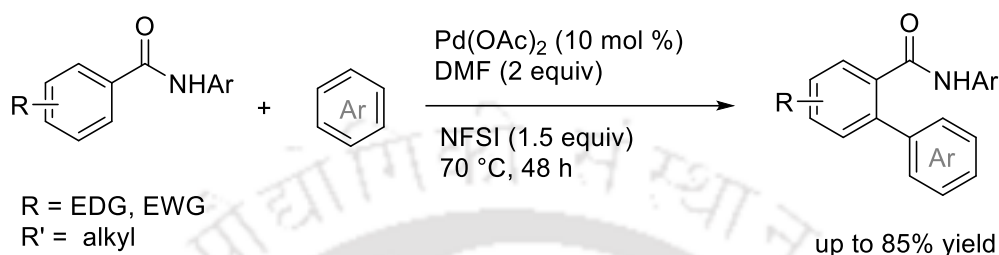
Shi and co-workers have demonstrated site-selective C4-arylation of indoles under the Pd(II)-catalysis using iodoarenes as aryl source (Scheme 8).¹³ The reaction was carried out with stoichiometric Ag₂O as an oxidant and DBU as an additive. The procedure was highlighted by the use of removable DG and good functional group tolerance.



Scheme 8. C4-H Arylation of Indoles with Iodoarenes

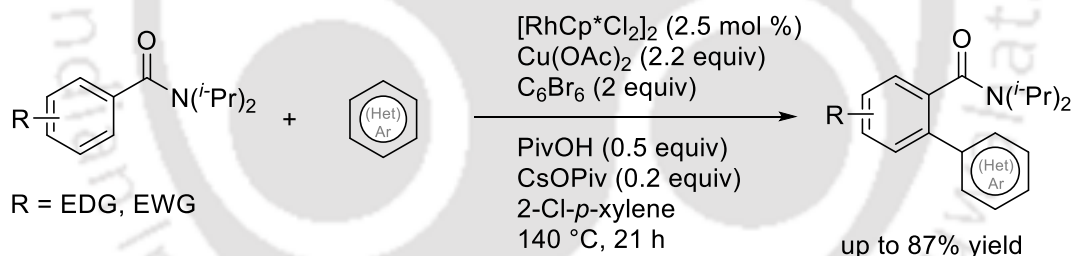
2.2.2 Using Simple Arenes

Yu group explored the C-H/C-H coupling of benzamides and monosubstituted arenes under Pd-catalysis (Scheme 9).²⁰ The use of bystanding F⁺ reagent as oxidant is crucial for achieving *para*-selectivity. Site-selectivity, substrate scope and functional group compatibility are the key aspects.



Scheme 9. Pd-Catalyzed Regioselective Arylation of Benzamides

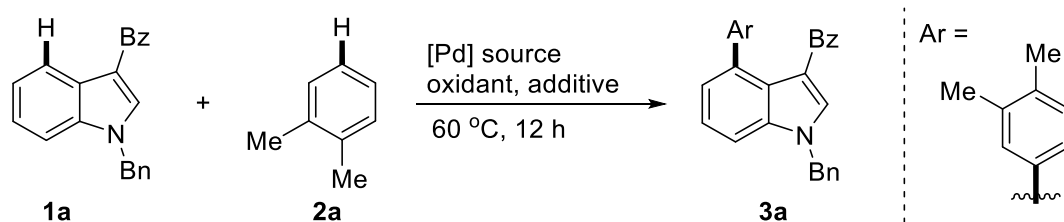
Glorius and co-workers accomplished the Rh(III)-catalyzed dehydrogenative cross-coupling of simple arenes with carboxamides to afford biphenyl-2-carboxamide derivatives (Scheme 10).²¹ The utilization of Cu(OAc)₂ together with C₆Br₆ as a complex catalyst modifier played an important role to deliver chemo- and regio-selectivity.



Scheme 10. Rh-Catalyzed Site-selective Arylation of Benzamides

2.3 Present Study

This chapter presents a Pd-catalyzed weak chelating benzoyl (Bz) DG assisted C4-H arylation of indole using arene as the arylating agent *via* 2-fold C-H activation and C-C bond formation. Initially, the optimization studies began with (1-benzyl-1*H*-indol-3-yl)(phenyl)methanone **1a** and *o*-xylene **2a** as the standard substrates utilizing Bz as the DG in the presence of varied Pd-sources, oxidants and additives (Table 1). Delightfully, the reaction occurred to produce **3a** in 12% yield, when **1a** and **2a** were stirred in presence of 10 mol % Pd(OAc)₂ and 10 equiv

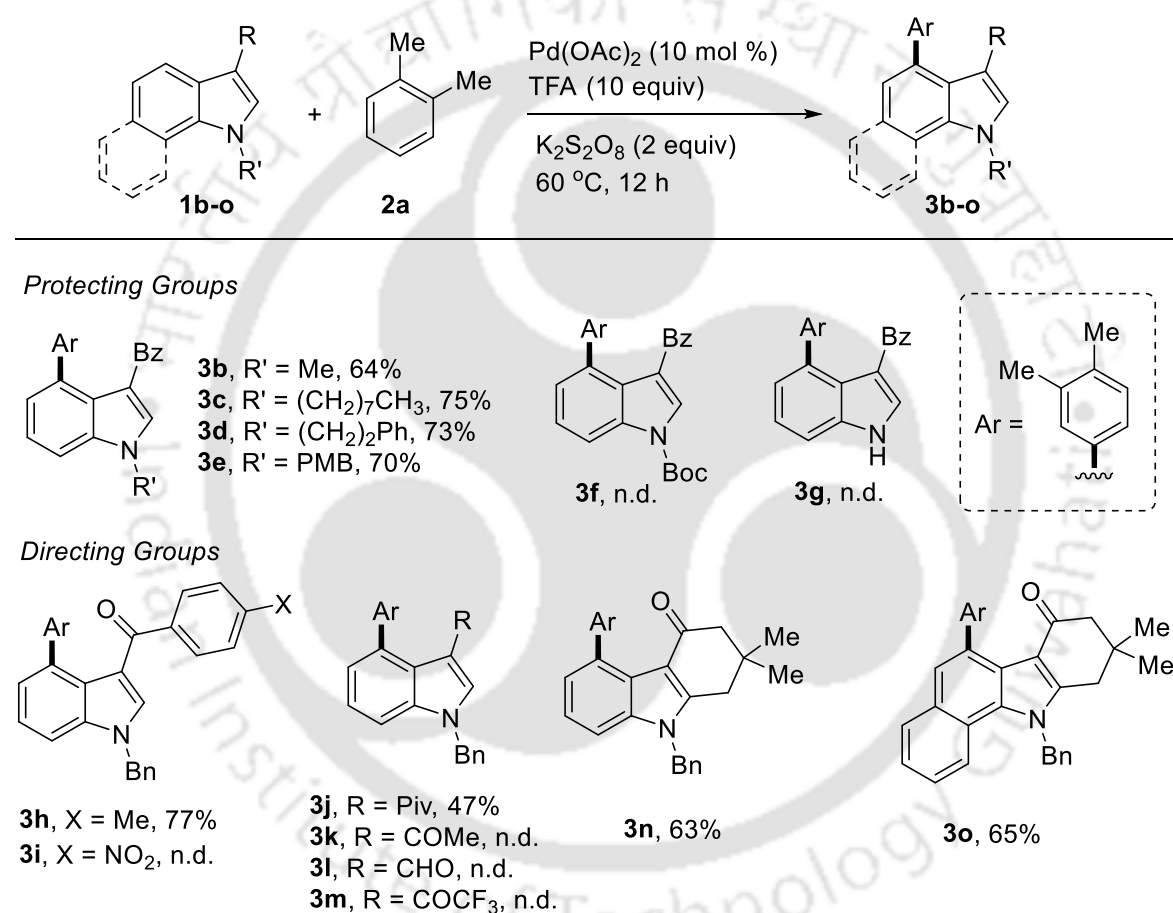
Table 1. Optimization of the Reaction Conditions^a

Entry	[Pd] Source	Oxidant	Additive	Yield (%) ^b
1	Pd(OAc) ₂	air	TFA	12
2	Pd(OAc) ₂	BQ	TFA	13
3 ^c	Pd(OAc) ₂	O ₂	TFA	68
4	Pd(OAc) ₂	<i>m</i> -CPBA	TFA	63
5	Pd(OAc) ₂	PIDA	TFA	10
6	Pd(OAc) ₂	Ag ₂ O	TFA	12
7	Pd(OAc) ₂	Cu(OAc) ₂	TFA	70
8	Pd(OAc) ₂	Na ₂ S ₂ O ₈	TFA	71
9	Pd(OAc)₂	K₂S₂O₈	TFA	83
10	Pd(OAc) ₂	K ₂ S ₂ O ₈	TfOH	n.d.
11	Pd(OAc) ₂	K ₂ S ₂ O ₈	AcOH	n.d.
12	Pd(TFA) ₂	K ₂ S ₂ O ₈	TFA	61
13	Pd(PPh ₃) ₂ Cl ₂	K ₂ S ₂ O ₈	TFA	n.d.
14	PdCl ₂	K ₂ S ₂ O ₈	TFA	n.d.
15 ^d	Pd(OAc) ₂	K ₂ S ₂ O ₈	TFA	65
16 ^e	Pd(OAc) ₂	K ₂ S ₂ O ₈	TFA	68
17 ^f	Pd(OAc) ₂	K ₂ S ₂ O ₈	---	n.d.
18	---	K ₂ S ₂ O ₈	TFA	n.d.
19 ^g	Pd(OAc) ₂	O ₂	TFA	73
20 ^h	Pd(OAc) ₂	O ₂	TFA	69
21 ⁱ	Pd(OAc) ₂	K ₂ S ₂ O ₈	TFA	65

^a Reaction conditions: **1a** (0.1 mmol), **2a** (1.0 mL), [Pd] source (10 mol %), oxidant (0.2 mmol), additive (1 mmol), 60 °C, 12 h, air. ^b Isolated yield. ^c O₂ balloon. ^d 5.0 equiv TFA used. ^e 1.0 equiv K₂S₂O₈ used. ^f Reaction temperature 100 °C. ^g Cu(OTf)₂ (20 mol %) used ^h AgOAc (20 mol %) used. ⁱ **2a** (0.5 mL) used. TFA= Trifluoroacetic acid. n.d. = not detected.

trifluoroacetic acid (TFA) at 60 °C for 12 h under aerobic condition (entry 1). In a set of subsequent oxidants screened, BQ, O₂, *m*-CPBA, PIDA, Ag₂O, Cu(OAc)₂, Na₂S₂O₈ and K₂S₂O₈, the latter led to improve the yield to 83% (entries 2-9). The reaction using TFA was superior to triflic acid (TfOH) and acetic acid (AcOH) (entries 10-11). Among the Pd-sources, Pd(OAc)₂ was found to be more effective compared to Pd(TFA)₂, Pd(PPh₃)₂Cl₂ and PdCl₂ (entries 12-14). Control experiments confirmed that the combination of the oxidant and additive was crucial to accomplish the cross-dehydrogenative *sp*² C-C coupling (entries 15-21).

Table 2. *N*-Protecting and Directing Groups Screening^{a,b}

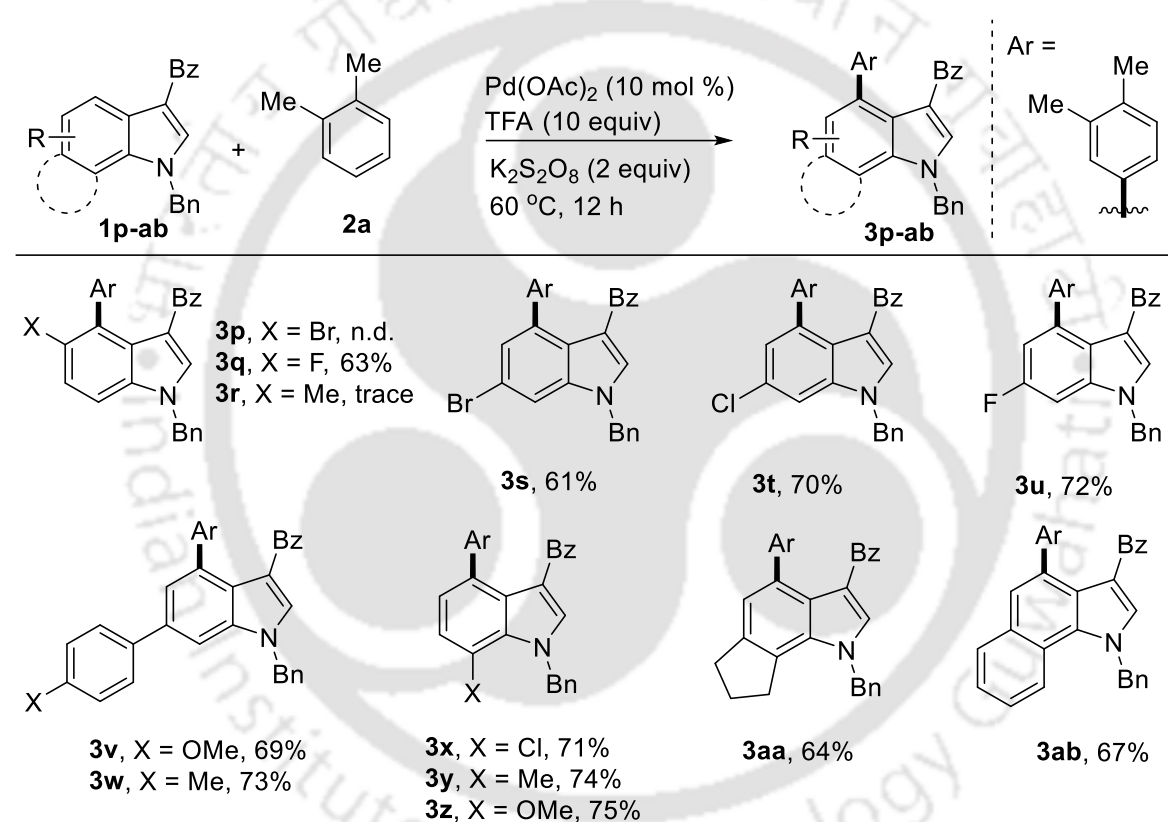


^aReaction conditions: **1b-o** (0.1 mmol), **2a** (1.0 mL), Pd(OAc)₂ (10 mol %), K₂S₂O₈ (0.2 mmol), TFA (1 mmol), 60 °C, 12 h, air. ^bIsolated yield. n.d. = not detected.

Further, the effect of the *N*-protecting and DGs was evaluated (Table 2). The substrates having methyl **1b**, octyl **1c**, phenylethyl **1d** and *p*-methoxybenzyl **1e** protecting groups were compatible, producing **3b-e** in 64-75% yields. In contrast, Boc-protected **1f** was an unsuccessful substrate, which might be attributed to the deprotection of Boc group. Owing to the possible chelation of the NH group with Pd-catalyst, the unprotected indole **1g** failed to

deliver the target product. In the context of the DGs, the substrate having 4-methyl group in aryl ring underwent reaction to provide **3h** in 77% yield, whereas electron withdrawing 4-nitro substituted **1i** conveyed no arylation. In addition, C3-pivaloyl indole **1j** showed moderate reactivity with longer reaction time (48 h), whereas acetyl **1k**, formyl **1l** and trifluoro acetyl **1m** DGs were ineffective. However, indoles having cyclic carbonyl congeners **1n** and **1o** were amenable to furnish **3n** and **3o** in 63% and 65% yields, respectively. These results suggest that the electronic nature of the chelating carbonyl group is crucial to accomplish the C4-H arylation.

Table 3. Scope of Indoles^{a,b}

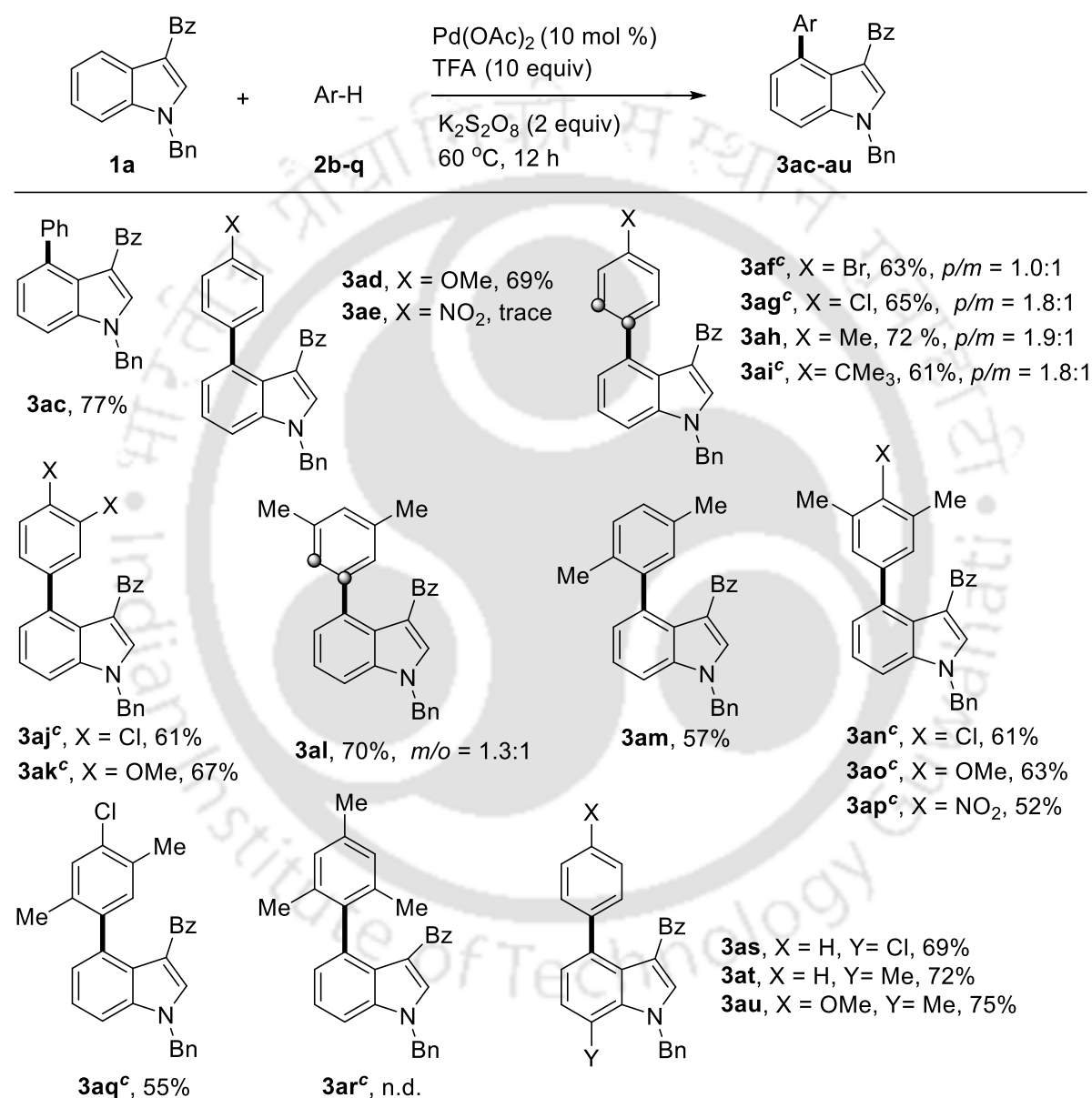


^aReaction conditions: **1p-ab** (0.1 mmol), **2a** (1.0 mL), $\text{Pd}(\text{OAc})_2$ (10 mol %), $\text{K}_2\text{S}_2\text{O}_8$ (0.2 mmol), TFA (1 mmol), 60 °C, 12 h, air. ^bIsolated yield. n.d. = not detected.

Having the optimal reaction conditions, the substrate scope was examined with an array of substituted indoles **1p-ab** with *o*-xylene **2a** as a test substrate (Table 3). Indoles with 5-bromo **1p** and 5-methyl **1r** substituents were the unsuccessful substrates, which might be due to the steric hindrance near the reaction site. In contrast, 5-fluoroindole **1q** underwent reaction to afford **3q** in 63% yield. Moreover, indoles having bromo **1s**, chloro **1t**, fluoro **1u**, *p*-methoxyphenyl **1v** and *p*-tolyl **1w** substituents at the 6-position reacted to deliver **3s-w** in 61-

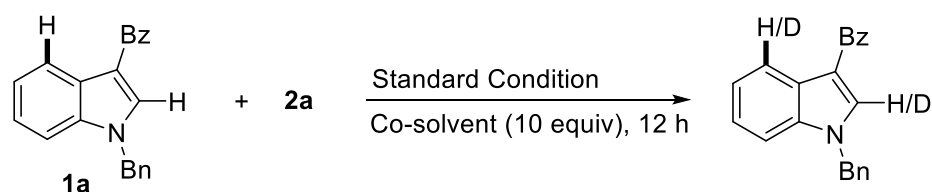
73% yields. A pertinent outcome was perceived with indoles bearing chloro **1x**, methyl **1y** and methoxy **1z** groups at the C7-site, giving **3x-z** in 71-75% yields. Further, fused indole analogues **1aa** and **1ab** arylated to afford **3aa** and **3ab** in 64% and 67% yields, respectively.

Table 4. Scope of Arenes^{a,b}



^aReaction conditions: **1a** (0.1 mmol), **2b-q** (1.0 mL), Pd(OAc)₂ (10 mol %), K₂S₂O₈ (0.2 mmol), TFA (1 mmol), 60 °C, 12 h, air. ^bIsolated yield. ^cReaction at 100 °C for 18 h. n.d. = not detected.

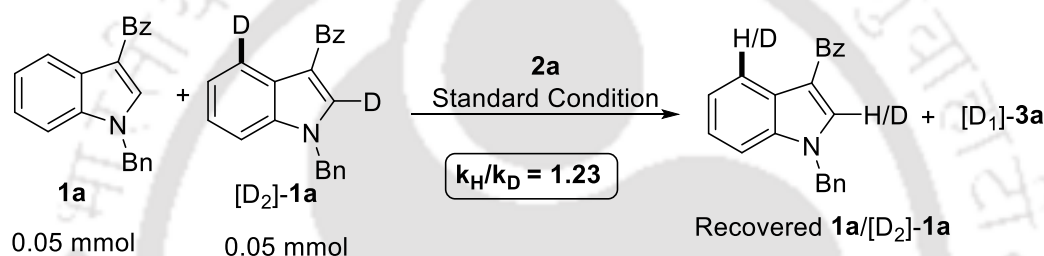
a. H/D-exchange experiments



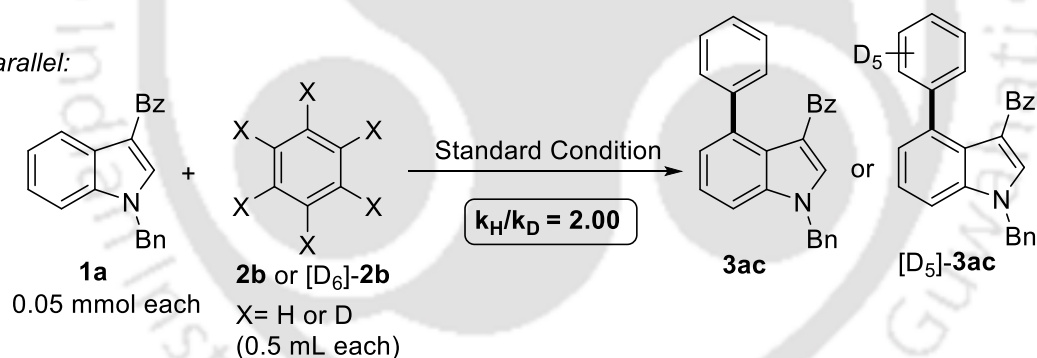
Co-solvent	C2-H deuteration	C4-H deuteration
with CD ₃ COOD	no deuteration	no deuteration
with CD ₃ OD	no deuteration	no deuteration

b. Kinetic Isotope Experiments

Intermolecular:



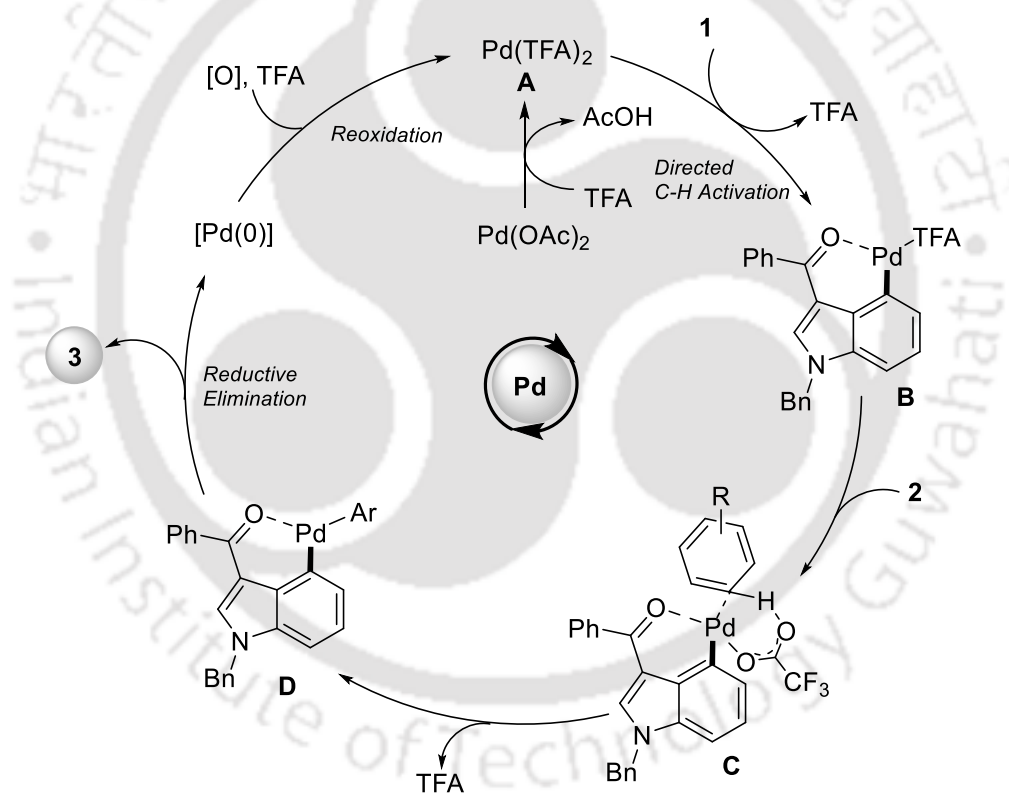
Parallel:



Scheme 11. Preliminary Mechanistic Findings

Next, the arylation procedure was extended to the coupling of arenes **2b-q** using **1a** as a standard substrate (Scheme 5). Benzene **2b** was successfully coupled to afford **3ac** in 77% yield. The reaction using anisole **2c** furnished **3ad** in 69% yield with *para* selectivity, whereas electron deficient nitrobenzene **2d** was proved to be an unsuccessful substrate. However, the coupling of toluene **2g** delivered a 1.9:1 (*p/m*) mixture of **3ah** in 72% yield, while monosubstituted arenes with bromo **2e**, chloro **2f** and *t*-butyl **2h** groups reacted at 100 °C with longer time to yield **3af** (63%, *p/m* = 1.0:1), **3ag** (65%, *p/m* = 1.8:1) and **3ai** (61%, *p/m* = 1.8:1), respectively. These outcomes indicate that the steric effect of the substituents rather than the electronic factor plays a pivotal role in determining the selectivity. In addition, the reaction of

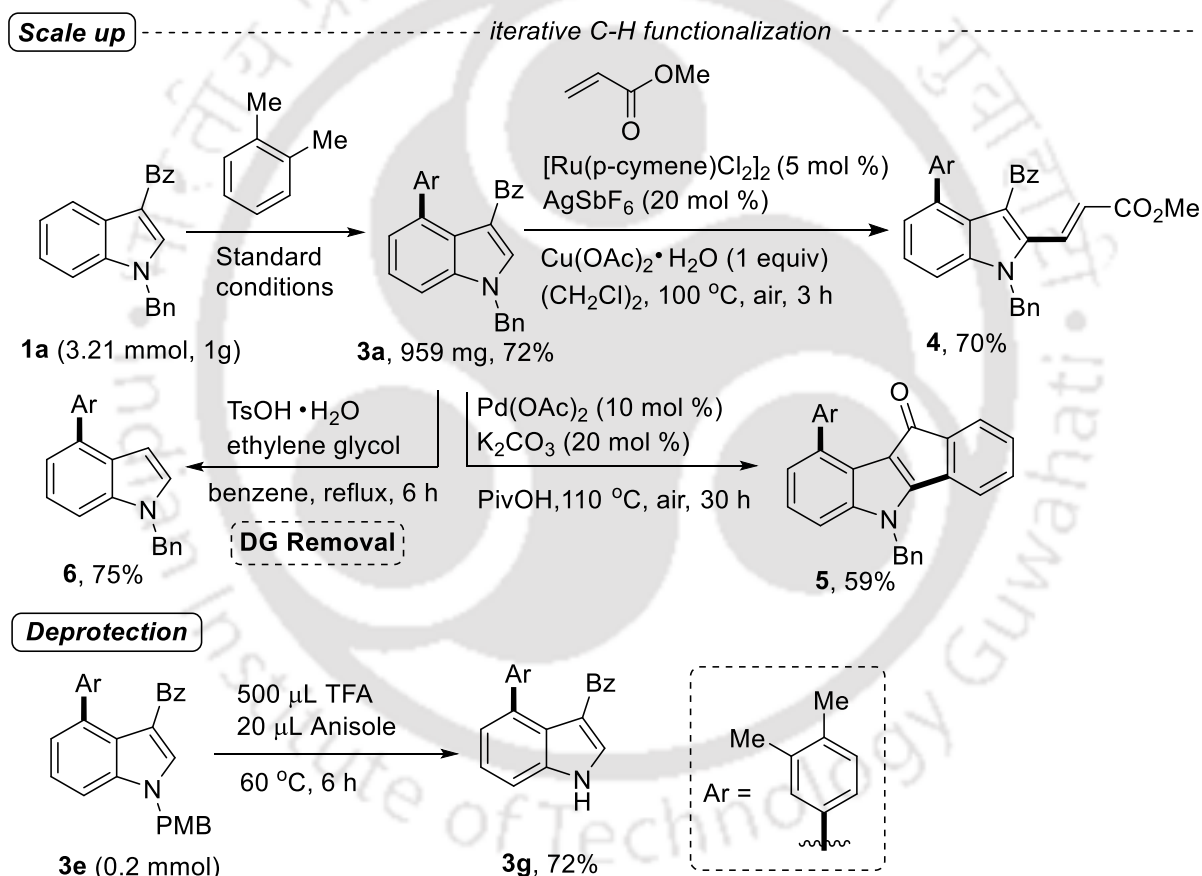
arenes having 1,2-dichloro **2i** and 1,2-dimethoxy **2j** groups furnished **3aj** and **3ak** in 61% and 67% yields, respectively. Further, *m*-xylene **2k** underwent reaction to produce a 1.3:1 mixture of regioisomers **3al** in 70% yield, whereas *p*-xylene **2l** coupled to deliver **3am** in 57% yield. However, 1,2,3-trisubstituted arenes **2m-o** with chloro, methyl, methoxy and nitro groups were reacted at the elevated temperature (100 °C), affording **3an-ap** in 52-63% yields. Pertinently, 1,2,5-trisubstituted arene **2p** with chloro and methyl substituents produced **3aq** in 55% yield, whose structure was determined using a single crystal X-ray analysis. Due to the steric hindrance, mesitylene **2q** was found to be an unsuccessful coupling partner. However, the arenes **2b-c** successfully coupled with indoles having substitution at the 7-position with chloro **1x** and methyl **1y** groups to afford **3as-au** in 69-75% yields.



Scheme 12. Proposed Catalytic Cycle

To shed light on the reaction mechanism, H/D exchange and kinetic isotope experiments were executed (Scheme 11). No H/D scrambling was observed either at C4 or C2 position in presence D₃COOD or CD₃OD as the co-solvents, respectively, indicating the irreversibility of the initial C-H activation step (Scheme 11a). When **2a** was treated with CD₃COOD under standard conditions, no deuterium incorporation was detected. Moreover, the intermolecular

kinetic isotope experiments of **1a** and [D₂]-**1a** utilizing **2a** yielded $k_H/k_D = 1.23$, which indicates that the first C-H bond cleavage might not be involved in the rate-determining step (Scheme 11b). However, the parallel experiment of **2b** or [D₆]-**2b** using **1a** $k_H/k_D = 2.00$, which suggests that the arene C-H bond activation might be the rate limiting step. These experimental results and literatures reports²² suggest that the *in-situ* generated active Pd(II) complex²³ **A** activates the C4-H bond of **1** with the aid of directing auxiliary to form a six membered palladacycle **B** (Scheme 12). Subsequently, the coordination of arene **2** to the metal centre may produce **C** that can seamlessly undergo non-directed C(sp²)-H cleavage of arene to afford **D**. Reductive elimination can give C4-arylated indole and Pd(0) species, which can be oxidized by K₂S₂O₈ in the presence of TFA to regenerate of active Pd(II) catalyst and complete the cycle.



Scheme 13. Post-Synthetic Utilities

To demonstrate the scale-up of the procedure, the direct coupling of **1a** with **2a** was investigated as the representative examples (Scheme 13). The target product **3a** was obtained in 72% (959 mg) yield, implied the reaction is scalable. Moreover, the C-4 arylated indoles **3a** was subjected to a series of synthetic transformations to afford diverse scaffolds. For instances, the Ru-catalyzed C2-H alkenylation of **3a** using methyl acrylate delivered **4** in 70% yield,

whereas the intramolecular C-C coupling furnished **5** in 59% yield. Further, the Bz auxiliary was successfully removed using TsOH to give **6** in 75 % yield. Moreover, the removal of PMB was accomplished to furnish **3g** in 72% yield.

In summary, we have developed the Pd-catalyzed weak chelating Bz DG enabled C4-H arylation of indoles using arenes as the aryl source. The two-fold C-H activation/C-C bond formation, exclusive site-selectivity, functional group tolerance and late-stage modifications are the salient features.

2.4 Experimental Section

General Information. Indole, Pd(OAc)₂ (≥99.9%), Pd(TFA)₂ (97%), Pd(PPh₃)₂Cl₂ (98%), PdCl₂ (>98%), [Ru(*p*-cymene)Cl₂]₂ (>95%), AgSbF₆ (99%), Cu(OAc)₂·H₂O (≥98%), BQ (>97%), *m*-CPBA (≥77%), PIDA (98%), Ag₂O (99%), Cu(OAc)₂ (≥98%), Na₂S₂O₈ (≥98.0%) and K₂S₂O₈ (≥99.9%) and arenes (**2a-q**) of Aldrich and TCI Chemicals used as received. The substrates *N*-alkyl 3-acyl indoles **1** were prepared according to the reported procedures.²⁴ Merck silica gel G/GF254 plates used for analytical thin-layer chromatography (TLC). Rankem silica gel (60-120 mesh) utilized for column chromatography. Bruker Avance III 600, 500 and 400 MHz spectrometers used for NMR spectra using tetramethylsilane (Me₄Si) as an internal standard. Chemical shifts (δ) and spin-spin coupling constant (*J*) are reported in parts per million and hertz (Hz), respectively, and other data are reported as follows: s = singlet, d = doublet, t = triplet, m = multiplet, dd = double doublet. Melting points were determined using a Büchi B-540 apparatus and are uncorrected. IR spectra were collected on a PerkinElmer Fourier transform infrared (FT-IR) spectrometer. Quadrupole time-of-flight electrospray ionization (ESI) mass spectrometer (model HAB 273) used for recording HRMS. Single-crystal X-ray data collected on a Bruker APEX II equipped with a charge-coupled device area detector Mo-K α radiation, and the structure was solved by direct method using SHELXL-2014 (Göttingen, Germany).

General Procedure for Pd(II)-Catalyzed C4-Arylation of Indoles. Indole **1** (0.1 mmol), arene **2** (1 mL), Pd(OAc)₂ (10 mol %, 2.24 mg), K₂S₂O₈ (0.2 mmol, 54 mg) and TFA (1 mmol) were stirred at 60 °C in a preheated oil bath for 12 h under air. The progress of the reaction was monitored using TLC. After completion, the reaction mixture was cooled to room temperature and extracted with EtOAc (3 x 10 mL). The combined organic layer was washed with saturated NaHCO₃ (2 x 5 mL) and water (2 x 5 mL). Drying (Na₂SO₄) and evaporation of the solvent

gave a residue that was purified on silica gel column chromatography using hexane and ethyl acetate as an eluent to afford C4-arylated indole **3** in good to moderate yield.

H/D Exchange Experiment of **1a with CD₃COOD or CD₃OD in presence of **2a**.** To a stirred solution of (1-benzyl-1*H*-indol-3-yl)(phenyl)methanone **1a** (0.1 mmol, 31 mg), *o*-xylene **2a** (1 mL), Pd(OAc)₂ (10 mol %, 0.01 mmol, 2.24 mg), K₂S₂O₈ (0.2 mmol, 54 mg), TFA (1 mmol) and deuterated solvent (CD₃COOD or CD₃OD, 1 mmol) were added. The reaction mixture was stirred at 60 °C in a preheated oil bath for 12 h under air. The resulting reaction mixture was cooled to room temperature, extracted with EtOAc (3 x 10 mL) and washed with saturated NaHCO₃ solution (2 x 5 mL) and water (2 x 5 mL). The purification was carried out according to the general procedure as described above. No deuterium incorporation was observed either at C4 and C2 position of recovered **1a**, based on 600 MHz ¹H NMR spectrum.

Preparation of (1-Benzyl-1*H*-indol-3-yl-2,4-*d*₂)(phenyl)methanone [D₂]-1a**.** In a Teflon capped sealed tube, (1-benzyl-1*H*-indol-3-yl)(phenyl)methanone **1a** (0.1 mmol, 31 mg), [Cp**Rh*Cl₂]₂ (2.5 mol %, 0.0025 mmol, 1.5 mg), AgSbF₆ (0.02 mmol, 6.8 mg), Cu(OAc)₂ (0.1 mmol, 18 mg) and D₂O (0.4 mmol, 80 μL) was stirred in 1,4-dioxane (1.5 mL) at 120 °C in a preheated oil bath for 14 h. The resulting mixture was diluted with CH₂Cl₂ (10 mL) and passed through a short pad of celite using CH₂Cl₂ (2 x 10 mL). Drying (Na₂SO₄) and evaporation of the solvent gave a residue that was purified on silica gel column chromatography using hexane and ethyl acetate as an eluent to afford [D₂]-**1a** as an orange solid in 87% yield (27 mg). The deuterium incorporation was determined using 600 MHz ¹H NMR as 82% at C4-H.

Kinetic Isotope Effect Experiments.

Intermolecular Experiment. (1-Benzyl-1*H*-indol-3-yl)(phenyl) methanone **1a** (0.05 mmol, 15.5 mg) and (1-benzyl-1*H*-indol-3-yl-2,4-*d*₂)(phenyl)methanone [D₂]-**1a** (0.05 mmol, 15.6 mg) were stirred with *o*-xylene **2a** (1 mL) for 30 min under above reported standard reaction conditions. The resulting mixture was cooled to room temperature, extracted with EtOAc (3 x 10 mL) and washed with saturated NaHCO₃ (2 x 5 mL) and water (2 x 5 mL). Drying (Na₂SO₄) and evaporation of the solvent gave a residue that was purified on silica gel column chromatography using hexane and ethyl acetate as an eluent to afford [D₁]-**3a** and a mixture of unreacted **1a** and [D₂]-**1a** as a colourless solid. The intermolecular *k_H/k_D* was found to be 1.23, based on 400 MHz ¹H NMR of the recovered substrate **1a** and [D₂]-**1a**.

Parallel Experiment. Two sets of experiments were performed: in the first set, **1a** (0.05 mmol, 15.5 mg) and **2b** (0.5 mL) were reacted, and in another set, **1a** (0.05 mmol, 15.5 mg) and [D₆]-

2b (0.5 mL) were reacted at 60 °C for 0.5 h in an oil bath. For both reactions, the work up was followed as described in the general procedure. The conversions of **3ac** and [D₅]-**3ac** were determined using 600 MHz ¹H NMR analysis of the crude product using mesitylene (0.025 mmol, 3.50 μL) as an internal standard and the *k_H/k_D* value was found to be 2.00.

Scale-up synthesis of 3a. (1-Benzyl-1*H*-indol-3-yl)(phenyl)methanone **1a** (3.21 mmol, 1 g), *o*-xylene **2a** (30 mL), Pd(OAc)₂ (10 mol %, 70 mg), K₂S₂O₈ (6.42 mmol, 1.7 g) and TFA (32 mmol) were stirred at 60 °C in a preheated oil bath for 12 h under air. After completion (monitored by TLC), the reaction mixture was cooled to room temperature and extracted with EtOAc (3 x 20 mL). The combined organic layer was washed with saturated NaHCO₃ (2 x 10 mL) and water (2 x 10 mL). Drying (Na₂SO₄) and evaporation of the solvent gave a residue that was purified on silica gel column chromatography using *n*-hexane and ethyl acetate as an eluent to afford **3a** in 72 % (959 mg) yield.

Synthesis of 4.²⁵ (1-Benzyl-4-(3,4-dimethylphenyl)-1*H*-indol-3-yl)(phenyl)methanone **3a** (0.1 mmol, 41 mg), [Ru(*p*-cymene)Cl₂]₂ (5 mol %, 3 mg), AgSbF₆ (0.02 mmol, 6.8 mg), Cu(OAc)₂·H₂O (0.1 mmol, 20 mg) and methyl acrylate (0.12 mmol) were stirred at 100 °C in 1,2-dichloroethane (2 mL) under air for an appropriate time. After completion (monitored by TLC), the reaction mixture was cooled to room temperature and diluted with CH₂Cl₂ (10 mL) and passed through a short pad of celite using CH₂Cl₂ (20 mL). Evaporation of the solvent gave a residue that was purified on silica gel column chromatography using *n*-hexane and ethyl acetate as an eluent to afford **4** in 70 % (35 mg) yield.

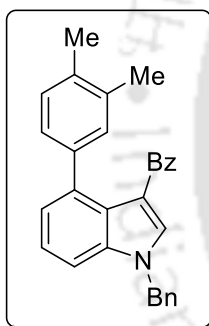
Synthesis of 5.²⁶ (1-Benzyl-4-(3,4-dimethylphenyl)-1*H*-indol-3-yl)(phenyl)methanone **3a** (0.1 mmol, 41mg), Pd(OAc)₂ (0.01 mmol, 2.24 mg), K₂CO₃ (0.02 mmol, 3 mg) and pivalic acid (100 μL) were stirred at 110 °C in a preheated oil bath for 30 h under air. After completion (monitored by TLC), the reaction mixture was cooled to room temperature and extracted with EtOAc (3 x 10 mL) and washed with saturated Na₂CO₃ (1 x 5 mL) and water (2 x 5 mL). Drying (Na₂SO₄) and evaporation of the solvent gave a residue that was purified on silica gel column chromatography using *n*-hexane and ethyl acetate as an eluent to afford **5** in 59 % (24 mg) yield.

Removal of Benzoyl DG.⁶ (1-Benzyl-4-(3,4-dimethylphenyl)-1*H*-indol-3-yl)(phenyl)methanone **3a** (0.1 mmol, 41 mg), ethylene glycol (0.1 mL) and *p*-toluenesulfonic acid monohydrate (0.1 mmol, 21 mg) were stirred for 6 h in benzene (2 mL) under reflux. After the completion (monitored by TLC), the reaction mixture was cooled to room temperature and extracted using

EtOAc (3 x 10 mL) and washed with saturated NaHCO₃ (2 x 5 mL) and water (2 x 5 mL). Drying (Na₂SO₄) and evaporation of the solvent gave a residue that was purified on silica gel column chromatography using n-hexane and ethyl acetate as an eluent to afford **6** in 75 % (23 mg) yield.

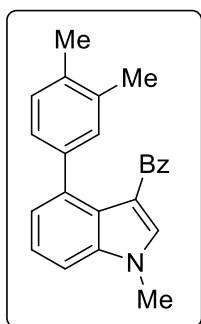
Synthetic Procedure of 3g.²⁷ (4-(3,4-Dimethylphenyl)-1-(4-methoxybenzyl)-1H-indol-3-yl)(phenyl)methanone **3e** (0.2 mmol, 89 mg), TFA (500 μ L) and anisole (20 μ L) were stirred at 60 °C for 6 h under air. After completion (monitored by TLC), the resultant mixture was cooled to room temperature and extracted with EtOAc (3 x 10 mL). The organic layer was washed with saturated NaHCO₃ (2 x 10 mL) and water (2 x 10 mL). Drying (Na₂SO₄) and evaporation of the solvent gave a residue that was purified on silica gel column chromatography using n-hexane and ethyl acetate as an eluent to afford **3g** in 72 % (46.8 mg) yield.

2.5 Characterization Data of the Products



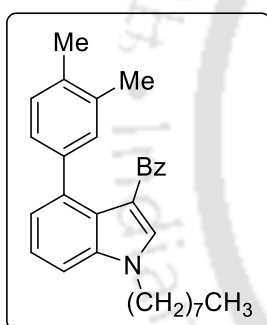
(1-Benzyl-4-(3,4-dimethylphenyl)-1H-indol-3-yl)(phenyl)methanone **3a**.

Analytical TLC on silica gel, 1:5 ethyl acetate/hexane R_f = 0.50; light brown solid; mp 153-154 °C; yield 83% (34.4 mg); ¹H NMR (400 MHz, CDCl₃) δ 7.57 (s, 1H), 7.51-7.48 (m, 2H), 7.36-7.30 (m, 6H), 7.21-7.13 (m, 5H), 6.98-6.97 (m, 2H), 6.89-6.87 (m, 1H), 5.40 (s, 2H), 2.15 (s, 3H), 2.07 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 191.7, 139.8, 139.5, 137.6, 136.9, 136.2, 136.0, 134.9, 134.6, 131.3, 130.0, 129.5, 129.4, 129.1, 128.2, 127.5, 127.1, 126.0, 125.1, 123.5, 123.2, 118.0, 109.0, 50.9, 19.7, 19.5; FT-IR (KBr) 2921, 2853, 1732, 1640, 1522, 1450, 1387, 1263, 1174, 742 cm⁻¹; HRMS (ESI) m/z [M+H]⁺ calcd for C₃₀H₂₆NO: 416.2009, found 416.2009.



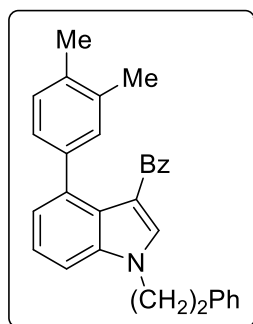
(4-(3,4-Dimethylphenyl)-1-methyl-1*H*-indol-3-yl)(phenyl)methanone 3b.

Analytical TLC on silica gel, 1:5 ethyl acetate/hexane $R_f = 0.54$; light yellow solid; mp 175-176 °C; yield 64% (21 mg); $^1\text{H NMR}$ (600 MHz, CDCl_3) δ 7.51-7.50 (m, 3H), 7.41-7.34 (m, 3H), 7.21-7.16 (m, 3H), 6.98-6.97 (m, 2H), 6.89-6.87 (m, 1H), 3.88 (s, 3H), 2.15 (s, 3H), 2.08 (s, 3H); $^{13}\text{C NMR}$ (150 MHz, CDCl_3) δ 191.5, 139.9, 139.5, 138.1, 136.8, 135.9, 135.6, 134.8, 131.3, 129.9, 129.5, 129.3, 127.5, 126.0, 124.8, 123.4, 123.1, 117.4, 108.4, 33.6, 19.8, 19.5; FT-IR (KBr) 2920, 1637, 1522, 1445, 1365, 1237, 1154, 1068, 868, 791, 744, 711 cm^{-1} ; HRMS (ESI) m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{24}\text{H}_{22}\text{NO}$: 340.1696, found 340.1696.



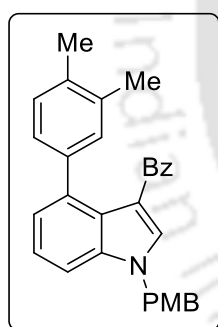
(4-(3,4-Dimethylphenyl)-1-octyl-1*H*-indol-3-yl)(phenyl)methanone

3c. Analytical TLC on silica gel, 1:5 ethyl acetate/hexane $R_f = 0.55$; light brown solid; mp 92-93 °C; yield 75% (32.8 mg); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.53 (s, 1H), 7.51-7.49 (m, 2H), 7.37-7.33 (m, 3H), 7.21-7.14 (m, 3H), 6.99-6.98 (m, 2H), 6.89-6.87 (m, 1H), 4.18 (t, $J = 7.2$ Hz, 2H), 2.15 (s, 3H), 2.08 (s, 3H), 1.93-1.89 (m, 2H), 1.35-1.26 (m, 10H), 0.89-0.86 (m, 3H); $^{13}\text{C NMR}$ (125 MHz, CDCl_3) δ 191.6, 140.0, 139.6, 137.4, 136.9, 135.9, 134.8, 134.5, 131.2, 129.9, 129.5, 129.4, 127.5, 126.0, 125.0, 123.2, 123.0, 117.4, 108.6, 47.2, 31.8, 30.0, 29.28, 29.26, 27.1, 22.7, 19.7, 19.5, 14.1; FT-IR (KBr) 2922, 2855, 1732, 1638, 1521, 1455, 1387, 1261, 1174, 737 cm^{-1} ; HRMS (ESI) m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{31}\text{H}_{36}\text{NO}$: 438.2791, found 438.2791.



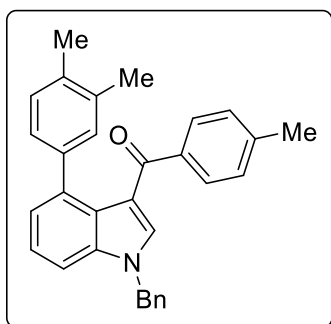
(4-(3,4-Dimethylphenyl)-1-phenethyl-1H-indol-3-

yl)(phenyl)methanone 3d. Analytical TLC on silica gel, 1:5 ethyl acetate/hexane $R_f = 0.49$; colorless solid; mp 123-124 °C; yield 73% (31.3 mg); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.34-7.32 (m, 2H), 7.29-7.24 (m, 3H), 7.22-7.14 (m, 4H), 7.11-7.07 (m, 3H), 7.00-6.99 (m, 2H), 6.90-6.88 (m, 2H), 6.81-6.80 (m, 1H), 4.32 (t, $J = 7.2$ Hz, 2H), 3.09 (t, $J = 7.2$ Hz, 2H), 2.07 (s, 3H), 2.00 (s, 3H); $^{13}\text{C NMR}$ (150 MHz, CDCl_3) δ 191.2, 139.8, 139.5, 137.9, 137.0, 136.9, 135.9, 135.1, 134.8, 131.2, 129.8, 129.4, 129.3, 129.0, 128.8, 127.5, 127.0, 126.0, 125.0, 123.3, 123.2, 117.1, 108.5, 48.8, 36.3, 19.8, 19.5; FT-IR (KBr) 2918, 2851, 1733, 1639, 1521, 1457, 1389, 1264, 1175, 746 cm^{-1} ; HRMS (ESI) m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{31}\text{H}_{28}\text{NO}$: 430.2165, found 430.2188.



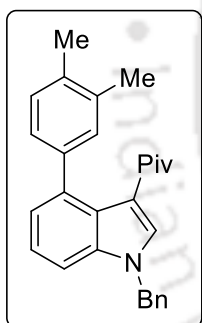
(4-(3,4-Dimethylphenyl)-1-(4-methoxybenzyl)-1H-indol-3-

yl)(phenyl)methanone 3e. Analytical TLC on silica gel, 1:5 ethyl acetate/hexane $R_f = 0.43$; orange thick liquid; yield 70% (31 mg); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.48 (s, 1H), 7.44 (d, $J = 7.6$ Hz, 2H), 7.29-7.24 (m, 3H), 7.13-7.07 (m, 5H), 6.92-6.90 (m, 2H), 6.82-6.79 (m, 3H), 5.24 (s, 2H), 3.71 (s, 3H), 2.08 (s, 3H), 2.01 (s, 3H); $^{13}\text{C NMR}$ (125 MHz, CDCl_3) δ 191.7, 159.5, 139.8, 139.5, 137.6, 136.8, 135.9, 134.8, 134.5, 131.3, 129.9, 129.5, 129.3, 128.6, 128.0, 127.5, 126.0, 125.2, 123.4, 123.1, 117.8, 114.5, 109.0, 55.4, 50.4, 19.7, 19.4; FT-IR (neat) 2925, 1638, 1514, 1441, 1385, 1245, 1172, 1029, 819, 745 cm^{-1} ; HRMS (ESI) m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{31}\text{H}_{28}\text{NO}_2$: 446.2115, found 446.2115.



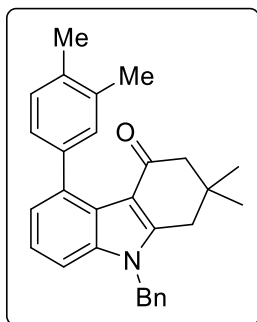
(1-Benzyl-4-(3,4-dimethylphenyl)-1H-indol-3-yl)(p-

tolyl)methanone 3h. Analytical TLC on silica gel, 1:5 ethyl acetate/hexane $R_f = 0.50$; light brown solid; mp 142-143 °C; yield 77% (33 mg); ^1H NMR (600 MHz, CDCl_3) δ 7.46 (s, 1H), 7.35 (d, $J = 7.8$ Hz, 2H), 7.25-7.20 (m, 5H), 7.11-7.09 (m, 2H), 7.07-7.05 (m, 1H), 6.91-6.90 (m, 4H), 6.81-6.79 (m, 1H), 5.28 (s, 2H), 2.24 (s, 3H), 2.07 (s, 3H), 1.99 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 191.4, 142.0, 139.5, 137.6, 137.3, 136.9, 136.2, 136.0, 134.8, 134.4, 130.0, 129.6, 129.3, 129.1, 128.2, 128.1, 127.1, 126.1, 125.1, 123.4, 123.1, 118.1, 108.9, 50.8, 21.6, 19.7, 19.5; FT-IR (KBr) 2919, 2852, 1733, 1638, 1523, 1447, 1388, 1260, 1174, 748 cm^{-1} ; HRMS (ESI) m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{31}\text{H}_{28}\text{NO}$: 430.2165, found 430.2175.

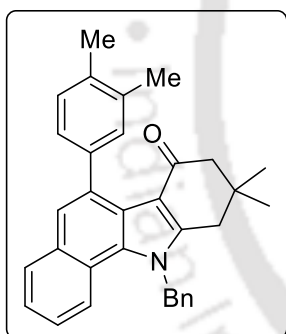


1-(1-Benzyl-4-(3,4-dimethylphenyl)-1H-indol-3-yl)-2,2-dimethylpropan-

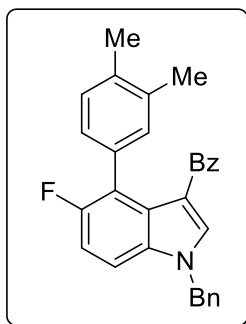
1-one 3j. Analytical TLC on silica gel, 1:5 ethyl acetate/hexane $R_f = 0.60$; brown solid; mp 136-137 °C; yield 47% (18.5 mg); ^1H NMR (400 MHz, CDCl_3) δ 7.36 (s, 1H), 7.28-7.19 (m, 3H), 7.18-7.13 (m, 2H), 7.09-7.04 (m, 6H), 5.28 (s, 2H), 2.21 (d, $J = 6$ Hz, 6H), 1.03 (s, 9H); ^{13}C NMR (100 MHz, CDCl_3) δ 205.7, 139.7, 137.1, 136.7, 136.5, 135.8, 135.0, 130.2, 129.5, 129.3, 129.0, 128.1, 126.9, 126.1, 125.0, 123.3, 123.1, 117.0, 108.7, 50.6, 44.5, 28.0, 19.9, 19.6; FT-IR (KBr) 2919, 2852, 1732, 1659, 1525, 1458, 1265, 1179, 746 cm^{-1} ; HRMS (ESI) m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{28}\text{H}_{30}\text{NO}$: 396.2322, found 396.2322.

**9-Benzyl-5-(3,4-dimethylphenyl)-2,2-dimethyl-1,2,3,9-tetrahydro-**

4H-carbazol-4-one 3n. Analytical TLC on silica gel, 1:5 ethyl acetate/hexane $R_f = 0.54$; colorless solid; mp 118-119 °C; yield 63% (25.6 mg); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.34-7.28 (m, 3H), 7.25-7.22 (m, 2H), 7.21-7.15 (m, 3H), 7.11-7.09 (m, 1H), 7.03-7.02 (m, 2H), 5.39 (s, 2H), 2.76 (s, 2H), 2.37 (s, 2H), 2.34 (d, $J = 6.4$ Hz, 6H), 1.09 (s, 6H); $^{13}\text{C NMR}$ (150 MHz, CDCl_3) δ 190.7, 151.1, 140.7, 138.3, 137.2, 136.1, 135.1, 134.7, 130.3, 129.2, 128.3, 128.0, 127.3, 126.0, 125.3, 123.0, 122.5, 112.8, 108.3, 53.0, 47.0, 36.8, 35.1, 28.7, 20.1, 19.8; FT-IR (KBr) 2920, 2852, 1732, 1658, 1463, 1267, 1174, 753 cm^{-1} ; HRMS (ESI) m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{29}\text{H}_{30}\text{NO}$: 408.2322, found 408.2321.

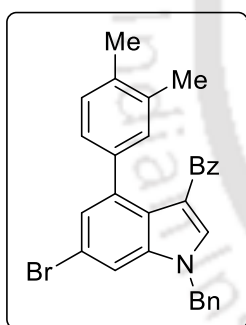
**11-Benzyl-6-(3,4-dimethylphenyl)-9,9-dimethyl-8,9,10,11-**

tetrahydro-7H-benzo[a]carbazol-7-one 3o. Analytical TLC on silica gel, 1:5 ethyl acetate/hexane $R_f = 0.53$; colorless solid; mp 129-130 °C; yield 65% (30 mg); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 8.05 (d, $J = 8.4$ Hz, 1H), 7.92 (d, $J = 8.0$ Hz, 1H), 7.60 (s, 1H), 7.39-7.35 (m, 3H), 7.33-7.28 (m, 3H), 7.19 (s, 2H), 7.15-7.13 (m, 2H), 5.83 (s, 2H), 2.80 (s, 2H), 2.40 (s, 2H), 2.36 (d, $J = 3.6$ Hz, 6H), 1.10 (s, 6H); $^{13}\text{C NMR}$ (150 MHz, CDCl_3) δ 191.4, 149.6, 141.0, 136.2, 136.0, 135.4, 134.8, 132.1, 131.7, 129.9, 129.49, 129.40, 128.6, 128.0, 126.7, 125.8, 125.7, 125.6, 124.3, 120.9, 120.7, 120.6, 113.7, 53.2, 50.1, 36.8, 35.2, 28.6, 20.1, 19.9; FT-IR (KBr) 2922, 2853, 1734, 1660, 1503, 1451, 1396, 1265, 736 cm^{-1} ; HRMS (ESI) m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{33}\text{H}_{32}\text{NO}$: 458.2478, found 458.2478.



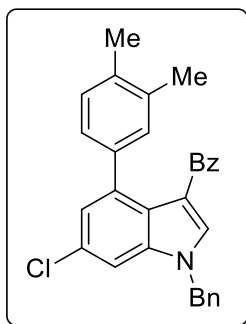
(1-Benzyl-4-(3,4-dimethylphenyl)-5-fluoro-1H-indol-3-

yl)(phenyl)methanone 3q. Analytical TLC on silica gel, 1:5 ethyl acetate/hexane $R_f = 0.48$; brown solid; mp 140-141 °C; yield 63% (27 mg); ^1H NMR (400 MHz, CDCl_3) δ 7.57 (s, 1H), 7.41-7.31 (m, 6H), 7.24-7.15 (m, 5H), 7.07 (t, $J = 9.6$ Hz, 1H), 6.93-6.86 (m, 3H), 5.37 (s, 2H), 2.14 (s, 3H), 2.04 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 191.6, 156.3 ($J_{\text{C-F}} = 235.1$ Hz), 139.3, 135.8 ($J_{\text{C-F}} = 5.0$ Hz), 135.3, 135.0, 133.6, 132.0, 131.2, 130.9, 129.4, 129.1 ($J_{\text{C-F}} = 12.1$ Hz), 128.2, 127.3, 127.0, 126.9, 126.84, 126.80, 122.0 ($J_{\text{C-F}} = 18.2$ Hz), 118.1, 118.0, 112.1 ($J_{\text{C-F}} = 28.0$ Hz), 110.0 ($J_{\text{C-F}} = 9.8$ Hz), 50.9, 19.5, 19.4; ^{19}F NMR (471 MHz, CDCl_3) δ -126.72.; FT-IR (KBr) 2923, 2854, 1732, 1641, 1521, 1444, 1389, 1259, 1186, 736 cm^{-1} ; HRMS (ESI) m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{30}\text{H}_{25}\text{FNO}$: 434.1915, found 434.1910.



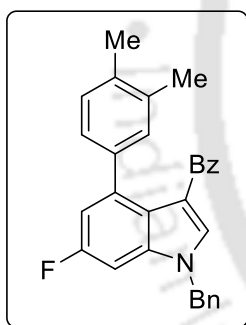
(1-Benzyl-6-bromo-4-(3,4-dimethylphenyl)-1H-indol-3-

yl)(phenyl)methanone 3s. Analytical TLC on silica gel, 1:5 ethyl acetate/hexane $R_f = 0.48$; Colorless solid; mp 118-119 °C; yield 61% (30.1 mg); ^1H NMR (400 MHz, CDCl_3) δ 7.45 (s, 1H), 7.38-7.36 (m, 3H), 7.32-7.23 (m, 4H), 7.19-7.18 (m, 1H), 7.13-7.08 (m, 4H), 6.86-6.84 (m, 2H), 6.80-6.78 (m, 1H), 5.27 (s, 2H), 2.07 (s, 3H), 1.99 (s, 3H).; ^{13}C NMR (150 MHz, CDCl_3) δ 191.5, 139.4, 138.34, 138.30, 138.1, 136.2, 135.6, 135.5, 134.7, 131.6, 129.8, 129.6, 129.3, 129.2, 128.4, 127.6, 127.0, 126.0, 125.9, 124.1, 118.1, 117.0, 111.8, 50.9, 19.7, 19.5. FT-IR (KBr) 2919, 2851, 1733, 1642, 1521, 1461, 1265, 1175, 747 cm^{-1} ; HRMS (ESI) m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{30}\text{H}_{25}\text{BrNO}$: 494.1114, found 494.1117.



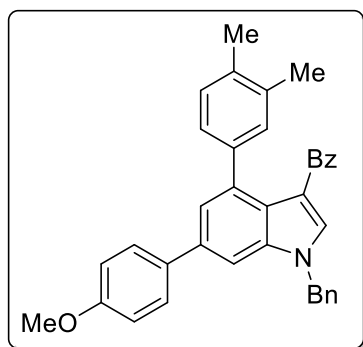
(1-Benzyl-6-chloro-4-(3,4-dimethylphenyl)-1H-indol-3-

yl)(phenyl)methanone **3t**. Analytical TLC on silica gel, 1:5 ethyl acetate/hexane $R_f = 0.47$; light brown solid; mp 108-109 °C; yield 70% (31.4 mg); ^1H NMR (400 MHz, CDCl_3) δ 7.54 (s, 1H), 7.46 (d, $J = 7.2$ Hz, 2H), 7.38 -7.29 (m, 5H), 7.20- 7.16 (m, 4H), 7.13-7.12 (m, 1H), 6.94-6.92 (m, 2H), 6.87-6.85 (m, 1H), 5.35 (s, 2H), 2.14 (s, 3H), 2.06 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 191.4, 139.5, 138.2, 138.09, 138.01, 136.2, 135.7, 135.5, 134.8, 131.6, 129.8, 129.6, 129.4, 129.3, 129.2, 128.4, 127.6, 127.1, 125.9, 123.8, 123.5, 118.1, 108.9, 50.9, 19.7, 19.5; FT-IR (neat) 2919, 2852, 1732, 1643, 1521, 1453, 1265, 1174, 886, 751 cm^{-1} ; HRMS (ESI) m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{30}\text{H}_{25}\text{ClNO}$: 450.1619, found 450.1626.



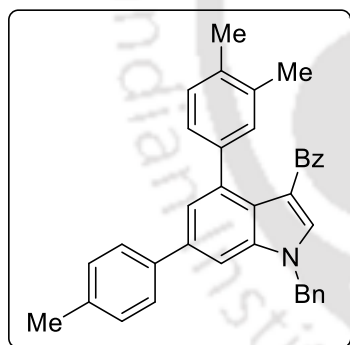
(1-Benzyl-4-(3,4-dimethylphenyl)-6-fluoro-1H-indol-3-

yl)(phenyl)methanone **3u**. Analytical TLC on silica gel, 1:5 ethyl acetate/hexane $R_f = 0.48$; colorless solid; mp 134-135 °C; yield 72% (31.2 mg); ^1H NMR (400 MHz, CDCl_3) δ 7.54 (s, 1H), 7.51-7.49 (m, 2H), 7.38-7.32 (m, 4H), 7.22-7.18 (m, 4H), 6.98-6.93 (m, 4H), 6.91-6.88 (m, 1H), 5.33 (s, 2H), 2.15 (s, 3H), 2.07 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 191.3, 161.5 ($J_{\text{C-F}} = 238.9$ Hz), 139.5, 138.4, 138.3 ($J_{\text{C-F}} = 9.7$ Hz), 137.8 ($J_{\text{C-F}} = 12.4$ Hz), 136.2, 135.7, 135.5, 134.9 ($J_{\text{C-F}} = 2.8$ Hz), 131.6, 129.8, 129.6, 129.3, 129.2, 128.4, 127.6, 127.0, 125.9, 121.6, 118.1, 111.7 ($J_{\text{C-F}} = 24.2$ Hz), 95.6 ($J_{\text{C-F}} = 26.1$ Hz), 51.0, 19.7, 19.5; ^{19}F NMR (377 MHz, CDCl_3) δ -118.68; FT-IR (KBr) 2922, 2853, 1732, 1641, 1523, 1451, 1265, 1168, 737 cm^{-1} ; HRMS (ESI) m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{30}\text{H}_{25}\text{FNO}$: 434.1915, found 434.1915.



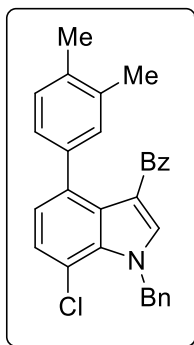
(1-Benzyl-4-(3,4-dimethylphenyl)-6-(4-methoxyphenyl)-1H-

indol-3-yl)(phenyl) methan-one 3v. Analytical TLC on silica gel, 1:5 ethyl acetate/hexane $R_f = 0.43$; light brown solid; mp 158-159 °C; yield 69% (35.9 mg); ^1H NMR (600 MHz, CDCl_3) δ 7.58 (s, 1H), 7.56-7.52 (m, 4H), 7.44 (s, 1H), 7.37-7.34 (m, 4H), 7.32-7.30 (m, 1H), 7.24-7.23 (m, 2H), 7.19 (t, $J = 7.8$ Hz, 2H), 7.03-7.02 (m, 2H), 6.97 (d, $J = 9.0$ Hz, 2H), 6.90-6.89 (m, 1H), 5.43 (s, 2H), 3.84 (s, 3H), 2.16 (s, 3H), 2.09 (s, 3H); ^{13}C NMR (150 MHz, CDCl_3) δ 191.6, 159.1, 139.8, 139.5, 138.3, 137.0, 136.7, 136.1, 136.0, 135.08, 135.04, 134.2, 131.4, 130.0, 129.5, 129.4, 129.1, 128.5, 128.2, 127.5, 127.1, 126.1, 124.0, 122.8, 117.9, 114.3, 106.8, 55.5, 50.8, 19.7, 19.5; FT-IR (neat) 2920, 2852, 1733, 1638, 1518, 1460, 1262, 1177, 737 cm^{-1} ; HRMS (ESI) m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{37}\text{H}_{32}\text{NO}_2$: 522.2428, found 522.2422.



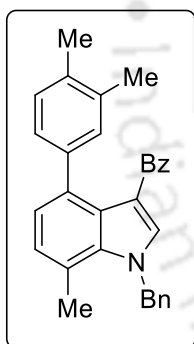
(1-Benzyl-4-(3,4-dimethylphenyl)-6-(p-tolyl)-1H-indol-3-

yl)(phenyl)methanone 3w. Analytical TLC on silica gel, 1:5 ethyl acetate/hexane $R_f = 0.52$; light yellow solid; mp 163-164 °C; yield 73% (36.9 mg); ^1H NMR (400 MHz, CDCl_3) δ 7.51 (s, 1H), 7.45 (d, $J = 8.0$ Hz, 4H), 7.40-7.39 (m, 1H), 7.325-7.322 (m, 1H), 7.29-7.27 (m, 2H), 7.25-7.22 (m, 1H), 7.17-7.09 (m, 7H), 6.95-6.94 (m, 2H), 6.82-6.80 (m, 1H), 5.35 (s, 2H), 2.31 (s, 3H), 2.08 (s, 3H), 2.01 (s, 3H); ^{13}C NMR (150 MHz, CDCl_3) δ 191.6, 139.8, 139.4, 138.8, 138.3, 137.07, 137.03, 136.9, 136.1, 136.0, 135.1, 135.0, 131.4, 130.0, 129.6, 129.5, 129.4, 129.1, 128.2, 127.5, 127.4, 127.1, 126.1, 124.2, 122.9, 117.9, 107.1, 50.8, 21.2, 19.7, 19.5; FT-IR (neat) 2923, 2854, 1732, 1639, 1519, 1452, 1264, 1175, 737 cm^{-1} ; HRMS (ESI) m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{37}\text{H}_{32}\text{NO}$: 506.2478, found 506.2478.



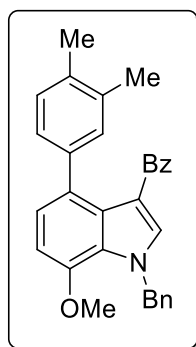
(1-Benzyl-7-chloro-4-(3,4-dimethylphenyl)-1H-indol-3-

yl)(phenyl)methanone 3x. Analytical TLC on silica gel, 1:5 ethyl acetate/hexane $R_f = 0.47$; colorless solid; mp 148-149 °C; yield 71% (31.9 mg); ^1H NMR (600 MHz, CDCl_3) δ 7.50 (s, 1H), 7.40-7.39 (m, 2H), 7.35-7.32 (m, 3H), 7.30-7.27 (m, 2H), 7.17 (t, $J = 7.8$ Hz, 2H), 7.13-7.12 (m, 2H), 7.01 (d, $J = 7.8$ Hz, 1H), 6.90-6.89 (m, 1H), 6.87-6.85 (m, 2H), 5.85 (s, 2H), 2.14 (s, 3H), 2.03 (s, 3H); ^{13}C NMR (150 MHz, CDCl_3) δ 191.7, 139.2, 138.6, 137.8, 136.3, 136.2, 135.7, 135.2, 132.5, 131.6, 129.8, 129.7, 129.2, 129.0, 128.1, 127.9, 127.5, 126.5, 125.9, 125.3, 123.5, 118.2, 116.0, 52.6, 19.6, 19.5; FT-IR (KBr) 2920, 2852, 1733, 1644, 1531, 1452, 1264, 1176, 741 cm^{-1} ; HRMS (ESI) m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{30}\text{H}_{25}\text{ClNO}$: 450.1619, found 450.1619.



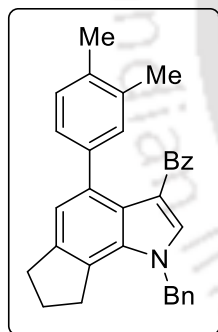
(1-Benzyl-4-(3,4-dimethylphenyl)-7-methyl-1H-indol-3-

yl)(phenyl)methanone 3y. Analytical TLC on silica gel, 1:5 ethyl acetate/hexane $R_f = 0.50$; light brown solid; mp 156-157 °C; yield 74% (31.7 mg); ^1H NMR (400 MHz, CDCl_3) δ 7.40 (s, 1H), 7.37-7.35 (m, 2H), 7.26-7.17 (m, 4H), 7.10-7.07 (m, 2H), 6.96-6.91 (m, 4H), 6.87-6.83 (m, 2H), 6.79-6.77 (m, 1H), 5.57 (s, 2H), 2.51 (s, 3H), 2.07 (s, 3H), 1.97 (s, 3H); ^{13}C NMR (150 MHz, CDCl_3) δ 192.09, 139.64, 139.63, 138.3, 136.1, 136.0, 134.8, 134.6, 131.3, 129.9, 129.5, 129.3, 129.1, 128.8, 127.8, 127.4, 126.6, 126.2, 126.0, 125.6, 123.1, 120.2, 117.9, 52.9, 19.7, 19.58, 19.53; FT-IR (KBr) 2920, 2852, 1733, 1634, 1531, 1450, 1382, 1261, 1177, 737 cm^{-1} ; HRMS (ESI) m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{31}\text{H}_{28}\text{NO}$: 430.2165, found 430.2173.



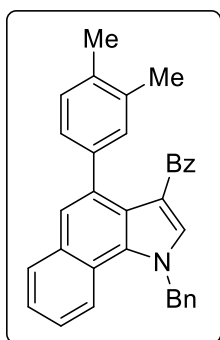
(1-Benzyl-4-(3,4-dimethylphenyl)-7-methoxy-1H-indol-3-

yl)(phenyl)methanone **3z**. Analytical TLC on silica gel, 1:5 ethyl acetate/hexane $R_f = 0.43$; yellow solid; mp 181-182 °C; yield 75% (33.4 mg); ^1H NMR (600 MHz, CDCl_3) δ 7.45-7.44 (m, 3H), 7.34-7.30 (m, 3H), 7.27 (s, 1H), 7.18-7.15 (m, 4H), 7.01 (d, $J = 7.8$ Hz, 1H), 6.92-6.89 (m, 2H), 6.85-6.84 (m, 1H), 6.77-6.75 (m, 1H), 5.69 (s, 2H), 3.87 (s, 3H), 2.14 (s, 3H), 2.05 (s, 3H); ^{13}C NMR (150 MHz, CDCl_3) δ 191.9, 146.8, 139.7, 139.5, 138.5, 135.9, 135.2, 134.3, 131.3, 129.9, 129.5, 129.4, 129.3, 128.8, 127.6, 127.5, 127.4, 127.3, 126.9, 126.0, 123.3, 118.1, 104.6, 55.6, 53.3, 19.7, 19.5; FT-IR (KBr) 2920, 2852, 1733, 1642, 1494, 1453, 1385, 1262, 1174, 736 cm^{-1} ; HRMS (ESI) m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{31}\text{H}_{28}\text{NO}_2$: 446.2115, found 446.2115.



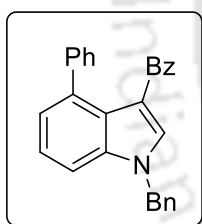
(1-Benzyl-4-(3,4-dimethylphenyl)-1,6,7,8-tetrahydrocyclopenta[g]indol-

3-yl)(phenyl) methanone **3aa**. Analytical TLC on silica gel, 1:5 ethyl acetate/hexane $R_f = 0.50$; light brown solid; mp 198-199 °C; yield 64% (29.1 mg); ^1H NMR (400 MHz, CDCl_3) δ 7.45 (s, 1H), 7.43-7.41 (m, 2H), 7.33-7.28 (m, 4H), 7.16-7.12 (m, 2H), 7.09-7.07 (m, 2H), 7.03 (s, 1H), 6.93-6.90 (m, 2H), 6.84-6.82 (m, 1H), 5.55 (s, 2H), 3.17 (t, $J = 7.6$ Hz, 2H), 3.01 (t, $J = 7.6$ Hz, 2H), 2.17-2.15 (m, 1H), 2.14 (s, 3H), 2.11-2.10 (m, 1H), 2.05 (s, 3H); ^{13}C NMR (150 MHz, CDCl_3) δ 192.2, 141.1, 139.9, 139.8, 138.0, 136.0, 135.2, 134.9, 134.57, 134.54, 131.2, 130.0, 129.5, 129.3, 129.1, 127.9, 127.3, 126.1, 124.6, 124.3, 120.1, 118.5, 51.9, 32.8, 31.3, 25.4, 19.7, 19.5; FT-IR (KBr) 2919, 2851, 1734, 1640, 1528, 1459, 1265, 1176, 739 cm^{-1} ; HRMS (ESI) m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{33}\text{H}_{30}\text{NO}$: 456.2322, found 456.2324.



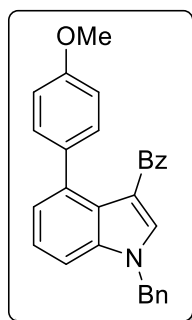
(1-Benzyl-4-(3,4-dimethylphenyl)-1H-benzo[g]indol-3-

yl)(phenyl)methanone 3ab. Analytical TLC on silica gel, 1:5 ethyl acetate/hexane $R_f = 0.49$; brown solid; mp 195-196 °C; yield 67% (31.1 mg); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 8.16 (d, $J = 8.4$ Hz, 1H), 7.93-7.91 (m, 1H), 7.57 (s, 1H), 7.48 (s, 1H), 7.43-7.30 (m, 8H), 7.21-7.19 (m, 2H), 7.16-7.12 (m, 2H), 7.01-6.99 (m, 1H), 6.96 (s, 1H), 6.88-6.86 (m, 1H), 5.91 (s, 2H), 2.17 (s, 3H), 2.06 (s, 3H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 192.9, 139.5, 139.4, 136.6, 136.2, 135.6, 135.0, 133.5, 132.1, 131.4, 131.1, 129.9, 129.7, 129.3, 128.1, 127.4, 126.3, 126.0, 125.7, 124.5, 123.9, 123.5, 121.5, 121.1, 119.0, 54.4, 19.6, 19.5; FT-IR (KBr) 2919, 2852, 1645, 1529, 1453, 1266, 1174, 743 cm^{-1} ; HRMS (ESI) m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{34}\text{H}_{28}\text{NO}$: 466.2165, found 466.2165.



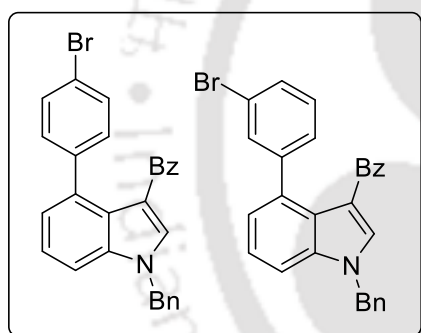
(1-Benzyl-4-phenyl-1H-indol-3-yl)(phenyl)methanone 3ac.

Analytical TLC on silica gel, 1:5 ethyl acetate/hexane $R_f = 0.47$; light brown solid; mp 173-174 °C; yield 77% (29.8 mg); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.50 (s, 1H), 7.48 (s, 2H), 7.31-7.23 (m, 5H), 7.21-7.19 (m, 3H), 7.17-7.15 (m, 2H), 7.13-7.06 (m, 6H), 5.31 (s, 2H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 190.9, 142.1, 139.9, 137.8, 136.9, 136.1, 135.5, 131.6, 129.5, 129.1, 128.6, 128.2, 128.0, 127.9, 127.0, 126.8, 124.9, 123.7, 123.6, 117.7, 109.3, 50.9; FT-IR (KBr) 2920, 2852, 1733, 1640, 1521, 1451, 1388, 1264, 1172, 741 cm^{-1} ; HRMS (ESI) m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{28}\text{H}_{22}\text{NO}$: 388.1696, found 388.1697.



(1-Benzyl-4-(4-methoxyphenyl)-1H-indol-3-yl)(phenyl)methanone 3ad.

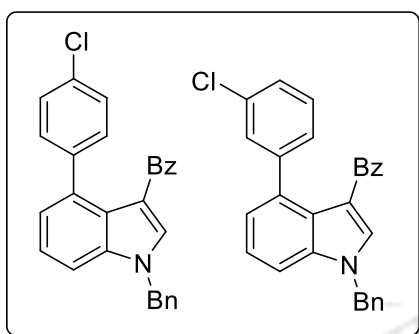
Analytical TLC on silica gel, 1:5 ethyl acetate/hexane $R_f = 0.43$; colorless solid; mp 153-154 °C; yield 69% (28.8 mg); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.53-7.51 (m, 3H), 7.34-7.26 (m, 5H), 7.21-7.19 (m, 2H), 7.17-7.12 (m, 5H), 7.10-7.08 (m, 1H), 6.66 (d, $J = 8.8$ Hz, 2H), 5.35 (s, 2H), 3.71 (s, 3H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 191.2, 158.4, 139.9, 137.7, 136.5, 136.1, 135.2, 134.7, 131.6, 129.6, 129.5, 129.1, 128.2, 127.8, 127.1, 125.1, 123.6, 123.5, 117.8, 113.6, 108.9, 55.2, 50.9; FT-IR (KBr) 2919, 2851, 1733, 1640, 1522, 1460, 1262, 1176, 746 cm^{-1} ; HRMS (ESI) m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{29}\text{H}_{24}\text{NO}_2$: 418.1802, found 418.1802.



(1-Benzyl-4-(4-bromophenyl)-1H-indol-3-

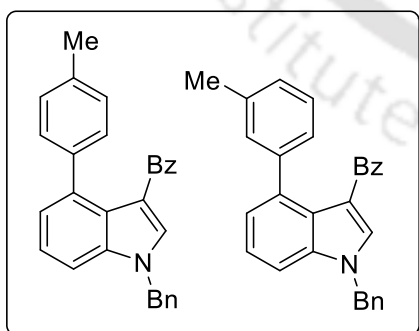
yl)(phenyl)methanone 3af and **(1-benzyl-4-(3-bromophenyl)-1H-indol-3-yl)(phenyl)methanone 3af'**. Analytical TLC on silica gel, 1:5 ethyl acetate/hexane $R_f = 0.48$; colorless solid; mp 205-206 °C; yield 63% (29 mg); An inseparable mixture of regioisomers was found and the isomeric ratio (p/m) was 1:1 as determined by $^{13}\text{C NMR}$; $^1\text{H NMR}$ (600 MHz, CDCl_3) δ 7.62 (s, 1H), 7.61-7.58 (m, 2.64H), 7.55-7.54 (m, 2.29H), 7.43-7.38 (m, 2.18H), 7.36-7.28 (m, 13.71H), 7.25-7.23 (m, 3.80H), 7.19-7.16 (m, 8.05H), 7.13-7.11 (m, 1.85H), 7.04-7.01 (m, 1.26H), 5.416-5.411 (m, 3.83H); $^{13}\text{C NMR}$ (150 MHz, CDCl_3) δ 191.2, 190.9, 144.0, 142.0, 139.9, 139.6, 137.79, 137.70, 136.8, 136.0, 135.9, 135.79, 135.76, 135.0, 131.8, 131.7, 131.4, 131.1, 130.1, 129.7, 129.57, 129.54, 129.4, 129.18, 129.14, 128.5, 128.3, 128.2, 128.08, 128.02, 127.9, 127.2, 127.03, 127.01, 126.8, 124.8, 124.7, 123.8, 123.69, 123.64, 123.62, 122.3, 117.6, 117.4, 109.9, 109.3, 50.97, 50.92; FT-IR (KBr) 2955, 2919, 1638,

1520, 1455, 1382, 1251, 1170, 749 cm^{-1} ; HRMS (ESI) m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{28}\text{H}_{21}\text{BrNO}$: 466.0801, found 466.0801.



(1-Benzyl-4-(4-chlorophenyl)-1H-indol-3-

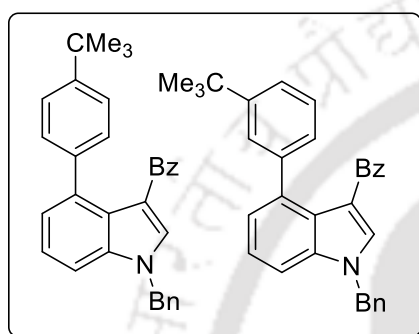
yl)(phenyl)methanone **3ag** and (1-benzyl-4-(3-chlorophenyl)-1H-indol-3-yl)(phenyl)methanone **3ag'**. Analytical TLC on silica gel, 1:5 ethyl acetate/hexane $R_f = 0.48$; colorless solid; mp 163-164 $^{\circ}\text{C}$; yield 65% (27 mg); An inseparable mixture of regioisomers was found and the isomeric ratio (p/m) was 1.8:1 as determined by ^{13}C NMR;³ ^1H NMR (400 MHz, CDCl_3) δ 7.54 (s, 0.54H), 7.52 (s, 1H), 7.50-7.46 (m, 3.01H), 7.35-7.31 (m, 1.82H), 7.29-7.25 (m, 6.94H), 7.23-7.22 (m, 1.28H), 7.20-7.15 (m, 3.42H), 7.13-7.10 (m, 5.16H), 7.07-7.04 (m, 3.88H), 7.02-7.00 (m, 1.11H), 5.33 (s, 3.26H); ^{13}C NMR (150 MHz, CDCl_3) δ 191.2, 191.0, 143.9, 140.6, 140.0, 139.8, 137.87, 137.81, 137.7, 136.0, 135.6, 135.5, 135.35, 135.33, 134.0, 132.7, 131.8, 131.7, 129.9, 129.5, 129.4, 129.29, 129.21, 128.7, 128.3, 128.2, 128.0, 127.9, 127.14, 127.13, 126.93, 126.91, 124.9, 124.8, 123.7, 123.66, 123.62, 117.7, 117.6, 109.9, 109.7, 51.0; FT-IR (KBr) 2955, 2919, 1638, 1520, 1455, 1382, 1252, 1170, 889, 749 cm^{-1} ; HRMS (ESI) m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{28}\text{H}_{21}\text{ClNO}$: 422.1306, found 422.1295.



(1-Benzyl-4-(p-tolyl)-1H-indol-3-yl)(phenyl)methanone

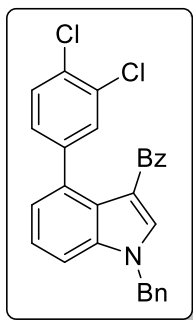
3ah and (1-benzyl-4-(m-tolyl)-1H-indol-3-yl)(phenyl)methanone **3ah'**. Analytical TLC on silica gel, 1:5 ethyl acetate/hexane $R_f = 0.49$; light brown solid; mp 160-161 $^{\circ}\text{C}$; yield 72% (29 mg); An inseparable mixture of regioisomers was found and the isomeric ratio (p/m) was 1.9:1 as determined by ^{13}C NMR;³ ^1H NMR (600 MHz, CDCl_3) δ 7.57-7.56 (m, 3.37H), 7.53 (d, J

= 7.8 Hz, 1.27H), 7.39-7.29 (m, 10.06H), 7.24-7.23 (m, 1.77H), 7.22-7.19 (m, 4.42H), 7.17-7.15 (m, 3.62H), 7.06-7.02 (m, 1.81H), 6.97-6.96 (m, 2.05H), 6.92-6.91 (m, 0.60H), 5.406-5.400 (m, 3.25H), 2.28 (s, 3H), 2.19 (s, 1.53H); ^{13}C NMR (150 MHz, CDCl_3) δ 191.5, 191.1, 141.9, 140.0, 139.8, 139.1, 137.8, 137.7, 137.5, 136.94, 136.92, 136.2, 136.17, 136.15, 135.4, 134.9, 131.6, 131.5, 129.5, 129.45, 129.42, 129.1, 128.8, 128.4, 128.2, 128.1, 127.8, 127.7, 127.6, 127.1, 127.0, 125.7, 125.09, 125.00, 123.68, 123.62, 123.5, 123.4, 117.8, 109.2, 109.1, 50.9, 21.4, 21.3; FT-IR (KBr) 2920, 2852, 1734, 1640, 1522, 1448, 1387, 1239, 1170, 734 cm^{-1} ; HRMS (ESI) m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{29}\text{H}_{24}\text{NO}$: 402.1852, found 402.1848.



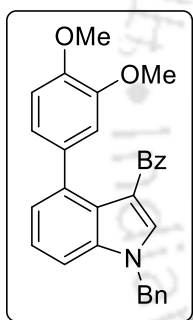
(1-Benzyl-4-(4-(*tert*-butyl)phenyl)-1*H*-indol-3-

yl)(phenyl)- methanone **3ai** and (1-benzyl-4-(3-(*tert*-butyl)phenyl)-1*H*-indol-3-yl)(phenyl)methanone **3ai'**. Analytical TLC on silica gel, 1:5 ethyl acetate/hexane R_f = 0.50; colorless solid; mp 133-134 °C; yield 61% (27 mg); An inseparable mixture of regioisomers was found and the isomeric ratio (*p*/*m*) was 1.8:1 as determined by ^{13}C NMR;³ ^1H NMR (600 MHz, CDCl_3) δ 7.63 (s, 0.74H), 7.58-7.55 (m, 2.32H), 7.39-7.38 (m, 1.45H), 7.36-7.29 (m, 8.27H), 7.24-7.17 (m, 6.80H), 7.15-7.13 (m, 2.40H), 7.11-7.07 (m, 4.92H), 5.41 (s, 2.92H), 1.25 (s, 9H), 1.15 (s, 6.68H); ^{13}C NMR (150 MHz, CDCl_3) δ 192.3, 191.1, 150.2, 149.2, 141.6, 139.7, 139.6, 139.0, 137.7, 137.4, 137.3, 136.7, 136.19, 136.17, 134.8, 134.0, 131.8, 131.4, 129.6, 129.4, 129.17, 129.16, 128.28, 128.27, 128.1, 127.8, 127.7, 127.2, 127.1, 125.7, 125.6, 125.2, 125.1, 125.0, 123.9, 123.59, 123.57, 123.4, 123.2, 118.0, 117.8, 109.2, 109.1, 50.9, 34.5, 34.4, 31.4, 31.2; FT-IR (KBr) 2921, 2853, 1732, 1640, 1523, 1456, 1263, 1173, 737 cm^{-1} ; HRMS (ESI) m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{32}\text{H}_{30}\text{NO}$: 444.2322, found 444.2320.



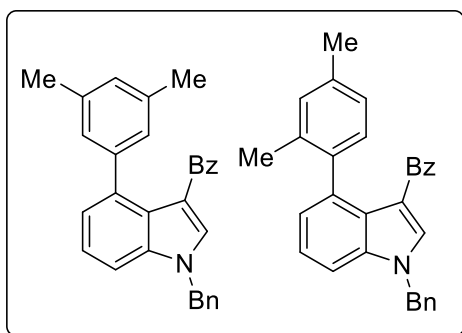
(1-Benzyl-4-(3,4-dichlorophenyl)-1H-indol-3-yl)(phenyl)methanone 3aj.

Analytical TLC on silica gel, 1:4 ethyl acetate/hexane $R_f = 0.30$; brown solid; mp 118-119 °C; yield 61% (27.8 mg); ^1H NMR (400 MHz, CDCl_3) δ 7.56 (s, 1H), 7.46 (d, $J = 7.6$ Hz, 2H), 7.37-7.33 (m, 1H), 7.31-7.23 (m, 5H), 7.21-7.17 (m, 4H), 7.13-7.11 (m, 3H), 7.04-6.98 (m, 2H), 5.34 (s, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 191.2, 142.1, 139.8, 137.7, 135.9, 135.7, 134.2, 132.1, 131.9, 130.8, 130.5, 130.0, 129.3, 129.2, 128.4, 128.0, 127.9, 127.1, 124.7, 123.65, 123.60, 117.5, 110.2, 51.0; FT-IR (KBr) 2919, 2851, 1734, 1637, 1464, 1264, 1176, 751 cm^{-1} ; HRMS (ESI) m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{28}\text{H}_{20}\text{Cl}_2\text{NO}$: 456.0916, found 456.0916.

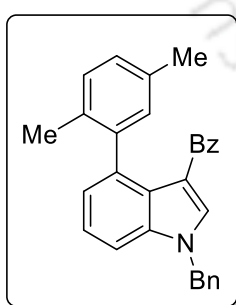


(1-Benzyl-4-(3,4-dimethoxyphenyl)-1H-indol-3-yl)(phenyl)methanone 3ak.

Analytical TLC on silica gel, 1:4 ethyl acetate/hexane $R_f = 0.35$; brown solid; mp 122-123 °C; yield 67% (30 mg); ^1H NMR (400 MHz, CDCl_3) δ 7.60 (s, 1H), 7.51 (d, $J = 7.2$ Hz, 2H), 7.37-7.31 (m, 6H), 7.23-7.13 (m, 5H), 6.80-6.77 (m, 1H), 6.725-6.720 (m, 1H), 6.63-6.61 (m, 1H), 5.40 (s, 2H), 3.81 (s, 3H), 3.67 (s, 3H); ^{13}C NMR (150 MHz, CDCl_3) δ 192.1, 148.2, 147.8, 139.7, 137.6, 136.4, 136.1, 134.9, 134.3, 131.7, 129.4, 129.1, 128.2, 127.7, 127.1, 125.2, 123.5, 122.9, 120.8, 117.8, 111.9, 111.2, 109.1, 55.9, 55.5, 50.9; FT-IR (KBr) 2921, 2851, 1733, 1640, 1521, 1454, 1249, 1174, 1028, 736 cm^{-1} ; HRMS (ESI) m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{30}\text{H}_{26}\text{NO}_3$: 448.1907, found 448.1916.



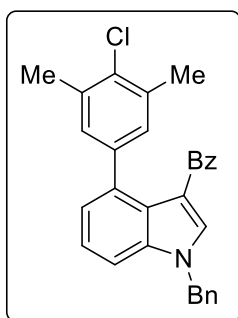
(1-Benzyl-4-(3,5-dimethylphenyl)-1H-indol-3-yl)(phenyl)methanone 3al and **(1-benzyl-4-(2,4-dimethylphenyl)-1H-indol-3-yl)(phenyl)methanone 3al'**. Analytical TLC on silica gel, 1:5 ethyl acetate/hexane $R_f = 0.50$; light brown solid; mp 154-155 °C; yield 70% (29 mg); An inseparable mixture of regioisomers was found and the isomeric ratio (*m/o*) was 1.3:1 as determined by ^{13}C NMR;³ ^1H NMR (600 MHz, CDCl_3) δ 7.58 (s, 1H), 7.52 (s, 0.86H), 7.47 (t, $J = 7.2$ Hz, 3.65H), 7.36 -7.33 (m, 5.36H), 7.31 -7.28 (m, 5.65H), 7.24-7.20 (m, 5.64H), 7.18-7.15 (m, 2.13H), 7.14-7.12 (m, 1.16H), 7.06-7.05 (m, 0.88H), 6.98-6.97 (m, 0.88H), 6.83-6.82 (m, 2.77H), 6.77 (s, 0.85H), 6.68 (s, 1.06H), 5.40-5.38 (m, 3.46H), 2.25 (s, 2.32H), 2.13 (s, 6H), 1.98 (s, 2.29H); ^{13}C NMR (150 MHz, CDCl_3) δ 192.0, 191.4, 140.2, 139.5, 138.6, 137.57, 137.53, 137.3, 136.9, 136.36, 136.31, 136.2, 136.1, 135.2, 135.0, 134.2, 131.4, 131.2, 130.6, 129.5, 129.2, 129.18, 129.15, 129.14, 128.5, 128.25, 128.24, 127.7, 127.5, 126.5, 126.2, 125.9, 125.2, 124.1, 123.4, 123.2, 122.9, 118.1, 117.9, 109.1, 109.0, 50.9, 21.3, 21.2, 20.3; FT-IR (KBr) 2920, 2852, 1733, 1640, 1523, 1452, 1387, 1262, 1173, 741 cm^{-1} ; HRMS (ESI) m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{30}\text{H}_{26}\text{NO}$: 416.2009, found 416.2009.



(1-Benzyl-4-(2,5-dimethylphenyl)-1H-indol-3-yl)(phenyl)methanone

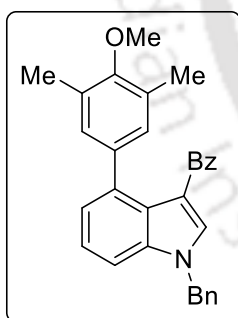
3am. Analytical TLC on silica gel, 1:5 ethyl acetate/hexane $R_f = 0.49$; yellow thick liquid; yield 57% (23.6 mg); ^1H NMR (400 MHz, CDCl_3) δ 7.53 (s, 1H), 7.46-7.44 (m, 2H), 7.37-7.30 (m, 6H), 7.22-7.19 (m, 4H), 7.07-7.05 (m, 1H), 6.86-6.85 (m, 3H), 5.40-5.39 (m, 2H), 2.17 (s, 3H), 1.96 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 191.6, 141.1, 140.0, 137.2, 136.3, 136.1, 134.62, 134.60, 132.3, 131.3, 130.4, 129.7, 129.2, 129.1, 128.2, 127.8, 127.7, 127.1, 125.8, 123.9, 123.2, 118.2, 109.1, 50.8, 21.0, 19.8; FT-IR (neat) 2924, 2854, 1730, 1639, 1523, 1450,

1263, 1173, 736 cm^{-1} ; HRMS (ESI) m/z $[M+H]^+$ calcd for $\text{C}_{30}\text{H}_{26}\text{NO}$: 416.2009, found 416.2008.



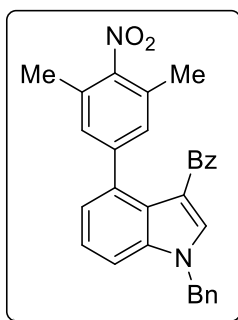
(1-Benzyl-4-(4-chloro-3,5-dimethylphenyl)-1H-indol-3-

yl)(phenyl)methanone 3an. Analytical TLC on silica gel, 1:5 ethyl acetate/hexane R_f = 0.45; light yellow solid; mp 149-150 $^{\circ}\text{C}$; yield 61% (27.4 mg); ^1H NMR (600 MHz, CDCl_3) δ 7.62 (s, 1H), 7.41 (d, J = 7.2 Hz, 2H), 7.36-7.28 (m, 6H), 7.22-7.21 (m, 2H), 7.16 (t, J = 7.8 Hz, 2H), 7.09 (d, J = 7.8 Hz, 1H), 6.87 (s, 2H), 5.41 (s, 2H), 2.17 (s, 6H); ^{13}C NMR (150 MHz, CDCl_3) δ 192.2, 139.7, 139.5, 137.4, 136.0, 135.8, 135.7, 134.3, 133.2, 131.3, 129.18, 129.13, 128.7, 128.3, 127.5, 127.1, 125.2, 123.4, 122.8, 117.8, 109.5, 50.9, 20.6; FT-IR (KBr) 2922, 2854, 1640, 1522, 1459, 1262, 753 cm^{-1} ; HRMS (ESI) m/z $[M+H]^+$ calcd for $\text{C}_{30}\text{H}_{25}\text{ClNO}$: 450.1619, found 450.1618.



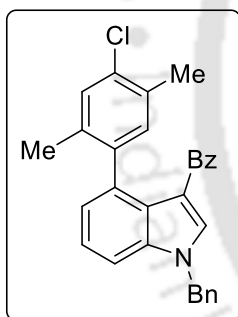
(1-Benzyl-4-(4-methoxy-3,5-dimethylphenyl)-1H-indol-3-

yl)(phenyl)methanone 3ao. Analytical TLC on silica gel, 1:5 ethyl acetate/hexane R_f = 0.44; light brown solid; mp 140-141 $^{\circ}\text{C}$; yield 63% (28 mg); ^1H NMR (400 MHz, CDCl_3) δ 7.54 (s, 1H), 7.35 (d, J = 7.2 Hz, 2H), 7.30-7.21 (m, 6H), 7.18-7.15 (m, 2H), 7.05-6.99 (m, 3H), 6.71 (s, 2H), 5.32 (s, 2H), 3.55 (s, 3H), 2.00 (s, 6H); ^{13}C NMR (100 MHz, CDCl_3) δ 192.4, 155.6, 139.5, 137.5, 137.4, 136.5, 136.2, 133.6, 131.1, 130.4, 129.18, 129.17, 128.2, 127.6, 127.2, 125.4, 123.3, 122.6, 118.0, 109.0, 59.5, 50.9, 16.0; FT-IR (KBr) 2919, 2851, 1734, 1640, 1522, 1466, 1251, 1174, 741 cm^{-1} ; HRMS (ESI) m/z $[M+H]^+$ calcd for $\text{C}_{31}\text{H}_{28}\text{NO}_2$: 446.2115, found 446.2127.



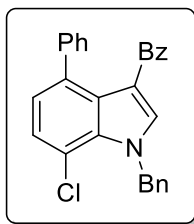
(1-Benzyl-4-(3,5-dimethyl-4-nitrophenyl)-1H-indol-3-

yl)(phenyl)methanone 3ap. Analytical TLC on silica gel, 1:5 ethyl acetate/hexane $R_f = 0.35$; brown thick liquid; yield 52% (24 mg); ^1H NMR (400 MHz, CDCl_3) δ 7.59 (s, 1H), 7.46-7.44 (m, 2H), 7.41-7.29 (m, 6H), 7.24-7.20 (m, 4H), 7.13 (d, $J = 8.0$ Hz, 1H), 7.01 (d, $J = 6.8$ Hz, 1H), 6.95 (d, $J = 8.0$ Hz, 1H), 5.40 (s, 2H), 2.23 (s, 3H), 1.92 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 191.4, 141.2, 139.9, 137.4, 135.9, 135.3, 133.9, 132.0, 131.2, 129.2, 128.9, 128.4, 128.1, 127.78, 127.74, 127.2, 127.0, 125.7, 124.3, 123.3, 117.8, 110.0, 51.0, 17.3, 15.5; FT-IR (neat) 2923, 2855, 1640, 1524, 1457, 1263, 753 cm^{-1} ; HRMS (ESI) m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{30}\text{H}_{25}\text{N}_2\text{O}_3$: 461.1860, found 461.1854.



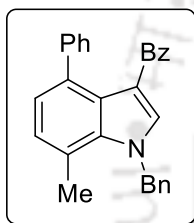
(1-Benzyl-4-(4-chloro-2,5-dimethylphenyl)-1H-indol-3-

yl)(phenyl)methanone 3aq. Analytical TLC on silica gel, 1:5 ethyl acetate/hexane $R_f = 0.45$; colorless solid; mp 145-146 $^\circ\text{C}$; yield 55% (24.7 mg); ^1H NMR (400 MHz, CDCl_3) δ 7.56 (s, 1H), 7.40-7.29 (m, 8H), 7.24-7.20 (m, 4H), 7.01 (d, $J = 7.2$ Hz, 1H), 6.88 (s, 1H), 6.84 (s, 1H), 5.40-5.39 (m, 2H), 2.16 (s, 3H), 1.92 (s, 3H); ^{13}C NMR (150 MHz, CDCl_3) δ 192.0, 139.9, 139.8, 137.1, 136.0, 134.9, 134.7, 134.6, 132.7, 132.5, 132.1, 131.5, 130.1, 129.1, 129.0, 128.2, 127.6, 127.1, 125.6, 123.7, 123.2, 117.9, 109.5, 50.9, 19.7, 19.5; FT-IR (KBr) 2920, 2853, 1733, 1639, 1523, 1450, 1385, 1260, 1171, 1051, 738 cm^{-1} ; HRMS (ESI) m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{30}\text{H}_{25}\text{ClNO}$: 450.1619, found 450.1619.



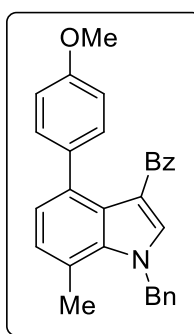
(1-Benzyl-7-chloro-4-phenyl-1H-indol-3-yl)(phenyl)methanone 3as.

Analytical TLC on silica gel, 1:5 ethyl acetate/hexane $R_f = 0.45$; colorless solid; mp 155-156 °C; yield 69% (29 mg); ^1H NMR (400 MHz, CDCl_3) δ 7.50 (s, 1H), 7.49-7.48 (m, 1H), 7.47-7.46 (m, 1H), 7.39-7.33 (m, 2H), 7.32-7.29 (m, 3H), 7.23-7.17 (m, 4H), 7.15-7.10 (m, 5H), 7.04 (d, $J = 8.0$ Hz, 1H), 5.86 (s, 2H); ^{13}C NMR (150 MHz, CDCl_3) δ 191.0, 141.2, 139.4, 137.8, 137.1, 135.7, 132.7, 131.9, 129.4, 129.0, 128.4, 128.2, 127.97, 127.95, 127.90, 127.0, 126.4, 125.4, 124.2, 118.0, 116.3, 52.7; FT-IR (KBr) 2919, 2851, 1735, 1646, 1530, 1458, 1393, 1266, 1177, 752 cm^{-1} ; HRMS (ESI) m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{28}\text{H}_{21}\text{ClNO}$: 422.1306, found 422.1306.



(1-Benzyl-7-methyl-4-phenyl-1H-indol-3-yl)(phenyl)methanone 3at.

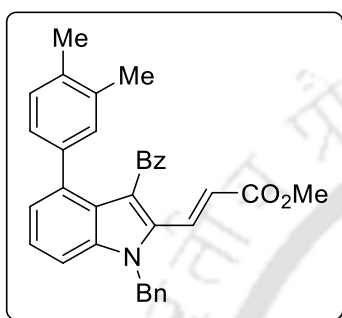
Analytical TLC on silica gel, 1:5 ethyl acetate/hexane $R_f = 0.49$; light yellow solid; mp 162-163 °C; yield 72% (28.9 mg); ^1H NMR (600 MHz, CDCl_3) δ 7.52-7.51 (m, 2H), 7.49 (s, 1H), 7.37-7.31 (m, 3H), 7.29-7.28 (m, 1H), 7.24-7.20 (m, 4H), 7.16-7.12 (m, 3H), 7.06-7.03 (m, 2H), 7.00-6.99 (m, 2H), 5.66 (s, 2H), 2.60 (s, 3H); ^{13}C NMR (150 MHz, CDCl_3) δ 191.3, 142.2, 139.8, 138.3, 137.0, 136.4, 134.9, 131.6, 129.4, 129.2, 128.5, 128.1, 127.9, 127.8, 126.7, 126.6, 126.0, 125.6, 123.8, 120.5, 117.8, 53.0, 19.6; FT-IR (KBr) 2921, 2852, 1733, 1640, 1530, 1451, 1379, 1259, 1175, 885, 735 cm^{-1} ; HRMS (ESI) m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{29}\text{H}_{24}\text{NO}$: 402.1852, found 402.1852.



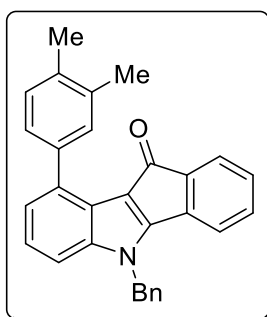
(1-Benzyl-4-(4-methoxyphenyl)-7-methyl-1H-indol-3-

yl)(phenyl)methanone 3au. Analytical TLC on silica gel, 1:5 ethyl acetate/hexane $R_f = 0.46$;

colorless solid; mp 185-186 °C; yield 75% (32.3 mg); ^1H NMR (400 MHz, CDCl_3) δ 7.44 (s, 1H), 7.42-7.40 (m, 2H), 7.29-7.18 (m, 4H), 7.15-7.11 (m, 2H), 7.06-7.04 (m, 2H), 6.96-6.90 (m, 4H), 6.59-6.57 (m, 2H), 5.58 (s, 2H), 3.68 (s, 3H), 2.51 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 191.7, 158.3, 139.9, 138.3, 136.5, 136.3, 134.9, 134.5, 131.6, 129.6, 129.4, 129.2, 127.9, 127.7, 126.6, 126.3, 125.6, 123.4, 120.1, 118.0, 113.7, 55.3, 53.0, 19.5; FT-IR (KBr) 2918, 2851, 1735, 1633, 1531, 1491, 1456, 1250, 1177, 753 cm^{-1} ; HRMS (ESI) m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{30}\text{H}_{26}\text{NO}_2$: 432.1958, found 432.1958.

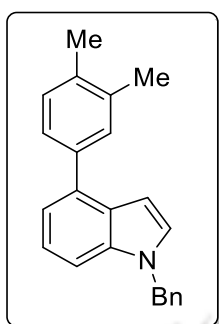


Methyl (E)-3-(3-benzoyl-1-benzyl-4-(3,4-dimethylphenyl)-1H-indol-2-yl)acrylate 4. Analytical TLC on silica gel, 1:5 ethyl acetate/hexane R_f = 0.41; yellow solid; mp 157-158 °C; yield 70% (35 mg); ^1H NMR (400 MHz, CDCl_3) δ 7.76 (d, J = 16.0 Hz, 1H), 7.38-7.33 (m, 2H), 7.32-7.29 (m, 3H), 7.27-7.26 (m, 1H), 7.21-7.19 (m, 2H), 7.17-7.15 (m, 2H), 7.09-7.05 (m, 2H), 7.02-7.00 (m, 1H), 6.79-6.75 (m, 2H), 6.71 (s, 1H), 6.30 (d, J = 16.0 Hz, 1H), 5.56 (s, 2H), 3.67 (s, 3H), 2.14 (s, 3H), 1.99 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 194.5, 166.8, 138.8, 138.6, 138.5, 137.2, 136.5, 136.0, 135.2, 135.1, 131.9, 131.5, 130.3, 129.5, 129.3, 129.2, 128.0, 127.4, 126.3, 126.1, 125.9, 125.0, 122.7, 122.5, 119.7, 109.0, 51.8, 48.1, 19.5, 19.4; FT-IR (KBr) 1714, 1635, 1485, 1435, 1233, 1171, 975, 736 cm^{-1} ; HRMS (ESI) m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{34}\text{H}_{30}\text{NO}_3$: 500.2220, found 500.2220.



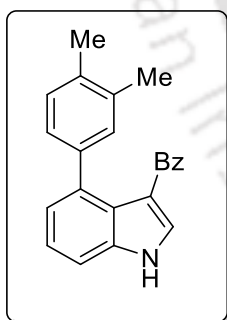
5-Benzyl-9-(3,4-dimethylphenyl)indeno[1,2-b]indol-10(5H)-one 5. Analytical TLC on silica gel, 1:5 ethyl acetate/hexane R_f = 0.49; yellow solid; mp 202-203 °C; yield 59% (24 mg); ^1H NMR (400 MHz, CDCl_3) δ 8.00-7.98 (m, 1H), 7.53-7.52 (m, 1H), 7.40-7.35 (m, 3H), 7.34 (d, J = 7.6 Hz, 1H), 7.30-7.28 (m, 2H), 7.24-7.22 (m, 1H), 7.04 (t, J = 7.6

Hz, 3H), 6.88-6.86 (m, 1H), 6.80-6.77 (m, 2H), 5.19 (s, 2H), 2.13 (s, 3H), 2.02 (s, 3H); ^{13}C NMR (150 MHz, CDCl_3) δ 193.4, 147.4, 142.3, 140.1, 139.6, 137.5, 136.2, 134.7, 134.1, 131.9, 131.0, 129.9, 129.7, 129.6, 129.1, 128.7, 128.6, 127.2, 125.9, 123.8, 123.3, 123.2, 122.6, 108.9, 108.3, 48.9, 19.6, 19.4; FT-IR (KBr) 2922, 2854, 1737, 1634, 1548, 1451, 1392, 1248, 1169, 749 cm^{-1} ; HRMS (ESI) m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{30}\text{H}_{24}\text{NO}$: 414.1852, found 414.1860.



1-Benzyl-4-(3,4-dimethylphenyl)-1H-indole 6. Analytical TLC on silica

gel, 1:19 ethyl acetate/hexane $R_f = 0.49$; yellow liquid; yield 75% (23 mg); ^1H NMR (600 MHz, CDCl_3) δ 7.41 (s, 1H), 7.38 (d, $J = 7.2$ Hz, 1H), 7.23-7.21 (m, 2H), 7.19-7.15 (m, 4H), 7.09-7.05 (m, 4H), 6.65-6.64 (m, 1H), 5.26 (s, 2H), 2.27 (s, 3H), 2.26 (s, 3H); ^{13}C NMR (150 MHz, CDCl_3) δ 138.9, 137.6, 136.8, 136.7, 135.4, 134.8, 130.2, 129.9, 128.9, 128.5, 127.7, 127.0, 126.9, 126.3, 122.1, 119.5, 108.6, 101.4, 50.3, 20.0, 19.6; FT-IR (neat) 2922, 2852, 1637, 1454, 1261, 801, 747 cm^{-1} ; HRMS (ESI) m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{23}\text{H}_{22}\text{N}$: 312.1747, found 312.1755.



(4-(3,4-Dimethylphenyl)-1H-indol-3-yl)(phenyl)methanone 3g.

Analytical TLC on silica gel, 1:3 ethyl acetate/hexane $R_f = 0.40$; brown solid; mp 110-111 $^\circ\text{C}$; yield 72% (46.8 mg); ^1H NMR (600 MHz, CDCl_3) δ 8.92 (s, 1H), 7.54-7.51 (m, 3H), 7.37-7.36 (m, 2H), 7.32-7.30 (m, 1H), 7.20 (t, $J = 7.8$ Hz, 2H), 7.15 (d, $J = 7.2$ Hz, 1H), 6.97-6.96 (m, 2H), 6.88-6.86 (m, 1H), 2.12 (s, 3H), 2.05 (s, 3H); ^{13}C NMR (150 MHz, CDCl_3) δ 192.2, 139.6, 139.5, 137.1, 136.5, 136.0, 134.9, 131.5, 129.9, 129.5, 129.4, 127.6, 126.0, 124.2, 123.7, 123.1, 118.8, 114.4, 110.3, 19.7, 19.5; FT-IR (KBr) 2924, 2855, 1623, 1511, 1450, 1413, 885, 795, 752 cm^{-1} ; HRMS (ESI) m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{23}\text{H}_{20}\text{NO}$: 326.1539, found 326.1534.

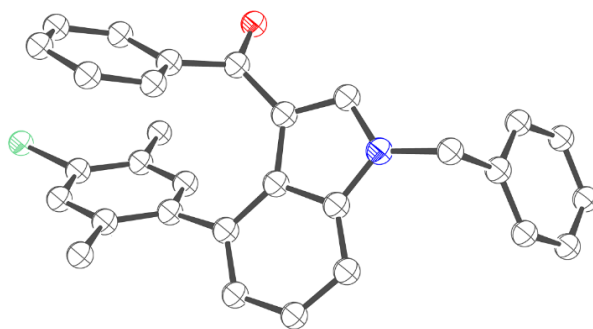
Crystal Data and Structure Refinement for **3aq**

Figure S1. ORTEP diagram of (1-benzyl-4-(4-chloro-2,5-dimethylphenyl)-1H-indol-3-yl)(phenyl)methanone **3aq** with 50% ellipsoid (CCDC 2120084). H-Atoms are omitted for clarity.

Identification code	3aq
Empirical formula	C ₃₀ H ₂₄ ClNO
Solvent for crystal growth	Acetonitrile
Formula weight	449.95
Crystal habit, colour	block and colourless
Temperature, <i>T</i> /K	296 K
Wavelength, $\lambda/\text{\AA}$	0.71073
Crystal system	triclinic
Space group	'P -1'
Unit cell dimensions	$a = 8.759(3) \text{ \AA}$ $b = 8.804(3) \text{ \AA}$ $c = 16.112(5) \text{ \AA}$ $\alpha = 78.42(2)$ $\beta = 80.71(2)$ $\gamma = 79.64(2)$
Volume, $V/\text{\AA}^3$	1187.0(7)
<i>Z</i>	2
Calculated density, Mg·m ⁻³	1.259
Absorption coefficient, μ/mm^{-1}	0.184
<i>F</i> (000)	472.0
θ range for data collection	1.30 to 24.49°
Limiting indices	$-10 \leq h \leq 9, -10 \leq k \leq 10, -18 \leq l \leq 18$

Reflection collected / unique	3947 / 2009
Completeness to θ	99.90% ($\theta = 24.49^\circ$)
Absorption correction	none
Refinement method	'SHELXL-2014/7 (Sheldrick 2014)'
Data / restraints / parameters	3947/0/301
Goodness-of-fit on F^2	0.827
Final R indices [$I > 2\sigma(I)$]	$R1 = 0.1368$, $wR2 = 0.2468$
R indices (all data)	$R1 = 0.0755$, $wR2 = 0.1929$

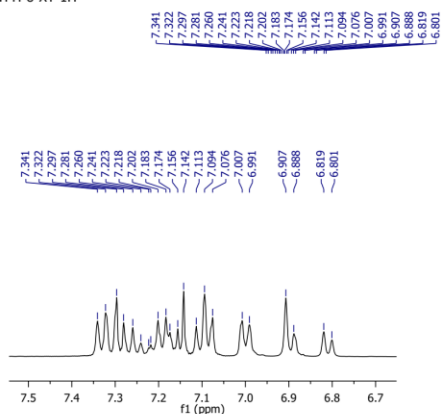
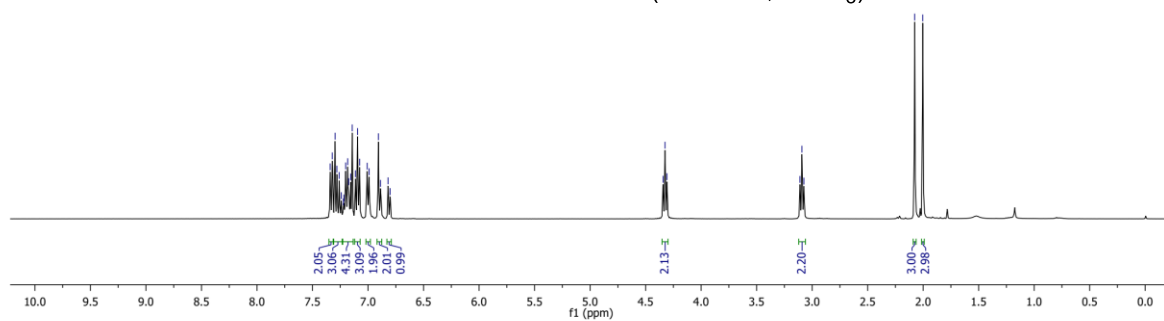
2.6 References

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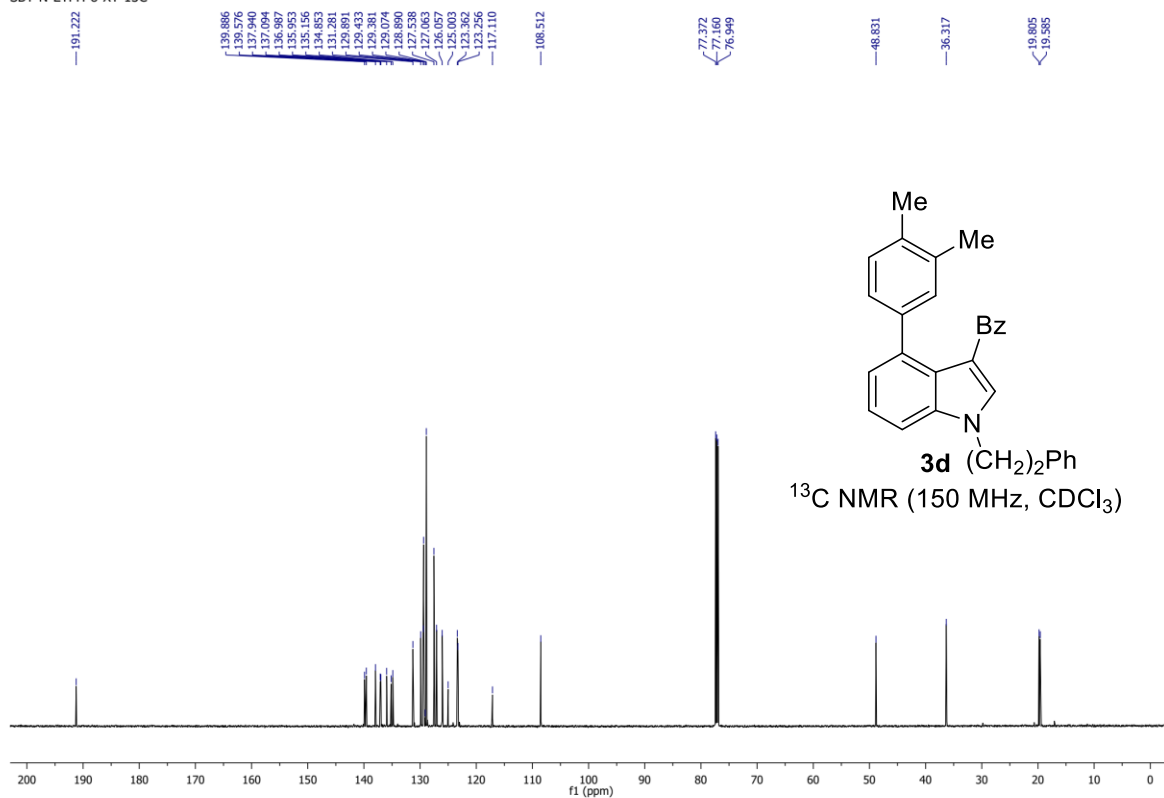
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2.7 Selected NMR Spectra

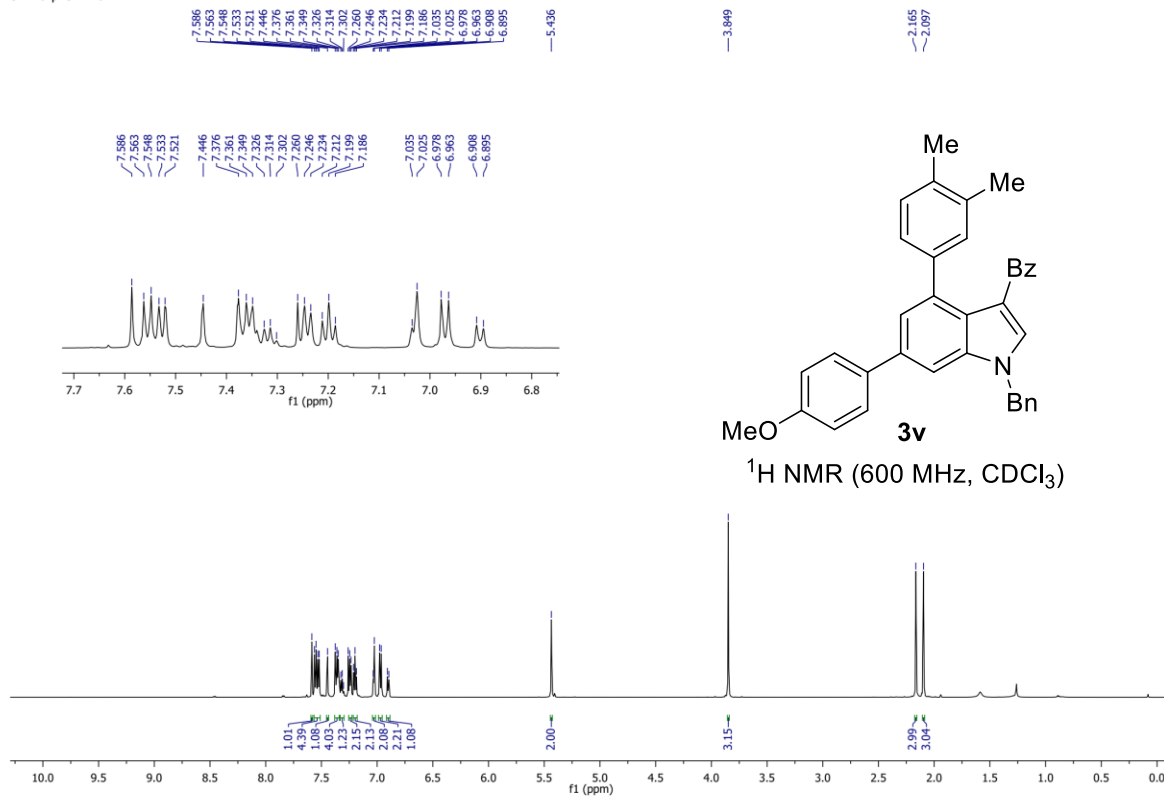
SBT-N-ETPH-o-XY-1H

 ^1H NMR (400 MHz, CDCl_3)

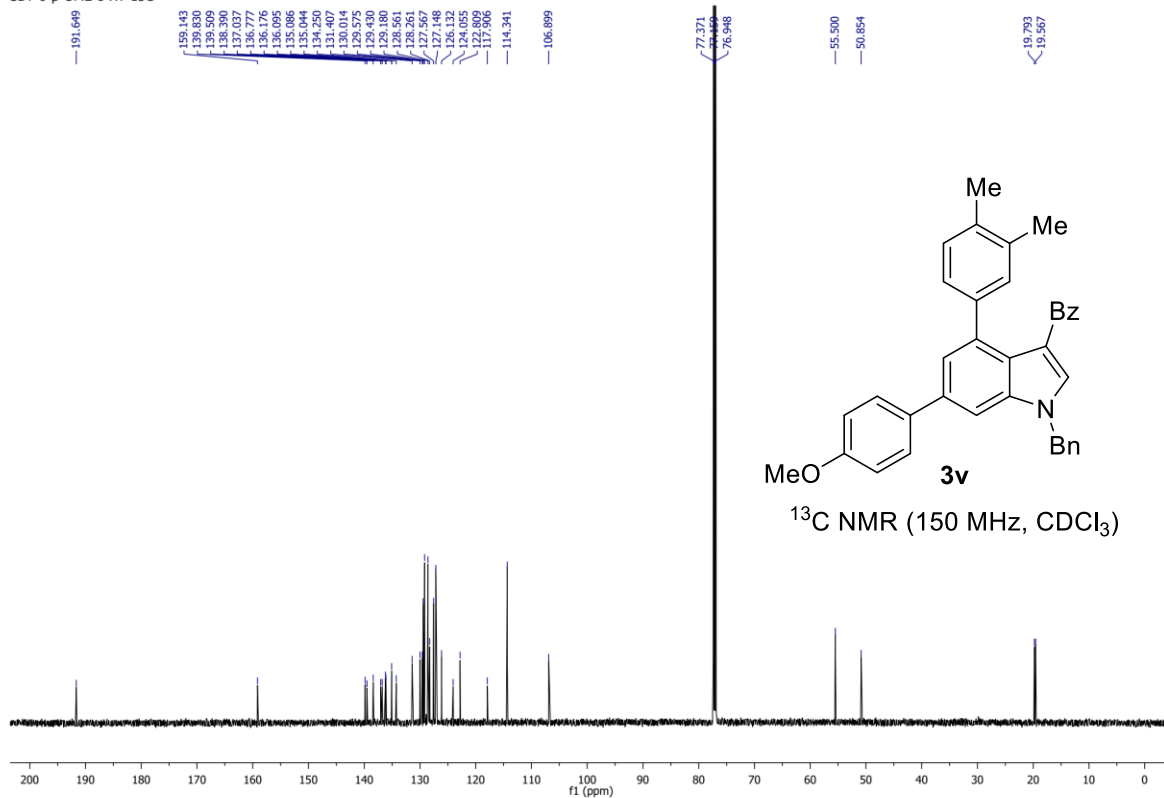
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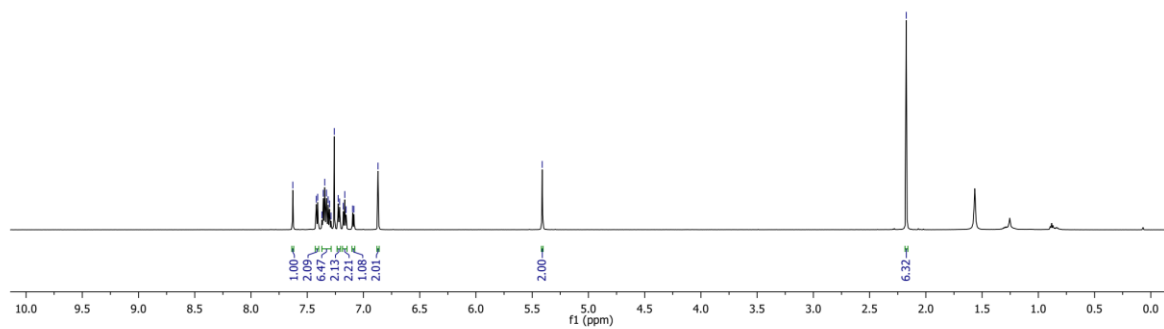
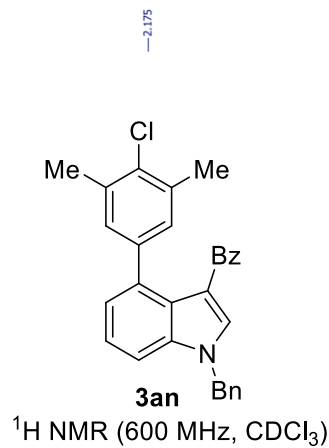
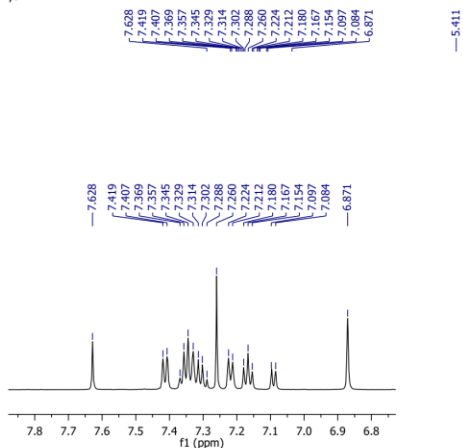
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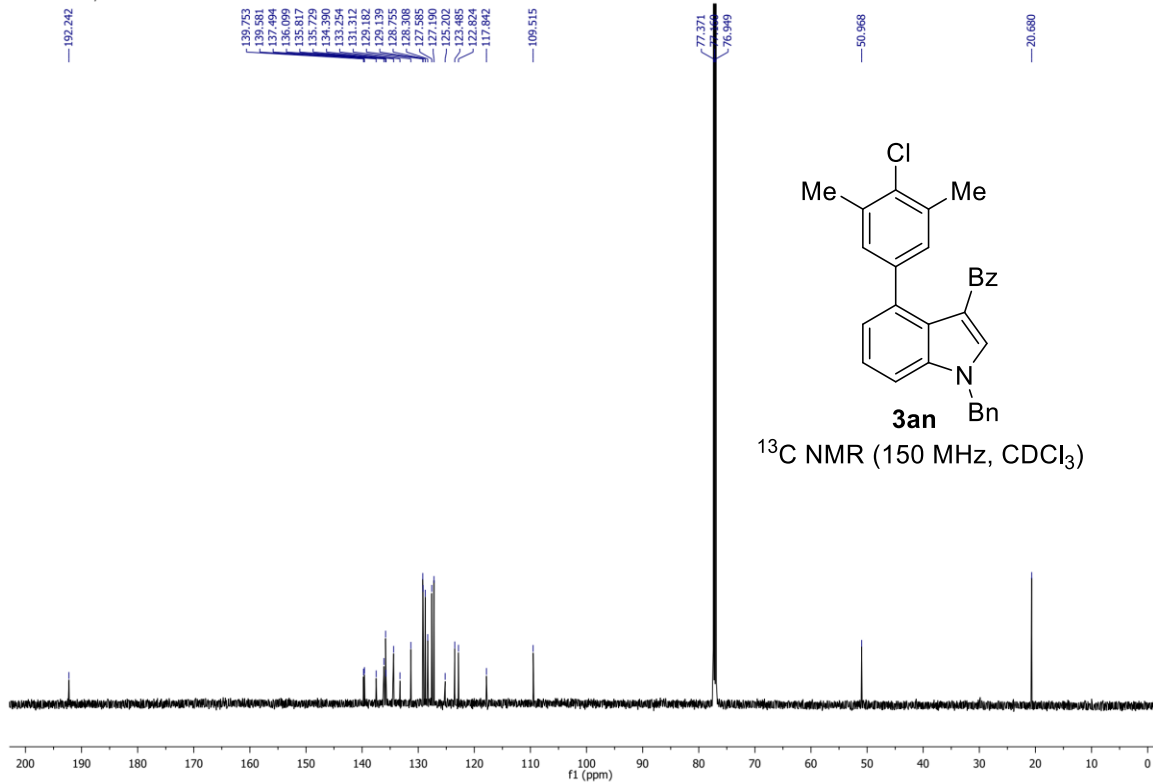
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SBT-BZ-2CL-1,3DIME-BEN-1H

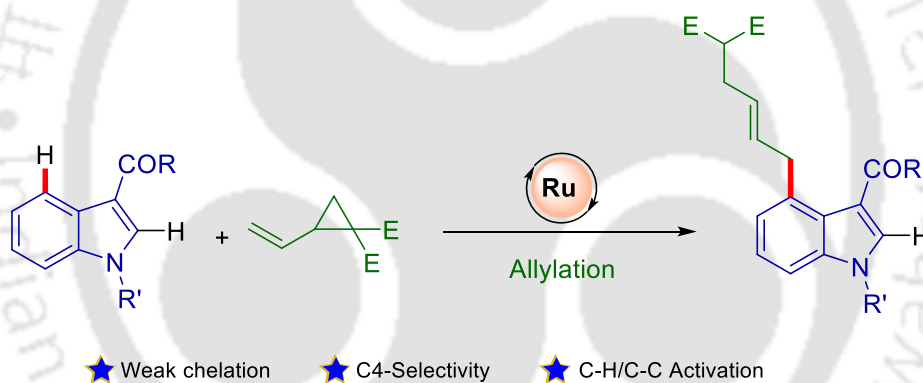


SBT-BZ-2CL-1,3DIME-BEN-13C



Chapter III

Ruthenium-Catalyzed C4-H Allylation of Indoles with Vinylcyclopropanes



Chem. Commun. **2023**, *59*, 11568.



Ruthenium-Catalyzed C4-H Allylation of Indoles with Vinylcyclopropanes

Functionalized indoles are ubiquitous in biologically potent molecules and natural products, showcasing a broad spectrum of pharmacological activities such as antibacterial, anti-inflammatory and antitumor properties.¹ Consequently, there has been a great surge of research interest for the diversification of indole nucleus employing directing group (DG) enabled transition-metal catalysis.² Moreover, the C-H functionalization at the C2- and C3-positions of indole are well-established due to the inherent reactivity of the pyrrole core,³ whereas selective functionalization at the less reactive C-H bonds (C4-C7) of benzenoid ring remains underexplored.⁴ Further, the remote C4-modification of indole in presence of free reactive C2-site endures as a substantial hurdle in catalytic transformations. The challenges to achieve C4-H functionalization involve a competing six membered cyclometalation process at the C4-site over a favorable five membered metallacycle formation at C2-position in presence of DG at C3-site. To address this issue, the exploitation of an appropriately tailored DG at C3-site can facilitate to bring about C4-selectivity, overriding the tendency towards C2-metallation. In this paradigm, the C4-H functionalization of indole has emerged as a burgeoning area of research.^{4a,d} In addition, the C4-allylated indoles are the building blocks of ergot alkaloids, which showcase significant applications in biochemistry and medicinal sciences (Figure 1).⁵ Comprehending the wide applications of C4-allylated indoles, the development of an efficient method for their synthesis would thus be advantageous. Moreover, the utilization of strained small-ring systems has gained considerable interest as the strain-release energy associated with the cleavage serve as a substantial driving force, rendering them ideal scaffolds for TM-catalyzed C-C activation.⁶ Contextually, three-membered vinylcyclopropanes (VCPs) which are readily accessible, can function as the versatile building blocks for the synthetic elaboration of organic scaffolds.⁷ In addition, the facile ring opening may involve β -carbon elimination to execute C-C bond cleavage. Accordingly, the integration of C-H activation and C-C cleavage in a unified tandem process employing strained rings furnishes a potential approach to access complex molecular architecture. In this line, the groups of Ackermann^{7b} and Glorius^{7c} have reported the 2-pyridyl DG-assisted C2-H allylation of indoles employing VCPs under Co- and Mn-catalysis, respectively. In continuation of our efforts, we accomplished an acyl DG guided C4-H allylation of indoles using VCPs *via* merging C-H/C-C bond activation under redox-

neutral Ru-catalysis. The use of weak chelating removable DG, redox-neutral conditions, distal selectivity and mutation of the medicinal molecules are the salient features.

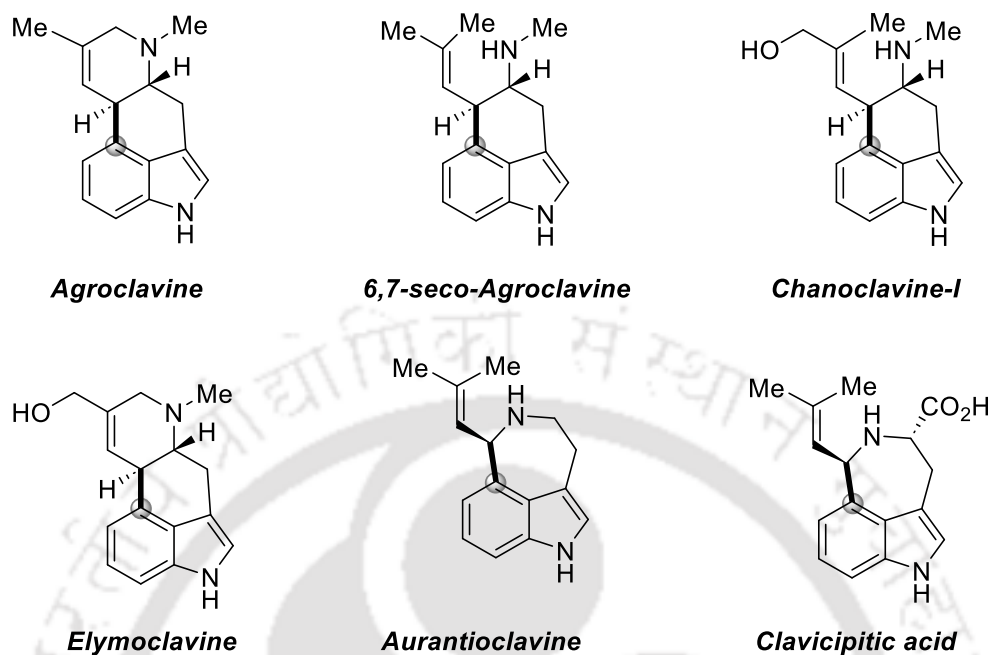
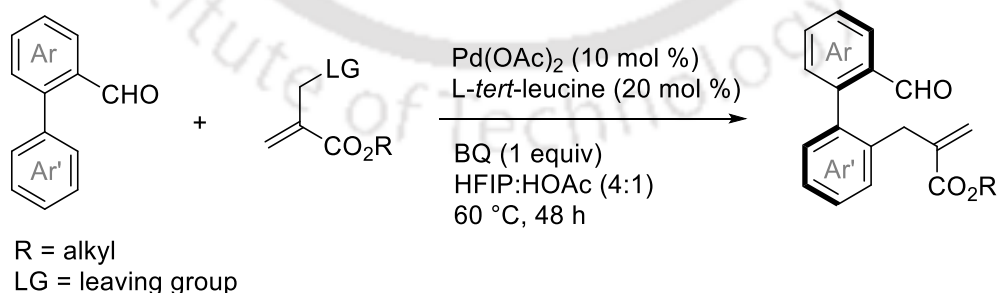


Figure 1. Representative Natural Products of C4-Allylated Indoles.

3.1 C-H Alkylation of (Hetero)arenes

3.1.1 Using Morita-Baylis-Hillman (MBH) Adducts

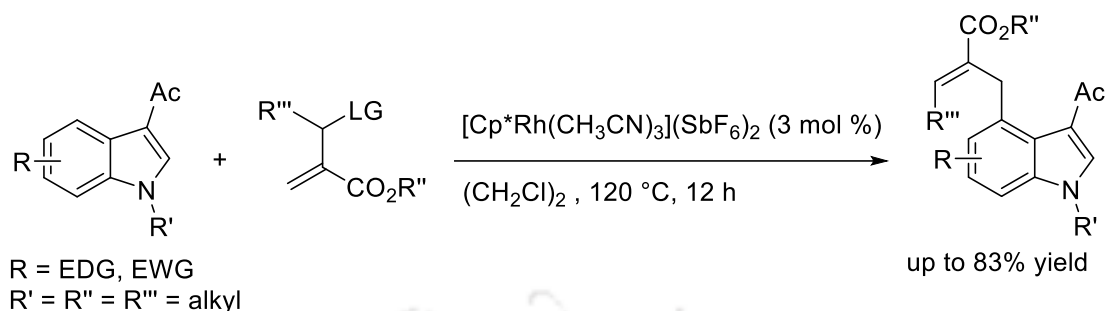
Shi group documented an efficient Pd-catalyzed atroposelective C-H alkylation using MBH adducts via β -O elimination (Scheme 1).⁸ The *tert*-leucine served as transient auxiliary, enabling the synthesis of a wide range of biaryl aldehydes in good to excellent yields and high enantiopurity.



Scheme 1. Pd-Catalyzed Atroposelective C-H Alkylation

Our group developed the Rh-catalyzed distal C4-H alkylation of indole exploiting MBH adducts under redox-neutral conditions (Scheme 2).⁹ The reaction exhibited broad substrate

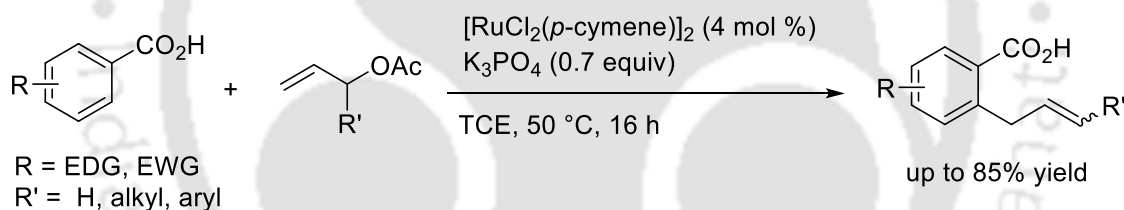
scope, functional group compatibility and late-stage natural product diversification as the notable features.



Scheme 2. Rh-Catalyzed C4-H Alkylation of Indole

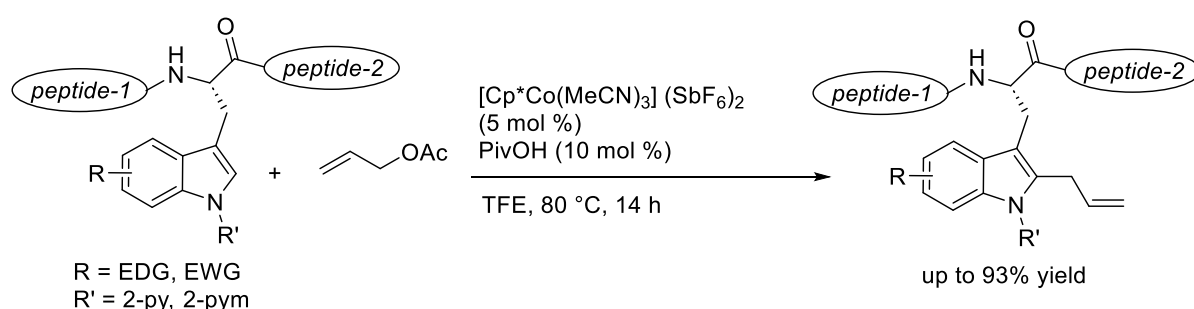
3.1.2 Using Allyl Acetate

Gooßen group disclosed carboxylate-directed regioselective *ortho*-C-H alkylation of benzoic acids with allyl acetates (Scheme 3).¹⁰ Benzoic acids bearing both electron-rich and electron deficient substituents in combination with linear and branched allyl acetates are well tolerated under the mild reaction conditions.



Scheme 3. Ru-Catalyzed *ortho*-C-H Alkylation with Allyl Acetate

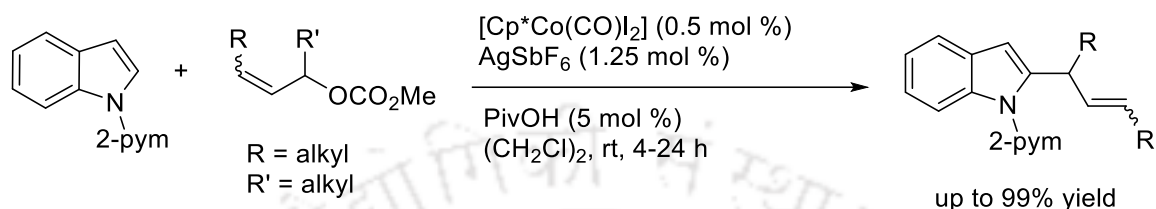
Ackermann and co-workers accomplished the Co(III)-catalyzed biorthogonal C-H alkylation for the late-stage diversification of structurally complex peptides using allyl acetates (Scheme 4).¹¹ The multimetallic merger of C-H activation/olefin metathesis/hydrogenation for the rapid synthesis of cyclic peptides highlights the potentiality of the methodology.



Scheme 4. Co-Catalyzed Late-stage C-H Alkylation of Peptides

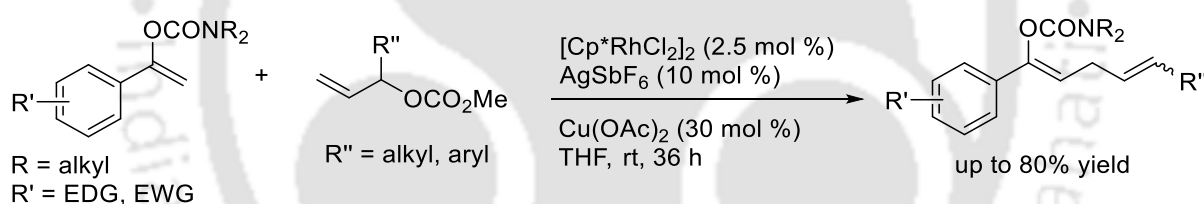
3.1.3 Using Allyl Carbonate

The Co(III)-catalyzed 2-pyrimidyl guided C2-selective allylation of indoles was developed by Glorius group utilizing a variety of substituted allyl carbonates (Scheme 5).¹² The geometry of the product was governed by the conformation of carbonate at the step of olefin insertion to cobaltacycle intermediate.



Scheme 5. Co-Catalyzed C2-H Allylation of Indoles with Allyl Carbonates

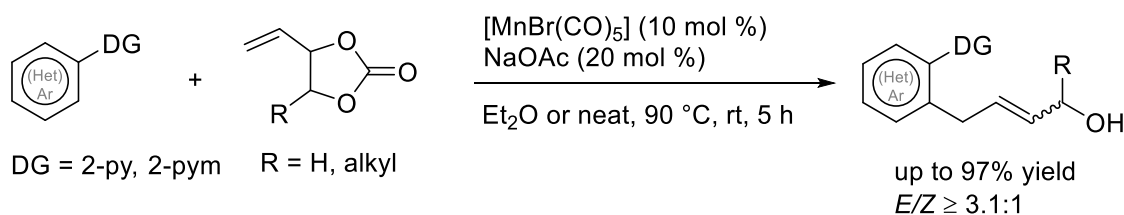
Kim group reported a site-selective C-H allylation of enol carbamates under Rh-catalysis for the direct access of biologically and synthetically convenient allylated enol carbamates under ambient temperature (Scheme 6).¹³ Diverse alkyl, aryl and heteroaryl enol carbamates were well compatible under the reaction conditions.



Scheme 6. Rh-Catalyzed C-H Allylation of Enol Carbamates

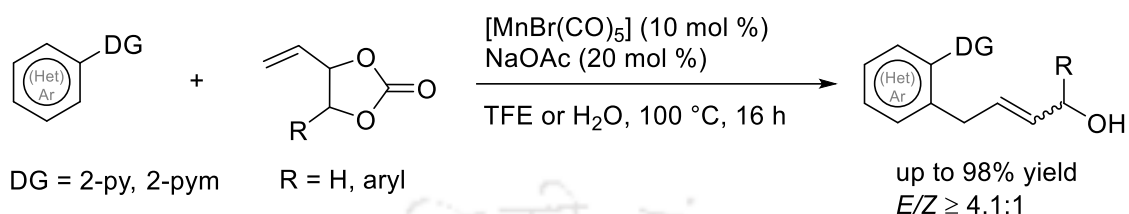
3.1.4 Using Dioxolanone

An elegant approach for the Mn-catalyzed chelation assisted C-H allylation of (hetero)arenes with dioxolanones was disclosed by Glorius and co-workers (Scheme 7).^{7c} The methodology worked efficiently under solvent free conditions. A wide range of allylic alcohols and skipped dienes could be formed in high yields and *E/Z*-selectivity.



Scheme 7. Mn-Catalyzed C-H Allylation with Dioxolanones

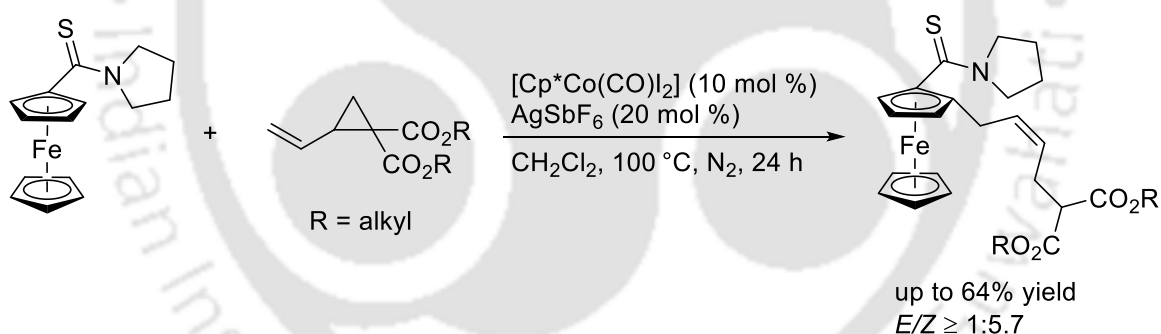
Concurrently, Ackermann group established an unprecedented Mn-catalyzed C-H allylation of (hetero)arenes with dioxolanones (Scheme 8).¹⁴ Excellent chemo-, site- and regioselectivity, ample substrate scope and direct modification of amino acids under racemization free conditions are the notable features.



Scheme 8. Mn-Catalyzed C-H Allylation of (Hetero)arenes

3.1.5 Using Vinylcyclopropanes

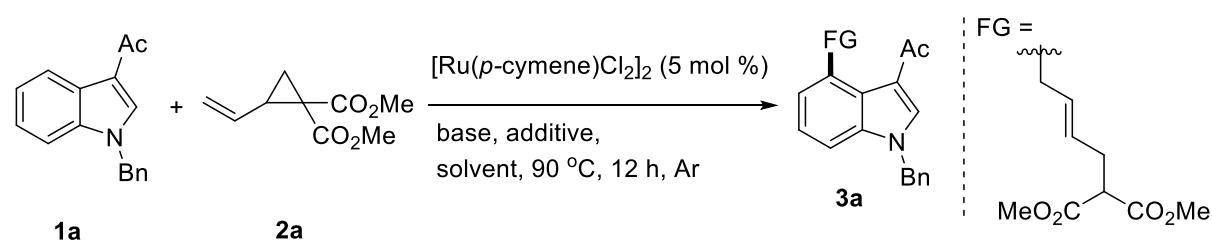
Shi group developed a potential approach for the thioamide directed Co(III)-catalyzed C-H allylation of ferrocenes with VCPs *via* sequential C-H and C-C activation (Scheme 9).¹⁵ The method furnished a diverse array of allylated ferrocene derivatives with high yields, selectivity and functional group compatibility.



Scheme 9. Co-Catalyzed C-H Allylation of Ferrocenes with VCPs

3.2 Present Study

Herein, we have demonstrated an acyl DG assisted C4-H allylation of indoles utilizing VCPs as allyl surrogate *via* successive C-H and C-C bond activation under redox-neutral Ru(II)-catalysis. The method was extended to the site-selective allylation of benzothiophene, tetrahydroquinoline, carbazole, α -tetralone and indoline. At the outset, the optimization studies were commenced with 1-(1-benzyl-1*H*-indol-3-yl)ethan-1-one **1a** and dimethyl 2-vinylcyclopropane-1,1-dicarboxylate **2a** as the standard substrates utilizing [Ru(*p*-cymene)Cl₂]₂ as a catalyst with varied bases, additives and solvents (Table 1). To our delight, the C4-allylated

Table 1. Optimization of the Reaction Conditions^a

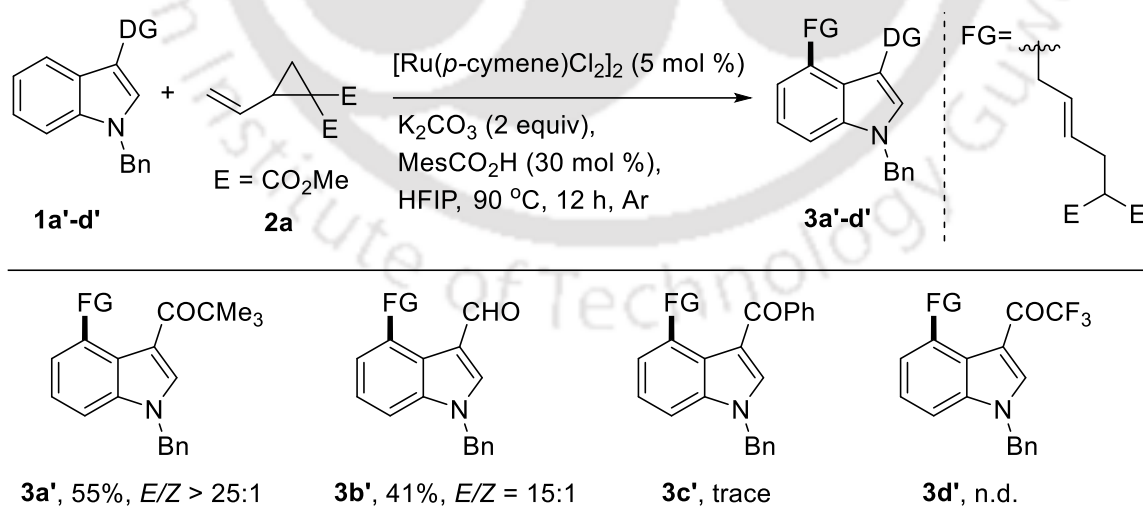
Entry	Base	Additive	Solvent	Yield (%) ^b	<i>E/Z</i> ratio ^c
1	K ₃ PO ₄	---	HFIP	32	8:1
2	CS ₂ CO ₃	---	HFIP	41	12:1
3	K ₂ CO ₃	---	HFIP	65	14:1
4	Na ₂ CO ₃	---	HFIP	50	10:1
5	K₂CO₃	MesCO₂H	HFIP	79	25:1
6	K ₂ CO ₃	1-AdCO ₂ H	HFIP	68	18:1
7	K ₂ CO ₃	PivOH	HFIP	64	16:1
8	K ₂ CO ₃	TsOH	HFIP	61	13:1
9	K ₂ CO ₃	(PhO) ₂ POOH	HFIP	52	10:1
10	K ₂ CO ₃	MesCO ₂ H	TFE	25	7:1
11	K ₂ CO ₃	MesCO ₂ H	MeOH	trace	---
12	K ₂ CO ₃	MesCO ₂ H	H ₂ O	n.d.	---
13	K ₂ CO ₃	MesCO ₂ H	(CH ₂ Cl) ₂	45	5:1
14	K ₂ CO ₃	MesCO ₂ H	THF	trace	---
15	K ₂ CO ₃	MesCO ₂ H	PhCl	n.d.	---
16 ^d	K ₂ CO ₃	MesCO ₂ H	HFIP	41	25:1
17 ^e	K ₂ CO ₃	MesCO ₂ H	HFIP	23	25:1
18 ^f	K ₂ CO ₃	MesCO ₂ H	HFIP	55	25:1
19 ^g	K ₂ CO ₃	MesCO ₂ H	HFIP	n.d.	---
20 ^h	K ₂ CO ₃	MesCO ₂ H	HFIP	trace	---
21 ⁱ	K ₂ CO ₃	MesCO ₂ H	HFIP	n.d.	---
22 ^j	K ₂ CO ₃	MesCO ₂ H	HFIP	n.d.	---
23 ^k	K ₂ CO ₃	MesCO ₂ H	HFIP	n.d.	---
24	---	MesCO ₂ H	HFIP	n.d.	---

^aReaction conditions: **1a** (0.1 mmol), **2a** (0.2 mmol) $[\text{Ru}(p\text{-cymene})\text{Cl}_2]_2$ (5 mol %), base (0.2 mmol), additive (30 mol %), solvent (1 mL), 90 °C, 12 h, Ar, pressure tube. ^b Isolated yield.

^cDetermined by ¹H NMR. ^d 1.0 equiv base used. ^e Reaction at 25 °C. ^f under air. ^g 5 mol % RuCl₃ • 3H₂O used. ^hUsing 10 mol % [Cp*Co(CO)I₂]. ⁱUsing 3 mol % [Cp*RhCl₂]₂. ^jUsing 3 mol % [IrCp*Cl₂]₂. ^kWithout [Ru]-catalyst. n.d. = not detected

3a was obtained in 79% yield (*E/Z* = 25:1), when the reaction was performed in presence of 5 mol % [Ru(*p*-cymene)Cl₂]₂, 2 equiv K₂CO₃ and 30 mol % MesCO₂H in HFIP at 90 °C for 12 h (entry 5). Among the bases examined, K₂CO₃ produced the best outcome compared to K₃PO₄, Cs₂CO₃ and Na₂CO₃ (entries 1-4). The reaction using MesCO₂H as an additive was superior to those of 1-AdCO₂H, PivOH, TsOH and (PhO)₂POOH (entries 6-9). Solvent screening showed that HFIP was the solvent of choice, while TFE, MeOH, H₂O, (CH₂Cl)₂, THF and PhCl gave inferior results (entries 10-15). Decreasing the base amount or temperature as well as reaction under air exhibit the detrimental results in the yield (entries 16-18). Moreover, the use of RuCl₃ • 3H₂O, [Cp*Co(CO)I₂], [Cp*RhCl₂]₂ and [Cp*IrCl₂]₂ failed to catalyze the reaction (entry 19-22). Control experiments in the absence of the Ru-catalyst or base conveyed no allylation, which indicates their major influence in the reaction (entry 23-24). In addition, to examine the efficiency, a set of C3-tailored carbonyl DGs were studied (Table 2). Among them, acetyl DG produced the best result compared to pivaloyl and benzoyl which might be due to the minimal steric hindrance, whereas formyl and trifluoroacetyl groups are electronically less favorable.¹⁶ These results suggest the vital role of DG in achieving the C4-allylation.

Table 2. Directing Groups Screening^{a,b}

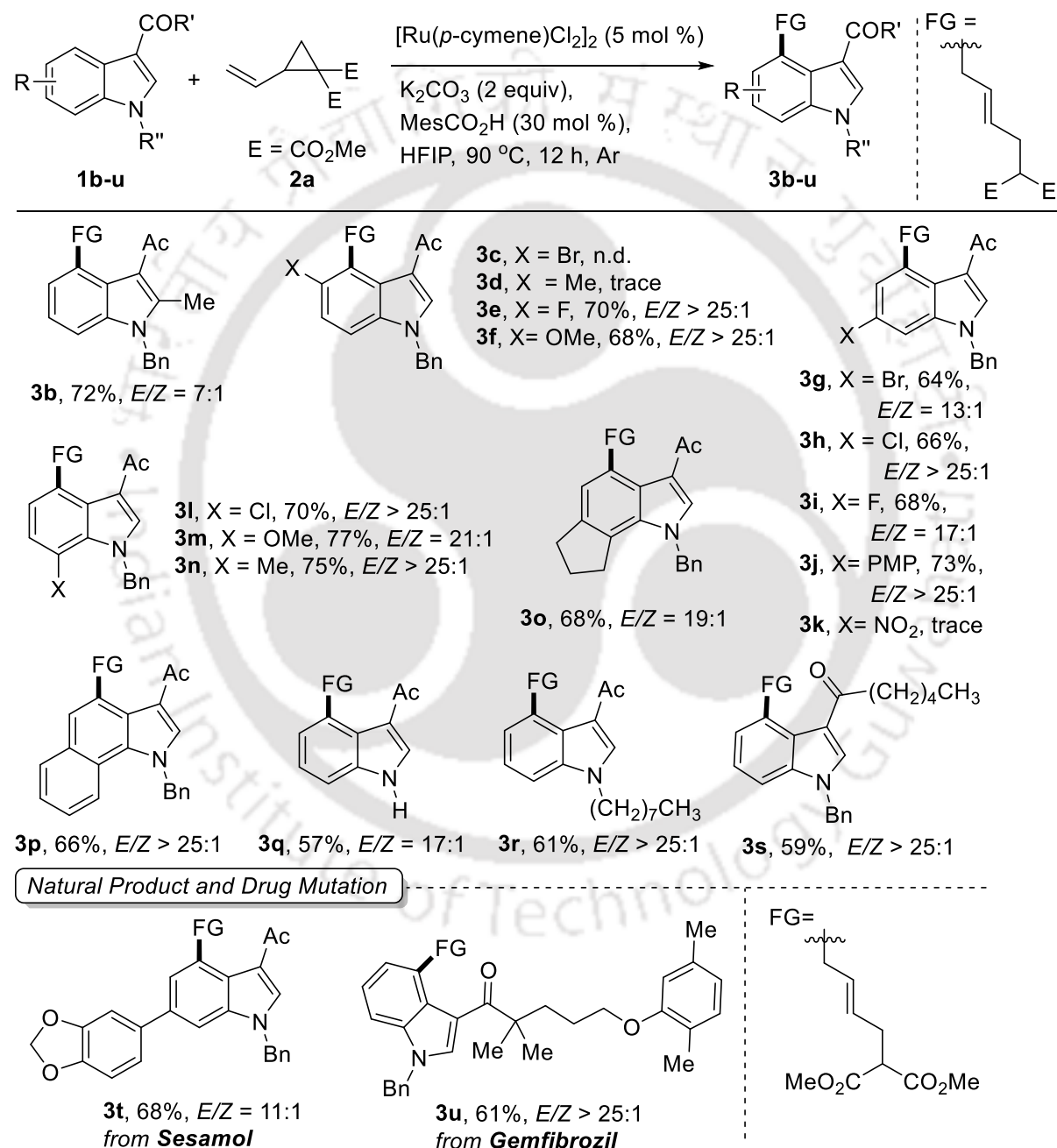


^aReaction conditions: **1a'-d'** (0.1 mmol), **2a** (0.2 mmol), [Ru(*p*-cymene)Cl₂]₂ (5 mol %), K₂CO₃ (0.2 mmol), MesCO₂H (30 mol %), HFIP (1 mL), 90 °C, 12 h, Ar, pressure tube.

^bIsolated yield.

With the optimal reaction conditions, we examined the generality of the reaction using an array of diversely substituted indoles **1b-u** with **2a** as a model substrate (Table 3). The reaction of 2-methylindole **1b** furnished **3b** in 72% yield with reduced diastereoselectivity ($E/Z = 7:1$) which might be due to the steric effect of methyl group.^{7b,c} The substrates having 5-fluoro **1e** and 5-methoxy **1f** groups underwent reaction to give allylated **3e-f** in 68-70% yields with E/Z

Table 3. Substrate Scope of Indoles^{a,b}

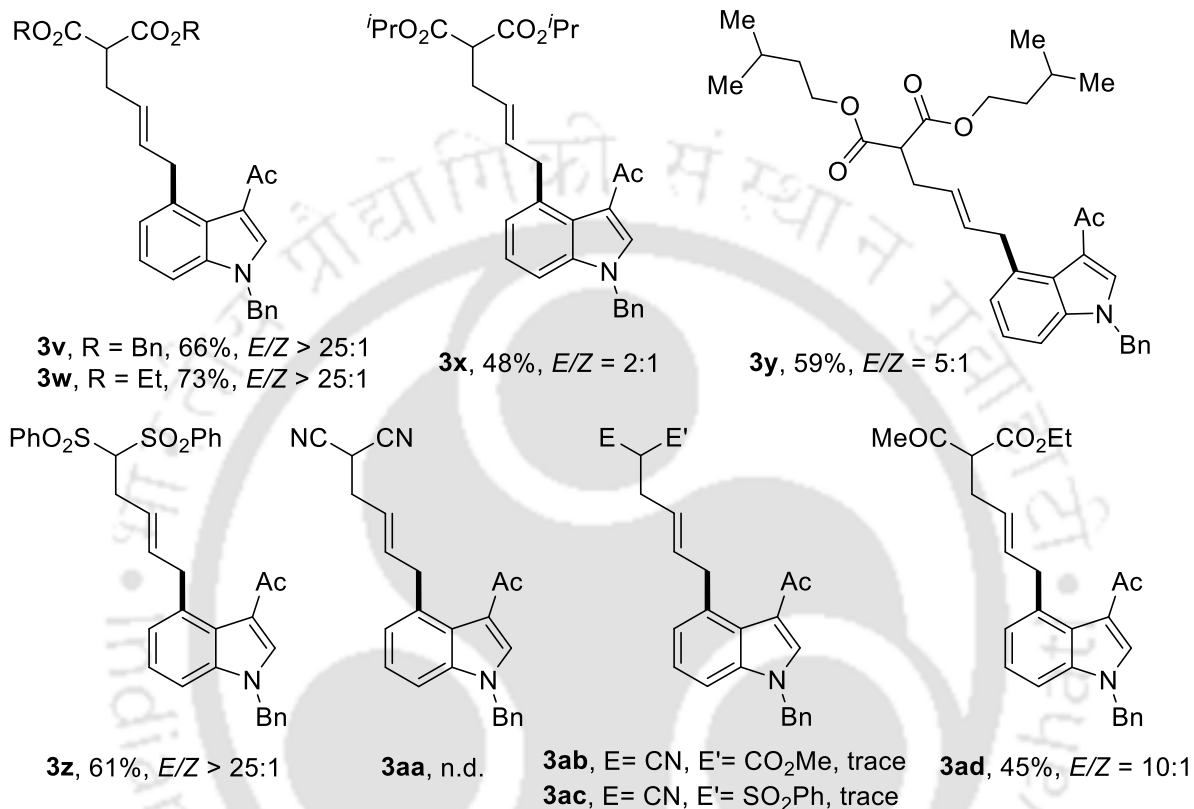
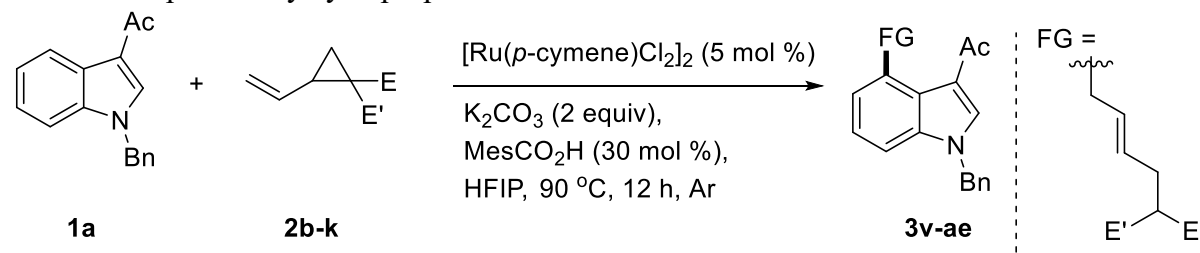


^aReaction conditions: **1b-u** (0.1 mmol), **2a** (0.2 mmol), $[\text{Ru}(p\text{-cymene})\text{Cl}_2]_2$ (5 mol %), K_2CO_3 (0.2 mmol), MesCO_2H (30 mol %), HFIP (1 mL), 90 °C, 12 h, Ar, pressure tube. ^b Isolated yield.

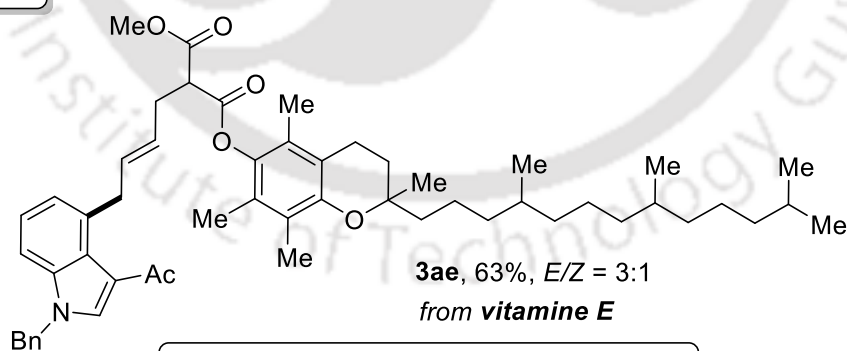
of >25:1. In contrast, 5-bromo **1c** and 5-methyl **1d** substituted indoles failed to afford the product, which was presumably for the steric congestions near C4-position. However, indoles having C6-substitution with bromo **1g**, chloro **1h**, fluoro **1i** and *p*-methoxy-phenyl (PMP) **1j** groups were amenable to deliver **3g-j** in 64-73% yields and $\geq 13:1$ (*E/Z*)-diastereoselectivities, whereas electron-deficient 6-nitro substituted **1k** produced a trace amount of **3k**. In addition, 7-chloro **1l**, 7-methoxy **1m** and 7-methyl **1n** substituted indoles reacted to afford **3l-n** in 70-77% yields with *E/Z* of $\geq 21:1$. Intriguingly, fused indole congeners **1o** and **1p** underwent allylation to provide **3o** and **3p** in 68% and 66% yields, respectively, with *E/Z* of $\geq 19:1$. Moreover, NH-free indole **1q** furnished **3q** in 57% yield and *E/Z* of 17:1. Pertinent results were obtained with *N*-octyl **1r** and C3-hexanoyl **1s** indoles, giving **3r** and **3s** in 61% and 59% yields, respectively, with *E/Z* of >25:1. In addition, the substrates tethered with naturally occurring sesamol **1t** and gemfibrozil **1u** units participated in the reaction to deliver **3t** and **3u** in 68% and 61% yields, respectively, with $\geq 11:1$ (*E/Z*)-diastereoselectivities, which demonstrates the captivating potential of the procedure for the late-stage modifications of biorelevant molecules.

With these intriguing results, the allylation procedure was extended to the coupling of a series of VCPs **2b-k** with indole **1a** as a test substrate (Table 4). A variety of ester containing VCPs such as benzyl **2b** and ethyl **2c** successfully coupled to give **3v** and **3w** in 66% and 73% yields, respectively, with >25:1 (*E/Z*)-diastereoselectivities. In addition, VCPs with isopropyl **2d** and isoamyl **2e** groups furnished **3x-y** in 48-59% yields, with *E/Z* of $\geq 2:1$. The reduced *E/Z* ratio may result from the influence of the substituents of VCP in β -carbon elimination step.^{7b} Moreover, VCP with diphenylsulfonyl group **2f** afforded **3z** in 61% yield with *E/Z* of >25:1, whereas the reactions using cyano group bearing VCPs **2g-i** were unsuccessful, which may be attributed to the chelation of the cyano group to the Ru-catalyst. However, VCP with keto-ester **2j** underwent allylation to afford **3ad** in 45% yield, with 10:1 (*E/Z*)-diastereoselectivities. In addition, vitamin E bound VCP **2k** successfully coupled to deliver **3ae** in 63% yield and *E/Z* of 3:1. The scope of the procedure was further examined with reaction of 1-tosyl-2-vinylaziridine **2A** and 2-vinylloxirane **2B**. The former was amenable to deliver **3A** in 50% yield with *E/Z* of >25:1, whereas the latter produced a trace amount of **3B**.

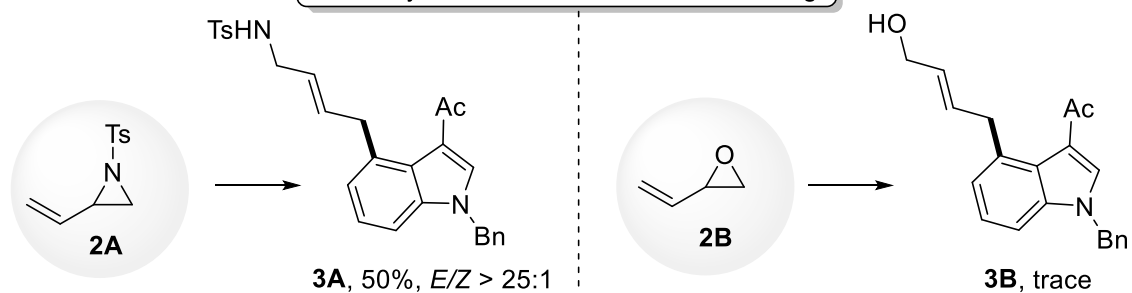
Further, the success of the procedure could be demonstrated by the potential viability to other weak carbonyl DG-tethered (hetero)aryl substrates (Table 5). For examples, benzothiophene **1A**, indoline **1B**, 1,2,3,4-tetrahydroquinoline **1C**, 3,4-dihydronaphthalen-1(2*H*)-one **1D** and carbazole **1E** underwent allylation to afford **4A-E** in 36-70% yields and $\geq 2:1$ *E/Z*-diastereoselectivities.

Table 4. Scope of Vinylcyclopropanes^{a,b}

Drug Conjugate

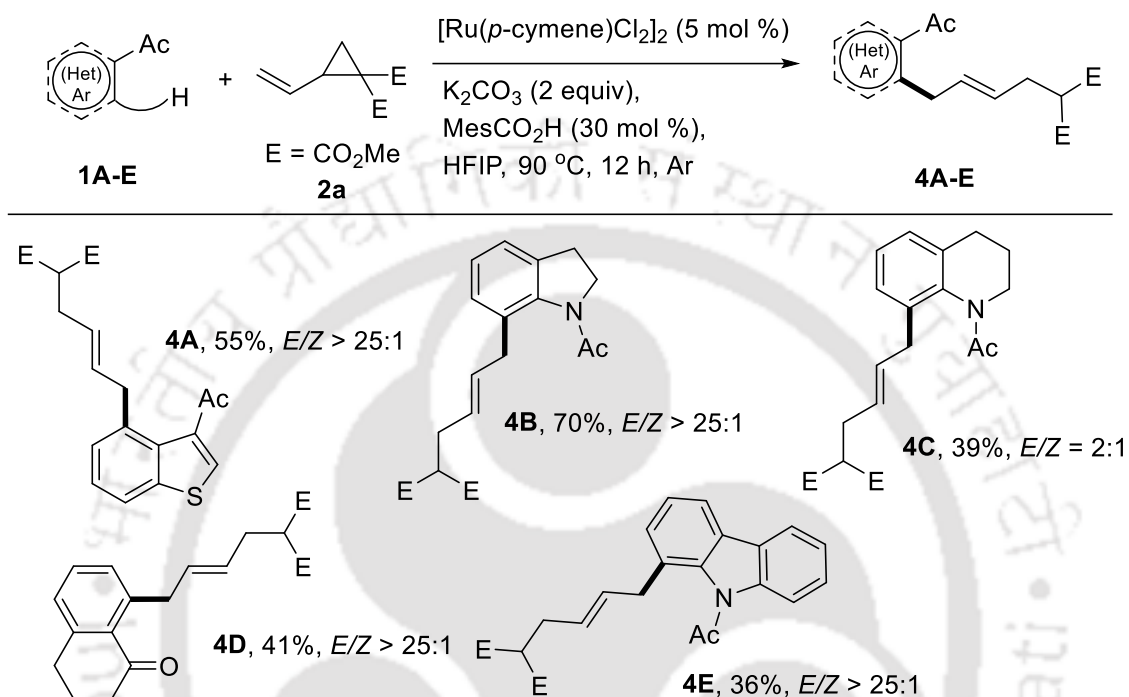


other vinyl substituted three membered rings



^aReaction conditions: **1a** (0.1 mmol), **2b-k** or **2A-B** (0.2 mmol), [Ru(*p*-cymene)Cl₂]₂ (5 mol %), K₂CO₃ (0.2 mmol), MesCO₂H (30 mol %), HFIP (1 mL), 90 °C, 12 h, Ar, pressure tube. ^b Isolated yield.

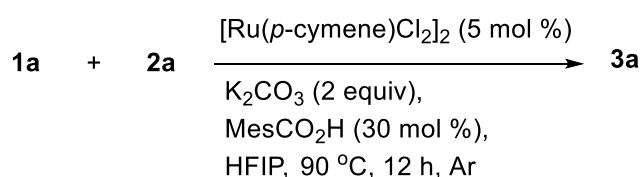
Table 5. Scope of Other Weak-chelating Substrates ^{a,b}



^aReaction conditions: **1A-E** (0.1 mmol), **2a** (0.2 mmol), [Ru(*p*-cymene)Cl₂]₂ (5 mol %), K₂CO₃ (0.2 mmol), MesCO₂H (30 mol %), HFIP (1 mL), 90 °C, 12 h, Ar, pressure tube. ^b Isolated yield.

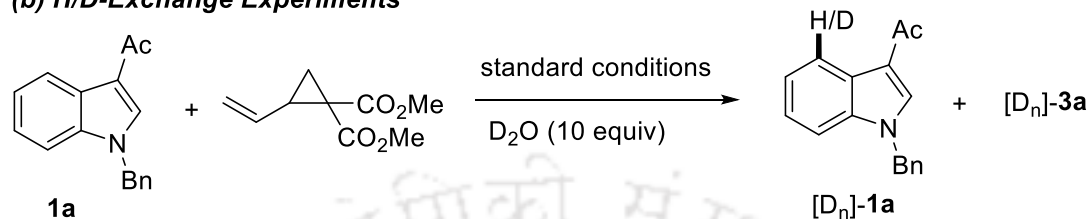
To get insight into the reaction pathway, a set of preliminary investigations were performed (Scheme 11). The allylation reaction of **1a** with **2a** in presence of 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO) and 2,6-di-*tert*-butyl-4-methylphenol (BHT) as radical scavengers, proceeded well to produce **3a**, which ruled out the involvement of radical pathway (Scheme 11a). Moreover, the H/D exchange experiments in the presence or absence of **2a** using D₂O as a co-solvent, showed 15% and 26% deuterium incorporation, respectively, at the C4-site (Scheme 11b). The lower deuterium scrambling was probably due to the rapid deuterium exchange from the protic HFIP. The intermolecular kinetic isotope experiment using **1a** and [D₂]-**1a** with **2a** revealed k_H/k_D of 2.18, which indicates that C4-H bond activation may be the rate-determining step (Scheme 11c).

(a) Radical Trapping Experiments



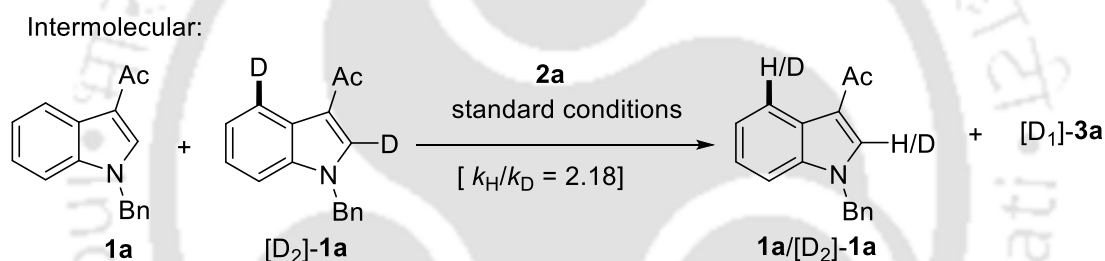
radical scavengers (1 equiv)	yield of 3a
TEMPO	68%
BHT	64%

(b) H/D-Exchange Experiments



variation	C-4 deuteration	C-2 deuteration
none	15%	5%
without 2a	26%	11%

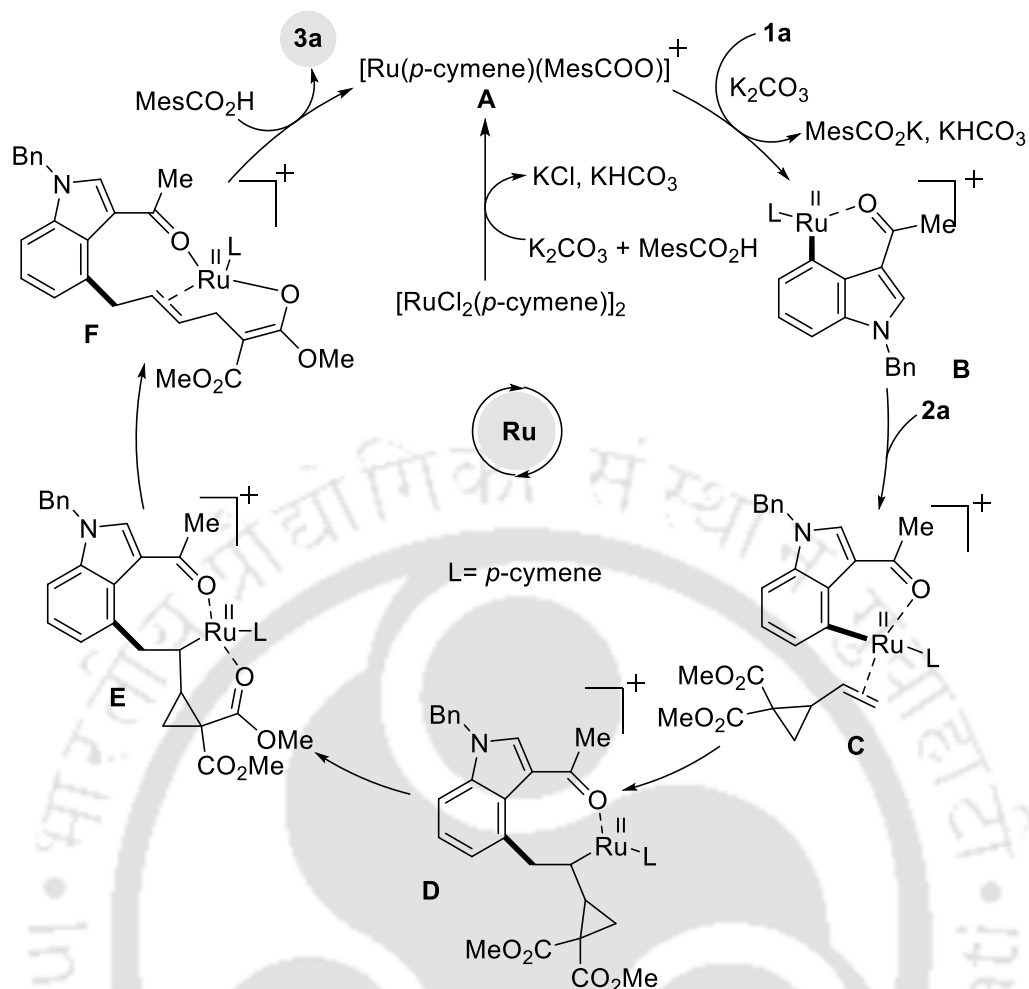
(c) Kinetic Isotope Experiment



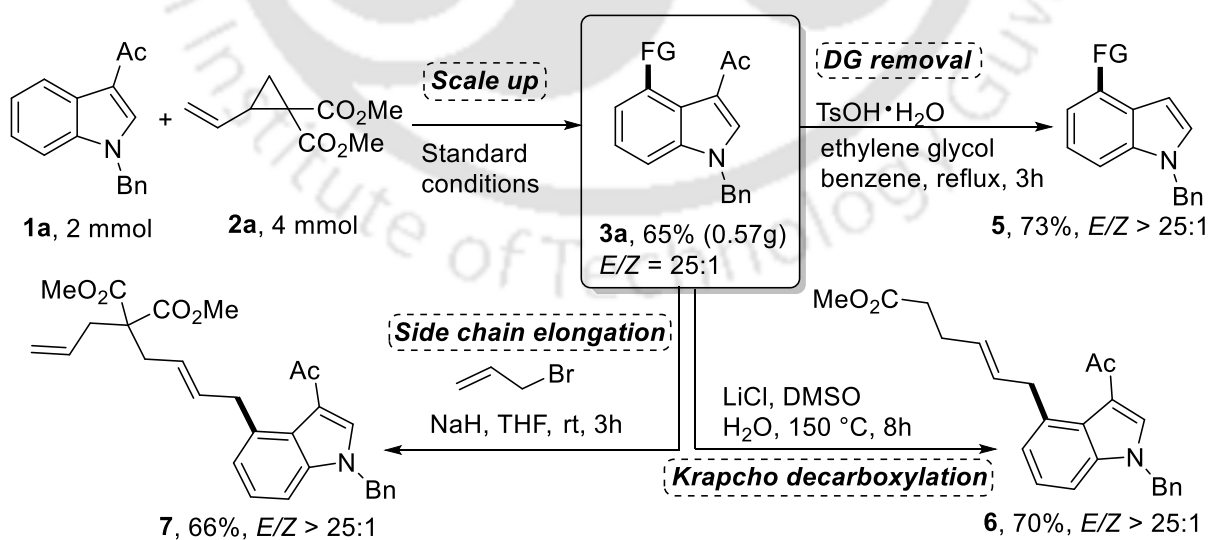
Scheme 11. Preliminary Mechanistic Investigations

Based on these experimental results and literature precedents¹⁷ a plausible mechanism is depicted in Scheme 12. Initially, $[\text{Ru}(p\text{-cymene})\text{Cl}_2]_2$ with K_2CO_3 and MesCO_2H may generate the active cationic $\text{Ru}(\text{II})$ -species **A** that can activate C4-H bond of **1a** to produce the ruthenacycle **B**.^{17a,b} Coordination of **2a** followed by subsequent 1,2-migratory insertion leads to the intermediate **D**. The chelation of ester group of **2a** can afford **E** that can seamlessly undergo β -carbon elimination to give **F**. The protodemetalation of **F** can furnish the target product **3a** and regenerate the active catalyst.

The scalability of the procedure was investigated by the direct coupling of **1a** (2 mmol) with **2a** as the representative substrates to afford **3a** in 65% yield (Scheme 13). In addition, the acetyl DG from **3a** can be uninstalled *via* reverse Friedel-Crafts reaction in presence of $\text{TsOH} \cdot \text{H}_2\text{O}$ and ethylene glycol to give **5** in 73% yield. In addition, Krapcho decarboxylation of **3a** delivered the mono-ester **6** in 70% yield and side chain elongation with allyl bromide afforded **7** in 66% yield.



Scheme 12. Plausible Reaction Mechanism



Scheme 13. Scale-up and Post-synthetic Utilities

In conclusion, we have described the Ru-catalyzed auxiliary guided redox-neutral C4-H alkylation of indoles with VCPs *via* successive C-H and C-C bond activation. The use of weak

chelating removable DG, redox-neutral conditions, distal selectivity, substrate scope and mutation of the medicinal molecules are the important features.

3.3 Experimental Section

General Information. Indoles, [Ru(*p*-cymene)Cl₂]₂ (>97%), RuCl₃·3H₂O (>98%), MesCO₂H (99%), 1-AdCO₂H (99%), PivOH (99%), K₃PO₄ (98%), CS₂CO₃ (98%), K₂CO₃ (≥98%), Na₂CO₃ (99.5%), 3,4-dihydro-1(2*H*)-naphthalenone (97%), 3,4-epoxy-1-butene (98%), TFE and HFIP of Aldrich and TCI Chemicals were used as received. The substrates *N*-alkyl 3-acyl indoles **1**,¹⁸ VCPs **2**^{7,19} and vinylaziridine **2A**²⁰ were prepared according to the reported procedures. Methanol, tetrahydrofuran, 1,2-dichloroethane and chlorobenzene were dried prior as per the standard procedure. Merck silica gel G/GF254 plates were used for analytical thin-layer chromatography. Column chromatography was carried out using Rankem silica gel (60-120 mesh). Bruker Avance III 400, 500 and 600 MHz NMR spectrometers were used to record spectra using CDCl₃ as the solvent and tetramethylsilane (Me₄Si) as an internal standard. Chemical shifts (δ) and spin-spin coupling constant (*J*) are reported in parts per million and hertz (Hz), respectively, and to describe peak patterns following abbreviations were used when appropriate: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = double doublet. Melting points were determined using a Büchi B-540 apparatus and are uncorrected. IR spectra were recorded on a PerkinElmer Fourier transform infrared spectrometer. Quadrupole time-of-flight electrospray ionization mass spectrometer (Agilent 6546) and Xevo XS mass spectrometer were used for recording HRMS.

General Procedure for Ru(II)-Catalyzed C4-Allylation of Indoles. In an oven-dried pressure tube, a mixture of indole **1** (0.1 mmol), VCP **2** (0.2 mmol), [Ru(*p*-cymene)Cl₂]₂ (5 mol %, 0.005 mmol, 3 mg), K₂CO₃ (0.2 mmol, 28 mg) and MesCO₂H (0.03 mmol, 5 mg) were stirred in HFIP (1 mL) at 90 °C in a preheated oil bath for 12 h under Ar atmosphere. The reaction progress was monitored by TLC using ethyl acetate and hexane as an eluent. Upon completion, the reaction mixture was allowed to cool to room temperature and was diluted with EtOAc and passed through a celite pad. The filtrate was concentrated under reduced pressure and the residue was purified on silica gel column chromatography using *n*-hexane and ethyl acetate as an eluent to afford C4-allylated indole **3** in moderate to good yields.

Radical Trapping Experiments. In an oven-dried pressure tube, a mixture of indole **1a** (0.1 mmol, 24.9 mg), dimethyl 2-vinylcyclopropane-1,1-dicarboxylate **2a** (0.2 mmol, 36.8 mg), [Ru(*p*-cymene)Cl₂]₂ (5 mol %, 0.005 mmol, 3 mg), K₂CO₃ (0.2 mmol, 28 mg), MesCO₂H (0.03 mmol, 5 mg) and TEMPO (0.1 mmol, 15.6 mg) or BHT (0.1 mmol, 22 mg) were stirred in

HFIP (1 mL) at 90 °C in a preheated oil bath for 12 h under Ar atmosphere. Upon completion, the reaction mixture was allowed to cool to room temperature and was diluted with EtOAc and passed through a celite pad. The purification was performed as described in the general procedure to afford **3a**.

H/D Exchange Experiment of 1a with D₂O in Presence of 2a. In an oven-dried pressure tube, a mixture of indole **1a** (0.1 mmol, 24.9 mg), dimethyl 2-vinylcyclopropane-1,1-dicarboxylate **2a** (0.2 mmol, 36.8 mg), [Ru(*p*-cymene)Cl₂]₂ (5 mol %, 0.005 mmol, 3 mg), K₂CO₃ (0.2 mmol, 28 mg), MesCO₂H (0.03 mmol, 5 mg), D₂O (1 mmol, 0.2 mL) and HFIP (1 mL) were stirred at 90 °C in a preheated oil bath for 12 h under Ar atmosphere. Upon completion, the reaction mixture was allowed to cool to room temperature and was diluted with EtOAc and passed through a celite pad. The purification was performed as described in the general procedure to afford [D_n]-**1a** and [D_n]-**3a**. The deuterium incorporation was observed as 15% at C4-H, 5% at C2-H of **1a** based on 500 MHz ¹H NMR spectrum.

H/D Exchange Experiment of 1a with D₂O in Absence of 2a. In an oven-dried pressure tube, a mixture of indole **1a** (0.1 mmol, 24.9 mg), [Ru(*p*-cymene)Cl₂]₂ (5 mol %, 0.005 mmol, 3 mg), K₂CO₃ (0.2 mmol, 28 mg), MesCO₂H (0.03 mmol, 5 mg), D₂O (1 mmol, 0.2 mL) and HFIP (1 mL) were stirred at 90 °C in a preheated oil bath for 12 h under Ar atmosphere. Upon completion, the reaction mixture was allowed to cool to room temperature and was diluted with EtOAc and passed through celite pad. The purification was performed as described in the general procedure to give [D_n]-**1a**. The deuterium incorporation was observed as 26% at C4-H and 11% at C2-H based on 500 MHz ¹H NMR spectrum.

Preparation of 1-(1-Benzyl-1*H*-indol-3-yl-2,4-*d*₂)ethan-1-one [D₂]-1a**.** In an oven-dried pressure tube, 1-(1-benzyl-1*H*-indol-3-yl)ethan-1-one **1a** (0.1 mmol, 24.9 mg), [Cp**Rh*Cl₂]₂ (2.5 mol %, 0.0025 mmol, 1.5 mg), AgSbF₆ (0.02 mmol, 6.8 mg), Cu(OAc)₂ (0.1 mmol, 18 mg), D₂O (0.4 mmol, 80 μL) and 1,4-dioxane (1.5 mL) were stirred at 120 °C in a preheated oil bath for 14 h. The resulting reaction mixture was allowed to cool to room temperature, diluted with CH₂Cl₂ (10 mL) and passed through a short pad of celite. Drying over Na₂SO₄ and evaporation of the solvent gave a residue that was purified on silica gel column chromatography using *n*-hexane and ethyl acetate as an eluent to afford [D₂]-**1a** as a light-yellow solid. The deuterium incorporation was determined using 600 MHz ¹H NMR as 85% at C4-H.

Kinetic Isotope Effect Experiment. A mixture of 1-(1-benzyl-1*H*-indol-3-yl)ethan-1-one **1a** (0.05 mmol, 12.4 mg) and 1-(1-benzyl-1*H*-indol-3-yl-2,4-*d*₂)ethan-1-one [D₂]-**1a** (0.05 mmol, 12.5 mg) was stirred with dimethyl 2-vinylcyclopropane-1,1-dicarboxylate **2a** (0.2 mmol, 36.8 mg) for 0.5 h under standard reaction condition. The reaction mixture was allowed to cool to room temperature and was diluted with EtOAc (5 mL) and passed through celite pad. The purification was performed as described in the general procedure to afford [D₁]-**3a** and a mixture of unreacted **1a** and [D₂]-**1a** as a colorless solid. The intermolecular k_H/k_D was found to be 2.18, based on 400 MHz ¹H NMR of the recovered substrate **1a** and [D₂]-**1a**.

Scale-up Synthesis of 3a. In an oven-dried pressure tube, a mixture of 1-(1-benzyl-1*H*-indol-3-yl)ethan-1-one **1a** (2 mmol, 498 mg), dimethyl 2-vinylcyclopropane-1,1-dicarboxylate **2a** (4 mmol, 736 mg), [Ru(*p*-cymene)Cl₂]₂ (5 mol%, 0.1 mmol, 61 mg), K₂CO₃ (4 mmol, 552 mg), MesCO₂H (0.6 mmol, 98 mg) and HFIP (15 mL) were subjected to the aforementioned general procedure. Upon completion, monitored by TLC, the reaction mixture was cooled to room temperature and was diluted with EtOAc (5 mL) and passed through a short pad of celite. Evaporation of the solvent gave a residue that was purified on silica gel column chromatography using *n*-hexane and ethyl acetate as an eluent (85/15, v/v) to afford **3a** in 65% (0.56 g) yield.

Procedures for the Post-Synthetic Modifications

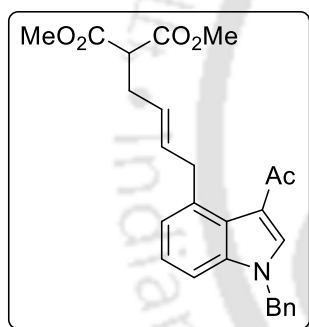
Removal of Acetyl Directing Group.¹⁸ In an oven-dried round bottom flask, a mixture of dimethyl (*E*)-2-(4-(3-acetyl-1-benzyl-1*H*-indol-4-yl)but-2-en-1-yl)malonate **3a** (0.1 mmol, 43 mg), ethylene glycol (0.1 mL) and *p*-toluenesulfonic acid monohydrate (0.1 mmol, 21 mg) was refluxed in benzene (2 mL) for 3 h. After completion, monitored by TLC, the reaction mixture was cooled to room temperature, washed with saturated NaHCO₃ solution (5 mL) and extracted using EtOAc (3 x 10 mL). Drying over Na₂SO₄ and evaporation of the solvent under reduced pressure gave a residue that was purified on silica gel column chromatography using *n*-hexane and ethyl acetate (97/3, v/v) as an eluent to afford **5** in 73 % (28.5 mg) yield.

Synthesis of 6.²¹ In an oven-dried round bottom flask, a mixture of dimethyl (*E*)-2-(4-(3-acetyl-1-benzyl-1*H*-indol-4-yl)but-2-en-1-yl)malonate **3a** (0.1 mmol, 43 mg) and LiCl (0.5 mmol, 21 mg) in DMSO (1 mL) and H₂O (0.5 mmol, 10 μL) was stirred at 150 °C for 12 h under Ar atmosphere. Upon completion, the reaction mixture was cooled to room temperature and extracted with EtOAc (3 x 10 mL). The organic layer was washed with brine (1 x 10 mL) and water (1 x 10 mL). Drying over Na₂SO₄ and evaporation of the solvent gave a residue that was

purified on silica gel column chromatography using *n*-hexane and ethyl acetate (90/10, v/v) as an eluent to afford **6** in 70 % (26.2 mg) yield.

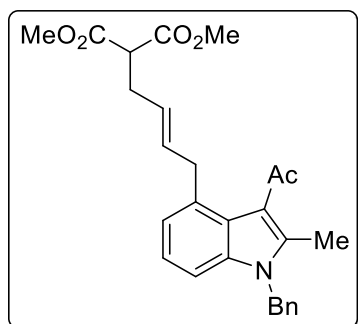
Synthesis of 7.²² To a stirred solution of dimethyl (*E*)-2-(4-(3-acetyl-1-benzyl-1*H*-indol-4-yl)but-2-en-1-yl)malonate **3a** (0.1 mmol, 43 mg) and a suspension of NaH (0.11 mmol, 4.5 mg, 60 % dispersion in mineral oil) in THF (2 mL) at 0 °C for 20 min, allyl bromide (0.1 mmol, 9 μL) was added and the stirring was continued for 3 h at room temperature. Upon completion, monitored by TLC, the reaction mixture was quenched with saturated aq. NH₄Cl solution (1 mL) and diluted with EtOAc (5 mL) and water (5 mL). The organic layer was extracted using EtOAc (2 x 10 mL), dried over Na₂SO₄ and evaporation of the solvent under reduced pressure gave a residue that was purified on silica gel column chromatography using *n*-hexane and ethyl acetate (90/10, v/v) as an eluent to afford **7** in 66 % (31.2 mg) yield.

3.4 Characterization Data of the Products

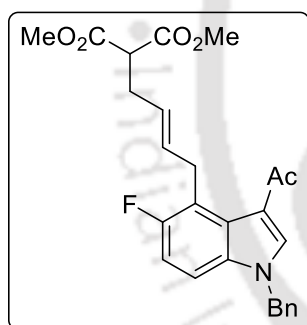


Dimethyl (*E*)-2-(4-(3-acetyl-1-benzyl-1*H*-indol-4-yl)but-2-en-1-

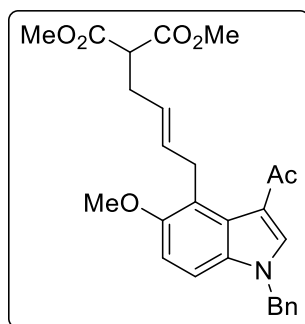
yl)malonate 3a. Analytical TLC on silica gel, 1:2 ethyl acetate/hexane $R_f = 0.45$; brown sticky liquid; yield 79% (34.2 mg, *E/Z* = 25:1); ¹H NMR (600 MHz, CDCl₃) δ 7.78 (s, 1H), 7.35-7.30 (m, 3H), 7.19-7.17 (m, 1H), 7.14-7.13 (m, 3H), 7.05-7.03 (m, 1H), 5.79-5.74 (m, 1H), 5.39-5.34 (m, 1H), 5.33 (s, 2H), 4.07 (d, *J* = 7.2 Hz, 2H), 3.64 (s, 6H), 3.39 (t, *J* = 7.8 Hz, 1H), 2.57 (t, *J* = 7.2 Hz, 2H), 2.52 (s, 3H); ¹³C NMR (150 MHz, CDCl₃) δ 192.2, 169.6, 138.3, 136.7, 136.2, 135.8, 134.2, 129.1, 128.3, 127.0, 125.3, 124.5, 124.0, 123.8, 119.2, 108.2, 52.4, 52.1, 50.8, 38.7, 32.1, 28.7; FT-IR (neat) 2922, 1732, 1654, 1524, 1438, 1376, 1231, 1191, 972, 749 cm⁻¹; HRMS (ESI) *m/z* [M+H]⁺ calcd for C₂₆H₂₈NO₅: 434.1962, found 434.1967.



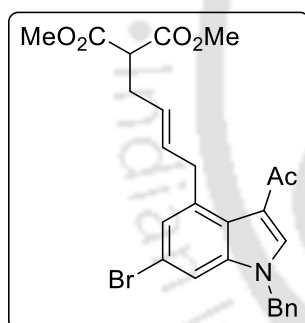
Dimethyl (*E*)-2-(4-(3-acetyl-1-benzyl-2-methyl-1*H*-indol-4-yl)but-2-en-1-yl)malonate 3b. Analytical TLC on silica gel, 1:2 ethyl acetate/hexane $R_f = 0.48$; ; brown sticky liquid; yield 72% (32 mg, $E/Z = 7:1$); $^1\text{H NMR}$ (600 MHz, CDCl_3) δ 7.29-7.26 (m, 2H), 7.24-7.23 (m, 1H), 7.16-7.09 (m, 2H), 6.98-6.97 (m, 3H), 5.70-5.65 (m, 1H), 5.42-5.37 (m, 1H), 5.32 (s, 2H), 3.76-3.66 (m, 8H), 3.42 (t, $J = 7.8$ Hz, 1H), 2.61-2.58 (m, 5H), 2.50 (s, 3H); $^{13}\text{C NMR}$ (150 MHz, CDCl_3) δ 198.9, 169.5, 139.1, 137.1, 136.5, 133.2, 132.7, 129.0, 127.7, 126.5, 126.0, 124.2, 122.8, 122.7, 118.3, 107.8, 52.5, 51.9, 46.7, 37.5, 32.5, 32.1, 12.3; FT-IR (neat) 2952, 1733, 1653, 1435, 1351, 1230, 1195, 972, 734 cm^{-1} ; HRMS (ESI) m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{27}\text{H}_{30}\text{NO}_5$: 448.2118, found 448.2124.



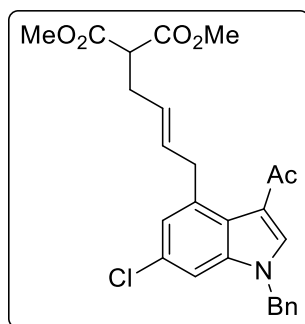
Dimethyl (*E*)-2-(4-(3-acetyl-1-benzyl-5-fluoro-1*H*-indol-4-yl)but-2-en-1-yl)malonate 3e. Analytical TLC on silica gel, 1:2 ethyl acetate/hexane $R_f = 0.44$; ; brown sticky liquid; yield 70% (31.5 mg, $E/Z > 25:1$); $^1\text{H NMR}$ (600 MHz, CDCl_3) δ 7.81 (s, 1H), 7.36-7.31 (m, 3H), 7.14-7.12 (m, 2H), 7.06-7.04 (m, 1H), 6.99-6.96 (m, 1H), 5.74-5.69 (m, 1H), 5.36-5.31 (m, 3H), 4.11 (d, $J = 6$ Hz, 2H), 3.61 (s, 6H), 3.34 (t, $J = 7.8$ Hz, 1H), 2.53-2.50 (m, 5H); $^{13}\text{C NMR}$ (150 MHz, CDCl_3) δ 191.7, 169.6, 158.6 ($J_{\text{C-F}} = 234.4$ Hz), 137.8, 135.5, 134.5, 133.0, 129.2, 128.4, 127.0, 125.8 ($J_{\text{C-F}} = 6.0$ Hz), 125.2, 121.7 ($J_{\text{C-F}} = 18.4$ Hz), 119.3 ($J_{\text{C-F}} = 4.3$ Hz), 112.4 ($J_{\text{C-F}} = 28.5$ Hz), 108.9 ($J_{\text{C-F}} = 10.3$ Hz), 52.3, 52.1, 51.0, 32.1, 30.0 ($J_{\text{C-F}} = 4.5$ Hz), 28.6; $^{19}\text{F NMR}$ (565 MHz, CDCl_3) δ -124.53; FT-IR (neat) 2952, 1730, 1655, 1523, 1438, 1392, 1204, 970, 796 cm^{-1} ; HRMS (ESI) m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{26}\text{H}_{27}\text{FNO}_5$: 452.1868, found 452.1866.



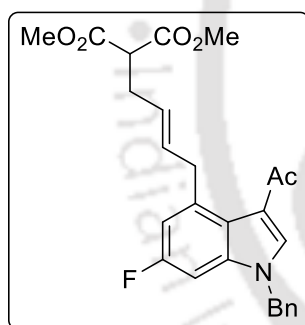
Dimethyl (E)-2-(4-(3-acetyl-1-benzyl-5-methoxy-1H-indol-4-yl)but-2-en-1-yl)malonate 3f. Analytical TLC on silica gel, 1:2 ethyl acetate/hexane $R_f = 0.39$; brown sticky liquid; yield 68% (31.4 mg, $E/Z > 25:1$); ^1H NMR (600 MHz, CDCl_3) δ 7.77 (s, 1H), 7.35-7.29 (m, 3H), 7.14-7.13 (m, 2H), 7.07-7.06 (m, 1H), 6.94-6.93 (m, 1H), 5.73-5.68 (m, 1H), 5.31-5.26 (m, 3H), 4.14 (d, $J = 6.6$ Hz, 2H), 3.82 (s, 3H), 3.60 (s, 6H), 3.33 (t, $J = 7.8$ Hz, 1H), 2.51-2.49 (m, 5H); ^{13}C NMR (150 MHz, CDCl_3) δ 191.9, 169.6, 153.9, 137.8, 135.9, 133.9, 133.6, 129.1, 128.3, 127.0, 126.0, 124.4, 123.8, 118.8, 110.6, 108.4, 57.6, 52.3, 50.9, 32.2, 30.5, 28.8; FT-IR (neat) 2952, 1733, 1656, 1506, 1435, 1385, 1265, 1091, 943, 730 cm^{-1} ; HRMS (ESI) m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{27}\text{H}_{30}\text{NO}_6$: 464.2068, found 464.2064.



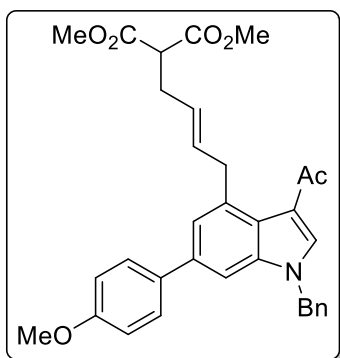
Dimethyl (E)-2-(4-(3-acetyl-1-benzyl-6-bromo-1H-indol-4-yl)but-2-en-1-yl)malonate 3g. Analytical TLC on silica gel, 1:2 ethyl acetate/hexane $R_f = 0.43$; light yellow sticky liquid; yield 64% (32.7 mg, $E/Z = 13:1$); ^1H NMR (600 MHz, CDCl_3) δ 7.72 (s, 1H), 7.37-7.33 (m, 3H), 7.29 (s, 1H), 7.15-7.12 (m, 3H), 5.74-5.69 (m, 1H), 5.40-5.36 (m, 1H), 5.29 (s, 2H), 4.01 (d, $J = 6.6$ Hz, 2H), 3.67 (s, 6H), 3.40 (t, $J = 7.8$ Hz, 1H), 2.58 (t, $J = 7.2$ Hz, 2H), 2.50 (s, 3H); ^{13}C NMR (150 MHz, CDCl_3) δ 192.0, 169.5, 139.0, 138.1, 136.9, 135.3, 133.3, 129.3, 128.5, 127.0, 126.8, 126.1, 123.6, 119.3, 117.6, 111.1, 52.5, 52.0, 50.8, 38.4, 32.1, 28.7; FT-IR (neat) 2918, 1730, 1657, 1523, 1432, 1376, 1254, 1189, 923, 701 cm^{-1} ; HRMS (ESI) m/z $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{26}\text{H}_{26}\text{BrNaNO}_5$: 534.0887, found 534.0878.



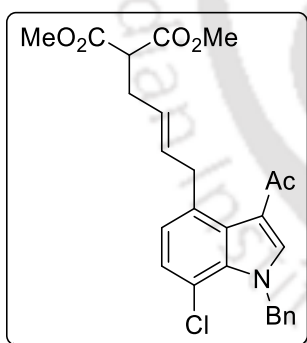
Dimethyl (*E*)-2-(4-(3-acetyl-1-benzyl-6-chloro-1H-indol-4-yl)but-2-en-1-yl)malonate 3h. Analytical TLC on silica gel, 1:2 ethyl acetate/hexane $R_f = 0.41$; brown sticky liquid; yield 66% (30.8 mg, $E/Z > 25:1$); $^1\text{H NMR}$ (600 MHz, CDCl_3) δ 7.74 (s, 1H), 7.37-7.33 (m, 3H), 7.13-7.12 (m, 3H), 7.01 (s, 1H), 5.74-5.70 (m, 1H), 5.41-5.36 (m, 1H), 5.29 (s, 2H), 4.02 (d, $J = 6.6$ Hz, 2H), 3.67 (s, 6H), 3.40 (t, $J = 7.8$ Hz, 1H), 2.58 (t, $J = 7.8$ Hz, 2H), 2.51 (s, 3H); $^{13}\text{C NMR}$ (150 MHz, CDCl_3) δ 192.1, 169.5, 138.7, 137.9, 137.0, 135.3, 133.2, 129.8, 129.3, 128.5, 126.9, 126.2, 124.1, 123.2, 119.3, 108.1, 52.5, 52.0, 50.9, 38.4, 32.1, 28.7; FT-IR (neat) 2924, 1732, 1657, 1524, 1434, 1375, 1187, 1028, 972, 700 cm^{-1} ; HRMS (ESI) m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{26}\text{H}_{27}\text{ClNO}_5$: 468.1572, found 468.1578.



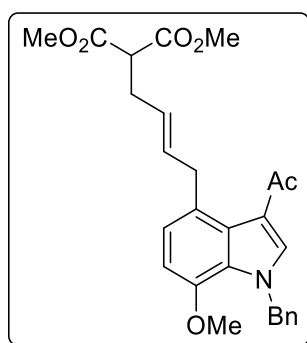
Dimethyl (*E*)-2-(4-(3-acetyl-1-benzyl-6-fluoro-1H-indol-4-yl)but-2-en-1-yl)malonate 3i. Analytical TLC on silica gel, 1:2 ethyl acetate/hexane $R_f = 0.42$; brown sticky liquid; yield 68% (30.6 mg, $E/Z = 17:1$); $^1\text{H NMR}$ (600 MHz, CDCl_3) δ 7.76 (s, 1H), 7.36-7.32 (m, 3H), 7.13 (d, $J = 7.2$ Hz, 2H), 6.81-6.78 (m, 2H), 5.75-5.70 (m, 1H), 5.42-5.37 (m, 1H), 5.27 (s, 2H), 4.03 (d, $J = 6.6$ Hz, 2H), 3.67 (s, 6H), 3.40 (t, $J = 7.8$ Hz, 1H), 2.59 (t, $J = 7.2$ Hz, 2H), 2.51 (s, 3H); $^{13}\text{C NMR}$ (150 MHz, CDCl_3) δ 192.1, 169.5, 161.3 ($J_{\text{C-F}} = 239.7$ Hz), 138.5 ($J_{\text{C-F}} = 12.0$ Hz), 138.4, 137.0 ($J_{\text{C-F}} = 2.5$ Hz), 135.4, 133.2, 129.2, 128.5, 127.0, 126.3, 121.0, 119.4, 112.1 ($J_{\text{C-F}} = 23.5$ Hz), 94.7 ($J_{\text{C-F}} = 25.9$ Hz), 52.5, 52.0, 51.0, 38.4, 32.1, 28.6; $^{19}\text{F NMR}$ (471 MHz, CDCl_3) δ -118.34.; FT-IR (neat) 2917, 1734, 1657, 1526, 1435, 1378, 1258, 1101, 955, 729 cm^{-1} ; HRMS (ESI) m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{26}\text{H}_{27}\text{FNO}_5$: 452.1868, found 452.1869.



Dimethyl (*E*)-2-(4-(3-acetyl-1-benzyl-6-(4-methoxyphenyl)-1H-indol-4-yl)but-2-en-1-yl)malonate **3j.** Analytical TLC on silica gel, 1:2 ethyl acetate/hexane $R_f = 0.36$; brown sticky liquid; yield 73% (39.3 mg, $E/Z > 25:1$); ^1H NMR (600 MHz, CDCl_3) δ 7.77 (s, 1H), 7.51 (d, $J = 8.4$ Hz, 2H), 7.35-7.31 (m, 3H), 7.26-7.25 (m, 2H), 7.17 (d, $J = 7.2$ Hz, 2H), 6.96 (d, $J = 9.0$ Hz, 2H), 5.83-5.78 (m, 1H), 5.43-5.38 (m, 1H), 5.36 (s, 2H), 4.11 (d, $J = 6.6$ Hz, 2H), 3.83 (s, 3H), 3.60 (s, 6H), 3.39 (t, $J = 7.8$ Hz, 1H), 2.58 (t, $J = 7.2$ Hz, 2H), 2.52 (s, 3H); ^{13}C NMR (150 MHz, CDCl_3) δ 192.1, 169.6, 159.1, 139.0, 137.1, 137.0, 136.4, 135.8, 134.2, 134.1, 129.2, 128.5, 128.3, 127.0, 125.4, 123.5, 123.4, 119.1, 114.3, 106.0, 55.5, 52.4, 52.1, 50.8, 38.8, 32.1, 28.6; FT-IR (neat) 2919, 1735, 1656, 1520, 1435, 1247, 1183, 1030, 733 cm^{-1} ; HRMS (ESI) m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{33}\text{H}_{34}\text{NO}_6$: 540.2381, found 540.2380.

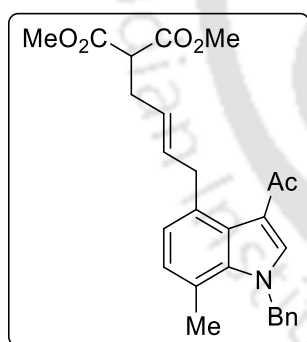


Dimethyl (*E*)-2-(4-(3-acetyl-1-benzyl-7-chloro-1H-indol-4-yl)but-2-en-1-yl)malonate **3l.** Analytical TLC on silica gel, 1:2 ethyl acetate/hexane $R_f = 0.42$; brown sticky liquid; yield 70% (32.6 mg, $E/Z > 25:1$); ^1H NMR (600 MHz, CDCl_3) δ 7.71 (s, 1H), 7.33-7.27 (m, 3H), 7.15 (d, $J = 7.8$ Hz, 1H), 7.04 (d, $J = 7.2$ Hz, 2H), 6.94 (d, $J = 7.8$ Hz, 1H), 5.82 (s, 2H), 5.72-5.67 (m, 1H), 5.36-5.32 (m, 1H), 3.97 (d, $J = 6.6$ Hz, 2H), 3.66 (s, 6H), 3.38 (t, $J = 7.8$ Hz, 1H), 2.57 (t, $J = 7.2$ Hz, 2H), 2.51 (s, 3H); ^{13}C NMR (150 MHz, CDCl_3) δ 192.3, 169.5, 139.0, 137.6, 135.0, 133.5, 133.3, 129.0, 128.0, 127.4, 126.3, 125.91, 125.90, 124.5, 119.3, 115.1, 53.0, 52.5, 52.0, 38.1, 32.1, 29.0; FT-IR (neat) 2925, 1733, 1662, 1532, 1435, 1383, 1205, 968, 735 cm^{-1} ; HRMS (ESI) m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{26}\text{H}_{27}\text{ClNO}_5$: 468.1572, found 468.1577.



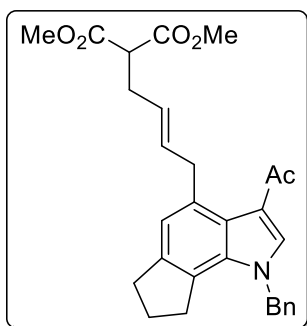
Dimethyl (E)-2-(4-(3-acetyl-1-benzyl-7-methoxy-1H-indol-4-

yl)but-2-en-1-yl)malonate 3m. Analytical TLC on silica gel, 1:2 ethyl acetate/hexane $R_f = 0.38$ brown sticky liquid; yield 77% (35.6 mg, $E/Z = 21:1$); $^1\text{H NMR}$ (600 MHz, CDCl_3) δ 7.65 (s, 1H), 7.31-7.29 (m, 2H), 7.27-7.26 (m, 1H), 7.10 (d, $J = 7.8$ Hz, 2H), 6.91 (d, $J = 7.8$ Hz, 1H), 6.65 (d, $J = 8.4$ Hz, 1H), 5.74-5.70 (m, 1H), 5.65 (s, 2H), 5.34-5.30 (m, 1H), 3.94 (d, $J = 6.6$ Hz, 2H), 3.76 (s, 3H), 3.65 (s, 6H), 3.38 (t, $J = 7.8$ Hz, 1H), 2.56 (t, $J = 7.2$ Hz, 2H), 2.49 (s, 3H); $^{13}\text{C NMR}$ (150 MHz, CDCl_3) δ 192.4, 169.6, 146.0, 138.2, 137.6, 134.5, 128.8, 127.9, 127.8, 127.7, 126.7, 126.6, 124.9, 123.9, 119.2, 105.1, 55.6, 53.6, 52.4, 52.2, 38.0, 32.1, 28.8; FT-IR (neat) 2952, 1733, 1656, 1506, 1435, 1385, 1265, 943, 730 cm^{-1} ; HRMS (ESI) m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{27}\text{H}_{30}\text{NO}_6$: 464.2068, found 464.2059.

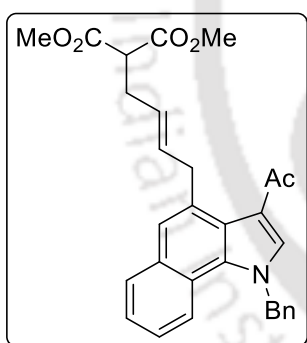


Dimethyl (E)-2-(4-(3-acetyl-1-benzyl-7-methyl-1H-indol-4-

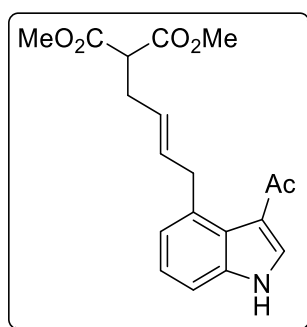
yl)but-2-en-1-yl)malonate 3n. Analytical TLC on silica gel, 1:2 ethyl acetate/hexane $R_f = 0.46$; light brown sticky liquid; yield 75% (33.5 mg, $E/Z > 25:1$); $^1\text{H NMR}$ (600 MHz, CDCl_3) δ 7.70 (s, 1H), 7.32-7.27 (m, 3H), 6.93-6.89 (m, 4H), 5.76-5.72 (m, 1H), 5.61 (s, 2H), 5.38-5.33 (m, 1H), 3.99 (d, $J = 6.6$ Hz, 2H), 3.67 (s, 6H), 3.39 (d, $J = 7.8$ Hz, 1H), 2.57 (t, $J = 7.2$ Hz, 2H), 2.52 (s, 3H), 2.48 (s, 3H); $^{13}\text{C NMR}$ (150 MHz, CDCl_3) δ 192.5, 169.6, 138.6, 138.0, 136.9, 134.2, 133.9, 129.2, 127.9, 127.2, 125.5, 125.3, 123.9, 119.19, 119.17, 53.2, 52.5, 52.1, 38.3, 32.1, 28.9, 19.5; FT-IR (neat) 2953, 1733, 1656, 1534, 1436, 1375, 1206, 1154, 944, 731 cm^{-1} ; HRMS (ESI) m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{27}\text{H}_{30}\text{NO}_5$: 448.2118, found 448.2101.



Dimethyl (E)-2-(4-(3-acetyl-1-benzyl-1,6,7,8-tetrahydrocyclopenta[g]indol-4-yl)but-2-en-1-yl)malonate 3o. Analytical TLC on silica gel, 1:2 ethyl acetate/hexane $R_f = 0.44$; brown sticky liquid; yield 68% (32.1 mg, $E/Z = 19:1$); ^1H NMR (600 MHz, CDCl_3) δ 7.66 (s, 1H), 7.33-7.28 (m, 3H), 7.00-6.96 (m, 3H), 5.78-5.74 (m, 1H), 5.50 (s, 2H), 5.40-5.35 (m, 1H), 4.01 (d, $J = 6.6$ Hz, 2H), 3.67 (s, 6H), 3.40 (t, $J = 7.8$ Hz, 1H), 3.05 (t, $J = 7.8$ Hz, 2H), 2.93 (t, $J = 7.8$ Hz, 2H), 2.58 (t, $J = 7.2$ Hz, 2H), 2.50 (s, 3H), 2.07-2.03 (m, 2H); ^{13}C NMR (150 MHz, CDCl_3) δ 192.4, 169.6, 141.6, 137.7, 137.1, 135.7, 134.4, 134.2, 129.1, 128.0, 125.9, 125.1, 123.5, 123.3, 120.8, 119.6, 52.5, 52.2, 52.0, 38.5, 32.6, 32.2, 31.3, 28.8, 25.4; FT-IR (neat) 2952, 1732, 1656, 1529, 1436, 1378, 1206, 1155, 965, 731 cm^{-1} ; HRMS (ESI) m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{29}\text{H}_{32}\text{NO}_5$: 474.2275, found 474.2283.



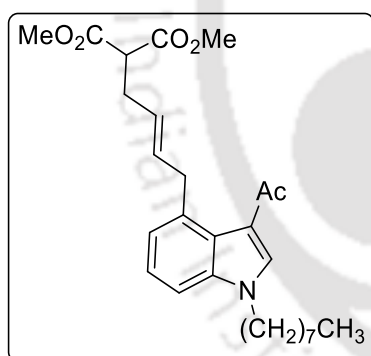
Dimethyl (E)-2-(4-(3-acetyl-1-benzyl-1H-benzo[g]indol-4-yl)but-2-en-1-yl)malonate 3p. Analytical TLC on silica gel, 1:2 ethyl acetate/hexane $R_f = 0.40$; colorless amorphous solid; mp 110-111 $^\circ\text{C}$; yield 66% (31.8 mg, $E/Z > 25:1$); ^1H NMR (600 MHz, CDCl_3) δ 8.04 (d, $J = 8.4$ Hz, 1H), 7.88 (d, $J = 8.4$ Hz, 1H), 7.77 (s, 1H), 7.45 (s, 1H), 7.39-7.36 (m, 1H), 7.35-7.32 (m, 2H), 7.31-7.28 (m, 2H), 7.11 (d, $J = 7.8$ Hz, 2H), 5.85 (s, 2H), 5.83-5.80 (m, 1H), 5.45-5.40 (m, 1H), 4.10 (d, $J = 6.6$ Hz, 2H), 3.66 (s, 6H), 3.42 (t, $J = 7.8$ Hz, 1H), 2.62 (t, $J = 7.8$ Hz, 2H), 2.59 (s, 3H); ^{13}C NMR (150 MHz, CDCl_3) δ 193.2, 169.6, 136.6, 136.3, 134.4, 133.5, 132.2, 132.1, 129.3, 128.6, 128.1, 126.1, 126.0, 125.3, 124.6, 124.0, 123.1, 120.92, 120.91, 120.0, 54.6, 52.5, 52.1, 38.6, 32.2, 29.3; FT-IR (neat) 2952, 1732, 1661, 1529, 1435, 1369, 1231, 1151, 945, 736 cm^{-1} ; HRMS (ESI) m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{30}\text{H}_{30}\text{NO}_5$: 484.2118, found 484.2126.



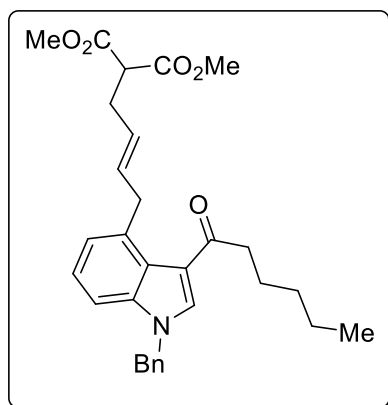
Dimethyl

(E)-2-(4-(3-acetyl-1H-indol-4-yl)but-2-en-1-

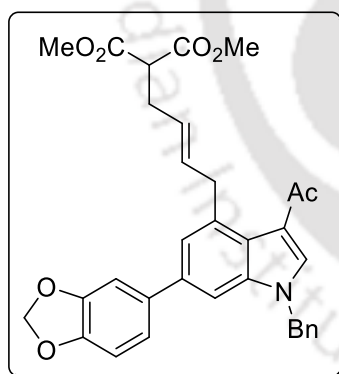
yl)malonate 3q. Analytical TLC on silica gel, 1:1 ethyl acetate/hexane $R_f = 0.35$; brown amorphous solid; mp 115-116 °C; yield 57% (19.5 mg, $E/Z = 17:1$); ^1H NMR (600 MHz, CDCl_3) δ 8.62 (s, 1H), 7.86 (s, 1H), 7.23-7.19 (m, 2H), 7.04 (d, $J = 7.2$ Hz, 1H), 5.78-5.73 (m, 1H), 5.37-5.32 (m, 1H), 4.05 (d, $J = 6.6$ Hz, 2H), 3.65 (s, 6H), 3.38 (t, $J = 7.8$ Hz, 1H), 2.58-2.56 (m, 5H); ^{13}C NMR (150 MHz, CDCl_3) δ 192.6, 169.6, 137.6, 135.9, 134.2, 132.9, 125.3, 124.2, 123.8, 123.5, 120.4, 109.5, 52.5, 52.1, 38.6, 32.1, 28.7; FT-IR (KBr) 2954, 1733, 1634, 1518, 1408, 1232, 1155, 934, 751 cm^{-1} ; HRMS (ESI) m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{19}\text{H}_{22}\text{NO}_5$: 344.1492, found 344.1505.

Dimethyl **(E)-2-(4-(3-acetyl-1-octyl-1H-indol-4-yl)but-2-en-**

1-yl)malonate 3r. Analytical TLC on silica gel, 1:2 ethyl acetate/hexane $R_f = 0.46$; light yellow sticky liquid; yield 61% (27.7 mg, $E/Z > 25:1$); ^1H NMR (600 MHz, CDCl_3) δ 7.75 (s, 1H), 7.23-7.18 (m, 2H), 7.04 (d, $J = 6.6$ Hz, 1H), 5.78-5.73 (m, 1H), 5.39-5.34 (m, 1H), 4.12 (t, $J = 7.8$ Hz, 2H), 4.06 (d, $J = 6.6$ Hz, 2H), 3.65 (s, 6H), 3.38 (t, $J = 7.8$ Hz, 1H), 2.57-2.54 (m, 5H), 1.89-1.84 (m, 2H), 1.34-1.25 (m, 10H), 0.89-0.85 (m, 3H); ^{13}C NMR (150 MHz, CDCl_3) δ 192.0, 169.6, 137.9, 136.5, 136.2, 134.3, 125.2, 124.5, 123.7, 123.6, 118.5, 107.9, 52.5, 52.1, 47.3, 38.7, 32.1, 32.0, 31.8, 29.8, 29.2, 28.6, 27.0, 22.7, 14.2; FT-IR (neat) 2925, 1734, 1654, 1524, 1434, 1376, 1275, 1152, 749 cm^{-1} ; HRMS (ESI) m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{27}\text{H}_{38}\text{NO}_5$: 456.2744, found 456.2750.

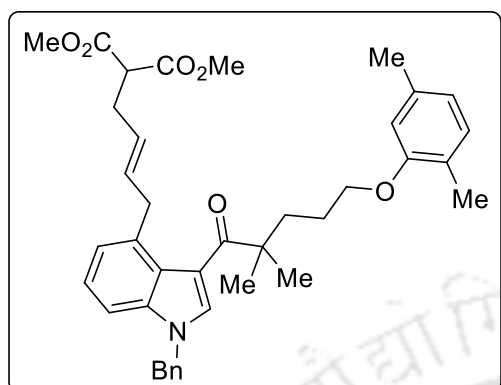


Dimethyl (*E*)-2-(4-(1-benzyl-3-hexanoyl-1*H*-indol-4-yl)but-2-en-1-yl)malonate 3s. Analytical TLC on silica gel, 1:2 ethyl acetate/hexane $R_f = 0.47$; colorless sticky liquid; yield 59% (28.8 mg, $E/Z > 25:1$); ^1H NMR (600 MHz, CDCl_3) δ 7.77 (s, 1H), 7.36-7.30 (m, 3H), 7.19-7.16 (m, 1H), 7.13-7.12 (m, 3H), 7.04 (d, $J = 7.2$ Hz, 1H), 5.78-5.74 (m, 1H), 5.42-5.36 (m, 1H), 5.34 (s, 2H), 4.05 (d, $J = 6.6$ Hz, 2H), 3.65 (s, 6H), 3.39 (t, $J = 7.8$ Hz, 1H), 2.82 (t, $J = 7.8$ Hz, 2H), 2.57 (t, $J = 7.2$ Hz, 2H), 1.76-1.73 (m, 2H), 1.37-1.33 (m, 4H), 0.91-0.87 (m, 3H); ^{13}C NMR (150 MHz, CDCl_3) δ 195.5, 169.6, 138.2, 136.2, 136.0, 135.8, 134.1, 129.1, 128.3, 126.9, 125.5, 124.7, 123.9, 123.6, 119.1, 108.2, 52.5, 52.1, 50.8, 40.9, 38.6, 32.1, 31.8, 25.3, 22.7, 14.1; FT-IR (neat) 2921, 2852, 1735, 1657, 1524, 1455, 1260, 1019, 799 cm^{-1} ; HRMS (ESI) m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{30}\text{H}_{36}\text{NO}_5$: 490.2588, found 490.2593.



Dimethyl (*E*)-2-(4-(3-acetyl-6-(benzo[*d*][1,3]dioxol-5-yl)-1-benzyl-1*H*-indol-4-yl)but-2-en-1-yl)malonate 3t. Analytical TLC on silica gel, 1:2 ethyl acetate/hexane $R_f = 0.37$; brown sticky liquid; yield 68% (37.6 mg, $E/Z = 11:1$); ^1H NMR (600 MHz, CDCl_3) δ 7.78 (s, 1H), 7.36-7.31 (m, 3H), 7.23-7.22 (m, 2H), 7.17 (d, $J = 7.6$ Hz, 2H), 7.05-7.03 (m, 2H), 6.87 (d, $J = 7.8$ Hz, 1H), 5.98 (s, 2H), 5.82-5.77 (m, 1H), 5.43-5.39 (m, 1H), 5.37 (s, 2H), 4.10 (d, $J = 6.6$ Hz, 2H), 3.61 (s, 6H), 3.39 (t, $J = 7.8$ Hz, 1H), 2.58 (t, $J = 7.8$ Hz, 2H), 2.53 (s, 3H); ^{13}C NMR (150 MHz, CDCl_3) δ 192.1, 169.6, 148.1, 147.0, 138.9, 137.2, 137.1, 136.5, 135.9, 135.8, 134.1, 129.2, 128.4, 127.0, 125.5, 123.6, 123.5, 120.9, 119.1, 108.6, 108.0, 106.2, 101.2, 52.4, 52.1, 50.8, 38.8, 32.1, 28.6; FT-IR (neat) 2924, 1733, 1655,

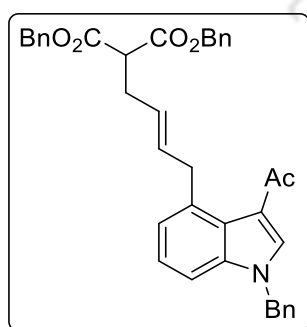
1524, 1478, 1377, 1231, 1038, 933, 749 cm^{-1} ; HRMS (ESI) m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{33}\text{H}_{32}\text{NO}_7$: 554.2173, found 554.2179.



Dimethyl (E)-2-(4-(1-benzyl-3-(5-(2,5-

dimethylphenoxy)-2,2-dimethylpentanoyl)-1H-indol-4-yl)but-2-en-1-yl)malonate 3u.

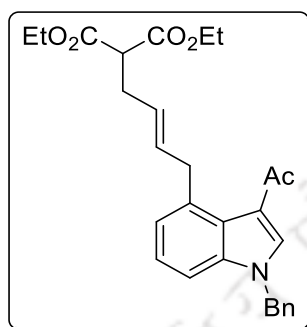
Analytical TLC on silica gel, 1:3 ethyl acetate/hexane R_f = 0.42; colorless amorphous solid; mp 105-106 $^{\circ}\text{C}$; yield 61% (38.0 mg, $E/Z > 25:1$); ^1H NMR (600 MHz, CDCl_3) δ 7.61 (s, 1H), 7.31-7.28 (m, 3H), 7.18-7.15 (m, 1H), 7.13-7.08 (m, 3H), 7.00-6.96 (m, 2H), 6.64 (d, J = 7.2 Hz, 1H), 6.57 (s, 1H), 5.78-5.73 (m, 1H), 5.43-5.38 (m, 1H), 5.29 (s, 2H), 3.90 (t, J = 6.0 Hz, 2H), 3.69-3.68 (m, 8H), 3.42 (t, J = 7.8 Hz, 1H), 2.60 (t, J = 7.2 Hz, 2H), 2.27 (s, 3H), 2.11 (s, 3H), 1.98-1.95 (m, 2H), 1.84-1.80 (m, 2H), 1.37 (s, 6H); ^{13}C NMR (150 MHz, CDCl_3) δ 204.5, 169.5, 157.0, 136.9, 136.6, 136.3, 135.1, 133.0, 130.7, 130.3, 129.0, 128.1, 126.8, 126.4, 125.7, 123.5, 123.4, 122.7, 120.8, 116.6, 112.1, 108.2, 68.2, 52.5, 52.0, 50.6, 48.0, 38.0, 37.3, 32.1, 29.8, 27.0, 25.2, 21.5, 15.9; FT-IR (KBr) 2953, 1736, 1649, 1253, 1436, 1389, 1264, 1156, 1129, 1042, 731 cm^{-1} ; HRMS (ESI) m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{39}\text{H}_{46}\text{NO}_6$: 624.3320, found 624.3328.



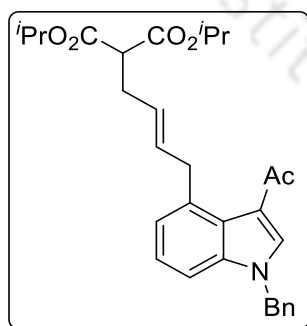
Dibenzyl (E)-2-(4-(3-acetyl-1-benzyl-1H-indol-4-yl)but-2-en-1-

yl)malonate 3v. Analytical TLC on silica gel, 1:2 ethyl acetate/hexane R_f = 0.42; brown sticky liquid; yield 66% (38.6 mg, $E/Z > 25:1$); ^1H NMR (600 MHz, CDCl_3) δ 7.78 (s, 1H), 7.33-7.28 (m, 9H), 7.23-7.22 (m, 4H), 7.18-7.15 (m, 1H), 7.13-7.12 (m, 3H), 7.03 (d, J = 7.2 Hz, 1H),

5.78-5.74 (m, 1H), 5.41-5.36 (m, 1H), 5.32 (s, 2H), 5.07-5.02 (m, 4H), 4.05 (d, $J = 6.6$ Hz, 2H), 3.48 (t, $J = 7.8$ Hz, 1H), 2.61 (t, $J = 7.2$ Hz, 2H), 2.51 (s, 3H); ^{13}C NMR (150 MHz, CDCl_3) δ 192.2, 168.8, 138.3, 136.7, 136.2, 135.8, 135.5, 134.3, 129.1, 128.6, 128.33, 128.31, 128.2, 127.0, 125.2, 124.5, 124.0, 123.9, 119.2, 108.2, 67.0, 52.4, 50.8, 38.7, 32.0, 28.7; FT-IR (neat) 2925, 1731, 1655, 1524, 1453, 1389, 1207, 1151, 748 cm^{-1} ; HRMS (ESI) m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{38}\text{H}_{36}\text{NO}_5$: 586.2588, found 586.2595.

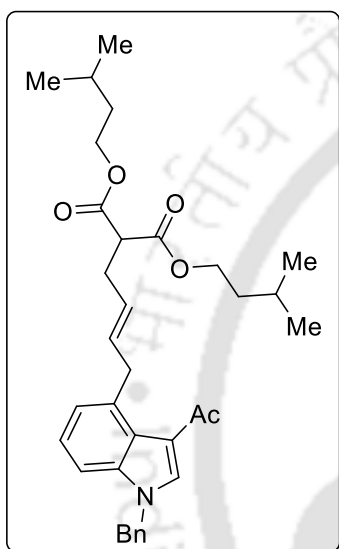


Diethyl (*E*)-2-(4-(3-acetyl-1-benzyl-1*H*-indol-4-yl)but-2-en-1-yl)malonate 3w. Analytical TLC on silica gel, 1:2 ethyl acetate/hexane $R_f = 0.46$; brown sticky liquid; yield 73% (33.6 mg, $E/Z > 25:1$); ^1H NMR (600 MHz, CDCl_3) δ 7.77 (s, 1H), 7.35-7.29 (m, 3H), 7.19-7.16 (m, 1H), 7.15-7.12 (m, 3H), 7.05 (d, $J = 7.2$ Hz, 1H), 5.78-5.74 (m, 1H), 5.40-5.36 (m, 1H), 5.33 (s, 2H), 4.14-4.08 (m, 4H), 4.06 (d, $J = 6.6$ Hz, 2H), 3.34 (t, $J = 7.8$ Hz, 1H), 2.56 (t, $J = 7.2$ Hz, 2H), 2.52 (s, 3H), 1.19 (t, $J = 7.2$ Hz, 6H); ^{13}C NMR (150 MHz, CDCl_3) δ 192.2, 169.2, 138.3, 136.6, 136.3, 135.8, 133.9, 129.1, 128.3, 127.0, 125.6, 124.5, 124.0, 123.9, 119.2, 108.2, 61.3, 52.4, 50.8, 38.7, 32.1, 28.7, 14.1; FT-IR (neat) 2918, 2850, 1729, 1656, 1524, 1441, 1373, 1150, 1030, 748 cm^{-1} ; HRMS (ESI) m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{28}\text{H}_{32}\text{NO}_5$: 462.2275, found 462.2279.

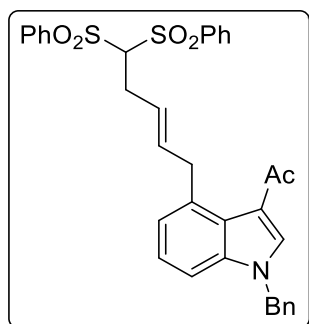


Diisopropyl (*E*)-2-(4-(3-acetyl-1-benzyl-1*H*-indol-4-yl)but-2-en-1-yl)malonate 3x. Analytical TLC on silica gel, 1:2 ethyl acetate/hexane $R_f = 0.45$; light brown sticky liquid; yield 46% (22.4 mg, $E/Z = 2:1$); ^1H NMR (600 MHz, CDCl_3) δ 7.79 (s, 0.56H), 7.77 (s, 1H), 7.40-7.30 (m, 5.42H), 7.19-7.11 (m, 6.38H), 7.05-7.04 (m, 1.05H), 6.09-6.04 (m, 0.63H), 5.77-5.72 (m, 1.17H), 5.42-5.39 (m, 0.60H), 5.38-5.35 (m, 1.14H), 5.34-5.33 (m,

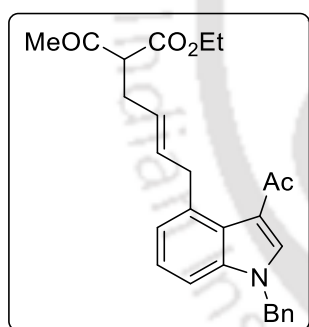
3.28H), 5.07-5.03 (m, 1.25H), 5.00-4.95 (m, 2.31H), 4.15 (d, $J = 6.6$ Hz, 0.85H), 4.06 (d, $J = 6.6$ Hz, 1.93H), 3.38 (t, $J = 7.8$ Hz, 0.63H), 3.27 (t, $J = 7.8$ Hz, 1.16H), 2.55-2.51 (m, 6.49H), 2.39-2.35 (m, 0.64H), 2.13-2.10 (m, 1.19H), 1.25-1.15 (m, 18H); ^{13}C NMR (150 MHz, CDCl_3) δ 192.3, 192.2, 169.3, 168.8, 138.4, 138.4, 138.3, 137.0, 136.6, 136.3, 135.9, 135.8, 133.8, 133.7, 132.5, 129.38, 129.36, 129.1, 128.3, 127.0, 126.9, 125.7, 124.6, 124.03, 124.00, 123.9, 123.6, 120.3, 119.3, 119.2, 108.9, 108.2, 68.8, 68.7, 52.8, 52.0, 50.8, 38.6, 31.9, 31.0, 28.75, 28.72, 21.8, 21.76, 21.74, 21.6; FT-IR (neat) 2926, 1724, 1656, 1524, 1441, 1374, 1189, 1102, 746 cm^{-1} ; HRMS (ESI) m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{30}\text{H}_{36}\text{NO}_5$: 490.2588, found 490.2595.



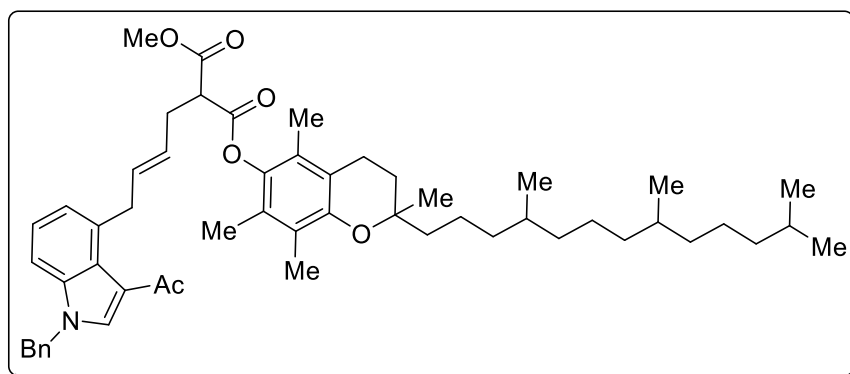
Diisopentyl (E)-2-(4-(3-acetyl-1-benzyl-1H-indol-4-yl)but-2-en-1-yl)malonate 3y. Analytical TLC on silica gel, 1:4 ethyl acetate/hexane $R_f = 0.46$; brown sticky liquid; yield 52% (28.3 mg, $E/Z = 5:1$); ^1H NMR (600 MHz, CDCl_3) δ 7.77 (s, 1H), 7.35-7.30 (m, 3H), 7.19-7.12 (m, 4H), 7.05 (d, $J = 7.2$ Hz, 1H), 5.79-5.74 (m, 1H), 5.41-5.36 (m, 1H), 5.33 (s, 2H), 4.12-4.05 (m, 4H), 3.74-3.70 (m, 2H), 3.38-3.33 (m, 1H), 2.58-2.55 (m, 2H), 2.52 (s, 3H), 1.66-1.62 (m, 2H), 1.52-1.45 (m, 4H), 0.90-0.85 (m, 12H); ^{13}C NMR (150 MHz, CDCl_3) δ 192.2, 169.3, 138.3, 136.6, 136.3, 135.8, 133.9, 129.1, 128.3, 127.1, 127.0, 125.6, 124.6, 124.0, 123.9, 108.2, 64.0, 52.6, 50.8, 38.6, 37.2, 32.1, 28.7, 25.0, 22.5; FT-IR (neat) 2957, 1729, 1655, 1525, 1440, 1388, 1190, 971, 746 cm^{-1} ; HRMS (ESI) m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{34}\text{H}_{44}\text{NO}_5$: 546.3214, found 546.3218.



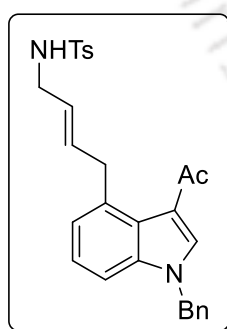
(E)-1-(1-benzyl-4-(5,5-bis(phenylsulfonyl)pent-2-en-1-yl)-1H-indol-3-yl)ethan-1-one 3z. Analytical TLC on silica gel, 1:2 ethyl acetate/hexane $R_f = 0.41$; colorless sticky liquid; yield 61% (36.4 mg, $E/Z > 25:1$); ^1H NMR (400 MHz, CDCl_3) δ 7.91-7.88 (m, 4H), 7.81 (s, 1H), 7.64-7.60 (m, 2H), 7.51-7.47 (m, 4H), 7.34-7.29 (m, 3H), 7.20-7.14 (m, 4H), 7.01-6.99 (m, 1H), 5.64-5.57 (m, 1H), 5.35-5.28 (m, 3H), 4.41 (t, $J = 6.4$ Hz, 1H), 4.01 (d, $J = 6.4$ Hz, 2H), 2.80 (t, $J = 6.4$ Hz, 2H), 2.53 (s, 3H); ^{13}C NMR (150 MHz, CDCl_3) δ 192.2, 138.3, 138.1, 137.0, 135.85, 135.81, 135.6, 134.5, 129.8, 129.2, 129.1, 128.3, 127.0, 124.6, 124.2, 124.0, 123.4, 119.1, 108.4, 84.2, 50.9, 38.7, 29.8, 29.0, 28.7; FT-IR (neat) 2924, 2854, 1652, 1524, 1447, 1376, 1330, 1153, 1079, 734 cm^{-1} ; HRMS (ESI) m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{34}\text{H}_{32}\text{S}_2\text{NO}_5$: 598.1716, found 598.1719.



Ethyl (E)-2-acetyl-6-(3-acetyl-1-benzyl-1H-indol-4-yl)hex-4-enoate 3ad. Analytical TLC on silica gel, 1:2 ethyl acetate/hexane $R_f = 0.44$; light yellow sticky liquid; yield 45% (19.3 mg, $E/Z = 10:1$); ^1H NMR (400 MHz, CDCl_3) δ 7.78 (s, 1H), 7.35-7.30 (m, 3H), 7.18-7.12 (m, 4H), 7.04-7.02 (m, 1H), 5.79-5.72 (m, 1H), 5.37-5.29 (m, 3H), 4.21-4.09 (m, 2H), 4.08-4.04 (m, 2H), 3.44 (t, $J = 7.6$ Hz, 1H), 2.52 (s, 3H), 2.27-2.21 (m, 2H), 2.16 (s, 3H), 1.18 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 203.2, 192.2, 169.5, 138.3, 136.7, 136.2, 135.8, 134.0, 129.1, 128.3, 127.0, 125.6, 124.5, 124.0, 123.9, 119.1, 108.2, 61.3, 60.0, 50.8, 38.6, 31.5, 29.3, 28.7, 14.1; FT-IR (neat) 2923, 2853, 1712, 1653, 1524, 1440, 1373, 1189, 1022, 970, 736 cm^{-1} ; HRMS (ESI) m/z $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{27}\text{H}_{29}\text{NaNO}_4$: 454.1989, found 454.1986.

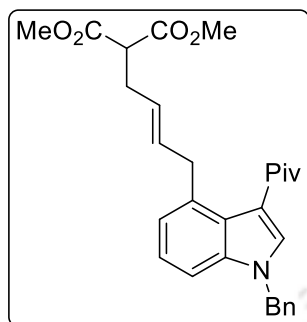
**1-Methyl 3-(2,5,7,8-**

tetramethyl-2-(4,8,12-trimethyltridecyl)chroman-6-yl) (E)-2-(4-(3-acetyl-1-benzyl-1H-indol-4-yl)but-2-en-1-yl)malonate 3ae. Analytical TLC on silica gel, 1:2 ethyl acetate/hexane $R_f = 0.43$; brown sticky liquid; yield 57% (47.4 mg, $E/Z = 3:1$); ^1H NMR (600 MHz, CDCl_3) δ 7.78 (s, 1H), 7.35-7.30 (m, 3H), 7.20-7.14 (m, 4H), 7.07 (d, $J = 7.2$ Hz, 1H), 5.88-5.84 (m, 1H), 5.49-5.44 (m, 1H), 5.33 (s, 2H), 4.11-4.09 (m, 2H), 3.70 (s, 3H), 3.66 (t, $J = 7.8$ Hz, 1H), 2.73 (t, $J = 7.2$ Hz, 2H), 2.58-2.54 (m, 2H), 2.53 (s, 3H), 2.06 (s, 3H), 1.98-1.92 (m, 6H), 1.82-1.77 (m, 2H), 1.56-1.49 (m, 3H), 1.37-1.22 (m, 14H), 1.15-1.09 (m, 7H), 0.87-0.84 (m, 12H); ^{13}C NMR (150 MHz, CDCl_3) δ 192.2, 169.4, 167.6, 149.6, 140.4, 138.3, 136.7, 136.1, 135.8, 134.4, 132.9, 129.1, 128.3, 127.0, 125.4, 124.6, 124.0, 123.1, 120.4, 119.2, 117.5, 109.0, 108.2, 75.2, 52.4, 52.2, 50.8, 39.5, 38.7, 37.7, 37.6, 37.5, 37.4, 32.93, 32.91, 32.8, 32.2, 28.7, 28.1, 24.95, 24.94, 24.5, 22.8, 22.7, 21.1, 20.7, 19.9, 19.8, 19.79, 19.76, 19.72, 11.9; FT-IR (neat) 2925, 1740, 1658, 1525, 1440, 1376, 1191, 1151, 741 cm^{-1} ; HRMS (ESI) m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{54}\text{H}_{74}\text{NO}_6$: 832.5511, found 832.5501.

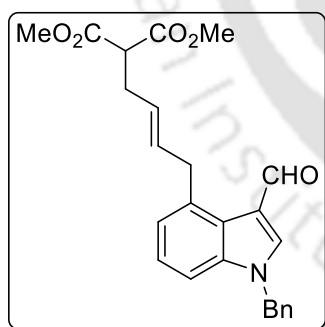


(E)-N-(4-(3-acetyl-1-benzyl-1H-indol-4-yl)but-2-en-1-yl)-4-methylbenzenesulfonamide 3A. Analytical TLC on silica gel, 1:2 ethyl acetate/hexane $R_f = 0.35$; brown sticky liquid; yield 50% (23.6 mg, $E/Z > 25:1$); ^1H NMR (600 MHz, CDCl_3) δ 7.79 (s, 1H), 7.69 (d, $J = 8.4$ Hz, 2H), 7.35-7.30 (m, 4H), 7.26 (s, 1H), 7.19-7.14 (m, 4H), 6.98-6.97 (m, 1H), 5.85-5.81 (m, 1H), 5.34 (s, 2H), 5.30-5.25 (m, 1H), 4.28 (t, $J = 6.0$ Hz, 1H), 4.02 (d, $J = 6.6$ Hz, 2H), 3.47 (t, $J = 6.6$ Hz, 2H), 2.50 (s, 3H), 2.40 (s, 3H); ^{13}C NMR (150 MHz, CDCl_3) δ 192.2, 143.4, 138.3, 137.1, 137.0, 135.9, 135.7, 135.3, 129.7, 129.2, 128.4, 127.2,

127.0, 126.6, 124.5, 124.3, 124.0, 118.9, 108.5, 50.9, 45.6, 38.5, 28.6, 21.6; FT-IR (neat) 3267, 2924, 1644, 1524, 1442, 1379, 1326, 1157, 1093 cm^{-1} ; HRMS (ESI) m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{28}\text{H}_{29}\text{N}_2\text{O}_3\text{S}$: 473.1893, found 473.1893.

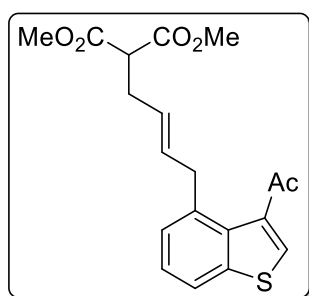


Dimethyl (E)-2-(4-(1-benzyl-3-pivaloyl-1H-indol-4-yl)but-2-en-1-yl)malonate 3a'. Analytical TLC on silica gel, 1:4 ethyl acetate/hexane $R_f = 0.46$; light brown amorphous solid; mp 103-104 °C; yield 55% (26.1 mg, $E/Z > 25:1$); ^1H NMR (500 MHz, CDCl_3) δ 7.55 (s, 1H), 7.33-7.28 (m, 3H), 7.18-7.11 (m, 4H), 6.99 (d, $J = 6.5$ Hz, 1H), 5.75-5.69 (m, 1H), 5.41-5.35 (m, 1H), 5.33 (s, 2H), 3.68-3.65 (m, 8H), 3.41 (t, $J = 8.0$ Hz, 1H), 2.59 (t, $J = 7.5$ Hz, 2H), 1.36 (s, 9H); ^{13}C NMR (150 MHz, CDCl_3) δ 205.6, 169.6, 136.9, 136.3, 135.0, 132.9, 130.6, 129.1, 128.1, 126.9, 126.3, 125.7, 123.4, 122.5, 116.3, 108.2, 52.5, 52.0, 50.6, 44.8, 37.1, 32.1, 28.7; FT-IR (KBr) 2953, 1735, 1650, 1524, 1437, 1390, 1183, 971, 731 cm^{-1} ; HRMS (ESI) m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{29}\text{H}_{34}\text{NO}_5$: 476.2431, found 476.2438.

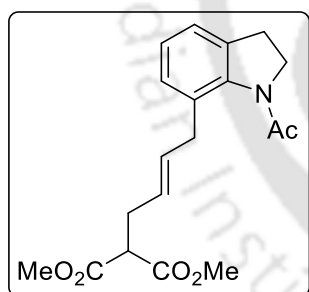


Dimethyl (E)-2-(4-(1-benzyl-3-formyl-1H-indol-4-yl)but-2-en-1-yl)malonate 3b'. Analytical TLC on silica gel, 1:3 ethyl acetate/hexane $R_f = 0.44$; brown sticky liquid; yield 41% (17.1 mg, $E/Z = 15:1$); ^1H NMR (600 MHz, CDCl_3) δ 9.98 (s, 1H), 7.81 (s, 1H), 7.36-7.32 (m, 3H), 7.23-7.17 (m, 4H), 7.08 (d, $J = 6.6$ Hz, 1H), 5.83-5.78 (m, 1H), 5.43-5.38 (m, 1H), 5.34 (s, 2H), 3.99 (d, $J = 6.0$ Hz, 2H), 3.66 (s, 6H), 3.39 (t, $J = 7.8$ Hz, 1H), 2.59 (t, $J = 7.2$ Hz, 2H); ^{13}C NMR (150 MHz, CDCl_3) δ 184.4, 169.5, 139.2, 138.3, 135.3, 135.1, 132.7, 129.2, 128.5, 127.3, 126.5, 124.6, 124.1, 123.8, 119.7, 108.8, 52.5, 52.0, 51.2,

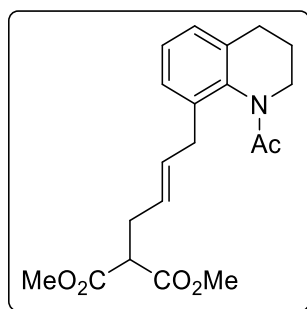
38.4, 32.0; FT-IR (neat) 1734, 1669, 1526, 1439, 1389, 1275, 1162, 750 cm^{-1} ; HRMS (ESI) m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{25}\text{H}_{26}\text{NO}_5$: 420.1805, found 420.1811.



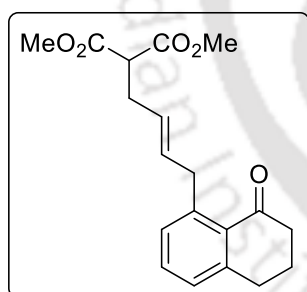
Dimethyl (E)-2-(4-(3-acetylbenzo[b]thiophen-4-yl)but-2-en-1-yl)malonate 4A. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.50; light yellow liquid; yield 55% (19.8 mg, $E/Z > 25:1$); ^1H NMR (500 MHz, CDCl_3) δ 7.96 (s, 1H), 7.74 (d, $J = 8.0$ Hz, 1H), 7.34 (t, $J = 8.0$ Hz, 1H), 7.24-7.22 (m, 1H), 5.63-5.57 (m, 1H), 5.31-5.26 (m, 1H), 3.70 (d, $J = 6.5$ Hz, 2H), 3.66 (s, 6H), 3.38 (t, $J = 8.0$ Hz, 1H), 2.66 (s, 3H), 2.57 (t, $J = 7.5$ Hz, 2H); ^{13}C NMR (150 MHz, CDCl_3) δ 196.3, 169.4, 141.4, 140.1, 137.3, 134.2, 132.9, 132.4, 127.3, 127.0, 125.6, 120.9, 52.5, 51.8, 38.1, 32.0, 30.3; FT-IR (neat) 2923, 1735, 1681, 1435, 1209, 1155, 975, 760 cm^{-1} ; HRMS (ESI) m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{19}\text{H}_{21}\text{O}_5\text{S}$: 361.1104, found 361.1113.



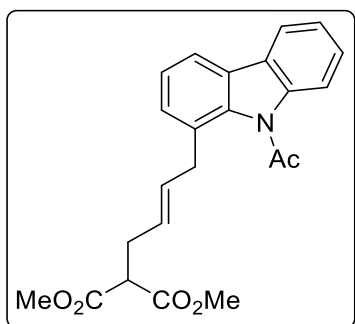
Dimethyl (E)-2-(4-(1-acetylidolin-7-yl)but-2-en-1-yl)malonate 4B. Analytical TLC on silica gel, 1:2 ethyl acetate/hexane R_f = 0.48; brown sticky liquid; yield 70% (24.1 mg, $E/Z > 25:1$); ^1H NMR (600 MHz, CDCl_3) δ 7.07-6.99 (m, 3H), 5.63-5.58 (m, 1H), 5.47-5.43 (m, 1H), 4.07-4.04 (m, 2H), 3.70 (s, 6H), 3.42 (t, $J = 7.8$ Hz, 1H), 3.35-3.34 (m, 2H), 3.01 (t, $J = 7.2$ Hz, 2H), 2.61 (t, $J = 7.2$ Hz, 2H), 2.26 (s, 3H); ^{13}C NMR (150 MHz, CDCl_3) δ 169.5, 140.9, 131.8, 128.8, 126.9, 125.4, 122.3, 52.5, 52.0, 51.3, 37.0, 32.0, 30.1, 23.9; FT-IR (neat) 2954, 1733, 1662, 1435, 1386, 1232, 1152, 974, 732 cm^{-1} ; HRMS (ESI) m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{19}\text{H}_{24}\text{NO}_5$: 346.1649, found 346.1643.



Dimethyl (*E*)-2-(4-(1-acetyl-1,2,3,4-tetrahydroquinolin-8-yl)but-2-en-1-yl)malonate 4C. Analytical TLC on silica gel, 1:2 ethyl acetate/hexane $R_f = 0.49$; brown liquid; yield 39% (14.0 mg, $E/Z = 2:1$); $^1\text{H NMR}$ (600 MHz, CDCl_3) δ 7.17-7.14 (m, 1.36H), 7.11-7.08 (m, 1.53H), 7.06-6.99 (m, 1.63H), 5.62-5.54 (m, 1.57H), 5.47-5.41 (m, 1.57H), 4.81-4.76 (m, 1.57H), 3.74-3.70 (m, 8.95H), 3.44-3.41 (m, 1.49H), 3.37-3.33 (m, 1.55H), 3.21 (d, $J = 7.2$ Hz, 1H), 3.18 (d, $J = 7.2$ Hz, 0.51H), 2.78-2.73 (m, 1.57H), 2.66-2.63 (m, 1.49H), 2.62-2.59 (m, 3.25H), 2.44-2.39 (m, 1.61H), 2.29-2.23 (m, 3.13H), 1.86 (s, 3.64H); $^{13}\text{C NMR}$ (150 MHz, CDCl_3) δ 171.13, 171.10, 169.43, 169.40, 139.5, 137.7, 135.6, 132.1, 131.3, 130.5, 128.1, 127.7, 127.4, 127.0, 126.9, 126.5, 126.3, 126.2, 125.8, 122.9, 52.65, 52.63, 52.0, 51.8, 46.1, 41.5, 35.2, 34.0, 32.0, 31.9, 26.6, 26.0, 24.7, 24.0, 22.5, 21.6; FT-IR (neat) 2924, 1736, 1659, 1437, 1378, 1234, 1154, 971, 766 cm^{-1} ; HRMS (ESI) m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{20}\text{H}_{26}\text{NO}_5$: 360.1805, found 360.1813.

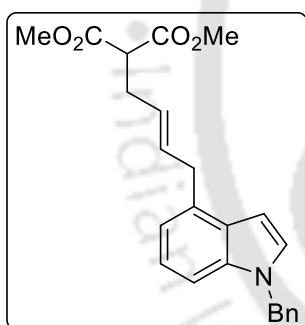


Dimethyl (*E*)-2-(4-(8-oxo-5,6,7,8-tetrahydronaphthalen-1-yl)but-2-en-1-yl)malonate 4D. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane $R_f = 0.46$; colorless sticky liquid; yield 41% (13.5 mg, $E/Z > 25:1$); $^1\text{H NMR}$ (600 MHz, CDCl_3) δ 7.30 (t, $J = 7.8$ Hz, 1H), 7.11 (d, $J = 7.2$ Hz, 1H), 7.08 (d, $J = 7.2$ Hz, 1H), 5.77-5.72 (m, 1H), 5.43-5.38 (m, 1H), 3.76 (d, $J = 6.6$ Hz, 2H), 3.68 (s, 6H), 3.40 (t, $J = 7.8$ Hz, 1H), 2.94 (t, $J = 6.0$ Hz, 2H), 2.64 (t, $J = 6.6$ Hz, 2H), 2.59 (t, $J = 7.2$ Hz, 2H), 2.10-2.04 (m, 2H); $^{13}\text{C NMR}$ (150 MHz, CDCl_3) δ 200.1, 169.5, 146.0, 143.4, 132.9, 132.5, 130.8, 129.5, 127.3, 126.3, 52.5, 52.0, 41.1, 38.0, 32.0, 31.2, 23.0; FT-IR (neat) 2925, 2853, 1737, 1678, 1591, 1436, 1273, 1155, 762 cm^{-1} ; HRMS (ESI) m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{19}\text{H}_{23}\text{O}_5$: 331.1540, found 331.1546.



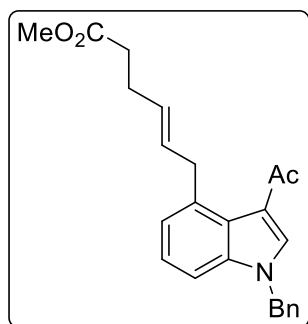
Dimethyl (E)-2-(4-(9-acetyl-9H-carbazol-1-yl)but-2-en-1-

yl)malonate 4E. Analytical TLC on silica gel, 1:2 ethyl acetate/hexane $R_f = 0.43$; colorless liquid; yield 36% (14.4 mg, $E/Z > 25:1$); ^1H NMR (600 MHz, CDCl_3) δ 7.97 (d, $J = 7.8$ Hz, 1H), 7.85 (t, $J = 7.8$ Hz, 2H), 7.45 (t, $J = 7.8$ Hz, 1H), 7.37-7.34 (m, 2H), 7.28-7.27 (m, 1H), 5.59-5.55 (m, 1H), 5.52-5.47 (m, 1H), 3.66 (s, 6H), 3.58 (d, $J = 6.0$ Hz, 2H), 3.42 (t, $J = 7.8$ Hz, 1H), 2.74 (s, 3H), 2.62 (t, $J = 7.2$ Hz, 2H); ^{13}C NMR (150 MHz, CDCl_3) δ 170.7, 169.4, 139.6, 138.3, 131.1, 129.3, 129.1, 128.0, 127.7, 127.1, 126.9, 124.4, 123.4, 120.2, 117.9, 114.4, 52.6, 51.8, 37.7, 31.9, 27.2; FT-IR (neat) 2924, 2853, 1737, 1435, 1364, 1272, 1205, 758 cm^{-1} ; HRMS (ESI) m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{23}\text{H}_{24}\text{NO}_5$: 394.1649, found 394.1650.



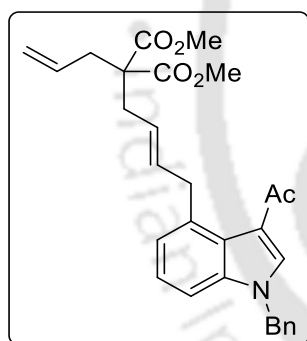
Dimethyl (E)-2-(4-(1-benzyl-1H-indol-4-yl)but-2-en-1-

yl)malonate 5. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane $R_f = 0.46$; yellow sticky liquid; yield 73% (28.5 mg, $E/Z > 25:1$); ^1H NMR (400 MHz, CDCl_3) δ 7.30-7.24 (m, 3H), 7.15-7.07 (m, 5H), 6.88 (d, $J = 6.4$ Hz, 1H), 6.55-6.54 (m, 1H), 5.85-5.78 (m, 1H), 5.58-5.50 (m, 1H), 5.30 (s, 2H), 3.67 (s, 6H), 3.61 (d, $J = 6.8$ Hz, 2H), 3.44 (t, $J = 7.6$ Hz, 1H), 2.62 (t, $J = 6.8$ Hz, 2H); ^{13}C NMR (125 MHz, CDCl_3) δ 169.5, 137.6, 136.4, 132.7, 132.4, 128.8, 128.1, 127.8, 127.7, 126.9, 126.5, 122.0, 119.0, 108.0, 100.2, 52.5, 52.0, 50.3, 36.6, 32.0; FT-IR (neat) 2961, 1732, 1493, 1435, 1259, 1152, 1017, 795 cm^{-1} ; HRMS (ESI) m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{24}\text{H}_{26}\text{NO}_4$: 392.1856, found 392.1862.



Methyl (*E*)-6-(3-acetyl-1-benzyl-1*H*-indol-4-yl)hex-4-enoate 6.

Analytical TLC on silica gel, 1:3 ethyl acetate/hexane $R_f = 0.46$; yellow sticky liquid; yield 70% (26.2 mg, $E/Z > 25:1$); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.77 (s, 1H), 7.36-7.30 (m, 3H), 7.21-7.17 (m, 1H), 7.15-7.13 (m, 3H), 7.08 (d, $J = 7.2$ Hz, 1H), 5.74-5.67 (m, 1H), 5.46-5.39 (m, 1H), 5.33 (s, 2H), 4.07 (d, $J = 6.8$ Hz, 2H), 3.61 (s, 3H), 2.52 (s, 3H), 2.37-2.27 (m, 4H); $^{13}\text{C NMR}$ (125 MHz, CDCl_3) δ 192.2, 173.9, 138.3, 136.6, 135.8, 131.8, 129.1, 128.32, 128.30, 127.0, 124.6, 124.0, 123.8, 119.2, 108.2, 51.5, 50.8, 38.6, 34.3, 28.7, 28.1; FT-IR (neat) 2920, 1731, 1652, 1524, 1438, 1374, 1190, 970, 735 cm^{-1} ; HRMS (ESI) m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{24}\text{H}_{26}\text{NO}_3$: 376.1907, found 376.1914.



Dimethyl (*E*)-2-(4-(3-acetyl-1-benzyl-1*H*-indol-4-yl)but-2-en-1-yl)-2-allylmalonate 7.

Analytical TLC on silica gel, 1:3 ethyl acetate/hexane $R_f = 0.47$; colorless sticky liquid; yield 66% (31.2 mg, $E/Z > 25:1$); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.79 (s, 1H), 7.34-7.30 (m, 3H), 7.20-7.16 (m, 1H), 7.13-7.11 (m, 3H), 7.05 (d, $J = 6.8$ Hz, 1H), 5.76-5.69 (m, 1H), 5.64-5.55 (m, 1H), 5.34 (s, 2H), 5.25-5.17 (m, 1H), 5.03-4.97 (m, 2H), 4.09 (d, $J = 6.4$ Hz, 2H), 3.59 (s, 6H), 2.57-2.55 (m, 4H), 2.53 (s, 3H); $^{13}\text{C NMR}$ (125 MHz, CDCl_3) δ 192.1, 171.4, 138.33, 138.30, 136.8, 136.2, 135.9, 135.8, 132.7, 129.1, 128.3, 126.9, 124.6, 124.0, 123.4, 119.2, 119.0, 108.2, 58.1, 52.3, 50.8, 38.8, 36.9, 35.9, 28.7; FT-IR (neat) 2924, 1732, 1656, 1525, 1440, 1376, 1207, 748 cm^{-1} ; HRMS (ESI) m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{29}\text{H}_{32}\text{NO}_5$: 474.2275, found 474.2283.

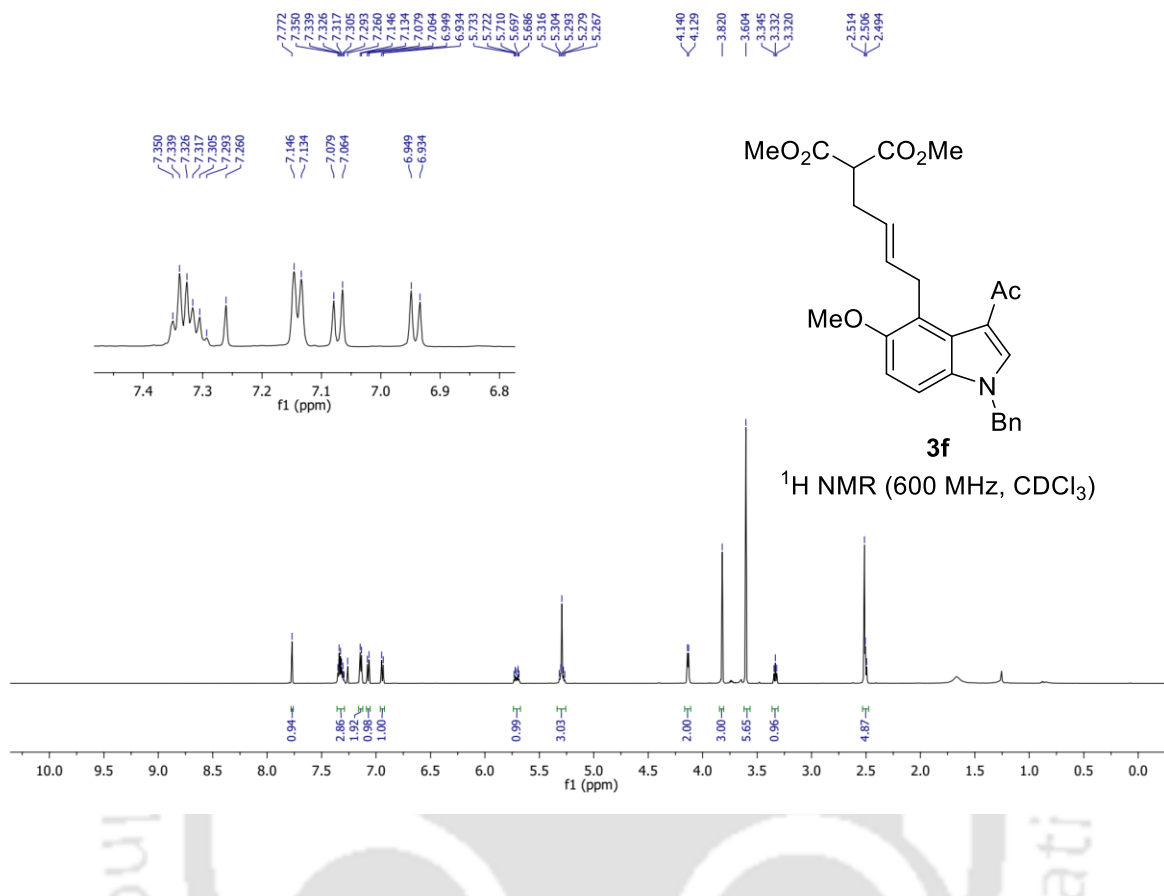
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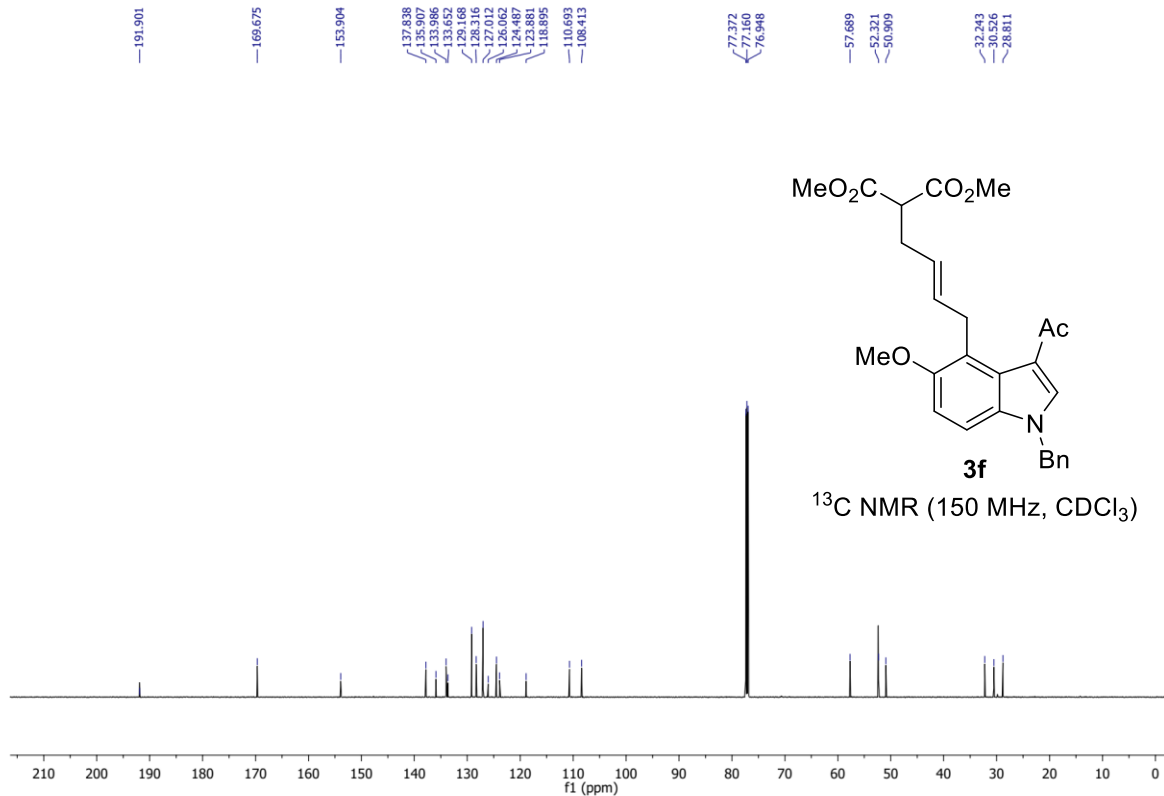
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3.6 Selected NMR Spectra

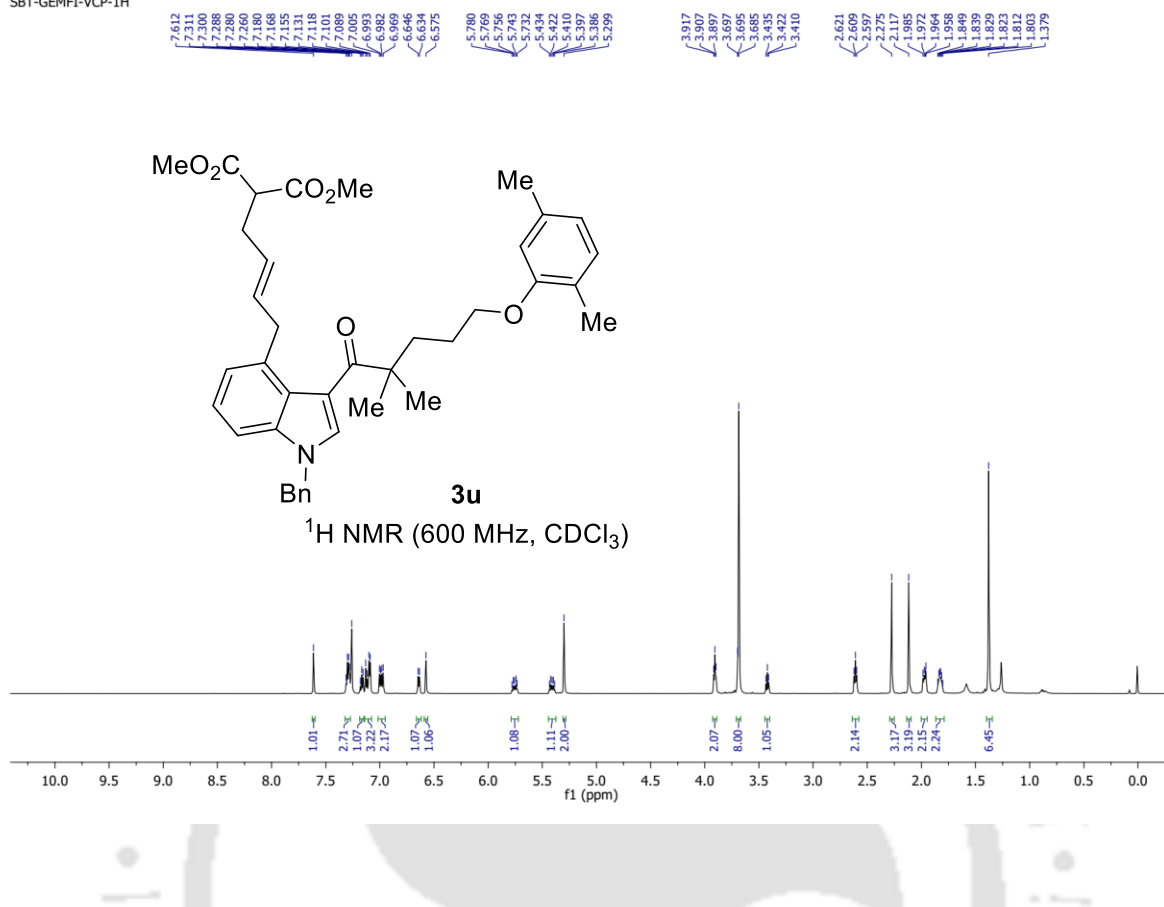
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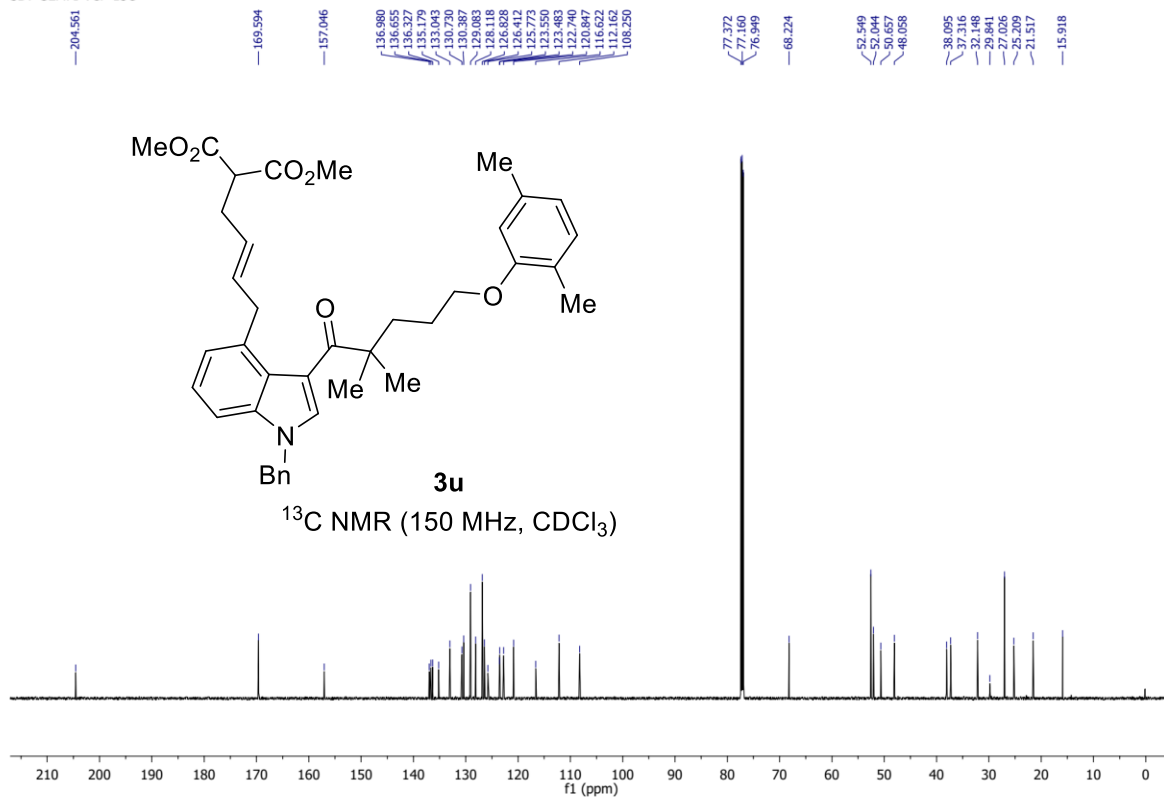
SBT-50ME-VCP-13C



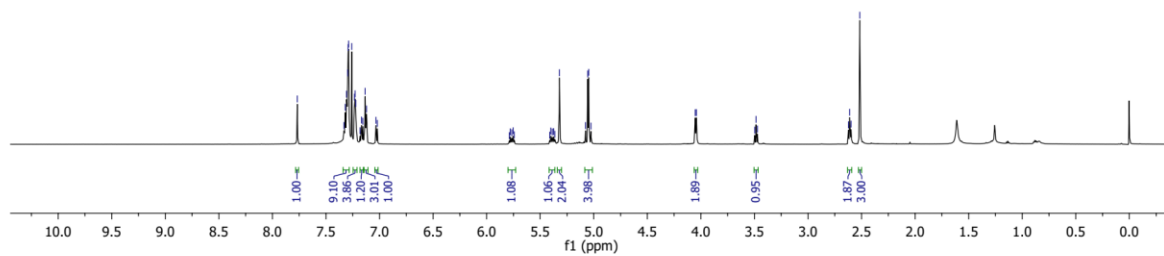
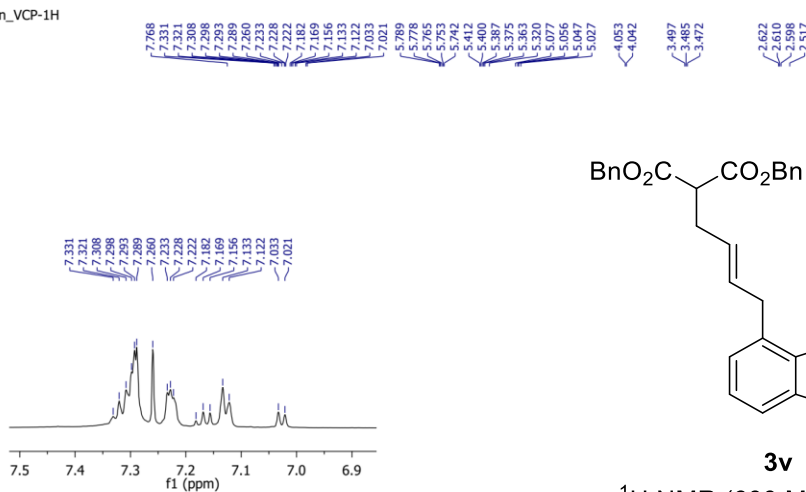
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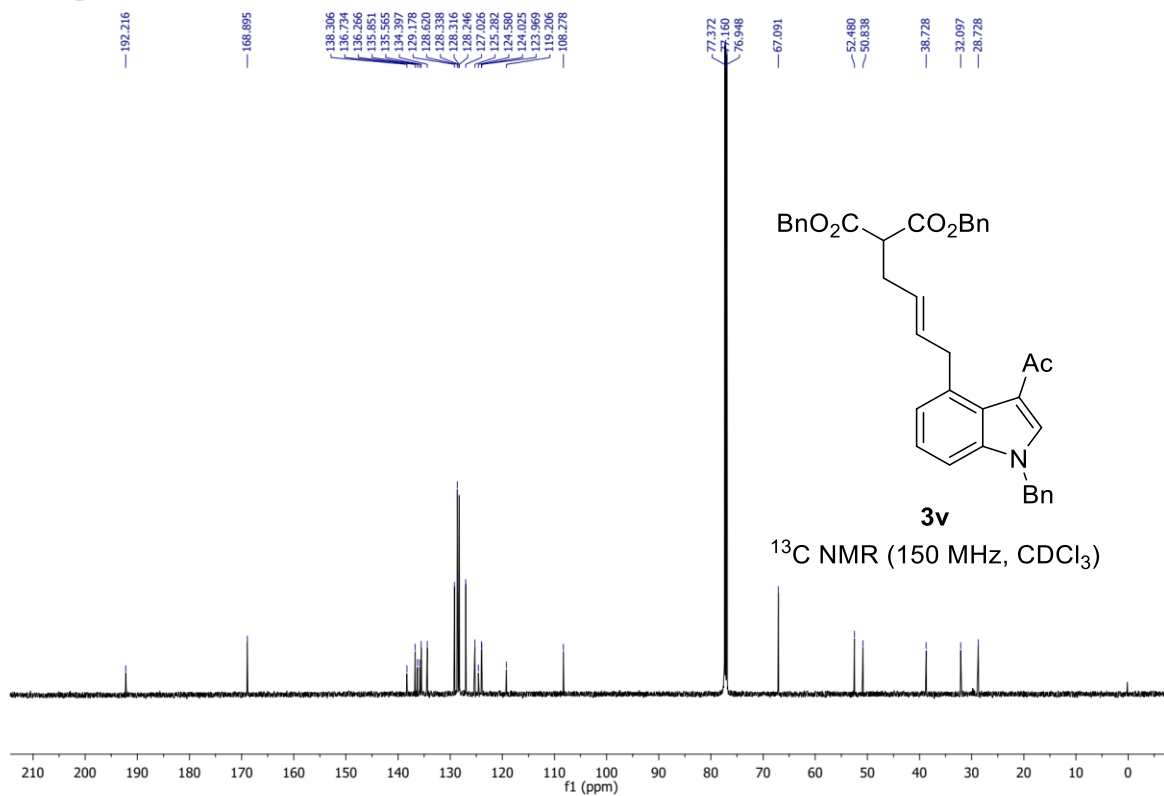
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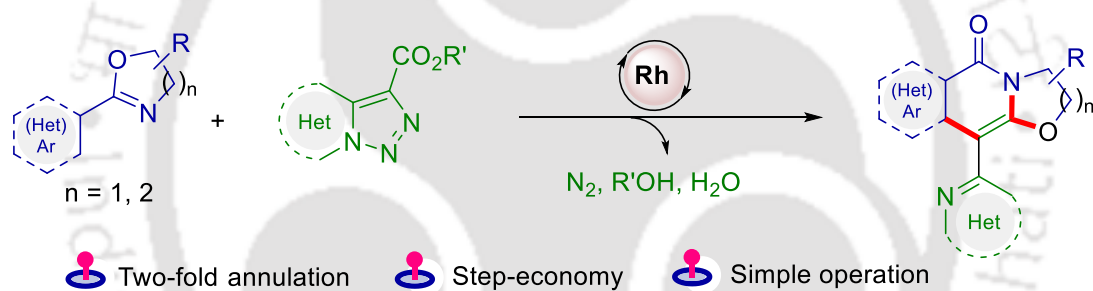


SBT-AC-Bn_VCP-13C



Chapter IV

Rhodium-Catalyzed Cascade C-H Activation and Annulation of (Hetero)arenes with Pyridotriazoles



Chem. Commun. **2025**, *61*, 1693.



Rhodium-Catalyzed Cascade C-H Activation and Annulation of (Hetero)-arenes with Pyridotriazoles

The site-selective C-H functionalization employing transition-metal-catalysis has evolved as a promising and versatile strategy for the synthetic transformation of simple substrates to the complex molecular scaffolds.¹ Recently, the chelation-assisted C-H functionalization and annulation under metal-catalysis has garnered considerable interest due to the rapid formation of C-C/C-heteroatom bonds in a predictable way, leading to the important cyclic frameworks.² In this context, the construction of polycyclic isoquinolinones has attracted much attention due to their ubiquity in pharmacologically potent compounds, molecular materials and agrochemicals.³ Notably, the ring-fused oxazolo- and oxazino-isoquinolinones exhibit the intriguing biological features such as anti-inflammatory, antimycobacterial and analgesic activities (Figure 1).⁴ Despite the important synthetic value, the traditional methods for the preparation of such scaffolds is often faced limitation by the harsh experimental conditions, prefunctionalized substrates and lengthy reaction steps. The concise synthetic method design to access these polycyclic isoquinolinone frameworks would thus be valuable. In this paradigm, 2-aryloxazolines can act as important structural frameworks for the auxiliary-assisted C-H functionalization to fabricate intricate structural motifs. Alongside, pyridotriazoles, a congener of 1,2,3-triazoles, are the versatile scaffolds as they undergo tautomerization to the diazoimine form, which can be trapped by organometallic species to afford reactive pyridyl carbene intermediate.⁵ Further, the potential pyridyl ring offers a significant advantage in the annulation sequence by chelation with the metal, rather poisoning the catalyst. In this vein, Glorius group has reported the C-H activation/annulation of 2-arylpyridines with pyridotriazoles as the stable carbene precursor to access novel fluorescent compounds.⁶ In order to meet the upsurge for the single step structural diversification, enabling the formation of the heteroaryl-tethered oxazoloisoquinolinones, the denitrogenative coupling of pyridotriazoles with 2-aryloxazolines would be stimulating. This chapter demonstrates a Rh(III)-catalyzed tandem C-H activation/2-fold annulation reaction of 2-aryloxazolines and pyridotriazoles for the synthesis of heteroaryl-tethered oxazoloisoquinolinones. The salient features include step-economic transformation, consecutive annulation sequence and production of N₂, alcohol and H₂O as the green by-products.

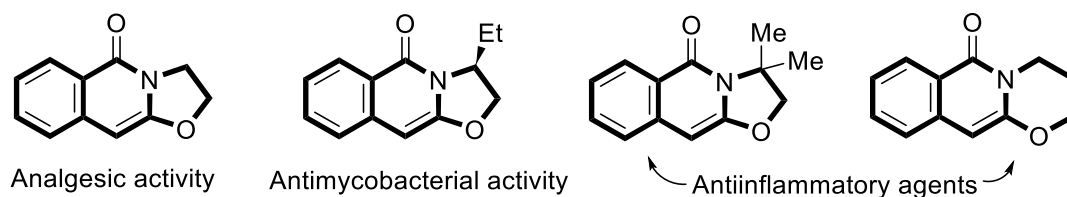
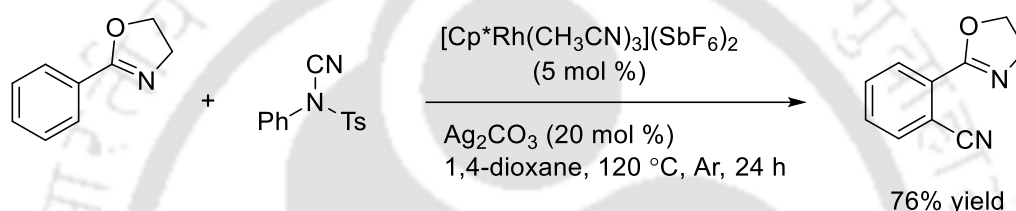


Figure 1. Examples of Bioactive Oxazolo- and Oxazino-Isoquinolinone Scaffolds

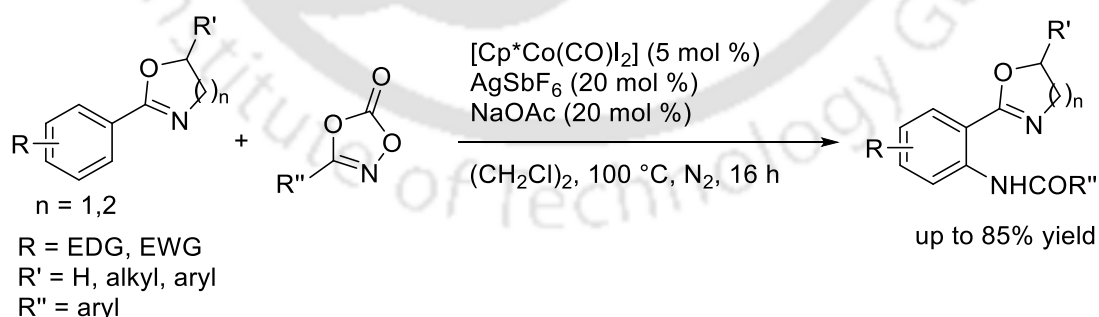
4.1. C-H Functionalization of 2-Aryloxazolines

The Rh(III)-catalyzed *ortho*-cyanation of 2-aryloxazolines was reported with *N*-cyano-*N*-phenyl-*p*-toluenesulfonamide (NCTS) with good functional group tolerance (Scheme 1).⁷ The procedure was extended to arene C-H cyanation utilizing a varied *N*-chelating functionalities such as oxime, pyridines and pyrazoles.



Scheme 1. Rh(III)-Catalyzed *ortho*-Cyanation of 2-Aryloxazolines

Ackermann and co-workers developed an elegant method for the oxazoliny-assisted direct C-H amidation at the *ortho*-position of aryl ring of 2-aryloxazolines with dioxazolones using economically viable Co(III)-catalysis (Scheme 2).⁸ A diverse array of amidated aryloxazolines were synthesized in good yields with regio- and chemo-selectivity. In addition, post synthetic transformation was realized to afford aminated quinazolines.

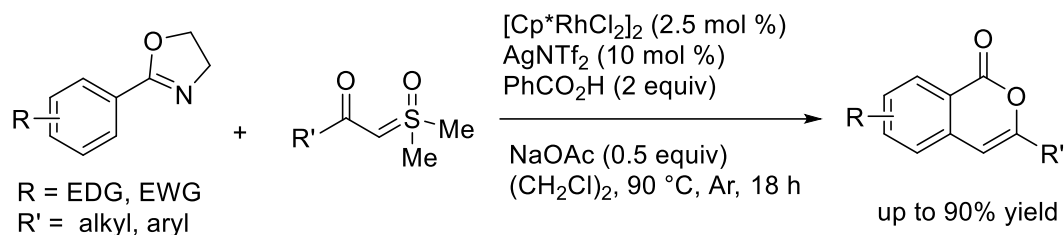


Scheme 2. Oxazoliny-Assisted Direct Amidation of 2-Aryloxazolines

4.2 Ring-Opening Annulation of 2-Aryloxazolines

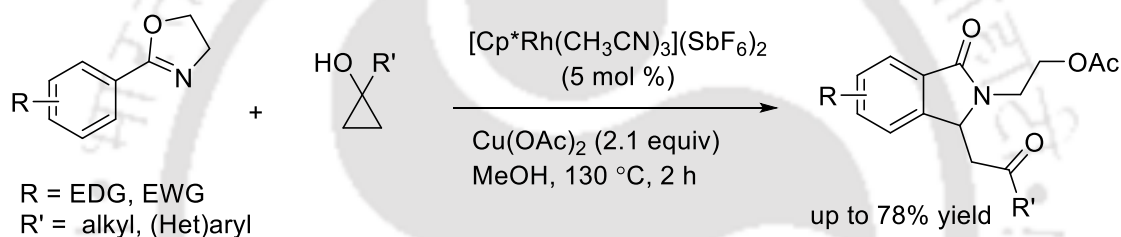
The Rh(III)-catalyzed C-H activation and annulative coupling of 2-aryloxazolines and sulfoxonium ylide was described for the synthesis of isocoumarins (Scheme 3).⁹ The reaction pathway is proposed to proceed with sequential C-H activation and nucleophilic addition of

enol *O*-atom to the imine followed by hydrolysis. A wide variety of isocoumarins was obtained with good yield and functional group compatibility.



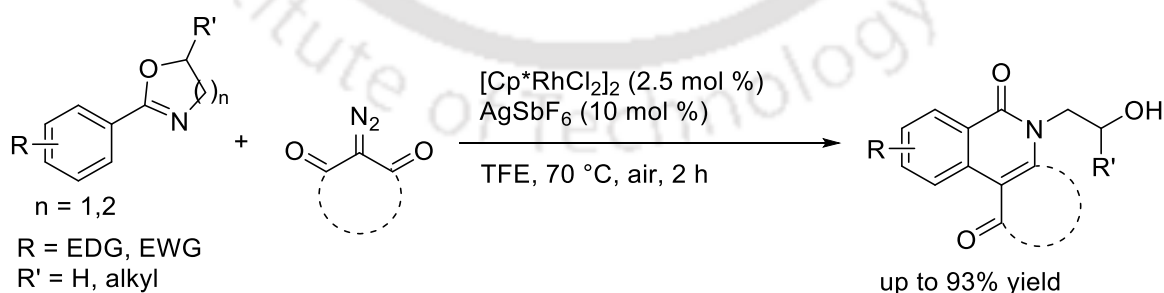
Scheme 3. Expedient Synthesis of Isocoumarins

Liu and co-workers developed oxazoliny-assisted C-H oxidative cyclization of 2-aryloxazolines and cyclopropanols utilizing Rh(III)-catalysis to afford C3-substituted isoindolin-1-ones (Scheme 4).¹⁰ The transformation involves the cleavage of three chemical bonds, which leads to sequential formation C-C/ C-N and C-O bonds.



Scheme 4. Synthesis of Substituted Isoindolin-1-ones

The Rh-catalyzed tandem C-H activation/[4+2]-cyclization of 2-aryloxazolines with α -1,3-diazodiones was demonstrated to access indenoisoquinolinones with broad substrate diversity (Scheme 5).¹¹ The one-pot strategy proceeded with the C-H functionalization/intramolecular annulation/elimination and oxazoline ring opening in a sequence to furnish the target product.

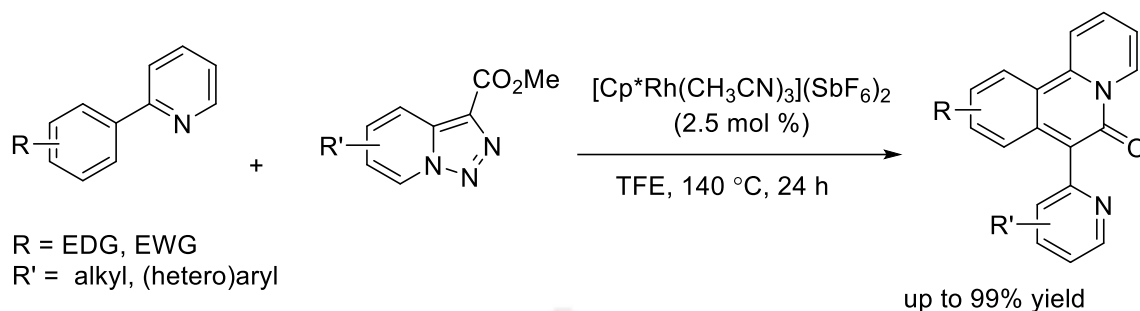


Scheme 5. Synthesis of Functionalized Indenoisoquinolinones

4.3 Reactivity of Pyridotriazoles

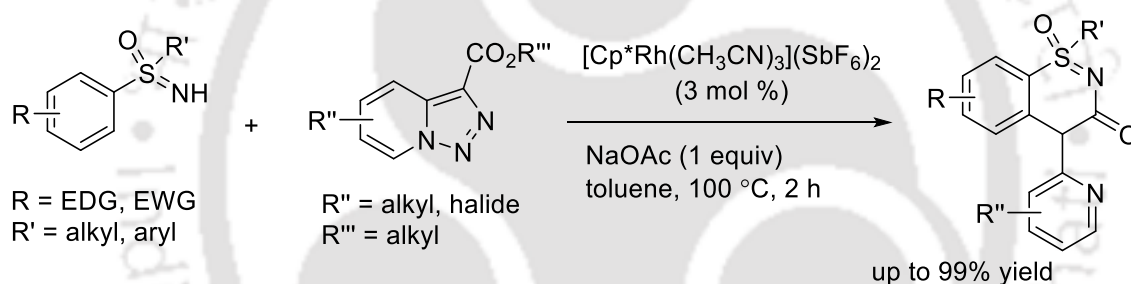
Glorius and co-workers reported C-H activation/annulation of 2-phenylpyridine utilizing pyridotriazole as stable carbene precursor under Rh(III)-catalysis (Scheme 6).⁶ The reaction

was guided by 2-pyridyl DG and provides access to a new family of π -extended fluorophores, which can find application in chemo- and bio-sensing.



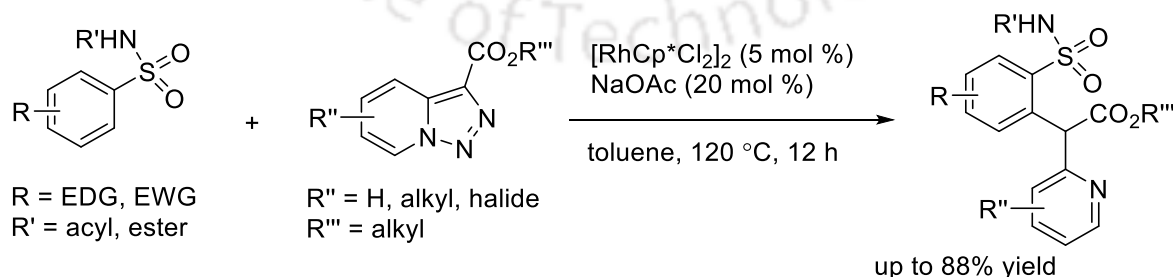
Scheme 6. Synthesis of π -Extended Fluorophores under Rh-Catalysis

Lee group described a practical approach for the synthesis of 2-pyridyl-tethered carbonyl group bearing 1,2-benzothiazines *via* the denitrogenative coupling of pyridotriazoles with *S*-aryl sulfoximines under Rh-catalysis (Scheme 7).¹² The reaction proceeded with N-H/C-H activation with a good site-selectivity and functional group tolerance.



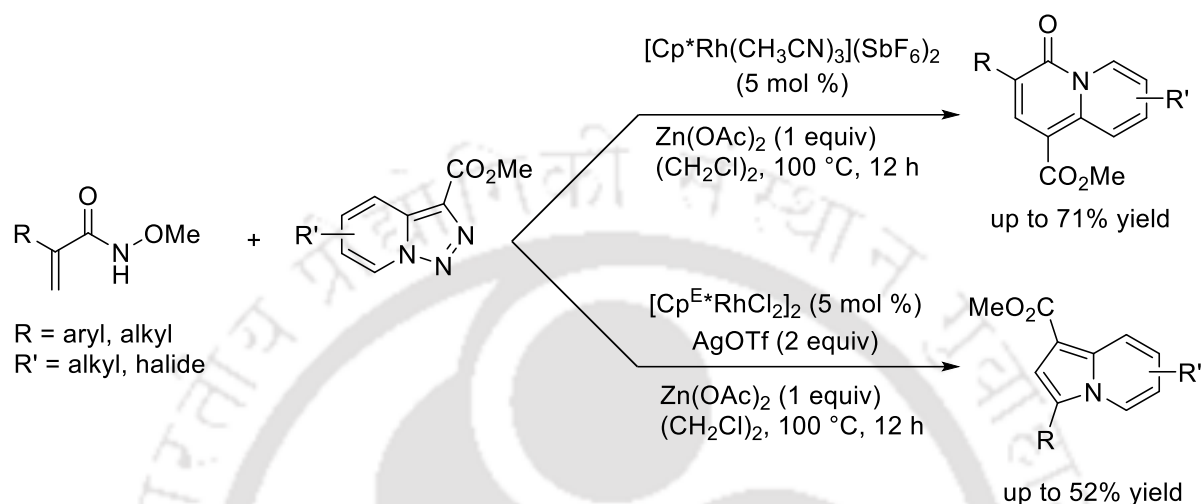
Scheme 7. Synthesis of Functionalized 1,2-Benzothiazines

A sulfonamide-assisted C-H activation and carbene insertion was reported to access benzylpyridyl sulfonamides utilizing Rh-catalysis (Scheme 8).¹³ The procedure featured with the formation of dual-pharmacophore compounds and the late-stage diversification of sulfonamide drugs.



Scheme 8. Sulfonamide-assisted Benzylpyridylation of Arenes

The divergent catalytic methods were developed for the synthesis of quinolizinone and indolizine using enamide and triazole derivatives (Scheme 9).¹⁴ The reaction pathway involving Rh(III) catalyzed terminal olefinic C-H activation of enamide followed by a cascade [3+3] and [3+2]-cyclization of triazoles leading to quinolizinone and indolizine, respectively, was proposed.



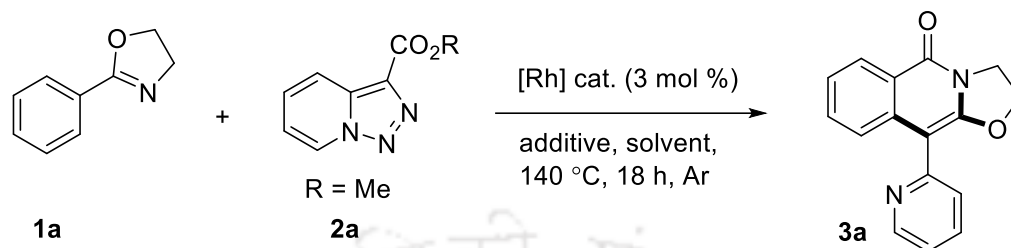
Scheme 9. Catalytic-condition Controlled Synthesis of Quinolizinones and Indolizines

4.4 Present Study

Herein, the Rh(III)-catalyzed cascade C-H activation and 2-fold annulative coupling of 2-aryl-oxazolines with pyridotriazoles is described for the construction of heteroaryl-tethered oxazoloisoquinolinones. The procedure was extended to the reaction of aryl 1,3-oxazine to afford oxazinoisoquinolinone. The optimization studies were initiated with 2-phenyl-4,5-dihydrooxazole **1a** and methyl [1,2,3]triazolo[1,5-*a*]pyridine-3-carboxylate **2a** as the test substrates utilizing a varied Rh-catalysts, additives and solvents (Table 1). Gratifyingly, the target product **3a** was obtained in 82% yield when the substrates were reacted using 3 mol % $[\text{Cp}^*\text{RhCl}_2]_2$ and 50 mol % NaOAc in TFE at 140 °C for 18 h (entry 1). Screening of the additives revealed that the use of NaOAc as base is superior to that of KOAc, AgOAc, CsOAc, Na_2CO_3 , $\text{Cu}(\text{OAc})_2$ and AcOH (entries 2-7). Among the solvent examined, TFE produced the best outcome, while HFIP, MeOH, H_2O , $(\text{CH}_2\text{Cl})_2$, PhMe and THF gave inferior results (entries 8-13). The use of $[\text{Cp}^*\text{Rh}(\text{CH}_3\text{CN})_3](\text{SbF}_6)_2$ showed a drop in the yield to 59%, whereas $\text{Rh}_2(\text{OAc})_4$ failed to catalyze the reaction (entries 14-15). Moreover, the reaction with ethyl [1,2,3]triazolo[1,5-*a*]pyridine-3-carboxylate **2a'**, instead of **2a** have led to a slight decrease in the yield to 73% (entry 16). In addition, lowering reaction temperature (70 °C) or amount (20 mol %) of additive showed a sluggish outcome (entries 17-18). Control experiments confirmed

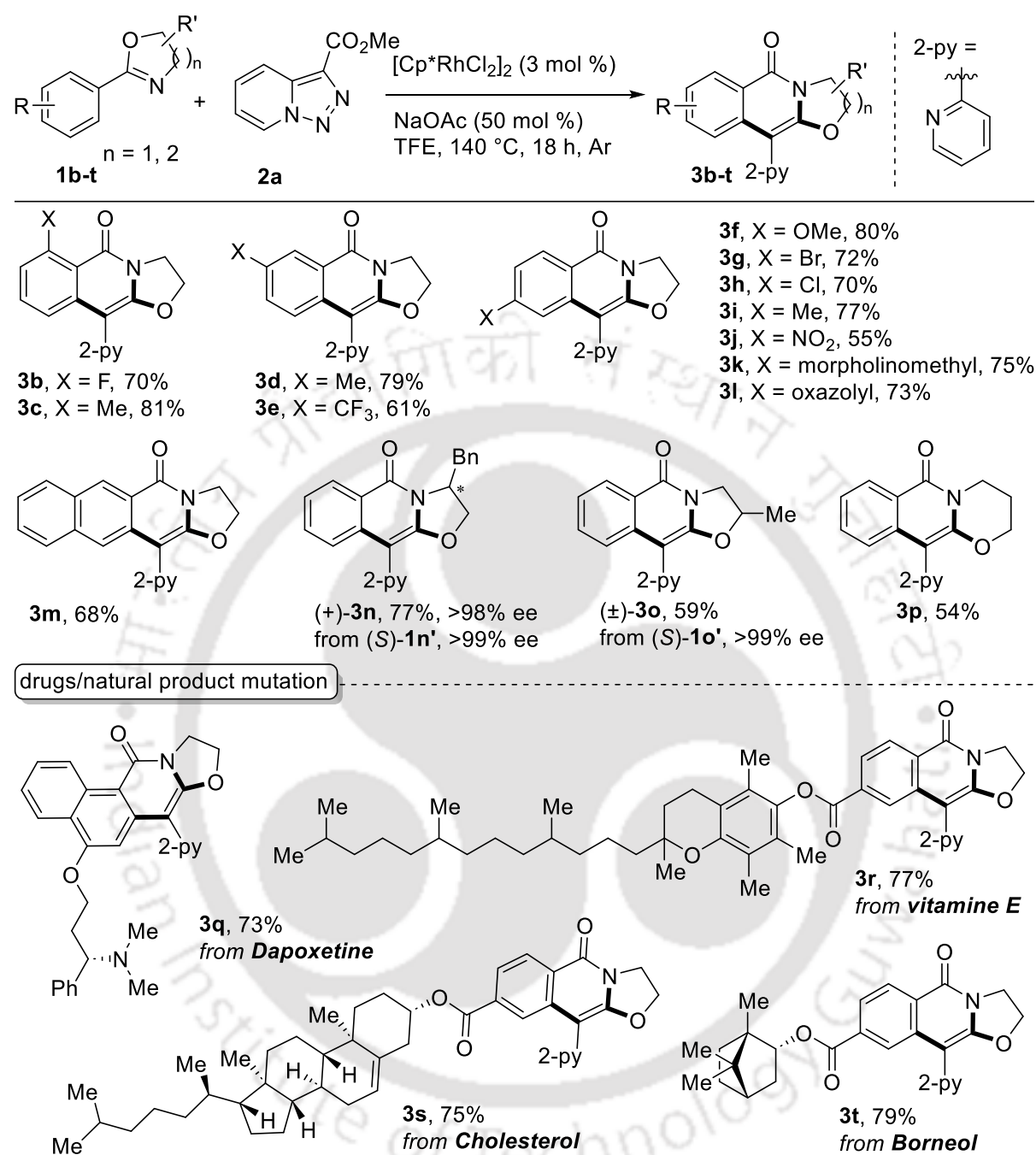
that the combination of the Rh-catalyst and basic additive is essential to realize the annulation in good yield (entries 19-20).

Tables 1. Optimization of the Reaction Conditions^a



Entry	Catalyst	Additive	Solvent	Yield (%)
1	[Cp*RhCl ₂] ₂	NaOAc	TFE	82
2	[Cp*RhCl ₂] ₂	KOAc	TFE	72
3	[Cp*RhCl ₂] ₂	AgOAc	TFE	57
4	[Cp*RhCl ₂] ₂	CsOAc	TFE	55
5	[Cp*RhCl ₂] ₂	Na ₂ CO ₃	TFE	n.d.
6	[Cp*RhCl ₂] ₂	Cu(OAc) ₂	TFE	trace
7	[Cp*RhCl ₂] ₂	AcOH	TFE	25
8	[Cp*RhCl ₂] ₂	NaOAc	HFIP	54
9	[Cp*RhCl ₂] ₂	NaOAc	MeOH	27
10	[Cp*RhCl ₂] ₂	NaOAc	H ₂ O	n.d.
11	[Cp*RhCl ₂] ₂	NaOAc	(CH ₂ Cl) ₂	trace
12	[Cp*RhCl ₂] ₂	NaOAc	PhMe	n.d.
13	[Cp*RhCl ₂] ₂	NaOAc	THF	n.d.
14	[Cp*Rh(CH ₃ CN) ₃](SbF ₆) ₂	NaOAc	TFE	59
15	Rh ₂ (OAc) ₄	NaOAc	TFE	n.d.
16 ^c	[Cp*RhCl ₂] ₂	NaOAc	TFE	73
17 ^d	[Cp*RhCl ₂] ₂	NaOAc	TFE	21
18 ^e	[Cp*RhCl ₂] ₂	NaOAc	TFE	57
19	[Cp*RhCl ₂] ₂	---	TFE	48
20	---	NaOAc	TFE	n.d.

^aReaction conditions: **1a** (0.2 mmol), **2a** (0.3 mmol), [Rh] (3 mol %), additive (50 mol %), solvent (1 mL), 140 °C, 18 h, Ar, pressure tube. ^bIsolated yield. ^cWith **2a'** (when R = Et). ^dReaction at 70 °C. ^eUsing 20 mol % NaOAc. n.d. = not detected.

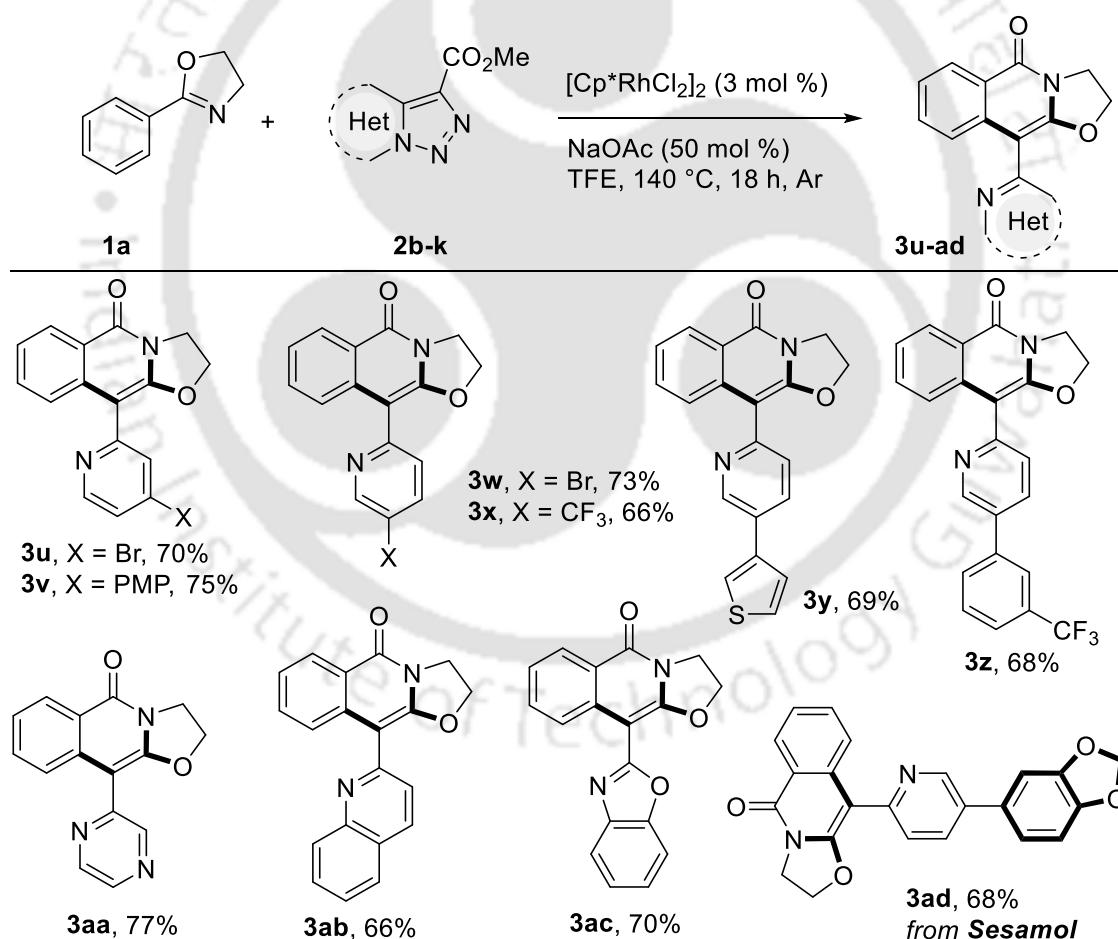
Table 2. Scope of 2-Aryloxazolines^{a,b}

^aReaction conditions: **1b-t** (0.2 mmol), **2a** (0.3 mmol), [Cp*RhCl₂]₂ (3 mol %), NaOAc (50 mol %), TFE (1 ml), 140 °C, 18 h, Ar, pressure tube. ^bIsolated yield.

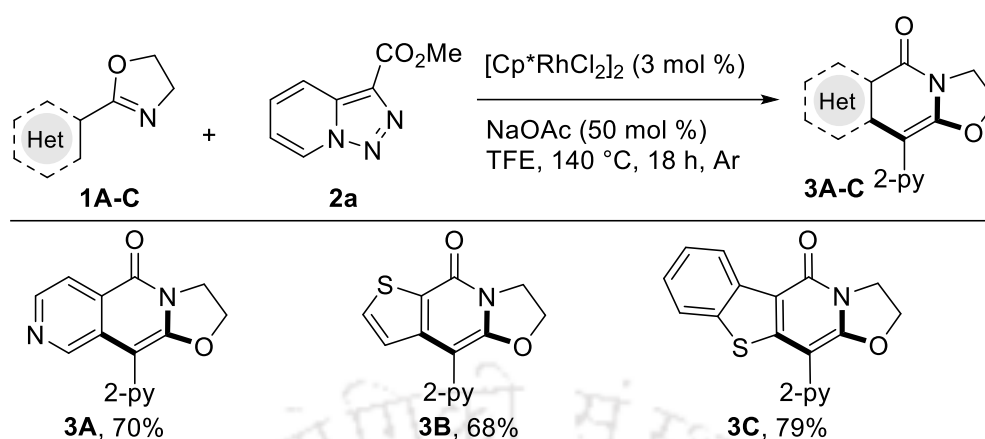
With the optimized conditions established, the viability of the procedure was examined for a set of 2-aryloxazolines **1b-t** employing **2a** as a model substrate (Table 2). Aryloxazolines having fluoro **1b** and methyl **1c** groups at the *o*-position were tolerated to afford **3b-c** in 70–81% yields. The substrate bearing *m*-methyl **1d** substitution delivered **3d** in 79% yield, while electron-withdrawing *m*-trifluoromethyl substituted **1e** produced **3e** in 61% yield. Further,

aryloxazolines bearing methoxy **1f**, bromo **1g**, chloro **1h** and methyl **1i**, nitro **1j**, benzylmorpholine **1k** and oxazole **1l** groups at *p*-position underwent annulation, delivering **3f-l** in 55-80% yields. The structure of **3f** was confirmed by single-crystal X-ray analysis. A similar result was observed with fused 2-naphthyloxazoline **1m**, giving **3m** in 68% yield. When the optically pure substrates bearing substitution on oxazoline ring such as 4-benzyl **1n'** and 5-methyl **1o'** were subjected to the reaction, the former produced (+)-**3n** in 77% yield with >98% ee, while the latter afforded (±)-**3o** in 59% yield, respectively. Intriguingly, six-membered phenyl 1,3-oxazine **1p** was compatible to provide **3p** in 54% yield. The selective serotonin reuptake inhibitor dapoxetine derived aryloxazoline **1q** was amenable to produce **3q** in 73% yield. Moreover, aryloxazolines tethered with vitamine E **1r**, cholesterol **1s** as well as naturally occurring (-)-borneol **1t** motifs at the *p*-position reacted to deliver **3r-t** in 75-79% yields.

Table 3. Scope of Heteroaryl Triazoles.^{a,b}



^aReaction conditions: **1a** (0.2 mmol), **2b-k** (0.3 mmol), [Cp*RhCl₂]₂ (3 mol %), NaOAc (50 mol %), TFE (1 ml), 140 °C, 18 h, Ar, pressure tube. ^bIsolated yield.

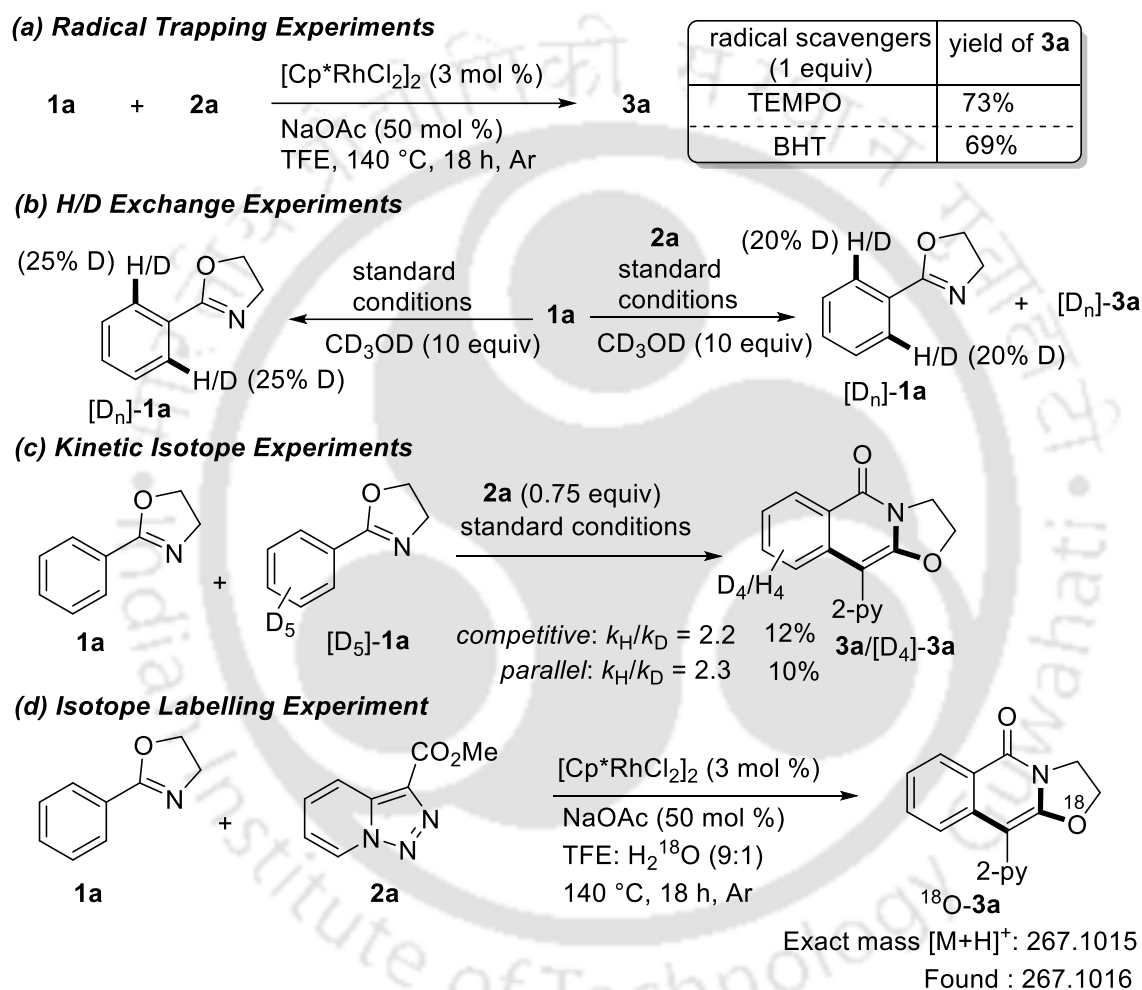
Table 4. Scope of Heteroaryl Oxazolines.^{a,b}

^aReaction conditions: **1A-C** (0.2 mmol), **2a** (0.3 mmol), [Cp*RhCl₂]₂ (3 mol %), NaOAc (50 mol %), TFE (1 ml), 140 °C, 18 h, Ar, pressure tube. ^bIsolated yield.

Encouraged by these intriguing results, we next surveyed the scope of the procedure employing a set of heteroaryl *N*-fused 1,2,3-triazoles **2b-k** with 2-phenyloxazoline **1a** as a model substrate (Table 3). The reaction of pyridotriazoles with 5-bromo **2b** and 5-*p*-methoxyphenyl (PMP) **2c** groups proceeded smoothly to afford **3u** and **3v** in 70% and 75% yields, respectively. A pertinent result was obtained with 6-bromo **2d** substituted pyridotriazole, furnishing **3w** in 73% yield. In contrast, electron-withdrawing 6-trifluoromethyl substituted **2e** gave **3x** in 66% yield, whereas pyridotriazoles having 3-thienyl **2f** and 3-trifluoromethylphenyl **2g** substitution at the 6-position underwent annulation to give **3y** and **3z** in 69% and 68% yields, respectively. In addition, the 1,2,3-triazoles having pyrazinyl **2h**, quinolinyl **2i** and benzo[*d*]oxazoliny **2j** units reacted to produce **3aa-ac** in 66-77% yields, while pyridotriazole tethered with naturally occurring sesamol **2k** successfully annulated to afford **3ad** in 68% yield. The synthetic versatility of the procedure was extended to the reaction of heteroaryl oxazolines such as 4-pyridinyl **1A**, 2-thienyl **1B** and 3-benzo[*b*]thiophenyl **1C** with **2a**, affording the annulated **3A-C** in 68-79% yields (Table 4). These results suggest that the annulation procedure is general for a broad spectrum of (hetero)aryl-oxazolines and pyridotriazoles with good functional group tolerance.

To elucidate the mechanistic pathway, the radical trapping experiments employing **1a** with **2a** using 2,6-di-*tert*-butyl-4-methylphenol (BHT) as well as 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) were investigated (Scheme 10a). The reaction occurred to furnish the annulated **3a** in good yield, suggesting the radical pathway is unlikely. In addition, the H/D exchange experiments independently in absence and presence of **2a** using CD₃OD as a co-solvent,

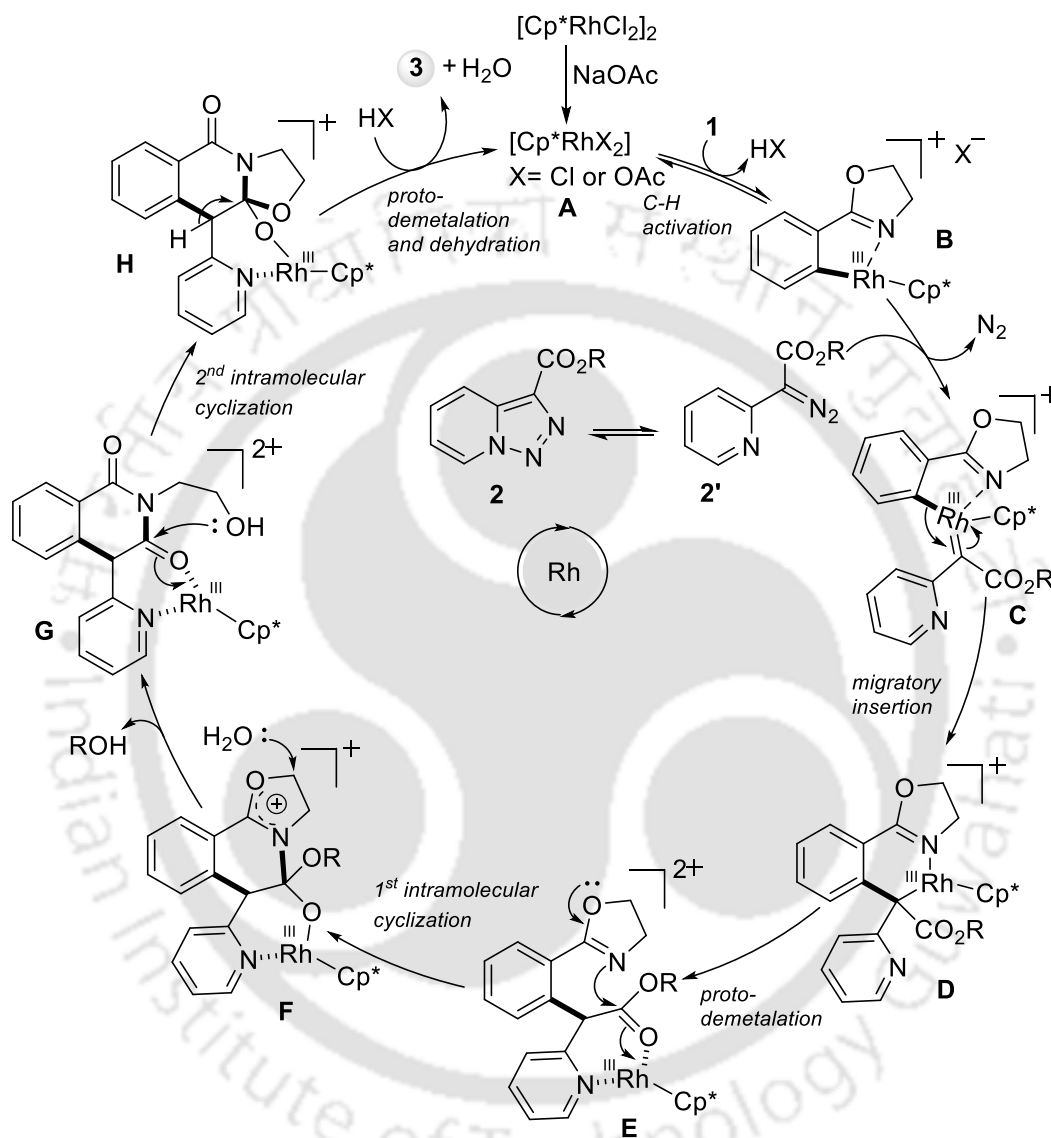
showed 25% and 20% deuterium incorporation at the *o*-positions of the aryl ring, respectively, indicating the reversibility in the C-H activation step (Scheme 10b). Moreover, the competitive and parallel kinetic isotope experiments¹⁵ using **1a** and [D₅]-**1a** with **2a** produced a k_H/k_D of 2.2 and 2.3, respectively, which entails that the *o*-C-H bond cleavage may be the rate-determining step (Scheme 10c). Further, the isotope labelling experiment utilizing TFE/H₂¹⁸O (9:1, v/v) afforded ¹⁸O-labelled **3a** (detected by HRMS analysis), which implies that the *O*-atom may come from water which may originate from the solvent TFE (Scheme 10d).^{11,16}



Scheme 10. Preliminary Mechanistic Studies

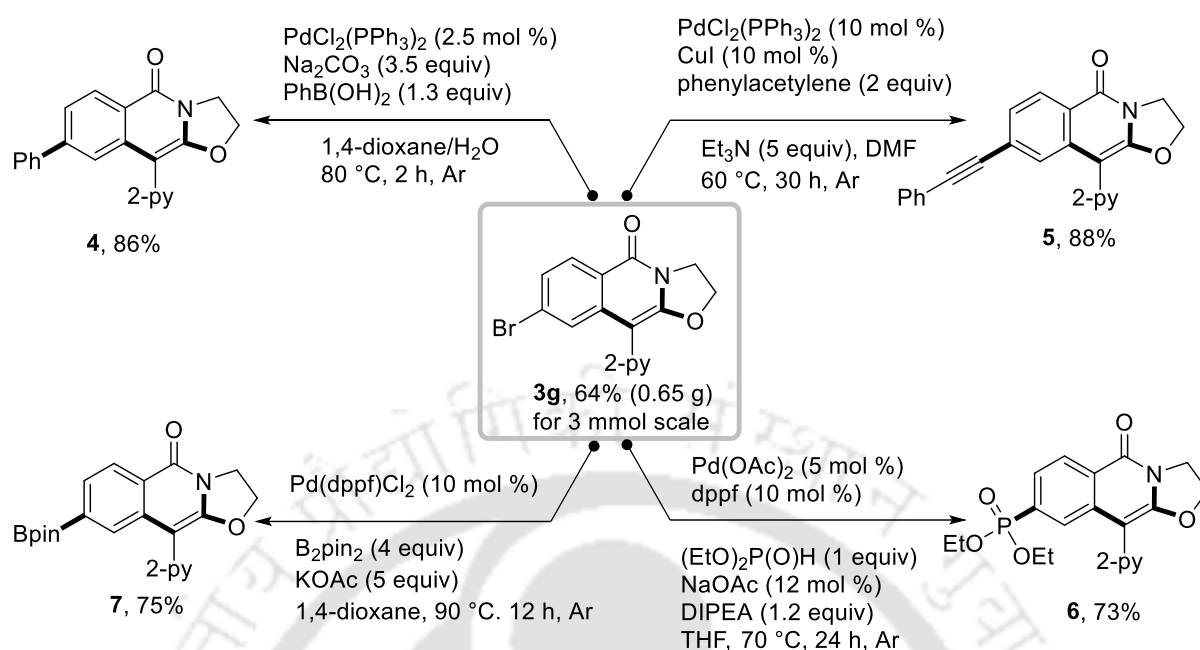
These experimental results and literatures^{6,17} suggest that [Cp*RhCl₂]₂ with NaOAc may form the active Rh-catalyst **A** (Scheme 11), which can activate the *o*-C-H bond of **1** to generate rhodacycle **B**. The latter can react with the *in situ* formed diazoimine **2'** from pyridotriazole **2** to furnish rhodium carbene species **C** by the liberation of N₂. Subsequent migratory insertion, followed by protodemetalation may lead to generation of **E**. Intramolecular addition to the activated ester carbonyl group may produce **F**, which can undergo oxazoline ring opening to afford **G** and liberate ROH. Nucleophilic attack of hydroxy group to the amide carbonyl which

was activated by $\text{Cp}^*\text{Rh(III)}$, may trigger further intramolecular cyclization, leading to the intermediate **H**. Subsequent protonation and dehydration of **H** delivered the annulated **3** and regenerate the active catalyst to complete the cycle.



Scheme 11. Plausible Reaction Mechanism

To illustrate the synthetic usefulness, a scale-up reaction taking **1g** (3 mmol) with **2a** was carried out and the target product **3g** was obtained in 64 % (0.65 g) yield (Scheme 12). Further, a set of Pd-catalyzed cross-coupling reactions were performed with the annulated **3g** to fabricate molecular intricacy. For instances, Suzuki coupling of **3g** with phenyl boronic acid delivered **4** in 86% yield, whereas Sonagashira coupling with phenyl acetylene furnished **5** in 88% yield. In addition, the phosphorylation of **3g** with diethyl phosphite afforded **6** in 73% yield, while the borylation conveyed **7** in 75% yield.



Scheme 12. Scale-up and Post-synthetic Utilities.

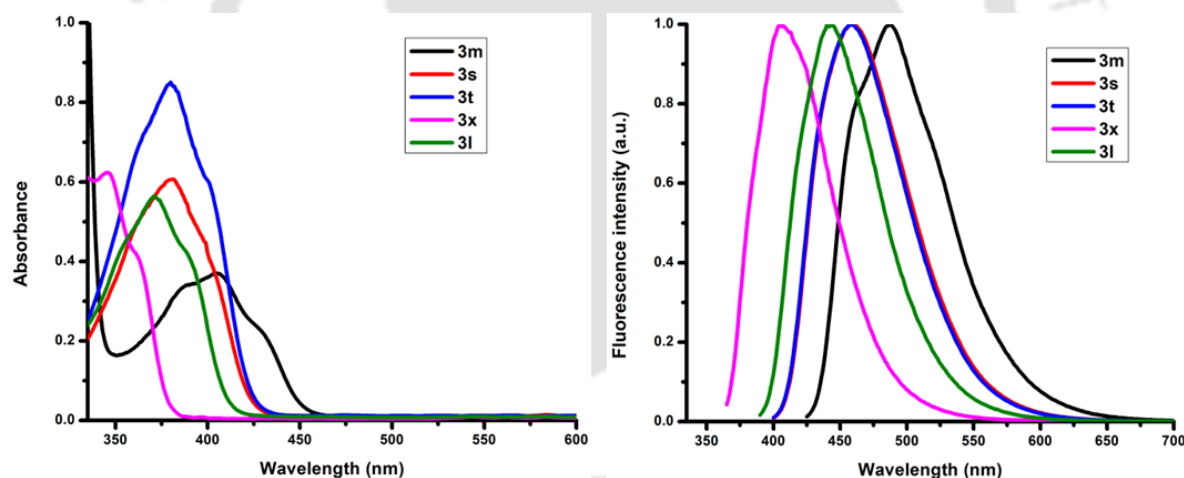


Figure 2. Absorption (left) and Normalized Emission (right) Spectra of **3m**, **3s**, **3t**, **3x** and **3l** in CH₂Cl₂ (1.0 × 10⁻⁵ M)

Additionally, photophysical properties were investigated for the compounds **3m**, **3s**, **3t**, **3x** and **3l** as the model examples.^{3a,c,6} The absorption and emission spectra are shown in Figure 2. A sharp photoluminescence was observed with emission wavelength in the range of 406–487 nm upon excitation, irrespective of the substitutions. These outcomes indicate that the products may gain a suitable position in organic electronic materials.

In summary, we have developed the Rh(III)-catalyzed cascade C-H activation/2-fold annulation of 2-aryloxazolines with pyridotriazoles to afford heteroaryl-tethered oxazoloisoquinolinones. The 2-fold synergistic annulation, substrate scope, step-economy, production of N₂, alcohol and H₂O as green byproducts and the late-stage modification of the bio-relevant compounds are the important features.

4.5 Experimental Section

General Information. [Cp*RhCl₂]₂ (>97%), Rh₂(OAc)₄ (>98%), AgOAc (≥99.99%), Cu(OAc)₂ (>98%), KOAc, NaOAc, CsOAc, Na₂CO₃, 2,2,2-trifluoroethanol (TFE) and 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) of Aldrich and TCI Chemicals were used as received. Aryloxazolines¹⁸ and pyridotriazoles⁶ were synthesized according to the reported procedure. Methanol, 1,2-dichloroethane, toluene and tetrahydrofuran were dried prior to use as per the standard procedure. Merck silica gel G/GF254 plates were used for analytical thin-layer chromatography (TLC). Column chromatography was carried out using Rankem silica gel (100-200 mesh). Bruker Avance III 400, 500 and 600 MHz NMR spectrometers were used to record spectra using CDCl₃ as the solvent and tetramethylsilane (Me₄Si) as an internal standard. Chemical shifts (δ) and spin-spin coupling constant (*J*) are reported in parts per million and hertz (Hz), respectively, and to describe peak patterns following abbreviations were used when appropriate: s = singlet, d = doublet, t = triplet, q = quartet, dd = double doublet, m = multiplet. Melting points were determined using a Büchi B-540 apparatus and are uncorrected. FT-IR spectra were recorded on a PerkinElmer FT-IR spectrometer. Quadrupole time-of-flight electrospray ionization (ESI) mass spectrometer (Agilent 6546) was used for recording HRMS. Single crystal X-ray data was collected on a Bruker SMART APEX equipped with a CCD area detector using Mo/Kα radiation and the structure was solved by direct method using SHELXT-2018/2 (Göttingen, Germany).

General Procedure for Rh(III)-Catalyzed C-H Activation/2-fold Annulation. In an oven-dried pressure tube, a mixture of aryl-/heteroaryl-oxazoline **1** (0.2 mmol), heteroaryl *N*-fused 1,2,3-triazole **2** (0.3 mmol, 1.5 equiv), [Cp*RhCl₂]₂ (3 mol %, 0.006 mmol, 3.70 mg), NaOAc (0.1 mmol, 0.5 equiv, 8.2 mg) in TFE (1 mL) was stirred at 140 °C for 18 h under Ar atmosphere. The progress of the reaction was monitored by TLC utilizing acetone and CH₂Cl₂ as an eluent. Upon completion, the resulting solution was cooled to room temperature, diluted with ethyl acetate (10 mL) and passed through a short celite pad. The filtrate was concentrated under reduced pressure and the residue was purified on silica gel column chromatography using acetone and CH₂Cl₂ as an eluent to afford the annulated product **3**.

Radical Trapping Experiments. In an oven-dried pressure tube, a mixture of 2-phenyl-4,5-dihydrooxazole **1a** (0.2 mmol, 29 mg), methyl [1,2,3]triazolo[1,5-*a*]pyridine-3-carboxylate **2a** (0.3 mmol, 1.5 equiv, 53 mg), [Cp*RhCl₂]₂ (3 mol %, 0.006 mmol, 3.70 mg), NaOAc (0.1 mmol, 0.5 equiv, 8.2 mg) and) and TEMPO (0.2 mmol, 31.2 mg) or BHT (0.2 mmol, 44 mg) in TFE (1 mL) was stirred at 140 °C for 18 h under Ar atmosphere. Upon completion, the resulting solution was cooled to room temperature, diluted with ethyl acetate (10 mL) and passed through a short celite pad. The purification was performed as described in the general procedure to afford **3a**.

H/D Exchange Experiment of 1a with CD₃OD in Absence of 2a. In an oven-dried pressure tube, a mixture of 2-phenyl-4,5-dihydrooxazole **1a** (0.2 mmol, 29 mg), [Cp*RhCl₂]₂ (3 mol %, 0.006 mmol, 3.70 mg), NaOAc (0.1 mmol, 0.5 equiv, 8.2 mg) and CD₃OD (2 mmol, 10 equiv, 82 μL) in TFE (1 mL) was stirred at 140 °C for 18 h under Ar atmosphere. The resulting solution was cooled to room temperature, diluted with ethyl acetate (10 mL) and passed through a short celite pad. The purification was performed as described in the general procedure to afford [D_n]-**1a**. The deuterium incorporation was observed as 25% at the *ortho*-position of aryl ring based on 600 MHz ¹H NMR spectrum.

H/D Exchange Experiment of 1a with CD₃OD in Presence of 2a. In an oven-dried pressure tube, a mixture of 2-phenyl-4,5-dihydrooxazole **1a** (0.2 mmol, 29 mg), methyl [1,2,3]triazolo[1,5-*a*]pyridine-3-carboxylate **2a** (0.3 mmol, 1.5 equiv, 53 mg), [Cp*RhCl₂]₂ (3 mol %, 0.006 mmol, 3.70 mg), NaOAc (0.1 mmol, 0.5 equiv, 8.2 mg) and CD₃OD (2 mmol, 10 equiv, 82 μL) in TFE (1 mL) was stirred at 140 °C for 18 h under Ar atmosphere. The resulting solution was cooled to room temperature, diluted with ethyl acetate (10 mL) and passed through a short celite pad. The purification was performed as described in the general procedure to afford [D_n]-**1a** and [D_n]-**3a**. The deuterium incorporation in [D_n]-**1a** was observed as 20% at the *ortho*-position of aryl ring based on 600 MHz ¹H NMR spectrum.

Preparation of 2-(Phenyl-d₅)-4,5-dihydrooxazole [D₅]-1a.

Step-I:^{19a} To a stirred solution of sulfuric acid (0.6 mL) in water (2 mL), benzene-d₆ (3 mmol, 265 μL) was added dropwise at 0 °C, which was treated with NaBrO₃ (3.3 mmol, 1.1 equiv, 498 mg) at the same temperature in two portions with an interval of 1 h and stirred for another 10 h at room temperature. Then, the mixture was quenched with ice water and extracted with Et₂O (3 x 20 mL). The combined organic layer was washed with brine (15 mL) and water (15 mL). Drying (Na₂SO₄) and evaporation of the solvent gave crude 1-bromobenzene-d₅ that was used for the next step without further purification (73% yield, 353 mg).

Step-II:^{19b} To a stirred solution of 1-bromobenzene-*d*₅ (2.0 mmol, 320 mg) in THF (10 mL), *n*-BuLi (2.4 mmol, 1.2 mL, 2M in hexane) was added dropwise at -78 °C for a period of 10 min under Ar atmosphere. The solution was allowed to stir for 30 min and then *N,N*-dimethylformamide (20 mmol, 1.5 mL) was added and continued the stirring at the same temperature for 10 min. Upon completion (monitored by TLC), the resulting mixture was quenched with H₂O and extracted with EtOAc (3 x 20 mL). The combined organic layer was washed with brine (2 x 10 mL) and water (10 mL). Drying (Na₂SO₄) and evaporation of the solvent gave crude bezaldehyde-*d*₅ that was used for the next step without further purification (55% yield, 122 mg).

Step-III:^{18a} To a stirred solution of bezaldehyde-*d*₅ (1 mmol, 111 mg) in *tert*-butyl alcohol (10 mL), 2-aminoethan-1-ol (1.1 mmol, 1.1 equiv, 67 mg) was added. The mixture was stirred at room temperature for 30 min under Ar atmosphere. K₂CO₃ (3 mmol, 3 equiv, 414 mg) and I₂ (2 mmol, 2 equiv, 506 mg) were then added and was further stirred at the same temperature for 18 h. Upon completion (monitored by TLC), the reaction mixture was allowed to cool and was quenched with saturated aqueous Na₂S₂O₃ solution until the colour of iodine was disappeared. The mixture was extracted with ethyl acetate (3 x 10 mL). The combined organic layer was washed with brine (2 x 5 mL) and water (5 mL). Drying (Na₂SO₄) and evaporation of the solvent gave a residue that was purified on silica gel column chromatography using *n*-hexane and ethyl acetate (80/20, v/v) as an eluent to afford 2-(phenyl-*d*₅)-4,5-dihydrooxazole [D₅]-**1a** in 75% (114 mg) yield.

Kinetic Isotope Effect Experiments.

Competitive Experiment. In an oven-dried pressure tube, a mixture of 2-phenyl-4,5-dihydrooxazole **1a** (0.1 mmol, 14.7 mg) and 2-(phenyl-*d*₅)-4,5-dihydrooxazole [D₅]-**1a** (0.1 mmol, 17.6 mg) was reacted with methyl [1,2,3]triazolo[1,5-*a*]pyridine-3-carboxylate **2a** (0.15 mmol, 0.75 equiv, 26.5 mg) for 2 h under standard reaction conditions. The resulting mixture was cooled to room temperature, diluted with ethyl acetate (10 mL) and passed through a short pad of celite. The purification was performed as described in the general procedure to afford a mixture of **3a** and [D₄]-**3a** in 12% yield. The intermolecular k_H/k_D was found to be 2.2, based on 400 MHz ¹H NMR of the product **3a** and [D₄]-**3a**.

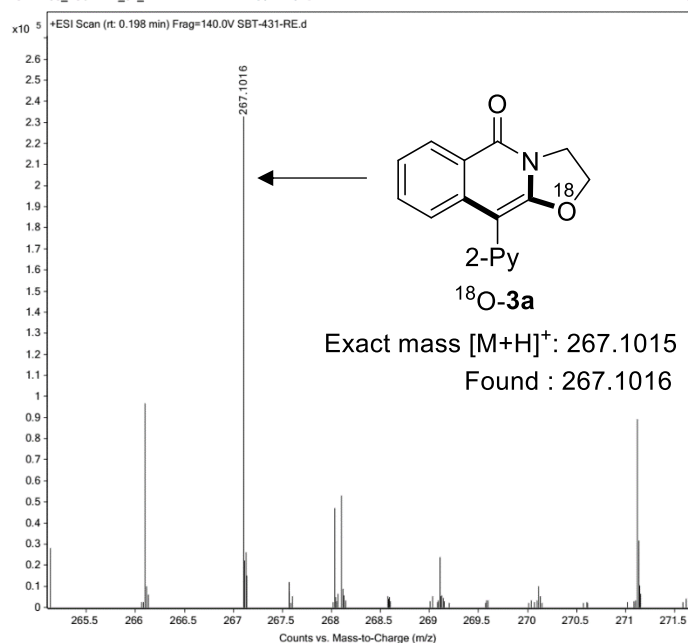
Parallel Experiments. Three sets of experiments were carried out, each having a mixture of 2-phenyl-4,5-dihydrooxazole **1a** (0.1 mmol, 14.7 mg) or 2-(phenyl-*d*₅)-4,5-dihydrooxazole [D₅]-**1a** (0.1 mmol, 17.6 mg) was reacted with methyl [1,2,3]triazolo[1,5-*a*]pyridine-3-carboxylate **2a** (0.075 mmol, 0.75 equiv, 13.3 mg) for 1 h (Set 1), 2h (Set 2) and 3h (Set 3),

respectively, under standard reaction conditions. The resulting mixture was cooled to room temperature, diluted with ethyl acetate (10 mL) and passed through a short pad of celite. The purification was performed as described in the general procedure to afford a mixture of **3a** and [D₄]-**3a**. The KIE value was calculated using 600 MHz ¹H NMR spectroscopy.

Reaction Set	Time	k_H/k_D	Yield of 3a /[D ₄]- 3a
Set 1	1h	2.3	10 %
Set 2	2h	2.3	14 %
Set 3	3h	2.4	19 %

Isotope Labelling Experiment. In an oven-dried pressure tube, a mixture of 2-phenyl-4,5-dihydrooxazole **1a** (0.2 mmol, 29 mg), methyl [1,2,3]triazolo[1,5-*a*]pyridine-3-carboxylate **2a** (0.3 mmol, 1.5 equiv, 53 mg), [Cp**Rh*Cl₂]₂ (3 mol %, 0.006 mmol, 3.70 mg) and NaOAc (0.1 mmol, 0.5 equiv, 8.2 mg) was stirred in TFE/ H₂¹⁸O (9:1, v/v) at 140 °C for 18 h under Ar atmosphere. The resultant solution was cooled to room temperature, diluted with ethyl acetate (10 mL) and passed through a short celite pad. The formation of ¹⁸O-**3a** was confirmed by HRMS. HRMS (ESI) m/z [M+H]⁺ calcd for C₁₆H₁₃N₂O¹⁸: 267.1015, found 267.1016.

Sample Name	SBT-431-RE	Position	P1-A1	Instrument Name	QTOF
User Name	SYSTEM (SYSTEM)	Inj Vol	5	InjPosition	
Sample Type	Sample	IRM Calibration Status	Success	Data Filename	SBT-431-RE.d
ACQ Method	DIRECT MASS_POSITIVE_01_1.m	Comment		Acquired Time	11-07-2024 10:03:36 (UTC+05:30)



Scale-up Synthesis of 3g. In an oven-dried pressure tube, a mixture of 2-(4-bromophenyl)-4,5-dihydrooxazole **1g** (3 mmol, 674 mg), methyl [1,2,3]triazolo[1,5-*a*]pyridine-3-carboxylate **2a** (4.5 mmol, 1.5 equiv, 796 mg), [Cp**RhCl*₂]₂ (3 mol %, 0.09 mmol, 55 mg), NaOAc (1.5 mmol, 0.5 equiv, 123 mg) in TFE (10 mL) was stirred at 140 °C for 18 h under Ar atmosphere. The progress of the reaction was monitored by TLC utilizing acetone and CH₂Cl₂ as an eluent. Upon completion, the resulting solution was cooled to room temperature, diluted with ethyl acetate (20 mL) and passed through a short celite pad. The filtrate was concentrated under reduced pressure and the residue was purified on silica gel column chromatography using acetone and CH₂Cl₂ (10/90, v/v) as an eluent to afford the annulated product **3g** in 64% (0.65 g) yield.

Synthesis of 4.¹¹ To an oven-dried round bottom flask, a mixture of compound **3g** (0.1 mmol, 34 mg), phenyl boronic acid (0.13 mmol, 1.3 equiv, 16 mg), PdCl₂(PPh₃)₂ (2.5 mol %, 0.0025 mmol, 1.75 mg) and Na₂CO₃ (0.35 mmol, 3.5 equiv, 37 mg) in dioxane/H₂O (1:1, v/v) was stirred at 80 °C in a preheated oil bath for 2 h under Ar atmosphere. Upon completion, monitored by TLC, the resulting mixture was quenched with saturated aqueous NH₄Cl solution and extracted with EtOAc (3 x 10 mL). The combined organic layer was washed with brine (2 x 5 mL) and water (1 x 5 mL). Drying (Na₂SO₄) and evaporation of the solvent gave a residue that was purified on silica gel column chromatography using acetone and CH₂Cl₂ (15/85, v/v) as an eluent to afford **4** in 86% (29 mg) yield.

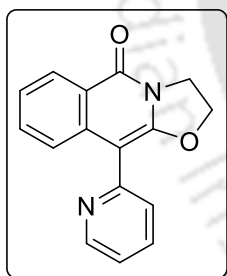
Synthesis of 5.²⁰ In an oven-dried pressure tube, a mixture of **3g** (0.1 mmol, 34 mg), phenylacetylene (0.2 mmol, 2 equiv, 20.4 mg), PdCl₂(PPh₃)₂ (10 mol %, 0.01 mmol, 7.0 mg), CuI (0.01 mmol, 10 mol %, 1.9 mg) and Et₃N (0.5 mmol, 5 equiv, 70 μL) in DMF (1 mL) was stirred at 60 °C in a preheated oil bath for 30 h under Ar atmosphere. Upon completion, monitored by TLC, the resulting mixture was quenched with H₂O and extracted with EtOAc (3 x 10 mL). The combined organic layer was washed with brine (2 x 5 mL) and water (1 x 5 mL). Drying (Na₂SO₄) and evaporation of the solvent gave a residue that was purified on silica gel column chromatography using acetone and CH₂Cl₂ (15/85, v/v) as an eluent to afford **5** in 88% (32 mg) yield.

Synthesis of 6.²¹ To an oven-dried round bottom flask, a mixture of compound **3g** (0.1 mmol, 34 mg), diethyl phosphite (0.1 mmol, 1 equiv, 14 mg), Pd(OAc)₂ (5 mol %, 0.005 mmol, 1 mg

mg), dppf (0.01 mmol, 10 mol %, 6 mg), NaOAc (0.012 mmol, 12 mol %, 1 mg) and DIPEA (0.12 mmol, 1.2 equiv, 16 mg) in THF (1 mL) was stirred at 70 °C in a preheated oil bath for 24 h under Ar atmosphere. Upon completion, monitored by TLC, the resulting solution was cooled to room temperature, diluted with ethyl acetate (10 mL) and passed through a short celite pad. The filtrate was concentrated under reduced pressure and the residue was purified on silica gel column chromatography using acetone and CH₂Cl₂ (25/75, v/v) as an eluent to afford the phosphorylated **6** in 73% (29 mg) yield.

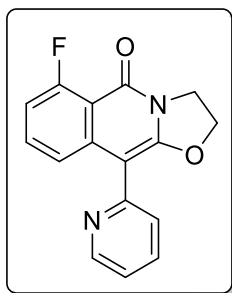
Synthesis of 7.²⁰ To an oven-dried round bottom flask, a mixture of compound **3g** (0.1 mmol, 34 mg), B₂pin₂ (0.4 mmol, 4 equiv, 101 mg), Pd(dppf)Cl₂ (10 mol %, 0.01 mmol, 7.3 mg) and KOAc (0.5 mmol, 5 equiv, 49 mg) in dioxane (1 mL) was stirred at 90 °C in a preheated oil bath for 12 h under Ar atmosphere. Upon completion, monitored by TLC, the resulting solution was cooled to room temperature, diluted with ethyl acetate (10 mL) and passed through a short celite pad. The filtrate was concentrated under reduced pressure and the residue was purified on silica gel column chromatography using acetone and CH₂Cl₂ (20/80, v/v) as an eluent to afford the borylated **7** in 75% (29 mg) yield.

4.6 Characterization Data of the Products

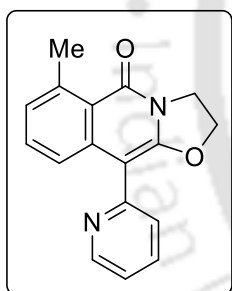


10-(Pyridin-2-yl)-2,3-dihydro-5H-oxazolo[3,2-b]isoquinolin-5-one 3a.

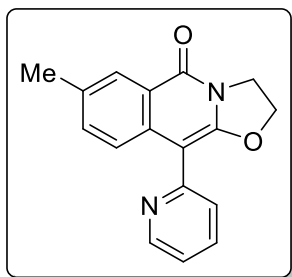
Analytical TLC on silica gel, 1:5 acetone/CH₂Cl₂ R_f = 0.50; light yellow solid; mp 180-181 °C; yield 82% (43.2 mg); ¹H NMR (600 MHz, CDCl₃) δ 8.76 (d, *J* = 4.2 Hz, 1H), 8.37 (d, *J* = 8.4 Hz, 1H), 7.80-7.77 (m, 1H), 7.64 (d, *J* = 8.4 Hz, 1H), 7.54-7.52 (m, 1H), 7.50 (d, *J* = 7.8 Hz, 1H), 7.33-7.30 (m, 1H), 7.28-7.27 (m, 1H), 4.70 (t, *J* = 8.4 Hz, 2H), 4.41 (t, *J* = 7.8 Hz, 2H); ¹³C NMR (150 MHz, CDCl₃) δ 160.2, 153.1, 150.1, 149.8, 138.3, 136.6, 132.9, 127.6, 126.4, 124.3, 123.6, 122.3, 122.0, 94.8, 68.2, 43.8; FT-IR (KBr) 2922, 2853, 1665, 1602, 1586, 1486, 1341, 1088, 1016, 983, 786, 764 cm⁻¹; HRMS (ESI) *m/z* [M+H]⁺ calcd for C₁₆H₁₃N₂O₂: 265.0972, found 265.0971.

**6-Fluoro-10-(pyridin-2-yl)-2,3-dihydro-5H-oxazolo[3,2-b]isoquinolin-**

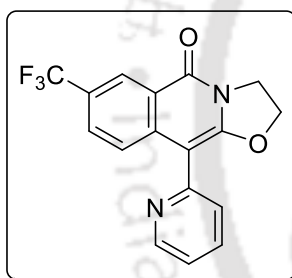
5-one 3b. Analytical TLC on silica gel, 1:5 acetone/CH₂Cl₂ R_f = 0.47; brown solid; mp 200-201 °C; yield 70% (39 mg); ¹H NMR (600 MHz, CDCl₃) δ 8.75 (d, *J* = 4.2 Hz, 1H), 7.79 (t, *J* = 7.8 Hz, 1H), 7.47 (d, *J* = 7.8 Hz, 1H), 7.44-7.40 (m, 1H), 7.33 (d, *J* = 7.8 Hz, 1H), 7.29-7.27 (m, 1H), 6.95-6.91 (m, 1H), 4.70 (t, *J* = 9.6 Hz, 2H), 4.38 (t, *J* = 8.4 Hz, 2H); ¹³C NMR (150 MHz, CDCl₃) δ 163.9 (*J*_{C-F} = 261.1 Hz), 157.5 (*J*_{C-F} = 3.9 Hz), 152.9, 150.8, 149.9, 141.3, 136.7, 133.6 (*J*_{C-F} = 10.3 Hz), 126.5, 122.3, 119.3 (*J*_{C-F} = 4.2 Hz), 111.6 (*J*_{C-F} = 6.3 Hz), 111.0 (*J*_{C-F} = 21.1 Hz), 94.2, 68.3, 43.8; ¹⁹F NMR (565 MHz, CDCl₃) δ -111.52; FT-IR (KBr) 2923, 2853, 1669, 1628, 1585, 1547, 1487, 1246, 1111, 1061, 808, 751 cm⁻¹; HRMS (ESI) *m/z* [M+H]⁺ calcd for C₁₆H₁₂FN₂O₂: 283.0877, found 283.0870.

**6-Methyl-10-(pyridin-2-yl)-2,3-dihydro-5H-oxazolo[3,2-b]isoquinolin-**

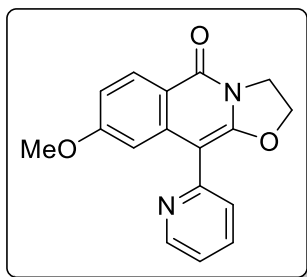
5-one 3c. Analytical TLC on silica gel, 1:5 acetone/CH₂Cl₂ R_f = 0.55; light yellow solid; mp 160-161 °C; yield 81% (45 mg); ¹H NMR (600 MHz, CDCl₃) δ 8.75 (d, *J* = 4.2 Hz, 1H), 7.78 (t, *J* = 7.8 Hz, 1H), 7.46 (d, *J* = 7.8 Hz, 1H), 7.36-7.32 (m, 2H), 7.28-7.27 (m, 1H), 7.06 (d, *J* = 6.6 Hz, 1H), 4.67 (t, *J* = 8.4 Hz, 2H), 4.36 (t, *J* = 8.4 Hz, 2H), 2.92 (s, 3H); ¹³C NMR (150 MHz, CDCl₃) δ 161.1, 153.7, 149.9, 149.7, 141.9, 140.3, 136.6, 131.9, 127.5, 126.6, 122.0, 121.7, 120.8, 94.7, 68.1, 43.9, 23.9; FT-IR (KBr) 2919, 2851, 1731, 1667, 1601, 1586, 1483, 1376, 1405, 1109, 1059, 802 cm⁻¹; HRMS (ESI) *m/z* [M+H]⁺ calcd for C₁₇H₁₅N₂O₂: 279.1128, found 279.1132.



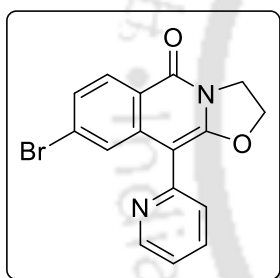
7-Methyl-10-(pyridin-2-yl)-2,3-dihydro-5H-oxazolo[3,2-*b*]isoquinolin-5-one 3d. Analytical TLC on silica gel, 1:5 acetone/CH₂Cl₂ R_f = 0.54; colorless solid; mp 156-157 °C; yield 79% (43.9 mg); ¹H NMR (600 MHz, CDCl₃) δ 8.76-8.74 (m, 1H), 8.17 (s, 1H), 7.78 (t, J = 7.8 Hz, 1H), 7.56 (d, J = 7.8 Hz, 1H), 7.50 (d, J = 7.8 Hz, 1H), 7.37 (d, J = 8.4 Hz, 1H), 7.27-7.25 (m, 1H), 4.69 (t, J = 7.8 Hz, 2H), 4.41 (t, J = 7.8 Hz, 2H), 2.43 (s, 3H); ¹³C NMR (150 MHz, CDCl₃) δ 160.2, 153.3, 149.7, 149.4, 136.5, 135.9, 134.4, 134.1, 127.1, 126.3, 123.5, 122.2, 121.9, 94.7, 68.1, 43.8, 21.1; FT-IR (KBr) 2921, 1662, 1629, 1586, 1499, 1468, 1434, 1348, 1104, 1017, 824, 609 cm⁻¹; HRMS (ESI) m/z [M+H]⁺ calcd for C₁₇H₁₅N₂O₂: 279.1128, found 279.1130.



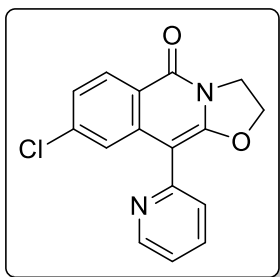
10-(Pyridin-2-yl)-7-(trifluoromethyl)-2,3-dihydro-5H-oxazolo[3,2-*b*]isoquinolin-5-one 3e. Analytical TLC on silica gel, 1:6 acetone/CH₂Cl₂ R_f = 0.56; colorless solid; mp 176-177 °C; yield 61% (40 mg); ¹H NMR (600 MHz, CDCl₃) δ 8.77 (d, J = 4.8 Hz, 1H), 8.64 (s, 1H), 7.83-7.78 (m, 2H), 7.71-7.69 (m, 1H), 7.51 (d, J = 7.8 Hz, 1H), 7.31-7.29 (m, 1H), 4.76 (t, J = 8.4 Hz, 2H), 4.45 (t, J = 8.4 Hz, 2H); ¹³C NMR (150 MHz, CDCl₃) δ 159.6, 152.4, 151.8, 149.9, 141.0, 136.8, 128.9 (J_{C-F} = 3.4 Hz), 126.4 (J_{C-F} = 277.2 Hz), 126.1, 125.4 (J_{C-F} = 4.3 Hz), 122.3, 121.9, 94.7, 68.6, 43.8; ¹⁹F NMR (565 MHz, CDCl₃) δ -62.22; FT-IR (KBr) 2922, 1670, 1626, 1586, 1507, 1469, 1435, 1325, 1166, 1121, 1017, 952 cm⁻¹; HRMS (ESI) m/z [M+H]⁺ calcd for C₁₇H₁₂F₃N₂O₂: 333.0845, found 333.0848.



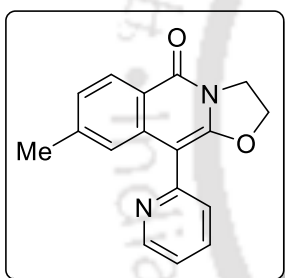
8-Methoxy-10-(pyridin-2-yl)-2,3-dihydro-5H-oxazolo[3,2-b]isoquinolin-5-one 3f. Analytical TLC on silica gel, 1:5 acetone/CH₂Cl₂ R_f = 0.42; colorless solid; mp 196-197 °C; yield 80% (47 mg); ¹H NMR (600 MHz, CDCl₃) δ 8.76 (d, *J* = 4.2 Hz, 1H), 8.29 (d, *J* = 8.4 Hz, 1H), 7.80-7.77 (m, 1H), 7.51 (d, *J* = 7.8 Hz, 1H), 7.28-7.26 (m, 1H), 7.08-7.07 (m, 1H), 6.91 (dd, *J* = 9.0, 2.4 Hz, 1H), 4.69 (t, *J* = 8.4 Hz, 2H), 4.39 (t, *J* = 8.4 Hz, 2H), 3.77 (s, 3H); ¹³C NMR (150 MHz, CDCl₃) δ 163.4, 159.8, 153.3, 150.7, 149.7, 140.5, 136.6, 129.7, 126.4, 122.0, 116.2, 113.2, 105.6, 94.5, 68.3, 55.4, 43.7; FT-IR (KBr) 2923, 1661, 1606, 1489, 1469, 1434, 1339, 1235, 1111, 1021, 774, 683 cm⁻¹; HRMS (ESI) *m/z* [M+H]⁺ calcd for C₁₇H₁₅N₂O₃: 295.1077, found 295.1072.



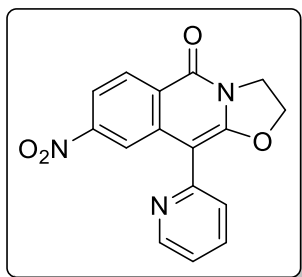
8-Bromo-10-(pyridin-2-yl)-2,3-dihydro-5H-oxazolo[3,2-b]isoquinolin-5-one 3g. Analytical TLC on silica gel, 1:5 acetone/CH₂Cl₂ R_f = 0.55; light yellow solid; mp 190-191 °C; yield 72% (49.2 mg); ¹H NMR (600 MHz, CDCl₃) δ 8.77 (d, *J* = 4.8 Hz, 1H), 8.21 (d, *J* = 8.4 Hz, 1H), 7.81-7.79 (m, 2H), 7.49 (d, *J* = 7.8 Hz, 1H), 7.42 (d, *J* = 8.4 Hz, 1H), 7.30-7.28 (m, 1H), 4.72 (t, *J* = 8.4 Hz, 2H), 4.40 (t, *J* = 8.4 Hz, 2H); ¹³C NMR (150 MHz, CDCl₃) δ 159.7, 152.4, 151.0, 149.9, 139.8, 136.8, 129.3, 128.6, 127.6, 126.3, 126.2, 122.3, 120.9, 94.1, 68.4, 43.8; FT-IR (KBr) 2922, 1660, 1627, 1588, 1536, 1478, 1433, 1334, 1296, 1207, 1099, 865 cm⁻¹; HRMS (ESI) *m/z* [M+H]⁺ calcd for C₁₆H₁₂BrN₂O₂: 343.0077, found 343.0072.



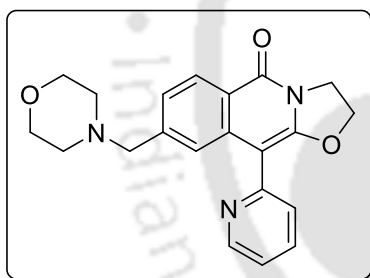
8-Chloro-10-(pyridin-2-yl)-2,3-dihydro-5H-oxazolo[3,2-*b*]isoquinolin-5-one 3h. Analytical TLC on silica gel, 1:5 acetone/CH₂Cl₂ $R_f = 0.53$; colorless solid; mp 195-196 °C; yield 70% (41.7 mg); ¹H NMR (600 MHz, CDCl₃) δ 8.77 (d, $J = 4.2$ Hz, 1H), 8.29 (d, $J = 8.4$ Hz, 1H), 7.82-7.79 (m, 1H), 7.65 (s, 1H), 7.50 (d, $J = 7.8$ Hz, 1H), 7.30-7.27 (m, 2H), 4.72 (t, $J = 8.4$ Hz, 2H), 4.41 (t, $J = 7.8$ Hz, 2H); ¹³C NMR (150 MHz, CDCl₃) δ 159.6, 152.5, 151.1, 149.9, 139.75, 139.73, 136.8, 129.3, 126.3, 124.9, 123.2, 122.2, 120.6, 94.2, 68.4, 43.8; FT-IR (KBr) 2921, 1664, 1627, 1597, 1482, 1434, 1208, 1100, 948, 869 cm⁻¹; HRMS (ESI) m/z [M+H]⁺ calcd for C₁₆H₁₂ClN₂O₂: 299.0582, found 299.0586.



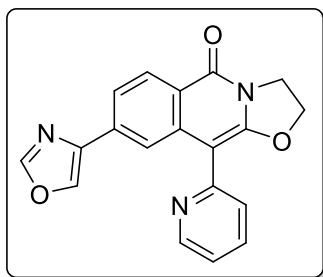
8-Methyl-10-(pyridin-2-yl)-2,3-dihydro-5H-oxazolo[3,2-*b*]isoquinolin-5-one 3i. Analytical TLC on silica gel, 1:5 acetone/CH₂Cl₂ $R_f = 0.56$; yellow solid; mp 150-151 °C; yield 77% (42.8 mg); ¹H NMR (600 MHz, CDCl₃) δ 8.76 (d, $J = 4.2$ Hz, 1H), 8.25 (d, $J = 7.8$ Hz, 1H), 7.79 (t, $J = 7.8$ Hz, 1H), 7.49 (d, $J = 7.8$ Hz, 1H), 7.37 (s, 1H), 7.29-7.27 (m, 1H), 7.14 (d, $J = 8.4$ Hz, 1H), 4.68 (t, $J = 8.4$ Hz, 2H), 4.39 (t, $J = 8.4$ Hz, 2H), 2.35 (s, 3H); ¹³C NMR (150 MHz, CDCl₃) δ 160.2, 153.2, 150.1, 149.7, 143.6, 138.4, 136.6, 127.6, 126.5, 126.0, 123.2, 122.0, 120.0, 94.6, 68.2, 43.7, 22.2; FT-IR (KBr) 2920, 2848, 1662, 1626, 1586, 1486, 1276, 1102, 750 cm⁻¹; HRMS (ESI) m/z [M+H]⁺ calcd for C₁₇H₁₅N₂O₂: 279.1128, found 279.1132.



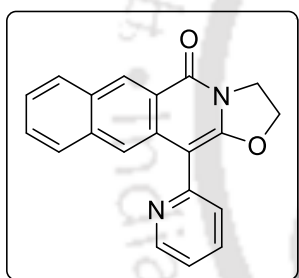
8-Nitro-10-(pyridin-2-yl)-2,3-dihydro-5H-oxazolo[3,2-*b*]isoquinolin-5-one 3j. Analytical TLC on silica gel, 1:5 acetone/CH₂Cl₂ R_f = 0.44; orange solid; mp 245-246 °C; yield 55% (34 mg); ¹H NMR (600 MHz, CDCl₃) δ 8.79 (d, J = 4.2 Hz, 1H), 8.66 (s, 1H), 8.51 (d, J = 9.0 Hz, 1H), 8.06 (d, J = 9.0 Hz, 1H), 7.84 (t, J = 7.8 Hz, 1H), 7.55 (d, J = 7.8 Hz, 1H), 7.34-7.32 (m, 1H), 4.79 (t, J = 8.4 Hz, 2H), 4.46 (t, J = 7.8 Hz, 2H); ¹³C NMR (150 MHz, CDCl₃) δ 159.0, 151.9, 151.8, 150.9, 150.0, 139.2, 137.0, 129.5, 126.2, 125.8, 122.5, 119.8, 117.9, 95.0, 68.7, 44.0; FT-IR (KBr) 2922, 2854, 1665, 1619, 1585, 1523, 1483, 1346, 1083, 1021, 835, 786 cm⁻¹; HRMS (ESI) m/z [M+H]⁺ calcd for C₁₆H₁₂N₃O₄: 310.0822, found 310.0823.



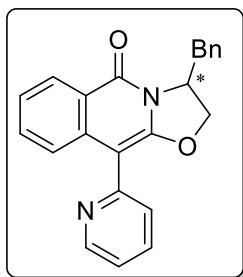
8-(Morpholinomethyl)-10-(pyridin-2-yl)-2,3-dihydro-5H-oxazolo[3,2-*b*]isoquinolin-5-one 3k. Analytical TLC on silica gel, 1:2 acetone/CH₂Cl₂ R_f = 0.35; brown solid; mp 146-147 °C; yield 75% (54.4 mg); ¹H NMR (600 MHz, CDCl₃) δ 8.76 (d, J = 4.8 Hz, 1H), 8.31 (d, J = 7.8 Hz, 1H), 7.79 (t, J = 7.8 Hz, 1H), 7.55 (s, 1H), 7.49 (d, J = 7.8 Hz, 1H), 7.35 (d, J = 8.4 Hz, 1H), 7.29-7.27 (m, 1H), 4.69 (t, J = 8.4 Hz, 2H), 4.40 (t, J = 7.8 Hz, 2H), 3.67-3.66 (m, 4H), 3.51 (s, 2H), 2.42-2.41 (m, 4H); ¹³C NMR (150 MHz, CDCl₃) δ 160.0, 153.1, 150.3, 149.7, 143.2, 138.3, 136.6, 127.7, 126.4, 125.2, 123.5, 122.0, 121.4, 94.7, 68.2, 67.0, 63.3, 53.7, 43.7; FT-IR (KBr) 2921, 2853, 1662, 1628, 1586, 1549, 1348, 1172, 1115, 914, 864, 782 cm⁻¹; HRMS (ESI) m/z [M+H]⁺ calcd for C₂₁H₂₂N₃O₃: 364.1656, found 364.1654.



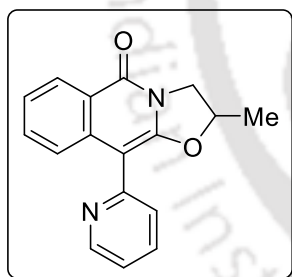
8-(Oxazol-4-yl)-10-(pyridin-2-yl)-2,3-dihydro-5H-oxazolo[3,2-*b*]isoquinolin-5-one 3l. Analytical TLC on silica gel, 1:4 acetone/CH₂Cl₂ *R_f* = 0.38; brown solid; mp 178-179 °C; yield 73% (48.3 mg); ¹H NMR (600 MHz, CDCl₃) δ 8.80 (d, *J* = 4.2 Hz, 1H), 8.41 (d, *J* = 8.4 Hz, 1H), 7.97 (s, 1H), 7.90 (s, 1H), 7.83 (t, *J* = 7.8 Hz, 1H), 7.58 (d, *J* = 8.4 Hz, 1H), 7.55 (d, *J* = 7.8 Hz, 1H), 7.40 (s, 1H), 7.33-7.31 (m, 1H), 4.73 (t, *J* = 7.8 Hz, 2H), 4.43 (t, *J* = 7.8 Hz, 2H); ¹³C NMR (150 MHz, CDCl₃) δ 159.7, 152.8, 151.2, 151.1, 150.8, 149.9, 138.9, 136.7, 131.6, 128.6, 126.4, 123.5, 122.2, 121.9, 120.2, 119.1, 94.7, 68.3, 43.8; FT-IR (KBr) 2920, 2852, 1661, 1626, 1585, 1549, 1489, 1341, 1199, 1104, 1020, 867 cm⁻¹; HRMS (ESI) *m/z* [M+H]⁺ calcd for C₁₉H₁₄N₃O₃: 332.1030, found 332.1022.



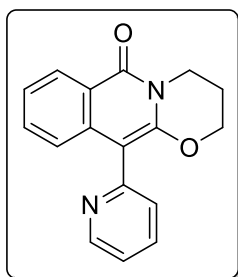
12-(Pyridin-2-yl)-2,3-dihydro-5H-benzo[*g*]oxazolo[3,2-*b*]isoquinolin-5-one 3m. Analytical TLC on silica gel, 1:5 acetone/CH₂Cl₂ *R_f* = 0.51; yellow solid; mp 210-211 °C; yield 68% (42.7 mg); ¹H NMR (400 MHz, CDCl₃) δ 8.98 (s, 1H), 8.82 (d, *J* = 4.8 Hz, 1H), 8.02 (s, 1H), 8.00 (d, *J* = 8.4 Hz, 1H), 7.85-7.81 (m, 1H), 7.75 (d, *J* = 8.0 Hz, 1H), 7.58 (d, *J* = 8.0 Hz, 1H), 7.50-7.46 (m, 1H), 7.43-7.39 (m, 1H), 7.33-7.30 (m, 1H), 4.69 (t, *J* = 8.0 Hz, 2H), 4.41 (t, *J* = 8.0 Hz, 2H); ¹³C NMR (150 MHz, CDCl₃) δ 160.9, 153.5, 149.8, 149.3, 136.7, 136.0, 133.8, 130.2, 129.4, 129.1, 128.2, 127.7, 126.6, 125.3, 122.1, 121.9, 121.4, 93.9, 68.2, 43.6; FT-IR (KBr) 2923, 1663, 1586, 1497, 1469, 1432, 1358, 1183, 1017, 896, 780 cm⁻¹; HRMS (ESI) *m/z* [M+H]⁺ calcd for C₂₀H₁₅N₂O₂: 315.1128, found 315.1127.



3-Benzyl-10-(pyridin-2-yl)-2,3-dihydro-5H-oxazolo[3,2-*b*]isoquinolin-5-one (+)-3n. Analytical TLC on silica gel, 1:6 acetone/CH₂Cl₂ R_f = 0.52; brown solid; mp 140-141 °C; yield 77% (54 mg); ¹H NMR (600 MHz, CDCl₃) δ 8.73 (d, *J* = 4.8 Hz, 1H), 8.41 (d, *J* = 7.8 Hz, 1H), 7.73 (t, *J* = 7.8 Hz, 1H), 7.65 (d, *J* = 7.8 Hz, 1H), 7.53 (t, *J* = 7.8 Hz, 1H), 7.35-7.28 (m, 4H), 7.24-7.22 (m, 4H), 5.12-5.09 (m, 1H), 4.48-4.46 (m, 1H), 4.41 (t, *J* = 8.4 Hz, 1H), 3.61-3.59 (m, 1H), 2.97-2.94 (m, 1H); ¹³C NMR (150 MHz, CDCl₃) δ 160.1, 153.2, 150.1, 149.7, 138.3, 136.5, 136.0, 132.9, 129.6, 129.0, 127.7, 127.3, 126.5, 124.3, 123.7, 122.6, 121.9, 94.7, 71.8, 57.3, 37.0; FT-IR (KBr) 2919, 2851, 1665, 1629, 1585, 1549, 1485, 1434, 1334, 1086, 994, 749 cm⁻¹; HRMS (ESI) *m/z* [M+H]⁺ calcd for C₂₃H₁₉N₂O₂: 355.1441, found 355.1443; [α]_D^{23.4} = + 44.62 (c = 0.13, CHCl₃); HPLC: >99% ee [CHIRALCEL AD-H, hexane/ⁱPrOH = 70:30, flow rate: 1 mL/min, λ = 254 nm, t_R = 17.38 min (minor), 38.53 min (major)].

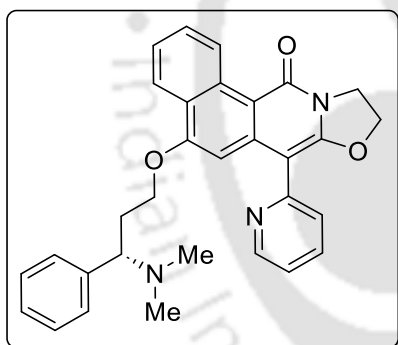


2-Methyl-10-(pyridin-2-yl)-2,3-dihydro-5H-oxazolo[3,2-*b*]isoquinolin-5-one (±)-3o. Analytical TLC on silica gel, 1:6 acetone/CH₂Cl₂ R_f = 0.55; colorless solid; mp 149-150 °C; yield 59% (32 mg); ¹H NMR (600 MHz, CDCl₃) δ 8.79 (d, *J* = 4.2 Hz, 1H), 8.40 (d, *J* = 8.4 Hz, 1H), 7.81 (t, *J* = 7.8 Hz, 1H), 7.70 (d, *J* = 8.4 Hz, 1H), 7.57-7.52 (m, 2H), 7.34 (t, *J* = 7.8 Hz, 1H), 7.30-7.29 (m, 1H), 5.11-5.05 (m, 1H), 4.57-4.54 (m, 1H), 3.98-3.95 (m, 1H), 1.60 (d, *J* = 6.0 Hz, 3H); ¹³C NMR (150 MHz, CDCl₃) δ 160.3, 153.3, 150.0, 149.7, 138.4, 136.6, 132.9, 127.6, 126.5, 124.2, 123.6, 122.2, 121.9, 94.5, 77.4, 50.0, 20.1; FT-IR (KBr) 2921, 2853, 1666, 1630, 1586, 1486, 1377, 1049, 823, 787, 695 cm⁻¹; HRMS (ESI) *m/z* [M+H]⁺ calcd for C₁₇H₁₅N₂O₂: 279.1128, found 279.1135; HPLC: [CHIRALCEL AD-H, hexane/ⁱPrOH = 70:30, flow rate: 1 mL/min, λ = 254 nm, t_R = 18.94 min, 30.02 min].



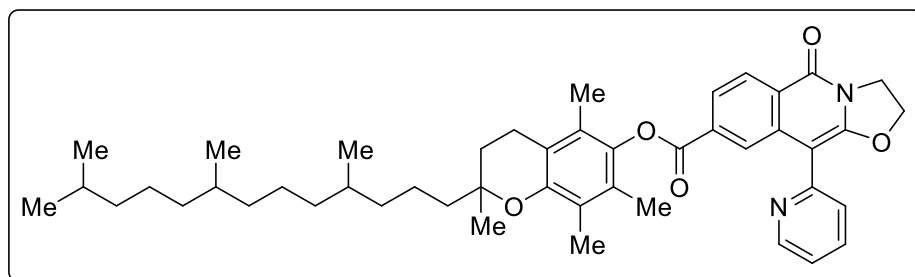
11-(Pyridin-2-yl)-3,4-dihydro-2H,6H-[1,3]oxazino[3,2-b]isoquinolin-

6-one 3p. Analytical TLC on silica gel, 1:6 acetone/CH₂Cl₂ R_f = 0.53; light yellow solid; mp 190-191 °C; yield 54% (30 mg); ¹H NMR (600 MHz, CDCl₃) δ 8.77 (d, *J* = 4.8 Hz, 1H), 8.37 (d, *J* = 7.8 Hz, 1H), 7.79 (t, *J* = 7.8 Hz, 1H), 7.47 (t, *J* = 7.8 Hz, 1H), 7.41 (d, *J* = 7.8 Hz, 1H), 7.30-7.27 (m, 2H), 7.20 (d, *J* = 7.8 Hz, 1H), 4.24-4.19 (m, 4H), 2.28-2.24 (m, 2H); ¹³C NMR (150 MHz, CDCl₃) δ 162.2, 154.3, 149.8, 147.4, 137.6, 136.5, 132.7, 127.9, 127.3, 124.2, 123.2, 122.0, 121.0, 97.3, 65.5, 39.8, 22.1; FT-IR (KBr) 2922, 1654, 1610, 1586, 1549, 1492, 1337, 1143, 700 cm⁻¹; HRMS (ESI) *m/z* [M+H]⁺ calcd for C₁₇H₁₅N₂O₂: 279.1128, found 279.1125.

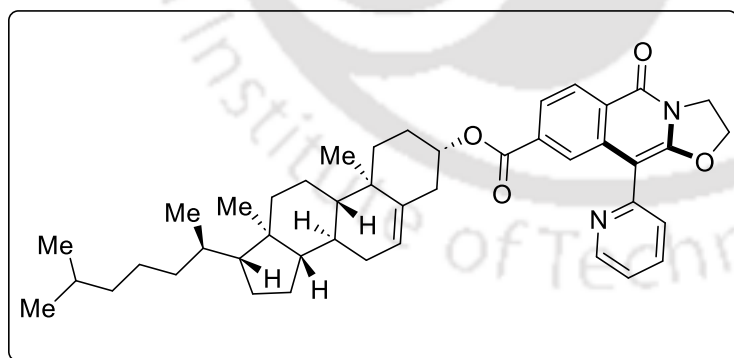


(S)-5-(3-(Dimethylamino)-3-phenylpropoxy)-7-(pyridin-

2-yl)-9,10-dihydro-12H-benzo[h]oxazolo[3,2-b]isoquinolin-12-one 3q. Analytical TLC on silica gel, 1:1 acetone/CH₂Cl₂ R_f = 0.35; brown solid; mp 126-127 °C; yield 73% (71.6 mg); ¹H NMR (600 MHz, CDCl₃) δ 10.08 (d, *J* = 9.0 Hz, 1H), 8.72 (d, *J* = 4.8 Hz, 1H), 8.24 (d, *J* = 7.8 Hz, 1H), 7.77 (t, *J* = 7.8 Hz, 1H), 7.70 (t, *J* = 8.4 Hz, 1H), 7.52 (t, *J* = 7.8 Hz, 1H), 7.46 (d, *J* = 7.8 Hz, 1H), 7.30-7.25 (m, 4H), 7.21 (d, *J* = 7.2 Hz, 2H), 6.77 (s, 1H), 4.71 (t, *J* = 7.8 Hz, 2H), 4.49 (t, *J* = 8.4 Hz, 2H), 3.94-3.90 (m, 1H), 3.74-3.70 (m, 1H), 3.50-3.48 (m, 1H), 2.58-2.52 (m, 1H), 2.20 (s, 6H), 2.18-2.16 (m, 1H); ¹³C NMR (150 MHz, CDCl₃) δ 159.8, 157.9, 153.5, 151.2, 149.8, 142.4, 139.6, 136.6, 133.6, 128.8, 128.5, 128.3, 127.4, 126.7, 126.2, 125.0, 124.3, 122.0, 121.8, 109.0, 99.7, 95.7, 68.3, 67.8, 65.6, 44.4, 43.0, 32.8; FT-IR (KBr) 2923, 1756, 1661, 1589, 1544, 1468, 1439, 1241, 1154, 1089, 914, 772 cm⁻¹; HRMS (ESI) *m/z* [M+H]⁺ calcd for C₃₁H₃₀N₃O₃: 492.2282, found 492.2286.

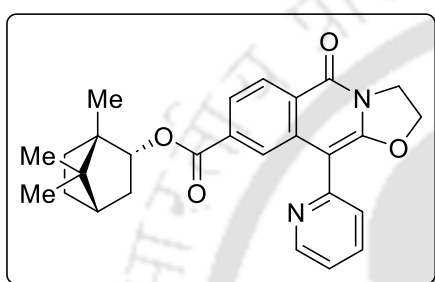
**2,5,7,8-Tetra-**

methyl-2-(4,8,12-trimethyltridecyl)chroman-6-yl 5-oxo-10-(pyridin-2-yl)-2,3-dihydro-5H-oxazolo[3,2-b]isoquinoline-8-carboxylate 3r. Analytical TLC on silica gel, 1:6 acetone/CH₂Cl₂ R_f = 0.54; yellow solid; mp 153-154 °C; yield 77% (111 mg); ¹H NMR (600 MHz, CDCl₃) δ 8.75 (d, J = 4.2 Hz, 1H), 8.59 (s, 1H), 8.50 (d, J = 8.4 Hz, 1H), 8.12 (d, J = 8.4 Hz, 1H), 7.79 (t, J = 7.8 Hz, 1H), 7.54 (d, J = 7.8 Hz, 1H), 7.28-7.27 (m, 1H), 4.75 (t, J = 8.4 Hz, 2H), 4.46 (t, J = 8.4 Hz, 2H), 2.59 (t, J = 6.6 Hz, 2H), 2.10 (s, 3H), 2.02 (s, 3H), 1.98 (s, 3H), 1.84-1.73 (m, 2H), 1.55-1.49 (m, 2H), 1.46-1.36 (m, 3H), 1.31-1.21 (m, 12H), 1.15-1.03 (m, 7H), 0.86-0.83 (m, 12H); ¹³C NMR (150 MHz, CDCl₃) δ 164.9, 159.7, 152.5, 150.8, 149.9, 149.6, 140.7, 138.4, 136.7, 133.4, 128.2, 126.9, 126.5, 126.3, 125.3, 125.2, 124.7, 123.3, 122.3, 117.6, 95.1, 75.2, 68.4, 43.9, 39.5, 37.69, 37.67, 37.58, 37.52, 37.4, 32.9, 32.8, 28.1, 24.95, 24.93, 24.5, 22.8, 22.7, 21.1, 20.7, 19.89, 19.82, 19.7, 13.2, 12.3, 11.9; FT-IR (KBr) 2923, 1734, 1665, 1585, 1549, 1465, 1376, 1230, 1199, 1093, 958, 751 cm⁻¹; HRMS (ESI) m/z [M+H]⁺ calcd for C₄₆H₆₁N₂O₅: 721.4575, found 721.4568.

**(3S,8S,9S,10R,13R,14S,17R)-**

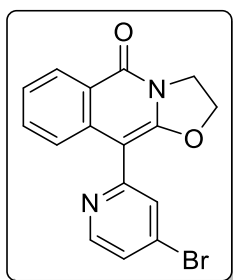
10,13-Dimethyl-17-((R)-6-methylheptan-2-yl)-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1H-cyclopenta[a]phenanthren-3-yl 5-oxo-10-(pyridin-2-yl)-2,3-dihydro-5H-oxazolo[3,2-b]isoquinoline-8-carboxylate 3s. Analytical TLC on silica gel, 1:6 acetone/CH₂Cl₂ R_f = 0.51; light yellow solid; mp 230-231 °C; yield 75% (101 mg); ¹H NMR (600 MHz, CDCl₃) δ 8.77 (d, J = 4.2 Hz, 1H), 8.41 (d, J = 8.4 Hz, 1H), 8.38 (s, 1H), 7.90-7.89 (m, 1H), 7.82-7.79 (m, 1H), 7.52 (d, J = 7.8 Hz, 1H), 7.30-7.28 (m, 1H), 5.40-5.39 (m, 1H),

4.83-4.77 (m, 1H), 4.73 (t, $J = 8.4$ Hz, 2H), 4.43 (t, $J = 8.4$ Hz, 2H), 2.43-2.41 (m, 2H), 2.02-1.95 (m, 3H), 1.91-1.87 (m, 1H), 1.85-1.79 (m, 1H), 1.72-1.66 (m, 2H), 1.60-1.54 (m, 2H), 1.53-1.48 (m, 2H), 1.47-1.42 (m, 2H), 1.37-1.30 (m, 2H), 1.28-1.24 (m, 2H), 1.20-1.07 (m, 6H), 1.04 (s, 3H), 1.02-0.95 (m, 3H), 0.91-0.90 (m, 3H), 0.86-0.85 (m, 6H), 0.67 (s, 3H); ^{13}C NMR (150 MHz, CDCl_3) δ 165.7, 159.7, 152.6, 150.6, 149.9, 139.7, 138.2, 136.7, 134.6, 127.9, 126.3, 125.8, 124.8, 124.2, 122.9, 122.2, 95.1, 75.3, 68.3, 56.8, 56.2, 50.1, 43.9, 42.4, 39.8, 39.6, 38.2, 37.1, 36.7, 36.3, 35.9, 32.06, 32.00, 28.3, 28.1, 27.8, 24.4, 23.9, 22.9, 22.7, 21.1, 19.5, 18.8, 12.0; FT-IR (KBr) 2926, 1716, 1664, 1630, 1585, 1550, 1468, 1252, 1204, 1107, 962, 756 cm^{-1} ; HRMS (ESI) m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{44}\text{H}_{57}\text{N}_2\text{O}_4$: 677.4313, found 677.4306.



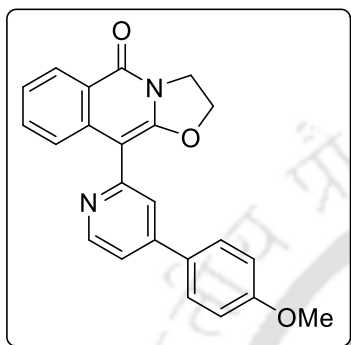
(1*S*,2*R*,4*S*)-1,7,7-Trimethylbicyclo[2.2.1]heptan-2-yl 5-oxo-10-(pyridin-2-yl)-2,3-dihydro-5*H*-oxazolo[3,2-*b*]isoquinoline-8-carboxylate **3t**.

Analytical TLC on silica gel, 1:6 acetone/ CH_2Cl_2 $R_f = 0.45$; light yellow solid; mp 192-193 $^\circ\text{C}$; yield 79% (70 mg); ^1H NMR (600 MHz, CDCl_3) δ 8.76-8.75 (m, 1H), 8.464-8.462 (m, 1H), 8.42 (d, $J = 7.8$ Hz, 1H), 7.92-7.90 (m, 1H), 7.80-7.78 (m, 1H), 7.53 (d, $J = 7.8$ Hz, 1H), 7.28-7.26 (m, 1H), 5.07-5.04 (m, 1H), 4.74 (t, $J = 8.4$ Hz, 2H), 4.44 (t, $J = 8.4$ Hz, 2H), 2.45-2.40 (m, 1H), 2.03-1.98 (m, 1H), 1.80-1.74 (m, 1H), 1.72-1.70 (m, 1H), 1.37-1.32 (m, 1H), 1.26-1.22 (m, 1H), 1.09-1.06 (m, 1H), 0.93 (s, 3H), 0.89 (s, 3H), 0.86 (s, 3H); ^{13}C NMR (150 MHz, CDCl_3) δ 166.5, 159.7, 152.6, 150.6, 149.8, 138.2, 136.6, 134.5, 127.9, 126.3, 125.9, 124.8, 124.1, 122.1, 95.0, 81.0, 68.4, 49.2, 47.9, 45.0, 43.8, 36.9, 28.1, 27.3, 19.8, 19.0, 13.6; FT-IR (KBr) 2923, 1715, 1664, 1630, 1585, 1551, 1485, 1255, 1203, 1108, 1016, 755 cm^{-1} ; HRMS (ESI) m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{27}\text{H}_{29}\text{N}_2\text{O}_4$: 445.2122, found 445.2126.

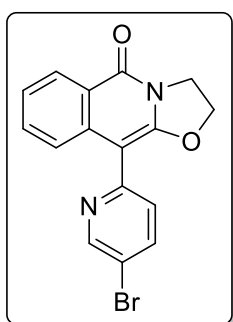


10-(4-Bromopyridin-2-yl)-2,3-dihydro-5*H*-oxazolo[3,2-*b*]isoquinolin-5-one **3u**. Analytical TLC on silica gel, 1:5 acetone/ CH_2Cl_2 $R_f = 0.48$; colorless solid; mp 164-

165 °C; yield 70% (47.8 mg); ^1H NMR (600 MHz, CDCl_3) δ 8.56 (d, $J = 4.8$ Hz, 1H), 8.36 (d, $J = 8.4$ Hz, 1H), 7.70-7.67 (m, 2H), 7.56-7.54 (m, 1H), 7.44-7.43 (m, 1H), 7.34-7.32 (m, 1H), 4.72 (t, $J = 7.8$ Hz, 2H), 4.41 (t, $J = 8.4$ Hz, 2H); ^{13}C NMR (150 MHz, CDCl_3) δ 160.2, 154.6, 150.5, 150.2, 137.8, 133.14, 133.12, 129.5, 127.7, 125.2, 124.5, 123.4, 122.2, 93.6, 68.4, 43.8; FT-IR (KBr) 2921, 1664, 1564, 1486, 1421, 1339, 1124, 1087, 1017, 984, 767 cm^{-1} ; HRMS (ESI) m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{16}\text{H}_{12}\text{BrN}_2\text{O}_2$: 343.0077, found 343.0074.

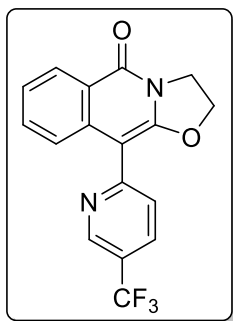


10-(4-(4-Methoxyphenyl)pyridin-2-yl)-2,3-dihydro-5H-oxazolo[3,2-*b*]isoquinolin-5-one 3v. Analytical TLC on silica gel, 1:5 acetone/ CH_2Cl_2 $R_f = 0.40$; brown solid; mp 222-223 °C; yield 75% (55.5 mg); ^1H NMR (600 MHz, CDCl_3) 8.75 (d, $J = 4.8$ Hz, 1H), 8.38 (d, $J = 7.8$ Hz, 1H), 7.68-7.67 (m, 2H), 7.64 (d, $J = 8.4$ Hz, 2H), 7.55-7.52 (m, 1H), 7.46-7.45 (m, 1H), 7.34-7.31 (m, 1H), 7.02 (d, $J = 9.0$ Hz, 2H), 4.70 (t, $J = 8.4$ Hz, 2H), 4.42 (t, $J = 7.8$ Hz, 2H), 3.86 (s, 3H); ^{13}C NMR (150 MHz, CDCl_3) δ 160.7, 160.2, 153.5, 150.2, 150.1, 148.6, 138.4, 132.9, 130.4, 128.3, 127.7, 124.3, 123.8, 123.6, 122.3, 119.5, 114.6, 94.9, 68.2, 55.5, 43.8; FT-IR (KBr) 2922, 1666, 1596, 1546, 1515, 1487, 1250, 1182, 1022, 826 cm^{-1} ; HRMS (ESI) m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{23}\text{H}_{19}\text{N}_2\text{O}_3$: 371.1390, found 371.1395.

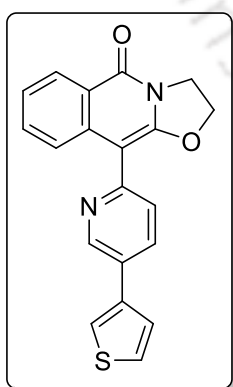


10-(5-Bromopyridin-2-yl)-2,3-dihydro-5H-oxazolo[3,2-*b*]isoquinolin-5-one 3w. Analytical TLC on silica gel, 1:5 acetone/ CH_2Cl_2 $R_f = 0.47$; light brown solid; mp 154-155 °C; yield 73% (50 mg); ^1H NMR (600 MHz, CDCl_3) δ 8.80-8.79 (m, 1H), 8.37-8.35 (m, 1H), 7.90 (dd, $J = 8.4, 2.4$ Hz, 1H), 7.67 (d, $J = 7.8$ Hz, 1H), 7.56-7.53 (m, 1H), 7.42 (d, $J = 8.4$ Hz, 1H), 7.34-7.32 (m, 1H), 4.71 (t, $J = 8.4$ Hz, 2H), 4.41 (t, $J = 8.4$ Hz, 2H); ^{13}C NMR

(150 MHz, CDCl₃) δ 160.1, 151.6, 150.7, 150.2, 139.2, 137.8, 133.0, 127.7, 127.6, 124.5, 123.4, 122.3, 118.9, 93.6, 68.3, 43.8; FT-IR (KBr) 2922, 1663, 1568, 1547, 1485, 1462, 1367, 1341, 1090, 1013, 864, 769 cm⁻¹; HRMS (ESI) m/z [M+H]⁺ calcd for C₁₆H₁₂BrN₂O₂: 343.0077, found 343.0083.

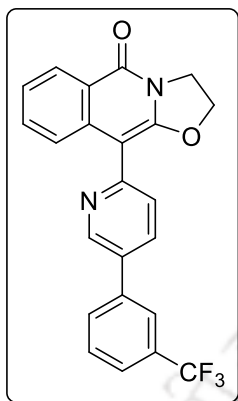


10-(5-(Trifluoromethyl)pyridin-2-yl)-2,3-dihydro-5H-oxazolo[3,2-b]isoquinolin-5-one 3x. Analytical TLC on silica gel, 1:6 acetone/CH₂Cl₂ R_f = 0.54; light yellow solid; mp 183-184 °C; yield 66% (43.8 mg); ¹H NMR (600 MHz, CDCl₃) δ 8.99-8.98 (m, 1H), 8.37 (d, J = 7.2 Hz, 1H), 8.00-7.98 (m, 1H), 7.75 (d, J = 7.8 Hz, 1H), 7.66 (d, J = 7.8 Hz, 1H), 7.57-7.54 (m, 1H), 7.35-7.32 (m, 1H), 4.71 (t, J = 8.4 Hz, 2H), 4.41 (t, J = 8.4 Hz, 2H); ¹³C NMR (150 MHz, CDCl₃) δ 160.1, 157.0, 150.8, 146.4 (J_{C-F} = 4.0 Hz), 137.5, 133.6 (J_{C-F} = 3.3 Hz), 133.1, 127.7 (J_{C-F} = 270.4 Hz), 124.6, 124.5 (J_{C-F} = 33.0 Hz), 123.4, 122.8, 122.3, 93.7, 68.4, 43.7; ¹⁹F NMR (565 MHz, CDCl₃) δ -62.26; FT-IR (KBr) 2923, 1662, 1603, 1488, 1329, 1125, 1081, 1017, 866, 762 cm⁻¹; HRMS (ESI) m/z [M+H]⁺ calcd for C₁₇H₁₂F₃N₂O₂: 333.0845, found 333.0847.

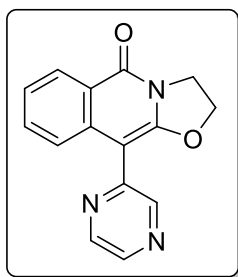


10-(5-(Thiophen-3-yl)pyridin-2-yl)-2,3-dihydro-5H-oxazolo[3,2-b]isoquinolin-5-one 3y. Analytical TLC on silica gel, 1:5 acetone/CH₂Cl₂ R_f = 0.41; yellow solid; mp 209-210 °C; yield 69% (47.7 mg); ¹H NMR (600 MHz, CDCl₃) δ 9.01 (s, 1H), 8.39 (d, J = 8.4 Hz, 1H), 7.98 (d, J = 7.8 Hz, 1H), 7.72 (d, J = 7.8 Hz, 1H), 7.58 (s, 1H), 7.57-7.54 (m, 2H), 7.47-7.45 (m, 2H), 7.34 (t, J = 7.8 Hz, 1H), 4.73 (t, J = 7.8 Hz, 2H), 4.43 (t, J = 7.8

Hz, 2H); ^{13}C NMR (150 MHz, CDCl_3) δ 160.2, 151.5, 150.2, 147.5, 138.7, 138.3, 134.1, 133.0, 129.8, 127.7, 127.2, 126.3, 126.0, 124.4, 123.6, 122.3, 121.6, 94.5, 68.3, 43.8; FT-IR (KBr) 2923, 2855, 1663, 1629, 1549, 1486, 1334, 1089, 1017, 864, 787, 760 cm^{-1} ; HRMS (ESI) m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{20}\text{H}_{15}\text{N}_2\text{O}_2\text{S}$: 347.0849, found 347.0850.

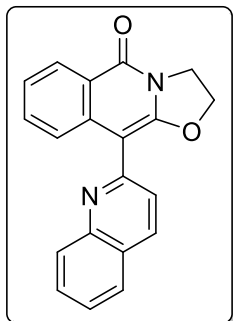


10-(5-(3-(Trifluoromethyl)phenyl)pyridin-2-yl)-2,3-dihydro-5H-oxazolo[3,2-*b*]isoquinolin-5-one 3z. Analytical TLC on silica gel, 1:5 acetone/ CH_2Cl_2 R_f = 0.48; light yellow solid; mp 217-218 $^\circ\text{C}$; yield 68% (55.4 mg); ^1H NMR (600 MHz, CDCl_3) δ 8.99 (s, 1H), 8.40 (d, J = 7.8 Hz, 1H), 8.01 (d, J = 8.4 Hz, 1H), 7.89 (s, 1H), 7.85 (d, J = 7.8 Hz, 1H), 7.76 (d, J = 8.4 Hz, 1H), 7.69-7.68 (m, 1H), 7.64 (t, J = 8.4 Hz, 2H), 7.57 (t, J = 7.8 Hz, 1H), 7.35 (t, J = 7.8 Hz, 1H), 4.74 (t, J = 8.4 Hz, 2H), 4.44 (t, J = 8.4 Hz, 2H); ^{13}C NMR (150 MHz, CDCl_3) δ 160.2, 152.9, 150.4, 148.1, 138.6, 138.1, 135.0, 133.4, 133.0, 131.9 ($J_{\text{C-F}}$ = 32.1 Hz), 130.4, 129.8, 127.8 ($J_{\text{C-F}}$ = 210.4 Hz), 125.0, 124.9 ($J_{\text{C-F}}$ = 3.9 Hz), 124.5, 124.1 ($J_{\text{C-F}}$ = 3.7 Hz), 123.6, 123.2, 122.4, 94.3, 68.3, 43.8; ^{19}F NMR (565 MHz, CDCl_3) δ -62.65; FT-IR (KBr) 2919, 2851, 1729, 1664, 1550, 1486, 1335, 1266, 1166, 1124, 1016, 763 cm^{-1} ; HRMS (ESI) m/z $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{23}\text{H}_{16}\text{F}_3\text{N}_2\text{O}_2$: 409.1158, found 409.1162.



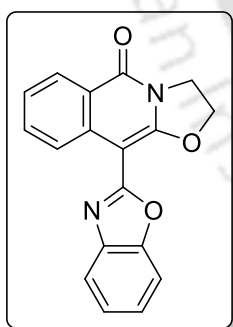
10-(Pyrazin-2-yl)-2,3-dihydro-5H-oxazolo[3,2-*b*]isoquinolin-5-one 3aa. Analytical TLC on silica gel, 1:5 acetone/ CH_2Cl_2 R_f = 0.42; light yellow solid; mp 247-248 $^\circ\text{C}$; yield 77% (40.8 mg); ^1H NMR (600 MHz, CDCl_3) δ 8.80 (s, 1H), 8.70 (s, 1H), 8.50 (s, 1H), 8.38 (d, J = 8.4 Hz, 1H), 7.75 (d, J = 8.4 Hz, 1H), 7.57 (t, J = 7.8 Hz, 1H), 7.35 (t, J = 7.8 Hz, 1H), 4.74 (t, J = 8.4 Hz, 2H), 4.43 (t, J = 7.8 Hz, 2H); ^{13}C NMR (150 MHz, CDCl_3) δ

160.2, 151.0, 149.6, 147.4, 144.1, 142.2, 137.5, 133.2, 127.9, 124.7, 123.1, 122.4, 91.3, 68.4, 43.8; FT-IR (KBr) 2922, 1668, 1626, 1548, 1486, 1423, 1341, 1121, 1092, 1015, 866, 761 cm^{-1} ; HRMS (ESI) m/z $[M+H]^+$ calcd for $\text{C}_{15}\text{H}_{12}\text{N}_3\text{O}_2$: 266.0924, found 266.0928.



10-(Quinolin-2-yl)-2,3-dihydro-5H-oxazolo[3,2-*b*]isoquinolin-5-one

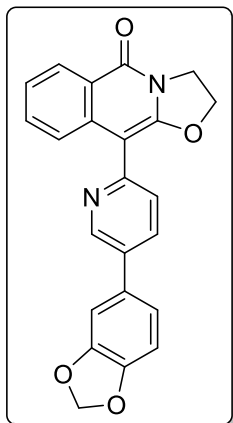
3ab. Analytical TLC on silica gel, 1:5 acetone/ CH_2Cl_2 R_f = 0.43; light brown solid; mp 225-226 $^\circ\text{C}$; yield 66% (41.4 mg); ^1H NMR (600 MHz, CDCl_3) δ 8.40 (d, J = 7.8 Hz, 1H), 8.25 (d, J = 8.4 Hz, 1H), 8.16 (d, J = 8.4 Hz, 1H), 7.88 (d, J = 7.8 Hz, 1H), 7.76-7.73 (m, 2H), 7.62 (d, J = 8.4 Hz, 1H), 7.58 (t, J = 7.8 Hz, 1H), 7.54 (t, J = 7.8 Hz, 1H), 7.34 (t, J = 7.8 Hz, 1H), 4.72 (t, J = 8.4 Hz, 2H), 4.44 (t, J = 8.4 Hz, 2H). ^{13}C NMR (150 MHz, CDCl_3) δ 160.3, 153.6, 150.6, 148.3, 138.3, 136.4, 133.0, 129.8, 129.5, 127.7, 127.6, 127.0, 126.7, 124.4, 124.3, 123.8, 122.4, 95.1, 68.3, 43.8; FT-IR (KBr) 2919, 2850, 1736, 1664, 1596, 1486, 1459, 1089, 1019 cm^{-1} ; HRMS (ESI) m/z $[M+H]^+$ calcd for $\text{C}_{20}\text{H}_{15}\text{N}_2\text{O}_2$: 315.1128, found 315.1133.



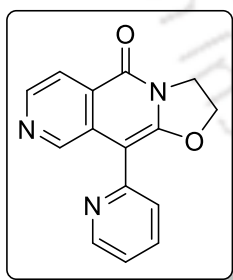
10-(Benzo[*d*]oxazol-2-yl)-2,3-dihydro-5H-oxazolo[3,2-*b*]isoquinolin-5-one

3ac. Analytical TLC on silica gel, 1:7 acetone/ CH_2Cl_2 R_f = 0.49; brown solid; mp 230-231 $^\circ\text{C}$; yield 70% (42.5 mg); ^1H NMR (400 MHz, CDCl_3) δ 8.74 (d, J = 8.4 Hz, 1H), 8.40 (d, J = 8.0 Hz, 1H), 7.82-7.80 (m, 1H), 7.74-7.70 (m, 1H), 7.61-7.59 (m, 1H), 7.41 (t, J = 7.6 Hz, 1H), 7.37-7.33 (m, 2H), 4.91 (t, J = 8.4 Hz, 2H), 4.46 (t, J = 8.4 Hz, 2H); ^{13}C NMR (150 MHz, CDCl_3) δ 160.0, 159.5, 154.3, 149.9, 141.7, 135.9, 133.7, 127.7, 125.1, 124.8, 124.7, 124.4, 121.9, 119.7, 110.4, 83.6, 69.1, 43.7; FT-IR (KBr) 2921, 1664, 1624, 1534, 1488, 1454, 1337,

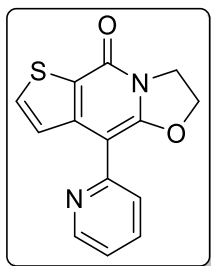
1246, 1092, 957, 690 cm^{-1} ; HRMS (ESI) m/z $[M+H]^+$ calcd for $\text{C}_{18}\text{H}_{13}\text{N}_2\text{O}_3$: 305.0921, found 305.0925.



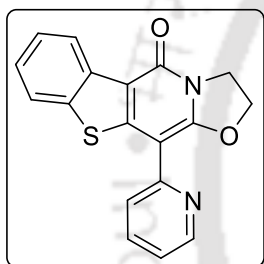
10-(5-(Benzo[*d*][1,3]dioxol-5-yl)pyridin-2-yl)-2,3-dihydro-5H-oxazolo[3,2-*b*]isoquinolin-5-one 3ad. Analytical TLC on silica gel, 1:5 acetone/ CH_2Cl_2 R_f = 0.36; light brown solid; mp 235-236 $^\circ\text{C}$; yield 68% (52.2 mg); ^1H NMR (600 MHz, CDCl_3) δ 8.92 (d, J = 2.4 Hz, 1H), 8.39 (d, J = 7.8 Hz, 1H), 7.91 (dd, J = 7.8, 2.4 Hz, 1H), 7.72 (d, J = 8.4 Hz, 1H), 7.57-7.54 (m, 2H), 7.34 (t, J = 7.8 Hz, 1H), 7.13-7.12 (m, 2H), 6.95 (d, J = 8.4 Hz, 1H), 6.04 (s, 2H), 4.73 (t, J = 7.8 Hz, 2H), 4.44 (t, J = 8.4 Hz, 2H); ^{13}C NMR (150 MHz, CDCl_3) δ 160.3, 151.5, 150.2, 148.6, 147.99, 147.91, 138.3, 134.67, 134.65, 133.0, 131.9, 127.7, 126.2, 124.4, 123.7, 122.3, 120.9, 109.1, 107.5, 101.5, 94.4, 68.3, 43.8; FT-IR (KBr) 2922, 1724, 1663, 1631, 1548, 1475, 1230, 1089, 1038, 862, 811 cm^{-1} ; HRMS (ESI) m/z $[M+H]^+$ calcd for $\text{C}_{23}\text{H}_{17}\text{N}_2\text{O}_4$: 385.1183, found 385.1177.



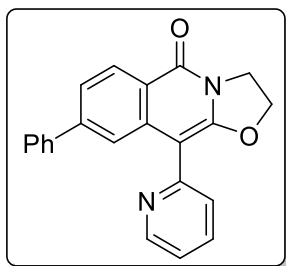
10-(Pyridin-2-yl)-2,3-dihydro-5H-oxazolo[3,2-*b*][2,6]naphthyridin-5-one 3A. Analytical TLC on silica gel, 1:1 acetone/ CH_2Cl_2 R_f = 0.40; brown solid; mp 197-198 $^\circ\text{C}$; yield 70% (37 mg); ^1H NMR (600 MHz, CDCl_3) δ 9.17 (s, 1H), 8.77 (d, J = 4.2 Hz, 1H), 8.54 (d, J = 4.8 Hz, 1H), 8.10 (d, J = 5.4 Hz, 1H), 7.81 (t, J = 7.8 Hz, 1H), 7.55 (d, J = 7.8 Hz, 1H), 7.31-7.29 (m, 1H), 4.76 (t, J = 8.4 Hz, 2H), 4.44 (t, J = 8.4 Hz, 2H); ^{13}C NMR (150 MHz, CDCl_3) δ 159.2, 151.7, 150.8, 149.9, 148.0, 144.0, 136.8, 132.5, 126.9, 126.1, 122.4, 119.4, 93.3, 68.4, 43.9; FT-IR (KBr) 2921, 1667, 1626, 1586, 1534, 1481, 1092, 1012, 984, 794 cm^{-1} ; HRMS (ESI) m/z $[M+H]^+$ calcd for $\text{C}_{15}\text{H}_{12}\text{N}_3\text{O}_2$: 266.0924, found 266.0925.



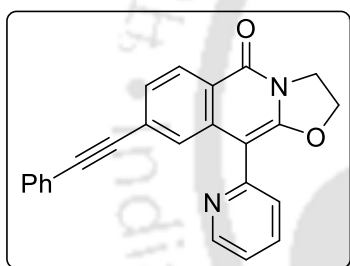
9-(Pyridin-2-yl)-2,3-dihydro-5H-oxazolo[3,2-a]thieno[3,2-d]pyridin-5-one 3B. Analytical TLC on silica gel, 1:5 acetone/CH₂Cl₂ R_f = 0.42; colorless solid; mp 186-187 °C; yield 68% (36.7 mg); ¹H NMR (600 MHz, CDCl₃) δ 8.70 (d, *J* = 4.8 Hz, 1H), 7.76-7.72 (m, 2H), 7.68 (d, *J* = 5.4 Hz, 1H), 7.64 (d, *J* = 7.8 Hz, 1H), 7.21-7.19 (m, 1H), 4.81 (t, *J* = 8.4 Hz, 2H), 4.45 (t, *J* = 8.4 Hz, 2H); ¹³C NMR (150 MHz, CDCl₃) δ 155.5, 153.3, 152.5, 149.4, 146.8, 136.4, 133.8, 124.9, 124.5, 123.6, 121.5, 95.6, 69.1, 43.8; FT-IR (KBr) 2921, 2850, 1659, 1586, 1514, 1467, 1059, 967, 852, 797 cm⁻¹; HRMS (ESI) *m/z* [M+H]⁺ calcd for C₁₄H₁₁N₂O₂S: 271.0536, found 271.0544.



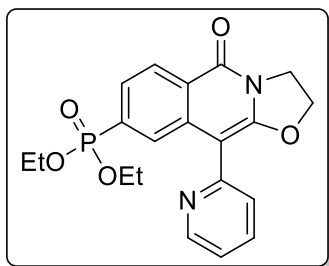
11-(Pyridin-2-yl)-2,3-dihydro-5H-benzo[4,5]thieno[2,3-d]oxazolo[3,2-a]pyridin-5-one 3C. Analytical TLC on silica gel, 1:5 acetone/CH₂Cl₂ R_f = 0.60; yellow solid; mp 225-226 °C; yield 79% (50.5 mg); ¹H NMR (600 MHz, CDCl₃) δ 8.93 (d, *J* = 8.4 Hz, 1H), 8.72-8.71 (m, 1H), 7.86 (d, *J* = 7.2 Hz, 1H), 7.75-7.72 (m, 1H), 7.67 (d, *J* = 7.8 Hz, 1H), 7.32-7.27 (m, 2H), 7.14-7.12 (m, 1H), 4.94 (t, *J* = 9.0 Hz, 2H), 4.45 (t, *J* = 9.0 Hz, 2H); ¹³C NMR (150 MHz, CDCl₃) δ 156.9, 153.7, 151.7, 146.4, 140.5, 136.2, 131.8, 129.8, 125.4, 125.1, 122.8, 121.7, 121.6, 120.3, 109.6, 101.2, 70.1, 44.3; FT-IR (KBr) 2923, 1722, 1651, 1584, 1516, 1465, 1257, 1097, 1002, 943, 793, 733 cm⁻¹; HRMS (ESI) *m/z* [M+H]⁺ calcd for C₁₈H₁₃N₂O₂S: 321.0692, found 321.0690.



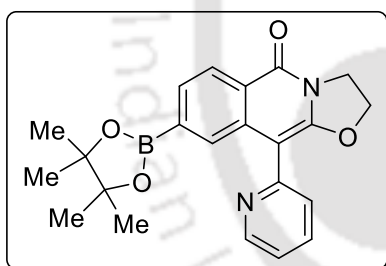
8-Phenyl-10-(pyridin-2-yl)-2,3-dihydro-5H-oxazolo[3,2-*b*]isoquinolin-5-one 4. Analytical TLC on silica gel, 1:5 acetone/CH₂Cl₂ *R_f* = 0.48; colorless solid; mp 238-239 °C; yield 86% (29 mg); ¹H NMR (600 MHz, CDCl₃) δ 8.78 (d, *J* = 4.8 Hz, 1H), 8.43 (d, *J* = 8.4 Hz, 1H), 7.82-7.78 (m, 2H), 7.57-7.52 (m, 4H), 7.40 (t, *J* = 7.8 Hz, 2H), 7.36-7.33 (m, 1H), 7.29-7.27 (m, 1H), 4.71 (t, *J* = 8.4 Hz, 2H), 4.43 (t, *J* = 8.4 Hz, 2H); ¹³C NMR (150 MHz, CDCl₃) δ 160.1, 153.1, 150.5, 149.9, 145.6, 140.7, 138.7, 136.6, 128.8, 128.2, 128.0, 127.6, 126.4, 123.7, 122.1, 122.0, 121.2, 94.9, 68.3, 43.8; FT-IR (KBr) 2922, 2855, 1663, 1626, 1546, 1481, 1436, 1339, 1199, 1104, 760, 699 cm⁻¹; HRMS (ESI) *m/z* [M+H]⁺ calcd for C₂₂H₁₇N₂O₂: 341.1285, found 341.1290.



8-(Phenylethynyl)-10-(pyridin-2-yl)-2,3-dihydro-5H-oxazolo[3,2-*b*]isoquinolin-5-one 5. Analytical TLC on silica gel, 1:5 acetone/CH₂Cl₂ *R_f* = 0.50; light brown solid; mp 260-261 °C; yield 88% (32 mg); ¹H NMR (600 MHz, CDCl₃) δ 8.79 (d, *J* = 4.8 Hz, 1H), 8.34 (d, *J* = 8.4 Hz, 1H), 7.83-7.80 (m, 1H), 7.77 (s, 1H), 7.52-7.49 (m, 3H), 7.45-7.43 (m, 1H), 7.33-7.32 (m, 3H), 7.31-7.29 (m, 1H), 4.71 (t, *J* = 8.4 Hz, 2H), 4.42 (t, *J* = 8.4 Hz, 2H); ¹³C NMR (150 MHz, CDCl₃) δ 159.8, 152.8, 150.6, 150.0, 138.3, 136.7, 131.8, 128.7, 128.5, 127.9, 127.7, 127.2, 126.7, 126.5, 122.9, 122.2, 121.5, 94.5, 91.9, 89.4, 68.3, 43.8; FT-IR (KBr) 2920, 1661, 1539, 1478, 1336, 1206, 1100, 1024, 963, 884, 755 cm⁻¹; HRMS (ESI) *m/z* [M+H]⁺ calcd for C₂₄H₁₇N₂O₂: 365.1285, found 365.1281.



Diethyl (5-oxo-10-(pyridin-2-yl)-2,3-dihydro-5H-oxazolo[3,2-b]isoquinolin-8-yl)phosphonate 6. Analytical TLC on silica gel, 1:4 acetone/CH₂Cl₂ R_f = 0.34; brown solid; mp 140-141 °C; yield 73% (29 mg); ¹H NMR (600 MHz, CDCl₃) δ 8.73 (d, *J* = 4.2 Hz, 1H), 8.43-8.41 (m, 1H), 8.16 (d, *J* = 15.6 Hz, 1H), 7.78 (t, *J* = 7.2 Hz, 1H), 7.65-6.62 (m, 1H), 7.49 (d, *J* = 7.8 Hz, 1H), 7.28-7.26 (m, 1H), 4.71 (t, *J* = 8.4 Hz, 2H), 4.41 (t, *J* = 8.4 Hz, 2H), 1.27 (t, *J* = 7.2 Hz, 6H); ¹³C NMR (150 MHz, CDCl₃) δ 159.6, 152.4, 150.8, 149.9, 138.1 (*J*_{C-P} = 6.6 Hz), 136.7, 133.5 (*J*_{C-P} = 183.6 Hz), 128.3 (*J*_{C-P} = 12.1 Hz), 127.9 (*J*_{C-P} = 14.8 Hz), 126.3, 126.0 (*J*_{C-P} = 9.4 Hz), 124.5 (*J*_{C-P} = 2.7 Hz), 122.3, 94.9, 68.3, 62.5 (*J*_{C-P} = 5.4 Hz), 43.8, 16.3 (*J*_{C-P} = 6.4 Hz); ³¹P NMR (243 MHz, CDCl₃) δ 17.67; FT-IR (KBr) 2920, 1662, 1541, 1477, 1339, 1242, 1022, 966, 795, 686 cm⁻¹; HRMS (ESI) *m/z* [M+H]⁺ calcd for C₂₀H₂₂N₂O₅P: 401.1261, found 401.1268.



10-(Pyridin-2-yl)-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydro-5H-oxazolo[3,2-b]isoquinolin-5-one 7. Analytical TLC on silica gel, 1:5 acetone/CH₂Cl₂ R_f = 0.42; colorless solid; mp 165-166 °C; yield 75% (29 mg); ¹H NMR (600 MHz, CDCl₃) δ 8.77 (d, *J* = 4.8 Hz, 1H), 8.35 (d, *J* = 7.8 Hz, 1H), 8.04 (s, 1H), 7.81-7.78 (m, 1H), 7.73 (d, *J* = 8.4 Hz, 1H), 7.51 (d, *J* = 7.8 Hz, 1H), 7.29-7.27 (m, 1H), 4.68 (t, *J* = 8.4 Hz, 2H), 4.41 (t, *J* = 8.4 Hz, 2H), 1.30 (s, 12H); ¹³C NMR (150 MHz, CDCl₃) δ 160.3, 153.1, 150.0, 149.8, 137.3, 136.5, 130.3, 129.9, 126.6, 126.5, 124.0, 122.0, 95.1, 84.2, 68.1, 43.8, 24.9; FT-IR (KBr) 2923, 1664, 1586, 1541, 1476, 1364, 1147, 1094, 967, 754 cm⁻¹; HRMS (ESI) *m/z* [M+H]⁺ calcd for C₂₂H₂₄BN₂O₄: 391.1824, found 391.1816.

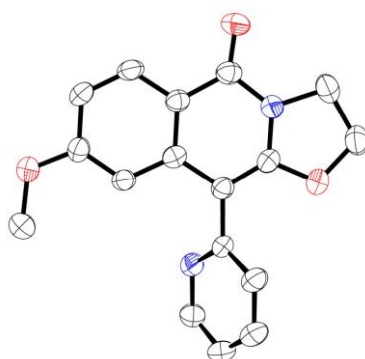
Crystal Data and Structure Refinement for **3f**

Figure S3. ORTEP diagram of 8-Methoxy-10-(pyridin-2-yl)-2,3-dihydro-5H-oxazolo[3,2-*b*]isoquinolin-5-one **3f** with 50% ellipsoid (CCDC 2382549). H-Atoms are omitted for clarity.

Identification code	3f
Empirical formula	C ₁₇ H ₁₄ N ₂ O ₃
Formula weight	294.30
Crystal habit, color	block and colorless
Temperature, <i>T</i> /K	297 K
Wavelength, λ /Å	0.71073
Crystal system	triclinic
Space group	'P -1'
Unit cell dimensions	$a = 8.7677(7)$ Å $b = 9.1717(8)$ Å $c = 10.1712(9)$ Å $\alpha = 64.119(2)$ $\beta = 76.342(2)$ $\gamma = 77.008(2)$
Volume, $V/\text{Å}^3$	708.10(11)
<i>Z</i>	2
Calculated density, g·cm ⁻³	1.380
Absorption coefficient, μ/mm^{-1}	0.096
<i>F</i> (000)	308
θ range for data collection	2.414 to 24.998 °
Limiting indices	$-10 \leq h \leq 10$, $-10 \leq k \leq 10$, $-12 \leq l \leq 12$
Reflection collected / unique	2456 / 1921

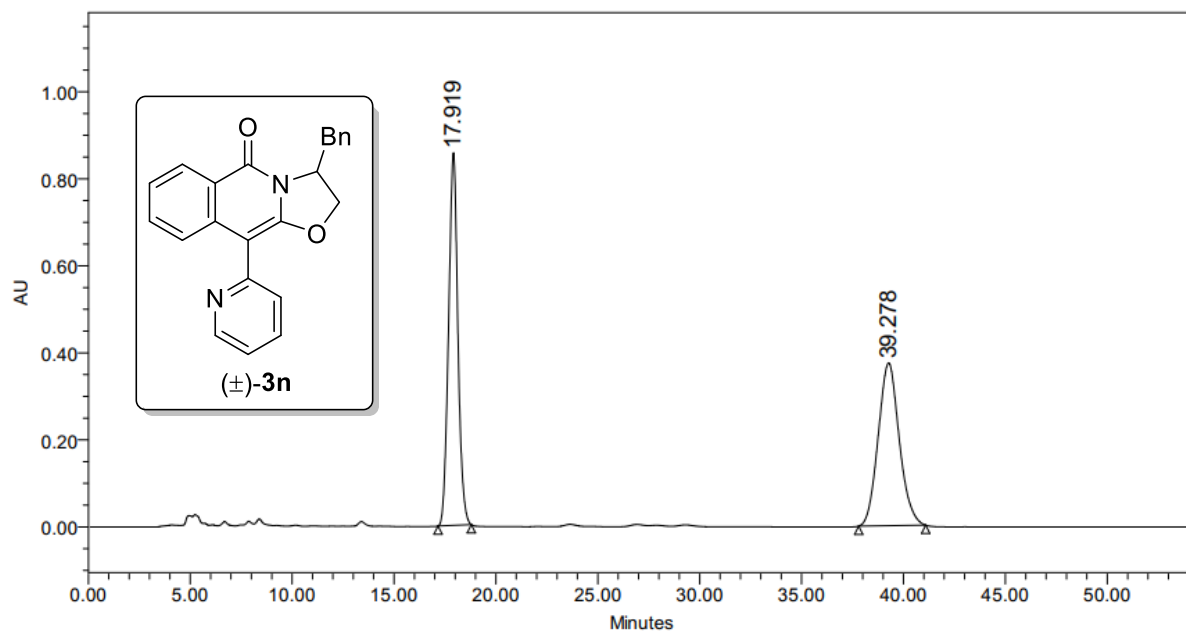
Completeness to θ	98.40% ($\theta = 24.998^\circ$)
Absorption correction	multi-scan
Refinement method	'SHELXT 2018/2 (Sheldrick, 2018)'
Data / restraints / parameters	2456/0/200
Goodness-of-fit on F^2	1.189
Final R indices [$I > 2\sigma(I)$]	$R1 = 0.0605$, $wR2 = 0.1097$
R indices (all data)	$R1 = 0.0819$, $wR2 = 0.1161$

4.7 References

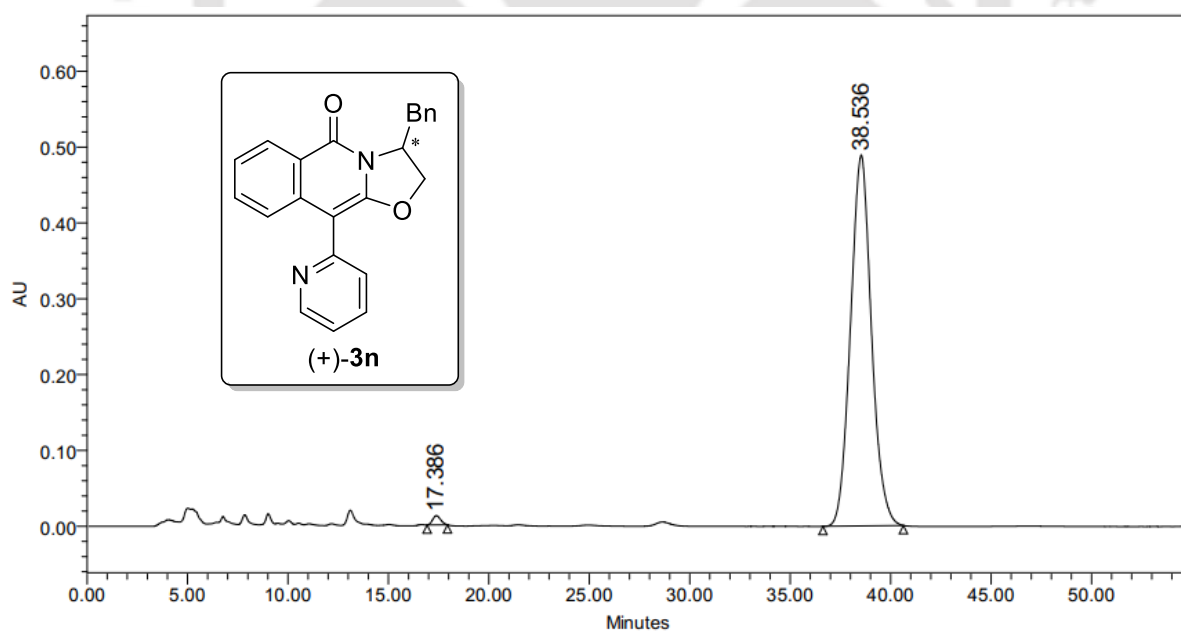
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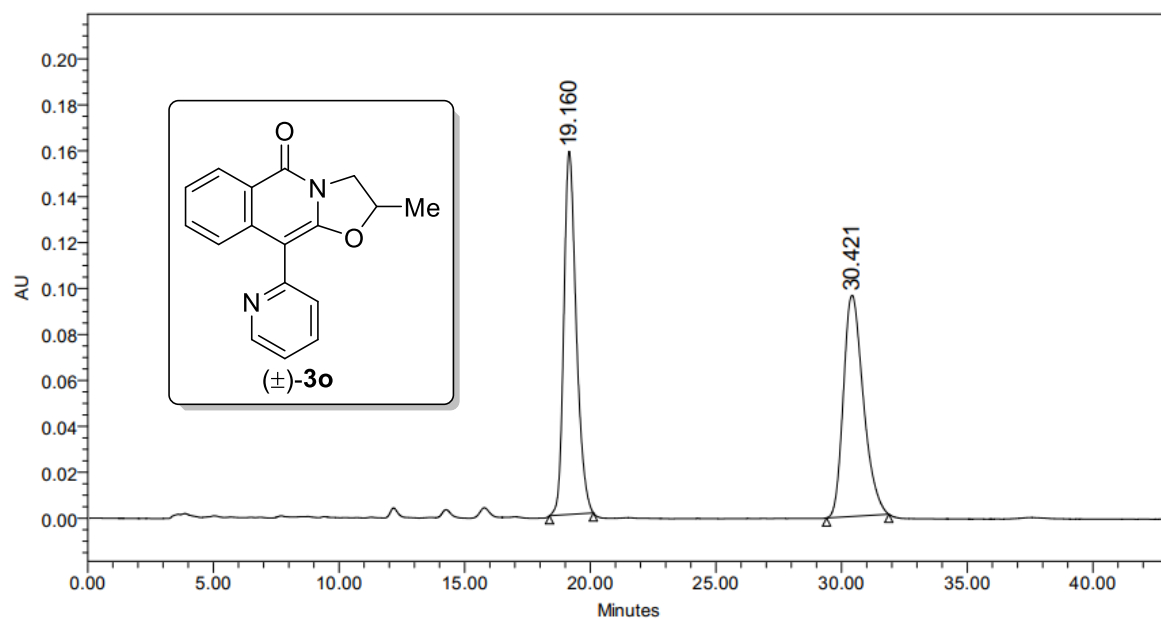
4.8 HPLC Chromatograms



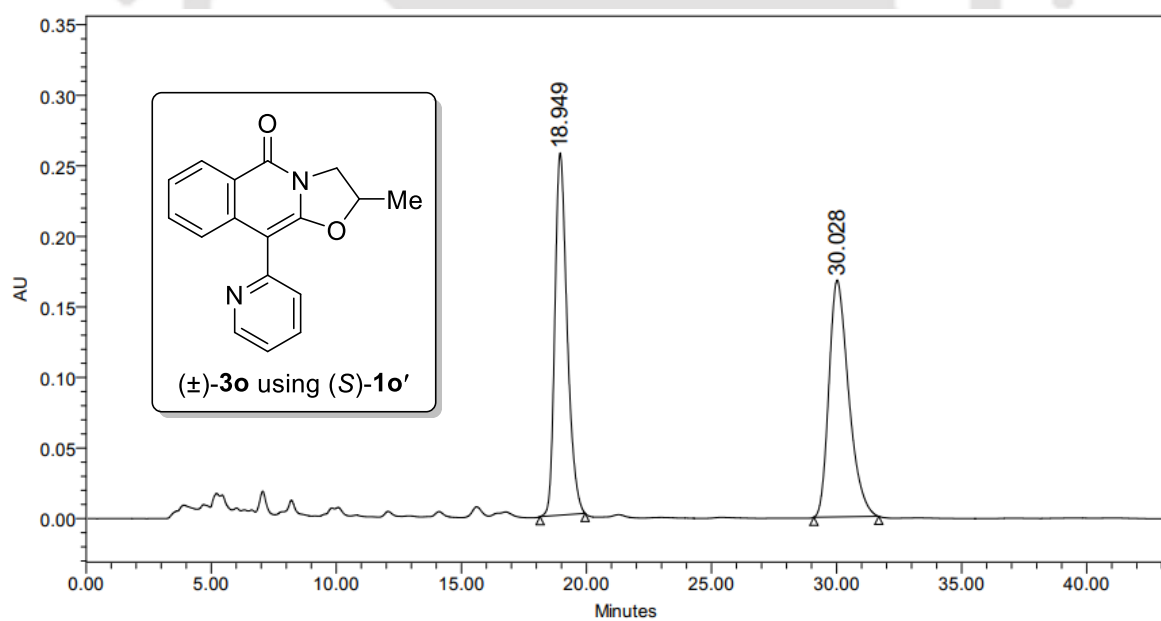
	RT	Area	% Area	Height
1	17.919	27118746	50.23	856049
2	39.278	26871875	49.77	374223



	RT	Area	% Area	Height
1	17.386	337003	0.94	12233
2	38.536	35420037	99.06	489286



RT	Area	% Area	Height
1 19.160	5433569	50.55	158077
2 30.421	5314729	49.45	96289



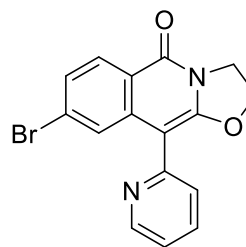
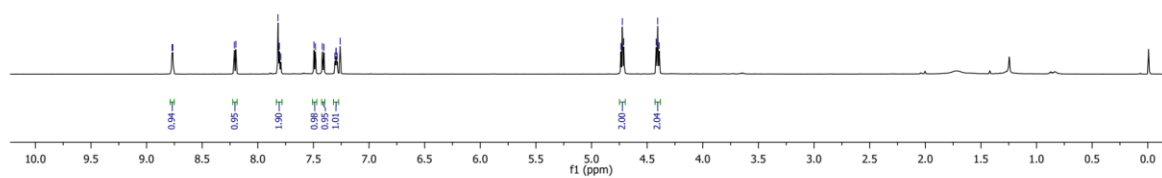
RT	Area	% Area	Height
1 18.949	8778292	48.84	256668
2 30.028	9196816	51.16	167797

4.9 Selected NMR Spectra

SBT-4Br-OXA-PYTR-1H

8.772
8.774
8.111
8.137
7.818
7.806
7.805
7.482
7.485
7.307
7.296
7.287
7.280

4.377
4.375
4.419
4.415
4.392

**3g**¹H NMR (600 MHz, CDCl₃)

SBT-4Br-OXA-PYTR-13C

159.738

152.477

151.045

149.925

139.853

136.844

129.339

128.621

127.856

126.253

122.898

121.975

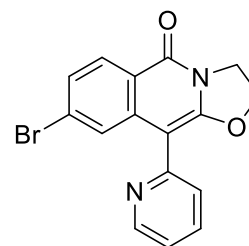
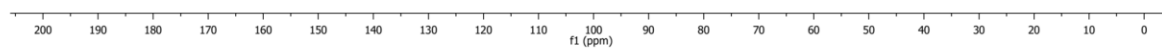
94.118

77.371

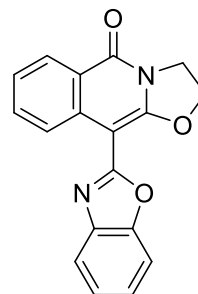
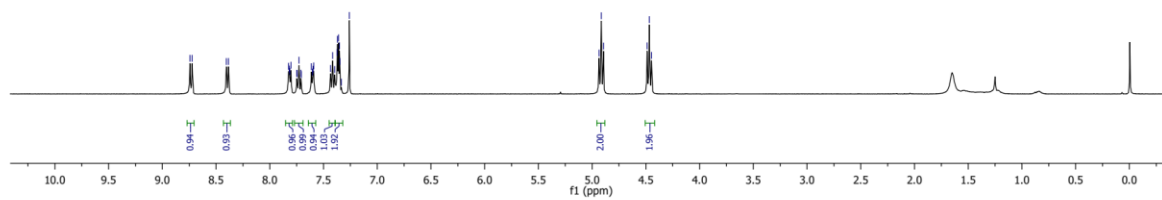
76.948

68.461

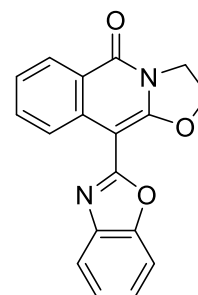
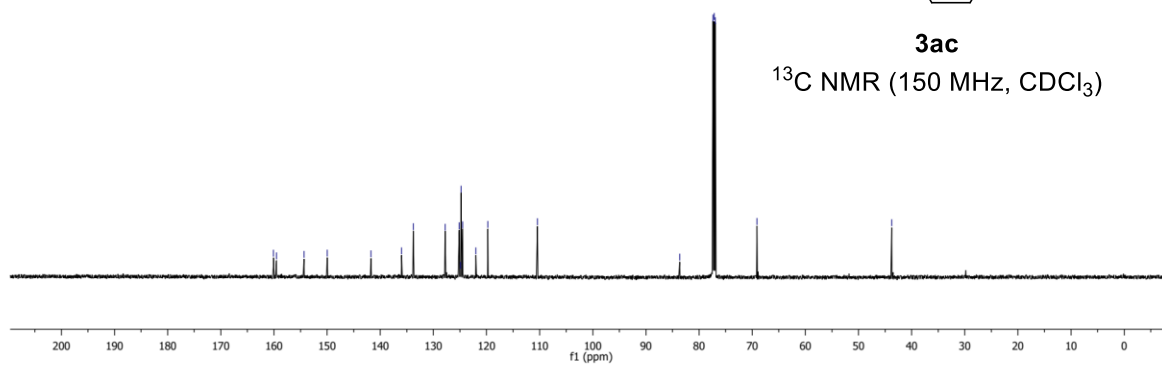
43.827

**3g**¹³C NMR (150 MHz, CDCl₃)

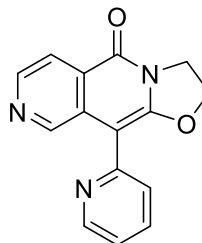
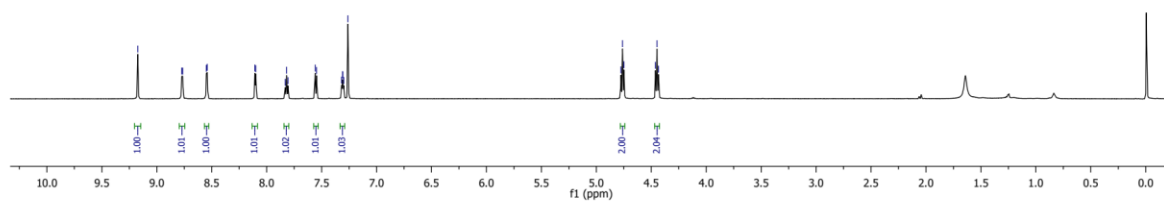
SBT-OXA-BENZOXA-PYTR-P2-1H

**3ac**¹H NMR (400 MHz, CDCl₃)

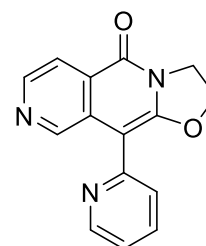
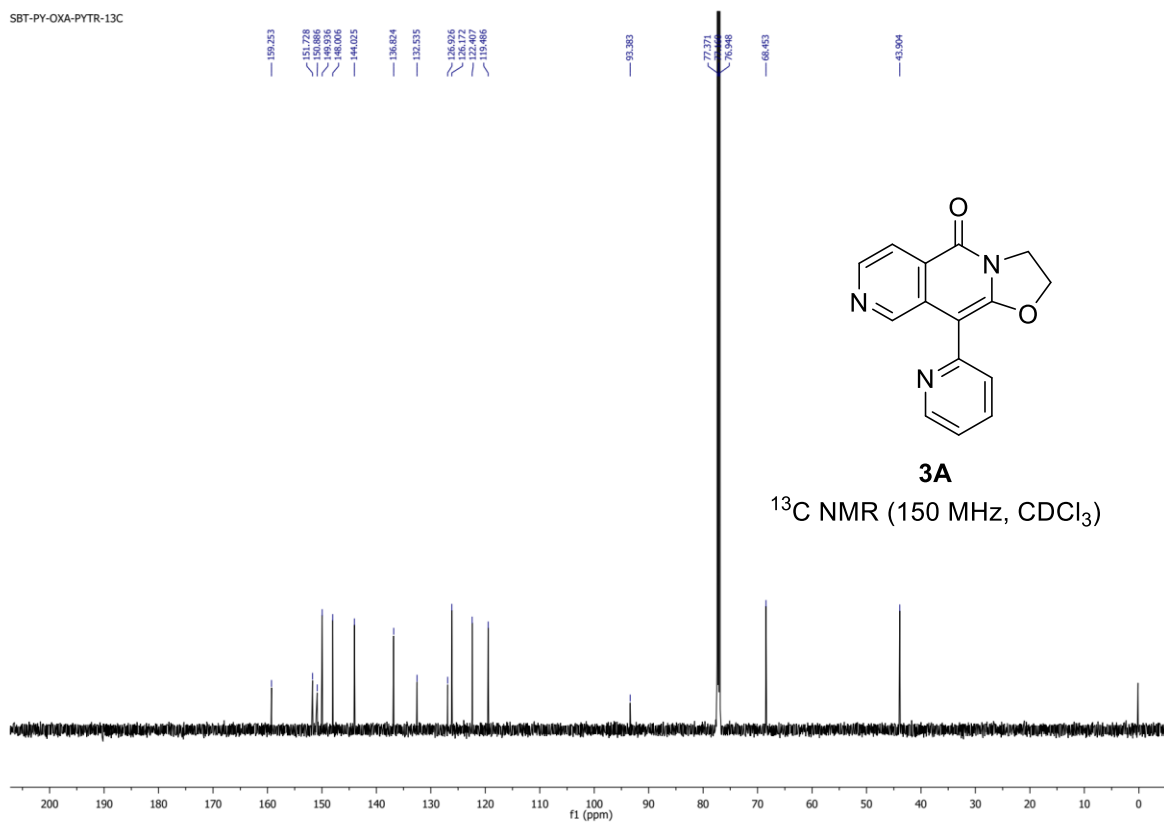
SBT-OXA-BENZOXA-PYTR-P2-13C

**3ac**¹³C NMR (150 MHz, CDCl₃)

SBT-PY-OXA-PYTR-1H

**3A** $^1\text{H NMR}$ (600 MHz, CDCl_3)

SBT-PY-OXA-PYTR-13C

**3A** $^{13}\text{C NMR}$ (150 MHz, CDCl_3)



Summary

Functionalized *N*-heterocycles are the structural backbone of a large number of biologically active compounds and natural products. Thus, the synthetic elaboration of the *N*-heterocycles has attracted notable attention over the years.

Chapter I aims to describe the auxiliary-assisted C-H activation utilizing TM-catalysis for the synthesis of functionalized *N*-heterocycles. The methodologies discussed are viable with a varied metal catalysts with good functional group tolerance. However, most of the methods offer C-H functionalization at the proximal position with the aid of DG which can lead to advance the field for distal C-H functionalization.

Chapter II illustrates a Pd-catalyzed 2-fold C-H functionalization of indoles with arenes to furnish C4-H arylation utilizing weak chelation assistance. A wide range indoles as well as arenes having electronically varied substituents were coupled to test the generality of the procedure. The use of arenes as arylating source, site-selectivity and post-synthetic transformations are the important practical features.

Chapter III presents a Ru-catalyzed weak acyl DG-assisted C4-H allylation of indoles employing vinylcyclopropanes *via* sequential C-H/C-C bond activation under redox-neutral conditions. The procedure was extended to the regioselective C-H allylation of benzothiophene, tetrahydroquinoline, carbazole, α -tetralone and indoline scaffolds as well as using vinylaziridine as allyl surrogate. The important aspects include the redox-neutral conditions, distal selectivity, use of removable DG and late stage-diversification of drug molecules.

Chapter IV delineates a Rh-catalyzed cascade C-H activation/ two-fold annulation of 2-aryl-oxazolines with pyridotriazoles for the rapid access of heteroaryl-tethered oxazolo-isoquinolinones. The procedure was extended to the heteroaryl oxazolines and aryl oxazines which showcase the viability of the method. In addition, this one-pot strategy featured a 2-fold annulation sequence, production of N₂, alcohol and H₂O as green by-products and the late-stage modification of the bio-relevant compounds.



List of Publications

1. **S. Basak**, T. Paul and T. Punniyamurthy, Palladium-Catalyzed 2-fold C–H Activation/C–C Coupling for C4-Arylation of Indoles Using Weak Chelation, *Org. Lett.* **2022**, *24*, 554.
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12. T. Paul, **S. Basak**, M. V. Nanjegowda and T. Punniyamurthy, Cascade Heteroarylation/Annulation of Arylphosphonic Acid Monoesters with Benzo-thiophenes: Access to Benzothieno-fused Oxaphosphacycles, *Chem. Commun.* **2025**, 61, 9480.

Conference Attended

Oral Presentation:

1. **S. Basak**, T. Paul and T. Punniyamurthy, "Palladium-Catalyzed 2-fold C-H Activation/C-C Coupling for C4-Arylation of Indoles Using Weak Chelation" XVII-J-NOST, University of Hyderabad, Jan 6-9, 2022.

Poster Presentation:

2. **S. Basak**, T. Paul and T. Punniyamurthy, "Palladium-Catalyzed Auxiliary Guided C4-Selective Arylation of Indoles via C-H/C-H Bond Functionalization" FICS, IIT Guwahati, Dec 2-4, 2022.
3. **S. Basak**, T. Paul and T. Punniyamurthy, "Palladium-Catalyzed Auxiliary Guided C4-Arylation of Indoles via C-H/C-H Bond Functionalization" NERC, IIT Guwahati, May 20-22, 2022.
4. **S. Basak**, T. Paul and T. Punniyamurthy, "Palladium-Catalyzed Two-fold C-H Functionalization for C4-Selective Arylation of Indoles Utilizing Weak Coordination" CRSI NSC-28, IIT Guwahati, Feb 4-6, 2022.
5. **S. Basak**, T. Paul and T. Punniyamurthy, "Palladium-Catalyzed Weak Coordination Guided C4-Selective Arylation of Indoles via Twofold C-H Activation" RIC (virtual), IIT Guwahati, Jan 20-23, 2022.