Studies Towards Auxiliary Assisted Positional-Selective C-H Functionalization: A Quest for C-C and C-N Bond Formation

A Thesis Submitted

in Partial Fulfilment of the Requirements

for the Degree of

DOCTOR OF PHILOSOPHY

by

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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
October 2019

Sourav Pradhan

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CERTIFICATE

This is to certify that Mr. Sourav Pradhan has been working under my supervision since July 2014. I am forwarding his thesis entitled "*Studies Towards Auxiliary Assisted Positional-Selective C-H Functionalization: A Quest for C-C and C-N Bond Formation*" being submitted for the Ph.D. degree of this institute. I certify that he has fulfilled all the requirements according to the rules of this institute, and regarding the investigations embodied in his thesis and this work has not been submitted elsewhere for a degree.

Guwahati
October 2019

Prof. Tharmalingam Punniyamurthy
Supervisor

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God bless you all!

Sourav Pradhan

List of Abbreviations

AQ	aminoquinoline
acac	acetylacetone
Å	angstrom (10^{-8} cm)
Bn	benzyl
Boc	*tert*-butoxycarbonyl
BQ	benzoquinone
Bz	benzoyl
Cp*	1,2,3,4,5-pentamethylcyclopentadiene
CCDC	Cambridge crystallographic data center
CCE	constant current
p-cymene	4-isopropyltoluene
DG	directing group
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DMSO	dimethylsulfoxide
DMF	*N*,*N*-dimethylformamide
dtbpy	4,4′-di-*tert*-butyl-2,2′-bipyridyl
EDG	electron donating group
eq	equation
equiv	equivalent
ESI	electrospray ionization
EWG	electron wthdrawing group
FT-IR	Fourier transform infrared spectroscopy
F-dppbz	1,2-bis[bis(4-fluorophenyl)phosphino]benzene
FG	functional group
HFIP	hexafluoroisopropanol
het	heterocyclic
HRMS	high-resolution mass spectrometry
Hz	hertz
LG	leaving group

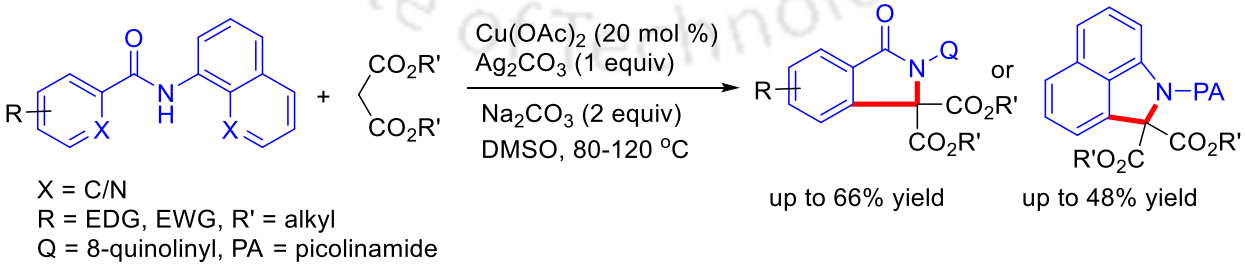
m/z	mass to charge ratio
mp	melting point
mA	milliampere
MesCOOH	2,4,6-trimethylbenzoic acid
MsOH	methanesulfonic acid
MHz	megahertz
NMR	nuclear magnetic resonance
NMP	*N*-methyl-2-pyrrolidone
NMO	*N*-methylmorpholine-N-oxide
NHPI	*N*-Hydroxyphthalimide
ORTEP	oak ridge thermal ellipsoid plot
PA	picolinamide
R_f	retardation factor
rt	room temperature
Piv	pivaloyl
py	pyridine
pym	pyrimidine
1, 10-Phen	1, 10-phenanthroline
PivOH	pivalic acid
Q	8-quinolinyl
SET	single-electron transfer
TBAI	tetrabutylammonium iodide
TFE	2,2,2-trifluoroethanol
TCE	2,2,2-trichloroethanol
Tf	trifluoromethanesulfonyl
TMEDA	tetramethylethylenediamine
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 a Cu(II)-catalyzed oxidative coupling of aromatic amides with malonates *via* C(sp^2)–H activation followed by an intramolecular oxidative N–C bond formation for the construction of isoindolinones and dihydrobenzoindoles. The second chapter deals with the picolinamide directed Cu(II)-mediated regioselective *N*-(hetero)arylation of indoles, pyrazoles and pyrrole *via* dehydrogenative cross-coupling. The third chapter demonstrates a Rh(III)-catalyzed weak-coordination facilitated C4-selective redox-neutral allylation of indoles expending Morita-Baylis-Hillman (MBH) adducts. The fourth chapter focuses on a Rh(III)-catalyzed switchable reactivity between C4-selective oxidative alkenylation and alkylation of indoles with allylic alcohols depending on the directing group and reaction conditions.

Chapter I. Cu(II)-Catalyzed Oxidative C-H/N-H Annulation of Benzamides with Dialkyl Malonates

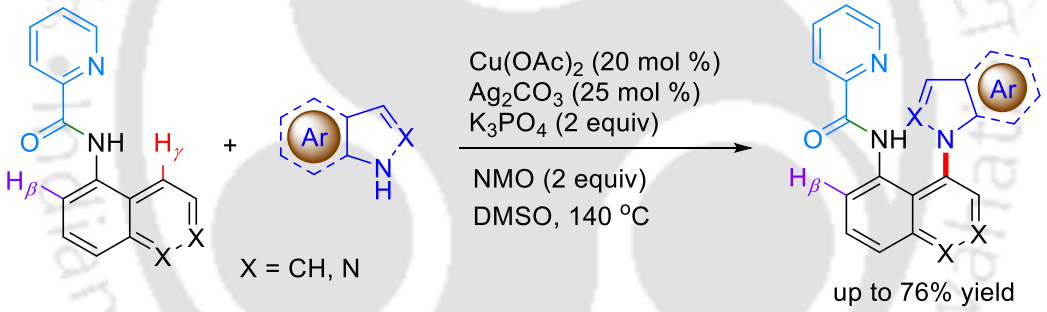
Over the past few decades, exploiting transition-metal-catalyzed C−H functionalization reactions, construction of C−C and C−heteroatom bonds is achieved considerably. In this context, enabling single catalytic system for two-fold oxidative C-C and C-N bond formation remains attractive for heterocycle synthesis. Isoindolinones and dihydrobenzoindoles are privileged building blocks and ubiquitous in natural products and pharmaceuticals. Construction of such heterocycles via oxidative C-C and C-N bond formation is thus desirable. The present chapter describes a copper(II)-catalyzed, direct two-fold C-C/C-N oxidative coupling of C(sp^2)-H bonds of aromatic amides with dialkyl malonates (Scheme 1). The reaction proceeds *via* an intramolecular oxidative C−N bond formation of the initially formed C-C coupling product.



Scheme 1. Cu(II)-Catalyzed C-H/N-H Annulation of Benzamides with Malonates

Chapter II. Cu(II)-Mediated *N*-Arylation of Azoles through Dehydrogenative Cross-Coupling

Transition-metal-catalyzed chelation guided direct C-H functionalization of pervasive C_{Ar}-H bond affords an elegant synthetic tool for the selective carbon-carbon and carbon-heteroatom bond formation in a step- and atom-economical manner. Among them, C-N bond formation remains striking as this motif, in specific *N*-arylated azoles are prevalent in plentiful compounds that are vital in biological, medicinal and material sciences. Exploiting the directed C-H functionalization for C-N bond formation, in this chapter, we have established an efficient copper-mediated regioselective C-H/N-H dehydrogenative cross-coupling of naphthylamides with indoles, pyrazoles and pyrrole using removable picolinamide as a directing group under aerobic conditions (Scheme 2). This reaction provides a prospective route for directly installing imperative heterocycles, such as, indoles, pyrazoles and pyrrole components into naphthyl scaffolds that are important in biological and medicinal sciences.



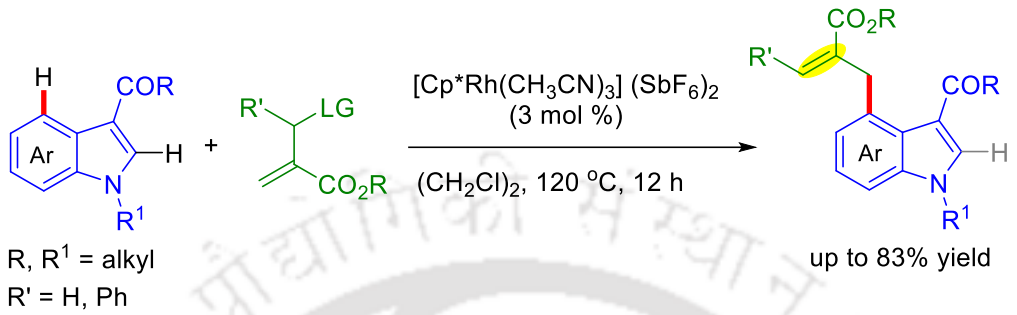
J. Org. Chem. **2017**, *82*, 4883.

Scheme 2. Cu(II)-Mediated Regioselective *N*-Arylation of Azoles

Chapter III. Rh(III)-Catalyzed C4-Selective Allylation of Indoles Exploiting MBH Adducts

Among many nitrogen-containing heterocyclic scaffolds, the indole nucleus is one of the most recurring subunit in natural products, and is the fourth-most prevalent heteroatomic motif in marketed pharmaceuticals. Thus, significant efforts have been made for the transition metal-catalyzed direct functionalization at the C2 and C3 positions due to its innate reactivity of the pyrrole type ring. In stark contrast, the site-selective functionalization of remote, less activated C–H bonds in the benzenoid core of indole derivatives continues to be challenging. Thus, selective C–H functionalization at the poor nucleophilic C4 position of the indole has been far less reported. This chapter demonstrates a weak coordination facilitated Rh(III)-catalyzed C4-selective redox-

neutral allylation of indoles with MBH acetates (Scheme 3). Indoles with versatile functional groups are well tolerated to give the target products in good yields and late-stage modification of the natural products has also been accomplished.

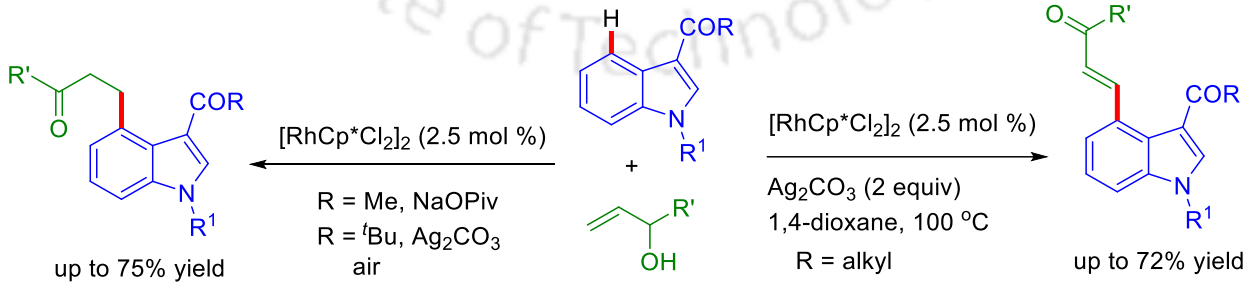


Org. Lett. **2019**, *21*, 9898.

Scheme 3. Rh(III)-Catalyzed C4-Allylation of Indoles with MBH Adducts

Chapter IV. Rh(III)-Catalyzed Switchable C4-Alkenylation and Alkylation of Indoles with Allylic Alcohols

Indoles and their synthetic analogues symbolize a pivotal class of heterocycles being featured in plentiful natural products and biologically active compounds and thus turn out to be one of the most extensively studied organic models. Due to the inherent reactivity of pyrrole type ring, functionalization at the C2 and C3 position of indoles are comparatively expedient than the benzenoid (C4 to C7) positions. In exploration of C4-selective modification of indoles, we have achieved switchable reactivity between C4-alkenylation vs C4-alkylation with allylic alcohols under a robust tunable Rh(III)-catalysis by varying the reaction conditions or directing groups (Scheme 4). Broad scope, functional group tolerance and late-stage drug modification are the important practical features.



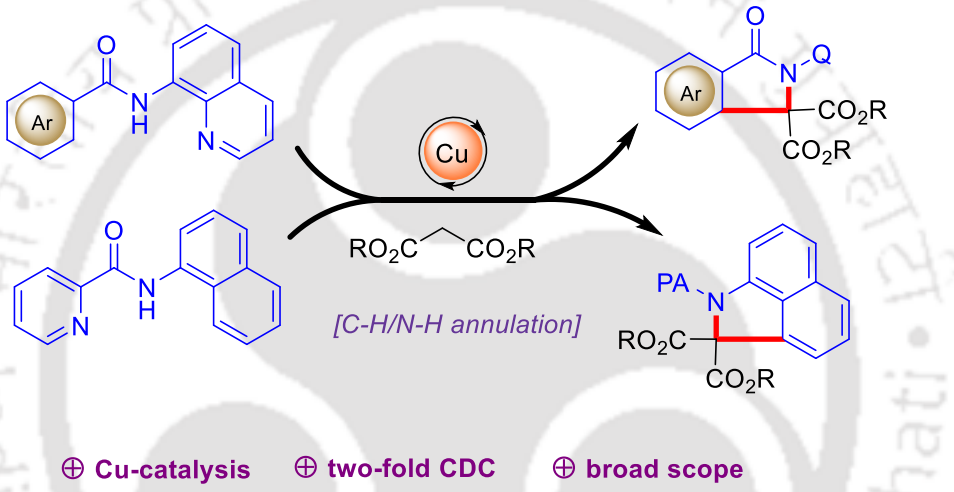
Org. Lett. **2020**, *22*, 1720.

Scheme 4. Rh(III)-Catalyzed C4-Alkenylation *vs* Alkylation of Indoles with Allylic Alcohols

Contents

Chapter I

Cu(II)-Catalyzed Oxidative C-H/N-H Annulation of Benzamides with Dialkyl Malonates



Cu(II)-Catalyzed Oxidative C-H/N-H Annulation of Benzamides with Dialkyl Malonates

C–H functionalization[1] surges an atom economical approach for streamlining the transformation of one of the most fundamental and ubiquitous linkages in organic substrates into a huge selection of functional groups. Achieving site selectivity in C–H functionalization is a vital challenge owing to the subtle reactivity differences of innumerable C–H bonds within a given molecule. Over the past few decades, exploiting transition-metal-catalyzed positional selective direct C−H functionalization[2] for the construction of C−C and C−heteroatom bonds have reached its pinnacle owing to the proximity-driven reactivity and selectivity that is aided by a chelating group. In this context, enabling single component catalytic system for two-fold oxidative C-C and C-heteroatom bond formation[3] remains as an attractive facet for heterocycle synthesis. Among the nitrogen containing heterocycles, isoindolinones are regarded as privileged building blocks and pervasive in natural products and pharmaceuticals (Figure 1).[4] Construction of such heterocycles *via* an oxidative C-C and C-N bond formation is thus desirable. On the other hand, the direct C-C coupling of C−H bonds with carbon centered nucleophiles compared to classical organometallic reagents, *via* redox catalysis thus far proven elusive. The difficulty associated with transfer of the nucleophilic carbon fragment *via* transmetalation or direct displacement to the organometallic intermediate, as well as the subsequent reductive elimination, has been realized as a challenging task. Despite a series of advancements in direct coupling of the arene C−H bonds with organometallic reagents,[5] the coupling of the same with C(sp^3)-H bonds of malonate nucleophile as well as C-H/N-H annulative cyclizations remained underdeveloped. Most of the reported annulations[6] are limited to the coupling of amides with alkynes or electron deficient olefins. Being a first-row transition-metal, Cu-catalyzed C−H functionalizations[7] have attracted considerable attention. This chapter describes a copper(II)-catalyzed, direct two-fold C-C/C-N oxidative coupling of C(sp^2)-H bond of benzamides with malonates employing 8-aminoquinoline as a bidentate directing group to afford isoindolinones. The reaction proceeds *via* an intramolecular oxidative C−N bond formation of the initially formed C-C coupling product. The scope was extended for the coupling of 1-naphthylamides[8] with malonates to give dihydrobenzoindoles.

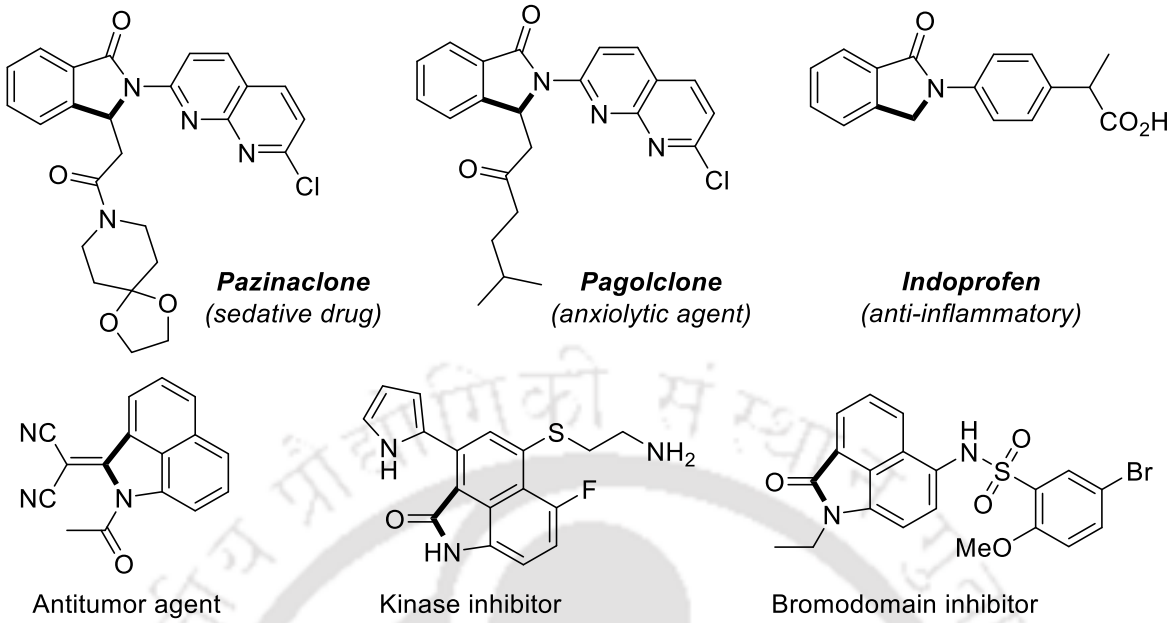
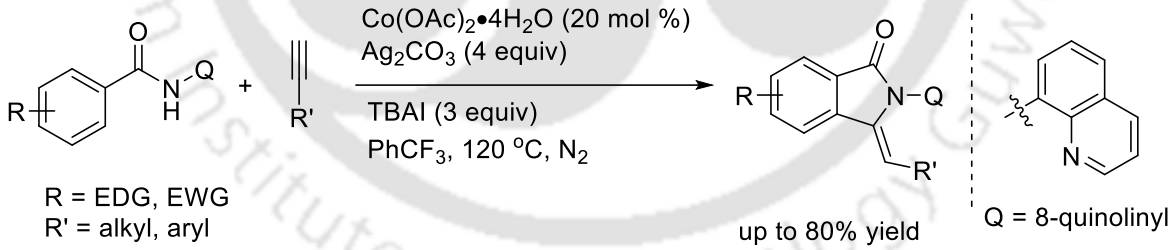


Figure 1. Biologically Active Isoindolinones and Dihydrobenzoindoles

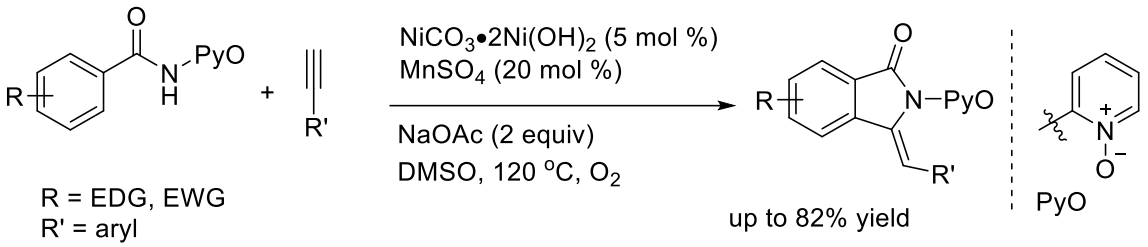
1.1 Metal-Catalyzed Annulation with Alkynes

Zhang and co-workers reported a Co-catalyzed oxidative annulation of terminal alkynes with aromatic amides using 8-aminoquinoline as a bidentate auxiliary using Ag_2CO_3 as a stoichiometric oxidant to access a variety of isoindolinones (Scheme 1).[9] The method was extended to aliphatic amides to afford pyrrolidinoes and tolerates a wide variety of functional groups.



Scheme 1. Co(II)-Catalyzed Oxidative Annulation of Benzamides

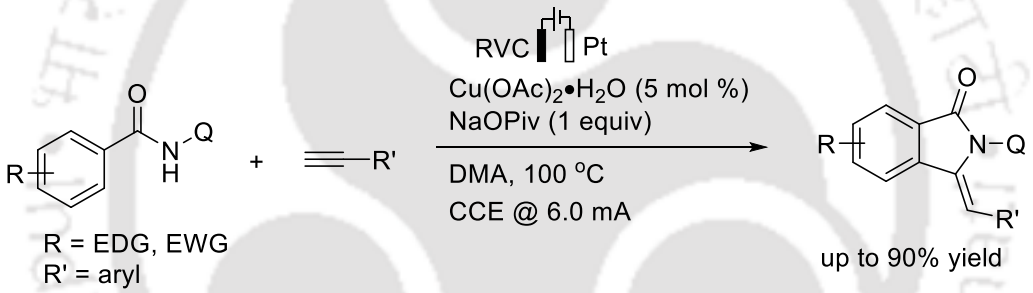
A Ni(II)-catalyzed removable *N,O*-bidentate directing group assisted alkynylation/annulation cascade *via* a double C–H cleavage was developed for the construction of 3-methyleneisoindolin-1-ones using O_2 as the external oxidant (Scheme 2).[10] This methodology is tolerated with a broad range of amide substrates and terminal alkynes.



Scheme 2. Ni(II)-Catalyzed C-C/C-N Annulation of Benzamides

1.2 Electro-Oxidative Annulation with Alkynes

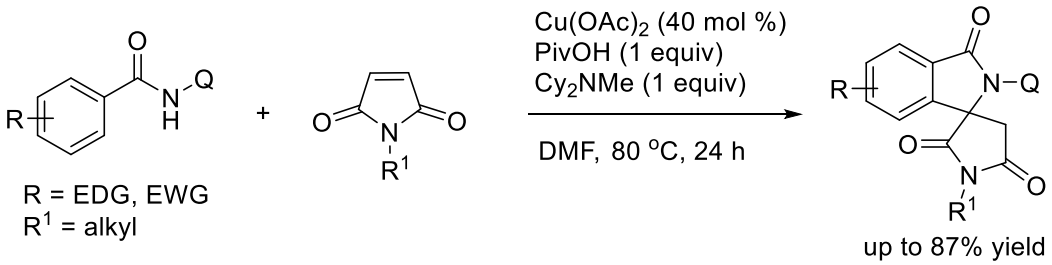
Biologically important isoindolones were synthesized by a cupraelectro-catalyzed C−H activation with electricity as a terminal oxidant (Scheme 3).[11] Thus, a versatile, inexpensive, and nontoxic $Cu(OAc)_2$ catalyst permitted widely applicable C−H/N−H functionalizations on electron-rich and electron-deficient aromatic amides with distinct functional group tolerance and resource-economy.



Scheme 3. Electrochemical Oxidative Annulation of Benzamides

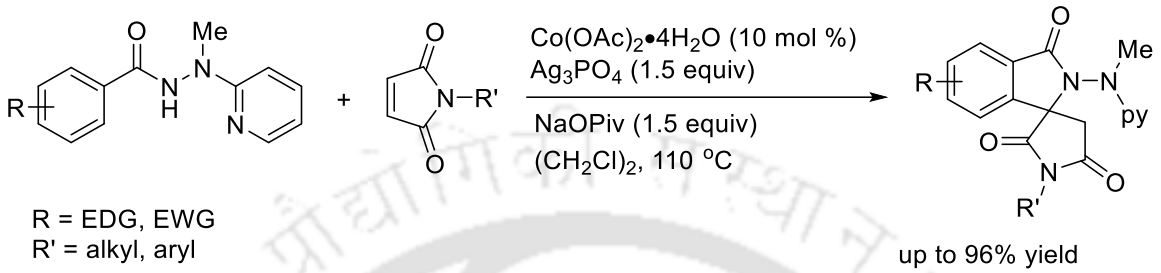
1.3 Metal-Catalyzed Annulation with Maleimides

A $Cu(OAc)_2$/Cy_2NMe-mediated direct oxidative coupling of benzamides with maleimides was reported to furnish the isoindolone-fused spirosuccinimides, which are of potent interest in medicinal chemistry (Scheme 4).[12] The reaction involves C(sp^2)–H alkenylation with the aid of 8-aminoquinoline directing group followed by an intramolecular aza-Michael-type addition.



Scheme 4. Cu(II)-Catalyzed Oxidative Coupling of Maleimides

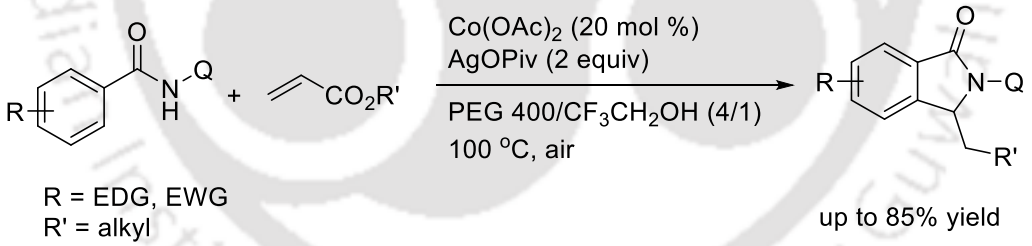
A Co(II)-catalyzed oxidative coupling of benzoic hydrazides with maleimides was accomplished utilizing 2-(1-methylhydrazinyl)pyridine as a bidentate directing group (Scheme 5).[13] This tandem C–H functionalization/spirocyclization reaction displays high efficiency and good functional group tolerance, and the ubiquitous spirosuccinimides were obtained with high regioselectivity.



Scheme 5. Annulative Coupling of Maleimides under Co(II)-Catalysis

1.4 Metal-Catalyzed Annulation with Alkenes

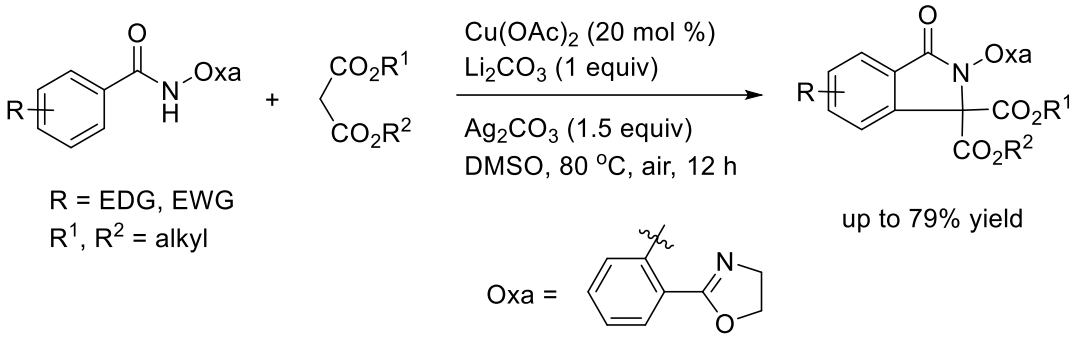
Ackerman and co-workers accomplished the synthesis of isoindolinones through a C−H/N−H functionalization process utilizing a Co(II)-based catalytic system (Scheme 6).[14] The carboxylate assisted oxidative annulation of benzamides occurred selectively with differently substituted electron-deficient alkenes.



Scheme 6. Co(II)-Catalyzed C-H/N-H Functionalization with Alkenes

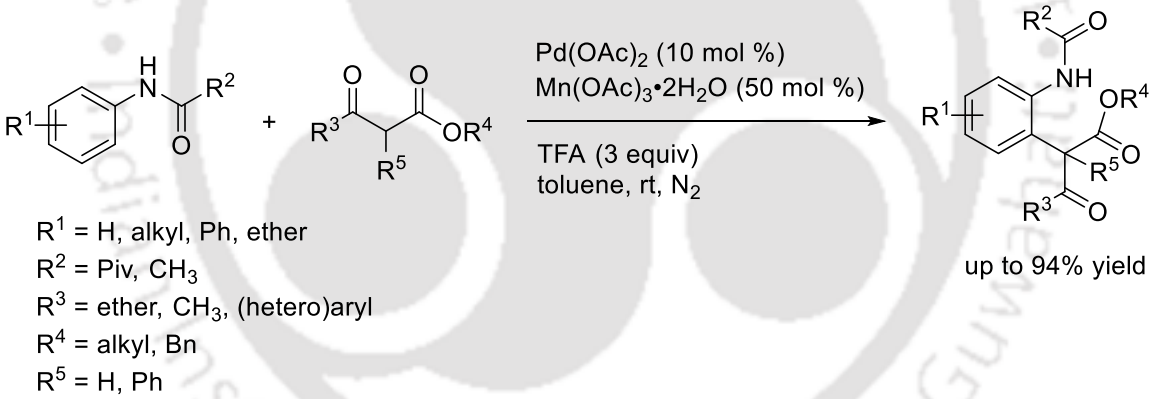
1.5 Metal-Catalyzed Alkylation/Annulation with C(sp^3)-H Bonds

Dai and Yu group reported a Cu(II)-catalyzed oxidative annulation of arenes with malonates using an amideoxazoline directing group (Scheme 7).[15] The reaction involves sequential C(sp^2)-H activation and malonate coupling, followed by an intramolecular oxidative N−C bond formation. Diversely substituted arenes and malonates are shown to be compatible with this cyclization.



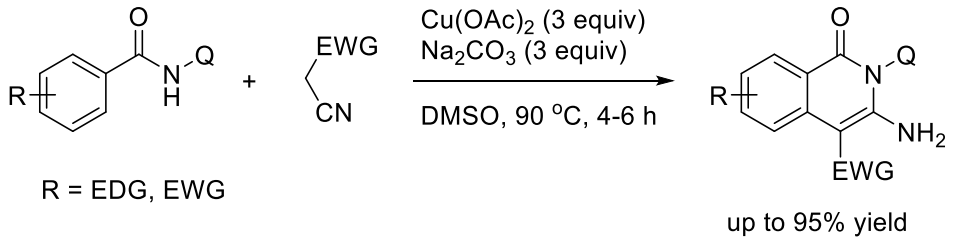
Scheme 7. Cu(II)-Catalyzed Oxidative Annulation with Malonates

A Pd(II)-catalyzed direct oxidative C(sp^2)–H/C(sp^3)–H coupling of anilides with β-keto esters has been developed using $Mn(OAc)_3 \cdot 2H_2O$ as the oxidant (Scheme 8).[16] The method offers facile access to α-aryl malonates with functional group diversity. The reaction pathway involving the coupling of a cyclopalladated complex with the enolate radical, generated from the 1,3-dicarbonyls was proposed.



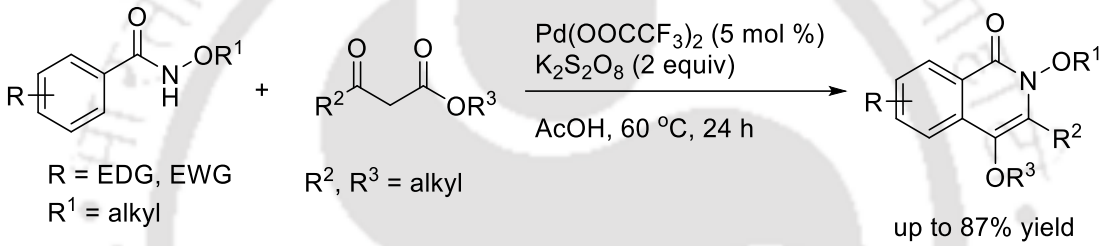
Scheme 8. Pd(II)-Catalyzed Coupling of β-Keto Esters with Anilides

Liu and co-workers disclosed a Cu(II)-mediated, dehydrogenative C–H(sp^2)/C–H(sp^3) coupling and intramolecular annulation of benzamides with ethyl cyanoacetate by the aid of 8-aminoquinoline moiety as a bidentate directing group (Scheme 9).[17] The strategy provides a straightforward route for the construction of privileged isoquinolinone scaffolds with wide generality and functional group tolerance.



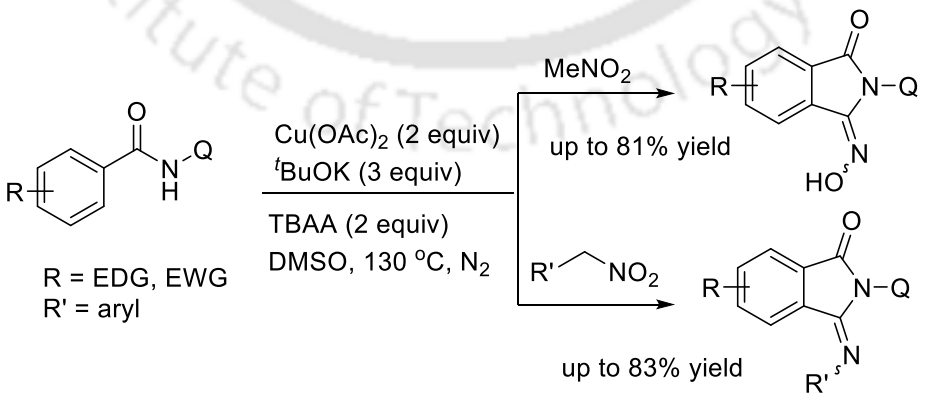
Scheme 9. Cu-Promoted Synthesis of Isoquinolinone

Huang and co-workers described a cascade dehydrogenative cross-coupling /annulation reaction of *N*-alkoxybenzamides with *β*-keto esters for the synthesis of isoquinolinone derivatives under Pd(II)-catalysis using $K_2S_2O_8$ as an oxidant (Scheme 10).[18] A plausible mechanism involving *ortho*-C(sp^2)–H activation followed by intramolecular condensation was proposed.



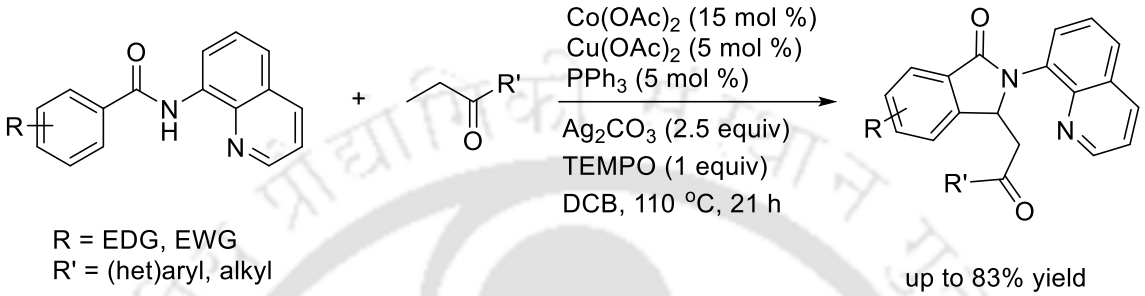
Scheme 10. Pd(II)-Catalyzed Dehydrogenative Coupling with *β*-Keto Esters

An efficient Cu-promoted annulation of benzamides with nitroalkanes was achieved to construct versatile isoindolinone derivatives by employing an 8-aminoquinoline directing group (Scheme 11).[19] The reaction was believed to go through sequential C–H activation, nitroalkylation followed by intramolecular cyclization.



Scheme 11. Cu-Promoted Annulation of Benzamides with Nitroalkanes

A Co(II)/Cu(II)-based dual metal-catalyzed oxidative C–H/N–H annulation of benzamides with substituted aliphatic ketones was developed utilizing 8-aminoquinoline moiety as the bidentate directing group (Scheme 12).[20] The tandem protocol displays broad functional group tolerance with aromatic amides as well as with ketones. Structurally diverse biologically important isoindolin-1-ones were synthesized by the reaction of substituted benzamides with ketones.

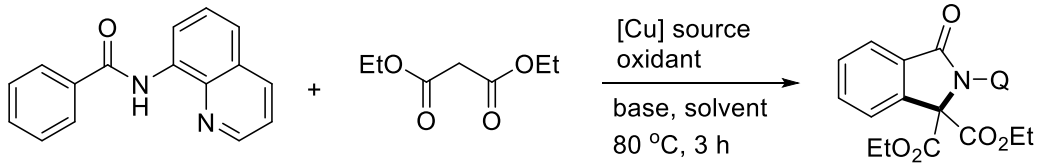


Scheme 12. Co(II)/Cu(II)-Catalyzed Oxidative Annulation with Ketones

1.6 Present Study

Herein, a Cu(II)-catalyzed oxidative C-C/C-N annulation of benzamides with dialkyl malonates is presented utilizing 8-aminoquinoline as a bidentate auxiliary for the construction of synthetically and medicinally valuable isoindolinones with broad scope and functional group diversity. At the outset, we conducted optimization studies by employing *N*-(quinolin-8-yl)benzamide **1a** and diethyl malonate **2a** as the test substrates for the desired annulation under varied Cu-sources, bases, oxidants and solvents (Table 1). Initial screening with the Cu-sources such as $CuCl_2$ and $CuBr_2$ failed to produce the target product (entries 1-2). Whereas, using 20 mol % $Cu(OAc)_2$, 2 equiv Na_2CO_3, 1 equiv Ag_2CO_3 in DMSO the formation of **3a** was achieved in 65% yield (entry 3). Using CuOAc as a catalyst **3a** was obtained in 16% yield (entry 4). Further screening of bases, such as K_2CO_3, Cs_2CO_3 and K_3PO_4 revealed Na_2CO_3 as the optimal base in providing best results (entries 5-7). Among the oxidants tested, Ag_2CO_3 was effective, whereas AgOAc, Ag_2O, NMO, NHPI and O_2 did not improve the yield (entries 8-12). DMSO was found to be the solvent of choice, whereas DMF, NMP and *m*-xylene afforded <10% yield (entries 13-15). A control experiment without $Cu(OAc)_2$ resulted in no product formation and the starting material **1a** was recovered (entry 16). This result explains the crucial role of $Cu(OAc)_2$ for two-fold oxidative annulation to realize the target products.

Table 1. Optimization of the Reaction Conditions[a]

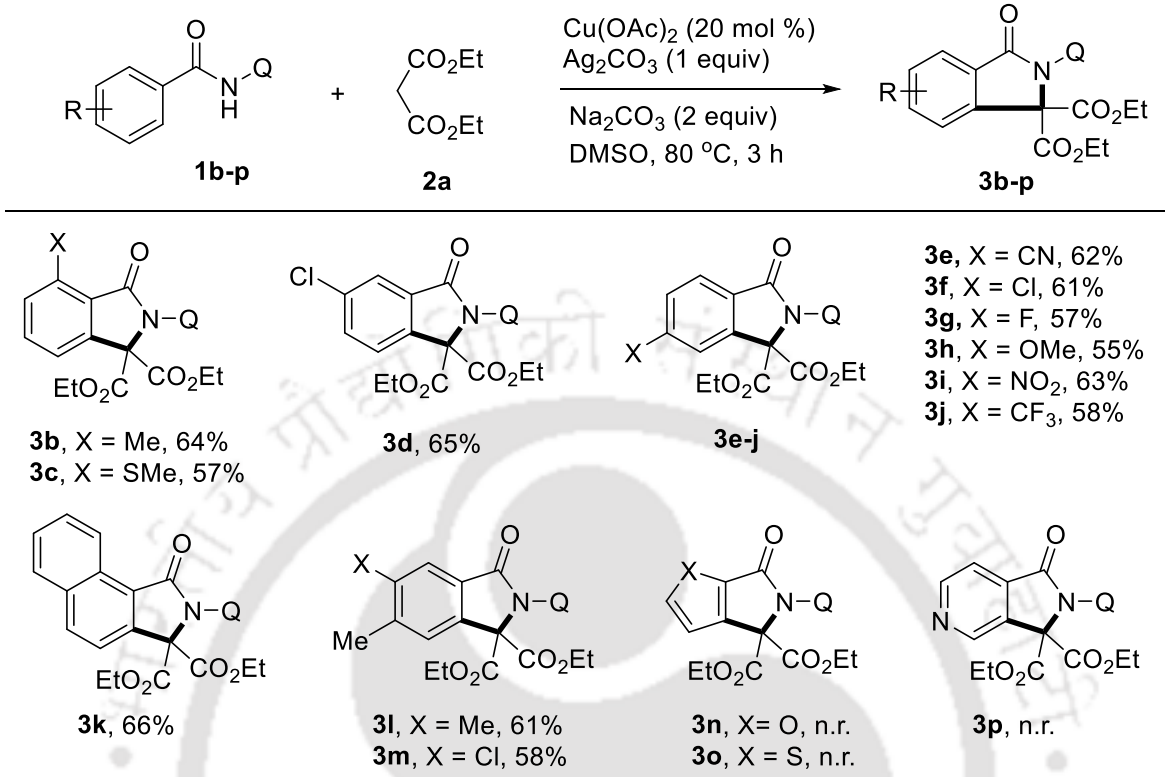


1a **2a** **3a**

Entry	[Cu] Source	Base	Oxidant	Solvent	Yield (%)[b]
1	$CuCl_2$	Na_2CO_3	Ag_2CO_3	DMSO	n.d.
2	$CuBr_2$	Na_2CO_3	Ag_2CO_3	DMSO	n.d.
3	**$Cu(OAc)_2$**	**Na_2CO_3**	**Ag_2CO_3**	**DMSO**	**65%**
4	CuOAc	Na_2CO_3	Ag_2CO_3	DMSO	16
5	$Cu(OAc)_2$	K_2CO_3	Ag_2CO_3	DMSO	31
6	$Cu(OAc)_2$	Cs_2CO_3	Ag_2CO_3	DMSO	n.d.
7	$Cu(OAc)_2$	K_3PO_4	Ag_2CO_3	DMSO	trace
8	$Cu(OAc)_2$	Na_2CO_3	AgOAc	DMSO	15
9	$Cu(OAc)_2$	Na_2CO_3	Ag_2O	DMSO	n.d.
10	$Cu(OAc)_2$	Na_2CO_3	NMO	DMSO	18
11	$Cu(OAc)_2$	Na_2CO_3	NHPI	DMSO	n.d.
12	$Cu(OAc)_2$	Na_2CO_3	O_2	DMSO	12
13	$Cu(OAc)_2$	Na_2CO_3	Ag_2CO_3	DMF	trace
14	$Cu(OAc)_2$	Na_2CO_3	Ag_2CO_3	NMP	n.d.
15	$Cu(OAc)_2$	Na_2CO_3	Ag_2CO_3	*m*-xylene	10
16	-	Na_2CO_3	Ag_2CO_3	DMSO	n.d.

[a]Reaction conditions: **1a** (0.1 mmol), **2a** (0.2 mmol), [Cu] (0.02 mmol), base (0.2 mmol), oxidant (0.1 mmol), solvent (2 mL), 80 °C, air, 3 h. [b]Isolated yield. n.d. = not detected.

Table 2. Substrate Scope of 8-Aminoqinolinamides[a,b]

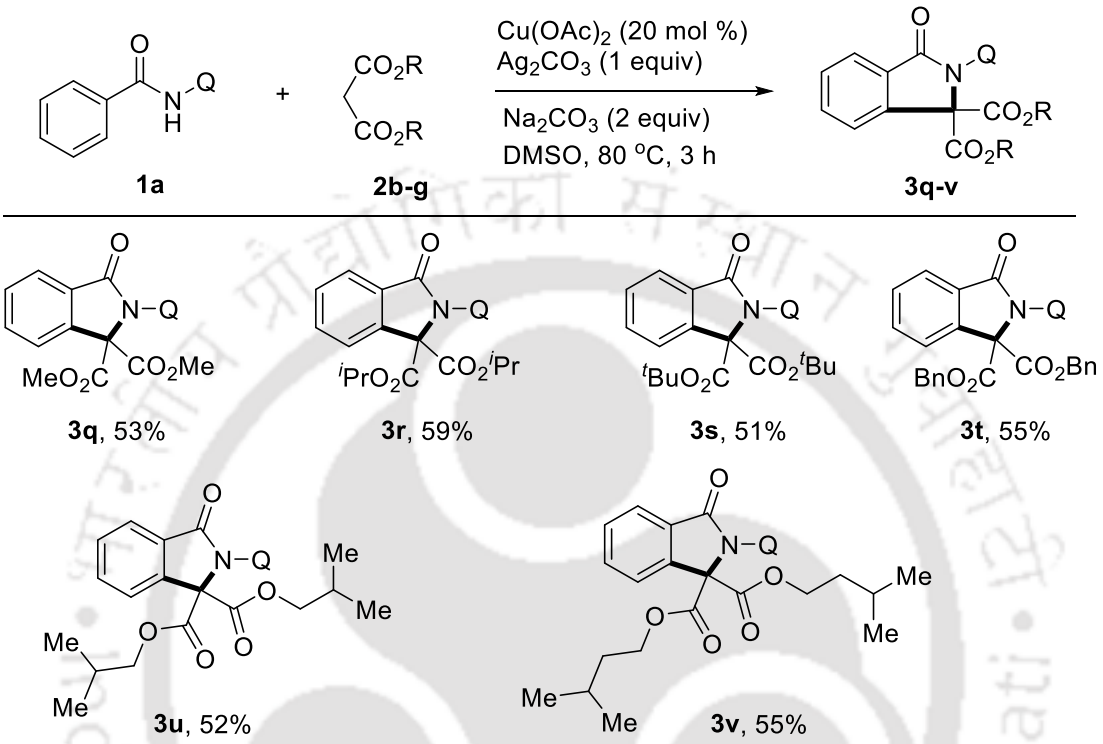


[a]Reaction conditions: **1b-p** (0.1 mmol), **2a** (0.2 mmol), $Cu(OAc)_2$ (0.02 mmol), Na_2CO_3 (0.2 mmol), Ag_2CO_3 (0.1 mmol), DMSO (2 mL), 80 °C, air, 3 h. [b]Isolated yield.

Having optimized the reaction conditions, the scope of the procedure was investigated using substituted benzamides **1b-p** with diethyl malonate **2a** as a standard substrate (Table 2). Thus, the reaction of *ortho*-substituted benzamides bearing methyl **1b** and thiomethyl **1c** groups afforded isoindolinones **3b** and **3c** in 64 and 57% yields, respectively. A 3-chloro derivative **1d** gave **3d** in 65% yield. Similar results were observed with benzamides bearing substitution at the *para*-position of the aryl ring with cyano **1e**, chloro **1f**, fluoro **1g** and methoxy **1h** groups, delivering **3e-h** in 55-62% yields. Notably, strong electron-withdrawing groups such as 4-nitro **1i** and 4-trifluoromethyl **1j** containing benzamide congeners were compatible, affording **3i** and **3j** in 63 and 58% yields, respectively. 1-Naphthyl carboxamide derivative **1k** selectively furnished **3k** in 66% yield. Notably, di-substituted benzamides **1l** and **1m** successfully delivered **3l** and **3m** in 61 and 58% yields, respectively. However, heterocyclic benzamides, such as 2-furanyl **1n**, 2-thienyl **1o** and 4-pyridyl **1p** derivatives failed to produce the coupling products and the starting materials were

recovered intact. The heteroatom poisoning effect is believed to hamper the coordination of the transition-metal for C-H activation.

Table 3. Substrate Scope of Alkyl Malonates[a,b]



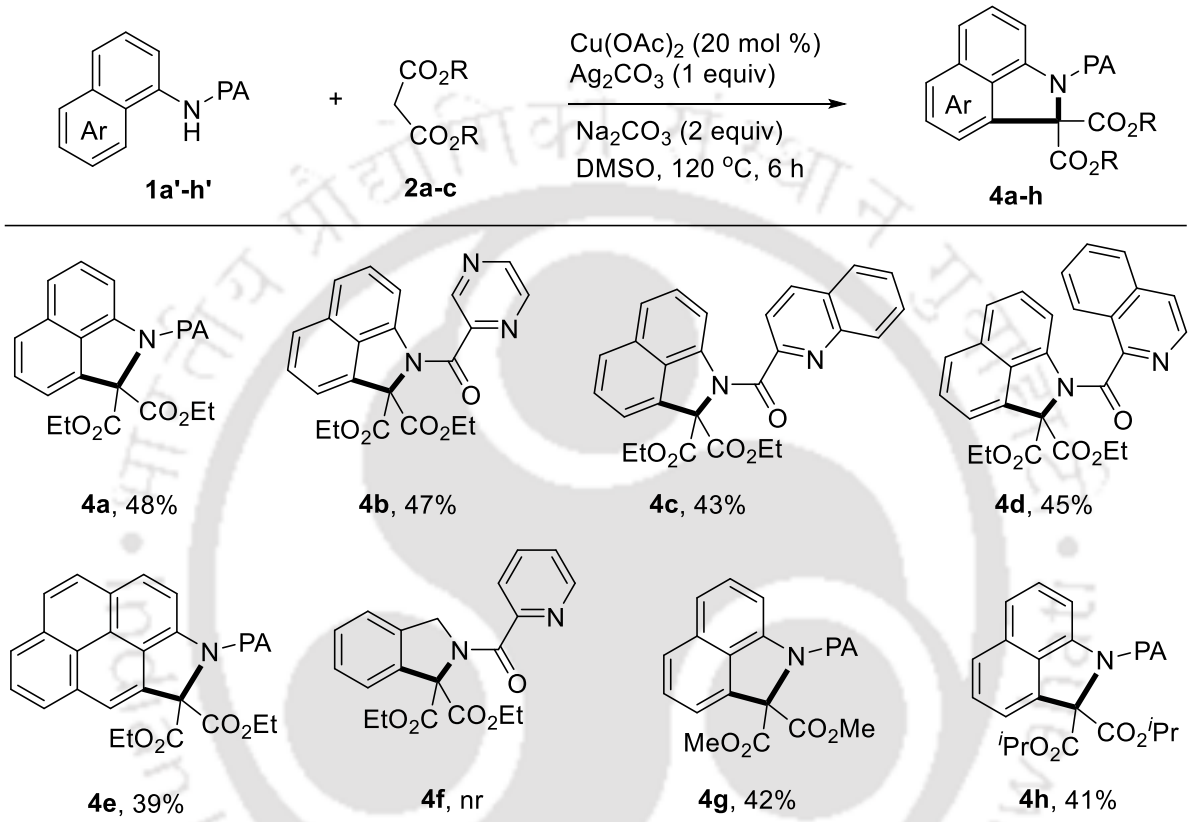
[a]Reaction conditions: **1a** (0.1 mmol), **2b-g** (0.2 mmol), $Cu(OAc)_2$ (0.02 mmol), Na_2CO_3 (0.2 mmol), Ag_2CO_3 (0.1 mmol), DMSO (2 mL), 80 °C, air, 3 h. [b]Isolated yield.

Next, the scope of the method was extended for the oxidative coupling of substituted dialkyl malonates **2b-g** with benzamide **1a** as the standard substrate (Table 3). Dialkyl malonates bearing methyl **2b**, isopropyl **2c**, *tert*-butyl **2d** and benzyl **2e** groups were coupled efficiently to furnish **3q-t** in 51-59% yields. Likewise, long chain alcohol derived alkyl malonates such as **2f** and **2g** were also proven amenable to the optimal conditions, delivering **3u** and **3v** in 52 and 55% yields, respectively.

With these exciting results, we inspected a series of 1-naphthylamides **1a′-h′** in the oxidative annulation with malonates to synthesize biologically important dihydrobenzoindoles (Table 4). Gratifyingly, at an elevated temperature the coupling of **1a′** and **2a** proceeded to give **4a** in 48% yield. Similarly, naphthylamides **1b′-d′** having analogous directing groups as that of **1a′** was found compatible and afforded **4b-d** in 43-47% yields. 1-Aminopyrene derivative **1e′** gave **4e** in 39%

yield. A benzyl amine derivative **1f′** was unsuccessful in the coupling, due to the flexible nature of amine. The oxidative coupling of malonates **2b** and **2c** independently with **1a′** delivered **4g** and **4h** in 42 and 41% yields, respectively.

Table 4. Substrate Scope for Coupling of 1-Naphthylamides with Malonates[a,b]

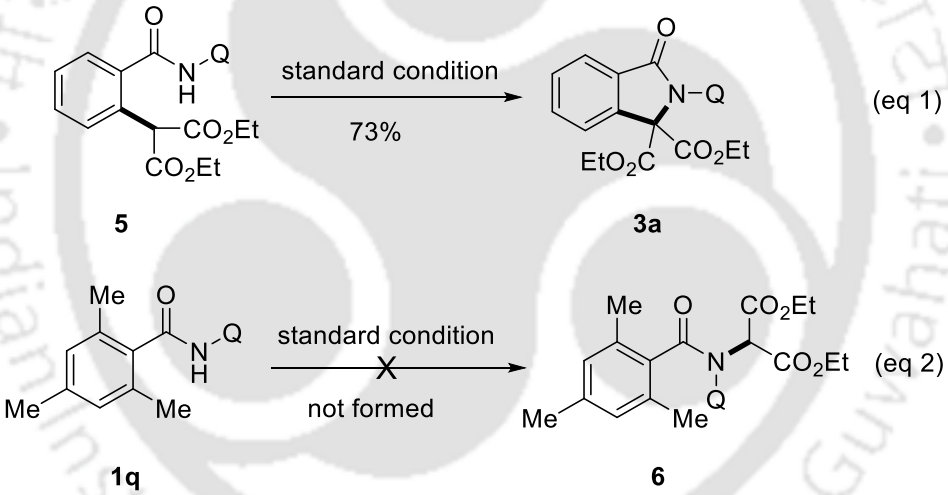


[a]Reaction conditions: **1a′-h′** (0.1 mmol), **2a-c** (0.2 mmol), $Cu(OAc)_2$ (0.02 mmol), Na_2CO_3 (0.2 mmol), Ag_2CO_3 (0.1 mmol), DMSO (2 mL), 120 °C, air, 6 h. [b]Isolated yield. PA = picolinamide.

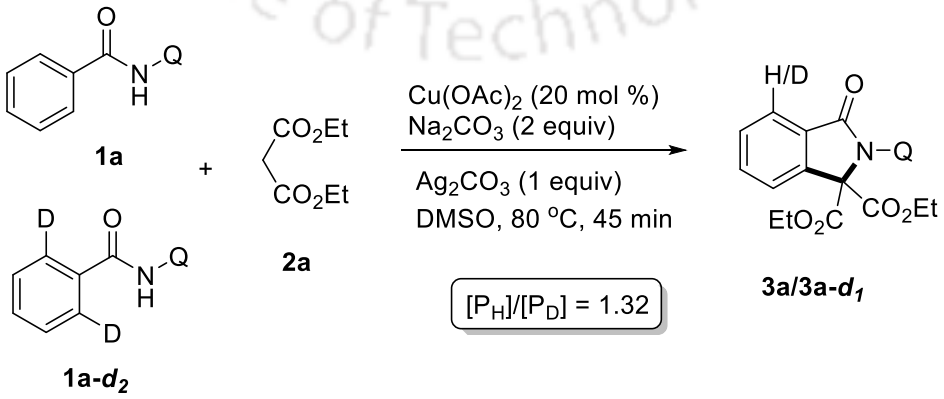
To shed light into the reaction pathway, the reaction of benzamides **5** and **1q** were conducted under standard conditions (Scheme 13). It was observed that the benzamide **5** successfully converted to the target product **3a** in 73% yield (eq 1), whereas the *ortho*-protected benzamide **1q** failed to deliver the N−C coupled intermediate **6** and was recovered in 93% yield (eq 2). These results indicate that this oxidative cyclization initially underwent through a direct oxidative C(sp^2)-H/C(sp^3)-H cross-coupling followed by an intramolecular N−H/C(sp^3)-H dehydrogenative cross-coupling to furnish the target heterocyclic scaffold. Further, the kinetic isotope effect (KIE)

experiment with **1a** and **1a-*d*$_2$** under standard conditions resulted a $[P_H]/[P_D]$ = 1.32 (Scheme 14). This result suggests that C−H bond cleavage might not be involved in the rate-limiting step.[7a]

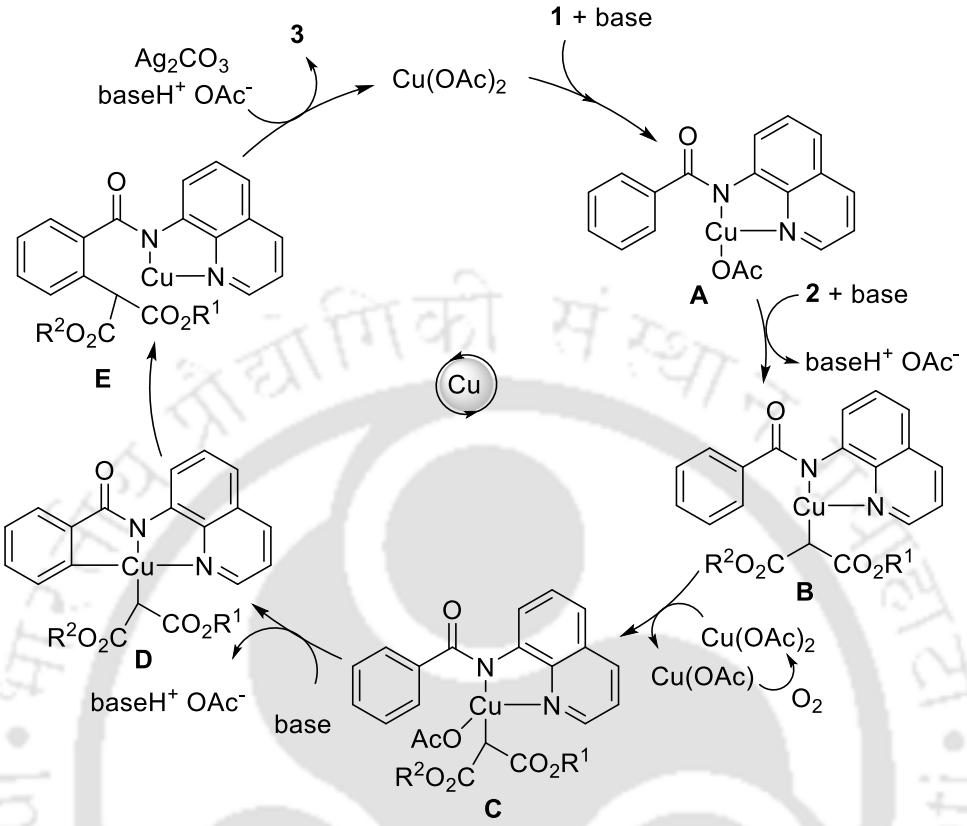
Based on preliminary mechanistic investigation and literature,[7] a plausible catalytic cycle is depicted in Scheme 14. Initial *N*-cupration of the substrate **1** with $Cu(OAc)_2$ in the presence of a base may give **A**, which may undergo substitution with malonate nucleophile to give the copper(II) intermediate **B** (Scheme 15). The latter may undergo the Cu-assisted oxidation to produce a copper(III) intermediate **C**, which can lead to *ortho*-C(sp^2)-H cupration of benzamide to deliver an organocopper(III) intermediate **D**.[7] Reductive elimination of **D** can give **E**, which further undergoes an intramolecular base mediated N−H/C(sp^3)-H dehydrogenative cross-coupling to give the target product **3**. The imminent Cu-species oxidized[7] to copper(II) with the help of Ag_2CO_3 to complete the catalytic cycle. The proposed reaction pathway also explains the requirement of excess base and oxidant to realize the product formation in good yields.



Scheme 13. Preliminary Mechanistic Investigations

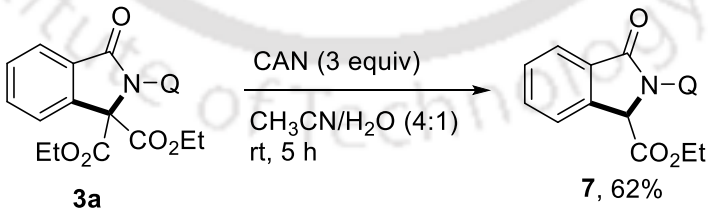


Scheme 14. Kinetic Isotope Experiment



Scheme 15. Proposed Catalytic Cycle

To demonstrate the synthetic utility of the method, the product **3a** was converted to an isoindolinone carboxylate **7** in 62% yield *via* ceric ammonium nitrate (CAN) promoted Krapcho-type decarboxylation (Scheme 16).



Scheme 16. Synthetic Utility

In summary, we have developed a Cu-catalyzed oxidative coupling of aromatic amides with dialkyl malonates to construct synthetically valuable isoindolinones and dihydrobenzoindoles. The reaction proceeds through direct oxidative C(sp^2)-H/C(sp^3)-H cross-coupling followed by an

intramolecular N−H/C(sp^3)-H dehydrogenative cross-coupling to furnish the target heterocyclic scaffolds. Good substrate scope, functional group compatibility, and aerobic conditions are the important practical features.

1.7 Experimental Section

General Information. $Cu(OAc)_2$ (98%), CuOAc (97%), AgOAc (99%), NMO (97%) and Ag_2CO_3 (98%) were purchased from Aldrich and used as received. All the solvents were dried prior to use according to the standard procedure. Merck silica gel G/GF254 plates were utilized for analytical thin-layer chromatography (TLC). Rankem silica gel (60−120 mesh) was employed for column chromatography. Bruker Avance III 600 and 400 MHz spectrometers were used for recording NMR (^1H and ^{13}C) spectra utilizing $CDCl_3$ 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 other data are reported as follows: s = singlet, d = doublet, t = triplet, m = multiplet, q = quartet and br s = broad singlet. Melting points were determined using a Büchi B-540 apparatus and are uncorrected. IR spectra were collected on a PerkinElmer Fourier transform infrared (FT-IR) spectrometer. Quadrupole time-of-flight electrospray ionization (ESI) mass spectrometry instrument (model HAB 273) was used for mass spectra.

General Procedure for the Preparation of Amide Directing Groups. To a stirred solution of amine (2 mmol) and Et_3N (2.4 mmol) in CH_2Cl_2 (10 mL) at 0 °C was added acid chloride (2 mmol) in CH_2Cl_2 (5 mL) dropwise. The mixture was allowed to warm up to room temperature, and the stirring was continued for 10-12 h. The progress of the reaction was monitored by TLC using ethyl acetate and hexane as an eluent. After completion, the reaction mixture was diluted with CH_2Cl_2 (30 mL) and washed with brine (2 x 10 mL) and water (10 mL). Drying (Na_2SO_4) and evaporation of the solvent gave a residue that was purified on a silica gel column chromatography using ethyl acetate and hexane as an eluent.

Procedure for Cu(II)-Catalyzed Coupling of Benzamides with Malonates. A mixture of quinolinamide **1** (0.1 mmol), malonate **2** (0.2 mmol), $Cu(OAc)_2$ (3.6 mg, 0.02 mmol), Ag_2CO_3 (27.6 mg, 0.1 mmol) and Na_2CO_3 (21.2 mg, 0.2 mmol) in DMSO (2 mL) were stirred at 80 ^oC in a preheated oil bath for 3 h under air. The progress of the reaction was monitored by TLC using hexane and ethyl acetate as an eluent. Upon completion, the reaction mixture was cooled to room temperature, diluted with ethyl acetate (10 mL), washed with aq. NH_3 (10 mL) and brine (2 x 5

mL). The aqueous phase was extracted with ethyl acetate (3 x 10 mL). Drying (Na_2SO_4) and evaporation of the solvent gave a residue that was purified by a silica gel column chromatography using ethyl acetate/hexane as the eluent to afford the product **3**.

Procedure for Cu(II)-Catalyzed Coupling of 1-Naphthylamides with Malonates. A mixture of 1-naphthylamide **1′** (0.1 mmol), malonate **2** (0.2 mmol), $Cu(OAc)_2$ (3.6 mg, 0.02 mmol), Ag_2CO_3 (27.6 mg, 0.1 mmol) and Na_2CO_3 (21.2 mg, 0.2 mmol) in DMSO (2 mL) were stirred at 120 ^oC in a preheated oil bath for 6 h under air. Then, the above described work-up procedure was followed. Purification by a silica gel column chromatography using ethyl acetate/hexane as the eluent afforded the target product **4**.

Preparation of Diethyl 2-(2-(quinolin-8-ylcarbamoyl)phenyl)malonate 5. A Schlenk tube was charged with 2-bromo-*N*-(quinolin-8-yl)benzamide (65.4 mg, 0.2 mmol), CuI (8 mg, 0.04 mmol), L-proline (10 mg, 0.08 mmol) and cesium carbonate (26 mg, 0.08 mmol) under argon. Diethyl malonate (38.4 mg, 0.24 mmol) and DMSO (1.0 mL) were then added. The reaction mixture was stirred at 50 ^oC in a preheated oil bath for 24 h. The mixture was cooled, diluted with ethyl acetate (10 mL), washed with brine (10 mL) and extracted using ethyl acetate (2 x 10 mL). Drying (Na_2SO_4) and evaporation of the solvent gave a residue that was purified by a silica gel column chromatography using ethyl acetate/hexane as the eluent to afford **5** in 15% yield (12 mg).

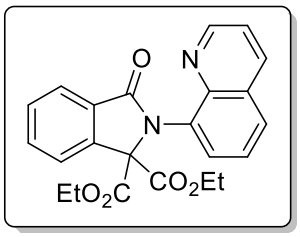
Preparation of *N*-(Quinolin-8-yl)benzamide-2,6-d_2 (1a-d_2).[21] The titled compound was prepared according to the reported procedure:[1] 1:9 ethyl acetate/hexane; R_f = 0.40; white solid; yield 82%. The deuterium incorporation was found to be 77% as estimated by ^1H NMR analysis.

Intermolecular Kinetic Isotope Effect Study. Diethyl malonate (0.2 mmol, 32 mg) was allowed to react with a mixture of *N*-(quinolin-8-yl)benzamide **1a** (0.1 mmol, 24.8 mg) and *N*-(quinolin-8-yl)benzamide-2,6-d_2 **1a-*d*$_2$** (0.1 mmol, 25 mg) under standard reaction conditions for 45 min. Then, the standard work-up procedure was followed. Purification by a silica gel column chromatography using ethyl acetate/hexane as the eluent afforded a mixture of **3a** and **3a-*d*$_1$** as a colorless solid in 17% yield. The $[P_H]/[P_D]$ was determined using 400 MHz ^1H NMR as 1.32.

Synthesis of Ethyl 3-oxo-2-(quinolin-8-yl)isoindoline-1-carboxylate 7. To a stirred a solution of **3a** (0.05 mmol, 20.2 mg) in MeCN/H_2O (4/1, v/v, 3 mL), ceric ammonium nitrate (0.15 mmol, 82.2 mg) was added and the mixture was stirred at room temperature for 5 h. The reaction mixture

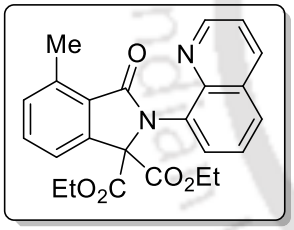
was diluted with water (5 mL) and extracted using ethyl acetate (10 mL). Drying (Na_2SO_4) and evaporation of the solvent gave a residue that was purified by a silica gel column chromatography using ethyl acetate/hexane as the eluent to afford **7** in 62% yield (10.3 mg).

Diethyl 3-oxo-2-(quinolin-8-yl)isoindoline-1,1-dicarboxylate 3a. Analytical TLC on silica gel,



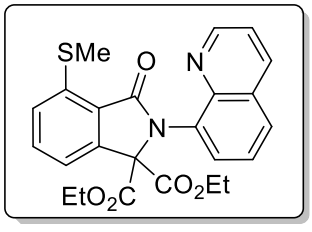
1:2 ethyl acetate/hexane R_f = 0.41; colorless solid; mp 155-156 °C; yield 65% (26 mg); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.74 (dd, *J* = 4.2, 1.8 Hz, 1H), 8.26 (dd, *J* = 7.4, 1.2 Hz, 1H), 8.17 (dd, *J* = 8.3, 1.6 Hz, 1H), 7.97 (d, *J* = 7.3 Hz, 1H), 7.88 (dd, *J* = 8.3, 1.2 Hz, 1H), 7.79 (d, *J* = 7.5 Hz, 1H), 7.71-7.58 (m, 3H), 7.37-7.33 (m, 1H), 4.07-3.96 (m, 2H), 3.87-3.76 (m, 2H), 0.87 (t, *J* = 7.1 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.4, 166.0, 150.2, 146.0, 140.4, 136.2, 134.9, 132.5, 131.6, 131.3, 130.0, 128.9, 128.8, 126.6, 124.8, 124.6, 121.4, 77.3, 62.5, 13.5; FT-IR (KBr) 2925, 2853, 1745, 1713, 1400 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{23}H_{21}N_2O_5$: 405.1455, found 405.1452.

Diethyl 4-methyl-3-oxo-2-(quinolin-8-yl)isoindoline-1,1-dicarboxylate 3b. Analytical TLC on



silica gel, 1:2 ethyl acetate/hexane R_f = 0.42; colorless solid; mp 148-149°C; yield 64% (26.7 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.77 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.25 (dd, *J* = 7.4, 1.4 Hz, 1H), 8.17 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.88 (dd, *J* = 8.3, 1.4 Hz, 1H), 7.65-7.60 (m, 2H), 7.54 (t, *J* = 7.7 Hz, 1H), 7.36-7.34 (m, 2H), 4.05-4.00 (m, 2H), 3.84-3.79 (m, 2H), 2.74 (s, 3H), 0.88 (t, *J* = 7.2 Hz, 6H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 170.1, 166.2, 150.3, 146.2, 140.6, 138.6, 136.1, 134.8, 132.1, 131.9, 131.8, 128.9, 128.8, 128.1, 126.5, 122.2, 121.4, 76.0, 62.4, 17.3, 13.5; FT-IR (KBr) 2996, 2953, 1771, 1744, 1709, 1472, 1397 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{24}H_{23}N_2O_5$: 419.1601, found 419.1609.

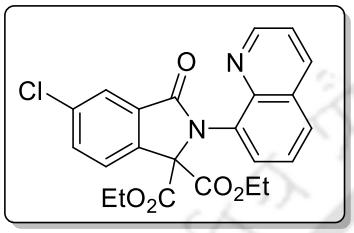
Diethyl 4-(methylthio)-3-oxo-2-(quinolin-8-yl)isoindoline-1,1-dicarboxylate 3c. Analytical



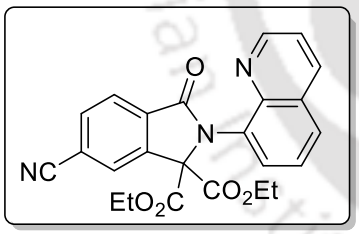
TLC on silica gel, 1:2 ethyl acetate/hexane R_f = 0.41; colorless liquid; yield 57% (25.6 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.74 (dd, *J* = 4.1, 1.6 Hz, 1H), 8.26 (dd, *J* = 7.4, 1.3 Hz, 1H), 8.15 (dd, *J* = 8.3, 1.6 Hz, 1H), 7.86 (dd, *J* = 8.3, 1.2 Hz, 1H), 7.64-7.56 (m, 2H), 7.52-7.50 (m,

1H), 7.35-7.31 (m, 2H), 4.06-3.98 (m, 2H), 3.87-3.79 (m, 2H), 2.52 (s, 3H), 0.88 (t, *J* = 7.1 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.1, 166.0, 150.1, 146.0, 141.4, 140.3, 136.1, 134.8, 132.5, 131.5, 130.4, 128.9, 128.6, 126.5, 124.6, 121.3, 120.0, 76.8, 62.4, 14.2, 13.5; FT-IR (neat) 2926, 2853, 1760, 1744, 1701, 1473, 1399 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{24}H_{23}N_2O_5S$: 451.1322, found 451.1340.

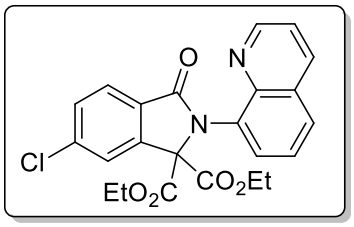
Diethyl 5-chloro-3-oxo-2-(quinolin-8-yl)isoindoline-1,1-dicarboxylate 3d. Analytical TLC on silica gel, 1:2 ethyl acetate/hexane R_f = 0.40; light yellow solid; mp 140-141°C; yield 65% (28.4 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.74 (dd, *J* = 4.1, 1.7 Hz, 1H), 8.24 (dd, *J* = 7.4, 1.3 Hz, 1H), 8.18 (dd, *J* = 8.3, 1.6 Hz, 1H), 7.94-7.88 (m, 2H), 7.74 (d, *J* = 8.2 Hz, 1H), 7.66-7.62 (m, 2H), 7.37 (dd, *J* = 8.3, 4.2 Hz, 1H), 4.07-3.99 (m, 2H), 3.87-3.79 (m, 2H), 0.89 (t, *J* = 7.1 Hz, 6H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 168.0, 165.4, 150.2, 145.7, 138.3, 136.4, 136.1, 134.3, 132.9, 132.6, 131.5, 128.9, 128.8, 126.4, 126.1, 124.5, 121.4, 76.3, 62.6, 13.4; FT-IR (KBr) 2931, 2851, 1749, 1716, 1400, 1310 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{23}H_{20}ClN_2O_5$ 439.1055, found 439.1053.



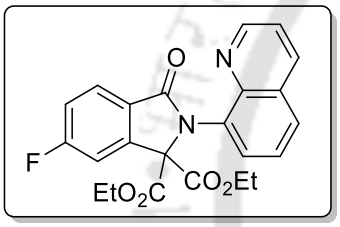
Diethyl 6-cyano-3-oxo-2-(quinolin-8-yl)isoindoline-1,1-dicarboxylate 3e. Analytical TLC on silica gel, 1:2 ethyl acetate/hexane R_f = 0.39; light yellow solid; mp 190-191 °C; yield 62% (26.5 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.73 (dd, *J* = 4.1, 1.6 Hz, 1H), 8.25 (dd, *J* = 7.4, 1.2 Hz, 1H), 8.20 (dd, *J* = 8.3, 1.6 Hz, 1H), 8.11 (s, 1H), 8.07 (d, *J* = 7.8 Hz, 1H), 7.92-7.90 (m, 2H), 7.67-7.64 (m, 1H), 7.39-7.37 (m, 1H), 4.07-4.02 (m, 2H), 3.89-3.84 (m, 2H), 0.91 (t, *J* = 7.1 Hz, 6H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 167.5, 165.0, 150.5, 145.7, 140.8, 136.3, 135.0, 133.9, 133.9, 131.7, 129.3, 129.1, 128.9, 126.6, 125.4, 121.6, 118.1, 116.1, 76.4, 63.1, 13.5; FT-IR (KBr) 2233, 1746, 1723, 1473, 1400, 1246 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{24}H_{20}N_3O_5$ 430.1397, found 430.1397.



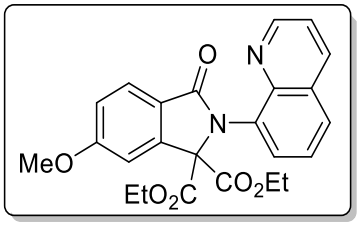
Diethyl 6-chloro-3-oxo-2-(quinolin-8-yl)isoindoline-1,1-dicarboxylate 3f. Analytical TLC on silica gel, 1:2 ethyl acetate/hexane R_f = 0.41; light yellow solid; mp 160-161°C; yield 61% (26.7 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.75 (dd, *J* = 4.1, 1.6 Hz, 1H), 8.24 (dd, *J* = 7.4, 1.2 Hz, 1H), 8.18 (dd, *J* = 8.3, 1.5 Hz, 1H), 7.90-7.89 (m, 2H), 7.79 (d, *J* = 1.4 Hz, 1H), 7.66-7.63 (m, 1H), 7.60 (dd, *J* = 8.1, 1.8 Hz, 1H), 7.38-7.36 (m, 1H), 4.06-4.01 (m, 2H), 3.87-3.81 (m, 2H), 0.89 (t, *J* = 7.1 Hz, 6H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 168.4, 165.5, 150.4, 145.9, 141.7, 138.9, 136.2, 134.4, 131.7, 130.7, 129.7, 129.0, 128.9, 126.6, 125.7, 125.3, 121.5, 76.3, 62.8, 13.5; FT-IR (KBr) 2932, 2853, 1751, 1716, 1400 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{23}H_{20}ClN_2O_5$ 439.1055, found 439.1052.



Diethyl 6-fluoro-3-oxo-2-(quinolin-8-yl)isoindoline-1,1-dicarboxylate 3g. Analytical TLC on silica gel, 1:2 ethyl acetate/hexane R_f = 0.43; colorless solid; mp 170-171°C; yield 57% (24 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.77 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.27 (dd, *J* = 7.4, 1.4 Hz, 1H), 8.21 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.99-7.97 (dd, *J* = 8.4, 5.0 Hz, 1H), 7.92 (dd, *J* = 8.3, 1.4 Hz, 1H), 7.68-7.65 (m, 1H), 7.51 (dd, *J* = 8.1, 2.3 Hz, 1H), 7.40-7.38 (m, 1H), 7.35-7.32 (m, 1H), 4.08-4.03 (m, 2H), 3.89-3.84 (m, 2H), 0.92 (t, *J* = 7.1 Hz, 6H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 168.4, 166.3 (J_{C-F} = 251.1), 165.5, 150.3, 145.9, 142.6 (J_{C-F} = 10.3), 139.4, 136.2, 134.5, 131.7, 129.0, 128.9, 127.3 (J_{C-F} = 2.2), 126.6, 126.6, 121.5, 118.0 (J_{C-F} = 23.5), 114.2, 112.5 (J_{C-F} = 25.3), 76.3, 62.7, 13.5; FT-IR (KBr) 2925, 2854, 1748, 1721, 1400 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{23}H_{20}FN_2O_5$ 423.1351, found 423.1357.

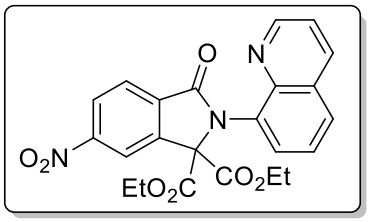


Diethyl 6-methoxy-3-oxo-2-(quinolin-8-yl)isoindoline-1,1-dicarboxylate 3h. Analytical TLC on silica gel, 1:2 ethyl acetate/hexane R_f = 0.44; light brown solid; mp 155-156 °C; yield 55% (23.8 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.75 (dd, *J* = 4.1, 1.6 Hz, 1H), 8.25 (dd, *J* = 7.4, 1.2 Hz, 1H), 8.17 (dd, *J* = 8.2, 1.5 Hz, 1H), 7.89-7.86 (m, 2H), 7.64-7.62 (m, 1H), 7.36 (dd, *J* = 8.2, 4.1 Hz, 1H), 7.27 (d, *J* = 2.2 Hz, 1H), 7.13 (dd, *J* = 8.4, 2.2 Hz, 1H), 4.06-4.00 (m, 2H), 3.93 (s, 3H), 3.84-3.79 (m, 2H), 0.87 (t, *J* = 7.1 Hz, 6H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 166.0, 163.4, 150.2, 146.0, 142.4, 136.2, 135.0, 131.5, 128.9, 128.7, 126.6, 125.9, 123.8, 121.4,

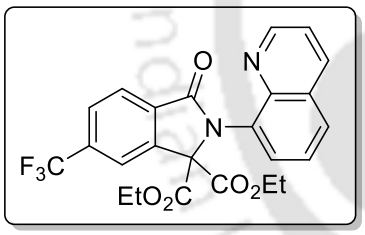


116.7, 114.2, 109.6, 76.4, 62.4, 55.9, 13.5; FT-IR (KBr) 2923, 2853, 1741, 1716, 1400 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{24}H_{23}N_2O_6$: 435.1551, found 435.158.

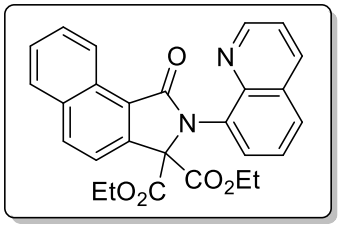
Diethyl 6-nitro-3-oxo-2-(quinolin-8-yl)isoindoline-1,1-dicarboxylate 3i. Analytical TLC on silica gel, 1:2 ethyl acetate/hexane R_f = 0.41; light yellow solid; mp 165-166 °C; yield 63% (28 mg); ^1H NMR (600 MHz, $CDCl_3$) δ 8.74 (dd, *J* = 4.1, 1.7 Hz, 1H), 8.67-8.65 (m, 1H), 8.51 (dd, *J* = 8.3, 2.0 Hz, 1H), 8.26 (dd, *J* = 7.4, 1.4 Hz, 1H), 8.20 (dd, *J* = 8.3, 1.7 Hz, 1H), 8.13 (dd, *J* = 8.3, 0.6 Hz, 1H), 7.93 (dd, *J* = 8.4, 1.4 Hz, 1H), 7.68-7.65 (m, 1H), 7.40-7.38 (dd, *J* = 8.3, 4.1 Hz, 1H), 4.10-4.04 (m, 2H), 3.90-3.84 (m, 2H), 0.92 (t, *J* = 7.1 Hz, 6H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 167.2, 164.9, 150.7, 150.5, 145.6, 141.4, 136.4, 136.3, 133.9, 131.7, 129.4, 128.9, 126.6, 125.7, 125.6, 121.6, 120.8, 76.5, 63.1, 13.5; FT-IR (KBr) 2931, 2853, 1748, 1725, 1537, 1399 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{23}H_{20}N_3O_7$: 450.1296, found 450.1295.



Diethyl 3-oxo-2-(quinolin-8-yl)-6-(trifluoromethyl)isoindoline-1,1-dicarboxylate 3j. Analytical TLC on silica gel, 1:2 ethyl acetate/hexane R_f = 0.42; colorless solid; mp 178-179 °C; yield 58% (27 mg); ^1H NMR (600 MHz, $CDCl_3$) δ 8.74 (dd, *J* = 4.1, 1.7 Hz, 1H), 8.26 (dd, *J* = 7.4, 1.4 Hz, 1H), 8.19 (dd, *J* = 8.3, 1.8 Hz, 1H), 8.09-8.07 (m, 2H), 7.92-7.89 (m, 2H), 7.66 (t, *J* = 7.8 Hz, 1H), 7.39-7.37 (m, 1H), 4.08-4.03 (m, 2H), 3.87-3.82 (m, 2H), 0.89 (t, *J* = 7.1 Hz, 6H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 168.0, 165.3, 150.4, 145.8, 140.8, 136.3, 134.8 (J_{C-F} = 31.9), 134.2, 131.7, 129.2, 128.9, 127.3 (J_{C-F} = 3.4), 126.6, 125.2, 122.4 (J_{C-F} = 3.7), 121.6, 76.6, 62.9, 13.5; FT-IR (KBr) 2923, 2855, 1770, 1748, 1721, 1400 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{24}H_{20}F_3N_2O_5$: 473.1319, found 473.1316.

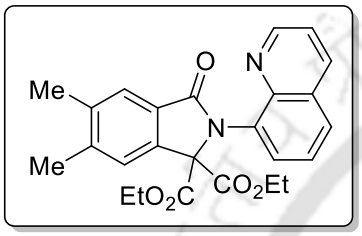


Diethyl 1-oxo-2-(quinolin-8-yl)-1,2-dihydro-3H-benzo[*e*]isoindole-3,3-dicarboxylate 3k. Analytical TLC on silica gel, 1:2 ethyl acetate/hexane R_f = 0.44; light yellow solid; mp 160-161 °C; yield 66% (30 mg); ^1H NMR (600 MHz, $CDCl_3$) δ 9.23 (d, *J* = 8.3 Hz, 1H), 8.74 (dd, *J* = 4.1, 1.7 Hz, 1H), 8.31 (dd, *J* = 7.4, 1.4 Hz, 1H), 8.19 (dd, *J* = 8.3, 1.7 Hz, 1H),

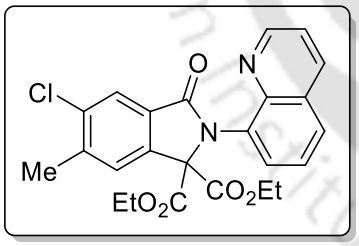


8.15-8.13 (m, 1H), 7.98 (d, *J* = 8.3 Hz, 1H), 7.91 (dd, *J* = 8.3, 1.4 Hz, 1H), 7.87 (d, *J* = 8.5 Hz, 1H), 7.69-7.66 (m, 2H), 7.64-7.61 (m, 1H), 7.36 (dd, *J* = 8.3, 4.1 Hz, 1H), 4.08-4.03 (m, 2H), 3.90-3.84 (m, 2H), 0.92 (t, *J* = 7.1 Hz, 6H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 170.4, 166.1, 150.3, 146.2, 140.7, 136.2, 134.8, 134.1, 133.3, 131.8, 129.4, 129.0, 128.9, 128.4, 128.2, 127.4, 126.6, 125.7, 124.5, 121.4, 121.2, 76.5, 62.6, 13.6; FT-IR (KBr) 2857, 1772, 1741, 1705, 1400 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{27}H_{23}N_2O_5$: 455.1601, found 455.1606.

Diethyl 5,6-dimethyl-3-oxo-2-(quinolin-8-yl)isoindoline-1,1-dicarboxylate 3l. Analytical TLC on silica gel, 1:2 ethyl acetate/hexane R_f = 0.42; colorless solid; mp 148-149 °C; yield 61% (26 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.74 (dd, *J* = 4.1, 1.8 Hz, 1H), 8.25 (dd, *J* = 7.4, 1.4 Hz, 1H), 8.16 (dd, *J* = 8.3, 1.8 Hz, 1H), 7.87 (dd, *J* = 8.3, 1.4 Hz, 1H), 7.74 (s, 1H), 7.64-7.61 (m, 1H), 7.55 (s, 1H), 7.35 (dd, *J* = 8.2, 4.1 Hz, 1H), 4.04-3.98 (m, 2H), 3.82-3.77 (m, 2H), 2.42 (s, 3H), 2.39 (s, 3H) 0.86 (t, *J* = 7.1 Hz, 6H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 169.8, 166.3, 150.2, 146.1, 142.2, 139.2, 138.2, 136.1, 135.1, 131.5, 129.0, 128.9, 128.6, 126.6, 125.4, 125.1, 121.4, 76.5, 62.3, 20.9, 20.2, 13.5; FT-IR (KBr) 2928, 2851, 1741, 1715, 1400 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{25}H_{25}N_2O_5$: 433.1758, found 433.1766.



Diethyl 5-chloro-6-methyl-3-oxo-2-(quinolin-8-yl)isoindoline-1,1-dicarboxylate 3m. Analytical TLC on silica gel, 1:2 ethyl acetate/hexane R_f = 0.42; colorless solid; mp 152-153 °C; yield 58% (26 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.74 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.23 (dd, *J* = 7.4, 1.3 Hz, 1H), 8.17 (dd, *J* = 8.3, 1.6 Hz, 1H), 7.94 (s, 1H), 7.88 (dd, *J* = 8.3, 1.3 Hz, 1H), 7.66-7.61 (m, 2H), 7.36 (dd, *J* = 8.3, 4.2 Hz, 1H), 4.06-3.98 (m, 2H), 3.85-3.77 (m, 2H), 2.54 (s, 3H), 0.87 (t, *J* = 7.1 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.3, 165.8, 150.3, 145.9, 141.3, 138.6, 136.8, 136.2, 134.8, 131.4, 130.6, 128.99, 128.90, 127.0, 126.6, 125.0, 121.5, 76.4, 62.6, 21.2, 13.5; FT-IR (KBr) 2927, 2853, 1769, 1746, 1716, 1400, 1278 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{24}H_{22}ClN_2O_5$: 453.1212, found 453.1214.



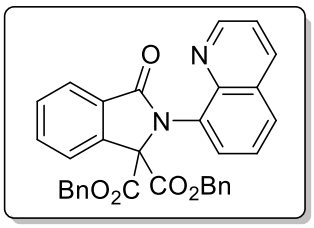
Dimethyl 3-oxo-2-(quinolin-8-yl)isoindoline-1,1-dicarboxylate 3q. Analytical TLC on silica gel, 1:2 ethyl acetate/hexane R_f = 0.43; light yellow solid; mp 156-157 °C; yield 53% (20 mg); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.75 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.26 (dd, *J* = 7.4, 1.3 Hz, 1H), 8.19 (dd, *J* = 8.3, 1.6 Hz, 1H), 7.99 (d, *J* = 7.0 Hz, 1H), 7.90 (dd, *J* = 8.2, 1.2 Hz, 1H), 7.79 (d, *J* = 7.5 Hz, 1H), 7.72-7.60 (m, 3H), 7.37 (dd, *J* = 8.3, 4.2 Hz, 1H), 3.51 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.3, 166.5, 150.1, 145.8, 140.2, 136.3, 134.5, 132.6, 131.7, 131.3, 130.1, 129.0, 129.0, 126.6, 124.7, 124.7, 121.3, 76.7, 53.2; FT-IR (KBr) 2926, 2851, 1746, 1715, 1400 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{21}H_{17}N_2O_5$: 377.1132, found 377.1136.

Diisopropyl 3-oxo-2-(quinolin-8-yl)isoindoline-1,1-dicarboxylate 3r. Analytical TLC on silica gel, 1:2 ethyl acetate/hexane R_f = 0.43; light brown solid; mp 109-110 °C; yield 59% (25.3 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.76 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.28 (dd, *J* = 7.4, 1.4 Hz, 1H), 8.16 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.97 (d, *J* = 7.7 Hz, 1H), 7.88 (dd, *J* = 8.3, 1.4 Hz, 1H), 7.80 (d, *J* = 7.5 Hz, 1H), 7.69-7.66 (m, 1H), 7.65-7.59 (m, 2H), 7.36 (dd, *J* = 8.2, 4.2 Hz, 1H), 4.80-4.77 (m, 2H), 1.11 (d, *J* = 6.2 Hz, 6H), 0.62 (d, *J* = 6.3 Hz, 6H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 169.5, 165.4, 150.4, 146.1, 140.5, 136.1, 135.0, 132.4, 131.5, 131.3, 129.9, 129.0, 128.7, 126.5, 124.8, 124.6, 121.5, 70.5, 21.4, 20.7; FT-IR (KBr) 2935, 2857, 1741, 1719, 1469, 1400 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{25}H_{25}N_2O_5$: 433.1758, found 433.1763.

Di-*tert*-butyl 3-oxo-2-(quinolin-8-yl)isoindoline-1,1-dicarboxylate 3s. Analytical TLC on silica gel, 1:2 ethyl acetate/hexane R_f = 0.44; light brown solid; mp 115-116 °C; yield 51% (23.4 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.77 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.30 (dd, *J* = 7.4, 1.4 Hz, 1H), 8.18 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.97 (d, *J* = 7.5 Hz, 1H), 7.88 (dd, *J* = 8.3, 1.4 Hz, 1H), 7.79 (d, *J* = 7.7 Hz, 1H), 7.69-7.66 (m, 1H), 7.63-7.58 (m, 2H), 7.36 (dd, *J* = 8.3, 4.2 Hz, 1H), 1.10 (s, 18H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 169.5, 164.7, 150.6, 145.9, 140.6, 136.1, 135.9, 132.3, 131.5, 130.9, 129.8, 129.0, 128.5, 126.5, 124.8, 124.5, 121.5, 83.3, 78.3, 27.4; FT-IR (KBr) 2977, 2929,

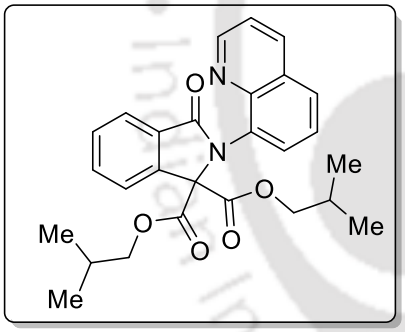
1760, 1740, 1709, 1398, 1154 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{27}H_{29}N_2O_5$: 461.2071, found 461.2072.

Dibenzyl 3-oxo-2-(quinolin-8-yl)isoindoline-1,1-dicarboxylate 3t. Analytical TLC on silica gel,



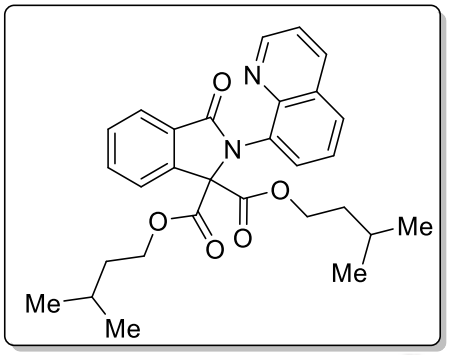
1:2 ethyl acetate/hexane R_f = 0.45; light brown liquid; yield 55% (29 mg); ^1H NMR (600 MHz, $CDCl_3$) δ 8.65-8.64 (m, 1H), 8.22 (dd, *J* = 7.4, 1.4 Hz, 1H), 8.08-8.06 (m, 1H), 8.01-7.96 (m, 2H), 7.82-7.72 (m, 3H), 7.63-7.60 (m, 2H), 7.55-7.52 (m, 1H), 7.28 (dd, *J* = 8.2, 4.1 Hz, 1H), 7.23 (t, *J* = 7.4 Hz, 2H), 7.16 (t, *J* = 7.6 Hz, 3H), 6.86-6.85 (m, 3H), 5.01 (d, *J* = 12.3 Hz, 2H), 4.71 (d, *J* = 12.3 Hz, 2H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 165.6, 150.9, 149.9, 145.4, 139.8, 136.1, 134.3, 134.24, 134.23, 132.5, 131.2, 130.0, 128.6, 128.3, 128.2, 127.8, 126.4, 124.6, 124.5, 123.9, 121.2, 76.6, 68.0; FT-IR (neat) 2851, 1762, 1741, 1716, 1400 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{33}H_{25}N_2O_5$: 529.1758, found 529.1768.

Diisobutyl 3-oxo-2-(quinolin-8-yl)isoindoline-1,1-dicarboxylate 3u. Analytical TLC on silica

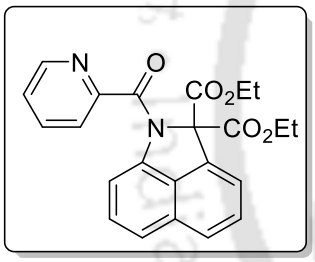


gel, 1:2 ethyl acetate/hexane R_f = 0.42; light yellow solid; mp 105-106 °C; yield 52% (24 mg); ^1H NMR (600 MHz, $CDCl_3$) δ 8.74 (dd, *J* = 4.1, 1.7 Hz, 1H), 8.29 (dd, *J* = 7.4, 1.2 Hz, 1H), 8.17 (dd, *J* = 8.3, 1.6 Hz, 1H), 7.98-7.96 (m, 1H), 7.87-7.86 (m, 1H), 7.82-7.80 (m, 1H), 7.70-7.66 (m, 1H), 7.65-7.60 (m, 2H), 7.36 (dd, *J* = 8.2, 4.1 Hz, 1H), 3.79-3.76 (m, 2H), 3.53-3.50 (m, 2H), 1.56-1.49 (m, 2H), 0.64 (d, *J* = 2.3 Hz, 6H), 0.63 (d, *J* = 2.3 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.4, 166.0, 150.1, 145.9, 140.5, 136.2, 134.8, 132.5, 131.5, 131.3, 130.0, 129.1, 128.8, 126.6, 124.8, 124.6, 121.3, 100.1, 72.6, 27.4, 18.8; FT-IR (KBr) 2894, 2878, 1742, 1721, 1470, 1400 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{27}H_{29}N_2O_5$: 461.2071, found 461.2078.

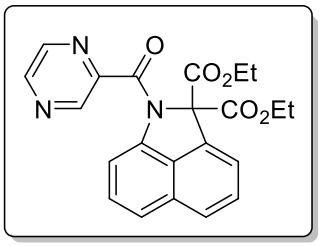
Diisopentyl 3-oxo-2-(quinolin-8-yl)isoindoline-1,1-dicarboxylate 3v. Analytical TLC on silica gel, 1:2 ethyl acetate/hexane R_f = 0.44; light brown solid; mp 100-101 °C; yield 55% (26.8 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.75 (dd, *J* = 4.1, 1.6 Hz, 1H), 8.28-8.25 (m, 1H), 8.18-8.16 (m, 1H), 7.97 (d, *J* = 7.4 Hz, 1H), 7.89-7.86 (m, 1H), 7.82-7.78 (m, 1H), 7.70-7.66 (m, 1H), 7.64-7.59 (m, 2H), 7.36 (dd, *J* = 8.3, 4.2 Hz, 1H), 4.02-3.96 (m, 2H), 3.82-3.76 (m, 2H), 1.33-1.27 (m, 2H), 1.12-1.06 (m, 4H), 0.74-0.69 (m, 12H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.2, 164.9, 149.0, 144.8, 139.2, 135.0, 133.7, 131.3, 130.3, 130.1, 128.8, 127.9, 127.6, 125.4, 123.6, 123.4, 120.2, 64.0, 35.5, 23.7, 21.2, 21.1; FT-IR (KBr) 2960, 2871, 1746, 1722, 1467, 1400 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{29}H_{33}N_2O_5$: 489.2384, found 489.2389.



Diethyl 1-picolinoylbenzo[*cd*]indole-2,2(1*H*)-dicarboxylate 4a. Analytical TLC on silica gel, 1:2 ethyl acetate/hexane R_f = 0.44; light brown solid; mp 164-165 °C; yield 48% (19.4 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.48 (d, *J* = 4.0 Hz, 1H), 8.46 (d, *J* = 7.9 Hz, 1H), 8.41 (d, *J* = 7.3 Hz, 1H), 7.93-7.90 (m, 1H), 7.78 (d, *J* = 8.1 Hz, 1H), 7.74 (d, *J* = 7.0 Hz, 1H), 7.60 (t, *J* = 7.8 Hz, 1H), 7.57-7.54 (m, 2H), 7.43-7.41 (m, 1H), 4.08-4.03 (m, 2H), 3.94-3.88 (m, 2H), 0.90 (t, *J* = 7.1 Hz, 6H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 165.8, 164.4, 151.2, 145.9, 144.2, 137.6, 135.0, 131.1, 129.8, 128.2, 127.2, 125.9, 125.5, 125.3, 120.3, 118.5, 112.9, 80.7, 62.2, 13.7; FT-IR (KBr) 2924, 2851, 1752, 1728, 1659, 1399 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{23}H_{21}N_2O_5$: 405.1455, found 405.1479.

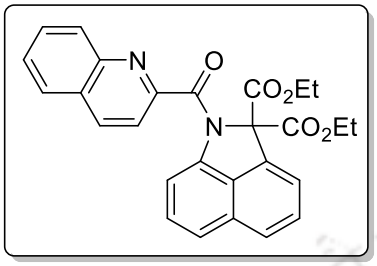


Diethyl 1-(pyrazine-2-carbonyl)benzo[*cd*]indole-2,2(1*H*)-dicarboxylate 4b. Analytical TLC on silica gel, 1:2 ethyl acetate/hexane R_f = 0.43; light yellow liquid; yield 47% (19 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.66 (s, 1H), 8.73 (d, *J* = 2.4 Hz, 1H), 8.48-8.38 (m, 2H), 7.80 (d, *J* = 8.2 Hz, 1H), 7.74 (d, *J* = 7.1 Hz, 1H), 7.64-7.55 (m, 3H), 4.10-4.05 (m, 2H), 4.00-3.95 (m, 2H), 0.97 (t, *J* = 7.1 Hz, 6H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 165.6, 163.2, 147.3, 146.5, 146.4, 143.7, 140.2, 134.6, 131.1, 129.8, 128.3, 127.0, 125.7, 120.8, 118.7, 113.2,

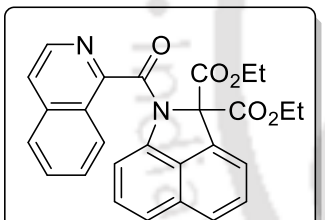


80.5, 62.6, 13.7; FT-IR (neat) 2926, 2853, 1774, 1743, 1720, 1654, 1400 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{22}H_{20}N_3O_5$: 406.1397, found 406.1399.

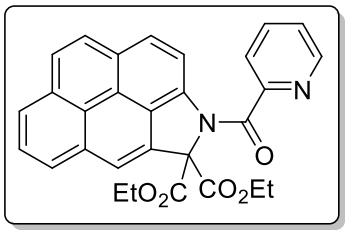
Diethyl 1-(quinoline-2-carbonyl)benzo[*cd*]indole-2,2(1*H*)-dicarboxylate 4c. Analytical TLC on silica gel, 1:2 ethyl acetate/hexane R_f = 0.43; light yellow liquid; yield 43% (19.5 mg); ^1H NMR (600 MHz, $CDCl_3$) δ 8.54 (d, *J* = 8.5 Hz, 1H), 8.47 (d, *J* = 7.3 Hz, 1H), 8.35 (d, *J* = 8.6 Hz, 1H), 8.31 (d, *J* = 8.4 Hz, 1H), 7.88 (d, *J* = 7.6 Hz, 1H), 7.83-7.77 (m, 3H), 7.67-7.54 (m, 4H), 4.03-3.97 (m, 2H), 3.85-3.79 (m, 2H), 0.74 (t, *J* = 7.1 Hz, 6H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 166.2, 164.5, 150.7, 145.7, 144.3, 137.5, 135.0, 131.2, 130.5, 129.9, 128.9, 128.6, 128.6, 128.3, 127.6, 127.3, 125.5, 121.3, 120.4, 118.5, 113.0, 80.8, 62.2, 13.6; FT-IR (neat) 2941, 2855, 1752, 1737, 1652, 1400 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{27}H_{23}N_2O_5$: 455.1601, found 455.1601.



Diethyl 1-(isoquinoline-1-carbonyl)benzo[*cd*]indole-2,2(1*H*)-dicarboxylate 4d. Analytical TLC on silica gel, 1:2 ethyl acetate/hexane R_f = 0.42; brown thick liquid; yield 45% (20.4 mg); ^1H NMR (400 MHz, $CDCl_3$) δ 8.54 (d, *J* = 8.6 Hz, 1H), 8.47 (d, *J* = 7.2 Hz, 1H), 8.33 (dd, *J* = 13.9, 8.7 Hz, 2H), 7.88 (d, *J* = 8.2 Hz, 1H), 7.81-7.77 (M, 3H), 7.68-7.55 (m, 4H), 4.04-3.96 (m, 2H), 3.87-3.79 (m, 2H), 0.75 (t, *J* = 7.1 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.2, 164.5, 150.8, 145.8, 137.5, 135.1, 131.2, 130.5, 129.9, 129.0, 128.6, 128.3, 127.6, 127.3, 125.5, 121.4, 120.4, 118.5, 116.6, 113.4, 113.0, 72.2, 62.2, 13.6; FT-IR (neat) 2928, 2853, 1753, 1670, 1495, 1401 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{27}H_{23}N_2O_5$: 455.1601, found 455.1604.

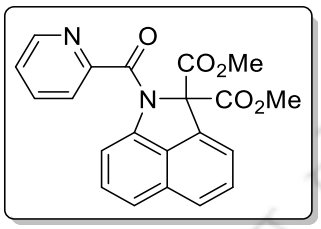


Diethyl 3-picolinoylphenaleno[2,1,9-*cde*]indole-4,4(3*H*)-dicarboxylate 4e. Analytical TLC on silica gel, 1:2 ethyl acetate/hexane R_f = 0.45; greenish liquid; yield 39% (18.6 mg); ^1H NMR (400 MHz, $CDCl_3$) δ 8.95 (d, *J* = 8.2 Hz, 1H), 8.46 (dd, *J* = 15.5, 6.1 Hz, 2H), 8.23-8.13 (m, 3H), 8.06 (d, *J* = 7.5 Hz, 1H), 7.97 (d, *J* = 9.1 Hz, 1H), 7.95-7.85 (m, 3H), 7.39 (dd, *J* = 7.0, 5.2 Hz, 1H), 4.09-3.97 (m, 2H), 3.92-3.82 (m, 2H), 0.84 (t, *J* = 7.1 Hz, 6H); ^{13}C NMR (101



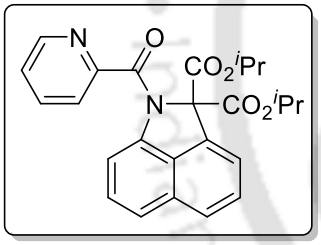
MHz, $CDCl_3$) δ 165.6, 151.3, 148.3, 146.1, 141.7, 137.9, 137.7, 134.6, 132.8, 131.5, 128.0, 126.9, 126.7, 126.3, 126.0, 125.8, 125.3, 124.7, 122.7, 120.4, 120.2, 118.9, 116.0, 77.3, 62.3, 13.7; FT-IR (neat) 2926, 2853, 1763, 1654, 1400, 1364 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{29}H_{23}N_2O_5$: 479.1601, found 479.1614.

Dimethyl 1-picolinoylbenzo[*cd*]indole-2,2(1*H*)-dicarboxylate 4g. Analytical TLC on silica gel,



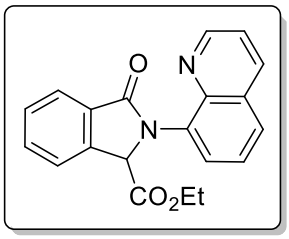
1:2 ethyl acetate/hexane R_f = 0.45; light brown solid; mp 168-169 °C; yield 42% (15.8 mg); ^1H NMR (400 MHz, $CDCl_3$) δ 8.55-8.32 (m, 3H), 7.94-7.89 (m, 1H), 7.78 (d, *J* = 8.2 Hz, 1H), 7.73 (d, *J* = 7.0 Hz, 1H), 7.62-7.54 (m, 3H), 7.46-7.39 (m, 1H), 3.50 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.3, 151.2, 145.9, 137.7, 134.8, 131.2, 129.9, 129.8, 128.3, 125.9, 125.6, 125.4, 125.3, 124.7, 120.4, 118.6, 113.0, 77.3, 53.2; FT-IR (KBr) 2926, 2852, 1758, 1738, 1661, 1588, 1400 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{21}H_{17}N_2O_5$: 377.1132, found 377.1138.

Diisopropyl 1-picolinoylbenzo[*cd*]indole-2,2(1*H*)-dicarboxylate 4h. Analytical TLC on silica



gel, 1:2 ethyl acetate/hexane R_f = 0.42; brown thick liquid; yield 41% (17.7 mg); ^1H NMR (300 MHz, $CDCl_3$) δ 8.47-8.45 (m, 2H), 8.40 (d, *J* = 6.9 Hz, 1H), 7.93-7.87 (m, 1H), 7.77 (d, *J* = 8.2 Hz, 1H), 7.71 (d, *J* = 7.0 Hz, 1H), 7.62-7.52 (m, 3H), 7.42-7.38 (m, 1H), 4.87-4.79 (m, 2H), 1.06 (d, *J* = 6.2 Hz, 6H), 0.89 (d, *J* = 6.2 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.3, 164.4, 158.1, 145.9, 144.4, 137.5, 131.2, 129.85, 129.80, 128.1, 125.8, 125.4, 125.3, 122.7, 120.1, 118.3, 112.9, 69.9, 21.6, 21.0; FT-IR (neat) 2932, 2855, 1745, 1715, 1400 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{25}H_{25}N_2O_5$ 433.1758, found 433.1765.

Ethyl 1-picolinoyl-1,2-dihydrobenzo[*cd*]indole-2-carboxylate 7. Analytical TLC on silica gel,



1:4 ethyl acetate/hexane R_f = 0.42; colorless solid; mp 111-112 °C; yield 62% (10.3 mg); ^1H NMR (400 MHz, $CDCl_3$) δ 8.84 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.21 (dd, *J* = 8.4, 1.7 Hz, 1H), 8.13 (dd, *J* = 7.4, 1.4 Hz, 1H), 8.03-7.98 (m, 1H), 7.86-7.82 (m, 1H), 7.75-7.71 (m, 1H), 7.70-7.62 (m, 2H), 7.58 (t, *J* = 7.4 Hz, 1H), 7.42 (dd, *J* = 8.3, 4.2 Hz, 1H), 6.87 (d, *J* = 0.9 Hz, 1H), 4.17-4.09 (m, 1H), 4.02-3.94 (m, 1H), 1.12 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz,

$CDCl_3$) δ 168.9, 168.8, 150.0, 144.1, 140.5, 136.6, 134.3, 132.4, 131.9, 130.6, 129.4, 129.2, 127.7, 126.6, 124.7, 122.9, 121.4, 65.4, 61.8, 14.1; FT-IR (KBr) 2933, 2853, 1737, 1704, 1471, 1398 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{20}H_{17}N_2O_3$: 333.1234, found 333.1265.

Crystal Data and Structure Refinement for 4h at 296(2) K

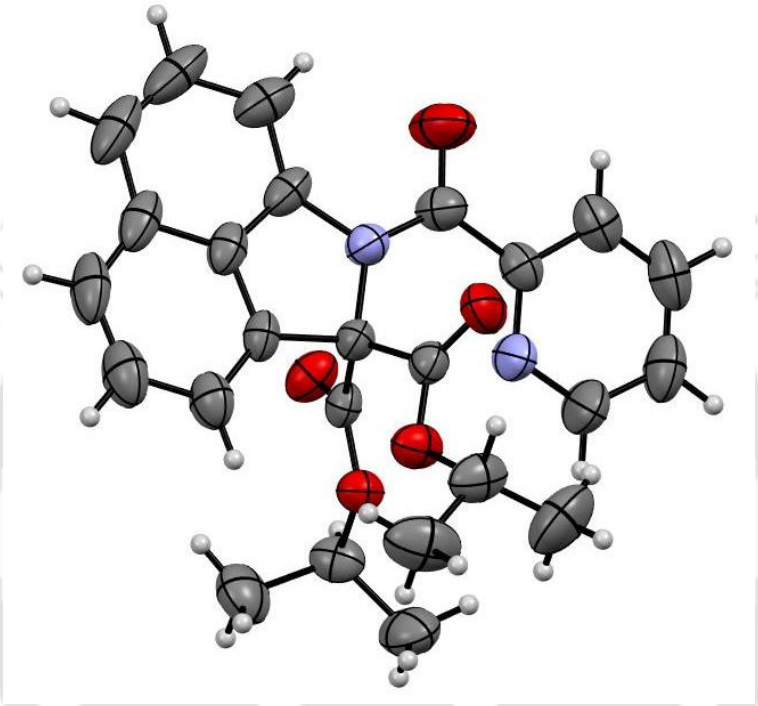


Figure S2. ORTEP diagram of diisopropyl 1-picolinoylbenzo[*cd*]indole-2,2(1*H*)-dicarboxylate **4h** with 50% ellipsoid (**CCDC 1981569**).

Identification code	**4h**
CCDC No.	**1981569**
Empirical formula	$C_{25}H_{24}N_2O_5$
Solvent for crystal growth	Acetonitrile
Formula weight	432.46
Crystal habit, colour	needle /colorless
Temperature, *T*/K	296(2) K
Wavelength, *λ*/Å	0.71073

Crystal system	triclinic
Space group	'P -1'
Unit cell dimensions	a = 9.2898(8) Å
	b = 11.6784(9) Å
	c = 12.1295(10) Å
	α = 92.062(3)
	β = 112.040(3)
	γ = 110.021(3)
Volume, V/Å^3	1125.43(17)
Z	2
Calculated density, Mg·m^{-3}	1.276
Absorption coefficient, μ/mm^{-1}	0.090
F(000)	456
θ range for data collection	2.38 to 20.95°
Limiting indices	$-11 \leq h \leq 11$, $-13 \leq k \leq 13$, $-14 \leq l \leq 14$
Reflection collected / unique	3959/2803
Completeness to θ	100% (θ = 24.995°)
Absorption correction	none
Refinement method	'SHELXL-2014 (Sheldrick, 2014)'
Data / restraints / parameters	3960/0/ 293
Goodness−of−fit on F^2	1.024
Final R indices [I>2sigma(I)]	R1 = 0.0520, wR2 = 0.1222
R indices (all data)	R1 = 0.0805, wR2 = 0.1443

1.8 References

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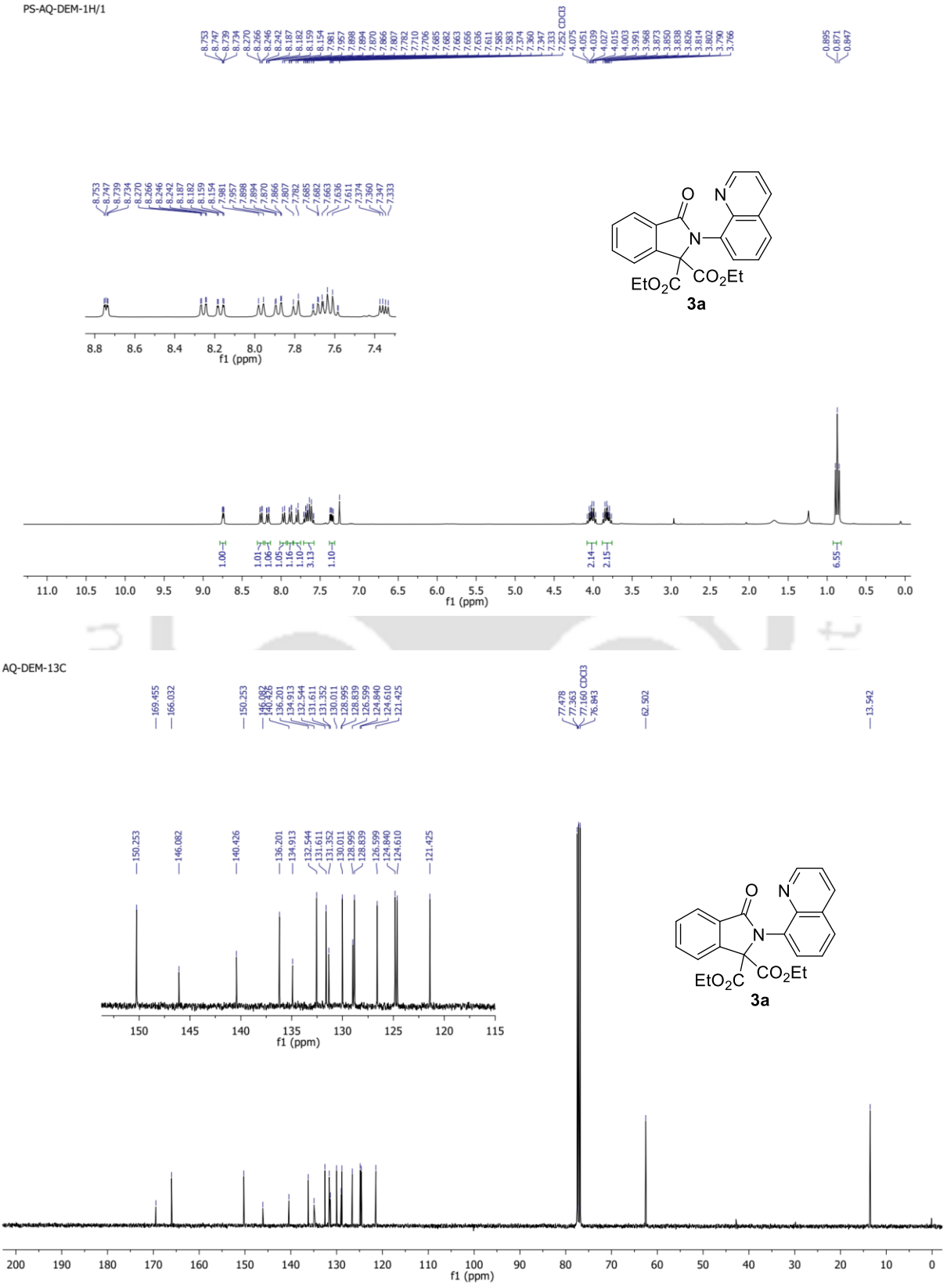
1.9 Selected NMR Spectra



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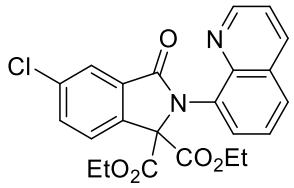

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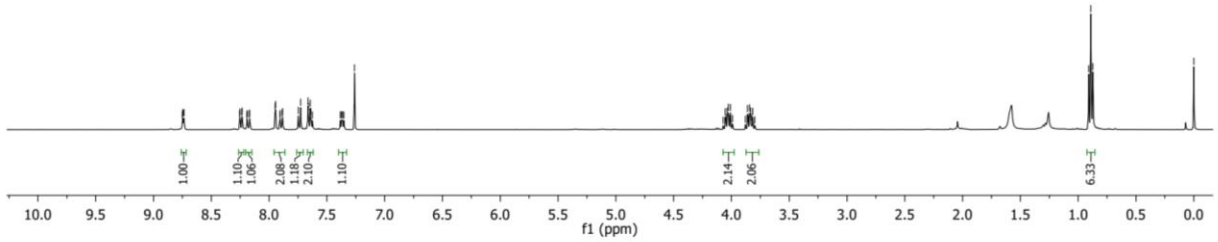

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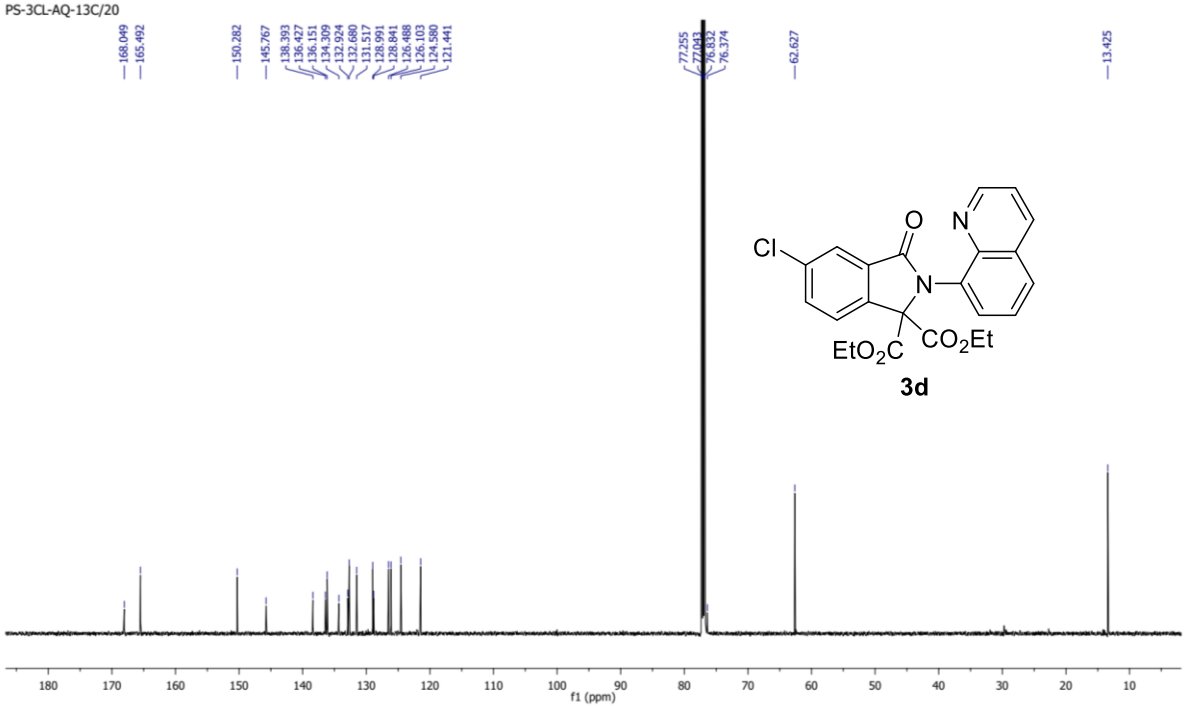

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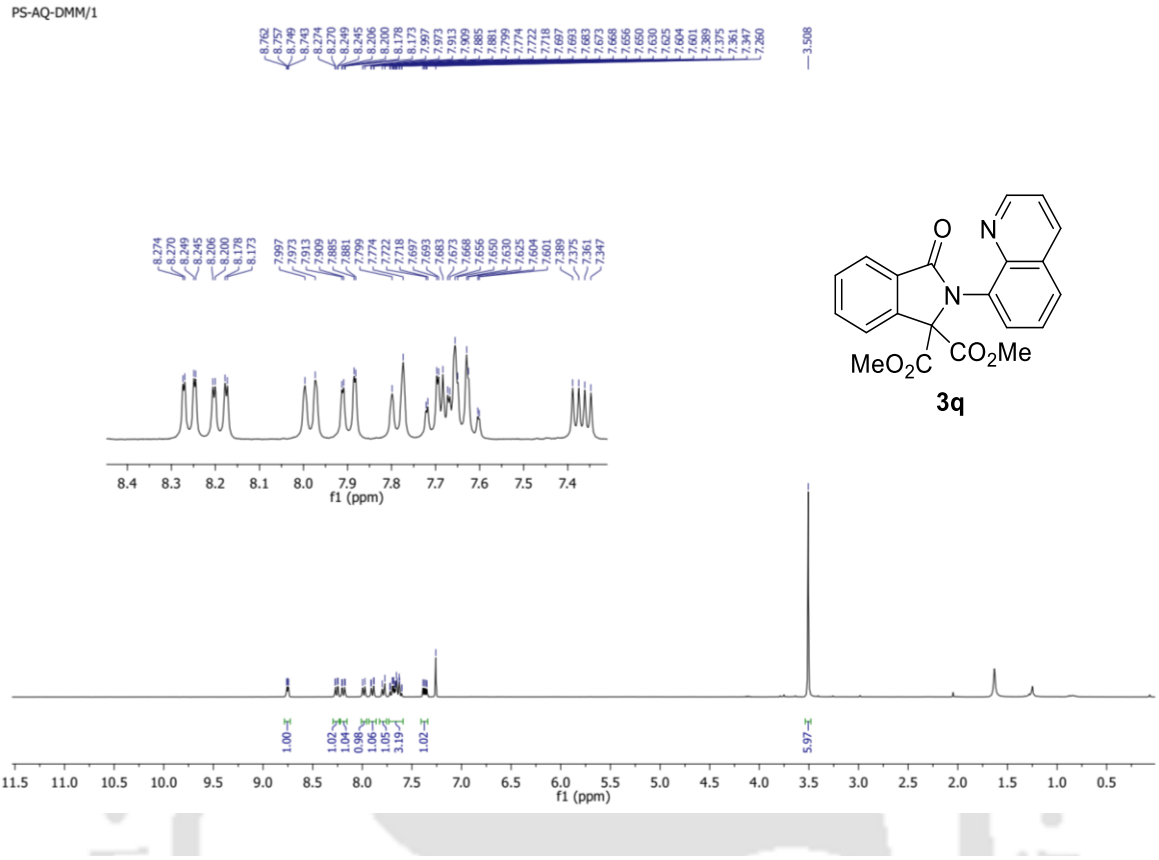
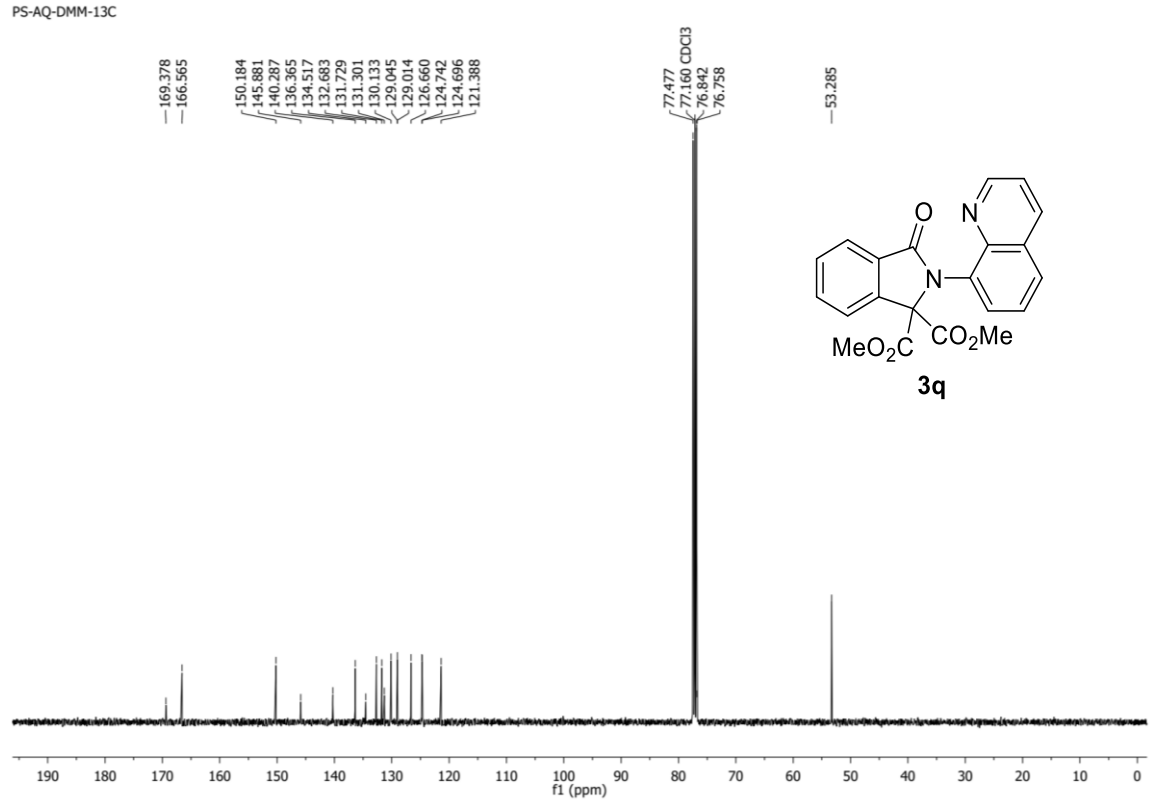
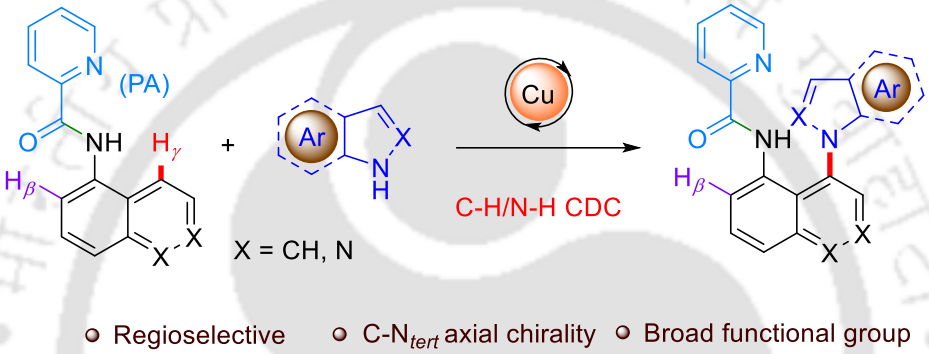




Chapter II

Cu(II)-Mediated N-Arylation of Azoles through Dehydrogenative Cross-Coupling



- Regioselective
- C-N_{tert} axial chirality
- Broad functional group

J. Org. Chem. **2017**, *82*, 4883.

Cu(II)-Mediated *N*-Arylation of Azoles through Dehydrogenative Cross-Coupling

Transition-metal-catalyzed chelation-guided direct C-H functionalization[1] appeared as an efficient and reliable synthetic tool to revolutionize regioselective carbon-carbon and carbon-heteroatom bond formation from readily available precursors obviating prefunctionalization steps. Among them, the C-N bond formation[2] is appealing from an academic as well as industrial standpoints, owing to the copious presence of the nitrogen-containing heterocycles as the core subunits in a wide variety of medicinal and bioactive natural products. In particular, *N*-arylated azoles are present among plentiful organic substrates that are important in biological, medicinal and material sciences.[3] Traditionally, cross-coupling[4] of azoles with aryl halides,[5] aryl boronic acids,[6] aryl bismuths[7] and aryl lead[8] reagents were adapted thoroughly to construct *N*-arylated azoles. However, the routine use of prefunctionalized substrates limit their potential applications. With the emergence of directing-group assisted C-H functionalization, directed C-N bond formation reaction has appeared in a step- and atom-economical manner. In this direction, several studies have been focused on the direct amination of arenes mostly with alkyl amines using a variety of directing groups under Pd, Ru, Co, Ni, Cu and Fe-based catalytic systems. In sharp contrast, utilization of NH-azoles as a coupling partner *via* a cross-dehydrogenative strategy[9] remained underdeveloped due to the associated thermodynamic limitations (the reductive elimination and/or the transmetalation step are known to be energetically difficult).[10] Thereby very few reports exist for the direct C-N bond formation of azoles with arenes *via* cross-dehydrogenative coupling using a directing group strategy. Driven by the distinguished significance of the *N*-naphthylated azoles (Figure 1),[11] development of streamlined strategies for the *N*-naphthylation of azoles is thus attractive. This chapter describes an efficient copper-mediated regioselective cross-coupling of 1-naphthylamides with indoles, pyrazoles and pyrrole using picolinamide as a directing group via γ-selective C-H functionalization. This reaction affords a potential route for directly installing indoles, pyrazoles and pyrrole units at C8-H position of the versatile naphthyl scaffolds that will find applications in biological and medicinal sciences. Remarkably, the reaction of indoles leads to the formation of chiral C-N cross-coupled products with a new kind of C-N_{tert} axial chirality.

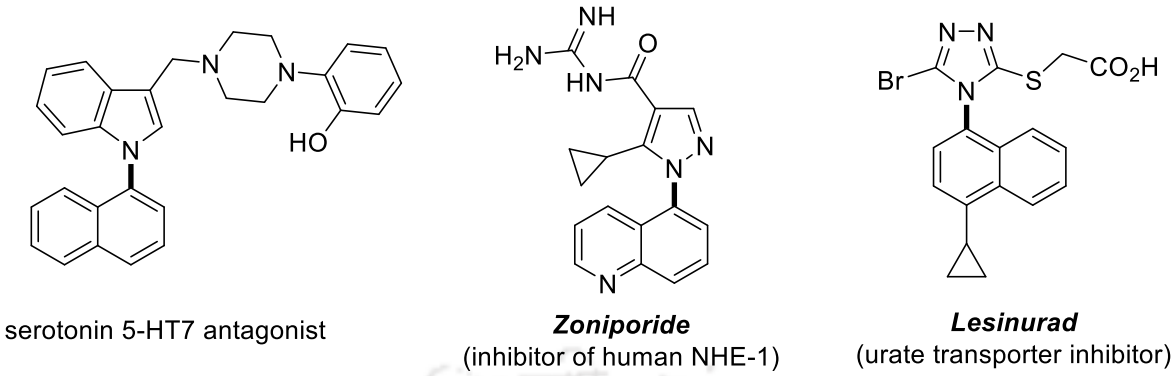
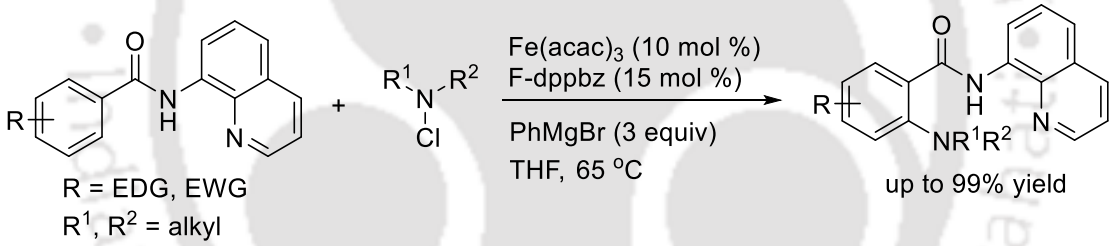


Figure 1. Examples of Biologically Important *N*-Naphthylated Azoles.

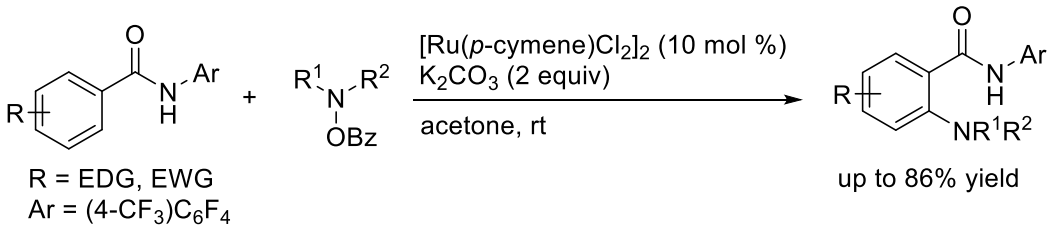
2.1 Metal-Catalyzed Amination with Prefunctionalized Amines

Nakamura and co-workers reported an Fe(III)/diphosphine ligand F-dppbz catalyzed amination of benzamides using 8-quinolinylamide as a directing group with *N*-chloroamines in the presence of an organometallic base (Scheme 1).[12] A variety of chloroamines participated in the reaction to give the anthranilic acid derivatives with high yields.



Scheme 1. Fe-Catalyzed *ortho*-Amination of Carboxamides

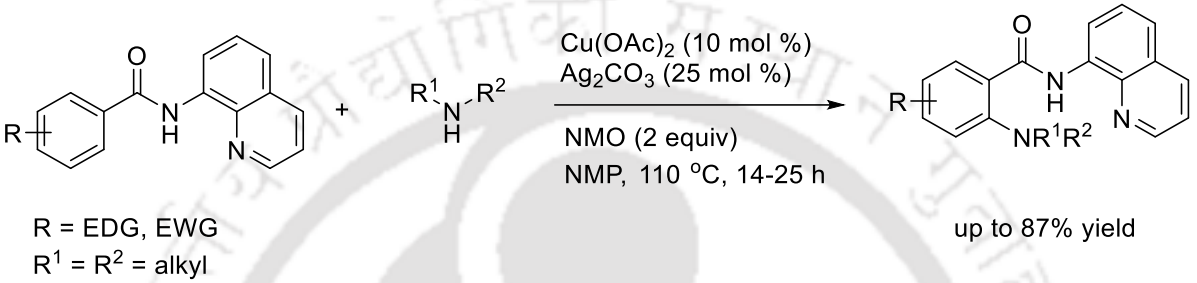
Yu and co-workers achieved a Ru(II)-catalyzed *ortho*-C–H amination utilizing a weakly coordinating amide auxiliary with *O*-benzoyl hydroxylamines at room temperature (Scheme 2).[13] The established method was found to be compatible with heterocyclic amides, such as pyrazole, thiophene, benzothiophene, furan, benzofuran and indole.



Scheme 2. Ru-Catalyzed *ortho*-Selective Amination of Benzamides

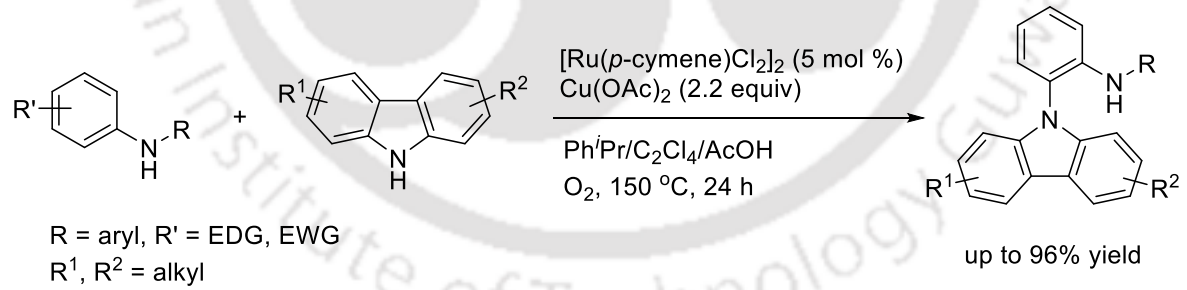
2.2 Metal-Catalyzed Cross-Dehydrogenative Amination

Daugulis and co-workers developed a removable 8-aminoquinoline auxiliary-assisted amination of β-C(sp^2)-H bonds of benzoic acid derivatives employing a Cu(II)-catalyst in combination with Ag_2CO_3 as a co-catalyst, using *N*-methyl-2-pyrrolidone (NMP) solvent, and *N*-methylmorpholine-*N*-oxide (NMO) as an oxidant (Scheme 3).[14] The reaction displays high generality, functional group tolerance and delivers a straightforward route to afford *ortho*-aminobenzoic acid derivatives.



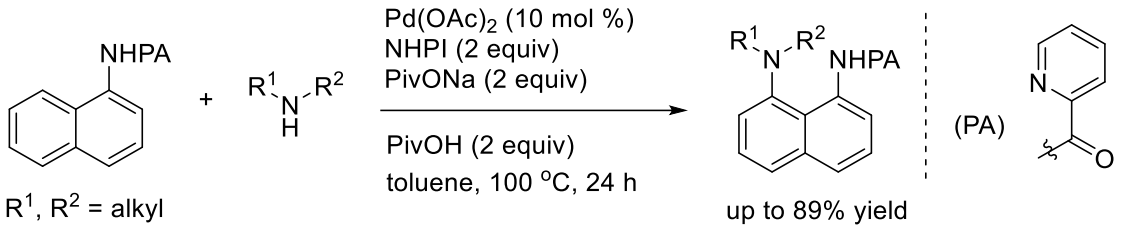
Scheme 3. Cu-Catalyzed Amination of 8-Aminoquinolinamides

A Ru(II)-catalyzed dehydrogenative *ortho* C–N cross-coupling of diarylanilines with substituted carbazoles was achieved with O_2 as the terminal oxidant for the synthesis of unsymmetrical diamines (Scheme 4).[15] Late-stage drug modification and C-N_{tert} axial chirality was also demonstrated to showcase the utility of the method.



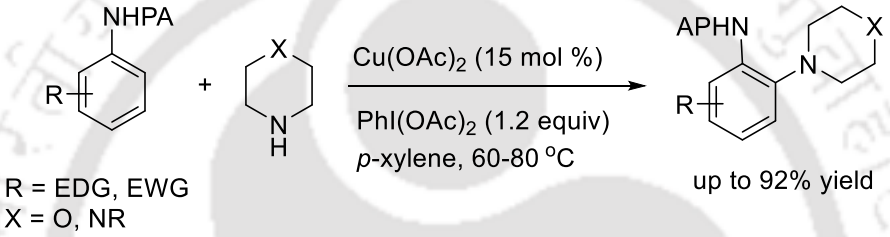
Scheme 4. Ru-Catalyzed Dehydrogenative Amination with Carbazoles

A facile method for Pd(II)-catalyzed picolinamide-directed C8–H amination of 1-naphthylamides was developed with secondary aliphatic amines (Scheme 5).[16] A variety of morpholine derivatives were coupled regioselectively and the removal of the picolinamide group was also presented by the authors.



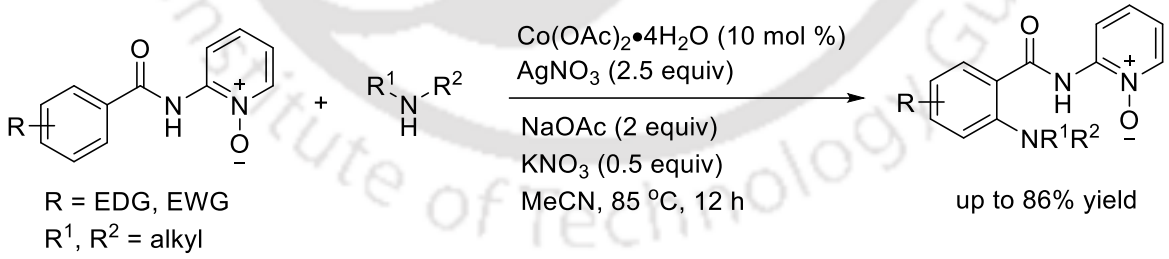
Scheme 5. Pd-Catalyzed C8-H Amination of 1-Naphthylamides

Carretero and co-workers reported a practical Cu(II)-catalyzed picolinamide-directed *o*-amination of anilines using secondary alkyl amines (Scheme 6).[17] The reaction displayed excellent mono-selectivity and good functional group tolerance.



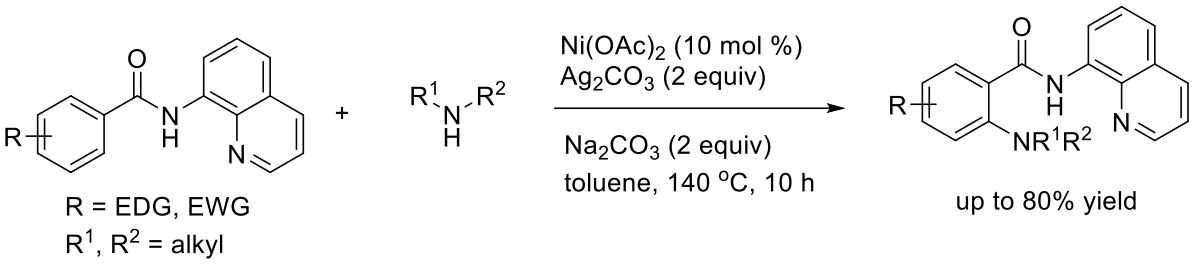
Scheme 6. Picolinamide Directed *ortho*-Amination of Anilines

Song and co-workers described a Co(II)-catalyzed cross-dehydrogenative amination of arylamides with alkylamines *via* C(sp^2)–H functionalization utilizing 2-aminopyridine 1-oxide as a removable directing group (Scheme 7).[18] Use of an inexpensive cobalt catalyst, removal of the directing group and high functional group tolerance were highlighted by the methodology.



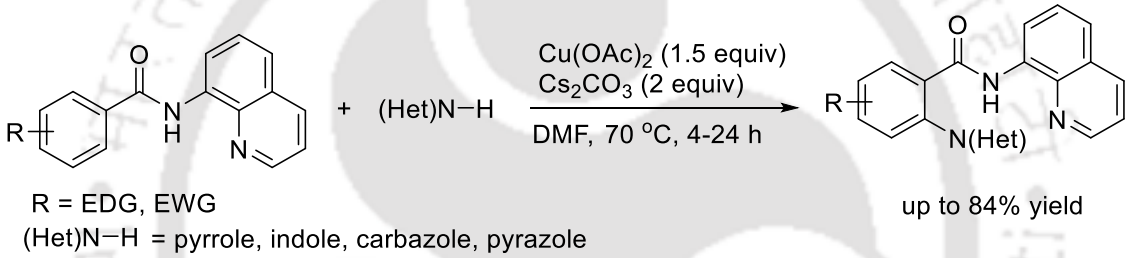
Scheme 7. Co-Catalyzed Cross-Dehydrogenative Amination of Arylamides

An efficient Ni(II)-catalyzed direct regioselective amination of benzamides with alkylamines was achieved with the assistance of 8-aminoquinolinamide auxiliary using Ag_2CO_3 as an oxidant (Scheme 8).[19] Radical trapping experiments and a kinetic isotope experiment provided insight into the reaction pathway.



Scheme 8. Amination of *N*-(Quinolin-8-yl)benzamides using Ni-Catalysis

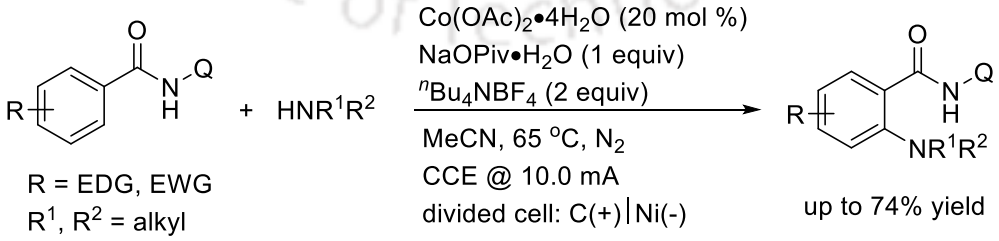
Our group developed a Cu(II)-mediated regioselective *N*-arylation of NH-heterocycles guided by 8-aminoquinoline amide as a directing group (Scheme 9).[20] This reaction displayed broad substrate scope with versatile azoles, such as pyrroles, indoles, pyrazoles and carbazole with moderate to good yields.



Scheme 9. Cu-Mediated Dehydrogenative Amination using NH-Heterocycles

2.3 Electrochemical Cross-Dehydrogenative Amination

Li and co-workers developed an eco-benign electrochemical cobalt-catalyzed dehydrogenative amination of arenes with a range of alkyl amines (Scheme 10).[21] A wide variety of arenes and alkylamines were coupled efficiently without using external oxidants, which avoids the formation of undesired byproducts and exhibits a high atom-economy.



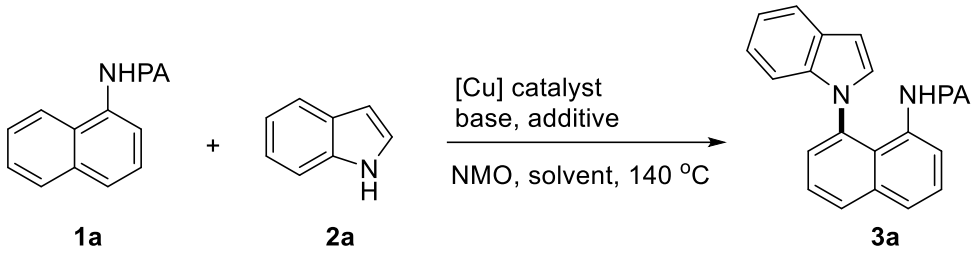
Scheme 10. Electrochemical Co-Catalyzed Dehydrogenative Amination

2.4 Present Study

We here present a robust copper(II)-mediated regioselective cross-dehydrogenative C-N coupling of 1-naphthylamides with a variety of NH-azoles, such as indoles, pyrazoles and pyrrole using removable picolinamide as a bidentate directing group *via* γ-C(sp^2)-H functionalization. This methodology delivers a straightforward route for incorporating indoles, pyrazoles and pyrrole heterocyclic fragments into naphthyl backbone with broad scope and functional group diversity. Our optimization studies initiated employing *N*-(naphthalen-1-yl)picolinamide **1a** with indole **2a** as the test substrates under varied copper sources, additives, bases and solvents (Table 1). To our delight, the reaction proceeded selectively to deliver the C-N cross-coupled product **3a** in 10% conversion when the substrates **1a** and **2a** were stirred with 20 mol % $CuCl_2$, 25 mol % Ag_2CO_3, 2 equiv NMO and 2 equiv K_3PO_4 at 140 °C in DMSO under air (entry 1). Subsequent screening of the copper sources led to an increase to 95% conversion using $Cu(OAc)_2$, whereas other copper sources, such as $CuBr_2$, CuO and CuI gave inferior results (entries 2-5). In a set of additives studied, Ag_2CO_3, Ag_2O and AgOAc, the former afforded the best results (entries 5-7). Among the bases surveyed, K_3PO_4 was superior to Na_2CO_3, K_2CO_3 and Cs_2CO_3 (entries 8-10). DMSO was found to be the solvent of choice, whereas DMF and NMP produced a trace amount of the product (entry 11-12). In the absence of NMO, **3a** was formed in 32% conversion (entry 13). Instead of NMO, using O_2 balloon as an external oxidant resulted in 51 % conversion (entry 14). A similar result was observed without Ag_2CO_3 (entry 15). While in the absence of K_3PO_4 no product formation was observed (entry 16). This signifies the crucial role of Ag-additive and the base in the product formation. A control experiment in the absence of copper salt revealed no product formation and the starting material was recovered intact (entry 17).

To disclose the reactivity mode of the directing group, a series of archetypal directing groups **1b-i** was inspected under optimal reaction conditions (Table 2). Quinaldic acid derived substrate **1b** underwent reaction as that of **1a** to produce the target product **3a′** in 71% yield. Whereas, the substrates **1c-f** bearing *N*- and *N*,*O*-chelating groups, and the flexible amine substrates **1g-i** having the picolinamide directing group revealed no product formation. These results confide that the combination of *N*,*N*-bidentate coordination with the relatively acidic N-H of the picolinamide and the rigid planar naphthyl system play a crucial role in this regioselective transformation.

Table 1. Optimization of the Reaction Conditions[a]

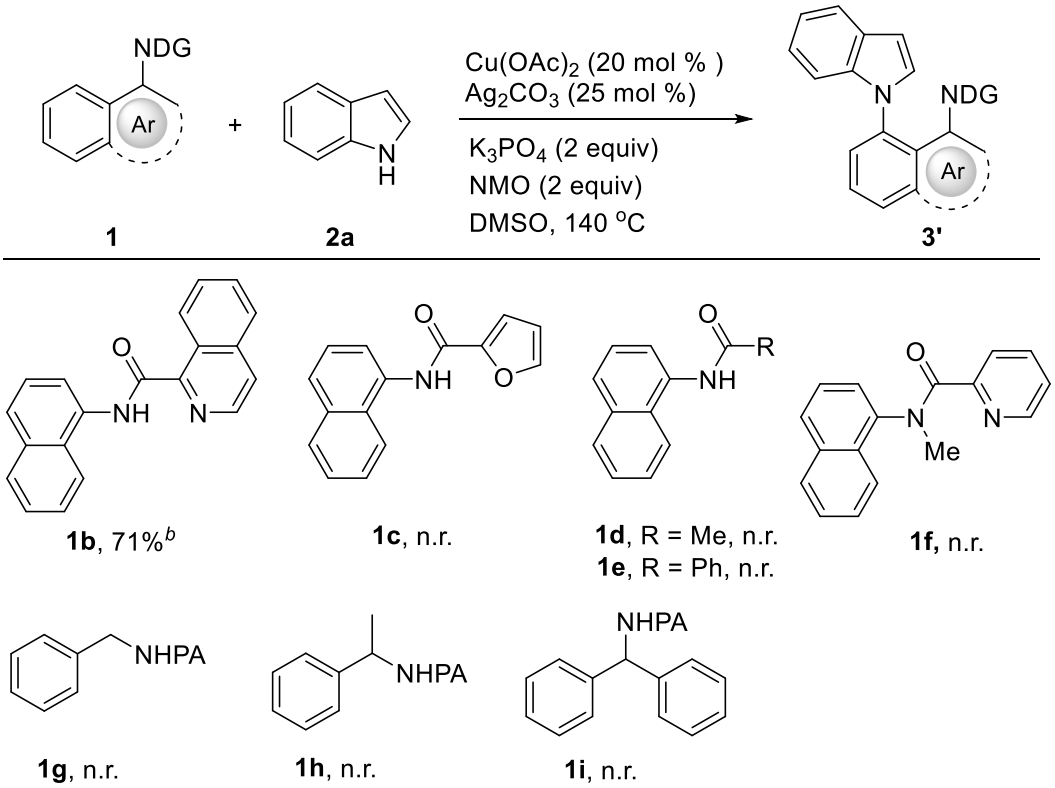


1a **2a** **3a**

Entry	[Cu] Source	Additive	Base	Solvent	Conv (%)[b]
1	$CuCl_2$	Ag_2CO_3	K_3PO_4	DMSO	10
2	$CuBr_2$	Ag_2CO_3	K_3PO_4	DMSO	9
3	CuO	Ag_2CO_3	K_3PO_4	DMSO	5
4	CuI	Ag_2CO_3	K_3PO_4	DMSO	n.d.
5	**$Cu(OAc)_2$**	**Ag_2CO_3**	**K_3PO_4**	**DMSO**	**95(72)[c]**
6	$Cu(OAc)_2$	Ag_2O	K_3PO_4	DMSO	12
7	$Cu(OAc)_2$	AgOAc	K_3PO_4	DMSO	21
8	$Cu(OAc)_2$	Ag_2CO_3	Na_2CO_3	DMSO	46
9	$Cu(OAc)_2$	Ag_2CO_3	K_2CO_3	DMSO	55
10	$Cu(OAc)_2$	Ag_2CO_3	Cs_2CO_3	DMSO	37
11	$Cu(OAc)_2$	Ag_2CO_3	K_3PO_4	DMF	16
12	$Cu(OAc)_2$	Ag_2CO_3	K_3PO_4	NMP	12
13	$Cu(OAc)_2$	Ag_2CO_3	K_3PO_4	DMSO	32[d]
14	$Cu(OAc)_2$	Ag_2CO_3	K_3PO_4	DMSO	51[e]
15	$Cu(OAc)_2$	-	K_3PO_4	DMSO	53
16	$Cu(OAc)_2$	Ag_2CO_3	-	DMSO	0
17	-	Ag_2CO_3	K_3PO_4	DMSO	0

[a]Reaction conditions: **1a** (0.2 mmol), **2a** (0.4 mmol), [Cu] (0.04 mmol), additive (0.05 mmol), base (0.4 mmol), NMO (0.4 mmol), solvent (1 mL), 140 °C, air, 7 h. [b]Estimated using 600 MHz ^{1}H NMR analysis. [c]Isolated yield. [d]Without NMO. [e]O_2 balloon without NMO. NMO = *N*-Methylmorpholine *N*-oxide.

Table 2. Investigation on Reactivity of Directing Groups and Amine Substrates[a]

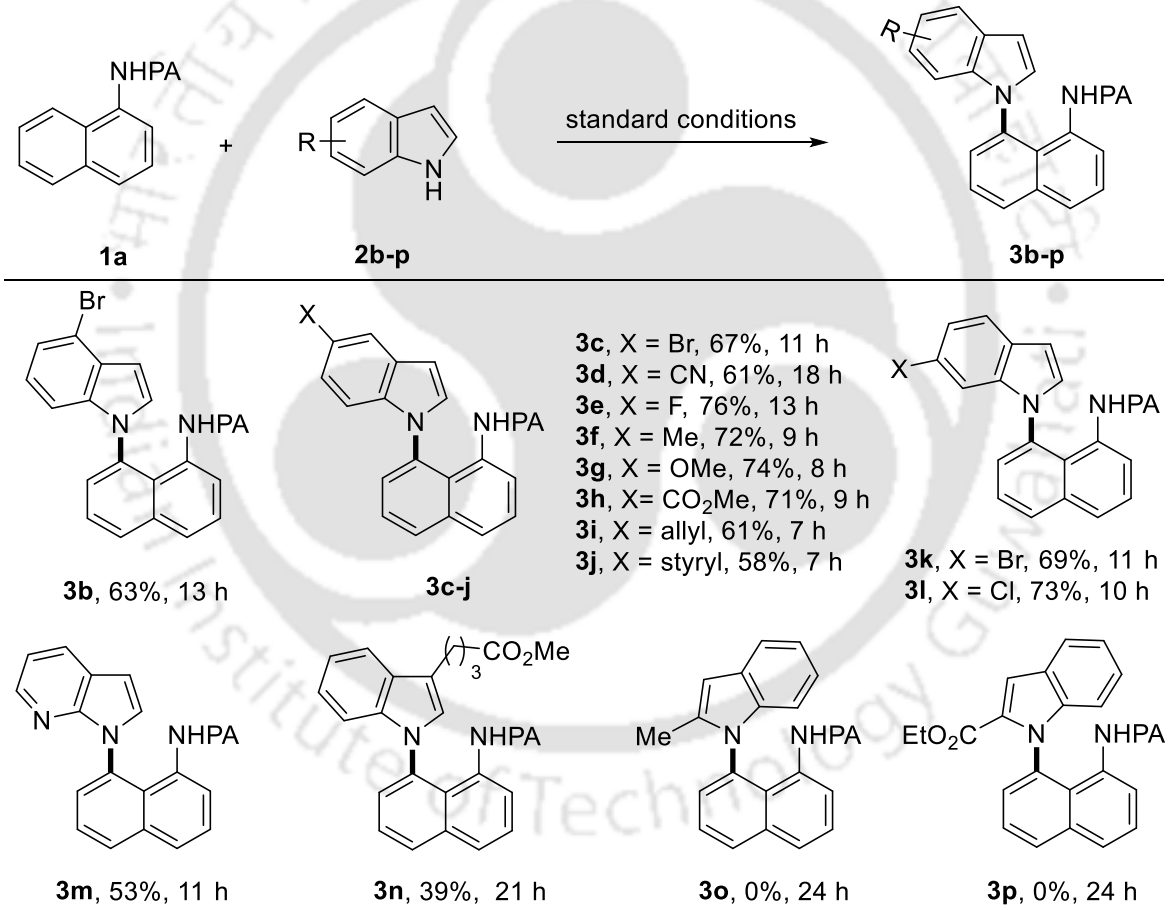


[a]Reaction conditions: Directing groups **1b-i** (0.2 mmol), indole **2a** (0.4 mmol), $Cu(OAc)_2$ (0.04 mmol), Ag_2CO_3 (0.05 mmol), K_3PO_4 (0.4 mmol), NMO (0.4 mmol), DMSO (1 mL), 140 °C, air. [b]Isolated yield. n.r. = no reaction.

Next, to assess the practicality of the method, the scope of the procedure was investigated using *N*-(naphthalen-1-yl)picolinamide **1a** with substituted indoles **2b-p** (Table 3). The substrates **2b** and **2c** bearing 4-Br and 5-Br substituents underwent the C-N cross-coupling to convey the aminated products **3b** and **3c** in 63% and 67% yields, respectively. A systematic examination revealed that electronically dissimilar functional groups were tolerated under the optimal conditions. Thus, the substrates **2d-j** bearing functional groups at the 5-position of indole, such as cyano (**3d**, 61%), fluoro (**3e**, 76%), methyl (**3f**, 72%), methoxy (**3g**, 74%), ester (**3h**, 71%), allyl (**3i**, 61%) and styrenyl (**3j**, 58%), readily afforded the desired products. The structure of **3h** was determined using single crystal X-ray analysis. Substrates **2k-l** bearing functional groups at the 6-position on indoles such as 6-Br and 6-Cl were readily converted to the target products **3k** and **3l** in 69% and 73% yields, respectively. A heterocyclic coupling partner 7-azaindole **2m** was readily converted to **3m** in 53% yield. Interestingly, the methyl ester of indole-3-butyric acid **2n**, which is a plant

hormone in the auxin family, was also amenable to the reaction conditions and gave **3n** in 39% yield. This showcase the significant potential feature of the protocol for natural product modifications. As anticipated, 2-substituted indole failed to produce the desired products **3o** and **3p**, irrespective of the electronic nature of the substituent, which may be attributed to the steric influence encountered near the C-N coupling site. Remarkably, the C-N cross-coupled products exhibit a new kind of C-N_{tert} axial chirality due to constrained rotation about the C-N_{tert} axis. For example, chiral HPLC analyses of **3a** and **3f** were investigated as representative substrates, which were readily separated into their enantiomers on a chiral stationary phase (OD column, Figure 2).

Table 3. Substrate Scope of Indoles[a,b]



[a]Reaction conditions: *N*-(naphthalen-1-yl)picolinamide **1a** (0.2 mmol), indole **2b-p** (0.4 mmol), $Cu(OAc)_2$ (0.04 mmol), Ag_2CO_3 (0.05 mmol), K_3PO_4 (0.4 mmol), NMO (0.4 mmol), DMSO (1 mL), 140 °C, air. [b]Isolated yield.

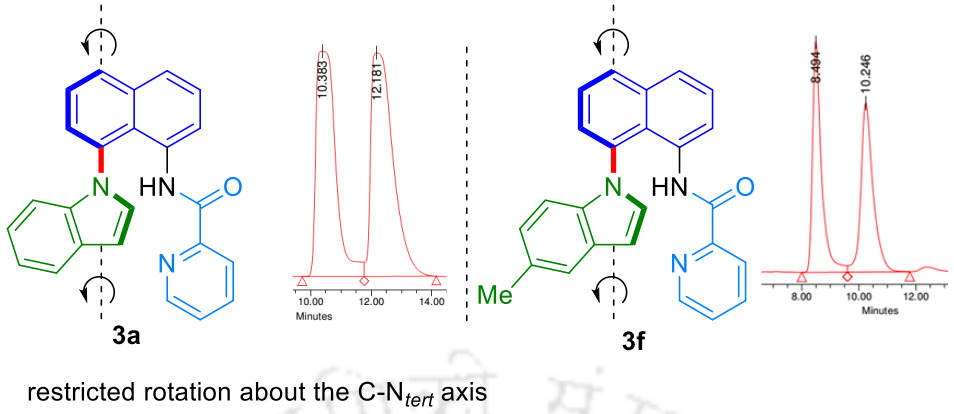
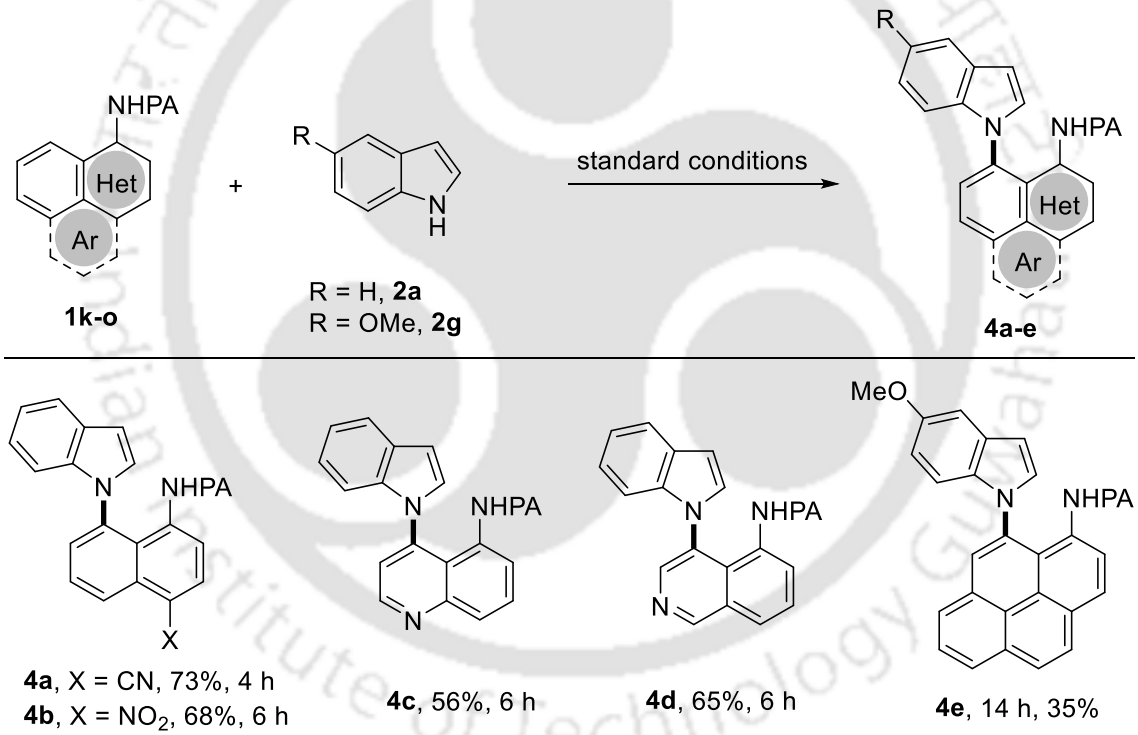


Figure 2. Chiral HPLC's profile of **3a** and **3f**.

Table 4. Substrate Scope of *N*-(naphthalen-1-yl)picolinamides[a,b]



[a]Reaction conditions: *N*-(naphthalen-1-yl)picolinamide **1k-o** (0.2 mmol), indole (0.4 mmol), $Cu(OAc)_2$ (0.04 mmol), Ag_2CO_3 (0.05 mmol), K_3PO_4 (0.4 mmol), NMO (0.4 mmol), DMSO (1 mL), 140 °C, air. [b]Isolated yield.

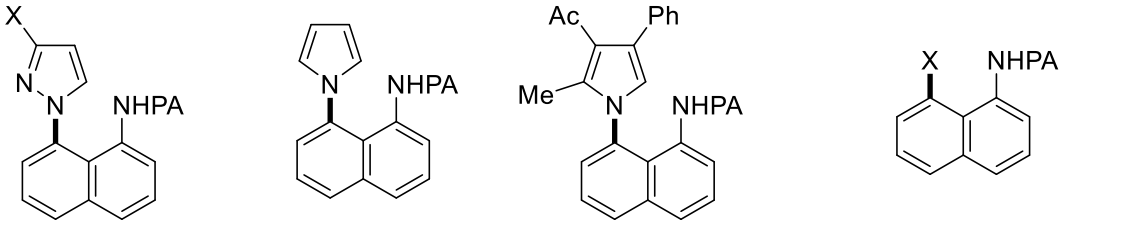
The scope of the reaction was then surveyed for the *N*-naphthylation of indoles with substituted *N*-(naphthalen-1-yl)picolinamides (Table 4). Reaction of the substrates **1k** and **1l** with electron-withdrawing groups at the 4-position proceeded efficiently to afford **4a** and **4b** in 73% and 68%

yields, respectively. The aminoquinoline derivatives **1m** and **1n** were successfully aminated to give the corresponding products **4c** and **4d** in 56% and 65% yields, respectively, exhibiting the overriding potential of this reaction in heteroatom poisoning for catalyst deactivation. A conjugated π-cycle like *N*-(pyren-1-yl)picolinamide **1o** was also aminated to give **4e** in 35% yield.

Table 5. Substrate Scope of Azoles[a,b]

1a **5a-f** **6a-f**

scope of azole nucleophiles



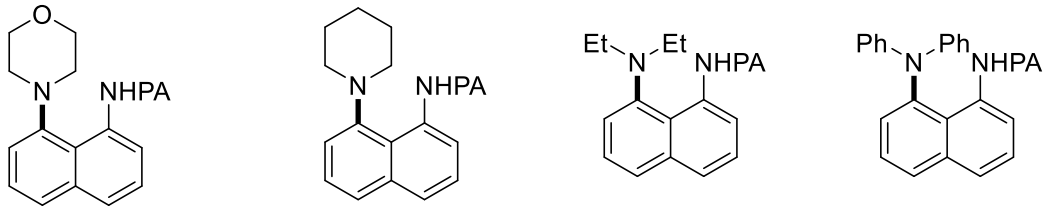
6a, X = H, 63%, 9 h
6b,X = Me, 69%, 8 h

6c, 18 h, 51%

6d, 0%

6e, X = 2-phenyl imidazolyl, 0%
6f, X = carbazolyl, 0%

scope of amine nucleophiles



6g, 23 %, 18 h

6h, 0%, 24 h

6i, 0%, 24 h

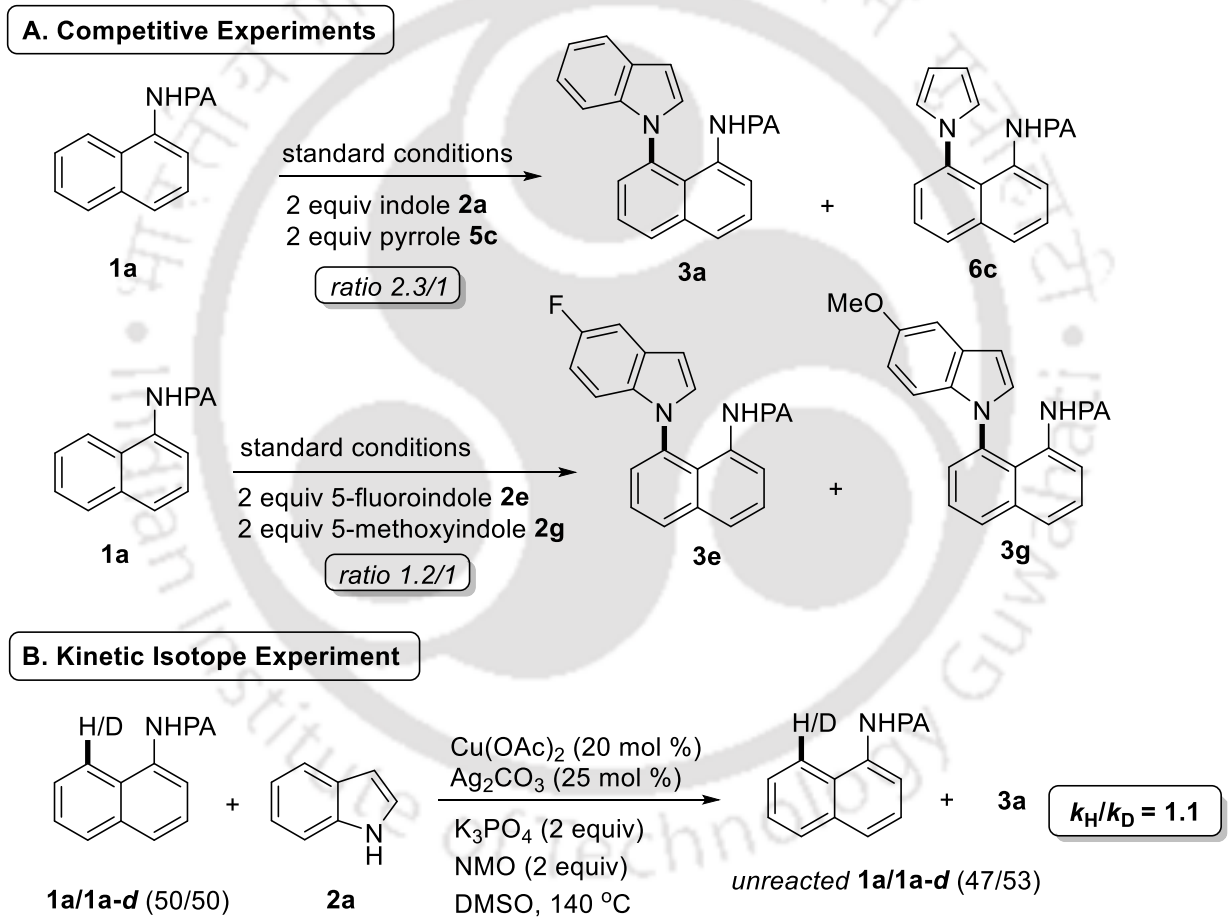
6j, 0%, 24 h

[a]Reaction conditions: *N*-(naphthalen-1-yl)picolinamide **1a** (0.2 mmol), azole (0.4 mmol), $Cu(OAc)_2$ (0.04 mmol), Ag_2CO_3 (0.05 mmol), K_3PO_4 (0.4 mmol), NMO (0.4 mmol), DMSO (1 mL), 140 °C, air. [b]Isolated yield.

We further extended the scope of the reaction by employing various azoles with naphthalenyl picolinamide **1a** (Table 5). Pleasingly, the C-N cross-coupling of pyrazole, 3-methylpyrazole and pyrrole proved to be quite successful. The reaction occurred to furnish the corresponding *N*-

naphthylated products **6a-c** in 51-69% yields. Moreover, the occurrence of such azole motifs in a hefty array of bioactive molecules highlights the synthetic efficacy of this setup. In contrast, the reaction of tri-substituted pyrrole **5d**, 2-phenylimidazole **5e** and carbazole **5f** were unsuccessful, which may be due to the steric congestion associated with the substituents.

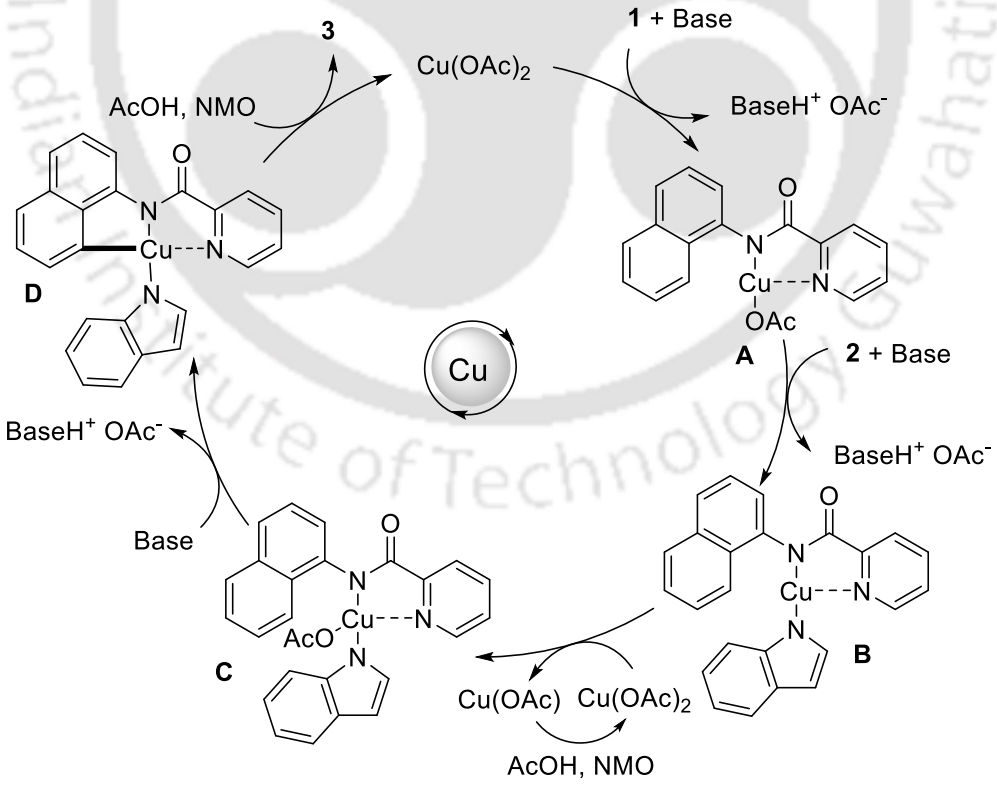
Next, the direct coupling protocol was instigated using a number of aliphatic as well as arylamines. Morpholine was found to be a successful substrate to afford **6g,** albeit in a lower yield. Other amine coupling partners like piperidine, diethylamine and diphenylamine was incompetent under the standard reaction conditions.



Scheme 11. Preliminary Mechanistic Investigations

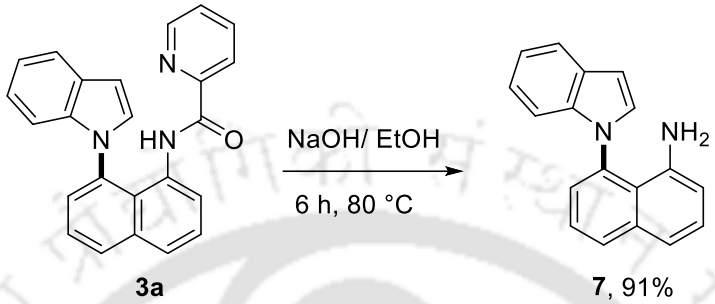
To get insight into the reaction pathway, the intermolecular competition experiments were performed (Scheme 11A). The competitive *N*-naphthylation of indole **2a** and pyrrole **5c** with **1a** suggests that indole is more reactive compared to pyrrole as reflected by their pK_a values. The

reaction was favored by more nucleophilic nature of the NH-heterocycles.[14b] On the other hand, when a 1:1 mixture of 5-fluoroindole **2e** and 5-methoxyindole **2f** was allowed to react with **1a**, a 1.2:1 mixture of **3e** and **3g** was obtained, indicating the electron-withdrawing group facilitates the reaction compared to electron-donating group, likely because of the increase of acidity of NH bond which facilitates effective nucleophilic substitution.[14b] Moreover, the intermolecular kinetic isotope experiment of **1a** and **1a-*d*** with **2a** yielded k_H/k_D = 1.1 (Scheme 11B), which indicates that the C−H bond cleavage might not be involved in the rate-determining step.[22] Thus, *N*-cupration of the substrate **1** with $Cu(OAc)_2$ may give **A**, which may undergo substitution with azole to provide the copper(II) intermediate **B** (Scheme 12). The latter may undergo oxidation to produce copper(III) intermediate **C**, which can lead to naphthyl C(γ)-H cupration to produce organocopper(III) **D**.[23] Reductive elimination of **D** can give the *N*-naphthyl azoles **3** and copper(I) species, which can be oxidized to copper(II) with NMO to complete the catalytic cycle. The presence of Ag_2CO_3 may facilitate the formation of Cu(III) species **D** by accelerating the ligand substitution process with NH-heterocycles.[19,23d-f] The proposed reaction pathway also explains the requirement of excess base and oxidant to realize products in good yields.



Scheme 12. Proposed Reaction Mechanism

Finally, to reveal the synthetic utility of the protocol, the removal of the directing group was accomplished (Scheme 13). The product **3a** was treated with NaOH in EtOH for 6 h to give the 8-(1*H*-indol-1-yl)naphthalen-1-amine in 91% yield, which suggests that the products can be converted into γ-azole α-naphthylamines.



3a **7**, 91%

Scheme 13. Removal of the PA Auxiliary

In summary, we have developed an efficient copper-mediated picolinamide directed regioselective cross-coupling of 1-naphthylamides with indoles, pyrazoles and pyrrole via C(γ)-H functionalization and C-N bond formation. A series of naphthylamines and indoles were cross-coupled with broad substrate scope and functional group tolerance. The reaction can be extended to the cross-coupling of pyrrole and pyrazoles with good yields.

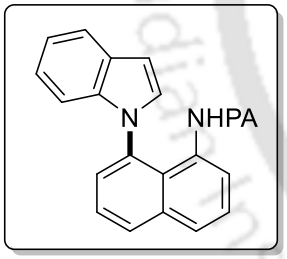
2.5 Experimental Section

General Information. $Cu(OAc)_2$ (98%), indoles, Ag_2CO_3 (99%), Ag_2O (99%), AgOAc (99.9%), K_3PO_4, Cs_2CO_3 and NMO (97%) were purchased from Aldrich and were used as received. The solvents were purchased and dried according to standard procedure prior to use. Substituted naphthalenyl picolinamides were prepared according to literature.[16] Purification of the reaction products was carried out on column chromatography using Merck silica gel (60-120 mesh). Analytical TLC was performed on Merck silica gel G/GF 254 plate. NMR spectra were recorded on Bruker Avance III 600 MHz and Varian 400 MHz using $CDCl_3$ as solvent and Me_4Si as an internal standard. Chemical shifts (δ) were reported in ppm and spin-spin coupling constants (J) were given in Hz. Melting points were determined using Buchi B-540 melting point apparatus and are uncorrected. HPLC analysis was carried out using Waters-2489 with Daicel Chiralcel OD

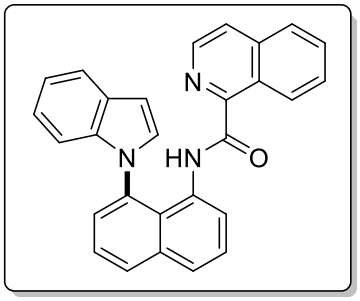
column using isopropanol and hexane as eluent. FT-IR spectra were recorded using Thermo Fisher Scientific spectrometer. Mass spectra were recorded on a Q-Tof ESI-MS Instrument (model HAB 273). Single crystal X-ray data were collected on a Bruker SMART APEX equipped with a CCD area detector using Mo/Kα radiation and the structure was solved by direct method using *SHELXL-97* (Göttingen, Germany).

General Procedure for Copper-Mediated Cross-Coupling of Napthylamines with Azoles. To a stirred solution of *N*-(naphthalen-1-yl)picolinamide (0.2 mmol), $Cu(OAc)_2$ (20 mol %, 0.04 mmol, 3.6 mg), Ag_2CO_3 (25 mol %, 0.05 mmol, 13.7 mg), K_3PO_4 (0.4 mmol, 84.8 mg) and NMO (0.4 mmol, 46.8 mg) in DMSO (1 mL) under air, azole (0.4 mmol) was added. The mixture was stirred at 140 ^oC and the progress of the reaction was monitored by TLC using ethyl acetate and hexane as an eluent. After an appropriate time, the resulting solution was diluted with ethyl acetate (3 x 10 mL) and then washed with brine (2 x 5 mL) and water (1 x 5 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 analytically pure substituted *N*-arylated azoles.

***N*-(8-(1*H*-Indol-1-yl)naphthalen-1-yl)picolinamide 3a.** Light green solid; purification (*n*-hexane/ethyl acetate 95/5); yield 72% (52 mg); mp 124-125 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 10.93 (br s, 1H), 8.43 (d, *J* = 7.8 Hz, 1H), 8.00 (d, *J* = 7.8 Hz, 1H), 7.92 (d, *J* = 7.8 Hz, 1H), 7.86-7.85 (m, 2H), 7.67-7.62 (m, 2H), 7.52 (t, *J* = 7.8 Hz, 1H), 7.45 (d, *J* = 7.8 Hz, 1H), 7.34 (d, *J* = 7.2 Hz, 1H), 7.25-7.24 (m, 1H), 7.22-7.20 (m, 1H), 7.13-7.10 (m, 1H), 7.08-7.07 (m, 1H), 7.05 (t, *J* = 7.8 Hz, 1H), 6.524-6.520 (m, 1H) ;^{13}C NMR (150 MHz, $CDCl_3$) δ 162.6, 149.5, 147.2, 139.4, 136.9, 136.3, 134.4, 132.5, 130.3, 130.0, 129.6, 128.5, 126.8, 126.2, 125.8, 125.6, 123.6, 122.8, 122.7, 121.8, 120.8, 120.5, 111.0, 104.8; FT-IR (KBr) 3298, 3279, 1684, 1446, 1529, 1498, 1268, 1151, 1031, 829 cm^{-1}; HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{24}H_{17}N_3O$ 364.1450, found 364.1457. HPLC: Daicel CHIRALCEL OD, hexane/*i*PrOH = 90:10, flow rate: 1 mL /min, λ = 215 nm, first enantiomer (t_R = 10.38 min, 47.2% of integration), second enantiomer (t_R = 12.18 min, 52.7% of integration).

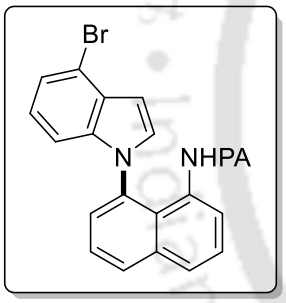


***N*-(8-(1*H*-Indol-1-yl)naphthalen-1-yl)isoquinoline-1-carboxamide 3a′.** Brown solid;



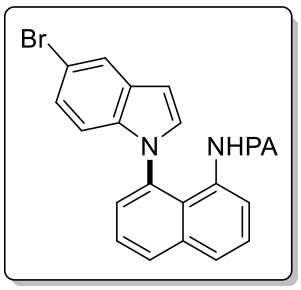
purification (*n*-hexane/ethyl acetate 95/5); yield 71% (58 mg); mp 133-134 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.72 (br s, 1H), 9.29 (d, *J* = 8.8 Hz, 1H), 8.37 (d, *J* = 7.6 Hz, 1H), 8.03 (d, *J* = 8.4 Hz, 1H), 7.90 (d, *J* = 8.0 Hz, 1H), 7.85 (d, *J* = 5.6 Hz, 1H), 7.79 (d, *J* = 8.4 Hz, 1H), 7.69-7.65 (m, 2H), 7.62-7.59 (m, 2H), 7.54 (t, *J* = 7.2 Hz, 1H), 7.37 (d, *J* = 7.2 Hz, 1H), 7.24 (d, *J* = 3.2 Hz, 1H), 7.13 (d, *J* = 7.6 Hz, 1H), 7.04-6.99 (m, 2H), 6.75- 6.71 (m, 1H), 6.32 (d, *J* = 3.2 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 164.1, 147.9, 139.8, 139.1, 137.3, 136.4, 134.3, 132.4, 130.3, 130.2, 129.9, 128.9, 128.5, 128.4, 127.7, 126.8, 126.76, 126.72, 126.4, 125.6, 124.4, 124.0, 123.6, 122.9, 120.7, 120.2, 104.3; FT-IR (KBr) 3385, 1677, 1600, 1489, 1384, 1136, 1019, 822 cm^{-1}; HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{28}H_{19}N_3O$ 414.1606, found 414.1598.

***N*-(8-(4-Bromo-1*H*-indol-1-yl)naphthalen-1-yl)picolinamide 3b.** Brown oily liquid;



purification (*n*-hexane/ethyl acetate 96/4); yield 63% (55 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.80 (br s, 1H), 8.40 (d, *J* = 7.2 Hz, 1H), 8.16 (d, *J* = 7.8 H, 1H), 8.11 (s, 1H), 8.01 (t, *J* = 9.6 Hz, 2H), 7.82 (t, *J* = 6.0 Hz, 1H), 7.77 (t, *J* = 7.8 Hz, 1H), 7.66 (t, *J* = 7.66 Hz, 1H), 7.46-7.42 (m, 3H), 7.30 (d, *J* = 7.2 Hz, 1H), 7.11-7.06 (m, 2 H), 6.64 (br s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 162.7, 149.1, 147.5, 139.4, 137.0, 136.4, 133.8, 132.0, 130.8, 130.6, 130.1, 128.7, 126.9, 126.7, 126.3, 125.6, 124.08, 124.06, 123.8, 123.3, 121.8, 114.8, 110.2, 104.6; FT-IR (KBr) 3326, 1683, 1599, 1526, 1495, 1319, 1283, 1177, 825 cm^{-1}; HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{24}H_{16}BrN_3O$ 442.0555, found 442.0558.

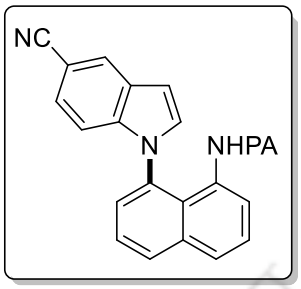
***N*-(8-(5-Bromo-1*H*-indol-1-yl)naphthalen-1-yl)picolinamide 3c.** White solid; purification (*n*-



hexane/ethyl acetate 95/5); yield 67% (59 mg); mp 160-161°C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.60 (br s, 1H), 8.24 (d, *J* = 7.2 hz, 1H), 8.01 (d, *J* = 8.4 Hz, 1H), 7.96-7.95 (m, 1H), 7.89 (d, *J* = 7.2 Hz, 2H), 7.73 (t, *J* = 7.8 Hz, 1H), 7.64 (t, *J* = 7.8 Hz, 1H), 7.54 (t, *J* = 7.8 Hz, 1H), 7.43 (s, 1H), 7.35 (d, *J* = 7.2 Hz, 1H), 7.30-7.29 (m, 1H), 7.17 (d, *J* = 8.4 Hz, 1H), 6.92 (d, *J* = 8.4 Hz, 1H), 6.40 (br s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 162.7, 149.5, 147.2,

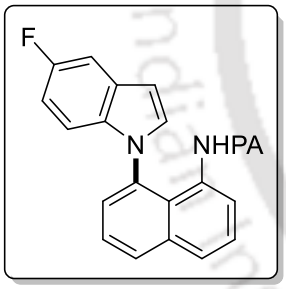
137.9, 137.1, 136.4, 133.7, 132.0, 131.4, 131.0, 130.5, 128.6, 126.9, 126.7, 126.1, 125.6, 125.5, 124.2, 124.1, 123.2, 121.9, 113.8, 112.5, 103.9; FT-IR (KBr) 3100, 1680, 1519, 1498, 1318, 1192, 1042, 889 cm^{-1}; HRMS (APCI) *m/z*: $[M+H]^+$ calcd for $C_{24}H_{16}BrN_3O$ 442.0555, found 442.0562.

***N*-(8-(5-Cyano-1*H*-indol-1-yl)naphthalen-1-yl)picolinamide 3d**. Grey solid; purification (*n*-



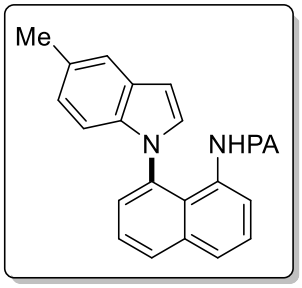
hexane/ethyl acetate 80/20); yield 61% (47 mg); mp 162-163°C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.43 (br s, 1H), 8.16 (d, *J* = 7.8 Hz, 1H), 8.07 (d, *J* = 8.4 Hz, 1H), 7.92-7.91 (m, 2H), 7.88 (d, *J* = 7.8 Hz, 1H), 7.73 (t, *J* = 7.8 Hz, 1H), 7.66 (t, *J* = 7.8 Hz, 2H), 7.57 (t, *J* = 7.8 Hz, 1H), 7.37-7.36 (m, 2H), 7.33-7.29 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 162.5, 149.2, 147.1, 140.5, 137.3, 136.4, 133.0, 132.6, 131.6, 130.9, 129.0, 128.6, 127.1, 127.0, 126.3, 126.2, 125.7, 125.6, 125.0, 124.3, 122.0, 111.9, 104.8, 103.5, 100.2; FT-IR (KBr) 3347, 2923, 2218, 1681, 1522, 1430, 1328, 1019, 818 cm^{-1}; HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{25}H_{16}N_4O$ 389.1402, found 389.1401.

***N*-(8-(5-Fluoro-1*H*-indol-1-yl)naphthalen-1-yl)picolinamide 3e.** Brown solid; purification (*n*-



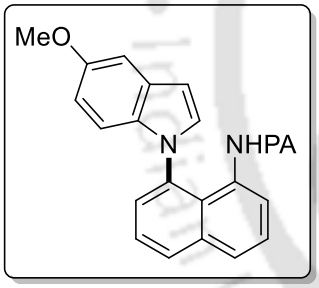
hexane/ethyl acetate 96/4); yield 76% (58 mg); mp 109-110°C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.85 (br s, 1H), 8.36 (d, *J* = 7.2 Hz, 1H), 8.01 (d, *J* = 7.8 Hz, 1H), 7.96 (br s, 1H), 7.93 (d, *J* = 7.8 Hz, 1H), 7.87 (d, *J* = 7.8 Hz, 1H), 7.70 (t, *J* = 7.8 Hz, 1H), 7.64 (t, *J* = 8.4 Hz, 1H), 7.53 (t, *J* = 8.4 Hz, 1H), 7.33 (d, *J* = 7.2 Hz, 1H), 7.29 (br s, 1H), 7.27-7.26 (m, 1H), 7.03 (d, *J* = 9.6 Hz, 1H), 6.96-6.95 (m, 1H), 6.83 (t, *J* = 9.6 Hz, 1H), 6.47 (br s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 162.6, 159.2 (J_{C-F} = 233.8 Hz), 149.5, 147.2, 137.0, 136.4, 136.0, 134.1, 132.2, 131.9, 130.3, 129.9 (J_{C-F} = 10.2 Hz), 128.5, 126.9, 126.4, 126.0, 125.6, 123.8, 123.4, 121.9, 111.8 (J_{C-F} = 9.4 Hz), 111.1 (J_{C-F} = 25.9 Hz), 105.6 (J_{C-F} = 23.2 Hz), 104.53 (J_{C-F} = 4.2 Hz); FT-IR (KBr) 3096, 1679, 119, 1497, 1330, 1281, 1115, 825 cm^{-1}; HRMS (APCI) *m/z*: $[M+H]^+$ calcd for $C_{24}H_{16}FN_3O$ 382.1356, found 382.1358.

***N*-(8-(5-Methyl-1*H*-indol-1-yl)naphthalen-1-yl)picolinamide 3f.** Green oily liquid; purification



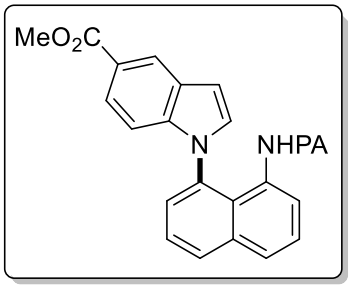
(*n*-hexane/ethyl acetate 94/6); yield 72% (54 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.99 (br s, 1H), 8.40 (d, *J* = 7.8 Hz, 1H), 7.99 (d, *J* = 8.4 Hz, 1H), 7.90-7.89 (m, 2H), 7.85 (d, *J* = 7.8 Hz, 1H), 7.69 (td, *J* = 7.8 Hz, 1.8 Hz, 1H), 7.63 (t, *J* = 8.4 Hz, 1H), 7.51 (t, *J* = 7.8 Hz, 1H), 7.32 (d, *J* = 7.2 Hz, 1H), 7.24 (td, *J* = 6.6 Hz, *J* = 1.2 Hz, 1H), 7.21 (d, *J* = 3.0 Hz, 1H), 7.18 (br s, 1H), 6.94-6.90 (m, 2H), 6.44 (d, *J* = 3.0 Hz, 1H), 2.36 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 162.7, 149.7, 147.2, 137.9, 136.8, 136.4, 134.6, 132.5, 130.4, 130.0, 129.9, 129.6, 128.5, 126.8, 126.2, 125.8, 125.6, 124.4, 123.8, 122.9, 121.8, 120.5, 110.7, 104.4, 21.5; FT-IR (KBr) 2922, 1684, 1530, 1429, 1321, 1220, 1129, 1034, 824 cm^{-1}; HRMS (APCI) *m/z*: $[M+H]^+$ calcd for $C_{25}H_{19}N_3O$ 378.1606, found 378.1601. HPLC: Daicel CHIRALCEL OD, hexane/*i*PrOH = 90:10, flow rate: 1 mL /min, λ = 215 nm, first enantiomer (t_R = 8.49 min, 50.1% of integration), second enantiomer (t_R = 10.24 min, 49.9% of integration).

***N*-(8-(5-Methoxy-1*H*-indol-1-yl)naphthalen-1-yl)picolinamide 3g.** Green solid; purification (*n*-



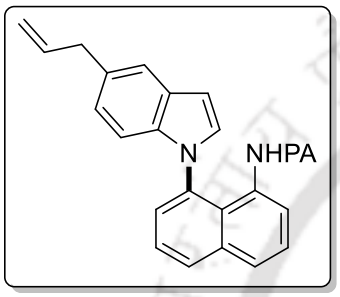
hexane/ethyl acetate 85/15); yield 74% (58 mg); mp 132-133°C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 10.02 (br s, 1H), 8.40 (d, *J* = 7.8 Hz, 1H), 7.99 (d, *J* = 8.4 Hz, 1H), 7.96-7.95 (m, 1H), 7.92 (d, *J* = 7.8 Hz, 1H), 7.85 (d, *J* = 8.4 Hz, 1H), 7.68 (t, *J* = 7.8 Hz, 1H), 7.63 (t, *J* = 7.8 Hz, 1H), 7.52 (t, *J* = 7.2 Hz, 1H), 7.33 (d, *J* = 7.2 Hz, 1H), 7.25-7.23 (m, 2H), 6.94 (d, *J* = 8.4 Hz, 1H), 6.86 (s, 1H), 6.75-6.73 (m, 1H), 6.46-6.45 (m, 1H), 3.78 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 162.7, 154.7, 147.3, 136.9, 136.4, 134.9, 134.6, 132.5, 131.0, 130.1, 130.0, 128.4, 126.8, 126.2, 125.8, 125.6, 123.7, 122.8, 121.9, 112.6, 111.7, 104.5, 102.9, 100.2, 56.1; FT-IR (KBr) 3139, 1671, 1530, 1498, 1430, 1336, 1268, 1192, 1150, 1029, 829 cm^{-1}; HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{25}H_{19}N_3O_2$ 394.1556, found 394.1563.

Methyl 1-(8-(picolinamido)naphthalen-1-yl)-1*H*-indole-5-carboxylate 3h. Grey solid; purification (*n*-hexane/ethyl acetate 88/12); yield 71% (59 mg); mp 116-117°C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.71 (br s, 1H), 8.30 (d, *J* = 7.2 Hz, 1H), 8.17 (br s, 1H), 8.04 (d, *J* = 7.8 Hz, 1H), 7.89-7.87 (m, 2H), 7.83-7.80 (m, 2H), 7.66 (d, *J* = 7.8 Hz, 2H), 7.55 (t, *J* = 7.8 Hz, 1H), 7.36 (d, *J* = 7.2 Hz, 1H), 7.29 (s, 1H), 7.24-7.23 (m, 1H), 7.08 (d, *J* = 8.4 Hz, 1H), 6.56 (br s, 1H), 3.92 (s,



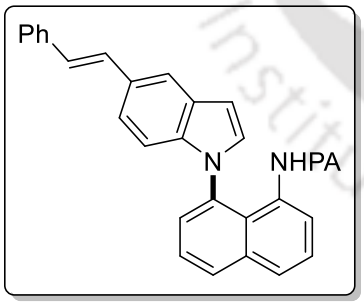
3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 168.2, 162.62, 149.3, 147.2, 141.6, 137.0, 136.4, 1333.7, 132.0, 131.8, 130.6, 129.1, 128.6, 127.0, 126.7, 126.1, 125.6, 124.2, 124.0, 123.9, 123.8, 122.5, 121.9, 110.7, 105.7; 52.1; FT-IR (KBr) 3056, 1708, 1689, 1424, 1432, 1326, 1277, 1189, 1083, 821 cm^{-1}; HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{26}H_{19}N_3O_3$ 422.1505, found 422.1505.

***N*-(8-(5-Allyl-1H-indol-1-yl)naphthalen-1-yl)picolinamide 3i**. Colorless oil; purification (*n*-



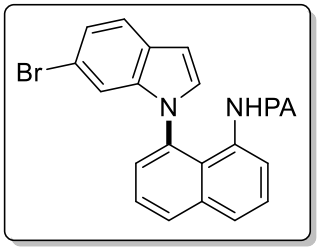
hexane/ethyl acetate 90/10); yield 61% (49 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.98 (br s, 1H), 8.39 (d, *J* = 7.2 Hz, 1H), 7.99 (d, *J* = 7.8 Hz, 1H), 7.90-7.844 (m, 3H), 7.68-7.62 (m, 2H), 7.52 (t, *J* = 7.8 Hz, 1H), 7.33 (d, *J* = 7.2 Hz, 1H), 7.23-7.21 (m, 3H), 6.98 (d, *J* = 8.4 Hz, 1H), 6.93 (d, *J* = 8.4 Hz, 1H), 6.46 (d, *J* = 3.0 Hz, 1H), 6.00-5.93 (m, 1H), 5.04-5.02 (m, 2H), 3.41 (d, *J* = 6.6 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 162.6, 149.7, 147.3, 138.7, 138.2, 136.9, 136.4, 134.6, 132.5, 131.9, 130.5, 130.0, 129.9, 128.4, 126.8, 126.2, 125.7, 125.6, 123.9, 123.8, 122.9, 121.8, 120.3, 115.2, 110.9, 104.5, 40.5; FT-IR (KBr) 3056, 3012, 2922, 1685, 1580, 1527, 1497, 1432, 1381, 1324, 1280, 1134, 997; HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{27}H_{21}N_3O$ 404.1763, found 404.1767.

(*E*)-*N*-(8-(5-Styryl-1*H*-indol-1-yl)naphthalen-1-yl)picolinamide 3j. Colorless oily liquid;

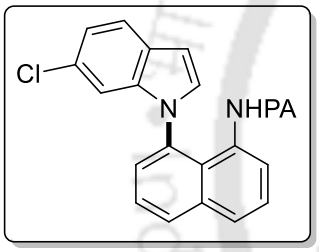


purification (*n*-hexane/ethyl acetate 88/12); yield 58% (54 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.87 (br s, 1H), 8.36 (d, *J* = 7.8 Hz, 1H), 8.02 (d, *J* = 7.8 Hz, 1H), 7.89-7.87 (m, 3H), 7.65 (t, *J* = 7.8 Hz, 2H), 7.56-7.53 (m, 3H), 7.49 (s, 1H), 7.38-7.37 (m, 3H), 7.36-7.35 (m, 1H), 7.23-7.22 (m, 3H), 7.19-7.16 (m, 1H), 7.06 (d, *J* = 8.4 Hz, 1H), 7.03 (d, *J* = 16.2 Hz, 1H), 6.49 (d, *J* = 3.0 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 167.7, 149.6, 147.3, 139.1, 138.1, 136.9, 136.4, 134.2, 132.3, 132.0, 131.0, 130.2, 130.1, 130.0, 129.9, 129.8, 128.9, 128.5, 127.3, 126.9, 126.45, 126.41, 126.4, 125.9, 125.6, 124.0, 123.4, 121.9,121.6, 119.4, 111.3, 104.9; FT-IR (KBr) 3309, 1682, 1597, 1529, 1496, 1432, 1326, 961, 826 cm^{-1}; HRMS (APCI) *m/z*: $[M+H]^+$ calcd for $C_{32}H_{23}N_3O$ 466.1919, found 466.1922.

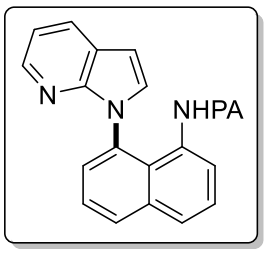
***N*-(8-(6-Bromo-1*H*-indol-1-yl)naphthalen-1-yl)picolinamide 3k.** Oily liquid; purification (*n*-hexane/ethyl acetate 94/6); yield 69% (60 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.83 (br s, 1H), 8.35 (d, *J* = 7.8 Hz, 1H), 8.03 (d, *J* = 8.4 Hz, 1H), 7.97 (d, *J* = 7.8 Hz, 1H), 7.88-7.85 (m, 2H), 7.70 (td, *J* = 7.8 Hz, 1.2 Hz, 1H), 7.64 (t, *J* = 7.8 Hz, 1H), 7.54 (t, *J* = 7.8 Hz, 1H), 7.33 (d, *J* = 7.2 Hz, 1H), 7.30 (d, *J* = 8.4 Hz, 1H), 7.25 (br s, 1H), 7.24-7.22 (m, 1H), 7.18 (d, *J* = 3.6 Hz, 1H), 7.03 (d, *J* = 8.4 Hz, 1.2 Hz, 1H), 6.43 (d, *J* = 3.0 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 162.6, 149.5, 147.2, 140.0, 137.1, 136.4, 133.6, 132.1, 131.1, 130.5, 128.6, 128.4, 127.0, 126.6, 125.9, 125.6, 123.9, 123.8, 123.6, 122.0, 121.9, 116.3, 114.0, 104.6; FT-IR (KBr) 3322, 2924, 1682, 1599, 1526, 1463, 1321, 1263, 1040, 804 cm^{-1}; HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{24}H_{16}BrN_3O$ 442.0555, found 442.0551.



***N*-(8-(6-Chloro-1*H*-indol-1-yl)naphthalen-1-yl)picolinamide 3l.** Sticky colorless liquid; purification (*n*-hexane/ethyl acetate 92/8); yield 73% (58 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.86 (br s, 1H), 8.37 (d, *J* = 7.8 Hz, 1H), 8.02 (d, *J* = 8.4 Hz, 1H), 7.97 (d, *J* = 7.8 Hz, 1H), 7.88-7.86 (m, 2H), 7.69 (t, *J* = 7.2 Hz, 1H), 7.64 (t, *J* = 7.8 Hz, 1H), 7.53 (t, *J* = 8.4 Hz, 1H), 7.35-7.32 (m, 2H), 7.23-7.20 (m, 2H), 7.10 (s, 1H), 7.03 (d, *J* = 8.4 Hz, 1H), 6.44 (br s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 162.6, 149.5, 147.2, 139.6, 137.1, 136.4, 133.7, 132.2, 131.2, 130.5, 128.7, 128.5, 128.1, 126.9, 126.5, 125.9, 125.6, 123.8, 123.5, 121.9, 121.6, 121.2, 111.0; FT-IR (KBr) 3330, 1683, 1600, 1526, 1495, 1463, 1384, 1323, 899, 823 cm^{-1}; HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{24}H_{16}ClN_3O$ 398.1060, found 398.1051.

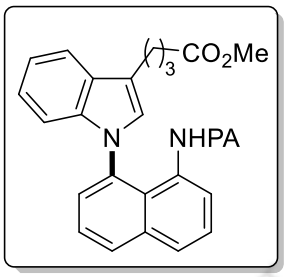


***N*-(8-(1*H*-Pyrrolo[2,3-*b*]pyridin-1-yl)naphthalen-1-yl)picolinamide 3m.** Pale brown solid; purification (*n*-hexane/ethyl acetate 88/12); yield 53% (38 mg); mp 165-166°C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.71 (br s, 1H), 8.33 (d, *J* = 4.8 Hz, 1H), 8.19 (d, *J* = 7.8 Hz, 1H), 8.01 (d, *J* = 7.8 Hz, 1H), 7.98 (d, *J* = 7.8 Hz, 1H), 7.88 (d, *J* = 8.4 Hz, 1H), 7.79 (d, *J* = 4.8 Hz, 1H), 7.77 (d, *J* = 7.8 Hz, 1H), 7.69 (t, *J* = 7.8 Hz, 1H), 7.61 (t, *J* = 7.8 Hz, 1H), 7.4 (t, *J* = 7.2 Hz, 1H), 7.36 (d, *J* = 7.2 Hz, 1H), 7.28 (d, *J* = 3.6 Hz, 1H), 7.21-7.18 (m, 1H), 7.08-7.05 (m, 1H), 6.35 (d, *J* = 3.6 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 162.5, 150.3, 149.6, 147.2, 144.3, 137.1, 136.5,



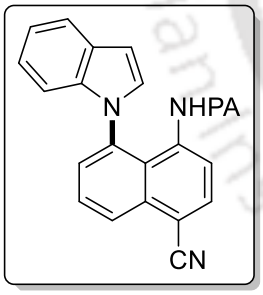
133.1, 132.1, 131.0, 130.4, 129.0, 128.9, 127.0, 126.7, 125.8, 125.6, 125.0, 124.3, 121.9, 121.7, 116.6, 102.2; FT-IR (KBr) 3369, 1689, 170, 121, 1493, 1434, 1341, 1274, 1119, 823 cm^{-1}; HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{23}H_{16}N_4O$ 365.1402, found 365.1409.

Methyl 4-(1-(8-(picolinamido)naphthalen-1-yl)-1*H*-indol-3-yl)butanoate 3n. Grey solid;



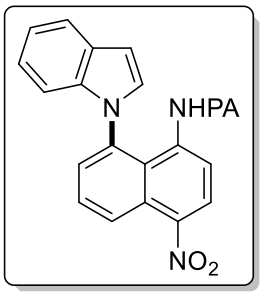
purification (*n*-hexane/ethyl acetate 95/5); yield 39% (36 mg); mp 99-100°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.02 (br s, 1H), 8.38 (dd, *J* = 7.6 Hz, 1.2 Hz, 1H), 7.97 (dd, *J* = 8.4 Hz, 1.6 Hz, 1H), 7.94-7.92 (m, 1H), 7.84 (dd, *J* = 8.4 Hz, 1.2 Hz, 1H), 7.76-7.75 (m, 1H), 7.66 (td, *J* = 7.6 Hz, 1.6 Hz, 1H), 7.62 (t, *J* = 8.0 Hz, 1H), 7.52 (t, *J* = 7.6 Hz, 1H), 7.43 (d, *J* = 8.0 Hz, 1H), 7.35 (dd, *J* = 7.2 Hz, 1.6 Hz, 1H), 7.22-7.18 (m, 1H), 7.17-7.05 (m, 3H), 7.00 (s, 1H), 3.64 (s, 3H), 2.62-2.48 (m, 2H), 2.31-2.26 (m, 2H), 1.90-1.80 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 174.1, 162.6, 149.6, 147.3, 139.7, 137.0, 136.4, 134.5, 132.5, 129.8, 129.3, 128.3, 127.7, 126.8, 126.3, 125.8, 125.6, 123.8, 123.0, 122.8, 121.9, 120.0, 119.0, 117.8, 111.1, 51.7, 33.8, 25.0, 24.; FT-IR (KBr) 3304, 1723, 1678, 12, 1497, 1230, 1135, 830 cm^{-1}; HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{29}H_{25}N_3O_3$ 464.1974, found 464.1966.

***N*-(4-Cyano-8-(1*H*-indol-1-yl)naphthalen-1-yl)picolinamide 4a.** Light brown solid; purification



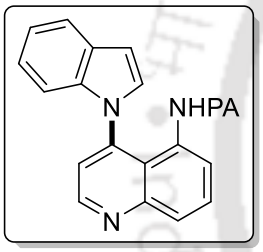
(*n*-hexane/ethyl acetate 94/6); yield 73% (56 mg); mp 216-217°C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 10.74 (br s, 1H), 8.71 (d, *J* = 8.4 Hz, 1H), 8.26 (d, *J* = 8.4 Hz, 1H), 7.91 (d, *J* = 8.0 Hz, 1H), 7.79 (d, *J* = 8.0 Hz, 1H), 7.58-7.49 (m, 3H), 7.41 (d, *J* = 7.6 Hz, 1H), 7.27 (d, *J* = 7.2 Hz, 1H), 7.09-7.08 (m, 1H), 7.06-7.03 (m, 1H), 6.97-6.91 (m, 3H); 6.52 (d, *J* = 3.2 Hz, 1H); ^{13}C{H} NMR (150 MHz, $CDCl_3$) δ 162.8, 148.8, 147.3, 139.6, 138.2, 137.3, 135.7, 135.5, 134.3, 130.5, 130.2, 129.7, 128.3, 127.0, 126.4, 123.4, 122.1, 121.9, 121.2, 121.1, 118.6, 118.3, 111.1, 106.4, 106.3; FT-IR (KBr) 3224, 1691, 1527, 1502, 1318, 1122, 842 cm^{-1}; HRMS (APCI) *m/z*: $[M+H]^+$ calcd for $C_{25}H_{16}N_4O$ 389.1402, found 389.1411.

***N*-(8-(1*H*-Indol-1-yl)-4-nitronaphthalen-1-yl)picolinamide 4b.** Pale yellow solid; purification



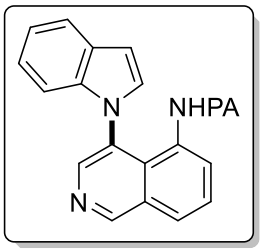
(*n*-hexane/ethyl acetate 92/8); yield 68% (55 mg); mp 231-232°C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 10.90 (br s, 1H), 8.89 (d, *J* = 8.4 Hz, 1H), 8.43 (dd, *J* = 8.4 Hz, 1.2 Hz, 1H), 8.08 (d, *J* = 7.8 Hz, 1H), 7.96 (d, *J* = 7.8 Hz, 1H), 7.75-7.772 (m, 2H), 7.69 (td, *J* = 7.8 Hz, 1.8 Hz, 1H), 7.58 (d, *J* = 7.8 Hz, 1H), 7.44-7.43 (m, 1H), 7.26 (br s, 1H), 7.23-7.21 (m, 1H), 7.16-7.09 (m, 3H), 6.70 (d, *J* = 3.0 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 162.8, 148.8, 147.3, 143.4, 139.4, 138.9, 137.3, 135.5, 130.4, 130.2, 129.4, 128.8, 128.4, 126.4, 125.9, 124.4, 123.4, 122.3, 122.1, 121.2, 121.1, 117.6, 111.1, 106.4; FT-IR (KBr) 3253, 2214, 1692, 1526, 1460, 1323, 1126, 819 cm^{-1}; HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{24}H_{16}N_4O_3$ 409.1301, found 409.1304.

***N*-(4-(1*H*-Indol-1-yl)quinolin-5-yl)picolinamide 4c.** Oily liquid; purification (*n*-hexane/ethyl



acetate 92/8); yield 56% (40 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 10.31, 8.97 (d, *J* = 4.2 Hz, 1H), 8.60 (d, *J* = 7.8 Hz, 1H), 8.13 (d, *J* = 8.4 Hz, 1H), 7.94 (d, *J* = 7.8 Hz, 1H), 7.88 (t, *J* = 8.4 Hz, 1H), 7.78 (d, *J* = 4.8 Hz, 1H), 7.68 (t, *J* = 7.8 Hz, 1H), 7.48 (d, *J* = 7.8 Hz), 7.31 (d, *J* = 4.2 Hz, 1H), 7.27-7.26 (m, 1H), 7.22-7.20 (m, 1H), 7.16-7.13 (m, 2H), 7.09-7.06 (m, 1H), 6.62 (d, *J* = 3.6 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 162.4, 151.4, 150.4, 149.2, 147.2, 143.3, 138.5, 137.1, 132.8, 130.6, 130.0, 129.5, 127.1, 126.1, 123.5, 121.9, 121.7, 121.3, 121.1, 121.0, 110.8, 106.45, 100.2; FT-IR (KBr) 3104, 1681, 1587, 1528, 1491, 1457, 1331, 1127, 812 cm^{-1}; HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{23}H_{16}N_4O$ 365.1402 , found 365.1403.

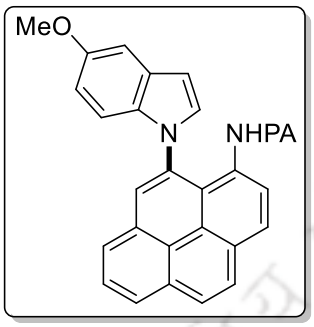
***N*-(4-(1*H*-Indol-1-yl)isoquinolin-5-yl)picolinamide 4d.** Oily liquid; purification (*n*-hexane/ethyl



acetate 70/30); yield 65% (47 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 10.25 (br s, 1H), 9.33 (s, 1H), 8.79 (d, *J* = 7.8 Hz, 1H), 8.34 (s, 1H), 7.98 (d, *J* = 8.4 Hz, 1H), 7.93 (d, *J* = 7.8 Hz, 1H), 7.87 (d, *J* = 4.8 Hz, 1H), 7.79 (t, *J* = 8.4 Hz, 1H), 7.67 (t, *J* = 7.8 Hz, 1H), 7.53 (d, *J* = 7.8 Hz, 1H), 7.30 (d, *J* = 3.0 H, 1H), 7.24-7.21 (m, 1H), 7.10 (t, *J* = 7.2 Hz, 1H), 7.06 (t, *J* = 7.8 Hz, 1H), 7.02 (d, *J* = 7.8 Hz, 1H), 6.67 (d, *J* = 3.0 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 162.7, 153.8, 149.1, 147.3, 144.7, 139.7, 137.1, 132.2, 130.6, 130.2, 129.8, 129.4, 128.6, 126.1, 125.9, 125.4,

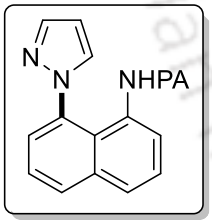
125.0, 123.2, 121.9, 120.9, 110.7, 105.6; FT-IR (KBr) 3284, 3122, 2924, 2854, 1685, 1576, 1522, 1479, 1455, 1350, 1321, 1277, 1205, 1126, 1099 cm^{-1}; HRMS (APCI) *m/z*: $[M+H]^+$ calcd for $C_{23}H_{16}N_4O$ 365.1402, found 365.1403.

***N*-(10-(5-Methoxy-1*H*-indol-1-yl)pyren-1-yl)picolinamide 4e.** Oily liquid; purification (*n*-



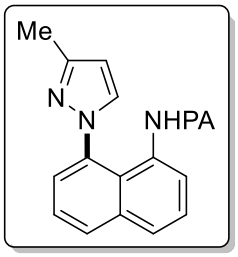
hexane/ethyl acetate 92/8); yield 35% (32 mg); ^1H NMR (600 MHz, $CDCl_3$) δ 10.15 (br s, 1H), 8.85 (d, *J* = 8.4 Hz, 1H), 8.34 (d, *J* = 8.4 Hz, 1H), 8.26 (d, *J* = 7.8 Hz, 1H), 8.15 (d, *J* = 9.0 Hz, 1H), 8.10-8.09 (m, 2H), 8.04-8.02 (m, 2H), 7.97-7.96 (m, 2H), 7.71 (dd, *J* = 7.2 Hz, 1.2 Hz, 1H), 7.37 (d, *J* = 3.0 Hz, 1H), 7.29-7.27 (m, 1H), 7.06 (d, *J* = 9.0 Hz, 1H), 6.87-6.86 (m, 1H), 6.77 (dd, *J* = 9.0 Hz, 2.4 Hz, 1H), 6.50 (d, *J* = 3.0 Hz, 1H), 3.80 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 162.8, 154.8, 149.8, 147.3, 137.0, 134.6, 133.8, 131.7, 131.4, 130.8, 130.5, 130.2, 129.5, 129.4, 128.1, 127.2, 127.0, 126.9, 126.8, 126.3, 125.9, 125.0, 124.7, 123.9, 122.0, 120.2, 112.7, 111.8, 104.6, 103.1, 56.1; FT-IR (KBr) 3050, 2925, 1681, 1605, 1516, 1382, 1321, 1260, 1229, 1150, 1031 cm^{-1}; HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{31}H_{21}N_3O_2$ 468.1712, found 468.1703.

***N*-(8-(1*H*-Pyrazol-1-yl)naphthalen-1-yl)picolinamide 6a.** Grey liquid; purification (*n*-



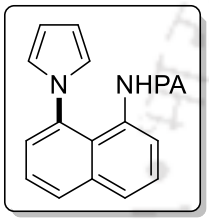
hexane/ethyl acetate 80/20); yield 63% (39 mg); ^1H NMR (400 MHz, $CDCl_3$) δ 9.61 (br s, 1H), 8.50 (d, *J* = 4.8 Hz, 1H), 8.11 (d, *J* = 7.6 Hz, 1H), 8.04 (d, *J* = 7.6 Hz, 1H), 8.01 (d, *J* = 8.4 Hz, 1H), 7.87 (d, *J* = 8.0 Hz, 1H), 7.80 (t, *J* = 7.6 Hz, 1H), 7.67 (br s, 1H), 7.63-7.60 (m, 2H), 7.49 (t, *J* = 7.6 Hz, 1H), 7.42-7.39 (m, 1H), 7.38 (d, *J* = 7.2 Hz, 1H), 6.06 (d, *J* = 2.0 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 163.5, 150.1, 147.6, 142.0, 137.2, 136.2, 135.7, 133.1, 131.7, 130.9, 127.5, 127.1, 126.7, 126.3, 126.0, 125.0, 124.3, 122.4, 106.8; FT-IR (KBr) 3057, 2924, 2854, 1680, 1598, 1495, 1464, 1435, 1395, 1343, 1274, 1133, 1042 cm^{-1}; HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{19}H_{14}N_4O$ 315.1246, found 315.1237.

***N*-(8-(3-Methyl-1*H*-pyrazol-1-yl)naphthalen-1-yl)picolinamide 6b.** Grey liquid; purification



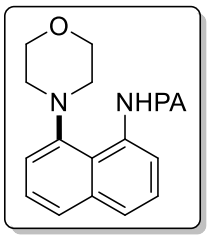
(*n*-hexane/ethyl acetate 80/20); yield 69% (45 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.67 (br s, 1H), 8.52 (d, *J* = 4.8 Hz, 1H), 8.13 (d, *J* = 7.8 Hz, 1H), 7.99 (d, *J* = 7.2 Hz, 1H), 7.97 (d, *J* = 8.4 Hz, 1H),7.85 (d, *J* = 8.4 Hz), 7.82 (td, *J* = 7.8 Hz, 1.2 Hz, 1H), 7.60 (t, *J* = 7.8 Hz, 1H), 7.51-7.50 (m, 1H), 7.47 (t, *J* = 7.8 Hz, 1H), 7.42-7.40 (m, 1H), 7.35 (d, *J* = 6.6 Hz, 1H), 5.87 (d, *J* = 2.4 Hz, 1H), 2.30 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 163.5, 151.5, 150.5, 147.7, 137.3, 136.2, 135.8, 133.7, 131.7, 130.6, 127.3, 127.1, 126.7, 126.3, 126.2, 125.0, 124.5, 122.6, 106. 9, 14.0; FT-IR (KBr) 3316, 1681, 1526, 1494, 1433, 1337, 1277, 1129, 1043, 998, 823 cm^{-1}; HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{20}H_{16}N_4O$ 329.1402, found 329.1404.

***N*-(8-(1*H*-Pyrrol-1-yl)naphthalen-1-yl)picolinamide 6c.** Sticky brown liquid; purification (*n*-



hexane/ethyl acetate 90/10); yield 51% (32 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.68 (br s, 1H), 8.41 (d, *J* = 4.8 Hz, 1H), 8.31 (d, *J* = 8.0 Hz, 1H), 8.13 (d, *J* = 8.0 Hz, 1H), 7.94 (d, *J* = 8.4 Hz, 1H), 7.82-7.79 (m, 2H), 7.60 (t, *J* = 7.6 Hz, 1H), 7.47 (t, *J* = 7.6 Hz, 1H), 7.41-7.37 (m, 1H), 7.34 (d, *J* = 7.2 Hz, 1H), 6.88 (br s, 1H), 6.05 (br s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 163.3, 150.4, 147.6, 137.2, 136.3, 136.1, 132.3, 129.7, 127.5, 126.7, 126.4, 126.2, 125.2, 123.9, 123.7, 123.3, 122.2, 110.3; FT-IR (KBr) 3056, 2921, 2852, 1682, 1597, 1525, 1499, 1432, 1380, 1314, 1261, 1094, 1041 cm^{-1}; HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{20}H_{15}N_3O$ 314.1293, found 314.1287.

***N*-(8-Morpholinonaphthalen-1-yl)picolinamide 6g**. Yellowish solid; purification (*n*-



hexane/ethyl acetate 88/12); yield 23% (15 mg); mp 162-163°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 13.83 (br s, 1H), 9.14 (d, *J* = 7.6 Hz, 1H), 8.75 (d, *J* = 4.8 Hz, 1H), 8.40 (d, *J* = 8.0 Hz, 1H), 7.94 (t, *J* = 8.0 Hz, 1H), 7.67 (d, *J* = 8.0 Hz, 1H), 7.62 (d, *J* = 8.0 Hz, 1H), 7.54-7.49 (m, 2H), 7.44 (t, *J* = 7.6 Hz, 1H), 7.39 (d, *J* = 7.6 Hz, 1H), 4.27-4.21 (m, 2H), 3.86-3.83 (m, 2H), 3.21-3.18 (m, 2H), 3.06-3.00 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 163.4, 151.5, 149.4, 148.1, 142.4, 137.7, 136.6, 135.6, 126.6, 126.5, 125.7, 124.7, 123.6, 120.0, 117.4, 100.2, 65.8, 54.7; FT-IR (KBr) 3053, 2960, 2842, 1657, 1527, 1494, 1428, 1343, 1262, 113, 1024, 996 cm^{-1}; HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{20}H_{19}N_3O_2$ 334.1556, found 334.1561.

8-(1*H*-Indol-1-yl)naphthalen-1-amine 7. Green liquid; purification (*n*-hexane/ethyl acetate 96/4): yield 91% (47 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, *J* = 8.0 Hz, 1H), 7.71 (d, *J* = 7.6 Hz, 1H), 7.41 (t, *J* = 7.6 Hz, 1H), 7.35 (d, *J* = 7.6 Hz, 1H), 7.30 (d, *J* = 7.2 Hz, 1H), 7.24-7.20 (m, 2H), 7.19-7.11 (m, 2H), 6.98 (d, *J* = 8.0 Hz, 1H), 6.74-6.73 (m, 1H), 6.57-6.55 (m, 1H), 3.34 (br s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.8, 138.8, 136.9, 134.5, 130.2, 129.8, 128.2, 127.3, 126.8, 125.2, 122.9, 121.1, 120.7, 120.3, 118.6, 112.1, 111.3, 103.5; FT-IR (KBr) 3456, 1622, 1454, 1401, 1325, 1214, 1010, 822 cm^{-1}; HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{18}H_{14}N_2$ 259.1235, found 259.1232.

Procedure for the Removal of Directing Group. To a stirred solution of NaOH (1.4 mmol, 56 mg) in EtOH (1.5 mL) added *N*-(8-(1*H*-indol-1-yl)naphthalen-1-yl)picolinamide **3a** (0.2 mmol, 51.7 mg). The resultant solution was stirred at room temperature for 2 min and then at 80 °C for 6 h. After completion, the reaction mixture was cooled to room temperature and diluted with ethyl acetate (4 x 15 mL). The mixture was successively washed with 0.5 N HCl (4 x 5mL), brine (2 x 5 mL) and water (5 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 (96/4 v/v) as an eluent to afford analytically pure **7** as a pale green liquid.

Preparation of *N*-(naphthalen-1-yl-8-*d*)picolinamide (1a-*d*).[22a] The titled compound was prepared according to the reported procedure as pale yellow solid. The deuterium incorporation was determined using 600 MHz ^{1}H NMR as 93%.

Intermolecular Kinetic Isotope Effect Study. Indole **2a** (0.4 mmol, 46.8 mg) was reactaed with *N*-(naphthalen-1-yl)picolinamide **1a** (0.2 mmol, 49.6 mg) and *N*-(naphthalen-1-yl-8-d)picolinamide **1a-*d*** (0.2 mmol, 49.8 mg) for 2 h under standard conditions. The resulting solution was then diluted with ethyl acetate (3 x 10 mL) and washed with brine (2 x 5 mL) and water (5 mL). Drying (Na_2SO_4) and evaporation of the solvent gave a residue that was purified on silica column chromatography using *n*-hexane and ethyl acetate as eluent to afford **3a** and a mixture of unreacted **1a** and **1a-*d*** as a white solid. The intermolecular k_H/k_D was found to be 1.1, based on 600 MHz ^{1}H NMR of the recovered substrates **1a** and **1a-*d***.

Crystal Data and Structure Refinement for 3h at 293(2) K

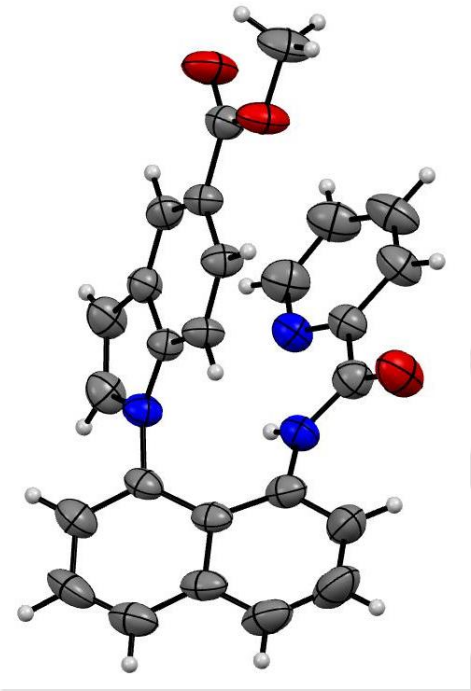


Figure 3. ORTEP diagram of methyl 1-(8-(picolinamido)naphthalen-1-yl)-1*H*-indole-5-carboxylate **3h** with 50% ellipsoid (**CCDC 1528745**).

Identification code	**3h**
Empirical formula	$C_{26}H_{19}N_3O_3$
Formula weight	421.44
Crystal habit, colour	Needle / colorless
Crystal size, mm^3	0.32 x 0.24 x 0.12
Temperature, *T*/K	296 (2)
Wavelength, λ/Å	0.71073
Crystal system	Triclinic
Space group	'P -1
Unit cell dimensions	*a* = 8.8838(6)Å
	b = 8.9296(11)Å
	c = 13.3506(8)Å

	α = 97.838(7)°
	β = 98.644(5)°
	γ = 91.067(8)°
Volume, V/Å^3	1036.44(16)
Z	2
Calculated density, Mg·m^{-3}	1.350
Absorption coefficient, μ/mm^{-1}	0.090
F(000)	440
θ range for data collection	3.92 to 27.65°
Limiting indices	$-10 \le h \le 7$, $-8 \le k \le 9$, $-10 \le l \le 16$
Reflection collected / unique	3740 / 2930 [R(int) = 0.0149]
Completeness to θ	99.70 % (θ = 25.25°)
Max. and min. transmission	0.974 and 0.989
Refinement method	SHELXL-97 (Sheldrick, 1997)'
Data / restraints / parameters	3740/0/ 290
Goodness–of–fit on F^2	1.048
Final R indices [I>2sigma(I)]	R1 = 0.0491, wR2 = 0.1001
R indices (all data)	R1 = 0.0630, wR2 = 0.1076

2.6 References

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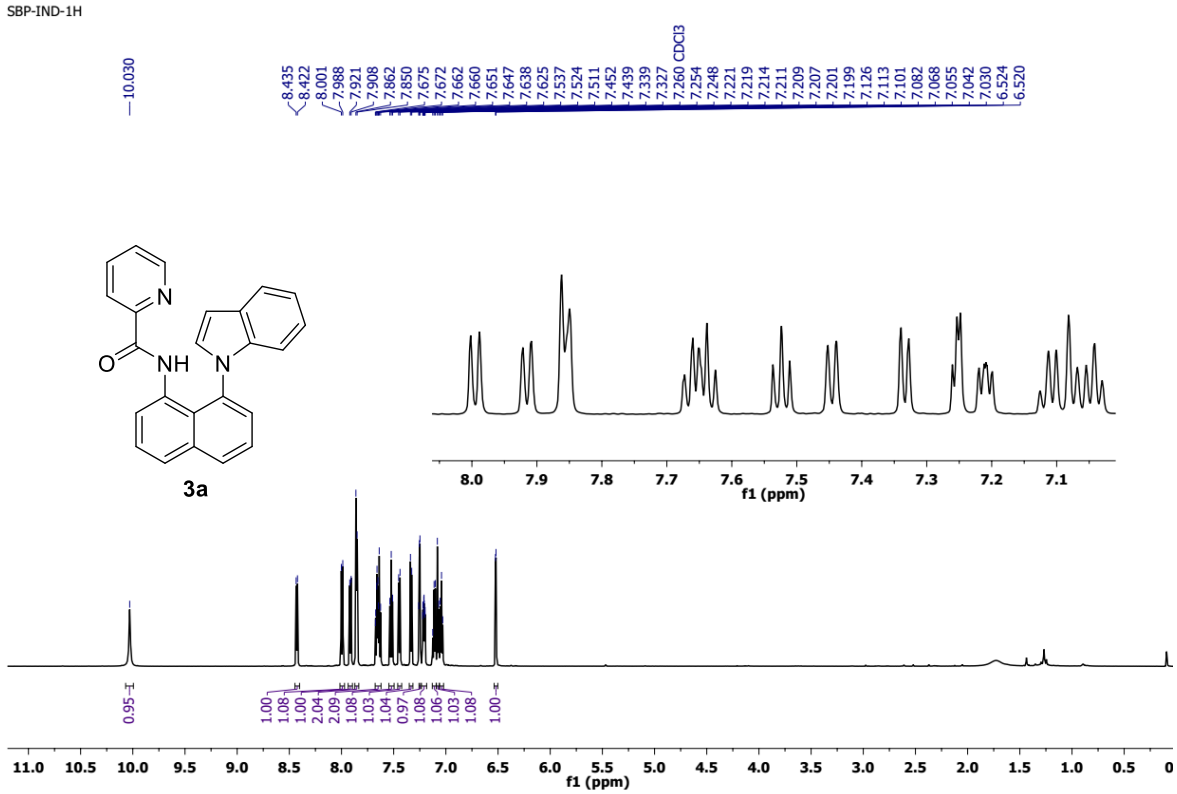
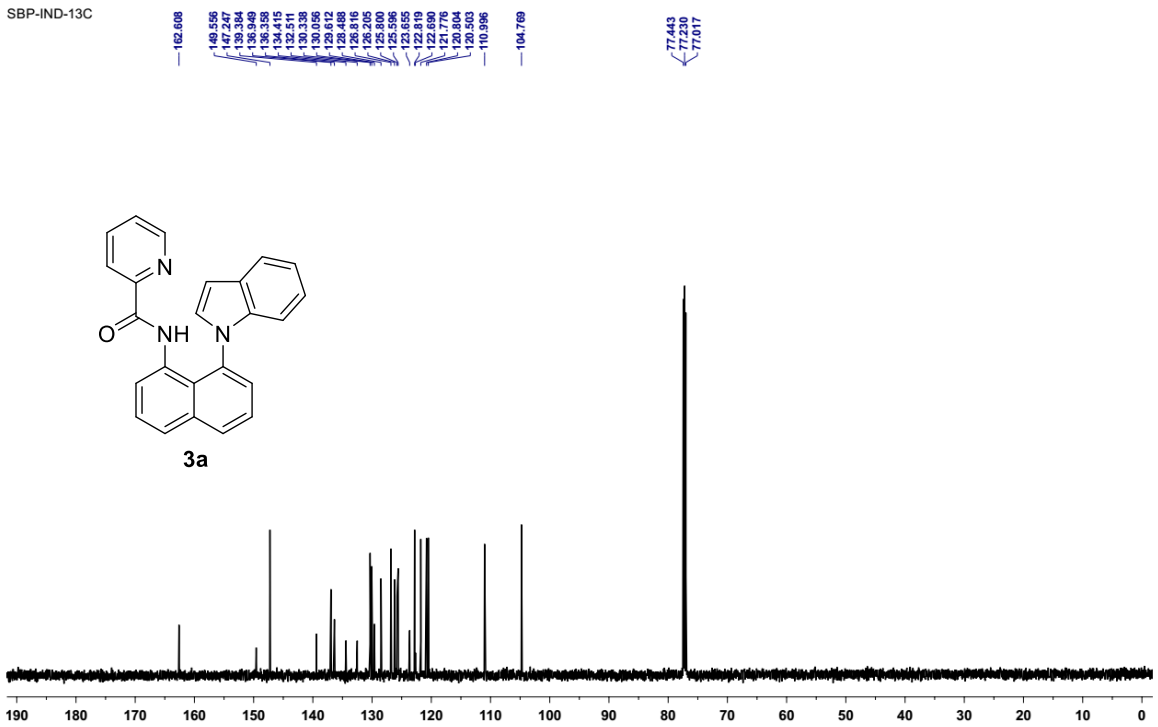
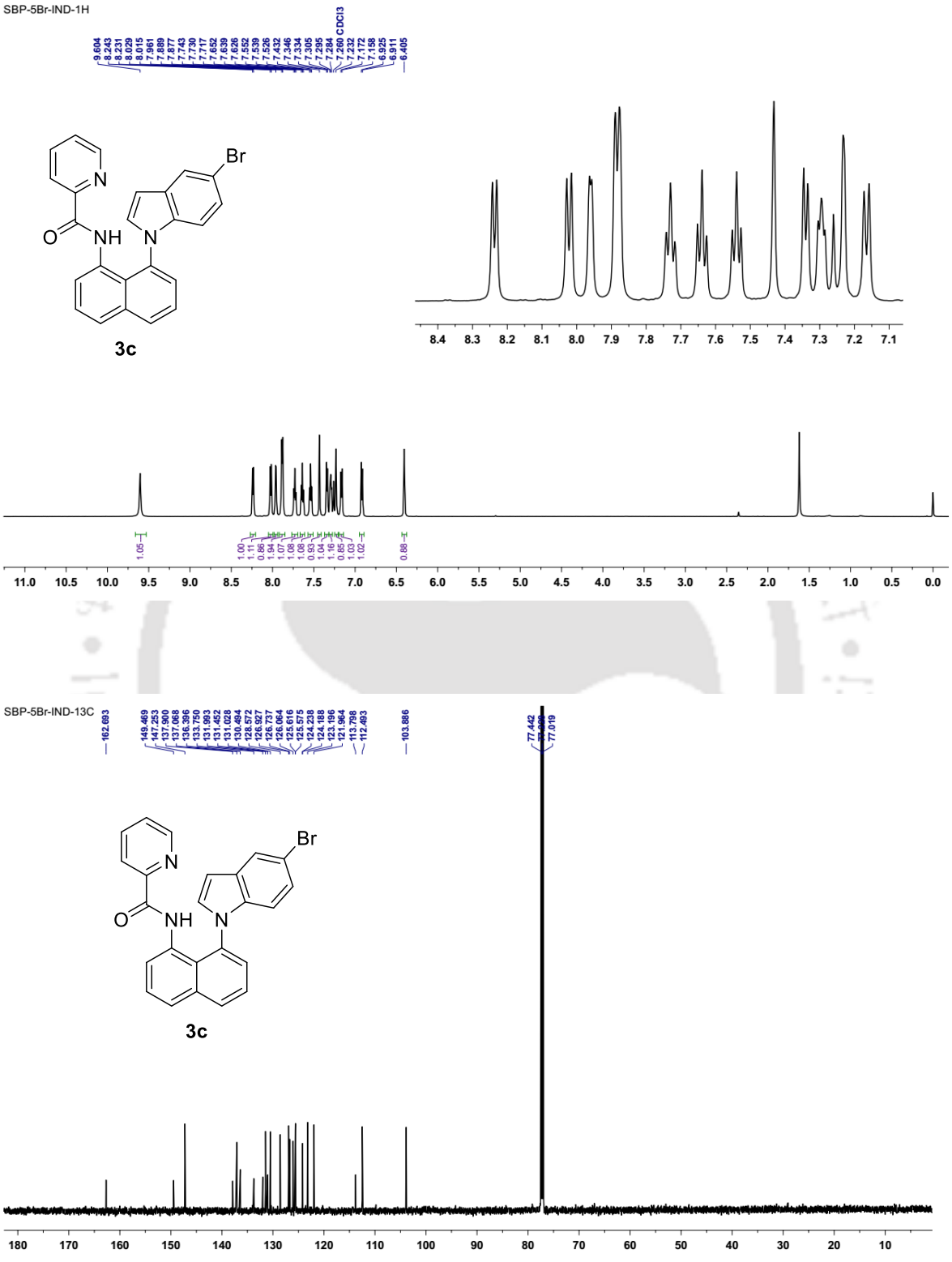
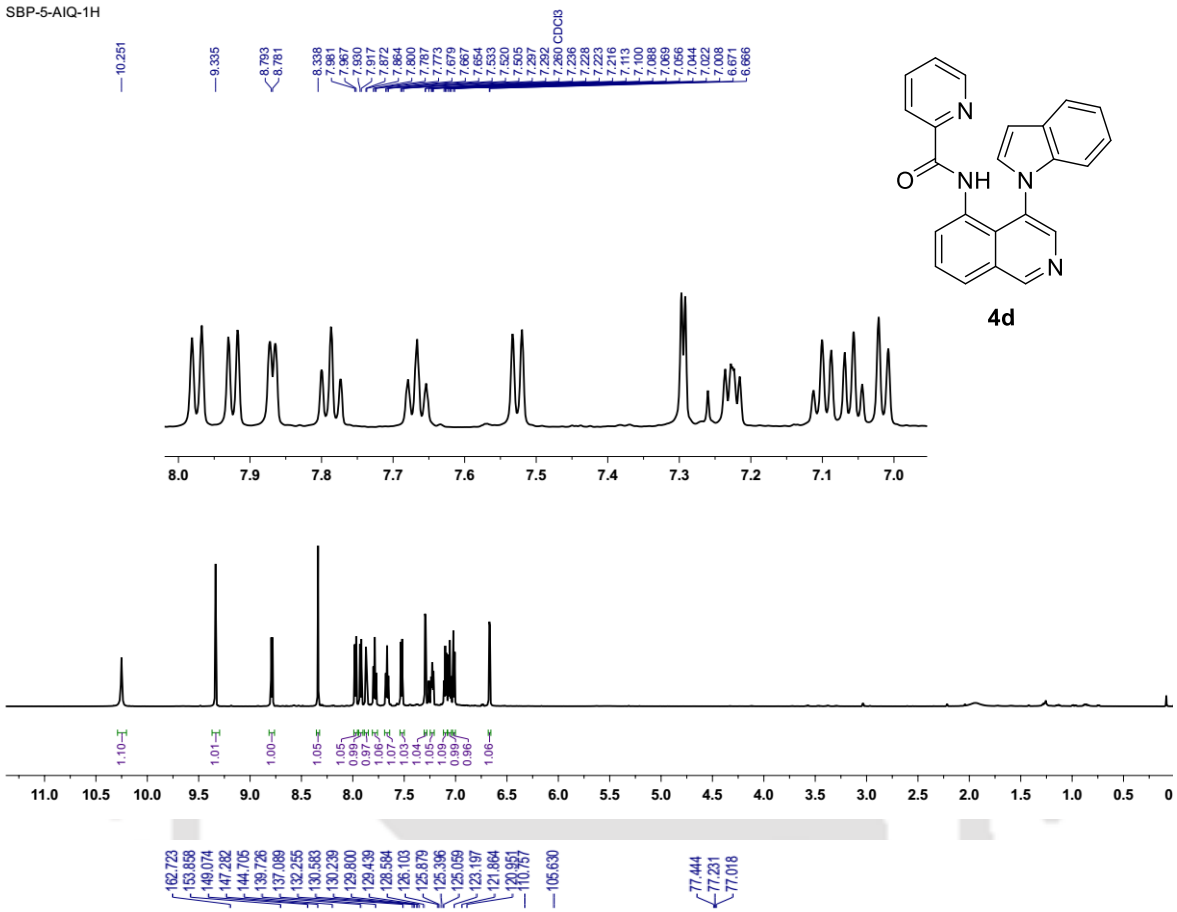
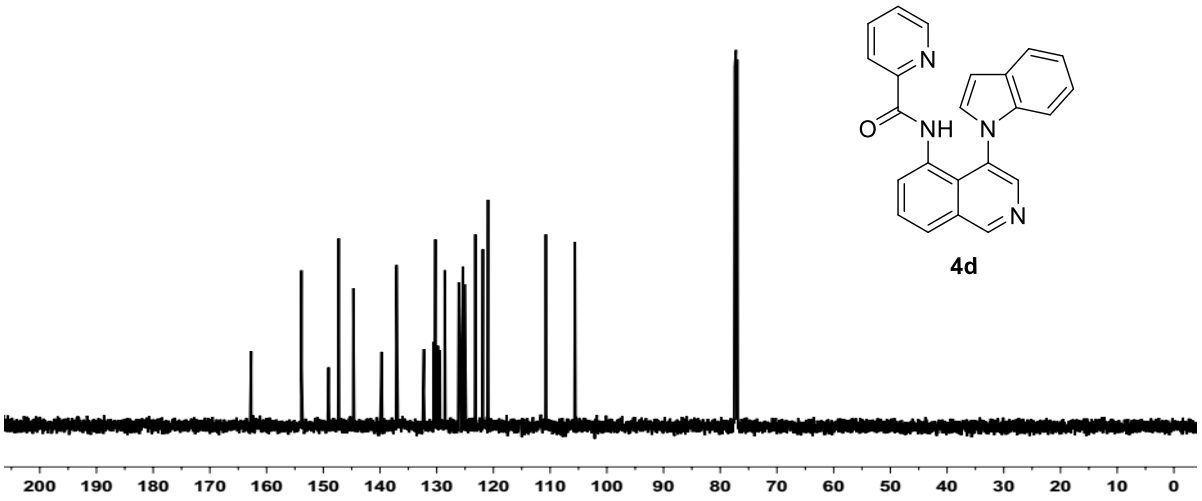
2.7 Selected NMR Spectra





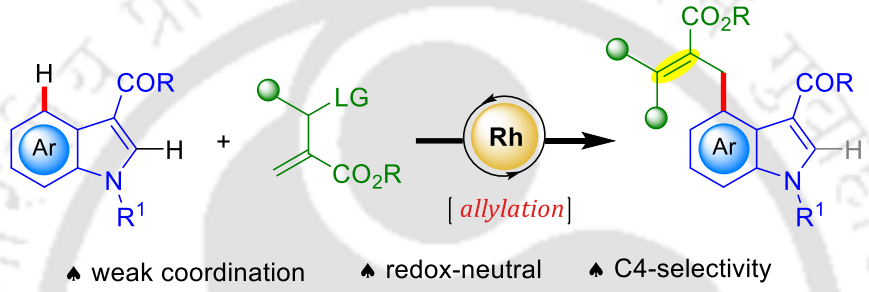






Chapter III

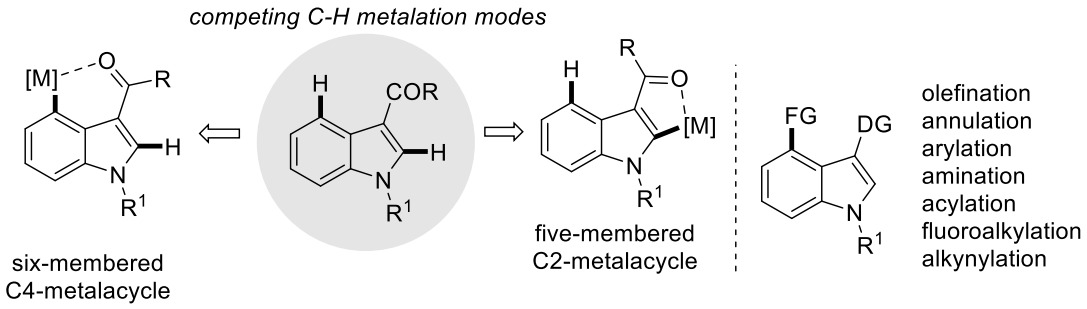
Rh(III)-Catalyzed C4-Selective Allylation of Indoles Exploiting MBH Adducts



Org. Lett. **2019**, *21*, 9898.

Rh(III)-Catalyzed C4-Selective Allylation of Indoles Exploiting MBH Adducts

The heteroaromatic scaffold indole is ubiquitous in a wide variety of functional molecules, bio-active natural products, and is reputed as the fourth most prevalent building block among the currently marketed pharmaceuticals.[1] Accordingly, the quest for elegant techniques to diversify six distinctive C-H functionalization sites across the indole nucleus has been the frontline areas of research. Due to the inherent nucleophilicity of the pyrrole core, the C2 and C3 functionalization has been studied considerably.[2] In sharp contrast, the selective modification of remote and less-reactive C-H bonds in the benzenoid core (C4 to C7) remained underexplored.[3] Hence, selective C-H functionalization at instinctually poor nucleophilic C4-site continues to be an inexplicable task. With a suitable directing group at the C3-position followed by selective cyclometalation will be a potential approach to address this issue. The implicit challenge for achieving C4-selectivity arises from the preferential formation of five-membered cyclometalation at C2 as compared to the corresponding six-membered cyclometalation at C4 site (Scheme 1). Driven by the remarkable importance of C4-substituted indole fragments in alkaloids and medicinal science (Figure 1),[4] development of selective C4-functionalization with a versatile functional precursor is valuable. Early stage development on C4 functionalization was realized through metal-catalyzed cross-coupling of prefunctionalized substrates.[5] In recent years, there has been an impetus for the exploration of the direct C-H functionalization method at the relatively less studied C4 position.[6] The initial breakthrough was achieved by Jia and co-workers[7] for Pd-catalyzed C4-olefination of tryptophan derivatives. Later on, phenomenal progress was addressed for the C4 functionalization, such as olefination,[8] annulation,[9] arylation,[10] amination,[11] acylation,[12] fluoroalkylation,[13] thiolation[14] and alkynylation (Scheme 1).[15] Direct allylation[16] of organic substrates are of substantial value due to its efficacious alteration of olefins upon allylation. In addition, C-H activation through weak coordinating directing groups[17] and/or redox-neutral approach is the essence of contemporary organometallic research. This chapter describes a Rh(III)-catalyzed redox-neutral C4-allylation of indoles leveraging weakly coordinating acetyl group with Morita-Baylis-Hillman (MBH) adducts as an allylating agent. The notable features of our findings include oxidant/base free C4-allylation and introduction of a synthetically useful α,β-unsaturated ester residue at C4-site of indole for late-stage modifications.



Scheme 1. Challenges and Developments of C4-Functionalization of Indoles

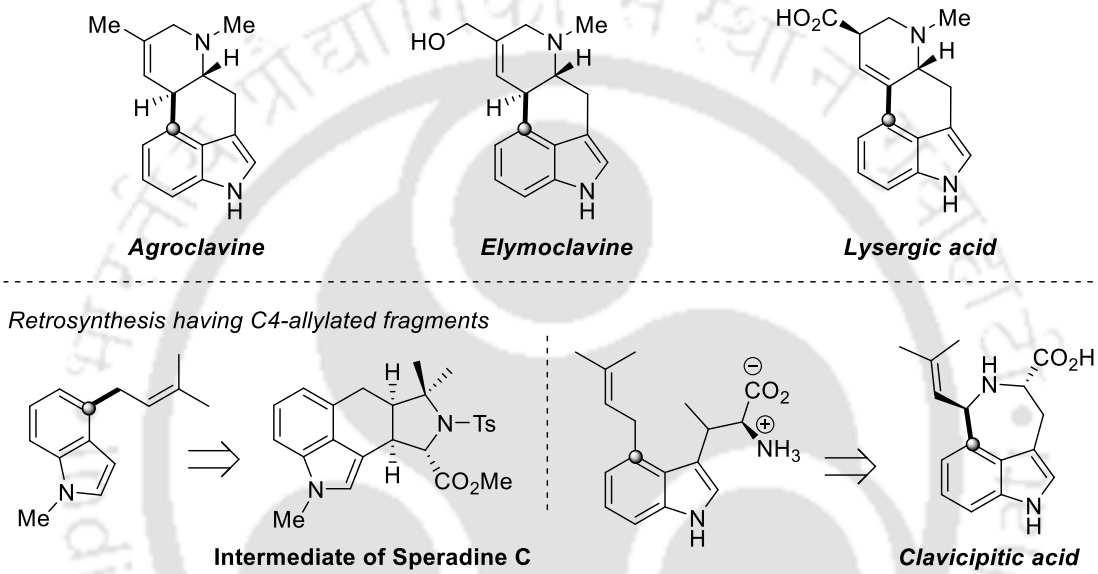
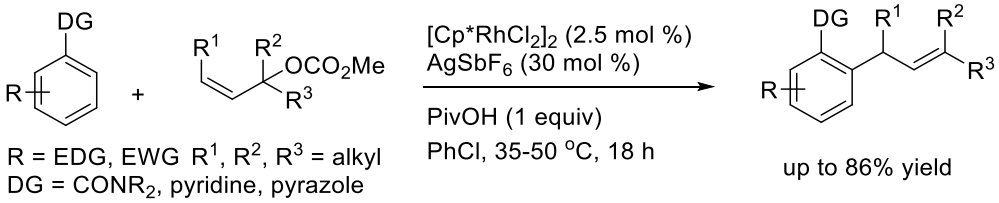


Figure 1. Selected examples of bio-active C4-substituted indoles

3.1 Allylation of Arenes

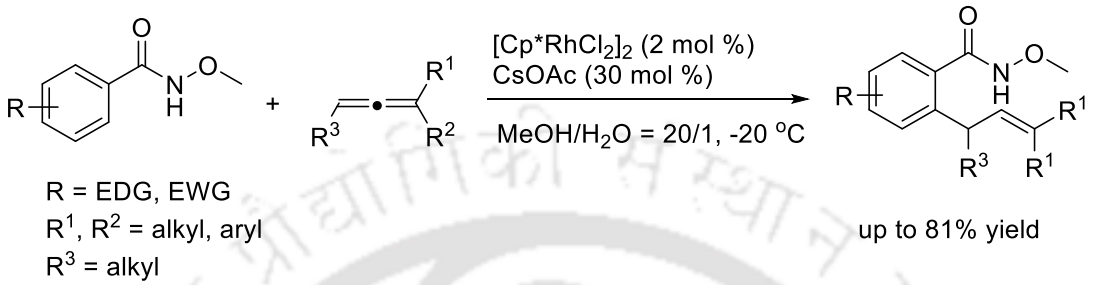
3.1.1 Rh-Catalyzed Reactions

Glorius and co-workers reported a Rh(III)-catalyzed oxidative C-H allylation of arenes with readily accessible allyl carbonates (Scheme 2).[18] This expedient method provides a facile route for the allylation of electron-neutral arenes, with exclusive γ-selectivity, high isomeric ratio and excellent functional group compatibility.



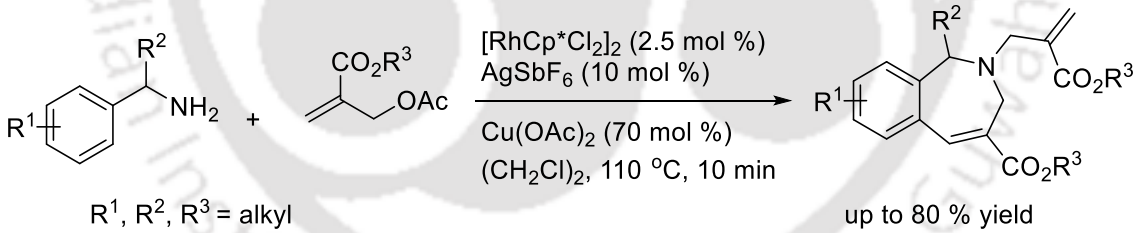
Scheme 2. Rh-Catalyzed *ortho*-Allylation of Arenes

Ma and co-workers reported a potential approach for the Rh(III)-catalyzed allylation of *N*-methoxybenzamides with 1,1- disubstituted or internal allenes as allyl sources (Scheme 3).[19] The reaction was compatible with both electron-rich and -poor benzamides and was extended to naphthylamides and benzofuran derivative.



Scheme 3. Rh-Catalyzed Allylation of Benzamides with Allenes

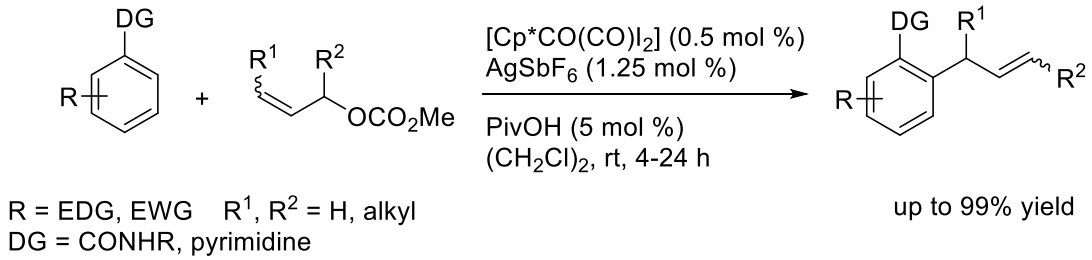
A Rh(III)-catalyzed annulation reaction of benzylamines with Morita–Baylis–Hillman (MBH) adducts was described to access 2-benzazepines *via* C(sp^2)–H activation of *N*-allylated benzylamines and subsequent intramolecular olefin insertion followed by intramolecular *N*-allylation (Scheme 4).[20] The reaction showed broad scope, high level of chemoselectivity and functional group tolerance.



Scheme 4. Rh-Catalyzed Annulation with MBH adducts

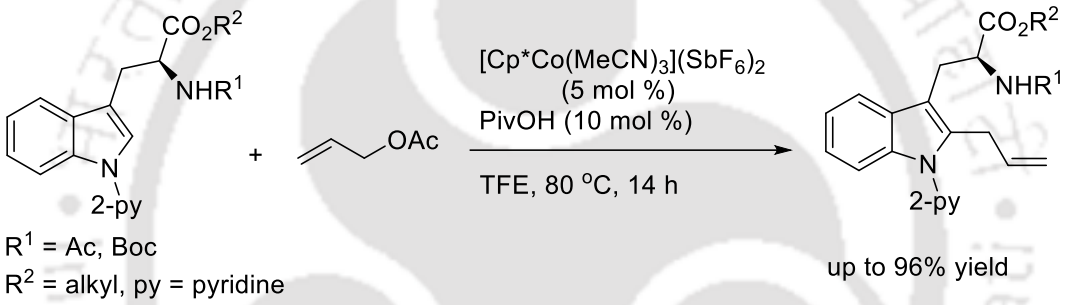
3.1.2 Co-Catalyzed Reactions

Glorius group explored minimally toxic and less expensive Co(III)-catalyzed amide directed sp^2 C-H allylation of arenes, heteroarenes, and olefins employing allyl carbonates (Scheme 5).[21] A variety of allyl sources was reacted successfully to introduce allyl moiety with broad scope and functional group diversity.



Scheme 5. Co-Catalyzed Direct C-H Allylation of Arenes

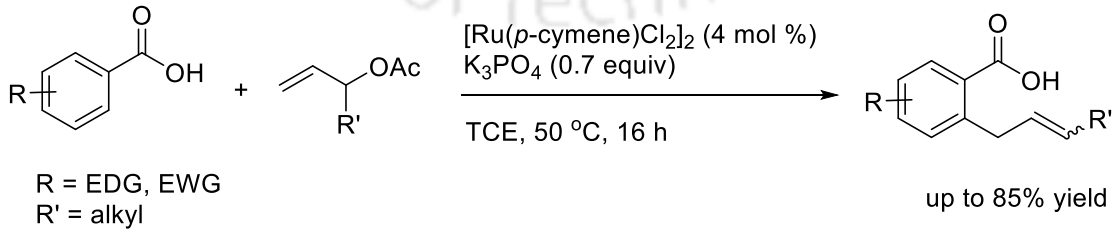
Ackermann and co-workers established an unprecedented Co(III)-catalyzed C−H allylation of tryptophan derivatives and structurally complex peptides (Scheme 6).[22] The method was highlighted for a multicatalytic C−H activation/alkene metathesis/hydrogenation strategy for the synthesis of novel cyclic peptides.



Scheme 6. Late-Stage Allylation of Peptides under Co-Catalysis

3.1.3 Ru-Catalyzed Reactions

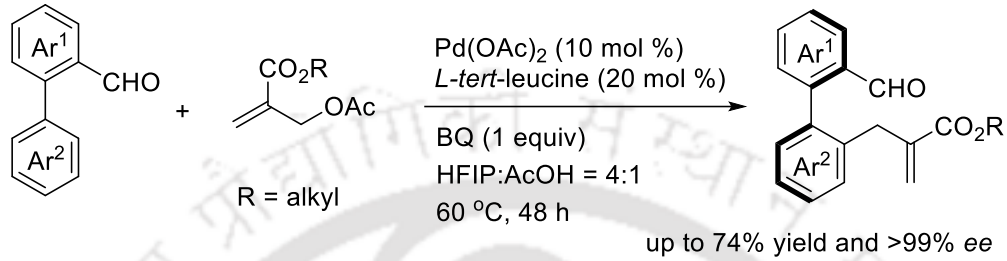
Gooßen and co-workers developed an elegant protocol for Ru-catalyzed direct regiospecific *ortho*-allylation of benzoic acids via carboxylate-directed sp^2 C−H functionalization in 2,2,2-trichloroethanol (TCE) at 50 °C (Scheme 7).[23] The method was compatible with both electron-rich and electron-poor benzoic acids in combination with linear and branched allyl acetates.



Scheme 7. Ru-Catalyzed Allylation of Benzoic Acids

3.1.4 Pd-Catalyzed Reactions

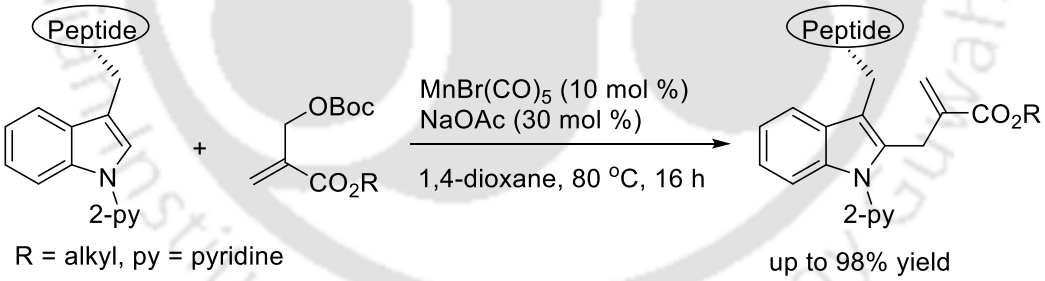
Shi and co-workers described a Pd(II)-catalyzed atropselective C−H allylation of biaryl aldehydes with *tert*-leucine as an efficient catalytic chiral transient auxiliary using MBH-adducts as an allylation source (Scheme 8).[24] A wide variety of enantioenriched biaryl aldehydes were synthesized with functional group diversity and excellent enantioselectivity *via* β-O elimination.



Scheme 8. Pd-Catalyzed Atropselective Allylation of Aldehydes

3.1.5 Mn-Catalyzed Reactions

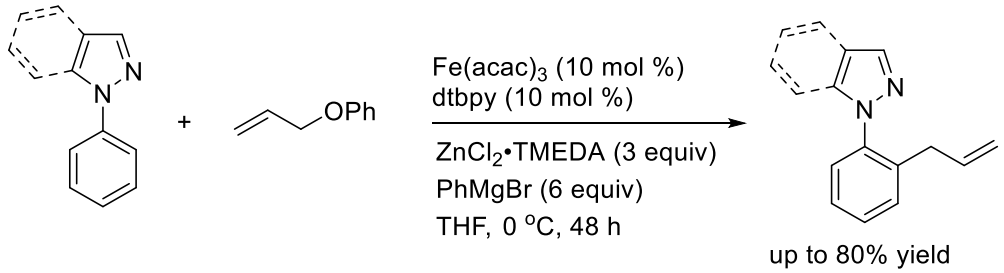
Ackermann and co-workers accomplished a Mn(I)-catalyzed bioorthogonal C−H allylation for the late-stage diversification of structurally complex peptides using MBH adducts (Scheme 9).[25] This robust manganese(I) catalysis manifold enabled the synthesis of C−H fused peptide hybrids featuring steroids, drug molecules, natural products, nucleobases, and saccharides.



Scheme 9. Mn-Catalyzed Late-Stage C-H Allylation of Peptides

3.1.6 Fe-Catalyzed Reactions

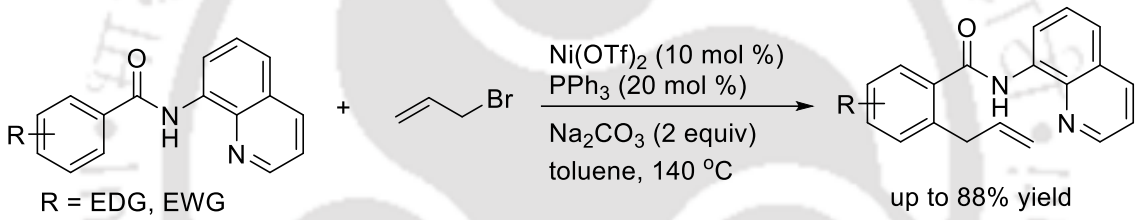
Nakamura and co-workers demonstrated *ortho*-allylation of 1-arylpyrazoles with allyl phenyl ether under Fe(III)-catalysis with 4,4′-di-*tert*-butyl-2,2′-bipyridyl (dtbpy) ligand and diphenylzinc as a base at 0 °C (Scheme 10).[26] The method was beneficial for the synthesis of functionalized allylated pyrazoles with the allylating agents bearing a better leaving group.



Scheme 10. Fe-Catalyzed *ortho*-Allylation of Pyrazoles

3.1.7 Ni-Catalyzed Reactions

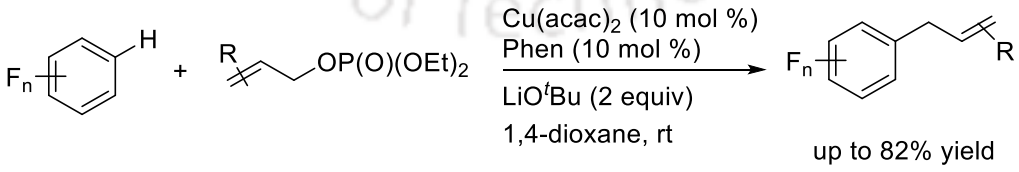
Chatani and co-workers realized direct allylation 8-aminoquinolinamides with allyl bromides as the allylating reagent using $Ni(OTf)_2$ as a catalyst precursor with PPh_3 as a ligand and Na_2CO_3 as a base in toluene (Scheme 11).[27] The amides bearing electron-donating and withdrawing groups were tolerated.



Scheme 11. Ni-Catalyzed *ortho*-Allylation of Quinolinamides

3.1.8 Cu-Catalyzed Reactions

Owing to the importance of highly electron-deficient polyfluoroarenes in materials and life sciences, Miura and co-workers developed an efficient Cu-catalyzed direct C−H allylation of polyfluoroarenes with allyl phosphates in a highly stereospecific fashion (Scheme 12).[28] The method offers a potential route to access allylarenes with a strongly electron-deficient nature.



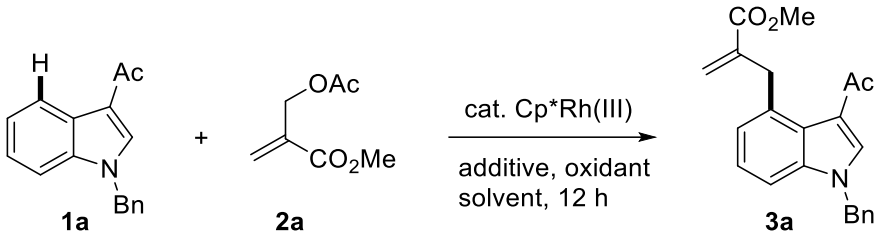
Scheme 12. Cu-Catalyzed Direct Allylation of Polyfluoroarenes

3.2 Present Study

Herein, a Rh(III)-catalyzed redox-neutral C4-selective allylation of indoles was developed leveraging weakly coordinating acetyl directing group using MBH-adducts with broad scope and functional group diversity. At the outset, our investigation was carried out using 1-(1-benzyl-1*H*-indol-3-yl)ethan-1-one **1a** and MBH-adduct **2a** as the test substrates under varied additives, oxidants and solvents (Table 1). To our delight, the target C4-allylated product **3a** was obtained in 21% yield, when the substrates were stirred with 3 mol % $[Cp^*RhCl_2]_2$, 10 mol % $AgSbF_6$ and 1 equiv $Cu(OAc)_2$ in THF at 120 ^oC for 12 h (entry 1). Further screening of the solvents revealed that $(CH_2Cl)_2$ is the solvent of choice, providing **3a** in 73% yield, while solvents such as 1,4-dioxane, PhCl and toluene produced inferior results (entries 2-5). Among the additives screened, $AgSbF_6$ was superior in delivering the target product efficiently, whereas AgOTf and $AgBF_4$ was found to be ineffective (entries 6-7). Subsequently, a survey among the oxidants such as Ag_2CO_3 and Ag_2O led to drop the yield to <41% (entries 8-9). In the absence of $Cu(OAc)_2$ 69% **3a** was obtained (entry 10). A control experiment without $AgSbF_6$ drastically lowered the product formation to 15%, indicating the formation of a cationic Rh-species (entry 11). Interestingly, when the reaction was carried out with 3 mol % of $[Cp^*Rh(CH_3CN)_3](SbF_6)_2$, **3a** was obtained in 78% yield (entry 12), while in the absence of $Cu(OAc)_2$ the yield was increased to 82% (entry 13). These results suggest that the allylation proceeds smoothly without any external oxidant or base (acetate source), where the OAc group of **2a** acts as an internal base. Lowering in temperature retarded the product formation (entry 14). No allylation was observed in the absence of the catalyst and the starting material was recovered intact (entry 15). In addition, C3-attached carbonyl based directing groups such as formyl **1a′**, pivaloyl **1b′**, benzoyl **1c′** and trifluoromethylacetyl **1d′** were found to be ineffective (Scheme 13). Thus, the electronic nature of the coordinating groups is crucial to bring out successful allylation.

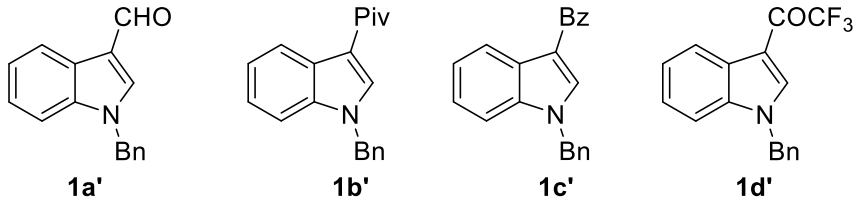
With the optimized reaction conditions, the scope of the method was investigated using diversely substituted indoles **1b-q** with MBH-adduct **2a** as a standard substrate (Table 2). The reaction of 2-methyl substituted indole **1b** delivered **3b** in 71% yield. Similarly, 5-fluoro substituted indole **1c** provided **3c** in 73% yield. However, 5-bromo, 5-iodo and 5-methyl substituted indoles **1d-f** failed to give **3d-f**, owing to the steric factor of the substituent near the C4-coupling site. Electron-donating 5-benzyloxy **1g** and 5-methoxy **1h** groups containing indoles successfully delivered allylated **3g** and **3h** in 69 and 74% yields, respectively.

Table 1. Optimization of the Reaction Conditions[a]



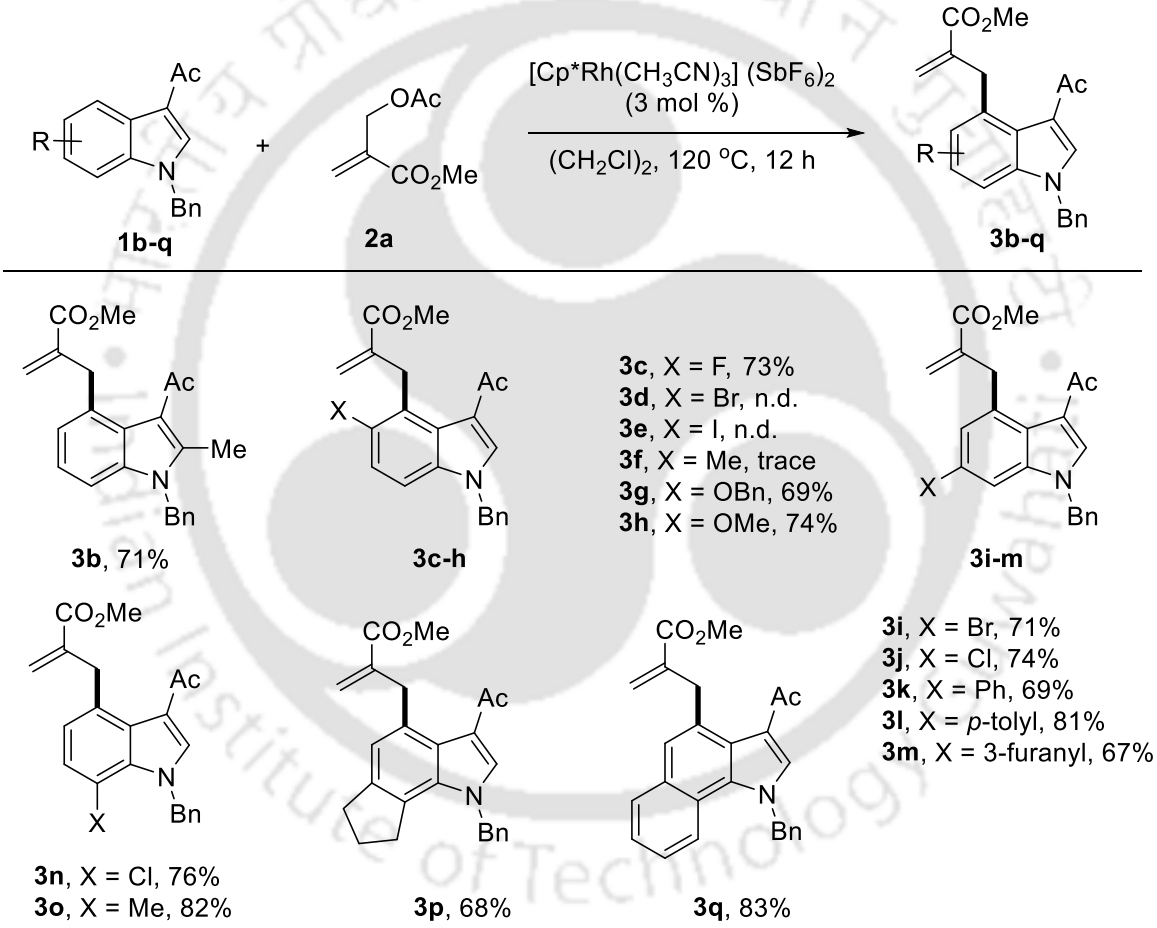
Entry	Additive	Oxidant	Solvent	Yield (%)[b]
1	$AgSbF_6$	$Cu(OAc)_2$	THF	21
2	$AgSbF_6$	$Cu(OAc)_2$	1,4-dioxane	18
3	$AgSbF_6$	$Cu(OAc)_2$	$(CH_2Cl)_2$	71
4	$AgSbF_6$	$Cu(OAc)_2$	PhCl	trace
5	$AgSbF_6$	$Cu(OAc)_2$	toluene	n.d.
6	AgOTf	$Cu(OAc)_2$	$(CH_2Cl)_2$	32
7	$AgBF_4$	$Cu(OAc)_2$	$(CH_2Cl)_2$	trace
8	$AgSbF_6$	Ag_2CO_3	$(CH_2Cl)_2$	41
9	$AgSbF_6$	Ag_2O	$(CH_2Cl)_2$	23
10	$AgSbF_6$	-	$(CH_2Cl)_2$	69
11	-	$Cu(OAc)_2$	$(CH_2Cl)_2$	15
12[c]	-	$Cu(OAc)_2$	$(CH_2Cl)_2$	78
13[c]	-	-	**$(CH_2Cl)_2$**	**82**
14[c,d]	-	-	$(CH_2Cl)_2$	37
15	-	-	$(CH_2Cl)_2$	n.d.

[a]Reaction conditions: **1a** (0.1 mmol), **2a** (0.2 mmol), $[Cp^*RhCl_2]_2$ (3 mol %), additive (10 mol %), oxidant (0.1 mmol), solvent (1.5 mL), 120 °C, 12 h, air. [b]Isolated yield. [c]Using 3 mol % $[Cp^*Rh(CH_3CN)_3](SbF_6)_2$. [d]At 90 °C. n.d. = not detected.



Scheme 13. Screening of Directing Groups

Table 2. Substrate Scope of Indoles[a,b]

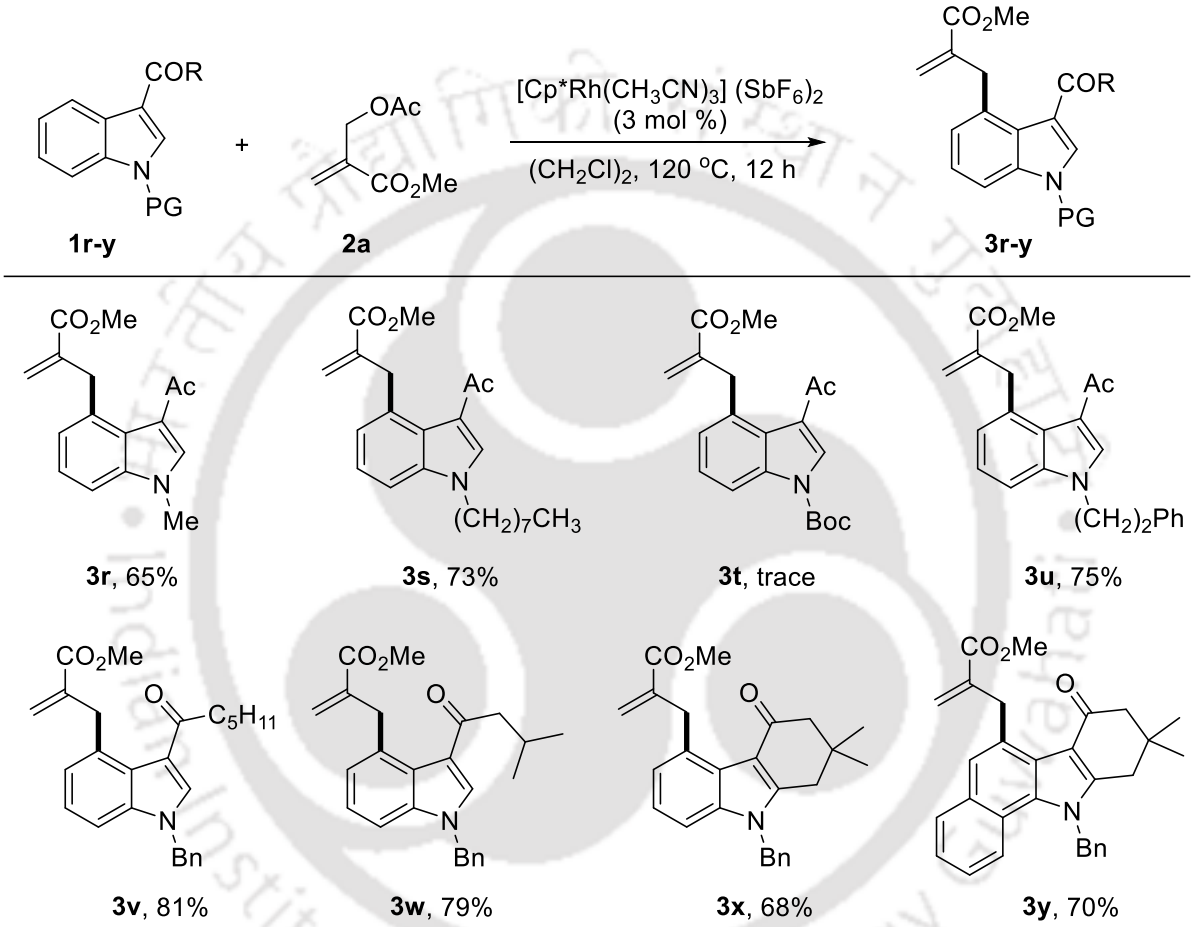


[a]Reaction conditions: **1b-q** (0.1 mmol), **2a** (0.2 mmol), $[Cp^*Rh(CH_3CN)_3](SbF_6)_2$ (3 mol %), $(CH_2Cl)_2$ (1.5 mL), 120 °C, air, 12 h. [b]Isolated yield. n.d. = not detected.

Similar results were observed with 6-substituted indoles, bearing bromo **1i**, chloro **1j**, phenyl **1k** and *p*-tolyl **1l** groups, affording **3i-l** in 69-81% yields. Intriguingly, 3-furanyl containing 6-substituted indole **1m** was found amenable, delivering **3m** in 67% yield. This showcase the

potential of the strategy by circumventing the heteroatom poisoning effect. Pertinently, 7-chloro **1n** and 7-methyl **1o** substituted indoles efficiently furnished the target allylated **3n** and **3o** in 76 and 82% yields, respectively. Amusingly, fused indole derivatives **1p** and **1q** were compatible substrates, conveying **3p** and **3q** in 68 and 83% yields, respectively.

Table 3. Effect of Protecting Group and Directing Groups of Indoles[a,b]



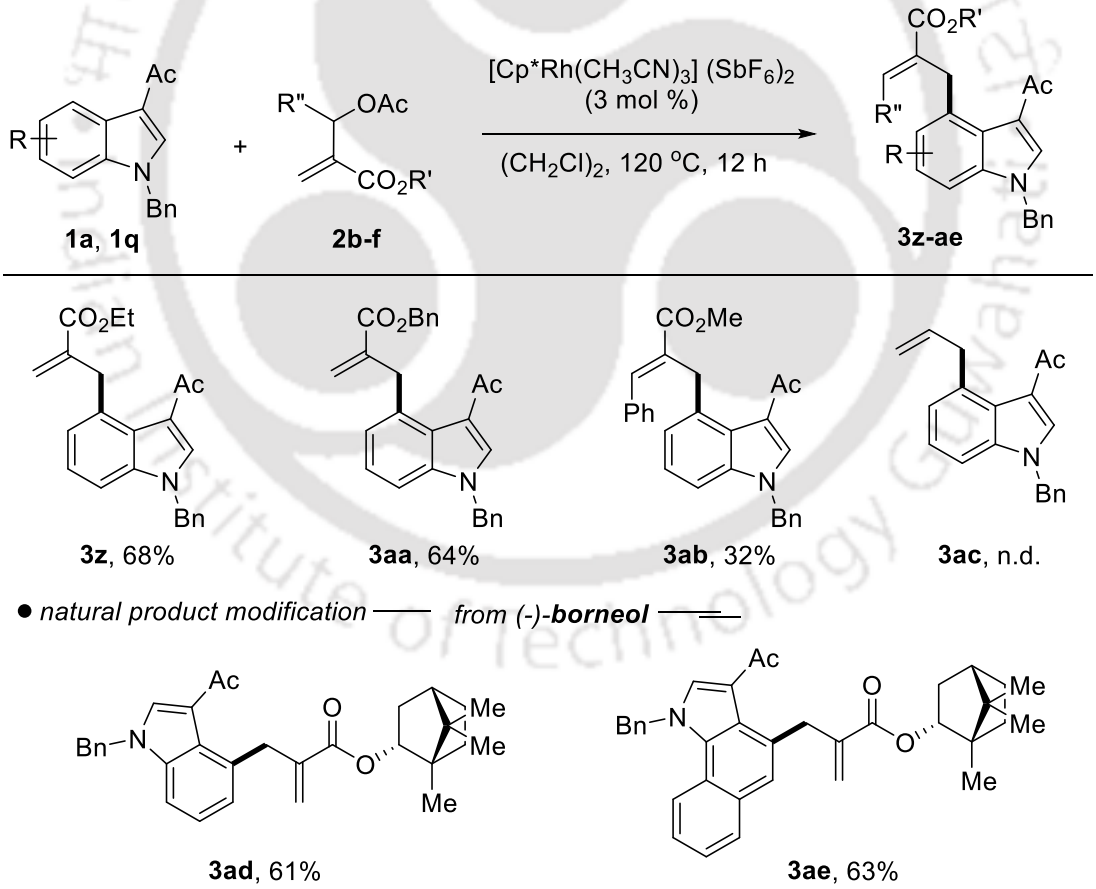
[a]Reaction conditions: **1r-y** (0.1 mmol), **2a** (0.2 mmol), $[Cp^*Rh(CH_3CN)_3](SbF_6)_2$ (3 mol %), $(CH_2Cl)_2$ (1.5 mL), 120 °C, air, 12 h. [b]Isolated yield.

Encouraged by the effective results, we turned our attention to the scope of indoles with different *N*-protecting groups and substituted C3-acyl group (Table 3). *N*-Substituted indoles such as methyl **1r**, *n*-octyl **1s** and phenylethyl **1u** successfully participated in the reaction furnishing **3r-s** and **3u** in 65-75% yields, while Boc-protected indole **1t** produced a trace amount of **3t**. Delightfully, hexanoyl **1v** and isovaleryl **1w** substituted indoles successfully transformed to allylated **3v** and **3w** in 81 and 79% yields, respectively. Moreover, enaminone derived indoles **1x** and **1y** were smoothly

allylated to **3x** and **3y** in good yields. These results confide that differentiated *N*-substitution patterns and the electronic nature of the acyl group can be accessed to display the practicality of the protocol.

Next, the allylation strategy was explored with substituted MBH-adducts, including those derived from a natural product (Table 4). Acyl indole **1a** on reaction with MBH-adducts **2b-d** afforded **3z-ab** in 32-68% yields. The structure of **3aa** was determined using single crystal X-ray analysis. The reaction of allyl acetate **2e** failed to produce the desired allylated product. This result confides the crucial role of the ester moiety in this transformation by facilitating the migratory insertion step in the catalytic cycle.[20] Borneol derived MBH-adduct **2f** successfully coupled with indoles **1a** and **1q** to give **3ad** and **3ae** in 61 and 63% yields, respectively. These results illustrate the expedited potential of the method for late-stage modification of natural products.

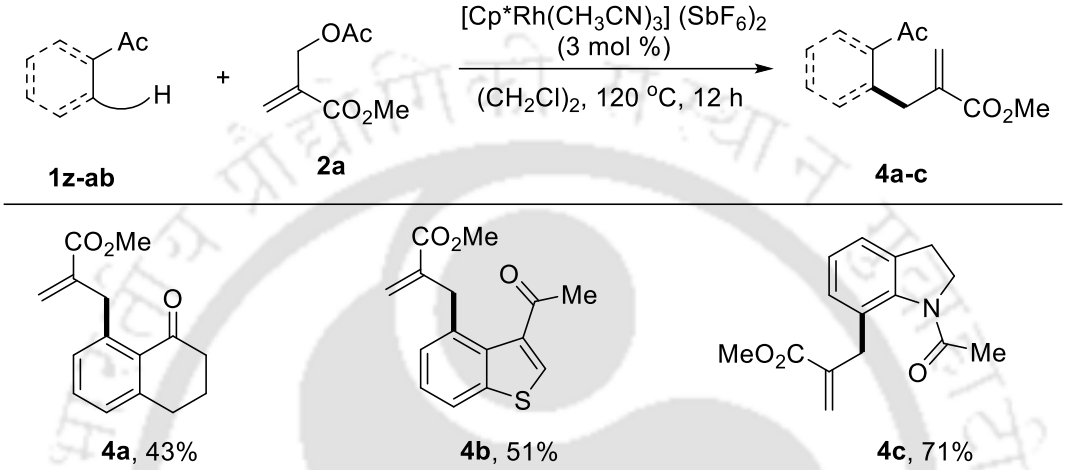
Table 4. Scope of MBH-Adducts[a,b]



[a]Reaction conditions: **1a, 1q** (0.1 mmol), **2b-f** (0.2 mmol), $[Cp^*Rh(CH_3CN)_3](SbF_6)_2$ (3 mol %), $(CH_2Cl)_2$ (1.5 mL), 120 °C, air, 12 h. [b]Isolated yield.

Further, the weak carbonyl coordination-guided allylation strategy was extended to site-selective allylation of α-tetralone **1z**, 3-benzo[*b*]thiophene **1aa** and indoline **1ab** in good yields (Table 5). To mention, **1z** gave **4a** in 43% yield, whereas **1aa** afforded C4-allylated **4b** in 51% yield and **1ab** conveyed C7-allylated **4c** in 71% yield.

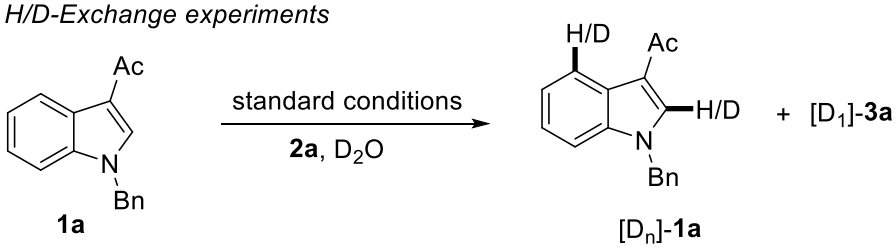
Table 5. Scope of Weakly Coordinating Arene Substrates[a,b]



[a]Reaction conditions: **1z-ab** (0.1 mmol), **2a** (0.2 mmol), $[Cp^*Rh(CH_3CN)_3](SbF_6)_2$ (3 mol %), $(CH_2Cl)_2$ (1.5 mL), 120 °C, air, 12 h. [b]Isolated yield.

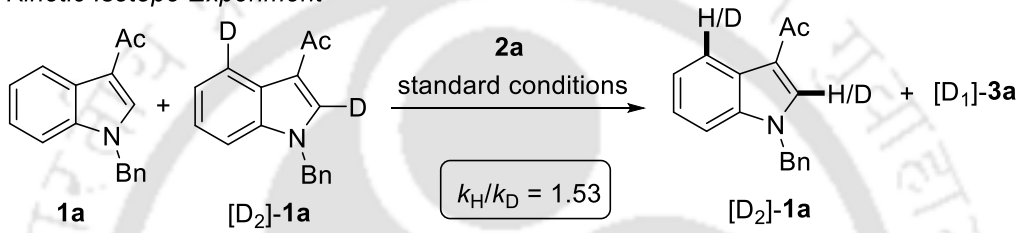
To gain insight into the reaction pathway, H/D-exchange experiments and kinetic isotope experiment were conducted (Scheme 14). In the absence of $[Cp^*Rh(CH_3CN)_3](SbF_6)_2$ catalyst, no H/D exchange was detected at both the C4-H and C2-H sites, implying an essential role of the Rh-catalyst in C-H activation process. Whereas, H/D-scrambling experiment independently in the presence or absence of **2a** using D_2O as a co-solvent, revealed a significant deuterium incorporation at the C4 C-H bond, indicating the reversibility of the C4 C-H activation step. In the absence of **2a** 32% deuterium incorporation was detected at the C4 C-H bond, while as in the presence of **2a** a substantial deuterium incorporation at C4-H was noticed (89%), which entails the involvement of acetate group of the MBH-adduct in the C-H activation/deprotonation pathway.[18] Additionally, no deuterium incorporation was observed at the allyl residue of $[D_1]$-**3a**, which ruled out the formation of a π-allyl rhodium complex. The kinetic isotope experiment was performed using **1a** and $[D_2]$-**1a** with **2a**, giving a k_H/k_D = 1.53 at the C4 position. This result revealed that the C4-H bond cleavage might not be involved in the rate-determining step.

● *H/D-Exchange experiments*

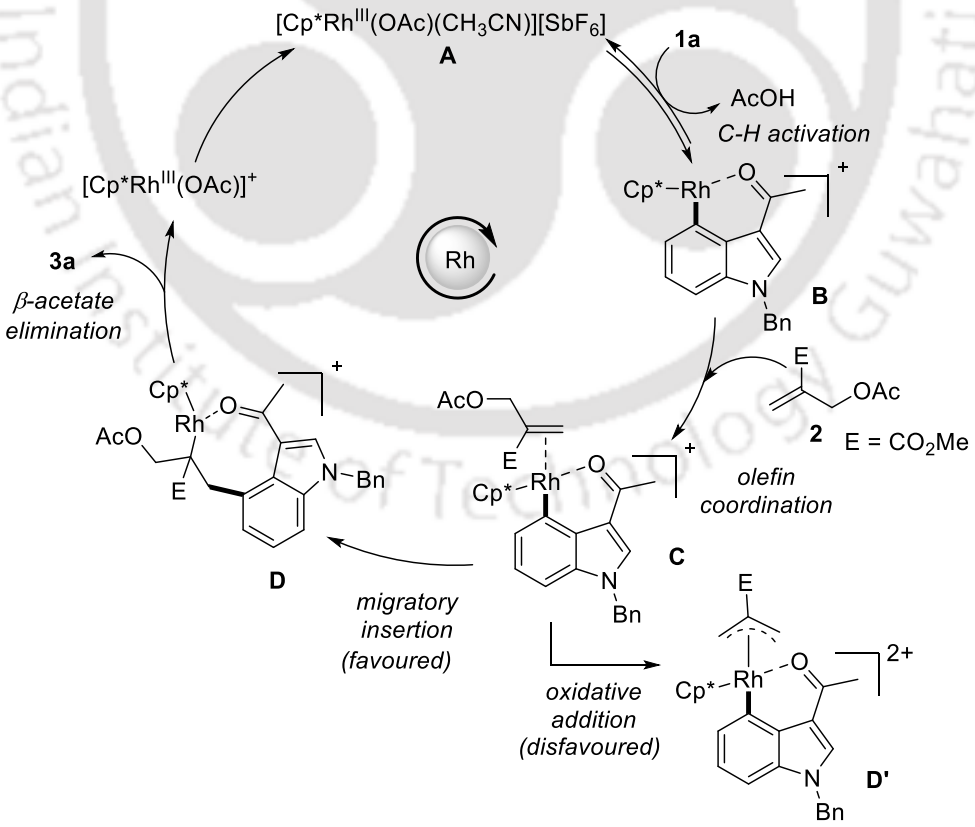


variation	C2-H deuteration	C4-H deuteration
no Rh-catalyst	0%	0%
none	51%	89%
no **2a**	65%	32%

● *Kinetic Isotope Experiment*



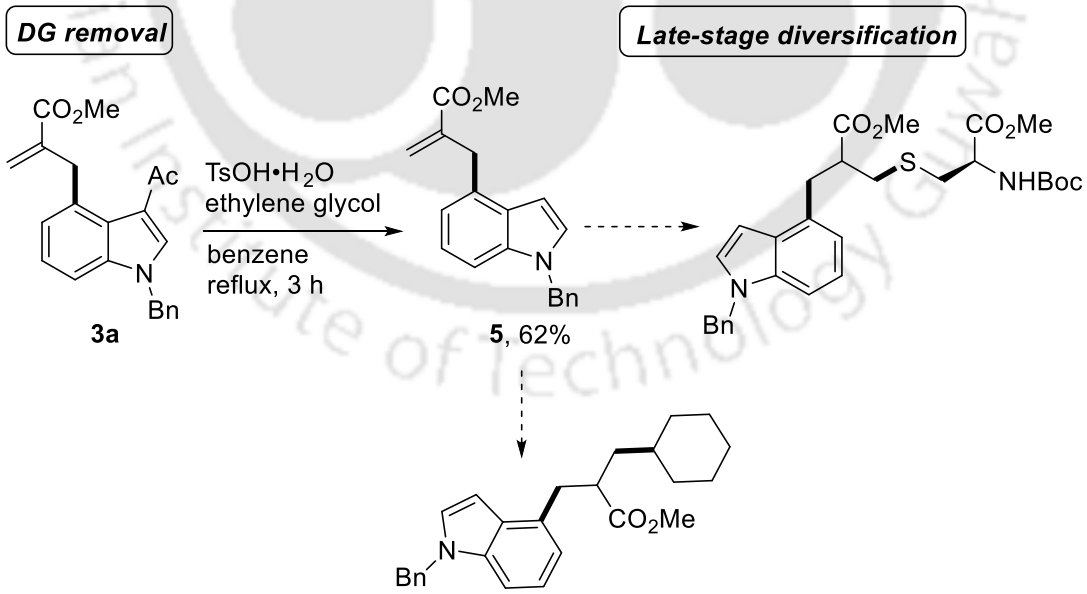
Scheme 14. Preliminary Mechanistic Investigations



Scheme 15. Proposed Reaction Mechanism

Based on the preliminary mechanistic investigations and previous literature,[20] a plausible mechanism is depicted in scheme 15. The weak precoordination of carbonyl group of 3-acetyl indole **1a** with a cationic rhodium species **A** followed by deprotonation may deliver a rhodium intermediate **B**. Later, the coordinative insertion of the double bond of MBH-adduct with intermediate **B** provides an eight-membered rhodacycle intermediate **D,** *via* **C**. The intermediate **D** undergoes intramolecular *β*-acetate elimination to furnish C4-allylated indole **3** and regenerates the active catalyst **A**. On the other hand, the allylation may proceed *via* the oxidative addition of the allyl electrophile which would generate a π-allyl rhodium complex **D′**.[18] However, the formation **D′** is less favored which is supported by the H/D-exchange experiment in the presence of **2a**. It is evident that, the rhodium species with +III oxidation state is involved throughout the catalytic cycle, and the allylation reaction proceeds in the redox-neutral version. Hence, the current developed allylation method does not require any external oxidant or base.

To demonstrate the synthetic utility of the procedure, the removal of acetyl directing group was accomplished by a reverse Friedel-Crafts reaction in the presence of TsOH and ethylene glycol, giving **5** in 62% yield (Scheme 16). It is noteworthy to mention that the embedded *α,β*-unsaturated ester at the C4-site of indole can serve as a multipurpose functional handle for downstream synthetic modifications.[25]



Scheme 16. Post-Synthetic Utility

In summary, we have presented a Rh(III)-catalyzed site-selective C4-allylation of indoles with versatile MBH-adducts in a redox-neutral fashion. The functional group compatibility, mechanistic aspects, wide substrate scope and late-stage natural product modifications are the important practical features.

3.3 Experimental Section

General Information. Indoles, $[Cp^*RhCl_2]_2$, $AgSbF_6$ (99%), $Cu(OAc)_2$ (98%), AgOTf (≥98.0%), $AgBF_4$ (98%), Ag_2CO_3 (98%) and Ag_2O (99%) were purchased from Aldrich and used as received, whereas $[Cp^*Rh(CH_3CN)_3](SbF_6)_2$ was prepared according the literature. All the solvents were dried prior to use according to the standard procedure. Merck silica gel G/GF254 plates were utilized for analytical thin-layer chromatography (TLC). Rankem silica gel (60−120 mesh) was employed for column chromatography. Bruker Avance III 600 and 400 MHz spectrometers were used for recording NMR (^1H and ^{13}C) spectra utilizing $CDCl_3$ as the solvent and tetramethylsilane (Me_4Si) as an internal standard. Chemical shifts (δ) and spin−spin coupling constants (*J*) are reported in parts per million and hertz (Hz), respectively, and other data are reported as follows: s = singlet, d = doublet, t = triplet, m = multiplet, q = quartet and br s = broad singlet. Melting points were determined using a Büchi B-540 apparatus and are uncorrected. IR spectra were collected on a PerkinElmer Fourier transform infrared (FT-IR) spectrometer. Quadrupole time-of-flight electrospray ionization (ESI) mass spectrometry instrument (model HAB 273) was used for mass spectra. Single crystal X-ray data were 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-97* (Göttingen, Germany).

General Procedure for the Preparation of Directing Groups. To a stirred solution of indole (2 mmol) in CH_2Cl_2 (10 mL), was added Et_2AlCl (1.5 mL, 3 mmol, 2 mol/L in hexane) dropwise at 0 °C. The resulting mixture was stirred at 0 °C for 30 min. Then, the solution of acetyl chloride (3 mmol) CH_2Cl_2 (5 mL) was added dropwise at 0 °C. The resulting mixture was further stirred at the same temperature for an appropriate time (2-4 hrs). After completion, as judged by TLC, the reaction mixture was quenched with aqueous buffer (pH 7) and extracted with CH_2Cl_2 (2 x 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 3-acetylindoles.

Then, to a suspension of NaH (1.05 mmol, 60% dispersion in mineral oil) in THF at 0 °C, a solution of 3-acetylindole (1 mmol) in THF (5 mL) was added dropwise. The corresponding alkyl bromide (1.1 equiv) was then added dropwise to this solution and allowed to stir at room temperature for an appropriate time. After completion of the reaction, it was quenched with water and extracted by EtOAc. 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 *N*-protected 3-acetyl indoles.

General Procedure for the Rh(III)-Catalyzed C4-Allylation of Indoles. A mixture of *N*-alkyl 3-acetyl indole **1** (0.1 mmol), $[Cp^*Rh(CH_3CN)_3](SbF_6)_2$ (3 mol %, 0.003 mmol, 2.5 mg) and MBH-adduct **2** (0.2 mmol) in $(CH_2Cl)_2$ (1.5 mL) was stirred at 120 °C in a preheated oil bath under air for 12 h. The progress of the reaction was monitored by TLC using ethyl acetate and hexane as an eluent. The reaction mixture was then cooled to room temperature, diluted with CH_2Cl_2 (10 mL) and passed through a short pad of celite using CH_2Cl_2 (2 x 10 mL). Drying (Na_2SO_4) and evaporation of the solvent gave a residue that was purified by silica gel column chromatography using *n*-hexane and ethyl acetate as an eluent to afford C4-allylated indoles. For the substrates other than indoles such as **1z**, **1aa** and **1ab** the above mentioned procedure was followed to get the corresponding allylated products.

H/D Exchange Experiment with D_2O. To a stirred solution of 1-(1-benzyl-1*H*-indol-3-yl)ethan-1-one **1a** (0.1 mmol, 24.9 mg) and $[Cp^*Rh(CH_3CN)_3](SbF_6)_2$ (3 mol %, 0.003 mmol, 2.5 mg) in $(CH_2Cl)_2$ (1.5 mL), D_2O (0.4 mmol, 80 μL) was added. The reaction mixture was stirred at 120 °C in a preheated oil bath under air for 12 h under air. The reaction mixture was cooled to room temperature, diluted with dichloromethane (10 mL), and passed through a short pad of celite using dichloromethane (25 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 give $[D_2]$-**1a** in 89% (22.3 mg) yield with 32% and 65% deuterium incorporation at C4-H and C2-H respectively, as estimated by 400 MHz ^{1}H NMR.

H/D Exchange Experiment with D_2O in the Presence of MBH-adduct. To a stirred solution of 1-(1-benzyl-1*H*-indol-3-yl)ethan-1-one **1a** (0.1 mmol, 24.9 mg), MBH-adduct **2a** and $[Cp^*Rh(CH_3CN)_3](SbF_6)_2$ (3 mol %, 0.003 mmol, 2.5 mg) in $(CH_2Cl)_2$ (1.5 mL), D_2O (0.4 mmol, 80 μL) was added. The reaction mixture was stirred at 120 °C in a preheated oil bath under air for

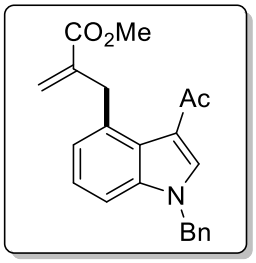
10 h under air. Then, the standard work procedure was followed. Drying (Na_2SO_4) and evaporation of the solvent produced a residue, which was purified on silica gel column chromatography using *n*-hexane and ethyl acetate as an eluent to give [D_2]-**1a** and [D_1]-**3a**. The deuterium incorporation was observed as 89% at C4-H and 51% at C2-H from 400 MHz ^{1}H NMR of recovered [D_2]-**1a**.

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 a mixture of 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 %, 1.6 mg), $AgSbF_6$ (0.02 mmol, 6.9 mg), $Cu(OAc)_2$ (0.1 mmol, 18 mg) and D_2O (0.4 mmol, 80 μL) in 1,4-dioxane (1.5 mL) was stirred at 120 ^{o}C in a preheated oil bath for 14 h. The resulting mixture was then diluted with CH_2Cl_2 (10 mL) and passed through a short pad of celite using CH_2Cl_2 (2 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 to afford [D_2]-**1a** as a light yellow solid in 91% yield (22.8 mg). The deuterium incorporation was determined using 400 MHz ^{1}H NMR as 79% at C4-H.

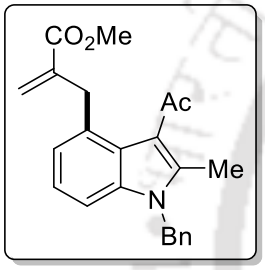
Kinetic Isotope Effect Experiment. A mixture of 1-(1-benzyl-1*H*-indol-3-yl)ethan-1-one **1a** (0.1 mmol, 24.9 mg) and 1-(1-benzyl-1*H*-indol-3-yl-2,4-*d*$_2$)ethan-1-one [D_2]-**1a** (0.1 mmol, 25.1 mg) was reacted with MBH-adduct **2a** (0.2 mmol, 31.6 mg) for 45 min under standard reaction conditions. The resulting mixture was then diluted with CH_2Cl_2 (10 mL) and passed through a short pad of celite using CH_2Cl_2 (2 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 to afford [D_1]-**3a** and a mixture of unreacted **1a** and [D_2]-**1a** as a colorless solid. The intermolecular k_H/k_D was found to be 1.53 after 45 min at 14% conversion, based on 400 MHz ^{1}H NMR of the recovered substrates **1a** and [D_2]-**1a**.

Procedure for the Removal of Acetyl Directing Group. A mixture of methyl 2-((3-acetyl-1-benzyl-1*H*-indol-4-yl)methyl)acrylate **3a** (0.1 mmol), ethylene glycol (0.1 mL) and *p*-toluenesulfonic acid monohydrate (0.11 mmol, 21 mg) in benzene (2 mL) was stirred under reflux for 3 h and the progress of the reaction was monitored by TLC using *n*-hexane and ethyl acetate as an eluent. The reaction mixture was then cooled to room temperature, saturated sodium bicarbonate (5 mL) was added and extracted with ethyl acetate (2 x 5 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 **5**.

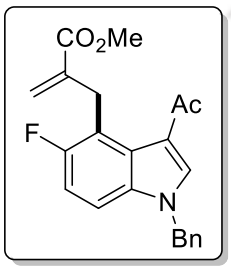
Methyl 2-((3-acetyl-1-benzyl-1*H*-indol-4-yl)methyl)acrylate 3a. Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.44; brown thick liquid; yield 82% (28.4 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (s, 1H), 7.37-7.31 (m, 3H), 7.22-7.19 (m, 2H), 7.17-7.14 (m, 2H), 7.07-7.05 (m, 1H), 6.12 (d, *J* = 1.2 Hz, 1H), 5.35 (s, 2H), 5.00 (d, *J* = 1.6 Hz, 1H), 4.37 (s, 2H), 3.78 (s, 3H), 2.47 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 191.9, 168.2, 141.6, 138.3, 136.8, 135.8, 134.1, 129.2, 128.3, 127.0, 125.1, 125.0, 124.8, 123.9, 119.0, 108.7, 52.0, 50.8, 37.7, 28.5; FT-IR (neat) 1715, 1652, 1525, 1400, 1260 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{22}H_{22}NO_3$: 348.1594, found 348.1592.



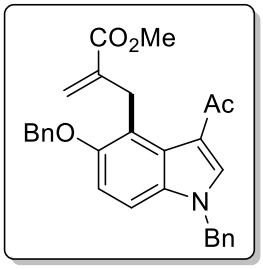
Methyl 2-((3-acetyl-1-benzyl-2-methyl-1*H*-indol-4-yl)methyl)acrylate 3b. Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.43; colorless solid; mp 121-122 °C; yield 71% (25.6 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23-7.15 (m, 3H), 7.07-7.02 (m, 2H), 6.93-6.89 (m, 3H), 6.07 (d, *J* = 1.2 Hz, 1H), 5.25 (s, 2H), 5.03 (d, *J* = 1.6 Hz, 1H), 3.95 (s, 2H), 3.68 (s, 3H), 2.45 (s, 3H), 2.42 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 198.7, 167.9, 140.2, 139.2, 137.2, 136.5, 131.4, 129.0, 127.7, 126.0, 125.4, 124.5, 124.0, 122.7, 118.5, 108.2, 51.9, 46.7, 36.8, 32.1, 12.5; FT-IR (KBr) 1716, 1657, 1524, 1400, 1191 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{23}H_{24}NO_3$: 362.1751, found 362.1756.



Methyl 2-((3-acetyl-1-benzyl-5-fluoro-1*H*-indol-4-yl)methyl)acrylate 3c. Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.45; colorless solid; mp 136-137 °C; yield 73% (26.6 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (s, 1H), 7.38-7.30 (m, 3H), 7.15-7.11 (m, 3H), 7.01 (t, *J* = 9.6 Hz, 1H), 6.08 (d, *J* = 1.6 Hz, 1H), 5.33 (s, 2H), 4.86 (s, 1H), 4.40 (d, *J* = 1.6 Hz, 2H), 3.82 (s, 3H), 2.45 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 191.6, 167.9, 159.3 (J_{C-F} = 235.0 Hz), 140.4, 137.9, 135.4, 134.5, 129.2, 128.5, 127.0, 126.58 (J_{C-F} = 5.0 Hz), 123.6, 119.6 (J_{C-F} = 19.0 Hz), 119.34 (J_{C-F} = 5.0 Hz), 112.43 (J_{C-F} = 29.0 Hz), 109.7 (J_{C-F} = 10.0 Hz), 51.9, 51.0, 29.4 (J_{C-F} = 5.0 Hz), 28.4; ^{19}F NMR (377 MHz, $CDCl_3$) δ -123.88; FT-IR (KBr) 1716, 1657, 1523, 1400, 1256 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{22}H_{21}FNO_3$: 366.1500, found 366.1502.

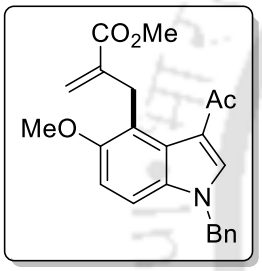


Methyl 2-((3-acetyl-1-benzyl-5-(benzyloxy)-1*H*-indol-4-yl)methyl)acrylate 3g. Analytical



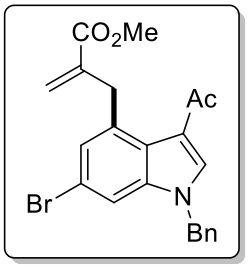
TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.43; brown solid; mp 111-112 °C; yield 69% (31.2 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (s, 1H), 7.39-7.32 (m, 7H), 7.29 (d, *J* = 7.2 Hz, 1H), 7.16-7.10 (m, 3H), 7.00 (d, *J* = 8.8 Hz, 1H), 6.05 (d, *J* = 1.6 Hz, 1H), 5.30 (s, 2H), 5.05 (s, 2H), 4.83 (d, *J* = 1.6 Hz, 1H), 4.47 (s, 2H), 3.80 (s, 3H), 2.45 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 191.6, 168.4, 153.2, 141.3, 137.9, 137.8, 135.7, 133.7, 129.2, 128.5, 128.3, 127.7, 127.2, 127.06, 127.03, 123.1, 122.5, 111.8, 109.0, 72.2, 51.9, 50.9, 30.2, 28.5; FT-IR (KBr) 1713, 1651, 1522, 1400, 1257 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{29}H_{28}NO_4$: 454.2013, found 454.2017.

Methyl 2-((3-acetyl-1-benzyl-5-methoxy-1*H*-indol-4-yl)methyl)acrylate 3h. Analytical TLC



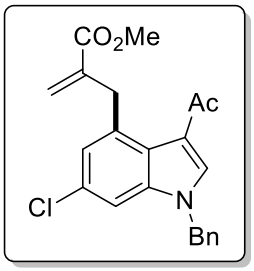
on silica gel, 1:4 ethyl acetate/hexane R_f = 0.43; light yellow solid; mp 104-105 °C; yield 74% (27.8 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.77 (s, 1H), 7.36-7.30 (m, 3H), 7.15-7.13 (m, 3H), 6.98 (d, *J* = 8.4 Hz, 1H), 6.033-6.030 (m, 1H), 5.31 (s, 2H), 4.79-4.78 (m, 1H), 4.39 (s, 2H), 3.83 (s, 3H), 3.79 (s, 3H), 2.45 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 191.6, 168.4, 154.2, 141.3, 137.9, 135.8, 133.5, 129.2, 128.3, 127.0, 126.9, 122.9, 121.8, 118.8, 110.4, 109.0, 57.6, 51.9, 50.9, 30.1, 28.5; FT-IR (KBr) 1712, 1648, 1523, 1400, 1256 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{23}H_{24}NO_4$: 378.1700, found 378.1700.

Methyl 2-((3-acetyl-1-benzyl-6-bromo-1*H*-indol-4-yl)methyl)acrylate 3i. Analytical TLC on

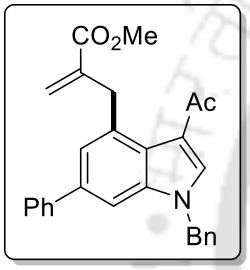


silica gel, 1:4 ethyl acetate/hexane R_f = 0.42; light yellow solid; mp 135-136 °C; yield 71% (30.1 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (s, 1H), 7.39-7.34 (m, 4H), 7.18 (d, *J* = 1.6 Hz, 1H), 7.14-7.12 (m, 2H), 6.147-6.144 (m, 1H), 5.29 (s, 2H), 5.055-5.051 (m, 1H), 4.32 (s, 2H), 3.78 (s, 3H), 2.46 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 191.8, 167.8, 140.8, 139.1, 137.08, 136.1, 135.2, 129.3, 128.5, 127.8, 127.0, 125.3, 124.1, 119.2, 117.5, 111.6, 100.1, 52.0, 50.9, 37.5, 28.5; FT-IR (KBr) 1706, 1661, 1525, 1400, 1261 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{22}H_{21}BrNO_3$: 426.0699, found 426.0693.

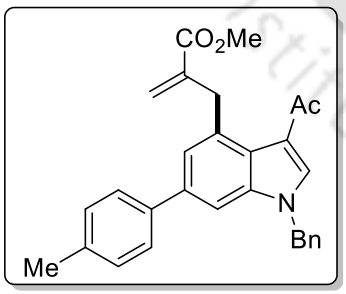
Methyl 2-((3-acetyl-1-benzyl-6-chloro-1*H*-indol-4-yl)methyl)acrylate 3j. Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.41; colorless solid; mp 127-128 °C; yield 74% (28.2 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (s, 1H), 7.39-7.33 (m, 3H), 7.17 (d, *J* = 1.6 Hz, 1H), 7.14-7.12 (m, 2H), 7.04 (d, *J* = 1.6 Hz, 1H), 6.15-6.14 (m, 1H), 5.29 (s, 2H), 5.062-5.062 (m, 1H), 4.33 (s, 2H), 3.78 (s, 3H), 2.46 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 191.8, 167.8, 140.8, 138.7, 137.2, 135.8, 135.2, 129.7, 129.3, 128.5, 127.0, 125.3, 125.1, 123.8, 119.2, 108.6, 52.0, 50.9, 37.5, 28.5; FT-IR (KBr) 1714, 1654, 1523, 1400, 1261 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{22}H_{21}ClNO_3$: 382.1204, found 382.1205.



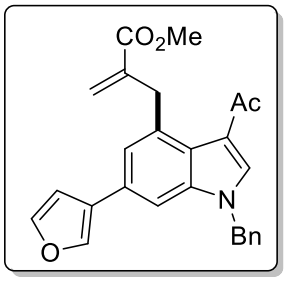
Methyl 2-((3-acetyl-1-benzyl-6-phenyl-1*H*-indol-4-yl)methyl)acrylate 3k. Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.45; brown thick liquid; yield 69% (29.1 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (s, 1H), 7.58-7.55 (m, 2H), 7.41 (t, *J* = 7.2 Hz, 3H), 7.37-7.36 (m, 2H), 7.34-7.30 (m, 3H), 7.19-7.17 (m, 2H), 6.145-6.142 (m, 1H), 5.39 (s, 2H), 5.079-5.075 (m, 1H), 4.43 (s, 2H), 3.80 (s, 3H), 2.48 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 191.9, 168.2, 141.5, 141.3, 139.0, 137.3, 137.2, 135.7, 134.3, 129.2, 128.9, 128.4, 127.4, 127.2, 127.0, 124.9, 124.7, 124.4, 118.9, 107.0, 52.0, 50.8, 37.9, 28.5; FT-IR (neat) 1715, 1653, 1523, 1400, 1260, 1191 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{28}H_{26}NO_3$: 424.1907, found 424.1903.



Methyl 2-((3-acetyl-1-benzyl-6-(*p*-tolyl)-1*H*-indol-4-yl)methyl)acrylate 3l. Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.44; light yellow solid; mp 155-156 °C; yield 81% (35.3 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (s, 1H), 7.47 (d, *J* = 8.4 Hz, 2H), 7.38-7.32 (m, 5H), 7.23 (d, *J* = 8.0 Hz, 2H), 7.19 (d, *J* = 6.4 Hz, 2H), 6.14 (d, *J* = 1.2 Hz, 1H), 5.38 (s, 2H), 5.08 (d, *J* = 1.6 Hz, 1H), 4.43 (s, 2H), 3.80 (s, 3H), 2.48 (s, 3H), 2.38 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 191.8, 168.2, 141.5, 139.0, 138.4, 137.2, 137.0, 135.7, 134.3, 129.6, 129.2, 128.4, 127.2, 127.1, 124.9, 124.6, 124.2, 119.0, 106.7, 52.0, 50.8, 37.8, 28.5, 21.2; FT-IR (KBr) 1716, 1655, 1522, 1400, 1259 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{29}H_{28}NO_3$: 438.2064, found 438.2064.

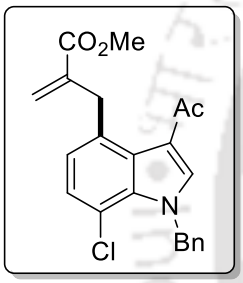


Methyl 2-((3-acetyl-1-benzyl-6-(furan-3-yl)-1*H*-indol-4-yl)methyl)acrylate 3m. Analytical



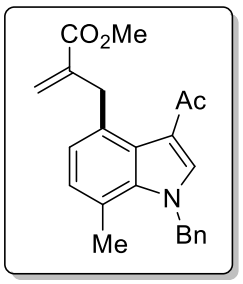
TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.43; light brown liquid; yield 67% (27.6 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (s, 1H), 7.69 (s, 1H), 7.45 (t, *J* = 1.6 Hz, 1H), 7.39-7.32 (m, 3H), 7.25 (s, 1H), 7.21 (s, 1H), 7.18 (d, *J* = 6.4 Hz, 2H), 6.667-6.665 (m, 1H), 6.127-6.124 (m, 1H), 5.37 (s, 2H), 5.036-5.033 (m, 1H), 4.38 (s, 2H), 3.80 (s, 3H), 2.46 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 191.8, 168.1, 143.7, 141.5, 138.9, 138.6, 137.1, 135.7, 134.5, 129.2, 128.46, 128.40, 127.1, 126.6, 124.8, 124.3, 123.6, 119.1, 109.1, 105.7, 52.0, 50.8, 37.8, 28.5; FT-IR (neat) 1714, 1634, 1524, 1400, 1259 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{26}H_{24}NO_4$: 414.1700, found 414.1701.

Methyl 2-((3-acetyl-1-benzyl-7-chloro-1*H*-indol-4-yl)methyl)acrylate 3n. Analytical TLC on



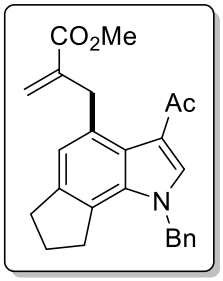
silica gel, 1:4 ethyl acetate/hexane R_f = 0.45; light brown solid; mp 95-96 °C; yield 76% (28.9 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (s, 1H), 7.35-7.27 (m, 3H), 7.18 (d, *J* = 7.6 Hz, 1H), 7.05-7.03 (m, 2H), 6.97 (d, *J* = 8.0 Hz, 1H), 6.12 (d, *J* = 1.2 Hz, 1H), 5.83 (s, 2H), 5.03 (d, *J* = 1.6 Hz, 1H), 4.30 (s, 2H), 3.77 (s, 3H), 2.46 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 192.1, 167.9, 141.0, 139.2, 137.5, 133.4, 132.9, 129.0, 128.0, 127.9, 126.3, 125.8, 125.6, 124.9, 119.2, 115.6, 53.0, 52.0, 37.4, 28.9; FT-IR (KBr) 1717, 1622, 1531, 1400, 1258 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{22}H_{21}ClNO_3$: 382.1204, found 382.1204.

Methyl 2-((3-acetyl-1-benzyl-7-methyl-1*H*-indol-4-yl)methyl)acrylate 3o. Analytical TLC on



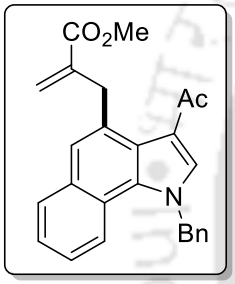
silica gel, 1:4 ethyl acetate/hexane R_f = 0.43; light yellow solid; mp 119-120 °C; yield 82% (29.6 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (s, 1H), 7.34-7.28 (m, 3H), 6.94-6.90 (m, 4H), 6.11 (d, *J* = 1.6 Hz, 1H), 5.62 (s, 2H), 5.01 (d, *J* = 1.6 Hz, 1H), 4.31 (s, 2H), 3.78 (s, 3H), 2.50 (s, 3H), 2.47 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 192.2, 168.2, 141.5, 138.9, 138.0, 137.0, 131.7, 129.2, 127.9, 127.1, 126.0, 125.4, 125.1, 124.6, 119.7, 118.9, 53.2, 51.9, 37.5, 28.7, 19.6; FT-IR (KBr) 1717, 1658, 1534, 1503, 1400, 1208 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{23}H_{24}NO_3$: 362.1751, found 362.1750.

Methyl 2-((3-acetyl-1-benzyl-1,6,7,8-tetrahydrocyclopenta[*g*]indol-4-yl)methyl)acrylate 3p.



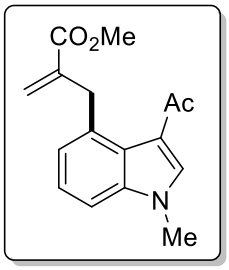
Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.41; colorless solid; mp 149-150 °C; yield 68% (26.3 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (s, 1H), 7.35-7.28 (m, 3H), 7.00 (d, *J* = 6.8 Hz, 2H), 6.96 (s, 1H), 6.11 (d, *J* = 1.6 Hz, 1H), 5.50 (s, 2H), 5.03 (d, *J* = 1.6 Hz, 1H), 4.33 (s, 2H), 3.79 (s, 3H), 3.08 (t, *J* = 7.2 Hz, 2H), 2.93 (t, *J* = 7.6 Hz, 2H), 2.45 (s, 3H), 2.10-2.02 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 192.1, 168.3, 141.8, 141.6, 137.7, 137.2, 135.8, 132.1, 129.2, 128.0, 125.9, 124.6, 124.1, 123.8, 122.0, 119.5, 52.0, 51.9, 37.6, 32.6, 31.4, 28.6, 25.3; FT-IR (KBr) 1652, 1530, 1400, 1261, 1120 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{25}H_{26}NO_3$: 388.1907, found 388.1916.

Methyl 2-((3-acetyl-1-benzyl-1*H*-benzo[*g*]indol-4-yl)methyl)acrylate 3q. Analytical TLC on



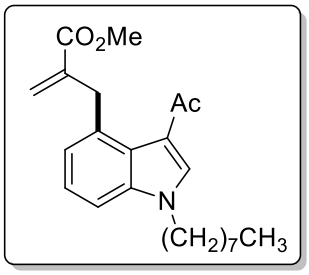
silica gel, 1:4 ethyl acetate/hexane R_f = 0.44; colorless solid; mp 165-166 °C; yield 83% (32.9 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (d, *J* = 8.4 Hz, 1H), 7.87 (d, *J* = 7.6 Hz, 1H), 7.77 (s, 1H), 7.46 (s, 1H), 7.41 (d, *J* = 6.8 Hz, 1H), 7.37-7.30 (m, 4H), 7.11 (d, *J* = 7.2 Hz, 2H), 6.15 (d, *J* = 1.2 Hz, 1H), 5.85 (s, 2H), 5.08 (d, *J* = 1.6 Hz, 1H), 4.42 (s, 2H), 3.80 (s, 3H), 2.53 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 192.9, 168.2, 141.1, 136.9, 136.2, 132.3, 132.2, 132.0, 129.3, 128.7, 128.1, 126.1, 125.6, 125.4, 124.8, 124.6, 123.3, 121.1, 120.9, 119.8, 54.6, 52.0, 38.1, 29.1; FT-IR (KBr) 1717, 1662, 1529, 1400, 1261 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{26}H_{24}NO_3$: 398.1751, found 398.1751.

Methyl 2-((3-acetyl-1-methyl-1*H*-indol-4-yl)methyl)acrylate 3r. Analytical TLC on silica gel,

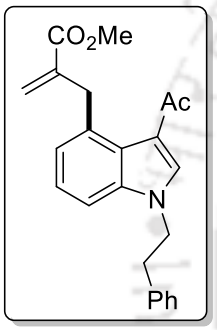


1:4 ethyl acetate/hexane R_f = 0.46; light brown solid; mp 130-131 °C; yield 65% (17.6 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (s, 1H), 7.22-7.18 (m, 2H), 7.16-7.14 (m, 1H), 7.01 (d, *J* = 6.8 Hz, 1H), 6.03 (d, *J* = 1.6 Hz, 1H), 4.90 (d, *J* = 1.6 Hz, 1H), 4.30 (s, 2H), 3.76 (s, 3H), 3.71 (s, 3H), 2.41 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 191.6, 168.2, 141.7, 138.8, 137.6, 134.1, 125.0, 124.9, 124.7, 123.8, 118.5, 108.1, 51.9, 37.7, 33.7, 28.4; FT-IR (KBr) 1716, 1640, 1528, 1400, 1135 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{16}H_{18}NO_3$: 272.1281, found 272.1283.

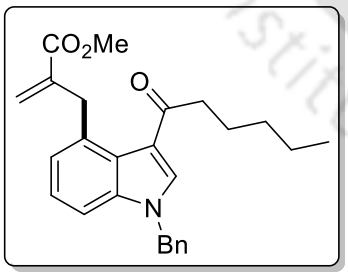
Methyl 2-((3-acetyl-1-octyl-1*H*-indol-4-yl)methyl)acrylate 3s. Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.45; brown thick liquid; yield 73% (26.9 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (s, 1H), 7.24-7.23 (m, 2H), 7.07-7.04 (m, 1H), 6.105-6.102 (m, 1H), 4.987-4.983 (m, 1H), 4.37 (s, 2H), 4.13 (t, *J* = 7.2 Hz, 2H), 3.78 (s, 3H), 2.49 (s, 3H), 1.91-1.84 (m, 2H), 1.34-1.25 (m, 12H), 0.87 (t, *J* = 6.4 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 191.7, 168.2, 141.6, 138.0, 136.6, 134.1, 125.1, 124.78, 124.76, 123.6, 118.4, 108.3, 51.9, 47.3, 37.7, 31.8, 29.8, 29.2, 28.5, 27.0, 22.7, 14.2; FT-IR (neat) 1718, 1654, 1524, 1400, 1141 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{23}H_{32}NO_3$: 370.2377, found 370.2376.



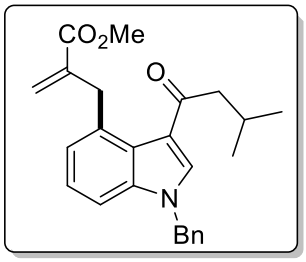
Methyl 2-((3-acetyl-1-phenethyl-1*H*-indol-4-yl)methyl)acrylate 3u. Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.47; brown thick liquid; yield 75% (27 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (s, 1H), 7.22-7.16 (m, 5H), 7.00-6.98 (m, 1H), 6.96-6.93 (m, 2H), 6.03 (d, *J* = 1.6 Hz, 1H), 4.89 (d, *J* = 1.6 Hz, 1H), 4.32-4.28 (m, 4H), 3.71 (s, 3H), 3.05 (t, *J* = 7.2 Hz, 2H), 2.26 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 191.7, 168.2, 141.7, 137.8, 137.7, 137.0, 134.2, 128.9, 128.8, 127.1, 125.2, 124.9, 124.6, 123.7, 118.2, 108.2, 51.9, 48.9, 37.8, 36.2, 28.3; FT-IR (neat) 1715, 1652, 1524, 1400, 1140 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{23}H_{24}NO_3$: 362.1751, found 362.1756.



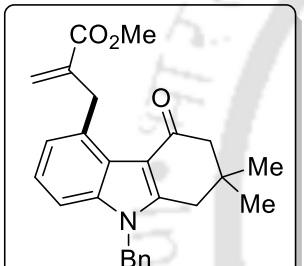
Methyl 2-((1-benzyl-3-hexanoyl-1*H*-indol-4-yl)methyl)acrylate 3v. Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.48; brown thick liquid; yield 81% (32.6 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (s, 1H), 7.36-7.30 (m, 3H), 7.19-7.18 (m, 2H), 7.16-7.13 (m, 2H), 7.06-7.04 (m, 1H), 6.10 (d, *J* = 1.2 Hz, 1H), 5.34 (s, 2H), 5.04 (d, *J* = 1.6 Hz, 1H), 4.38 (s, 2H), 3.76 (s, 3H), 2.77 (t, *J* = 7.6 Hz, 2H), 1.73-1.66 (m, 3H), 1.33-1.30 (m, 3H), 0.89 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (151 MHz, CDCl3) δ 195.4, 168.1, 141.1, 138.2, 135.9, 135.8, 134.1, 129.1, 128.2, 127.0, 125.2, 125.0, 124.6, 123.8, 119.0, 108.7, 51.9, 50.8, 40.9, 37.6, 31.7, 25.4, 22.7, 14.1; FT-IR (neat) 1717, 1654, 1524, 1400, 1200 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{26}H_{30}NO_3$: 404.2220, found 404.2218.



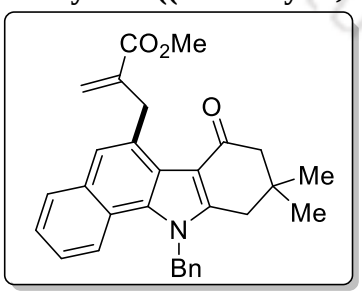
Methyl 2-((1-benzyl-3-(3-methylbutanoyl)-1*H*-indol-4-yl)methyl)acrylate 3w. Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.49; light yellow liquid; yield 79% (30.7 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (s, 1H), 7.36-7.31 (m, 3H), 7.21-7.18 (m, 2H), 7.16-7.13 (m, 2H), 7.06-7.04 (m, 1H), 6.10 (d, *J* = 1.2 Hz, 1H), 5.35 (s, 2H), 5.03 (d, *J* = 1.6 Hz, 1H), 4.39 (s, 2H), 3.76 (s, 3H), 2.65 (d, *J* = 7.2 Hz, 2H), 2.30-2.20 (m, 1H), 0.96 (s, 3H), 0.94 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 194.9, 168.1, 141.3, 138.3, 135.97, 135.96, 134.3, 129.1, 128.3, 127.0, 125.2, 125.0, 124.7, 123.8, 119.7, 108.7, 51.8, 50.8, 50.0, 37.7, 26.2, 22.9; FT-IR (neat) 1717, 1652, 1524, 13991194 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{25}H_{28}NO_3$: 390.2064, found 390.2066.



Methyl 2-((9-benzyl-2,2-dimethyl-4-oxo-2,3,4,9-tetrahydro-1*H*-carbazol-5-yl)methyl)acrylate 3x. Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.46; colorless solid; mp 150-151°C; yield 68% (27.2 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33-7.27 (m, 3H), 7.17-7.11 (m, 2H), 7.05-7.03 (m, 1H), 6.99-6.98 (m, 2H), 6.134-6.131 (m, 1H), 5.33 (s, 2H), 5.04 (d, *J* = 1.6 Hz, 1H), 4.50 (s, 2H), 3.79 (s, 3H), 2.73 (s, 2H), 2.45 (s, 2H), 1.10 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 191.8, 168.2, 151.2, 141.8, 138.3, 136.0, 133.6, 129.1, 127.9, 125.9, 124.9, 124.8, 124.5, 123.4, 113.0, 108.1, 53.2, 51.9, 47.0, 37.6, 36.8, 34.6, 28.6; FT-IR (KBr) 1717, 1647, 1400, 1259, 1137 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{26}H_{28}NO_3$: 402.2064, found 402.2064.

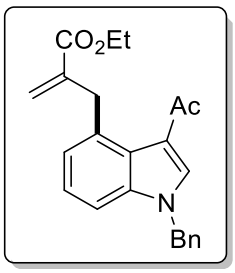


Methyl 2-((11-benzyl-9,9-dimethyl-7-oxo-8,9,10,11-tetrahydro-7*H*-benzo[*a*]carbazol-6-yl)-methyl)acrylate 3y. Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.46; colorless solid; mp 189-190 °C; yield 70% (31.5 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.99 (d, *J* = 9.0 Hz, 1H), 7.86 (d, *J* = 7.8 Hz, 1H), 7.46 (s, 1H), 7.37-7.34 (m, 3H), 7.31 (t, *J* = 7.8 Hz, 1H), 7.28-7.27 (m, 1H), 7.11 (d, *J* = 7.8 Hz, 2H), 6.149-6.147 (m, 1H), 5.79 (s, 2H), 5.06 (s, 1H), 4.57 (s, 2H), 3.82 (s, 3H), 2.78 (s, 2H), 2.49 (s, 2H), 1.12 (s, 6H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 192.5, 168.3, 150.0, 141.6, 136.1, 132.2, 132.0, 129.5, 128.8, 128.0, 125.6, 125.5, 125.2, 124.7, 124.2, 122.6, 120.7, 114.0, 53.6, 52.0, 50.1, 38.4,

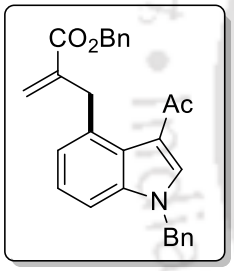


37.0, 34.7, 28.5; FT-IR (KBr) 1631, 1400, 1262, 1112 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{30}H_{30}NO_3$: 452.2220, found 452.221.

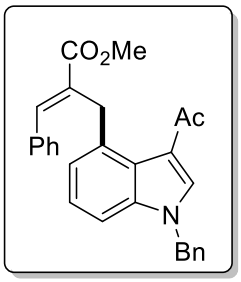
Ethyl 2-((3-acetyl-1-benzyl-1*H*-indol-4-yl)methyl)acrylate 3z. Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.44; light yellow solid; mp 108-109 °C; yield 68% (24.5 mg); ^1H NMR (400 MHz, $CDCl_3$) δ 7.77 (s, 1H), 7.36-7.31 (m, 3H), 7.22-7.18 (m, 2H), 7.16-7.13 (m, 2H), 7.07-7.05 (m, 1H), 6.12 (d, *J* = 1.2 Hz, 1H), 5.34 (s, 2H), 5.03 (d, *J* = 1.6 Hz, 1H), 4.38 (s, 2H), 4.23 (q, *J* = 7.2 Hz, 2H), 2.47 (s, 3H), 1.28 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 192.0, 167.7, 141.8, 138.3, 136.8, 135.8, 134.2, 129.1, 128.3, 127.0, 125.1, 124.9, 124.5, 123.8, 119.0, 108.6, 60.6, 50.8, 37.6, 28.5, 14.3; FT-IR (KBr) 1710, 1653, 1524, 1400, 1256 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{23}H_{24}NO_3$: 362.1751, found 362.1753.



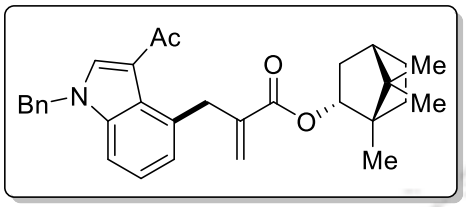
Benzyl 2-((3-acetyl-1-benzyl-1*H*-indol-4-yl)methyl)acrylate 3aa. Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.46; brown solid; mp 105-106 °C; yield 64% (27 mg); ^1H NMR (400 MHz, $CDCl_3$) δ 7.77 (s, 1H), 7.37-7.28 (m, 8H), 7.19-7.18 (m, 2H), 7.16-7.14 (m, 2H), 7.07-7.05 (m, 1H), 6.187-6.185 (m, 1H), 5.34 (s, 2H), 5.23 (s, 2H), 5.09 (d, *J* = 1.2 Hz, 1H), 4.43 (s, 2H), 2.46 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 191.9, 167.4, 141.5, 138.3, 136.8, 136.5, 135.8, 134.1, 129.1, 128.5, 128.3, 127.97, 127.95, 127.0, 125.2, 125.1, 124.8, 123.8, 119.1, 108.7, 66.3, 50.8, 37.7, 28.5; FT-IR (KBr) 1713, 1654, 1524, 1400, 1254 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{28}H_{26}NO_3$: 424.1907, found 424.1911.



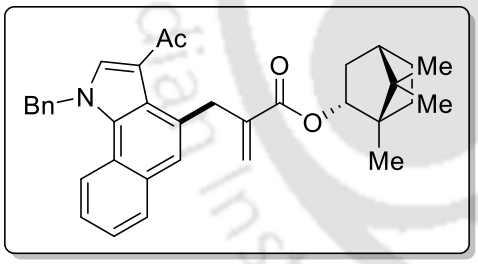
Methyl (*Z*)-2-((3-acetyl-1-benzyl-1*H*-indol-4-yl)methyl)-3-phenylacrylate 3ab. Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.41; brown thick liquid; yield 32% (13 mg); ^1H NMR (400 MHz, $CDCl_3$) δ 7.99 (s, 1H), 7.79 (s, 1H), 7.38-7.32 (m, 6H), 7.24 (d, *J* = 2.0 Hz, 1H), 7.19-7.16 (m, 5H), 7.02-7.00 (m, 1H), 5.35 (s, 2H), 4.68 (s, 2H), 3.70 (s, 3H), 2.52 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 192.4, 169.3, 141.3, 138.3, 136.4, 135.8, 135.7, 135.0, 131.2, 129.6, 129.2, 128.6, 128.5, 128.3, 127.1, 124.9, 124.1, 120.9, 119.6, 108.4, 52.1, 50.9, 33.9, 28.8;



FT-IR (neat) 1706, 1653, 1521, 1400, 1252 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{28}H_{26}NO_3$: 424.1907, found 424.1902.

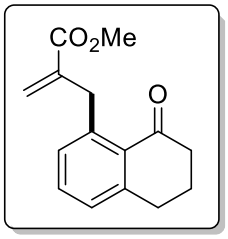
(1S,2R,4S)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl 2-((3-acetyl-1-benzyl-1*H*-indol-4-yl)-methyl)acrylate 3ac. 

Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.41; brown thick liquid; yield 61% (28.6 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (s, 1H), 7.36-7.30 (m, 3H), 7.20-7.16 (m, 2H), 7.14-7.12 (m, 2H), 7.07-7.05 (m, 1H), 6.186-6.182 (m, 1H), 5.34 (s, 2H), 5.16 (d, *J* = 1.6 Hz, 1H), 4.93-4.89 (m, 1H), 4.42 (d, *J* = 4.0 Hz, 2H), 2.48 (s, 3H), 2.36-2.28 (m, 1H), 1.83-1.76 (m, 1H), 1.63-1.60 (m, 3H), 1.18-1.11 (m, 1H), 1.07-1.01 (m, 1H), 0.88 (s, 3H), 0.83 (s, 3H), 0.74 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 192.0, 167.9, 141.8, 138.3, 136.5, 135.9, 134.7, 129.1, 128.3, 127.0, 125.1, 125.0, 124.1, 123.9, 119.3, 108.5, 80.0, 50.8, 48.9, 47.8, 45.0, 37.8, 36.7, 28.6, 28.0, 27.2, 19.8, 19.0, 13.4; FT-IR (neat) 1704, 1654, 1523, 1400, 1259 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{31}H_{36}NO_3$: 470.2690, found 470.2692.

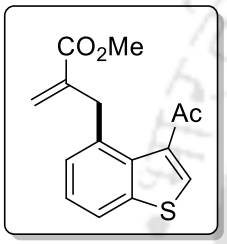
(1S,2R,4S)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl 2-((3-acetyl-1-benzyl-1*H*-benzo[*g*]indol-4-yl)methyl)acrylate 3ad. 

Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.39; colorless solid; mp 185-186 °C; yield 63% (32.6 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, *J* = 8.4 Hz, 1H), 7.85 (d, *J* = 7.6 Hz, 1H), 7.75 (s, 1H), 7.45 (s, 1H), 7.39-7.35 (m, 1H), 7.33-7.29 (m, 4H), 7.10 (d, *J* = 6.8 Hz, 2H), 6.222-6.220 (m, 1H), 5.85 (s, 2H), 5.21 (d, *J* = 1.6 Hz, 1H), 4.95-4.91 (m, 1H), 4.48-4.38 (m, 2H), 2.53 (s, 3H), 2.37-2.29 (m, 1H), 1.87-1.81 (m, 1H), 1.67-1.61 (m, 3H), 1.21-1.13 (m, 1H), 1.07-1.01 (m, 1H), 0.88 (s, 3H), 0.83 (s, 3H), 0.75 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 193.0, 167.9, 141.4, 136.5, 136.3, 132.8, 132.2, 132.1, 129.3, 128.7, 128.1, 126.1, 125.5, 124.9, 124.6, 124.5, 123.3, 121.1, 120.9, 120.2, 80.1, 54.6, 49.0, 47.8, 45.1, 38.1, 36.7, 29.2, 28.0, 27.3, 19.8, 19.0, 13.5; FT-IR (KBr) 1703, 1663, 1529, 1400, 1261, 1159 cm^{-1} HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{35}H_{38}NO_3$: 520.2846, found 520.2850.

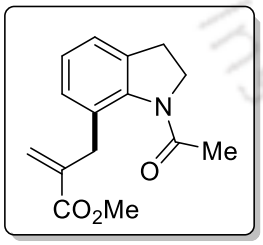
Methyl 2-((8-oxo-5,6,7,8-tetrahydronaphthalen-1-yl)methyl)acrylate 4a. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.46; light brown liquid; yield 43% (10.4 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (t, *J* = 7.6 Hz, 1H), 7.17 (d, *J* = 7.6 Hz, 1H), 7.09 (d, *J* = 7.6 Hz, 1H), 6.13 (d, *J* = 1.2 Hz, 1H), 5.14 (d, *J* = 1.2 Hz, 1H), 4.06 (s, 2H), 3.77 (s, 3H), 2.96 (t, *J* = 6.0 Hz, 2H), 2.62 (t, J = 6.4 Hz, 2H), 2.10-2.04 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 199.6, 167.9, 146.2, 141.2, 140.5, 132.5, 131.1, 130.4, 127.8, 124.9, 52.0, 41.0, 36.9, 31.1, 23.0; FT-IR (neat) 1719, 1677, 1632, 1591, 1400, 1270 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{15}H_{17}O_3$: 245.1172, found 245.1176.



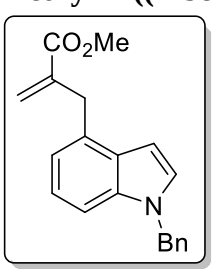
Methyl 2-((3-acetylbenzo[*b*]thiophen-4-yl)methyl)acrylate 4b. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.46; light brown liquid; yield 51% (14 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.96 (s, 1H), 7.78 (d, *J* = 8.4 Hz, 1H), 7.36 (t, *J* = 7.8 Hz, 1H), 7.26-7.25 (m, 1H), 6.13 (d, *J* = 1.2 Hz, 1H), 5.01 (d, *J* = 1.2 Hz, 1H), 4.06 (s, 2H), 3.75 (s, 3H), 2.60 (s, 3H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 196.3, 167.6, 141.5, 140.19, 140.18, 135.3, 134.4, 133.1, 128.3, 125.6, 125.5, 121.4, 52.1, 37.6, 30.1; FT-IR (neat) 1718, 1678, 1632, 1400, 1259 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{15}H_{15}O_3S$: 275.0736, found 275.0737.



Methyl 2-((1-acetylindolin-7-yl)methyl)acrylate 4c. Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.43; colorless solid; mp 85-86 °C; yield 71% (18.3 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.09-7.07 (m, 1H), 7.05-7.03 (d, *J* = 7.6 Hz, 1H), 7.01-6.99 (m, 1H), 6.19 (s, 1H), 5.46 (d, *J* = 1.2 Hz, 1H), 4.04 (t, *J* = 7.2 Hz, 2H), 3.73 (s, 2H), 3.66 (s, 3H), 3.01 (t, *J* = 7.2 Hz, 2H), 2.24 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 167.6, 141.3, 139.1, 134.8, 129.5, 129.0, 126.0, 125.45, 125.41, 122.6, 51.8, 51.3, 36.6, 30.0, 23.8; FT-IR (KBr) 1722, 1633, 1400, 1117 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{15}H_{18}NO_3$: 260.1281, found 260.1288.



Methyl 2-((1-benzyl-1*H*-indol-4-yl)methyl)acrylate 5. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.46; brown thick liquid; yield 62% (18.9 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33-7.26 (m, 3H), 7.19 (d, *J* = 8.2 Hz, 1H), 7.13 (dd, *J* = 6.8, 2.6 Hz, 4H), 6.94 (d, *J* = 7.0 Hz, 1H), 6.53 (d, *J* = 3.8 Hz, 1H), 6.24 (s, 1H), 5.40 (d, *J* = 1.5 Hz, 1H), 5.32 (s, 2H), 3.93 (s, 2H), 3.77 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.9, 139.5, 137.6, 136.5, 131.0, 128.8, 128.4, 128.0, 127.7, 127.0, 126.3, 121.9, 120.2, 108.3, 100.3, 52.0, 50.3, 35.3; FT-IR (neat) 1629, 100, 1139 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{20}H_{20}NO_2$: 306.1489, found 306.1497.



Crystal Data and Structure Refinement for 3aa at 293(2) K

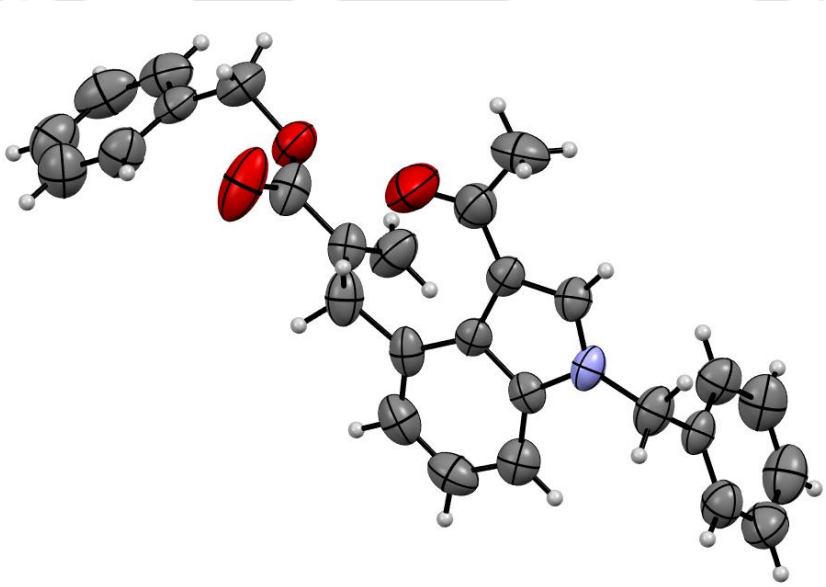


Figure 2. ORTEP diagram of methyl benzyl 2-((3-acetyl-1-benzyl-1*H*-indol-4-yl)methyl)acrylate **3aa** with 50% ellipsoid (**CCDC 1960464**).

Identification code	**3aa**
Empirical formula	C_{28} H_{25} N O_3
Formula weight	423.49
Crystal habit, colour	block /Colorless

Temperature, *T*/K	296 K
Wavelength, λ/Å	0.71073
Crystal system	monoclinic
Space group	'P 21/c'
Unit cell dimensions	a = 9.8397(6)Å
	b = 25.7051(16)Å
	c = 9.5292(6)Å
	α = 90, β = 110.975(2)
	γ = 90
Volume, *V*/Å^3	2250.5(2)
Z	4
Calculated density, Mg·m^{-3}	1.250
Absorption coefficient, μ/mm^{-1}	0.081
F(000)	896
θ range for data collection	2.35 to 19.63°
Limiting indices	$-9 \leq h \leq 9$, $-24 \leq k \leq 24$, $-9 \leq l \leq 9$
Reflection collected / unique	2040/1557
Completeness to θ	100% (θ = 19.78°)
Absorption correction	Multi-scan
Refinement method	'SHELXL-2014/7 (Sheldrick, 2014)'
Data / restraints / parameters	3782/0/ 273
Goodness–of–fit on F^2	1.040
Final *R* indices [*I*>2sigma(*I*)]	R1 = 0.0426, wR2 = 0.1350
R indices (all data)	R1 = 0.0585, wR2 = 0.1501

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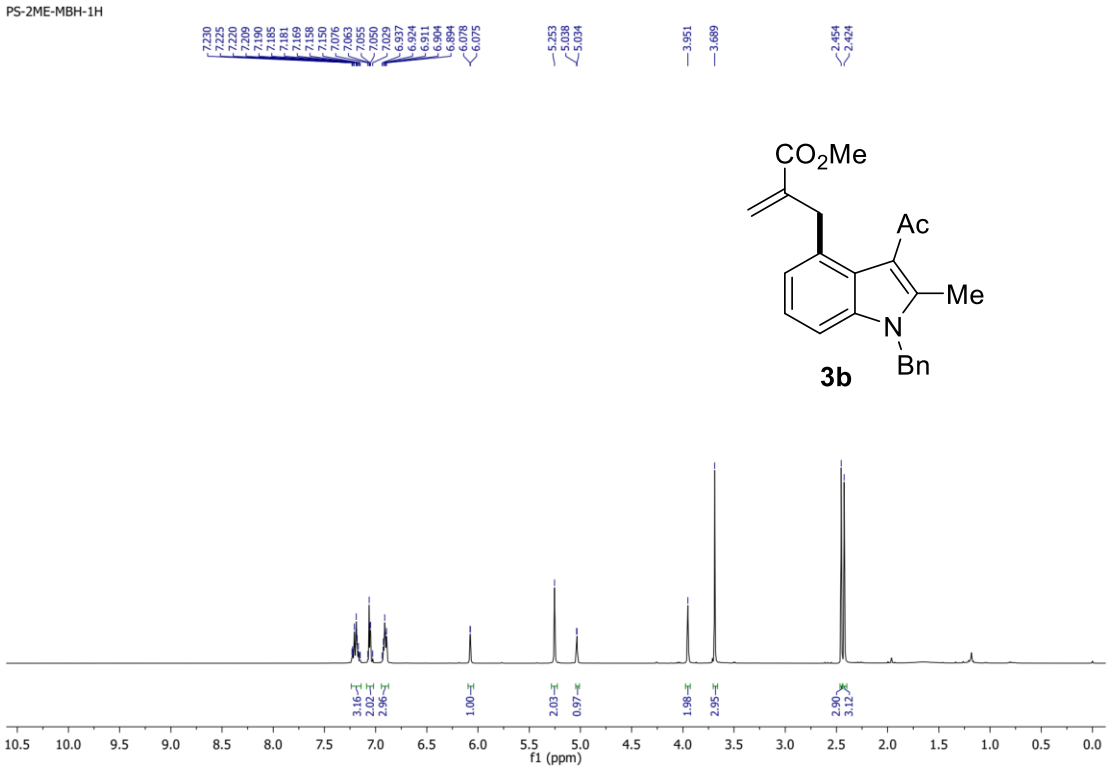
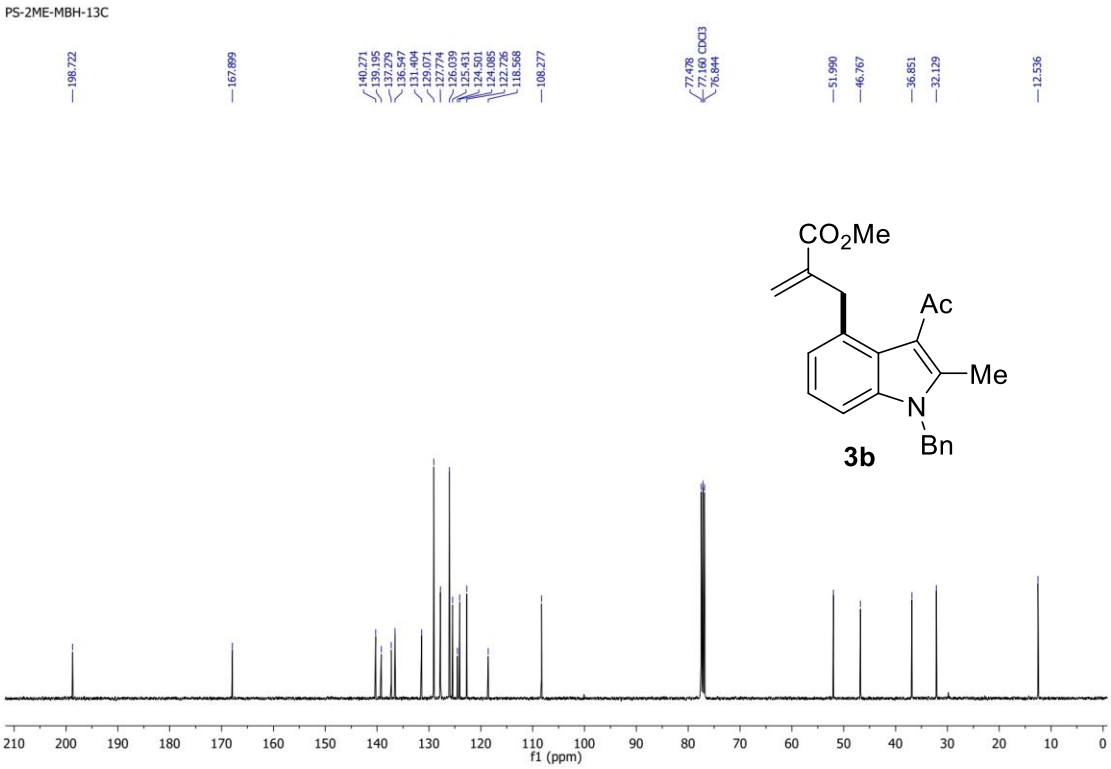
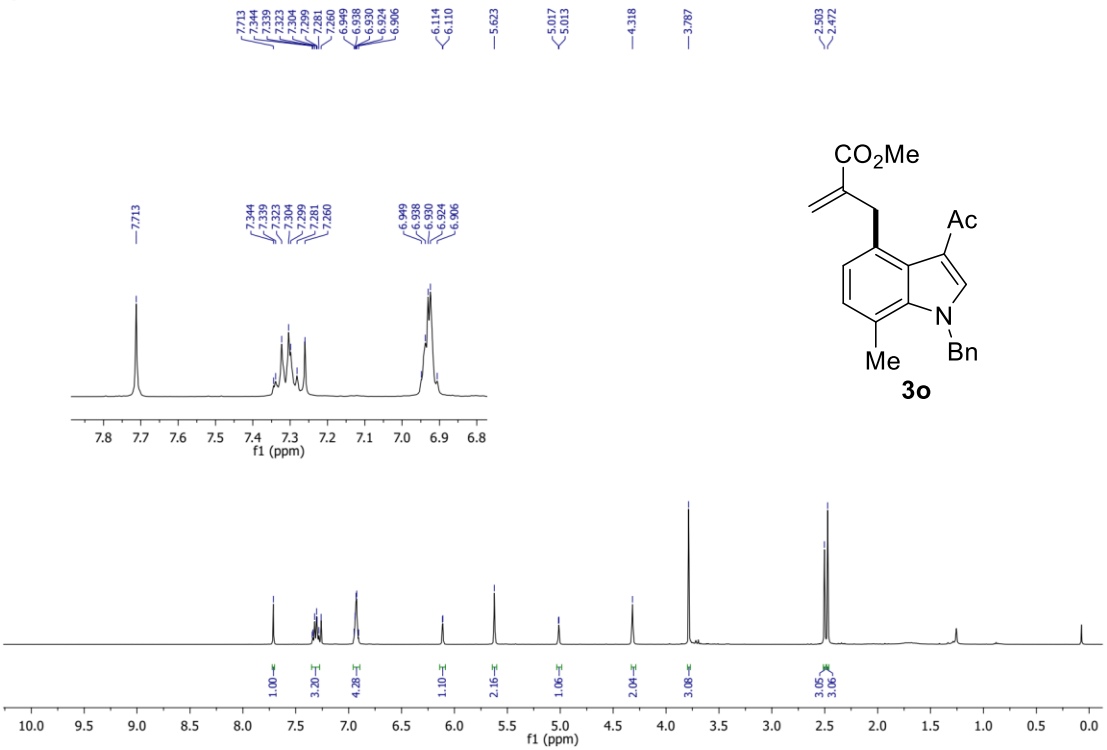
3.5 Selected NMR Spectra





PS-7-ME-MBH-1H



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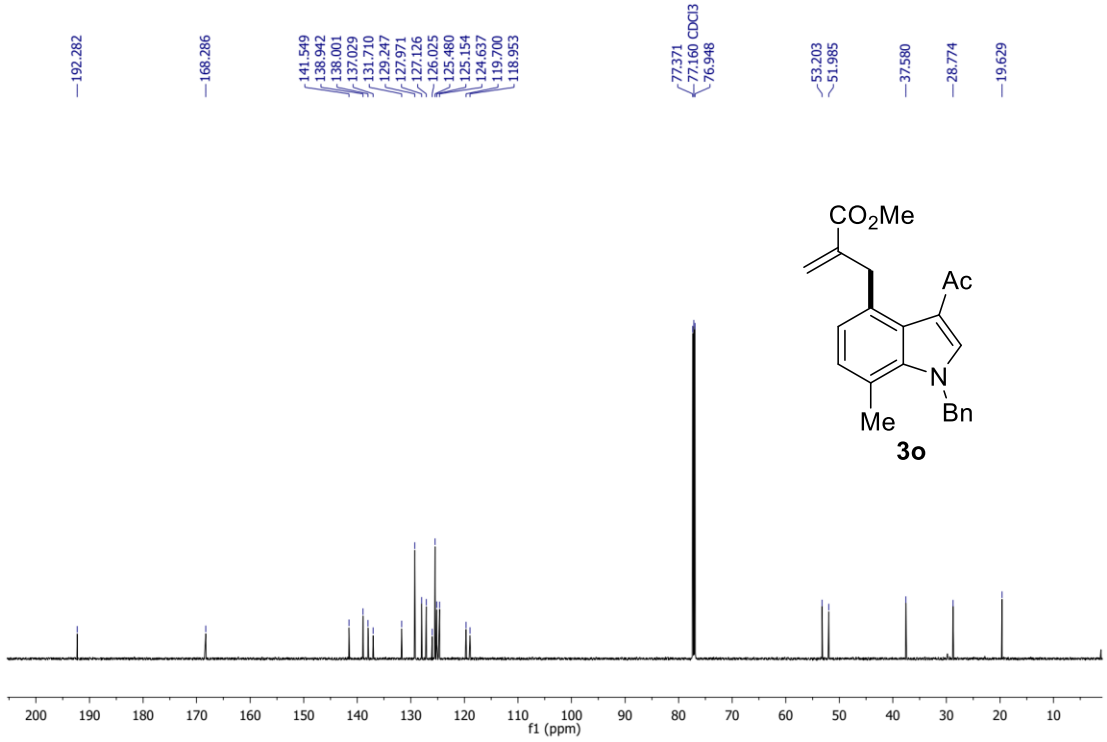
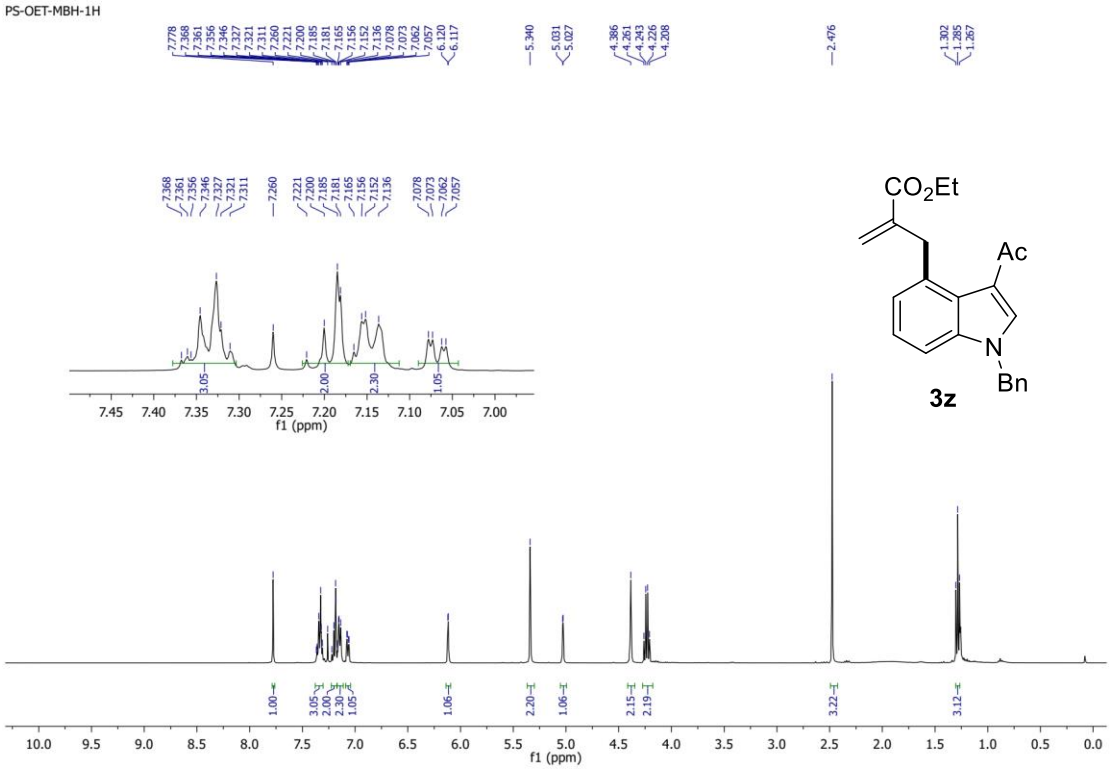
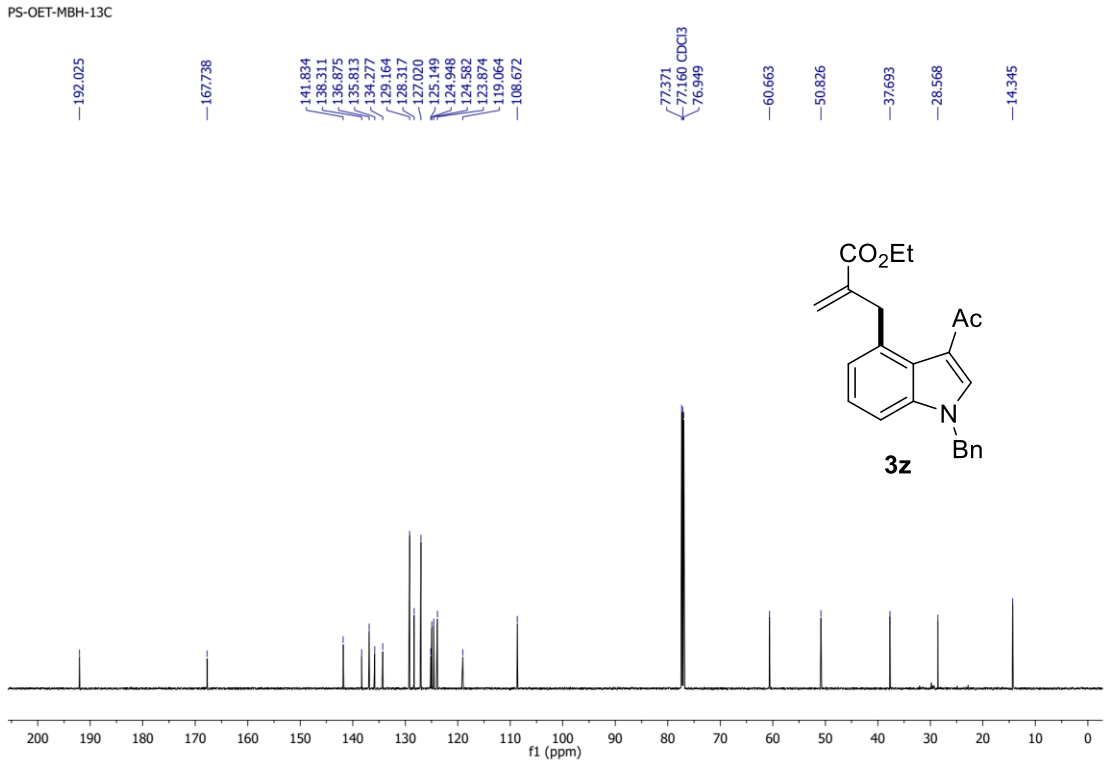
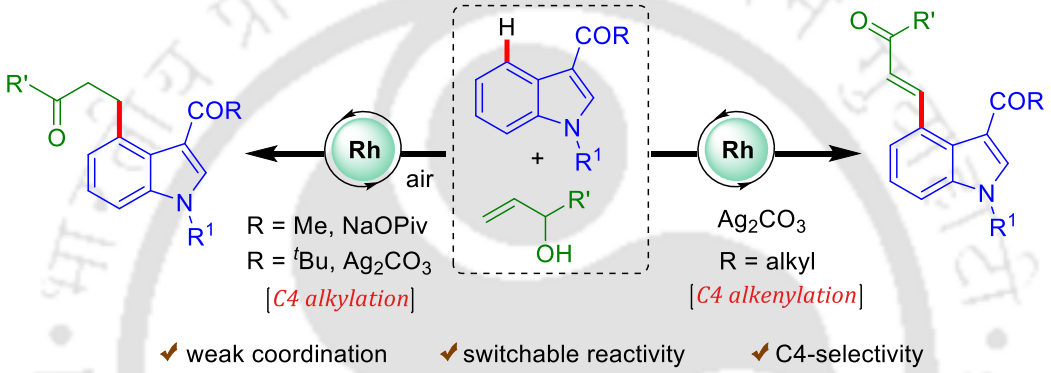






Chapter IV

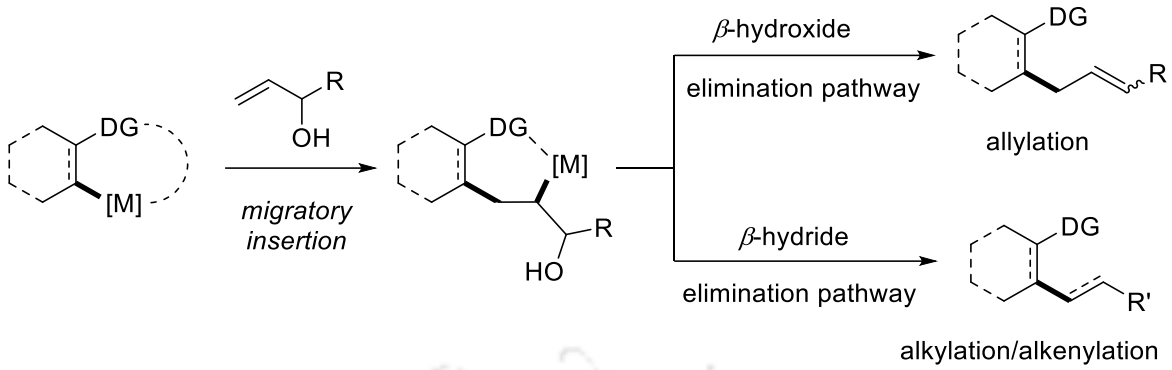
Rh(III)-Catalyzed Switchable C4-Alkenylation and Alkylation of Indoles with Allylic Alcohols



Org. Lett. **2020**, *22*, 1720.

Rh(III)-Catalyzed Switchable C4-Alkenylation and Alkylation of Indoles with Allylic Alcohols

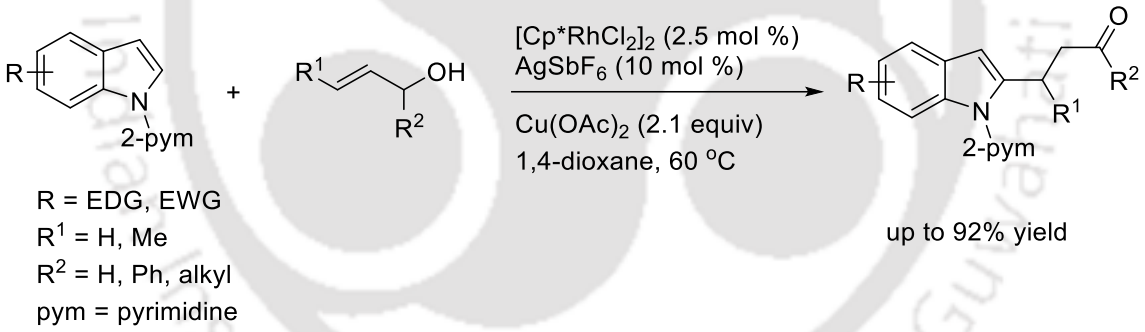
The heteroaromatic scaffold indole has been one of the most studied organic templates in the realm of organic synthesis,[1] as it features in plentiful natural products and pharmaceuticals.[2] Thus, the pursuit for site-selective expedited synthetic elaborations of the six available C-H functionalization site on the indole backbone has emerged as a burgeoning research area. Owing to the inherent nucleophilic nature of the pyrrole type ring, C2 and C3 C-H functionalizations[3,4] are replete with examples in the literature. In contrast, the C-H functionalization around the benzenoid segment (C4 to C7) remained underdeveloped.[5] In this line, selective editing at the C4-site of indole requires a directing group at the C3 position, which imposes a substantial challenge by prompting a competing C-H metalation pathway. The formation of five-membered cyclometalation at C2 is kinetically favored as compared to the corresponding six-membered cyclometalation at C4. Hence, C4 functionalization of indole has garnered much attention.[6] However, the development of an efficient and robust catalytic system which enables multiple reactive pathways by tuning the reactivity of substrates is highly desirable. In this context, allylic alcohols are realized as staple coupling partners in C−H functionalization as they are capable of selectively undergoing manifold reaction pathways.[7] The reaction involves the formation of a metal alkyl intermediate *via* migratory insertion of the metal aryl species into the olefin partner. The resulting organometallic intermediate can now choose the β-hydride elimination or protonolysis pathways to deliver alkenylation and alkylated products (Scheme 1).[8] The group of Glorius, Kanai/Matsunaga and others demonstrated the use of allylic alcohols for C-H functionalization regulating by either β-hydride elimination or β-hydroxy elimination pathway using suitable transition metals. However, the use of weakly coordinating directing group[9] to achieve such tunable reactivity are scarce. Weakly coordinating directing groups are generally intrinsic part of the substrate and the resulting metallacycles are less thermodynamically stable, thus a broad range of nucleophiles and electrophiles can be coupled efficiently.[9] Herein, we report an efficient weak coordination guided Rh-catalyzed controllable reactivity switch between C4-alkenylation and C4-alkylation by judicious modification of reaction parameters or electronic nature of the directing groups. Broad substrate scope, functional group compatibility and mechanistic aspects are the important practical features.



Scheme 1. Diverse Reactivity Features of Allylic Alcohols

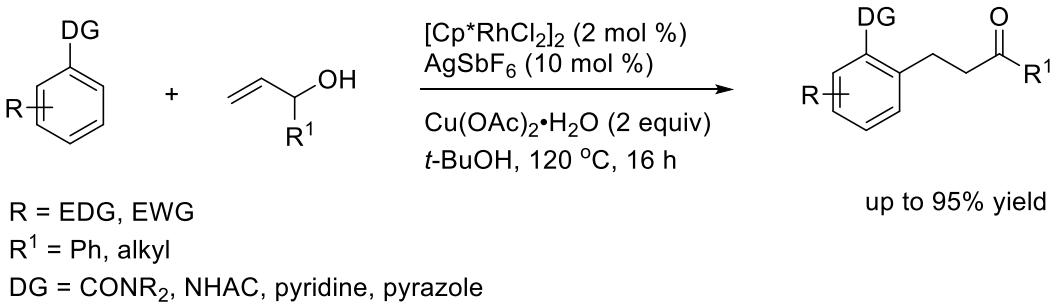
4.1 Oxidative Alkylation of Arenes with Allylic Alcohols

Glorius and co-workers described an efficient Rh(III)-catalyzed oxidative alkylation of indoles with allylic alcohols as coupling partners using 2-pyrimidyl directing group (Scheme 2).[10] The reaction provides a general route to synthesize diverse *β*-aryl ketones and aldehydes. The strategy was further extended to the dehydrogenative coupling with several arene systems, such as 2-phenylpyridine, aryl ketones and acetanilide to afford a class of value-added scaffolds.



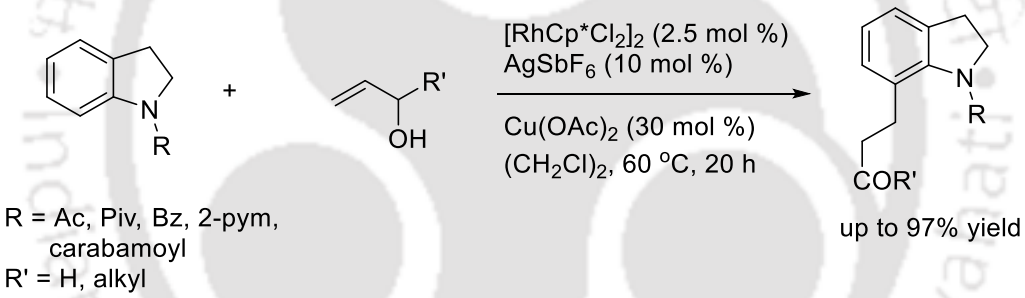
Scheme 2. Rh(III)-Catalyzed Oxidative C2-Alkylation of Indoles

Jiang and co-workers developed a robust Rh(III)-catalyzed direct oxidative C(sp^2)-H alkylation of *N*,*N*-disubstituted aryl amides and oxidative cyclization of acetanilides with allylic alcohols to afford functional *β*-aryl ketones and indolines with excellent regioselectivity (Scheme 3).[11] The strategy was extended to the alkylation of 2-phenylpyridine and 1-phenylpyrazole derivatives. A tentative mechanism with C-H activation, 1,2-migratory insertion followed by *β*-hydride elimination was proposed.



Scheme 3. Oxidative Alkylation of Arenes under Rh(III)-Catalysis.

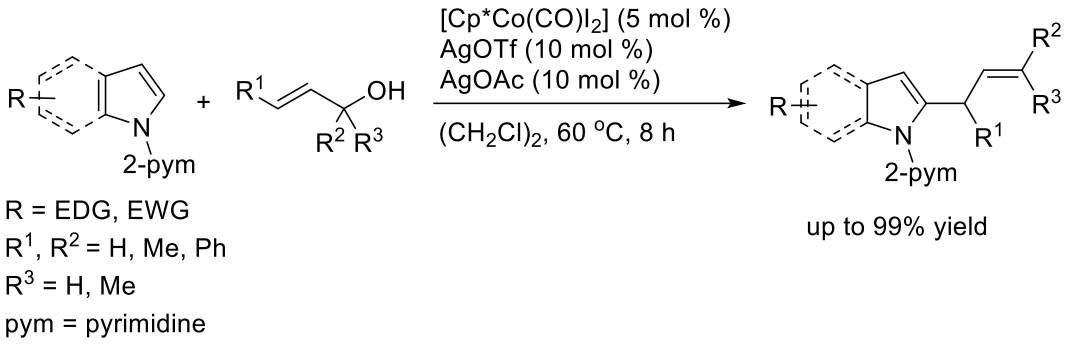
Kim and co-workers described a Rh(III)-catalyzed C7-alkylation of indolines with allylic alcohols using a variety of directing groups (Scheme 4). The compatibility of alkylation was extended to other *N*-heterocycles, such as carbazoles and pyrroles.[12] This method permits the synthesis of heterocyclic frameworks containing a *β*-aryl carbonyl moiety, which is known to be effective structural motif of biologically active compounds.



Scheme 4. Rh(III)-Catalyzed C7-Alkylation of Indolines

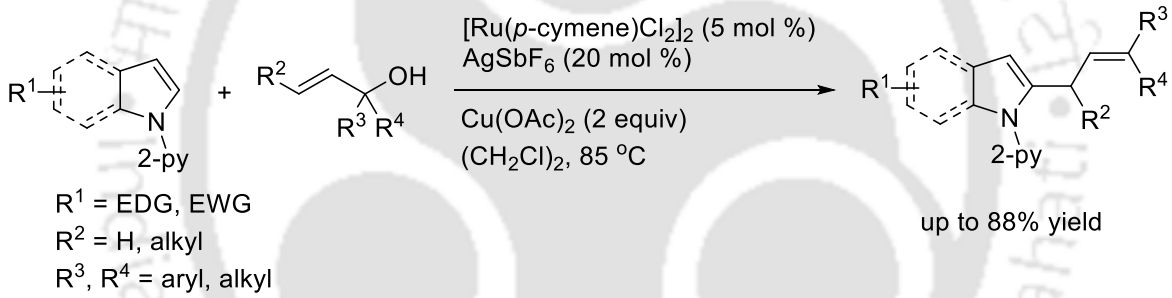
4.2 Oxidative Allylation of Arenes with Allylic Alcohols

Matsunaga and Kanai group demonstrated the unique reactivity of a cationic [Cp*Co^{III}]-catalyzed dehydrative C-H allylation of indoles, pyrrole and 1-phenylpyrazole with non-activated allylic alcohols (Scheme 5).[13] The unique [Cp*Co^{III}] catalyst favored *β*-hydroxide elimination rather than *β*-hydride elimination compared with analogous [Cp*Rh^{III}] catalyst, which was otherwise ineffective. The mechanistic pathway involving C-H metalation and insertion of a C-C double bond with subsequent *β*-hydroxide elimination was proposed.



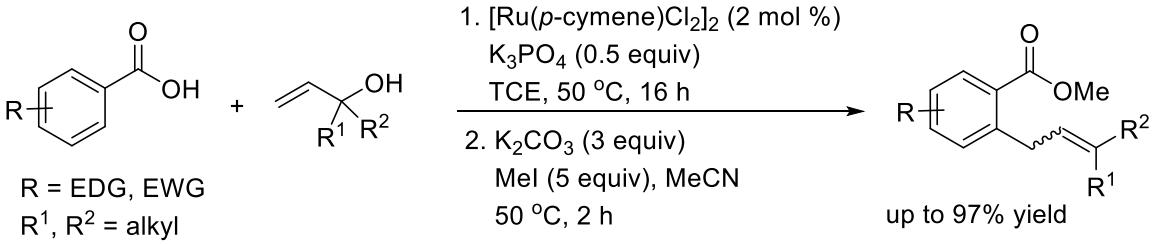
Scheme 5. Co(III)-Catalyzed Allylation of Heterocycles

A Ru(II)-catalyzed C2-allylation of indoles and pyrrole was presented using a removable 2-pyridyl directing group with substituted allylic alcohol *via* *β*-hydroxide elimination (Scheme 6).[14] Indoles bearing electron-donating and withdrawing substituents tolerated well and in case of substituted allylic alcohol good *E*-selectivity was observed of the olefin.



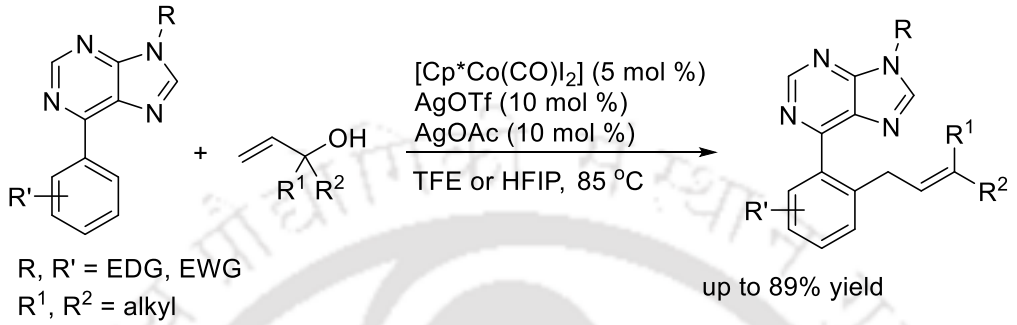
Scheme 6. Ru(II)-Catalyzed C2-Selective Allylation of Indoles

Ru(II)-catalyzed *ortho*-C–H allylation of aromatic and heteroaromatic carboxylates with versatile allylic alcohols was described (Scheme 7).[15] A wide variety of carboxylic acid derivatives and naturally occurring allylic alcohols efficiently coupled to afford allylarenes at 50 °C in phosphate-buffered 2,2,2-trichloroethanol (TCE).



Scheme 7. Ru(II)-Catalyzed Carboxylate-Directed Allylation

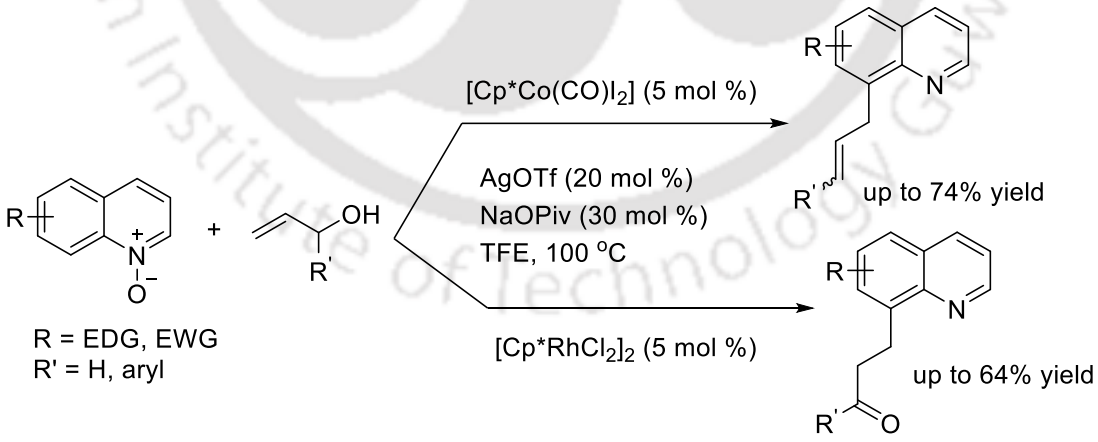
Matsunaga and Yoshino reported the mono-selective allylation of biologically active 6-arylpurine derivatives using allylic alcohols under Co(III) catalysis (Scheme 8).[16] Diverse array of functional groups on the aryl ring and substituted benzamides were compatible. With tertiary allylic alcohols as a coupling partners *γ*-selective prenylated products were obtained.



Scheme 8. Co(III)-Catalyzed Allylation of 6-Arylpurines

4.3 Switchable Reactivity of Arenes with Allylic alcohols

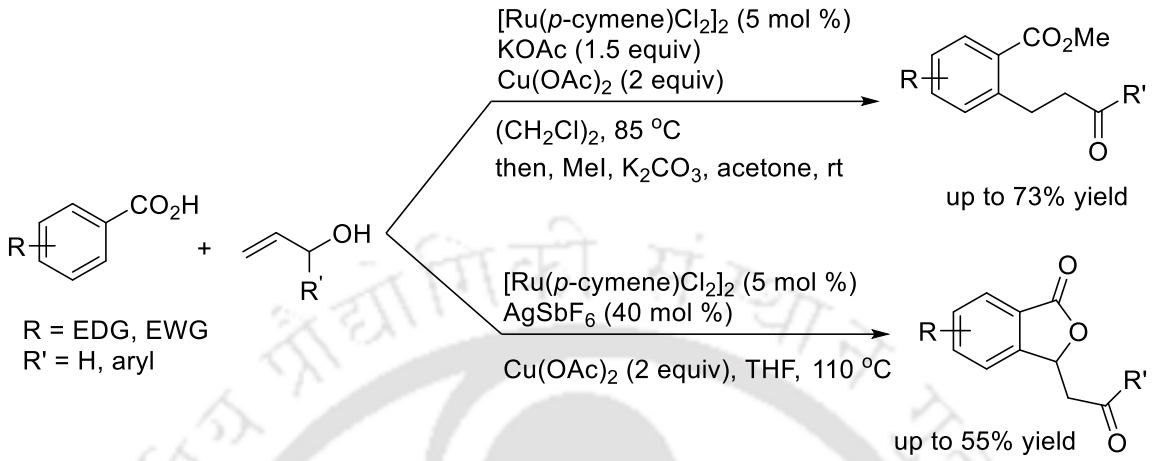
A comparative study between allylation and alkylation of C(8)-H bond of quinolines with allylic alcohols was demonstrated using a traceless directing group (Scheme 9).[17] Under an identical non-oxidative condition, the presence of Co(III)-catalyst resulted in C8-allylation, whereas the Cp*Rh(III) complex delivered the corresponding *β*-aryl ketone instead of allylated products, highlighting the unique features of cobalt(III) catalysis.



Scheme 9. C8-H Allylation *vs* Alkylation of Quinolines

Switchable reactivity between regioselective C−H alkylation and alkenylation of benzoic acids with allylic alcohols under a Ru(II)-catalysis was developed (Scheme 10).[18] By regulating the

reactivity of the organometallic intermediate in the carboxylate-directed C−H functionalization, unified access to diverse motifs such as 2-alkylbenzoic acids and phthalides was achieved.

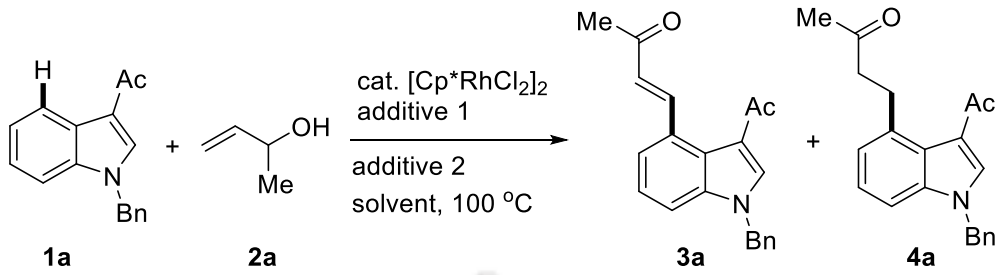


Scheme 10. Ru(II)-Catalyzed Alkylation *vs* Alkenylation of Benzoic Acids

4.4 Present Study

Herein, we report a C4-selective C-H functionalization of indoles guided by a weak coordination under Rh(III)-catalysis, in which a switchable reactivity between C4-alkenylation and C4-alkylation was achieved by judicious modification of the reaction parameters and the directing groups. At the outset, we carried out our investigation employing 1-(1-benzyl-1*H*-indol-3-yl)ethan-1-one **1a** with but-3-en-2-ol **2a** as the test substrates (Table 1). The reaction occurred to give the C4-alkenylated product **3a** in 17% yield along with a trace amount of alkylated **4a** when the substrates were stirred with 2.5 mol % $[Cp^*RhCl_2]_2$, 20 mol % $AgSbF_6$ and 2 equiv $Cu(OAc)_2$ in $(CH_2Cl)_2$ at 100 °C (entry 1). Screening of the ethereal solvents, such as THF and 1,4-dioxane, revealed that the formation of **3a** was facilitated (entries 2-4). Addition of Ag_2CO_3 in the place of $Cu(OAc)_2$ led to improve the yield of **3a** to 74%, whereas AgOAc produced inferior result (entries 5-6). Thus, Ag_2CO_3 was found to be the optimal additive to furnish the alkenylation product selectively. Further screening of the alcoholic solvents such as, HFIP, TFE, and ^{t}BuOH favored the formation of **4a** compared to **3a** (entries 7-9). Switching the additive from Ag_2CO_3 to NaOPiv•H_2O and a combination with AgOTf selectively produced the alkylated **4a** as the sole product (entries 10-11). PivOH was also found to be effective, delivering **4a** in 61% yield, whereas AcOH and 1-AdCO_2H were ineffective (entries 12-14). Thus, NaOPiv•H_2O was beneficial to achieve alkylation selectively.

Table 1. Optimization of the Reaction Conditions[a]



Entry	Additive 1	Additive 2	Solvent	Yield[b]	
				3a	**4a**
1	$AgSbF_6$	$Cu(OAc)_2$	$(CH_2Cl)_2$	17	trace
2	$AgSbF_6$	$Cu(OAc)_2$	THF	57	12
3	$AgSbF_6$	$Cu(OAc)_2$	1,4-dioxane	68	trace
4	AgOTf	$Cu(OAc)_2$	1,4-dioxane	61	10
5	**$AgSbF_6$**	**Ag_2CO_3**	**1,4-dioxane**	**74**	**trace**
6	$AgSbF_6$	AgOAc	1,4-dioxane	43	trace
7	$AgSbF_6$	Ag_2CO_3	HFIP	41	47
8	$AgSbF_6$	Ag_2CO_3	TFE	23	55
9	$AgSbF_6$	Ag_2CO_3	^{t}BuOH	21	59
10	AgOTf	Ag_2CO_3	^{t}BuOH	16	61
11	**AgOTf**	**$NaOPiv•H_2O$**	**^{t}BuOH**	**trace**	**69**
12	AgOTf	PivOH	^{t}BuOH	trace	61
13	AgOTf	1-$AdCO_2H$	^{t}BuOH	n.d.	trace
14	AgOTf	AcOH	^{t}BuOH	n.d.	n.d.
15[c]	-	Ag_2CO_3	1,4-dioxane	n.d.	n.d.
16[d]	-	$NaOPiv•H_2O$	1,4-dioxane	n.d.	n.d.
17[e]	$AgSbF_6$	Ag_2CO_3	^{t}BuOH	n.d.	n.d.
18[e]	AgOTf	$NaOPiv•H_2O$	^{t}BuOH	n.d.	n.d.

[a]Reaction conditions: **1a** (0.1 mmol), **2a** (0.2 mmol), $[Cp^*RhCl_2]_2$ (2.5 mol %), additive 1 (20 mol %), additive 2 (0.2 mmol), solvent (1.5 mL), 100 °C, 6 h, air. [b]Isolated yields. [c]Without $AgSbF_6$. [d]Without AgOTf. [e]Without Rh-catalyst. n.d. = not detected. Ac = acetyl.

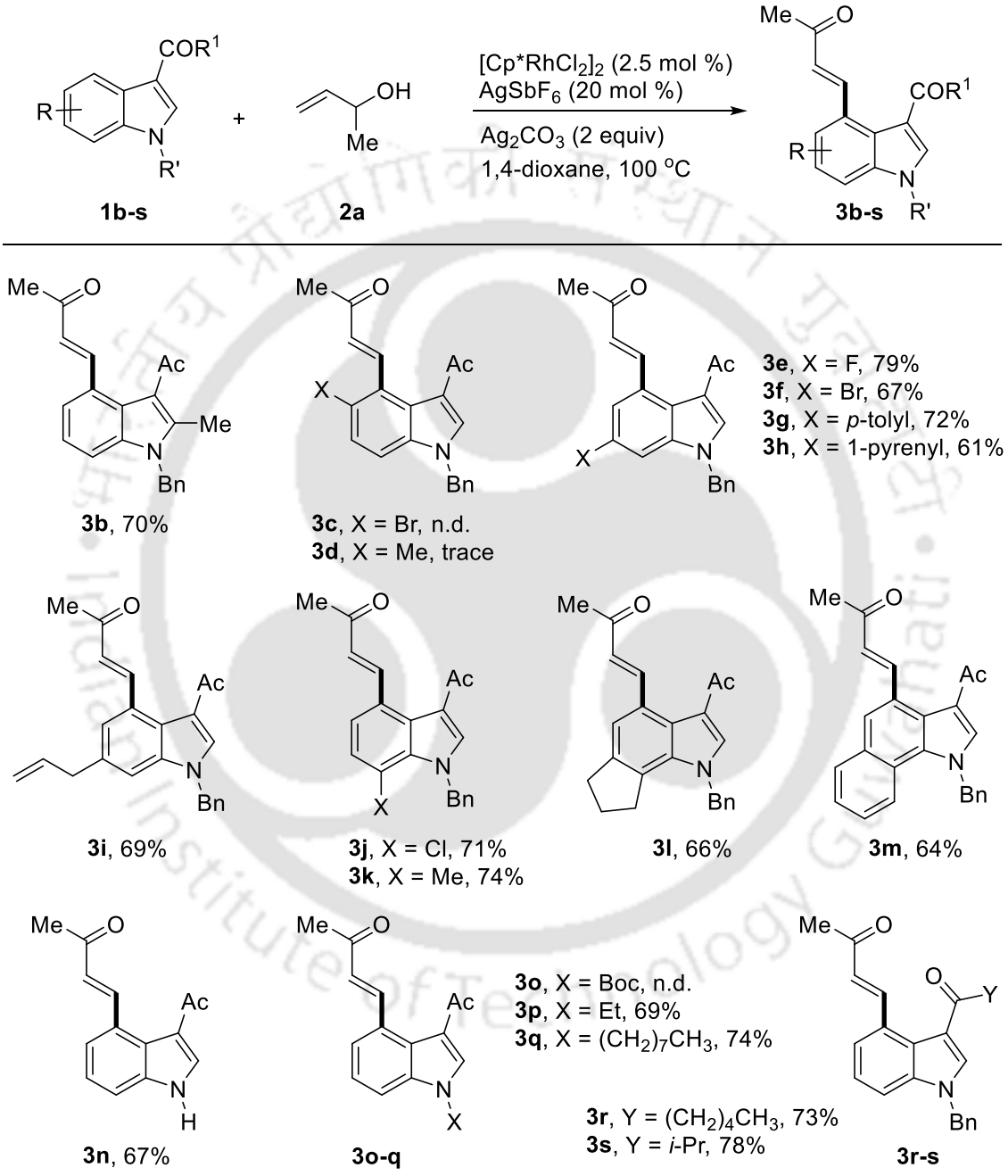
Control experiments confirmed that the combination of $AgSbF_6$ or AgOTf and the Rh(III)-catalyst is decisive and no product formation was observed in its absence (entries 15-18). Notably, C4 functionalization of indole was occurred selectively and no C2 functionalized product was detected. From the density functional theory (DFT) calculation, it was proposed that introducing a carbonyl group at the C3 C-H site can significantly increase the electron density at C4 site compared to the C2 site.[19] This may drive the selective C4 functionalization by an electrophilic metalation-type process.

With the optimal reaction conditions established, the scope of C4-alkenylation was assessed for substituted indoles **1b-s** with allylic alcohol **2a** as a standard substrate (Table 2). The reaction of 2-methyl indole **1b** afforded **3b** in 70% yield. 5-Substituted indoles bearing bromo **1c** and methyl **1d** functionalities were unsuccessful, which presumably due to the steric congestion near the C4 site. However, the substrates containing substitution at the 6 position of indole, with fluoro **1e**, bromo **1f**, *p*-tolyl **1g** and 1-pyrenyl **1h** groups afforded the target alkenylated products **3e-h** in 61-79% yields. Delightfully, sensitive 6-allylated indole **1i** afforded **3i** in 69% yield. Similar results were obtained with 7-chloro **1j** and 7-methyl **1k** substituted indoles furnishing **3j** and **3k** in 71 and 74% yields, respectively. Fused indole congeners **1l** and **1m** produced **3l** and **3m** in 66 and 64% yields, respectively. Interestingly, NH-free indole was successfully coupled to give **3n** in 67% yield. Variation in *N*-protecting groups such as, Boc **1o**, ethyl **1p** and octyl **1q**, the former was ineffective, while as others was amenable, delivering **3p** and **3q** in 69 and 74% yields, respectively. Likewise, 3-hexanoyl derivative **1r** and isobutyryl derivative **1s** conveyed **3r** and **3s** in 73 and 78% yields, respectively. These results suggest that C4 alkenylation of indoles can be accomplished with functional group tolerance.

With this intriguing results, the alkenylation scope was further explored using substituted allylic alcohols **2b-i** with indole **1a** as a standard substrate (Table 3). 1-Phenylprop-2-en-1-ol **2b** underwent reaction to afford **3t** in 64% yield. The reaction of 3-trifluoromethyl analogue **2c** produced **3u** in 58% yield. Whereas, 4-chloro **2d** and 4-fluro **2e** derivatives, delivered the corresponding alkenylated product **3v** and **3w** in 63 and 51% yields, respectively. Similar results were perceived with alkyl substitutions at the carbinol carbon of the allylic alcohols **2f-h**, delivering **3x-z** in 53-68% yields. Naturally occurring terpene alcohol isophytol **2i** participated in the reaction to give the C4-allylated product **3aa** in 41% yield. The reaction of tertiary allylic alcohol precludes the *β*-hydride elimination pathway and the reaction proceeds *via β*-hydroxide

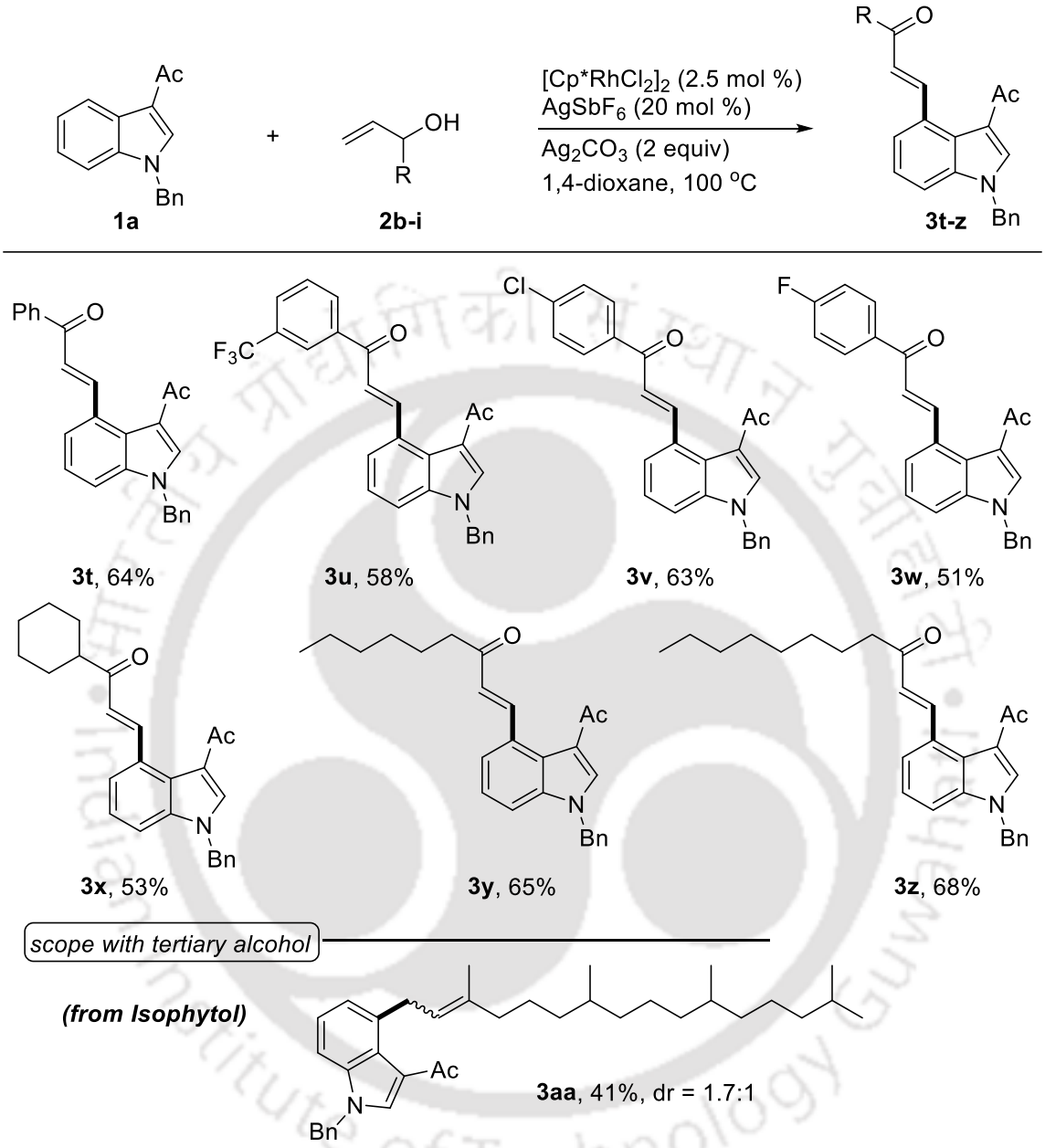
elimination pathway to deliver allylated product.[15] This result confides that C4-selective allylation of indoles can be achieved employing *tert*-allylic alcohols as a coupling partner.

Table 2. Scope of C4-Alkenylation with Substituted Indoles[a,b]



[a]Reaction conditions: **1b-s** (0.1 mmol), **2a** (0.2 mmol), $[Cp^*RhCl_2]_2$ (2.5 mol %), $AgSbF_6$ (20 mol %), Ag_2CO_3 (0.2 mmol), 1,4-dioxane (1.5 mL), 100 °C, 6 h, air. [b]Isolated yields.

Table 3. Scope of C4-Alkenylation with Allylic Alcohols[a,b]

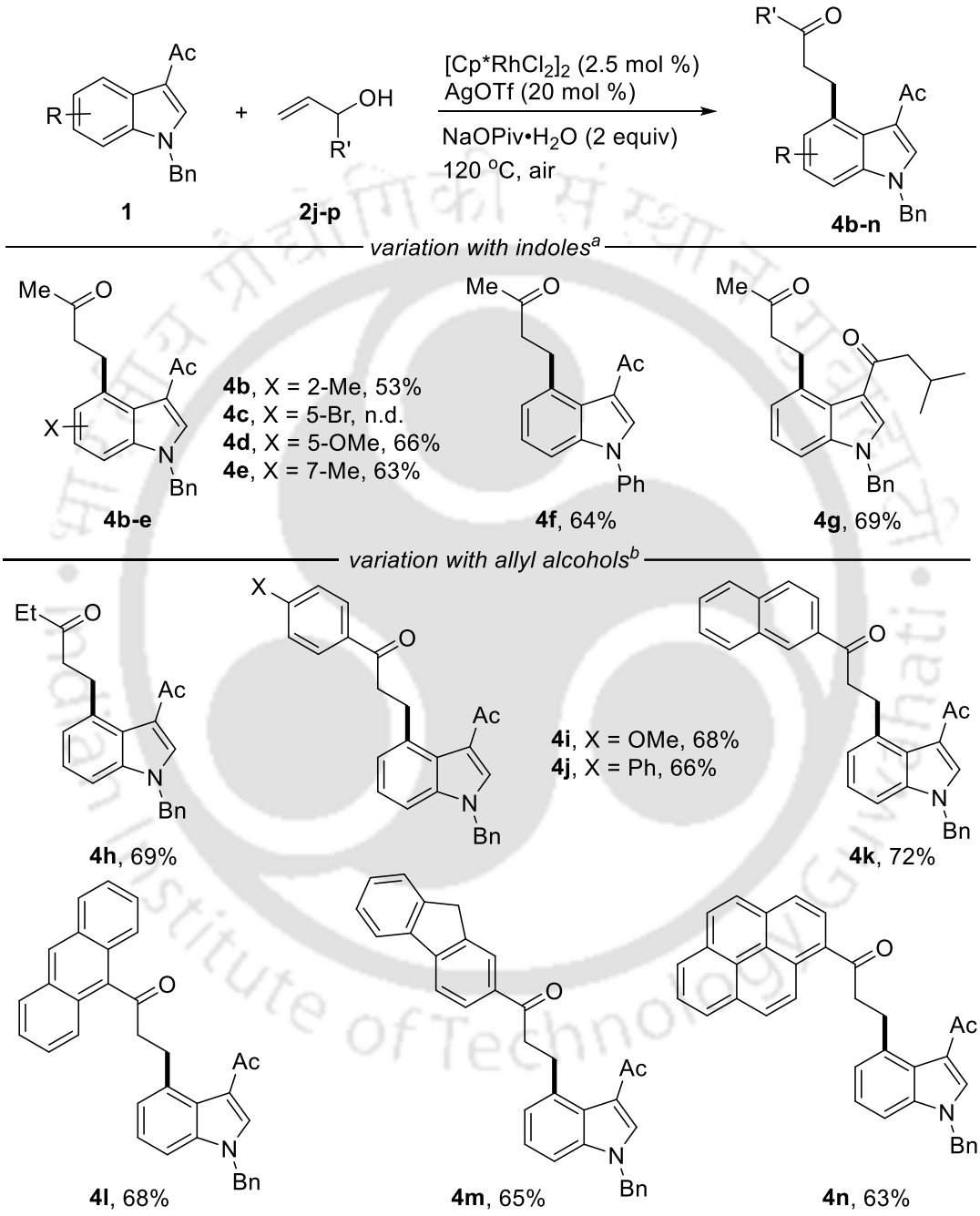


[a]Reaction conditions: **1a** (0.1 mmol), **2b-i** (0.2 mmol), $[Cp^*RhCl_2]_2$ (2.5 mol %), $AgSbF_6$ (20 mol %), Ag_2CO_3 (0.2 mmol), 1,4-dioxane (1.5 mL), 100 °C, 6 h, air. [b]Isolated yields.

Next, the C4-alkylation scope was investigated utilizing diversely substituted indoles with allylic alcohol **2a** as a standard coupling partner (Table 4). The reaction of 2-methyl indole **1b** furnished the C4 alkylated product **4b** in 53% yield. Likewise, 5-methoxy **1t**, 7-methyl **1k**, *N*-phenyl **1u** and

3-isovaleryl **1v** containing indoles converted to the alkylated scaffolds **4d-g** in 63-69% yields. Whereas 5-bromo indole **1c** was unsuccessful substrate, which may be due to steric hindrance.

Table 4. Scope of C4-Alkylation with Indoles and Allylic Alcohols[a,b]

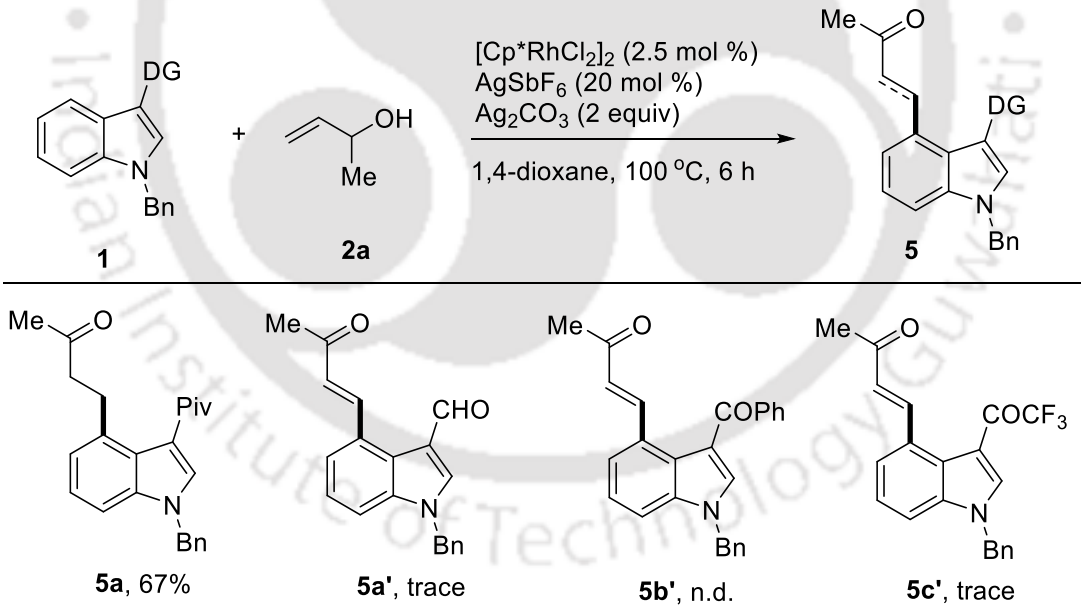


[a]Reaction conditions: **1** (0.1 mmol), **2j-p** (0.2 mmol), $[Cp^*RhCl_2]_2$ (2.5 mol %), AgOTf (20 mol %), $NaOPiv•H_2O$ (0.2 mmol), solvent (1.5 mL), 120 °C, 12 h, air. [b]Isolated yields. [a]*t*-BuOH used. [b]TFE used.

The reaction conditions were extended to the coupling of substituted allylic alcohols **2j-p** with indole **1a** as a standard substrate (Table 4). The reaction of pent-1-en-3-ol **2j** gave **4h** in 69% yield. Similarly, substitution of the phenyl ring at the carbinol carbon with 4-methoxy **2k** and 4-phenyl **2l** groups underwent reaction to afford **4i** and **4j** in 68 and 66% yields, respectively. Remarkably, conjugated π-system based allylic alcohols **2m-p** efficiently conveyed the alkylation products **4k-n** in 63-72% yields. These results displayed the captivating potential of the method for C4-alkylation of indoles to synthesize *β*-arylated ketones.

To divulge the importance of carbonyl based coordinating groups, the reaction of **2a** was conducted with a series of C3-carbonyl attached indole derivatives. Pivaloyl indole **1A**, conveyed the C4 alkylated product **5a** in 67% yield, whereas formyl, **1a′**, benzoyl **1b′** and trifluoromethylacetyl **1c′**, were unsuccessful substrates (Table 5). These results indicate that, depending on the directing group a switch in product distribution between C4-selective alkenylation and alkylation can be achieved under identical reaction conditions.[20]

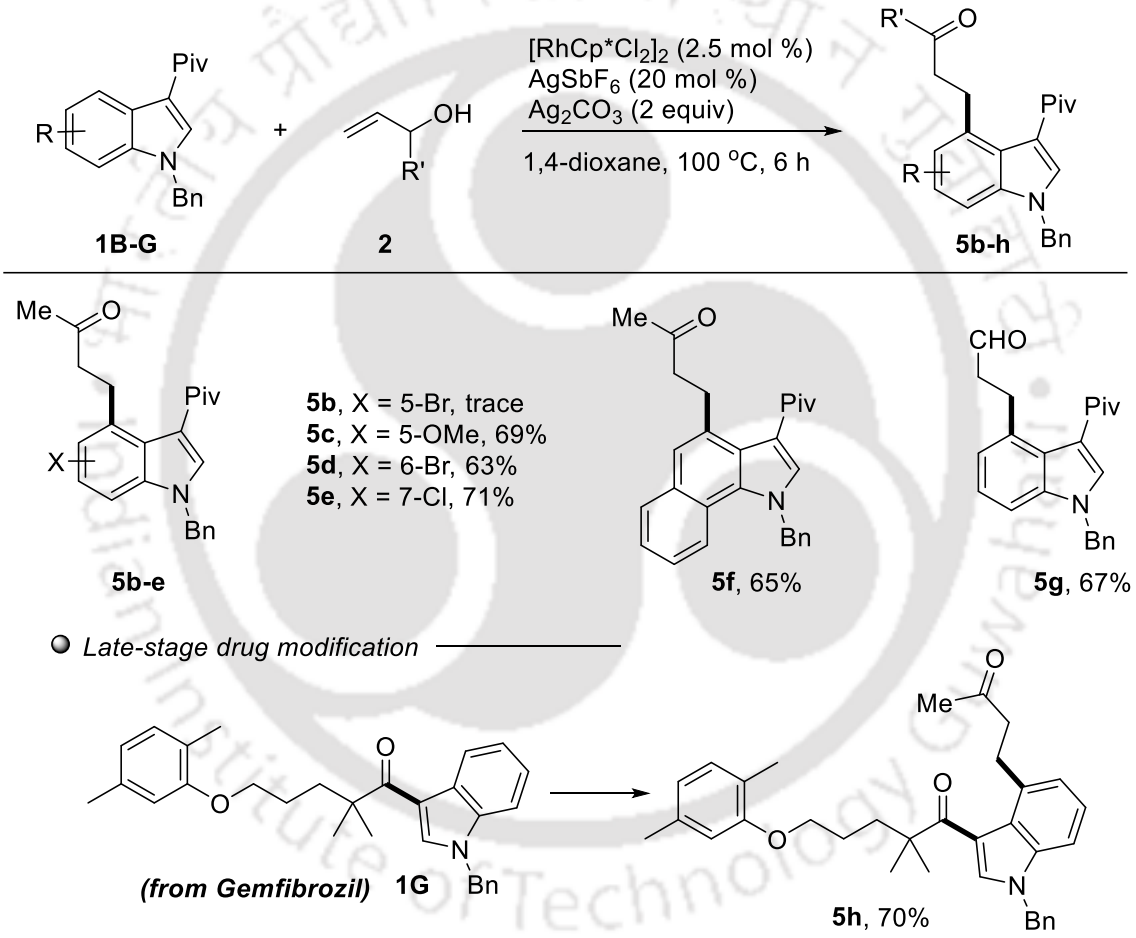
Table 5. Evaluation of Different Directing Groups



We then turned our attention to assess the generality of C4-alkylation with respect to pivaloyl indoles **1B-G** with **2a** as a standard substrate (Table 6). 5-Bromo derivative **1B** was an unsuccessful substrate, which may be due to the steric hindrance near coupling site. However, 5-methoxy **1C**, 6-bromo **1D** and 7-chloro **1E** indoles underwent reaction to deliver the alkylated

products **5c-e** in 63-71% yields. The structure of **5d** was determined using single crystal X-ray analysis. The reaction of a fused indole derivative **1F** gave **5f** in 65% yield. Interestingly, prop-2-en-1-ol **2q** was smoothly coupled with **1A** to give the *β*-aryl aldehyde **5g** in 67% yield. In addition, fibrate drug gemfibrozil derived indole **1G** was alkylated to furnish **5h** in 70% yield. This showcase the remarkable potential of the method for the late-stage drug modification and the chemoselectivity can be altered depending on the directing group.[20]

Table 6. Scope of C4-Alkylation with Pivaloyl Indoles[a,b]

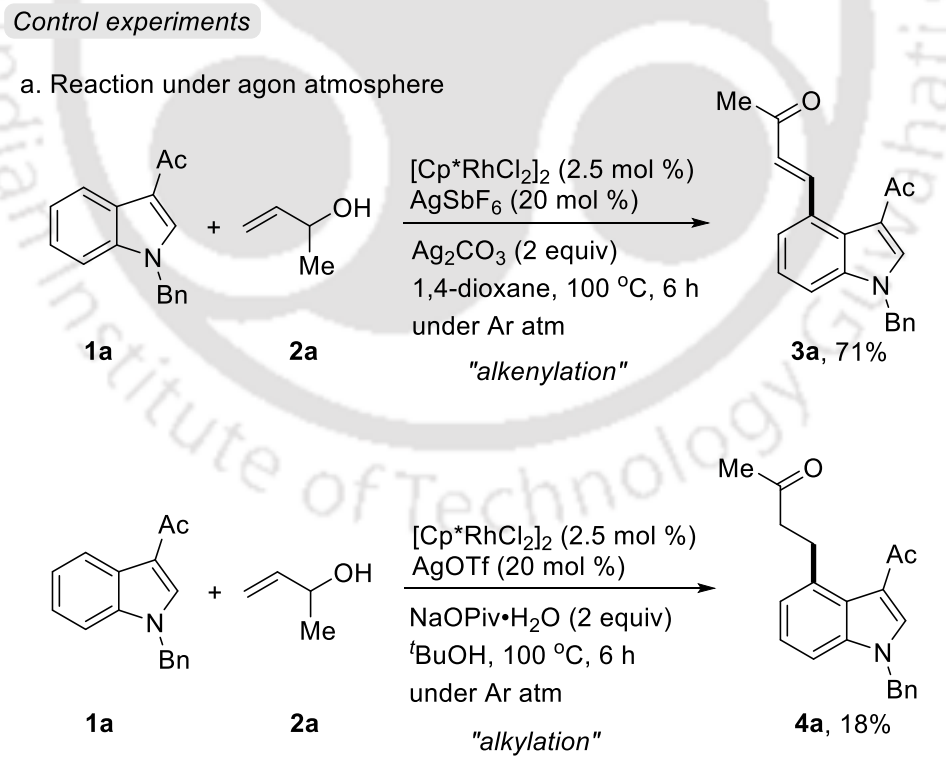


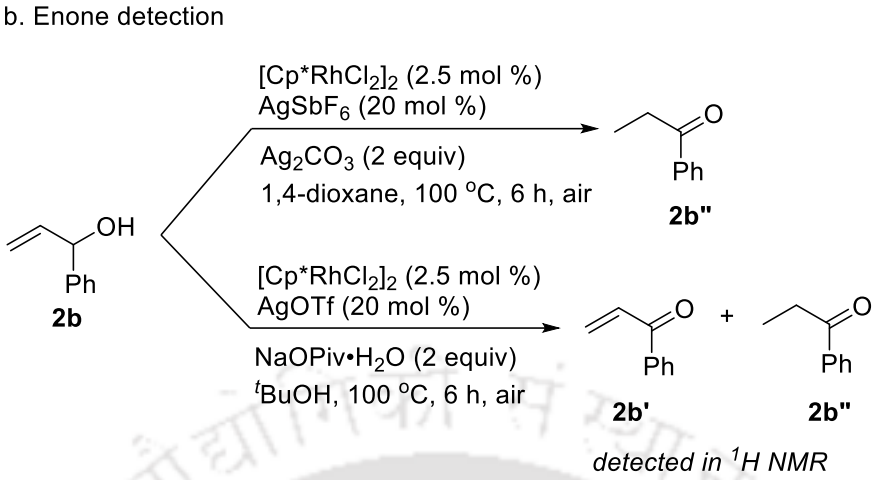
[a]Reaction conditions: **1B-G** (0.1 mmol), **2** (0.2 mmol), $[Cp^*RhCl_2]_2$ (2.5 mol %), $AgSbF_6$ (20 mol %), Ag_2CO_3 (0.2 mmol), 1,4-dioxane (1.5 mL), 100 °C, 6 h, air. [b]Isolated yield.

To gain insight into the reaction pathway, control, H/D-exchange and kinetic isotope experiments were conducted. The alkenylation and alkylation reaction of **1a** and **2a** was performed independently under argon atmosphere. The C4-alkenylation product **3a** was obtained in 71%

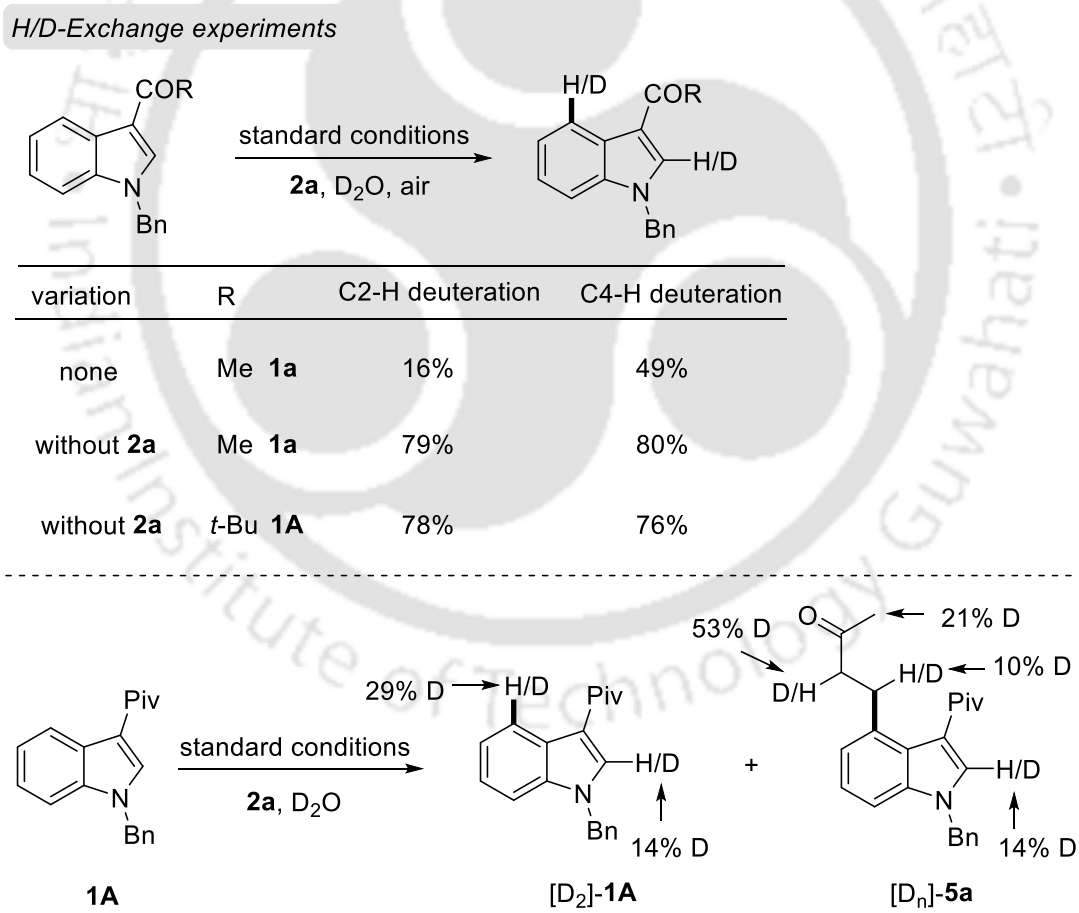
yield, whereas the C4-alkylation product **4a** was obtained albeit in lower yield (Scheme 11a). These results suggest that air might be playing as an oxidant in case of alkylation. Under both the standard reaction conditions allylic alcohol **2b** afforded isomerization products 1-phenylprop-2-en-1-one **2b′** and propiophenone **2b"**, as detected in NMR (Scheme 11b), which indicates that the reaction may proceed through the isomerized enone intermediate.[21]

In the absence of $[Cp^*RhCl_2]_2$, no H/D exchange was detected at both C4-H and C2-H bonds, implying the essential role of the Rh-catalyst in C-H activation. Whereas, H/D exchange experiments of **1a** and **1A** independently in the presence or absence of **2a** using D_2O as a co-solvent revealed significant deuterium incorporation at C4 site (Scheme 12), signifying the reversibility of the C-H activation step. The H-D exchange of **1A** with **2a** revealed significant deuterium incorporation at the α-carbon of the carbonyl group of $[D_n]$-**5a**, thereby indicating the formation of a rhodium-oxa-π alllyl species.[18,22b] Further, kinetic isotope experiment using **1a** and $[D_2]$-**1a** with **2a**, yielded a k_H/k_D = 1.48 (Scheme 13) at C4 position. This result confides that the C4 C-H bond cleavage might not be involved in the rate-determining step.[23]

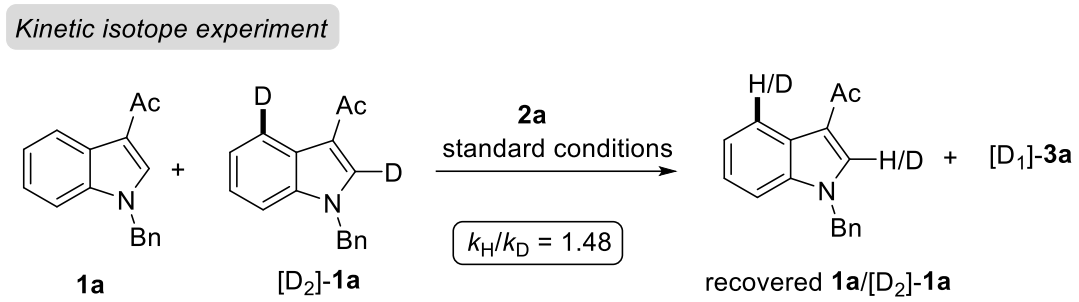




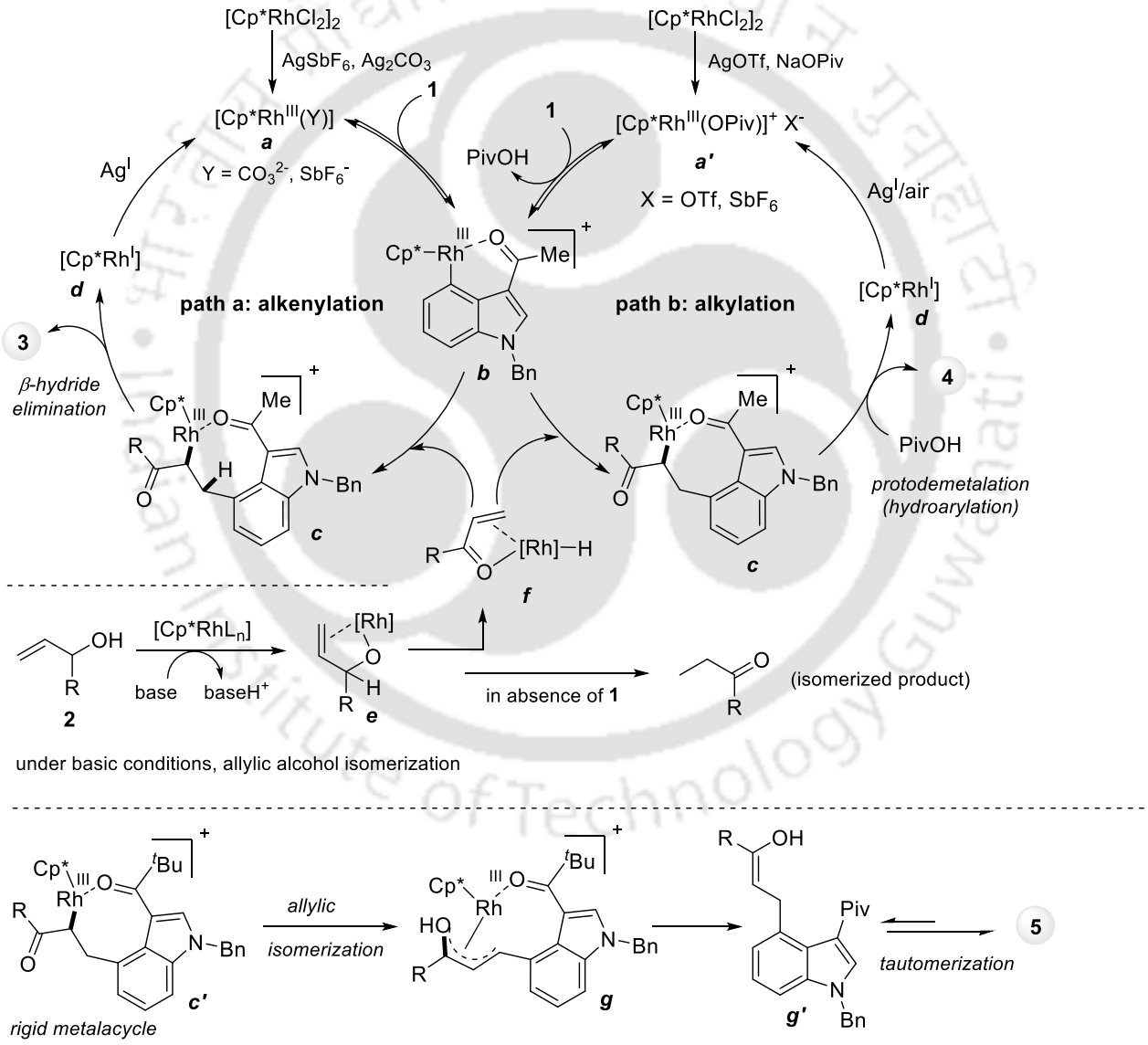
Scheme 11. Control Experiments



Scheme 12. H-D Exchange Experiments



Scheme 13. Kinetic Isotope Experiment



Scheme 14. Proposed Reaction Mechanism

On the basis of mechanistic considerations and literature,[10,11,18] a plausible mechanism is depicted in scheme 14. The catalytic cycle commenced with the generation of a cationic rhodium species ***a*** or ***a'*** by the reaction of dimeric Rh(III)-catalyst in the presence of Ag(I) salts (AgOTf or $AgSbF_6$), and additives Ag_2CO_3 or NaOPiv. Allylic alcohols under basic condition may give the isomerized enone intermediate ***f***.[21] The weak precoordination of carbonyl oxygen of **1** with ***a***, may deliver rhodacycle ***b***, whereas coordination of **1** with ***a'*** furnished ***b*** along with the generation of PivOH. Subsequent reaction of ***b*** with ***f*** may lead to the formation of ***c***. The latter may undergo reaction in two distinct pathways to provide the target products. When Ag_2CO_3 is present as a base additive in the medium, the intermediate ***c*** may undergo β-hydride elimination (path a) to deliver the alkenylated indoles **3**. On the other hand, the intermediate ***c*** may undergo preferential protodemetalation in the presence of PivOH (path b) to give the alkylated products **4**.[22a] In case of pivaloyl indoles **1A-G**, the electron-rich and bulkier carbonyl group may yield a rigid metalacycle ***c'*** which can prevent the β-hydride elimination due to difficulty to align in a requisite syn-coplanar conformation, and thus undergo isomerization to give the Rh-oxa-π allyl species ***g***.[18,20] Further tautomerization afforded the alkylated product **5**. The active Rh-catalyst may be regenerated with the help of Ag(I) and air to complete the catalytic cycle.

In summary, we have demonstrated a robust Rh(III)-catalyzed oxidative tunable C4-selective alkenylation and alkylation of indoles engaging readily accessible allylic alcohols with high selectivity and functional group diversity. The dichotomy in product distribution can be achieved by switching the additives or directing group. Broad substrate scope, mechanistic underpinnings and late-stage diversification of the bio-active molecule are the highlighting features.

4.5 Experimental Section

General Information. Followed as reported in chapter 3.

General Procedure for the Preparation of Directing Groups. To a stirred solution of indole (2 mmol) in CH_2Cl_2 (10 mL), was added Et_2AlCl (1.5 mL, 3 mmol, 2 mol/L in hexane) dropwise at 0 °C. The resulting mixture was stirred at 0 °C for 30 min. Then a solution of acetyl chloride (3 mmol) in CH_2Cl_2 (5 mL) was added dropwise at 0 °C. The resulting mixture was further stirred at the same temperature for an appropriate of time (2-4 h). After completion, as judged by TLC, the reaction mixture was quenched with aqueous buffer (pH 7) and extracted with CH_2Cl_2 (2 x 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 3-acetylindoles. Then, to a suspension of NaH (1.05 mmol, 60% dispersion in mineral oil) in THF at 0 ^{o}C, a solution of 3-acetylindole (1 mmol) in THF (5 mL) was added dropwise. The corresponding alkyl bromide (1.1 equiv) was then added dropwise to this solution and allowed to stir at room temperature for an appropriate time. After completion of the reaction, it was quenched with water and extracted using EtOAc (2 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 to afford *N*-protected 3-acetyl indoles.

General Procedure for the Rh(III)-Catalyzed C4-Alkenylation of Indoles. A mixture of *N*-alkyl 3-acetyl indole **1** (0.1 mmol), $[Cp^*RhCl_2]_2$ (2.5 mol %, 0.0025 mmol, 1.5 mg), $AgSbF_6$ (0.02 mmol, 7 mg), Ag_2CO_3 (0.2 mmol, 55 mg) and allyl alcohol **2** (0.2 mmol) in 1,4-dioxane (1.5 mL) was stirred at 100 ^{o}C in a preheated oil bath under air for 6 h. The progress of the reaction was monitored by TLC using ethyl acetate and hexane as an eluent. The reaction mixture was then cooled to room temperature, diluted with CH_2Cl_2 (10 mL) and passed through a short pad of celite using CH_2Cl_2 (2 x 10 mL). Drying (Na_2SO_4) and evaporation of the solvent gave a residue that was purified by silica gel column chromatography using *n*-hexane and ethyl acetate as an eluent to afford C4-alkenylated indoles **3a-z**.

General Procedure for the Rh(III)-Catalyzed C4-Alkylation of Indoles. A mixture of *N*-alkyl 3-acetyl indole **1** (0.1 mmol), $[Cp^*RhCl_2]_2$ (2.5 mol %, 0.0025 mmol, 1.5 mg), AgOTf (0.02 mmol, 5 mg), NaOPiv•H_2O (0.2 mmol, 25 mg) and allyl alcohol **2** (0.2 mmol, 14.5 mg) in 2,2,2-trifluoroethanol (TFE) or ^{t}BuOH (1.5 mL) was stirred at 120 ^{o}C in a preheated oil bath under air for 12 h. The reaction mixture was then cooled to room temperature, diluted with CH_2Cl_2 (10 mL) and passed through a short pad of celite using CH_2Cl_2 (2 x 10 mL). Drying (Na_2SO_4) and evaporation of the solvent gave a residue that was purified by silica gel column chromatography using *n*-hexane and ethyl acetate as an eluent to afford C4-alkylated indoles **4a-n**.

General Procedure for the Rh(III)-Catalyzed C4-Alkylation of 3-Pivaloyl Indoles. A mixture of *N*-alkyl 3-pivaloyl indole **1A-G** (0.1 mmol), $[Cp^*RhCl_2]_2$ (2.5 mol %, 0.0025 mmol, 1.5 mg), $AgSbF_6$ (0.02 mmol, 7 mg), Ag_2CO_3 (0.2 mmol, 55 mg) and allyl alcohol **2** (0.2 mmol) in 1,4-

dioxane (1.5 mL) was stirred at 100 °C in a preheated oil bath under air for 6 h. The work up was followed as described earlier. Purification by silica gel column chromatography using *n*-hexane and ethyl acetate afforded C4-alkylated indoles **5a-h**.

H/D Exchange Experiment of 1a with D_2O in the 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), $[Cp^*RhCl_2]_2$ (2.5 mol %, 1.6 mg), $AgSbF_6$ (0.02 mmol, 6.9 mg) and Ag_2CO_3 (0.2 mmol, 55 mg) in 1,4-dioxane (1.5 mL), D_2O (0.4 mmol, 80 μL) was added. The reaction mixture was stirred at 100 °C in a preheated oil bath under air for 6 h under air. The reaction mixture was then cooled to room temperature, diluted with CH_2Cl_2 (10 mL), and passed through a short pad of celite using CH_2Cl_2 (25 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 give [D_2]-**1a** in 89% (22.3 mg) yield with 80% and 79% deuterium incorporation at C4-H and C2-H, respectively, as estimated by 400 MHz ^{1}H NMR.

H/D Exchange Experiment of 1a with D_2O in the 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), but-3-en-2-ol **2a** (0.2 mmol, 14.5 mg), $[Cp^*RhCl_2]_2$ (2.5 mol %, 1.6 mg), $AgSbF_6$ (0.02 mmol, 6.9 mg) and Ag_2CO_3 (0.2 mmol, 55 mg) in 1,4-dioxane (1.5 mL), D_2O (0.4 mmol, 80 μL) was added. The reaction mixture was stirred at 100 °C in a preheated oil bath under air for 4 h under air. Work up as described above was followed. Drying (Na_2SO_4) and evaporation of the solvent produced a residue, which was purified on silica gel column chromatography using *n*-hexane and ethyl acetate as an eluent to give [D_2]-**1a** and [D_1]-**3a**. The deuterium incorporation was observed as 49% at C4-H and 16% at C2-H from 400 MHz ^{1}H NMR analysis of recovered [D_2]-**1a**.

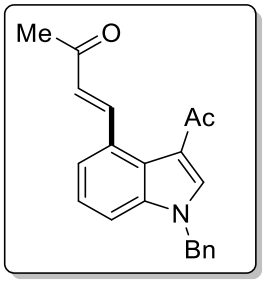
H/D Exchange Experiment of 1A with D_2O in the Absence of 2a. To a stirred solution of 1-(1-benzyl-1*H*-indol-3-yl)-2,2-dimethylpropan-1-one **1A** (0.1 mmol, 29.1 mg), $[Cp^*RhCl_2]_2$ (2.5 mol %, 1.6 mg), $AgSbF_6$ (0.02 mmol, 6.9 mg) and Ag_2CO_3 (0.2 mmol, 55 mg) in 1,4-dioxane (1.5 mL), D_2O (0.4 mmol, 80 μL) was added. The reaction mixture was stirred at 100 °C in a preheated oil bath under air for 6 h under air. Work up as described above was followed. Drying (Na_2SO_4) and evaporation of the solvent produced a residue, which was purified on silica gel column

chromatography using *n*-hexane and ethyl acetate as an eluent to give [D_2]-**1A** in 91% yield. The deuterium incorporation was observed as 76% at C4-H and 78% at C2-H from ^{1}H NMR analysis of recovered [D_2]-**1A**.

H/D Exchange Experiment of 1A with D_2O in the Presence of 2a. To a stirred solution of 1-(1-benzyl-1*H*-indol-3-yl)-2,2-dimethylpropan-1-one **1A** (0.1 mmol, 29.1 mg), but-3-en-2-ol **2a** (0.2 mmol, 14.5 mg), $[Cp^*RhCl_2]_2$ (2.5 mol %, 1.6 mg), $AgSbF_6$ (0.02 mmol, 6.9 mg) and Ag_2CO_3 (0.2 mmol, 55 mg) in 1,4-dioxane (1.5 mL), D_2O (0.4 mmol, 80 μL) was added. The reaction mixture was stirred at 100 ^{o}C in a preheated oil bath under air for 4 h under air. Work up as described above was followed. Drying (Na_2SO_4) and evaporation of the solvent produced a residue, which was purified on silica gel column chromatography using *n*-hexane and ethyl acetate as an eluent to give [D_2]-**1A** and [D_n]-**5a**. The deuterium incorporation was observed as 29% at C4-H and 14% at C2-H from 600 MHz ^{1}H NMR analysis of recovered [D_2]-**1A**.

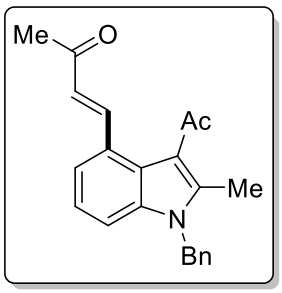
Kinetic Isotope Effect Experiment. A mixture of 1-(1-benzyl-1*H*-indol-3-yl)ethan-1-one **1a** (0.1 mmol, 24.9 mg) and 1-(1-benzyl-1*H*-indol-3-yl-2,4-d_2)ethan-1-one [D_2]-**1a** (0.1 mmol, 25.1 mg) were reacted with but-3-en-2-ol **2a** (0.2 mmol, 14.5 mg) for 35 min under the standard reaction conditions. The resulting mixture was then diluted with CH_2Cl_2 (10 mL) and passed through a short pad of celite using CH_2Cl_2 (2 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 to afford [D_1]-**3a** and a mixture of unreacted **1a** and [D_2]-**1a** as a colourless solid. The intermolecular k_H/k_D was found to be 1.48 after 35 min at 15% conversion, based on 600 MHz ^{1}H NMR of the recovered substrate **1a** and [D_2]-**1a**.

(*E*)-4-(3-Acetyl-1-benzyl-1*H*-indol-4-yl)but-3-en-2-one 3a. Analytical TLC on silica gel, 1:2 ethyl acetate/hexane R_f = 0.42; light yellow solid; mp 165-166 °C; yield 74% (23.5 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.49 (d, *J* = 16.4 Hz, 1H), 7.93 (s, 1H), 7.60 (d, *J* = 7.6 Hz, 1H), 7.37-7.27 (m, 5H), 7.15-7.13 (m, 2H), 6.59 (d, *J* = 16.4 Hz, 1H), 5.39 (s, 2H), 2.58 (bs, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 200.9, 192.3, 147.2, 138.7, 138.4, 135.3, 130.4, 129.3, 128.6, 128.5, 126.9, 125.1, 124.1, 121.4, 118.8, 112.1, 51.0, 28.6, 26.3; FT-IR (KBr) 2925, 2853,



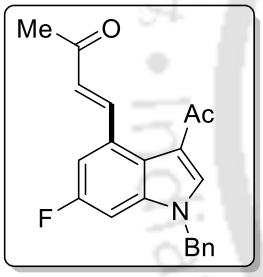
1667, 1650, 1524, 1440, 1395 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{21}H_{20}NO_2$: 318.1489, found 318.1495.

(*E*)-4-(3-Acetyl-1-benzyl-2-methyl-1*H*-indol-4-yl)but-3-en-2-one 3b. Analytical TLC on silica



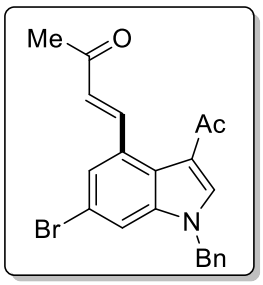
gel, 1:2 ethyl acetate/hexane R_f = 0.46; colorless solid; mp 155-156 °C; yield 70% (23 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (d, *J* = 16.0 Hz, 1H), 7.47 (d, *J* = 7.6 Hz, 1H), 7.32-7.26 (m, 4H), 7.24-7.20 (m, 1H), 6.98-6.96 (m, 2H), 6.67 (d, *J* = 16.0 Hz, 1H), 5.38 (s, 2H), 2.57 (s, 6H), 2.44 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.3, 197.9, 144.7, 142.2, 137.3, 136.0, 129.2, 128.0, 128.0, 128.0, 125.9, 124.8, 122.9, 121.4, 118.0, 111.6, 46.9, 32.3, 27.0, 12.5; FT-IR (KBr) 2925, 1659, 1639, 1509, 1494, 1401, 1263 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{22}H_{22}NO_2$: 332.1645, found 332.1640.

(*E*)-4-(3-Acetyl-1-benzyl-6-fluoro-1*H*-indol-4-yl)but-3-en-2-one 3e. Analytical TLC on silica



gel, 1:2 ethyl acetate/hexane R_f = 0.43; colorless solid; mp 167-168 °C; yield 79% (26.5 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.41 (d, *J* = 17.6 Hz, 1H), 7.92 (s, 1H), 7.39-7.34 (m, 3H), 7.30 (dd, *J* = 10.8, 2.4 Hz, 1H), 7.14-7.12 (m, 2H), 7.00 (dd, *J* = 8.4, 2.4 Hz, 1H), 6.53 (d, *J* = 16.4 Hz, 1H), 5.33 (s, 2H), 2.573 (s, 3H), 2.571 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.5, 192.2, 161.4 (J_{C-F} = 240.8 Hz), 145.7, 139.0 (J_{C-F} = 2.1 Hz), 138.9 (J_{C-F} = 11.9 Hz), 134.8, 131.9 (J_{C-F} = 9.1 Hz), 129.5, 129.4, 128.7, 126.9, 121.7, 119.0, 109.4 (J_{C-F} = 24.3 Hz), 98.8 (J_{C-F} = 26.3 Hz), 51.2, 28.5, 26.4; ^{19}F NMR (377 MHz, $CDCl_3$) δ -117.28; FT-IR (KBr) 2923, 1667, 1649, 1526, 1488, 1399, 1264 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{21}H_{19}FNO_2$: 336.1394, found 336.1397.

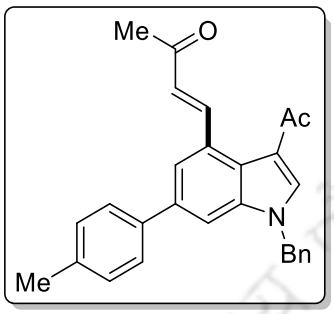
(*E*)-4-(3-Acetyl-1-benzyl-6-bromo-1*H*-indol-4-yl)but-3-en-2-one 3f. Analytical TLC on silica



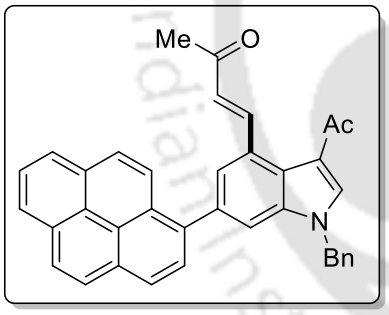
gel, 1:2 ethyl acetate/hexane R_f = 0.43; grey solid; mp 170-171°C; yield 67% (26 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.33 (d, *J* = 16.4 Hz, 1H), 7.87 (s, 1H), 7.66 (d, *J* = 1.6 Hz, 1H), 7.47 (d, *J* = 1.6 Hz, 1H), 7.38-7.35 (m, 3H), 7.14-7.12 (m, 2H), 6.54 (d, *J* = 16.4 Hz, 1H), 5.34 (s, 2H), 2.563 (s, 3H), 2.561 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.2, 191.9, 145.3,

139.0, 138.6, 134.7, 131.9, 129.5, 129.3, 128.6, 126.8, 124.2, 123.8, 118.8, 117.6, 114.5, 50.9, 28.4, 26.3; FT-IR (KBr) 2924, 2852, 1710, 1638, 1528, 1470, 1399 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{21}H_{19}BrNO_2$: 396.0594, found 396.0595.

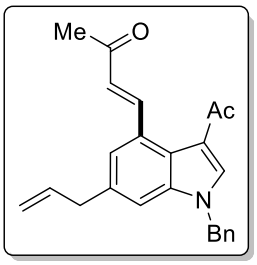
(*E*)-4-(3-Acetyl-1-benzyl-6-(*p*-tolyl)-1*H*-indol-4-yl)but-3-en-2-one 3g. Analytical TLC on silica gel, 1:2 ethyl acetate/hexane R_f = 0.45; yellow solid; mp 155-156 °C; yield 72% (29 mg); ^1H NMR (600 MHz, $CDCl_3$) δ 9.52 (d, *J* = 16.2 Hz, 1H), 7.93 (s, 1H), 7.82 (s, 1H), 7.49-7.46 (m, 3H), 7.37-7.32 (m, 3H), 7.26-7.24 (m, 2H), 7.17 (d, *J* = 7.2 Hz, 2H), 6.66 (d, *J* = 16.2 Hz, 1H), 5.42 (s, 2H), 2.60 (s, 3H), 2.59 (s, 3H), 2.39 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 200.9, 192.3, 147.2, 139.1, 138.9, 137.7, 137.5, 135.3, 130.9, 130.6, 129.7, 129.3, 128.9, 128.6, 127.2, 126.9, 124.1, 120.9, 118.7, 110.1, 51.0, 28.5, 26.3, 21.2; FT-IR (KBr) 2925, 2854, 1651, 1636, 1520, 1399, 1264 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{28}H_{26}NO_2$: 408.1958, found 408.1962.



(*E*)-4-(3-Acetyl-1-benzyl-6-(pyren-1-yl)-1*H*-indol-4-yl)but-3-en-2-one 3h. Analytical TLC on silica gel, 1:2 ethyl acetate/hexane R_f = 0.45; light yellow liquid; yield 61% (31.5 mg); ^1H NMR (400 MHz, $CDCl_3$) δ 9.59 (d, *J* = 16.4 Hz, 1H), 8.23-8.20 (m, 2H), 8.17 (d, *J* = 7.2 Hz, 1H), 8.10 (s, 2H), 8.04 (s, 1H), 8.02-7.98 (m, 2H), 7.98-7.92 (m, 2H), 7.896-7.894 (m, 1H), 7.595-7.592 (m, 1H), 7.39-7.37 (m, 3H), 7.20-7.18 (m, 2H), 6.65 (d, *J* = 16.4 Hz, 1H), 5.44 (s, 2H), 2.66 (s, 3H), 2.61 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 200.7, 192.3, 146.9, 139.0, 138.6, 137.2, 136.8, 135.2, 131.6, 131.0, 131.0, 130.9, 130.4, 129.4, 129.0, 128.68, 128.65, 128.0, 127.8, 127.7, 127.5, 127.1, 126.2, 125.4, 125.1, 125.0, 124.9, 124.8, 124.8, 124.3, 118.9, 114.2, 51.3, 28.6, 26.4; FT-IR (neat) 2927, 1644, 1638, 1400, 1262 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{37}H_{28}NO_2$: 518.2115, found 518.2119.

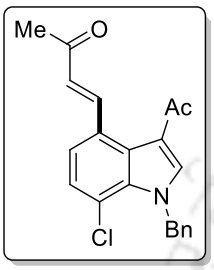


(*E*)-4-(3-Acetyl-6-allyl-1-benzyl-1*H*-indol-4-yl)but-3-en-2-one 3i. Analytical TLC on silica gel, 1:2 ethyl acetate/hexane R_f = 0.43; colorless solid; mp 135-136 °C; yield 69% (24.6 mg); ^1H NMR (600 MHz, $CDCl_3$) δ 9.48 (d, *J* = 16.2 Hz, 1H), 7.86 (s, 1H), 7.44 (s, 1H), 7.38-7.33 (m, 3H), 7.15-



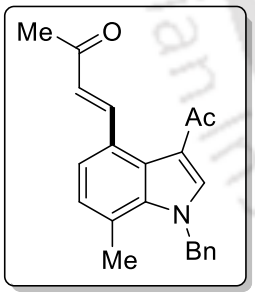
7.13 (m, 3H), 6.58 (d, *J* = 16.8 Hz, 1H), 5.97-5.90 (m, 1H), 5.36 (s, 2H), 5.09-5.08 (m, 1H), 5.07-5.06 (m, 1H), 3.47 (d, *J* = 6.6 Hz, 2H), 2.58 (s, 3H), 2.56 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 200.9, 192.2, 147.2, 138.9, 138.4, 137.0, 136.4, 135.4, 130.2, 129.3, 128.7, 128.5, 127.0, 123.5, 122.5, 118.8, 116.5, 111.8, 50.8, 40.2, 28.5, 26.2; FT-IR (KBr) 2927, 1648, 1638, 1524, 1399, 1265 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{24}H_{24}NO_2$: 358.1802, found 358.1801.

(*E*)-4-(3-Acetyl-1-benzyl-7-chloro-1*H*-indol-4-yl)but-3-en-2-one 3j. Analytical TLC on silica



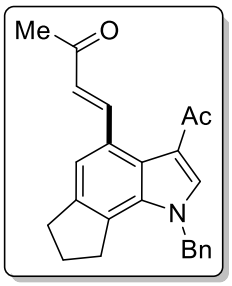
gel, 1:2 ethyl acetate/hexane R_f = 0.43; light grey liquid; yield 71% (25 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.27 (d, *J* = 16.4 Hz, 1H), 7.87 (s, 1H), 7.46 (d, *J* = 8.4 Hz, 1H), 7.36-7.30 (m, 3H), 7.27-7.25 (m, 1H), 7.04-7.01 (m, 2H), 6.53 (d, *J* = 16.4 Hz, 1H), 5.86 (s, 2H), 2.57 (s, 3H), 2.55 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.5, 192.2, 146.0, 141.1, 137.0, 133.6, 129.4, 129.2, 128.8, 128.2, 127.7, 126.3, 126.2, 122.2, 119.1, 118.8, 53.3, 28.9, 26.4; FT-IR (neat) 2961, 2853, 1710, 1658, 1638, 1590, 1388 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{21}H_{19}ClNO_2$: 352.1099, found 352.1098.

(*E*)-4-(3-Acetyl-1-benzyl-7-methyl-1*H*-indol-4-yl)but-3-en-2-one 3k. Analytical TLC on silica



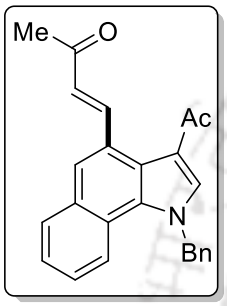
gel, 1:2 ethyl acetate/hexane R_f = 0.44; light yellow liquid; yield 74% (25 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.40 (d, *J* = 16.4 Hz, 1H), 7.87 (s, 1H), 7.48 (d, *J* = 7.6 Hz, 1H), 7.35-7.28 (m, 3H), 7.03 (d, *J* = 8.0 Hz, 1H), 6.93-6.91 (m, 2H), 6.56 (d, *J* = 16.4 Hz, 1H), 5.66 (s, 2H), 2.58 (s, 3H), 2.57 (s, 3H), 2.54 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 200.9, 192.4, 147.2, 140.8, 137.5, 137.1, 129.4, 128.5, 128.2, 127.9, 127.6, 126.1, 125.4, 123.8, 121.8, 118.6, 53.4, 28.8, 26.3, 19.9; FT-IR (neat) 2931, 1650, 1637, 1588, 1532, 1400, 1260 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{22}H_{22}NO_2$: 332.1645, found 332.1650.

(*E*)-4-(3-Acetyl-1-benzyl-1,6,7,8-tetrahydrocyclopenta[*g*]indol-4-yl)but-3-en-2-one 3l. Analytical TLC on silica gel, 1:2 ethyl acetate/hexane R_f = 0.44; yellow solid; mp 152-153 °C; yield 66% (23.6 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.48 (d, *J* = 16.8 Hz, 1H), 7.83 (s, 1H), 7.51

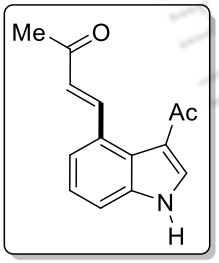


(s, 1H), 7.35-7.29 (m, 3H), 6.98 (d, *J* = 7.2 Hz, 2H), 6.56 (d, *J* = 16.2 Hz, 1H), 5.54 (s, 2H), 3.10 (t, *J* = 7.2 Hz, 2H), 2.98 (t, *J* = 7.2 Hz, 2H), 2.577 (s, 3H), 2.570 (s, 3H), 2.10 (p, *J* = 7.2 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 201.0, 192.4, 147.6, 142.0, 139.3, 137.2, 135.8, 129.3, 128.7, 128.3, 128.2, 127.7, 125.7, 124.4, 119.0, 118.3, 52.2, 32.5, 31.6, 28.7, 26.3, 25.3; FT-IR (KBr) 2926, 1648, 1639, 1596, 1529, 1400, 1261 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{24}H_{24}NO_2$: 358.1802, found 358.1805.

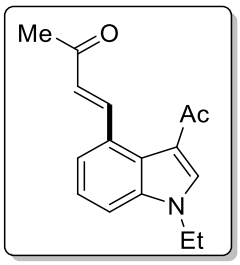
(*E*)-4-(3-Acetyl-1-benzyl-1*H*-benzo[*g*]indol-4-yl)but-3-en-2-one 3m. Analytical TLC on silica gel, 1:2 ethyl acetate/hexane R_f = 0.45; light yellow liquid; yield 64% (23 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.26 (d, *J* = 16.4 Hz, 1H), 8.08 (d, *J* = 8.0 Hz, 1H), 7.95-7.93 (m, 2H), 7.90 (s, 1H), 7.46-7.41 (m, 1H), 7.39-7.37 (m, 1H), 7.35-7.29 (m, 3H), 7.11-7.09 (m, 2H), 6.68 (d, *J* = 16.4 Hz, 1H), 5.90 (s, 2H), 2.63 (s, 3H), 2.60 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 200.6, 193.0, 147.4, 138.1, 135.9, 132.4, 131.7, 129.9, 129.53, 129.50, 128.9, 128.4, 127.1, 126.1, 125.2, 123.5, 122.5, 122.3, 121.0, 119.4, 54.8, 28.9, 26.4; FT-IR (neat) 1582, 1655, 1638, 1529, 1400, 1261 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{25}H_{22}NO_2$: 368.1645, found 368.1644.



(*E*)-4-(3-Acetyl-1*H*-indol-4-yl)but-3-en-2-one 3n. Analytical TLC on silica gel, 1:1 ethyl acetate/hexane R_f = 0.48; colorless solid; mp 147-148 °C; yield 67% (15.2 mg); ^{1}H NMR (600 MHz, DMSO-d_6) δ 12.3 (s, 1H), 9.51 (d, *J* = 16.2 Hz, 1H), 8.56 (s, 1H), 7.65 (d, *J* = 7.8 Hz, 1H), 7.57 (d, *J* = 7.8 Hz, 1H), 7.29 (t, *J* = 7.8 Hz, 1H), 6.57 (d, *J* = 16.2 Hz, 1H), 2.56 (s, 3H), 2.42 (s, 3H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 199.2, 192.9, 147.2, 138.8, 138.6, 128.7, 127.2, 124.4, 123.7, 120.7, 118.5, 114.9, 28.8, 26.7; FT-IR (KBr) 2923, 2256, 2129, 1643, 1625, 1504, 1400 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{14}H_{14}NO_2$: 228.1019, found 228.1013.

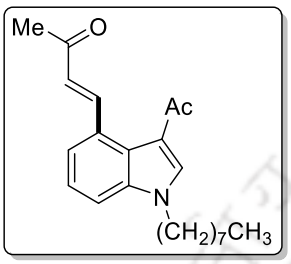


(*E*)-4-(3-Acetyl-1-ethyl-1*H*-indol-4-yl)but-3-en-2-one 3p. Analytical TLC on silica gel, 1:2 ethyl acetate/hexane R_f = 0.47; brown thick liquid; yield 69% (18 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.50 (d, *J* = 16.4 Hz, 1H), 7.92 (s, 1H), 7.58 (d, *J* = 7.6 Hz, 1H), 7.41 (d, *J* = 7.6 Hz, 1H), 7.34-7.30 (m, 1H), 6.57 (d, *J* = 16.4 Hz, 1H), 4.24 (q, *J* = 7.2 Hz, 2H), 2.58 (s, 3H), 2.57 (s, 3H),

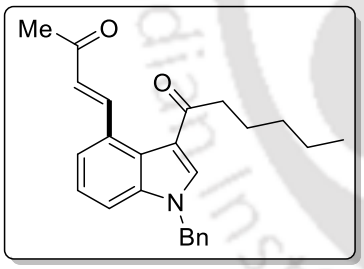


1.54 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.9, 192.1, 147.3, 137.9, 137.7, 130.3, 128.4, 125.1, 123.8, 121.2, 118.3, 111.6, 42.0, 28.5, 26.3, 15.1; FT-IR (neat) 2930, 1663, 1637, 1524, 1399 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{16}H_{18}NO_2$: 256.1332, found 256.1332.

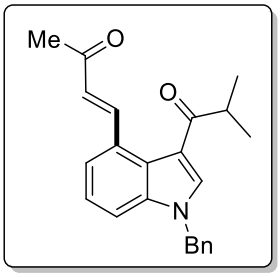
(*E*)-4-(3-Acetyl-1-octyl-1*H*-indol-4-yl)but-3-en-2-one 3q. Analytical TLC on silica gel, 1:2 ethyl acetate/hexane R_f = 0.47; brown thick liquid; yield 74% (25 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.50 (d, *J* = 16.4 Hz, 1H), 7.89 (s, 1H), 7.58 (d, *J* = 7.2 Hz, 1H), 7.40 (d, *J* = 7.2 Hz, 1H), 7.32 (t, *J* = 7.6 Hz, 1H), 6.57 (d, *J* = 16.4 Hz, 1H), 4.16 (t, *J* = 7.2 Hz, 2H), 2.58 (s, 3H), 2.57 (s, 3H), 1.89-1.84 (m, 2H), 1.33-1.24 (m, 10H), 0.86 (t, *J* = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.9, 192.1, 147.3, 138.4, 138.1, 130.3, 128.5, 125.0, 123.8, 121.2, 118.2, 111.8, 47.4, 31.8, 29.85, 29.82, 29.2, 28.5, 26.9, 26.2, 22.7, 14.1; FT-IR (neat) 2917, 2850, 1521, 1638, 1395 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{22}H_{30}NO_2$: 340.2271, found 340.2273.



(*E*)-1-(1-Benzyl-4-(3-oxobut-1-en-1-yl)-1*H*-indol-3-yl)hexan-1-one 3r. Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.43; yellow thick liquid; yield 73% (27.6 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.40 (d, *J* = 16.4 Hz, 1H), 7.92 (s, 1H), 7.58 (d, *J* = 7.2 Hz, 1H), 7.37-7.32 (m, 4H), 7.29 (d, *J* = 7.2 Hz, 1H), 7.14-7.12 (m, 2H), 6.58 (d, *J* = 16.4 Hz, 1H), 5.39 (s, 2H), 2.86 (t, *J* = 7.2 Hz, 2H), 2.57 (s, 3H), 1.81-1.73 (m, 2H), 1.38-1.33 (m, 4H), 0.90 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.9, 195.6, 147.0, 138.3, 137.6, 135.4, 130.4, 129.2, 128.6, 128.5, 126.9, 125.2, 124.0, 121.3, 118.6, 112.1, 51.0, 40.9, 31.8, 26.3, 25.7, 22.6, 14.1; FT-IR (neat) 2926, 2855, 1664, 1651, 1638, 1399 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{25}H_{28}NO_2$: 374.2115, found 374.2115.

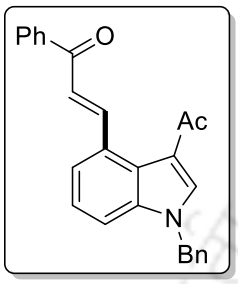


(*E*)-4-(1-Benzyl-3-isobutyryl-1*H*-indol-4-yl)but-3-en-2-one 3s. Analytical TLC on silica gel, 1:2 ethyl acetate/hexane R_f = 0.45; colorless solid; mp 145-146 °C; yield 78% (27 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.31 (d, *J* = 16.2 Hz, 1H), 7.93 (s, 1H), 7.56 (d, *J* = 7.8 Hz, 1H), 7.36-7.31 (m, 4H), 7.27 (t, *J* = 7.8 Hz, 1H), 7.13 (d, *J* = 6.6 Hz, 2H), 6.57 (d, *J* = 16.2 Hz, 1H), 5.39 (s, 2H),

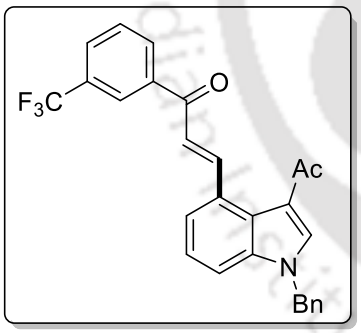


3.39-3.32 (m, 1H), 2.56 (s, 3H), 1.25 (s, 3H), 1.24 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 200.8, 199.7, 146.9, 138.4, 137.0, 135.5, 130.4, 129.2, 128.5, 128.4, 126.8, 125.5, 124.0, 121.3, 117.6, 112.1, 51.0, 38.0, 26.3, 20.2; FT-IR (neat) 2969, 2928, 1646, 1601, 1522, 1391 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{23}H_{24}NO_2$: 346.1802, found 346.1805.

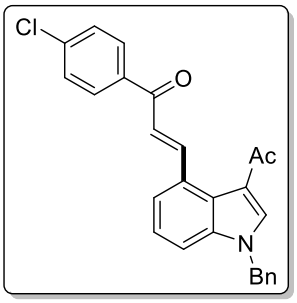
(*E*)-3-(3-Acetyl-1-benzyl-1*H*-indol-4-yl)-1-phenylprop-2-en-1-one 3t. Analytical TLC on silica gel, 1:2 ethyl acetate/hexane R_f = 0.43; brown thick liquid; yield 64% (24 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.30 (d, *J* = 15.6 Hz, 1H), 8.09-8.06 (m, 2H), 7.86 (s, 1H), 7.67-7.65 (m, 1H), 7.58-7.54 (m, 1H), 7.51-7.47 (m, 2H), 7.35-7.28 (m, 6H), 7.15-7.13 (m, 2H), 5.38 (s, 2H), 2.53 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.9, 191.7, 147.3, 138.7, 138.4, 137.5, 135.5, 132.3, 131.2, 129.2, 128.9, 128.53, 128.51, 127.0, 125.1, 123.9, 123.4, 121.7, 119.2, 112.0, 51.0, 28.4; FT-IR (neat) 2927, 2853, 1654, 1523, 1398 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{26}H_{22}NO_2$: 380.1645, found 380.1648.



(*E*)-3-(3-Acetyl-1-benzyl-1*H*-indol-4-yl)-1-(3-(trifluoromethyl)phenyl)prop-2-en-1-one 3u. Analytical TLC on silica gel, 1:2 ethyl acetate/hexane R_f = 0.43; yellow thick liquid; yield 58% (26 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.37 (d, *J* = 16.0 Hz, 1H), 8.29-8.25 (m, 2H), 7.88 (s, 1H), 7.82 (d, *J* = 7.6 Hz, 1H), 7.68-7.62 (m, 2H), 7.38-7.32 (m, 5H), 7.30-7.29 (m, 1H), 7.15-7.13 (m, 2H), 5.39 (s, 2H), 2.53 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.9, 191.0, 148.8, 139.2, 138.4, 137.8, 135.4, 132.2, 130.7, 130.1, 129.3, 129.1, 128.8 (J_{C-F} = 3.7 Hz), 128.5, 126.9, 125.8 (J_{C-F} = 3.0 Hz), 125.2, 123.9, 123.0, 121.8, 119.1, 112.4, 51.0, 28.3; ^{19}F NMR (377 MHz, $CDCl_3$) δ -62.60; FT-IR (neat) 2849, 1654, 1590, 1523, 1400, 1332 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{27}H_{21}F_3NO_2$: 448.1519, found 448.1521.

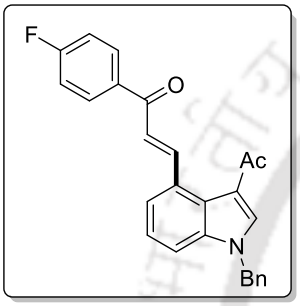


(*E*)-3-(3-Acetyl-1-benzyl-1*H*-indol-4-yl)-1-(4-chlorophenyl)prop-2-en-1-one 3v. Analytical TLC on silica gel, 1:2 ethyl acetate/hexane R_f = 0.45; yellow thick liquid; yield 63% (26 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.30 (d, *J* = 15.6 Hz, 1H), 8.05-8.01 (m, 2H), 7.87 (s, 1H), 7.66 (d, *J*



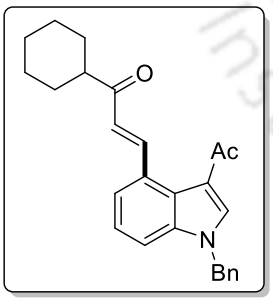
= 6.8 Hz, 1H), 7.48-7.46 (m, 2H), 7.36-7.32 (m, 3H), 7.30-7.24 (m, 3H), 7.15-7.12 (m, 2H), 5.39 (s, 2H), 2.54 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.9, 190.7, 147.9, 138.7, 138.4, 137.7, 136.9, 135.4, 131.0, 130.4, 129.3, 128.8, 128.5, 127.0, 125.2, 123.9, 123.1, 121.8, 119.2, 112.1, 51.0, 28.4; FT-IR (neat) 1654, 1591, 1565, 1523, 1399 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{26}H_{21}ClNO_2$: 414.1255, found 414.1262.

(*E*)-3-(3-Acetyl-1-benzyl-1*H*-indol-4-yl)-1-(4-fluorophenyl)prop-2-en-1-one 3w. Analytical



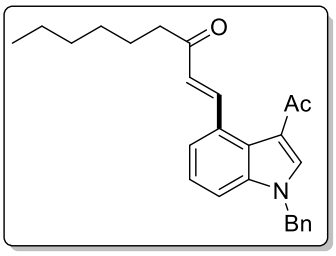
TLC on silica gel, 1:2 ethyl acetate/hexane R_f = 0.45; light yellow liquid; yield 51% (21.4 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.30 (d, *J* = 15.6 Hz, 1H), 8.13-8.09 (m, 2H), 7.88 (s, 1H), 7.66 (d, *J* = 7.2 Hz, 1H), 7.36-7.32 (m, 5H), 7.303-7.300 (m, 1H), 7.189-7.184 (m, 1H), 7.16-7.13 (m, 3H), 5.39 (s, 2H), 2.53 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 191.9, 190.4, 166.3 (J_{C-F} = 251.5 Hz), 147.6, 138.4, 137.7, 135.4, 134.9 (J_{C-F} = 2.8 Hz), 131.5 (J_{C-F} = 9.0 Hz), 131.0, 129.2, 128.5, 126.9, 125.1, 123.9, 123.1, 121.7, 119.1, 115.6 (J_{C-F} = 21.6 Hz), 112.1, 51.0, 28.4; FT-IR (neat) 3017, 2853, 1654, 1598, 1524, 1400 cm^{-1}; HRMS (ESI) *m/z* $[M+Na]^+$ calcd for $C_{26}H_{20}FNNaO_2$: 420.1370, found 420.1358.

(*E*)-3-(3-Acetyl-1-benzyl-1*H*-indol-4-yl)-1-cyclohexylprop-2-en-1-one 3x. Analytical TLC on

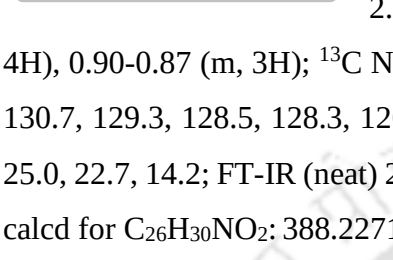


silica gel, 1:4 ethyl acetate/hexane R_f = 0.45; colorless solid; mp 134-135 °C; yield 53% (20.4 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.40 (d, *J* = 16.2 Hz, 1H), 7.90 (s, 1H), 7.60 (d, *J* = 7.2 Hz, 1H), 7.36-7.30 (m, 4H), 7.28 (d, *J* = 7.8 Hz, 1H), 7.13 (d, *J* = 7.2 Hz, 2H), 6.58 (d, *J* = 16.2 Hz, 1H), 5.38 (s, 2H), 3.23-3.19 (m, 1H), 2.57 (s, 3H), 1.96-1.95 (m, 2H), 1.84-1.82 (m, 2H), 1.76-1.72 (m, 1H), 1.63-1.62 (m, 2H), 1.53-1.46 (m, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 205.7, 192.1, 145.0, 138.4, 138.1, 135.4, 130.7, 129.2, 128.5, 126.9, 126.7, 125.1, 124.0, 121.3, 119.0, 111.9, 51.0, 46.7, 29.6, 28.6, 26.2, 26.0; FT-IR (KBr) 2930, 2853, 1650, 1598, 1523, 1399 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{26}H_{28}NO_2$: 386.2115, found 386.2112.

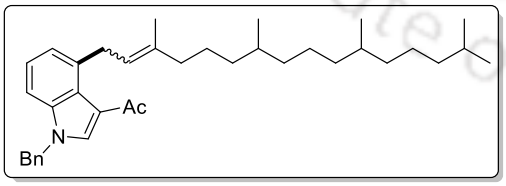
(*E*)-1-(3-Acetyl-1-benzyl-1*H*-indol-4-yl)non-1-en-3-one 3y. Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.44; light yellow liquid; yield 65% (25 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.42 (d, *J* = 16.4 Hz, 1H), 7.90 (s, 1H), 7.59 (d, *J* = 6.4 Hz, 1H), 7.35-7.28 (m, 5H), 7.15-7.13 (m, 2H), 6.58 (d, *J* = 16.4 Hz, 1H), 5.38 (s, 2H), 2.94 (t, *J* = 7.2 Hz, 2H), 2.57 (s, 3H), 1.77-1.69 (m, 2H), 1.45-1.38 (m, 2H), 1.35-1.31 (m, 4H), 0.90-0.87 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.0, 192.1, 145.6, 138.4, 138.3, 135.4, 130.7, 129.3, 128.5, 128.3, 126.9, 125.1, 124.1, 121.4, 119.0, 111.9, 51.0, 38.7, 31.9, 29.3, 28.5, 25.0, 22.7, 14.2; FT-IR (neat) 2925, 2853, 1714, 1650, 1602, 1399 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{26}H_{30}NO_2$: 388.2271, found 388.2278.



(*E*)-1-(3-Acetyl-1-benzyl-1*H*-indol-4-yl)undec-1-en-3-one 3z. Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.44; yellow liquid; yield 68% (28 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.42 (d, *J* = 16.4 Hz, 1H), 7.91 (s, 1H), 7.59 (d, *J* = 8.0 Hz, 1H), 7.38-7.28 (m, 5H), 7.15-7.13 (m, 2H), 6.58 (d, *J* = 16.4 Hz, 1H), 5.38 (s, 2H), 2.94 (t, *J* = 7.2 Hz, 2H), 2.57 (s, 3H), 1.77-1.69 (m, 2H), 1.43-1.25 (m, 10H), 0.89-0.83 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.1, 192.1, 145.6, 138.4, 138.3, 135.4, 130.8, 129.3, 128.5, 128.4, 126.9, 124.1, 121.4, 119.0, 111.9, 100.1, 51.0, 38.7, 32.0, 29.7, 29.6, 29.3, 28.5, 25.1, 22.8, 14.2; FT-IR (neat) 2923, 2854, 1653, 1647, 1522, 1398 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{28}H_{34}NO_2$: 416.2584, found 416.2590.

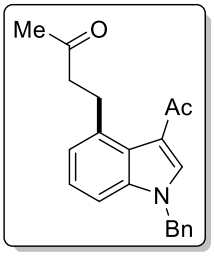


1-(1-Benzyl-4-(3,7,11,15-tetramethylhexadec-2-en-1-yl)-1*H*-indol-3-yl)ethan-1-one 3aa. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.47; light yellow liquid; yield 41% (21.6 mg); dr = 1.7:1; ^{1}H NMR (400 MHz, $CDCl_3$) δ (*E*+*Z*) 7.77-7.76 (m, 1H), 7.36-7.30 (m, 3H), 7.20-7.09 (m, 5H), 5.33 (s, 2H), 4.08 (d, *J* = 7.2 Hz, 2H), 2.53 (s, 3H), 2.15 (t, *J* = 7.6 Hz, 1H), 1.98 (t, *J* = 7.6 Hz, 1H), 1.72-1.70 (m, 3H), 1.42-1.32 (m, 5H), 1.29-1.24 (m, 6H), 1.15-1.00 (m, 8H), 0.86-0.82 (m, 13H); ^{13}C NMR (150 MHz, $CDCl_3$) δ (*E*+*Z*) 192.25, 192.24, 138.3, 138.2, 137.8, 137.7, 136.5, 136.4, 135.96, 135.94, 135.8, 135.6, 129.1, 128.2, 127.0, 124.7, 124.69, 124.63, 124.0, 123.97, 123.91, 123.5,

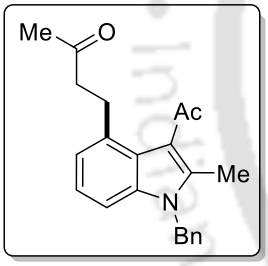


123.1, 119.4, 119.3, 107.9, 50.8, 40.3, 39.5, 37.6, 37.59, 37.58, 37.55, 37.52, 37.4, 37.3, 37.2, 37.0, 36.9, 33.9, 32.94, 32.92, 32.88, 32.86, 32.4, 28.85, 28.81, 28.1, 25.75, 25.74, 25.67, 25.66, 24.97, 24.96, 24.6, 23.7, 22.8, 22.7, 19.9, 19.88, 19.84, 19.81, 16.3; FT-IR (neat) 3017, 2925, 2857, 1655, 1525, 1400, 1259 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{37}H_{54}NO$: 528.4200, found 528.4206.

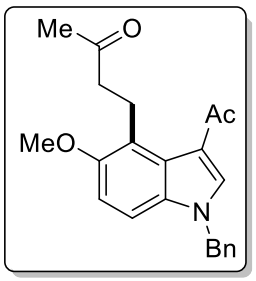
4-(3-acetyl-1-benzyl-1*H*-indol-4-yl)butan-2-one 4a. Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.41; thick brown liquid; yield 69% (22 mg); ^1H NMR (400 MHz, $CDCl_3$) δ 7.81 (s, 1H), 7.37-7.29 (m, 3H), 7.19-7.14 (m, 4H), 7.09 (dd, *J* = 6.4, 1.6 Hz, 1H), 5.33 (s, 2H), 3.55 (t, *J* = 7.6 Hz, 2H), 2.79 (t, *J* = 8.0 Hz, 2H), 2.53 (s, 3H), 2.18 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.6, 192.0, 138.4, 137.1, 137.0, 135.7, 129.2, 128.3, 127.0, 124.4, 124.4, 124.0, 118.7, 108.4, 50.8, 46.9, 30.9, 30.1, 28.6.; FT-IR (neat) 2923, 2851, 1706, 1658, 1521, 1400 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{21}H_{22}NO_2$: 320.1645, found 320.1641.



4-(3-Acetyl-1-benzyl-2-methyl-1*H*-indol-4-yl)butan-2-one 4b. Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.45; yellow liquid; yield 53% (17.6 mg); ^1H NMR (400 MHz, $CDCl_3$) δ 7.31-7.27 (m, 3H), 7.14-7.09 (m, 2H), 7.03-6.97 (m, 3H), 5.34 (s, 2H), 3.23 (t, *J* = 7.6 Hz, 2H), 2.78 (t, *J* = 8.0 Hz, 2H), 2.62 (s, 3H), 2.53 (s, 3H), 2.15 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 209.0, 198.8, 139.4, 137.3, 136.4, 134.3, 129.1, 127.8, 126.0, 124.0, 123.1, 122.9, 118.2, 107.9, 46.8, 45.2, 32.6, 30.0, 29.1, 12.6; FT-IR (neat) 2926, 2854, 2090, 1710, 1637, 1400 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{22}H_{24}NO_2$: 334.1802, found 334.1810.

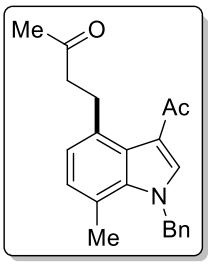


4-(3-Acetyl-1-benzyl-5-methoxy-1*H*-indol-4-yl)butan-2-one 4d. Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.43; colorless solid; mp 115-116 °C; yield 66% (23 mg); ^1H NMR (400 MHz, $CDCl_3$) δ 7.78 (s, 1H), 7.36-7.30 (m, 3H), 7.15-7.13 (m, 2H), 7.09 (d, *J* = 9.2 Hz, 1H), 6.93 (d, *J* = 8.8 Hz, 1H), 5.29 (s, 2H), 3.82 (s, 3H), 3.54 (t, *J* = 7.6 Hz, 2H), 2.77 (t, *J* = 8.0 Hz, 2H), 2.50 (s, 3H), 2.23 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.2, 191.8, 153.8, 138.0, 135.8, 133.5, 129.1, 128.3, 127.0, 126.2, 124.2, 118.6, 109.8, 108.4, 57.1, 50.9, 45.3,

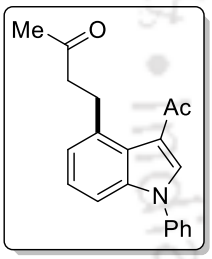


29.8, 28.6, 23.4; FT-IR (KBr) 2925, 2853, 1709, 1658, 1526, 1399 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{22}H_{24}NO_3$: 350.1751, found 350.1755.

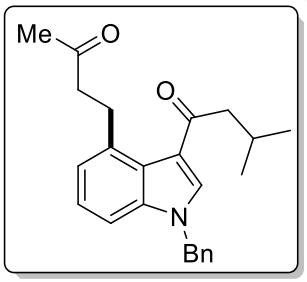
4-(3-Acetyl-1-benzyl-7-methyl-1*H*-indol-4-yl)butan-2-one 4e. Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.44; light yellow solid; mp 110-111 °C; yield 63% (21 mg); ^1H NMR (400 MHz, $CDCl_3$) δ 7.75 (s, 1H), 7.34-7.32 (m, 1H), 7.30-7.28 (m, 2H), 6.98-6.94 (m, 2H), 6.93-6.88 (m, 2H), 5.62 (s, 2H), 3.51 (t, *J* = 7.6 Hz, 2H), 2.78 (t, *J* = 8.0 Hz, 2H), 2.53 (s, 3H), 2.49 (s, 3H), 2.18 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 209.7, 192.2, 139.2, 137.9, 137.2, 134.7, 129.2, 128.0, 127.3, 125.5, 125.4, 124.6, 119.3, 118.7, 53.2, 46.8, 30.5, 30.1, 28.8, 19.6; FT-IR (KBr) 2924, 2852, 1704, 1652, 1533, 1401 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{22}H_{24}NO_2$: 334.1802, found 334.1799.



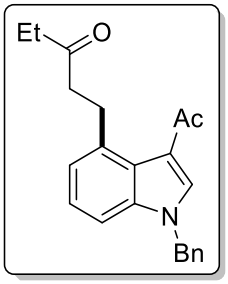
4-(3-Acetyl-1-phenyl-1*H*-indol-4-yl)butan-2-one 4f. Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.46; colorless solid; mp 145-146 °C; yield 64% (19.5 mg); ^1H NMR (400 MHz, $CDCl_3$) δ 7.94 (s, 1H), 7.56-7.52 (m, 2H), 7.47-7.44 (m, 3H), 7.24-7.22 (m, 1H), 7.19-7.15 (m, 1H), 7.11 (d, *J* = 7.2 Hz, 1H), 3.54 (t, *J* = 7.6 Hz, 2H), 2.79 (t, *J* = 7.6 Hz, 2H), 2.57 (s, 3H), 2.17 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.5, 192.4, 138.6, 138.3, 136.99, 136.91, 130.1, 130.0, 128.4, 125.6, 124.8, 124.4, 120.0, 109.1, 46.9, 30.8, 30.1, 28.7; FT-IR (KBr) 1704, 1659, 1596, 1522, 1400 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{20}H_{20}NO_2$: 306.1489, found 306.1492.



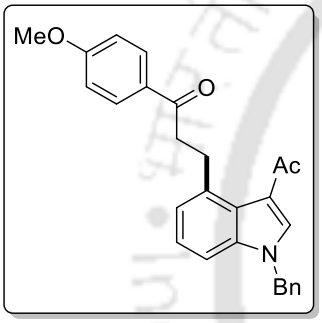
1-(1-Benzyl-4-(3-oxobutyl)-1*H*-indol-3-yl)-3-methylbutan-1-one 4g. Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.48; colorless solid; mp 120-121 °C; yield 69% (25 mg); ^1H NMR (600 MHz, $CDCl_3$) δ 7.81 (s, 1H), 7.35-7.31 (m, 3H), 7.18-7.13 (m, 4H), 7.09 (d, *J* = 6.6 Hz, 1H), 5.34 (s, 2H), 3.56 (t, *J* = 7.2 Hz, 2H), 2.78 (t, *J* = 7.8 Hz, 2H), 2.71 (d, *J* = 7.2 Hz, 2H), 2.33-2.26 (m, 1H), 2.17 (s, 3H), 1.00 (s, 3H), 0.99 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.6, 194.9, 138.4, 137.0, 136.4, 135.8, 129.1, 128.3, 126.9, 124.5, 124.3, 123.9, 119.2, 108.4, 50.8, 49.9, 46.7, 30.8, 30.1, 26.4, 22.9; FT-IR (KBr) 2955, 2924, 2868, 1705, 1646, 1397 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{24}H_{28}NO_2$: 362.2115, found 362.2112.



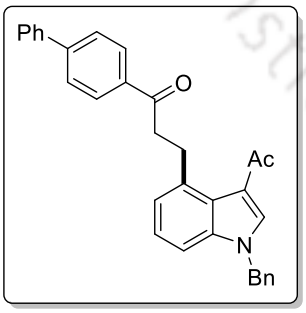
1-(3-Acetyl-1-benzyl-1*H*-indol-4-yl)pentan-3-one 4h. Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.44; colorless solid; mp 118-119 °C; yield 69% (23 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (s, 1H), 7.37-7.31 (m, 3H), 7.19-7.14 (m, 4H), 7.10-7.08 (m, 1H), 5.34 (s, 2H), 3.55 (t, *J* = 7.6 Hz, 2H), 2.76 (t, *J* = 7.6 Hz, 2H), 2.52 (s, 3H), 2.47 (q, *J* = 7.6 Hz, 2H), 1.03 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 212.1, 192.0, 138.4, 137.2, 137.1, 135.7, 129.2, 128.3, 127.0, 124.54, 124.51, 124.0, 108.4, 50.9, 45.6, 36.0, 30.9, 28.6, 7.9; FT-IR (KBr) 2851, 1709, 1644, 1525, 1397 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{22}H_{24}NO_2$: 334.1802, found 334.1805.



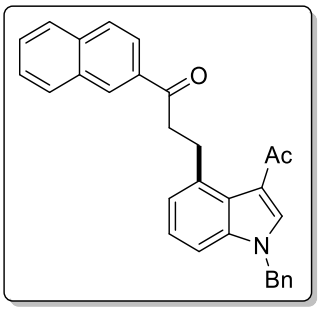
3-(3-Acetyl-1-benzyl-1*H*-indol-4-yl)-1-(4-methoxyphenyl)propan-1-one 4i. Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.41; brown thick liquid; yield 68% (28 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97-7.93 (m, 2H), 7.81 (s, 1H), 7.37-7.29 (m, 3H), 7.20-7.13 (m, 5H), 6.89-6.86 (m, 2H), 5.33 (s, 2H), 3.83 (s, 3H), 3.70 (t, *J* = 7.6 Hz, 2H), 3.32 (t, *J* = 7.6 Hz, 2H), 2.51 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.9, 192.0, 163.2, 138.4, 137.5, 137.0, 135.8, 130.6, 130.5, 129.1, 128.3, 127.0, 124.7, 124.6, 124.0, 118.9, 113.5, 108.3, 55.5, 50.8, 41.5, 30.9, 28.5; FT-IR (neat) 2931, 2838, 1656, 1599, 1524, 1395, 1259, 1170 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{27}H_{26}NO_3$: 412.1907, found 412.1912.



1-([1,1'-Biphenyl]-4-yl)-3-(3-acetyl-1-benzyl-1*H*-indol-4-yl)propan-1-one 4j. Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.41; brown thick liquid; yield 66% (30.2 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.05 (d, *J* = 8.4 Hz, 2H), 7.83 (s, 1H), 7.63-7.60 (m, 4H), 7.45 (t, *J* = 7.2 Hz, 2H), 7.38-7.31 (m, 4H), 7.19-7.15 (m, 5H), 5.35 (s, 2H), 3.74 (t, *J* = 7.2 Hz, 2H), 3.41 (t, *J* = 7.8 Hz, 2H), 2.53 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 199.9, 192.0, 145.3, 140.2, 138.4, 137.4, 137.1, 136.1, 135.7, 129.2, 129.0, 128.9, 128.3, 128.1, 127.4, 127.3, 127.1, 127.0, 124.7, 124.0, 118.8, 108.4, 50.8, 42.0, 30.8, 28.6; FT-IR (neat) 1651, 1603, 1524, 1400, 1265 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{32}H_{28}NO_2$: 458.2115, found 458.2120.

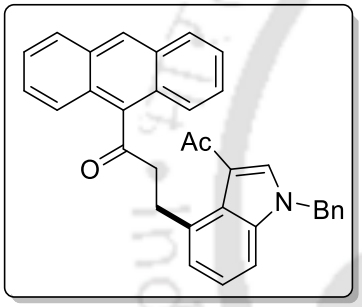


3-(3-Acetyl-1-benzyl-1*H*-indol-4-yl)-1-(naphthalen-2-yl)propan-1-one 4k. Analytical TLC on



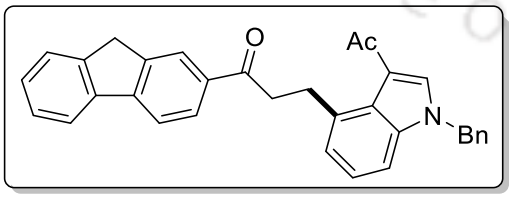
silica gel, 1:4 ethyl acetate/hexane R_f = 0.46; brown thick liquid; yield 72% (31 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.49 (s, 1H), 8.06 (dd, *J* = 8.8, 1.6 Hz, 1H), 7.90 (d, *J* = 8.0 Hz, 1H), 7.85-7.83 (m, 3H), 7.58-7.48 (m, 3H), 7.35-7.31 (m, 3H), 7.20-7.15 (m, 4H), 5.34 (s, 2H), 3.78 (t, *J* = 7.2 Hz, 2H), 3.52 (t, *J* = 7.6 Hz, 2H), 2.53 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.3, 192.1, 138.4, 137.4, 137.0, 135.7, 135.5, 134.8, 132.7, 129.9, 129.6, 129.2, 128.3, 128.2, 128.2, 127.8, 127.08, 127.04, 126.5, 124.8, 124.3, 124.0, 118.9, 108.4, 50.9, 42.1, 31.0, 28.6; FT-IR (neat) 2927, 2851, 1677, 1655, 1525, 1399 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{30}H_{26}NO_2$: 432.1958, found 432.1964.

3-(3-Acetyl-1-benzyl-1*H*-indol-4-yl)-1-(anthracen-9-yl)propan-1-one 4l. Analytical TLC on



silica gel, 1:4 ethyl acetate/hexane R_f = 0.43; brown thick liquid; yield 68% (32.7 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.39 (s, 1H), 7.96 (d, *J* = 8.4 Hz, 2H), 7.77-7.75 (m, 3H), 7.41 (t, *J* = 7.2 Hz, 2H), 7.37-7.34 (m, 2H), 7.31-7.30 (m, 3H), 7.28-7.26 (m, 1H), 7.20 (t, *J* = 7.8 Hz, 1H), 7.16 (d, *J* = 8.4 Hz, 1H), 7.11-7.10 (m, 2H), 5.31 (s, 2H), 3.99 (t, *J* = 7.2 Hz, 2H), 3.39 (t, *J* = 7.8 Hz, 2H), 2.49 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 210.2, 191.9, 138.3, 137.2, 137.1, 136.8, 135.8, 131.0, 129.1, 128.5, 128.2, 127.7, 127.07, 127.04, 126.9, 126.4, 125.4, 124.9, 124.5, 124.0, 118.8, 108.5, 50.8, 49.3, 30.2, 28.6; FT-IR (neat) 2925, 1694, 1653, 1523, 1398 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{34}H_{28}NO_2$: 482.2115, found 482.2120.

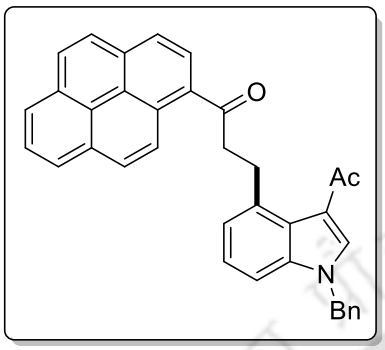
3-(3-Acetyl-1-benzyl-1*H*-indol-4-yl)-1-(9*H*-fluoren-2-yl)propan-1-one 4m. Analytical TLC on



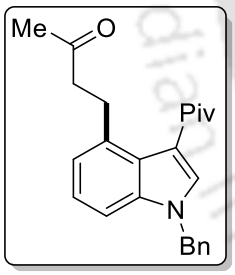
silica gel, 1:4 ethyl acetate/hexane R_f = 0.44; brown thick liquid; yield 65% (30 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (s, 1H), 8.03 (d, *J* = 8.0 Hz, 1H), 7.82-7.77 (m, 3H), 7.57 (d, *J* = 7.2 Hz, 1H), 7.40-7.33 (m, 5H), 7.19-7.14 (m, 5H), 5.34 (s, 2H), 3.90 (s, 2H), 3.75 (t, *J* = 7.2 Hz, 2H), 3.44 (t, *J* = 7.6 Hz, 2H), 2.53 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.1, 192.0, 145.9, 144.6, 143.2, 140.8, 138.4, 137.5, 137.0, 136.0, 135.8, 129.2, 128.3, 127.8, 127.6, 127.0, 125.3, 125.0, 124.8, 124.6, 124.0,

120.8, 119.6, 118.9, 108.4, 50.9, 42.0, 37.0, 30.9, 28.6; FT-IR (neat) 2927, 1675, 1656, 1606, 1438, 1399 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{33}H_{28}NO_2$: 470.2115, found 470.2119.

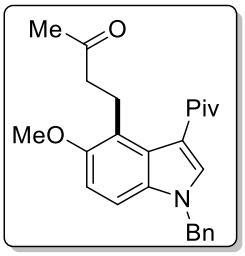
3-(3-Acetyl-1-benzyl-1*H*-indol-4-yl)-1-(pyren-1-yl)propan-1-one 4n. Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.42; brown thick liquid; yield 63% (31.8 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.83 (d, *J* = 9.6 Hz, 1H), 8.30 (d, *J* = 8.0 Hz, 1H), 8.22 (dd, *J* = 7.6, 2.8 Hz, 2H), 8.15-8.09 (m, 3H), 8.05-8.01 (m, 2H), 7.76 (s, 1H), 7.34-7.30 (m, 3H), 7.19-7.12 (m, 5H), 5.30 (s, 2H), 3.88 (t, *J* = 7.2 Hz, 2H), 3.59 (t, *J* = 7.6 Hz, 2H), 2.49 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.4, 192.0, 138.4, 137.2, 137.0, 135.8, 133.7, 133.4, 131.2, 130.8, 129.24, 129.22, 129.20, 129.1, 128.3, 127.2, 127.0, 126.3, 126.2, 126.0, 125.8, 125.3, 125.0, 124.7, 124.6, 124.5, 124.1, 124.0, 118.9, 108.4, 50.8, 45.7, 31.5, 28.5; FT-IR (neat) 2925, 2851, 1721, 1655, 1524, 1400 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{36}H_{28}NO_2$: 506.2115, found 506.2119.



4-(1-Benzyl-3-pivaloyl-1*H*-indol-4-yl)butan-2-one 5a. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.45; colorless solid; mp 120-121 °C; yield 67% (24 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (s, 1H), 7.35-7.27 (m, 3H), 7.18-7.12 (m, 4H), 7.03-7.01 (m, 1H), 5.32 (s, 2H), 3.20 (t, *J* = 7.6 Hz, 2H), 2.80 (t, *J* = 8.0 Hz, 2H), 2.17 (s, 3H), 1.37 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.1, 205.8, 137.0, 136.2, 135.6, 130.6, 129.0, 128.1, 126.9, 125.7, 123.4, 122.9, 115.9, 108.3, 50.6, 45.2, 44.9, 29.9, 29.0, 28.6; FT-IR (KBr) 2982, 2886, 1709, 1646, 1524, 1400 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{24}H_{28}NO_2$: 362.2115, found 362.2112.

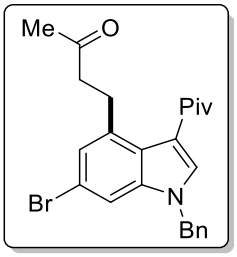


4-(1-Benzyl-5-methoxy-3-pivaloyl-1*H*-indol-4-yl)butan-2-one 5c. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.43; brown thick liquid; yield 69% (27 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (s, 1H), 7.35-7.28 (m, 3H), 7.14-7.12 (m, 2H), 7.08 (d, *J* = 8.8 Hz, 1H), 6.92 (d, *J* = 8.8 Hz, 1H), 5.27 (s, 2H), 3.82 (s, 3H), 3.07-3.03 (m, 2H), 2.84-2.80 (m, 2H), 2.21 (s, 3H), 1.35 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 209.9, 206.2, 153.0, 136.4, 132.4, 131.0, 129.0,



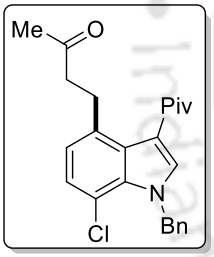
128.1, 127.3, 126.9, 122.7, 115.9, 109.6, 108.2, 57.2, 50.7, 44.9, 43.6, 29.7, 28.5, 22.4; FT-IR (KBr) 2925, 2853, 1709, 1658, 1524, 1436, 1399 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{25}H_{30}NO_3$: 392.2220, found 392.2223.

4-(1-Benzyl-6-bromo-3-pivaloyl-1*H*-indol-4-yl)butan-2-one 5d. Analytical TLC on silica gel,



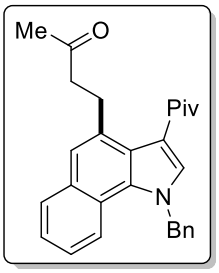
1:9 ethyl acetate/hexane R_f = 0.43; colorless solid; mp 160-161 °C; yield 63% (27.6 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (s, 1H), 7.37-7.31 (m, 3H), 7.29 (d, *J* = 1.6 Hz, 1H), 7.13-7.09 (m, 3H), 5.27 (s, 2H), 3.11 (t, *J* = 7.2 Hz, 2H), 2.79 (t, *J* = 8.0 Hz, 2H), 2.17 (s, 3H), 1.34 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.3, 205.7, 137.7, 137.5, 135.7, 130.7, 129.2, 128.3, 126.8, 125.9, 124.7, 117.0, 116.2, 111.1, 50.6, 45.0, 44.9, 29.9, 28.58, 28.51; FT-IR (KBr) 2961, 2929, 1710, 1655, 1526, 1401, 1359 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{24}H_{27}BrNO_2$: 440.1220, found 440.1226.

4-(1-Benzyl-7-chloro-3-pivaloyl-1*H*-indol-4-yl)butan-2-one 5e. Analytical TLC on silica gel,



1:9 ethyl acetate/hexane R_f = 0.44; colorless solid; mp 99-100 °C; yield 71% (28 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (s, 1H), 7.26-7.18 (m, 3H), 7.05 (d, *J* = 7.6 Hz, 1H), 6.96-6.94 (m, 2H), 6.83 (d, *J* = 7.6 Hz, 1H), 5.71 (s, 2H), 2.97 (t, *J* = 7.2 Hz, 2H), 2.71 (t, *J* = 8.0 Hz, 2H), 2.08 (s, 3H), 1.26 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 208.5, 206.6, 138.0, 134.1, 132.14, 132.12, 129.0, 128.6, 127.8, 126.3, 125.2, 123.2, 116.5, 115.1, 52.6, 45.2, 44.7, 29.9, 28.2, 28.1; FT-IR (KBr) 2963, 2928, 1715, 1707, 1655, 1643, 1401 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{24}H_{27}ClNO_2$: 396.1725, found 396.1725.

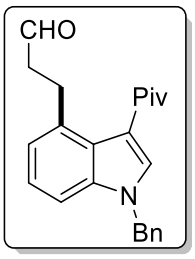
4-(1-Benzyl-3-pivaloyl-1*H*-benzo[*g*]indol-4-yl)butan-2-one 5f. Analytical TLC on silica gel, 1:9



ethyl acetate/hexane R_f = 0.45; colorless solid; mp 138-139 °C; yield 65% (26.7 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (d, *J* = 8.8 Hz, 1H), 7.84 (d, *J* = 7.6 Hz, 1H), 7.45 (s, 1H), 7.39-7.38 (m, 1H), 7.36-7.33 (m, 2H), 7.32-7.26 (m, 3H), 7.11 (d, *J* = 6.8 Hz, 2H), 5.83 (s, 2H), 3.20 (t, *J* = 7.2 Hz, 2H), 2.90 (t, *J* = 8.0 Hz, 2H), 2.20 (s, 3H), 1.39 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 208.7, 208.0, 136.7, 133.8, 131.9, 130.7, 129.5, 129.3, 128.6, 128.0, 126.2, 125.3, 124.3, 123.9, 122.8,

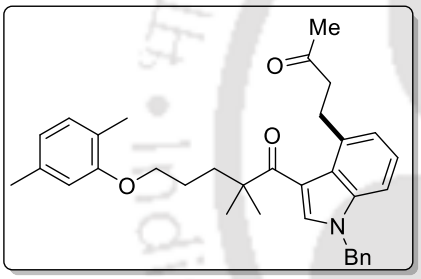
121.1, 120.9, 117.3, 54.2, 45.3, 44.6, 30.0, 28.7, 28.3; FT-IR (KBr) 2958, 2925, 2853, 1706, 1650, 1531, 1400 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{28}H_{30}NO_2$: 412.2271, found 412.2270.

3-(1-Benzyl-3-pivaloyl-1*H*-indol-4-yl)propanal 5g. Analytical TLC on silica gel, 1:9 ethyl



acetate/hexane R_f = 0.42; colorless solid; mp 100-101 °C; yield 67% (23 mg); ^1H NMR (400 MHz, $CDCl_3$) δ 9.81 (t, *J* = 1.6 Hz, 1H), 7.61 (s, 1H), 7.36-7.29 (m, 3H), 7.17-7.16 (m, 2H), 7.14-7.12 (m, 2H), 7.03-7.01 (m, 1H), 5.33 (s, 2H), 3.31 (t, *J* = 7.2 Hz, 2H), 2.77 (t, *J* = 7.6 Hz, 2H), 1.37 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 205.4, 202.9, 137.1, 136.2, 135.1, 131.1, 129.1, 128.2, 126.9, 125.7, 123.5, 123.0, 116.0, 108.5, 50.7, 45.1, 44.9, 28.8, 27.4; FT-IR (KBr) 2931, 2725, 1717, 1650, 1523, 1399 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{23}H_{26}NO_2$: 348.1958, found 348.1957.

1-(1-Benzyl-4-(3-oxobutyl)-1*H*-indol-3-yl)-5-(2,5-dimethylphenoxy)-2,2-dimethylpentan-1-



one 5h. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.43; colorless liquid; yield 70% (35.6 mg); ^1H NMR (400 MHz, $CDCl_3$) δ 7.62 (s, 1H), 7.33-7.27 (m, 3H), 7.18-7.10 (m, 4H), 7.04-7.02 (m, 1H), 6.99 (d, *J* = 7.6 Hz, 1H), 6.65 (d, *J* = 7.6 Hz, 1H), 6.58 (s, 1H), 5.30 (s, 2H), 3.91 (t, *J* = 6.4 Hz, 2H), 3.22 (t, *J* = 7.6 Hz, 2H), 2.84 (t, *J* = 8.0 Hz, 2H), 2.28 (s, 3H), 2.18 (s, 3H), 2.12 (s, 3H), 2.01-1.96 (m, 2H), 1.86-1.81 (m, 2H), 1.39 (s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 209.0, 204.7, 157.0, 137.1, 136.6, 136.2, 135.8, 130.7, 130.4, 129.0, 128.1, 126.8, 126.1, 125.8, 123.5, 123.1, 120.8, 116.3, 112.2, 108.3, 68.2, 50.6, 48.1, 45.4, 38.0, 29.9, 29.1, 26.9, 25.2, 21.4, 15.8; FT-IR (neat) 2963, 2925, 1713, 1647, 1524, 1399 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{34}H_{40}NO_3$: 510.3003, found 510.3009.

Crystal Data and Structure Refinement for 5d at 293(2) K

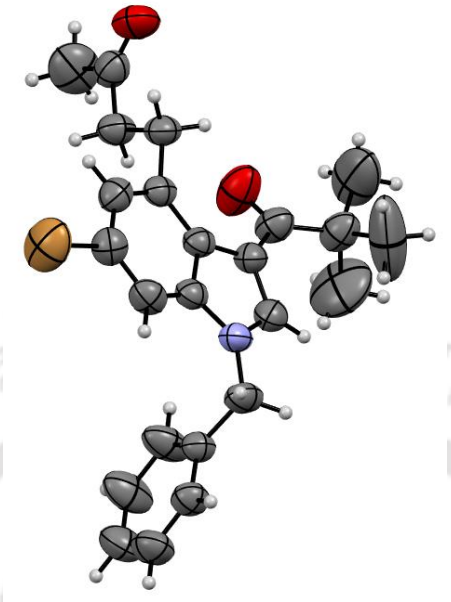


Figure 3. ORTEP diagram of methyl 4-(1-benzyl-6-bromo-3-pivaloyl-1*H*-indol-4-yl)butan-2-one **5d** with 50% ellipsoid (**CCDC 1959139**).

Identification code	**5d**
Empirical formula	$C_{24}H_{26}BrNO_2$
Formula weight	440.36
Crystal habit, colour	block /colorless
Temperature, *T*/K	296 K
Wavelength, λ/Å	0.71073
Crystal system	monoclinic
Space group	'P 21/c'
Unit cell dimensions	a = 20.911(3)Å
	b = 10.7246(13)Å
	c = 10.0860(12)Å
	α = 90
	β = 102.188(4)
	γ = 90
Volume, *V*/Å^3	2211.0(5)

Z	4
Calculated density, $Mg \cdot m^{-3}$	1.323
Absorption coefficient, μ/mm^{-1}	1.877
$F(000)$	996
θ range for data collection	2.14 to 17.10°
Limiting indices	$-25 \leq h \leq 25, -13 \leq k \leq 13, -12 \leq l \leq 12$
Reflection collected / unique	4198/1880
Completeness to θ	99.80% (θ = 25.96°)
Absorption correction	multi-scan
Refinement method	'SHELXL-2014/7 (Sheldrick, 2014)'
Data / restraints / parameters	4198/0/ 258
Goodness–of–fit on F^2	0.958
Final R indices [I>2sigma(I)]	R1 = 0.1564, wR2 = 0.1987
R indices (all data)	R1 = 0.0558, wR2 = 0.1437

4.6 References

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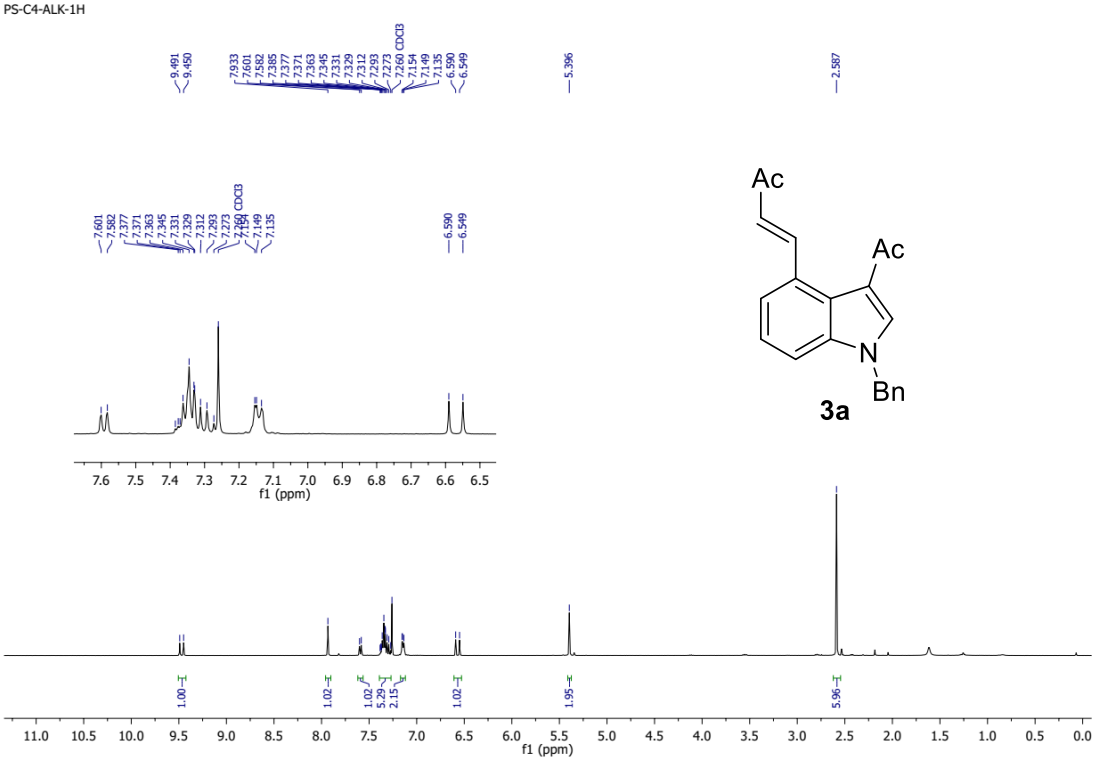
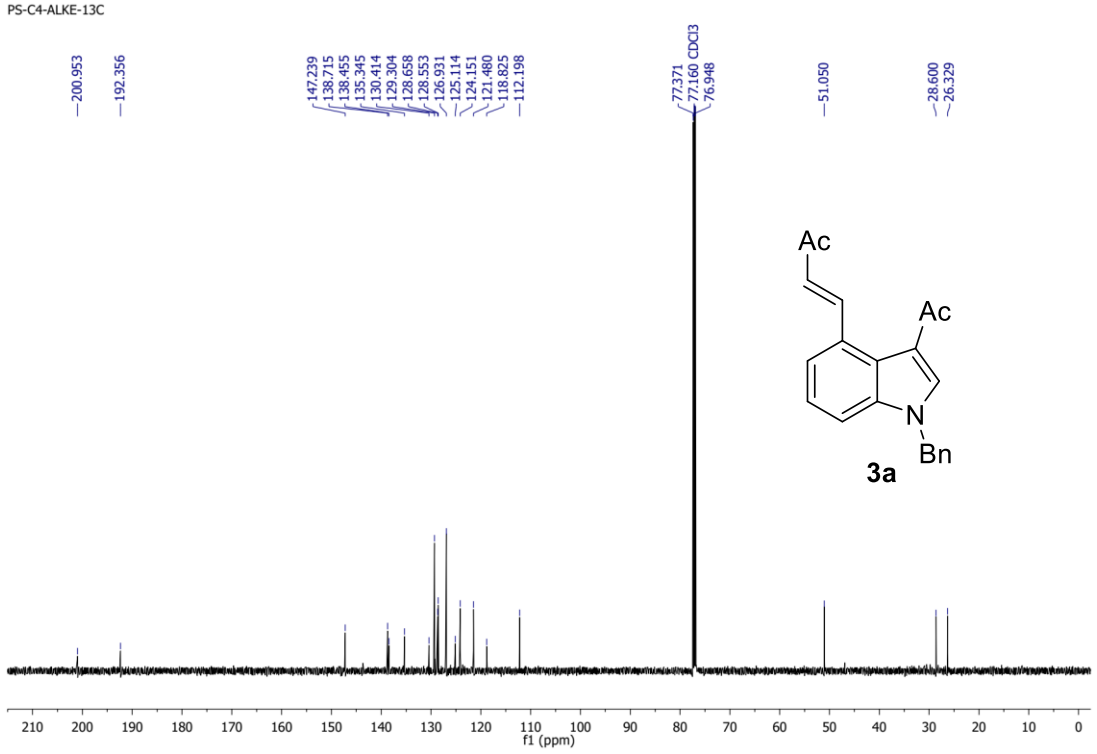
4.7 Selected NMR Spectra





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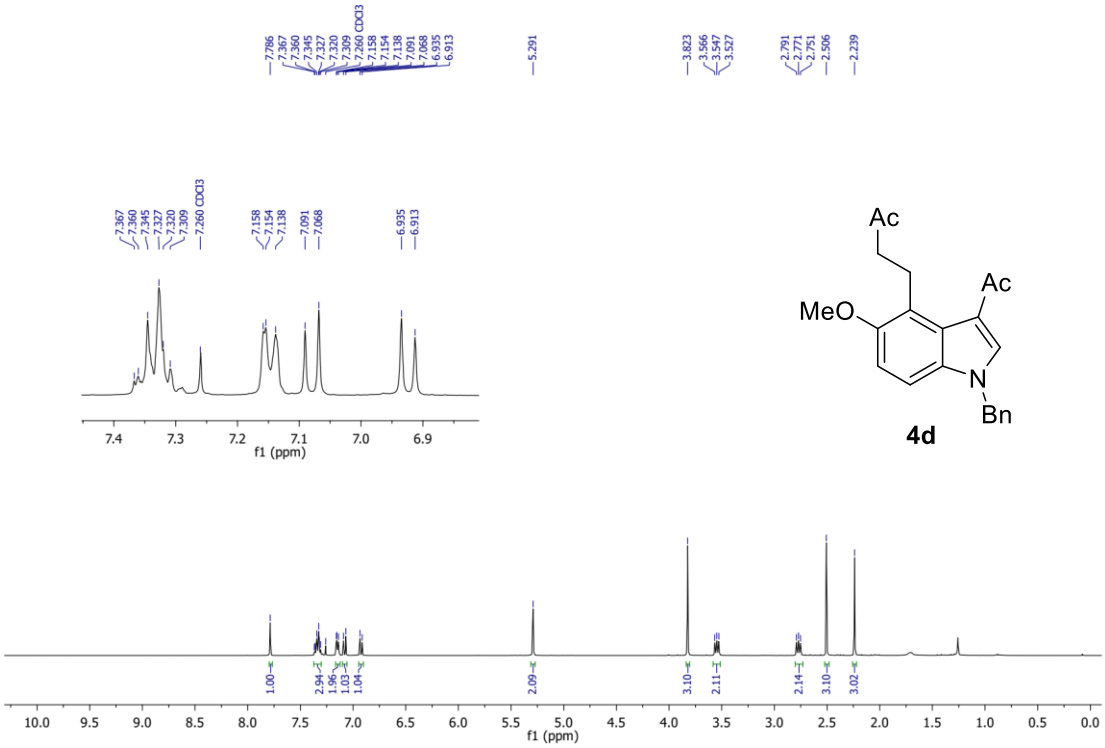

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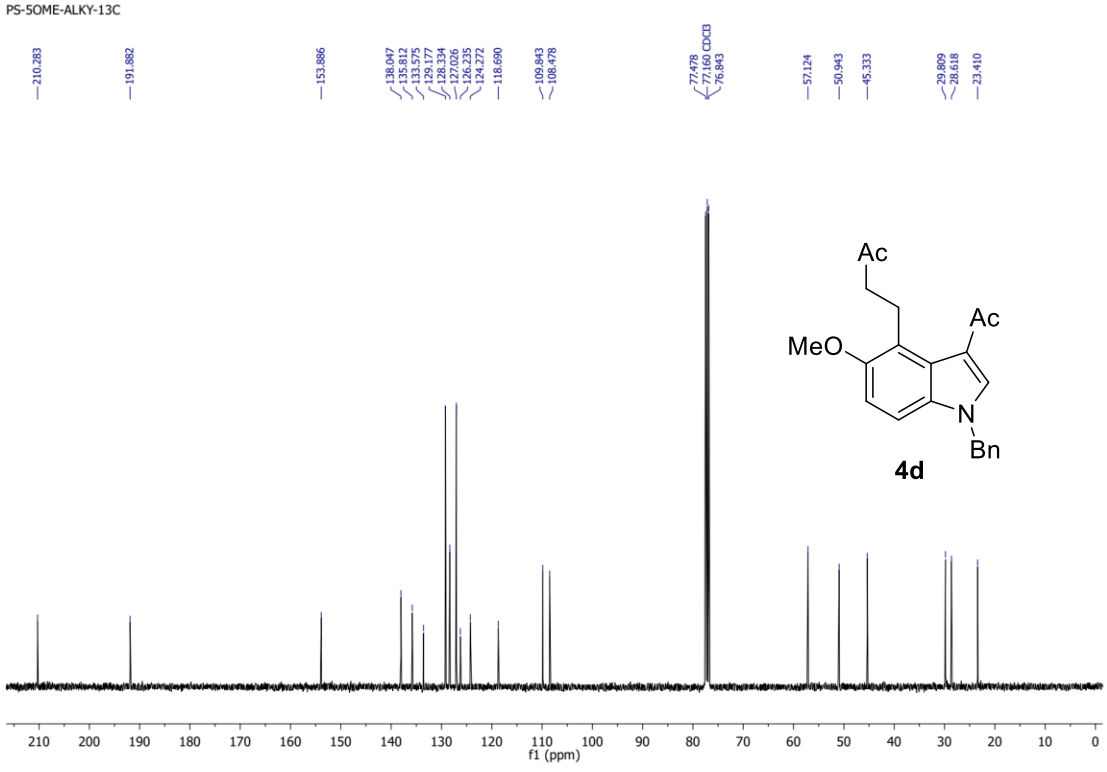
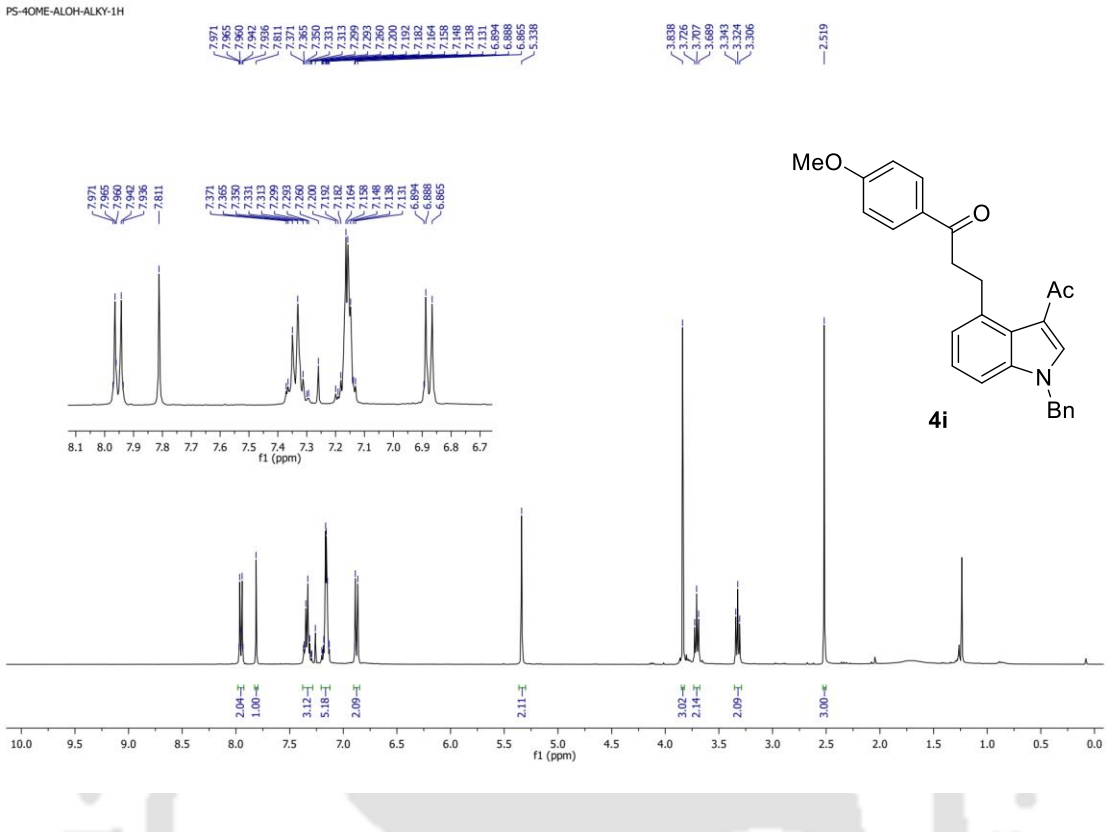
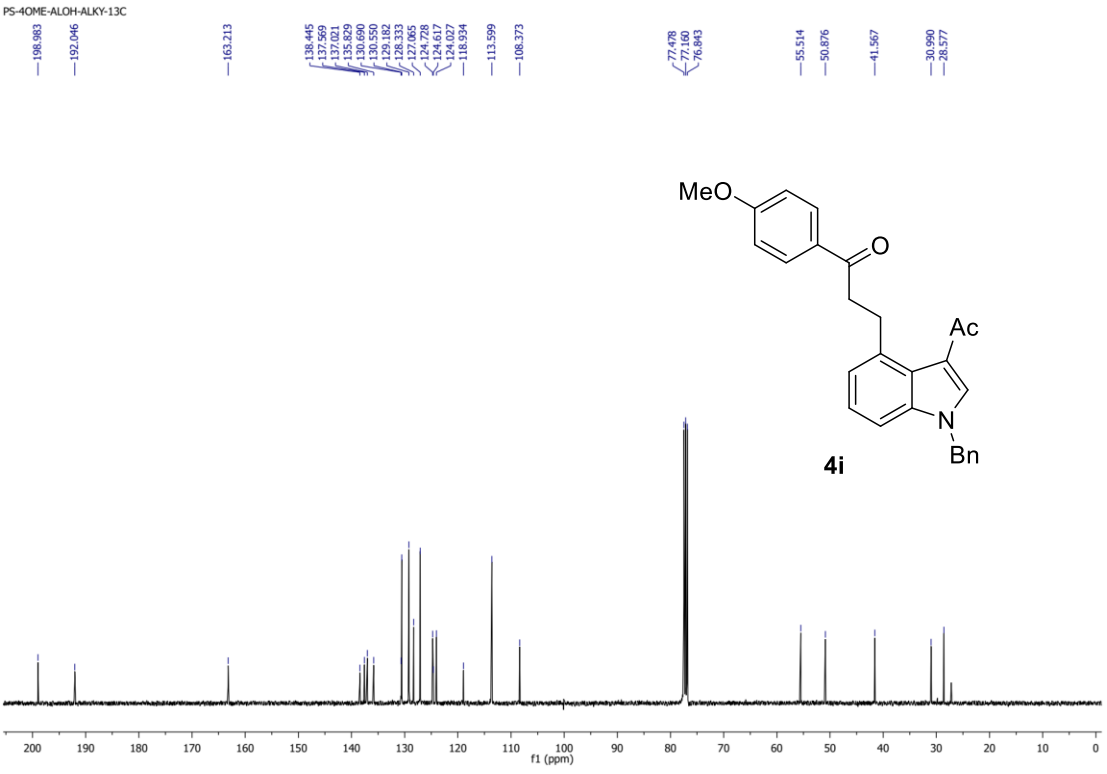
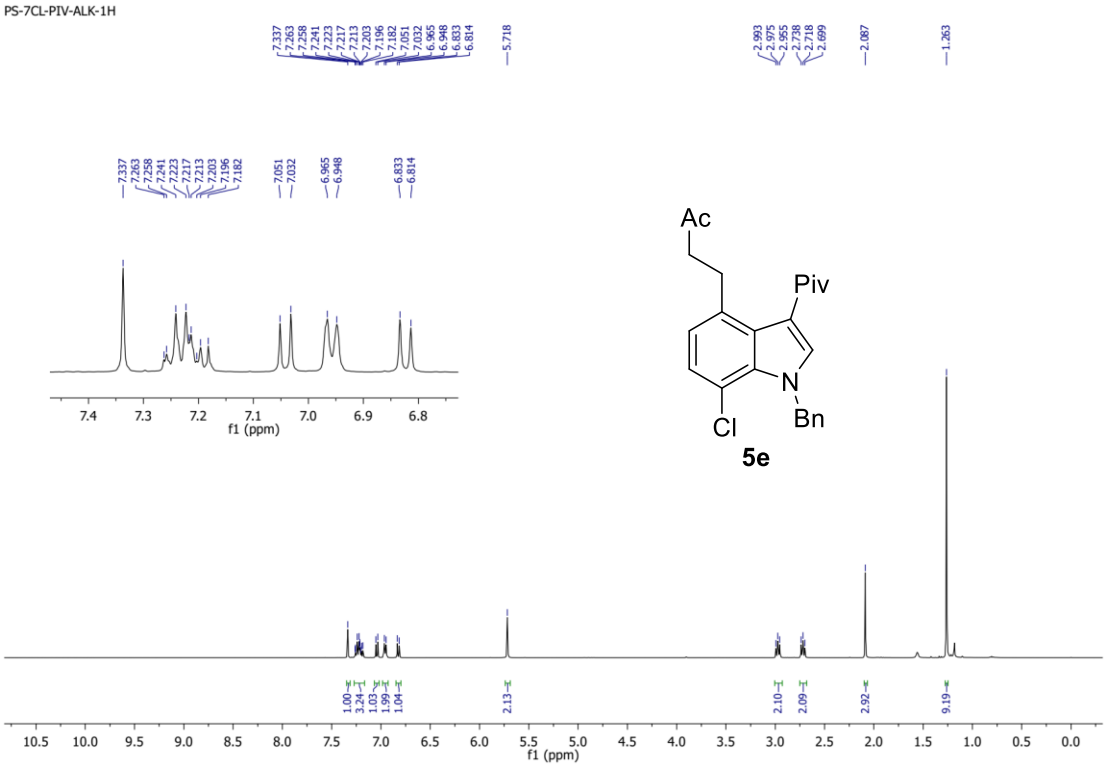
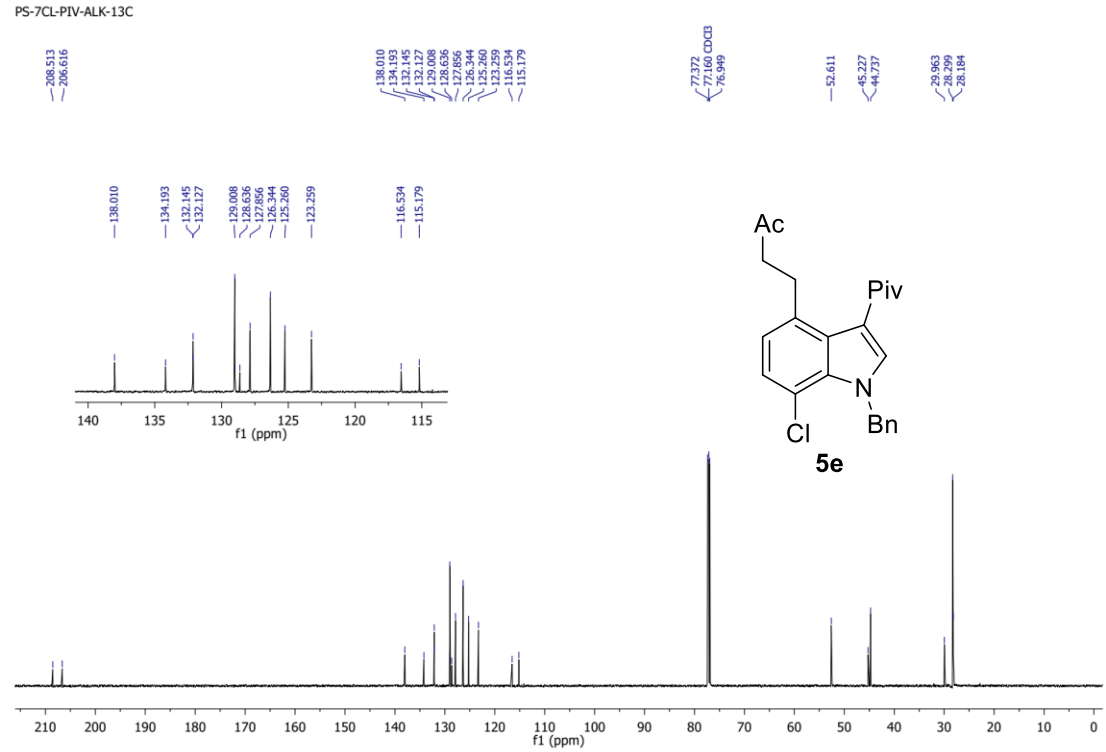


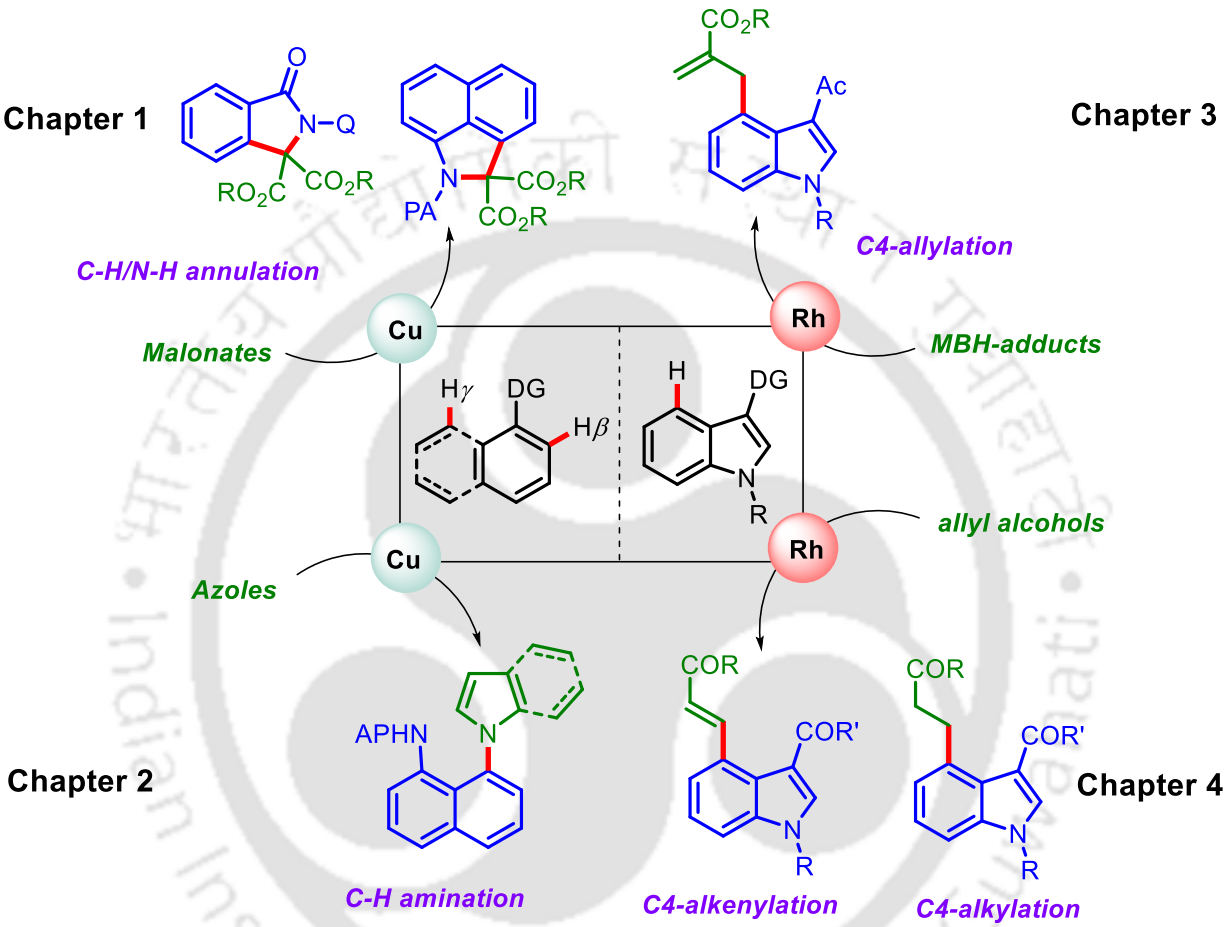








Thesis Overview



Summary

In chapter 1, we have presented a Cu(II)-catalyzed oxidative C-H/N-H annulation of benzamides with dialkyl malonates through cross-dehydrogenative strategy to construct synthetically useful isoindolinones. The reaction proceeds via an intramolecular oxidative C-N bond formation of the initially formed C-C coupling product. The method was extended for the coupling of 1-naphthylamides to afford dihydrobenzoindoles.

In chapter 2, a copper-mediated regioselective C-H/N-H dehydrogenative cross-coupling of 1-naphthylamides with indoles, pyrazoles and pyrrole was developed using picolinamide as a directing group. This reaction provides a prospective route for directly installing imperative heterocycles, such as, indoles, pyrazoles and pyrrole components into naphthyl backbone that are important in biological and medicinal sciences.

In chapter 3, we have demonstrated a weak carbonyl coordination enabled Rh(III)-catalyzed C4-selective redox-neutral allylation of indoles with versatile MBH acetates. Indoles bearing distinct functional groups are well endured to give the target allylated products. Exclusive C4-selectivity, functional group tolerance, mechanistic underpinnings and late-stage modification of the natural products are the significant practical findings.

In chapter 4, a weak carbonyl coordination guided Rh(III)-catalyzed switchable reactivity between oxidative C4-alkenylation and C4-alkylation of indoles was achieved utilizing allylic alcohols. Tuning the reactivity of the substrates by modification of the reaction parameters and directing group the target C4-alkenylated and C4-alkylated products was accessed. The elegant features of our findings comprise of late-stage drug modification, mechanistic aspects and broad scope with functional group diversity.

List of Publications

1 Copper(II)-Catalyzed Oxidative C-H/C-N Annulation of Benzamides with Malonates: A Facile Route to Isoindolinones

Pradhan, S.; Roy, S.; Banerjee, S.; De, P. B.; Punniyamurthy, T. (*Manuscript submitted*).

2 Weak Coordination-Guided Regioselective Direct Redox-Neutral C4 Allylation of Indoles with Morita–Baylis–Hillman Adducts

Pradhan, S.; De, P. B.; Punniyamurthy, T. *Org. Lett.*, **2019**, *21*, 9898.

3 Weak Coordination Enabled Switchable C4-Alkenylation and Alkylation of Indoles with Allyl Alcohols

Pradhan, S.; De, P. B.; Mishra, M.; Banerjee, S.; Punniyamurthy, T. *Org. Lett.* 2**020**, *22*, 1720.

4 Copper(II)-Mediated Chelation-Assisted Regioselective *N*-Naphthylation of Indoles, Pyrazoles and Pyrrole Through Dehydrogenative Cross-Coupling

Pradhan, S.; De, P. B.; Punniyamurthy, T. *J. Org. Chem.* **2017**, *82*, 4883.

5 Stereoselective Copper-Catalyzed Cross-Coupling of Aziridines with Benzimidazoles *via* Nucleophilic Ring Opening and C(sp^2)-H Functionalization

De, P. B.; **Pradhan, S**.; Punniyamurthy, T. *J. Org. Chem.* **2017**, *82*, 3183.

6 Recent Advances in Radical Dioxygenation of Olefins

Bag, R.; De, P. B.; **Pradhan, S**.; Punniyamurthy, T. *Eur. J. Org. Chem*. **2017**, 5424.

7 Chiral Fe-Dendrimer Catalyzed Domino Michael and Aldol Reactions of Chalcones with 1,4-Dithiane-2,5-diol

Kannan, M.; De, P. B.; **Pradhan, S**.; Punniyamurthy, T. *Chem. Select.* **2018**, *3*, 859.

8 Expedient Cobalt(II)-Catalyzed Site-Selective C7-Arylation of Indolines with Arylboronic Acids

De, P. B.; **Pradhan, S**.; Banerjee, S.; Punniyamurthy, T. *Chem. Commun*. **2018**, *54*, 2494.

9 Iodine-Mediated Intramolecular C-H Amination of Benzimidazoles: A Metal-Free Route to Dihydroimidazobenzimidazoles

De, P. B.; **Pradhan, S**.; Shah, T. A.; Punniyamurthy, T. *Synthesis* **2018**. *50*, 3224.

10 Copper-Mediated Regioselective C–H Etherification of Naphthylamides with Arylboronic Acids Using Water as an Oxygen Source

Roy, S.; **Pradhan**, **S**.; Punniyamurthy, T. *Chem. Commun*. **2018**, *54*, 3899.

11 Stereospecific Ring Opening and Cycloisomerization of Aziridines with Propargylamines: Synthesis of Functionalized Piperazines and Tetrahydropyrazines

Das, B. K.; **Pradhan, S.**; Punniyamurthy, T. *Org. Lett*. **2018**, *20*, 4444.

12 Ru(II)-Catalyzed C7-Acyloxylation of Indolines with Carboxylic Acids

De, P. B.; Banerjee, S.; **Pradhan, S**.; Punniyamurthy, T. *Org. Biomol. Chem.* **2018**, *16*, 5889.

13 Transition-Metal-Catalyzed Site-Selective C7-Functionalization of Indoles: Advancement and Future Prospects

Shah, T. A.; De, P. B.; **Pradhan, S**.; Punniyamurthy, T. *Chem. Commun*. **2019**, *55*, 572.

14 Ru(II)-Catalyzed Regioselective C-N Bond Formation of Indolines and Carbazole with Acyl Azides

Banerjee, S.; De, P. B.; **Pradhan, S**.; Shah, T. A.; Punniyamurthy, T. *Eur. J. Org. Chem*. **2019**, 1677.

15 Stereospecific Copper(II)-Catalyzed Tandem Ring Opening/Oxidative Alkylation of Donor-Acceptor Cyclopropanes with Hydrazones: Synthesis of Tetrahydropyridazines

Mishra, M.; De, P. B.; **Pradhan, S**.; Punniyamurthy, T. *J. Org. Chem.* **2019**, *84*, 10901.

16 Stereospecific Assembly of Tetrahydroquinolines via Tandem Ring-Opening/Oxidative Cyclization of Donor-Acceptor Cyclopropanes with *N*-Alkyl Anilines

Das, B. K.; **Pradhan, S**.; Punniyamurthy, T. *Chem. Commun*. **2019**, *55*, 8083.

17 Iron-Catalyzed Regioselective Remote C(sp^2)-H Carboxylation of Naphthyl and Quinoline Amides

Kumar, S.; **Pradhan, S**.; Roy, S.; De, P. B.; Punniyamurthy, T. *J. Org. Chem.* **2019**, *84*, 10481.

18 Cp*Co(III)-Catalyzed Regioselective C2-Amidation of Indoles Using Acyl Azides

Shah, T. A.; De, P. B.; **Pradhan, S**.; Banerjee, S.; Punniyamurthy, T. *J. Org. Chem.* **2019**, *84*, 16278.

Conference Attended

Oral Presentations:

1. **Sourav Pradhan**, "Weak Coordination Guided Distal C4 Functionalization of Indoles". Organic Colloquium, 2020, IIT Guwahati, 05th March 2020.
2. **Sourav Pradhan**, "Transition-Metal Catalyzed Direct C-H Functionalization: A Quest for Carbon-Carbon and Carbon-Heteroatom Bond Formation". Royal Society of Chemistry Roadshow, 2019, IIT Guwahati, 06th Nov 2019.

Poster Presentation:

1. **Sourav Pradhan**, Pinaki Bhusan De and Tharmalingam Punniyamurthy, "Copper(II)-Mediated Picolinamide Directed Regioselective *N*-Naphthylation of Azoles via Dehydrogenative Cross-Coupling" XIII J-NOST, Banaras Hindu University, Varanasi, Nov 9-12, 2017.
2. **Sourav Pradhan**, Pinaki Bhusan De and Tharmalingam Punniyamurthy, "Picolinamide Directed Copper(II)-Mediated Regioselective *N*-Naphthylation of Azoles via Dehydrogenative Cross-Coupling" Chemconvene, IIT Guwahati, July 27th 2017.