Studies Towards C-C, C-N and C-O Bond Formation *via* C-H Functionalization: Expedient Synthesis of Functionalized Heterocycles

A Thesis Submitted

in Partial Fulfilment of the Requirements

for the Degree of

DOCTOR OF PHILOSOPHY

by

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September 2019

Dedicated To

My Family Members

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   Pinaki Bhusan De

September 2019

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Department of Chemistry

CERTIFICATE

This is to certify that Mr. Pinaki Bhusan De has been working under my supervision since July 2014. I am forwarding his thesis entitled "*Studies Towards C-C, C-N and C-O Bond Formation via C-H Functionalization: Expedient Synthesis of Functionalized Heterocycles*" being submitted for the Ph.D. degree of this institute. I certify that he has fulfilled all the requirements according to the rules of this institute, and regarding the investigations embodied in his thesis and this work has not been submitted elsewhere for a degree.

Guwahati
September 2019

Prof. Tharmalingam Punniyamurthy
Supervisor

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Pinaki Bhusan De

List of Abbreviations

AcOH	acetic acid
Ac_2O	acetic anhydride
Ac	acetyl
acac	acetylacetone
Å	angstrom (10^{-8} cm)
$AgBF_4$	silver tetrafluoroborate
AgOTf	silver trifluoromethanesulfonate
$AgSbF_6$	silver hexafluoroantimonate
Ag_2CO_3	silver carbonate
aq.	Aqueous
aq. HCl	aqueous hydrochloric acid
Ar	aryl
BHT	2,6-di-*tert*-butyl-4-methylphenol
Bn	benzyl
Boc	*tert*-butoxycarbonyl
Boc-Val-OH	*N*-(*tert*-butoxycarbonyl)-L-valine
Cp*	1,2,3,4,5-pentamethylcyclopentadiene
CCDC	Cambridge crystallographic data centre
CH_3CN	acetonitrile
PhCl	chlorobenzene
$CHCl_3$	chloroform
CH_2Cl_2	dichloromethane
$(CH_2Cl)_2$	1,2-dichloroethane
p-cymene	4-isopropyltoluene
DG	Directing group
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DMSO	dimethylsulfoxide
DMF	*N*,*N*-dimethylformamide
dr	diastereomeric ratio

EDG	electron donating group
equiv	equivalent
Et_3N	triethylamine
ESI	electrospray ionization
Et	ethyl
EWG	electron wthdrawing group
FT-IR	fourier transform infrared spectroscopy
H_2O_2	hydrogen peroxide
HFIP	hexafluoroisopropanol
HRMS	high-resolution mass spectrometry
Hz	hertz
*i*PrOH	isopropyl alcohol
KBr	potassium bromide
KPF_6	potassium hexafluorophosphate
K_2CO_3	potassium carbonate
K_3PO_4	Potassium phosphate tribasic
$K_2S_2O_8$	potassium persulfate
m/z	mass to charge ratio
mp	melting point
MesCOOH	2,4,6-trimethylbenzoic acid
Me	methyl
MeOH	methanol
MsOH	Methanesulfonic acid
MHz	megahertz
NMR	nuclear magnetic resonance
nm	nanometer
ORTEP	oak ridge thermal ellipsoid plot
Ph	phenyl
R_f	retardation factor
rt	room temperature
Pcy_3	tricyclohexylphosphine

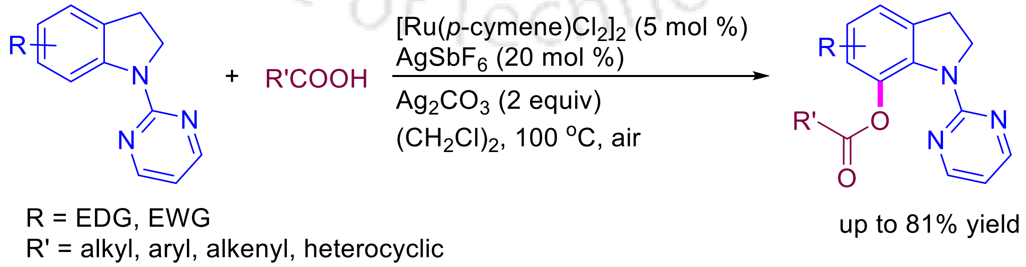
PIDA	phenyliodonium diacetate
PPh_3	triphenyphosphine
1, 10-Phen	1, 10-phenanthroline
PivOH	pivalic acid
SET	single-electron transfer
TFE	trifluoroethanol
TFAA	Trifluoro acetic anhydride
TBAI	tetrabutylammonium iodide
TBHP	*tert*-butyl hydroperoxide
TEMPO	2,2,6,6-tetramethylpiperidine 1-oxyl
THF	tetrahydrofuran
TLC	thin layer chromatography
TsOH	*p*-toluenesulfonic acid
TMS	trimethylsilyl
TM	transition metal
μl	microliter

Abstract

The thesis contains four chapters. The first chapter describes C7-acyloxylation of indolines with versatile carboxylic acids using pyrimidine as directing group under Ru(II)-catalysis. The second chapter deals with the Co(II)-PCy3-catalyzed C7-arylation of indolines using arylboronic acids as arylating agents utilizing a removable pyrimidyl directing group. The third chapter focuses on the air stable Cp*Co(III)-catalyzed auxiliary assisted ring opening of *N*-sulfonyl aziridines with indolines at its C7 position, enabling site-selective C-H activation at moderate temperature. The fourth chapter represents a Cu(II)-catalyzed aziridine ring opening reaction with benzimidazoles followed by cyclization to construct imidazobenzimidazole moiety using air as an oxidant.

Chapter I. Ru(II)-Catalyzed C7-Acyloxylation of Indolines with Carboxylic Acids

Indoles and their synthetic scaffolds epitomize a class of privileged heterocycles being present in many natural products and biologically active compounds and thus have become one of the most extensively studied organic templates. Due to the inherent reactivity of pyrrole type ring, functionalization at the C2 and C3 position of indoles are comparatively convenient than the other positions. Current developments focuses on the carbon-carbon and carbon-heteroatom bond formation to diversify the indoles at the C7-H bond. Among them, C-H acyloxylation using carboxylic acids as oxygenating source is attractive due to the prevalence of C-O bonds in pharmaceuticals and material sciences. The present chapter describes Ru(II)-catalyzed C7-oxygenation of indolines with versatile carboxylic acids and consequent oxidation to yield C7-oxygenated indole (Scheme 1).

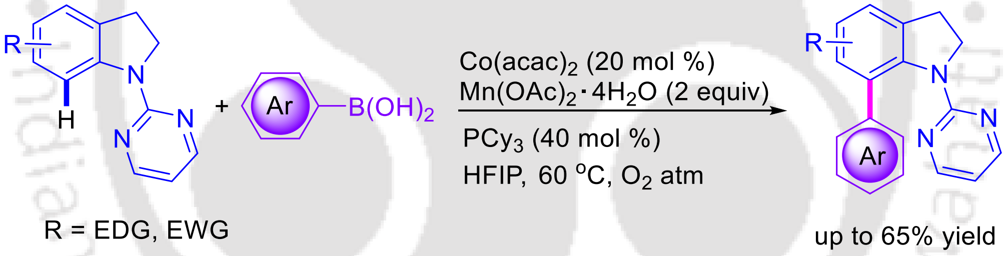


Org. Biomol. Chem. **2018**, *16*, 5889

Scheme 1. Ru(II)-Catalyzed C-H Acyloxylation of Indolines utilizing Carboxylic Acids

Chapter II. Co(II)-Catalyzed Site-Selective C7-Arylation of Indolines with Arylboronic Acids

Transition-metal-catalyzed C-H functionalization has recently appeared a prospetic synthetic tool for the carbon-carbon and carbon-heteroatom bond formation guided by chelation. Among them, C-H arylation is attractive as this core moiety is found in many bio-active molecules. Cobalt being less-expensive, air stable and minimally toxic shows a new dimension for the C-H arylation. Exploiting the functionalization on biologically imperative indole moiety, in this chapter, we established a Co(II)-PCy_3-catalyzed C7 arylation of indolines with arylboronic acids as an arylating agent using a removable pyrimidyl coordinating group, which can be further oxidized to C7-arylated indoles (Scheme 2). The broad substrate scope with functional group diversity, using of minimally-toxic and inexpensive cobalt catalyst and late-stage removal of directing group are the important features of the protocol.

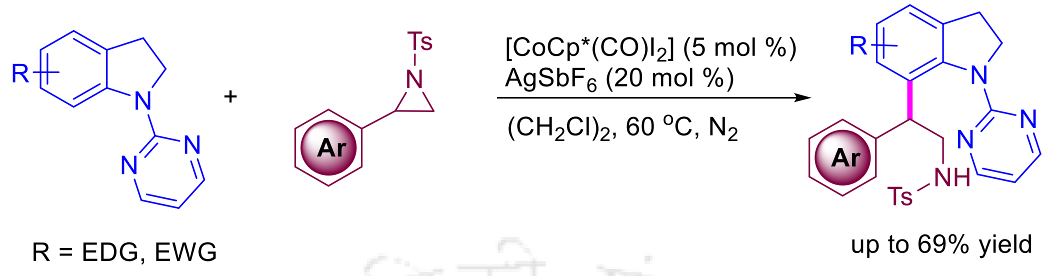


Chem. Commun. **2018**, *54*, 2494

Scheme 2. C-H Arylation of Indolines at the C7 Position under Co(II)-PCy_3 Catalyst

Chapter III. Cp*Co(III)-Catalyzed C-C Coupling of Indolines at C-7 Position with Aziridines *via* C-H Activation

Aziridines has recently been used as an appealing target for the selective synthesis of many diverse scaffolds due to the ring strain and electrophilic nature by merging C-H activation and ring-cleavage. In this direction, it can serve as an alkylating agent to construct bio-relevent β-branched amines in presence of transition metal catalyst. This chapter demonstrates air-stable Cp*Co(III)-catalyzed C7-alkylation of indolines with aziridines utilizing pyrimidyl directing group in the regime of concomitant C-H activation and ring opening (Scheme 3). The key findings involve use of cost-effective and air-stable cobalt catalysis, detection of a Co(III) intermediate, and late-stage removal of directing group.

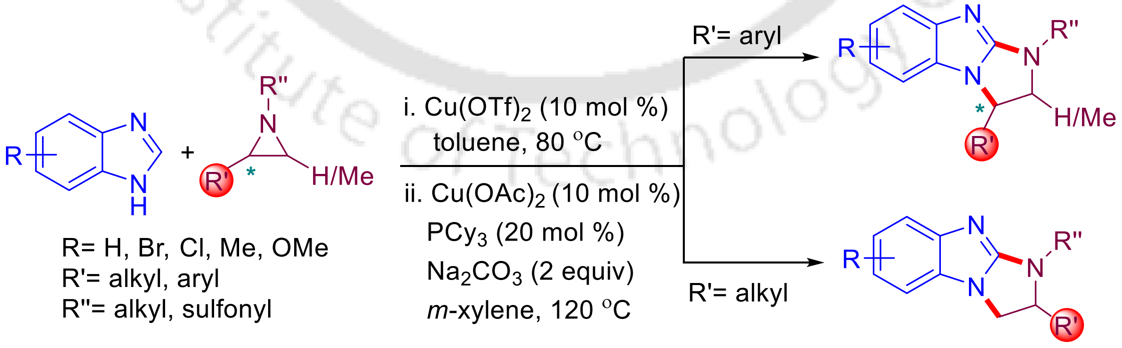


Manuscript submitted

Scheme 3. Co(III)-Catalyzed C7-Alkylation of Indolines with Aziridines

Chapter IV. Regioselective Cu(II)-Catalyzed Coupling of Aziridines with Benzimidazoles

Functionalized nitrogen and oxygen containing heterocycles play a predominant role in medicinal chemistry and have been extensively used as modular frameworks for drug development. In particular, imidazo-fused heterocycles such as tricyclic benzo imidazole derivatives exhibit antimycobacterial, anticancer, antiarrhythmic, analgesic, neuropsychiatric disorders and human TNF modulator. In this chapter, we disclosed an efficient synthetic route to functionalized dihydroimidazobenzimidazoles *via* copper(II)-catalyzed stereo-invertive coupling of 2-alkyl/-arylaziridines with benzimidazoles (Scheme 4). The use of relatively cheaper copper(II) catalyst, and air as an oxidant, regioselectivity and high enantiomeric purity are the significant practical features.



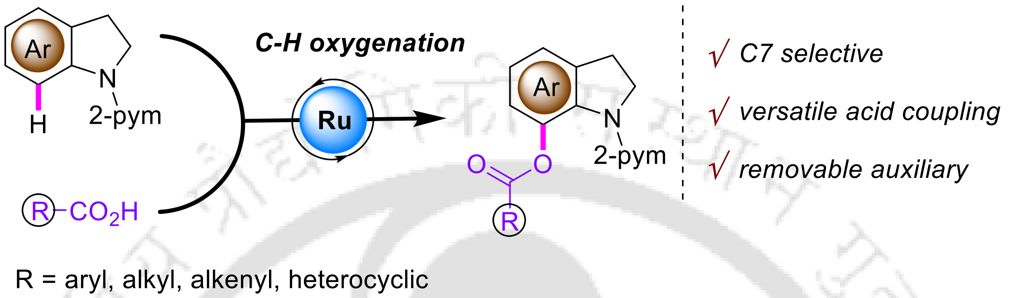
J. Org. Chem. **2017**, *82*, 3183

Scheme 4. Stereospecific Cu(II)-Catalyzed Intramolecular C-H Amination of Benzimidazoles

Contents

Chapter I

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



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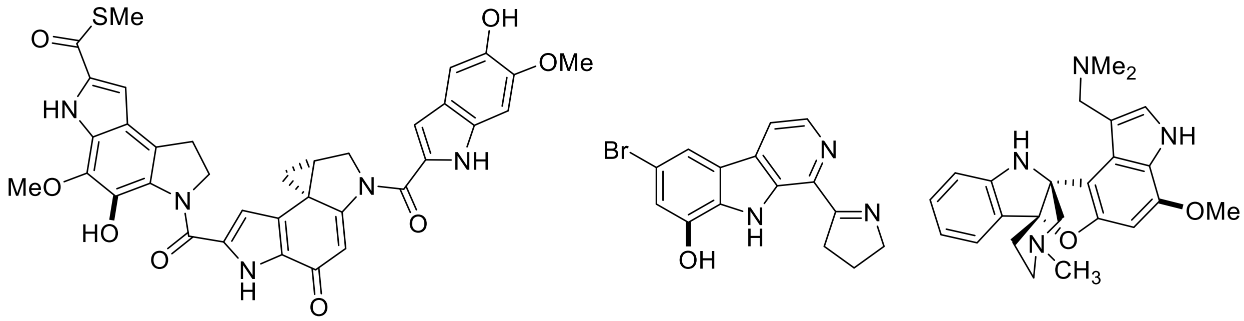
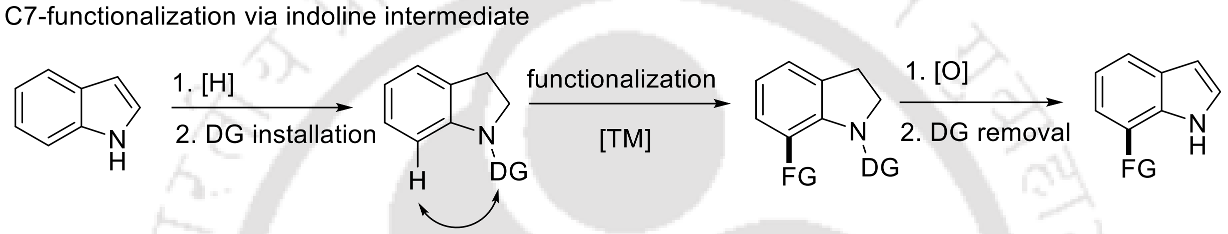
Ru(II)-Catalyzed C7-Acyloxylation of Indolines with Carboxylic Acids

Indoles and their synthetic scaffolds epitomize a class of privileged heterocycles present in a plethora of natural products and biologically active compounds[1]. It offers six distinctive sites for C-H bond functionalization and to this end transition-metal-catalyzed chelation assisted C-H functionalization has paved a unique pathway for further modification of its core moiety. The inherent reactivity of pyrrole type ring in indole drives functionalization at the C2 and C3 position and is well established.[2] Thus facilitating site-selective C-H functionalizations on the less reactive benzenoid ring has remained an inexplicable assignment owing to the selectivity concerns at C2, C3 and C7 positions. However, pushing selectivity towards C7 site over C2 position executes a significant task owing to the preferable realization of a five membered metallacycle at C2 position than the corresponding six membered metallacycle at C7 position (Scheme 1).[3] To resolve the selectivity issue, development of C7 functionalization of indoles enabling site-selective C-H activation is approved by installing directing group at the *N*-atom of indolines followed by oxidation and late-stage auxiliary removal. Current developments focuses on the carbon-carbon and carbon-heteroatom bond formation to diversify the indoles at the C7-H bond employing various transition-metal-catalysts (Scheme 2).[4,5] Among them, C-H acyloxylation is attractive due to the prevalence of C-O bond in pharmaceutical and material sciences (Figure. 1).[6] Several studies on acyloxylation of C−H bonds have been described utilizing Pd-and Cu-based catalytic systems with $PhI(OAc)_2$,[7] anhydride,[8] *tert*-butyl peroxyacetate,[9a] sodium carboxylate[9b] and acid halide.[9c] However, the directed acyloxylation of C−H bonds with carboxylic acid as an acyl source is scarce.[10] Hitherto, this type of transformation has been successfully achieved by using mostly Rh, Ru, Pd, Cu and Co catalysts. Importantly, the reaction of carboxylic acids as oxygenating source is attractive as it is less expensive, minimally toxic and atom economical. This chapter describes Ru(II)-catalyzed C7-oxygenation of indolines with versatile carboxylic acids and consequent oxidation to yield C7-oxygenated indole.

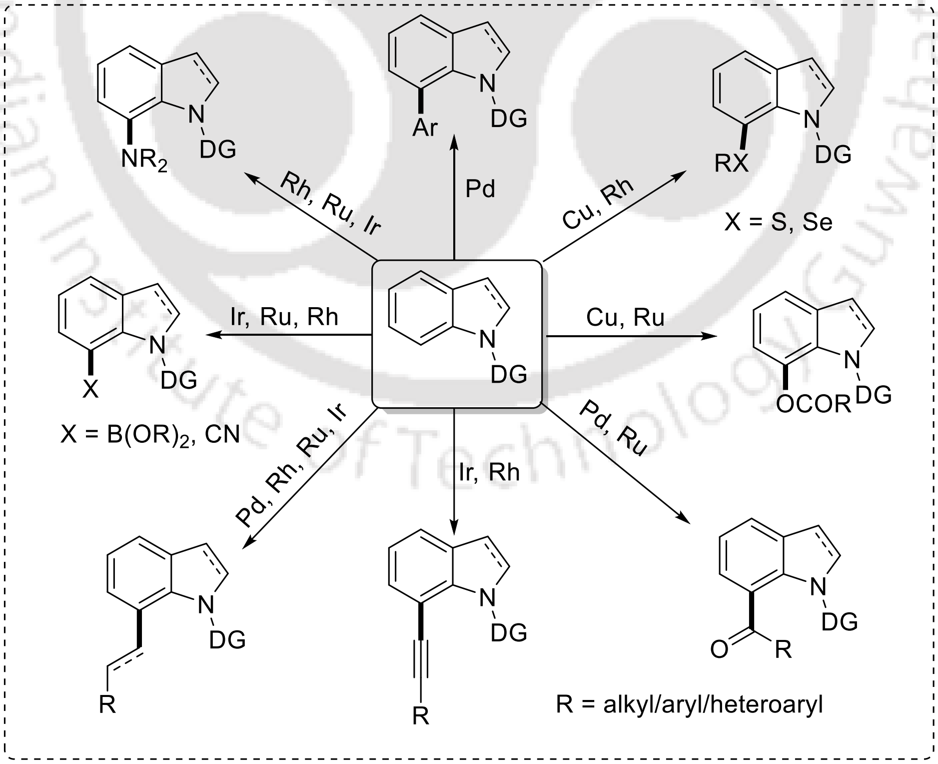


(+)-Yatakemycin Eudistomidin-A Phalarine

Figure 1. Representative examples of bio-active compounds



Scheme 1. Achieving Regioselective C7-Functionalization of Indoles

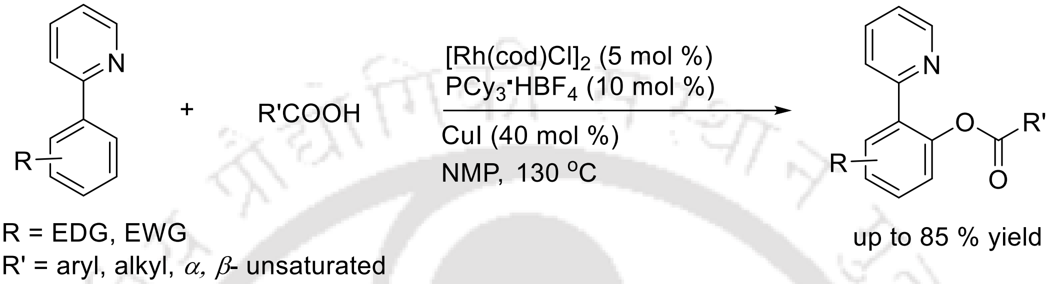


Scheme 2. Transition-Metal-Catalyzed C7 Functionalization of Indoles/Indolines

1.1 Literature

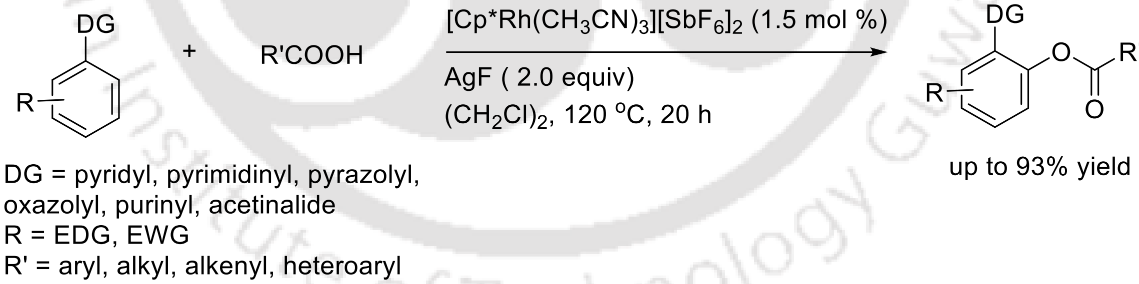
1.1.1 Rh-Catalyzed C-H Oxygenation of Arenes

Cheng and co-workers reported a Rh(I)-catalyzed direct *ortho*-acyloxylation of aromatic C-H bond at high temperature providing corresponding esters in moderate yields (Scheme 3).[11] The reaction offers broad substrate scope as alkyl and *α, β*-unsaturated carboxylic acids are well tolerated.



Scheme 3. Rh-Catalyzed C-H Oxygenation of 2-Aryl Pyridines

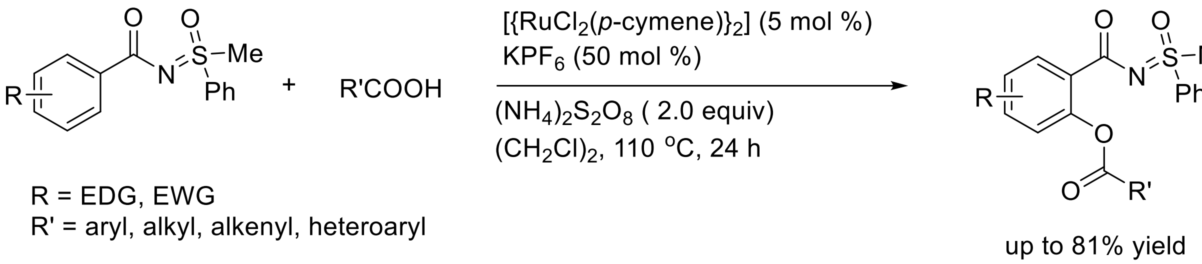
Li and co-workers established direct regioselective oxygenation of sp^2 C-H bonds with various carboxylic acids utilizing variety of *N*- and *O*-coordinating directing groups employing a cationic Rh(III)-complex and silver source as an oxidant (Scheme 4).[12] The authors extended the synthetic utility of this protocol for the late-stage modification of many biologically active compounds such as fenbufen, dehydrocholic acid and glycyrrhetinic acid.



Scheme 4. Directed Rh-Catalyzed C-H Oxygenation with Carboxylic Acids

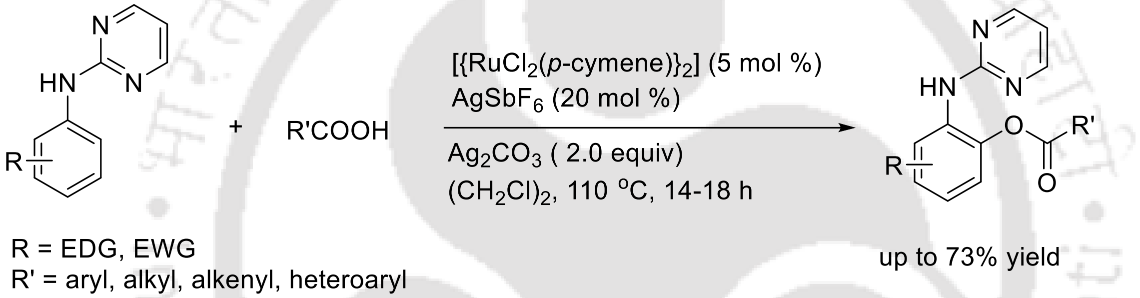
1.1.2 Ru-Catalyzed C-H Oxygenation of Arenes

Ackermann and co-workers developed a Ru(II)-catalyzed *ortho* C-H oxygenation of sufoximines with diverse (hetero)aromatic carboxylic acids in moderate to good yields (Scheme 5).[13] The final product can be easily transformed into the corresponding salicylic acids under acidic conditions.



Scheme 5. Regioselective Ru-Catalyzed C-H Oxygenation of Sulfoximines

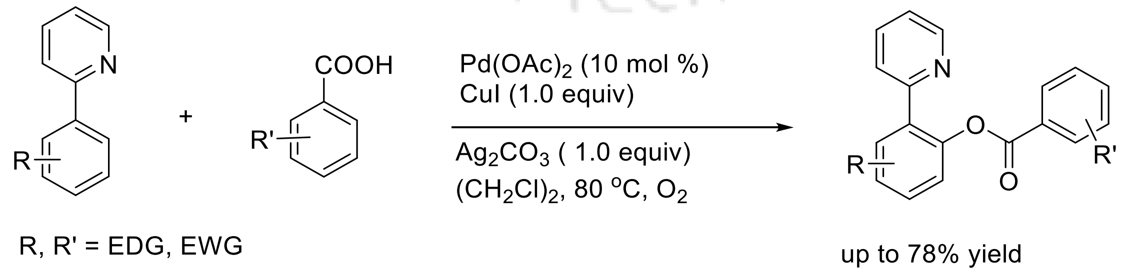
Our group reported a Ru-catalyzed positional selective C–H acyloxylation of *N*-aryl-2-pyrimidines with carboxylic acids in the presence of $AgSbF_6$ as an additive (Scheme 6).[14] Several alkyl, aryl, heteroaryl and *α,β*–unsaturated carboxylic acids, and a series of functionalized N-aryl-2-pyrimidines were utilized to found the general applicability of the methodology.



Scheme 6. *Ortho*-Selective C-H Oxygenation using Ru-Catalysis

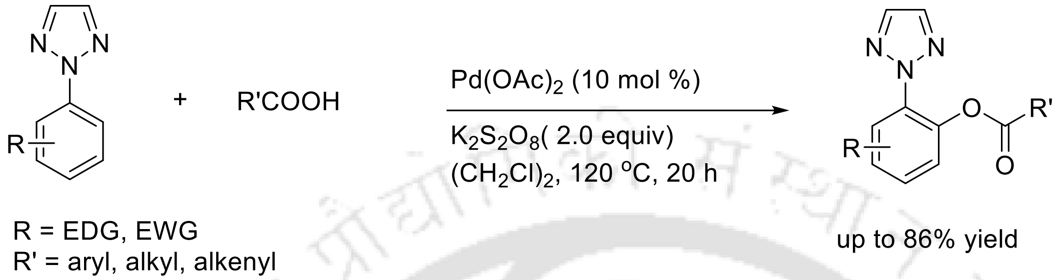
1.1.3 Pd-Catalyzed C-H Acyloxylation of Arenes

Zhong and co-workers demonstrated *ortho*-selective benzoxylation of 2-phenyl pyridines with aromatic carboxylic acids utilizing Pd(II) catalysis in $(CH_2Cl)_2$ under oxygen atmosphere (Scheme 7).[15] Both electron-donating and electron-withdrawing 2-arylpyridines showed good reactivity in this regioselective protocol. However, strong electron-withdrawing carboxylic acids (e.g., NO_2) failed to account for the desired product.



Scheme 7. Pd-Catalyzed C-H Benzoxylation of 2-Aryl Pyridines

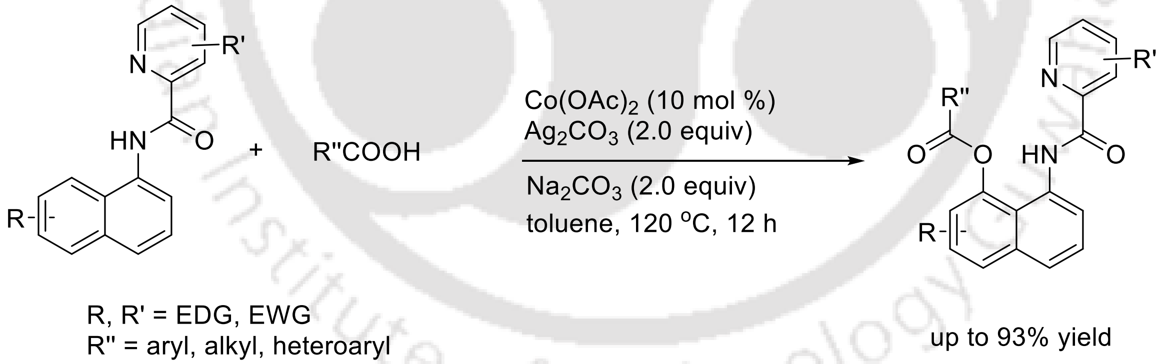
A Pd(II)-catalyzed *ortho*-acyloxylation of 2-substituted 1,2,3-triazoles with aryl, alkyl and alkenyl carboxylic acids was presented by Wang group (Scheme 8).[16] A higher kinetic isotope effect ($k_H/k_D = 3.0$) was obtained, suggesting that the cleavage of C–H bond was involved in the rate determining step.



Scheme 8. Regioselective Pd-Catalyzed C-O Coupling with Carboxylic Acids

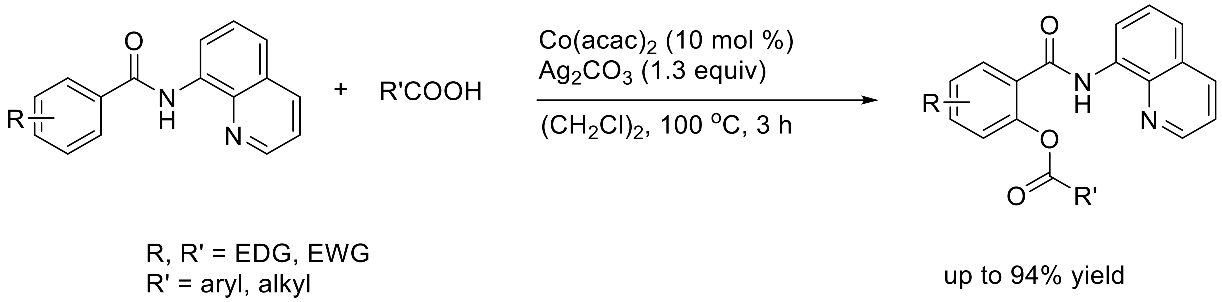
1.1.4 Co-Catalyzed C-H Acyloxylation of Arenes

Zeng and co-workers reported a Co(II)-catalyzed C-O bond formation through C-H oxygenation employing alkyl/aryl/heteroaryl carboxylic acids to produce the corresponding mono-acyloxylated product in moderate to good yields (Scheme 9).[17] However, 4-nitro-2-pyridyl carboxamide and 4-alkoxybenzoic acid failed to produce oxygenated product under this reaction system.



Scheme 9. Positional-Selective Co-Catalyzed C-H Acyloxylation

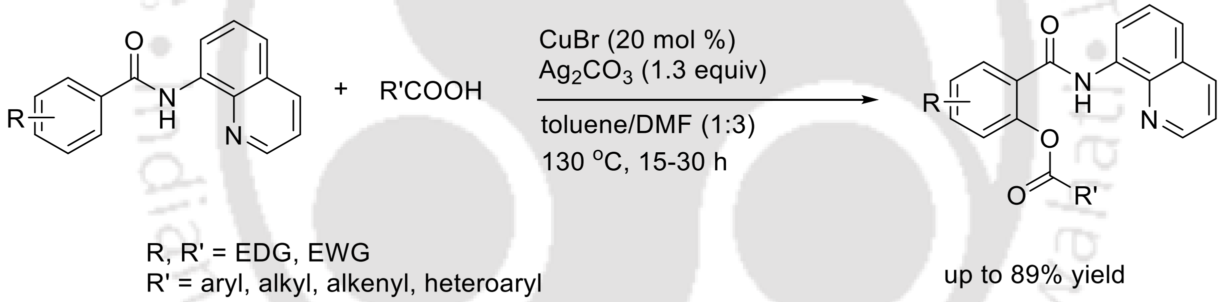
Chatani and co-workers reported that the reaction of *N*-(quinolin-8-yl)benzamides with aryl and alkyl carboxylic acids in the presence of $Co(acac)_2$ as catalyst and Ag_2CO_3 in $(CH_2Cl)_2$ under air leads to the formation of mono-acyloxylated N-(quinolin-8-yl)benzamide derivatives in relatively low to excellent yields (Scheme 10).[18] The use of cost-effective and minimally toxic cobalt catalyst and broad substrate scope with electronically dissimilar functional groups are the important practical features.



Scheme 10. Co-Catalyzed C-H Oxygenation of N-(quinolin-8-yl)benzamides

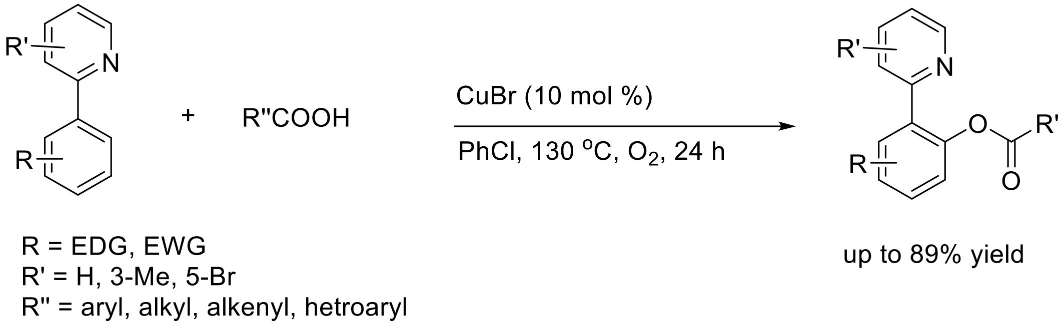
1.1.5 Cu-Catalyzed C-H Acyloxylation of Arenes

An efficient directed C–O coupling of *N*-(quinolin-8-yl)benzamides with various carboxylic acids was reported utilizing commercially available Cu(I)-catalyst and Ag_2CO_3 as oxidant in the binary toluene/DMF at elevated temperature by Zhang group (Scheme 11).[19a] The effect of directing group, radical scavenger experiment and kinetic studies were investigated to understand the reaction mechanism.



Scheme 11. *Ortho*-Selective C-H Oxygenation by Cu-Catalysis

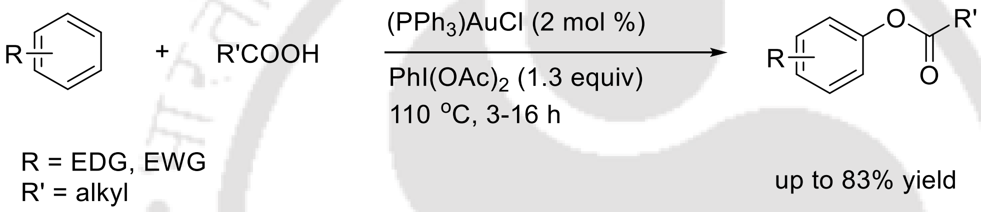
The same group explored a Cu-catalyzed *ortho* C–H oxygenation of 2-arylpyridines with carboxylic acids using oxygen as the oxidant (Scheme 12).[19b] The authors showed that 2-arylpyridines bearing electron-donating groups gave relatively higher yields compared to the electron-withdrawing ones. Moreover, aryl carboxylic acids were found to be more reactive as compared to alkyl carboxylic acids in terms of stabilization of conjugate base of corresponding acids.



Scheme 12. Cu-Catalyzed C-H Oxygenation of 2-Aryl Pyridines

1.1.6 Au-Catalyzed C-H Benzoxylation of Arenes

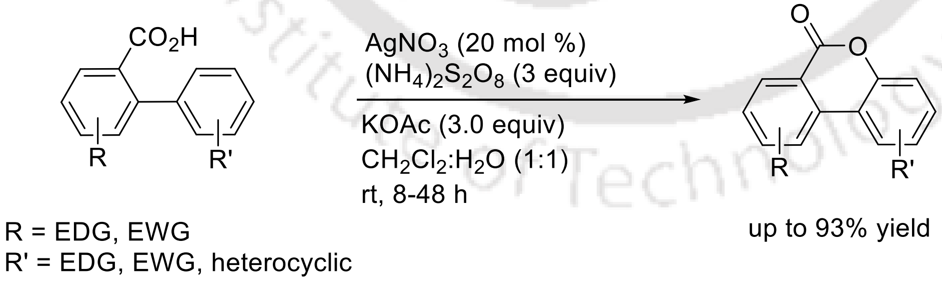
Michelet and co-workers developed a Au-catalyzed direct C-H acyloxylation of arenes with alkyl carboxylic acids employing PhI(OAc)$_2$ as an oxidant under solvent free conditions (Scheme 13).[20]



Scheme 13. Au-Catalyzed C-H Acyloxylation of Arenes

1.1.7 Ag-Catalyzed C-O Cross-Coupling of Arenes

Xu and co-workers demonstrated an intramolecular C-O bond formation of biaryl-2-carboxylic acids *via* C–H functionalization using silver catalyst to afford corresponding lactones (Scheme 14).[21] This protocol was also applicable for larger-scale synthesis.



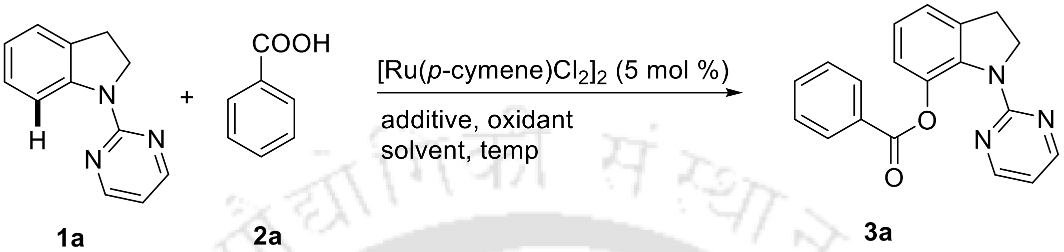
Scheme 14. Ag-Catalyzed Intramolecular C-H Oxygenation to Lactones

1.2 Present Study

We here present C7-oxygenation of *N*-pyrimidylindolines utilizing a variety of carboxylic acids as an oxygenating source under Ru(II)-catalysis. This reaction offers broad substrate scope as alkyl, aryl, alkenyl and heterocyclic organic acids are well tolerated with broad functional group diversity. Our optimization studies initiated by employing *N*-pyrimidyl indoline **1a** with benzoic acid **2a** as the model substrates using Ru(II) as catalyst with diverse additives, oxidants and solvents at various temperature (Table 1). Delightfully, the C7 oxygenated indoline **3a** was formed in 7% yield utilizing 5 mol % [Ru(*p*-cymene)Cl_2]$_2$ and 20 mol % KPF_6 as an additive in $(CH_2Cl)_2$ at 100 °C. Upon addition of 2 equiv Ag_2CO_3 as an oxidant, the yield dramatically improved to 64%, whereas $Cu(OAc)_2$•H_2O, $K_2S_2O_8$ and $Na_2S_2O_8$ furnished inferior results (entries 2-5). Among the additives screened, $AgSbF_6$ gave 77% yield, whereas NaOAc offorded 34% yield (entries 6-7). $(CH_2Cl)_2$ was found to be the optimal solvent, while toluene, DMSO and 1,4-dioxane produced <48% yield (entries 8-10). Varying the reaction temperature (80 °C and 120 °C) led to the drop in the yield to 51% (entry 11-12). A control experiment in the absence of the Ru-catalyst showed no desired C-H oxygenated product (entry 13). To disclose the reactivity mode of the directing group, the reaction was executed by incorporating *O*-co-ordinating groups on the *N*-atom of indoline, such as acetyl (**1A'**), pivalyl (**1B'**), *N*,*N*-dimethyl carbamoyl (**1C'**) and boc (**1D'**) (Scheme 15). The substrates **1A'-C'** were successful to afford **3A'-C'** in 46-62% yields, while **1D'** did not produce the target product.

With the optimal reaction conditions, we explored the substrate scope using variously substituted carboxylic acids with indoline **1a** as a representative substrate (Scheme 16). Both electron-donating and electron-withdrawing groups were compatible under the given reaction conditions. *Ortho*-substituted benzoic acids such as 2-chloro **2b** and 2-iodo **2c** underwent reaction to deliver **3b** and **3c** in 73 and 55% yields, respectively. Gratifyingly, medicinally important drug aspirin **2d** was effectively survived to construct **3d** in 40% yield. Similar results were observed with substituted benzoic acids at the *meta*-position, such as 3-chloro **2e**, 3-methyl **2f** and 3-methoxy **2g** groups, giving **3e-g** in 68-73% yields. Similarly, *para*-substituted benzoic acids such as chloro **2h**, fluoro **2i**, methyl **2j** and nitro **2k** groups underwent coupling to afford **3h-k** in 74-81% yields. A strong electron-withdrawing group, 4-CF_3 substituted benzoic acid **2l** was also reacted smoothly to provide **3l** in 80% yield. Moreover, di-substituted benzoic acid bearing 3,4-dimethyl group **2m** and 1-naphthoic acid **2n** underwent reaction to furnish **3m** and **3n** in 69 and 54% yields, respectively. The heterocyclic coupling partners like 2-thienyl carboxylic acid **2o** was also operative, giving **3o** in 64% yield, while picolinic acid **2p** and isonicotinic acid **2q** failed to provide the desired product **3p-q**, owing to chelation of nitrogen lone pair with the Ru-complex.

Table 1. Optimization of Reaction Conditions[a]

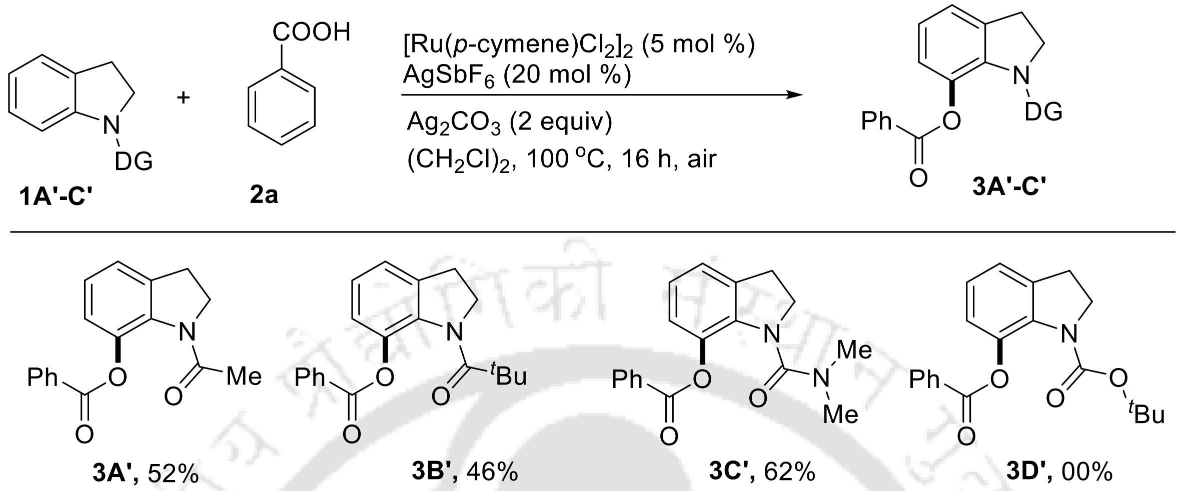


Entry	Additive	Oxidant	Solvent	Yield(%)[b]
1	KPF_6	-	$(CH_2Cl)_2$	7
2	KPF_6	Ag_2CO_3	$(CH_2Cl)_2$	64
3	KPF_6	$Cu(OAc)_2•H_2O$	$(CH_2Cl)_2$	trace
4	KPF_6	$K_2S_2O_8$	$(CH_2Cl)_2$	13
5	KPF_6	$Na_2S_2O_8$	$(CH_2Cl)_2$	n.d.
6	$AgSbF_6$	Ag_2CO_3	$(CH_2Cl)_2$	77
7	NaOAc	Ag_2CO_3	$(CH_2Cl)_2$	34
8	$AgSbF_6$	Ag_2CO_3	toluene	48
9	$AgSbF_6$	Ag_2CO_3	DMSO	9
10	$AgSbF_6$	Ag_2CO_3	1,4-dioxane	6
11	$AgSbF_6$	Ag_2CO_3	$(CH_2Cl)_2$	51[c]
12	$AgSbF_6$	Ag_2CO_3	$(CH_2Cl)_2$	74[d]
13[e]	$AgSbF_6$	Ag_2CO_3	$(CH_2Cl)_2$	n.d.

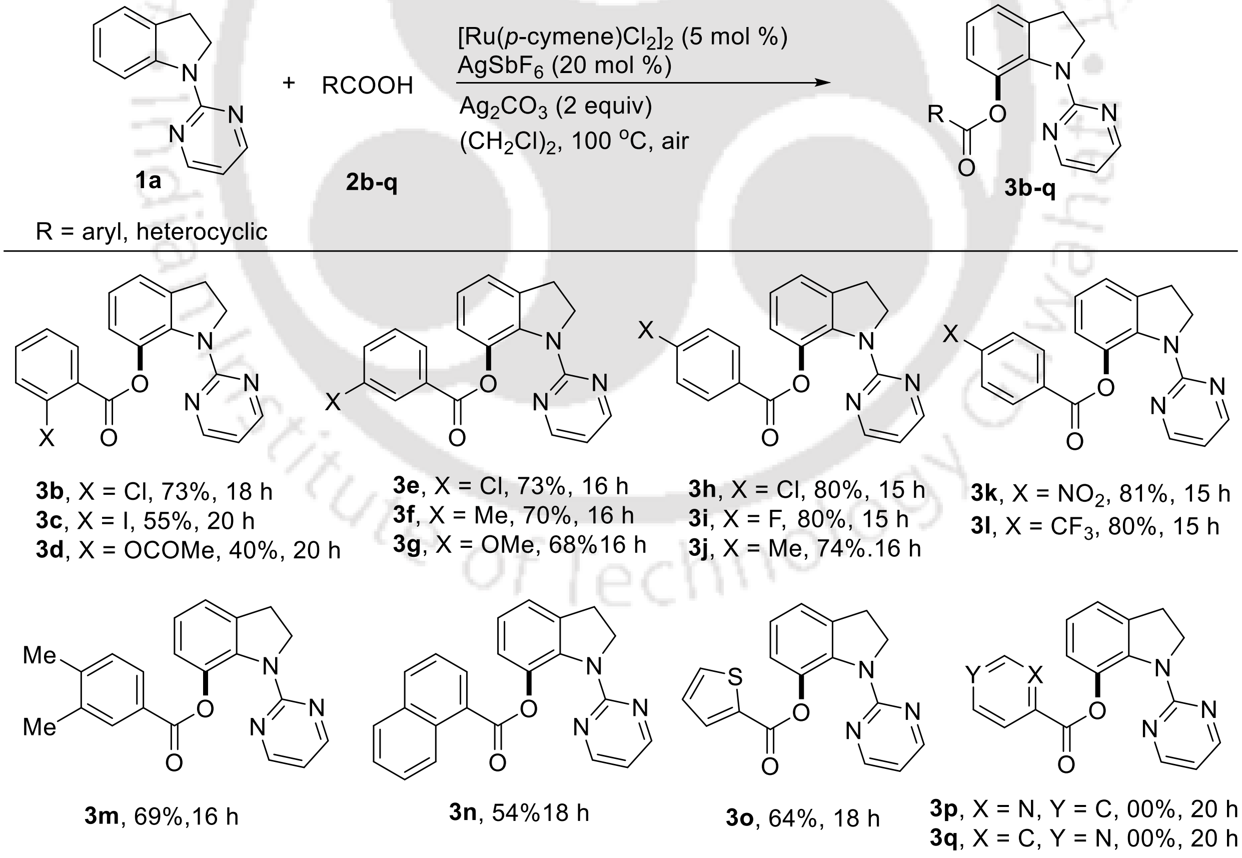
[a]Reaction conditions: **1a** (0.2 mmol), **2a** (0.4 mmol), [Ru(*p*-cymene)Cl_2]$_2$ (5 mol %), additive (20 mol %), oxidant (2 equiv), solvent (2 mL), 100 °C, 16 h. [b]Isolated yield. [c]Reaction at 80 °C. [d]Reaction at 120 °C. [e]Without [Ru] catalyst. n.d. = not detected.

However, the coupling of *α,β*-unsaturated and alkyl carboxylic acids can be readily accomplished (Scheme 17). For example, crotonic acid **2r** and cinnamic acid **2s** underwent reaction to produce **3r** and **3s** in 65 and 67% yields, whereas ethanoic acid **2t**, pivalic acid

2u and 1-adamentylcarboxylic acid **2v** delivered the corresponding oxygenated product **3t-v** in 69-70% yields.

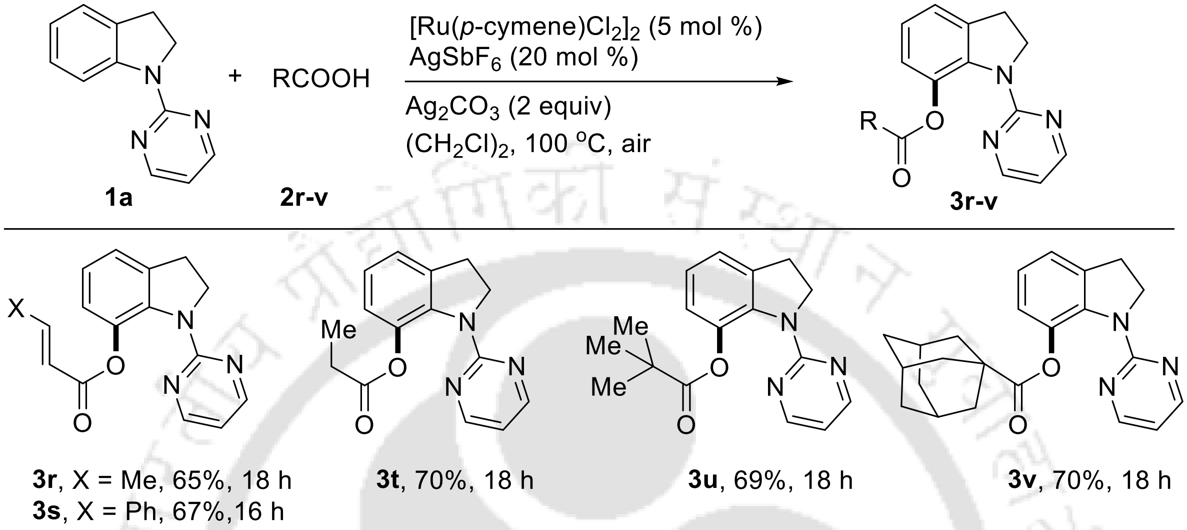


Scheme 15. Screening of Directing Groups



Reaction Conditions: **1a** (0.2 mmol), **2b–q** (0.4 mmol), [Ru(*p*-cymene)Cl_2]$_2$ (5 mol %), $AgSbF_6$ (20 mol %), Ag_2CO_3 (0.4 mmol), $(CH_2Cl)_2$ (2 mL),100 °C, 15–20 h.

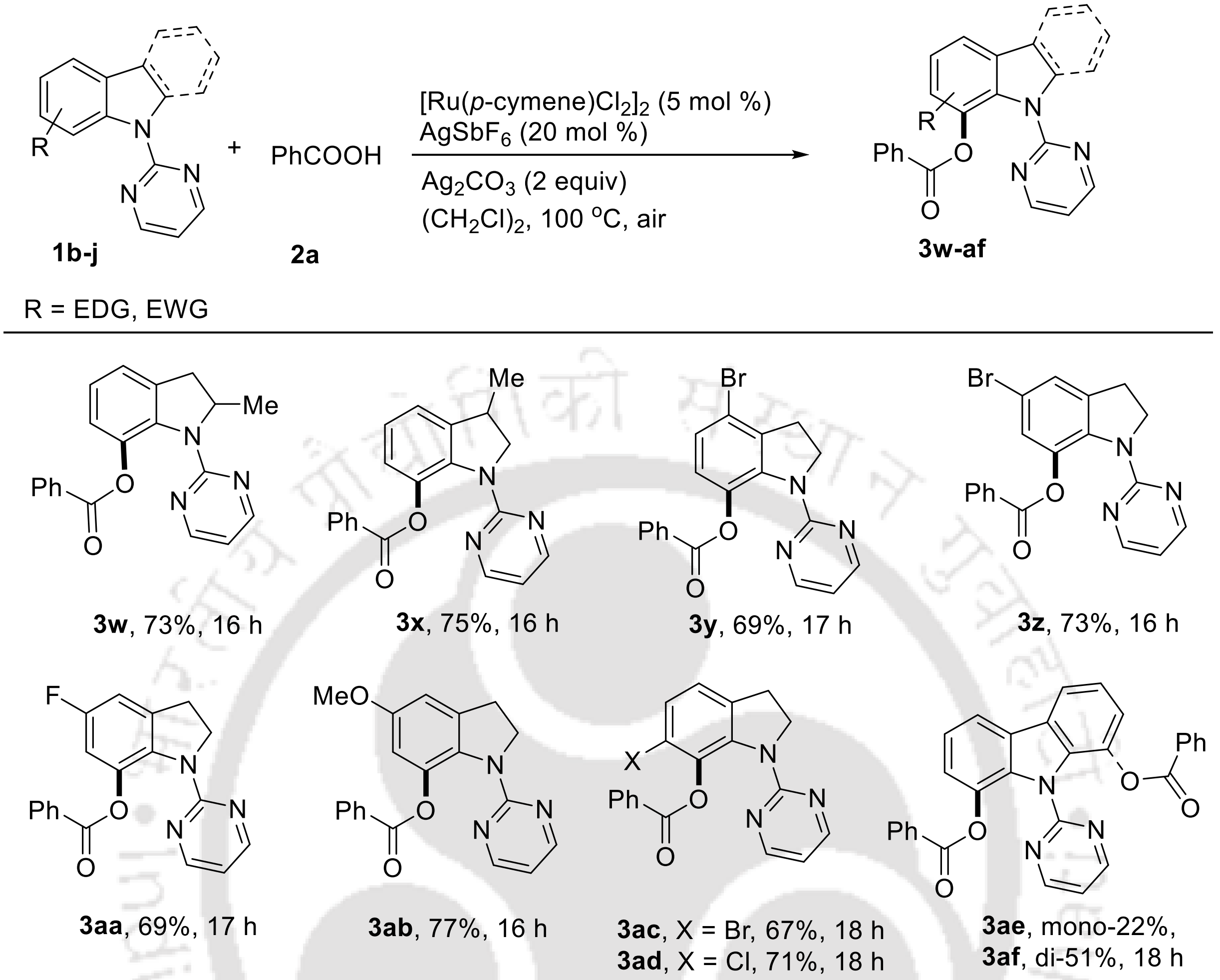
Scheme 16. Substrate Scope of Aryl Carboxylic Acids **2b-q** with Indoline **1a**



Reaction Conditions: **1a** (0.2 mmol), **2r–v** (0.4 mmol), [Ru(*p*-cymene)Cl_2]$_2$ (5 mol %), $AgSbF_6$ (20 mol %), Ag_2CO_3 (0.4 mmol), $(CH_2Cl)_2$ (2 mL),100 °C, 15–20 h.

Scheme 17. Substrate Scope of Alkyl Carboxylic Acids **2r-v** with Indoline **1a**

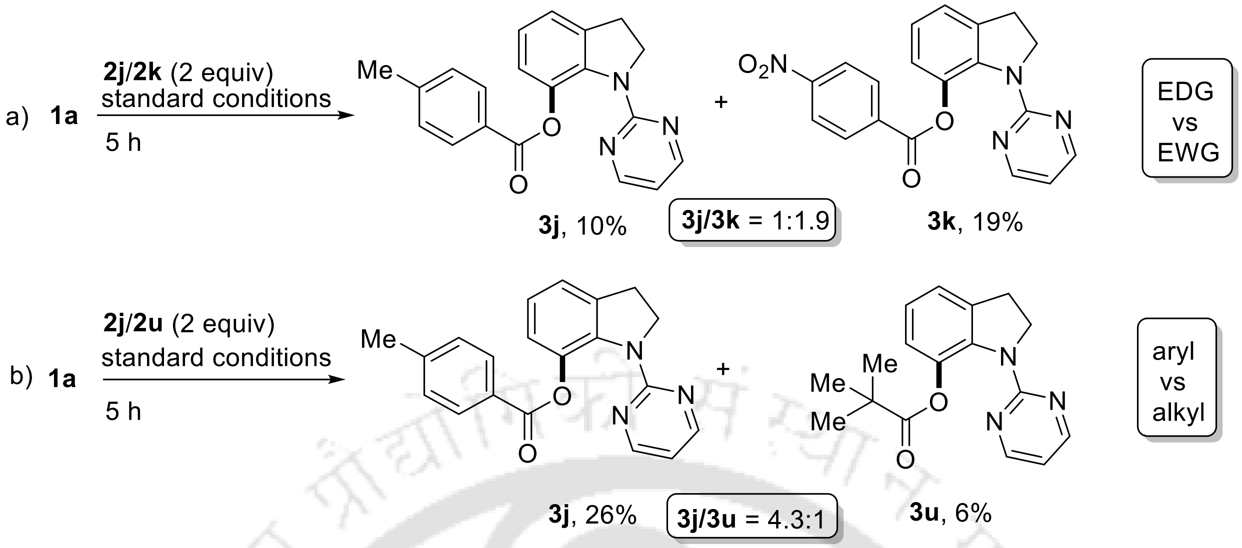
Finally, the substrate scope with respect to electronically varied indolines was surveyed using benzoic acid **2a** as a representative substrate (Scheme 18). Various functionalities ranging from 2 to 6 positions on the indoline moiety responded smoothly to provide the target oxygenated product. Indolines bearing 2-methyl **1b**, 3-methyl **1c** and 4-bromo **1d** substituents delivered the target products **3w-y** in 69-75% yields. Further, 5-substituted indolines with bromo **1e**, fluoro **1f** and methoxy **1g** groups underwent reaction to furnish **3z-ab** in 69-77% yields. The sterically challenging indoline substrates having 6-bromo **1h** and 6-chloro **1i** groups were found to be well tolerated under this optimal conditions, giving **3ac** and **3ad** in 67 and 71% yields, respectively. Additionally, the acetoxylation of a carbazole derivative **1j** was amenable delivering **3ae** (mono) in 22% yield and **3af** (di) in 51% yield, respectively.



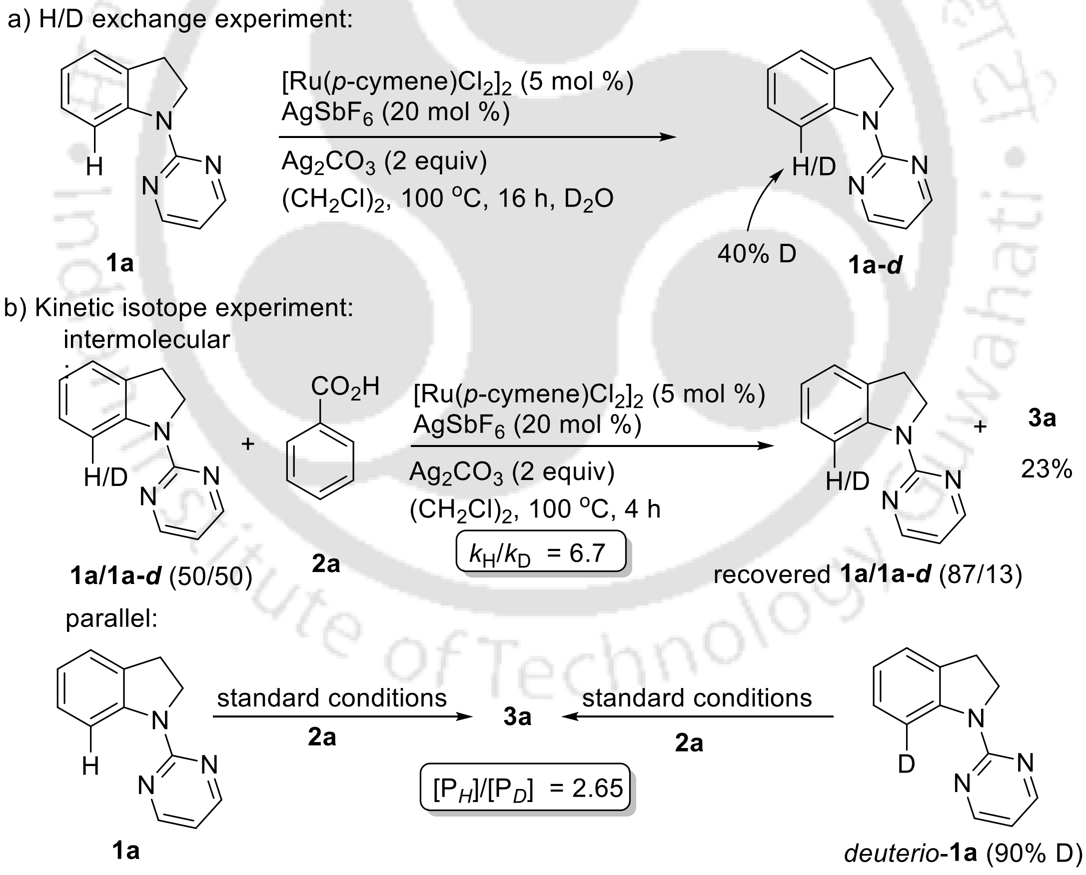
Reaction Conditions: **1b-j** (0.2 mmol), **2b** (0.4 mmol), [Ru(*p*-cymene)Cl_2]$_2$ (5 mol %), $AgSbF_6$ (20 mol %), Ag_2CO_3 (0.4 mmol), $(CH_2Cl)_2$ (2 mL),100 °C, 15–20 h.

Scheme 18. Substrate Scope of Indolines **1b-j** with Benzoic Acids **2a**

To shed light in the reaction mechanism, intermolecular competitive experiments have been achieved using electronically different benzoic acids **2j** and **2k** with indoline **1a** as a representative substrate. The results disclosed that electron-deficient benzoic acid reacts at a higher rate which may be reflected in terms of lower pK_a value of *p*-NO_2-benzoic acid **2k** (Scheme 19a). Additionally, the competition experiment between aryl and alkyl carboxylic acids **2j** and **2u** revealed that the former facilitates the reaction to a greater extent, due to the resonance stabilization of the corresponding conjugate base of the acid (Scheme 19b). A significant H/D exchange (40%) was perceived at the C7 position of indoline using D_2O as the co-solvent, confessing the reversibility of the C-H bond cleavage (Scheme 20).



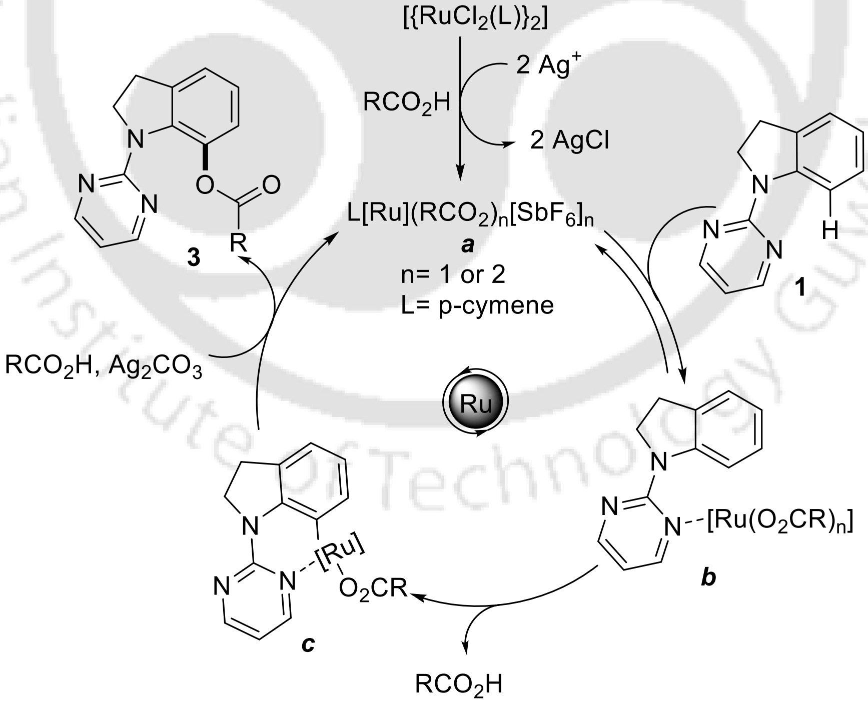
Scheme 19. Competitive Experiment



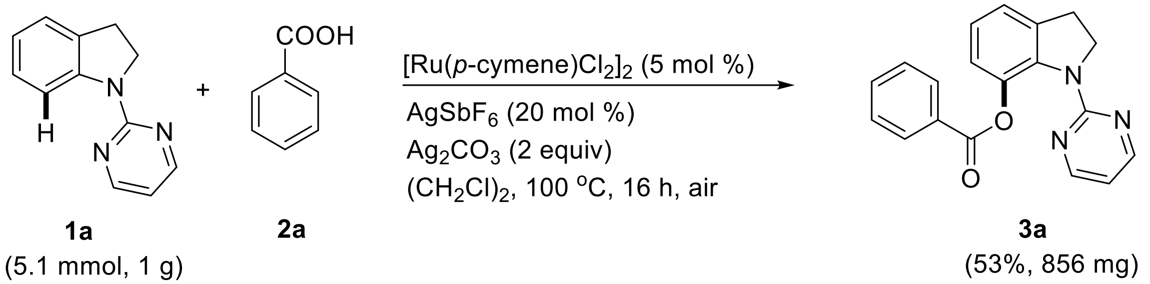
Scheme 20. Kinetic Isotope Experiments

Further, kinetic isotope experiments using **1a** and **1a-*d*** with **2a** in one pot (k_H/k_D = 6.7) and parallel (k_H/k_D =2.65) suggests that the C−H bond cleavage may be involved in the rate-determining step. Thus, the reactive Ru(II) carboxylate ***a*** may originate from the reaction of [Ru(*p*-cymene)Cl_2]$_2$ with silver salt (Scheme 21). Chelation of the pyrimidyl-nitrogen of **1** with Ru(II) carboxylate ***a*** may produce intermediate ***b*** along with exclusion of RCOOH to yield a six-membered ruthenacycle ***c*** *via* C-H activation. Further, reductive elimination of the intermediate **c** may deliver the functionalized product **3** and regenerate the catalyst upon oxidation with silver salt to complete the catalytic cycle.

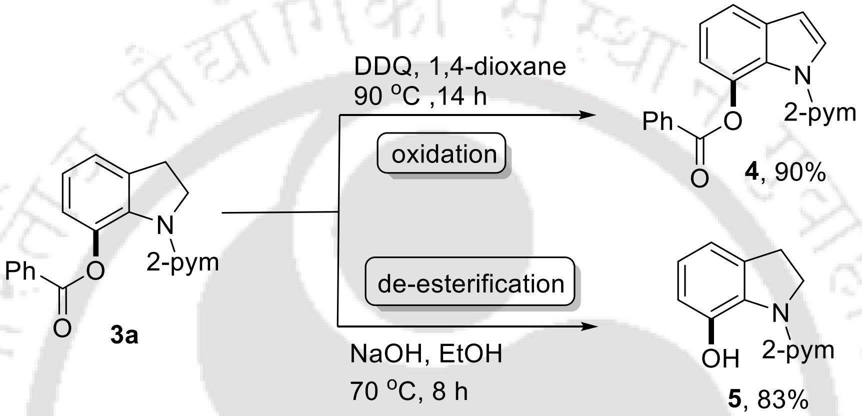
To disclose the scale-up of this protocol, the reaction of **1a** with **2a** was examined as the representative example (Scheme 22). The reaction readily occurred to furnish **3a** in 53% yield, which suggests that the reaction can be employed for the gram scale synthesis. Finally, compound **3a** was further oxidized to construct indole **4** in presence of DDQ, providing 90% yield. Additionally, the ester can be hydrolysed utilizing base to produce 7-hydroxy indole **5** in 83% yield (Scheme 23).



Scheme 21. Plausible Catalytic Cycle



Scheme 22. Gram-Scale Synthesis of **3a**



Scheme 23. Post-Synthetic Application

In conclusion, we have established a Ru(II)-catalyzed C7-acyloxylation of indolines with carboxylic acids as oxygenating source under air and consequent oxidation to yield C7-oxygenated indole. Aryl, alkyl *α,β*-unsaturated and heterocyclic carboxylic acids can be proficient under this reaction conditions.

1.3 Experimental Section

General Information. 2-Chloropyrimidine (95%), [Ru(*p*-cymene)Cl$_2$]$_2$, AgSbF$_6$ (98%), KPF$_6$ (≥99%), Ag$_2$CO$_3$ (99%), Cu(OAc)$_2$·2H$_2$O and DDQ (98%) were purchased from Aldrich. NaCNBH$_3$ was procured from Spectrochem. K$_2$S$_2$O$_8$ and Na$_2$S$_2$O$_8$ were obtained from Molychem. Merck silica gel G/GF 254 plates were utilized for analytical TLC. Rankem silica gel (100-200 mesh) was employed for column chromatography. DRX-400 Varian, and Bruker Avance III 600 and 400 spectrometers were used for recording NMR (^{1}H and ^{13}C) spectra utilizing CDCl$_3$ as solvent and TMS as an internal standard. Chemical shifts (δ) and spin-spin coupling constant (*J*) are reported in ppm and in 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. FT-IR spectra were collected on PerkinElmer IR spectrometer. Q-Tof ESI-MS instrument (model HAB 273) was used mass spectra.

General Procedure for the Preparation of *N*-Pyrimidyl Indolines 1. Indole (5.0 mmol) and $NaBH_3CN$ (25.0 mmol) were stirred in AcOH (25 mL) at room temperature. The progress of the reaction was monitored using TLC with ethyl acetate and hexane as an eluent. The resultant mixture was treated with water (15 mL) and neutralized using aq. NaOH. The solution was extracted with ethyl acetate (3 x 30 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 to give indoline. Indoline (1.0 mmol) was then stirred with 2-chloropyrimidine (1.2 mmol) at 100 ^{o}C in DMSO (3 mL). The reaction was monitored using TLC with a mixture of ethyl acetate and hexane. After completion, the reaction mixture was diluted with ethyl acetate (30 mL) and 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 1-(pyrimidin-2-yl)indoline.

General Procedure for Ruthenium(II)-Catalyzed C7-Oxygenation of Indolines. To a stirred solution of 1-(pyrimidin-2-yl)indoline (0.2 mmol), $[Ru(p\text{-cymene})Cl_2]_2$ (5 mol %, 0.01 mmol, 6.1 mg), $AgSbF_6$ (20 mol%, 0.04 mmol, 13.7 mg) and Ag_2CO_3 (2 equiv, 0.4 mmol, 110.2 mg) in $(CH_2Cl)_2$ (2 mL) under air, carboxylic acid (0.4 mmol) was added. The resultant mixture was stirred at 100 ^{o}C and the progress of the reaction was monitored by TLC using a mixture of ethyl acetate and hexane. The reaction mixture was then diluted with dichloromethane (30 mL) and passed through a short pad of celite. 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 C7 oxygenated indolines.

Procedure for the Synthesis of 1-(Pyrimidin-2-yl)-1H-indol-7-yl benzoate 4. To a stirred solution of 1-(pyrimidin-2-yl)indolin-7-yl benzoate **3a** (0.1 mmol, 31.7 mg) in 1,4-dioxane, DDQ (0.2 mmol, 45.4 mg) was added at room temperature. The resultant solution was further stirred at 90 ^{o}C for 14 h. After completion, as indicated by TLC, the reaction mixture was cooled to room temperature and diluted with ethyl acetate (15 mL). The mixture was successively 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 gel column chromatography using *n*-hexane and ethyl acetate as an eluent to afford 1-(pyrimidin-2-yl)-1H-indol-7-yl benzoate **4** as a colorless liquid in 84% yield (56.7 mg).

Procedure for the Synthesis of 1-(Pyrimidin-2-yl)indolin-7-ol 5. 1-(Pyrimidin-2-yl)indolin-7-yl benzoate **3a** (0.1 mmol, 31.7 mg) and NaOH (40% solution, 2 mL) (2 mL) were stirred at 70 ^{o}C for 2 h in ethanol (4 mL). The resultant mixture was treated with water (2 mL) and the stirring was continued at 70 ^{o}C for 6 h. After completion, as indicated by TLC, the reaction mixture was neutralized using 1N HCL. Ethanol was removed on a rotary evaporator and aqueous solution was extracted with ethyl acetate (3 x 15 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 1-(pyrimidin-2-yl)indolin-7-ol **5** as a yellow solid in 83% yield (42.6 mg).

Competition Experiment using Acids 2j and 2k. 1-(Pyrimidin-2-yl)indoline **1a** (19.7 mg, 0.1 mmol), **2j** (13.6 mg, 0.1 mmol), **2k** (16.7 mg, 0.1 mmol), $[RuCl_2(p\text{-cymene})]_2$ (3.0 mg, 5.0 mol %), $AgSbF_6$ (7.0 mg, 20 mol %) and Ag_2CO_3 (55.2 mg, 0.2 mmol) in $(CH_2Cl)_2$ (1.0 mL) were subjected to the reaction conditions described in the general procedure (100 ^{o}C) for 5 h and **3j** and **3k** were formed in 10 and 19% yields, respectively.

Competition Experiment using Acids 2j and 2u. The reaction of 1-(pyrimidin-2-yl)indoline **1a** (19.7 mg, 0.1 mmol) was performed with **2j** (13.6 mg, 0.1 mmol) and **2u** (10.2 mg, 0.1 mmol) in the presence of $[RuCl_2(p\text{-cymene})]_2$ (3.0 mg, 5.0 mol %), $AgSbF_6$ (7.0 mg, 20 mol %) and Ag_2CO_3 (55.2 mg, 0.2 mmol) for 5 h in $(CH_2Cl)_2$ (1.0 mL) as described above to produce **3j** and **3u** in 26 and 6% yields, respectively.

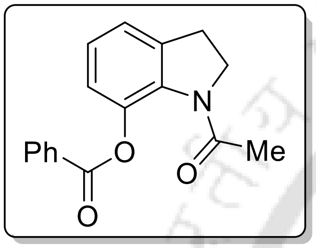
H/D Exchange with D_2O. 1-(Pyrimidin-2-yl)indoline **1a** (19.7 mg, 0.2 mmol), [$RuCl_2$(*p*-cymene)$]_2$] (6.0 mg, 5.0 mol %), $AgSbF_6$ (13.7 mg, 20 mol %) and Ag_2CO_3 (110 mg, 0.4 mmol) were stirred at 100 °C for 16 h in 1,2-dichloroethane:D_2O (1.8:0.2) under air. The reaction mixture was cooled 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 using column chromatography on silica gel to give **1a-*d*** in 87% (34.4 mg) yield with 40% deuterium incorporation as estimated by 400 MHz ^{1}H NMR.

Preparation of 1-(Pyrimidin-2-yl)indoline-7-d (1a-*d*).[5b] The titled compound was prepared according to the reported procedure as a pale yellow liquid. The deuterium incorporation was determined using 600 MHz ^{1}H NMR as 90%.

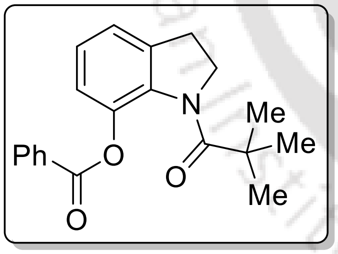
Intermolecular Kinetic Isotope Study. Benzoic acid **2a** (0.2 mmol, 24.4 mg) was reacted with 1-(pyrimidin-2-yl)indoline **1a** (0.1 mmol, 19.7 mg) and 1-(pyrimidin-2-yl)indoline-7-*d* **1a-*d*** (0.1 mmol, 19.8 mg) for 4 h under standard reaction condition. The reaction mixture was cooled to room temperature, 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 afford **3a** and a mixture of unreacted **1a** and **1a-*d*** as a yellowish liquid. The intermolecular k_H/k_D was found to be 6.67 after 4 h at 23% conversion, based on 400 MHz ^{1}H NMR of the recovered substrates **1a** and **1a-*d***.

Parallel Kinetic Isotope Effect Study. In a set of two experiments: in first set, benzoic acid **2a** (0.2 mmol, 24.4 mg) was reacted with 1-(pyrimidin-2-yl)indoline **1a** (0.1 mmol, 19.7 mg) under standard reaction conditions. Whereas in another set, 1-(pyrimidin-2-yl)indoline-7-d **1a-*d*** (0.1 mmol, 19.8 mg, 90% D) was used instead of **1a** in the reaction with benzoic acid **2a** under the standard reaction conditions. The two reactions were allowed to stir at 100 □C for 4 h. For the both cases, 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 afford **3a**. The yield of **3a** was obtained as 18% and 43% yields respectively. The KIE value of 2.65 was determined by the ratio of obtained yield of **3a** (KIE = 43%/18%/90% = 2.65).

1.4 Characterization Data

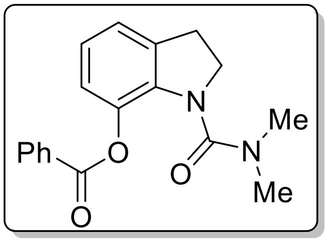


1-Acetylindolin-7-yl benzoate 3A'. Analytical TLC on silica gel, 1:3 ethyl acetate/hexane R_f = 0.18; colorless solid; yield 52% (29.2 mg); mp 120-121°C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.19 (d, *J* = 7.2 Hz, 2H), 7.60 (t, *J* = 7.2 Hz, 1H), 7.49 (t, *J* = 7.8 Hz, 2H), 7.13-7.11 (m, 2H), 7.07–7.06 (m, 1H), 4.15 (t, *J* = 7.8 Hz, 2H), 3.13 (t, *J* = 7.8 Hz, 2H), 2.15 (s, 3H).; ^{13}C NMR (150 MHz, $CDCl_3$) δ 163.9, 139.6, 136.7, 134.3, 133.5, 130.4, 129.8, 128.7, 125.6, 122.7, 122.4, 50.8, 29.5, 23.5; FT-IR (KBr) 2963, 2924, 2892, 1736, 1674, 1607, 1474, 1454, 1395, 1265, 1231, 1065 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{17}H_{16}NO_3$:282.1125, found: 282.1138.

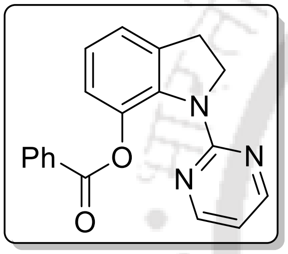


1-Pivaloylindolin-7-yl benzoate 3B'. Analytical TLC on silica gel, 1:3 ethyl acetate/hexane R_f = 0.45; colorless solid; yield 46% (29.7 mg); mp 142-143°C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.19 – 8.18 (m, 2H), 7.57 (t, *J* = 7.2 Hz, 1H), 7.46 (t, *J* = 7.8 Hz, 2H), 7.13 – 7.08 (m, 3H), 4.18 (t, *J* = 7.8 Hz, 2H), 3.13 (t, *J* = 7.8 Hz, 2H), 1.18 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 177.0, 163.6, 140.5, 136.0, 135.9, 133.2, 130.4, 130.0, 128.4, 125.2, 122.3, 121.8, 51.1, 39.9, 31.1, 28.3; FT-IR (KBr) 2958, 2924, 2853, 1742, 1647, 1474, 1263, 1095 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{20}H_{22}NO_3$:324.1594, found: 324.1603.

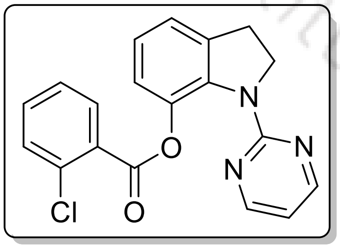
1-(Dimethylcarbamoyl)indolin-7-yl benzoate 3C'. Analytical TLC on silica gel, 1:3 ethyl acetate/hexane R_f = 0.14; yellow liquid; yield 62% (38.4 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.17 – 8.15 (m, 2H), 7.59 (t, *J* = 7.2 Hz, 1H), 7.47 (t, *J* = 7.8 Hz, 2H), 7.08-7.05 (m, 2H), 7.05 – 6.97 (m, 1H), 3.91 (t, *J* = 7.8 Hz, 2H), 3.15 (t, *J* = 7.8 Hz, 2H), 2.74 (s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 164.1, 160.3, 138.8, 137.1, 135.2, 133.4, 130.3, 129.9, 128.5, 123.3 , 122.2, 121.9, 52.4, 37.6, 30.2; FT-IR (neat) 2959, 2924, 2853, 1738, 1643, 1478, 1385, 1262, 1090, 1065 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{18}H_{19}N_2O_3$:311.1390, found: 311.1396.



1-(Pyrimidin-2-yl)indolin-7-yl benzoate 3a. Analytical TLC on silica gel, 1:3 ethyl acetate/hexane R_f = 0.49; colorless solid; mp 124-125 °C; yield 77% (48.8 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.05 (d, *J* = 4.8 Hz, 2H), 8.01-8.00 (m, 2H), 7.54 (t, *J* = 7.8 Hz, 1H), 7.39 (t, *J* = 7.8 Hz, 2H), 7.14 (t, *J* = 8.4 Hz, 2H), 7.08-7.06 (m, 1H), 6.39 (t, *J* = 4.8 Hz, 1H), 4.41 (t, *J* = 7.8 Hz, 2H), 3.18 (t, *J* = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.9, 159.9, 157.5, 139.2, 136.9, 135.2, 133.2, 130.5, 130.0, 128.5, 123.8, 123.3, 122.2, 112.1, 52.4, 29.4; FT-IR (KBr) 2958, 2923, 2852, 1740, 1636, 1577, 1552, 1473, 1431, 1382, 1265,1240, 1191, 1174, 1085, 1067, 1024 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{19}H_{16}N_3O_2$: 318.1237, found: 318.1257.

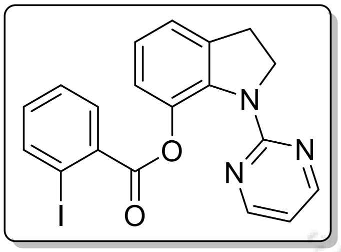


1-(Pyrimidin-2-yl)indolin-7-yl 2-chlorobenzoate 3b. Analytical TLC on silica gel, 1:3 ethyl acetate/hexane R_f = 0.47; colorless solid; yield 73% (51.2 mg); mp 115-116 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.20 (d, *J* = 4.8 Hz, 2H), 7.85 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.46 (d, *J* = 7.2 Hz, 1H), 7.42–7.39 (m, 1H), 7.24–7.23 (m, 1H), 7.16 – 7.14 (m, 2H), 7.09–7.06 (m, 1H), 6.50 (t, *J* = 4.8 Hz, 1H), 4.43 (t, *J* = 7.8 Hz, 2H), 3.17 (t, *J* = 7.8 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 162.9, 160.1, 157.6, 139.1, 137.0, 135.2, 135.0, 133.2, 132.5, 131.6, 129.0, 126.6, 123.9, 123.1, 122.4, 112.3, 52.4, 29.4; FT-IR (KBr) 2958, 2923, 2852, 1750, 1578,1553, 1471, 1433, 1383, 1281, 1237,

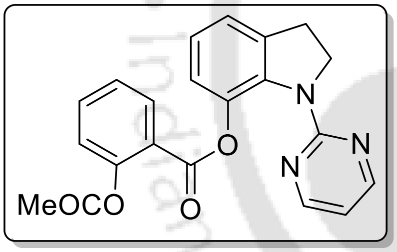


1215, 1190, 1110, 1037 cm^{-1}; HRMS (ESI) m/z [M+H]$^+$ calcd for $C_{19}H_{15}ClN_3O_2$: 352.0847, found: 352.0852.

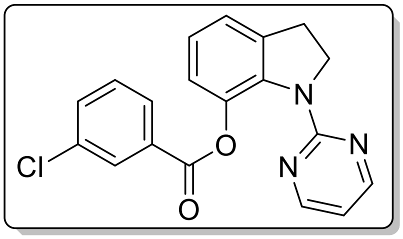
1-(Pyrimidin-2-yl)indolin-7-yl 2-iodobenzoate 3c. Analytical TLC on silica gel, 1:3 ethyl acetate/hexane R_f = 0.39; colorless solid; mp 148-149 °C; yield 55% (48.7 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.20 (d, *J* = 4.8 Hz, 2H), 8.05 (d, *J* = 7.8 Hz, 1H), 7.88 (dd, *J* = 7.8 , 1.8 Hz, 1H), 7.32 (t, *J* = 7.8 Hz, 1H), 7.16-7.12 (m, 3H), 7.09-7.06 (m, 1H), 6.50 (t, *J* = 4.8 Hz, 1H), 4.43 (t, *J* = 7.8 Hz, 2H), 3.17 (t, *J* = 7.8 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 163.5, 160.0, 157.7, 142.2, 139.1, 137.0, 135.1, 133.3, 133.2, 132.2, 128.0, 123.9, 123.1, 122.4, 112.3, 95.4, 52.4, 29.4; FT-IR (KBr) 2926, 2654, 1658, 1440, 1390, 1256, 1101 cm^{-1}; HRMS (ESI) m/z [M+H]$^+$ calcd for $C_{19}H_{15}IN_3O_2$: 444.0203, found: 444.0203.



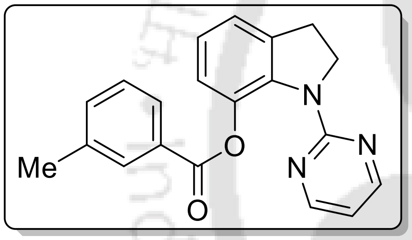
1-(Pyrimidin-2-yl)indolin-7-yl 2-acetoxybenzoate 3d. Analytical TLC on silica gel, 1:3 ethyl acetate/hexane R_f = 0.37; colorless liquid; yield 40% (30 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.16 (d, *J* = 4.8 Hz, 2H), 7.95 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.56-7.53 (m, 1H), 7.21 (t, *J* = 7.8 Hz, 1H), 7.14 (d, *J* = 6.6 Hz, 1H), 7.11 (d, *J* = 8.4 Hz, 2H), 7.07-7.05 (m, 1H), 6.45 (t, *J* = 4.8 Hz, 1H), 4.40 (t, *J* = 7.8 Hz, 2H), 3.16 (t, *J* = 7.8 Hz, 2H), 2.33 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.1, 162.5, 160.0, 157.7, 151.6, 138.9, 137.0, 135.2, 134.4, 132.4, 126.1, 124.3, 123.8, 123.5, 122.9, 122.3, 112.4, 52.4, 29.4, 21.2; FT-IR (neat) 2924, 2853, 1745, 1639, 1578, 1554, 1471, 1433, 1240, 1191cm^{-1}; HRMS (ESI) m/z [M+H]$^+$ calcd for $C_{21}H_{18}N_3O_4$: 376.1292, found: 376.1307.



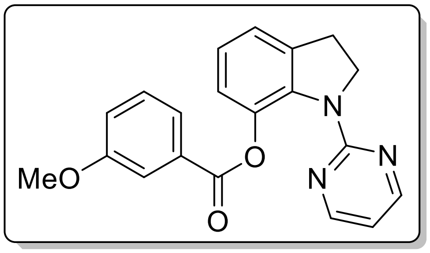
1-(Pyrimidin-2-yl)indolin-7-yl 3-chlorobenzoate 3e. Analytical TLC on silica gel, 1:3 ethyl acetate/hexane R_f = 0.40; colorless solid; yield 73% (51.2 mg); mp 117-118°C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.08 (d, *J* = 4.8 Hz, 2H), 7.99 (t, *J* = 1.8 Hz, 1H), 7.89 (d, *J* = 7.8 Hz, 1H), 7.52 (d, *J* = 9.0 Hz, 1H), 7.34 (t, *J* = 7.8 Hz, 1H), 7.17 (d, *J* = 7.2 Hz, 1H), 7.12 (d, *J* = 7.8 Hz, 1H), 7.09 – 7.06 (m, 1H), 6.44 (t, *J* = 4.8 Hz, 1H), 4.42 (t, *J* = 7.8 Hz, 2H), 3.18 (t, *J* = 7.8 Hz, 2H).; ^{13}C NMR (150 MHz, $CDCl_3$) δ 163.7, 159.9, 157.6, 138.9, 137.0, 135.1, 134.6, 133.3, 132.2, 130.1, 129.8, 128.1, 123.9, 123.1, 122.5, 112.2, 52.4, 29.4 ; FT-IR (KBr) 2961, 2924, 2853, 1732, 1636, 1577, 1554, 1466, 1417, 1254, 1109 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{19}H_{15}ClN_3O_2$: 352.0847, found: 352.0856.



1-(Pyrimidin-2-yl)indolin-7-yl 3-methylbenzoate 3f. Analytical TLC on silica gel, 1:3 ethyl acetate/hexane R_f = 0.43; colorless solid; mp 91-92°C; yield 70% (46.3 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.10 (d, *J* = 4.8 Hz, 2H), 7.84 (s, 1H), 7.82 (d, *J* = 7.2 Hz, 1H), 7.37 (d, *J* = 7.8 Hz, 1H), 7.30 (d, *J* = 7.8 Hz, 1H), 7.16 (t, *J* = 8.4 Hz, 2H), 7.10–7.08 (m, 1H), 6.43 (t, *J* = 4.8 Hz, 1H), 4.44 (t, *J* = 7.8 Hz, 2H), 3.20 (t, *J* = 7.8 Hz, 2H), 2.38 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 165.0, 159.9, 157.6, 139.2, 138.2, 136.8, 135.2, 134.0, 130.5, 130.3, 128.3, 127.2, 123.8, 123.3, 122.2, 112.1, 52.4, 29.4, 21.4; FT-IR (KBr) 2956, 2924, 2853, 1739, 1578, 1553, 1472, 1443, 1383, 1275, 1186, 1092, 1073 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{20}H_{18}N_3O_2$: 332.1394, found: 332.1400.

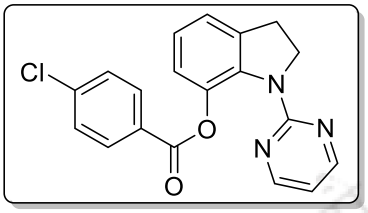


1-(Pyrimidin-2-yl)indolin-7-yl 3-methoxybenzoate 3g. Analytical TLC on silica gel, 1:3 ethyl acetate/hexane R_f = 0.34; colorless solid; yield 68% (47.1 mg); mp 119-120 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.07 (d, *J*=4.8 Hz, 2H), 7.60(d, *J* =7.2 Hz, 1H), 7.51 (s,1H), 7.29 (t, *J* =7.8 Hz, 1H), 7.16 – 7.12(m, 2H), 7.09 -7.06(m, 2H), 6.41 (t, *J* =4.8 Hz, 1H), 4.41 (t, *J* = 8.4 Hz, 2H), 3.79(s, 3H), 3.18 (t, *J* = 7.8Hz, 2H) ; ^{13}C NMR (150 MHz, $CDCl_3$) δ 164.7, 159.6,

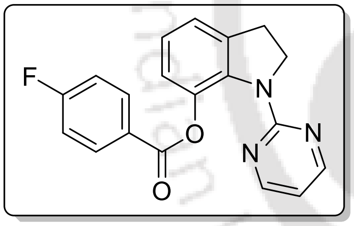


157.6, 139.1, 136.9, 135.2, 131.7, 129.5, 123.8, 123.3, 122.6, 122.3, 120.0, 114.1, 112.1, 55.6, 52.4, 29.4 ; FT-IR (KBr) 2924, 2853, 1737, 1639, 1576, 1551, 1466, 1424, 1277, 1107 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{20}H_{18}N_3O_3$: 348.1343, found: 348.1357.

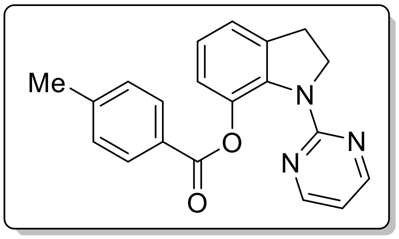
1-(Pyrimidin-2-yl)indolin-7-yl 4-chlorobenzoate 3h. Analytical TLC on silica gel, 1:3 ethyl acetate/hexane R_f = 0.41; colorless solid; mp 137-138 °C; yield 80% (56.1 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.06 (d, *J* = 4.8 Hz, 2H), 7.95 (d, *J* = 8.4 Hz, 2H), 7.37 (d, *J* = 8.4 Hz, 2H), 7.16-7.15 (m, 1H), 7.13 (d, *J* = 7.2Hz, 1H), 7.08-7.06 (m, 1H), 6.43 (t, *J* = 4.8 Hz, 1H), 4.41 (t, *J* = 8.4 Hz, 2H), 3.17 (t, *J* = 7.8 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 164.1, 159.9, 157.6, 139.6, 139.0, 137.0, 135.1, 131.4, 128.93, 128.91, 123.9, 123.1, 122.4, 112.2, 52.4, 29.4; FT-IR (KBr) 2958, 2924, 2853, 1741, 1591, 1578, 1553, 1471, 1433, 1400, 1263, 1171, 1089, 1014 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{19}H_{15}ClN_3O_2$: 352.0847, found: 352.0856.



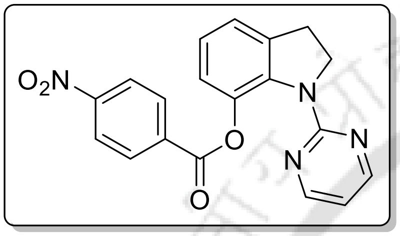
1-(Pyrimidin-2-yl)indolin-7-yl 4-fluorobenzoate 3i. Analytical TLC on silica gel, 1:3 ethyl acetate/hexane R_f = 0.44; colorless solid, mp 151-152 °C; yield 80% (53.6 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.06 (d, *J* = 4.8 Hz, 2H), 8.04-8.01 (m, 2H), 7.16-7.12 (m, 2H), 7.08-7.05 (m, 3H), 6.42 (t, *J* = 4.8 Hz, 1H), 4.41 (t, *J* = 7.8 Hz, 2H), 3.17 (t, *J* = 7.8 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 166.7 (J_{C-F} = 252.76 Hz), 163.9, 159.9, 157.5, 139.0, 136.9, 135.1, 132.6 (J_{C-F} = 9.3 Hz), 126.7 (J_{C-F} = 3.15 Hz), 123.9, 123.2, 122.4, 115.7 (J_{C-F} = 21.75 Hz), 112.2, 52.4, 29.4; FT-IR (KBr) 2956, 2924, 2854, 1735, 1637, 1603, 1552, 1488, 1446, 1271, 1234, 1160, 1108, 991 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{19}H_{15}FN_3O_2$: 336.1143, found: 336.1152.



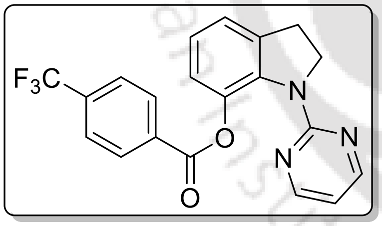
1-(Pyrimidin-2-yl)indolin-7-yl 4-methylbenzoate 3j. Analytical TLC on silica gel, 1:3 ethyl acetate/hexane R_f = 0.46; colorless solid, mp 172-173 °C; yield 74% (48.9 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.09 (d, *J* = 4.8 Hz, 2H), 7.92 (d, *J* = 7.4 Hz, 2H), 7.21 (d, *J* = 8.4 Hz, 2H), 7.16 (t, *J* = 7.2 Hz, 2H), 7.10-7.07 (m, 1H),



6.43 (t, *J* = 4.8 Hz, 1H), 4.43 (t, *J* = 8.4 Hz, 2H), 3.20 (t, *J* = 8.4 Hz, 2H), 2.42 (s, 3H); ^{13}C NMR (150 MHz,) δ 165.0, 159.9, 157.5, 143.9, 139.2, 136.8, 135.2, 130.1, 129.2, 127.7, 123.8, 123.4, 122.2, 112.1, 52.4, 29.4, 21.9; FT-IR (KBr) 2923, 2853, 1730, 1610, 1576, 1549, 1485, 1471, 1445, 1433, 1270, 1140, 1173, 1085, 1018 cm^{-1}; HRMS (ESI) *m/z* [M+H]$^+$ calcd for $C_{20}H_{18}N_3O_2$: 332.1394, found: 332.1398.

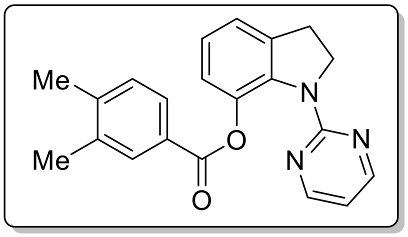


1-(Pyrimidin-2-yl)indolin-7-yl 4-nitrobenzoate 3k. Analytical TLC on silica gel, 1:3 ethyl acetate/hexane R$_f$ = 0.41; yellow solid; mp 159-160 °C; yield 81% (58.6 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (d, *J* = 8.4 Hz, 2H), 8.20 (d, *J* = 8.4 Hz, 2H), 8.04 (d, *J* = 4.0 Hz, 2H), 7.20 – 7.10 (m, 3H), 6.42 (t, *J* = 4.0 Hz, 1H), 4.43 (t, *J* = 8.0 Hz, 2H), 3.19 (t, *J* = 7.6 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 163.0, 159.9, 157.6, 150.7, 138.8, 137.2, 135.9, 135.0, 131.1, 124.0, 123.7, 122.9, 122.8, 112.3, 52.4, 29.3; FT-IR (KBr) 2958, 2923, 2852, 1744, 1638, 1578, 1527, 1472, 1432, 1347, 1265, 1240, 1191, 1088, 1014 cm^{-1}; HRMS (ESI) *m/z* [M+H]$^+$ calcd for $C_{19}H_{15}N_4O_4$: 363.1088, found: 363.1091.

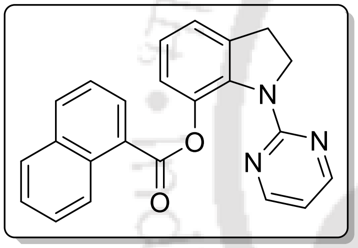


1-(Pyrimidin-2-yl)indolin-7-yl 4-(trifluoromethyl)benzoate 3l. Analytical TLC on silica gel, 1:3 ethyl acetate/hexane R$_f$ = 0.40; colorless solid, mp 126-127 °C; yield 80% (61.6 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.13 (d, *J* = 7.8 Hz, 2H), 8.05 (d, *J* = 4.8 Hz, 2H), 7.67 (d, *J* = 8.4 Hz, 2H), 7.18 (d, *J* = 7.2 Hz, 1H), 7.14 (d, *J* = 7.8 Hz, 1H), 7.10-7.07 (m, 1H), 6.42 (t, *J* = 4.8 Hz, 1H), 4.42 (t, *J* = 8.4 Hz, 2H), 3.18 (t, *J* = 7.8 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 163.7, 159.9, 157.6, 138.9, 137.1, 135.0, 134.7 (q, *J* = 32.7 Hz), 133.7, 130.4, 125.6 (q, *J* = 3.9 Hz), 124.0, 123.8 (q, *J* = 271.05 Hz), 123.0, 122.6, 112.2, 52.4, 29.4; FT-IR (KBr) 2956, 2921, 2850, 1743, 1638, 1579, 1471, 1434, 1263, 1130, 1109, 966 cm^{-1}; HRMS (ESI) *m/z* [M+H]$^+$ calcd for $C_{20}H_{15}F_3N_3O_2$: 386.1111, found: 386.1118.

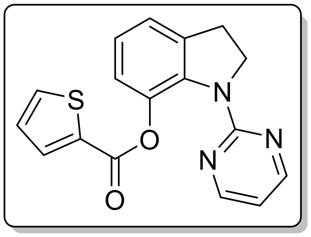
1-(Pyrimidin-2-yl)indolin-7-yl 3,4-dimethylbenzoate 3m. Analytical TLC on silica gel, 1:3 ethyl acetate/hexane $R_f = 0.43$; colorless solid, mp 135-136 °C; yield 69% (47.6 mg); ^{1}H NMR (600 MHz, CDCl$_3$) δ 8.08 (d, *J* = 4.8 Hz, 2H), 7.76 (s, 1H), 7.71 (d, *J* = 7.8 Hz, 1H), 7.13 (t, *J* = 7.2 Hz, 3H), 7.07-7.05 (m, 1H), 6.41 (t, *J* = 4.8 Hz, 1H), 4.41 (t, *J* = 7.8 Hz, 2H), 3.17 (t, *J* = 7.8 Hz, 2H), 2.29 (s, 3H), 2.25 (s, 3H); ^{13}C NMR (150 MHz, CDCl$_3$) δ 165.1, 160.0, 157.6, 142.5, 139.3, 136.8, 135.3, 131.1, 129.7, 128.0, 127.7, 123.8, 123.4, 122.1, 112.1, 52.4, 29.4, 20.2, 19.8; FT-IR (KBr) 2957, 2923, 2853, 1734, 1611, 1578, 1553, 1479, 1469, 1432, 1405, 1286, 1260, 1169, 1088 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{21}H_{20}N_3O_2$: 346.1550, found: 346.1553.



1-(Pyrimidin-2-yl)indolin-7-yl 1-naphthoate 3n. Analytical TLC on silica gel, 1:3 ethyl acetate/hexane $R_f = 0.41$; colorless liquid; yield 54% (39.6 mg); ^{1}H NMR (600 MHz, CDCl$_3$) δ 9.09 (d, *J* = 9.0 Hz, 1H), 8.20 (dd, *J* = 7.2, 1.2 Hz, 1H), 8.03 – 8.01 (m, 3H), 7.89 (d, *J* = 8.4 Hz, 1H), 7.61 – 7.59 (m, 1H), 7.54 (t, *J* = 7.2 Hz, 1H), 7.41 (t, *J*=7.8 Hz, 1H), 7.21- 7.17 (m, 2H), 7.11 (t, *J* = 7.8 Hz, 1H), 6.29 (t, *J* = 4.8 Hz, 1H), 4.45 (t, *J* = 8.4 Hz, 2H), 3.20 (t, *J* = 7.8 Hz, 2H).; ^{13}C NMR (150 MHz, CDCl$_3$) δ 165.0, 160.0, 157.6, 139.2, 137.0, 135.3, 134.1, 133.9, 131.8, 131.4, 128.7, 128.2, 126.4, 126.2, 126.0, 124.5, 123.9, 123.4, 122.3, 112.2, 52.4, 29.4; FT-IR (neat) 2963, 2924, 2853, 1732, 1639, 1577, 1552, 1471, 1432, 1236, 1186, 1120 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{23}H_{18}N_3O_2$: 368.1394, found: 368.1408.

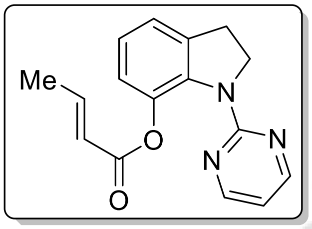


1-(Pyrimidin-2-yl)indolin-7-yl thiophene-2-carboxylate 3o. Analytical TLC on silica gel, 1:3 ethyl acetate/hexane $R_f = 0.40$; colorless solid, mp 102-103 °C; yield 64% (41.3 mg); ^{1}H NMR (600 MHz, CDCl$_3$) δ 8.13 (d, *J* = 4.8 Hz, 2H), 7.80 (dd, *J* = 3.6, 1.2 Hz, 1H), 7.53 (dd, *J* = 5.4, 1.8 Hz, 1H), 7.14 (t, J = 6.0 Hz, 2H), 7.07-7.04 (m, 2H), 6.45 (t, *J* = 4.8 Hz, 1H), 4.40 (t, *J* = 7.8 Hz, 2H), 3.17 (t, *J* = 8.4 Hz, 2H); ^{13}C NMR (150 MHz, CDCl$_3$) δ 160.3, 159.9, 157.5, 138.8, 136.9, 135.2, 134.1, 134.0,

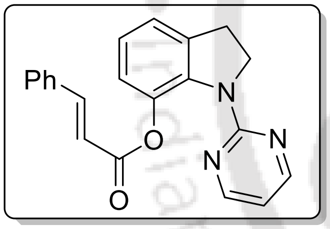


132.9, 127.8, 123.8, 123.3, 122.4, 112.2, 52.3, 29.4; FT-IR (KBr) 2922, 2851, 1730, 1639, 1577, 1553, 1472, 1442, 1432, 1416, 1383, 1239, 1190, 1070, 1030 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{17}H_{14}N_3O_2S$: 324.0801, found: 324.0801.

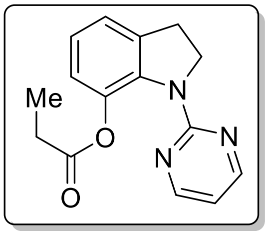
1-(Pyrimidin-2-yl)indolin-7-yl (*E*)-but-2-enoate 3r. Analytical TLC on silica gel, 1:3 ethyl acetate/hexane R_f = 0.28; colorless solid; yield 61% (34.2 mg); mp 112-113^{o}C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.32 (d, *J* = 4.2 Hz, 2H), 7.11 – 7.09 (m, 1H), 7.04 – 6.97 (m, 3H), 6.64 (t, *J* = 4.8 Hz, 1H), 5.88 (dd, *J* = 15.6, 1.8 Hz, 1H), 4.38 (t, *J* = 7.8 Hz, 2H), 3.14 (t, *J* = 8.4 Hz, 2H), 1.86 (dd, *J* =7.2, 1.8 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 164.5, 160.0, 157.7, 145.8, 139.1, 136.8, 135.1, 123.8, 123.1, 122.8, 122.0, 112.2, 52.3, 29.4, 18.2; FT-IR (KBr) 2961, 2924, 2854, 1733, 1653, 1577, 1554, 1467, 1102 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{16}H_{16}N_3O_2$:282.1237, found: 282.1249.



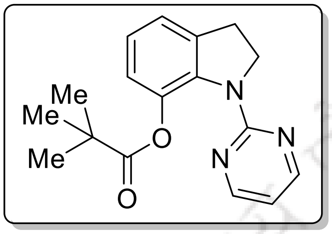
1-(Pyrimidin-2-yl)indolin-7-yl cinnamate 3s. Analytical TLC on silica gel, 1:3 ethyl acetate/hexane R_f = 0.38; colorless solid; mp 101-102 ^{o}C; yield 67% (46 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.31 (d, *J* = 4.8 Hz, 2H), 7.73 (d, *J* = 15.6 Hz, 1H), 7.50-7.48 (m, 2H), 7.39-7.38 (m, 3H), 7.14 (d, *J* = 7.8 Hz, 1H), 7.09-7.04 (m, 2H), 6.57 (t, *J* = 4.8 Hz, 1H), 6.48 (d, *J* = 16.2 Hz, 1H), 4.41 (t, *J* = 8.4 Hz, 2H), 3.16 (t, *J* = 7.8 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 165.1, 160.0, 157.7, 145.6, 139.1, 136.9, 135.1, 134.4, 130.6, 129.1, 128.3, 123.8, 123.2, 122.2, 118.2, 112.3, 52.3, 29.4; FT-IR (KBr) 2956, 2923, 2852, 1731, 1637, 1577, 1552, 1472, 1442, 1383, 1328, 1309, 1237, 1191, 1138, 1065, 990 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{21}H_{18}N_3O_2$: 344.1394, found: 344.1400.



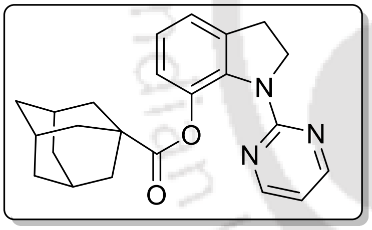
1-(Pyrimidin-2-yl)indolin-7-yl propionate 3t. Analytical TLC on silica gel, 1:3 ethyl acetate/hexane R_f = 0.35; yellow liquid; yield 70% (37.6 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.39 (d, *J* = 4.8 Hz, 2H), 7.11 (d, *J* = 7.2 Hz, 1H), 7.02 (t, *J* = 7.8 Hz, 1H), 6.99 (d, *J* = 8.4 Hz, 1H), 6.70 (t, *J* = 4.8 Hz, 1H), 4.39 (t, *J* = 7.8 Hz, 2H), 3.13 (t, *J* = 7.8 Hz, 2H), 2.37 (q, *J* = 7.2 Hz, 2H), 1.10 (t, *J* = 7.8 Hz, 3H); ^{13}C NMR (150 MHz,



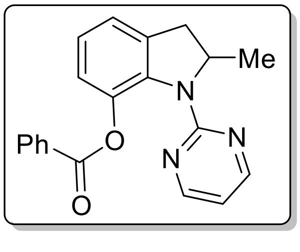
$CDCl_3$) δ 172.3, 160.2, 157.6, 139.3, 136.9, 135.1, 124.0, 122.9, 122.1, 112.4, 52.5, 29.5, 28.0, 9.0; FT-IR (neat) 2956, 2924, 2853, 1761, 1638, 1578, 1551, 1470, 1432, 1382, 1243, 1139, 1080 cm-1; HRMS (ESI) m/z [M+H]+ calcd for: $C_{15}H_{16}N_3O_2$: 270.1237, found: 270.1239.



1-(Pyrimidin-2-yl)indolin-7-yl pivalate 3u. Analytical TLC on silica gel, 1:3 ethyl acetate/hexane R_f = 0.35; colorless liquid; yield 69% (41 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.41 (d, *J* = 4.8 Hz, 2H), 7.10 (d, J = 7.2 Hz, 1H), 7.03 (t, *J* = 7.8 Hz, 1H), 6.93 (d, *J* = 8.4 Hz, 1H), 6.70 (t, *J* = 4.8 Hz, 1H), 4.38 (t, *J* = 7.8 Hz, 2H), 3.12 (t, *J* = 7.8 Hz, 2H), 1.12 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 176.2, 160.8, 157.9, 140.2, 136.8, 135.6, 124.3, 122.2, 122.0, 112.5, 52.9, 39.2, 29.8, 27.2; FT-IR (neat) 2959, 2924, 2853, 1750, 1592, 1577, 1552, 1472, 1400, 1382, 1243, 1120, 1030 cm^{-1}; HRMS (ESI) *m/z* [M+H]$^+$ calcd for $C_{17}H_{20}N_3O_2$: 298.1550, found: 298.1559.

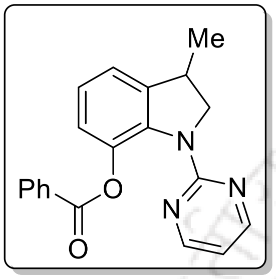


1-(Pyrimidin-2-yl)indolin-7-yl (3r,5r,7r)-adamantane-1-carboxylate 3v. Analytical TLC on silica gel, 1:3 ethyl acetate/hexane R_f = 0.34; yellow liquid; yield 70% (52.5 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.43 (d, *J* = 4.8 Hz, 2H), 7.09-7.08 (m, 1H), 7.02 (t, *J* = 8.4 Hz, 1H), 6.93 – 6.91 (m, 1H), 6.71 (t, *J* = 4.8 Hz, 1H), 4.38 (t, *J* = 8.4 Hz, 2H), 3.11 (t, *J* = 8.4 Hz, 2H), 1.94 – 1.91 (m, 4H), 1.795-1.791 (m, 5H), 1.72-1.62 (m, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 175.2, 160.8, 157.9, 140.2, 136.7, 135.6, 124.2, 122.2, 121.8, 112.4, 52.9, 41.1, 38.8, 36.6, 29.8, 28.0; FT-IR (neat) 2920, 2852, 1747, 1578, 1552, 1479, 1433, 1382, 1211, 1179, 1103, 1065 cm^{-1}; HRMS (ESI) *m/z* [M+H]$^+$ calcd for $C_{23}H_{26}N_3O_2$: 376.2020, found: 376.2029.

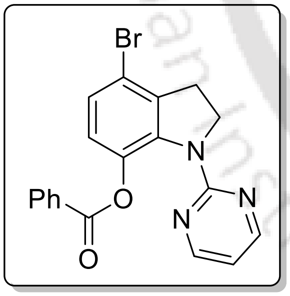


2-Methyl-1-(pyrimidin-2-yl)indolin-7-yl benzoate 3w. Analytical TLC on silica gel, 1:3 ethyl acetate/hexane R_f = 0.51; brown liquid; yield 73% (48.3 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.05 (d, *J* = 4.8 Hz, 2H), 8.02-8.01 (m, 2H), 7.54-7.52 (m, 1H), 7.40-7.38 (m, 2H), 7.15 (d, *J* = 7.8 Hz, 2H), 7.09-7.07 (m, 1H), 6.37 (t, *J* = 4.8 Hz, 1H), 4.96-4.93 (m, 1H), 3.51 (dd, *J* = 15.0, 8.4 Hz, 1H), 2.64 (d, *J* = 15.6 Hz, 1H), 1.47 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 164.7, 159.7, 157.6, 139.8, 135.8, 133.9, 133.1, 130.5, 130.1, 128.4, 123.9, 123.2, 122.7, 112.1, 60.0, 36.9, 21.2; FT-IR (neat) 2957, 2923, 2851, 1740, 1578, 1552, 1479, 1433, 1385, 1265, 1242, 1199, 1086, 1068, 1025 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{20}H_{18}N_3O_2$: 332.1394, found: 332.1399.

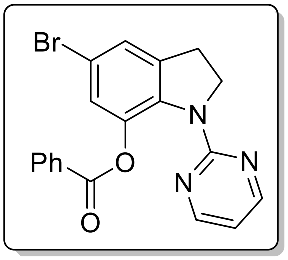
3-Methyl-1-(pyrimidin-2-yl)indolin-7-yl benzoate 3x. Analytical TLC on silica gel, 1:3 ethyl acetate/hexane R_f = 0.51; yellow liquid; yield 75% (49.6 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05-8.00 (m, 4H), 7.54 (t, *J* = 7.2 Hz, 1H), 7.39 (t, *J* = 7.6 Hz, 2H), 7.14-7.08 (m, 3H), 6.38 (t, *J* = 4.8 Hz, 1H), 4.60 (t, *J*= 9.6 Hz, 1H), 3.94-3.90 (m, 1H), 3.53-3.48 (m, 1H), 1.37 (d, *J* = 6.4 Hz, 3H).; ^{13}C NMR (150 MHz, $CDCl_3$) δ 164.8, 159.9, 157.6, 142.0, 139.1, 134.8, 133.2, 130.5, 130.0, 128.4, 124.0, 123.4, 121.0, 112.0, 60.1, 36.0, 19.0.; FT-IR (neat) 2959, 2925, 2854, 1742, 1578, 1553, 1470, 1434, 1383, 1265, 1242, 1190, 1087, 1023 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{20}H_{18}N_3O_2$: 332.1394, found: 332.1397.



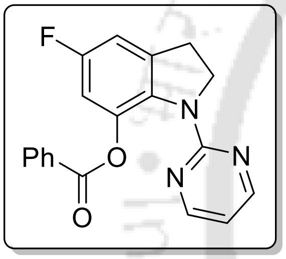
4-Bromo-1-(pyrimidin-2-yl)indolin-7-yl benzoate 3y. Analytical TLC on silica gel, 1:3 ethyl acetate/hexane R_f = 0.49; colorless solid; mp 86-87 °C; yield 69% (54.5 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.06 (d, *J* = 4.8 Hz, 2H), 7.98 (d, *J* = 8.4 Hz, 2H), 7.54 (t, *J* = 7.8 Hz, 1H), 7.39 (t, *J* = 7.8 Hz, 2H), 7.21 (d, *J* = 8.4 Hz, 1H), 7.05 (d, *J* = 8.4 Hz, 1H), 6.43 (t, *J* = 4.8 Hz, 1H), 4.42 (t, *J* = 8.4 Hz, 2H), 3.17 (t, *J* = 7.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.6, 159.8, 157.6, 138.1, 136.9, 136.4, 133.4, 130.16, 130.10, 128.5, 126.4, 125.1, 116.0, 112.6, 51.7, 31.0; FT-IR (KBr) 2961, 2924, 2853, 1741, 1640, 1563, 1551, 1460, 1407, 1261, 1238, 1100, 1023 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{19}H_{15}BrN_3O_2$: 396.0342, found: 396.0343.



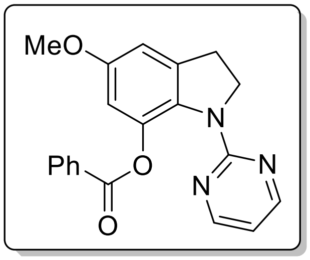
5-Bromo-1-(pyrimidin-2-yl)indolin-7-yl benzoate 3z. Analytical TLC on silica gel, 1:3 ethyl acetate/hexane R_f = 0.44; yellow solid, mp 98-99 °C; yield 73% (57.6 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.05 (d, *J* = 4.8 Hz, 2H), 7.99-7.97 (m, 2H), 7.55 (t, *J* = 7.8 Hz, 1H), 7.39 (t, J = 8.4 Hz, 2H), 7.30 (s, 1H), 7.27 (s, 1H), 6.41 (t, *J* = 4.8 Hz, 1H), 4.41 (t, *J* = 7.8 Hz, 2H), 3.17 (t, *J* = 8.4 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 164.5, 159.7, 157.6, 139.2, 138.5, 134.8, 133.4, 130.1, 129.9, 128.5, 126.3, 125.4, 115.1, 112.5, 52.4, 29.2; FT-IR (KBr) 2951, 2923, 2852, 1746, 1578, 1552, 1477, 1451, 1411, 1380, 1262, 1250, 1239, 1191, 1078, 996 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{19}H_{15}BrN_3O_2$: 396.0342, found: 396.0344.



5-Fluoro-1-(pyrimidin-2-yl)indolin-7-yl benzoate 3aa. Analytical TLC on silica gel, 1:3 ethyl acetate/hexane R_f = 0.58; yellowish solid; mp 175-176 °C; yield 69% (46.2 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.05 (d, *J* = 4.8 Hz, 2H), 7.99-7.98 (m, 2H), 7.56-7.53 (m, 1H), 7.40-7.37 (m, 2H), 6.92-6.90 (m, 2H), 6.39 (t, *J* = 4.8 Hz, 1H), 4.43 (t, *J* = 8.4 Hz, 2H), 3.15 (t, *J* = 7.8 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 164.5, 159.9, 159.8 (J_{C-F} = 241.5 Hz), 157.6, 139.1(J_{C-F} =11.55 Hz), 138.0 (J_{C-F} =9.45 Hz), 133.4, 131.7 (J_{C-F} =2.7 Hz), 130.1, 130.0, 128.5, 112.2, 110.5 (J_{C-F} =25.8 Hz), 110.0 (J_{C-F} =23.7 Hz), 52.5, 29.7 (J_{C-F} =2.1 Hz); FT-IR (KBr) 2956, 2924, 2853, 1736, 1596, 1580, 1552, 1490, 1467, 1424, 1386, 1255, 1124, 1083, 1026 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{19}H_{15}FN_3O_2$: 336.1143, found: 336.1151.

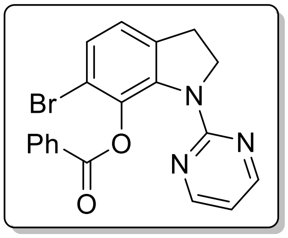


5-Methoxy-1-(pyrimidin-2-yl)indolin-7-yl benzoate 3ab. Analytical TLC on silica gel, 1:3 ethyl acetate/hexane R_f = 0.44; yellow liquid; yield 77% (53.4 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 – 8.01 (m, 4H), 7.54 (t, *J* = 7.6 Hz, 1H), 7.39 (t, *J* = 8.0 Hz, 2H), 6.77 (s, 1H), 6.70-6.69 (m, 1H), 6.35 (t, *J* = 4.8 Hz, 1H), 4.40 (t, *J* = 8.0 Hz, 2H), 3.81 (s, 3H), 3.13 (t, *J* = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.8, 160.1, 157.6, 156.8, 139.4, 137.8, 133.2, 130.4, 130.1, 128.8, 128.5, 111.7, 109.7, 107.8, 56.1, 52.3, 29.8; FT-IR (neat) 2958, 2924, 2852, 1739, 1622, 1579, 1550, 1488, 1424, 1381,

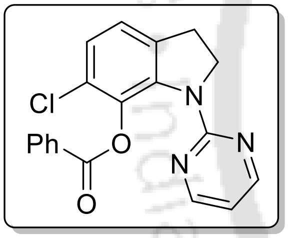


1261, 1190, 1140, 1088, 1069, 1026 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{20}H_{18}N_3O_3$: 348.1343, found: 348.1347.

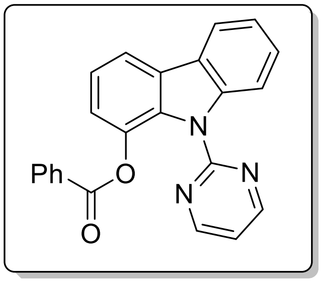
6-Bromo-1-(pyrimidin-2-yl)indolin-7-yl benzoate 3ac. Analytical TLC on silica gel, 1:3 ethyl acetate/hexane R_f = 0.40; yellow liquid; yield 67% (53 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.10 – 8.06 (m, 4H), 7.57 – 7.54 (m, 1H), 7.42 (t, *J* = 7.8 Hz, 2H), 7.30 (d, *J* = 8.4 Hz, 1H), 7.02 (d, *J* = 8.4 Hz, 1H), 6.44 (t, *J* = 4.2 Hz, 1H), 4.40 (s, 2H), 3.12 (t, *J* = 7.8 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 163.3, 159.5, 157.5, 137.3, 136.7, 136.4, 133.4, 130.2, 129.9, 128.5, 127.6, 123.2, 117.1, 112.5, 52.9, 29.1; FT-IR (neat) 2923, 2852, 1744, 1576, 1553, 1438, 1381, 1260, 1221, 1108 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{19}H_{15}BrN_3O_2$: 396.0342, found: 396.0361.



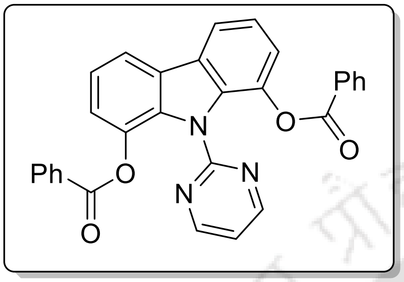
6-Chloro-1-(pyrimidin-2-yl)indolin-7-yl benzoate 3ad. Analytical TLC on silica gel, 1:3 ethyl acetate/hexane R_f = 0.43; colorless solid; mp 129-130 °C; yield 71% (49.8 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09-8.05 (m, 4H), 7.55 (t, *J* = 7.2 Hz, 1H), 7.41 (t, *J* = 7.6 Hz, 2H), 7.14 (d, *J* = 7.6 Hz, 1H), 7.08 (d, *J* = 7.6 Hz, 1H), 6.44 (t, *J* = 4.8 Hz, 1H), 4.41 (s, 2H), 3.13 (t, *J* = 7.2 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 163.6, 159.6, 157.5, 137.3, 135.8, 135.6, 133.4, 130.2, 129.9, 128.5, 127.9, 124.4, 122.6, 112.5, 53.0, 29.0; FT-IR (KBr) 2958, 2922, 2852, 1748, 1635, 1577, 1554, 1468, 1383, 1261, 1223, 1175, 1080, 1024 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{19}H_{15}ClN_3O_2$: 352.0847, found: 352.0852.



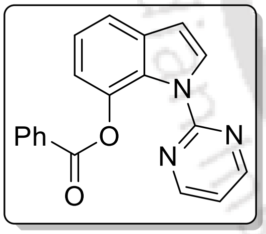
9-(Pyrimidin-2-yl)-9H-carbazol-1-yl benzoate 3ae. Analytical TLC on silica gel, 1:3 ethyl acetate/hexane R_f = 0.44; colorless solid; yield 22% (16 mg); mp 150-151°C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.44 (d, *J* = 4.8 Hz, 2H), 8.18 (d, *J* = 8.4 Hz, 1H), 8.10 (d, *J* = 7.2 Hz, 1H), 8.03 (d, *J* = 7.2 Hz, 1H), 7.91 (d, *J* = 7.2 Hz, 2H), 7.58 (t, *J* = 7.8 Hz, 1H), 7.46 -7.35 (m, 6H), 6.77 (t, *J* = 4.8 Hz, 1H).; ^{13}C NMR (150 MHz, $CDCl_3$) δ 164.3, 158.2, 140.9, 137.7, 133.6, 131.0, 130.0, 129.8, 128.9, 128.6,



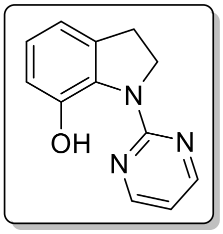
127.2, 125.1, 122.5, 122.4, 121.6, 120.2, 117.8, 117.2, 112.9 ; FT-IR (KBr) 2963, 2924, 2852, 1729, 1637, 1566, 1452, 1413, 1211, 1090 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{23}H_{16}N_3O_2$:366.1237, found: 366.1251.



9-(Pyrimidin-2-yl)-9H-carbazole-1,8-diyl dibenzoate 3af. Analytical TLC on silica gel, 1:3 ethyl acetate/hexane R_f = 0.24; colorless solid; yield 51% (49.4 mg); mp 240-241°C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.08 (dd, *J* = 8.4, 1.2 Hz, 2H), 7.99 (d, *J* = 4.8 Hz, 2H), 7.77 – 7.76 (m, 4H), 7.53 (t, *J* = 7.21 Hz, 2H), 7.39 (t, *J* = 7.8 Hz, 2H), 7.34 (t, *J* = 7.8 Hz, 4H), 7.28 (d, *J* = 7.8, 2H), 6.32 (t, *J* = 4.8 Hz, 1H) ; ^{13}C NMR (150 MHz, $CDCl_3$) δ 164.4, 159.2, 158.1, 136.5, 133.6, 132.9, 130.1, 129.2, 128.4, 127.3, 121.7, 121.3, 118.9, 118.3; FT-IR (KBr) 2924, 2853, 1748, 1632, 1583, 1566, 1450, 1432, 1408, 1260, 1213, 1174, 1062, 1051 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{30}H_{20}N_3O_4$:486.1448, found: 486.1458.



1-(Pyrimidin-2-yl)-1H-indol-7-yl benzoate 4. Analytical TLC on silica gel, 1:3 ethyl acetate/hexane R_f = 0.50; colorless liquid; yield 84% (56.7 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.15 (d, *J* = 4.8 Hz, 2H), 8.10 – 8.08 (m, 2H), 8.03 (d, *J* = 3.6 Hz, 1H), 7.62 – 7.59 (m, 1H), 7.57-7.55 (m, 1H), 7.47 – 7.45 (m, 2H), 7.28 (t, *J* = 7.8 Hz, 1H), 7.16-7.15 (m, 1H), 6.76 – 6.73 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 165.2, 158.2, 157.4, 137.8, 134.9, 133.3, 130.5, 130.2, 129.5, 128.6, 127.0, 122.7, 119.2, 118.9, 116.7, 107.2; FT-IR (neat) 2923, 2852, 1738, 1637, 1572, 1482, 1421, 1357, 1264, 1217, 1093 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{19}H_{14}N_3O_2$: 316.1081, found: 316.1097.



1-(Pyrimidin-2-yl)indolin-7-ol 5. Analytical TLC on silica gel, 1:3 ethyl acetate/hexane R_f = 0.55; yellow solid; yield 83% (42.6 mg); mp 98-99 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 13.0 (br s, 1H), 8.49-8.26 (m, 2H), 6.94 (t, *J* = 7.8 Hz, 1H), 6.81 (d, *J* = 8.4 Hz, 1H), 6.73 (d, *J* = 7.8 Hz, 1H), 6.63 (t, *J* = 4.8 Hz, 1H), 4.26 (t, *J* = 8.4 Hz, 2H), 3.14 (t, *J* = 8.4 Hz, 2H); ^{13}C NMR

(150 MHz, $CDCl_3$) δ 160.3, 157.4, 145.5, 135.2, 129.6, 125.4, 117.9, 116.1, 110.3, 49.7, 28.2; FT-IR (KBr) 3436, 2925, 2854, 1633, 1596, 1554, 1482, 1465, 1424 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{12}H_{12}N_3O$: 214.0975, found: 214.0982.

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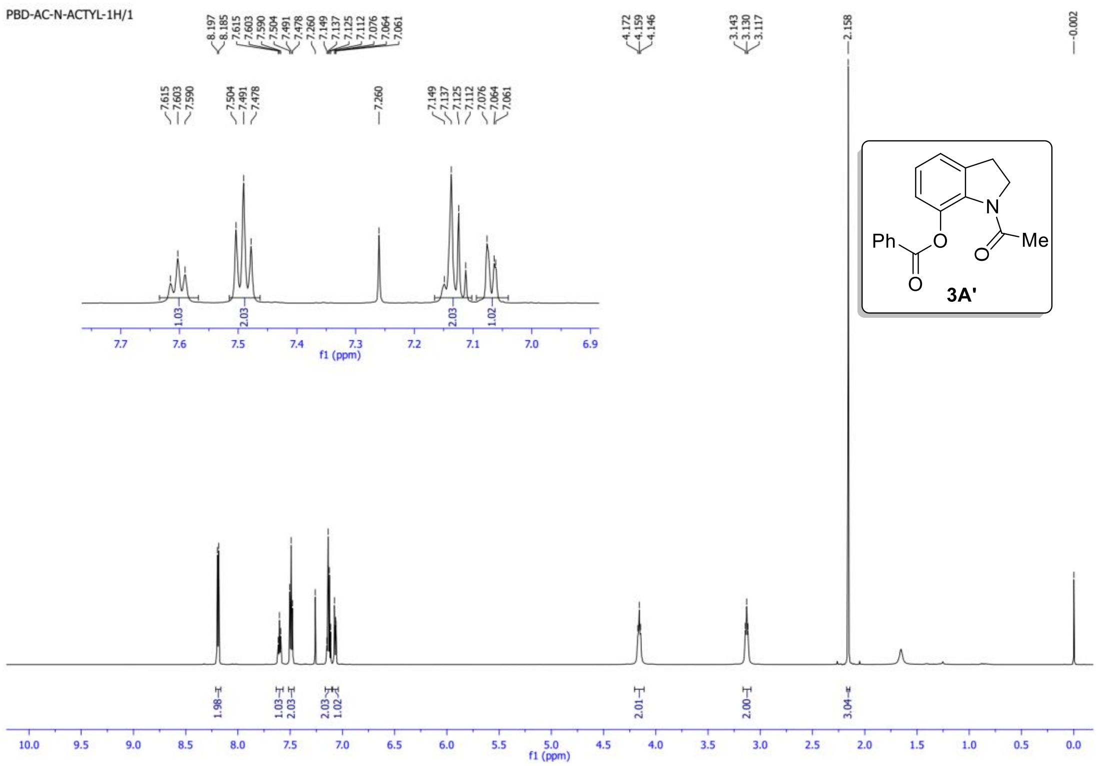
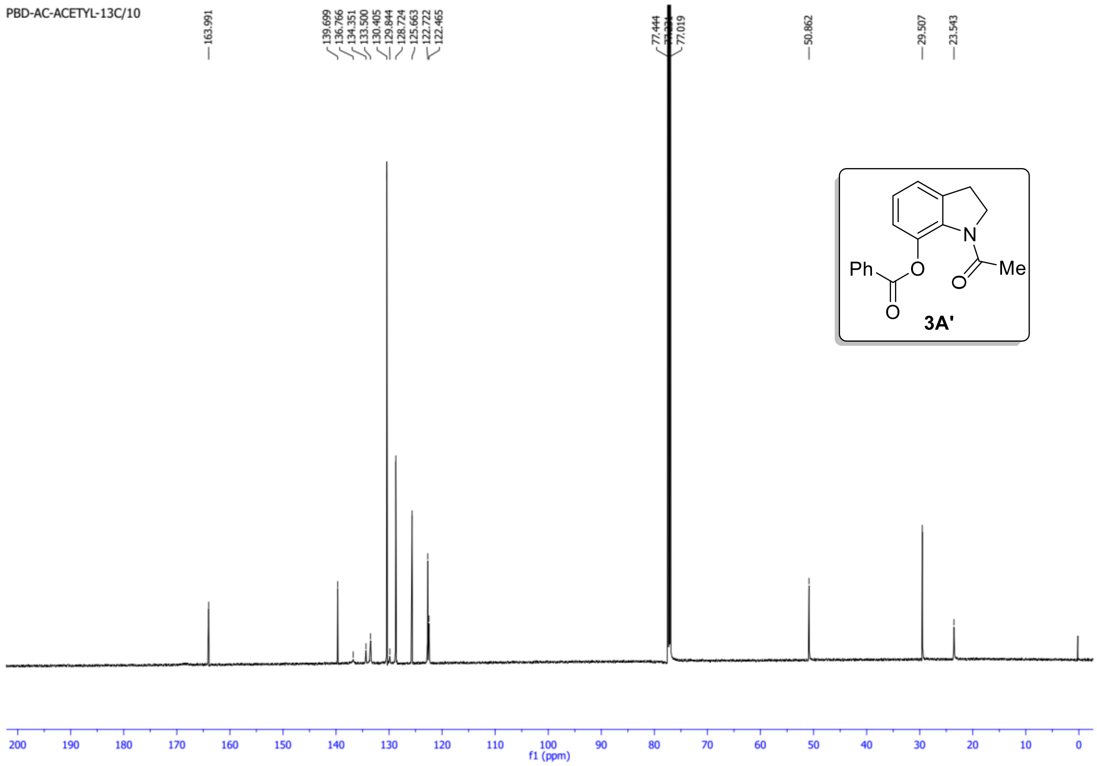
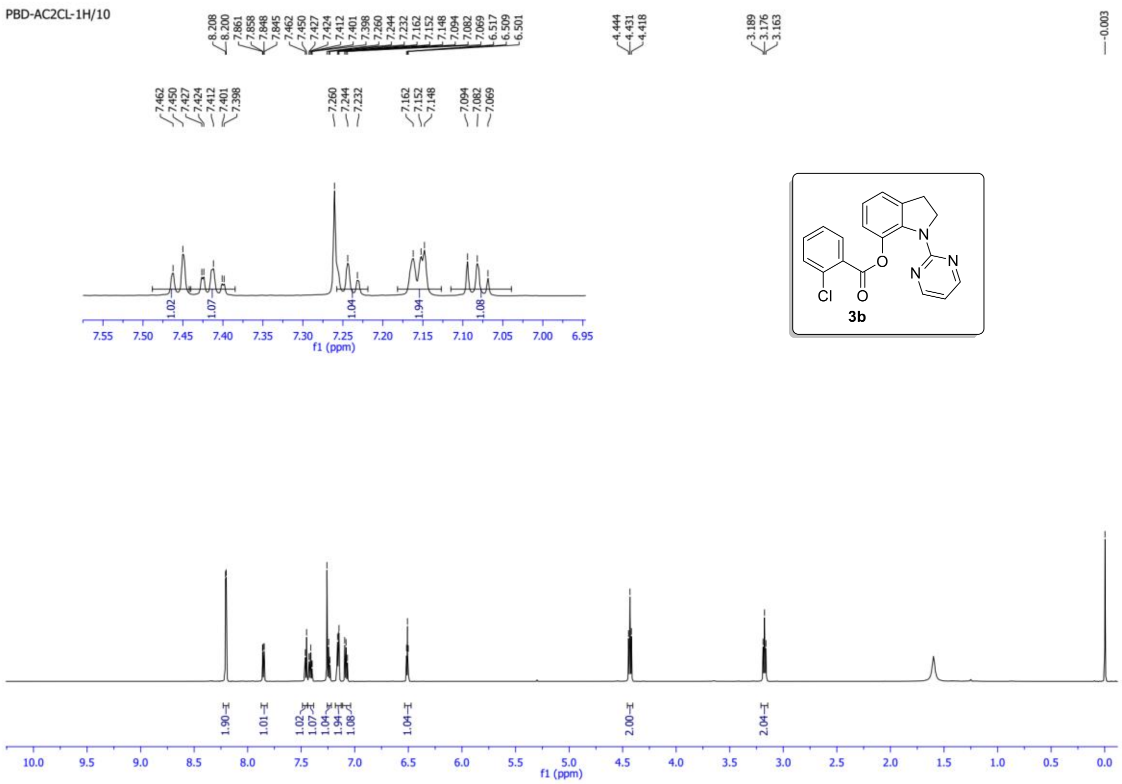
1.6 Selected NMR Spectra



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7.424
7.412
7.401
7.398
7.260
7.244
7.232
7.162
7.152
7.148
7.094
7.082
7.069
6.517
6.509
6.501
4.444
4.431
4.418
3.189
3.176
3.163
-0.003
1.02
1.07
1.04
1.94
1.08
f1 (ppm)
Cl
O
O
N
N
N
3b
1.90
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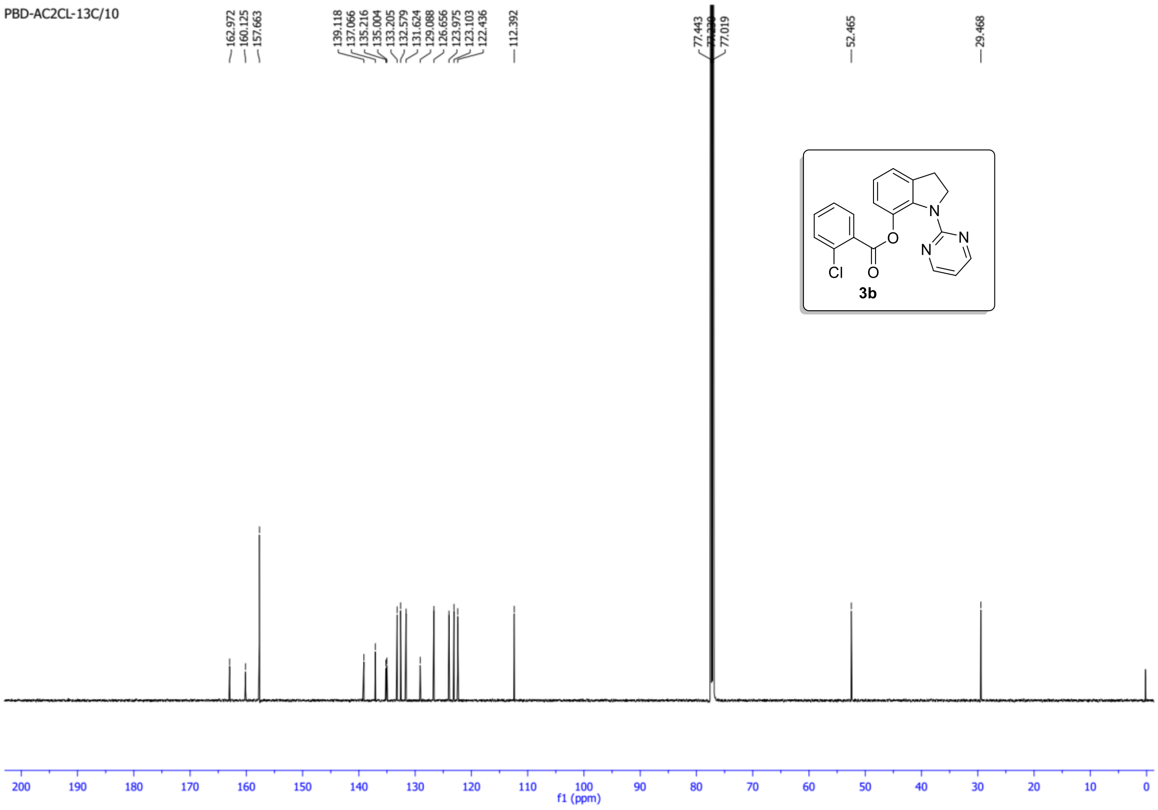
1.02
1.07
1.04
1.94
1.08
1.04
2.00
2.04
f1 (ppm)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157.663
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133.205
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131.624
129.088
126.656
123.975
123.103
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Cl
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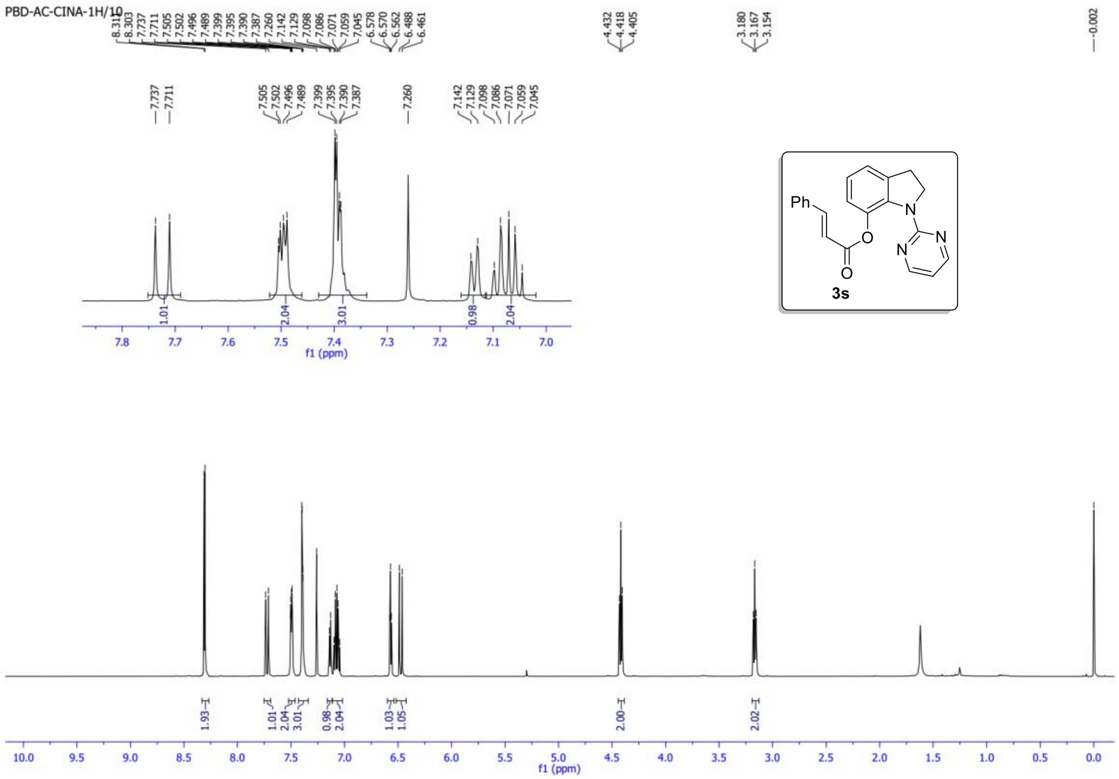
O
N
N
N
3b
f1 (ppm)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3.154
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Ph
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O
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2.04
f1 (ppm)
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1.01
2.04
3.01
0.98
2.04
1.03
1.05
2.00
2.02
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9.5
9.0
8.5
8.0
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6.0
5.5
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2.5
2.0
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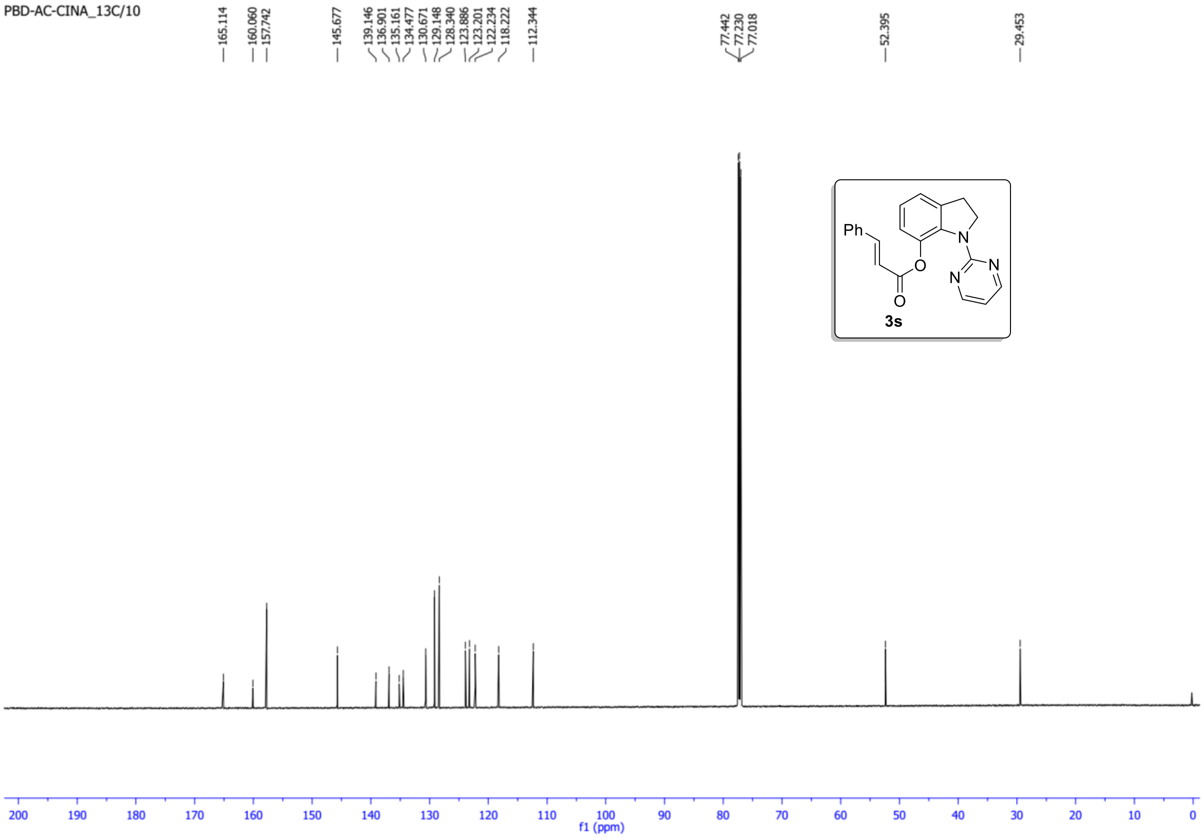
1.0
0.5
0.0
f1 (ppm)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Ph
O
N
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N
O
3s
200
190
180
170
160
150
140
130
120
110
100
90
80
70
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50
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30
20
10
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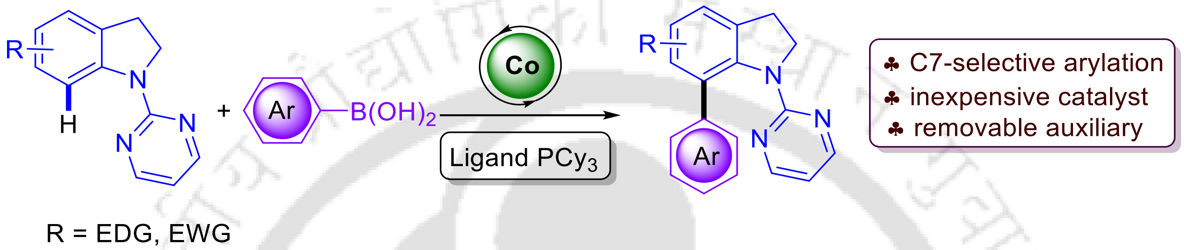
f1 (ppm)

Chapter II

Co(II)-Catalyzed Site-Selective C7-Arylation of Indolines with Arylboronic Acids



♣ C7-selective arylation
♣ inexpensive catalyst
♣ removable auxiliary

Chem. Commun. **2018**, *54*, 2494

Co(II)-Catalyzed Site-Selective C7-Arylation of Indolines with Arylboronic Acids

Transition-metal-catalyzed C-H functionalization[1] has recently appeared a trustworthy synthetic tool for the carbon-carbon and carbon-heteroatom bond formation enabled by chelation. Among them, C-H arylation is attractive as this core moiety is found in many bio-active molecules and natural products. However, this transformation is mostly limited to Pd and other noble transition metals.[2] In this context, exploitation of eco-benign and cost-effective metals to achieve comparable C-H arylation efficiencies continue to garner much attention. Cobalt being less-expensive, air stable and minimally toxic guided this methodology into new dimension for achieving varied modifications.[3] Many groups showcased the utilization of Co-based catalyst systems with Grignard reagents as the bases and reductants.[4] This limits the practicality and the scope of aryl electrophiles, which often leads to unwanted coupling products. Therefore, enabling sustainable and elegant approaches for C-H arylation is extremely desirable. The biological prevalence and ubiquity of the indole moiety has pushed it to the forefront of organic synthesis (Figure 1).[5] Several studies have thus appeared, for the functionalization of of indoles.[6-8] However, due to the innate reactivity of pyrrole type ring, mainly C2 and C3 functionalizations[6,7] have been accomplished and hence direct C7 functionalization of indoles remained elusive.[8] Recently, the C7 decorated indoles have been triggered *via* chelation supported functionalization of indolines, followed by oxidation. The existing C7 functionalizations mainly rely on precious metal catalysts, such as Pd,[9] Rh,[10] Ir[11] and Ru[12] based homogeneous catalytic systems. Exploiting the functionalization on biologically imperative indole moiety this chapter describes a Co(II)-PCy_3-catalyzed C7 arylation of indolines with arylboronic acids as an arylating agent using a removable pyrimidyl coordinating group, which can be further oxidized to deliver C7-arylated indoles in good yields. The addition of the PCy_3 ligand, oxygen and HFIP as solvent had a profound effect on the product yield. To the best of our knowledge, this is the first example for the C-H functionalization at the C7 position of indoles using inexpensive cobalt catalyst.

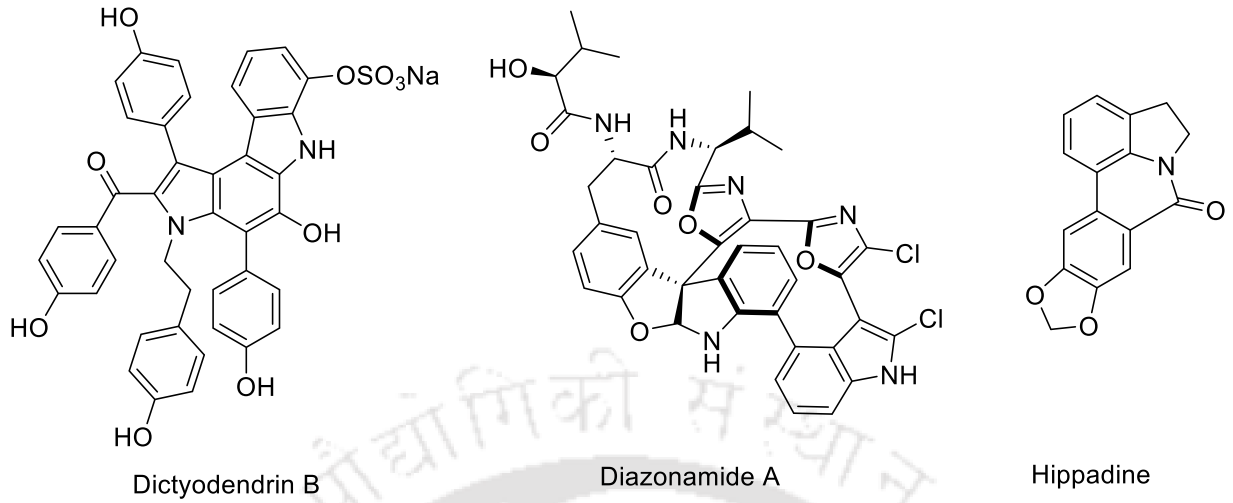
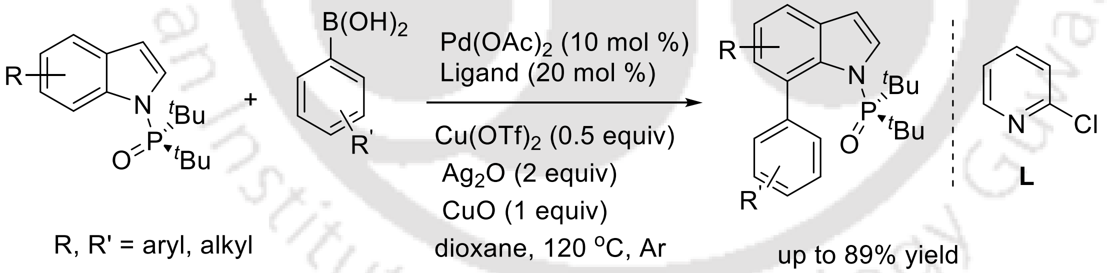


Figure 1. Selected examples of bio-active C7-arylated indoles

2.1 Literature

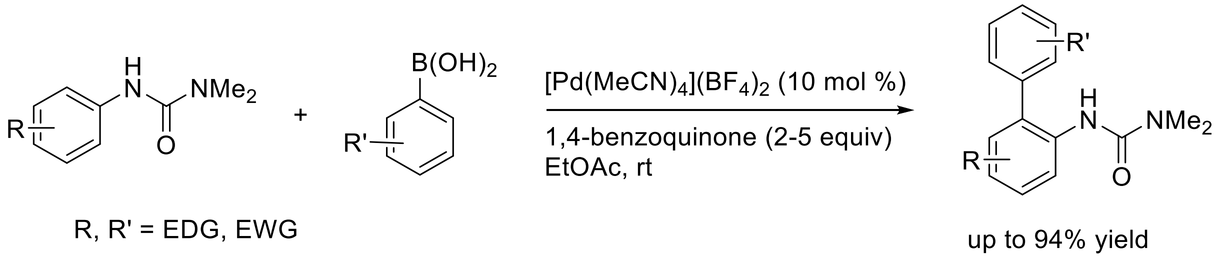
2.1.1 Metal-Catalyzed/Mediated C-H Arylation of Arenes

Shi and co-workers reported a direct C7-arylation of indoles using a di-*tert*-butyl phosphine oxide as directing group under Pd(II)-catalysis at high temperature in presence of Ag_2O and CuO as oxidants (Scheme 1).[13] The use of pyridine based ligand was found to have a profound effect as it accelerates the product yield.



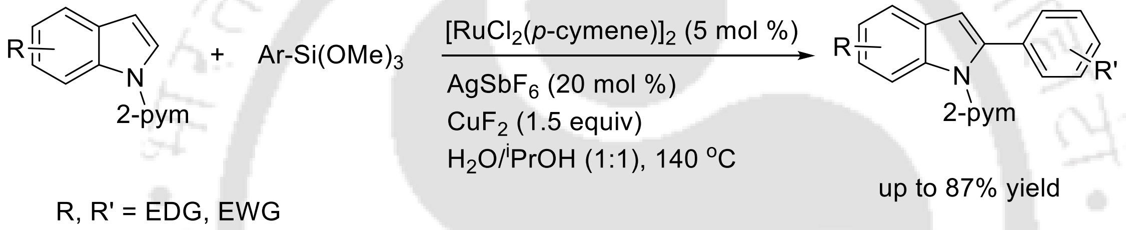
Scheme 1. Pd-Catalyzed C7-Arylation of Indoles using Arylboronic Acids

Lipshutz and co-workers described Suzuki Miyaura coupling reaction *via* C-H activation with aryl ureas using cationic Pd(II)-complex as active catalyst at room temperature. The directing group can be removed by base hydrolysis to afford corresponding aniline derivatives in quantitative yields (Scheme 2).[14]



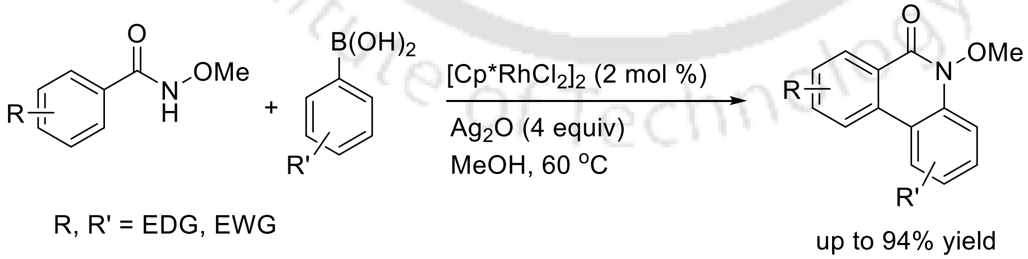
Scheme 2. Pd-Catalyzed Direct Suzuki Miyaura Coupling using Arylboronic Acids

Szostak and co-workers reported a Ru-catalyzed site-selective directed Hiyama cross-coupling of indoles using arylsilanes as a coupling partner at high temperature in water (Scheme 3). The reaction took place exclusively at the C-2 position of indoles and provided broad substrate scope with respect to both the indole and arylsilane component.[15]



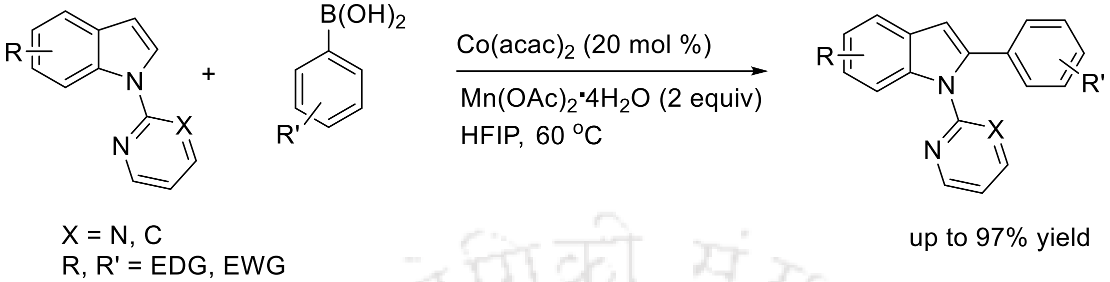
Scheme 3. Ru-Catalyzed C2-Arylation of Indoles using Arylsilanes

Cheng and co-workers reported a Rh-catalyzed dual oxidative C-C/C-N bond formation of *N*-methoxybenzamides and aryl boronic acids for the synthesis of phenanthridinone derivatives. This one-pot reaction involves regioselective C-C bond formation through *ortho*-arylation followed by C-N bond formation (Scheme 4).[16]



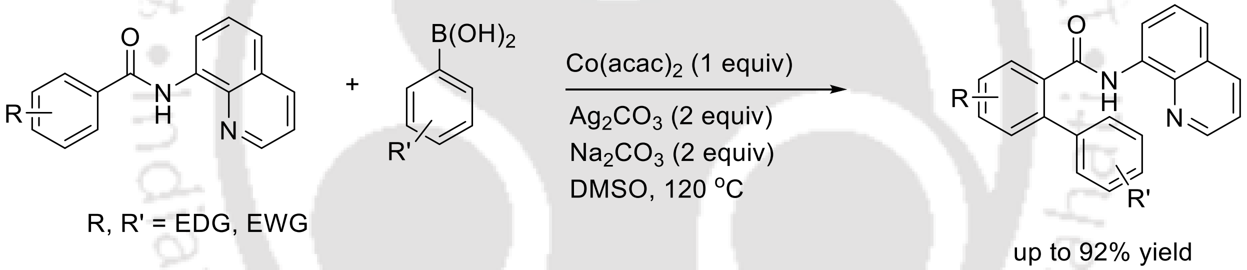
Scheme 4. Rh-Catalyzed C-C/C-N Bond Formation Towards Phenanthridinones

A cobalt(II)-catalazed oxidative C2-arylation of indoles with boronic acids through monodentate chelation assistance in HFIP at moderate temperature was accomplished.[17] This reaction proceeds under Grignard reagent-free mild reaction conditions with high C2 selectivity using inexpensive catalyst (Scheme 5).



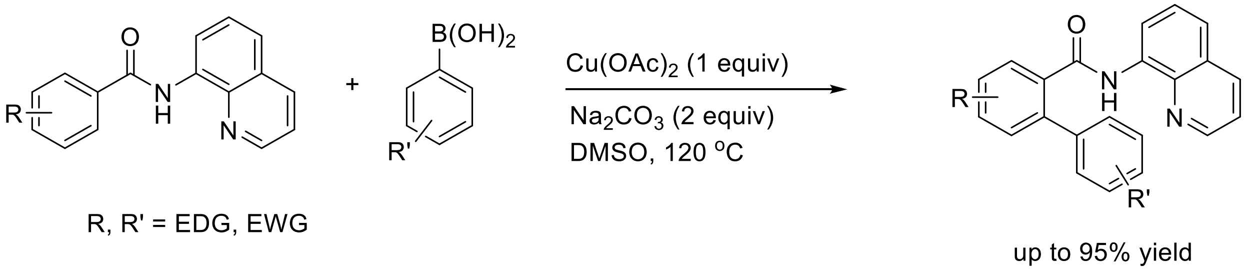
Scheme 5. Co-Catalyzed C2-Arylation of Indoles using Arylboronic Acids

Tan and co-workers reported a Co-mediated *ortho*-arylation of benzamides using 8-aminoquinolone as directing group utilizing arylboronic acid at elevated temperature (Scheme 6).[18a] Additionally, the authors extended this protocol for the arylation of acrylamides utilizing stoichiometric amount of cobalt source.



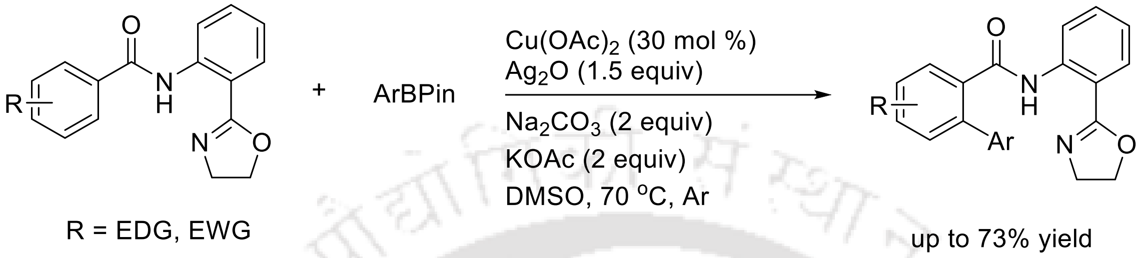
Scheme 6. Co-Mediated Positional-Selective C-H Arylation of Benzamides

Later, the same group accomplished a Cu-promoted bidentated auxiliary assisted *ortho*-C-H arylation using arylboronic acids as arylating agent in good to excellent yields (Scheme 7).[18b] The 8-aminoquinoline directing group was successfully extruded by *N*-methylation of amide followed by base hydrolysis to provide 2-aryl benzoic acids.



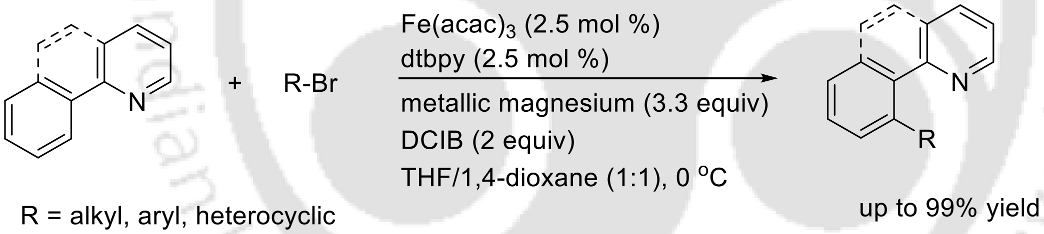
Scheme 7. Cu-Promoted *ortho*-C-H arylation using Arylboronic acids

Yu and co-workers reported a Cu-catalyzed C-C coupling reaction of benzamide derivatives with aryl boron reagents for the synthesis of bi-aryl substructures employing removable directing group (Scheme 8). The authors readily synthesized 2-aryl aldehydes and carboxylic acids from the Boc-protected product.[19]



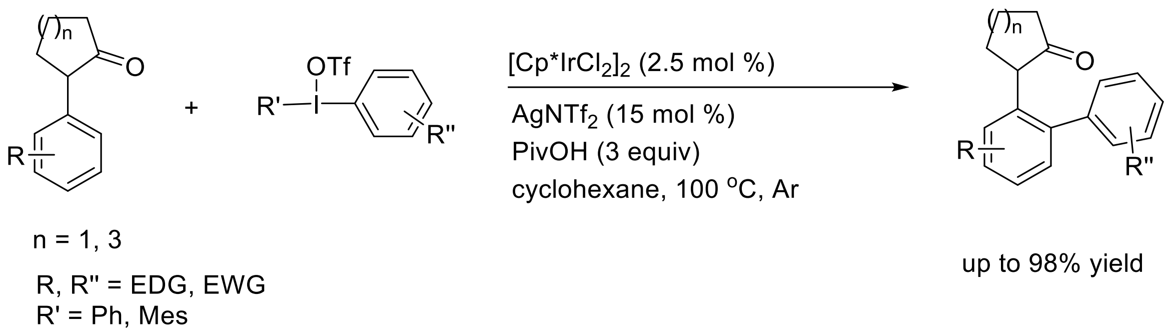
Scheme 8. Cu-Catalyzed *ortho*-Arylation using Arylboron Reagents

Nakamura and co-workers reported nitrogen co-ordinated direct cross-coupling of arenes with aryl bromides in the presence of an iron catalyst and diamine as ligand. The reaction employs metallic magnesium as an additive and 1,2-dichloroisobutane (DCIB) as an oxidant at 0 °C. The use of 1,4-dioxane as a co-solvent is vital for this transformation (Scheme 9).[20]



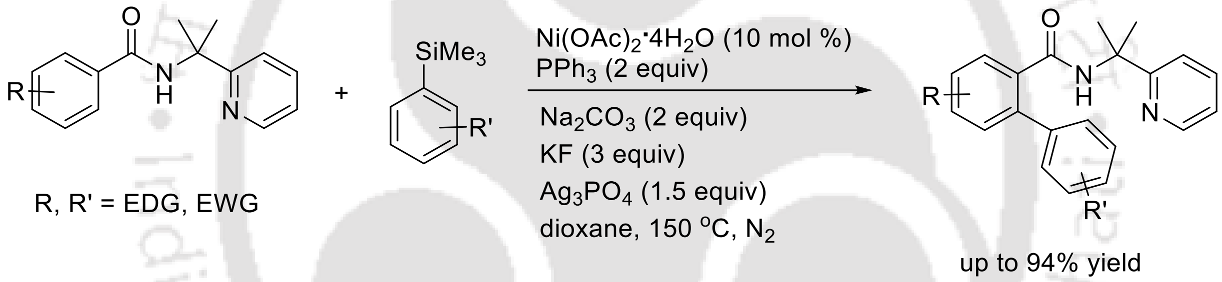
Scheme 9. Fe-Catalyzed Regioselective C-C Bond Formation of Arenes

The regioselective C-H arylation of arenes has been described by Shi and co-workers using diaryliodonium salts as the arylating source in the presence of a iridium(III) catalyst (Scheme 10).[21] This study provided easy access to biaryl motifs and displays high functional group tolerance with excellent yield.



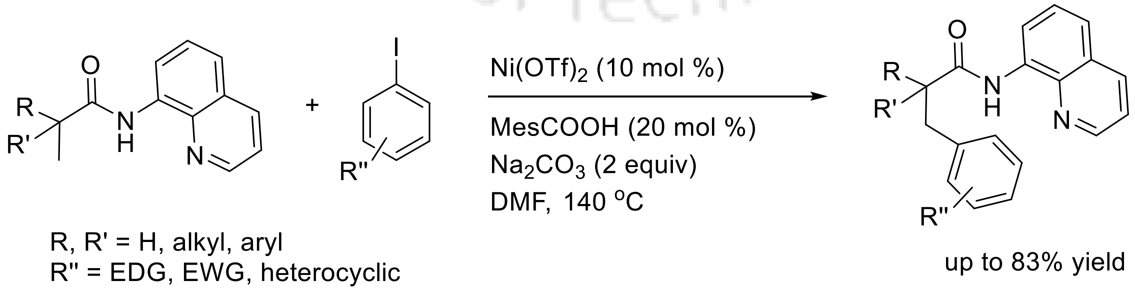
Scheme 10. Ir-Catalyzed Coupling of Arenes using Diaryliodonium Salts

Shi and co-workers reported a Ni-catalyzed *ortho*-arylation of carboxamides with organosilicon reagent *via* bidentate chelation assistance. This study features the usage of nontoxic arylsilanes as arylating agent, broad substrate scope with functional group compatibility and the late-stage DG removal (Scheme 11).[22]



Scheme 11. Directed *ortho*-Arylation of Benzamides under Ni-Catalysis

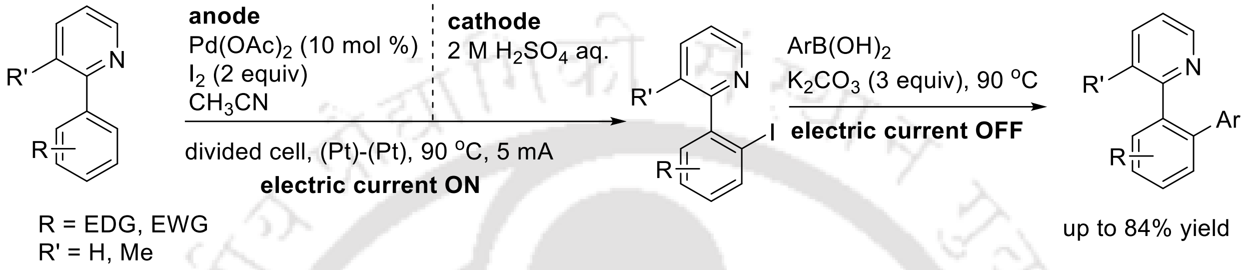
Chatani and co-workers reported a Ni(II)-catalyzed 8-aminoquinoline directed C(sp^3)-H arylation in aliphatic amides using aryl iodides as an arylating agent. The detailed mechanistic studies shows that reversible C-H activation step may not involve in the rate determining step (Scheme 12).[23]



Scheme 12. Ni-Catalyzed sp^3 C-H Arylation using Aryl Iodides

2.1.2 Electrochemical Direct C-H Arylation of Arenes

Electrochemical Pd-catalyzed *ortho*-arylation of 2-aryl pyridines via C-H iodination has been developed by Kakiuchi group. The authors achieved this arylation employing arylboronic acids as arylating source in a one-pot fashion in presence of a palladium catalyst. This Suzuki−Miyaura coupling operates by ON/OFF switching of electric current with two dissimilar catalytic cycles (Scheme 13).[24]

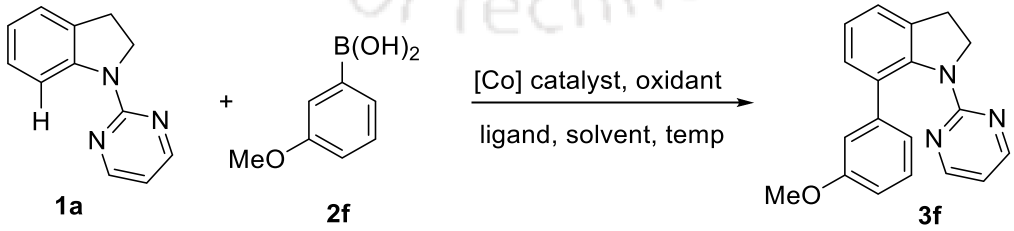


Scheme 13. Electrochemical Pd-Catalyzed Cross-coupling of Arenes

2.2 Present study

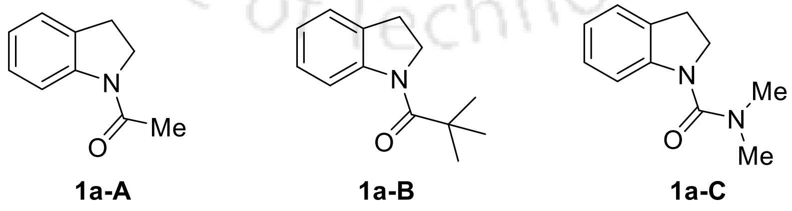
Herein, an expedient C7 arylation of indolines with arylboronic acids as coupling partner has been developed under Co(II)-PCy_3 catalyst regime using a removable pyrimidyl auxiliary at moderate temperature. At the outset of our studies, the reaction was investigated introducing *N*- and *O*-coordinating groups (DG) on the *N*-atom of indoline, such as pyrimidyl **1a**, acetyl **1a-A**, pivaloyl **1a-B** and *N*, *N*-dimethylcarbamoyl **1a-C**. The O-coordinating directing groups failed to produce the desired C7 arylated indoline, whereas the *N*-coordinating pyrimidyl group **1a** was found to be crucial for the transformation (Table 1).

Table 1. Optimization of Reaction Conditions[a]



Entry	[Co] Catalyst	Oxidant	Ligand	Solvent	Yield [b](%)
1	Co(acac)$_2$	Mn(OAc)$_2$·4H$_2$O	-	HFIP	27
2	Co(OAc)$_2$	Mn(OAc)$_2$·4H$_2$O	-	HFIP	12
3	Co(OAc)$_2$·4H$_2$O	Mn(OAc)$_2$·4H$_2$O	-	HFIP	10
4	Co(acac)$_2$	Mn(acac)$_3$	-	HFIP	15
5	Co(acac)$_2$	Mn(OAc)$_3$·2H$_2$O	-	HFIP	7
6	Co(acac)$_2$	MnO$_2$	-	HFIP	n.d.
7	Co(acac)$_2$	K$_2$S$_2$O$_8$	-	HFIP	n.d.
8	Co(acac)$_2$	Mn(OAc)$_2$·4H$_2$O	1,10-phen	HFIP	17
9	Co(acac)$_2$	Mn(OAc)$_2$·4H$_2$O	PCy$_3$	HFIP	56
10	Co(acac)$_2$	Mn(OAc)$_2$·4H$_2$O	P(O)Cy$_3$	HFIP	11
11	Co(acac)$_2$	Mn(OAc)$_2$·4H$_2$O	PPh$_3$	HFIP	25
12	Co(acac)$_2$	Mn(OAc)$_2$·4H$_2$O	P(*o*-tolyl)$_3$	HFIP	29
13	Co(acac)$_2$	Mn(OAc)$_2$·4H$_2$O	DPPF	HFIP	45
14	Co(acac)$_2$	Mn(OAc)$_2$·4H$_2$O	DPPM	HFIP	54
15	Co(acac)$_2$	Mn(OAc)$_2$·4H$_2$O	Boc-val-OH	HFIP	19
16	Co(acac)$_2$	Mn(OAc)$_2$·4H$_2$O	PCy$_3$	HFIP	77[d](60)[c]
17	Co(acac)$_2$	Mn(OAc)$_2$·4H$_2$O	PCy$_3$	TFE	28
18	Co(acac)$_2$	Mn(OAc)$_2$·4H$_2$O	PCy$_3$	MeOH	trace
19	Co(acac)$_2$	Mn(OAc)$_2$·4H$_2$O	PCy$_3$	(CH$_2$Cl)$_2$	trace
20	Co(acac)$_2$	Mn(OAc)$_2$·4H$_2$O	PCy$_3$	HFIP	38[e]
21	Co(acac)$_2$	Mn(OAc)$_2$·4H$_2$O	PCy$_3$	HFIP	41[f]
22	-	Mn(OAc)$_2$·4H$_2$O	PCy$_3$	HFIP	n.d.

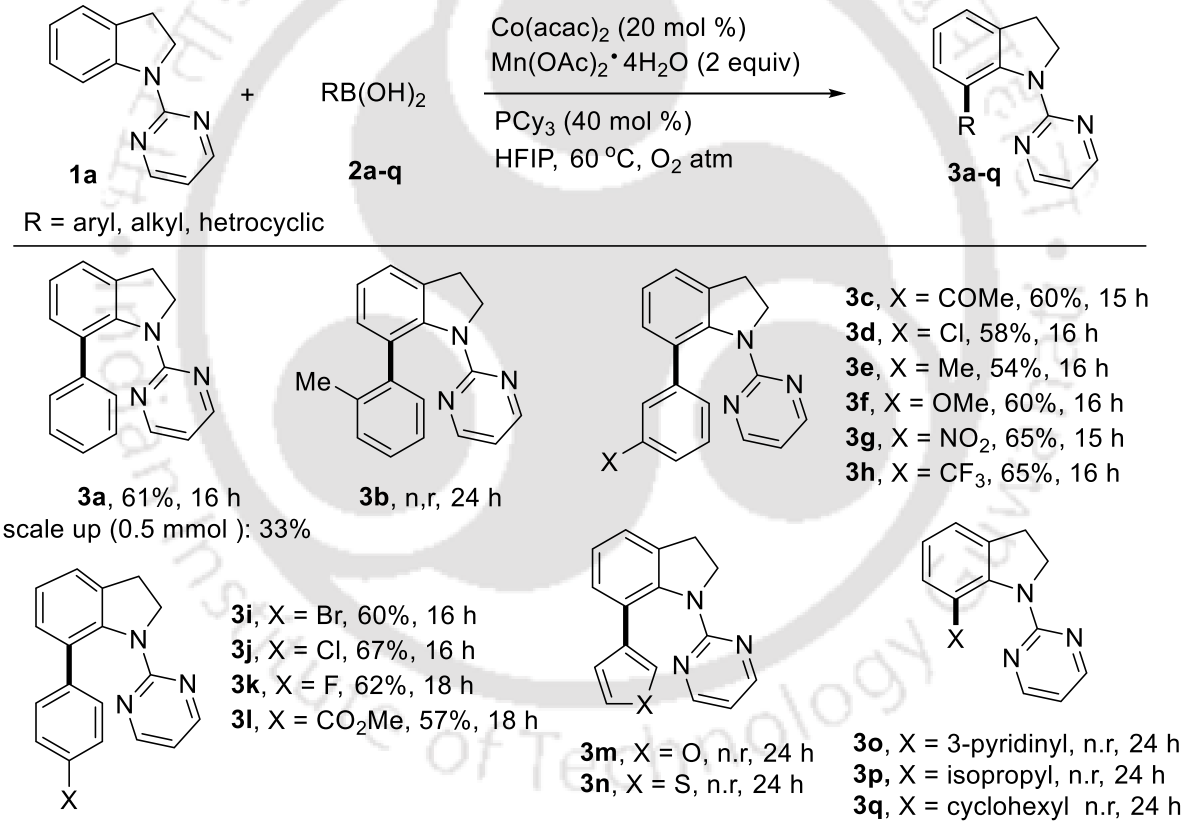
screening of directing groups



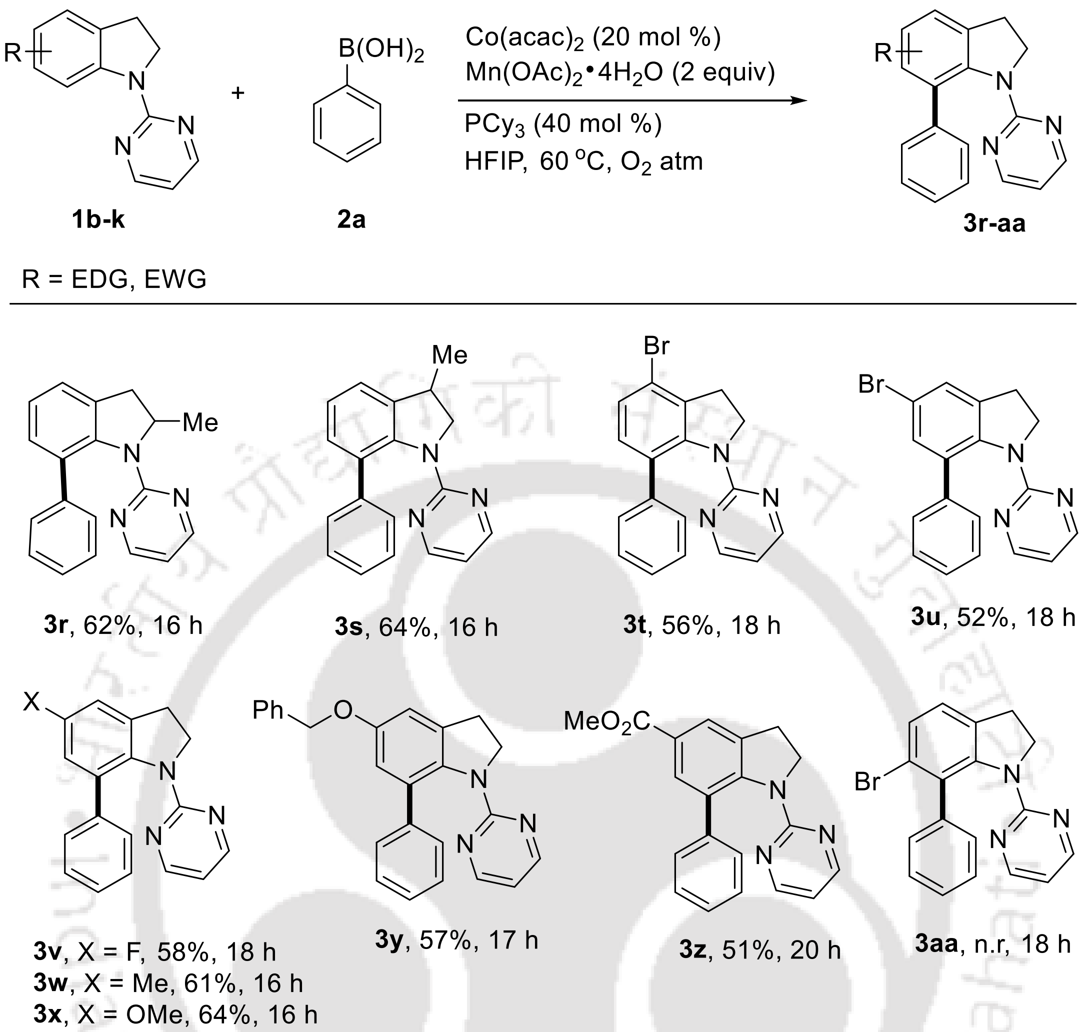
[a]Reaction Conditions: **1a** (0.1 mmol), **2f** (0.2 mmol), [Co] catalyst (20 mol %), oxidant (2 equiv), ligand (40 mol%), solvent (0.5 mL), 60 °C, 16 h. [b] Determined by 400 MHz ^{1}H NMR. [c]Isolated yield. [d] Using oxygen balloon. [e] Co(acac)$_2$ (10 mol %) was used. [f] Reaction at 45 °C. n.d. = not detected.

With this findings, we commenced our optimization studies using *N*-pyrimidyl indoline **1a** and (3-methoxyphenyl)boronic acid **2f** as the model substrates in the presence of various cobalt salts, ligands, oxidants and solvents at different temperatures (Table 1). To our delight, the reaction occurred to afford the C7 arylated **3f** in 27% yield, when the substrates **1a** and **2f** were stirred with 20 mol % Co(acac)$_2$ and 2 equiv Mn(OAc)$_2$·4H$_2$O at 60 °C in HFIP under air (entry 1). The replacement of Co(acac)$_2$ with Co(OAc)$_2$ or Co(OAc)$_2$·4H$_2$O as the cobalt source only resulted in inferior yield (entry 2-3). Similar results were witnessed when Mn(acac)$_3$, Mn(OAc)$_3$·2H$_2$O, MnO$_2$ and K$_2$S$_2$O$_8$ were used as an oxidant (entries 4-7). A drastic enhancement in the conversion was noticed by the introduction of phosphine based ligands. Among the screened ligands such as PCy$_3$, P(O)Cy$_3$, 1,10-phen, PPh$_3$, P(*o*-tolyl)$_3$, DPPF (1,1'-bis(diphenylphosphino)ferrocene), DPPM (1,1-bis(diphenylphosphino)methane) and Boc-Val-OH, the former produced best result in 56% yield (entries 8-15). The optimal efficiency was accelerated the yield to 77% employing oxygen balloon (entry 16). Finally, our optimization studies concluded with the finding that 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) was the solvent of choice, while 2,2,2-trifluoroethanol (TFE), methanol and 1,2-dichloroethane gave inferior results (entries 17-19). Lowering the catalyst amount (10 mol %) or temperature (45 °C) led to drop in yield to <41% (entries 20-21). A control experiment without the cobalt source resulted in no C7 arylation of the parent indoline (entry 22).

After establishing the effective conditions for C7 arylation, the practicality of the protocol was assessed engaging electronically varied arylboronic acids with indoline **1a** as a standard substrate (Scheme 14). The reaction of phenylboronic acid **2a** gave the C7 arylated **3a** in 61% yield. When this reaction was performed on a scale-up (0.5 mmol) provided **3a** in 33% yield. 2-Me substituted boronic acid **2b** was unsuccessful substrate under the reaction conditions due to steric effect resided at the *ortho* position. Thorough examination of the substituent pattern at the *meta*-position on arylboronic acid such as acetyl **2c**, chloro **2d**, methyl **2e**, methoxy **2f** and nitro **2g** groups efficiently delivered the corresponding arylated **3c-g** in 54-65% yields irrespective of their electronic effects. Notably, strong electron-withdrawing 3-trifluoromethyl substituted boronic acid **2h** was also operative to the reaction condition and provided **3h** in 65% yield. Whereas, *para*-substituted arylboronic acids like 4-bromo **2i**, 4-chloro **2j** and 4-fluoro **2k** groups furnished the C-H arylation products **3i-k** in 60-67 % yields. Additionally, the substrate **2l** bearing methyl ester at the 4-position successfully reacted to afford **3l** in 57% yield. A number of heteroaryl boronic acids **2m-o** were also examined in the reaction, but they were recognized to be ineffective substrates under the optimal reaction condition. Alkylboronic acid coupling partners such as **2p-q** exhibited no reaction under these conditions, and the starting materials were recovered intact.

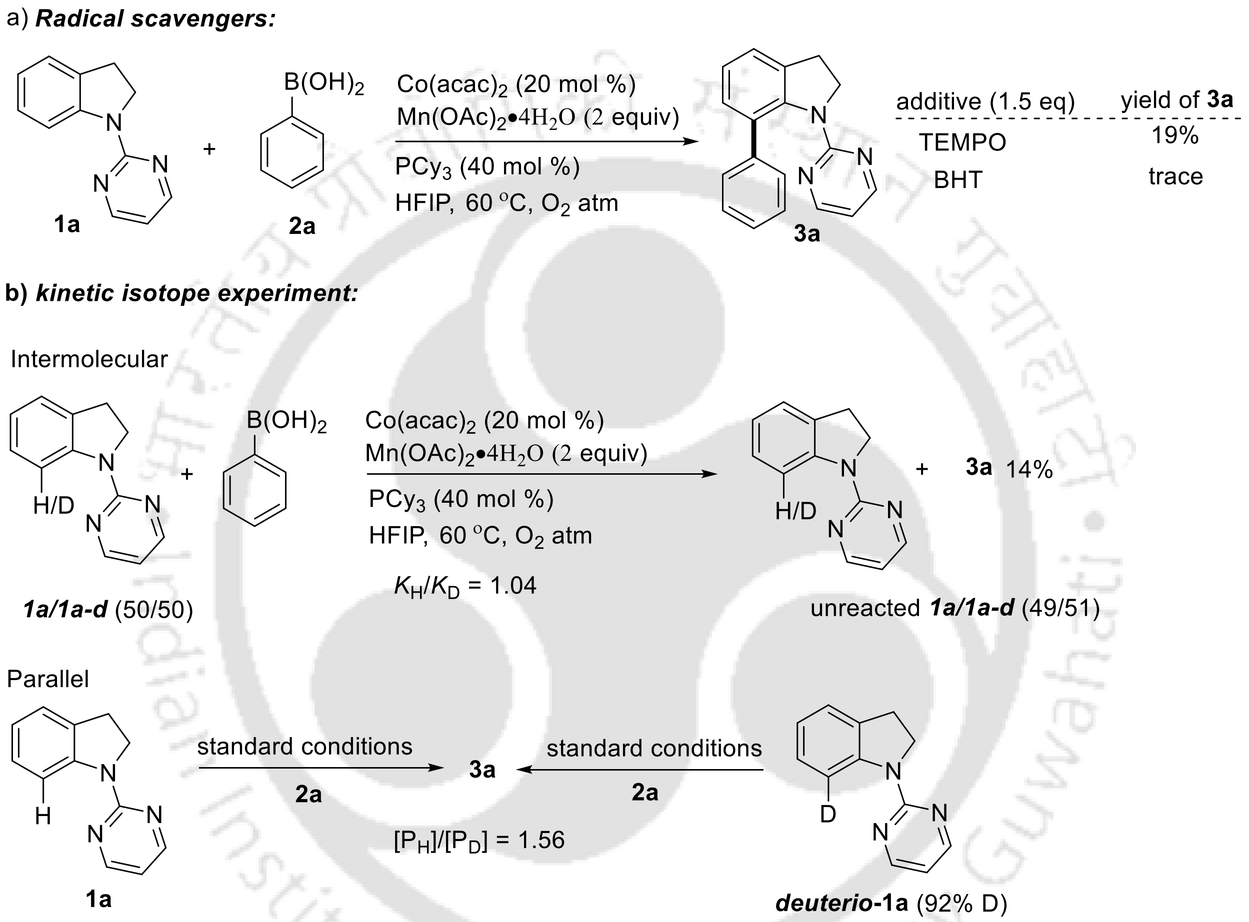


Scheme 14. Substrate Scope of Arylboronic Acids **2a-q** with Indoline **1a**.[a,b] [a]Reaction Conditions: **1a** (0.1 mmol), **2a-q** (0.2 mmol), Co(acac)$_2$ (20 mol %), Mn(OAc)$_2$·4H$_2$O (2 equiv), PCy$_3$ (40 mol %), HFIP (0.5 mL), 15-24 h. [b]Isolated yield. n.r = no reaction.



Scheme 15. Substrate Scope of Indolines **1b-k** with Phenylboronic acid **2a.**[a,b] [a]Reaction Conditions: **1b-k** (0.1 mmol), **2a** (0.2 mmol), Co(acac)$_2$ (20 mol %), Mn(OAc)$_2$·4H$_2$O (2 equiv), PCy$_3$ (40 mol %), HFIP (0.5 mL), 16-20 h. [b]Isolated yield.

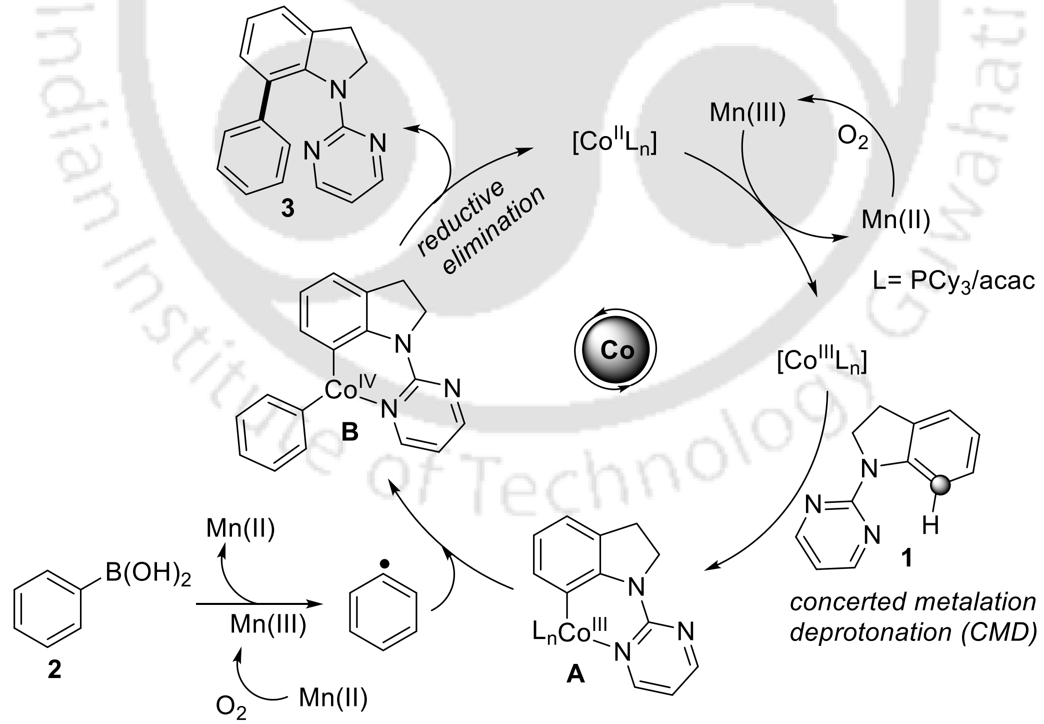
Next, the robustness of the methodology was harnessed by extending the scope of the site-selective arylation of a series of substituted indolines with phenylboronic acid **2a** as standard substrate (Scheme 15). The substrates having 2-methyl **1b**, 3-methyl **1c** and 4-bromo **1d** substituents went on arylation in 62, 64, and 56% yields, respectively. Moreover, 5-substituted indolines such as 5-bromo **1e**, 5-fluoro **1f**, 5-methyl **1g**, 5-methoxy **1h**, 5-benzylether **1i** and 5-ester **1j** groups were found to be well tolerated under identical conditions giving **3q-v** in 51-64% yields. Surprisingly, the substrate **1k** bearing 6-Br functionality did not react to afford the target product. This may be attributed to the steric congestion encountered near C-H functionalization site by the bromo group. It is noteworthy that the cobalt based catalytic system tolerated an array of functionalities on both the coupling partners, comprising of further synthetically modifiable halo and nitro groups.



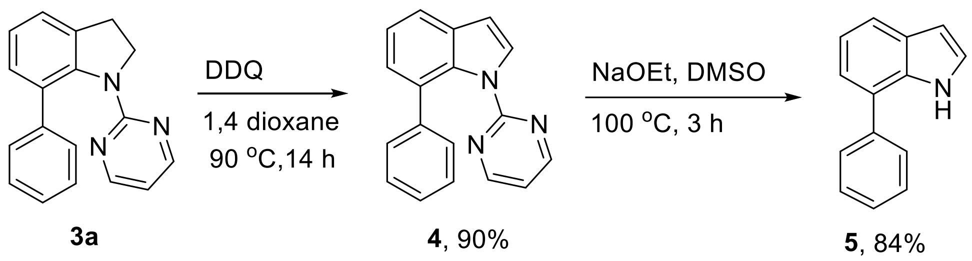
Scheme 16. Preliminary Mechanistic Investigations

To gain insight into the reaction mechanism, radical scavenging and kinetic isotope experiments were conducted. Introducing radical scavengers like TEMPO and BHT into the reaction medium utilizing indoline **1a** and arylboronic acid **2a** as the representative substrates, significantly inhibited the outcome of the arylation process (Scheme 16a). These results confide that a SET-type mechanism may be operative during the course of the reaction.[6h] Moreover, the intermolecular kinetic isotope experiment with equimolar mixture of **1a** and **1a-*d*** with **2a** under optimal reaction conditions gave $k_H/k_D = 1.04$ (Scheme 16b). Next, parallel reactions of **1a** and ***deuterio*-1a** with **2a** under standard reaction conditions exhibited $P_H/P_D = 1.56$, which suggests that the C−H activation step might not be involved in the rate-determining step. On the basis of the preliminary mechanistic investigation and previous literature, a plausible mechanism is depicted in scheme 17. First, Mn^{II} is oxidized to Mn^{III} complex under oxygen atmosphere, which reacts with Co^{II} to form Co^{III} species. The latter may react with the substrate **1** to form the six membered cobaltocycle **A** *via* the CMD (concerted metalation deprotonation) process. The aryl radical,[25] genarated by the reaction of arylboronic acid **2** with Mn^{III} may undergo reaction with **A** to give the cobalt(IV) species **B**. Lastly, the reductive elimination of **B** may produce the target product with the regeneration of cobalt(II) species to fulfil the catalytic cycle.

Finally, to disclose the synthetic utility of the Co-catalyzed arylation protocol, the facile late-stage removal of the pyrimidyl counterpart was accomplished. The target C7 arylated indoline **3a** was oxidized to indole **4** in presence of DDQ followed by base promoted C-N bond cleavage to furnish the 7-phenyl-indole **5** in 84% yield (Scheme 18). Therefore, bio-relevant C-7 decorated aryl indole frameworks can be accessed efficiently through present strategy.



Scheme 17. Plausible Catalytic Cycle



Scheme 18. Late-State Removal of Directing Group

In summary, we have demonstrated an efficient Co(II)-catalyzed site-selective C7 arylation of indolines with arylboronic acids using a removable pyrimidyl chelating group and subsequent oxidation with DDQ followed by directing group removal to assemble bio-relevant C7-arylated indoles in good yields. The methodology was highlighted in the implementation of readily accessible reagents, cost-effective cobalt catalyst and late-stage removal of directing group.

2.3 Experimental Section

General Information. Indoles, 2-chloropyrimidine (95%), boronic acids, $Co(acac)_2$ (97%), $Co(OAc)_2$ (99.995%), PCy_3, 1,1,1,3,3,3-hexafluoro-2-propanol (99%), 2,2,2-trifluoroethanol, DDQ (98%) and 2,2,6,6-tetramethylpiperdine-1-oxyl (99%) purchased of Aldrich, $NaCNBH_3$ procured of Spectrochem, $Mn(OAc)_2{\cdot}4H_2O$ and butylated hydroxytoluene (BHT) of Merck were used as received. Merck silica gel G/GF 254 plates for analytical TLC and Rankem silica gel (100-200 mesh) for column chromatography were used. DRX-400 Varian spectrometer and Bruker Avance III 600 and 400 spectrometers were used for recording NMR (^1H and ^{13}C) spectra using $CDCl_3$ and as solvent and TMS as an internal standard. Chemical shifts (δ) and spin-spin coupling constant (J) are reported in ppm and in 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 with a Büchi B-540 apparatus and are uncorrected. FT-IR were collected on PerkinElmer IR spectrometer. Q-Tof ESI-MS instrument (model HAB 273) was used for recording mass spectra.

General Procedure for the Preparation of Directing Groups 1. To a stirred solution of indoles (1.0 equiv, 5.0 mmol) in AcOH (25 mL) at 0 °C was added $NaBH_3CN$ (5.0 equiv, 25.0 mmol) in portions. Then, the reaction mixture was stirred at room temperature until completion. Then the resulted mixture was diluted with water and basified with aq. NaOH solution, and extracted with ethyl acetate (3 x 30 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 corresponding indolines.

Then, the indolines (1.0 equiv) and 2-chloropyrimidine (1.2 equiv) were dissolved in DMSO. The resultant mixture was stirred at 100 ^{o}C and 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 and diluted with ethyl acetate (3 x 30 mL) and then washed with brine (2 x 10 mL) and water (1 x 10 mL). Drying (Na_2SO_4) and evaporation of the solvent gave a residue that was purified on silica gel column chromatography using n-hexane and ethyl acetate as an eluent to afford substituted 1-(Pyrimidin-2-yl)indolines **1**.

General Procedure for the Synthesis of *N*-Acetyl, *N*-Pivaloyl and *N*-Carbamoyl Indolines (1a-A-C). To a stirred solution of indoline (0.7 mmol, 1.0 equiv) and triethylamine (2.1 mmol, 3.0 equiv) in CH_2Cl_2 (5 mL) was added dropwise a solution of corresponding acid chloride or *N*-carbamoyl chloride (0.84 mmol, 1.2 equiv) in CH_2Cl_2 (3 mL) at 0 °C. The reaction mixture was stirred at this temperature for 15 min and further stirred at room temperature for 3 h. The resulting mixture was extracted between CH_2Cl_2 and H_2O. The organic layer was dried over 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 corresponding directing groups.

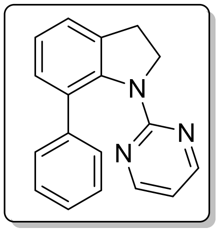
General Procedure for Cobalt(II)-Catalyzed C7 Arylation of Indolines. To a stirred solution of 1-(pyrimidin-2-yl)indoline (0.1 mmol), $Co(acac)_2$ (20 mol %, 0.02 mmol, 5.1 mg), $Mn(OAc)_2.4H_2O$ (0.2 mmol, 49 mg) and PCy_3 (40 mol %, 0.04 mmol, 11.2 mg) in HFIP (0.5 mL) under O_2 atmosphere, boronic acid (0.2 mmol) was added. The resultant mixture was stirred at 60 ^{o}C and 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 and 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 C7 arylated indolines.

Intermolecular Kinetic Isotope Effect Study. Phenylboronic acid **2a** (0.2 mmol, 24 mg) was reacted with 1-(pyrimidin-2-yl)indoline **1a** (0.1 mmol, 19.7 mg) and 1-(pyrimidin-2-yl)indoline-7-*d* **1a-*d*** (0.1 mmol, 19.8 mg) for 3 h under standard reaction condition. 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 gel column chromatography using *n*-hexane and ethyl acetate as an eluent to afford **3a** and a mixture of unreacted **1a** and **1a-*d*** as a yellowish liquid. The intermolecular k_H/k_D was found to be 1.04 after 3 h at 14% conversion, based on 400 MHz ^{1}H NMR of the recovered substrates **1a** and **1a-*d***.

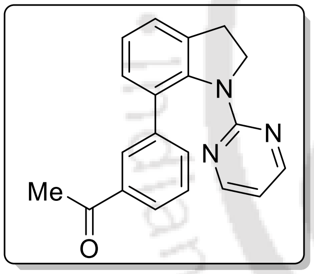
Parallel Kinetic Isotope Effect Study. In a set of two experiments: in first set, phenylboronic acid **2a** (0.2 mmol, 24 mg) was reacted with 1-(pyrimidin-2-yl)indoline **1a** (0.1 mmol, 19.7 mg) for 3 h under standard reaction conditions. Whereas in another set, 1-(pyrimidin-2-yl)indoline-7-*d* **1a-*d*** (0.1 mmol, 19.8 mg, 93% D) was used instead of **1a** in the reaction with phenyl boronic acid **2a** under the standard reaction conditions. The two reactions were allowed to stir at 60 °C for 3 h. For the both cases, 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 gel column chromatography using *n*-hexane and ethyl acetate as an eluent to afford **3a**. The yield of **3a** was obtained as 16% and 11% yields respectively. The KIE value of 1.56 was determined by ratio of obtained **3a** yield (KIE = 16%/11%/93% = 1.56).

Procedure for the Late-stage Removal of Pyrimidyl Directing Group. To a stirred solution of 7-phenyl-1-(pyrimidin-2-yl)indoline **3a** (0.1 mmol, 27.3 mg) in 1,4-dioxane, DDQ (0.2 mmol, 45.4 mg) was added at room temperature. The resultant solution was further stirred at 90 °C for 14 h. After completion, as indicated by TLC, the reaction mixture was cooled to room temperature and diluted with ethyl acetate (1 x 15 mL). The mixture was successively 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 gel column chromatography using *n*-hexane and ethyl acetate as an eluent to afford 7-phenyl-1-(pyrimidin-2-yl)-1H-indole **4** as a colorless liquid. Next, indole **4** (0.1 mmol, 27.1 mg) was dissolved in DMSO (1 mL) and NaOEt (5 equiv.) in EtOH (0.2 mL) was added to the mixture. The mixture was stirred at 100 °C for 3 h. After completion, the reaction mixture was cooled to room temperature and diluted with ethyl acetate (1 x 15 mL). The mixture was then washed with 2 N HCl (1 x 5 mL), 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 as an eluent to afford 7-phenyl-1H-indole **5** as a brown liquid.

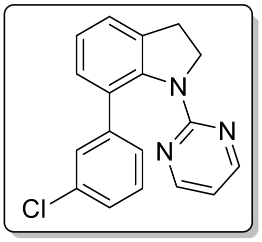
2.4 Characterization Data of Products



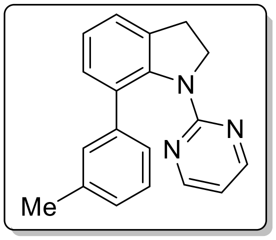
7-Phenyl-1-(pyrimidin-2-yl)indoline 3a. Analytical TLC on silica gel, 1:4 ethyl acetate/hexane $R_f = 0.43$; yellowish liquid; yield 61% (16.4 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, *J* = 4.8 Hz, 2H), 7.35 (d, *J* = 7.2 Hz, 2H), 7.28-7.23 (m, 2H), 7.17-7.07 (m, 4H), 6.37 (t, *J* = 4.8 Hz, 1H), 4.45 (t, *J* = 7.6 Hz, 2H), 3.18 (t, *J* = 7.6 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 159.3, 156.6, 142.4, 141.2, 135.1, 130.5, 129.1, 128.0, 126.8, 126.2, 123.9, 123.8, 111.9, 52.3, 29.7; FT-IR (neat) 2917, 2851, 1696, 1577, 1550, 1458, 1443, 1439, 1105 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{18}H_{16}N_3$: 274.1339, found: 274.1349.



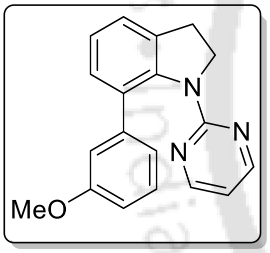
1-(3-(1-(Pyrimidin-2-yl)indolin-7-yl)phenyl)ethan-1-one 3c. Analytical TLC on silica gel, 1:4 ethyl acetate/hexane $R_f = 0.39$; colorless sticky oil; yield 60% (18.9 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, *J* = 4.8 Hz, 3H), 7.73-7.70 (m, 1H), 7.56-7.53 (m, 1H), 7.30-7.23 (m, 3H), 7.13 (t, *J* = 7.6 Hz, 1H), 6.37 (t, *J* = 4.8 Hz, 1H), 4.48 (t, *J* = 8.0 Hz, 2H), 3.20 (t, *J* = 8.0 Hz, 2H), 2.49 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 198.4, 159.2, 156.7, 142.9, 141.2, 137.1, 135.4, 131.5, 129.3, 129.0, 128.4, 127.2, 125.9, 124.3, 124.1, 112.2, 52.4, 29.6, 26.8; FT-IR (neat) 2958, 2924, 2853, 1682, 1575, 1550, 1455, 1433, 1110 cm^{-1}; HRMS (ESI) m/z [M+H]+ calcd for $C_{20}H_{18}N_3O$: 316.1444, found: 316.1443.



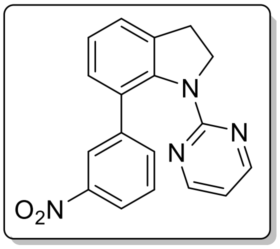
7-(3-Chlorophenyl)-1-(pyrimidin-2-yl)indoline 3d. Analytical TLC on silica gel, 1:4 ethyl acetate/hexane $R_f = 0.43$; yellow liquid; yield 58% (17.8 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, *J* = 4.8 Hz, 2H), 7.366-7.361 (m, 1H), 7.26-7.22 (m, 2H), 7.21-7.18 (m, 1H), 7.12 (d, *J* = 7.2 Hz, 1H), 7.08-7.02 (m, 2H), 6.43 (t, *J* = 4.8 Hz, 1H), 4.45 (t, *J* = 8.0 Hz, 2H), 3.18 (t, *J* = 8.0 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 159.3, 156.8, 144.3, 141.2, 135.3, 134.0, 129.2, 129.1, 128.9, 127.0, 126.2, 125.1, 124.3, 124.0, 112.2, 52.3, 29.6; FT-IR (neat) 2960, 2923, 2852, 1637, 1576, 1550, 1455, 1432, 1110 cm^{-1}; HRMS (ESI) *m/z* [M+H]$^+$ calcd for $C_{18}H_{15}ClN_3$: 308.0949, found: 308.0946.



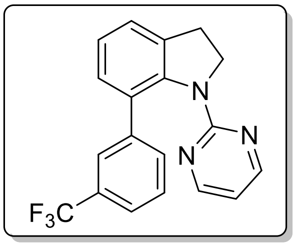
1-(Pyrimidin-2-yl)-7-(*m*-tolyl)indoline 3e. Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.42; yellowish gummy liquid; yield 54% (15.5 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, *J* = 4.8 Hz, 2H), 7.28-7.26 (m, 1H), 7.23-7.21 (m, 1H), 7.15-7.07 (m, 3H), 7.03 (t, *J* = 7.6 Hz, 1H), 6.91 (d, *J* = 7.6 Hz, 1H), 6.38 (t, *J* = 4.8 Hz, 1H), 4.44 (t, *J* = 8.0 Hz, 2H), 3.18 (t, *J* = 8.0 Hz, 2H), 2.20 (s, 3H); ^{13}C NMR (150 MHz,) δ 159.3, 156.6, 142.2, 141.2, 137.6, 135.0, 130.3, 129.1, 127.9, 127.5, 126.9, 124.0, 123.8, 123.7, 111.9, 52.4, 29.7, 21.4; FT-IR (neat) 2958, 2924, 2953, 1637, 1597, 1576, 1550, 1441, 1261, 1222, 1198, 1108 cm^{-1}; HRMS (ESI) *m/z* [M+H]$^+$ calcd for $C_{19}H_{18}N_3$: 288.1495, found: 288.1496.



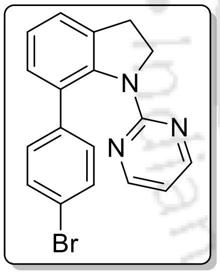
7-(3-Methoxyphenyl)-1-(pyrimidin-2-yl)indoline 3f. Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.40; brown sticky liquid; yield 60% (18.1 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.00 (d, *J* = 4.8 Hz, 2H), 7.29 (d, *J* = 7.8 Hz, 1H), 7.24 (d, *J* = 6.6 Hz, 1H), 7.10 (t, *J* = 7.2 Hz, 1H), 7.05 (t, *J* = 7.8 Hz, 1H), 6.94 (d, *J* = 7.8 Hz, 1H), 6.918-6.915 (m, 1H), 6.66-6.64 (m, 1H), 6.40 (t, *J* = 4.8 Hz, 1H), 4.45 (t, *J* = 7.8 Hz, 2H), 3.68 (s, 3H), 3.18 (t, *J* = 7.8 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.6, 159.4, 157.3, 156.7, 143.7, 141.1, 135.1, 130.1, 129.0, 123.95, 123.90, 119.5, 112.6, 112.0, 111.7, 55.4, 52.4, 29.7; FT-IR (neat) 2960, 2923, 2851, 1602, 1575, 1550, 1457, 1435, 1380, 1224, 1176, 1042 cm^{-1}; HRMS (ESI) *m/z* [M+H]$^+$ calcd for $C_{19}H_{18}N_3O$: 304.1444, found: 304.1455.



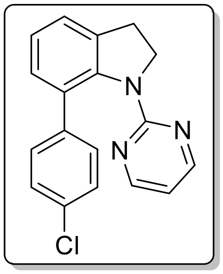
7-(3-Nitrophenyl)-1-(pyrimidin-2-yl)indoline 3g. Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.41; brown liquid; yield 65% (20.6 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (t, *J*= 1.6 Hz, 1H), 7.98-7.95 (m, 3H), 7.66 (d, *J* = 7.6 Hz, 1H), 7.31-7.26 (m, 3H), 7.15 (t, *J* = 7.2 Hz, 1H), 6.41 (t, *J* = 4.8 Hz, 1H), 4.49 (t, *J* = 8.0 Hz, 2H), 3.20 (t, *J* = 8.0 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 159.2, 156.9, 148.3, 144.4, 141.3, 135.6, 133.0, 128.86, 128.84, 128.3, 124.9, 124.3, 121.8, 121.0, 112.4, 52.3, 29.5; FT-IR (neat) 2958, 2923, 2852, 1575, 1551, 1527, 1455, 1434, 1350, 1261, 1003 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{18}H_{15}N_4O_2$: 319.1189, found: 319.1187.



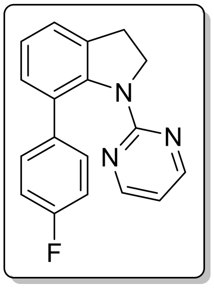
1-(Pyrimidin-2-yl)-7-(3-(trifluoromethyl)phenyl)indoline 3h. Analytical TLC on silica gel, 1:4 ethyl acetate/hexane $R_f = 0.44$; yellow liquid; yield 65% (22.1 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, *J* = 4.8 Hz, 2H), 7.60 (s, 1H), 7.50 (d, *J* = 7.6 Hz, 1H), 7.36 (d, *J* = 7.6 Hz, 1H), 7.29-7.23 (m, 4H), 7.13 (t, *J* = 7.6 Hz, 1H), 6.39 (t, *J* = 4.8 Hz, 1H), 4.47 (t, *J* = 7.6 Hz, 2H), 3.19 (t, *J* = 8.0 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 159.1, 156.7, 143.3, 141.3, 135.4, 130.9 (q, J_{C-F} = 31.65 Hz), 130.126, 130.120, 128.94, 128.91, 128.4, 124.5, 124.07, 124.00 (q, J_{C-F} = 3.6 Hz), 122.83 (q, J_{C-F} = 3.75 Hz), 112.27, 52.3, 29.6; FT-IR (neat) 2956, 2923, 2852, 1638, 1575, 1552, 1456, 1440, 1339, 1260, 1163, 1122, 1071 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{19}H_{15}F_3N_3$: 342.1212, found: 342.1219.



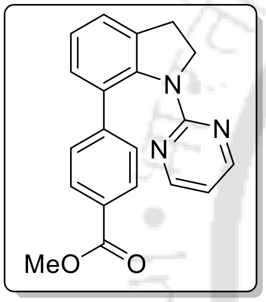
7-(4-Bromophenyl)-1-(pyrimidin-2-yl)indoline 3i. Analytical TLC on silica gel, 1:4 ethyl acetate/hexane $R_f = 0.43$; colorless gummy liquid; yield 60% (21 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.03 (d, *J* = 4.8 Hz, 2H), 7.31-7.29 (m, 2H), 7.28-7.24 (m, 4H), 7.12 (t, *J* = 7.2 Hz, 1H), 6.47 (t, *J* = 4.8 Hz, 1H), 4.47 (t, *J* = 7.8 Hz, 2H), 3.20 (t, *J* = 7.8 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.3, 156.8, 141.4, 141.1, 135.3, 131.1, 129.3, 128.8, 128.5, 124.1, 124.0, 120.0, 112.3, 52.3, 29.6; FT-IR (KBr) 2957, 2924, 2852, 1574, 1548, 1451, 1427, 1261, 1065 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{18}H_{15}BrN_3$: 352.0443, found: 352.0423.



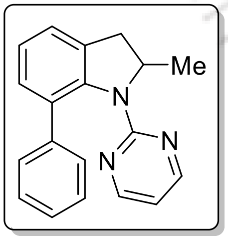
7-(4-Chlorophenyl)-1-(pyrimidin-2-yl)indoline 3j. Analytical TLC on silica gel, 1:4 ethyl acetate/hexane $R_f = 0.45$; yellowish sticky liquid; yield 67% (20.5 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (d, *J* = 4.8 Hz, 2H), 7.29-7.21 (m, 4H), 7.14-7.08 (m, 3H), 6.44 (t, *J* = 4.4 Hz, 1H), 4.45 (t, *J* = 8.0 Hz, 2H), 3.17 (t, *J* = 8.0 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 159.4, 156.8, 141.2, 141.0, 135.3, 132.0, 129.4, 128.9, 128.2, 128.1, 124.1, 124.0, 112.3, 52.4, 29.7; FT-IR (neat) 2954, 2922, 2852, 1638, 1576, 1551, 1453, 1429, 1112, 1068 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{18}H_{15}ClN_3$: 308.0949, found: 308.0954.



7-(4-Fluorophenyl)-1-(pyrimidin-2-yl)indoline 3k. Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.41; colorless sticky liquid; yield 62% (18 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.00 (d, J = 4.8 Hz, 2H), 7.31 – 7.29 (m, 2H), 7.24-7.22 (m, 2H), 7.10 (t, J = 7.8 Hz, 1H), 6.86–6.83 (m, 2H), 6.42 (t, J = 4.8 Hz, 1H), 4.45 (t, J = 7.8 Hz, 2H), 3.17 (t, J = 7.8 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 162.2(J_{C-F} = 243.3), 159.1, 156.6, 141.0, 138.3(J_{C-F} = 3.3), 135.1, 129.4, 128.7, 128.2 (J_{C-F} = 7.8), 123.8, 123.7, 114.7(J_{C-F} = 21.3), 112.0, 52.2, 29.5; FT-IR (KBr) 2955, 2924, 2853, 1636, 1575, 1549, 1508, 1455, 1426, 1377, 1283, 1153, 1093 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{18}H_{15}FN_3$: 292.1244, found: 292.1251.

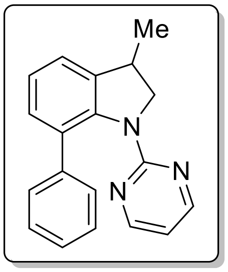


Methyl 4-(1-(pyrimidin-2-yl)indolin-7-yl)benzoate 3l. Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.40; sticky liquid; yield 57% (18.8 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, J = 4.8 Hz, 2H), 7.85-7.82 (m, 2H), 7.44-7.41(m, 2H), 7.28-7.26(m, 2H), 7.14 – 7.10 (m, 1H), 6.38 (t, J = 4.8 Hz, 1H), 4.47 (t, J = 8.0 Hz, 2H), 3.88 (s, 3H), 3.19 (t, J = 7.6 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 167.3, 159.3, 156.8, 147.4, 141.2, 135.3, 129.5, 129.4, 128.9, 127.7, 126.7, 124.5, 124.0, 112.4, 52.2, 52.1, 29.6; FT-IR (neat) 2952, 2924, 2853, 1721, 1609, 1575, 1551, 1454, 1434, 1275, 1103 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{20}H_{18}N_3O_2$: 332.1393, found: 332.1397.

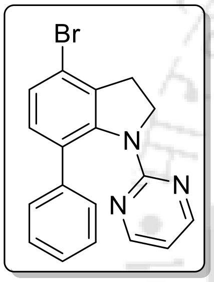


2-Methyl-7-phenyl-1-(pyrimidin-2-yl)indoline 3r. Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.42; Purification (hexane/ethyl acetate 88/12); yellow liquid; yield 62% (17.7 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.95 (d, J = 4.8 Hz, 2H), 7.34 (d, J = 7.2 Hz, 2H), 7.29 (d, J = 7.8 Hz, 1H), 7.24-7.22 (m, 1H), 7.16 (t, J = 7.2 Hz, 2H), 7.13-7.08 (m, 2H), 6.36 (t, J = 4.8 Hz, 1H), 4.94-4.89 (m, 1H), 3.52 (dd, J = 15.0, 8.4 Hz, 1H), 2.65 (d, J = 15.6 Hz, 1H), 1.55 (d, J = 6.6 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 158.9, 156.7, 142.5, 139.7, 133.9, 130.9, 129.0, 128.1, 126.7, 126.1, 124.3, 124.0, 111.9, 59.7, 37.0, 21.3; FT-IR (neat) 3054, 3031, 2972, 2923, 2851, 1638, 1598, 1577, 1549, 1461, 1436, 1384, 1209 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{19}H_{18}N_3$: 288.1495, found: 288.1512.

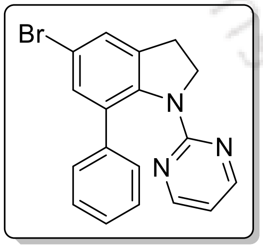
3-Methyl-7-phenyl-1-(pyrimidin-2-yl)indoline 3s. Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.43; yellow liquid; yield 64% (18.3 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.96 (d, *J* = 4.8 Hz, 2H), 7.35 (d, *J* = 7.2 Hz, 2H), 7.29 (d, *J* = 7.8 Hz, 1H), 7.21 (d, *J* = 7.2 Hz, 1H), 7.16-7.13 (m, 3H), 7.08 (t, *J* = 7.2 Hz, 1H), 6.37 (t, *J* = 4.8 Hz, 1H), 4.61 (dd, *J* = 10.8, 8.4 Hz, 1H), 3.99 (dd, *J* = 10.8, 7.2 Hz, 1H), 3.52-3.46 (m, 1H), 1.37 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 159.4, 156.7, 142.3, 140.8, 140.3, 130.4, 129.2, 128.0, 126.9, 126.2, 124.1, 122.6, 111.9, 60.2, 36.4, 19.2; FT-IR (neat) 2958, 2924, 2854, 1597, 1576, 1550, 1459, 1441, 1380, 1261, 1222, 1108 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{19}H_{18}N_3$: 288.1495, found: 288.1509.



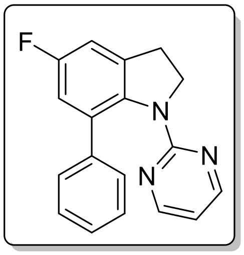
4-Bromo-7-phenyl-1-(pyrimidin-2-yl)indoline 3t. Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.43; colorless sticky liquid; yield 56% (19.6 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.96 (d, *J* = 4.8 Hz, 2H), 7.29-7.28 (m, 2H), 7.25 (d, *J* = 8.4 Hz, 1H), 7.14 (t, *J* = 8.4 Hz, 3H), 7.08 (t, *J* = 7.8 Hz, 1H), 6.41 (t, *J* = 4.8 Hz, 1H), 4.46 (t, *J* = 7.8 Hz, 2H), 3.19 (t, *J* = 7.8 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 159.2, 156.7, 142.2, 141.5, 135.5, 130.8, 129.3, 128.2, 126.7, 126.6, 126.5, 118.4, 112.5, 51.6, 31.1; FT-IR (neat) 2954, 2923, 2852, 1638, 1576, 1552, 1467, 1434, 1407, 1286, 1078 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{18}H_{15}BrN_3$: 352.0443, found: 352.0441.



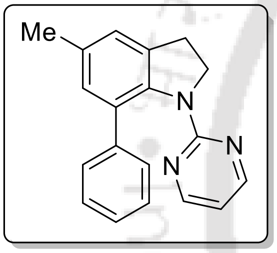
5-Bromo-7-phenyl-1-(pyrimidin-2-yl)indoline 3u. Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.41; colorless solid; mp 122-123 °C; yield 52% (18.2 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.96 (d, *J* = 4.8 Hz, 2H), 7.407-7.404 (m, 1H), 7.344-7.340 (m, 1H), 7.30-7.28 (m, 2H), 7.16-7.13 (m, 2H), 7.11-7.08 (m, 1H), 6.40 (t, *J* = 4.8 Hz, 1H), 4.44 (t, *J* = 8.4 Hz, 2H), 3.17 (t, *J* = 8.4 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 159.1, 156.7, 141.1, 140.5, 137.4, 132.0, 131.7, 128.2, 126.77, 126.71, 126.6, 116.2, 112.3, 52.4, 29.5; FT-IR (KBr) 2924, 2852, 1644, 1637, 1576, 1459, 1439, 1112 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{18}H_{15}BrN_3$: 352.0443, found: 352.0459.



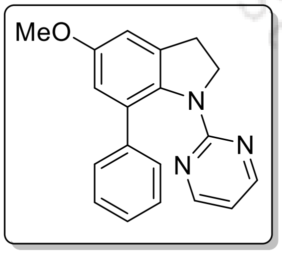
5-Fluoro-7-phenyl-1-(pyrimidin-2-yl)indoline 3v. Analytical TLC on silica gel, 1:4 ethyl acetate/hexane $R_f = 0.42$; yellow liquid; yield 58% (16.8 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.96 (d, *J* = 4.2 Hz, 2H), 7.34 (d, *J* = 7.2 Hz, 2H), 7.16 (t, *J* = 7.2 Hz, 2H), 7.11 (t, *J* = 7.2 Hz, 1H), 7.00-6.98 (m, 1H), 6.96 (d, *J* = 7.8 Hz, 1H), 6.38 (t, *J* = 4.8 Hz, 1H), 4.47 (t, *J* = 7.8 Hz, 2H), 3.15 (t, *J* = 7.8 Hz, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 160.7($J_{C\text{-}F}$ = 240), 159.4, 156.7, 141.3, 137.3($J_{C\text{-}F}$ = 1.95), 137.2($J_{C\text{-}F}$ = 8.85), 131.7($J_{C\text{-}F}$ = 7.95), 128.2, 126.78, 126.70, 115.2 ($J_{C\text{-}F}$ = 23.55), 112.0, 111.1($J_{C\text{-}F}$ = 23.7), 52.6, 30.03($J_{C\text{-}F}$ = 1.95); FT-IR (neat) 2962, 2924, 2853, 1636, 1578, 1551, 1462, 1443, 1433, 1149 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{18}H_{15}FN_3$: 292.1244, found: 292.1254.



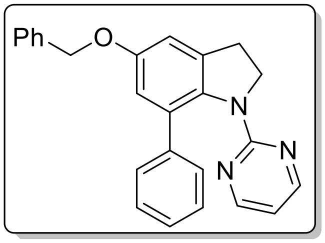
5-Methyl-7-phenyl-1-(pyrimidin-2-yl)indoline 3w. Analytical TLC on silica gel, 1:4 ethyl acetate/hexane $R_f = 0.42$; yellow liquid; yield 61% (17.5 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.94 (d, *J* = 4.8 Hz, 2H), 7.34 (d, *J* = 7.8 Hz, 2H), 7.14 (t, *J* = 7.8 Hz, 2H), 7.09-7.06 (m, 3H), 6.34 (t, *J* = 4.8 Hz, 1H), 4.44 (t, *J* = 7.8 Hz, 2H), 3.13 (t, *J* = 7.8 Hz, 2H), 2.36 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 159.5, 156.7, 142.4, 138.9, 135.3, 133.6, 130.3, 129.5, 128.0, 126.8, 126.1, 124.6, 111.7, 52.4, 29.8, 21.2; FT-IR (neat) 2952, 2922, 2852, 1577, 1549, 1465, 1441, 1222, 1104 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{19}H_{18}N_3$: 288.1501, found: 288.1507.



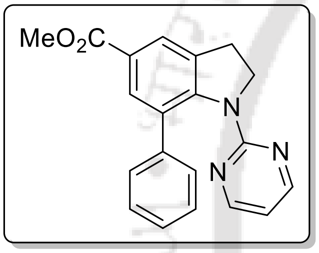
5-Methoxy-7-phenyl-1-(pyrimidin-2-yl)indoline 3x. Analytical TLC on silica gel, 1:4 ethyl acetate/hexane $R_f = 0.39$; colorless stick liquid; yield 64% (19.3 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.94 (d, *J* = 4.8 Hz, 2H), 7.38 (d, *J* = 7.2 Hz, 2H), 7.16 (t, *J* = 7.2 Hz, 2H), 7.10 (t, *J* = 7.2 Hz, 1H), 6.84-6.83 (m, 2H), 6.34 (t, *J* = 4.8 Hz, 1H), 4.45 (t, *J* = 7.8 Hz, 2H), 3.83 (s, 3H), 3.13 (t, *J* = 7.8 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 159.4, 156.7, 156.5, 142.0, 136.6, 134.6, 131.2, 127.9, 126.6, 126.2, 113.39, 111.38, 110.2, 55.8, 52.3, 30.0; FT-IR (neat) 2961, 2921, 2850, 1637, 1578, 1548, 1463, 1443, 1261, 1160, 1104 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{19}H_{18}N_3O$: 304.1444, found: 304.1455.



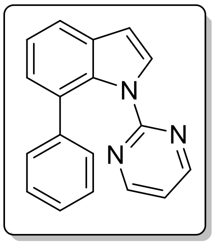
5-(Benzyloxy)-7-phenyl-1-(pyrimidin-2-yl)indoline 3y. Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.40; yellowish sticky liquid; yield 57% (21.6 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.94 (d, *J* = 4.8 Hz, 2H), 7.45 (d, *J* = 7.8 Hz, 2H), 7.39 (t, *J* = 7.2 Hz, 2H), 7.37-7.31 (m, 3H), 7.16 (t, *J* = 7.8 Hz, 2H), 7.09 (t, *J* = 7.2 Hz, 1H), 6.93-6.90 (m, 2H), 6.34 (t, *J* = 4.2 Hz, 1H), 5.08 (s, 2H), 4.45 (t, *J* = 7.8 Hz, 2H), 3.13 (t, *J* = 7.8 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 159.5, 156.7, 156.1, 142.2, 137.4, 136.8, 135.0, 131.4, 128.7, 128.1, 127.6, 126.8, 126.4, 114.8, 111.6, 111.2, 70.8, 52.5, 30.2; FT-IR (neat) 2956, 2921, 2849, 1635, 1578, 1462, 1443, 1431, 1166, 1110 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{25}H_{22}N_3O$: 380.1757, found: 380.1769.

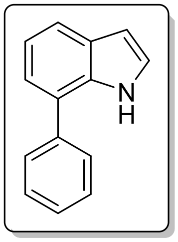


Methyl 7-phenyl-1-(pyrimidin-2-yl)indoline-5-carboxylate 3z. Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.3; yellowish sticky liquid; yield 51% (16.8 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00-7.97 (m, 3H), 7.89 (s, 1H), 7.30 (d, *J* = 7.2 Hz, 2H), 7.16-7.09 (m, 3H), 6.45 (t, *J* = 4.4 Hz, 1H), 4.47 (t, *J* = 8.0 Hz, 2H), 3.90 (s, 3H), 3.23 (t, *J* = 8.0 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 167.2, 158.8, 156.7, 145.5, 141.6, 135.2, 132.0, 129.3, 128.1, 126.8, 126.5, 125.1, 125.0, 112.9, 52.6, 52.1, 29.0; FT-IR (neat) 2958, 2922, 2854, 1652, 1638, 1464, 1386, 1179, 1113, 990 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{20}H_{18}N_3O_2$: 332.1393, found: 332.1398.



7-Phenyl-1-(pyrimidin-2-yl)-1H-indole 4. Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.44; Colourless liquid; yield 90% (24.4 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.19 (d, *J* = 4.2 Hz, 2H), 7.79 (d, *J* = 3.6 Hz, 1H), 7.66-7.65 (m, 1H), 7.33–7.29 (m, 2H), 7.22-7.20 (m, 2H), 7.10-7.09 (m, 3H), 6.80-6.78 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 157.2, 157.1, 142.3, 132.9, 132.2, 129.4, 128.7, 127.9, 127.7, 126.1, 125.8, 122.3, 120.4, 116.9, 106.6; FT-IR (neat) 2958, 2921, 1639, 1652, 1435, 1386, 1183, 1114 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{18}H_{14}N_3$: 272.1182, found: 272.1180.





7-Phenyl-1H-indole 5. Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.53; brown liquid; yield 84% (16.3 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.44 (br s, 1H), 7.66 (d, *J* = 7.2 Hz, 3H), 7.51 (t, *J* = 7.2 Hz, 2H), 7.40 (t, *J* = 7.2 Hz, 1H), 7.22-7.19 (m, 3H), 6.63 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 139.4, 133.9, 129.3, 128.47, 128.45, 127.6, 125.8, 124.5, 122.1, 120.5, 120.2, 103.2; FT-IR (neat) 2952, 2924, 2853, 1637, 1476, 1461, 1420, 1338, 1113, 1027 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{14}H_{12}N$: 194.0964, found: 194.0956.

2.5 References

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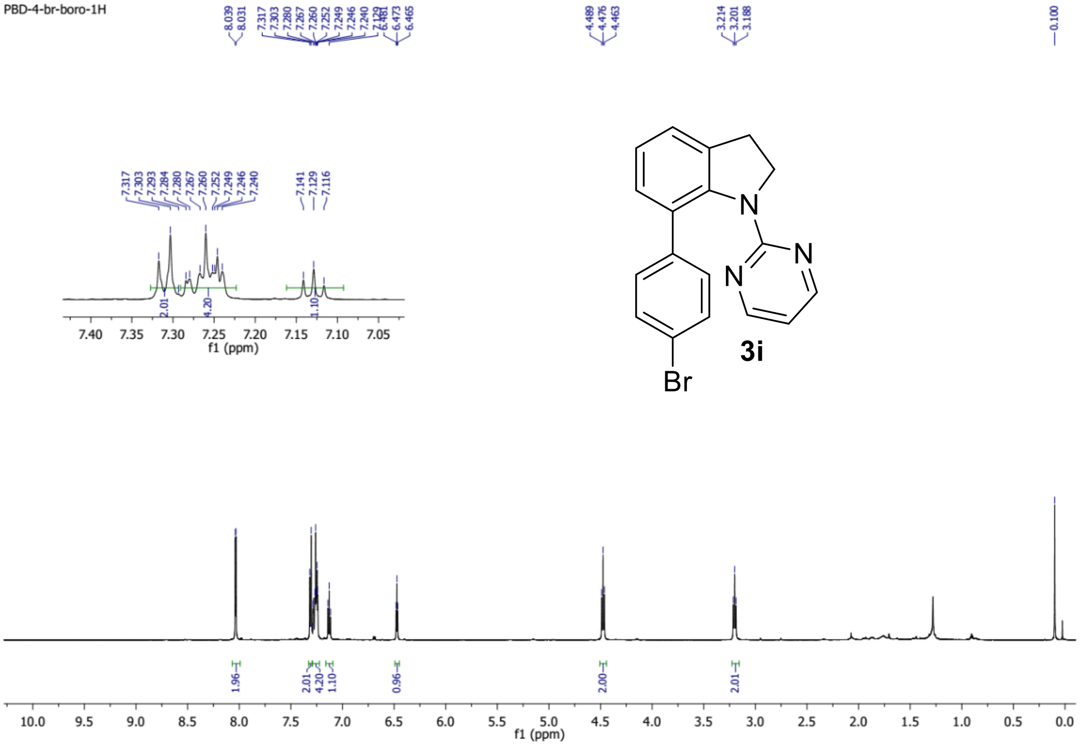
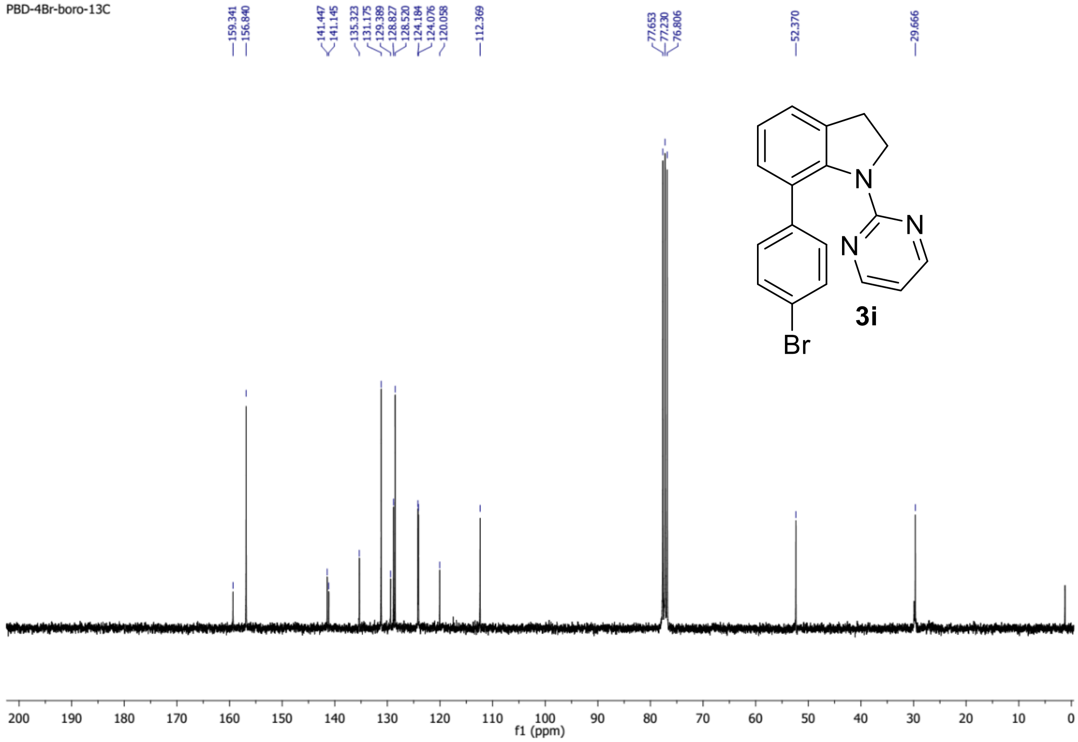
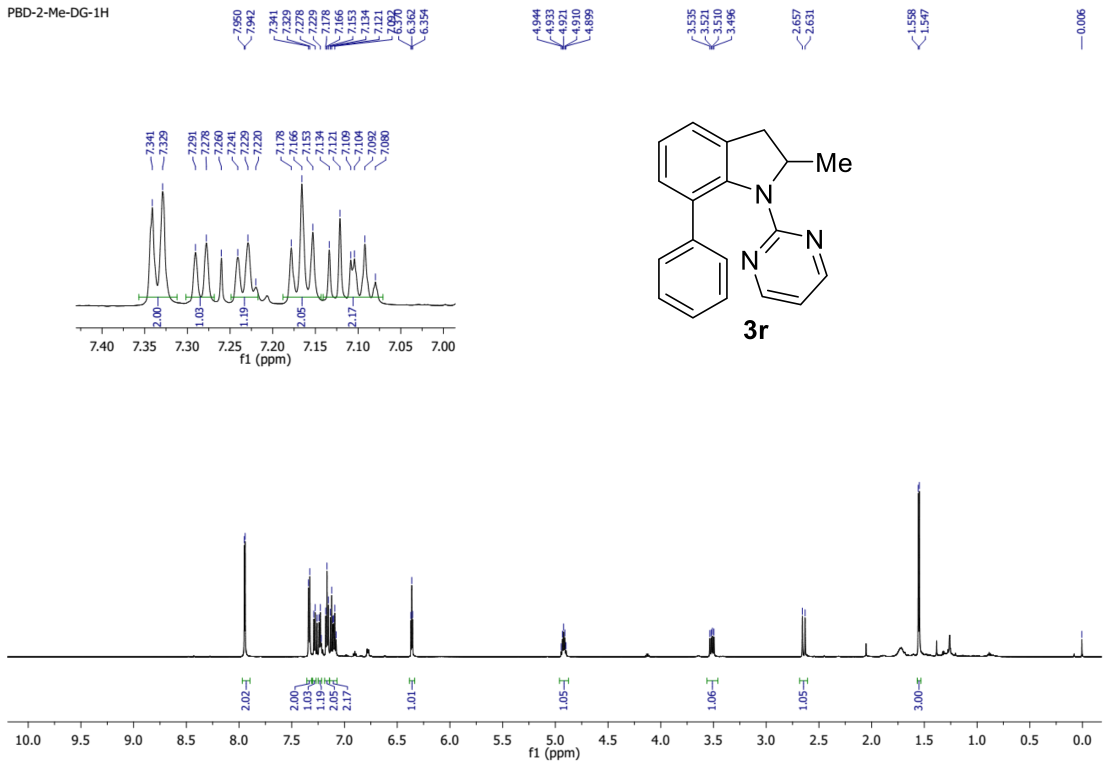
2.6 Selected NMR Spectra



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7.121
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2.05
2.17
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f1 (ppm)
Me
N
N
N
3r
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2.00
1.03
1.19
2.05
2.17
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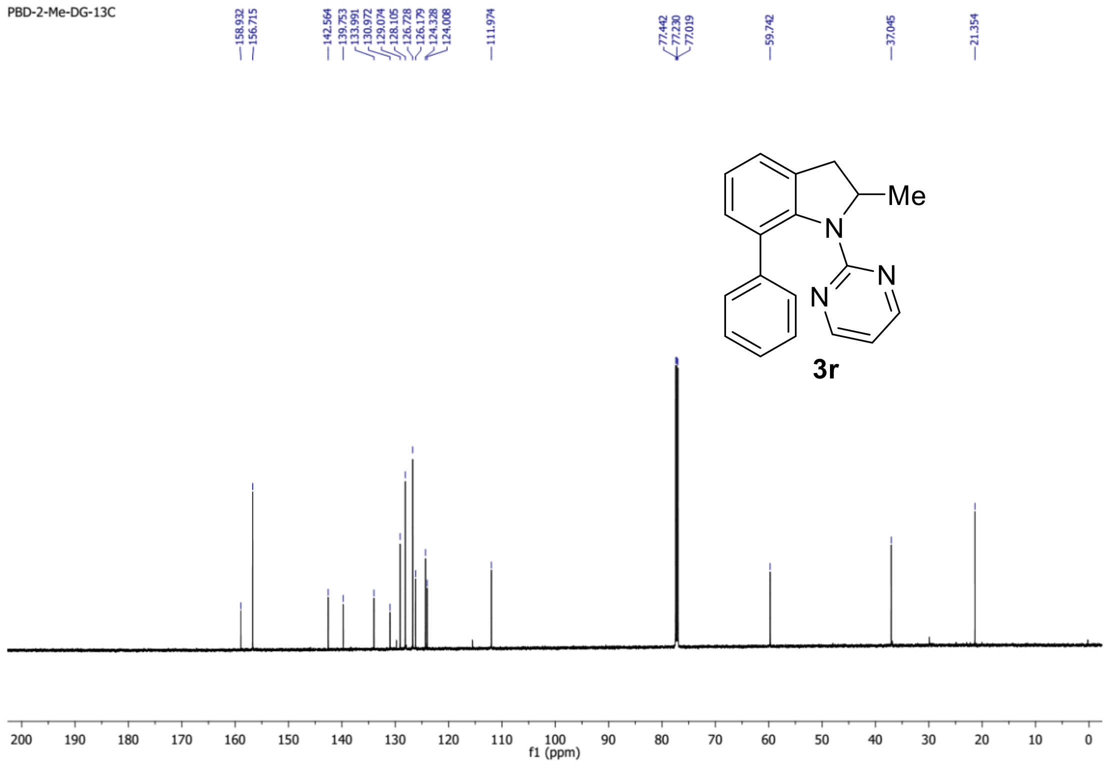
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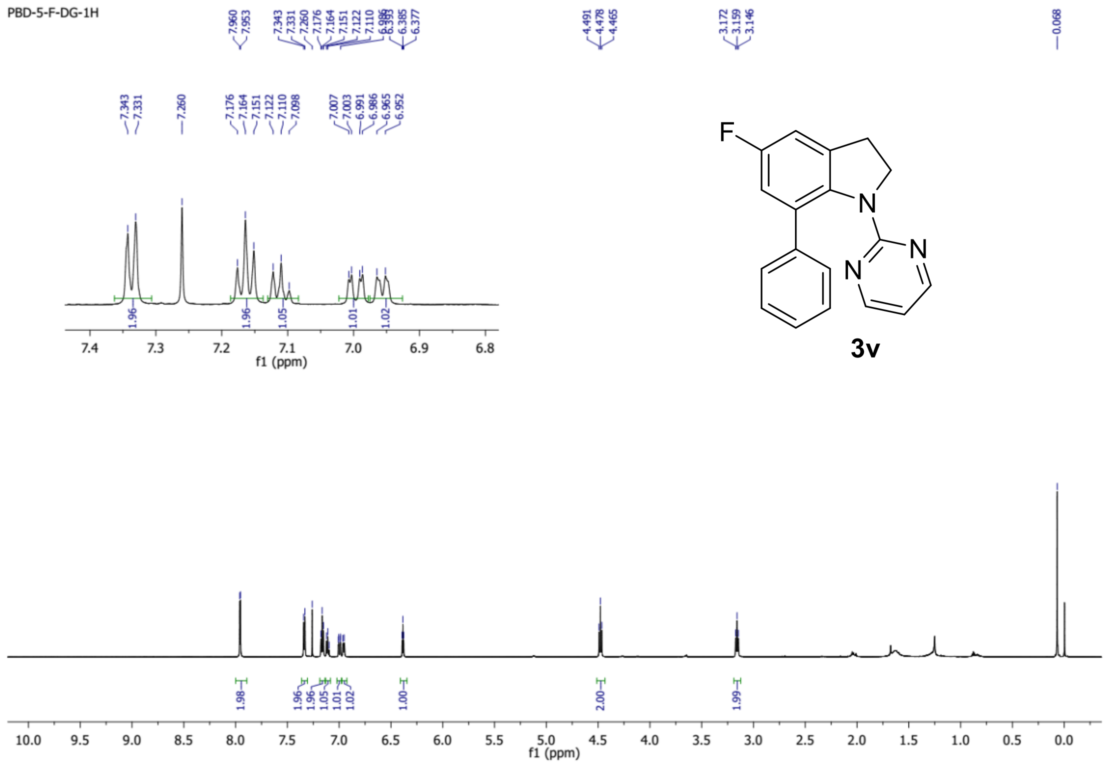
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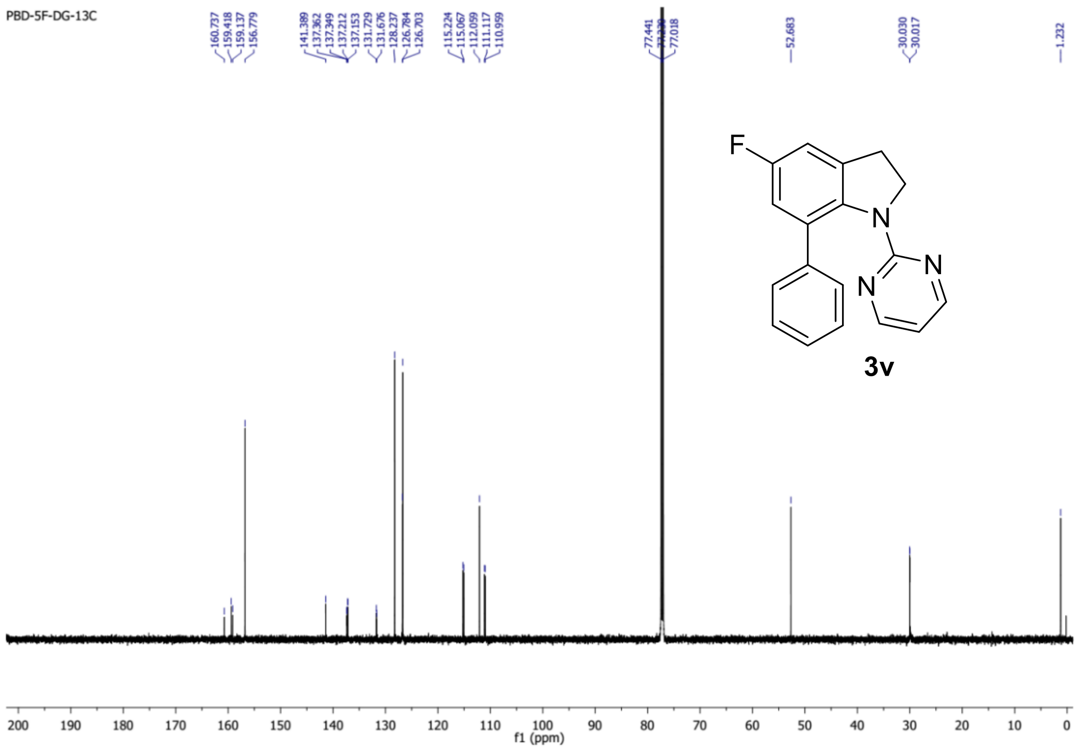
f1 (ppm)

3v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10
0
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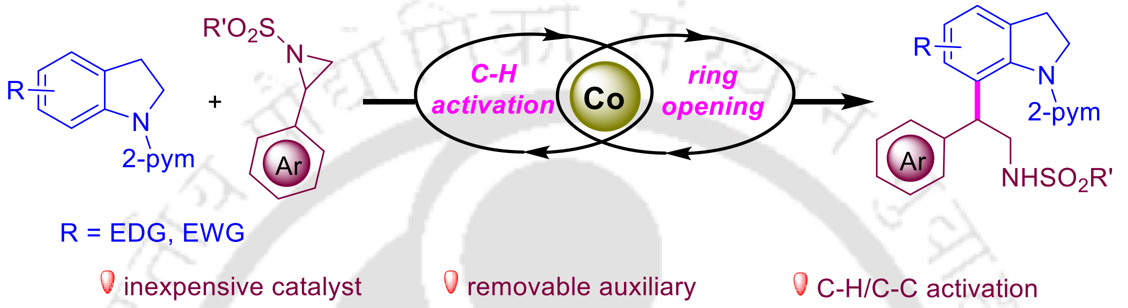
Chapter III

*Cp*Co(III)-Catalyzed C-C Coupling of Indolines at C-7 Position with Aziridines via C-H Activation*

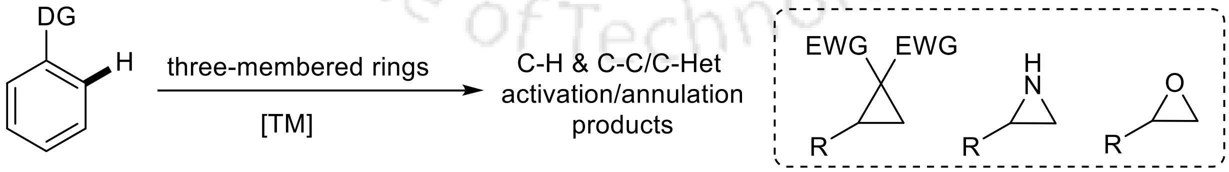


Manuscript submitted

Cp*Co(III)-Catalyzed C-C Coupling of Indolines at C-7 Position with Aziridines *via* C-H Activation

Owing to the importance of biologically significant indole moiety, C-H functionalization of its core is extremely valuable from synthetic viewpoint.[1] Direct C-7 functionalization of indoles is relatively challenging compared to functionalization at C-2 and C-3 positions due to the inherent reactivity of the pyrrole-type ring as already discussed in chapter 1.[2] However, several transition-metal catalyzed chelation guided elegant methods are documented in literature for the construction of C-C bond formation at the inert C7-H bond of indoles viz; alkylation,[3] arylation,[4] alkenylation,[5] alkynylation,[6] allylation[7] and acylation.[8] Among various transition-metal-catalysts, Cp*Co(III) catalyzed C-H functionalization[9] recently gained a plentiful progress for achieving the varied functionalizations with remarkable contribution by several groups owing to the cost-effective and air stable nature of the catalyst.[10]

Due to the ring strain and electrophilic nature, three membered carbocycles/heterocycles such as cyclopropanes, oxiranes, aziridines, etc. has recently been used as an appealing target for the selective synthesis of many diverse scaffolds by merging C-H activation and ring-scission (Scheme 1).[11] In particular, aziridine ring being a versatile synthetic precursor, can serve as an alkylating agent to construct bio-relevent *β*-branched amines. Lewis acid catalyzed nucleophilic ring opening or cycloaddtion of aziridines has been well documented in literature. In contrast, direct ring opening of aziridines by integrating C-H activation is scarce. This chapter demonstrates air-stable Cp*Co(III)-catalyzed C7-alkylation of indolines with aziridines utilizing removable pyrimidyl directing group in the regime of concomitant C-H activation and ring opening.

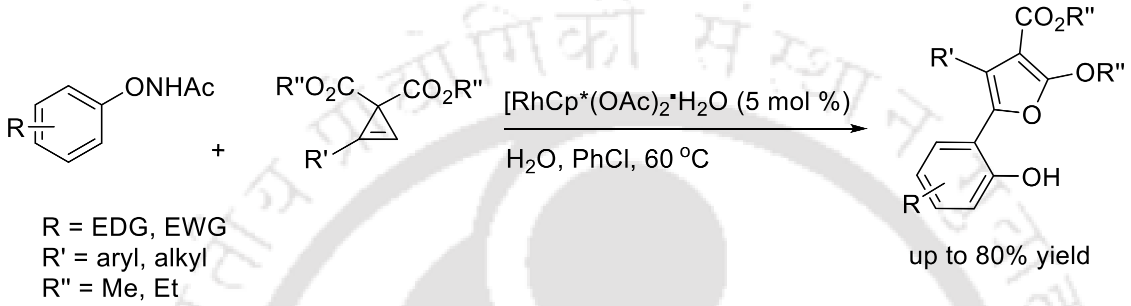


Scheme 1. Transition-Metal-Catalyzed Ring Opening of Strained Three Membered Ring

3.1 Literature

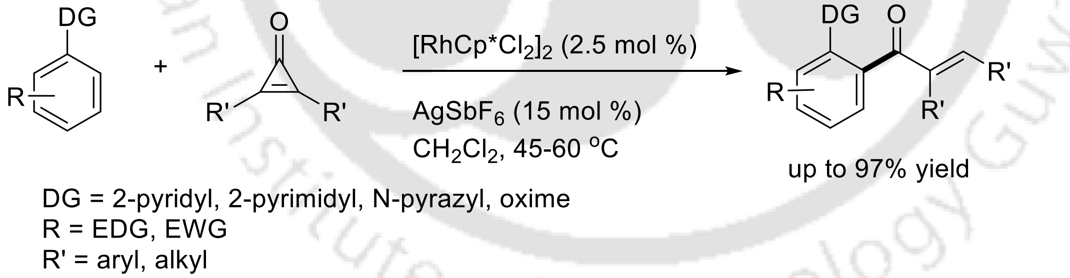
3.1.1 Reaction of Three Membered Carbocycles with Arenes

Glorius and co-workers developed Rh(III)-catalyzed synthesis of arylated furans by reaction of cyclopropenyl esters and *N*-phenoxyacetamides (Scheme 2).[12] The methodology besides being mild and additive-free, offers further transformation to benzofuran-3(2H)-one and butenolide derivatives.



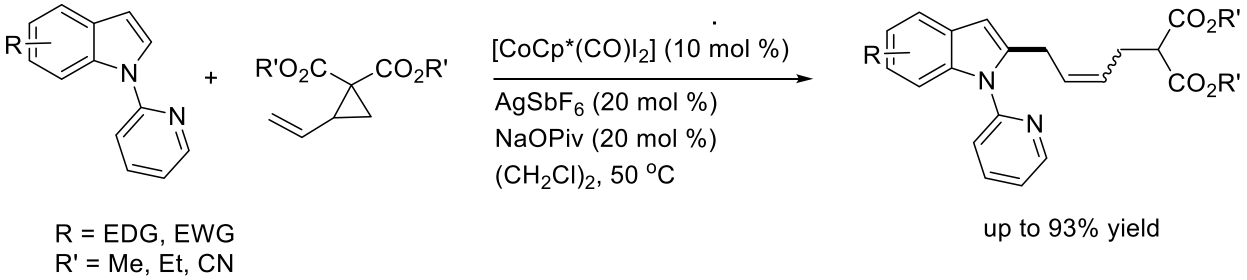
Scheme 2. Rh-Catalyzed Synthesis of Arylated Furans

Li and co-workers reported a mild protocol for the synthesis of chalcones via a Rh(III)-catalyzed C-H activation using cyclopropenones as coupling partners with arenes (Scheme 3).[13] Various DG installed arenes such as 2-pyridyl, 2-pyrimidyl, N-pyrazyl and oximes could be applicable under this reaction condition.



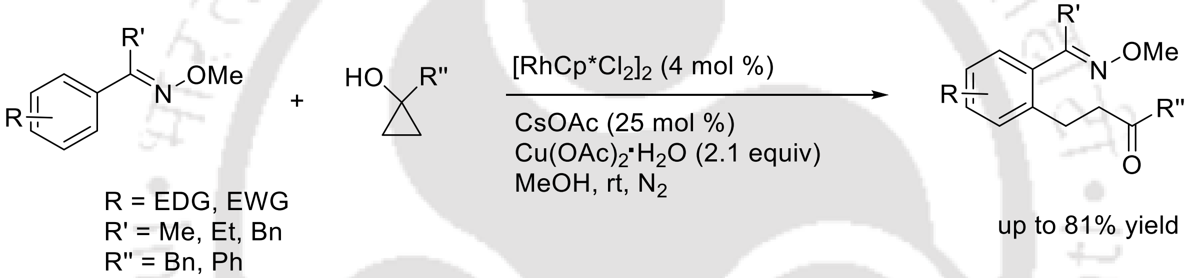
Scheme 3. Directed Rh-Catalyzed C-C bond Formation using Cyclopropenones

Ackermann and co-workers reported a Co-catalyzed regioselective functionalization of 2-pyridylindoles using vinyl cyclopropanes as coupling partners at room temperature (Scheme 4).[14] DFT calculations rationalized the formation of thermodynamically less favorable Z alkenes with excellent diastreoselectivity.



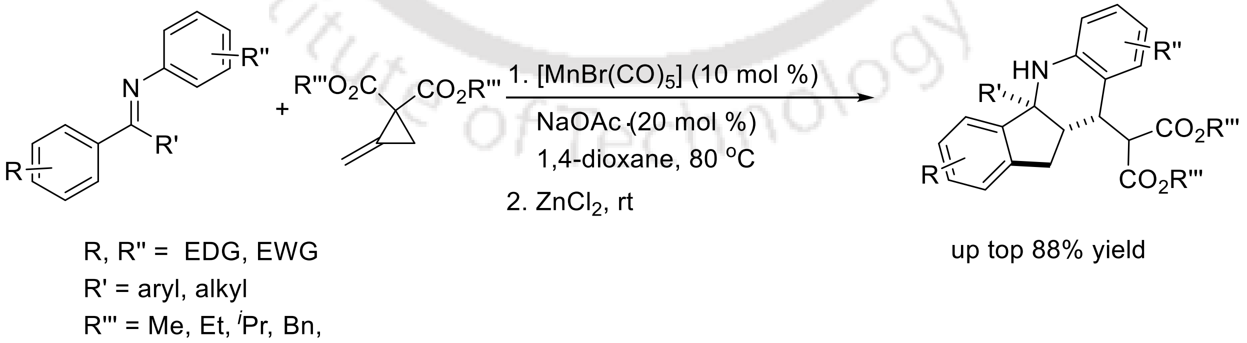
Scheme 4. Co-Catalyzed C2-Alkylation of Indoles using Vinyl Cyclopropanes

Li and co-workers reported a Rh-catalyzed chelation assisted C-C coupling of arenes with cyclopropanols as coupling partner to provide *β*-aryl ketones *via* C-H activation and ring opening (Scheme 5).[15] The authors extended their strategy for the indoles substrates by varying the additives and temperature.



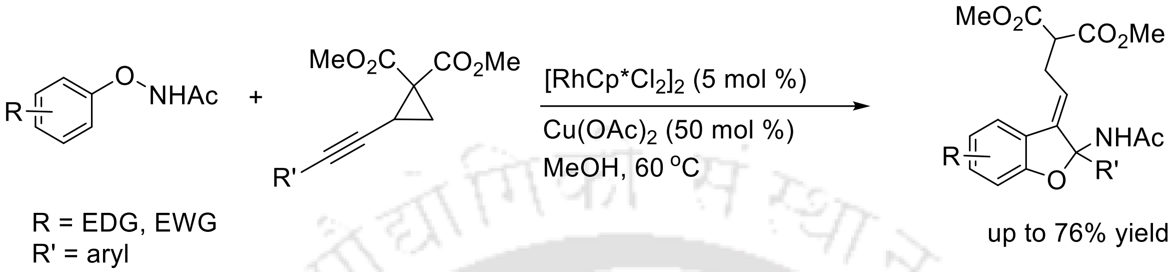
Scheme 5. Rh-Catalyzed C-C Coupling of Arenes with Cyclopropanols

Ackermann and co-workers described a stereoselective annulation of methylenecyclopropanes (MCPs) *via* C-H/C-C activation with ketimines to provide polycyclic anilines (Scheme 6).[16] The authors showed detailed mechanistic studies for a facile C-H manganation.



Scheme 6. Stereoselective Annulation of Methylenecyclopropanes

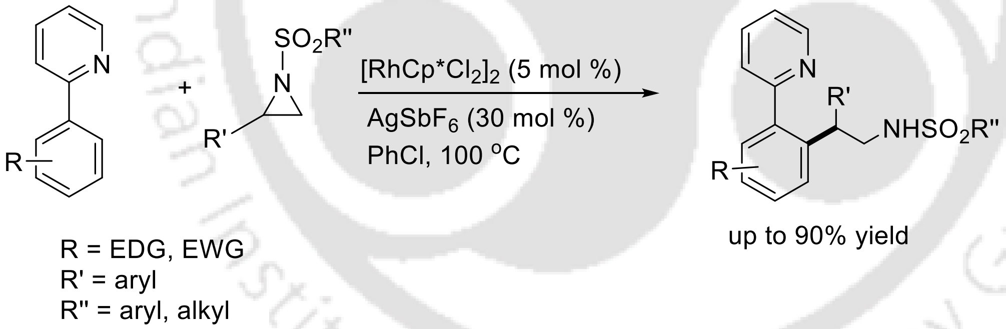
Alkynylcyclopropanes have been utilized for annulation reaction with *N*-aryloxyamides *via* redox-neutral C−H/C−C activation employing Rh(III)-catalyst to furnish a highly functionalized benzofurans with (*E*)-exocyclic carbon−carbon double bond and a tetrasubstituted carbon center (Scheme 7).[17]



Scheme 7. Rh-Catalyzed Annulation of *N*-Aryloxyamides with Alkynylcyclopropanes

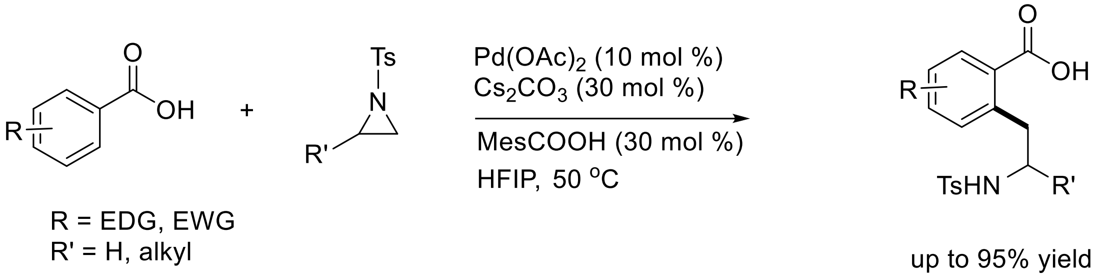
3.1.2 Reaction of Three Membered Heterocycles with Arenes

Li and co-workers reported an *ortho*-selective C-C coupling of 2-arylpyridines with aziridines under Rh(III)-catalysis for the synthesis of *β*-branched *N*-sulfonylethylamines in moderate to good yields (Scheme 8).[18] Notably, in this transformation silver salt activates both the aziridine and the Rh catalyst.



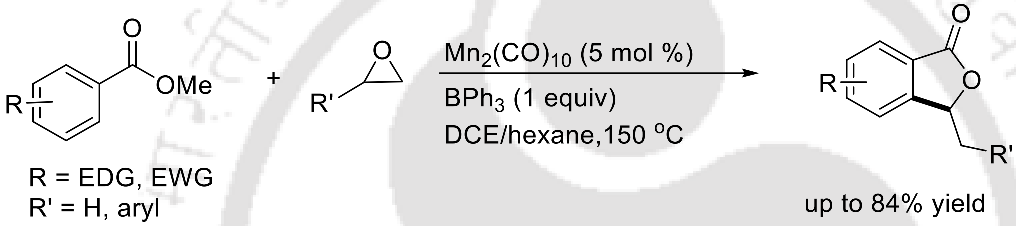
Scheme 8. *ortho*-Selective C-C Coupling of 2-Arylpyridines with Aziridines

Zhao and co-workers reported a carboxylic acid co-ordinated Pd(II)-catalyzed late-stage functionalization of aromatic acids with alkyl aziridines to construct *β*-arylethylamine *via* C-H activation (Scheme 9).[19] The enantioenriched aliphatic aziridines could also be transformed into the desired product without loss of ee.



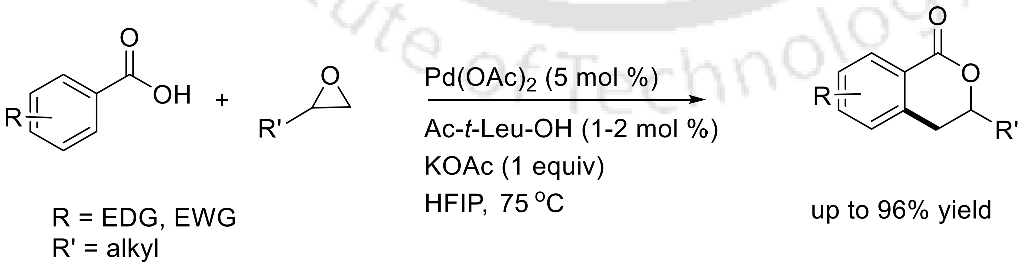
Scheme 9. Pd-Catalyzed Regioselective C-H Alkylation using Aziridines

Kuninobu and co-workers reported a manganese catalyzed synthesis of isobenzofuranones from aromatic esters and oxiranes (Scheme 10).[20] Notably, triphenylborane was found to play a essential role in cooperatively acceralating the annulation reaction.



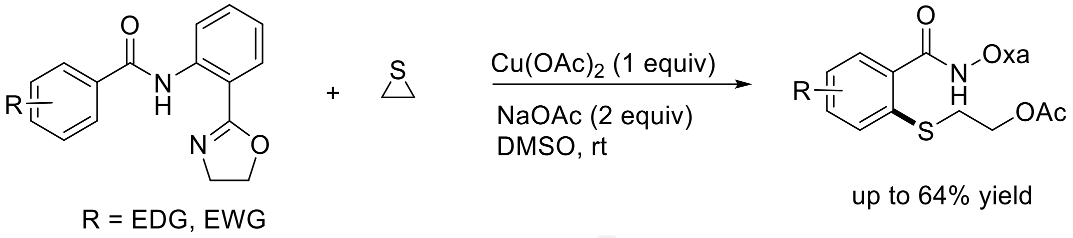
Scheme 10. Mn-Catalyzed Ring Opening of Oxiranes via C-H Activation

Yu and co-workers reported a carboxylic acid directed Pd-catalyzed *ortho*-alkylation using a wide range of terminal and internal epoxides to construct 3,4-dihydroisocoumarins via ring opening with subsequent lactonization (Scheme 11).[21] The use of counterions (K^+) and amino acids as ligands significantly promoted C-H functionalization/annulation strategy. The authors realised inversion of stereochemistry in the ring opening step, thereby indicating the S_N2 nucleophilic ring opening pathway.



Scheme 11. Pd-catalyzed *ortho*-Alkylation Towards 3,4-Dihydroisocoumarins

Dai and co-workers reported a selective thioetherification of arenes at ambient temperature using Cu as catalyst by employing thiarenes as thiolating agent (Scheme 12).[22] This amide-oxazoline directed thioetherification tolerated various functional groups and the resulting products could be easily transformed to seven-membered benzoxathiepinone derivatives.



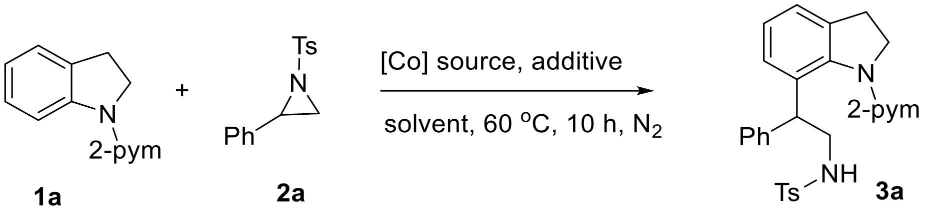
Scheme 12. Cu-Promoted Selective Thioetherification of Arenes

Present Study

This chapter presents, an air stable Cp*Co(III)-catalyzed C-C coupling of indolines at the C7 position with aziridines using a removable pyrimidyl chelating group by integrating C-H activation. The key findings involve use of cost-effective and air-stable cobalt catalysis, detection of a Co(III) intermediate, mechanistic study and late-stage removal of directing group. Initially, our optimization studies commenced by employing *N*-pyrimidyl indoline **1a** with 2-phenyl-1-tosylaziridine as the test substrates for the desired C-H alkylation at the C-7 position (Table 1). Gratifyingly, the C7 alkylated product was obtained in 15% yield, when the substrates were stirred with 10 mol % $Co(acac)_2$ catalyst and $AgSbF_6$ as an additive in $(CH_2Cl)_2$ under N_2 atmosphere (entry 1). Probing the catalytic system, it was found that 5 mol % $Cp^*Co(CO)I_2$ in combination with 20 mol % $AgSbF_6$ served our purpose best (entry 2-4). Among the screened additives such as $AgSbF_6$, $AgBF_4$, AgOTf and KPF_6, the $AgSbF_6$ produced 66% yield, whereas others giving inferior results (entry 4-7). Next, screening of solvents concluded that $(CH_2Cl)_2$ was solvent of choice (entry 8-12) and reaction at room temperature led to the drop in yield to 29% (entry 13). A control experiment without catalyst showed no product formation (entry 14).

After optimizing the reaction conditions in hand, the practicality of the protocol was assessed engaging various *N*-sulphonyl aziridines with indoline **1a** as standard substrate (Scheme 13). The reaction of *ortho*-substituted *N*-tosyl aziridines having bromo **2b** and fluoro **2c** delivered the desired products **3b and 3c** in 52 and 58% yields respectively. Similar results were observed with the *meta*-substituted aziridines bearing bromo **2d**, chloro **2e**, fluoro **2f** and methyl **2g** groups, providing **3d-g** 60-65% yields. Surprisingly, strong electron withdrawing group 3-nitro substituted aziridine **2h** failed to produce **3h** under the given reaction condition. However, substrates having

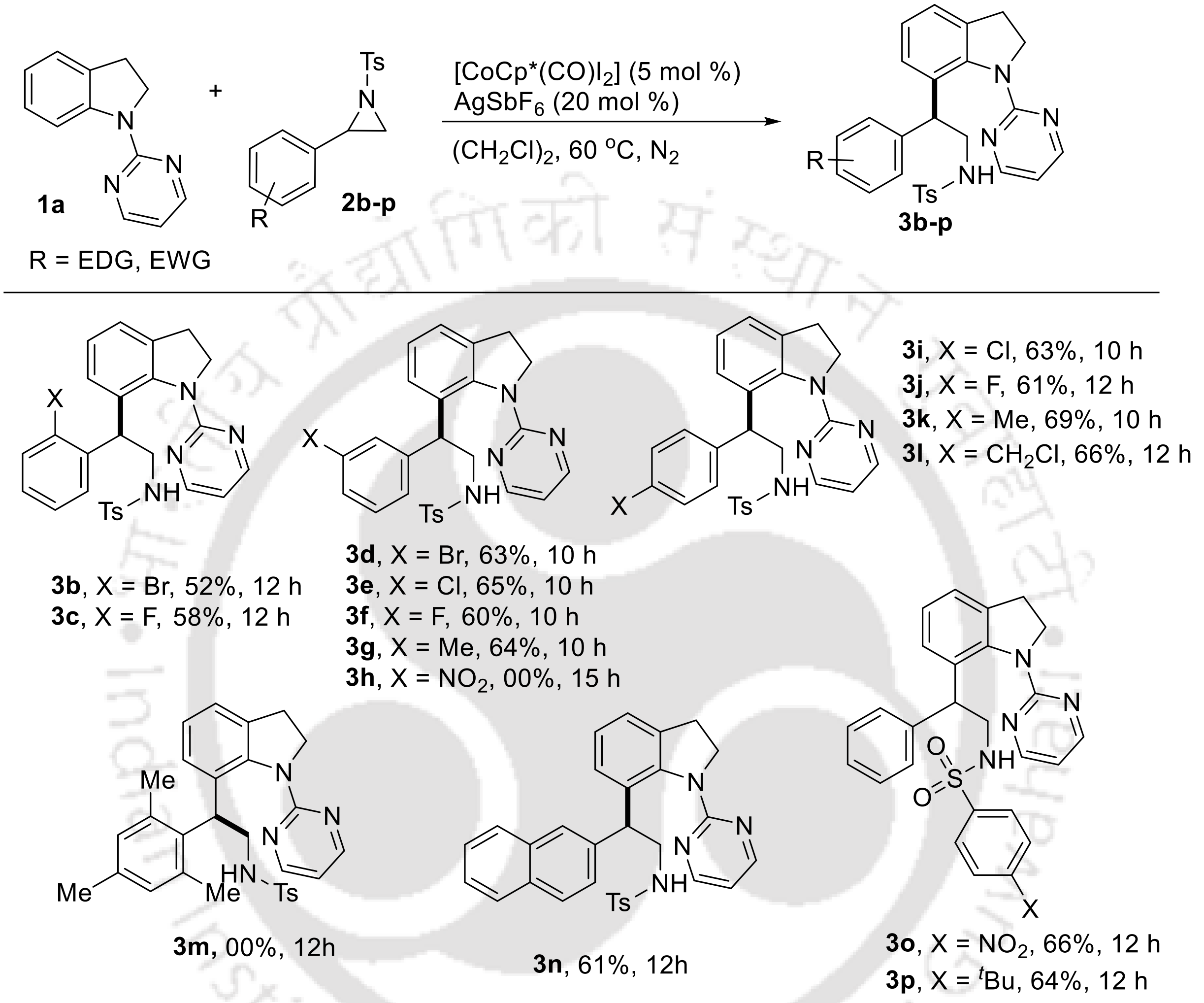
Table 1. Optimization of Reaction Conditions[a]



Entry	[Co] source	Additive	Solvent	Yield (%)
1	$Co(acac)_2$	$AgSbF_6$	$(CH_2Cl)_2$	15
2	$Co(acac)_3$	$AgSbF_6$	$(CH_2Cl)_2$	21
3	$Co(OAc)_2 \cdot 4H_2O$	$AgSbF_6$	$(CH_2Cl)_2$	n.d
4	$[Cp^*Co(CO)I_2]$	$AgSbF_6$	$(CH_2Cl)_2$	66
5	$[Cp^*Co(CO)I_2]$	$AgBF_4$	$(CH_2Cl)_2$	trace
6	$[Cp^*Co(CO)I_2]$	AgOTf	$(CH_2Cl)_2$	13
7	$[Cp^*Co(CO)I_2]$	KPF_6	$(CH_2Cl)_2$	n.d
8	$[Cp^*Co(CO)I_2]$	$AgSbF_6$	Toluene	trace
9	$[Cp^*Co(CO)I_2]$	$AgSbF_6$	MeOH	n.d
10	$[Cp^*Co(CO)I_2]$	$AgSbF_6$	DMF	n.d
11	$[Cp^*Co(CO)I_2]$	$AgSbF_6$	PhCl	49
12	$[Cp^*Co(CO)I_2]$	$AgSbF_6$	THF	n.d
13[c]	$[Cp^*Co(CO)I_2]$	$AgSbF_6$	$(CH_2Cl)_2$	29
14[d]	-	$AgSbF_6$	$(CH_2Cl)_2$	n.d

[a]Reaction conditions: **1a** (0.15 mmol), **2a** (0.18 mmol), [Co] source (5 mol %), additive (20 mol %), solvent (2 mL), 60 °C, 10 h. [b]Isolated yield. [c]Room temperature. [d]Without [Co] catalyst. n.d. = not detected.

para-substituents such as chloro **2i,** fluoro **2j**, methyl **2k** and chloromethyl **2l** groups were smoothly participated to furnish **3i-l** in 61-69% yields. Sterically hindered substrate 2,4,6-tri methyl substituted aziridine **2m** was found to be unsuccessful. In addition, 2-naphthyl substituted aziridine **2n** was also amenable to the reaction condition and provided **3n** in 61% yield. The reaction of substituted *N*-sulphonyl 2-phenyl aziridines such as 4-nitro **2o** and 4-*tert*-butyl **2p** groups successfully reacted to afford **3o-p** in 64 and 66% yields respectively. The structure of **3j** was determined using X-ray analysis (Figure 1). These results suggest that the functional group competence of the devised protocol for the C7 modification of indoline motifs.

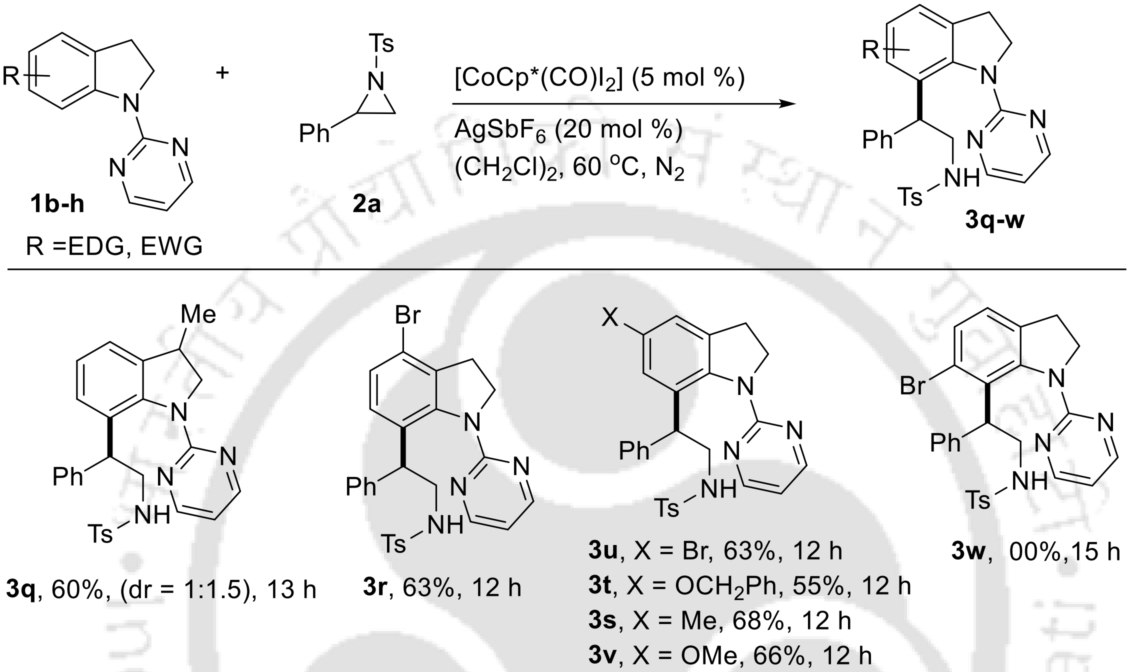


^{a}Reaction conditions: **1a** (0.15 mmol), **2b-p** (0.18 mmol), [Cp*Co(CO)I$_2$] (5 mol %), AgSbF$_6$ (20 mol %), (CH$_2$Cl)$_2$ (2 mL), 60 °C, N$_2$ atmosphere. n.d. = not detected.

Scheme 13. Substrate Scope of Aziridines **2b-p** with Indoline **1a**

Next, we investigated the substrate scope with respect to substituted indolines with aziridines **2a** as representative substrate (Scheme 14). Indolines bearing 3-methyl substituent **1b** gave a diastereomeric mixture (1:1.5) **3q** in 60% yield, while as 4-bromo **1c** provided the desired product **3r** in 63% yields. Moreover, 5-substituted indolines like 5-bromo **1d**, 5-benzoloxy **1e**, 5-methyl **1f** and 5-methoxy **1g** were found to be well tolerated under identical conditions giving **3u-v** in 55-

68% yields. Surprisingly, the substrate **1h** bearing 6-Br functionality did not react to afford the target product. This may be attributed to the steric congestion encountered near C-H functionalization site by the bromo group.



[a]Reaction conditions: **1b-h** (0.15 mmol), **2a** (0.18 mmol), [Cp*Co(CO)I$_2$] (5 mol %), AgSbF$_6$ (20 mol %), (CH$_2$Cl)$_2$ (2 mL), 60 °C, N$_2$ atmosphere. n.d. = not detected.

Scheme 14. Substrate Scope of Indolines **1b-h** with Aziridine **2a**

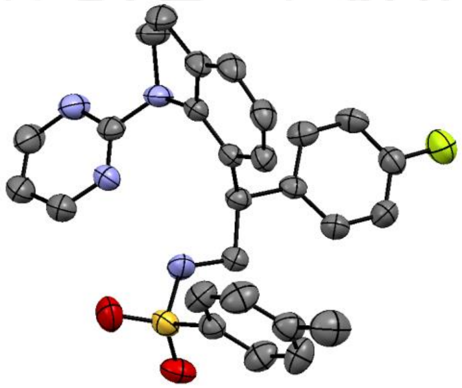
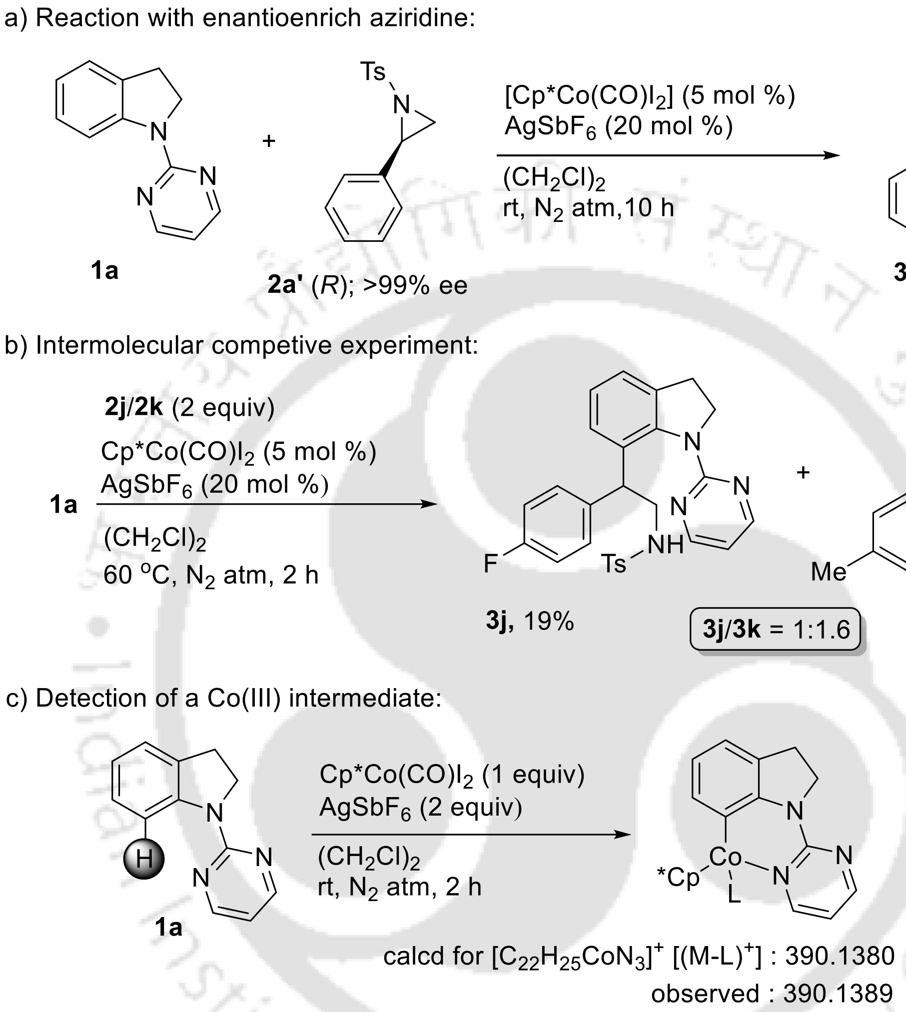
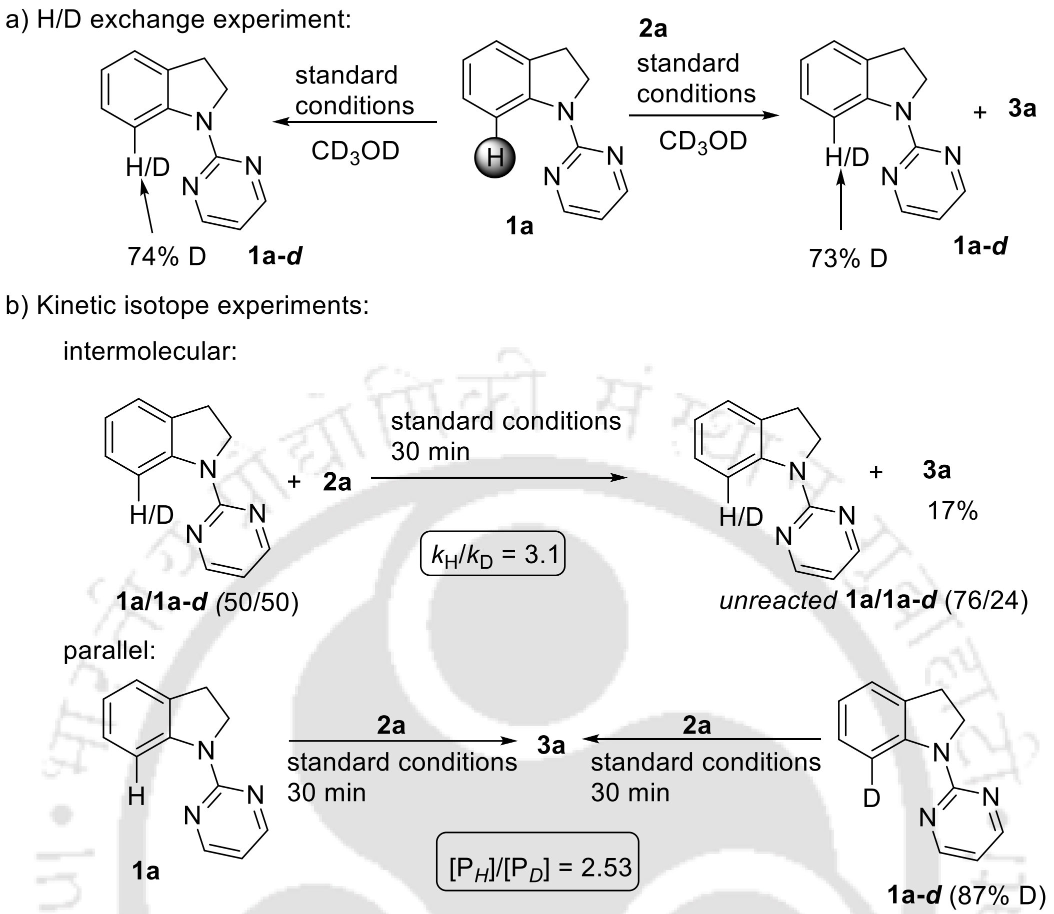


Figure 1. ORTEP diagram of *N*-(2-(4-fluorophenyl)-2-(1-(pyrimidin-2-yl)indolin-7-yl)ethyl)-4-methylbenzenesulfonamide **3j** with 50% ellipsoid. H-Atoms are omitted for clarity (CCDC 1954602).

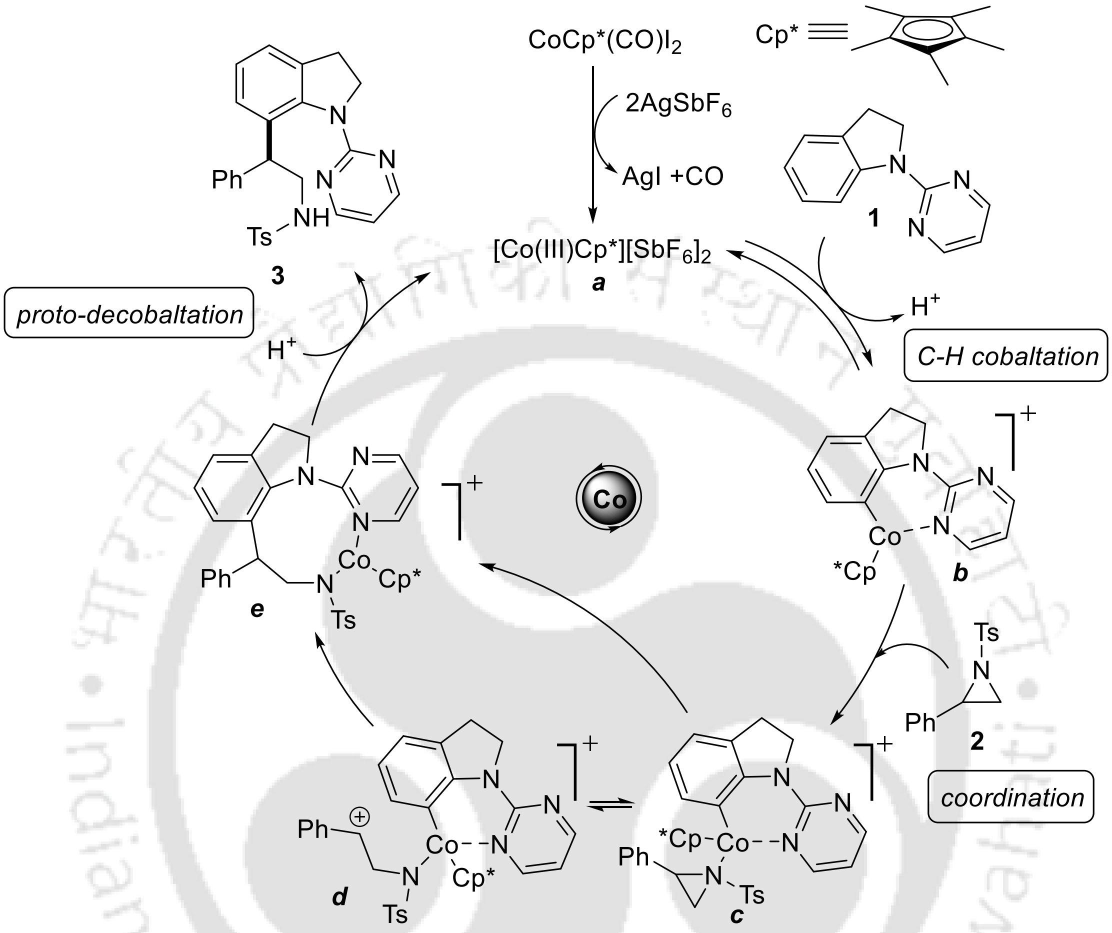


Scheme 15. Mechanistic Studies



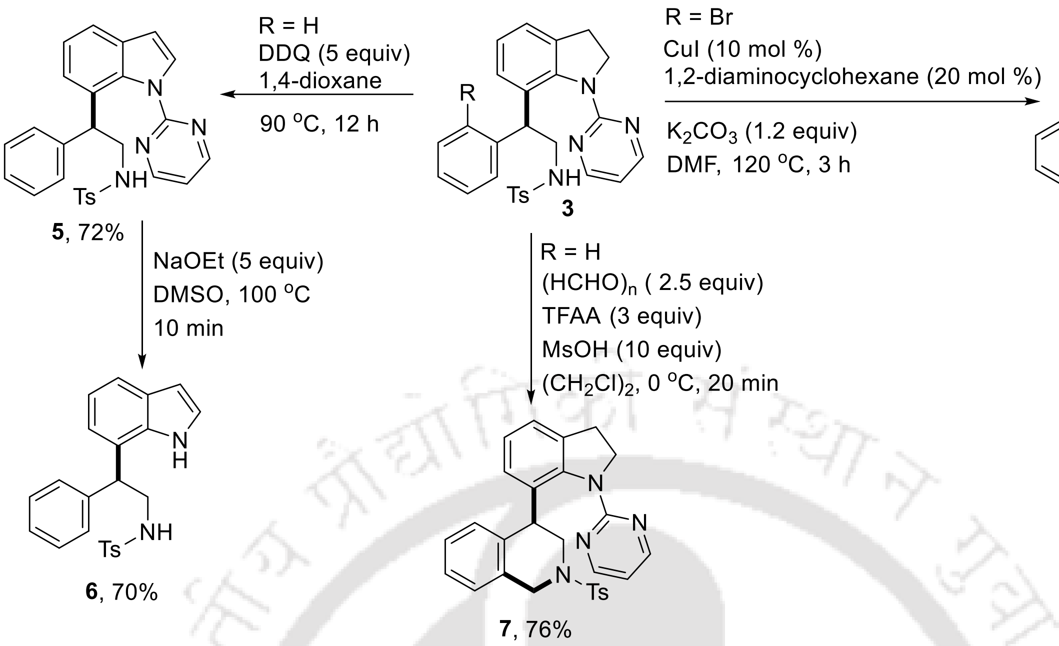
Scheme 16. Kinetic Isotope Studies

To get insight on the reaction pathway, we performed the reaction of indoline **1a** with enantioenriched aziridine **2a′** as a standard substrate and only 30% ee was observed in the desired product. The significant loss of ee supports the formation of a partial planer carbocation intermediate (Scheme 15a). The intermolecular competitive experiment between electronically dissimilar *N*-tosyl aziridines **2h** and **2i** with **1a** as a representative example shows that the former reacted slightly faster than the other one (Scheme 15b). We were pleased to detect a Co(III) intermediate by ESI-MS, suggesting the existence of six membered cobaltacycle in the reaction mechanism (Scheme 15c). A significant H/D exchange (74% D) was remarkably witnessed upon addition of CD_3OD as co-solvent under the optimal reaction condition, whereas 73% deuterium incorporation was observed in presence of aziridine, thereby indicating that the C-H cobaltation may be reversible (Scheme 16a). Moreover, the kinetic isotope studies from intermolecular experiment (k_H/k_D = 3.1) and parallel experiment ($[P_H]/[P_D]$ = 2.5) implies that the C−H bond cleavage may be involved in the rate-determining step (Scheme 16b).[23]



Scheme 17. Proposed Catalytic Cycle

On the basis of the preliminary mechanistic investigation and previous literature,[23] a plausible mechanism is depicted in scheme 17. The reaction mechanism involves generation of the cataionic Co(III) species ***a*** by the reaction of CoCp*(CO)I$_2$ with AgSbF$_6$, which may coordinate with **1** to give six membered cobaltocycle ***b***. The latter can chelate with nitrogen atom of aziridine ring **2** to form ***c*,** which may produce complex ***e*** or alternatively Ag^I may enables elongation of the C-N bond to construct a benzylic carbocation species ***d***, leading to the formation of ***e***. Finally, proto de-metalation of ***e*** may give the desired product **3** and regenerate the active Co(III) species ***a*** to fulfill the catalytic cycle.



Scheme 18. Post-Synthetic Application

Finally, to disclose the synthetic utility of this protocol, some post-synthetic transformation has been accomplished in good yields (Scheme 18). Cu-catalyzed cross-coupling of **3b** was also performed to construct bi-indoline derivative **4** in 85% yields. The late-stage directing group removal was successfully achieved by oxidation of **3a** to give **5**, which was further transformed to the C7-functionalized indole **6** in 70% yield by base promoted C-N bond cleavage. Additionally, the synthesized C7-alkylated product can be transformed to tetrahydroisoquinoline substituted indoline **7** in 76% yield while reacting with paraformaldehyde under acidic conditions. Therefore, bio-relevant C-7 decorated indole frameworks can be accessed efficiently by present strategy.

In summary, we have demonstrated a cost-effective and air-stable Cp*Co(III)-catalyzed site-selective C7 alkylation of indolines with aziridines using a removable pyrimidyl directing group and consequent oxidation to assemble C7-alkylated indoles in good yields. The protocol offers divergent pathways to ensemble plethora of bio-relevent C7-decorated indolines.

2.3 Experimental Section

General Information. Indoles, 2-chloropyrimidine (95%), alkenes, Co(acac)$_2$ (97%), Co(OAc)$_2$ (99.995%), DDQ (98%), Co$_2$(CO)$_8$, AgSbF$_6$ (98%), AgOTf (≥99.95%) and 1,2,3,4,5-pentamethylcyclopentadiene (95%) purchased of Aldrich, NaCNBH$_3$ procured of Spectrochem, Chloramine T trihydrate and paraformaldehyde (97%) of Merck were used as received. Merck silica gel G/GF 254 plates for analytical TLC and Rankem silica gel (100-200 mesh) for column chromatography were used. DRX-400 Varian spectrometer and Bruker Avance III 600 and 400 spectrometers were used for recording NMR (^{1}H and ^{13}C) spectra using $CDCl_3$ and as solvent and TMS as an internal standard. Chemical shifts (δ) and spin-spin coupling constant (*J*) are reported in ppm and in 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 with a Büchi B-540 apparatus and are uncorrected. HPLC analysis was carried out using Waters-2489 with Daicel Chiralcel OD-H column using *iso*-propanol and *n*-hexane as an eluent. FT-IR were collected on PerkinElmer IR spectrometer. Q-Tof ESI-MS instrument (model HAB 273) was used for recording mass spectra. X-ray crystallographic data were collected using Super Nova, Single source at offset, Eos diffractometer. The data refinement and cell reductions were carried out by CrysAlisPro.

General Procedure for the Preparation of Directing Groups 1. To a stirred solution of indoles (1.0 equiv, 5.0 mmol) in AcOH (25 mL) at 0 °C was added $NaBH_3CN$ (5.0 equiv, 25.0 mmol) in portions. Then, the reaction mixture was stirred at room temperature until completion. Then the resulted mixture was diluted with water and basified with aq. NaOH solution, and extracted with ethyl acetate (3 x 30 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 corresponding indolines. Then, the indolines (1.0 equiv) and 2-chloropyrimidine (1.2 equiv) were dissolved in DMSO. The resultant mixture was stirred at 100 °C and 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 and diluted with ethyl acetate (3 x 30 mL) and then washed with brine (2 x 10 mL) and water (1 x 10 mL). Drying (Na_2SO_4) and evaporation of the solvent gave a residue that was purified on silica gel column chromatography using n-hexane and ethyl acetate as an eluent to afford substituted 1-(pyrimidin-2-yl)indolines **1**.

General Procedure for Cobalt(III)-Catalyzed C7 Alkylation of Indolines. To a stirred solution of 1-(pyrimidin-2-yl)indoline (0.15 mmol), $Cp^{*}Co(CO)I_2$ (5 mol %, 0.0075 mmol, 3.6 mg) and $AgSbF_6$ (20 mol %, 0.03 mmol, 10.3 mg) in $(CH_2Cl)_2$ (1 mL) under N_2 atmosphere, aziridines

(0.18 mmol) was added. The resultant mixture was stirred at 60 °C and 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 and diluted with CH_2Cl_2 (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 C7 alkylated indolines.

Competition Experiment using Aziridines 2j and 2k. 1-(Pyrimidin-2-yl)indoline **1a** (19.7 mg, 0.1 mmol), **2j** (34.9 mg, 0.12 mmol), **2k** (34.4 mg, 0.12 mmol), [Cp*Co(CO)I_2] (2.4 mg, 0.005 mmol, 5.0 mol %) and $AgSbF_6$ (6.8 mg, 0.02 mmol, 20 mol %) in $(CH_2Cl)_2$ (1.0 mL) were subjected to the reaction conditions described in the standard procedure (60 °C) for 2 h and **3j** and **3k** were formed in 19 and 30% yields, respectively.

Intermolecular Kinetic Isotope Effect Study. 2-Phenyl-1-tosylaziridine **2a** (0.12 mmol, 32.7 mg) was reacted with 1-(pyrimidin-2-yl)indoline **1a** (0.1 mmol, 19.7 mg) and 1-(pyrimidin-2-yl)indoline-7-*d* **1a-*d*** (0.1 mmol, 19.8 mg) for 30 min under standard reaction condition. The resulting solution was then diluted with CH_2Cl_2 (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 gel column chromatography using *n*-hexane and ethyl acetate as an eluent to afford **3a** and a mixture of unreacted **1a** and **1a-*d*** as a yellowish liquid. The intermolecular k_H/k_D was found to be 3.1 after 30 min at 17% conversion, based on 600 MHz ^1H NMR of the recovered substrates **1a** and **1a-*d***.

Parallel Kinetic Isotope Effect Study. In a set of two experiments: in first set, 2-phenyl-1-tosylaziridine **2a** (0.12 mmol, 32.7 mg) was reacted with 1-(pyrimidin-2-yl)indoline **1a** (0.1 mmol, 19.7 mg) for 30 min under standard reaction conditions. Whereas in another set, 1-(pyrimidin-2-yl)indoline-7-*d* **1a-*d*** (0.1 mmol, 19.8 mg, 87% D) was used instead of **1a** in the reaction with 2-phenyl-1-tosylaziridine **2a** (0.12 mmol, 32.7 mg) under the standard reaction conditions. The two reactions were allowed to stir at 60 °C for 3 h. For the both cases, the resulting solution was then diluted with CH_2Cl_2 (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 gel column chromatography using *n*-hexane and ethyl acetate as an eluent to afford **3a**. The yield of **3a** was obtained as 22% and 10% yields respectively. The KIE value of 2.52 was determined by ratio of obtained **3a** yield (KIE = 22%/10%/87% = 2.52).

Procedure for the Synthesis of 1'-(Pyrimidin-2-yl)-1-tosyl-3,7'-biindoline 4. To a stirred solution of N-(2-(2-bromophenyl)-2-(1-(pyrimidin-2-yl)indolin-7-yl)ethyl)-4-methylbenzenesulfonamide **3b** (0.05 mmol, 27.4 mg), 1,2-diaminocyclohexane (1.2 mg, 0.01 mmol, 20 mol %), K_2CO_3 (10 mg, 0.075 mmol, 1.5 equiv) in DMF, CuI (1 mg, 0.005 mmol, 10 mol %) was added at room temperature. The resultant solution was further stirred at 120 ^{o}C for 3 h. After completion, as indicated by TLC, the reaction mixture was cooled to room temperature and diluted with ethyl acetate (15 mL). The mixture was successively washed with brine (2 x 5 mL) and cold 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 as an eluent to afford 1'-(pyrimidin-2-yl)-1-tosyl-3,7'-biindoline **4** as a colorless liquid in 85% yield (19.9 mg).

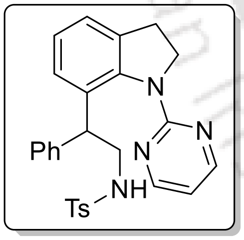
Procedure for the Late-stage Removal of Pyrimidyl Directing Group. To a stirred solution of 4-methyl-N-(2-phenyl-2-(1-(pyrimidin-2-yl)indolin-7-yl)ethyl)benzenesulfonamide **3a** (0.1 mmol, 47 mg) in 1,4-dioxane, DDQ (0.2 mmol, 45.4 mg) was added at room temperature. The resultant solution was further stirred at 90 °C for 14 h. After completion, as indicated by TLC, the reaction mixture was cooled to room temperature and diluted with ethyl acetate (1 x 15 mL). The mixture was successively 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 gel column chromatography using *n*-hexane and ethyl acetate as an eluent to afford 4-methyl-N-(2-phenyl-2-(1-(pyrimidin-2-yl)-1H-indol-7-yl)ethyl)benzenesulfonamide **5** as a colorless solid in 72% yield (33.7 mg). Next, indole **5** (0.05 mmol, 23.4 mg) was dissolved in DMSO (1 mL) and freshly prepared NaOEt (5 equiv) in EtOH (0.2 mL) was added to the mixture. The mixture was stirred at 100 ^{o}C for 8 min. After completion, the reaction mixture was cooled to room temperature and diluted with ethyl acetate (1 x 15 mL). The mixture was then washed with 2 N HCl (1 x 5 mL), 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 as an eluent to afford N-(2-

(1H-indol-7-yl)-2-phenylethyl)-4-methylbenzenesulfonamide **6** as a brown liquid in 70% yield (13.6 mg).

Procedure for the Synthesis of 4-(1-(Pyrimidin-2-yl)indolin-7-yl)-2-tosyl-1,2,3,4-tetrahydroisoquinoline 7. To a stirred solution of 4-methyl-N-(2-phenyl-2-(1-(pyrimidin-2-yl)indolin-7-yl)ethyl)benzenesulfonamide **3a** (0.05 mmol, 23.5 mg), paraformaldehyde ($(HCHO)_n$, 3.8 mg, 0.125 mmol, 2.5 equiv) and trifluoroacetic anhydride (TFAA, 22 µL, 0.15 mmol, 3 equiv) in $(CH_2Cl)_2$, MsOH (33 µL, 0.5 mmol, 10 equiv) was slowly added and the solution was stirred at 0 °C for 20 min. Then, 2 mL of H_2O was added and the mixture was stirred for an additional 5 min at 0 °C and 10 min at room temperature and diluted with CH_2Cl_2 (3 x 10 mL). The mixture was successively 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 gel column chromatography using *n*-hexane and ethyl acetate as an eluent to afford 4-(1-(pyrimidin-2-yl)indolin-7-yl)-2-tosyl-1,2,3,4-tetrahydroisoquinoline **7** as a colorless solid in 76% yield (18.3 mg).

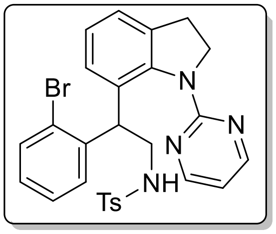
3.4 Characterization Data

4-Methyl-N-(2-phenyl-2-(1-(pyrimidin-2-yl)indolin-7-yl)ethyl)benzenesulfonamide 3a.

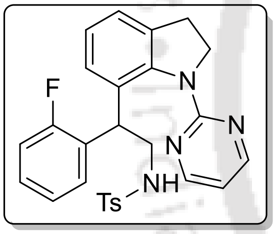


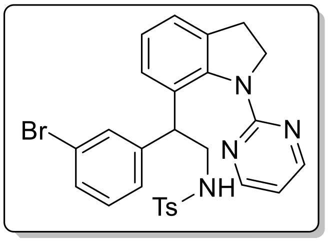
Analytical TLC on silica gel, 3:7 ethyl acetate/hexane $R_f = 0.40$; colorless solid; mp 181-183 °C; yield 66% (36.5 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.52 (d, *J* = 4.8 Hz, 2H), 7.65 (d, *J* = 8.0 Hz, 2H), 7.25 (d, *J* = 8.0 Hz, 2H), 7.20-7.16 (m, 2H), 7.14-7.10 (m, 2H), 7.04 (d, *J* = 7.2 Hz, 2H), 6.94-6.92 (m, 1H), 6.87-6.81 (m, 2H), 6.77 (d, *J* = 8.0 Hz, 1H), 4.90-4.84 (m, 1H), 4.46-4.42 (m, 1H), 4.13-4.06 (m, 1H), 3.76-3.63 (m, 2H), 3.21-3.13 (m, 1H), 2.88-2.79 (m, 1H), 2.45 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 161.6, 158.1, 143.5, 143.0, 141.8, 137.0, 136.4, 132.3, 129.7, 128.7, 127.45, 127.43, 126.8, 125.5, 125.4, 123.4, 113.0, 54.0, 46.2, 44.6, 30.2, 21.7; FT-IR (KBr) 3039, 2936, 2846, 1580, 1554 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{27}H_{27}N_4O_2S^+$: 471.1849, found: 471.1849.

N-(2-(2-Bromophenyl)-2-(1-(pyrimidin-2-yl)indolin-7-yl)ethyl)-4-methylbenzenesulfonamide 3b. Analytical TLC on silica gel, 3:7 ethyl acetate/hexane R_f = 0.39; colorless solid; mp 157-159 °C; yield 52% (42.7 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.38 (d, *J* = 4.8 Hz, 2H), 7.66 (d, *J* = 8.4 Hz, 2H), 7.43 (d, *J* = 8.4 Hz, 1H), 7.27 (d, *J* = 7.8 Hz, 2H), 7.17 – 7.14 (m, 3H), 7.02-7.00 (m, 1H), 6.95-6.90 (m, 2H), 6.75 (t, *J* = 4.8 Hz, 1H), 6.41 (s, 1H), 4.82-4.80 (m, 1H), 4.72-4.69 (m, 1H), 4.10-4.05 (m, 1H), 3.69-3.65 (m, 1H), 3.58-3.54 (m, 1H), 3.20-3.15 (m, 1H), 2.87-2.82 (m, 1H), 2.46 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 161.0, 157.9, 143.5, 143.2, 140.6, 136.8, 136.5, 133.3, 129.7, 129.1, 128.4, 128.3, 127.7, 127.4, 126.3, 125.4, 124.8, 123.8, 112.7, 53.5, 46.1, 44.3, 29.9, 21.7; FT-IR (KBr) 3012, 2852, 2784, 1582, 1554 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{27}H_{26}BrN_4O_2S^+$: 549.0954, found: 549.0955.

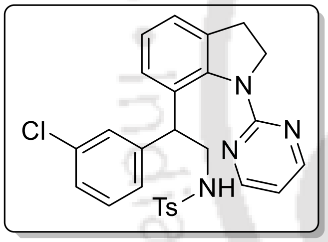


N-(2-(2-Fluorophenyl)-2-(1-(pyrimidin-2-yl)indolin-7-yl)ethyl)-4-methylbenzenesulfonamide 3c. Analytical TLC on silica gel, 3:7 ethyl acetate/hexane R_f = 0.40; colorless solid; mp 145-147 °C; yield 58% (42.4 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.42 (d, *J* = 4.8 Hz, 2H), 7.61 (d, *J* = 8.4 Hz, 2H), 7.22 (d, *J* = 7.8 Hz, 2H), 7.12-7.08 (m, 2H), 7.05 (t, *J* = 7.8 Hz, 1H), 6.96 (t, *J* = 7.8 Hz, 1H), 6.88-6.83 (m, 3H), 6.80 (br s, 1H), 6.75 (t, *J* = 4.8 Hz, 1H), 4.79-4.76 (m, 1H), 4.63 (dd, *J* = 10.2, 5.4 Hz, 1H), 4.09-4.04 (m, 1H), 3.74-3.71 (m, 1H), 3.63-3.59 (m, 1H), 3.17-3.11 (m, 1H), 2.79 (dd, *J* = 15.8, 9.6 Hz, 1H), 2.43 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 161.3 (J_{C-F} = 245.4 Hz), 161.0, 157.8, 143.2, 142.9, 136.7, 136.3, 129.9, 129.5, 128.5 (J_{C-F} = 14.5 Hz), 128.3 (J_{C-F} = 8.2 Hz), 128.0 (J_{C-F} = 4.2 Hz), 127.1, 125.8, 124.9, 124.1 (J_{C-F} = 3.3 Hz), 123.4, 115.5 (J_{C-F} = 22.2 Hz), 112.6, 53.5, 45.4 (J_{C-F} = 2.1 Hz), 38.4, 29.9, 21.5; FT-IR (KBr) 3028, 2930, 2885, 1578, 1552 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{27}H_{26}FN_4O_2S^+$: 489.1755, found: 489.1760.

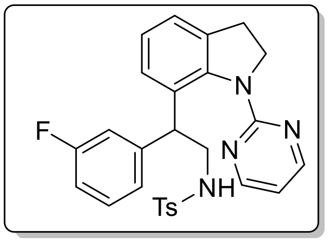




N-(2-(3-Bromophenyl)-2-(1-(pyrimidin-2-yl)indolin-7-yl)ethyl)-4-methylbenzenesulfonamide 3d. Analytical TLC on silica gel, 3:7 ethyl acetate/hexane $R_f = 0.40$; colorless solid; mp 139-141 °C; yield 63% (51.8 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.52 (d, *J* = 4.8 Hz, 2H), 7.63 (d, *J* = 7.8 Hz, 2H), 7.27-7.24 (m, 3H), 7.15 (s, 1H), 7.14 (d, *J* = 7.2 Hz, 1H), 7.06 (t, *J* = 7.8 Hz, 1H), 6.98 (d, *J* = 7.8 Hz, 1H), 6.88-6.83 (m, 3H), 6.74 (d, *J* = 7.8 Hz, 1H), 4.88-4.84 (m, 1H), 4.42-4.39 (m, 1H), 4.15-4.10 (m, 1H), 3.69-3.65 (m, 1H), 3.63-3.60 (m, 1H), 3.20-3.14 (m, 1H), 2.87-2.83 (m, 1H), 2.46 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 161.5, 158.1, 144.1, 143.4, 143.2, 136.7, 136.6, 131.4, 130.4, 130.2, 130.0, 129.7, 127.3, 126.1, 125.6, 125.4, 123.7, 122.8, 113.2, 54.0, 46.0, 44.2, 30.2, 21.7; FT-IR (KBr) 3022, 2854, 1630, 1580, 1496 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{27}H_{26}BrN_4O_2S^+$: 549.0949, found: 549.0963.

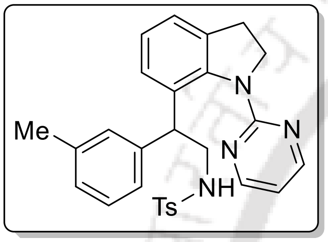


N-(2-(3-Chlorophenyl)-2-(1-(pyrimidin-2-yl)indolin-7-yl)ethyl)-4-methylbenzenesulfonamide 3e. Analytical TLC on silica gel, 3:7 ethyl acetate/hexane $R_f = 0.40$; thick colorless liquid; yield 65% (49.1 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.52 (d, *J* = 4.8 Hz, 2H), 7.64 (d, *J* = 8.4 Hz, 2H), 7.26 (d, *J* = 7.8 Hz, 2H), 7.14-7.11 (m, 3H), 7.00 (s, 1H), 6.93-6.92 (m, 1H), 6.87 (t, *J* = 7.2 Hz, 1H), 6.84 (t, *J* = 4.8 Hz, 2H), 6.74 (d, *J* = 7.8 Hz, 1H), 4.88-4.84 (m, 1H), 4.41 (dd, *J* = 10.8, 6.0 Hz, 1H), 4.15-4.10 (m, 1H), 3.70-3.66 (m, 1H), 3.64-3.63 (m, 1H), 3.20-3.14 (m, 1H), 2.87-2.83 (m, 1H), 2.46 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 161.5, 158.1, 143.8, 143.5, 143.2, 136.9, 136.6, 134.5, 131.5, 129.9, 129.7, 127.6, 127.4, 127.1, 125.7, 125.6, 125.5, 123.7, 113.2, 54.0, 46.1, 44.4, 30.2, 21.7; FT-IR (neat) 3024, 2928, 1609, 1554, 1494 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{27}H_{26}ClN_4O_2S^+$: 505.1460, found: 505.1460.



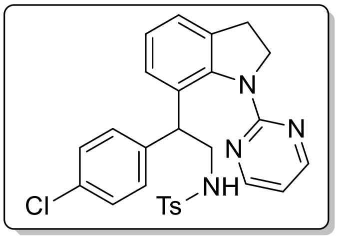
N-(2-(3-Fluorophenyl)-2-(1-(pyrimidin-2-yl)indolin-7-yl)ethyl)-4-methylbenzenesulfonamide 3f. Analytical TLC on silica gel, 3:7 ethyl acetate/hexane $R_f = 0.41$; colorless solid; mp 139-141 °C; yield 60% (43.9 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.50 (d, *J* = 4.8 Hz, 2H), 7.61 (d, *J* = 8.4 Hz, 2H), 7.23 (d, *J* = 7.8 Hz, 2H), 7.14-7.10 (m, 2H), 6.89 (br s, 1H), 6.85-6.79 (m, 4H), 6.70-6.68 (m, 2H), 4.86-4.83 (m, 1H), 4.40 (dd, *J* = 10.8, 6.0 Hz, 1H), 4.12-4.07 (m, 1H), 3.68-3.61 (m, 2H), 3.18-3.12 (m, 1H), 2.84-2.80 (m, 1H), 2.43 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 163.5 ($J_{C\text{-}F}$ = 244.5 Hz), 161.3, 157.9, 144.2 ($J_{C\text{-}F}$ = 6.6 Hz), 143.3, 143.0, 136.5 ($J_{C\text{-}F}$ = 21.6 Hz), 136.4, 131.4, 129.9 ($J_{C\text{-}F}$ = 8.2 Hz), 129.8, 129.5, 127.2, 127.0, 125.3 ($J_{C\text{-}F}$ = 21.6 Hz), 123.5, 122.8 ($J_{C\text{-}F}$ = 2.7 Hz), 114.3 ($J_{C\text{-}F}$ = 21.6 Hz), 113.6 ($J_{C\text{-}F}$ = 20.8 Hz), 113.0, 53.8, 45.8, 44.0, 30.0, 21.5; FT-IR (KBr) 3030, 2850, 2794, 1613, 1556 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{27}H_{26}FN_4O_2S^+$: 489.1755, found: 489.1758.

4-Methyl-N-(2-(1-(pyrimidin-2-yl)indolin-7-yl)-2-(m-tolyl)ethyl)benzenesulfonamide 3g.

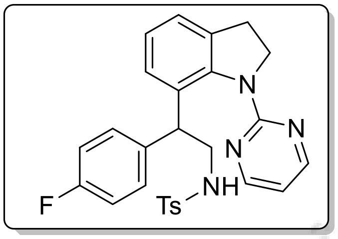


Analytical TLC on silica gel, 3:7 ethyl acetate/hexane R_f = 0.40; colorless solid; mp 79-81 °C; yield 64% (46.5 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.53 (d, *J* = 4.8 Hz, 2H), 7.64 (d, *J* = 7.8 Hz, 2H), 7.25 (d, *J* = 7.8 Hz, 2H), 7.11 (d, *J* = 7.2 Hz, 1H), 7.06 (t, *J* = 7.8 Hz, 1H), 6.99-6.97 (m, 1H), 6.95 (d, *J* = 7.2 Hz, 1H), 6.85-6.81 (m, 4H), 6.77 (d, *J* = 7.8 Hz, 1H), 4.90-4.86 (m, 1H), 4.38 (dd, *J* = 10.8, 5.4 Hz, 1H), 4.12-4.07 (m, 1H), 3.75-3.70 (m, 1H), 3.65-3.61 (m, 1H), 3.20-3.14 (m, 1H), 2.81 (dd, *J* = 15.0, 7.2 Hz, 1H), 2.45 (s, 3H), 2.23 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 161.6, 158.1, 143.3, 143.0, 141.7, 138.3, 136.8, 136.3, 132.3, 129.6, 128.6, 128.1, 127.6, 127.3, 125.5, 125.4, 124.3, 123.3, 113.0, 54.0, 46.2, 44.4, 30.2, 21.7, 21.6; FT-IR (KBr) 3034, 2862, 2799, 1582, 1553 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{28}H_{29}N_4O_2S^+$: 485.2006, found: 485.2028.

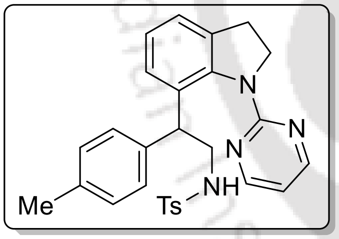
N-(2-(4-Chlorophenyl)-2-(1-(pyrimidin-2-yl)indolin-7-yl)ethyl)-4-methylbenzenesulfonamide 3i. Analytical TLC on silica gel, 3:7 ethyl acetate/hexane R_f = 0.41;



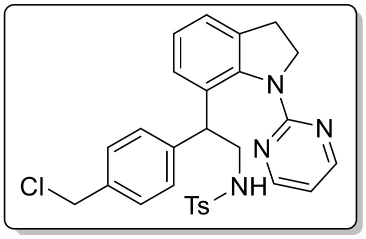
thick yellow liquid; yield 63% (47.6 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.49 (d, *J* = 4.8 Hz, 2H), 7.62 (d, *J* = 8.4 Hz, 2H), 7.23 (d, *J* = 7.6 Hz, 2H), 7.13-7.09 (m, 3H), 6.95 (d, *J* = 8.8 Hz, 2H), 6.86-6.78 (m, 3H), 6.71 (d, *J* = 7.6 Hz, 1H), 4.86-4.80 (m, 1H), 4.41-3.37 (m, 1H), 4.12-4.04 (m, 1H), 3.69-3.57 (m, 2H), 3.18-3.10 (m, 1H), 2.84-2.78 (m, 1H), 2.43 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.4, 157.8, 143.3, 142.9, 140.1, 136.6, 136.3, 132.4, 131.6, 129.5, 128.5, 127.1, 125.3, 125.1, 123.4, 112.9, 53.7, 45.8, 43.8, 30.0, 21.5; FT-IR (neat) 3028, 2850, 2797, 1554, 1584 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{27}H_{26}ClN_4O_2S^+$: 505.1460, found: 505.1463.



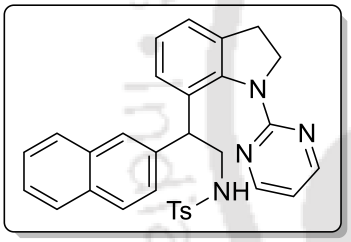
N-(2-(4-Fluorophenyl)-2-(1-(pyrimidin-2-yl)indolin-7-yl)ethyl)-4-methylbenzenesulfonamide 3j. Analytical TLC on silica gel, 3:7 ethyl acetate/hexane $R_f = 0.40$; colorless solid; mp 138-140 °C; yield 61% (44.6 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.52 (d, *J* = 4.8 Hz, 2H), 7.64 (d, *J* = 8.4 Hz, 2H), 7.25 (d, *J* = 8.4 Hz, 2H), 7.13 (d, *J* = 7.2 Hz, 1H), 7.00-6.97 (m, 2H), 6.90 (s, 1H), 6.88-6.83 (m, 4H), 6.73 (d, *J* = 7.8 Hz, 1H), 4.88-4.85 (m, 1H), 4.42-4.40 (m, 1H), 4.12-4.07 (m, 1H), 3.69-3.61 (m, 2H), 3.20-3.14 (m, 1H), 2.85-2.81 (m, 1H), 2.45 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 162.5 ($J_{C\text{-}F}$ = 243.9 Hz), 161.5, 158.1, 143.4, 143.1, 137.5 ($J_{C\text{-}F}$ = 3.3 Hz), 136.7, 136.5, 132.1, 129.7, 128.9 ($J_{C\text{-}F}$ = 7.8 Hz), 127.4, 125.5, 125.3, 123.6, 115.5 ($J_{C\text{-}F}$ = 21.0 Hz), 113.1, 54.0, 46.2, 43.8, 30.2, 21.7; FT-IR (KBr) 3026, 2934, 2856, 1583, 1556, 1507 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{27}H_{26}FN_4O_2S^+$: 489.1755, found: 489.1762.



4-Methyl-N-(2-(1-(pyrimidin-2-yl)indolin-7-yl)-2-(p-tolyl)ethyl)benzenesulfonamide 3k. Analytical TLC on silica gel, 3:7 ethyl acetate/hexane $R_f = 0.42$; colorless solid; mp 157-159 °C; yield 69% (50.1 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.51 (d, *J* = 4.8 Hz, 2H), 7.62 (d, *J* = 8.4 Hz, 2H), 7.22 (d, *J* = 7.8 Hz, 2H), 7.08 (d, *J* = 7.2 Hz, 1H), 6.97 (d, *J* = 8.4 Hz, 3H), 6.90 (d, *J* = 7.8 Hz, 2H), 6.82-6.79 (m, 2H), 6.73 (d, *J* = 7.8 Hz, 1H), 4.88-4.84 (m, 1H), 4.37-4.35 (m, 1H), 4.08-4.03 (m, 1H), 3.71-3.67 (m, 1H), 3.62-3.59 (m, 1H), 3.18-3.12 (m, 1H), 2.80-2.76 (m, 1H), 2.43 (s, 3H), 2.22 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 161.5, 158.1, 143.3, 143.0, 138.8, 136.8, 136.4, 136.3, 132.5, 129.6, 129.4, 127.4, 127.2, 125.4, 125.4, 123.3, 113.0, 53.9, 46.1, 44.1, 30.2, 21.7, 21.1; FT-IR (KBr) 3028, 2954, 2918, 1583, 1557 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{28}H_{29}N_4O_2S^+$: 485.2006, found: 485.2022.

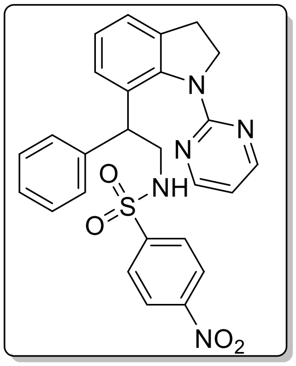


N-(2-(4-(Chloromethyl)phenyl)-2-(1-(pyrimidin-2-yl)indolin-7-yl)ethyl)-4-methylbenzenesulfonamide 3l. Analytical TLC on silica gel, 3:7 ethyl acetate/hexane R_f = 0.40; colorless solid; mp 160-162 °C; yield 66% (51.3 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.52 (d, *J* = 4.8 Hz, 2H), 7.64 (d, *J* = 8.4 Hz, 2H), 7.25 (d, *J* = 8.4 Hz, 2H), 7.21 (d, *J* = 8.4 Hz, 2H), 7.12 (d, *J* = 7.8 Hz, 1H), 7.03 (d, *J* = 8.4 Hz, 2H), 6.95 (s, 1H), 6.86-6.82 (m, 2H), 6.74 (d, *J* = 7.8 Hz, 1H), 4.89-4.86 (m, 1H), 4.50 (s, 2H), 4.43 (dd, *J* = 11.4, 5.4 Hz, 1H), 4.12-4.07 (m, 1H), 3.73-3.68 (m, 1H), 3.66-3.63 (m, 1H), 3.20-3.14 (m, 1H), 2.84-2.81 (m, 1H), 2.45 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 161.5, 158.1, 143.4, 143.1, 142.1, 136.8, 136.5, 136.0, 131.9, 129.7, 129.0, 127.8, 127.4, 125.5, 125.4, 123.5, 113.1, 54.0, 46.0, 44.3, 30.2, 21.7; FT-IR (KBr) 3016, 2926, 2858, 1578, 1556 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{28}H_{28}ClN_4O_2S^+$: 519.1616, found: 519.1617.



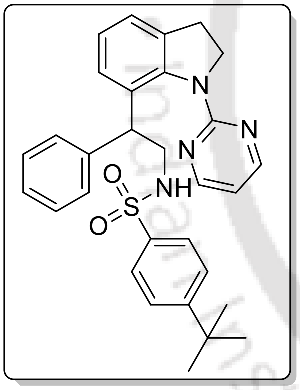
4-methyl-N-(2-(naphthalen-2-yl)-2-(1-(pyrimidin-2-yl)indolin-7-yl)ethyl)benzenesulfonamide 3n. Analytical TLC on silica gel, 3:7 ethyl acetate/hexane R_f = 0.39; colorless solid; mp 141-143 °C; yield 61% (47.6 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.55 (d, *J* = 4.8 Hz, 2H), 7.73-7.69 (m, 2H), 7.66 (d, *J* = 8.4 Hz, 3H), 7.45 (s, 1H), 7.43-7.39 (m, 2H), 7.25 (d, *J* = 7.8 Hz, 2H), 7.17 (d, *J* = 8.4 Hz, 1H), 7.12 (d, *J* = 7.2 Hz, 1H), 6.99 (br s, 1H), 6.86-6.83 (m, 2H), 6.81 (d, *J* = 7.8 Hz, 1H), 4.92-4.88 (m, 1H), 4.58 (dd, *J* = 10.2, 5.4 Hz, 1H), 4.18-4.13 (m, 1H), 3.86-3.83 (m, 1H), 3.80-3.77 (m, 1H), 3.22-3.16 (m, 1H), 2.87-2.83 (m, 1H), 2.45 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 161.4, 157.9, 143.2, 142.9, 139.1, 136.6, 136.2, 133.2, 132.1, 132.0, 129.5, 128.2, 127.7, 127.4, 127.2, 126.3, 126.1, 125.7, 125.5, 125.3, 124.7, 123.3, 112.9, 53.8, 45.8, 44.3, 30.0, 21.5; FT-IR (KBr) 3014, 2938, 2851, 1631, 1584, 1551 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{31}H_{29}N_4O_2S^+$: 521.2006, found: 521.2021.

4-Nitro-N-(2-phenyl-2-(1-(pyrimidin-2-yl)indolin-7-yl)ethyl)benzenesulfonamide 3o.



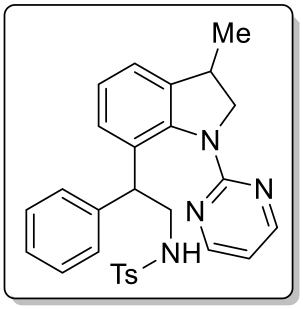
Analytical TLC on silica gel, 3:7 ethyl acetate/hexane $R_f = 0.40$; yellow solid; mp 161-163 °C; yield 66% (49.6 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.58 (d, J = 4.8 Hz, 2H), 8.28 (s, 1H), 8.21 (d, J = 9.0 Hz, 2H), 7.86 (d, J = 8.4 Hz, 2H), 7.19 (t, J = 7.2 Hz, 2H), 7.14 (t, J = 7.2 Hz, 1H), 7.10 (d, J = 7.2 Hz, 1H), 7.02 (d, J = 6.6 Hz, 2H), 6.88 (t, J = 4.8 Hz, 1H), 6.69 (t, J = 7.8 Hz, 1H), 6.62 (d, J = 7.8 Hz, 1H), 4.98-4.95 (m, 1H), 4.44 (dd, J = 11.4, 4.2 Hz, 1H), 4.11-4.06 (m, 1H), 3.83-3.80 (m, 1H), 3.76-3.71 (m, 1H), 3.23-3.17 (m, 1H), 2.84-2.80 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 161.3, 158.1, 149.8, 146.0, 143.3, 141.3, 136.9, 132.1, 128.8, 128.3, 127.1, 127.0, 125.4, 125.1, 124.2, 123.7, 113.1, 54.3, 46.4, 43.9, 30.2; FT-IR (KBr) 3028, 2852, 1584, 1556 cm^{-1}; HRMS (ESI) m/z [M+H]$^+$ calcd for $C_{26}H_{24}N_5O_4S^+$: 502.1544, found: 502.1562.

4-(*tert*-Butyl)-N-(2-phenyl-2-(1-(pyrimidin-2-yl)indolin-7-yl)ethyl)benzenesulfonamide 3p.



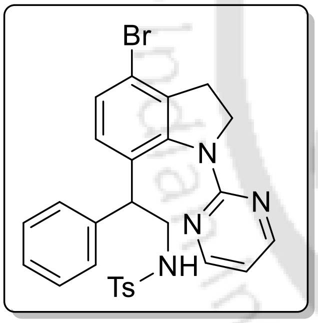
Analytical TLC on silica gel, 3:7 ethyl acetate/hexane $R_f = 0.40$; yellowish solid; mp 174-176 °C; yield 64% (49.1 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.50 (d, J = 4.8 Hz, 2H), 7.65 (d, J = 8.4 Hz, 2H), 7.43 (d, J = 8.4 Hz, 2H), 7.16 (t, J = 7.2 Hz, 2H), 7.11-7.07 (m, 2H), 7.02-7.00 (m, 3H), 6.81-6.79 (m, 2H), 6.73 (d, J = 7.8 Hz, 1H), 4.88-4.84 (m, 1H), 4.42 (dd, J = 11.4, 6.0 Hz, 1H), 4.09-4.04 (m, 1H), 3.75-3.70 (m, 1H), 3.68-3.65 (m, 1H), 3.18-3.13 (m, 1H), 2.81-2.78 (m, 1H), 1.35 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 161.5, 158.1, 156.0, 143.4, 141.8, 136.7, 136.4, 132.2, 128.7, 127.4, 127.2, 126.8, 126.0, 125.5, 125.4, 123.4, 113.0, 54.0, 46.1, 44.4, 35.2, 31.3, 30.2; FT-IR (KBr) 3037, 2852, 2786, 1584, 1550 cm^{-1}; HRMS (ESI) m/z [M+H]$^+$ calcd for $C_{30}H_{33}N_4O_2S^+$: 513.2319, found: 513.2062.

4-**Methyl-N-(2-(3-methyl-1-(pyrimidin-2-yl)indolin-7-yl)-2-phenylethyl)benzenesulfonamide**

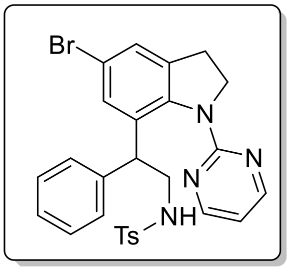


3q. Analytical TLC on silica gel, 3:7 ethyl acetate/hexane R$_f$ = 0.38; yellowish liquid; yield 60% (43.6 mg); ^{1}H NMR (600 MHz, CDCl$_3$) δ 8.45 (d, *J* = 4.8 Hz, 2H), 8.40 (d, *J* = 4.8 Hz, 1.28H), 7.54 (d, *J* = 8.0 Hz, 3.53H), 7.15 (d, *J* = 8.0 Hz, 3.67H), 7.10-7.03 (m, 6.79 H), 6.79 (q, *J* = 7.1 Hz, 2H), 6.99-6.92 (m, 5.39H), 6.82-6.67 (m, 1.90H), 6.74-6.67 (m, 3.63H), 6.53-6.50 (m, 1H), 4.94-4.90 (m, 1H), 4.36-4.32 (m, 2H), 4.29-4.28 (m, 0.69H), 4.23-4.18 (m, 1H), 3.69-3.62 (m, 1.84H), 3.60-3.58 (m, 2.59H), 3.51-3.45 (m, 1.61H), 3.38-3.32 (m, 1.58H), 3.06-3.02 (m, 1H), 2.36 (s, 3H), 2.35 (s, 2.32H), 1.20-1.18 (m, 3H), 1.09 (d, *J* = 7.0 Hz, 2.32H); ^{13}C NMR (150 MHz, CDCl$_3$) δ 161.3, 157.9, 157.9, 143.2, 141.68, 141.3, 136.6, 132.0, 129.5, 129.4, 128.5, 128.5, 127.3, 127.2, 127.1, 126.6, 125.5, 125.4, 125.2, 122.3, 121.6, 112.8, 61.7, 60.8, 45.8, 44.8, 44.0, 36.8, 36.4, 21.5, 19.8, 16.4; FT-IR (KBr) 3036, 2851, 1552 cm^{-1}; HRMS (ESI) m/z [M+H]$^+$ calcd for C$_{28}$H$_{29}$N$_4$O$_2$S$^+$: 485.2006, found: 485.2018.

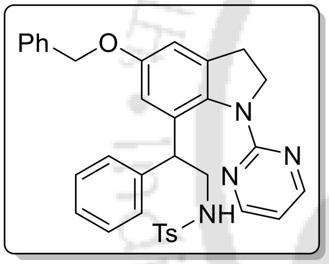
N-(2-(4-Bromo-1-(pyrimidin-2-yl)indolin-7-yl)-2-phenylethyl)-4-methylbenzenesulfonamide



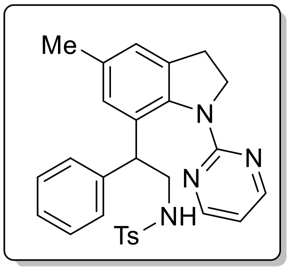
3r. Analytical TLC on silica gel, 3:7 ethyl acetate/hexane R$_f$ = 0.38; colorless liquid; yield 63% (51.8 mg); ^{1}H NMR (600 MHz, CDCl$_3$) δ 8.50 (d, *J* = 4.8 Hz, 2H), 7.65 (d, *J* = 8.4 Hz, 2H), 7.43 (d, *J* = 8.4 Hz, 2H), 7.16 (t, *J* = 7.2 Hz, 2H), 7.11-7.07 (m, 2H), 7.02-7.00 (m, 3H), 6.81-6.79 (m, 2H), 6.73 (d, *J* = 7.8 Hz, 1H), 4.88-4.84 (m, 1H), 4.42 (dd, *J* = 11.4, 6.0 Hz, 1H), 4.09-4.04 (m, 1H), 3.75-3.70 (m, 1H), 3.68-3.65 (m, 1H), 3.18-3.13 (m, 1H), 2.81-2.78 (m, 1H), 1.35 (s, 9H); ^{13}C NMR (151 MHz, CDCl$_3$) δ 161.5, 158.1, 156.0, 143.4, 141.8, 136.7, 136.4, 132.2, 128.7, 127.4, 127.2, 126.8, 126.0, 125.5, 125.4, 123.4, 113.0, 54.0, 46.1, 44.4, 35.2, 31.3, 30.2; FT-IR (neat) 3035, 2850, 1552 cm^{-1}; HRMS (ESI) m/z [M+H]$^+$ calcd for C$_{27}$H$_{26}$N$_4$O$_2$S$^+$: 549.0954, found: 549.0962.



N-(2-(5-Bromo-1-(pyrimidin-2-yl)indolin-7-yl)-2-phenylethyl)-4-methylbenzenesulfonamide 3s. Analytical TLC on silica gel, 3:7 ethyl acetate/hexane R$_f$ = 0.40; colorless solid; mp 201-203 °C; yield 63% (51.8 mg); ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.47 (d, *J* = 4.8 Hz, 2H), 7.56 (d, *J* = 8.0 Hz, 2H), 7.21-7.19 (m, 2H), 7.13-7.04 (m, 4H), 6.95-6.90 (m, 3H), 6.77 (t, *J* = 4.8 Hz, 1H), 6.73-6.72 (m, 1H), 4.83-4.78 (m, 1H), 4.32 (dd, *J* = 10.8, 5.6 Hz, 1H), 4.04-3.96 (m, 1H), 3.61-3.50 (m, 2H), 3.12 – 3.03 (m, 1H), 2.74-2.68 (m, 1H), 2.37 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 161.3, 158.2, 143.4, 142.8, 141.1, 138.8, 136.5, 134.4, 129.9, 128.9, 128.4, 127.2, 127.2, 127.1, 126.7, 118.3, 113.4, 54.1, 45.9, 44.5, 30.0, 21.8; FT-IR (KBr) 3020, 2934, 2856, 1590, 1552 cm^{-1}; HRMS (ESI) m/z [M+H]$^+$ calcd for C$_{27}$H$_{26}$BrN$_4$O$_2$S$^+$: 549.0954, found: 549.0961.

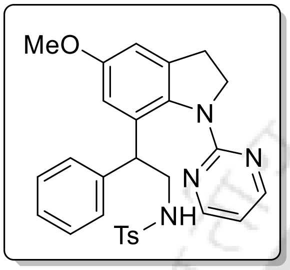


N-(2-(5-(Benzyloxy)-1-(pyrimidin-2-yl)indolin-7-yl)-2-phenylethyl)-4-methylbenzenesulfonamide 3t. Analytical TLC on silica gel, 3:7 ethyl acetate/hexane R$_f$ = 0.40; colorless solid; mp 133-135 °C; yield 55% (47.5 mg); ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.52 (d, *J* = 4.8 Hz, 2H), 7.66 (d, *J* = 8.4 Hz, 2H), 7.39-7.34 (m, 5H), 7.23 (d, *J* = 8.0 Hz, 2H), 7.16-7.12 (m, 4H), 7.00-6.98 (m, 2H), 6.81-6.78 (m, 2H), 6.40 (d, *J* = 2.4 Hz, 1H), 4.93-4.88 (m, 1H), 4.85-4.78 (m, 2H), 4.45-4.41 (m, 1H), 4.11-4.04 (m, 1H), 3.66-3.64 (m, 2H), 3.19-3.11 (m, 1H), 2.80-2.74 (m, 1H), 2.32 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 161.8, 158.1, 156.9, 143.1, 141.6, 138.0, 137.2, 137.2, 137.1, 133.4, 129.6, 128.8, 128.7, 128.1, 127.5, 127.41, 127.40, 126.8, 112.8, 111.5, 110.8, 54.2, 46.2, 44.7, 30.7, 21.6; FT-IR (KBr) 3034, 2920, 2855, 1664, 1581, 1552 cm^{-1}; HRMS (ESI) m/z [M+H]$^+$ calcd for C$_{34}$H$_{33}$N$_4$O$_3$S$^+$: 577.2268, found: 577.2277.

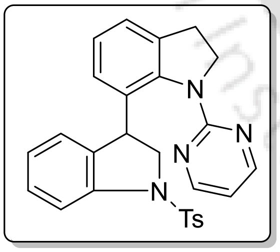


4-Methyl-N-(2-(5-methyl-1-(pyrimidin-2-yl)indolin-7-yl)-2-phenylethyl)benzenesulfonamide 3u. Analytical TLC on silica gel, 3:7 ethyl acetate/hexane R$_f$ = 0.39; colorless solid; mp 184-186 °C; yield 68% (49.4 mg); ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.50 (d, *J* = 4.8 Hz, 2H), 7.63 (d, *J* = 8.4 Hz, 2H), 7.23 (d, *J* = 8.0 Hz, 2H), 7.16 (t, *J* = 6.8 Hz, 2H), 7.12-7.08 (m, 2H), 7.02 (d, *J* = 7.2 Hz, 2H), 6.90 (s, 1H), 6.77 (t, *J* = 4.8

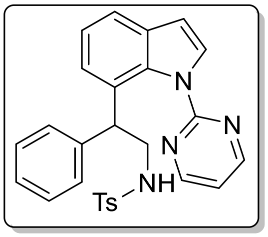
Hz, 1H), 6.51 (s, 1H), 4.89-4.83 (m, 1H), 4.39 (dd, *J* = 10.0, 6.4 Hz, 1H), 4.08-4.01(m, 1H), 3.69-3.65 (m, 2H), 3.15-3.07 (m, 1H), 2.77-2.71 (m, 1H), 2.42 (s, 3H), 2.09 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.7, 158.0, 142.9, 142.0, 141.2, 137.0, 136.5, 135.0, 131.9, 129.6, 128.6, 127.4, 127.3, 126.7, 125.9, 124.4, 112.8, 54.1, 46.1, 44.2, 30.2, 21.7, 21.3; FT-IR (KBr) 3034, 2932, 2852, 1586, 1550 cm^{-1}; HRMS (ESI) m/z [M+H]$^+$ calcd for $C_{28}H_{29}N_4O_2S^+$: 485.2006, found: 485.2014.



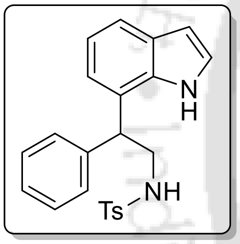
N-(2-(5-Methoxy-1-(pyrimidin-2-yl)indolin-7-yl)-2-phenylethyl)-4-methylbenzenesulfonamide 3v. Analytical TLC on silica gel, 3:7 ethyl acetate/hexane R$_f$ = 0.41; colorless thick liquid; yield 66% (49.5 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.51 (d, *J* = 4.8 Hz, 2H), 7.62 (d, *J* = 8.4 Hz, 2H), 7.26-7.24 (m, 1H), 7.21-7.15 (m, 4H), 7.11 (t, *J* = 6.8 Hz, 1H), 7.03 (d, *J* = 6.8 Hz, 2H), 6.77 (t, *J* = 4.8 Hz, 1H), 6.67-6.66 (m, 1H), 6.24-6.23 (m, 1H), 4.92-4.87 (m, 1H), 4.40 (t, *J* = 7.6 Hz, 1H), 4.08-4.01 (m, 1H), 3.69-3.64 (m, 2H), 3.57 (s, 3H), 3.17-3.09 (m, 1H), 2.77-2.72 (m, 1H), 2.41 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 161.8, 158.1, 157.6, 143.0, 141.7, 138.0, 136.9, 136.8, 133.4, 129.6, 128.7, 127.3, 127.3, 126.9, 112.8, 110.4, 109.6, 55.4, 54.2, 46.1, 44.4, 30.7, 21.7; FT-IR (neat) 3016,. 2932, 2852, 1617, 1582 cm^{-1}; HRMS (ESI) m/z [M+H]$^+$ calcd for $C_{28}H_{29}N_4O_3S^+$: 501.1955, found: 501.1976.



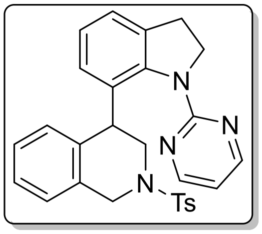
1'-(Pyrimidin-2-yl)-1-tosyl-3,7'-biindoline 4. Analytical TLC on silica gel, 3:7 ethyl acetate/hexane R$_f$ = 0.45; colorless solid; mp 180-182 °C; yield 85% (19.9 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.40 (d, *J* = 4.8 Hz, 2H), 7.72 (d, *J* = 8.0 Hz, 1H), 7.66 (d, *J* = 8.0 Hz, 2H), 7.22-7.15 (m, 3H), 7.07 (d, *J* = 7.2 Hz, 1H), 6.93 (t, *J* = 6.8 Hz, 1H), 6.87 (d, *J* = 7.2 Hz, 1H), 6.76-6.71 (m, 2H), 6.18 (d, *J* = 7.6 Hz, 1H), 4.60-4.53 (m, 1H), 4.50-4.45 (m, 1H), 4.41-4.30 (m, 2H), 3.93 (dd, *J* = 10.8, 7.2 Hz, 1H), 3.14-3.06 (m, 1H), 3.01-2.94 (m, 1H), 2.36 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 161.9, 157.8, 144.1, 142.7, 142.5, 136.5, 135.0, 134.6, 134.1, 129.8, 128.1, 127.5, 127.3, 126.0, 125.1, 124.3, 123.2, 115.2, 112.9, 58.8, 53.1, 43.2, 30.0, 21.7; FT-IR (KBr) 3026, 2868, 1597, 1579, 1555 cm^{-1}; HRMS (ESI) m/z [M+H]$^+$ calcd for $C_{27}H_{25}N_4O_2S^+$: 469.1693, found: 469.1692.



4-Methyl-N-(2-phenyl-2-(1-(pyrimidin-2-yl)-1H-indol-7-yl)ethyl)benzenesulfonamide 5. Analytical TLC on silica gel, 3:7 ethyl acetate/hexane R_f = 0.40; colorless solid; mp 95-97 °C; yield 72% (33.7 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.73 (d, *J* = 4.8 Hz, 2H), 7.81 (d, *J* = 3.6 Hz, 1H), 7.62 (d, *J* = 7.8 Hz, 2H), 7.52 (d, *J* = 7.8 Hz, 1H), 7.27 (d, *J* = 7.8 Hz, 2H), 7.20 (t, *J* = 4.8 Hz, 1H), 7.14-7.12 (m, 3H), 7.09 (t, *J* = 7.8 Hz, 1H), 6.92 (d, *J* = 7.2 Hz, 1H), 6.84-6.82 (m, 2H), 6.71 (d, *J* = 3.6 Hz, 1H), 5.27 (s, 1H), 4.97 (t, *J* = 7.8 Hz, 1H), 3.76-3.74 (m, 1H), 3.61-3.57 (m, 1H), 2.45 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 158.4, 158.2, 143.2, 141.2, 136.5, 134.0, 132.9, 131.1, 129.6, 128.5, 127.6, 127.1, 126.7, 123.1, 122.5, 120.0, 117.6, 107.2, 99.9, 46.9, 45.4, 21.5; FT-IR (KBr) 3022, 2856, 1633, 1643 cm^{-1}; HRMS (ESI) m/z [M+H]$^+$ calcd for $C_{27}H_{25}N_4O_2S^+$: 469.1693, found: 469.1693.



N-(2-(1H-Indol-7-yl)-2-phenylethyl)-4-methylbenzenesulfonamide 6. Analytical TLC on silica gel, 3:7 ethyl acetate/hexane R_f = 0.45; brown liquid; yield 70% (13.6 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.42 (s, 1H), 7.70 (d, *J* = 8.4 Hz, 2H), 7.57 (d, *J* = 8.4 Hz, 1H), 7.34 (t, *J* = 7.2 Hz, 2H), 7.30-7.28 (m, 3H), 7.25 (d, *J* = 7.2 Hz, 2H), 7.18-7.17 (m, 1H), 7.05 (t, *J* = 7.8 Hz, 1H), 6.84 (d, *J* = 7.2 Hz, 1H), 6.56-6.55 (m, 1H), 4.63-4.61 (m, 1H), 4.58-4.55 (m, 1H), 3.73-3.68 (m, 1H), 3.66-3.61 (m, 1H), 2.44 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 143.9, 139.9, 137.2, 134.9, 130.1, 129.4, 128.8, 128.6, 127.8, 127.3, 124.8, 123.8, 120.3, 120.2, 120.2, 103.3, 47.6, 47.0, 21.8; FT-IR (neat) 3028, 2926, 1599, 1494 cm^{-1}; HRMS (ESI) m/z [M+H]$^+$ calcd for $C_{23}H_{23}N_2O_2S^+$: 391.1475, found: 391.1481.



4-(1-(Pyrimidin-2-yl)indolin-7-yl)-2-tosyl-1,2,3,4-tetrahydroisoquinoline 7. Analytical TLC on silica gel, 3:7 ethyl acetate/hexane R_f = 0.43; colorless solid; mp 212-214 °C; yield 76% (18.3 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.46 (d, *J* = 4.8 Hz, 2H), 7.62 (d, *J* = 8.4 Hz, 2H), 7.23 (d, *J* = 8.0 Hz, 2H), 7.09 (d, *J* = 7.2 Hz, 1H), 7.02 (t, *J* = 6.8 Hz, 1H), 6.94 (t, J = 6.8 Hz, 2H), 6.85 (t, *J* = 7.6 Hz, 1H), 6.72 (d, *J* = 7.2 Hz, 1H), 6.67 (t, *J* = 4.8 Hz, 1H), 6.58 (d, *J* = 7.6 Hz, 1H), 4.61-4.56 (m, 1H), 4.51 (d, *J* = 14.8 Hz, 1H), 4.41-4.34 (m, 2H), 4.32-4.27 (m, 1H), 3.96 (d, *J* = 14.8 Hz, 1H), 3.13-3.05 (m, 1H), 2.97-2.90 (m, 1H), 2.87-2.81 (m, 1H), 2.35 (s, 3H);

^{13}C NMR (150 MHz, $CDCl_3$) δ 161.7, 157.9, 143.6, 143.5, 137.8, 135.3, 132.9, 132.8, 131.6, 129.6, 129.5, 128.3, 127.9, 126.7, 126.1, 125.8, 124.6, 123.2, 112.8, 53.2, 50.0, 48.3, 41.6, 30.0, 21.5; FT-IR (KBr) 3022, 2854, 1638, 1577, 1551 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{28}H_{27}N_4O_2S^+$: 483.1849, found: 483.1850.

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

Identification code	**3j**
Empirical formula	$C_{27}H_{25}FN_4O_2S$
Formula weight	488.57
Crystal habit, colour	Needle / colorless
Crystal size, mm^3	0.21 x 0.17 x 0.15
Temperature, T/K	293 (2)
Wavelength, λ/Å	0.71073
Crystal system	monoclinic
Space group	‘P 21/c’
Unit cell dimensions	a = 15.9019(11)Å, b = 15.1890(10)Å c = 9.7547(4)Å $\alpha = \gamma$ = 90.00°, β = 95.855(6)
Volume, V/Å^3	2343.8(2)
Z	4
Calculated density, Mg·m^{-3}	1.385
Absorption coefficient, μ/mm^{-1}	0.180
F(000)	1024
θ range for data collection	2.98 to 25.00°
Limiting indices	$-18 \le h \le 15$, $-17 \le k \le 18$, $-11 \le l \le 11$
Reflection collected / unique	4092/ 2337 [R(int) = 0.0632]
Completeness to θ	99.30 % (θ = 25.00°)
Absorption correction	Multi-scan
Max. and min. transmission	0.973 and 0.964
Refinement method	SHELXL-97
Data / restraints / parameters	4092/0/ 317

Goodness–of–fit on F^2	0.956
Final R indices [I>2sigma(I)]	$R1 = 0.0745$, $wR2 = 0.1685$
R indices (all data)	$R1 = 0.1295$, $wR2 = 0.2036$

3.5 References

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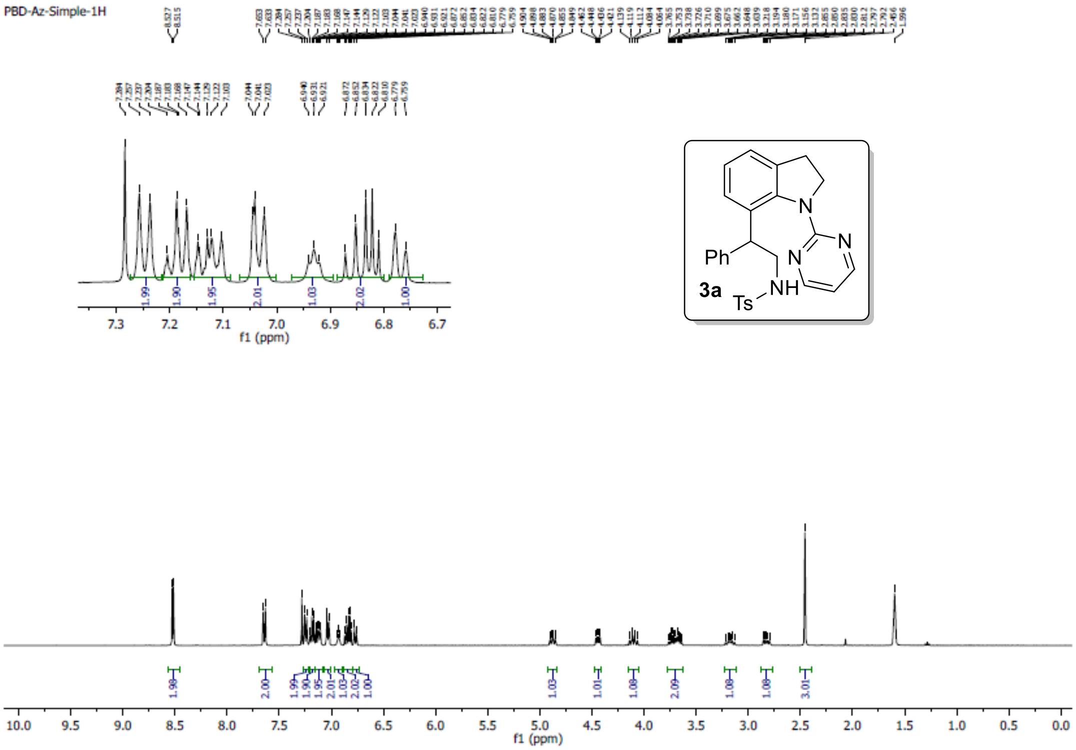
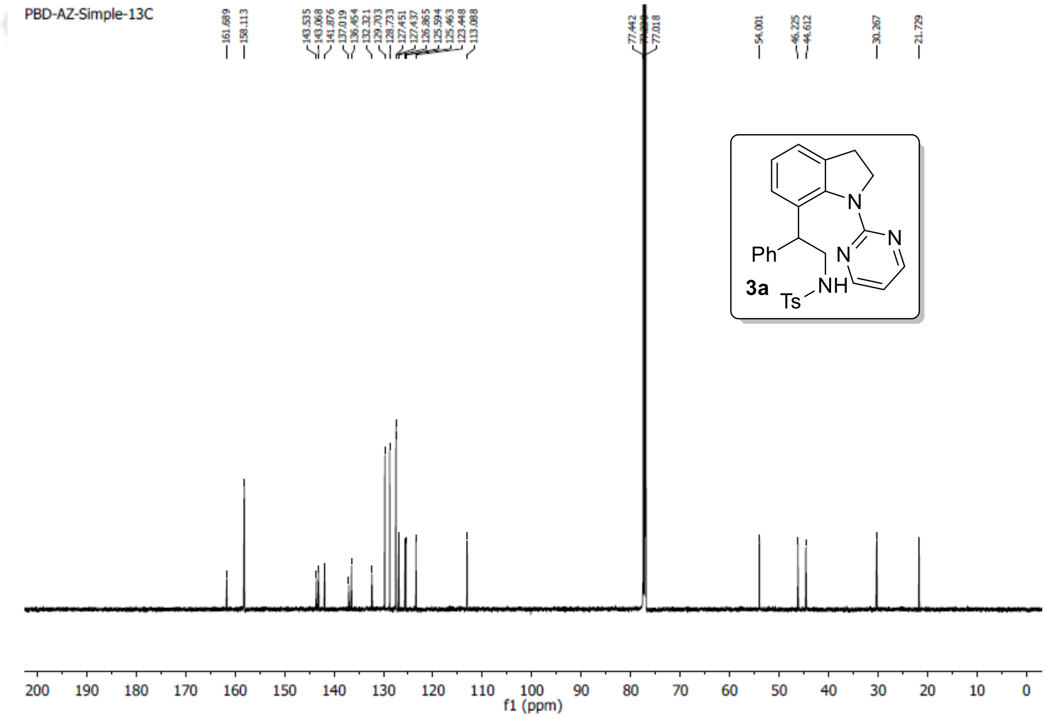
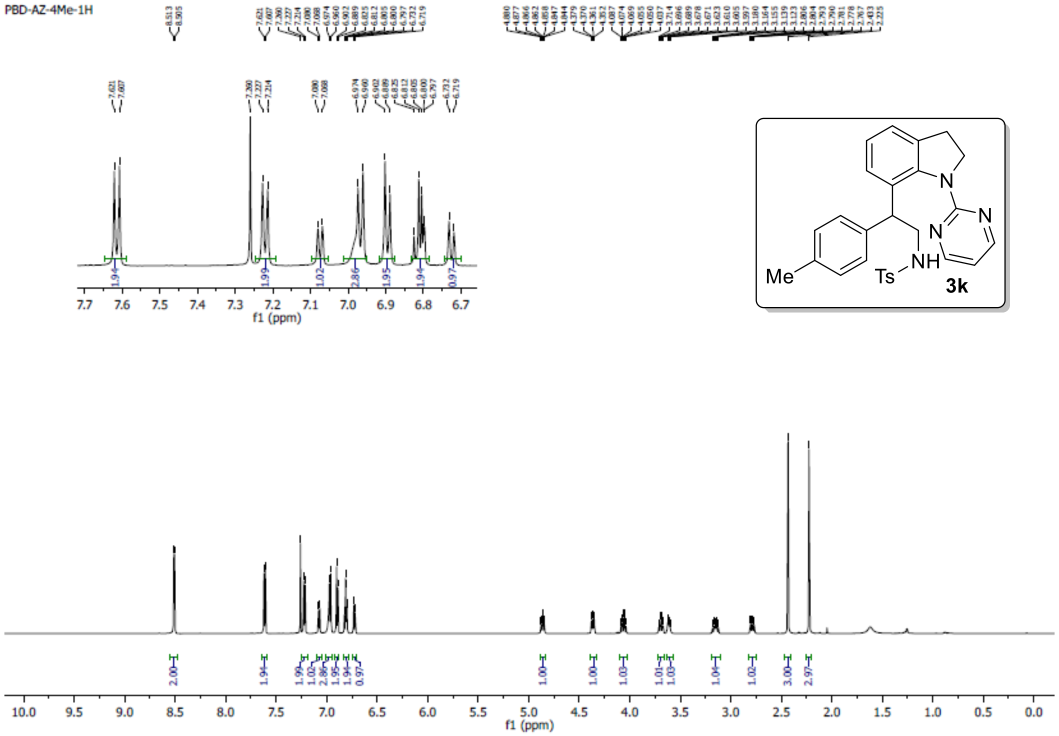
3.6 Selected NMR Spectra



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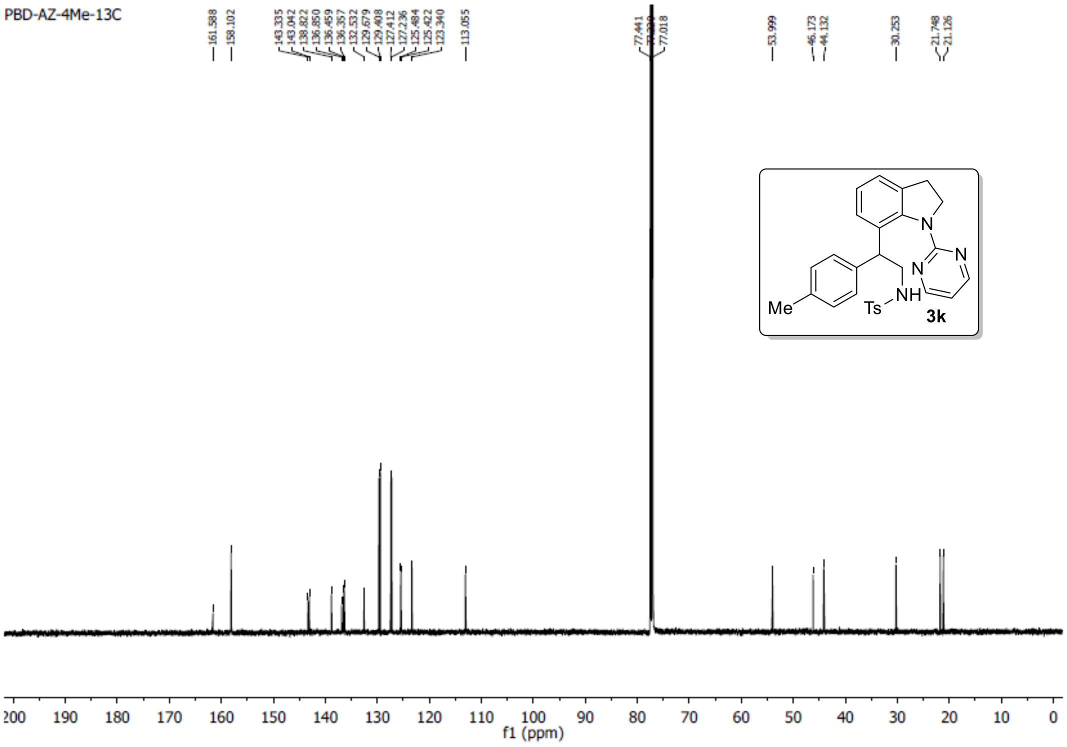
6.960
6.902
6.889
6.825
6.812
6.805
6.800
6.732
6.719
1.94
1.99
1.02
2.86
1.95
1.94
0.97
7.7 7.6 7.5 7.4 7.3 7.2 7.1 7.0 6.9 6.8 6.7
f1 (ppm)
N
N
N
Me
Ts
NH
3k
2.00
1.94
1.99
1.02
2.86
1.95
1.94
0.97
1.00
1.00
1.03
1.01
1.03
1.04
1.02
3.00
2.97
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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125.422
123.340
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53.999
46.173
44.132
30.253
21.748
21.126
N
N
N
Me
Ts
NH
3k
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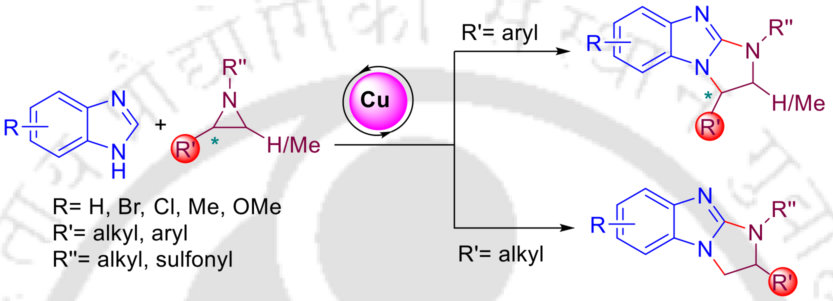
f1 (ppm)

Chapter IV

Regioselective Cu(II)-Catalyzed Coupling of Aziridines with Benzimidazoles

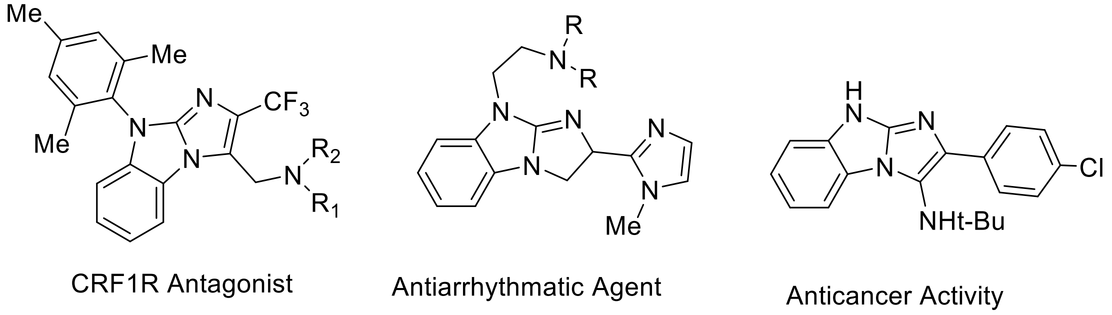


J. Org. Chem. **2017**, *82*, 3183

Regioselective Cu(II)-Catalyzed Coupling of Aziridines with Benzimidazoles

Heterocyclic compounds are of huge importance owing to their application in pharmaceutical and material sciences.[1] Functionalized nitrogen and oxygen containing heterocycles play a predominant role in medicinal chemistry and have been extensively used as modular frameworks for drug development.[2] In particular, imidazo-fused heterocycles such as tricyclic benzo imidazole derivatives exhibit antimycobacterial, anticancer, antiarrhythmic, analgesic, neuropsychiatric disorders and human TNF modulator (Figure 1).[3] Thus, the functionalization of benzimidazoles and its core would be valuable from the synthetic and biological point of view. Recently, transition metal catalysts have heralded a new era in synthetic organic chemistry by contributing to the dramatic resurgence of interest in carbon-carbon or carbon-heteroatom bond formation *via* C-H bond cleavage.[4] Among various transition metals, copper being cost effective and less toxic is advantageous for achieving the same.[5]

The aziridine moiety[6] signifies one of the most appreciated three membered ring structures and flexible building blocks, which have a wide application in synthetic chemistry to construct nitrogen containing complex scaffolds due to inherent ring strain *via* nucleophilic ring opening or cycloaddtion. Hitherto, great developments have been accomplished in the ring opening of aziridines with various carbon- and heteroatom based nucleophiles[7] and many such reactions proceed through high stereo-and regioselective manner. Here a case study with benzimidazoles as nucleophile has been carried out for the ring opening to access functionalized benzimidazoles of biological importance.[8] The beauty of this reaction is that switchable regioselectivity can be observed by varying substitution pattern on the aziridine ring (Figure 2). The reaction of 2-arylazirdines takes place at the aryl substituted 2-carbon owing to the electronic effect, while 2-alkylaziridines undergo reaction at the 3-carbon due to lower steric hindrance. In this chapter, we disclosed an efficient route to functionalize dihydroimidazobenzimidazoles *via* copper(II)-catalyzed stereo-invertive cross-coupling of *N*-alkyl/-sulfonyl 2-alkyl/- arylaziridines with benzimidazoles. In this two-step reaction sequence $Cu(OTf)_2$, stereo- and regioselectively catalyzes the ring opening of aziridines to provide benzoimidazolylethylamines followed by the intramolecular C-H amination in the presence of $Cu(OAc)_2-PCy_3$ catalyst regime.



CRF1R Antagonist Antiarrhythmatic Agent Anticancer Activity

Figure 1. Some examples of bio-active benzofused azoles

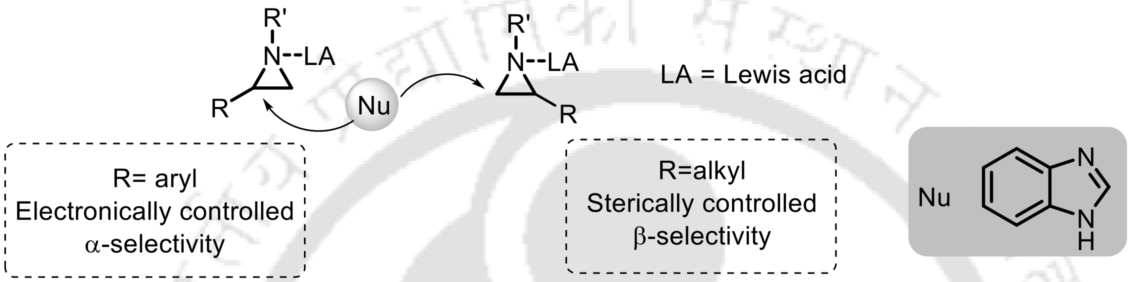
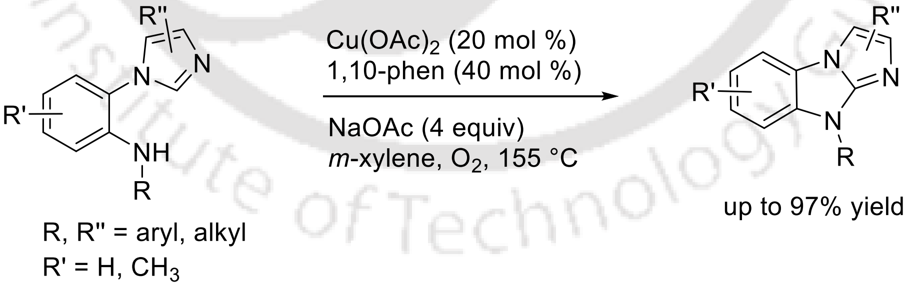


Figure 2. Switchable regioselectivity of aziridines

4.1 Literature

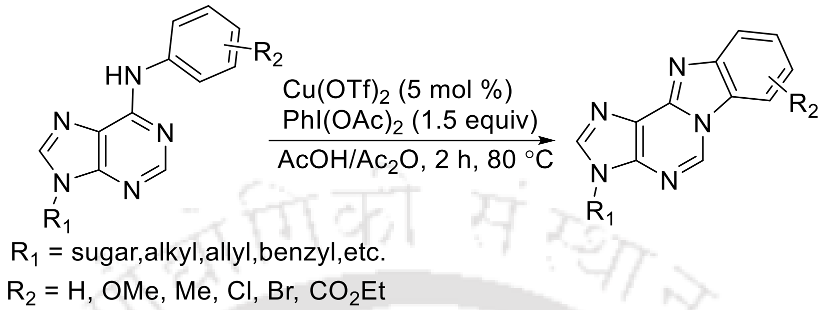
4.1.1 Metal-Catalyzed/Mediated C-H Amination of Azoles

Fu and co-workers reported the synthesis of imidazobenzimidazole derivatives *via* copper(II)-mediated aerobic oxidative intramolecular sp^2 C-H amination reaction at high temperature.[9] This atom economical process uses oxygen as an oxidant. (Scheme 1).



Scheme 1. Cu-Catalyzed Intramolecular C-H Amination of Azoles

Fossey and co-workers developed a novel method for the synthesis of multi heterocyclic compounds from purine based compounds though copper catalyzed direct C-N bond formation *via* C-H amination. (Scheme 2).[10]

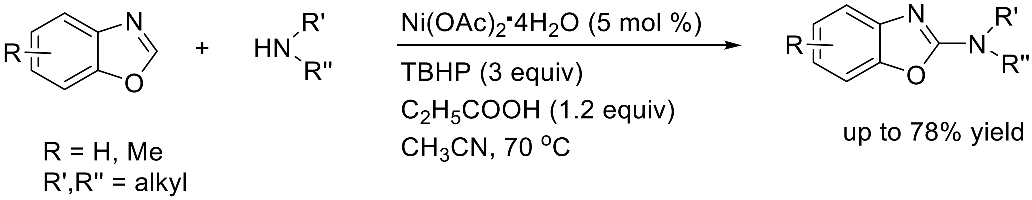


Scheme 2. Cu-Catalyzed C-N Bond Formation of Purine Compounds

Yu and co-workers reported direct aerobic Fe-mediated intermolecular C-H amination of substituted benzoxazoles using formamide or amines as nitrogen surrogates *via* decarbonylative coupling at high temperature (Scheme 3).[11] Imidazole as additive and oxygen in air as oxidant are crucial for this transformation.

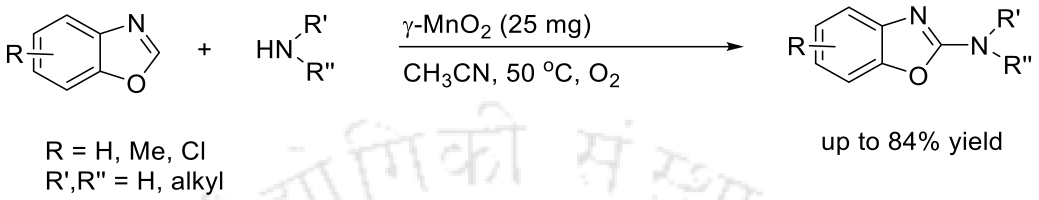
Scheme 3. Regioselective Fe-Catalyzed Intermolecular C-H Amination

Duan and co-workers reported Ni-catalyzed intermolecular C-H amination of benzoxazoles with secondary amines using TBHP as oxidant and propanoic acid as additive at moderate temperature (Scheme 4).[12]



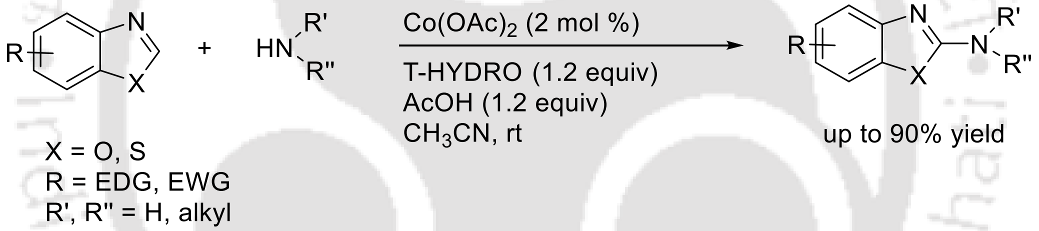
Scheme 4. Ni-Catalyzed Intramolecular C-H Amination of Benzoxazoles

An efficient heterogeneous γ-MnO_2-catalyzed regioselective C-N bond formation of benzoxazoles with a series of primary and secondary amines using molecular oxygen as oxidant has been recently accomplished by Panda group. The catalyst can be reused several times after separating by filtration without a significant loss of its catalytic activity (Scheme 5).[13]



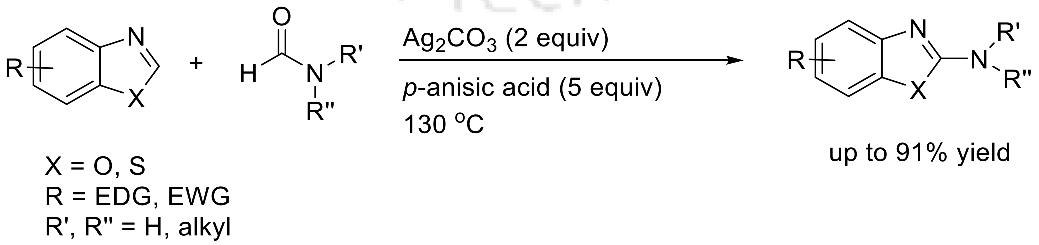
Scheme 5. MnO_2-Catalyzed C2-Amination of Benzoxazoles

Chang and co-workers reported Co-catalyzed direct C-H amination of benzo fused azoles with amines at room temperature. Kinetic isotope study experiment ($k_H/k_D = 1$) confided that C2-H bond cleavage of azoles may not involved in the rate determining step (Scheme 6).[14]



Scheme 6. Co-Catalyzed C-H Amination of Benzofused Azoles

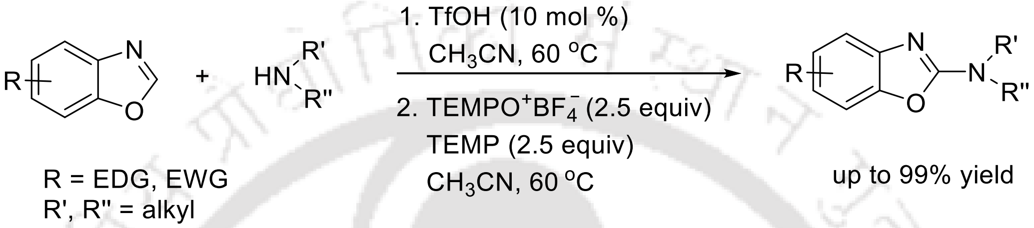
The same group later, reported a silver mediated C-H amination of azoles with formamides as nitrogen source. One of the important substrates coumarinyl piperazine dereivates can easily undergo reaction with benzaoxazoles to afford corrrsponding aminated product, which shows high anti-HIV and antitumor activities (Scheme 7).[15]



Scheme 7. Ag-Mediated C-H amination of Azoles with Formamides

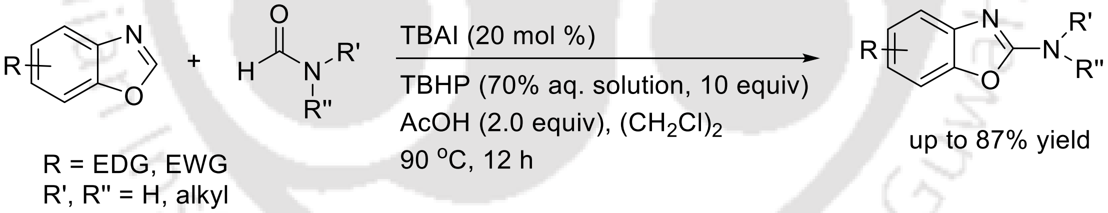
4.1.2 Amination of Azoles under Metal-free Approach

Studer and co-workers reported a metal-free protocol for the synthesis of 2-amino benzoxazoles *via* intermolecular C-N bond formation of benzoxazoles with secondary amines by sacrificing catalytic amount of triflic acid and *N*-oxoammonium salt (TEMPO$^+$BF$_4^-$) as oxidant. The authors showed the synthetic application of the protocol for the synthesis of racemic MK-4305 in good yield (Scheme 8).[16]



Scheme 8. Synthesis of 2-Amino Benzoxazoles using N-Oxoammonium Salt

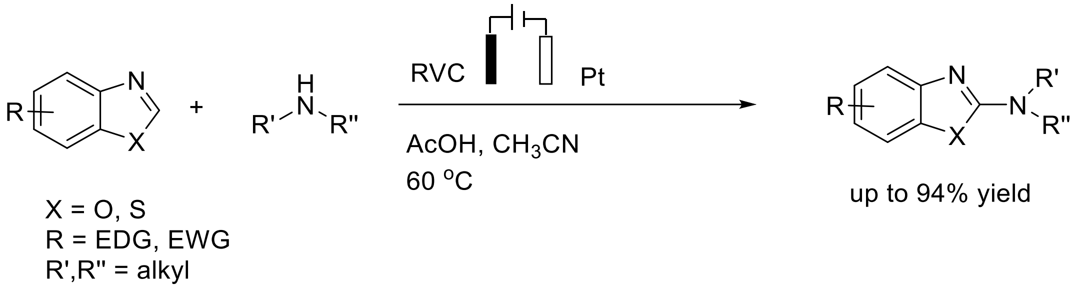
Another metal-free approach for the C2-amination of benzoxazoles with formamides was accomplished by Wang group using the combination of TBAI-TBHP catalytic system. Mechanistic studies concluded that a radical reaction pathway was effective for this intramolecular amination (Scheme 9).[17]



Scheme 9. TBAI-TBHP-Catalyzed Intramolecular C-H Amination of Azoles

4.1.3 Electrochemical C-H Amination of Azoles

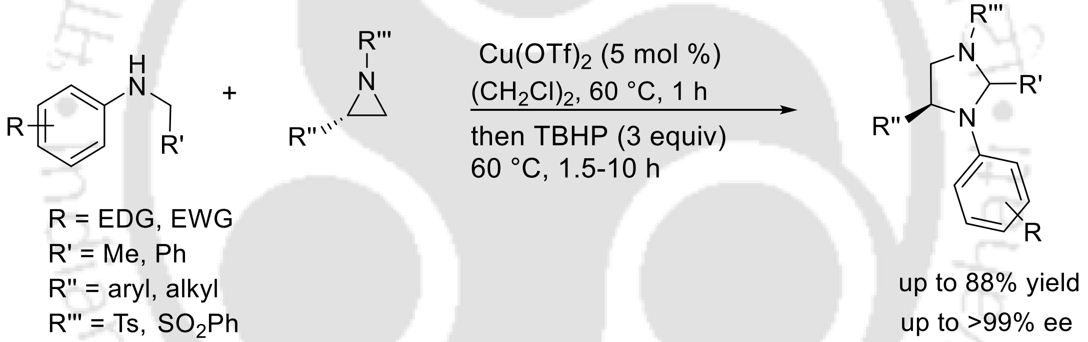
Ackermann and co-workers disclosed electrochemical C-H amination of benzofused azoles with cyclic and acyclic amines at moderate temperature under catalyst and oxidant-free conditions. This method provides a detailed mechanistic studies, indicating the strong support for SET-type reaction pathway (Scheme 10).[18]



Scheme 10. Electrochemical C-H Amination of Benzofused Azoles

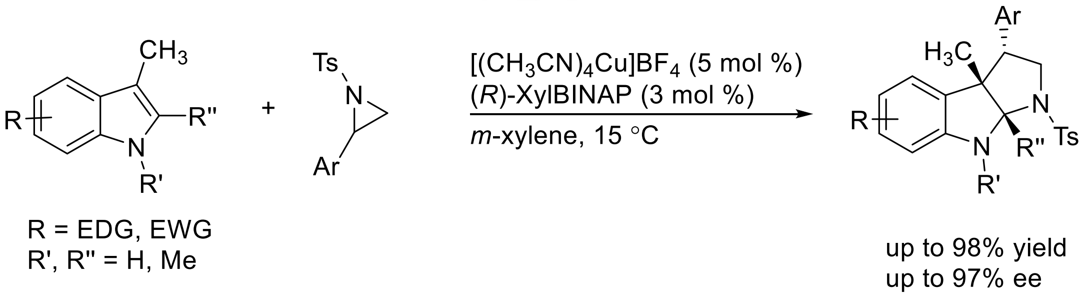
4.1.4 Lewis Acid Catalyzed Aziridine Ring Opening/Cyclization

Our group developed a stereoselective Cu-catalyzed domino ring opening of aryl and alkyl aziridine ring opening with N-substituted anilines followed by sp^3 C-H functionalization (Scheme 11).[19] This reaction was also extended for the reaction of enantioenriched aziridines to give chiral imidazolidines with high enantiomeric excess.



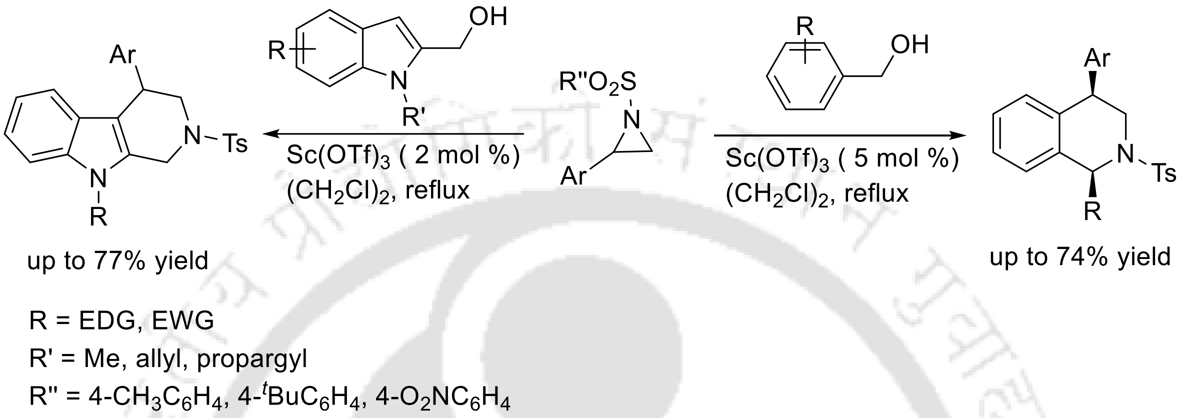
Scheme 11. Cu-Catalyzed Ring Opening of Aziridines with N-Methyl Anilines

Yang and co-workers reported the asymmetric Lewis acid catalyzed [3+2] annulation reaction of indoles and 2-aryl-*N*-tosylaziridines for the construction of pyrroloindolines. The reaction proceeds *via* regioselective ring opening of aziridines followed by cyclization (Scheme 12).[20]



Scheme 12. Cu-Catalyzed Ring Opening/Cyclization of Aziridines

A Sc(OTf)$_3$ catalyzed [3+3]-annulation process for the construction of tetrahydro-β-carbolines and tetrahydroisoquinolnes was presented by Wei and co-workers. The authors employed readily available benzyl alcohols and aziridines as a starting materials (Scheme 13).[21]

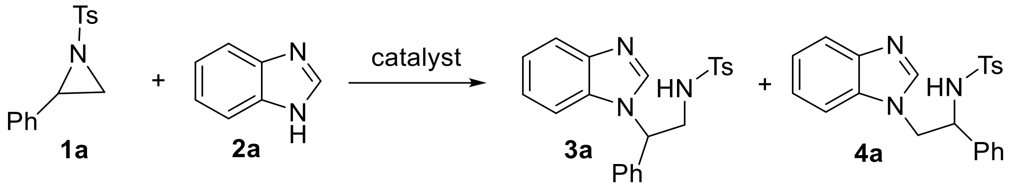


Scheme 13. Ring Opening of Aziridines with Benzyl Alcohols

4.2 Present Study

This chapter presents a stereo and regioselective Cu(II)-catalyzed nucleophilic ring opening of aziridines with benzimidazoles to furnish benzoimidazolylethylamines that can be cyclized to dihydroimidazobenzimidazoles under Cu(OAc)$_2$−PCy$_3$ catalyst regime using air as an oxidant. The optimization of the reaction was initiated by utilizing aziridine **1a** and benzimidazole **2a** as the standard substrates employing various Lewis acids at different temperatures (Table 1). Gratifyingly, the reaction readily underwent selectively to provide 2-benzoimidazolylethylamine derivative **3a** in 41% conversion, when the substrates **1a** and **2a** were stirred with 10 mol % Cu(OTf)$_2$ for 3 h at 70 °C in (CH$_2$Cl)$_2$ (entry 1). Toluene was found to be the solvent of choice, whereas 1,2-dichloroethane, and m-xylene produced 41-63% conversion. Increase of the reaction temperature to 80 °C led to completion the reaction in 2 h with 100% conversion (entry x). In a set of screened Lewis acids, Cu(OTf)$_2$, Sc(OTf)$_3$, Bi(OTf)$_3$ and Yb(OTf)$_3$, the former afforded the superior result (entries xx). In compare, Cu(OAc)$_2$ furnished a mixture of regioisomers **3a** and **4a** (2:1) in 90% conversion (entry 7). Decreasing the catalyst loading (5 mol %) led to the drop in yield. A control experiment confirmed that without Lewis acid catalyst the product **3a** was not formed as a sole product (entry 10).

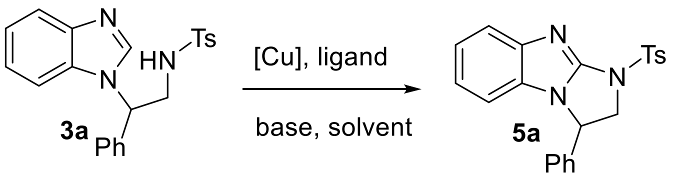
Table 1. Regioselective Reaction of 2-Arylaziridine **1a** with Benzimidazole **2a**



Entry	Catalyst	Solvent	Temp (°C)	Time (h)	Conv. (%)^{a,b}	
					3a	**4a**
1	Cu(OTf)$_2$	(CH$_2$Cl)$_2$	70	3	41	n.d.
2	Cu(OTf)$_2$	toluene	70	3	72	n.d.
3	Cu(OTf)$_2$	*m*-xylene	70	3	63	n.d.
4	Cu(OTf)$_2$	toluene	80	2	100 (82)^c	n.d.
5	Sc(OTf)$_3$	toluene	80	2	74	n.d.
6	Bi(OTf)$_3$	toluene	80	2	57	n.d.
7	Yb(OTf)$_3$	toluene	80	2	64	n.d.
8	Cu(OAc)$_2$	toluene	80	2	60	30
9	Cu(OTf)$_2$	toluene	80	2	70^d	n.d.
10	-	toluene	80	2	n.d.	n.d.

^{a}Aziridine **1a** (0.2 mmol), benzimidazole **2a** (0.24 mmol), catalyst (10 mol %) and solvent (1.5 mL) were stirred. ^{b}Determined by 400 MHz ^{1}H NMR. ^{c}Yield. ^{d}Cu(OTf)$_2$ (5 mol %) is used. n.d. = not detected.

Table 2. Cross-Coupling of *N*-(2-Benzoimidazolyl-2-phenylethyl)-*p*-tolylsulfonamide **3a**

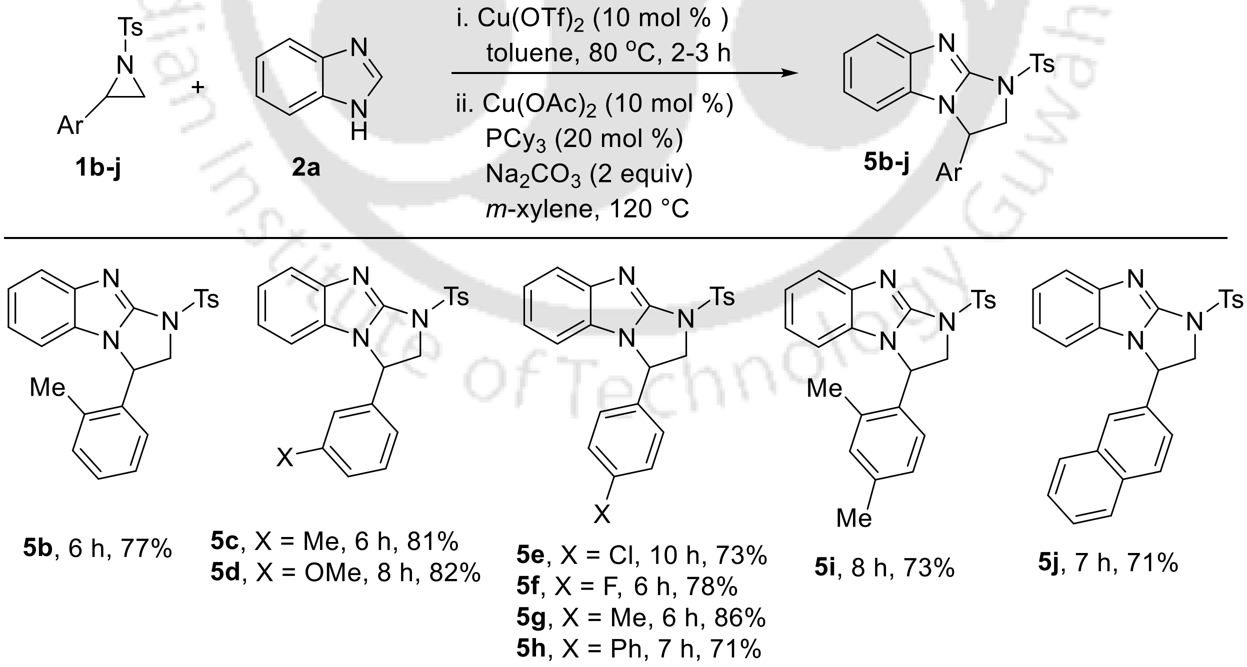


Entry	[Cu] Source	Ligand	Base	Solvent	Conv (%)^{a,b}
1	$Cu(OTf)_2$	-	NaOAc	*m*-xylene	n.d.
2	$Cu(OAc)_2$	-	NaOAc	*m*-xylene	30
3	$Cu(OAc)_2$	1,10-phen	NaOAc	*m*-xylene	68
4	$Cu(OAc)_2$	Ethylene glycol	NaOAc	*m*-xylene	32
5	$Cu(OAc)_2$	PPh_3	NaOAc	*m*-xylene	69
6	$Cu(OAc)_2$	DPPE	NaOAc	*m*-xylene	72
7	$Cu(OAc)_2$	PCy_3	NaOAc	*m*-xylene	75
8	$Cu(OAc)_2\cdot H_2O$	PCy_3	NaOAc	*m*-xylene	56
9	$CuCl_2$	PCy_3	NaOAc	*m*-xylene	43
10	$Cu(OAc)_2$	PCy_3	Na_2CO_3	*m*-xylene	100 (87)^{c}
11	$Cu(OAc)_2$	PCy_3	K_2CO_3	*m*-xylene	85
12	$Cu(OAc)_2$	PCy_3	K_3PO_4	*m*-xylene	92
13	$Cu(OAc)_2$	PCy_3	Na_2CO_3	toluene	57
14	$Cu(OAc)_2$	PCy_3	Na_2CO_3	DMSO	90
15^{d}	$Cu(OAc)_2$	PCy_3	Na_2CO_3	*m*-xylene	74
16^{e}	$Cu(OAc)_2$	PCy_3	Na_2CO_3	*m*-xylene	72
17	-	PCy_3	Na_2CO_3	*m*-xylene	n.d.

^{a}Substrate **3a** (0.2 mmol), Cu-source (10 mol %), ligand (20 mol %), base (2 equiv), solvent (1 mL), 120 °C, 6 h. ^{b}Determined by 400 MHz ^{1}H NMR. ^{c}Yield. ^{d}$Cu(OAc)_2$ (5 mol %) was used. ^{e}Temperature (110 °C) was used. n.d.= not detected.

Next, the oxidative C-H amination of **3a** was studied using copper(II) salts, bases and solvents at various temperatures (Table 2). Interestingly, the reaction proceeded to yield dihydroimidazobenzimidazole **5a** in 30% conversion when the substrate **3a** was stirred with 10 mol % $Cu(OAc)_2$ and 2 equiv NaOAc at 120 °C for 6 h in *m*-xylene, while $Cu(OTf)_2$ showed no reaction (entries 1-2). Incorporating the ligand led to the increasing in conversion and screening of ligands revealed that PCy_3 produced the superior result, while PPh_3, DPPE (Ethylenebis(diphenylphosphine)), 1,10-phenanthroline (1,10-phen) and ethylene glycol provided 32-72% conversions (entries 3-7). In a series of copper sources studied, $Cu(OAc)_2$, $Cu(OAc)_2$•H_2O and $CuCl_2$, the former gave the paramount results (entries 7-9). Subsequent screening of the bases such as Na_2CO_3, K_2CO_3 and K_3PO_4, the former produced 100% conversions (entries 10-12). Among the screened solvents, *m*-xylene gave best result, while toluene and DMSO produced 57-90% conversions (entries 13-14). Decreasing the temperature (110 °C) or the catalyst loading (5 mol %) led to the drop in product formation in 72-74% conversions (entries 15-16). A control experiment confirmed that the product formation took place in absence of the copper source (entry 17).

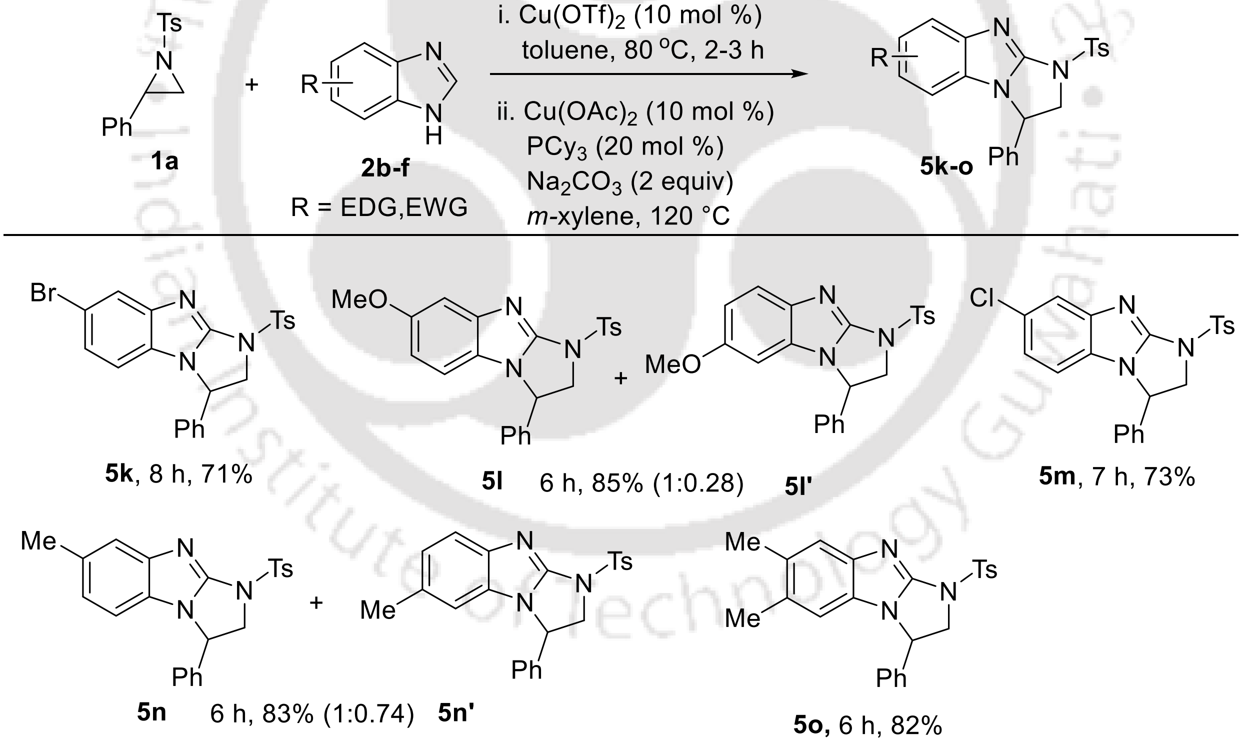
After optimization of the reaction conditions, the substrate scope was investigated with a series of 2-arylaziridines **1b-j** using benzimidazole **2a** as a representative substrate (Scheme 14). Aziridine **1b** having methyl group at the *ortho* position on the aryl ring formed **5b** in 77% yield. Similar results were observed with aziridines bearing 3-methyl **1c** and 3-methoxy **1d** substitutions at the aryl ring, delivering the heterocyclic frameworks **5c** and **5d** in 81 and 82% yields, respectively. Aziridines bearing 4-chloro **1e**, 4-fluoro **1f**, 4-methyl **1g** and 4-phenyl **1h** groups at the aryl ring produce the target heterocycles **5e-h** in 71-85% yields, whereas di-substituted aziridine **2i** with 2,4-dimethyl groups in the aryl ring afforded **5i** in 73% yield. However, 2-naphthylaziridine **1j** underwent cyclization, providing **5j** in 71% yield. The structure of **5e** was determined using X-ray analysis (Figure 3).



[a]Reaction conditions: i. **1b-j** (0.2 mmol), **2a** (0.24 mmol), $Cu(OTf)_2$ (10 mol %), toluene (1.5 mL), 2-3 h; ii. $Cu(OAc)_2$ (10 mol %), PCy_3 (20 mol %), Na_2CO_3 (2 equiv), *m*-xylene (1 mL), 120 °C, 6-15 h. [b]Yield.

Scheme 14. Substrate Scope of 2-Arylaziridines **1b-j** with Benzimidazole **2a** [a,b]

Next, the reaction of substituted benzimidazoles **2b-f** was also studied with 2-phenylaziridine **1a** as a regular substrate (Scheme 15). The reaction of 5-Bromobenzimidazole **2b** produced the heterocycle **5k** in 71% yield, while 5-methoxy **2c** and 5-methyl **2e** benzimidazoles gave **5l, 5l', 5n** and **5n'** in 83-85% yields as a mixture of regioisomers, which may be due to the existence of **2c** and **2e** as a mixture of tautomers. However, 5-chloro **2d** and 5,6-dimethyl **2f** benzimidazoles underwent reaction to furnish **5m** and **5o** in 73% and 82% yields, respectively.



[a]Reaction conditions: i. **1a** (0.2 mmol), **2b-f** (0.24 mmol), $Cu(OTf)_2$ (10 mol %), toluene (1.5 mL), 2-3 h, 80 °C; ii. $Cu(OAc)_2$ (10 mol %), PCy_3 (20 mol %), Na_2CO_3 (2 equiv), *m*-xylene (1 mL), 120 °C, 6-8 h. [b]Yield.

Scheme 15. Substrate Scope of Benzimidazoles **2b-f** with Aziridine **1a**^{a,b}

The effect of *N*-substitution on aziridine ring was next investigated (Scheme 16). *N*-sulfonylaziridines **1k** and **1l** reacted efficiently to provide the heterocycles **5p** and **5q** in 79 and 78% yields, respectively. However, *N*-alkylaziridines such as 1-benzyl-2-phenylaziridine **1m**, 1-cyclohexyl-2-phenylaziridine **1n**, 2-(2,4-dimethylphenyl)-1-isopropropyl aziridine **1o** and 1-hexyl-2-(*p*-tolyl)aziridine **1p**, underwent reaction to furnish the corresponding products **5r-u** in 62-72% yields. These results confide that the activated and unactivated aziridines can be coupled in good to moderate yields.

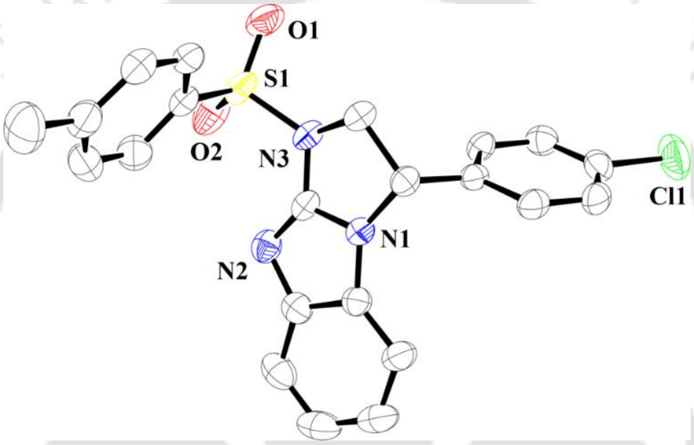


Figure 3. ORTEP diagram of 3-(4-chlorophenyl)-1-tosyl-2,3-dihydro-1H-benzo[d]imidazo[1,2-a]imidazole **5e** with 50% ellipsoid. H-Atoms are omitted for clarity (CCDC 1517716).

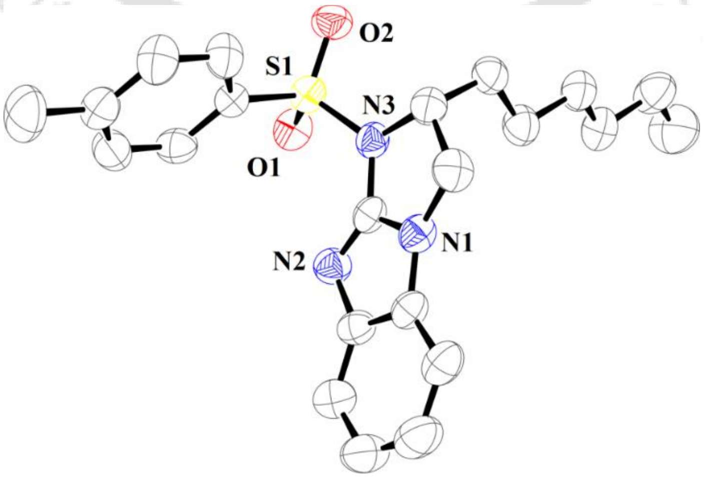
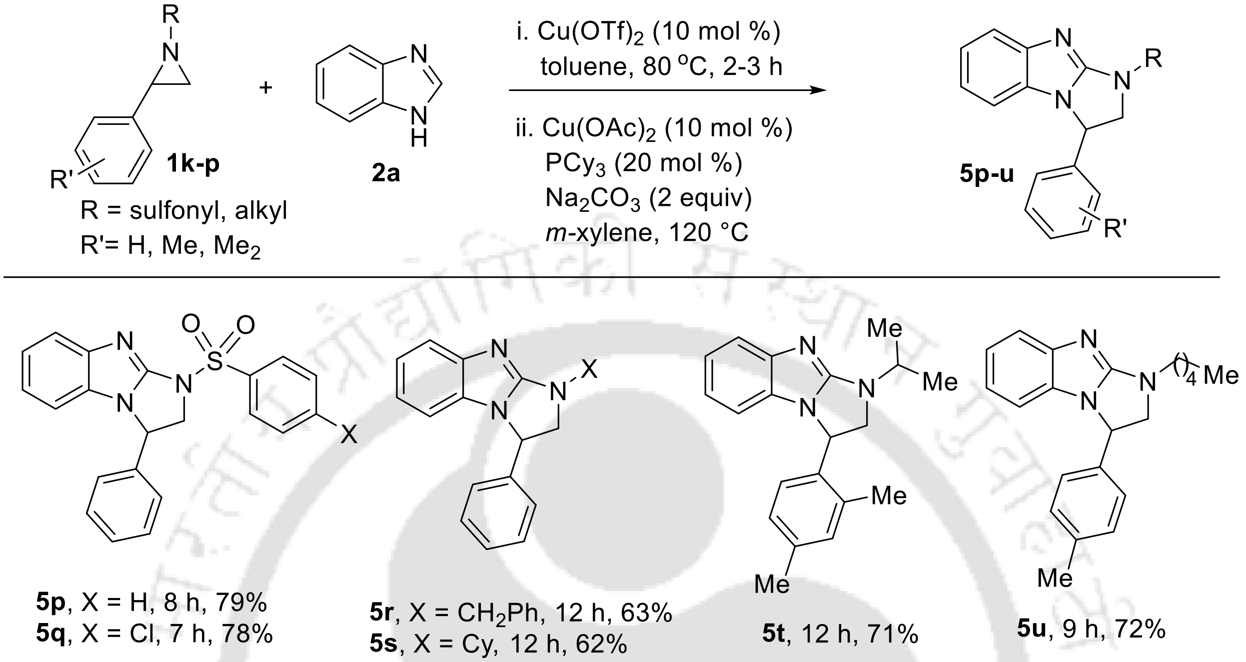


Figure 4. ORTEP diagram of 2-hexyl-1-tosyl-2,3-dihydro-1H-benzo[d]imidazo[1,2-a]imidazole **6a** with 50% ellipsoid. H-Atoms are omitted for clarity (CCDC 1519075).



[a]Reaction conditions: i. **1k-p** (0.2 mmol), **2a** (0.24 mmol), $Cu(OTf)_2$ (10 mol %), toluene (1.5 mL), 2-3 h, 80 °C; ii. $Cu(OAc)_2$ (10 mol %), PCy_3 (20 mol %), Na_2CO_3 (2 equiv), *m*-xylene (1 mL), 120 °C, 7-12 h. [b]Yield.

Scheme 16. Substrate Scope of *N*-Substituted Aziridines **1k-p** with Benzimidazole **2a**[a,b]

Finally, the scope of the protocol was extended for the reaction of 2-alkylaziridines **1q-v** with benzimidazole **2a** as a representative substrate (Scheme 17). These substrates were slightly less reactive related to 2-arylaziridines and the ring opening occurred exclusively only at the sterically less hindered 3-carbon of the aziridines to provide the respective 1-alkyl-2-benzoimidazolylethylamine derivatives followed by cyclization to furnish the corresponding dihydroimidobenzimidazoles. Thus, 2-hexylaziridine **1q** reacted to provide the target heterocycle **6a** in 69% yield, whereas 2-octyl **1r** and 2-decyl **1s** aziridines gave **6b** and **6c** in 67 and 66% yields, respectively. Moreover, the reaction of 2-isobutyl-, 2-benzyl and 2-(cyclohexylmethyl)aziridines **1t-v** underwent reaction to furnish the corresponding heterocycles **6d-f** in 62-71% yields. The regiochemistry of the compound **6a** was revealed using single-crystal X-ray analysis (Figure 5).

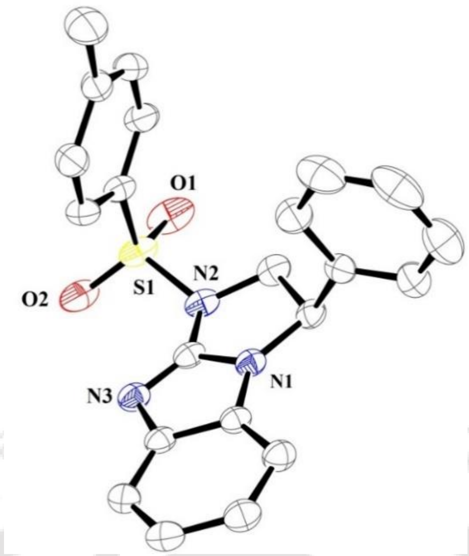
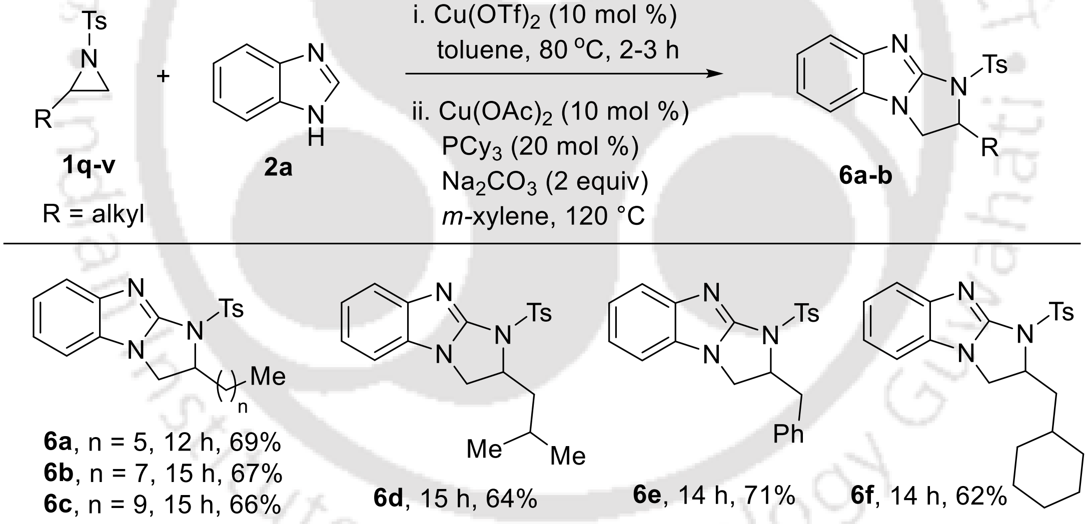
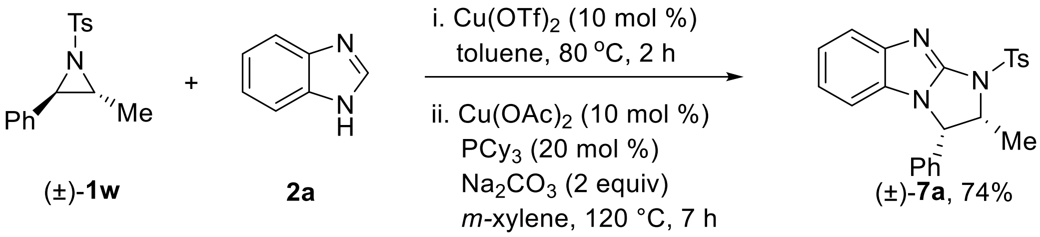


Figure 5. ORTEP diagram of (*R*)-3-phenyl-1-tosyl-2,3-dihydro-1*H*-benzo[*d*]imidazo[1,2-*a*]imidazole **5aa'** with 35% ellipsoid. H-Atoms are omitted for clarity (CCDC 1526881).

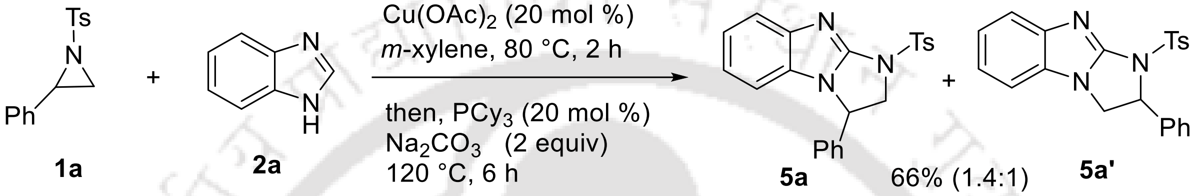


[a]Reaction conditions: i. **1q-v** (0.2 mmol), **2a** (0.24 mmol), Cu(OTf)$_2$ (10 mol %), toluene (1.5 mL), 1-2 h, 90 °C; ii. Cu(OAc)$_2$ (10 mol %), PCy$_3$ (20 mol %), Na$_2$CO$_3$ (2 equiv), 120 °C, 6-15 h [b]Yield.

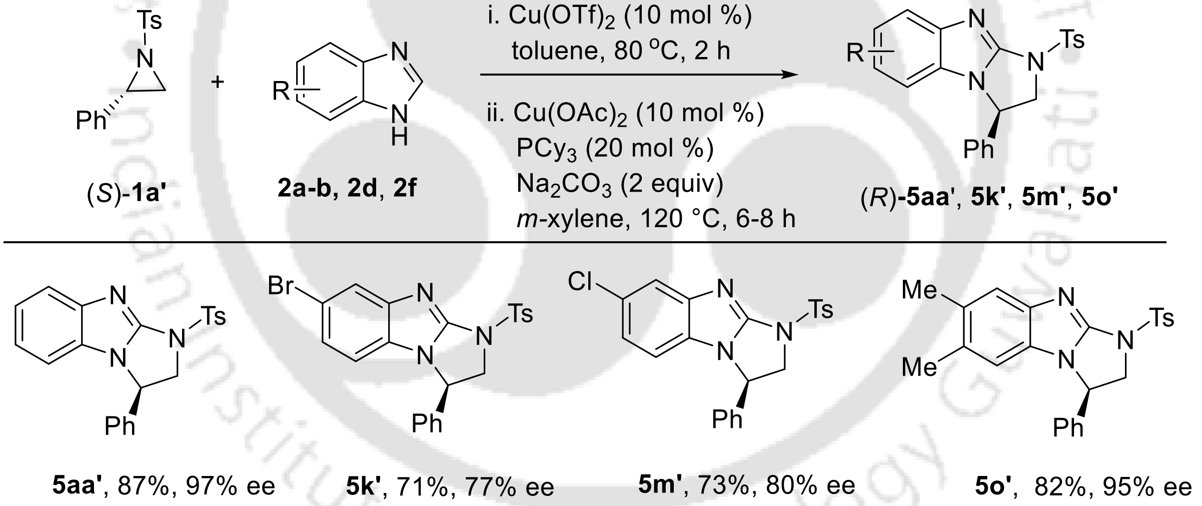
Scheme 17. Substrate Scope of 2-Alkylaziridines **1q-v** with Benzimidazole **2a** [a.b]



Scheme 18. Reaction of 2,3-Disubstituted *N*-Tosylaziridine **1w** with Benzimidazole **2a**

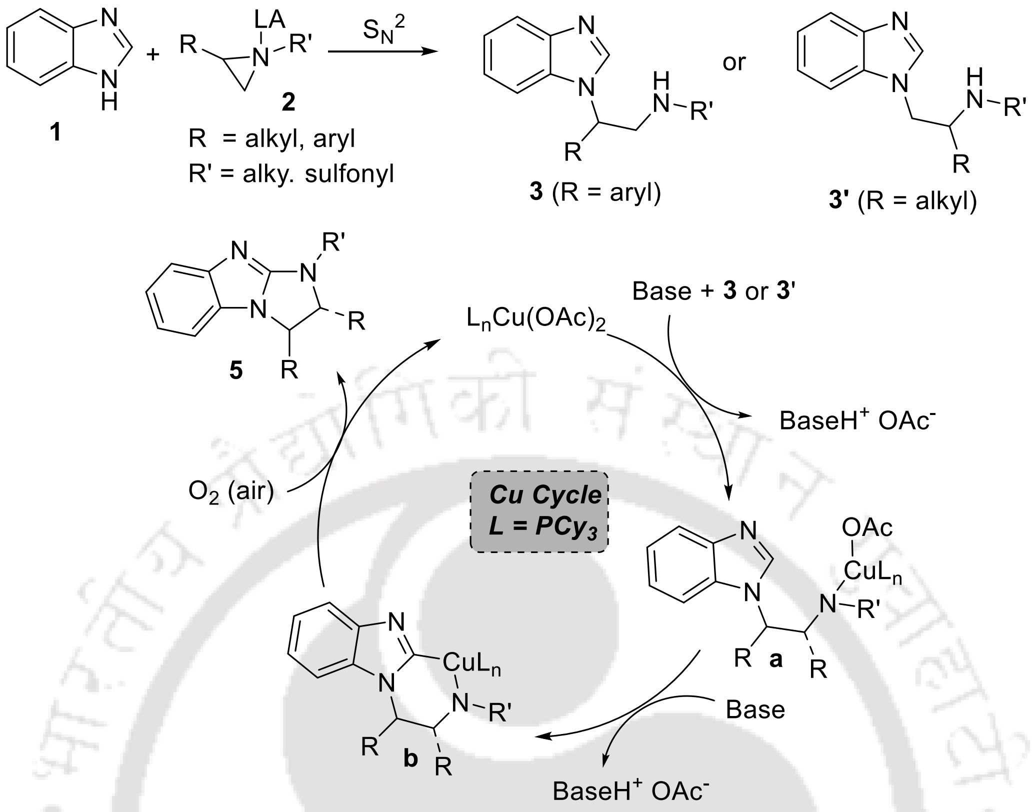


Scheme 19. One-Pot Cross-Coupling of Aziridine **1a** with Benzimidazole **2a**



Scheme 20. Reaction of Optically Active Substrates

This methodology were further investigated for the coupling of *trans*-(±)-2-methyl-3-phenyl-1-tosylaziridine **1w** with benzimidazole **2a** (Scheme 18). The reaction took place to construct the corresponding heterocycle **7a** as a single diastereoisomer in 74% yield. In addition, the one-pot reaction of aziridine **1a** with benzimidazole **2a** was also examined. The reaction occurred to produce a mixture of regioisomers (Scheme 19).



Scheme 21. Proposed Catalytic Cycle

To investigate the mechanism, the reaction of enantio-enriched (*S*)-2-phenylaziridine **1a'** with variety of benzimidazoles were studied to realize the mode of ring opening of aziridines (Scheme 20). Benzimidazole **2a** reacted smoothly with **1a'** to deliver **5aa'** in 97% ee, whose absolute configuration was determined using single-crystal X-ray analysis. Next, 5-bromo **2b** and 5-chloro **2d** substituted benzimidazoles gave **5k' and 5m'** with 77 and 80% ee, respectively. The drop in the *ee* may be reflected the partial participation of S$_N$1 reaction pathway. However, 5,6-dimethylbenzimidazole **2f** underwent reaction to give the target heterocyclic **5o'** in 95% ee. These results disclose that optically active 2-arylaziridines can be reacted with benzimidazoles *via* stero-invertive manner with high enantiomeric purities. Thus, the chelation of Cu(OTf)$_2$ with aziridines **2** may result in the S$_N$2 ring opening at the more electrophilic carbon of aziridines by benzimidazoles **1** giving benzoimidazolylethylamines **3** or **3**' (Scheme 21). Then, the latter with Cu(OAc)$_2$L$_n$ (L = PCy$_3$) may lead to the construction of the copper(II) species **a**, which may convert into the copper(II) metallocycle **b** *via* C-H activation. Finally, the target heterocycles **5** can produce *via* the reductive elimination of **b** along with regeneration of Cu(II) catalyst to complete the catalytic cycle.

In summary, we have presented a stereospecific copper(II)-catalyzed coupling of the aziridines with benzimidazoles as nucleophiles to construct dihydroimidazobenzimidazoles via the regioselective ring opening of aziridines followed by an intramolecular C-H amination. The use of relatively cheaper copper(II) catalyst, and air as an oxidant, switchable regioselectivity and high enantiomeric purity are the important practical features.

4.3 Experimental Section

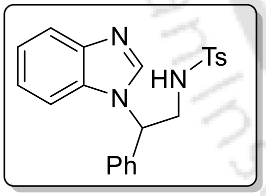
General Information. Benzimidazole (98%), $Cu(OTf)_2$ (98%), $Cu(OAc)_2$ (98%), $Cu(OAc)_2{\cdot}H_2O$ (>98%), $CuCl_2$ (>99.99%), PCy_3, PPh_3, DPPE, 1,10-phenanthroline, alkenes and amines were purchased from Aldrich and used as received. Chloramine-T trihydrate was purchased from Merck and L-phenylglycine was obtained from SRL. Aziridines were prepared according to the literature.[7d] SRL G/GF 254 plates for analytical TLC and silica gel 60-120 mesh for column chromatography were used. DRX-400 Varian and Bruker Avance III 600 spectrometers were used for recording NMR (^1H and ^{13}C) spectra using $CDCl_3$ as a solvent and TMS as an internal standard. Chemical shifts (δ) and spin-spin coupling constant (J) are reported in ppm and in Hz, respectively, and other data are reported as follows: s = singlet, d = doublet, t = triplet, m = multiplet, q = quartet, dd = doublet of doublets, td = triplet of doublets and br s = broad singlet. Melting points were determined with a Büchi B-540 apparatus and are uncorrected. Optical rotations were determined by using Perkin Elmer-343 Polarimeter with a 50 mm path length cell at 589 nm at 25 °C. HPLC analysis was carried out using Waters-2489 with Daicel Chiralcel OD column using *iso*-propanol and *n*-hexane as an eluent. FT-IR spectra were collected on Thermo Fisher Scientific IR spectrometer. Q-Tof ESI-MS instrument (model HAB 273) was used for recording mass spectra. Single crystal X-ray data were determined using Bruker SMART APEX-II CCD diffractometer, which is equipped with 1.75 kW sealed-tube Mo-Kα irradiation ($\lambda = 0.71073$ Å) at 298(2) K. The crystal structure was solved by direct method using SHELXL-97 (Göttingen, Germany) and refined with full-matrix least squares on F^2 using SHELXL-2014/7.

General Procedure for the Coupling of Aziridines with Benzimidazoles. Aziridine **1** (0.2 mmol), benzimidazole **2** (0.24 mmol) and $Cu(OTf)_2$ (10 mol %, 0.02 mmol, 7.22 mg) were stirred in toluene (1.5 mL) for 2-3 h at 80-90 ^{o}C using $CaCl_2$ guard tube. After completion, the reaction mixture was passed through a short pad of silica gel (60-120 mesh) using ethyl acetate and hexane. After evaporating the solvent, the residue was treated with $Cu(OAc)_2$ (10 mol %, 0.02 mmol, 3.6 mg), PCy_3 (20 mol %, 0.04 mmol, 11.2 mg), Na_2CO_3 (0.4 mmol, 42.4 mg) and *m*-xylene (1 mL) and stirred at 120 °C for the appropriate time. The reaction mixture was transferred to column chromatography and *m*-xylene was eluted using hexane. Then, the resultant material on the column was purified using a mixture of *n*-hexane and ethyl acetate to produce analytically pure dihydroimidazobenzimidazoles.

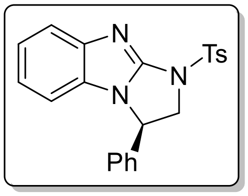
General procedure for the One-Pot Cross-Coupling of Aziridine 1a with Benzimidazole 2a. Aziridine **1a** (0.2 mmol, 54.6 mg), benzimidazole **2a** (0.24 mmol, 28.3 mg) and $Cu(OAc)_2$ (20 mol %, 0.04 mmol, 7.2 mg) were stirred in *m*-xylene (1 mL) for 2 h at 80 °C using $CaCl_2$ guard tube. After cooling the reaction mixture to room temperature, PCy_3 (20 mol %, 0.04 mmol, 11.2 mg), Na_2CO_3 (2 equiv, 0.4 mmol, 42.4 mg) were added in the same pot and stirred the reaction mixture at 120 °C for 6 h. The reaction mixture was transferred to column chromatography and *m*-xylene was eluted using hexane. Then, the resultant material on the column was purified using a mixture of *n*-hexane and ethyl acetate to produce mixture of regioisomers.

4.4 Characterization Data of Products

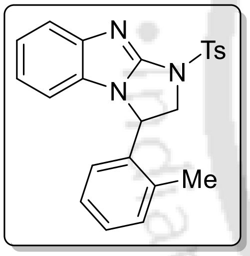
***N*-(2-(1*H*-Benzo[*d*]imidazole-1-yl)-2-phenylethyl)-4-methylbenzenesulfonamide 3a.**



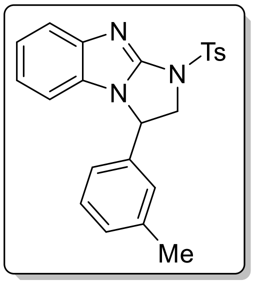
Analytical TLC on silica gel, $R_f = 0.32$; white solid; mp 90-91 °C; yield 82% (64 mg); ^1H NMR (600 MHz, $CDCl_3$) δ 7.87 (s, 1H), 7.72 (d, *J* = 7.8 Hz, 2H), 7.64 (d, *J* = 7.2 Hz, 1H), 7.34-7.33 (m, 3H), 7.28 (d, *J* = 8.4 Hz, 2H), 7.18-7.16 (m, 5H), 5.98 (br s, 1H), 5.68-5.65 (m, 1H), 3.89-3.80 (m, 2H), 2.42 (s, 3H); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 143.7, 141.6, 137.4, 136.3, 133.4, 130.0, 129.4, 128.9, 127.0, 126.7, 123.5, 122.9, 119.88, 119.86, 110.8, 60.3, 46.0, 21.7; FT-IR (KBr) 3273, 3061, 2923, 2855, 1613, 1598, 1494, 1456, 1398, 1328, 1287, 1216, 1157, 1092, 1030 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{22}H_{21}N_3O_2S$: 392.1433, found: 392.1437.



(*R*)-3-Phenyl-1-tosyl-2,3-dihydro-1*H*-benzo[*d*]imidazo[1,2-*a*]imidazole 5aa'. Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.41; white solid; mp 218-219 °C; yield 87% (67 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.99 (d, *J* = 7.8 Hz, 2H), 7.72 (d, *J* = 7.8 Hz, 1H), 7.34 (t, *J* = 7.2 Hz, 1H), 7.29-7.27 (m, 4H), 7.15 (t, *J* = 7.2 Hz, 1H), 6.98-6.96 (m, 3H), 6.66 (d, *J* = 7.8 Hz, 1H), 5.40 (dd, *J* = 8.4, 6.6 Hz, 1H), 4.76 (dd, *J* = 10.2, 8.4 Hz, 1H), 4.11 (dd, *J* = 10.2, 6.6 Hz, 1H), 2.40 (s, 3H); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 153.1, 147.8, 145.4, 136.5, 133.5, 131.0, 130.1, 129.5, 129.4, 128.2, 126.3, 122.4, 122.0, 119.9, 109.3, 60.5, 56.9, 21.8; FT-IR (KBr) 2923, 2850, 1622, 1595, 1532, 1499, 1454, 1435, 1373, 1291, 1272, 1186, 1171, 1108, 1091, 1042, 1004 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{22}H_{19}N_3O_2S$: 390.1276, found: 390.1283; $[\alpha]_D^{25}$ = -44.44 (c= 0.135, $CHCl_3$); HPLC analysis: 97% ee [Daicel CHIRALCEL OD column, hexane/*i*PrOH = 75:25, flow rate: 1 mL /min, λ = 215 nm, t_R = 11.69 min (major), 15.28 min (minor)].



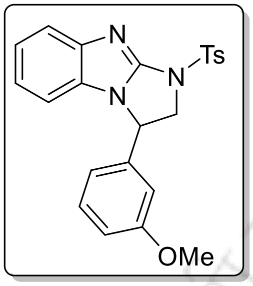
3-(*o*-Tolyl)-1-tosyl-2,3-dihydro-1*H*-benzo[*d*]imidazo[1,2-*a*]imidazole 5b. Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.35; white solid; mp 185-186 °C; yield 77% (62 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, *J* = 8.4 Hz, 2H); 7.74 (d, *J* = 8.4 Hz, 1H), 7.26-7.24 (m, 2H), 7.22-7.15 (m, 3H), 7.00-6.95 (m, 2H), 6.68 (d, *J* = 8.0 Hz, 1H), 6.53 (d, *J* = 7.2 Hz, 1H), 5.62 (dd, *J* = 8.0, 6.8 Hz, 1H), 4.78 (dd, *J* = 10.0, 8.8 Hz, 1H), 4.00 (dd, *J* = 10.4, 6.8 Hz, 1H), 2.38 (s, 3H), 2.31 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 153.2, 147.7, 145.4, 134.9, 134.4, 133.4, 131.4, 130.1, 128.9, 128.1, 127.1, 122.4, 121.9, 119.9, 109.4, 59.5, 54.0, 21.8, 19.2; FT-IR (KBr) 3055, 2948, 1937, 1623, 1587, 1584, 1487, 1466, 1436, 1369, 1315, 1285, 1264, 1217, 1174, 1106, 1091, 1075, 1058, 1019, 1004 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{23}H_{21}N_3O_2S$: 404.1433, found: 404.1433.



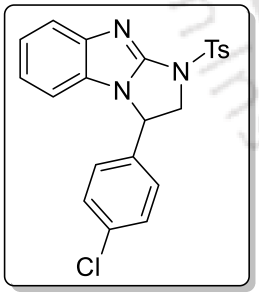
3-(*m*-Tolyl)-1-tosyl-2,3-dihydro-1*H*-benzo[*d*]imidazo[1,2-*a*]imidazole 5c. Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.38; white solid; mp 147-148 °C; yield 81% (65 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.00 (d, *J* = 7.8 Hz, 2H), 7.72 (d, *J* = 7.8 Hz, 1H), 7.30 (d, *J* = 7.2 Hz, 2H), 7.17-7.14 (m, 3H), 6.97 (t, *J* = 7.8 Hz, 1H), 6.79-6.77 (m, 2H), 6.68 (d, *J* = 7.8 Hz, 1H), 5.35 (t, *J* = 7.8 Hz, 1H), 4.74 (t, *J* = 9.6 Hz, 1H), 4.12-4.09 (m, 1H), 2.40 (s, 3H), 2.24

(s, 3H); ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$) δ 153.0, 147.7, 145.4, 139.4, 136.5, 133.3, 130.2, 130.1, 129.3, 128.2, 126.8, 123.5, 122.3, 121.9, 119.8, 109.3, 60.5, 56.7, 21.8, 21.5; FT-IR (KBr) 3061, 2922, 2856, 1622, 1589, 1537, 1491, 1475, 1455, 1434, 1374, 1334, 1273, 1183, 1169, 1108, 1090, 1062, 1005 cm^{-1}; HRMS (ESI) *m/z* [M+H]$^+$ calcd for $C_{23}H_{21}N_3O_2S$: 404.1433, found: 404.1435.

3-(3-Methoxyphenyl)-1-tosyl-2,3-dihydro-1*H*-benzo[*d*]imidazo[1,2-*a*]imidazole 5d.

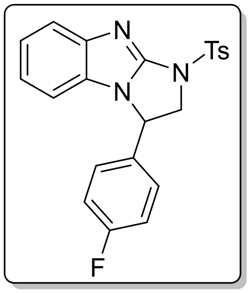


Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R$_f$ = 0.39; white solid; mp 166-167 °C; yield 82% (69 mg); ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.98 (d, J = 8.4 Hz, 2H), 7.71 (d, J = 8.0 Hz, 1H), 7.26 (dd, J = 8.8, 8.4 Hz, 2H), 7.21-7.13 (m, 2H), 6.97 (t, J = 8.0 Hz, 1H), 6.86 (dd, J = 8.4, 2.8 Hz, 1H), 6.70 (d, J = 8.0 Hz, 1H), 6.55 (d, J = 8.0 Hz, 1H), 6.49-6.48 (m, 1H), 5.35 (dd, J = 8.8, 6.8 Hz, 1H), 4.73 (dd, J = 10.4, 8.8 Hz, 1H), 4.09 (dd, J = 10.0, 6.4 Hz, 1H), 3.68 (s, 3H), 2.39 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$) δ 160.4, 153.0, 147.7, 145.4, 138.1, 133.3, 131.0, 130.6, 130.1, 128.1, 122.4, 121.9, 119.8, 118.4, 114.5, 112.0, 109.3, 60.4, 56.7, 55.4, 21.8; FT-IR (KBr) 1621, 1598, 1541, 1508, 1457, 1379, 1340, 1279, 1174, 1149, 1090, 1073, 1057, 1036 cm^{-1}; HRMS (ESI) *m/z* [M+H]$^+$ calcd for $C_{23}H_{21}N_3O_3S$: 420.1382, found: 420.1385.

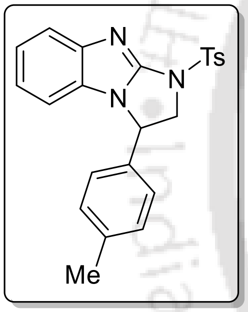


3-(4-Chlorophenyl)-1-tosyl-2,3-dihydro-1*H*-benzo[*d*]imidazo[1,2-*a*]imidazole 5e. Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R$_f$ = 0.40; white solid; mp 185-186 °C; yield 73% (62 mg); ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.97 (d, J = 8.0 Hz, 2H), 7.72 (d, J = 8.0 Hz, 1H), 7.29-7.23 (m, 4H), 7.19-7.15 (m, 1H), 7.01-6.97 (m, 1H), 6.90 (d, J = 8.4 Hz, 2H), 6.67 (d, J = 8.0 Hz, 1H), 5.39 (dd, J = 8.4, 6.4 Hz, 1H), 4.75 (dd, J = 10.4, 8.4 Hz, 1H), 4.05 (dd, J = 10.4, 6.0 Hz, 1H), 2.41 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$) δ 153.0, 147.7, 145.6, 135.4, 135.1, 133.3, 130.8, 130.1, 129.7, 128.1, 127.6, 122.6, 122.1, 120.0, 109.1, 60.4, 56.2, 21.8; FT-IR (KBr) 2953, 2926, 2853, 1739, 1624, 1595, 1550, 1491, 1464, 1455, 1440, 1408, 1366, 1317, 1281, 1215, 1187, 1172, 1149, 1107, 1089, 1014, 1005 cm^{-1}; HRMS (ESI) *m/z* [M+H]$^+$ calcd for $C_{22}H_{18}ClN_3O_2S$: 424.0887, found: 424.0890.

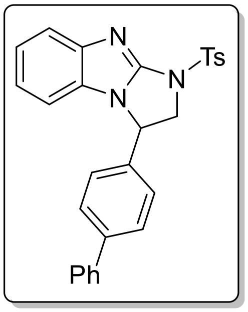
3-(4-Fluorophenyl)-1-tosyl-2,3-dihydro-1*H*-benzo[*d*]imidazo[1,2-*a*]imidazole 5f. Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.44; white solid; mp 201-202 °C; yield 78% (63 mg); ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.97 (d, *J* = 8.4 Hz, 2H), 7.71 (d, *J* = 8.0 Hz, 1H), 7.28 (d, *J* = 8.0 Hz, 2H), 7.17- 7.13 (m, 1H), 6.99-6.94 (m, 5H), 6.65 (d, *J* = 8.0 Hz, 1H), 5.39 (dd, *J* = 8.4, 6.4 Hz, 1H), 4.73 (dd, *J* = 10.4, 8.4 Hz, 1H), 4.05 (dd, *J* = 10.4, 6.4 Hz, 1H), 2.40 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$) δ 164.4 ($J_{C\text{-}F}$ = 247.6 Hz), 152.9, 147.7, 145.5, 133.3 ($J_{C\text{-}F}$ = 87.5 Hz), 130.8, 130.1, 128.2, 128.19, 128.17, 122.5, 122.0, 119.9, 116.7 ($J_{C\text{-}F}$ = 22.0 Hz), 109.1, 60.5, 56.1, 21.8; FT-IR (KBr) 3072, 2920, 1620, 1605, 1543, 1510, 1480, 1466, 1441, 1421, 1370, 1265, 1234, 1187, 1174, 1100, 1049, 1017, 1003 cm^{-1}; HRMS (ESI) *m/z* [M+H]$^{+}$ calcd for $C_{22}H_{18}FN_3O_2S$: 408.1182, found: 408.1184.



3-(*p*-Tolyl)-1-tosyl-2,3-dihydro-1*H*-benzo[*d*]imidazo[1,2-*a*]imidazole 5g. Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.41; white solid; mp 184-185 °C; yield 86% (69 mg); ^{1}H NMR (600 MHz, CDCl$_3$) δ 7.99 (d, *J* = 8.4 Hz, 2H), 7.71 (d, *J* = 7.8 Hz, 1H), 7.29 (d, *J* = 7.8 Hz, 2H), 7.14 (t, *J* = 7.8 Hz, 1H), 7.09 (d, *J* = 7.8 Hz, 2H), 6.96 (t, *J* = 7.8 Hz, 1H), 6.87 (d, *J* = 7.8 Hz, 2H), 6.66 (d, *J* = 7.8 Hz, 1H), 5.37-5.35 (m, 1H), 4.74-4.71 (m, 1H), 4.07 (dd, *J* = 10.2, 6.6 Hz, 1H), 2.40 (s, 3H), 2.32 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$) δ 153.0, 147.7, 145.4, 139.4, 133.4, 133.3, 130.9, 130.1, 128.2, 126.3, 122.3, 121.9, 119.8, 109.3, 60.6, 56.6, 21.8, 21.3; FT-IR (KBr) 3045, 2919, 2256, 1623, 1593, 1547, 1515, 1469, 1435, 1369, 1336, 1310, 1276, 1265, 1213, 1185, 1172, 1106, 1091, 1059, 1004 cm^{-1}; HRMS (ESI) *m/z* [M+H]$^{+}$ calcd for $C_{23}H_{21}N_3O_2S$: 404.1433, found: 404.1435.

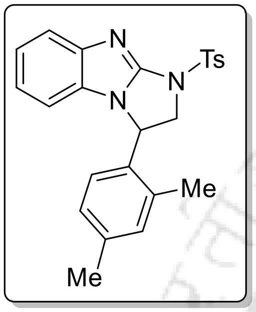


3-([1,1'-Biphenyl]-4-yl)-1-tosyl-2,3-dihydro-1*H*-benzo[*d*]imidazo[1,2-*a*]imidazole 5h. Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.53; white solid; mp 211-212 °C; yield 71% (66 mg); ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.01 (d, *J* = 8.4 Hz, 2H), 7.74 (d, *J* = 8.4 Hz, 1H), 7.54-7.49 (m, 4H), 7.46-7.42 (m, 2H), 7.39-7.34 (m, 1H), 7.30 (d, *J* = 8.4 Hz, 2H), 7.17 (td, *J* = 7.6, 1.2 Hz, 1H), 7.05 (d, *J* = 8.4 Hz, 2H), 7.01-6.97 (m, 1H), 6.74 (d, *J* = 8.0 Hz, 1H), 5.45 (dd, *J* = 8.4, 6.8 Hz, 1H), 4.78 (dd, *J* = 10.4, 8.8 Hz, 1H), 4.13 (dd, *J* =



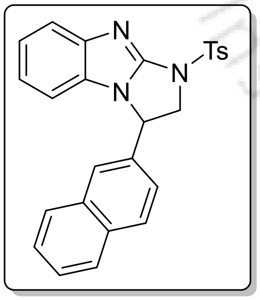
10.4, 6.8 Hz, 1H), 2.39 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 153.1, 147.8, 145.4, 142.4, 140.1, 135.3, 133.4, 131.0, 130.19, 130.16, 129.1, 128.2, 128.0, 127.2, 126.8, 122.4, 122.0, 119.9, 109.3, 60.5, 56.6, 21.8; FT-IR (KBr) 3057, 3034, 2925, 1623, 1583, 1547, 1487, 1451, 1437, 1411, 1376, 1333, 1309, 1279, 1260, 1188, 1173, 1107, 1093, 1074, 1005 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{28}H_{23}N_3O_2S$: 466.1589, found: 466.1585.

3-(2,4-Dimethylphenyl)-1-tosyl-2,3-dihydro-1*H*-benzo[*d*]imidazo[1,2-*a*]imidazole 5i.



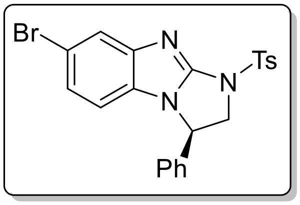
Analytical TLC on silica gel, 1:4 ethyl acetate/hexane $R_f = 0.50$; white solid; mp 153-154 °C; yield 73% (61 mg); ^1H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, *J* = 7.6 Hz, 2H), 7.73 (d, *J* = 8.0 Hz, 1H), 7.27-7.25 (m, 2H), 7.18-7.14 (m, 1H), 7.02 (s, 1H), 7.00-6.96 (m, 1H), 6.80 (d, *J* = 8.0 Hz, 1H), 6.68 (d, *J* = 8.0 Hz, 1H), 6.46 (d, *J* = 7.6 Hz, 1H), 5.59 (t, *J* = 7.6 Hz, 1H), 4.78-4.74 (m, 1H), 3.97 (dd, *J* = 9.2, 6.8 Hz, 1H), 2.39 (s, 3H), 2.28 (s, 3H), 2.26 (s, 3H); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 153.2, 147.8, 145.3, 138.9, 134.8, 133.6, 132.1, 131.3, 131.1, 130.1, 128.2, 127.7, 125.6, 122.3, 121.9, 119.9, 109.4, 59.7, 54.0, 21.8, 21.1, 19.1; FT-IR (KBr) 3064, 2922, 2853, 1625, 1596, 1543, 1506, 1432, 1371, 1319, 1274, 1244, 1214, 1188, 1175, 1146, 1090, 1064, 1004 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{24}H_{23}N_3O_2S$: 418.1589, found: 418.1588.

3-(Naphthalen-2-yl)-1-tosyl-2,3-dihydro-1*H*-benzo[*d*]imidazo[1,2-*a*]imidazole 5j.



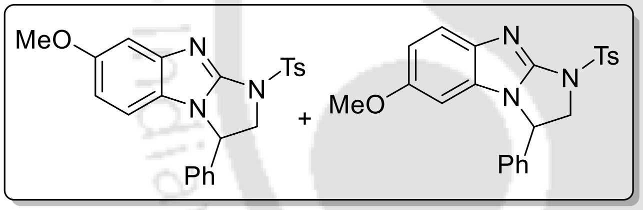
Analytical TLC on silica gel, 1:4 ethyl acetate/hexane $R_f = 0.35$; white solid; mp 217-218 °C; yield 71% (62 mg); ^1H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, *J* = 7.6 Hz, 2H), 7.80 (d, *J* = 7.2 Hz, 1H), 7.73 (d, *J* = 8.4 Hz, 2H), 7.68 (d, *J* = 7.6 Hz, 1H), 7.50-7.48 (m, 3H), 7.26 (d, *J* = 8.4 Hz, 2H), 7.13 (t, *J* = 7.6 Hz, 1H), 6.95-6.89 (m, 2H), 6.64 (d, *J* = 8.0 Hz, 1H), 5.57-5.53 (m, 1H), 4.83-4.79 (m, 1H), 4.19-4.15 (m, 1H), 2.37 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 153.1, 147.8, 145.5, 133.8, 133.6, 133.4, 133.1, 131.0, 130.1, 129.9, 128.24, 128.21, 128.0, 127.19, 127.14, 126.1, 123.0, 122.5, 122.0, 119.9, 109.3, 60.4, 57.0, 21.8; FT-IR (KBr) 3048, 2921, 2853, 1625, 1597, 1588, 1545, 1474, 1435, 1390, 1371, 1331, 1269, 1184, 1170, 1110, 1093, 1080, 1064, 1007 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{26}H_{21}N_3O_2S$: 440.1433, found: 440.1432.

(*R*)-7-Bromo-3-phenyl-1-tosyl-2,3-dihydro-1*H*-benzo[*d*]imidazo[1,2-*a*]imidazole 5k'.

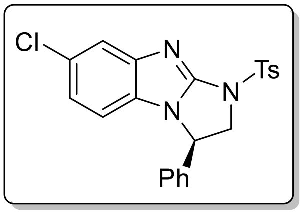


Analytical TLC on silica gel, 1:4 ethyl acetate/hexane $R_f = 0.49$; white solid; mp 212-213 °C; yield 71% (66 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.97 (d, *J* = 7.8 Hz, 2H), 7.82 (s, 1H), 7.34 (t, *J* = 7.2 Hz, 1H), 7.30-7.27 (m, 4H), 7.07 (d, *J* = 8.4 Hz, 1H), 6.94 (d, *J* = 7.2 Hz, 2H), 6.51 (d, *J* = 8.4 Hz, 1H), 5.41-5.38 (m, 1H), 4.78-4.75 (m, 1H), 4.12 (dd, *J* = 10.2, 6.6 Hz, 1H), 2.41 (s, 3H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 153.9, 149.1, 145.6, 136.1, 133.4, 130.2, 129.9, 129.6, 128.2, 126.2, 124.9, 122.8, 115.4, 110.3, 60.6, 57.0, 21.8; FT-IR (KBr) 2920, 2856, 1625, 1534, 1451, 1415, 1375, 1335, 1306, 1271, 1189, 1172, 1120, 1090, 1056 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{22}H_{18}BrN_3O_2S$: 468.0381, found: 468.0363; $[\alpha]_D^{25} = -37.5$ (c = 0.16, $CHCl_3$); HPLC analysis: 77% ee [Daicel CHIRALCEL OD column, hexane/*i*PrOH = 75:25, flow rate: 1 mL /min, λ = 215 nm, t_R = 12.20 min (major), 16.26 min (minor)].

7-Methoxy-3-phenyl-1-tosyl-2,3-dihydro-1*H*-benzo[*d*]imidazo[1,2-*a*]imidazole 5l and 6-Methoxy-3-phenyl-1-tosyl-2,3-dihydro-1*H*-benzo[*d*]imidazo[1,2-*a*]imidazole 5l'. Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.28; white solid; yield 85% (71 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.96 (d, *J* = 7.8 Hz, 2H), 7.60 (d, *J* = 9.0 Hz, 0.88H), 7.34-7.32 (m, 1.16H), 7.28-7.26 (m, 4.72H), 6.95 (d, *J* = 7.2 Hz, 2.12H), 6.77 (d, *J* = 7.2 Hz, 0.85H), 6.60 (d, *J* = 6.6 Hz, 0.23H), 6.54 (d, *J* = 8.4 Hz, 0.24H), 6.17 (s, 0.86H), 5.35 (dd, *J* = 13.8, 6.0 Hz, 1.09H), 4.74-4.71 (m, 1.06H), 4.07 (dd, *J* = 9.6, 6.0 Hz, 1.11H), 3.80 (s, 0.74H), 3.64 (s, 2.64H), 2.40 (s, 3.13H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 155.7, 152.4, 145.4, 141.9, 136.5, 133.4, 131.5, 130.1, 129.5, 129.4, 128.2, 126.3, 120.1, 110.6, 109.7, 109.5, 103.7, 94.8, 60.5, 57.0, 56.7, 56.0, 21.8; FT-IR (KBr) 2942, 2837, 1622, 1593, 1548, 1488, 1473, 1441, 1426, 1374, 1264, 1239, 1203, 1183, 1169, 1110, 1107, 1091, 1081, 1069, 1056, 1032, 1001 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{23}H_{21}N_3O_3S$: 420.1382, found: 420.1380.

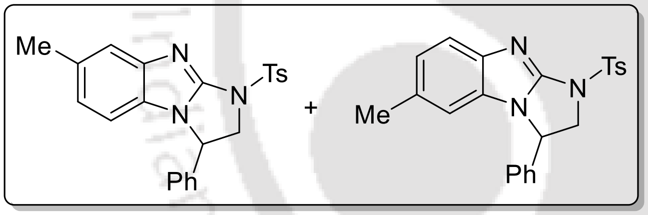


(*R*)-7-Chloro-3-phenyl-1-tosyl-2,3-dihydro-1*H*-benzo[*d*]imidazo[1,2-*a*]imidazole 5m'.

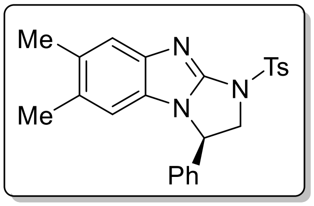


Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.53; white solid; mp 188-189 °C; yield 73% (62 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.97 (d, *J* = 7.8 Hz, 2H), 7.66 (s, 1H), 7.34 (t, *J* = 7.2 Hz, 1H), 7.30-7.27 (m, 4H), 6.94-6.92 (m, 3H), 6.55 (d, *J* = 8.4 Hz, 1H), 5.40 (dd, *J* = 8.4, 6.6 Hz, 1H), 4.76 (dd, *J* = 10.2, 9.0 Hz, 1H), 4.10 (dd, *J* = 10.2, 6.6 Hz, 1H), 2.41 (s, 3H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 154.0, 148.6, 145.6, 136.2, 133.4, 130.2, 129.6, 129.5, 128.2, 128.1, 126.2, 122.2, 119.8, 109.8, 60.5, 57.0, 21.8; FT-IR (KBr) 2923, 2853, 1624, 1559, 1540, 1508, 1495, 1449, 1419, 1375, 1307, 1189, 1172, 1120, 1090, 1054 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{22}H_{18}ClN_3O_2S$: 424.0887, found: 424.0888; $[\alpha]_D^{25}$ = -14 (c= 0.1, $CHCl_3$); HPLC analysis: 80% ee [Daicel CHIRALCEL OD column, hexane/iPrOH = 75:25, flow rate: 1 mL /min, λ = 215 nm, t_R = 12.25 min (major), 16.18 min (minor)].

7-Methyl-3-phenyl-1-tosyl-2,3-dihydro-1*H*-benzo[*d*]imidazo[1,2-*a*]imidazole 5n and 6-Methyl-3-phenyl-1-tosyl-2,3-dihydro-1*H*-benzo[*d*]imidazo[1,2-*a*]imidazole 5n'. Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.44; white solid; yield 83% (67 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97-7.95 (m, 1.83H), 7.59 (d, *J* = 8.4 Hz, 0.41H), 7.51 (s, 0.53H), 7.34-7.30 (m, 1.20H), 7.28-7.24 (m, 4.01H), 6.96-6.93 (m, 2.11H), 6.80 (d, *J* = 7.6 Hz, 0.57H), 6.55 (d, *J* = 8.4 Hz, 0.55H), 6.45 (s, 0.38H), 5.38-5.33 (m, 1H), 4.75-4.70 (m, 1.02H), 4.07 (dd, *J* = 10.4, 6.4 Hz, 1.01H), 2.40 (s, 2.66H), 2.39 (s, 1.46H), 2.25 (s, 1.18H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) 153.1, 152.7, 148.0, 145.6, 145.3, 136.7, 136.6, 133.3, 132.1, 131.9, 130.1, 129.5, 129.4, 129.3, 128.9, 128.2, 126.3, 126.2, 123.6, 123.0, 120.0, 119.4, 109.4, 108.8, 60.5, 56.8, 56.7, 21.8, 21.7, 21.6; FT-IR (KBr) 2923, 2856, 1629, 1596, 1586, 1540, 1473, 1438, 1373, 1308, 1272, 1184, 1169, 1121, 1092, 1056 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{23}H_{21}N_3O_2S$: 404.1433, found: 404.1435.

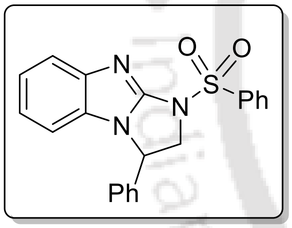


(*R*)-6,7-Dimethyl-3-phenyl-1-tosyl-2,3-dihydro-1*H*-benzo[*d*]imidazo[1,2-*a*]imidazole 5o'.



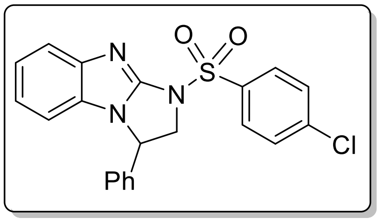
Analytical TLC on silica gel, 1:4 ethyl acetate/hexane $R_f = 0.43$; white solid; mp 229-230 °C; yield 82% (68 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, *J* = 8.4 Hz, 2H), 7.48 (s, 1H), 7.35-7.31 (m, 1H), 7.28-7.24 (m, 4H), 6.93 (d, *J* = 7.6 Hz, 2H), 6.43 (s, 1H), 5.32 (dd, *J* = 8.4, 6.4 Hz, 1H), 4.71 (dd, *J* = 10.0, 8.4 Hz, 1H), 4.04 (dd, *J* = 10.0, 6.0 Hz, 1H), 2.38 (s, 3H), 2.28 (s, 3H), 2.14 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 152.5, 146.1, 145.3, 136.8, 133.2, 131.0, 130.8, 130.1, 129.4, 129.2, 128.2, 126.2, 120.3, 109.7, 60.6, 56.6, 21.8, 20.4, 20.3; FT-IR (KBr) 2922, 1632, 1596, 1578, 1545, 1493, 1458, 1440, 1375, 1306, 1276, 1185, 1171, 1117, 1092, 1039, 1020, 992 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{24}H_{23}N_3O_2S$: 418.1589, found: 418.1580; $[\alpha]_D^{25}$ = -61.74 (c= 0.23, $CHCl_3$); HPLC analysis: 95% ee [Daicel CHIRALCEL OD column, hexane/*i*PrOH = 75:25, flow rate: 1 mL /min, λ = 215 nm, t_R = 9.22 min (major), 14.30 min (minor)].

3-Phenyl-1-(phenylsulfonyl)-2,3-dihydro-1*H*-benzo[*d*]imidazo[1,2-*a*]imidazole 5p. Analytical



TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.40; white solid; mp 209-210 °C; yield 79% (59 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (d, *J* = 7.6 Hz, 2H), 7.73 (d, *J* = 8.4 Hz, 1H), 7.64 (t, *J* = 7.6 Hz, 1H), 7.51 (t, *J* = 7.6 Hz, 2H), 7.34-7.26 (m, 3H), 7.16 (t, *J* = 7.6 Hz, 1H), 6.98 (t, *J* = 8.4 Hz, 3H), 6.67 (d, *J* = 8.0 Hz, 1H), 5.43-5.39 (m, 1H), 4.80-4.75 (m, 1H), 4.11 (dd, *J* = 10.0, 6.4 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 152.9, 147.8, 136.4, 134.3, 131.0, 129.6, 129.58, 129.53, 128.1, 126.3, 122.5, 122.0, 119.9, 109.3, 60.5, 56.9; FT-IR (KBr) 3072, 3039, 2920, 1621, 1587, 1540, 1495, 1462, 1448, 1428, 1368, 1265, 1173, 1105, 1090, 1051, 1004 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{21}H_{17}N_3O_2S$: 376.1120, found: 376.1119.

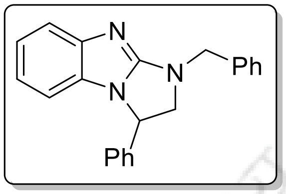
1-((4-Chlorophenyl)sulfonyl)-3-phenyl-2,3-dihydro-1*H*-benzo[*d*]imidazo[1,2-*a*]imidazole 5q.



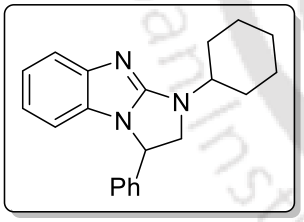
Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.57; white solid; mp 220-221 °C; yield 78% (64 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.06 (d, *J* = 9.0 Hz, 2H), 7.71 (d, *J* = 7.8 Hz, 1H), 7.43 (d, *J* = 8.4 Hz, 2H), 7.35 (t, *J* = 7.2 Hz, 1H), 7.30 (t, *J* = 7.2 Hz, 2H), 7.17 (t, *J* = 7.8 Hz, 1H), 6.99 (t, *J* = 7.8 Hz, 1H), 6.97 (d, *J* = 7.8 Hz, 2H), 6.69 (d, *J* =

7.8 Hz, 1H), 5.45-5.43 (m, 1H), 4.80-4.77 (m, 1H), 4.11 (dd, *J* = 10.2, 6.0 Hz, 1H); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 152.7, 147.7, 141.1, 136.4, 134.9, 131.0, 129.8, 129.66, 129.62, 129.5, 126.2, 122.6, 122.2, 120.0, 109.4, 60.6, 56.9; FT-IR (KBr) 3095, 2923, 2856, 1621, 1585, 1538, 1495, 1475, 1464, 1450, 1428, 1398, 1372, 1263, 1180, 1174, 1145, 1092, 1084, 1048, 1016, 1004 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{21}H_{16}ClN_3O_2S$: 410.0730, found: 410.0731.

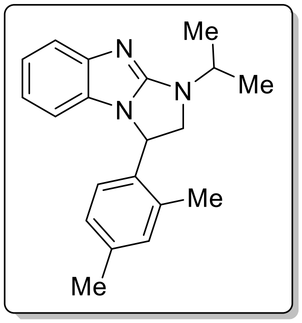
1-Benzyl-3-phenyl-2,3-dihydro-1*H*-benzo[*d*]imidazo[1,2-*a*]imidazole 5r. Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.40; white solid; mp 154-155 °C; yield 63% (41 mg); ^1H NMR (400 MHz, $CDCl_3$) δ 7.51 (d, *J* = 7.6 Hz, 1H), 7.39-7.29 (m, 7H), 7.27-7.26 (m, 3H), 7.08 (t, *J* = 7.6 Hz, 1H), 6.89 (t, *J* = 7.6 Hz, 1H), 6.65 (d, *J* = 8.0 Hz, 1H), 5.40 (t, *J* = 8.4 Hz, 1H), 4.77 (d, *J* = 14.8 Hz, 1H), 4.60 (d, *J* = 14.8 Hz, 1H), 4.12 (t, *J* = 9.2 Hz, 1H), 3.57 (t, *J* = 8.8 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 161.9, 148.6, 137.8, 136.3, 132.0, 129.3, 128.98, 128.95, 128.6, 128.1, 126.6, 121.5, 120.0, 117.3, 108.3, 61.3, 58.0, 51.0; FT-IR (KBr) 3034, 2931, 2854, 1639, 1597, 1568, 1493, 1467, 1447, 1378, 1365, 1360, 1342, 1313, 1281, 1265, 1211, 1178, 1106, 1078, 1027, 1005 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{22}H_{19}N_3$: 326.1657, found: 326.1659.



1-Cyclohexyl-3-phenyl-2,3-dihydro-1*H*-benzo[*d*]imidazo[1,2-*a*]imidazole 5s. Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.53; yellowish liquid; yield 62% (39 mg); ^1H NMR (400 MHz, $CDCl_3$) δ 7.44 (d, *J* = 8.0 Hz, 1H), 7.38-7.35 (m, 3H), 7.31-7.29 (m, 2H), 7.05-7.01 (m, 1H), 6.84 (t, *J* = 8.0 Hz, 1H), 6.61 (d, *J* = 8.0 Hz, 1H), 5.38 (t, *J* = 8.0 Hz, 1H), 4.27 (t, *J* = 8.8 Hz, 1H), 3.86-3.83 (m, 1H), 3.72 (dd, *J* = 9.2, 7.6 Hz, 1H), 2.02-1.98 (m, 2H), 1.85-1.78 (m, 3H), 1.70-1.67 (m, 1H), 1.46-1.40 (m, 3H), 1.16-1.07 (m, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 161.1, 148.6, 138.0, 131.6, 129.1, 128.7, 126.3, 121.0, 119.4, 116.7, 107.8, 57.9, 57.2, 54.2, 30.4, 29.8, 25.5, 25.3; FT-IR (neat) 2929, 2854, 1634, 1596, 1567, 1451, 1379, 1360, 1333, 1312, 1267, 1213, 1128, 1083, 1029, 1008 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{21}H_{23}N_3$: 318.1970, found: 318.1973.

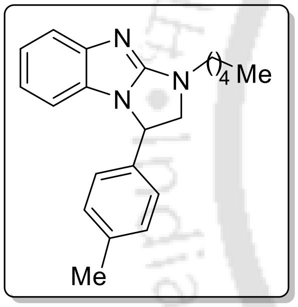


3-(2,4-Dimethylphenyl)-1-isopropyl-2,3-dihydro-1*H*-benzo[*d*]imidazo[1,2-*a*]imidazole 5t.

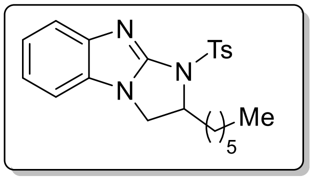


Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.3; yellowish liquid; yield 71% (43 mg); ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.46 (d, *J* = 8.0 Hz, 1H), 7.06-7.03 (m, 2H), 6.99 (q, *J* = 8.4 Hz, 2H), 6.86 (t, *J* = 7.6 Hz, 1H), 6.64 (d, *J* = 7.6 Hz, 1H), 5.59 (t, *J* = 8.4 Hz, 1H), 4.29-4.24 (m, 2H), 3.57 (t, *J* = 8.4 Hz, 1H), 2.37 (s, 3H), 2.32 (s, 3H), 1.31 (d, *J* = 6.8 Hz, 3H), 1.26 (d, *J* = 6.4 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$) δ 161.4, 148.8, 138.2, 134.8, 133.1, 131.9, 127.6, 126.0, 121.2, 119.6, 116.9, 108.2, 55.4, 55.0, 46.7, 21.2, 20.1, 19.4, 19.3; FT-IR (neat) 2969, 2926, 2878, 1631, 1597, 1564, 1505, 1451, 1382, 1366, 1312, 1268, 1216, 1126, 1043, 1007 cm^{-1}; HRMS (ESI) *m/z* [M+H]$^+$ calcd for $C_{20}H_{23}N_3$: 306.1970, found: 306.1972.

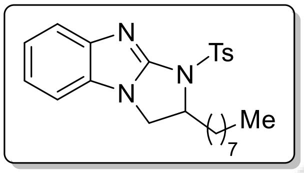
1-Pentyl-3-(*p*-tolyl)-2,3-dihydro-1*H*-benzo[*d*]imidazo[1,2-*a*]imidazole 5u. Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.32; yellowish liquid; yield 72% (46 mg); ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.44 (d, *J* = 7.6 Hz, 1H), 7.22-7.17 (m, 4H), 7.03 (t, *J* = 8.0 Hz, 1H), 6.85 (t, *J* = 7.6 Hz, 1H), 6.62 (d, *J* = 7.6 Hz, 1H), 5.38 (t, *J* = 7.6 Hz, 1H), 4.25 (t, *J* = 8.8 Hz, 1H), 3.69-3.65 (m, 1H), 3.54-3.47 (m, 1H), 3.42-3.35 (m, 1H), 2.36 (s, 3H), 1.68-1.65 (m, 2H), 1.37-1.35 (m, 4H), 0.91-0.88 (m, 3H); ^{13}C{^{1}H} NMR (150 MHz, CDCl$_3$) δ 148.6, 138.8, 135.0, 131.9, 130.0, 126.6, 121.3, 119.8, 117.0, 108.2, 62.1, 57.9, 47.1, 29.2, 27.6, 22.6, 21.3, 14.2; FT-IR (neat) 2959, 2923, 2860, 1634, 1569, 1515, 1452, 1379, 1313, 1266, 1209, 1183, 1114, 1063, 1008 cm^{-1}; HRMS (ESI) *m/z* [M+H]$^+$ calcd for $C_{21}H_{25}N_3$: 320.2127, found: 320.2127.



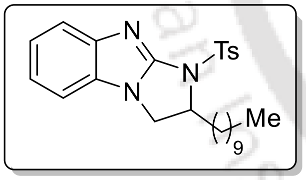
2-Hexyl-1-tosyl-2,3-dihydro-1*H*-benzo[*d*]imidazo[1,2-*a*]imidazole 6a. Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.50; white solid; mp 145-146 °C; yield 69% (55 mg); ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.93 (d, *J* = 8.0 Hz, 2H), 7.71 (d, *J* = 8.0 Hz, 1H), 7.24 (d, *J* = 8.0 Hz, 2H), 7.18 (td, *J* = 7.2, 1.6 Hz, 1H), 7.12 (td, *J* = 8.0, 1.2 Hz, 1H), 7.09-7.07 (m, 1H), 4.74-4.68 (m, 1H), 4.05-4.01 (m, 1H), 3.77 (dd, *J* = 9.6, 4.4 Hz, 1H), 2.35 (s, 3H), 2.10-2.06 (m, 1H), 1.95-1.90 (m, 1H), 1.80-1.76 (m, 1H), 1.35-1.26 (m, 7H), 0.87 (t, *J* = 6.8 Hz, 3H); ^{13}C{^{1}H}



NMR (100 MHz, $CDCl_3$) δ 153.2, 147.5, 145.1, 134.9, 131.4, 130.0, 127.8, 122.2, 121.9, 119.9, 108.6, 65.8, 45.5, 35.7, 31.8, 29.1, 24.3, 22.7, 21.7, 14.2; FT-IR (KBr) 2957, 2926, 2852, 1626, 1597, 1587, 1540, 1500, 1441, 1368, 1301, 1275, 1185, 1166, 1107, 1089, 1052, 1006 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{22}H_{27}N_3O_2S$: 398.1902, found: 398.1903.

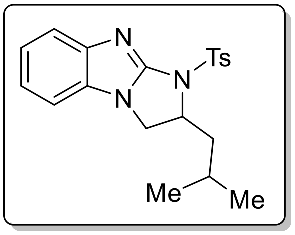


2-Octyl-1-tosyl-2,3-dihydro-1*H*-benzo[*d*]imidazo[1,2-*a*]imidazole 6b. Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.65; white solid; mp 131-132 °C; yield 67% (57 mg); ^1H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, *J* = 8.4 Hz, 2H), 7.70 (d, *J* = 7.6 Hz, 1H), 7.23 (d, *J* = 8.0 Hz, 2H), 7.19-7.15 (m, 1H), 7.13-7.09 (m, 1H), 7.09-7.06 (m, 1H), 4.73-4.66 (m, 1H), 4.04-4.00 (m, 1H), 3.77 (dd, *J* = 9.6, 4.4 Hz, 1H), 2.34 (s, 3H), 2.10-2.03 (m, 1H), 1.96-1.87 (m, 1H), 1.32-1.24 (m, 12H), 0.86 (t, *J* = 6.4 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 153.1, 147.4, 145.1, 134.7, 131.3, 130.0, 127.7, 122.1, 121.8, 119.7, 108.6, 65.7, 45.5, 35.6, 31.9, 29.5, 29.4, 29.3, 24.2, 22.7, 21.7, 14.2; FT-IR (KBr) 2961, 2924, 2852, 1623, 1596, 1536, 1501, 1466, 1442, 1370, 1296, 1277, 1187, 1172, 1107, 1091, 1043, 1028, 1004 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{24}H_{31}N_3O_2S$: 426.2215, found: 426.2224.

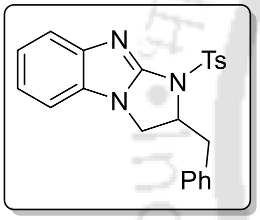


2-Decyl-1-tosyl-2,3-dihydro-1*H*-benzo[*d*]imidazo[1,2-*a*]imidazole 6c. Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.65; white solid; mp 119-120 °C; yield 66% (60 mg); ^1H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, *J* = 8.4 Hz, 2H), 7.71 (d, *J* = 8.0 Hz, 1H), 7.24-7.22 (m, 2H), 7.20-7.16 (m, 1H), 7.12 (td, *J* = 7.6, 1.2 Hz, 1H), 7.09-7.07 (m, 1H), 4.73-4.67 (m, 1H), 4.05-4.00 (m, 1H), 3.77 (dd, *J* = 9.6, 4.4 Hz, 1H), 2.35 (s, 3H), 2.12-2.04 (m, 1H), 1.97-1.87 (m, 1H), 1.32-1.24 (m, 16H), 0.87 (t, *J* = 6.4 Hz, 3H); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 153.2, 147.5, 145.1, 134.9, 131.4, 130.0, 127.8, 122.2, 121.9, 119.8, 108.6, 65.8, 45.5, 35.7, 32.0, 29.7, 29.69, 29.61, 29.4, 24.3, 22.8, 21.7, 14.2; FT-IR (KBr) 2956, 2924, 2854, 1624, 1596, 1537, 1500, 1468, 1440, 1368, 1336, 1297, 1277, 1186, 1171, 1106, 1091, 1045, 1006 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{26}H_{35}N_3O_2S$: 454.2528, found: 454.2536.

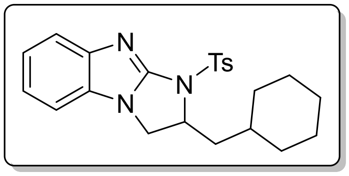
2-Isobutyl-1-tosyl-2,3-dihydro-1*H*-benzo[*d*]imidazo[1,2-*a*]imidazole 6d. Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.55; white solid; mp 191-192 °C; yield 64% (47 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, *J* = 8.4 Hz, 2H), 7.71 (d, *J* = 7.6 Hz, 1H), 7.23-7.21 (m, 2H), 7.18 (td, *J* = 7.2, 1.2 Hz, 1H), 7.12 (td, *J* = 7.6, 1.2 Hz, 1H), 7.08-7.06 (m, 1H), 4.74-4.67 (m, 1H), 4.03-3.99 (m, 1H), 3.73 (dd, *J* = 9.6, 4.4 Hz, 1H), 2.35 (s, 3H), 2.14-2.12 (m, 1H), 1.80-1.70 (m, 2H), 1.02 (t, *J* = 6.8 Hz, 6H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 153.1, 147.6, 145.1, 134.8, 131.5, 130.0, 127.9, 122.2, 121.9, 119.9, 108.6, 64.6, 46.2, 45.1, 24.8, 23.4, 22.0, 21.7; FT-IR (KBr) 2961, 2878, 1921, 1653, 1624, 1587, 1539, 1500, 1479, 1461, 1440, 1374, 1361, 1332, 1308, 1299, 1275, 1215, 1187, 1166, 1107, 1050, 1018, 1000 cm^{-1}; HRMS (ESI) *m/z* [M+H]$^+$ calcd for $C_{20}H_{23}N_3O_2S$: 370.1589, found: 370.1590.



2-Benzyl-1-tosyl-2,3-dihydro-1*H*-benzo[*d*]imidazo[1,2-*a*]imidazole 6e. Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.54; white solid; mp 182-183 °C; yield 71% (57 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (d, *J* = 8.4 Hz, 2H), 7.70 (d, *J* = 8.0 Hz, 1H), 7.36-7.33 (m, 2H), 7.29-7.25 (m, 5H), 7.20-7.15 (m, 1H), 7.12-7.09 (m, 1H), 7.03 (d, *J* = 7.6 Hz, 1H), 4.95-4.88 (m, 1H), 3.84 (d, *J* = 6.8 Hz, 2H), 3.68 (dd, *J* = 13.6, 3.6 Hz, 1H), 3.06 (dd, *J* = 13.6, 10.4 Hz, 1H), 2.36 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 153.0, 147.4, 145.3, 135.4, 134.7, 131.4, 130.1, 129.6, 129.2, 127.9, 127.6, 122.2, 121.9, 119.9, 108.6, 66.4, 44.8, 41.8, 21.8; FT-IR (KBr) 3031, 2923, 2856, 1624, 1596, 1540, 1498, 1457, 1439, 1365, 1296, 1271, 1185, 1169, 1107, 1090, 1054, 1025 cm^{-1}; HRMS (ESI) *m/z* [M+H]$^+$ calcd for $C_{23}H_{21}N_3O_2S$: 404.1433, found: 404.1436.

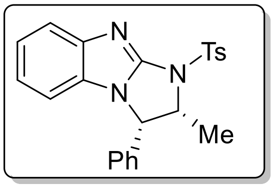


2-(Cyclohexylmethyl)-1-tosyl-2,3-dihydro-1*H*-benzo[*d*]imidazo[1,2-*a*]imidazole 6f. Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.62; white solid; mp 189-190 °C; yield 62% (51 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, *J* = 8.4 Hz, 2H), 7.71 (d, *J* = 8.0 Hz, 1H), 7.24 (d, *J* = 8.0 Hz, 2H), 7.19 (td, *J* = 7.6 Hz, 1.6 Hz, 1H), 7.13 (td, *J* = 8.0, 1.2 Hz, 1H), 7.09-7.06 (m, 1H), 4.78-4.71 (m, 1H), 4.04-4.00 (m, 1H), 3.74 (dd, *J* = 9.6, 4.4 Hz, 1H), 2.36 (s, 3H), 2.20-2.13 (m, 1H), 1.77-1.69 (m, 6H), 1.45-1.42 (m, 1H), 1.26-1.21 (m, 3H), 1.09-1.03 (m, 2H); ^{13}C{^{1}H}



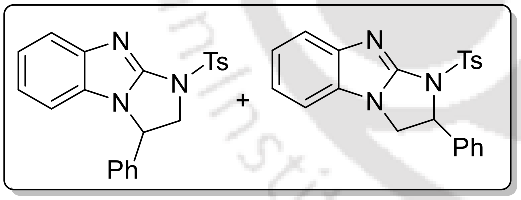
NMR (100 MHz, $CDCl_3$) δ 153.2, 147.6, 145.1, 134.8, 131.5, 130.1, 127.9, 122.2, 121.9, 120.0, 108.6, 64.1, 46.4, 43.8, 34.2, 34.0, 32.7, 26.5, 26.3, 26.2, 21.8; FT-IR (KBr) 2925, 2842, 1625, 1590, 1540, 1497, 1439, 1370, 1325, 1296, 1273, 1215, 1185, 1171, 1091, 1048, 1004 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{23}H_{27}N_3O_2S$: 410.1902, found: 410.1903.

(±)-2-Methyl-3-phenyl-1-tosyl-2,3-dihydro-1*H*-benzo[*d*]imidazo[1,2-*a*]imidazole 7a.



Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.53; white solid; mp 230-231 °C; yield 74% (60 mg); ^1H NMR (600 MHz, $CDCl_3$) δ 8.03 (d, *J* = 7.8 Hz, 2H), 7.74 (d, *J* = 8.4 Hz, 1H), 7.37-7.35 (m, 3H), 7.29 (d. *J* = 8.4 Hz, 2H), 7.16 (t, *J* = 7.8 Hz, 1H), 7.07 (d, *J* = 4.2 Hz, 2H), 6.98 (t, *J* = 7.8 Hz, 1H), 6.65 (d, *J* = 7.8 Hz, 1H), 5.40 (d, *J* = 8.4 Hz, 1H), 4.96-4.91 (m, 1H), 2.39 (s, 3H), 1.19 (d, *J* = 6.6 Hz, 3H); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 153.4, 147.8, 145.2, 135.0, 132.9, 131.2, 130.1, 129.4, 129.1, 128.0, 127.8, 122.4, 121.8, 119.8, 109.8, 65.8, 61.6, 21.8, 18.3; FT-IR (KBr) 1619, 1533, 1454, 1434, 1370, 1274, 1188, 1174, 1085, 1022, 1004 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{23}H_{21}N_3O_2S$: 404.1433, found: 404.1434.

3-Phenyl-1-tosyl-2,3-dihydro-1*H*-benzo[*d*]imidazo[1,2-*a*]imidazole 5a and 2-phenyl-1-tosyl-2,3-dihydro-1*H*-benzo[*d*]imidazo[1,2-*a*]imidazole 5a'. Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.41; white solid; mp 212-213 °C; yield 66% (51 mg); ^1H NMR (400 MHz, $CDCl_3$) δ 7.99 (d, *J* = 8.4 Hz, 1.86H), 7.72 (t, *J* = 8.0 Hz, 3.05H), 7.36-7.24 (m, 9.39H), 7.23-7.19 (m, 1.02H),7.17-7.08 (m, 4.08H), 6.99-6.95 (m, 2.88H), 6.67 (d, *J* = 8.0 Hz, 0.93H), 5.77 (dd, *J* = 8.8, 4.4 Hz, 0.72H), 5.40 (dd, *J* = 8.4, 6.4 Hz, 1H), 4.75 (dd, *J* = 10.4, 8.8 Hz, 1.01H), 4.53-4.48 (m, 0.72H), 4.10 (dd, *J* = 10.4, 6.4 Hz, 1H), 4.02 (dd, *J* = 9.6, 4.4 Hz, 0.71H), 2.40 (s, 2.87H), 2.34 (s, 2.07H); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 153.3, 153.1, 147.8, 145.4, 144.8, 138.7, 136.5, 135.3, 133.5, 131.5, 131.0, 130.1, 129.7, 129.5, 129.4, 129.2, 129.1, 128.2, 127.9, 126.8, 126.3, 122.4, 122.3, 122.0, 121.9, 119.9, 109.3, 108.6, 68.1, 60.5, 56.9, 49.4, 21.8, 21.7; FT-IR (KBr) 2923, 2850, 1622, 1595, 1532, 1499, 1454, 1435, 1373, 1291, 1272, 1186, 1171, 1108, 1091, 1042, 1004 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{22}H_{19}N_3O_2S$: 390.1276, found: 390.1283.



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

Identification code	**5e**
Empirical formula	$C_{22}H_{18}N_3O_2SCl$
Formula weight	423.90
Crystal habit, colour	Needle / colorless
Crystal size, mm^3	0.29 x 0.24 x 0.18
Temperature, T/K	293 (2)
Wavelength, λ/Å	0.71073
Crystal system	monoclinic
Space group	‘P 21/n’
Unit cell dimensions	a = 9.7527(6)Å, b = 8.3311(6)Å
	c = 24.3083(18)Å
	$\alpha = \gamma$ = 90.00°, β = 100.212(6)
Volume, V/Å^3	1943.8(2)
Z	4
Calculated density, $Mg \cdot m^{-3}$	1.449
Absorption coefficient, μ/mm^{-1}	0.329
F(000)	880
θ range for data collection	2.98 to 25.25°
Limiting indices	$-11 \leq h \leq 11$, $-10 \leq k \leq 6$, $-25 \leq l \leq 29$
Reflection collected / unique	3518/ 2667 [R(int) = 0.0351]
Completeness to θ	99.90 % (θ = 25.25°)
Absorption correction	Multi-scan
Max. and min. transmission	0.942 and 0.910
Refinement method	SHELXL-2014/7
Data / restraints / parameters	3518/0/ 263
Goodness–of–fit on F^2	1.081
Final R indices [I>2sigma(I)]	$R1$ = 0.0496, $wR2$ = 0.1295
R indices (all data)	$R1$ = 0.0679, $wR2$ = 0.1380

Crystal Data and Structure Refinement for 6a at 298(2) K

Identification code	**6a**
Empirical formula	$C_{22}H_{27}N_3O_2S$
Formula weight	397.53
Crystal habit, colour	Needle / colorless
Crystal size, mm^3	0.29 x 0.24 x 0.18
Temperature, T/K	298 (2)
Wavelength, λ/Å	0.71073
Crystal system	monoclinic
Space group	P 21/c
Unit cell dimensions	a = 13.4172(13)Å, b = 6.0529(4)Å c = 28.871(2)Å α = γ = 90.00°, β = 117.325(6)
Volume, V/Å^3	2083.1(3)
Z	4
Calculated density, Mg·m^{-3}	1.268
Absorption coefficient, μ/mm^{-1}	0.178
F(000)	848.0
θ range for data collection	1.59 to 24.99°
Limiting indices	$-15 \leq h \leq 15$, $-6 \leq k \leq 7$, $-34 \leq l \leq 34$
Reflection collected / unique	3597/1607 [R(int) = 0.1390]
Completeness to θ	98.00% (θ = 24.99°)
Absorption correction	Multi-scan
Max. and min. transmission	0.968 and 0.950
Refinement method	SHELXL-2014/7
Data / restraints / parameters	3597/0/ 255
Goodness–of–fit on F^2	0.800
Final R indices [I>2sigma(I)]	R1 = 0.0445, wR2 = 0.0852
R indices (all data)	R1 = 0.1077, wR2 = 0.0953

Crystal Data and Structure Refinement for 5aa' at 296(2) K

Identification code	**5aa'**
Empirical formula	$C_{22}H_{19}N_3O_2S$
Formula weight	389.46
Crystal habit, colour	plates / colorless
Crystal size, mm^3	0.25 x 0.18 x 0.14
Temperature, T/K	296 (2)
Wavelength, λ/Å	0.71073
Crystal system	monoclinic
Space group	P 2(1)
Unit cell dimensions	a = 11.1987(4)Å, b = 8.5305(4)Å
	c = 11.2494(4)Å
	α = γ = 90.00°, β = 114.071(2)
Volume, V/Å^3	981.21(7)
Z	2
Calculated density, Mg·m^{-3}	1.318
Absorption coefficient, μ/mm^{-1}	0.188
F(000)	408
θ range for data collection	1.98 to 24.99°
Limiting indices	$-12 \le h \le 13$, $-10 \le k \le 10$, $-13 \le l \le 13$
Reflection collected / unique	3411 /2817 [R(int) = 0.0360]
Completeness to θ	99.00% (θ = 24.99°)
Absorption correction	none
Max. and min. transmission	0.974 and 0.960
Refinement method	SHELXL-97 (Sheldrick, 1997)
Data / restraints / parameters	3411/1/ 254
Goodness–of–fit on F^2	0.815
Final R indices [I>2sigma(I)]	R1 = 0.0357, wR2 = 0.1024
R indices (all data)	R1 = 0.0459, wR2 = 0.1122

4.5 References

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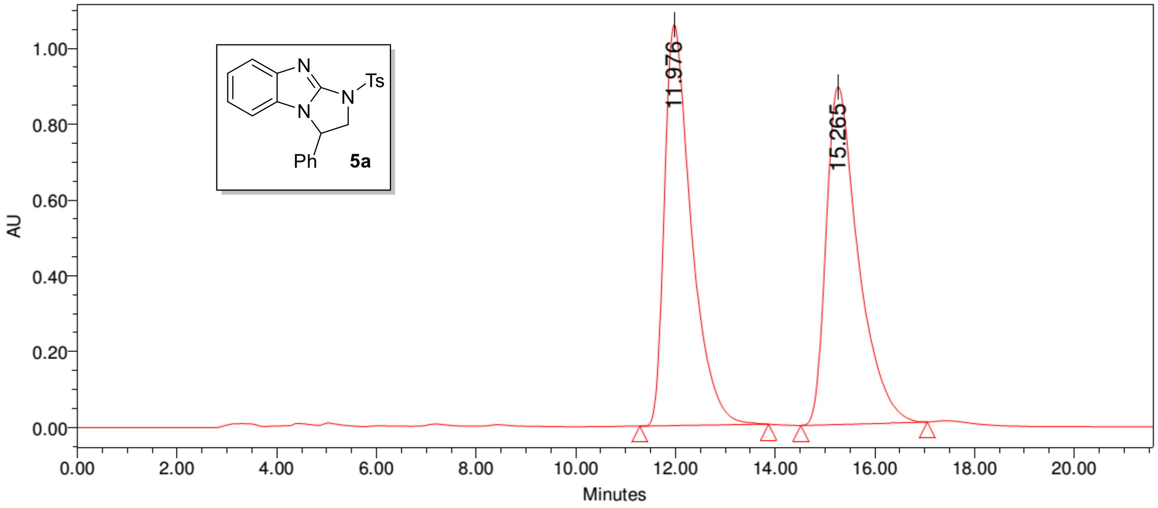
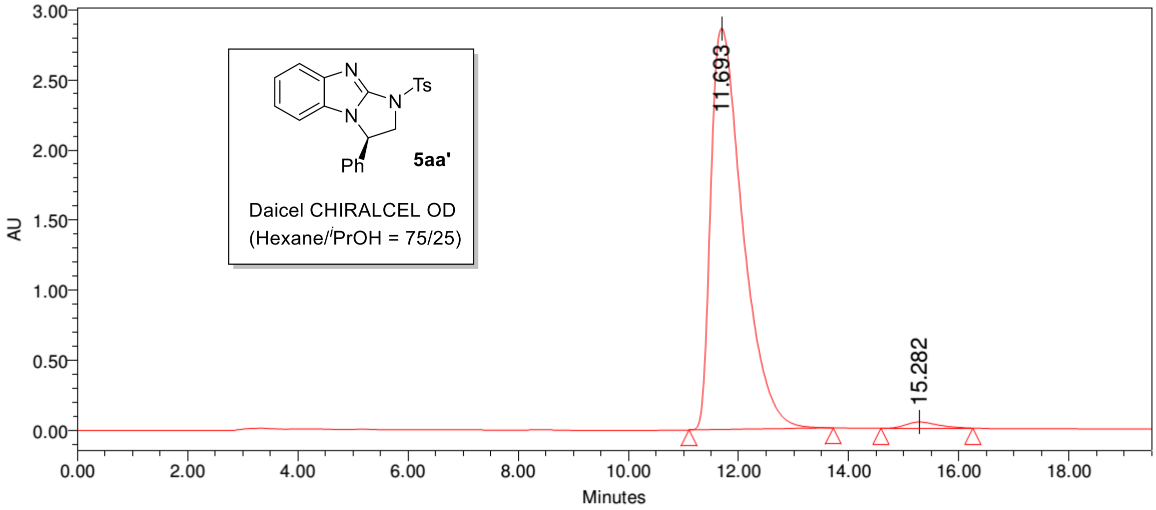
4.6 HPLC Chromatogram



Peak Results

	RT	Height (µV)	% Area
1	11.976	1058375	49.80
2	15.265	891647	50.20



Peak Results

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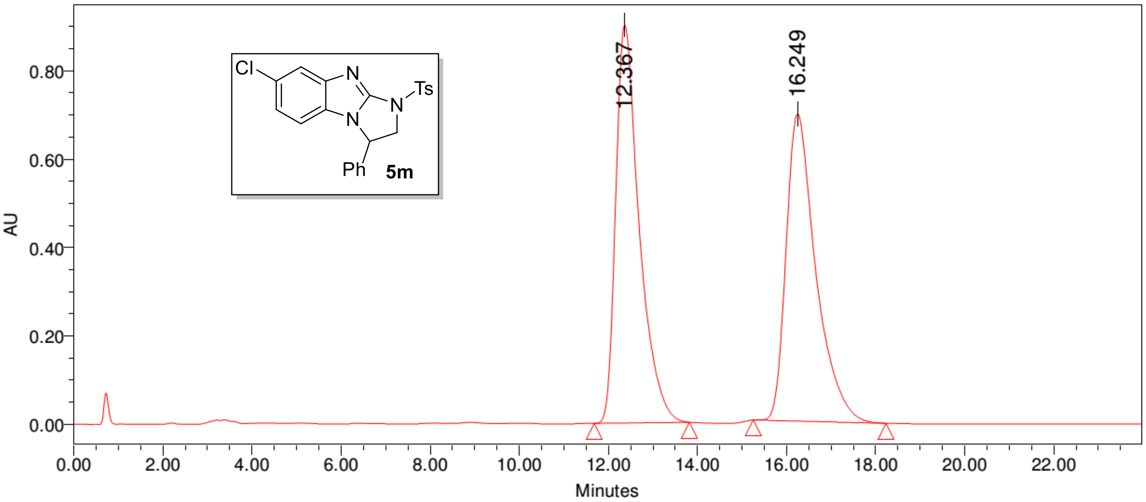
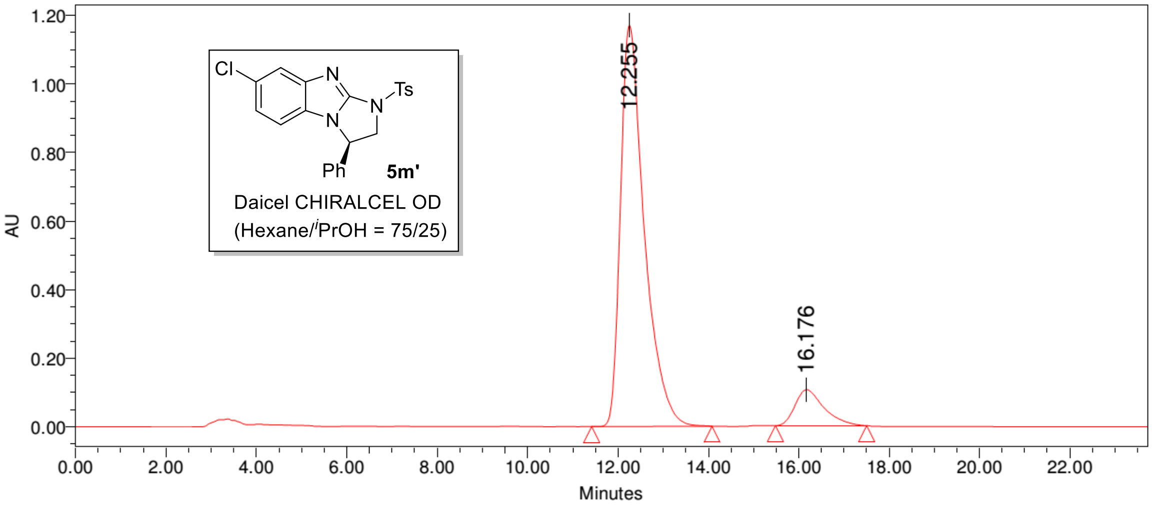
1	11.693	2865049	98.46
2	15.282	44449	1.54



Peak Results

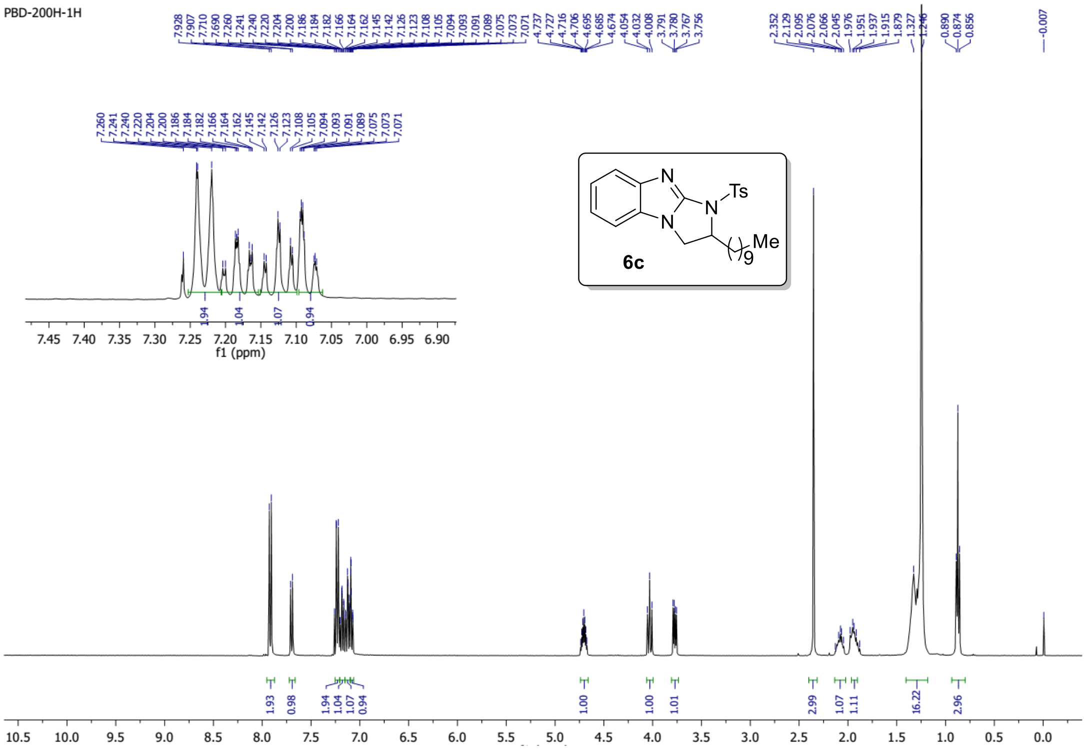
	RT	Height (μV)	% Area
1	12.367	901238	50.56
2	16.249	695252	49.44

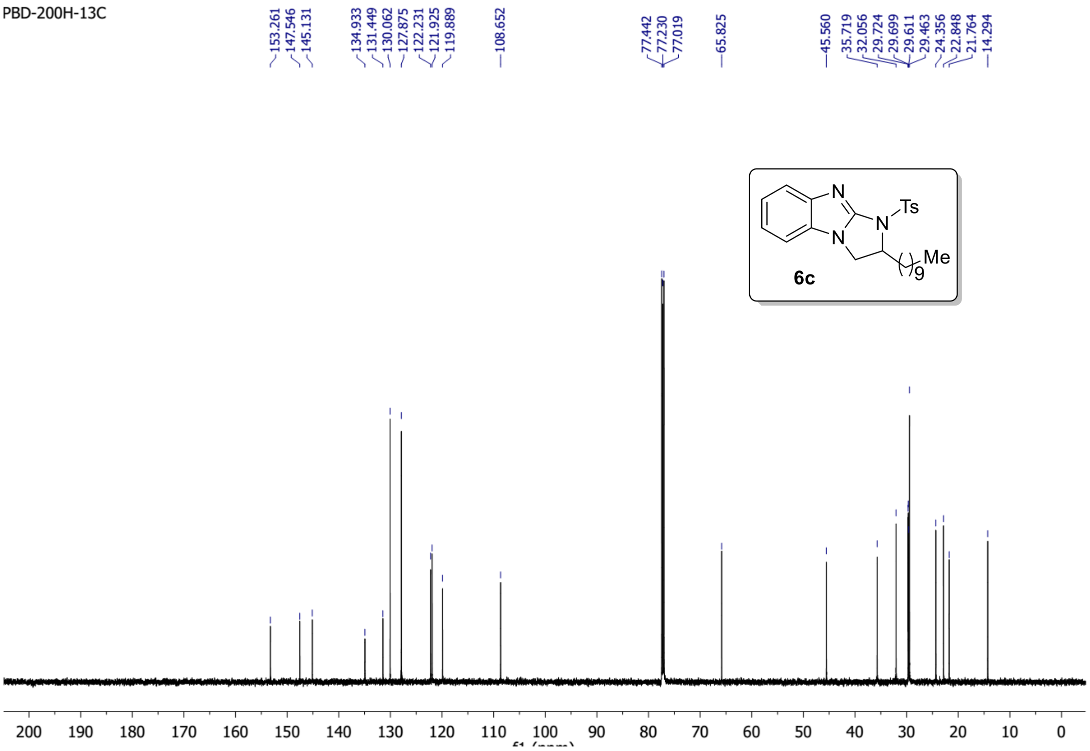


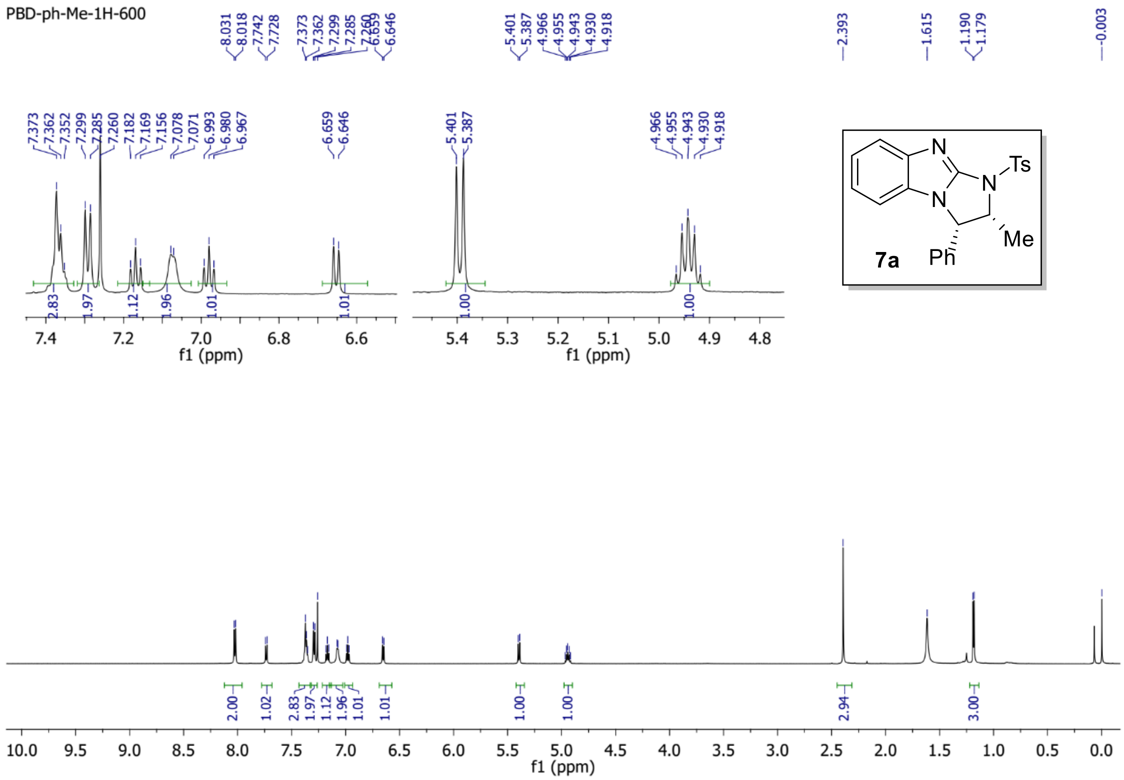
Peak Results

	RT	Height (μV)	% Area
1	12.255	1171237	90.12
2	16.176	105159	9.88

4.7 Selected NMR Spectra






PBD-ph-Me-1H-600
8.031
8.018
7.742
7.728
7.373
7.362
7.352
7.299
7.285
7.260
7.182
7.169
7.156
7.078
7.071
6.993
6.980
6.967
6.659
6.646
5.401
5.387
4.966
4.955
4.943
4.930
4.918
2.393
1.615
1.190
1.179
-0.003
2.83
1.97
1.12
1.96
1.01
1.01
1.00
1.00
2.00
1.02
2.94
3.00
N
N
N
Ts
Me
Ph
7a
f1 (ppm)
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
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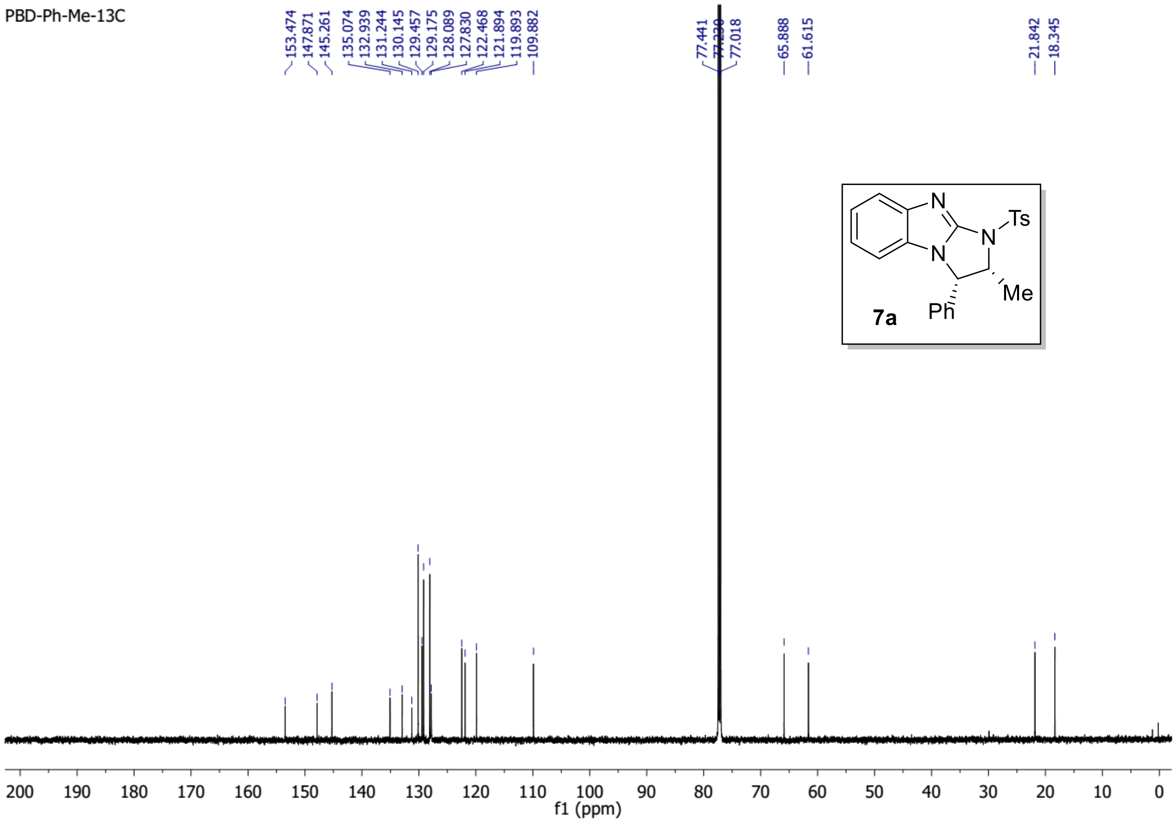
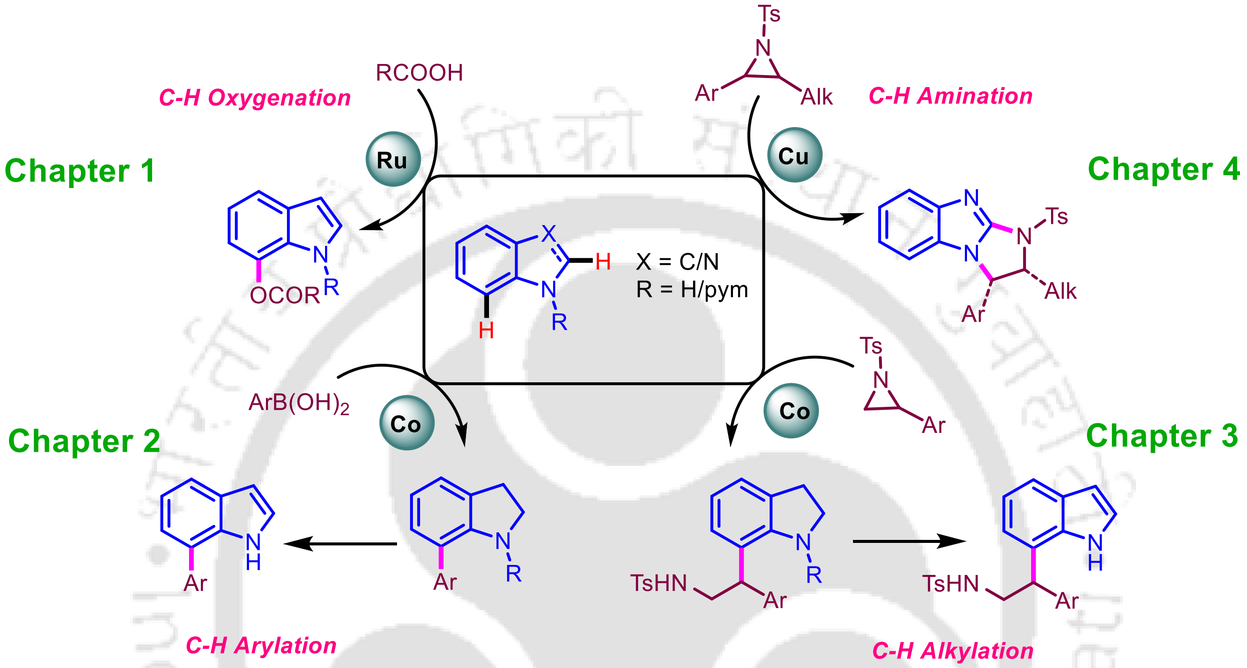
1.0
0.5
0.0


PBD-Ph-Me-13C
153.474
147.871
145.261
135.074
132.939
131.244
130.145
129.457
129.175
128.089
127.830
122.468
121.894
119.893
109.882
77.441
77.230
77.018
65.888
61.615
21.842
18.345
N
N
N
Ts
Me
Ph
7a
f1 (ppm)
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

Thesis Overview



Summary

In chapter 1, we presented Ru-catalyzed the C-H oxygenation of indolines at the C7 position with carboxylic acids as coupling partner and consequent oxidation to give C7-oxygenated indoles in good yields. This protocol is expedient and a series of alkyl, aryl, α, β-unsaturated and heterocyclic carboxylic acids having electron donating and electron withdrawing groups proceeded reaction with good to high yields.

In chapter 2, a Co-catalyzed C7-arylation of iondolines with arylboronic acids has been described using a removable pyrimidyl coordinating group, which can be further oxidized to C7-arylated indoles. The addition of the PCy_3 ligand, oxygen and HFIP as the solvent had a profound effect on the yield. The mechanistic studies concluded that the reaction may progress *via* a radical intermediate.

In chapter 3, we developed chelation assisted C7-alkylation of indolines using aziridines as an alkylating agent in presence of cost-effective cobalt as catalyst by merging C-H activation with ring cleavage at moderate temperature. This methodology offers the use of air stable Cp*Co(III)-catalysis, detection of a Co(III)-species by ESI-MS, post-synthetic application and late-stage removal of the directing group.

In chapter 4, a copper(II)-catalyzed stereo-invertive cross-coupling of *N*-alkyl/-sulfonyl 2-alkyl/-arylaziridines with benzimidazoles to construct functionalized dihydroimidazobenzimidazoles is presented via a ring opening followed by intramolecular C-H amination. Optically active 2-arylaziridines can be reacted to give functionalized heterocycles with high enantiomeric purities (77−97% ee). Switchable regioselectivity was perceived by varying substitution pattern on the aziridine ring.

List of Publications

1 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.

2 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.

3 Recent Advances in Radical Dioxygenation of Olefins

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

4 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.

5 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.

6 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.

7 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.

8 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.

9 Ru(II)-Catalysed 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.

10 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.

11 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.

12 Exploiting Strained Rings in Chelation Guided C-H Functionalization: Integration of C-H Activation with Ring Cleavage

Shah, T. A.; **De, P. B.;** Pradhan, S.; Banerjee, S.; Punniyamurthy, T. *Chem. Asian. J.* **2019** (DOI: 10.1002/asia.201901067).

Conferences

Oral Presentation

1 “Expedient Cobalt(II)-Catalyzed Site-Selective C7-Arylation of Indolines with Boronic Acids” **De, P. B.;** Pradhan, S.; Banerjee, S.; Punniyamurthy, T. *ORGANIX*, Tezpur University, Tezpur, Dec 20-21, 2018.

2 “Expedient Co(II)-Catalyzed Regioselective C7-Arylation of Indolines with Boronic Acids” **De, P. B.;** Pradhan, S.; Banerjee, S.; Punniyamurthy, T. *FICS*, IIT Guwahati, Guwahati, Dec 6-8, 2018.

3 “Copper-Catalyzed Regioselective Ring Opening of Aziridines/Aerobic Oxidative C-H Amination: A Facile Rote to Imidazobenzimidazoles” **De, P. B.;** Pradhan, S.; Punniyamurthy, T. *XIII J-NOST*, Banaras Hindu University, Varanasi, Nov 9-12, 2017.

Poster Presenatation

4 “Ligand-Accelerated Robust Cobalt(II)-Catalyzed Site-Selective C7-Arylation of Indolines with Boronic Acids” **De, P. B.;** Pradhan, S.; Banerjee, S.; Punniyamurthy, T. *Research Conclave*, IIT Guwahati, Guwahati, Mar 8-11, 2018.

5 “Ligand-Accelerated Expedient Cobalt(II)-Catalyzed Regio-Selective C7-Arylation of Indolines with Boronic Acids” **De, P. B.;** Pradhan, S.; Banerjee, S.; Punniyamurthy, T. *ICCHD*, University of Calcutta and Heritage Institute of Technology, Kolkata, Jan 8-10, 2018.

6 “Regioselective 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. *Chemconvene*, IIT Guwahati, July 27th 2017.

7 “Stereo-invertive 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. *Research Conclave*, IIT Guwahati, March 16-19th 2017.

8 “Copper-Catalyzed Streospecific Ring Opening of Aziridines/Aerobic Oxidative C-H Amination: A Facile Route to Imidazobenzimidazoles” **De, P. B.;** Pradhan, S.; Punniyamurthy, T. *20th CRSI National Symposium in Chemistry*, Gauhati University, Feb 2-5th, 2017.

9 “Copper-catalyzed regioselective ring opening of aziridines/aerobic oxidative C-H amination: a facile route to imidazobenzimidazoles” **De, P. B.;** Pradhan, S.; Punniyamurthy, T. *21st International Conference on Organic Synthesis (ICOS 21)*, IIT Bombay, Dec 11-16th, 2016.