Transition-Metal Catalyzed Regioselective C-C/C-Heteroatom Bond Formations: Access to Functionalized Arenes and Heterocycles

A Thesis Submitted

in Partial Fulfilment of the Requirements

for the Degree of

DOCTOR OF PHILOSOPHY

by

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Dedicated To

My Mother

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 — Tanumay Sarkar

December 2021

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CERTIFICATE

This is to certify that Mr. Tanumay Sarkar has been working under my supervision since July 2016. I am forwarding his thesis entitled "*Transition-Metal Catalyzed Regioselective C-C/C-Heteroatom Bond Formations: Access to Functionalized Arenes and 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
December 2021

Prof. Tharmalingam Punniyamurthy
Supervisor

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Tanumay Sarkar

List of Abbreviations

AcOH	acetic acid
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
AgF	silver fluoride
Ag_2O	silver oxide
1-$AdCO_2H$	1-adamantanecarboxylic acid
aq.	Aqueous
aq. HCl	aqueous hydrochloric acid
Ar	aryl
Bn	benzyl
Boc	*tert*-butoxycarbonyl
BQ	benzoquinone
Bz	benzoyl
B_2Pin_2	bis(pinacolato)diboron
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
COD	cyclooctadiene
Cy	cyclohexyl
p-cymene	4-isopropyltoluene

DG	directing group
D_2O	deuterium oxide
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DMSO	dimethylsulfoxide
DMAP	4-dimethylaminopyridine
DMF	*N*,*N*-dimethylformamide
DBU	diazabicyclo[5.4.0]undec-7-ene
DPPF	1,1'-bis(diphenylphosphino)ferrocene
EDG	electron donating group
eq	equation
equiv	equivalent
Et_3N	triethylamine
ESI	electrospray ionization
Et	ethyl
EWG	electron wthdrawing group
FT-IR	fourier transform infrared spectroscopy
FG	Functional group
het	heterocyclic
HRMS	high-resolution mass spectrometry
Hz	hertz
*i*PrOH	isopropyl alcohol
KBr	potassium bromide
K_2CO_3	potassium carbonate
K_3PO_4	Potassium phosphate tribasic
KOAc	potassium acetate
m/z	mass to charge ratio
mp	melting point
MS	molecular sieve
Me	methyl
MeOH	methanol
MHz	megahertz

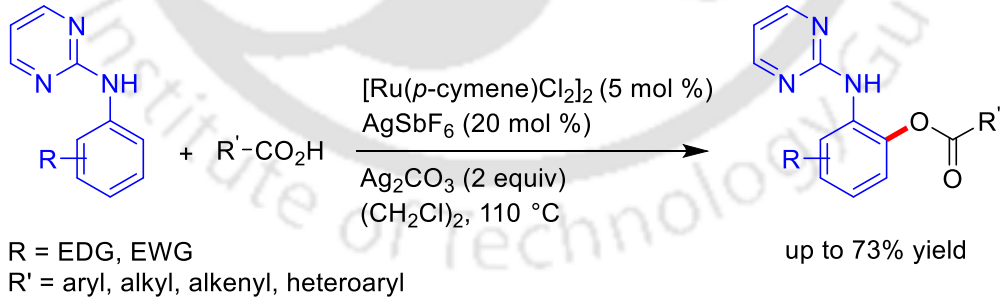
NMR	nuclear magnetic resonance
NMP	*N*-methyl-2-pyrrolidone
NBD	bicyclo[2.2.1]hepta-2,5-diene
ORTEP	oak ridge thermal ellipsoid plot
Oxa	2-phenyl-4,5-dihydrooxazole
Ph	phenyl
PA	picolinamide
R_f	retardation factor
rt	room temperature
py	pyridine
pym	pyrimidine
PPh_3	triphenyphosphine
PivOH	pivalic acid
SET	single-electron transfer
TFA	trifluoroacetic acid
Tf	trifluoromethanesulfonyl
TBHP	*tert*-butyl hydroperoxide
THF	tetrahydrofuran
TLC	thin layer chromatography
TsOH	*p*-toluenesulfonic acid
TMS	trimethylsilyl
TM	transition metal
μL	microliter
μW	microwave

Abstract

The thesis is divided into four chapters. The first chapter illustrates a Ru(II)-catalyzed site-selective C-H acyloxylation of *N*-aryl-2-pyrimidines with carboxylic acids as the acyl source. The second chapter describes a Ni(II)-catalyzed oxidative C-H heteroarylation of arenes with azoles utilizing a removable oxazoline-based directing auxiliary. The third chapter deals with the Bi(III)-catalyzed annulation of 2-naphthols with *N*-sulfonylaziridines. The fourth chapter demonstrates (3+3)-cycloaddition of aziridines with diaziridines for the stereospecific synthesis of triazines under Fe(III)-catalysis.

Chapter I. Ru(II)-Catalyzed Site-Selective C-H Acyloxylation of *N*-Aryl-2-pyrimidines with Carboxylic Acids

The transition-metal-catalyzed directing group assisted proximity-induced C−H functionalizations for the construction of C−C and C−heteroatom bonds have recently witnessed impeccable advancements. In this realm, the directed C-H oxygenation is one of the fascinating chemical transformations in synthetic community owing to the immense ubiquity of C-O bonds in bio-active natural products and pharmaceuticals. The utilization of carboxylic acids as the acyloxylating agent is appealing since it is less expensive and atom efficient. The present chapter describes a Ru(II)-catalyzed C-H acyloxylation of anilines with carboxylic acids with the aid of pyrimidine as a directing group (Scheme 1). This method offers a straightforward route for directly installing aryl, alkyl, heteroaryl, and α,β-unsaturated carboxylic acids with good yields.

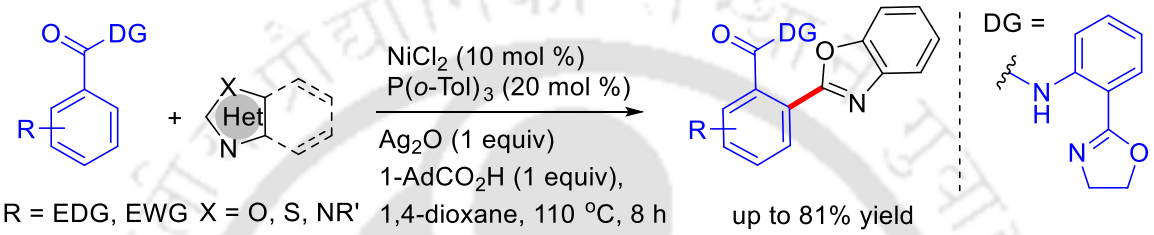


Scheme 1. Ru(II)-Catalyzed C-H Acyloxylation of *N*-Aryl-2-pyrimidines with Carboxylic Acids

Chapter II. Ni(II)-Catalyzed Cross-Dehydrogenative Coupling of Aromatic Amides with Azoles

Azoles and their synthetic scaffolds are the privileged building blocks and omnipresent in myriads of natural products, bio-active compounds and functional materials. The construction of hetero-

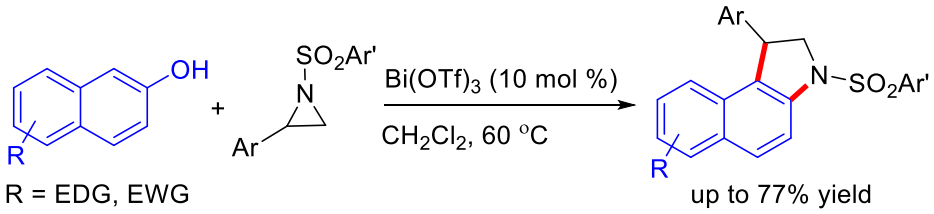
biaryl compounds comprising an azole unit are thus in great demand for drug discovery. On the other hand, being less-expensive and minimally toxic, the Ni-catalyzed C-H functionalizations has recently appeared as a sustainable synthetic tool. This chapter demonstrates a Ni(II)-catalyzed oxidative C-H/C-H cross-coupling of carboxamides with azoles using a removable oxazoline-based directing group (Scheme 2). The broad substrate scope with functional group diversity, mechanistic insights and late-stage modification of xanthine-derived drugs are the important features of the protocol.



Scheme 2. Ni(II)-Catalyzed Oxidative C-H/C-H Cross-Coupling of Carboxamides with Azoles

Chapter III. Bi(III)-Catalyzed Annulation of Aziridines with 2-Naphthols: Synthesis of Functionalized Benzoindolines and Benzoindoles

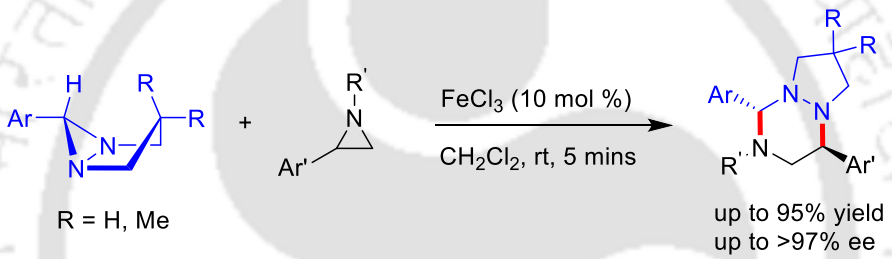
In the realm of aza-heterocyclic compounds, indolines and their synthetic congeners play a predominant role and exhibit potential therapeutic applications. Consequently, the designing of synthetic strategies for their construction using simple building blocks is highly desirable. In this vein, the Lewis acid catalyzed cycloaddition of aziridines provides a potential route to access a library of nitrogen-containing heterocycles. In this chapter, we disclosed a regioselective Bi(III)-catalyzed annulation of 2-naphthols with *N*-sulfonylaziridines to access a library of benzoindoline derivatives (Scheme 3). The scope was extended to the one-pot construction of functionalized benzoindoles in the presence of DDQ as an oxidant. The reaction proceeds *via* an S_N1 pathway, involving regioselective ring-opening of aziridine, followed by nucleophilic addition with 2-naphthol and subsequent dehydrative intramolecular cyclization.



Scheme 3. Bi(III)-Catalyzed Annulation of Aziridines with 2-Naphthols

Chapter IV. Fe(III)-Catalyzed (3+3)-Cycloaddition of Aziridines with Diaziridines: Stereospecific Synthesis of Triazines

[1,2,4]-Triazines represent a pivotal class of aza-heterocycles being featured in the potent and value-added pharmacophores. The metal-catalyzed (3+n)-cycloaddition reactions using three-membered rings have emerged as a powerful means for synthesizing heterocyclic scaffolds as the release of considerable ring strain provides thermodynamic driving force for ring cleavage. Diaziridines, having two adjacent nitrogen centres, serve as a versatile 1,3-zwitterionic component in a diverse array of cycloaddition reactions. In this chapter, we have established a convenient method to synthesize [1,2,4]-triazines via (3+3)-cycloaddition of bicyclic diaziridines with *N*-alkyl aziridines under Fe(III)-catalysis (Scheme 4). This protocol paves the way for the annulation of two distinct three-membered rings, resulting in a new class of fused heterocycles.

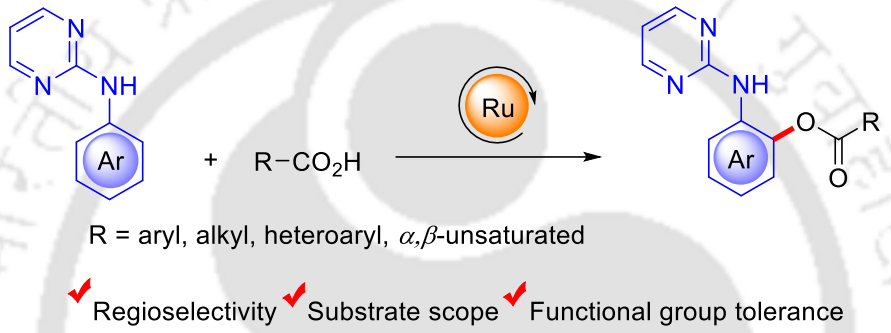


Scheme 4. Fe(III)-Catalyzed (3+3)-Cycloaddition of Aziridines with Diaziridines

Contents

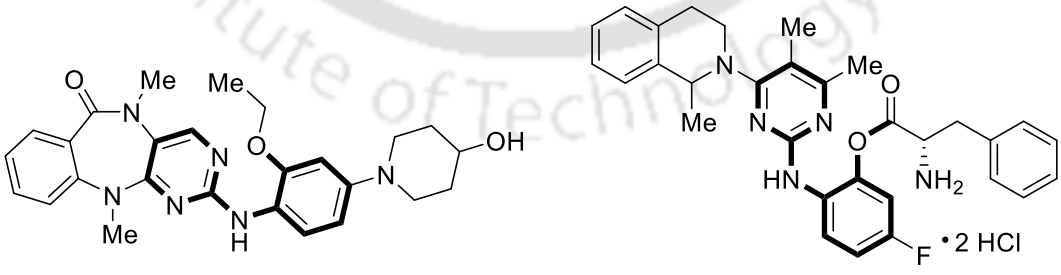
Chapter I

Ru(II)-Catalyzed Site-Selective C-H Acyloxylation of N-Aryl-2-pyrimidines with Carboxylic Acids



Ru(II)-Catalyzed Site-Selective C-H Acyloxylation of *N*-Aryl-2-pyrimidines with Carboxylic Acids

The transition-metal-catalyzed proximity-induced functionalization of unreactive C-H bonds using directing group (DG) has emerged as a potential synthetic tool to synthesize various carbogenic scaffolds.[1] The aim of DG is to coordinate with the metal and bring it into the close proximity of a particular C-H bond, resulting in selective cleavage and subsequent functionalization. In this realm, the directed C-H oxygenation[2] is one of the highly sought-after transformations due to the ubiquity of C-O bonds in bio-active pharmaceuticals, agrochemicals and functional materials (Figure 1).[3] Despite significant advances made in directed C-H acyloxylation using Cu- and Pd-based catalytic systems with $PhI(OAc)_2$, acid halide, anhydride, sodium carboxylate and *tert*-butyl peroxyacetate as acyl sources,[4-6] the reaction with carboxylic acid as the acyl source is scarce. The utilization of carboxylic acids as the acyloxylating agent is attractive as it is readily available.[7] In general, this sort of transformation has been accomplished primarily through the use of Pd, Cu, Co, Rh and Ru based catalysts. On the other hand, as an imperative moiety in value-added and potent pharmacophores,[8] the pyrimidine based strong σ-coordinating DG is used for the C-H functionalizations.[9] In this chapter, we described an efficient Ru(II)-catalyzed[10,11] acyloxylation of anilines with carboxylic acids *via ortho*-C(sp^2)-H functionalization using pyrimidine as a DG. This approach offers a viable way for directly introducing aryl, alkyl, heteroaryl and *α,β*-unsaturated carboxylic acids at the *ortho*-position of aniline moieties, which will have uses in biological and medical sciences.



retinoid X receptor antagonist

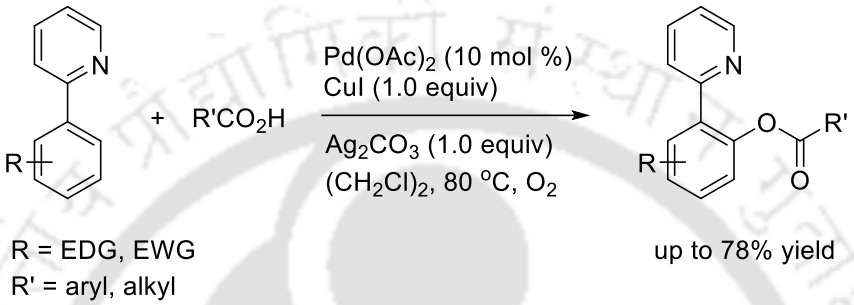
anti-secretory activity

Figure 1. Examples of Biologically Active Aminopyrimidine Derivatives.

1.1 Literature Study

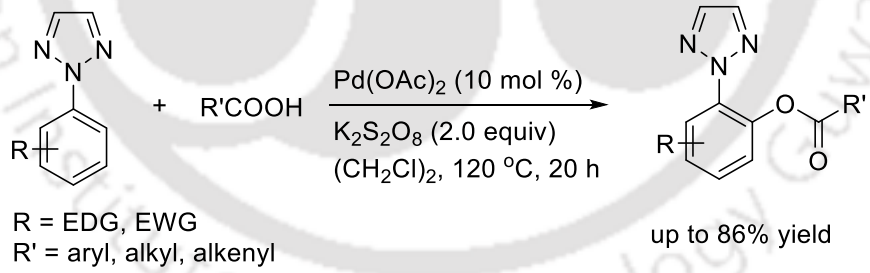
1.1.1 Pd-Catalyzed C-H Acyloxylation of Arenes

A Pd(II)-catalyzed regioselective acyloxylation of 2-arylpyridines was demonstrated by Zhong and co-workers using diversely substituted carboxylic acids under oxygen atmosphere (Scheme 1).[12] Notably, electron-donating carboxylic acids showed good reactivity, while strong electron-withdrawing functionalities failed to deliver the desired products.



Scheme 1. Pd(II)-Catalyzed Acyloxylation of 2-Arylpyridines

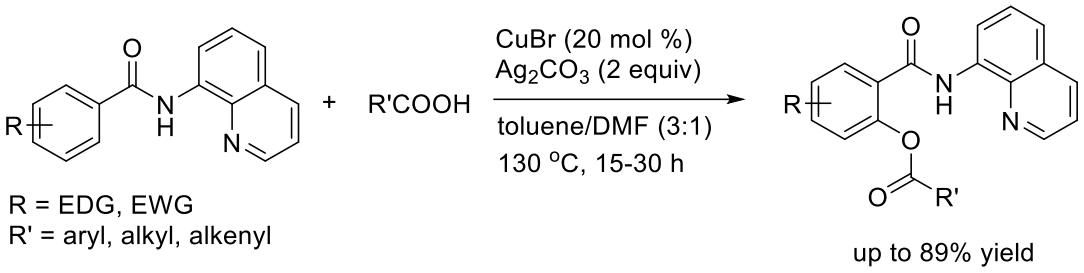
Kuang and co-workers described the *ortho*-selective acyloxylation of 1,2,3-triazoles with aryl, alkyl and α,β-unsaturated carboxylic acids under Pd(II)-catalysis (Scheme 2).[13] A variety of substituents with diverse electronic properties were well compatible in delivering the desired targets in moderate to good yields.



Scheme 2. Pd(II)-Catalyzed Acyloxylation of 1,2,3-Triazoles

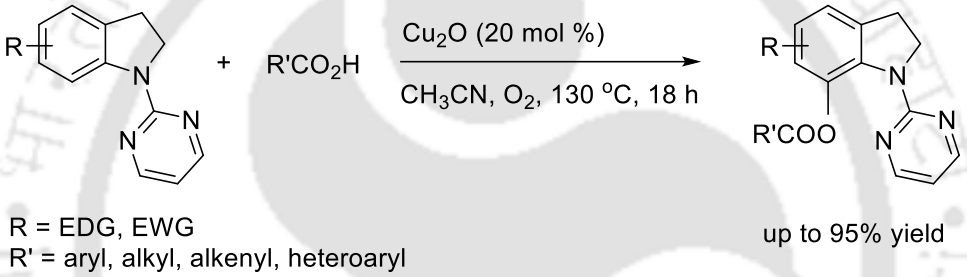
1.1.2 Cu-Catalyzed C-H Acyloxylation of Arenes

A Cu(I)-catalyzed 8-aminoquinolinamide-directed *ortho*-acyloxylation of aryl amides was reported by Zhang and co-workers (Scheme 3).[14] This additive free protocol exhibited good functional group tolerance and mono-selectivity.



Scheme 3. Cu(I)-Catalyzed Acyloxylation of Aromatic Amides

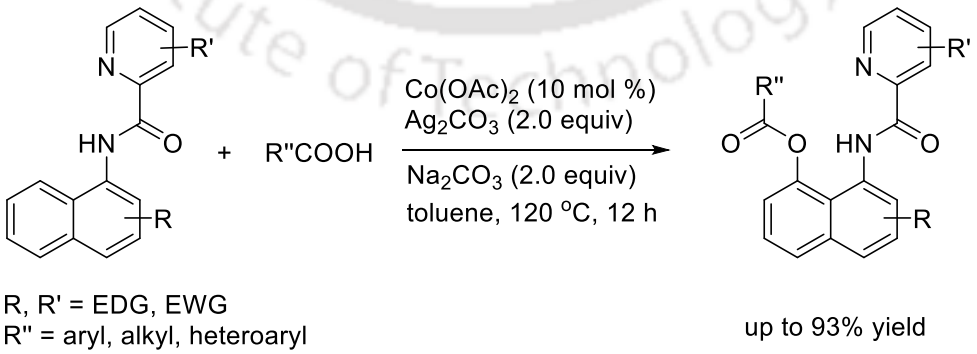
Koley and co-workers disclosed a Cu-catalyzed dehydrogenative coupling of indoline with a diverse array of aryl, alkyl, heteroaryl and α,β-unsaturated carboxylic acids using 2-pyrimidine moiety as a DG and oxygen as the oxidant (Scheme 4).[15] Radical trapping studies and H/D exchange experiment shed light into the reaction pathway.



Scheme 4. Cu-Catalyzed C7-Selective C-H Oxygenation of Indolines

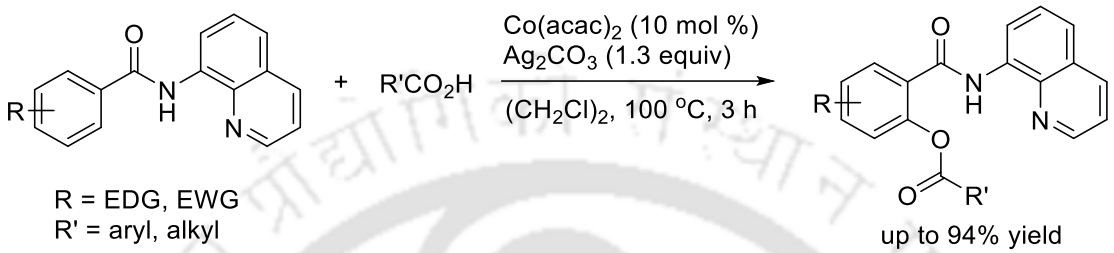
1.1.3 Co-Catalyzed C-H Acyloxylation of Arenes

Zeng and co-workers described a picolinamide-directed C(sp^2)-H oxygenation of naphthylamines employing various carboxylic acids to afford the corresponding acyloxylated products in moderate to good yields under Co(II)-catalysis (Scheme 5).[16] The utilization of inexpensive cobalt salt as catalyst and broad functional group tolerance are the important practical features.



Scheme 5. Co(II)-Catalyzed Acyloxylation of 1-Naphthylamines

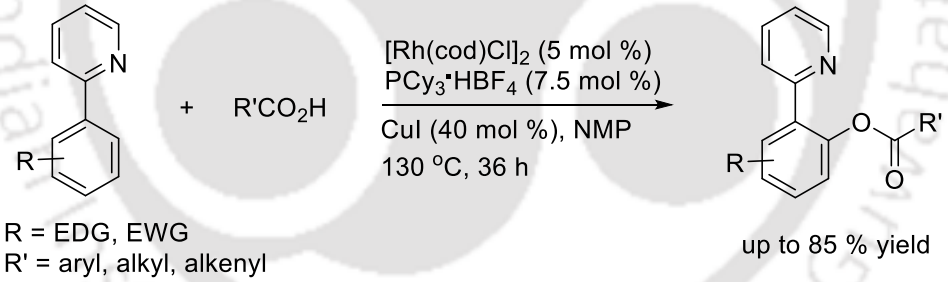
Acyloxylation of benzamides with substituted aryl and alkyl carboxylic acids in the presence of $Co(acac)_2$ as catalyst was developed using 8-aminoquinoline moiety as the bidentate DG under aerobic condition (Scheme 6).[17] The method offers facile access to mono-acyloxylated *N*-(quinolin-8-yl)benzamides with functional group diversities. Kinetic isotope experiment revealed that C-H bond cleavage may not be involved in the rate determining step.



Scheme 6. Co(II)-Catalyzed C-H Oxygenation of Aromatic Amides

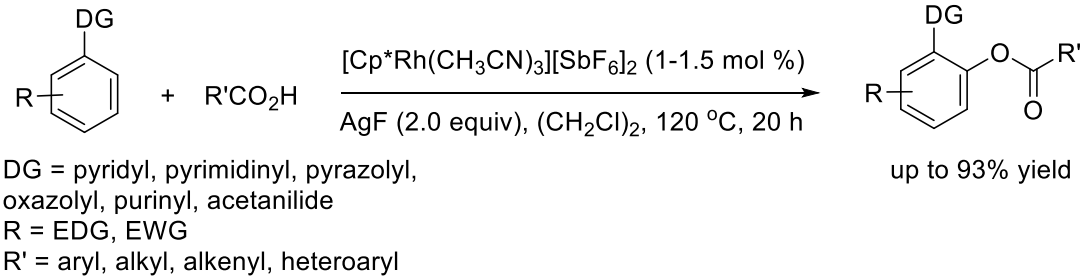
1.1.4 Rh-Catalyzed C-H Acyloxylation of Arenes

Cheng and co-workers demonstrated a Rh(I)-catalyzed *ortho*-acyloxylation of 2-arylpyridines (Scheme 7).[18] This strategy was found to be compatible with aryl, alkyl and α,β-unsaturated carboxylic acids with good yields.



Scheme 7. Rh(I)-Catalyzed *ortho*-Acyloxylation of 2-Arylpyridines

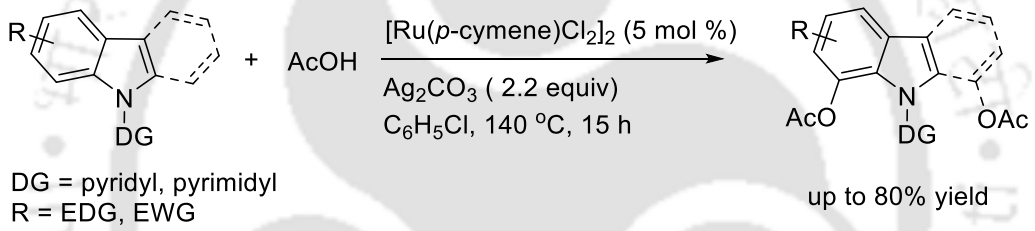
A Rh-complex catalyzed regioselective oxygenation of C(sp^2)-H bonds utilizing diverse *N*- and *O*-coordinating DGs was achieved by Li and co-workers using AgF as the sole oxidant (Scheme 8).[19] Late-stage modification of bio-active compounds such as fenbufen, dehydrocholic, glycyrrhetinic and estrone-derived carboxylic acid were demonstrated to showcase the efficacy of the protocol.



Scheme 8. Rh-Catalyzed Acyloxylation using Carboxylic Acids

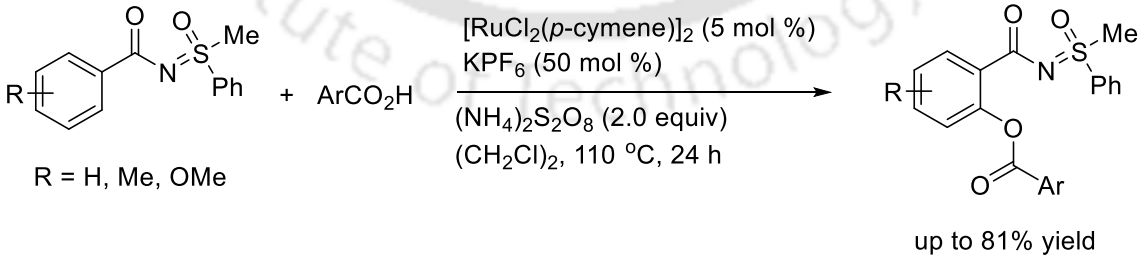
1.1.5 Ru-Catalyzed C-H Acyloxylation of Arenes

Miura and co-workers reported a facile Ru(II)-catalyzed positional selective acetoxylation of indoles and carbazoles with acetic acid (Scheme 9).[20] The methodology lays forth a straightforward route for the construction of privileged scaffolds with broad functional group tolerance.



Scheme 9. Ru(II)-Catalyzed C-H Acetoxylation of Indoles and Carbazoles

Ackermann and co-workers reported a removable sulfoximine-assisted *ortho* C-H acyloxylation of benzoic acid derivatives employing Ru(II)-catalyst in combination with KPF_6 as an additive and $(NH_4)_2S_2O_8$ as an oxidant (Scheme 10).[21] The reaction displays high functional group tolerance and the removal of the DG highlights the utility of the procedure.



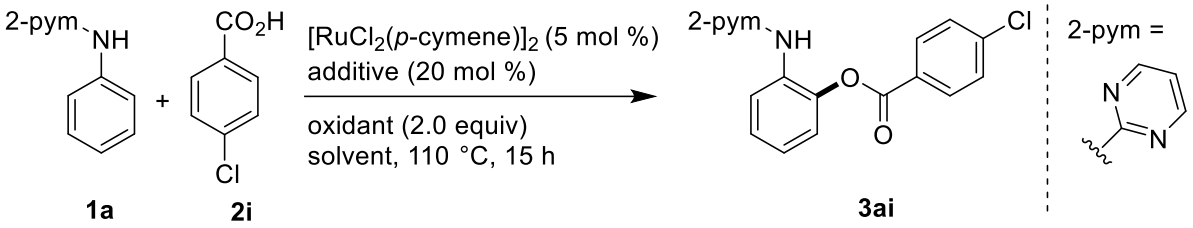
Scheme 10. Ru(II)-Catalyzed Acyloxylation of Sulfoximine Benzamides

1.2 Present Study

Herein a Ru(II)-catalyzed *ortho*-selective acyloxylation of *N*-aryl-2-pyrimidines with carboxylic acids is described utilizing 2-pyrimidine as a DG auxiliary. We commenced the optimization studies using *N*-phenylpyrimidin-2-amine **1a** and 4-chlorobenzoic acid **2i** as the standard substrates with a series of catalysts, additives, oxidants and solvents (Table 1). Gratifyingly, **3ai** was formed in 39% yield when the mixture of **1a** and **2a** was stirred in 1,2-dichloroethane using 5 mol % $[RuCl_2(p\text{-cymene})]_2$, 20 mol % AgOTf and 2 equiv Ag_2CO_3 at 110 °C for 15 h under inert atmosphere (entry 1). Screening of additives led to an improvement in yield to 72% using $AgSbF_6$, while $AgBF_4$ and KPF_6 showed inferior results (entries 2-4). Among the oxidants screened, Ag_2CO_3, $Cu(OAc)_2$, $K_2S_2O_8$, AgOAc and Ag_2O, Ag_2CO_3 furnished the best result (entries 5-8). In a set of solvents surveyed, 1,2-dichloroethane was found to be superior than 1,4-dioxane, THF, MeOH and DMF (entries 9-12). The reactions using $RuCl_3$, $RuCl_2(PPh_3)_3$, $Co(OAc)_2$ and $Pd(OAc)_2$ failed to produce the intended product (entries 13-16). Control experiments without entailing $AgSbF_6$ and Ag_2CO_3 did not give the oxygenated product, which suggest the crucial role of Ag_2CO_3 and $AgSbF_6$ (entries 17-18).

With the optimized reaction conditions, the scope of the protocol was investigated employing diversely functionalized carboxylic acids (Table 2). Aryl and alkyl carboxylic acids comprising both electron-donating and electron-withdrawing functionalities were compatible. The reaction of unsubstituted benzoic acid **2a** delivered **3aa** in 72% yield. Similarly, 2-bromo **2b**, 2-chloro **2c**, 2-methyl **2d**, 2-acetoxy **2e**, 3-chloro **2f** and 3-nitro **2g** substituted benzoic acids provided **3ab-ag** in 61-71% yields. 4-Substituted benzoic acids having bromo **2h**, fluoro **2j**, methyl **2k**, methoxy **2l**, trifluoromethyl **2m** and phenyl **2n** groups successfully delivered **3ah-an** in 59-73% yields. Further, 3,4-dimethyl **2o** and 1-naphthyl **2p** carboxylic acids were amenable, delivering **3ao** and **3ap** in 63 and 64% yields, respectively. With these intriguing results, the scope of the procedure was extended for alkyl carboxylic acids. Acetic acid **2q**, propionic acid **2r**, pivalic acid **2s** and the sterically encumbered 1-adamantanecarboxylic acid **2t** underwent reaction to give **3aq-at** in 62-73% yields. The reactions using 2-phenylacetic acid **2u**, 2-(4-methoxyphenyl)acetic acid **2v** and 1-naphthylacetic acid **2w** underwent efficiently to afford **3au-aw** in 63-67% yields.

Table 1. Optimization of Reaction Conditions[a]

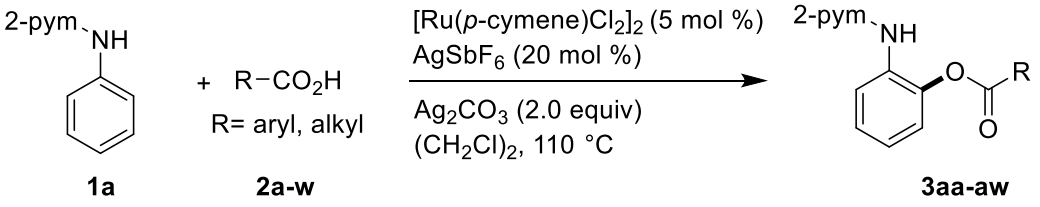


1a **2i** **3ai**

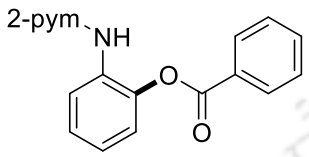
Entry	Additive	Oxidant	Solvent	Yield (%)[b]
1	AgOTf	Ag_2CO_3	$(CH_2Cl)_2$	39
2	$AgBF_4$	Ag_2CO_3	$(CH_2Cl)_2$	25
3	KPF_6	Ag_2CO_3	$(CH_2Cl)_2$	43
4	**$AgSbF_6$**	**Ag_2CO_3**	**$(CH_2Cl)_2$**	**72**
5	$AgSbF_6$	$Cu(OAc)_2$	$(CH_2Cl)_2$	0
6	$AgSbF_6$	$K_2S_2O_8$	$(CH_2Cl)_2$	27
7	$AgSbF_6$	AgOAc	$(CH_2Cl)_2$	21
8	$AgSbF_6$	Ag_2O	$(CH_2Cl)_2$	12
9	$AgSbF_6$	Ag_2CO_3	1,4-dioxane	59
10	$AgSbF_6$	Ag_2CO_3	THF	64
11	$AgSbF_6$	Ag_2CO_3	MeOH	23
12	$AgSbF_6$	Ag_2CO_3	DMF	47
13	$AgSbF_6$	Ag_2CO_3	$(CH_2Cl)_2$	0[c]
14	$AgSbF_6$	Ag_2CO_3	$(CH_2Cl)_2$	18[d]
15	$AgSbF_6$	Ag_2CO_3	$(CH_2Cl)_2$	0[e]
16	$AgSbF_6$	Ag_2CO_3	$(CH_2Cl)_2$	0[f]
17	$AgSbF_6$	-	$(CH_2Cl)_2$	0
18	-	Ag_2CO_3	$(CH_2Cl)_2$	0

[a]Reaction conditions: **1a** (0.2 mmol), **2i** (0.24 mmol), $[RuCl_2(p\text{-cymene})]_2$ (5 mol %), additive (20 mol %), oxidant (0.4 mmol), solvent (2.0 mL), 110 °C, 15 h, N_2. [b]Isolated yield. [c]$RuCl_3$ used. [d]$RuCl_2(PPh_3)_3$ used. [e]$Co(OAc)_2$ used. [f]$Pd(OAc)_2$ used.

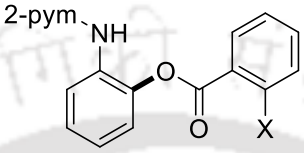
Table 2. Reaction of Aryl and Alkyl Carboxylic Acids with **1a**[a,b]



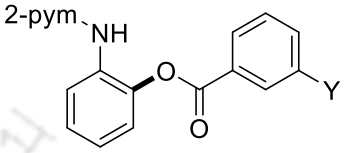
aryl carboxylic acids



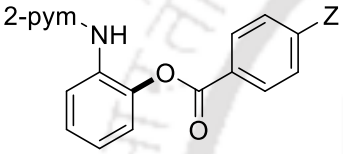
3aa, 72%, 15 h



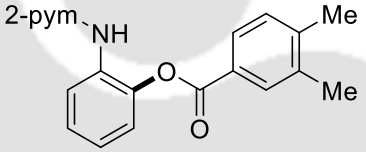
X= Br, **3ab**, 63%, 16 h
X= Cl, **3ac**, 65%, 16 h
X= Me,**3ad**, 69%, 14 h
X= OCOMe, **3ae**, 66%, 17 h



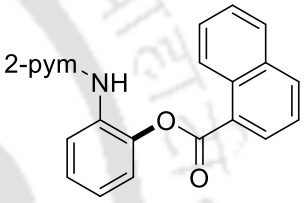
Y= Cl, **3af**, 71%, 15 h
Y= NO_2, **3ag**, 61%, 16 h



Z= Br, **3ah**, 67%, 14 h
Z= F, **3aj**, 65%, 17 h
Z= Me, **3ak**, 73%, 14 h
Z= OMe, **3al**, 68%, 15 h
Z= CF_3, **3am**, 59%, 18 h
Z= Ph, **3an**, 67%, 15 h

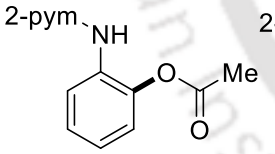


3ao, 63%, 15 h

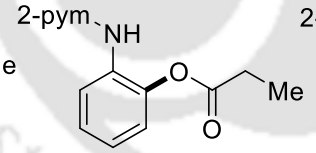


3ap, 64%, 16 h

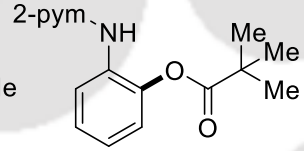
alkyl carboxylic acids



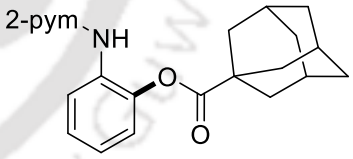
3aq, 73%, 14 h



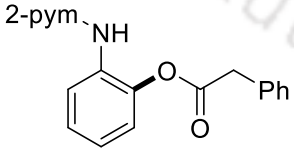
3ar, 62%, 15 h



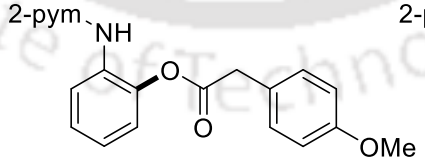
3as, 69%, 15 h



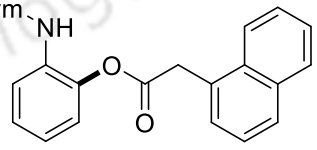
3at, 65%, 18 h



3au, 63%, 17 h



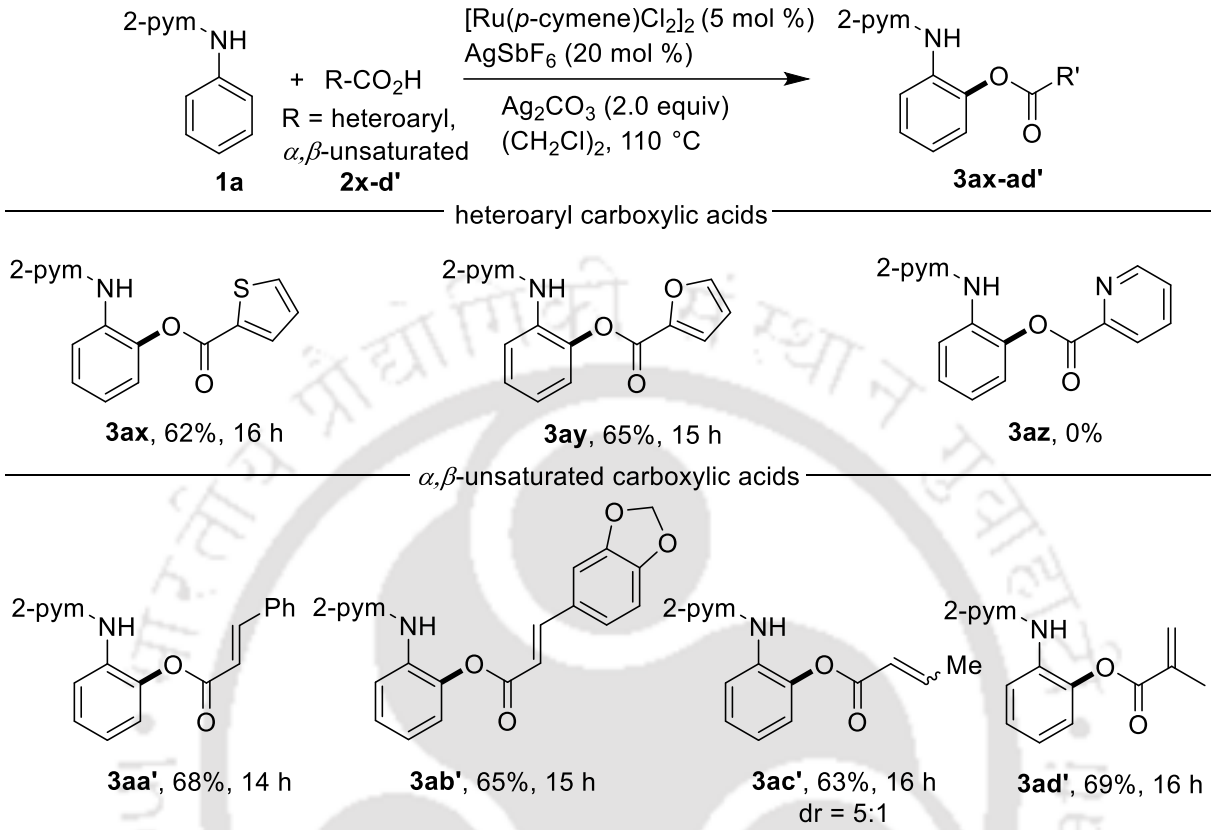
3av, 66%, 15 h



3aw, 67%, 16 h

[a]Reaction conditions: **1a** (0.2 mmol), **2a-w** (0.24 mmol), $[RuCl_2(p\text{-cymene})]_2$ (5 mol %), $AgSbF_6$ (20 mol %), Ag_2CO_3 (0.4 mmol), $(CH_2Cl)_2$ (2.0 mL), 110 °C, N_2. [b]Isolated yield.

Table 3. Reaction of heteroaryl and α,β-unsaturated Carboxylic Acids with **1a**[a,b]

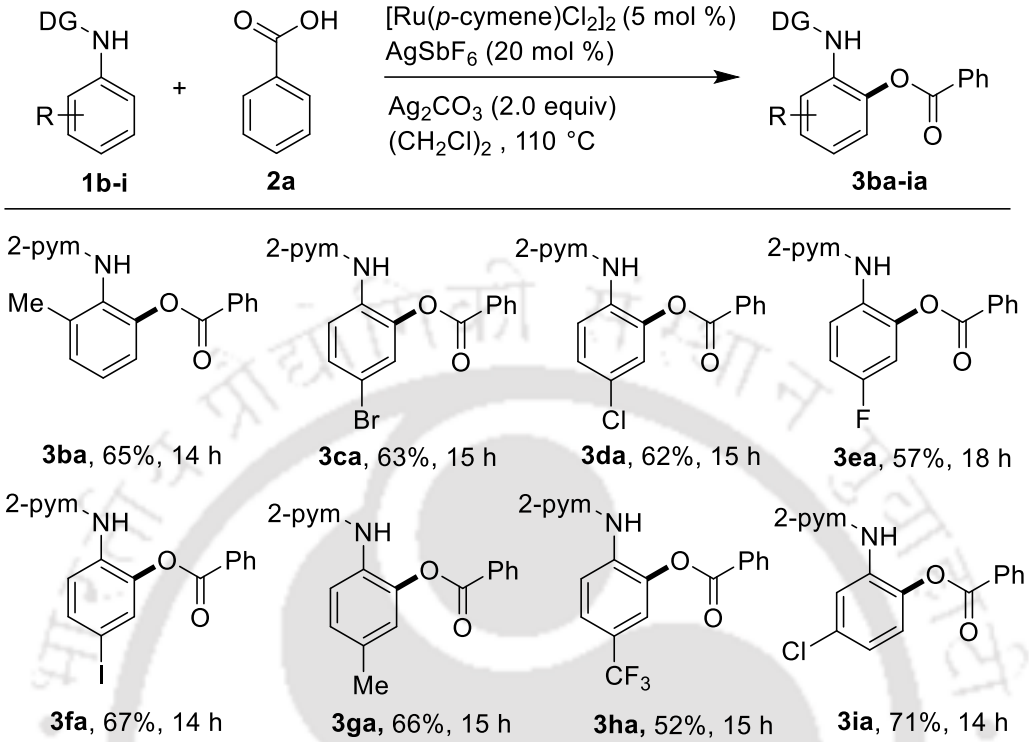


[a]Reaction conditions: **1a** (0.2 mmol), **2x-d'** (0.24 mmol), $[RuCl_2(p\text{-cymene})]_2$ (5 mol %), $AgSbF_6$ (20 mol %), Ag_2CO_3 (0.4 mmol), $(CH_2Cl)_2$ (2.0 mL), 110 °C, N_2. [b]Isolated yield.

The scope of the method was expanded for the coupling of heteroaryl and α,β-unsaturated carboxylic acids (Table 3). Carboxylic acids bearing 2-thiophenyl **2x** and 2-furanyl **2y** successfully coupled to give **3ax** and **3ay** in 62 and 65% yields, respectively. In contrary, 2-picolinic acid **2z** was an unsuccessful substrate, which may be because of the complex formation with Ru-species. However, α,β-unsaturated substrates, cinnamic **2a'** and (*E*)-3-(benzo[*d*][1,3]dioxol-5yl)acrylic **2b'** and methacrylic **2d'** acids, participated to deliver **3aa', 3ab'** and **3ad'** in 68%, 65% and 69% yields, respectively, while but-2-enoic acid **2c'** gave **3ac** in a 5:1 mixture of isomers.

Next, the reaction of a series of diversely substituted *N*-aryl-2-pyrimidines **1b-i** was examined employing benzoic acid **2a** as the standard substrate (Table 4). The substrate **1b** with a methyl group at the 2-position of the aryl ring furnished **3ba** in 65% yield. Similarly, the substrates having

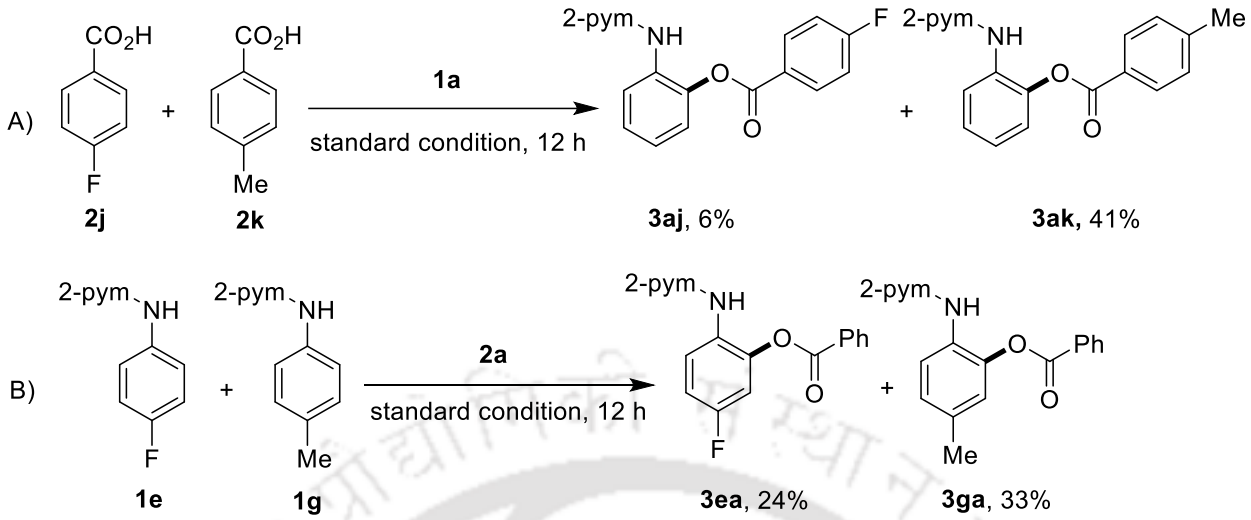
Table 4. Reaction of *N*-aryl-2-pyrimidines with **2a**[a,b]



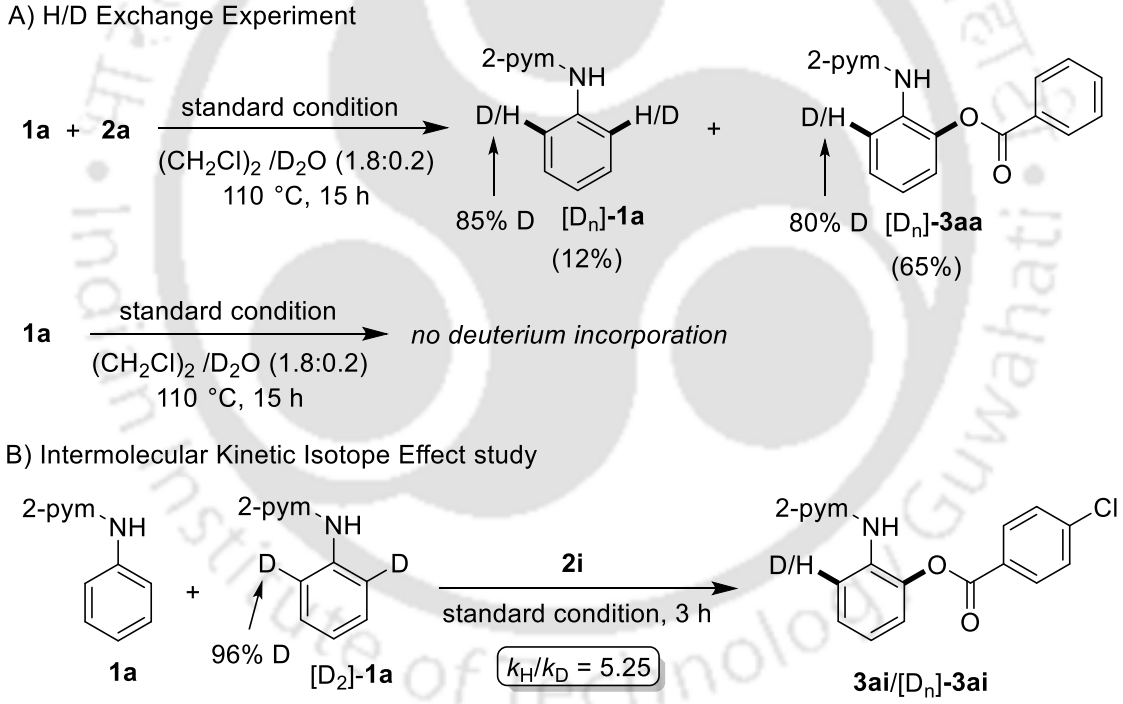
[a]Reaction conditions: **1b-i** (0.2 mmol), **2a** (0.24 mmol), $[RuCl_2(p\text{-cymene})]_2$ (5 mol %), $AgSbF_6$ (20 mol %), Ag_2CO_3 (0.4 mmol), $(CH_2Cl)_2$ (2.0 mL), 110 °C, 15 h, N_2. [b]Isolated yield.

4-bromo **1c**, 4-chloro **1d**, 4-fluoro **1e**, 4-iodo **1f**, 4-methyl **1g** and 4-trifluoromethyl **1h** groups in the aryl ring participated to afford **3ca-ha** in 52-67% yields. Further, the 3-chloro substituted **1i** produced **3ia** in 71% yield. These findings indicate that a wide variety of aryl, alkyl, heteroaryl and α,β-unsaturated carboxylic acids capable of delivering the oxygenated products in high yields.

To get an understanding of the reaction pathway, intermolecular competitive experiments were performed. The reaction of benzoic acid with an electron-rich 4-methyl group **2k** showed greater efficacy than that of benzoic acid with electron-withdrawing 4-fluoro group **2j** (Scheme 11A). This might be due to the higher nucleophilicity of the conjugate base of carboxylic acid with high pKa value which could aid in the rapid formation of active Ru-carboxylate species **I**. In addition, the electron-donating 4-methyl group **1g** in *N*-aryl-2-pyrimidine was found to be more reactive than the electron deficient 4-fluoro group **1e**, suggesting the involvement of an electrophilic substitution



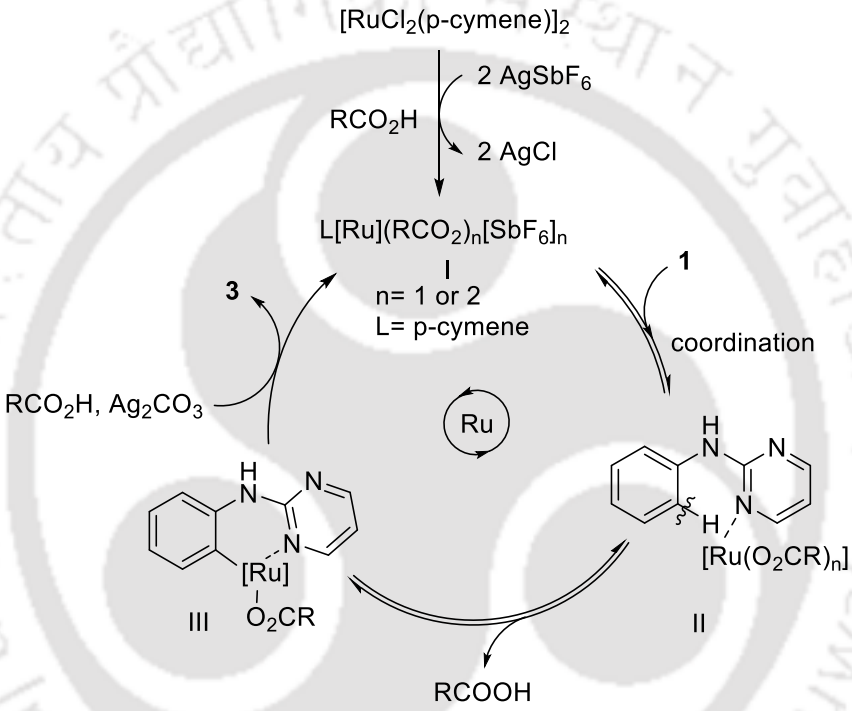
Scheme 11. Intermolecular Competition Experiments



Scheme 12. Mechanistic Investigations

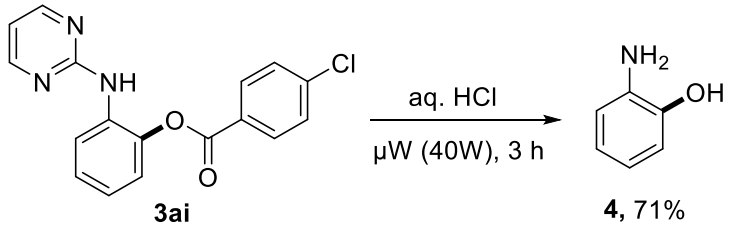
type C-H metalation (Scheme 11B). The H/D scrambling experiment of **1a** in the absence of **2a** using D_2O as the co-solvent showed no deuterium incoporation, while in the presence of **2a**, significant deuterium incorporation was witnessed in the re-isolated [D_n]-**1a** and the acyloxylated [D_n]-**3aa**, implying the reversible cleavage of the C-H bond (Scheme 12A). Further, intermolecular kinetic isotope experiment using **1a** and [D_2]-**1a** with **2i** gave a k_H/k_D = 5.25 (Scheme 12B). This

result suggests that the C-H bond cleavage might be involved in the rate-determining step. The mechanism proceeds through the formation of Ru-complex **I** using $[RuCl_2(p\text{-cymene})]_2$ and $AgSbF_6$ with carboxylic acid (Scheme 13).[7b,f] Subsequent reversible co-ordination with the pyrimidyl-nitrogen may give intermediate **II**, which can lead to *ortho*-C(sp^2)-H activation to furnish six-membered ruthenacycle intermedaite **III**. The eductive elimination of **III** can give the target product and the Ag(I)-mediated oxidation can regenerate the active Ru-species to complete the catalytic cycle



Scheme 13. Plausible Catalytic Cycle

To illustrate the synthetic utility of the procedure, acid hydrolysis of **3ai** was accomplished in the presence of aq. HCl (Scheme 14).[9d] The reaction occurred efficiently under microwave irradiation to produce 2-aminophenol **4** in 71% yield.



Scheme 14. Acid Hydrolysis of **3ai**

In summary, a Ru-catalyzed site-selective C-H acyloxylation of *N*-aryl-2-pyrimidines using carboxylic acids as the acyl source was demonstrated. The reaction of a broad range of aryl, alkyl, heteroaryl and *α,β*-unsaturated carboxylic acids has been accomplished with good functional group tolerance. The substrate scope, mechanistic insights and regioselectivity are the important practical features.

1.3 Experimental Section

General Information. Carboxylic acids, $[RuCl_2(p\text{-cymene})]_2$ (97%), $RuCl_3$ (45-55%), $RuCl_2(PPh_3)_3$ (97%), $Co(OAc)_2$ (99.995%), $Pd(OAc)_2$ (99.9%), $AgSbF_6$ (98%) and Ag_2CO_3 (99%) were purchased from Aldrich and used as received. *N*-Aryl-2-pyrimidines[9a,b] were prepared according to literature procedure. SRL silica gel G/GF 254 plates were used for analytical TLC and SRL silica gel (100-200 mesh) was used for column chromatography. NMR spectra were recorded with Varian DRX-400, Bruker Ascend 400 and Bruker Avance III 600 MHz spectrometers using $CDCl_3$ or DMSO-d_6 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, dd = doublet of doublets. Melting points were determined using a Büchi B-540 apparatus and are uncorrected. FT-IR spectra were collected on Perkin Elmer IR spectrometer. Q-Tof ESI-MS instrument (model HAB 273) was used for recording mass spectra. Single crystal X-ray data were collected on a Bruker SMART APEX equipped with a CCD area detector using Mo/Kα radiation and the structure was solved by direct method using *SHELXL-14* (Göttingen, Germany). Microwave reaction was carried out in sealed vessel using CEM Discover Microwave reactor fitted with external IR sensor that monitor the surface temperature of the reaction vessel.

Procedure for C-H Oxygenation of Arenes with Carboxylic acids. *N*-Aryl-2-pyrimidine (0.2 mmol), carboxylic acid (0.24 mmol), $[RuCl_2(p\text{-cymene})]_2$ (5.0 mol %, 6 mg), $AgSbF_6$ (20 mol %, 13.7 mg) and Ag_2CO_3 (0.4 mmol, 110 mg) were stirred at 110 °C in 1,2-dichloroethane (2.0 mL) under inert atmosphere for the appropriate time. The progress of the reaction was monitored by TLC using hexane and ethyl acetate as eluent. After completion, it was cooled to room temperature, diluted with dichloromethane (10 mL) and passed through a short pad of celite using dichloromethane (50 mL). Drying (Na_2SO_4) and evaporation of the solvent gave a residue that was purified on silica gel column chromatography using ethyl acetate and hexane as eluent.

Competition Experiment using Acids 2j and 2k. *N*-Phenylpyrimidin-2-amine **1a** (17 mg, 0.1 mmol), **2j** (14 mg, 0.1 mmol), **2k** (13.6 mg, 0.1 mmol), $[RuCl_2(p\text{-cymene})]_2$ (3.0 mg, 5.0 mol %), $AgSbF_6$ (7.0 mg, 20 mol %), Ag_2CO_3 (55.2 mg, 0.2 mmol) and 1,2-dichloroethane (1.0 mL) were subjected to the reaction conditions described in the general procedure for 12 h and **3aj** and **3ak** were formed in 6 and 41% yields, respectively.

Competition Experiment using *N*-Aryl-2-pyrimidines 1e and 1g. The reaction of **1e** (18.9 mg, 0.1 mmol) and **1g** (18.5 mg, 0.1 mmol) with benzoic acid **2a** (12.2 mg, 0.1 mmol) was performed 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) in 1,2-dichloroethane (1.0 mL) as described above for 12 h to give **3ea** and **3ga** in 24 and 33% yields, respectively.

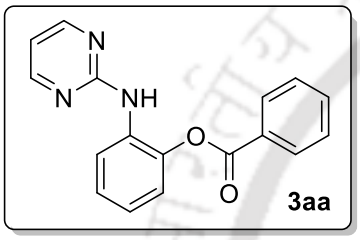
H/D Exchange with D_2O. *N*-Phenylpyrimidin-2-amine **1a** (34.2 mg, 0.2 mmol), benzoic acid **2a** (29.2 mg, 0.24 mmol), $[RuCl_2(p\text{-cymene})]_2$ (6.0 mg, 5.0 mol %), $AgSbF_6$ (13.7 mg, 20 mol %) and Ag_2CO_3 (110 mg, 0.4 mmol) were stirred at 110 °C for 15 h in 1,2-dichloroethane:D_2O (1.8:0.2) under inert atmosphere. 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 yield $[D_n]$-**1a** in 12% (4 mg) and $[D_n]$-**3aa** in 65% (38 mg) yield. Deuterium incorporation was calculated by ^{1}H NMR analysis.

Preparation of Deuterated Substrate $[D_2]$-**1a**. *N*-Phenylpyrimidin-2-amine **1a** (34.2 mg, 0.2 mmol), $[RuCl_2(p\text{-cymene})]_2$ (6 mg, 5.0 mol %), $AgSbF_6$ (13.7 mg, 20 mol %), AcOH (5.0 μL, 50.0 mol %) and Ag_2CO_3 (110 mg, 0.4 mmol) were stirred at 110 °C for 3 h in 1,2-dichloroethane:D_2O (1.8:0.2) under inert atmosphere. The reaction mixture was cooled to room temperature, diluted with dichloromethane (10 mL) and passed through a short pad of celite using dichloromethane (50 mL). Drying (Na_2SO_4) and evaporation of the solvent gave a residue that was purified using column chromatography on silica gel to yield the deuterated product $[D_2]$-**1a** as a white solid (19 mg, 57%). Deuterium incorporation in the *ortho*-position was found to be 96% as estimated by ^{1}H NMR analysis.

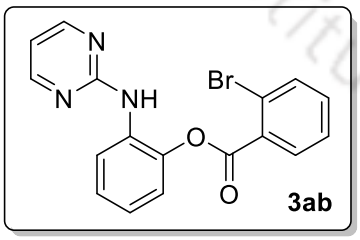
Intermolecular Kinetic Isotope Effect Study. *N*-Phenylpyrimidin-2-amine **1a** (17 mg, 0.1 mmol), $[D_2]$-**1a** (17.3 mg, 0.1 mmol), **2i** (18.8 mg, 0.12 mmol), $[RuCl_2(p\text{-cymene})]_2$ (3.0 mg, 5.0

mol %), $AgSbF_6$ (7.0 mg, 20 mol %), Ag_2CO_3 (55.2 mg, 0.2 mmol) and 1,2-dichloroethane (1.0 mL) were stirred at 110 °C for 3 h under inert atmosphere. The resulting reaction mixture was then 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 ethyl acetate and hexane as an eluent to afford a mixture of **3ai** and [D_n]-**3ai** as a white solid. The intermolecular k_H/k_D was found to be 5.25, based on 600 MHz ^{1}H NMR analysis.

1.4 Characterization Data of Products

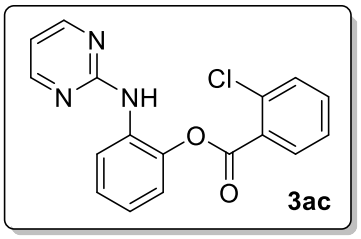


2-(Pyrimidin-2-ylamino)phenyl benzoate 3aa. Analytical TLC on silica gel, 1:5 ethyl acetate/hexane R_f = 0.52; colorless solid; mp 136-137 °C; yield 72% (42 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.38-8.37 (m, 3H), 8.20 (d, *J* = 7.2 Hz, 2H), 7.64 (t, *J* = 7.6 Hz, 1H), 7.51 (t, *J* = 7.6 Hz, 2H), 7.32-7.28 (m, 1H), 7.27-7.24 (m, 1H), 7.22 (br s, 1H), 7.15-7.10 (m, 1H), 6.70 (t, *J* = 4.8 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 164.8, 160.1, 158.1, 140.9, 134.1, 131.8, 130.5, 129.1, 128.9, 126.6, 123.4, 122.6, 122.0, 113.1; FT-IR (KBr) 3408, 1726 cm^{-1}. HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{17}H_{14}N_3O_2$: 292.1086, found: 292.1083.

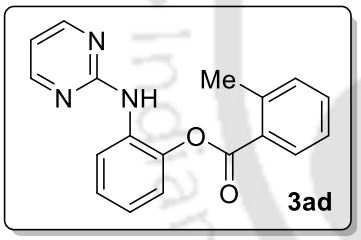


2-(Pyrimidin-2-ylamino)phenyl 2-bromobenzoate 3ab. Analytical TLC on silica gel, 1:5 ethyl acetate/hexane R_f = 0.48; colorless solid; mp 119-120 °C; yield 63% (47 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.43-8.39 (m, 3H), 7.96 (dd, *J* = 7.2, 2.4 Hz, 1H), 7.73 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.53 (s, 1H), 7.43-7.38 (m, 2H), 7.33-7.29 (m, 2H), 7.13-7.11 (m, 1H), 6.71 (t, *J* = 4.2 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 164.4, 160.2, 158.1, 140.6, 134.7, 133.5, 132.1, 131.7, 131.3, 127.6, 126.7,

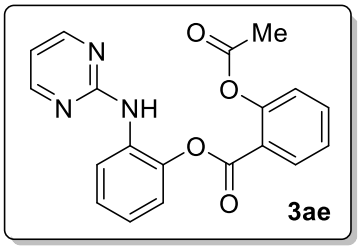
123.1, 122.3, 122.2, 121.9, 113.1; FT-IR (KBr) 3402, 1725 cm^{-1}. HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{17}H_{13}BrN_3O_2$: 370.0191, found: 370.0198.



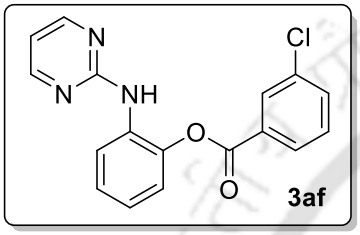
2-(Pyrimidin-2-ylamino)phenyl 2-chlorobenzoate 3ac. Analytical TLC on silica gel, 1:5 ethyl acetate/hexane R_f = 0.50; colorless solid; mp 157-158 °C; yield 65% (42 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.45-8.40 (m, 3H), 8.01-7.99 (m, 1H), 7.54-7.50 (m, 2H), 7.48-7.46 (m, 1H), 7.40-7.36 (m, 1H), 7.33-7.29 (m, 2H), 7.14-7.10 (m, 1H), 6.72 (t, *J* = 4.8 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 163.9, 160.2, 158.1, 140.5, 134.3, 133.6, 132.3, 131.7, 131.5, 129.2, 127.1, 126.7, 123.1, 122.3, 121.8, 113.1; FT-IR (KBr) 3413, 1723 cm^{-1}. HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{17}H_{13}ClN_3O_2$: 326.0696, found: 326.0695.



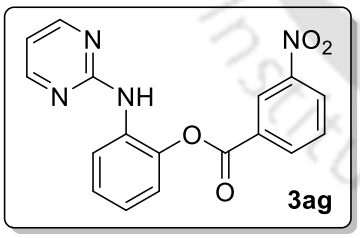
2-(Pyrimidin-2-ylamino)phenyl 2-methylbenzoate 3ad. Analytical TLC on silica gel, 1:5 ethyl acetate/hexane R_f = 0.54; thick liquid; yield 69% (42 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.40-8.38 (m, 3H), 8.17-8.15 (m, 1H), 7.51-7.47 (m, 1H), 7.33-7.24 (m, 5H), 7.15-7.11 (m, 1H), 6.71 (t, *J* = 4.8 Hz, 1H), 2.66 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 165.3, 160.2, 158.1, 141.9, 141.0, 133.2, 132.2, 131.9, 131.4, 128.1, 126.4, 126.2, 123.3, 122.6, 122.0, 113.0, 22.2; FT-IR (neat) 3435, 1740 cm^{-1}. HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{18}H_{16}N_3O_2$: 306.1243, found: 306.1250.



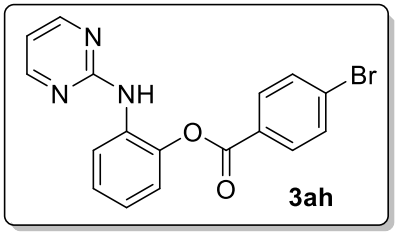
2-(Pyrimidin-2-ylamino)phenyl 2-acetoxybenzoate 3ae. Analytical TLC on silica gel, 1:5 ethyl acetate/hexane R_f = 0.42; thick liquid; yield 66% (46 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.42-8.38 (m, 3H), 8.20-8.17 (m, 1H), 8.67-7.62 (m, 1H), 7.40-7.35 (m, 1H), 7.32-7.28 (m, 2H), 7.23-7.17 (m, 2H), 7.13-7.08 (m, 1H), 6.72-6.69 (m, 1H), 2.28 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.1, 162.8, 160.1, 158.1, 151.2, 140.3, 135.0, 132.4, 131.8, 129.2, 126.8, 126.5, 124.2, 123.2, 122.6, 121.9, 113.1, 21.2; FT-IR (neat) 3435, 1765, 1745 cm^{-1}. HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{19}H_{16}N_3O_4$: 350.1141, found: 350.1124.



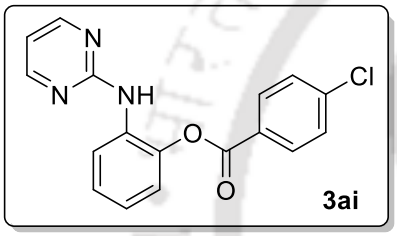
2-(Pyrimidin-2-ylamino)phenyl 3-chlorobenzoate 3af. Analytical TLC on silica gel, 1:5 ethyl acetate/hexane R_f = 0.48; colorless solid; mp 155-156 °C; yield 71% (46 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.38-8.31 (m, 1H), 8.138-8.134 (m, 1H), 8.06 (d, *J* = 7.6 Hz, 1H), 7.61 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.46-7.42 (m, 1H), 7.33-7.29 (m, 1H), 7.25-7.12 (m, 3H), 6.71 (t, *J* = 4.8 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 163.7, 160.2, 158.2, 141.1, 135.0, 134.1, 131.7, 130.9, 130.4, 130.2, 128.5, 126.8, 123.7, 122.56, 122.54, 113.1; FT-IR (KBr) 3429, 1740 cm^{-1}. HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{17}H_{13}ClN_3O_2$: 326.0696, found: 326.0703.



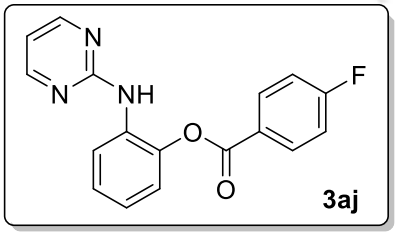
2-(Pyrimidin-2-ylamino)phenyl 3-nitrobenzoate 3ag. Analytical TLC on silica gel, 1:5 ethyl acetate/hexane R_f = 0.44; thick liquid; yield 61% (41 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.97-8.96 (m, 1H), 8.49-8.46 (m, 2H), 8.37-8.35 (m, 2H), 8.28-8.26 (m, 1H), 7.70 (t, *J* = 8.0 Hz, 1H), 7.36-7.32 (m, 1H), 7.27-7.25 (m, 1H), 7.21-7.15 (m, 2H), 6.72-6.69 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.9, 160.2, 158.2, 148.5, 141.2, 135.9, 131.5, 131.0, 130.1, 128.4, 127.1, 125.3, 124.0, 123.0, 122.4, 113.2; FT-IR (neat) 3433, 1746, 1531, 1350 cm^{-1}. HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{17}H_{13}N_4O_4$: 337.0937, found: 337.0924.



2-(Pyrimidin-2-ylamino)phenyl 4-bromobenzoate 3ah. Analytical TLC on silica gel, 1:5 ethyl acetate/hexane R_f = 0.46; brown solid; mp 153-154 °C; yield 67% (49 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.37-8.32 (m, 3H), 8.04-8.01 (m, 2H), 7.65-7.61 (m, 2H), 7.33-7.29 (m, 1H), 7.26-7.23 (m, 2H), 7.15-7.11 (m, 1H), 6.70 (t, *J* = 4.8 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 164.1, 160.1, 158.1, 141.0, 132.2, 131.8, 131.7, 129.3, 128.0, 126.7, 123.5, 122.5, 122.3, 113.1; FT-IR (KBr) 3440, 1740 cm^{-1}. HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{17}H_{13}BrN_3O_2$: 370.0191, found: 370.0195.

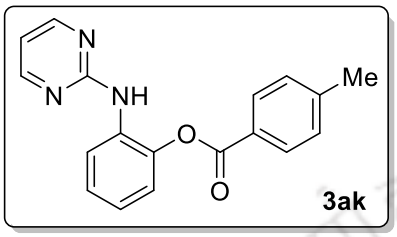


2-(Pyrimidin-2-ylamino)phenyl 4-chlorobenzoate 3ai. Analytical TLC on silica gel, 1:5 ethyl acetate/hexane R_f = 0.48; yellow solid; mp 156-157 °C; yield 72% (46 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.38-8.33 (m, 3H), 8.12 (d, *J* = 8.4 Hz, 2H), 7.48 (d, *J* = 7.8 Hz, 2H), 7.32-7.29 (m, 1H), 7.25-7.23 (m, 1H), 7.15-7.12 (m, 2H), 6.71 (t, *J* = 4.8 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 164.0, 160.1, 158.1, 141.0, 140.6, 131.8, 131.7, 129.2, 127.6, 126.7, 123.6, 122.5, 122.3, 113.1; FT-IR (KBr) 3430, 1740 cm^{-1}. HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{17}H_{13}ClN_3O_2$: 326.0696, found: 326.0699.

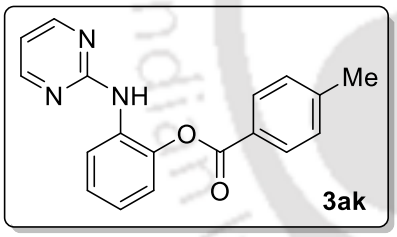


2-(Pyrimidin-2-ylamino)phenyl 4-fluorobenzoate 3aj. Analytical TLC on silica gel, 1:5 ethyl acetate/hexane R_f = 0.52; colorless solid; mp 121-122 °C; yield 65% (40 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.38-8.35 (m, 3H), 8.22-8.19 (m, 2H), 7.33-7.29 (m, 1H), 7.25-7.23 (m, 1H), 7.20-7.11

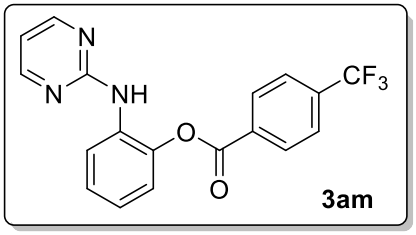
(m, 4H), 6.71 (t, J = 4.8 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 167.3 (J_{C-F} = 254.2 Hz), 163.9, 160.1, 158.1, 141.0, 133.16 (J_{C-F} = 9.4 Hz), 131.7, 126.7, 125.4, 123.5, 122.5, 122.2, 116.2 (J_{C-F} = 22.0 Hz), 113.1; ^{19}F NMR (377 MHz, $CDCl_3$) δ -103.7; FT-IR (KBr) 3419, 1732 cm^{-1}. HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{17}H_{13}FN_3O_2$: 310.0992, found: 310.0998.



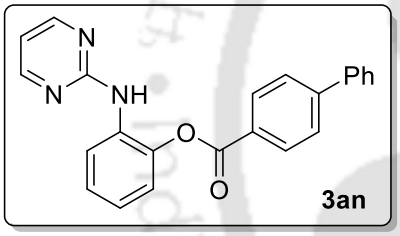
2-(Pyrimidin-2-ylamino)phenyl 4-methylbenzoate 3ak. Analytical TLC on silica gel, 1:5 ethyl acetate/hexane R_f = 0.51; colorless solid; mp 139-140 °C; yield 73% (44 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.40-8.37 (m, 3H), 8.09 (d, J = 8.4 Hz, 2H), 7.31-7.23 (m, 5H), 7.13-7.09 (m, 1H), 6.69 (t, J = 4.8 Hz, 1H), 2.44 (s, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 164.8, 160.1, 158.1, 145.0, 140.9, 131.8, 130.5, 129.6, 126.4, 126.3, 123.2, 122.6, 121.8, 113.0, 21.9; FT-IR (KBr) 3450, 1735 cm^{-1}. HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{18}H_{16}N_3O_2$: 306.1243, found: 306.1255.



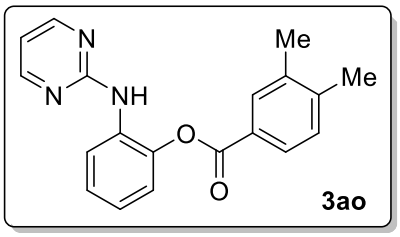
2-(Pyrimidin-2-ylamino)phenyl 4-methoxybenzoate 3al. Analytical TLC on silica gel, 1:5 ethyl acetate/hexane R_f = 0.38; colorless solid; mp 125-126 °C; yield 68% (44 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.39-8.36 (m, 3H), 8.15-8.13 (m, 2H), 7.31-7.23 (m, 3H), 7.13-7.09 (m, 1H), 6.98-6.95 (m, 2H), 6.69 (t, J = 4.8 Hz, 1H), 3.88 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 164.5, 164.3, 160.1, 158.1, 140.9, 132.6, 131.9, 126.3, 123.2, 122.6, 121.8, 121.3, 114.1, 113.0, 55.7; FT-IR (KBr) 3440, 1730 cm^{-1}. HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{18}H_{16}N_3O_3$: 322.1192, found: 322.1199.



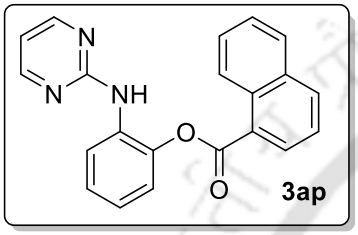
2-(Pyrimidin-2-ylamino)phenyl 4-(trifluoromethyl)benzoate 3am. Analytical TLC on silica gel, 1:5 ethyl acetate/hexane R_f = 0.52; colorless solid; mp 117-118 °C; yield 59% (42 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.38-8.28 (m, 5H), 7.78 (d, *J* = 8.0 Hz, 2H), 7.33 (t, *J* = 7.6 Hz, 1H), 7.28-7.26 (m, 1H), 7.15 (t, *J* = 7.2 Hz, 2H), 6.71 (t, *J* = 4.8 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 163.7, 160.1, 158.2, 141.0, 135.5 (J_{C-F} = 32.5 Hz), 132.455, 132.451, 131.6, 130.8, 126.9, 125.95 (J_{C-F} = 3.7 Hz), 124.5 (J_{C-F} = 271.0 Hz), 123.7, 122.58, 122.51, 113.2; ^{19}F NMR (377 MHz, $CDCl_3$) δ -63.2; FT-IR (KBr) 3453, 1742 cm^{-1}. HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{18}H_{13}F_3N_3O_2$: 360.0960, found: 360.0967.



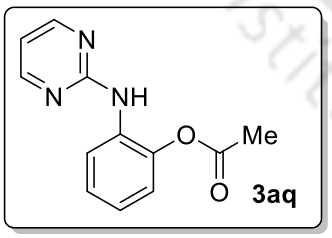
2-(Pyrimidin-2-ylamino)phenyl [1,1'-biphenyl]-4-carboxylate 3an. Analytical TLC on silica gel, 1:5 ethyl acetate/hexane R_f = 0.43; colorless solid; mp 145-146 °C; yield 67% (49 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41-8.38 (m, 3H), 8.27 (d, *J* = 8.0 Hz, 2H), 7.73 (d, *J* = 8.0 Hz, 2H), 7.66 (d, *J* = 7.2 Hz, 2H), 7.50 (t, *J* = 7.2 Hz, 2H), 7.44-7.41 (m, 1H), 7.35-7.26 (m, 3H), 7.16-7.13 (m, 1H), 6.70 (t, *J* = 4.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.7, 160.2, 158.2, 146.8, 140.9, 139.9, 131.8, 131.0, 129.2, 128.5, 127.8, 127.58, 127.55, 126.6, 123.4, 122.6, 122.0, 113.1; FT-IR (KBr) 3434, 1738, 1728 cm^{-1}. HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{23}H_{18}N_3O_2$: 368.1399, found: 368.1392.



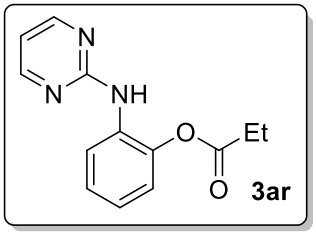
2-(Pyrimidin-2-ylamino)phenyl 3,4-dimethylbenzoate 3o. Analytical TLC on silica gel, 1:5 ethyl acetate/hexane R_f = 0.48; colorless solid; mp 178-179 °C; yield 63% (40 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.39-8.37 (m, 3H), 7.95-7.91 (m, 2H), 7.31-7.28 (m, 2H), 7.26-7.23 (m, 2H), 7.14-7.10 (m, 1H), 6.70 (t, *J* = 4.8 Hz, 1H), 2.35 (s, 3H), 2.33 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 165.1, 160.1, 158.1, 143.7, 141.0, 137.3, 131.9, 131.4, 130.1, 128.1, 126.6, 126.4, 123.3, 122.6, 121.9, 113.0, 20.3, 19.8; FT-IR (KBr) 3440, 1728 cm^{-1}. HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{19}H_{18}N_3O_2$: 320.1399, found: 320.1393.



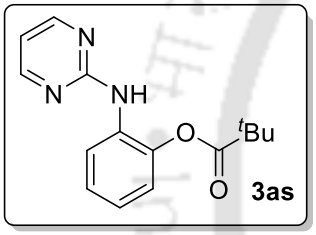
2-(Pyrimidin-2-ylamino)phenyl 1-naphthoate 3ap. Analytical TLC on silica gel, 1:5 ethyl acetate/hexane R_f = 0.47; colorless solid; mp 111-112 °C; yield 64% (44 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.04 (d, *J* = 8.4 Hz, 1H), 8.47 (d, *J* = 7.2 Hz, 1H), 8.41-8.35 (m, 3H), 8.11 (d, *J* = 8.0 Hz, 1H), 7.93 (d, *J* = 8.0 Hz, 1H), 7.63 (t, *J* = 6.8 Hz, 1H), 7.58-7.52 (m, 2H), 7.43 (br s, 1H), 7.34 (t, *J* = 7.6 Hz, 2H), 7.18 (t, *J* = 7.6 Hz, 1H), 6.67 (t, *J* = 4.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.3, 160.2, 158.1, 141.1, 134.9, 134.1, 132.0, 131.6, 128.9, 128.5, 126.7, 126.6, 125.9, 125.3, 124.7, 123.4, 122.7, 122.2, 113.1; FT-IR (KBr) 3450, 1733 cm^{-1}. HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{21}H_{16}N_3O_2$: 342.1243, found: 342.1246.



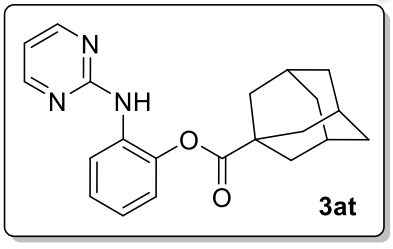
2-(Pyrimidin-2-ylamino)phenyl acetate 3aq. Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.52; colorless liquid; yield 73% (33 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.43 (d, *J* = 4.8 Hz, 2H), 8.37-8.35 (m, 1H), 7.28-7.23 (m, 1H), 7.16-7.14 (m, 2H), 7.09-7.04 (m, 1H), 6.74 (t, *J* = 4.8 Hz, 1H), 2.35 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.0, 160.1, 158.2, 140.7, 131.5, 126.4, 123.2, 122.4, 121.9, 113.1, 21.2; FT-IR (neat) 3434, 1767 cm^{-1}. HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{12}H_{12}N_3O_2$: 230.0930, found: 230.0932.



2-(Pyrimidin-2-ylamino)phenyl propionate 3ar. Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.48; colorless liquid; yield 62% (33 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41 (d, *J* = 4.6 Hz, 2H), 8.33-8.31 (m, 1H), 7.27-7.22 (m, 2H), 7.16-7.13 (m, 1H), 7.09-7.04 (m, 1H), 6.73 (t, *J* = 4.8 Hz, 1H), 2.64 (q, *J* = 7.6 Hz, 2H), 1.27 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.5, 160.1, 158.1, 140.8, 131.5, 126.3, 123.2, 122.4, 121.9, 113.0, 27.9, 9.30; FT-IR (neat) 3432, 1764 cm^{-1}. HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{13}H_{14}N_3O_2$: 244.1086, found: 244.1110.

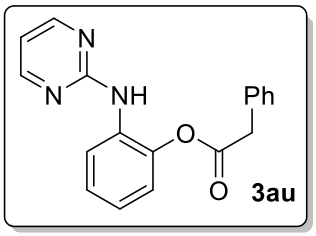


2-(Pyrimidin-2-ylamino)phenyl pivalate 3as. Analytical TLC on silica gel, 1:5 ethyl acetate/hexane R_f = 0.48; colorless liquid; yield 69% (34 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41 (d, *J* = 4.8 Hz, 2H), 8.27-8.24 (m, 1H), 7.27-7.23 (m, 1H), 7.12-7.06 (m, 2H), 7.00 (br s, 1H), 6.72 (t, *J* = 5.2 Hz, 1H), 1.38 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.6, 160.3, 158.2, 141.4, 131.6, 126.3, 123.5, 122.35, 122.33, 113.0, 39.5, 27.4; FT-IR (neat) 3375, 1756 cm^{-1}. HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{15}H_{18}N_3O_2$: 272.1399, found: 272.1401.

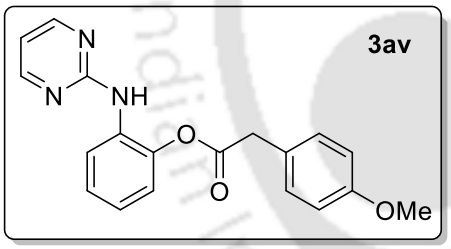


2-(Pyrimidin-2-ylamino)phenyl (3r,5r,7r)-adamantane-1-carboxylate 3at. Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.54; colorless liquid; yield 65% (45 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.40 (d, *J* = 4.8 Hz, 2H), 8.27-8.25 (m, 1H), 7.26-7.21 (m, 1H), 7.10-7.04 (m, 3H),

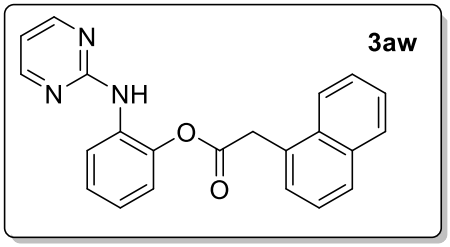
6.71 (t, *J* = 4.8 Hz, 1H), 2.09-2.06 (m, 9H), 1.76 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.6, 160.3, 158.1, 141.2, 131.6, 126.2, 123.4, 122.3, 122.1, 112.9, 41.4, 38.9, 36.5, 28.0; FT-IR (neat) 3432, 1748 cm^{-1}. HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{21}H_{24}N_3O_2$: 350.1869, found: 350.1887.



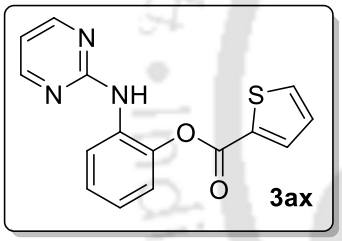
2-(Pyrimidin-2-ylamino)phenyl 2-phenylacetate 3au. Analytical TLC on silica gel, 1:5 ethyl acetate/hexane R_f = 0.51; thick liquid; yield 63% (38 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.39 (d, *J* = 4.8 Hz, 2H), 8.29-8.27 (m, 1H), 7.37-7.34 (m, 4H), 7.32-7.30 (m, 1H), 7.25-7.21 (m, 2H), 7.12-7.09 (m, 1H), 7.06-7.02 (m, 1H), 6.71 (t, *J* = 4.8 Hz, 1H), 3.89 (s, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.6, 160.1, 158.1, 140.8, 133.3, 131.4, 129.4, 129.1, 127.6, 126.4, 123.2, 122.2, 122.0, 113.0, 41.5; FT-IR (neat) 3427, 1760 cm^{-1}. HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{18}H_{16}N_3O_2$: 306.1243, found: 306.1257.



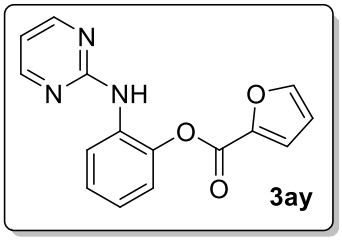
2-(Pyrimidin-2-ylamino)phenyl 2-(4-methoxyphenyl)acetate 3av. Analytical TLC on silica gel, 1:5 ethyl acetate/hexane R_f = 0.51; thick liquid; yield 66% (44 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.39 (d, *J* = 4.8 Hz, 2H), 8.31-8.29 (m, 1H), 7.31-7.27 (m, 2H), 7.25-7.21 (m, 1H), 7.12-7.08 (m, 2H), 7.05-7.01 (m, 1H), 6.91-6.88 (m, 2H), 6.72 (t, *J* = 4.8 Hz, 1H), 3.83 (s, 2H), 3.80 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.9, 160.1, 159.1, 158.1, 140.7, 131.5, 130.4, 126.4, 125.3, 123.1, 122.2, 121.8, 114.5, 113.1, 55.4, 40.7; FT-IR (neat) 3434, 1758 cm^{-1}. HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{19}H_{18}N_3O_3$: 336.1348, found: 336.1373.



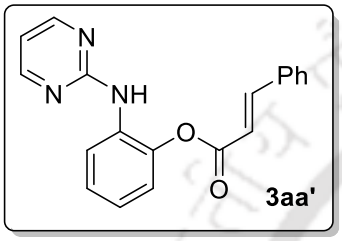
2-(Pyrimidin-2-ylamino)phenyl 2-(naphthalen-1-yl)acetate 3aw. Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.46; colorless liquid; yield 67% (47 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.34 (d, *J* = 4.8 Hz, 2H), 8.24-8.21 (m, 1H), 8.08-8.06 (m, 1H), 7.88-7.86 (m, 1H), 7.82 (d, *J* = 8.0 Hz, 1H), 7.56-7.42 (m, 4H), 7.23-7.18 (m, 1H), 7.09-7.05 (m, 2H), 7.02-6.98 (m, 1H), 6.68-6.65 (m, 1H), 4.32 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.6, 160.1, 158.0, 141.0, 134.1, 132.1, 131.4, 129.8, 129.0, 128.6, 128.3, 126.9, 126.4, 126.0, 125.7, 123.6, 123.2, 122.2, 122.1, 113.0, 39.3; FT-IR (neat) 3411, 1761 cm^{-1}. HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{22}H_{18}N_3O_2$: 356.1399, found: 356.1408.



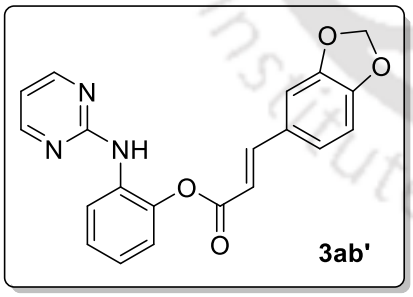
2-(Pyrimidin-2-ylamino)phenyl thiophene-2-carboxylate 3ax. Analytical TLC on silica gel, 1:5 ethyl acetate/hexane R_f = 0.47; colorless solid; mp 137-138 °C; yield 62% (37 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.39-8.36 (m, 3H), 7.98 (d, *J* = 2.8 Hz, 1H), 7.67 (d, *J* = 4.4 Hz, 1H), 7.32-7.26 (m, 3H), 7.17 (t, *J* = 4.4 Hz, 1H), 7.13-7.09 (m, 1H), 6.71 (t, *J* = 4.8 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 160.1, 158.1, 140.5, 135.2, 134.1, 132.3, 131.8, 128.4, 126.6, 123.2, 122.5, 121.9, 113.1; FT-IR (KBr) 3403, 1717 cm^{-1}. HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{15}H_{12}N_3O_2S$: 298.0650, found: 298.0659.



2-(Pyrimidin-2-ylamino)phenyl furan-2-carboxylate 3ay. Analytical TLC on silica gel, 1:5 ethyl acetate/hexane R_f = 0.50; colorless solid; mp 148-149 °C; yield 65% (36 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41-8.39 (m, 3H), 7.67 (s, 1H), 7.40 (d, *J* = 2.8 Hz, 1H), 7.32-7.26 (m, 3H), 7.10 (t, *J* = 7.6 Hz, 1H), 6.72 (t, *J* = 4.8 Hz, 1H), 6.59 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 160.1, 158.1, 156.4, 147.6, 143.6, 139.9, 131.8, 126.7, 123.1, 122.4, 121.8, 120.2, 113.1, 112.5; FT-IR (KBr) 3411, 1736 cm^{-1}. HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{15}H_{12}N_3O_3$: 282.0879, found: 282.0890.

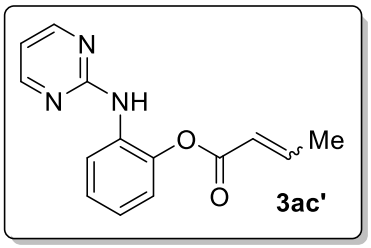


2-(Pyrimidin-2-ylamino)phenyl cinnamate 3aa'. Analytical TLC on silica gel, 1:5 ethyl acetate/hexane R_f = 0.42; colorless solid; mp 112-113 °C; yield 68% (43 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41-8.38 (m, 3H), 7.90 (d, *J* = 16.0 Hz, 1H), 7.58-7.56 (m, 2H), 7.45-7.41 (m, 4H), 7.30-7.23 (m, 2H), 7.12-7.08 (m, 1H), 6.72 (t, *J* = 4.8 Hz, 1H), 6.68 (d, *J* = 16.0 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 165.0, 160.1, 158.1, 147.6, 140.5, 134.1, 131.7, 131.0, 129.1, 128.5, 126.3, 123.1, 122.4, 121.7, 116.7, 113.0; FT-IR (KBr) 3452, 1737 cm^{-1}. HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{19}H_{16}N_3O_2$: 318.1243, found: 318.1247.

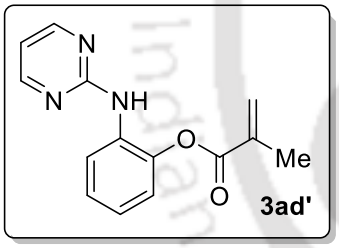


2-(Pyrimidin-2-ylamino)phenyl (*E*)-3-(benzo[*d*][1,3]dioxol-5-yl)acrylate 3ab'. Analytical TLC on silica gel, 1:5 ethyl acetate/hexane R_f = 0.38; colorless solid; mp 169-170 °C; yield 65% (47 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41 (s, 3H), 7.80 (d, *J* = 16.0 Hz, 1H), 7.31-7.20 (m, 3H), 7.08-7.04 (m, 3H), 6.84 (d, *J* = 7.2 Hz, 1H), 6.72 (s, 1H), 6.49 (d, *J* = 15.6 Hz, 1H), 6.03 (s, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 165.2, 160.1, 158.1, 150.3, 148.6, 147.3, 140.5, 131.7, 128.6,

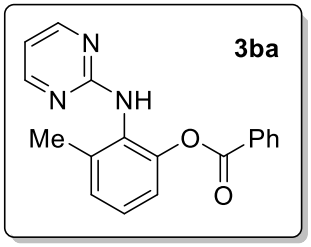
126.3, 125.3, 123.0, 122.4, 121.6, 114.5, 113.0, 108.8, 106.8, 101.9; FT-IR (KBr) 3439, 1745 cm^{-1}. HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{20}H_{16}N_3O_4$: 362.1141, found: 362.1153.



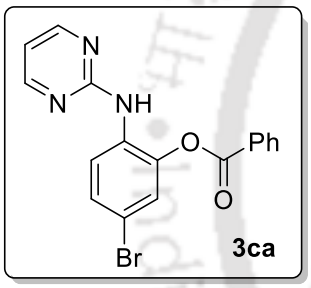
2-(Pyrimidin-2-ylamino)phenyl but-2-enoate 3ac'. Analytical TLC on silica gel, 1:5 ethyl acetate/hexane R_f = 0.50; thick liquid; *dr* = 5:1; yield 63% (32 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41-8.34 (m, 3H), 7.53 (s, 1.04H), 7.27-7.15 (m, 3.21H), 7.07 (t, *J* = 7.6 Hz, 1.06H), 6.73 (s, 1.08H), 6.10 (d, *J* = 15.6 Hz, 1.02H), 5.88 (d, *J* = 15.2 Hz, 0.21H), 1.96 (d, *J* = 6.4 Hz, 2.91H), 1.91 (d, *J* = 6.8 Hz, 0.59H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.2, 164.4, 160.0, 158.1, 148.0, 145.8, 140.6, 131.6, 126.2, 123.1, 123.0, 122.4, 121.8, 121.7, 112.9, 18.4, 18.2; FT-IR (neat) 3437, 1736 cm^{-1}. HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{14}H_{14}N_3O_2$: 256.1086, found: 256.1099.



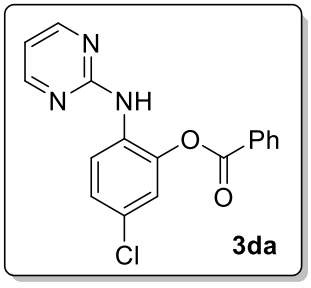
2-(Pyrimidin-2-ylamino)phenyl methacrylate 3ad'. Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.46; colorless liquid; yield 69% (35 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41 (d, *J* = 4.8 Hz, 2H), 8.35-8.32 (m, 1H), 7.28-7.24 (m, 1H), 7.18-7.16 (m, 2H), 7.10-7.06 (m, 1H), 6.72 (t, *J* = 4.8 Hz, 1H), 6.378-6.372 (m, 1H), 5.79-5.77 (m, 1H), 2.06 (t, J = 1.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.4, 160.1, 158.1, 140.9, 135.6. 131.6, 128.1, 126.4, 123.3, 122.4, 121.9, 113.1, 18.6; FT-IR (neat) 3434, 1738 cm^{-1}. HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{14}H_{14}N_3O_2$: 256.1086, found: 256.1107.



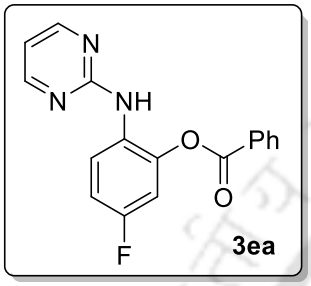
3-Methyl-2-(pyrimidin-2-ylamino)phenyl benzoate 3ba. Analytical TLC on silica gel, 1:5 ethyl acetate/hexane R_f = 0.52; thick liquid; yield 65% (39 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (d, *J* = 4.4 Hz, 2H), 7.97 (d, *J* = 7.2 Hz, 2H), 7.55 (t, *J* = 7.6 Hz, 1H), 7.38 (t, *J* = 8.0 Hz, 2H), 7.29-7.25 (m, 1H), 7.23-7.21 (m, 1H), 7.18-7.16 (m, 1H), 6.60 (s, 1H), 6.54 (t, *J* = 4.4 Hz, 1H), 2.32 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.9, 161.4, 158.3, 147.5, 138.1, 133.6, 130.2, 129.6, 129.4, 128.6, 128.4, 127.5, 120.6, 112.1, 18.6; FT-IR (neat) 3436, 1738 cm^{-1}. HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{18}H_{16}N_3O_2$: 306.1243, found: 306.1246.



5-Bromo-2-(pyrimidin-2-ylamino)phenyl benzoate 3ca. Analytical TLC on silica gel, 1:5 ethyl acetate/hexane R_f = 0.46; colorless solid; mp 132-133 °C; yield 63% (46 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.38-8.35 (m, 3H), 8.19 (d, *J* = 6.8 Hz, 2H), 7.66-7.65 (m, 1H), 7.54-7.52 (m, 2H), 7.42-7.40 (m, 2H), 7.19 (s, 1H), 6.74 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 164.4, 159.8, 158.2, 140.9, 134.4, 131.2, 130.5, 139.5, 129.0, 128.6, 125.7, 122.7, 114.6, 113.5; FT-IR (KBr) 3430, 1746 cm^{-1}. HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{17}H_{13}BrN_3O_2$: 370.0191, found: 370.0193.

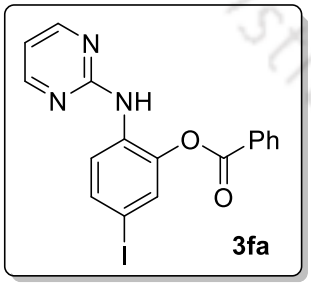


5-Chloro-2-(pyrimidin-2-ylamino)phenyl benzoate 3da. Analytical TLC on silica gel, 1:5 ethyl acetate/hexane R_f = 0.45; colorless solid; mp 139-140 °C; yield 62% (40 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.39-8.38 (m, 3H), 8.19 (d, *J* = 7.6 Hz, 2H), 7.68-7.64 (m, 1H), 7.52 (t, *J* = 7.6 Hz, 2H), 7.29-722 (m, 3H), 6.73 (t, *J* = 4.8 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 164.4, 159.9, 158.1, 140.9, 134.3, 130.7, 130.5, 129.0, 128.7, 127.6, 126.6, 122.9, 122.5, 113.4; FT-IR (KBr) 3436, 1744 cm^{-1}. HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{17}H_{13}ClN_3O_2$: 326.0696, found: 326.0696.



3ea

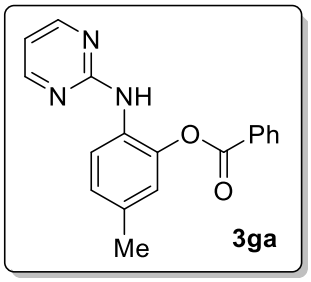
5-Fluoro-2-(pyrimidin-2-ylamino)phenyl benzoate 3ea. Analytical TLC on silica gel, 1:5 ethyl acetate/hexane R_f = 0.47; colorless solid; mp 106-107 °C; yield 57% (35 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36 (d, *J* = 4.8 Hz, 2H), 8.22-8.19 (m, 1H), 8.16-8.14 (m, 2H), 7.64 (t, *J* = 7.6 Hz, 1H), 7.51-7.47 (m, 2H), 7.17 (br s, 1H), 7.07-7.01 (m, 2H), 6.69 (t, *J* = 4.8 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 164.4, 160.3, 159.3 (J_{C-F} = 242.8 Hz), 158.2, 142.2 (J_{C-F} = 10.8 Hz), 134.2, 130.5, 128.9, 128.8, 128.0, 123.9 (J_{C-F} = 8.7 Hz), 113.3 (J_{C-F} = 21.7 Hz), 113.0, 110.6 (J_{C-F} = 25.5 Hz); ^{19}F NMR (377 MHz, $CDCl_3$) δ -117.2; FT-IR (KBr) 3442, 1741 cm^{-1}. HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{17}H_{13}FN_3O_2$: 310.0992, found: 310.0996.



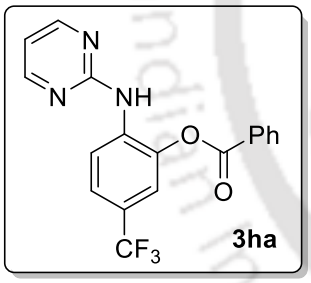
3fa

5-Iodo-2-(pyrimidin-2-ylamino)phenyl benzoate 3fa. Analytical TLC on silica gel, 1:5 ethyl acetate/hexane R_f = 0.49; brown solid; mp 147-148 °C; yield 67% (56 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.40 (d, *J* = 4.4 Hz, 2H), 8.26 (d, *J* = 8.8 Hz, 1H), 8.19 (d, *J* = 7.6 Hz, 2H), 7.67 (t, *J* = 7.2 Hz, 1H), 7.60-7.57 (m, 2H), 7.52 (t, *J* = 7.6 Hz, 2H), 7.18 (s, 1H), 6.74 (t, *J* = 4.4 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 164.5, 159.8, 158.1, 140.8, 135.5, 134.3, 132.0, 131.3, 130.5, 129.0,

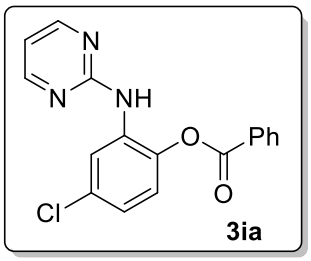
128.6, 123.0, 113.5, 84.3; FT-IR (KBr) 3427, 1749 cm^{-1}. HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{17}H_{13}IN_3O_2$: 418.0052, found: 418.0059.



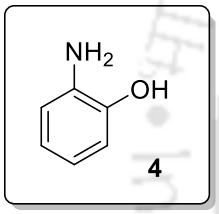
5-Methyl-2-(pyrimidin-2-ylamino)phenyl benzoate 3ga. Analytical TLC on silica gel, 1:5 ethyl acetate/hexane R_f = 0.51; colorless solid; mp 121-122 °C; yield 66% (40 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35 (d, *J* = 4.8 Hz, 2H), 8.17-8.09 (m, 3H), 7.63 (t, *J* = 7.2 Hz, 1H), 7.49 (t, *J* = 7.6 Hz, 2H), 7.12-7.08 (m, 3H), 6.66 (t, *J* = 4.8 Hz, 1H), 2.36 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 164.9, 160.4, 158.1, 141.5, 134.09, 134.01, 130.4, 129.2, 129.0, 128.8, 127.2, 123.1, 122.9, 112.7, 21.0; FT-IR (KBr) 3449, 1732 cm^{-1}. HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{18}H_{16}N_3O_2$: 306.1243, found: 306.1244.



2-(Pyrimidin-2-ylamino)-5-(trifluoromethyl)phenyl benzoate 3ha. Analytical TLC on silica gel, 1:5 ethyl acetate/hexane R_f = 0.46; thick liquid; yield 52% (37 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.75 (d, *J* = 8.4 Hz, 1H), 8.46-8.44 (m, 2H), 8.23-8.21 (m, 2H), 7.71-7.66 (m, 1H), 7.58-7.53 (m, 4H), 7.45 (br s, 1H), 6.81 (t, *J* = 4.8 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 164.5, 159.5, 158.2, 139.2, 135.2, 134.5, 130.5, 129.0, 128.5, 124.9 (J_{C-F} = 269.8 Hz), 124.3 (J_{C-F} = 33.0 Hz), 123.75 (J_{C-F} = 3.7 Hz), 120.4, 119.98 (J_{C-F} = 3.9 Hz), 118.5, 114.1; ^{19}F NMR (377 MHz, $CDCl_3$) δ -61.7; FT-IR (neat) 3433, 1746 cm^{-1}. HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{18}H_{13}F_3N_3O_2$: 360.0960, found: 360.0964.



4-Chloro-2-(pyrimidin-2-ylamino)phenyl benzoate 3ia. Analytical TLC on silica gel, 1:5 ethyl acetate/hexane R_f = 0.47; colorless solid; mp 137-138 °C; yield 71% (46 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.65 (d, *J* = 2.4 Hz, 1H), 8.43 (d, *J* = 4.8 Hz, 2H), 8.21-8.19 (m, 2H), 7.67 (t, *J* = 7.6 Hz, 1H), 7.52 (t, *J* = 8.0 Hz, 2H), 7.30 (br s, 1H), 7.18 (d, *J* = 8.8 Hz, 1H), 7.07-7.04 (m, 1H), 6.77 (t, *J* = 4.8 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 164.6, 159.6, 158.1, 138.4, 134.3, 133.0, 131.8, 130.5, 129.0, 128.8, 123.3, 122.4, 120.7, 113.7; FT-IR (KBr) 3435, 1750 cm^{-1}. HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{17}H_{13}ClN_3O_2$: 326.0696, found: 326.0697.



Acid Hydrolysis of 3ai. 2-(Pyrimidin-2-ylamino)phenyl-4-chlorobenzoate **3ai** (65 mg, 0.2 mmol) and aqueous HCl (37%, 1 mL) were added to a sealed microwave vial and heated up to 150 °C (40 W) for 3 h in the microwave reactor. The reaction mixture was cooled to room temperature and diluted with ethyl acetate (5 mL). The resultant solution was treated with saturated $NaHCO_3$ until the pH was adjusted to 7. The aqueous layer was extracted with ethyl acetate (3 × 5 mL), and the combined organic solution was dried over Na_2SO_4. Removal of the solvent gave a residue, which was purified by column chromatography on silica gel to afford 2-aminophenol **4** as a brown solid in 71% yield (15 mg). Analytical TLC on silica gel, 1:1 ethyl acetate/hexane R_f = 0.48; mp 180-182 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.92 (br s, 1H), 6.64-6.62 (m, 1H), 6.58-6.51 (m, 2H), 6.40-6.36 (m, 1H), 4.44 (br s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 144.4, 136.9, 119.9, 116.9, 114.9, 114.8; FT-IR (KBr) 3466, 3376, 3305 cm^{-1}. HRMS (ESI) *m/z* $[M+H]^+$ calcd for C_6H_8NO: 110.0606, found: 110.0607.

Crystal Structure and Data of 3af

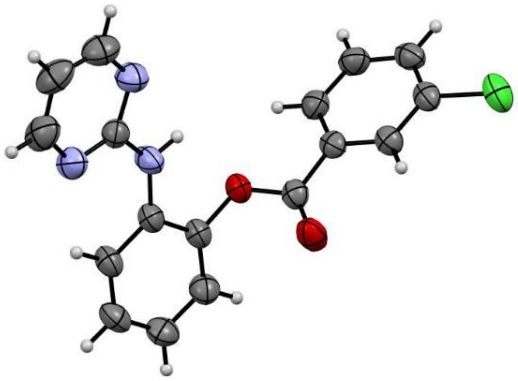


Figure 2. ORTEP diagram of 2-(Pyrimidin-2-ylamino)phenyl-3-chlorobenzoate **3af** (CCDC 1812578).

Identification code	**3af**
Empirical formula	$C_{17}H_{12}ClN_3O_2$
Formula weight	325.75
Crystal habit, colour	Rectangular, colourless
Crystal size, mm^3	0.32 x 0.27 x 0.22
Temperature, *T*/K	296 (2)
Wavelength, λ/Å	0.71073
Crystal system	Monoclinic
Space group	'P2(1)/c '
Unit cell dimensions	a = 17.1569(10) Å b = 7.1445(4) Å c = 12.2275(8) Å $\alpha = \gamma = 90.00^o$, $\beta = 90.144(4)$
Volume, *V*/$Å^3$	1498.81(16)
Z	4
Calculated density, $Mg \cdot m^{-3}$	1.444
Absorption coefficient, μ/mm^{-1}	0.268

F(000)	672.00
θ range for data collection	2.37 to 25.00 ^{o}
Limiting indices	$-20 \leq h \leq 20$, $-8 \leq k \leq 8$, $-14 \leq l \leq 14$
Reflection collected / unique	2648/2129 [R(int) = 0.0285]
Completeness to θ	100 % (θ = 25.00)
Absorption correction	Multi-scan
Max. and min. transmission	0.943 and 0.918
Refinement method	SHELXL-97 (Sheldrick, 1997)
Data / restraints / parameters	2648/0/212
Goodness–of–fit on F^2	1.045
Final *R* indices [*I*>2sigma(*I*)]	R1 = 0.0345, *w*R2 = 0.0873
R indices (all data)	R1 = 0.0448, *w*R2 = 0.0937

1.5 References

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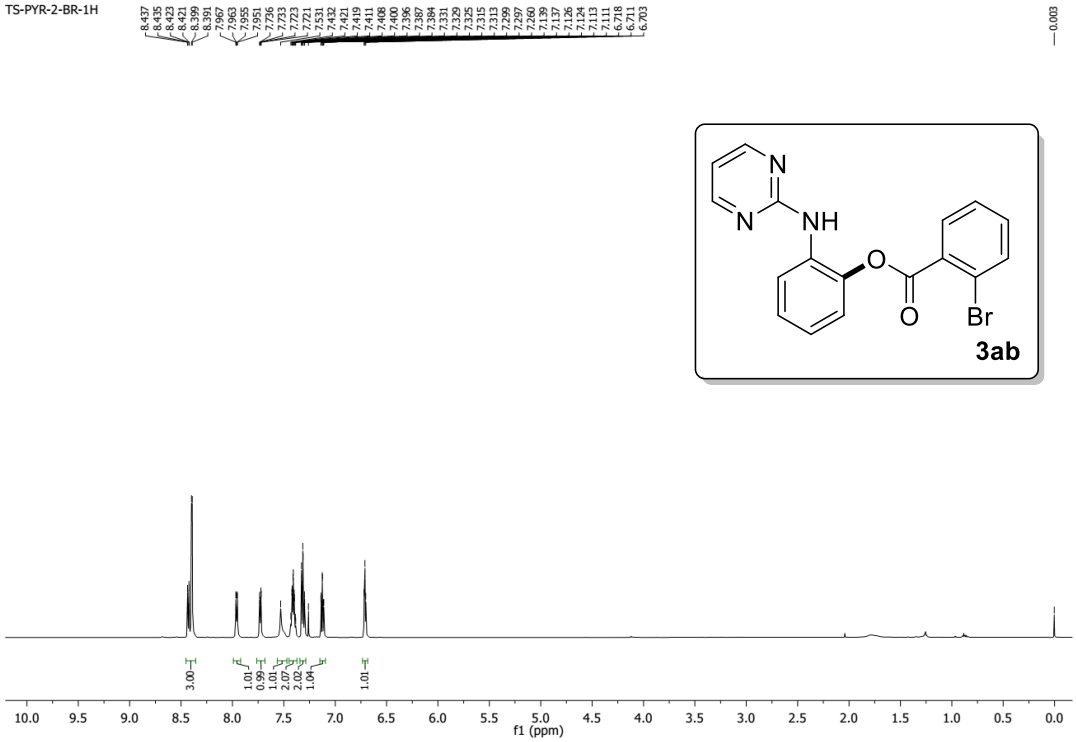
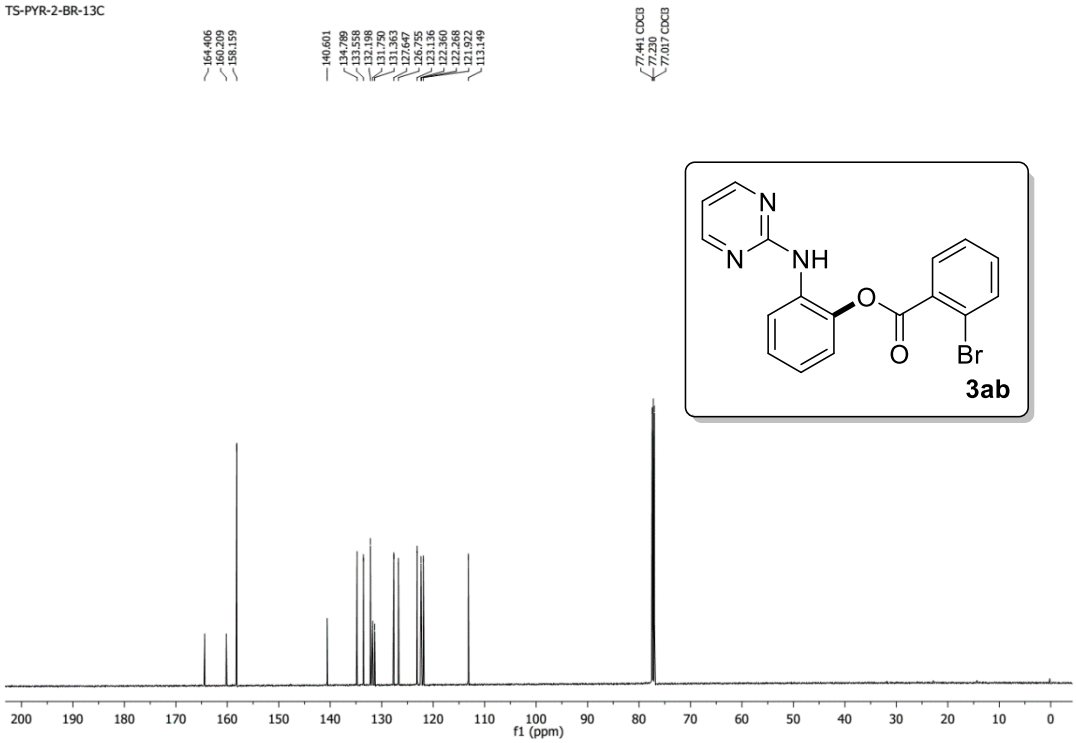
1.6 Selected NMR Spectra





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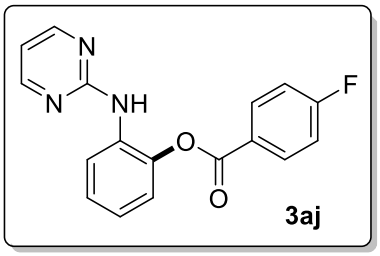

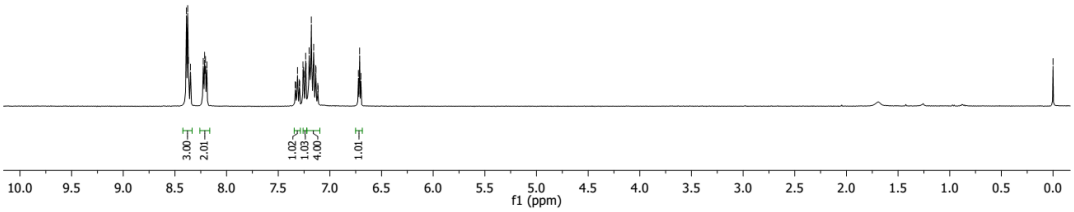

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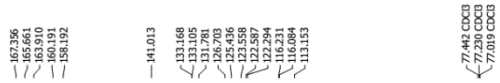

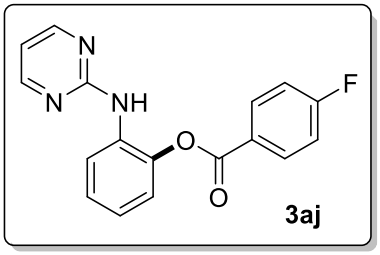

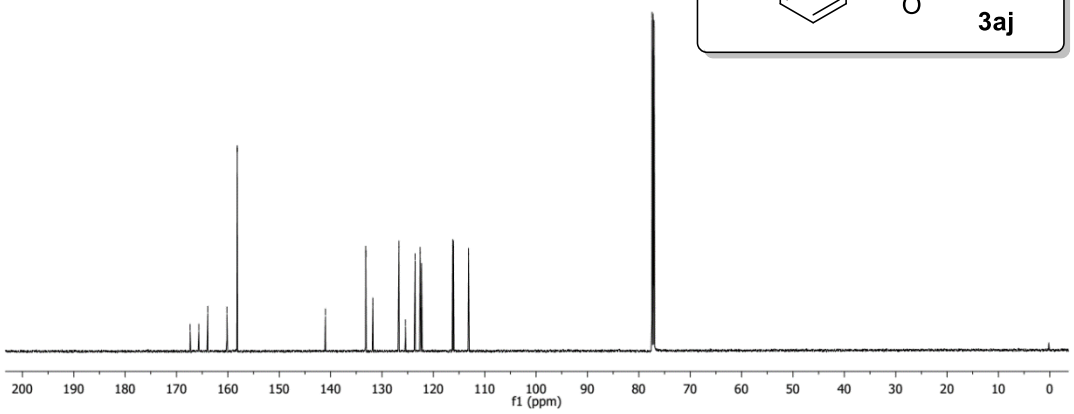

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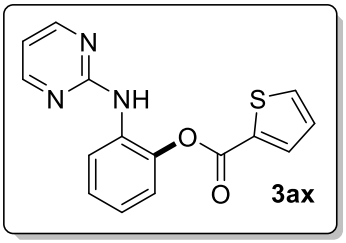

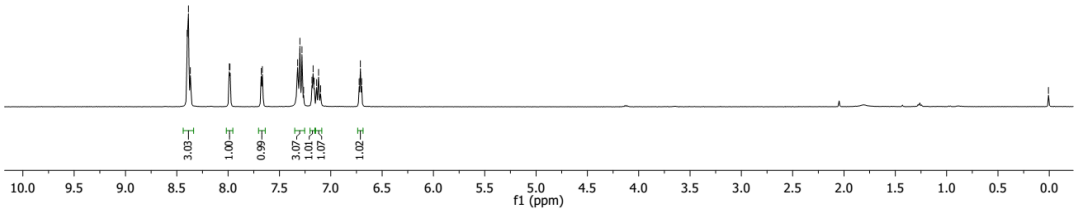

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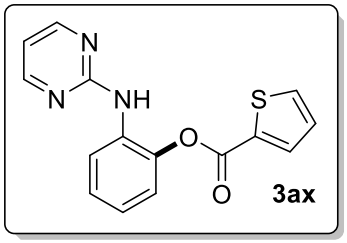
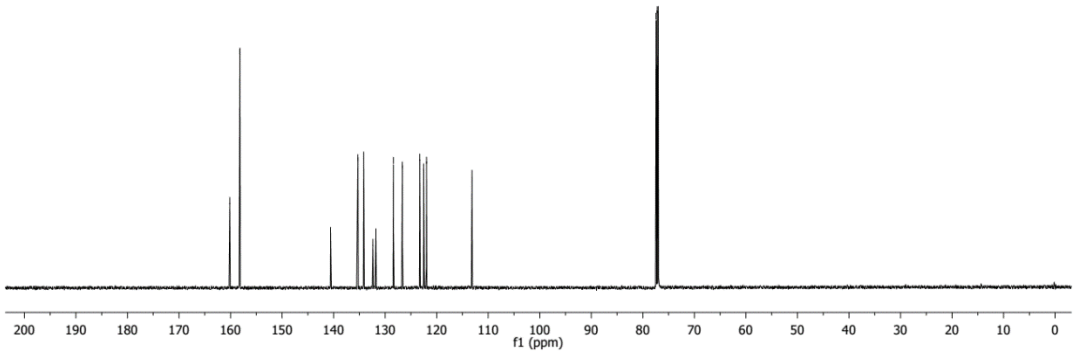
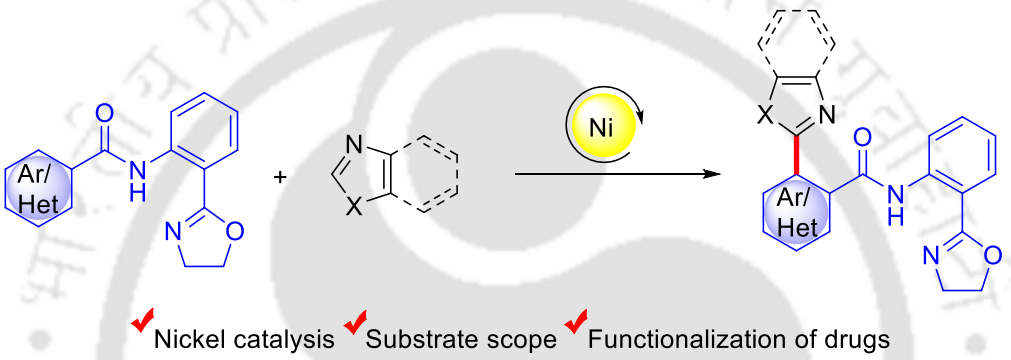




Chapter II

Ni(II)-Catalyzed Cross-Dehydrogenative Coupling of Aromatic Amides with Azoles



Ni(II)-Catalyzed Cross-Dehydrogenative Coupling of Aromatic Amides with Azoles

Hetero-biaryl compounds comprising an azole subunit are the privileged scaffolds due to their presence in bio-active natural products and applications for the functional materials and pharmaceuticals (Figure 1).[1] The development of effective synthetic strategies to enable the installation of azoles into arenes can lead to sought-after transformations for drug molecules in late stage diversifications. The majority of the classical concepts, for instances, the conventional cross-coupling reactions for preparing the bi-(hetero)aryl compounds hinges on the utilization of pre-defined feedstocks and precious late transition metals.[2] To surmount these shortcomings, the oxidative C-H/C-H cross-coupling of two (hetero)arenes *via* the dual C-H bond activation strategy has been realized in recent years for the assembly of bi-(hetero)aryl compounds by means of transition-metal or photoredox catalysis.[3] Despite the advances, the positional-selective functionalization remains an imperative task owing to the profuse prominence of C-H bonds in organic molecules. Therefore, the implementation of DG strategy comprising a coordinating moiety which can direct the metal centre into the close proximity of a specific C-H bond and thereby leading to selective functionalization is highly desirable.[4,5] This chapter describes an efficient Ni(II)-catalyzed[6] oxidative C-H/C-H cross-coupling of benzamides with azoles using a removable oxazoline-derived[7] bidentate DG. The notable features of the methodology include the direct installation of marketed drugs such as natural CNS stimulant caffeine, anti-peripheral vascular disease (PVD) drug pentoxyfylline and anti-asthmatic drug doxofylline that will be useful in medicinal sciences.

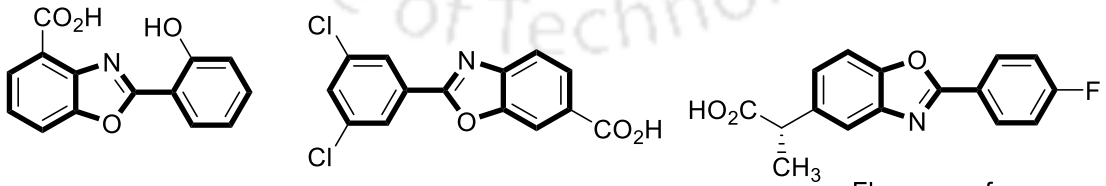
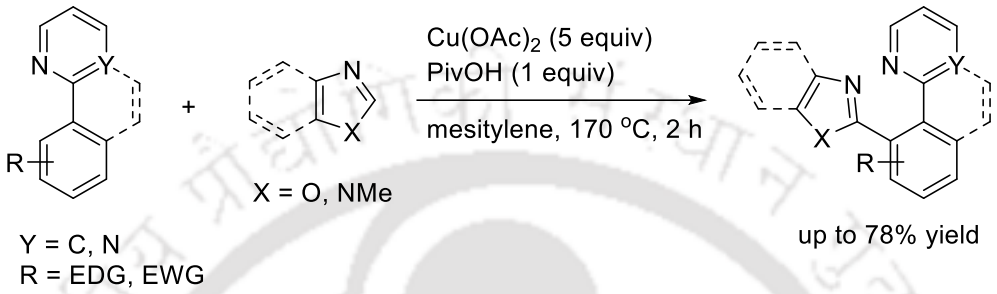


Figure 1. Examples of Biologically Active Azole derivatives.

2.1 Literature

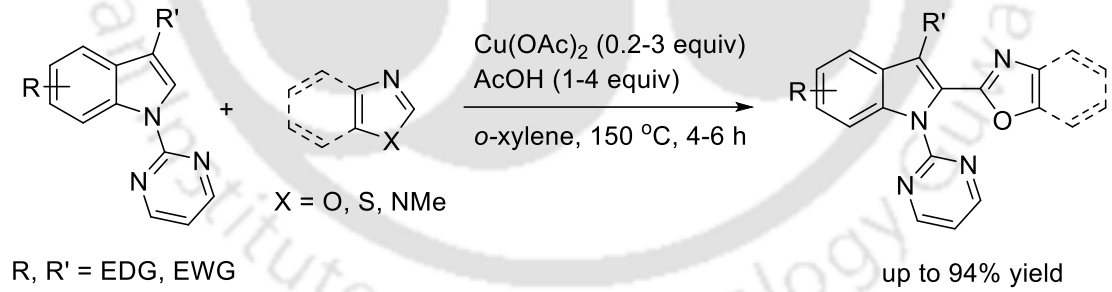
2.1.1 Cu-Catalyzed/Mediated C-H Heteroarylation

Miura and co-workers reported a Cu-mediated biaryl coupling of azoles with arylazines (Scheme 1).[8] The reaction involves carboxylate assisted reversible C(sp^2)-H metalation of azole, followed by C-H activation of arylazine and reductive elimination.



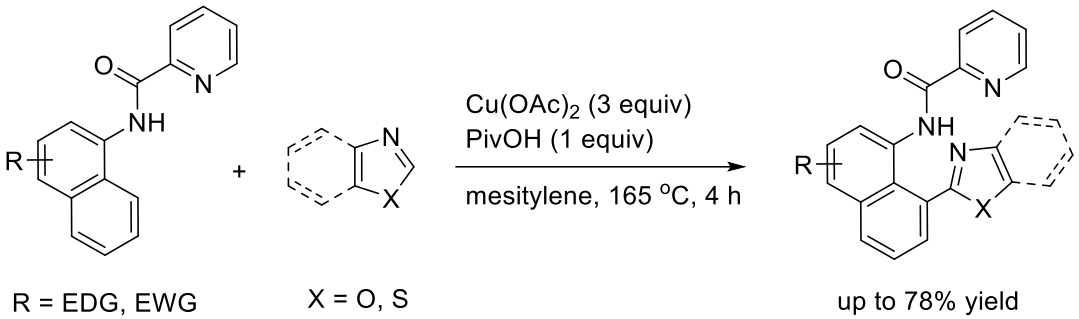
Scheme 1. Cu(II)-Mediated Oxidative Heteroarylation of Arylazines

The same group developed the oxidative C2-heteroarylation of indoles with azoles for the synthesis of bi-heteroaryl substructures in presence of $Cu(OAc)_2$ using 2-pyrimidyl DG (Scheme 2).[9] The catalytic version of this transformation has been accomplished employing aerobic oxygen as oxidant. The removal of the DG, mechanistic insights and broad substrate scope with functional group diversity has been accomplished.



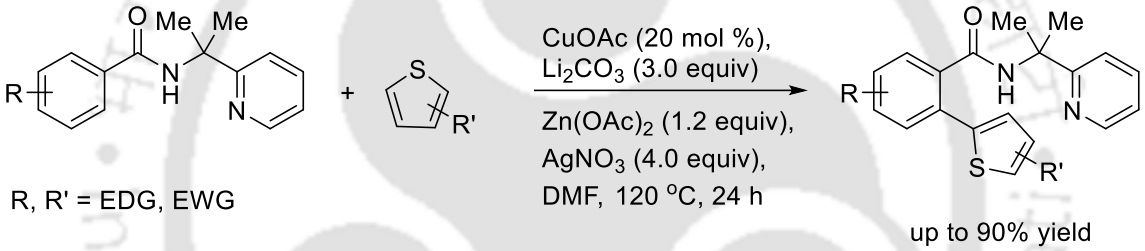
Scheme 2. C2-Heteroarylation of Indoles using Azoles

A Cu-mediated picolinamide directed cross-dehydrogenative coupling of 1,3-azoles with 1-naphthylamines *via* a double C-H bond cleavage was described for the construction of naphthalene-azoles using pivalic acid as additive (Scheme 3).[10] This procedure tolerated a wide range of naphthylamine substrates and azoles.



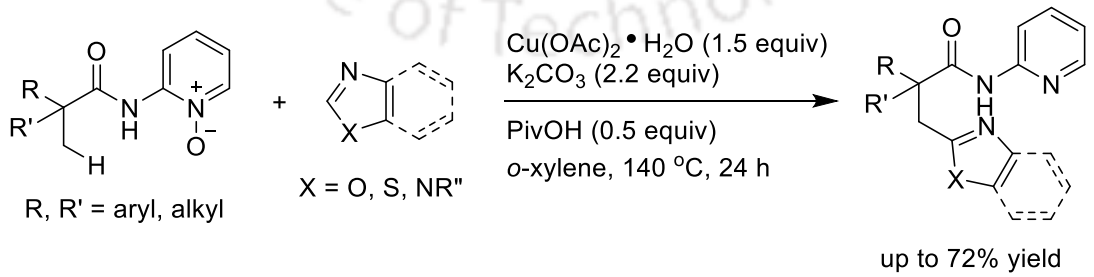
Scheme 3. Cu(II)-Mediated Heteroarylation of Naphthylamines

Shi and co-workers demonstrated a *N*,*N*-bidentate chelation assisted oxidative coupling of benzamides with thiophenes to furnish hetero-biaryl compounds under Cu-catalysis (Scheme 4).[11] This methodology features the usage of inexpensive copper catalyst, high functional group tolerance and late-stage removal of the DG.



Scheme 4. Directed *ortho*-Heterorylation of Benzamides under Cu-Catalysis

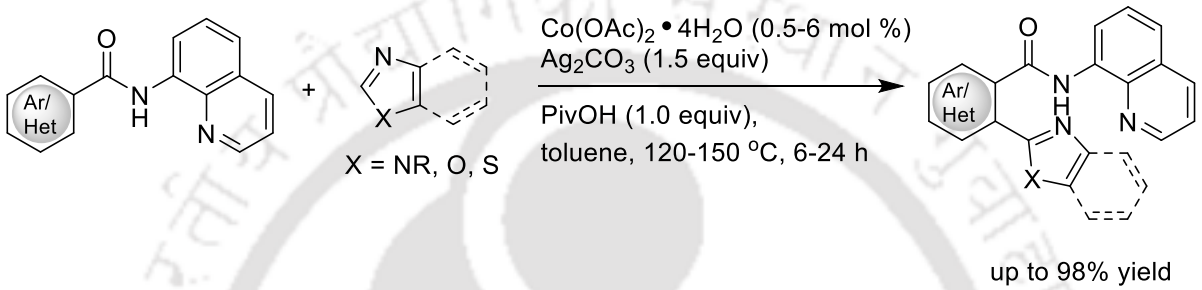
A Cu(II)-promoted direct oxidative C(sp^3)-H/C(sp^2)-H coupling of carboxamide-pyridine *N*-oxides with azoles has been demonstrated *via* *N*,*O*-bidentate chelation assistance (Scheme 5).[12] Diversely substituted amides and azoles were found to be compatible. The removal of the DG provides a straightforward route to access privileged *β*-azolyl propanoic acid derivatives, which are of potent interest in medicinal sciences.



Scheme 5. Cu(II)-Promoted Coupling of Carboxamide-Pyridine *N*-Oxides with Azoles

2.1.2 Co-Catalyzed C-H Heteroarylation

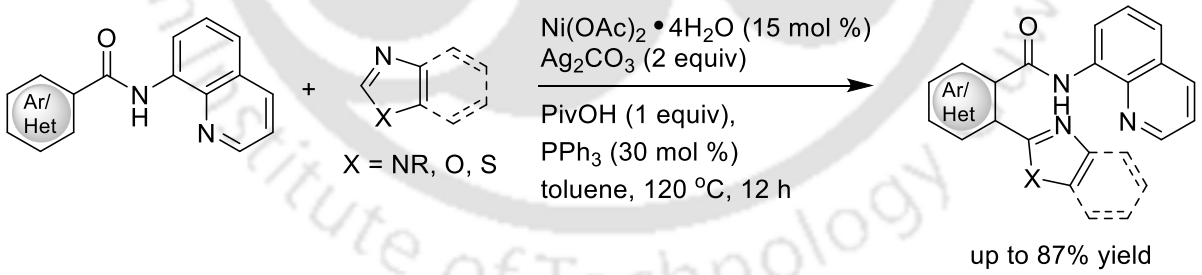
You and co-workers explored a Co(II)-catalyzed oxidative C-H heteroarylation of carboxamides with the aid of 8-aminoquinolinamide DG (Scheme 6).[13] A variety of azole substrates were reacted successfully with broad scope and functional group diversity. Further, H/D exchange experiments, kinetic isotope effect, radical trapping experiments and electron paramagnetic resonance (EPR) provided insight into the reaction pathway. The reaction was believed to proceed through a single electron transfer (SET) pathway and the removal of the DG illustrated the synthetic utility.



Scheme 6. Co(II)-Catalyzed Coupling of Carboxamides with Azoles

2.1.3 Ni-Catalyzed C-H Heteroarylation

The same group reported an efficient Ni(II)-catalyzed direct *ortho*-selective heteroarylation using 8-aminoquinoline as DG auxiliary, Ag_2CO_3 as oxidant and PivOH as additive (Scheme 7).[14] This reaction displays high efficiency and broad substrate scope with good functional group tolerance.

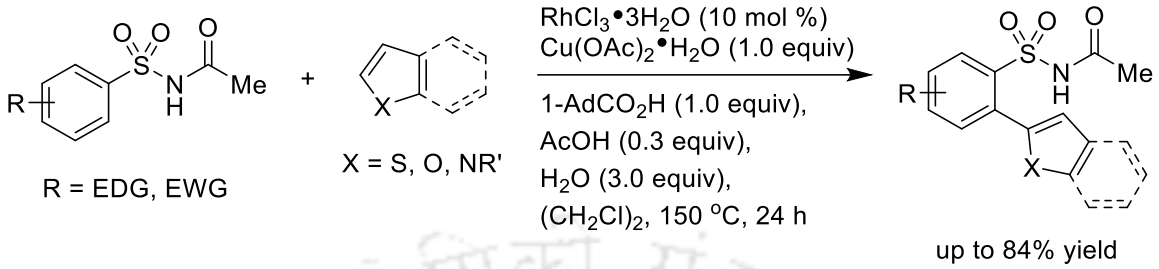


Scheme 7. Ni(II)-Catalyzed Oxidative Coupling of Carboxamides with Azoles

2.1.4 Rh-Catalyzed C-H Heteroarylation

A Rh-catalyzed dehydrogenative cross-coupling of aromatic sulfonamides and substituted heteroarenes was achieved for the synthesis of hetero-biaryl derivatives using $Cu(OAc)_2 \cdot H_2O$ as the oxidant (Scheme 8).[15] This strategy was found to be compatible with diverse heteroarenes, such as benzothiophene, thiophene, benzofuran, furan, pyrrole and indolizine with moderate to

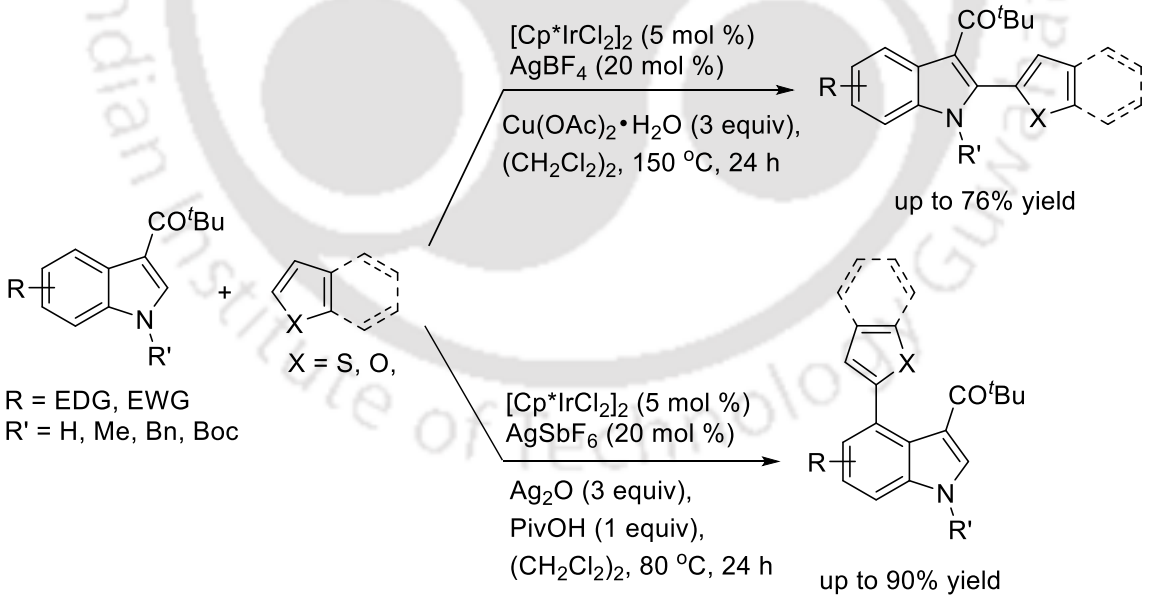
good yields. The late-stage functionalization of COX-2 inhibitor Celecoxib was demonstrated to showcase the efficacy.



Scheme 8. Rh(III)-Catalyzed Coupling of Aromatic Sulfonamides with Heteroarenes

2.1.5 Ir-Catalyzed C-H Heteroarylation

An Ir-catalyzed pivaloyl group directed C2/C4 regioselective dual C-H/C-H oxidative cross-coupling of indoles with heteroarenes was accomplished by fine tuning of oxidants (Scheme 9).[16] The selection of oxidant was found to play a crucial role as $Cu(OAc)_2 \cdot H_2O$ delivered the C2-heteroarylated product via a concerted metalation-deprotonation (CMD) process while C4-heteroarylation was achieved via a S_E3 pathway using Ag_2O as oxidant. A wide variety of indole derivatives were synthesized with functional group diversity and regioselectivity.



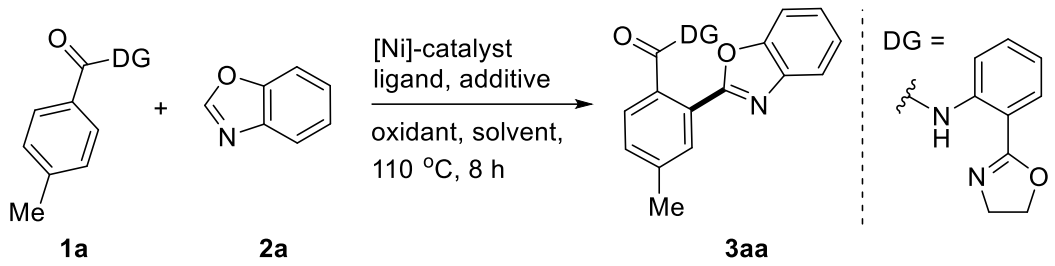
Scheme 9. Ir(III)-Catalyzed Regioselective Heteroarylation of Indoles

2.2 Present Study

This chapter presents a Ni(II)-catalyzed regioselective C-H heteroarylation of carboxamides using a removable oxazoline-based DG to afford hetero-biaryl compounds under aerobic condition. The optimization of the reaction was initiated by employing 4-methylbenzamide **1a** and benzoxazole **2a** as the standard substrates using a series of nickel catalysts, ligands, additives, oxidants and solvents (Table 1). The desired **3aa** was formed in 52% yield, when substrates **1a** and **2a** were stirred in presence of $NiCl_2$ (10 mol %), PPh_3 (20 mol %), 1-$AdCO_2H$ (1.0 equiv) and Ag_2CO_3 (1 equiv) in toluene at 110 ^oC for 8 h (entry 1). In a set of nickel catalysts screened, $NiCl_2$, $Ni(OAc)_2{\cdot}4H_2O$, $NiCl_2(PPh_3)_2$ and $Ni(COD)_2$, the former yielded the best result (entries 2-4). Among the various phosphine-based ligands studied, PCy_3, P(*o*-Tol)$_3$ and DPPE, P(*o*-Tol)$_3$ led to increase the overall yield to 69% (entries 5-7). Control experiment suggests that the presence of ligand is crucial for the formation of **3aa** (entry 8). In case of the additive, 1-$AdCO_2H$ was found to be superior in comparison with PivOH, TFA and KOAc (entries 9-11). Control experiment in absence of the additive failed to produce the desired product (entry 12). Subsequent screening of oxidants, Ag_2CO_3, Ag_2O, 1,4-benzoquione (BQ) and $Cu(OAc)_2$, led to improve the yield to 75% using Ag_2O (entries 13-15). The presence of oxidant was found to be essential to deliver the target adduct (entry 16). 1,4-Dioxane was found to be the solvent of choice, whereas $(CH_2Cl)_2$ and DMF exhibited inferior results (entries 17-19). The influence of the DG on the efficiency of reaction was investigated using a set of amide-tethered dihydrooxazole and pyrazole moieties (Table 2). Sulfonamide-oxazoline **1a'** was not effective while 2-(4-isopropyl-4,5-dihydrooxazol-2-yl)aniline **1b'**, 2-(4-methyl-4,5-dihydrooxazol-2-yl)aniline **1c'** and 2-(1H-pyrazol-1-yl)aniline **1d'** were successful to afford **3b'a-d'a** in 55-71% yields.

Having the optimal reaction condition in hand, the scope of the protocol was investigated using a series of substituted carboxamides **1b-p** with benzoxazole **2a** as a test substrate (Table 3). Unsubstituted benzoic acid **1b** gave the target **3ba** in 77% yield, whereas 2-substituted benzoic acids such as 2-methyl **1c** and 2-fluoro **1d** groups furnished **3ca** and **3da** in 67 and 69% yields, respectively. Similarly, benzamides bearing substituents at the 3-position with methyl **1e** and chloro **1f** groups participated efficiently to afford **3ea** and **3fa** in 74 and 76% yields, respectively. 4-Substituted benzamides such as 4-choloro **1g**, 4-fluoro **1h**, 4-phenyl **1i** and 4-trifluoromehyl **1j**

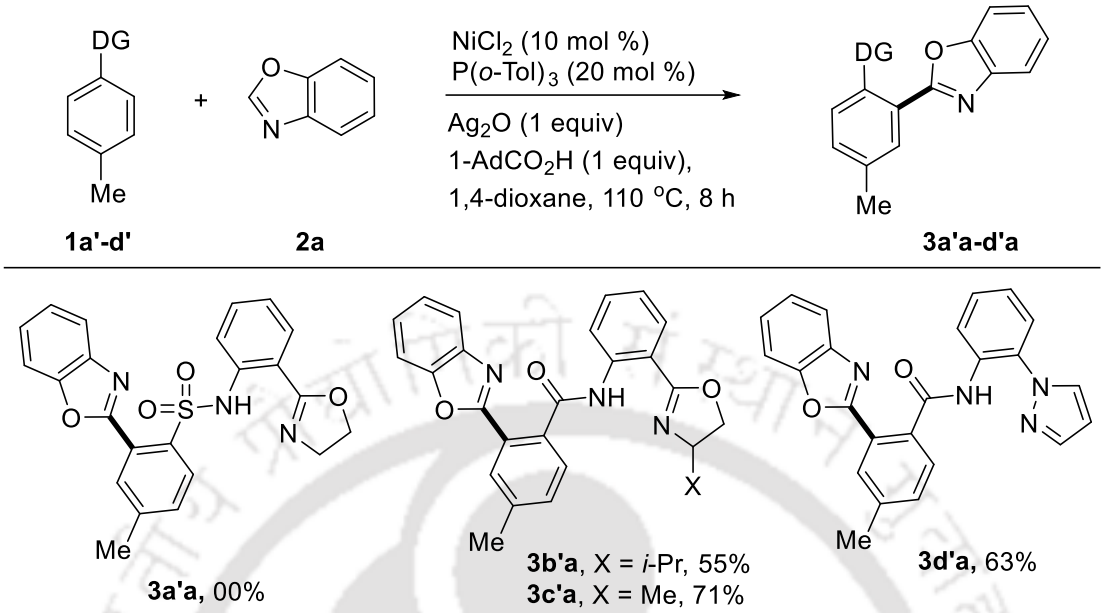
Table 1. Optimization of the Reaction Conditions[a]



Entry	Catalyst	Ligand	Additive	Oxidant	Solvent	Yield (%)[b]
1	$NiCl_2$	PPh_3	1-$AdCO_2H$	Ag_2CO_3	Toluene	52
2	$Ni(OAc)_2•4H_2O$	PPh_3	1-$AdCO_2H$	Ag_2CO_3	Toluene	17
3	$NiCl_2(PPh_3)_2$	PPh_3	1-$AdCO_2H$	Ag_2CO_3	Toluene	33
4	$Ni(COD)_2$	PPh_3	1-$AdCO_2H$	Ag_2CO_3	Toluene	11
5	$NiCl_2$	PCy_3	1-$AdCO_2H$	Ag_2CO_3	Toluene	61
6	$NiCl_2$	P(*o*-Tol)$_3$	1-$AdCO_2H$	Ag_2CO_3	Toluene	69
7	$NiCl_2$	DPPE	1-$AdCO_2H$	Ag_2CO_3	Toluene	n.r.
8	$NiCl_2$	-	1-$AdCO_2H$	Ag_2CO_3	Toluene	n.r.
9	$NiCl_2$	P(*o*-Tol)$_3$	PivOH	Ag_2CO_3	Toluene	62
10	$NiCl_2$	P(*o*-Tol)$_3$	TFA	Ag_2CO_3	Toluene	n.r.
11	$NiCl_2$	P(*o*-Tol)$_3$	KOAc	Ag_2CO_3	Toluene	12
12	$NiCl_2$	P(*o*-Tol)$_3$	-	Ag_2CO_3	Toluene	n.r.
13	$NiCl_2$	P(*o*-Tol)$_3$	1-$AdCO_2H$	Ag_2O	Toluene	75
14	$NiCl_2$	P(*o*-Tol)$_3$	1-$AdCO_2H$	BQ	Toluene	n.r.
15	$NiCl_2$	P(*o*-Tol)$_3$	1-$AdCO_2H$	$Cu(OAc)_2$	Toluene	18
16	$NiCl_2$	P(*o*-Tol)$_3$	1-$AdCO_2H$	-	Toluene	n.r.
17	$NiCl_2$	P(*o*-Tol)$_3$	1-$AdCO_2H$	Ag_2O	$(CH_2Cl)_2$	53
18	**$NiCl_2$**	**P(*o*-Tol)$_3$**	**1-$AdCO_2H$**	**Ag_2O**	**1,4-Dioxane**	**81**
19	$NiCl_2$	P(*o*-Tol)$_3$	1-$AdCO_2H$	Ag_2O	DMF	55

[a]Reaction conditions: **1a** (0.2 mmol), **2a** (0.24 mmol), catalyst (10 mol %), ligand (20 mol %), additive (1 equiv), oxidant (1 equiv), solvent (2 mL), 110 °C, 8 h. [b]Isolated yield. n.r. = no reaction.

Table 2. Investigation on Reactivity of DG[a]



[a]Reaction conditions: DGs **1a'-d'** (0.2 mmol), **2a** (0.24 mmol), $NiCl_2$ (10 mol %), P(*o*-Tol)$_3$ (20 mol %), Ag_2O (1 equiv), 1-$AdCO_2H$ (1 equiv), 1,4-dioxane (2 mL), 110 °C, 8 h. [b]Isolated yield.

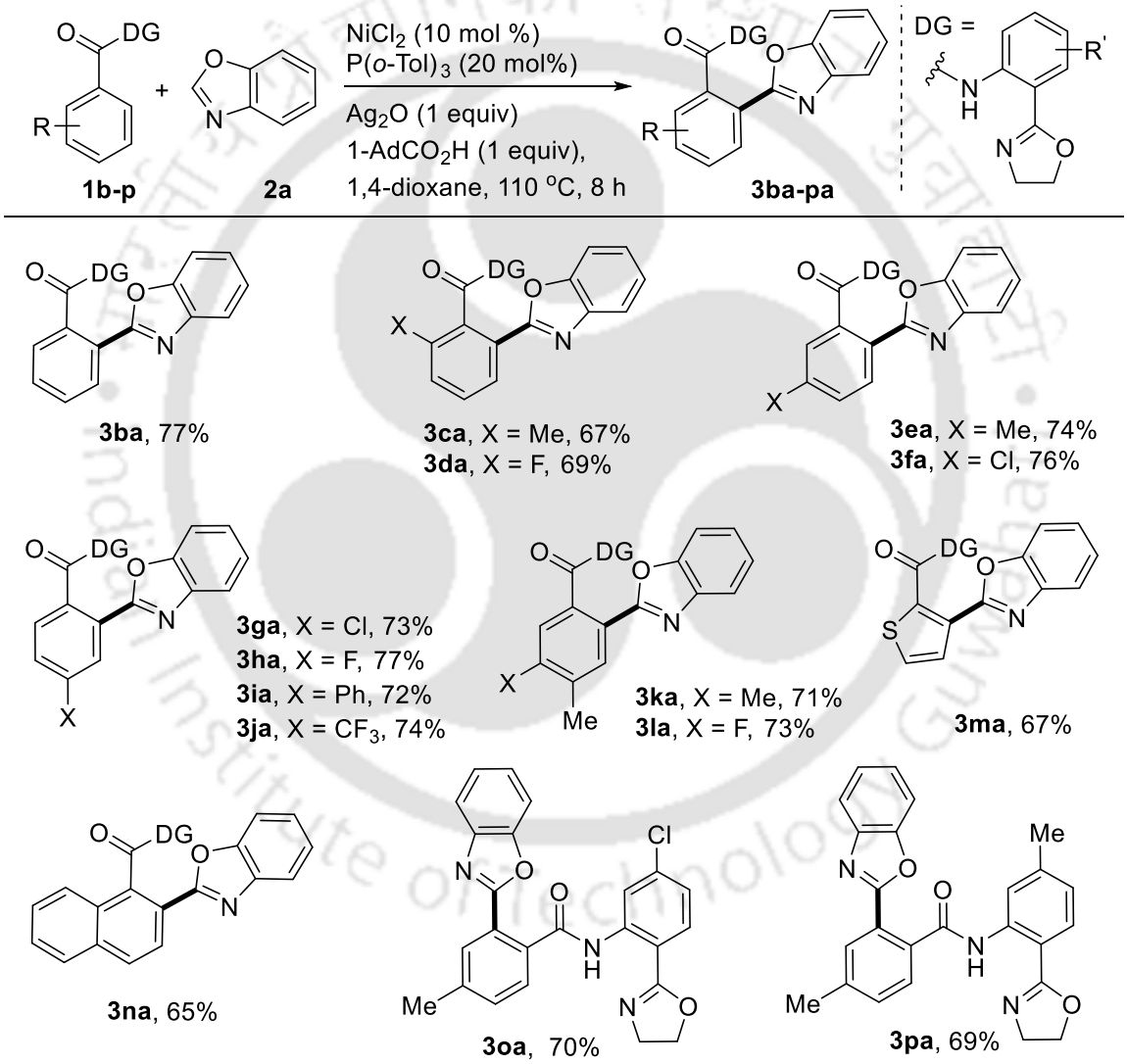
functionalities gave **3ga-ja** in 72-77% yields. The reaction of di-substituted benzamides **1k** and **1l** proceeded smoothly, furnishing **3ka** and **3la** in 71 and 73% yields, respectively. Furthermore, heterocyclic **1m** and polyaromatic carboxamide **1n** were amenable to deliver **3ma** and **3na** in 67 and 65% yields, respectively. In addition, the influence of different functionalities on the phenyl ring of the 2-phenyl-4,5-dihydrooxazole was also investigated. For examples, 4-chloro **1o** and 4-methyl **1p** groups on the phenyl ring afforded **3oa** and **3pa** in 70 and 69% yields, respectively.

The scope was expanded to the coupling of substituted azoles **2b-m** with 4-methylbenzamide **1a** as a standard substrate (Table 4). Benzoxazoles with 5-chloro **2b**, 5-methyl **2c**, 5-nitro **2d** and 6-nitro **2e** functionalities at the aryl ring were participated efficiently to afford **3ab-3ae** in 71-79% yields. In addition, 5-aryloxazoles having substituents at the phenyl ring such as 2-nitro **2f**, 3-nitro **2g**, 3-trifluoromethyl **2h**, 4-chloro **2i**, 4-fluoro **2j**, 4-phenyl **2k** and 4-nitro **2l** groups were compatible, furnishing the **3af-al** in 69-78% yields. Moreover, benzothiazole **2m** delivered **3am** in 71% yield.

The viability of the protocol for the late-stage modification in drug molecules was exemplified by C-H arylation of marketed drugs (Scheme 10). It is noteworthy that C-H functionalization using drug molecules as a functional group remains significantly challenging owing to the omnipresence

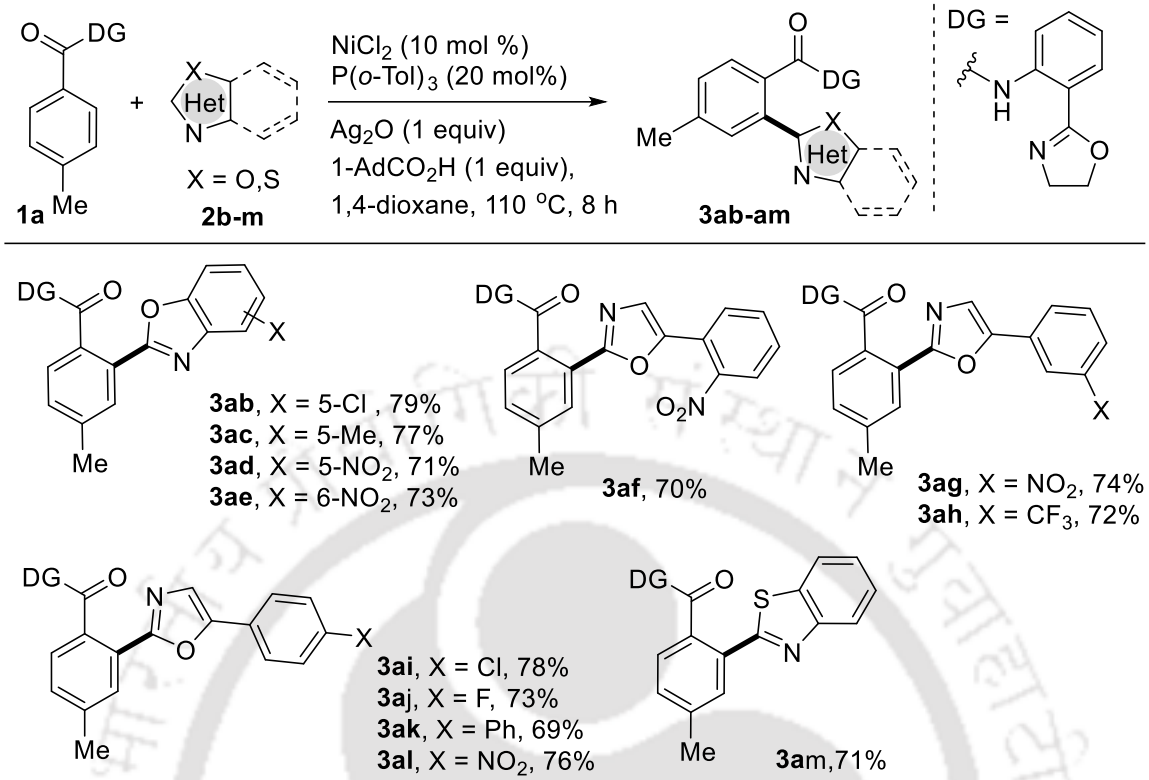
of multiple heterocyclic cores. In this direction, the methylxanthine derived natural CNS stimulant caffeine **2n** coupled with **1a** to furnish **3an** in 69% yield. Moreover, commercially available anti-peripheral vascular disease (PVD) drug pentoxyfylline **2o** and anti-asthmatic drug doxofylline **2p** were paricipated, affording **3ao** and **3ap** in 67 and 61% yields, respectively. These results suggest the remarkable potential of the hypothesis in regioselective C-H functionalizations using potent phamacophoric units as a functional handle.

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



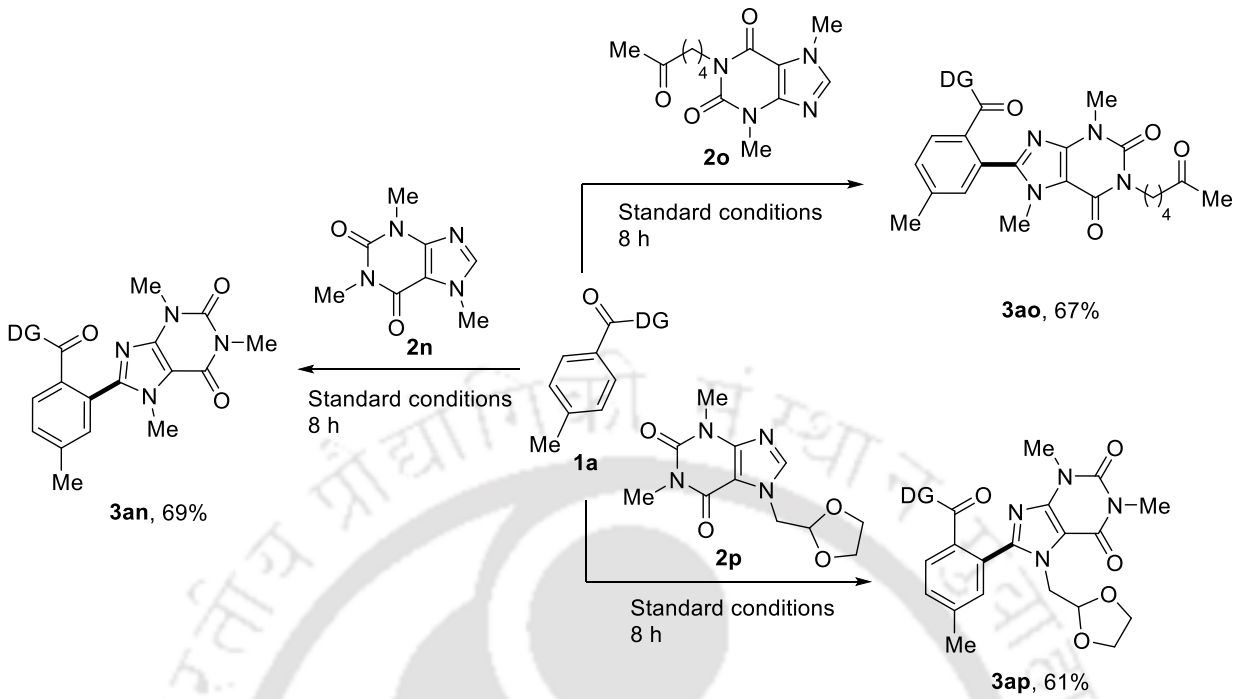
[a]Reaction conditions: **1b-p** (0.2 mmol), **2a** (0.24 mmol), $NiCl_2$ (10 mol %), P(*o*-Tol)$_3$ (20 mol %), Ag_2O (1 equiv), 1-AdCO_2H (1 equiv), 1,4-dioxane (2 mL), 110 °C, 8 h. [b]Isolated yield.

Table 4. Substrate Scope of Azoles [a,b]

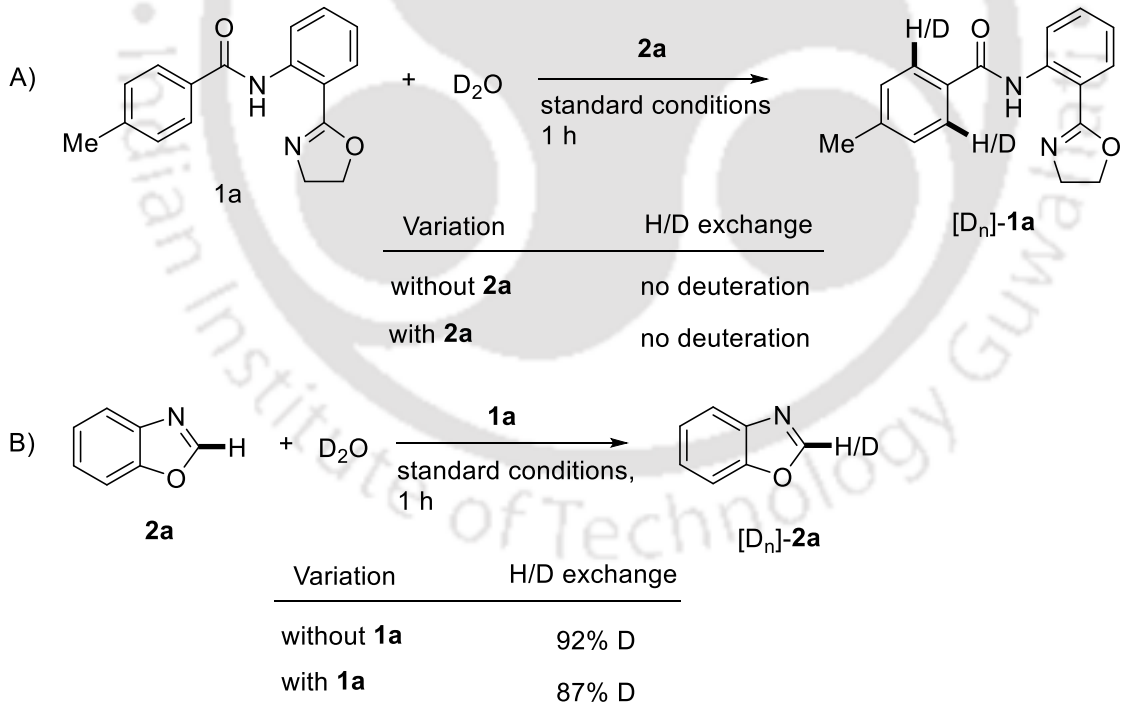


[a]Reaction conditions: **1a** (0.2 mmol), **2b-m** (0.24 mmol), $NiCl_2$ (10 mol %), P(*o*-Tol)$_3$ (20 mol %), Ag_2O (1 equiv), 1-AdCO_2H (1 equiv), 1,4-dioxane (2 mL), 110 °C, 8 h. [b]Isolated yield.

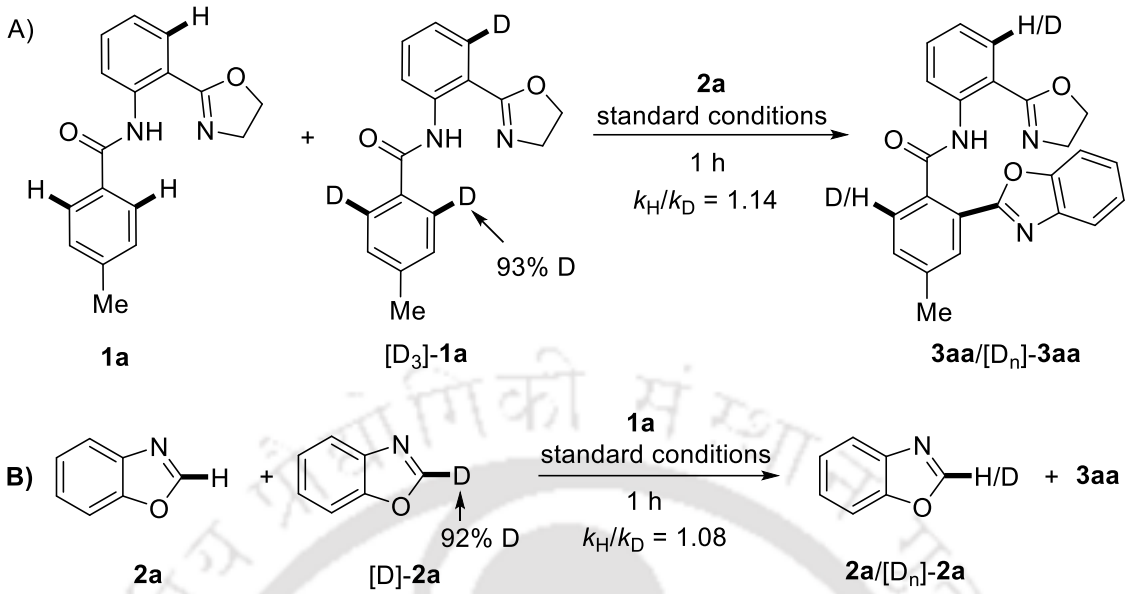
To shed light into the reaction pathway, H/D-exchange and kinetic isotope experiments were accomplished. The H/D scrambling experiment using *N*-(2-(4,5-dihydrooxazol-2-yl)phenyl)-4-methylbenzamide **1a** and D_2O as a co-solvent was performed and no deuteration was observed after 1 h (Scheme 11A). On the other hand, 92% deuterium incorporation was observed when benzoxazole **2a** reacted with D_2O in absence of **1a** (Scheme 11B). The deuterium labelling experiment using both **1a** and **2a** in presence of D_2O showed 87% H/D scrambling for [D_n]-**2a** and no deuterium incorporation for the recovered [D_n]-**1a**. These outcomes suggest the irreversible cleavage of the C-H bond in **1a** wherein the C-H bond activation step in **2a** could be a reversible process. Intermolecular kinetic isotope experiment using **1a** and [D_3]-**1a** with **2a** yielded k_H/k_D = 1.14, while k_H/k_D of 1.08 was attained using **2a** and [D]-**2a** with **1a**. This outcomes revealed that the C-H bond cleavage of benzamide and azole might not be involved in the rate determining step (Scheme 12A and 12B).



Scheme 10. Functionalization of Drug Molecules



Scheme 11. H/D Exchange Experiments

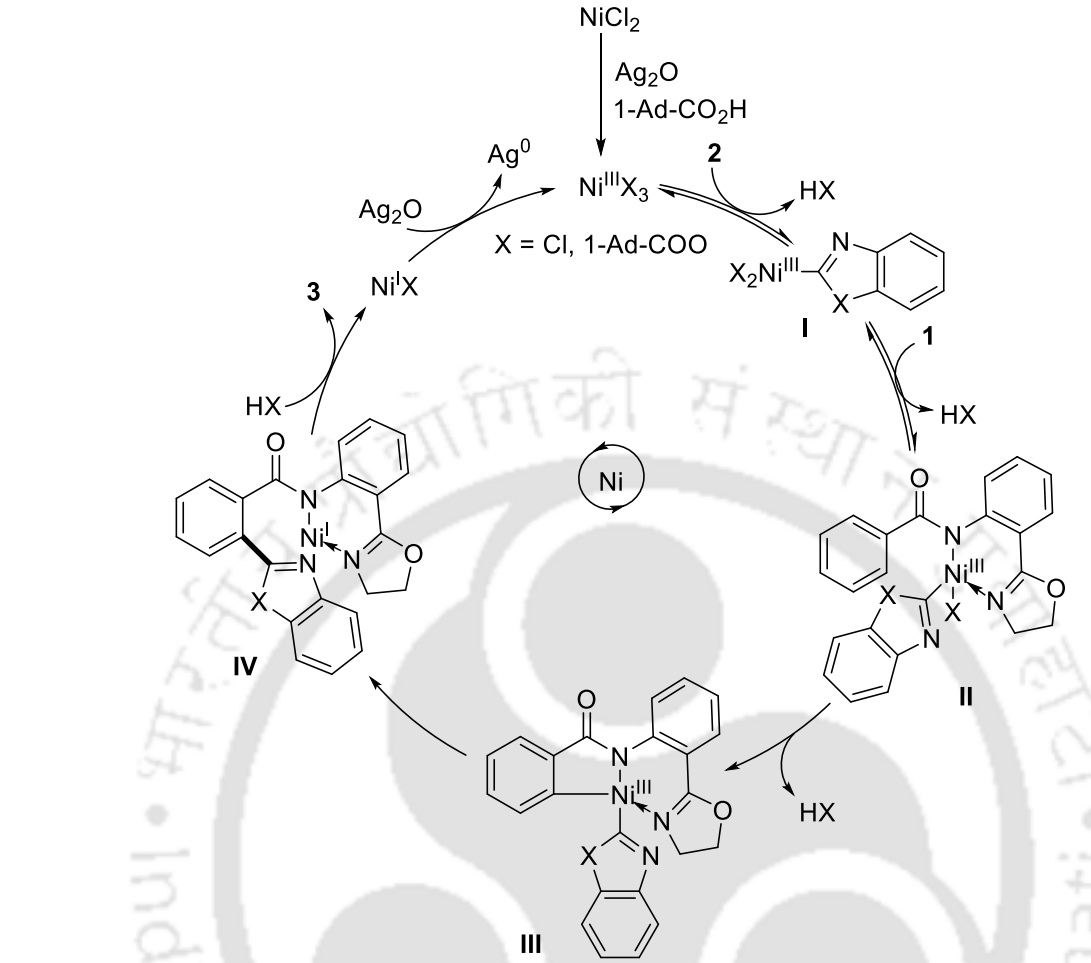


Scheme 12. Intermolecular Kinetic Isotope Experiments

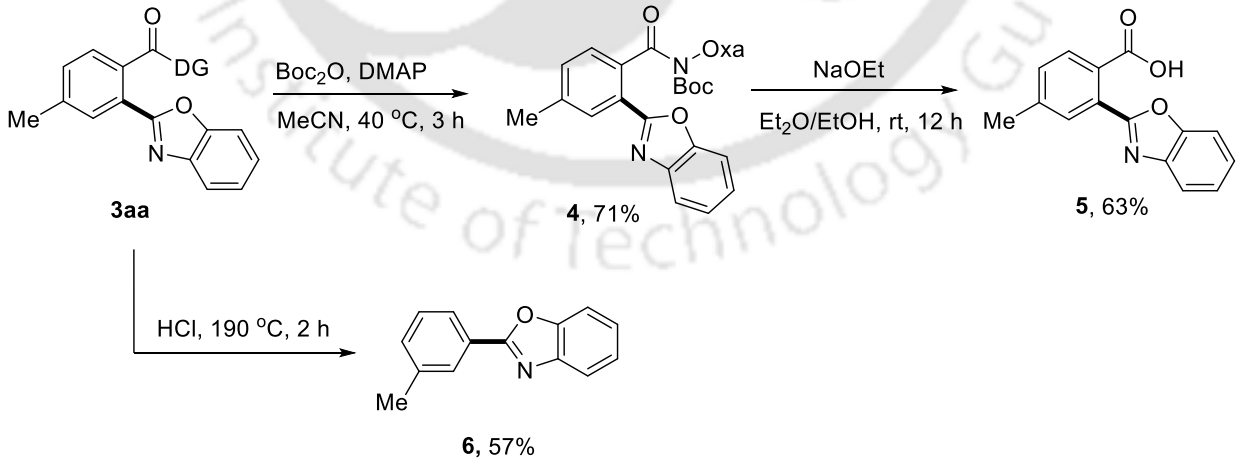
On the basis of the preliminary mechanistic investigations and reported precedents,[7,14] a plausible mechanism was demonstrated in scheme 13. The activation of C-H bond of azole **2** by the Ni(III)-complex can lead to the formation of intermediate **I**. Subsequently, **1** can undergo coordination to the Ni(III) centre, affording intermediate **II**. The intramolecular cyclometalation of the latter can provide **III**, which in turn, may undergo reductive elimination to furnish the Ni(I)-species **IV**. Protodemetalation of the latter can deliver the target **3** and the Ag(I)-mediated oxidation of the Ni(I)-species can regenerate the Ni(III)-complex.

To highlight the synthetic utilities, post synthetic transformations were performed (Scheme 14). The amide-oxazoline DG of **3aa** was removed in a tandem reaction sequence, producing the carboxylic acid **5** in 63% yield, whereas the acid mediated removal of the DG furnished the bi-heteroaryl product **6** in 57% yield.

In summary, we have demonstrated a Ni-catalyzed regioselective dehydrogenative C(sp^2)-H/C(sp^2)-H cross-coupling of aromatic amides with of azoles using oxazoline-based DG. This method is tolerated with a broad range of functional groups with different electronic properties and substitution patterns. In addition, the utilization of inexpensive nickel(II) catalyst, substrate scope and late-stage modification of xanthine-derived drugs are the important practical features.



Scheme 13. Plausible reaction mechanism



Scheme 14. Post-Synthetic Utilities

2.3 Experimental Section

General Information. $NiCl_2$ (99%), $Ni(OAc)_2•4H_2O$ (99.99%), $Ni(PPh_3)_2Cl_2$ (99.99%), $Ni(COD)_2$ (99%), Ag_2O (99.99%), P(*o*-Tol)$_3$ (97%) and 1-AdCO_2H (99%) were purchased from Aldrich and used as received. All the solvents were dried prior to use according to the standard procedure. Carboxamides[7] and azoles[8-10] were prepared according to reported procedure. SRL silica gel G/GF 254 plates were used for analytical TLC and SRL silica gel (100-200 mesh) was used for column chromatography. NMR (^{1}H, ^{13}C and ^{19}F) spectra were recorded with Bruker Avance III 600, Ascend 400 and 500 MHz spectrometer using $CDCl_3$ 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, dd = doublet of doublets. Melting points were determined using a Büchi B-540 apparatus and are uncorrected. FT-IR spectra were collected on Perkin Elmer IR spectrometer. Q-Tof ESI-MS instrument (model HAB 273) was used for recording mass spectra.

Procedure for the Oxidative C-H Heteroarylation. A mixture of amide **1** (0.2 mmol), azole **2** (0.24 mmol), $NiCl_2$ (0.02 mmol, 3 mg), P(*o*-Tol)$_3$ (0.04 mmol, 12 mg), Ag_2O (0.2 mmol, 46 mg) and 1-AdCO_2H (0.2 mmol, 36 mg) was stirred in 1,4-dioxane (2 mL) at 110 ^oC for 8 h under air. Upon completion, the reaction mixture was cooled to room temperature, diluted with ethyl acetate (20 mL) and passed through a short pad of celite. The organic layer was washed with brine (2 × 5 mL) and water (2 × 5 mL). Drying (Na_2SO_4) and evaporation of the solvent gave a residue that was purified on silica gel column chromatography using ethyl acetate/hexane as an eluent to afford the product **3**.

Synthesis of 4 and 5.[7b] Di-*tert*-butyl dicarbonate (1 mmol, 218 mg) was added to a solution of 2-(benzo[d]oxazol-2-yl)-*N*-(2-(4,5-dihydrooxazol-2-yl)phenyl)-4-methylbenzamide **3aa** (0.1 mmol, 40 mg) and DMAP (0.2 mmol, 24 mg) in CH_3CN (2 mL) and was stirred at 40 ^oC for 3 h under air. The solvent was evaporated under reduced pressure to give a residue, which was purified by silica gel column chromatography using ethyl acetate/*n*-hexane as the eluent to furnish **4** as a yellow solid. Next, to a stirred a solution of **4** (0.07 mmol, 35 mg) in Et_2O/EtOH (4/1, v/v, 3 mL), EtONa (20% w/w in EtOH, 0.21 mmol, 71 mg) was added at 0 ^oC under inert atmosphere and the resultant mixture was stirred at room temperature for 12 h. The reaction mixture was then diluted with ethyl acetate (10 mL) and washed with 1 N HCl (1 × 5 mL), brine (2 × 5 mL) and water (5

mL). Drying (Na_2SO_4) and evaporation of the solvent gave a residue that was purified by a silica gel column chromatography using ethyl acetate/hexane as the eluent to afford **5** in 63% yield (11 mg).

Synthesis of 6.[7e] A mixture of 2-(benzo[d]oxazol-2-yl)-*N*-(2-(4,5-dihydrooxazol-2-yl)phenyl)-4-methylbenzamide **3aa** (0.1 mmol, 40 mg) in conc. HCl (1 mL) was stirred at 190 ^oC for 2 h in a sealed tube. The mixture was cooled to room temperature and treated with NaOH solution until the pH was adjusted to 9. The aqueous layer was extracted with dichloromethane (3 × 5 mL). Drying (Na_2SO_4) and evaporation of the solvent gave a residue, which was purified on silica gel column chromatography to afford 2-(*m*-tolyl)benzo[d]oxazole **6** as a brown solid in 57% yield (12 mg).

Synthesis of [D_3]-1a. *N*-(2-(4,5-Dihydrooxazol-2-yl)phenyl)-4-methylbenzamide **1a** (0.2 mmol, 56 mg), $Pd(TFA)_2$ (0.01 mmol, 3 mg), D_2O (4 mmol, 80 mg) and toluene (1 mL) were stirred at 130 ^oC for 1 h in a sealed tube. The resultant mixture was extracted with ethyl acetate (2 × 5 mL) and the organic layer was dried over Na_2SO_4. Evaporation of the solvent gave a residue that was purified on silica gel column chromatography using ethyl acetate/hexane to afford [D_3]-**1a** in 98% yield. The deuterium incorporation was determined using 400 MHz ^1H NMR as 93% D was incorporated into the two *ortho* positions of the carboxamide aryl ring.

H/D exchange Experiment of 1a with D_2O in the Absence of 2a. *N*-(2-(4,5-Dihydrooxazol-2-yl)phenyl)-4-methylbenz-amide **1a** (0.2 mmol, 56 mg), $NiCl_2$ (0.02 mmol, 3 mg), P(*o*-Tol)$_3$ (0.04 mmol, 12 mg), Ag_2O (0.2 mmol, 46 mg), 1-$AdCO_2H$ (0.2 mmol, 36 mg) and D_2O (4 mmol, 80 mg) was stirred in 1,4-dioxane (2 mL) at 110 ^oC for 1 h under air. The reaction mixture was cooled to room temperature, diluted with ethyl acetate (2 × 5 mL) and passed through a short pad of celite. The work-up and purification were performed as described in the general procedure. 400 MHz ^1H NMR analysis of the product showed no deuterium incorporation.

H/D exchange Experiment of 2a with D_2O in the Absence of 1a. Benzoxazole **2a** (0.2 mmol, 24 mg), $NiCl_2$ (0.02 mmol, 3 mg), P(*o*-Tol)$_3$ (0.04 mmol, 12 mg), Ag_2O (0.2 mmol, 46 mg), 1-$AdCO_2H$ (0.2 mmol, 36 mg) and D_2O (4 mmol, 80 mg) was stirred in 1,4-dioxane (2 mL) at 110 ^oC for 1 h under air. The reaction mixture was cooled, diluted with ethyl acetate (2 × 5 mL) and passed through a short pad of celite. The work-up and purification were performed as described in

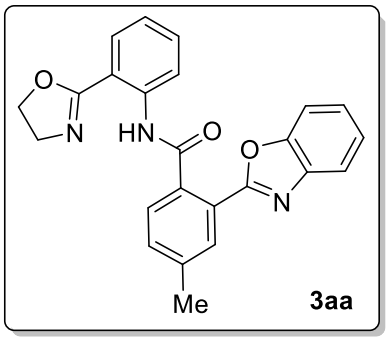
the general procedure. The deuterium incorporation was calculated using 400 MHz ^{1}H NMR as 92%.

H/D Exchange Experiment of 1a with D_2O in the Presence of 2a. A mixture of *N*-(2-(4,5-dihydrooxazol-2-yl)phenyl)-4-methylbenz-amide **1a** (0.2 mmol, 56 mg), benzoxazole **2a** (0.24 mmol, 28 mg), $NiCl_2$ (0.02 mmol, 3 mg), P(*o*-Tol)$_3$ (0.04 mmol, 12 mg), Ag_2O (0.2 mmol, 46 mg), 1-AdCO_2H (0.2 mmol, 36 mg) and D_2O (4 mmol, 80 mg) was stirred in 1,4-dioxane (2 mL) at 110 ^oC for 1 h under air. The reaction mixture was cooled to room temperature, diluted with ethyl acetate (2 × 5 mL) and passed through a short pad of celite. The work-up and purification were performed as described in the general procedure. 400 MHz ^{1}H NMR analysis revealed no deuterium incorporation into carboxamide while 87% D was observed at the 2-position of benzoxazole.

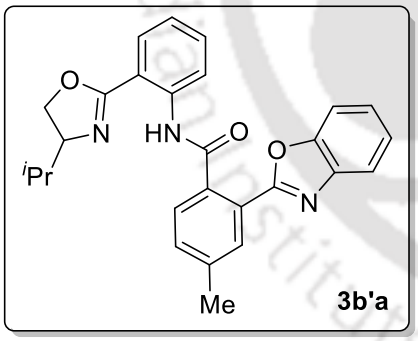
Intermolecular Kinetic Isotope Effect Experiment using 1a and [D_3]-1a. A mixture of **1a** (0.2 mmol, 56 mg) and [D_3]-**1a** (0.2 mmol, 57 mg) was reacted with **2a** (0.2 mmol, 24 mg) for 1 h under standard reaction condition. The resulting solution was then diluted with ethyl acetate (2 x 5 mL), passed through a short pad of celite, washed with brine (2 x 5 mL) and water (5 mL). Drying (Na_2SO_4) and evaporation of the solvent produced a residue, which was purified on silica gel column chromatography using ethyl acetate/hexane as the eluent to afford a mixture of **3aa**/[D_2]-**3aa**. The intermolecular k_H/k_D was found to be 1.14, based on the 400 MHz ^{1}H NMR spectroscopy.

Intermolecular Kinetic Isotope Effect Experiment using 2a and [D]-2a. *N*-(2-(4,5-Dihydrooxazol-2-yl)phenyl)-4-methylbenzamide **1a** (0.2 mmol, 56 mg) was reacted with **2a** (0.2 mmol, 24 mg) and [D]-**2a** (0.2 mmol, 24 mg) for 1 h under the standard reaction condition. The resulting solution was diluted with ethyl acetate (2 x 5 mL), passed through a short pad of celite, washed with brine (2 x 5 mL) and water (5 mL). Drying (Na_2SO_4) and evaporation of the solvent produced a residue, which was purified on silica gel column chromatography using ethyl acetate/hexane as the eluent to afford a mixture of unreacted **2a** and [D]-**2a**. The intermolecular k_H/k_D was found to be 1.08, based on the 400 MHz ^{1}H NMR spectroscopy analysis.

2.4 Characterization Data of Products

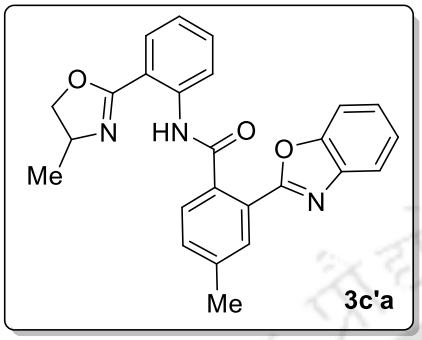


2-(Benzo[d]oxazol-2-yl)-N-(2-(4,5-dihydrooxazol-2-yl)phenyl)-4-methylbenzamide 3aa. Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.48; colorless solid; mp 161-162 ^oC; yield 81% (64 mg); ^1H NMR (400 MHz, $CDCl_3$) δ 12.35 (s, 1H), 8.79 (d, *J* = 8.4 Hz, 1H), 7.97 (s, 1H), 7.69-7.61 (m, 3H), 7.47-7.43 (m, 1H), 7.37 (d, *J* = 7.6 Hz, 1H), 7.25-7.16 (m, 3H), 7.02 (t, *J* = 7.2 Hz, 1H), 3.91 (t, *J* = 9.6 Hz, 2H), 3.63 (t, *J* = 9.6 Hz, 2H), 2.43 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 167.9, 164.4, 162.6, 151.1, 141.9, 140.7, 139.9, 135.3, 132.6, 132.1, 130.9, 129.2, 129.0, 125.3, 125.0, 124.5, 122.7, 120.5, 120.1, 113.8, 110.7, 66.1, 54.4, 21.4; FT-IR (KBr) 3006, 2921, 1636, 1610, 1535, 1449, 1306, 1275, 1260, 749 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{24}H_{20}N_3O_3$: 398.1499, found: 398.1508.

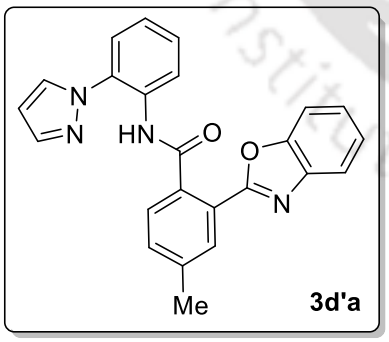


2-(Benzo[d]oxazol-2-yl)-N-(2-(4-isopropyl-4,5-dihydrooxazol-2-yl)phenyl)-4-methylbenzamide 3b'a. Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.54; colorless solid; mp 173-174 ^oC; yield 55% (48 mg); ^1H NMR (400 MHz, $CDCl_3$) δ 12.76 (s, 1H), 8.89 (d, *J* = 8.4 Hz, 1H), 8.03 (s, 1H), 7.81-7.78 (m, 1H), 7.72-7.68 (m, 2H), 7.54-7.50 (m, 1H), 7.41-7.36 (m, 2H), 7.32-7.26 (m, 2H), 7.13-7.09 (m, 1H), 4.17-4.13 (m, 1H), 3.91-3.79 (m, 2H), 2.49 (s, 3H), 1.60-1.51 (m, 1H), 0.75-0.72 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.8, 163.3, 162.5, 151.1, 141.9, 140.5, 140.2, 135.4, 132.6, 131.8, 130.8, 129.1, 128.6, 125.27, 125.22, 124.5, 122.6, 120.3, 120.1,

113.6, 110.7, 72.5, 69.4, 33.0, 21.3, 18.7, 18.5; FT-IR (KBr) 3009, 2962, 1683, 1635, 1610, 1536, 1449, 1275, 1260, 749 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{27}H_{26}N_3O_3$: 440.1969, found: 440.1969.

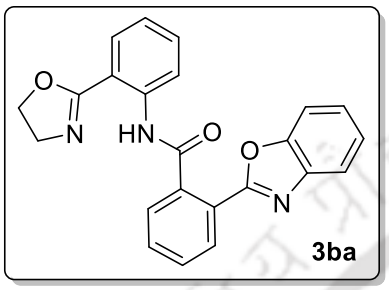


2-(Benzo[d]oxazol-2-yl)-4-methyl-N-(2-(4-methyl-4,5-dihydrooxazol-2-yl)phenyl)benzamide 3c'a. Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.52; colorless solid; mp 169-170 ^oC; yield 71% (58 mg); ^1H NMR (400 MHz, $CDCl_3$) δ 12.64 (s, 1H), 8.89 (d, *J* = 8.4 Hz, 1H), 8.06-8.05 (m, 1H), 7.82-7.79 (m, 1H), 7.76-7.72 (m, 2H), 7.56-7.52 (m, 1H), 7.47-7.44 (m, 1H), 7.39-7.37 (m, 1H), 7.34-7.27 (m, 2H), 7.15-7.11 (m, 1H), 4.19-4.09 (m, 2H), 3.74-3.71 (m, 1H), 2.52 (s, 3H), 1.14 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.7, 163.2, 162.6, 151.1, 141.9, 140.7, 140.1, 135.3, 132.6, 131.9, 131.0, 129.0, 128.8, 125.3, 125.2, 124.5, 122.6, 120.3, 120.2, 113.7, 110.7, 72.6, 61.7, 21.4, 21.3; FT-IR (KBr) 3009, 2988, 1683, 1634, 1610, 1536, 1447, 1275, 1260, 749 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{25}H_{22}N_3O_3$: 412.1656, found: 412.1657.

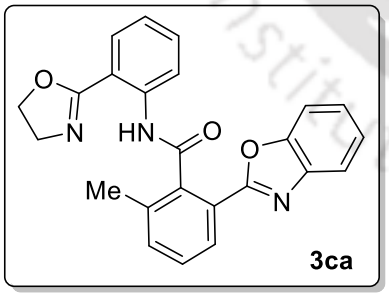


***N*-(2-(1H-Pyrazol-1-yl)phenyl)-2-(benzo[d]oxazol-2-yl)-4-methylbenzamide 3d'a**. Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.46; colorless solid; mp 154-155 ^oC; yield 63% (50 mg); ^1H NMR (400 MHz, $CDCl_3$) δ 10.61 (s, 1H), 8.58 (d, *J* = 8.0 Hz, 1H), 7.93 (s, 1H), 7.59-7.57 (m, 1H), 7.53 (d, *J* = 7.6 Hz, 1H), 7.42-7.33 (m, 4H), 7.30-7.27 (m, 1H), 7.21-7017 (m, 3H),

7.14-7.09 (m, 1H), 6.03-6.02 (m, 1H), 2.41 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.3, 161.9, 151.0, 141.9, 140.9, 140.8, 134.9, 132.1, 131.6, 130.8, 129.5, 129.4, 128.6, 128.0, 125.2, 124.8, 124.48, 124.46, 123.6, 122.2, 120.4, 110.6, 106.7, 21.4; FT-IR (KBr) 3006, 1681, 1599, 1529, 1513, 1452, 1275, 1260, 749 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{24}H_{19}N_4O_2$: 395.1503, found: 395.1505.

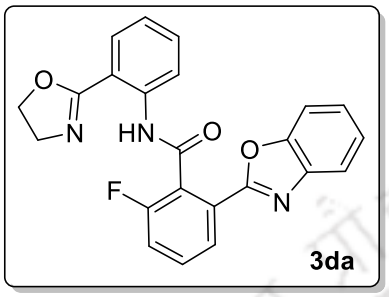


2-(Benzo[d]oxazol-2-yl)-N-(2-(4,5-dihydrooxazol-2-yl)phenyl)benzamide 3ba. Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.42; colorless solid; mp 180-181 °C; yield 77% (59 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.47 (s, 1H), 8.87 (d, *J* = 8.4 Hz, 1H), 8.26-8.22 (m, 1H), 7.84-7.80 (m, 1H), 7.77-7.75 (m, 1H), 7.71-7.69 (m, 1H), 7.65-7.60 (m, 2H), 7.55-7.51 (m, 1H), 7.34-7.24 (m, 3H), 7.13-7.09 (m, 1H), 3.99 (t, *J* = 9.6 Hz, 2H), 3.71 (t, *J* = 9.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.8, 164.4, 162.2, 151.1, 141.9, 139.8, 137.9, 132.6, 131.4, 130.3, 129.1, 129.0, 125.3, 125.0, 124.5, 122.8, 120.5, 120.2, 113.8, 110.7, 66.1, 54.4; FT-IR (KBr) 2976, 1681, 1634, 1610, 1532, 1448, 1303, 1058, 747 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{23}H_{18}N_3O_3$: 384.1343, found: 384.1346.

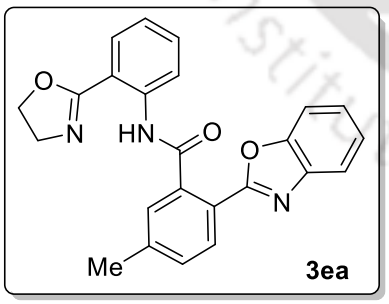


2-(Benzo[d]oxazol-2-yl)-N-(2-(4,5-dihydrooxazol-2-yl)phenyl)-6-methylbenzamide 3ca. Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.52; colorless solid; mp 148-149 °C; yield 67% (53 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.14 (s, 1H), 8.83 (d, *J* = 8.4 Hz, 1H), 8.17-8.15 (m, 1H), 7.78-7.76 (m, 1H), 7.65-7.62 (m, 1H), 7.60-7.55 (m, 1H), 7.50-7.43 (m, 2H), 7.29-7.21 (m, 3H), 7.13 (t, *J* = 7.6 Hz, 1H), 3.99-3.94 (m, 2H), 3.66 (t, *J* = 9.2 Hz, 2H), 2.55 (s, 3H);

^{13}C NMR (150 MHz, $CDCl_3$) δ 168.1, 164.2, 162.1, 150.8, 141.9, 139.6, 137.4, 136.5, 133.6, 132.4, 129.3, 129.1, 127.1, 125.2, 124.5, 124.1, 122.9, 121.2, 120.2, 114.2, 110.5, 66.0, 54.4, 19.6; FT-IR (KBr) 2978, 1684, 1528, 1446, 1300, 1056, 743 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{24}H_{20}N_3O_3$: 398.1499, found: 398.1502.

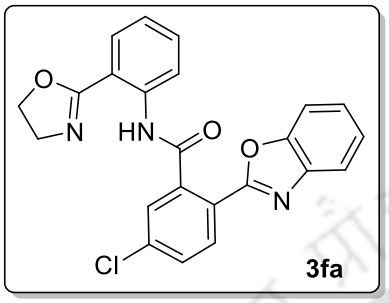


2-(Benzo[d]oxazol-2-yl)-N-(2-(4,5-dihydrooxazol-2-yl)phenyl)-6-fluorobenzamide 3da. Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.46; colorless solid; mp 153-154 °C; yield 69% (55 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.47 (s, 1H), 8.84 (d, *J* = 8.4 Hz, 1H), 8.13 (d, *J* = 8.0 Hz, 1H), 7.81-7.79 (m, 1H), 7.69-7.66 (m, 1H), 7.61-7.55 (m, 2H), 7.38-7.27 (m, 4H), 7.18-7.14 (m, 1H), 4.03 (t, *J* = 9.6 Hz, 2H), 3.71 (t, *J* = 9.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.4, 162.9, 161.2 (J_{C-F} = 247.9 Hz), 160.8 (J_{C-F} = 3.4 Hz), 151.0, 141.9, 139.6, 132.6, 131.2 (J_{C-F} = 8.6 Hz), 129.1, 126.6 (J_{C-F} = 4.3 Hz), 126.1 (J_{C-F} = 20.8 Hz), 125.7, 125.4 (J_{C-F} = 3.2 Hz), 124.8, 123.2, 121.1, 120.6, 119.1 (J_{C-F} = 22.1 Hz), 114.2, 110.8, 66.2, 54.5; ^{19}F NMR (377 MHz, $CDCl_3$) δ -114.5; FT-IR (KBr) 2979, 1690, 1635, 1535, 1448, 1307, 1244, 945, 748 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{23}H_{17}FN_3O_3$: 402.1248, found: 402.1251.

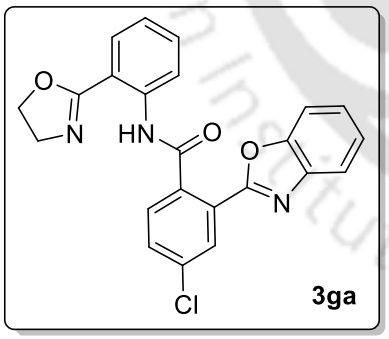


2-(Benzo[d]oxazol-2-yl)-N-(2-(4,5-dihydrooxazol-2-yl)phenyl)-5-methylbenzamide 3ea. Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.50; colorless solid; mp 182-183 °C; yield 74% (59 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.42 (s, 1H), 8.88 (d, *J* = 8.4 Hz, 1H), 8.17 (d, *J* = 8.0 Hz, 1H), 7.78-7.76 (m, 1H), 7.71-7.68 (m, 1H), 7.65 (s, 1H), 7.58-7.54 (m, 1H), 7.47-7.44 (m, 1H), 7.33-7.24 (m, 3H), 7.15-7.11 (m, 1H), 3.95 (t, *J* = 10 Hz, 2H), 3.68 (t, *J* = 9.2 Hz, 2H),

2.51 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 168.1, 164.3, 162.4, 151.0, 142.1, 142.0, 139.8, 137.8, 132.5, 131.1, 130.2, 129.8, 129.0, 125.1, 124.4, 122.7, 122.0, 120.6, 120.0, 113.9, 110.6, 66.0, 54.3, 21.6.; FT-IR (KBr) 2976, 1682, 1611, 1533, 1448, 1305, 1059, 749 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{24}H_{20}N_3O_3$: 398.1499, found: 398.1514.

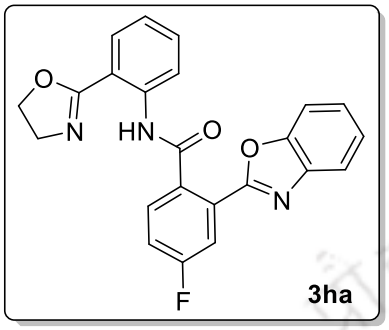


2-(Benzo[d]oxazol-2-yl)-5-chloro-N-(2-(4,5-dihydrooxazol-2-yl)phenyl)benzamide 3fa. Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.46; colorless solid; mp 186-187 °C; yield 76% (63 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.53 (s, 1H), 8.82 (d, *J* = 8.4 Hz, 1H), 8.20 (d, *J* = 8.4 Hz, 1H), 7.80-7.52 (m, 5H), 7.33-7.25 (m, 3H), 7.13 (t, *J* = 7.6 Hz, 1H), 3.99 (t, *J* = 9.6 Hz, 2H), 3.70 (t, *J* = 9.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.3, 164.4, 161.2, 151.0, 141.8, 139.5, 139.1, 137.7, 132.6, 131.6, 130.5, 129.3, 129.1, 125.5, 124.7, 123.4, 123.0, 120.6, 120.3, 113.9, 110.7, 66.1, 54.3; FT-IR (KBr) 2981, 1681, 1611, 1531, 1448, 1304, 1058, 745 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{23}H_{17}ClN_3O_3$: 418.0953, found: 418.0962.

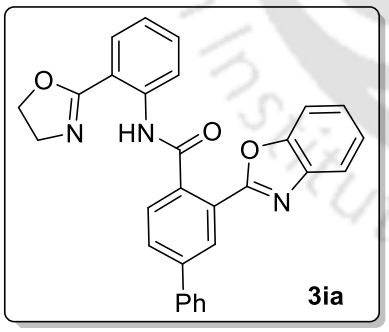


2-(Benzo[d]oxazol-2-yl)-4-chloro-N-(2-(4,5-dihydrooxazol-2-yl)phenyl)benzamide 3ga. Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.42; colorless solid; mp 145-146 °C; yield 73% (61 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.51 (s, 1H), 8.84 (d, *J* = 8.4 Hz, 1H), 8.25-8.24 (m, 1H), 7.78-7.74 (m, 2H), 7.71-7.69 (m, 1H), 7.61-7.58 (m, 1H), 7.55-7.51 (m, 1H), 7.35-7.29 (m, 3H), 7.12 (t, *J* = 7.6 Hz, 1H), 4.00 (t, *J* = 9.6 Hz, 2H), 3.71 (t, *J* = 9.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.8, 164.4, 160.8, 151.1, 141.7, 139.7, 136.4, 136.2, 132.6, 131.4, 130.5,

130.1, 129.1, 126.7, 125.7, 124.8, 123.0, 120.49, 120.44, 113.8, 110.7, 66.1, 54.3; FT-IR (KBr) 2978, 1683, 1635, 1535, 1449, 1307, 1059, 748 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{23}H_{17}ClN_3O_3$: 418.0953, found: 418.0960.

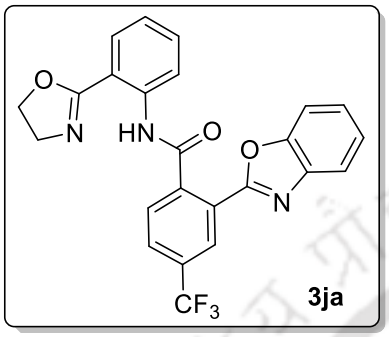


2-(Benzo[d]oxazol-2-yl)-N-(2-(4,5-dihydrooxazol-2-yl)phenyl)-4-fluorobenzamide 3ha. Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.54; colorless solid; mp 187-188 °C; yield 77% (62 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.48 (s, 1H), 8.85 (d, *J* = 8.4 Hz, 1H), 7.95-7.92 (m, 1H), 7.83-7.76 (m, 2H), 7.71-7.69 (m, 1H), 7.56-7.52 (m, 1H), 7.39-7.27 (m, 4H), 7.14-7.10 (m, 1H), 3.99 (t, *J* = 9.6 Hz, 2H), 3.70 (t, *J* = 9.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.9 (J_{C-F} = 241.4 Hz), 162.0, 161.0, 151.1, 141.8, 139.8, 134.2 (J_{C-F} = 3.6 Hz), 132.7, 131.4 (J_{C-F} = 8.6 Hz), 129.1, 127.4 (J_{C-F} = 8.8 Hz), 125.8, 124.8, 122.9, 120.5, 120.4, 118.5 (J_{C-F} = 21.4 Hz), 117.3 (J_{C-F} = 24.3 Hz), 113.8, 110.8, 66.2, 54.4; FT-IR (KBr) 3006, 1691, 1635, 1535, 1449, 1275, 749 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{23}H_{17}FN_3O_3$: 402.1248, found: 402.1244.

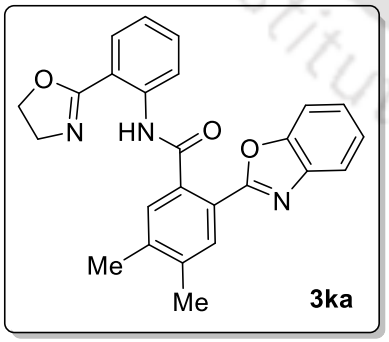


3-(Benzo[d]oxazol-2-yl)-N-(2-(4,5-dihydrooxazol-2-yl)phenyl)-[1,1'-biphenyl]-4-carboxamide 3ia. Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.40; colorless solid; mp 166-167 °C; yield 72% (66 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.53 (s, 1H), 8.89 (d, *J* = 8.4 Hz, 1H), 8.476-8.472 (m, 1H), 7.92-7.85 (m, 2H), 7.79-7.71 (m, 4H), 7.57-7.48 (m, 3H), 7.45-7.40 (m, 1H), 7.36-7.28 (m, 3H), 7.14-7.10 (m, 1H), 4.00 (t, *J* = 9.6 Hz, 2H), 3.74 (t, *J* = 9.2 Hz, 2H); ^{13}C

NMR (100 MHz, $CDCl_3$) δ 167.6, 164.4, 162.3, 151.2, 143.3, 142.0, 139.9, 139.3, 136.6, 132.6, 129.8, 129.7, 129.1, 129.0, 128.4, 127.4, 125.7, 125.4, 124.6, 122.8, 120.5, 120.3, 113.8, 110.7, 66.1, 54.4; FT-IR (KBr) 3031, 1681, 1635, 1534, 1448, 1305, 1060, 749 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{29}H_{22}N_3O_3$: 460.1656, found: 46.1657.

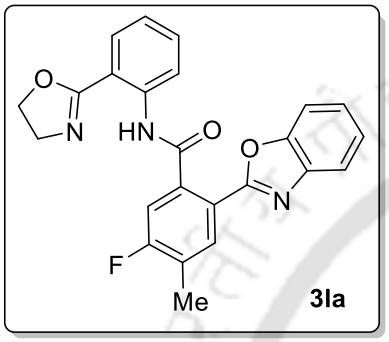


2-(benzo[d]oxazol-2-yl)-N-(2-(4,5-dihydrooxazol-2-yl)phenyl)-4-(trifluoromethyl)benzamide 3ja. Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.46; colorless solid; mp 139-140 °C; yield 74% (67 mg); ^1H NMR (400 MHz, $CDCl_3$) δ 12.59 (s, 1H), 8.85 (d, *J* = 8.4 Hz, 1H), 8.55 (s, 1H), 7.94-7.87 (m, 2H), 7.80-7.78 (m, 1H), 7.73-7.70 (m, 1H), 7.58-7.54 (m, 1H), 7.37-7.29 (m, 3H), 7.17-7.13 (m, 1H), 4.02 (t, *J* = 9.6 Hz, 2H), 3.71 (t, *J* = 9.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.5, 164.5, 160.7, 151.1, 141.8, 140.8, 139.6, 132.7, 132.4, 129.7, 129.2, 128.0 (J_{C-F} = 3.4 Hz), 127.4 (J_{C-F} = 3.8 Hz), 125.9, 125.8, 124.9, 123.2, 122.1, 120.67, 120.60, 114.0, 110.8, 66.2, 54.4; ^{19}F NMR (377 MHz, $CDCl_3$) δ -63.0; FT-IR (KBr) 2978, 1687, 1636, 1536, 1449, 1309, 1278, 1131, 749 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{24}H_{17}F_3N_3O_3$: 452.1217, found: 452.1229.

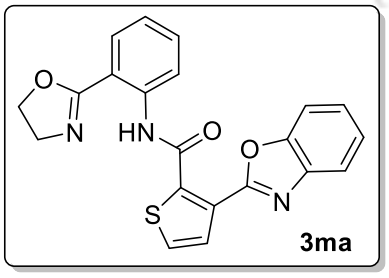


2-(Benzo[d]oxazol-2-yl)-N-(2-(4,5-dihydrooxazol-2-yl)phenyl)-4,5-dimethylbenzamide 3ka. Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.54; colorless solid; mp 182-183 °C; yield 71% (58 mg); ^1H NMR (400 MHz, $CDCl_3$) δ 12.37 (s, 1H), 8.87 (d, *J* = 8.4 Hz, 1H), 8.02 (s,

1H), 7.74-7.72 (m, 1H), 7.69-7.67 (m, 1H), 7.60 (s, 1H), 7.55-7.50 (m, 1H), 7.30-7.21 (m, 3H), 7.11-7.07 (m, 1H), 3.91 (t, J = 9.6 Hz, 2H), 3.64 (t, J = 9.6 Hz, 2H), 2.40-2.39 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.1, 164.3, 162.7, 151.1, 141.9, 140.8, 139.9, 139.4, 135.4, 132.5, 131.2, 130.5, 129.0, 125.0, 124.4, 122.6, 122.2, 120.5, 119.9, 113.8, 110.6, 66.0, 54.3, 19.9, 19.7; FT-IR (KBr) 2973, 1681, 1609, 1531, 1447, 1305, 1058, 748 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{25}H_{22}N_3O_3$: 412.1656, found: 412.1657.

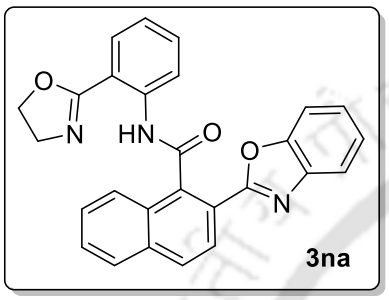


2-(Benzo[d]oxazol-2-yl)-N-(2-(4,5-dihydrooxazol-2-yl)phenyl)-5-fluoro-4-methylbenzamide 3la. Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.46; colorless solid; mp 165-166 ^{o}C; yield 73% (60 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.44 (s, 1H), 8.76 (d, J = 8.0 Hz, 1H), 8.03 (d, J = 7.2 Hz, 1H), 7.70-767 (m, 1H), 7.62-7.60 (m, 1H), 7.48-7.44 (m, 1H), 7.41 (d, J = 9.2 Hz, 1H), 7.25-7.16 (m, 3H), 7.08-7.02 (m, 1H), 3.91 (t, J = 9.6 Hz, 2H), 3.63 (t, J = 9.2 Hz, 2H), 2.35 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.4, 164.4, 164.0, 161.8, 161.5, 151.1, 141.9, 139.7, 137.6 ($J_{C\text{-}F}$ = 7.5 Hz), 133.9, 133.8, 132.7, 129.1, 128.0, 127.8, 125.3, 124.6, 123.0, 120.9 ($J_{C\text{-}F}$ = 3.8 Hz), 120.5, 120.1, 116.3 ($J_{C\text{-}F}$ = 24.7 Hz), 113.9, 110.7, 66.1, 54.3, 14.6 ($J_{C\text{-}F}$ = 3.0 Hz); ^{19}F NMR (377 MHz, $CDCl_3$) δ -111.5; FT-IR (KBr) 2987, 1683, 1635, 1533, 1448, 1312, 1059, 749 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{24}H_{19}FN_3O_3$: 416.1405, found: 416.1407.

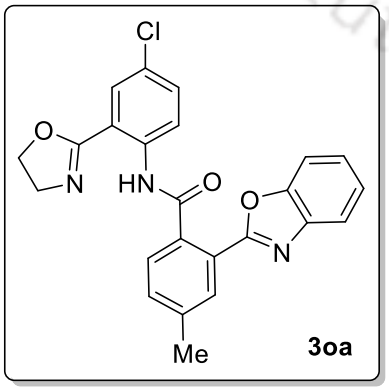


3-(Benzo[d]oxazol-2-yl)-N-(2-(4,5-dihydrooxazol-2-yl)phenyl)thiophene-2-carboxamide 3ma. Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.40; thick liquid; yield 67% (52

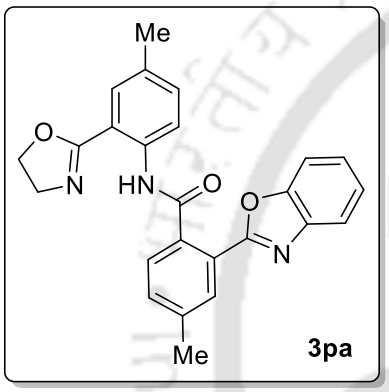
mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.89 (s, 1H), 8.88 (d, *J* = 8.4 Hz, 1H), 7.81-7.78 (m, 1H), 7.77-7.73 (m, 2H), 7.57-7.52 (m, 2H), 7.38-7.29 (m, 3H), 7.16-7.12 (m, 1H), 3.86 (t, *J* = 9.6 Hz, 2H), 3.27 (t, *J* = 9.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.2, 160.4, 158.9, 150.7, 142.1, 141.7, 139.4, 132.6, 129.7, 129.3, 128.8, 126.8, 125.6, 124.8, 123.1, 120.6, 120.2, 114.2, 110.8, 66.2, 54.1; FT-IR (neat) 2922, 1637, 1614, 1538, 1450, 1275, 1260, 749 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{21}H_{16}N_3O_3S$: 390.0907, found: 390.0909.



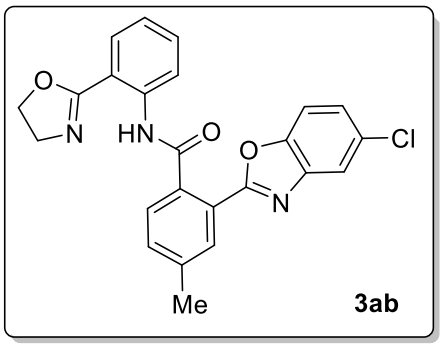
2-(Benzo[d]oxazol-2-yl)-N-(2-(4,5-dihydrooxazol-2-yl)phenyl)-1-naphthamide **3na**. Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.42; colorless solid; mp 188-189 °C; yield 65% (56 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.45 (s, 1H), 9.01 (d, *J* = 8.4 Hz, 1H), 8.44 (d, *J* = 8.4 Hz, 1H), 8.31-8.29 (m, 1H), 8.09 (d, *J* = 8.8 Hz, 1H), 7.98-7.96 (m, 1H), 7.82-7.80 (m, 1H), 7.73-7.72 (m, 1H), 7.69-7.63 (m, 3H), 7.35-7.28 (m, 3H), 7.21 (t, *J* = 7.6 Hz, 1H), 4.12-4.07 (m, 1H), 3.83-3.78 (m, 1H), 3.58-3.51 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.6, 164.1, 162.2, 151.1, 142.0, 139.7, 136.1, 134.8, 132.5, 130.6, 129.9, 129.1, 128.25, 128.22, 127.9, 126.8, 125.4, 125.2, 124.6, 123.1, 121.4, 121.1, 120.3, 114.4, 110.7, 66.0, 54.3; FT-IR (KBr) 2987, 1684, 1636, 1531, 1448, 1300, 1260, 1061, 750 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{27}H_{20}N_3O_3$: 434.1499, found: 434.1499.



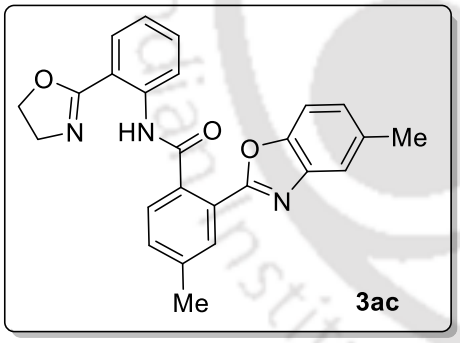
2-(Benzo[d]oxazol-2-yl)-N-(4-chloro-2-(4,5-dihydrooxazol-2-yl)phenyl)-4-methylbenzamide 3oa. Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.38; colorless solid; mp 179-180 ^oC; yield 70% (60 mg); ^1H NMR (400 MHz, $CDCl_3$) δ 12.49 (s, 1H), 8.967-8.962 (m, 1H), 8.05-8.04 (m, 1H), 7.72-7.66 (m, 3H), 7.46-7.44 (m, 1H), 7.36-7.27 (m, 3H), 7.09-7.06 (m, 1H), 3.98 (t, *J* = 10 Hz, 2H), 3.70 (t, *J* = 9.2 Hz, 2H), 2.51 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.0, 163.8, 162.4, 151.1, 141.9, 141.0, 140.8, 138.6, 134.8, 132.2, 130.9, 130.0, 129.3, 125.4, 125.0, 124.6, 122.9, 120.4, 120.2, 112.0, 110.7, 66.2, 54.4, 21.4; FT-IR (KBr) 2988, 1685, 1637, 1576, 1523, 1408, 1275, 1260, 1059, 749 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{24}H_{19}ClN_3O_3$: 432.1109, found: 432.1115.



2-(Benzo[d]oxazol-2-yl)-N-(2-(4,5-dihydrooxazol-2-yl)-4-methylphenyl)-4-methylbenzamide 3pa. Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.42; colorless solid; mp 161-162 ^oC; yield 69% (57 mg); ^1H NMR (400 MHz, $CDCl_3$) δ 12.45 (s, 1H), 8.72 (s, 1H), 8.06 (s, 1H), 7.75-7.72 (m, 2H), 7.66 (d, *J* = 8.0 Hz, 1H), 7.47-7.44 (m, 1H), 7.3-7.26 (m, 3H), 6.95-6.92 (m, 1H), 3.96 (t, *J* = 9.6 Hz, 2H), 3.69 (t, *J* = 9.6 Hz, 2H), 2.52 (s, 3H), 2.46 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.8, 164.4, 162.6, 151.1, 143.3, 141.9, 140.7, 139.8, 135.3, 132.1, 130.9, 129.2, 128.9, 125.2, 124.9, 124.5, 123.6, 120.9, 120.1, 111.2, 110.7, 65.9, 54.3, 22.1, 21.4; FT-IR (KBr) 2981, 1680, 1632, 1577, 1535, 1451, 1297, 1242, 1056, 747 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{25}H_{22}N_3O_3$: 412.1656, found: 412.1657.

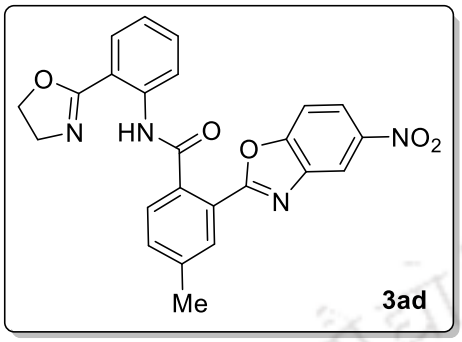


2-(5-Chlorobenzo[d]oxazol-2-yl)-N-(2-(4,5-dihydrooxazol-2-yl)phenyl)-4-methylbenzamide 3ab. Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.44; colorless solid; mp 164-165 ^oC; yield 79% (68 mg); ^1H NMR (400 MHz, $CDCl_3$) δ 12.50 (s, 1H), 8.85 (d, *J* = 8.4 Hz, 1H), 7.99 (s, 1H), 7.79-7.77 (m, 1H), 7.73 (d, *J* = 8.0 Hz, 1H), 7.68-7.67 (m, 1H), 7.53-7.49 (m, 1H), 7.45-7.43 (m, 1H), 7.26-7.21 (m, 2H), 7.12-7.08 (m, 1H), 4.08 (t, *J* = 9.6 Hz, 2H), 3.77 (t, *J* = 9.6 Hz, 2H), 2.49 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.5, 164.5, 164.0, 149.7, 143.0, 140.8, 139.9, 135.3, 132.6, 132.4, 131.0, 129.9, 129.1, 129.0, 125.5, 124.7, 122.7, 120.2, 120.0, 113.6, 111.4, 66.1, 54.4, 21.3; FT-IR (KBr) 2987, 1677, 1609, 1531, 1446, 1301, 1258, 1056, 751 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{24}H_{19}ClN_3O_3$: 432.1109, found: 432.1111.



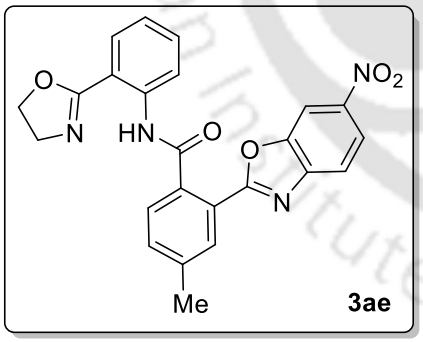
N-(2-(4,5-Dihydrooxazol-2-yl)phenyl)-4-methyl-2-(5-methylbenzo[d]oxazol-2-yl)benzamide 3ac. Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.52; colorless solid; mp 156-157 ^oC; yield 77% (63 mg); ^1H NMR (400 MHz, $CDCl_3$) δ 12.42 (s, 1H), 8.86 (d, *J* = 8.4 Hz, 1H), 8.02 (s, 1H), 7.76-7.74 (m, 1H), 7.71 (d, *J* = 8.0 Hz, 1H), 7.53-7.47 (m, 2H), 7.42-7.40 (m, 1H), 7.18 (d, *J* = 8.4 Hz, 1H), 7.11-7.04 (m, 2H), 3.98 (t, *J* = 9.6 Hz, 2H), 3.71 (t, *J* = 9.6 Hz, 2H), 2.48 (s, 3H), 2.43 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.9, 164.3, 162.6, 149.4, 142.1, 140.6, 139.9, 135.2, 134.3, 132.5, 131.9, 130.8, 129.1, 129.0, 126.3, 125.1, 122.6, 120.4, 119.9, 113.7, 110.0,

66.0, 54.4, 21.5, 21.3; FT-IR (KBr) 2984, 1682, 1609, 1531, 1446, 1301, 1261, 1057, 945, 765 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{25}H_{22}N_3O_3$: 412.1656, found: 412.1652.



N-(2-(4,5-Dihydrooxazol-2-yl)phenyl)-4-methyl-2-(5-nitrobenzo[d]oxazol-2-yl)benzamide

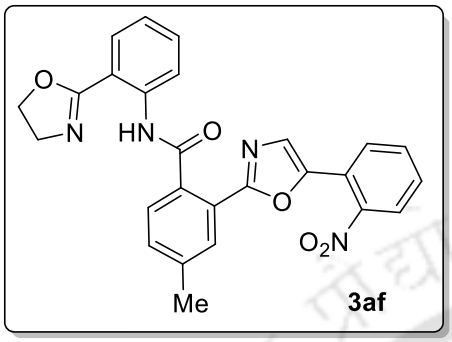
3ad. Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.46; yellow solid; mp 191-192 ^oC; yield 71% (63 mg); ^1H NMR (400 MHz, $CDCl_3$) δ 12.65 (s, 1H), 8.84 (d, *J* = 8.8 Hz, 1H), 8.60-8.59 (m, 1H), 8.26-8.23 (m, 1H), 8.00 (s, 1H), 7.83-7.81 (m, 1H), 7.77 (d, *J* = 8.0 Hz, 1H), 7.56-7.46 (m, 3H), 7.15-7.11 (m, 1H), 4.18 (t, *J* = 9.6 Hz, 2H), 3.87 (t, *J* = 9.6 Hz, 2H), 2.52 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.2, 165.9, 164.7, 154.6, 145.4, 142.3, 141.1, 139.9, 135.5, 132.9, 132.8, 131.4, 129.3, 128.9, 124.5, 122.9, 121.3, 120.1, 116.5, 113.6, 110.9, 66.2, 54.5, 21.4; FT-IR (KBr) 3108, 2984, 1680, 1610, 1525, 1305, 1058, 750 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{24}H_{19}N_4O_5$: 443.1350, found: 443.1337.



N-(2-(4,5-Dihydrooxazol-2-yl)phenyl)-4-methyl-2-(6-nitrobenzo[d]oxazol-2-yl)benzamide

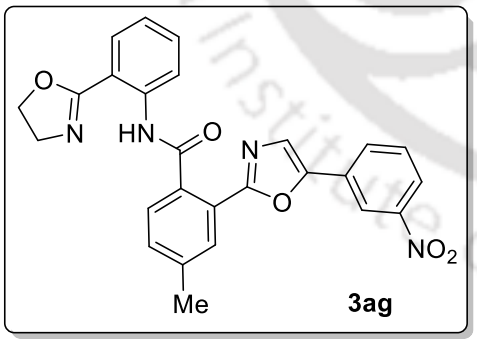
3ae. Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.48; yellow solid; mp 188-189 ^oC; yield 73% (64 mg); ^1H NMR (400 MHz, $CDCl_3$) δ 12.69 (s, 1H), 8.84 (d, *J* = 8.4 Hz, 1H), 8.31-8.26 (m, 2H), 8.00 (s, 1H), 7.84-7.75 (m, 3H), 7.55-7.50 (m, 2H), 7.14 (t, *J* = 7.6 Hz, 1H), 4.20 (t, *J* = 9.6 Hz, 2H), 3.89 (t, *J* = 9.6 Hz, 2H), 2.52 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.3, 167.1, 164.8, 150.2, 147.2, 145.3, 141.1, 139.9, 135.8, 133.1, 132.8, 131.5, 129.3, 128.9,

124.6, 123.0, 120.7, 120.2, 120.1, 113.6, 107.4, 66.2 54.6, 21.4; FT-IR (KBr) 2992, 1682, 1583, 1523, 1447, 1305, 1274, 1059, 764 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{24}H_{19}N_4O_5$: 443.1350, found: 443.1336.



N-(2-(4,5-Dihydrooxazol-2-yl)phenyl)-4-methyl-2-(5-(2-nitrophenyl)oxazol-2-yl)benzamide

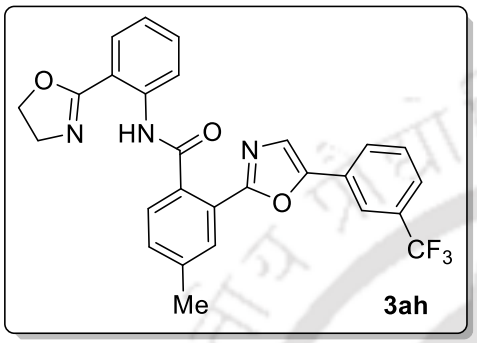
3af. Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.42; yellow solid; mp 199-200 ^oC; yield 70% (65 mg); ^1H NMR (400 MHz, $CDCl_3$) δ 12.54 (s, 1H), 8.91 (d, *J* = 8.4 Hz, 1H), 7.96 (s, 1H), 7.72-7.69 (m, 2H), 7.64 (d, *J* = 7.6 Hz, 1H), 7.52-7.44 (m, 3H), 7.40-7.37 (m, 1H), 7.33-7.29 (m, 1H), 7.23-7.19 (m, 1H), 7.06-7.02 (m, 1H), 4.24 (t, *J* = 9.6 Hz, 2H), 3.85 (t, *J* = 9.6 Hz, 2H), 2.48 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.3, 164.4, 161.4, 146.7, 146.0, 140.6, 140.1, 134.4, 132.4, 132.4, 131.7, 129.9, 129.2, 128.8, 128.5, 124.2, 124.1, 122.7, 121.3, 120.2, 113.6, 66.2, 54.5, 21.4; FT-IR (KBr) 2987, 1681, 1530, 1306, 1275, 1261, 1057, 749 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{26}H_{21}N_4O_5$: 469.1506, found: 469.1508.



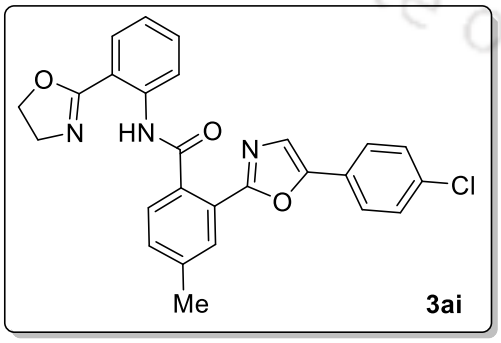
N-(2-(4,5-Dihydrooxazol-2-yl)phenyl)-4-methyl-2-(5-(3-nitrophenyl)oxazol-2-yl)benzamide

3ag. Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.44; yellow solid; mp 194-195 ^oC; yield 74% (69 mg); ^1H NMR (400 MHz, $CDCl_3$) δ 12.56 (s, 1H), 8.95 (d, *J* = 8.4 Hz, 1H), 8.29-8.28 (m, 1H), 8.05-8.02 (m, 1H), 7.986-7.980 (m, 1H), 7.72-7.70 (m, 1H), 7.67-7.61 (m, 2H), 7.54-7.49 (m, 2H), 7.41-7.39 (m, 1H), 7.32 (t, *J* = 8.0 Hz, 1H), 7.08-7.03 (m, 1H), 4.22 (t, *J* = 9.6

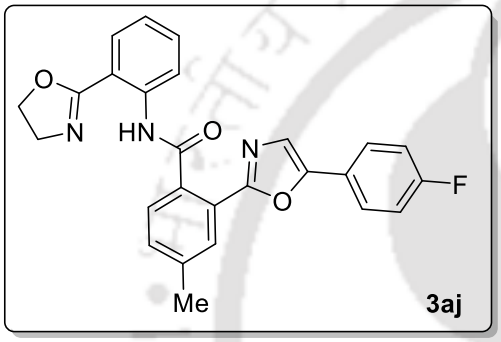
Hz, 2H), 3.88 (t, *J* = 9.6 Hz, 2H), 2.50 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.2, 164.5, 161.3, 149.6, 148.6, 140.6, 140.0, 134.5, 132.7, 131.7, 129.9, 129.8, 129.5, 129.2, 128.8, 125.1, 124.3, 122.79, 122.73, 120.2, 118.7, 113.5, 66.2, 54.5, 21.4; FT-IR (KBr) 3009, 1681, 1526, 1348, 1305, 1261, 1060, 750 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{26}H_{21}N_4O_5$: 469.1506, found: 469.1507.



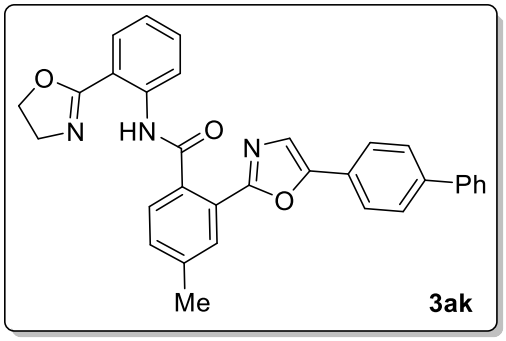
N-(2-(4,5-Dihydrooxazol-2-yl)phenyl)-4-methyl-2-(5-(3-(trifluoromethyl)phenyl)oxazol-2-yl)benzamide 3ah. Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.48; colorless solid; mp 157-158 °C; yield 72% (71 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.53 (s, 1H), 8.95 (d, *J* = 8.4 Hz, 1H), 7.97 (s, 1H), 7.75-7.70 (m, 2H), 7.66 (d, *J* = 8.0 Hz, 1H), 7.55-7.49 (m, 2H), 7.45-7.43 (m, 2H), 7.40-7.37 (m, 1H), 7.31-7.27 (m, 1H), 7.08-7.04 (m, 1H), 4.21 (t, *J* = 10.0 Hz, 2H), 3.87 (t, *J* = 9.2 Hz, 2H), 2.49 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.3, 164.6, 161.0, 150.6, 140.6, 140.1, 134.6, 132.7, 131.9 (J_{C-F} = 32.6 Hz), 131.4, 129.8, 129.4, 129.2, 128.8, 128.5, 127.9 (J_{C-F} = 270.6 Hz), 127.2, 124.9 (J_{C-F} = 3.8 Hz), 124.6, 124.4, 122.7, 120.9 (J_{C-F} = 3.9 Hz), 120.1, 113.5, 66.2, 54.6, 21.4; ^{19}F NMR (377 MHz, $CDCl_3$) δ -62.9; FT-IR (KBr) 2984, 1682, 1609, 1532, 1447, 1304, 1262, 1124, 1060, 751 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{27}H_{21}F_3N_3O_3$: 492.1530, found: 492.1533.



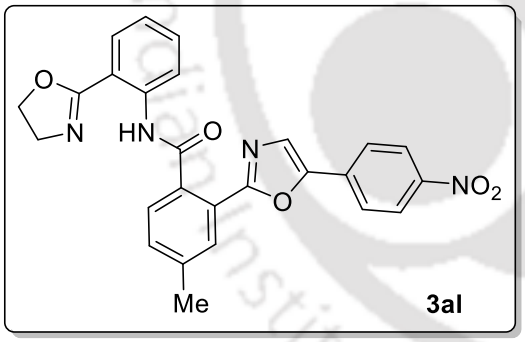
2-(5-(4-Chlorophenyl)oxazol-2-yl)-N-(2-(4,5-dihydrooxazol-2-yl)phenyl)-4-methylbenzamide 3ai. Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.54; colorless solid; mp 191-192 ^oC; yield 78% (71 mg); ^1H NMR (400 MHz, $CDCl_3$) δ 12.51 (s, 1H), 8.95 (d, *J* = 8.4 Hz, 1H), 7.96 (s, 1H), 7.76-7.73 (m, 1H), 7.64 (d, *J* = 7.6 Hz, 1H), 7.56-7.52 (m, 1H), 7.38-7.35 (m, 2H), 7.32-7.29 (m, 2H), 7.16-7.08 (m, 3H), 4.21 (t, *J* = 9.6 Hz, 2H), 3.86 (t, *J* = 9.6 Hz, 2H), 2.48 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.4, 164.5, 160.5, 151.0, 140.4, 140.1, 134.4, 134.1, 132.6, 131.3, 129.6, 129.3, 129.0, 128.7, 126.1, 125.3, 124.6, 123.5, 122.7, 120.2, 113.6, 66.2, 54.6, 21.4; FT-IR (KBr) 2992, 1682, 1635, 1533, 1447, 1305, 1261, 1057, 750 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{26}H_{21}ClN_3O_3$: 458.1266, found: 458.1257.



N-(2-(4,5-Dihydrooxazol-2-yl)phenyl)-2-(5-(4-fluorophenyl)oxazol-2-yl)-4-methylbenzamide 3aj. Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.52; colorless solid; mp 116-117 ^oC; yield 73% (64 mg); ^1H NMR (400 MHz, $CDCl_3$) δ 12.52 (s, 1H), 8.95 (d, *J* = 8.4 Hz, 1H), 7.96-7.95 (m, 1H), 7.74-7.72 (m, 1H), 7.63 (d, *J* = 7.6 Hz, 1H), 7.55-7.50 (m, 1H), 7.37-7.30 (m, 3H), 7.30 (s, 1H), 7.10-7.06 (m, 1H), 6.86 (t, *J* = 8.8 Hz, 2H), 4.18 (t, *J* = 9.6 Hz, 2H), 3.84 (t, *J* = 9.6 Hz, 2H), 2.47 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.5, 164.4, 163.8 (J_{C-F} = 247.2 Hz), 160.2, 151.1, 140.4, 140.1, 134.3, 132.6, 131.2, 129.5, 129.2, 128.7, 126.0, 125.9, 124.6, 123.9 (J_{C-F} = 3.4 Hz), 122.7, 122.7, 122.7, 120.2, 115.9 (J_{C-F} = 21.9 Hz), 113.6, 66.2, 54.5, 21.4; ^{19}F NMR (377 MHz, $CDCl_3$) δ -112.3; FT-IR (KBr) 2987, 1679, 1609, 1497, 1303, 1261, 1232, 1056, 750 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{26}H_{21}FN_3O_3$: 442.1561, found: 442.1564.

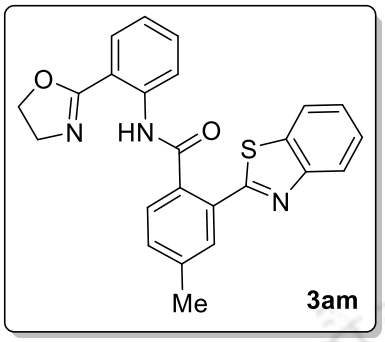


2-(5-([1,1'-Biphenyl]-4-yl)oxazol-2-yl)-N-(2-(4,5-dihydrooxazol-2-yl)phenyl)-4-methylbenzamide 3ak. Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.40; thick liquid; yield 69% (69 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.55 (s, 1H), 9.00 (d, *J* = 8.0 Hz, 1H), 7.99 (s, 1H), 7.75-7.72 (m, 1H), 7.66 (d, *J* = 7.6 Hz, 1H), 7.57-7.53 (m, 3H), 7.47-7.40 (m, 7H), 7.38-7.34 (m, 2H), 7.10-7.06 (m, 1H), 4.18 (t, *J* = 9.6 Hz, 2H), 3.85 (t, *J* = 9.6 Hz, 2H), 2.49 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.5, 164.4, 160.2, 151.7, 140.9, 140.4, 140.3, 140.2, 134.3, 132.5, 131.1, 129.5, 129.2, 128.9, 128.7, 127.6, 127.4, 127.0, 126.5, 124.6, 124.5, 123.2, 122.6, 120.2, 113.6, 66.2, 54.5, 21.4; FT-IR (neat) 2926, 1679, 1583, 1531, 1446, 1303, 1261, 1056, 750 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{32}H_{26}N_3O_3$: 500.1969, found: 500.1966.

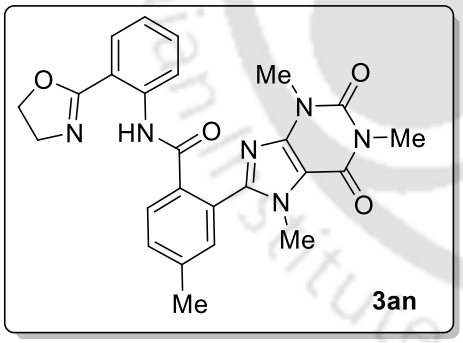


N-(2-(4,5-Dihydrooxazol-2-yl)phenyl)-4-methyl-2-(5-(4-nitrophenyl)oxazol-2-yl)benzamide 3al. Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.42; yellow solid; mp 196-197 ^{o}C; yield 76% (71 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.58 (s, 1H), 8.95 (d, *J* = 8.4 Hz, 1H), 8.03-7.98 (m, 3H), 7.75-7.73 (M, 1H), 7.66 (d, *J* = 8.0 Hz, 1H), 7.58-7.54 (m, 2H), 7.51-7.49 (m, 2H), 7.42-7.40 (m, 1H), 7.13-7.09 (m, 1H), 4.22 (t, *J* = 9.6 Hz, 2H), 3.87 (t, *J* = 9.6 Hz, 2H), 2.49 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.3, 164.5, 162.0, 149.7, 147.0, 140.6, 140.0, 134.6, 133.3, 132.7, 131.8, 129.9, 129.3, 128.7, 126.4, 125.5, 124.7, 124.4, 124.3, 124.2, 123.0, 120.1,

113.6, 66.2, 54.5, 21.4; FT-IR (KBr) 2987, 1678, 1606, 1516, 1335, 1261, 1058, 750 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{26}H_{21}N_4O_5$: 469.1506, found: 469.1509.

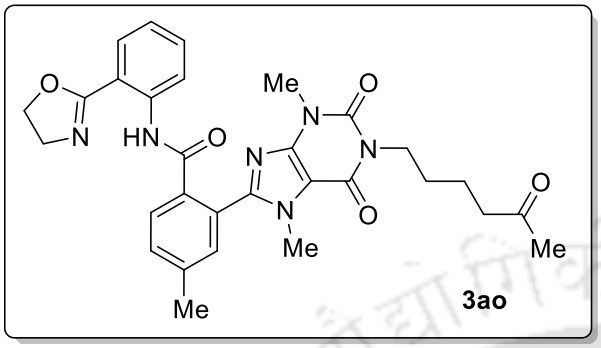


2-(Benzo[d]thiazol-2-yl)-N-(2-(4,5-dihydrooxazol-2-yl)phenyl)-4-methylbenzamide 3am. Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.50; thick liquid; yield 71% (59 mg); ^1H NMR (400 MHz, $CDCl_3$) δ 12.51 (s, 1H), 8.83 (d, *J* = 8.8 Hz, 1H), 7.95 (d, *J* = 8.0 Hz, 1H), 7.84-7.68 (m, 4H), 7.50-7.32 (m, 4H), 7.08 (t, *J* = 7.6 Hz, 1H), 4.12 (t, *J* = 9.6 Hz, 2H), 3.87 (t, *J* = 9.2 Hz, 2H), 2.49 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.9, 166.7, 164.3, 153.6, 140.7, 140.0, 136.2, 135.0, 132.5, 132.1, 131.3, 131.1, 129.0, 128.9, 126.1, 125.2, 123.5, 122.6, 121.5, 120.3, 113.7, 66.1, 54.6, 21.4; FT-IR (neat) 3006, 1680, 1636, 1534, 1447, 1305, 1275, 1261, 1057, 750 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{24}H_{20}N_3O_2S$: 414.1271, found: 414.1274.

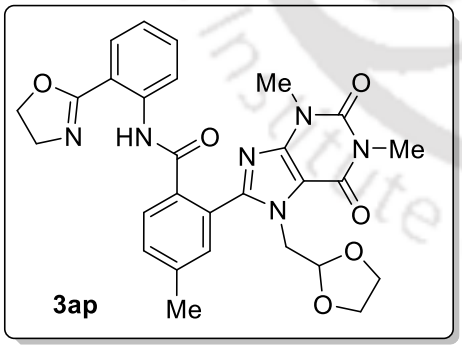


N-(2-(4,5-Dihydrooxazol-2-yl)phenyl)-4-methyl-2-(1,3,7-trimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-8-yl)benzamide 3an. Analytical TLC on silica gel, 1:1 ethyl acetate/hexane R_f = 0.58; colorless solid; mp >200 °C; yield 69% (65 mg); ^1H NMR (400 MHz, $CDCl_3$) δ 12.92 (s, 1H), 8.66 (d, *J* = 8.8 Hz, 1H), 7.92-7.86 (m, 2H), 7.47-7.41 (m, 2H), 7.35-7.34 (m, 1H), 7.12-7.08 (m, 1H), 4.40 (t, *J* = 9.6 Hz, 2H), 4.13 (t, *J* = 9.6 Hz, 2H), 3.79 (s, 3H), 3.56 (s, 3H), 3.42 (s, 3H), 2.48 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.7, 165.0, 155.7, 152.3, 151.9, 148.2, 141.9, 139.8, 134.5, 132.8, 132.6, 131.3, 129.4, 128.9, 128.2, 122.9, 119.8, 113.6, 108.1,

66.4, 54.7, 33.0, 29.9, 28.0, 21.4; FT-IR (KBr) 3005, 1702, 1659, 1541, 1275, 1260, 1063, 749 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{25}H_{25}N_6O_4$: 473.1932, found: 473.1948.

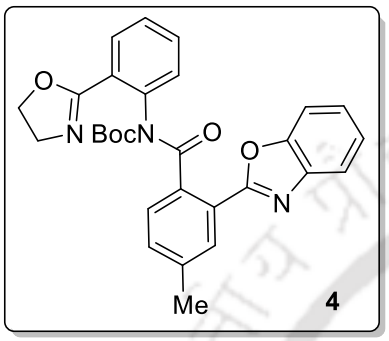


***N*-(2-(4,5-Dihydrooxazol-2-yl)phenyl)-2-(3,7-dimethyl-2,6-dioxo-1-(5-oxohexyl)-2,3,6,7-tetrahydro-1H-purin-8-yl)-4-methylbenzamide 3ao**. Analytical TLC on silica gel, 1:1 ethyl acetate/hexane R_f = 0.54; colorless solid; mp 195-196 °C; yield 67% (74 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.91 (s, 1H), 8.66 (d, *J* = 8.4 Hz, 1H), 7.92-7.86 (m, 2H), 7.46-7.41 (m, 2H), 7.33 (s, 1H), 7.09 (t, *J* = 8.0 Hz, 1H), 4.40 (t, *J* = 9.2 Hz, 2H), 4.13 (t, *J* = 9.2 Hz, 2H), 4.03-4.00 (m, 2H), 3.77 (s, 3H), 3.53 (s, 3H), 2.52-2.47 (m, 5H), 2.14 (s, 3H), 1.68-1.67 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.9, 165.7, 165.0, 155.5, 152.40, 151.6, 148.26, 141.9, 139.8, 134.4, 132.8, 132.6, 131.3, 129.4, 128.9, 128.1, 122.9, 119.9, 113.6, 108.1, 66.4, 54.7, 43.4, 40.9, 33.0, 30.0, 29.8, 27.6, 21.4, 21.2; FT-IR (KBr) 2955, 1700, 1656, 1541, 1308, 1062, 751 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{30}H_{33}N_6O_5$: 557.2507, found: 557.2510.

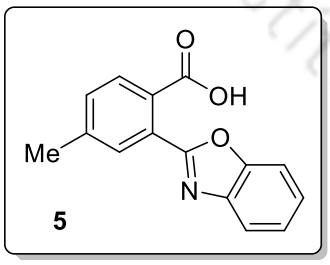


2-(7-((1,3-Dioxolan-2-yl)methyl)-1,3-dimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-8-yl)-N-(2-(4,5-dihydrooxazol-2-yl)phenyl)-4-methylbenzamide 3ap. Analytical TLC on silica gel, 1:1 ethyl acetate/hexane R_f = 0.42; colorless solid; mp 189-190 °C; yield 61% (66 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.85 (s, 1H), 8.63 (d, *J* = 8.4 Hz, 1H), 7.90-7.85 (m, 2H), 7.45-7.40 (m, 3H), 7.10-7.06 (m, 1H), 5.33 (t, *J* = 4.8 Hz, 1H), 4.40 (t, *J* = 9.6 Hz, 2H), 4.30 (d, *J* = 5.2 Hz, 2H), 4.13

(t, *J* = 9.6 Hz, 2H), 3.80 (s, 4H), 3.54 (s, 3H), 3.42 (s, 3H), 2.47 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.6, 165.0, 155.5, 152.6, 151.9, 148.3, 141.4, 139.9, 134.5, 133.4, 132.7, 131.2, 129.3, 129.1, 128.0, 122.8, 120.0, 113.7, 107.8, 101.8, 66.4, 64.9, 54.8, 48.2, 29.9, 28.1, 21.4; FT-IR (KBr) 2953, 1702, 1659, 1541, 1308, 1060, 750 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{28}H_{29}N_6O_6$: 545.2143, found: 545.2150.

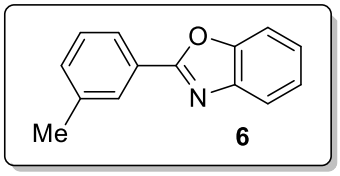


***tert*-Butyl (2-(benzo[d]oxazol-2-yl)-4-methylbenzoyl)(2-(4,5-dihydrooxazol-2-yl)phenyl)carbamate 4**. Analytical TLC on silica gel, 1:1 ethyl acetate/hexane R_f = 0.44; colorless solid; mp >200 °C; yield 71% (35 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08-8.06 (m, 2H), 7.84-7.80 (m, 2H), 7.67-7.63 (m, 1H), 7.61-7.58 (m, 1H), 7.54 (d, *J* = 8.0 Hz, 1H), 7.49-7.45 (m, 1H), 7.42-7.36 (m, 3H), 4.43-4.32 (m, 2H), 4.14-4.00 (m, 2H), 2.49 (s, 3H), 1.01 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.1, 162.5, 161.9, 151.4, 150.7, 142.2, 138.8, 138.1, 136.8, 131.86, 131.81, 130.6, 129.8, 128.9, 128.2, 127.0, 125.9, 125.3, 124.7, 123.1, 120.3, 110.6, 82.8, 67.0, 55.3, 27.4, 21.4; FT-IR (KBr) 2925, 1746, 1677, 1452, 1365, 1249, 1156, 1049, 1025, 748 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{29}H_{28}N_3O_5$: 498.2023, found: 498.2035.



2-(Benzo[d]oxazol-2-yl)-4-methylbenzoic acid 5. Analytical TLC on silica gel, 1:1 ethyl acetate/hexane R_f = 0.52; colorless solid; mp 155-156 °C; yield 63% (11 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.49 (d, *J* = 8.4 Hz, 1H), 8.18 (s, 1H), 7.83-7.80 (m, 1H), 7.68-7.66 (m, 1H), 7.52-7.46 (m, 3H), 2.53 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.8, 162.6, 149.9, 143.3, 138.6, 135.7,

133.2, 131.0, 128.8, 126.9, 125.9, 123.9, 119.8, 111.2, 21.5; FT-IR (KBr) 2989, 1716, 1455, 1275, 1260, 749 cm^{-1}; HRMS (ESI) *m/z* $[M-H]^-$ calcd for $C_{15}H_{10}NO_3$: 252.0666, found: 252.0663.



2-(*m*-Tolyl)benzo[d]oxazole 6. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.58; brown solid; mp 72-73 °C; yield 57% (12 mg); ^1H NMR (400 MHz, $CDCl_3$) δ 8.19-8.17 (m, 1H), 7.83-7.79 (m, 1H), 7.62-7.57 (m, 1H), 7.44-7.33 (m, 5H), 2.82 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.5, 150.4, 142.2, 138.9, 131.9, 131.0, 130.0, 126.3, 126.1, 125.1, 124.5, 120.2, 110.6, 22.3; FT-IR (KBr) 2923, 1615, 1549, 1452, 1241, 1029, 472 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{14}H_{12}NO$: 210.0913, found: 210.0931.

2.5 References

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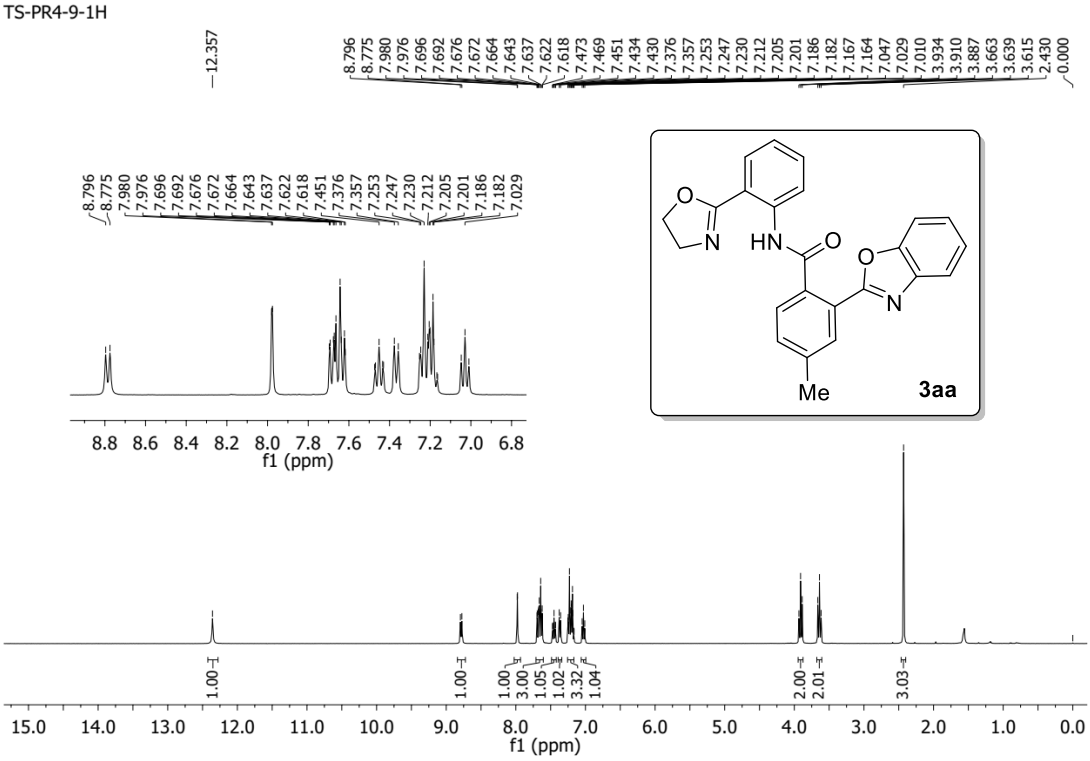
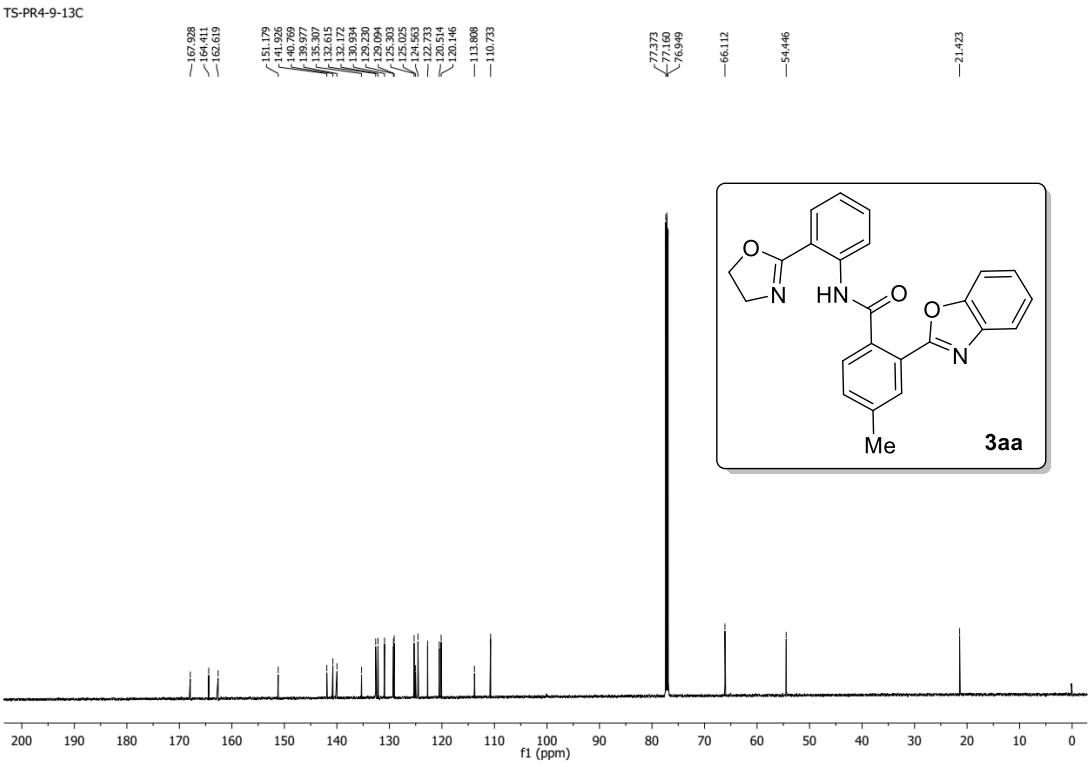
2.6 Selected NMR Spectra





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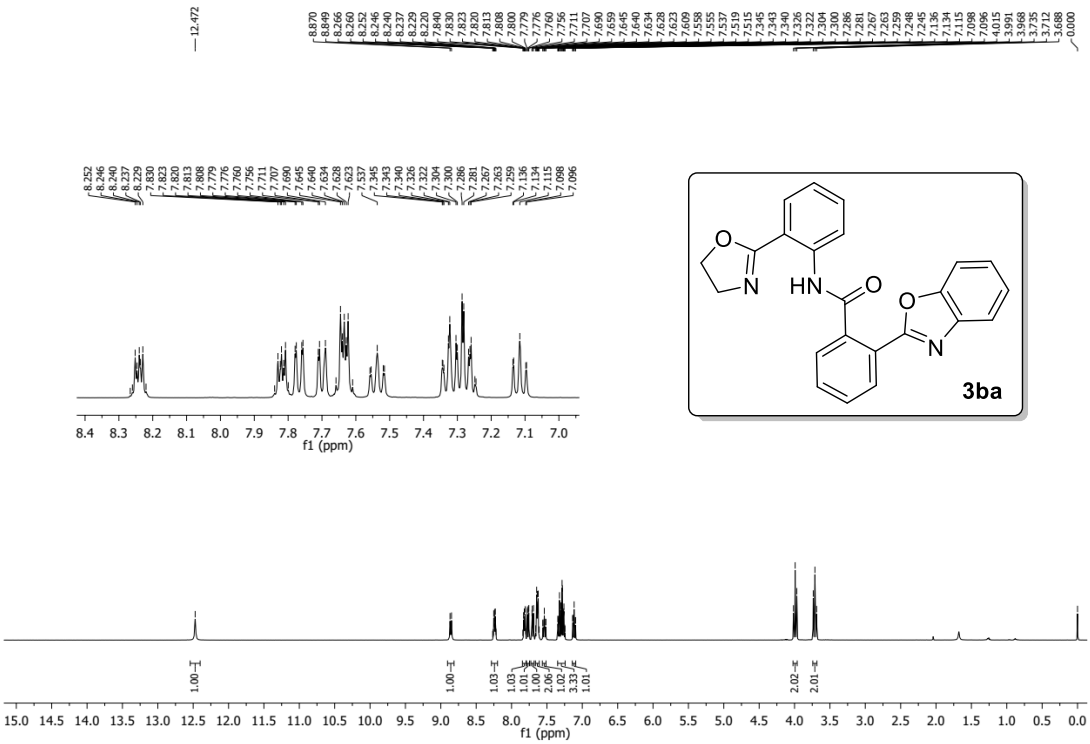

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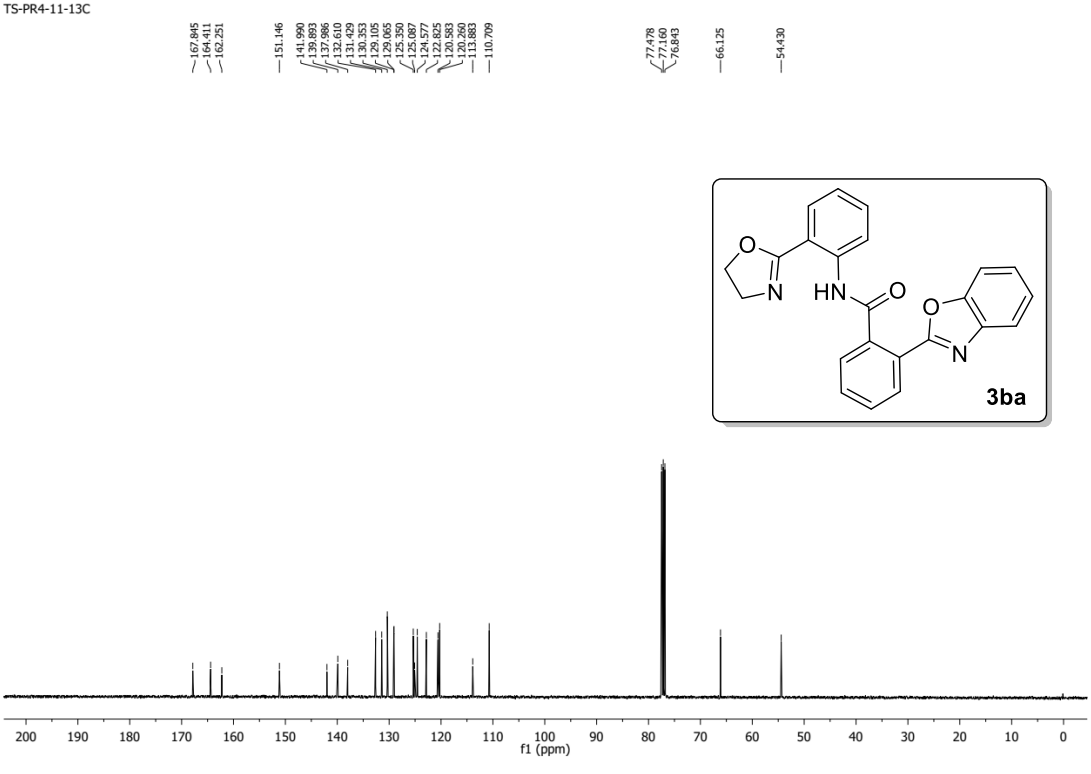

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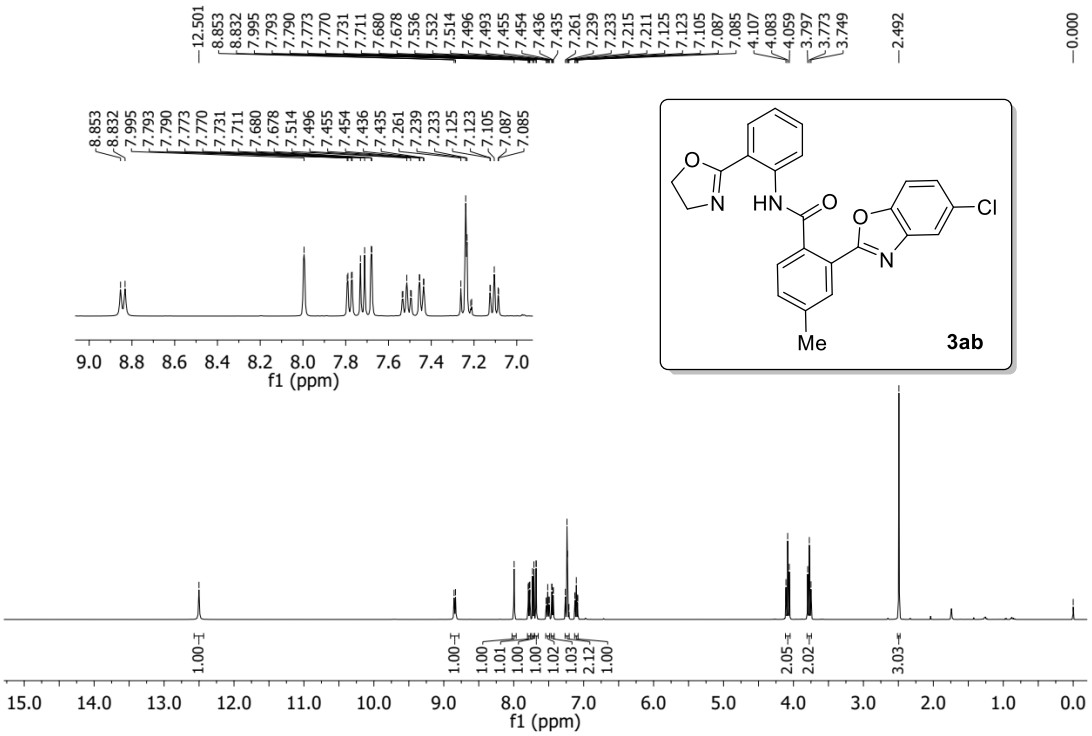

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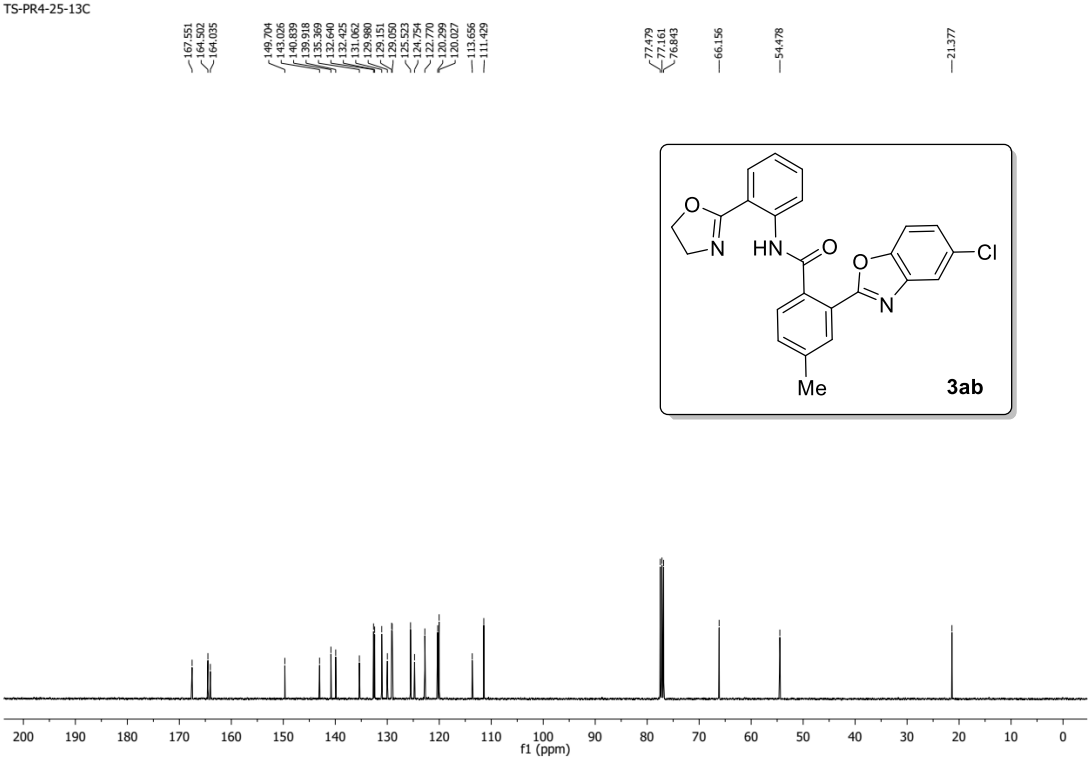
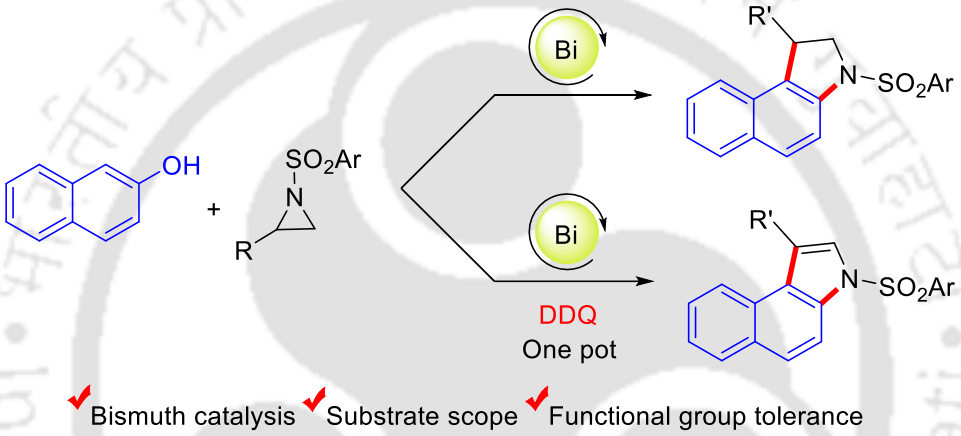


Chapter III

Bi(III)-Catalyzed Annulation of Aziridines with 2-Naphthols: Synthesis of Functionalized Benzoindolines and Benzoindoles



Bi(III)-Catalyzed Annulation of Aziridines with 2-Naphthols: Synthesis of Functionalized Benzoindolines and Benzoindoles

Indolines and their synthetic congeners represent a pivotal class of nitrogen containing heterocycles that are ubiquitous in natural isolates and pharmaceuticals (Figure 1).[1] They have also been extensively utilized as a synthetic precursor to access complex molecular assemblies.[2] Therefore, countless synthetic strategies have been made for the development of the newer methodologies to construct functionalized indoline-based structural scaffolds. Commonly, the direct reduction of indoles either by transfer hydrogenation[3] or by classical hydrogenation[4] and transition-metal-catalyzed C-H functionalization[5] strategies deliver typical approaches to access the above targets. Despite the significant advancements, the development of a milder protocol to construct these structural scaffolds is highly desirable. In recent years, Lewis acid catalyzed (3+n)-cycloaddition reactions have emerged as a potential and reliable synthetic tool for the assembly of versatile heterocyclic frameworks.[6] In this realm, aziridines are recognized as a masked 1,3-zwitterionic component for synthesizing nitrogen-bearing heterocycles. Owing to their inherent ring strain, they can undergo Lewis acid catalyzed tandem ring-opening/cyclization or (3+n)-cycloaddition to furnish a library of cycloadducts.[7] On the other hand, the use of $Bi(OTf)_3$ as a Lewis acid catalyst has attracted considerable attention owing to its low toxicity, water-stability and cost-effectiveness.[8] Herein, we report an efficient route to construct functionalized benzoindolines and benzoindoles *via* Bi(III)-catalyzed (3+2)-annulation of aziridines with 2-naphthols. The substrate scope, functional group diversity and mechanistic insights are the important practical features.

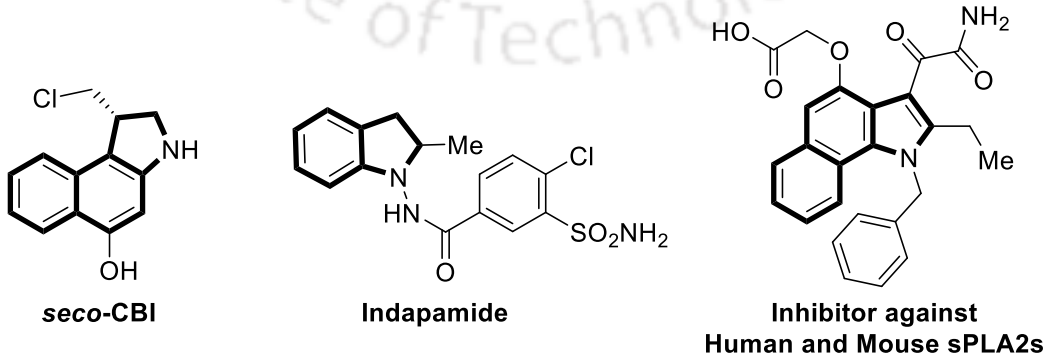
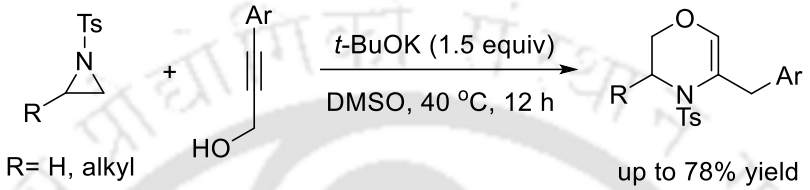


Figure 1. Examples of Biologically Active Indoline and Indole derivatives.

3.1 Literature Study

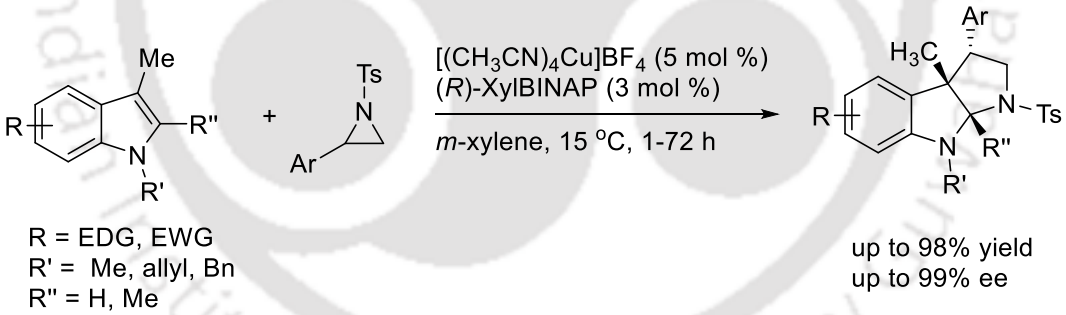
3.1.1 Tandem Ring Opening/Cyclization of Aziridines

Zhou and co-workers disclosed a base-promoted coupling of 2-alkyl-*N*-tosylaziridines with propargyl alcohols for the construction of dihydroxazine derivatives (Scheme 1).[9] A plausible mechanism involving regioselective ring-opening of aziridine, followed by intramolecular cyclization was proposed.



Scheme 1. Base Promoted Coupling of Aziridines and Propargyl Alcohols

Yang and co-workers demonstrated the asymmetric synthesis of pyrroloindolines employing 2-aryl-*N*-tosylaziridines and substituted indoles in presence of Cu(I)-catalyst and chiral diphosphine ligand (Scheme 2).[10] The tandem reaction displays a functional group tolerance with good yields and enantioselectivities.

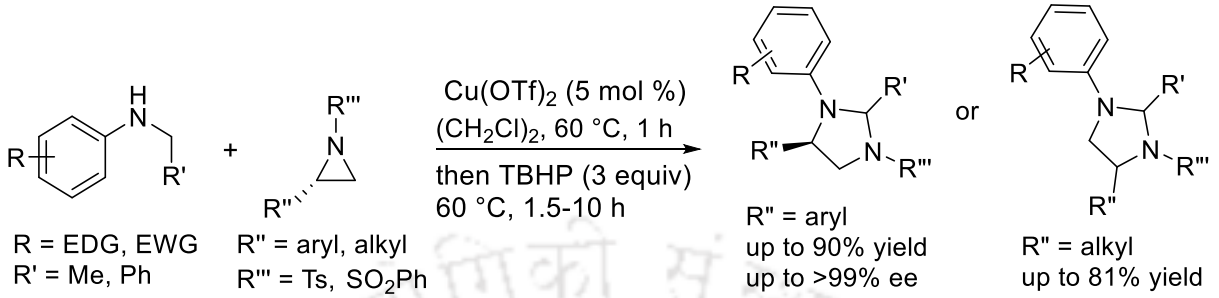


Scheme 2. Cu(I)-Catalyzed Asymmetric Coupling of Aziridines with Indoles

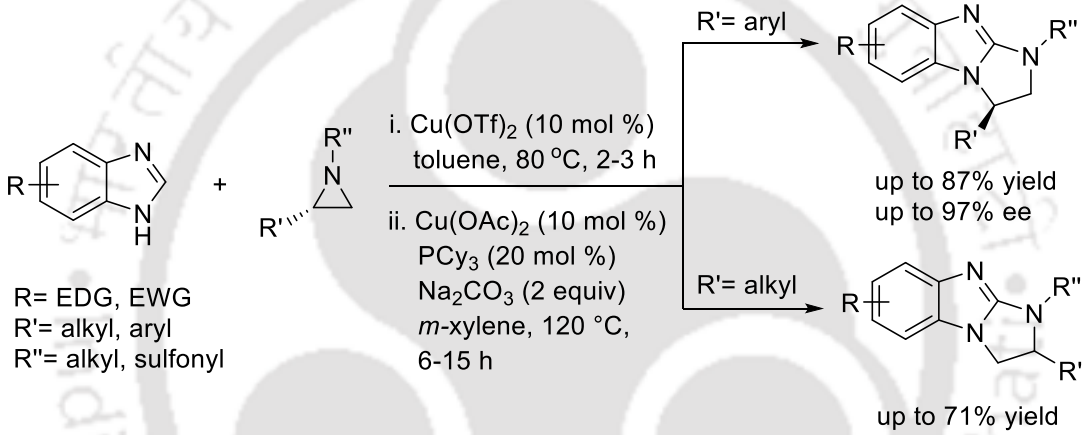
Our group described a Cu(II)-catalyzed stereospecific synthesis of 1,3-imidazolidines employing aryl/alkyl *N*-sulfonylaziridines and *N*-alkylanilines in presence of TBHP as oxidant (Scheme 3).[11] The method was extended for the reaction of optically pure aziridines to produce enantioenriched imidazolidines. The reaction proceeded through sequential nucleophilic ring opening of aziridine, followed by intramolecular C-N bond formation *via* single-electron transfer (SET) pathway.

A Cu(II)-catalyzed stereo- and regioselective nucleophilic ring opening of aziridines with benzimidazoles, followed by intramolecular C-N coupling to afford functionalized dihydroimida-

zobenzimidazoles was documented using air as the oxidant (Scheme 4).[12] The reaction was found to be compatible with a diverse array of both the activated and unactivated aziridines.

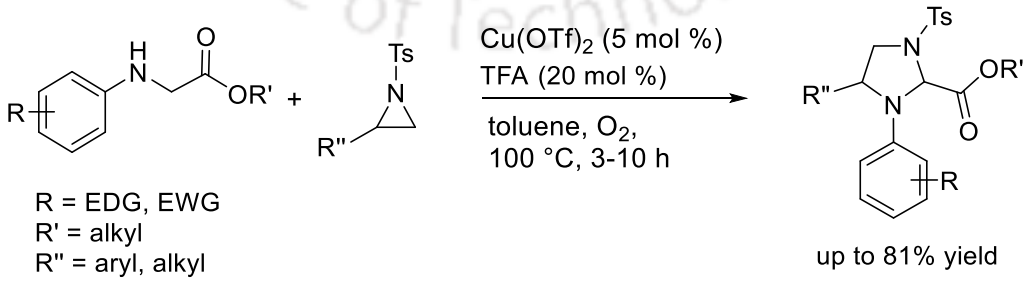


Scheme 3. Cu(II)-Catalyzed Annulation of Aziridines with *N*-Alkylanilines



Scheme 4. Cu(II)-Catalyzed Coupling of Aziridines with Benzimidazoles

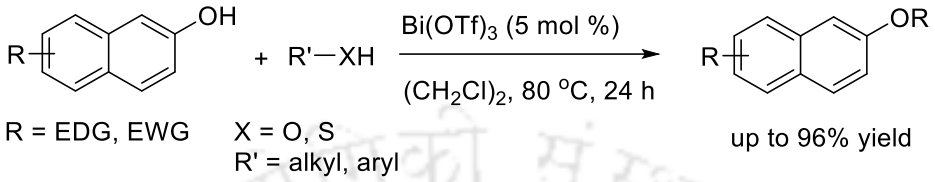
Huo group reported an oxidative dehydrogenative coupling of *N*-sulfonylaziridines with glycine esters to furnish a library of functionalized imidazolidines in moderate to good yields under O_2 atmosphere (Scheme 5).[13] The mechanism involves Cu(II)-catalyzed regioselective ring-opening of aziridine and subsequent O_2-promoted intramolecular C–N bond formation.



Scheme 5. Cu(II)-Catalyzed Oxidative Coupling of Aziridines with Glycine Esters

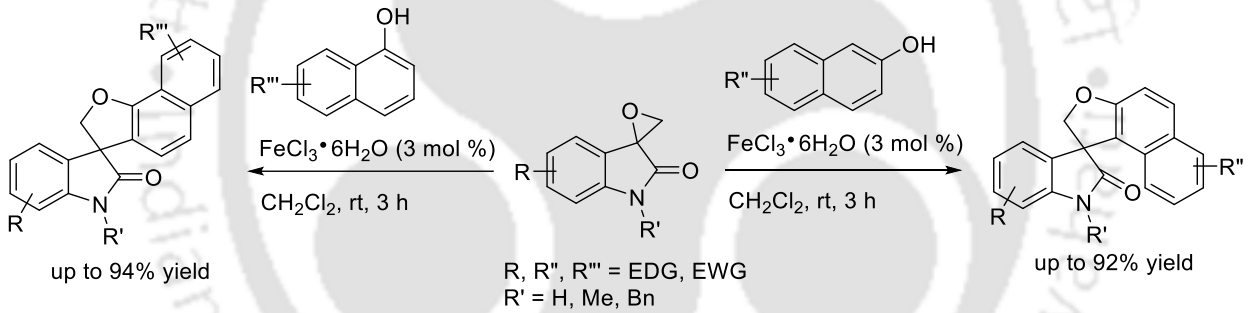
3.1.2 Lewis Acid Catalyzed Dehydrative Reactions of Naphthols

A $Bi(OTf)_3$ catalyzed dehydrative etherification and thioetherification process was presented by Murai and co-workers (Scheme 6).[14] The reaction offers a straightforward route by employing readily accessible alcohols and thiols as the starting materials.



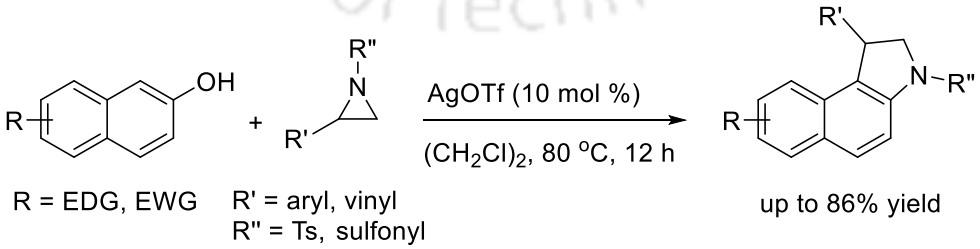
Scheme 6. Bi(III)-Catalyzed Dehydrative Etherification and Thioetherification

Wei group demonstrated the dehydrative annulation of naphthols with spiro-epoxyoxindoles for the construction of naphthofuranyl-spirooxindoles alcohols under Fe(III)-catalysis (Scheme 7).[15] The mechanistic pathway proceeded via sequential Friedel-Crafts-type arylation and O-cyclization in presence of Fe-catalysis.



Scheme 7. Fe(III)-Catalyzed Annulation of Naphthols with Spiro-epoxyoxindoles

During the preparation of our manuscript Biju group reported a Ag(I)-catalyzed (3+2)-annulation of aziridines with 2-naphthols for synthesizing functionalized benzoindolines (Scheme 8).[16] A wide range of functional groups with diverse electronic properties were found to be well tolerated.

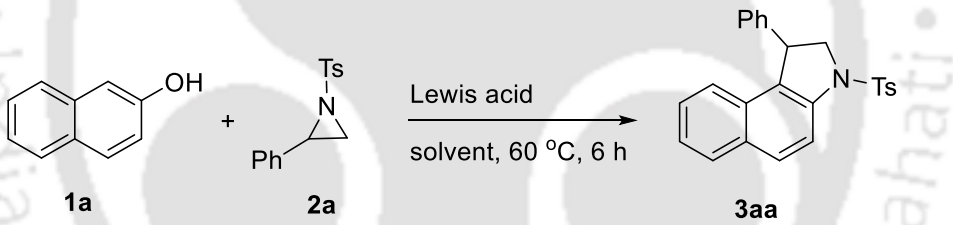


Scheme 8. Ag(I)-Catalyzed Annulation of 2-Naphthols with Aziridines

3.2 Present Study

This chapter demonstrated the Bi(III)-catalyzed regioselective annulation of 2-naphthols with *N*-sulfonylaziridines to access a library of benzoindoline derivatives. The protocol was extended to the one-pot preparation of benzoindoles in the presence of DDQ as the oxidant. Our optimization studies commenced by employing 2-naphthol **1a** and *N*-tosyl-2-phenyl aziridine **2a** as the test substrates utilizing a series of Lewis acids and solvents (Table 1). Gratifyingly, the reaction proceeded selectively to furnish the annulated product **3aa** in 61% yield when **1a** and **2a** were stirred with 5 mol % $Bi(OTf)_3$ in 1,2-dichloroethane at 60 °C for 6 h (entry 1). In a set of Lewis acids screened, $Bi(OTf)_3$, $Yb(OTf)_3$, $Sc(OTf)_3$ and $Cu(OTf)_2$, the former afforded the superior result (entries 2-4). Subsequent screening of the solvents revealed that dichloromethane was the solvent of choice while CH_3CN, toluene and *m*-xylene showed inferior results (entries 5-8). Further, increasing the amount of the catalyst led to improve the overall yield to 75% yield (entry 10). The structure of the cycloadduct **3aa** was determined using single crystal X-ray analysis.

Table 1. Optimization of the Reaction Conditions[a]

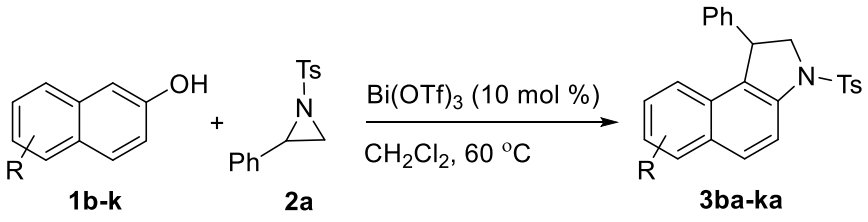


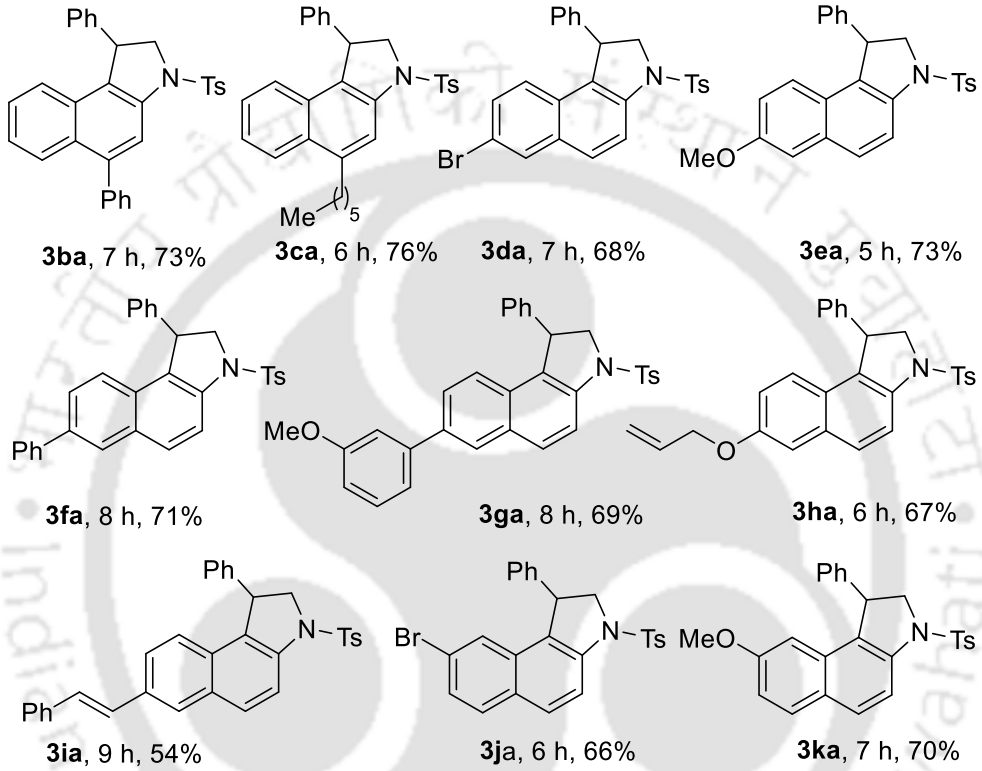
1a **2a** **3aa**

Entry	Lewis acid (5 mol %)	Solvent	Yield (%)[b]
1	$Bi(OTf)_3$	$(CH_2Cl)_2$	61
2	$Yb(OTf)_3$	$(CH_2Cl)_2$	trace
3	$Sc(OTf)_3$	$(CH_2Cl)_2$	trace
4	$Cu(OTf)_2$	$(CH_2Cl)_2$	10
5	$Bi(OTf)_3$	CH_2Cl_2	73
6	$Bi(OTf)_3$	CH_3CN	trace
7	$Bi(OTf)_3$	toluene	63
8	$Bi(OTf)_3$	*m*-xylene	69
9	$Bi(OTf)_3$	CH_2Cl_2	67[c]
10	**$Bi(OTf)_3$**	**CH_2Cl_2**	**75**[d]

[a]Reaction conditions: **1a** (0.2 mmol), **2a** (0.24 mmol), catalyst (5 mol %), solvent (1.5 mL). [b]Isolated yield. [c]$Bi(OTf)_3$ (2 mol %) is used. [d]$Bi(OTf)_3$ (10 mol %) is used.

Table 2. Substrate scope of 2-Naphthols[a,b]

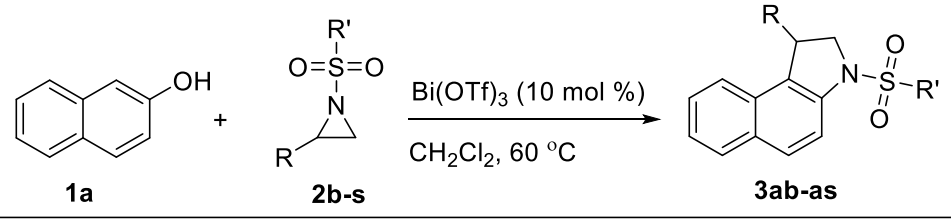


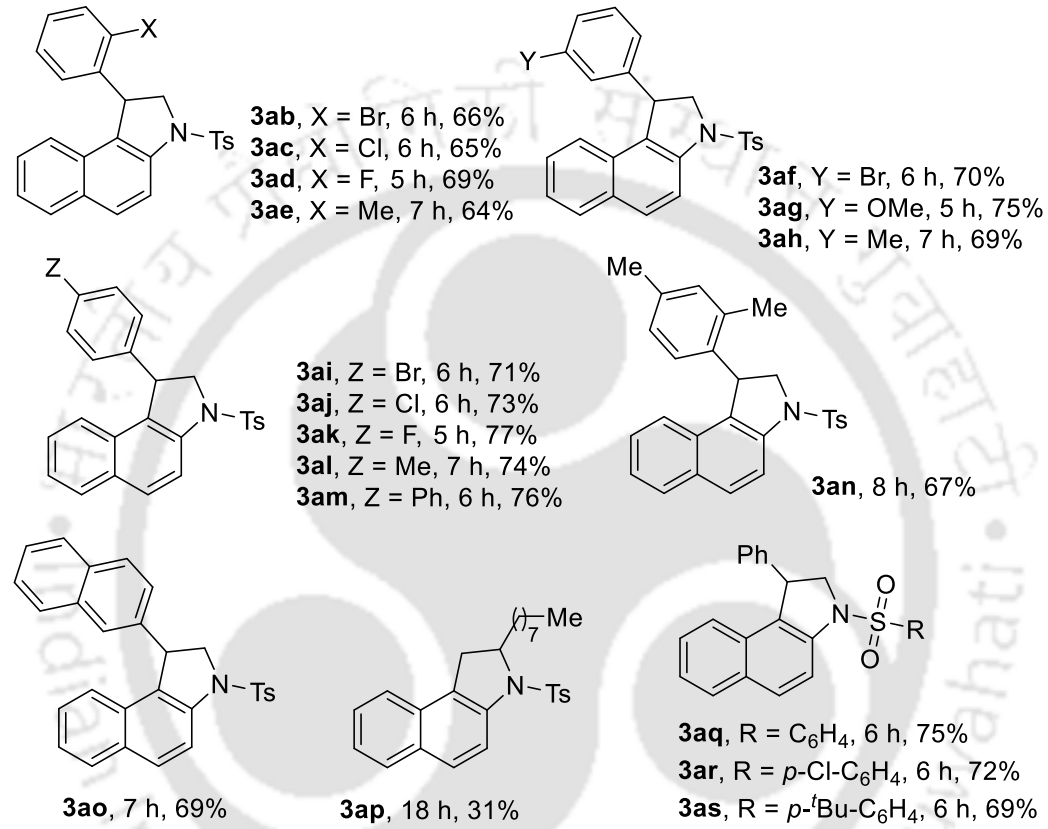


[a]Reaction conditions: **1b-k** (0.2 mmol), **2a** (0.24 mmol), $Bi(OTf)_3$ (10 mol %), CH_2Cl_2 (1.5 mL), 60 °C. [b]Isolated yield. n. r. = no reaction.

Having the optimized reaction conditions, the generality of this protocol was investigated using a series of 2-naphthols **1b-k** with *N*-tosyl-2-phenylaziridine **2a** as a standard substrate (Table 2). The substrates having 4-phenyl **1b** and 4-hexyl **1c** groups underwent the reaction efficiently to produce **3ba** and **3ca** in 73 and 76% yields, respectively. The reaction of the substrates bearing diverse functional groups at the 6-position such as bromo **1d**, methoxy **1e**, phenyl **1f**, 3-methoxyphenyl **1g**, allyl ether **1h** and styrenyl **1i** substituents proceeded smoothly, affording the cycloadducts **3da-ia** in 54-73% yields. In addition, the C7-substituted 2-naphthols with bromo **1j** and methoxy **1k** groups were compatible to give **3ja** and **3ka** in 66 and 70% yields, respectively.

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



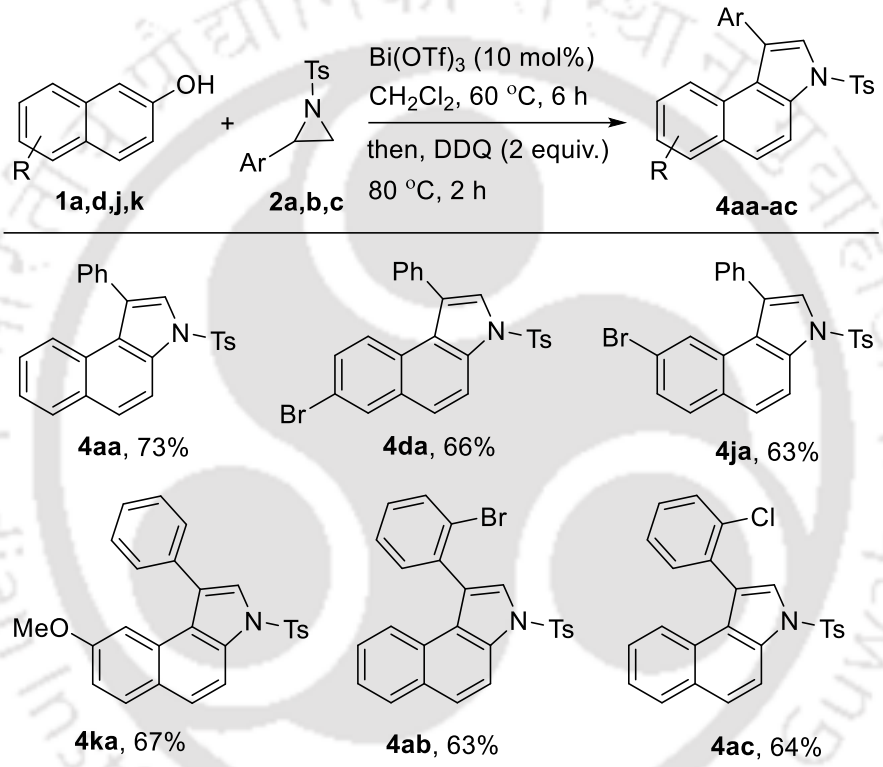


[a]Reaction conditions: **1a** (0.2 mmol), **2b-s** (0.24 mmol), $Bi(OTf)_3$ (10 mol %), CH_2Cl_2 (1.5 mL), 60 °C. [b]Isolated yield.

The scope of the method was extended for the reaction of 2-naphthol **1a** with a library of substituted aziridines **2b-s** (Table 3). Aziridines bearing 2-bromo **2b**, 2-chloro **2c**, 2-fluoro **2d** and 2-methyl **2e** groups on the aryl ring afforded the desired **3ad-ae** in 64-69% yields. Similarly, the reaction of aziridines having substitution at the 3-position of the aryl ring with bromo **2f**, methoxy **2g** and methyl **2h** functionalities gave the target heterocycles **3af-ah** in 69-75% yields. In addition, the substrates with 4-bromo **2i**, 4-chloro **2j** and 4-fluoro **2k** functionalities produced the annulated **3ai-ak** in 71-77% yields, while the aziridines having 4-methyl **2l** and 4-phenyl **2m** substituents successfully reacted to furnish the benzoindolines **3al** and **3am** in 74 and 76% yields, respectively.

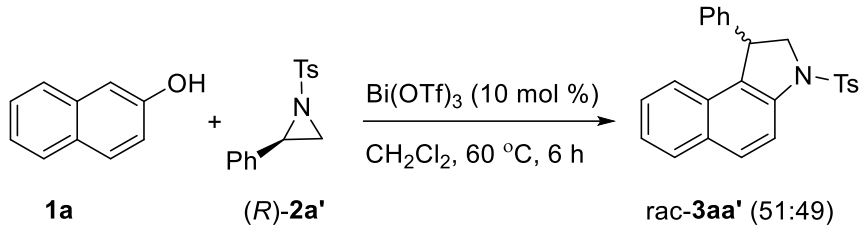
Moreover, 2,4-dimethylphenylaziridine **2n** and 2-naphthylaziridine **2o** were amenable, producing **3an** and **3ao** in 67% and 69%, yields, respectively. Intriguingly, 2-octylaziridine **2p** was tested and the regiochemical outcome of **3ap** was different to those of aryl analogues.[11,12] Further, *N*-sulfonylaziridines with electronically divergent groups **2q-s** delivered benzoindolines **3aq-as** in 69-75% yields. These results highlight the functional group tolerance in accommodating the bio-relevant heterocyclic frameworks.

Table 4. Synthesis of Benzoindoles [a,b]



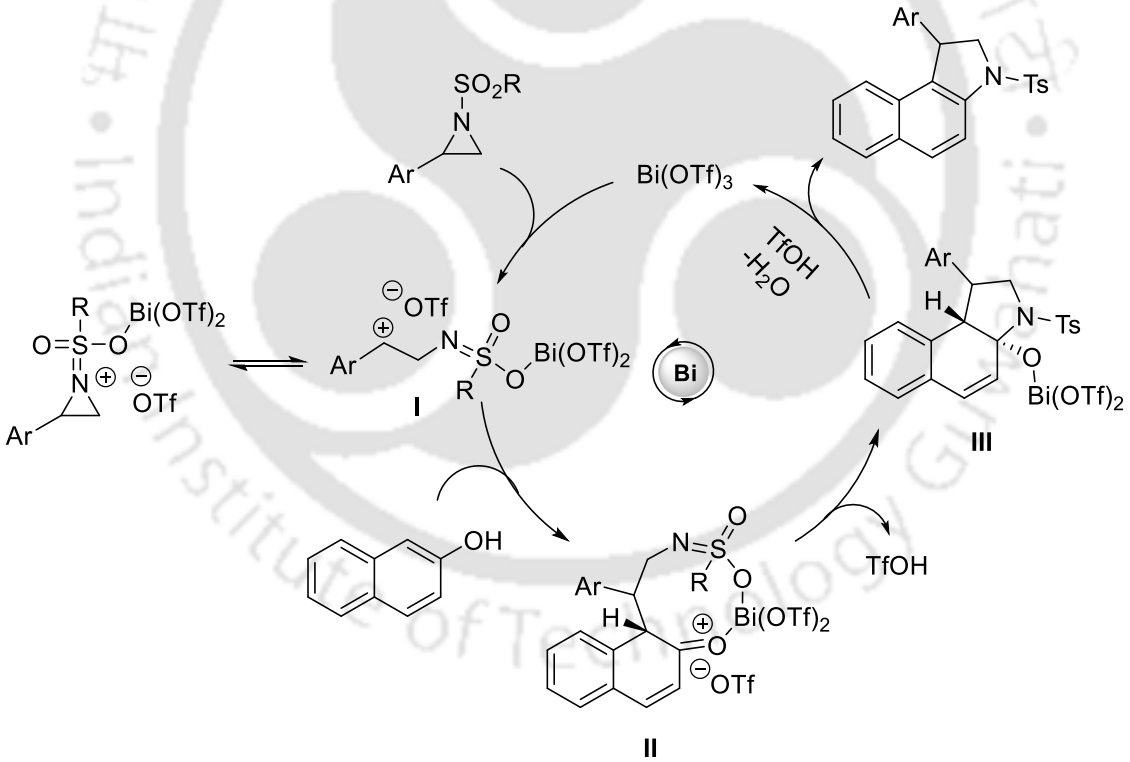
[a]Reaction conditions: **1** (0.2 mmol), **2** (0.24 mmol), $Bi(OTf)_3$ (10 mol%), CH_2Cl_2 (1.5 mL) 60 °C, 6 h, then DDQ (0.4 mmol), 80 °C, 2 h. [b]Isolated yield.

We further extended the scope of the methodology towards the one-pot construction of functionalized benzoindoles in the presence of DDQ as an oxidant. The reaction of 2-naphthols **1a**, **1d**, **1j** and **1k** with aziridines **2a-c** were investigated as the representative examples (Table 4). The reactions took place efficiently to produce the functionalized benzoindoles **4aa-ac** in 63-73% yields. The bromo-containing benzoindole derivatives could be further modified for potential structure-activity relationship studies.



Scheme 9. Reaction with Chiral Aziridine

To shed light into the reaction pathway, the reaction of enantiopure aziridine (*R*)-**2a'** was examined with 2-naphthol **1a** as a representative example (Scheme 9). The reaction took place to produce a 1:1 mixture of enantiomers, which suggests the involvement of an S_N1 pathway.[7b] Thus, the chelation of $Bi(OTf)_3$ with aziridine may lead to the regioselective ring opening and therefore producing a stable benzylic carbocation **I** (Scheme 10).[7] Nucleophilic addition of **I** with 2-naphthol may give the oxocarbenium ion **II**.[14,15] The latter may undergo intramolecular cyclization to produce **III**, which can deliver the target heteroycle *via* dehydration to complete the catalytic cycle.



Scheme 10. Plausible Reaction Mechanism

In summary, we have described an efficient Bi(III)-catalyzed annulation of 2-naphthols with *N*-sulfonylaziridines to produce benzoindolines *via* a tandem nucleophilic ring opening of aziridine

followed by an intramolecular dehydrative cyclization. The scope was expanded for the construction of benzoindoles in high yields. The use of simple substrates and functional group diversity are the important practical features.

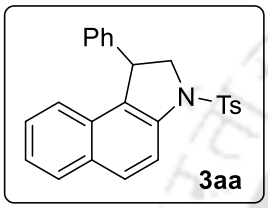
3.3 Experimental Section

General Information. 2-Naphthol (99%), $Bi(OTf)_3$ (99%), styrenes and 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ) were purchased from Aldrich and chloramine-T trihydrate (98%) was purchased from Merck and used as received. 2-Naphthols[17] and aziridines[18] were prepared according to the reported procedure. SRL silica gel G/GF 254 plates and Merck silica gel (100-200 mesh) were used for analytical TLC and column chromatography, respectively. Varian DRX-400, Bruker Ascend 300, 400 and Bruker Avance III 600 MHz spectrometer 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. HPLC analysis was carried out using Waters-2489 with Chiralcel OD using isopropanol and hexane as 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. The X-ray diffraction data were collected at 296 K with Mo Kα radiation (λ = 0.71073 Å) using a Bruker SMART APEX II CCD diffractometer equipped with a graphite monochromator. The structure was solved by direct methods and refined by full-matrix least-squares calculations using SHELXL software.

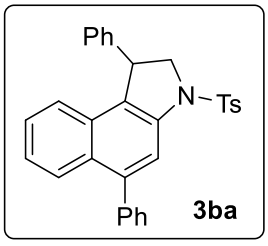
Procedure for the Synthesis of Benzoindolines. To a mixture of 2-naphthols **1** (0.2 mmol) and aziridines **2** (0.24 mmol) in CH_2Cl_2 (1.5 mL) was added $Bi(OTf)_3$ (10 mol %, 13.12 mg) at room temperature under air. The resultant mixture was stirred at 60 ^oC for the appropriate time. The progress of the reaction was monitored by TLC using hexane and ethyl acetate as an eluent. After completion, the reaction mixture was cooled to room temperature and diluted with CH_2Cl_2 (10 mL). The solution was washed with brine (2 x 5 mL) and water (1 x 5 mL). Drying (Na_2SO_4) and evaporation of the solvent furnished a residue that was purified on silica gel column chromatography using hexane and ethyl acetate as eluent.

Procedure for the Synthesis of Benzoindoles. 2-Naphthol **1** (0.2 mmol), aziridine **2** (0.24 mmol) and $Bi(OTf)_3$ (10 mol %, 13.12 mg) were stirred in CH_2Cl_2 (1.5 mL) at 60 °C for 6h. The reaction mixture was then treated with DDQ (0.4 mmol, 90.8 mg) in the same pot and stirred at 80 °C for 2 h. The resultant mixture was cooled to room temperature and treated with CH_2Cl_2 (1 x 10 mL). The resultant mixture was washed successively with brine (2 x 5 mL) and water (1 x 5 mL). Drying (Na_2SO_4) and evaporation of the solvent produced a residue that was purified using a silica gel column chromatography with hexane and ethyl acetate as an eluent.

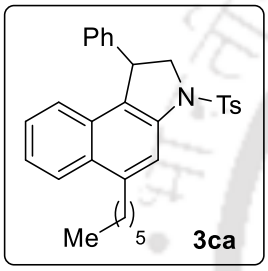
3.4 Characterization Data



1-Phenyl-3-tosyl-2,3-dihydro-1*H*-benzo[*e*]indole 3aa. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.51; colorless solid; mp 184-185 °C; yield 75% (60 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.10 (d, *J* = 9.0 Hz, 1H), 7.85 (d, *J* = 8.4 Hz, 1H), 7.81 (d, *J* = 7.8 Hz, 1H), 7.64 (d, *J* = 7.8 Hz, 2H), 7.30-7.27 (m, 1H), 7.24-7.21 (m, 2H), 7.14-7.12 (m, 3H), 7.08 (t, *J* = 7.8 Hz, 2H), 6.74 (d, *J* = 7.2 Hz, 2H), 4.73 (dd, *J* = 10.2 Hz, 4.8 Hz, 1H), 4.46 (t, *J* = 10.8 Hz, 1H), 3.97 (dd, *J* = 11.4 Hz, 4.8 Hz, 1H), 2.34 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 144.2, 143.4, 140.4, 133.7, 131.4, 130.3, 130.1, 129.9, 128.9, 128.8, 127.5, 127.4, 127.3, 127.0, 126.9, 124.6, 123.7, 115.7, 59.6, 45.6, 21.6; FT-IR (KBr) 3061, 2919, 1925, 1812, 1624, 1594, 1512, 1493, 1468, 1456, 1354, 1254, 1167, 1090, 1065, 1018 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{25}H_{22}NO_2S$: 400.1371, found: 400.1370. HPLC analysis: Daicel CHIRALCEL OD column, hexane/iPrOH = 90:10, flow rate: 1 mL /min, λ = 215 nm, first enantiomer (^{t}R = 8.51 min, 51% of integration), second enantiomer (^{t}R = 14.71 min, 49% of integration).

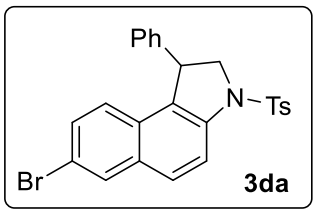


1,5-Diphenyl-3-tosyl-2,3-dihydro-1*H*-benzo[*e*]indole 3ba. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.47; thick yellow liquid; yield 73% (69 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.05 (s, 1H), 7.82-7.81 (m, 1H), 7.67 (d, *J* = 8.4 Hz, 2H), 7.55-7.52 (m, 4H), 7.49-7.46 (m, 1H), 7.32-7.30 (m, 1H), 7.24-7.21 (m, 2H), 7.17-7.10 (m, 5H), 6.81 (d, *J* = 7.2 Hz, 2H), 4.78 (dd, *J* = 10.2 Hz, 4.8 Hz, 1H), 4.49 (t, *J* = 10.8 Hz, 1H), 4.01 (dd, *J* = 10.8 Hz, 4.2 Hz, 1H), 2.36 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.1, 143.3, 142.5, 140.4, 139.7, 133.5, 130.5, 130.1, 129.7, 129.6, 128.8, 128.4, 127.6, 127.4, 127.3, 127.1, 126.8, 126.7, 126.5, 124.5, 123.8, 116.3, 59.5, 45.5, 21.5; FT-IR (neat) 3059, 3030, 2924, 2849, 1619, 1594, 1493, 1453, 1400, 1352, 1311, 1165, 1091, 1073, 1031 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{31}H_{26}NO_2S$: 476.1684, found: 476.1684.



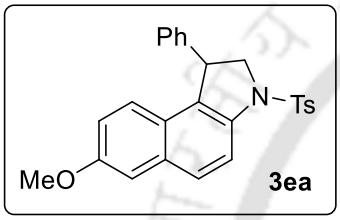
3ca

5-Hexyl-1-phenyl-3-tosyl-2,3-dihydro-1*H*-benzo[*e*]indole 3ca. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.56; colorless solid; mp 116-117 °C; yield 76% (73 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.99-7.97 (m, 2H), 7.63-7.61 (m, 2H), 7.30 (t, *J* = 6.6 Hz, 1H), 7.25-7.23 (m, 1H), 7.21-7.18 (m, 1H), 7.11-7.10 (m, 3H), 7.06 (t, *J* = 7.2 Hz, 2H), 6.72 (d, *J* = 7.2 Hz, 2H), 4.68 (dd, *J* = 10.2 Hz, 4.2 Hz, 1H), 4.42 (t, *J* = 10.8 Hz, 1H), 3.94 (dd, *J* = 11.4 Hz, 3.6 Hz, 1H), 3.14-3.12 (m, 2H), 2.32 (s, 3H), 1.81-1.79 (m, 2H), 1.49-1.47 (m, 2H), 1.38-1.37 (m, 4H), 0.94-0.92 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.9, 143.4, 141.5, 139.7, 133.4, 130.4, 129.6, 129.5, 128.5, 127.3, 127.1, 126.5, 126.2, 125.1, 124.7, 124.2, 124.1, 115.4, 59.3, 45.3, 33.7, 31.7, 31.0, 29.4, 22.6, 21.4, 14.1; FT-IR (KBr) 3029, 2957, 2929, 2854, 1621, 1596, 1581, 1492, 1466, 1454, 1353, 1266, 1182, 1169, 1091, 1030 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{31}H_{34}NO_2S$: 484.2310, found: 484.2305.

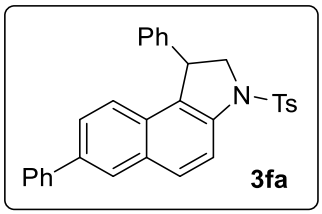


3da

7-Bromo-1-phenyl-3-tosyl-2,3-dihydro-1*H*-benzo[*e*]indole 3da. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.50; colorless solid; mp 201-202 °C; yield 68% (65 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.10 (d, *J* = 9.0 Hz, 1H), 7.94 (s, 1H), 7.74 (d, *J* = 9.0 Hz, 1H), 7.62 (d, *J* = 8.4 Hz, 2H), 7.27-7.25 (m, 1H), 7.14-7.12 (m, 3H), 7.09-7.07 (m, 3H), 6.70 (d, *J* = 7.8 Hz, 2H), 4.70 (dd, *J* = 10.2 Hz, 4.2 Hz, 1H), 4.45 (t, *J* = 10.8 Hz, 1H), 3.94 (dd, *J* = 11.4 Hz, 4.8 Hz, 1H), 2.34 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 144.4, 143.1, 140.8, 133.7, 132.5, 130.7, 130.3, 129.9, 129.1, 129.0, 128.8, 127.6, 127.5, 127.4, 127.1, 125.4, 118.4, 116.7, 59.5, 45.6, 21.7; FT-IR (KBr) 3059, 3028, 2955, 1623, 1583, 1501, 1464, 1451, 1348, 1253, 1161, 1088, 1073, 981 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{25}H_{21}BrNO_2S$: 478.0476, found: 478.0474.

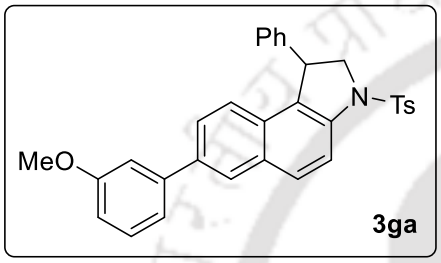


7-Methoxy-1-phenyl-3-tosyl-2,3-dihydro-1*H*-benzo[*e*]indole 3ea. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.42; brown solid; mp 152-153 °C; yield 73% (63 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.06 (d, *J* = 9.0 Hz, 1H), 7.74 (d, *J* = 9.0 Hz, 1H), 7.62 (d, *J* = 8.4 Hz, 2H), 7.14-7.11 (m, 5H), 7.07 (t, *J* = 7.8 Hz, 2H), 6.91-6.89 (m, 1H), 6.71 (d, *J* = 7.8 Hz, 2H), 4.68 (dd, *J* = 10.2 Hz, 4.8 Hz, 1H), 4.44 (t, *J* = 10.8 Hz, 1H), 3.93 (dd, *J* = 11.4 Hz, 4.8 Hz, 1H), 3.85 (s, 3H), 2.34 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 156.7, 144.1, 143.5, 138.7, 133.7, 132.7, 129.8, 128.9, 128.7, 127.8, 127.6, 127.5, 126.9, 125.7, 125.2, 119.7, 116.3, 106.9, 59.5, 55.4, 45.8, 21.6; FT-IR (KBr) 3065, 3010, 2968, 2932, 2835, 1894, 1629, 1602, 1515, 1467, 1453, 1424, 1374, 1350, 1344, 1270, 1240, 1232, 1165, 1089, 1022 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{26}H_{24}NO_3S$: 430.1477, found: 430.1468.

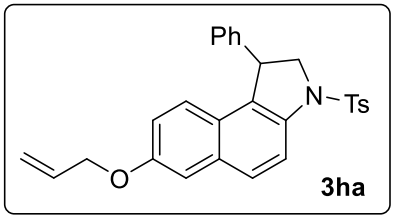


1,7-Diphenyl-3-tosyl-2,3-dihydro-1*H*-benzo[*e*]indole 3fa. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.49; colorless solid; mp 171-172 °C; yield 71% (67 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.15-8.13 (m, 1H), 8.01 (s, 1H), 7.92 (d, *J* = 9.0 Hz, 1H), 7.67 (d, *J* = 8.4 Hz, 2H),

7.62 (d, *J* = 7.8 Hz, 2H), 7.51-7.49 (m, 1H), 7.44 (t, *J* = 7.8 Hz, 2H), 7.35 (t, *J* = 7.8 Hz, 1H), 7.32 (d, *J* = 9.0 Hz, 1H), 7.17-7.15 (m, 3H), 7.11 (t, *J* = 7.2 Hz, 2H), 6.78 (d, *J* = 7.2 Hz, 2H), 4.76 (dd, *J* = 10.2 Hz, 4.2 Hz, 1H), 4.49 (t, *J* = 10.8 Hz, 1H), 3.99 (dd, *J* = 10.8 Hz, 4.8 Hz, 1H), 2.35 (s, 3H) ; ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.0, 143.1, 140.5, 140.1, 137.0, 133.3, 131.4, 130.1, 129.6, 129.2, 128.7, 128.6, 127.29, 127.23, 127.09, 127.06, 126.7, 126.4, 126.3, 123.9, 115.8, 59.3, 45.3, 21.4 ; FT-IR (KBr) 3060, 3028, 2923, 1953, 1628, 1596, 1568, 1493,1473, 1446, 1353, 1260, 1186, 1164, 1091, 1072, 1060, 1019, 994 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{31}H_{26}NO_2S$: 476.1684, found: 476.1694.

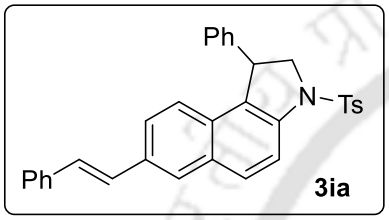


7-(3-Methoxyphenyl)-1-phenyl-3-tosyl-2,3-dihydro-1*H*-benzo[*e*]indole 3ga. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.44; colorless solid; mp 168-169 °C; yield 69% (70 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.13 (d, *J* = 9.0 Hz, 1H), 8.003-8.001 (m, 1H), 7.90 (d, *J* = 9.0 Hz, 1H), 7.65 (d, *J* = 7.8 Hz, 2H), 7.49-7.47 (m, 1H), 7.35 (t, *J* = 7.8 Hz, 1H), 7.30 (d, *J* = 8.4 Hz, 1H), 7.19 (d, *J* = 7.2 Hz, 1H), 7.16-7.13 (m, 4H), 7.10 (t, *J* = 7.2 Hz, 2H), 6.90-6.88 (m, 1H), 6.77 (d, *J* = 7.2 Hz, 2H), 4.75 (dd, *J* = 10.2 Hz, 4.2 Hz, 1H), 4.48 (t, *J* = 10.8 Hz, 1H), 3.98 (dd, *J* = 11.4 Hz, 4.8 Hz, 1H), 3.85 (s, 3H), 2.35 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.1, 144.3, 143.4, 142.4, 140.5, 137.2, 133.6, 131.7, 130.4, 130.0, 129.9, 129.5, 128.9, 127.58, 127.51, 127.3, 127.0, 126.7, 126.6, 124.2, 119.8, 116.1, 113.0, 112.8, 59.6, 55.5, 45.6, 21.7 ; FT-IR (KBr) 3080, 2997, 2947, 2832, 1578, 1509, 1489, 1463, 1447, 1434, 1415, 1350, 1293, 1253, 1208, 1165, 1090, 1068, 1033, 981 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{32}H_{28}NO_3S$: 506.1790, found:506.1787.

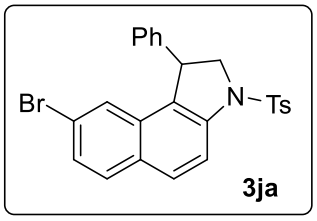


7-(Allyloxy)-1-phenyl-3-tosyl-2,3-dihydro-1*H*-benzo[*e*]indole 3ha. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.47; thick brown liquid; yield 67% (61 mg); ^{1}H NMR (600

MHz, $CDCl_3$) δ 8.05 (d, *J* = 9.0 Hz, 1H), 7.72 (d, *J* = 9.0 Hz, 1H), 7.61 (d, *J* = 8.4 Hz, 2H), 7.14-7.11 (m, 5H), 7.07 (t, *J* = 7.8 Hz, 2H), 6.94-6.92 (m, 1H), 6.71 (d, *J* = 7.2 Hz, 2H), 6.09-6.03 (m, 1H), 5.43-5.40 (m, 1H), 5.30 (d, *J* = 10.2 Hz, 1H), 4.67 (dd, *J* = 10.2 Hz, 4.8 Hz, 1H), 4.58-4.57 (m, 2H), 4.43 (t, *J* = 10.8 Hz, 1H), 3.93 (dd, *J* = 10.8 Hz, 4.2 Hz, 1H), 2.34 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.6, 144.1, 143.4, 138.6, 133.4, 133.1, 132.5, 129.8, 128.8, 128.6, 127.7, 127.5, 127.4, 126.8, 125.6, 125.2, 119.9, 117.9, 116.2, 108.0, 68.9, 59.4, 45.7, 21.6 ; FT-IR (neat) 3063, 3027, 2925, 2870, 1914, 1628, 1598, 1516, 1493, 1453, 1424, 1353, 1268, 1238, 1166, 1061, 1019, 1001 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{28}H_{26}NO_3S$: 456.1633, found: 456.1642.

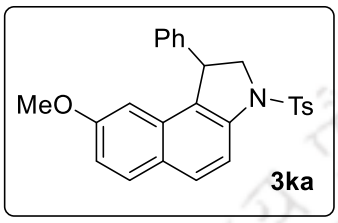


(*E*)-1-Phenyl-7-styryl-3-tosyl-2,3-dihydro-1*H*-benzo[*e*]indole 3ia. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.51; colorless solid; mp 189-190 °C; yield 54% (54 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.09 (d, *J* = 9.0 Hz, 1H), 7.84-7.82 (m, 2H), 7.64 (d, *J* = 8.4 Hz, 2H), 7.50-7.48 (m, 3H), 7.35 (t, *J* = 7.2 Hz, 2H), 7.26-7.24 (m, 2H), 7.21-7.18 (m, 1H), 7.15-7.13 (m, 3H), 7.11-7.07 (m, 3H), 6.75 (d, *J* = 7.2 Hz, 2H), 4.72 (dd, *J* = 10.8 Hz, 4.8 Hz, 1H), 4.47 (t, *J* = 10.8 Hz, 1H), 3.96 (dd, *J* = 4.8 Hz, 10.8 Hz, 1H), 2.35 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.3, 143.4, 140.4, 137.3, 133.69, 133.62, 131.7, 130.1, 129.9, 129.8, 128.94, 128.91, 128.5, 127.8, 127.6, 127.5, 127.4, 127.3, 127.0, 126.6, 124.7, 124.1, 116.1, 59.5, 45.6, 21.7; FT-IR (KBr) 3027, 2924, 2852, 1915, 1595, 1492, 1470, 1444, 1353, 1255, 1164, 1089, 1028, 964 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{33}H_{28}NO_2S$: 502.1841, found:502.1830.

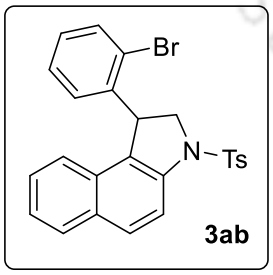


8-Bromo-1-phenyl-3-tosyl-2,3-dihydro-1*H*-benzo[*e*]indole 3ja. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.48; colorless solid; mp 204-205 °C; yield 66% (63 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.10 (d, *J* = 9.0 Hz, 1H), 7.80 (d, *J* = 9.0 Hz, 1H), 7.64 (t, *J* = 9.0 Hz, 3H), 7.384-7.382 (m, 1H), 7.35-7.33 (m, 1H), 7.17-7.14 (m, 3H), 7.12-7.10 (m, 2H), 6.74-6.73 (m, 2H),

4.66 (dd, *J* = 10.2 Hz, 4.8 Hz, 1H), 4.44 (t, *J* = 10.8 Hz, 1H), 3.98 (dd, *J* = 11.4 Hz, 4.8 Hz, 1H), 2.35 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 144.4, 142.9, 141.3, 133.7, 131.5, 130.4, 130.0, 129.9, 129.7, 129.0, 128.0, 127.5, 127.3, 127.2, 126.5, 125.8, 121.4, 115.9, 59.6, 45.4, 21.7; FT-IR (KBr) 3056, 3012, 2979, 2918, 1909, 1751, 1640, 1619, 1598, 1575, 1504, 1457, 1447, 1350, 1302, 1263, 1253, 1162, 1147, 1087, 1075, 1033, 1017, 987 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{25}H_{21}BrNO_2S$: 478.0476, found: 478.0472.

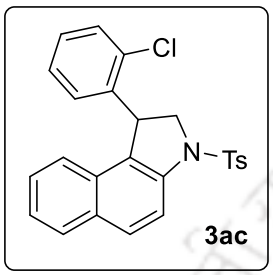


8-Methoxy-1-phenyl-3-tosyl-2,3-dihydro-1*H*-benzo[*e*]indole 3ka. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.46; colorless solid; mp 157-158 °C; yield 70% (60 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.94 (d, *J* = 8.4 Hz, 1H), 7.75 (d, *J* = 9.0 Hz, 1H), 7.69-7.65 (m, 3H), 7.16-7.10 (m, 5H), 6.93-6.92 (m, 1H), 6.80 (d, *J* = 7.2 Hz, 2H), 6.455-6.453 (m, 1H), 4.66 (dd, *J* = 10.2 Hz, 5.4 Hz, 1H), 4.47 (t, *J* = 10.8 Hz, 1H), 3.95 (dd, *J* = 11.4 Hz, 5.4 Hz, 1H), 3.5 (s, 3H), 2.35 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 158.3, 144.2, 143.3, 140.8, 133.7, 131.6, 130.2, 129.9, 129.7, 128.9, 127.67, 127.64, 127.0, 126.8, 126.3, 117.2, 113.1, 102.2, 59.5, 55.1, 45.9, 21.7; FT-IR (KBr) 3061, 3022, 2958, 2832, 1910, 1627, 1598, 1581, 1513, 1492, 1469, 1453, 1431, 1356, 1254, 1224, 1169, 1158, 1058, 1030, 1001 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{26}H_{24}NO_3S$: 430.1477, found: 430.1472.

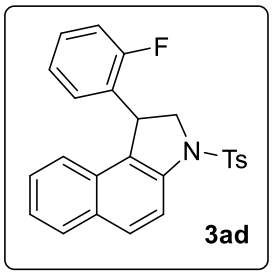


1-(2-Bromophenyl)-3-tosyl-2,3-dihydro-1*H*-benzo[*e*]indole 3ab. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.48; brown solid; mp 131-132 °C; yield 66% (63 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (d, *J* = 8.8 Hz, 1H), 7.89 (d, *J* = 9.2 Hz, 1H), 7.84 (d, *J* = 8.0 Hz, 1H), 7.58 (d, *J* = 8.0 Hz, 3H), 7.32 (t, *J* = 7.2 Hz, 1H), 7.28-7.25 (m, 1H), 7.15 (d, *J* = 8.0 Hz, 1H), 7.07 (d, *J* = 8.0 Hz, 2H), 6.97 (t, *J* = 7.6 Hz, 1H), 6.69 (t, *J* = 6.8 Hz, 1H), 5.93 (d, *J* = 6.8 Hz, 1H), 5.12

(dd, *J* = 10.4 Hz, 3.6 Hz, 1H), 4.49 (t, *J* = 11.2 Hz, 1H), 3.98 (dd, *J* = 11.6 Hz, 3.6 Hz, 1H), 2.30 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 144.2, 142.0, 141.1, 133.8, 132.8, 131.4, 130.3, 130.2, 129.8, 128.9, 128.8, 128.3, 127.7, 127.4, 127.3, 126.4, 124.8, 123.8, 123.6, 116.0, 58.6, 44.5, 21.6; FT-IR (KBr) 3057, 2919, 2886, 1921, 1738, 1628, 1590, 1512, 1469, 1457, 1361, 1256, 1183, 1171, 1090, 1075, 1018, 996 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{25}H_{21}BrNO_2S$: 478.0476, found: 478.0466.

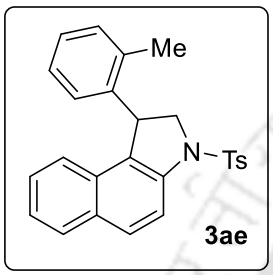


1-(2-Chlorophenyl)-3-tosyl-2,3-dihydro-1*H*-benzo[*e*]indole 3ac. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.47; colorless solid; mp 148-149 °C; yield 65% (56 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (d, *J* = 9.2 Hz, 1H), 7.88-7.82 (m, 2H), 7.58 (d, *J* = 8.0 Hz, 2H), 7.38 (d, *J* = 8.0 Hz, 1H), 7.32 (t, *J* = 7.6 Hz, 1H), 7.28-7.25 (m, 1H), 7.16 (d, *J* = 8.4 Hz, 1H), 7.07-7.04 (m, 3H), 6.65 (t, *J* = 8.0 Hz, 1H), 5.96-5.95 (m, 1H), 5.13 (dd, *J* = 10.4 Hz, 3.2 Hz, 1H), 4.49 (t, *J* = 10.8 Hz, 1H), 4.0 (dd, *J* = 11.2 Hz, 3.2 Hz, 1H), 2.29 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 144.2, 141.0, 140.3, 133.8, 133.0, 131.4, 130.3, 130.2, 129.8, 129.5, 128.87, 128.82, 128.0, 127.4, 127.3, 127.1, 126.3, 124.8, 123.7, 116.0, 58.5, 41.9, 21.6; FT-IR (KBr) 3059, 2953, 2925, 1901, 1627, 1594, 1492, 1470, 1440, 1348, 1252, 1182, 1161, 1063, 1032, 977 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{25}H_{21}ClNO_2S$: 434.0982, found: 434.0972.

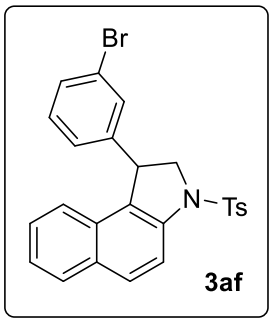


1-(2-Fluorophenyl)-3-tosyl-2,3-dihydro-1*H*-benzo[*e*]indole 3ad. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.49; colorless solid; mp 142-143 °C; yield 69% (57 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.09 (d, *J* = 9.0 Hz, 1H), 7.87 (d, *J* = 9.0 Hz, 1H), 7.84 (d, *J* = 7.8 Hz, 1H), 7.60 (d, *J* = 8.4 Hz, 2H), 7.34-7.31 (m, 1H), 7.29-7.27 (m, 1H), 7.25-7.24 (m, 1H), 7.12-7.07 (m,

3H), 7.05-7.02 (m, 1H), 6.61 (t, *J* =7.2 Hz, 1H), 6.11-6.08 (m, 1H), 5.04 (dd, *J* = 10.2 Hz, 3.6 Hz, 1H), 4.43 (t, *J* = 10.8 Hz, 1H), 4.04 (dd, *J* = 11.4 Hz, 3.6 Hz, 1H), 2.31 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.3 (J_{C-F} = 243.8 Hz), 144.0, 140.4, 133.3, 131.0, 129.9, 129.7, 129.5, 128.59, 128.51, 128.2 (J_{C-F} = 8.25 Hz), 127.1, 127.0, 125.8, 124.5, 124.2, 124.1, 123.2, 115.6, 115.2 (J_{C-F} = 21.6 Hz), 58.4, 37.3, 21.4; FT-IR (KBr) 3059, 2954, 2923, 1627, 1593, 1515, 1486, 1451, 1352, 1256, 1225, 1166, 1091, 1070, 1033, 981 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{25}H_{21}FNO_2S$: 418.1277, found: 418.1278.

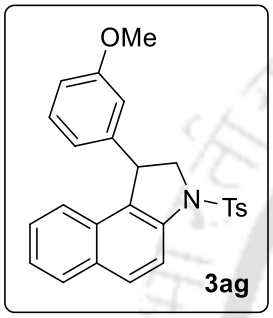


1-(*o*-Tolyl)-3-tosyl-2,3-dihydro-1*H*-benzo[*e*]indole 3ae. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.49; colorless solid; mp 165-166 °C; yield 64% (53 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.10 (d, *J* = 9.0 Hz, 1H), 7.87-7.82 (m, 2H), 7.60 (d, *J* = 8.4 Hz, 2H), 7.30 (t, *J* = 7.2 Hz, 1H), 7.22 (t, *J* = 7.2 Hz, 1H), 7.18 (d, *J* = 7.8 Hz, 1H), 7.09 (d, *J* = 8.4 Hz, 3H), 7.03 (t, *J* = 7.2 Hz, 1H), 6.63 (s, 1H), 5.92 (s, 1H), 4.91 (dd, *J* = 10.2 Hz, 4.8 Hz, 1H), 4.52 (t, *J* = 10.8 Hz, 1H), 3.87 (dd, *J* = 10.8 Hz, 4.8 Hz, 1H), 2.45 (s, 3H), 2.32 (s, 3H) ; ^{13}C NMR (150 MHz, $CDCl_3$) δ 144.2, 141.3, 140.8, 134.8, 133.8, 131.4, 130.5, 130.4, 129.9, 129.8, 128.8, 127.5, 127.4, 127.0, 126.7, 126.5, 124.7, 123.8, 115.9, 58.7, 41.7, 21.6, 20.1; FT-IR (KBr) 3058, 2947, 2893, 2922, 1930, 1626, 1593, 1515, 1491, 1459, 1349, 1335, 1256, 1182, 1161, 1089, 1070, 1035 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{26}H_{24}NO_2S$: 414.1528, found: 414.1524.

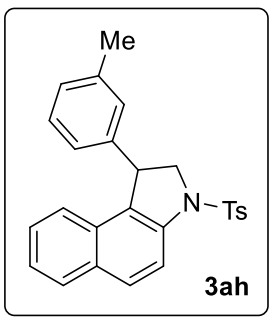


1-(3-Bromophenyl)-3-tosyl-2,3-dihydro-1*H*-benzo[*e*]indole 3af. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.48; colorless solid; mp 123-124 °C; yield 70% (67 mg); ^{1}H NMR

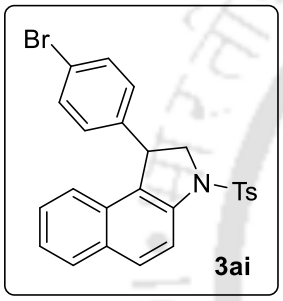
(400 MHz, $CDCl_3$) δ 8.10 (d, *J* = 9.2 Hz, 1H), 7.87-7.81 (m, 2H), 7.64 (d, *J* = 8.0 Hz, 2H), 7.33-7.29 (m, 1H), 7.28-7.25 (m, 2H), 7.21-7.19 (m, 1H), 7.16 (d, *J* = 8.0 Hz, 2H), 6.95 (t, *J* = 7.6 Hz, 1H), 6.89 (s, 1H), 6.66 (d, *J* = 7.6 Hz, 1H), 4.70 (dd, *J* = 10.0 Hz, 4.0 Hz, 1H), 4.45 (t, *J* = 10.8 Hz, 1H), 3.95 (dd, *J* = 11.2 Hz, 4.4 Hz, 1H), 2.34 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 145.8, 144.5, 140.5, 133.5, 131.4, 130.5, 130.4, 130.3, 130.2, 129.9, 128.9, 127.5, 127.2, 126.3, 126.2, 124.8, 123.5, 123.0, 115.7, 59.3, 45.2, 21.8.; FT-IR (KBr) 3054, 2952, 2900, 1910, 1627, 1595, 1565, 1515, 1466, 1351, 1294, 1251, 1169, 1160, 1091, 1072, 1030, 996 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{25}H_{21}BrNO_2S$: 478.0476, found: 478.0472.



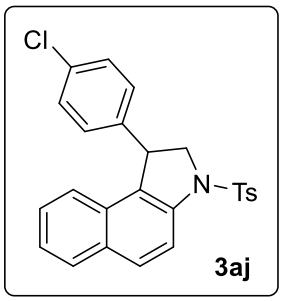
1-(3-Methoxyphenyl)-3-tosyl-2,3-dihydro-1*H*-benzo[*e*]indole 3ag. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.45; colorless solid; mp 151-152 °C; yield 75% (64 mg); ^1H NMR (600 MHz, $CDCl_3$) δ 8.08 (d, *J* = 9.0 Hz, 1H), 7.83-7.78 (m, 2H), 7.63 (d, *J* = 8.4 Hz, 2H), 7.28-7.20 (m, 3H), 7.12 (d, *J* = 8.4 Hz, 2H), 6.99 (t, *J* = 8.4 Hz, 1H), 6.67-6.66 (m, 1H), 6.32-6.31 (m, 2H), 4.68 (dd, *J* = 10.2 Hz, 4.2 Hz, 1H), 4.43 (t, *J* = 10.8 Hz, 1H), 3.97 (dd, *J* = 10.8 Hz, 4.2 Hz, 1H), 3.63 (s, 3H), 2.31 (s, 3H) ; ^{13}C NMR (150 MHz, $CDCl_3$) δ 159.9, 145.1, 144.3, 140.4, 133.6, 131.4, 130.4, 130.1, 129.9, 129.8, 128.7, 127.5, 127.1, 127.0, 124.6, 123.7, 119.9, 115.6, 113.6, 111.9, 59.5, 55.2, 45.6, 21.7; FT-IR (KBr) 3055, 2991, 2958, 2833, 1918, 1629, 1609, 1595, 1582, 1513, 1487, 1454, 1352, 1252, 1168, 1161, 1152, 1088, 1065, 1051, 995 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{26}H_{24}NO_3S$: 430.1477, found: 430.1472.



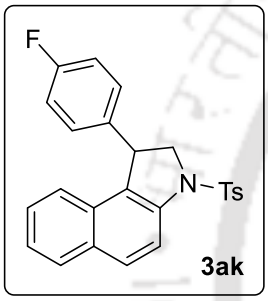
1-(*m*-Tolyl)-3-tosyl-2,3-dihydro-1*H*-benzo[*e*]indole 3ah. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.48; colorless solid; mp 176-177 °C; yield 69% (57 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.09 (d, *J* = 9.0 Hz, 1H), 7.83-7.78 (m, 2H), 7.65 (d, *J* = 8.4 Hz, 2H), 7.28-7.20 (m, 3H), 7.14 (d, *J* = 8.4 Hz, 2H), 6.98-6.93 (m, 2H), 6.59 (s, 1H), 6.54 (d, *J* = 7.2 Hz, 1H), 4.68 (dd, *J* = 10.2 Hz, 4.8 Hz, 1H), 4.44 (t, *J* = 10.8 Hz, 1H), 3.94 (dd, *J* = 10.8 Hz, 4.8 Hz, 1H), 2.33 (s, 3H), 2.15 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 144.2, 143.5, 140.4, 138.6, 133.9, 131.4, 130.4, 130.0, 129.8, 128.77, 128.75, 128.1, 127.8, 127.6, 127.3, 126.9, 124.6, 124.5, 123.7, 115.6, 59.6, 45.7, 21.6, 21.5; FT-IR (KBr) 3059, 2990, 2922, 1913, 1629, 1595, 1514, 1466, 1457, 1349, 1254, 1183, 1166, 1090, 1068, 1031, 1001 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{26}H_{24}NO_2S$: 414.1528, found: 414.1527.



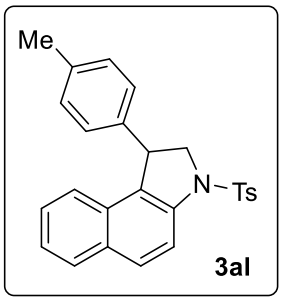
1-(4-Bromophenyl)-3-tosyl-2,3-dihydro-1*H*-benzo[*e*]indole 3ai. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.49; colorless solid; mp 168-169 °C; yield 71% (68 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (d, *J* = 8.8 Hz, 1H), 7.87-7.81 (m, 2H), 7.58-7.56 (m, 2H), 7.33-7.29 (m, 1H), 7.27-7.23 (m, 1H), 7.20-7.14 (m, 3H), 7.11 (d, *J* = 8.0 Hz, 2H), 6.56-6.54 (m, 2H), 4.68 (dd, *J* = 10.4 Hz, 4.0 Hz, 1H), 4.45 (t, *J* = 11.2 Hz, 1H), 3.94 (dd, *J* = 11.2 Hz, 4.0 Hz, 1H) 2.34 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 144.5, 142.4, 140.5, 133.7, 131.9, 131.5, 130.3, 130.2, 129.8, 129.1, 128.9, 127.4, 127.2, 126.7, 124.8, 123.5, 120.8, 115.9, 59.4, 44.9, 21.7; FT-IR (KBr) 3048, 2958, 2895, 1910, 1898, 1626, 1591, 1574, 1485, 1466, 1352, 1335, 1166, 1142, 1066, 1029, 982 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{25}H_{21}BrNO_2S$: 478.0476, found: 478.0476.



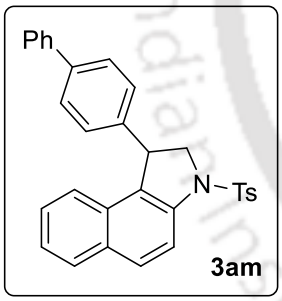
1-(4-Chlorophenyl)-3-tosyl-2,3-dihydro-1*H*-benzo[*e*]indole 3aj. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.48; brown solid; mp 150-151 °C; yield 73% (63 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.08 (d, *J* = 9.0 Hz, 1H), 7.85-7.80 (m, 2H), 7.59 (d, *J* = 7.8 Hz, 2H), 7.31-7.29 (m, 1H), 7.24 (t, *J* = 7.8 Hz, 1H), 7.19-7.18 (m, 1H), 7.11 (d, *J* = 7.8 Hz, 2H), 7.02 (d, *J* = 8.4 Hz, 2H), 6.63 (d, *J* = 8.4 Hz, 2H), 4.69 (dd, *J* = 10.2 Hz, 4.2 Hz, 1H), 4.44 (t, *J* = 10.8 Hz, 1H), 3.94 (dd, *J* = 11.4 Hz, 4.2 Hz, 1H), 2.34 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 144.4, 141.9, 140.5, 133.9, 132.7, 131.5, 130.3, 130.2, 129.8, 129.0, 128.9, 128.7, 127.5, 127.2, 126.7, 124.7, 123.5, 115.8, 59.4, 44.9, 21.6; FT-IR (KBr) 3048, 2958, 2922, 2856, 1626, 1592, 1513, 1489, 1467, 1376, 1352, 1243, 1166, 1092, 1068, 1030, 1013, 983 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{25}H_{21}ClNO_2S$: 434.0982, found: 434.0973.



1-(4-Fluorophenyl)-3-tosyl-2,3-dihydro-1*H*-benzo[*e*]indole 3ak. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.49; colorless solid; mp 191-192 °C; yield 77% (64 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (d, *J* = 8.8 Hz, 1H), 7.86-7.80 (m, 2H), 7.62 (d, *J* = 8.0 Hz, 2H), 7.32-7.19 (m, 3H), 7.13 (d, *J* = 8.0 Hz, 2H), 6.75 (t, *J* = 8.8 Hz, 2H), 6.68-6.64 (m, 2H), 4.71 (dd, *J* = 10.4 Hz, 4.0 Hz, 1H), 4.43 (t, *J* = 10.8 Hz, 1H), 3.93 (dd, *J* = 11.2 H, 4.0 Hz, 1H), 2.33 (s, 3H) ; ^{13}C NMR (150 MHz, $CDCl_3$) δ 162.5 (J_{C-F} = 244.2 Hz), 144.4, 140.3, 139.2, 133.7, 131.4, 130.28, 130.25, 129.9, 128.9 (J_{C-F} = 7.95 Hz), 128.8, 127.5, 127.16, 127.12, 124.7, 123.6, 115.8 (J_{C-F} = 3.3 Hz), 115.6, 59.5, 44.8, 21.6; FT-IR (KBr) 3058, 1629, 1598, 1506, 1470, 1457, 1355, 1256, 1215, 1168, 1160, 1092, 1068, 1019 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{25}H_{21}FNO_2S$: 418.1277, found: 418.1275.

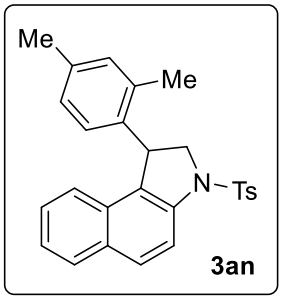


1-(*p*-Tolyl)-3-tosyl-2,3-dihydro-1*H*-benzo[*e*]indole 3al. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.51; colorless solid; mp 179-180 °C; yield 74% (61 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.08 (d, *J* = 9.0 Hz, 1H), 7.83-7.78 (m, 2H), 7.63 (d, *J* = 7.8 Hz, 2H), 7.29-7.20 (m, 3H), 7.13 (d, *J* = 8.4 Hz, 2H), 6.89 (d, *J* = 7.8 Hz, 2H), 6.64 (d, *J* = 7.8 Hz, 2H), 4.68 (dd, *J* = 10.2 Hz, 4.8 Hz, 1H), 4.42 (t, *J* = 10.8 Hz, 1H), 3.3.93 (dd, *J* = 11.4 Hz, 4.8 Hz, 1H), 2.33 (s, 3H), 2.25 (s, 3H) ; ^{13}C NMR (150 MHz, $CDCl_3$) δ 144.2, 140.5, 140.3, 136.5, 133.7, 131.4, 130.4, 129.9, 129.8, 129.5, 128.7, 127.59, 127.57, 127.3, 126.9, 124.6, 123.7, 115.7, 59.7, 45.3, 21.7, 21.2; FT-IR (KBr) 3047, 2924, 2895, 1908, 1624, 1590, 1511, 1466, 1455, 1375, 1354, 1253, 1167, 1090, 1064, 1008, 954 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{26}H_{24}NO_2S$: 414.1528, found: 414.1522.

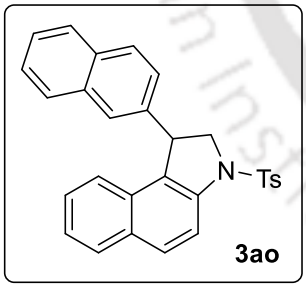


1-([1,1'-Biphenyl]-4-yl)-3-tosyl-2,3-dihydro-1*H*-benzo[*e*]indole 3am. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.47; colorless solid; mp 176-177 °C; yield 76% (72 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.11 (d, *J* = 9.0 Hz, 1H), 7.86 (d, *J* = 9.0 Hz, 1H), 7.83 (d, *J* = 8.4 Hz, 1H), 7.64 (d, *J* = 8.4 Hz, 2H), 7.50 (d, *J* = 7.2 Hz, 2H), 7.40 (t, *J* = 7.8 Hz, 2H), 7.33-7.29 (m, 5H), 7.26-7.24 (m, 1H), 7.13 (d, *J* = 7.8 Hz, 2H), 6.81 (d, *J* = 8.4 Hz, 2H), 4.77 (dd, *J* = 10.2 Hz, 4.2 Hz, 1H), 4.48 (t, *J* = 10.8 Hz, 1H), 4.02 (dd, *J* = 10.8 Hz, 4.2 Hz, 1H), 2.29 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.3, 142.4, 140.7, 140.4, 139.8, 133.7, 131.4, 130.3, 130.1, 129.8, 128.9, 128.8, 127.8, 127.5, 127.4, 127.3, 127.09, 127.05, 124.7, 123.7, 115.7, 59.6, 45.2, 21.6 ; FT-IR (KBr)

3053, 3027, 2922, 2852, 1591, 1514, 1485, 1467, 1365, 1355, 1267, 1168, 1099, 1037, 996 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{31}H_{26}NO_2S$: 476.1684, found: 476.1679.

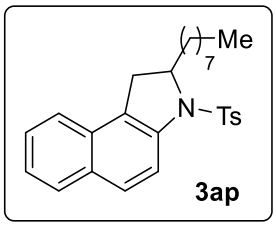


1-(2,4-Dimethylphenyl)-3-tosyl-2,3-dihydro-1*H*-benzo[*e*]indole 3an. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.49; colorless solid; mp 138-139 °C; yield 67% (57 mg); ^1H NMR (400 MHz, $CDCl_3$) δ 8.08 (d, *J* = 8.8 Hz, 1H), 7.82 (t, *J* = 9.6 Hz, 2H), 7.58 (d, *J* = 8.0 Hz, 2H), 7.29 (t, *J* = 7.6 Hz, 1H), 7.24-7.19 (m, 1H), 7.10-7.06 (m, 3H), 6.97 (s, 1H), 6.42 (s, 1H), 5.82 (s, 1H), 4.85 (dd, J= 10.4 Hz, 4.8 Hz, 1H), 4.48 (t, *J* = 10.4 Hz, 1H), 3.83 (dd, *J* = 10.8 Hz, 4.8 Hz, 1H), 2.37 (s, 3H), 2.31 (s, 3H), 2.21 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.9, 140.4, 138.0, 135.8, 134.3, 133.5, 131.1, 131.0, 130.1, 129.57, 129.51, 128.4, 127.3, 127.1, 127.0, 126.8, 126.7, 124.3, 123.5, 115.6, 58.5, 41.3, 21.4, 20.8, 19.7; FT-IR (KBr) 2916, 1910, 1629, 1595, 1494, 1470, 1399, 1352, 1305, 1167, 1183, 1137, 1090, 1075, 1028, 984 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{27}H_{26}NO_2S$: 428.1684, found: 428.1687.

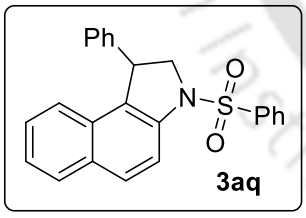


1-(Naphthalen-2-yl)-3-tosyl-2,3-dihydro-1*H*-benzo[*e*]indole 3ao. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.46; colorless solid; mp 192-193 °C; yield 69% (62 mg); ^1H NMR (600 MHz, $CDCl_3$) δ 8.14 (d, *J* = 8.4 Hz, 1H), 7.87 (d, *J* = 9.0 Hz, 1H), 7.80 (d, *J* = 8.4 Hz, 1H), 7.72-7.71 (m, 1H), 7.60 (d, *J* = 7.8 Hz, 2H), 7.55 (d, *J* = 8.4 Hz, 1H), 7.49-7.48 (m, 1H), 7.39-7.38 (m, 2H), 7.24-7.21 (m, 2H), 7.15-7.14 (m, 2H), 7.02 (d, *J* = 7.8 Hz, 2H), 6.84 (d, *J* = 7.8 Hz, 1H), 4.87 (dd, *J* = 10.2 Hz, 4.2 Hz, 1H), 4.53 (t, *J* = 10.8 Hz, 1H), 4.04 (dd, *J* = 10.8 Hz, 3.6 Hz, 1H), 2.21 (s, 3H) ; ^{13}C NMR (150 MHz, $CDCl_3$) δ 144.4, 140.9, 140.5, 133.7, 133.4, 132.5, 131.5,

130.5, 130.2, 129.8, 128.9, 128.8, 128.0, 127.8, 127.5, 127.2, 127.1, 126.3, 126.2, 126.0, 125.5, 124.7, 123.8, 115.9, 59.5, 45.8, 21.6; FT-IR (KBr) 3058, 2960, 2921, 1627, 1594, 1514, 1467, 1357, 1303, 1166, 1151, 1093, 1031, 996 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{29}H_{24}NO_2S$: 450.1528, found: 450.1530.

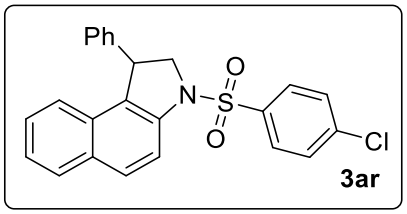


2-Octyl-3-tosyl-2,3-dihydro-1*H*-benzo[*e*]indole 3ap. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.64; thick yellow liquid; yield 31% (27 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.00 (d, *J* = 9.0 Hz, 1H), 7.83 (d, *J* = 8.4 Hz, 1H), 7.76 (d, *J* = 9.0 Hz, 1H), 7.69 (d, *J* = 8.4 Hz, 2H), 7.62 (d, *J* = 8.4 Hz, 1H), 7.45-7.42 (m, 1H), 7.35 (t, *J* = 7.8 Hz, 1H), 7.19 (d, *J* = 7.8 Hz, 2H), 3.99-3.91 (m, 2H), 3.51-3.48 (m, 1H), 2.32 (s, 3H), 1.63-1.61 (m, 1H), 1.31-1.20 (m, 13H), 0.89 (t, *J* = 7.2 Hz, 3H) ; ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.2, 138.8, 133.8, 131.2, 129.9, 129.8, 129.6, 129.1, 128.9, 127.4, 126.8, 124.4, 123.0, 115.6, 55.3, 39.7, 34.7, 32.0, 29.69, 29.65, 29.4, 27.3, 22.8, 21.6, 14.3; FT-IR (neat) 3060, 2925, 2854, 1916, 1628, 1594, 1576, 1516, 1467, 1358, 1256, 1184, 1167, 1093, 1067, 1018 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{27}H_{34}NO_2S$: 436.2310, found: 436.2311.

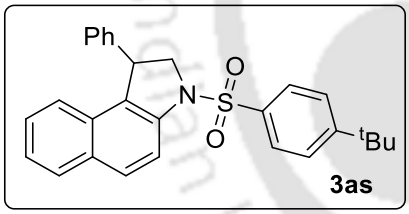


1-Phenyl-3-(phenylsulfonyl)-2,3-dihydro-1*H*-benzo[*e*]indole 3aq. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.51; colorless solid; mp 153-154 °C; yield 75% (58 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.11 (d, *J* = 9.0 Hz, 1H), 7.85 (d, *J* = 9.0 Hz, 1H), 7.80 (d, *J* = 7.8 Hz, 1H), 7.76 (d, *J* = 7.8 Hz, 2H), 7.49 (t, *J* = 7.2 Hz, 1H), 7.34 (t, *J* = 8.4 Hz, 2H), 7.29-7.26 (m, 1H), 7.24-7.19 (m, 2H), 7.12-7.06 (m, 3H), 6.73 (d, *J* = 7.2 Hz, 2H), 4.72 (dd, *J* = 10.8 Hz, 4.8 Hz, 1H), 4.46 (t, *J* = 10.8 Hz, 1H), 3.97 (dd, *J* = 10.8 Hz, 4.2 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 143.4, 140.2, 136.7, 133.4, 131.5, 130.3, 130.1, 129.3, 129.0, 128.8, 127.5, 127.47, 127.45, 127.3, 127.1, 124.7, 123.7, 115.5, 59.6, 45.7 ; FT-IR (KBr) 3057, 3021, 2999, 1943, 1627, 1590, 1574, 1516,

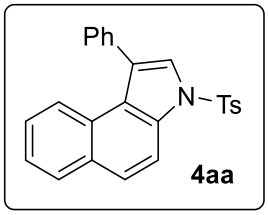
1492, 1469, 1453, 1358, 1334, 1264, 1254, 1169, 1141, 1091, 1068, 994 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{24}H_{20}NO_2S$: 386.1215, found: 386.1218.



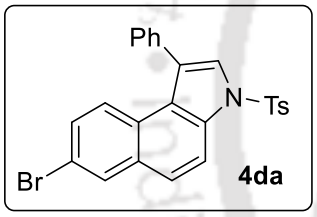
3-((4-Chlorophenyl)sulfonyl)-1-phenyl-2,3-dihydro-1*H*-benzo[*e*]indole 3ar. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.50; colorless solid; mp 163-164 °C; yield 72% (60 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.07 (d, *J* = 9.0 Hz, 1H), 7.87-7.82 (m, 2H), 7.63-7.62 (m, 2H), 7.33-7.31 (m, 1H), 7.27-7.25 (m, 4H), 7.16-7.13 (m, 1H), 7.09 (t, *J* = 7.8 Hz, 2H), 6.66 (d, *J* = 7.2 Hz, 2H), 4.75 (dd, *J* = 10.2 Hz, 4.2 Hz, 1H), 4.50 (t, *J* = 10.8 Hz, 1H), 3.98 (dd, *J* = 11.4 Hz, 4.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.9, 139.7, 139.6, 134.8, 131.3, 130.1, 130.0, 129.2, 128.7, 128.55, 128.50, 127.3, 127.0, 126.9, 126.7, 124.6, 123.6, 115.4, 59.5, 45.2 ; FT-IR (KBr) 3087, 3060, 2924, 1922, 1624, 1581, 1513, 1492, 1471, 1394, 1361, 1255, 1174, 1094, 1082, 1067, 1012 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{24}H_{19}ClNO_2S$: 420.0825, found: 420.0818.



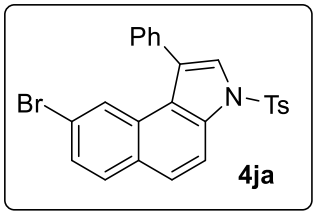
3-((4-(*tert*-Butyl)phenyl)sulfonyl)-1-phenyl-2,3-dihydro-1*H*-benzo[*e*]indole 3as. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.52; colorless solid; mp 196-197 °C; yield 69% (61 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.13 (d, *J* = 9.0 Hz, 1H), 7.85 (d, *J* = 9.0 Hz, 1H), 7.80 (d, *J* = 8.4 Hz, 1H), 7.70 (d, *J* = 8.4 Hz, 2H), 7.37 (d, *J* = 9.0 Hz, 2H), 7.28-7.19 (m, 3H), 7.13-7.06 (m, 3H), 6.77 (d, *J* = 7.2 Hz, 2H), 4.74 (dd, *J* = 10.2 Hz, 4.2 Hz, 1H), 4.44 (t, *J* = 10.8 Hz, 1H), 3.96 (dd, *J* = 10.8 Hz, 4.8 Hz, 1H), 1.26 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.0, 143.4, 140.2, 133.5, 131.2, 130.2, 129.9, 128.8, 128.6, 127.3, 127.0, 126.9, 126.8, 126.1, 124.4, 123.5, 115.3, 59.3, 45.4, 35.1, 31.0 cm^{-1}; FT-IR (KBr) 3064, 2965, 2870, 1930, 1738, 1626, 1592, 1514, 1472, 1457, 1350, 1257, 1172, 1113, 1087, 1022 cm^{-1} ; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{28}H_{28}NO_2S$: 442.1841, found: 442.1845.



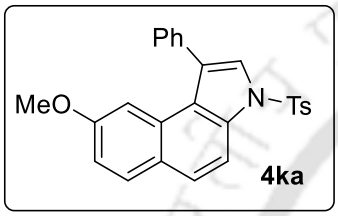
1-Phenyl-3-tosyl-3*H*-benzo[*e*]indole 4aa. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.62; colorless solid; mp 157-158 °C; yield 73% (58 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.21 (d, *J* = 9.0 Hz, 1H), 7.90-7.86 (m, 2H), 7.83 (d, *J* = 7.8 Hz, 2H), 7.76 (d, *J* = 9.0 Hz, 1H), 7.59 (s, 1H), 7.53-7.52 (m, 2H), 7.49-7.44 (m, 3H), 7.38 (t, *J* = 7.2 Hz, 1H), 7.27-7.25 (m, 1H), 7.23-7.21 (m, 2H), 2.32 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.1, 135.4, 134.9, 132.3, 130.8, 130.0, 129.9, 128.7, 128.5, 128.0, 127.9, 126.9, 126.1, 126.0, 125.9, 124.7, 123.8, 123.6, 113.5, 21.6; FT-IR (KBr) 3135, 3059, 2921, 1595, 1518, 1493, 1485, 1441, 1373, 1300, 1272, 1189, 1176, 1140, 1094, 1024, 946 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{25}H_{20}NO_2S$: 398.1215, found: 398.1208.



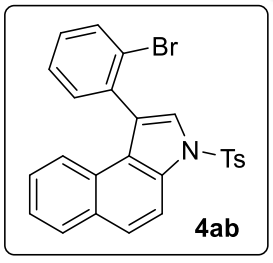
7-Bromo-1-phenyl-3-tosyl-3*H*-benzo[*e*]indole 4da. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.61; brown solid; mp 177-178 °C; yield 66% (63 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.22 (d, *J* = 9.6 Hz, 1H), 7.993-7.990 (m, 1H), 7.83 (d, *J* = 7.8 Hz, 2H), 7.75 (d, *J* = 9.0 Hz, 1H), 7.63 (d, *J* = 9.6 Hz, 1H), 7.60 (s, 1H), 7.49-7.44 (m, 5H), 7.32-7.30 (m, 1H), 7.23 (d, *J* = 8.4 Hz, 2H), 2.31 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.3, 135.2, 134.5, 132.2, 132.1, 130.6, 130.1, 129.8, 129.2, 128.7, 128.1, 126.9, 126.5, 125.5, 125.3, 125.1, 124.0, 123.8, 118.4, 114.5, 21.6,; FT-IR (KBr) 3078, 2925, 2852, 1597, 1583, 1510, 1486, 1444, 1376, 1340, 1294, 1270, 1174, 1143, 1093, 1025 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{25}H_{19}BrNO_2S$: 476.0320, found: 476.0319.



8-Bromo-1-phenyl-3-tosyl-3*H*-benzo[*e*]indole 4ja. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.60; green solid; mp 140-141 °C; yield 63% (60 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.21 (d, *J* = 9.0 Hz, 1H), 8.04 (s, 1H), 7.83 (d, *J* = 8.4 Hz, 2H), 7.71-7.68 (m, 2H), 7.60 (s, 1H), 7.50-7.47 (m, 5H), 7.45-7.43 (m, 1H), 7.23 (d, *J* = 8.4 Hz, 2H), 2.32 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.3, 135.2, 134.1, 132.7, 130.2, 130.0, 129.8, 129.2, 129.1, 128.7, 128.2, 128.0, 126.9, 126.1, 125.8, 125.6, 123.7, 122.9, 120.2, 113.8, 21.6; FT-IR (KBr) 3126, 3054, 2922, 1607, 1507, 1492, 1444, 1369, 1337, 1284, 1176, 1155, 1138, 1095, 956 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{25}H_{19}BrNO_2S$: 476.0320, found: 476.0328.

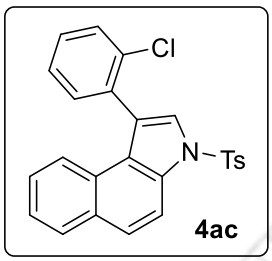


8-Methoxy-1-phenyl-3-tosyl-3*H*-benzo[*e*]indole 4ka. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.58; thick liquid; yield 67% (57 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.06 (d, *J* = 9.0 Hz, 1H), 7.82 (d, *J* = 8.4 Hz, 2H), 7.73 (d, *J* = 9.0 Hz, 1H), 7.66 (d, *J* = 9.0 Hz, 1H), 7.57 (s, 1H), 7.53-7.51 (m, 2H), 7.46 (t, *J* = 7.2 Hz, 2H), 7.42-7.40 (m, 1H), 7.21-7.16 (m, 3H), 7.01-6.99 (m, 1H), 3.41 (s, 3H), 2.28 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.7, 145.1, 135.4, 134.9, 132.7, 130.2, 130.07, 130.0, 129.1, 128.4, 127.9, 126.9, 125.8, 125.78, 125.75, 123.2, 123.0, 116.9, 111.0, 103.0, 54.7, 21.5; FT-IR (neat) 3121, 3061, 2954, 2832, 1912, 1625, 1595, 1580, 1519, 1492, 1467, 1424, 1370, 1306, 1291, 1229,1175, 1134, 1095, 1030, 975 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{26}H_{22}NO_3S$: 428.1320, found: 428.1317.



1-(2-Bromophenyl)-3-tosyl-3*H*-benzo[*e*]indole 4ab. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.61; colorless solid; mp 162-163 °C; yield 63% (60 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.19 (d, *J* = 9.0 Hz, 1H), 7.86 (d, *J* = 7.8 Hz, 1H), 7.80 (d, *J* = 8.4 Hz, 2H), 7.76-7.74 (m, 2H), 7.62 (s, 1H), 7.46-7.41 (m, 3H), 7.39-7.34 (m, 2H), 7.27-7.24 (m, 1H), 7.21 (d, *J* = 8.4

Hz, 2H), 2.31 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.1, 136.0, 135.3, 132.9, 132.2, 132.0, 130.7, 129.97, 129.91, 128.6, 128.0, 127.5, 126.8, 126.4, 126.2, 125.4, 124.8, 124.5, 124.3, 124.2, 123.0, 113.5, 21.6; FT-IR (KBr) 3126, 3058, 2920, 2852, 1924, 1626, 1593, 1518, 1445, 1366, 1296, 1172, 1135, 1094, 1026, 947 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{25}H_{19}BrNO_2S$: 476.0320, found: 476.0325.



1-(2-Chlorophenyl)-3-tosyl-3*H*-benzo[*e*]indole 4ac. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.61; colorless solid; mp 175-176 °C; yield 64% (55 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.19 (d, *J* = 9.0 Hz, 1H), 7.87 (d, *J* = 8.4 Hz, 1H), 7.80 (d, *J* = 7.8 Hz, 2H), 7.75 (d, *J* = 9.0 Hz, 1H), 7.62 (s, 1H), 7.57 (d, *J* = 7.8 Hz, 1H), 7.50 (d, *J* = 8.4 Hz, 1H), 7.46-7.42 (m, 2H), 7.38 (t, *J* = 7.2 Hz, 2H), 7.27-7.24 (m, 1H), 7.22 (d, *J* = 8.4 Hz, 2H), 2.32 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.2, 135.3, 135.0, 133.9, 132.3, 132.1, 130.7, 129.9, 129.79, 129.75, 128.6, 128.0, 126.9, 126.8, 126.4, 126.2, 124.8, 124.4, 124.2, 123.0, 122.6, 113.5, 21.5,; FT-IR (KBr) 3129, 3061, 2922, 2852, 1915, 1518, 1464, 1432, 1368, 1298, 1188, 1173, 1137, 1094, 1079, 1044, 1026, 949 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{25}H_{19}ClNO_2S$: 432.0825, found: 432.0829.

Crystal Structure and Data of 3aa

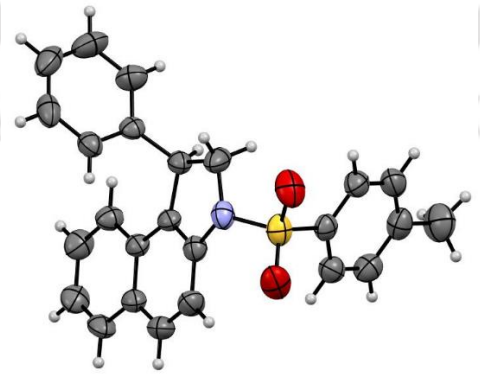


Figure 2. ORTEP diagram of 1-phenyl-3-tosyl-2,3-dihydro-1*H*-benzo[*e*]indole **3aa** (CCDC 1561710).

Identification code	**3aa**
Empirical formula	$C_{25}H_{21}NO_2S$
Formula weight	399.49
Crystal habit, colour	Triangular plates, colorless
Crystal size, mm^3	0.30 x 0.24 x 0.20
Temperature, *T*/K	296 (2)
Wavelength, λ/Å	0.71073
Crystal system	monoclinic
Space group	'P n'
Unit cell dimensions	a = 9.1781(3) Å b = 11.5113(4) Å c = 9.9117(3) Å $\alpha = \gamma = 90.00^o$, $\beta = 106.669(2)$
Volume, *V*/$Å^3$	1003.18(6)
Z	2
Calculated density, $Mg \cdot m^{-3}$	1.322
Absorption coefficient, μ/mm^{-1}	0.183
F(000)	420
θ range for data collection	1.76 to 25.00 ^{o}
Limiting indices	$-10 \leq h \leq 9$, $-13 \leq k \leq 13$, $-11 \leq l \leq 11$
Reflection collected / unique	3154/2826 [R(int) = 0.0338]
Completeness to θ	98.8 % (θ = 25.00)
Absorption correction	Multiscan
Max. and min. transmission	0.964 and 0.949
Refinement method	SHELXL-2014/7
Data / restraints / parameters	3154/2/263
Goodness−of−fit on F^2	0.849
Final *R* indices [*I*>2sigma(*I*)]	R1 = 0.0354, *w*R2 = 0.0999
R indices (all data)	R1 = 0.0416, *w*R2 = 0.1079

3.5 References

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Zhou, S.; Wang, S.; Zhu, X.; Wei, Y. *Org. Lett.* **2013**, *15*, 2628. (h) Craig, R. A.; O'Connor, N. R.; Goldberg, A. F. G.; Stoltz, B. M. *Chem. Eur. J.* **2014**, *20*, 4806. (i) Chai, Z.; Zhu, Y.-M.; Yang, P. J.; Wang, S.; Wang, S.; Liu, Z.; Yang, G. *J. Am. Chem. Soc.* **2015**, *137*, 10088.

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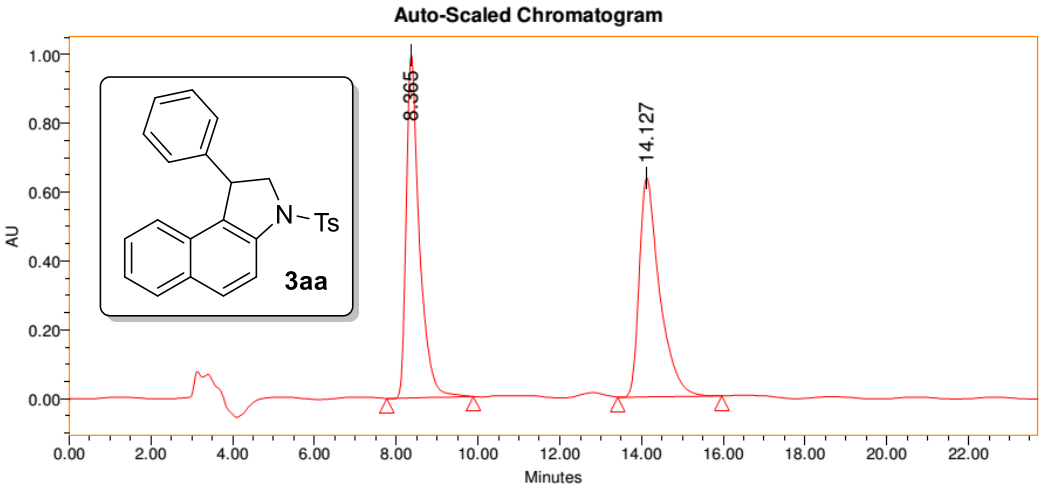
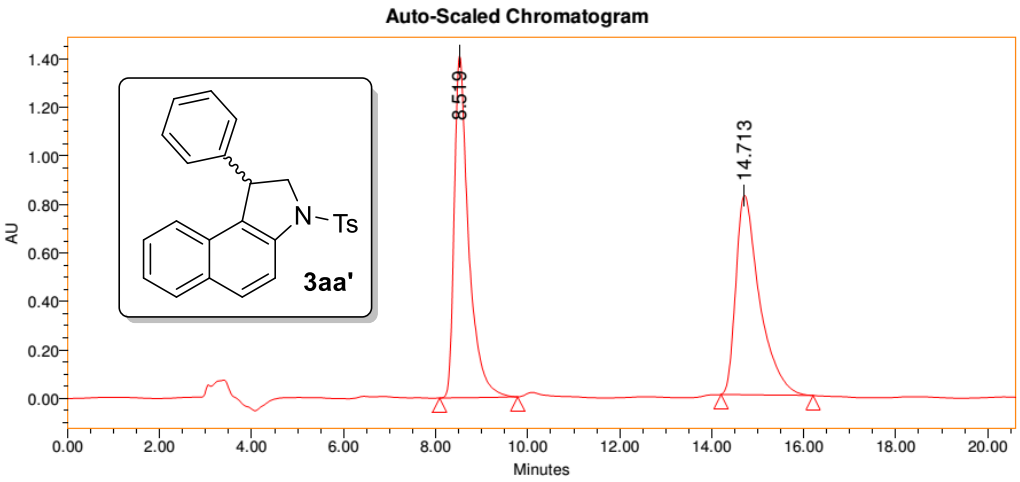
3.6 HPLC chromatograms



Peak Results

	RT	Height (μV)	% Area
1	8.365	996206	50.24
2	14.127	637083	49.76



Peak Results

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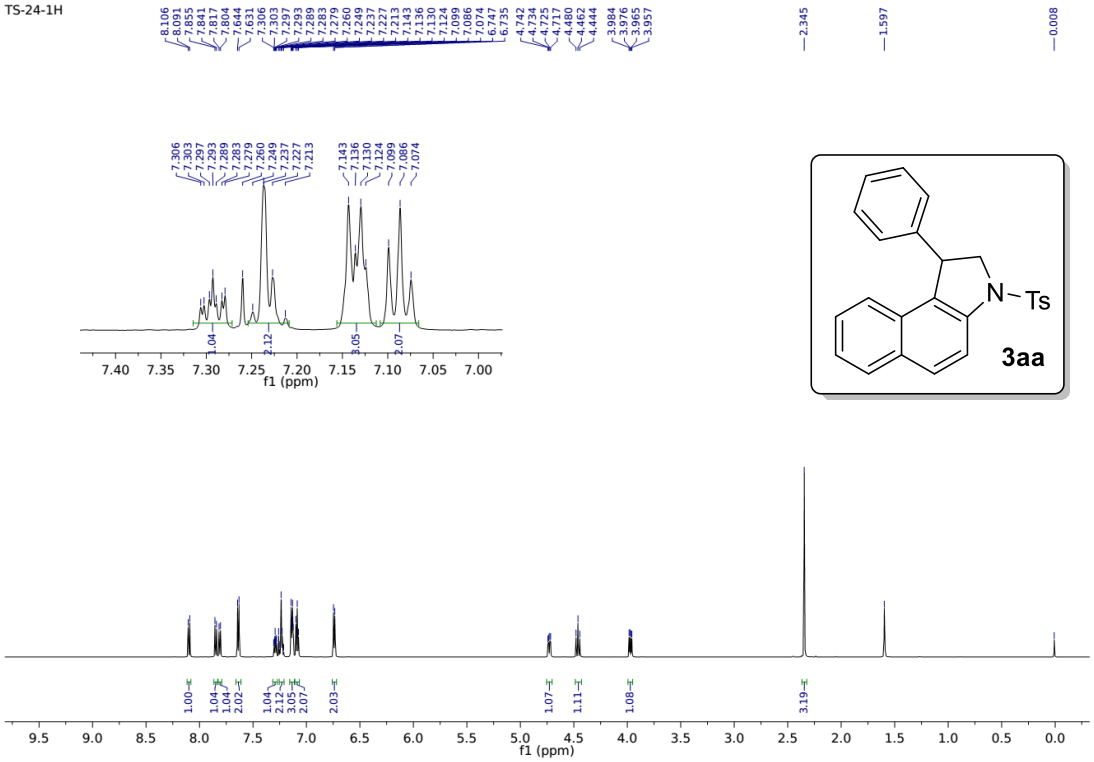
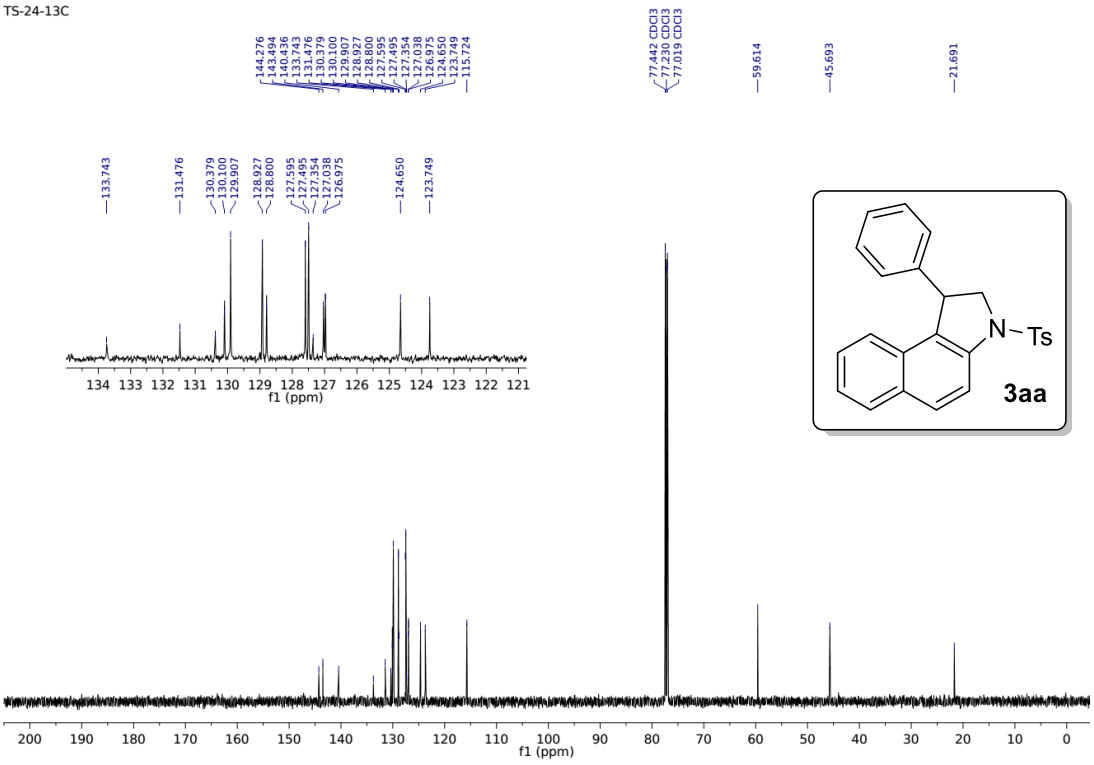
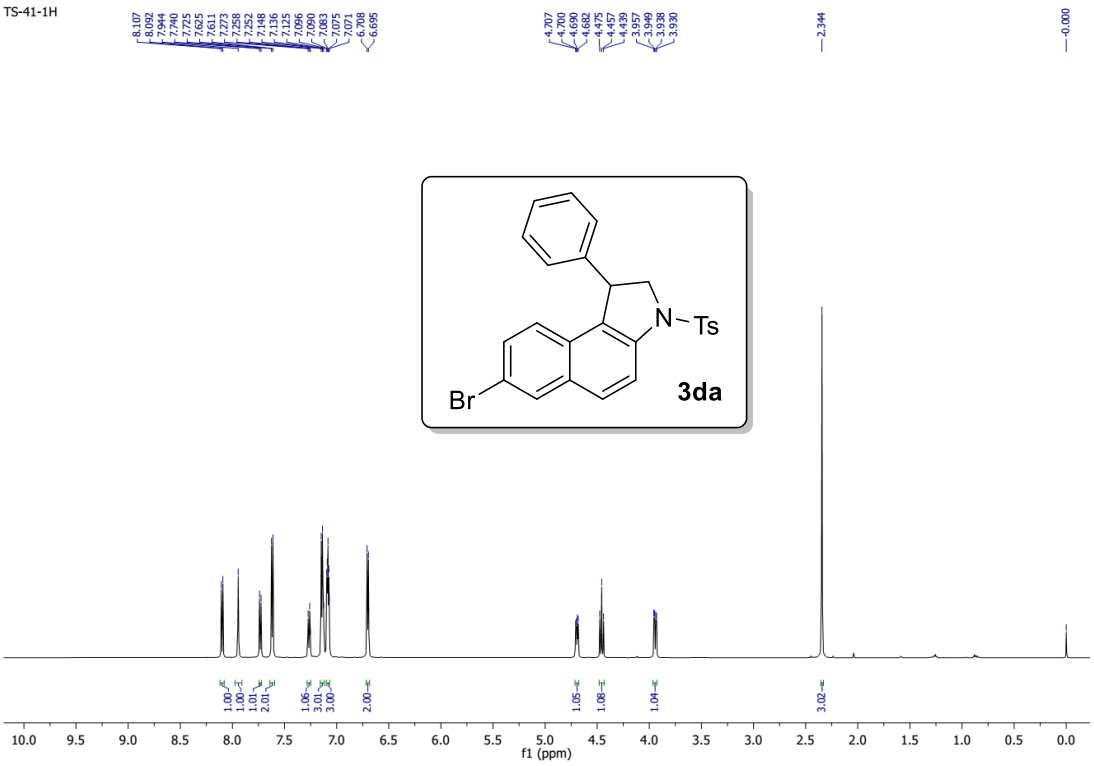
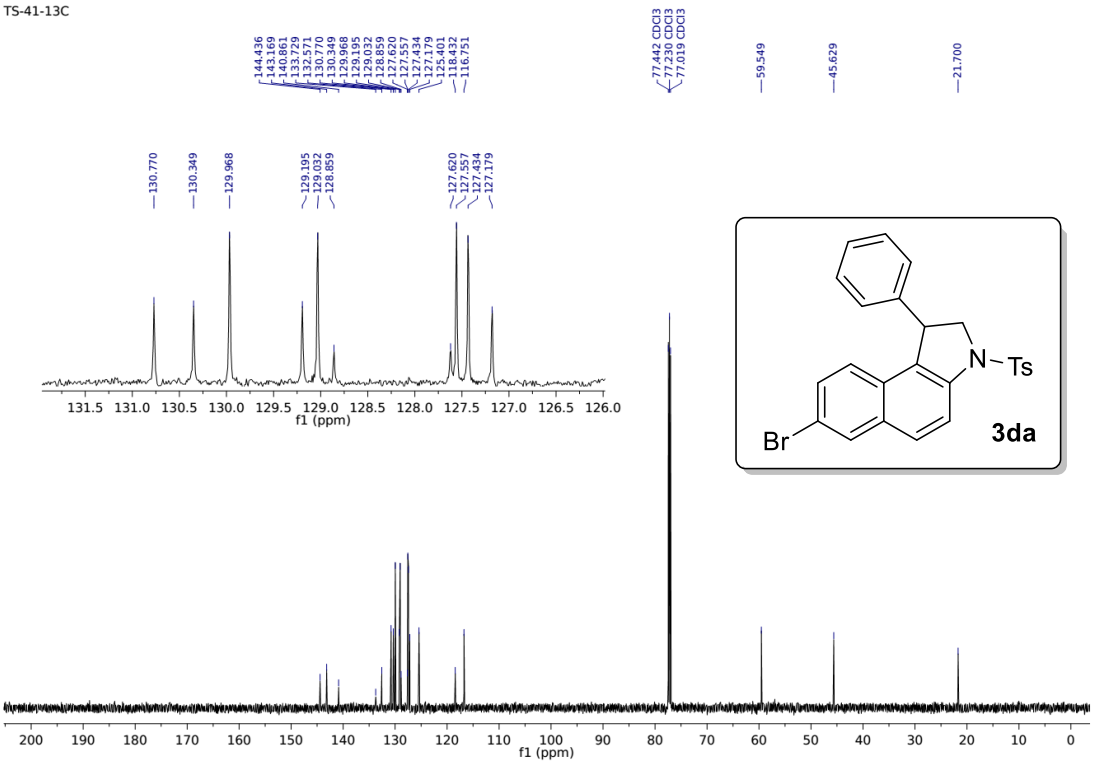
2	14.713	822581	49.04

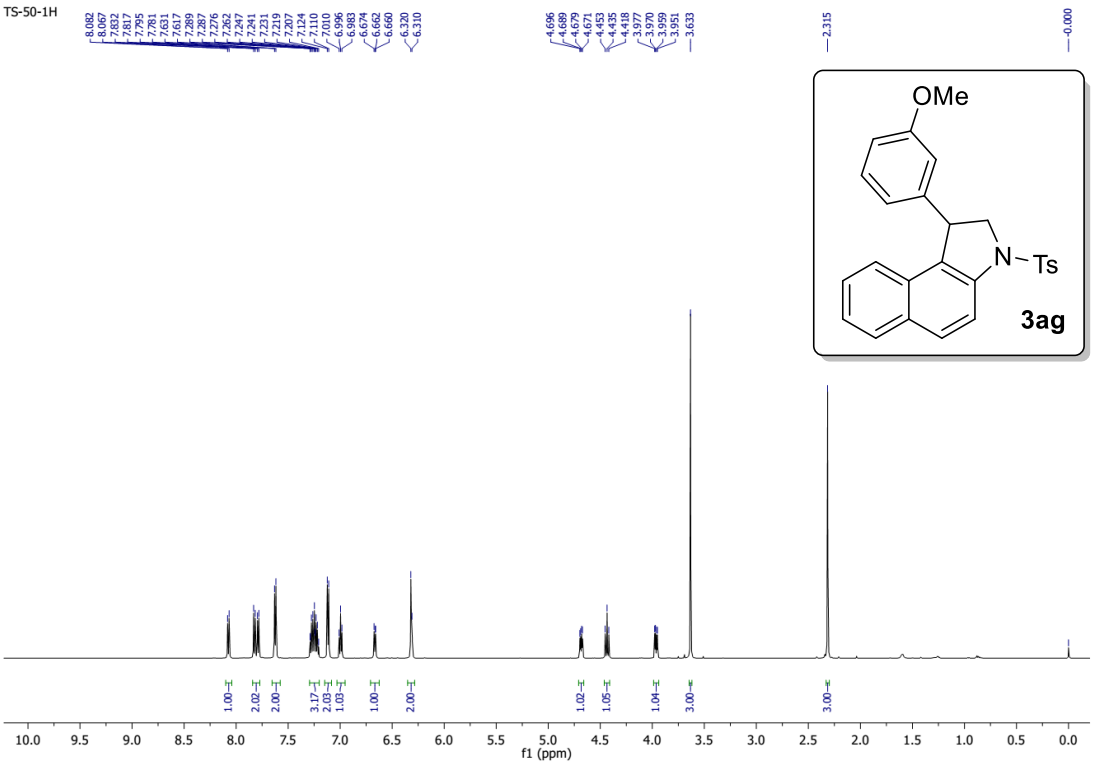
3.7 Selected NMR Spectra

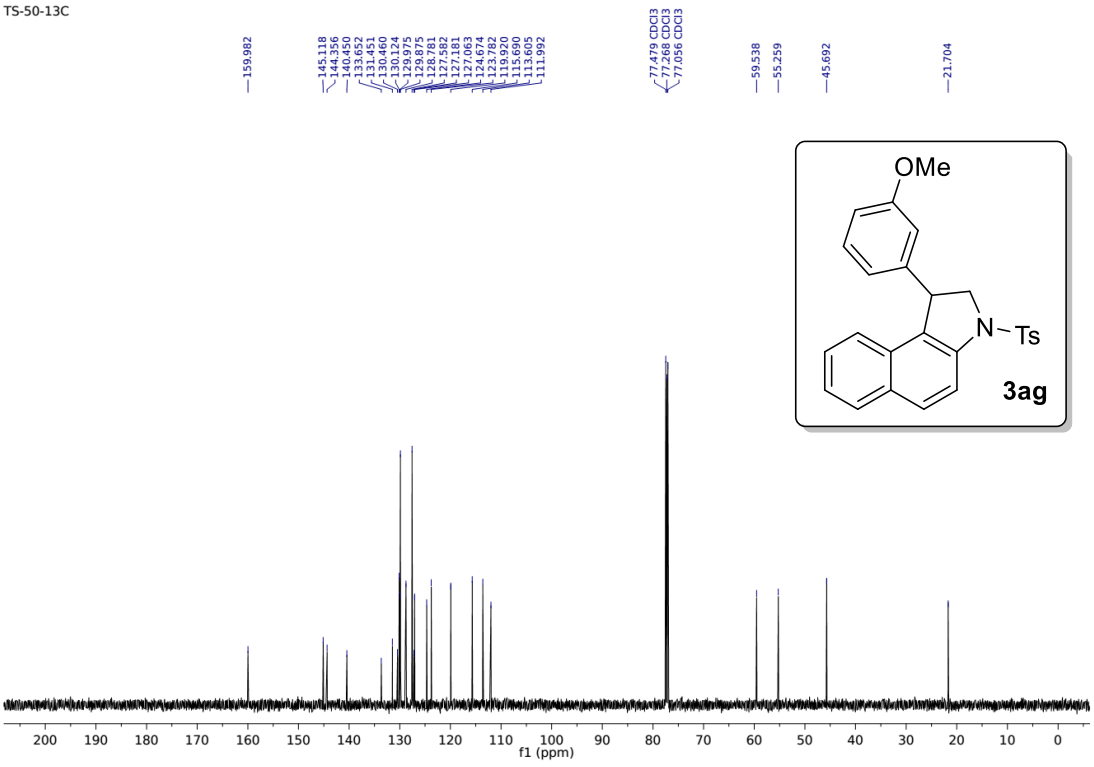






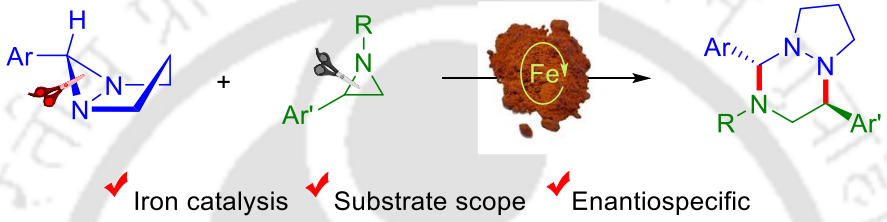






Chapter IV

Fe(III)-Catalyzed (3+3)-Cycloaddition of Aziridines with Diaziridines: Stereospecific Synthesis of Triazines



Fe(III)-Catalyzed (3+3)-Cycloaddition of Aziridines with Diaziridines: Stereospecific Synthesis of Triazines

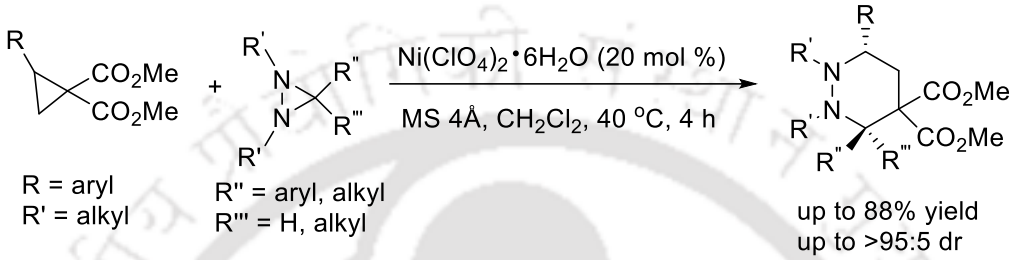
[1,2,4]-Triazines are the previledged aza-heterocyclic compounds that display broad bio-active spectrum in myriads of natural products, pharmaceuticals and functional materials (Figure 1).[1] The development of elegant strategies for their synthesis using simple building blocks would thus be highly desirable. In this direction, (3+n)-cycloaddition using three-membered rings have emerged as a powerful means for the assembly of heterocyclic scaffolds owing to their apparent simplicity and staple architectures.[2] The innate ring strain provides thermodynamic driving force for their facile ring-cleavage in presence of Lewis acids and renders them susceptible to undergo (3+n)-cycloaddition. Contextually, diaziridines with two contiguous nitrogen atoms represent an imperative class of aza-heterocycles that can be cleaved heterolytically in presence of Lewis acid and serve as a versatile 1,3-zwitterionic component in a range of cycloaddition.[3] Consequently, cycloaddition by engaging diaziridines and aziridines can provide a straightforward method to access a library of aza-cyclic scaffolds. Iron catalysts, on the other hand, have stimulated the interest of contemporary cycloaddition due to their low toxicity, renewability and low cost.[4] This chapter describes an Fe(III)-catalyzed (3+3)-annulation of bicyclic diaziridines with aziridines to enable the stereospecific synthesis of [1,2,4]-triazines in high yields. The scope was investigated with a wide variety of substrates having diverse substitution patterns. The key features of this strategy includes the construction of enantioenriched [1,2,4]-triazine derivatives with high optical purities and post-synthetic transformations.

Figure 1. Examples of Biologically Active Triazine derivatives.

4.1 Literature

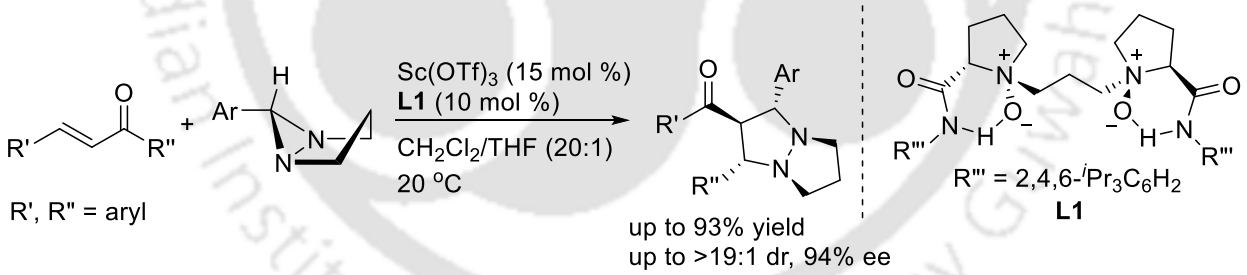
4.1.1 Metal-Catalyzed Reaction with Diaziridines

Trushkov and co-workers reported a concise method for the synthesis of perhydropyridazines in high yields *via* Ni(II)-catalyzed (3+3)-annulation of donor-acceptor (DA) cyclopropanes with diaziridines (Scheme 1).[5] This protocol provides a convenient route to furnish non-symmetrically substituted six-membered rings.



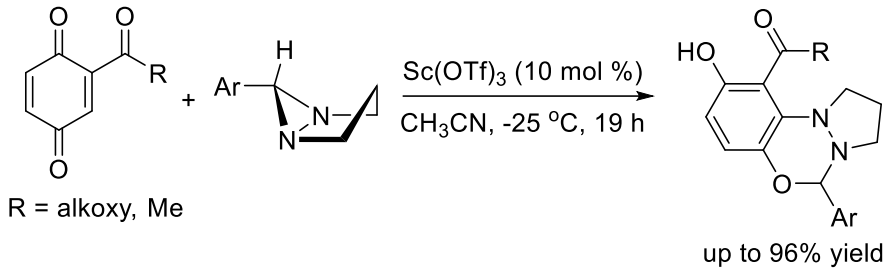
Scheme 1. Ni(II)-Catalyzed (3+3)-Cycloaddition of Diaziridines with DA-Cyclopropanes

Feng and co-workers described the asymmetric *N,N′*-dioxide/scandium(III)-complex catalyzed (3+2)-annulation of diaziridines with chalcones to provide chiral 1,5-diazabicylo[3.3.0]octanes in good yields with excellent enantio- and diastereoselectivities (Scheme 2).[6] The stereoselectivity was governed by the preferential 1,3-diploar cycloaddition on the Re-face of chalcone.



Scheme 2. Sc(III)-Catalyzed Enantioselective Annulation of Diaziridines with Chalcones

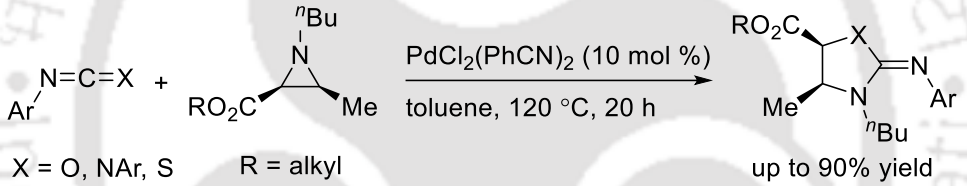
An efficient Sc(III)-catalyzed (3+3)-annulation for the construction of benzo[e][1,3,4]oxadiazine derivatives was presented by Luo and co-workers (Scheme 3).[7] The authors employed diaziridines and quinones as the starting materials. The synergistic role of $Sc(OTf)_3$ was found to be crucial for the activation of diaziridines and quinones.



Scheme 3. Sc(III)-Catalyzed (3+3)-Cycloaddition of Diaziridines with Quinones

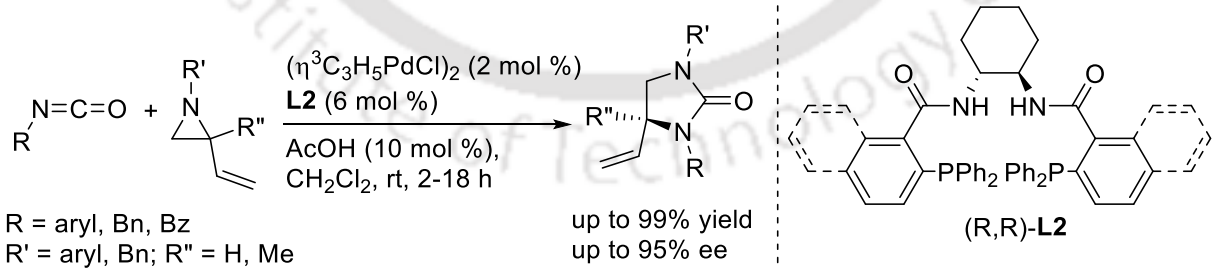
4.1.2 Cycloaddition Reactions of Unactivated Aziridines

Alper and co-workers described a Pd(II)-catalyzed (3+2)-cycloaddition of aziridines with heterocumulenes such as isocyanates, isothiocyanates and carbodiimides to enable the enantioselective synthesis of five-membered azacyclic derivatives (Scheme 4).[8] Further, the authors employed optically pure 1,2-disubstituted aziridines to afford the heterocycles with retention of configuration.



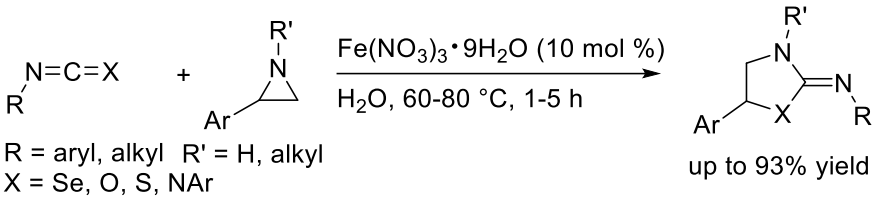
Scheme 4. Pd(II)-Catalyzed Cycloaddition of Aziridines and Heterocumulenes.

Trost and co-workers documented the asymmetric (3+2)-annulation of 2-vinylaziridines with isocyanates in presence of $(\eta^3\text{-}C_3H_5PdCl)_2$ and chiral ligand **L2** (Scheme 5).[9] This method furnished a wide range of imidazolidin-2-ones in high yields and enantioselectivities.



Scheme 5. Pd(II)-Catalyzed (3+2)-Cycloaddition of Vinylaziridines with Isocyanates

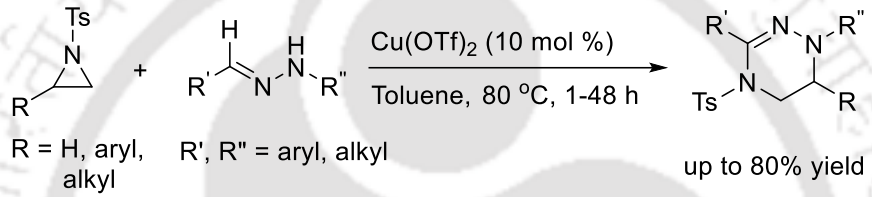
Our group reported a Fe(III)-catalyzed cycloaddition of aziridines with isoselenocyanates isocyanates, isothiocyanates and carbodiimides under aqueous condition at moderate temperature. (Scheme 6).[10] Various *N*-alkyl aziridines were well tolerated.



Scheme 6. Fe(III)-Catalyzed (3+3)-Cycloaddition of Aziridines with Heterocumulenes

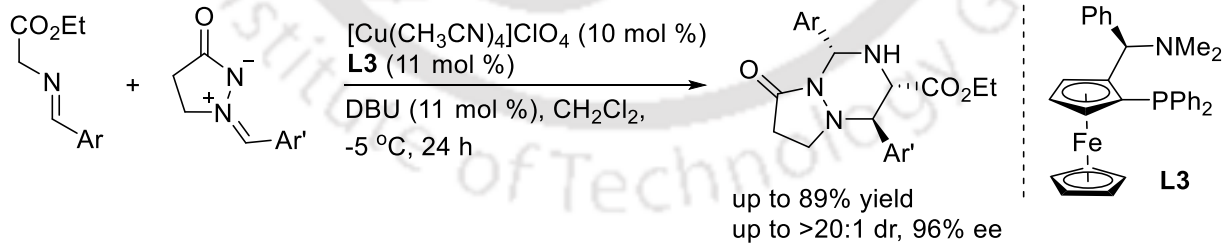
4.1.3 Metal-Catalyzed Synthesis of Triazines

Wang and co-workers demonstrated the synthesis of tetrahydrotriazines *via* Cu(II)-catalyzed nucleophilic ring-opening of *N*-tosylaziridines with hydrazones followed by oxidative amidation (Scheme 7).[11] This procedure utilizes oxygen as an oxidant.



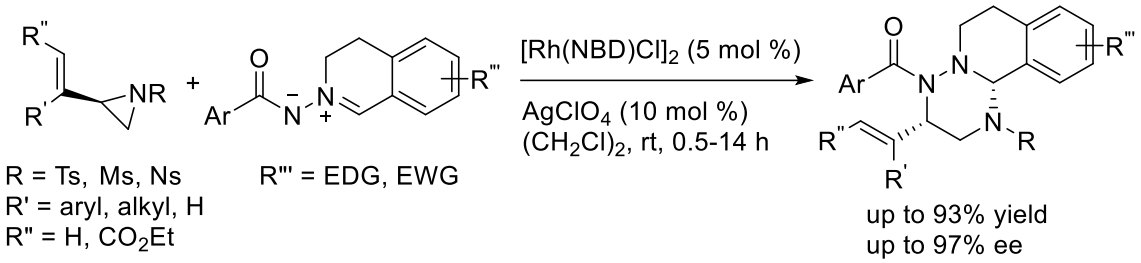
Scheme 7. Cu(II)-Catalyzed Ring Opening/Cyclization of Aziridines with Hydrazones

Guo and co-workers reported an asymmetric (3+3)-annulation of azomethine imines and azomethine ylides in the presence of copper complex and chiral ferrocenyl ligand for the enantioselective synthesis of 8-oxohexahydro-6H-pyrazolo[1,2-a][1,2,4]triazine-3-carboxylates with high diastereoselectivity (Scheme 8).[12] This methodology tolerated functional groups and the resulting cycloadduct could be epimerized under acidic condition.



Scheme 8. Cu(I)-Catalyzed (3+3)-Cycloaddition of Azomethine Ylides with Azomethine Imines

Zhang and co-workers disclosed a (3+3)-cycloaddition of vinylaziridines with azomethine imines for the construction of enantioenriched 1,2,4-hexahydrotriazines in good yields under Rh(I)-catalysis (Scheme 9).[13] The enantiospecificity of the cycloadduct was achieved via efficient chirality transfer utilizing optically pure vinylaziridines.



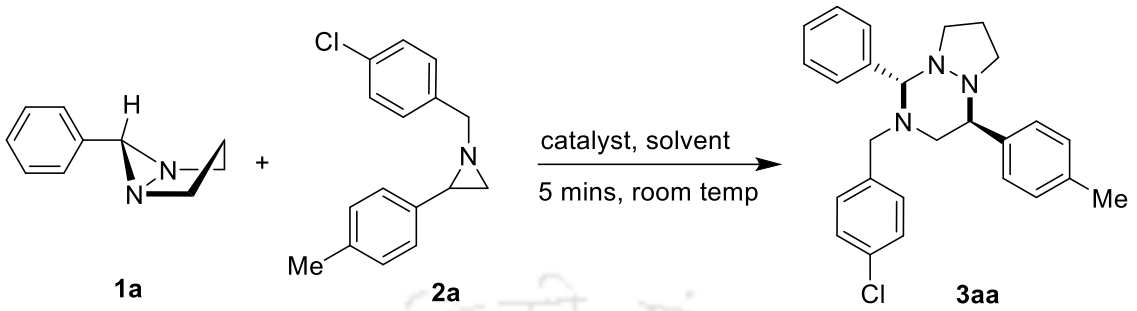
Scheme 9. Rh(I)-Catalyzed (3+3)-Cycloaddition of vinylaziridines with Azomethine Imines

4.2 Present Study

Herein we described the stereospecific synthesis of [1,2,4]-triazines *via* the Fe(III)-catalyzed (3+3)-annulation of *N*-alkyl aziridines with bicyclic diaziridines. The present methodology offers an imperative route for the annulation of two distinct strained ring heterocycles to afford a new class of heterocycles. At the outset, we carried out our investigation by employing diaziridine **1a** and 1-(4-chlorobenzyl)-2-(*p*-tolyl)aziridine **2a** as the model substrates utilizing a set of iron catalysts and solvents (Table 1). Delightfully, **3aa** was formed in 95% yield when **1a** and **2a** were stirred in dichloromethane at room temperature for 5 minutes using 10 mol % $FeCl_3$ (entry 1). In a series of iron salts surveyed, $FeCl_3$ was superior to $FeCl_3 \cdot 6H_2O$, $FeCl_2 \cdot 4H_2O$, $Fe(NO_3)_3 \cdot 9H_2O$ and $Fe(acac)_3$ (entries 2-5). Among the solvent studied, CH_2Cl_2, $(CH_2Cl)_2$, MeOH, DMSO, THF, toluene and H_2O, the former afforded the best result (entries 6-11). A control experiment suggested the crucial role of $FeCl_3$ in delivering the intended heterocycle (entry 12). In addition, 1-benzyl-1,2-diazaspiro[2.5]octane **1b**, 1-benzyl-3-phenyl-diaziridine **1c**, 2-phenylaziridine **2b,** *N*-tosylaziridine **2b′** and donor-acceptor aziridine **2c** were reluctant under these conditions.

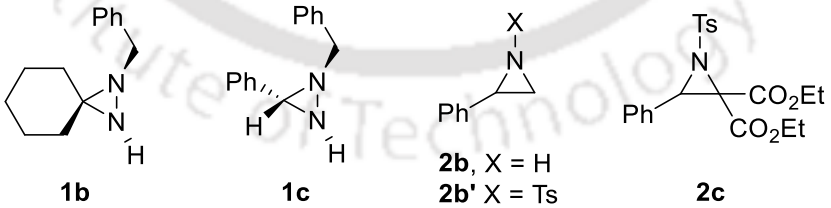
Having optimized the reaction conditions, the scope of the methodology was investigated using a series of diaziridines **1d-s** with 1-(4-chlorobenzyl)-2-(*p*-tolyl)aziridine **2a** as a standard substrate (Table 2). The reaction of diaziridines bearing substituents at the 3-position with nitro **1d** and trifluoromethyl **1e** groups afforded the target products **3da** and **3ea** in 83 and 85% yields, respectively. Similar results were observed with diaziridines having substitution at the 4-position of the aryl ring with electron-rich and electron-deficient substituents such as bromo **1f**, cyano **1g**, methoxycarbonyl **1h**, methoxy **1i**, nitro **1j** and phenyl **1k** groups, delivering **3fa-ka** in 77-94% yields. In addition, heteroaryl diaziridines **1l** and **1m** participated efficiently to furnish **3la** and **3ma** in 91 and 93% yields, respectively. Moreover, polycyclic-aromatic diaziridines such as 2-

Table 1. Optimization of the Reaction Conditions[a]



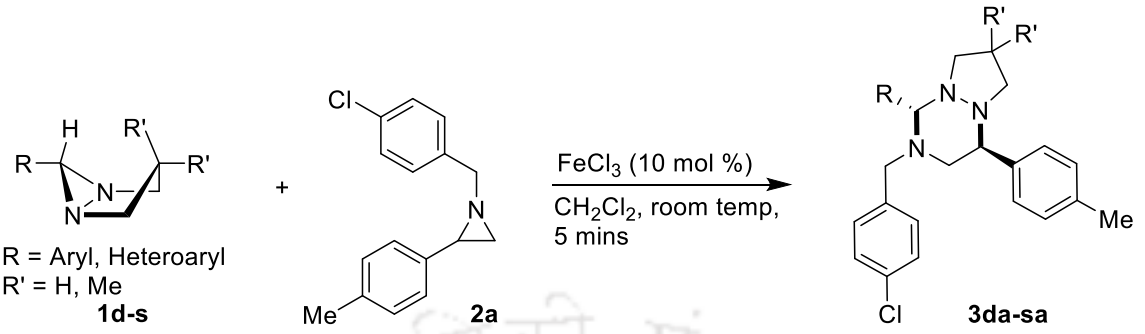
Entry	Catalyst (10 mol %)	Solvent	Yield (%)[b]
1	**$FeCl_3$**	**CH_2Cl_2**	**95**
2	$FeCl_3·6H_2O$	CH_2Cl_2	79
3	$Fe(NO_3)_3·9H_2O$	CH_2Cl_2	32
4	$FeCl_2·4H_2O$	CH_2Cl_2	n.r.
5	$Fe(acac)_3$	CH_2Cl_2	n.r.
6	$FeCl_3$	$(CH_2Cl)_2$	86
7	$FeCl_3$	MeOH	54
8	$FeCl_3$	DMSO	n.r.
9	$FeCl_3$	THF	72
10	$FeCl_3$	Toluene	81
11	$FeCl_3$	H_2O	n.r.
12	-	CH_2Cl_2	n.r.

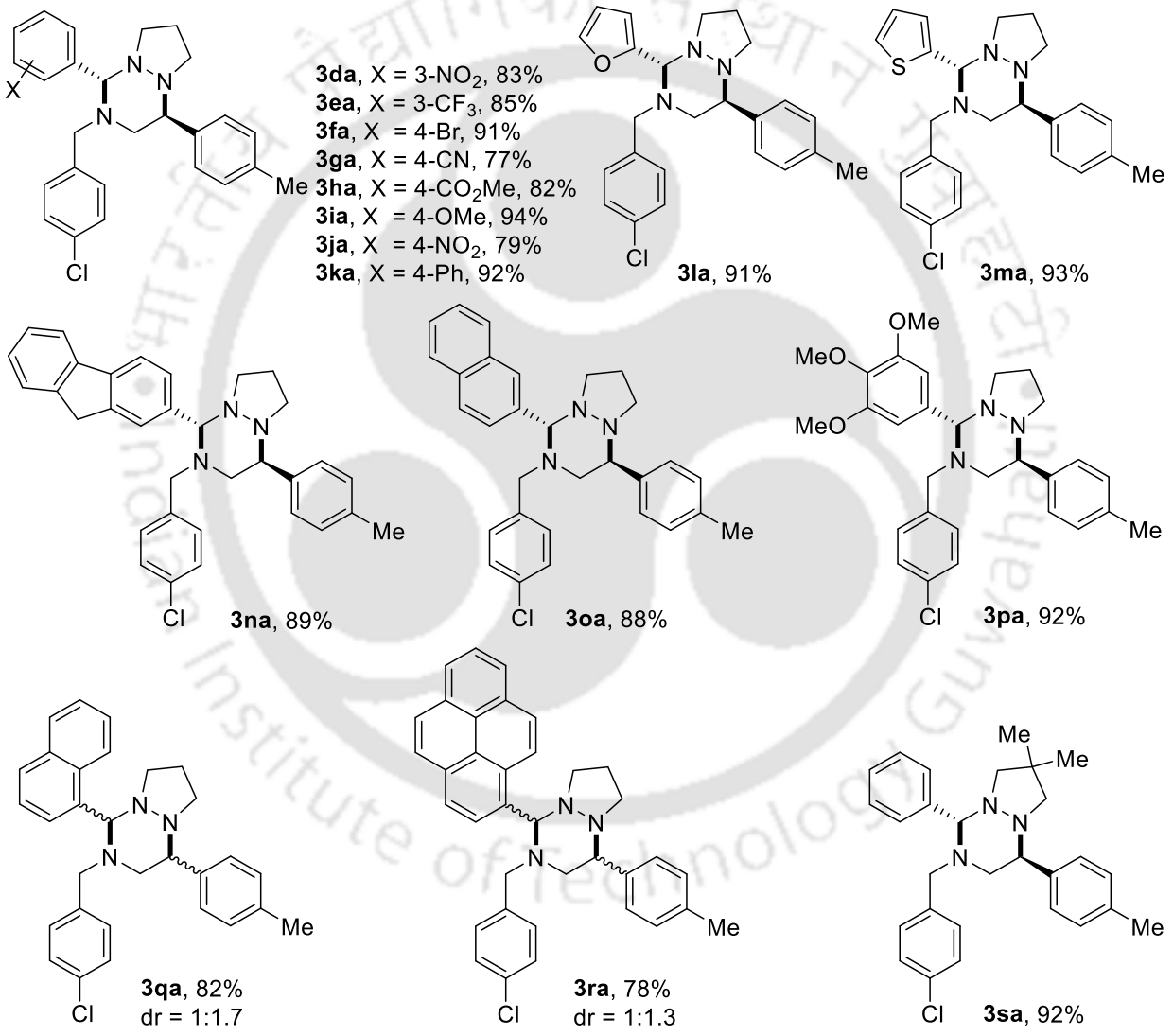
unsuccessful substrates



[a]Reaction conditions: **1a** (0.2 mmol), **2a** (0.2 mmol), catalyst (10 mol %), solvent (2 mL), 5 minutes, room temperature. [b]Isolated yield. n.r. = no reaction.

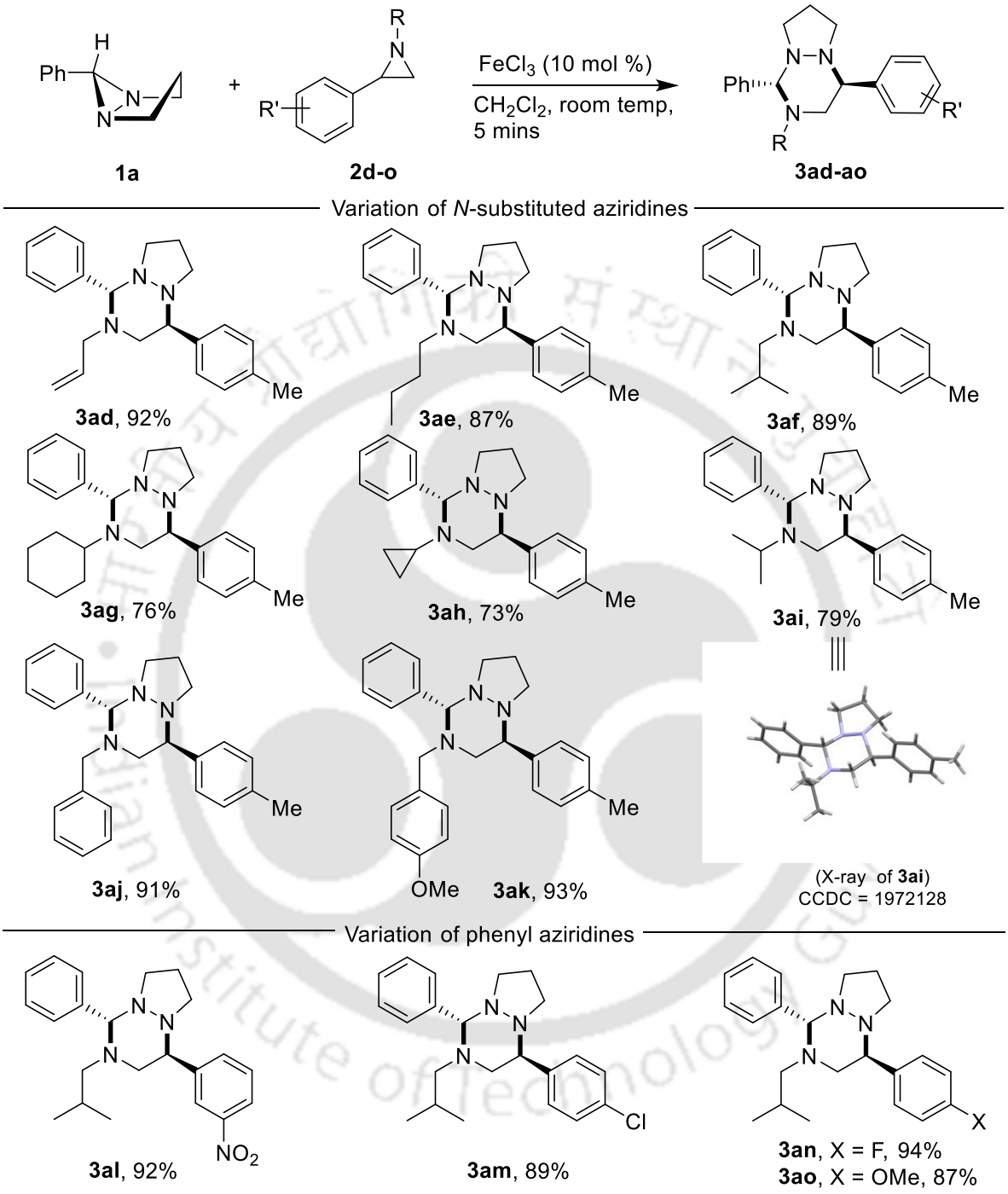
Table 2. Substrate scope of Diaziridines[a,b]





[a]Reaction conditions: **1d-s** (0.2 mmol), **2a** (0.2 mmol), $FeCl_3$ (10 mol %), CH_2Cl_2 (2 mL), 5 minutes, room temp. [b]Isolated yield.

Table 3. Substrate Scope of *N*-Substituted Aziridines[a,b]



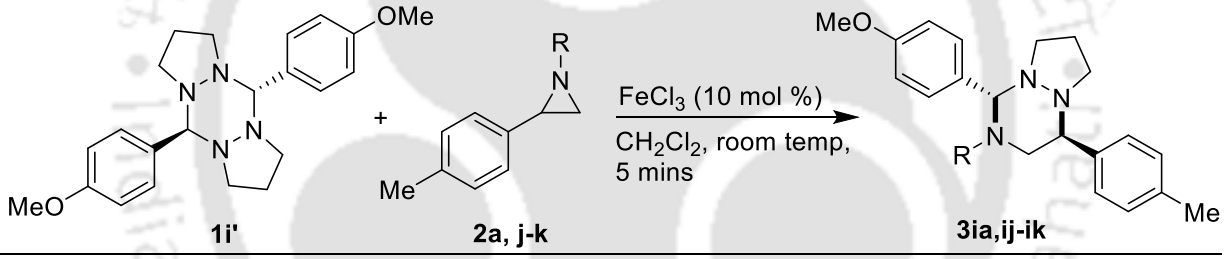
[a]Reaction conditions: **1a** (0.2 mmol), **2d-o** (0.2 mmol), $FeCl_3$ (10 mol %), CH_2Cl_2 (2 mL), 5 minutes, room temp. [b]Isolated yield.

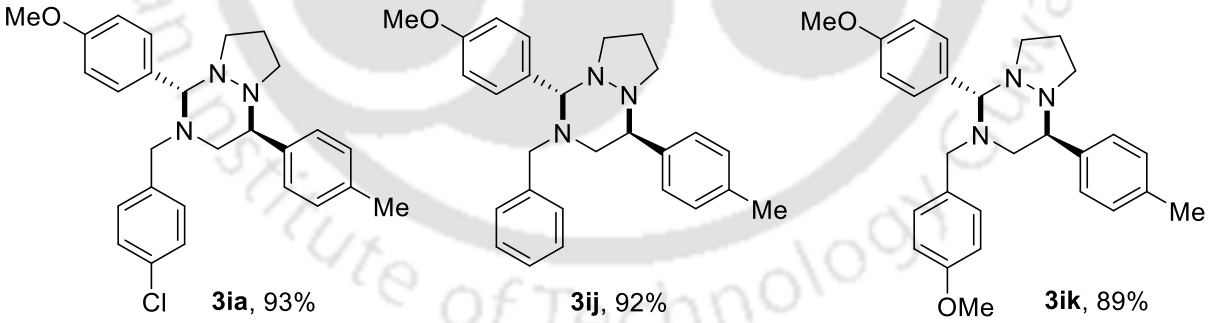
fluorene **1n**, 2-naphthyl **1o** and trimethoxyphenyl diaziridine **1p** successfully delivered **3na-pa** in 88-92% yields. Notably, 1-naphthyl **1q** and 1-pyrene **1r** substituted diaziridines produced **3qa** and

3ra as a mixture of isomers. Further, 3,3-disubstituted diaziridine **1s** selectively furnished **3sa** in 92% yield. These findings confide that diaziridines with various substitution sequences can be reacted.

The scope of the protocol was extended for the annulation of a series of *N*-substituted aziridines **2d-o** with 6-phenyl-1,5-diazabicyclo-[3.1.0]hexane **1a** as the standard substrate (Table 3). The reaction of substrates having allyl **2d**, *n*-butyl **2e**, isobutyl **2f**, cyclohexyl **2g**, cyclopropyl **2h** and isopropyl **2i** substituents on nitrogen underwent efficiently to convey **3ad-ai** in 73-92% yields. The single-crystal X-ray analysis of **3ai** revealed the stereochemistry of the cycloadduct (CCDC = 1972128). Similarly, aziridines bearing benzyl **2j** and 4-methoxybenzyl **2k** groups readily afforded the desired **3aj** and **3ak** in 91% and 93% yields, respectively. Further, the reaction of *N*-isobutyl aziridines with substitution on the aryl ring with 3-nitro **2l**, 4-chloro **2m**, 4-fluoro **2n** and 4-methoxy **2o** groups proceeded smoothly to produce **3al-ao** in 87-94% yields.

Table 4. Scope of Cyclodimers [a,b]



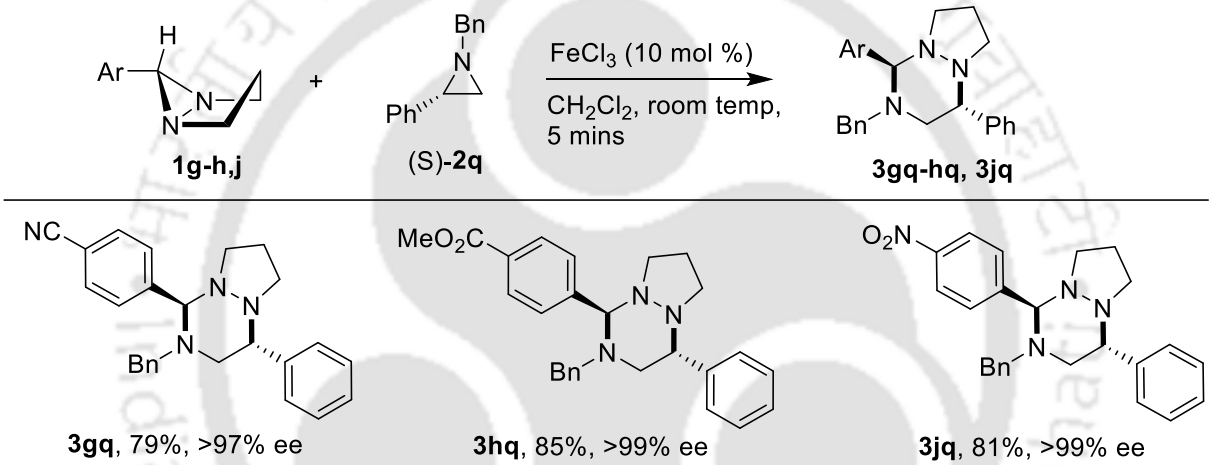


[a]Reaction conditions: **1i′** (0.1 mmol), **2a,j-k** (0.2 mmol), $FeCl_3$ (10 mol %), CH_2Cl_2 (2 mL), 5 minutes, room temp. [b]Isolated yield.

To showcase the practicality of the method, the annulation of the cyclodimer of 6-(4-methoxyphenyl)-1,5-diazabicyclo-[3.1.0]hexane **1i′** with *N*-alkyl aziridines **2a** and **2j-k** were performed (Table 4). Aziridines with 4-chloro **2a**, 4-hydrogen **2j** and 4-methoxy **2k** groups at the

N-benzyl ring were well compatible and delivered **3ia-ik** as a single diastereoisomer in 89-93% yields. The structure of **3ik** was determined using single-crystal X-ray analysis (CCDC = 1972182). The formation of the identical azomethine imine **A** from the cyclodimer **1i′** was principally responsible for the observed diasteroselectivity.[3,5] In order to divulge the stereoselectivity, the reaction of optically active aziridine (*S*)-**2q** was examined with a set of diaziridines (Table 5). Diaziridines bearing 4-cyano **1g**, 4-methoxycarbonyl **1h** and 4-nitro **1j** groups coupled efficiently to afford **3gq**, **3hq** and **3jq** in >97% *ee*. These results suggest the potential of the method for enantiospecific synthesis of [1,2,4]-triazines with high optical purities.

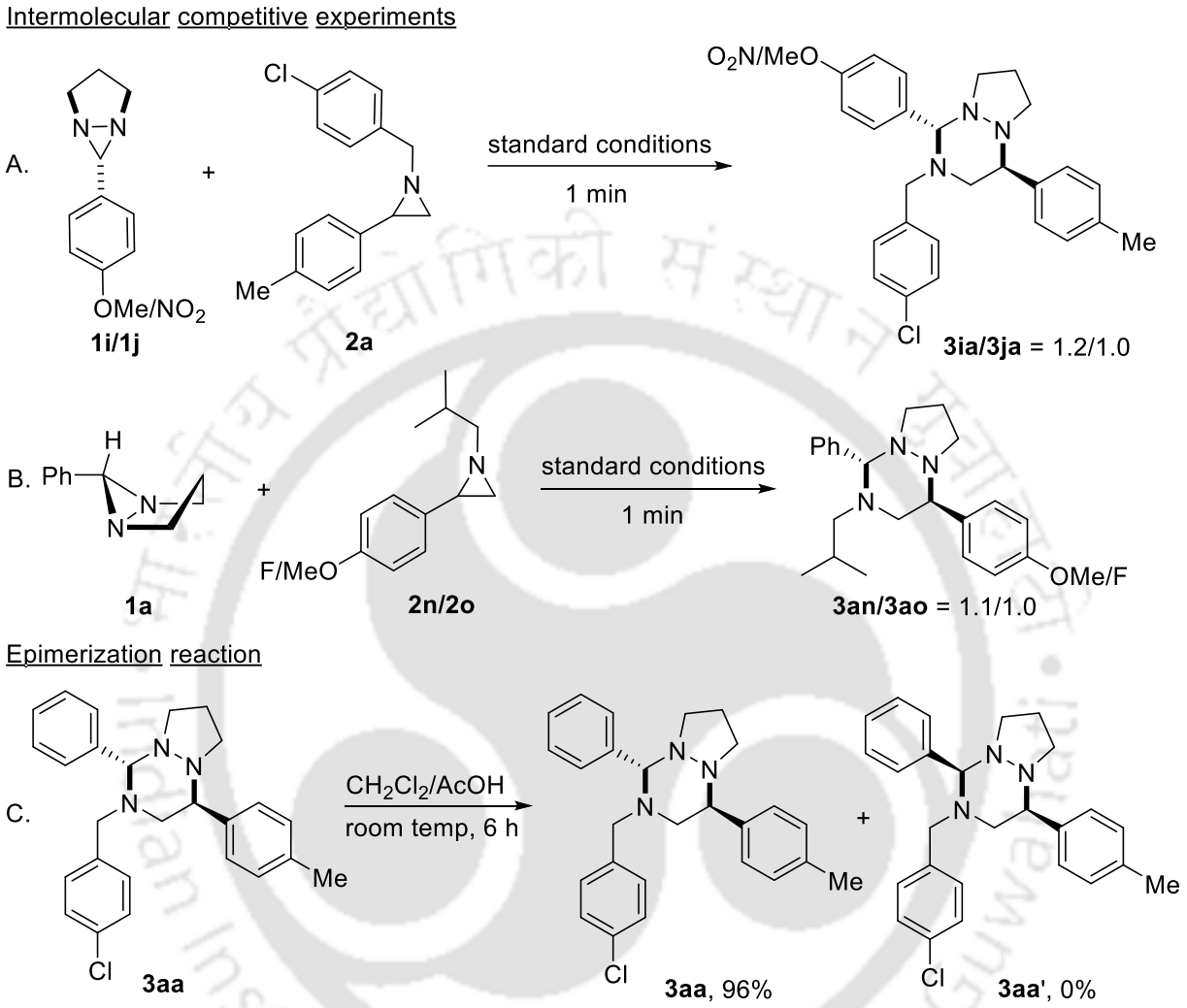
Table 5. Reaction of Substituted Diaziridines with Chiral Aziridine[a,b]



[a]Reaction conditions: **1g-h** and **1j** (0.2 mmol), (*S*)-**2q** (0.2 mmol), $FeCl_3$ (10 mol %), CH_2Cl_2 (2 mL), 5 minutes, room temp. [b]Isolated yield.

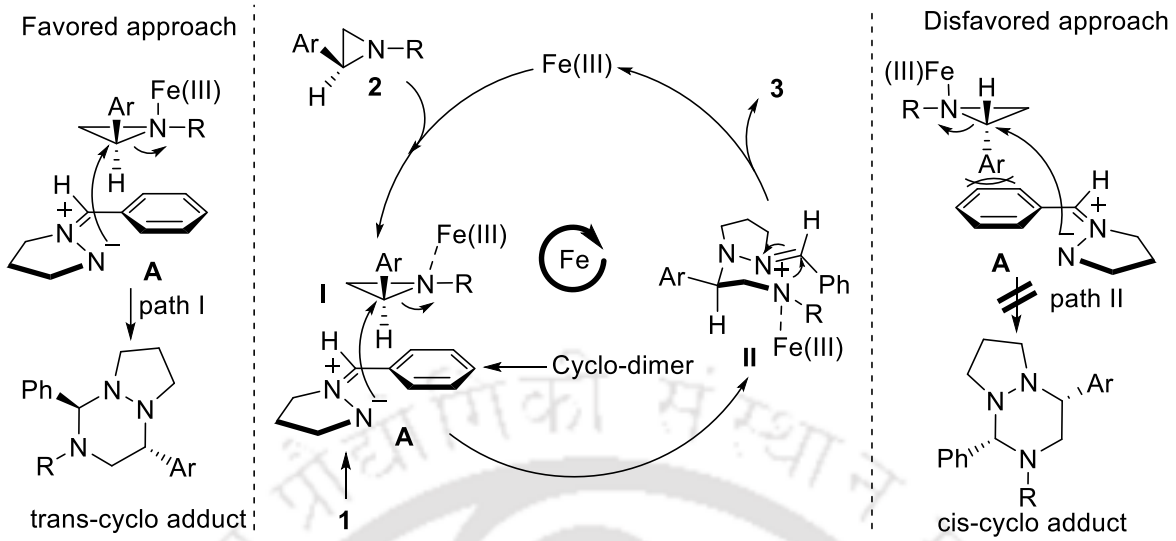
To shed light into the mechanism, control experiments were accomplished (Scheme 10). Diaziridine with an electron donating 4-methoxy **1i** group showed superior reactivity than its electron withdrawing 4-nitro **1j** counterpart (Scheme 10A). Likewise, aziridine bearing an electron-withdrawing 4-fluoro **2o** group exhibited higher reactivity (Scheme 10B). In addition, no epimerized product was realised in the presence of AcOH (Scheme 10C).[14] Thus, chelation of the aziridine with $FeCl_3$ may lead to the formation of **I** that can undergo stereospecific ring opening using azomethine imine **A** to afford **II** (Scheme 11).[5,10] Intramolecular cyclization may deliver the desired heterocycles with regeneration of the catalyst. The diasteroselectivity of the cycloadduct is presumably due to the arising steric factors during the approaches of aziridine with the

azomethine imine **A.** The sterically preferred pathway (*path I*) favoured the formation of the *trans*-cycloadduct while steric encumbrance forbid the *cis*-selectivity (*path II*).[5,15]

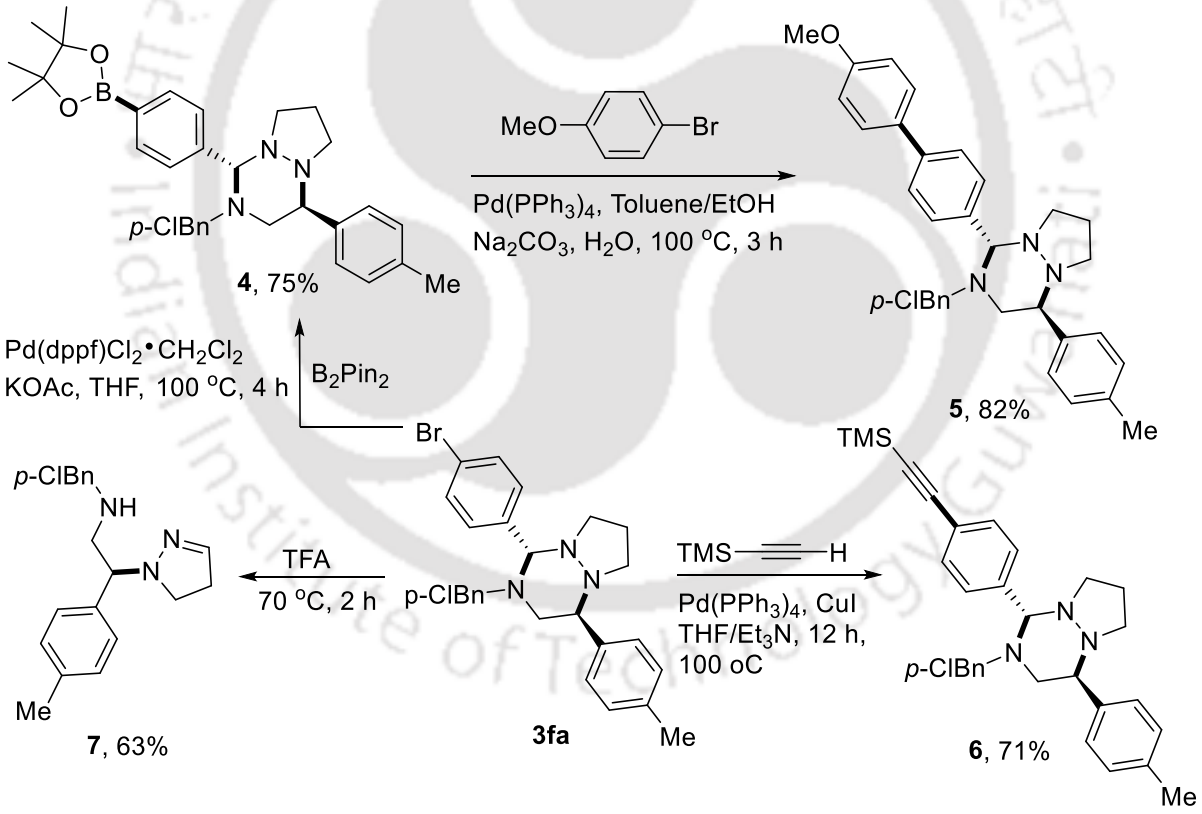


Scheme 10. Control experiments

To demonstrate the synthetic utilities, the bromo-containing **3fa** was converted to a borylated **4** in 75% yield (Scheme 12). Further, Pd-catalyzed Suzuki coupling of **4** was performed to construct **5** in 82% yield. Gratifyingly, a similar result was observed when the reaction of **3fa** was carried out with trimethylsilylacetylene, delivering **6** in 71% yield. Notably, the benzyl group between two nitrogen centres was removed selectively by the acid mediated debenzylation reaction using trifluoroacetic acid, affording the dihydro-pyrazole **7** in 63% yield.



Scheme 11. Plausible Reaction Mechanism



Scheme 12. Post-Synthetic Applications

In summary, we have documented an Fe(III)-catalyzed (3+3)-cycloaddition of diaziridines with unactivated azirdines to enable the synthesis of functionalized [1,2,4]-triazines in high yields. The

broad substrate scope, use of earth-abundant iron salt as catalyst and post synthetic utilities are the important practical features.

4.3 Experimental Section

General Information. Alkenes, amines, (*S*)-(+)-2-phenylglycinol (99%), $FeCl_3 \cdot 6H_2O$ (>98%), $FeCl_2 \cdot 4H_2O$ (98%), $Fe(acac)_3$ (97%), $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (>99%) and $Pd(PPh_3)_4$ (99%) were purchased from Aldrich and used as received. $Fe(NO_3)_3 \cdot 9H_2O$ (98%) was purchased from Merck and $FeCl_3$ (96%) was purchased from Rankem. Diaziridines[3,5,16] and aziridines[17] were prepared according to reported procedure. SRL silica gel G/GF 254 plates were used for analytical TLC and SRL silica gel (100-200 mesh) was used for column chromatography. NMR (^1H, ^{13}C and ^{19}F) spectra were recorded with Bruker Ascend 400 MHz spectrometer using $CDCl_3$ as solvent and Me_4Si 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. Melting points were determined using a Büchi B-540 apparatus and are uncorrected. FT-IR spectra were collected on Perkin Elmer IR spectrometer. Q-Tof ESI-MS instrument (model HAB 273) was used for recording mass spectra. Optical rotation was determined by using Rudolph autopol I automatic polarimeter. HPLC analysis was carried out using Waters-2489 with Daicel Chiralcel AD column using *iso*-propanol and hexane as eluent. Single crystal X-ray data of **3ai** was determined using Bruker SMART APEX-II CCD diffractometer, which is equipped with 1.75 kW sealed-tube Mo-Kα irradiation and the crystal structure was solved by direct method using SHELXL-14 (Göttingen, Germany) and refined with full-matrix least squares on F^2 using SHELXL-14, while single crystal X-ray data of **3ik** was collected on a Bruker SMART APEX equipped with a CCD area detector using Mo/Kα radiation and the structure was solved by direct method using SHELXL-16 (Göttingen, Germany).

Procedure for the Synthesis of [1,2,4]-Triazines. Diaziridine **1** (0.2 mmol), *N*-substituted aziridine **2** (0.2 mmol) and $FeCl_3$ (3 mg, 0.02 mmol) were stirred in dichloromethane (2.0 mL) at room temperature (25 ^oC) for 5 minutes. The reaction mixture was then diluted using dichloromethane (5 mL) and passed through a short pad of celite using dichloromethane (10 mL). Evaporation of the solvent gave a residue that was purified on silica gel column chromatography using ethyl acetate and hexane as an eluent to afford [1,2,4]-triazine motifs.

Procedure for the Synthesis of [1,2,4]-Triazines from Cyclodimer 1i′. A mixture of cyclo-dimer **1i′** (0.1 mmol), *N*-alkyl aziridine **2** (0.2 mmol) and $FeCl_3$ (3 mg, 0.02 mmol) was stirred in dichloromethane (2.0 mL) at room temperature (25 ^oC) for 5 minutes. The purification was carried as above described in general procedure.

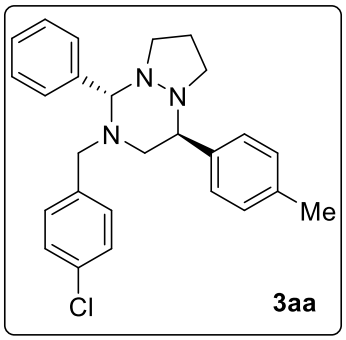
Procedure for the Enantiospecific Synthesis of [1,2,4]-Triazines. A mixture of diaziridine **1** (0.2 mmol), (*S*)-1-benzyl-2-phenylaziridine **2q** (0.2 mmol) and $FeCl_3$ (3 mg, 0.02 mmol) was stirred in dichloromethane (2.0 mL) at room temperature (25 ^oC) for 5 minutes. The purification was performed as above presented in general procedure. The enantiomeric excess was determined using chiral HPLC.

Intermolecular Competitive Experiment Using 1i and 1j. 1-(4-Chlorobenzyl)-2-(*p*-tolyl)aziridine **2a** (52 mg, 0.2 mmol), **1i** (38 mg, 0.2 mmol), **1j** (42 mg, 0.2 mmol) and $FeCl_3$ (3 mg, 0.02 mmol) were stirred in dichloromethane (2.0 mL) at room temperature (25 ^oC) for 1 minute. Next, the reaction mixture was diluted with dichloromethane (5 mL) and passed through a short pad of celite using dichloromethane (10 mL) as solvent. Evaporation of the solvent gave a residue that was purified on silica gel column chromatography using ethyl acetate and hexane as eluent to give **3ia** and **3ja** in 50 and 42% yields, respectively.

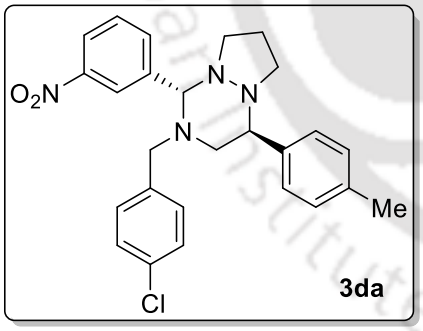
Intermolecular Competitive Experiment Using 2n and 2o. 6-Phenyl-1,5-diazabicyclo[3.1.0]-hexane **1a** (32 mg, 0.2 mmol), **2n** (38 mg, 0.2 mmol), **2o** (42 mg, 0.2 mmol) and $FeCl_3$ (3 mg, 0.02 mmol) were stirred in dichloromethane (2.0 mL) at room temperature (25 ^oC) for 1 minute. Next, the reaction mixture was diluted with dichloromethane (5 mL) and passed through a short pad of celite using dichloromethane (10 mL) as solvent. Evaporation of the solvent gave a residue that was purified on silica gel column chromatography using ethyl acetate and hexane as eluent to give **3an** and **3ao** in 47 and 42% yields, respectively.

Epimerization Reaction of 3aa.[18] Acetic acid (6 μL, 0.1 mmol) was added to a stirring solution of **3aa** (42 mg, 0.1 mmol) in dichloromethane (2 mL) and the reaction mixture was stirred at room temperature (25 ^oC) for 6 h. Next, the reaction mixture was quenched by using saturated aq. $NaHCO_3$ solution (10 mL) and extracted with CH_2Cl_2 (3×10 mL). Drying (Na_2SO_4) and evaporation of the solvent gave a residue that was purified on silica gel column chromatography using ethyl acetate and hexane as an eluent to give **3aa** as a sole product in 96% yield (40 mg).

4.4 Characterization Data

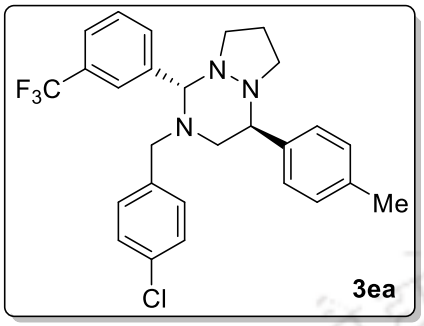


2-(4-Chlorobenzyl)-1-phenyl-4-(*p*-tolyl)hexahydro-6H-pyrazolo[1,2-a][1,2,4]triazine 3aa. Analytical TLC on silica gel, 1:24 ethyl acetate/hexane R_f = 0.52; colorless solid; mp 138-139 °C; yield 95% (79 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55-7.53 (m, 2H), 7.32-7.24 (m, 3H), 7.19-7.17 (m, 2H), 7.10-7.05 (m, 4H), 7.03 (d, *J* = 7.6 Hz, 2H), 3.72 (s, 1H), 3.55-3.51 (m, 2H), 2.83-2.77 (m, 3H), 2.44-2.38 (m, 1H), 2.37-2.32 (m, 1H), 2.30-2.23 (m, 5H), 1.71-1.63 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.4, 137.59, 137.54, 137.1, 132.4, 130.0, 129.19, 129.15, 128.9, 128.6, 128.3, 127.9, 89.7, 68.0, 59.1, 56.6, 51.9, 50.8, 22.0, 21.2; FT-IR (KBr) 2824, 2768, 1514, 1451, 1355, 1127, 1017 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{26}H_{29}ClN_3$: 418.2045, found: 418.2044.

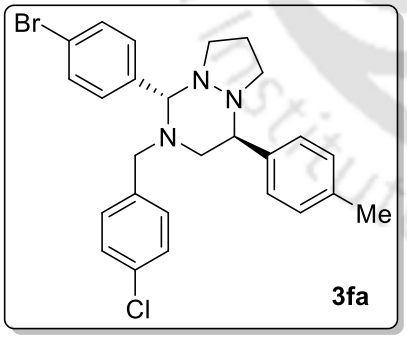


2-(4-Chlorobenzyl)-1-(3-nitrophenyl)-4-(*p*-tolyl)hexahydro-6H-pyrazolo[1,2-a][1,2,4]triazine 3da. Analytical TLC on silica gel, 1:24 ethyl acetate/hexane R_f = 0.50; thick liquid; yield 83% (76 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41 (s, 1H), 8.15-8.12 (m, 1H), 7.93-7.91 (m, 1H), 7.49 (t, *J* = 8.0 Hz, 1H), 7.19-7.17 (m, 2H), 7.11-7.09 (m, 2H), 7.04-7.02 (m, 4H), 3.84 (s, 1H), 3.55-3.51 (m, 1H), 3.44 (d, *J* = 13.2 Hz, 1H), 2.89-2.79 (m, 3H), 2.41-2.20 (m, 7H), 1.73-1.65 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.5, 142.1, 137.7, 136.8, 135.3, 132.8, 129.8, 129.6, 129.2, 128.5, 127.9, 124.3, 124.0, 88.5, 67.8, 58.9, 56.7, 51.9, 50.8, 22.0, 21.2; FT-IR (neat) 2830, 1633,

1530, 1352, 1129, 1092, 1014 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{26}H_{28}ClN_4O_2$: 463.1895, found: 463.1896.

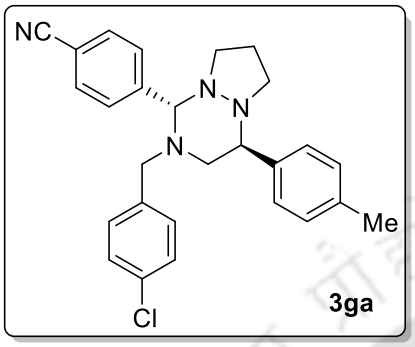


2-(4-Chlorobenzyl)-4-(*p*-tolyl)-1-(3-(trifluoromethyl)phenyl)hexahydro-6H-pyrazolo[1,2-a]-[1,2,4]triazine 3ea. Analytical TLC on silica gel, 1:24 ethyl acetate/hexane R_f = 0.48; thick liquid; yield 85% (82 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82-7.76 (m, 2H), 7.55 (d, *J* = 8.0 Hz, 1H), 7.43 (t, *J* = 7.6 Hz, 1H), 7.19-7.17 (m, 2H), 7.11-7.08 (m, 2H), 7.04-7.02 (m, 4H), 3.78 (s, 1H), 3.54-3.51 (m, 1H), 3.45 (d, *J* = 13.2 Hz, 1H), 2.84-2.78 (m, 3H), 2.42-2.36 (m, 1H), 2.35-2.28 (m, 2H), 2.26-2.21 (m, 4H), 1.72-1.65 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.8, 137.7, 137.1, 136.9, 132.7, 132.6, 131.5 (J_{C-F} = 32.3 Hz), 129.9, 129.2, 129.1, 128.4, 128.2 (J_{C-F} = 270.6 Hz), 127.9, 126.1 (J_{C-F} = 3.0 Hz), 125.9 (J_{C-F} = 3.7 Hz), 89.0, 67.9, 59.0, 56.7, 51.9, 50.8, 22.0, 21.2; ^{19}F NMR (377 MHz, $CDCl_3$) δ -62.3; FT-IR (neat) 2829, 1638, 1514, 1490, 1324, 1165, 1128, 1071 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{27}H_{28}ClF_3N_3$: 486.1918, found: 486.1912.

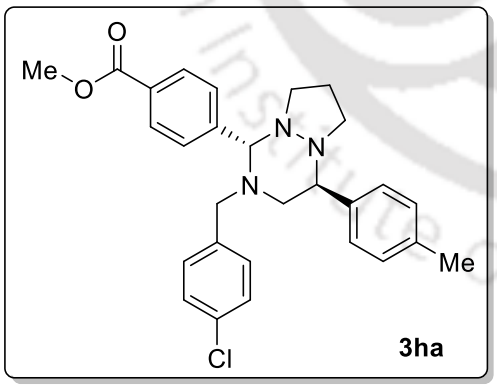


1-(4-Bromophenyl)-2-(4-chlorobenzyl)-4-(*p*-tolyl)hexahydro-6H-pyrazolo[1,2-a][1,2,4]tria-zine 3fa. Analytical TLC on silica gel, 1:24 ethyl acetate/hexane R_f = 0.52; colorless solid; mp 162-163 °C; yield 91% (90 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (s, 4H), 7.18-7.16 (m, 2H), 7.11-7.09 (m, 2H), 7.05-7.01 (m, 4H), 3.68 (s, 1H), 3.50-3.47 (m, 2H), 2.81-2.76 (m, 3H), 2.44-2.39 (m, 1H), 2.33-2.20 (m, 6H), 1.71-1.64 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.6, 137.6,

137.2, 137.0, 132.6, 131.8, 130.8, 129.9, 129.1, 128.4, 127.9, 122.8, 88.9, 68.0, 59.0, 56.6, 51.9, 50.8, 22.0, 21.2; FT-IR (KBr) 2827, 1638, 1591, 1488, 1314, 1128, 1012 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{26}H_{28}BrClN_3$: 496.1150, found: 496.1157.

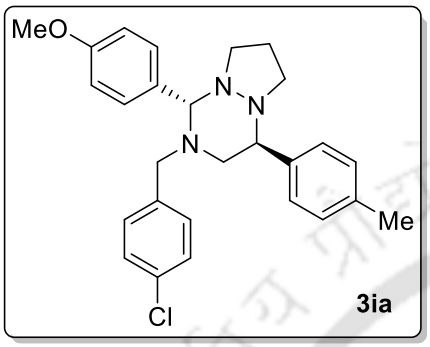


4-(2-(4-Chlorobenzyl)-4-(*p*-tolyl)hexahydro-6H-pyrazolo[1,2-a][1,2,4]triazin-1-yl)benzonitrile 3ga. Analytical TLC on silica gel, 1:16 ethyl acetate/hexane R_f = 0.48; colorless solid; mp 180-181 °C; yield 77% (68 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77-7.75 (m, 2H), 7.70 – 7.67 (m, 2H), 7.25 (d, *J* = 8.0 Hz, 2H), 7.20-7.16 (m, 2H), 7.11-7.09 (m, 4H), 3.84 (s, 1H), 3.59-3.56 (m, 1H), 3.49 (d, *J* = 13.2 Hz, 1H), 2.93-2.84 (m, 3H), 2.46-2.40 (m, 1H), 2.38-2.26 (m, 6H), 1.80-1.72 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.0, 137.7, 136.7, 132.8, 132.4, 130.0, 129.8, 129.2, 128.5, 127.9, 118.6, 112.8, 88.8, 67.9, 58.8, 56.6, 51.8, 50.7, 22.0, 21.2; FT-IR (KBr) 2830, 2228, 1609, 1543, 1489, 1300, 1128, 1015 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{27}H_{28}ClN_4$: 443.1997, found: 443.1998.

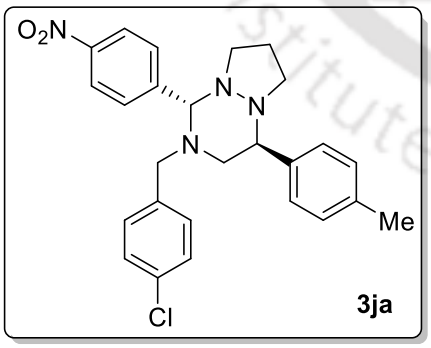


Methyl 4-(2-(4-chlorobenzyl)-4-(*p*-tolyl)hexahydro-6H-pyrazolo[1,2-a][1,2,4]triazin-1-yl)-benzoate 3ha. Analytical TLC on silica gel, 1:16 ethyl acetate/hexane R_f = 0.46; colorless solid; mp 184-185 °C; yield 82% (78 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00-7.98 (m, 2H), 7.65-7.63 (m, 2H), 7.19-7.17 (m, 2H), 7.10-7.08 (m, 2H), 7.05-7.01 (m, 4H), 3.84 (s, 3H), 3.77 (s, 1H), 3.54-3.50 (m, 1H), 3.46 (d, *J* = 13.6 Hz, 1H), 2.83-2.77 (m, 3H), 2.41-2.35 (m, 1H), 2.33-2.21 (m, 6H),

1.71-1.64 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.9, 144.6, 137.6, 137.1, 136.9, 132.6, 130.8, 130.0, 129.9, 129.3, 129.1, 128.4, 127.9, 89.1, 68.0, 58.9, 56.6, 52.3, 51.8, 50.7, 22.0, 21.2; FT-IR (KBr) 2822, 1722, 1611, 1432, 1276, 1102, 1014 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{28}H_{31}ClN_3O_2$: 476.2099, found: 476.2116.

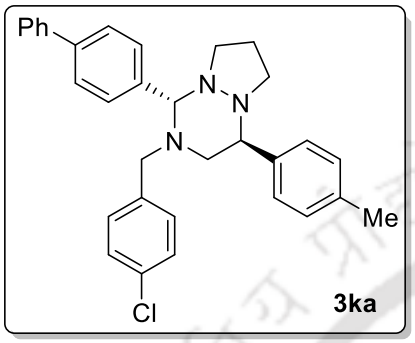


2-(4-Chlorobenzyl)-1-(4-methoxyphenyl)-4-(*p*-tolyl)hexahydro-6H-pyrazolo[1,2-a][1,2,4]triazine 3ia. Analytical TLC on silica gel, 1:16 ethyl acetate/hexane R_f = 0.46; colorless solid; mp 169-170 °C; yield 94% (84 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46-7.45 (m, 2H), 7.19-7.17 (m, 2H), 7.10-7.05 (m, 4H), 7.03 (d, *J* = 8.0 Hz, 2H), 6.84 (d, *J* = 8.8 Hz, 2H), 3.73 (s, 3H), 3.68 (s, 1H), 3.58-3.50 (m, 2H), 2.83-2.77 (m, 3H), 2.47-2.42 (m, 1H), 2.36-2.23 (m, 6H), 1.71-1.64 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.0, 137.67, 137.60, 137.1, 132.4, 131.5, 130.2, 130.0, 129.1, 128.3, 127.9, 113.9, 89.1, 68.1, 59.1, 56.5, 55.3, 52.0, 50.8, 21.9, 21.2; FT-IR (KBr) 2825, 1611, 1510, 1239, 1126 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{27}H_{31}ClN_3O$: 448.2150, found: 448.2164.

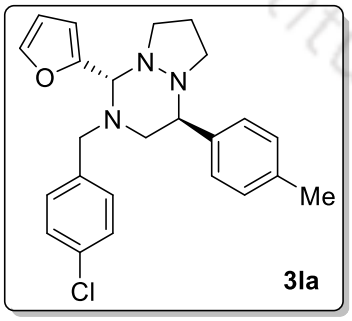


2-(4-Chlorobenzyl)-1-(4-nitrophenyl)-4-(*p*-tolyl)hexahydro-6H-pyrazolo[1,2-a][1,2,4]triazine 3ja. Analytical TLC on silica gel, 1:16 ethyl acetate/hexane R_f = 0.42; yellow solid; mp 122-123 °C; yield 79% (73 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19-8.17 (m, 2H), 7.77-7.75 (m, 2H), 7.19-7.16 (m, 2H), 7.12-7.09 (m, 2H), 7.04-7.02 (m, 4H), 3.82 (s, 1H), 3.53-3.50 (m, 1H), 3.41 (d,

J = 13.6 Hz, 1H), 2.87-2.78 (m, 3H), 2.39-2.19 (m, 7H), 1.73-1.65 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.4, 147.0, 137.8, 136.78, 136.71, 132.9, 130.2, 129.8, 129.2, 128.5, 127.9, 123.8, 88.5, 67.9, 58.8, 56.6, 51.8, 50.7, 22.0, 21.2; FT-IR (KBr) 2964, 2828, 1607, 1519, 1489, 1342, 1127, 1014 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{26}H_{28}ClN_4O_2$: 463.1895, found: 463.1892.

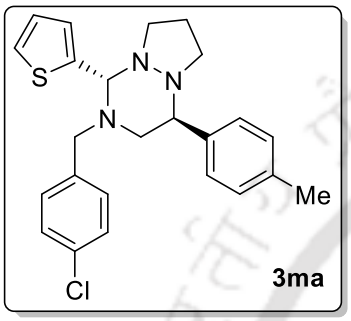


1-([1,1'-Biphenyl]-4-yl)-2-(4-chlorobenzyl)-4-(*p*-tolyl)hexahydro-6H-pyrazolo[1,2-a][1,2,4]-triazine 3ka. Analytical TLC on silica gel, 1:24 ethyl acetate/hexane R_f = 0.48; colorless solid; mp 158-159 ºC; yield 92% (90 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61-7.59 (m, 2H), 7.54-7.51 (m, 4H), 7.37-7.33 (m, 2H), 7.27-7.23 (m, 1H), 7.20-7.16 (m, 2H), 7.09 (s, 4H), 7.03 (d, *J* = 8.0 Hz, 2H), 3.76 (s, 1H), 3.62 (d, *J* = 13.2 Hz, 1H), 3.56-3.52 (m, 1H), 2.85-2.79 (m, 3H), 2.52-2.47 (m, 1H), 2.40-2.33 (m, 1H), 2.30-2.25 (m, 2H), 2.23 (s, 3H), 1.72-1.64 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.7, 140.8, 138.5, 137.6, 137.5, 137.1, 132.5, 130.0, 129.5, 129.1, 128.9, 128.3, 127.9, 127.5, 127.3, 127.2, 89.4, 68.1, 59.1, 56.7, 51.9, 50.8, 22.0, 21.2; FT-IR (KBr) 2824, 1511, 1487,1314, 1129, 1014 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{32}H_{33}ClN_3$: 494.2358, found: 494.2368.

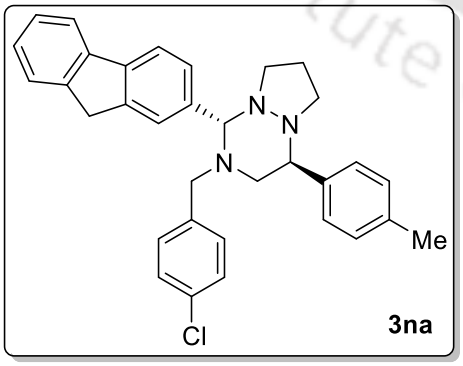


2-(4-Chlorobenzyl)-1-(furan-2-yl)-4-(*p*-tolyl)hexahydro-6H-pyrazolo[1,2-a][1,2,4]triazine 3la. Analytical TLC on silica gel, 1:24 ethyl acetate/hexane R_f = 0.48; colorless solid; mp 123-124 ºC; yield 91% (74 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.388-7.383 (m, 1H), 7.18-7.09 (m, 6H),

7.02 (d, *J* = 8.0 Hz, 2H), 6.44-6.43 (m, 1H), 6.29-6.28 (m, 1H), 3.90 (s, 1H), 3.60-3.53 (m, 2H), 2.96 (d, *J* = 13.2 Hz, 1H), 2.82-2.74 (m, 2H), 2.65-2.59 (m, 1H), 2.40-2.33 (m, 1H), 2.31-2.21 (m, 5H), 1.77-1.68 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.4, 142.8, 137.6, 137.2, 136.9, 132.5, 130.2, 129.1, 128.3, 127.9, 110.4, 110.1, 82.2, 67.6, 58.9, 56.5, 51.9, 50.4, 21.9, 21.2; FT-IR (KBr) 2846, 2823, 2736, 1491, 1336, 1151, 1128, 1077 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{24}H_{27}ClN_3O$: 408.1837, found: 408.1856.

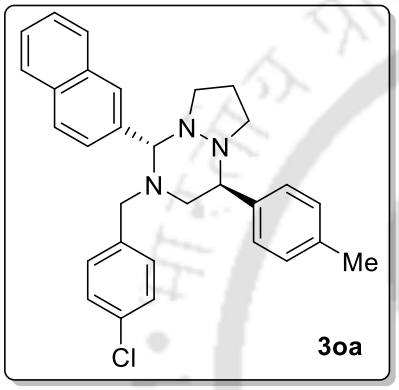


2-(4-Chlorobenzyl)-1-(thiophen-2-yl)-4-(*p*-tolyl)hexahydro-6H-pyrazolo[1,2-a][1,2,4]triazine 3ma. Analytical TLC on silica gel, 1:24 ethyl acetate/hexane R_f = 0.46; thick liquid; yield 93% (79 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (d, *J* = 4.8 Hz, 1H), 7.18-7.15 (m, 2H), 7.14-7.08 (m, 5H), 7.02 (d, *J* = 8.0 Hz, 2H), 6.90-6.88 (m, 1H), 4.03 (s, 1H), 3.71 (d, *J* = 13.2 Hz, 1H), 3.55-3.51 (m, 1H), 2.84-2.786 (m, 2H), 2.781-2.74 (m, 1H), 2.62-2.57 (m, 1H), 2.40-2.32 (m, 1H), 2.30-2.23 (m, 5H), 1.74-1.67 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.3, 137.6, 137.3, 136.9, 132.6, 130.1, 129.1, 128.3, 127.9, 127.2, 126.9, 125.8, 84.5, 67.8, 59.0, 56.6, 52.1, 51.0, 21.8, 21.2; FT-IR (neat) 2973, 2826, 1591, 1488, 1291, 1127, 1012 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{24}H_{27}ClN_3S$: 424.1609, found: 424.1608.

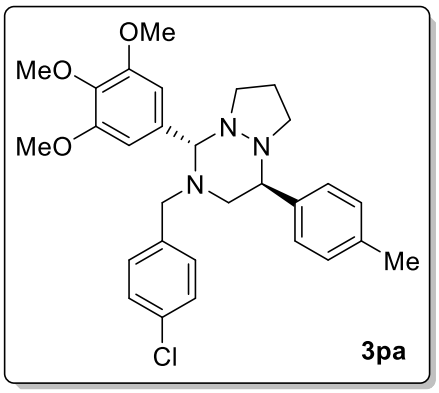


2-(4-Chlorobenzyl)-1-(9H-fluoren-2-yl)-4-(*p*-tolyl)hexahydro-6H-pyrazolo[1,2-a][1,2,4]triazine 3na. Analytical TLC on silica gel, 1:24 ethyl acetate/hexane R_f = 0.46; colorless solid; mp

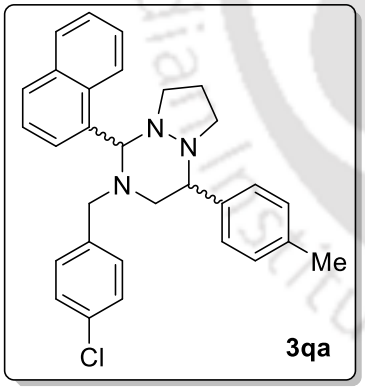
189-190 °C; yield 89% (90 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81-7.68 (m, 3H), 7.50-7.44 (m, 2H), 7.29-7.25 (m, 1H), 7.22-7.18 (m, 3H), 7.09-7.07 (m, 4H), 7.03 (d, *J* = 7.6 Hz, 2H), 3.84 (s, 2H), 3.78 (s, 1H), 3.62 (d, *J* = 13.2 Hz, 1H), 3.56-3.53 (m, 1H), 2.84-2.79 (m, 3H), 2.49-2.44 (m, 1H), 2.41-2.34 (m, 1H), 2.31-2.26 (m, 2H), 2.22 (s, 3H), 1.70-1.63 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.7, 143.6, 142.5, 141.3, 138.0, 137.59, 137.56, 137.1, 132.4, 130.0, 129.1, 128.3, 127.9, 126.9, 126.8, 125.4, 125.1, 120.0, 119.8, 89.8, 68.2, 59.1, 56.7, 51.9, 50.9, 36.9, 22.0, 21.2; FT-IR (KBr) 2852, 2819, 1723, 1613, 1513, 1123 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{33}H_{33}ClN_3$: 506.2358, found: 506.2376.



2-(4-Chlorobenzyl)-1-(naphthalen-2-yl)-4-(*p*-tolyl)hexahydro-6H-pyrazolo[1,2-a][1,2,4]triazine 3oa. Analytical TLC on silica gel, 1:24 ethyl acetate/hexane R_f = 0.52; colorless solid; mp 177-178 °C; yield 88% (82 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (s, 1H), 7.91-7.84 (m, 4H), 7.53-7.48 (m, 2H), 7.31 (d, *J* = 7.6 Hz, 2H), 7.18-7.11 (m, 6H), 3.97 (s, 1H), 3.71-3.62 (m, 2H), 2.94 – 2.89 (m, 3H), 2.54-2.44 (m, 2H), 2.43-2.36 (m, 2H), 2.33 (s, 3H), 1.80-1.72 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.6, 137.4, 137.1, 137.0, 133.9, 133.2, 132.5, 130.0, 129.1, 128.65, 128.62, 128.3, 128.1, 128.0, 127.8, 126.3, 126.2, 89.8, 68.1, 59.1, 56.7, 52.0, 50.9, 22.0, 21.2; FT-IR (KBr) 2823, 2800, 1489, 1289, 1139, 1092, 1014 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{30}H_{31}ClN_3$: 468.2201, found: 468.2204.

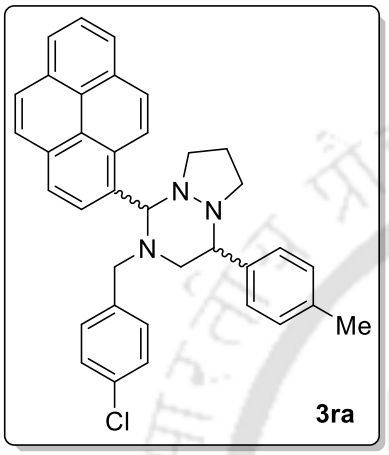


2-(4-Chlorobenzyl)-4-(*p*-tolyl)-1-(3,4,5-trimethoxyphenyl)hexahydro-6H-pyrazolo[1,2-a]-[1,2,4]triazine 3pa. Analytical TLC on silica gel, 1:16 ethyl acetate/hexane R_f = 0.44; colorless solid; mp 159-160 ºC; yield 92% (93 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19-7.17 (m, 2H), 7.12-7.07 (m, 4H), 7.05-7.01 (m, 2H), 6.77 (s, 2H), 3.82 (s, 6H), 3.77 (s, 3H), 3.62-3.51 (m, 3H), 2.83-2.77 (m, 3H), 2.54-2.49 (m, 1H), 2.36-2.32 (m, 1H), 2.30-2.23 (m, 5H), 1.73-1.65 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.2, 138.2, 137.6, 137.5, 137.0, 134.9, 132.5, 129.8, 129.1, 128.3, 127.9, 106.8, 105.9, 90.0, 67.8, 60.9, 59.3, 56.6, 56.3, 51.9, 50.7, 22.0, 21.2; FT-IR (KBr) 2829, 1592, 1504, 1490, 1462, 1356, 1230, 1127, 1013 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{29}H_{35}ClN_3O_3$: 508.2361, found: 508.2369.

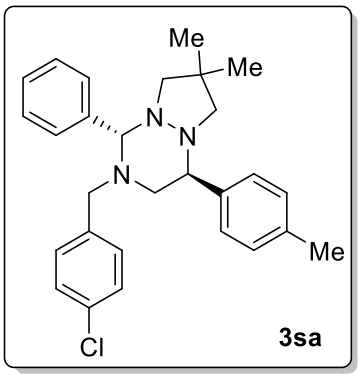


2-(4-Chlorobenzyl)-1-(naphthalen-1-yl)-4-(*p*-tolyl)hexahydro-6H-pyrazolo[1,2-a][1,2,4]tri-azine 3qa. Analytical TLC on silica gel, 1:16 ethyl acetate/hexane R_f = 0.48; thick liquid; yield 82% (76 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.64 (d, *J* = 8.4 Hz, 1H), 8.38 (d, *J* = 8.4 Hz, 0.57H), 8.18-8.16 (m, 0.57H), 7.82-7.73 (m, 3.23H), 7.52-7.40 (m, 5H), 7.32-7.15 (m, 5.01H), 7.11-6.97 (m, 8H), 6.88 (d, *J* = 8.4 Hz, 2.01H), 4.80 (s, 0.59H), 4.06 (s, 1H), 3.68-3.65 (m, 1.02H), 3.63-3.59 (m, 0.58H), 3.55 – 3.43 (m, 0.97H), 3.36 (d, *J* = 13.2 Hz, 1H), 2.90-2.73 (m, 5H), 2.46-2.19 (m, 12.02H), 1.69-1.56 (m, 4.01H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.64, 137.62, 137.5, 137.3,

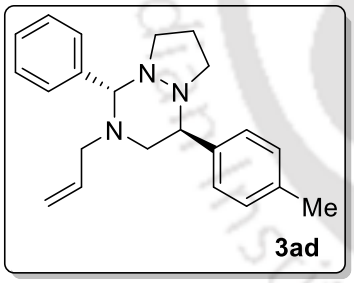
137.1, 135.1, 134.9, 134.5, 133.6, 132.7, 132.4, 132.3, 131.6, 130.3, 129.9, 129.6, 129.2, 129.1, 128.8, 128.7, 128.5, 128.2, 128.1, 128.0, 127.8, 127.0, 126.2, 126.07, 126.02, 125.5, 125.0, 124.7, 122.7, 93.1, 81.9, 68.6, 67.8, 59.4, 57.2, 56.0, 52.3, 51.9, 50.7, 50.1, 29.8, 22.2, 21.9, 21.28, 21.25; FT-IR (KBr) 2853, 2828, 1634, 1512, 1489, 1128, 1014 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{30}H_{31}ClN_3$: 468.2201, found: 468.2209.



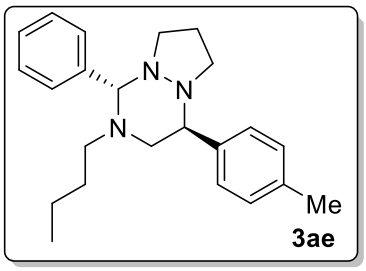
2-(4-Chlorobenzyl)-1-(pyren-1-yl)-4-(*p*-tolyl)hexahydro-6H-pyrazolo[1,2-a][1,2,4]triazine 3ra. Analytical TLC on silica gel, 1:16 ethyl acetate/hexane R_f = 0.46; colorless solid; mp >200 ^oC; yield 78% (84 mg); ^1H NMR (400 MHz, $CDCl_3$) δ 10.03 (d, *J* = 9.42 Hz, 1H), 8.80-8.72 (m, 1.71H), 8.33-8.01 (m, 14.53H), 7.40-7.38 (m, 3.66H), 7.18-7.09 (m, 7.24H), 7.06-6.98 (m, 4H), 5.16 (s, 0.81H), 4.43 (s, 1H), 3.90-3.87 (m, 1.02H), 3.81-3.78 (m, 0.86H), 3.58 (d, *J* = 13.6 Hz, 0.89H), 3.47 (d, *J* = 13.2 Hz, 1.03H), 3.06-2.89 (m, 5.79H), 2.63 (t, *J* = 10.8 Hz, 0.92H), 2.57-2.36 (m, 11.52H), 2.29-2.24 (m, 120H), 1.78-1.65 (m, 4.72H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.67, 137.62, 137.4, 137.3, 137.2, 133.0, 132.9, 132.4, 132.36, 132.34, 131.9, 131.4, 131.36, 131.30, 130.6, 130.3, 130.28, 130.25, 130.0, 129.9, 129.24, 129.21, 129.1, 128.2, 128.1, 128.0, 127.99, 127.95, 127.8, 127.7, 127.6, 127.3, 126.7, 126.2, 126.1, 126.0, 125.728, 125.721, 125.6, 125.3, 125.2, 125.0, 124.9, 124.7, 124.6, 124.2, 122.3, 93.2, 82.5, 68.6, 68.1, 59.6, 59.4, 57.4, 56.2, 52.3, 52.0, 50.9, 50.2, 22.2, 22.0, 21.2; FT-IR (KBr) 2834, 1512, 1489, 1313, 1126, 1014 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{36}H_{33}ClN_3$: 542.2358, found: 542.2379.



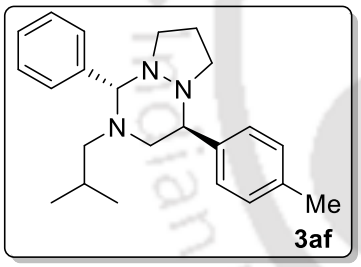
2-(4-Chlorobenzyl)-7,7-dimethyl-1-phenyl-4-(*p*-tolyl)hexahydro-6H-pyrazolo[1,2-a][1,2,4]-triazine 3sa. Analytical TLC on silica gel, 1:24 ethyl acetate/hexane R_f = 0.52; colorless solid; mp 139-140 ºC; yield 92% (82 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53-7.51 (m, 2H), 7.31-7.23 (m, 3H), 7.18 (d, *J* = 8.0 Hz, 2H), 7.09-7.00 (m, 6H), 3.67 (s, 1H), 3.52-3.48 (m, 2H), 2.78-2.74 (m, 2H), 2.54 (d, *J* = 8.8 Hz, 1H), 2.24-2.07 (m, 7H), 0.94 (s, 3H), 0.88 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.5, 137.5, 137.44, 137.40, 132.4, 130.1, 129.2, 129.1, 128.8, 128.5, 128.2, 127.8, 89.7, 67.9, 67.2, 66.2, 59.3, 56.6, 36.2, 29.1, 28.9, 21.2; FT-IR (KBr) 2959, 2823, 1642, 1514, 1490, 1450, 1130, 1015 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{28}H_{33}ClN_3$: 446.2358, found: 446.2360.



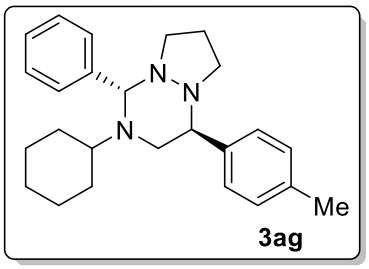
2-Allyl-1-phenyl-4-(*p*-tolyl)hexahydro-6H-pyrazolo[1,2-a][1,2,4]triazine 3ad. Analytical TLC on silica gel, 1:24 ethyl acetate/hexane R_f = 0.50; colorless solid; mp 110-111 ºC; yield 92% (61 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53-7.51 (m, 2H), 7.37-7.32 (m, 5H), 7.15 (d, *J* = 7.6 Hz, 2H), 5.78-5.67 (m, 1H), 5.02-4.97 (m, 2H), 3.71 (s, 1H), 3.68-3.65 (m, 1H), 3.13-3.05 (m, 2H), 2.92-2.86 (m, 1H), 2.57- 2.28 (m, 8H), 1.77-1.69 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.3, 137.5, 137.4, 135.1, 129.2, 129.1, 128.7, 128.4, 128.0, 117.5, 89.2, 68.1, 59.1, 56.1, 51.9, 50.7, 22.0, 21.2; FT-IR (KBr) 2828, 1641, 1512, 1128, 1021 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{22}H_{28}N_3$: 334.2278, found: 334.2287.



2-Butyl-1-phenyl-4-(*p*-tolyl)hexahydro-6H-pyrazolo[1,2-a][1,2,4]triazine 3ae. Analytical TLC on silica gel, 1:24 ethyl acetate/hexane R_f = 0.56; thick liquid; yield 87% (61 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44- 7.43 (m, 2H), 7.28-7.25 (m, 5H), 7.09 (d, *J* = 7.6 Hz, 2H), 3.61-3.58 (m, 2H), 3.10-3.06 (m, 1H), 2.84-2.79 (m, 1H), 2.40-2.36 (m, 1H), 2.35-2.29 (m, 2H), 2.27 (s, 3H), 2.26-2.21 (m, 2H), 1.90-1.83 (m, 1H), 1.69-1.61 (m, 2H), 1.28-1.19 (m, 2H), 1.13-1.05 (m, 1H), 1.03 – 0.92 (m, 1H), 0.64 (t, *J* = 7.6 Hz, 3H).; ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.7, 137.57, 137.54, 129.2, 129.1, 128.5, 128.3, 128.0, 89.8, 68.2, 59.1, 52.5, 52.0, 50.7, 28.7, 22.0, 21.3, 20.4, 14.0; FT-IR (neat) 2827, 1636, 1513, 1315, 1129, 1021 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{23}H_{32}N_3$: 350.2591, found: 350.2605.

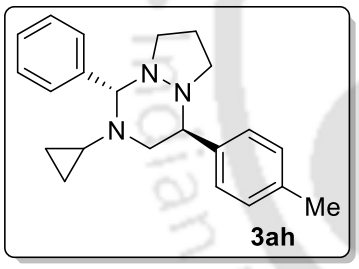


2-Isobutyl-1-phenyl-4-(*p*-tolyl)hexahydro-6H-pyrazolo[1,2-a][1,2,4]triazine 3af. Analytical TLC on silica gel, 1:24 ethyl acetate/hexane R_f = 0.52; thick liquid; yield 89% (62 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (s, 2H), 7.28-7.24 (m, 5H), 7.09 (d, *J* = 8.0 Hz, 2H), 3.61-3.57 (m, 1H), 3.54 (s, 1H), 3.08-3.05 (m, 1H), 2.84-2.79 (m, 1H), 2.38-2.33 (m, 1H), 2.30-2.21 (m, 6H), 1.88-1.82 (m, 1H), 1.75-1.71 (m, 1H), 1.69-1.61 (m, 2H), 1.60-1.52 (m, 1H), 0.71 (d, *J* = 6.4 Hz, 3H), 0.57 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.8, 137.58, 137.55, 129.5, 129.1, 128.5, 128.2, 128.0, 90.3, 68.2, 60.9, 59.7, 51.9, 50.8, 25.7, 21.9, 21.29, 21.20, 20.3; FT-IR (neat) 2954, 2826, 1638, 1514, 1451, 1127, 1022 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{23}H_{32}N_3$: 350.2591, found: 350.2608.



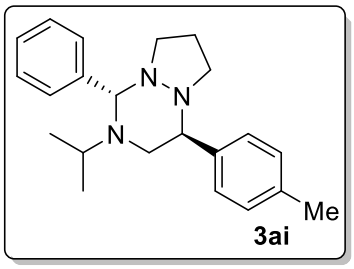
3ag

2-Cyclohexyl-1-phenyl-4-(*p*-tolyl)hexahydro-6H-pyrazolo[1,2-a][1,2,4]triazine 3ag. Analytical TLC on silica gel, 1:24 ethyl acetate/hexane R_f = 0.54; thick liquid; yield 76% (57 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.51-7.49 (m, 2H), 7.35-7.33 (m, 5H), 7.16 (d, *J* = 7.6 Hz, 2H), 4.05 (s, 1H), 3.62 (d, *J* = 10.4 Hz, 1H), 3.01-2.98 (m, 1H), 2.90-2.85 (m, 1H), 2.71 (t, *J* = 10.8 Hz, 1H), 2.43-2.38 (m, 1H), 2.34-2.33 (m, 3H), 2.31-2.21 (m, 2H), 1.76-1.53 (m, 8H), 1.44-1.39 (m, 1H), 1.36-1.29 (m, 1H), 1.25-1.14 (m, 1H), 1.01-0.88 (m, 1H), 0.86-0.73 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.5, 137.9, 137.4, 129.1, 129.0, 128.5, 128.4, 128.0, 87.0, 68.6, 57.3, 52.5, 51.9, 50.8, 31.9, 26.6, 26.4, 25.9, 24.9, 22.0, 21.2; FT-IR (neat) 2928, 2852, 2826, 1514, 1450, 1125, 1020 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{25}H_{34}N_3$: 376.2747, found: 376.2746.

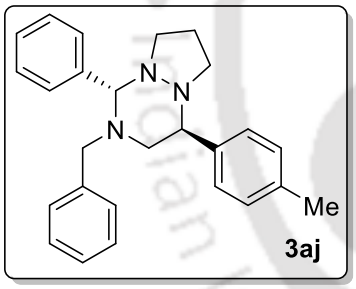


3ah

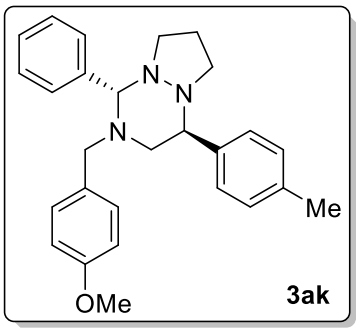
2-Cyclopropyl-1-phenyl-4-(*p*-tolyl)hexahydro-6H-pyrazolo[1,2-a][1,2,4]triazine 3ah. Analytical TLC on silica gel, 1:24 ethyl acetate/hexane R_f = 0.52; thick liquid; yield 73% (49 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49-7.47 (m, 2H), 7.34-7.30 (m, 5H), 7.16 (d, *J* = 8.0 Hz, 2H), 3.83 (s, 1H), 3.65-3.62 (m, 1H), 3.15-3.12 (m, 1H), 2.93-2.88 (m, 1H), 2.70-2.60 (m, 2H), 2.34 (s, 3H), 2.32-2.23 (m, 2H), 1.78-1.71 (m, 2H), 1.61-1.56 (m, 1H), 0.23-0.12 (m, 2H), -0.05- -0.12 (m, 1H), -0.22--0.28 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.5, 137.5, 137.3, 129.6, 129.2, 128.3, 127.9, 127.8, 90.6, 67.8, 61.2, 51.9, 50.5, 35.0, 22.1, 21.2, 8.8, 4.8; FT-IR (neat) 2827, 1633, 1513, 1315, 1133, 1021 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{22}H_{28}N_3$: 334.2278, found: 334.2280.



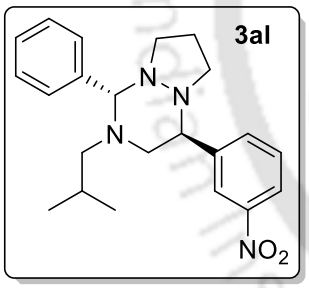
2-Isopropyl-1-phenyl-4-(*p*-tolyl)hexahydro-6H-pyrazolo[1,2-a][1,2,4]triazine 3ai. Analytical TLC on silica gel, 1:24 ethyl acetate/hexane R_f = 0.54; colorless solid; mp 130-131 ^oC; yield 79% (53 mg); ^1H NMR (400 MHz, $CDCl_3$) δ 7.44 (s, 2H), 7.29-7.27 (m, 5H), 7.10 (d, *J* = 7.6 Hz, 2H), 3.87 (s, 1H), 3.57-3.54 (m, 1H), 2.89-2.85 (m, 1H), 2.84-2.79 (m, 1H), 2.70-2.63 (m, 1H), 2.55 (t, *J* = 10.8 Hz, 1H), 2.36-2.31 (m, 1H), 2.30-2.20 (m, 5H), 1.67-1.62 (m, 2H), 0.90 (d, *J* = 6.8 Hz, 3H), 0.76 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.5, 137.8, 137.5, 129.18, 129.12, 128.6, 128.5, 128.0, 87.4, 68.5, 51.9, 50.8, 50.4, 47.7, 22.0, 21.7, 21.2, 13.2; FT-IR (KBr) 2966, 2822, 1629, 1511, 1361, 1309, 1127, 1009 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{22}H_{30}N_3$: 336.2434, found: 336.2445.



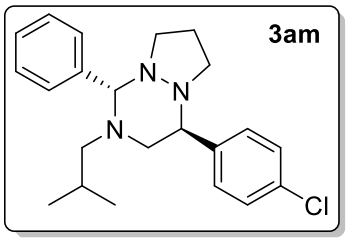
2-Benzyl-1-phenyl-4-(*p*-tolyl)hexahydro-6H-pyrazolo[1,2-a][1,2,4]triazine 3aj. Analytical TLC on silica gel, 1:24 ethyl acetate/hexane R_f = 0.50; colorless solid; mp 147-148 ^oC; yield 91% (70 mg); ^1H NMR (400 MHz, $CDCl_3$) δ 7.58 – 7.56 (m, 2H), 7.32-7.23 (m, 3H), 7.20-7.10 (m, 6H), 7.08-7.04 (m, 1H), 7.02 (d, *J* = 7.6 Hz, 2H), 3.73 (s, 1H), 3.62 (d, *J* = 13.2 Hz, 1H), 3.56-3.52 (m, 1H), 2.87-2.77 (m, 3H), 2.46-2.40 (m, 1H), 2.38-2.31 (m, 1H), 2.30 – 2.25 (m, 2H), 2.22 (s, 3H), 1.71-1.63 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.6, 139.0, 137.5, 137.2, 129.2, 129.1, 128.8, 128.7, 128.5, 128.2, 128.0, 126.8, 89.8, 68.1, 59.0, 57.3, 51.9, 50.8, 22.0, 21.2; FT-IR (KBr) 2826, 1631, 1491, 1314, 1126, 1066 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{26}H_{30}N_3$: 384.2434, found: 384.2439.



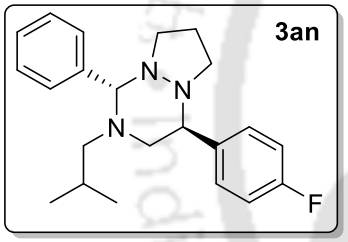
2-(4-Methoxybenzyl)-1-phenyl-4-(*p*-tolyl)hexahydro-6H-pyrazolo[1,2-a][1,2,4]triazine 3ak. Analytical TLC on silica gel, 1:16 ethyl acetate/hexane R_f = 0.46; colorless solid; mp 153-154 ^oC; yield 93% (77 mg); ^1H NMR (400 MHz, $CDCl_3$) δ 7.56 (s, 2H), 7.32-7.23 (m, 3H), 7.20-7.17 (m, 2H), 7.02 (t, *J* = 8.4 Hz, 4H), 6.68 – 6.65 (m, 2H), 3.70 (s, 1H), 3.65 (s, 3H), 3.55-3.51 (m, 2H), 2.86-2.82 (m, 1H), 2.80-2.74 (m, 2H), 2.45-2.39 (m, 1H), 2.37-2.30 (m, 1H), 2.29-2.21 (m, 5H), 1.70-1.63 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.5, 139.7, 137.4, 137.3, 130.9, 129.9, 129.2, 129.1, 128.7, 128.5, 128.0, 113.5, 89.8, 68.1, 58.9, 56.7, 55.3, 51.9, 50.8, 22.0, 21.2; FT-IR (KBr) 2824, 1611, 1512, 1251, 1125, 1035 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{27}H_{32}N_3O$: 414.2540, found: 414.2549.



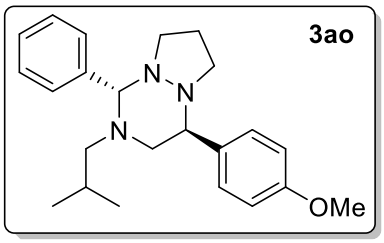
2-Isobutyl-4-(3-nitrophenyl)-1-phenylhexahydro-6H-pyrazolo[1,2-a][1,2,4]triazine 3al. Analytical TLC on silica gel, 1:24 ethyl acetate/hexane R_f = 0.48; thick liquid; yield 92% (70 mg); ^1H NMR (400 MHz, $CDCl_3$) δ 8.34-8.33 (m, 1H), 8.16-8.13 (m, 1H), 7.80 (d, *J* = 7.6 Hz, 1H), 7.53-7.49 (m, 3H), 7.35-7.32 (m, 3H), 3.82-3.78 (m, 1H), 3.63 (s, 1H), 3.16-3.13 (m, 1H), 2.88-2.83 (m, 1H), 2.46-2.41 (m, 1H), 2.39-2.24 (m, 3H), 1.97-1.91 (m, 1H), 1.83-1.70 (m, 3H), 1.67-1.57 (m, 1H), 0.78 (d, *J* = 6.4 Hz, 3H), 0.64 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.5, 142.8, 139.4, 134.3, 129.4, 128.7, 128.3, 123.0, 122.9, 90.0, 67.7, 60.7, 59.6, 51.9, 50.7, 25.7, 21.9, 21.1, 20.3; FT-IR (neat) 2958, 2832, 1628, 1530, 1352, 1127, 1024 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{22}H_{29}N_4O_2$: 381.2285, found: 381.2286.



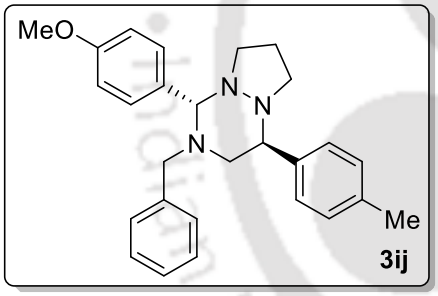
4-(4-Chlorophenyl)-2-isobutyl-1-phenylhexahydro-6H-pyrazolo[1,2-a][1,2,4]triazine 3am. Analytical TLC on silica gel, 1:24 ethyl acetate/hexane R_f = 0.54; thick liquid; yield 89% (66 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49-7.48 (m, 2H), 7.40-7.37 (m, 2H), 7.34-7.26 (m, 5H), 3.68-3.65 (m, 1H), 3.60 (s, 1H), 3.13-3.09 (m, 1H), 2.88-2.83 (m, 1H), 2.45-2.22 (m, 4H), 1.95-1.90 (m, 1H), 1.82-1.78 (m, 1H), 1.76-1.68 (m, 2H), 1.67-1.57 (m, 1H), 0.77 (d, *J* = 6.4 Hz, 3H), 0.64 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.6, 139.0, 133.4, 129.4, 128.68, 128.61, 128.2, 90.2, 67.8, 60.8, 59.6, 51.9, 50.7, 25.7, 21.9, 21.1, 20.3; FT-IR (neat) 2956, 2829, 1491, 1292, 1127, 1090, 1015 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{22}H_{29}ClN_3$: 370.2045, found: 370.2057.



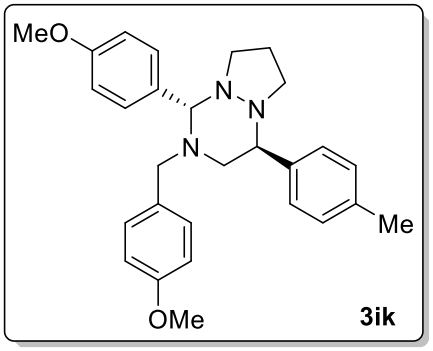
4-(4-Fluorophenyl)-2-isobutyl-1-phenylhexahydro-6H-pyrazolo[1,2-a][1,2,4]triazine 3an. Analytical TLC on silica gel, 1:24 ethyl acetate/hexane R_f = 0.52; thick liquid; yield 94% (66 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (s, 2H), 7.44-7.40 (m, 2H), 7.34-7.31 (m, 3H), 7.01 (t, *J* = 8.8 Hz, 2H), 3.69-3.65 (m, 1H), 3.60 (s, 1H), 3.14-3.10 (m, 1H), 2.87-2.81 (m, 1H), 2.45-2.24 (m, 4H), 1.96-1.90 (m, 1H), 1.82-1.78 (m, 1H), 1.75-1.58 (m, 3H), 0.78 (d, *J* = 6.4 Hz, 3H), 0.65 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.6 (J_{C-F} = 244.2 Hz), 139.7, 136.3 (J_{C-F} = 3.1 Hz), 129.6 (J_{C-F} = 7.8 Hz), 129.5, 128.5, 128.2, 115.4 (J_{C-F} = 21.0 Hz), 90.3, 67.7, 60.9, 59.7, 51.9, 50.8, 25.7, 21.9, 21.1, 20.3; ^{19}F NMR (377 MHz, $CDCl_3$) δ -114.7; FT-IR (neat) 2957, 2827, 1607, 1510, 1223, 1127, 1105 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{22}H_{29}FN_3$: 354.2340, found: 354.2348.



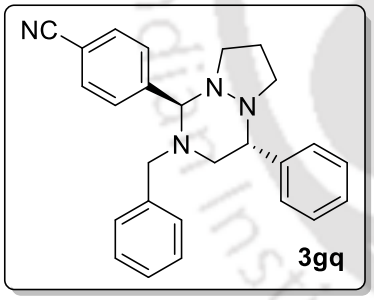
2-Isobutyl-4-(4-methoxyphenyl)-1-phenylhexahydro-6H-pyrazolo[1,2-a][1,2,4]triazine 3ao. Analytical TLC on silica gel, 1:16 ethyl acetate/hexane R_f = 0.48; thick liquid; yield 87% (63 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (s, 2H), 7.39-7.30 (m, 5H), 6.89-6.85 (m, 2H), 3.80 (s, 3H), 3.66-3.62 (m, 1H), 3.61 (s, 1H), 3.15-3.11 (m, 1H), 2.88-2.83 (m, 1H), 2.45-2.39 (m, 1H), 2.37-2.27 (m, 3H), 1.95-1.89 (m, 1H), 1.82-1.78 (m, 1H), 1.75-1.68 (m, 2H), 1.66-1.59 (m, 1H), 0.78 (d, *J* = 6.8 Hz, 3H), 0.64 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.2, 139.8, 132.7, 129.5, 129.1, 128.5, 128.2, 113.8, 90.3, 67.8, 60.9, 59.6, 55.3, 51.9, 50.8, 25.7, 21.9, 21.1, 20.3; FT-IR (neat) 2955, 2830, 1611, 1513, 1248, 1172, 1128, 1036 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{23}H_{32}N_3O$: 366.2540, found: 366.2542.



2-Benzyl-1-(4-methoxyphenyl)-4-(*p*-tolyl)hexahydro-6H-pyrazolo[1,2-a][1,2,4]triazine 3ij. Analytical TLC on silica gel, 1:16 ethyl acetate/hexane R_f = 0.44; colorless solid; mp 160-161 °C; yield 92% (76 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49-7.47 (m, 2H), 7.19-7.17 (m, 2H), 7.15-7.10 (m, 4H), 7.08-7.03 (m, 1H), 7.02 (d, *J* = 7.6 Hz, 2H), 6.84-6.82 (m, 2H), 3.73 (s, 3H), 3.68-3.61 (m, 2H), 3.54-3.51 (m, 1H), 2.86-2.77 (m, 3H), 2.48-2.43 (m, 1H), 2.36-2.22 (m, 6H), 1.70-1.63 (m, 2H); 13C NMR (100 MHz, $CDCl_3$) δ 159.9, 139.1, 137.4, 137.3, 131.8, 130.2, 129.1, 128.7, 128.1, 128.0, 126.8, 113.9, 89.2, 68.1, 59.1, 57.3, 55.3, 52.0, 50.8, 22.0, 21.2; FT-IR (KBr) 2831, 1610, 1585, 1512, 1300, 1248, 1128, 1037 cm^{-1}; HRMS (ESI) m/z [M+H]+ calcd for $C_{27}H_{32}N_3O$: 414.2540, found: 414.2541.

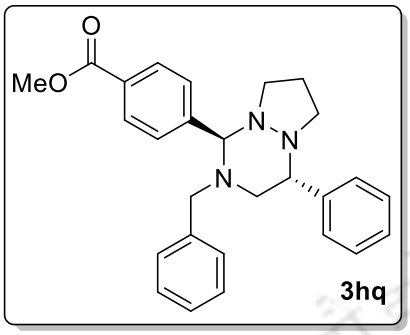


2-(4-Methoxybenzyl)-1-(4-methoxyphenyl)-4-(*p*-tolyl)hexahydro-6H-pyrazolo[1,2-a][1,2,4]-triazine 3ik. Analytical TLC on silica gel, 1:16 ethyl acetate/hexane R_f = 0.42; colorless solid; mp 161-162 ^oC; yield 89% (79 mg); ^1H NMR (400 MHz, $CDCl_3$) δ 7.48-7.46 (m, 2H), 7.19-7.17 (m, 2H), 7.04-7.00 (m, 4H), 6.85-6.82 (m, 2H), 6.68-6.65 (m, 2H), 3.74 (s, 3H), 3.65 (s, 4H), 3.57-3.49 (m, 2H), 2.85-2.73 (m, 3H), 2.47-2.42 (m, 1H), 2.35-2.21 (m, 6H), 1.70-1.62 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.9, 158.5, 137.45, 137.40, 131.9, 131.1, 130.2, 129.9, 129.0, 128.0, 113.8, 113.6, 89.2, 68.1, 59.0, 56.6, 55.38, 55.33, 52.0, 50.8, 22.0, 21.2; FT-IR (KBr) 2953, 2831, 1510, 1585, 1510, 1300, 1245, 1127, 1036 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{28}H_{34}N_3O_2$: 444.2646, found: 444.2650.

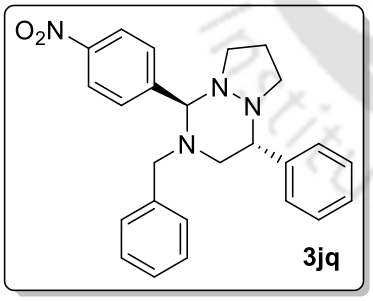


4-((1R,4R)-2-Benzyl-4-phenylhexahydro-6H-pyrazolo[1,2-a][1,2,4]triazin-1-yl)benzonitrile 3gq. Analytical TLC on silica gel, 1:16 ethyl acetate/hexane R_f = 0.52; colorless solid; mp >200 ^oC; yield 79% (62 mg); ^1H NMR (400 MHz, $CDCl_3$) δ 7.73-7.71 (m, 2H), 7.63 (d, *J* = 8.8 Hz, 2H), 7.30-7.28 (m, 2H), 7.23-7.07 (m, 8H), 3.79 (s, 1H), 3.57-3.53 (m, 1H), 3.48 (d, *J* = 13.2 Hz, 1H), 2.89-2.85 (m, 2H), 2.83-2.77 (m, 1H), 2.40-2.20 (m, 4H), 1.73-1.65 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ145.2, 139.9, 138.2, 132.4, 130.1, 128.56, 128.50, 128.3, 128.1, 127.9, 127.1, 118.7, 112.7, 89.0, 68.2, 58.8, 57.4, 51.8, 50.7, 22.0; FT-IR (KBr) 2830, 2227, 1607, 1494, 1452, 1301, 1128, 1027 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{26}H_{27}N_4$: 395.2230, found: 395.2234;

$[\alpha]_D^{20.8}$ = -24.00 (c = 0.02, $CHCl_3$); HPLC: >97% *ee* [CHIRALCEL AD, hexane/^{i}PrOH = 98:2, flow rate: 1 mL /min, λ = 254 nm, t_R = 8.52 min (minor), 12.66 min (major)].

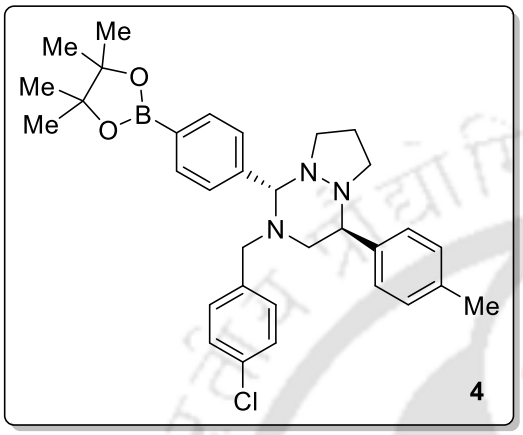


Methyl 4-((1R,4R)-2-benzyl-4-phenylhexahydro-6H-pyrazolo[1,2-a][1,2,4]triazin-1-yl)benzoate 3hq. Analytical TLC on silica gel, 1:16 ethyl acetate/hexane R_f = 0.48; colorless solid; mp 182-183 °C; yield 85% (72 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (d, *J* = 8.8 Hz, 2H), 7.78-7.76 (m, 2H), 7.41-7.38 (m, 2H), 7.33-7.15 (m, 8H), 3.94 (s, 3H), 3.89 (s, 1H), 3.68-3.60 (m, 2H), 2.99-2.87 (m, 3H), 2.53-2.32 (m, 4H), 1.82-1.74 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.0, 144.8, 140.1, 138.5, 130.7, 129.9, 129.3, 128.6, 128.4, 128.2, 128.1, 127.9, 127.0, 89.2, 68.3, 58.9, 57.3, 52.2, 51.9, 50.7, 22.0; FT-IR (KBr) 2831, 1724, 1636, 1276, 1127, 1018 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{27}H_{30}N_3O_2$: 428.2333, found: 428.2334; $[\alpha]_D^{21.5}$ = -70.00 (c = 0.02, $CHCl_3$); HPLC: >99% *ee* [CHIRALCEL AD, hexane/^{i}PrOH = 98:2, flow rate: 1 mL /min, λ = 254 nm, t_R = 7.96 min (minor), 11.62 min (major)].

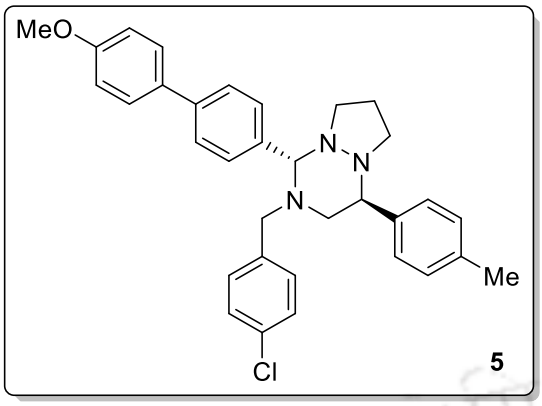


(1R,4R)-2-Benzyl-1-(4-nitrophenyl)-4-phenylhexahydro-6H-pyrazolo[1,2-a][1,2,4]triazine 3jq. Analytical TLC on silica gel, 1:16 ethyl acetate/hexane R_f = 0.46; yellow solid; mp 193-194 °C; yield 81% (67 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19-8.17 (m, 2H), 7.79-7.77 (m, 2H), 7.30-7.28 (m, 2H), 7.23-7.06 (m, 8H), 3.85 (s, 1H), 3.58-3.55 (m, 1H), 3.48 (d, *J* = 13.2 Hz, 1H), 2.90-2.87 (m, 2H), 2.83-2.78 (m, 1H), 2.40-2.20 (m, 4H), 1.74-1.65 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.4, 147.1, 139.8, 138.1, 130.2, 128.56, 128.51, 128.3, 128.1, 128.0, 127.1, 123.8,

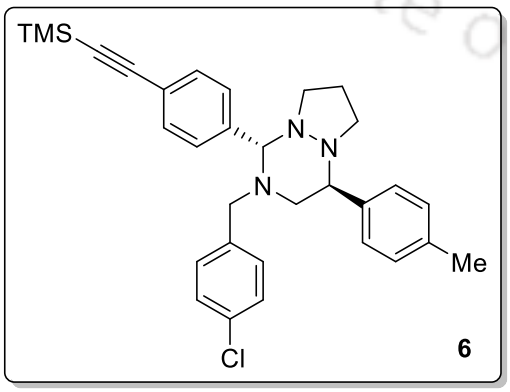
88.6, 68.2, 58.8, 57.4, 51.8, 50.7, 22.0; FT-IR (KBr) 2830, 1606, 1522, 1493, 1346, 1314, 1128, 1026 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{25}H_{27}N_4O_2$: 415.2129, found: 415.2129; $[\alpha]_D^{21.4}$ = -25.00 (c = 0.02, $CHCl_3$); HPLC: >99% *ee* [CHIRALCEL AD, hexane/*i*PrOH = 98:2, flow rate: 1 mL /min, λ = 254 nm, t_R = 6.76 min (minor), 8.51 min (major)].



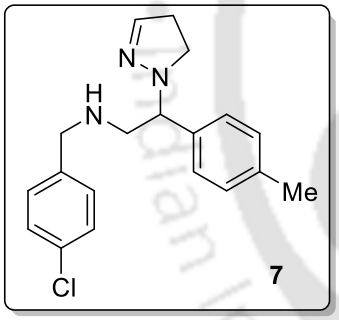
2-(4-Chlorobenzyl)-1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-4-(*p*-tolyl)hexahydro-6H-pyrazolo[1,2-a][1,2,4]triazine 4.[19] The cyclo-adduct **3fa** (100 mg, 0.2 mmol), bis(pinacolato)diboron (50 mg, 0.2 mmol), KOAc (40 mg, 0.4 mmol), $Pd(dppf)Cl_2 \bullet CH_2Cl_2$ (8 mg, 0.01 mmol) and dry THF (3 mL) were heated to reflux at 100 °C for 4 h under nitrogen atmosphere. After completion, the reaction mixture was cooled to room temperature and passed through a short pad of celite with CH_2Cl_2 (15 ml). Evaporation of the solvent gave a residue that was purified on silica gel column chromatography using hexane and ethyl acetate as an eluent to give **4**. Analytical TLC on silica gel, 1:16 ethyl acetate/hexane R_f = 0.48; colorless solid; mp 194-195 °C; yield 75% (81 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, *J* = 7.6 Hz, 2H), 7.56 (s, 2H), 7.19-7.17 (m, 2H), 7.09-7.01 (m, 6H), 3.72 (s, 1H), 3.54-3.47 (m, 2H), 2.83-2.76 (m, 3H), 2.45-2.39 (m, 1H), 2.35-2.22 (m, 6H), 1.70-1.63 (m, 2H), 1.27 (s, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.5, 137.6, 137.4, 137.1, 135.1, 132.5, 130.1, 129.1, 128.6, 128.3, 128.0, 89.7, 84.0, 68.1, 59.1, 56.6, 51.9, 50.7, 25.05, 25.02, 22.0, 21.2; FT-IR (KBr) 2977, 2827, 1612, 1489, 1360, 1143, 1016 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{32}H_{40}BClN_3O_2$: 544.2897, found: 544.2893.



2-(4-Chlorobenzyl)-1-(4'-methoxy-[1,1'-biphenyl]-4-yl)-4-(*p*-tolyl)hexahydro-6H-pyrazolo-[1,2-a][1,2,4]triazine 5.[19] The coupled adduct **4** (54 mg, 0.1 mmol), 4-bromoanisole (19 mg, 0.1 mmol), $Pd(PPh_3)_4$ (2.3 mg, 0.002), Na_2CO_3 (22 mg, 0.2 mmol), H_2O (50 μL) and toluene:EtOH (1:1, 2 mL) were heated to reflux at 100 ^oC for 3 h under nitrogen atmosphere. After completion, the reaction mixture was cooled to room temperature and passed through a short pad of celite with CH_2Cl_2 (10 ml). Evaporation of the solvent gave a residue that was purified on silica gel column chromatography using hexane and ethyl acetate as an eluent to give **5**. Analytical TLC on silica gel, 1:12 ethyl acetate/hexane R_f = 0.46; colorless solid; mp 173-174 ^oC; yield 82% (43 mg); ^1H NMR (400 MHz, $CDCl_3$) δ 7.65 (s, 2H), 7.55 (t, *J* = 8.4 Hz, 4H), 7.28-7.26 (m, 2H), 7.17 (s, 4H), 7.12 (d, *J* = 8.0 Hz, 2H), 6.99-6.96 (m, 2H), 3.85-3.83 (m, 4H), 3.70 (d, *J* = 13.6 Hz, 1H), 3.63-3.60 (m, 1H), 2.93-2.87 (m, 3H), 2.61-2.56 (m, 1H), 2.48-2.41 (m, 1H), 2.38-2.31 (m, 5H), 1.80-1.73 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.3, 141.3, 137.8, 137.6, 137.1, 133.3, 132.5, 130.0, 129.5, 129.1, 128.3, 128.2, 128.0, 126.8, 114.3, 89.4, 68.1, 59.1, 56.7, 55.4, 52.0, 50.9, 22.0, 21.2; FT-IR (KBr) 3831, 1610, 1496, 1248, 1180, 1128, 1015 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{33}H_{35}ClN_3O$: 524.2463, found: 524.2463.



2-(4-Chlorobenzyl)-4-(*p*-tolyl)-1-(4-((trimethylsilyl)ethynyl)phenyl)hexahydro-6H-pyrazolo-[1,2-a][1,2,4]triazine 6.[19] The cyclo-adduct **3fa** (50 mg, 0.1 mmol), trimethylsilylacetylene (12 mg, 0.12 mmol), CuI (2 mg, 0.01 mmol), $Pd(PPh_3)_4$ (6 mg, 0.005) and dry THF/Et_3N (1:1, 2 mL) were heated to reflux at 100 ^oC for 12 h under nitrogen atmosphere. After completion, the reaction mixture was cooled to room temperature and passed through a short pad of celite with CH_2Cl_2 (10 ml). Evaporation of the solvent gave a residue that was purified on silica gel column chromatography using hexane and ethyl acetate as an eluent to give **5**. Analytical TLC on silica gel, 1:24 ethyl acetate/hexane R_f = 0.46; thick liquid; yield 71% (36 mg); ^1H NMR (400 MHz, $CDCl_3$) δ 7.61-7.56 (m, 2H), 7.50-7.48 (m, 2H), 7.26-7.23 (m, 2H), 7.17-7.15 (m, 2H), 7.11-7.08 (m, 4H), 3.76 (s, 1H), 3.58-3.52 (m, 2H), 2.89-2.83 (m, 3H), 2.50-2.45 (m, 1H), 2.40-2.27 (m, 6H), 1.78-1.70 (m, 2H), 0.24 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.0, 137.6, 137.2, 137.0, 132.6, 132.3, 130.0, 129.19, 129.13, 128.4, 127.9, 123.7, 104.8, 94.9, 89.2, 68.0, 59.0, 56.6, 51.9, 50.7, 22.0, 21.2, 0.09; FT-IR (neat) 2828, 2157, 1634, 1490, 1249, 1128, 1015 cm-1; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{31}H_{37}ClN_3Si$: 514.2440, found: 514.2444.



***N*-(4-Chlorobenzyl)-2-(4,5-dihydro-1H-pyrazol-1-yl)-2-(*p*-tolyl)ethan-1-amine 7**. 1-(4-Bromophenyl)-2-(4-chlorobenzyl)-4-(*p*-tolyl)hexahydro-6H-pyrazolo[1,2-a][1,2,4]triazine **3fa** (50 mg, 0.1 mmol) and TFA (2 mL) were stirred at 70 ^oC for 2 h under air. The reaction mixture was then cooled to room temperature and diluted with ethyl acetate (5 mL). The resultant solution was treated with saturated aq. $NaHCO_3$ solution (10 mL) and extracted with ethyl acetate (3×10 mL). Drying (Na_2SO_4) and evaporation of the solvent gave a residue that was purified on silica gel column chromatography using ethyl acetate and hexane as an eluent to give **7**. Analytical TLC on silica gel, 1:1 ethyl acetate/hexane R_f = 0.42; thick liquid; yield 63% (21 mg); ^1H NMR (400 MHz, $CDCl_3$) δ 7.19-7.11 (m, 6H), 7.06-7.04 (m, 2H), 6.699-6.690 (m, 1H), 3.94-3.91 (m, 1H), 3.75-3.68 (m, 2H), 3.37-3.32 (m, 1H), 2.91-2.87 (m, 1H), 2.78-2.73 (m, 2H), 2.52-2.37 (m, 2H), 2.25

(s, 3H), 1.95 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.1, 139.0, 137.4, 136.2, 132.5, 129.5, 129.1, 128.57, 128.54, 68.0, 53.7, 53.2, 50.7, 33.3, 21.2; FT-IR (neat) 3320, 2919, 2839, 1490, 1407, 1286, 1088, 1014 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{19}H_{23}ClN_3$: 328.1575, found: 328.1593.

Crystal Structure and Data of 3ai

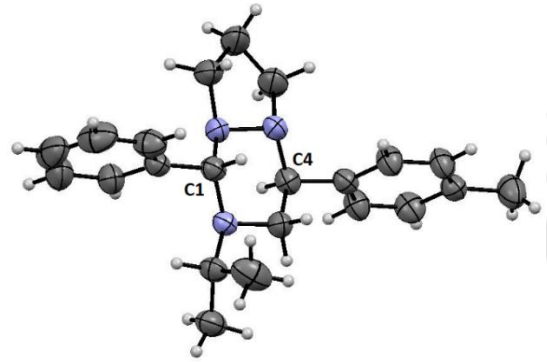


Figure 2. ORTEP diagram of 2-isopropyl-1-phenyl-4-(*p*-tolyl)hexahydro-6H-pyrazolo[1,2-a][1,2,4]triazine **3ai** (CCDC 1972128).

Identification code	**3ai**
Empirical formula	'C22 H29 N3'
Formula weight	335.48
Crystal habit, colour	block/Colorless
Temperature, *T*/K	293 K
Wavelength, *λ*/Å	0.71073
Crystal system	'monoclinic'
Space group	'P 21/n'
Unit cell dimensions	a = 16.2354(8) Å
	b = 5.8866(4) Å
	c = 20.5287(11) Å
	α = 90
	β = 93.513(4)
	γ = 90
Volume, *V*/Å^3	1958.3(2)

Z	4
Calculated density, $Mg \cdot m^{-3}$	1.138
Absorption coefficient, μ/mm^{-1}	0.067
$F(000)$	428
θ range for data collection	2.51 to 25°
Limiting indices	$-19 \leq h \leq 19, -3 \leq k \leq 7, -24 \leq l \leq 21$
Reflection collected / unique	3450/2277
Completeness to θ	99.9%
Absorption correction	Multi-scan
Max. and min. transmission	1.000 and 0.839
Refinement method	'SHELXL-2014/7 (Sheldrick, 2014)'
Data / restraints / parameters	3450/0/ 229
Goodness–of–fit on F^2	1.024
Final R indices [I>2sigma(I)]	R1 = 0.0532, wR2 = 0.1448
R indices (all data)	R1 = 0.0846, wR2 = 0.1764

Crystal Structure and Data of 3ik

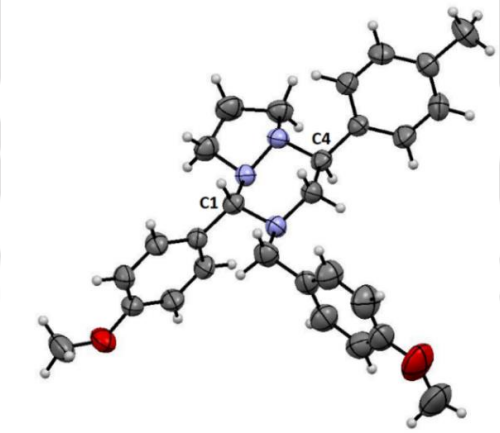


Figure 3. ORTEP diagram of 2-(4-methoxybenzyl)-1-(4-methoxyphenyl)-4-(*p*-tolyl)hexahydro-6H-pyrazolo[1,2-a][1,2,4]triazine **3ik** (CCDC 1972182).

Identification code	**3ik**
Empirical formula	'C28 H33 N3 O2'

Formula weight	443.57
Crystal habit, colour	block/Colorless
Temperature, *T*/K	298 K
Wavelength, λ/Å	0.71073
Crystal system	'triclinic'
Space group	'P -1'
Unit cell dimensions	a = 6.1688(8) Å
	b = 10.0037(13) Å
	c = 20.560(3) Å
	α = 103.548(5)
	β = 91.180(5)
	γ = 95.599(5)
Volume, *V*/Å^3	1226.4(3)
Z	2
Calculated density, Mg·m^{-3}	1.201
Absorption coefficient, μ/mm^{-1}	0.076
F(000)	476
θ range for data collection	2.23 to 25°
Limiting indices	-7 ≤ h ≤ 7, –11 ≤ k ≤ 11, –23 ≤ l ≤ 23
Reflection collected / unique	3951/2297
Completeness to θ	100%
Absorption correction	Multi-scan
Max. and min. transmission	0.989 and 0.977
Refinement method	'SHELXL-2016/6 (Sheldrick, 2016)'
Data / restraints / parameters	3951/0/ 301
Goodness–of–fit on F^2	1.047
Final *R* indices [*I*>2sigma(*I*)]	R1 = 0.0668, wR2 = 0.1608
R indices (all data)	R1 = 0.1299, wR2 = 0.2092

4.5 References

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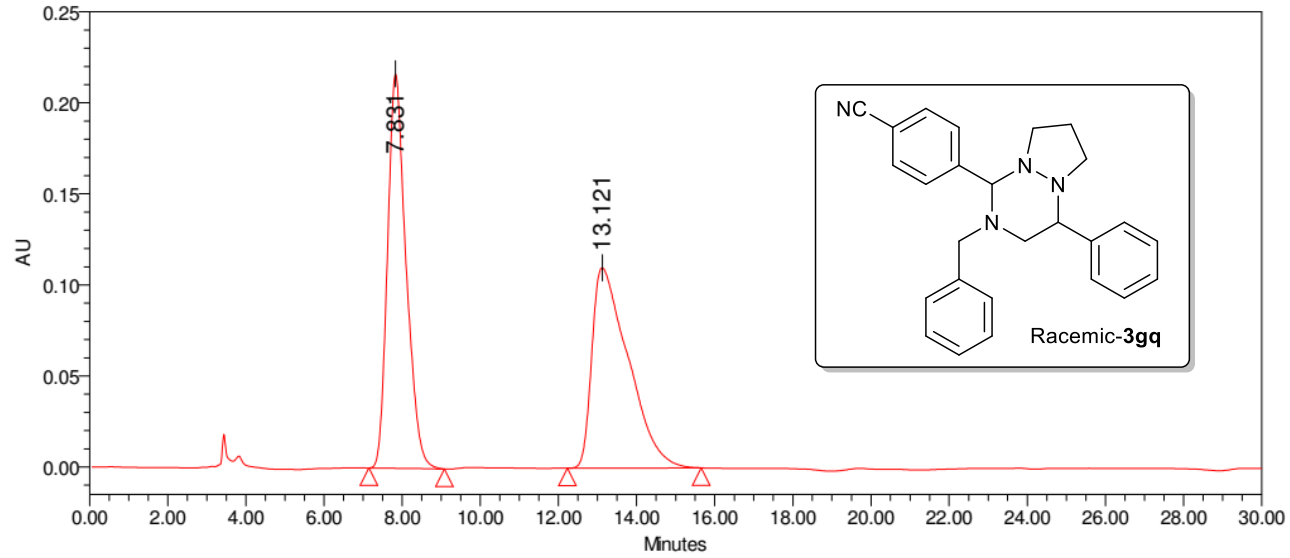
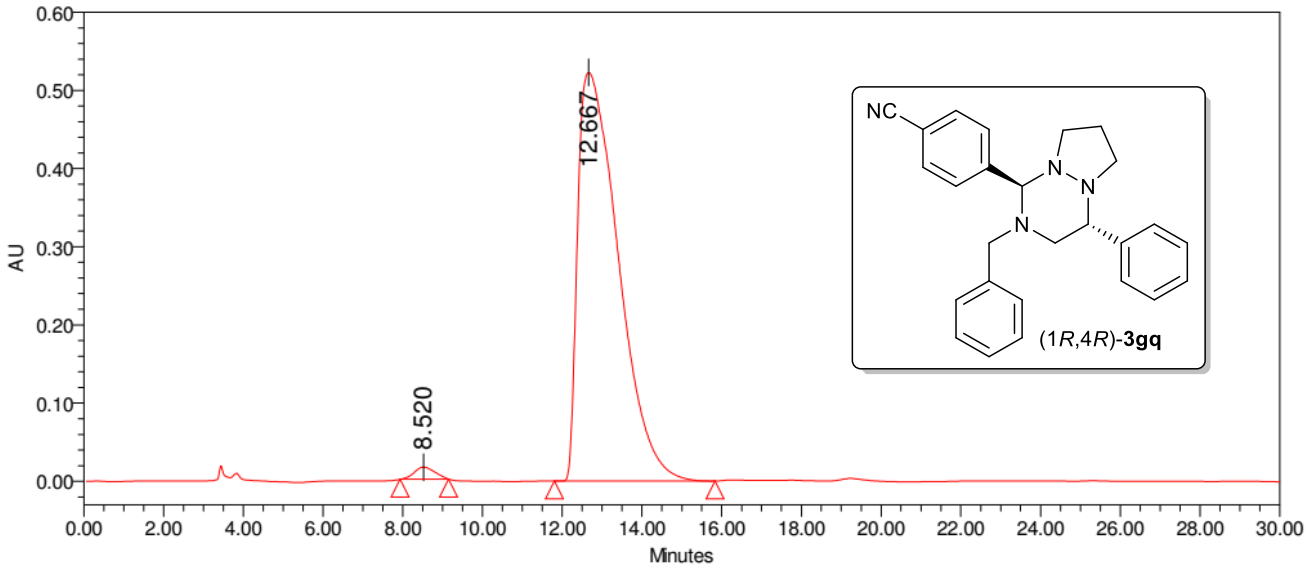
4.6 HPLC chromatograms



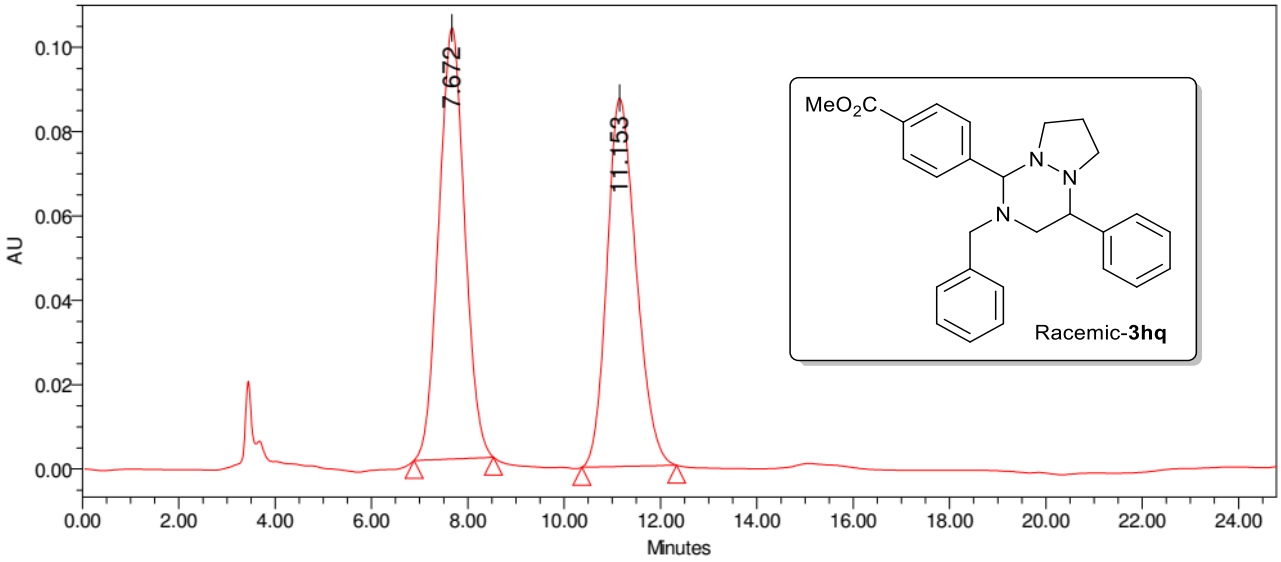
Peak Results

	RT	% Area
1	7.831	50.09
2	13.121	49.91



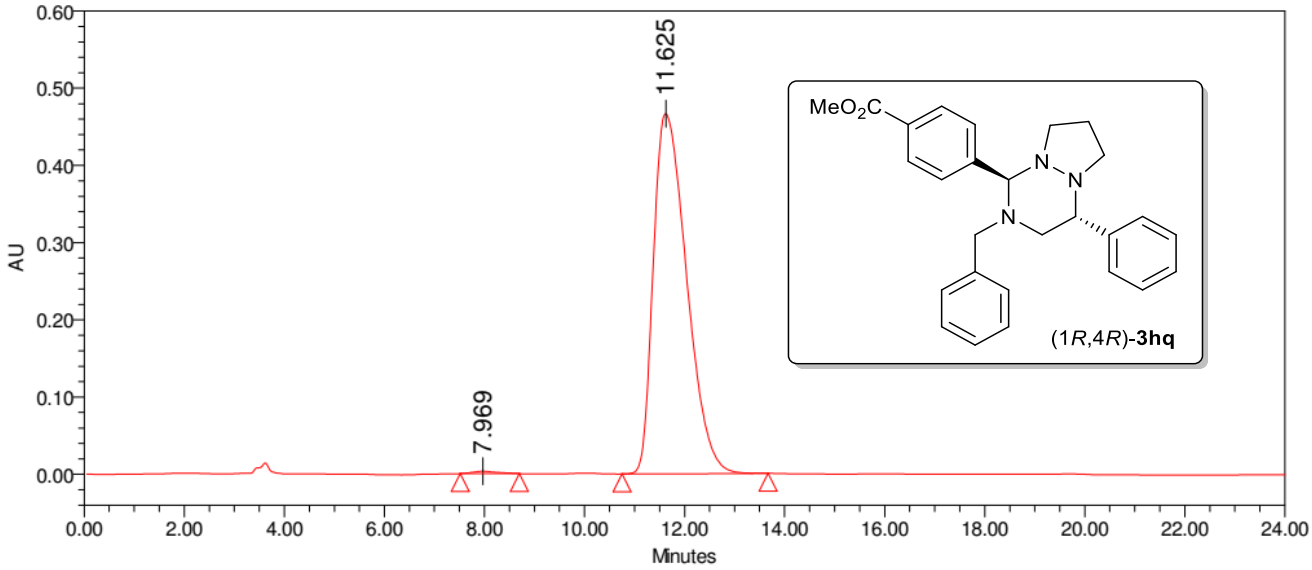
Peak Results

	RT	% Area
1	8.520	1.49
2	12.667	98.51



Peak Results

	RT	% Area
1	7.672	50.89
2	11.153	49.11



Peak Results

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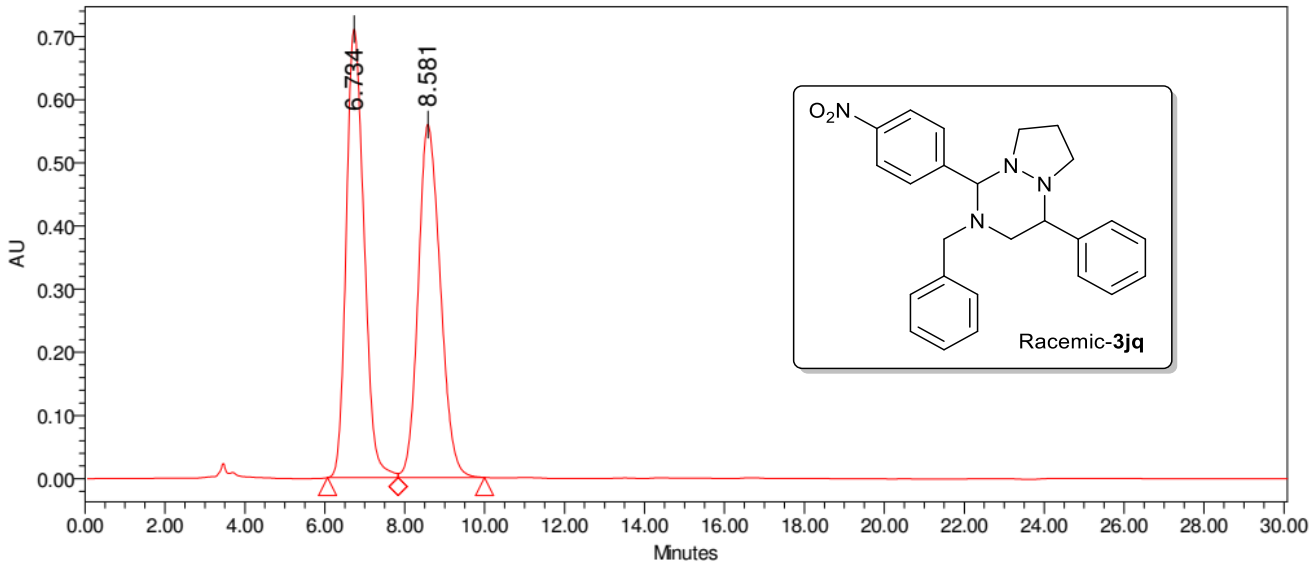
1	7.969	0.48
2	11.625	99.52



Peak Results

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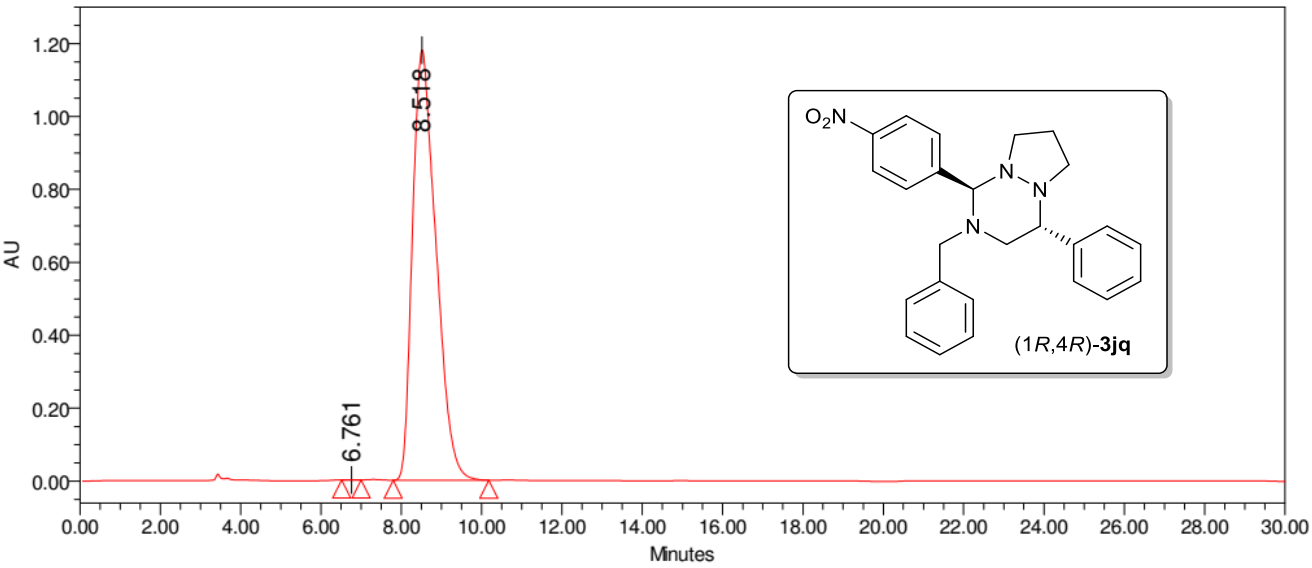
1	6.734	50.57
2	8.581	49.43



Peak Results

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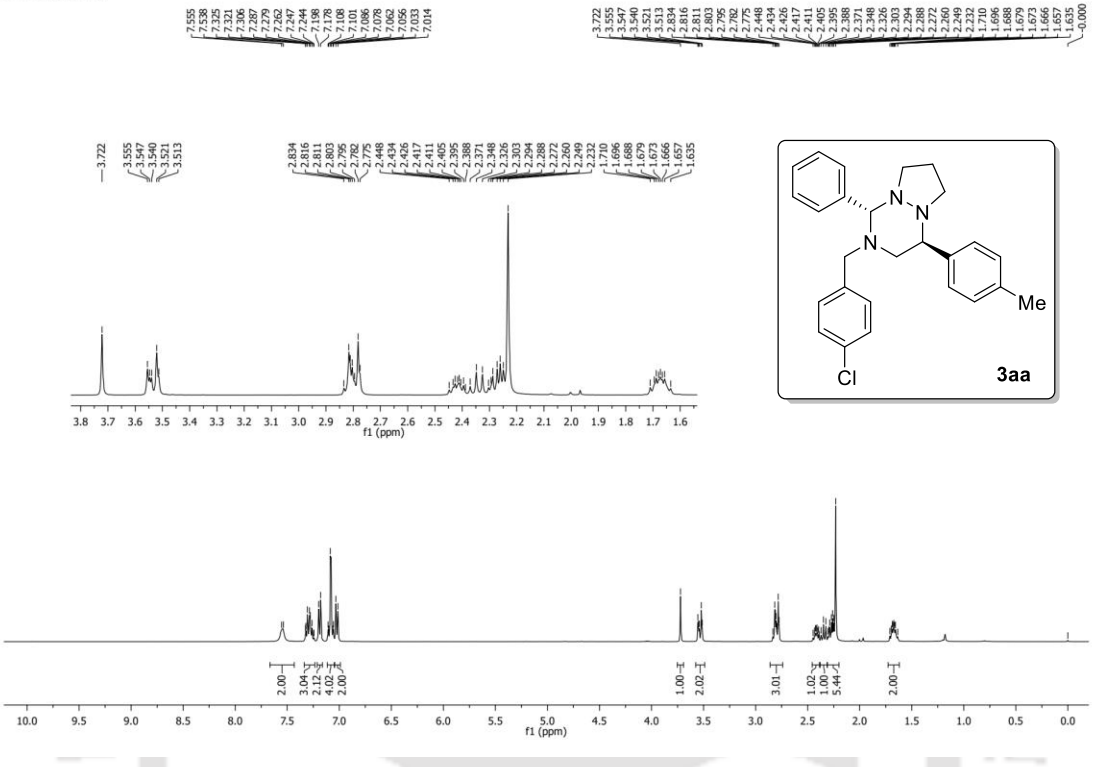
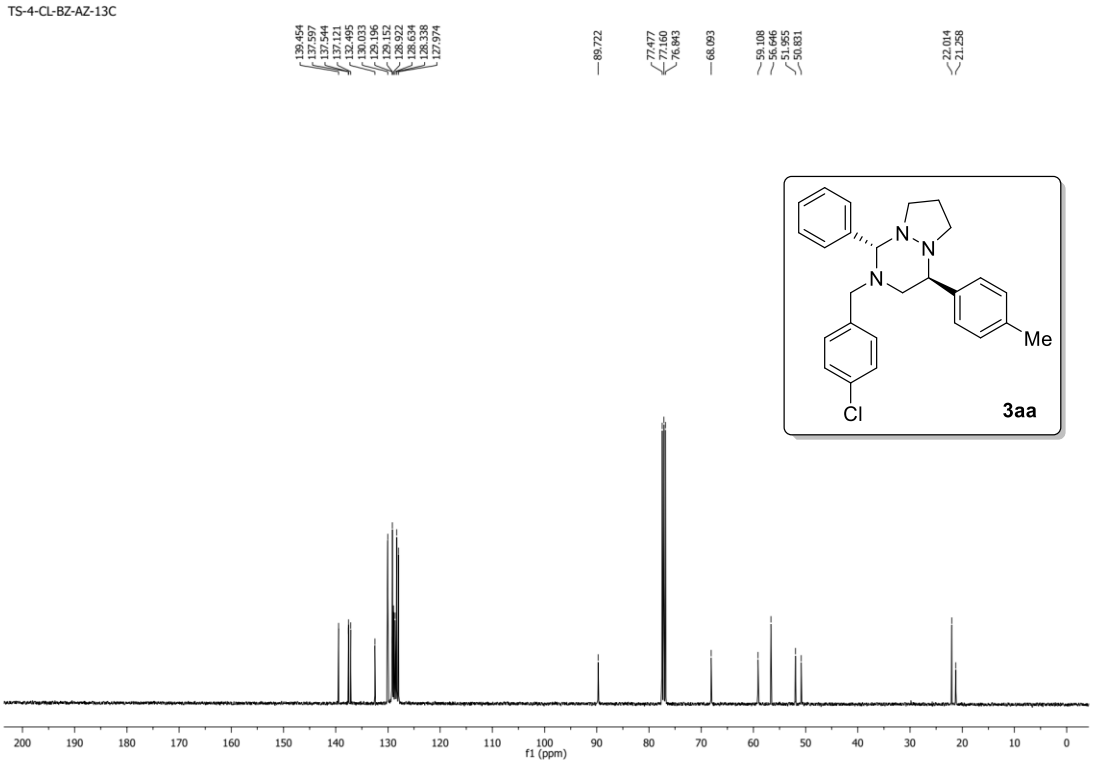
1	6.761	0.01
2	8.518	99.99

4.7 Selected NMR Spectra

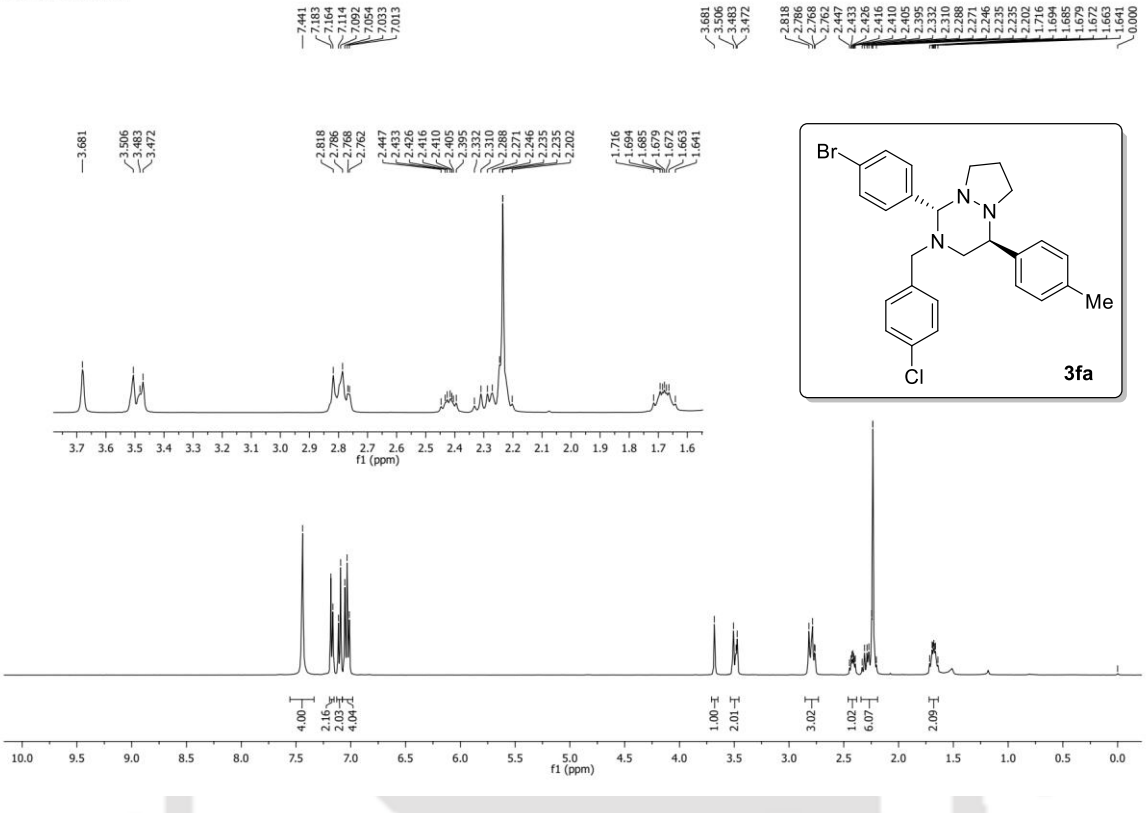
TS-4-CL-BZ-AZ-1H



TS-4-CL-BZ-AZ-13C



TS-4-BR-DIAZ-AZ-1H



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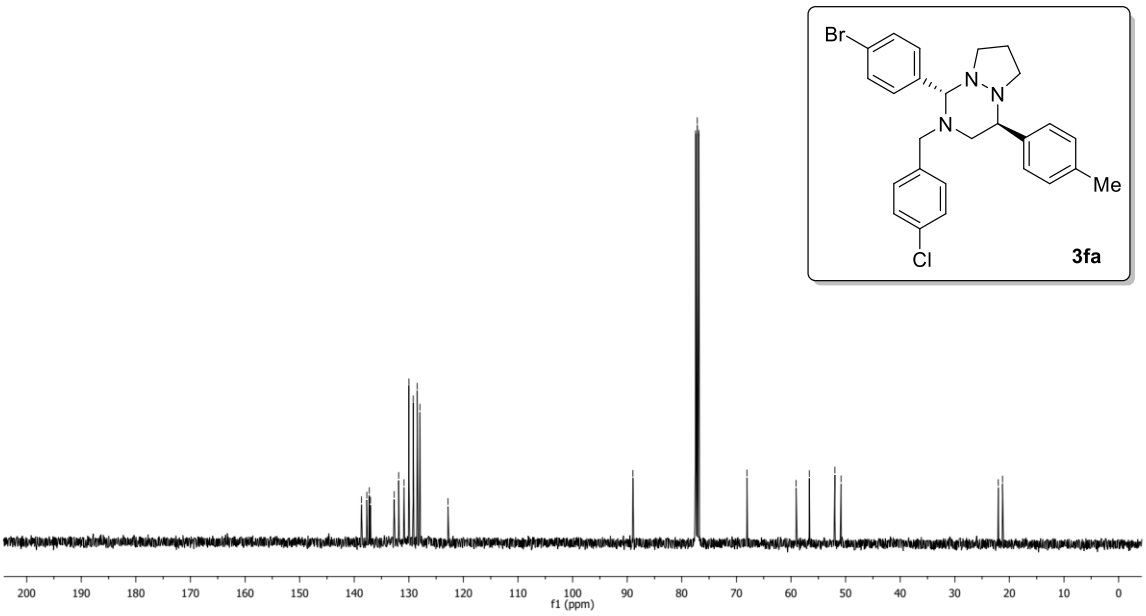
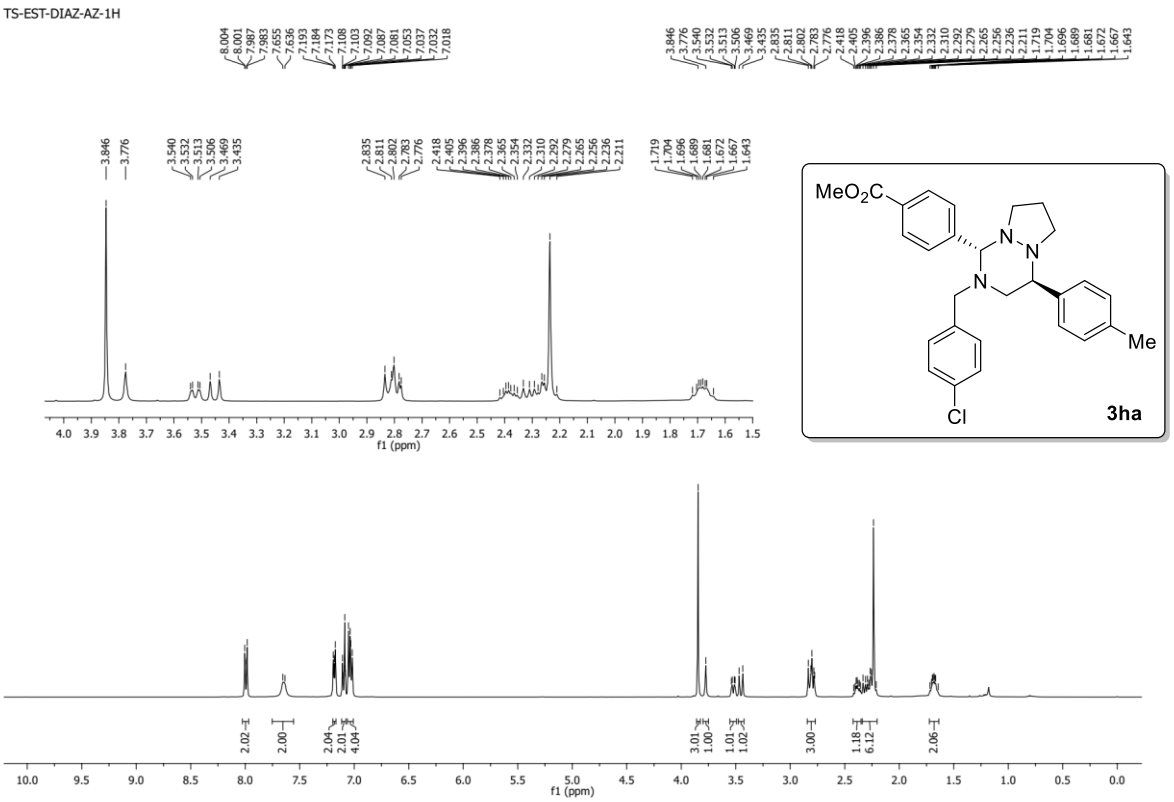


TS-EST-DIAZ-AZ-1H



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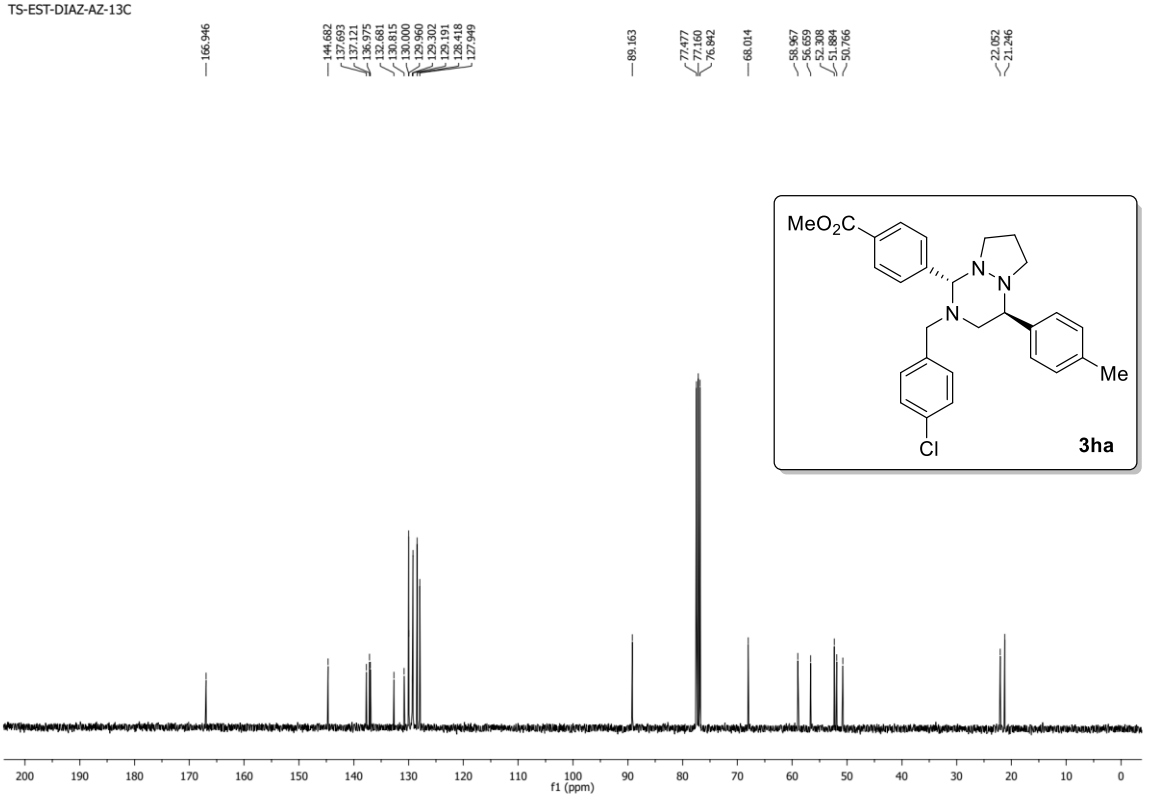


Conclusions

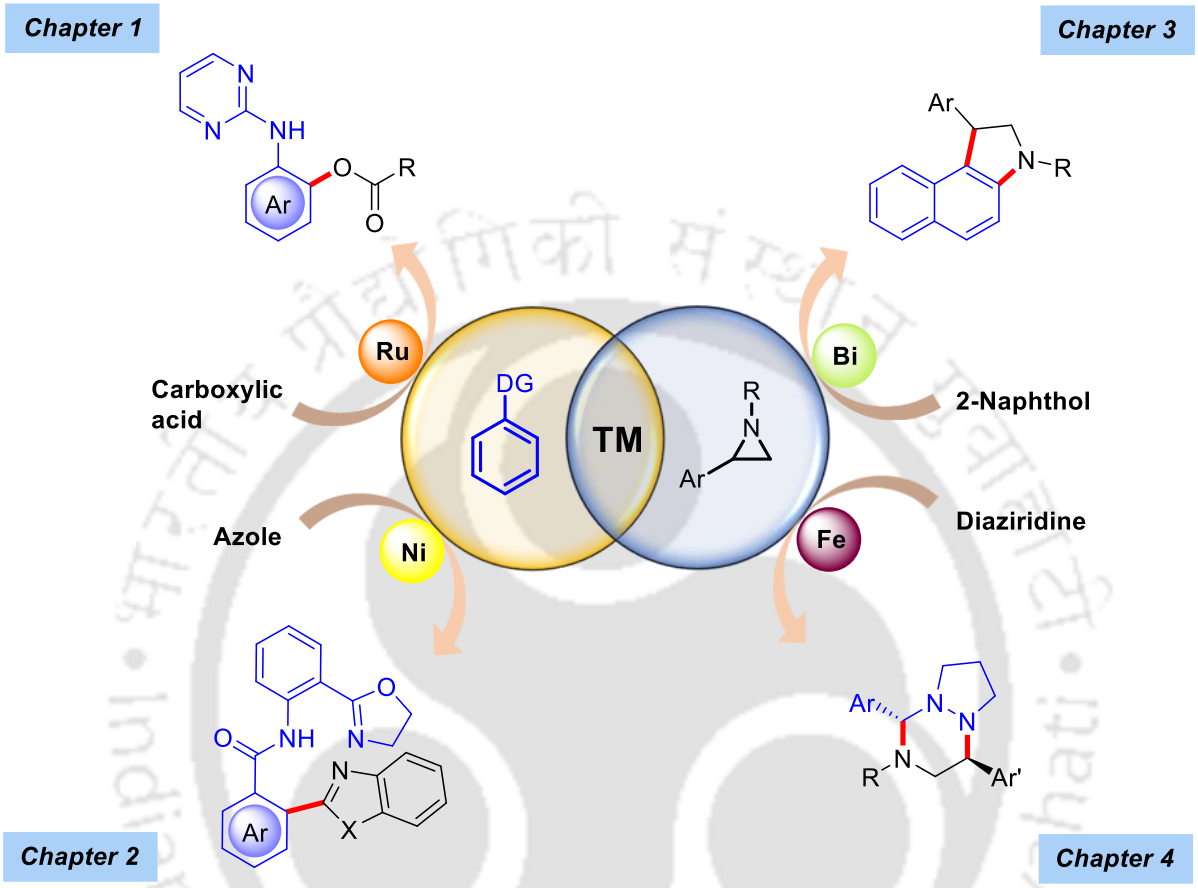
In chapter 1, we have presented a Ru(II)-catalyzed *ortho*-selective C-H acyloxylation of *N*-aryl-2-pyrimidines with carboxylic acids as the acyl source utilizing 2-pyrimidine as a directing group auxiliary. The reaction of a broad range of aryl, alkyl, heteroaryl and *α,β*-unsaturated carboxylic acids having electron donating and electron withdrawing groups has been accomplished with good to high yields.

In chapter 2, a Ni(II)-catalyzed regioselective dehydrogenative $C(sp^2)$-H/$C(sp^2)$-H cross-coupling of aromatic amides with azoles was developed using a removable oxazoline-based directing group to afford hetero-biaryl compounds under aerobic condition. This method provides a straightforward route for directly installing privileged heterocyclic scaffolds, such as, benzoxazole, benzothiazole, 5-aryloxazole and xanthine-derived drugs that will be useful in medicinal sciences.

In chapter 3, we have demonstrated an efficient route to construct functionalized benzoindolines *via* Bi(III)-catalyzed tandem nucleophilic ring opening of aziridines with 2-naphthols followed by intramolecular dehydrative cyclization. The protocol was extended to the one-pot preparation of benzoindoles in the presence of DDQ as the oxidant. The use of simple substrates, broad substrate scope and functional group diversity are the important practical features.

In chapter 4, an effecient Fe(III)-catalyzed (3+3)-annulation of bicyclic diaziridines with aziridines was described that enables the stereospecific synthesis of [1,2,4]-triazines in high yields at room temperature. The scope was investigated with a wide variety of substrates having diverse substitution patterns. The elegant features of our findings include the construction of enantioenriched [1,2,4]-triazine derivatives with high optical purities, mechanistic insights and post-synthetic transformations.

Thesis Overview



List of Publications

1 Ruthenium(II)-Catalyzed Positional Selective C–H Oxygenation of *N*-Aryl-2-pyrimidines **Sarkar, T**.; Pradhan, S.; Punniyamurthy, T. *J. Org. Chem*. **2018**, *83*, 6444.

2 BINOL Accelerated Ru(II)-Catalyzed Regioselective C-H Functionalization of Arenes with Disulfides and Diselenides, Bag, R.; **Sarkar, T**.; Kumar, S. V.; Talukdar, K.; Punniyamurthy, T. *J. Chem. Sci*. **2019**, *131*, 115.

3 Expedient Iron-Catalyzed Stereospecific Synthesis of Triazines *via* Cycloaddition of Aziridines with Diaziridines, **Sarkar**, **T**.; Talukdar, K.; Roy, S.; Punniyamurthy, T. *Chem. Commun*. **2020**, *56*, 3381.

4 Stereospecific Oxidative Annulative Coupling of Indolines with Aziridines, Karjee, P.; **Sarkar, T**.; Kar, S.; Punniyamurthy, T. *J. Org. Chem*. **2020**, *85*, 8261.

5 Recent Advances in Stereoselective Ring-Expansions of Spirocyclopropanes: Access to the Spirocyclic Compounds, **Sarkar, T**.; Das, B. K.; Talukdar, K.; Shah, T. A.; Punniyamurthy, T. *ACS Omega*. **2020**, *5*, 26316.

6 Pd-Catalyzed sp^3 C–H Alkoxycarbonylation of 8-Methylquinolines using $Mo(CO)_6$ as a CO Surrogate, Talukdar, K.; **Sarkar**, **T**.; Roy, S.; Punniyamurthy, T. *Chem. Commun*. **2021**, *57*, 3359.

7 The Transition-Metal-Catalyzed Stereoselective Ring-Expansion of Vinylaziridines and Vinyloxiranes, **Sarkar**, **T**.; Talukdar, K.; Das, B. K.; Shah, T. A.; Debnath, B.; Punniyamurthy, T. *Org. Biomol. Chem*. **2021**, *19*, 3776.

8 Transition-Metal-Catalyzed Directing Group Assisted (Hetero)Aryl C-H Functionalization: Construction of C-C/C-Heteroatom Bonds, **Sarkar**, **T**.; Shah, T. A.; Maharana, P. K.; Talukdar, K.; Das, B. K.; Punniyamurthy, T. *Chem. Rec.* **2021**, DOI: 10.1002/tcr.202100143.

9 Copper-Catalysed sp^3 C-H Bond Functionalization, Karjee, P.; **Sarkar**, **T**.; Talukdar, K.; Shah, T. A.; Das, B. K.; Punniyamurthy, T. Wiley-VCH, **2021**.

10 Pd-Catalyzed Bidentate Auxiliary Assisted Remote C(sp^3)–H Functionalization, Talukdar, K.; Shah, T. A.; **Sarkar**, **T**.; Roy, S.; Maharana, P. K.; Punniyamurthy, T. *Chem. Commun*. **2021**, *57*, 13221.

11 Expedient Ni-Catalyzed C–H/C–H Cross-Dehydrogenative Coupling of Aryl Amides with Azoles, **Sarkar**, **T.;** Maharana, P. K.; Roy, S.; Punniyamurthy, T. *Chem. Commun*. **2022**, *58*, 5980.

12 Bi-Catalyzed 1,2-Reactivity of Spirocyclopropyl Oxindoles with Dithianediol: Access to Spiroheterocycles, Kar, S.; **Sarkar**, **T.;** Maharana, P. K.; Guha, A. K.; Punniyamurthy, T. *Org. Lett*. **2022**, DOI:10.1021/acs.orglett.2c01928.

13 Dual Metallaphotoredox Catalyzed Directed C(sp^2)-H Functionalization: Access to C-C/C-Heteroatom Bonds, **Sarkar**, **T.;** Shah, T. A.; Maharana, P. K.; Debnath, B.; Punniyamurthy, T. *Eur. J. Org. Chem*. **2022**, DOI:10.1039/d2cc01926d.

14 Transition-Metal-Catalyzed C-H Functionalization of Benzofused Azoles with Two or More Heteroatoms in Transition-Metal-Catalyzed C-H Functionalization of Heterocycles, **Sarkar**, **T.;** Kar, S.; Maharana, P. K.; Shah, T. A.; Punniyamurthy, T. Wiley-VCH, **2022**.

Conferences

Oral Presentation

1. "Iron-Catalyzed [3+3]-Cycloaddition of Aziridines with Diaziridines: Stereospecific Synthesis of Triazines" **Sarkar**, **T**.; Punniyamurthy, T. *FOMC*, MNIT Jaipur, Rajasthan, January 20-22, 2021.

Poster Presentations

2. "Bismuth-Catalyzed Annulation of Aziridines with 2-Naphthols for the Synthesis of Functionalized Benzoindolines and Benzoindoles" **Sarkar**, **T**.; Punniyamurthy, T. *ICCHD*, Heritage Institute of Technology, Kolkata, January 8-10, 2018.
3. "Ruthenium-Catalyzed Positional Selective C-H Oxygenation of Aniline Derivatives Using Removable Pyrimidine Auxilliary" **Sarkar**, **T**.; Pradhan, S.; Punniyamurthy, T. *FICS*, IIT Guwahati, Assam, December 6-8, 2018.
4. "Ruthenium-Catalyzed Site Selective C-H Oxygenation of Aniline Derivatives Using Removable Pyrimidine Auxilliary" **Sarkar**, **T**.; Pradhan, S.; Punniyamurthy, T. *Research Conclave*, IIT Guwahati, Assam, March 14-17, 2019.
5. "Ruthenium-Catalyzed Positional Selective C-H Oxygenation of Aniline Derivatives Using Removable Pyrimidine Auxilliary" **Sarkar**, **T**.; Pradhan, S.; Punniyamurthy, T. *XV J-NOST*, University of Delhi, Delhi, October 18-21, 2019.
6. "Expedient Iron-Catalyzed Stereospecific Synthesis of Triazines via [3+3]-Cycloaddition of Aziridines with Diaziridines" **Sarkar**, **T**.; Punniyamurthy, T. *PFEOS*, Tezpur University, Assam, January 7-8, 2021.
7. "Expedient Iron-Catalyzed Stereospecific (3+3)-Cycloaddition of Aziridines with Diaziridines" **Sarkar**, **T**.; Talukdar, K.; Roy, S.; Punniyamurthy, T. *CRSI NSC-28*, IIT Guwahati, Assam, March 25-27, 2022.