Studies Towards Weak Chelation Assisted Regioselective C-H Activation/C-C Bond Formation: Exploration to Functionalized Heterocycles

A Thesis Submitted

in Partial Fulfilment of the Requirements

for the Degree of

DOCTOR OF PHILOSOPHY

by

Tripti Paul

Roll No. 196122042

Department of Chemistry
Indian Institute of Technology Guwahati
Guwahati- 781039
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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 — Tripti Paul

January 2025

INDIAN INSTITUTE OF TECHNOLOGY GUWAHATI

Department of Chemistry

CERTIFICATE

This is to certify that Ms. Tripti Paul has been working under my supervision since July 2019. I am forwarding her thesis entitled "*Studies Towards Weak Chelation Assisted Regioselective C-H Activation/C-C Bond Formation: Exploration to Functionalized Heterocycles*" being submitted for the Ph.D. degree of this institute. I certify that she has fulfilled all the requirements according to the rules of this institute, and regarding the investigations embodied in her thesis and this work has not been submitted elsewhere for a degree.

Guwahati
January 2025

Prof. Tharmalingam Punniyamurthy
Supervisor

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Last but not the least my words are insufficient to thank my guiding power Lord Shiva and I surrender myself to Him, for showering His blessings upon me for making me able to sew up this thesis work.

May God bless you all!

Tripti Paul

List of Abbreviations

Ac	acetyl
Å	angstrom (10^{-8} cm)
Bn	benzyl
Boc	*tert*-butoxycarbonyl
BHT	butylated hydroxytoluene
cat.	catalyst
Cp*	1,2,3,4,5-pentamethylcyclopentadiene
CCDC	Cambridge crystallographic data center
CMD	concerted bis-metalation deprotonation
p-cymene	4-isopropyltoluene
DCE	1,2-dichloroethane
DCM	dichloromethane
DG	directing group
DME	dimethoxyethane
DMSO	dimethylsulfoxide
DMF	*N*,*N*-dimethylformamide
EDG	electron donating group
eq	equation
equiv	equivalent
ESI	electrospray ionization
EWG	electron wthdrawing group
FT-IR	Fourier transform infrared spectroscopy
FG	functional group
GC	gas chromatograms
HFIP	hexafluoroisopropanol
het	heterocyclic
HRMS	high-resolution mass spectrometry
Hz	hertz
L	ligand
LG	leaving group
Leu	leucine
m/z	mass to charge ratio

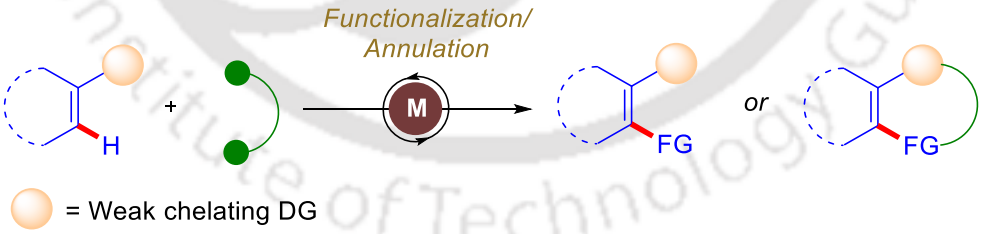
mL	milliliter
mp	melting point
MHz	megahertz
NMR	nuclear magnetic resonance
NFSI	*N*-fluorobenzenesulfonimide
ORTEP	oak ridge thermal ellipsoid plot
OH	hydroxyl
PIDA	phenyliodine(III) diacetate
R_f	retardation factor
rt	room temperature
Piv	pivaloyl
py	pyridyl
pym	pyrimidyl
1, 10-Phen	1, 10-phenanthroline
PivOH	pivalic acid
SET	single-electron transfer
THF	tetrahydrofuran
TFE	2,2,2-trifluoroethanol
TCD	thermal conductivity detector
TCE	2,2,2-trichloroethanol
TEMPO	2,2,6,6-tetramethylpiperidine-1-oxyl
TLC	thin layer chromatography
TsOH	*p*-toluenesulfonic acid
TMS	trimethylsilyl
TM	transition metal
μL	microliter

Abstract

The thesis is divided into four chapters. The first chapter describes the transition-metal (TM)-catalyzed weak chelation assisted regioselective C-H functionalization and annulation reactions. The second chapter deals with the weak chelation-guided Rh-catalyzed C4-H alkylation of indoles with cyclopropanols *via* merging C-H/C-C bond activation. The third chapter demonstrates a biorelevant weakly coordinating directing group (DG) assisted C-H alkenylation with cyclopropanols. The fourth chapter focuses on weak chelation assisted oxidative C-H/C-H coupling/annulation cascade of aryl phosphonic acid monoesters and benzothiophenes.

Chapter I. Transition-Metal-Catalyzed Weak Chelation Assisted Regio-selective C-H Functionalization and Annulation

The widespread presence of C-H bonds in organic molecules makes the site-selective functionalization of a specific C-H bond a challenging endeavor. Over the past decade, elegant methods for C-H activation have been developed using TM-catalyzed DG assistance. However, most of these methods rely on strong chelating DGs, which forms thermodynamically stable metallacycle, making them less reactive for further functionalization. In contrast, weak chelating DGs offer an ideal approach, as they form less thermodynamically stable and more reactive metallacycle for coupling with the incoming coupling partners. This chapter focuses on the TM-catalyzed weak chelation assisted regioselective C-H functionalization and annulation reactions for efficient molecular diversification.

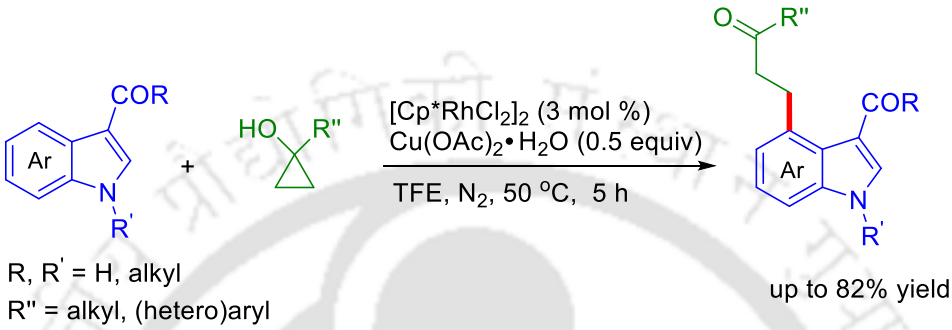


Scheme 1. Metal Catalyzed C(sp^2)-H Bond Functionalization/Annulation

Chapter II. Rh-Catalyzed C4-H Alkylation of Indoles with Cyclopropanols

Indole nucleus is the skeletal framework of numerous natural products, therapeutic agents, agrochemicals and advanced materials. Thus, unstinting efforts have been made by the scientific community for the site-selective functionalization of indole core. Functionalization of C2 and C3-positions of indole has been well achieved owing to the innate reactivity of pyrrole core.

However, site-selective C-H functionalization of less reactive distal benzenoid core (C4-C7) continues to be increasingly challenging. Alongside merging C-H/C-C activation represents a cornerstone for advancing synthetic methodologies. Cyclopropanols serve as a staple coupling partner due to its high strain energy and ready availability. This chapter demonstrates a Rh-catalyzed weak chelation assisted C4-alkylation of indoles using cyclopropanols as an alkylating agent *via* the tandem C-H and C-C bond activation.

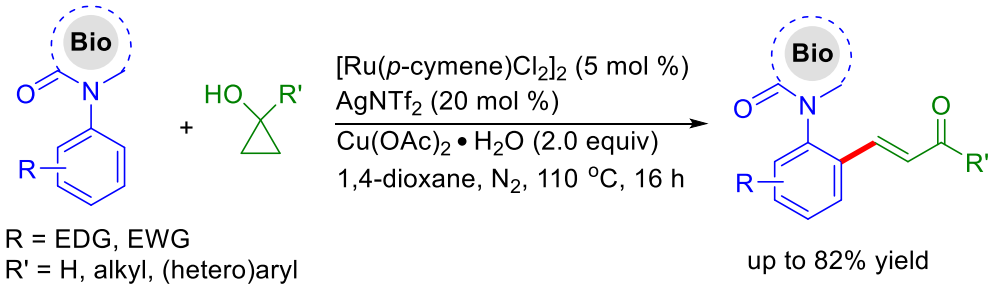


Org. Lett. **2022**, *24*, 6000.

Scheme 2. Rh(III)-Catalyzed C4-Alkylation of Indoles with Cyclopropanols

Chapter III. Ru-Catalyzed C-H Alkenylation of Arenes Exploiting Cyclopropanols

Transition-metal-catalyzed auxiliary assisted C-H functionalization has emerged as a transformative tool for the late-stage functionalization of complex organic molecules. However, installation and removal of DGs remain labour-intensive. In this context, utilization of bioactive scaffolds as intrinsic DG for C-H activation is particularly appealing from the sustainability perspective. In this chapter, we have established an efficient Ru(II)-catalyzed regioselective arene C-H alkenylation leveraging weakly coordinating biorelevant intrinsic DG and readily accessible cyclopropanols as alkenyl surrogate. β- and, γ-Lactam, ε-caprolactam, isoindolinone, morpholinone and pyridones acted as effective DG in our protocol, providing the alkenylated products in synthetically useful yields. The utilization of intrinsic DG, site-selectivity, functional group tolerance, ample substrate scope, late-stage natural product and drug mutations are the significant practical features.

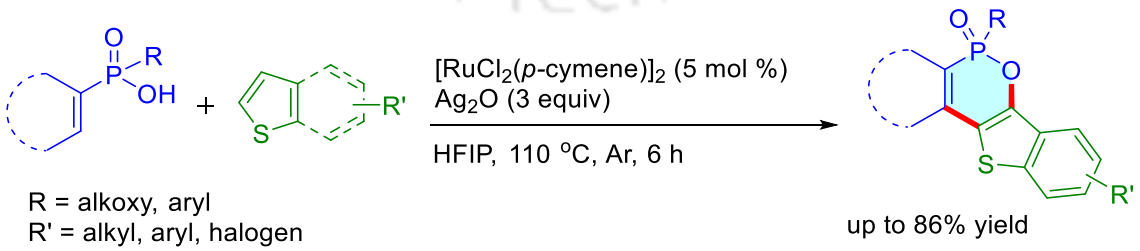


Org. Lett. **2023**, *25*, 8975.

Scheme 3. Ru(II)-Catalyzed Arene C-H Alkenylation with Cyclopropanols

Chapter IV. Ru-Catalyzed C-H/C-H Coupling/Annulation Cascade with Benzothiophenes

The development of efficient methods for the rapid assembly of complex molecular architecture from readily accessible chemical feedstocks has always been a core objective in synthetic organic chemistry. In this context, chelation guided C-H/C-H coupling under TM-catalysis has proven to be a potential strategy for the construction of C-C bonds as it eliminates the need for the prefunctionalization steps, thereby enhances both step- and atom-economy. Moreover, cascade C-H/C-H coupling and annulation strategy to achieve cyclic complex molecules in a single step will streamline organic synthesis and hence desirable. However, subtle reactivity difference among multiple C-H bonds present in a molecule renders the process quite challenging. Bezothiophenes adorn the core subunit of numerous biologically active compounds and optoelectronic materials. In this chapter, we have established a weak chelation assisted Ru(II)-catalyzed one-pot cascade C-H/C-H cross-coupling/annulation of aryl/vinyl phosphonic acid monoesters with benzothiophenes. Diversely aryl/vinyl phosphonic acid monoesters and benzothiophenes are well tolerated, affording the benzothiophene fused phosphaisocoumarins in good to excellent yields.



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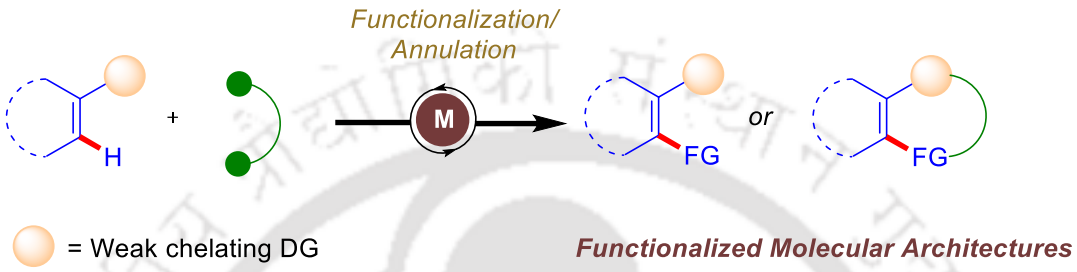
Scheme 4. Ru(II)-Catalyzed 2-Fold C-H Activation/Annulation with Benzothiophenes

Contents

Chapter I

Transition-Metal-Catalyzed Weak Chelation Assisted Regioselective C-H Functionalization and Annulation

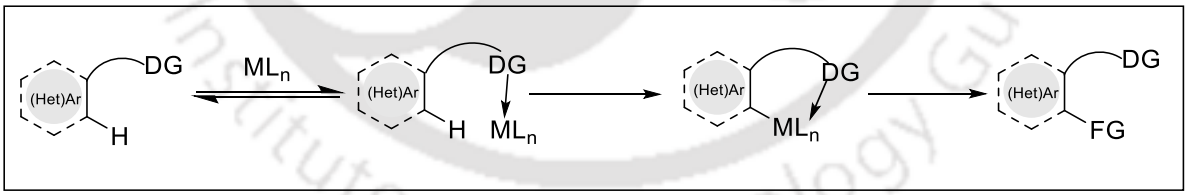


Transition-Metal-Catalyzed Weak Chelation Assisted Regio-selective C-H Functionalization and Annulation

Transition-metal-catalyzed C-H activation/functionalization has emerged as flagship technology as it offers operationally simple, step- and atom-economic routes to access important structural scaffolds that are present in pharmaceuticals, agrochemicals and organic materials.[1] However, overabundance of C-H bonds in organic molecules with subtle reactivity difference poses tremendous obstacle to achieve a smooth synthetic pathway for regioselective C-H activation. In the initial stages of C-H bond activation research, regioselectivity was largely dictated by the steric and electronic characteristics of the C-H bonds. Transition-metal catalysts preferentially targeted less sterically hindered and more acidic C-H bonds, while achieving site-selective functionalization of unbiased C-H bonds posed a considerable challenge.[2] Along this line, functional groups with pre-coordination ability to the transition-metal catalysts, profoundly termed as directing groups (DGs), have shown great potentiality in exerting site-selective C-H activation of complex organic molecules.[3]

1.1 DG Assisted C-H Functionalization

The coordination of DG to the transition-metal-catalysts brings the metal to proximity of a certain C-H bonds in the substrate, which leads to site-selective C-H bond cleavage *via* key metallacycle and enables subsequent functionalization (Scheme 1).[3]

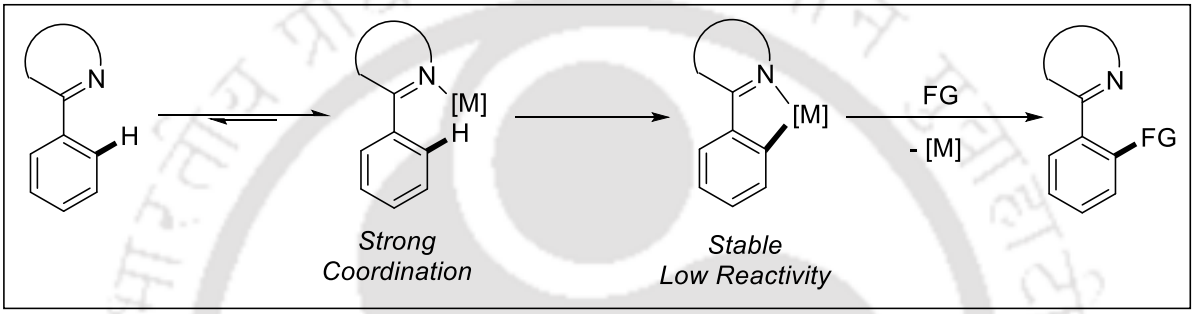


Scheme 1. DG Assisted C-H Activation/Functionalization

The DG approach allows the override of inherent reactivity in (hetero)arenes. Moreover, it has revolutionized synthetic methodologies, enabling site-selective transformations of complex molecular architectures that were previously deemed inaccessible. A wide array of functional groups such as amides, ketones, imines, oximes, carboxylic acids, esters, hydroxyl groups and amines have successfully been employed as DG for the catalytic C-H bond functionalizations.[3,4] Based on the coordinating atom present, DGs can be broadly categorized as strong chelating DG and weak chelating DG.

1.1.1 Strong Chelating DG

DGs with nitrogen (N) or phosphorus (P) as the chelating atoms are typically referred as strong chelating DG.[5] The strong electron donating ability of these atoms enables them to form thermodynamically stable metallacycle and hence less reactive for further functionalization (Scheme 2). Pyridin-2-yl, oxazoline-2-yl and pyrazole-1-yl etc. are typical examples of strong chelating DGs (Figure 1). Moreover, removal of such DG is often labor-intensive, necessitates additional synthetic steps, thereby undermining the atom-and step-economy for the C-H bond activation/functionalization process.



Scheme 2. C-H Functionalization *via* Strong Chelation Assistance

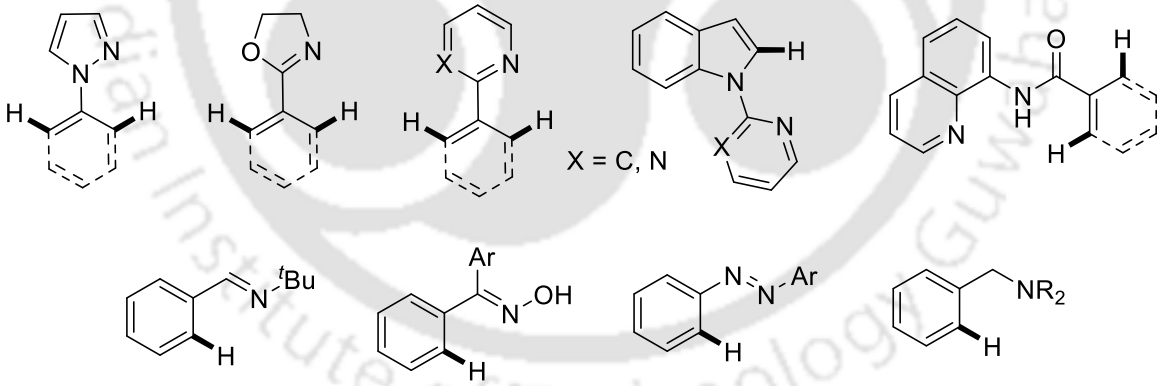
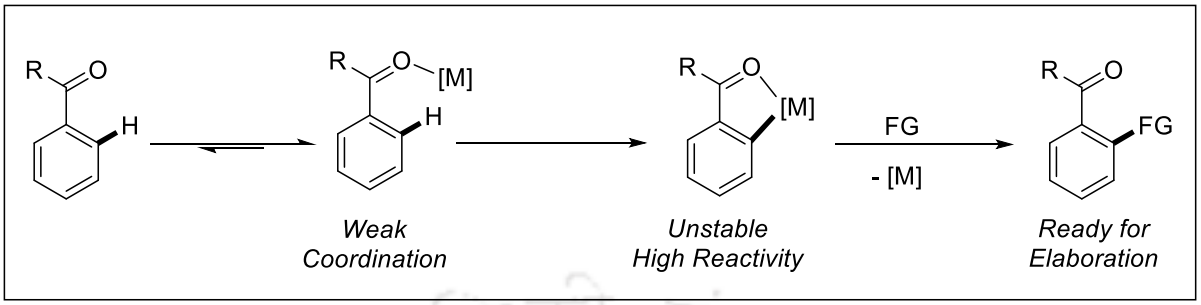


Figure 1. Examples of Strong Chelating DGs

1.1.2 Weak Chelating DG

Weakly (oxygen and sulphur) coordinating DGs would ideally be employed for C-H activation reactions *via* less thermodynamically stable and more reactive metallacycle for coupling with the coupling partners (Scheme 3).[6] Ketone, acid, ester, ether and alcohol functionalities are some representative examples of weak chelating DGs (Figure 2). Installation or removal of these weakly coordinating DGs are very facile and offers a diverse scope for the post synthetic

transformations. Thus, the rational design of DGs permits the synthesis functionalized products of synthetic importance from simple chemical inputs.



Scheme 3. C-H Functionalization *via* Weak Chelation Assistance

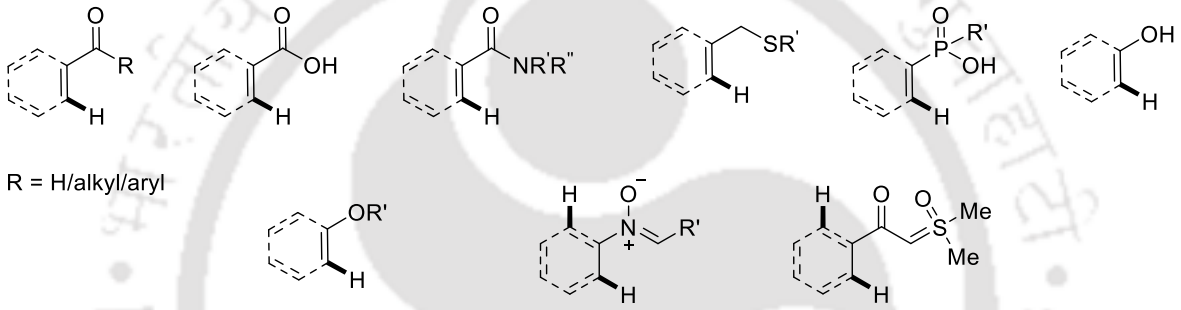
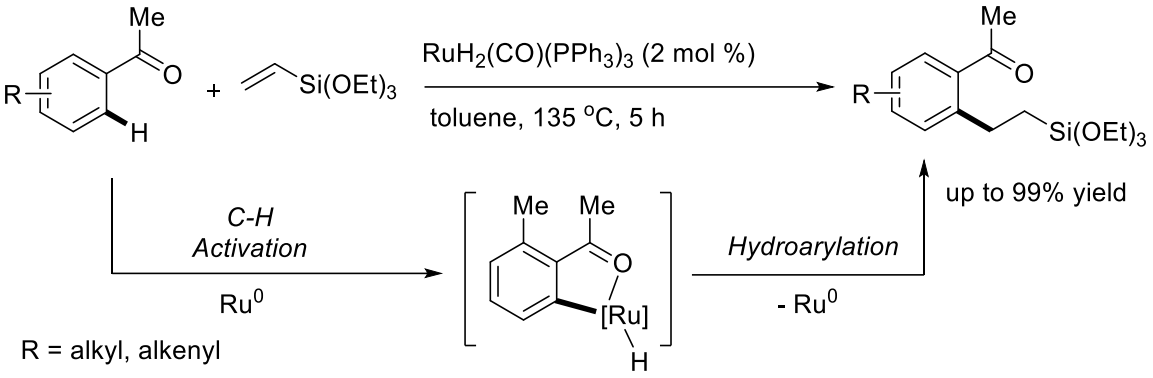


Figure 2. Examples of Weak Chelating DGs

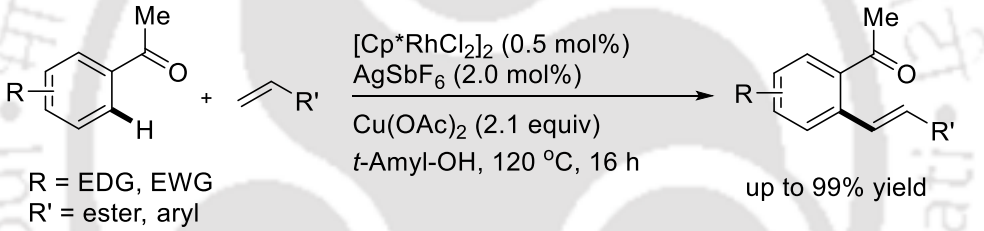
1.1.2.1 Ketone as DG

Ketones are readily introducible functional groups and offers numerous opportunities for diverse synthetic transformations. Hence, leveraging ketone as DG can unlock new avenues for the development of efficient methodologies in organic synthesis. Pioneering work by Murai demonstrated *ortho*-C-H alkylation of aryl ketones utilizing $RuH_2(CO)(PPh_3)_3$ as catalyst (Scheme 4).[7] The metal precursor first reduced to Ru(0), that coordinates with ketones to facilitate the oxidative addition of C-H bond to metal center, followed by insertion of double bond and reductive elimination leads to the alkylated product.



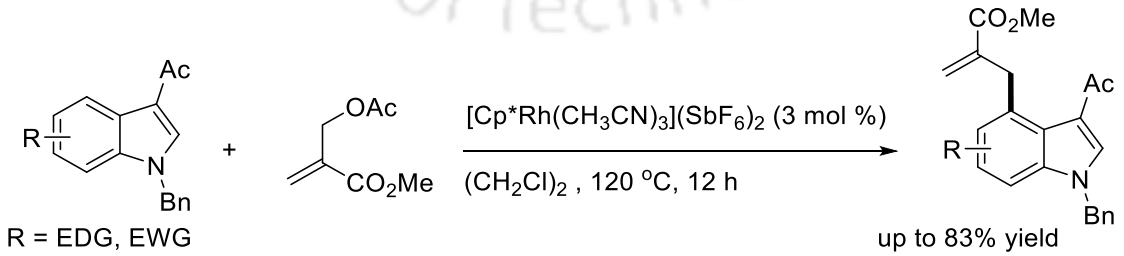
Scheme 4. Ru-Catalyzed C-H Alkylation of Aryl Ketones

Glorius group unveiled weakly coordinating ketone directed arene C-H alkenylation with excellent functional group tolerance and broad substrate scope (Scheme 5).[8] The obtained products are highly valuable due to their extensive synthetic utility from biological and synthetic context.



Scheme 5. Rh-Catalyzed C-H Alkenylation of Acetophenones

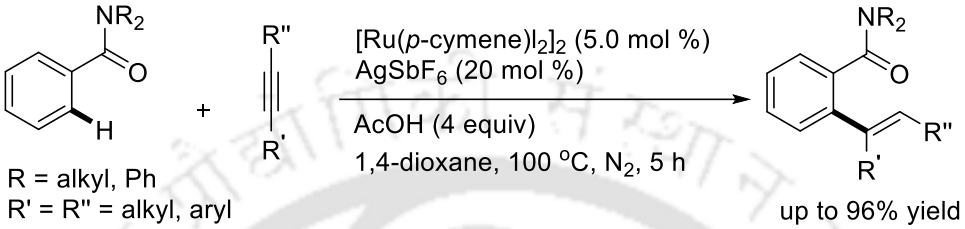
Very recently, our groups exploited Rh-catalyzed distal C4-H allylation of indoles with the assistance of weakly coordinating acetyl group (Scheme 6).[9] The reaction exhibited a wide scope for indole, showcasing excellent functional group tolerance. The oxidant free character and post-synthetic transformations are the key practical aspects of the reaction.



Scheme 6. Ketone-directed Regioselective C4-H Allylation of Indoles

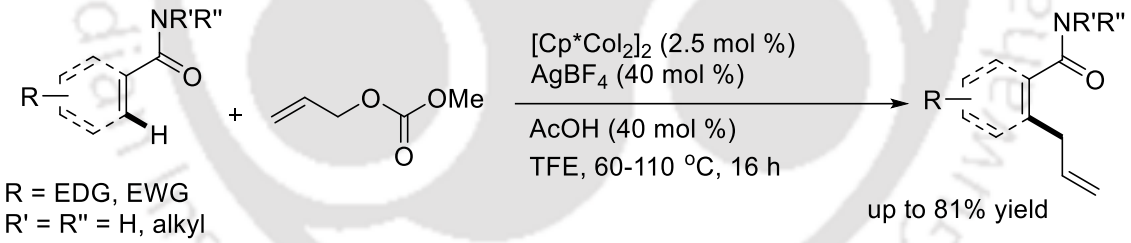
1.1.2.2 Amide as DG

Amide directed C-H functionalization is a rapidly growing field within the chemistry community, due to its easy installation and removal. Satoh and Miura group explored the amide DG assisted arene C-H alkenylation with alkyne as coupling partner under Ru-catalysis (Scheme 7).[10a] Of note, unsymmetrical internal alkynes were found to be suitable substrates, affording regioselective products in good yields, whereas terminal alkynes resulted diminished yields.



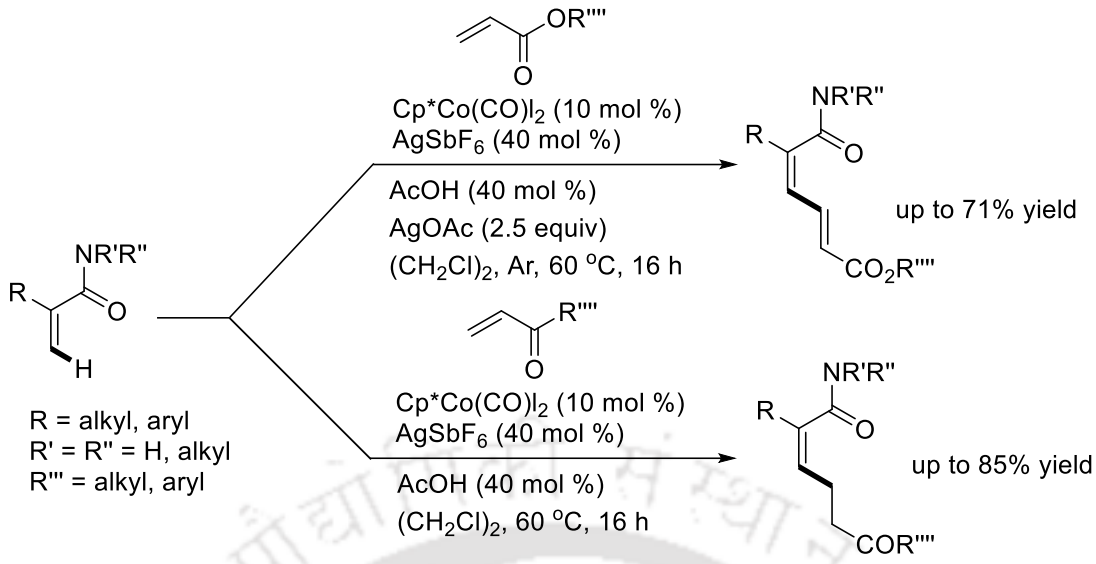
Scheme 7. Ru-Catalyzed Regio- and Stereo-selective Arene C-H Alkenylation

An elegant work on the Co-catalyzed site-selective C-H allylation of (hetero)arylamides and acrylamides was reported using allyl carbonates as coupling partner (Scheme 8).[10b] The reaction exhibits broad substrate scope and good functional group compatibility, yielding products in good to excellent yields.



Scheme 8. Co-Catalyzed Amide Directed C-H Allylation

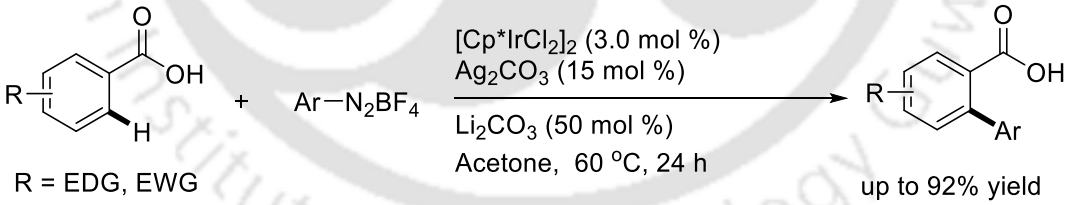
Zhang and Zhong groups accomplished the Co-catalyzed regio- and stereo-selective olefinic C-H alkenylation and alkylation by prudent choice of coupling partners (Scheme 9).[10c] Acrylates yielded conjugated dienes through β-hydride elimination, whereas α,β-unsaturated ketones furnished alkylated product *via* protodemetalation.



Scheme 9. Co-Catalyzed Olefinic C-H Alkenylation and Alkylation

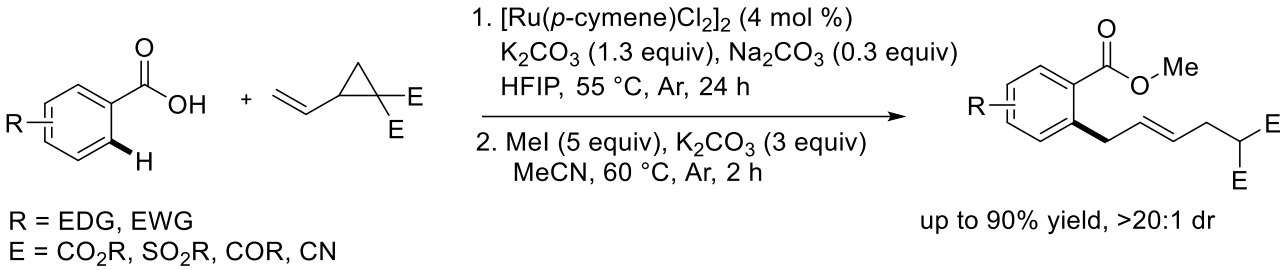
1.1.2.3 Acid as DG

Carboxylic acids, being one of the most prevalent functional groups in organic molecules, serve as a versatile DG in chelation assisted C-H functionalization for further elaboration. In this context, Gooβen and co-workers developed an efficient Ir-catalyzed *ortho*-arylation of benzoic acids with arenediazonium salts for the synthesis of a diverse range of diarylcarboxylates (Scheme 10).[11a] Traceless removal of the DG after reaction or its use in subsequent functionalization, demonstrated the potential utility of the methodology.



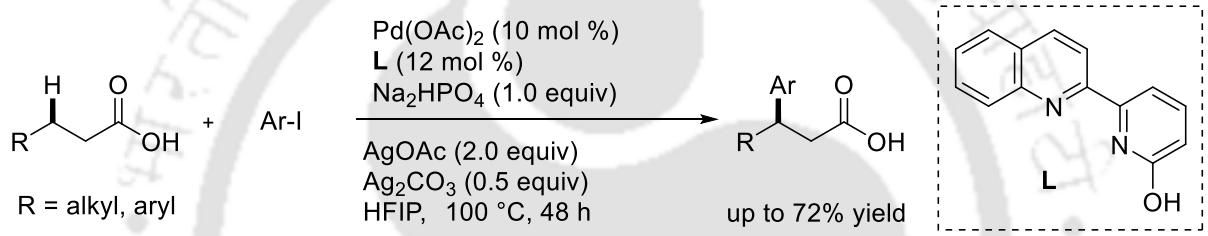
Scheme 10. Ir-Catalyzed *ortho*-Arylation of Benzoic Acids

The Ru-catalyzed *ortho*-allylation of benzoic acids with vinyl cyclopropanes by merging C-H/C-C activation was disclosed (Scheme 11).[11b] The redox-neutral oxidant free approach underscores the practical advantage of the methodology both in terms of sustainability and operational simplicity. In addition, the reaction exhibits good functional group compatibility and follow-up transformations.



Scheme 11. Ru-Catalyzed *ortho*-Allylation with VCPs

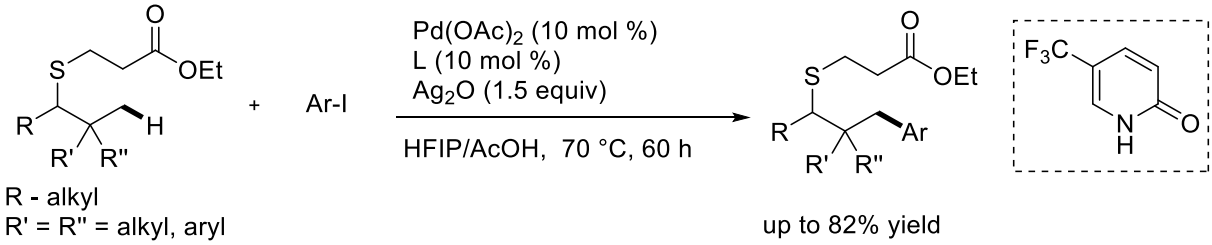
Yu group demonstrated a free-carboxylic-acid directed ligand-enabled Pd-catalyzed *β*-methylene C(sp^3)-H arylation employing iodoarenes (Scheme 12).[11c] The bite angle of the ligand has been found to be the crucial determinant for the success of reaction. A wide variety of arylated carboxylic acid were synthesized, showcasing the broad scope and versatility of the method.



Scheme 12. Pd-Catalyzed *β*-Methylene (sp^3) C-H Arylation

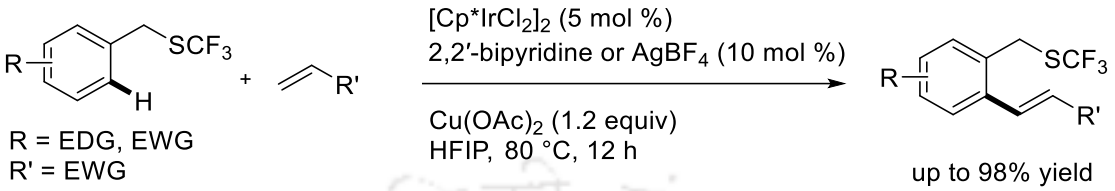
1.1.2.4 Thioether as DG

Thiols can be easily transformed into a variety of sulfur-based functional groups that are widely present in natural products and pharmaceuticals.[12a] Thus, site-selective C-H functionalization using thiols as DG offers a highly appealing strategy for broadening their synthetic utility. Dong group represented Pd-catalyzed *γ*-C(sp^3)-H arylation of thioethers using iodoarenes (Scheme 13).[12b] Due to the convenient installation and removal of ethyl acrylate derived DGs, a one-pot protection/*γ*-C(sp^3)-H arylation/deprotection strategy was successfully implemented to achieve the arylated product in a synthetically useful yield, which further highlights the practicality.



Scheme 13. Sulfur-directed Pd-Catalyzed *γ*-C(sp^3)-H Arylation

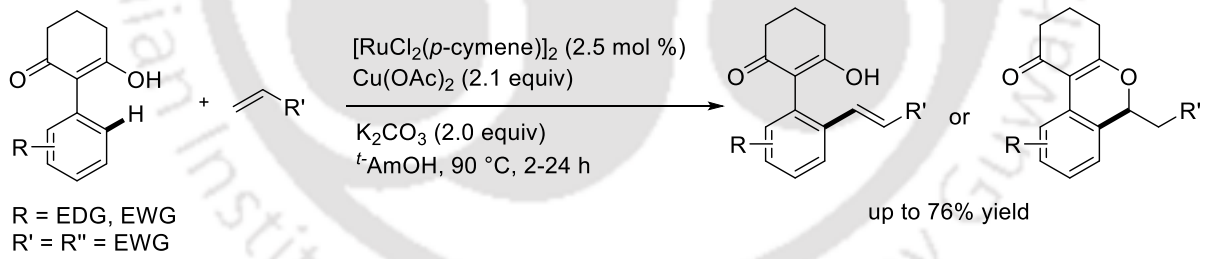
Li and Wang groups utilized -SCF_3 as weak chelating DG for the olefination of aryl C-H bonds utilizing alkene under Ir-catalysis (Scheme 14).[12c] The catalytic activity of substrates with varying electronic properties can be controlled by using 2,2′-bipyridine for electron rich substrates or $AgBF_4$ for electron-deficient ones.



Scheme 14. Ir-Catalyzed mono-C-H Olefination of Arenes

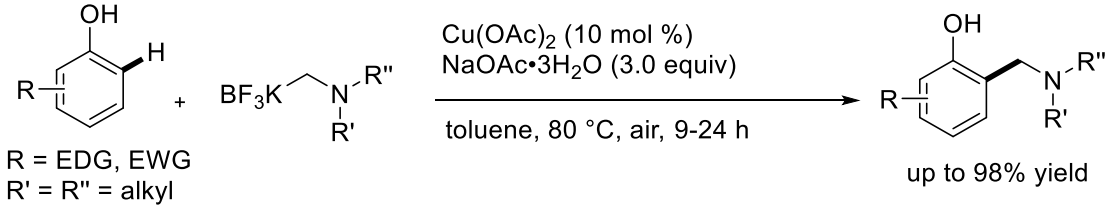
1.1.2.5 Hydroxyl Assistance

Site-selective C-H functionalization using hydroxyl assistance offers an indispensable tool in synthetic chemistry because of their omnipresence in bioactive compounds and interconversion ability. Lam group reported the enol-directed oxidative alkenylations of arene C-H bonds using terminal alkenes under Ru-catalysis (Scheme 15).[13a] Contrastive study between Ru(II)- and Pd(II)-catalysts were conducted, revealing that the Ru(II)-complex was more suitable. In case of electron-deficient alkenes, a subsequent oxa-Michael type addition resulted in the formation of benzopyrans in good yields, while styrenes led to the alkene products.



Scheme 15. Enol Directed Oxidative Alkenylation of Arene C-H Bonds

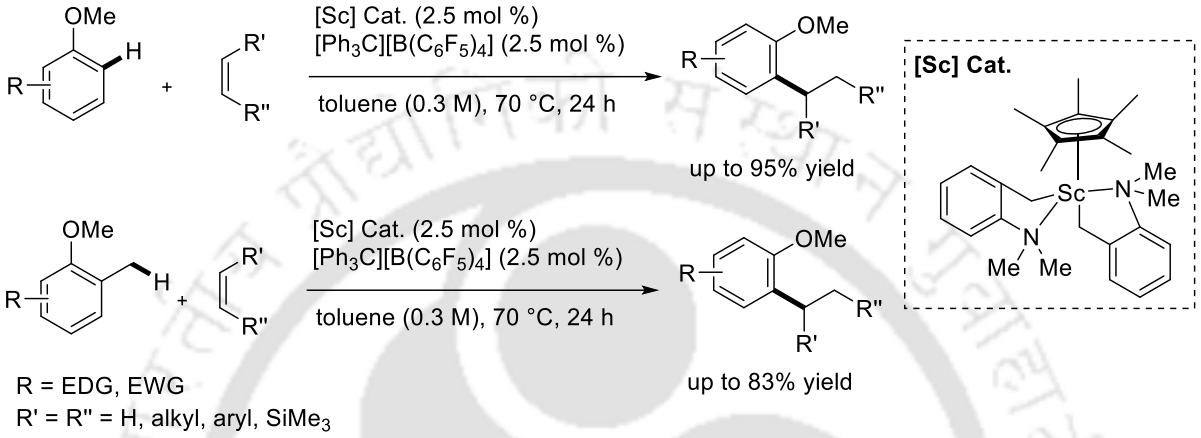
Wang group accomplished the Cu(II)-catalyzed *ortho*-aminomethylation of free phenols with trifluoroborates (Scheme 16).[13b] The method permits the facile synthesis of serine hydrolases inhibitors for MAGL and ABHD6, which are found to be common in enzyme modulators.



Scheme 16. Cu-Catalyzed C-H Aminomethylation of Free Phenols

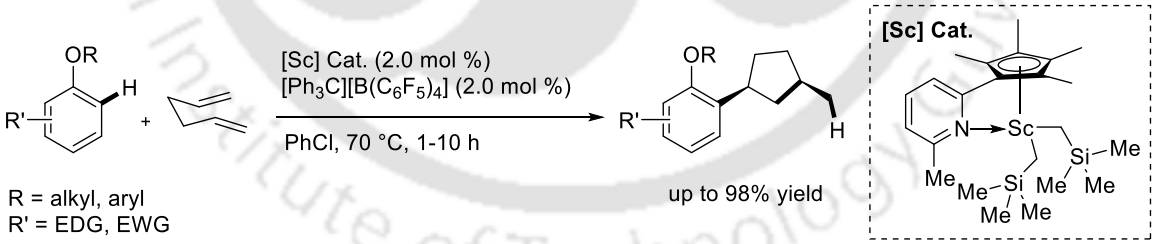
1.1.2.6 Alkoxy DG

Hou and co-workers introduced a half-sandwich scandium dialkyl complex-catalyzed arene C-H alkylation using alkoxy as weak chelating DG (Scheme 17).[14a] However, the use of $[Ph_3C][B(C_6H_5)_4]$ is essential, as it facilitates the formation of a cationic alkyl species when combined with the scandium complex, the active catalyst for the transformation. For 2-methyl anisole derivatives, alkylation selectively occurred at the benzylic C(sp^3)-H bond.



Scheme 17. Directed C-H Alkylation of Anisoles

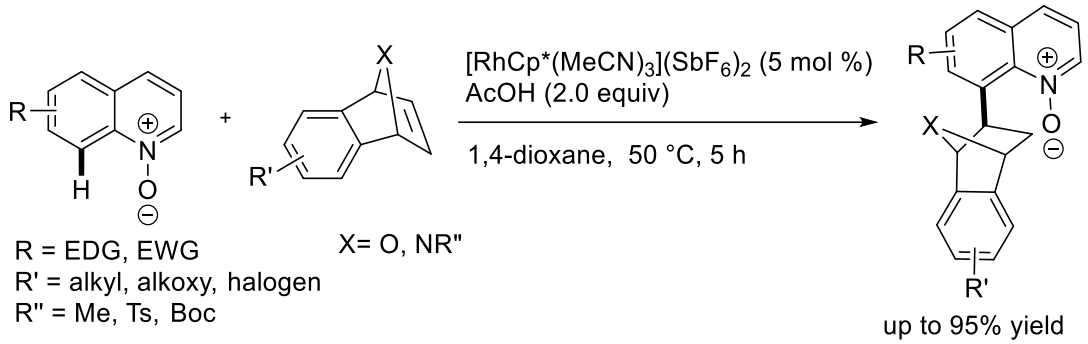
Chen group demonstrated alkoxy directed tandem cyclization/hydroarylation of 1,5-dienes catalyzed by cationic 2-picoline-tethered-half-sandwich-scandium alkyl catalyst (Scheme 18).[14b] High regio- and diastereo-selectivity, mild reaction conditions, substrate scope and atom-economy are the important practical features.



Scheme 18. Alkoxy Directed C-H Hydroarylation of Dienes

1.1.2.7 *N*-oxide as DG

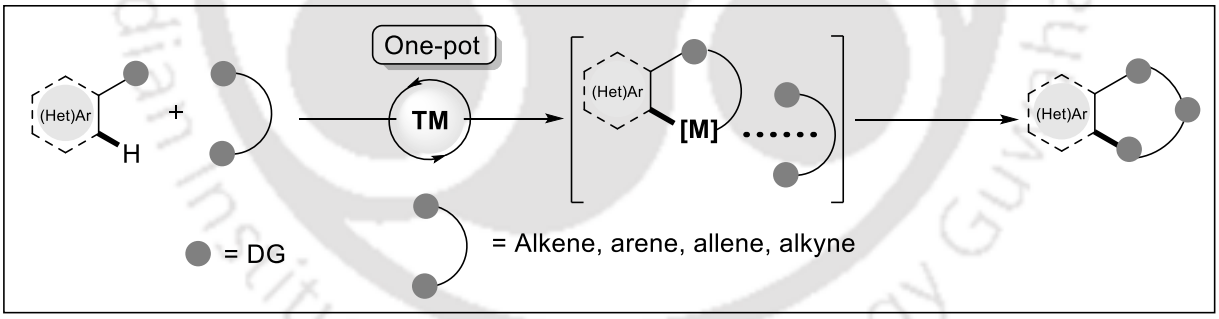
N-Heterocycles are prevalent in pharmaceuticals and functional materials. Utilizing simple *N*-oxide as weak chelating DG, the site selective C-H functionalization is advantageous. Liu group realized an efficient C8-H alkylation of quinoline-*N*-oxides with oxa-/aza-benzonorbornadienes under Rh-catalysis (Scheme 19).[15] The notable features of the protocol include the retention of strained heterobicyclic core in the hydroarylation, regioselectivity, downstream transformations and one-step access to epibatidine synthesis.



Scheme 19. *N*-Oxide Directed C8-H Functionalization of Quinolines

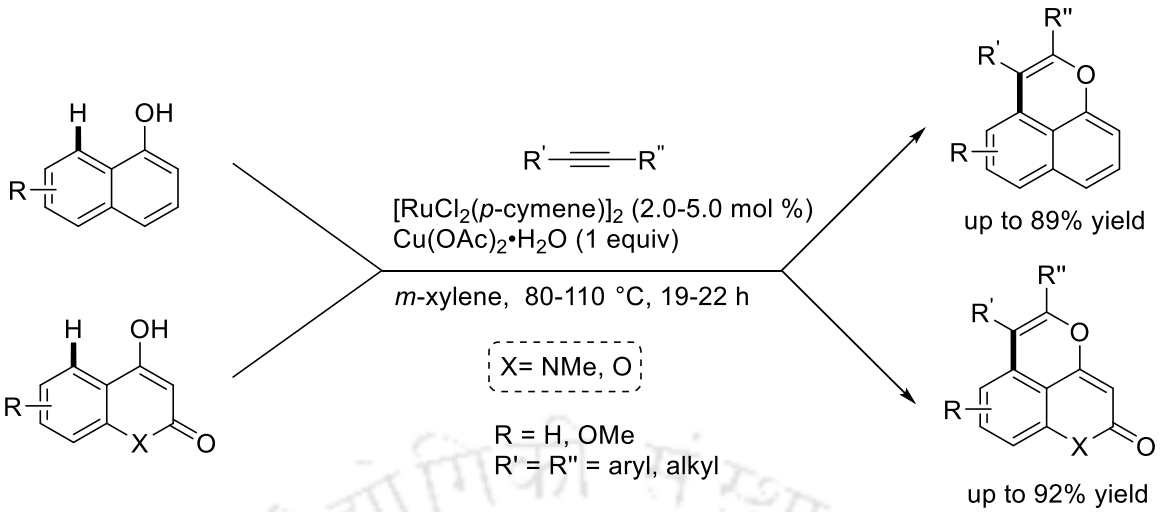
1.2 DG Assisted C-H Functionalization/Annulation

One-pot C-H functionalization and subsequent annulation have emerged as an increasingly effective and attractive strategy to meet the increasing demand for affording diverse heterocycles of synthetic importance in a step- and atom-economic manner (Scheme 20).[16] Functional groups like alcohols, nitrones, carboxylic acids, α-carbonyl sulfoxonium ylides, enaminones etc. serve as potent directing auxiliaries, facilitating the cascade C-H activation and annulation process with exceptional efficiency and selectivity. Alongside, readily accessible and staple coupling partners such as alkynes, alkenes, allenes and diazo compounds have proven to be reliable coupling partners for these transformations.



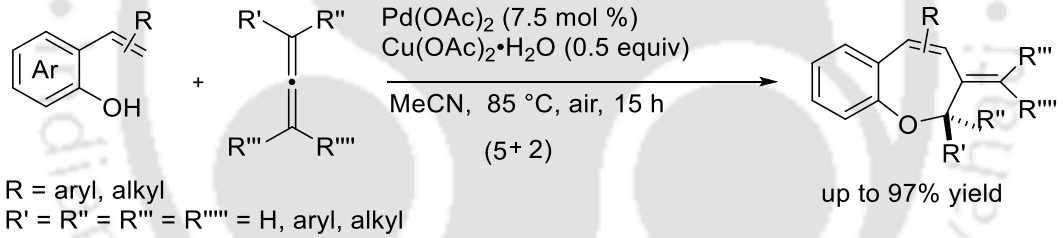
Scheme 20. TM-Catalyzed C-H Functionalization/Annulation Cascade

Ackermann group described the synthesis of fluorescent pyrans *via* hydroxyl assisted Ru-catalyzed oxidative C-H functionalization/annulation of naphthols with alkynes (Scheme 21).[17] The reaction is also feasible for 4-hydroxycoumarin and 4-hydroxy quinoline-2-ones delivering the annulated products with good to excellent yields.



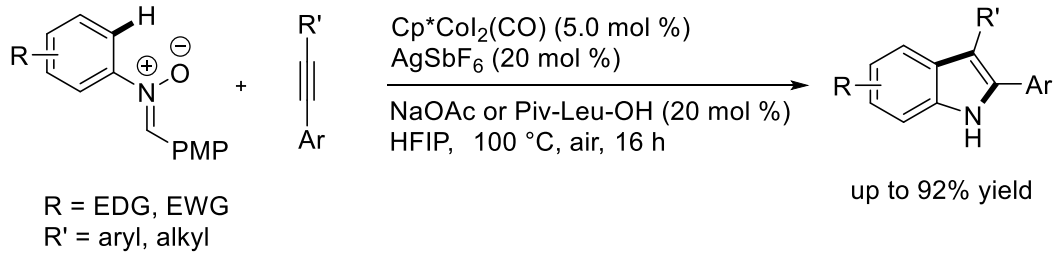
Scheme 21. Hydroxyl Directed Oxidative Annulation with Alkynes

The formal (5+2) annulative coupling of *ortho*-alkenylphenols and allenes for the synthesis of highly appealing benzoxepine has been demonstrated under Pd-catalysis (Scheme 22).[18] Computational studies revealed that the square planner geometry of Pd-catalyst is essential for the reaction, favoring reductive elimination step to generate benzoxepine products.



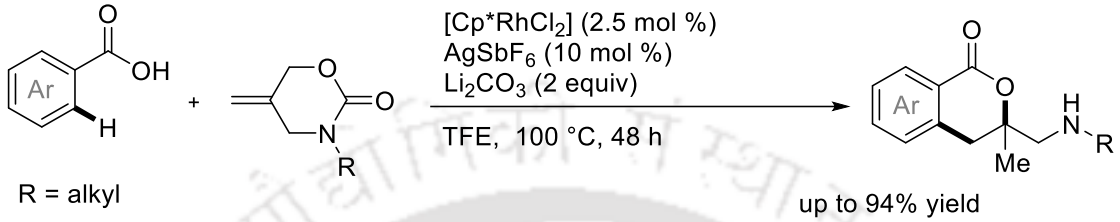
Scheme 22. Pd-Catalyzed (5+2) Annulation of *ortho*-Alkenylphenols with Allenes

Ackermann and co-workers disclosed an elegant approach for the synthesis of indoles *via* redox-neutral C-H/N-O functionalization of nitrones with alkynes under the Co-catalysis (Scheme 23).[19] Broad spectrum of nitrones along with both symmetrical and unsymmetrical alkynes exhibit good compatibility, affording diversely substituted indoles in good yields.



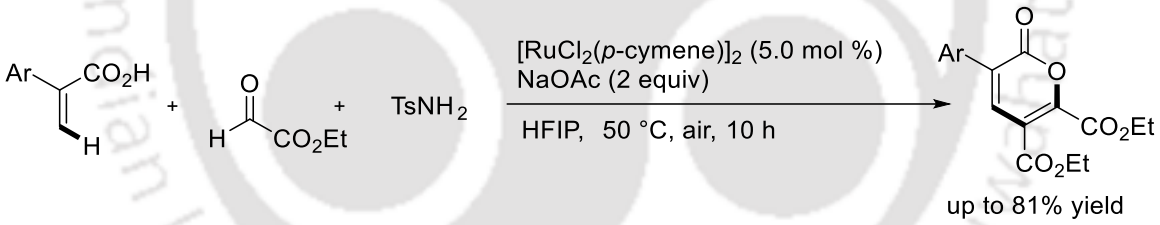
Scheme 23. Co-Catalyzed Redox-neutral Annulation of Nitrones with Alkynes

Huang group reported the Rh-catalyzed redox-neutral C-H/O-H annulation of aryl carboxylic acids with *N*-functionalized cyclic carbonate to access amino-isocoumarins (Scheme 24).[20] The potentiality of the protocol was reflected by late-stage modification of bio-active compounds. Interestingly, an amino-isocoumarin estrone conjugated with selenocyano functionality was found to be fourfold more reactive than the marketed drug abiraterone against T47D cancer cells.



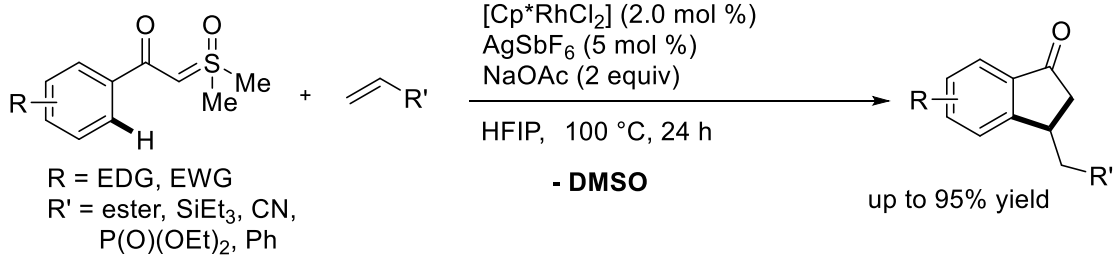
Scheme 24. Rh-Catalyzed Redox-neutral C-H/O-H Annulation

Concurrently, a three-component cascade C-H functionalization/annulation with acrylic acid, ethyl glyoxylate, and *p*-toluenesulfonamide has been reported for the synthesis of pyranones (Scheme 25).[21] The reaction is initiated by the carboxyl directed Ru-catalyzed addition of vinylic C-H bonds to aldehydes. $TsNH_2$ plays a pivotal role for the synthesis of six-membered pyranones.



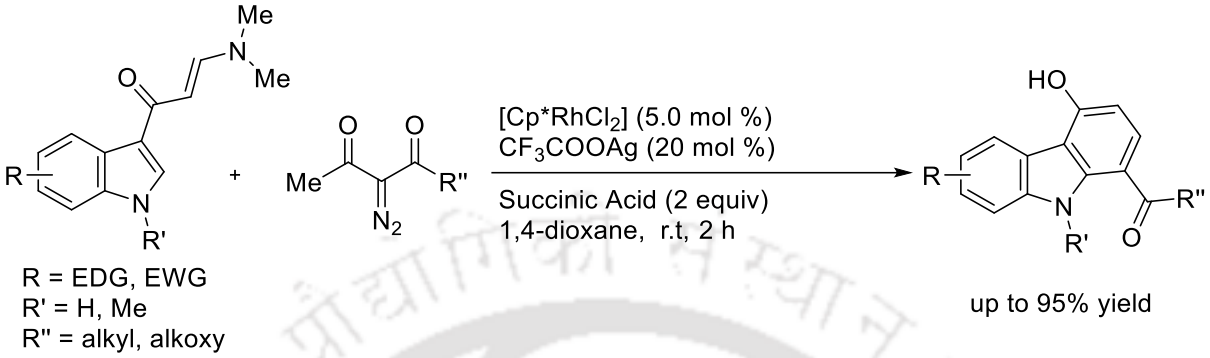
Scheme 25. Ru-Catalyzed Synthesis of Pyranones

Chatani and co-workers demonstrated an efficient synthesis of indanones *via* Rh-catalyzed formal [4 + 1]-annulation of α-carbonyl sulfoxonium ylides with activated alkenes (Scheme 26).[22] Low catalyst loading, dual C-C bond formation and broad functional group compatibility are key practical features of the methodology.



Scheme 26. Rh(III)-Catalyzed [4 + 1] Annulation for the Synthesis of Indanones

Liu and Zhou groups exploited the Rh-catalyzed C-H activation/annulation involving indole-enaminones and diazo compounds to furnish functionalized carbazoles with pharmacological interests (Scheme 27).[23] The protocol featured good functional group tolerance and substrate scope.



Scheme 27. C-H Activation/Annulation of Indole-enaminones with Diazo Compounds

1.3 Objective of the Thesis

The TM-catalyzed weak chelating DG assisted regioselective C-H functionalization has provided an increasingly viable tool in organic synthesis. Most of the procedures demonstrate exceptional functional group tolerance and proceed with excellent yields. However, further exciting developments are yet to be explored in this rapidly growing research arena.

- The utilization of biorelevant molecules as intrinsic DG for the regioselective C-H functionalization are still in their infancy. More research on this area will streamline organic synthesis and offer novel approaches to construct complex molecular architectures in step- and atom-economic manner.
- Although a significant progress has been made in exploring *ortho*-C-H activation, the distal C-H activation remains underdeveloped, requiring further investigations and attention in future studies.
- The C-C Bonds are the strongest and most prevalent in organic molecules. As such, integrating C-H and C-C activation into a unified platform would provide considerable advantages.
- The reliance on activated coupling partners experiences a significant limitation. Approaching towards sequential C-H/C-H cross-coupling and annulation reactions for the one-pot access to pharmaceutically and industrially potent molecules without the need for substrate pre-activation will provide a substantial reward.

- To fully unlock the potential of these methodologies, several issues, such as, developing methods that operate under mild conditions with low catalyst loading and introducing functional groups that are primed for iterative transformations must be addressed.

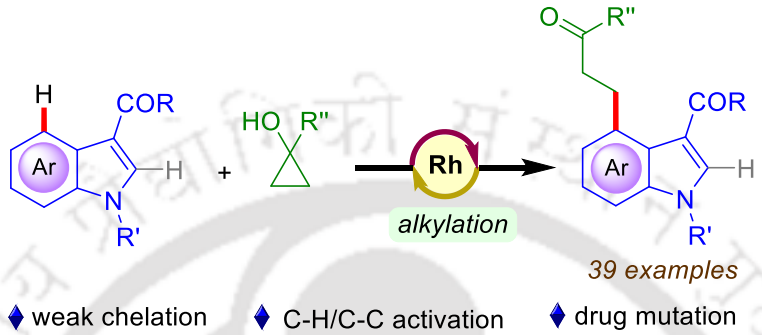
1.4 References

1. For reviews see: (a) Crabtree, R. H. *J. Chem. Soc., Dalton Trans.* **2001**, *17*, 2437. (b) Sun, C.-L.; Li, B.-J.; Shi, Z.-J. *Chem. Rev.* **2011**, *111*, 1293. (c) Kuhl, N.; Hopkinson, M. N.; Wencel-Delord, J.; Glorius, F. *Angew. Chem., Int. Ed.* **2012**, *51*, 10236. (d) Collins, K. D.; Glorius, F. *Nat. Chem.* **2013**, *5*, 597.
2. (a) Furukawa, T.; Tobisu, M.; Chatani, N. *J. Am. Chem. Soc.* **2015**, *137*, 12211. (b) Crabtree, R. H.; Lei, A. *Chem. Rev.* **2017**, *117*, 8481.
3. For reviews see: (a) Wencel-Delord, J.; Glorius, F. *Nat. Chem.* **2013**, *5*, 369. (b) Chen, Z.; Wang, B.; Zhang, J.; Yu, W.; Liu, Z.; Zhang, Y. *Org. Chem. Front.* **2015**, *2*, 1107. (c) Gensch, T.; Hopkinson, M. N.; Glorius, F.; Wencel-Delord, J. *Chem. Soc. Rev.* **2016**, *45*, 2900. (d) Hartwig, J. F.; Larsen, M. A. *ACS Cent. Sci.* **2016**, *2*, 281. (e) Yang, Y.; Lan, J.; You, J. *Chem. Rev.* **2017**, *117*, 8787. (f) Sambiagio, C.; Schonbauer, D.; Blieck, R.; Dao-Huy, T.; Pototschnig, G.; Schaaf, P.; Wiesinger, T.; Zia, M. F.; Wencel-Delord, J.; Besset, T.; Maes, B. U. W.; Schnurch, M. *Chem. Soc. Rev.* **2018**, *47*, 6603. (g) Rej, S.; Das, A.; Chatani, N. *Coord. Chem. Rev.* **2021**, *431*, 213683.
4. For examples see: (a) Murphy, J. M.; Liao, X.; Hartwig, J. F. *J. Am. Chem. Soc.* **2007**, *129*, 15434. (b) Zhang, Y.-H.; Shi, B.-F.; Yu, J.-Q. *J. Am. Chem. Soc.* **2009**, *131*, 5072.
5. (a) Ma, W.; Ackermann, L. *Chem.-Eur. J.* **2013**, *19*, 13925. (b) Ogiwara, Y.; Tamura, M.; Kochi, T.; Matsuura, Y.; Chatani, N.; Kakiuchi, F. *Organometallics* **2014**, *33*, 402. (c) Liu, B.; Li, J.; Hu, P.; Zhou, X.; Bai, D.; Li, X. *ACS Catal.* **2018**, *8*, 9463. (d) Aslam, M.; Mohandoss, S.; Lee, Y. R. *Org. Lett.* **2021**, *23*, 6206.
6. (a) Engle, K. M.; Mei, T.-S.; Wasa, M.; Yu, J.-Q. *Acc. Chem. Res.* **2012**, *45*, 788. (b) De Sarkar, S.; Liu, W.; Kozhushkov, S. I.; Ackermann, L. *Adv. Synth. Catal.* **2014**, *356*, 1461. (c) Martinez de Salinas, S.; Sanjosé-Orduna, J.; Odena, C.; Barranco, S.; Benet-Buchholz, J.; Pérez-Temprano, M. H. *Angew. Chem., Int. Ed.* **2020**, *59*, 6239.
7. Kakiuchi, F.; Sato, T.; Tsujimoto, T.; Yamauchi, M.; Chatani, N.; Murai, S. *Chem. Lett.* **1998**, 27, 1053.
8. Patureau, F. W.; Besset, T.; Glorius, F.; *Angew. Chem., Int. Ed.*, **2011**, *50*, 1064.
9. Pradhan, S.; De, P. B.; Punniyamurthy, T. *Org. Lett.* **2019**, *21*, 9898.

10. (a) Hashimoto, Y.; Hirano, K.; Satoh, T.; Kakiuchi, F.; Miura, M. *Org. Lett.* **2012**, *14*, 2058. (b) Gensch, T.; Vásquez-Céspedes, S.; Yu, D.-G.; Glorius, F. *Org. Lett.* **2015**, *17*, 3714. (c) Li, T.; Shen, C.; Sun, Y.; Zhang, J.; Xiang, P.; Lu, X.; Zhong, G. *Org. Lett.* **2019**, *21*, 7772.
11. (a) Huang, L.; Hackenberger, D.; Gooßen, L. J. *Angew. Chem., Int. Ed.* **2015**, *54*, 12607. (b) Hu, Z.; Hu, X.-Q.; Zhang, G.; Gooßen, L. J. *Org. Lett.* **2019**, *21*, 6770. (c) Hu, L.; Meng, G.; Yu, J.-Q. *J. Am. Chem. Soc.* **2022**, *144*, 20550.
12. (a) Landelle, G.; Panossian, A.; Leroux, F. R. *Curr. Top. Med. Chem.* **2014**, *14*, 941. (b) Jin, L.; Wang, J.; Dong, G. *Angew. Chem. Int. Ed.* **2018**, *57*, 12352. (c) Bao, R.-P.; Chen, X.; Li, C.; Wang, D.-H. *Org. Lett.* **2019**, *21*, 8116.
13. (a) Reddy Chidipudi, S.; Wieczysty, M. D.; Khan, I.; Lam, H. W. *Org. Lett.* **2013**, *15*, 570. (b) Dai, J.-L.; Shao, N.-Q.; Zhang, J.; Jia, R.-P.; Wang, D.-H. *J. Am. Chem. Soc.* **2017**, *139*, 12390.
14. (a) Oyamada, J.; Hou, Z. *Angew. Chem., Int. Ed.* **2012**, *51*, 12828. (b) Tang, B.; Hu, X.; Liu, C.; Jiang, T.; Alam, F.; Chen, Y. *ACS Catal.* **2019**, *9*, 599.
15. Li, D.-Y.; Huang, Z.-L.; Liu, P.-N. *Org. Lett.* **2018**, *20*, 2028.
16. For reviews on C-H functionalization/annulation see: (a) Ackermann, L. *Acc. Chem. Res.* **2014**, *47*, 281. (b) Liang, Y. F.; Yang, L.; Rogge, T.; Ackermann, L. *Chem. Eur. J.* **2018**, *24*, 16548. (c) Song, L.; Van der Eycken, E. V. *Chem. Eur. J.* **2021**, *27*, 121.
17. Thirunavukkarasu, V. S.; Donati, M.; Ackermann, L. *Org. Lett.* **2012**, *14*, 3416.
18. Casanova, N.; Del Rio, K. P.; García-Fandiño, R.; Mascareñas, J. L.; Gulías, M. *ACS Catal.* **2016**, *6*, 3349.
19. Wang, H.; Moselage, M.; González, M. J.; Ackermann, L. *ACS Catal.* **2016**, *6*, 2705.
20. Zhang, Y.; Wang, H.; Bai, J.; Liu, Q.; Cui, J.; Huang, Y. *Org. Lett.* **2022**, *24*, 9222.
21. Yu, S.; Hong, C.; Liu, Z.; Zhang, Y. *Org. Lett.* **2022**, *24*, 4871.
22. Kommagalla, Y.; Ando, S.; Chatani, N. *Org. Lett.* **2020**, *22*, 1375.
23. Jiang, Z.; Zhou, J.; Zhu, H.; Liu, H.; Zhou, Y. *Org. Lett.* **2021**, *23*, 4406.

Chapter II

Rh-Catalyzed C4-H Alkylation of Indoles with Cyclopropanols



♦ weak chelation ♦ C-H/C-C activation ♦ drug mutation

Org. Lett. **2022**, *24*, 6000.

Rh-Catalyzed C4-H Alkylation of Indoles with Cyclopropanols

The indole framework is one of the cardinal constituents in a myriad of natural products, pharmaceuticals and functional materials.[1] Thus, the development of concise and efficient methods for facile diversification of the six different C-H bonds present in indole core have consistently captivated the interest of scientific chemistry community.[2] The C2 and C3 functionalizations of indole core have been well documented due to the inherent nucleophilicity of the pyrrole ring.[3] However, the selective functionalization of remote and less-reactive C-H bonds at the benzenoid segment (C4-C7) remains elusive.[4,5] Especially, there is a growing impetus within the scientific community towards C4-modification of indole because of their profound biological relevance (Figure 1).[6] However, a substantial challenge arises to access the remote C4-site from the preferential formation of five-membered metallacycle at the C2-position over six-membered metallacycle at C4-position, with a directing group (DG) installed at the C3-site of indole (Scheme 1). To overcome this obstacle, a suitably tailored C3-tethered DG is highly sought-after that can lead to the exclusive C4-selective functionalization over the competing C2-functionalization. In this context, elegant approaches have been made for the TM-catalyzed directed C4-H functionalization of indoles, such as amidation,[7a] olefination,[7b,f] borylation,[7c] allylation[7d] and arylation[7g]. Particularly, C4-alkylated indoles have remarkable importance in natural product synthesis and medicinal science.[6] Consequently, devising an efficient protocol for their synthesis is highly desirable. Meanwhile, the strained ring chemistry has emerged as a powerful platform for the development of molecular complexity in a step- and atom-economic manner.[8] In this context, cyclopropanols are considered as the most attractive coupling partners for the site-selective alkylation *via* C-C bond activation because of their easy preparation and rich reactivity.[9] Hence merging C-H and C-C activations for molecular diversification, although challenging in practice, offers considerable potential. This chapter describes a Rh(III)-catalyzed weak coordination guided C4-H alkylation of indoles with easily accessible and bench stable cyclopropanols as coupling partner *via* tandem C-H/C-C bond activation. The reaction can be extended for the site-selective C-H alkylation of other heteroaromatics, such as benzo[*b*]thiophene, indoline and tetrahydroisoquinoline. The key advantages include regioselectivity, tandem C-H functionalization/C-C bond cleavage, ample substrate scope and post-synthetic utilities.

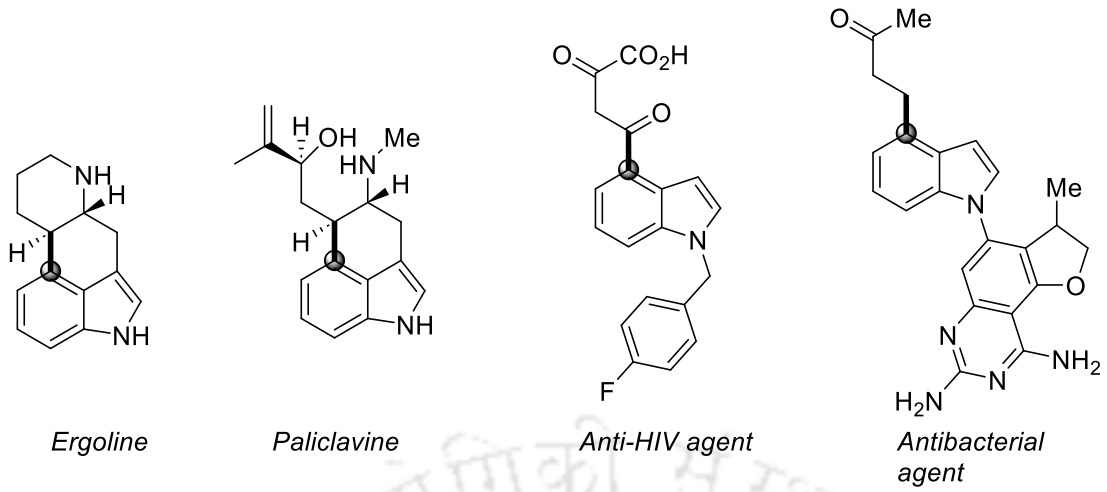
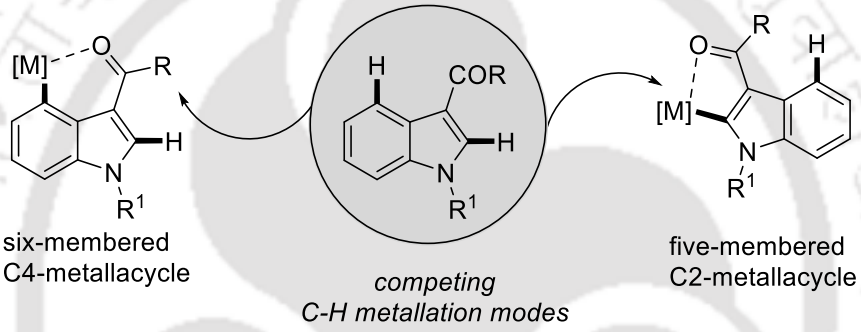


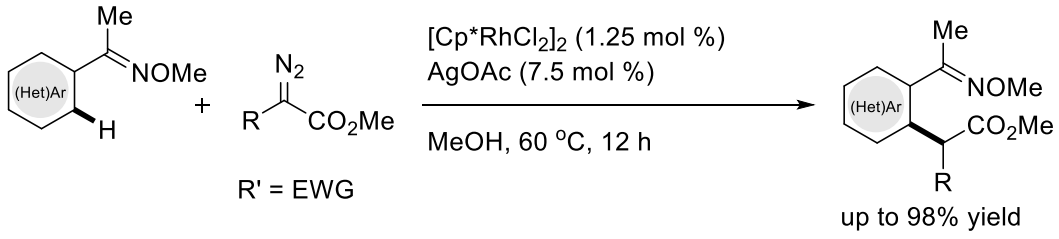
Figure 1. Selected Examples of Biologically Potent C4-Alkylated Indoles.



Scheme 1. Challenges of C4-Functionalization of Indoles

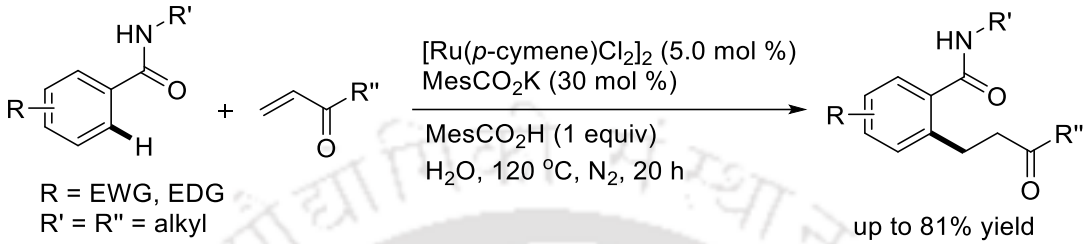
2.1. TM-Catalyzed C-H Alkylation of (Hetero)arenes

Yu and co-workers demonstrated oxime directed base free Rh-catalyzed *ortho*-C-H alkylation of arenes with α-diazomalonates (Scheme 2).[10] The reaction produces environmentally benign N_2 as the sole byproduct. A wide variety of alkylated products were obtained in good to excellent yields, showcasing functional group compatibility. Moreover, the method provides a highly efficient route to naphthalene.



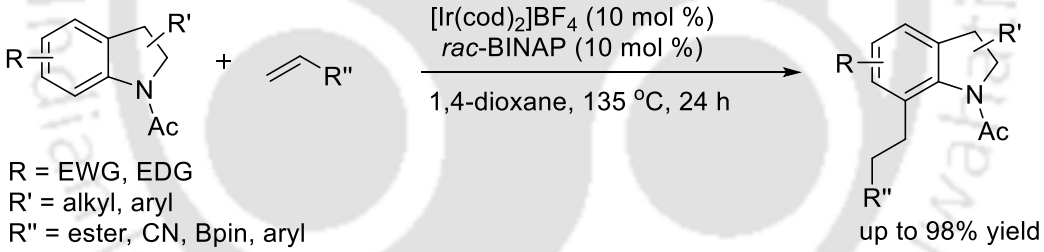
Scheme 2. Rh-Catalyzed *ortho*-Alkylation of Arenes

Ackermann and co-workers documented the Ru-catalyzed oxidative C-H alkylation of acetanilides with α,β-unsaturated ketones (Scheme 3).[11] The reaction proceeds *via* carboxylate assistance and the aqueous conditions render the method environmentally benign. Further, the procedure provides a step-economic approach for the synthesis of diverse quinolines.



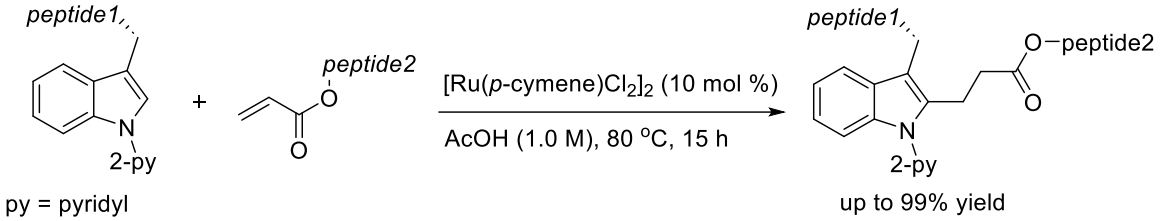
Scheme 3. Ru-Catalyzed *ortho*-Alkylation of Arenes

The carbonyl directed a cationic Ir-catalyzed C7-alkylation of indolines with alkenes was reported by Shibata and co-workers (Scheme 4).[12] A diverse array of C7-alkylated indoles were obtained in moderate to good yields.



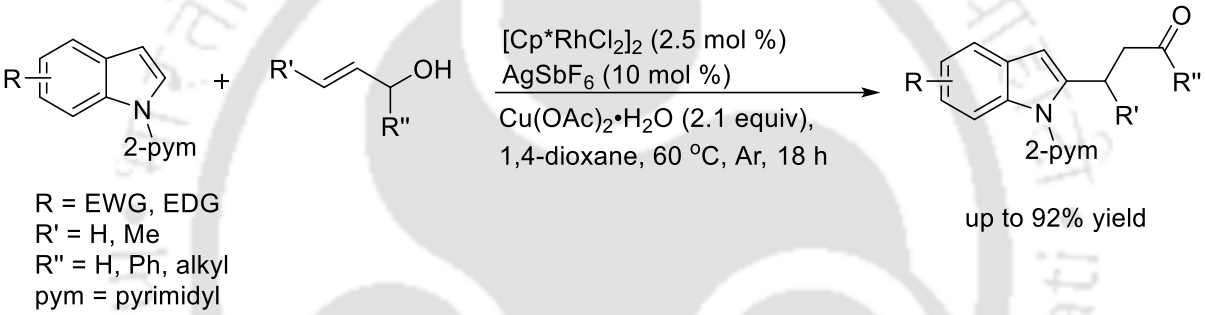
Scheme 4. Ir-Catalyzed C7-Alkylation of Indolines

Ackermann and co-workers accomplished an efficient methodology for the Ru(II)-catalyzed late-stage peptide C-H alkylation on user-friendly resin support (Scheme 5).[13] The detailed mechanistic study revealed that the reaction involves acid-enabled C-H ruthenation, alkene coordination, migratory insertion and protodemetalation to deliver the alkylated product. The method showcased a broad substrate scope with excellent tolerance to reactive functional groups such as ketone, ester, amide and nitro.



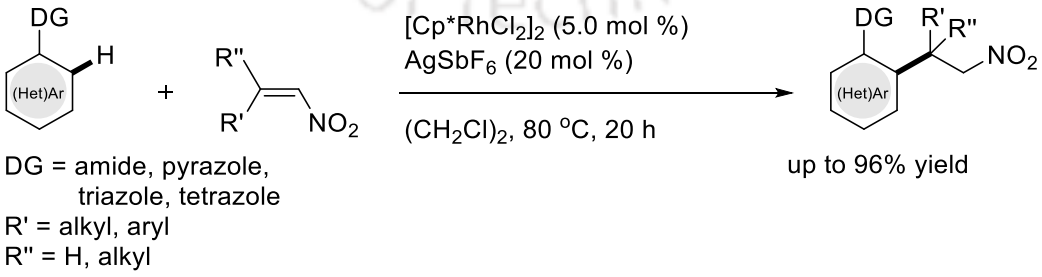
Scheme 5. Ru-Catalyzed Late-stage Peptide C-H Alkylation

Glorius and co-workers developed a robust Rh(III)-catalyzed dehydrogenative C2-alkylation of indoles with allylic alcohols (Scheme 6).[14] The reaction provides diverse array of *β*-aryl ketones and aldehydes with good to excellent yields. The strategy was further extended to arene systems, including 2-phenylpyridine, aryl ketones and acetanilides, yielding a variety of value-added scaffolds.



Scheme 6. Rh-Catalyzed C2-H Alkylation of Indoles

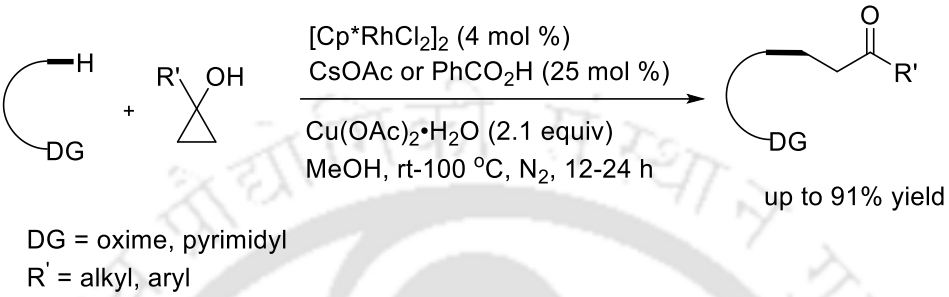
Ellman and co-workers realized arene C-H bond addition to diverse nitroalkenes under Rh-catalysis (Scheme 7).[15] Different DGs, such as amide, pyrazole, triazole and tetrazole proved effective. Selected nitroalkane products were seamlessly converted to dihydroisoquinolones and dihydropyridones through iron-mediated reduction followed by in-situ cyclization.



Scheme 7. Rh-Catalyzed *ortho*-Alkylation of (Hetero)arenes

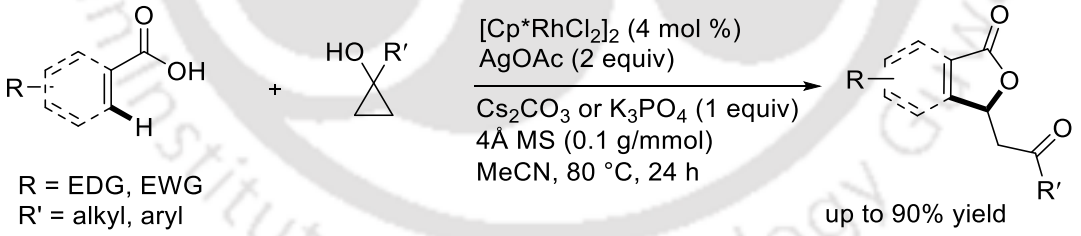
2.2 Reactivity of Arenes with Cyclopropanols

Li and co-workers employed cyclopropanols in the Rh-catalyzed oxidative arene C-H alkylation (Scheme 8).[9b] The method offers an effective route to access diverse range of *β*-aryl ketones, potentially merging the C-H activation and ring opening of cyclopropanol. In addition, the reaction was extended for C(sp^3)-H alkylation of 8-methylquinolines.



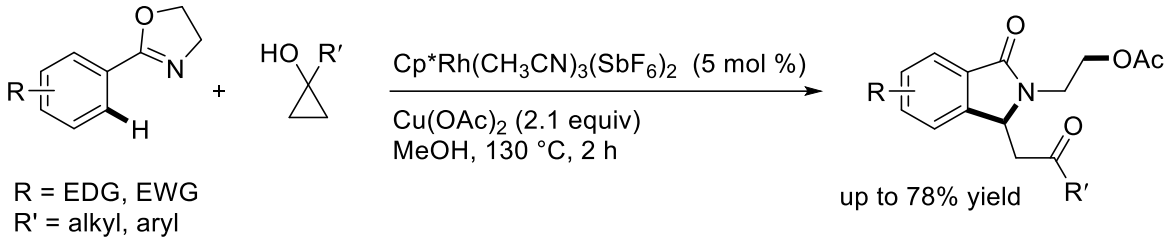
Scheme 8. Rh-Catalyzed C-H Alkylation with Cyclopropanols

The Rh(III)-catalyzed annulation of benzoic acids with cyclopropanols was described to access 3-substituted phthalides and *α,β*-butenolides *via* tandem C(sp^2)-H activation, ring opening C-C cleavage and cyclization (Scheme 9).[16] The reaction displayed versatile substrate scope and showcased its utility by the rapid synthesis of bioactive compounds by late-stage functionalization.



Scheme 9. Rh-Catalyzed Annulation with Cyclopropanols

Liu and Liu groups described the synthesis of C3-substituted isoindoline-1-ones by the Rh(III)-catalyzed oxidative cyclization of oxazolines with cyclopropanols (Scheme 10).[17] The reaction showed broad scope and functional group tolerance on both the substrates.



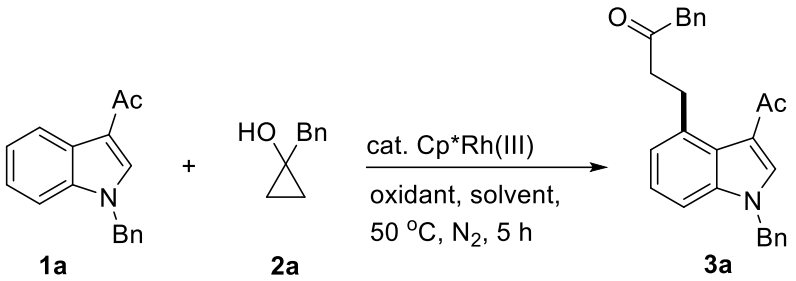
Scheme 10. Rh-Catalyzed Tandem C-H/C-C Activation/Annulation with Cyclopropanols

2.3 Present Study

Herein, we demonstrated the Rh(III)-catalyzed weak carbonyl chelation-assisted distal C4-H alkylation of indoles using cyclopropanols as a coupling partner *via* a cascade C-H/C-C bond activation. At the outset, our optimization studies were carried out using 1-(1-benzyl-1*H*-indol-3-yl)ethan-1-one **1a** and 1-benzylcyclopropan-1-ol **2a** as the test substrates under varied oxidants and solvents (Table 1). A combination of 3 mol % $[Cp^*RhCl_2]_2$ and 50 mol % AgOAc in the presence of substrates **1a** and **2a** in TFE at 50 °C for 5 h under N_2 provided the target product **3a** in 23% yield (entry 1). The structure of **3a** was determined using single crystal X-ray analysis. Further screening of oxidants revealed that $Cu(OAc)_2 \cdot H_2O$ was most effective affording 81% yield, while oxidants like Ag_2CO_3, Ag_2O, $K_2S_2O_8$, $Cu(OAc)_2$, Cu_2O produced inferior outcomes (entries 2-7). A survey of solvents with varying polarities showed TFE as the solvent of choice, whereas MeOH, HFIP, toluene, $(CH_2Cl)_2$, THF did not improve the yield (entries 8-12). $Rh_2(OAc)_4$ was ineffective in producing the desired product, while $[Cp^*Rh(CH_3CN)_3](SbF_6)_2$ gave 52% yield (entries 13-14). Reducing the amount of oxidant or lowering temperature led to a decrease in product yield (entries 15-16). Control experiments confirmed that no alkylation occurred in the absence of catalyst or oxidant (entries 17-18). Thereafter, we examined the efficacy of different weak DGs. Among formyl **1a′**, trifluoroacetyl **1b′**, benzoyl **1c′** and carboxyl **1d′**, only the former delivered product **3a′** in 57% yield, which suggests electronic nature of DG is crucial for successful alkylation (Table 2).

With the optimized reaction conditions, we tested the scope of the method with diversely substituted indoles **1b-v** using **2a** as the standard substrate (Table 3). 2-Methylindole **1b** underwent the reaction to deliver **3b** in 73% yield, whereas indoles with 5-bromo **1c** and 5-methyl **1d** groups were unreactive, likely due to the steric hindrance. However, substrates having 5-fluoro **1e** and 5-methoxy **1f** afforded the target products **3e-f** in 66-72% yields. Further, indoles having substituents at the C6-position such as bromo **1g**, chloro **1h**, fluoro **1i** and *p*-methoxy phenyl (PMP) **1j** gave the target products **3g-j** in 68-75% yields. Intriguingly,

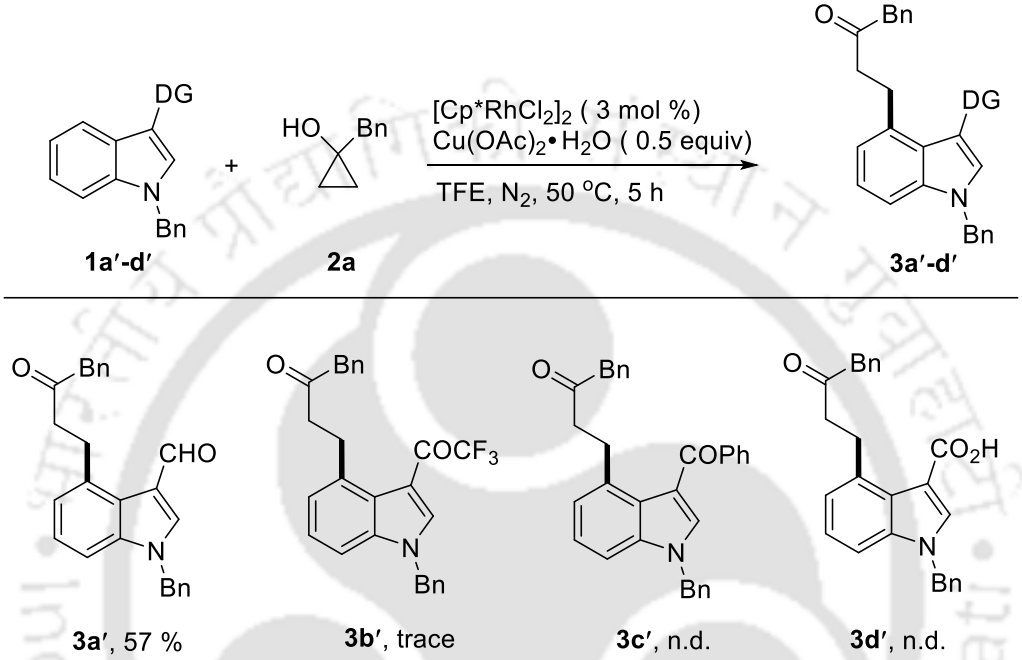
Table 1. Optimization of the Reaction Conditions[a]



Entry	Oxidant	Solvent	Yield (%) [b]
1	AgOAc	TFE	23
2	Ag_2CO_3	TFE	30
3	Ag_2O	TFE	n.d.
4	$K_2S_2O_8$	TFE	n.d.
5	**$Cu(OAc)_2·H_2O$**	**TFE**	**81**
6	$Cu(OAc)_2$	TFE	41
7	Cu_2O	TFE	n.d.
8	$Cu(OAc)_2·H_2O$	MeOH	32
9	$Cu(OAc)_2·H_2O$	HFIP	trace
10	$Cu(OAc)_2·H_2O$	toluene	n.d.
11	$Cu(OAc)_2·H_2O$	$(CH_2Cl)_2$	n.d.
12	$Cu(OAc)_2·H_2O$	THF	n.d.
13[c]	$Cu(OAc)_2·H_2O$	TFE	n.d.
14[d]	$Cu(OAc)_2·H_2O$	TFE	52
15[e]	$Cu(OAc)_2·H_2O$	TFE	61
16[f]	$Cu(OAc)_2·H_2O$	TFE	45
17[g]	$Cu(OAc)_2·H_2O$	TFE	n.d.
18	-	TFE	n.d.

[a]Reaction conditions: **1a** (0.1 mmol), **2a** (0.2 mmol), $[Cp^*RhCl_2]_2$ (3 mol %), oxidant (0.05 mmol), solvent (1 ml), 50 °C, 5 h, N_2. [b]Isolated yield. [c]Using 3 mol % $Rh_2(OAc)_4$. [d]Using 3 mol % $[Cp^*Rh(CH_3CN)_3](SbF_6)_2$. [e]Using 20 mol % $Cu(OAc)_2 \cdot H_2O$ [f]Room temperature 25 °C. [g]Without $[Cp^*RhCl_2]_2$. n.d. = not detected.

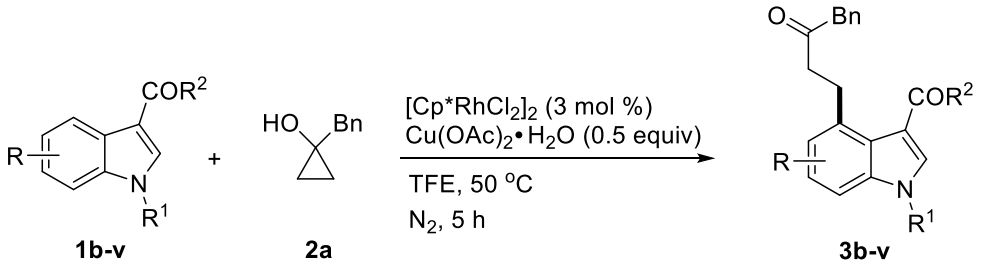
Table 2. Screening of Different Weak Chelating Directing Groups[a,b]

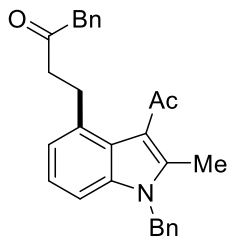


[a]Reaction conditions: **1a′-d′** (0.1 mmol), **2a** (0.2 mmol), $[Cp^*RhCl_2]_2$ (3 mol %), $Cu(OAc)_2 \cdot H_2O$ (0.05 mmol), TFE (1 ml), 50 °C, 5 h, N_2. [b]Isolated yield.

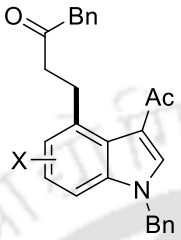
heterocyclic 3-furanyl substituted indole **1k** at the C6-site was amenable to furnish **3k** in 59% yield. Similar results were observed for the substrates with chloro **1l**, methyl **1m**, and methoxy **1n** at the C7-position providing **3l-m** in 73-75% yields. In addition, fused indoles **1o** and **1p** smoothly alkylated to give **3o** and **3p** in 64% and 61 % respectively. Delightfully, *N*H-free indole substrate **1q** was compatible to deliver **3q** in 54% yield. Other *N*-substituted indole, *N*-octyl **1r** provided **3r** in 68% of yield, while *N*-Boc **1s** was unsuccessful substrate. The reaction of 3-hexanoyl indole **1t** took place efficiently to give **3t** in 77% yield. Moreover, the strategy can be expanded to the late-stage modifications of natural products and drug molecules, such as sesamol and gemfibrozil derived indoles **1u** and **1v** afforded **3u** and **3v** in 70% and 68% yields, respectively, showcasing the applicability of the process.

Table 3. Substrate Scope of Indoles

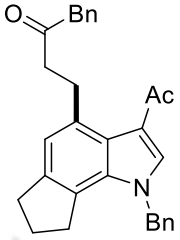




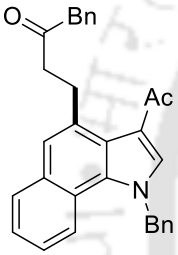
3b, 73%



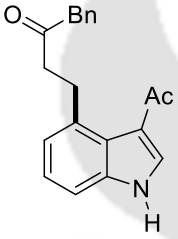
X = 5-Br, **3c**, n.d.
= 5-Me, **3d**, trace
= 5-F, **3e**,72%
= 5-OMe, **3f**, 66%
= 6-Br, **3g**, 68%
= 6-Cl, **3h**, 70%
= 6-F, **3i**, 72%
= 6-PMP, **3j**, 75%
= 6-(3-furanyl), **3k**, 59%
= 7-Cl, **3l**, 74%
= 7-Me, **3m**, 73%
= 7-OMe, **3n**, 75%



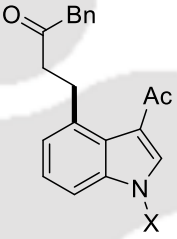
3o, 64%



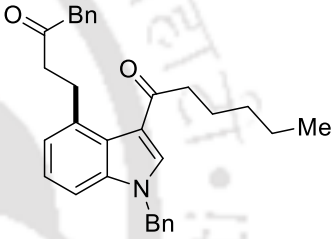
3p, 61%



3q, 54%

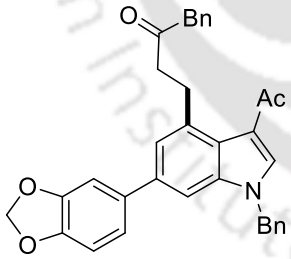


3r, X = $(CH_2)_7CH_3$, 68%
3s, X = Boc, n.d.

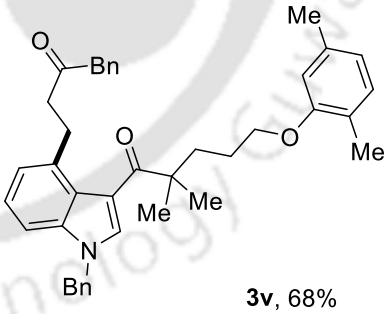


3t,77%

natural product and drug mutation



3u, 70%
from ***Sesamol***

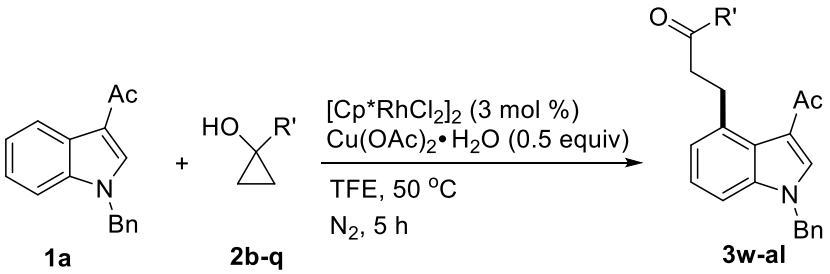


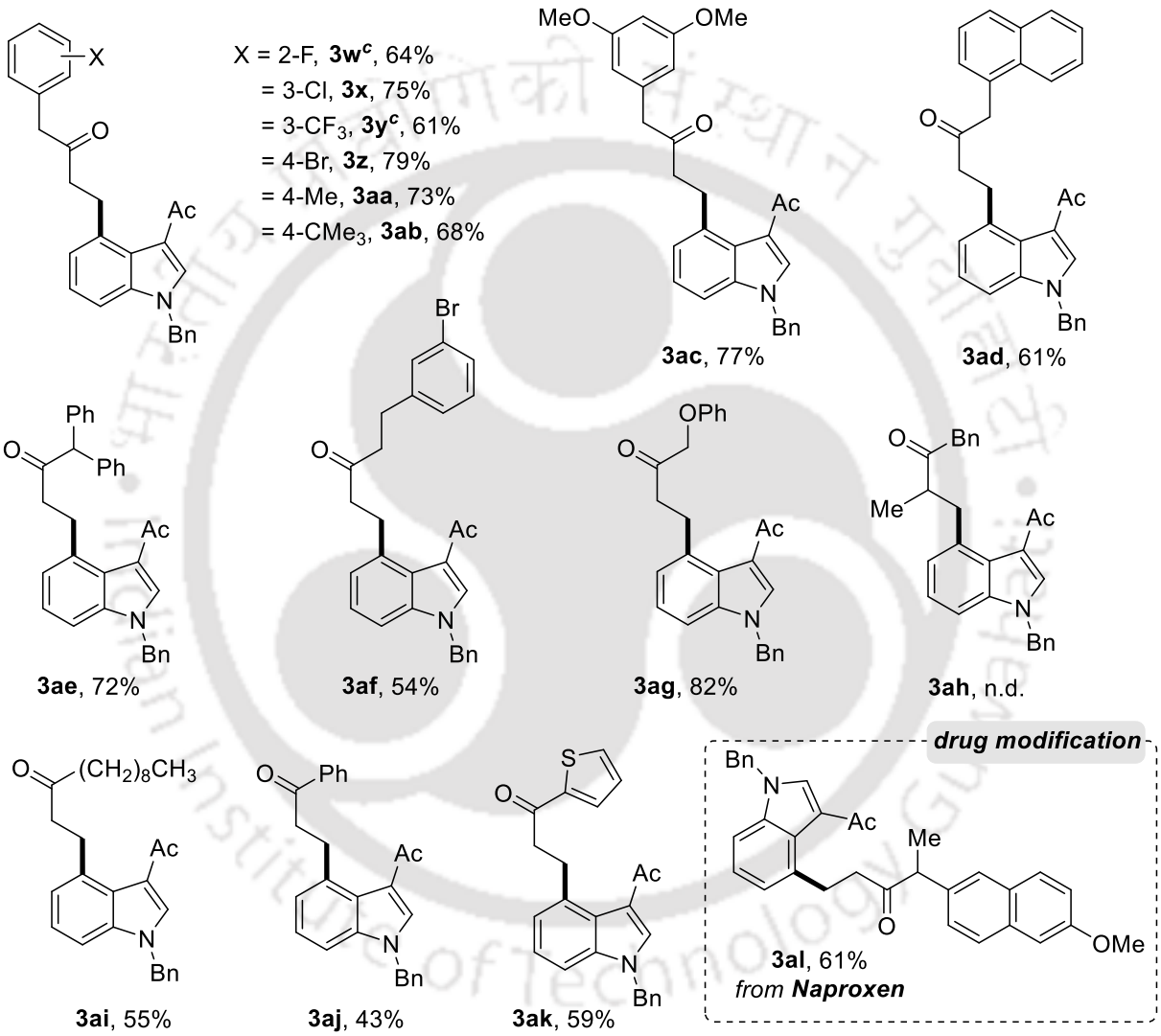
3v, 68%
from ***Gemfibrozil***

[a]Reaction conditions: **1b-m** (0.1 mmol), **2a** (0.2 mmol), $[Cp^*RhCl_2]_2$ (3 mol %), $Cu(OAc)_2 \cdot H_2O$ (0.05 mmol), TFE (1 ml), 50 °C, 5 h, N_2. [b]Isolated yield.

Scope of the method was further explored for a series of cyclopropanols **2b-q** with **1a** as the standard substrate. Diverse electronic substituents on the phenyl ring of cyclopropanol **2b-h** coupled smoothly, yielding **3w-3ac** in 61-79% yields. 1-Methylnaphthyl **2i**, diphenylmethyl **2j**, 1-bromo-3-ethylphenyl **2k** and 1-phenoxymethyl **2l** substituted cyclopropanols found to

Table 4. Substrate Scope of Cyclopropanols[a,b,c]

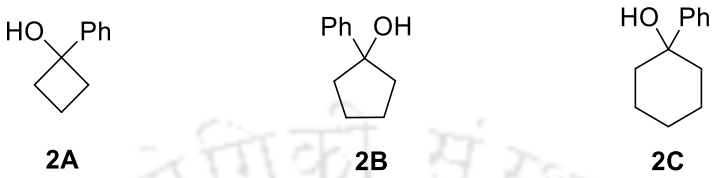




[a]Reaction conditions: **1a** (0.1 mmol), **2b-m** (0.2 mmol), $[Cp^*RhCl_2]_2$ (3 mol %), $Cu(OAc)_2 \cdot H_2O$ (0.05 mmol), TFE (1 ml), 50 °C, 5 h, N_2. [b]Isolated yield. [c]Reaction for 12 h.

be amenable, giving the target products **3ad-ag** in 54-82% yields. 1,2-Disubstituted cyclopropanol **2m** was unsuccessful substrate, which might be attributed to the steric encumbrance. However, aliphatic 1-nonyl substituted cyclopropanol **2n** delivered **3ai** in 55%

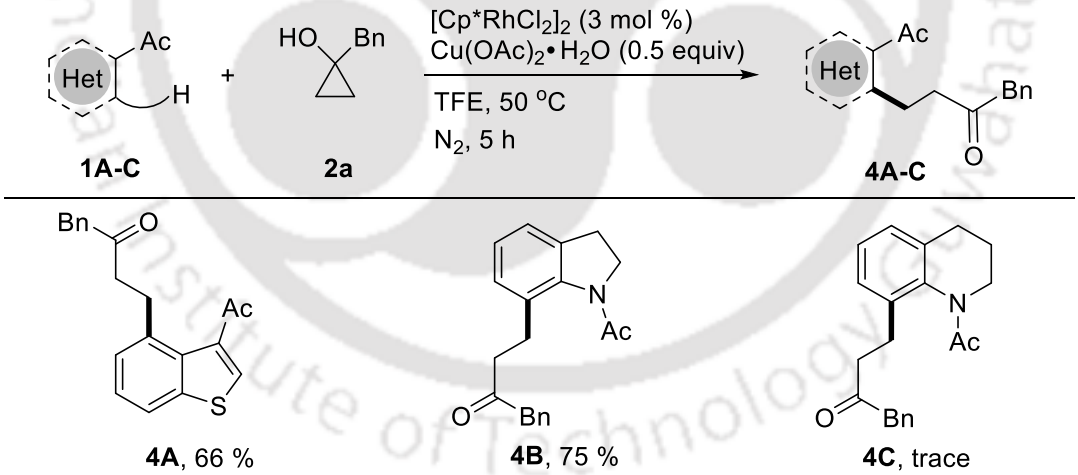
yield. Aryl and heteroaryl-substituted cyclopropanols **2o-p** were compatible, providing **3aj-ak** in 43-59% yields. The reaction exhibits significant tolerance towards substrates derived from the drug molecule, naproxen derivative **2q** reacted to furnish **3al** in 61% yield. Notably, cycloalkanols with lower strain, 1-phenylcyclobutan-1-ol **2A**, 1-phenylcyclopentan-1-ol **2B** and 1-phenylcyclohexan-1-ol **2C** remained silent under the reaction conditions (Scheme 11).



Scheme 11. Investigation on Reactivity of Less Strained Cycloalkanols

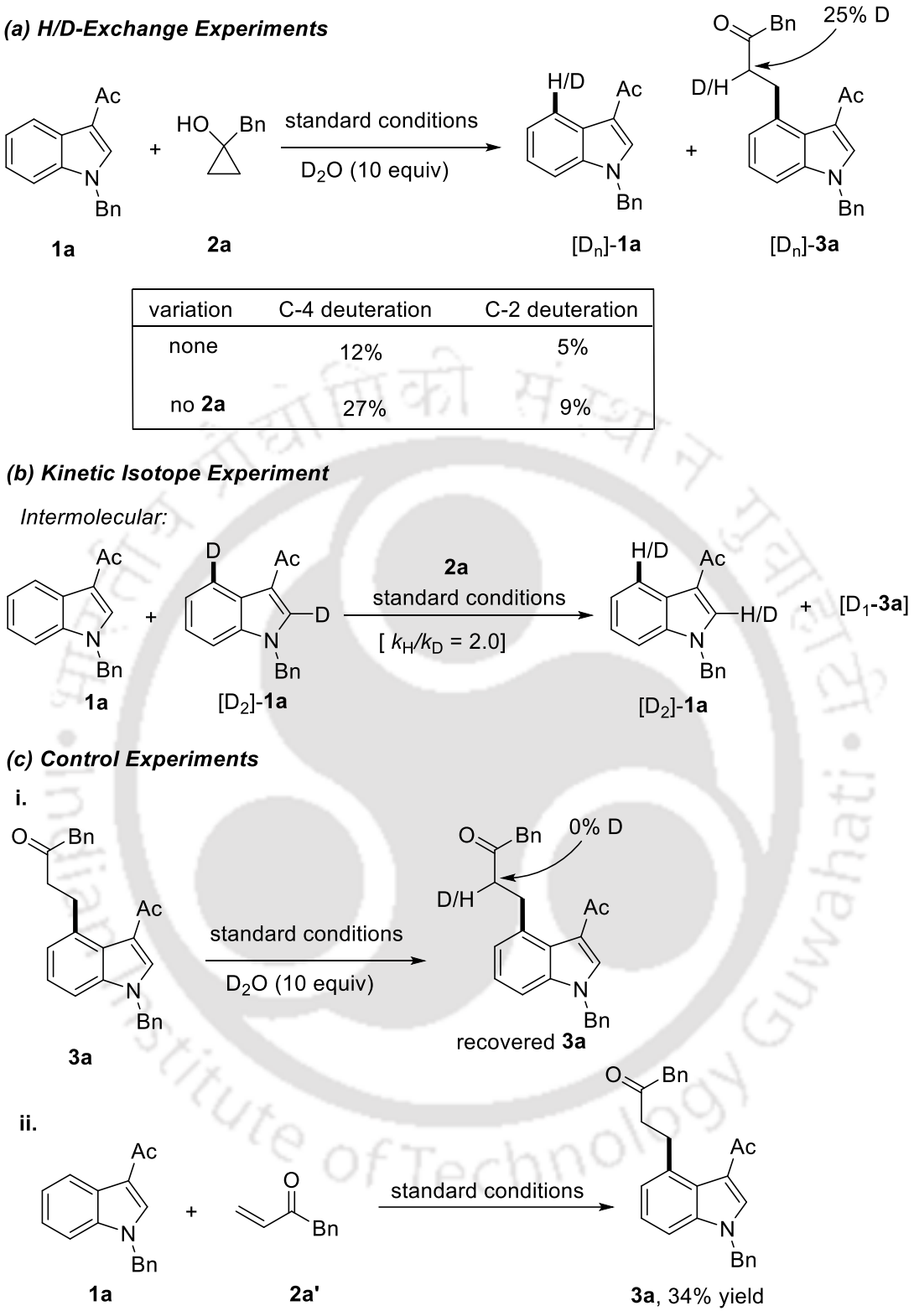
Next, to diversify the scope of the method, we explored the alkylation on heteroaromatics, such as benzo[*b*]thiophene **1A**, indoline **1B** and tetrahydroisoquinoline **1C** (Table 5). Substrates **1A-B** coupled smoothly to afford **4A-B** in 66-75% yields, whereas the reaction with 1,2,3,4-tetrahydroquinoline **1C** gave a trace amount of alkylated product.

Table 5. Scope of Weak-coordinating Substrates[a,b]



[a]Reaction conditions: **1A-C** (0.1 mmol), **2a** (0.2 mmol), $[Cp^*RhCl_2]_2$ (3 mol %), $Cu(OAc)_2 \cdot H_2O$ (0.05 mmol), TFE (1 ml), 50 °C, 5 h, N_2. [b]Isolated yield.

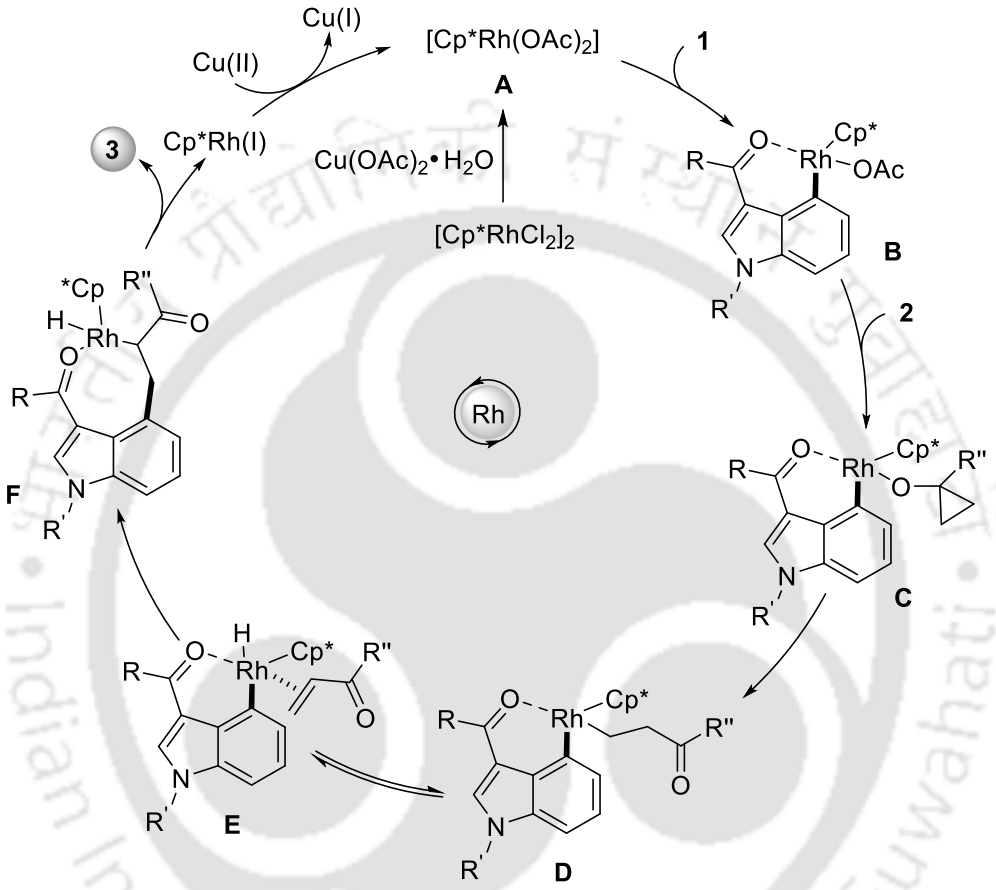
To gain insight into the reaction pathway, H/D exchange and kinetic isotope experiments were conducted. H/D scrambling experiments with D_2O as a cosolvent showed 12% and 27% deuterium incorporation at the C4-site in presence and absence of **2a**, respectively (Scheme 12a). Moreover, deuterium incorporation was observed at one of the α-carbons of carbonyl



Scheme 12. Preliminary Mechanistic Investigations

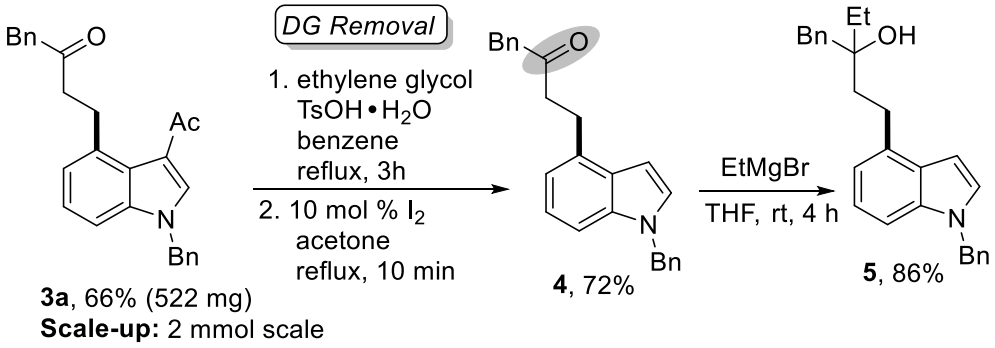
group of [Dₙ]-**3a**, thereby indicating the reaction may proceed through *β*-hydride elimination and olefin intermediate. The intermolecular kinetic isotope experiment produced a k_H/k_D of 2.0, which indicates the C4-H bond cleavage might be involved in the rate-determining step (Scheme

12b). Control experiment on **3a** with D_2O confirmed that the deuterium incorporation in $[D_n]$-**3a** was not due to post-coupling H/D scrambling (Scheme 12c.i). In addition, the reaction of **1a** with 1-phenylbut-3-en-2-one **2a′**, produced the C4-alkylated product **3a** in 34% yield, which further revealed the presence of an α,β-unsaturated ketone intermediate in the catalytic cycle (Scheme 12c.ii).



Scheme 13. Plausible Reaction Mechanism

Based on these preliminary mechanistic investigations and previous literatures,[16,18] a plausible catalytic cycle proposed (Scheme 13). The weak precoordination of the carbonyl group of indole DG with active catalyst **A** and subsequent C-H bond activation may give a six-membered rhodacycle **B**. Ligand exchange with cyclopropanol may lead to the formation of alkoxide **C**, followed by a β-carbon elimination of **C** may afford a Rh(III) alkyl species **D**, which can undergo reversible β-hydride elimination to give **E**. Further, the reaction may involve a migratory insertion of the aryl into the double bond to form an eight-membered rhodacycle **F**. Protonolysis of the later delivers the C4-alkylated product and Cu(II)-aided oxidation of Rh(I)-species regenerates the active catalyst **A** to complete the cycle.



Scheme 14. Scale-up and Post-Synthetic Utilities

To demonstrate the synthetic utility of the protocol, scale-up reaction was performed with 2 mmol of **1a**, yielding **3a** 66% of yield (522 mg) (Scheme 13). The removal of auxiliary was performed by reverse Friedel-Crafts reaction and subsequent ketal deprotection provided **4** in 72% yield. The embedded ketone functionality in **4** can act as a versatile functional handle for further downstream synthetic transformations. Treatment of **4** with EtMgBr in THF resulted in the formation of tertiary alcohol **5** in 86% yield.

In summary, a Rh(III)-catalyzed C4-alkylation of indoles with versatile cyclopropanols has been accomplished. The reaction demonstrates remarkable regioselectivity, sequential C-H/C-C activation, functional group compatibility and post-synthetic utilities.

2.4 Experimental Section

General Informations. Indoles, $[Cp^*RhCl_2]_2$, $Cu(OAc)_2 \cdot H_2O$ (>98%), $Cu(OAc)_2$ (98%), AgOAc (≥99.99%), Ag_2CO_3 (98%), Ag_2O (99%), $K_2S_2O_8$ (≥99.9%) Cu_2O (≥99.99%), TFE and HFIP were purchased from Aldrich and TCI Chemicals and used as received. Methanol (MeOH), tetrahydrofuran (THF), 1,2-dichloroethane and toluene were dried prior to use according to 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 (60-120 mesh). Bruker Avance III 400, 500 and 600 MHz NMR spectrometers were utilized to record spectra using $CDCl_3$ as solvent and tetramethylsilane (Me_4Si) 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, 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 (FT-IR) spectrometer. Quadrupole

time-of-flight electrospray ionization (ESI) mass spectrometer (Agilent 6545) and Xevo XS mass spectrometer were used to record HRMS. Single-crystal X-ray data collected on a Bruker D8 VENTURE APEX 3 equipped with a charge-coupled device area detector Mo-Kα radiation and the structure was solved by direct method using SHELXL-2019 (Göttingen, Germany). Indole substrates[7f,19] and cyclopropanols[9] were prepared according to the reported procedures.

General Procedure for Rh(III)-Catalyzed C4-Alkyation of Indoles. A mixture of indole **1** (0.1 mmol), cyclopropanol **2** (0.20 mmol), $[Cp^*RhCl_2]_2$ (3 mol%, 0.003 mmol, 1.8 mg) and $Cu(OAc)_2 \cdot H_2O$ (0.05 mmol, 10 mg) in TFE (1 ml) was stirred at 50 °C in a preheated oil bath for 5 h under N_2 atmosphere. The progress of the reaction was monitored by TLC utilizing ethyl acetate and hexane as an eluent. After completion, the reaction mixture was cooled to room temperature, diluted with CH_2Cl_2 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 *n*-hexane and ethyl acetate as an eluent to afford C4-alkylated indole **3**. For the substrates **1A-C** above mentioned procedure was followed to get the corresponding alkylated products **4A-C**.

H/D Exchange Experiment of 1a with D_2O in Presence of 2a. To a stirred solution of 1-(1-benzyl-1*H*-indol-3-yl)ethan-1-one **1a** (0.1 mmol, 24.9 mg), 1-benzylcyclopropan-1-ol **2a** (0.20 mmol, 29.6 mg), $[Cp^*RhCl_2]_2$ (3 mol%, 0.003 mmol, 1.8 mg) and $Cu(OAc)_2 \cdot H_2O$ (0.05 mmol, 10 mg) in TFE (1 ml), (D_2O, 0.4 mmol, 80 μL) was added. The reaction mixture was stirred at 50 °C in a preheated oil bath for 5 h under N_2 atmosphere. After reaction, the resulting mixture was cooled to room temperature, diluted with CH_2Cl_2 and passed through celite. The purification was performed as described in the general procedure to give $[D_n]$-**1a** and $[D_n]$-**3a**. The deuterium incorporation was observed as 12% at C4-H, 5% at C2-H of **1a** and 25% at one of the α-carbons of carbonyl group of $[D_n]$-**3a** based on 600 MHz ^{1}H NMR spectrum.

H/D Exchange Experiment of 1a with D_2O in Absence of 2a. To a stirred solution of 1-(1-benzyl-1*H*-indol-3-yl)ethan-1-one **1a** (0.1 mmol, 24.9 mg), $[Cp^*RhCl_2]_2$ (3 mol%, 0.003 mmol, 1.8 mg) and $Cu(OAc)_2 \cdot H_2O$ (0.05 mmol, 10 mg) in TFE (1 ml), D_2O (0.4 mmol, 80 μL) was added and stirred at 50 °C for 5 h under N_2 atmosphere. After reaction, the mixture was cooled to room temperature, diluted with CH_2Cl_2 and passed through celite. The purification was performed as described in the general procedure to give $[D_n]$-**1a**. The deuterium incorporation was observed as 27% at C4-H and 9% at C2-H based on 600 MHz ^{1}H NMR spectrum.

Preparation of 1-(1-Benzyl-1*H*-indol-3-yl-2,4-*d*$_2$)ethan-1-one [D$_2$]-**1a.** In a teflon capped sealed tube was charged with 1-(1-benzyl-1*H*-indol-3-yl)ethan-1-one **1a** (0.1 mmol, 24.9 mg), [Cp*RhCl$_2$]$_2$ (2.5 mol %, 0.0025 mmol, 1.5 mg), $AgSbF_6$ (0.02 mmol, 6.8 mg), Cu(OAc)$_2$ (0.1 mmol, 18 mg), D_2O (0.4 mmol, 80 μL) and 1,4-dioxane (1.5 mL). The mixture was stirred at 120 ^oC in a preheated oil bath for 14 h. Upon completion, the resulting mixture was cooled to room temperature, diluted with CH_2Cl_2 (10 mL) and passed through a short pad of celite using CH_2Cl_2 (20 mL). Drying (Na_2SO_4) 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 [D$_2$]-**1a** as a light yellow solid. The deuterium incorporation was determined using 600 MHz ^{1}H NMR as 93% 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 [D$_2$]-**1a** (0.05 mmol, 12.5 mg) was reacted with 1-benzylcyclopropan-1-ol **2a** (0.20 mmol, 29.6 mg) for 0.5 h at standard reaction conditions. The resulting mixture was then cooled to room temperature, diluted with CH_2Cl_2 (10 mL) and passed through a short celite pad. The purification was performed as described in the general procedure to afford [D$_1$]-**3a** and a mixture of unreacted **1a** and [D$_2$]-**1a**. The intermolecular k_H/k_D was found to be 2.00, based on 500 MHz ^{1}H NMR of the recovered substrates **1a** and [D$_2$]-**1a**.

Control Experiments.

i. **H/D Exchange Experiment of 3a with D$_2$O.** A mixture of 4-(3-acetyl-1-benzyl-1H-indol-4-yl)-1-phenylbutan-2-one **3a** (0.1 mmol, 39.5 mg), [Cp*RhCl$_2$]$_2$ (3 mol%, 0.003 mmol, 1.8 mg), Cu(OAc)$_2$·H$_2$O (0.05 mmol, 10 mg) and D_2O (0.4 mmol, 80 μL) was stirred in TFE (1 ml) at 50 ^oC for 5 h under N_2 atmosphere. The resulting mixture was cooled to room temperature, diluted with CH_2Cl_2 (10 mL) and passed through a short celite pad. The purification was performed as described in the general procedure and **3a** was recovered in 97% yield.

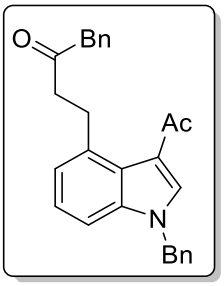
ii. **Reaction of 1a with 2a′.** A mixture of 1-(1-benzyl-1*H*-indol-3-yl)ethan-1-one **1a** (1 mmol, 24.9 mg), 1-phenylbut-3-en-2-one **2a′** (0.20 mmol, 29 mg), [Cp*RhCl$_2$]$_2$ (3 mol%, 0.003 mmol, 1.8 mg) and Cu(OAc)$_2$·H$_2$O (0.05 mmol, 10 mg) was stirred in TFE (1 ml) at 50 ^oC in a preheated oil bath for 5 h under N_2 atmosphere. The reaction mixture was cooled to room temperature, diluted with CH_2Cl_2 (10 mL) and passed

through a short celite pad. The purification of the product was performed as described in the general procedure to afford **3a** in 34% yield.

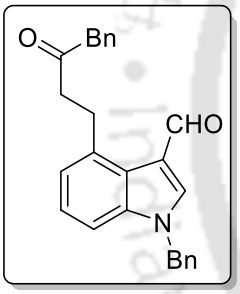
Procedures for Removal of Acetyl Directing Group. A mixture of 4-(3-acetyl-1-benzyl-1*H*-indol-4-yl)-1-phenylbutan-2-one **3a** (0.2 mmol, 79 mg), ethylene glycol (0.2 mL) and *p*-toluenesulfonic acid monohydrate (0.2 mmol, 42 mg) was stirred in benzene (4 mL) under reflux for 3 h. Upon completion (monitored by TLC), the resulting solution was cooled to room temperature, saturated $NaHCO_3$ (5 mL) was added and extracted using ethyl acetate (3 x 10 mL), washed with brine (2 x 10 mL) and water (1 x 10 mL). Drying (Na_2SO_4) 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 as an eluent (96/4, v/v) to afford **3′** in 75 % (60 mg) yield. Next, the ketal **3′** (0.14 mmol, 55 mg) and iodine (3.5 mg, 0.014mmol) in acetone (1 mL) were stirred for 10 min at refluxing temperature (56 °C). Removal of the solvent gave a residue, which was treated with CH_2Cl_2 (15 mL) and successively washed with 5% aqueous $Na_2S_2O_3$ (5 mL), brine (2 x 10 mL) and H_2O (10 mL). The resulting organic solution was dried over Na_2SO_4 and evaporated *in vacuo* to give a residue, that was purified by column chromatography on silica gel using *n*-hexane and ethyl acetate as an eluent (92/8, v/v) to afford **4** in 72% (35.6 mg) yield.

Synthesis of 5. To a stirred solution of 4-(1-benzyl-1*H*-indol-4-yl)-1-phenylbutan-2-one **4** (0.1 mmol, 35 mg) in THF (5 ml), EtMgBr (44 μL, 0.13 mmol, 3.0 M in Et_2O) was added dropwise at 0 ^oC under N_2 atmosphere. The reaction mixture was allowed to warm to room temperature and stirred for 4 h. Saturated aqueous NH_4Cl (5 mL) was slowly added at 0 °C to quench and the resultant mixture was extracted with ethyl acetate (2 x 10 mL). The combined organic layer was washed with brine (2 x 20 mL) and water (1 x 20 mL). Drying (Na_2SO_4) and evaporation of solvent gave a residue that was purified by silica gel column chromatography using ethyl acetate/*n*-hexane as the eluent (10/90, v/v) to provide **5** in 86% (33 mg) yield.

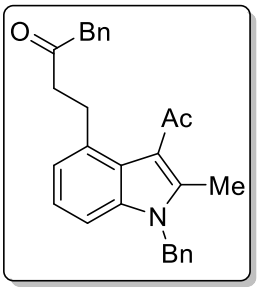
Characterization Data of the Products



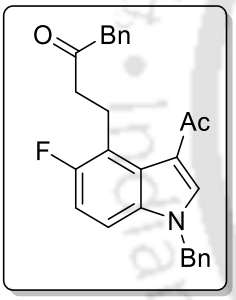
4-(3-Acetyl-1-benzyl-1*H*-indol-4-yl)-1-phenylbutan-2-one 3a. Analytical TLC on silica gel, 1:3 ethyl acetate/hexane R_f = 0.42; yellow solid; mp 115-116 °C; yield 81% (32.0 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (s, 1H), 7.37-7.31 (m, 3H), 7.27-2.26 (m, 1H), 7.25-7.24 (m, 1H) 7.21-7.19 (m, 1H), 7.17-7.14 (m, 6H), 7.06-7.04 (m, 1H), 5.33 (s, 2H), 3.71 (s, 2H), 3.56 (t, *J* = 7.6 Hz, 2H), 2.80 (t, *J* = 8 Hz, 2H), 2.51 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.7, 191.9, 138.4, 137.0, 136.9, 135.7, 134.8, 129.7, 129.2, 128.5, 128.4, 127.0, 126.7, 124.6, 124.4, 124.0, 118.8, 108.4, 50.9, 50.2, 45.1, 30.9, 28.6; FT-IR (KBr) 2922, 1711, 1654, 1525, 1445, 1376, 1195, 1029, 740 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{27}H_{26}NO_2$: 396.1958, found 396.1963.



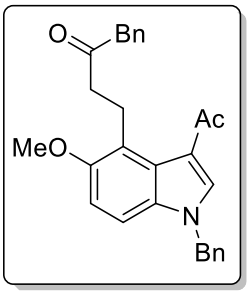
1-Benzyl-4-(3-oxo-4-phenylbutyl)-1*H*-indole-3-carbaldehyde 3a′. Analytical TLC on silica gel, 1:3 ethyl acetate/hexane R_f = 0.45; brown thick liquid; yield 57% (21.7 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.90 (s, 1H), 7.77 (s, 1H), 7.38-7.32 (m, 3H), 7.27 (s, 1H), 7.24 (s, 1H), 7.21-7.18 (m, 5H), 7.15-7.14 (m, 2H), 7.10-7.07 (m, 1H), 5.34 (s, 2H), 3.72 (s, 2H), 3.52 (t, *J* = 9 Hz, 2H), 2.83 (t, *J* = 8 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 208.2, 183.8, 140.9, 138.7, 136.3, 135.1, 134.5, 129.6, 129.2, 128.67, 128.60, 127.4, 126.8, 124.33, 124.31, 124.0, 119.6, 108.7, 51.1, 50.3, 44.3, 30.4; FT-IR (neat) 2919, 2851, 1734, 1668, 1527, 1463, 1264, 1177, 1110, 1049, 738 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{26}H_{24}NO_2$: 382.1802, found 382.1802.



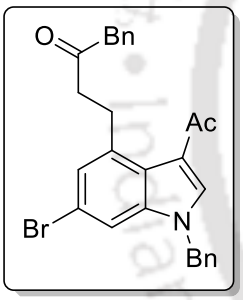
4-(3-Acetyl-1-benzyl-2-methyl-1*H*-indol-4-yl)-1-phenylbutan-2-one 3b. Analytical TLC on silica gel, 1:3 ethyl acetate/hexane R_f = 0.41; brown solid; mp 135-136 °C; yield 73% (29.8 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.29-7.26 (m, 5H), 7.23-7.21 (m, 1H), 7.15-7.14 (m, 2H), 7.09-7.07 (m, 2H), 6.98-6.95 (m, 3H), 5.33 (s, 2H), 3.67 (s, 2H), 3.23 (t, *J* = 7.8 Hz, 2H), 2.79 (t, *J* = 7.8 Hz, 2H), 2.55 (s, 3H), 2.51 (s, 3H).^{13}C NMR (150 MHz, $CDCl_3$) δ 208.2, 198.7, 139.4, 137.3, 136.4, 134.5, 134.1, 129.6, 129.1, 128.7, 127.8, 126.9, 126.0, 124.0, 123.2, 122.9, 118.2, 107.9, 50.2, 46.8, 43.3, 32.5, 29.1, 12.6; FT-IR (KBr) 2923, 2853, 1712, 1651, 1495, 1452, 1407, 1360, 1149, 732 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{28}H_{28}NO_2$: 410.2115, found 410.2119.



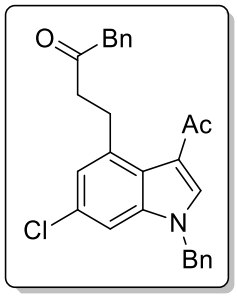
4-(3-Acetyl-1-benzyl-5-fluoro-1*H*-indol-4-yl)-1-phenylbutan-2-one 3e. Analytical TLC on silica gel, 1:3 ethyl acetate/hexane R_f = 0.43; brown solid; mp 115-116 °C; yield 72% (29.7 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.80 (s, 1H), 7.36-7.31 (m, 3H), 7.29-7.27 (m, 2H), 7.22-7.20 (m, 3H), 7.13-7.12 (m, 2H), 7.05-7.03 (m, 1H), 6.97-6.94 (m, 1H), 5.30 (s, 2H), 3.79 (s, 2H), 3.57-3.54 (m, 2H), 2.79 (t, *J* = 8.4 Hz, 2H), 2.50 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 208.3, 191.8, 158.6 (J_{C-F} = 234.1 Hz), 137.9, 135.4, 134.8, 134.5, 129.7, 129.2, 128.6, 128.5, 127.0, 126.7, 125.8 (J_{C-F} = 6.0 Hz), 122.4 (J_{C-F} = 18.6 Hz), 119.2 (J_{C-F} = 4.5 Hz), 112.4 (J_{C-F} = 28.5 Hz), 109.1 (J_{C-F} = 10.3 Hz), 51.0, 49.9, 43.6, 28.5, 22.3 (J_{C-F} = 4.5 Hz); ^{19}F NMR (471 MHz, $CDCl_3$) δ -124.58; FT-IR (KBr) 2922, 1713, 1657, 1524, 1450, 1393, 1189, 964, 798 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{27}H_{25}FNO_2$: 414.1864, found 414.1869.



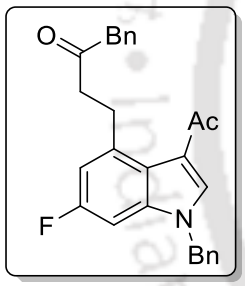
4-(3-Acetyl-1-benzyl-5-methoxy-1*H*-indol-4-yl)-1-phenylbutan-2-one 3f. Analytical TLC on silica gel, 1:3 ethyl acetate/hexane R_f = 0.40; brown solid; mp 118-119 °C; yield 66% (28.0 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.77 (s, 1H), 7.35-7.27 (m, 5H), 7.23-7.20 (m, 3H), 7.14-7.13 (m, 2H), 7.07 (d, *J* = 9 Hz, 1H), 6.91 (d, *J* = 9 Hz, 1H), 5.29 (s, 2H), 3.81 (s, 2H), 3.77 (s, 3H), 3.55 (t, *J* = 7.8 Hz, 2H), 2.78 (t, *J* = 7.8 Hz, 2H), 2.50 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 209.3, 191.8, 153.8, 137.9, 135.8, 135.2, 133.5, 129.8, 129.1, 128.5, 128.3, 127.0, 126.6, 126.2, 124.2, 118.7, 109.8, 108.4, 57.1, 50.9, 49.8, 43.6, 28.6, 23.3; FT-IR (KBr) 2922, 2853, 1712, 1652, 1524, 1454, 1250, 1185, 1080, 961, 799 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{28}H_{28}NO_3$: 426.2064, found 426.2076.



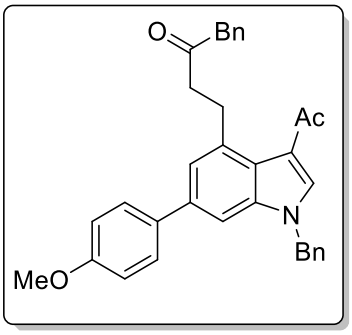
4-(3-Acetyl-1-benzyl-6-bromo-1*H*-indol-4-yl)-1-phenylbutan-2-one 3g. Analytical TLC on silica gel, 1:3 ethyl acetate/hexane R_f = 0.43; colorless solid; mp 134-135 °C; yield 68% (32.2 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.73 (s, 1H), 7.38-7.33 (m, 3H), 7.288-7.280 (m, 1H), 7.26 (s, 1H), 7.25 (s, 1H), 7.21-7.19 (m, 1H), 7.16-7.12 (m, 3H), 7.13-7.12 (m, 2H), 5.28 (s, 2H), 3.71 (s, 2H), 3.48 (t, *J* = 7.8 Hz, 2H), 2.78 (t, *J* = 7.8 Hz, 2H), 2.49 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 208.1, 191.8, 139.1, 138.8, 137.2, 135.2, 134.6, 129.6, 129.3, 128.66, 128.61, 127.4, 127.0, 126.8, 123.4, 118.9, 117.5, 111.3, 50.9, 50.2, 44.7, 30.5, 28.6; FT-IR (KBr) 2921, 2852, 1713, 1659, 1524, 1452, 1374, 1187, 1080, 823 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{27}H_{25}BrNO_2$: 474.1063, found 474.1072.



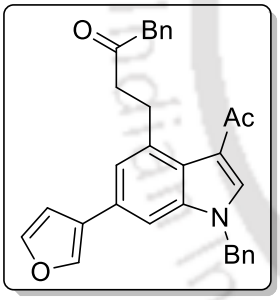
4-(3-Acetyl-1-benzyl-6-chloro-1*H*-indol-4-yl)-1-phenylbutan-2-one 3h. Analytical TLC on silica gel, 1:3 ethyl acetate/hexane R_f = 0.42; brown thick liquid; yield 70% (30.0 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.75 (s, 1H), 7.38-7.33 (m, 3H), 7.27 (s, 1H), 7.25 (s, 1H), 7.21-7.19 (m, 1H), 7.16-7.12 (m, 5H), 7.029-7.026 (m, 1H), 5.28 (s, 2H), 3.71 (s, 2H), 3.49 (t, *J* = 7.8 Hz, 2H), 2.78 (t, *J* = 7.8 Hz, 2H), 2.49 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 208.1, 191.9, 138.8, 138.5, 137.3, 135.2, 134.6, 129.7, 129.6, 129.3, 128.66, 128.61, 127.0, 126.8, 124.8, 123.1, 118.9, 108.3, 50.9, 50.2, 44.7, 30.5, 28.6; FT-IR (neat) 2921, 2852, 1715, 1658, 1603, 1524, 1451, 1259, 1187, 1082, 970 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{27}H_{25}ClNO_2$: 430.1568, found 430.1568.



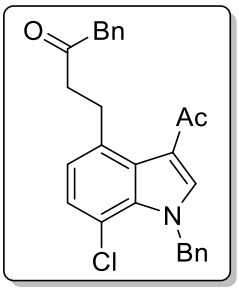
4-(3-Acetyl-1-benzyl-6-fluoro-1*H*-indol-4-yl)-1-phenylbutan-2-one 3i. Analytical TLC on silica gel, 1:3 ethyl acetate/hexane R_f = 0.43; brown solid; mp 98-99 °C; yield 72% (29.7 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.77 (s, 1H), 7.37-7.31 (m, 3H), 7.27 (s, 1H), 7.25 (s, 1H), 7.21-7.19 (m, 1H), 7.16-7.13 (m, 4H), 6.82-6.77 (m, 2H), 5.26 (s, 2H), 3.71 (s, 2H), 3.51 (t, *J* = 7.8 Hz, 2H), 2.79 (t, *J* = 7.8 Hz, 2H), 2.49 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 208.2, 191.9, 161.0 ($J_{C\text{-}F}$ = 240.1 Hz), 139.0 ($J_{C\text{-}F}$ = 9.1 Hz), 138.6 ($J_{C\text{-}F}$ = 12.0 Hz), 137.3 ($J_{C\text{-}F}$ = 2.5 Hz), 135.2, 134.6, 129.6, 129.3, 128.6, 128.5, 127.0, 126.8, 120.9, 118.9, 112.9 ($J_{C\text{-}F}$ = 23.2 Hz), 94.9 ($J_{C\text{-}F}$ = 25.8 Hz), 51.0, 50.2, 44.6, 30.6, 28.5; ^{19}F NMR (471 MHz, $CDCl_3$) δ -118.26; FT-IR (KBr) 2923, 2854, 1713, 1657, 1612, 1526, 1453, 1378, 1186, 953 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{27}H_{25}FNO_2$: 414.1864, found 414.1878.



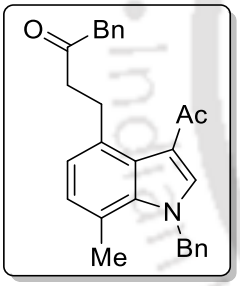
4-(3-Acetyl-1-benzyl-6-(4-methoxyphenyl)-1*H*-indol-4-yl)-1-phenylbutan-2-one 3j. Analytical TLC on silica gel, 1:3 ethyl acetate/hexane R_f = 0.40; colorless solid; mp 147-148 °C; yield 75% (37.6 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.79 (s, 1H), 7.47 (d, *J* = 9 Hz, 2H), 7.36-7.30 (m, 3H), 7.274-7.270 (m, 2H), 7.24-7.22 (m, 2H), 7.19-7.17 (m, 3H), 7.15-7.14 (m, 2H), 6.95 (d, *J* = 9 Hz, 2H), 5.37 (s, 2H), 3.84 (s, 3H), 3.72 (s, 2H), 3.60 (t, *J* = 7.8 Hz, 2H), 2.84 (t, *J* = 7.8 Hz, 2H), 2.52 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 208.7, 191.9, 159.2, 139.1, 137.3, 137.1, 137.0, 135.7, 134.7, 133.8, 129.7, 129.2, 128.6, 128.46, 128.43, 127.1, 126.7, 124.1, 123.2, 118.7, 114.3, 106.2, 55.5, 50.8, 50.3, 45.2, 31.1, 28.5; FT-IR (KBr) 2921, 2852, 1734, 1654, 1521, 1463, 1375, 1264, 1181, 1046, 738 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{34}H_{32}NO_3$: 502.2377, found 502.2366.



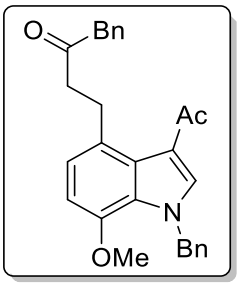
4-(3-Acetyl-1-benzyl-6-(furan-3-yl)-1*H*-indol-4-yl)-1-phenylbutan-2-one 3k. Analytical TLC on silica gel, 1:3 ethyl acetate/hexane R_f = 0.41; brown thick liquid; yield 59% (27.2 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.77 (s, 1H), 7.678-7.675 (m, 1H), 7.45-7.44 (m, 1H), 7.37-7.33 (m, 3H), 7.25-7.24 (m, 2H), 7.20-7.19 (m, 3H), 7.18-7.15 (m, 4H), 6.649-6.644 (m, 1H), 5.35 (s, 2H), 3.73 (s, 2H), 3.57 (t, *J* = 7.8, 2H), 2.82 (t, *J* = 7.8 Hz, 2H), 2.51 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 208.7, 191.9, 143.7, 139.0, 138.6, 137.3, 135.6, 134.7, 129.7, 129.2, 128.6, 128.5, 128.4, 127.1, 126.7, 126.5, 123.5, 123.1, 118.9, 109.1, 105.4, 50.8, 50.2, 45.1, 31.0, 28.5; FT-IR (neat) 2924, 2853, 1713, 1654, 1524, 1452, 1381, 1264, 1190, 752 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{31}H_{28}NO_3$: 462.2064, found 462.2071.



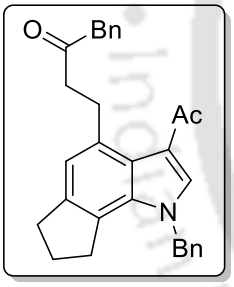
4-(3-Acetyl-1-benzyl-7-chloro-1*H*-indol-4-yl)-1-phenylbutan-2-one 3l. Analytical TLC on silica gel, 1:3 ethyl acetate/hexane R_f = 0.42; brown solid; mp 117-118 °C; yield 74% (31.8 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.73 (s, 1H), 7.34-7.29 (m, 3H), 7.27 (s, 1H), 7.24 (s, 1H), 7.21-7.19 (m, 1H), 7.14-7.13 (m, 2H), 7.11 (d, *J* = 7.8 Hz, 1H), 7.05-7.03 (m, 2H), 6.95 (d, *J* = 7.8 Hz, 1H), 5.82 (s, 2H), 3.69 (s, 2H), 3.48 (t, *J* = 7.8 Hz, 2H), 2.77 (t, *J* = 7.8 Hz, 2H), 2.49 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 208.3, 192.0, 139.5, 137.5, 135.7, 134.6, 133.5, 129.6, 129.1, 128.6, 128.0, 127.3, 126.8, 126.3, 125.9, 125.3, 118.8, 115.2, 53.0, 50.3, 44.6, 30.2, 28.9; FT-IR (KBr) 2921, 2852, 1715, 1658, 1524, 1451, 1259, 1187, 1082, 1027, 970, 804 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{27}H_{25}ClNO_2$: 430.1568, found 430.1568.



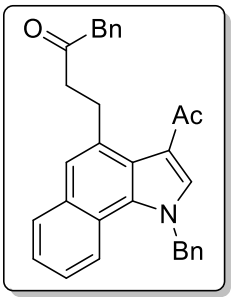
4-(3-Acetyl-1-benzyl-7-methyl-1*H*-indol-4-yl)-1-phenylbutan-2-one 3m. Analytical TLC on silica gel, 1:3 ethyl acetate/hexane R_f = 0.41; light brown solid; mp 120-121 °C; yield 73% (29.8 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (s, 1H), 7.34-7.28 (m, 3H), 7.27-7.26 (m, 1H), 7.25-7.24 (m, 1H), 7.22-7.20 (m, 1H), 7.17-7.15 (m, 2H), 6.94-6.92 (m, 3H), 6.88-6.86 (m, 1H), 5.62 (s, 2H), 3.72 (s, 2H), 3.51 (t, *J* = 7.6 Hz, 2H), 2.79 (t, *J* = 8 Hz, 2H), 2.51 (s, 3H), 2.48 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.8, 192.1, 139.1, 137.9, 137.1, 134.8, 134.6, 129.7, 129.3, 128.6, 128.0, 127.2, 126.7, 125.6, 125.4, 124.7, 119.3, 118.7, 53.2, 50.2, 45.0, 30.5, 28.8, 19.6; FT-IR (KBr) 2919, 1720, 1651, 1532, 1449, 1378, 1275, 1179, 974, 739 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{28}H_{28}NO_2$: 410.2115, found 410.2115.



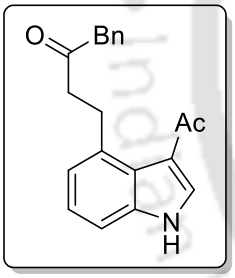
4-(3-Acetyl-1-benzyl-7-methoxy-1*H*-indol-4-yl)-1-phenylbutan-2-one 3n. Analytical TLC on silica gel, 1:3 ethyl acetate/hexane R_f = 0.40; brown solid; mp 130-131 °C; yield 75% (31.9 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.67 (s, 1H), 7.32-7.30 (m, 2H), 7.28-7.26 (m, 1H), 7.24-7.23 (m, 2H), 7.20-7.17 (m, 1H), 7.14-7.13 (m, 2H), 7.11-7.10 (m, 2H), 6.93 (d, *J* = 7.8 Hz, 1H), 6.61 (d, *J* = 7.8 Hz, 1H), 5.66 (s, 2H), 3.76 (s, 3H), 3.69 (s, 2H), 3.46 (t, *J* = 7.8 Hz, 2H), 2.75 (t, *J* = 7.8 Hz, 2H), 2.48 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 209.1, 192.1, 146.1, 138.17, 138.15, 134.8, 129.7, 128.9, 128.5, 127.9, 127.7, 126.79, 126.73, 126.4, 124.7, 118.8, 105.0, 55.6, 53.7, 50.2, 45.2, 30.3, 28.7; FT-IR (KBr) 2921, 2851, 1711, 1657, 1506, 1385, 1261, 1209, 1189, 1088, 946 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{28}H_{28}NO_3$: 426.2064, found 426.2072.



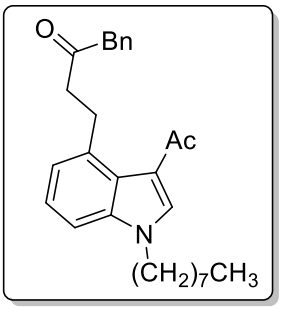
4-(3-Acetyl-1-benzyl-1,6,7,8-tetrahydrocyclopenta[*g*]indol-4-yl)-1-phenylbutan-2-one 3o. Analytical TLC on silica gel, 1:3 ethyl acetate/hexane R_f = 0.45; colorless thick liquid; yield 64% (27.8 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.69 (s, 1H), 7.34-7.26 (m, 5H), 7.25 (s, 1H), 7.21-7.19 (m, 1H), 7.17-7.16 (m, 1H), 7.00 (d, *J* = 6.6 Hz, 2H), 6.96 (s, 1H), 5.50 (s, 2H), 3.72 (s, 2H), 3.52 (t, *J* = 7.8 Hz, 2H), 3.05 (t, *J* = 7.8 Hz, 2H), 2.90 (t, *J* = 7.8 Hz, 2H), 2.80 (t, *J* = 7.8 Hz, 2H), 2.50 (s, 3H), 2.07-2.02 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 209.0, 192.1, 141.7, 137.6, 135.9, 134.9, 134.8, 129.7, 129.2, 128.5, 128.0, 126.7, 125.9, 123.5, 123.4, 121.6, 119.1, 52.0, 50.2, 45.3, 32.6, 31.4, 30.8, 28.7, 25.3; FT-IR (neat) 2923, 2853, 1712, 1655, 1530, 1496, 1449, 1377, 1273, 1206, 1082, 751 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{30}H_{30}NO_2$: 436.2271, found 436.2265.



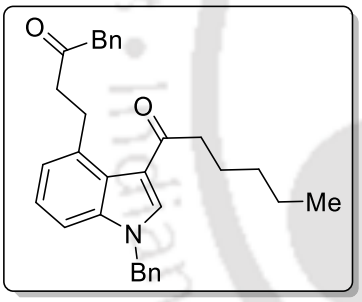
4-(3-Acetyl-1-benzyl-1H-benzo[*g*]indol-4-yl)-1-phenylbutan-2-one 3p. Analytical TLC on silica gel, 1:3 ethyl acetate/hexane R_f = 0.44; light brown solid; mp 148-149 °C; yield 61% (27.1 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.03 (d, *J* = 8.4 Hz, 1H), 7.818-7.811 (m, 2H), 7.44 (s, 1H), 7.38-7.33 (m, 3H), 7.31-7.28 (m, 2H), 7.24-7.23 (m, 2H), 7.20-7.18 (m, 1H), 7.15-7.14 (m, 2H), 7.12-7.11 (m, 2H), 5.87 (s, 2H), 3.72 (s, 2H), 3.64 (t, *J* = 7.8 Hz, 2H), 2.86 (t, *J* = 7.8 Hz, 2H), 2.57 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 208.6, 192.8, 137.3, 136.2, 134.9, 134.7, 132.4, 132.1, 129.6, 129.4, 128.6, 128.2, 126.8, 126.2, 125.4, 124.8, 124.7, 122.8, 120.9, 119.5, 54.7, 50.3, 44.4, 30.9, 29.1; FT-IR (KBr) 2922, 2854, 1712, 1665, 1529, 1457, 1371, 1261, 1184, 1081, 969, 746 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{31}H_{28}NO_2$: 446.2115, found 446.2116.



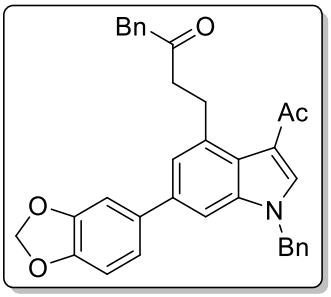
4-(3-Acetyl-1*H*-indol-4-yl)-1-phenylbutan-2-one 3q. Analytical TLC on silica gel, 1:1 ethyl acetate/hexane R_f = 0.40; brown solid; mp 122-123 °C; yield 54% (16.4 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.70 (s, 1H), 7.88 (s, 1H), 7.24-7.13 (m, 7H), 7.04-7.03 (m, 1H), 3.71 (s, 2H), 3.55 (t, *J* = 7.8 Hz, 2H), 2.79 (t, *J* = 7.8 Hz, 2H), 2.54 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 208.9, 192.5, 137.7, 136.5, 134.7, 133.4, 129.7, 128.6, 126.7, 124.5, 124.2, 123.4, 119.9, 109.7, 50.2, 45.1, 30.9, 28.6; FT-IR (KBr) 2922, 2852, 1709, 1631, 1518, 1408, 1260, 1169, 1082, 1017, 796 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{20}H_{20}NO_2$: 306.1489, found 306.1469.



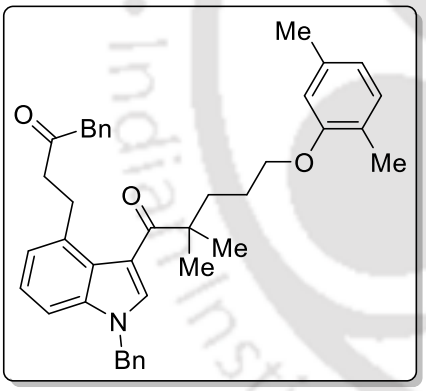
4-(3-Acetyl-1-octyl-1*H*-indol-4-yl)-1-phenylbutan-2-one 3r. Analytical TLC on silica gel, 1:3 ethyl acetate/hexane R_f = 0.5; brown thick liquid; yield 68% (28.3 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.77 (s, 1H), 7.26 (s, 1H), 7.24 (s, 1H), 7.20-7.18 (m, 3H), 7.15-7.14 (m, 2H), 7.05-7.04 (m, 1H), 4.12 (t, *J* = 7.8 Hz, 2H), 3.71 (s, 2H), 3.55 (t, *J* = 7.8 Hz, 2H), 2.79 (t, *J* = 7.8 Hz, 2H), 2.53 (s, 3H), 1.88-1.86 (m, 2H), 1.34-1.25 (m, 10H), 0.88-0.86 (m, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 208.8, 191.8, 138.0, 136.9, 134.8, 129.7, 128.5, 126.7, 124.4, 123.7, 118.1, 108.1, 50.2, 47.3, 45.1, 31.8, 31.0, 29.8, 29.2, 28.5, 27.0, 22.7, 14.2; FT-IR (neat) 2921, 2852, 1732, 1654, 1524, 1464, 1375, 1263, 1176, 1047, 738 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{28}H_{36}NO_2$: 418.2741, found 418.2743.



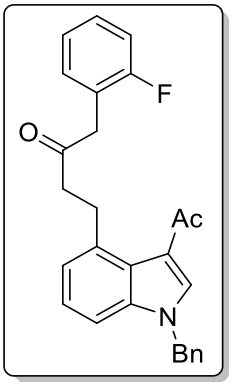
1-(1-Benzyl-4-(3-oxo-4-phenylbutyl)-1*H*-indol-3-yl)hexan-1-one 3t. Analytical TLC on silica gel, 1:3 ethyl acetate/hexane R_f = 0.46; Colorless solid; mp 95-96 °C; yield 77% (34.7 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.72 (s, 1H), 7.28-7.23 (m, 3H), 7.18-7.16 (m, 2H), 7.13-7.11 (m, 1H), 7.08-7.06 (m, 6H), 6.99-6.97 (m, 1H), 5.26 (s, 2H), 3.63 (s, 2H), 3.49 (t, *J* = 7.8 Hz, 2H), 2.75-2.71 (m, 4H), 1.68-1.66 (m, 2H), 1.30-1.28 (m, 4H), 0.85-0.82 (m, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 208.8, 195.3, 138.3, 136.8, 136.1, 135.8, 134.8, 129.6, 129.2, 128.5, 128.3, 127.0, 126.7, 124.6, 124.5, 123.9, 118.6, 108.4, 50.8, 50.2, 44.9, 40.8, 31.8, 30.9, 25.6, 22.7, 14.1; FT-IR (KBr) 2927, 2856, 1712, 1655, 1525, 1451, 1391, 1188, 1087, 731 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{31}H_{34}NO_2$: 452.2584, found 452.2603.



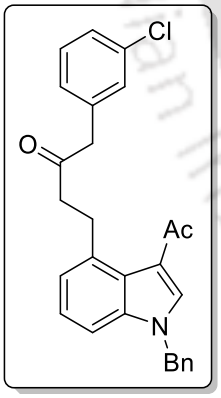
4-(3-Acetyl-6-(benzo[*d*][1,3]dioxol-5-yl)-1-benzyl-1*H*-indol-4-yl)-1-phenylbutan-2-one 3u. Analytical TLC on silica gel, 1:2 ethyl acetate/hexane R_f = 0.41; brown solid; mp 149-150 °C; yield 70% (36.0 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (s, 1H), 7.38-7.32 (m, 3H), 7.24-7.23 (m, 4H), 7.20-7.14 (m, 5H), 7.01-6.99 (m, 2H), 6.86-6.83 (m, 1H), 5.98 (s, 2H), 5.36 (s, 2H), 3.72 (s, 2H), 3.59 (t, *J* = 7.6 Hz, 2H), 2.84 (t, *J* = 7.6 Hz, 2H), 2.51 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.7, 191.9, 148.2, 147.1, 139.0, 137.4, 137.16, 137.13, 135.67, 135.66, 134.7, 129.6, 129.2, 128.6, 128.4, 127.0, 126.7, 124.1, 123.4, 120.9, 118.7, 108.6, 107.9, 106.4, 101.2, 50.8, 50.2, 45.1, 31.1, 28.5; FT-IR (KBr) 2922, 2855, 1714, 1651, 1509, 1451, 1376, 1249, 1107, 1037, 939 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{34}H_{30}NO_4$: 516.2169, found 516.2184.



1-(1-Benzyl-4-(3-oxo-4-phenylbutyl)-1*H*-indol-3-yl)-5-(2,5-dimethylphenoxy)-2,2-dimethylpentan-1-one 3v. Analytical TLC on silica gel, 1:5 ethyl acetate/hexane R_f = 0.42; yellow liquid; yield 68% (39.8 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.60 (s, 1H), 7.33-7.26 (m, 5H), 7.18-7.15 (m, 3H), 7.13-7.09 (m, 4H), 6.99-6.96 (m, 2H), 6.64 (d, *J* = 7.5 Hz, 1H), 6.56 (s, 1H), 5.29 (s, 2H), 3.89 (t, *J* = 6.0 Hz, 2H), 3.71 (s, 1H), 3.64 (s, 1H), 3.21 (t, *J* = 8 Hz, 2H), 2.86 (t, *J* = 7.5 Hz, 2H), 2.27 (s, 3H), 2.11 (s, 3H), 1.97-1.94 (m, 2H), 1.83-1.77 (m, 2H), 1.35 (s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 208.3, 204.6, 157.0, 137.0, 136.6, 136.2, 135.7, 134.6, 130.7, 130.4, 129.6, 129.1, 128.7, 128.6, 128.1, 126.8, 125.8, 123.5, 123.3, 120.8, 116.3, 112.1, 108.3, 68.2, 50.6, 50.1, 48.1, 43.8, 38.0, 29.1, 26.9, 25.2, 21.5, 15.9; FT-IR (neat) 2925, 1706, 1647, 1609, 1519, 1451, 1389, 1262, 1183, 1038, 806 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{40}H_{44}NO_3$: 586.3316, found 586.3316.

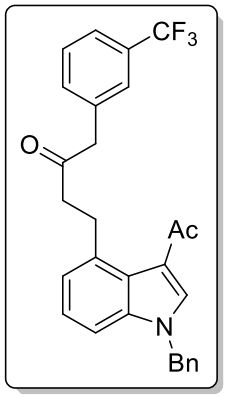


4-(3-Acetyl-1-benzyl-1*H*-indol-4-yl)-1-(2-fluorophenyl)butan-2-one 3w. Analytical TLC on silica gel, 1:3 ethyl acetate/hexane R_f = 0.44; brown solid; mp 141-142 °C; yield 64% (26.4 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.80 (s, 1H), 7.36-7.31 (m, 3H), 7.16-7.13 (m, 5H), 7.09-7.07 (m, 1H), 7.05-6.98 (m, 3H), 5.34 (s, 2H), 3.76 (s, 2H), 3.58 (t, *J* = 7.8 Hz, 2H), 2.85 (t, *J* = 7.8 Hz, 2H), 2.52 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 207.4, 192.0, 138.4 (J_{C-F} = 233.4 Hz), 136.8, 135.7, 131.9 (J_{C-F} = 4.3 Hz), 129.2, 128.7 (J_{C-F} = 8.2 Hz), 128.4, 127.09, 127.03, 124.6, 124.4, 124.1 (J_{C-F} = 3.4 Hz), 124.0, 122.2 (J_{C-F} = 16.0 Hz), 118.8, 115.4, 115.2, 108.5, 50.9, 45.3, 43.1 (J_{C-F} = 1.6 Hz), 30.9, 28.6; ^{19}F NMR (471 MHz, $CDCl_3$) δ -117.11; FT-IR (KBr) 2921, 2853, 1714, 1657, 1492, 1455, 1377, 1231, 1187, 756 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{27}H_{25}FNO_2$: 414.1864, found 414.1862.

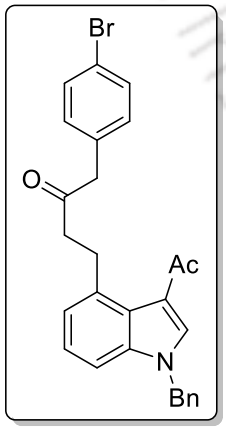


4-(3-Acetyl-1-benzyl-1*H*-indol-4-yl)-1-(3-chlorophenyl)butan-2-one 3x. Analytical TLC on silica gel, 1:3 ethyl acetate/hexane R_f = 0.44; Colorless solid; mp 102-103 °C; yield 75% (32.2 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.82 (s, 1H), 7.36-7.30 (m, 3H), 7.18-7.15 (m, 6H), 7.12 (s, 1H), 7.06-7.05 (m, 1H), 7.02-7.01 (m, 1H), 5.34 (s, 2H), 3.69 (s, 2H), 3.55 (t, *J* = 7.8 Hz, 2H), 2.80 (t, *J* = 7.8 Hz, 2H), 2.53 (s, 3H);^{13}C NMR (150 MHz, $CDCl_3$) δ 208.1, 192.1, 138.3, 137.3, 136.58, 136.56, 135.6, 134.2, 129.8, 129.7, 129.2, 128.3, 127.9, 127.0, 126.9, 124.7, 124.3, 124.0, 118.6, 108.6, 50.8, 49.6, 45.3, 31.1, 28.6; FT-IR (KBr) 2922,

1714, 1653, 1527, 1444, 1377, 1260, 1080, 1018, 796 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{27}H_{25}ClNO_2$: 430.1568, found 430.1564.

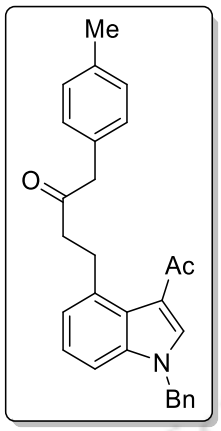


4-(3-Acetyl-1-benzyl-1*H*-indol-4-yl)-1-(3-(trifluoromethyl)phenyl)-butan-2-one 3y. Analytical TLC on silica gel, 1:3 ethyl acetate/hexane R_f = 0.41; light yellow solid; mp 116-117 °C; yield 61% (28.2 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.82 (s, 1H), 7.46-7.45 (m, 1H), 7.39-7.38 (m, 1H), 7.37-7.32 (m, 5H), 7.16-7.14 (m, 4H), 7.07-7.06 (m, 1H), 5.34 (s, 2H), 3.79 (s, 2H), 3.58 (t, *J* = 7.8, 2H), 2.83 (t, *J* = 7.8, 2H), 2.52 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 207.8, 192.0, 138.4, 137.2, 136.6, 135.6, 135.5, 133.2, 130.8 (J_{C-F} = 32.9 Hz), 129.2, 128.9, 128.4, 127.0, 126.5 (J_{C-F} = 3.9 Hz), 125.1 (J_{C-F} = 270.7 Hz), 124.7, 124.4, 124.0, 123.6 (J_{C-F} = 3.7 Hz), 118.6, 108.6, 50.9, 49.5, 45.6, 31.2, 28.5; ^{19}F NMR (471 MHz, $CDCl_3$) δ -62.50; FT-IR (KBr) 2921, 2852, 1715, 1653, 1525, 1446, 1378, 1330, 1163, 1122, 1075, 738 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{28}H_{25}F_3NO_2$: 464.1832, found 464.1830.

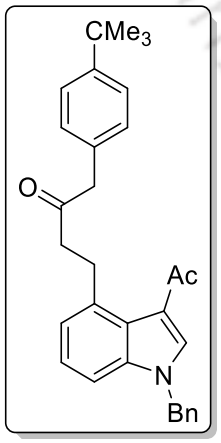


4-(3-Acetyl-1-benzyl-1*H*-indol-4-yl)-1-(4-bromophenyl)butan-2-one 3z. Analytical TLC on silica gel, 1:3 ethyl acetate/hexane R_f = 0.44; colorless solid; mp 123-124 °C; yield 79% (37.4 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.80 (s, 1H), 7.35-7.30 (m, 5H), 7.15-7.14 (m, 4H), 7.05-7.04 (m, 1H), 6.99 (d, *J* = 8.4 Hz, 2H), 5.34 (s, 2H), 3.66 (s, 2H), 3.55 (t, *J* = 7.8 Hz, 2H), 2.79 (t, *J* = 7.8 Hz, 2H), 2.51 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 208.1, 192.0, 138.4, 137.1, 136.6, 135.7, 133.6, 131.5, 131.4, 129.2, 128.4, 127.0, 124.7, 124.4, 124.0,

120.7, 118.7, 108.5, 50.9, 49.4, 45.1, 31.0, 28.6; FT-IR (KBr) 2922, 2852, 1713, 1655, 1488, 1376, 1188, 1071, 1012, 802 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{27}H_{25}BrNO_2$: 474.1063, found 474.1064.

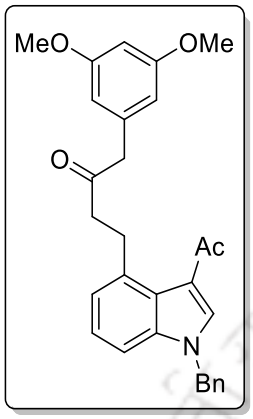


4-(3-Acetyl-1-benzyl-1*H*-indol-4-yl)-1-(*p*-tolyl)butan-2-one 3aa. Analytical TLC on silica gel, 1:3 ethyl acetate/hexane R_f = 0.43; colorless solid; mp 120-121 °C; yield 73% (29.8 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.79 (s, 1H), 7.36-7.31 (m, 3H), 7.15-7.13 (m, 4H), 7.07-7.03 (m, 5H), 5.33 (s, 2H), 3.67 (s, 2H), 3.54 (t, *J* = 7.8 Hz, 2H), 2.79 (t, *J* = 7.8 Hz, 2H), 2.51 (s, 3H), 2.29 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 209.0, 192.0, 138.4, 137.05, 137.00, 136.3, 135.7, 131.7, 129.5, 129.3, 129.2, 128.4, 127.0, 124.6, 124.4, 124.0, 118.8, 108.4, 50.9, 49.8, 45.0, 30.9, 28.6, 21.2; FT-IR (KBr) 2920, 2851, 1713, 1656, 1524, 1377, 1260, 1020, 800 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{28}H_{28}NO_2$: 410.2115, found 410.2114.

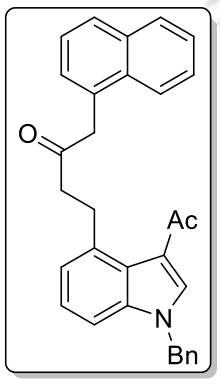


4-(3-Acetyl-1-benzyl-1*H*-indol-4-yl)-1-(4-(*tert*-butyl)phenyl)butan-2-one 3ab. Analytical TLC on silica gel, 1:3 ethyl acetate/hexane R_f = 0.44; yellow thick liquid; yield 68% (30.7 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.79 (s, 1H), 7.36-7.31 (m, 3H), 7.29-7.28 (m, 2H), 7.17-7.13 (m, 4H), 7.10-7.08 (m, 2H), 7.06-7.05 (m, 1H), 5.33 (s, 2H), 3.68 (s, 2H), 3.56 (t, *J* = 8 Hz, 2H), 2.80 (t, *J* = 7.5 Hz, 2H), 2.51 (s, 3H), 1.29 (s, 9H); ^{13}C NMR (150 MHz,

$CDCl_3$) δ 209.0, 192.0, 149.5, 138.4, 137.0, 135.7, 131.7, 129.3, 129.2, 128.3, 127.0, 125.5, 124.6, 124.4, 124.0, 118.8, 108.4, 50.9, 49.7, 45.1, 34.5, 31.4, 30.9, 28.6; FT-IR (neat) 2923, 2855, 1710, 1654, 1443, 1375, 1191, 1152, 1024, 953 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{31}H_{34}NO_2$: 452.2584, found 452.2583.

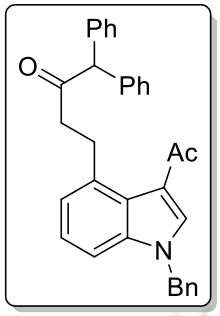


4-(3-Acetyl-1-benzyl-1*H*-indol-4-yl)-1-(3,5-dimethoxyphenyl)butan-2-one 3ac. Analytical TLC on silica gel, 1:2 ethyl acetate/hexane R_f = 0.40; brown solid; mp 94-95 °C; yield 77% (35.0 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.79 (s, 1H), 7.35-7.30 (m, 3H), 7.15-7.12 (m, 4H), 7.05-7.04 (m, 1H), 6.30 (s, 3H), 5.33 (s, 2H), 3.73 (s, 6H), 3.63 (s, 2H), 3.54 (t, *J* = 7.8 Hz, 2H), 2.80 (t, *J* = 7.8 Hz, 2H), 2.51 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 208.7, 192.0, 160.8, 138.3, 137.1, 136.88, 136.80, 135.7, 129.2, 128.3, 127.0, 124.6, 124.3, 123.9, 118.6, 108.4, 107.5, 99.1, 55.4, 50.8, 50.6, 44.8, 30.9, 28.5; FT-IR (KBr) 2920, 2850, 1710, 1652, 1596, 1455, 1375, 1204, 1152, 1062, 801 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{29}H_{30}NO_4$: 456.2169, found 456.2180.

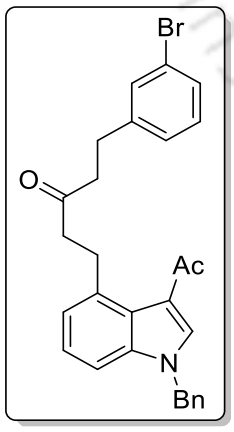


4-(3-Acetyl-1-benzyl-1*H*-indol-4-yl)-1-(naphthalen-1-yl)butan-2-one 3ad. Analytical TLC on silica gel, 1:3 ethyl acetate/hexane R_f = 0.40; colorless thick liquid; yield 61% (27.1 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.85-7.84 (m, 1H), 7.82-7.80 (m, 1H), 7.76 (s, 1H), 7.72 (d, *J* = 7.8 Hz, 1H), 7.45-7.44 (m, 2H), 7.36-7.31 (m, 4H), 7.28-7.27 (m, 1H), 7.15-7.10 (m, 4H), 7.02-7.00 (m, 1H), 5.31 (s, 2H), 4.14 (s, 2H), 3.57 (t, *J* = 7.8 Hz, 2H),

2.80 (t, *J* = 7.8 Hz, 2H), 2.47 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 209.0, 191.9, 138.3, 137.0, 136.8, 135.7, 133.9, 132.4, 131.5, 129.2, 128.6, 128.37, 128.34, 127.7, 127.0, 126.3, 125.7, 125.5, 124.6, 124.4, 124.3, 123.9, 118.7, 108.4, 50.8, 48.5, 44.5, 31.0, 28.5; FT-IR (neat) 2919, 2850, 1712, 1653, 1524, 1444, 1378, 1195, 783 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{31}H_{28}NO_2$: 446.2115, found 446.2122.

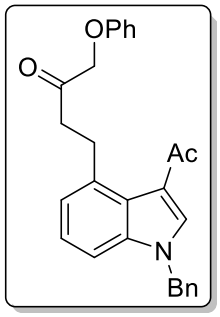


(4-(3-Acetyl-1-benzyl-1*H*-indol-4-yl)-1,1-diphenylbutan-2-one 3ae. Analytical TLC on silica gel, 1:3 ethyl acetate/hexane R_f = 0.40; light yellow solid; mp 105-106 °C; yield 72% (33.9 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.77 (s, 1H), 7.35-7.30 (m, 4H), 7.25 (s, 1H), 7.23-7.22 (m, 3H), 7.19-7.17 (m, 2H), 7.14-7.13 (m, 8H), 7.07-7.06 (m, 1H), 5.33 (s, 2H), 5.20 (s, 1H), 3.61 (t, *J* = 7.8 Hz, 2H), 2.84 (t, *J* = 7.8 Hz, 2H), 2.48 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 209.0, 191.9, 138.8, 138.3, 137.0, 136.6, 135.7, 129.2, 129.1, 128.5, 128.3, 127.0, 126.9, 124.8, 124.3, 123.9, 118.7, 108.4, 64.0, 50.8, 45.6, 31.2, 28.6; FT-IR (KBr) 2919, 2850, 1713, 1657, 1453, 1378, 1186, 1079, 970 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{33}H_{30}NO_2$: 472.2271, found 472.2277.

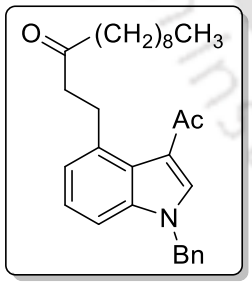


1-(3-Acetyl-1-benzyl-1*H*-indol-4-yl)-5-(3-bromophenyl)pentan-3-one 3af. Analytical TLC on silica gel, 1:3 ethyl acetate/hexane R_f = 0.43; brown liquid; yield 54% (26.3 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.81 (s, 1H), 7.35-7.32 (m, 3H), 7.31-7.28 (m, 2H), 7.17-7.14 (m, 4H), 7.12-7.09 (m, 2H), 7.07-7.06 (m, 1H), 5.34 (s, 2H), 3.55 (t, *J* = 7.8 Hz, 2H), 2.84 (t, *J* = 7.8 Hz, 2H), 2.77-2.71 (m, 4H), 2.52 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 210.1,

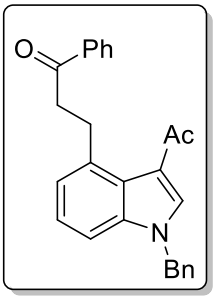
192.0, 144.0, 138.4, 137.2, 136.9, 135.7, 131.5, 130.0, 129.2, 129.1, 128.4, 127.2, 127.0, 124.5, 124.4, 124.0, 122.5, 118.7, 108.5, 50.9, 46.0, 44.1, 31.0, 29.4, 28.6; FT-IR (neat) 2922, 2852, 1710, 1655, 1525, 1444, 1375, 1190, 1073, 784 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{28}H_{27}BrNO_2$: 488.1220, found 488.1241.



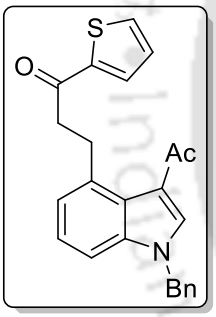
4-(3-Acetyl-1-benzyl-1*H*-indol-4-yl)-1-phenoxybutan-2-one 3ag. Analytical TLC on silica gel, 1:2 ethyl acetate/hexane R_f = 0.43; brown solid; mp 137-138 °C; yield 82% (33.7 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.80 (s, 1H), 7.35-7.30 (m, 3H), 7.25-7.22 (m, 2H), 7.18-7.14 (m, 4H), 7.10-7.09 (m, 1H), 6.94-6.92 (m, 1H), 6.84-6.83 (m, 2H), 5.33 (s, 2H), 4.62 (s, 2H), 3.60 (t, *J* = 7.8 Hz, 2H), 2.92 (t, *J* = 7.8 Hz, 2H), 2.50 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 207.5, 192.0, 158.1, 138.4, 137.2, 136.6, 135.7, 129.6, 129.2, 128.3, 127.0, 124.6, 124.4, 124.0, 121.4, 118.7, 114.7, 108.6, 73.0, 50.9, 42.2, 30.5, 28.5; FT-IR (KBr) 2919, 2851, 1722, 1653, 1494, 1376, 1243, 1080, 801 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{27}H_{26}NO_3$: 412.1907, found 412.1925.



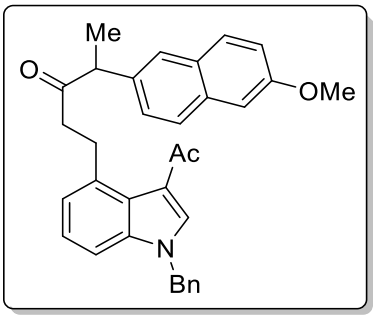
1-(3-Acetyl-1-benzyl-1*H*-indol-4-yl)dodecan-3-one 3ai. Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.45; brown liquid; yield 55% (23.7 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.80 (s, 1H), 7.36-7.30 (m, 3H), 7.18-7.13 (m, 4H), 7.10-7.07 (m, 1H), 5.34 (s, 2H), 3.54 (t, *J* = 7.8 Hz, 2H), 2.76 (t, *J* = 7.8 Hz, 2H), 2.53 (s, 3H), 2.41 (t, *J* = 7.8 Hz, 2H), 2.34 (t, *J* = 7.8 Hz, 2H), 1.30-1.24 (m, 12H), 0.89-0.86 (m, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 211.8, 192.0, 138.4, 137.3, 137.0, 135.7, 129.2, 128.3, 127.0, 124.5, 124.0, 118.8, 108.3, 50.9, 45.8, 43.0, 33.5, 32.0, 30.8, 29.8, 29.6, 28.6, 24.8, 23.9, 22.8, 14.2; FT-IR (neat) 2922, 2852, 1709, 1655, 1526, 1459, 1379, 1276, 1264, 1187, 750 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{29}H_{38}NO_2$: 432.2897, found 432.2871.



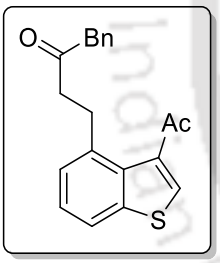
3-(3-Acetyl-1-benzyl-1*H*-indol-4-yl)-1-phenylpropan-1-one 3aj. Analytical TLC on silica gel, 1:3 ethyl acetate/hexane R_f = 0.40; colorless thick liquid; yield 43% (16.4 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.97-7.95 (m, 2H), 7.81 (s, 1H), 7.51-7.46 (m, 1H), 7.41-7.38 (m, 2H), 7.35-7.31 (m, 3H), 7.17-7.15 (m, 5H), 5.34 (s, 2H), 3.71 (t, J = 7.5 Hz, 2H), 3.38 (t, *J* = 7.5 Hz, 2H), 2.51 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.3, 180.6, 137.5, 137.4, 137.0, 135.8, 132.7, 129.2, 128.4, 128.38, 128.33, 127.0, 124.7, 124.6, 124.0, 118.9, 108.4, 50.9, 41.9, 30.7, 28.6. FT-IR (neat) 2922, 2853, 1682, 1656, 1525, 1448, 1376, 1260, 1081, 799 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{26}H_{24}NO_2$: 382.1802, found 382.1778.



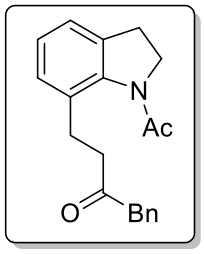
3-(3-Acetyl-1-benzyl-1*H*-indol-4-yl)-1-(thiophen-2-yl)propan-1-one 3ak. Analytical TLC on silica gel, 1:2 ethyl acetate/hexane R_f = 0.44; brown solid; mp 130-131 °C; yield 59% (22.8 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.82 (s, 1H), 7.70-7.69 (m, 1H), 7.56-7.55 (m, 1H), 7.36-7.30 (m, 3H), 7.19-7.15 (m, 5H), 7.05-7.04 (m, 1H), 5.34 (s, 2H), 3.71 (t, *J* = 7.8 Hz, 2H), 3.31 (t, *J* = 7.8 Hz, 2H), 2.53 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 193.4, 192.1, 144.9, 138.4, 137.09, 137.07, 135.7, 133.0, 132.0, 129.2, 128.3, 128.0, 127.0, 124.9, 124.5, 124.0, 118.8, 108.5, 50.9, 42.6, 31.1, 28.6; FT-IR (KBr) 2923, 2854, 1713, 1656, 1523, 1445, 1415, 1375, 1205, 729 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{24}H_{22}NO_2S$: 388.1366, found 388.1373.



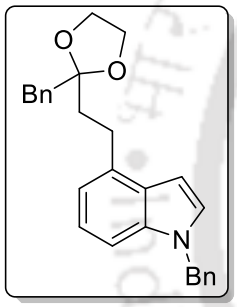
1-(3-Acetyl-1-benzyl-1*H*-indol-4-yl)-4-(6-methoxynaphthalen-2-yl)pentan-3-one 3al. Analytical TLC on silica gel, 1:2 ethyl acetate/hexane R_f = 0.46; yellow thick liquid; yield 61% (29.8 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.64 (s, 1H), 7.60-7.55 (m, 2H), 7.46 (s, 1H), 7.33-7.29 (m, 3H), 7.18-7.16 (m, 1H), 7.11-7.04 (m, 6H), 6.99-6.97 (m, 1H), 5.29-5.21 (m, 3H), 3.90 (s, 3H), 3.65-3.60 (m, 1H), 3.42-3.37 (m, 1H), 2.80-2.74 (m, 1H), 2.66-2.61 (m, 1H), 2.40 (s, 3H), 1.42 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 211.1, 191.8, 157.5, 138.2, 136.85, 136.81, 136.3, 135.7, 133.5, 129.3, 129.18, 129.14, 128.3, 127.2, 127.0, 126.7, 126.6, 124.6, 123.8, 118.8, 118.7, 108.3, 105.6, 55.4, 52.9, 50.7, 43.8, 31.0, 28.5, 17.5; FT-IR (neat) 2924, 1708, 1654, 1605, 1525, 1446, 1386, 1265, 745 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{33}H_{32}NO_3$: 490.2377, found 490.2372.



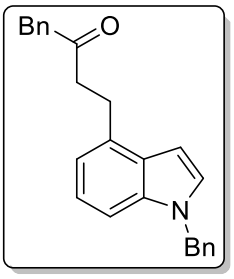
4-(3-Acetylbenzo[*b*]thiophen-4-yl)-1-phenylbutan-2-one 4A. Analytical TLC on silica gel, 1:8 ethyl acetate/hexane R_f = 0.44; brown liquid; yield 66% (21.2 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.97 (d, *J* = 7.8 Hz, 1H), 7.75 (d, *J* = 7.8 Hz, 1H), 7.42-7.39 (m, 1H), 7.34-7.32 (m, 1H), 7.30-7.27 (m, 2H), 7.25-7.22 (m, 1H), 7.19-7.17 (m, 2H), 3.71 (s, 2H), 3.33 (t, *J* = 7.2 Hz, 2H), 2.94 (t, *J* = 7.8 Hz, 2H), 2.64 (s, 3H);^{13}C NMR (150 MHz, $CDCl_3$) δ 206.4, 196.6, 152.2, 137.8, 133.9, 133.6, 129.5, 128.9, 127.2, 125.3, 124.5, 123.3, 122.2, 50.3, 43.2, 31.8, 24.6; FT-IR (neat) 2923, 2851, 1714, 1669, 1495, 1456, 1431, 1358, 1198, 760 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{20}H_{19}O_2S$: 323.1100, found 323.1104.



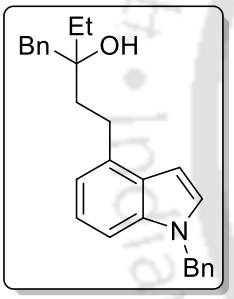
4-(1-Acetylindolin-7-yl)-1-phenylbutan-2-one 4B. Analytical TLC on silica gel, 1:3 ethyl acetate/hexane R_f = 0.41; yellow thick liquid; yield 75% (23.0 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.31-7.28 (m, 2H), 7.25-7.22 (m, 1H), 7.16-7.15 (m, 2H), 7.06-7.05 (m, 1H), 7.01 (t, *J* = 7.8 Hz, 1H), 6.97-6.96 (m, 1H), 4.01-3.99 (m, 2H), 3.68 (s, 2H), 2.99 (t, *J* = 7.8 Hz, 2H), 2.91-2.89 (m, 2H), 2.82-2.80 (m, 2H), 2.24 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 208.2, 140.9, 134.5, 129.5, 128.77, 128.70, 127.0, 125.6, 122.4, 51.2, 50.1, 41.9, 30.1, 28.0, 24.0; FT-IR (neat) 2923, 2851, 1713, 1665, 1451, 1388, 1188, 780 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{20}H_{22}NO_2$: 308.1645, found 308.1656.



1-Benzyl-4-(2-(2-benzyl-1,3-dioxolan-2-yl)ethyl)-1*H*-indole 3′. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.57; colorless thick liquid; yield 75% (60 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.24-7.22 (m, 2H), δ 7.21-7.12 (m, 6H), 7.04-6.98 (m, 5H), 6.82 (d, *J* = 7.2 Hz, 1H), 6.46-6.45 (m, 1H), 5.20 (s, 2H), 3.91-3.85 (m, 2H), 3.71-3.65 (m, 2H), 2.96-2.93 (m, 2H), 2.91 (s, 2H), 2.01-1.98 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 137.6, 136.9, 136.3, 134.7, 130.7, 128.8, 128.1, 127.7, 127.6, 126.9, 126.4, 121.9, 118.8, 111.4, 107.7, 100.1, 65.5, 50.2, 44.0, 38.9, 27.5; FT-IR (neat) 2918, 2851, 1531, 1491, 1456, 1242, 1250, 1177, 1075, 753 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{27}H_{28}NO_2$: 398.2115, found 398.2117.



4-(1-Benzyl-1*H*-indol-4-yl)-1-phenylbutan-2-one 4. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.50; colorless solid; mp 113-114 °C; yield 72% (35.6 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31-7.27 (m, 5H), 7.25-7.24 (m, 1H), 7.17-7.13 (m, 3H), 7.11-7.10 (m, 3H), 7.09-7.05 (m, 1H), 6.87 (d, *J* = 7 Hz, 1H), 6.488-6.482 (m, 1H), 5.30 (s, 2H), 3.67 (s, 2H), 3.16 (t, *J* = 8 Hz, 2H), 2.90 (t, *J* = 8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.2, 137.5, 136.3, 134.3, 133.3, 129.5, 128.9, 128.8, 128.0, 127.8, 127.7, 127.1, 126.9, 122.0, 118.9, 108.1, 99.9, 50.5, 50.3, 42.8, 27.6; FT-IR (KBr) 1714, 1635, 1485, 1435, 1233, 1171, 975, 736 cm^{-1}; FT-IR (KBr) 2924, 2855, 1713, 1494, 1451, 1357, 1299, 1159, 1079, 748 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{25}H_{24}NO$: 354.1852, found 354.1832.



3-Benzyl-1-(1-benzyl-1*H*-indol-4-yl)pentan-3-ol 5. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.41; green liquid; yield 86% (33 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32-7.22 (m, 9H), 7.14-7.07 (m, 5H), 6.93 (d, *J* = 7 Hz, 1H), 6.568-6.562 (m, 1H), 5.29 (s, 2H), 3.00 (t, *J* = 8.5 Hz, 2H), 2.869-2.864 (m, 2H), 1.96-1.84 (m, 2H), 1.64-1.55 (m, 3H), 1.02 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 137.6, 137.3, 136.3, 134.9, 130.7, 128.8, 128.4, 128.0, 127.8, 127.6, 126.9, 126.6, 122.0, 118.7, 107.7, 100.0, 74.7, 50.2, 45.2, 39.0, 31.0, 27.5, 8.5; FT-IR (neat) 3360, 2920, 2852, 1734, 1601, 1494, 1453, 1436, 1354, 1276, 1029, 749 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{27}H_{30}NO$: 384.2322; $[[M-H_2O]+H]^+$ $C_{27}H_{28}N$: 366.2216; found 366.2220.

Crystal Data and Structure Refinement for 3a

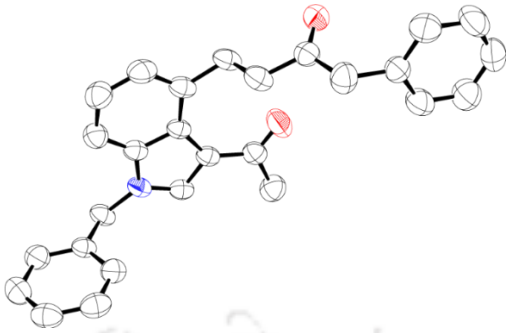


Figure 2. ORTEP diagram of 4-(3-acetyl-1-benzyl-1*H*-indol-4-yl)-1-phenylbutan-2-one **3a** with 50% ellipsoid (**CCDC 2178663**).

Identification code	**3a**
Empirical formula	$C_{27}H_{25}NO_2$
Solvent for crystal growth	Acetonitrile
Formula weight	395.48
Crystal habit, colour	block and yellow
Temperature, *T*/K	296 K
Wavelength, λ/Å	0.71073
Crystal system	triclinic
Space group	'P -1'
Unit cell dimensions	a = 10.0339(7) Å
	b = 11.0257(7) Å
	c = 11.1550(8) Å
	α = 110.081(2)
	β = 107.586(2)
	γ = 98.718(2)
Volume, *V*/Å^3	1059.02(13)
Z	2
Calculated density, g·cm^{-3}	1.240
Absorption coefficient, μ/mm^{-1}	0.078
F(000)	420.0
θ range for data collection	2.25 to 28.36°
Limiting indices	$-13 \leq h \leq 13$, $-14 \leq k \leq 14$, $-14 \leq l \leq 14$

Reflection collected / unique	5276 / 3387
Completeness to θ	99.80% (θ = 25.24°)
Absorption correction	none
Refinement method	'SHELXL-2019/1 (Sheldrick 2019)'
Data / restraints / parameters	5276/0/272
Goodness-of-fit on F^2	1.027
Final *R* indices [*I* >2sigma(*I*)]	*R*1 = 0.0884, *wR*2 = 0.1350
R indices (all data)	*R*1 = 0.0512, *wR*2 = 0.1174

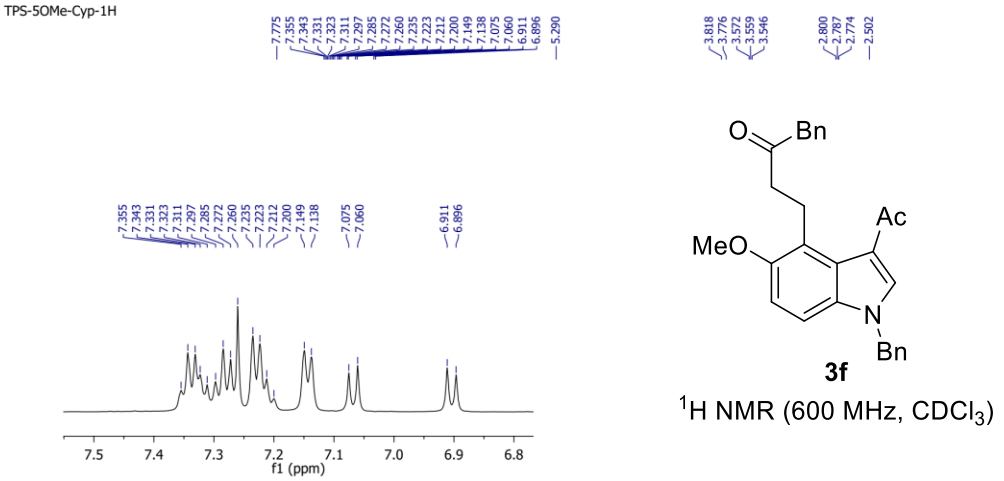
2.5 References

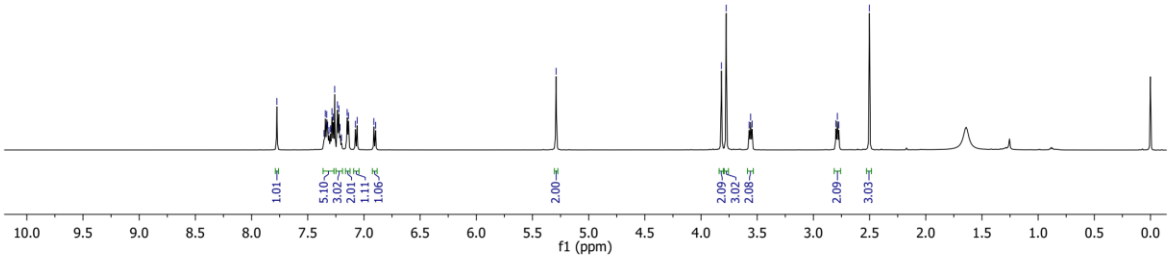
1. (a) Somei, M.; Yamada, F. *Nat. Prod. Rep.* **2005**, *22*, 73. (b) Taylor, R. D.; MacCoss, M.; Lawson, A. D. G. *J. Med. Chem.* **2014**, *57*, 5845. (c) Zhang, M.-Z.; Chen, Q.; Yang, G.-F. *Eur. J. Med. Chem.* **2015**, *89*, 421. (d) Chadha, N.; Silakari, O. *Eur. J. Med. Chem.* **2017**, *134*, 159.
2. (a) Bandini, M.; Eichholzer, A. *Angew. Chem., Int. Ed.* **2009**, *48*, 9608. (b) Dalpozzo, R. *Chem. Soc. Rev.* **2015**, *44*, 742. (c) Corsello, M. A.; Kim, J.; Garg, N. K. *Chem. Sci.* **2017**, *8*, 5836.
3. (a) Stuart, D. R.; Villemure, E.; Fagnou, K. *J. Am. Chem. Soc.* **2007**, *129*, 12072. (b) Toutov, A. A.; Liu, W.-B.; Betz, K. N.; Fedorov, A.; Stoltz, B. M.; Grubbs, R. H. *Nature* **2015**, *518*, 80. (c) Jacob, N.; Zaid, Y.; Oliveira, J. C. A.; Ackermann, L.; Wencel-Delord, J. *J. Am. Chem. Soc.* **2022**, *144*, 798. For a review, see: (d) Sandtorv, A. H. *Adv. Synth. Catal.* **2015**, *357*, 2403.
4. For selected reviews, see: (a) Leitch, J. A.; Bhonoah, Y.; Frost, C. G. *ACS Catal.* **2017**, *7*, 5618. (b) Pradhan, S.; de, P. B.; Shah, T. A.; Punniyamurthy, T. *Chem.-Asian J.* **2020**, *15*, 4184. (c) Prabagar, B.; Yang, Y.; Shi, Z. *Chem. Soc. Rev.* **2021**, *50*, 11249.
5. For seminal publications, see: (a) Yang, G.; Lindovska, P.; Zhu, D.; Kim, J.; Wang, P.; Tang, R.-Y.; Movassaghi, M.; Yu, J.-Q. *J. Am. Chem. Soc.* **2014**, *136*, 10807. (b) Yang, Y.; Qiu, X.; Zhao, Y.; Mu, Y.; Shi, Z. *J. Am. Chem. Soc.* **2016**, *138*, 495. (c) Choi, I.; Messinis, A. M.; Ackermann, L. *Angew. Chem., Int. Ed.* **2020**, *59*, 12534.
6. (a) Garg, N. K.; Sarpong, R.; Stoltz, B. M. *J. Am. Chem. Soc.* **2002**, *124*, 13179. (b) Wallwey, C.; Matuschek, M.; Xie, X.- L.; Li, S.-M. *Org. Biomol. Chem.* **2010**, *8*, 3500.

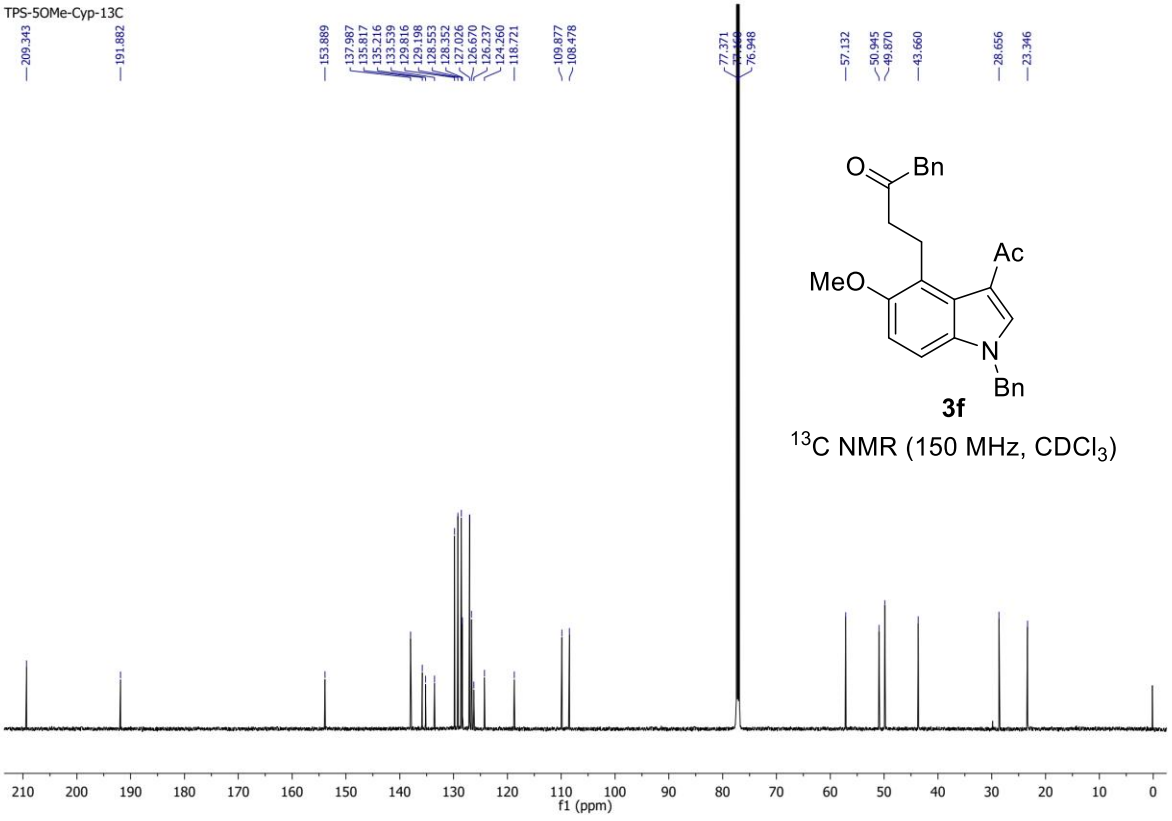
(c) Maimone, T. J.; Ishihara, Y.; Baran, P. S. *Tetrahedron* **2015**, *71*, 3652. (d) Liu, H.; Jia, Y. *Nat. Prod. Rep.* **2017**, *34*, 411.

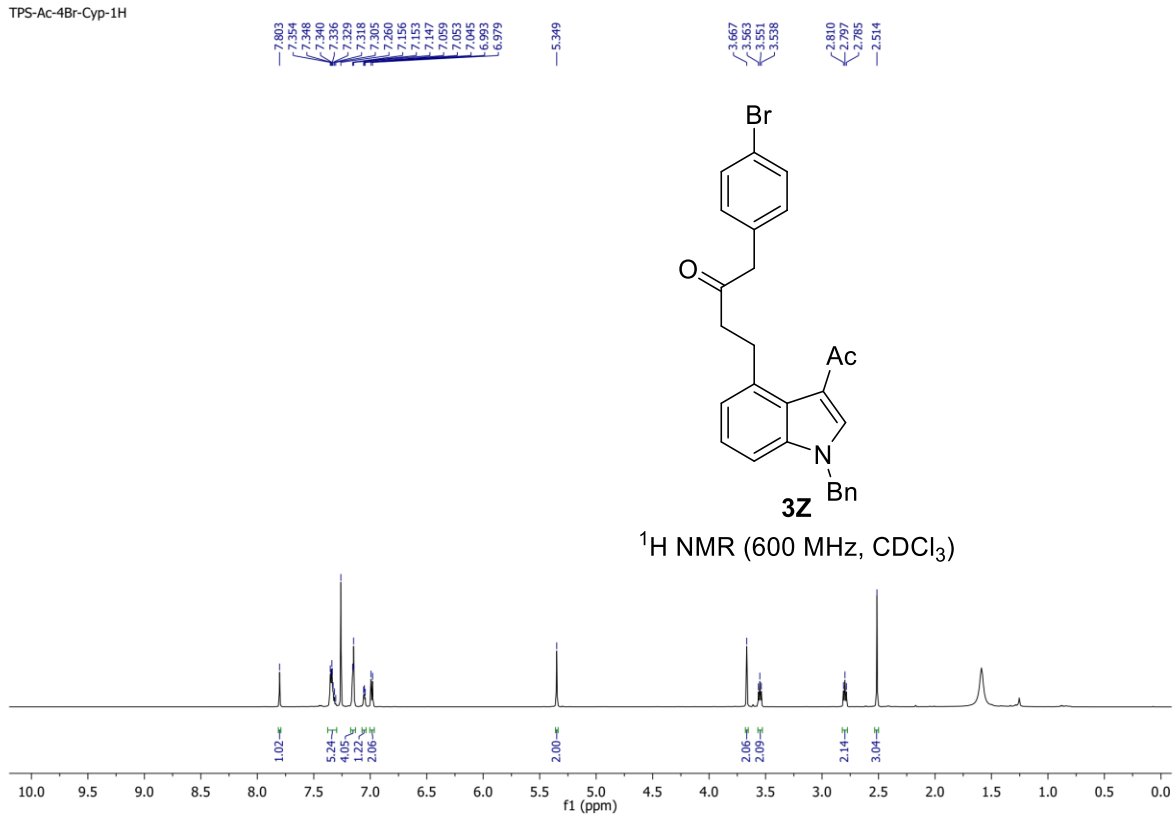
7. For examples, see: (a) Lanke, V.; Prabhu, K. R. *Chem. Commun.* **2017**, *53*, 5117. (b) Lv, J.; Wang, B.; Yuan, K.; Wang, Y.; Jia, Y. *Org. Lett.* **2017**, *19*, 3664. (c) Lv, J.; Chen, X.; Xue, X.-S.; Zhao, B.; Liang, Y.; Wang, M.; Jin, L.; Yuan, Y.; Han, Y.; Zhao, Y.; Lu, Y.; Zhao, J.; Sun, W.-Y.; Houk, K. N.; Shi, Z. *Nature* **2019**, *575*, 336. (d) Pradhan, S.; De, P. B.; Punniyamurthy, T. *Org. Lett.* **2019**, *21*, 9898. (e) Harada, S.; Yanagawa, M.; Nemoto, T. *ACS Catal.* **2020**, *10*, 11971. (f) Pradhan, S.; Mishra, M.; De, P. B.; Banerjee, S.; Punniyamurthy, T. *Org. Lett.* **2020**, *22*, 1720. (g) Basak, S.; Paul, T.; Punniyamurthy, T. *Org. Lett.* **2022**, *24*, 554. For review see: (h) Kalepu, J.; Gandeepan, P.; Ackermann, L.; Pilarski, L. T. *Chem. Sci.* **2018**, *9*, 4203.
8. (a) Wang, F.; Yu, S.; Li, X. *Chem. Soc. Rev.* **2016**, *45*, 6462. (b) Nairoukh, Z.; Cormier, M.; Marek, I. *Nat. Rev. Chem.*, **2017**, *1*, 0035. (c) Shah, T. A.; De, P. B.; Pradhan, S.; Banerjee, S.; Punniyamurthy, T. *Chem. Asian J.* **2019**, *14*, 4520.
9. (a) Rosa, D.; Orellana, A. *Chem. Commun.*, **2012**, *48*, 1922. (b) Zhou, X.; Yu, S.; Kong, L.; Li, X. *ACS Catal.* **2016**, *6*, 647. (c) Lee, M.; Heo, J.; Kim, D.; Chang, S. *J. Am. Chem. Soc.* **2022**, *144*, 3667. For selected reviews, see: (d) Kulinkovich, O. G. *Chem. Rev.* **2003**, *103*, 2597. (e) McDonald, T. R.; Mills, L. R.; West, M. S.; Rousseaux, S. A. L. *Chem. Rev.* **2021**, *121*, 3.
10. Chan, W.-W.; Lo, S.-F.; Zhou, Z.; Yu, W.-Y. *J. Am. Chem. Soc.* **2012**, *134*, 13565.
11. Li, J.; Ackermann, L. *Org. Chem. Front.* **2015**, *2*, 1035.
12. Pan, S.; Ryu, N.; Shibata, T. *Adv. Synth. Catal.* **2014**, *356*, 929.
13. Schischko, A.; Kaplaneris, N.; Rogge, T.; Sirvinskaite, G.; Son, J.; Ackermann, L. *Nat. Commun.* **2019**, *10*, 3553.
14. Shi, Z.; Boultadakis-Arapinis, M.; Glorius, F. *Chem. Commun.* **2013**, *49*, 6489.
15. Potter, T. J.; Kamber, D. N.; Mercado, B. Q.; Ellman, J. A. *ACS Catal.* **2017**, *7*, 150.
16. Wang, S.; Miao, E.; Wang, H.; Song, B.; Huang, W.; Yang, W. *Chem. Commun.* **2021**, *57*, 5929.
17. Liu, J.; Yang, Z.; Jiang, J.; Zeng, Q.; Zheng, L.; Liu, Z.-Q. *Org. Lett.* **2021**, *23*, 5927.
18. Seoane, A.; Casanova, N.; Quiñones, N.; Mascareñas, J. L.; Gulías, M. *J. Am. Chem. Soc.* **2014**, *136*, 834.
19. Borah, A. J.; Shi, Z. *Chem. Commun*. **2017**, *53*, 3945.

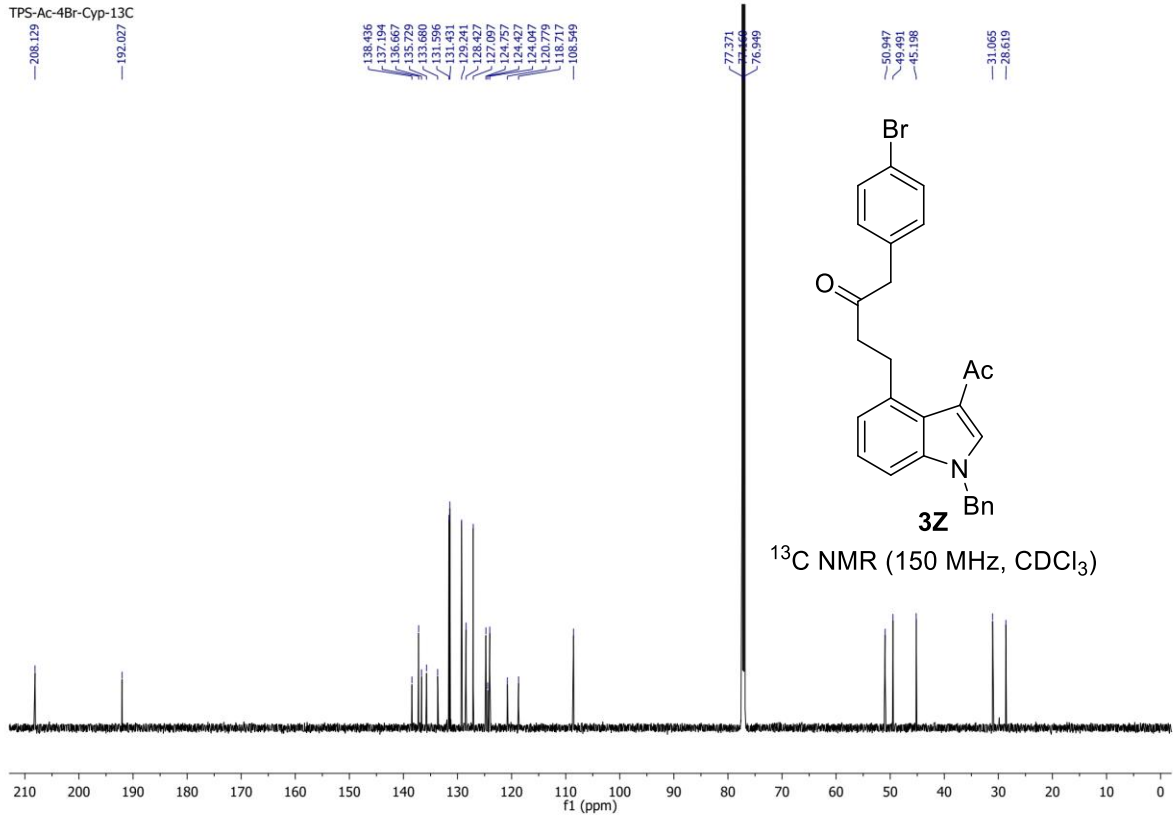
2.6 Selected NMR Spectra

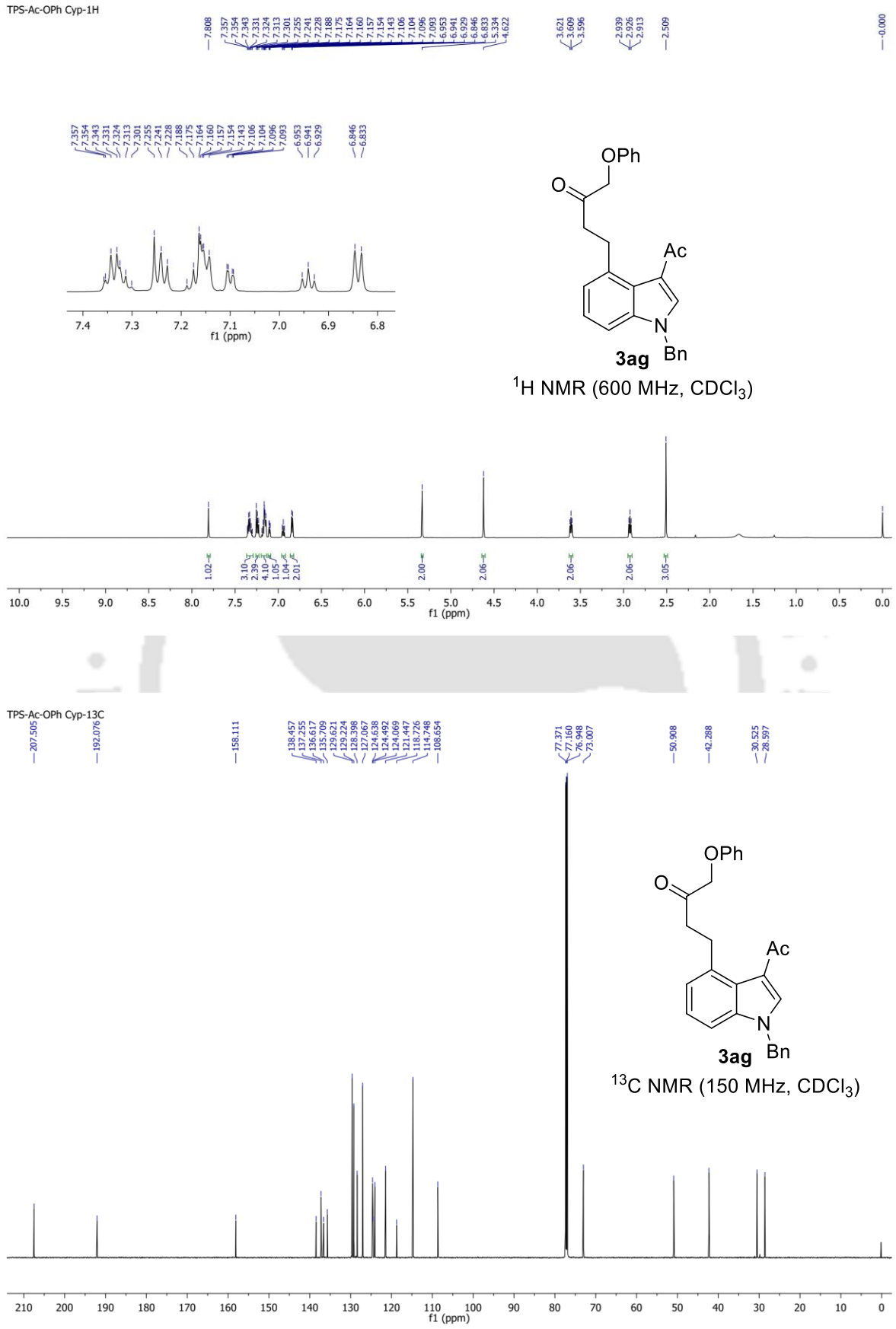






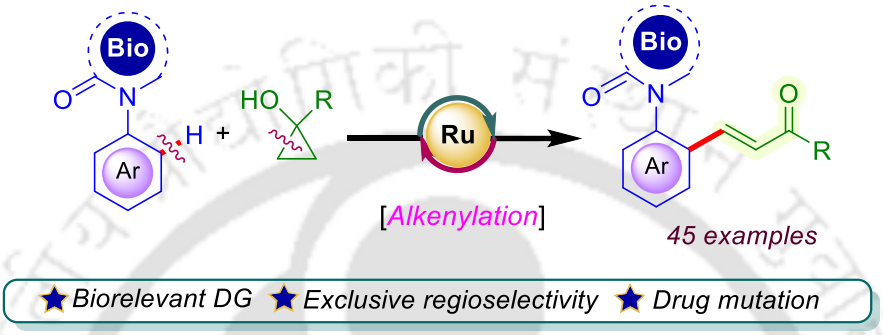






Chapter III

Ru-Catalyzed C-H Alkenylation of Arenes exploiting Cyclopropanols



Org. Lett. **2023**, *25*, 8975.

Chapter III

Ru-Catalyzed C-H Alkenylation of Arenes Exploiting Cyclopropanols

Implementation of synthetic routes that allows rapid modification of organic scaffolds into lead compounds in a step- and atom-economical manner has sparked great attention in scientific community in recent times. In this context, transition-metal-catalyzed chelation assisted C-H functionalization has emerged as powerful tool.[1] Further, lactams are key structural motifs in plenty of natural products and drug molecules. Since the groundbreaking discovery of penicillin by Fleming, β-lactams has become cornerstone of antibiotics development.[2a,c] Likewise, γ-lactam derivatives have emerged as essential structural motif in therapeutics, including $\alpha_v\beta_3$-antagonists and brivaracetam drugs.[2b,4a] In addition, ε-caprolactam is a key component in the production of industrially potent compounds *viz.* nylon, paint and plastic.[3] Moreover, morpholinones, pyridones and isoindolin-1-ones are privileged among wide variety of bioactive products and functional molecules.[4] In this realm, development of a unified approach for the utilization of these easily accessible bioactive agents as intrinsic weak coordinating DGs for the site-selective C-H bond functionalization would serve as a pivotal tool in organic synthesis. Further, *N*-arylated derivatives of these aforementioned molecules received enormous attention due to their overabundance in natural products, drug molecules and agrochemicals.[4] The intrinsic DG assisted selective modulation of *N*-arylated bioactive molecules would thus be highly appealing. Meanwhile, α,β-unsaturated ketones are the essential functional handle in synthetic organic chemistry.[5] Thus, the development of advanced synthetic methods for their incorporation is a primary focus of contemporary research. Alongside, the strained ring systems, due to their distinctive architecture and rich reactivity have been widely exploited as organic synthons in synthetic chemistry.[6] Among them, readily accessible cyclopropanol stands out as a staple coupling partner due to their propensity for ring-strain release *via* C-C bond activation under TM-catalysis.[7] Interestingly, cyclopropanol shows manifold reactivity in presence of different catalytic system. However, merging C-H and C-C bond activation in a cascade process, although a formidable task, hold significant value from a synthetic viewpoint. In chapter II, we successfully demonstrated the use of cyclopropanol as alkyl surrogate. In this work, we describe a Ru(II)-catalyzed C-H alkenylation with cyclopropanols utilizing bioactive structural motifs as weak chelating DG *via* the sequential C-H and C-C activation. The salient features of our

protocol include high regioselectivity, broad substrate scope and late-stage diversifications of bioactive molecules.

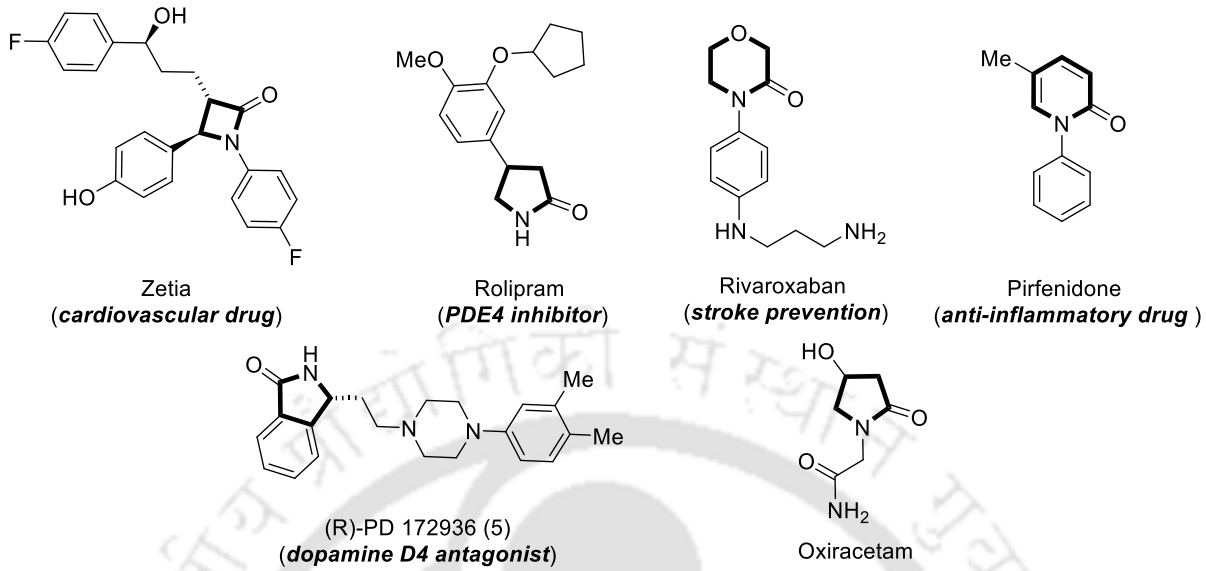
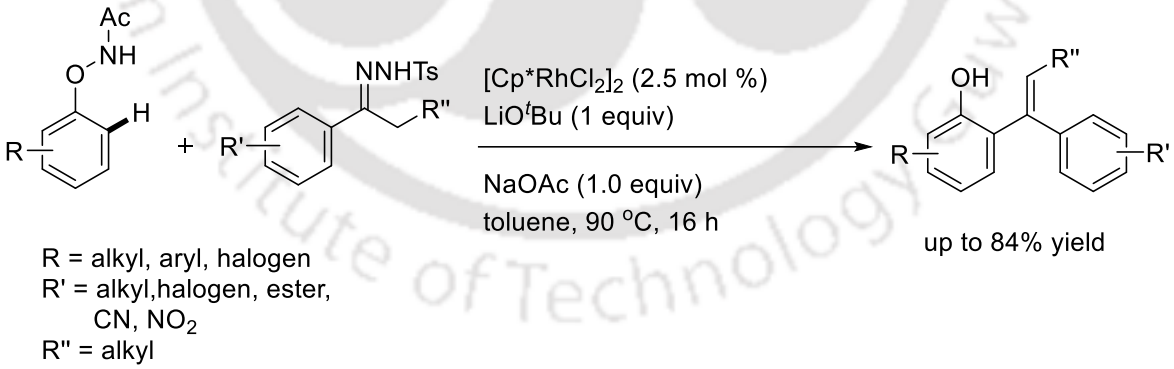


Figure 1. Examples of Pharmacologically Active Compounds

3.1 Alkenylation of Arenes

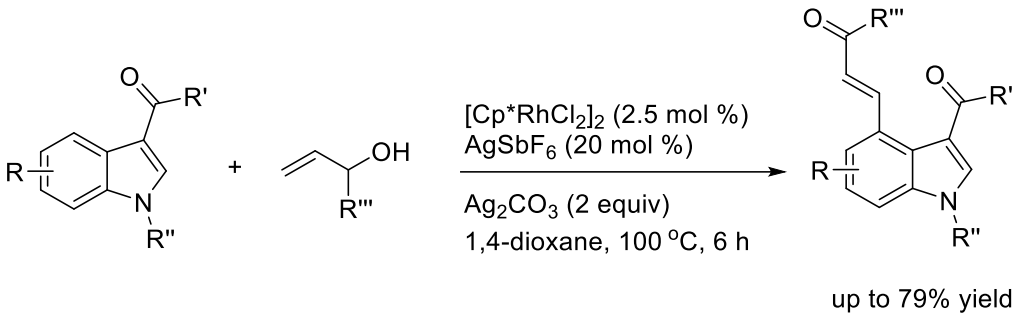
3.1.1 Rh-Catalyzed Reactions

Wang and co-workers reported Rh-catalyzed C-H alkenylation of *N*-phenoxyacetamides with *N*-tosylhydrazones (Scheme 1).[8] The reaction proceeded under mild and oxidant free conditions. A variety of substrates were well tolerated and provided the desired products in good yields.



Scheme 1. Rh-Catalyzed Alkenylation of *N*-Phenoxyacetamides

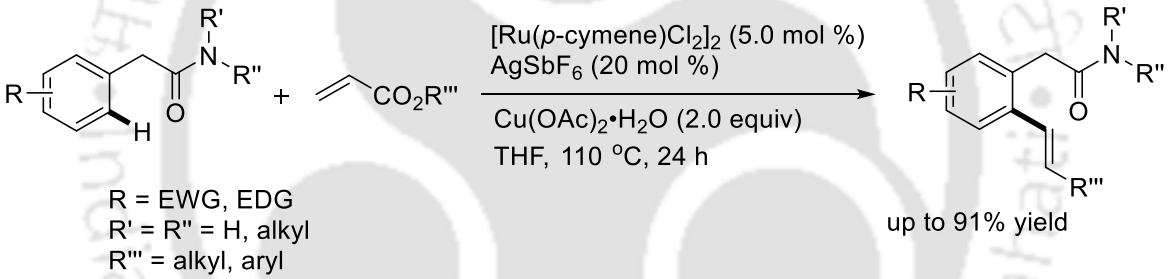
The Rh-catalyzed C4-H alkenylation of indoles with allyl alcohols utilizing weak carbonyl assistance has been developed (Scheme 2).[9] A diverse range of indole substrates were compatible and for allyl alcohols, both aryl and alkyl substituents at the carbinol carbon reacted efficiently to give the desired product. Naturally occurring tertiary terpene alcohol isophytol furnished the C4-allylated product under the standard reaction conditions.



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

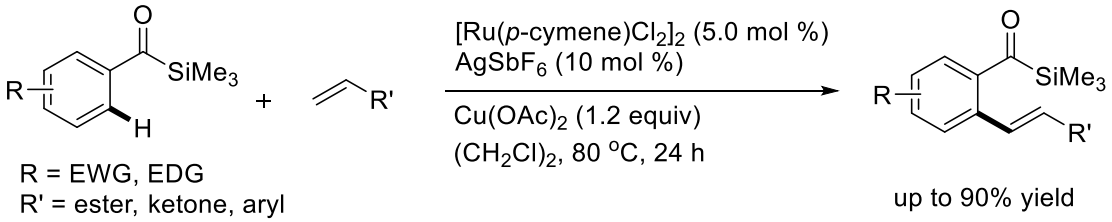
3.1.2 Ru-Catalyzed Reactions

Ackermann group devised a method for the Ru-catalyzed arene C-H alkenylation with alkenes by distal weak coordinating *O*-acetamide assistance (Scheme 3).[10] A variety of substrates with electron deficient and rich substituents were compatible. Detailed mechanistic investigations and DFT studies revealed that a challenging six-membered metallacycle was formed through carboxylate-mediated base-assisted internal electrophilic-type substitution of the C-H bond.



Scheme 3. Ru-Catalyzed Acetamide Directed C-H Alkenylation of Arenes

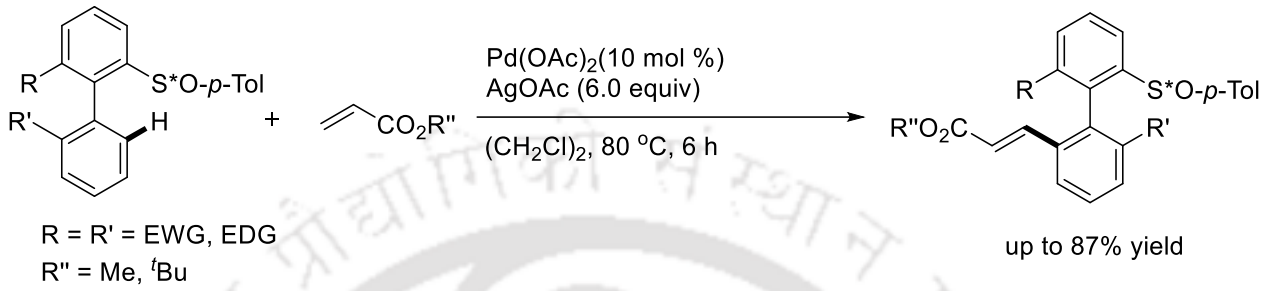
The Ru-catalyzed oxidative C-H alkenylation of aroylsilanes with activated alkenes was described for the access of diverse array styrene derivatives bearing acylsilanes with excellent regio- and stereo-selcetivities (Scheme 4).[11] Interestingly, the acylsilane DG was efficiently transformed into aldehyde and carboxylic acid, demonstrating its versatility.



Scheme 4. Ru-Catalyzed Acylsilane-directed C-H Alkenylation of Arenes

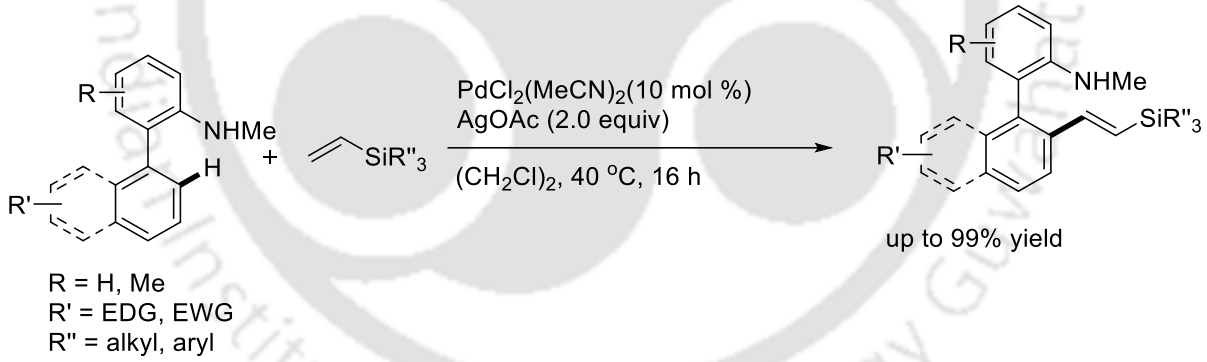
3.1.3 Pd-Catalyzed Reactions

The development of Pd-catalyzed atropodiastereoselective C-H olefination with acrylates for the synthesis of axially chiral biaryls was reported by Colobert group (Scheme 5).[12] Enantiopure *p*-tolyl-sulfoxide was employed as both DG and chiral auxiliary. The observed atroposelectivity presumably attributed to the diastereomeric discrimination during the cyclometallation step.



Scheme 5. Pd-Catalyzed Chiral Auxiliary Assisted Atroposelective C-H Alkenylation

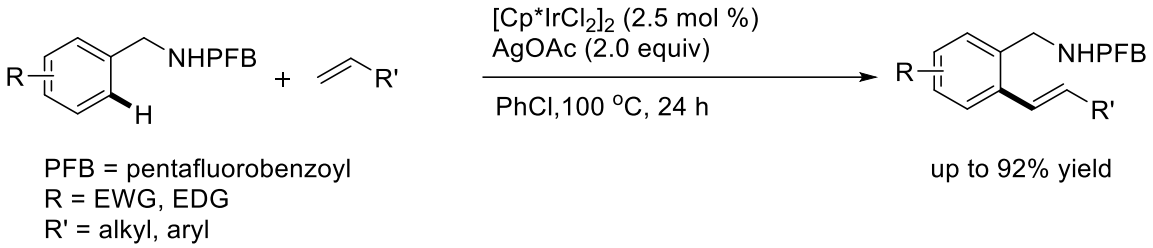
Cui and Xu groups explored Pd-catalyzed amino-chelation-assisted arene C-H olefination using unactivated vinylsilanes (Scheme 6).[13] The reaction offers ligand-free conditions to access broad range of arylated vinyl silanes in good yields exclusive (*E*)-selectivities.



Scheme 6. Pd-Catalyzed Olefination 2-Amino Biaryls with Vinylsilanes

3.1.4 Ir-Catalyzed Reaction

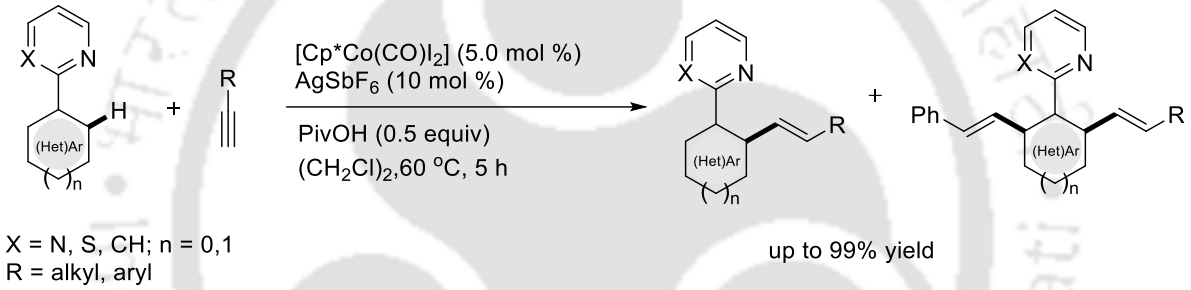
Ir-catalyzed oxidative alkenylation of benzylamine with acrylates has been demonstrated using pentafluorobenzoyl as the chelation assistance (Scheme 7).[14] Diversely substituted benzylamine and acrylates were found to be compatible. The reaction is scalable and the post-synthetic transformations illustrate its potential.



Scheme 7. Ir-Catalyzed Olefination of Benzylamine

3.1.5 Co-Catalyzed Reaction

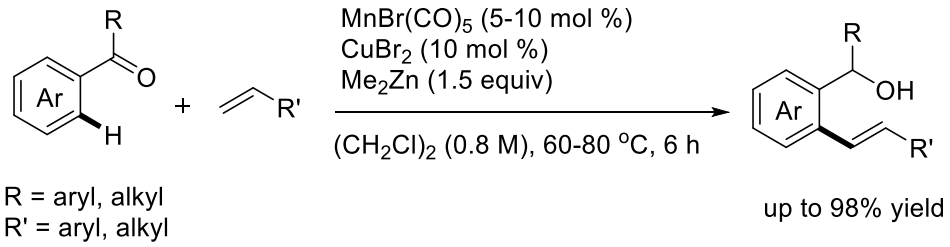
Chen and Yu groups described the Co-catalyzed alkenylation of arenes and 6-arylpurines with terminal alkynes with exclusive *E*-selectivity (Scheme 8).[15] This approach enabled the efficient synthesis of a mitochondria-targeted imaging dye, showcasing the versatility of Co-catalyzed alkenylation in designing functional dyes.



Scheme 8. Co-Catalyzed Alkenylation with Terminal Alkynes

3.1.6 Mn-Catalyzed Reaction

Chen and Wang groups developed an efficient Mn-catalyzed redox-neutral pathway for the directed C-H alkenylation of ketones with unactivated alkenes (Scheme 9).[16] The carbonyl group of ketone serves dual role, as weak coordinating DG and a hydrogen acceptor, thereby synthesizing C-H olefinated benzylic alcohols. Mechanistic studies and DFT calculations unveiled a distinctive concerted bis-metalation deprotonation (CMBD) underlying the Mn-Zn-enabled C-H activation.



Scheme 9. Mn-Catalyzed C-H Olefination with Unactivated Olefins

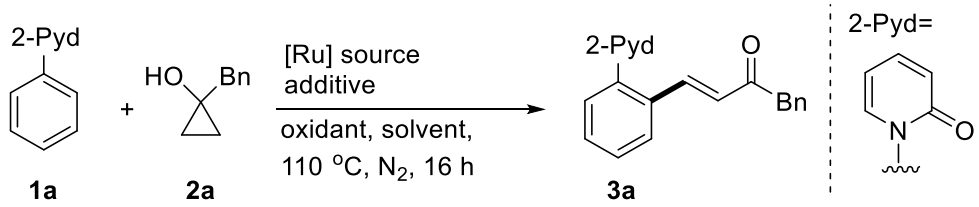
3.2 Present Study

On account of the salient synthetic importance of alkenyl functionality, herein, we report the Ru(II)-catalyzed arene C-H alkenylation with cyclopropanols exploiting bioactive weak chelating structural motifs *via* sequential C-H and C-C activation. We started our optimization with 1-phenyl-pyridin-2(1*H*)-one **1a** and 1-benzylcyclopropan-1-ol **2a** as standard substrates (Table 1). To our delight, the target alkenylated **3a** was obtained in 25% yield and 86:14 (*E/Z*)-diastereoselectivity, when the substrates were stirred with 5 mol % of $[RuCl_2(p\text{-cymene})]_2$, 20 mol % of $AgSbF_6$ and 2 equiv of Ag_2CO_3 in 1,4-dioxane at 110 ^oC for 16 h under N_2. For further optimization, we varied different additives, oxidants and solvents. Initially, among the oxidants we screened such as Ag_2O, AgOAc, $Cu(OAc)_2$ and $Cu(OAc)_2{\cdot}H_2O$, the later gave the best result with 61% yield and 93:7 (*E/Z*)-diastereoselectivity (entries 2-5). Further, the different Ag-salts were examined and $AgNTf_2$ was found to provide the highest yield of 82% and 96:4 (*E/Z*)-diastereoselectivity (entry 7). Subsequent solvent screening revealed that 1,4-dioxane is the optimal solvent, while other solvents like THF, DME, MeOH, H_2O, $(CH_2Cl)_2$ and toluene were less effective (entries 8-13). The reaction did not proceed without the catalyst, Ag-source or oxidant, implying their necessity for the alkenylation (entries 14-16). The use of $RuCl_3{\cdot}3H_2O$ as catalyst failed to provide the target product (entry 17). Moreover, decreasing the oxidant amount or reaction temperature adversely affected the product yield (entries 18-19).

With the optimal reaction conditions, the scope with various weakly coordinating bioactive DGs **1A-J** was investigated (Table 2). Remarkably, *N*-aryl *β*-lactam **1A-B** coupled smoothly with **2a** to afford the alkenylated products **3A-B** in 46-52% yields and *E/Z* ≥ 88:12. However, *p*-nitro substituent **1C** produced trace amount of desired product. Moreover, *N*-Aryl-*γ*-lactams **1D-E** trigger the reaction efficiently, providing **3D-E** in 72-77% yields with *E/Z* ratio of > 96:4. *N*-Phenyl isoindolin-1-one **1F**, *N*-(hetero)aryl morpholinones **1G-H**, 2-phenylisoquinoline-1(2*H*)-one **1I** reacted to furnish the products **3F-I** in 41-70% yields and *E/Z* ≥ 83:17. Of note, seven membered *ε*-caprolactam assisted alkenylation occurred yielding **3J** in 79% with *E/Z* ratio of > 96:4. Gratifyingly, *N*-phenyl *γ*-lactam **1D** and morpholinone **1G** reacted smoothly with gemfibrozil and felbinac-derived cyclopropanols to afford **3K-L** in 54-75% yields with *E/Z* of ≥ 91:9, showcasing the potentiality of the protocol for late-stage drug modifications.

With these intriguing results, a diverse array of electronically varied functionalized *N*-aryl pyridones were examined to investigate substituent effects (Table 3). The substrates with 3-chloro **1b**, 3-trifluoromethyl **1c**, 3-trimethylsilyl **1d**, 4-benzyloxy **1e** and 5-fluoro **1f** substitution at the pyridone ring were susceptible to the reaction conditions, giving **3b- f** in 57-68% yields

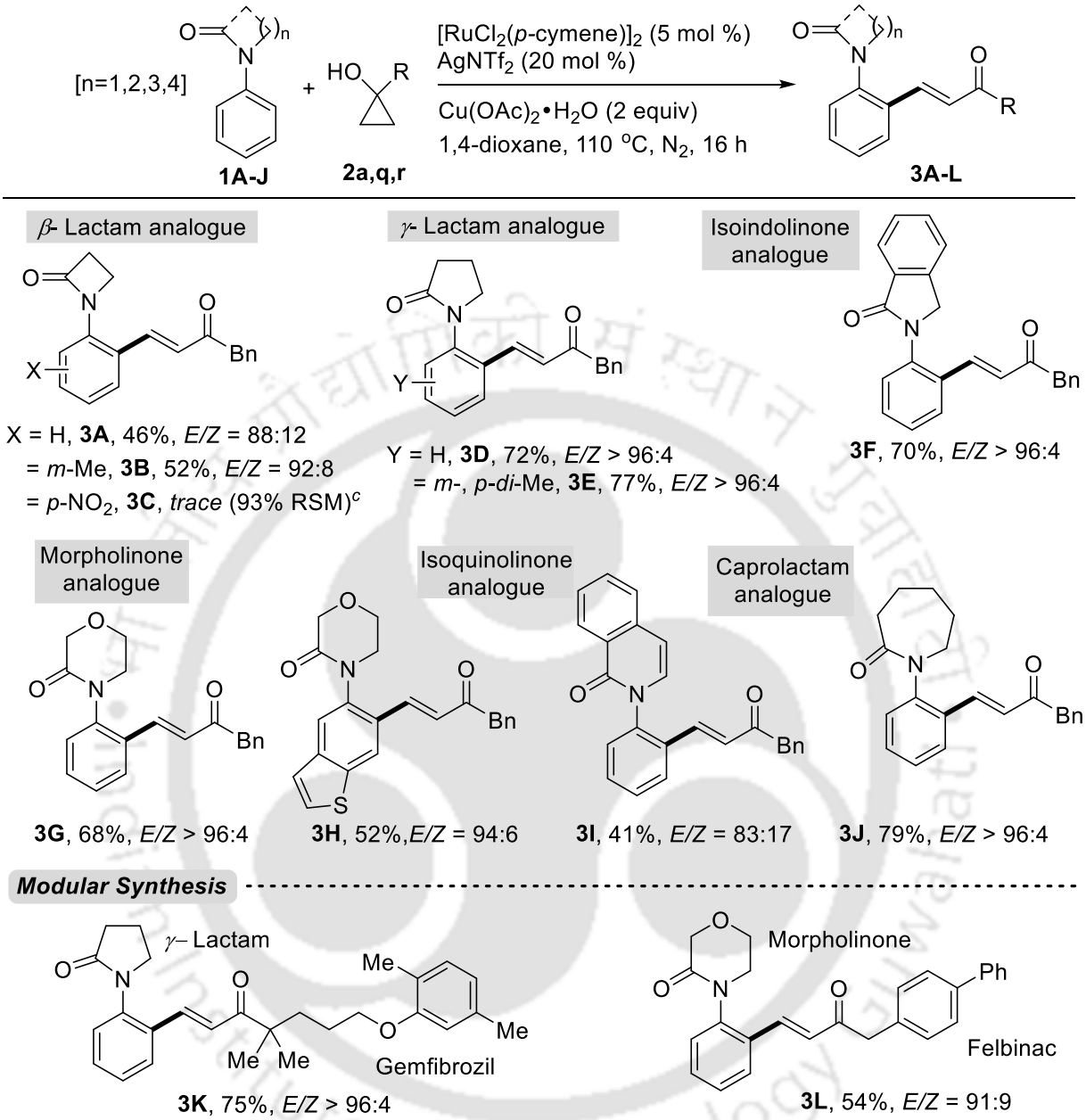
Table 1. Optimization of the Reaction Conditions[a]



Entry	Additive	Oxidant	Solvent	Yield[b] (%)	*E/Z*[c]
1	$AgSbF_6$	Ag_2CO_3	1,4-dioxane	25	86:14
2	$AgSbF_6$	Ag_2O	1,4-dioxane	n.d.	-
3	$AgSbF_6$	AgOAc	1,4-dioxane	32	89:11
4	$AgSbF_6$	$Cu(OAc)_2$	1,4-dioxane	52	91:9
5	$AgSbF_6$	$Cu(OAc)_2{\cdot}H_2O$	1,4-dioxane	61	93:7
6	$AgBF_4$	$Cu(OAc)_2{\cdot}H_2O$	1,4-dioxane	trace	-
7	**$AgNTf_2$**	**$Cu(OAc)_2{\cdot}H_2O$**	**1,4-dioxane**	**82**	**96:4**
8	$AgNTf_2$	$Cu(OAc)_2{\cdot}H_2O$	THF	30	67:33
9	$AgNTf_2$	$Cu(OAc)_2{\cdot}H_2O$	DME	21	67:33
10	$AgNTf_2$	$Cu(OAc)_2{\cdot}H_2O$	MeOH	n.d.	-
11	$AgNTf_2$	$Cu(OAc)_2{\cdot}H_2O$	H_2O	n.d.	-
12	$AgNTf_2$	$Cu(OAc)_2{\cdot}H_2O$	$(CH_2Cl)_2$	56	89:11
13	$AgNTf_2$	$Cu(OAc)_2{\cdot}H_2O$	toluene	37	91:9
14[d]	$AgNTf_2$	$Cu(OAc)_2{\cdot}H_2O$	1,4-dioxane	n.d.	-
15	-	$Cu(OAc)_2{\cdot}H_2O$	1,4-dioxane	trace	-
16	$AgNTf_2$	-	1,4-dioxane	n.d.	-
17[e]	$AgNTf_2$	$Cu(OAc)_2{\cdot}H_2O$	1,4-dioxane	n.d.	-
18[f]	$AgNTf_2$	$Cu(OAc)_2{\cdot}H_2O$	1,4-dioxane	52	96:4
19[g]	$AgNTf_2$	$Cu(OAc)_2{\cdot}H_2O$	1,4-dioxane	36	96:4

[a]Reaction conditions: **1a** (0.2 mmol), **2a** (0.4 mmol), $[RuCl_2(p\text{-cymene})]_2$ (5 mol %), additive (20 mol %), oxidant (0.4 mmol), solvent (1.5 mL), 110 °C, 16 h, N_2. [b]Isolated yield. [c] Determined by ^1H NMR. [d]Without $[RuCl_2(p\text{-cymene})]_2$. [e]Using 5 mol % $RuCl_3{\cdot}3H_2O$. [f]Using 1 equiv $Cu(OAc)_2{\cdot}H_2O$ [g]At 60°C. n.d. = not detected.

Table 2. Scope of Arene C-H Alkenylation with Weak-chelating Bioactive DGs[a,b,d]

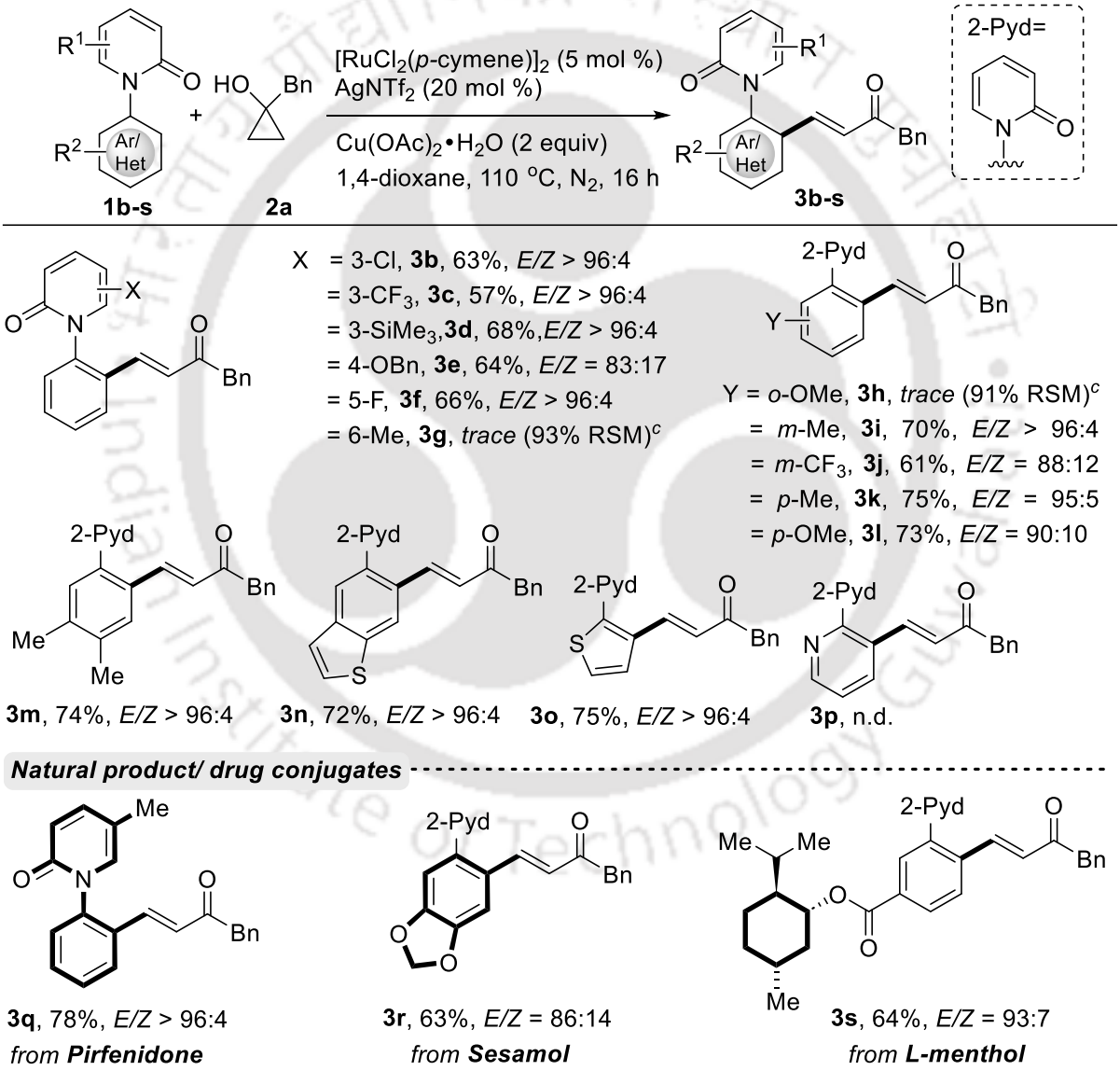


[a]Reaction conditions: **1A-J** (0.2 mmol), **2a** or **2q** or **2r** (0.4 mmol), $[RuCl_2(p\text{-cymene})]_2$ (5 mol %), $AgNTf_2$ (20 mol %), $Cu(OAc)_2 \cdot H_2O$ (2 equiv), 1,4-dioxane (1.5 mL), 110 °C, 16 h, N_2. [b]Isolated yield. [c]Reisolated starting material are shown in parentheses. [d]*E/Z* ratio determined by ^1H NMR.

and *E/Z* ratio of ≥ 83:17. However, the reaction with 6-methyl **1g** and *o*-methoxy **1h** substrates provided trace amount of product, which might be attributed to the steric reason. Further, substrates with various functional groups, including *m*-methyl **1i**, *m*-trifluoromethyl **1j**, *p*-

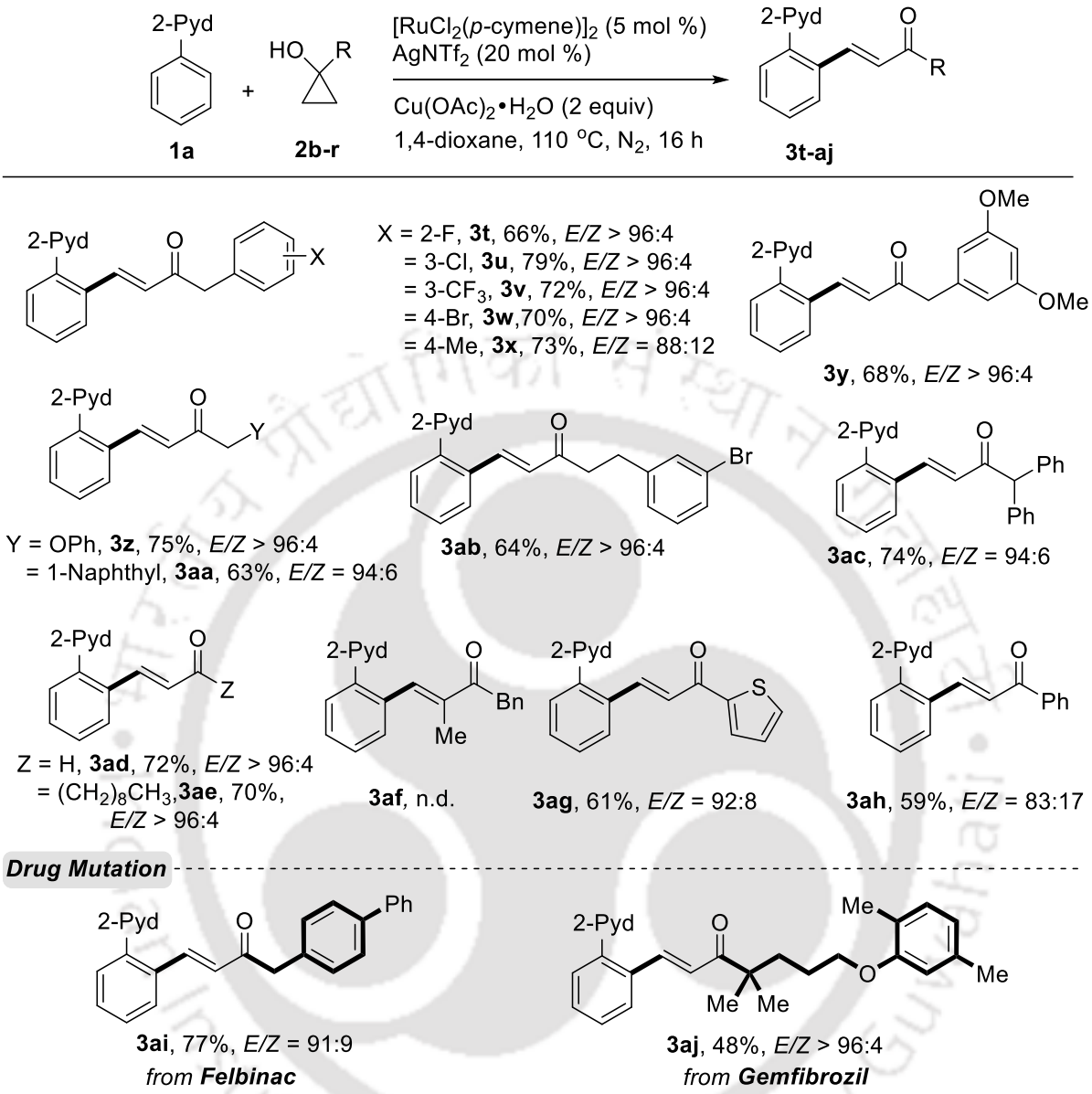
methyl **1k**, *p*-methoxy **1l** and *m*-*p*-di-methyl **1m** successfully coupled, leading to **3i-m** in 61-75% yields and *E/Z* ratio of ≥ 88:12. *N*-Heteroaryl rings such as benzo[*b*]thiophene **1n** and 2-thiophene **1o** were compatible, resulting the products **3n** and **3o** in 72% and 75% yields, respectively, with *E/Z* ratio of >96:4, whereas *N*-pyridyl pyridone **1p** remained unsuccessful. Gratifyingly, anti-inflammatory drug pirfenidone **1q** and naturally occurring sesamol **1r**, menthol **1s** tethered pyridones provided **3q-s** in 63-78% yields and with *E/Z* ≥ 86:14.

Table 3. Substrate Scope of *N*-(Hetero)arylpyridine-2(1*H*)-ones[a,b,c,d]



[a]Reaction conditions: **1b-s** (0.2 mmol), **2a** (0.4 mmol), $[RuCl_2(p\text{-cymene})]_2$ (5 mol %), $AgNTf_2$ (20 mol %), $Cu(OAc)_2 \cdot H_2O$ (2 equiv), 1,4-dioxane (1.5 mL), 110 °C, 16 h, N_2. [b]Isolated yield. [c]Reisolated starting material are shown in parentheses. [d]*E/Z* ratio determined by ^1H NMR.

Table 4. Substrate Scope of Cyclopropanols[a,b,c]

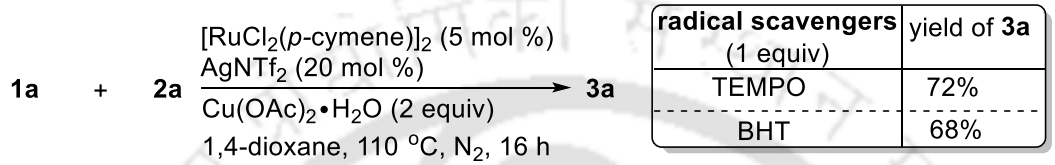


[a]Reaction conditions: **1a** (0.2 mmol), **2b-r** (0.4 mmol), $[RuCl_2(p\text{-cymene})]_2$ (5 mol %), $AgNTf_2$ (20 mol %), $Cu(OAc)_2 \cdot H_2O$ (2 equiv), 1,4-dioxane (1.5 mL), 110 °C, 16 h, N_2. [b]Isolated yield. [c]*E/Z* ratio determined by ^1H NMR.

The scope of the alkenylation process was then explored with decorated cyclopropanols **2b-r** (Table 4). Cyclopropanols with 2-fluoro **2b**, 3-chloro **2c** and 3-trifluoromethyl **2d**, 4-bromo **2e**, 4-methyl **2f** substituents in the aryl ring smoothly converted to alkenylated derivatives **3t-x** in 66-79% yields and *E/Z* ≥ 88:12. The structure of **3t** was determined using single crystal X-ray analysis. Further, the substrates with 3,5-dimethoxy **2g**, 1-phenoxymethyl **2h**, 1-bromo-3-ethylphenyl **2i**, 1-methylnaphthyl **2j** and diphenylmethyl **2k** functionalities were amenable,

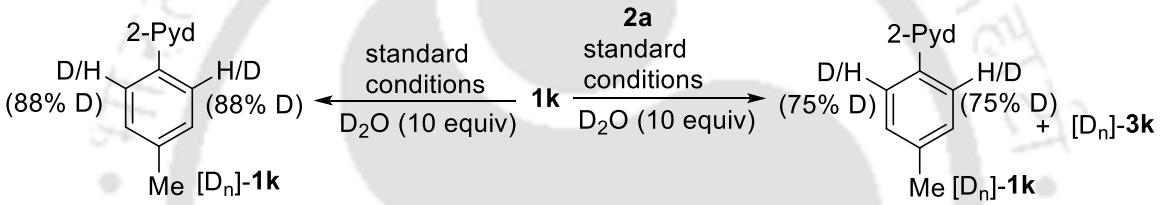
delivering **3y-ac** in 63-75% yields with *E/Z* ≥94:6. Moreover, unsubstituted **2l** and long alkyl chain bearing **2m** were compatible, providing **3ad-ae** in 70-72% yields with *E/Z* >96:4. Sterically hindered 1,2-disubstituted **2n** showed no reaction. However, (hetero)aryl containing **2o-p** were proved to be competent coupling partner, affording **3ag-ah** in 59-61% yields with *E/Z* ≥83:17. Amusingly, nonsteroidal anti-inflammatory drug felbinac **2q** and fibrate drug gemfibrozil **2r** bound cyclopropanols underwent the reaction to give **3ai-aj** in 48-77% yields with E/Z ≥91:9.

(a) Radical Trapping Experiments



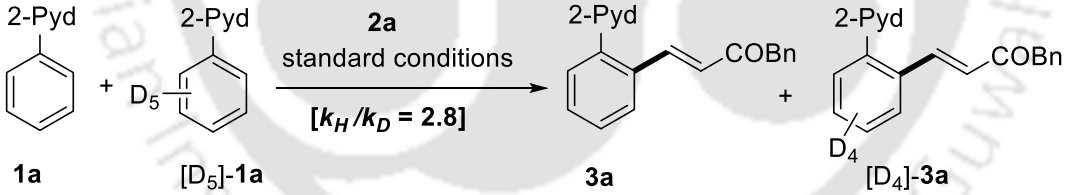
radical scavengers (1 equiv)	yield of **3a**
TEMPO	72%
BHT	68%

(b) H/D Exchange Experiments

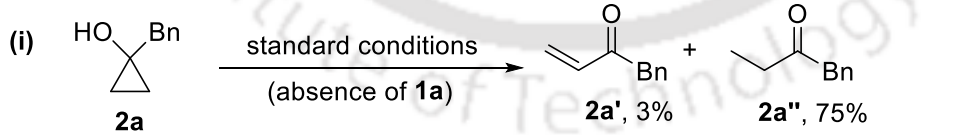


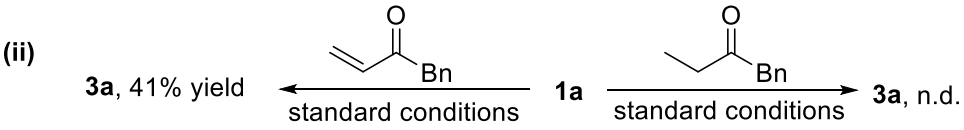
(c) Kinetic Isotope Experiment

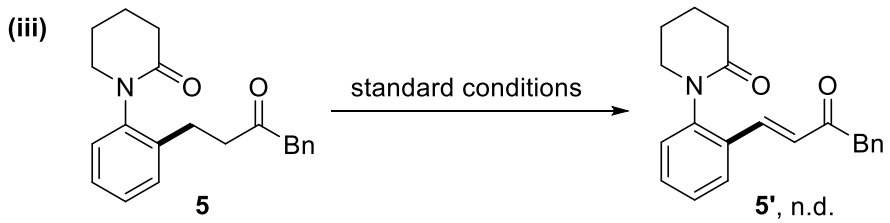
Intermolecular



(d) Control Experiments

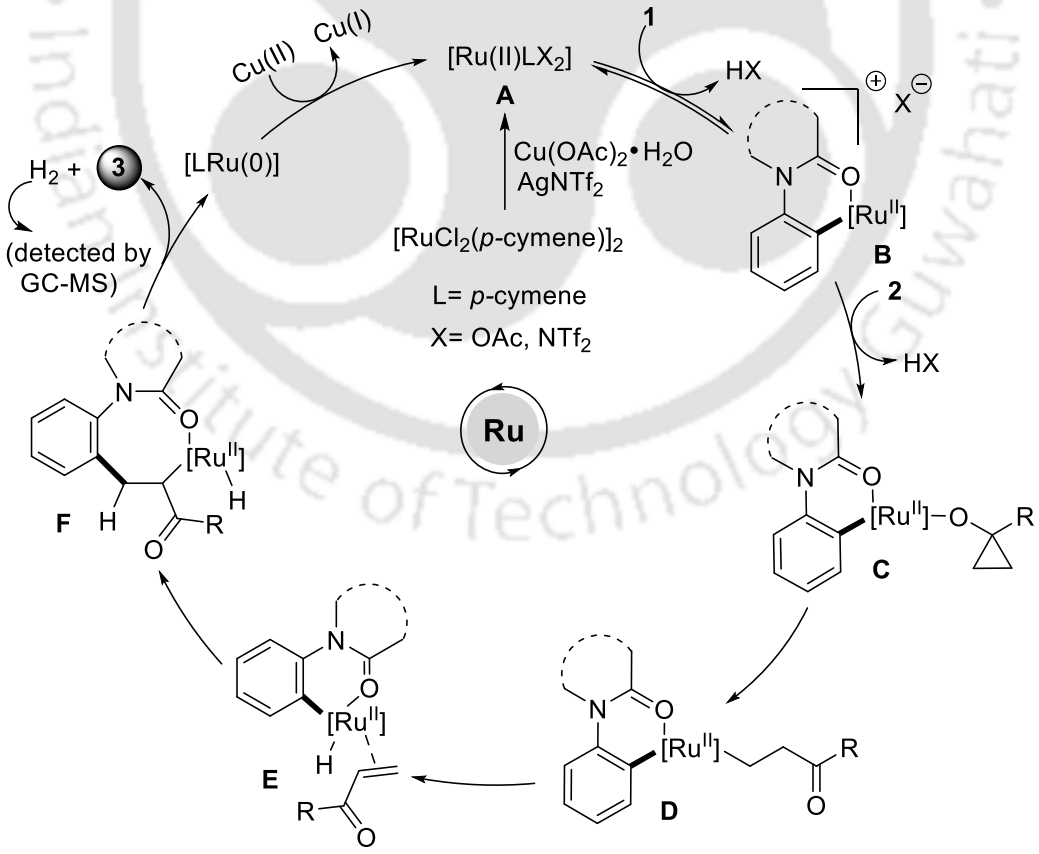






Scheme 10. Preliminary Mechanistic Investigations

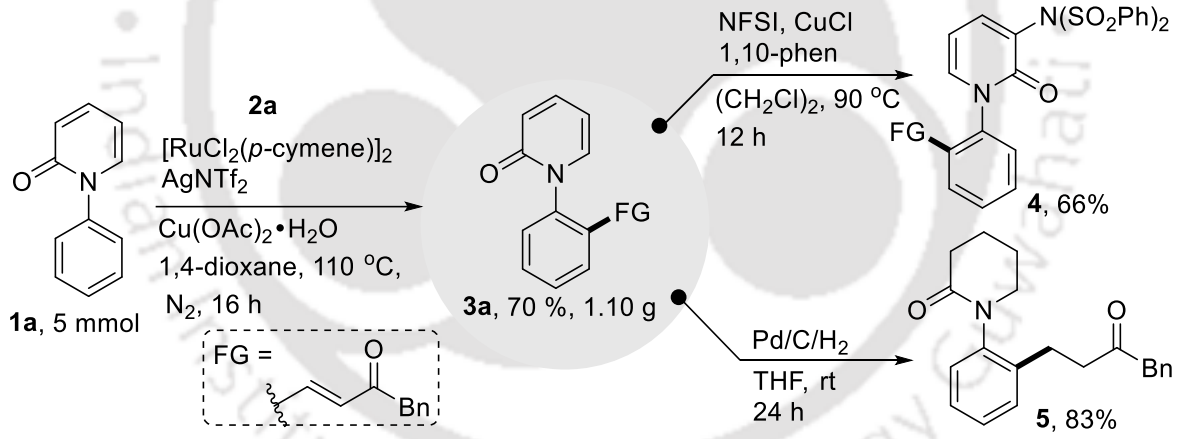
To get insight into the reaction pathway, radical trapping experiments were conducted in presence of radical scavengers such as, 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) and 2,6-di-*tert*-butyl-4-methylphenol (BHT) (Scheme 10a). The reaction took place to provide the target product **3a** in comparable yields, indicating the radical pathway might not be involved. The H/D-exchange experiment with D_2O, in absence of **2a** showed 88% deuterium incorporation at the *o*-position of aryl ring, while the deuterium incorporation was found to be 75% at *o*-position in the presence of **2a** (Scheme 10b). These results indicate the reversibility of the C-H activation step. In addition, *o*-C-H bond cleavage was likely to be involved in the rate determining step, as evidenced by the k_H/k_D value of 2.8 (Scheme 10c). Next, a set of control experiments were performed to investigate the involvement of α,β-unsaturated ketone as an intermediate. Cyclopropanol **2a** afforded 1-phenylbut-3-en-2-one **2a′** (3%) and 1-phenylbutan-2-one **2a″** (75%) under standard reaction conditions as detected in NMR analysis (Scheme 10d.i). Further, coupling of **1a** with **2a′** conditions furnished **3a** in reduced yield of 41%, however reaction with **2a″** was unsuccessful (Scheme 10d.ii). These results suggest the presence of an *in-situ* generated enone in the catalytic cycle, while initial oxidative conversion of cyclopropanol to enone seems



Scheme 11. Proposed Reaction Mechanism

unlikely. Further, compound **5** was subjected under standard reaction conditions (Scheme 10d, iii), no alkenylation was observed, which implies *β*-hydride elimination followed by H_2 liberation (detected by GC-MS) might be involved in the reaction. Based on the mechanistic investigations and literature precedents,[17] a plausible mechanism is proposed (Scheme 11). Initially, six-membered ruthenacycle **B** was formed *via* reversible C-H activation of substrate **1** with active Ru-catalyst **A**. Subsequently, ligand exchange with the cyclopropanol **2**, followed by *β*-carbon elimination generated Ru(II) alkyl species **D**. *β*-Hydride elimination of **D** may form **E**, which further undergoes migratory insertion to produce an eight membered ruthenacycle **F**. Finally, *β*-hydride elimination of **F** leads to the target product **3** and Ru(0) species, which can be oxidized with the aid of Cu(II) salt to regenerate the active Ru(II) species completing the catalytic cycle.

To demonstrate the practicality, gram-scale reaction was carried out with 5 mmol **1a** and **2a** under the standard reaction conditions, producing the target product **3a** in 70% yield (Scheme 12). C3-Amidation of **3a** with NFSI provided **4** in 66% yield. The reduction of **3a** with Pd/C and H_2 delivered piperidin-2-one derivative **5** in 83% yield.



Scheme 12. Scale-up and Post-Synthetic Utilities

In summary, we have shown a bioactive DG assisted arene C-H alkenylation under the Ru-catalysis with cyclopropanols. Excellent chemo-, site- and stereo-selectivities, substrate scope, good functional group compatibility, sequential C-H/C-C activation and late-stage functionalization of bioactive compounds are the notable practical features.

3.3 Experimental Section

General Information. $[RuCl_2(p\text{-cymene})]_2$ (>97%), $RuCl_3{\cdot}3H_2O$ (>98%), $Cu(OAc)_2{\cdot}H_2O$ (>98%), $Cu(OAc)_2$ (98%), AgOAc (≥99.99%), Ag_2CO_3 (98%), Ag_2O (99%), $AgSbF_6$ (>98%), $AgBF_4$ (98%), $AgNTf_2$ (>98%) and dimethoxyethane (DME) of Aldrich and TCI Chemicals were used as received. Methanol, 1,4-dioxane, tetrahydrofuran, 1,2-dichloroethane and toluene were dried prior 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 (60-120 mesh). Bruker Avance III 400, 500 and 600 MHz NMR spectrometers were used to record spectra using $CDCl_3$ as the solvent and tetramethylsilane (Me_4Si) 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, 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). *N*-Aryl substrates were prepared according to the reported procedures.[18]

Procedure for Ru(II)-Catalyzed C-H Alkenylation. *N*-Aryl substrate **1** (0.2 mmol), cyclopropanol **2** (0.4 mmol), $[RuCl_2(p\text{-cymene})]_2$ (5 mol %, 0.010 mmol, 6 mg), $AgNTf_2$ (20 mol %, 0.04 mmol, 15 mg) and $Cu(OAc)_2{\cdot}H_2O$ (2 equiv, 80 mg) were stirred in 1,4-dioxane (1.5 ml) at 110 ^oC in a preheated oil bath for 16 h under N_2 atmosphere. The progress of the reaction was monitored by TLC utilizing ethyl acetate and hexane as an eluent. Upon completion, the reaction mixture 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 *n*-hexane and ethyl acetate as an eluent to afford alkenylated product **3**.

Radical Trapping Experiments. 1-Phenylpyridin-2(1*H*)-one **1a** (0.2 mmol, 34.2 mg), 1-benzylcyclopropan-1-ol **2a** (0.4 mmol, 59.2 mg), $[RuCl_2(p\text{-cymene})]_2$ (5 mol %, 0.010 mmol, 6 mg), $AgNTf_2$ (20 mol %, 0.04 mmol, 15 mg), $Cu(OAc)_2{\cdot}H_2O$ (2 equiv, 80 mg) and TEMPO (0.2 mmol, 31.2 mg) or BHT (0.2 mmol, 44 mg) were stirred in 1,4-dioxane (1.5 ml) at 110

^{o}C in a preheated oil bath for 16 h under N_2 atmosphere. Upon completion, the reaction mixture was allowed to cool to ambient 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 1k with D_2O in Absence of 2a. To a stirred solution of 1-(*p*-tolyl)pyridin-2(1*H*)-one **1k** (0.2 mmol, 37 mg), $[RuCl_2(p\text{-cymene})]_2$ (5 mol %, 0.010 mmol, 6 mg), $AgNTf_2$ (20 mol %, 0.04 mmol, 15 mg) and $Cu(OAc)_2 \cdot H_2O$ (2 equiv, 80 mg) in 1,4-dioxane (1.5 ml), D_2O (1.0 mmol, 0.2mL) was added and stirred at 110 ^{o}C in a preheated oil bath for 16 h under N_2 atmosphere. 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 give $[D_n]$-**1k**. The deuterium incorporation was observed as 88% at the *ortho*-position of aryl ring based on 600 MHz ^{1}H NMR spectrum.

H/D Exchange Experiment of 1k with D_2O in Presence of 2a. To a stirred solution of 1-(*p*-tolyl)pyridin-2(1*H*)-one **1k** (0.2 mmol, 37 mg), 1-benzylcyclopropan-1-ol **2a** (0.40 mmol, 59.2 mg), $[RuCl_2(p\text{-cymene})]_2$ (5 mol %, 0.010 mmol, 6 mg), $AgNTf_2$ (20 mol %, 0.04 mmol, 15 mg) and $Cu(OAc)_2 \cdot H_2O$ (2 equiv, 80 mg) in 1,4-dioxane (1.5 ml), D_2O (1.0 mmol, 0.2mL) was added and stirred at 110 ^{o}C in a preheated oil bath for 16 h under N_2 atmosphere. The resulting mixture was cooled to room temperature, diluted with ethyl acetate and passed through a short pad of celite. The purification was performed as described in the general procedure to give $[D_n]$-**1k** and $[D_n]$-**3k**. The deuterium incorporation was observed as 75% at the *ortho*-position of aryl ring based on 600 MHz ^{1}H NMR spectrum.

Preparation of 1-(Phenyl-*d*$_5$)pyridin-2(1*H*)-one [D$_5$]-**1a.**

Step-I: To a stirred solution of sulfuric acid (0.4 mL) in water (1.3 mL), benzene-d_6 (2 mmol, 0.2 mL) was added dropwise at 0 ^{o}C, which was treated with $NaBrO_3$ (2.2 mmol, 331 mg) at the same temperature in two portions with an interval of 1 h and allowed to stir for another 10 h at room temperature. After completion, ice water was added into the mixture and extracted with diethyl ether (3 x 10 mL). The combined organic layer was washed with brine (1 x 10 mL) and water (1 x 10 mL). Drying (Na_2SO_4) and evaporation of the solvent gave a residue that was used for the next step without further purification (75% yield, 243 mg).

Step-II: Pyridin-2(1*H*)-one (1.0 mmol), 1-bromobenzene-d_5 (2.0 mmol, 2 equiv), K_2CO_3 (1.0 mmol, 1 equiv) and CuI (10 mol %) were stirred in DMF (2 mL) at 150 °C in a preheated oil

bath for 6 h under N_2 atmosphere. After completion, the reaction mixture was cooled to room temperature and extracted with ethyl acetate (3 x 10 mL). The combined organic layer was washed with brine (2 x 10 mL) and water (1 x 10 mL). Drying (Na_2SO_4) and evaporation of the solvent gave a residue that was purified on silica gel column chromatography using *n*-hexane and ethyl acetate (60/40, v/v) as an eluent to afford 1-(phenyl-d_5)pyridin-2(1*H*)-one [D_5]-**1a** in 81% (142 mg) yield.

Kinetic Isotope Effect Experiment. A mixture of 1-phenylpyridin-2(1*H*)-one **1a** (0.1 mmol, 17.1 mg) and 1-(phenyl-d_5)pyridin-2(1*H*)-one [D_5]-**1a** (0.1 mmol, 17.6 mg) was reacted with 1-benzylcyclopropan-1-ol **2a** (0.40 mmol, 59.2 mg) for 0.5 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 [D_4]-**3a**. The intermolecular k_H/k_D was found to be 2.80, based on 500 MHz ^{1}H NMR of the product **3a** and [D_4]-**3a**.

Preparation of 1-Phenylbut-3-en-2-one 2a′.[19]

Step-I: *N*,*O*-Dimethylhydroxylamine hydrochloride (590 mg, 6 mmol, 1.2 equiv) was suspended in dry $(CH_2Cl)_2$ (20 mL). 2-Phenylacetyl chloride (0.7 mL, 5 mmol, 1 equiv) was added dropwise at 0 ^oC and pyridine (0.9 mL, 11 mmol, 2.2 equiv) was added *via* syringe within 5 min. The reaction mixture was allowed to stir for 1 h at room temperature. After completion, 2 M HCl (10 mL) was added into the mixture and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layer was washed with brine (1 x 10 mL) and water (1 x 10 mL). Drying (Na_2SO_4) and evaporation of the solvent gave a residue *N*-methoxy-*N*-methyl-2-phenylacetamide that was used for the next step without further purification.

Step-II: To a solution of *N*-methoxy-*N*-methyl-2-phenylacetamide in dry THF (25 mL), vinylmagnesium bromide (1.0 M in THF, 8 mL, 8 mmol, 1.6 equiv) was added dropwise at 0 ^oC. The solution was allowed to warm to room temperature and stirred for 2 h. After completion, the reaction mixture was cooled to 0 °C and quenched with slow addition of saturated NH_4Cl solution (10 mL). The mixture was extracted with diethyl ether (20 mL x 3) and washed with brine (2 x 20 mL) and water (1 x 20 mL). Drying (Na_2SO_4) and evaporation of the solvent gave a residue that was purified by silica gel column chromatography using ethyl acetate/*n*-hexane (10/90, v/v) as an eluent to provide 1-phenylbut-3-en-2-one **2a′** in 51% (372 mg) yield.

Control Experiments

i. **Reaction of 2a under standard conditions in absence of 1a:** 1-Benzylcyclopropan-1-ol **2a** (0.20 mmol, 29.6 mg), $[RuCl_2(p\text{-cymene})]_2$ (5 mol %, 0.005 mmol, 3 mg), $AgNTf_2$ (20 mol %, 0.02 mmol, 7 mg) and $Cu(OAc)_2 \cdot H_2O$ (2 equiv, 40 mg) in 1,4-dioxane (1.0 ml) were stirred at 110 °C in a preheated oil bath for 16 h under N_2 atmosphere. The resulting mixture was cooled to room temperature, diluted with ethyl acetate and passed through a short pad of celite. The products 1-phenylbut-3-en-2-one **2a′** (3% yield) and 1-phenylbutan-2-one **2a′′** (75% yield) were detected in ^1H NMR analysis of crude reaction mixture.

ii. **Reaction of 1a with 2a′:** 1-Phenylpyridin-2(1*H*)-one **1a** (0.20 mmol, 34.2 mg), 1-phenylbut-3-en-2-one **2a′** (0.40 mmol, 58 mg), $[RuCl_2(p\text{-cymene})]_2$ (5 mol %, 0.010 mmol, 6 mg), $AgNTf_2$ (20 mol %, 0.04 mmol, 15 mg) and $Cu(OAc)_2 \cdot H_2O$ (2 equiv, 80 mg) were stirred in 1,4-dioxane (1.5 ml) at 110 °C in a preheated oil bath for 16 h under N_2 atmosphere. The reaction mixture was cooled to room temperature and the crude mixture was diluted with ethyl acetate and passed through a short of pad of celite. The purification of the product was performed as described in the general procedure to afford **3a** in 41% yield.

iii. **Reaction of 1a with 2a′′:** 1-Phenylpyridin-2(1*H*)-one **1a** (0.20 mmol, 34.2 mg), 1-phenylbutan-2-one **2a′′** (0.40 mmol, 59.2 mg), $[RuCl_2(p\text{-cymene})]_2$ (5 mol %, 0.010 mmol, 6 mg), $AgNTf_2$ (20 mol %, 0.04 mmol, 15 mg) and $Cu(OAc)_2 \cdot H_2O$ (2 equiv, 80 mg) were stirred in 1,4-dioxane (1.5 ml) at 110 °C in a preheated oil bath for 16 h under N_2 atmosphere. No desired product was formed.

iv. **Reaction of 5 under standard conditions:** A solution of 1-(2-(3-oxo-4-phenylbutyl)phenyl)piperidin-2-one **5** (0.10 mmol, 32.1 mg), $[RuCl_2(p\text{-cymene})]_2$ (5 mol %, 0.005 mmol, 3 mg), $AgNTf_2$ (20 mol %, 0.02 mmol, 7 mg) and $Cu(OAc)_2 \cdot H_2O$ (2 equiv, 40 mg) in 1,4-dioxane (1.0 ml) was stirred in a preheated oil bath at 110 °C under N_2 atmosphere for 16 h under N_2 atmosphere. No desired alkenylated product was formed.

Procedure for the Determination of H_2 gas Evolution by GC. 1-Phenylpyridin-2(1*H*)-one **1a** (5 mmol, 855 mg), 1-benzylcyclopropan-1-ol **2a** (10 mmol, 1.5 g), $[RuCl_2(p\text{-cymene})]_2$ (5 mol %, 0.25 mmol, 153 mg), $AgNTf_2$ (20 mol %, 1 mmol, 388 mg) and $Cu(OAc)_2 \cdot H_2O$ (2 equiv, 1.9 g) were stirred in 1,4-dioxane (20 mL) at 110 °C in a preheated oil bath for 16 h. After completion, the pressure tube was cooled at 0 °C, the evolved gas was syringed out and detected from PerkinElmer clarus-590 GC instrument using Elite Plot-Q column (30 m length x 530 μm x 20 μm ID) employing the following method:

TCD starting temperature: 40 °C

Oven temperature: 60 °C

Time at starting temperature: 0 min

Hold time: 5 min

Ramp: 28 °C/ min up to 200 °C

Flow rate: 5 ml/ min (N_2)

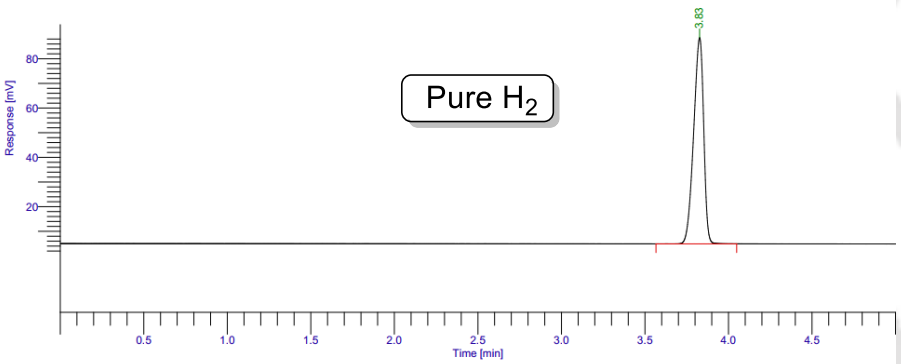
Split ration: 20

Inlet temperature: 40 °C

Detector temperature TCD: 200 °C

Gas Chromatograms:

Sequence File : D:\GC Data\STD H2.seq



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Peak #	Component Name	Time [min]	Area [uV*sec]	Height [uV]	Area [%]
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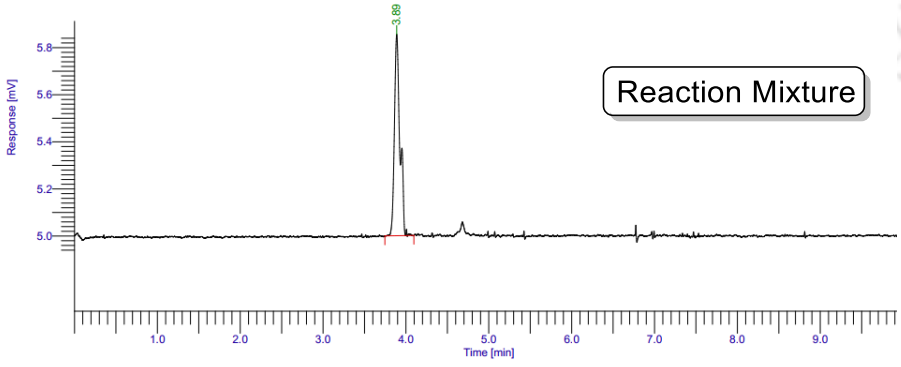
			348996.67	83657.50	100.00

Sequence File : D:\GC Data\TPS-RM-1.seq



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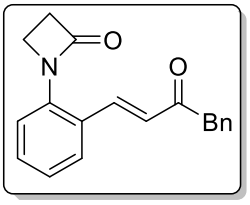
Peak #	Component Name	Time [min]	Area [uV*sec]	Height [uV]	Area [%]
1		3.888	3973.42	855.01	100.00
			3973.42	855.01	100.00

Scale-up Synthesis of 3a. 1-Phenylpyridin-2(1*H*)-one **1a** (5 mmol, 855 mg), 1-benzylcyclopropan-1-ol **2a** (10 mmol, 1.5 g), $[RuCl_2(p\text{-cymene})]_2$ (5 mol %, 0.25 mmol, 153 mg), $AgNTf_2$ (20 mol %, 1 mmol, 388 mg) and $Cu(OAc)_2 \cdot H_2O$ (2 equiv, 1.9 g) were stirred in 1,4-dioxane (20 mL) at 110 °C in a preheated oil bath for 16 h under N_2 atmosphere. After completion (monitored by TLC), the reaction mixture was cooled to room temperature and diluted with ethyl acetate (20 mL) and passed through a celite pad. Evaporation of the solvent gave a residue that was purified on silica gel column chromatography using *n*-hexane and ethyl acetate as an eluent (40/60, v/v) to afford **3a** in 70% (1.10 g) yield.

Synthesis of 4. Compound **3a** (0.1 mmol, 31.5 mg), CuCl (10 mol %, 1 mg), 1,10-phenanthroline (10 mol %, 1.8 mg) and NFSI (1.5 equiv, 47 mg) were stirred in 1,2-dichloroethane (1 mL) at 90 °C for 12 h. After completion (monitored by TLC), the reaction mixture was cooled to room temperature, diluted with CH_2Cl_2 (10 mL) and passed through a short celite pad. Evaporation of the solvent gave a residue that was purified by silica gel column chromatography using ethyl acetate/*n*-hexane as the eluent (70/30, v/v) to provide **4** in 66% (40.2 mg) yield.

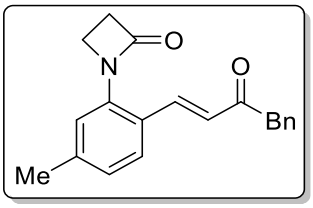
Synthesis of 5. Compound **3a** (0.1 mmol, 31.5 mg) and Pd/C (2.2 mg, 20 mol%) were stirred in THF (1 mL) at room temperature for 15 h under H_2 balloon. After completion (monitored by TLC), the reaction mixture diluted with CH_2Cl_2 (10 mL) and passed through a short celite pad. Evaporation of solvent the gave a residue that was purified by silica gel column chromatography using ethyl acetate/*n*-hexane as the eluent (40/60, v/v) to provide **5** in 83% (26.6 mg) yield.

Characterization Data of the Products

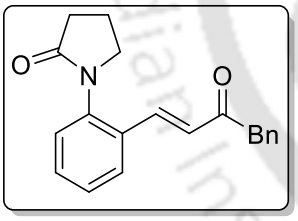


(*E*)-1-(2-(3-Oxo-4-phenylbut-1-en-1-yl)phenyl)azetidin-2-one 3A. Analytical TLC on silica gel, 3:1 ethyl acetate/hexane R_f = 0.52; yellow liquid; yield 46% (26.7 mg, *E/Z* = 88:12); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, *J* = 16.0 Hz, 1H), 7.54-7.51 (m, 1H), 7.41-7.38 (m, 1H), 7.37-7.35 (m, 1H), 7.34-7.32 (m, 2H), 7.28-7.27 (m, 3H), 7.21-7.17 (m, 1H), 6.67 (d, *J* = 16.0 Hz, 1H), 3.98 (s, 2H), 3.68 (t, *J* = 4.4 Hz, 2H), 3.14 (t, *J* = 4.8 Hz, 2H);

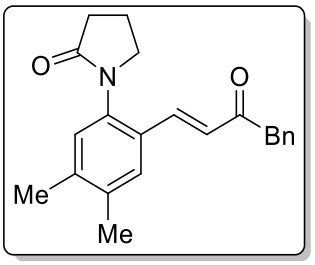
^{13}C NMR (100 MHz, $CDCl_3$) δ 197.7, 165.8, 140.3, 137.3, 134.6, 131.0, 129.6, 128.9, 127.9, 127.6, 127.2, 127.1, 126.1, 122.1, 48.0, 41.7, 36.6; FT-IR (neat) 2922, 1747, 1686, 1602, 1492, 1454, 1356, 1278, 1263, 751 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{19}H_{18}NO_2$: 292.1333, found 292.1326.



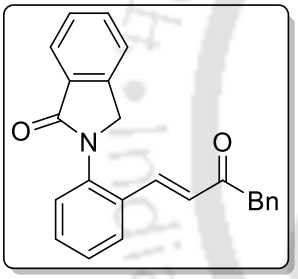
(*E*)-1-(5-Methyl-2-(3-oxo-4-phenylbut-1-en-1-yl)phenyl)azetidin-2-one 3B. Analytical TLC on silica gel, 3:1 ethyl acetate/hexane R_f = 0.50; yellow liquid; yield 52% (31.7 mg, *E/Z* = 92:8); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.96 (d, *J* = 15.6 Hz, 1H), 7.44 (d, *J* = 7.8 Hz, 1H), 7.34-7.32 (m, 2H), 7.28-7.27 (m, 3H), 7.21 (s, 1H), 7.01 (d, *J* = 7.8 Hz, 1H), 6.63 (d, *J* = 16.2 Hz, 1H), 3.97 (s, 2H), 3.67 (t, *J* = 4.8 Hz, 2H), 3.13 (t, *J* = 4.8 Hz, 2H), 2.34 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 197.7, 165.9, 141.8, 140.2, 137.3, 134.8, 129.6, 128.8, 127.7, 127.2, 127.0, 126.2, 124.8, 122.7, 47.9, 41.8, 36.6, 21.5; FT-IR (neat) 2923, 1743, 1716, 1601, 1454, 1354, 1278, 1199 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{20}H_{20}NO_2$: 306.1489, found 306.1491.



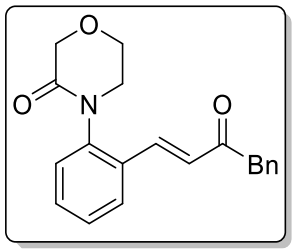
(*E*)-1-(2-(3-Oxo-4-phenylbut-1-en-1-yl)phenyl)pyrrolidin-2-one 3D. Analytical TLC on silica gel, 3:1 ethyl acetate/hexane R_f = 0.45; yellow liquid; yield 72% (43.9 mg, *E/Z* >96:4); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64-7.62 (m, 1H), 7.58 (d, *J* = 16.0 Hz, 1H), 7.44-7.40 (m, 1H), 7.36-7.31 (m, 3H), 7.29-7.26 (m, 1H), 7.24-7.20 (m, 3H), 6.76 (d, *J* = 16.0 Hz, 1H), 3.92 (s, 2H), 3.64 (t, *J* = 7.2 Hz, 2H), 2.57 (t, *J* = 8.4 Hz, 2H), 2.22-2.14 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.3, 175.1, 138.8, 138.7, 134.5, 131.9, 131.3, 129.4, 128.9, 128.1, 127.6, 127.3, 127.1, 126.9, 51.5, 48.6, 31.3, 19.1; FT-IR (neat) 2890, 1691, 1601, 1489, 1456, 1405, 1305, 1237, 1087, 979, 763 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{20}H_{20}NO_2$: 306.1489, found 306.1490.



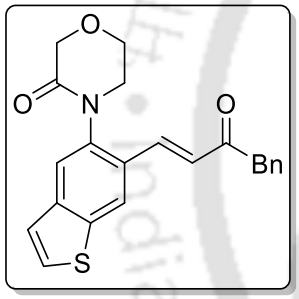
(*E*)-1-(4,5-Dimethyl-2-(3-oxo-4-phenylbut-1-en-1-yl)phenyl)pyrrolidin-2-one 3E. Analytical TLC on silica gel, 3:1 ethyl acetate/hexane R_f = 0.43; yellow liquid; yield 77% (51.3 mg, *E/Z* >96:4); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.53 (d, *J* = 16.2 Hz, 1H), 7.41 (s, 1H), 7.34-7.32 (m, 2H), 7.27-7.24 (m, 3H), 6.98 (s, 1H), 6.72 (d, *J* = 16.2 Hz, 1H), 3.91 (s, 2H), 3.60 (t, *J* = 7.2 Hz, 2H), 2.56 (t, *J* = 8.4 Hz, 2H), 2.25 (s, 6H), 2.19-2.14 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 197.4, 175.3, 141.0, 138.7, 137.0, 136.5, 134.6, 129.4, 129.1, 128.8, 128.5, 128.4, 127.0, 125.9, 51.7, 48.4, 31.2, 19.9, 19.5, 19.0; FT-IR (neat) 2923, 1688, 1601, 1496, 1453, 1414, 1301, 1253, 1090, 980, 738 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{22}H_{24}NO_2$: 334.1802, found 334.1805.



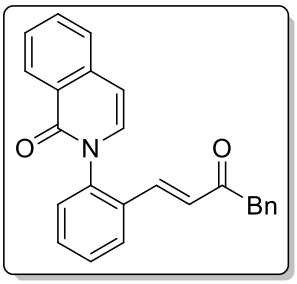
(*E*)-2-(2-(3-Oxo-4-phenylbut-1-en-1-yl)phenyl)isoindolin-1-one 3F. Analytical TLC on silica gel, 3:1 ethyl acetate/hexane R_f = 0.41; yellow solid; mp 116-117 °C; yield 70% (49.4 mg, *E/Z* >96:4); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.99 (d, *J* = 7.8 Hz, 1H), 7.70-7.69 (m, 1H), 7.67-7.64 (m, 1H), 7.58-7.56 (m, 2H), 7.50-7.46 (m, 2H), 7.40-7.37 (m, 1H), 7.32-7.31 (m, 1H), 7.14-7.12 (m, 3H), 7.09-7.08 (m, 2H), 6.73 (d, *J* = 16.2 Hz, 1H), 4.62 (s, 2H), 3.84 (s, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 197.6, 168.4, 141.6, 139.2, 138.2, 134.5, 132.7, 132.2, 131.9, 131.3, 129.2, 128.7, 128.6, 128.5, 128.3, 127.6, 127.4, 126.9, 124.6, 123.0, 53.8, 48.2; FT-IR (KBr) 2924, 1692, 1601, 1487, 1455, 1385, 1332, 1303, 1215, 1165, 1113, 977, 704 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{24}H_{20}NO_2$: 354.1489, found 354.1488.



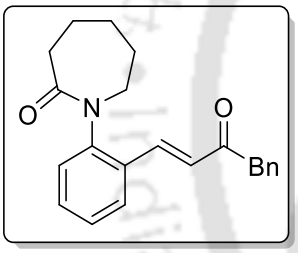
(*E*)-4-(2-(3-Oxo-4-phenylbut-1-en-1-yl)phenyl)morpholin-3-one 3G. Analytical TLC on silica gel, 3:1 ethyl acetate/hexane R_f = 0.48; yellow liquid; yield 68% (43.7 mg, *E/Z* >96:4); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67-7.65 (m, 1H), 7.60 (d, *J* = 16.0 Hz, 1H), 7.48- 7.44 (m, 1H), 7.39-7.33 (m, 3H), 7.29-7.27 (m, 2H), 7.24-7.23 (m, 2H), 6.79 (d, *J* = 16.0 Hz, 1H), 4.34 (s, 2H), 3.96-3.92 (m, 4H), 3.68 (bs, 1H), 3.42 (bs, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 197.1, 167.1, 141.2, 137.8, 134.3, 132.0, 131.8, 129.5, 129.0, 128.8, 128.3, 127.8, 127.5, 127.2, 68.5, 64.1, 50.7, 48.8; FT-IR (neat) 2930, 1663, 1602, 1485, 1454, 1428, 1344, 1323, 1284, 1125, 995, 763 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{20}H_{20}NO_3$: 322.1438, found 322.1437.



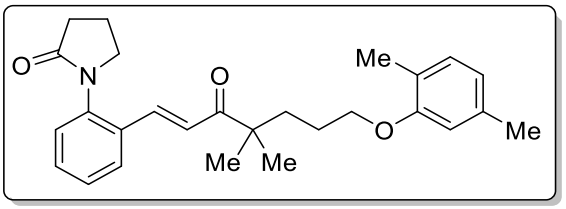
(*E*)-4-(6-(3-Oxo-4-phenylbut-1-en-1-yl)benzo[*b*]thiophen-5-yl)morpholin-3-one 3H. Analytical TLC on silica gel, 3:1 ethyl acetate/hexane R_f = 0.41; yellow liquid; yield 52% (39.2 mg, *E/Z* = 94:6); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.18 (s, 1H), 7.69-7.66 (m, 2H), 7.59 (d, *J* = 5.4 Hz, 1H), 7.37-7.35 (m, 2H), 7.32-7.26 (m, 4H), 6.86 (d, *J* = 15.6 Hz, 1H), 4.39-4.38 (m, 2H), 4.05-4.03 (m, 1H), 3.96-3.93 (m, 3H), 3.79-3.75 (m, 1H), 3.47-3.45 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 196.8, 167.5, 141.9, 140.0, 138.0, 137.7, 134.2, 130.4, 129.4, 128.9, 127.8, 127.1, 126.7, 123.7, 123.0, 121.8, 68.5, 64.0, 51.1, 48.8; FT-IR (neat) 2923, 1662, 1596, 1479, 1426, 1319, 1118, 990, 904 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{22}H_{20}NO_3S$: 378.1159, found 378.1158.



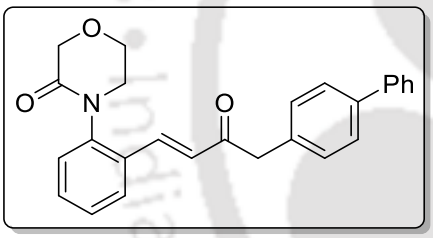
(*E*)-2-(2-(3-Oxo-4-phenylbut-1-en-1-yl)phenyl)isoquinolin-1(2*H*)-one 3I. Analytical TLC on silica gel, 3:2 ethyl acetate/hexane R_f = 0.45; yellow solid; mp 150-151 °C; yield 41% (29.9 mg, *E/Z* = 83:17); ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.14 (d, *J* = 16.2 Hz, 1H), 7.65-7.62 (m, 1H), 7.59-7.58 (m, 1H), 7.54-7.50 (m, 4H), 7.46-7.40 (m, 3H), 7.31-7.27 (m, 3H), 7.23-7.20 (m, 2H), 6.57-6.56 (m, 1H), 6.45 (d, *J* = 16.8 Hz, 1H), 4.08 (s, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 198.5, 162.5, 146.3, 141.5, 139.1, 139.0, 134.9, 132.8, 132.3, 129.8, 129.6, 129.4, 129.1, 128.6, 128.5, 128.3, 128.1, 127.7, 127.1, 126.8, 124.1, 106.4, 46.3; FT-IR (KBr) 2922, 2852, 1654, 1624, 1592, 1493, 1454, 1276, 1171, 1078, 966 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{25}H_{20}NO_2$: 366.1489, found 366.1491.



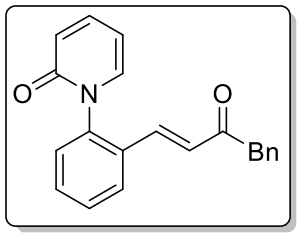
(*E*)-1-(2-(3-Oxo-4-phenylbut-1-en-1-yl)phenyl)azepan-2-one 3J. Analytical TLC on silica gel, 3:1 ethyl acetate/hexane R_f = 0.43; brown liquid; yield 79% (52.6 mg, *E/Z* >96:4); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.64-7.61 (m, 2H), 7.42-7.39 (m, 1H), 7.35-7.33 (m, 2H), 7.30-7.24 (m, 4H), 7.16-7.14 (m, 1H), 6.75 (d, *J* = 16.2 Hz, 1H), 3.95-3.89 (m, 2H), 3.59-3.55 (m, 1H), 3.46-3.42 (m, 1H), 2.74-2.66 (m, 2H), 1.96-1.86 (m, 2H), 1.82-1.69 (m, 4H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 197.2, 176.2, 144.8, 139.0, 134.5, 131.58, 131.56, 129.5, 128.9, 128.3, 127.8, 127.3, 127.1, 126.8, 53.2, 48.6, 37.5, 30.0, 28.5, 23.5; FT-IR (neat) 2926, 1653, 1605, 1454, 1409, 1334, 1197, 1081, 979, 760 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{22}H_{24}NO_2$: 334.1802, found 334.1807.



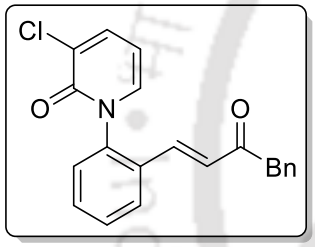
(*E*)-1-(2-(7-(2,5-Dimethylphenoxy)-4,4-dimethyl-3-oxohept-1-en-1-yl)phenyl)pyrrolidin-2-one 3K. Analytical TLC on silica gel, 3:1 ethyl acetate/hexane R_f = 0.67; yellow liquid; yield 75% (62.8 mg, *E/Z* >96:4); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.74 (d, *J* = 7.8 Hz, 1H), 7.68 (d, *J* = 15.6 Hz, 1H), 7.47-7.44 (m, 1H), 7.37-7.34 (m, 1H), 7.28-7.27 (m, 1H), 7.17 (d, *J* = 15.6 Hz, 1H), 7.00 (d, *J* = 7.8 Hz, 1H), 6.66-6.65 (m, 1H), 6.61 (s, 1H), 3.93 (t, *J* = 6.6 Hz, 2H), 3.74 (t, *J* = 7.2 Hz, 2H), 2.64 (t, *J* = 8.4 Hz, 2H), 2.32-2.25 (m, 5H), 2.17 (s, 3H), 1.85-1.83 (m, 2H), 1.75-1.70 (m, 2H), 1.26 (s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 203.7, 175.3, 156.9, 139.0, 138.1, 136.5, 132.4, 131.1, 130.3, 128.1, 127.7, 127.4, 123.5, 122.5, 120.7, 112.0, 67.9, 51.7, 46.5, 36.4, 31.3, 25.0, 24.3, 21.5, 19.1, 15.8; FT-IR (neat) 2954, 1697, 1606, 1460, 1399, 1263, 1158, 1129, 1036, 805, 763 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{27}H_{34}NO_3$: 420.2534, found 420.2538.



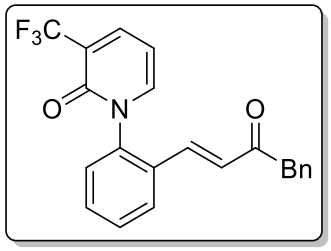
(*E*)-4-(2-(4-([1,1'-Diphenyl]-4-yl)-3-oxobut-1-en-1-yl)phenyl)morpholin-3-one 3L. Analytical TLC on silica gel, 3:1 ethyl acetate/hexane R_f = 0.43; brown liquid; yield 54% (42.8 mg, *E/Z* =91:9); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.71 (d, *J* = 7.8 Hz, 1H), 7.64-7.59 (m, 5H), 7.50-7.49 (m, 1H), 7.47-7.44 (m, 2H), 7.41-7.39 (m, 1H), 7.37-7.34 (m, 3H), 7.28-7.27 (m, 1H), 6.84 (d, *J* = 15.6 Hz, 1H), 4.38 (s, 2H), 3.99 (s, 4H), 3.73-3.69 (m, 1H), 3.45 (bs, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 197.1, 167.2, 141.2, 140.7, 140.2, 137.9, 133.3, 131.9, 131.8, 129.9, 128.9, 128.3, 127.8, 127.7, 127.5, 127.4, 127.1, 68.5, 64.0, 50.7, 48.4; FT-IR (neat) 2925, 1664, 1606, 1484, 1321, 1125, 761, 697 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{26}H_{24}NO_3$: 398.1751, found 398.1752.



(*E*)-1-(2-(3-Oxo-4-phenylbut-1-en-1-yl)phenyl)pyridin-2(1*H*)-one 3a. Analytical TLC on silica gel, 3:1 ethyl acetate/hexane R_f = 0.45; brown solid; mp 149-150 °C; yield 82% (51.6 mg, *E/Z* = 96:4); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.72-7.71 (m, 1H), 7.52-7.50 (m, 1H), 7.48-7.45 (m, 2H), 7.34 (d, *J* = 16.2 Hz, 1H), 7.30-7.27 (m, 3H), 7.25-7.22 (m, 1H), 7.15-7.12 (m, 3H), 6.71-6.66 (m, 2H), 6.26-6.24 (m, 1H), 3.86-3.80 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 197.1, 162.4, 140.6, 140.5, 138.0, 137.5, 134.2, 131.8, 131.5, 129.6, 129.4, 128.9, 128.4, 128.1, 127.7, 127.1, 122.1, 106.4, 48.2; FT-IR (KBr) 2922, 1713, 1663, 1599, 1534, 1492, 1458, 1377, 1260, 1187, 1080, 968, 764 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{21}H_{18}NO_2$: 316.1333, found 316.1339.

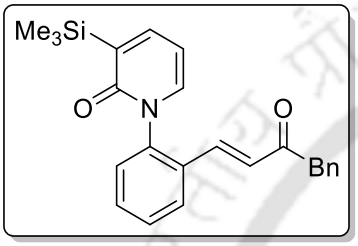


(*E*)-3-Chloro-1-(2-(3-oxo-4-phenylbut-1-en-1-yl)phenyl)pyridin-2(1*H*)-one 3b. Analytical TLC on silica gel, 3:1 ethyl acetate/hexane R_f = 0.43; brown liquid; yield 63% (43.9 mg, *E/Z* >96:4); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.71-7.70 (m, 1H), 7.65-7.64 (m, 1H), 7.52-7.46 (m, 2H), 7.31-7.26 (m, 4H), 7.24-7.23 (m, 1H), 7.16-7.15 (m, 2H), 7.10-7.08 (m, 1H), 6.68 (d, *J* = 16.2 Hz, 1H), 6.20 (t, *J* = 7.2 Hz, 1H), 3.87-3.80 (m, 2H);^{13}C NMR (150 MHz, $CDCl_3$) δ 197.0, 158.7, 140.1, 138.5, 137.1, 136.6, 134.2, 131.7, 131.4, 129.9, 129.4, 128.9, 128.4, 128.3, 127.9, 127.6, 127.1, 105.6, 48.5; FT-IR (neat) 2923, 1663, 1606, 1529, 1486, 1454, 1344, 1264, 1102, 1079, 977, 754 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{21}H_{17}ClNO_2$: 350.0943, found 350.0948.

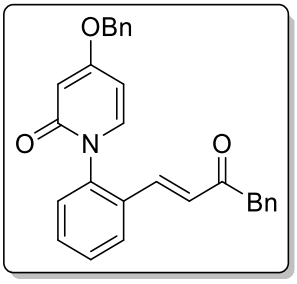


(*E*)-1-(2-(3-Oxo-4-phenylbut-1-en-1-yl)phenyl)-3-(trifluoromethyl)pyridin-2(1*H*)-one 3c. Analytical TLC on silica gel, 3:1 ethyl

acetate/hexane R_f = 0.48; yellow liquid; yield 57% (43.6 mg, *E/Z* >96:4); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.87-7.85 (m, 1H), 7.71-7.70 (m, 1H), 7.53-7.47 (m, 2H), 7.35-7.33 (m, 1H), 7.30-7.28 (m, 4H), 7.24-7.23 (m, 1H), 7.16-7.14 (m, 2H), 6.67 (d, *J* = 15.6 Hz, 1H), 6.29 (t, *J* = 7.2 Hz, 1H), 3.86-3.81 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 196.9, 158.1, 141.9, 139.9 (J_{C-H} = 4.8 Hz), 139.2, 137.0, 134.1, 131.8, 131.4, 130.3, 130.1, 129.4, 129.0, 128.9, 128.6, 128.4, 128.0, 127.1, 104.4, 48.4; ^{19}F NMR (471 MHz, $CDCl_3$) δ -65.95; FT-IR (neat) 2925, 1676, 1611, 1555, 1486, 1453, 1376, 1318, 1134, 1052, 973, 763 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{22}H_{17}F_3NO_2$: 384.1206, found 384.1204.

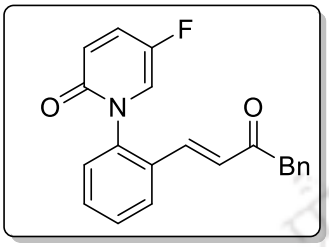


(*E*)-1-(2-(3-Oxo-4-phenylbut-1-en-1-yl)phenyl)-3-(trimethylsilyl)pyridin-2(1*H*)-one 3d. Analytical TLC on silica gel, 2:3 ethyl acetate/hexane R_f = 0.41; brown liquid; yield 68% (52.6 mg, *E/Z* >96:4); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.70-7.69 (m, 1H), 7.59-7.58 (m, 1H), 7.51-7.47 (m, 1H), 7.44-7.41 (m, 1H), 7.38-7.36 (m, 1H), 7.34-7.33 (m, 1H), 7.30-7.26 (m, 3H), 7.24-7.22 (m, 1H), 7.18-7.17 (m, 1H), 7.14-7.13 (m, 1H), 6.67-6.64 (m, 1H), 6.27-6.23 (m, 1H), 3.86-3.79 (m, 2H), 0.28 (s, 9H);^{13}C NMR (150 MHz, $CDCl_3$) δ 197.1, 164.6, 146.8, 141.0, 138.8, 138.1, 134.3, 133.9, 131.8, 131.4, 129.5, 129.2, 128.9, 128.4, 128.0, 127.6, 127.0, 106.5, 47.9, -1.6; FT-IR (neat) 2924, 1646, 1591, 1529, 1494, 1454, 1342, 1245, 1174, 1028, 840, 762 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{24}H_{26}NO_2Si$: 388.1728, found 388.1722.

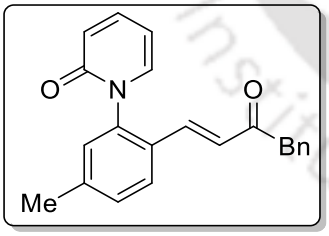


(*E*)-4-(Benzyloxy)-1-(2-(3-oxo-4-phenylbut-1-en-1-yl)phenyl)pyridin-2(1*H*)-one 3e. Analytical TLC on silica gel, 3:1 ethyl acetate/hexane R_f = 0.43; yellow solid; mp 115-116 °C; yield 64% (53.8 mg, *E/Z* = 83:17); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.71-7.70 (m, 1H), 7.50-7.48 (m, 1H), 7.45-7.41 (m, 5H), 7.40-7.36 (m, 2H), 7.30-7.26 (m, 3H), 7.25-7.22 (m, 1H), 7.17-7.16 (m, 2H), 7.01-7.00 (m, 1H), 6.70 (d, *J* = 16.2 Hz,

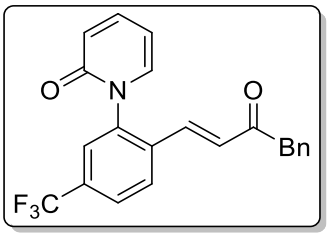
1H), 6.10-6.05 (m, 2H), 5.09-5.04 (m, 2H), 3.88-3.81 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 197.2, 167.8, 163.9, 140.3, 137.8, 135.1, 134.3, 132.1, 131.4, 130.3, 129.5, 128.9, 128.8, 128.76, 128.73, 128.1, 128.0, 127.9, 127.6, 127.1, 102.0, 98.7, 70.6, 48.2; FT-IR (KBr) 2922, 1659, 1609, 1542, 1474, 1453, 1338, 1226, 1209, 824, 739 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{28}H_{24}NO_3$: 422.1751, found 422.1759.



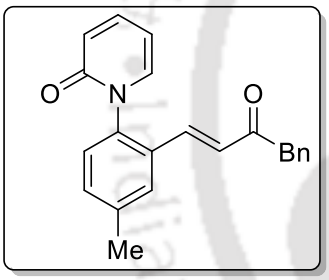
(*E*)-5-Fluoro-1-(2-(3-oxo-4-phenylbut-1-en-1-yl)phenyl)pyridin-2(1*H*)-one 3f. Analytical TLC on silica gel, 3:1 ethyl acetate/hexane R_f = 0.47; brown solid; mp 140-141 °C; yield 66% (44.0 mg, *E/Z* >96:4); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.71-7.70 (m, 1H), 7.54-7.46 (m, 2H), 7.44-7.40 (m, 1H), 7.34-7.27 (m, 4H), 7.25-7.23 (m, 1H), 7.16-7.15 (m, 2H), 7.08-7.07 (m, 1H), 6.70-6.64 (m, 2H), 3.88-3.81 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 196.9, 160.6, 148.2 (J_{C-F} = 233.2 Hz), 139.9, 137.1, 134.1, 133.0 (J_{C-F} = 24.1 Hz), 131.8, 131.6, 129.9, 129.4, 128.9, 128.3 (J_{C-F} = 4.0 Hz), 127.8, 127.1, 123.5, 123.3, 122.6 (J_{C-F} = 7.3 Hz), 48.5; ^{19}F NMR (471 MHz, $CDCl_3$) δ -148.26; FT-IR (KBr) 2921, 1682, 1609, 1541, 1486, 1452, 1362, 1278, 1182, 1084, 829, 754 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{21}H_{17}FNO_2$: 334.1238, found 334.1256.



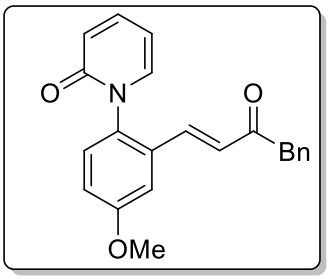
(*E*)-1-(5-Methyl-2-(3-oxo-4-phenylbut-1-en-1-yl)phenyl)pyridin-2(1*H*)-one 3i. Analytical TLC on silica gel, 3:1 ethyl acetate/hexane R_f = 0.44; brown liquid; yield 70% (46.0 mg, *E/Z* >96:4); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.62 (d, *J* = 8.4 Hz, 1H), 7.47-7.44 (m, 1H), 7.31-7.29 (m, 1H), 7.28-7.26 (m, 3H), 7.24-7.21 (m, 1H), 7.14-7.09 (m, 4H), 6.71 (d, *J* = 9.6 Hz, 1H), 6.64 (d, *J* = 16.2 Hz, 1H), 6.24 (t, *J* = 6.6 Hz, 1H), 3.85-3.78 (m, 2H), 2.39 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 197.2, 162.5, 142.4, 140.6, 140.5, 138.1, 137.5, 134.3, 130.5, 129.4, 128.9, 128.86, 128.81, 127.6, 127.2, 127.0, 122.0, 106.3, 48.1, 21.4; FT-IR (neat) 2921, 1662, 1596, 1535, 1498, 1452, 1275, 1177, 1139, 980, 766 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{22}H_{20}NO_2$: 330.1489, found 330.1485.



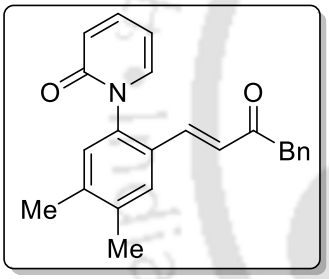
(*E*)-1-(2-(3-Oxo-4-phenylbut-1-en-1-yl)-5-(trifluoromethyl)phenyl)pyridin-2(1*H*)-one 3j. Analytical TLC on silica gel, 3:1 ethyl acetate/hexane R_f = 0.47; brown liquid; yield 61% (46.7 mg, *E/Z* = 88:12); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.82-7.80 (m, 1H), 7.71-7.70 (m, 1H), 7.55 (s, 1H), 7.51-7.47 (m, 1H), 7.33-7.29 (m, 4H), 7.16-7.12 (m, 3H), 6.74-6.68 (m, 2H), 6.29 (t, *J* = 6.6 Hz, 1H), 3.88-3.82 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 196.6, 162.1, 140.9, 140.7, 137.5, 136.0, 135.7, 133.8, 133.2 (J_{C-H} = 33.4 Hz), 129.9, 129.5, 129.0, 128.4, 127.3, 126.4 (J_{C-H} = 3.4 Hz), 125.8 (J_{C-H} = 3.9 Hz), 124.1, 122.3, 106.8, 48.5; ^{19}F NMR (471 MHz, $CDCl_3$) δ -62.86; FT-IR (neat) 2917, 2849, 1664, 1590, 1538, 1423, 1332, 1261, 1171, 1129, 1074, 763 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{22}H_{17}F_3NO_2$: 384.1206, found 384.1219.



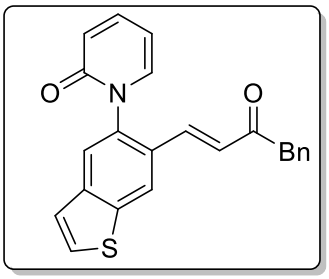
(*E*)-1-(4-Methyl-2-(3-oxo-4-phenylbut-1-en-1-yl)phenyl)pyridin-2(1*H*)-one 3k. Analytical TLC on silica gel, 3:1 ethyl acetate/hexane R_f = 0.44; brown solid; mp 160-161 °C; yield 75% (49.3 mg, *E/Z* = 95:5); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44 (s, 1H), 7.40-7.36 (m, 1H), 7.25-7.15 (m, 5H), 7.10-7.04 (m, 4H), 6.62-6.56 (m, 2H), 6.17-6.14 (m, 1H), 3.79-3.72 (m, 2H), 2.34 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 197.1, 162.6, 140.5, 139.7, 138.2, 138.1, 137.8, 134.2, 132.3, 131.3, 129.4, 128.8, 128.2, 128.1, 128.0, 127.0, 122.0, 106.2, 48.1, 21.3; FT-IR (KBr) 2925, 1661, 1592, 1533, 1494, 1453, 1280, 1135, 1082, 977, 764 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{22}H_{20}NO_2$: 330.1489, found 330.1492.



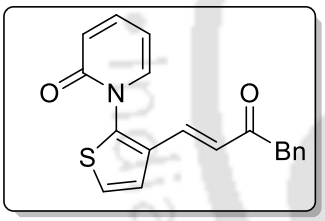
(*E*)-1-(4-Methoxy-2-(3-oxo-4-phenylbut-1-en-1-yl)phenyl)pyridin-2(1*H*)-one 3l. Analytical TLC on silica gel, 3:1 ethyl acetate/hexane R_f = 0.42; brown liquid; yield 73% (50.4 mg, *E/Z* = 90:10); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.46-7.43 (m, 1H), 7.29-7.27 (m, 3H), 7.24-7.23 (m, 1H), 7.20-7.17 (m, 2H), 7.14-7.11 (m, 3H), 7.03-7.01 (m, 1H), 6.69 (d, *J* = 9.0 Hz, 1H), 6.64 (d, *J* = 16.2 Hz, 1H), 6.24-6.21 (m, 1H), 3.88-3.78 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.1, 162.8, 160.0, 140.5, 138.5, 137.7, 134.1, 133.5, 132.7, 129.5, 129.4, 128.8, 128.3, 127.0, 122.0, 117.1, 112.3, 106.2, 55.8, 48.0; FT-IR (neat) 2924, 1660, 1582, 1534, 1495, 1454, 1285, 1234, 1166, 1039, 998, 766 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{22}H_{20}NO_3$: 346.1438, found 346.1440.



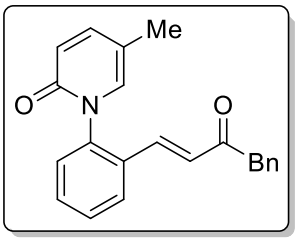
(*E*)-1-(4,5-Dimethyl-2-(3-oxo-4-phenylbut-1-en-1-yl)phenyl)pyridin-2(1*H*)-one 3m. Analytical TLC on silica gel, 3:1 ethyl acetate/hexane R_f = 0.43; brown solid; mp 160-161 °C; yield 74% (50.7 mg, *E/Z* >96:4); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.68 (s, 1H), δ 7.67-7.64 (m, 1H), 7.50-7.42 (m, 5H), 7.35-7.31 (m, 3H), 6.90 (d, *J* = 9.0 Hz, 1H), 6.83 (d, *J* = 16.2 Hz, 1H), 6.43 (t, *J* = 6.6 Hz, 1H), 4.06-3.99 (m, 2H), 2.51(s, 3H), 2.50 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 197.2, 162.7, 141.2, 140.5, 138.4, 138.39, 138.32, 137.7, 134.4, 129.5, 129.3, 128.9, 128.8, 128.7, 127.1, 127.0, 122.0, 106.1, 48.0, 19.9, 19.7; FT-IR (KBr) 2922, 1659, 1595, 1533, 1495, 1452, 1275, 1139, 975, 764 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{23}H_{22}NO_2$: 344.1646, found 344.1655.



(*E*)-1-(6-(3-Oxo-4-phenylbut-1-en-1-yl)benzo[b]thiophen-5-yl)pyridin-2(1*H*)-one 3n. Analytical TLC on silica gel, 3:1 ethyl acetate/hexane R_f = 0.41; brown solid; mp 120-121 °C; yield 72% (53.4 mg, *E/Z* >96:4); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.22 (s, 1H), 7.72 (s, 1H), 7.62 (d, *J* = 5.4 Hz, 1H), 7.50-7.47 (m, 1H), 7.42 (d, *J* = 16.2 Hz, 1H), 7.34 (d, *J* = 5.4 Hz, 1H), 7.31-7.29 (m, 2H), 7.24-7.23 (m, 1H), 7.21-7.20 (m, 1H), 7.17-7.16 (m, 2H), 6.73-6.70 (m, 2H), 6.28-6.26 (m, 1H), 3.87-3.80 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 196.9, 162.8, 141.6, 140.8, 140.7, 138.4, 138.0, 137.4, 134.3, 130.9, 129.5, 128.9, 127.8, 127.4, 127.1, 123.9, 123.1, 122.0, 121.9, 106.4, 48.3; FT-IR (KBr) 2923, 1660, 1590, 1533, 1285, 1085, 973, 759 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{23}H_{18}NO_2S$: 372.1053, found 372.1056.

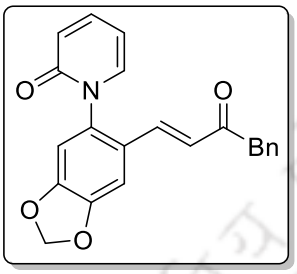


(*E*)-1-(3-(3-Oxo-4-phenylbut-1-en-1-yl)thiophen-2-yl)pyridin-2(1H)-one 3o. Analytical TLC on silica gel, 3:1 ethyl acetate/hexane R_f = 0.43; brown sticky liquid; yield 75% (48.2 mg, *E/Z* >96:4); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.44-7.41 (m, 1H), 7.30-7.28 (m, 3H), 7.25-7.22 (m, 1H), 7.21-7.16 (m, 5H), 6.67 (d, *J* = 9.6 Hz, 1H), 6.57 (d, *J* = 15.6 Hz, 1H), 6.25-6.22 (m, 1H), 3.83 (s, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 197.2, 162.3, 142.0, 140.6, 138.8, 134.2, 132.9, 132.4, 129.4, 128.8, 127.1, 126.9, 125.1, 124.1, 122.1, 106.6, 48.6; FT-IR (neat) 2923, 1669, 1594, 1534, 1458, 1278, 1138, 1083, 968 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{19}H_{16}NO_2S$: 322.0897, found 322.0900.

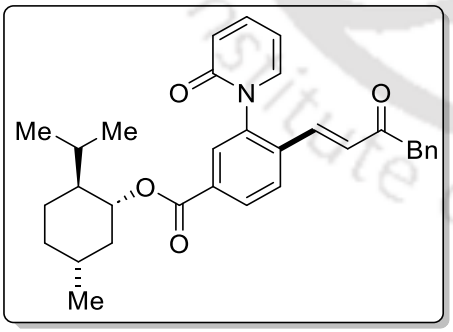


(*E*)-5-Methyl-1-(2-(3-oxo-4-phenylbut-1-en-1-yl)phenyl)pyridin-2(1*H*)-one 3q. Analytical TLC on silica gel, 3:1 ethyl acetate/hexane R_f = 0.44; yellow solid;

mp 206-207 °C; yield 78% (51.3 mg, *E/Z* >96:4); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72-7.69 (m, 1H), 7.52-7.43 (m, 2H), 7.36-7.27 (m, 5H), 7.25-7.21 (m, 1H), 7.16-7.14 (m, 2H), 6.91 (s, 1H), 6.69-6.63 (m, 2H), 3.88-3.78 (m, 2H), 2.08 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.2, 161.8, 143.4, 140.8, 137.8, 135.2, 134.2, 131.8, 131.5, 129.5, 129.4, 128.8, 128.4, 128.0, 127.7, 127.0, 121.5, 115.4, 48.2, 17.1; FT-IR (KBr) 2875, 1671, 1611, 1533, 1489, 1454, 1278, 1142, 983, 829, 757 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{22}H_{20}NO_2$: 330.1489, found 330.1480.

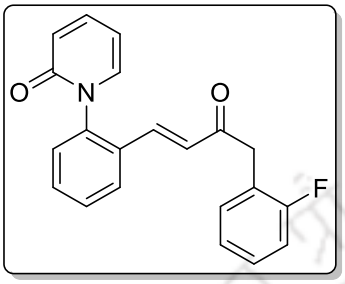


(*E*)-1-(6-(3-Oxo-4-phenylbut-1-en-1-yl)benzo[*d*][1,3]dioxol-5-yl)pyridin-2(1*H*)-one 3r. Analytical TLC on silica gel, 3:1 ethyl acetate/hexane R_f = 0.38; yellow liquid; yield 63% (45.2 mg, *E/Z* = 86:14); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.49-7.40 (m, 1H), 7.29-7.26 (m, 3H), 7.23-7.21 (m, 1H), 7.15-7.13 (m, 3H), 7.05 (s, 1H), 6.89-6.87 (m, 1H), 6.76-6.73 (m, 1H), 6.68-6.66 (m, 1H), 6.25-6.22 (m, 1H), 6.15-6.12 (m, 2H), 3.85- 3.78 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.6, 162.8, 148.5, 147.7, 140.6, 138.5, 134.4, 134.3, 132.7, 130.7, 129.5, 128.8, 127.0, 121.9, 121.4, 115.4, 109.6, 106.3, 102.6, 48.3; FT-IR (neat) 2920, 1663, 1586, 1534, 1455, 1242, 1072, 1024, 932, 767 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{22}H_{18}NO_4$: 360.1231, found 360.1237.

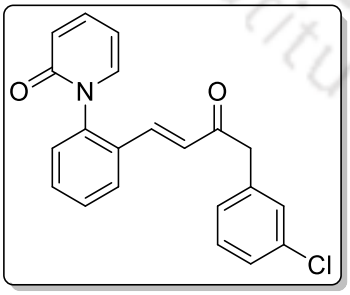


(1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyl 4-((*E*)-3-oxo-4-phenylbut-1-en-1-yl)-3-(2-oxopyridin-1(2*H*)-yl)benzoate 3s. Analytical TLC on silica gel, 3:1 ethyl acetate/hexane R_f = 0.52; brown sticky liquid; yield 64% (63.6 mg, *E/Z* = 93:7); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.11-8.09 (m, 1H), 7.93-7.90 (m, 1H), 7.77-7.75 (m, 1H), 7.50-7.47 (m, 1H), 7.34-7.28 (m, 3H), 7.25-7.23 (m, 1H), 7.16-7.14 (m, 3H), 6.74-6.69 (m, 2H), 6.28 (t, *J* = 6.6 Hz, 1H), 4.97-4.92 (m, 1H), 3.88-3.82 (m, 2H), 2.09-2.04 (m, 1H), 1.93-1.85 (m, 1H), 1.73-1.71 (m, 2H), 1.55-1.51 (m, 2H), 1.15-1.06 (m, 3H), 0.93-0.89 (m, 6H),

0.78 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.8, 164.5, 162.3, 140.8, 140.5, 137.8, 136.5, 136.1, 133.9, 133.7, 130.4, 129.65, 129.62, 129.5, 128.9, 127.7, 127.2, 122.1, 106.6, 75.8, 48.4, 47.2, 41.0, 34.3, 31.5, 26.6, 23.7, 22.1, 20.9, 16.4 cm^{-1}; FT-IR (neat) 2942, 1712, 1667, 1596, 1533, 1495, 1453, 1417, 1294, 1243, 1097, 962, 843 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{32}H_{36}NO_4$: 498.2639, found 498.2649.

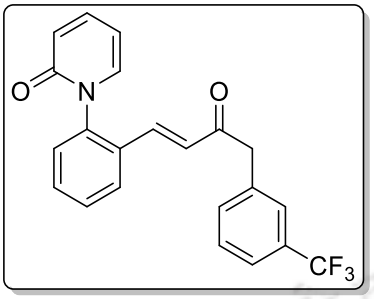


(*E*)-1-(2-(4-(2-Fluorophenyl)-3-oxobut-1-en-1-yl)phenyl)pyridin-2(1*H*)-one 3t. Analytical TLC on silica gel, 3:1 ethyl acetate/hexane R_f = 0.46; brown solid; mp 160-161 °C; yield 66% (43.9 mg, *E/Z* >96:4); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.69 (d, *J* = 7.8 Hz, 1H), 7.46-7.37 (m, 3H), 7.30 (d, *J* = 16.2 Hz, 1H), 7.23 (d, *J* = 7.8 Hz, 1H), 7.18-7.15 (m, 1H), 7.11-7.08 (m, 2H), 7.02-6.94 (m, 2H), 6.66-6.60 (m, 2H), 6.19 (t, *J* = 7.2 Hz, 1H), 3.84-3.76 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 195.8, 162.5, 161.8 (J_{C-F} = 244.3 Hz), 140.7, 140.6, 138.0, 137.5, 131.8, 131.7 (J_{C-F} = 4.0 Hz), 131.5, 129.6, 129.1 (J_{C-F} = 8.1 Hz), 128.5, 127.9, 127.8, 124.4 (J_{C-F} = 3.4 Hz), 122.1, 121.5 (J_{C-F} = 15.9 Hz), 115.6 (J_{C-F} = 21.9 Hz), 106.3, 41.1; ^{19}F NMR (471 MHz, $CDCl_3$) δ -117.02; FT-IR (KBr) 2922, 1663, 1595, 1532, 1490, 1457, 1337, 1280, 1232, 1082, 846 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{21}H_{17}FNO_2$: 334.1238, found 334.1240.

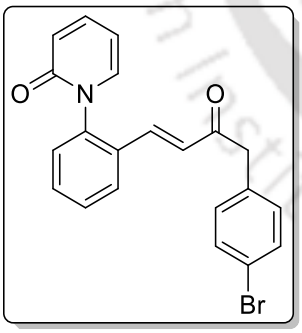


(*E*)-1-(2-(4-(3-Chlorophenyl)-3-oxobut-1-en-1-yl)phenyl)pyridin-2(1*H*)-one 3u. Analytical TLC on silica gel, 3:1 ethyl acetate/hexane R_f = 0.45; brown liquid; yield 79% (55.2 mg, *E/Z* >96:4); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.86-7.84 (m, 1H), 7.66-7.58 (m, 3H), 7.45-7.38 (m, 3H), 7.34-7.33 (m, 2H), 7.27-7.26 (m, 1H), 7.16-7.14 (m, 1H), 6.82 (d, *J* = 9 Hz, 1H), 6.78 (d, *J* = 16.2 Hz, 1H), 6.38 (t, *J* = 6.6 Hz, 1H), 3.96-6-3.88 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 196.3, 162.4, 140.7, 140.6, 138.1, 138.0, 136.1,

134.5, 131.6, 130.0, 129.6, 129.5, 128.5, 128.0, 127.9, 127.6, 127.3, 122.0, 106.4, 47.4; FT-IR (neat) 2921, 1662, 1595, 1532, 1480, 1279, 1145, 1080, 975, 763 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{21}H_{17}ClNO_2$: 350.0943, found 350.0951.

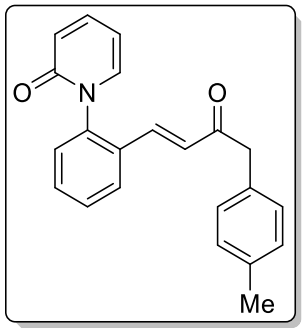


(*E*)-1-(2-(3-Oxo-4-(3-(trifluoromethyl)phenyl)but-1-en-1-yl)phenyl)pyridin-2(1*H*)-one 3v. Analytical TLC on silica gel, 3:1 ethyl acetate/hexane R_f = 0.42; brown liquid; yield 72% (55.1 mg, *E/Z* >96:4); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.75-7.74 (m, 1H), 7.55-7.45 (m, 4H), 7.43-7.41 (m, 2H), 7.36-7.33 (m, 2H), 7.30 (d, *J* = 7.8 Hz, 1H), 7.17-7.15 (m, 1H), 6.70-6.67 (m, 2H), 6.26 (t, *J* = 6.6 Hz, 1H), 3.93-3.87 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 196.1, 162.5, 140.7, 140.6, 138.1, 138.0, 135.1, 133.0, 131.7, 131.6, 131.1 (J_{C-F} = 31.9 Hz), 129.7, 129.2, 128.5, 128.0, 127.8, 126.3 (J_{C-F} = 3.7 Hz), 125.0 (J_{C-F} = 270.7 Hz), 124.0 (J_{C-F} = 3.7 Hz), 122.0, 106.4, 47.4; ^{19}F NMR (471 MHz, $CDCl_3$) δ -62.52; FT-IR (neat) 2922, 1664, 1605, 1533, 1489, 1454, 1330, 1275, 1168, 1123, 1075, 763 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{22}H_{17}F_3NO_2$: 384.1206, found 384.1218.

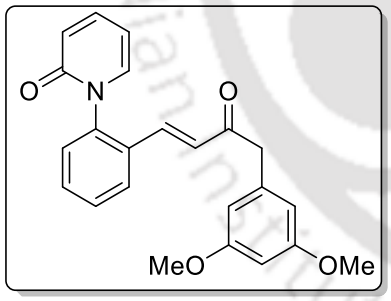


(*E*)-1-(2-(4-(4-Bromophenyl)-3-oxobut-1-en-1-yl)phenyl)pyridin-2(1*H*)-one 3w. Analytical TLC on silica gel, 3:1 ethyl acetate/hexane R_f = 0.45; brown sticky liquid; yield 70% (55.1 mg, *E/Z* >96:4); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.73-7.71 (m, 1H), 7.54-7.51 (m, 1H), 7.49-7.46 (m, 2H), 7.42-7.39 (m, 2H), 7.33 (d, *J* = 16.2 Hz, 1H), 7.29-7.27 (m, 1H), 7.14-7.12 (m, 1H), 7.03-7.01 (m, 2H), 6.70 (d, *J* = 9.6 Hz, 1H), 6.65 (d, *J* = 16.2 Hz, 1H), 6.27-6.24 (m, 1H), 3.82-3.75 (m, 2H);^{13}C NMR (150 MHz, $CDCl_3$) δ 196.5, 162.4, 140.7, 140.6, 138.09, 138.05, 133.2, 132.0, 131.7, 131.6, 131.1, 129.7, 128.5, 128.1, 127.8, 122.1,

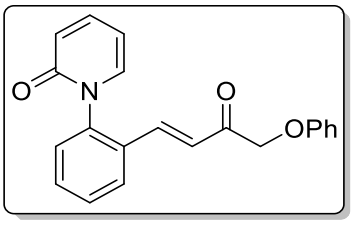
121.1, 106.4, 47.4; FT-IR (KBr) 2924, 1658, 1608, 1533, 1486, 1279, 1070, 1011, 762 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{21}H_{17}BrNO_2$: 394.0438, found 394.0434.



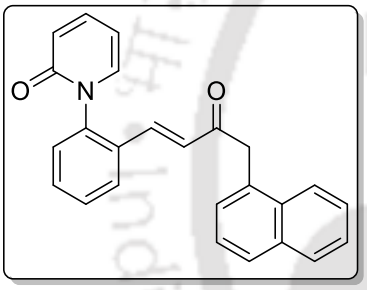
(*E*)-1-(2-(3-Oxo-4-(p-tolyl)but-1-en-1-yl)phenyl)pyridin-2(1*H*)-one 3x. Analytical TLC on silica gel, 3:1 ethyl acetate/hexane R_f = 0.44; brown liquid; yield 73% (48.0 mg, *E/Z* = 88:12); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.72 (d, *J* = 7.8 Hz, 1H), 7.52-7.43 (m, 3H), 7.33 (d, *J* = 16.2 Hz, 1H), 7.28 (d, *J* = 7.2 Hz, 1H), 7.14-7.09 (m, 3H), 7.04-7.02 (m, 2H), 6.70-6.65 (m, 2H), 6.25 (t, *J* = 7.2 Hz, 1H), 3.82-3.75 (m, 2H), 2.31 (s, 3H);^{13}C NMR (150 MHz, $CDCl_3$) δ 197.3, 162.5, 140.6, 140.5, 138.1, 137.4, 136.7, 131.8, 131.4, 131.1, 130.4, 129.6, 129.3, 128.4, 128.2, 127.8, 122.1, 106.3, 47.8, 21.2; FT-IR (KBr) 2923, 1656, 1603, 1534, 1486, 1451, 1277, 974, 764 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{22}H_{20}NO_2$: 330.1489, found 330.1487.



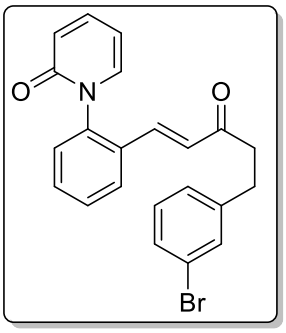
(*E*)-1-(2-(4-(3,5-Dimethoxyphenyl)-3-oxobut-1-en-1-yl)phenyl)pyridin-2(1*H*)-one 3y. Analytical TLC on silica gel, 3:1 ethyl acetate/hexane R_f = 0.40; brown liquid; yield 68% (51 mg, *E/Z* >96:4); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.72 (d, *J* = 7.8 Hz, 1H), 7.52-7.44 (m, 3H), 7.33-7.28 (m, 2H), 7.13-7.12 (m, 1H), 6.68-6.65 (m, 2H), 6.35-6.30 (m, 3H), 6.23 (t, *J* = 6.6 Hz, 1H), 3.77-3.71 (m, 8H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 196.9, 162.5, 161.1, 140.7, 140.6, 138.0, 137.6, 136.3, 131.8, 131.5, 129.6, 128.5, 127.98, 127.96, 122.0, 107.5, 106.4, 99.2, 55.4, 48.6; FT-IR (neat) 2926, 1662, 1596, 1534, 1459, 1431, 1324, 1278, 1205, 1153, 1067, 841, 763 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{23}H_{22}NO_4$: 376.1544, found 376.1540.



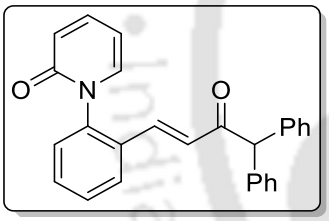
(*E*)-1-(2-(3-Oxo-4-phenoxybut-1-en-1-yl)phenyl)pyridin-2(1*H*)-one 3z. Analytical TLC on silica gel, 3:1 ethyl acetate/hexane R_f = 0.36; brown solid; mp 160-161 °C; yield 75% (49.6 mg, *E/Z* >96:4); ^{1}H NMR (500 MHz, $CDCl_3$) 7.80-7.78 (m, 1H), 7.56-7.48 (m, 3H), 7.45-7.42 (m, 1H), 7.31-7.27 (m, 3H), 7.17-7.16 (m, 1H), 7.02-6.97 (m, 2H), 6.88-6.86 (m, 2H), 6.68 (d, *J* = 9.5 Hz, 1H), 6.27-6.24 (m, 1H), 4.72-4.65 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 195.7, 162.5, 157.9, 140.9, 140.6, 138.5, 137.9, 131.8, 131.7, 129.7, 129.6, 128.6, 128.0, 124.0, 122.1, 121.8, 114.7, 106.4, 72.5; FT-IR (KBr) 2923, 1662, 1597, 1532, 1491, 1456, 1278, 1243, 1051, 844, 757 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{21}H_{18}NO_3$: 332.1282, found 332.1290.



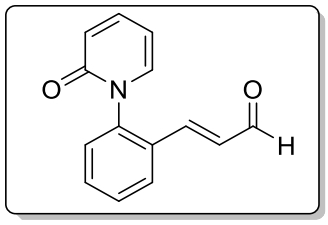
(*E*)-1-(2-(4-(Naphthalen-1-yl)-3-oxobut-1-en-1-yl)phenyl)pyridin-2(1*H*)-one 3aa. Analytical TLC on silica gel, 3:1 ethyl acetate/hexane R_f = 0.40; brown liquid; yield 63% (45.9 mg, *E/Z* = 94:6); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.75-7.72 (m, 2H), 7.67 (d, *J* = 8.4 Hz, 1H), 7.52-7.51 (m, 1H), 7.38-7.34 (m, 3H), 7.31-7.27 (m, 2H), 7.23-7.19 (m, 2H), 7.13-7.12 (m, 2H), 6.94-6.93 (m, 1H), 6.59 (d, *J* = 16.2 Hz, 1H), 6.49 (d, *J* = 9.6 Hz, 1H), 6.02-6.00 (m, 1H), 4.16-4.09 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 197.1, 162.4, 140.6, 140.5, 137.9, 137.4, 134.0, 132.3, 131.7, 131.4, 130.8, 129.5, 128.8, 128.4, 128.2, 128.1, 127.9, 127.4, 126.6, 126.0, 125.7, 124.0, 121.9, 106.2, 46.6; FT-IR (neat) 2925, 1633, 1594, 1532, 1485, 1454, 1278, 1143, 1087, 975, 734 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{25}H_{20}NO_2$: 366.1489, found 366.1495.



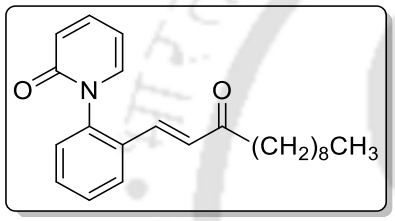
(*E*)-1-(2-(5-(3-Bromophenyl)-3-oxopent-1-en-1-yl)phenyl)pyridin-2(1*H*)-one 3ab. Analytical TLC on silica gel, 3:1 ethyl acetate/hexane R_f = 0.45; brown solid; mp 127-128 °C; yield 64% (52.2 mg, *E/Z* >96:4); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76-7.74 (m, 1H), 7.55-7.46 (m, 3H), 7.32-7.28 (m, 3H), 7.26-7.25 (m, 1H), 7.20-7.18 (m, 1H), 7.15-7.09 (m, 2H), 6.70 (d, *J* = 9.5 Hz, 1H), 6.66 (d, *J* = 16 Hz, 1H), 6.29 (t, *J* = 6.5 Hz, 1H), 2.91-2.83 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.4, 162.4, 143.4, 140.7, 140.5, 138.0, 136.9, 131.8, 131.5, 131.4, 130.1, 129.6, 129.3, 128.7, 128.4, 127.7, 127.2, 122.5, 122.1, 106.4, 42.1, 29.7; FT-IR (KBr) 2925, 1664, 1595, 1532, 1482, 1280, 1099, 998, 764 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{22}H_{19}BrNO_2$: 408.0594, found 408.0596.



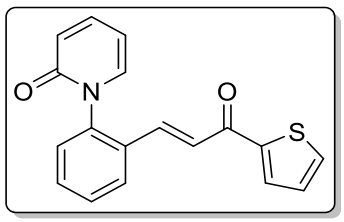
(*E*)-1-(2-(3-Oxo-4,4-diphenylbut-1-en-1-yl)phenyl)pyridin-2(1*H*)-one 3ac. Analytical TLC on silica gel, 3:1 ethyl acetate/hexane R_f = 0.41; brown liquid; yield 74% (57.8 mg, *E/Z* = 94:6); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57-7.55 (m, 1H), 7.38-7.35 (m, 1H), 7.32-7.27 (m, 3H), 7.20-7.12 (m, 7H), 7.07-7.04 (m, 4H), 6.95-6.94 (m, 1H), 6.61 (d, *J* = 16.0 Hz, 1H), 6.54 (d, *J* = 9.5 Hz, 1H), 6.07-6.04 (m, 1H), 5.17 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 197.1, 162.5, 140.6, 140.5, 138.33, 138.30, 137.9, 137.3, 131.7, 131.4, 129.5, 129.3, 129.2, 128.9, 128.8, 128.5, 128.0, 127.9, 127.4, 127.3, 122.0, 106.3, 63.1; FT-IR (neat) 2923, 2852, 1690, 1658, 1600, 1451, 1277, 1083, 760 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{27}H_{22}NO_2$: 392.1646, found 392.1650.



(*E*)-3-(2-(2-Oxopyridin-1(2*H*)-yl)phenyl)acrylaldehyde 3ad. Analytical TLC on silica gel, 3:1 ethyl acetate/hexane R_f = 0.51; brown liquid; yield 72% (32.4 mg, *E/Z* >96:4); ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.57 (d, *J* = 7.8 Hz, 1H), 7.81-7.79 (m, 1H), 7.60-7.57 (m, 1H), 7.55-7.49 (m, 2H), 7.33-7.32 (m, 1H), 7.23-7.19 (m, 2H), 6.73 (d, *J* = 9.0 Hz, 1H), 6.68-6.64 (m, 1H), 6.34-6.31 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 193.6, 162.4, 146.4, 140.8, 140.4, 138.0, 132.3, 131.4, 131.1, 129.8, 128.5, 127.9, 122.2, 106.6; FT-IR (neat) 2923, 1666, 1590, 1532, 1484, 1455, 1278, 1127, 972, 766 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{14}H_{12}NO_2$: 226.0863, found 226.0865.

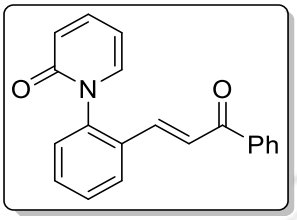


(*E*)-1-(2-(3-Oxododec-1-en-1-yl)phenyl)pyridin-2(1*H*)-one 3ae. Analytical TLC on silica gel, 3:1 ethyl acetate/hexane R_f = 0.54; brown solid; yield 70% (49.1 mg, *E/Z* >96:4); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80-7.78 (m, 1H), 7.56-7.47 (m, 3H), 7.34-7.32 (m, 1H), 7.29-7.28 (m, 1H), 7.22-7.20 (m, 1H), 6.73 (d, *J* = 9.5 , 2H), 6.68 (d, *J* = 16.5 , 2H), 6.31-6.28 (m, 1H), 2.54 (t, *J* = 7.5 Hz, 2H), 1.61-1.59 (m, 2H), 1.33-1.27 (m, 10H), 0.90 (t, *J* = 7 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 200.4, 162.5, 140.6, 140.5, 138.1, 136.4, 132.1, 131.3, 129.6, 129.2, 128.4, 127.7, 122.1, 106.2, 41.0, 32.0, 29.56, 29.55, 29.42, 29.41, 24.4, 22.8, 14.2; FT-IR (KBr) 2924, 1665, 1606, 1594, 1532, 1485, 1456, 1278, 1131, 1084, 999, 762 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{23}H_{30}NO_2$: 352.2272, found 352.2275.

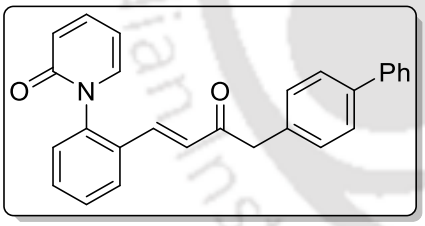


(*E*)-1-(2-(3-Oxo-3-(thiophen-2-yl)prop-1-en-1-yl)phenyl)pyridin-2(1*H*)-one 3ag. Analytical TLC on silica gel, 3:1 ethyl acetate/hexane R_f = 0.40; brown liquid; yield 61% (37.4 mg, *E/Z* = 92:8); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.87-7.86 (m, 1H), 7.77-7.76 (m, 1H), 7.67-7.66 (m, 1H), 7.55-7.51 (m, 3H), 7.48-7.45 (m, 1H), 7.34 (d,

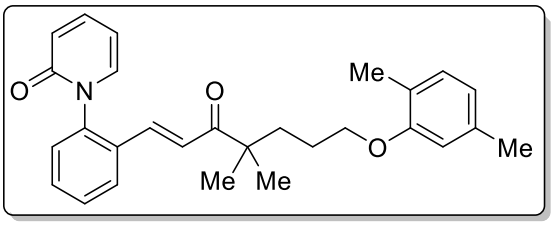
J = 7.2 Hz, 1H), 7.29 (d, *J* = 15.6 Hz, 1H), 7.22-7.21 (m, 1H), 7.15-7.14 (m, 1H), 6.71 (d, *J* = 9.6 Hz, 1H), 6.29 (t, *J* = 7.2 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 181.9, 162.6, 145.2, 140.6, 138.2, 138.1, 138.0, 134.3, 132.3, 132.2, 131.4, 129.6, 128.6, 128.4, 128.3, 125.0, 122.2, 106.4; FT-IR (neat) 2923, 1658, 1592, 1532, 1485, 1454, 1413, 1284, 975 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{18}H_{14}NO_2S$: 308.0740, found 308.0736.



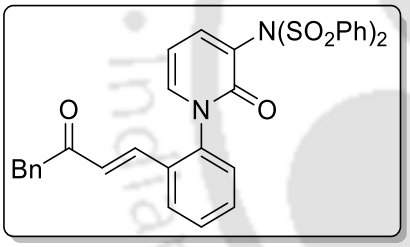
(*E*)-1-(2-(3-Oxo-3-phenylprop-1-en-1-yl)phenyl)pyridin-2(1*H*)-one 3ah. Analytical TLC on silica gel, 3:1 ethyl acetate/hexane R_f = 0.41; yellow thick liquid; yield 59% (35.5 mg, *E/Z* = 83:17); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.92-7.91 (m, 2H), 7.89-7.87 (m, 1H), 7.57-7.50 (m, 3H), 7.47-7.44 (m, 3H), 7.41-7.37 (m, 2H), 7.34-7.32 (m, 1H), 7.22-7.21 (m, 1H), 6.70 (d, *J* = 8.0 Hz, 1H), 6.29-6.26 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 190.5, 162.5, 140.7, 140.5, 139.0, 138.1, 137.8, 133.0, 132.4, 131.4, 129.6, 128.8, 128.7, 128.6, 128.1, 125.5, 122.2, 106.3; FT-IR (neat) 2923, 2853, 1662, 1598, 1533, 1449, 1281, 1217, 1016, 762 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{20}H_{16}NO_2$: 302.1176, found 302.1175.



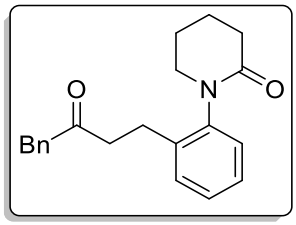
(*E*)-1-(2-(4-([1,1'-Biphenyl]-4-yl)-3-oxobut-1-en-1-yl)phenyl)pyridin-2(1*H*)-one 3ai. Analytical TLC on silica gel, 3:1 ethyl acetate/hexane R_f = 0.45; brown liquid; yield 77% (60.2 mg, *E/Z* = 91:9); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.62-7.60 (m, 1H), 7.45-7.44 (m, 2H), 7.40-7.37 (m, 3H), 7.36-7.29 (m, 4H), 7.23-7.20 (m, 1H), 7.16-7.09 (m, 4H), 7.02-7.01 (m, 1H), 6.59-6.57 (m, 2H), 6.13-6.10 (m, 1H), 3.79-3.72 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 197.0, 162.4, 140.8, 140.6, 140.5, 140.0, 138.0, 137.7, 133.2, 131.8, 131.5, 129.8, 129.6, 128.9, 128.4, 128.2, 127.8, 127.6, 127.4, 127.1, 122.0, 106.3, 47.8 ; FT-IR (neat) 2924, 1662, 1600, 1532, 1486, 1283, 1078, 848, 760 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{27}H_{22}NO_2$: 392.1646, found 392.1636.



(*E*)-1-(2-(7-(2,5-Dimethylphenoxy)-4,4-dimethyl-3-oxohept-1-en-1-yl)phenyl)pyridin-2(1*H*)-one 3aj. Analytical TLC on silica gel, 3:1 ethyl acetate/hexane R_f = 0.61; green sticky liquid; yield 48% (41.2 mg, *E/Z* >96:4); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.77-7.76 (m, 1H), 7.52-7.46 (m, 2H), 7.44-7.39 (m, 2H), 7.31-7.29 (m, 1H), 7.15-7.14 (m, 1H), 7.03 (d, *J* = 15.6 Hz, 1H), 6.98 (d, *J* = 7.2 Hz, 1H), 6.68 (d, *J* = 9.6 Hz, 1H), 6.64 (d, *J* = 7.2 Hz, 1H), 6.58 (s, 1H), 6.26-6.23 (m, 1H), 3.91-3.85 (m, 2H), 2.28 (s, 3H), 2.14 (s, 3H), 1.81-1.71 (m, 2H), 1.69-1.63 (m, 2H), 1.18 (s, 3H), 1.16 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 203.3, 162.6, 157.0, 140.5, 138.1, 137.1, 136.6, 132.2, 131.1, 130.4, 129.5, 128.7, 128.3, 123.8, 123.5, 122.2, 120.8, 112.0, 106.2, 67.9, 46.5, 36.3, 25.0, 24.4, 24.0, 21.5, 15.9; FT-IR (neat) 3380, 2924, 1661, 1607, 1584, 1534, 1457, 1377, 1263, 1129, 1082, 1037, 765 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{28}H_{32}NO_3$: 430.2377, found 430.2380.



(*E*)-*N*-(2-Oxo-1-(2-(3-oxo-4-phenylbut-1-en-1-yl)phenyl)-1,2-dihydropyridin-3-yl)-*N*-(phenylsulfonyl)benzenesulfonamide 4. Analytical TLC on silica gel, 3:1 ethyl acetate/hexane R_f = 0.50; yellow thick liquid; yield 66% (40.2 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.07-8.05 (m, 2H), 7.98-7.96 (m, 2H), 7.69-7.67 (m, 1H), 7.60-7.55 (m, 2H), 7.53-7.43 (m, 8H), 7.32 (d, *J* = 16.2 Hz, 1H), 7.24-7.19 (m, 4H), 7.14-7.13 (m, 2H), 6.61 (d, *J* = 16.2 Hz, 1H), 6.25 (t, *J* = 7.2 Hz, 1H), 3.97-3.94 (m, 1H), 3.86-3.84 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 197.7, 159.7, 145.1, 140.7, 139.5, 139.1, 139.0, 137.2, 134.5, 134.14, 134.12, 132.0, 131.4, 130.0, 129.64, 129.61, 129.3, 129.1, 128.9, 128.8, 128.7, 128.3, 128.1, 126.9, 125.6, 105.1, 47.2; FT-IR (neat) 2924, 1672, 1610, 1538, 1483, 1449, 1375, 1353, 1267, 1169, 1084, 889, 756 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{33}H_{27}N_2O_6S_2$: 611.1306, found 611.1300.



1-(2-(3-Oxo-4-phenylbutyl)phenyl)piperidin-2-one 5. Analytical TLC on silica gel, 3:2 ethyl acetate/hexane R_f = 0.50; yellow liquid; yield 83% (26.6 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31-7.28 (m, 2H), 7.25-7.20 (m, 3H), 7.19-7.16 (m, 3H), 7.09-7.07 (m, 1H), 3.69-3.62 (m, 2H), 3.53-3.49 (m, 1H), 3.36-3.34 (m, 1H), 2.86-2.76 (m, 2H), 2.74-2.71 (m, 2H), 2.52-2.40 (m, 2H), 1.92-1.84 (m, 4H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 207.4, 170.1, 141.7, 137.9, 134.0, 129.7, 129.3, 128.6, 127.9, 127.6, 127.5, 126.9, 51.8, 50.0, 41.9, 32.4, 24.6, 23.3, 21.3; FT-IR (neat) 2941, 1709, 1642, 1490, 1452, 1434, 1346, 1327, 1165, 1151, 1072, 761 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{21}H_{24}NO_2$: 322.1802, found 322.1806.

Crystal Data and Structure Refinement for 3t

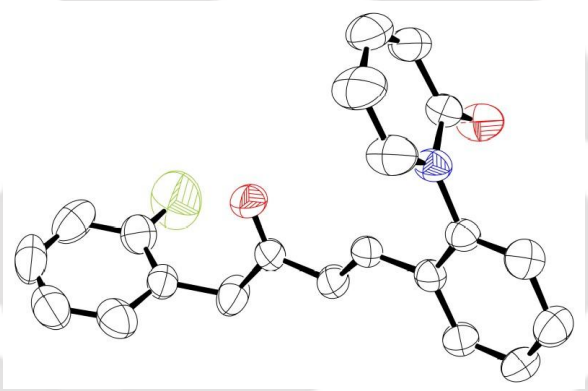


Figure 2. ORTEP diagram of (*E*)-1-(2-(4-(2-fluorophenyl)-3-oxobut-1-en-1-yl)phenyl) pyridin-2(1*H*)-one **3t** with 50% ellipsoid (**CCDC 2267567**).

Identification code	**3t**
Empirical formula	$C_{21}H_{16}FNO_2$
Solvent for crystal growth	Acetonitrile
Formula weight	333.35
Crystal habit, colour	block and brown
Temperature, *T*/K	297 K
Wavelength, *λ*/Å	0.71073
Crystal system	orthorhombic

Space group	'P 21 21 21'
Unit cell dimensions	a = 5.9995(3) Å
	b = 13.3944(6) Å
	c = 21.3076(9) Å
	α = 90
	β = 90
	γ = 90
Volume, V/Å^3	1712.27(14)
Z	4
Calculated density, g·cm^{-3}	1.293
Absorption coefficient, μ/mm^{-1}	0.091
F(000)	696
θ range for data collection	1.796 to 24.973°
Limiting indices	$-7 \leq h \leq 7$, $-15 \leq k \leq 15$, $-25 \leq l \leq 25$
Reflection collected / unique	2935 / 2695
Completeness to θ	97.60% (θ = 24.97°)
Absorption correction	none
Refinement method	'SHELXT 2018/2 (Sheldrick, 2018) '
Data / restraints / parameters	2935/0/226
Goodness-of-fit on F^2	1.086
Final R indices [I >2sigma(I)]	$R1$ = 0.0582, $wR2$ = 0.1525
R indices (all data)	$R1$ = 0.0530, $wR2$ = 0.1437

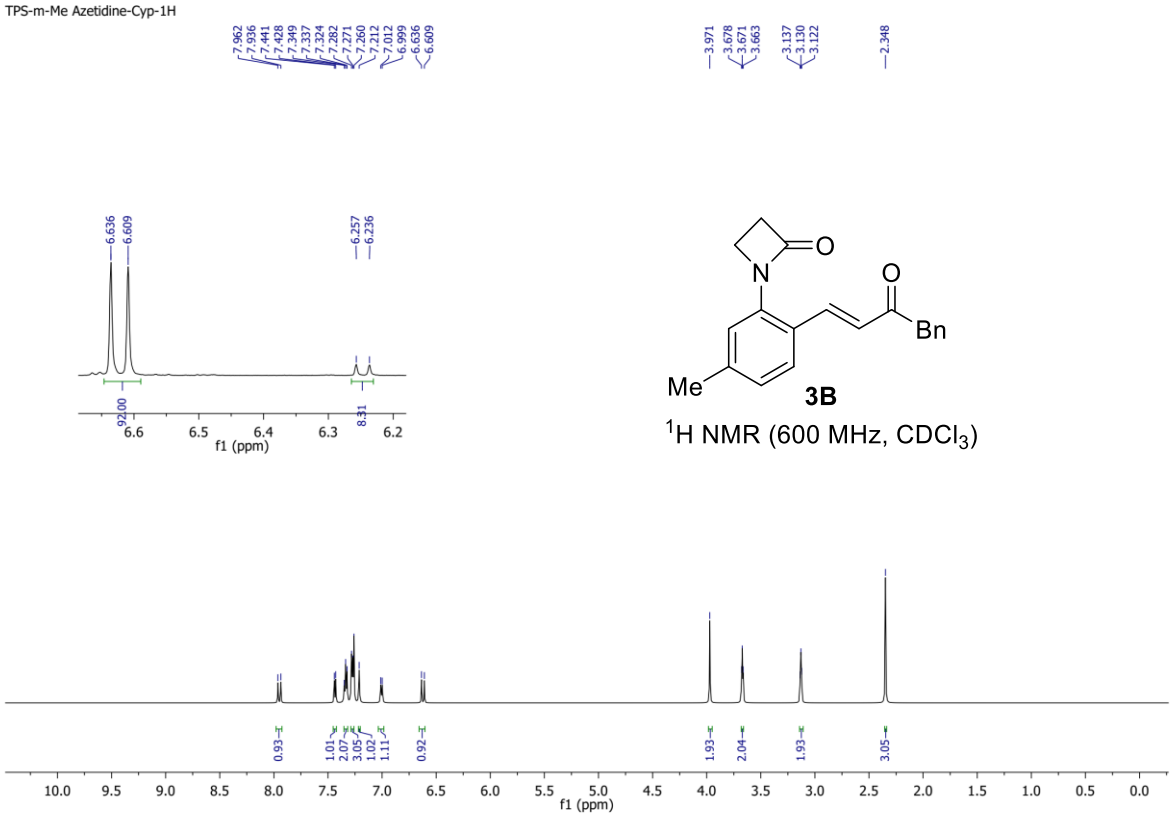
3.4 References

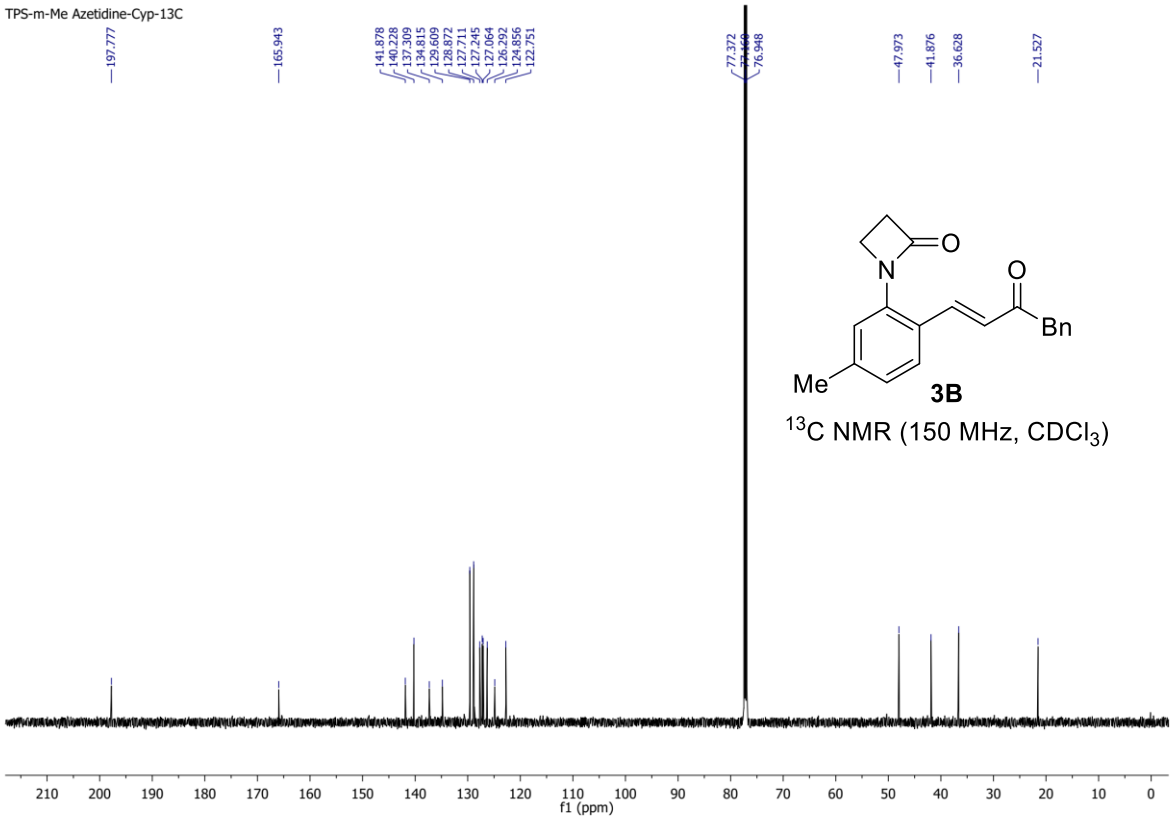
1. (a) De Sarkar, S.; Liu, W.; Kozhushkov, S. I.; Ackermann, L. *Adv. Synth. Catal.* **2014**, *356*, 1461. (b) Rej, S.; Ano, Y.; Chatani, N. *Chem. Rev.* **2020**, *120*, 1788. (c) Zhao, B.; Prabagar, B.; Shi, Z. *Chem.* **2021**, *7*, 2585.
2. (a) Willcox, D.; Chappell, B. G. N.; Hogg, K. F.; Calleja, J.; Smalley, A. P.; Gaunt, M. J. *Science.* **2016**, *354*, 851. (b) Liu, S.; Zhuang, Z.; Qiao, J. X.; Yeung, K.-S.; Su, S.; Cherney, E. C.; Ruan, Z.; Ewing, W. R.; Poss, M. A.; Yu, J.-Q. *J. Am. Chem. Soc.* **2021**, *143*, 21657. (c) Zhuang, Z.; Liu, S.; Cheng, J.-T.; Yeung, K.-S.; Qiao, J. X.; Meanwell, N. A.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2022**, *61*, e202207354.

3. Yan, C.; Fraga-Dubreuil, J.; Garcia-Verdugo, E.; Hamley, P. A.; Poliakoff, M.; Pearson, I.; Coote, A. S. *Green Chem.* **2008,** *10*, 98.
4. (a) Xi, N.; Arvedson, S.; Eisenberg, S.; Han, N.; Handley, M.; Huang, L.; Huang, Q.; Kiselyov, A.; Liu, Q.; Lu, Y.; Nunez, G.; Osslund, T.; Powers, D.; Tasker, A. S.; Wang, L.; Xiang, T.; Xu, S.; Zhang, J.; Zhu, J.; Kendall, R.; *Bioorg. Med. Chem. Lett.* **2004**, *14*, 2905. (b) Taniguchi, H.; Ebina, M.; Kondoh, Y.; Ogura, T.; Azuma, A.; Suga, M.; Taguchi, Y.; Takahashi, H.; Nakata, K.; Sato, A.; Takeuchi, M.; Raghu, G.; Kudoh, S.; Nukiwa, T. *Eur. Respir. J.* **2010**, *35*, 821. (c) Yuan, J.; Liu, K.; Li, L.; Yuan, Y.; Liu, X.; Li, Y. *Molecules.* **2014**, *19*, 14999. (d) Wang, Y.; Wang, H.; Jiang, X.; Jiang, Z.; Guo, T.; Ji, X.; Li, Y.; Li, Y.; Li, Z. *Molecules.* **2019**, *24*, 985. (e) Boucherdoud, A.; Kherroub, D.E. *Polym. Bull.* **2021**, *78*, 6367.
5. (a) Mielcke, T. R.; Mascarello, A.; Filippi-Chiela, E.; Zanin, R. F.; Lenz, G.; Leal, P. C.; Chirardia, L. D.; Yunes, R. A.; Nunes, R. J.; Battastini, A. M.; Morrone, F. B.; Campos, M. M. *Eur. J. Med. Chem.* **2012**, *48*, 255. (b) Zhuang, C.; Zhang, W.; Sheng, C.; Zhang, W.; Xing, C.; Miao, Z. *Chem. Rev.* **2017**, *117*, 7762.
6. (a) Masarwa, A.; Didier, D.; Zabrodski, T.; Schinkel, M.; Ackermann, L.; Marek, I. *Nature.* **2014**, *505*, 199. (b) Wang, H.-H.; Wang, X.-D.; Yin, G.-F.; Zeng, Y.-F.; Chen, J.; Wang, Z. *ACS Catal.* **2022**, *12*, 2330.
7. For examples, see: (a) Zhou, X.; Yu, S.; Qi, Z.; Kong, L.; Li, X. *J. Org. Chem.* **2016**, *81*, 4869. (b) Zhou, X.; Qi, Z.; Yu, S.; Kong, L.; Li, Y.; Tian, W.-F.; Li, X. *Adv. Synth. Catal.* **2017**, *359*, 1620. (c) Chen, H. M.; Liao, G.; Xu, C. K.; Yao, Q. J.; Zhang, S.; Shi, B.-F. *CCS Chem.* **2021**, *3*, 455. (d) Sekiguchi, Y.; Yoshikai, N. *J. Am. Chem. Soc.* **2021**, *143*, 4775.
8. Hu, F.; Xia, Y.; Ye, F.; Liu, Z.; Ma, C.; Zhang, Y.; Wang, J. *Angew. Chem., Int. Ed.* **2014**, *53*, 1364.
9. Pradhan, S.; Mishra, M.; De, P. B.; Banerjee, S.; Punniyamurthy, T. *Org. Lett.* **2020**, *22*, 1720.
10. Bu, Q.; Rogge, T.; Kotek, V.; Ackermann, L. *Angew. Chem. Int. Ed.* **2018**, *57*, 765.
11. Lu, X.; Shen, C.; Meng, K.; Zhao, L.; Li, T.; Sun, Y.; Zhang, J.; Zhong, G. *Chem. Commun.* **2019**, *55*, 826.
12. Wesch, T.; Leroux, F. R.; Colobert, F. *Adv. Synth. Catal.* **2013**, *355*, 2139.
13. Sun, Q.-Y.; Li, Z.; Xu, Z.; Zheng, Z.-J.; Cao, J.; Yang, K.-F.; Cui, Y.-M.; Xu, L.-W. *Chem. Commun.* **2019**, *55*, 6229.

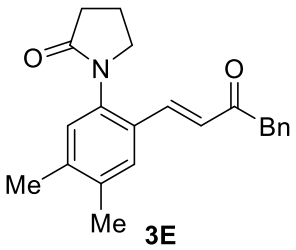
14. Yang, X.; Sun, R.; Zhang, C.; Zheng, X.; Yuan, M.; Fu, H.; Li, R.; Chen, H. *Org. Lett.* **2019**, *21*, 1002.
15. Wang, S.; Hou, J.-T.; Feng, M.-L.; Zhang, X.-Z.; Chen, S.-Y.; Yu, X.-Q. *Chem. Commun.* **2016**, *52*, 2709.
16. Hu, Y.; Zhou, B.; Chen, H.; Wang, C. *Angew. Chem., Int. Ed.* **2018**, *57*, 12071.
17. (a) Arockiam, P. B.; Bruneau, C.; Dixneuf, P. H. *Chem. Rev.* **2012**, *112*, 5879. (b) Kozhushkov, S. I.; Ackermann, L. *Chem. Sci.* **2013**, *4*, 886. (c) Shan, C.; Zhu, L.; Qu, L.-B.; Bai, R.; Lan, Y. *Chem. Soc. Rev.* **2018**, *47*, 7552 (d) Wang, S.; Miao, E.; Wang, H.; Song, B.; Huang, W.; Yang, W. *Chem. Commun.* **2021**, *57*, 5929.
18. (a) Klapars, A.; Antilla, J. C.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2001**, *123*, 7727. (b) Yuan, J.; Liu, K.; Li, L.; Yuan, Y.; Liu, X.; Li, Y. *Molecules*. **2014**, *19*, 14999. (c) Zhou, Y.; Chen, P.; Lv, X.; Niu, J.; Wang, Y.; Lei, M.; Hu, L. *Tetrahedron Lett.* **2017**, *58*, 2232. (d) Li, J.; Yang, Y.; Wang, Z.; Feng, F.; You, J. *Org. Lett*. **2017**, *19*, 3083.
19. Ploger, S.; Studer, A. *Org. Lett.* **2022**, *24*, 8568.

3.5 Selected NMR Spectra



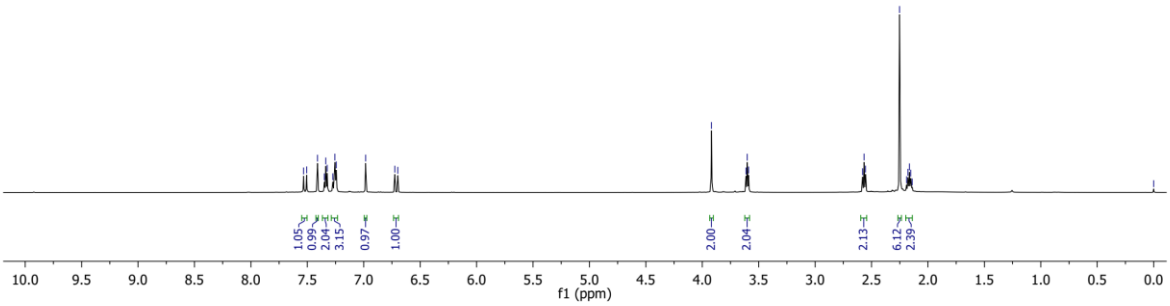


TPS-DiMe pyrrolidine-Cyp-1H

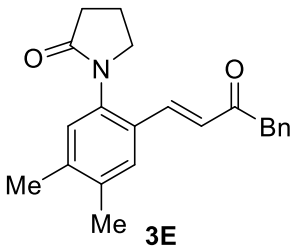


3E

^{1}H NMR (600 MHz, $CDCl_3$)

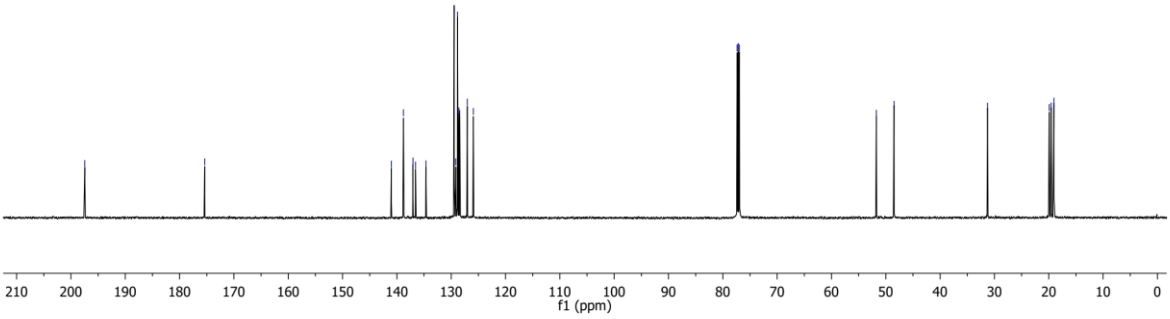


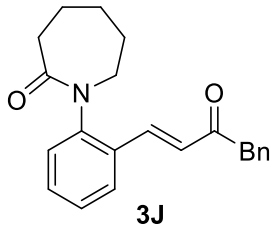
TPS-DiMe pyrrolidine-Cyp-13C



3E

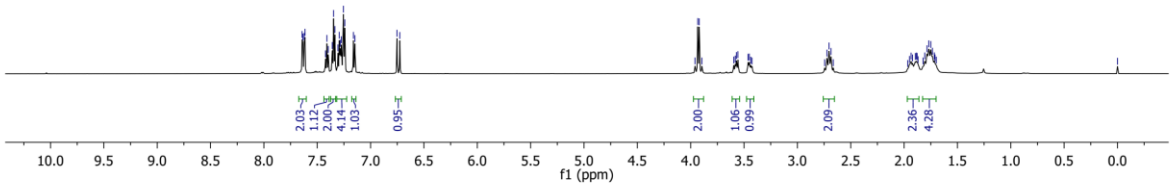
^{13}C NMR (150 MHz, $CDCl_3$)

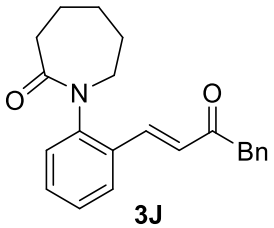




3J

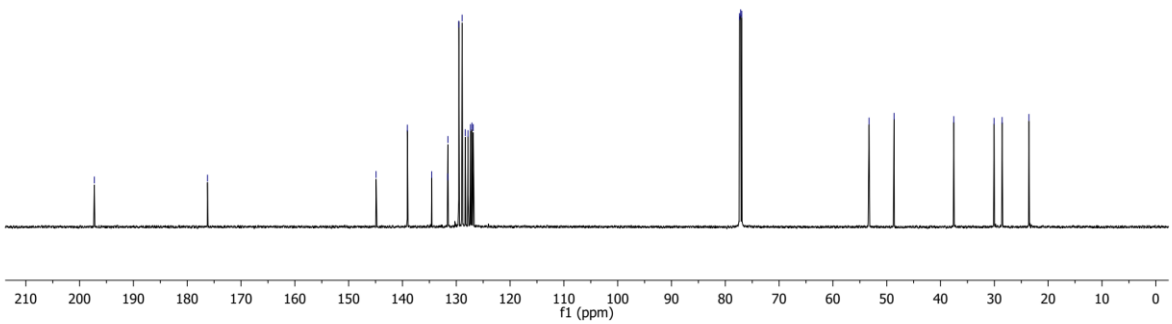
^{1}H NMR (600 MHz, $CDCl_3$)





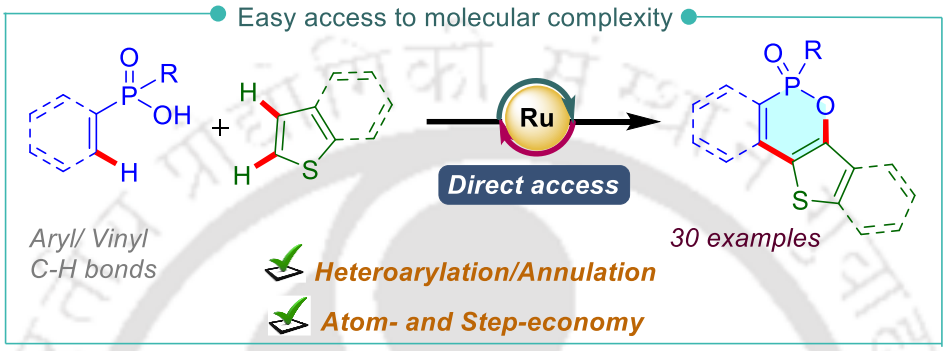
3J

^{13}C NMR (150 MHz, $CDCl_3$)



Chapter IV

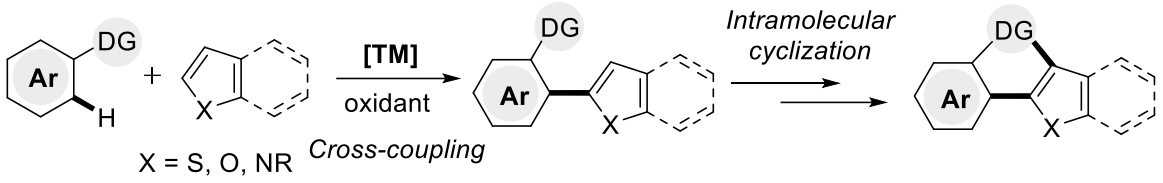
Ru-Catalyzed C-H/C-H Coupling/Annulation Cascade with Benzothiophenes



Chem. Commun. **2025**, DOI: 10.1039/D5CC02209F

Ru-Catalyzed C-H/C-H Coupling/Annulation Cascade with Benzothiophenes

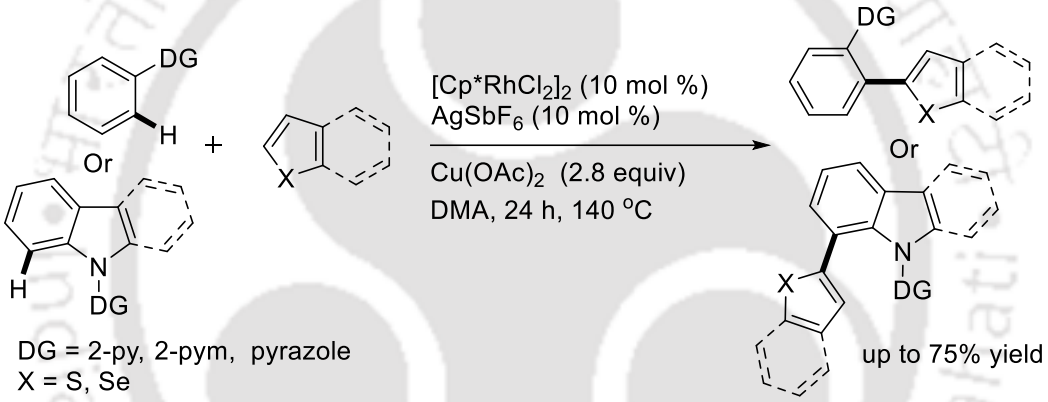
Transition-metal-catalyzed auxiliary assisted site-selective C-H functionalization has garnered significant attention over the years for rapid and straightforward access to functionally rich compounds of pharmaceutical relevance.[1] In particular, chelation guided oxidative C-H/C-H cross coupling for site-selective (hetero)arylation has received substantial importance as it circumvents the necessity for preactivation of coupling partners.[2] Along this line, one-pot (hetero)arylation/annulation will be more advantageous, providing a streamlined and efficient synthetic approach with high step- and atom-economy for the rapid synthesis of cyclic complex organic molecules of pharmaceutical and industrial interest.[3] However, tandem C-H/C-H cross coupling/annulation strategy is quite challenging as it requires controllable sequential multiple C-H bond activation. Owing to the good biocompatibity, air stability and interconversion ability phosphaheterocycles are omnipresent in biologically active compounds, functional materials, organocatalysts and ligands.[4] Given the importance on organophosphorus compounds, there has been continuous quest within the scientific community for their structural modification.[5] Meanwhile, among (hetero)arenes, benzothiophenes are regarded as privileged building blocks in natural products, organic functional materials. Regioselective functionalization of benzothiophene is especially arduous due to the subtle reactivity difference of C-H bonds present. Moreover, benzothiophene fused polyheterocycles are the structural units of various optoelectronic materials, semiconductors and bioactive compounds.[6] The traditional methods for their synthesis suffer from multiple intricate steps and stringent reaction conditions (Scheme 1). In this regard, one-step site-selective assembly of aryl phosphonic acid monoesters with benzothiophenes for the expeditious construction of benzothiophene fused phosphaisocoumarin frameworks would thus be valuable. In this chapter, we present Ru(II)-catalyzed weak chelation assisted cascade C-H/C-H cross coupling/cyclization of aryl/vinyl phosphonic acid monoesters with benzothiophenes, resulting in the formation of benzothiophene fused phosphaisocoumarin frameworks. In addition, vinylic C(sp^2)-H functionalization, which is typically challenging due to their propensity for polymerization and decomposition at elevated temperature, [7] proved to be an effective substrate under this protocol. Notable features of our findings include one-pot annulative π-extension, broad substrate scope, functional group tolerance and late-stage mutations of valuable drug molecules.



Scheme 1. Complementary Multistep Strategy

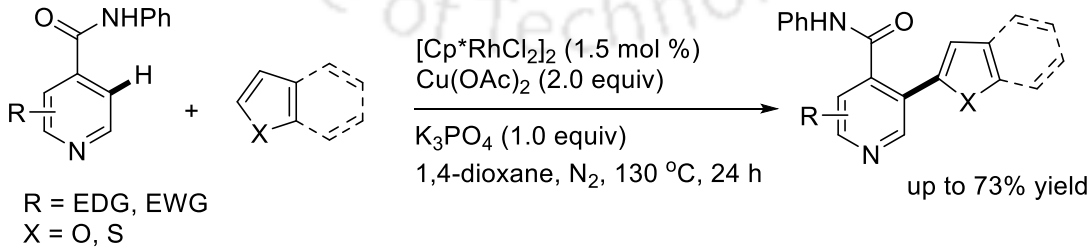
4.1 TM-Catalyzed C-H Heteroarylation

Kambe and co-workers described the chelation-assisted Rh-catalyzed oxidative C-H/C-H cross-coupling of (hetero)arenes with chalcogenophenes (Scheme 2).[8] A combination of $Cu(OAc)_2$ and $AgSbF_6$ proved to be the optimal oxidant. The reaction showed a broad substrate scope with (hetero)arenes and thiophenes. In addition, selenophenes proved to be effective substrates for the protocol.



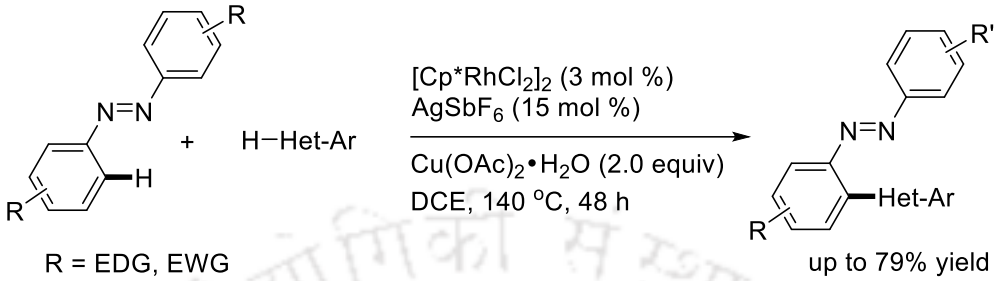
Scheme 2. Cross-coupling of (Hetero)arenes with Thio- and Selenophene Derivatives

Concurrently, Su and co-workers developed an amide directed Rh-catalyzed oxidative cross-coupling of pyridines with heteroarenes (Scheme 3).[9] The reaction was amenable to a variety of functional groups like aryl, alkyl, ester, cyano and halogens.



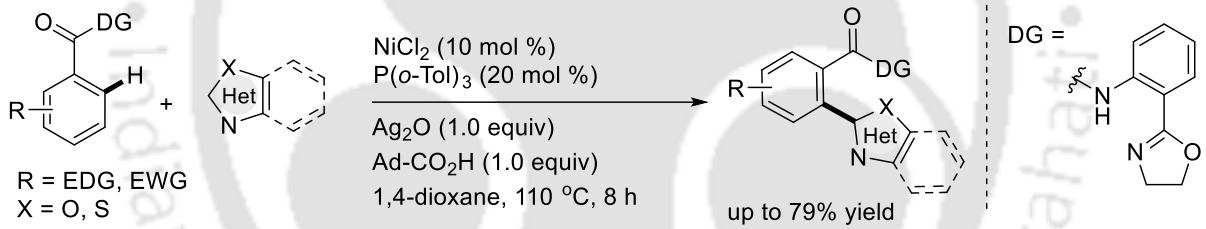
Scheme 3. Amide Directed Cross-coupling of Pyridines with (Hetero)arenes

Li and Wang disclosed oxidative cross-dehydrogenative coupling of azobenzenes with indoles, benzothiophenes or benzoxazoles affording a series of π-conjugated biaryls in good to excellent yields (Scheme 4).[10] The mechanistic studies suggested that the reaction is initiated by *ortho*-C-H activation of azobenzenes.



Scheme 4. Rh-Catalyzed Cross-coupling of Azobenzenes with Heteroarenes

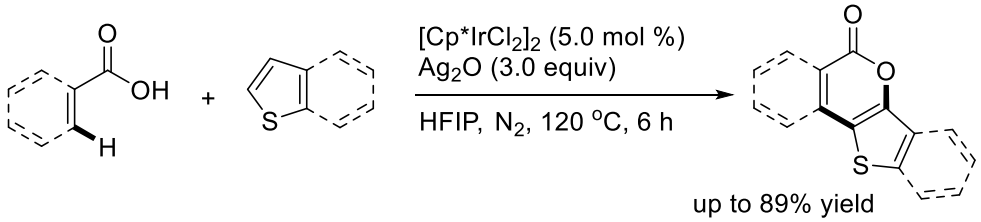
Our group demonstrated a Ni-catalyzed arene C-H heteroarylation utilizing easily removable oxazoline-aniline derived DG (Scheme 5).[11] The key features of the protocol include substrate scope, functional group compatibility and late-stage modifications of commercially available drug molecules such as caffeine, pentoxifylline, doxofylline.



Scheme 5. Ni-Catalyzed C-H/C-H Cross-coupling of Arenes with Azoles

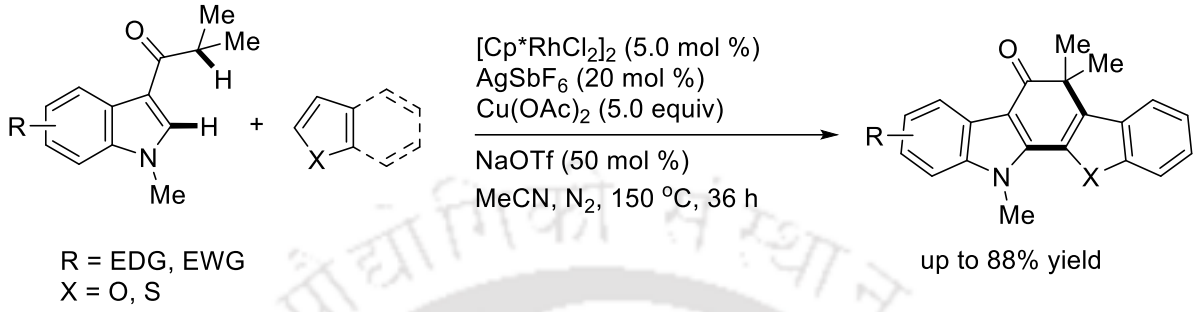
4.2 TM-Catalyzed C-H Heteroarylation/Annulation

Ir-catalyzed one-pot annulation of carboxylic acids with (benzo)thiophenes *via* a heck type pathway was realized by You and co-workers (Scheme 6).[12] The reaction provided a wide range of thiophene-fused coumarin-type frameworks. Moreover, the reactions of α,β-unsaturated carboxylic acids with 2-substituted thiophenes furnished dearomatized spirocyclic compounds.



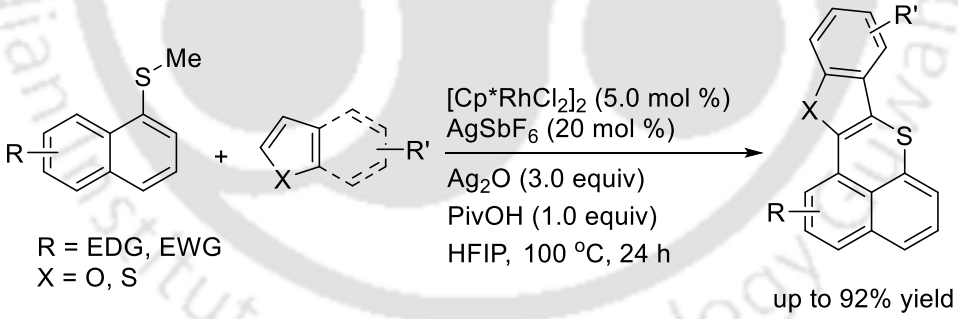
Scheme 6. Ir-Catalyzed C-H/C-H Cross-coupling/Cyclization of Carboxylic Acids

Lan and You groups demonstrated a tandem Rh(III)-catalyzed *ortho*-C-H heteroarylation of indolyl ketones and Cu(II)-promoted cyclization to access phenanthrone-type polyheterocycles (Scheme 7).[13] Compared to the uncyclized intermediates, cyclized products exhibit higher quantum yield and function as blue-emitting fluorophore, demonstrating potential applicability.



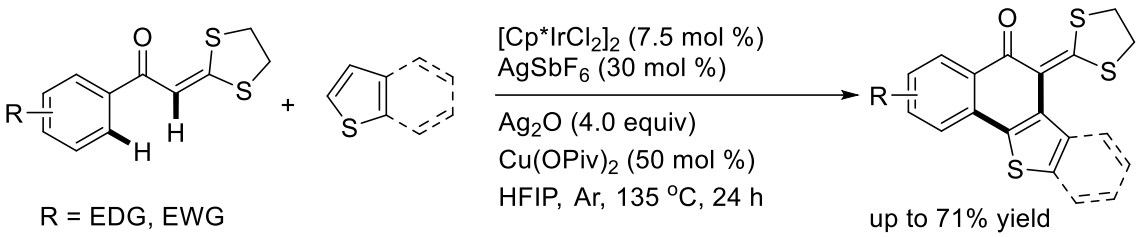
Scheme 7. Rh-Catalyzed Tandem Heteroarylation/Cyclization of Indolyl Ketones

Thioether directed Rh-catalyzed *peri*-selective heteroarylation/Ag-mediated cyclization of 1-(methylthio)naphthalenes with heteroarenes has been achieved to access benzo[*de*]thioacenes (Scheme 8).[14] Regioselectivity, π-extension, substrate scope, mechanistic studies are important features of the reaction. Importantly, the use of *t*-BuOH instead HFIP solvent delivered biaryl sulfides.



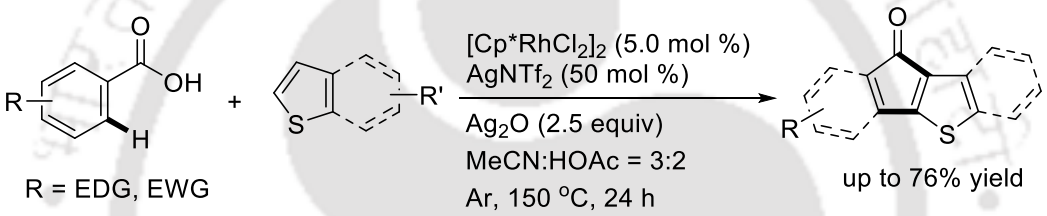
Scheme 8. Rh/Ag-Mediated *Peri*-selective Heteroarylation/Annulation Cascade

Ir-catalyzed tandem cross-dehydrogenative coupling/intramolecular cyclization of ketene dithioacetals with benzothiophenes was described by Yu and co-workers (Scheme 9).[15] Mechanistic study revealed that the reaction likely proceeds through C-H heteroarylation, followed by Ag_2O-promoted intramolecular cyclization *via* radical intermediate. The tandem protocol displays ample substrate scope and excellent tolerance for a wide range of functional groups.



Scheme 9. Ir-Catalyzed C-H/C-H Cross-coupling/Cyclization of Ketene Dithioacetals

Jiao and Shi groups reported Rh-catalyzed tandem oxidative cyclization of aromatic acids with (benzo)thiophenes to afford planar polycyclic heteroarenes (Scheme 10).[16] The reaction was proposed to proceed *via* intermolecular cross-dehydrogenative coupling followed by Fridel-Crafts acylation. Due to favorable biocompatibility and photostability the annulate products can selectively target lipid droplets, highlighting its potential for applications in biological imaging.

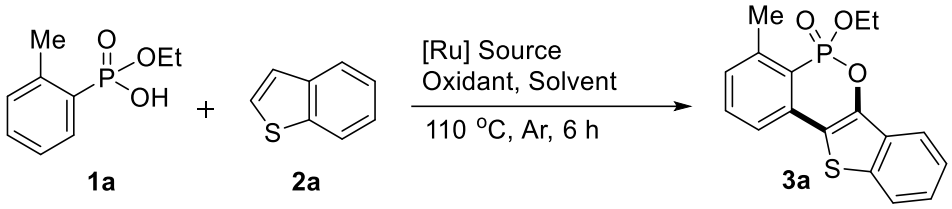


Scheme 10. Rh-Catalyzed C-H/C-H Cross-coupling/Cyclization of Aromatic Carboxylic Acids

4.3 Present Study

Herein, a Ru-catalyzed oxidative C-H/C-H heteroarylation/annulation of aryl/vinyl phosphonic acid monoesters with benzothiophenes is presented for the construction of benzothiophene fused phosphaisocoumarin frameworks. We initiated optimization studies with the annulation reaction between ethyl hydrogen *o*-tolylphosphonate **1a** and benzo[*b*]thiophene **2a** as the test substrates under varied Ru-sources, oxidants and solvents (Table 1). Gratifyingly, the annulated product was formed in 21% yield when the substrates **1a** and **2a** were stirred with 5 mol % [$RuCl_2$(*p*-cymene)]$_2$ and 3 equiv AgOAc in HFIP at 110 ^oC for 6 h under Ar atmosphere (entry 1). Further screening of oxidants, Ag_2CO_3, Ag_2O, $Cu(OAc)_2$ and $K_2S_2O_8$, revealed Ag_2O as the optimal oxidant, providing best result of 86% yield (entries 2-5). Among the solvents examined, HFIP, TFE, methanol, H_2O, 2-methyltetrahydrofuran, 1,4-dioxane, 1,2-dichloroethane, toluene and DMF (entries 6-13), HFIP yielded the best outcome. Further, the additional use of 20 mol % $AgSbF_6$ provided an adverse effect on the yield (entry 14). The product was not obtained using $RuCl_3$•3H_2O as catalyst (entry 15). Control experiments confirmed the absence of catalyst or

Table 1. Optimization of the Reaction Conditions[a]

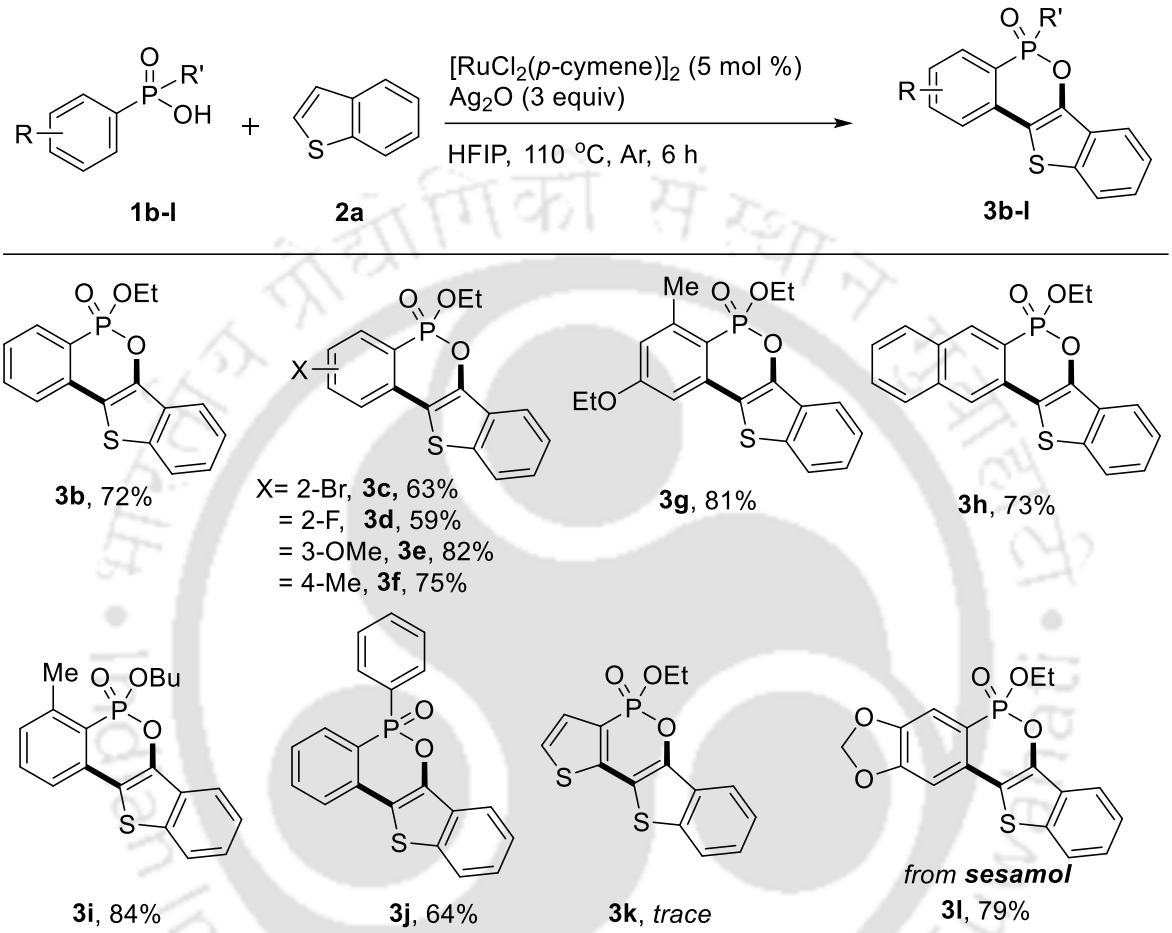


Entry	Catalyst	Oxidant	Solvent	Yield[b] (%)
1	$[RuCl_2(p\text{-cymene})]_2$	AgOAc	HFIP	21
2	$[RuCl_2(p\text{-cymene})]_2$	Ag_2CO_3	HFIP	66
3	**$[RuCl_2(p\text{-cymene})]_2$**	**Ag_2O**	**HFIP**	**86**
4	$[RuCl_2(p\text{-cymene})]_2$	$Cu(OAc)_2$	HFIP	n.d.
5	$[RuCl_2(p\text{-cymene})]_2$	$K_2S_2O_8$	HFIP	n.d.
6	$[RuCl_2(p\text{-cymene})]_2$	Ag_2O	TFE	52
7	$[RuCl_2(p\text{-cymene})]_2$	Ag_2O	MeOH	trace
8	$[RuCl_2(p\text{-cymene})]_2$	Ag_2O	H_2O	n.d.
9	$[RuCl_2(p\text{-cymene})]_2$	Ag_2O	2-Methyltetrahydofuran	n.d.
10	$[RuCl_2(p\text{-cymene})]_2$	Ag_2O	1,4-dioxane	n.d.
11	$[RuCl_2(p\text{-cymene})]_2$	Ag_2O	$(CH_2Cl)_2$	trace
12	$[RuCl_2(p\text{-cymene})]_2$	Ag_2O	toluene	n.d.
13	$[RuCl_2(p\text{-cymene})]_2$	Ag_2O	DMF	n.d.
14	$[RuCl_2(p\text{-cymene})]_2$/ $AgSbF_6$ (20 mol %)	Ag_2O	HFIP	43
15	$RuCl_3 \cdot 3H_2O$	Ag_2O	HFIP	n.d.
16	---	Ag_2O	HFIP	n.d.
17	$[RuCl_2(p\text{-cymene})]_2$	---	HFIP	n.d.
18[c]	$[RuCl_2(p\text{-cymene})]_2$	Ag_2O	HFIP	43
19[d]	$[RuCl_2(p\text{-cymene})]_2$	Ag_2O	HFIP	61
20[e]	$[RuCl_2(p\text{-cymene})]_2$	Ag_2O	HFIP	57
21[f]	$[RuCl_2(p\text{-cymene})]_2$	Ag_2O	HFIP	48

[a]Reaction conditions: **1a** (0.1 mmol), **2a** (0.2 mmol), $[RuCl_2(p\text{-cymene})]_2$ (5 mol %), oxidant (3 equiv), solvent (1.0 mL), 110 °C, 6 h, Ar. [b]Isolated yield. [c]Using 1 equiv Ag_2O. [d]Using 2 equiv Ag_2O. [e]Under O_2 atmosphere. [f]At 60 °C. n.d. = not detected.

oxidant failed to produce desired product (entries 16-17). Reducing the amount of oxidant or reaction temperature showed reduction in the yield (entries 18-20). Moreover, reaction under O_2 atmosphere resulted in a diminished product yield (entry 21).

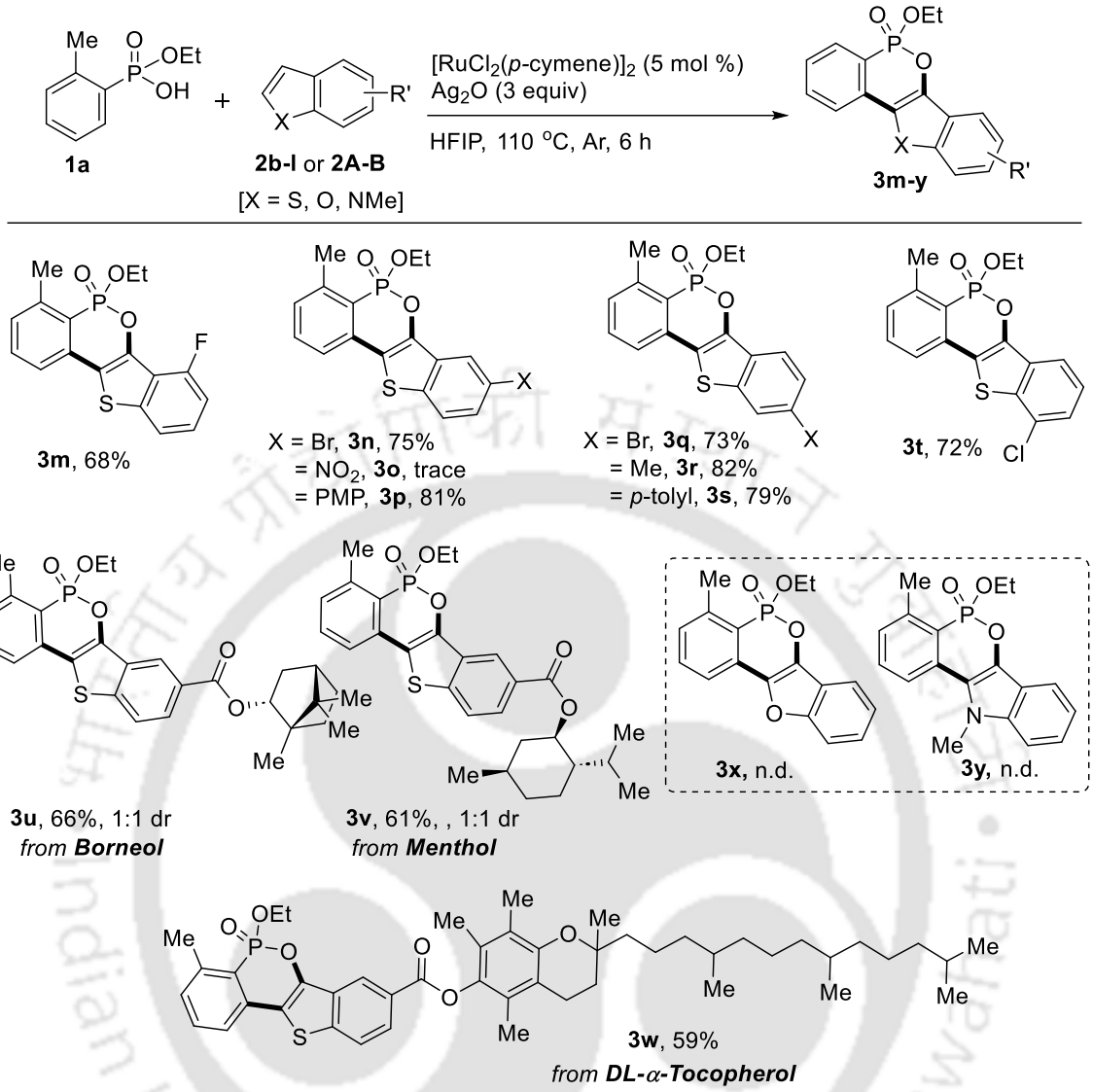
Table 2. Scope of Aryl Phosphonic Acid Monoesters[a,b]



[a]Reaction conditions: **1b-l** (0.1 mmol), **2a** (0.2 mmol), $[RuCl_2(p\text{-cymene})]_2$ (5 mol %), Ag_2O (0.3 mmol), HFIP (1.0 mL), 110 °C, 6 h, Ar. [b]Isolated yield.

With the optimal reaction conditions, the scope of the procedure with diversely substituted aryl phosphonic acid monoesters **1b-l** was evaluated using **2a** as a standard substrate. Phenyl phosphonic acid monoester **1b** smoothly participated in the reaction furnishing **3b** in 72% yield. Substrates equipped with 2-bromo **1c**, 2-fluoro **1d**, 3-methoxy **1e** and 4-methyl **1f** in the aryl ring reacted to deliver **3c-f** in 59-82% yields. Further, disubstituted phosphonic acid monoester **1g** and polycyclic naphthalen-2-ylphosphonate **1h** were competent to the reaction giving **3g** and **3h** in 81% and 73% yields, respectively. Substrate with butyloxy substitution on phosphorous**1i** reacted seamlessly to afford **3j** in 84% yield. Notably, diphenylphosphinic acid **1j** was suitable

Table 3. Scope of Benzothiophenes[a,b]

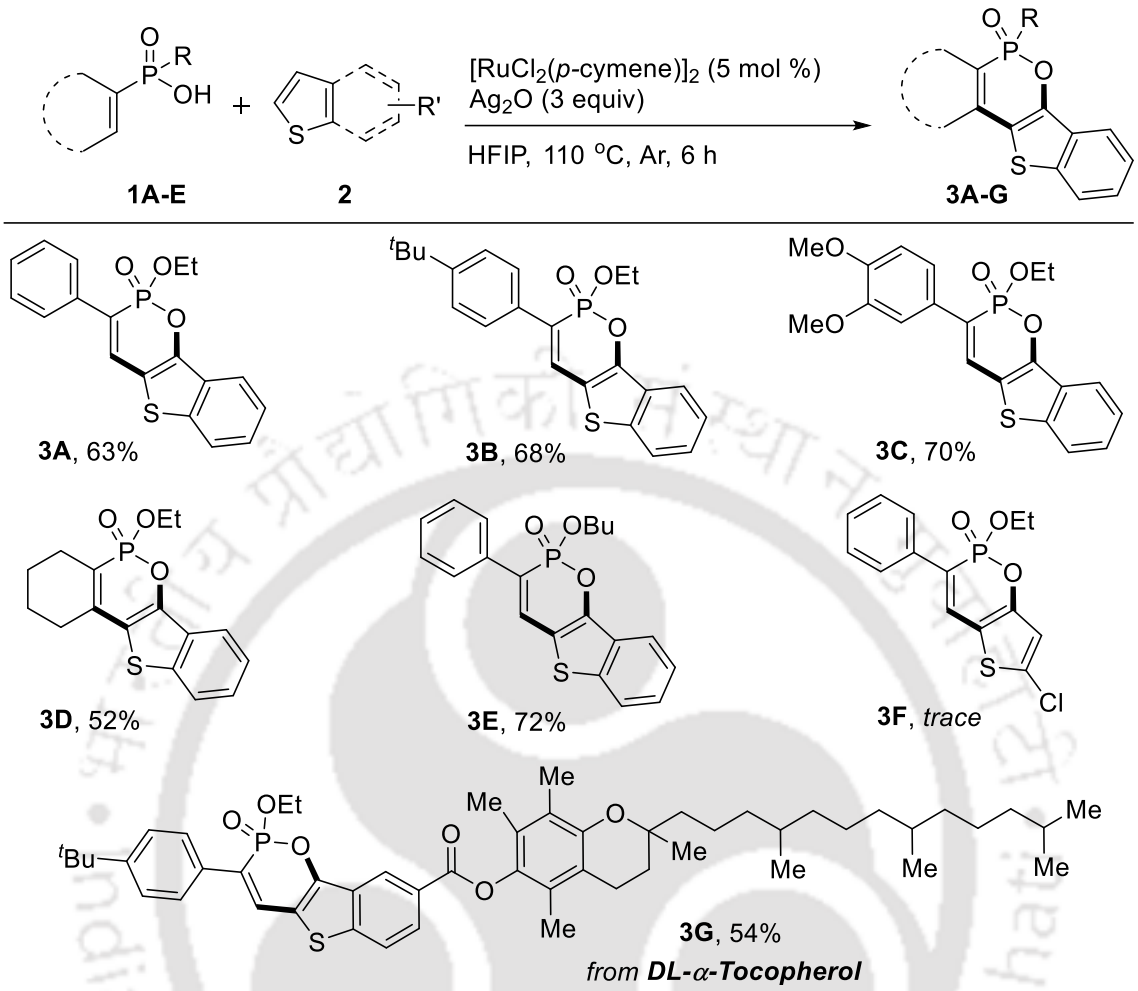


[a]Reaction conditions: **1a** (0.1 mmol), **2b-l** or **2A-B** (0.2 mmol), $[RuCl_2(p\text{-cymene})]_2$ (5 mol %), Ag_2O (0.3 mmol), HFIP (1.0 mL), 110 °C, 6 h, Ar. [b]Isolated yield.

substrate to provide **3j** in 64% yield. However, the reaction was sensitive towards heteroaryl compound thiophen-3-ylphosphonate **1k**, giving trace amount of **3k**. Interestingly, naturally occurring sesamol derived phosphomonoester **1l** is compatible, leading to annulated product **3l** in 79% yield.

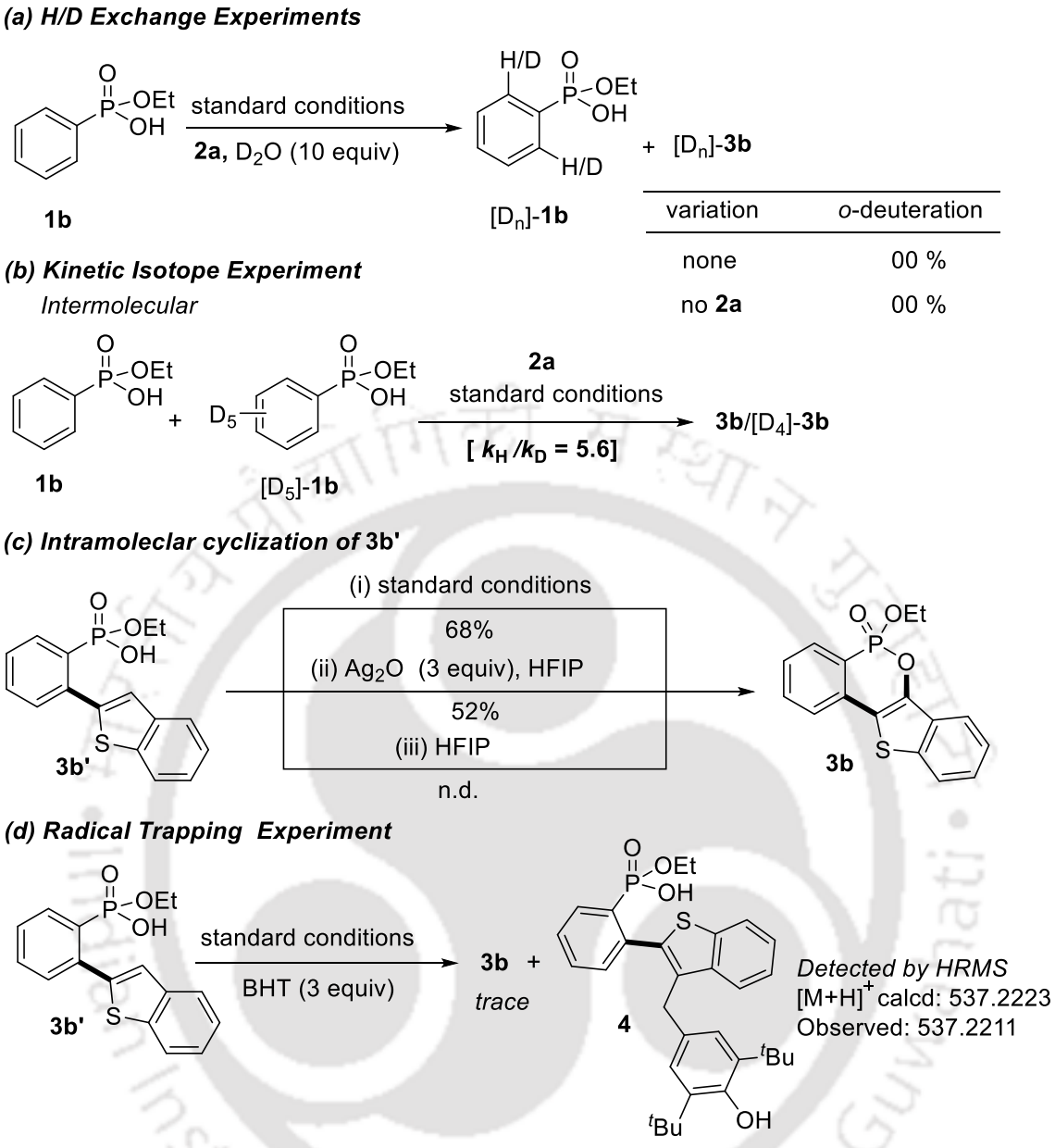
The scope of the reaction was then surveyed with substituted (benzo)thiophenes **2b-l** using **1a** as the standard substrate (Table 3). Benzothiophenes bearing 4-fluoro **2b** and 5-bromo **2c** substituents worked well to provide the desired products **3m-n** in 68-75% yields. The structure

Table 4. Scope of Vinyl Phosphonic Acid Monoesters[a,b]



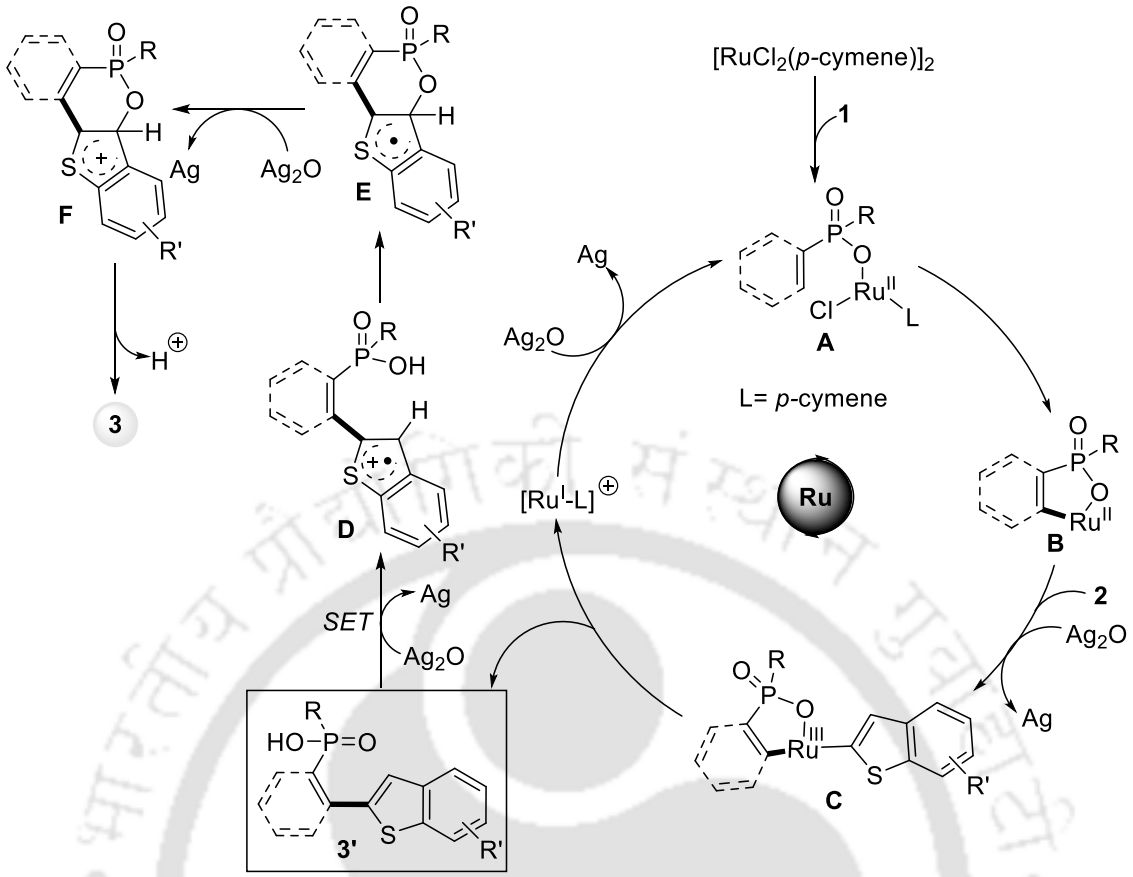
[a]Reaction conditions: **1A-E** (0.1 mmol), **2a** or **2l** or **2m** (0.2 mmol), $[RuCl_2(p\text{-cymene})]_2$ (5 mol %), Ag_2O (0.3 mmol), HFIP (1.0 mL), 110 °C, 6 h, Ar. [b]Isolated yield.

of **3m** was determined using single crystal X-ray analysis. However, electron-withdrawing nitro substituted **2d** yielded a trace amount of **3o**. Delightfully, 5-*p*-methoxyphenyl (PMP) **2e**, 6-bromo **2f**, 6-methyl **2g** and 6-*p*-tolyl **2h** and 7-chloro **2i** substituted benzothiophenes successfully transformed to annulated **3p-t** in 72-82% yields. Intriguingly, naturally occurring alcohols, (-)-borneol **2j** and L-menthol **2k** bound benzothiophenes were competent, affording the desired products **3u-v** in 61-66% yields and 1:1 dr, while DL-α-Tocopherol tethered benzothiophene **2l** afforded **3w** in 59% yield. These results demonstrate the potentiality of the method for late-stage natural product modifications. However, 2,3-benzofuran **2A** and 1-methyl-1*H*-indole **2B** failed to provide any product.



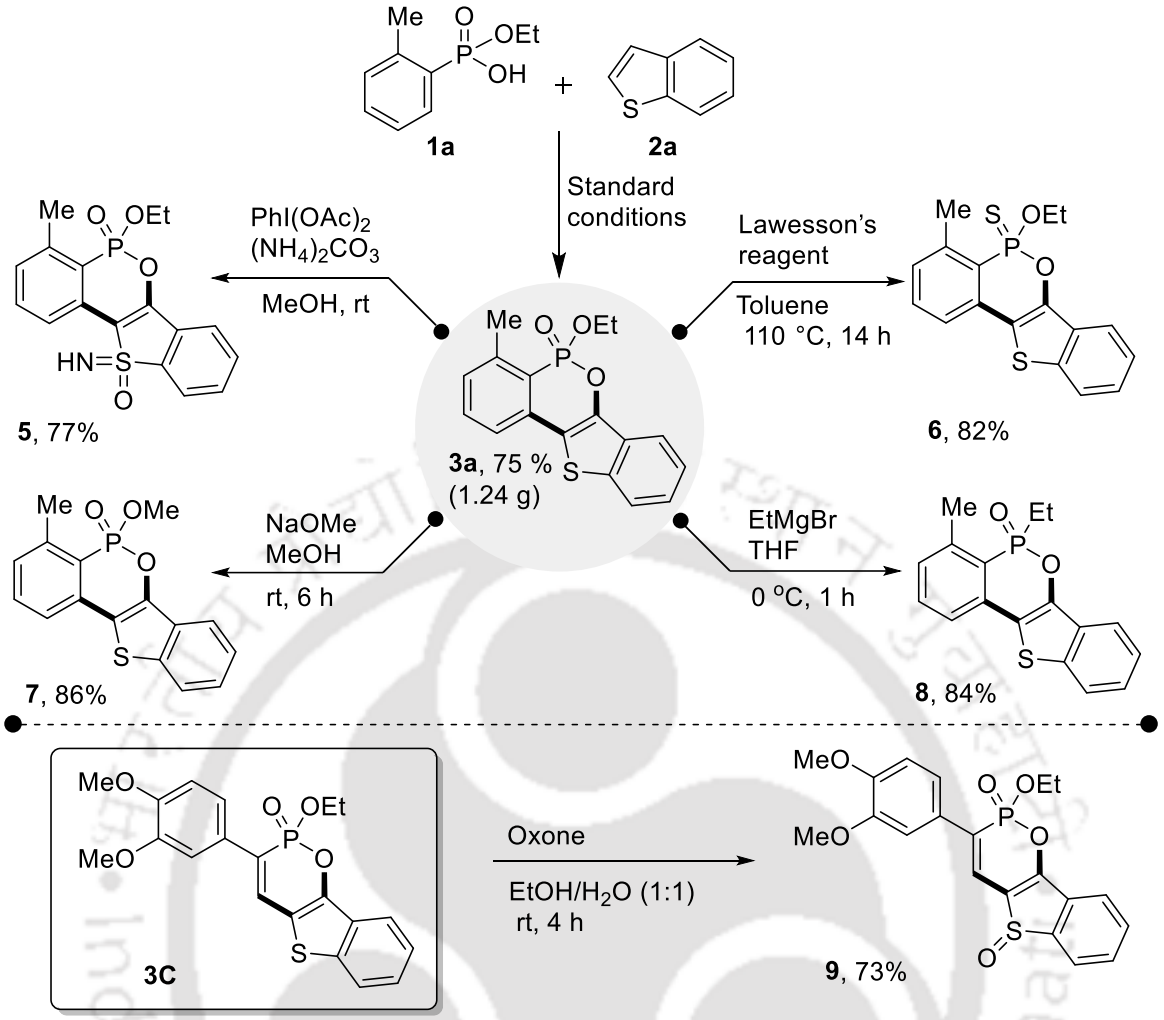
Scheme 10. Preliminary Mechanistic Investigations

To broaden diversity, the reaction was further explored with vinyl phosphonic acid monoesters **1A-E**. Ethyl hydrogen (1-phenylvinyl)phosphonate **1A** successfully reacted with **2a** to give **3A** in 63% yield. Pertinently, 4-^{t}butyl **1B** and 3,4-dimethoxy **1C** substituted derivatives participated well to furnish the annulated products **3B-C** in 68-70% yields. Amusingly, cyclohexene derivative **1D** was compatible to provide **3D** in 52% yield, whereas butyl ester variant **1E** conveyed **3E** in 72% yield. In contrast, the reaction of **1A** with 2-chlorothiophene **2m** gave a trace amount of **3F**. Delightedly, DL-α-Tocopherol tethered benzothiophene **2l** reacted with **1B** to furnish **3G** in 54% yield.



Scheme 11. Proposed Catalytic Cycle

In order to probe the reaction mechanism, H/D scrambling experiments was performed using D_2O as co-solvent (Scheme 10a). Both in presence or absence of **2a** no *o*-deuteration was observed, indicating the C-H activation step might be irreversible. The intermolecular kinetic isotope experiment was performed using **1b** and [D_5]-**1b** with **2a**, giving k_H/k_D 5.6. This result suggests the *o*-C-H bond cleavage might be involved in the rate-determining step (Scheme 10b). The reaction of ethyl hydrogen (2-(benzo[*b*]thiophen-2-yl)phenyl)phosphonate **3b′** was conducted and the annulated **3b** was observed in 68% yield. Subsequently, in the absence of catalyst **3b′** furnished **3b** in 52% yield, whereas the reaction ceased in presence of HFIP only. These findings depict that the reaction involves an initial oxidative C-H/C-H cross-coupling, followed by silver-mediated cyclization, leading to the annulated product. Further, radical trapping experiment was performed with **3b′** using 2,6-di-*tert*-butyl-4-methylphenol (BHT) as a radical scavenger (Scheme 10d). The product **3b** formation was impeded, instead a BHT adduct **4** was detected in HRMS analysis, which implies cyclization step may involve radical pathway. On the basis of literature reports[17] and experimental observations, a plausible mechanism is proposed (Scheme 11). First, the coordination of phosphonic acid monoester **1**



Scheme 12. Scale-up and Post-Synthetic Transformations

with Ru(II)-catalyst forms Ru(II) phosphonate **A**, which may trigger *ortho*-C-H bond activation leading to a five membered ruthenacycle **B**. Afterward, **B** reacts with benzothiophene **2** to produce intermediate **C**. The latter may undergo reductive elimination to afford C-H/C-H cross-coupled product **3′** and Ru(I) species, which can be oxidized by Ag_2O to complete the catalytic cycle. The intermediate **3′** underwent single electron oxidation by Ag_2O to deliver a cation-radical intermediate **D**, which further undergoes intramolecular cyclization to give the intermediate **E**. A subsequent SET and deprotonation may lead to aromatization, providing the annulated product **3**.

To showcase the synthetic utilities, scale-up synthesis of **3a** was performed using 5 mmol of **1a** with **2a** as the representative substrates (Scheme 12). The reaction afforded **3a** in 75% (1.24 g) yield. *N*H-Sulfoximidation of **3a** proceeded smoothly using PIDA to afford **5** in 77% yield. The reaction of **3a** with Lawesson's reagent readily accomplished to furnish phosphine sulfide **6** in 82% yield. Further, nucleophilic substitution of **3a** with NaOMe and EtMgBr produced **7**

and **8** in 86% and 84% yields, respectively. Oxidation of product **3C** with oxone provided **9** in 73% yield.

In summary, the Ru(II)-catalyzed regioselective one-pot heteroarylation/annulation reaction between aryl/vinyl phosphonic acid monoesters and benzothiophenes has been disclosed for the assembly of benzothiophene-fused phosphaisocoumarin frameworks. The important practical features of the protocol include cascade C-H/C-H cross-coupling/annulation strategy, functional group tolerance, broad substrate scope and late-stage functionalization of bioactive compounds.

4.4 Experimental Section

General Information. $[RuCl_2(p\text{-cymene})]_2$ (>97%), $RuCl_3 \bullet 3H_2O$ (>98%), $Cu(OAc)_2 \cdot H_2O$ (>98%), AgOAc (≥99.99%), Ag_2CO_3 (98%), Ag_2O (99%), $Cu(OAc)_2$ (98%), $K_2S_2O_8$ (≥99.0%), $AgSbF_6$ (>98%), 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP), 2,2,2-trifluoroethanol (TFE), 2-methyltetrahydrofuran, diphenylphosphinic acid (**1j**), benzothiophenes (**2a-d**, **2f-g** and **2i**), 2,3-benzofuran (**2A**) and 1-methyl-1*H*-indole (**2B**) of Aldrich and TCI Chemicals were used as received. Methanol, 1,4-dioxane, 1,2-dichloroethane, toluene and dimethylformamide (DMF) 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 (60-120 mesh). Bruker Avance III 400, 500 and 600 MHz NMR spectrometers were used to record spectra using $CDCl_3$ as the solvent and tetramethylsilane (Me_4Si) 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, bs = broad singlet, d = doublet, t = triplet, 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 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 SHELXL-2018/3 (Göttingen, Germany). Aryl/vinyl phosphonic acid monoesters[18] and substituted benzothiophenes[19] **2e** and **2h**, **2j-l** were prepared according to reported procedures.

General Procedure for Ru(II)-Catalyzed Annulation of Aryl/Vinyl Phosphonic Acid Monoesters. Aryl/vinyl phosphonic acid monoester **1** (0.1 mmol), benzothiophene **2** (0.2 mmol), $[RuCl_2(p\text{-cymene})]_2$ (3 mg, 5 mol %, 0.005 mmol) and Ag_2O (69.5 mg, 0.3 mmol, 3

equiv) were stirred in HFIP (1.0 ml) at 110 ^{o}C in a preheated oil bath for 6 h under Ar atmosphere. The progress of the reaction was monitored by TLC utilizing ethyl acetate and hexane as an eluent. Upon completion (monitored by TLC), the reaction mixture was cooled to room temperature, diluted with CH_2Cl_2 (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 *n*-hexane and ethyl acetate as an eluent to afford **3**.

Scale-up Synthesis of 3a. Ethyl hydrogen *o*-tolylphosphonate **1a** (5 mmol, 1.0 g), benzo[*b*]thiophene **2a** (10 mmol, 1.34 g), $[RuCl_2(p\text{-cymene})]_2$ (5 mol %, 0.25 mmol, 153 mg) and Ag_2O (3 equiv, 3.4 g) were stirred in HFIP (10.0 ml) at 110 ^{o}C in a preheated oil bath for 6 h under Ar atmosphere. The reaction mixture was cooled to room temperature and diluted with CH_2Cl_2 (20 mL) and passed through a celite pad. Evaporation of the solvent gave a residue that was purified on silica gel column chromatography using *n*-hexane and ethyl acetate as an eluent (70/30, v/v) to afford **3a** in 75% (1.24 g) yield.

Procedures for the Post-Synthetic Modifications

Synthesis of 5. Compound **3a** (33.0 mg, 0.1 mmol, 1 equiv), $PhI(OAc)_2$ (161.0 mg, 0.50 mmol, 5.0 equiv) and $(NH_4)_2CO_3$ (28.8 mg, 0.30 mmol, 3.0 equiv) were stirred in methanol (1 mL) at room temperature for overnight. After completion (monitored by TLC), the reaction mixture was diluted with ethyl acetate (10 mL) and passed through a short celite pad. Evaporation of the solvent gave a residue that was purified on silica gel column chromatography using ethyl acetate/*n*-hexane as the eluent (40/60, v/v) to provide **5** in 77% (27.8 mg) yield.

Synthesis of 6. Compound **3a** (33.0 mg, 0.1 mmol, 1 equiv) and Lawesson's reagent (81.0 mg, 0.2 mmol ,0.2 equiv) were stirred in toluene (1 mL) at 110 °C for 14 h under N_2 atmosphere. After completion (monitored by TLC), the reaction mixture diluted with ethyl acetate (10 mL) and passed through a short celite pad. Evaporation of solvent gave a residue that was purified on silica gel column chromatography using ethyl acetate/*n*-hexane as the eluent (10/90, v/v) to provide **6** in 82% (28.4 mg) yield.

Synthesis of 7. Compound **3a** (33.0 mg, 0.1 mmol, 1 equiv) and NaOMe (5 equiv, 27 mg) were stirred in MeOH (1 mL) at room temperature for 6 h. After completion (monitored by TLC), the reaction mixture was extracted with ethyl acetate (10 mL x 3) and washed with brine (2 x 10 mL) and water (1 x 10 mL). Drying (Na_2SO_4) and evaporation of the solvent gave a residue

that was purified by silica gel column chromatography using ethyl acetate/*n*-hexane (30/70, v/v) as an eluent to provide **7** in 86% (27.2 mg) yield.

Synthesis of 8. To a stirred solution of compound **3a** (33.0 mg, 0.1 mmol, 1 equiv) in THF (1 mL), EtMgBr (3 M in Et_2O, 50 μL, 0.15 mmol, 1.5 equiv) was added dropwise at 0 °C and continued stirring at the same temperature for additional 1 h. After completion (monitored by TLC), saturated aqueous solution of NH_4Cl (10 mL) was added to the reaction mixture and extracted with ethyl acetate (10 mL x 3), washed with brine (2 x 10 mL) and water (1 x 10 mL). Drying (Na_2SO_4) and evaporation of the solvent gave a residue that was purified by silica gel column chromatography using ethyl acetate/*n*-hexane (70/30, v/v) as an eluent to provide **8** in 84% (26.4 mg) yield.

Synthesis of 9. Compound **3C** (40.0 mg, 0.1 mmol, 1 equiv) and oxone (46.1 mg, 1.5 equiv, 0.15 mmol) were stirred in EtOH/H_2O (1 mL, 1:1, v/v) at room temperature for 4 h. After completion (monitored by TLC), the reaction mixture was filtered and the residue was washed with CH_2Cl_2/acetone (10 mL, 1:1, v/v), followed by CH_2Cl_2 (10 mL). Evaporation of the filtrate gave a residue that was purified by silica gel column chromatography using ethyl acetate/*n*-hexane as the eluent (70/30, v/v) to provide **9** in 73% (30.5 mg) yield.

Mechanistic Investigations

H/D Exchange Experiment of 1b with D_2O in Absence of 2a. To a stirred solution of ethyl hydrogen phenylphosphonate **1b** (18.6 mg, 0.1 mmol), $[RuCl_2(p\text{-cymene})]_2$ (3 mg, 5 mol %, 0.005 mmol) and Ag_2O (69.5 mg, 3 equiv, 0.3 mmol) in HFIP (1.0 ml), D_2O (1.0 mmol, 0.2 mL) was added and stirred at 110 ^oC in a preheated oil bath for 6 h under Ar atmosphere. The resulting mixture was cooled to room temperature, diluted with CH_2Cl_2 (10 mL) and passed through a short pad of celite. The purification was performed as described in the general procedure to give $[D_n]$-**1b**. No deuterium incorporation was observed at the *ortho*-position of aryl ring based on 600 MHz ^1H NMR spectrum.

H/D Exchange Experiment of 1b with D_2O in Presence of 2a. To a stirred solution of ethyl hydrogen phenylphosphonate **1b** (18.6 mg, 0.10 mmol), benzo[*b*]thiophene **2a** (0.20 mmol, 26.8 mg), $[RuCl_2(p\text{-cymene})]_2$ (3 mg, 5 mol %, 0.005 mmol) and Ag_2O (69.5 mg, 3 equiv, 0.3 mmol) in HFIP (1.0 ml), D_2O (1.0 mmol, 0.2 mL) was added and stirred at 110 ^oC in a preheated oil bath for 6 h under Ar atmosphere. The resulting mixture was cooled to room temperature, diluted with CH_2Cl_2 (10 mL) and passed through a short pad of celite. The purification was

performed as described in the general procedure to give [D_n]-**1b** and [D_n]-**3b**. The starting **1b** was analyzed using 600 MHz ^{1}H NMR and no deuterium incorporation was observed at the *ortho*-position of aryl ring.

Preparation of Ethyl hydrogen (phenyl-*d*$_5$)phosphonate [D_5]-**1b.**

Step-I:[20] To a stirred solution of sulfuric acid (0.6 mL) in water (2 mL), benzene-d_6 (0.3 mL, 3 mmol, 1 equiv) was added dropwise at 0 °C. Then, $NaBrO_3$ (497 mg, 3.3 mmol, 1.1 equiv) was added to the reaction mixture at the same temperature in two portions with an interval of 1 h and allowed to stir for 10 h at room temperature. After completion, ice water was added into the mixture and extracted with diethyl ether (3 x 20 mL). The combined organic layer was washed with brine (1 x 20 mL) and water (1 x 10 mL). Drying (Na_2SO_4) and evaporation of the solvent gave a residue that was used for the next step without further purification (75% yield, 364 mg).

Step-II:[20] A solution of 1-bromobenzene-d_5 (0.2 mL, 2.0 mmol, 1 equiv) in THF (10 mL) under N_2 atmosphere was cooled to -78 °C. Thereafter, *n*-BuLi (1 mL, 2 M in cyclohexane, 2.0 mmol) was added dropwise over 30 min. The mixture was then stirred at the same temperature and after 2 h triisopropyl borate (0.7 mL, 3.0 mmol, 1.5 equiv) dissolved in 1 mL of THF was added drop wise to the mixture. The solution was allowed to warm up to room temperature and stirred for 12 h. After completion (monitored by TLC), the reaction mixture was quenched with dilute HCl (20%, 4 mL) and stirred for 3 h at room temperature. The solution was extracted with diethyl ether (3 x 20 mL) and the combined organic layer was washed with brine (1 x 20 mL) and water (1 x 10 mL). Drying (Na_2SO_4) and evaporation of the solvent gave a residue, which was treated with 10 mL *n*-hexane. The colorless solid (phenyl-d_5)boronic acid precipitated, which was used for the next step without further purification (78% yield, 198 mg).

Step-III: A mixture of (phenyl-d_5)boronic acid (127 mg, 1.0 mmol, 1 equiv), diethyl phosphite (64 μL, 0.5 mmol, 0.5 equiv), 1,10-phenanthroline (9.0 mg, 0.05 mmol, 5 mol %) and Cu_2O (3.6 mg, 0.025 mmol, 2.5 mol %) was stirred in CH_3CN (10 mL) for 24 h under air. Upon completion, the reaction mixture was extracted with ethyl acetate (3 x 20 mL). The combined organic layer was washed with brine (2 x 10 mL) and water (1 x 10 mL). Drying (Na_2SO_4) 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 (70/30, v/v) to afford diethyl (phenyl-d_5)phosphonate in 79% (173 mg) yield.

***Step-IV*:** A mixture of diethyl(phenyl-d_5)phosphonate (109.5 mg, 0.50 mmol, 1 equiv) and NaOH (40 mg, 1.0 mmol, 2 equiv) was stirred in water (10 mL) at 80 °C in a preheated oil bath

for 12 h. Upon completion, (as monitored by TLC), the reaction mixture was allowed to cool to room temperature and neutralized with cooled conc. HCl (2 mL). The reaction mixture was then extracted with ethyl acetate (3 x 10 mL). The combined organic layer was washed with brine (2 x 10 mL) and water (1 x 10 mL). Drying (Na_2SO_4) and evaporation of the solvent gave ethyl hydrogen (phenyl-d_5)phosphonate [D_5]-**1b** in 82% (78.3 mg) yield.

Kinetic Isotope Effect Experiment. A mixture of ethyl hydrogen phenylphosphonate **1b** (0.1 mmol, 18.6 mg) and ethyl hydrogen (phenyl-d_5)phosphonate [D_5]-**1b** (0.1 mmol, 19.1 mg) was reacted with benzo[*b*]thiophene **2a** (0.40 mmol, 53.6 mg) for 0.5 h under standard reaction conditions. The resulting mixture was cooled to room temperature, diluted with CH_2Cl_2 (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 **3b** and [D_4]-**3b**. The intermolecular k_H/k_D was found to be 5.6, based on 600 MHz ^{1}H NMR of the product **3b** and [D_4]-**3b**.

Preparation of the Intermediate 3b′

Step-I: [19b] A mixture of diethyl (2-bromophenyl)phosphonate (586 mg, 2 mmol, 1 equiv), Na_2CO_3 (742 mg, 7.0 mmol, 3.5 equiv), $PdCl_2(PPh_3)_2$ (35 mg, 2.5 mol %) and benzo[*b*]thiophen-2-ylboronic acid (463 mg, 2.6 mmol, 1.3 equiv) was stirred in 1,4-dioxane : H_2O (1:1, v/v, 10 mL) under Ar atmosphere for 2 h at 80 °C. After completion, the reaction mixture was cooled to room temperature and added aqueous NH_4Cl (15 mL). The mixture was extracted with ethyl acetate (20 mL x 3) and washed with brine (2 x 20 mL) and water (1 x 20 mL). Drying (Na_2SO_4) and evaporation of the solvent gave a residue that was purified by silica gel column chromatography using ethyl acetate/*n*-hexane as an eluent (70/30, v/v) to provide diethyl (2-(benzo[*b*]thiophen-2-yl)phenyl)phosphonate in 73% (506 mg) yield.

Step-II: A mixture of diethyl (2-(benzo[*b*]thiophen-2-yl)phenyl)phosphonate (692 mg, 2.0 mmol, 1 equiv) and NaOH (80 mg, 4.0 mmol, 2 equiv) was stirred in water (10 mL) at 80 °C in a preheated oil bath for an appropriate time 12 h. Upon completion, (as monitored by TLC), the reaction mixture was allowed to cool to room temperature and neutralized with conc. HCl (5 mL). The reaction mixture was then extracted with ethyl acetate (3 x 20 mL). The combined organic layer was washed with brine (2 x 10 mL) and water (1 x 10 mL). Drying (Na_2SO_4) and evaporation of the solvent gave ethyl hydrogen (2-(benzo[*b*]thiophen-2-yl)phenyl)phosphornate **3b′** in 84% (534 mg) yield.

Intramolecular Lactonization of Ethyl Hydrogen (2-(Benzo[*b*]thiophen-2-yl)phenyl)-phosphonate 3b′.

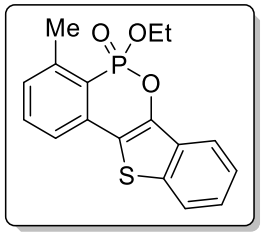
i. Ethyl hydrogen (2-(benzo[*b*]thiophen-2-yl)phenyl)phosphonate **3b′** (31.8 mg, 0.1 mmol), $[RuCl_2(p\text{-cymene})]_2$ (3 mg, 5 mol %, 0.005 mmol) and Ag_2O (69.5 mg, 3 equiv, 0.3 mmol) were stirred in HFIP (1.0 ml) at 110 ^oC in a preheated oil bath for 6 h under Ar atmosphere. The resulting mixture was cooled to room temperature, diluted with CH_2Cl_2 (10 mL) and passed through a short pad of celite. The purification was performed as described in the general procedure to give **3b** in 68% (21.6 mg) yield.

ii. Ethyl hydrogen (2-(benzo[*b*]thiophen-2-yl)phenyl)phosphonate **3b′** (31.8 mg, 0.1 mmol) and Ag_2O (69.5 mg, 3 equiv, 0.3 mmol) were stirred in HFIP (1.0 ml) at 110 ^oC in a preheated oil bath for 6 h under Ar atmosphere. The resulting mixture was cooled to room temperature, diluted with CH_2Cl_2 (10 mL) and passed through a short pad of celite. The purification was performed as described in the general procedure to give **3b** in 52% (16.5 mg) yield.

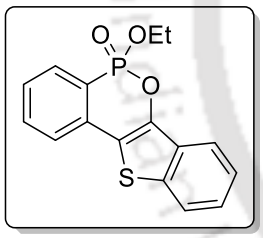
iii. Ethyl hydrogen (2-(benzo[*b*]thiophen-2-yl)phenyl)phosphonate **3b′** (31.8 mg, 0.1 mmol) in HFIP (1.0 ml) was stirred at 110 ^oC in a preheated oil bath for 6 h under Ar atmosphere. The resulting mixture was cooled to room temperature, diluted with CH_2Cl_2 (10 mL) and passed through a short pad of celite. No product was detected except for the recovery of **3b′**.

Radical Trapping Experiments. Ethyl hydrogen (2-(benzo[*b*]thiophen-2-yl)phenyl)-phosphornate **3b′** (31.8 mg, 0.1 mmol), $[RuCl_2(p\text{-cymene})]_2$ (3 mg, 5 mol %, 0.005 mmol), Ag_2O (69.5 mg, 3 equiv, 0.3 mmol) and BHT (0.3 mmol, 66 mg) were stirred in HFIP (1.0 ml) at 110 ^oC in a preheated oil bath for 6 h under Ar atmosphere. The resulting mixture was cooled to room temperature, diluted with CH_2Cl_2 (10 mL) and passed through a short pad of celite. The formation of BHT adduct **4** was confirmed by high-resolution mass spectrometry (HRMS) analysis of crude reaction mixture. HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{31}H_{38}O_4PS$: 537.2223, found 537.2211.

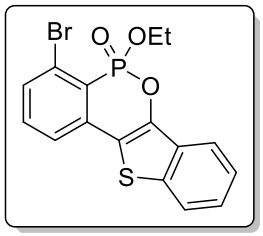
Characterization Data of the Products



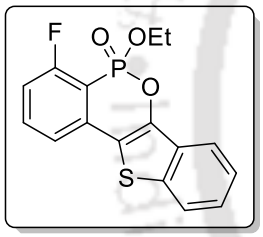
5-Ethoxy-4-methylbenzo[*c*]benzo[4,5]thieno[2,3-*e*][1,2]oxaphosphinine 5-oxide 3a. Analytical TLC on silica gel, 1:2 ethyl acetate/hexane R_f = 0.48; brown solid; mp 129-130 °C; yield 86% (28.4 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91-7.87 (m, 1H), 7.81-7.77 (m, 1H), 7.57-7.53 (m, 1H), 7.47-7.37 (m, 3H), 7.29-7.27 (m, 1H), 4.35-4.20 (m, 2H), 2.78 (d, *J* = 1.2 Hz, 3H), 1.36 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 142.7 (d, *J* = 9.6 Hz), 141.0 (d, *J* = 7.8 Hz), 135.7, 135.3 (d, *J* = 7.6 Hz), 133.4, 131.4 (d, *J* = 6.3 Hz), 130.8 (d, *J* = 14.8 Hz), 126.6, 125.2, 123.0, 122.1 (d, *J* = 10.8 Hz), 121.0, 119.0 (d, *J* = 178.2 Hz), 117.9 (d, *J* = 13.6 Hz), 63.2 (d, *J* = 6.9 Hz), 21.6 (d, *J* = 4.3 Hz), 16.5 (d, *J* = 6.1 Hz); ^{31}P NMR (243 MHz, $CDCl_3$) δ 12.48; FT-IR (KBr) 3060, 2972, 2924, 1715, 1590, 1458, 1370, 1263, 1153, 1029, 960, 853, 759 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{17}H_{16}O_3PS$: 331.0553, found 331.0556.



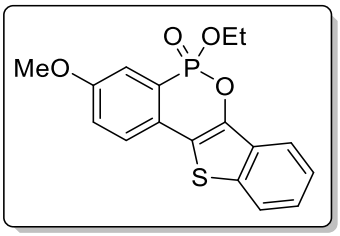
5-Ethoxybenzo[*c*]benzo[4,5]thieno[2,3-*e*][1,2]oxaphosphinine 5-oxide 3b. Analytical TLC on silica gel, 1:2 ethyl acetate/hexane R_f = 0.40; brown solid; mp 98-99 °C; yield 72% (22.8 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.99-7.96 (m, 1H), 7.90-7.87 (m, 1H), 7.80-7.79 (m, 1H), 7.68 (t, *J* = 7.8 Hz, 1H), 7.54 (t, *J* = 7.2 Hz, 1H), 7.50-7.47 (m, 1H), 7.46-7.42 (m, 2H), 4.28-4.23 (m, 2H), 1.30 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 141.5 (d, *J* = 7.9 Hz), 135.7, 134.7 (d, *J* = 7.0 Hz), 133.8 (d, *J* = 2.4 Hz), 131.5 (d, *J* = 6.3 Hz), 130.7 (d, *J* = 9.1 Hz), 128.3 (d, *J* = 15.4 Hz), 126.8, 125.3, 124.3 (d, *J* = 10.8 Hz), 123.1, 121.0, 120.5 (d, *J* = 182.5 Hz), 117.9 (d, *J* = 13.8 Hz), 63.4 (d, *J* = 6.6 Hz), 16.5 (d, *J* = 5.7 Hz); ^{31}P NMR (243 MHz, $CDCl_3$) δ 13.29; FT-IR (KBr) 3427, 2922, 2854, 1728, 1591, 1467, 1371, 1266, 1159, 1093, 1025, 961, 854, 757 cm^{-1}; ^{31}P NMR (243 MHz, $CDCl_3$) δ 13.29; HRMS (ESI) *m/z* $[M+Na]^+$ calcd for $C_{16}H_{13}NaO_3PS$: 339.0216, found 339.0218.



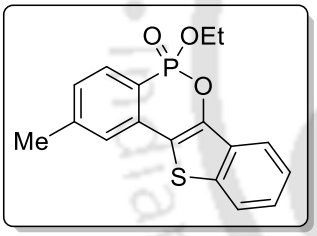
4-Bromo-5-ethoxybenzo[*c*]benzo[4,5]thieno[2,3-*e*][1,2]oxaphosphinine 5-oxide 3c. Analytical TLC on silica gel, 1:2 ethyl acetate/hexane R_f = 0.47; brown solid; mp 135-136 °C yield 63% (24.9 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.90-7.87 (m, 1H), 7.79-7.76 (m, 1H), 7.65-7.62 (m, 1H), 7.49-7.42 (m, 4H), 4.47-4.38 (m, 2H), 1.44 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 141.6 (d, *J* = 7.9 Hz), 137.3 (d, *J* = 6.1 Hz), 135.8, 134.2 (d, *J* = 1.8 Hz), 133.3 (d, *J* = 11.4 Hz), 131.2 (d, *J* = 6.6 Hz), 127.2, 125.7 (d, *J* = 3.3 Hz), 125.3, 123.4 (d, *J* = 10.0 Hz), 123.0, 121.7 (d, *J* = 187.2 Hz), 121.4, 116.4 (d, *J* = 13.2 Hz), 64.7 (d, *J* = 7.0 Hz), 16.5 (d, *J* = 4.4 Hz); ^{31}P NMR (243 MHz, $CDCl_3$) δ 8.37; FT-IR (KBr) 3424, 2921, 2860, 1723, 1583, 1450, 1371, 1266, 1194, 1156, 1104, 1033, 968, 852, 760 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{16}H_{13}BrO_3PS$: 394. 9501, found 394. 9502.



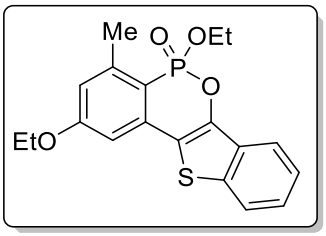
5-Ethoxy-4-fluorobenzo[*c*]benzo[4,5]thieno[2,3-*e*][1,2]oxaphosphinine 5-oxide 3d. Analytical TLC on silica gel, 1:2 ethyl acetate/hexane R_f = 0.46; brown solid; mp 123-124 °C; yield 59% (19.8 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.89-7.88 (m, 1H), 7.79-7.78 (m, 1H), 7.66-7.63 (m, 1H), 7.45-7.44 (m, 2H), 7.34-7.32 (m, 1H), 7.16-7.12 (m, 1H), 4.45-4.40 (m, 2H), 1.42 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 164.5 (d, *J* = 252.0 Hz), 141.9 (d, *J* = 7.5 Hz), 136.4 (d, *J* = 3.9 Hz), 135.8, 135.6 (d, *J* = 9.6 Hz), 131.2 (d, *J* = 6.7 Hz), 127.2, 125.4, 123.0, 121.3, 120.1 (dd, *J* = 10.0 Hz, *J* = 3.0 Hz), 116.3 (dd, *J* = 13.9 Hz, *J* = 3.3 Hz), 115.2 (dd, *J* = 22.0 Hz, *J* = 7.9 Hz), 109.0 (d, *J* = 181.0 Hz), 64.6 (d, *J* = 6.4 Hz), 16.5 (d, *J* = 6.3 Hz); ^{31}P NMR (243 MHz, $CDCl_3$) δ 7.10; ^{19}F NMR (565 MHz, $CDCl_3$) δ -103.09; FT-IR (KBr) 3403, 2919, 2853, 1732, 1601, 1539, 1463, 1371, 1263, 1174, 1114, 1028, 967, 859, 794 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{16}H_{13}FO_3PS$: 335.0302, found 335.0299.



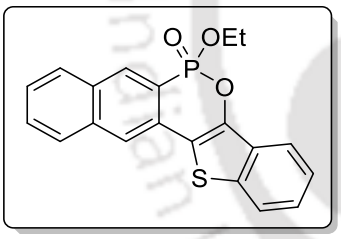
5-Ethoxy-3-methoxybenzo[*c*]benzo[4,5]thieno[2,3-*e*][1,2]oxaphosphinine 5-oxide 3e. Analytical TLC on silica gel, 1:2 ethyl acetate/hexane R_f = 0.39; brown solid; mp 142-143 °C; yield 82% (28.4 mg,); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.91-7.90 (m, 1H), 7.81- 7.80 (m, 1H), 7.64-7.61 (m, 1H), 7.49-7.45 (m, 1H), 7.44-7.40 (m, 2H), 7.25 (d, *J* = 8.4 Hz, 1H), 4.25-4.20 (m, 2H), 4.06 (s, 3H), 1.27 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 154.1 (d, *J* = 15.9 Hz), 141.0 (d, *J* = 7.9 Hz), 137.7, 130.2 (d, *J* = 6.0 Hz), 129.0 (d, *J* = 18.1 Hz), 126.1, 124.7, 124.3 (d, *J* = 7.6 Hz), 122.7 (d, *J* = 8.2 Hz), 122.4, 121.5 (d, *J* = 180.7 Hz), 120.5, 115.7 (d, *J* = 2.8 Hz), 114.4 (d, *J* = 14.2 Hz), 63.3 (d, *J* = 6.6 Hz), 56.1, 16.5 (d, *J* = 6.0 Hz); ^{31}P NMR (243 MHz, $CDCl_3$) δ 13.14; FT-IR (KBr) 3463, 2924, 2854, 1727, 1600, 1490, 1371, 1270, 1083, 1028, 964, 853, 760 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{17}H_{16}O_4PS$: 347.0502, found 347.0495.



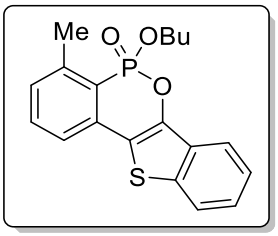
5-Ethoxy-2-methylbenzo[*c*]benzo[4,5]thieno[2,3-*e*][1,2]oxaphosphinine 5-oxide 3f. Analytical TLC on silica gel, 1:2 ethyl acetate/hexane R_f = 0.48; brown solid; mp 140-141 °C; yield 75% (24.8 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.88-7.84 (m, 2H), 7.80-7.79 (m, 1H), 7.46-7.41 (m, 2H), 7.34 (d, *J* = 5.4 Hz, 1H), 7.31-7.29 (s, 1H), 4.26-4.21 (m, 2H), 2.49 (s, 3H), 1.28 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 144.7 (d, *J* = 2.4 Hz), 141.6 (d, *J* = 7.6 Hz), 135.6, 134.7 (d, *J* = 7.3 Hz), 131.6 (d, *J* = 6.1 Hz), 130.7 (d, *J* = 9.6 Hz), 129.2 (d, *J* = 15.9 Hz), 126.7, 125.2, 124.8 (d, *J* = 11.2 Hz), 123.1, 121.0, 117.9 (d, *J* = 13.5 Hz), 117.4 (d, *J* = 185.1 Hz), 63.2 (d, *J* = 6.6 Hz), 22.0, 16.5 (d, *J* = 6.0 Hz); ^{31}P NMR (243 MHz, $CDCl_3$) δ 14.10; FT-IR (KBr) 3452, 2920, 2854, 1734, 1602, 1460, 1372, 1265, 1161, 1093, 1030, 964, 854, 756 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{17}H_{16}O_3PS$: 331.0553, found 331.0556.



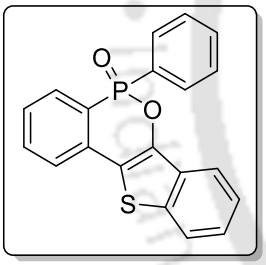
2,5-Diethoxy-4-methylbenzo[*c*]benzo[4,5]thieno[2,3-*e*][1,2]oxaphosphinine 5-oxide 3g. Analytical TLC on silica gel, 1:2 ethyl acetate/hexane R_f = 0.35; brown solid; mp 159-160 °C; yield 81% (30.3 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.87-7.85 (m, 1H), 7.77-7.75 (m, 1H), 7.44-7.40 (m, 2H), 6.829-6.822 (m, 1H), 6.76 (s, 1H), 4.27-4.16 (m, 2H), 4.14 (q, *J* = 7.2 Hz, 2H), 2.70 (s, 3H), 1.46 (t, *J* = 7.2 Hz, 3H), 1.32 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 162.6 (d, *J* = 2.8 Hz), 145.0 (d, *J* = 10.9 Hz), 141.3 (d, *J* = 7.8 Hz), 137.3 (d, *J* = 9.1 Hz), 135.6, 131.4 (d, *J* = 6.4 Hz), 126.7, 125.2, 123.0, 121.0, 117.7 (d, *J* = 13.3 Hz), 117.1 (d, *J* = 15.6 Hz), 110.5 (d, *J* = 186.1 Hz), 107.6 (d, *J* = 11.8 Hz), 63.9, 63.1 (d, *J* = 7.0 Hz), 21.8 (d, *J* = 4.2 Hz), 16.4 (d, *J* = 6.3 Hz), 14.7; ^{31}P NMR (243 MHz, $CDCl_3$) δ 14.09; FT-IR (KBr) 3452, 2924, 2857, 1731, 1596, 1454, 1377, 1263, 1197, 1100, 1030, 959, 850, 761 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{19}H_{20}O_4PS$: 375.0815, found 375.0817.



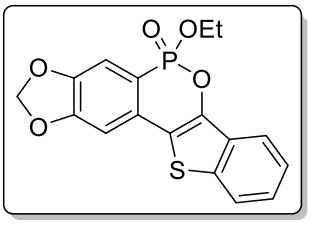
6-Ethoxybenzo[4,5]thieno[2,3-*e*]naphtho[2,3-*c*][1,2]oxaphosphinine 6-oxide 3h. Analytical TLC on silica gel, 1:2 ethyl acetate/hexane R_f = 0.46; brown solid; mp 209-210 °C; yield 73% (26.7 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.57 (d, *J* = 16.2 Hz, 1H), 7.97-7.93 (m, 3H), 7.89-7.88 (m, 1H), 7.82-7.81 (m, 1H), 7.65 (t, *J* = 7.8 Hz, 1H), 7.57 (t, *J* = 7.8 Hz, 1H), 7.47-7.43 (m, 2H), 4.30-4.25 (m, 2H), 1.29 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 141.3 (d, *J* = 7.6 Hz), 135.7, 135.6 (d, *J* = 2.1 Hz), 133.1 (d, *J* = 9.4 Hz), 132.1 (d, *J* = 16.8 Hz), 131.8 (d, *J* = 6.3 Hz), 129.8 (d, *J* = 7.3 Hz), 129.5, 129.2, 128.2, 127.3, 126.8, 125.3, 123.1, 122.8 (d, *J* = 10.5 Hz), 120.9 (d, *J* = 7.6 Hz), 119.1 (d, *J* = 183.0 Hz), 118.7 (d, *J* = 12.3 Hz), 63.4 (d, *J* = 6.6 Hz), 16.5 (d, *J* = 6.0 Hz); ^{31}P NMR (243 MHz, $CDCl_3$) δ 13.13; FT-IR (KBr) 3454, 2921, 2857, 1731, 1594, 1460, 1372, 1274, 1098, 1028, 958, 863, 757 cm^{-1}; HRMS (ESI) *m/z* $[M+Na]^+$ calcd for $C_{20}H_{15}NaO_3PS$: 389.0372, found 389.0374.



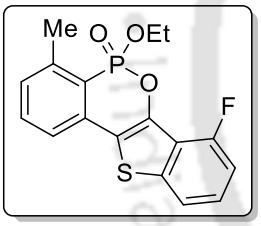
5-Butoxy-4-methylbenzo[*c*]benzo[4,5]thieno[2,3-*e*][1,2]oxaphosphinine 5-oxide 3i. Analytical TLC on silica gel, 1:2 ethyl acetate/hexane R_f = 0.80; yellow liquid; yield 84% (30.1 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.89 -7.87 (m, 1H), 7.79-7.78 (m, 1H), 7.54 (t, *J* = 7.8 Hz, 1H), 7.46-7.41 (m, 2H), 7.39-7.37 (m, 1H), 7.28-7.27 (m, 1H), 4.24-4.15 (m, 2H), 2.77 (s, 3H), 1.69-1.64 (m, 2H), 1.37-1.31 (m, 2H), 0.85 (t, *J* = 7.8 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 142.7 (d, *J* = 9.6 Hz), 141.0 (d, *J* = 7.9 Hz), 135.7, 135.3 (d, *J* = 7.6 Hz), 133.4, 131.4 (d, *J* = 6.3 Hz), 130.8 (d, *J* = 15.0 Hz), 126.6, 125.1, 123.0, 122.1 (d, *J* = 10.8 Hz), 121.0, 119.1 (d, *J* = 178.2 Hz), 117.9 (d, *J* = 13.8 Hz), 66.9 (d, *J* = 7.3 Hz), 32.5 (d, *J* = 6.1 Hz), 21.7 (d, *J* = 4.3 Hz), 18.7, 13.5; ^{31}P NMR (243 MHz, $CDCl_3$) δ 12.48; FT-IR (neat) 3449, 2957, 2871, 1728, 1589, 1460, 1369, 1268, 1065, 1022, 852, 756 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{19}H_{20}O_3PS$: 359.0866, found 359.0867.



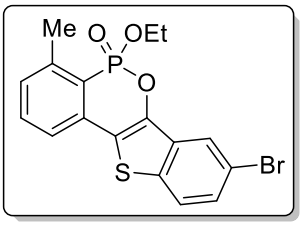
5-Phenylbenzo[*c*]benzo[4,5]thieno[2,3-*e*][1,2]oxaphosphinine 5-oxide 3j. Analytical TLC on silica gel, 1:2 ethyl acetate/hexane R_f = 0.41; brown solid; mp 245-246 °C; yield 64% (22.3 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.88-7.84 (m, 3H), 7.80-7.79 (m, 1H), 7.67-7.63 (m, 2H), 7.62-7.56 (m, 2H), 7.51-7.48 (m, 2H), 7.43-7.38 (m, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 141.3 (d, *J* = 9.0 Hz), 135.9, 133.8 (d, *J* = 5.5 Hz), 133.5, 133.3, 132.1 (d, *J* = 11.2 Hz), 131.8 (d, *J* = 5.5 Hz), 131.6 (d, *J* = 12.1 Hz), 130.7 (d, *J* = 144.1 Hz), 128.8 (d, *J* = 14.1 Hz), 128.3 (d, *J* = 14.2 Hz), 126.8, 125.2, 124.0 (d, *J* = 8.5 Hz), 123.2 (d, *J* = 127.6 Hz), 123.0, 121.4, 117.6 (d, *J* = 12.9 Hz); ^{31}P NMR (243 MHz, $CDCl_3$) δ 28.70; FT-IR (KBr) 3425, 2922, 2855, 1727, 1591, 1461, 1372, 1241, 1124, 1092, 979, 839, 754 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{20}H_{14}O_2PS$: 349.0447, found 349.0445.



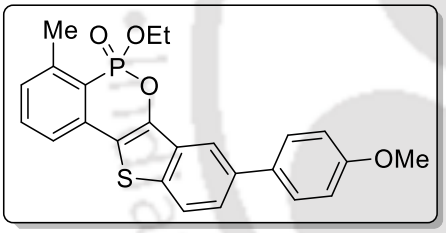
5-Ethoxy-[1,3]dioxolo[4',5':4,5]benzo[1,2-*c*]benzo[4,5]thieno-[2,3-*e*][1,2]oxaphosphinine 5-oxide 3l. Analytical TLC on silica gel, 1:2 ethyl acetate/hexane R_f = 0.36; colorless solid; mp 243-244 °C; yield 79% (28.4 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.90 (d, *J* = 7.2 Hz, 1H), 7.81 (d, *J* = 7.2 Hz, 1H), 7.58-7.54 (m, 1H), 7.47-7.42 (m, 2H), 6.95 (dd, *J* = 7.8 Hz, 3.0 Hz, 1H), 6.23 (d, *J* = 5.4 Hz, 2H), 4.25-4.20 (m, 2H), 1.27 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 151.9 (d, *J* = 3.3 Hz), 142.1 (d, *J* = 18.3 Hz), 141.8 (d, *J* = 7.8 Hz), 137.3, 130.5 (d, *J* = 6.0 Hz), 126.5, 126.4 (d, *J* = 10.3 Hz), 125.1, 122.9, 120.8, 117.2 (d, *J* = 9.4 Hz), 113.5 (d, *J* = 189.4 Hz), 113.2 (d, *J* = 13.3 Hz), 108.5 (d, *J* = 19.0 Hz), 102.6, 63.2 (d, *J* = 6.6 Hz), 16.5 (d, *J* = 5.8 Hz); ^{31}P NMR (243 MHz, $CDCl_3$) δ 13.09; FT-IR (KBr) 3490, 2983, 2917, 1764, 1624, 1453, 1372, 1260, 1120, 1028, 964, 909, 854, 758 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{17}H_{14}O_5PS$: 361.0295, found 361.0296.



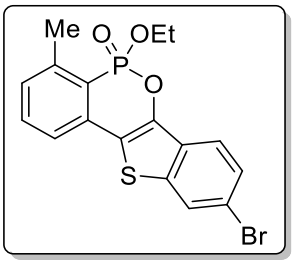
5-Ethoxy-7-fluoro-4-methylbenzo[*c*]benzo[4,5]thieno[2,3-*e*][1,2]oxa-phosphinine 5-oxide 3m. Analytical TLC on silica gel, 1:2 ethyl acetate/hexane R_f = 0.46; yellow solid; mp 160-161 °C; yield 68% (23.7 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.54-7.51 (m, 2H), 7.35-7.32 (m, 2H), 7.28-7.27 (m, 1H), 7.05 (t, *J* = 9.6, 1H), 4.34-4.29 (m, 2H), 2.75 (s, 3H), 1.38 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 158.2 (d, *J* = 255.3 Hz), 142.7 (d, *J* = 9.4 Hz), 139.2 (dd, *J* = 7.8 Hz, 3.0 Hz), 137.7 (d, *J* = 4.8 Hz), 134.7 (d, *J* = 7.6 Hz), 133.4 (d, *J* = 2.1 Hz), 131.1 (d, *J* = 15.0 Hz), 127.4 (d, *J* = 7.0 Hz), 122.3 (d, *J* = 10.8 Hz), 120.5 (dd, *J* = 16.0 Hz, 5.8 Hz), 119.0 (d, *J* = 179.1 Hz), 118.9 (d, *J* = 4.2 Hz), 118.2 (d, *J* = 14.2 Hz), 111.3 (d, *J* = 18.4 Hz), 63.4 (d, *J* = 7.0 Hz), 21.6 (d, *J* = 4.2 Hz), 16.4 (d, *J* = 5.8 Hz); ^{31}P NMR (243 MHz, $CDCl_3$) δ 11.59; ^{19}F NMR (565 MHz, $CDCl_3$) δ -119.16; FT-IR (KBr) 3474, 2921, 2857, 1731, 1587, 1459, 1359, 1262, 1026, 959, 848, 779 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{17}H_{15}FO_3PS$: 349.0459, found 349.0451.



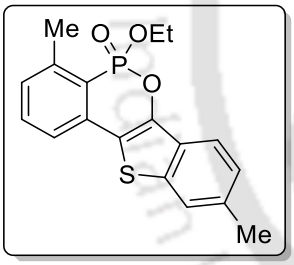
8-Bromo-5-ethoxy-4-methylbenzo[*c*]benzo[4,5]thieno[2,3-*e*][1,2]oxaphosphinine 5-oxide 3n. Analytical TLC on silica gel, 1:2 ethyl acetate/hexane R_f = 0.46; brown solid; mp 189-190 °C; yield 75% (30.7 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.99 (s, 1H), 7.62 (d, *J* = 8.4 Hz, 1H), 7.54-7.48 (m, 2H), 7.35-7.33 (m, 1H), 7.28-7.27 (m, 1H), 4.34-4.22 (m, 2H), 2.75 (s, 3H), 1.36 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 142.8 (d, *J* = 9.6 Hz), 139.8 (d, *J* = 7.8 Hz), 134.7 (d, *J* = 7.6 Hz), 134.1, 133.5 (d, *J* = 2.1 Hz), 132.9 (d, *J* = 6.1 Hz), 131.2 (d, *J* = 15.0 Hz), 129.7, 124.4, 123.6, 122.2 (d, *J* = 10.8 Hz), 119.5 (d, *J* = 13.8 Hz), 119.3, 119.2 (d, *J* = 178.2 Hz), 63.4 (d, *J* = 7.0 Hz), 21.6 (d, *J* = 4.5 Hz), 16.5 (d, *J* = 6.1 Hz); ^{31}P NMR (243 MHz, $CDCl_3$) δ 12.10; FT-IR (KBr) 3442, 2923, 2853, 1731, 1588, 1455, 1346, 1262, 1066, 1026, 961, 851, 788 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{17}H_{15}BrO_3PS$: 408.9658, found 408.9659.



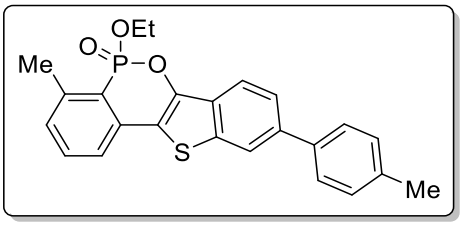
5-Ethoxy-8-(4-methoxyphenyl)-4-methylbenzo-[*c*]benzo[4,5]thieno[2,3-*e*][1,2]oxaphosphinine 5-oxide 3p. Analytical TLC on silica gel, 1:2 ethyl acetate/hexane R_f = 0.44; green liquid; yield 81% (35.3 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.03 (s, 1H), 7.80 (d, *J* = 8.4 Hz, 1H), 7.63-7.61 (m, 3H), 7.53 (t, *J* = 7.8 Hz, 1H), 7.37 (t, *J* = 7.2 Hz, 1H), 7.27 (s, 1H), 7.03 (d, *J* = 7.8 Hz, 2H), 4.33-4.20 (m, 2H), 3.87 (s, 3H), 2.77 (s, 3H), 1.34 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 159.5, 142.7 (d, *J* = 9.6 Hz), 141.0 (d, *J* = 7.9 Hz), 138.3, 135.3 (d, *J* = 7.6 Hz), 134.0, 133.5 (d, *J* = 1.5 Hz), 133.0, 132.0 (d, *J* = 6.3 Hz), 130.8 (d, *J* = 15.0 Hz), 128.4, 125.9, 123.3, 122.1 (d, *J* = 10.8 Hz), 118.9 (d, *J* = 178.2 Hz), 118.5, 118.4 (d, *J* = 13.6 Hz), 114.5, 63.3 (d, *J* = 7.0 Hz), 55.5, 21.6 (d, *J* = 4.3 Hz), 16.5 (d, *J* = 6.3 Hz); ^{31}P NMR (243 MHz, $CDCl_3$) δ 12.55; FT-IR (neat) 3402, 2919, 2852, 1731, 1597, 1515, 1452, 1362, 1252, 1179, 1028, 963, 851, 795 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{24}H_{22}O_4PS$: 437.0971, found 437.0969.



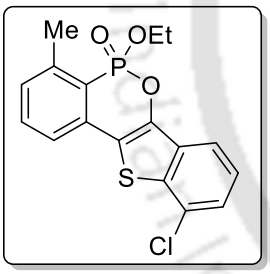
9-Bromo-5-ethoxy-4-methylbenzo[*c*]benzo[4,5]thieno[2,3-*e*][1,2]oxaphosphinine 5-oxide 3q. Analytical TLC on silica gel, 1:2 ethyl acetate/hexane R_f = 0.46; colorless solid; mp 155-156 °C; yield 73% (29.9 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.90 (s, 1H), 7.71 (d, *J* = 8.4 Hz, 1H), 7.54-7.51 (t, *J* = 7.5 Hz, 2H), 7.32 (t, *J* = 7.2 Hz, 1H), 7.28-7.27 (m, 1H), 4.33-4.22 (m, 2H), 2.75 (s, 3H), 1.35 (t, *J* = 7.2 Hz, 3H);^{13}C NMR (150 MHz, $CDCl_3$) δ 142.7 (d, *J* = 9.6 Hz), 140.5 (d, *J* = 7.8 Hz), 136.8, 134.8 (d, *J* = 7.8 Hz), 133.5 (d, *J* = 1.9 Hz), 131.1 (d, *J* = 15.0 Hz), 130.1 (d, *J* = 6.3 Hz), 128.7, 125.6, 122.1 (d, *J* = 10.9 Hz), 121.9, 120.6, 118.7 (d, *J* = 178.8 Hz), 118.3 (d, *J* = 13.8 Hz), 63.4 (d, *J* = 7.0 Hz), 21.6 (d, *J* = 4.3 Hz), 16.4 (d, *J* = 6.1 Hz); ^{31}P NMR (243 MHz, $CDCl_3$) δ 12.40; FT-IR (KBr) 3471, 2921, 2857, 1734, 1586, 1456, 1367, 1265, 1075, 1026, 961, 852, 764 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{17}H_{15}BrO_3PS$: 408.9658, found 408.9658.



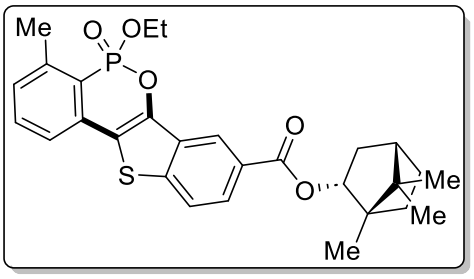
5-Ethoxy-4,9-dimethylbenzo[*c*]benzo[4,5]thieno[2,3-*e*][1,2]oxaphosphinine 5-oxide 3r. Analytical TLC on silica gel, 1:2 ethyl acetate/hexane R_f = 0.47; pink solid; mp 189-190 °C; yield 82% (28.2 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.77 (d, *J* = 8.4 Hz, 1H), 7.58 (s, 1H), 7.53 (t, *J* = 7.8 Hz, 1H), 7.35 (t, *J* = 7.2 Hz, 1H), 7.279-7.275 (m, 1H), 7.25-7.23 (m, 1H), 4.30-4.21 (m, 2H), 2.77 (s, 3H), 2.50 (s, 3H), 1.35 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 142.6 (d, *J* = 9.6 Hz), 141.0 (d, *J* = 8.1 Hz), 137.1, 136.0, 135.5 (d, *J* = 7.6 Hz), 133.4 (d, *J* = 2.2 Hz), 130.5 (d, *J* = 14.8 Hz), 129.2 (d, *J* = 6.4 Hz), 126.9, 122.9, 121.9 (d, *J* = 10.8 Hz), 120.6, 118.7 (d, *J* = 178.0 Hz), 116.7 (d, *J* = 13.8 Hz), 63.1 (d, *J* = 7.0 Hz), 21.9, 21.6 (d, *J* = 4.3 Hz), 16.4 (d, *J* = 6.1 Hz); ^{31}P NMR (243 MHz, $CDCl_3$) δ 12.60; FT-IR (KBr) 3474, 2922, 2857, 1734, 1589, 1537, 1457, 1369, 1266, 1028, 961, 838, 756 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{18}H_{18}O_3PS$: 345.0709, found 345.0710.



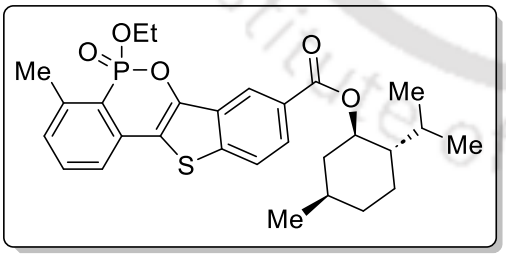
5-Ethoxy-4-methyl-9-(*p*-tolyl)benzo[*c*]benzo[4,5]-thieno[2,3-*e*][1,2]oxaphosphinine 5-oxide 3s. Analytical TLC on silica gel, 1:2 ethyl acetate/hexane R_f = 0.45; brown solid; mp 195-196 °C; yield 79% (33.2 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.96 (s, 1H), 7.92 (d, *J* = 8.4 Hz, 1H), 7.68 (d, *J* = 8.4 Hz, 1H), 7.57-7.53 (m, 3H), 7.38 (t, *J* = 7.2 Hz, 1H), 7.30-7.27 (m, 3H), 4.34-4.23 (m, 2H), 2.78 (s, 3H), 2.43 (s, 3H), 1.36 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 142.7 (d, *J* = 9.6 Hz), 140.9 (d, *J* = 7.9 Hz), 140.0, 137.7 (d, *J* = 7.6 Hz), 136.4, 135.4 (d, *J* = 7.6 Hz), 133.4 (d, *J* = 2.2 Hz), 130.7 (d, *J* = 15.0 Hz), 130.2 (d, *J* = 6.4 Hz), 129.8, 127.3, 124.8, 122.1 (d, *J* = 10.8 Hz), 121.1 (d, *J* = 10.9 Hz), 118.9 (d, *J* = 178.2 Hz), 117.9 (d, *J* = 13.8 Hz), 63.2 (d, *J* = 7.0 Hz), 21.6 (d, *J* = 4.3 Hz), 21.2, 16.5 (d, *J* = 6.1 Hz); ^{31}P NMR (243 MHz, $CDCl_3$) δ 12.50; FT-IR (KBr) 3472, 2921, 2863, 1731, 1588, 1457, 1372, 1265, 1027, 961, 855, 807 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{24}H_{22}O_3PS$: 421.1022, found 421.1024.



10-Chloro-5-ethoxy-4-methylbenzo[*c*]benzo[4,5]thieno[2,3-*e*][1,2]-oxaphosphinine 5-oxide 3t. Analytical TLC on silica gel, 1:2 ethyl acetate/hexane R_f = 0.47; brown solid; mp 145-146 °C; yield 72% (26.3 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.79-7.78 (m, 1H), 7.55 (t, *J* = 7.8 Hz, 1H), 7.42-7.38 (m, 3H), 7.29-7.27 (m, 1H), 4.32-4.21 (m, 2H), 2.76 (s, 3H), 1.34 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 142.8 (d, *J* = 9.6 Hz), 140.9 (d, *J* = 7.8 Hz), 134.8 (d, *J* = 7.6 Hz), 134.6, 133.5 (d, *J* = 2.1 Hz), 132.9 (d, *J* = 6.9 Hz), 131.2 (d, *J* = 15.0 Hz), 128.4, 126.5, 126.2, 122.2 (d, *J* = 10.8 Hz), 119.4, 119.27 (d, *J* = 13.8 Hz), 119.23 (d, *J* = 178.5 Hz), 63.3 (d, *J* = 7.0 Hz), 21.6 (d, *J* = 4.3 Hz), 16.4 (d, *J* = 6.1 Hz); ^{31}P NMR (243 MHz, $CDCl_3$) δ 12.20; FT-IR (KBr) 3465, 2922, 2857, 1734, 1591, 1460, 1372, 1267, 1028, 964, 854, 755 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{17}H_{15}ClO_3PS$: 365.0163, found 365.0162.

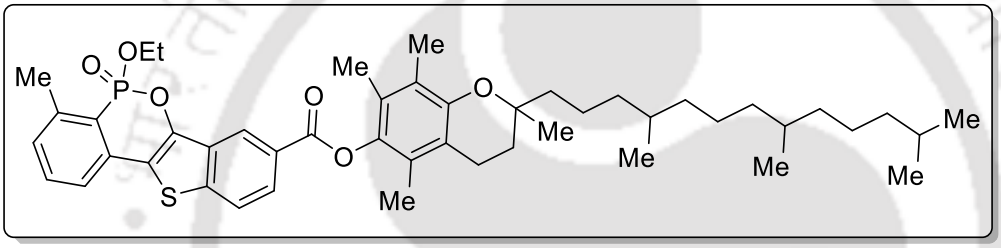


(1*S*,2*R*,4*S*)-1,7,7-Trimethylbicyclo[2.2.1]heptan-2-yl 5-ethoxy-4-methylbenzo[*c*]benzo[4,5]thieno[2,3-*e*][1,2]oxaphosphinine-8-carboxylate 5-oxide 3u. Analytical TLC on silica gel, 1:2 ethyl acetate/hexane R_f = 0.58; colorless solid; mp 152-153 °C; yield 66% (33.7 mg); An inseparable mixture of diasteroisomers (dr = 1:1); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.55-8.54 (m, 2H), 8.10 (s, 1H), 8.08 (s, 1H), 7.84 (d, *J* = 8.4 Hz, 2H), 7.55 (t, *J* = 7.8 Hz, 2H), 7.38 (t, *J* = 6.6 Hz, 2H), 7.30-7.28 (m, 2H), 5.19-5.17 (m, 2H), 4.37-4.25 (m, 4H), 2.77 (s, 6H), 2.54-2.48 (m, 2H), 2.21-2.15 (m, 2H), 1.88-1.81 (m, 2H), 1.77-1.76 (m, 2H), 1.49-1.44 (m, 2H), 1.40-1.34 (m, 8H), 1.19-1.16 (m, 2H), 0.99 (s, 6H), 0.96-0.95 (m, 6H), 0.94 (s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 166.66, 166.65, 142.8 (d, *J* = 9.6 Hz), 141.19 (d, *J* = 7.3 Hz), 141.18 (d, *J* = 7.8 Hz), 139.7, 139.6, 134.8 (d, *J* = 7.6 Hz), 133.56, 133.55, 131.3 (d, *J* = 6.4 Hz), 131.2 (d, *J* = 15.0 Hz), 128.3, 128.2, 127.1 (d, *J* = 3.6 Hz), 123.0, 122.58, 122.56, 122.1 (d, *J* = 10.8 Hz), 119.2 (d, *J* = 178.5 Hz), 119.1 (d, *J* = 178.5 Hz), 119.08 (d, *J* = 13.8 Hz), 119.06 (d, *J* = 13.8 Hz), 81.1, 63.5 (d, *J* = 6.9 Hz), 49.3 (d, *J* = 8.2 Hz), 48.1, 48.0, 45.12, 45.10, 37.0, 28.29, 28.27, 27.6 (d, *J* = 5.5 Hz), 21.6 (d, *J* = 4.3 Hz), 19.9, 19.0, 16.5 (d, *J* = 6.1 Hz), 13.85, 13.84; ^{31}P NMR (243 MHz, $CDCl_3$) δ 12.31, 12.28; FT-IR (KBr) 3427, 2923, 2855, 1714, 1591, 1457, 1359, 1264, 1122, 1026, 964, 846, 755 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{28}H_{32}O_5PS$: 511.1703, found 511.1697.

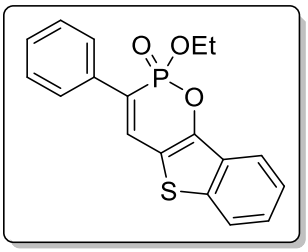


(1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyl 5-ethoxy-4-methylbenzo[*c*]benzo[4,5]thieno[2,3-*e*][1,2]oxaphosphinine-8-carboxylate 5-oxide 3v. Analytical TLC on silica gel, 1:2 ethyl acetate/hexane R_f = 0.56; colorless solid; mp 160-161 °C; yield 61% (31.2 mg); An inseparable mixture of diasteroisomers (dr = 1:1); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.57 (s, 1H), δ 8.55 (s, 1H), 8.10-8.07 (m, 2H), 7.83 (d, *J* = 8.4 Hz, 2H), 7.55 (t, *J* = 7.8 Hz, 2H), 7.38 (t, *J* = 7.2 Hz, 2H), 7.30-7.28 (m, 2H), 5.04-4.96 (m, 2H), 4.38-4.22 (m, 4H), 2.77 (s, 6H), 2.17-2.14 (m, 2H), 2.04-1.96 (m, 2H), 1.79-1.74 (m, 4H), 1.67-

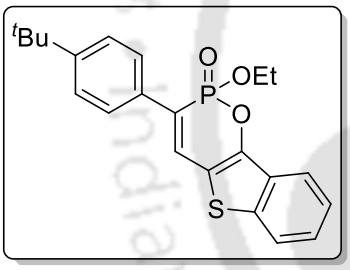
1.61 (m, 4H), 1.36 (t, *J* = 7.2 Hz, 6H), 1.20-1.15 (m, 4H), 0.99-0.93 (m, 14H), 0.83-0.80 (m, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 165.88, 165.86, 142.89 (d, *J* = 9.7 Hz), 142.86 (d, *J* = 9.6 Hz), 141.26 (d, *J* = 6.9 Hz), 141.21 (d, *J* = 6.6 Hz), 139.66, 139.65, 134.9 (d, *J* = 7.6 Hz), 133.56, 133.54, 131.35 (d, *J* = 6.1 Hz), 131.33 (d, *J* = 6.1 Hz), 131.2 (d, *J* = 15.0 Hz), 128.29, 128.25, 127.2 (d, *J* = 11.1 Hz), 122.9, 122.7 (d, *J* = 10.2 Hz), 122.2 (d, *J* = 10.8 Hz), 119.27 (d, *J* = 172.5 Hz), 119.23 (d, *J* = 171.9 Hz), 119.09 (d, *J* = 12.1 Hz), 119.06 (d, *J* = 13.9 Hz), 75.4, 75.3, 63.47 (d, *J* = 6.9 Hz), 63.45 (d, *J* = 6.9 Hz), 47.37, 47.33, 41.18, 41.12, 34.4, 31.67, 31.64, 29.8, 26.8, 26.4, 23.9, 23.5, 22.2 (d, *J* = 3.9 Hz), 21.6 (d, *J* = 4.2 Hz), 21.0, 20.8, 16.8, 16.5 (d, *J* = 5.2 Hz), 16.4 (d, *J* = 6.3 Hz); ^{31}P NMR (243 MHz, $CDCl_3$) δ 12.37, 12.23; FT-IR (KBr) 3430, 2923, 2855, 1716, 1591, 1459, 1371, 1266, 1122, 1032, 844, 755 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{28}H_{34}O_5PS$: 513.1860, found 513.1844.



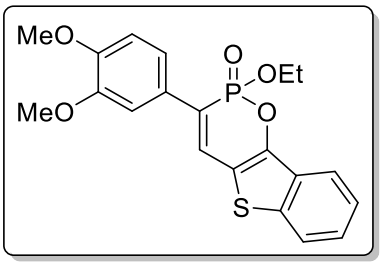
2,5,7,8-Tetramethyl-2-(4,8,12-trimethyltridecyl)chroman-6-yl 5-ethoxy-4-methylbenzo[*c*]benzo-[4,5]thieno[2,3-*e*][1,2]oxaphosphinine-8-carboxylate 5-oxide 3w. Analytical TLC on silica gel, 1:2 ethyl acetate/hexane R_f = 0.60; yellow liquid; yield 59% (46.4 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.79 (s, 1H), 8.26 (d, *J* = 8.4 Hz, 1H), 7.91 (d, *J* = 8.4 Hz, 1H), 7.57 (t, *J* = 7.8 Hz, 1H), 7.40 (t, *J* = 6.6 Hz, 1H), 7.31-7.29 (m, 1H), 4.39-4.27 (m, 2H), 2.77 (s, 3H), 2.64-2.62 (m, 2H), 2.13 (s, 3H), 2.09 (d, *J* = 9.0 Hz, 3H), 2.05 (d, *J* = 9.6 Hz, 3H), 1.88-1.78 (m, 2H), 1.53-1.50 (m, 2H), 1.38 (t, *J* = 7.2 Hz, 5H), 1.28-1.25 (m, 14H), 1.15-1.04 (m, 6H), 0.87-0.84 (m, 12H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 165.0, 149.7, 142.8 (d, *J* = 9.1 Hz), 141.2 (d, *J* = 6.9 Hz), 140.8, 140.2, 134.8 (d, *J* = 7.2 Hz), 133.5, 131.6 (d, *J* = 7.5 Hz), 131.3 (d, *J* = 15.0 Hz), 127.5, 127.0, 125.2, 123.3, 123.2, 122.2 (d, *J* = 10.9 Hz), 119.4 (d, *J* = 178.2 Hz), 119.2 (d, *J* = 14.1 Hz), 117.7, 75.2, 63.5 (d, *J* = 6.3 Hz), 39.5, 37.6, 37.5, 37.4, 32.9, 32.8, 29.8, 28.1, 24.9, 24.6, 22.8 (d, *J* = 13.5 Hz), 21.6 (d, *J* = 3.9 Hz), 21.2, 20.8, 19.9, 19.8, 19.79, 19.76, 16.5 (d, *J* = 5.85 Hz), 13.2, 12.4, 12.0; ^{31}P NMR (243 MHz, $CDCl_3$) δ 12.14; FT-IR (neat) 3432, 2923, 2858, 1732, 1591, 1456, 1372, 1222, 1084, 1028, 962, 849, 753 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{47}H_{64}O_6PS$: 787.4156, found 787.4153.



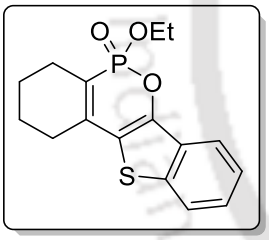
2-Ethoxy-3-phenylbenzo[4,5]thieno[2,3-*e*][1,2]oxaphosphinine 2-oxide 3A. Analytical TLC on silica gel, 1:2 ethyl acetate/hexane R_f = 0.60; brown sticky liquid; yield 63% (21.5 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.91 (d, *J* = 7.2 Hz, 1H), 7.79 (d, *J* = 7.8 Hz, 1H), 7.75 (d, *J* = 7.2 Hz, 2H), 7.53 (d, *J* = 37.8 Hz, 1H), 7.46-7.42 (m, 4H), 7.39-7.37 (m, 1H), 4.26-4.17 (m, 2H), 1.27 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 143.9 (d, *J* = 9.1 Hz), 137.6, 134.8 (d, *J* = 10.5 Hz), 132.6 (d, *J* = 5.1 Hz), 130.4 (d, *J* = 6.3 Hz), 129.1, 128.9, 127.4 (d, *J* = 7.0 Hz), 126.9, 125.3, 125.0 (d, *J* = 170.2 Hz), 123.2, 121.2, 116.1 (d, *J* = 19.6 Hz), 64.1 (d, *J* = 7.0 Hz), 16.4 (d, *J* = 6.1 Hz); ^{31}P NMR (243 MHz, $CDCl_3$) δ 11.65; FT-IR (neat) 3425, 3063, 2921, 2853, 1727, 1584, 1521, 1451, 1381, 1336, 1265, 1030, 967, 844, 759 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{18}H_{16}O_3PS$: 343.0553, found 343.0552.



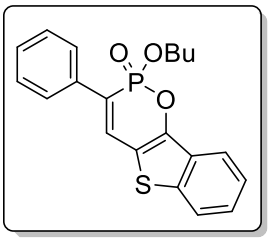
3-(4-(*tert*-Butyl)phenyl)-2-ethoxybenzo[4,5]thieno[2,3-*e*][1,2]-oxaphosphinine 2-oxide 3B. Analytical TLC on silica gel, 1:2 ethyl acetate/hexane R_f = 0.40; brown sticky liquid; yield 68% (27.1 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.88 (d, *J* = 7.8 Hz, 1H), 7.75 (d, *J* = 7.8 Hz, 1H), 7.67 (d, *J* = 7.2 Hz, 2H), 7.50 (d, *J* = 31.8 Hz, 1H), 7.44-7.39 (m, 4H), 4.27-4.17 (m, 2H), 1.33 (s, 9H), 1.28 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 152.1, 143.6 (d, *J* = 9.3 Hz), 137.4, 131.8 (d, *J* = 5.4 Hz), 131.6, 130.3 (d, *J* = 6.3 Hz), 128.5, 126.9 (d, *J* = 7.2 Hz), 126.7, 126.0, 125.2, 124.7 (d, *J* = 169.6 Hz), 123.1, 121.0, 119.1, 116.2 (d, *J* = 19.5 Hz), 63.8 (d, *J* = 7.0 Hz), 34.7, 31.2, 16.4 (d, *J* = 6.1 Hz); ^{31}P NMR (243 MHz, $CDCl_3$) δ 11.94; FT-IR (neat) 3454, 2958, 2868, 1690, 1585, 1517, 1461, 1376, 1263, 1025, 968, 839, 757 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{22}H_{24}O_3PS$: 399.1179, found 399.1174.



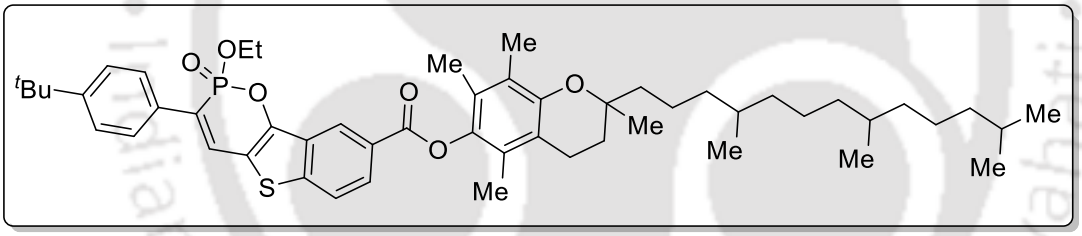
3-(3,4-Dimethoxyphenyl)-2-ethoxybenzo[4,5]thieno[2,3-*e*][1,2]oxaphosphinine 2-oxide 3C. Analytical TLC on silica gel, 1:2 ethyl acetate/hexane R_f = 0.30; brown sticky liquid; yield 70% (28.2 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.88 (d, *J* = 7.8 Hz, 1H), 7.75 (d, *J* = 7.8 Hz, 1H), 7.44-7.38 (m, 3H), 7.34-7.32 (m, 1H), 7.27-7.26 (m, 1H), 6.90 (d, *J* = 8.4 Hz, 1H), 4.24-4.14 (m, 2H), 3.94 (s, 3H), 3.90 (s, 3H), 1.26 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 149.9, 149.3, 143.4 (d, *J* = 9.0 Hz), 137.3, 131.0 (d, *J* = 5.4 Hz), 130.3 (d, *J* = 6.3 Hz), 127.5 (d, *J* = 10.8 Hz), 126.7, 125.2, 124.7 (d, *J* = 169.3 Hz), 123.1, 121.0, 120.3 (d, *J* = 7.3 Hz), 116.1 (d, *J* = 19.3 Hz), 111.4, 110.2 (d, *J* = 7.3 Hz), 63.9 (d, *J* = 7.0 Hz), 56.1 (d, *J* = 9.9 Hz), 16.4 (d, *J* = 6.0 Hz); ^{31}P NMR (243 MHz, $CDCl_3$) δ 11.76; FT-IR (neat) 3467, 2925, 2850, 1719, 1590, 1515, 1459, 1378, 1259, 1155, 1026, 964, 851, 761 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{20}H_{20}O_5PS$: 403.0764, found 403.0758.



5-Ethoxy-1,2,3,4-tetrahydrobenzo[*c*]benzo[4,5]thieno[2,3-*e*][1,2]oxa-phosphinine 5-oxide 3D. Analytical TLC on silica gel, 1:2 ethyl acetate/hexane R_f = 0.56; yellow liquid; yield 52% (16.6 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.84 (d, *J* = 7.8 Hz, 1H), 7.75 (d, *J* = 7.8 Hz, 1H), 7.43-7.37 (m, 2H), 4.26-4.21 (m, 2H), 2.71-2.66 (m, 1H), 2.57 (s, 2H), 2.48-2.43 (m, 1H), 1.88-1.79 (m, 4H), 1.36 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 143.2 (d, *J* = 5.1 Hz), 141.4 (d, *J* = 8.1 Hz), 135.6, 130.9 (d, *J* = 6.6 Hz), 126.3, 125.1, 123.0, 120.9, 117.9 (d, *J* = 173.2 Hz), 63.2 (d, *J* = 6.9 Hz), 29.8, 28.3 (d, *J* = 13.5 Hz), 23.4 (d, *J* = 8.5 Hz), 21.7 (d, *J* = 10.5 Hz), 21.6, 16.6 (d, *J* = 5.7 Hz); ^{31}P NMR (243 MHz, $CDCl_3$) δ 15.82; FT-IR (neat) 3391, 2922, 2863, 1720, 1591, 1455, 1375, 1239, 1090, 1034, 958, 860, 756 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{16}H_{18}O_3PS$: 321.0709, found 321.0697.

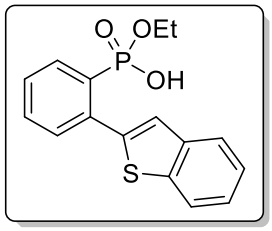


2-Butoxy-3-phenylbenzo[4,5]thieno[2,3-*e*][1,2]oxaphosphinine 2-oxide 3E. Analytical TLC on silica gel, 1:2 ethyl acetate/hexane R_f = 0.84; brown solid; mp 145-146 °C; yield 72% (26.6 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.91-7.89 (m, 1H), 7.78-7.70 (m, 1H), 7.74-7.73 (m, 2H), 7.52-7.45 (m, 2H), 7.44-7.42 (m, 3H), 7.39-7.37 (t, *J* = 7.3 Hz, 1H), 4.18-4.10 (m, 2H), 1.60-1.55 (m, 2H), 1.29-1.23 (m, 2H), 0.79 (t, *J* = 7.8 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 143.9 (d, *J* = 9.3 Hz), 137.6, 134.9 (d, *J* = 10.3 Hz), 132.5 (d, *J* = 4.9 Hz), 130.4 (d, *J* = 6.3 Hz), 129.1, 128.9, 127.4 (d, *J* = 7.0 Hz), 126.9, 125.3, 125.1 (d, *J* = 169.9 Hz), 123.2, 121.2, 116.1 (d, *J* = 19.5 Hz), 67.7 (d, *J* = 7.3 Hz), 32.4 (d, *J* = 6.0 Hz), 18.6, 13.5; ^{31}P NMR (243 MHz, $CDCl_3$) δ 11.56; FT-IR (KBr) 3449, 2923, 2865, 1734, 1580, 1520, 1460, 1380, 1337, 1267, 1025, 986, 843, 758 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{20}H_{20}O_3PS$: 371.0866, found 371.0862.

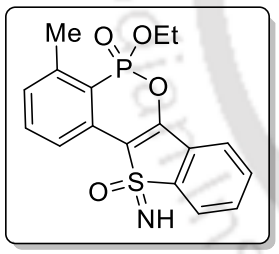


2,5,7,8-Tetramethyl-2-(4,8,12-trimethyltridecyl)chroman-6-yl 3-(4-(*tert*-butyl)phenyl)-2-ethoxybenzo[4,5]thieno[2,3-*e*][1,2]oxaphosphinine-8-carboxylate 2-oxide 3G. Analytical TLC on silica gel, 1:2 ethyl acetate/hexane R_f = 0.80; yellow liquid; yield 54% (46.2 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.81 (s, 1H), 8.26-8.25 (m, 1H), 7.91 (d, *J* = 8.4 Hz, 1H), 7.69 (d, *J* = 8.4 Hz, 2H), 7.52-7.45 (m, 3H), 4.33-4.23 (m, 2H), 2.65-2.62 (m, 2H), 2.14 (s, 3H), 2.09 (d, *J* = 6.0 Hz, 3H), 2.05 (d, *J* = 6.6 Hz, 3H), 1.87-1.80 (m, 2H), 1.54-1.49 (m, 2H), 1.35 (s, 9H), 1.31 (t, *J* = 7.2 Hz, 5H), 1.28-1.24 (m, 12H), 1.15-1.08 (m, 8H), 0.87-0.84 (m, 12H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 164.9, 152.5, 149.7, 143.8 (d, *J* = 8.8 Hz), 141.8, 140.7, 131.6 (d, *J* = 169.6 Hz), 131.1 (d, *J* = 4.9 Hz), 127.5, 127.1, 127.07, 127.01 (d, *J* = 6.6 Hz), 126.1, 125.2 (d, *J* = 4.2 Hz), 125.0, 123.5, 123.4, 123.3 (d, *J* = 8.4 Hz), 117.7 (d, *J* = 6.7 Hz),117.6, 117.5 (d, *J* = 19.6 Hz), 75.2, 64.3 (d, *J* = 7.0 Hz), 39.5, 37.7, 37.6, 37.5, 37.4, 34.8, 32.9 (d, *J* = 1.9 Hz), 31.3, 31.1, 28.1, 24.9 (d, *J* = 1.9 Hz), 24.5, 24.3, 23.8, 22.8, 22.7, 21.2, 20.7, 19.9 (d, *J* = 9.7 Hz), 19.7 (d, *J* = 5.2 Hz), 16.4 (d, *J* = 6.1 Hz), 13.2, 12.4, 12.0; ^{31}P NMR (243 MHz, $CDCl_3$) δ

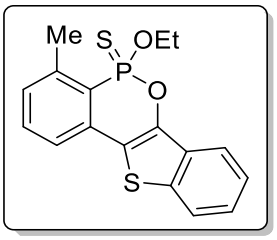
11.40; FT-IR (neat) 2927, 2863, 1733, 1458, 1371, 1326, 1269, 1224, 1090, 1029, 967, 837, 752 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{52}H_{72}O_6PS$: 855.4782, found 855.4753.



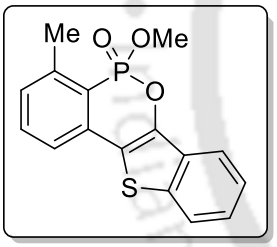
Ethyl hydrogen (2-(benzo[*b*]thiophen-2-yl)phenyl)phosphonate 3b′. Analytical TLC on silica gel, 1:2 methanol/ CH_2Cl_2 R_f = 0.70; colorless solid; yield 84% (534.0 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.87 (bs, 1H), 8.09-8.05 (m, 1H), 7.80 (dd, *J* = 25.8 Hz, 7.8 Hz, 2H), 7.58-7.55 (m, 3H), 7.45-7.42 (m, 1H), 7.34-7.30 (m, 2H), 3.81-3.77 (m, 2H), 0.94 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 141.5 (d, *J* = 4.6 Hz), 140.4, 140.1, 138.2 (d, *J* = 8.8 Hz), 134.1 (d, *J* = 9.6 Hz), 132.4 (d, *J* = 13.5 Hz), 132.0 (d, *J* = 2.4 Hz), 128.9 (d, *J* = 192.3 Hz), 128.5 (d, *J* = 15.1 Hz), 128.0 (d, *J* = 14.5 Hz), 125.5, 124.4 (d, *J* = 6.6 Hz), 124.1, 121.9, 62.0 (d, *J* = 6.1 Hz), 15.9 (d, *J* = 6.9 Hz); ^{31}P NMR (243 MHz, $CDCl_3$) δ 19.86; FT-IR (KBr) 3386, 2920, 2857, 2323, 1732, 1591, 1460, 1378, 1196, 1041, 986, 758 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{16}H_{16}O_3PS$: 319.0553, found 319.0545.



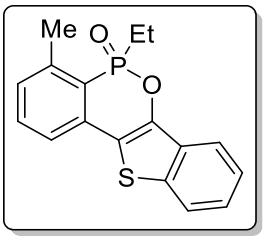
5-Ethoxy-11-imino-4-methyl-11*H*-11λ^4-benzo[*c*]benzo[4,5]thieno-[2,3-*e*][1,2]oxaphosphinine 5,11-dioxide 5. Analytical TLC on silica gel, 1:2 ethyl acetate/hexane R_f = 0.37; yellow solid; mp 192-193 °C; yield 77% (27.8 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.90-7.88 (m, 1H), 7.84 (d, *J* = 7.8 Hz, 1H), 7.73 (d, *J* = 7.2 Hz, 1H), 7.67-7.61 (m, 3H), 7.37-7.35 (m, 1H), 4.36-4.26 (m, 2H), 3.48 (bs, 1H), 2.73 (s, 3H), 1.40 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 148.4 (d, *J* = 8.1 Hz), 143.1 (d, *J* = 9.3 Hz), 141.7, 133.8 (d, *J* = 2.1 Hz), 133.1, 131.9 (d, *J* = 15.1 Hz), 131.7, 130.0 (d, *J* = 29.7 Hz), 127.3 (d, *J* = 6.3 Hz), 121.4 (d, *J* = 10.8 Hz), 121.3, 120.5, 118.8 (d, *J* = 187.0 Hz), 118.7 (d, *J* = 4.8 Hz), 64.2 (d, *J* = 7.2 Hz), 21.6 (d, *J* = 4.5 Hz), 16.4 (d, *J* = 6.3 Hz); ^{31}P NMR (243 MHz, $CDCl_3$) δ 11.95; FT-IR (KBr) 3466, 3247, 2922, 2855, 1722, 1624, 1586, 1459, 1364, 1248, 1112, 1022, 965, 804 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{17}H_{17}NO_4PS$: 362.0611, found 362.0610.



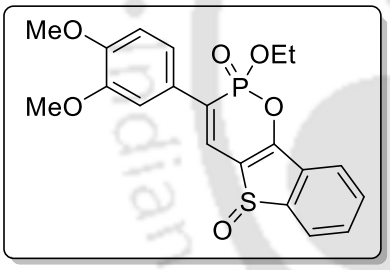
5-Ethoxy-4-methylbenzo[*c*]benzo[4,5]thieno[2,3-*e*][1,2]oxaphosphinine 5-sulfide 6. Analytical TLC on silica gel, 1:10 ethyl acetate/hexane R_f = 0.48; yellow solid; mp 102-103 °C; yield 82% (28.4 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.87-7.86 (m, 1H), 7.77-7.76 (m, 1H), 7.48 (t, *J* = 7.8 Hz, 1H), 7.43-7.39 (m, 2H), 7.36-7.34 (m, 1H), 7.25-7.23 (m, 1H), 4.43-4.32 (m, 2H), 2.76 (s, 3H), 1.42 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 141.5 (d, *J* = 11.2 Hz), 140.4 (d, *J* = 9.7 Hz), 135.8, 133.2 (d, *J* = 7.3 Hz), 132.8 (d, *J* = 2.2 Hz), 131.6 (d, *J* = 13.9 Hz), 126.6, 125.1, 123.4 (d, *J* = 140.4 Hz), 123.0, 122.3, 122.2, 121.0, 118.0 (d, *J* = 14.2 Hz), 64.0 (d, *J* = 7.9 Hz), 21.9 (d, *J* = 4.9 Hz), 16.3 (d, *J* = 7.2 Hz); ^{31}P NMR (243 MHz, $CDCl_3$) δ 76.13; FT-IR (KBr) 3465, 2920, 2857, 1733, 1588, 1457, 1367, 1247, 1022, 961, 836, 754 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{17}H_{16}O_2PS_2$: 347.0324, found 347.0324.



5-Methoxy-4-methylbenzo[*c*]benzo[4,5]thieno[2,3-*e*][1,2]oxaphosphinine 5-oxide 7. Analytical TLC on silica gel, 1:2 ethyl acetate/hexane R_f = 0.48; colorless solid; mp 125-126 °C; yield 86% (27.2 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.90-7.88 (m, 1H), 7.78-7.77 (m, 1H), 7.54 (t, *J* = 7.8 Hz, 1H), 7.46-7.41 (m, 2H), 7.38 (t, *J* = 7.2 Hz, 1H), 7.28-7.26 (m, 1H), 3.87 (d, *J* = 12.0 Hz, 3H), 2.76 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 142.8 (d, *J* = 9.7 Hz), 141.0 (d, *J* = 7.9 Hz), 135.7, 135.4 (d, *J* = 7.6 Hz), 133.5 (d, *J* = 2.2 Hz), 131.3 (d, *J* = 6.3 Hz), 130.8 (d, *J* = 15.0 Hz), 126.7, 125.2, 123.0, 122.2 (d, *J* = 10.9 Hz), 121.0, 118.5 (d, *J* = 177.9 Hz), 117.9 (d, *J* = 13.6 Hz), 53.2 (d, *J* = 6.9 Hz), 21.6 (d, *J* = 4.3 Hz); ^{31}P NMR (243 MHz, $CDCl_3$) δ 13.82; FT-IR (KBr) 3467, 2921, 2853, 1726, 1589, 1458, 1370, 1261, 1030, 858, 795, 732 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{16}H_{14}O_3PS$: 317.0396, found 317.0393.



5-Ethyl-4-methylbenzo[*c*]benzo[4,5]thieno[2,3-*e*][1,2]oxaphosphinine 5-oxide 8. Analytical TLC on silica gel, 1:2 ethyl acetate/hexane R_f = 0.30; yellow liquid; yield 84% (26.4 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.87-7.86 (m, 1H), 7.76-7.75 (m, 1H), 7.50 (t, *J* = 7.8 Hz, 1H), 7.44-7.39 (m, 2H), 7.35-7.33 (m, 1H), 7.24-7.22 (m, 1H), 2.76 (s, 3H), 2.28-2.13 (m, 2H), 1.15-1.09 (m, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 142.2 (d, *J* = 11.4 Hz), 140.9 (d, *J* = 8.7 Hz), 135.8, 134.4 (d, *J* = 5.8 Hz), 133.2 (d, *J* = 1.9 Hz), 131.5 (d, *J* = 5.2 Hz), 131.2 (d, *J* = 12.3 Hz), 126.6, 125.1, 123.0, 122.2 (d, *J* = 8.1 Hz), 121.1, 120.5 (d, *J* = 113.4 Hz), 117.8 (d, *J* = 12.1 Hz), 24.7 (d, *J* = 97.6 Hz), 21.6 (d, *J* = 3.9 Hz), 5.8 (d, *J* = 5.5 Hz); ^{31}P NMR (243 MHz, $CDCl_3$) δ 45.12; FT-IR (neat) 3446, 2922, 1715, 1587, 1456, 1368, 1218, 1108, 1067, 836, 753 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{17}H_{16}O_2PS$: 315.0604, found 315.0602.



3-(3,4-Dimethoxyphenyl)-2-ethoxybenzo[4,5]thieno[2,3-*e*][1,2]oxaphosphinine 2,5-dioxide 9. Analytical TLC on silica gel, 1:2 ethyl acetate/hexane R_f = 0.30; yellow liquid; yield 73% (30.5 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.95 (d, *J* = 7.8 Hz, 1H), 7.70-7.68 (m, 1H), 7.65 (t, *J* = 7.2 Hz, 1H), 7.61-7.58 (m, 1H), 7.53-7.45 (m, 1H), 7.38-7.34 (m, 1H), 7.23 (s, 1H), 6.92 (d, *J* = 8.4 Hz, 1H), 4.32-4.16 (m, 2H), 3.95 (s, 3H), 3.92 (s, 3H), 1.27 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 153.0 (d, *J* = 9.4 Hz), 150.5, 149.5, 144.4, 132.9, 131.5 (d, *J* = 6.6 Hz), 131.1, 128.5 (d, *J* = 5.5 Hz), 128.4 (d, *J* = 4.9 Hz), 127.0, 126.7 (d, *J* = 11.1 Hz), 126.3 (d, *J* = 168.7 Hz), 123.3 (d, *J* = 19.8 Hz), 122.1, 120.7 (d, *J* = 7.2 Hz), 111.5, 110.0 (d, *J* = 8.1 Hz), 65.0 (d, *J* = 7.2 Hz), 56.2 (d, *J* = 17.1 Hz), 16.3 (d, *J* = 6.0 Hz); ^{31}P NMR (243 MHz, $CDCl_3$) δ 11.46; FT-IR (neat) 2922, 2855, 1718, 1591, 1514, 1458, 1374, 1264, 1162, 1027, 867, 762 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{20}H_{20}O_6PS$: 419.0713, found 419.0699.

Crystal Data and Structure Refinement for 3m

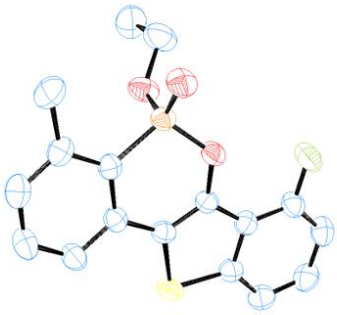


Figure 1. ORTEP diagram of 5-Ethoxy-7-fluoro-4-methylbenzo[*c*]benzo[4,5]thieno[2,3-*e*][1,2]oxaphosphinine 5-oxide **3m** with 50% ellipsoid (**CCDC 2388928**).

Identification code	**3m**
Empirical formula	$C_{17}H_{14}FO_3PS$
Solvent for crystal growth	Acetonitrile
Formula weight	348.31
Crystal habit, colour	block and yellow
Temperature, *T*/K	301 K
Wavelength, λ/Å	0.71073
Crystal system	orthorhombic
Space group	'P 21 21 21'
Unit cell dimensions	a = 7.7392(9) Å
	b = 13.4287(15) Å
	c = 15.1509(17) Å
	α = 90
	β = 90
	γ = 90
Volume, *V*/Å^3	1574.6(3)
Z	4
Calculated density, g·cm^{-3}	1.469
Absorption coefficient, μ/mm^{-1}	0.329
F(000)	720
θ range for data collection	2.026 to 26.365°
Limiting indices	$-9 \leq h \leq 9$, $-16 \leq k \leq 16$, $-18 \leq l \leq 18$

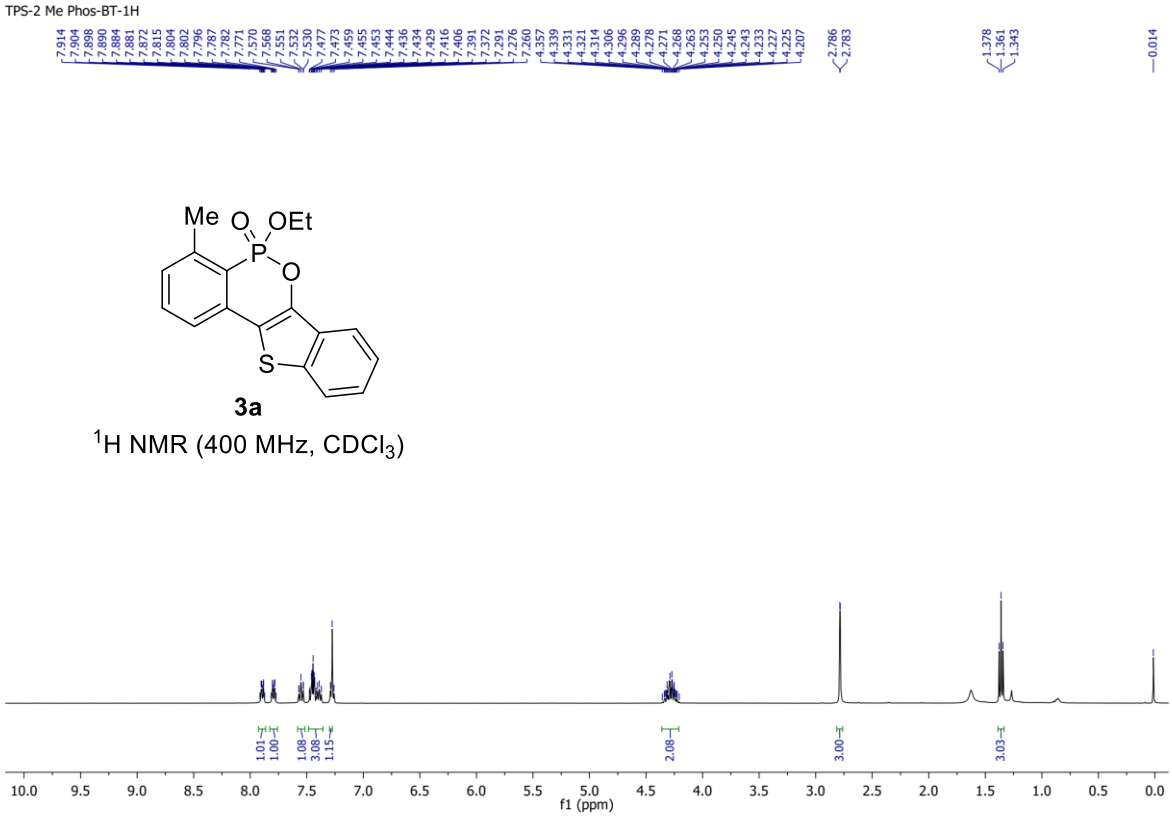
Reflection collected / unique	3220 / 3032
Completeness to θ	99.60% (θ = 26.36°)
Absorption correction	none
Refinement method	'SHELXL-2018/3 (Sheldrick, 2015) '
Data / restraints / parameters	3220/0/211
Goodness-of-fit on F^2	1.073
Final *R* indices [*I* >2sigma(*I*)]	*R*1 = 0.0348, *wR*2 = 0.0790
R indices (all data)	*R*1 = 0.0306, *wR*2 = 0.0740

4.5 References

1. (a) Engle, K. M.; Mei, T.-S.; Wasa, M.; Yu, J.-Q. *Acc. Chem. Res.* **2012**, *45*, 788. (b) Gensch, T.; Hopkinson, M. N.; Glorius, F.; Wencel-Delord, J. *Chem. Soc. Rev.* **2016**, *45*, 2900. (c) Sambiagio, C.; Schönbauer, D.; Blieck, R.; DaoHuy, T.; Pototschnig, G.; Schaaf, P.; Wiesinger, T.; Zia, M. F.; Wencel-Delord, J.; Besset, T.; Maes, B. U. W.; Schnürch, M. *Chem. Soc. Rev.* **2018**, *47*, 6603.
2. (a) Dong, J.; Long, Z.; Song, F.; Wu,N.; Guo, Q.; Lan, J.; You, J. *Angew. Chem., Int. Ed.* **2013**, *52*, 580. (b) Jiao, L.-Y.; Smirnov, P.; Oestreich, M. *Org. Lett.* **2014**, *16*, 6020. (c) Xu, H.; Shang, M.; Dai, H.-X.; Yu, J.-Q. *Org. Lett.* **2015**, *17*, 3830.
3. (a) Tan, G.; You, Q.; Lan, J.; You, J. *Angew. Chem., Int. Ed.* **2018**, *57*, 6309. (b) Chen, J.; Yin, C.; Zhou, J.; Yu, C. *Adv. Synth. Catal.* **2021**, *363*, 4360.
4. (a) Grembecka, J.; Mucha, A.; Cierpicki, T.; Kafarski, P. *J. Med. Chem.* **2003**, *46*, 2641. (b) Reddy, P. V. G.; Kiran, Y. B. R.; Reddy, C. S.; Reddy. C. D. *Chem. Pharm. Bull.* **2004**, *52*, 307. (c) Finkbeiner, P.; Hehn, J. P.; Gnamm, C. *J. Med. Chem.* **2020**, *63*, 7081.
5. (a) Liu, L.; Wu, H.-C.; Yu, J.-Q. *Chem.-Eur. J.* **2011**, *17*, 10828. (b) Chan, L. Y.; Cheong, L.; Kim, S. *Org. Lett.* **2013**, *15*, 2186. (c) Zhao, D.; Nimphius, C.; Lindale, M.; Glorius, F. *Org. Lett.* **2013**, *15*, 4504. (d) Feng, C.-G.; Ye, M.; Xiao, K.-J.; Li, S.; Yu, J.-Q. *J. Am. Chem. Soc.* **2013**, *135*, 9322. (e) Park, Y.; Seo, J.; Park, S.; Yoo, E. J.; Lee, P. H. *Chem.-Eur. J.* **2013**, *19*, 16461. (f) Baba, K.; Tobisu, M.; Chatani, N. *Org. Lett.* **2015**, *17*, 70. (g) Nguyen, T. T.; Grigorjeva, L.; Daugulis, O. *ACS Catal.* **2016**, 6, 551. (h) Qiu, X.; Wang, M.; Zhao, Y.; Shi, Z. *Angew. Chem., Int. Ed.* **2017**, *56*, 7233.

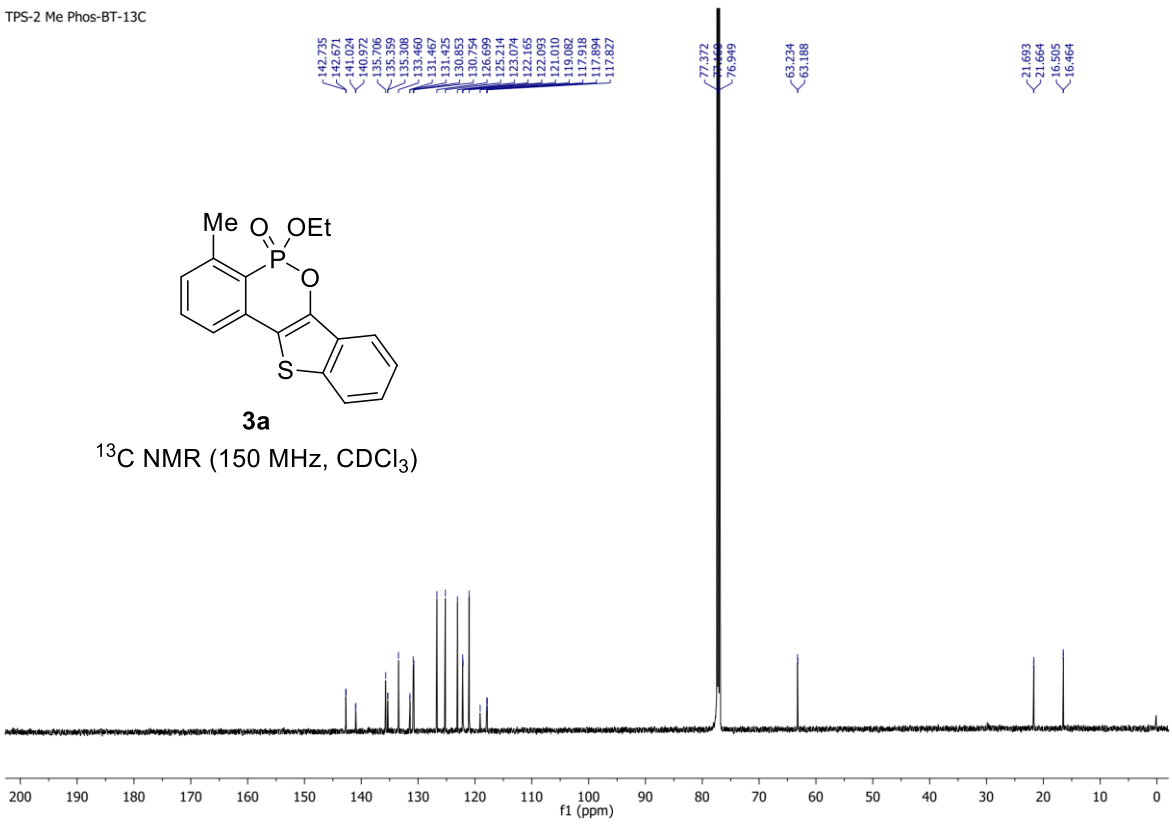
6. (a) Wang, C.; Dong, H.; Hu, W.; Liu, Y.; Zhu, D. *Chem. Rev.* **2012**, *112*, 2208. (b) Cinar, M. E.; Ozturk, T. *Chem. Rev.* **2015**, *115*, 3036. (c) Chen, W.; Dong, G.; He, S.; Xu, T.; Wang, X.; Liu, N.; Zhang, W.; Miao, C.; Sheng, C. *Bioorg. Med. Chem. Lett.* **2016**, *26*, 765. (d) Keri, R. S.; Chand, K.; Budagumpi, S.; Somappa, S. B.; Patil, S. A.; Nagaraja, B. M. A. *Eur. J. Med. Chem.* **2017**, *138*, 1002. (e) Venkateswarlu, S.; Lin, Y. D.; Lee, K. M.; Liau, K. L.; Tao, Y. T. *Acs Appl. Mater. Interfaces* **2020**, *12*, 50495.
7. (a) Rosenfeld, R. N.; Weiner, B. R. *J. Am. Chem. Soc.* **1983**, *105*, 6233. (b) Hu, X.-H.; Zhang, J.; Yang, X.-F.; Xu, Y.-H.; Loh, T.-P. *J. Am. Chem. Soc.* **2015**, *137*, 3169. (c) Lu, M.-Z.; Chen, X.-R.; Xu, H.; Dai, H.-X.; Yu, J.-Q. *Chem. Sci.* **2018**, *9*, 1311.
8. Reddy, V. P.; Qiu, R.; Iwasaki, T.; Kambe, N. *Org. Lett.* **2013**, *15*, 1290.
9. Shang, Y.; Jie, X.; Zhao, H.; Hu, P.; Su, W. *Org. Lett.* **2014**, *16*, 416.
10. Deng, H.; Li, H.; Wang, L. *Org. Lett.* **2016**, *18* , 3110.
11. Sarkar, T.; Maharana, P. K.; Roy, S.; Punniyamurthy, T. *Chem. Commun.* **2022**, *58* , 5980.
12. Tan, G.; You, Q.; Lan, J.; You, J. *Angew. Chem., Int. Ed.* **2018**, *57*, 6309.
13. Pu, X.; Zhang, M.; Lan, J.; Chen, S.; Liu, Z.; Liang, W.; Yang, Y.; Zhang, M.; You, J. *Org. Lett.* **2019**, *21*, 1139.
14. Yang, S.; Cheng, R.; Zhang, M.; Bin, Z.; You, J. *ACS Catal.* **2019**, *9*, 6188.
15. Chen, J.; Yin, C.; Zhou, J.; Yu, C. *Adv. Synth. Catal.* **2021**, *363*, 4360.
16. Li, W.-D.; Zhang, P.-J.; Jia, J.-W.; Zhang, X.-Y.; Ma, H.-Y.; He, K.-X.; Dang, D.-F.; Jiao, J.; Shi, X.-Y. *Org. Lett.* **2024**, *26*, 4857.
17. Kim, J.; Shin, K.; Jin, S.; Kim, D.; Chang, S. *J. Am. Chem. Soc.* **2019**, *141*, 4137.
18. (a) Zhuang, R.-Q.; Xu, J.; Cai, Z.-S.; Tang, G.; Fang, M.-J.; Zhao, Y.-F. *Org. Lett.* **2011**, *13*, 2110. (b) Seo, J.; Park, Y.; Jeon, I.; Ryu, T.; Park, S.; Lee, P. H. *Org. Lett.* **2013**, *15*, 3358. (c) Xin, N.; Lv, Y.; Lian, Y.; Lin, Z.; Huang, X.-Q.; Zhao**,** C.-Q.; Wang, Y. *J. Org. Chem.* **2023**, *88*, 2898.
19. (a) Kim, J. H.; Gensch, T.; Zhao, D.; Stegemann, L.; Strassert, C. A.; Glorius, F. *Angew. Chem., Int. Ed.* **2015**, *54*, 10975. (b) Chen, D.-F.; Bernsten, S.; Miyake, G. M. *Macromolecules* **2020**, *53*, 8352.
20. Thongpaen, J.; Schmid, T. E.; Toupet, L.; Dorcet, V.; Mauduit, M.; Baslé, O. *Chem. Commun.* **2018**, *54*, 8202.

4.6 Selected NMR Spectra



3a

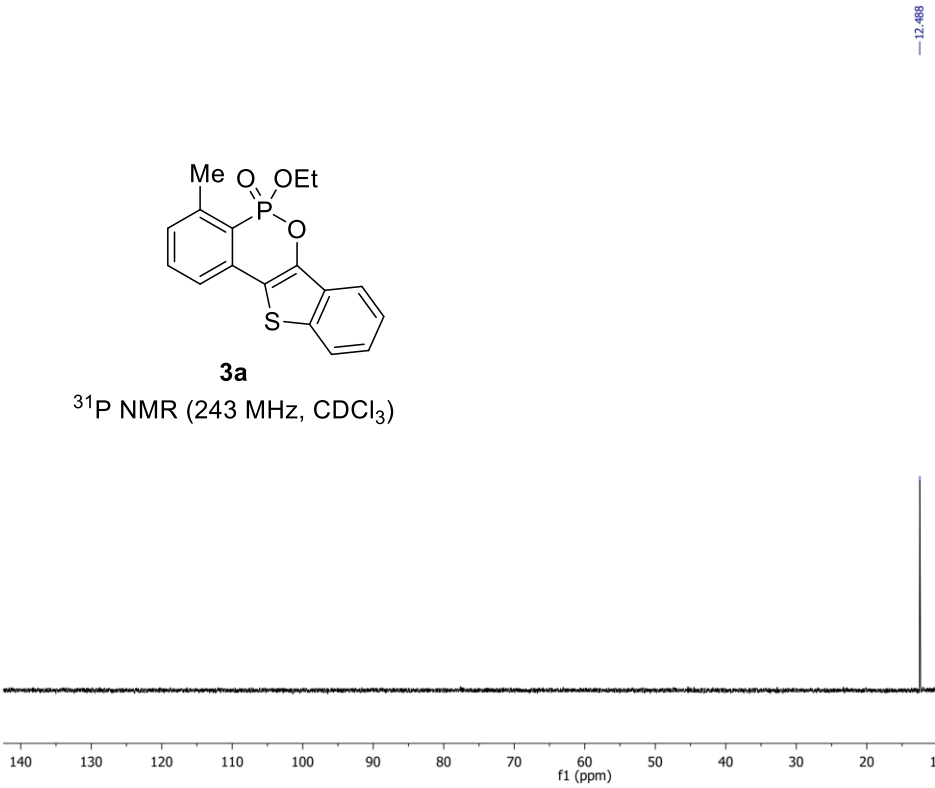
^{1}H NMR (400 MHz, $CDCl_3$)



3a

^{13}C NMR (150 MHz, $CDCl_3$)

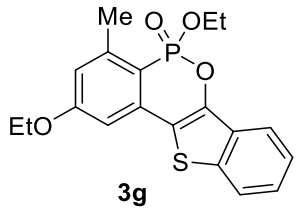
TPS-2 Me Phos-BT-31P



3a

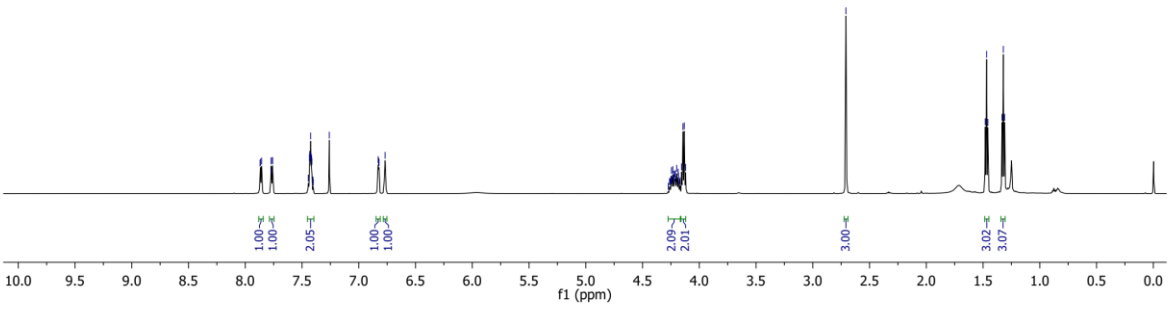
^{31}P NMR (243 MHz, $CDCl_3$)

TPS-Disub Phos-BT-1H

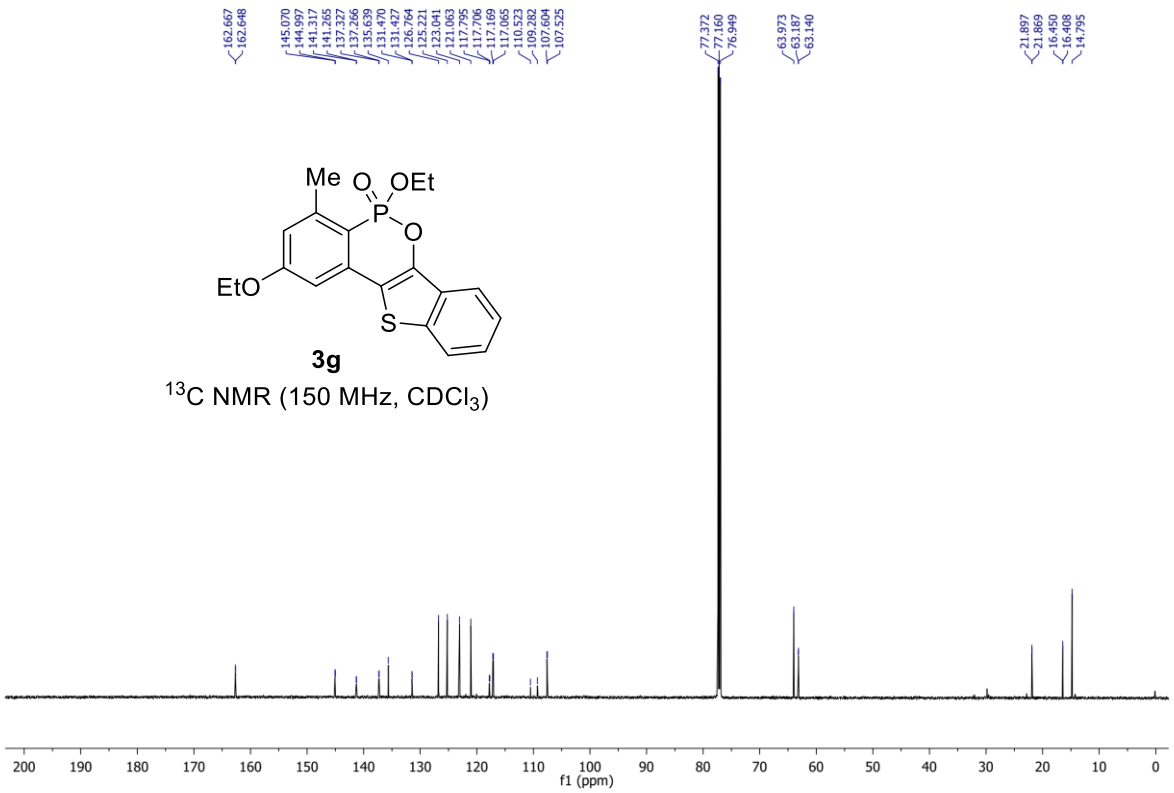


3g

^{1}H NMR (600 MHz, $CDCl_3$)



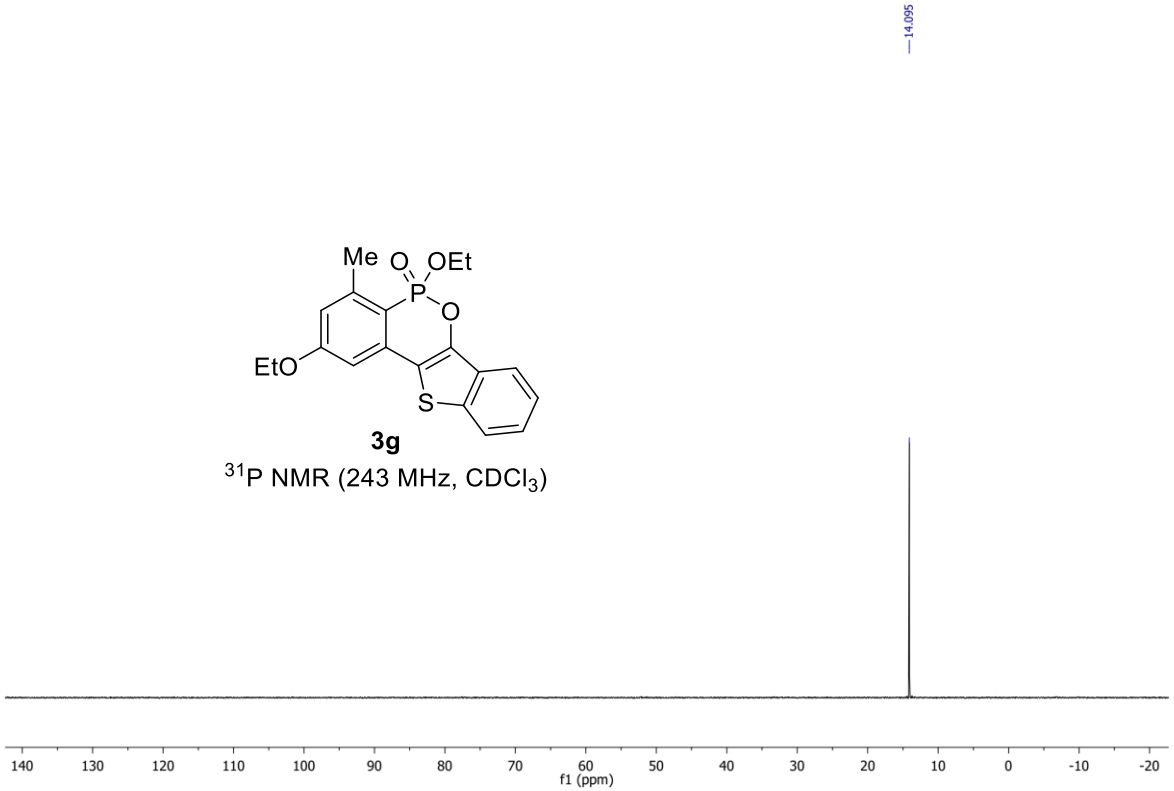
TPS-Disub Phos-BT-13C



3g

^{13}C NMR (150 MHz, $CDCl_3$)

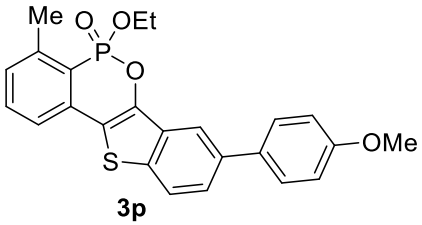
TPS-Disub Phos-BT-31P



3g

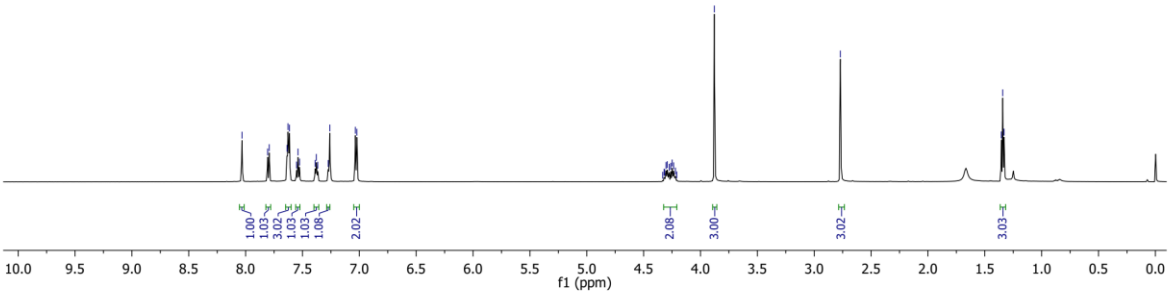
^{31}P NMR (243 MHz, $CDCl_3$)

TPS-Phos-PMP BT-1H



3p

^{1}H NMR (600 MHz, $CDCl_3$)



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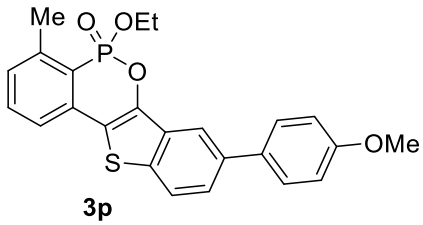
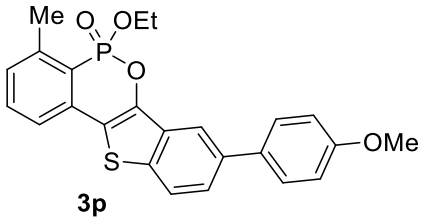


3p

^{13}C NMR (150 MHz, $CDCl_3$)

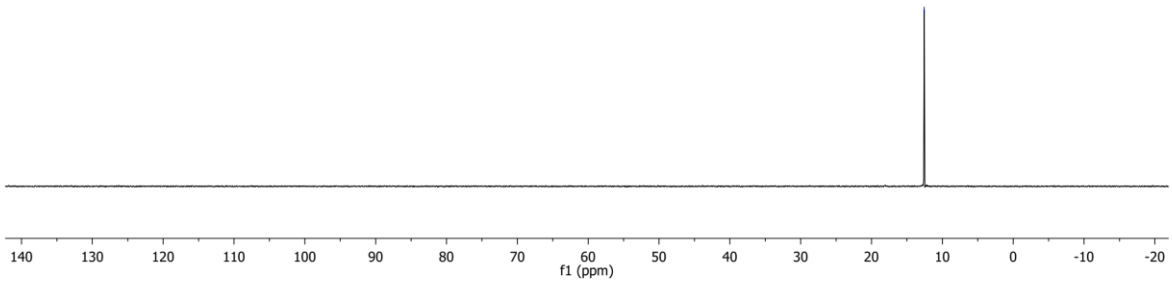
TPS-Phos-PMP BT-31P

12.557

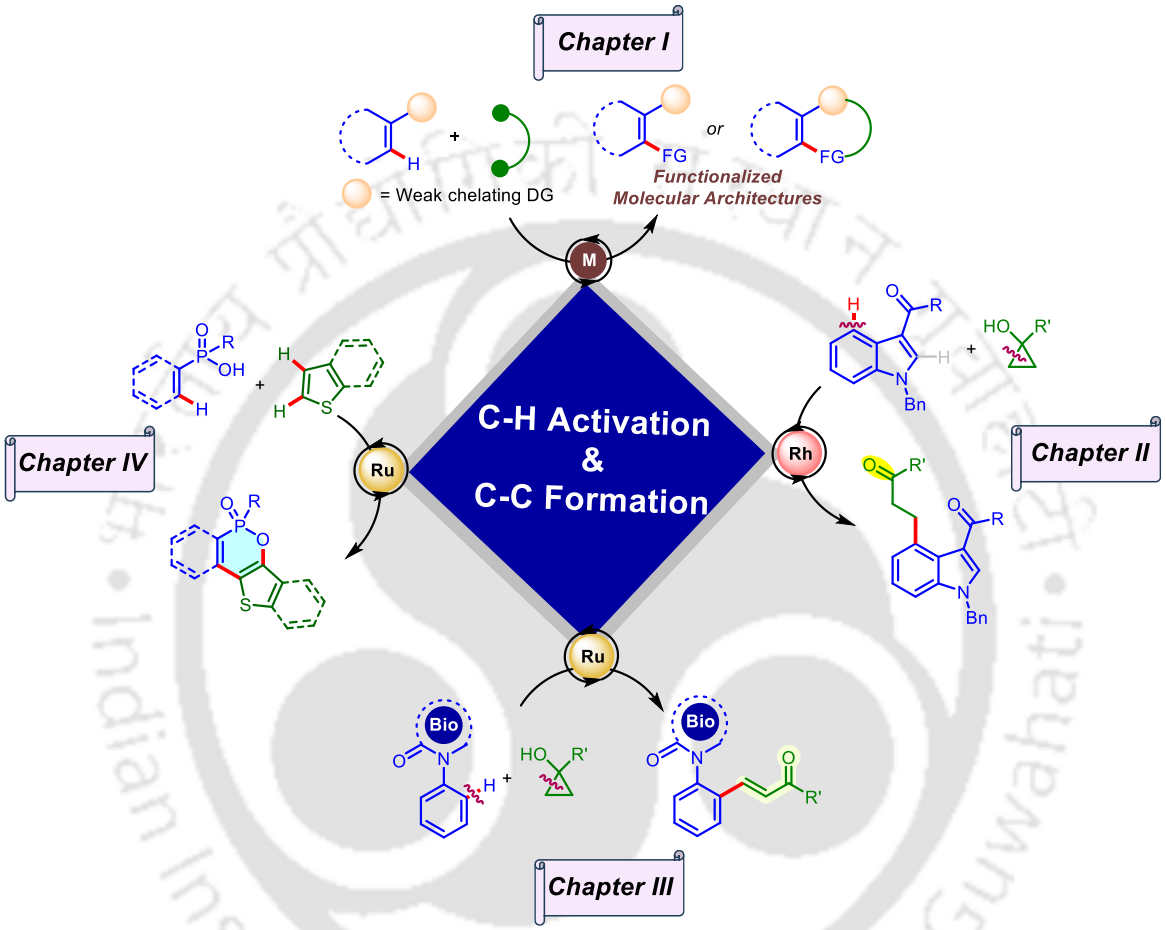


3p

^{31}P NMR (243 MHz, $CDCl_3$)



Thesis Overview



Summary

In chapter I, we have discussed the TM-catalyzed weak-chelation assisted regioselective C-H functionalization/annulation reactions. A variety of weakly coordinating functional groups have been employed as DGs for constructing C-C bonds. The procedures utilizing different TM-catalysts showed good selectivity and functional group compatibility. However, continued research interest in this area is expected to address the remaining research gaps and pave the way for new innovations.

In chapter II, a weak carbonyl coordination guided Rh(III)-catalyzed C4-selective alkylation of indole with cyclopropanols was achieved *via* cascade C-H and C-C bond activation. The method was extended to heteroaromatics *viz.* benzo[*b*]thiophene, tetrahydroisoquinoline and indoline. The elegant aspects of our findings comprise of regioselectivity, merging C-H/C-C activation, late-stage natural products and drug modifications with broad substrate scope.

In chapter III, we have demonstrated a biorelevant weak chelating intrinsic DG assisted arene C-H alkenylation under Ru(II)-catalysis using versatile cyclopropanols as coupling partner. The biologically potent β- and, γ-lactams, ε-caprolactam, isoindolinone, morpholinone and pyridones served as DGs. Site-selectivity, functional group tolerance, mechanistic underpinnings and late-stage drug modifications are the significant practical findings.

In chapter IV, a Ru(II)-catalyzed 2-fold C-H coupling/annulation of aryl/vinyl phosphonic acid monoesters with benzothiophenes has been described to afford benzothiophene fused phosphaisocoumarins. The potential of the procedure has been showcased *via* one-step heteroarylation followed by annulation with site-selectivity, functional group compatibility and post-synthetic transformations.

Future directions: Despite the considerable progress in weak-chelation assisted C-H functionalization and annulation reactions, several challenges and opportunities remain for future exploration. The development of methodologies that proceed under milder conditions, such as, at ambient temperature and in aqueous or solvent-free environments to reduce energy consumption and avoid hazardous solvents. Integration with enabling technologies such as flow chemistry, electrosynthesis, or photocatalysis could enhance the sustainability and efficiency of these processes.

List of Publications

1. Basak, S.; **Paul, T.**; Punniyamurthy, T. Palladium-Catalyzed 2-fold C-H Activation/C-C Coupling for C4-Arylation of Indoles Using Weak Chelation. *Org. Lett.* **2022**, *24*, 554.

2. **Paul, T.**; Basak, S.; Punniyamurthy, T. Weak Chelation-Assisted C4-Selective Alkylation of Indoles with Cyclopropanols *via* Sequential C-H/C-C Bond Activation. *Org. Lett.* **2022**, *24*, 6000.

3. **Paul, T.**; Basak, S.; Nanjegowda, M. V.; Punniyamurthy, T. Biorelevant Weakly Coordinating Directing Group Assisted C-H Alkenylation with Cyclopropanols *via* Sequential C-H/C-C Activation. *Org. Lett.* **2023**, *25*, 8975.

4. Mandal, S.; **Paul, T.**; Karjee, P.; Barman, M.; Punniyamurthy, T. Site-Selective C8-Alkylation of Quinolines with Cyclopropanols: Merging C-H/C-C Bond Activation. *Org. Lett.* **2023**, *25*, 7805.

5. Basak, S.; **Paul, T.**; Punniyamurthy, T. A Redox-Neutral Weak Carbonyl Chelation Assisted C4-H Allylation of Indoles with Vinylcyclopropanes. *Chem. Commun.* **2023**, *59*, 11568.

6. Basak, S.; **Paul, T.**; Mandal, S.; Karjee, P.; Nanjegowda, M. V.; Punniyamurthy, T. Transition-Metal-Catalyzed Directed C8–H Carbon–Carbon Bond Formation in Quinolines and 1,2,3,4-Tetrahydroquinolines. *Synthesis*, **2023**, *55*, 3454.

7. Basak, S.; **Paul, T.**; Maharana, P. K.; Debnath, B.; Punniyamurthy, T. Transition-Metal-Catalyzed Directing-Group-Assisted C4-H Carbon–Carbon Bond Formation of Indole. *Synlett* **2023**, *34*, 759.

8. Nanjegowda, M. V.; Basak, S.; **Paul, T.**; Punniyamurthy, T. Palladium-Catalyzed Weak Chelation-Assisted Site-Selective C-H Arylation of N-Aryl Pyridones *via* 2-fold C-H Activation. *J. Org. Chem.* **2024**, *89*, 6564.

9. Sahoo, A.; **Paul, T.**; Basak, S.; Punniyamurthy, T. Palladium Catalyzed C(sp^3)-H Alkylation of 8-Methylquinolines with Aziridines: Access to Functionalized γ-Quinolinylpropylamines. *Chem. Commun.* **2024**, *60*, 14818.

10. Basak, S.; **Paul, T.**; Nanjegowda, M. V.; Punniyamurthy, T. Integrating C-H Activation/2-fold Annulation: A Modular Access to Heteroaryl-Tethered Oxazoloiso-quinolinones. *Chem. Commun.* **2025**, *61*, 1693.

11. Basak, S.; **Paul, T.**; Mandal, S.; Barman, M.; Nanjegowda, M. V.; Punniyamurthy, T. Transition-Metal-Catalyzed Auxiliary-Assisted C-H Functionalization Using Vinylcyclopropanes and Cyclopropanols. *Chem. Commun.* **2025**, *61*, 6055.

12. Nanjegowda, M. V.; Basak, S.; **Paul, T.**; Barman, M.; Punniyamurthy, T. Directed Cascade C-H Functionalization/2-Fold Annulation with Vinylcyclopropanes: Access to Tetrahydrobenzo[*g*]isochromen-10-ones. *Org. Lett.* **2025,** *27*, 5379.

13. **Paul, T.**; Basak, S.; Nanjegowda, M. V.; Punniyamurthy, T. Cascade heteroarylation/annulation of arylphosphonic acid monoesters with benzo-thiophenes: access to benzothieno-fused oxaphosphacycles. *Chem. Commun.* **2025**, DOI: 10.1039/D5CC02209F.

Conference Attended

Poster Presentation

1. **Tripti Paul**, Shubhajit Basak and Tharmalingam Punniyamurthy, "Weak Chelation-Assisted C4-Selective Alkylation of Indoles with Cyclopropanols via Sequential C−H/C−C Bond Activation" FICS-2022, Indian Institute of Technology Guwahati, Assam, 2nd - 4th Dec., 2022.

Oral Presentation

2. **Tripti Paul**, Shubhajit Basak and Tharmalingam Punniyamurthy, "Weak Chelation Assisted C4-Selective Alkylation of Indoles with Cyclopropanol *via* Sequential C-H Functionalization/C-C Bond Cleavage" Research and Industrial Conclave-2023, Indian Institute of Technology Guwahati, Assam, 14th - 16th May, 2023.

3. **Tripti Paul** and Tharmalingam Punniyamurthy, "Weak Chelation Assisted Distal C4-H Functionalization of Indoles" Organic Colloquium 2023, Indian Institute of Technology Guwahati, Assam, 4th Nov., 2023.