Transition Metal Catalyzed Synthesis of Aza-fused Heterocycles and Hydroalkylation of Aryl-Substituted *N*-Heterocycles

THESIS

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by

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Under the supervision of

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Dedicated to

My Beloved Family

BIRLA INSTITUTE OF TECHNOLOGY AND SCIENCE,
PILANI (RAJASTHAN)

CERTIFICATE

This is to certify that the thesis titled "**Transition Metal Catalyzed Synthesis of Aza-fused Heterocycles and Hydroalkylation of Aryl-Substituted *N*-Heterocycles**" submitted by **Nipate Dhananjay Shrinivas** ID No **2019PHXF0014P** for the award of Ph.D. of the Institute embodies original work done by him under my supervision.

Signature of the Supervisor:

Name in capital letters: DR. ANIL KUMAR

Designation: Professor

Date:

Acknowledgment

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ABSTRACT

Heterocyclic compounds are pivotal in diverse scientific domains, including medicine, pharmaceuticals, and material chemistry. Transition-metal catalyzed C-H functionalization and oxidative annulation reactions play important roles in the synthesis of heterocyclic motifs in synthetic organic chemistry. The thesis, "**Transition Metal Catalyzed Synthesis of Aza-fused Heterocycles and Hydroalkylation of Aryl-Substituted *N*-Heterocycles,**" deals with the synthesis and C-H functionalization of heterocyclic compounds using transition-metal catalysts. The thesis is divided into five chapters.

The first chapter of the thesis demonstrates an Rh(III)-catalyzed [4+2] annulation of 2-aryl quinoxalines and 2-aryl-2*H*-indazoles with allyl alcohols for the synthesis of functionalized benzo[*a*]phenazines and indazolo[2,3-*a*]quinolines in moderate to good yields. The developed protocol features a broad substrate scope, excellent functional group tolerance, and scaled-up synthesis capability, thus providing easy access to medicinally valuable fused polyheterocyclic compounds. A tentative mechanism of annulation reaction has been proposed based on a preliminary mechanistic investigation.

The second chapter of the thesis demonstrates a Copper(II)-catalyzed cascade synthesis of 1*H*-pyrrolo[3,4-*b*]quinoline-1,3(2*H*)-diones has been accomplished using easily accessible *ortho*-amino carbonyl compounds and maleimides. This one-pot cascade approach contains a copper-catalyzed aza-Michael addition, subsequent condensation, and oxidation steps to produce the desired products. The developed protocol shows a wide range of substrate scope with high functional group tolerance yielded the desired products ranging from moderate to good (44−88%). A notable feature of the developed methods is that it can afford biologically active pyrrolo[3,4-b]quinolinediones in a single synthesis step from easily accessible starting materials.

The third chapter of the thesis describes a Ru(II)-catalyzed direct C-H/C-H annulation of 2-phenyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one, imidazopyridines and indazoles with vinylene carbonate is described. This one-pot cascade strategy provided the diverse substituted 7*H*-benzo[*h*]pyrido[2,1-*b*]quinazolin-7-one, naphtho[1',2':4,5]imidazo[1,2-*a*]pyridine, and indazolo[2,3-*a*]quinoline derivatives with moderate to excellent yields. The developed protocol exhibited a broad substrate scope with good functional group tolerance and acid/base-free

conditions. Based on a preliminary mechanistic investigation, a tentative mechanism of Ru(II)-catalyzed [4 + 2] annulation reaction has been proposed.

The fourth chapter of the thesis describes the *ortho*-functionalization of 2-aryl heterocycles. This chapter is divided into two parts: **Part A** describes a condition-based switchable regioselective hydroalkylation of 2-arylindoles with maleimides. The reaction in the presence of a Ru(II)-catalyst resulted in hydroalkylation at the *ortho* position of the C2-aryl ring via C–H activation, whereas the reaction in the absence of the catalyst in TFE resulted in C3-hydroalkylation. Various functional groups, both on the indole ring and on the 2-phenyl ring, were tolerated, and a wide range of hydroalkylated products were obtained in moderate to high (37–88%) yields**. Part B**, a regioselective manganese-catalyzed *ortho*-hydroalkylation of aryl-substituted *N*-heteroaromatic compounds with a range of maleimides, is described. The developed C–H bond functionalization protocol allowed the introduction of succinimide motif at the *ortho*-position of the aryl ring of N-heteroaromatic compounds, such as 2-arylimidazo[1,2-*a*]pyridines, 2-arylindazoles, 2-phenylpyridine, 2-phenylpyrimidine, 2-phenylimidazo[1,2-*a*]pyrimidine, 2-phenylimidazo[2,1-*b*]thiazole, 2-phenylbenzo[*d*]imidazo[2,1-*b*]thiazole, 1-phenylindazole and 1-phenylpyrazole to produce 3-(2-(*N*-heteroaryl)aryl)-pyrrolidine-2,5-diones in good yields. The protocol exhibited broad substrate scope, good functional group tolerance, and excellent regioselectivity under mild and additive-free reaction conditions.

Finally, in **the fifth chapter** of the thesis, a summary of the thesis is presented along with the future scope of the research work.

TABLE OF CONTENTS

Appendices

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVATIONS

Abbreviation	Description
AcOH	Acetic acid
acac	Acetylacetonate
ACN	Acetonitrile
Ar	Aryl
Aq	Aqueous
AgOAc	Silver acetate
AdCOOH	1-Adamantane carboxylic acid
atm	Atmosphere
BHT	Butylated hydroxy toluene
Bn	Benzyl
t-BuOK	Potassium *tert*-butoxide
^{13}C	Carbon-13
$CDCl_3$	Deuterated chloroform
Cp*	1,2,3,4,5-Pentamethylcyclopenta-1,3-diene
p-Cymene	1-Methyl-4-(propan-2-yl)benzene
$Cu(OAc)_2$	Cupric acetate
Calc.	Calculated
CCDC	Cambridge crystallographic data center
d	Doublet
dd	Doublet of doublet

DCB	1,4-Dichlorobenzene
DCE	1,2-Dichloroethane
DCM	Dichloromethane
DG	Directing group
DMA	Dimethylacetamide
DME	Dimethoxyethane
DMF	*N, N*-Dimethylformamide
DMSO-d_6	Deuterated dimethylsulfoxide
DMSO	Dimethylsulfoxide
ESI-MS	Electron spray ionization-mass spectrometry
Et_2O	Diethyl ether
EtOAc	Ethyl acetate
EtOH	Ethanol
EWG	Electron withdrawing group
EDG	Electron donating group
equiv.	Equivalent
FID	Free induction decay
FT-IR	Fourier transform infrared
g	Gram
h	Hours
HFIP	Hexafluoroisopropanol
HRMS	High resolution mass spectrometry

Hz	Hertz
^{i}Pr	Isopropyl
IBD	Iodobenzene diacetate
J	Coupling constant
KOAc	Potassium acetate
KIE	Kinetic isotopic effect
k_H	Protonated rate constant
k_D	Deuterated rate constant
Lit.	Literature
mp	Melting point
m	Meta
m	Multiplet
mL	Millilitre
mg	Milligram
MHz	Megahertz
min	Minutes
mmol	Millimole
mol %	Mole percent
MeOH	Methanol
NaOAc	Sodium acetate
NMR	Nuclear magnetic resonance
Nu	Nucleophile

o	Ortho
ORTEP	Oak ridge thermal ellipsoid plot
p	Para
Phen	1,10-Phenanthroline
PIDA	Phenyl iodonium diacetate
PivOH	Pivalic acid
ppm	Parts per million
Q-TOF	Quadrupole time of flight
rt	Room temperature
s	Singlet
t	Triplet
td	Triplet of doublets
TFA	Trifluoroacetic acid
TEMPO	(2,2,6,6-Tetramethylpiperidin-1-yl)oxyl
TFE	Trifluoroethanol
TBHP	*tert*-Butyl hydroperoxide
THF	Tetrahydrofuran
TLC	Thin layer chromatography
p-TSA or *p*-TsOH	*p*-Toluenesulfonic acid
UV	Ultraviolet
XRD	X-Ray diffraction
$Zn(OAc)_2$	Zinc acetate

Chapter 1

Rh(III)-Catalyzed Oxidative [4+2] Annulation of 2-Arylquinoxalines and 2-Aryl-2*H*-indazoles with Allyl Alcohols: Easy Access to Benzo[*a*]phenazines and Indazolo[2,3-*a*]quinolines

Chapter 1

1.1 INTRODUCTION

Heterocyclic compounds are highly desirable in chemistry due to their prevalence in natural products and extensive pharmaceutical usage.[1-3] The heterocyclic scaffolds are versatile building blocks in organic synthesis. Their distinct reactivity has been utilized to prepare pharmaceuticals, agrochemicals, dyes, polymers, and other industrially relevant molecules. For centuries, these compounds have been regarded as privileged substances, and their synthesis is often accomplished through functional group transformation.[3-5] Among them, phenazines constitute a broad class of nitrogen-containing heterocyclic compounds exhibiting a wide range of chemical structures and diverse biological properties.[6, 7] Natural phenazines are primarily sourced from microorganisms found in both marine and terrestrial environments. To date, researchers have examined over 100 natural phenazine derivatives and more than 6000 synthetic phenazine derivatives.[8-10] Phenazine derivatives exhibit variations in their chemical and physical characteristics broad on the nature and location of functional groups.[11] Notably, these derivatives have garnered considerable interest due to their redox and fluorescent properties. And used as efficient fluorescent probes for examining changes in biochemical profiles within living organisms.[12, 13] Benzo[*a*]phenazines have attracted much attention because of their important applications in the fields of medicinal chemistry and materials chemistry. Compounds containing benzo[*a*]phenazine core display various biological and pharmacological activities such as antitumor, antimalarial, antiviral, antibacterial, and antifungal.[14-16] For example, compound NC-182 is an antitumor agent, XR11576 and XR5944 are dual inhibitors of topoisomerases I and II that play an essential role in DNA replication and transcription, and 2,3-dihydro-1*H*-benzo[*a*]pyrano[2,3-*c*]phenazines are active against Trypanosoma cruzi trypomastigotes that cause Chagas disease and also act as an antimalarial agent (**Figure 1.1**).[11, 16-18]

The bacterial metabolites like phenazine-1-carboxylic acid (PCA), pyocyanin, and iodinin, which are naturally occurring phenazines, are generated by Pseudomonas microorganisms.[7, 19] In particular, PCA core is a promising lead structure for several disease areas, and its ability to efficiently intercalate DNA leads to the progression of PCA dimers into human clinical trials aimed at treating solid tumors.[20-22] This promising framework is being explored for a wide range of disease areas.

Moreover, the indazole skeleton is also an important class of *N*-containing fused heterocycles with a wide range of applications in medicinal sciences. These compounds possess interesting

properties, including anti-microbial, anti-HIV, anti-inflammatory, anti-cancer, and anti-depressant.[23-25] In medicinal chemistry, the indazole core is a "bioisostere" for heterocycle structures like an indole and benzimidazole.[24, 26, 27] As a result, this scaffold has been identified as a privileged pharmacophore with a broad range of biological functions. On the other hand, compounds with indazolo[2,3-*a*]quinoline core exhibit strong blue emission with high quantum yields. Because of their excellent optoelectronic properties, these compounds and their metal complexes have been used in organic light-emitting diode (OLED) devices (**Figure 1.1**).[28]

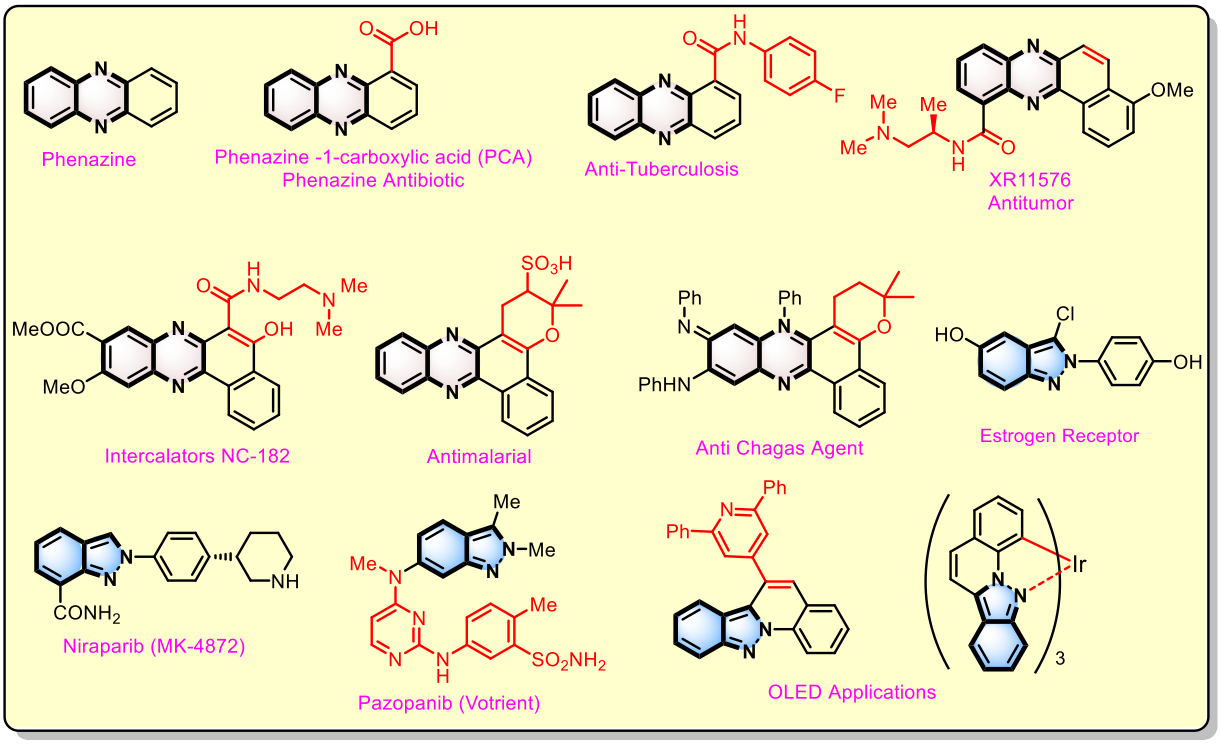


Figure 1.1: Structures of selected bioactive benzo[*a*]phenazines and naturally-occurring indazole-based drugs and fused indazolo[2,3-*a*]quinoline

1.1.1 Transition Metal-Catalyzed C-H Activation/Functionalization

The development of transition metal-catalyzed cross-coupling reactions renovated the field of organic synthesis. This technique provided a direct and efficient route to access valuable functionalized compounds from simple starting materials.[29, 30] The traditional cross-coupling reactions for the formation of C-C or C-X bonds utilized the reaction of an organometallic nucleophile with an organic electrophile in the presence of transition metal catalysts (**Figure 1.2**).[31-33 34-36] Examples of traditional cross-coupling reactions include the Suzuki-Miyaura, Stille, Kumada, Heck, Sonogashira, and Neghishi reactions.[37-39] Furthermore, the efficiency of

these methods was admired by the Noble Prize for Chemistry in 2010 when Heck, Negishi, and Suzuki's palladium-catalyzed cross-coupling processes were honored

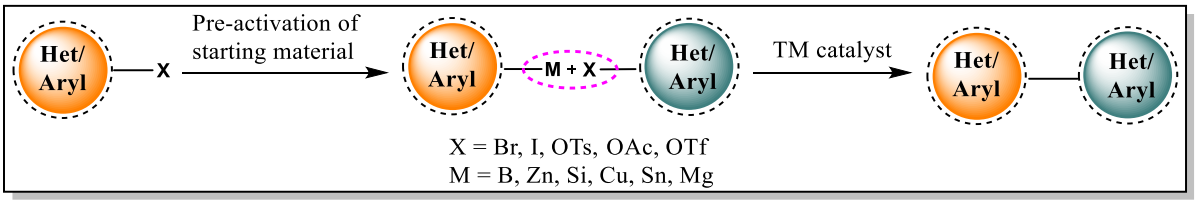


Figure 1.2: A general overview of transition metal-catalyzed traditional cross-coupling reactions

Metals such as nickel, iron, and copper are also used for cross-coupling reactions. Still, palladium shows better selectivity, robustness, stability, and tolerance for different functional groups in cross-coupling reactions.[40-42] The cross-coupling reactions had three general steps: (i) oxidative addition, (ii) transmetallation, and (iii) reductive elimination (**Figure 1.3)**. The oxidative addition of a metal catalyst into an organic halide initiates the reaction. In the next step, the coupling partner coordinates with a metal center and undergoes the transmetallation step. The active catalyst is regenerated after the reductive elimination of two-coupling species.[42] Although the cross-coupling reactions have been very successful in the generation of large number of useful compounds. These reactions often require pre-functionalization of the starting materials, adding an extra step to introduce a reactive group to the carbon atoms to be coupled. The requirement of a stoichiometric amount of organometallic reagent generates a large amount of metallic waste, shortening the utilization of these reactions to industrial scale.[43] Therefore, researchers have been investigating alternative cross-coupling methods that use direct C-H bond activation and oxidative coupling in the presence of transition metal catalysts. [44-49]

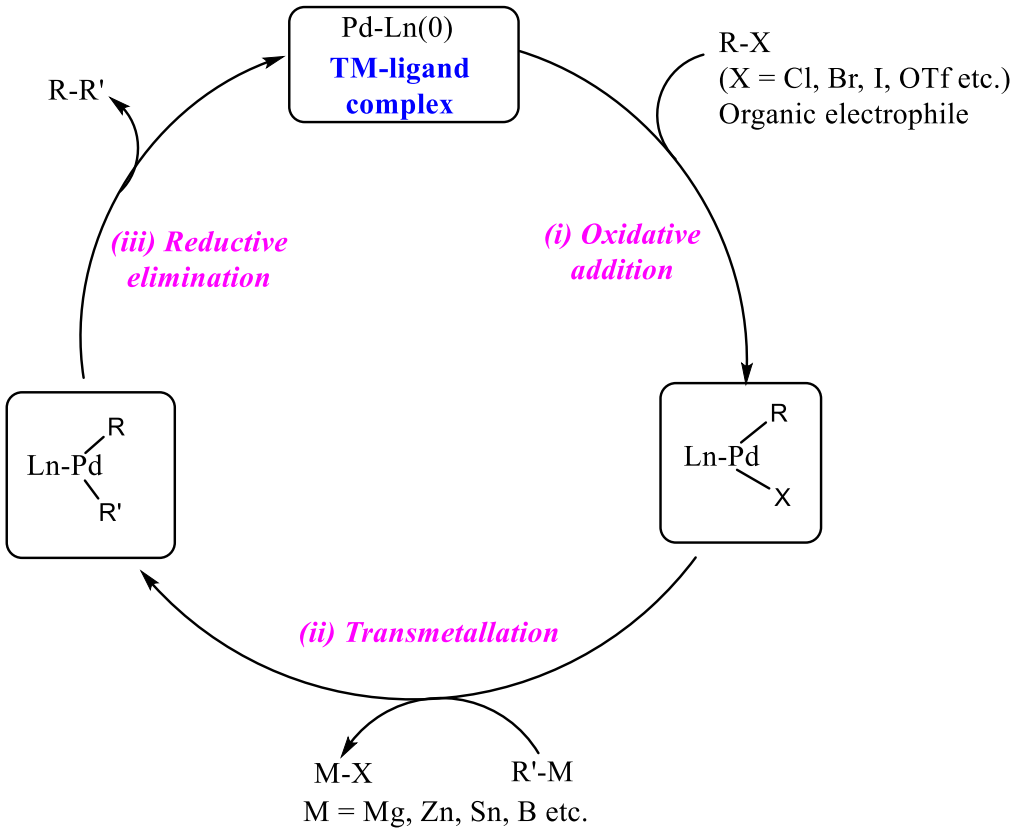


Figure 1.3: Generalized mechanistic pathway for the cross-coupling reactions

Moreover, new aspects of cross-coupling reactions in chemistry have emerged through cross-dehydrogenative couplings. These involve the activation of $C_{(sp^2)}$-H, $C_{(sp)}$-H, and $C_{(sp^3)}$-H bonds through transition metal catalysts.[50-52] This method effectively minimizes the production of undesirable by-products and leads to excellent step and atom economy. In this reaction the inert C-H bond cleaves in the presence of transitions metal catalyst to form the reactive C-M bond, which gives rise to functionalized products (**Figure 1.4)**. So, transition metal-catalyzed C-H functionalization proceeds through three main stages: C-H substrate activation, functionalization of the resulting organometallic species, and finally, regeneration of the active catalyst. Depending on the circumstances, an external oxidizing agent may be required to enable the catalytic cycle (**Figure 1.5)**.[53]

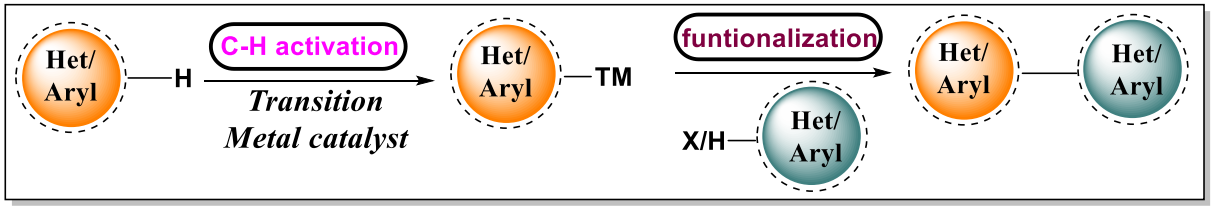


Figure 1.4: General strategy of C-H functionalization

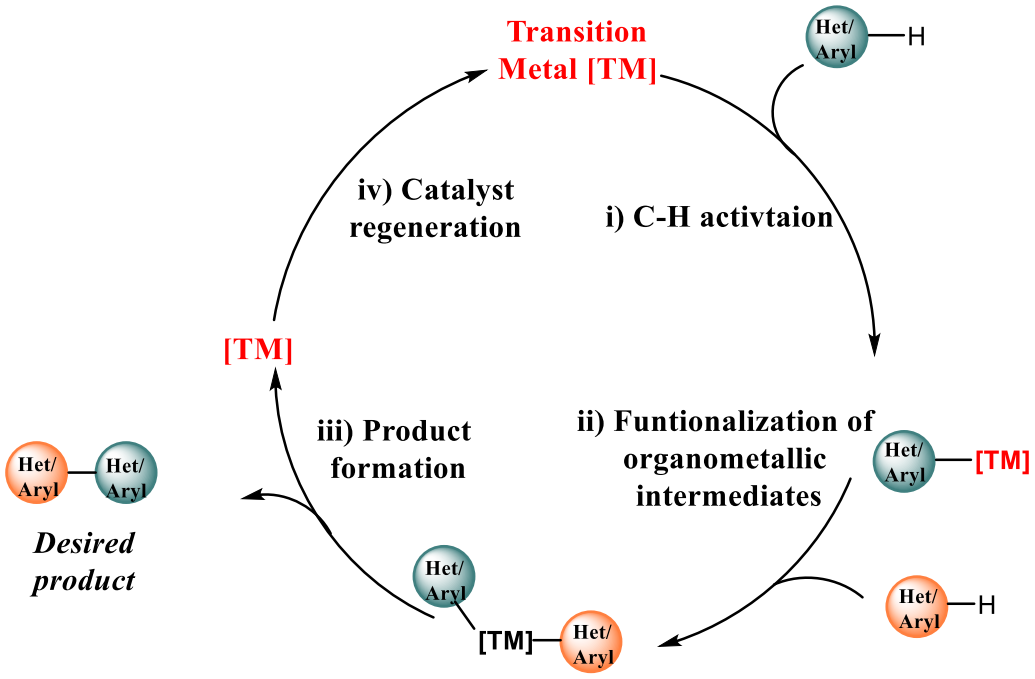


Figure 1.5: Generalized mechanistic pathway for C-H bond activation *via* transition metal catalyst

In general, transition metal-catalyzed C-H functionalization, a transformative method in organic synthesis, involves the direct conversion of C-H bonds into C-C, C-N, C-O, or C-X bonds. This versatile strategy has gained significant attention due to its efficiency and atom economy. The choice of coupling partner greatly influences the outcome of the reaction, allowing for diverse synthetic pathways. When C-H bonds are activated in the presence of other C-H bonds, elaborate skeletal rearrangements and complex molecular constructions can be achieved. Alternatively, coupling with C-X (heteroatom-containing) substrates expands the functional group compatibility, enabling the introduction of diverse functional groups. Moreover, coupling with metal-containing species (C-M) can lead to unique organometallic intermediates, facilitating subsequent transformations and enabling the synthesis of complex molecules with high

efficiency.[43, 54, 55] However, this approach faces certain drawbacks, including the necessity of preinstalling directing groups and activating typically inert C-H bonds, as well as the challenge of selectively functionalizing a specific C-H bond within a molecule. Hence, an ideal strategy for forming heteroaryl-heteroaryl carbon-carbon (C-C) bonds would involve replacing a C-X or C-M bond with a C-H bond. Due to the significance of fused heterocyclic compounds, synthetic chemists consistently try to discover more efficient routes for accessing carbon-carbon (C-C) bonds. In recent years, a particularly compelling and challenging goal in catalysis has emerged: the direct construction of C-C links from two simple carbon-hydrogen (C-H) bonds.[56] Generally termed as cross-dehydrogenative coupling (CDC), these reactions involve coupling between two nucleophilic C-H bonds (see **Figure 1.6**). To maintain electroneutrality throughout the process, these reactions necessitate an external (or internal) oxidant. This requirement arises because the evolution of H_2 gas is thermodynamically unfavorable and demands an external driving force in the form of an oxidant. Consequently, this type of reaction is also referred to as oxidative C-H/C-H coupling.[57-59]

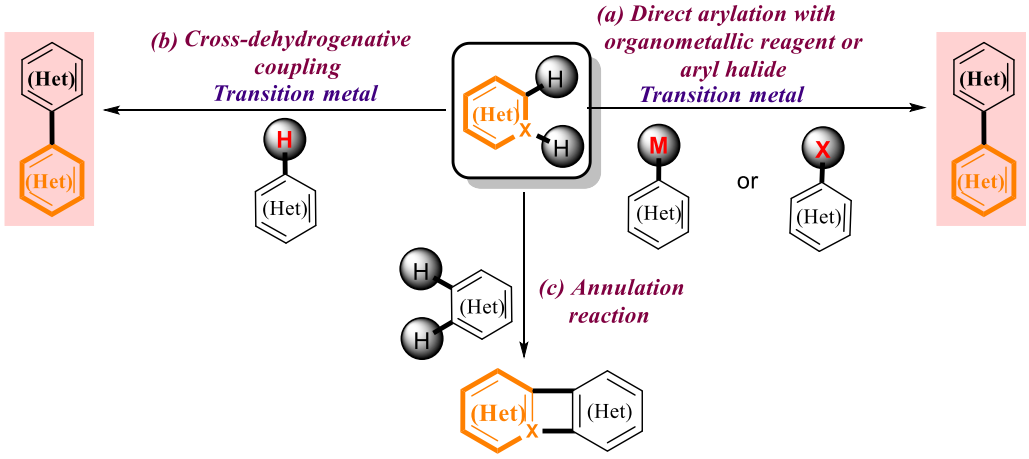


Figure 1.6: General strategy of C-H functionalization in the presence of different coupling partners

In this aspect, the annulation reaction plays the most vital role for the efficient synthesis of carbocyclic and heterocyclic molecules, enabling the construction of diverse chemical frameworks. This methodology finds extensive application in the synthesis of natural products, pharmaceutical-relevant heterocycles, and materials synthesized via metal-catalyzed C-H

activation processes. There is considerable interest in leveraging C-H functionalization, cross-dehydrogenative coupling, and annulation reactions for their synthetic potential.[42, 58, 60-65]

The progress of the metal-catalyzed annulation reactions consists of an initial formation of heterometallacyclic intermediates and, the migratory insertion of an unsaturated partner. Finally, reductive elimination occurs to access the product (**Figure 1.7**). Regenerating the transition metal-based catalysts in their active oxidation state requires the use of the equivalent number of external oxidants to re-oxidize and re-enter into the catalytic cycle. In most cases, a heteroatom in the substrate enhances both the reactivity and regioselectivity, which often enhances the metal complex to move to the reacting C-H site, and the heteroatom will become part of the final annulated ring. Thus, this C-H activation and annulation approach can enhance selectivity, reactivity, yield, good substrate scope, and a collective overall "greenness" of the process.

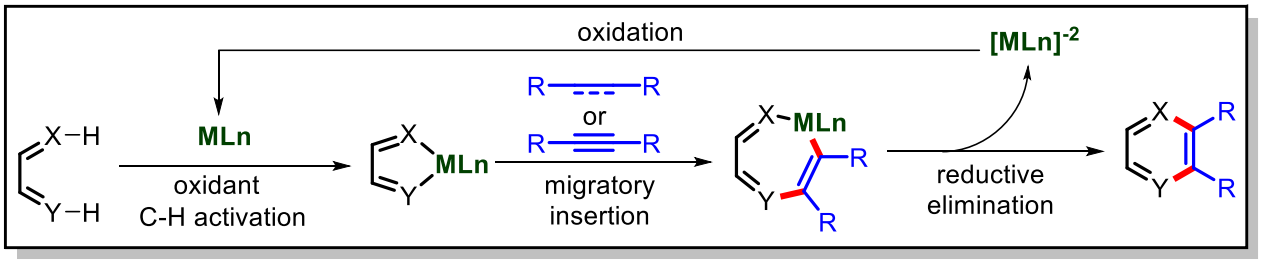


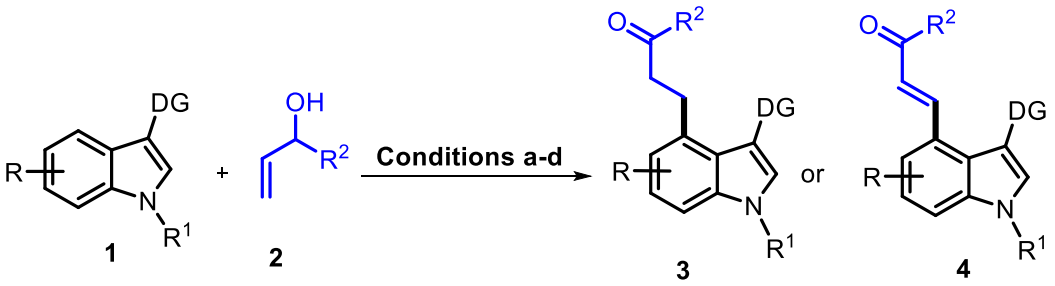
Figure 1.7: General mechanism for a metal-catalyzed annulation involving a formal C-H activation

In recent years various coupling partners such as diphenyl acetylene, styrene, acrylate, maleimide, vinylene carbonate, sulfoxonium ylide and α-diazo carbonyl compounds have been utilized for C-H functionalization reactions to synthesis of complex molecules. [66-72] Among various coupling partners, allyl alcohol has attracted considerable attention for a variety of C-H functionalization reactions. A brief overview of C-H functionalization reactions utilizing allyl alcohol as coupling partners is given below.

1.1.2 Direct C-H Alkylation/Allylation using Allyl Alcohols

In 2020 Punniyamurthy group reported Rh(III)-catalyzed switchable C-4 alkylation and alkenylation of indoles (**1**) using allyl alcohols (**2**) as substrates (**Scheme 1.1ab**).[73] This methodology relies on weak carbonyl coordination to facilitate tunable reactivity, allowing for alkylation (**3**) and alkenylation (**4**) of indoles. The method exhibited excellent tolerance to various functional groups and afforded good to excellent yield. The same year, Prabhu and Yu's

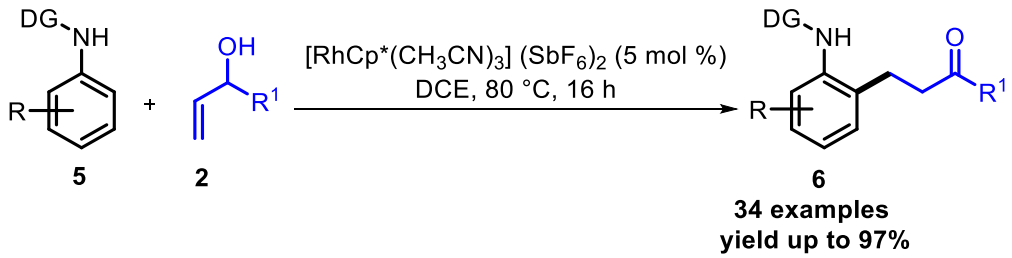
group (**Scheme 1.1cd**) independently reported the Rh(III)-catalyzed C-4 alkylation of indole (**1**) with allyl alcohols (**2**).[74, 75] The decoupled method useful for the late-stage functionalization.



No.	Reaction conditions	Examples of 3	Examples of 4	yield
a)	$[RhCp^*Cl_2]_2$ (2.5 mol %), $AgSbF_6$ (20 mol %), Ag_2CO_3 (2 equiv.), 1,4-dioxane, 100 °C, 6 h	-	25	up to 78%
b)	$[RhCp^*Cl_2]_2$ (2.5 mol %), AgOTf (20 mol %), $NaOPiv{\cdot}H_2O$ (2 equiv.), 1,4-dioxane, 120 °C, 12 h	20	-	up to 72%
c)	$[RhCp^*Cl_2]_2$ (5 mol %), $AgSbF_6$ (20 mol %), $Cu(OAc)_2{\cdot}H_2O$ (2.5 equiv.), AdCOOH (1.25 equiv.), HFIP, argon atmosphere, 55 °C, 24 h	24	-	up to 93%
d)	$[RhCp^*Cl_2]_2$ (5 mol %), $AgSbF_6$ (20 mol %), $Cu(OAc)_2$ (30 mol %), DCE, 40 °C, 48 h	27	-	up to 92%

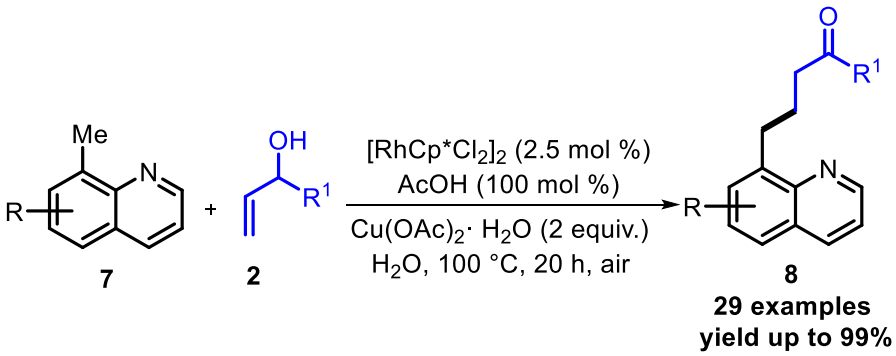
Scheme 1.1: Rh(III)-catalyzed selective C-H functionalization of indoles with allyl alcohols

Later, in 2022, Chatani and co-workers described a pyrimidine-directed Rh(III)-catalyzed C-H alkylation of aniline derivative (**5**) with allyl alcohols (**2**) as a coupling partner leading to the formation of *β*-aryl ketones (**6**) (**Scheme 1.2**).[76] In this reaction, there is no need for a metal oxidant when allyl alcohol with a methyl group at the α-hydroxy carbon. Moreover, when the methyl group is substituted with larger groups like ethyl, propyl, or phenyl, the reaction does not proceed efficiently unless Ag2CO3 is added. Mechanistic studies revealed that the regeneration step for the active catalytic species is influenced by the structure of allyl alcohols used as substrates.



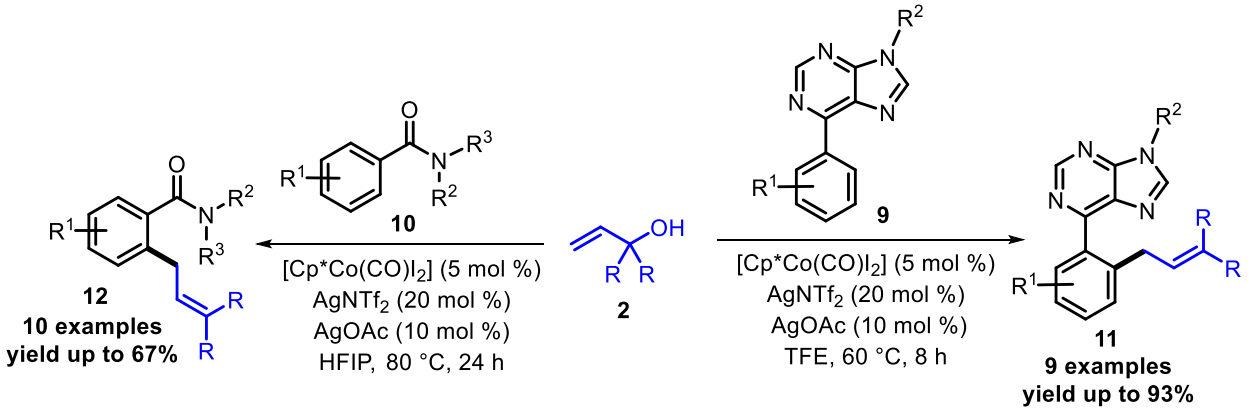
Scheme 1.2: Rh(III)-catalyzed alkylation of aniline derivatives with allyl alcohols

Li and co-workers reported the Rh(III)-catalyzed synthesis of γ-quinolinyl carbonyl compounds (**8**) through the cross-coupling reaction between the 8-methylquinolines (**7**) and various allylic alcohols (**2**) (**Scheme 1.3**).[77] These transformations have demonstrated broad applicability across diverse substrates with excellent chemoselectivity. This methodology reveals its scalability, enabling the efficient production of γ-quinolinyl carbonyl products, and these compounds show significant potential for further transformation into biologically active scaffolds.



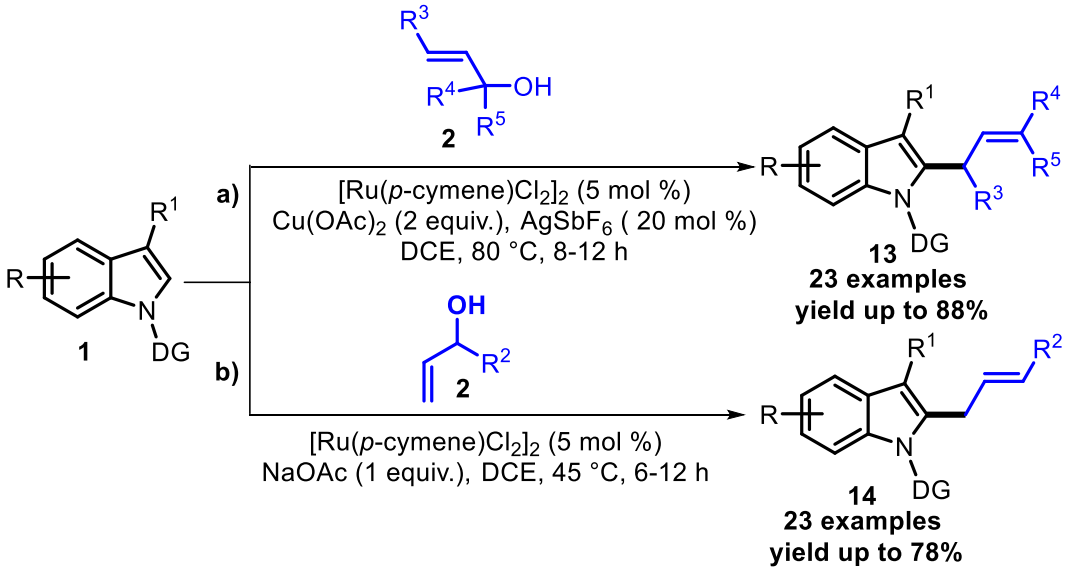
Scheme 1.3: Rh(III)-catalyzed alkylation of 8-methylquinolines derivatives with allyl alcohols

Matsunaga and team described the functionalization of 6-arylpurines (**9**) and benzamide (**10**) derivatives using allyl alcohols (**2**) as allylating agents through Cp*Co(III)-catalyzed C-H activation protocol (**Scheme 1.4**).[78] The easily accessible starting materials, compatibility of various functional groups, and mild reaction conditions are salient features of this protocol.



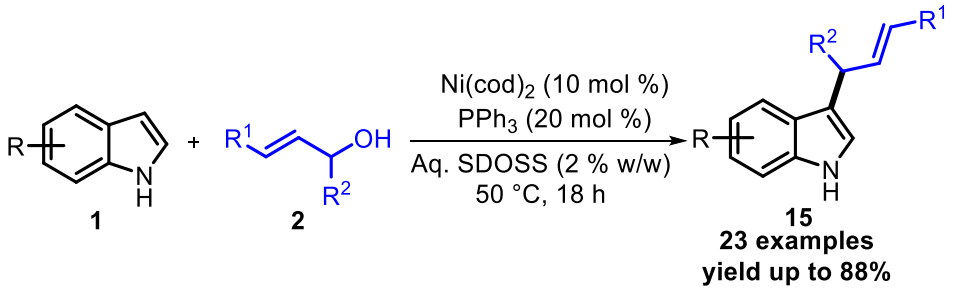
Scheme 1.4: Co(III)-catalyzed dehydrative C-H allylation of 6-arylpurines and benzamide with allyl alcohols

Kapur group developed the Ru(II)-catalyzed site-selective C-H allylation of indoles (**1**) with allyl alcohols (**2**) for the synthesis of C2-allylated indoles derivatives (**13**) (**Scheme 1.5a**).[79] In this protocol contains pyridine as removable directing groups at N-1 positions in the presence of Ru(II)-catalyst. Likewise, Ji and co-workers established a method for synthesizing C2-allylated indoles (**14**), achieving moderate to good yields along with excellent regioselectivity and stereoselectivity (**Scheme 1.5b**).[80]

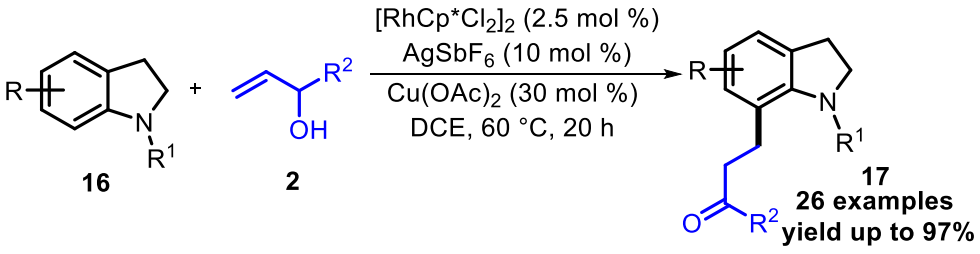


Scheme 1.5: Ru(II)-catalyzed selective C-H allylation of indolines with allyl alcohols

In 2022, Kumar *et al.* demonstrated chemoselective C3-allylation of indoles (**1**) using allyl alcohols (**2**) as a coupling partner under Ni-catalyzed conditions (**Scheme 1.6**).[81] The reaction is compatible with various indoles and allyl alcohols with excellent chemo, regio, and stereoselectivity. In this transformation, water plays a crucial role by activating allylic alcohols through hydrogen bonding. This activation leads to the stabilization of hydroxide ions, creating a solid solvation effect.



In 2015, Kim's group reported the synthesis of *β*-aryl carbonyl compound (**17**) by utilization of Rh(III)-catalyzed C-H functionalization of indolines (**16**) with allyl alcohols (**2**) (**Scheme 1.8**).[82] This protocol is also applicable for different *N*-heterocycles, such as pyrroles **Scheme 1.6:** Ni-catalyzed chemoselective allylation of indoles and carbazoles with allyl alcohols, to form the *β*-aryl carbonyl compound. Furthermore, this methodology offers the opportunity to synthesize 1,7-fused tricyclic indolinic compounds. These compounds constitute a vital structural motif that is found in biologically active molecules.



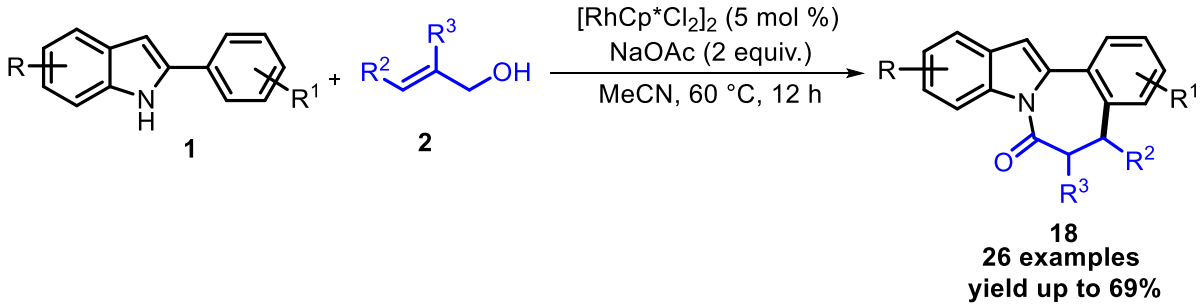
Scheme 1.8: Rh(III)-catalyzed site-selective C-H alkylation of indolines with allyl alcohols

1.1.3 Annulation Reactions using Allyl Alcohols

In recent years, the utilization of transition metal-catalyzed C-H/C-H, C-H/O-H, and C-H/N-H annulation reactions with diverse coupling partners has emerged as a potent and appealing method in organic synthesis.[83-86] This strategy, marked by high atom- and step-economy, enables

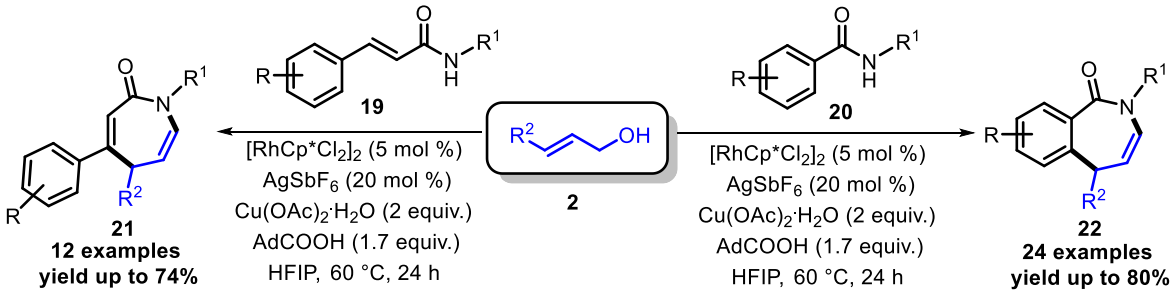
the efficient construction of diverse carbo- and heterocycles. By harnessing the inherent reactivity of C-H bonds and promoting intramolecular interactions, transition metal catalysts facilitate the formation of intricate ring structures, offering a streamlined approach to synthesizing complex organic compounds. The versatility of these annulation reactions has made them invaluable in the pursuit of sustainable and efficient synthetic routes, paving the way for the development of novel molecules with potential applications in various fields, including pharmaceuticals and materials science.[83, 84, 87-93]

Zhao group disclosed a Rh(III)-catalyzed cascade annulation of 2-arylindoles (**1**) with allyl alcohols (**2**) to access indolo[2,1-*a*]benzazepinones derivatives (**18**) with moderate to good yields (**Scheme 1.9**).[94] This method is notable for its efficiency as it requires no pre-functionalization of the substrates and forms two new bonds in a single step.



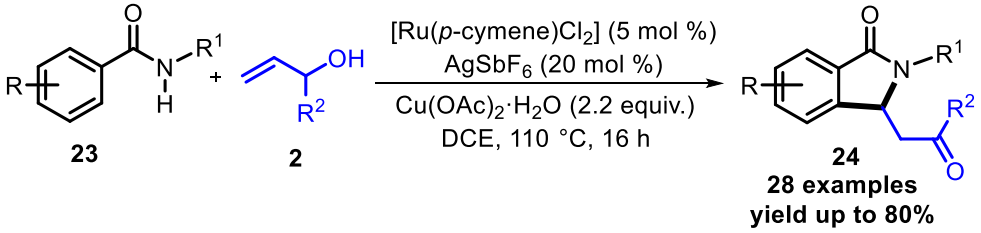
Scheme 1.9: Rh(III)-catalyzed annulation of 2-arylindoles with allyl alcohols

In 2021, Prabhu and co-workers demonstrated a Rh(III)-catalyzed oxidative [4+3] annulation strategy for the synthesis of benzazepinone (**21**) and azepinone (**22**) derivative from allyl alcohol (**1**) (**Scheme 1.10**).[95] Interestingly, catalysts played dual role in this reaction, firstly oxidizing allyl alcohol to carbonyl compounds. The *in situ*-generated carbonyl compound coordinated with the rhodacycle generated by the reaction of benzamide with $[RhCp^*Cl_2]_2$ in the presence of $AgSbF_6$. mechanistic studies revealed that $AgSbF_6$ also assisted in the cyclization step interestingly.



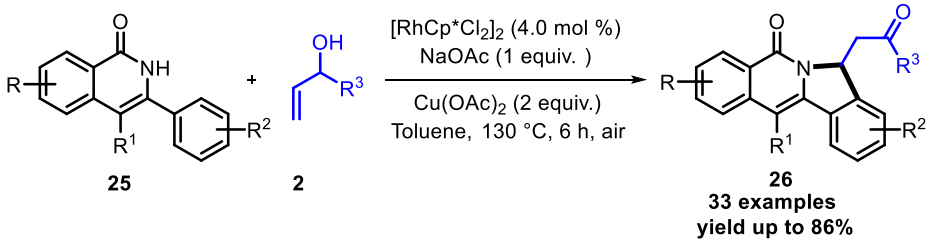
Scheme 1.10: Rh(III)-catalyzed [4+3] annulation of amide with allyl alcohols

Jeganmohan group reported the Ru(II)-catalyzed [4+1] annulative coupling between *N*-substituted aromatic amides (**23**) and allylic alcohols (**2**) for the synthesis of 3-substituted isoindolinone derivatives (**24**) (**Scheme 1.11**).[96] The experimental evidence strongly supported the proposed reaction mechanism, which involves a five-membered ruthenacycle intermediate. The notable features of the developed protocol consist of broad substrate scope, high atom economy, and wide functional group tolerance.



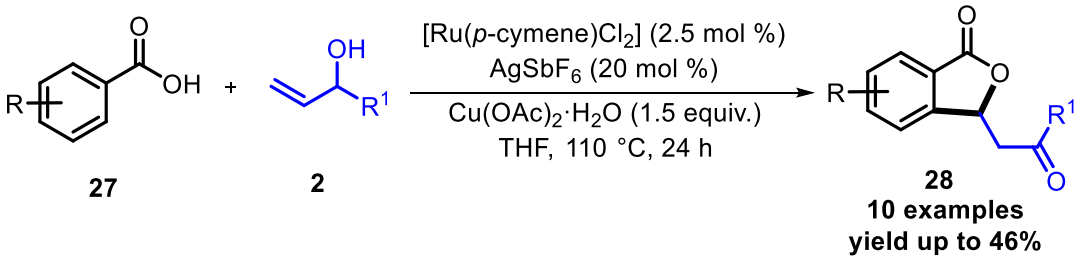
Scheme 1.11: Ru(II)-catalyzed spiro cyclization of *N*-substituted benzamides with allyl alcohols

Liu and co-workers established an Rh(III)-catalyzed [4+1] annulation of isoquinolines (**25**) with allyl alcohols (**2**), leading to the formation of isoindolo[2,1-*b*]isoquinolin-5(7*H*)-ones (**26**) (**Scheme 1.12**).[97] This methodology was efficiently applied to synthesize structurally diverse isoindolo[2,1-*b*]isoquinolin-5(7*H*)-ones with a high atom economy. It demonstrates remarkable versatility by accommodating a wide range of functional groups.



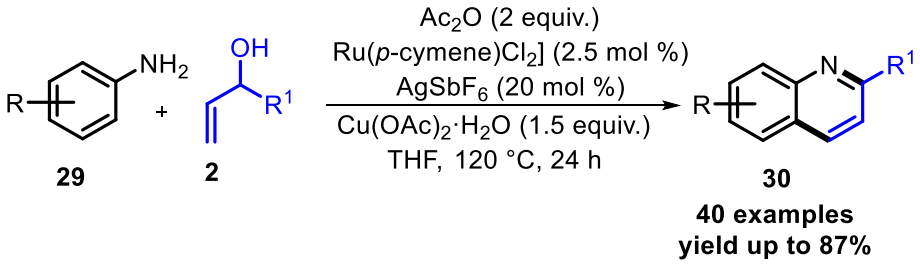
Scheme 1.12: Rh(III)-catalyzed [4+1] annulation of isoquinolines with allyl alcohols

Kapur and co-workers demonstrated the Ru(II)-catalyzed C−H functionalization of benzoic acids (**27**) with allyl alcohols (**2**) for the synthesis of annulated Phthalide derivatives (**28**) (**Scheme 1.13**).[98] The significant features exhibited protocol, broad substrate scope with the coupling partner, and excellent atom economy with high regioselectivity.



Scheme 1.13: Ru(II)-catalyzed cyclization of benzoic acids with allyl alcohols

In 2017, the Kapur group developed rapid access to substituted quinolines (**30**) *via* Ru(II) catalyzed oxidative [3+3] annulation of readily available aniline (**29**) with allyl alcohols (**2**) (**Scheme 1.14**).[99] In this methodology, a traceless directing group was used for the C−H bond functionalization, and mechanistic studies revealed that the cleavage of C(sp^2)−H was involved in the rate-limiting step. The sequential *ortho* C-H functionalization, *β*-hydride elimination, and olefin isomerization followed by condensation with the ketone functional group provided the desired product quinolines.

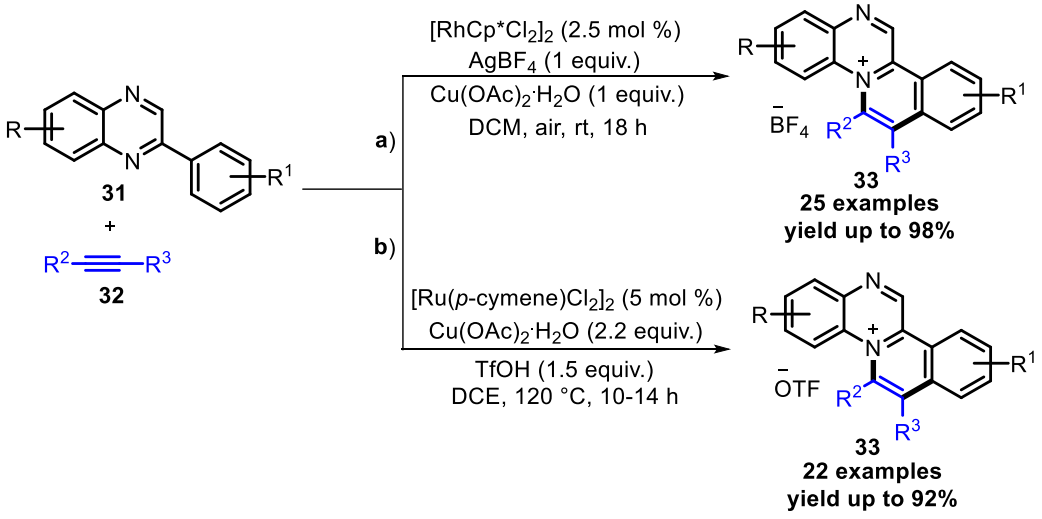


Scheme 1.14: Ru(II)-catalyzed annulation of anilines with allyl alcohols

On the other hand, the quinoxalines and 2-arylindazoles core represent a significant class of nitrogen-containing fused heterocycles with extensive applications in pharmaceutical chemistry. These compounds exhibit diverse properties, such as anti-inflammatory, antibacterial, anti-cancer, and antiviral activities. Furthermore, quinoxaline serves as a structural component in

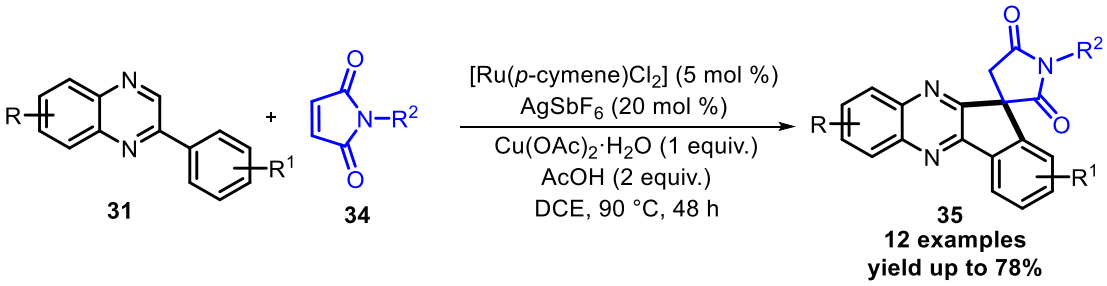
various antibiotics like levomycin, echinomycin, and actinomycin. Notably, these antibiotics are effective in inhibiting the growth of gram-positive bacteria.[100-103] Moreover, 2-arylindazole chromophores exhibit notable fluorescence characteristics, featuring large Stokes shifts, making them valuable candidates for applications as biological probes. Consequently, considerable efforts have been dedicated toward the direct C–H functionalization of 2-arylquinoxalines and 2-arylindazoles. [104-107]

There are a few reports available for the synthesis of fused heterocycles from these motifs through transition metal-catalyzed annulation reactions. In this context, in 2019, Punniyamurthy group disclosed the synthesis of variously substituted quaternary ammonium salt (**33**) *via* Rh(III)-catalyzed oxidative annulation reaction between the 2-arylquinoxaline (**31**) with 1,2-disubstituted alkynes (**32**) (**Scheme 1.15a**).[108] The developed protocol shows some significant features, such as mild reaction conditions and high functional group tolerance. Furthermore, in preliminary photophysical studies, specific structural scaffolds have the potential for use in developing organic light-emitting diodes (OLEDs). In the same year, the Patel group reported Ru(II)-catalyzed oxidative dehydrogenative coupling of 2-arylquinoxaline (**31**) with internal alkynes (**32**), leading to the formation of highly luminescent annulated quaternary ammonium salts (**33**) in good to excellent yield (**Scheme 1.15b**).[109]



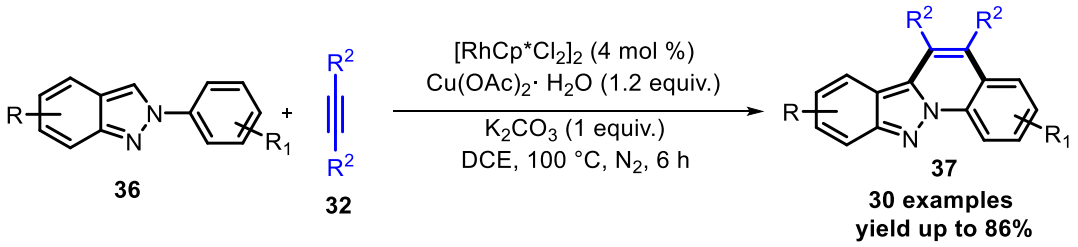
Scheme 1.15: Rh(III) and Ru(II)-catalyzed annulation 2-arylquinoxaline with alkynes for the synthesis of quaternary ammonium salts

In 2021, Hajra and co-workers demonstrated the Ru(II)-catalyzed spirocyclization of 2-arylquinoxalines (**31**) with maleimides (**34**) for the synthesis of various polyheterocycles containing spiro[indeno[1,2- *b*]quinoxaline-11,3′-pyrrolidine]-2′,5′-diones (**35**) (**Scheme 1.16**).[110] The sequential *ortho* C-H bond functionalization followed by carbon annulation resulted in the formation of diverse polyheterocyclic compounds. The notable features consist of a one-step synthesis of spiro cyclic compounds, broad substrate scope, high atom economy, and wide functional group tolerance.



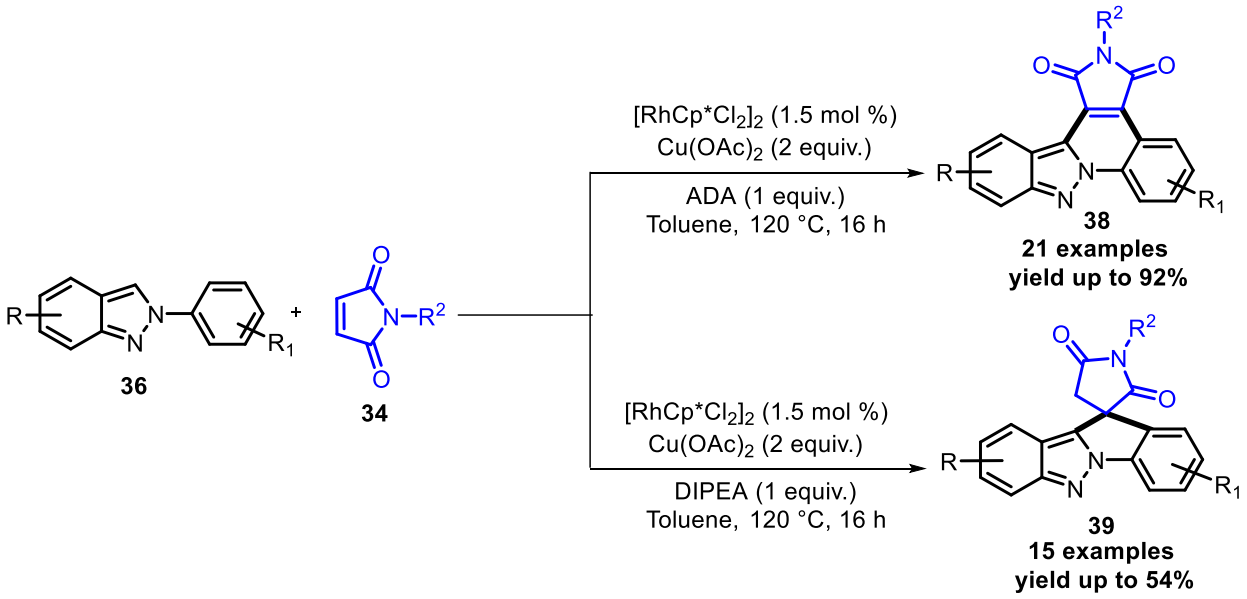
Scheme 1.16: Ru(II)-catalyzed spirocyclization of 2-arylquinoxalines with maleimide

In 2018, the Punniyamurthy group successfully developed a synthesis of indazolo[2,3-*a*]quinolines derivatives (**37**) by employing Rh(III)-catalyzed oxidative annulation of 2-aryl-2*H*-indazoles (**36**) and alkynes (**32**) using $Cu(OAc)_2 \cdot H_2O$ as the oxidant (**Scheme 1.17**).[106] The developed protocol yielded indazoloquinoline derivatives with moderate to good yields, emitting a strong blue emission with high quantum yields. The reaction pathway involved the sequential formation of a five-membered rhodacycle, alkyne insertion, rollover cyclometallation, and subsequent reductive elimination, resulting in the formation of the desired product.



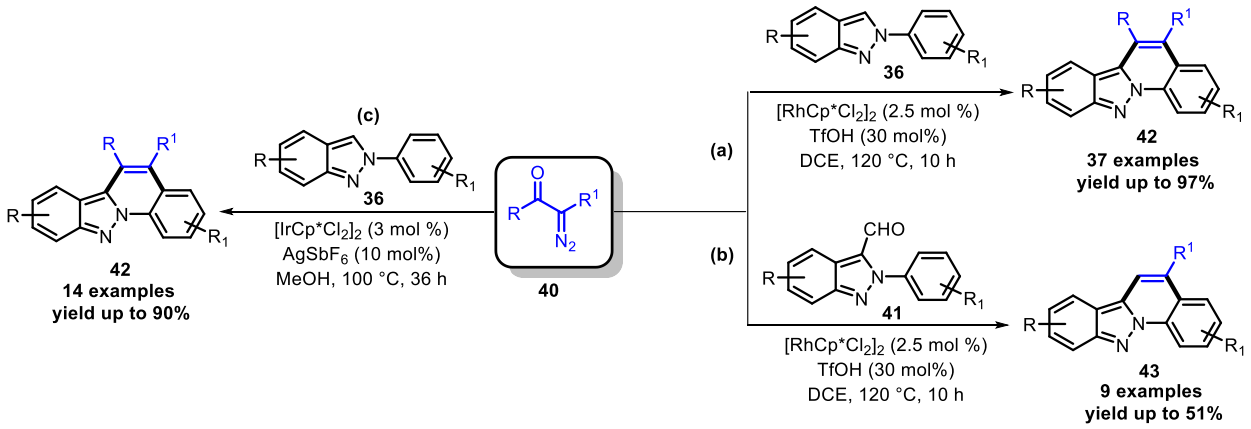
Scheme 1.17: Rh(III)-catalyzed annulation of 2-aryl-2*H*-indazoles with alkynes

Fan and colleagues illustrated Rh(III)-catalyzed, condition-dependent dehydrogenative annulation of 2-arylindazoles (**36**) with maleimides (**34**) to produce either indazolo[2,3-*a*]pyrrolo[3,4-*c*]quinolinones (**38**) or spiroindolo-[1,2-b]indazole-pyrrolidinones (**39**) (**Scheme 1.18**).[107] The choice of additives determined the selectivity between fused and spiro compounds. When 1-adamantane carboxylic acid (ADA) was used, fused indazoloquinolinones were predominantly formed. On the other hand, employing *N,N*-diisopropyl ethylamine (DIPEA) as an additive favored the spiro compound as the major product.



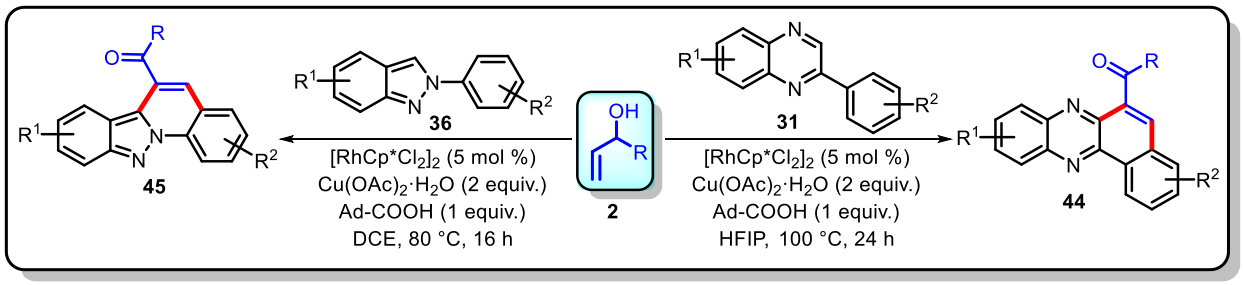
Scheme 1.18: Rh(III)-catalyzed cyclization of 2-arylindazoles with maleimides

In 2020, Fan and co-workers disclosed a facile route for the synthesis of 5,6-disubstituted (**42**) or 5-substituted indazolo[2,3-*a*]quinolones (**43**) *via* Rh(III)-catalyzed [4+2] and [4+1] annulation of 2-arylindazoles (**36**) with α-diazo carbonyl compounds (**40**) under oxidant-free conditions (**Scheme 1.19ab**).[104, 111] When utilizing 3-unsubstituted 2*H*-indazoles under standard reaction conditions [4+2], annulation with a diazo compound as a C2 synthon selectively yields 5,6-disubstituted indazolo[2,3-*a*]quinolines (**42**). On the other hand, employing 3-formylsubstituted 2*H*-indazoles (**41**) leads to the formation of 5-substituted indazolo[2,3-*a*]quinolines (**43**) through a fascinating [5+1] annulation pathway. At the same time, Reddy group also reported Ir(III)-catalyzed annulation of 2-arylindazoles (**36**) with α-diazocarbonyl compounds (**40**) (**Scheme 1.19c**).



Scheme 1.19: Rh(III)-catalyzed oxidative annulation of 2-arylindazoles with α-diazo carbonyl compounds

The use of allyl alcohols as a two-carbon synthon for C-H/N-H annulation reactions has seldom been demonstrated. For these motifs in our efforts toward the development of atom-economical synthetic approaches for polyheterocycles, herein, we have described the synthesis of benzo[*a*]phenazines (**44**) and indazolo[2,3-*a*]quinolones (**45**) *via* an Rh(III)-catalyzed oxidative [4+2] annulation of 2-arylquinoxalines (**31**) and 2-aryl-2*H*-indazoles (**36**) with allyl alcohols (**2**) (**Scheme 1.20**).



Scheme 1.20: Rh(III)-catalyzed oxidative [4+2] annulation of 2-arylquinoxalines and 2-aryl-2*H*-indazoles with allyl alcohols

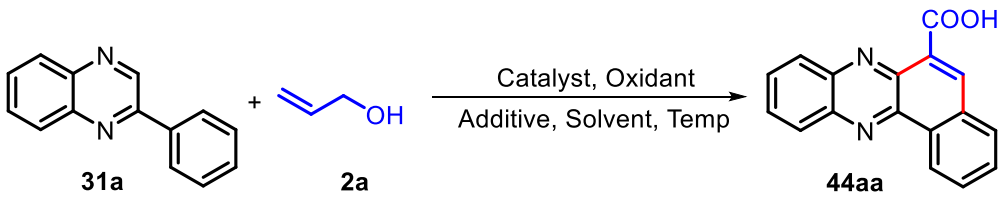
1.2 RESULTS AND DISCUSSION

We selected 2-phenylquinoxaline (**31a**) and allyl alcohol (**2a**) as model substrates to optimize the reaction conditions. Initially, annulated product benzo[*a*]phenazine-6-carboxylic acid (**44aa**) was obtained in a 41% yield from the reaction of **31a** and **2a** after 24 h using $[RhCp^*Cl_2]_2$ (5 mol %) as a catalyst and $Cu(OAc)_2{\cdot}H_2O$ (1 equiv.) as an oxidant in dichloroethane (DCE) at 100 °C (**Table 1.1**, entry 1). However, initially tested several metal catalysts, including [Ru(*p*-

cymene)$Cl_2]_2$ and $Pd(OAc)_2$, but found them to be ineffective for this transformation (**Table 1.1**, entries 2, 3). Next, increasing the amount of oxidant $Cu(OAc)_2.H_2O$ (2 equiv.) yield of **45aa** increases 58% yield, further increasing the amount of oxidant $Cu(OAc)_2.H_2O$ from 2.0 equiv. to 2.5 equiv., not much effective in increasing the yield of **44aa** (**Table 1.1**, entries 4, 5). For other oxidants such as $Cu(OAc)_2$, $Cu(OTf)_2$, $CuSO_4{\cdot}5H_2O$, and Ag_2CO_3 are much less effective than $Cu(OAc)_2.H_2O$ (**Table 1.1**, entries 6-9). To examine the effect of solvent in our reaction, we screened different solvents such as MeOH, DMA, DMF, DMSO, and HFIP (**Table 1.1**, entries 10-14); HFIP is the most suitable solvent for this transformation. Next, we tested the effectiveness of various acidic additives, such as ADA, PivOH, and AcOH (**Table 1.1**, entries 15-17), and found that ADA produced the best result. Next, we evaluated basic additive NaOAc and KOAc yield of **44aa** did not improve (**Table 1.1**, entries 18, 19). The efficiency of **44aa** decreased in the absence of an oxidant, and the desired product was not obtained when the reaction was carried out without the $[RhCp^*Cl_2]_2$ catalyst. So, both the experiments revealed that the oxidant and metal catalyst both are played a crucial role in this transformation (**Table 1.1**, entries 20, 21). After a set of experiments, the best yield of **44aa** was obtained using $[RhCp^*Cl_2]_2$ (5 mol %) as the catalyst in the presence of $Cu(OAc)_2{\cdot}H_2O$ (2 equiv.) and ADA (1 equiv.) as the additive in HFIP at 100 °C (**Table 1.1**, entry 15).

The structure of the **44aa** was fully elucidated by NMR and HRMS analysis. In ^1H NMR, the singlet peak for the C3 proton of the 2-arylquinoxalines disappeared, and a peak for the acidic proton appeared at 15.8 ppm (**Figure 1.8**). In ^{13}C NMR, the carbonyl carbon of acid was observed at 166.4 ppm. The proton and carbon signals corresponding to the remaining structure of compound **44aa** were detected at their specific positions in both the ^1H and $^{13}C\{^1H\}$ NMR spectra (**Figure 1.9**). In addition, a peak at (*m/z*) 275.0812 in HRMS corresponding to $C_{17}H_{11}N_2O_2$ $[M + H]^+$ ion confirmed the structure of **44aa**.

Table 1.1: Optimization of reaction conditions [a]



Entry	Catalyst	Oxidant	Solvent	Additive	% Yield[b]

1	$[RhCp^*Cl_2]_2$	$Cu(OAc)_2{\cdot}H_2O$	DCE	-	41
2	$[Ru(p\text{-cymene})Cl_2]_2$	$Cu(OAc)_2{\cdot}H_2O$	DCE	-	NR
3	$Pd(OAc)_2$	$Cu(OAc)_2{\cdot}H_2O$	DCE	-	NR
4	$[RhCp^*Cl_2]_2$	$Cu(OAc)_2{\cdot}H_2O$	DCE	-	58
5	$[RhCp^*Cl_2]_2$	$Cu(OAc)_2{\cdot}H_2O$	DCE	-	60
6	$[RhCp^*Cl_2]_2$	$Cu(OAc)_2$	DCE	-	54
7	$[RhCp^*Cl_2]_2$	$Cu(OTf)_2$	DCE	-	44
8	$[RhCp^*Cl_2]_2$	$CuSO_4{\cdot}5H_2O$	DCE	-	37
9	$[RhCp^*Cl_2]_2$	Ag_2CO_3	DCE	-	39
10	$[RhCp^*Cl_2]_2$	$Cu(OAc)_2{\cdot}H_2O$	MeOH	-	NR
11	$[RhCp^*Cl_2]_2$	$Cu(OAc)_2{\cdot}H_2O$	DMA	-	63
12	$[RhCp^*Cl_2]_2$	$Cu(OAc)_2{\cdot}H_2O$	DMF	-	57
13	$[RhCp^*Cl_2]_2$	$Cu(OAc)_2{\cdot}H_2O$	DMSO	-	54
14	$[RhCp^*Cl_2]_2$	$Cu(OAc)_2{\cdot}H_2O$	HFIP	-	69
15	**$[RhCp^*Cl_2]_2$**	**$Cu(OAc)_2{\cdot}H_2O$**	**HFIP**	**ADA**	**81**
16	$[RhCp^*Cl_2]_2$	$Cu(OAc)_2{\cdot}H_2O$	HFIP	PiOH	78
17	$[RhCp^*Cl_2]_2$	$Cu(OAc)_2{\cdot}H_2O$	HFIP	AcOH	74
18	$[RhCp^*Cl_2]_2$	$Cu(OAc)_2{\cdot}H_2O$	HFIP	NaOAc	67
19	$[RhCp^*Cl_2]_2$	$Cu(OAc)_2{\cdot}H_2O$	HFIP	KOAc	65
20	-	$Cu(OAc)_2{\cdot}H_2O$	HFIP	ADA	NR
21	$[RhCp^*Cl_2]_2$	-	HFIP	ADA	32

[a]Reaction conditions: **31a** (0.24 mmol), **2a** (0.97 mmol), catalyst (5 mol %), oxidant (2 equiv), additive (1 equiv), solvent (2 mL) in a sealed tube at 100 °C for 24 h. [b]Isolated yield.

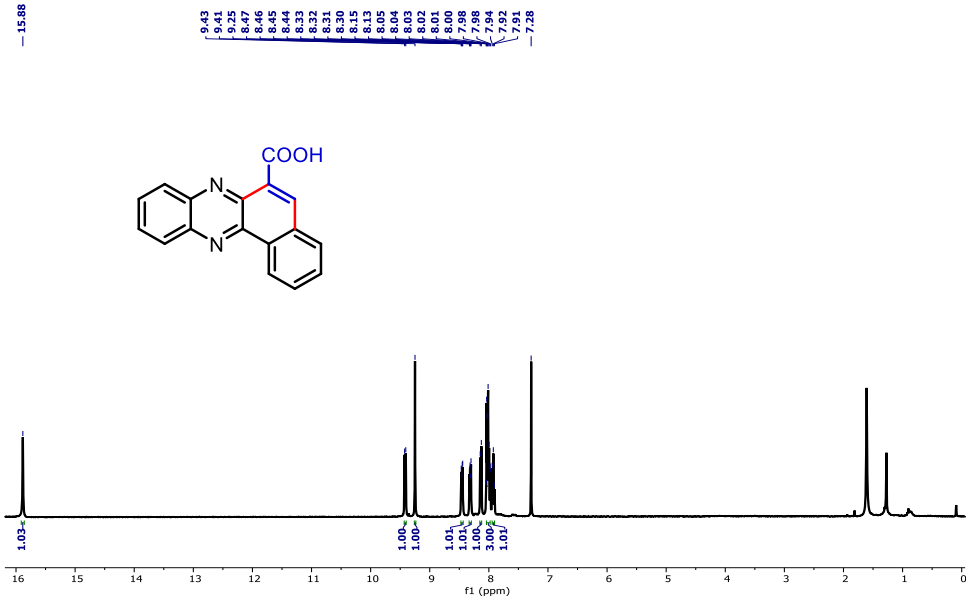


Figure 1.8: ^{1}H NMR spectra of benzo[*a*]phenazine-6 carboxylic acid (**44aa**) recorded in $CDCl_3$

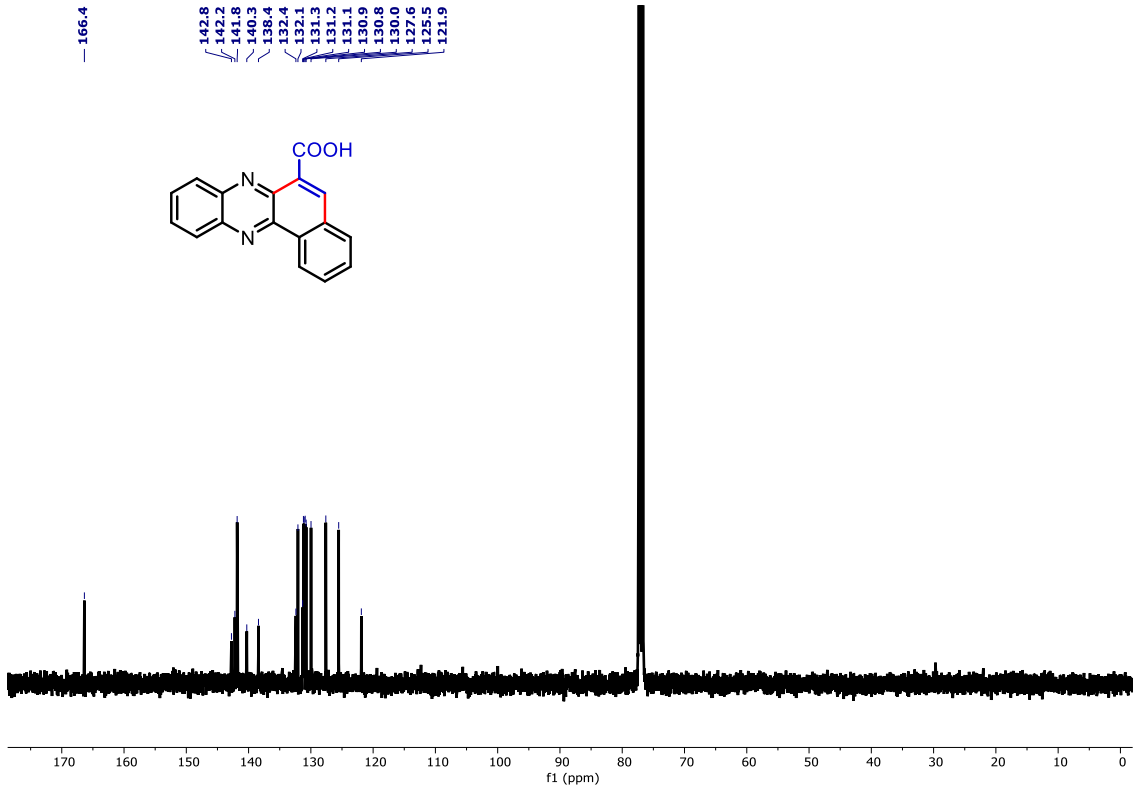
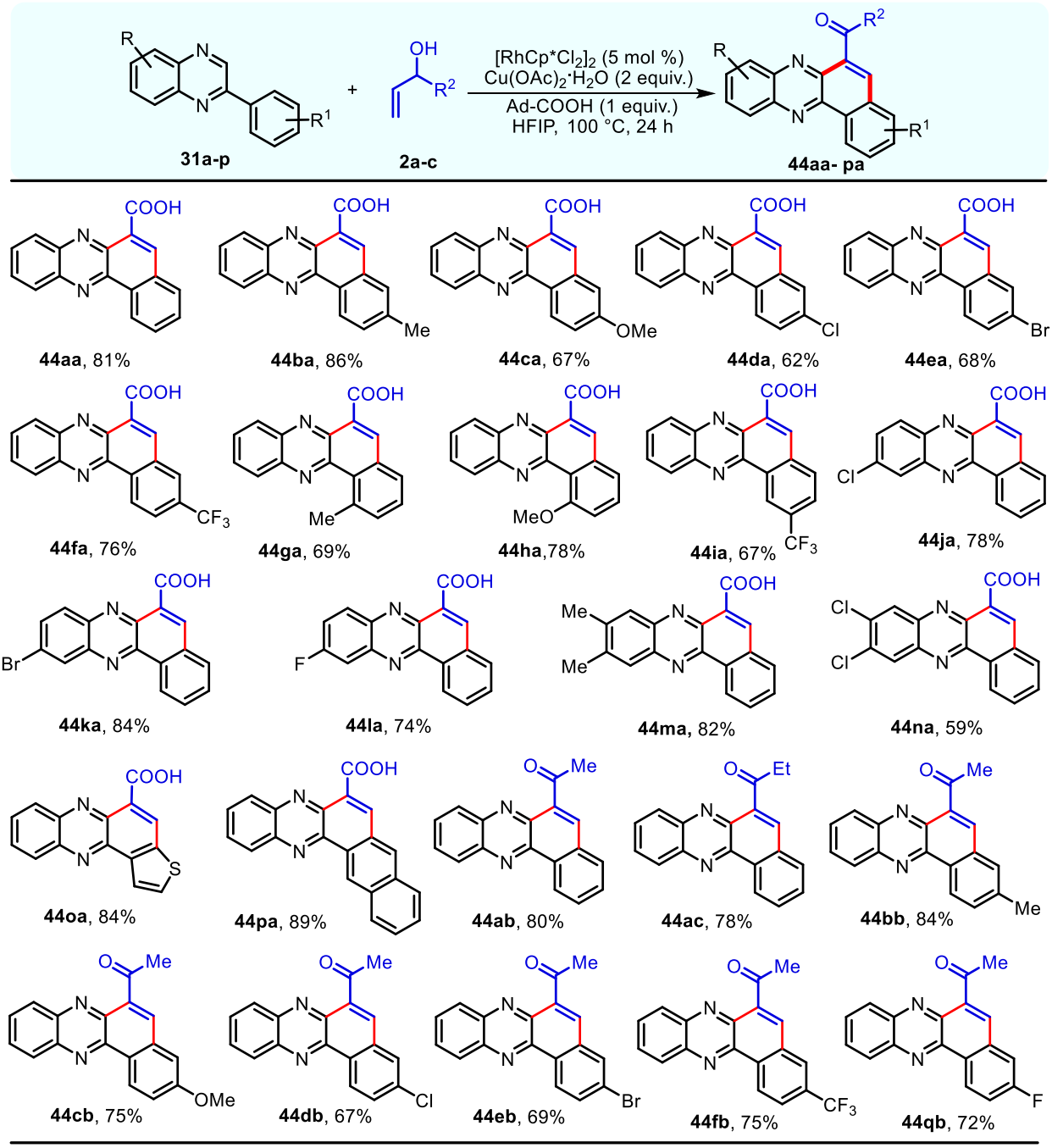


Figure 1.9: $^{13}C\{^{1}H\}$ NMR spectra of benzo[*a*]phenazine-6-carboxylic acid (**44aa**) in $CDCl_3$

With the optimized reaction conditions in hand, the scope and generality of this oxidative [4+2] annulation was examined (**Table 1.2**). Firstly, we investigated scope of this reaction with respect to 2-arylquinoxalines. Various 2-arylquinoxalines (**31a-n)** having different substituent such as Me, OMe, F, Cl, Br and CF_3 on 2-phenyl ring and/or quinoxaline nucleus reacted smoothly with **2a** to afford corresponding benzo[*a*]phenazine-6-carboxylic acids **44aa-na** in good to high (60-86%) yields. Interestingly, halo groups and *ortho*-substituents on 2-phenyl ring were well tolerated in this reaction. Additionally, 2-(thiophen-2-yl)quinoxaline (**31o**) and 2-(naphthalen-2-yl)quinoxaline (**31p**) also reacted with **2a** to give annulated product **44oa** and **44pa** in 84% and 89% yields, respectively. Next, scope of allyl alcohols was investigated.

Table 1.2: Substrate scope for 2-arylquinoxalines and allyl alcohols.[a,b]



[a]Reaction condition: **31** (0.24 mmol), **2** (0.97 mmol), $[Cp^*RhCl_2]_2$ (5 mol %), ADA (1 equiv.), $Cu(OAc)_2{\cdot}H_2O$ (2 equiv.), HFIP (2 mL) in sealed tube at 100 °C for 24 h. [b]Isolated yields

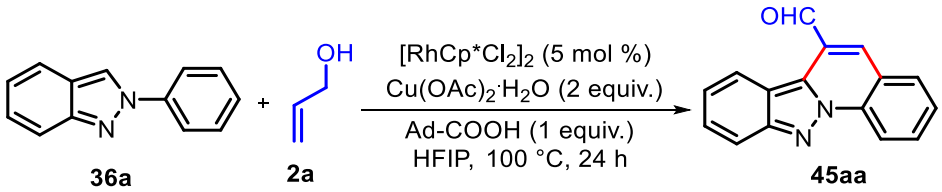
The reaction of 2-phenylquinoxaline (**31a**) with but-3-en-2-ol (**2b**) and pent-1-en-3-ol (**2c**) under optimized reaction condition produced 1-(benzo[*a*]phenazin-6-yl)ethan-1-one (**44ab**) and 1-(benzo[*a*]-phenazin-6-yl)propan-1-one (**44ac**) in 80% and 78% yields, respectively. Further,

other 2-arylquinoxalines (**31b-f, 31q**) having substituents at *para*-position of 2-phenyl ring underwent reaction with **2b** to furnish corresponding 1-(benzo[*a*]phenazin-6-yl)ethan-1-one derivatives (**44bb-fb, 44qb**) in 67-84% yields. Unfortunately, other allyl alcohols such as cinnamyl alcohol, crotyl alcohol, and geraniol failed to produce the desired products in our hands.

Having developed synthesis of benzo[*a*]phenazines, we became interested in the reaction of 2-aryl-2*H*-indazoles with allyl alcohol to prepare indazolo[2,3-*a*]quinolines. To our satisfaction, reaction of 2-phenyl-2*H*-indazole (**36a**) and **2a** in the presence of $[Cp^*RhCl_2]_2$ (5 mol %), $Cu(OAc)_2{\cdot}H_2O$ (2 equiv), ADA (1 equiv) in HFIP at 100 °C for 24 h furnished indazolo[2,3-*a*]quinoline-6-carbaldehyde (**45aa**) in 32% yield. The obtained annulated product was fully characterized by NMR and HRMS analysis. In the ^1H NMR of **45aa** aldehydic protons appeared at 10.3 ppm **(Figure 1.10)**. Likewise, aldehyde carbonyl carbon peaks was observed at 189.8 ppm in $^{13}C\{^1H\}$NMR (**Figure 1.11**). Furthermore, presence of peak at *m/z* 247.0877 in HRMS corresponding to molecular formula $C_{16}H_{11}N_2O$ $[M + H]^+$ ion confirmed the structure of **45aa**. Finally, the molecular structure of **45aa** was also confirmed by single crystal X-ray diffraction analysis (CCDC No **2294834**).

After slight modification in the reaction conditions (**Table 1.3**, entry 6), it was observed that with DCE as solvent and reaction temperature at 80 °C, the yield of **45aa** increased to 72%. Taking these as optimal reaction conditions, we examined scope of the reaction for the synthesis of indazolo[2,3-*a*]quinoline-6-carbaldehydes (**Table 1.4**). The 2-arylindazoles with substitutions at the *para*- and *meta*-position of the 2-phenyl ring (**36b-g**) underwent reaction with **2a** to afford desired annulated product **45ba-45ga** in yields ranging from 64% to 81%. In addition, 2-phenyl-2*H*-indazole bearing a chloro and fluoro groups at the C5-position of the indazolyl nucleus (**36h** and **36i**) also proved to be good substrate to give corresponding products **45ha** and **45ia** in 73% and 75% yields, respectively. Moreover, other allyl alcohols viz. but-3-en-2-ol (**2b**) and pent-1-en-3-ol (**2c**) also underwent reaction with **36a** to furnish corresponding annulated products, 1-(indazolo[2,3-*a*]quinolin-6-yl)ethan-1-one (**45ab**) and 1-(indazolo[2,3-*a*]quinolin-6-yl)propan-1-one (**45ac**) in 68% and 65% yields, respectively. Other substituted 2-aryl-2*H*-indazole (**36b-h**) also reacted smoothly with **2b** to afford the corresponding 1-(indazolo[2,3-*a*]quinolin-6-yl)ethan-1-ones (**45bb-45hb**) in good (64-71%) yields.

Table 1.3: Optimization of reaction conditions for **45aa**.[a,b]



Entry	Variation from standard conditions	% Yield 5aa[b]
1	none	38
2	80 °C and 24 h	49
3	80 °C and 16 h	58
4	60 °C and 16 h	46
5	toluene as solvent	63
6	**DCE as solvent**	**72**
7	2 equivalent of **2a**	57
8	3 equivalent of **2a**	71
9	[Ru(*p*-cymene)Cl_2]$_2$ as a catalyst	Trace
10	$Pd(OAc)_2$ as a catalyst	NR

[a]Reaction conditions: **36a** (0.25 mmol), **2a** (0.77 mmol), catalyst (5 mol %), oxidant (2 equiv.), additive (1 equiv.), solvent (2 mL) in a sealed tube at 80 °C for 16 h, [b]Isolated yield.

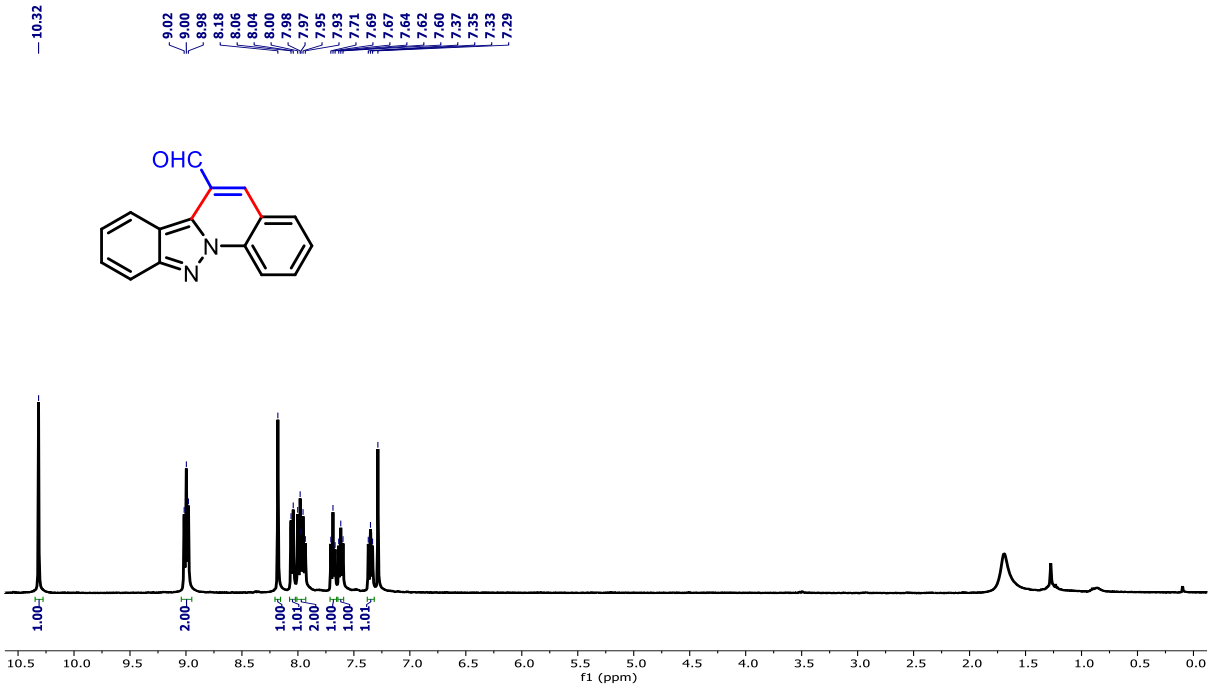


Figure 1.10: ^{1}H NMR spectra of indazolo[2,3-*a*]quinoline-6-carbaldehyde (**45aa**) recorded in $CDCl_3$

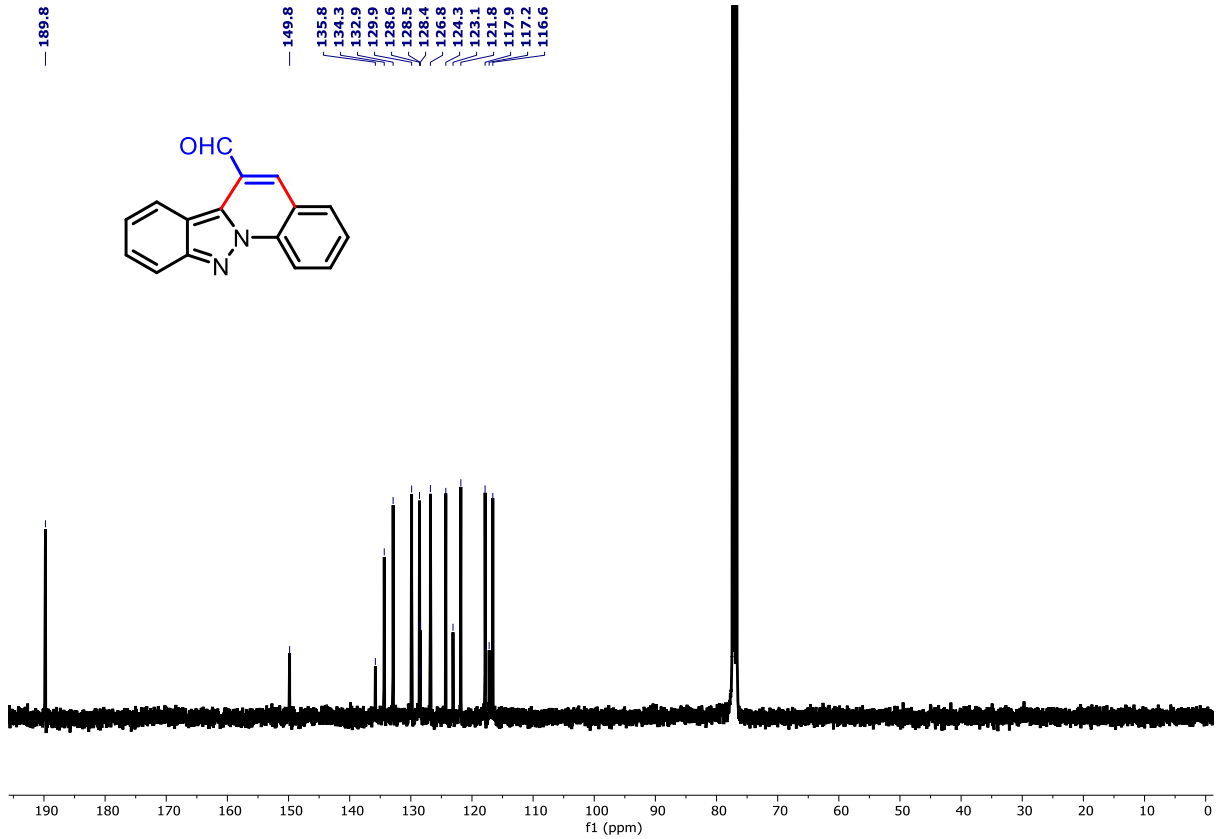


Figure 1.11: $^{13}C\{^{1}H\}$ NMR spectra of indazolo[2,3-*a*]quinoline-6-carbaldehyde (**45aa**) recorded in $CDCl_3$

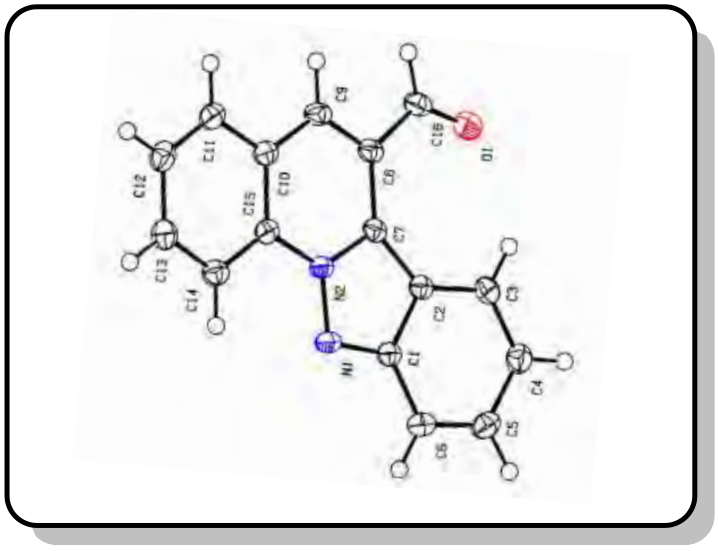
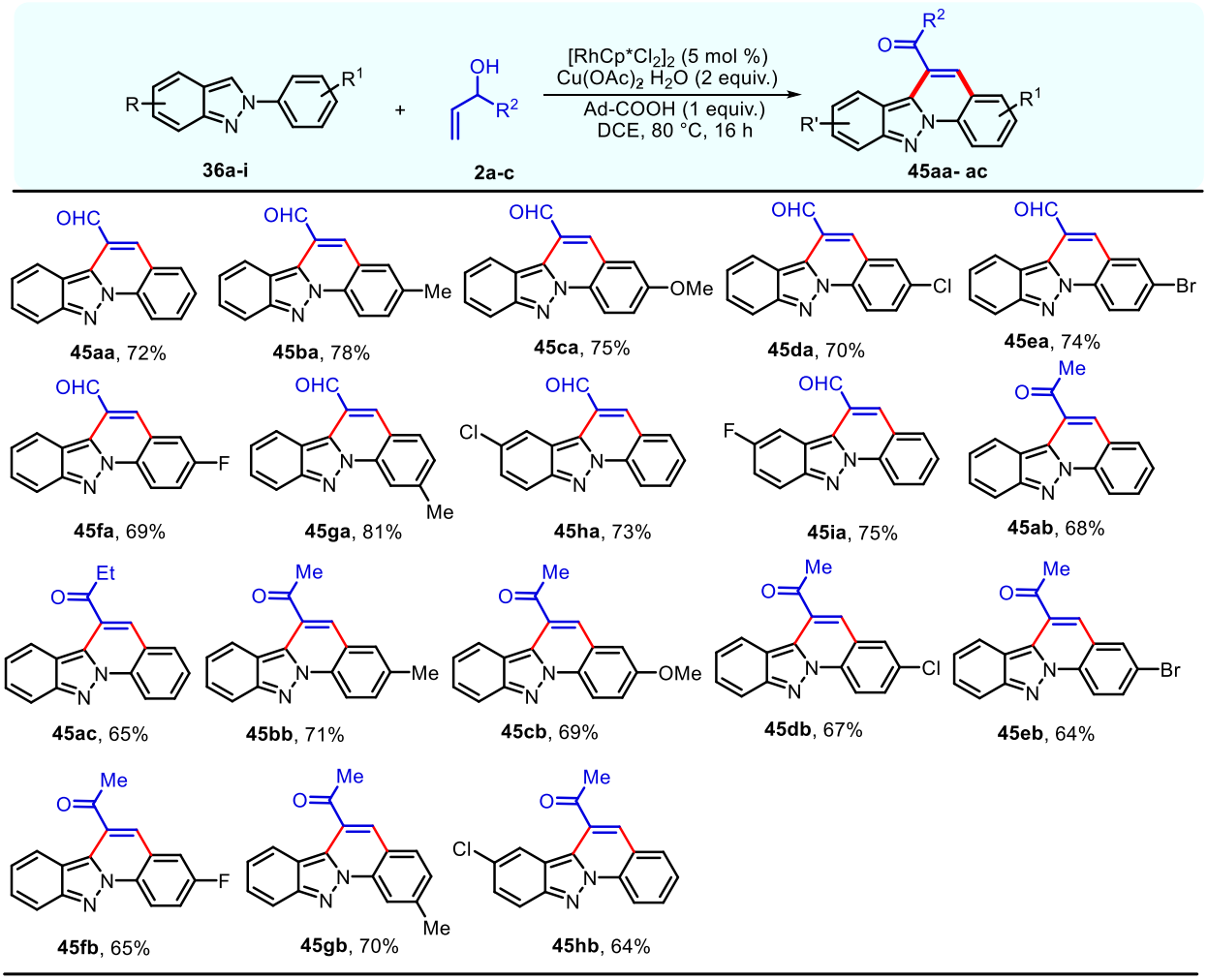


Figure 1.12: Single crystal ORTEP diagram of compound **45aa**. The thermal ellipsoids are drawn to a 50 % probability level (**CCDC No** 2294834)

Table 1.4: Substrate scope for the 2-phenyl-2*H*-indazole. [a,b]



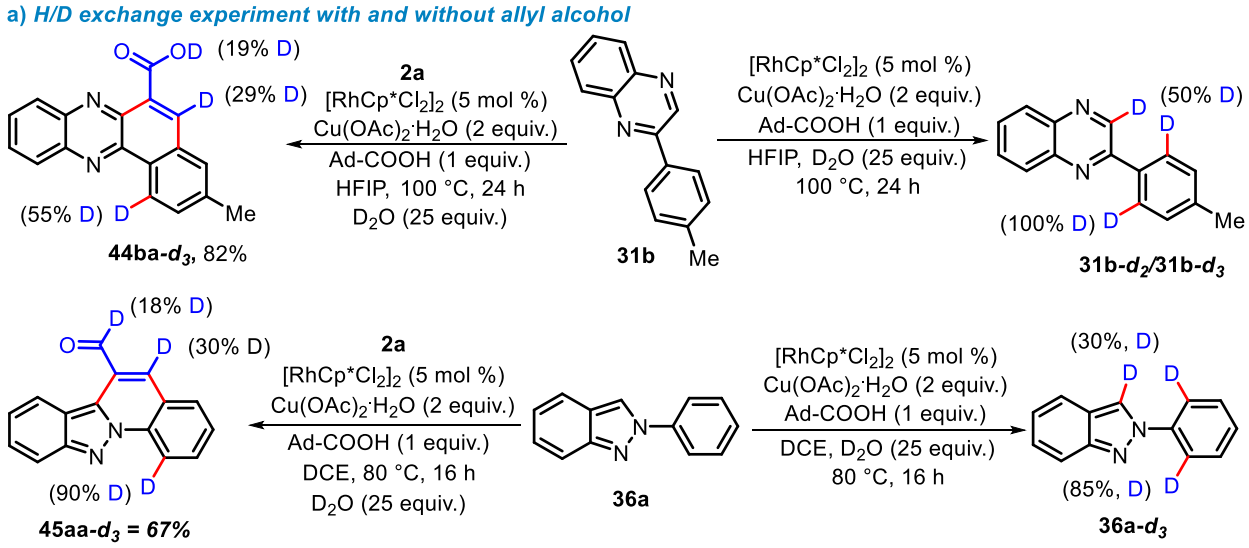
[a]Reaction condition: **36** (0.25 mmol), **2** (0.77 mmol), $[Cp^*RhCl_2]_2$ (5 mol %), ADA (1 equiv.), $Cu(OAc)_2 \cdot H_2O$ (2 equiv.), DCE (2 mL) sealed tube at 80 °C for 16 h. [b]Isolated yields

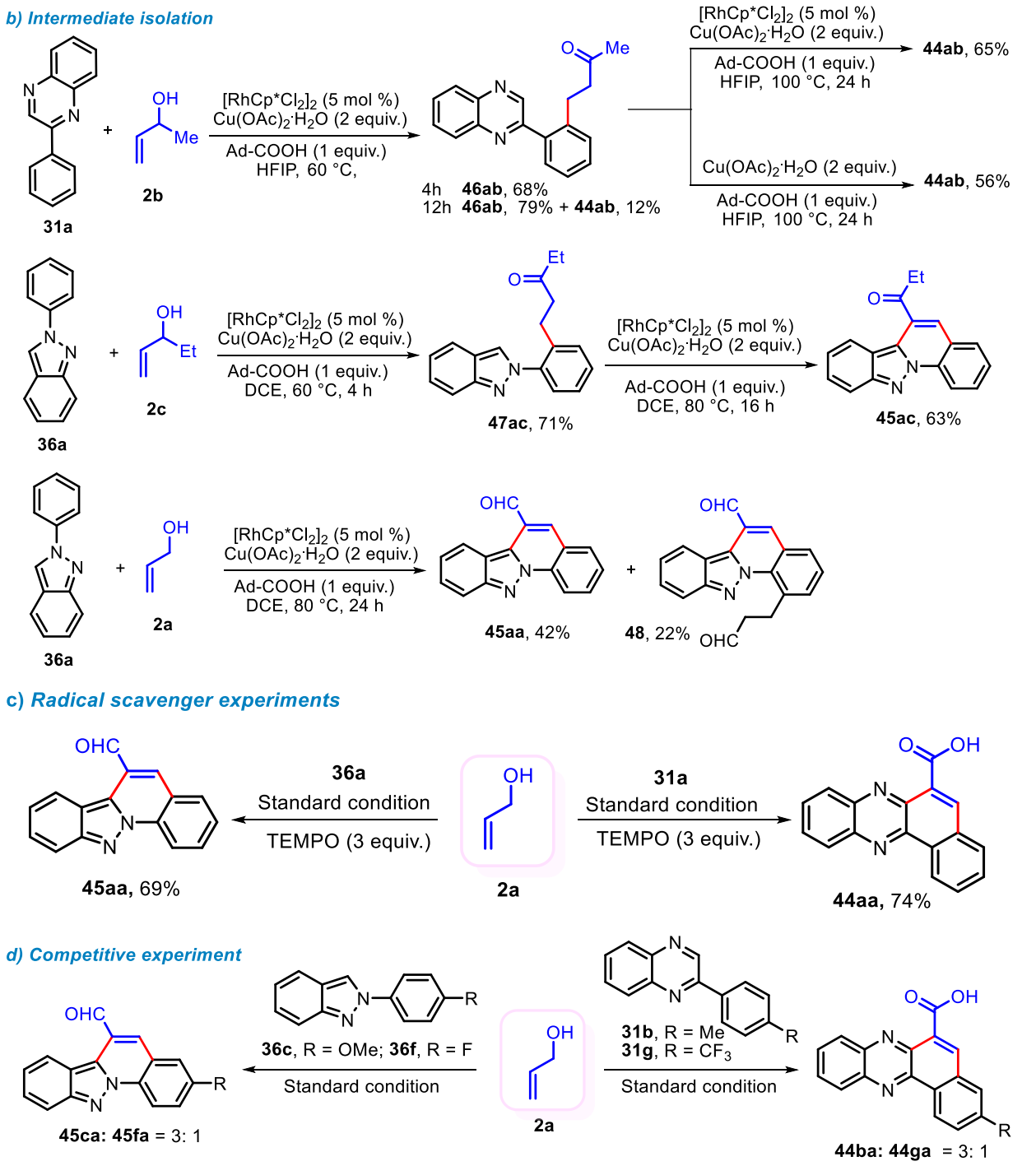
To understand the reaction mechanism, a few control experiments were conducted (**Scheme 1.21**). Incorporation of deuterium in significant quantity at the *ortho*-position of the 2-phneyl ring for both 2-(*p*-tolyl)quinoxaline (**31b**) and 2-phenyl-2*H*-indazole (**36a**) in the absence and presence of allyl alcohol (**2a**) under standard reaction conditions (**Scheme 1.21a**), indicated that the step of the *ortho*-C-H bond cleavage is reversible. Moreover, deuterium incorporation at the *β*-carbon of allyl alcohol in annulated products (**44ba-*d*$_3$** and **45aa-*d*$_3$**) indicates the formation of the stable rhodium–oxa-π-allyl intermediates.[98]

Next, performing the reaction of **31b** with **2b** and **36a** with **2c** at 60 °C for 4 h otherwise under standard conditions produced *ortho*-alkylated products **46ab** and **47ac** in 68% and 71% yields,

respectively (**Scheme 1.21b**). Formation of **46ab** and **47ac** can result from the reductive elimination of rhodacycle intermediate **B**. Furthermore, continuing the reaction of **31b** with **2b** at 60 °C for 12 h otherwise under the standard conditions produced **46ab** in a 79% yield along with **44ab** in a 12% yield. Carrying out the reaction of **46ab** and **47ac** under standard reaction conditions afforded **44ab** and **45ac** in 65% and 63% yields, respectively. Moreover, the reaction of **46ab** under the standard reaction conditions in the absence of the Rh-catalyst also afforded **44ab** in a 56% yield. These results indicated that the *ortho*-alkylated product could be the intermediate in this reaction.

Finally, carrying out the reaction of **36a** with **2a** at 80 °C for 24 h and otherwise under the standard conditions produced the desired product **45aa** in a 42% yield along with 1-(3-oxopropyl)indazolo[2,3-*a*]quinoline-6-carbaldehyde (**48**) in a 22% yield. Next, no significant reduction in the yields of **44aa** and **45aa** was noted when reactions of **31a** with **2a** and **36a** with **2a** were performed in the presence of radical scavenger TEMPO (**Scheme 1.21c**), suggesting that the reaction did not involve a radical pathway. Intermolecular competitive reaction of **31b** and **31g** with **2a** produced the corresponding annulated products **44ba** and **44ga** in a 3 : 1 ratio. Similarly, intermolecular competitive reaction of **36c** and **36f** with **2a** produced the corresponding annulated products **45ca** and **45fa** in a 3 : 1 ratio **(Scheme 1.21d)**. These results revealed that this reaction is more favorable for compounds with the electron-rich 2-aryl ring.

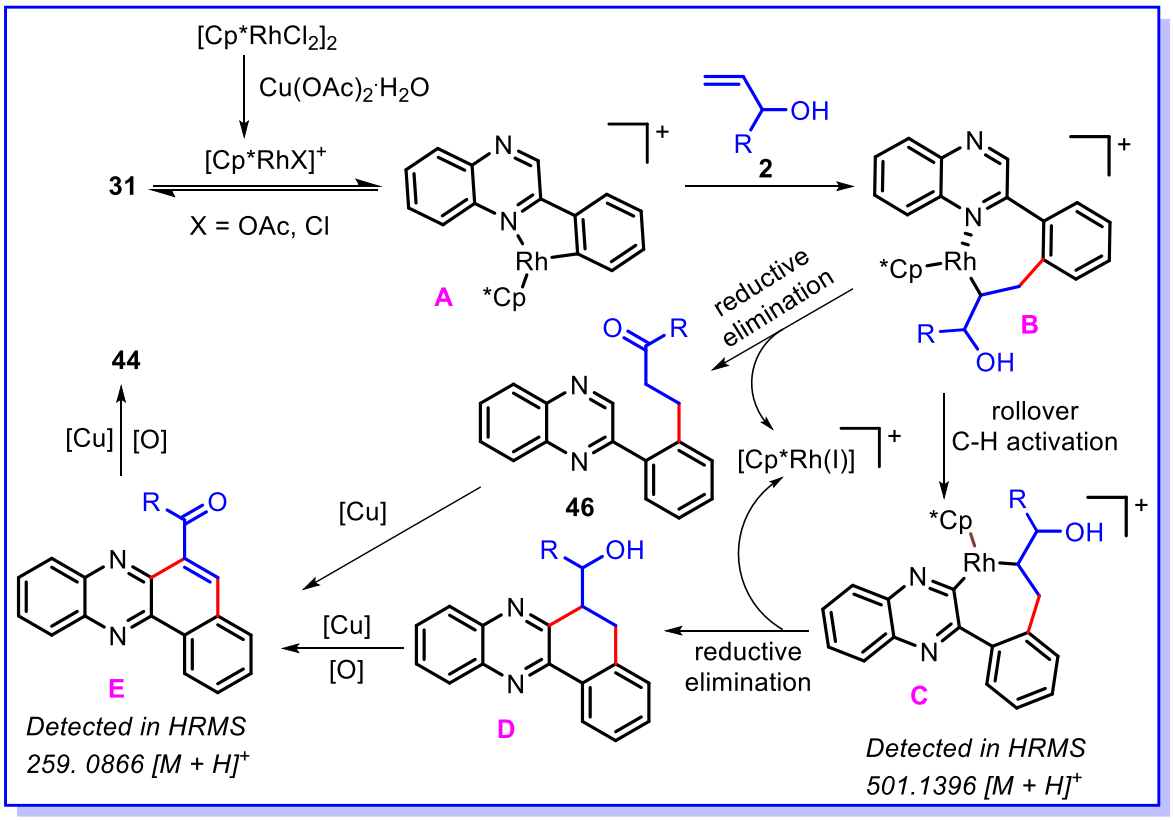




Scheme 1.21: Control experiment

Based on the above control experiment results and the previous literature reports,[112-114] a plausible mechanism of the developed annulation reaction is depicted in **Scheme 1.22**. Initially, coordination of the active Rh(III) catalyst with the nitrogen atom of **31** triggers cleavage of the *ortho*-C(sp^2)–H bond to form five-membered rhodacycle intermediate **A**. Subsequently,

coordination of **2** with Rh(III) of **A** followed by migratory insertion of it into the Rh–C bond of rhodacycle **A** produces seven membered rhodacycle intermediate **B**. Rollover cyclometallation of **B** may afford intermediate **C** (detected in LC-HRMS *m/z* 501.1396 $[M + H]^+$), which would undergo reductive elimination to produce intermediate **D** and Rh(I) species. Furthermore, oxidation of **D** gives benzo[a]phenazine-6-carbaldehyde intermediate **E** (detected in LC-HRMS *m/z* 259.0866 $[M + H]^+$). Alternatively, reductive elimination of intermediate **B** produces intermediate **46**, which then, on oxidative cyclization in the presence of copper, can provide intermediate **E**. Finally, oxidation of intermediate **E** takes place to produce the desired product **44**.

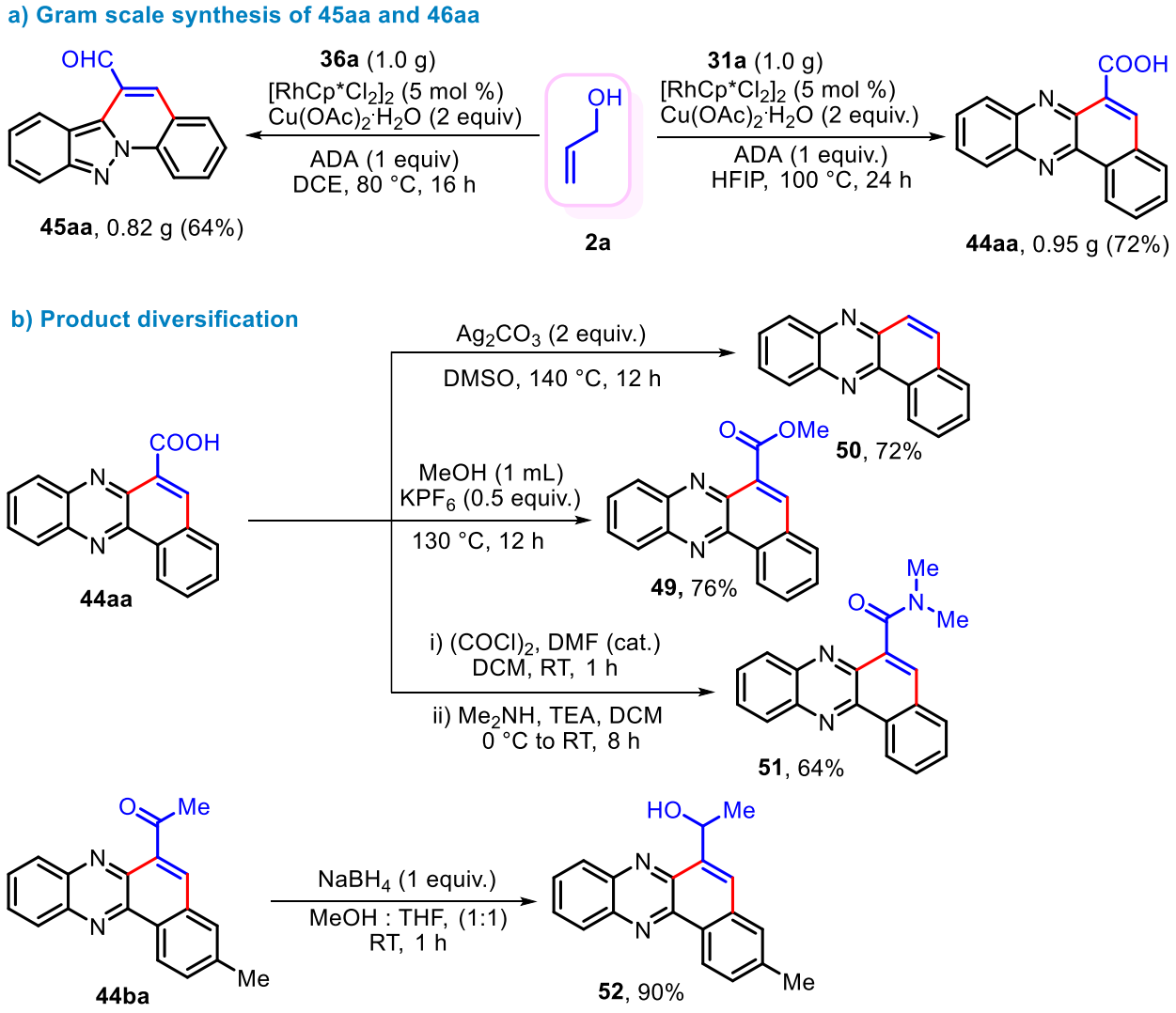


Scheme 1.22. Plausible mechanism for the Rh(III)-catalysed [4+2] annulation reaction

To evaluate the synthetic potential of this chemical reaction, gram-scale experiments has been demonstrated in (**Scheme 1.23**). The substrate **31a** or **36a** on reaction with **2a** under optimal conditions afforded the corresponding desired products benzo[*a*]phenazine-6-carboxylic acid **(44aa)** and indazolo[2,3-*a*]quinoline-6-carbaldehyde **(45aa)** in 72% and 64% yields, respectively. The reaction of **44aa** with methanol (1.0 mL) in the presence of KPF_6 (0.5 equiv.)

at 130 °C for 12 h afforded methyl benzo[*a*]phenazine-6-carboxylate (**49**) in 76% yield.[115] Next, **44aa** was readily converted to the benzo[*a*]phenazine (**50**) in 72% yield in the presence of Ag_2CO_3 (2 equiv.) in DMSO at 140 °C for 12 h.[116] Furthermore, the reaction of **44aa** with $(COCl)_2$ in the catalytic amount of DMF followed by reaction with dimethylamine produced acid amide coupled product *N, N*-dimethylbenzo[*a*]phenazine-6-carboxamide (**51**) with 64% yield[117]. Finally, treating **44ba** with $NaBH_4$ produced compound **52** in a 90% yield.

Scheme 1.23: Gram-scale synthesis and chemical transformation of product



1.3 CONCLUSIONS

In summary, we have developed a Rh(III)-catalyzed oxidative annulation of 2-aryl-2*H*-indazoles and 2-arylquinoxalines with allyl alcohols. The developed methodology produces functionalized

benzo[*a*]phenazines and indazolo[2,3-*a*]quinolines in moderate to good yields. The method features a broad substrate scope, excellent functional group tolerance and scaled-up synthesis capability, thus providing easy access to medicinally valuable fused polyheterocyclic compounds. Based on preliminary mechanistic investigation, a tentative mechanism of the annulation reaction has been proposed. Detailed study of the mechanism and synthetic applications of the annulation reaction are now under investigation.

1.4 EXPERIMENTAL SECTION

1.4.1. General Information:

All chemicals and solvents purchased from commercial suppliers and used without purification unless otherwise noted. 2-Arylquinoxalines and 2-aryl-2*H*-indazoles were synthesized by following the reported procedure.[118, 119] All reactions were monitored by thin layer chromatography (TLC) on pre-coated silica gel 60 F254 aluminium foils and visualized under a UV lamp (366 or 254 nm). Desired products were purified by column chromatography (silica gel 100-200 mesh size) using a gradient of ethyl acetate and hexanes as mobile phase. The ^{1}H and $^{13}C\{^{1}H\}$ NMR spectra were recorded on a 400 MHz spectrometer. Chemical shifts (δ) are reported in parts per million (ppm), and coupling constants (*J*) are reported in hertz (Hz). High-resolution mass spectra (HRMS) were recorded on a Q-TOF mass spectrometer. X-ray analysis was performed on a Rigaku Oxford XtaLAB AFC12 (RINC): Kappa dual home/near diffractometer.

1.4.2 Experimental Procedure

1.4.2.1. General Procedure for the Synthesis of 44.

A 10 mL oven-dried sealed tube was charged with compounds **31** (0.24 mmol) and **2** (0.97 mmol), $Cu(OAc)_2{\cdot}H_2O$ (0.48 mmol), Ad-COOH (0.24 mmol), $[RhCp^*Cl_2]_2$ (0.012 mmol, 5 mol %) and HFIP (2 mL) at room temperature. The reaction tube was capped tightly, and the reaction mixture was stirred at 100 °C in an oil bath for 24 h. The reaction mixture was cooled, diluted with water (5 mL), and then extracted with ethyl acetate (3 × 5 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The resulting crude mixture was purified by column chromatography (silica gel 100−200 mesh) using EtOAc-hexanes as an eluent to afford the desired product.

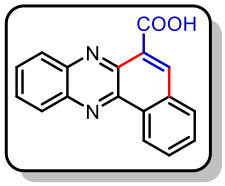
1.4.2.2. General Procedure for the Synthesis of 45.

A 10 mL oven-dried sealed tube was charged with compounds **36** (0.25 mmol) and **2** (0.77 mmol), $Cu(OAc)_2{\cdot}H_2O$ (0.51 mmol), Ad-COOH (0.25 mmol), $[RhCp^*Cl_2]_2$ (0.012 mmol, 5 mol %) and DCE (2 mL) at room temperature. The reaction tube was capped tightly, and the reaction mixture was stirred at 80 °C in an oil bath for 16 h. The reaction mixture was cooled, diluted with water (5 mL), and then extracted with ethyl acetate (3 × 5 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The resulting crude mixture was purified by column chromatography (silica gel 100−200 mesh) using EtOAc-hexanes as an eluent to afford the desired product.

1.4.2.3 Experimental Procedure for Isolation of 46ab: An oven-dried 10 mL pressure tube was charged with **31a** (50 mg, 0.24 mmol), **2b** (70 mg, 0.97 mmol), $Cu(OAc)_2{\cdot}H_2O$ (96 mg, 0.48 mmol), Ad-COOH (44 mg, 0.24 mmol), $[RhCp^*Cl_2]_2$ (7 mg, 0.012 mmol, 5 mol %) in HFIP (2 mL) at room temperature. The reaction mixture was stirred at 60 °C in an oil bath for 4 h. After that the reaction mixture was cooled to ambient temperature, quenched with water, and extracted in ethyl acetate (3 × 5 mL). The combined organic layer was dried over Na_2SO_4 and evaporated under reduced pressure. The resulting residue was purified by column chromatography using hexanes/EtOAc as eluent on (100-200 mm) size silica gel to afford the product **46ab** with 68% yield.

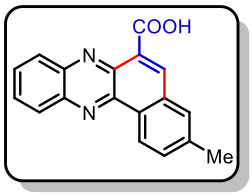
1.4.2.4 Experimental Procedure for Isolation of 47ac: An oven-dried 10 mL pressure tube charged with **36a** (50 mg, 0.25 mmol), **2c** (66 mg, 0.77 mmol) $Cu(OAc)_2{\cdot}H_2O$ (102 mg, 0.51 mmol), Ad-COOH (47 mg, 0.25 mmol), $[RhCp^*Cl_2]_2$ (8 mg, 0.012 mmol, 5 mol %) in DCE (2 mL) at room temperature. The reaction mixture was stirred at 60 °C in an oil bath for 4 h. After that the reaction mixture was cooled to ambient temperature, quenched with water, and extracted in ethyl acetate (3 × 5 mL). The combined organic layer was dried over Na_2SO_4 and evaporated under reduced pressure. The resulting residue was purified by column chromatography using hexanes/EtOAc as eluent on (100-200 mm) size silica gel to afford the product **47ac** with 71% yield.

Benzo[*a*]phenazine-6-carboxylic acid (44aa): The title compound was purified by column chromatography on silica gel using EtOAc/ hexanes (1: 4, *v/v*) as an eluent; yellow solid (54 mg, 81%); mp = 272-274 °C (Lit. mp 274-276 °C)[120]; ^1H



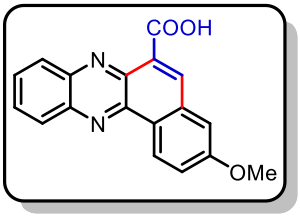
NMR (400 MHz, $CDCl_3$) δ 15.88 (s, 1H), 9.42 (d, *J* = 8.0 Hz, 1H), 9.25 (s, 1H), 8.45 (dd, *J* = 6.4, 3.6 Hz, 1H), 8.33 – 8.30 (m, 1H), 8.14 (d, *J* = 7.6 Hz, 1H), 8.04 – 7.97 (m, 3H), 7.94 – 7.91 (m, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 166.4, 142.8, 142.2, 141.8, 140.3, 138.4, 132.4, 132.1, 131.3, 131.2, 131.1, 130.9, 130.8, 129.1, 127.6, 125.5, 121.9; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{17}H_{11}N_2O_2^+$ 275.0810; Found 275.0812.

3-Methylbenzo[*a*]phenazine-6-carboxylic acid (44ba): The title compound was purified by



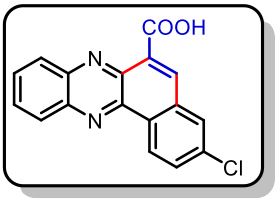
column chromatography on silica gel using EtOAc/ hexanes (1: 4, *v/v*) as an eluent; yellow solid (56 mg, 86%); mp = 276-278 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 15.94 (s, 1H), 9.28 (d, *J* = 8.2 Hz, 1H), 9.19 (s, 1H), 8.45 – 8.42 (m, 1H), 8.31 – 8.29 (m, 1H), 8.02 – 7.99 (m, 2H), 7.90 (s, 1H), 7.81 (d, *J* = 8.4 Hz, 1H), 2.69 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 166.5, 142.9, 142.2, 141.8, 141.6, 140.2, 138.2, 132.7, 131.8, 131.5, 131.1, 130.6, 130.1, 129.9, 127.6, 125.5, 121.8, 21.8; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{18}H_{13}N_2O_2^+$ 289.0972; Found 289.0981.

3-Methoxybenzo[*a*]phenazine-6-carboxylic acid (44ca): The title compound was purified by



column chromatography on silica gel using EtOAc/ hexanes (1: 3, *v/v*) as an eluent; yellow solid (43 mg, 67%); mp = 268-270 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 15.98 (s, 1H), 9.31 (d, *J* = 8.8 Hz, 1H), 9.18 (s, 1H), 8.42 – 8.40 (m, 1H), 8.29 – 8.27 (m, 1H), 8.01 – 7.96 (m, 2H), 7.56 (dd, *J* = 8.8, 2.4 Hz, 1H), 7.48 (d, *J* = 2.0 Hz, 1H), 4.06 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 166.5, 161.7, 142.8, 142.4, 141.5, 139.7, 137.9, 133.1, 131.5, 131.2, 129.8, 127.6, 127.4, 126.2, 122.4, 120.6, 111.6, 55.8; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{18}H_{13}N_2O_3^+$ 305.0921; Found 305.0924.

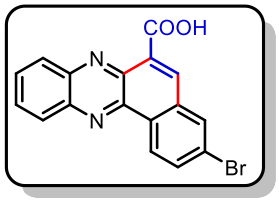
3-Chlorobenzo[*a*]phenazine-6-carboxylic acid (44da): The title compound was purified by



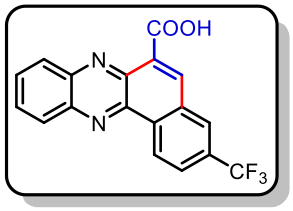
column chromatography on silica gel using EtOAc/ hexanes (1: 4, *v/v*) as an eluent; yellow solid (40 mg, 62%); mp = 282-284 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 15.81 (s, 1H), 9.39 (d, *J* = 8.8 Hz, 1H), 9.18 (s, 1H), 8.47 (dd, *J* = 6.6, 3.4 Hz, 1H), 8.34 (dd, *J* = 6.6, 3.4 Hz, 1H), 8.12 (d, *J* = 2.0 Hz, 1H), 8.06 (dd, *J* = 6.6, 3.4 Hz, 1H), 7.95 – 7.93 (m, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 165.9, 142.4, 142.3, 140.3, 140.0, 138.6, 137.2, 132.4, 131.6, 131.4, 130.7, 130.0,

129.7, 127.7, 127.2, 123.3; HRMS (ESI) *m/z*: $[M+H]^+$ Calcd for $C_{17}H_{10}ClN_2O_2^+$ 309.0425; Found 309.0421.

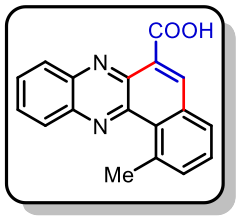
3-Bromobenzo[*a*]phenazine-6-carboxylic acid (44ea): The title compound was purified by column chromatography on silica gel using EtOAc/ hexanes (1: 4, *v/v*) as an eluent; yellow solid (42 mg, 68%); mp = 272-274 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 15.80 (s, 1H), 9.31 (d, *J* = 8.6 Hz, 1H), 9.18 (s, 1H), 8.48 – 8.46 (m, 1H), 8.35 – 8.33 (m, 1H), 8.29 (d, *J* = 3.6 Hz, 1H), 8.10 – 8.04 (m, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 165.8, 140.2, 140.0, 138.6, 134.1, 132.8, 132.6, 132.4, 131.6, 131.2, 131.0, 130.9, 130.8, 130.0, 127.7, 127.2, 125.6; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{17}H_{10}N_2BrN_2O_2^+$ 352.9920; Found 352.9923.



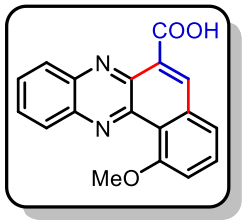
3-(Trifluoromethyl)benzo[*a*]phenazine-6-carboxylic acid (44fa): The title compound was purified by column chromatography on silica gel using EtOAc/ hexanes (1: 3, *v/v*) as an eluent; yellow solid (47 mg, 76%); mp = 244-246 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 15.71 (s, 1H), 9.56 (d, *J* = 8.4 Hz, 1H), 9.29 (s, 1H), 8.52 – 8.49 (m, 1H), 8.41 (s, 1H), 8.38 – 8.34 (m, 1H), 8.19 (d, *J* = 8.4 Hz, 1H), 8.13 – 8.04 (m, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 165.6, 142.5, 141.8, 140.6, 140.4, 138.9, 134.6, 133.0, 132.7 (q, $^2J_{C\text{-}F}$ = 31.6 Hz), 131.8, 131.0, 130.1, 127.7, 127.6 (q, $^4J_{C\text{-}F}$ = 4.5 Hz), 126.9 (q, $^4J_{C\text{-}F}$ = 3.5 Hz), 126.5, 123.5, 123.7 (q, $^1J_{C\text{-}F}$ = 279.3 Hz); HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{18}H_{10}F_3N_2O_2^+$ 343.0689; Found 343.0693.



1-Methylbenzo[*a*]phenazine-6-carboxylic acid (44ga): The title compound was purified by column chromatography on silica gel using EtOAc/ hexanes (1: 4, *v/v*) as an eluent; yellow solid (45 mg, 69%); mp = 254-258 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 16.07 (s, 1H), 9.15 (s, 1H), 8.41 – 8.38 (m, 1H), 8.26 – 8.23 (m, 1H), 8.01 – 7.95 (m, 3H), 7.78 – 7.73 (m, 2H), 3.38 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 166.3, 145.2, 143.0, 141.1, 140.7, 140.6, 136.4, 135.4, 132.5, 131.9, 130.7, 130.0, 129.95, 129.94, 129.92, 127.2, 121.4, 26.6; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{18}H_{13}N_2O_2^+$ 289.0972; Found 289.0983.

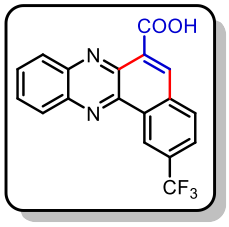


1-Methoxybenzo[*a*]phenazine-6-carboxylic acid (44ha): The title compound was purified by column chromatography on silica gel using EtOAc/ hexanes (1: 3 *v/v*) as an eluent; yellow solid (50 mg, 78%); mp = 276-278 °C; ^{1}H NMR (400 MHz,

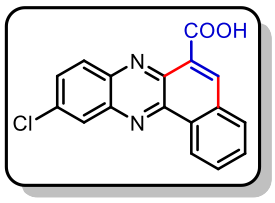


$CDCl_3$) δ 9.20 (s, 1H), 8.48 (dd, *J* = 6.6, 3.2 Hz, 1H), 8.28 (dd, *J* = 6.5, 3.3 Hz, 1H), 8.02 – 7.98 (m, 2H), 7.87 (t, *J* = 7.9 Hz, 1H), 7.77 (d, *J* = 7.4 Hz, 1H), 7.54 (d, *J* = 8.0 Hz, 1H), 4.29 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 166.3, 160.0, 144.0, 142.5, 141.8, 140.2, 136.4, 133.6, 132.0, 131.4, 130.8, 130.3, 127.1, 124.1, 122.2, 120.7, 114.6, 56.8; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{18}H_{13}N_2O_3^+$ 305.0921; Found 305.0918.

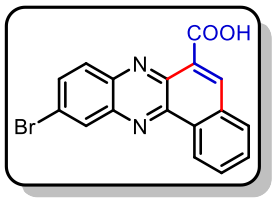
2-(Trifluoromethyl)benzo[*a*]phenazine-6-carboxylic acid (44ia): The title compound was purified by column chromatography on silica gel using EtOAc/ hexanes (1: 3 *v/v*) as an eluent; yellow solid (42 mg, 67%); mp = 264-266 °C;^{1}H NMR (400 MHz, $CDCl_3$) δ 15.80 (s, 1H), 9.72 (s, 1H), 9.29 (s, 1H), 8.53 (dd, *J* = 6.6, 3.4 Hz, 1H), 8.37 (dd, *J* = 6.4, 3.6 Hz, 1H), 8.29 (d, *J* = 8.4 Hz, 1H), 8.14 – 8.07 (m, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$: DMSO) δ 166.3, 142.4, 142.0, 140.2, 139.9, 138.9, 133.1, 132.9, 132.6, 132.3, 131.9, 131.4, 129.9, 127.6, 126.8 (q, $^4J_{C\text{-}F}$ = 3.0 Hz), 123.8 (q, $^1J_{C\text{-}F}$ = 271.2 Hz), 123.7, 122.7 (q, $^4J_{C\text{-}F}$ = 4.1 Hz); HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{18}H_{10}F_3N_2O_2^+$ 343.0689; Found 343.0687.



10-Chlorobenzo[*a*]phenazine-6-carboxylic acid (44ja): The title compound was purified by column chromatography on silica gel using EtOAc/ hexanes (1: 4, *v/v*) as an eluent; yellow solid (50 mg, 78%); mp = 276-278 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 15.50 (s, 1H), 9.37 (d, *J* = 7.6 Hz, 1H), 9.25 (s, 1H), 8.44 (d, *J* = 2.0 Hz, 1H), 8.26 (d, *J* = 8.8 Hz, 1H), 8.14 (d, *J* = 8.0 Hz, 1H), 8.02 – 7.98 (m, 1H), 7.96 – 7.92 (m, 2H); $^{13}C\{^1H\}$NMR (100 MHz, $CDCl_3$) δ 166.1, 143.4, 142.3, 142.2, 140.3, 137.4, 136.9, 133.3, 132.1, 131.5, 131.3, 131.31, 130.9, 128.8, 128.5, 125.7, 121.8; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{17}H_{10}ClN_2O_2^+$ 309.0425; Found 309.0431.

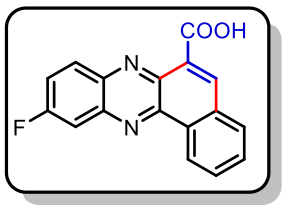


10-Bromobenzo[*a*]phenazine-6-carboxylic acid (44ka): The title compound was purified by column chromatography on silica gel using EtOAc/ hexanes (1: 4, *v/v*) as an eluent; yellow solid (52 mg, 84%); mp = 262-264 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 15.50 (s, 1H), 9.36 (d, *J* = 8.0 Hz, 1H), 9.26 (s, 1H), 8.63 (d, *J* = 2.0 Hz, 1H), 8.16 (dd, *J* = 17.0, 8.6 Hz, 2H), 8.07 (dd, *J* = 9.2, 2.0 Hz, 1H), 8.02 – 7.98 (m, 1H), 7.96 – 7.92 (m, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$ + MeOH) δ 166.3, 143.3, 142.4, 142.3, 140.3, 137.1, 135.7, 132.1, 131.9, 131.5, 131.3, 130.9, 128.7, 125.69,

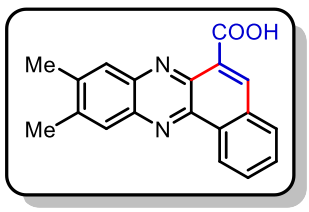


125.67, 121.6; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{17}H_{10}N_2BrN_2O_2^+$ 352.9920; Found 352.9904.

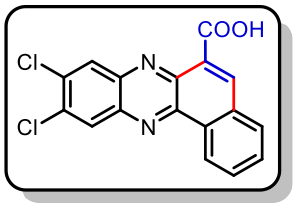
10-Fluorobenzo[*a*]phenazine-6-carboxylic acid (44la): The title compound was purified by column chromatography on silica gel using EtOAc/ hexanes (1: 2.3, *v/v*) as an eluent; yellow solid (48 mg, 74%); mp = 288-290 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 15.53 (s, 1H), 9.40 (d, *J* = 7.6 Hz, 1H), 9.24 (s, 1H), 8.34 (dd, *J* = 9.0, 5.4 Hz, 1H), 8.14 (d, *J* = 7.2 Hz, 1H), 8.06 (dd, *J* = 8.8, 2.4 Hz, 1H), 8.01 (t, *J* = 7.2 Hz, 1H), 7.95 (t, *J* = 7.0 Hz, 1H), 7.85 – 7.80 (m, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$ + MeOH) δ 166.48, 163.45 (d, $^1J_{C\text{-}F}$ = 255.2 Hz), 143.27, 142.84 (d, $^3J_{C\text{-}F}$ = 13.6 Hz), 141.84 (d, $^4J_{C\text{-}F}$ = 1.4 Hz), 139.70 (d, $^4J_{C\text{-}F}$ = 3.1 Hz), 135.74, 131.98, 131.48, 131.30, 131.25, 130.83, 129.82 (d, $^3J_{C\text{-}F}$ = 10.3 Hz), 125.66, 123.49 (d, $^2J_{C\text{-}F}$ = 27.3 Hz), 121.58, 112.74 (d, $^2J_{C\text{-}F}$ = 21.3 Hz); HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{17}H_{10}FN_2O_2^+$ 293.0721; Found 293.0727.



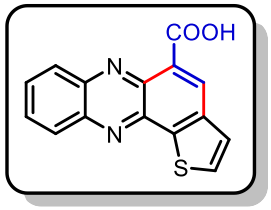
9,10-Dimethylbenzo[*a*]phenazine-6-carboxylic acid (44ma): The title compound was purified by column chromatography on silica gel using EtOAc/ hexanes (1: 4, *v/v*) as an eluent; yellow solid (53 mg, 82%); mp = 258-260 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 16.02 (s, 1H), 9.29 (d, *J* = 8.0 Hz, 1H), 9.14 (s, 1H), 8.09 (d, *J* = 8.4 Hz, 2H), 7.94 (t, *J* = 7.0 Hz, 2H), 7.87 (t, *J* = 7.2 Hz, 1H), 2.61 (s, 6H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 166.7, 143.8, 142.6, 141.8, 141.4, 140.6, 139.3, 137.4, 132.5, 131.1, 130.7, 130.5, 130.4, 128.4, 126.1, 125.2, 121.8, 20.8, 20.7; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{19}H_{15}N_2O_2^+$ 303.1128; Found 303.1139.



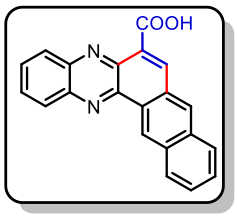
9,10-Dichlorobenzo[*a*]phenazine-6-carboxylic acid (44na): The title compound was purified by column chromatography on silica gel using EtOAc/ hexanes (1: 3, *v/v*) as an eluent; yellow solid (37 mg, 59%); mp = 282-284 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 15.26 (s, 1H), 9.37 (d, *J* = 7.2 Hz, 1H), 9.29 (s, 1H), 8.60 (s, 1H), 8.47 (s, 1H), 8.16 (d, *J* = 8.4 Hz, 1H), 8.03 (t, *J* = 7.6 Hz, 1H), 7.97 (t, *J* = 7.0 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 165.8, 143.5, 143.0, 141.0, 140.6, 137.3, 137.1, 136.4, 132.1, 131.54, 131.50, 131.0, 130.2, 128.0, 125.8, 121.8; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{17}H_9Cl_2N_2O_2^+$ 343.0036; Found 343.0027.



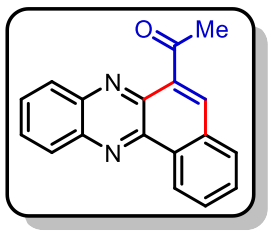
Thieno[3,2-*a*]phenazine-5-carboxylic acid (44oa): The title compound was purified by column chromatography on silica gel using EtOAc/ hexanes (1: 4, *v/v*) as an eluent; yellow solid (56 mg, 84%); mp = 248-250 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 15.77 (s, 1H), 9.30 (s, 1H), 8.49 (d, *J* = 5.2 Hz, 1H), 8.37 – 8.34 (m, 1H), 8.27 – 8.23 (m, 1H), 8.03 – 7.97 (m, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 166.2, 142.5, 140.2, 140.1, 139.3, 139.1, 138.4, 133.5, 132.7, 132.1, 131.4, 129.8, 127.7, 124.8, 120.1; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{15}H_9N_2O_2S^+$ 281.0379; Found 281.0382.



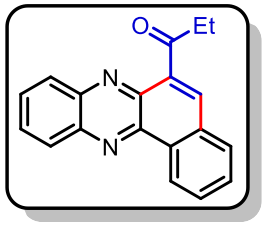
Naphtho[2,3-*a*]phenazine-6-carboxylic acid (44pa): The title compound was purified by column chromatography on silica gel using EtOAc/ hexanes (1: 3, *v/v*) as an eluent; yellow solid (56 mg, 89%); mp = 274-276 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 15.84 (s, 1H), 9.72 (s, 1H), 9.21 (s, 1H), 8.49 (s, 1H), 8.43 – 8.41 (m, 1H), 8.25 – 8.20 (m, 2H), 8.11 (d, *J* = 7.7 Hz, 1H), 8.03 – 7.95 (m, 2H), 7.78 – 7.69 (m, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 166.5, 144.0, 143.3, 141.7, 141.4, 137.9, 133.8, 133.7, 131.6, 131.4, 131.1, 129.7, 129.3, 128.8, 128.6, 128.5, 128.4, 128.1, 127.5, 126.0, 121.6; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{21}H_{13}N_2O_2^+$ 325.0972; Found 325.0969.



1-(Benzo[*a*]phenazin-6-yl)ethan-1-one (44ab): The title compound was purified by column chromatography on silica gel using EtOAc/ hexanes (1: 19, *v/v*) as an eluent; yellow solid (53 mg, 80%); mp = 188-190 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.36 (d, *J* = 7.6 Hz, 1H), 8.37 (s, 1H), 8.34 – 8.32 (m, 1H), 8.28 – 8.25 (m, 1H), 8.33, 7.98 (d, *J* = 7.2 Hz, 1H), 7.90 – 7.77 (m, 4H), 3.10 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 201.8, 142.0, 141.9, 141.5, 141.2, 137.0, 134.5, 132.4, 131.7, 130.4, 130.2, 130.1, 129.8, 129.6, 129.5, 125.4, 32.8; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{18}H_{13}N_2O^+$ 273.1022; Found 273.1020.

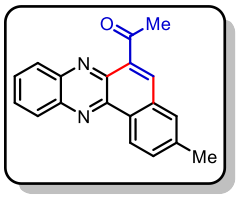


1-(Benzo[*a*]phenazin-6-yl)propan-1-one (44ac): The title compound was purified by column chromatography on silica gel using EtOAc/ hexanes (1: 19, *v/v*) as an eluent; yellow solid (54 mg, 78%); mp = 184-186 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.42 (d, *J* = 8.0 Hz, 1H), 8.39 – 8.36 (m, 1H), 8.32 (s, 1H), 8.31 – 8.28 (m, 1H), 8.02 (dd, *J* = 7.6, 0.8 Hz, 1H), 7.94 – 7.81 (m,



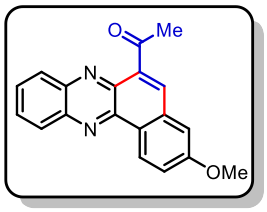
4H), 3.53 (q, *J* = 7.4 Hz, 2H), 1.37 (t, *J* = 7.2 Hz, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 205.7, 142.1, 142.0, 141.6, 141.3, 137.6, 133.9, 132.2, 131.9, 130.4, 130.3, 130.2, 129.7, 129.64, 129.62, 129.4, 125.5, 38.1, 8.7; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{19}H_{15}N_2O^+$ 287.1179; Found 287.1184.

1-(3-Methylbenzo[*a*]phenazin-6-yl)ethan-1-one (44bb): The title compound was purified by



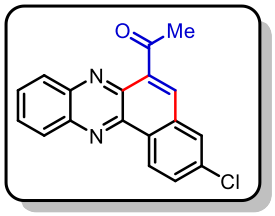
column chromatography on silica gel using EtOAc/ hexanes (1: 19, *v/v*) as an eluent; yellow solid (55 mg, 84%); mp = 184-186 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.23 (d, *J* = 8.4 Hz, 1H), 8.33 – 8.31 (m, 2H), 8.27 – 8.25 (m, 1H), 7.91 – 7.84 (m, 2H), 7.75 (s, 1H), 7.67 (d, *J* = 8.4 Hz, 1H), 3.10 (s, 3H), 2.62 (s, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 201.9, 142.2, 141.7, 141.1, 140.6, 137.0, 134.6, 131.8, 131.2, 130.3, 130.1, 130.0, 129.7, 129.6, 129.5, 125.4, 32.8, 21.7; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{19}H_{15}N_2O^+$ 287.1179; Found 287.1186.

1-(3-Methoxybenzo[*a*]phenazin-6-yl)ethan-1-one (44cb): The title compound was purified by



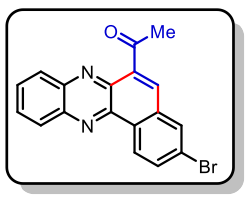
column chromatography on silica gel using EtOAc/ hexanes (1: 19, *v/v*) as an eluent; yellow solid (48 mg, 75%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.29 (d, *J* = 8.8 Hz, 1H), 8.33 – 8.30 (m, 2H), 8.26 (d, *J* = 8.0 Hz, 1H), 7.90 – 7.83 (m, 2H), 7.44 (d, *J* = 8.9 Hz, 1H), 7.37 (s, 1H), 4.01 (s, 3H), 3.09 (s, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 202.0, 161.2, 142.2, 141.7, 141.5, 140.6, 137.6, 134.2, 133.3, 130.4, 129.7, 129.6, 129.3, 127.3, 126.2, 119.0, 110.9, 55.7, 32.8; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{19}H_{15}N_2O_2^+$ 303.1128; Found 303.1136.

1-(3-Chlorobenzo[*a*]phenazin-6-yl)ethan-1-one (44db): The title compound was purified by



column chromatography on silica gel using EtOAc/ hexanes (1: 19, *v/v*) as an eluent; yellow solid (43 mg, 67%); mp = 242-244 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.36 (d, *J* = 8.4 Hz, 1H), 8.37 (d, *J* = 7.6 Hz, 1H), 8.32 – 8.28 (m, 2H), 8.00 (s, 1H), 7.95 – 7.91 (m, 2H), 7.83 (d, *J* = 8.8 Hz, 1H), 3.10 (s, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 201.7, 142.1, 141.7, 141.6, 140.9, 138.5, 136.4, 132.9, 132.8, 130.8, 130.7, 130.6, 129.9, 129.7, 129.6, 128.8, 127.1, 32.8; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{18}H_{12}ClN_2O^+$ 307.0633; Found 307.0641.

1-(3-Bromobenzo[*a*]phenazin-6-yl)ethan-1-one (44eb): The title compound was purified by



column chromatography on silica gel using EtOAc/ hexanes (1: 19, *v/v*) as

an eluent; yellow solid (43 mg, 69%); mp = 234-236 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.29 (d, J = 8.4 Hz, 1H), 8.39 – 8.37 (m, 1H), 8.33 – 8.31 (m, 1H), 8.28 (s, 1H), 8.17 (d, J = 1.2 Hz, 1H), 7.99 – 7.92 (m, 3H), 3.10 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 201.6, 142.2, 141.75, 141.72, 140.9, 138.5, 133.1, 132.8, 132.6, 132.0, 131.0, 130.9, 130.6, 129.7, 129.6, 127.2, 124.7, 32.7; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{11}H_{12}BrN_2O^+$ 351.0128; Found 351.0121.

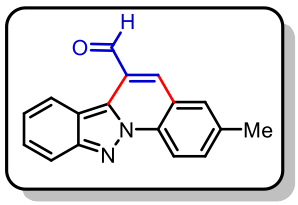
1-(3-(Trifluoromethyl)benzo[*a*]phenazin-6-yl)ethan-1-one (44fb): The title compound was purified by column chromatography on silica gel using EtOAc/ hexanes (1:19, *v/v*) as an eluent; Yellow solid (47 mg, 75%); mp = 190-192 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.49 (d, J = 8.5 Hz, 1H), 8.38 – 8.36 (m, 2H), 8.33 – 8.28 (m, 1H), 8.27 (s, 1H), 8.05 (d, J = 8.3 Hz, 1H), 7.98 – 7.93 (m, 2H), 3.10 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 201.3, 142.4, 141.7, 141.3, 141.1, 138.6, 134.5, 133.2, 131.8 (q, $^{2}J_{C-F}$ = 35.8 Hz), 131.4, 131.1, 131.0, 129.73, 129.68, 126.8 (q, $^{4}J_{C-F}$ = 4.0 Hz), 126.4, 125.3 (q, $^{4}J_{C-F}$ = 3.0 Hz), 122.6 (q, $^{1}J_{C-F}$ = 273.3 Hz), 32.7; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{19}H_{12}F_3N_2O^+$ 341.0896; Found 341.0889.

1-(3-Fluorobenzo[*a*]phenazin-6-yl)ethan-1-one (44qb): The title compound was purified by column chromatography on silica gel using EtOAc/ hexanes (1: 19, *v/v*) as an eluent; yellow solid (47 mg, 72%); mp = 196-198 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.41 (dd, J = 9.0, 5.8 Hz, 1H), 8.35 (dd, J = 7.2, 2.4 Hz, 1H), 8.31 – 7.28 (m, 2H), 7.95 – 7.89 (m, 2H), 7.65 (dd, J = 8.8, 2.4 Hz, 1H), 7.61 – 7.56 (m, 1H), 3.10 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 201.7, 163.6 (d, $^{1}J_{C-F}$ = 250.0 Hz), 141.9, 141.7, 140.7, 138.5, 133.4, 133.4, 133.1 (d, $^{4}J_{C-F}$ = 3.4 Hz), 130.7, 130.3, 129.7, 129.5, 128.8 (d, $^{4}J_{C-F}$ = 2.2 Hz), 128.2, 128.1, 118.0 (d, $^{2}J_{C-F}$ = 23.0 Hz), 114.5 (d, $^{2}J_{C-F}$ = 21.5 Hz), 32.7; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{18}H_{12}FN_2O^+$ 291.0928; Found 291.0934.

Indazolo[2,3-*a*]quinoline-6-carbaldehyde (45aa): The title compound was purified by column chromatography on silica gel using EtOAc/ hexanes (1: 9, *v/v*) as an eluent; yellow solid (46 mg, 72%); mp = 148-150 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.32 (s, 1H), 9.00 (t, J = 7.6 Hz, 2H), 8.18 (s, 1H), 8.05 (d, J = 7.6 Hz, 1H), 8.00 – 7.93 (m, 2H), 7.69 (t, J = 7.6 Hz, 1H), 7.62 (t, J = 7.6 Hz, 1H), 7.35 (t, J = 7.6 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 189.8, 149.8, 135.8, 134.3, 132.9, 129.9, 128.6, 128.5, 128.4, 126.8, 124.3, 123.1,

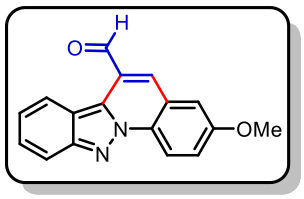
121.8, 117.9, 117.2, 116.6; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{16}H_{11}N_2O^+$ 247.0866; Found 247.0877.

3-Methylindazolo[2,3-*a*]quinoline-6-carbaldehyde (45ba): The title compound was purified



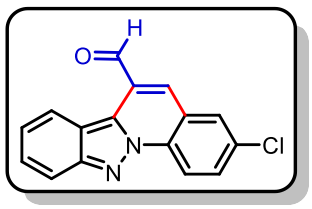
by column chromatography on silica gel using EtOAc/ hexanes (1: 9, *v/v*) as an eluent; yellow solid (49 mg, 78%); mp = 158-160 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.32 (s, 1H), 9.02 – 8.99 (m, 1H), 8.87 (d, *J* = 8.4 Hz, 1H), 8.12 (s, 1H), 7.99 (d, *J* = 8.7 Hz, 1H), 7.81 (s, 1H), 7.77 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.63 – 7.59 (m, 1H), 7.37 – 7.32 (m, 1H), 2.61 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 189.9, 149.7, 136.9, 134.6, 134.3, 134.0, 129.2, 128.5, 128.4, 128.2, 124.2, 123.2, 121.6, 117.6, 117.2, 116.5, 21.3; HRMS (ESI) *m/z:* $[M + H]^+$ Calcd for $C_{17}H_{13}N_2O^+$ 261.1022; Found 261.1025.

3-Methoxyindazolo[2,3-*a*]quinoline-6-carbaldehyde (45ca): The title compound was purified



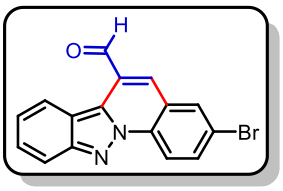
by column chromatography on silica gel using EtOAc/ hexanes (1: 4, *v/v*) as an eluent; yellow solid (46 mg, 75%); mp = 186-188 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.25 (s, 1H), 8.95 (d, *J* = 8.4 Hz, 1H), 8.85 (d, *J* = 9.2 Hz, 1H), 8.01 (s, 1H), 7.96 (d, *J* = 8.4 Hz, 1H), 7.60 (t, *J* = 7.6 Hz, 1H), 7.51 (dd, *J* = 9.2, 2.8 Hz, 1H), 7.35 – 7.29 (m, 2H), 3.98 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 189.8, 158.1, 149.5, 133.5, 130.6, 128.6, 128.2, 127.6, 124.2, 124.1, 122.9, 121.5, 119.3, 117.1, 116.3, 109.5, 55.8; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{17}H_{13}N_2O_2^+$ 277.0972; Found 277.0979.

3-Chloroindazolo[2,3-*a*]quinoline-6-carbaldehyde (45da): The title compound was purified by

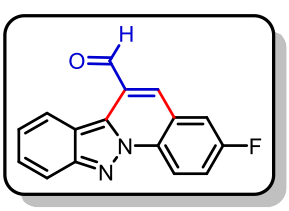


column chromatography on silica gel using EtOAc/ hexanes (1: 9, *v/v*) as an eluent; yellow solid (43 mg, 70%); mp = 192-194 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.24 (s, 1H), 8.91 (d, *J* = 8.6 Hz, 1H), 8.85 (d, *J* = 9.0 Hz, 1H), 7.96 – 7.92 (m, 3H), 7.83 (dd, *J* = 9.2, 2.4 Hz, 1H), 7.61 (t, *J* = 7.6 Hz, 1H), 7.34 (t, *J* = 7.6 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 189.4, 149.8, 134.0, 132.9, 132.6, 132.4, 129.2, 128.8, 128.5, 128.2, 124.1, 123.9, 122.2, 119.4, 117.2, 116.6; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{16}H_{10}ClN_2O^+$ 281.0476, Found 281.0485

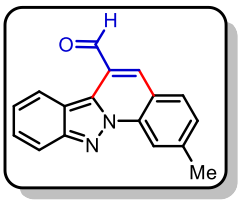
3-Bromoindazolo[2,3-*a*]quinoline-6-carbaldehyde (45ea): The title compound was purified by column chromatography on silica gel using EtOAc/ hexanes (1: 9, *v/v*) as an eluent; yellow solid (44 mg, 74%); mp = 208-210 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.30 (s, 1H), 8.96 (d, *J* = 8.8 Hz, 2H), 8.85 (d, *J* = 9.2 Hz, 1H), 8.18 (d, *J* = 2.0 Hz, 2H), 8.05 (s, 1H), 8.01 (dd, *J* = 9.2, 2.0 Hz, 1H), 7.97 (d, *J* = 8.8 Hz, 1H), 7.64 – 7.60 (m, 1H), 7.38 – 7.34 (m, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 189.4, 149.9, 135.6, 134.4, 132.4, 131.7, 129.3, 128.8, 128.3, 124.4, 124.1, 122.2, 120.3, 119.6, 117.2, 116.6; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{16}H_{10}BrN_2O^+$ 324.9971; Found 324.9977.



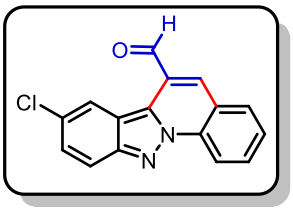
3-Fluoroindazolo[2,3-*a*]quinoline-6-carbaldehyde (45fa): The title compound was purified by column chromatography on silica gel using EtOAc/ hexanes (1: 9, *v/v*) as an eluent; yellow solid (43 mg, 69%); mp = 178-180 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.32 (s, 1H), 9.01 – 8.94 (m, 2H), 8.08 (s, 1H), 7.97 (d, *J* = 8.8 Hz, 1H), 7.69 (d, *J* = 8.0 Hz, 2H), 7.65 – 7.60 (m, 1H), 7.38 – 7.34 (m, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 189.5, 160.6 (d, $^{1}J_{C\text{-}F}$ = 247.2 Hz), 149.7, 132.7 (d, $^{4}J_{C\text{-}F}$ = 3.6 Hz), 132.4, 129.4, 128.6, 128.0, 124.2, 124.2, 124.1, 122.0, 121.3 (d, $^{2}J_{C\text{-}F}$ = 24.6 Hz), 120.2 (d, $^{3}J_{C\text{-}F}$ = 8.6 Hz), 117.2, 116.6, 114.0 (d, $^{2}J_{C\text{-}F}$ = 22.6 Hz); HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{16}H_{10}FN_2O^+$ 265.0772; Found 265.0771.



2-Methylindazolo[2,3-*a*]quinoline-6-carbaldehyde (45ga): The title compound was purified by column chromatography on silica gel using EtOAc/ hexanes (1: 9, *v/v*) as an eluent; yellow solid (51 mg, 81%); mp = 154-156 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.24 (s, 1H), 9.00 (d, *J* = 8.4 Hz, 1H), 8.76 (s, 1H), 8.09 (s, 1H), 7.97 (d, *J* = 8.4 Hz, 1H), 7.88 (d, *J* = 8.0 Hz, 1H), 7.60 (t, *J* = 7.6 Hz, 1H), 7.46 (d, *J* = 7.6 Hz, 1H), 7.33 (t, *J* = 7.6 Hz, 1H), 2.69 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 189.6, 149.8, 144.6, 135.7, 134.5, 129.6, 128.6, 128.52, 128.48, 127.6, 124.4, 121.5, 120.9, 117.5, 117.1, 116.4, 22.4; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{17}H_{13}N_2O^+$ 261.1022; Found 261.1014.

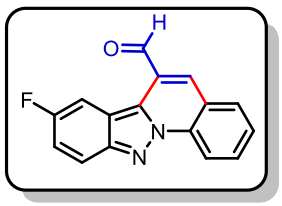


8-Chloroindazolo[2,3-*a*]quinoline-6-carbaldehyde (45ha): The title compound was purified by column chromatography on silica gel using EtOAc/ hexanes (1: 9, *v/v*) as an eluent; yellow solid (45 mg, 73%); mp = 196-198 °C; ^{1}H NMR

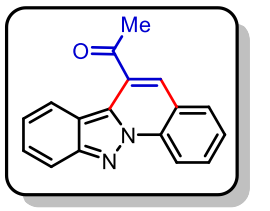


(400 MHz, $CDCl_3$) δ 10.27 (s, 1H), 9.07 (d, *J* = 1.6 Hz, 1H), 8.98 (d, *J* = 8.8 Hz, 1H), 8.22 (s, 1H), 8.08 (d, *J* = 8.0 Hz, 1H), 8.01 – 7.96 (m, 1H), 7.91 (d, *J* = 8.8 Hz, 1H), 7.75 – 7.70 (m, 1H), 7.53 (dd, *J* = 9.2, 2.0 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 189.7, 148.1, 135.8, 135.2, 133.2, 129.9, 129.8, 128.4, 127.9, 127.2, 127.1, 123.25, 123.22, 118.0, 117.9, 117.6; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{16}H_{10}ClN_2O^+$ 281.0476; Found 281.0482.

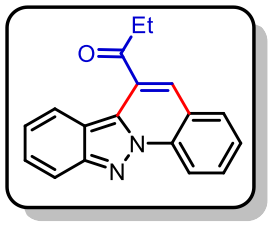
8-Fluoroindazolo[2,3-*a*]quinoline-6-carbaldehyde (45ia): The title compound was purified by column chromatography on silica gel using EtOAc/ hexanes (1: 9, *v/v*) as an eluent; yellow solid (47 mg, 75%); mp = 188-190 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 10.21 (s, 1H), 8.93 (d, *J* = 8.4 Hz, 1H), 8.67 (dd, *J* = 10.4, 2.0 Hz, 1H), 8.12 (s, 1H), 8.04 (d, *J* = 7.6 Hz, 1H), 7.97 – 7.91 (m, 2H), 7.71 – 7.67 (m, 1H), 7.42 – 7.37 (m, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 189.8, 157.9 (d, $^1J_{C\text{-}F}$ = 247.2 Hz), 147.41, 135.8, 134.7, 132.9, 129.8, 128.5, 128.46, 128.41, 127.0, 123.1, 119.7 (d, $^2J_{C\text{-}F}$= 28.8 Hz), 118.3 (d, $^3J_{C\text{-}F}$= 9.5 Hz), 117.7, 116.7 (d, $^3J_{C\text{-}F}$ = 12.6 Hz), 107.6 (d, $^2J_{C\text{-}F}$= 26.8 Hz); HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{16}H_{10}FN_2O^+$ 265.0772; Found 265.0777.



1-(Indazolo[2,3-*a*]quinolin-6-yl)ethan-1-one (45ab): The title compound was purified by column chromatography on silica gel using EtOAc/ hexanes (1: 4, *v/v*) as an eluent; yellow solid (46 mg, 68%); mp = 166-168 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.95 (d, *J* = 8.4 Hz, 1H), 8.62 (d, *J* = 8.8 Hz, 1H), 8.09 (s, 1H), 7.96 (t, *J* = 9.0 Hz, 2H), 7.90 – 7.86 (m, 1H), 7.65 – 7.56 (m, 2H), 7.31 – 7.27 (m, 1H), 2.87 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 197.3, 149.9, 135.2, 131.9, 129.7, 129.4, 128.9, 128.3, 127.1, 126.6, 124.2, 123.1, 121.5, 117.7, 116.6, 116.5, 28.3; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{17}H_{13}N_2O^+$ 261.1022; Found 261.1014.

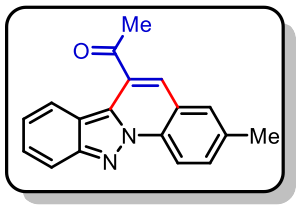


1-(Indazolo[2,3-*a*]quinolin-6-yl)propan-1-one (45ac): The title compound was purified by column chromatography on silica gel using EtOAc/ hexanes (1: 9, *v/v*) as an eluent; yellow solid (46 mg, 65%); mp = 172-174 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 9.00 (d, *J* = 8.4 Hz, 1H), 8.53 (d, *J* = 8.8 Hz, 1H), 8.10 (s, 1H), 7.99 (d, *J* = 8.4 Hz, 2H), 7.92 – 7.88 (m, 1H), 7.68 – 7.64 (m, 1H), 7.61 – 7.57 (m, 1H), 7.31 (d, *J* = 7.6 Hz, 1H), 3.26 (q, *J* = 7.2 Hz, 2H),



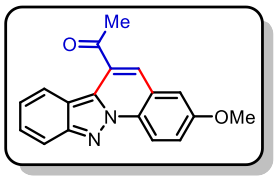
1.42 (t, J = 7.2 Hz, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 200.7, 149.9, 135.2, 131.6, 129.9, 129.3, 129.0, 128.2, 126.6, 125.6, 123.8, 123.3, 121.5, 117.7, 116.7, 116.6, 33.8, 8.5; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{18}H_{15}N_2O^+$ 275.1179; Found 275.1187.

1-(3-Methylindazolo[2,3-*a*]quinolin-6-yl)ethan-1-one (45bb): The title compound was



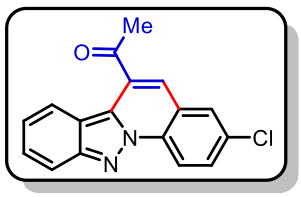
purified by column chromatography on silica gel using EtOAc/ hexanes (1: 9, *v/v*) as an eluent; yellow solid (47 mg, 71%); mp = 176-178 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.86 (d, J = 8.8 Hz, 1H), 8.64 (d, J = 8.8 Hz, 1H), 8.07 (s, 1H), 7.97 (d, J = 8.8 Hz, 1H), 7.75 (s, 1H), 7.72 (d, J = 8.8 Hz, 1H), 7.60 – 7.56 (m, 1H), 7.31 – 7.29 (m, 1H), 2.88 (s, 3H), 2.60 (s, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 197.4, 149.8, 136.7, 133.6, 129.7, 128.8, 128.7, 128.1, 127.0, 124.1, 123.2, 121.3, 117.5, 116.8, 116.5, 28.4, 21.3; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{18}H_{15}N_2O^+$ 275.1179; Found 275.1185.

1-(3-Methoxyindazolo[2,3-*a*]quinolin-6-yl)ethan-1-one (45cb): The title compound was



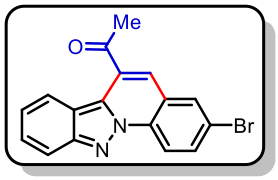
purified by column chromatography on silica gel using EtOAc/ hexanes (1: 4, *v/v*) as an eluent; yellow solid (45 mg, 69%); mp = 168-170 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.90 (d, J = 9.2 Hz, 1H), 8.62 (d, J = 8.4 Hz, 1H), 8.06 (s, 1H), 7.96 (d, J = 8.8 Hz, 1H), 7.58 (t, J = 7.6 Hz, 1H), 7.51 (dd, J = 9.2, 2.4 Hz, 1H), 7.32 – 7.29 (m, 2H), 4.00 (s, 3H), 2.88 (s, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 197.4, 158.1, 149.7, 130.2, 128.3, 127.9, 126.5, 124.3, 123.9, 121.9, 121.2, 119.2, 116.8, 116.3, 109.3, 55.8, 28.4; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{18}H_{15}N_2O_2^+$ 291.1128; Found 291.1137.

1-(3-Chloroindazolo[2,3-*a*]quinolin-6-yl)ethan-1-one (45db): The title compound was purified



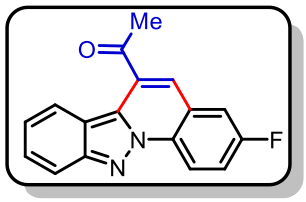
by column chromatography on silica gel using EtOAc/ hexanes (1: 9, *v/v*) as an eluent; yellow solid (43 mg, 67%); mp = 194-196 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.86 (d, J = 9.2 Hz, 1H), 8.55 (d, J = 8.8 Hz, 1H), 7.94 – 7.89 (m, 3H), 7.79 (dd, J = 9.0, 1.8 Hz, 1H), 7.58 (t, J = 7.6 Hz, 1H), 7.31 – 7.28 (m, 1H), 2.85 (s, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 197.0, 149.9, 133.5, 132.3, 132.0, 130.7, 128.7, 128.5, 128.2, 125.3, 124.02, 124.00, 121.8, 119.2, 116.8, 116.6, 28.4; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{17}H_{12}ClN_2O^+$ 295.0633; Found 295.0630.

1-(3-Bromoindazolo[2,3-*a*]quinolin-6-yl)ethan-1-one (45eb): The title compound was purified



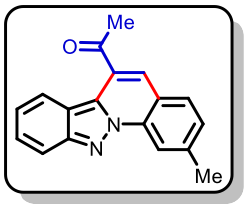
by column chromatography on silica gel using EtOAc/ hexanes (1: 9, *v/v*) as an eluent; yellow solid (40 mg, 64%); mp = 160-162 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.86 (d, *J* = 9.2 Hz, 1H), 8.58 (d, *J* = 8.4 Hz, 1H), 8.14 (s, 1H), 8.00 – 7.95 (m, 3H), 7.60 (t, *J* = 7.4 Hz, 1H), 7.33 – 7.29 (m, 1H), 2.88 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 197.1, 150.0, 134.7, 134.0, 131.4, 130.8, 128.8, 128.5, 125.2, 124.5, 124.0, 121.9, 120.1, 119.5, 116.9, 116.6, 28.4; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{17}H_{12}BrN_2O^+$ 339.0128; Found 339.0136.

1-(3-Fluoroindazolo[2,3-*a*]quinolin-6-yl)ethan-1-one (45fb): The title compound was purified



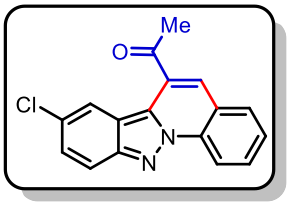
by column chromatography on silica gel using EtOAc/ hexanes (1: 9, *v/v*) as an eluent; yellow solid (42 mg, 65%); mp = 174-176 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.98 (dd, *J* = 10.0, 4.8 Hz, 1H), 8.57 (d, *J* = 8.8 Hz, 1H), 8.01 (s, 1H), 7.96 (d, *J* = 8.8 Hz, 1H), 7.63 – 7.57 (m, 3H), 7.33 – 7.29 (m, 1H), 2.88 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 197.2, 160.6 (d, $^{1}J_{C\text{-}F}$ = 246.4 Hz), 149.8, 131.9, 130.9, 128.5, 128.3, 125.5 (d, $^{4}J_{C\text{-}F}$ = 3.6 Hz), 124.3 (d, $^{3}J_{C\text{-}F}$ = 9.1 Hz), 123.9, 121.7, 120.3 (d, $^{2}J_{C\text{-}F}$ = 24.7 Hz), 120.0 (d, $^{3}J_{C\text{-}F}$ = 8.5 Hz), 116.9, 116.6, 113.6 (d, $^{2}J_{C\text{-}F}$ = 22.7 Hz), 28.5; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{17}H_{12}FN_2O^+$ 279.0928; Found 279.0934.

1-(2-Methylindazolo[2,3-*a*]quinolin-6-yl)ethan-1-one (45gb): The title compound was purified



by column chromatography on silica gel using EtOAc/ hexanes (1: 9, *v/v*) as an eluent; yellow solid (46 mg, 70%); mp = 162-164 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.77 (s, 1H), 8.67 (d, *J* = 8.4 Hz, 1H), 8.09 (s, 1H), 7.97 (d, *J* = 8.4 Hz, 1H), 7.84 (d, *J* = 8.0 Hz, 1H), 7.58 (t, *J* = 7.6 Hz, 1H), 7.45 (d, *J* = 8.0 Hz, 1H), 7.30 – 7.27 (m, 1H), 2.86 (s, 3H), 2.68 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 197.2, 149.9, 143.4, 135.2, 129.24, 129.18, 128.8, 128.4, 128.3, 127.4, 124.3, 121.3, 120.9, 117.4, 116.8, 116.4, 28.3, 22.3; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{18}H_{15}N_2O^+$ 275.1179; Found 275.1185.

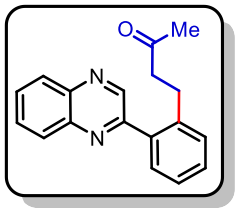
1-(8-Chloroindazolo[2,3-*a*]quinolin-6-yl)ethan-1-one (45hb): The title compound was purified



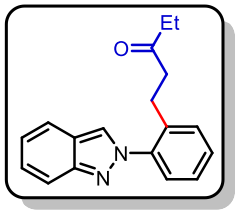
by column chromatography on silica gel using EtOAc/ hexanes (1:9, *v/v*) as an eluent; yellow solid (41 mg, 64%); mp = 172-174 °C; ^{1}H

NMR (400 MHz, $CDCl_3$) δ 8.95 (d, *J* = 8.4 Hz, 1H), 8.70 (d, *J* = 1.6 Hz, 1H), 8.18 (s, 1H), 8.00 (d, *J* = 7.6 Hz, 1H), 7.94 – 7.87 (m, 2H), 7.69 (t, *J* = 7.4 Hz, 1H), 7.50 (dd, *J* = 9.0, 2.2 Hz, 1H), 2.89 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 197.0, 148.2, 135.3, 132.2, 129.55, 129.47, 129. 4, 128.6, 127.9, 127.0, 126.8, 123.3, 123.2, 117.9, 117.7, 117.3, 28.2; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{17}H_{12}ClN_2O^+$ 295.0633; Found 295.0628.

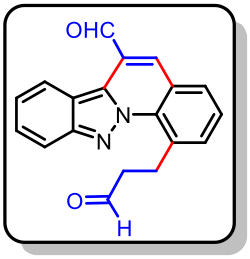
4-(2-(Quinoxalin-2-yl)phenyl)butan-2-one (46ab): The title compound was purified by column chromatography on silica gel using EtOAc/ hexanes (1: 4, *v/v*) as an eluent; yellow oily liquid (46 mg, 68%); ^1H NMR (400 MHz, $CDCl_3$) δ 9.04 (s, 1H), 8.19 – 8.17 (m, 1H), 8.12 – 8.10 (m, 1H), 7.85 – 7.80 (m, 2H), 7.56 – 7.53 (m, 1H), 7.48 – 7.39 (m, 3H), 3.07 (t, *J* = 8.0 Hz, 2H), 2.86 (t, *J* = 7.2 Hz, 2H), 2.10 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 207.8, 154.7, 145.8, 141.7, 141.1, 140.3, 136.9, 130.5, 130.4, 130.3, 129.9, 129.7, 129.5, 129.3, 126.7, 45.7, 29.9, 27.5; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{18}H_{17}N_2O^+$ 277.1335; Found 277.1344.



1-(2-(2*H*-Indazol-2-yl)phenyl)pentan-3-one (47ac): The title compound was purified by column chromatography on silica gel using EtOAc/ hexanes (1: 4, *v/v*) as an eluent; yellow oily liquid (51 mg, 71%); ^1H NMR (400 MHz, $CDCl_3$) δ 8.16 (d, *J* = 0.8 Hz, 1H), 7.80 – 7.75 (m, 2H), 7.47 – 7.35 (m, 5H), 7.19 – 7.15 (m, 1H), 2.84 (t, *J* = 7.6 Hz, 2H), 2.62 (t, *J* = 7.6 Hz, 2H), 2.30 (q, *J* = 7.4 Hz, 2H), 0.97 (t, *J* = 7.4 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 210.4, 149.3, 140.1, 137.5, 130.5, 129.5, 127.05, 127.00, 126.5, 124.6, 122.3, 122.0, 120.4, 117.9, 43.0, 35.9, 25.7, 7.7; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{18}H_{19}N_2O^+$ 279.1492; Found 279.1484.

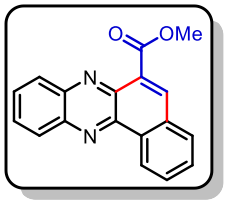


1-(3-Oxopropyl)indazolo[2,3-*a*]quinoline-6-carbaldehyde (48): The title compound was purified by column chromatography on silica gel using EtOAc/hexanes (1: 4, *v/v*) as an eluent; yellow oily liquid (17 mg, 22%); ^1H NMR (400 MHz, $CDCl_3$) δ 10.36 (s, 1H), 10.02 (s, 1H), 9.02 (d, *J* = 8.4 Hz, 1H), 8.20 (s, 1H), 7.98 (d, *J* = 7.2 Hz, 1H), 7.92 (d, *J* = 8.8 Hz, 1H), 7.81 (d, *J* = 6.8 Hz, 1H), 7.62 – 7.58 (m, 2H), 7.37 (t, *J* = 6.6 Hz, 2H), 4.15 (t, *J* = 7.2 Hz, 2H),

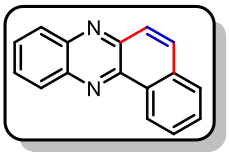


3.12 (t, J = 6.4 Hz, 2H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 202.2, 189.6, 149.3, 136.7, 135.2, 133.0, 129.7, 129.3, 128.2, 128.1, 127.3, 126.4, 125.1, 123.9, 122.0, 116.8, 115.9, 46.1, 29.8; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{19}H_{15}N_2O_2^+$ 303.1128; Found 303.1132

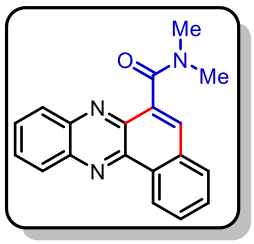
Methyl benzo[*a*]phenazine-6-carboxylate (49): The title compound was purified by column chromatography on silica gel using EtOAc/ hexanes (1: 4, *v/v*) as an eluent; off white solid (24 mg, 76%); mp = 122-124 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.46 (d, J = 8.0 Hz, 1H), 8.51 (s, 1H), 8.40 – 8.37 (m, 2H), 8.02 (d, J = 7.6 Hz, 1H), 7.94 – 7.89 (m, 3H), 7.87 – 7.83 (m, 1H), 4.16 (s, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 167.2, 142.6, 141.9, 141.7, 140.9, 135.6, 132.4, 131.4, 130.6, 130.2, 130.12, 130.10, 129.7, 129.5, 129.4, 129.2, 125.6, 52.7; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{18}H_{13}N_2O_2^+$ 289.0972; Found 289.0978.



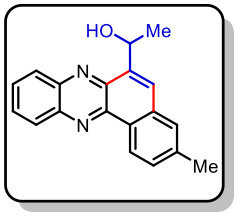
Benzo[*a*]phenazine (50): The title compound was purified by column chromatography on silica gel using EtOAc/ hexanes (1: 19, *v/v*) as an eluent; yellow solid (30 mg, 72%); mp = 232-234 °C (Lit. mp 236-237 °C)[121]; ^{1}H NMR (400 MHz, $CDCl_3$) 9.47 – 9.44 (m, 1H), 8.41 – 8.39 (m, 1H), 8.33 – 8.30 (m, 1H), 8.06 – 7.99 (m, 2H), 7.96 – 7.94 (m, 1H), 7.91 – 7.89 (m, 2H), 7.86 – 7.79 (m, 2H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 143.6, 142.7, 142.0, 133.4, 133.3, 131.2, 130.1, 129.90, 129.86, 129.7, 129.2, 128.3, 128.0, 127.2, 125.4; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{16}H_{11}N_2^+$ 231.0917; Found 231.0917.



***N*, *N*-Dimethylbenzo[*a*]phenazine-6-carboxamide (51):** The title compound was purified by column chromatography on silica gel using EtOAc/ hexanes (1: 3, *v/v*) as an eluent; off white solid (21 mg, 64%); mp = 118-120 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.45 (dd, J = 7.8, 1.4 Hz, 1H), 8.41 – 8.38 (m, 1H), 8.34 – 8.31 (m, 1H), 8.06 (s, 1H), 7.97 – 7.81 (m, 5H), 3.38 (s, 3H), 2.92 (s, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 169.4, 142.7, 142.0, 141.9, 140.8, 135.0, 132.3, 131.3, 131.0, 130.4, 130.1, 129.9, 129.6, 128.7, 128.6, 125.4, 38.8, 35.1; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{19}H_{16}N_3O^+$ 302.1288; Found 302.1292.



1-(3-Methylbenzo[*a*]phenazin-6-yl)ethan-1-ol (52): The title compound was purified by column chromatography on silica gel using EtOAc/ hexanes (1:4, *v/v*) as an eluent; off white solid (28 mg, 90%); mp = 184-186 °C; ^{1}H NMR (400



MHz, $CDCl_3$) δ 9.22 (d, *J* = 8.0 Hz, 1H), 8.36 – 8.34 (m, 1H), 8.25 – 8.23 (m, 1H), 7.91 – 7.83 (m, 3H), 7.67 (s, 1H), 7.60 (d, *J* = 8.4 Hz, 1H), 5.63 (q, *J* = 6.8 Hz, 1H), 5.37 (s, 1H), 2.62 (s, 3H), 1.86 (d, *J* = 6.8 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 143.2, 142.5, 141.6, 140.7, 140.4, 139.0, 132.9, 130.0, 129.9, 129.5, 129.4, 129.08, 129.07, 128.4, 128.2, 125.2, 69.0, 22.9, 21.8; HRMS (ESI) *m/z:* $[M + H]^+$ Calcd for $C_{19}H_{17}N_2O^+$ 289.133 5; Found 289.1341.

1.4.2.5 X-ray Crystallographic Analysis of Compound 45aa

The single crystal of the compound **45aa** ($C_{16}H_{10}N_2O$) was obtained from slow evaporation of chloroform: hexane solutions. A suitable crystal was selected and mounted on an XtaLAB AFC12 (RINC): Kappa dual home/near diffractometer. The crystal was kept at 123(2) K during data collection. Using Olex2,[122] the structure was solved with the SHELXT[123] structure solution program using Intrinsic Phasing and refined with the SHELXL[124] refinement package using Least Squares minimisation. The **45aa** was crystallized in a triclinic space-group crystal system with a P-1 space group. The crystal structure information of **45aa** is deposited to the Cambridge Crystallographic Data Center, and the CCDC number for the **45aa** is 2209858.

Table 1.5: Crystal data and structure refinement for **45aa**

Identification code	**45aa**
Empirical formula	$C_{16}H_{10}N_2O$
Formula weight	246.26
Temperature/K	123(2)
Crystal system	triclinic
Space group	P-1
a/Å	8.0807(2)
b/Å	11.4488(3)
c/Å	13.0502(4)
α/°	75.453(2)
β/°	79.894(2)

γ/°	79.458(2)
Volume/Å^3	1138.21(6)
Z	4
ρ_{calc}g/cm^3	1.437
μ/mm^{-1}	0.736
F(000)	512.0
Crystal size/mm^3	0.19 × 0.05 × 0.04
Radiation	Cu Kα (λ = 1.54184)
2Θ range for data collection/°	8.064 to 159.736
Index ranges	-9 ≤ h ≤ 6, -14 ≤ k ≤ 14, -16 ≤ l ≤ 15
Reflections collected	12496
Independent reflections	4788 [R_{int} = 0.0315, R_{sigma} = 0.0394]
Data/restraints/parameters	4788/0/343
Goodness-of-fit on F^2	1.066
Final R indexes [I>=2σ (I)]	R_1 = 0.0395, wR_2 = 0.1073
Final R indexes [all data]	R_1 = 0.0440, wR_2 = 0.1105
Largest diff. peak/hole / e Å^{-3}	0.21/-0.30

1.5 REFERENCES

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Chapter 2

Copper(II)-Catalysed Annulation of 2-Amino Carbonyl Compounds with Maleimides: Synthesis of Pyrrolo[3,4-*b*]quinolinediones

2.1 INTRODUCTION

Quinoline and pyrrole scaffolds containing heterocyclic compounds have received considerable attention in drug design as they exhibit a large spectrum of pharmacological activities such as antimicrobial, analgesic, antiviral, antiparasitic, cytotoxic hypnotic, anticholesterol, anticonvulsant, anti-Alzheimer and antitumor activities.[1-5] In particular, pyrrolo[3,4-*b*]quinolines are important hybrid of quinoline and pyrrole scaffolds, which constitute the core structure of many naturally occurring alkaloids and synthetic molecules such as luotonin A,[6] rosettacin,[7] camptothecin,[8] homocampthotecin,[9] topotecan[10] and mappicine[11-13] (**Figure 2.1**). Natural and synthetic molecules containing pyrrolo[3,4-*b*]quinolines skeleton are associated with a large spectrum of biological activities towards various targets.[14-17]

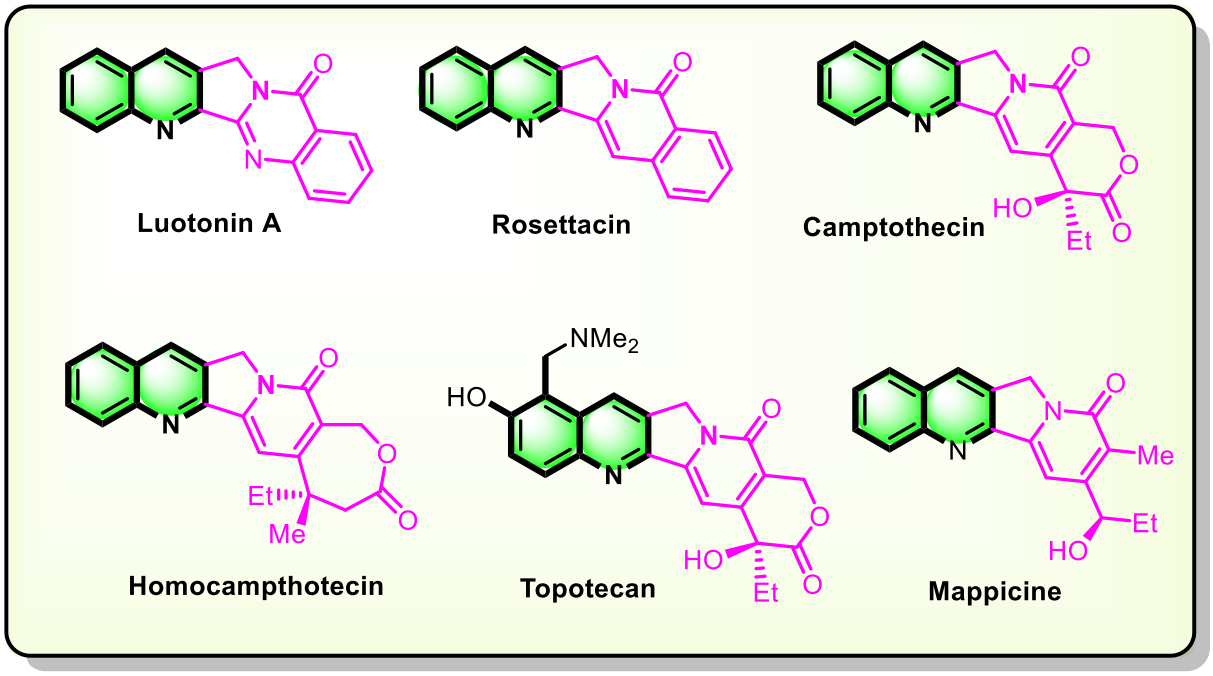
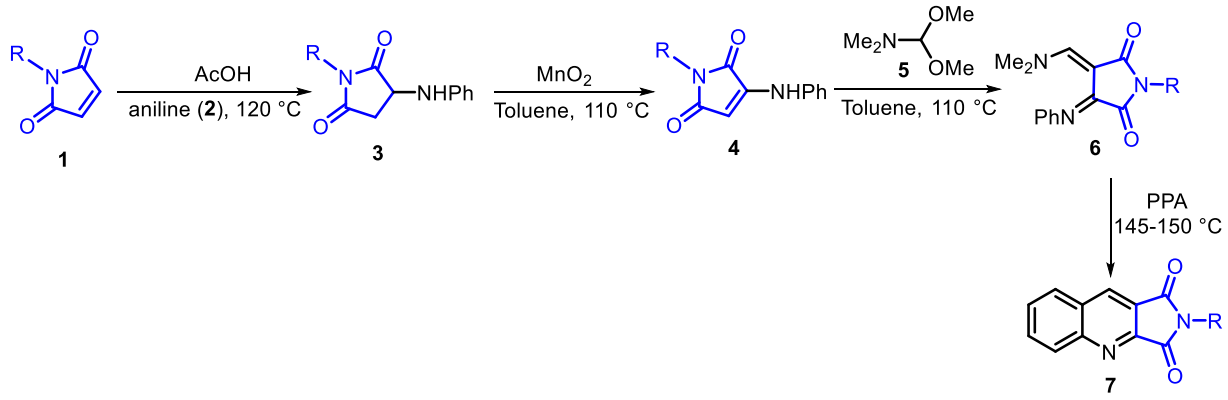


Figure 2.1: Representative bioactive molecules containing pyrroloquinoline skeleton

A large number of pyrrolo[3,4-*b*]quinoline-based alkaloids and other related bioactive compounds have been synthetically derived from pyrrolo[3,4-*b*]quinolinediones; however, there are very few reports available for the construction of pyrrolo[3,4-*b*]quinolinediones. Most of these methods rely on multistep reactions and start from the substituted quinoline or substituted maleimide precursors.

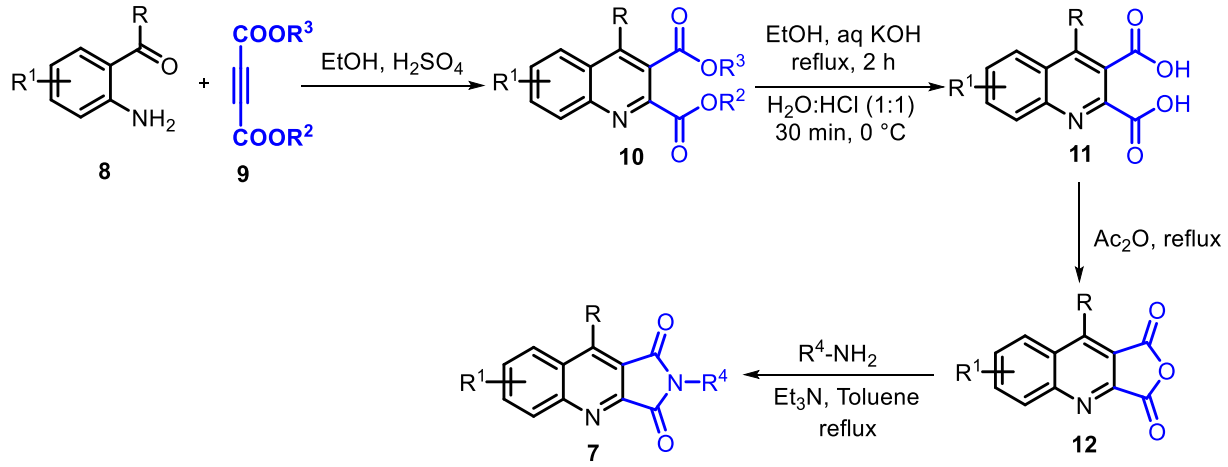
In 1988, Maulding group described the multistep synthesis of pyrrolo[3,4-*b*]quinolinediones (**7**) (**Scheme 2.1**).[18] First, the reaction of a maleimide (**1**) with aniline (**2**) in the presence of acetic acid resulted the formation of anilinosuccinimide (**3**). Subsequently, oxidation of (**3**) was oxidized with

manganese dioxide produced anilinomaleimide (**4**). This compound was then treated with 1,1-dimethoxy-*N*, *N*-dimethylmethanamine (**5**) to afford an intermediate (**6**). Which was the converted pyrrolo[3,4-*b*]quinolinediones (**7**) in the presence of polyphosphoric acid.



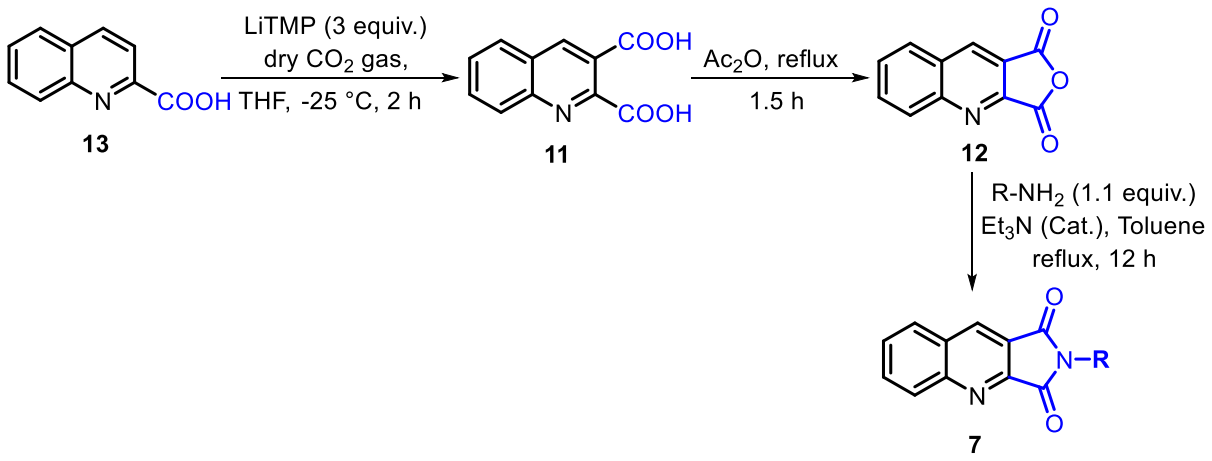
Scheme 2.1: Synthesis of pyrrolo[3,4-*b*]quinolinediones from maleimide and aniline

Imanzadeh *et al.* disclosed the synthesis of pyrrolo[3,4-*b*]quinolinediones (**7**) from *o*-ketoanilines (**8**) and dialkylacetylenedi-carboxylate (**9**). Initially the reaction of **8** and **9** in refluxing ethanol with an acid catalyst afforded the quinoline diesters intermediate (**10**). Then, alkaline hydrolysis of quinoline diesters (**10**) fallowed by acidification with HCl at low temperatures produced the dicarboxyquinoline derivative (**11**). Refluxing (**11**) with acetic anhydride give the corresponding anhydride derivative (**12**). Finally, the reaction of substituted aniline with anhydrides derivative (**12**) in the presence of Et_3N as a catalyst produced the desired pyrrolo[3,4-*b*]quinolinediones (**Scheme 2.2**).[19]



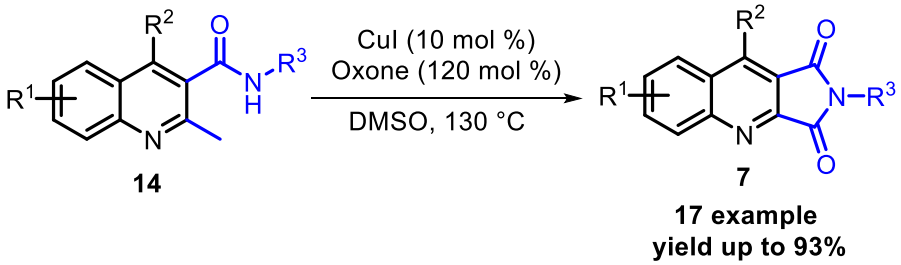
Scheme 2.2: Synthesis of pyrrolo[3,4-*b*]quinolinediones from *o*-ketoanilines and dialkylacetylenedi-carboxylate

Routier and co-workers developed the synthesis of pyrrolo[3,4-*b*]quinolinediones (**7**) by utilizing 2-quinolinyl carboxylic acid (**13**) with excess LiTMP and dry CO_2, resulting in the formation of the corresponding quinoline-2,3-dicarboxylic acid (**11**). Compound (**11**) was treated with acetic anhydride at reflux for 2 hours to produce an intermediate (**12**). Further, this anhydride intermediate was then condensed with amine over 12 hours, forming the desired product (**7**) with a 78% yield (**Scheme 2.3**).[20]



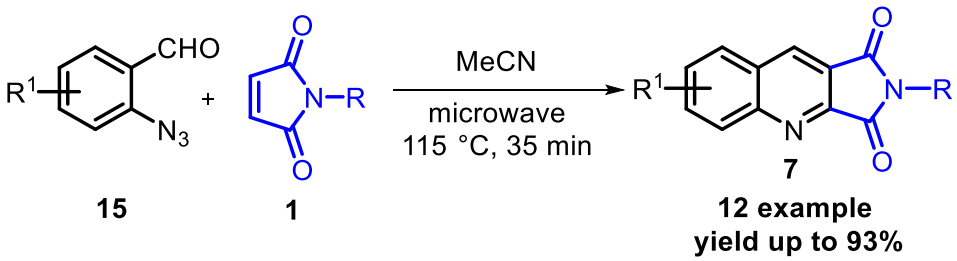
Scheme 2.3: Synthesis of pyrrolo[3,4-*b*]quinolinediones from 2-quinolinyl carboxylic acid

Zhang's group reported a copper(I)-catalyzed intramolecular direct oxidative amidation reaction to synthesize fused *N*-heterocyclic compounds (**Scheme 2.4**).[21] The 2-methyl-3-carbamoyl-quinoline (**14**) underwent intramolecular tandem amidation followed by oxidation to furnish the biologically active 1*H*-pyrrolo[3,4-*b*]quinoline-1,3(2*H*)-diones scaffold (**7**). This method's silent features are the minimally toxic reagent, cheap copper salt as a catalyst and good to excellent yields.



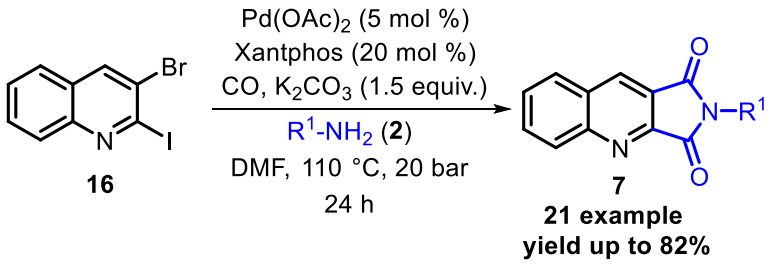
Scheme 2.4: Copper (I)-catalyzed synthesis pyrrolo[3,4-*b*]quinolinediones from 2-methyl-3-carbamoyl-quinoline

Zang *et al*. disclosed the microwave-mediated reaction of 2-azido benzaldehydes (**15**) with *N*-substituted maleimide (**1**) to afford the variety of pyrroloquinolinediones derivatives in moderate to good yields (**Scheme 2.5**).[22] The developed protocol involved a one-pot reaction, including denitrogenation of azide, benzisoxazole formation, and aza-Diels–Alder cycloaddition followed by dehydrative aromatization.



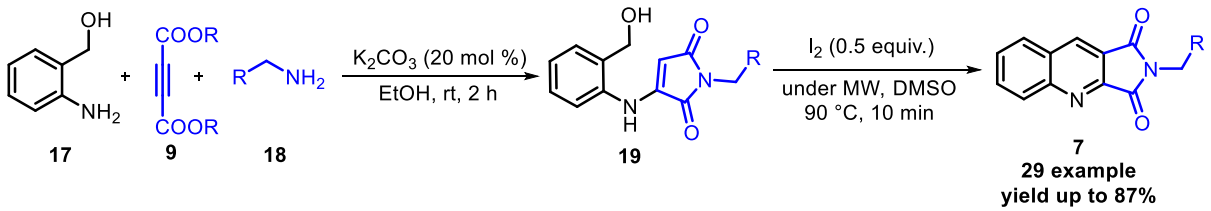
Scheme 2.5: microwave mediated synthesis of pyrrolo[3,4-*b*]quinolinediones from 2-azido benzaldehydes

Recently, Takács and co-workers reported the Pd(II)-catalyzed carbonylative cyclization of 3-bromo-2-iodoquinoline (**16**) with different substituted amines (**2**) to afford the *N*-substituted pyrrolo[3,4-*b*]quinoline-1,3-diones (**7**) (**Scheme 2.6**).[23] The developed protocol exhibited high efficiency and broad substrate scope with respect to a variety of amines.



Scheme 2.6: synthesis of pyrrolo[3,4-*b*]quinolinediones from of 3-bromo-2-iodoquinoline *via* Pd-catalysed carbonalative cyclization

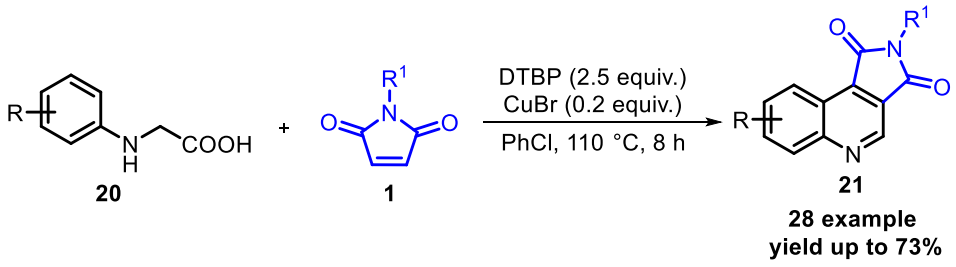
In 2023, Huang *et al.* developed a facile route for the synthesis of pyrrolo[3,4-*b*]quinolinediones (**7**) Initially the reaction of 2-amino benzyl alcohol (**17**) dialkylacetylenedi-carboxylate (**9**) and benzylamine (**18**) (**Scheme 2.7**).[24] Subsequently aminomaleimides intermediate (**19**) undergoes iodine-oxidized tandem annulations involving oxidation of alcohol and intramolecular cyclization, followed by aromatization reactions.



Scheme 2.7: Synthesis of pyrrolo[3,4-*b*]quinolinediones from 2-amino benzyl alcohol, dialkylacetylenedi-carboxylate and benzylamine

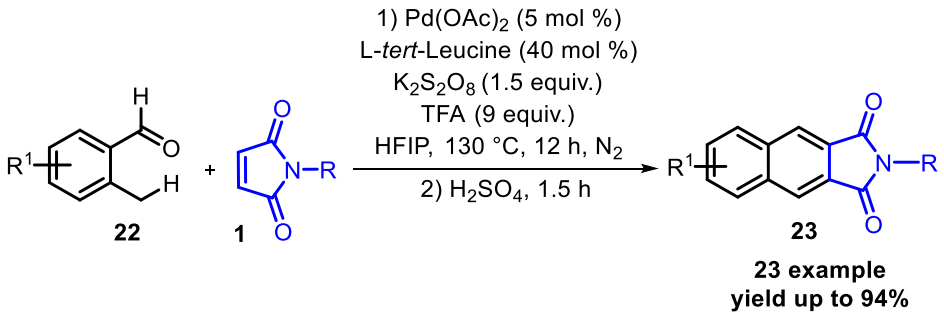
Maleimide structures have garnered significant attention across various fields including biomaterials, chemical probes, and organic dyes. Their versatility makes them valuable in pharmacology and agriculture, owing to their diverse biological activities.[25, 26] Maleimide motifs have been found to be invaluable pharmaceutical and bioactive natural compounds. Moreover, they are utilized in developing fluorescent probes for detecting biothiols[27] and labelling proteins, peptides, and other molecules containing free thiol groups[28]. Additionally, maleimide compounds have been investigated for their potential in anticancer activity and molecular docking.[29] Maleimide plays a dual role in organic transformations and used as a dienophile in electrocyclic reactions.[30, 31]

Additionally, it acts as a two-carbon electrophilic coupling partner in conjugate addition reactions and metal-catalyzed reactions such as C-H functionalization, spirocyclization, and annulation reactions.[32-41] The versatility of maleimide derivatives makes them essential in various scientific and industrial applications. In particular, the Yan group reported a 1*H*-pyrrolo[3,4-*c*]quinoline-1,3(2*H*)-diones (**21**) through Cu-catalyzed decarboxylative cyclization of *N*-phenylglycines (**20**) with maleimides (**1**) (**Scheme 2.8**).[42] This synthetic protocol involved consecutive oxidation-decarboxylation, 1,2-addition, intramolecular cyclization, and tautomerization, followed by aromatization reactions.



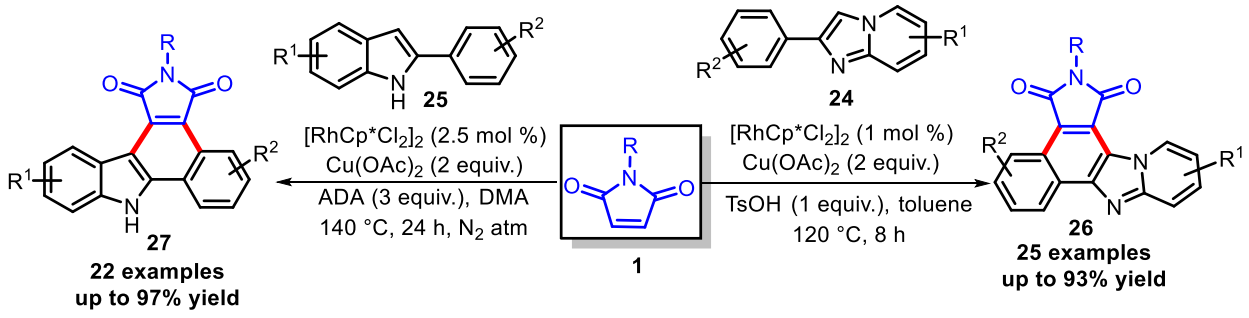
Scheme 2.8: Cu-catalyzed annulation of *n*-phenylglycines with maleimides

Zhang and co-workers demonstrated an efficient approach for the preparation of naphthalimides derivatives (**23**) *via* Pd(II)-catalyzed tandem process using *o*-methylbenzaldehydes (**22**) and maleimides (**1**) (**Scheme 2.9**).[43] The sequential reaction involves Pd(II)-catalyzed benzylic C(sp^3)−H oxidation by utilizing an amino acid as a transient directing group, followed by a Diels−Alder reaction. The succeeding dehydration step leads to the formation of naphthalimides derivatives.



Scheme 2.9: Pd(II)-catalyzed annulation of *o*-methylbenzaldehydes with maleimides

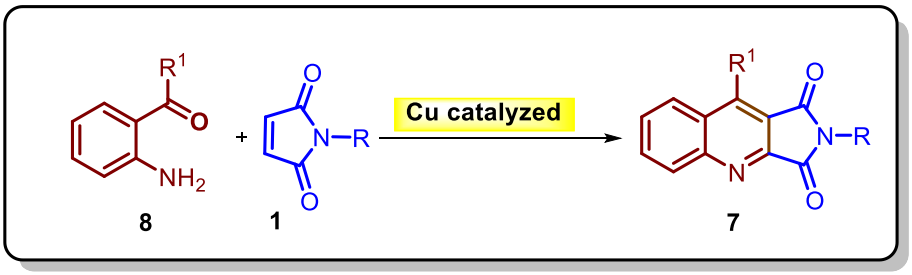
Our team also developed Rh(III)-catalyzed dehydrogenative annulation and a spirocyclization protocol for 2-arylimidazo[1,2-*a*]pyridines (**24**) and 2-arylindoles (**25**) with maleimides (**1**) to afford annulated and spirocyclized products with consistently good to excellent yields (**Scheme 2.10**).[44, 45] Additionally, the study explores the absorption and fluorescence properties of the annulated products, supported by quantum chemical calculations. Notably, the protocol demonstrates a wide substrate scope encompassing 2-arylimidazo[1,2-*a*]pyridines/indoles and maleimides.



Scheme 2.10: Rh(III)-catalyzed annulation of 2-arylimidazo[1,2-*a*]pyridines/2-arylindoles with maleimides

Thus, the development of efficient novel protocols for the construction of pyrrolo[3,4-*b*]quinolinediones from readily available substrates have become an important challenge for

chemists.[46-50] Thus, developing more flexible and efficient methods that lead to structurally diverse libraries of pyrrolo[3,4-*b*]quinolinediones is highly desirable in organic synthesis. However, to the best of our knowledge, there is no report for synthesizing Pyrrolo[3,4-*b*]quinolinediones by directly coupling *ortho*-amino carbonyl compounds with maleimide in a one-pot strategy. In continuation of our efforts toward developing methodologies for *N*-heterocyclic systems, herein we developed an efficient synthetic method for one-pot synthesis of pyrrolo[3,4-*b*]quinolinedione derivatives by copper(II)-catalyzed annulation of *ortho*-amino carbonyl compounds with maleimides (**Scheme 2.11**).

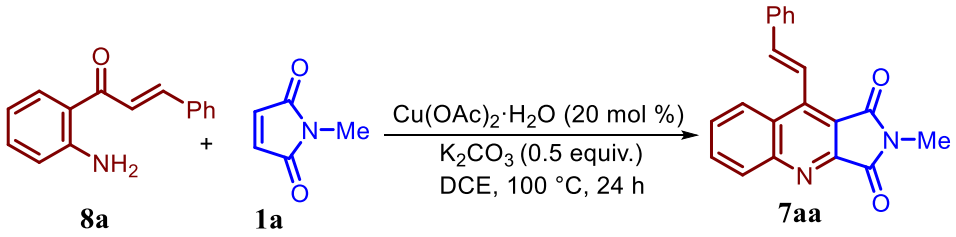


Scheme 2.11: Synthesis of pyrroloquinolinediones *via* Cu(II)-catalyzed annulation of *ortho*-amino carbonyl compound with maleimides

2.2 RESULTS AND DISCUSSION

Our initial investigation began by examining the reaction of (*E*)-1-(2-aminophenyl)-3-phenylprop-2-en-1-one (**8a**) and maleimide (**1a**) under different conditions to optimize the reaction conditions. The results are summarized in **Table 2.1**. Gratifyingly, the desired product (*E*)-2-methyl-9-styryl-1*H*-pyrrolo[3,4-*b*]quinoline-1,3(2*H*)-dione (**7aa**) was furnished in 83% yield from the reaction of **8a** and **1a** in the presence of $Cu(OAc)_2{\cdot}H_2O$ (1 equiv.), K_2CO_3 (1.5 equiv.) in DCE at 100 °C for 24 h (**Table 2.1**, entry 1). The structure product **7aa** was confirmed by NMR (^1H, $^{13}C\{^1H\}$) and HRMS data. In ^1H NMR spectrum of **7aa**, the characteristic peak C12-H *N*-methyl proton singlet appeared at 3.33 ppm and one trans double bond proton C14-H appeared at 8.03 ppm and rest of the aromatic protons well matched with the structure (**Figure 2.2**). In $^{13}C\{^1H\}$ NMR of **7aa**, carbonyl carbon of the *N*-methyl maleimide appeared at 166.8 ppm and 166.3 ppm, respectively along with other carbons (**Figure 2.3**). Finally, peak at *m/z* 315.1131 in the HRMS corresponding to molecular formula $C_{20}H_{15}N_2O_2$ $[M + H]^+$ ion confirmed the structure at **7aa**.

Table 2.1: Optimization of reaction conditions



8a **1a** **7aa**

Entry	Variation from standard conditions	% Yield 7aa[b]
1	**none**	**83**
2	reaction time 12 h	65
3	80 °C and 12 h	52
4	toluene as solvent	67
5	PhCl as solvent	59
6	DMF/ IPA/ TFE/ DMSO as solvent	NR
7	$Cu(OAc)_2·H_2O$ (50 mol%)	81
8	$Cu(OAc)_2·H_2O$ (10 mol%)	74
9	$CuSO_4·5H_2O$ (20 mol%) as catalyst	54
10	$Cu(OTf)_2$ (20 mol%) as catalyst	57
11	CuI/CuBr (20 mol%) as catalyst	NR
12	$Zn(OTf)_2/Yb(OTf)_2$ (20 mol%) as catalyst	NR
13	NaOAc as base	72
14	KOAc as base	77
15	CsOAc as base	63
16	Na_2CO_3 as base	77
17	Cs_2CO_3 as base	71
18	No base	53
19	No catalyst	NR

[a]Reaction conditions: **8a** (0.22 mmol), **1a** (0.45 mmol), copper salt (20 mol%), base (0.5 equiv.), solvent (2 mL), air. [b]Isolated yields.

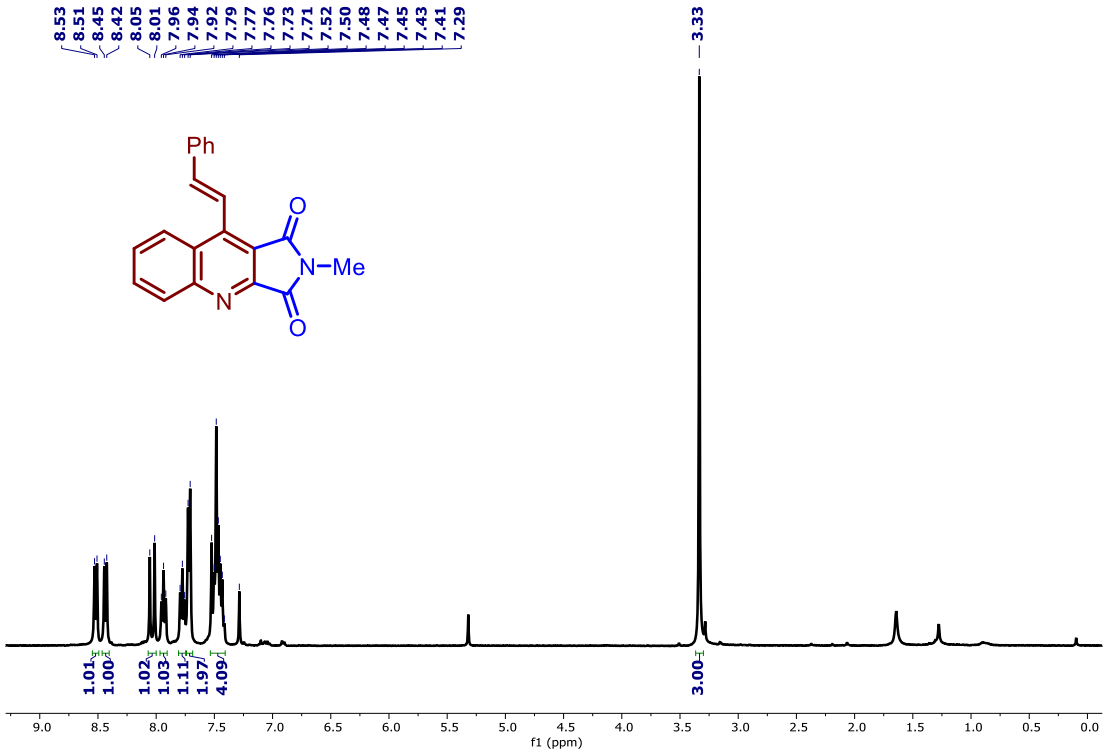


Figure 2.2: ^{1}H-NMR spectrum of (*E*)-2-methyl-9-styryl-1*H*-pyrrolo[3,4-*b*]quinoline-1,3(2*H*)-dione (**7aa**) recorded in $CDCl_3$

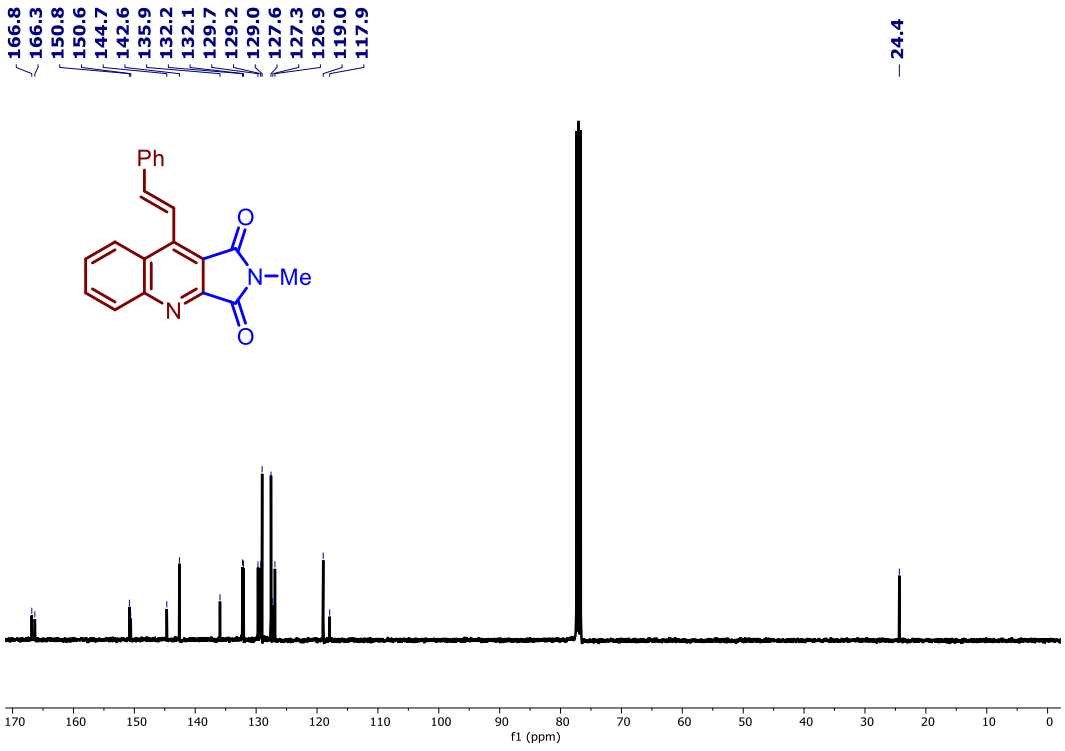


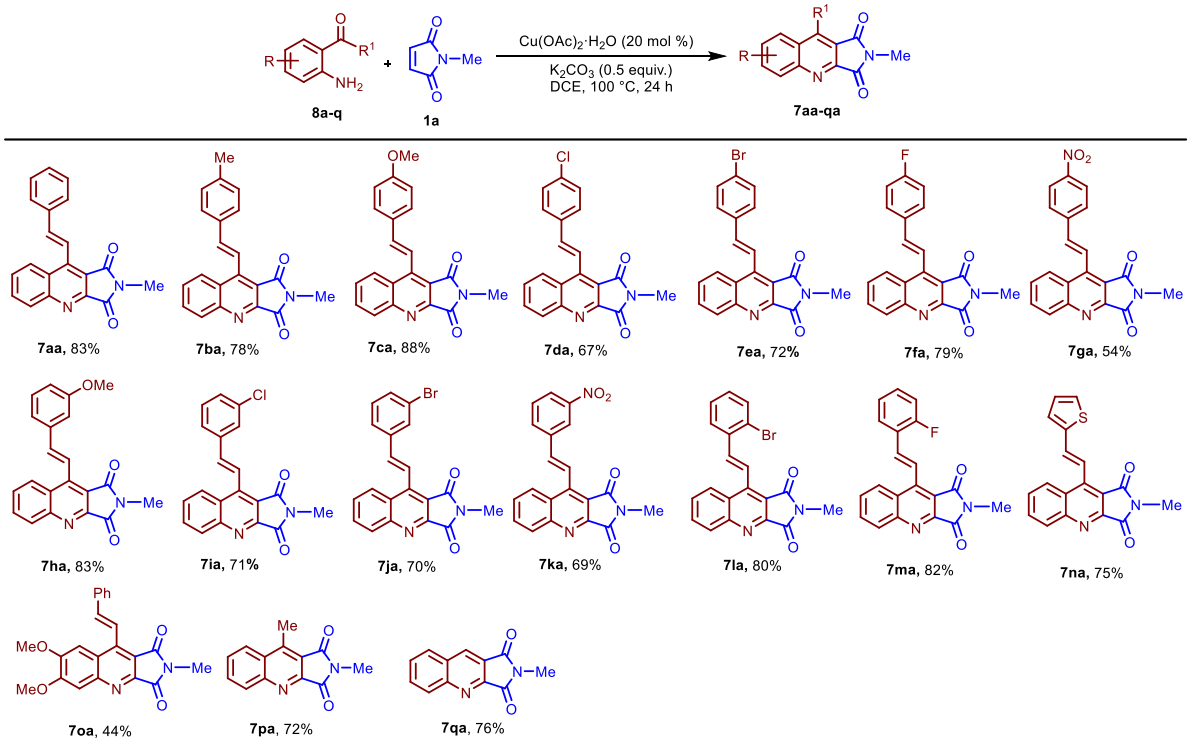
Figure 2.3: ^{13}C{^{1}H}-NMR spectrum of (*E*)-2-methyl-9-styryl-1*H*-pyrrolo[3,4-*b*]quinoline-1,3(2*H*)-dione **(7aa)** recorded in $CDCl_3$

Further yield of **7aa** decreased to 65% on decreasing reaction time to 12 h (**Table 2.1**, entry 2). Similarly, lowering the reaction temperature to 80 °C and reaction time to 12 h also produced **7aa** in low yield (**Table 2.1**, entry 3). Next, to examine the effect of solvent polarity on this reaction, we screened solvents with varying polarities, e.g., toluene, chlorobenzene, DMF, IPA, TFE, and DMSO (**Table 2.1**, entries 4-6). Interestingly, solvent polarity played a significant role in this reaction. The desired product **7aa** was obtained in good yields in non-polar solvents such as toluene and chlorobenzene albeit in lower yield than DCE, while the reaction failed to produce **7aa** in polar solvents such as DMF, IPA, TFE, and DMSO. Yield of **7aa** did not improve on increasing the amount of copper catalyst to 50 mol%, while it dropped to 74% on lowering the catalyst amount to 10 mol% (**Table 2.1**, entry 7-8). Other copper catalysts such as $CuSO_4 \cdot 5H_2O$ and $Cu(OTf)_2$ provided lower yields of **7aa**, whereas with CuBr and CuI reaction failed to produce **7aa** (**Table 1.1**, entry 8-11). Other Lewis acid catalysts, such as $Zn(OTf)_2$ and $Yb(OTf)_3$, failed to catalyze the reaction (**Table 2.1**, entry 12). Subsequently, the role of the base was examined. The use of NaOAc, KOAc, CsOAc, Na_2CO_3, and Cs_2CO_3 afforded lower yields of **7aa** in comparison with the K_2CO_3 (**Table 2.1**, entries 12-17). Further, the absence of K_2CO_3 led to a significant decrease in the yield of **3aa** (**Table 2.1**, entry 18). Importantly, the desired product **7aa** was not obtained in the absence of $Cu(OAc)_2 \cdot H_2O$ (**Table 2.1**, entry 19).

With the optimal reaction condition in hand (**Table 2.1**, entry 1) we next set out to examine the scope and generality of the reaction using diverse *ortho*-amino carbonyl compounds and maleimides (**Table 2.2**). At first, various (*E*)-1-(2-aminophenyl)-3-arylprop-2-en-1-one derivatives (2′-amino chalcones) (**8a-m**) were allowed to react with **1a**. To our satisfaction, various 2′-amino chalcones with substituents such as methyl, methoxy, bromo, chloro, fluoro, and nitro on different positions of the 3-aryl ring reacted efficiently with **1a** to afford the desired products **7aa-ma** in moderate to good (54-88%) yields. Generally, 2′-amino chalcones bearing electron-donating substituents on the 3-aryl ring produced corresponding products in slightly higher yields as compared to 2′-amino chalcones with electron-withdrawing substituents on the 3-aryl ring (compare **7ca** and **7ha** *vs* **7ga** and **7ka**). It is worth noting that the halo-substituted 2′-amino chalcones furnished the corresponding products in good yields, thereby enabling further functionalization. Chalcones with hetero-aromatic ring, (*E*)-1-(2-aminophenyl)-3-(thiophen-2-yl)prop-2-en-1-one, **8n** also responded well, delivering corresponding product **7na** in 75% yield. Next, substituted chalcone (*E*)-1-(2-amino-4,5-dimethoxyphenyl)-3-phenylprop-2-en-1-one (**8o**)

2-aminoacetophenone (**8p**) and 2-aminobenzaldehyde (**8q**) smoothly reacted with **1a** to afford desired product **7oa**, **7pa**, and **7qa** in moderate to good yield (44-76%). Structure of all new compounds was confirmed by NMR and Mass analysis. Structure of **7ea** was also unambiguously confirmed by the single crystal X-ray analysis (**CCDC No** 2209858).

Table 2.2: Substrate scope of *ortho*-amino carbonyl compounds.[a,b]



[a]Reaction conditions: **8** (0.22 mmol), **1** (0.45 mmol), $Cu(OAc)_2 \cdot H_2O$ (20 mol %), K_2CO_3 (0.5 equiv.), DCE (2 mL), 100 °C, 24 h. [b]Isolated yields

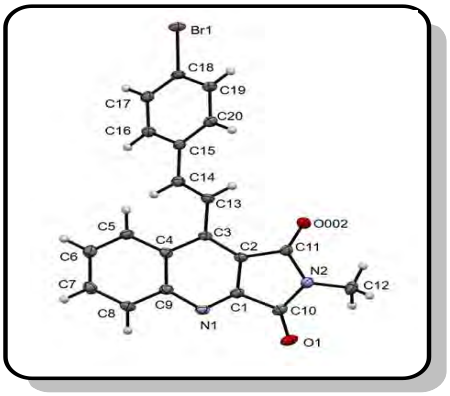
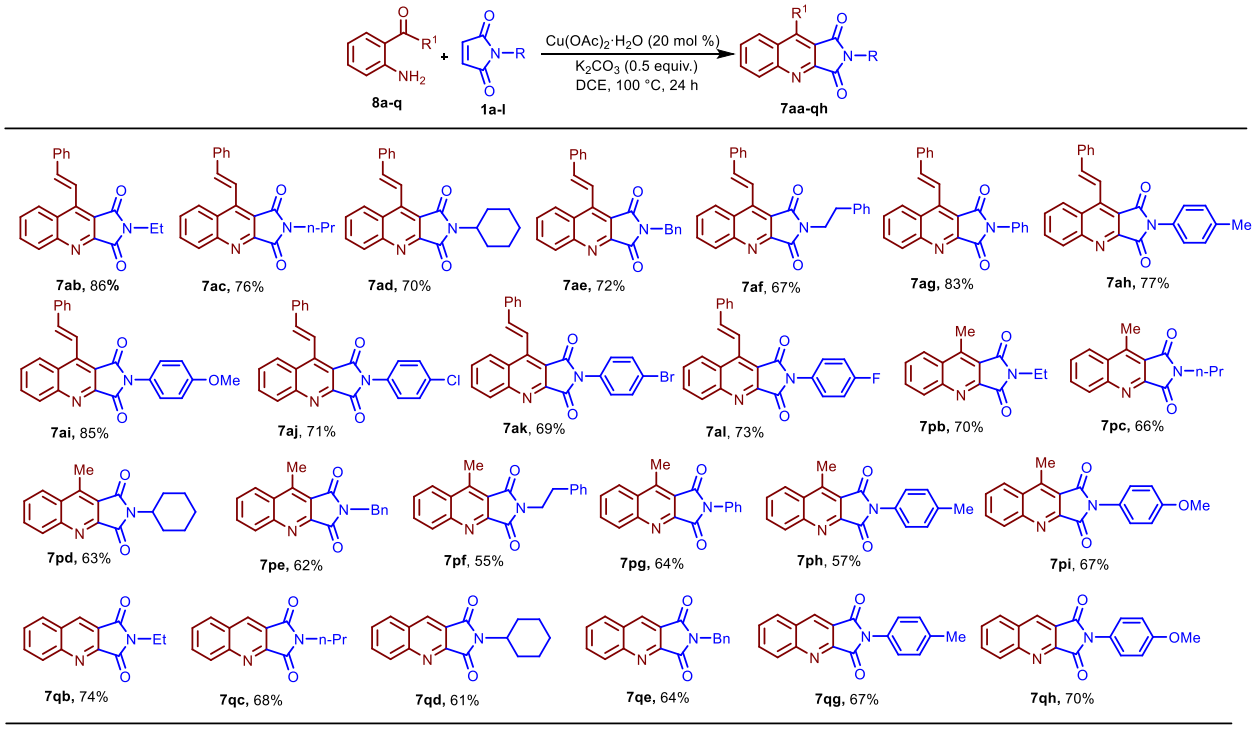


Figure 2.4: The ORTEP diagram of **7ea** [CCDC 2209858] thermal ellipsoids are drawn at 50% probability level.

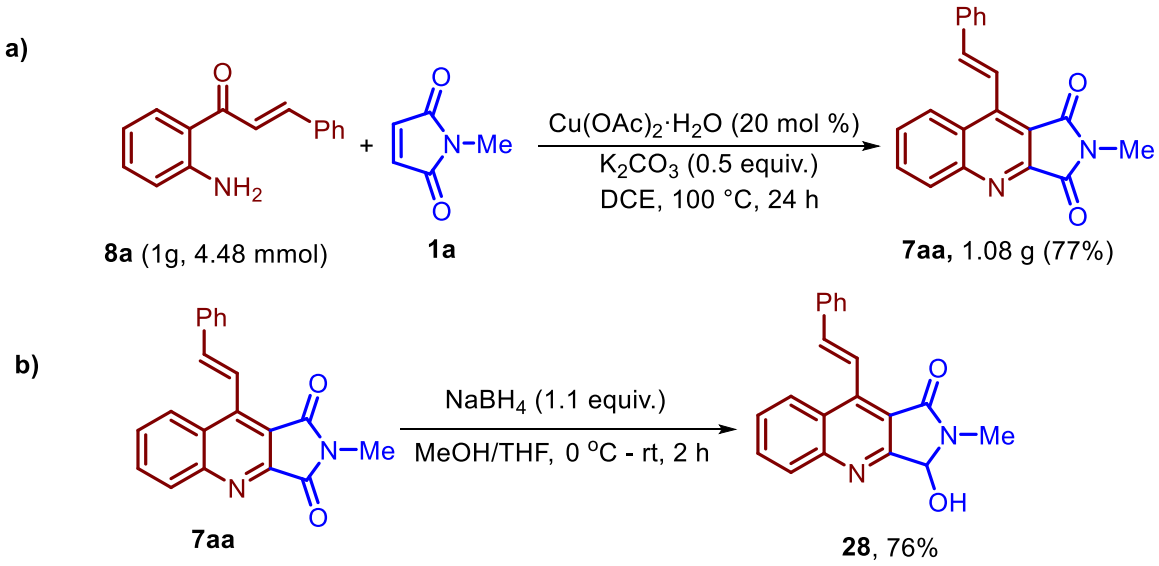
Table 2.3: Substrate scope of maleimides.[a,b]



[a]Reaction conditions: **8** (0.22 mmol), **1** (0.45 mmol), $Cu(OAc)_2 \cdot H_2O$ (20 mol %), K_2CO_3 (0.5 equiv.), DCE (2 mL), 100 °C, 24 h. [b]Isolated yields

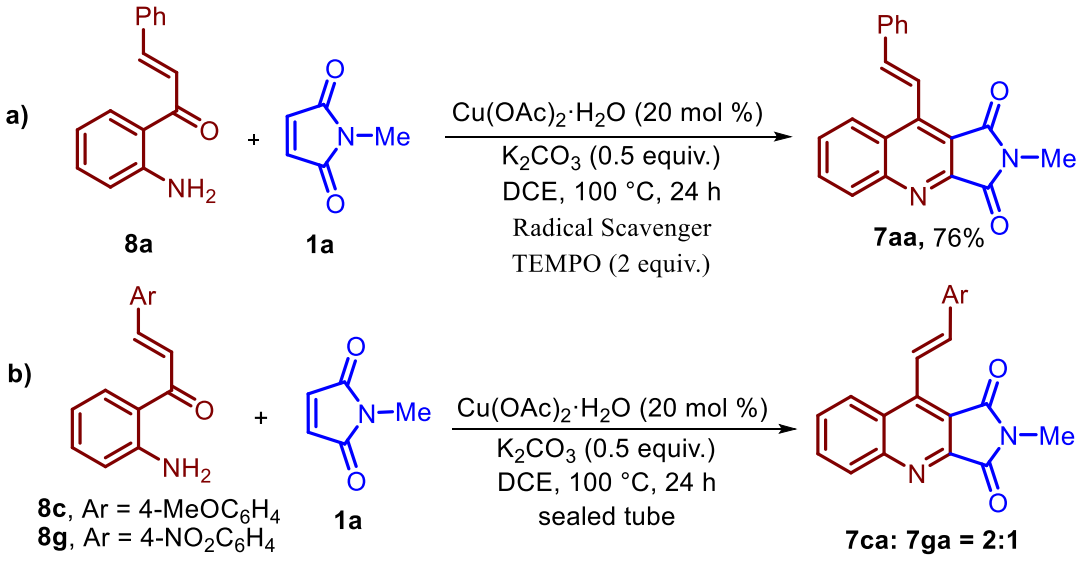
Next, to explore the substrate scope of maleimide various *N*-substituted maleimides (**1b-l**) were reacted with **8a** under standard reaction conditions (**Table 2.3**). Interestingly, maleimides with both *N*-alkyl and *N*-aryl substituents reacted efficiently to produce the corresponding products **7ab-al** in 67-86% yields. Subsequently, we explored the scope of the reaction of 2-aminoacetophenone (**8p**) and 2-aminobenzaldehyde (**8q**) with different maleimides **1a-i** under standard conditions. As can be seen in **Table 2.3**, **7p** and **7q** were found to be suitable reaction partners with **1a-i** to provide the corresponding pyrrolo[3,4-*b*]quinolinediones **7pa-pi** and **7qa-qh** in 55-72% and 61-76% yields, respectively.

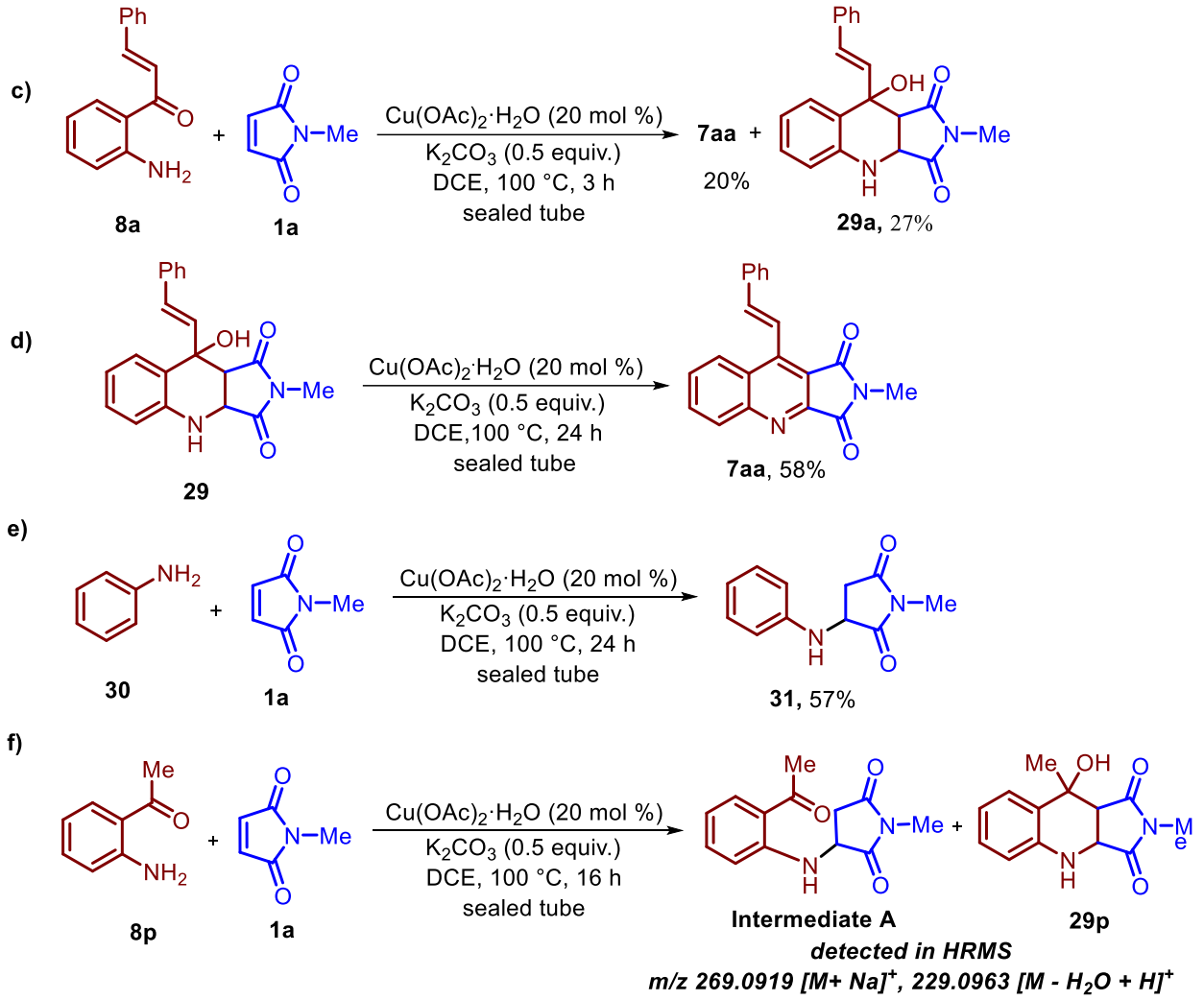
To highlight the practical utility of this method, upscaling of the reaction was explored (**Scheme 2.11a**). Interestingly, the method allowed the gram-scale (1.08 g) one-pot synthesis of **7aa** with excellent yield (77%) from the reaction of **8a** (1g, 4.48 mmol) with **1a** under the established conditions. The Cu-catalyzed reaction was performed on a benchtop without using glovebox techniques. Further, product **7aa** was regioselectively reduced with sodium borohydride to corresponding hydroxyl lactam **28** in 76% yield following reported conditions (**Scheme 2.11 b**).[51]



Scheme 2.11: Gram scale synthesis of 7aa and its reduction with $NaBH_4$.

To get more insight into the reaction mechanism of this reaction, some control experiments were conducted (**Scheme 2.12**). First, when a radical inhibitor 2,2,6,6-tetramethylpiperidine-*N*-oxyl (TEMPO) (2 equiv.) was employed for the reaction of **8a** with **1a** under standard reactions, the yield of the product **7aa** was only slightly decreased (76%), which indicated that a free radical pathway for this reaction (**Scheme 2.12a**). Intermolecular competitive reaction of **8c** and **8g** with **1a** produced corresponding products **7ca** and **7ga** in a 2: 1 ratio (**Scheme 2.12b**), indicating that electron-rich 2-amino chalcones are more favourable for this reaction. We could also isolate intermediate **29a** by quenching the reaction of **8a** and **1a** after 3h (**Scheme 2.12c**). Formation of the intermediate **29a** shows that the reaction involves nucleophilic addition to the carbonyl group.



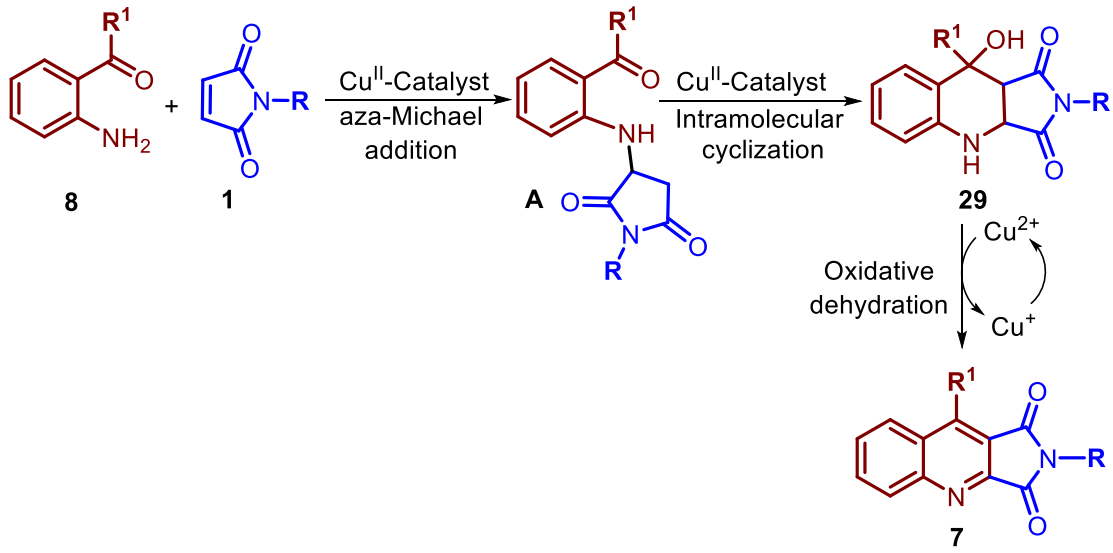


Scheme 2.12: Control experiments

Finally, the reaction of aniline (**30**) with **1a** under standard reaction conditions produced **31** in 57% yield (**Scheme 2.12d**), suggesting that aza-Michael adduct could be an intermediate in this transformation. Further, the reaction of intermediate **29a** in the presence of standard reaction conditions produced **7aa** in 58% yield (**Scheme 2.12e**). Finally, detection of two peaks at m/z 269.0919 and 229.0963 corresponding to $C_{13}H_{14}N_2NaO_3$ $[M + Na]^+$ and $C_{13}H_{13}N_2O_2$ $[M - H_2O + H]^+$, respectively, ions in the HRMS analysis of the reaction of **8p** with **1a** (**Scheme 2.12f**) also supported the idea that the reaction proceeds through aza-Michael addition as an intermediate step.

The mechanism of the developed tandem reaction is not clear; however, based on the results of the above control experiments and previous literature on copper(II)-catalyzed reactions, the plausible reaction mechanism for this tandem reaction is proposed in **Scheme 2.13**. Initially, the aza-Michael

addition of **8** with **1** under Cu(II) catalysis would generate intermediate **A**, which then undergoes copper-catalyzed intramolecular cyclization to form intermediate **29**. Finally, copper-catalyzed oxidative dehydration of intermediate **29** affords product **7**.



Scheme 2.13: Proposed mechanism for the developed reaction

2.3 CONCLUSION

In summary, we have described a cascade synthesis of valuable pyrrolo[3,4-*b*]quinolinediones by copper-catalysed reaction between *ortho*-amino carbonyl compounds and maleimides. This simple one-pot approach exhibited broad substrate scope high functional group tolerance, and yielded 1*H*-pyrrolo[3,4-*b*]quinoline-1,3(2*H*)-diones in moderate to good (54-88%) yields under mild conditions. A notable feature of the developed methods is that it can afford biologically active pyrrolo[3,4-*b*]quinolinediones in a single synthesis step from easily accessible starting materials. We are currently investigating application of this methodology for the synthesis of natural alkaloids.

2.4 EXPERIMENTAL SECTION

2.4.1 General Information

All chemicals and solvents purchased from commercial suppliers and used without purification, unless otherwise stated. 2-Amino chalcones were synthesized by following the reported procedure.[52, 53] All reactions were monitored by thin layer chromatography (TLC) on pre-coated silica gel 60 F254 aluminium foils and visualized under a UV lamp (366 or 254 nm). Desired

products were purified by column chromatography (silica gel 100-200 mesh size) using a gradient of ethyl acetate and hexanes as mobile phase. The ^{1}H, $^{13}C\{^{1}H\}$ NMR spectra were recorded on a 400 MHz spectrometer. Chemical shifts (δ) are reported in parts per million (ppm) and coupling constants (*J*) are reported in hertz (Hz). High-resolution mass spectra (HRMS) were recorded on a Q-TOF mass spectrometer.

2.4.2 General Procedure for the Synthesis of 7

A 10 mL oven-dried sealed tube was charged with compounds **8** (0.22 mmol and **1** (0.45 mmol, 2 equiv.), $Cu(OAc)_2{\cdot}H_2O$ (0.045 mmol, 0.2 equiv.), K_2CO_3 (0.11 mmol, 0.5 equiv.) and DCE (2 mL) at room temperature. The reaction tube was capped tightly, and the reaction mixture was stirred at 100 °C in an oil bath for 24 h. The reaction mixture was cooled, diluted with water (5 mL), and then extracted with ethyl acetate (3 × 5 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The resulting crude mixture was purified by column chromatography (silica gel 100−200 mesh) using EtOAc-hexanes as an eluent to afford the desired product **7**.

2.4.3 Experimental Procedure for Gram Scale Synthesis of 7aa

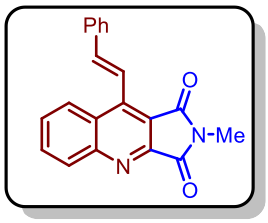
An oven-dried sealed tube was charged with compound **8a** (1g, 4.48 mmol, 1 equiv.) in **1a** (995 mg, 8.97 mmol, 2 equiv.), $Cu(OAc)_2{\cdot}H_2O$ (178 mg, 0.89 mmol, 0.2 equiv.), followed by K_2CO_3 (309 mg, 2.24 mmol, 0.5 equiv in DCE (8 mL) at room temperature, and the reaction mixture was stirred at 100 °C in an oil bath for 24 h. After completion of the reaction (monitored by TLC), the reaction mixture was allowed to attain room temperature. The reaction mixture was poured into water (50 mL) and extracted with ethyl acetate (3 × 30 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and evaporated under a vacuum. The resulting crude was purified by column chromatography (silica gel 100-200 mesh) using EtOAc-hexanes as an eluent to afford **7aa**.

2.4.4 Experimental Procedure for Isolation Intermediate 29a

A 10 mL oven-dried sealed tube was charged with compounds **8a** (50 mg, 0.22 mmol, 1 equiv.) and **1a** (50 mg, 0.44 mmol, 2 equiv.), $Cu(OAc)_2{\cdot}H_2O$ (9 mg, 0.04 mmol, 0.2 equiv.), K_2CO_3 (15 mg, 0.11 mmol, 0.5 equiv.) and DCE (2 mL) at room temperature. The reaction tube was capped tightly, and the reaction mixture was stirred at 100 °C in an oil bath for 3 h. The reaction mixture was cooled, diluted with water (5 mL), and then extracted with ethyl acetate (3 × 5 mL). The

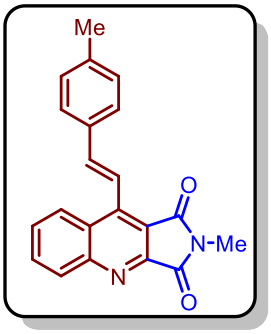
combined organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The resulting crude mixture was purified by column chromatography (silica gel 100−200 mesh) using EtOAc-hexanes as an eluent to get **7aa** and **29a** in 20 and 27% yields, respectively.

(*E*)-2-Methyl-9-styryl-1*H*-pyrrolo[3,4-*b*]quinoline-1,3(2*H*)-dione (7aa): The title compound



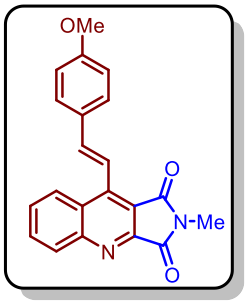
was purified by column chromatography on silica gel using EtOAc/ hexanes (1: 3, *v/v*) as an eluent; pale yellow solid (59 mg, 83%); mp = 174-176 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.52 (d, *J* = 8.8 Hz, 1H), 8.43 (d, *J* = 8.8 Hz, 1H), 8.03 (d, *J* = 16.8 Hz, 1H), 7.94 (t, *J* = 7.8 Hz, 1H), 7.77 (t, *J* = 7.8 Hz, 1H), 7.72 (d, *J* = 7.2 Hz, 2H), 7.52 – 7.41 (m, 4H), 3.33 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 166.8, 166.3, 150.8, 150.6, 144.7, 142.6, 135.9, 132.2, 132.0, 129.7, 129.2, 129.0, 127.5, 127.2, 126.9, 119.0, 117.9, 24.4; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{20}H_{15}N_2O_2^+$ 315.1128; Found 315.1131.

(*E*)-2-Methyl-9-(4-methylstyryl)-1*H*-pyrrolo[3,4-*b*]quinoline-1,3(2*H*)-dione (7ba): The title



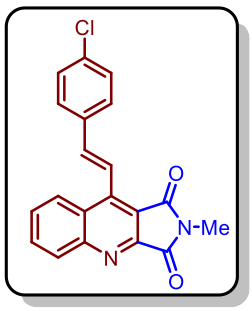
compound was purified by column chromatography on silica gel using EtOAc/ hexanes (1: 4, *v/v*) as an eluent; pale yellow solid (54 mg, 78%); mp = 246-248 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.51 (d, *J* = 8.4 Hz, 1H), 8.42 (d, *J* = 8.4 Hz, 1H), 7.99 (d, *J* = 16.4 Hz, 1H), 7.92 (t, *J* = 7.6 Hz, 1H), 7.76 (t, *J* = 7.6 Hz, 1H), 7.60 (d, *J* = 8.0 Hz, 2H), 7.49 (d, *J* = 16.8 Hz, 1H), 7.28 (d, *J* = 7.2 Hz, 2H), 3.32 (s, 3H), 2.43 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 166.9, 166.3, 150.8, 150.6, 144.9, 142.7, 140.0, 133.2, 132.1, 132.0, 129.7, 129.1, 127.5, 127.3, 126.9, 117.9, 117.7, 24.3, 21.4; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{21}H_{17}N_2O_2^+$ 329.1285; Found 329.1286.

(*E*)-9-(4-Methoxystyryl)-2-methyl-1*H*-pyrrolo[3,4-*b*]quinoline-1,3(2*H*)-dione (7ca): The title

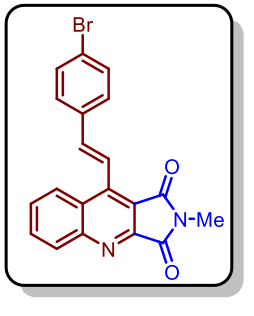


compound was purified by column chromatography on silica gel using EtOAc/ hexanes (1: 2.3, *v/v*) as an eluent; pale yellow solid (59 mg, 88%); mp = 258-260 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.53 (d, *J* = 8.4 Hz, 1H), 8.42 (d, *J* = 8.4 Hz, 1H), 7.95 – 7.90 (m, 2H), 7.78 – 7.74 (m, 1H), 7.67 (d, *J* = 8.8 Hz, 2H), 7.50 (d, *J* = 16.4 Hz, 1H), 7.00 (d, *J* = 8.8 Hz, 2H), 3.90 (s, 3H), 3.33 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 167.0, 166.4, 161.0, 150.8, 150.7, 145.1, 142.5, 132.1, 132.0, 130.3, 129.15, 129.07, 128.8, 127.3, 127.0, 116.6, 114.4, 55.4, 24.3; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{21}H_{17}N_2O_3^+$ 345.1234; Found 345.1238.

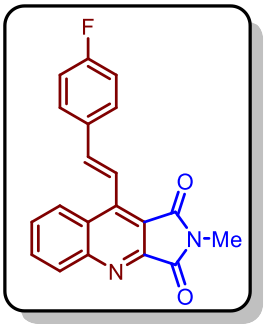
(*E*)-9-(4-Chlorostyryl)-2-methyl-1*H*-pyrrolo[3,4-*b*]quinoline-1,3(2*H*)-dione (7da): The title compound was purified by column chromatography on silica gel using EtOAc/ hexanes (1: 3, *v/v*) as an eluent; pale yellow solid (45 mg, 67%); mp = 234-236 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.47 (dd, *J* = 18.4, 8.4 Hz, 2H), 8.01 (d, *J* = 16.8 Hz, 1H), 7.95 (t, *J* = 7.6 Hz, 1H), 7.80 (d, *J* = 7.6 Hz, 1H), 7.65 (d, *J* = 8.4 Hz, 2H), 7.47 – 7.43 (m, 3H), 3.34 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 166.8, 166.2, 150.8, 150.5, 144.2, 141.1, 135.5, 134.4, 132.3, 132.1, 129.3, 129.2, 128.7, 127.1, 126.7, 119.5, 118.0, 24.4; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{20}H_{14}ClN_2O_2^+$ 349.0738; Found 349.0735.



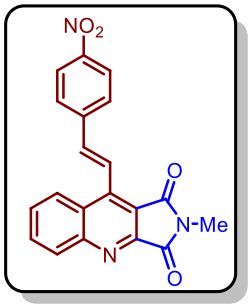
(*E*)-9-(4-Bromostyryl)-2-methyl-1*H*-pyrrolo[3,4-*b*]quinoline-1,3(2*H*)-dione (7ea): The title compound was purified by column chromatography on silica gel using EtOAc / hexanes (1: 2.3, *v/v*); as an eluent; pale yellow solid (47 mg, 72%); mp = 228-230 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.45 (dd, *J* = 16.4, 8.4 Hz, 2H), 8.00 (d, *J* = 16.4 Hz, 1H), 7.93 (t, *J* = 7.4 Hz, 1H), 7.78 (t, *J* = 7.6 Hz, 1H), 7.61 – 7.55 (m, 4H), 7.44 (d, *J* = 16.8 Hz, 1H), 3.33 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 166.8, 166.2, 150.8, 150.5, 144.2, 141.1, 134.8, 132.3, 132.2, 132.1, 129.4, 128.9, 127.1, 126.7, 123.8, 119.6, 118.0, 24.4; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{20}H_{14}BrN_2O_2^+$ 393.0233; Found 393.0231.



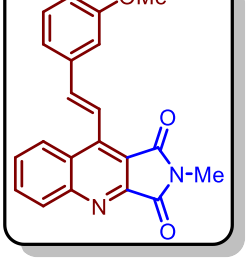
(*E*)-9-(4-Fluorostyryl)-2-methyl-1*H*-pyrrolo[3,4-*b*]quinoline-1,3(2*H*)-dione (7fa): The title compound was purified by column chromatography on silica gel using EtOAc / hexanes (1: 3, *v/v*); as an eluent; pale Yellow solid (55 mg, 79%); mp = 252-254 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.49 (d, *J* = 8.4 Hz, 1H), 8.43 (d, *J* = 8.4 Hz, 1H), 7.95 – 7.91 (m, 2H), 7.77 (t, *J* = 8.0 Hz, 1H), 7.71 – 7.67 (m, 2H), 7.47 (d, *J* = 16.8 Hz, 1H), 7.17 (t, *J* = 8.6 Hz, 2H), 3.33 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 166.9, 166.3, 163.6 (d, $^{1}J_{C\text{-}F}$ = 249.1 Hz), 150.8, 150.6, 144.4, 141.2, 132.25, 132.20 (d, $^{3}J_{C\text{-}F}$ = 3.4 Hz), 132.1, 129.36, 129.28, 127.2, 126.8, 118.7 (d, $^{3}J_{C\text{-}F}$ = 2.4 Hz), 117.9, 116.1 (d, $^{2}J_{C\text{-}F}$ = 21.6 Hz), 24.3; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{20}H_{14}FN_2O_2^+$ 333.1034; Found 333.1035.



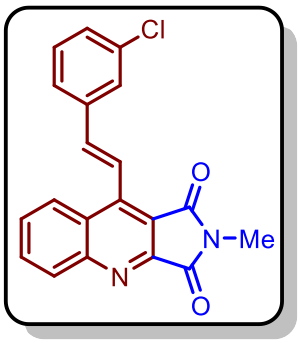
(*E*)-2-Methyl-9-(4-nitrostyryl)-1*H*-pyrrolo[3,4-*b*]quinoline-1,3(2*H*)-dione (7ga): The title compound was purified by column chromatography on silica gel using EtOAc / hexanes (1: 2.3, *v/v*); as an eluent; yellow solid (36 mg, 54%); mp = 254-256 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.48 (d, *J* = 8.4 Hz, 2H), 8.35 (d, *J* = 8.8 Hz, 2H), 8.15 (d, *J* = 16.4 Hz, 1H), 7.99 (t, *J* = 7.6 Hz, 1H), 7.87 – 7.80 (m, 3H), 7.54 (d, *J* = 16.8 Hz, 1H), 3.36 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 166.7, 166.1, 150.9, 150.5, 148.1, 143.2, 142.0, 139.5, 132.5, 132.3, 129.7, 128.0, 127.0, 126.5, 124.3, 123.3, 118.5, 24.4; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{20}H_{14}N_3O_4^+$ 360.0979; Found 360.0979.



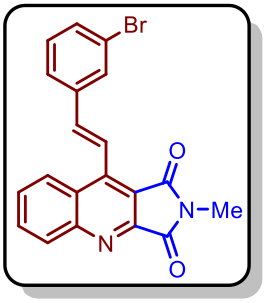
(*E*)-9-(3-Methoxystyryl)-2-methyl-1*H*-pyrrolo[3,4-*b*]quinoline-1,3(2*H*)-dione (7ha): The title compound was purified by column chromatography on silica gel using EtOAc / hexanes (1: 2.3, *v/v*); as an eluent; pale yellow solid (57 mg, 83%); mp = 194-196 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.51 (d, *J* = 8.4 Hz, 1H), 8.43 (d, *J* = 8.0 Hz, 1H), 8.00 (d, *J* = 16.4 Hz, 1H), 7.93 (t, *J* = 7.6 Hz, 1H), 7.78 (t, *J* = 7.6 Hz, 1H), 7.46 (d, *J* = 16.4 Hz, 1H), 7.39 (t, *J* = 8.0 Hz, 1H), 7.30 (d, *J* = 7.6 Hz, 1H), 7.22 (s, 1H), 6.98 (d, *J* = 8.0 Hz, 1H), 3.91 (s, 3H), 3.33 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 166.8, 166.3, 160.1, 150.8, 150.6, 144.6, 142.5, 137.3, 132.2, 132.0, 130.0, 129.2, 127.2, 126.9, 120.2, 119.2, 117.9, 115.4, 112.7, 55.4, 24.3; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{21}H_{17}N_2O_3^+$ 345.1234; Found 345.1236.



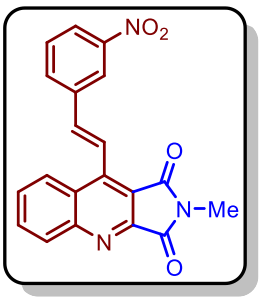
(*E*)-9-(3-Chlorostyryl)-2-methyl-1*H*-pyrrolo[3,4-*b*]quinoline-1,3(2*H*)-dione (7ia): The title compound was purified by column chromatography on silica gel using EtOAc / hexanes (1: 4, *v/v*); as an eluent; pale yellow solid (48 mg, 71%); mp = 216-218 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.45 (dd, *J* = 13.0, 8.6 Hz, 2H), 7.98 (d, *J* = 16.4 Hz, 1H), 7.93 (d, *J* = 7.6 Hz, 1H), 7.78 (t, *J* = 7.4 Hz, 1H), 7.68 (s, 1H), 7.58 – 7.56 (m, 1H), 7.44 – 7.39 (m, 3H), 3.33 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 166.7, 166.2, 150.8, 150.5, 144.0, 140.9, 137.7, 135.0, 132.3, 132.1, 130.2, 129.5, 129.4, 127.3, 127.1, 126.7, 125.6, 120.2, 118.1, 24.4; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{20}H_{14}ClN_2O_2^+$ 349.0738; Found 349.0740.



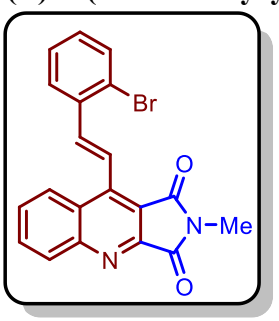
(*E*)-9-(3-Bromostyryl)-2-methyl-1*H*-pyrrolo[3,4-*b*]quinoline-1,3(2*H*)-dione (7ja): The title compound was purified by column chromatography on silica gel using EtOAc / hexanes (1: 4, *v/v*); as an eluent; pale yellow solid (46 mg, 70%); mp = 234-236 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.47 – 8.41 (m, 2H), 7.99 – 7.92 (m, 2H), 7.83 (s, 1H), 7.78 (t, *J* = 7.6 Hz, 1H), 7.62 (d, *J* = 7.6 Hz, 1H), 7.54 (d, *J* = 8.0 Hz, 1H), 7.41 (d, *J* = 16.4 Hz, 1H), 7.36 – 7.32 (m, 1H), 3.33 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 166.7, 166.2, 150.8, 150.5, 144.0, 140.7, 138.0, 132.4, 132.3, 132.1, 130.5, 130.3, 129.4, 127.1, 126.7, 126.0, 123.2, 120.3, 118.1, 24.4; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{20}H_{14}BrN_2O_2^+$ 393.0233; Found 393.0238.



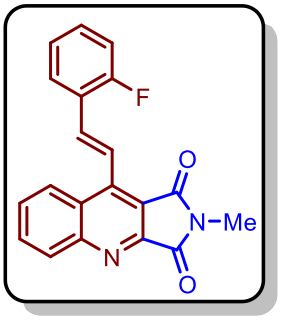
(*E*)-2-Methyl-9-(3-nitrostyryl)-1*H*-pyrrolo[3,4-*b*]quinoline-1,3(2*H*)-dione (7ka): The title compound was purified by column chromatography on silica gel using EtOAc / hexanes (1: 2.3, *v/v*); as an eluent; yellow solid (47 mg, 69%); mp = 244-246 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.54 (t, *J* = 1.8 Hz, 1H), 8.47 (dd, *J* = 8.4, 2.0 Hz, 2H), 8.28 (dd, *J* = 8.2, 1.2 Hz, 1H), 8.10 (d, *J* = 16.8 Hz, 1H), 8.05 (d, *J* = 8.0 Hz, 1H), 7.98 (t, *J* = 8.0 Hz, 1H), 7.83 (t, *J* = 8.0 Hz, 1H), 7.68 (t, *J* = 8.0 Hz, 1H), 7.55 (d, *J* = 16.8 Hz, 1H), 3.35 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 166.7, 166.1, 150.8, 150.5, 148.8, 143.3, 139.5, 137.6, 132.9, 132.5, 132.2, 130.0, 129.7, 127.1, 126.5, 123.9, 122.1, 121.8, 118.4, 24.4; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{20}H_{14}N_3O_4^+$ 360.0979; Found 360.0980.



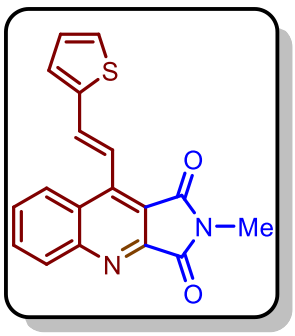
(*E*)-9-(2-Bromostyryl)-2-methyl-1*H*-pyrrolo[3,4-*b*]quinoline-1,3(2*H*)-dione (7la): The title compound was purified by column chromatography on silica gel using EtOAc / hexanes (1: 4, *v/v*); as an eluent; pale yellow solid (52 mg, 80%); mp = 226-228 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.60 (d, *J* = 8.0 Hz, 1H), 8.44 (d, *J* = 8.0 Hz, 1H), 7.98 – 7.91 (m, 3H), 7.82 – 7.74 (m, 2H), 7.66 (d, *J* = 8.0 Hz, 1H), 7.45 (t, *J* = 7.2 Hz, 1H), 7.29 – 7.25 (m, 1H), 3.34 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 166.8, 166.3, 151.0, 150.4, 143.9, 140.8, 136.2, 133.2, 132.3, 132.1, 130.6, 129.5, 128.0, 127.7, 127.0, 124.8, 122.1, 118.2, 24.4; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{20}H_{14}BrN_2O_2^+$ 393.0233; Found 393.0232.



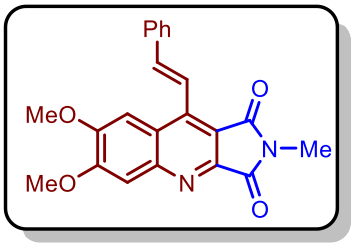
(*E*)-9-(2-Fluorostyryl)-2-methyl-1*H*-pyrrolo[3,4-*b*]quinoline-1,3(2*H*)-dione (7ma): The title compound was purified by column chromatography on silica gel using EtOAc / hexanes (1: 3, *v/v*); as an eluent; pale yellow solid (57 mg, 82%); mp = 228-230 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.49 (d, *J* = 8.4 Hz, 1H), 8.41 (d, *J* = 8.0 Hz, 1H), 8.05 (d, *J* = 16.8 Hz, 1H), 7.92 (t, *J* = 7.8 Hz, 1H), 7.81 – 7.74 (m, 2H), 7.62 (d, *J* = 16.8 Hz, 1H), 7.41 – 7.36 (m, 1H), 7.26 (t, *J* = 7.6 Hz, 1H), 7.16 (t, *J* = 9.4 Hz, 1H), 3.32 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 166.7, 166.2, 161.0 (d, $^{1}J_{C\text{-}F}$ = 250.5 Hz) 150.8, 150.5, 144.4, 134.8 (d, $^{3}J_{C\text{-}F}$ = 3.6 Hz), 132.2, 132.0, 131.0, 131.0, 129.4, 128.1 (d, $^{3}J_{C\text{-}F}$ = 3.0 Hz), 127.1, 126.8, 124.6 (d, $^{3}J_{C\text{-}F}$ = 3.5 Hz), 124.0, 123.89, 121.3 (d, $^{3}J_{C\text{-}F}$ = 5.5 Hz), 118.0, 116.1 (d, $^{2}J_{C\text{-}F}$ = 21.7 Hz), 24.3; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{20}H_{14}FN_2O_2^+$ 333.1034; Found 333.1031.



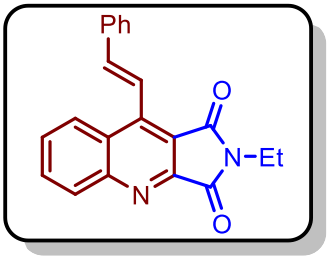
(*E*)-2-Methyl-9-(2-(thiophen-2-yl)vinyl)-1*H*-pyrrolo[3,4-*b*]quinoline-1,3(2*H*)-dione (7na): The title compound was purified by column chromatography on silica gel using EtOAc / hexanes (1: 3, *v/v*); as an eluent; pale yellow solid (63 mg, 75%); mp = 220-222 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.47 (d, *J* = 8.0 Hz, 1H), 8.41 (d, *J* = 8.0 Hz, 1H), 7.92 (t, *J* = 8.2 Hz, 1H), 7.80 (d, *J* = 6.0 Hz, 2H), 7.77 – 7.75 (m, 1H), 7.45 (d, *J* = 4.8 Hz, 1H), 7.34 (d, *J* = 2.8 Hz, 1H), 7.14 – 7.11 (m, 1H), 3.33 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 166.9, 166.2, 150.6, 144.0, 141.4, 135.7, 132.2, 132.1, 129.6, 129.2, 128.1, 127.8, 127.1, 126.5, 117.7, 117.5, 24.3; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{18}H_{13}N_2O_2S^+$ 321.0692; Found 321.0690.



(*E*)-6,7-Dimethoxy-2-methyl-9-styryl-1*H*-pyrrolo[3,4-*b*]quinoline-1,3(2*H*)-dione (7oa): The title compound was purified by column chromatography on silica gel using EtOAc / hexanes (2: 3, *v/v*); as an eluent; pale yellow solid (58 mg, 44%); mp = 220-222 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, *J* = 16.8 Hz, 1H), 7.71 – 7.69 (m, 3H), 7.67 (s, 1H), 7.55 – 7.43 (m, 4H), 4.09 (s, 3H), 4.05 (s, 3H), 3.29 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 167.3, 166.8, 154.3, 151.7, 148.8, 148.3, 142.0, 141.1, 136.0, 129.5, 129.1, 127.4, 123.0, 119.5, 117.1, 110.3, 104.4, 56.5, 56.2, 24.12; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for 375.1339; Found 375.1341.

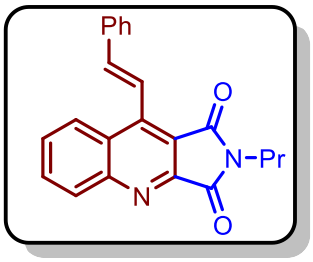


(*E*)- Ethyl 2-9-styryl-1*H*-pyrrolo[3,4-*b*]quinoline-1,3(2*H*)-dione (7ab): The title compound was



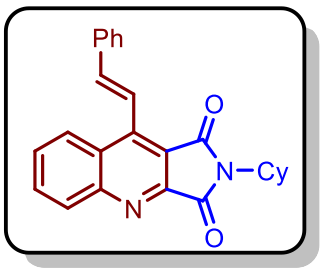
purified by column chromatography on silica gel using EtOAc / hexanes (1: 4, *v/v*); as an eluent; pale yellow solid (63 mg, 86%); mp = 176-178 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.51 (d, *J* = 8.4 Hz, 1H), 8.42 (d, *J* = 8.4 Hz, 1H), 8.04 (d, *J* = 16.8 Hz, 1H), 7.92 (t, *J* = 7.4 Hz, 1H), 7.76 (t, *J* = 8.2 Hz, 1H), 7.71 (d, *J* = 7.2 Hz, 2H), 7.51 – 7.40 (m, 4H), 3.90 (q, *J* = 7.2 Hz, 2H), 1.36 (t, *J* = 7.2 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 166.6, 166.0, 150.9, 150.6, 144.6, 142.5, 136.0, 132.1, 132.0, 129.7, 129.2, 129.0, 127.5, 127.3, 126.9, 119.0, 117.9, 33.4, 13.8; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{21}H_{17}N_2O_2^+$ 329.1285; Found 329.1281.

(*E*)-2-Propyl-9-styryl-1*H*-pyrrolo[3,4-*b*]quinoline-1,3(2*H*)-dione (7ac): The title compound



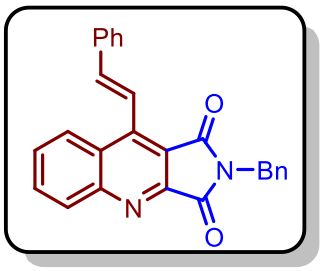
was purified by column chromatography on silica gel using EtOAc / hexanes (1: 4, *v/v*); as an eluent; pale yellow solid (59 mg, 76%); mp = 172-174 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.53 (d, *J* = 8.4 Hz, 1H), 8.44 (d, *J* = 8.4 Hz, 1H), 8.06 (d, *J* = 16.8 Hz, 1H), 7.94 (t, *J* = 7.6 Hz, 1H), 7.77 (t, *J* = 8.0 Hz, 1H), 7.72 (d, *J* = 6.8 Hz, 2H), 7.52 – 7.40 (m, 4H), 3.81 (t, *J* = 7.4 Hz, 2H), 1.80 (q, *J* = 7.2 Hz, 2H), 1.01 (t, *J* = 7.4 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 166.9, 166.3, 150.9, 150.5, 144.6, 142.5, 135.9, 132.2, 132.0, 129.7, 129.2, 129.0, 127.5, 127.3, 126.9, 119.1, 117.8, 40.0, 21.9, 11.4; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{22}H_{19}N_2O_2^+$ 343.1441; Found 343.1444.

(*E*)-2-Cyclohexyl-9-styryl-1*H*-pyrrolo[3,4-*b*]quinoline-1,3(2*H*)-dione (7ad): The title



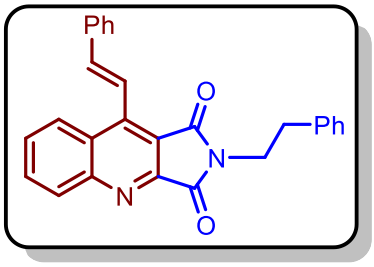
compound was purified by column chromatography on silica gel using EtOAc / hexanes (1: 4, v/v); as an eluent; pale yellow solid (60 mg, 70%); mp = 172-174 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.53 (d, *J* = 8.4 Hz, 1H), 8.44 (d, *J* = 8.4 Hz, 1H), 8.08 (d, *J* = 16.4 Hz, 1H), 7.95 – 7.91 (m, 1H), 7.78– 7.71 (m, 3H), 7.50 – 7.41 (m, 4H), 4.35 – 4.27 (m, 1H), 2.36 – 2.27 (m, 2H), 1.93 – 1.72 (m, 5H), 1.47 – 1.27 (m, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 167.0, 166.2, 151.0, 150.3, 144.5, 142.3, 136.0, 132.08, 132.01, 129.6, 129.09, 129.00, 127.5, 127.4, 126.9, 119.3, 117.8, 51.5, 29.8, 26.0, 25.0; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{25}H_{23}N_2O_2^+$ 383.1754; Found 383.1756.

(*E*)-2-Benzyl-9-styryl-1*H*-pyrrolo[3,4-*b*]quinoline-1,3(2*H*)-dione (7ae): The title compound



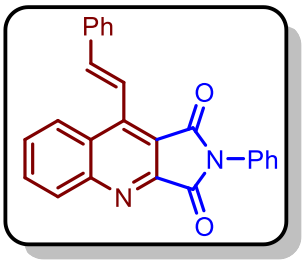
was purified by column chromatography on silica gel using EtOAc / hexanes (1: 2.3, *v/v*); as an eluent; pale yellow solid (64 mg, 72%); mp =170-172 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.50 (d, *J* = 8.4 Hz, 1H), 8.42 (d, *J* = 8.4 Hz, 1H), 8.03 (d, *J* = 16.8 Hz, 1H), 7.91 (t, *J* = 7.8 Hz, 1H), 7.75 (d, *J* = 7.6 Hz, 1H), 7.70 (d, *J* = 7.6 Hz, 2H), 7.53 (d, *J* = 7.2 Hz, 2H), 7.48 – 7.40 (m, 4H), 7.37 – 7.28 (m, 3H), 5.00 (s 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 166.4, 165.9, 150.9, 150.4, 144.8, 142.6, 136.0, 135.9, 132.2, 132.0, 129.7, 129.2, 129.0, 128.9, 128.7, 128.0, 127.6, 127.3, 126.9, 119.1, 117.9, 42.0; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{26}H_{19}N_2O_2^+$ 391.1441; Found 391.1375.

(*E*)-2-Phenethyl-9-styryl-1*H*-pyrrolo[3,4-*b*]quinoline-1,3(2*H*)-dione (7af): The title compound



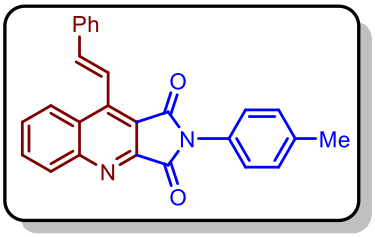
was purified by column chromatography on silica gel using EtOAc / hexanes (1: 3, *v/v*); as an eluent; pale yellow solid (61 mg, 67%); mp = 174-176 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.53 (d, *J* = 8.0 Hz, 1H), 8.45 (d, *J* = 8.4 Hz, 1H), 8.04 (d, *J* = 16.8 Hz, 1H), 7.96 – 7.92 (m, 1H), 7.80 – 7.76 (m, 1H), 7.72 (d, *J* = 7.2 Hz, 2H), 7.51 – 7.43 (m, 4H), 7.32 (d, *J* = 4.4 Hz, 4H), 7.26 – 7.23 (m, 1H), 4.10 – 4.07 (m, 2H), 3.11 – 3.07 (m, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 166.6, 166.0, 150.9, 150.4, 144.8, 142.6, 137.8, 135.9, 132.2, 132.1, 129.7, 129.2, 129.0, 128.9, 128.6, 127.6, 127.3, 126.9, 126.7, 119.0, 117.8, 39.7, 34.5; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{27}H_{21}N_2O_2^+$ 405.1598; Found 405.1596.

(*E*)-2-Phenyl-9-styryl-1*H*-pyrrolo[3,4-*b*]quinoline-1,3(2*H*)-dione (7ag): The title compound



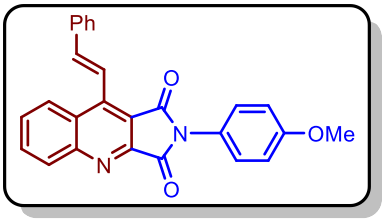
was purified by column chromatography on silica gel using EtOAc / hexanes (1: 3, *v/v*); as an eluent; pale yellow solid (70 mg, 83%); mp = 248-250 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.58 (d, *J* = 8.4 Hz, 1H), 8.49 (d, *J* = 8.4 Hz, 1H), 8.13 (d, *J* = 16.4 Hz, 1H), 7.98 (t, *J* = 7.8 Hz, 1H), 7.82 (t, *J* = 7.8 Hz, 1H), 7.72 (d, *J* = 7.2 Hz, 2H), 7.58 – 7.51 (m, 5H), 7.48 – 7.40 (m, 4H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 165.9, 165.1, 151.3, 150.0, 145.5, 142.9, 135.9, 132.49, 132.14, 131.4, 129.8, 129.4, 129.2, 129.0, 128.5, 127.6, 127.5, 127.0, 126.7, 119.1, 117.5; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{25}H_{17}N_2O_2^+$ 377.1285; Found 377.1300.

(*E*)-9-Styryl-2-(*p*-tolyl)-1*H*-pyrrolo[3,4-*b*]quinoline-1,3(2*H*)-dione (7ah): The title compound



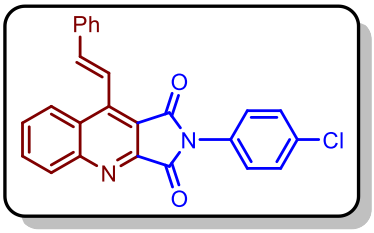
was purified by column chromatography on silica gel using EtOAc / hexanes (1: 2.3, *v/v*); as an eluent; pale yellow solid (68 mg, 77%); mp= 262-264 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.58 (d, *J* = 8.4 Hz, 1H), 8.49 (d, *J* = 8.4 Hz, 1H), 8.13 (d, *J* = 16.8 Hz, 1H), 7.98 (t, *J* = 8.4 Hz, 1H), 7.81 (t, *J* = 7.6 Hz, 1H), 7.72 (d, *J* = 6.8 Hz, 2H), 7.53 (d, *J* = 16.8 Hz, 1H), 7.49 – 7.33 (m, 7H), 2.45 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 166.0, 165.3, 151.2, 150.0, 145.4, 142.8, 138.6, 135.9, 132.4, 132.1, 129.8, 129.7, 129.4, 129.0, 128.7, 127.6, 127.5, 127.0, 126.5, 119.2, 117.5, 21.3; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{26}H_{19}N_2O_2^+$ 391.1441; Found 391.1438.

(*E*)-2-(4-Methoxyphenyl)-9-styryl-1*H*-pyrrolo[3,4-*b*]quinoline-1,3(2*H*)-dione (7ai): The title



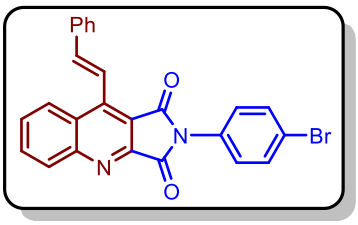
compound was purified by column chromatography on silica gel using EtOAc / hexanes (1: 2.3, *v/v*); as an eluent; pale yellow solid (78 mg, 85%); mp = 244-246 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.58 (d, *J* = 8.4 Hz, 1H), 8.49 (d, *J* = 8.4 Hz, 1H), 8.12 (d, *J* = 16.8 Hz, 1H), 7.98 (t, *J* = 7.0 Hz, 1H), 7.81 (t, *J* = 7.8 Hz, 1H), 7.72 (d, *J* = 6.8 Hz, 2H), 7.53 (d, *J* = 16.4 Hz, 1H), 7.48 – 7.40 (m, 5H), 7.07 (d, *J* = 8.8 Hz, 2H), 3.88 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 166.2, 165.4, 159.5, 151.2, 150.0, 145.3, 142.8, 135.9, 132.4, 132.1, 129.7, 129.4, 129.0, 127.9, 127.6, 127.0, 123.9, 119.2, 114.5, 55.6; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{26}H_{19}N_2O_3^+$ 407.1390; Found 407.1387.

(*E*)-2-(4-Chlorophenyl)-9-styryl-1*H*-pyrrolo[3,4-*b*]quinoline-1,3(2*H*)-dione (7aj): The title

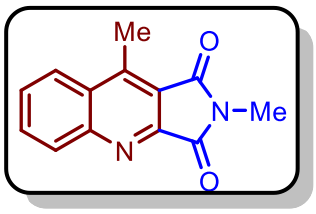


compound was purified by column chromatography on silica gel using EtOAc / hexanes (1: 2.3, *v/v*); as an eluent; pale yellow solid (65 mg, 71%); mp = 268-270 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.58 (d, *J* = 8.4 Hz, 1H), 8.48 (d, *J* = 8.4 Hz, 1H), 8.10 (d, *J* = 16.8 Hz, 1H), 7.99 (t, *J* = 7.4 Hz, 1H), 7.82 (t, *J* = 7.4 Hz, 1H), 7.72 (d, *J* = 6.8 Hz, 2H), 7.54 – 7.41 (m, 8H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 165.5, 164.9, 151.3, 149.7, 145.7, 143.0, 135.8, 134.3, 132.6, 132.2, 129.9, 129.8, 129.5, 129.4, 129.0, 127.8, 127.6, 127.5, 127.0, 119.0, 117.3; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{25}H_{16}ClN_2O_2^+$ 411.0895; Found 411.0897.

(*E*)-2-(4-Bromophenyl)-9-styryl-1*H*-pyrrolo[3,4-*b*]quinoline-1,3(2*H*)-dione (7ak): The title compound was purified by column chromatography on silica gel using EtOAc / hexanes (1: 4, *v/v*); as an eluent; pale yellow solid (70 mg, 69%); mp = 288-290 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.58 (d, *J* = 8.4 Hz, 1H), 8.49 (d, *J* = 8.4 Hz, 1H), 8.10 (d, *J* = 16.4 Hz, 1H), 7.99 (t, *J* = 7.4 Hz, 1H), 7.82 (t, *J* = 7.8 Hz, 1H), 7.73 – 7.67 (m, 4H), 7.54 – 7.41 (m, 6H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 165.5, 164.8, 151.3, 149.7, 145.7, 143.0, 135.8, 132.6, 132.4, 132.2, 130.4, 129.8, 129.5, 129.0, 128.0, 127.6, 127.0, 122.3, 119.0, 117.3; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{25}H_{16}BrN_2O_2^+$ 455.0390; Found 455.0393.

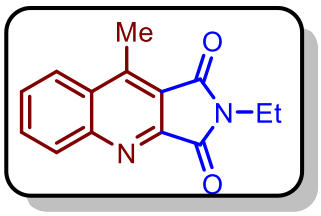


(*E*)-2-(4-Fluorophenyl)-9-styryl-1*H*-pyrrolo[3,4-*b*]quinoline-1,3(2*H*)-dione (7al): The title compound was purified by column chromatography on silica gel using EtOAc / hexanes (1: 4, *v/v*); as an eluent; pale yellow solid (65 mg, 73%); mp = 260-262 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.58 (d, *J* = 8.4 Hz, 1H), 8.49 (d, *J* = 8.0 Hz, 1H), 8.11 (d, *J* = 16.8 Hz, 1H), 7.99 (t, *J* = 8.0 Hz, 1H), 7.82 (t, *J* = 7.6 Hz, 1H), 7.72 (d, *J* = 6.8 Hz, 2H), 7.54 – 7.43 (m, 6H), 7.25 (t, *J* = 8.6 Hz, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 165.8, 165.1, 162.2 (d, $^{1}J_{C\text{-}F}$ = 247.1 Hz), 151.3, 149.8, 145.6, 143.0, 135.8, 132.6, 132.2, 129.8, 129.5, 129.0, 128.5 (d, $^{2}J_{C\text{-}F}$ = 8.7 Hz), 127.6, 127.5, 127.3 (d, $^{3}J_{C\text{-}F}$ = 3.2 Hz), 127.0, 119.0, 117.3, 116.2 (d, $^{2}J_{C\text{-}F}$ = 22.8 Hz); HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{25}H_{16}FN_2O_2^+$ 395.1190; Found 395.1185.



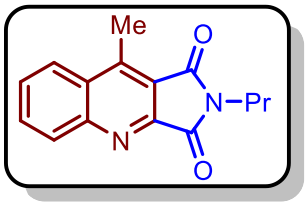
2,9-Dimethyl-1*H*-pyrrolo[3,4-*b*]quinoline-1,3(2*H*)-dione (7pa): The title compound was purified by column chromatography on silica gel using EtOAc / hexanes (1: 2.3, *v/v*); as an eluent; off white solid (60 mg, 72%); mp = 236-238 °C (Lit. mp 240-243 °C)[54]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41 (d, *J* = 8.4 Hz, 1H), 8.25 (d, *J* = 8.4 Hz, 1H), 7.92 (t, *J* = 7.8 Hz, 1H), 7.79 (t, *J* = 7.6 Hz, 1H), 3.33 (s, 3H), 3.15 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 167.4, 166.3, 150.3, 149.8, 146.5, 132.2, 132.1, 129.4, 129.2, 125.3, 120.0, 24.3, 13.3; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{13}H_{11}N_2O_2^+$ 227.0815; Found 227.0816.

2-Ethyl-9-methyl-1*H*-pyrrolo[3,4-*b*]quinoline-1,3(2*H*)-dione (7pb): The title compound was



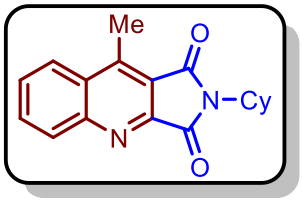
purified by column chromatography on silica gel using EtOAc / hexanes (1: 3, *v/v*); as an eluent; off white solid (63 mg, 70%); mp = 196-198 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41 (d, *J* = 8.4 Hz, 1H), 8.24 (d, *J* = 8.4 Hz, 1H), 7.92 (t, *J* = 7.6 Hz, 1H), 7.78 (t, *J* = 7.6 Hz, 1H), 3.90 (q, *J* = 7.2 Hz, 2H), 3.14 (s, 3H), 1.36 (t, *J* = 7.2 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 167.1, 166.0, 150.4, 149.8, 146.4, 132.1, 132.0, 129.4, 129.1, 125.3, 119.1, 33.3, 13.8, 13.2; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{14}H_{13}N_2O_2^+$ 241.0972; Found 241.0973.

9-Methyl-2-propyl-1*H*-pyrrolo[3,4-*b*]quinoline-1,3(2*H*)-dione (7pc): The title compound was



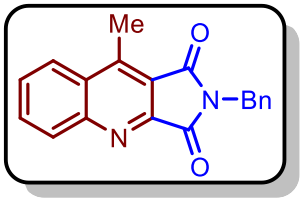
purified by column chromatography on silica gel using EtOAc / hexanes (1: 3, *v/v*); as an eluent; off white solid (62 mg, 66%); mp = 148-150 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41 (d, *J* = 8.4 Hz, 1H), 8.24 (d, *J* = 8.0 Hz, 1H), 7.92 (t, *J* = 7.4 Hz, 1H), 7.79 (t, *J* = 7.4 Hz, 1H), 3.81 (t, *J* = 7.2 Hz, 2H), 3.15 (s, 3H), (q, *J* = 7.2 Hz, 2H), 1.01 (t, *J* = 7.2 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 167.4, 166.3, 150.3, 149.8, 146.5, 132.1, 132.0, 129.4, 129.1, 125.3, 119.9, 39.9, 21.8, 13.2, 11.4; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{15}H_{15}N_2O_2^+$ 255.1128; Found 255.1124.

2-Cyclohexyl-9-methyl-1*H*-pyrrolo[3,4-*b*]quinoline-1,3(2*H*)-dione (7pd): The title compound



was purified by column chromatography on silica gel using EtOAc / hexanes (1: 6, *v/v*); as an eluent; off white solid (69 mg, 63%); mp = 244-246 °C;^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41 (d, *J* = 8.4 Hz, 1H), 8.24 (d, *J* = 8.4 Hz, 1H), 7.91 (t, *J* = 7.6 Hz, 1H), 7.78 (t, *J* = 7.6 Hz, 1H), 4.34 – 4.26 (m, 1H), 3.14 (s, 3H), 2.37 – 2.26 (m, 2H), 1.93 – 1.72 (m, 5H), 1.47 – 1.31 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.5, 166.1, 150.1, 149.9, 146.3, 132.0, 129.5, 129.0, 125.2, 119.7, 51.4, 29.7, 25.1, 25.0, 13.0; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{18}H_{19}N_2O_2^+$ 295.1441; found 295.1445.

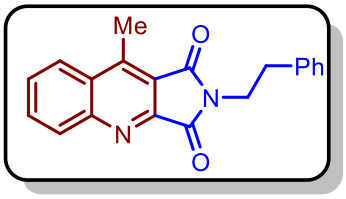
2-Benzyl-9-methyl-1*H*-pyrrolo[3,4-*b*]quinoline-1,3(2*H*)-dione (7pe): The title compound was



purified by column chromatography on silica gel using EtOAc / hexanes (1: 4, *v/v*); as an eluent; off white solid (70 mg, 62%); mp = 218-220 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41 (d, *J* = 8.4 Hz, 1H), 8.23 (d, *J* = 8.4 Hz, 1H), 7.92 (t, *J* = 7.4 Hz, 1H), 7.78 (t, *J* = 7.6 Hz, 1H), 7.52 (d, *J* = 7.2 Hz, 2H), 7.37 – 7.30 (m, 3H), 5.00 (s, 2H), 3.13 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ

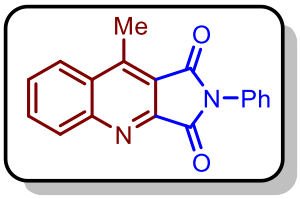
167.0 , 165.9, 150.2, 149.9, 146.8, 136.0, 132.2, 132.0, 129.2, 128.8, 128.7, 128.0, 125.3, 41.9, 13.3; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{19}H_{15}N_2O_2^+$ 303.1128; Found 303.1124.

9-Methyl-2-phenethyl-1*H*-pyrrolo[3,4-*b*]quinoline-1,3(2*H*)-dione (7pf): The title compound



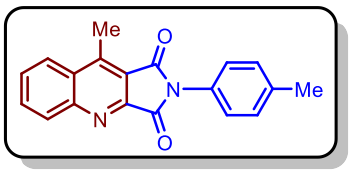
was purified by column chromatography on silica gel using EtOAc / hexanes (2: 3, *v/v*); as an eluent; pale yellow solid (64 mg, 55%); mp = 234-236 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41 (d, *J* = 8.4 Hz, 1H), 8.24 (d, *J* = 8.0 Hz, 1H), 7.94 – 7.90 (m, 1H), 7.81 – 7.77 (m, 1H), 7.31 (d, *J* = 4.4 Hz, 4H), 7.26 – 7.22 (m, 1H), 4.10 – 4.06 (m, 2H), 3.13 (s, 3H), 3.10 – 3.06 (m, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 167.1, 166.0, 150.2, 149.8, 146.6, 137.8, 132.2, 132.1, 129.4, 129.2, 128.9, 128.6, 126.7, 125.3, 119.8, 39.5, 34.5, 13.3; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{20}H_{17}N_2O_2^+$ 317.1285; Found 317.1288.

9-Methyl-2-phenyl-1*H*-pyrrolo[3,4-*b*]quinoline-1,3(2*H*)-dione (7pg): The title compound was



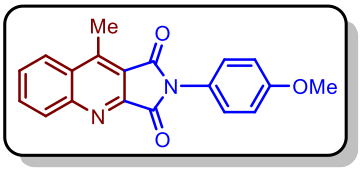
purified by column chromatography on silica gel using EtOAc / hexanes (1: 2.3, *v/v*); as an eluent; off white solid (68 mg, 64%); mp = 206-208 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.46 (d, *J* = 8.4 Hz, 1H), 8.30 (d, *J* = 8.4 Hz, 1H), 7.96 (t, *J* = 8.2 Hz, 1H), 7.83 (t, *J* = 8.0 Hz, 1H), 7.59 – 7.51 (m, 4H), 7.47 (t, *J* = 7.2 Hz, 1H), 3.21 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 166.3, 165.1, 150.2, 149.7, 147.5, 132.4, 132.2, 131.3, 129.6, 129.4, 129.2, 128.5, 126.7, 125.4, 119.5, 13.4; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{18}H_{13}N_2O_2^+$ 289.0972; Found 289.0975.

9-Methyl-2-(*p*-tolyl)-1*H*-pyrrolo[3,4-*b*]quinoline-1,3(2*H*)-dione (7ph): The title compound

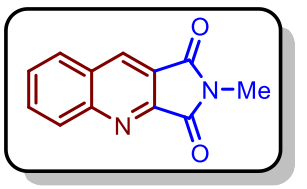


was purified by column chromatography on silica gel using EtOAc / hexanes (1: 2.3, *v/v*); as an eluent; off white solid (64 mg, 57%); mp = 252-254 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.46 (d, *J* = 8.4 Hz, 1H), 8.29 (d, *J* = 8.4 Hz, 1H), 7.96 (t, *J* = 7.8 Hz, 1H), 7.82 (t, *J* = 7.6 Hz, 1H), 7.43 (d, *J* = 8.8 Hz, 2H), 7.07 (d, *J* = 9.2 Hz, 2H), 3.89 (s, 3H), 3.20 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 166.5, 165.4, 159.5, 150.1, 149.8, 147.3, 132.3, 132.1, 129.6, 129.3, 128.0, 125.3, 123.9, 119.6, 114.6, 55.5, 13.3; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{19}H_{15}N_2O_2^+$ 303.1128; Found 303.1134.

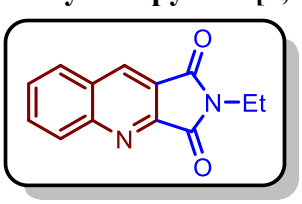
2-(4-Methoxyphenyl)-9-methyl-1*H*-pyrrolo[3,4-*b*]quinoline-1,3(2*H*)-dione (7pi): The title compound was purified by column chromatography on silica gel using EtOAc / hexanes (1: 1.5, *v/v*); as an eluent; off white solid (79 mg, 67%); mp = 238-240 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.47 (d, *J* = 8.4 Hz, 1H), 8.30 (d, *J* = 8.4 Hz, 1H), 7.96 (t, *J* = 7.6 Hz, 1H), 7.83 (t, *J* = 7.6 Hz, 1H), 7.43 (d, *J* = 9.2 Hz, 1H), 7.08 (d, *J* = 8.8 Hz, 2H), 3.89 (s, 3H), 3.21 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 166.6, 165.4, 159.5, 150.1, 149.8, 147.3, 132.4, 132.1, 129.6, 129.3, 128.0, 125.3, 123.9, 119.6, 114.6, 55.5, 13.4; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{19}H_{15}N_2O_3^+$ 319.1077; Found 319.1084.



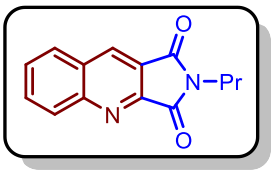
2-Methyl-1*H*-pyrrolo[3,4-*b*]quinoline-1,3(2*H*)-dione (7qa): The title compound was purified by column chromatography on silica gel using EtOAc / hexanes (1: 3, *v/v*); as an eluent; off white solid (66 mg, 76%); mp = 264-266 °C (Lit. mp 266-268 °C)[22]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.68 (s, 1H), 8.45 (d, *J* = 8.4 Hz, 1H), 8.09 (d, *J* = 8.4 Hz, 1H), 7.98 – 7.94 (m, 1H), 7.81 – 7.77 (m, 1H), 3.36 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 166.3, 166.1, 150.7, 150.6, 132.8, 132.5, 131.5, 129.5, 129.1, 128.7, 123.0, 24.5 HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{12}H_9N_2O_2^+$ 213.0659; Found 213.0660.



2-Ethyl-1*H*-pyrrolo[3,4-*b*]quinoline-1,3(2*H*)-dione (7qb): The title compound was purified by column chromatography on silica gel using EtOAc / hexanes (1: 6, *v/v*); as an eluent; off white solid (69 mg, 74%); mp = 212-214 °C (Lit. mp 210-212 °C)[22]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.64 (s, 1H), 8.42 (d, *J* = 8.4 Hz, 1H), 8.06 (d, *J* = 8.0 Hz, 1H), 7.94 (t, *J* = 7.8 Hz, 1H), 7.77 (t, *J* = 7.4 Hz, 1H), 3.91 (q, *J* = 7.2 Hz, 2H), 1.36 (t, *J* = 7.2 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 166.0, 165.8, 150.7, 150.6, 132.7, 132.5, 131.4, 129.9, 129.5, 128.7, 123.0, 33.5, 13.8; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{13}H_{11}N_2O_2^+$ 227.0815; Found 227.0818.

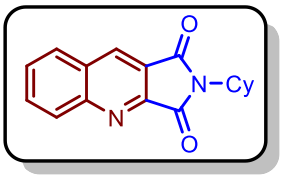


2-Propyl-1*H*-pyrrolo[3,4-*b*]quinoline-1,3(2*H*)-dione (7qc): The title compound was purified by column chromatography on silica gel using EtOAc / hexanes (1: 4, *v/v*); as an eluent; off white solid (68 mg, 68%); mp = 178-180 °C (Lit. mp 183-185 °C)[22]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.66 (s, 1H), 8.44 (d, *J* = 8.4 Hz, 1H), 8.08 (d, *J* = 8.4 Hz, 1H), 7.95 (t, *J* = 7.6 Hz, 1H), 7.78 (t, *J* = 7.6 Hz, 1H), 3.83 (t, *J* = 7.4 Hz, 2H), 1.80 (q, *J* = 7.6 Hz, 2H), 1.01 (t, *J* = 7.4 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 166.3,



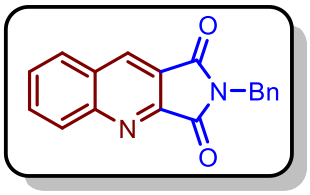
166.1, 150.8, 150.6, 132.7, 132.5, 131.5, 129.9, 129.5, 128.8, 122.9, 40.1, 21.8, 11.3; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{14}H_{13}N_2O_2^+$ 241.0972; Found 241.0973.

2-Cyclohexyl-1*H*-pyrrolo[3,4-*b*]quinoline-1,3(2*H*)-dione (7qd): The title compound was



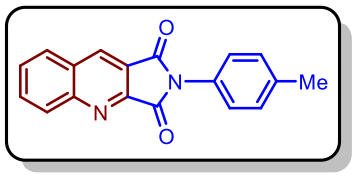
purified by column chromatography on silica gel using EtOAc / hexanes (1: 4, *v/v*); as an eluent; off white solid (71 mg, 61%); mp = 210-212 °C (Lit. mp 213-215 °C)[22]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.65 (s, 1H), 8.45 (d, *J* = 8.4 Hz, 1H), 8.08 (d, *J* = 8.0 Hz, 1H), 7.94 (t, *J* = 7.8 Hz, 1H), 7.78 (t, *J* = 7.4 Hz, 1H), 4.36 – 4.28 (m, 1H), 2.37 – 2.27 (m, 2H), 1.93 – 1.73 (m, 5H), 1.48 – 1.32 (m, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 166.2, 166.1, 150.9, 150.4, 132.6, 132.3, 132.1, 131.4, 129.8, 129.3, 128.9, 51.6, 29.7, 25.9, 25.0; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{17}H_{17}N_2O_2^+$ 281.1285; Found 281.1286.

2-Benzyl-1*H*-pyrrolo[3,4-*b*]quinoline-1,3(2*H*)-dione (7qe): The title compound was purified by



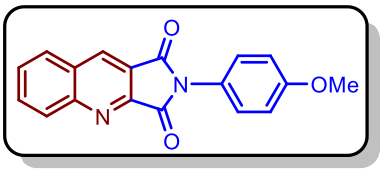
column chromatography on silica gel using EtOAc/ hexanes (1: 4, *v/v*) as an eluent; off white solid (76 mg, 64%); mp = 250-252 °C; (Lit. mp 248-251 °C)[22]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.67 (s, 1H), 8.44 (d, *J* = 8.4 Hz, 1H), 8.08 (d, *J* = 8.4 Hz, 1H), 7.96 (t, *J* = 7.8 Hz, 1H), 7.78 (t, *J* = 8.0 Hz, 1H), 7.52 (d, *J* = 6.8 Hz, 2H), 7.37 – 7.30 (m, 3H), 5.02 (s, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 165.9, 165.7, 150.8, 150.5, 135.8, 132.8, 132.7, 131.5, 129.9, 129.6, 128.9, 128.8, 128.0, 123.0, 42.1; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{18}H_{13}N_2O_2^+$ 289.0972; Found 289.0978.

2-(*p*-Tolyl)-1*H*-pyrrolo[3,4-*b*]quinoline-1,3(2*H*)-dione (7qg): The title compound was purified



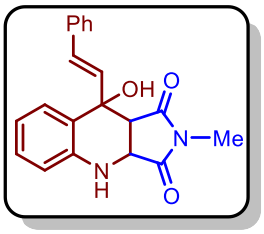
by column chromatography on silica gel using EtOAc/ hexanes (1: 4, *v/v*) as an eluent; off white solid (80 mg, 67%); mp = 274-276 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.80 (s, 1H), 8.50 (d, *J* = 8.4 Hz, 1H), 8.13 (d, *J* = 8.0 Hz, 1H), 8.00 (t, *J* = 7.8 Hz, 1H), 7.83 (t, *J* = 7.4 Hz, 1H), 7.42 – 7.36 (m, 4H), 2.46 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 165.3, 165.2, 151.2, 138.8, 133.2, 132.9, 131.6, 130.0, 129.9, 129.7, 129.0, 128.6, 126.4, 122.7, 122.0, 21.2; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{18}H_{13}N_2O_2^+$ 289.0972; Found 289.0974.

2-(4-Methoxyphenyl)-1*H*-pyrrolo[3,4-*b*]quinoline-1,3(2*H*)-dione (7qh): The title compound



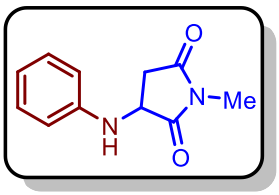
was purified by column chromatography on silica gel using EtOAc/ hexanes (1: 3, *v/v*) as an eluent; off white solid (88 mg, 70%); mp = 268-270 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.79 (s, 1H), 8.50 (d, *J* = 8.8 Hz, 1H), 8.13 (d, *J* = 8.4 Hz, 1H), 8.00 (t, *J* = 7.6 Hz, 1H), 7.84 (t, *J* = 7.4 Hz, 1H), 7.45 (d, *J* = 8.8 Hz, 2H), 7.08 (d, *J* = 8.8 Hz, 2H), 3.89 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 165.4, 165.3, 159.6, 151.2, 150.1, 133.2, 133.0, 131.6, 130.0, 129.7, 129.0, 127.9, 123.8, 122.7, 114.6, 55.6; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{18}H_{13}N_2O_3^+$ 305.0921; Found 305.0923.

(*E*)-9-Hydroxy-2-methyl-9-styryl-3*a*,4,9,9*a*-tetrahydro-1*H*-pyrrolo[3,4-*b*]quinoline-1,3 (2*H*)-



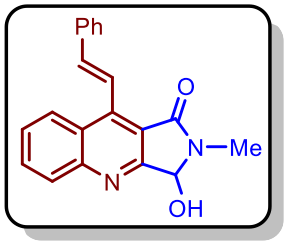
dione (29a): The title compound was purified by column chromatography on silica gel using EtOAc/ hexanes (1: 1.5, *v/v*) as an eluent; off white solid (20 mg, 27%); mp = 216-218 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.31 – 7.27 (m, 4H), 7.24 – 7.17 (m, 2H), 6.94 – 6.90 (m, 1H), 6.80 – 6.76 (m, 2H), 6.40 (d, *J* = 16.0 Hz, 1H), 4.59 (d, *J* = 4.0 Hz, 1H), 4.46 (dd, *J* = 9.2, 4.4 Hz, 1H), 3.63 (s, 1H), 3.41 (d, *J* = 9.2 Hz, 1H), 2.93 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 176.7, 175.4, 141.0, 136.2, 130.2, 128.9, 128.6, 127.9, 127.1, 127.0, 126.7, 124.2, 120.6, 115.5, 73.1, 53.0, 52.3, 24.6; HRMS (ESI) *m/z*: $[(M – H2O)+H]^+$ Calcd for $C_{20}H_{17}N_2O_2^+$ 317.1285; Found 317.1283.

1-Methyl-3-(phenylamino)pyrrolidine-2,5-dione (31): The title compound was purified by



column chromatography on silica gel using EtOAc/ hexanes (1: 2.3, *v/v*) as an eluent; off white solid (63 mg, 57%); mp = 140-142 °C (Lit. mp 138-140 °C)[55]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (t, *J* = 7.0 Hz, 2H), 6.88 (t, *J* = 7.0 Hz, 1H), 6.66 (d, *J* = 6.8 Hz, 2H), 4.46 (s, 1H), 4.34 (t, *J* = 7.6 Hz, 1H), 3.29 (dd, *J* = 17.6, 7.6 Hz, 1H), 3.11 (s, 3H), 2.68 (dd, *J* = 18.0, 5.2 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 176.9, 174.6, 146.1, 129.5, 119.6, 113.8, 53.0, 38.3, 25.2; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{11}H_{13}N_2O_2^+$ 205.0972; Found 205.0971.

(E)-3-Hydroxy-2-methyl-9-styryl-2,3-dihydro-1*H*-pyrrolo[3,4-*b*]quinolin-1-one (28): The



title compound was purified by column chromatography on silica gel using EtOAc/ hexanes (1: 0.3, *v/v*) as an eluent; off white solid (30 mg, 76%); mp = 252-254 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.53 (d, J = 7.8 Hz, 1H), 8.20 – 8.15 (m, 2H), 7.94 – 7.89 (m, 1H), 7.76 – 7.71 (m, 3H), 7.50 – 7.40 (m, 4H), 6.86 (d, J = 8.9 Hz, 1H), 5.76 (d, J = 8.8 Hz, 1H), 3.04 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 165.4, 163.2, 149.7, 142.7, 140.6, 136.9, 131.6, 130.1, 129.5, 129.3, 127.8, 127.7, 127.0, 126.0, 120.3, 118.8, 82.1, 26.4; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{20}H_{17}N_2O_2^+$ 317.1285; Found 317.1281.

2.4.5 X-ray Crystallographic Analysis of Compound 7ea:

The crystal data collection and data reduction were performed using CrysAlisPro software and suitable crystal of $C_{20}H_{13}BrN_2O_2$ [exp_884_DSN-499] was selected and mounted on a XtaLAB Pro: Kappa dual home/near diffractometer. The crystal was kept at 93(2) K during data collection. Using Olex2,[56] the structure was solved with the SHELXT[57] structure solution program using Intrinsic Phasing and refined with the SHELXL[58] refinement package using Least Squares minimization.

The single crystal of the compound **7ea** ($C_{20}H_{13}BrN_2O_2$) was obtained from slow evaporation of chloroform: Hexane solutions. The **7ea** was crystallized in triclinic crystal system with P-1 space group. The crystal structure information of **7ea** is deposited to Cambridge Crystallographic Data Center and the CCDC number for the **7ea** is 2209858.

Table 2.3: Crystal data and structure refinement for **7ea**.

Identification code	**7ea**
Empirical formula	$C_{20}H_{13}BrN_2O_2$
Empirical formula	393.23
Temperature/K	93(2)
Crystal system	triclinic
Space group	P-1
a/Å	7.5263(2)

b/Å	9.5684(3)
c/Å	12.2464(5)
α/°	112.583(3)
β/°	91.637(3)
γ/°	94.583(2)
Volume/Å^3	810.01(5)
Z	2
ρ_{calc}g/cm^3	1.612
μ/mm^{-1}	3.595
F(000)	396.0
Crystal size/mm^3	0.1 × 0.1 × 0.1
Radiation	Cu Kα (λ = 1.54184)
2Θ range for data collection/°	7.836 to 159.158
Index ranges	-9 ≤ h ≤ 8, -12 ≤ k ≤ 8, -14 ≤ l ≤ 15
Reflections collected	8188
Independent reflections	3402 [R_{int} = 0.0200, R_{sigma} = 0.0198]
Data/restraints/parameters	3402/0/227
Goodness-of-fit on F^2	1.059
Final R indexes [I>=2σ (I)]	R_1 = 0.0366, wR_2 = 0.0959
Final R indexes [all data]	R_1 = 0.0369, wR_2 = 0.0962
Largest diff. peak/hole / e Å^{-3}	1.58/-0.75

2.5 REFERENCES

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Chapter 3

Synthesis of Polyheterocycles by Ruthenium(II)-Catalyzed [4+2] Annulation of 2-Arylheteroarenes with Vinylene Carbonate

3.1 INTRODUCTION

Nitrogen-containing heterocycles are crucial building blocks found in many biologically significant natural products and synthetic pharmaceuticals. These compounds have garnered significant interest due to their substantial physiological and biological activities.[1-5] Within the array of *N*-heterocyclic structural motifs, the 4*H*-pyrido[1,2-*a*]pyrimidin-4-one skeleton is a distinctive class of fused nitrogen-containing heterocycles that is prevalent in various biologically active agents and assumes a pivotal role in medicinal chemistry.[6, 7] Specifically, scaffolds of 4*H*-pyrido[1,2-*a*]pyrimidin-4-one disclose a broad spectrum of pharmacological activities, including anti-cancer, antiallergic, antioxidant, aldose reductase inhibition, ERP α reverse agonism, and anti-ulcer properties.[8-15] Furthermore, indolopyridoquinazoline alkaloids like euxylophoricines B and F have been identified in Euxylophora paraensis, while 7,8-Dehydrorutaecarpine was initially isolated from Phellodendron amurense in 1998, demonstrating significant discoveries in alkaloid research (**Figure 3.1**)[16-18]

On the other hand, 2*H*-indazole and imidazo[1,2-*a*]pyridine are essential structural components found in numerous natural products, medicines, and agrochemicals.[19, 20] Molecules with an indazole and imidazo[1,2-*a*]pyridine framework exhibit diverse biological pharmacological activities. Many marketed drugs contain the imidazopyridine structure; for example, Zolpidem is utilized as a sedative to treat insomnia.[21] Necopidem and Saripidem bind to the central benzodiazepine receptor (CBR) and are used as anxiolytic agents.[22] Zolimidine, known for its gastroprotective properties, also incorporates the imidazopyridine structure.[23]

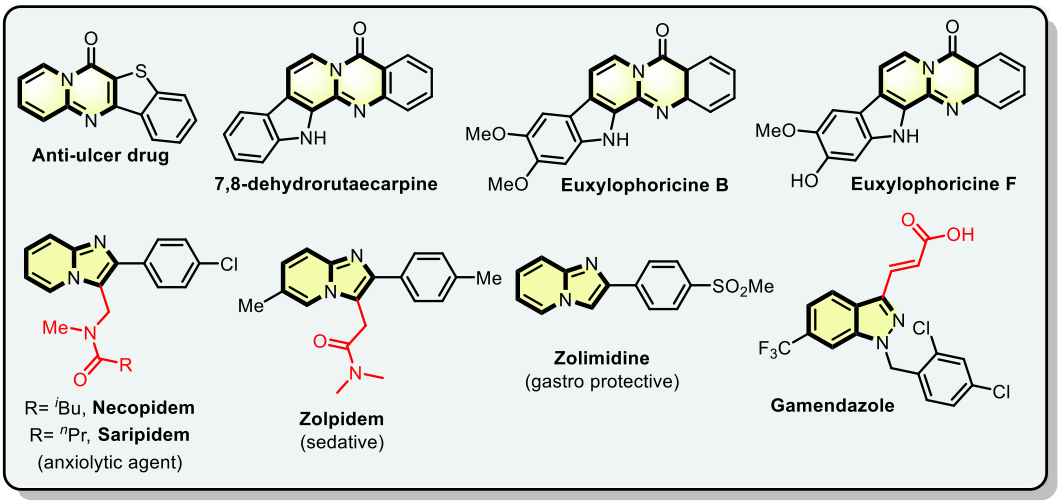
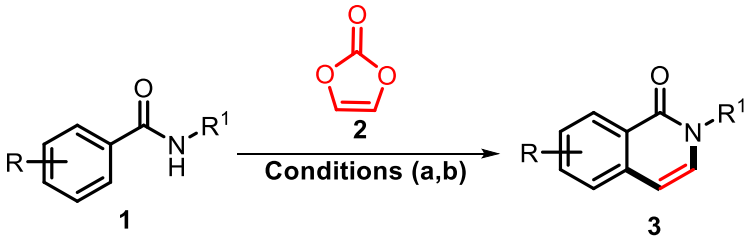


Figure 3.1: Selected examples of biologically active polyheterocycles

Transition-metal-catalyzed C-H/N-H, C-H/O-H, and C-H/C-H cascade annulation reactions have gained remarkable attention over the past few decades as a convincing and efficient method for synthesizing fused heterocyclic compounds.[24-28] This approach combines different pharmacophores and natural product scaffolds to create diverse structures, offering a straightforward and high-atom-economic strategy for the construction of complex polycycles.[29-31] Among the different coupling partners, vinylene carbonate has been widely used as a formylmethyl, ethynol, and acetylene equivalent for different metal-catalyzed C-H bond functionalization and annulation reactions to construct the fused heterocyclic compounds.[32-37]

In 2019, Miura and colleagues reported the Rh(III)-catalyzed C−H/N−H annulation of *N*-substituted benzamides (**1**) and vinylene carbonate (**2**) for the synthesis of quinolinone derivatives (**3**) (**Scheme 3.1a**).[38] In the following year, Xiao group disclosed the Co(III)-catalyzed [4+2] annulation of benzamides (**1**) with vinylene carbonate (**2**) for the construction of quinolinone derivatives (**3**) (**Scheme 3.1b**).[39] The present methodology has shown significant features like a broad substrate scope with good to excellent yields, no need for pre-functionalization of starting material, and no external oxidant necessary to produce the oxidative annulation.

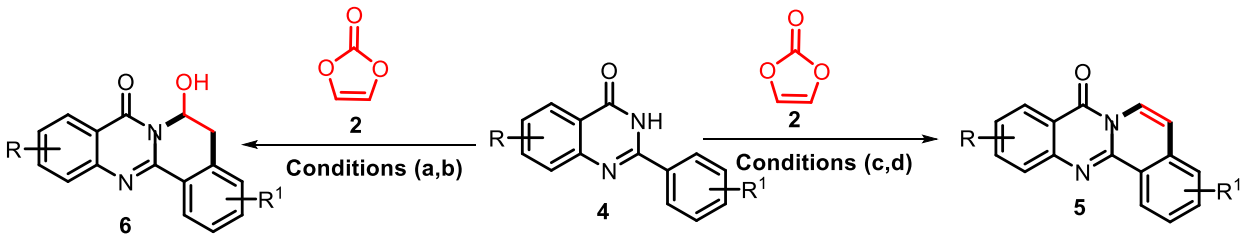


No	Condition	Examples	Yield%
a)	$[RhCp^*(MeCN)_3](SbF_6)_2$ (2 mol %), DCE, 70 °C 12 h	17	up to 90
b)	$[CoCp^*(CO)I_2]$ (10 mol %), $AgSbF_6$ (20 mol %), $Zn(OAc)_2$ (5 mol %), TFE, 100 °C 12 h	26	up to 95

Scheme 3.1: Rh(III) and Co(III)-catalyzed annulation of benzamides with vinylene carbonate

In 2021, Zhou and co-workers reported Ru(II)-catalyzed C-C and C-N annulation of 2-arylquinazolinones (**4**) with vinylene carbonate (**2**) for the construction of fused quinazolinone derivatives (**Scheme 3.2a**).[40] In the developed methodology, vinylene carbonate acts as an ethynol surrogate. Almost at the same time, Zhang group also synthesized 8*H*-isoquino[1,2-*b*]quinazolin-

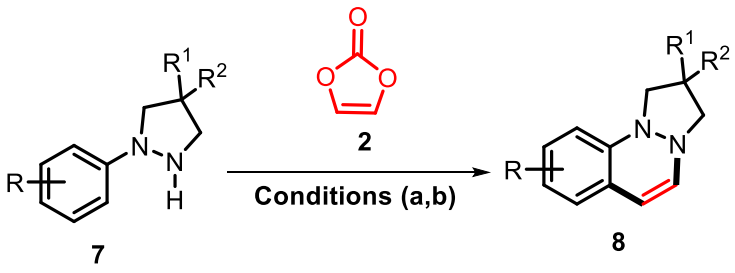
8-one(**5**) by utilizing 2-arylquinazolinones (**4**) and vinylene carbonate (**2**) used as coupling partners in the presence of a Rh(III) catalyst (**Scheme 3.2b**).[41] In this protocol, vinylene carbonate acts as an acetylene surrogate. Additionally, kinetic isotope effect (KIE) studies have shown a k_H/k_D value of 2.4, suggesting that the cleavage of the C-H bond could be the rate-determining step of the reaction.



No	Condition	Examples	Yield%
a)	[Ru(*p*-cymene)Cl_2]$_2$ (5 mol %), $AgSbF_6$ (20 mol %), NaOAc (2 equiv.), DCE, 80 °C, 12 h	28	up to 92
d)	[RhCp*Cl_2]$_2$ (2.5 mol %), AgOTf (10 mol %), γ-valerolactone, 130 °C, 24 h	18	up to 92

Scheme 3.2: Rh(III) and Ru(II)-catalyzed annulation of 2-arylquinazolinones with vinylene carbonate

Yu and Fan groups independently reported the construction of pyrazolo[1,2–*a*]cinnolines (**8**) through Rh(III)-catalyzed [4+2] cyclization of *N*-arylpyrazolidin-3-ones (**7**) and vinylene carbonate (**2**) (**Scheme 3.3ab**).[42, 43] Notably, the developed protocol offers several advantages, including readily available substrates with a broad scope, and excellent compatibility with diverse functional groups.

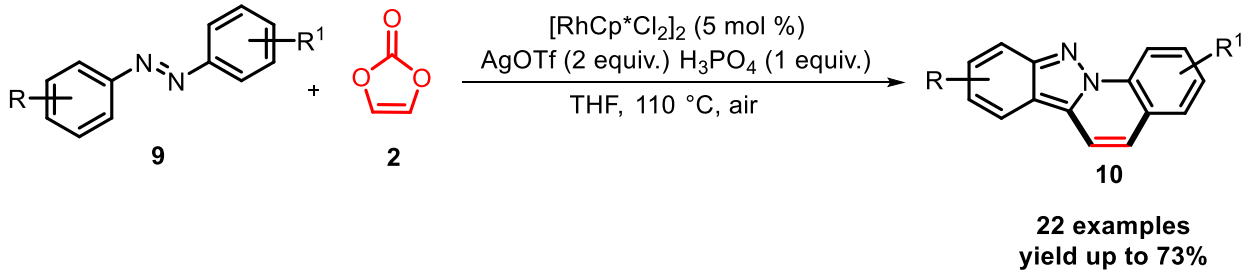


No	Condition	Examples	Yield%

a)	$[RhCp^*Cl_2]_2$ (2.5 mol %), $Zn(OAc)_2$ (0.5 equiv), AcOH (0.5 equiv.) DCM, 100 °C, 8 h	30	up to 98
b)	$[RhCp^*Cl_2]_2$ (3 mol %), $Zn(OAc)_2$ (0.2 equiv), toluene 100 °C 12 h	23	up to 83

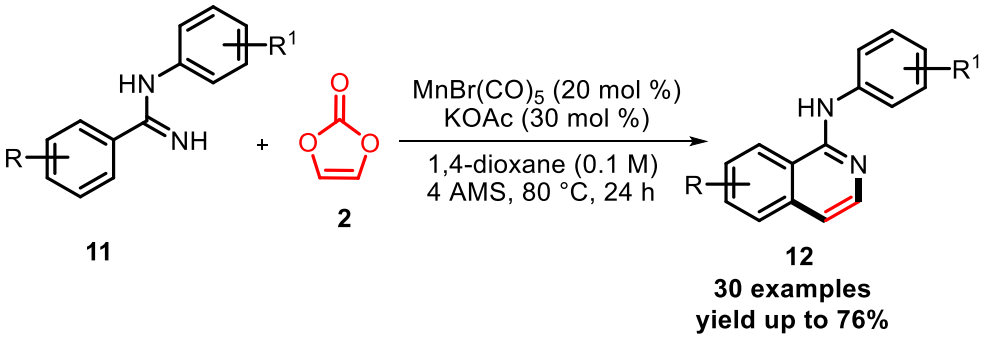
Scheme 3.3: Rh(III)-catalyzed oxidative coupling of *N*-arylpyrazolidin-3-ones with vinylene carbonate

Cui group explored the Rh(III)-catalyzed cyclization between the azobenzenes (**9**) and the vinylene carbonate (**2**) for the synthesis of structurally diverse indazolo[2,3-*a*]quinoline derivatives (**10**) with moderate to good yields (**Scheme 3.4**).[44] The established protocol utilizes vinylene carbonate to serve as both C1 and C2 synthons within a single reaction.



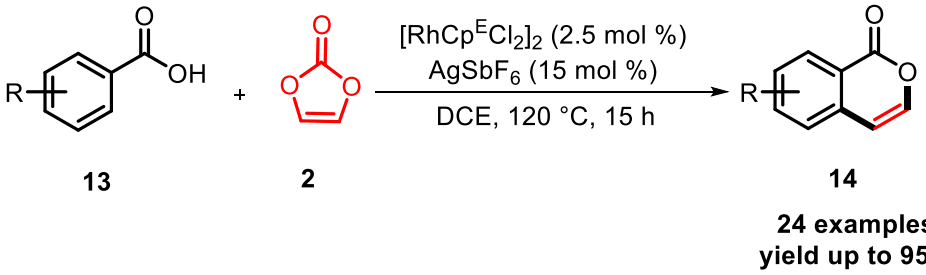
Scheme 3.4: Rh(III)-catalyzed cyclization of azobenzenes with vinylene carbonate

Li and co-workers developed an Mn(I)-catalyzed synthesis of 1-aminoisoquinoline derivatives (**12**) *via* the [4+2] annulation of *N*-phenylbenzimidamide (**11**) with vinylene carbonate (**2**) (**Scheme 3.5**).[45] The developed protocol removes the necessity for oxidants and demonstrates excellent tolerance towards functional groups, along with high atom efficiency.



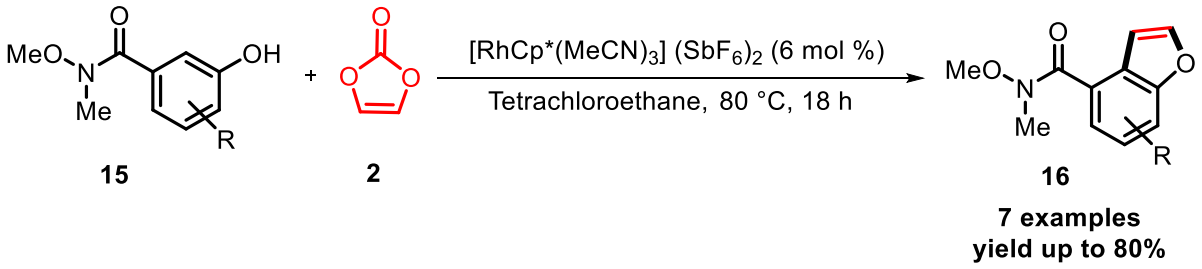
Scheme 3.5: Mn(I)-catalyzed annulation of imidines with vinylene carbonate

In 2020, the Miura group established a novel approach to synthesize isocoumarin derivatives (**14**) using a Rh(III)-catalyzed [4 + 2] cyclization reaction. This pioneering process involved the reaction of aryl carboxylic acids (**13**) with vinylene carbonate (**2**) (**Scheme 3.6**).[46] The developed protocol introduced an innovative "rhodium shift" phenomenon during the reaction, triggering a detailed investigation through Density Functional Theory (DFT) calculations. The electronic effect of the rhodium catalyst was efficiently evaluated, and the electron-deficient Cp^E–Rh proved to be a better choice than the commonly used Cp*–Rh catalyst.



Scheme 3.6: Rh(III)-catalyzed cyclization of carboxylic acids with vinylene carbonate

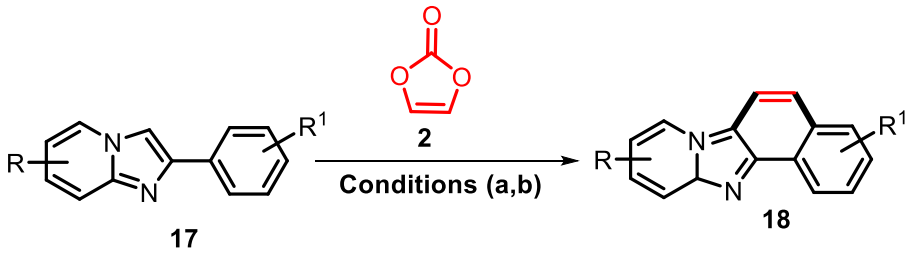
In 2022, the Miura research group extended their work by introducing an Rh(III)-catalyzed [3 + 2] annulation reaction. This innovative process involved the use of 3-hydroxy-*N*-methoxy-*N*-methylbenzamide (**15**) and vinylene carbonate (**2**) as substrates, leading to the efficient synthesis of C4-substituted benzofuran derivatives (**16**) (**Scheme 3.7**).[47] In this protocol, Weinreb amide is used as a directing group for the construction of C4-substituted benzofurans.



Scheme 3.7: Rh(III)-catalyzed annulation of benzamide with vinylene carbonate

In 2020, the Miura group utilized vinylene carbonate (**2**) as a coupling partner for the synthesis of naphtho[1',2':4,5]imidazo[1,2-*a*]pyridine (**18**) from 2-phenylimidazo[1,2-*a*]pyridines (**17**) under Rh(III)-catalysis (**Scheme 3.8a**).[48] This strategy offers an efficient and straightforward approach to construct biologically important polyaromatic scaffolds. The reaction demonstrates good

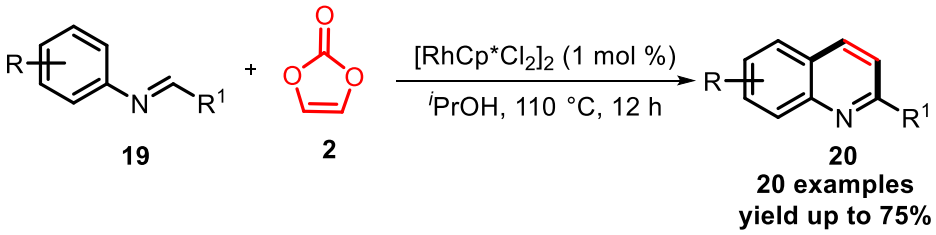
substrate scope, yielding annulated products in moderate to good yields. Yan group also established a similar strategy for the construction of naphtho[1',2':4,5]imidazo[1,2-*a*]pyridine (**18**) utilizing Co(III)-catalyst (**Scheme 3.8b**).[49]



No	Conditions	Examples	Yield%
a)	$[RhCp^*(MeCN)_3](SbF_6)_2$ (6 mol %), DCE, 120 °C 24 h	19	up to 86
b)	$[CoCp^*(MeCN)_3](SbF_6)_2$ (10 mol %), HFIP, 100 °C 12 h	24	up to 89

Scheme 3.8: Rh(III) and Co(III)-catalyzed annulation of 2-phenylimidazo[1,2-*a*]pyridines with vinylene carbonate

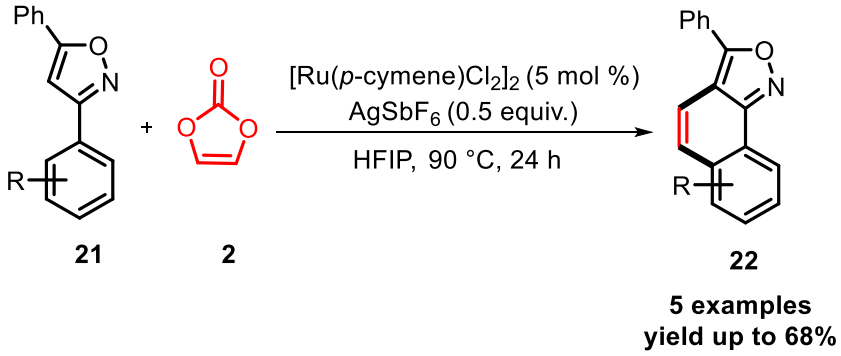
Ma and his co-workers demonstrated the construction of quinolines derivatives (**20**) *via* Rh(III) catalyzed [4 + 2] cyclization reaction between easily accessible *N*-arylimines (**19**) with vinylene carbonate(**2**) (**Scheme 3.9**).[50] This methodology resulted in the synthesis of quinoline derivatives, widely applicable in organic, material sciences, and pharmaceuticals. The process, a redox-neutral reaction, exhibited a straightforward system, reduced catalyst loading, and eliminated carbonic acid as a byproduct.



Scheme 3.9: Rh(III)-catalyzed [4 + 2] cyclization of *N*-arylimines with vinylene carbonate

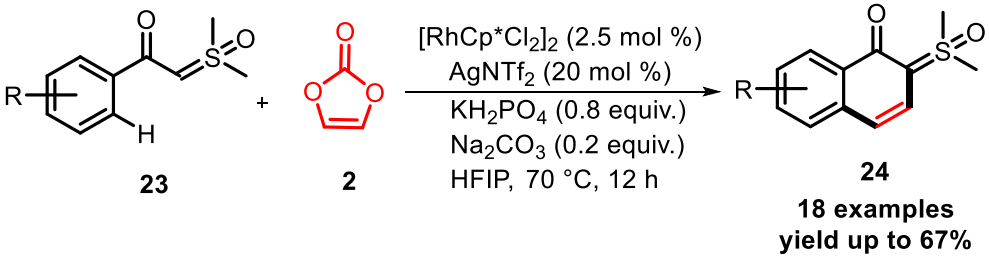
In 2022, the Kumar group disclosed the synthesis of fused-anthranilic derivatives (**22**) *via* Ru(II)-catalyzed oxidative coupling reaction between isoxazoles (**21**) and vinylene carbonate(**2**) (**Scheme**

3.10).[51] In this transformation, the author also achieved the formation of a C–H formylmethylated product by simple manipulation of the established reaction conditions. Furthermore, the vinylene carbonate acts as both an acetylene equivalent and a formylmethyl cation equivalent through a decarboxylation process.



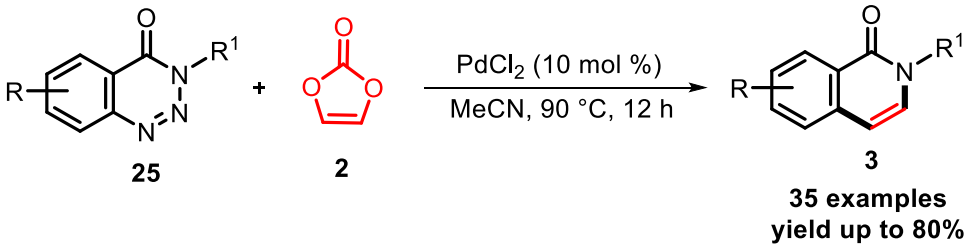
Scheme 3.10: Ru(II)-catalyzed oxidative coupling of isoxazoles with vinylene carbonate

Shu and colleagues developed Rh(III) catalyzed unprecedented C– H/C–H oxidative annulation of sulfoxonium ylides (**23**) with vinylene carbonate (**2**) to afford the desired annulated product, naphthalenone *β*-ketosulfoxonium ylide (**24**) (**Scheme 3.11**).[37] The innovative redox-neutral catalytic system demonstrates mild reaction conditions, wide range of substrates cope, and excellent compatibility with various functional groups.



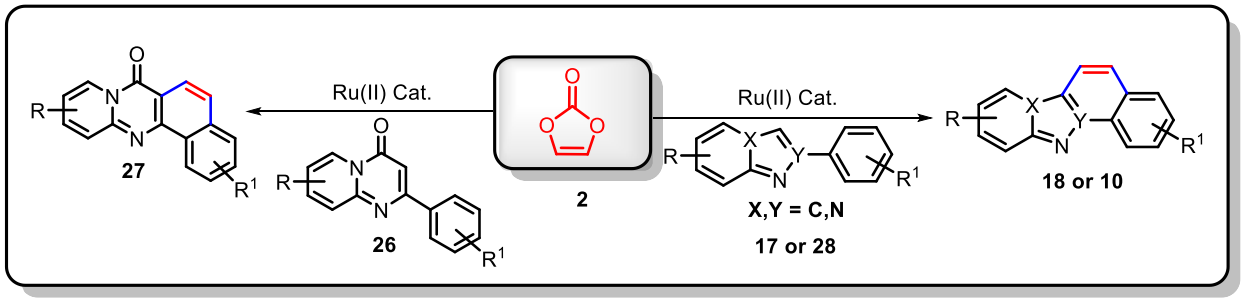
Scheme 3.11: Rh(III)-catalyzed C-H functionalization of sulfoxonium ylides with vinylene carbonate

In 2024, Ma and co-workers, for the first time, reported Pd(II) catalyzed synthesis of isoquinolinone derivatives (**3**) *via* the coupling between benzotriazinone (**25**) and vinylene carbonate (**2**) (**Scheme 3.12**).[52] The developed protocol enables the smooth synthesis of C3 and C4-non-substituted isoquinolinones with good to excellent yields. Moreover, this strategy has been applied for late-stage modification of bioactive molecules.



Scheme 3.12: Pd(II)-catalyzed vinylation of benzotriazinone with vinylene carbonate

A very few reports are available on Ru(II)-catalyzed direct C-H/C-H annulation of various heterocycles with vinylene carbonate. Inspired by elegant pioneering studies, herein we report the annulation of 2-Phenyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (**26**), 2-Phenyl-2*H*-indazole (**28**) and 2-Phenylimidazo[1,2-*a*]pyridine (**17**) with vinylene carbonate (**2**) in the presence of Ru(II)-catalyst for the construction of fused-polyheterocyclic compounds.



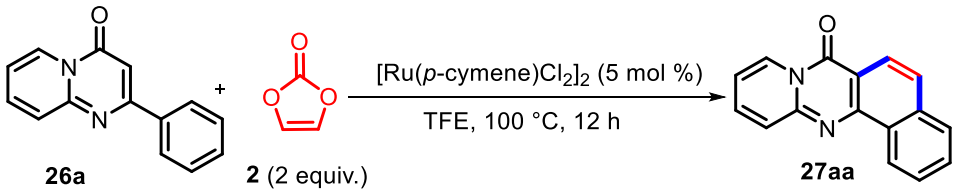
Scheme 3.13: Ru(II)-catalyzed [4 + 2] annulation of 2-arylheteroaryl with vinylene carbonate

3.2 RESULTS AND DISCUSSION

At the outset of our studies, we selected 2-phenyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (**26a**) and vinylene carbonate (**2**) as model substrates to optimize the reaction conditions for the [4+2] C-H/C-H annulation of vinylene carbonate (**Table 3.1**). To our satisfaction, the initial reaction of **26a** and **2** in the presence of [Ru(*p*-cymene)Cl_2]$_2$ (5 mol %) in toluene at 100 °C for 24 h delivered the desired product, 7*H*-benzo[*H*]pyrido[2,1-*b*]quinazolin-7-one, (**27aa**) in a promising 58% yield (**Table 3.1,** entry 1). The structure of **27aa** was confirmed by NMR (^{1}H and ^{13}C{^{1}H}) and HRMS spectroscopic data. In the ^{1}H NMR of **27aa**, all aromatic protons appeared at 9.18-6.97 ppm **(Figure 3.2)**. In the ^{13}C{^{1}H} NMR of **27aa**, carbonyl carbon of 2-phenyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one appeared at 158.6 ppm along with other expected carbons **(Figure 3.3)**. A peak at *m/z* 247.0866 in the HRMS corresponding to molecular formula $C_{16}H_{11}N_2O$ [M+H] ion confirmed the structure of **27aa**. Further, the molecular structure of **27aa** was unambiguously

confirmed by single-crystal X-ray analysis (**Figure 3.4, CCDC No**. 2354240). We investigated this model reaction in various solvents, including 1,4-dioxane, dichloroethane, trifluoroethanol (TFE), and DMF (**Table 3.1,** entries 2-5). The best yield of **27aa** (88%) was obtained in TFE (**Table 3.1,** entry 4). Furthermore, the reaction temperature was decreased to 80 °C (**Table 3.1,** entry 6), reducing the amount of **2** to 1.5 equiv. (**Table 3.1,** entry 7) and lowering the catalyst loading to 2.5 mol % (**Table 3.1,** entry 8) resulted in a decreased yield of **27aa**. Importantly, the annulated product **27aa** was not obtained when the reaction was performed using $[Ru(PPh_3)_3Cl_2]$ and $Pd(OAc)_2$ as the catalysts or in the absence of $[Ru(p\text{-cymene})Cl_2]_2$ (**Table 3.1**, entries 9-11).

Table 3.1: Optimization of reaction conditions.[a]



Entry	Variation from standard conditions	% Yield **3a**[b]
1	toluene as solvent	58
2	1,4-dioxane	64
3	DCE as solvent	71
4	none	88
5	DMF as solvent	NR
6	reaction at 80 °C	74
7	1.5 equivalent of 2	68
8	$[Ru(p\text{-cymene})Cl_2]_2$ (2.5 mol %)	48
9	$[Ru(PPh3)_3Cl_2]$ (5 mol %)	NR
10	$Pd(OAc)_2$ as a catalyst	NR
11	no Ru- catalyst	NR

[a]Reaction conditions: **26a** (0.259 mmol), **2** (0.518 mmol), catalyst (5 mol %), solvent (1 mL), in a sealed tube at 100 °C for 12 h. [b]Isolated yield.

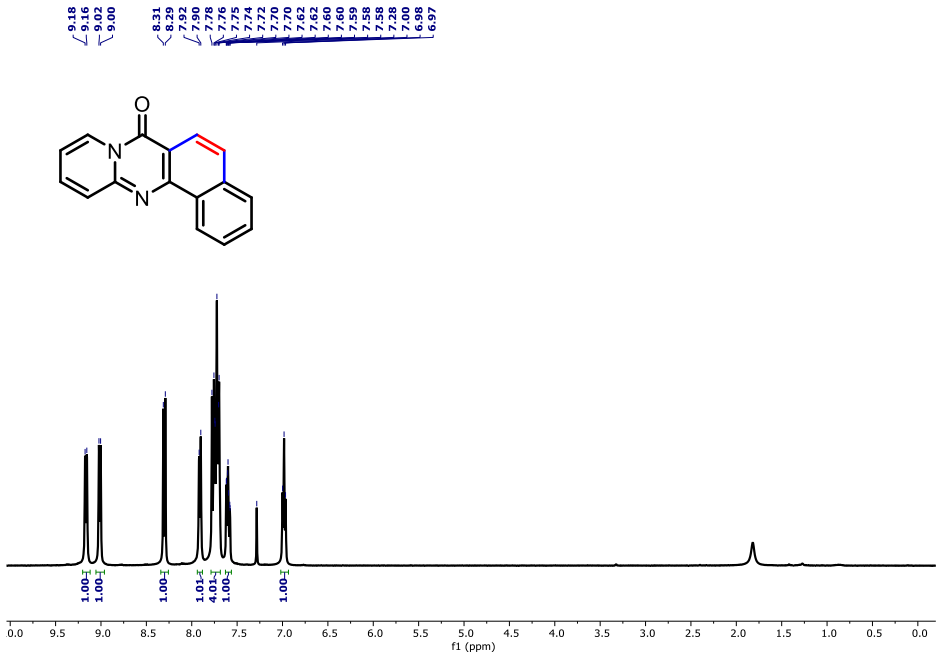


Figure 3.2: ^{1}H NMR spectra of 7*H*-benzo[*h*]pyrido[2,1-*b*]quinazolin-7-one (**27aa**) recorded in $CDCl_3$

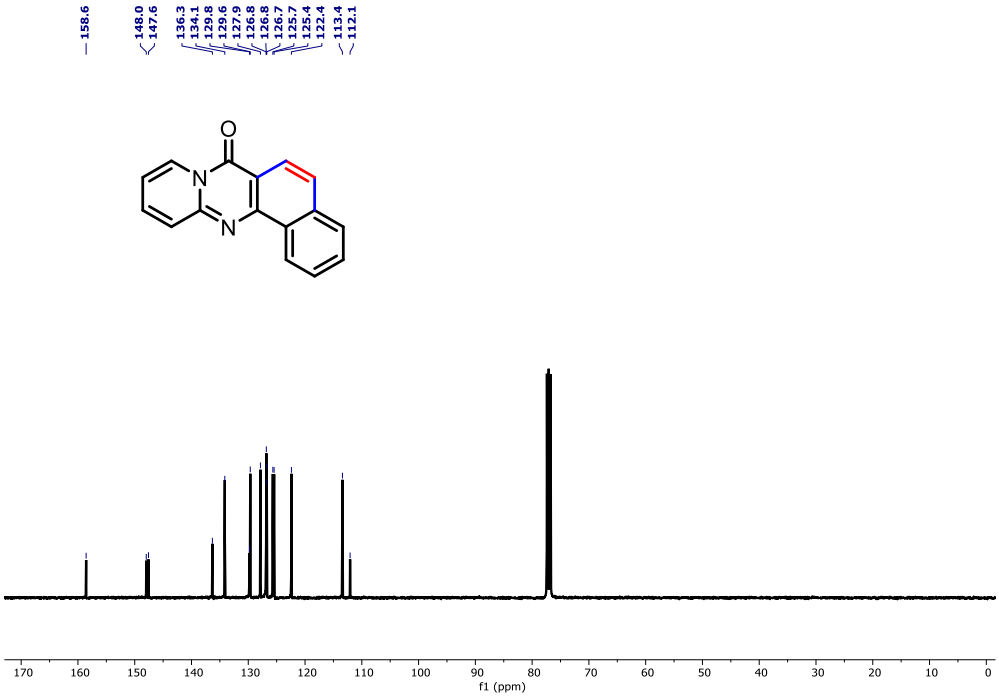


Figure 3.3: $^{13}C\{^{1}H\}$ NMR spectra of 7*H*-benzo[*h*]pyrido[2,1-*b*]quinazolin-7-one (**27aa**) recorded in $CDCl_3$

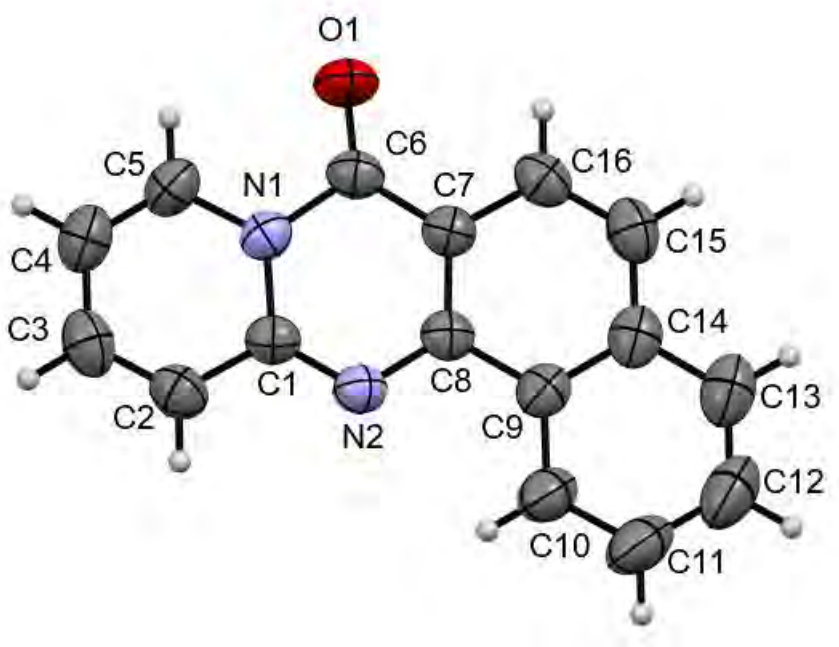
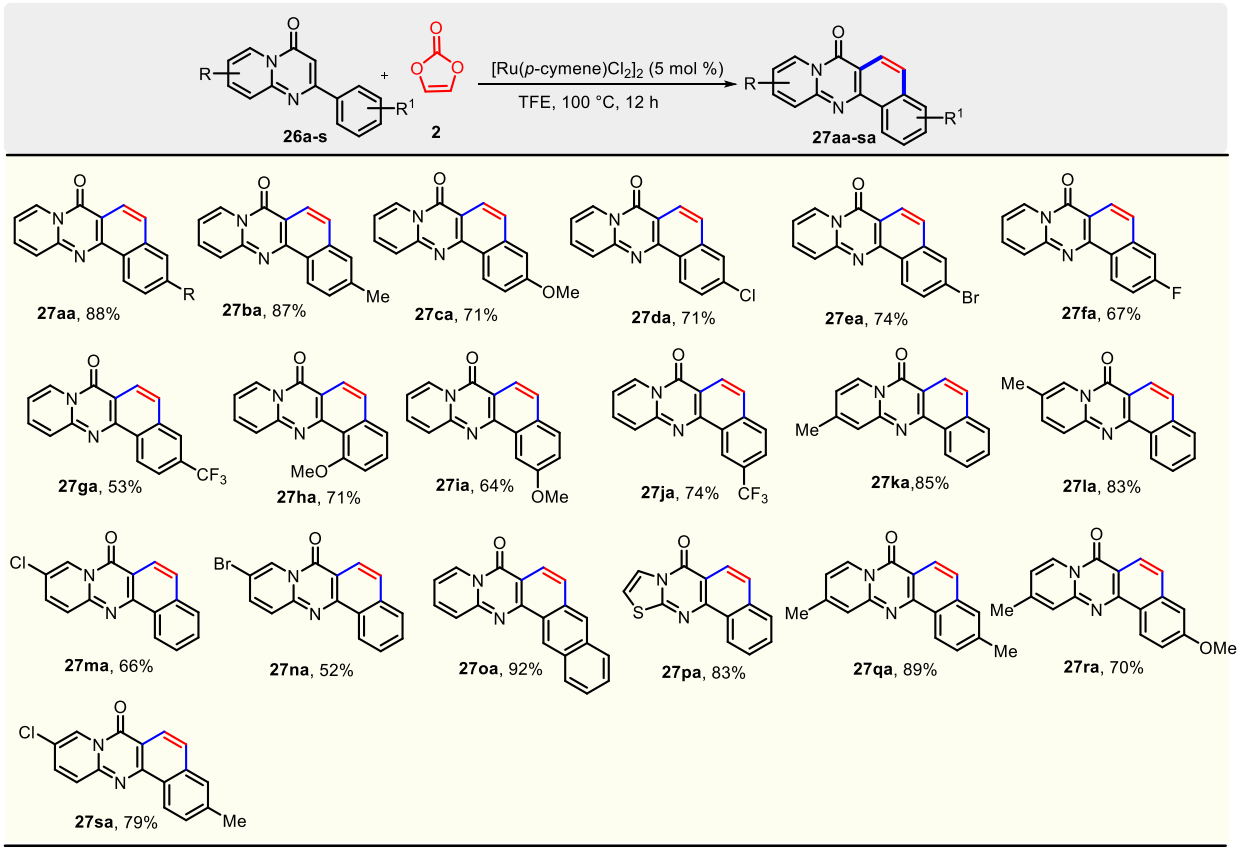


Figure 3.4: Single crystal ORTEP diagram of compound **27aa**. Thermal ellipsoids are drawn at a 50 % probability level (**CCDC No** 2354240)

With the appropriate reaction conditions in hand, we proceeded to employ various 2-aryl-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones to evaluate the scope of this reaction (**Table 3.2**). 2-Aryl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (**26a-26g**) with various functional groups such as Me, OMe, Cl, Br, F, and CF_3 on the para position of C2-phenyl ring underwent successful coupling with formation of corresponding 7*H*-benzo[*H*]pyrido[2,1-*b*]quinazolin-7-ones **27a-27g** in good to excellent (54-88%) yields. The optimized reaction conditions also exhibited excellent tolerance towards *ortho* and *meta*-substituted C2-phenyl rings, resulting in the formation of the corresponding cyclized product **27h-27j** in 57-74% yield. The reaction of 2-phenyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one with substituents such as Me, Cl, Br on the C-6 and C-7 position of pyrimidine ring (**26k-26n**) and 2-(naphthalen-2-yl)-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (**26o**) with **2** also produced the desired annulated products **27k-27o** in 61-92% yield. Similarly, the reaction of 2-phenyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones having substituents on both the pyrido[1,2-*a*]pyrimidin-4-one nucleus and 2-phenyl ring (**26p-26r)** with **2** worked well under optimized conditions and furnished the corresponding products **26p-26r** in 70-89% yield. Notably, the halogen substituents were well tolerated, which would offer numerous possible post-functionalization of benzo[*H*]pyrido[2,1-*b*]quinazolin-7-one scaffold. Gratifyingly, the reaction of 7-phenyl-5*H*-thiazolo[3,2-*a*]pyrimidin-5-one (**26s**) with **2** also produced corresponding annulated products **27s** in 83% yield.

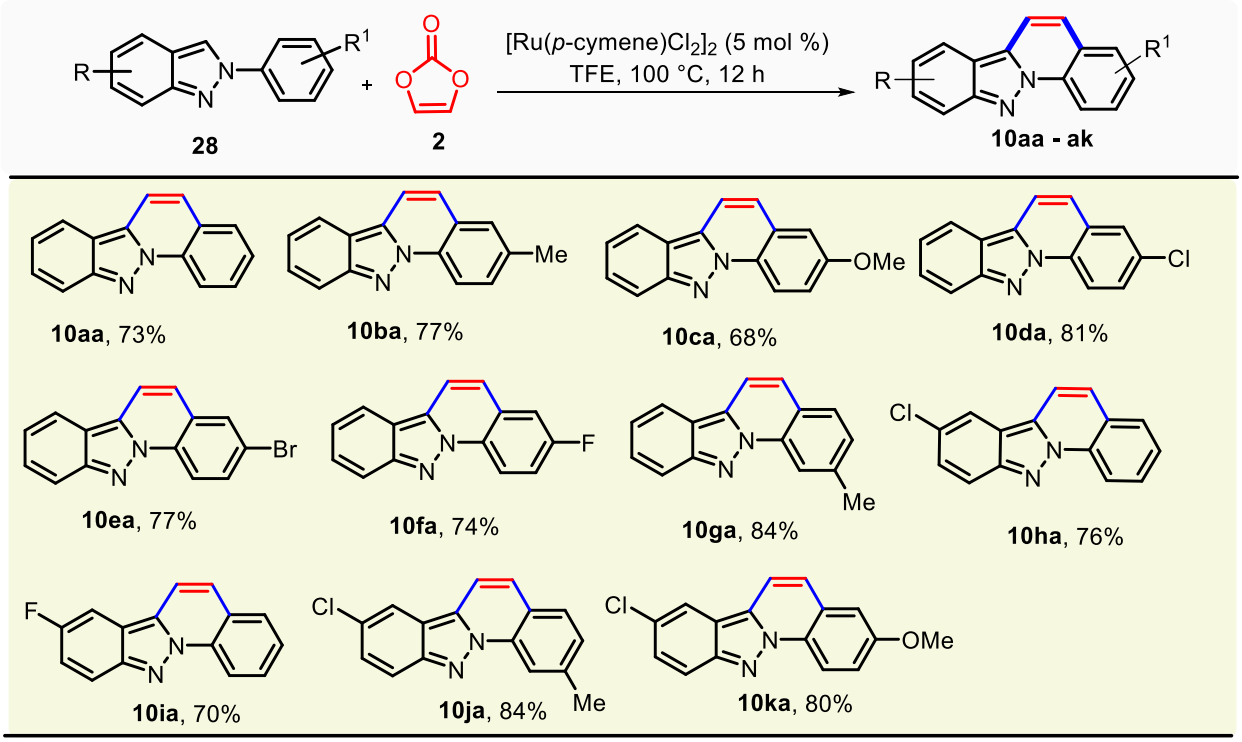
Table 3.2: Substrate scope for annulation of the 2-aryl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one with vinylene carbonate [a b]



Reaction conditions[a]: **26** (0.27 mmol), **2** (0.54 mmol), [Ru(*p*-cymene)Cl_2]$_2$ (5 mol %), TFE (1 mL), 100 °C, 12 h. [b]Isolated yields.

Next, we explored the possibility of using 2-aryl-2*H*-indazoles (**28**) as substrates for Ru(II)-catalyzed C-H/C-H annulation with vinylene carbonate (**Table 3.3**). To our satisfaction, various 2-aryl-2*H*-indazoles (**28a-28k**) with substituents such as Me, OMe, F, Cl, and Br both on the 2-phenyl ring as well as on the indazole nucleus reacted smoothly with **2** to afford corresponding indazolo[2,3-*a*]quinolines (**10aa-10ka**) in 68-84% yields under optimized reaction conditions.

Table 3.3: Substrate scope for the 2- aryl-2*H*-indazole [a, b]



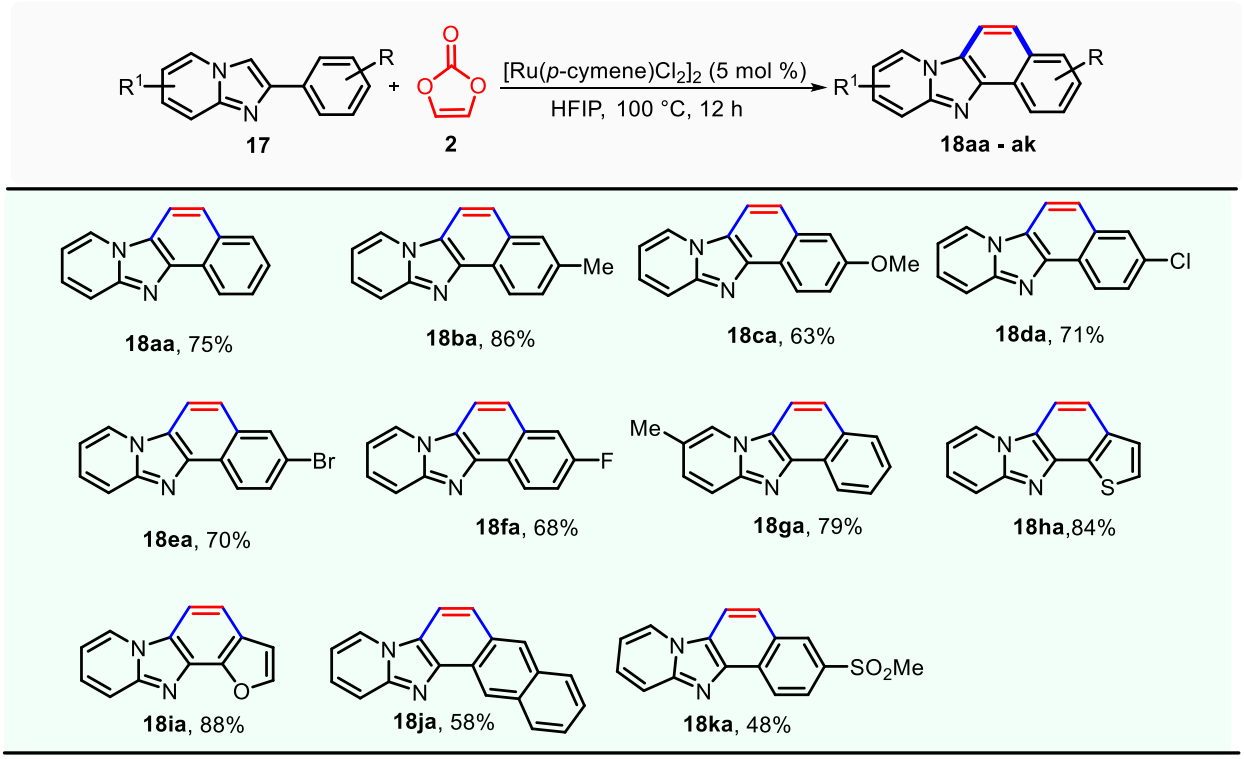
[a]Reaction conditions for preparation of **10**: **1** (0.27 mmol), **2** (0.54 mmol), [Ru(*p*-cymene)Cl_2]$_2$ (5 mol %), TFE (1 mL), 100 °C, 12 h. [b]Isolated yields.

To further expand the scope of this methodology, we examined 2-arylimidazo[1,2-*a*]pyridines (**17**) as substrates (**Table 3.4**). Initially, the reaction of 2-phenylimidazo[1,2-*a*]pyridine (**17a**) with **2** in the presence of [Ru(*p*-cymene)Cl_2]$_2$ (5 mol%) in TFE at 100 °C for 12 h produced annulated product, naphtho[1',2':4,5]imidazo[1,2-*a*]pyridine, (**18aa**) in low (64%) yield and thus the reaction conditions were re-optimized. To our satisfaction reaction of **17a** with **2** in the presence of [Ru(*p*-cymene)Cl_2]$_2$ (5 mol%) in HFIP at 100 °C for 12 h **18aa** in 75% yield. The reaction of other 2-arylimidazo[1,2-*a*]pyridine (**17b-17j**) with **2** in the presence of [Ru(*p*-cymene)Cl_2]$_2$ (5 mol%) in HFIP at 100 °C for 12 h produced corresponding annulated products **18ba-18ja** in 58-88% yields. Additionally, a commercial drug molecule, Zolimidine (**17k**), also underwent annulation with **2** to produce a cyclized product of **18ka** in 48% yield.

A series of functional groups such as Me, OMe, F, Cl, Br, and SO_2Me were well tolerated to produce the corresponding annulated products. Especially, the halogen substituents would offer

numerous possibilities for the late-stage functionalization of fused-polyheterocycles. The structure of all the products was ascertained by ^{1}H NMR, ^{13}C NMR, and HRMS data. The structure of **18ha** was also unambiguously confirmed by single-crystal X-ray analysis (**CCDC No** 2374059). Interestingly, the yields for indazolo[2,3-*a*]quinolines and naphtho[1',2':4,5]imidazo[1,2-*a*]pyridines were comparable with that obtained using Rh(III)-catalyst by Miura group.

Table 3.4: Substrate scope for the 2-phenylimidazo[1,2-*a*]pyridine [a,b]



[a]Reaction conditions for preparation of **18**: **1** (0.27 mmol), **2** (0.54 mmol), [Ru(*p*-cymene)Cl_2]$_2$ (5 mol %), HFIP (1 mL), 100 °C, 12 h. [b]Isolated yields.

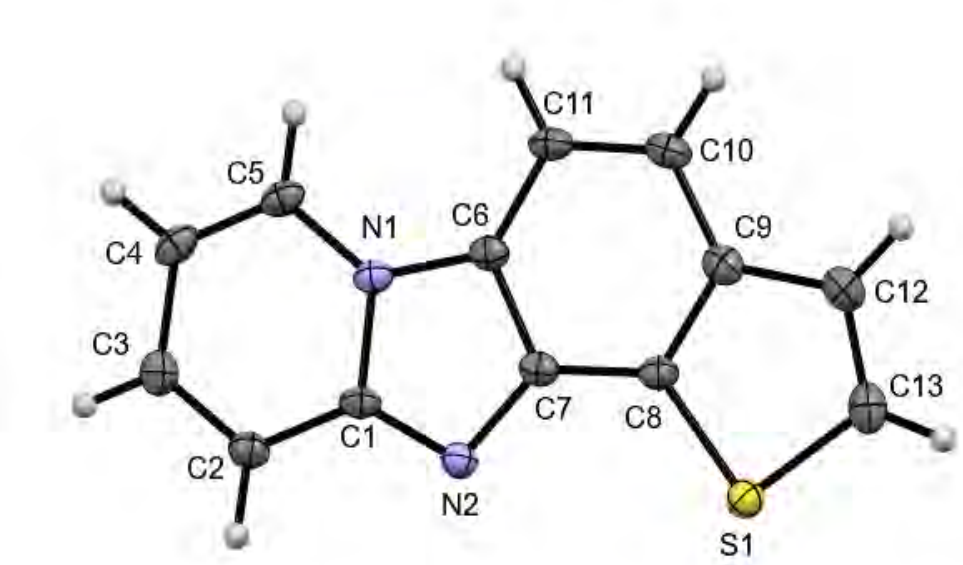
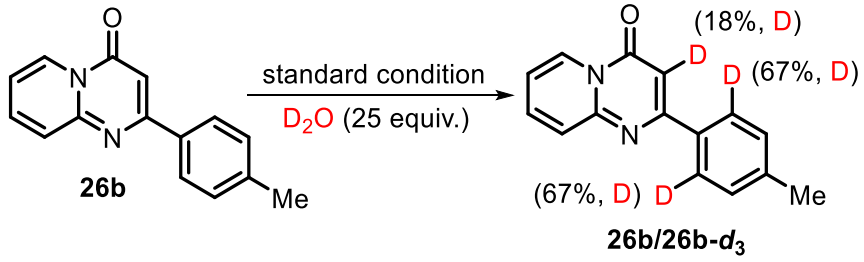


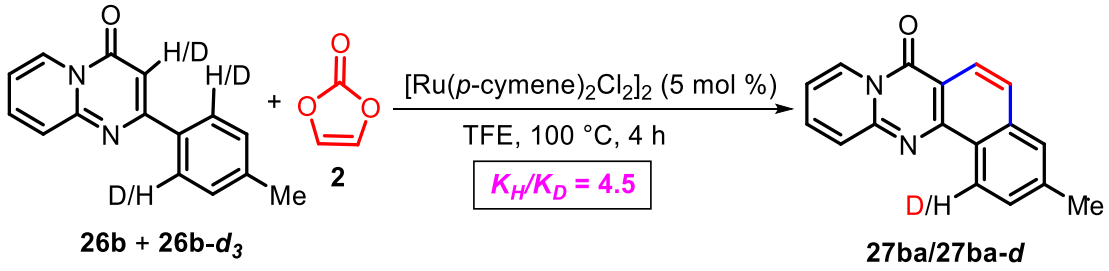
Figure 3.5. ORTEP diagram of **18ha** the thermal ellipsoids are drawn at a 50 % probability level [**CCDC No**: 2374059].

To gain some mechanistic insights, a few control experiments were performed (**Scheme 3.14**). At first, we performed a deuterium-labeling experiment (**Scheme 3.14a**). Incorporation of deuterium into the *ortho* C−H bond (67%), over the C3-H bond (18%) reveals that the cleavage of the *ortho* C−H bond is reversible and involves a concerted metalation-deprotonation (CMD) pathway. Next, we performed a kinetic isotope effect (KIE) study (**Scheme 3.14b**). An intermolecular competition reaction between **26b** and **26b-*D*$_3$** gave k_H/k_D = 4.5 for the formation of **27b**/**27b-*D***, suggesting that the C–H bond cleavage process is involved in the rate-limiting step. Intermediate cyclometalated complex **B** (**Ru-I**) was isolated by the stoichiometric reaction of **26b** with [Ru(*p*-cymene)Cl_2]$_2$ in methanol (**Scheme 3.14c**). Subsequently, the reaction of **26b** and **2** was conducted under optimized conditions using **Ru-I** as a catalyst instead of [Ru(*p*-cymene)Cl_2]$_2$ (**Scheme 3.14d**). The reaction produced the desired product **27ba** in 74% yield, indicating that the developed annulation reaction proceeds through cyclometalated complex **Ru-I**.

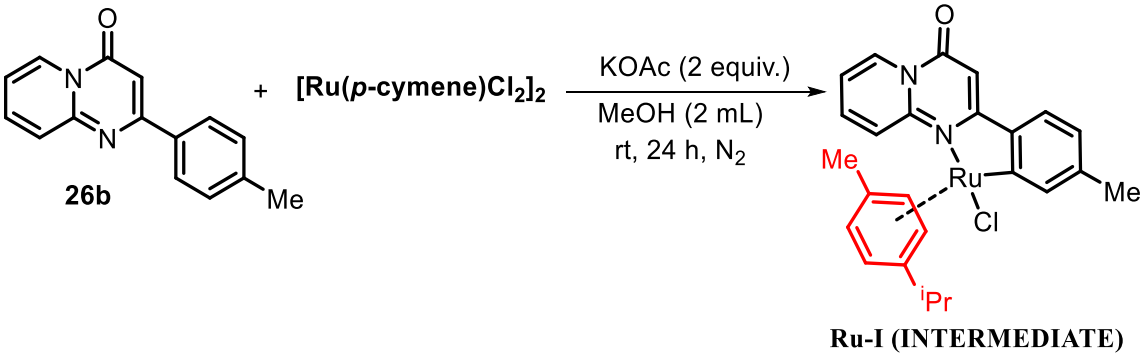
a) H/D exchange experiment without allyl alcohol



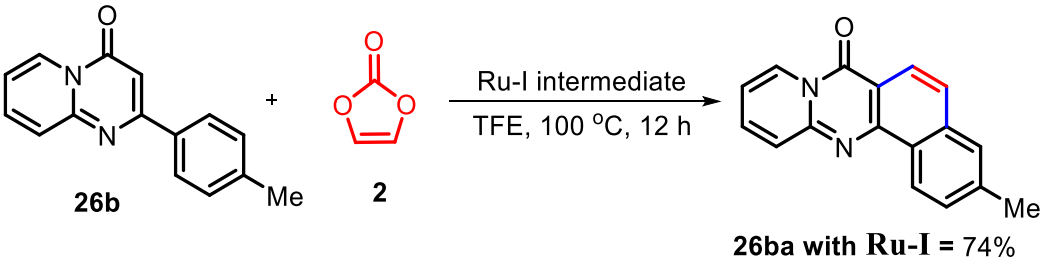
b) Kinetic isotope experiment



c) Ruthenium complex synthesis



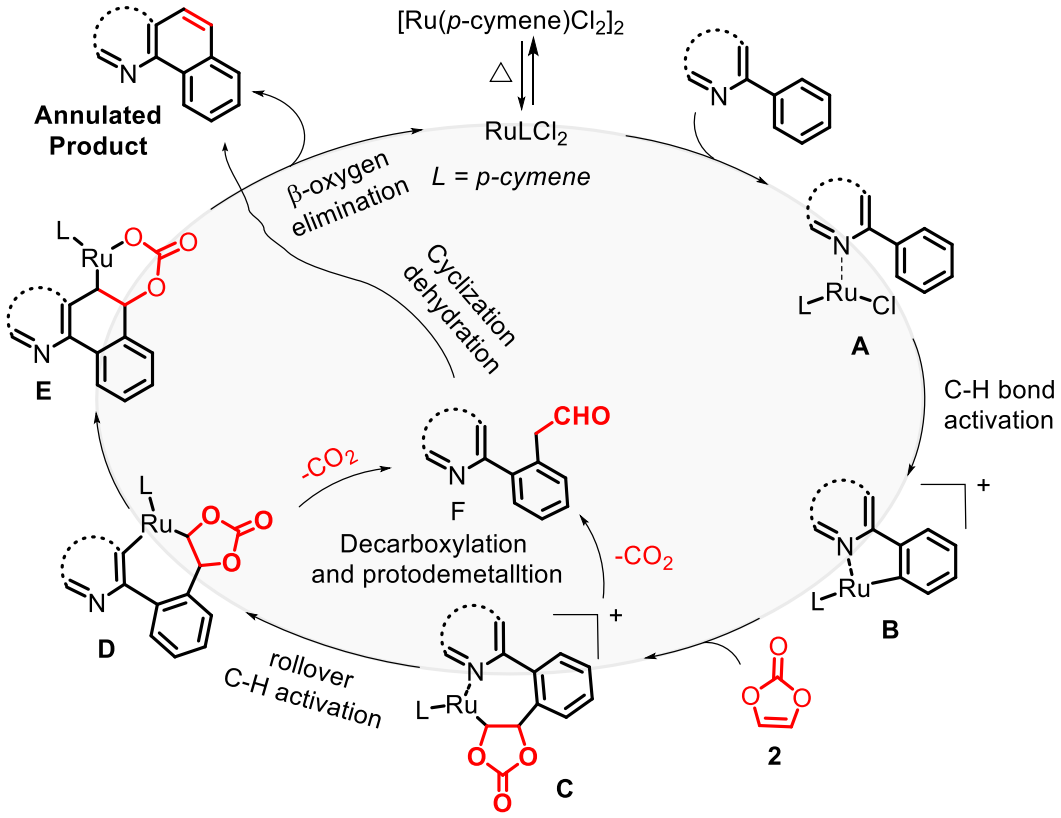
d) Standard reaction performed with Ru-I



Scheme 3.14: Control experiments

Based on the above control experiment results and the previous literature reports [48, 49] a plausible mechanistic pathway for Ru(II)-catalyzed annulation reaction is depicted in **Scheme 3.15**. Initially, after the formation of an active ruthenium complex, ruthenium metal coordinates with the nitrogen

atom of the 2-arylheteroarene to generate intermediate **A,** which, after the *ortho* C-H bond activation possibly through a CMD process generates a five-membered cyclometalated complex **B**. Coordination of **2** to the ruthenium center in intermediate **B** followed by migratory insertion of **2** into the Ru-C bond produces a seven-membered ruthenacycle intermediate **C**. Next, intermediate **C** undergoes 'rollover C-H activation' to produce a seven-membered ruthenacycle intermediate **D**. Subsequently, reductive elimination and oxidative addition into the adjacent C-O bond produces intermediate **E**. Finally, *β*-oxygen elimination of intermediate **E** gives the annulated product and regenerates the active Ru(II) catalyst. Alternatively, aldehyde intermediate **F** could be generated by *β*-oxygen elimination, decarboxylation, and protodemetalltion from intermediate **C** and /or **D**, which then produces an annulated product through cyclization followed by dehydration.



Scheme 3.15: Proposed reaction mechanism

3.3 CONCLUSIONS

In summary, we have successfully developed a simple and efficient protocol for the Ru(II)-catalyzed C-H/C-H [4+2] annulation of 2-arylheteroarenes using vinylene carbonate as an acetylene surrogate. The developed methodology allows convenient access to benzo[*h*]pyrido[2,1-

b]quinazolin-7-ones, naphtho[1',2':4,5]imidazo[1,2-*a*]pyridines and indazolo[2,3-*a*]quinolines from readily available 2-arylheteroarenes using vinylene carbonate *via* the construction of two C-C bonds in single step. The developed protocol exhibits a broad substrate scope with good functional group tolerance and provides desired [4+2] annulation products in good to high reaction yields. A preliminary mechanistic study indicates that the reaction involves *ortho* C-H bond activation, possibly through a CMD process and rollover C-H activation.

3.4 EXPERIMENTAL SECTION

3.4.1 General Information

All chemicals and solvents purchased from commercial suppliers and used without purification unless otherwise noted. 2-phenyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one, 2-aryl-2*H*-indazoles, and 2-phenylimidazo[1,2-*a*]pyridine were synthesized by following the reported procedure.[53-55] All reactions were monitored by thin layer chromatography (TLC) on pre-coated silica gel 60 F254 aluminium foils and visualized under a UV lamp (366 or 254 nm). Desired products were purified by column chromatography (silica gel 100-200 mesh size) using a gradient of ethyl acetate and hexanes as mobile phase. The ^{1}H and $^{13}C\{^{1}H\}$ NMR spectra were recorded on a 400 MHz spectrometer. Chemical shifts (δ) are reported in parts per million (ppm), and coupling constants (*J*) are reported in hertz (Hz). High-resolution mass spectra (HRMS) were recorded on a Q-TOF mass spectrometer. X-ray analysis was performed on a Rigaku Oxford XtaLAB AFC12 (RINC): Kappa dual home/near diffractometer.

3.4.2 General Procedure for the Synthesis of 27

A 10 mL oven-dried sealed tube was charged with compounds **26** (0.22 mmol) and **2** (0.45 mmol), $[Ru(p\text{-cymene})Cl_2]_2$ (0.011 mmol, 5 mol %) and TFE (1 mL) at room temperature. The reaction tube was capped tightly, and the reaction mixture was stirred at 100 °C in an oil bath for 12 h. The reaction mixture was cooled, diluted with water (5 mL), and then extracted with ethyl acetate (3 × 5 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The resulting crude mixture was purified by column chromatography (silica gel 100−200 mesh) using EtOAc-hexanes as an eluent to afford the desired product **27**.

3.4.3 General Procedure for the Synthesis of 10

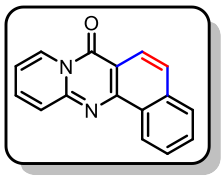
A 10 mL oven-dried sealed tube was charged with compounds **31** (0.25 mmol) and **2** (0.51 mmol), $[Ru(p\text{-cymene})Cl_2]_2$ (0.012 mmol, 5 mol %) and TFE (1 mL) at room temperature. The reaction

tube was capped tightly, and the reaction mixture was stirred at 100 °C in an oil bath for 12 h. The reaction mixture was cooled, diluted with water (5 mL), and then extracted with ethyl acetate (3 × 5 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The resulting crude mixture was purified by column chromatography (silica gel 100−200 mesh) using EtOAc-hexanes as an eluent to afford the desired product **10**.

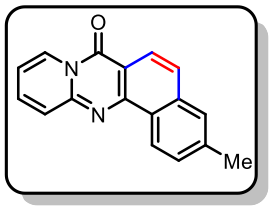
3.4.4 General Procedure for the Synthesis of 18

A 10 mL oven-dried sealed tube was charged with compounds **17** (0.2 mmol) and **2** (0.51 mmol) at room temperature. The reaction tube was capped tightly, and the reaction mixture was [Ru(*p*-cymene)Cl_2]$_2$ (0.012 mmol, 5 mol %) and HFIP (1 mL) stirred at 100 °C in an oil bath for 12 h. The reaction mixture was cooled, diluted with water (5 mL), and then extracted with ethyl acetate (3 × 5 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The resulting crude mixture was purified by column chromatography (silica gel 100−200 mesh) using EtOAc-hexanes as an eluent to afford the desired product **18**.

7*H*-Benzo[*h*]pyrido[2,1-*b*]quinazolin-7-one (27aa): The title compound was purified by column chromatography on silica gel using EtOAc/ hexanes (1: 4, *v/v*) as an eluent; pale yellow solid (49 mg, 88%); mp = 194-196 °C (Lit. mp 198-199 °C)[56]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.17 (d, *J* = 7.6 Hz, 1H), 9.01 (d, *J* = 7.2 Hz, 1H), 8.30 (d, *J* = 8.8 Hz, 1H), 7.91 (d, *J* = 7.2 Hz, 1H), 7.77 – 7.69 (m, 4H), 7.61 – 7.57 (m, 1H), 6.98 (t, *J* = 6.6 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 158.5, 148.0, 147.6, 136.3, 134.1, 129.8, 129.6, 127.9, 126.8, 126.8, 126.7, 125.7, 125.4, 122.4, 113.4, 112.1; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{16}H_{11}N_2O^+$ 247.0866; Found 247.0870.



3-Methyl-7*H*-benzo[*h*]pyrido[2,1-*b*]quinazolin-7-one (27ba): The title compound was purified by column chromatography on silica gel using EtOAc/ hexanes (1: 4, *v/v*) as an eluent; pale yellow solid (48 mg, 87%); mp = 204-206 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.05 – 9.01 (m, 2H), 8.28 (d, *J* = 8.8 Hz, 1H), 7.73 – 7.68 (m, 3H), 7.62 – 7.58 (m, 1H), 7.54 (dd, *J* = 8.4, 1.4 Hz, 1H), 7.00 – 6.96 (m, 1H), 2.60 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, CDCl3) δ 158.6, 148.0, 147.6, 140.0, 136.6, 134.0, 128.7, 127.7, 127.4, 126.9, 126.8, 125.4, 122.5, 113.3, 111.6, 21.9; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{17}H_{13}N_2O^+$ 261.1022; Found 261.0934.



3-Methoxy-7*H*-benzo[*h*]pyrido[2,1-*b*]quinazolin-7-one (27ca): The title compound was purified by column chromatography on silica gel using EtOAc/ hexanes (1: 3, *v/v*) as an eluent; pale yellow solid (39 mg, 71%); mp = 206-208 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.11 (d, *J* = 9.2 Hz, 1H), 9.06 – 9.03 (m, 1H), 8.32 (d, *J* = 8.8 Hz, 1H), 7.74 – 7.70 (m, 2H), 7.66 – 7.61 (m, 1H), 7.35 (dd, *J* = 9.0, 2.6 Hz, 1H), 7.27 (d, *J* = 2.4 Hz, 1H), 7.03 – 6.99 (m, 1H), 4.02 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 160.9, 158.5, 148.0, 147.7, 138.3, 134.2, 127.3, 126.9, 126.7, 125.1, 124.2, 123.3, 117.9, 113.2, 110.7, 107.3, 55.5; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{17}H_{13}N_2O_2^+$ 277.0972; Found 277.1025.

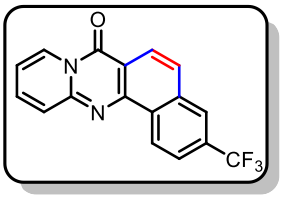
3-Chloro-7*H*-benzo[*h*]pyrido[2,1-*b*]quinazolin-7-one (27da): The title compound was purified by column chromatography on silica gel using EtOAc/ hexanes (1: 4, *v/v*) as an eluent; pale yellow solid (39 mg, 71%); mp = 217-219 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.13 (d, *J* = 8.4 Hz, 1H), 9.05 (d, *J* = 7.2 Hz, 1H), 8.34 (d, *J* = 8.8 Hz, 1H), 7.90 (s, 1H), 7.75 – 7.64 (m, 4H), 7.05 (t, *J* = 6.4 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 158.4, 147.9, 147.8, 137.2, 135.9, 134.6, 128.1, 127.4, 127.3, 127.0, 126.8, 124.5, 123.9, 113.6, 112.1; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{16}H_{10}ClN_2O^+$ 281.0476; Found 281.0476.

3-Bromo-7*H*-benzo[*h*]pyrido[2,1-*b*]quinazolin-7-one (27ea): The title compound was purified by column chromatography on silica gel using EtOAc/ hexanes (1: 4, *v/v*) as an eluent; pale yellow solid (40 mg, 74%); mp = 233-235 °C;^{1}H NMR (400 MHz, $CDCl_3$) δ 9.07 – 9.04 (m, 2H), 8.35 (d, *J* = 8.8 Hz, 1H), 8.09 (s, 1H), 7.80 (dd, *J* = 8.8, 2.0 Hz, 1H), 7.75 (d, *J* = 9.2 Hz, 1H), 7.70 – 7.65 (m, 2H), 7.07 – 7.04 (m, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 158.4, 147.9, 137.5, 134.6, 130.0, 130.0, 128.4, 127.4, 127.0, 126.8, 124.5, 124.4, 123.9, 113.7, 112.1; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{16}H_{10}BrN_2O^+$ 324.9971; Found 324.9974.

3-Fluoro-7*H*-benzo[*h*]pyrido[2,1-*b*]quinazolin-7-one (27fa): The title compound was purified by column chromatography on silica gel using EtOAc/ hexanes (1: 4, *v/v*) as an eluent; pale yellow solid (37 mg, 67%); mp = 219-221 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.15 (dd, *J* = 9.0, 5.8 Hz, 1H), 9.00 (d, *J* = 7.2 Hz, 1H), 8.29 (d, *J* = 9.2 Hz, 1H), 7.69 – 7.60 (m, 3H), 7.50 (dd, *J* = 9.4, 2.6 Hz, 1H), 7.45 – 7.38 (m, 1H), 7.02 – 6.98 (m, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 163.4 (d, $^1J_{C\text{-}F}$ = 248.9 Hz), 158.4, 147.8,

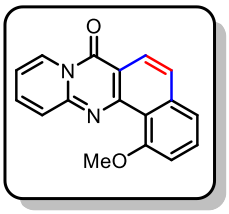
137.9 (d, $^{3}J_{C\text{-}F}$ = 9.7 Hz), 134.5, 128.4 (d, $^{3}J_{C\text{-}F}$ = 9.5 Hz), 126.9, 126.7, 126.4 (d, $^{4}J_{C\text{-}F}$ = 1.0 Hz), 124.7 (d, $^{3}J_{C\text{-}F}$ = 3.9 Hz), 123.8, 116.0 (d, $^{2}J_{C\text{-}F}$ = 23.7 Hz), 113.5, 111.8 (d, $^{2}J_{C\text{-}F}$ = 20.8 Hz), 111.5 (d, $^{4}J_{C\text{-}F}$ = 1.1 Hz); HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{16}H_{10}FN_2O^+$ 265.0772; Found 265.072.

3-(Trifluoromethyl)-7*H*-benzo[*H*]pyrido[2,1-*b*]quinazolin-7-one (27ga): The title compound



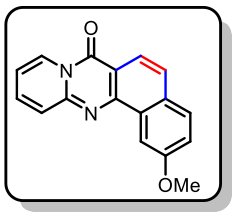
was purified by column chromatography on silica gel using EtOAc/ hexanes (1: 3, *v/v*) as an eluent; pale yellow solid (29 mg, 53%); mp = 243-245 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.29 (d, *J* = 8.8 Hz, 1H), 9.05 (d, *J* = 7.2 Hz, 1H), 8.39 (d, *J* = 8.8 Hz, 1H), 8.20 (s, 1H), 7.88 (d, *J* = 8.4 Hz, 1H), 7.82 (d, *J* = 8.8 Hz, 1H), 7.76 (d, *J* = 8.8 Hz, 1H) 7.70 – 7.67 (m, 1H), 7.07 (t, *J* = 6.4 Hz, 1H); ^{13}C{^{1}H) NMR (100 MHz, $CDCl_3$) δ 158.4, 148.0, 147.5, 135.5, 134.7, 131.7, 131.0, 127.2 (q, $^{1}J_{C\text{-}F}$= 245.9 Hz), 127.0, 126.9, 126.7, 125.4, 125.2 (q, $^{3}J_{C\text{-}F}$ = 4.4 Hz), 124.0, 122.4 (q, $^{3}J_{C\text{-}F}$ = 2.9 Hz), 113.9, 113.1; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{17}H_{10}F_3N_2O^+$ 315.0740; Found 315.072.

1-Methoxy-7*H*-benzo[*h*]pyrido[2,1-*b*]quinazolin-7-one (27ha): The title compound was



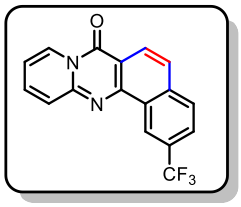
purified by column chromatography on silica gel using EtOAc/ hexanes (1: 3, *v/v*) as an eluent; pale yellow solid (39 mg, 71%); mp = 227-229 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.06 (d, *J* = 7.2 Hz, 1H), 8.40 (d, *J* = 8.8 Hz, 1H), 7.82 – 7.7 (m, 2H), 7.70 – 7.63 (m, 2H), 7.57 (d, *J* = 7.6 Hz, 1H), 7.20 (d, *J* = 7.8 Hz, 1H), 7.06 – 7.03 (m, 1H), 4.19 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 159.6, 158.6, 148.7, 146.5, 139.3, 133.9, 130.1, 127.4, 126.6, 126.5, 123.3, 121.4, 120.1, 113.8, 113.2, 109.6, 56.8; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{17}H_{13}N_2O_2^+$ 277.0972; Found 277.0968.

2-Methoxy-7*H*-benzo[*h*]pyrido[2,1-*b*]quinazolin-7-one (27ia): The title compound was purified



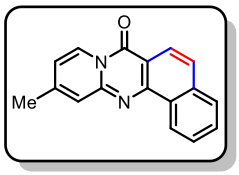
by column chromatography on silica gel using EtOAc/ hexanes (1: 3, *v/v*) as an eluent; pale yellow solid (35 mg, 64%); mp = 230-232 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.05 – 9.03 (m, 1H), 8.55 (d, *J* = 2.8 Hz, 1H), 8.21 (d, *J* = 8.8 Hz, 1H), 7.85 (d, *J* = 8.8 Hz, 1H), 7.76 – 7.74 (m, 2H), 7.64 – 7.60 (m, 1H), 7.40 (dd, *J* = 8.6, 2.6 Hz, 1H), 7.02 – 6.99 (m, 1H), 4.10 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 158.7, 158.6, 147.2, 147.0, 133.9, 131.3, 131.2, 129.4, 126.8, 126.8, 125.5, 121.3, 120.0, 113.3, 112.6, 104.6, 55.7; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{17}H_{13}N_2O_2^+$ 277.0972; Found 277.0978.

2-(Trifluoromethyl)-7*H*-benzo[*h*]pyrido[2,1-*b*]quinazolin-7-one (27ja): The title compound



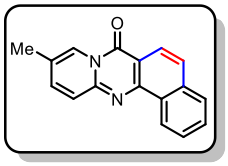
was purified by column chromatography on silica gel using EtOAc/ hexanes (1: 3, *v/v*) as an eluent; pale yellow solid (40 mg, 74%); mp = 238-240 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.51 (s, 1H), 9.06 (d, *J* = 7.2 Hz, 1H), 8.42 (d, *J* = 9.2 Hz, 1H), 8.04 (d, *J* = 8.4 Hz, 1H), 7.93 (dd, *J* = 8.6, 1.8 Hz, 1H), 7.83 – 7.79 (m, 2H), 7.74 – 7.70 (m, 1H), 7.11 – 7.07 (m, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 158.4, 148.0, 148.0, 137.9, 134.9, 128.7, 128.6, 128.3, 127.0, 126.5 (q, $^{1}J_{C-F}$= 197.0 Hz), 126.9, 125.4 (q, $^{3}J_{C-F}$ = 3.0 Hz), 124.9, 124.8, 123.4 (q, $^{3}J_{C-F}$ = 4.5 Hz), 113.9, 112.6; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{17}H_{10}F_3N_2O^+$ 315.0740; Found 315.0744.

11-Methyl-7*H*-benzo[*h*]pyrido[2,1-*b*]quinazolin-7-one (27ka): The title compound was



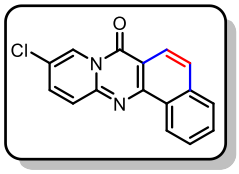
purified by column chromatography on silica gel using EtOAc/ hexanes (1: 4, *v/v*) as an eluent; pale yellow solid (47 mg, 85%); mp = 218-220 °C (Lit. mp 221-222 °C)[56]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.16 (d, *J* = 7.6 Hz, 1H), 8.92 (d, *J* = 7.6 Hz, 1H), 8.29 (d, *J* = 8.8 Hz, 1H), 7.92 – 7.90 (m, 1H), 7.76 – 7.69 (m, 3H), 7.49 (s, 1H), 6.82 (dd, *J* = 7.4, 1.4 Hz, 1H), 2.47 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 158.6, 148.4, 147.7, 146.0, 136.4, 129.8, 129.6, 127.8, 126.6, 126.1, 125.4, 125.1, 124.5, 122.5, 116.4, 111.6, 21.4; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{17}H_{13}N_2O^+$ 261.1022; Found 261.0934.

10-Methyl-7*H*-benzo[*h*]pyrido[2,1-*b*]quinazolin-7-one (27la): The title compound was purified



by column chromatography on silica gel using EtOAc/ hexanes (1: 4, *v/v*) as an eluent; pale yellow solid (46 mg, 83%); mp = 222-224 °C (Lit. mp 219-220 °C)[56]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.19 (dd, *J* = 7.4, 1.8 Hz, 1H), 8.85 (s, 1H), 8.33 (d, *J* = 8.8 Hz, 1H), 7.93 (dd, *J* = 6.4, 1.6 Hz, 1H), 7.79 – 7.72 (m, 3H), 7.69 (d, *J* = 9.6 Hz, 1H), 7.50 (dd, *J* = 9.2, 2.0 Hz, 1H), 2.44 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 158.4, 147.9, 146.8, 137.5, 136.3, 129.8, 129.5, 127.9, 126.7, 126.3, 125.5, 125.4, 123.9, 123.3, 122.5, 112.0, 18.4; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{17}H_{13}N_2O^+$ 261.1022; Found 261.0934.

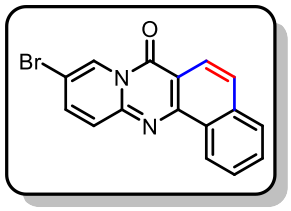
10-Chloro-7H-benzo[*h*]pyrido[2,1-*b*]quinazolin-7-one (27ma): The title compound was



purified by column chromatography on silica gel using EtOAc/ hexanes (1: 4, *v/v*) as an eluent; pale yellow solid (36 mg, 66%); mp = 234-236 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.13 (d, *J* = 8.4 Hz, 1H), 9.05 (d, *J* = 7.2 Hz, 1H), 8.34 (d, *J* = 8.8 Hz, 1H), 7.90 (s, 1H), 7.74 (d, *J* = 9.2 Hz, 1H), 7.69 – 7.64 (m, 3H), 7.05 (t, *J* =

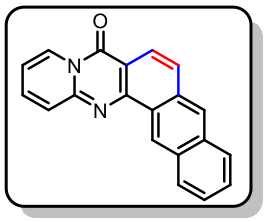
6.4 Hz, 1H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 158.4, 147.9, 147.8, 137.2, 135.9, 134.6, 128.1, 127.4, 127.3, 127.0, 126.8, 124.5, 123.9, 113.6, 112.1; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{16}H_{10}N_2O^+$ 281.0476; Found 281.0480

10-Bromo-7*H*-benzo[*h*]pyrido[2,1-*b*]quinazolin-7-one (27na): The title compound was purified



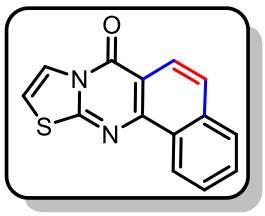
by column chromatography on silica gel using EtOAc/ hexanes (1: 4, *v/v*) as an eluent; pale yellow solid (28 mg, 52%); mp = 228-230 °C (Lit. mp 231-232 °C)[56]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.20 – 9.17 (m, 2H), 8.33 (d, *J* = 8.8 Hz, 1H), 7.97 – 7.95 (m, 1H), 7.85 (d, *J* = 8.8 Hz, 1H), 7.81 – 7.73 (m, 2H), 7.66 – 7.65 (m, 2H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 157.6, 147.7, 145.8, 137.6, 136.4, 129.9, 129.8, 128.0, 127.9, 127.0, 126.8, 126.5, 125.4, 122.3, 112.3, 108.7; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{16}H_{10}BrN_2O^+$ 324.9971; Found 324.9968.

6*H*-naphtho[2,3-*h*]pyrido[2,1-*b*]quinazolin-6-one (27oa): The title compound was purified by



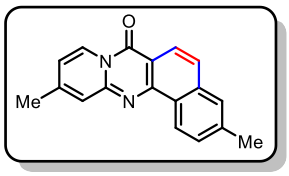
column chromatography on silica gel using EtOAc/ hexanes (1: 4, *v/v*) as an eluent; pale yellow solid (50 mg, 92%); mp = 252-254 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.73 (s, 1H), 9.08 (d, *J* = 7.2 Hz, 1H), 8.39 (s, 1H), 8.23 (d, *J* = 7.6 Hz, 1H), 8.19 (d, *J* = 9.2 Hz, 1H), 8.07 (d, *J* = 8.0 Hz, 1H), 7.85 – 7.81 (m, 2H), 7.70 – 7.66 (m, 1H), 7.64 – 7.56 (m, 2H), 7.07 – 7.04 (m, 1H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 158.1, 149.5, 147.9, 134.4, 133.8, 133.3, 131.9, 129.3, 128.2, 127.9, 127.1, 126.8, 126.3, 126.0, 125.9, 125.7, 121.5, 113.8, 111.1; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{20}H_{13}N_2O^+$ 297.1022; Found 297.1025.

7*H*-benzo[*h*]thiazolo[2,3-*b*]quinazolin-7-one (27pa): The title compound was purified by



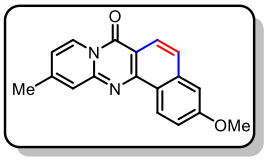
column chromatography on silica gel using EtOAc/ hexanes (1: 4, *v/v*) as an eluent; pale yellow solid (46 mg, 83%); mp = 196-198 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.03 (d, *J* = 7.6 Hz, 1H), 8.25 (d, *J* = 8.8 Hz, 1H), 8.05 (d, *J* = 4.8 Hz, 1H), 7.91 (d, *J* = 7.4 Hz, 1H), 7.78 (d, *J* = 8.8 Hz, 1H), 7.74 – 7.67 (m, 2H), 6.95 (d, *J* = 4.8 Hz, 1H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 158.7, 158.2, 147.6, 136.4, 129.5, 129.1, 127.8, 126.8, 125.6, 125.4, 121.9, 121.5, 112.3, 110.2; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{14}H_9N_2OS^+$ 253.0430; Found 253.0435.

3,11-Dimethyl-7*H*-benzo[*h*]pyrido[2,1-*b*]quinazolin-7-one (27qa): The compound was purified



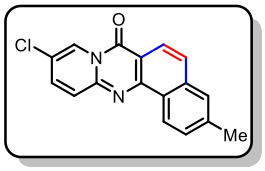
by column chromatography on silica gel using EtOAc / hexanes (1: 4, *v/v*); as an eluent; pale yellow solid (49 mg, 89%); mp = 228-230 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.03 (d, *J* = 8.4 Hz, 1H), 8.92 (d, *J* = 7.2 Hz, 1H), 8.26 (d, *J* = 8.8 Hz, 1H), 7.68 – 7.65 (m, 2H), 7.53 (dd, *J* = 8.4, 1.2 Hz, 1H), 7.48 (s, 1H), 6.81 (dd, *J* = 7.6, 1.6 Hz, 1H), 2.60 (s, 3H), 2.46 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 158.6, 148.4, 147.7, 145.8, 139.8, 136.6, 128.6, 127.8, 127.3, 126.1, 125.3, 124.8, 124.4, 122.5, 116.2, 111.2, 21.9, 21.4; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{18}H_{15}N_2O^+$ 275.1179; Found 275.1183.

3-Methoxy-11-methyl-7*H*-benzo[*h*]pyrido[2,1-*b*]quinazolin-7-one (27ra): The compound was



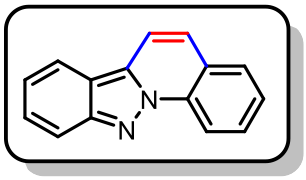
purified by column chromatography on silica gel using EtOAc / hexanes (1:3, *v/v*); as an eluent; pale yellow solid (38 mg, 70%); mp = 242-244 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.08 (d, *J* = 8.8 Hz, 1H), 8.94 (d, *J* = 7.2 Hz, 1H), 8.28 (d, *J* = 8.8 Hz, 1H), 7.66 (d, *J* = 8.8 Hz, 1H), 7.49 (s, 1H), 7.33 (dd, *J* = 9.0, 2.6 Hz, 1H), 7.25 (d, *J* = 2.4 Hz, 1H), 6.83 (dd, *J* = 7.4, 1.8 Hz, 1H), 4.01 (s, 3H), 2.49 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 160.8, 158.6, 148.4, 147.9, 146.0, 138.3, 127.2, 126.2, 124.5, 124.3, 124.2, 123.3, 117.7, 116.1, 110.3, 107.3, 55.5, 21.4; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{18}H_{15}N_2O_2^+$ 291.1228; Found 291.1231.

10-Chloro-3-methyl-7*H*-benzo[*H*]pyrido[2,1-*b*]quinazolin-7-one (27sa): The compound was



purified by column chromatography on silica gel using EtOAc / hexanes (1: 4, *v/v*); as an eluent; pale yellow solid (43 mg, 79%); mp = 258-260 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.06 – 9.03 (m, 2H), 8.29 (d, *J* = 9.2 Hz, 1H), 7.76 (d, *J* = 8.8 Hz, 1H), 7.73 (s, 1H), 7.70 – 7.67 (m, 1H), 7.58 – 7.53 (m, 2H), 2.63 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 157.7, 147.6, 145.8, 140.3, 136.6, 135.4, 129.0, 127.8, 127.7, 127.5, 127.4, 126.2, 125.3, 124.5, 122.4, 121.9, 21.9; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{17}H12ClN2O^+$ 295.0633; Found 295.0637.

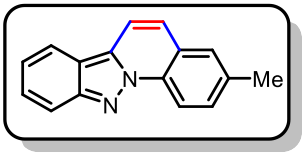
Indazolo[2,3-*a*]quinoline (10aa): The compound was purified by column chromatography on



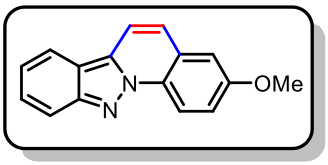
silica gel using EtOAc / hexanes (1: 4, *v/v*); as an eluent; pale yellow solid (41 mg, 73%); mp = 112-114 °C (Lit. mp 109-110 °C)[48]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.95 (d, *J* = 8.8 Hz, 1H), 8.08 (d, *J* = 8.4 Hz, 1H),

7.98 (dd, *J* = 8.6, 4.2 Hz, 2H), 7.91 (d, *J* = 8 Hz, 1H), 7.80 (t, *J* = 8 Hz, 1H), 7.65 – 7.55 (m, 3H), 7.29-7.26 (m, 1H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 149.2, 134.2, 132.4, 129.5, 128.5, 128.0, 126.1, 125.2, 123.1, 120.8, 119.7, 117.2, 116.7, 116.6, 115.6; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{15}H_{11}N_2^+$ 219.0917; Found 219.0922.

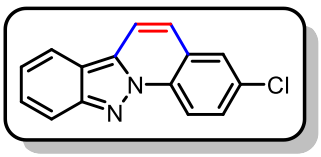
3-Methylindazolo[2,3-*a*]quinoline (10ba): The compound was purified by column chromatography on silica gel using EtOAc / hexanes (1: 4, *v/v*); as an eluent; pale yellow solid (43 mg, 77%); mp = 112-170 °C (Lit. mp 114-115 °C)[48] ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.84 (d, *J* = 8.4 Hz, 1H), 8.09 (d, *J* = 8.0 Hz, 1H), 7.99 – 7.95 (m, 2H), 7.71 (s, 1H), 7.64 (dd, *J* = 8.8, 1.6 Hz, 1H), 7.61 – 7.55 (m, 2H), 7.30 – 7.26 (m, 1H), 2.59 (s, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 149.1, 136.0, 132.4, 132.1, 131.1, 128.0, 127.9, 125.3, 123.0, 120.6, 119.7, 117.0, 116.8, 116.5, 115.5, 21.4; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{16}H_{13}N_2^+$ 233.1073; Found 233.1078.



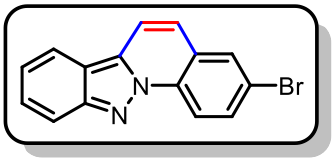
3-Methoxyindazolo[2,3-*a*]quinoline (10ca): The compound was purified by column chromatography on silica gel using EtOAc / hexanes (1: 4, *v/v*); as an eluent; pale yellow solid (38 mg, 68%); mp = 120-122; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.33 (s, 1H), 7.82-7.78 (m, 3H), 7.71 (d, *J* = 8.4 Hz, 1H), 7.33 (t, *J*=7.6 Hz,1H), 7.12 (t, *J*=7.6 Hz,1H), 7.04 7.71 (d, *J* = 9.2 Hz, 2H), 3.88 (s, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 159.3, 149.6, 134.1, 126.5, 122.7, 122.4, 122.2, 120.3, 120.2, 117.8, 114.6, 55.6; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{16}H_{13}N_2O^+$ 249.1022; Found 249.1025.



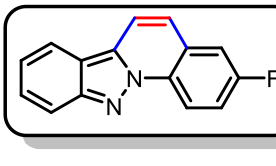
3-Chloroindazolo[2,3-*a*]quinoline (10da): The compound was purified by column chromatography on silica gel using EtOAc / hexanes (1: 4, *v/v*); as an eluent; pale yellow solid (45 mg, 81%); mp = 168-170 °C (Lit. mp 163-164 °C)[48]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.86 (d, *J* = 8.0 Hz, 1H), 8.05 (d, *J* = 7.2 Hz, 1H), 7.98 – 7.94 (m, 2H), 7.87 (d, *J* = 2 Hz, 1H), 7.72 (dd, *J* = 9.0, 1.8 Hz, 1H), 7.57 (t, *J*=7.6 Hz, 1H), 7.52 (d, *J* = 8.8 Hz, 1H), 7.30 – 7.26 (m, 2H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 149.3, 132.5, 132.2, 131.8, 129.7, 128.3, 127.4, 126.2, 122.0, 121.8, 121.2, 119.6, 118.8, 116.8, 116.7; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{15}H_{10}ClN_2^+$ 253.0527; Found 253.0533.



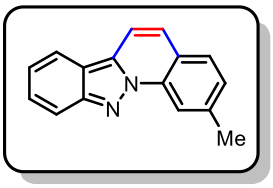
3-Bromoindazolo[2,3-*a*]quinoline (10ea): The compound was purified by column chromatography on silica gel using EtOAc / hexanes (1: 4, *v/v*); as an eluent; pale yellow solid (42 mg, 77%); mp = 132-134 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.81 (d, *J* = 9.2 Hz, 1H), 8.08 – 8.05 (m, 2H), 7.98 (t, *J* = 8.2 Hz, 2H), 7.87 (dd, *J* = 9.0, 1.8 Hz, 2H), 7.59 (t, *J* = 7.6 Hz, 1H), 7.31 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.3, 132.9, 132.4, 132.2, 130.6, 128.3, 126.6, 121.7, 121.2, 119.6, 119.7, 118.9, 116.8, 116.9, 116.7; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{15}H_{10}BrN_2^+$ 297.0022; Found 297.0025.



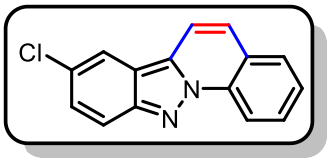
3-Fluoroindazolo[2,3-*a*]quinoline (10fa): The compound was purified by column chromatography on silica gel using EtOAc / hexanes (1: 4, *v/v*); as an eluent; pale yellow solid (41 mg, 74%); mp = 118-120 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.90 (dd, *J* = 7.4, 4.6 Hz, 1H), 8.03 (d, *J* = 8.0 Hz, 1H), 7.95 (dd, *J* = 8.2, 3.0 Hz, 2H), 7.58 – 7.48 (m, 4H), 7.29 (t, *J*= 7.0 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 160.4 (d, *J* = 247.0 Hz), 149.1, 131.8, 130.7, 128.1, 126.4 (d, *J* = 10.0 Hz), 122.1 (d, *J* = 3.0 Hz), 121.0, 119.6, 119.3 (d, *J* = 8.0 Hz), 118.1, 117.1, 116.8 (d, *J* = 4.0 Hz), 116.6, 112.8 (d, *J* = 23.0 Hz); HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{15}H_{10}FN_2^+$ 237.0823; Found 237.0827.



2-Methylindazolo[2,3-*a*]quinoline (10ja): The title compound was purified by column chromatography on silica gel using EtOAc/ hexanes (1: 4, *v/v*) as an eluent; yellow solid (47 mg, 84%); mp = 124-126 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.73 (s, 1H), 8.04 (d, *J* = 8.4 Hz, 1H), 7.97 (d, *J* = 8.4 Hz, 1H), 7.85 (d, *J* = 8.8 Hz, 1H), 7.74 (d, *J* = 8.4 Hz, 1H), 7.56 (t, *J* = 8.8 Hz, 2H), 7.37 (d, *J* = 8.4 Hz, 1H), 7.26 (d, *J* = 8.0 Hz, 1H), 2.63 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 149.2, 140.3, 134.0, 132.5, 128.2, 128.0, 127.7, 123.0, 123.0, 120.5, 119.7, 116.8, 116.7, 116.4, 114.4, 22.0; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{16}H_{14}N_2^+$ 234.1151; Found 234.1154.

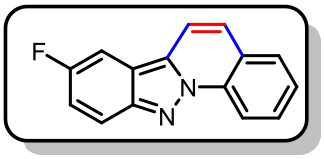


8-Chloroindazolo[2,3-*a*]quinoline (10ha): The compound was purified by column chromatography on silica gel using EtOAc / hexanes (1: 4, *v/v*); as an eluent; pale yellow solid (42 mg, 76%); mp = 116-118 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.87 (d, *J* = 8.4 Hz, 1H), 7.99 (d, *J* = 1.2 Hz, 1H), 7.89 – 7.84 (m, 3H), 7.81 – 7.77 (m, 1H), 7.62 – 7.58 (m, 2H), 7.47 (dd, *J* = 9.0, 1.8 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 147.4, 134.0, 131.8, 129.7, 129.1, 128.5, 126.4, 126.1, 125.2,



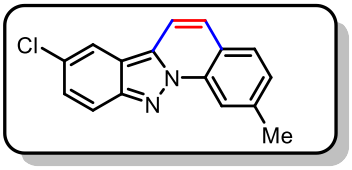
123.5, 118.7, 118.1, 117.1, 115.3; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{15}H_{10}ClN_2^+$ 253.0527; Found 253.0522.

8-Fluoroindazolo[2,3-*a*]quinoline (10ia): The compound was purified by column



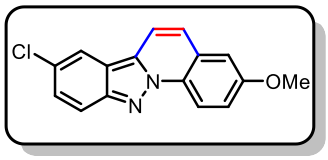
chromatography on silica gel using EtOAc / hexanes (1: 4, *v/v*); as an eluent; pale yellow solid (39 mg, 70%); mp = 108-110 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.89 (d, *J* = 8.4 Hz, 1H), 7.95 – 7.87 (m, 3H), 7.78 (t, *J* = 7.8 Hz, 1H), 7.65-7.58 (m, 3H), 7.37-7.32 (m, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 157.8 (d, *J* = 238.0 Hz), 146.4, 134.2, 132.4 (d, *J* = 8.0 Hz), 129.5, 128.5, 126.3, 125.2, 122.8, 120.9, 118.9 (d, *J* = 28.0 Hz), 118.5 (d, *J* = 9.0 Hz), 117.0, 115.9 (d, *J* = 11.0 Hz), 115.5, 102.9 (d, *J* = 25 Hz); HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{15}H_{10}FN_2^+$ 237.0823; Found 237.0825.

8-Chloro-2-methylindazolo[2,3-*a*]quinoline (10ja): The compound was purified by column



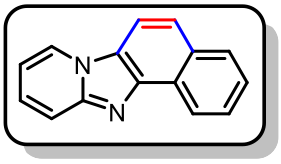
chromatography on silica gel using EtOAc / hexanes (1: 4, *v/v*); as an eluent; pale yellow solid (46 mg, 84%); mp = 134-136 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.68 (s, 1H), 7.99 (d, *J* = 0.8 Hz 1H), 7.86 (d, *J* = 9.2 Hz, 1H), 7.78 (t, *J* = 8.6 Hz, 2H), 7.58 (d, *J* = 9.2 Hz, 1H), 7.46 (dd, *J* = 9.2, 1.6 Hz, 1H), 7.42 (d, *J* = 8.0 Hz, 1H), 2.65 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 147.4, 140.6, 133.9, 131.1, 129.1, 128.3, 128.1, 125.9, 123.5, 123.1, 118.7, 117.9, 117.1, 116.8, 114.2, 21.1; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{16}H_{12}ClN_2^+$ 267.0684; Found 267.0689.

8-Chloro-3-methoxyindazolo[2,3-*a*]quinoline (10ka): The compound was purified by column



chromatography on silica gel using EtOAc / hexanes (1: 4, *v/v*); as an eluent; pale yellow solid (44 mg, 80%); mp = 126-128 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.78 (d, *J* = 9.2 Hz, 1H), 7.98 (s, 1H), 7.85 (t, *J*= 4.2 2H), 7.54 (d, *J* = 9.2 Hz, 1H), 7.46 (d, *J* = 8.8 Hz, 1H), 7.40 – 7.38 (m, 1H), 7.24 (s, 1H), 3.96 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 157.9, 147.2, 130.9, 128.9, 128.7, 126.5, 125.9, 123.1, 119.6, 118.6, 118.5, 117.8, 117.3, 115.8, 108.8, 55.7; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{16}H_{12}ClN_2O^+$ 283.0633; Found 283.0637.

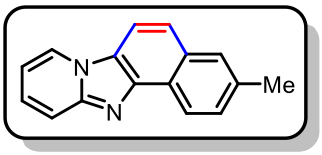
Naphtho[1',2':4,5]imidazo[1,2-*a*]pyridine (18aa): The title compound was purified by column



chromatography on silica gel using EtOAc/ hexanes (1: 3, *v/v*) as an eluent; white solid (42 mg, 75%); mp = 190-192 °C (Lit. mp 193-195 °C)[48]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.86 (d, *J* = 8.4 Hz, 1H), 8.55 (d, *J*

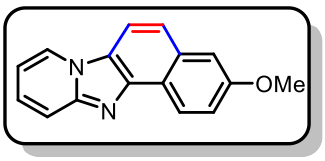
= 6.8 Hz, 1H), 8.04 (d, *J* = 8.0 Hz, 1H), 7.95 – 7.90 (m, 2H), 7.78 (d, *J* = 8.8 Hz, 1H), 7.74 (t, *J* = 7.4 Hz, 1H), 7.64 (t, *J* = 7.2 Hz, 1H), 7.48 – 7.44 (m, 1H), 6.99 (t, *J* = 6.6 Hz, 1H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 147.2, 141.1, 132.1, 128.6, 127.7, 126.8, 126.7, 126.0, 124.4, 124.3, 123.0, 122.5, 118.0, 111.3, 110.1; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{15}H_{11}N_2^+$ 219.0917; Found 219.0921.

3-Methylnaphtho[1',2':4,5]imidazo[1,2-*a*]pyridine (18ba): The title compound was purified by



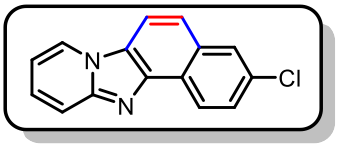
column chromatography on silica gel using EtOAc/ hexanes (1: 3, *v/v*) as an eluent; white solid (48 mg, 86%); mp = 152-154 °C (Lit. mp 156-158 °C)[48]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.75 (d, *J* = 8.4 Hz, 1H), 8.53 (d, *J* = 6.4 Hz, 1H), 7.92 – 7.86 (m, 2H), 7.81 (s, 1H), 7.70 (d, *J* = 8.8 Hz, 1H), 7.58 (d, *J* = 8.0 Hz, 1H), 7.45 (t, *J* = 7.8 Hz, 1H), 6.97 (t, *J* = 6.6 Hz, 1H), 2.61 (s, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 147.2, 141.2, 135.7, 132.3, 128.7, 127.9, 127.5, 124.7, 124.4, 123.9, 122.8, 122.1, 117.9, 111.2, 110.0, 21.8; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{16}H_{13}N_2^+$ 233.1073; Found 233.1068.

3-Methoxynaphtho[1',2':4,5]imidazo[1,2-*a*]pyridine (18ca): The compound was purified by



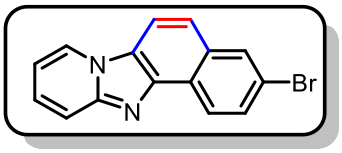
column chromatography on silica gel using EtOAc / hexanes (1: 3, *v/v*); as an eluent; white solid (37 mg, 63%); mp = 122-124 °C (Lit. mp 117-120 °C) [48]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.75 (d, *J* = 9.6 Hz, 1H), 8.52 (d, *J* = 6.0 Hz, 1H), 7.92 (d, *J* = 8.8 Hz, 1H), 7.86 (d, *J* = 8.8 Hz, 1H), 7.67 (d, *J* = 8.8 Hz, 1H), 7.44 (t, *J* = 8.0 Hz, 1H), 7.38 – 7.36 (m, 2H), 6.94 (t, *J* = 6.4 Hz, 1H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 157.1, 148.5, 147.3, 141.3, 133.4, 127.5, 124.5, 124.4, 121.6, 121.5, 117.1, 117.8, 111.1, 110.5, 108.1, 55.4; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{16}H_{13}N_2O^+$ 249.1022; Found 249.1028.

3-Chloronaphtho[1',2':4,5]imidazo[1,2-*a*]pyridine (18da): The compound was purified by

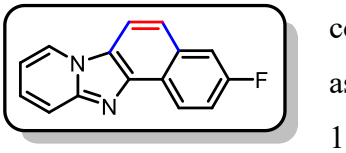


column chromatography on silica gel using EtOAc / hexanes (1: 3, *v/v*); as an eluent; white solid (42 mg, 71%); mp = 168-170 °C (Lit. mp 172-174 °C)[48]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.77 (d, *J* = 8.8 Hz, 1H), 8.53 (d, *J* = 6.8 Hz, 1H), 7.99 (d, *J* = 1.6 Hz, 1H), 7.96 (d, *J* = 8.8 Hz, 1H), 7.87 (d, *J* = 9.2 Hz, 1H), 7.66 (dd, *J* = 8.8, 2.0 Hz, 2H), 7.49 – 7.45 (m, 1H), 6.99 (t, *J* = 6.6 Hz, 1H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 147.5, 141.0, 132.8, 131.7, 128.2, 127.4, 127.2, 125.0, 124.6, 124.4, 124.4, 121.3, 118.03, 111.5, 111.2; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{15}H_{10}ClN_2^+$ 253.0527; Found 253.0531.

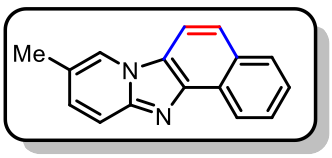
3-Bromonaphtho[1',2':4,5]imidazo[1,2-*a*]pyridine (18ea): The compound was purified by column chromatography on silica gel using EtOAc / hexanes (1: 3, *v/v*); as an eluent; pale yellow solid (40 mg, 70%); mp = 184-186 °C (Lit. mp 181-183 °C)[48]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.72 (d, *J* = 8.4 Hz, 1H), 8.55-8.52 (m, 1H), 8.18 (d, *J* = 2.0 Hz, 1H), 7.97 (d, *J* = 8.9 Hz, 1H), 7.89-7.86 (m, 1H), 7.80 (dd, *J* = 8.8, 2.0 Hz, 1H), 7.67 (d, *J* = 8.9 Hz, 1H), 7.50-7.46 (m, 1H), 7.02-6.98 (m, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 147.5, 141.4, 133.6, 130.6, 129.8, 128.0, 125.30, 124.7, 124.5, 124.4, 121.2, 119.1, 118.0, 111.6, 111.2; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{15}H_{10}BrN_2^+$ 297.0022; Found 297.0028.



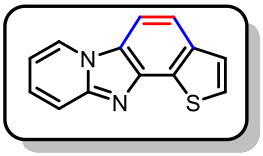
3-Fluoronaphtho[1',2':4,5]imidazo[1,2-*a*]pyridine (18fa): The compound was purified by column chromatography on silica gel using EtOAc / hexanes (1: 3, *v/v*); as an eluent; white solid (38 mg, 68%); mp = 190-192 °C (Lit. mp 188-187 °C)[49]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.85 – 8.79 (m, 1H), 8.52 (d, *J* = 6.0 Hz, 1H), 7.95 (d, *J* = 8.4 Hz, 1H), 7.86 (d, *J* = 8.9 Hz, 1H), 7.66 (dd, *J* = 16.4, 7.2 Hz, 2H), 7.46 (t, *J* = 7.0 Hz, 2H) , 6.98 (t, *J* = 5.8 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 161.0 (d, *J* = 244.0 Hz), 147.4, 141.2, 133.1 (d, *J* = 9.0 Hz), 127.9, 125.3 (d, *J* = 9.0 Hz), 124.5, 123.8, 123.5, 121.5 (d, *J* = 4.0 Hz), 117.9, 116.1 (d, *J* = 24.0 Hz), 112.2 (d, *J* = 21.0 Hz), 111.4, 111.3; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{15}H_9FN_2^+$ 237.0823; Found 237.0827.



9-Methylnaphtho[1',2':4,5]imidazo[1,2-*a*]pyridine (18ga): The compound was purified by column chromatography on silica gel using EtOAc / hexanes (1:3 , *v/v*); as an eluent; white solid (44 mg, 79%); mp = 172-174 °C (Lit. mp 170-171 °C)[49]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.83 (d, *J* = 8.0 Hz, 1H), 8.32 (s, 1H), 8.01 (d, *J* = 9.2 Hz, 1H), 7.91 (d, *J* = 9.2 Hz, 1H), 7.80 – 7.69 (m, 3H), 7.63 – 7.59 (m, 1H), 7.31 (dd, *J* = 9.4, 1.8 Hz, 1H), 2.46 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 146.4, 141.1, 131.9, 130.9, 128.5, 126.9, 126.5, 125.8, 124.1, 122.9, 122.2, 122.00, 121.0, 117.3, 110.0, 18.3; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{16}H_{13}N_2^+$ 233.1073; Found 233.1078.

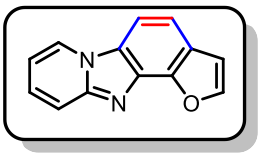


Thieno[3'',2'':5',6']benzo[1',2':4,5]imidazo[1,2-*a*]pyridine (18ha): The compound was purified by column chromatography on silica gel using EtOAc / hexanes (1: 3, *v/v*); as an eluent; white solid (47 mg, 84%); mp = 204-206 °C (Lit. mp 200-201 °C)[48]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.42 (d, *J* = 6.8 Hz, 1H), 7.86 – 7.67 (m, 3H), 7.54 – 7.50 (m, 2H), 7.41 – 7.37 (m, 1H), 6.87 (t, *J* = 6.6 Hz, 1H); ^{13}C{^{1}H}

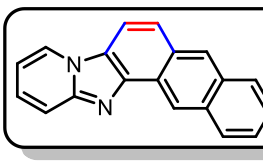


NMR (100 MHz, $CDCl_3$) δ 147.1, 139.7, 138.2, 129.1, 128.5, 125.4, 125.0, 124.9, 124.7, 117.8, 117.1, 110.1, 107.7; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{13}H_9N_2S^+$ 225.0481; Found 225.0485.

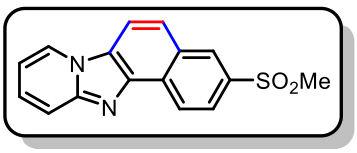
Benzofuro[7',6':4,5]imidazo[1,2-*a*]pyridine (18ia): The compound was purified by column chromatography on silica gel using EtOAc / hexanes (1: 3, *v/v*); as an eluent; white solid (50 mg, 88%); mp = 212-214 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.50 (d, *J* = 6.8 Hz, 1H), 7.83 – 7.75 (m, 3H), 7.57 (d, *J* = 8.4 Hz, 1H), 7.47 – 7.43 (m, 1H), 6.98 (d, *J* = 1.6 Hz, 1H), 6.92 (t, *J* = 6.6 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 148.2, 145.3, 144.6, 131.7, 128.7, 127.1, 125.0, 124.8, 118.1, 114.4, 110.9, 107.6, 106.0; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{13}H_9N_2O^+$ 209.0709; Found 209.0706.



Anthra[1',2':4,5]imidazo[1,2-*a*]pyridine (18ja): The compound was purified by column chromatography on silica gel using EtOAc / hexanes (1: 3, *v/v*); as an eluent; white solid (32 mg, 58%); mp = 220-222 °C (Lit. mp 215-217 °C)[48]; ^1H NMR (400 MHz, $CDCl_3$) δ 9.37 (s, 1H), 8.54 (s, 1H), 8.48 (d, *J* = 6.4 Hz, 1H), 8.19 (d, *J* = 7.2 Hz, 1H), 8.07 (d, *J* = 7.2 Hz, 1H), 7.90 (d, *J* = 9.2 Hz, 1H), 7.85 – 7.84 (m, 2H), 7.58 – 7.52 (m, 2H), 7.42 (t, *J* = 7.6 Hz, 1H), 6.98 (t, *J* = 6.4 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$ δ 146.8, 141.0, 132.0, 131.6, 130.7, 128.5, 128.1, 127.3, 126.9, 125.8, 125.51, 125.47, 124.0, 123.2, 123.1, 121.5, 117.8, 111.8, 110.7; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{19}H_{13}N_2^+$ 269.1073; Found 269.1079.



3-(Methylsulfonyl)naphtho[1',2':4,5]imidazo[1,2-*a*]pyridine (18ka): The compound was purified by column chromatography on silica gel using EtOAc / hexanes (1: 1, *v/v*); as an eluent; white solid (26 mg, 48%); mp = 208-210 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 9.02 (d, *J* = 8.4 Hz, 1H), 8.68 (s, 1H), 8.59 (d, *J* = 5.2 Hz, 1H), 8.15 (d, *J* = 6.8 Hz, 1H), 8.10 (d, *J* = 8.4 Hz, 1H), 7.90 (dd, *J* = 13.2, 9.2 Hz, 2H), 7.54 (t, *J* = 6.0 Hz, 1H), 7.06 (t, *J* = 6.6 Hz, 1H), 3.20 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 147.9, 140.5, 137.3, 130.9, 129.2, 128.8, 127.9, 126.6, 124.7, 124.7, 123.2, 122.9, 118.3, 112.2, 112.1, 44.7; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{16}H_{13}N_2O_2S^+$ 297.0692; Found 297.0695.



3.4.4 Sample Preparation and Crystal Measurement of 27aa and 18ha

A suitable crystal was selected and mounted on an XtaLAB Pro II AFC12 (RINC): Kappa single diffractometer. The crystal was kept at 298 K during data collection. Using Olex2[57], the

structure was solved with the SHELXT[58] structure solution program using Intrinsic Phasing and refined with the SHELXL[59] refinement package using Least Squares minimization.

Single crystals of **27aa** [$C_{16}H_{10}N_2O$] were grown from slow evaporation of chloroform: hexane solution.

Table 3.5: Crystal data and structure refinement for **27aa**

Identification code	**27aa**
Empirical formula	$C_{16}H_{10}N_2O$
Formula weight	246.26
Temperature/K	298
Crystal system	monoclinic
Space group	$P2_1/n$
a/Å	7.3145(3)
b/Å	11.4335(4)
c/Å	13.9053(5)
α/°	90
β/°	90.487(3)
γ/°	90
Volume/Å^3	1162.86(8)
Z	4
ρ_{calc}g/cm^3	1.407
μ/mm^{-1}	0.090
F(000)	512.0
Crystal size/mm^3	0.31 × 0.25 × 0.2
Radiation	Mo Kα (λ = 0.71073)

2Θ range for data collection/°	4.612 to 52.09
Index ranges	$-8 \leq h \leq 8, -9 \leq k \leq 13, -16 \leq l \leq 16$
Reflections collected	7419
Independent reflections	2170 [R_{int} = 0.0175, R_{sigma} = 0.0200]
Data/restraints/parameters	2170/0/172
Goodness-of-fit on F^2	1.068
Final R indexes [I>=2σ (I)]	R_1 = 0.0416, wR_2 = 0.1082
Final R indexes [all data]	R_1 = 0.0568, wR_2 = 0.1186
Largest diff. peak/hole / e $Å^{-3}$	0.10/-0.22

Single crystals of **18ha** [$C_{13}H_8N_2S$] were grown from slow evaporation of chloroform: hexane solution

Table 3.6: Crystal data and structure refinement for **18ha**

Identification code	**18ha**
Empirical formula	$C_{13}H_8N_2S$
Formula weight	224.27
Temperature/K	100(2)
Crystal system	orthorhombic
Space group	Pcab
a/Å	12.3042(5)
b/Å	7.7496(3)
c/Å	21.1003(8)
α/°	90

β/°	90
γ/°	90
Volume/Å^3	2011.97(14)
Z	8
ρ_{calc}g/cm^3	1.481
μ/mm^{-1}	0.289
F(000)	928.0
Crystal size/mm^3	0.28 × 0.2 × 0.13
Radiation	Mo Kα (λ = 0.71073)
2Θ range for data collection/°	3.86 to 56.17
Index ranges	-16 ≤ h ≤ 15, -10 ≤ k ≤ 7, -19 ≤ l ≤ 27
Reflections collected	12647
Independent reflections	2352 [R_{int} = 0.0524, R_{sigma} = 0.0452]
Data/restraints/parameters	2352/0/145
Goodness-of-fit on F^2	1.075
Final R indexes [I>=2σ (I)]	R_1 = 0.0453, wR_2 = 0.1140
Final R indexes [all data]	R_1 = 0.0537, wR_2 = 0.1254
Largest diff. peak/hole / e Å^{-3}	0.69/-0.41

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Chapter 4A

Switchable Regioselective Hydroalkylation of 2-Arylindoles with Maleimides

4.4A.1 INTRODUCTION

The transition metal-catalyzed C–H bond functionalization strategy represents a paradigm shift for constructing C– C and C–heteroatom bonds in organic synthesis.[1-3] Direct functionalization of the C–H bond provides an atom- or step-economical, cost-effective, and environmentally friendly synthesis of important building blocks, natural products, medicinally relevant molecules, and organic materials.[4, 5] This strategy is also advantageous for late-stage modifications enabling rapid diversification of complex molecules that are not easily feasible in traditional methods.[6]

Indole is one of the "privileged" structures that serve as a key framework in many pharmaceuticals, marketed drugs, and natural products with diverse biological activities. Its importance extends to being one of the top nitrogen heterocycles commonly incorporated into medicinal compounds.[7-9] Therefore, the construction and functionalization of the indole nucleus is an important field in heterocyclic chemistry and has been devoted to synthetic chemists for over a century and a half.[10-12] Most importantly, a large number of naturally occurring alkaloids, such as granulatimide and isogranulatimide, were isolated from the ascidian Didemnum granulatum, which contains indole and maleimide nuclei (**Figure 4.4A.1**).[13-16]

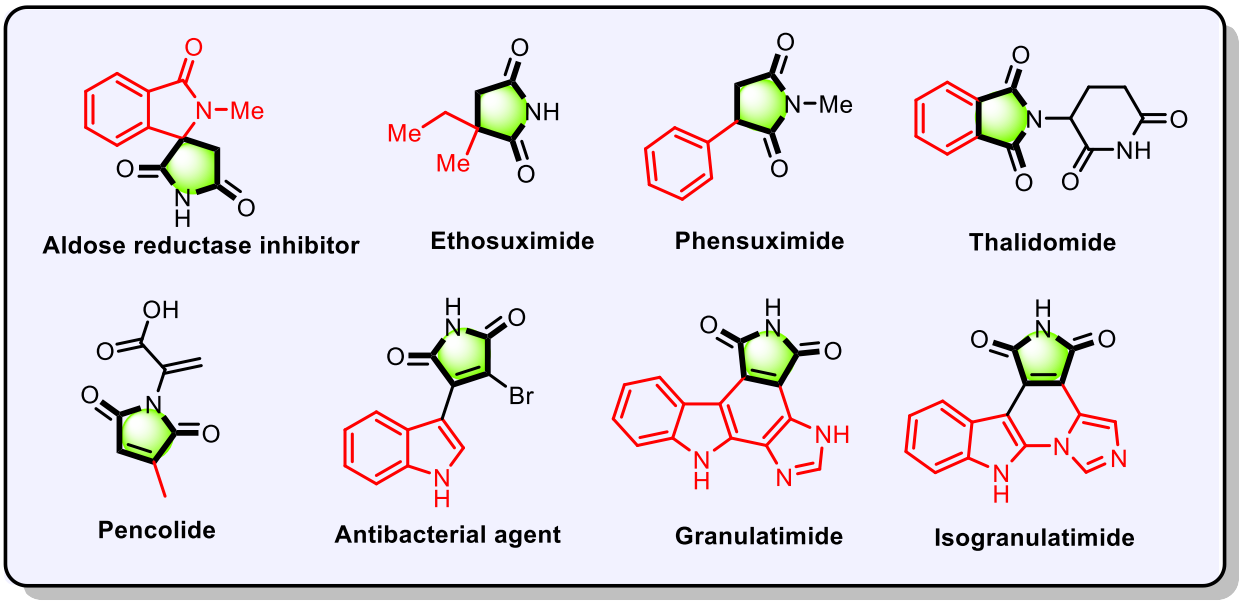
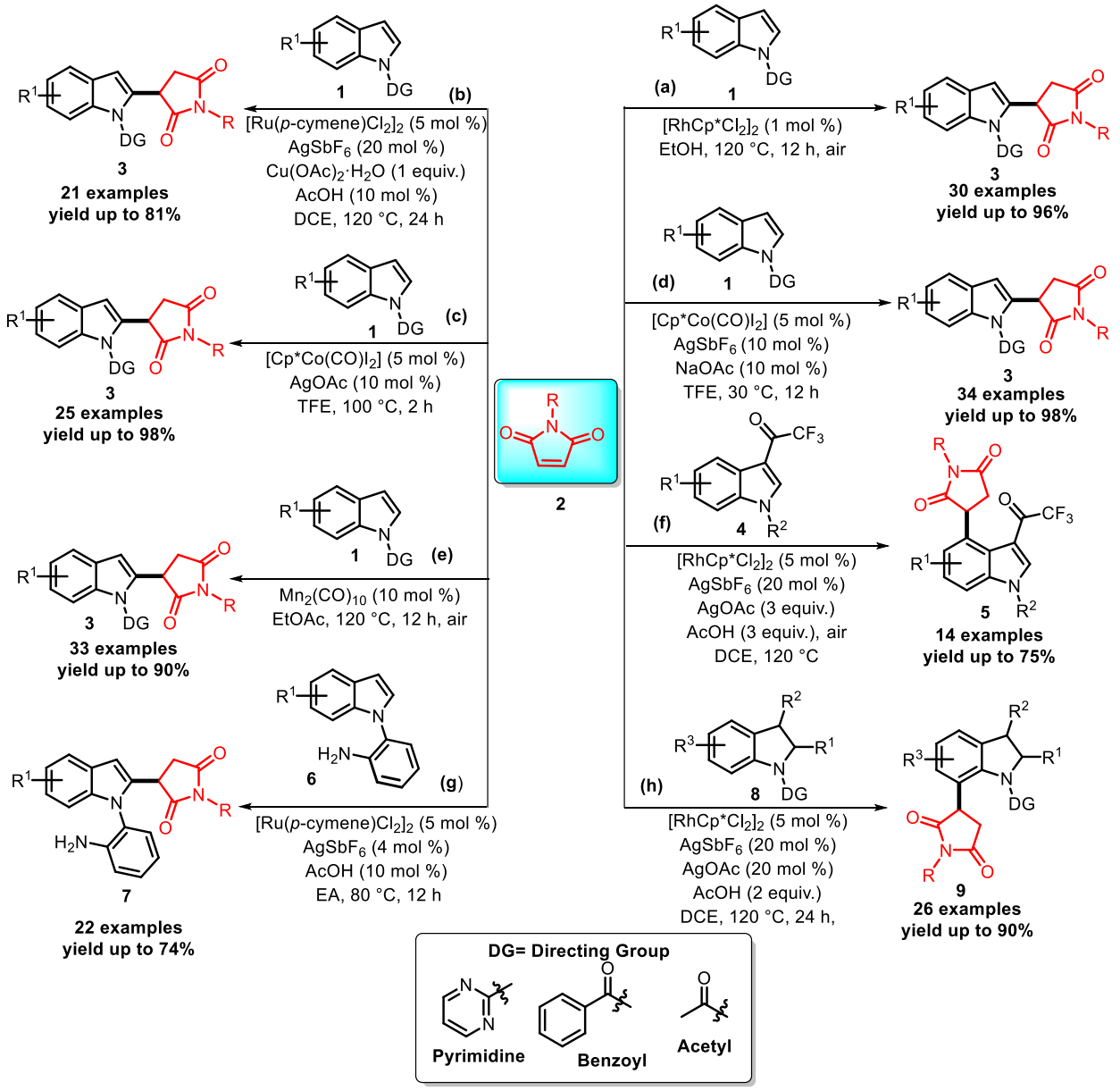


Figure 4.4A.1 Maleimide containing natural products and marine alkaloids

The maleimide structure is a versatile and important scaffold found in a broad range of natural products, functional materials, pharmaceutical ingredients, and biologically active molecules.[17-20] Additionally, maleimide-containing materials have been explored for applications in biosensing, targeted drug delivery, and tissue engineering. This versatile structural unit has shown promise in

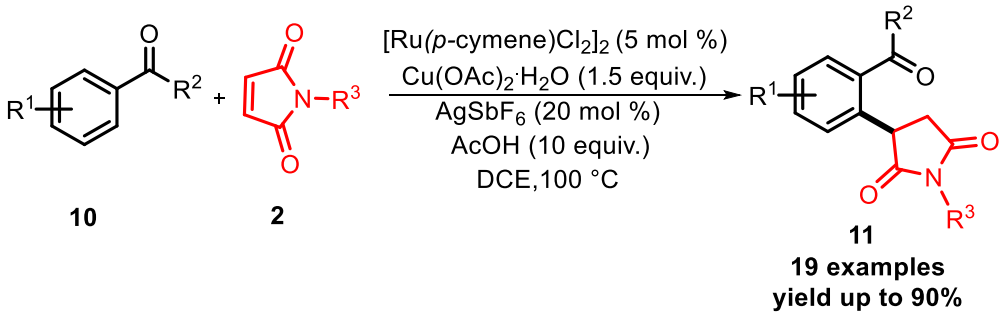
a wide array of practical applications, owing to its diverse biological activities and potential benefits.[21-23] The saturated form of the maleimide also plays a significant role in several natural products and drug molecules, such as ethosuximide, phensuximide, thalidomide, and lurasidone molecules.[24-26] Meanwhile, succinimide derivatives can be easily transformed into biologically applicable molecules, including pyrrolidines and ɣ-lactams (**Figure 4.4A.1**).[27-29]

For example, the group of Li, Song, and Prabhu independently reported transition metal (Rh, Ru Co, and Mn) catalyzed regioselective C-2 hydroalkylation of indole **(1)** with maleimides **(2)** by using different directing groups to produce 3-(indol-2-yl)succinimide derivatives **(3)** (**Scheme 4.4A.1abcde**).[30-34] Furthermore, in 2020 Prabhu *et al.* reported weakly co-ordinating $COCF_3$ group directed, Rh(III)-catalyzed coupling of indoles **(1)** with maleimides **(2)** to give C4-hydroalkylated products **(5)** (**Scheme 4.4A.1f**).[35] Both the additive and an oxidant play crucial roles in determining product selectivity. When a base additive (Ag_2CO_3) was added, Heck-type products were formed. When AgOAc and AcOH were used together, afford 1,4-addition products were obtained. Recently, Fan and co-workers described the Ru(II)-catalyzed alkylation of 2-(1*H*-indol1-yl)-anilines **(6)** with maleimides **(2)** leading to the regioselective synthesis of 3-(indol-2-yl)succinimides **(7)** in good yields with excellent functional group compatibility (**Scheme 4.4A.1g**).[36] Yu group disclosed rhodium(III)-catalyzed direct cross-coupling reaction between indolines **(8)** and maleimides **(2)** through C-H bond functionalization **(Scheme 4.4A.1h)**.[37] This innovative protocol enabling the efficient synthesis of C7-modified indoline derivatives also works well with different functional groups, showing its usefulness for making various kinds of molecules.



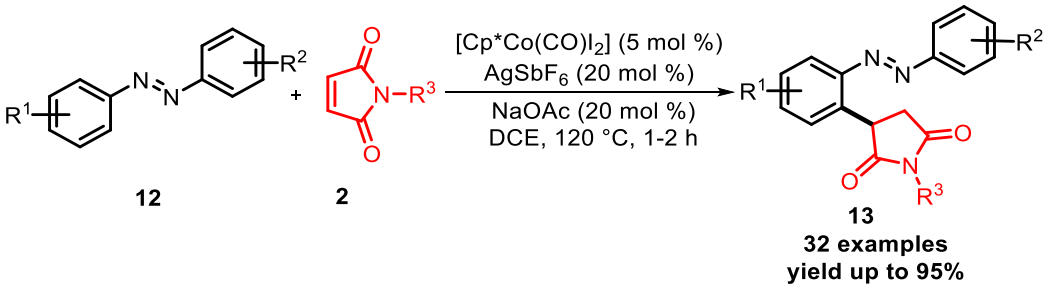
Scheme 4.4A.1: Transition metal-catalyzed hydroalkylation of indole and indoline with maleimides

Prabhu and co-workers developed a synthesis of 3-arylated succinimide derivatives **(11)** *via* Ru(II)- catalyzed C-H functionalization of acetophenone **(10)** with maleimide **(2)** using ketone as a directing group **(Scheme 4.4A.2)**.[38] Mechanistic studies indicated that the C-H activation proceeds through a concerted metalation-deprotonation mechanism, resulting in the formation of a crucial ruthenacycle intermediate. Subsequently, the olefin undergoes insertion into the C-Ru bond. This sequence of events constitutes the key steps in the overall reaction mechanism.



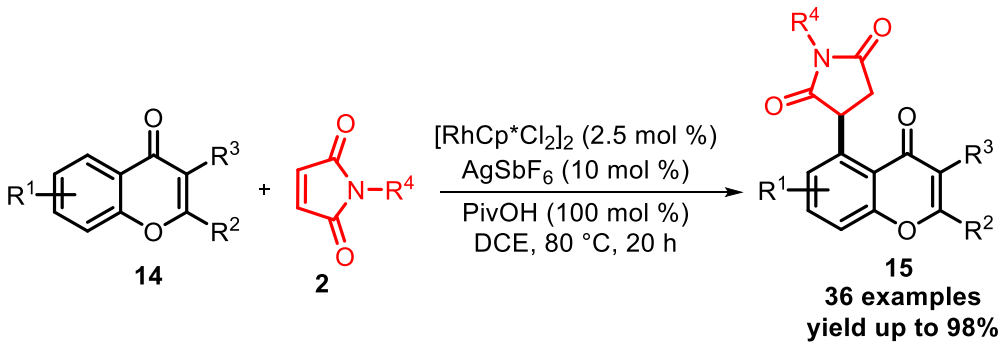
Scheme 4.4A.2: Ru(II)-catalyzed alkylation of acetophenone with maleimides

Prabhu group disclosed Co(III)-catalyzed strategy for functionalization of azobenzene **(12)** with maleimide **(2)** to produce the 3-arylated succinimides derivatives **(13)** in good to excellent yields **(Scheme 4.4A.3)**.[39] The developed protocol demonstrates a broad substrate scope with both symmetrical and unsymmetrical azobenzene derivatives, as well as maleimides and maleate esters.



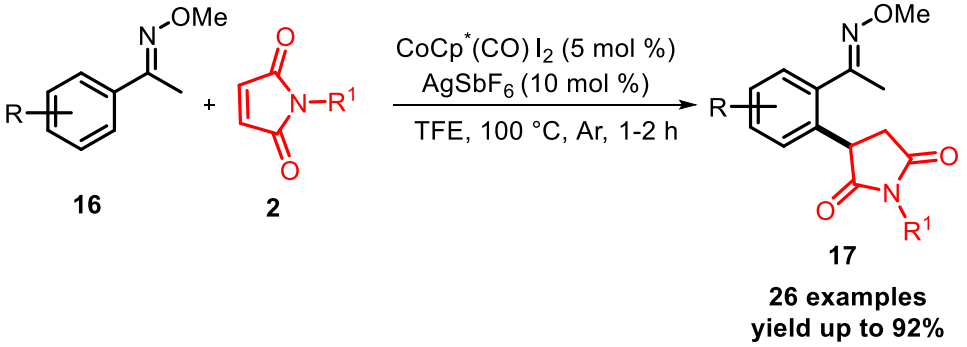
Scheme 4.4A.3: Co(III)-catalyzed alkylation of azobenzene with maleimides

Kim and group reported Rh(III)-catalyzed C-H alkylation reaction of chromones **(14)**, with different substituted maleimide **(2)** to produce the biologically relevant succinimide derivatives **(15)** (**Scheme 4.4A.4**).[40] In addition, the synthesized compound shows potential anticancer activity against human breast adenocarcinoma MCF-7 cell lines.



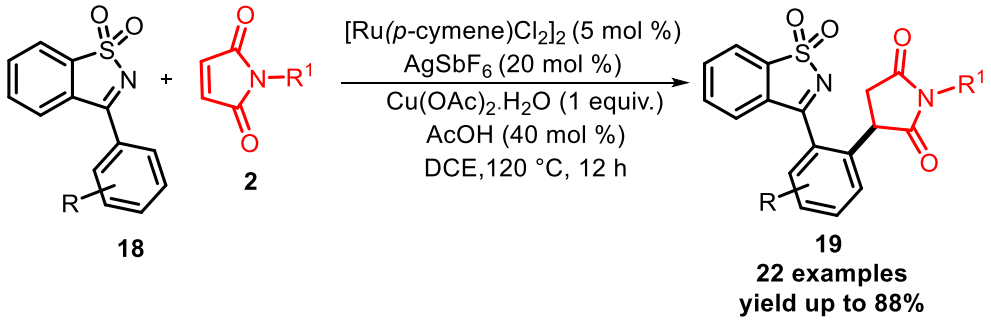
Scheme 4.4A.4: Rh(III)-catalyzed C-H alkylation of chromones with maleimides

Wu *et al.* reported the cobalt (III)-catalyzed the direct C-H arylation of aromatic oxime (**16**) with maleimides (**2**) to afford the various substituted succinimide derivatives (**17**) in moderate to good yields (**Scheme 4.4A.6**).[41] The highlighted features of this developed protocol are excellent regioselectivity, no external bases, and broad substrate scope.



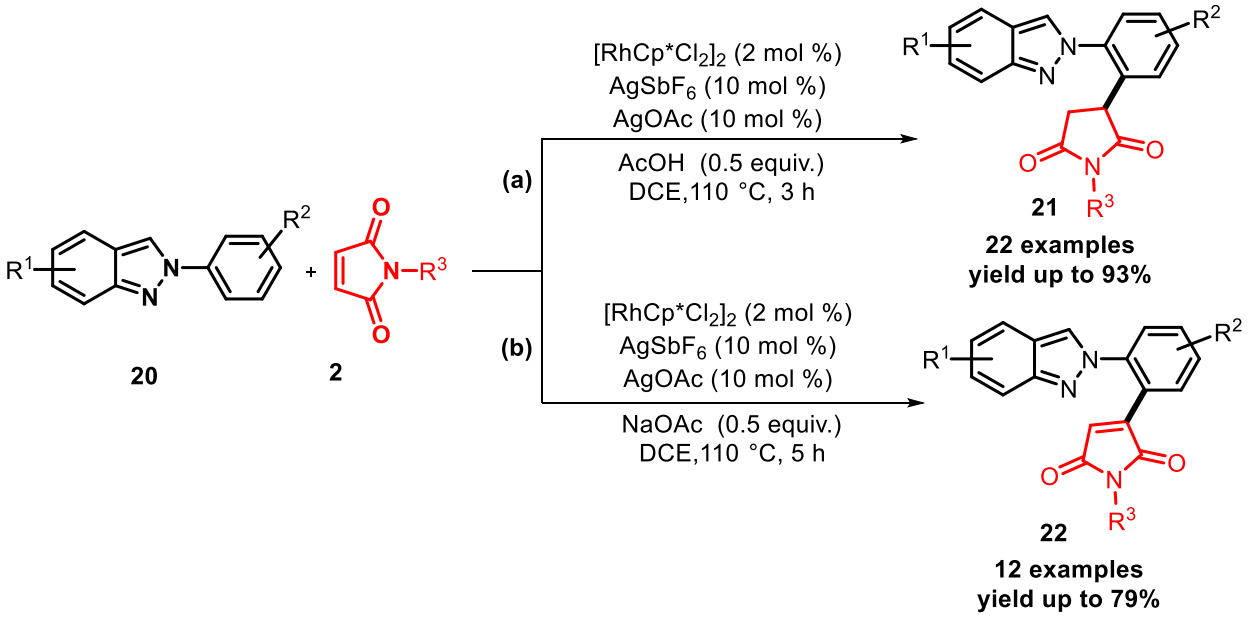
Scheme 4.4A.6: Co(III)-catalyzed alkylation of aromatic oxime with maleimides

In 2018, Reddy and co-workers elaborated the Ru(II)-catalyzed C−H alkylation of cyclic *N*-sulfonyl ketimines (**18**) with maleimides (**2**) to produced 3-[(isothiazol-3-yl)phenyl]succinimide derivatives (**19**) moderate to good yields (**Scheme 4.4A.6**).[42] The designed strategy provides straightforward and atom-efficient tool, yielding medically significant 3-arylsuccinimide derivatives.



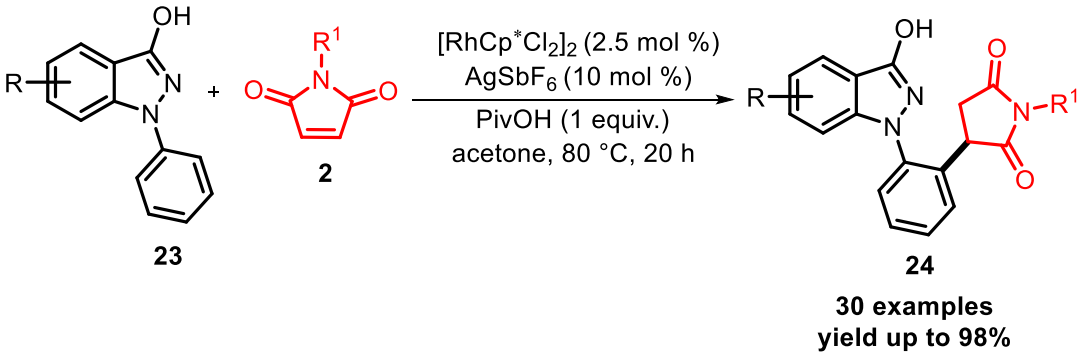
Scheme 4.4A.6: Ru(II)-catalyzed alkylation of *N*-sulfonyl ketimines with maleimides

In 2020, Hajra and group developed the additive control Rh(III)-catalyzed C-H alkylation and alkenylation of 2-arylindazoles **(20)** with maleimide **(2)** to produce 3-(2-(2*H*-indazol-2-yl)phenyl)succinimides **(21)** and 3-(2-(2*H*-indazol-2-yl)phenyl)maleimides **(22)** (**Scheme 4.4A.7**).[43] Interestingly, AgOAc and AcOH combination resulted in alkylated products through reductive elimination, while AgOAc and NaOAc led to the formation of a Heck-type product through E2-elimination of a seven-membered rhodacycle intermediate.



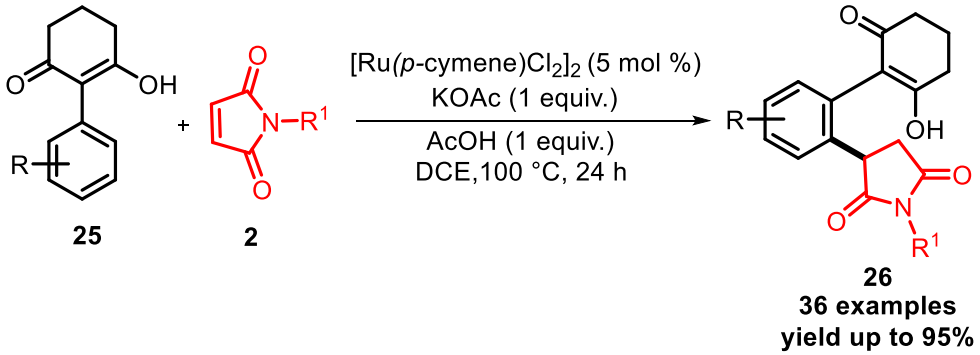
Scheme 4.4A.7: Rh(III)-catalyzed alkylation and alkenylation of 2-arylindazoles with maleimides

Kim and co-workers demonstrated the Rh(III)-catalyzed synthesis of succinimide-bearing indazol-3-ol derivatives (**24**) *via* 1, 4- addition of maleimide (**2**) with *N*-arylindazol-3-ols (**23**) (**Scheme 4.4A.8**).[44] Notably, the developed protocol shows high regioselectivity with good functional group tolerance.



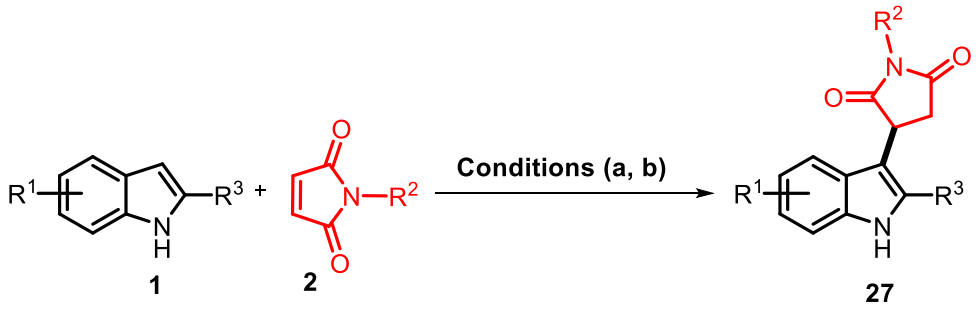
Scheme 4.4A.8: Rh(III)-catalyzed alkylation of *N*-aryl indazol-3-ol with maleimides

In 2023, Baidya group explored the Ru(II)-catalyzed C-H alkylation of enol directed arene (**25**) and maleimides (**2**) for the synthesis of structurally diverse 3-aryl succinimide derivatives (**26**) containing amino acid embedded scaffold in good to excellent yields (**Scheme 4.4A.9**).[45] This strategy has been applied for synthesizing resorcinol- incorporated biaryls in good yields.



Scheme 4.4A.9: Ru(II)-catalyzed alkylation of enol directed arene with maleimides

In 2013, Zhao and co-workers disclosed the Lewis acid-catalyzed synthesis of C3-substituted indole derivative *via* Michael addition of indole **(1)** with maleimides **(2)** (**Scheme 4.4A.10a**).[46] Likewise, the Adil group described the BF_3OEt_2 mediated C3-alkylation of indole **(1)** with maleimides **(2)** under mild reaction conditions, leading to the formation of indolylsuccinimides derivatives **(27)** in moderate to good yields (**Scheme 4.4A.10b**).[47] The developed protocol shows a broad substrate scope with excellent functional group tolerance. Moreover, the anti-proliferative efficacy of these conjugates was assessed against human cancer cell lines, including HT-29 (colorectal), HepG2 (liver), and A549 (lung).

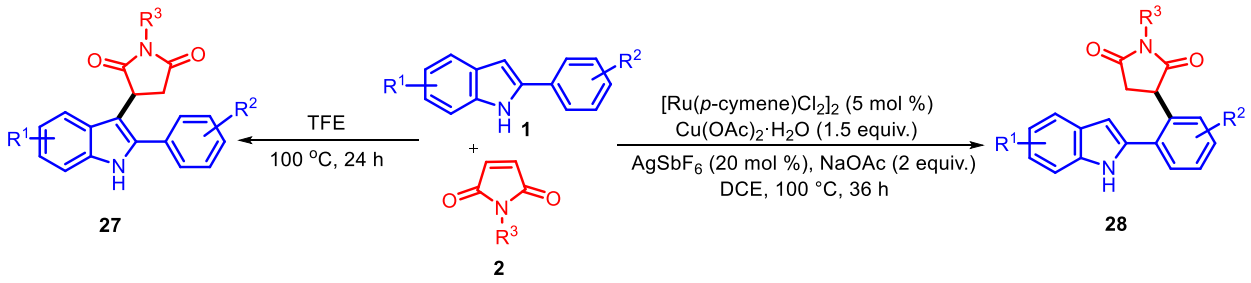


No.	Conditions	Examples	Yield%
a	$AlCl_3$ (10 mol %), DCE, 100 °C, 6-16 h	12	up to 90
b	BF_3OEt_2 (50 mol %), EtOAc, 60 °C, 6 h	25	up to 90

Scheme 4.4A.10: Lewis acid catalyzed C3-alkylation of indoles with maleimides

In continuation of functionalization of *N*-heterocycles, herein, in this chapter, we have described a switchable regioselective hydroalkylation of 2-arylindoles with maleimides In case of Ru(II)-

catalysis hydroalkylation at the *ortho* position of the C2-aryl ring *via* C–H activation, whereas the reaction in the absence of the catalyst in TFE resulted in C3-hydroalkylation.



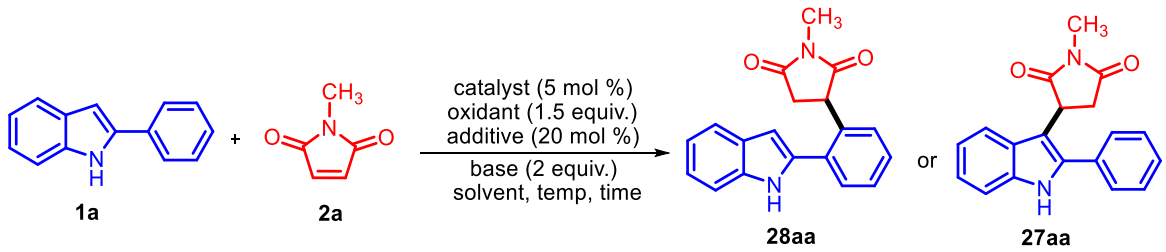
Scheme 4.4A.11: Switchable regioselective hydroalkylation of 2-arylindoles with maleimides

4.4A.2 RESULTS AND DISCUSSION

We started our exploration using 2-phenylindole **(1a)** and maleimide **(2a)** as the starting materials. To our delight, the initial reaction of **1a** and **2a** using [Ru(*p*-cymene)Cl_2]$_2$ (5 mol %) as the catalyst in the presence of Cu(OAc)$_2$ (1.5 equiv.), $AgSbF_6$ (20 mol%) and NaOAc (2 equiv.) in DCE at 100 °C for 24 h delivered 3-(2-(1*H*-indol-2-yl)phenyl)-1-methylpyrrolidine-2,5-dione **(28aa)** in 28% isolated yield **(Table 4.4A.1,** entry 1**)**. In the absence of the [Ru(*p*-cymene)Cl_2]$_2$ catalyst, 1-methyl-3-(2-phenyl-1*H*-indol- 3-yl)pyrrolidine-2,5-dione **(27aa)** was obtained in 52% yield instead of **28aa (Table 4.4A.1,** entry 2**)**. The structures of **27aa** and **28aa** were elucidated with NMR (^{1}H and ^{13}C{^{1}H}) and HRMS spectroscopic data. In ^{1}H NMR of **28aa** the C-3 proton of 2-phenylindole appeared at 6.6 ppm and NH proton appeared at 10.0 ppm along with *N*-methyl maleimide proton appeared at 3.1 ppm, rest of the aromatic proton well match with the structure **(Figure 4.4A.2)**. In ^{13}C{^{1}H} NMR of **28aa**, carbonyl carbon of *N*-methyl maleimide appeared at 180.0 ppm and 176.0 ppm along with other carbons (**Figure 4.4A.3**). In ^{1}H NMR of **27aa** the C-3 proton of 2-phenylindole has vanished and the methyl peak of C19-H of *N*-methyl maleimide appeared at 3.1 ppm. In ^{13}C{^{1}H} NMR of **27aa** the carbonyl carbon of *N*-methyl maleimide appeared at 178.8 ppm and 176.7 ppm. The remaining protons and carbons of the compound **27aa** were observed at their respective positions in ^{1}H and ^{13}C{^{1}H} NMR **(Figure 4.4A.4** and **4.4A.5)**. A peak at *m/z* 305.1288 in the HRMS corresponding to molecular formula $C_{19}H_{17}N_2O_2$ [M+H] ion confirmed the structure of **27aa** and **28aa**. The molecular structure of **28aa** was unambiguously confirmed by single crystal X-ray analysis **(Figure 4.4A.6**, CCDC 2068507). The single crystals of **28aa** were obtained as yellow blocks from a chloroform–hexane solvent mixture. It crystallized in a monoclinic, P21 space group. Two molecules appeared per asymmetric unit during the crystal structure solution with $Z' = 2$ and $Z = 4$.

After confirming the structure of **27aa** and **28aa**, a series of experiments were performed to optimize the reaction conditions. Different oxidants such as Ag_2CO_3, $K_2S_2O_8$, and Cu $(OAc)_2 \cdot H_2O$ were screened to improve the yield of **28aa** (**Table 4.4A.1**, entries 3–5). Among them, $Cu(OAc)_2 \cdot H_2O$ was found to be the most effective giving **28aa** in 52% yield. Furthermore, the yield of **28aa** increased to 69% on increasing the reaction time from 24 h to 36 h (**Table 4.4A.1**, entry 6). Notably, the C3-hydroalkylated product **27aa** and Heck-type product were not obtained when a model reaction was performed in the presence of [Ru(*p*- cymene)Cl_2]$_2$ as the catalyst. The yield of **28aa** was reduced significantly in the absence of $Cu(OAc)_2 \cdot H_2O$ or $AgSbF_6$ or NaOAc signifying the indispensable roles of oxidants and additives (**Table 4.4A.1**, entries 7–9). Furthermore, replacing NaOAc with other bases such as KOAc, CsOAc, Cs_2CO_3, and K_2CO_3 and replacing $AgSbF_6$ with KPF_6 were also found to be detrimental to the yield of hydroalkylated product **28aa** (**Table 4.4A.1**, entries 10–14). To examine the effect of the solvent on the yield of **28aa**, a model reaction was performed in different solvents (**Table 4.4A.1**, entries 15–20). Among them, toluene, nitrobenzene, DMF, and DMA were partially effective and the reaction did not proceed in trifluoroethanol (TFE). Thus, the best yield of **28aa** was obtained using [Ru(*p*-cymene)Cl_2]$_2$ (5 mol %) as the catalyst in the presence of $Cu(OAc)_2$ (1.5 equiv.) and $AgSbF_6$ (20 mol %) as the additive in DCE at 100 °C (**Table 4.4A.1**, entry 6)

Table 4.4A.1. Optimization of Reaction Conditions for the Hydroalkylation of 2-Arylindoles.[a]



Sr. No	oxidant	base	additive	solvent	time (h)	% yield[b]	
						28aa	**27aa**
1	$Cu(OAc)_2$	NaOAc	$AgSbF_6$	DCE	24	28	-
2	$Cu(OAc)_2 \cdot H_2O$	NaOAc	$AgSbF_6$	DCE	24	-	52[c]
3	Ag_2CO_3	NaOAc	$AgSbF_6$	DCE	24	trace	-
4	$K_2S_2O_8$	NaOAc	$AgSbF_6$	DCE	24	18	-
5	$Cu(OAc)_2.H_2O$	NaOAc	$AgSbF_6$	DCE	24	52	-
6	**$Cu(OAc)_2 \cdot H_2O$**	**NaOAc**	**$AgSbF_6$**	**DCE**	**36**	**69**	**-**
7	-	NaOAc	$AgSbF_6$	DCE	36	traces	-
8	$Cu(OAc)_2 \cdot H_2O$	-	$AgSbF_6$	DCE	36	67	-

9	$Cu(OAc)_2·H_2O$	NaOAc	-	DCE	36	57	-
10	$Cu(OAc)_2·H_2O$	KOAc	$AgSbF_6$	DCE	36	35	-
11	$Cu(OAc)_2·H_2O$	Cs_2CO_3	$AgSbF_6$	DCE	24	25	-
12	$Cu(OAc)_2·H_2O$	K_2CO_3	$AgSbF_6$	DCE	36	43	-
13	$Cu(OAc)_2·H_2O$	CsOAc	$AgSbF_6$	DCE	36	trace	-
14	$Cu(OAc)_2·H_2O$	NaOAc	KPF_6	DCE	36	40	-
15	$Cu(OAc)_2·H_2O$	NaOAc	$AgSbF_6$	$PhCH_3$	36	30	-
16	$Cu(OAc)_2·H_2O$	NaOAc	$AgSbF_6$	PhCl	36	33	-
17	$Cu(OAc)_2·H_2O$	NaOAc	$AgSbF_6$	$PhNO_2$	36	35	-
18	$Cu(OAc)_2·H_2O$	NaOAc	$AgSbF_6$	TFE	36	trace	-
19	$Cu(OAc)_2·H_2O$	NaOAc	$AgSbF_6$	DMF	36	39	-
20	$Cu(OAc)_2·H_2O$	NaOAc	$AgSbF_6$	DMA	36	45	-
21	-	NaOAc	$AgSbF_6$	DCE	24	-	56[c]
22	-	-	$AgSbF_6$	DCE	24	-	59[c]
23	-	-	-	DCE	24	-	32[c]
24	-	-	-	HFIP	24	-	61[c]
25	-	-	-	EtOH	24	-	39[c]
26	**-**	**-**	**-**	**TFE**	**24**	**-**	**79[c]**

[a]Reaction conditions: **1a** (0.259 mmol), **2a** (0.518 mmol), catalyst (5 mol %), additive (20 mol %), oxidant (1.5 equiv.), base (0.518 mmol), solvent (2 mL), air. [b]Isolated yield. [c]In the absence of a ruthenium catalyst.

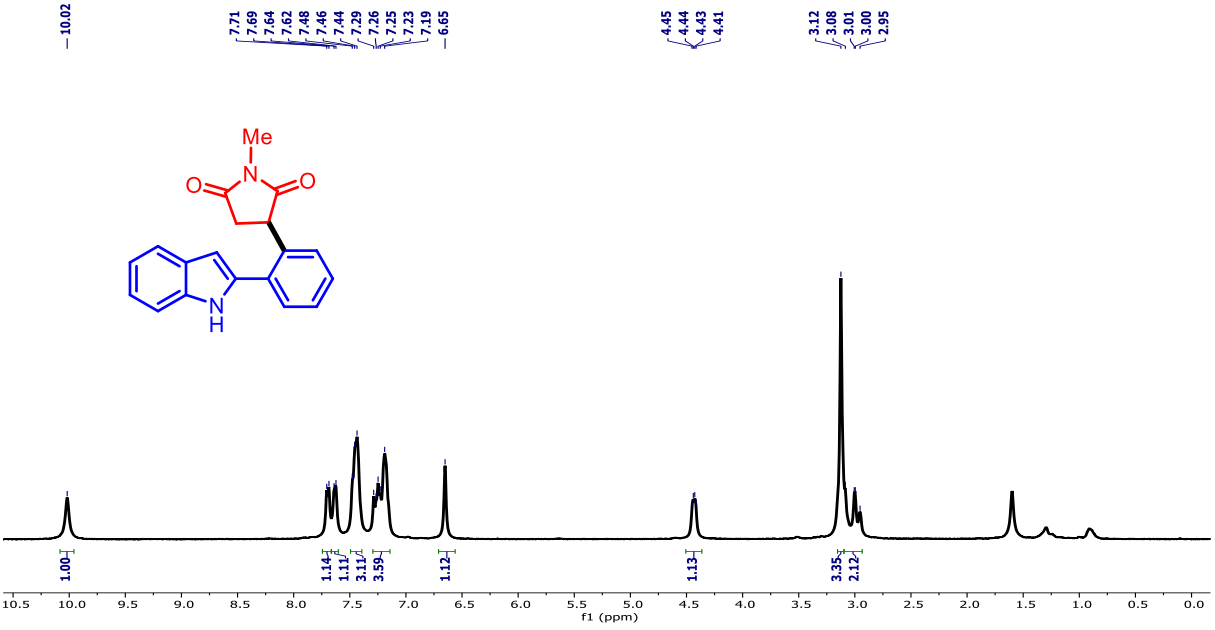


Figure 4.4A.2: ^{1}H-NMR spectrum of 3-(2-(1*H*-indol-2-yl)phenyl)-1-methylpyrrolidine-2,5-dione (**28aa**) recorded in $CDCl_3$

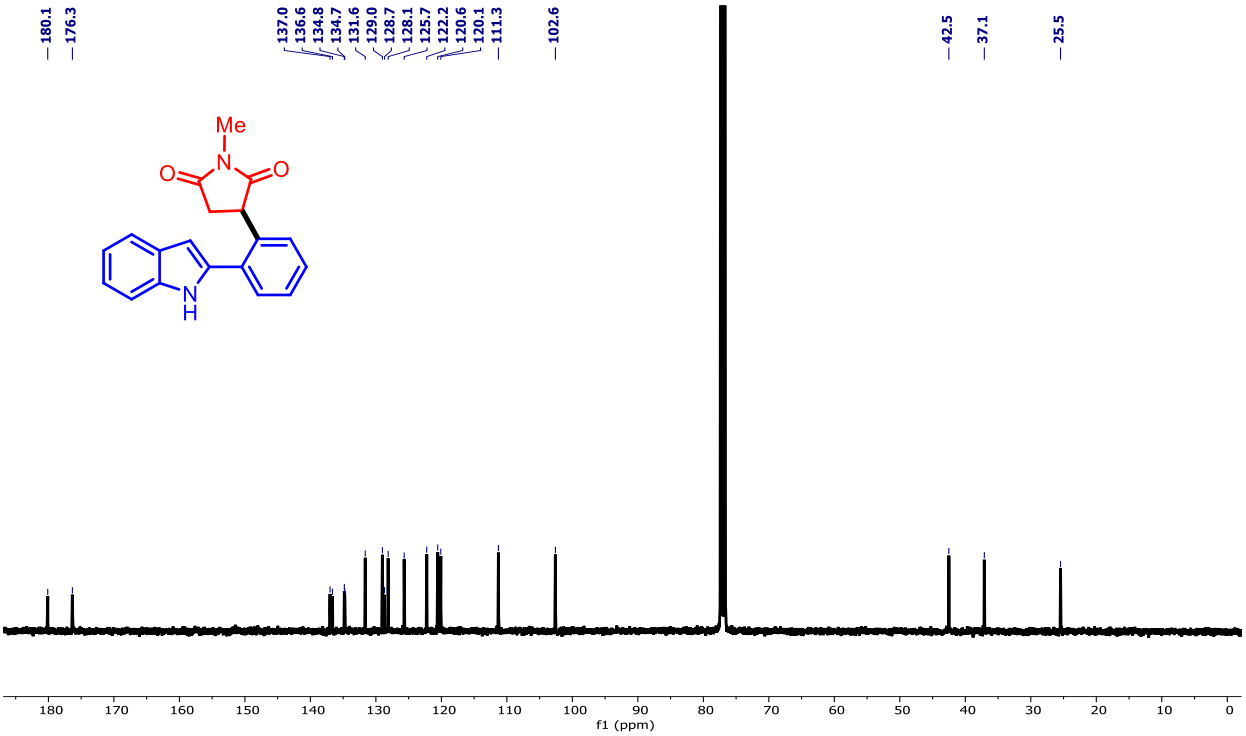


Figure 4.4A.3: $^{13}C\{^{1}H\}$-NMR spectrum of 3-(2-(1*H*-indol-2-yl)phenyl)-1-methylpyrrolidine-2,5-dione (**28aa)** recorded in $CDCl_3$

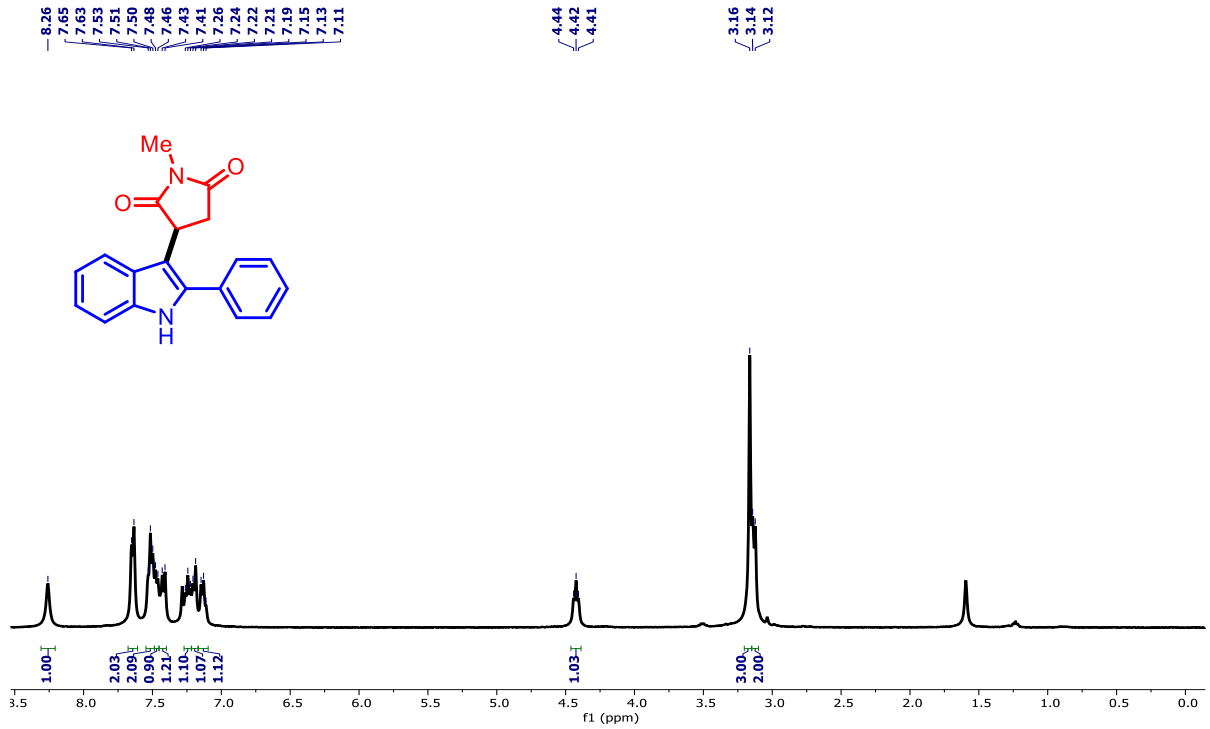


Figure 4.4A.4: ^{1}H-NMR spectrum of 1-methyl-3-(2-phenyl-1*H*-indol-3-yl)pyrrolidine-2,5-dione (**27aa**) recorded in $CDCl_3$

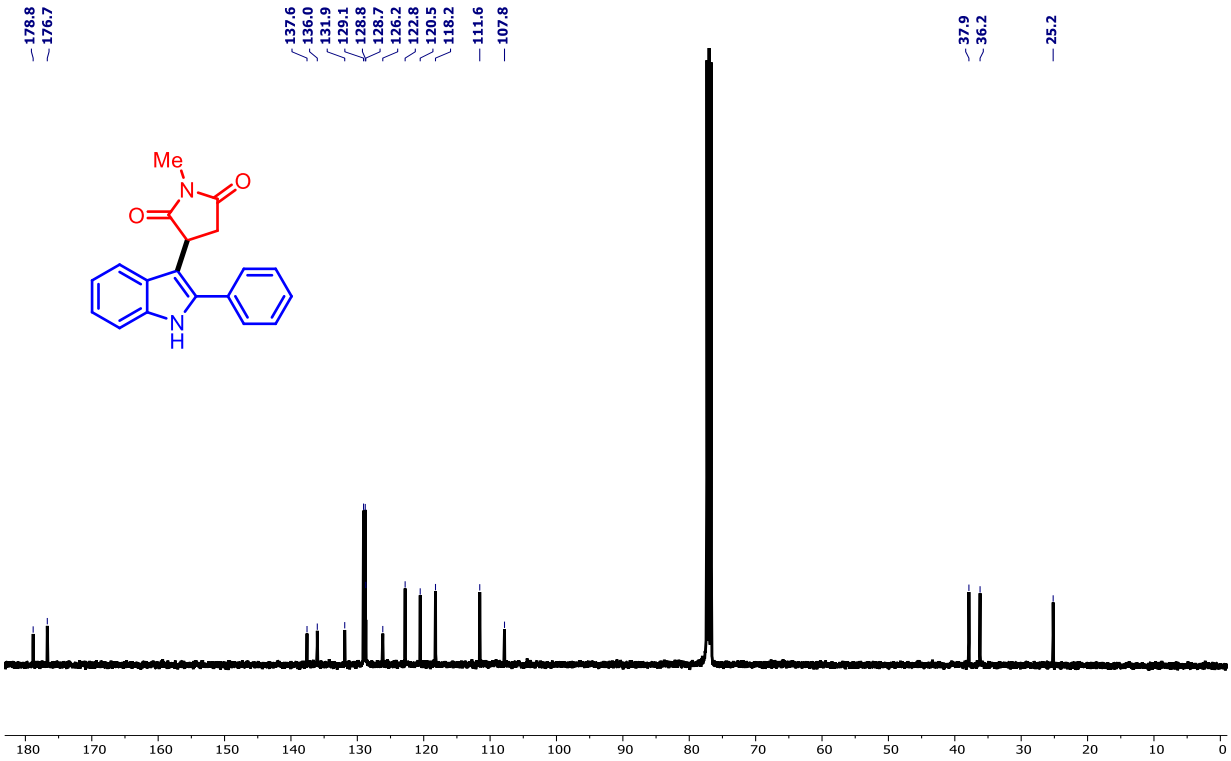


Figure 4.4A.5: ^{13}C-NMR spectrum of 1-methyl-3-(2-phenyl-1*H*-indol-3-yl)pyrrolidine-2,5-dione (**27aa)** recorded in $CDCl_3$

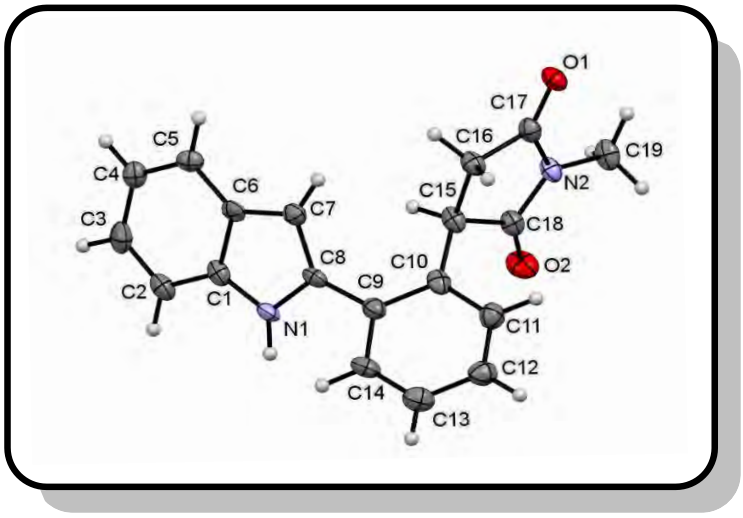
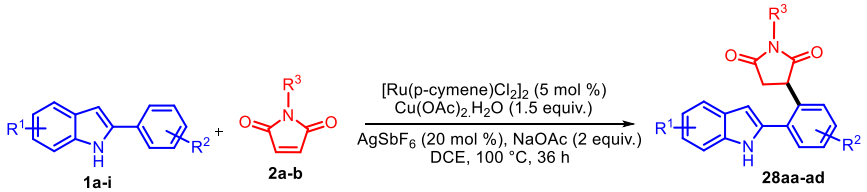


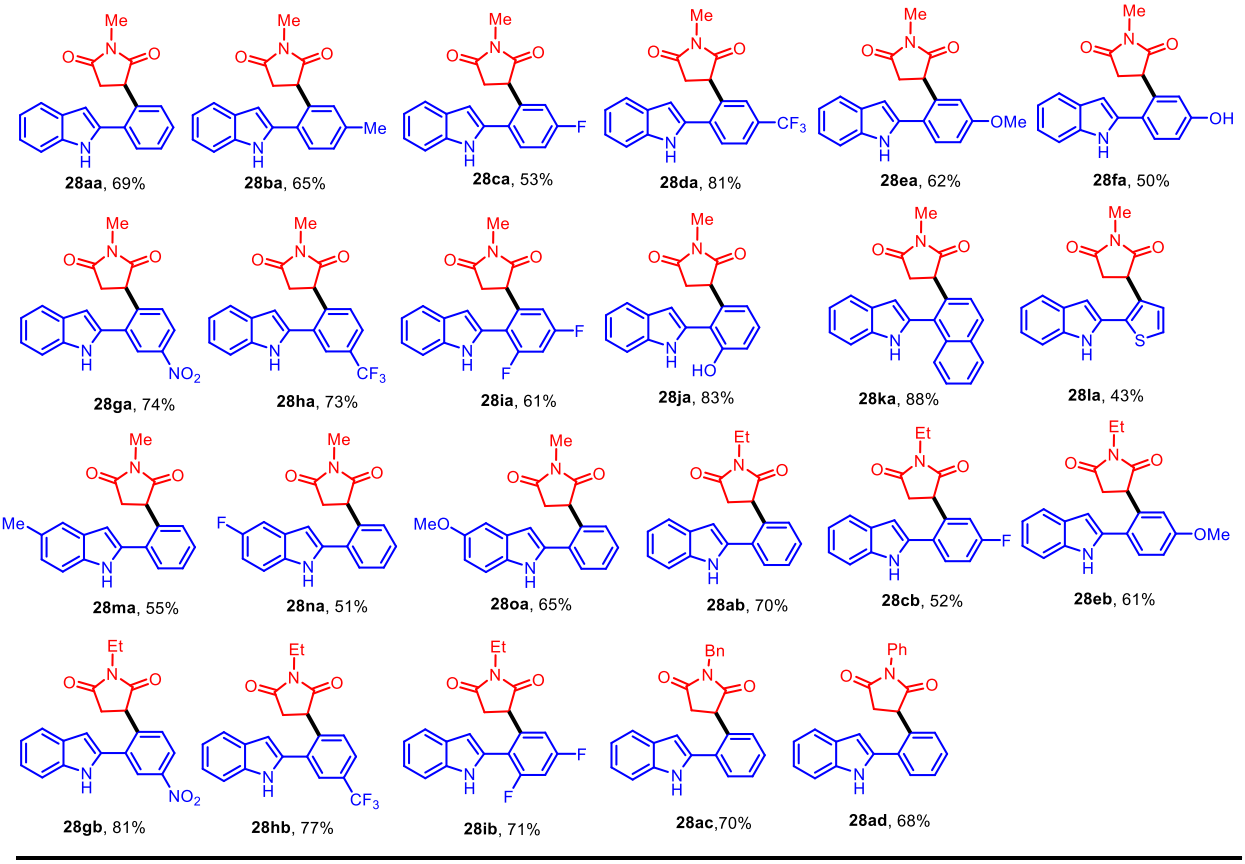
Figure 4.4A.6: ORTEP diagram of **28aa (CCDC NO** 2068507) the thermal ellipsoids are drawn at 50 % probability level.

With the optimized reaction conditions in hand, we investigated the scope of Ru(II)-catalyzed hydroalkylation **(Table 4.4A.2)**. 2-Arylindoles (**1a–1j)** with various functional groups such as methyl, methoxy, hydroxyl, fluoro, trifluoromethyl, and nitro on the C2-phenyl ring reacted smoothly with *n*-methylmaleimide **(2a)** to furnish the corresponding hydro alkylated products **28aa–28ja** in moderate to good (50–83%) yields. Higher yields of hydroalkylated products were obtained from 2-arylindoles with electron-withdrawing substituents at the meta-position of the C2-phenyl ring. Moreover, 2- (naphthyl-2-yl)indole **(1k)** and 2-(thiophen-2-yl)indole **(1l)** also reacted smoothly to afford the corresponding hydroalkylated products **28ka** and **28la** in 88 and 43% yields, respectively. The reaction of 2-phenylindole with a substituent on the indole ring **(1m–1o)** with **2a** also afforded the corresponding *ortho*-hydroalkylated products **28ma–28oa** in moderate to good (51–65%) yields. Unfortunately, *N*-methyl-2-phenylindole did not react under these conditions to afford the desired *ortho*-hydroalkylated product.

Next, we examined the scope of maleimides. To our satisfaction, different maleimides *viz. N*-ethylmaleimide **(2b)**, *N*-benzylmaleimide **(2c),** and *N*-phenylmaleimide **(2d)** reacted smoothly with **1a** under standard conditions to furnish the corresponding hydroalkylated products **28ab–28ad** in good yields. Similarly, the reaction of **2b** with other 2-arylindoles also afforded good to excellent yields of *ortho*-hydroalkylated products **28cb–28ib**. As mentioned earlier, the reaction of **2b** with substrates with electron-withdrawing groups on the C2-phenyl ring furnished higher yields as compared with those with electron-donating groups.

Table 4.4A.2: Substrate scope for Ru-catalyzed hydroalkylation of 2-arylindoles with maleimides.[a,b]





[a]Reaction conditions: **1** (0.259 mmol), **2** (0.518 mmol), $Cu(OAc)_2 \cdot H_2O$ (1.5 equiv.), NaOAc (0.518 mmol), $AgSbF_6$ (20 mol %), [Ru(*p*-cymene)Cl_2]$_2$ (5 mol %), DCE (2 mL), 100 °C, 36 h. [b]Isolated yields.

Compounds with the 3-(indol-3-*yl*)succinimide framework have been found to possess a diverse spectrum of biological activities such as high binding affinities for 5-HT1A receptors and selective inhibition of indoleamine 2,3-dioxygenase (IDO-1). The most common method to synthesize 3-(indol-3- *yl*)succinimides is the Michael addition reaction of indoles with maleimides; however, very few reactions are reported and they have many disadvantages such as the requirement of a strong Lewis acid, undesired side products, low or moderate yields and poor selectivity. Therefore,

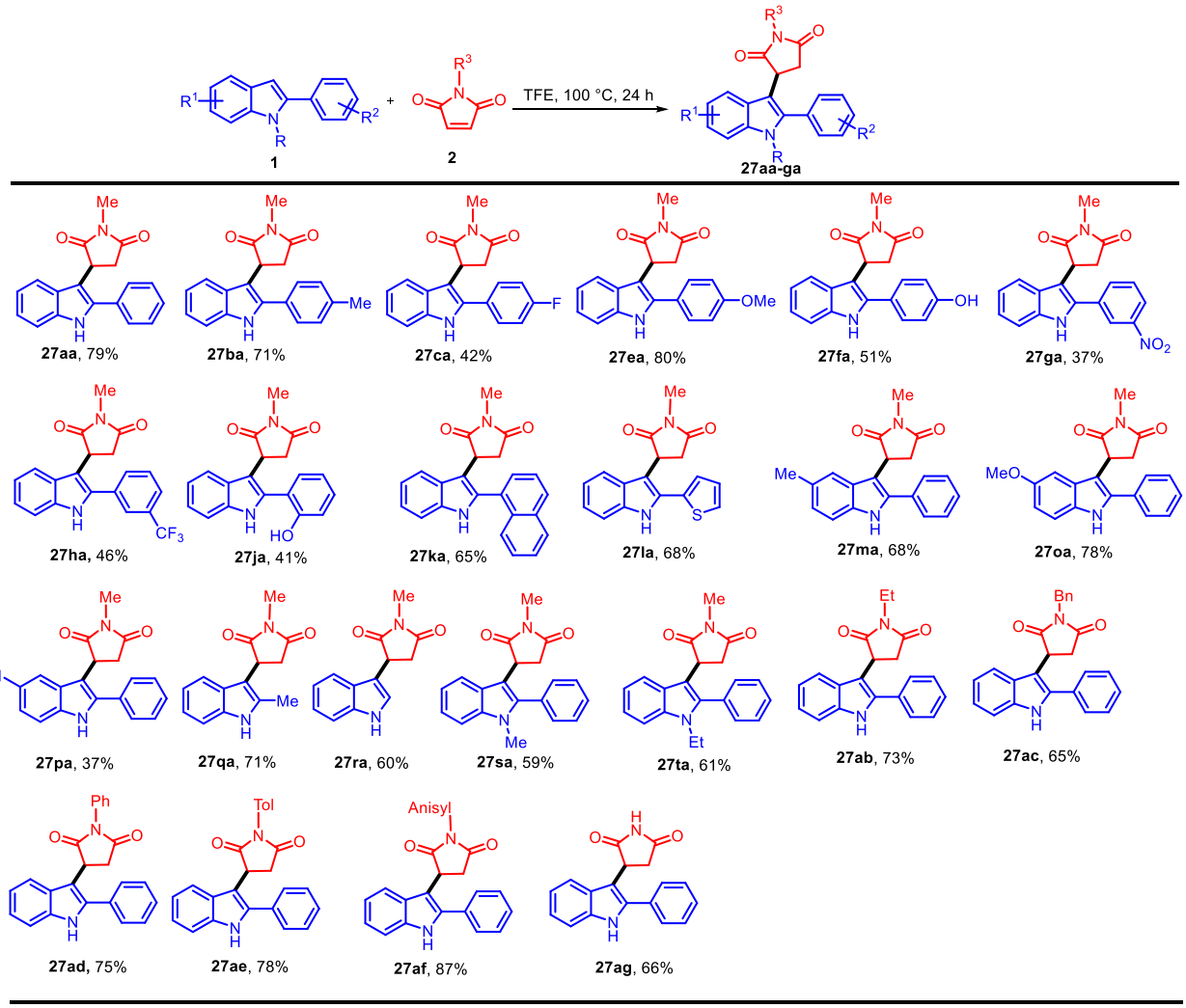
a simple and straightforward method for the preparation of 3-(indol-3-*yl*) succinimides by Michael addition of indoles with maleimides is highly desirable.

During our optimization for ruthenium-catalyzed hydroalkylation, *N*-methyl-3-(2-phenyl-1*H*-indol-3-yl)succinimide **(27aa)** was obtained in 52% yield in the absence of a ruthenium catalyst. Further optimization of the reaction conditions by performing a model reaction in different solvents and in the absence of additives led to the highest yield (79%) of **27aa** in TFE (**Table 4.4A.1**, entries 21–26).

Encouraged by these results, we investigated the substrate scope for the preparation of 3-(indol-3-*yl*)succinimides by the Michael addition of indoles with maleimides **(Table 4.4A.3)**. A wide variety of 2-aryl indoles (**1a**–**1j**) with substituents on the C2-phenyl ring reacted smoothly with *N*-methyl maleimide **(2a)** to provide the corresponding 3-(indol-3-yl)succinimides **(27aa–27ja)** in moderate to good (41–80%) yields. Indoles with electron-withdrawing groups on the C2-phenyl ring produced lower yields of the corresponding 3-(indol-3-yl)succinimides as compared to the indoles with electron-donating groups. 2- (Naphthyl-2-yl)indole **(1k)** and 2-(thiophen-2-yl)indole **(1l)** also reacted smoothly to afford the corresponding 3-(indol-3-*yl*)succinimides **27ka** and 2**7la** in 65 and 68% yields, respectively.

2-Phenylindoles with substituents on the indole ring **(1m–1p)** also reacted smoothly with **2a** to furnish the corresponding 3-(indol-3-yl)succinimides **(27ma–27pa)** in moderate to good yields. Interestingly, 2-methylindole **(1q)**, C2-unsubstituted indole **(1r)** and *N*-substituted indoles (**1s** and **1t**) also reacted with **2a** to afford the corresponding 3-(indol-3-*yl*)succinimides in 71%, 60%, 59% and 61% yields, respectively. Finally, the substrate scope of maleimides was investigated. Different *N*-substituted maleimides **(2b–2f)** and unsubstituted maleimide **(2g)** reacted with **1a** to furnish the corresponding 3-(indol-3-*yl*)succinimides **(27ab–ag)** in good (65–87%) yields.

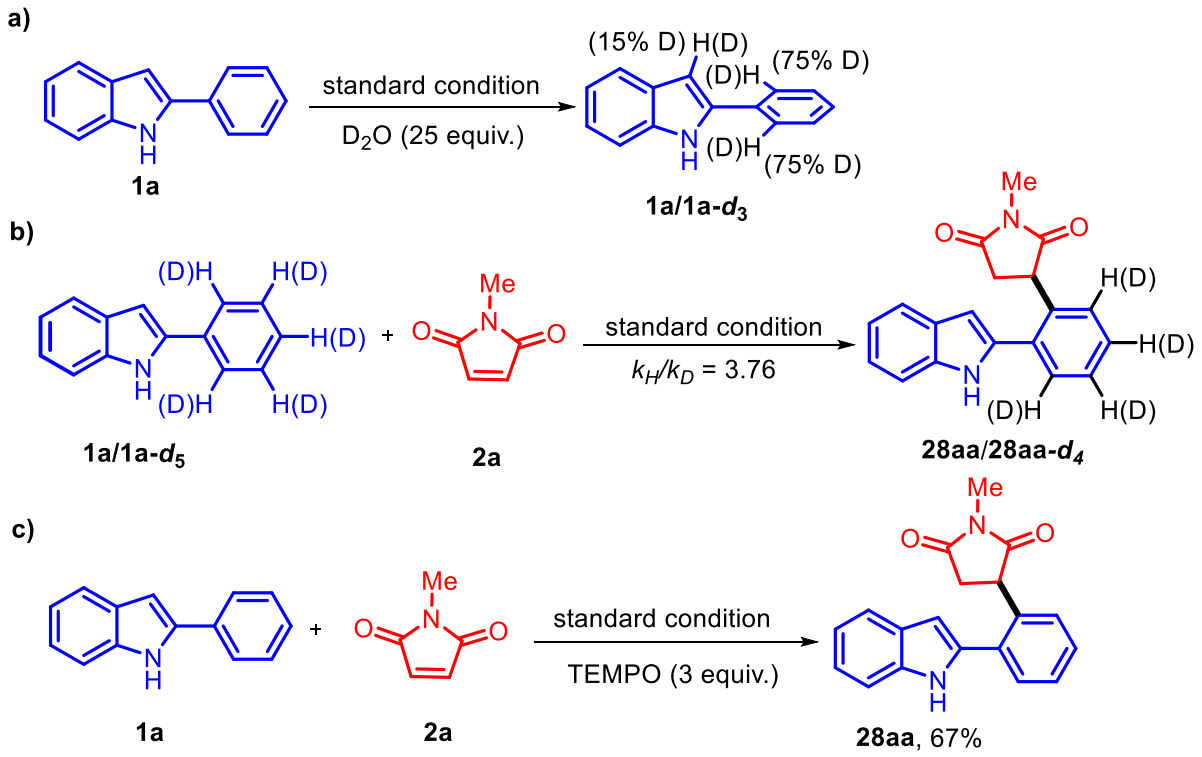
Table 4.4A.3: Substrate scope for synthesis of 3-(indol-3-yl)succinimides.[a,b]

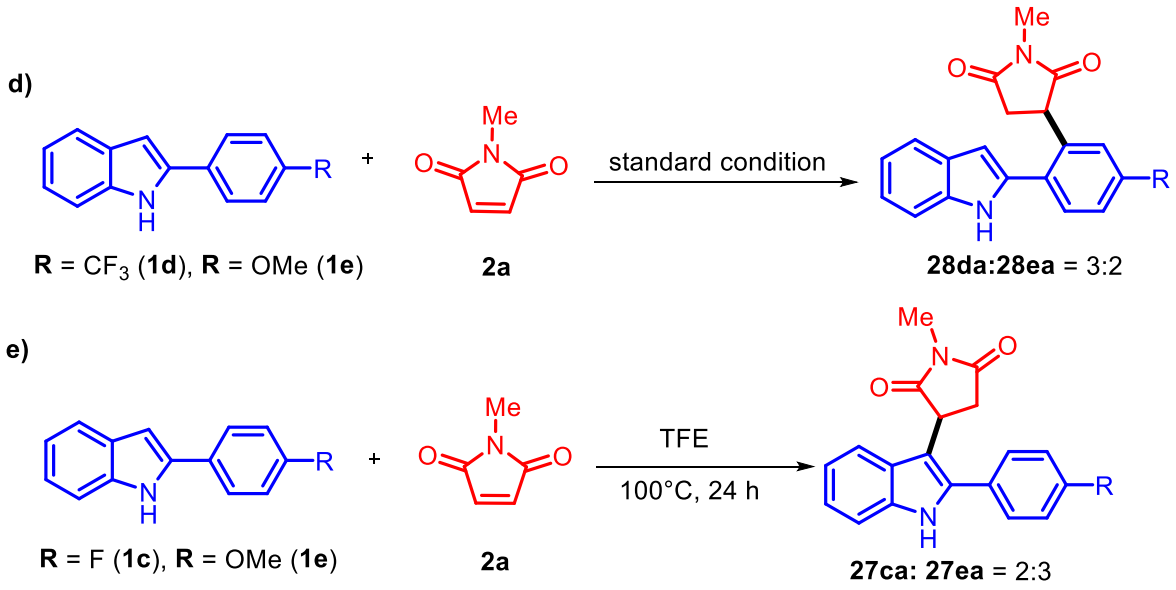


[a]Reaction conditions: **1** (0.259 mmol), **2** (0.518 mmol) in TFE (2 mL) under air at 100 °C for 24 h. [b]Isolated yields.

To know more about the reaction mechanisms, a few control experiments were performed **(Scheme 4.4A.10)**. When 2-phenylindole **(1a)** was treated with D_2O under similar reaction conditions in the presence of a Ru-catalyst without **2a**, 75% of deuterium incorporation was observed at both *ortho* C–H bonds of the 2-phenyl ring and 15% of deuterium incorporation was observed at the C3-position to give **1a-*d*$_3$ (Scheme 4.4A.10a)**. This result suggested that the ortho C(sp^2)–H activation of the 2-phenyl ring is reversible. Furthermore, a k_H/k_D value of approx. 3.76 was observed from the kinetic isotope experiment (KIE) for Ru-catalyzed hydroalkylation indicating that the rate-limiting step is the C–H bond activation **(Scheme 4.4A.10b)**. The reaction of **1a** with **2a** was performed in the presence of the (2,2,6,6-tetramethylpiperidin-1-yl)oxyl radical

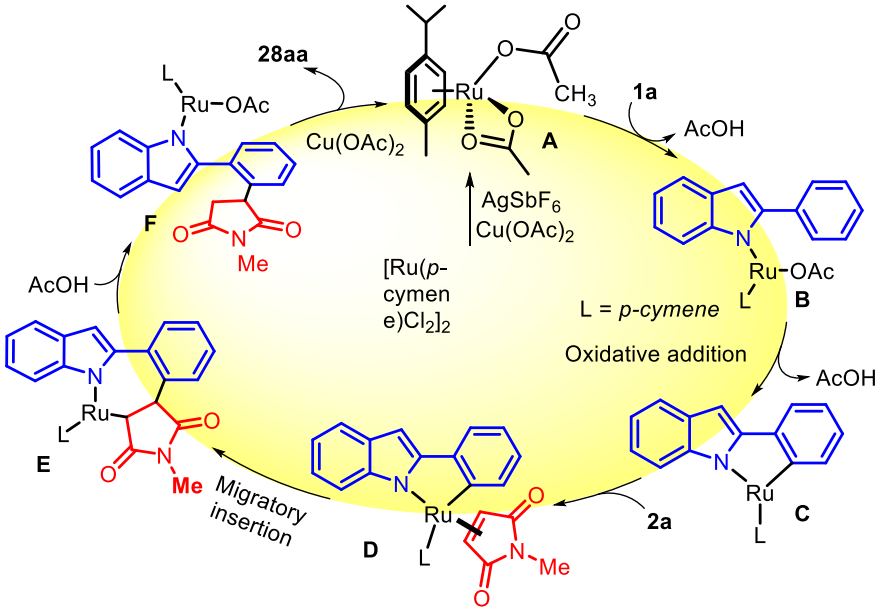
scavenger **(Scheme 4.4A.10c)**. Product **28aa** was isolated in 67% yield which confirmed that the reaction does not involve a radical intermediate. Finally, intermolecular competition experiments were performed for both *ortho*-hydroalkylation and C3-hydroalkylation reactions. Intermolecular competition experiments of **1d** and **1e** under Ru(II)-catalysis produced the corresponding products **28da** and **28ea** in a 3 : 2 ratio (**Scheme 4.4A.10d**) confirming the preference for substrates containing electron-withdrawing substituents on the C2-phenyl ring. This result supports the acetate-assisted, concerted metalation–deprotonation (CMD) step as the rate determining step in the mechanism and rules out electrophilic C–H bond activation to be the operative mechanism. On the other hand, intermolecular competition experiments of **1c** and **1e** in TFE provided a mixture of **27ca** and **27ea** in a 2 : 3 ratio **(Scheme 4.4A.10e)** supporting TFE-assisted nucleophilic addition of indole to maleimide *via* the Michael addition reaction.



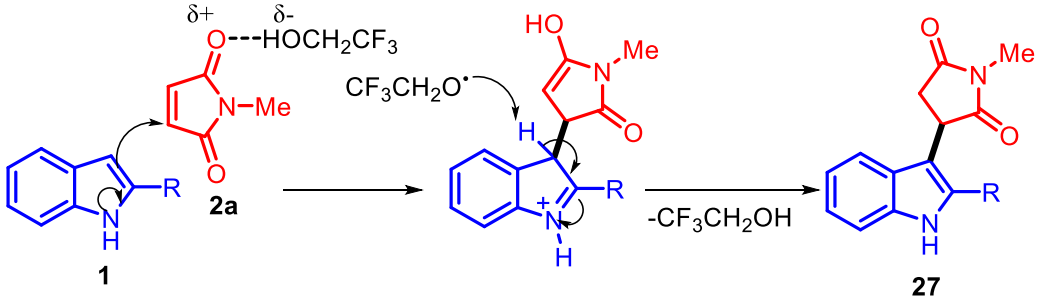


Scheme 4.4A.10: Control experiments

Based on the control experiments and literature reports,[48-50] a plausible mechanistic pathway for Ru(II)-catalysed orthohydroalkylation is shown in **Scheme 4.4A.11**. The reaction of [Ru(*p*-cymene)Cl_2]$_2$ with Cu(OAc)$_2$·H_2O generates the active Ru(II) precursor A with dissociation of Cl_2. The Ru(II) precursor **A** reacts with **1a** to provide ruthenium complex **B**, where a lone pair of the nitrogen atom of **1** coordinates with the ruthenium metal ion. Base-mediated deprotonation at the *ortho* C–H bond of complex **B** then generates the key ruthenacycle intermediate **C**. Intermediate **C** leads to a seven-membered ruthenacycle **E** *via* coordination with maleimide followed by migratory insertion. Finally, protonation of the C–Ru bond of intermediate **E** followed by dissociation of the catalyst provides product **28aa** and regenerates the active ruthenium catalyst. On the other hand, C3-hydroalkylation is believed to proceed through TFE-assisted Michael addition of nucleophilic indoles with maleimides **(Scheme 4.4A.11)**.



Scheme 4.4A.11: Proposed reaction mechanism *ortho*-hydroalkylation of 2-arylindoles



Scheme 4.4A.12: Proposed mechanism for TFE-mediated C3-hydroalkylation of indoles

4.4A.3 CONCLUSIONS

In summary, we have demonstrated an efficient and new pathway of switchable regioselective hydroalkylation of 2-arylindoles with maleimides. In the presence of a Ru(II)-catalyst, hydroalkylation at the *ortho*-position of the 2-aryl ring occurred *via* an *ortho* C–H activation pathway while in the absence of the catalyst, C3-hydroalkylation occurred using TFE as the solvent. The reaction provided hydroalkylated derivatives in good to moderate yields with good functional group tolerance.

4.4A.4 EXPERIMENTAL SECTION

4.4A.4.1 General Information

Unless specified, all materials were commercially available and were used without further purification. 2-Substituted indole derivatives were synthesized by using reported methods.[51] All reactions were performed under air and in a pressure tube. The ^{1}H NMR (400 MHz) and $^{13}C\{^{1}H\}$ NMR (100 MHz) spectra were recorded using $CDCl_3$ (TMS as an internal standard) or DMSO-d_6 as the solvent. The ^{1}H and $^{13}C\{^{1}H\}$ shifts were referenced at 7.26 ppm and 77.6 ppm for $CDCl_3$ and 2.50 ppm and 40.5 ppm for DMSO-d_6, respectively. Chemical shifts (δ) and coupling constants (J) are reported in parts per million (ppm) and hertz, respectively. The chemical multiplicities were reported as: singlet (s), doublet (d), triplet (t), quartet (q), quintet (quint), sextet (sext), septet (sept) and multiplet (m) and their combinations of them as well. HRMS data were recorded in electrospray ionization (ESI) mode on an Q-TOF LC-MS spectrometer. Column chromatography was performed on 100-200 mesh silica gel using EtOAc-hexanes as an eluent. Reactions were monitored by thin-layer chromatography (TLC) using 0.25 mm silica gel 60-F_{254} plates. The melting point were determined in open capillary tubes on an automated apparatus and were uncorrected.

4.4A.4.2 Procedure for Ru-catalyzed Hydroalkylation of 2-Arylindoles with Maleimides.

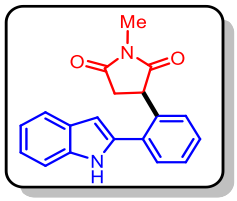
A 10 mL pressure tube was charged with 2-arylindole (0.26 mmol) and *N*-substituted maleimide (0.52 mmol), $Cu(OAc)_2{\cdot}H_2O$ (77 mg, 0.39 mmol), $AgSbF_6$ (18 mg, 20 mol %), NaOAc (43 mg, 0.52 mmol), $[Ru(p\text{-cymene})Cl_2]_2$ (8 mg, 2.5 mol %) in dichloroethane (2 mL). The reaction tube was caped tightly and stirred at 100 °C in an oil bath for 36 h. Upon completion of the reaction, the reaction mixture was cooled to ambient temperature, and diluted with water (2 mL). The reaction mixture was extracted in ethyl acetate (2 × 15 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and evaporated in a vacuum. The resulting residue was purified by column chromatography on silica gel using EtOAc-hexanes eluent to afford the desired hydroarylated products **28aa**.

4.4A.4.3 Procedure for C3-Hydroalkylation of Indoles with Maleimides.

A 10 mL pressure tube was charged with indole (0.26 mmol) *N*-substituted maleimide (0.52 mmol) and trifluoroethanol (2 mL). The reaction tube was caped tightly and stirred at 100 °C in an oil bath for 24 h. Upon completion of the reaction, the reaction mixture was cooled to ambient temperature and TFE was evaporated under vacuum. The resulting residue was purified by column

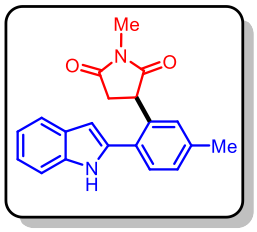
chromatography on silica gel using EtOAc-hexanes eluent to afford the desired C3-hydroarylated products **27aa**.

3-(2-(1*H*-Indol-2-yl)phenyl)-1-methylpyrrolidine-2,5-dione (28aa): The title compound was



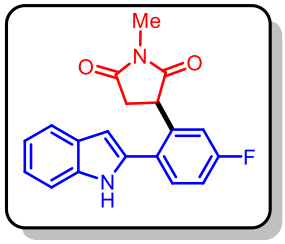
purified by column chromatography on silica gel using EtOAc/ hexanes (1: 4, *v/v*) as an eluent; off white solid (55 mg, 69%); mp = 156-158 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.02 (s, 1H), 7.70 (d, *J* = 7.6 Hz, 1H), 7.63 (d, *J* = 6.8 Hz, 1H), 7.48 – 7.44 (m, 3H), 7.29 – 7.19 (m, 3H), 6.65 (s, 1H), 4.43 (d, *J* = 5.2 Hz, 1H), 3.12 (s, 3H), 3.09 – 2.95 (m, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 180.1, 176.3, 137.0, 136.6, 134.8, 134.7, 131.6, 129.0, 128.7, 128.1, 125.7, 122.2, 120.6, 120.1, 111.3, 102.6, 42.5, 37.1, 25.5; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{19}H_{17}N_2O_2^+$ 305.1285; Found 305.1293.

3-(2-(1*H*-Indol-2-yl)-5-methylphenyl)-1-methylpyrrolidine-2,5-dione (28ba): The title



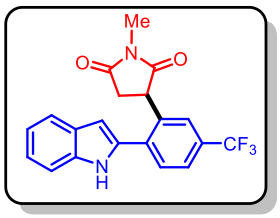
compound was purified by column chromatography on silica gel using EtOAc/ hexanes (1: 4, *v/v*) as an eluent; off white solid (50 mg, 65%); mp = 162-164 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.93 (s, 1H), 7.68 (d, *J* = 8.0 Hz, 1H), 7.51 (d, *J* = 7.6 Hz, 1H), 7.45 (d, *J* = 8.0 Hz, 1H), 7.29 – 7.14 (m, 3H), 6.96 (s, 1H), 6.61 (s, 1H), 4.40 (dd, *J* = 9.6, 4.0 Hz, 1H), 3.13 (s, 3H), 3.08 (d, *J* = 9.6 Hz, 1H), 2.97 (dd, *J* = 19.0, 3.8 Hz, 1H), 2.42 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 180.2, 176.5, 139.1, 137.1, 136.6, 134.6, 131.8, 131.5, 129.0, 128.7, 126.2, 122.1, 120.5, 120.0, 111.2, 102.3, 42.4, 37.1, 25.5, 21.3; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{20}H_{19}N_2O_2^+$ 319.1441; Found 319.1435.

3-(5-Fluoro-2-(1*H*-indol-2-yl)phenyl)-1-methylpyrrolidine-2,5-dione (28ca): The title



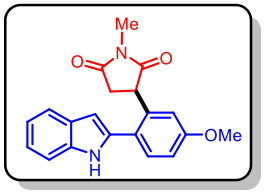
compound was purified by column chromatography on silica gel using EtOAc/ hexanes (1: 3, *v/v*) as an eluent; off white solid (41 mg, 53%); mp = 158-160 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.89 (s, 1H), 7.68 (d, *J* = 8.0 Hz, 1H), 7.60 (dd, *J* = 8.4, 5.6 Hz, 1H), 7.46 (d, *J* = 8.4 Hz, 1H), 7.25 (t, *J* = 7.6 Hz, 1H), 7.19 – 7.11 (m, 2H), 6.90 (dd, *J* = 9.6, 2.8 Hz, 1H), 6.61 (s, 1H), 4.40 (dd, *J* = 9.2, 3.6 Hz, 1H), 3.12 (s, 3H), 3.09 – 2.90 (m, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 179.4, 175.8, 162.9 (d, $^{1}J_{C\text{-}F}$ = 248.0 Hz), 137.0 (d, $^{3}J_{C\text{-}F}$ = 7.2 Hz), 136.6, 135.9, 133.5 (d, $^{3}J_{C\text{-}F}$ = 8.0 Hz), 130.8 (d, $^{4}J_{C\text{-}F}$ = 3.0 Hz), 128.6, 122.4, 120.6, 120.2, 115.4 (d, $^{2}J_{C\text{-}F}$ = 20.8 Hz), 112.8 (d, $^{2}J_{C\text{-}F}$ = 22.6 Hz), 111.3, 102.8, 42.6, 36.8, 25.6; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{19}H_{16}FN_2O_2^+$ 323.1190; Found 323.1182.

3-(2-(1*H*-Indol-2-yl)-5-(trifluoromethyl)phenyl)-1-methylpyrrolidine-2,5-dione (28da): The



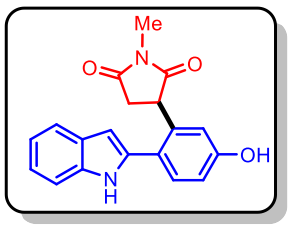
title compound was purified by column chromatography on silica gel using EtOAc/ hexanes (1: 3, *v/v*) as an eluent; off white solid (112 mg, 81%); mp = 154-156 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.05 (s, 1H), 7.76 (d, *J* = 8.0 Hz, 1H), 7.69 (t, *J* = 9.4 Hz, 2H), 7.47 (d, *J* = 8.4 Hz, 1H), 7.42 (s, 1H), 7.28 (d, *J* = 8.0 Hz, 1H), 7.19 (t, *J* = 7.4 Hz, 1H), 6.71 (s, 1H), 4.51 (dd, *J* = 9.4, 3.8 Hz, 1H), 3.19 (d, *J* = 10.0 Hz, 1H), 3.15 (s, 3H), 2.99 (dd, *J* = 19.0, 3.8 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 179.5, 175.6, 138.4, 136.1, 135.4, 135.4, 132.1, 131.2, 126.9 (q, $^1J_{C\text{-}F}$ = 268.0 Hz), 125.0, 124.9, 122.9, 122.8, 120.8, 120.4, 111.4, 103.6, 42.4, 36.8, 25.; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{20}H_{16}F_3N_2O_2^+$ 373.1158; Found 373.1081.

3-(2-(1*H*-Indol-2-yl)-5-methoxyphenyl)-1-methylpyrrolidine-2,5-dione (28ea): The title



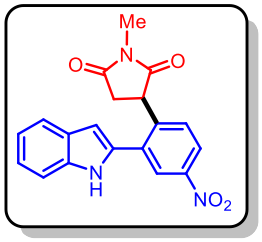
compound was purified by column chromatography on silica gel using EtOAc/ hexanes (1: 3, *v/v*) as an eluent; off white solid (46 mg, 62%); mp = 174-16 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.86 (s, 1H), 7.67 (d, *J* = 8.0 Hz, 1H), 7.55 (d, *J* = 8.4 Hz, 1H), 7.45 (d, *J* = 8.0 Hz, 1H), 7.22 (t, *J* = 7.2 Hz, 1H), 7.16 (t, *J* = 7.4 Hz, 1H), 6.95 (d, *J* = 8.4 Hz, 1H), 6.69 (s, 1H), 6.58 (s, 1H), 4.39 (d, *J* = 7.6 Hz, 1H), 3.87 (s, 3H), 3.11 (s, 3H), 3.07 – 2.94 (m, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 179.9, 176.2, 160.1, 136.9, 136.5, 136.3, 132.9, 128.7, 127.2, 122.0, 120.4, 120.0, 112.8, 112.1, 111.2, 102.2, 100.1, 55.5, 42.7, 36.9, 25.4; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{20}H_{19}N_2O_3^+$ 335.1390; Found 335.1369.

3-(5-Hydroxy-2-(1*H*-indol-2-yl)phenyl)-1-methylpyrrolidine-2,5-dione (28fa): The title



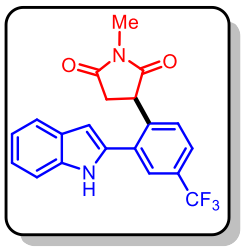
compound was purified by column chromatography on silica gel using EtOAc/ *n*-hexanes (1: 3, *v/v*) as an eluent; off white solid (38 mg, 50%); mp = 144-146 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.81 (s, 1H), 7.66 (d, *J* = 7.6 Hz, 1H), 7.47 (d, *J* = 8.4 Hz, 1H), 7.44 (d, *J* = 8.0 Hz, 1H), 7.22 (t, *J* = 6.9 Hz, 1H), 7.16 (t, *J* = 7.6 Hz, 1H), 6.86 (dd, *J* = 8.4, 2.4 Hz, 1H), 6.64 (d, *J* = 2.4 Hz, 1H), 6.57 – 6.56 (m, 1H), 5.50 (s, 1H), 4.38 (dd, *J* = 9.2, 3.6 Hz, 1H), 3.10 (s, 3H), 3.06 – 2.90 (m, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 179.8, 176.3, 156.3, 136.7, 136.6, 136.5, 133.0, 128.7, 127.2, 122.0, 120.4, 120.0, 115.4, 112.6, 111.2, 102.2, 42.6, 37.0, 25.5; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{19}H_{17}N_2O_3^+$ 321.1234; Found 321.1214.

3-(2-(1*H*-Indol-2-yl)-4-nitrophenyl)-1-methylpyrrolidine-2,5-dione (28ga): The title



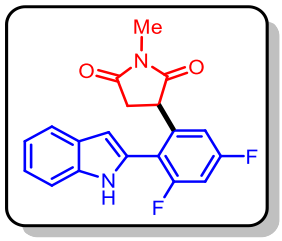
compound was purified by column chromatography on silica gel using EtOAc/ hexanes (1: 3, *v/v*) as an eluent; off white solid (55 mg, 74%); mp = 202-204 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.01 (s, 1H), 8.49 (d, *J* = 2.8 Hz, 1H), 8.26 (dd, *J* = 8.8, 2.8 Hz, 1H), 7.72 (d, *J* = 8.0 Hz, 1H), 7.48 (dd, *J* = 8.0, 0.8 Hz, 1H), 7.38 (d, *J* = 8.8 Hz, 1H), 7.31 – 7.27 (m, 1H), 7.22 – 7.18 (m, 1H), 6.77 (dd, *J* = 2.0, 0.8 Hz, 1H), 4.56 (dd, *J* = 9.2, 3.6 Hz, 1H), 3.22 – 3.18 (m, 1H), 3.15 (s, 3H), 2.99 (dd, *J* = 19.0, 4.0 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 178.8, 175.3, 147.3, 141.4, 137.0, 136.5, 134.3, 128.5, 127.1, 126.2, 123.4, 123.1, 120.9, 120.6, 111.5, 104.2, 42.6, 36.9, 25.7; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{19}H_{16}N_3O_4^+$ 350.1135; Found 350.1134.

3-(2-(1*H*-Indol-2-yl)-4-(trifluoromethyl)phenyl)-1-methylpyrrolidine-2,5-dione (28ha): The



title compound was purified by column chromatography on silica gel using EtOAc/ hexanes (1: 4, *v/v*) as an eluent; off white solid (51 mg, 73%); mp = 128-130 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.99 (s, 1H), 7.89 (s, 1H), 7.70 (t, *J* = 8.4 Hz, 2H), 7.47 (d, *J* = 8.0 Hz, 1H), 7.32 (d, *J* = 8.4 Hz, 1H), 7.29 – 7.25 (m, 1H), 7.19 (t, *J* = 7.6 Hz, 1H), 6.72 (s, 1H), 4.50 (dd, *J* = 9.6, 3.6 Hz, 1H), 3.17 (d, *J* = 10.4 Hz, 1H), 3.14 (s, 3H), 2.97 (dd, *J* = 18.4, 3.6 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 179.3, 175.7, 138.5, 141.4, 136.9, 135.6, 135.3, 130.6 (d, $^{2}J_{C\text{-}F}$ = 32.9 Hz), 128.5, 128.4 (q, $^{4}J_{C\text{-}F}$ = 3.5 Hz), 126.5, 125.5 (q, $^{4}J_{C\text{-}F}$ = 3.1 Hz), 123.5 (q,$^{1}J_{C\text{-}F}$ = 269.8 Hz), 122.8, 120.8, 120.4, 111.4, 103.5, 42.5, 36.9, 25.6; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{20}H_{16}F_3N_2O_2^+$ 373.1158; Found 373.1126.

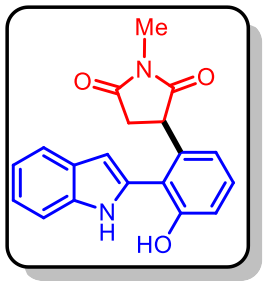
3-(3,5-Difluoro-2-(1*H*-indol-2-yl)phenyl)-1-methylpyrrolidine-2,5-dione (28ia): The title



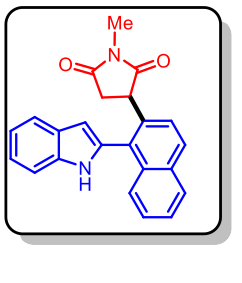
compound was purified by column chromatography on silica gel using EtOAc/ hexanes (1: 4, *v/v*) as an eluent; off white solid (46 mg, 61%); mp = 190-192 °C; H NMR (400 MHz, $CDCl_3$) δ 9.43 (s, 1H), 7.69 (d, *J* = 7.6 Hz, 1H), 7.45 (d, *J* = 8.0 Hz, 1H), 7.29 – 7.24 (m, 1H), 7.17 (t, *J* = 7.4 Hz, 1H), 6.95 (dd, *J* = 8.8, 2.4 Hz, 1H), 6.75 (d, *J* = 9.2 Hz, 1H), 6.68 (s, 1H), 4.26 (dd, *J* = 9.6, 4.4 Hz, 1H), 3.13 – 3.08 (m, 1H), 3.05 (s, 3H), 2.86 (dd, *J* = 18.8, 4.4 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 178.4, 175.4, 162.9 (d, $^{1}J_{C\text{-}F}$ = 249.8 Hz), 162.8 (d, $^{1}J_{C\text{-}F}$ = 253.1 Hz), 139.9 (dd, $^{3}J_{C\text{-}F}$ = 8.3, 8.8 Hz), 136.5, 128.2, 127.2, 122.7, 120.8, 120.3, 119.1 (dd, $^{3}J_{C\text{-}F}$ = 15.7, 14.5 Hz), 111.2, 109.2 (d, $^{2}J_{C\text{-}F}$ = 22.0 Hz), 109.2 (d, $^{2}J_{C\text{-}F}$ = 22.4 Hz), 105.3 (d, $^{4}J_{C\text{-}F}$ =

2.3 Hz), 104.4, 104.1, 103.8, 42.8, 37.0, 25.5; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{19}H_{15}F_2N_2O_2^+$ 341.1096; Found 341.1075.

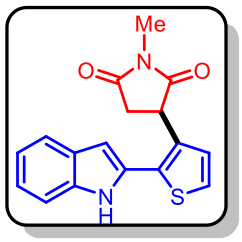
3-(3-Hydroxy-2-(1*H*-indol-2-yl)phenyl)-1-methylpyrrolidine-2,5-dione (28ja): The title compound was purified by column chromatography on silica gel using EtOAc/ hexanes (1: 3, *v/v*) as an eluent; off white solid (64 mg, 83%); mp = 188-190 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (s, 1H), 7.45 (d, *J* = 8.0 Hz, 1H), 7.38 (t, *J* = 8.6 Hz, 2H), 7.30 – 7.26 (m, 1H), 7.20 – 7.13 (m, 2H), 7.10 (d, *J* = 8.4 Hz, 1H), 7.05 (t, *J* = 7.6 Hz, 1H), 6.99 (s, 1H), 4.18 (dd, *J* = 5.2, 9.6 Hz, 1H), 3.21 (dd, *J* = 18.8, 5.2 Hz, 1H), 3.16 (s, 3H), 3.14 – 3.09 (m, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 184.1, 181.7, 159.8, 141.1, 138.8, 136.2, 134.8, 130.4, 126.7, 124.5, 124.4, 123.4, 122.3, 121.3, 116.6, 112.9, 42.9, 40.8, 29.7; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{19}H_{17}N_2O_3^+$ 321.1234; Found 321.1209.



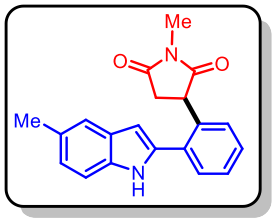
3-(1-(1*H*-Indol-2-yl)naphthalen-2-yl)-1-methylpyrrolidine-2,5-dione (28ka):): The title compound was purified by column chromatography on silica gel using EtOAc/ hexanes (1: 4, *v/v*) as an eluent; off white solid (64 mg, 88%); mp = 194-196 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.56 (s, 1H), 7.99 (t, *J* = 9.2 Hz, 2H), 7.90 (d, *J* = 8.0 Hz, 1H), 7.75 (d, *J* = 8.0 Hz, 1H), 7.55 (t, *J* = 7.4 Hz, 1H), 7.50 (d, *J* = 8.0 Hz, 2H), 7.30 – 7.22 (m, 3H), 6.70 (s, 1H), 4.20 (dd, *J* = 9.2, 4.8 Hz, 1H), 3.10 (s, 3H), 3.04 – 3.00 (m, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 179.4, 176.2, 136.3, 133.7, 133.3, 133.1, 132.7, 132.1, 130.2, 128.5, 127.9, 127.2, 126.9, 126.6, 122.2, 122.0, 120.5, 120.2, 111.3, 104.8, 43.5, 36.8, 25.4; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{23}H_{19}N_2O_2^+$ 355.1441; Found 355.1405.



3-(2-(1*H*-Indol-2-yl)thiophen-3-yl)-1-methylpyrrolidine-2,5-dione (28la): The title compound was purified by column chromatography on silica gel using EtOAc/ hexanes (1: 4, *v/v*) as an eluent; off white solid (34 mg, 43%); mp = 136-138 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.16 (s, 1H), 7.66 (d, *J* = 7.6 Hz, 1H), 7.46 (d, *J* = 8.0 Hz, 1H), 7.37 (d, *J* = 4.8 Hz, 1H), 7.25 (t, *J* = 7.6 Hz, 1H), 7.16 (t, *J* = 7.2 Hz, 1H), 6.92 (d, *J* = 5.2 Hz, 1H), 6.72 (s, 1H), 4.40 (dd, *J* = 8.4, 2.4 Hz, 1H), 3.22 – 3.17 (m, 1H), 3.15 (s, 3H), 3.06 – 3.01 (m, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 179.5, 176.0, 136.9, 134.4, 131.8, 129.9, 128.8, 126.3, 125.1, 122.7, 120.6, 120.3, 111.4, 103.3, 40.2, 36.1, 25.5; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{17}H_{15}N_2O_2S^+$ 311.0849; Found 311.0828.

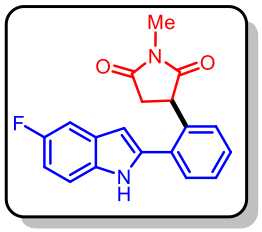


1-Methyl-3-(2-(5-methyl-1*H*-indol-2-yl)phenyl)pyrrolidine-2,5-dione (28ma): The title



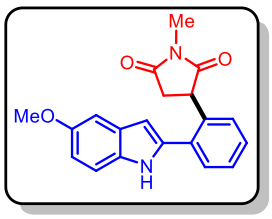
compound was purified by column chromatography on silica gel using EtOAc/ hexanes (1: 9, *v/v*) as an eluent; off white solid (43 mg, 55%); mp = 192-194 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.86 (s, 1H), 7.63 – 7.60 (m, 1H), 7.47 (s, 1H), 7.43 – 7.40 (m, 2H), 7.35 (d, *J* = 8.0 Hz, 1H), 7.19 – 7.17 (m, 1H), 7.07 (dd, *J* = 8.4, 1.8 Hz, 1H), 6.56 (s, 1H), 4.43 (dd, *J* = 9.2, 3.6 Hz, 1H), 3.11 (s, 3H), 3.09 – 2.93 (m, 2H), 2.49 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 180.1, 176.3, 137.0, 135.0, 134.9, 131.5, 129.3, 129.0, 128.9, 128.1, 125.7, 123.9, 120.1, 110.9, 102.1, 100.0, 42.5, 37.1, 25.4, 21.5; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{20}H_{19}N_2O_2^+$ 319.1441; Found 319.1426.

3-(2-(5-Fluoro-1*H*-indol-2-yl)phenyl)-1-methylpyrrolidine-2,5-dione (28na): The title



compound was purified by column chromatography on silica gel using EtOAc/ hexanes (1: 4, *v/v*) as an eluent; off white solid (39 mg, 51%); mp = 164-166 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.13 (s, 1H), 7.62 (d, *J* = 6.8 Hz, 1H), 7.44 – 7.29 (m, 4H), 7.19 (d, *J* = 7.2 Hz, 1H), 6.99 (t, *J* = 9.2 Hz, 1H), 6.61 (s, 1H), 4.40 (d, *J* = 6.8 Hz, 1H), 3.12 (s, 3H), 3.02 – 2.96 (m, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 180.2, 176.3, 158.1 (d, $^{1}J_{C\text{-}F}$ = 233.7 Hz), 138.8, 134.6, 134.4, 133.2, 131.6, 129.2, 129.0 (d, $^{3}J_{C\text{-}F}$ = 10.6 Hz), 128.2, 125.7, 111.9 (d, $^{3}J_{C\text{-}F}$ = 9.4 Hz), 110.6 (d, $^{2}J_{C\text{-}F}$ = 26.1 Hz), 105.2 (d, $^{2}J_{C\text{-}F}$ = 23.4 Hz), 102.6 (d, $^{4}J_{C\text{-}F}$ = 4.5 Hz), 42.5, 37.0, 25.5; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{19}H_{16}FN_2O_2^+$ 323.1190; Found 323.1156.

3-(2-(5-Methoxy-1*H*-indol-2-yl)phenyl)-1-methylpyrrolidine-2,5-dione (28oa): The title



compound was purified by column chromatography on silica gel using EtOAc/ hexanes (1: 3, *v/v*) as an eluent; semi solid (58 mg, 65%); mp = 174-176 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.48 – 7.40 (m, 3H), 7.30 (d, *J* = 6.8 Hz, 2H), 7.04 (s, 1H), 6.76 (d, *J* = 8.4 Hz, 1H), 6.48 (s, 1H), 4.58 – 4.54 (m, 1H), 3.73 (s, 3H), 3.18 (dd, *J* = 18.4, 9.6 Hz, 1H), 2.82 (s, 3H), 2.70 – 2.65 (m, 1H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 179.3, 177.0, 153.9, 137.0, 136.8, 134.0, 132.0, 130.4, 129.0, 128.1, 128.6, 127.1, 112.5, 112.2, 102.6, 102.0, 55.8, 43.4, 38.4, 25.2; HRMS (ESI) *m/z*: [M + H] Calcd for $C_{20}H_{19}N_2O_3^+$ 335.1390; Found 335.1333.

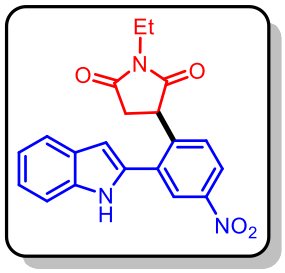
3-(2-(1*H*-Indol-2-yl)phenyl)-1-ethylpyrrolidine-2,5-dione (28ab): The title compound was purified by column chromatography on silica gel using EtOAc/ hexanes (1: 9, *v/v*) as an eluent; off white solid (58 mg, 70%); mp = 146-148 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.07 (s, 1H), 7.69 (d, *J* = 8.0 Hz, 1H), 7.63 (d, *J* = 7.6 Hz, 1H), 7.41 – 7.42 (m, 3H), 7.28 – 7.17 (m, 3H), 6.65 (s, 1H), 4.41 (d, *J* = 6.8 Hz, 1H), 3.6 (d, *J* = 5.6 Hz, 2H), 3.13 – 2.92 (m, 2H), 1.25 (t, *J* = 8.0 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 179.9, 176.2, 137.1, 136.6, 135.0, 134.8, 131.6, 129.0, 128.7, 128.1, 125.4, 122.2, 120.6, 120.1, 111.3, 102.5, 42.3, 37.2, 34.4, 13.0; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{20}H_{19}N_2O_2^+$ 319.1441; Found 319.1402.

1-Ethyl-3-(5-fluoro-2-(1*H*-indol-2-yl)phenyl)pyrrolidine-2,5-dione (28cb): The title compound was purified by column chromatography on silica gel using EtOAc/ hexanes (1: 4, *v/v*) as an eluent; off white solid (42 mg, 52%); mp = 124-126 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.95 (s, 1H), 7.69 (d, *J* = 8.0 Hz, 1H), 7.60 (dd, *J* = 8.4, 6.0 Hz, 1H), 7.46 (d, *J* = 8.0 Hz, 1H), 7.25 (t, *J* = 7.6 Hz, 1H), 7.25 (t, *J* = 7.8 Hz, 1H), 7.14 – 7.10 (m, 1H), 6.88 (dd, *J* = 9.6, 2.4 Hz, 1H), 6.61 (s, 1H), 4.38 (dd, *J* = 9.6, 4.0 Hz, 1H), 3.69 (q, *J* = 8.0 Hz, 2H), 3.11 (dd, *J* = 12.2, 9.6 Hz, 1H), 2.90 (dd, *J* = 18.8, 3.6 Hz, 1H), 1.26 (t, *J* = 8.0 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 179.2, 175.6, 163.0 (d, $^1J_{C\text{-}F}$ = 247.8 Hz), 137.2 (d, $^3J_{C\text{-}F}$ = 6.9 Hz), 136.6, 135.9, 133.4 (d, $^3J_{C\text{-}F}$ = 8.2 Hz), 130.9 (d, $^4J_{C\text{-}F}$ = 3.2 Hz), 128.6, 122.3, 120.6, 120.2, 115.3 (d, $^2J_{C\text{-}F}$ = 21.0 Hz), 112.6 (d, $^2J_{C\text{-}F}$ = 22.6 Hz), 111.3, 102.7, 42.5, 36.9, 34.5, 12.9; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{20}H_{18}FN_2O_2^+$ 337.1347; Found 337.1326.

3-(2-(1*H*-Indol-2-yl)-5-methoxyphenyl)-1-ethylpyrrolidine-2,5-dione (28eb): The title compound was purified by column chromatography on silica gel using EtOAc/ hexanes (1: 4, *v/v*) as an eluent; off white solid (48 mg, 61%); mp = 144-146 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.91 (s, 1H), 7.67 (d, *J* = 7.6 Hz, 1H), 7.55 (d, *J* = 8.4 Hz, 1H), 7.45 (d, *J* = 8.4 Hz, 1H), 7.23 (t, *J* = 7.4 Hz, 1H), 7.16 (t, *J* = 7.4 Hz, 1H), 6.97 – 6.94 (m, 1H), 6.67 (d, *J* = 2.8 Hz, 1H), 6.58 (s, 1H), 4.37 (dd, *J* = 10.0, 4.0 Hz, 1H), 3.86 (s, 3H), 3.68 (q, *J* = 7.2 Hz, 2H), 3.12 – 3.05 (m, 1H), 2.96 – 2.90 (m, 1H), 1.25 (t, *J* = 8.0 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 179.6, 176.0, 160.1, 136.9, 136.5, 136.5, 132.9, 128.8, 127.2, 122.0, 120.4, 120.0, 112.8,

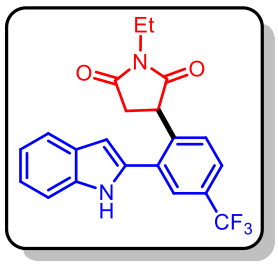
111.9, 111.2, 102.2, 55.5, 42.5, 37.0, 34.4, 13.0; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{21}H_{21}N_2O_3^+$, 349.1547; Found, 349.1538.

3-(2-(1*H*-Indol-2-yl)-4-nitrophenyl)-1-ethylpyrrolidine-2,5-dione (28gb): The title compound



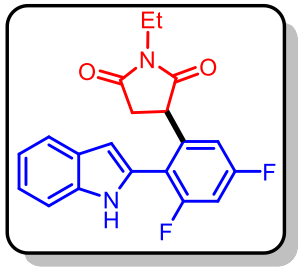
was purified by column chromatography on silica gel using EtOAc/ hexanes (1: 4, *v/v*) as an eluent; off white solid (62 mg, 81%); mp = 214-216 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.08 (s, 1H), 8.49 (d, *J* = 2.4 Hz, 1H), 8.27 (dd, *J* = 6.4, 2.4 Hz, 1H), 7.72 (d, *J* = 8.0 Hz, 1H), 7.49 (d, *J* = 8.0 Hz, 1H), 7.35 (d, *J* = 8.8 Hz, 1H), 7.31 – 7.28 (m, 1H), 7.20 (t, *J* = 7.4 Hz, 1H), 6.78 (s, 1H), 4.54 (dd, *J* = 9.6, 3.6 Hz, 1H), 3.71 (q, *J* = 8.0 Hz, 2H), 3.17 (dd, *J* = 18.8, 9.2 Hz, 1H), 2.96 (dd, *J* = 18.8, 3.6 Hz, 1H), 1.27 (t, *J* = 8.0 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 178.6, 175.2, 147.3, 141.6, 137.0, 136.5, 134.4, 128.5, 126.9, 126.3, 123.4, 123.1, 121.0, 120.6, 111.5, 104.1, 42.5, 36.9, 34.7, 13.0; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{20}H_{18}N_3O_4^+$ 364.1292; Found 364.1271.

3-(2-(1*H*-Indol-2-yl)-4-(trifluoromethyl)phenyl)-1-ethylpyrrolidine-2,5-dione (28hb): The



title compound was purified by column chromatography on silica gel using EtOAc/ hexanes (1: 4, *v/v*) as an eluent; off white solid (56 mg, 77%); mp = 142-144 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.07 (s, 1H), 7.90 (s, 1H), 7.70 (t, *J* = 8.4 Hz, 2H), 7.48 (d, *J* = 8.0 Hz, 1H), 7.31 – 7.26 (m, 2H), 7.19 (t, *J* = 7.4 Hz, 1H), 6.72 (s, 1H), 4.48 (dd, *J* = 9.6, 4.6 Hz, 1H), 3.70 (q, *J* = 8.0 Hz, 2H), 3.14 (dd, *J* = 19.0, 9.4 Hz, 1H), 2.94 (dd, *J* = 18.8, 4.0 Hz, 1H), 1.26 (t, *J* = 8.0 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 179.1, 175.6, 138.7, 136.9, 135.6, 135.3, 130.7, 130.4, 128.7, 128.4 (q, $^4J_{C\text{-}F}$ = 3.5 Hz), 126.2, 125.6 (q, $^4J_{C\text{-}F}$ = 3.5 Hz), 122.8, 123.6 (q, $^1J_{C\text{-}F}$ = 273.8 Hz), 120.8, 120.4, 111.4, 103.5, 42.3, 36.1, 34.6, 12.1; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{21}H_{18}F_3N_2O_2^+$ 387.1315; Found 387.1308.

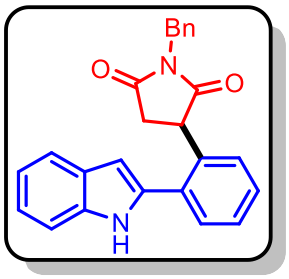
3-(3,5-Difluoro-2-(1*H*-indol-2-yl)phenyl)-1-ethylpyrrolidine-2,5-dione (28ib): The title



compound was purified by column chromatography on silica gel using EtOAc/ hexanes (1: 4, *v/v*) as an eluent; off white solid (55 mg, 71%); mp = 124-126 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.54 (s, 1H), 7.70 (d, *J* = 8.0 Hz, 1H), 7.47 (d, *J* = 8.4 Hz, 1H), 7.25 (d, *J* = 7.2 Hz, 1H), 7.20 – 7.16 (m, 1H), 6.95 (td, *J* = 8.8, 2.4 Hz, 1H), 6.72 (d, *J* = 9.2 Hz, 1H), 6.69 (s, 1H), 4.26 (dd, *J* = 9.4, 4.2 Hz, 1H), 3.64 (q, *J* = 8.0 Hz, 2H), 3.09 (dd, *J* = 18.6, 9.4 Hz,

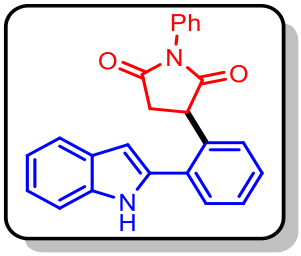
1H), 2.84 (dd, J = 18.8, 4.4 Hz, 1H), 1.22 (t, J = 8.0 Hz, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 178.3, 175.2, 162.9 (dd, $^{1}J_{C\text{-}F}$ = 250.2, 13.1 Hz), 161.2 (dd, $^{1}J_{C\text{-}F}$ = 249.7, 12.7 Hz), 140.1 (dd, $^{3}J_{C\text{-}F}$ = 8.4, 3.0 Hz), 136.5, 128.3, 127.3, 122.6, 120.8, 120.2, 119.2 (dd, $^{3}J_{C\text{-}F}$ = 16.4, 4.1 Hz), 111.3, 108.9 (dd, $^{2}J_{C\text{-}F}$ = 22.3, 3.8 Hz), 105.3 (d, $^{4}J_{C\text{-}F}$ = 2.4 Hz), 104.1 (dd, $^{2}J_{C\text{-}F}$ = 27.0, 25.1 Hz), 42.6, 37.0, 34.5, 12.9; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{20}H_{17}F_2N_2O_2^+$ 355.1253; Found 355.1215.

3-(2-(1*H*-Indol-2-yl)phenyl)-1-benzylpyrrolidine-2,5-dione (28ac): The title compound was



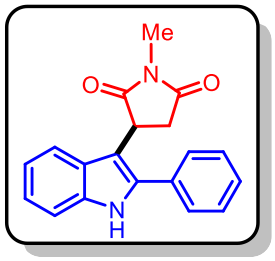
purified by column chromatography on silica gel using EtOAc/ hexanes (1: 4, *v/v*) as an eluent; off white solid (69 mg, 70%); mp = 88-90 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.53 – 7.41 (m, 5H), 7.31 – 7.25 (m, 5H), 7.12 – 7.02 (m, 3H), 6.58 (s, 1H), 4.68 – 4.66 (m, 1H), 4.56 (s, 2H), 3.32 – 3.25 (m, 1H), 2.77 (d, J = 18.4 Hz, 1H); $^{13}C\{^{1}H\}$ NMR (100 MHz, DMSO-d_6) δ 183.8, 181.6, 141.7, 141.6, 141.2, 140.9, 138.7, 135.3, 133.9, 133.8, 133.3, 132.9, 132.8, 132.7, 132.5, 126.8, 125.3, 124.6, 116.5, 107.5, 48.0, 47.0, 43.2; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{25}H_{21}N_2O_2^+$ 381.1598; Found 381.1535.

3-(2-(1*H*-Indol-2-yl)phenyl)-1-phenylpyrrolidine-2,5-dione (28ad): The title compound was



purified by column chromatography on silica gel using EtOAc/ hexanes (1: 4, *v/v*) as an eluent; off white solid (64 mg, 68%); mp = 106-108 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.35 (s, 1H), 7.56 (d, J = 7.6 Hz, 1H), 7.52 (d, J = 7.2 Hz, 2H), 7.47 – 7.40 (m, 6H), 7.20 (d, J = 7.2 Hz, 2H), 7.14 (t, J = 7.4 Hz, 1H), 7.04 (t, J = 7.4 Hz, 1H), 6.57 (s, 1H), 4.76 (dd, J = 9.2, 5.6 Hz, 1H), 3.36 (dd, J = 18.4, 9.6 Hz, 1H), 2.89 (dd, J = 18.4, 5.6 Hz, 1H); $^{13}C\{^{1}H\}$ NMR (100 MHz, DMSO-d_6) δ 178.3, 176.0, 137.1, 136.9, 136.3, 134.0, 132.9, 130.7, 129.3, 129.3, 129.1, 128.9, 128.6, 128.0, 127.7, 122.0, 120.5, 119.9, 111.8, 102.7, 43.1, 38.7; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{24}H_{19}N_2O_2^+$ 367.1441; Found 367.1381.

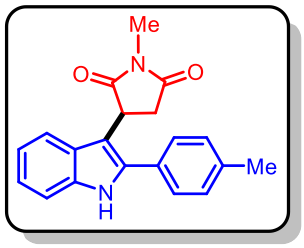
1-Methyl-3-(2-phenyl-1*H*-indol-3-yl)pyrrolidine-2,5-dione (27aa): The title compound was



purified by column chromatography on silica gel using EtOAc/ hexanes (1: 4, *v/v*) as an eluent; off white solid (62 mg, 79%); mp = 210-212 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (s, 1H), 7.64 (d, J = 6.8 Hz, 2H), 7.51 (t, J = 7.0 Hz, 2H), 7.47 (d, J = 7.2 Hz, 1H), 7.42 (d, J = 8.0 Hz, 1H), 7.24 (t, J = 7.4 Hz, 1H), 7.20 (d, J = 7.6 Hz, 1H), 7.13 (t, J = 7.2 Hz, 1H), 4.42 (t, J = 7.0 Hz, 1H), 3.16 (s, 3H), 3.13 (d, J = 7.6 Hz, 2H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ

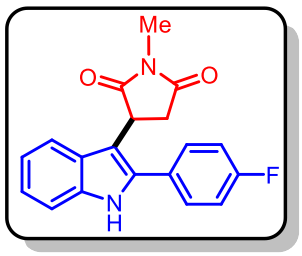
178.8, 176.7, 137.6, 136.0, 131.9, 129.1, 128.8, 128.7, 126.2, 122.8, 120.5, 118.2, 111.6, 107.8, 37.9, 36.2, 25.2; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{19}H_{17}N_2O_2^+$ 305.1285; Found 305.1293.

1-Methyl-3-(2-(*p*-tolyl)-1*H*-indol-3-yl)pyrrolidine-2,5-dione (27ba): The title compound was



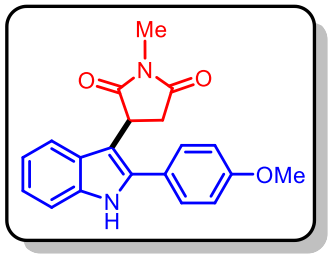
purified by column chromatography on silica gel using EtOAc/ hexanes (1: 4, *v/v*) as an eluent; off white solid (54 mg, 71%); mp = 124-126 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (s, 1H), 7.53 – 7.52 (m, 2H), 7.41 (dd, J = 7.6, 2.0 Hz, 1H), 7.32 – 7.28 (m, 2H), 7.24 – 7.21 (m, 1H), 7.19 (d, J = 7.2 Hz, 1H), 7.14 – 7.10 (m, 1H), 4.42 (t, J = 7.0 Hz, 1H), 3.17 (s, 3H), 3.12 (d, J = 5.6 Hz, 2H), 2.45 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 178.9, 176.8, 138.8, 137.7, 135.9, 129.8, 129.1, 128.7, 126.2, 122.6, 120.4, 118.1, 111.5, 107.5, 37.9, 36.2, 25.2, 21.3; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{20}H_{19}N_2O_2^+$ 319.1441; Found 319.1435.

3-(2-(4-Fluorophenyl)-1*H*-indol-3-yl)-1-methylpyrrolidine-2,5-dione (27ca): The title



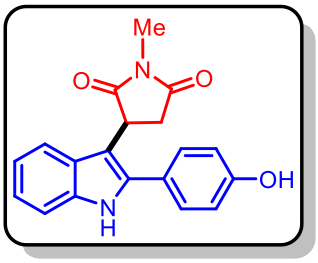
compound was purified by column chromatography on silica gel using EtOAc/ hexanes (1: 4, *v/v*) as an eluent; off white solid (30 mg, 42%); mp = 204-206 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (s, 1H), 7.66 – 7.62 (m, 2H), 7.42 (d, J = 8.4 Hz, 1H), 7.27 – 7.25 (m, 1H), 7.23 – 7.22 (m, 1H), 7.21 (d, J = 3.2 Hz, 1H), 7.19 (d, J = 2.4 Hz, 1H), 7.15 – 7.11 (m, 1H), 4.35 (t, J = 7.6 Hz, 1H), 3.17 (s, 3H), 3.14 (d, J = 7.2 Hz, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 178.8, 176.6, 163.0 (d, $^1J_{C\text{-}F}$ = 248 Hz), 136.6, 136.0, 130.7 (d, $^3J_{C\text{-}F}$ = 8.0 Hz), 127.9 (d, $^4J_{C\text{-}F}$ = 3.0 Hz), 126.0, 122.9, 120.6, 118.2, 116.2 (d, $^2J_{C\text{-}F}$ = 22.0 Hz), 111.6, 108.0, 37.8, 36.0, 25.2; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{19}H_{16}FN_2O_2^+$ 323.1190; Found 323.1182.

3-(2-(4-Methoxyphenyl)-1*H*-indol-3-yl)-1-methylpyrrolidine-2,5-dione (27ea): The title

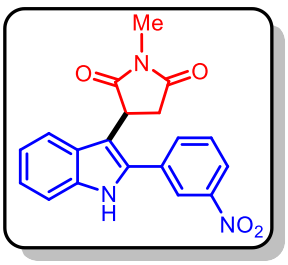


compound was purified by column chromatography on silica gel using EtOAc/ hexanes (1: 4, *v/v*) as an eluent; off white solid (47 mg, 62%); mp = 214-216 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (s, 1H), 7.56 (d, J = 8.8 Hz, 2H), 7.39 (d, J = 8.0 Hz, 1H), 7.24 – 7.20 (m, 1H), 7.18 (d, J = 8.0 Hz, 1H), 7.11 (t, J = 7.4 Hz, 1H), 7.03 (d, J = 8.8 Hz, 2H), 4.38 (t, J = 7.2 Hz, 1H), 3.89 (s, 3H), 3.16 (s, 3H), 3.12 (d, J = 7.2 Hz, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 179.0, 176.8, 160.1, 137.5, 135.9, 130.1, 126.2, 124.3, 122.5, 120.4, 118.0, 114.5, 111.4, 107.3, 55.4, 37.9, 36.1, 25.2; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{20}H_{19}N_2O_3^+$ 335.1390; Found 335.1376.

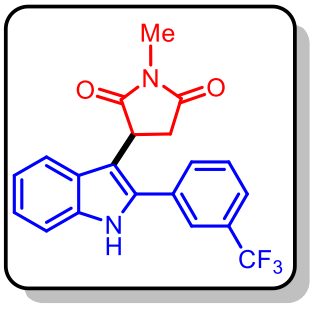
3-(2-(4-Hydroxyphenyl)-1*H*-indol-3-yl)-1-methylpyrrolidine-2,5-dione (27fa): The title compound was purified by column chromatography on silica gel using EtOAc/ hexanes (1: 3, *v/v*) as an eluent; off white solid (39 mg, 51%); mp = 238-240 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.28 (s, 1H), 9.73 (s, 1H), 7.45 (d, J = 6.0 Hz, 2H), 7.38 (d, J = 7.2 Hz, 1H), 7.08 (t, J = 7.0 Hz, 2H), 6..97 – 6.92 (m, 3H), 4.40 – 4.39 (m, 1H), 3.26 – 3.20 (m, 1H), 2.97 (s, 3H), 2.81 – 2.77 (m, 1H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 179.6, 177.2, 158.0, 138.0, 136.3, 130.4, 126.6, 123.2, 121.7, 119.7, 118.0, 116.1, 112.0, 106.6, 37.9, 36.5, 25.2; HRMS (ESI) *m/z*: [M + H]$^+$ Calcd for $C_{19}H_{17}N_2O_3^+$ 321.1234; Found 321.1212.



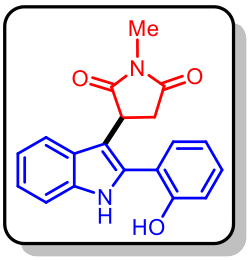
1-Methyl-3-(2-(3-nitrophenyl)-1*H*-indol-3-yl)pyrrolidine-2,5-dione (27ga): The title compound was purified by column chromatography on silica gel using EtOAc/ hexanes (1: 1, *v/v*) as an eluent; yellow solid (52 mg, 37%); mp = 162-164 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.45 (s, 1H), 8.30 (d, J = 8.0 Hz, 1H), 8.07 (d, J = 7.6 Hz, 1H), 7.84 (t, J = 7.8 Hz, 1H), 7.49 (d, J = 8.0 Hz, 1H), 7.23 – 7.16 (m, 2H), 7.06 (t, J = 7.4 Hz, 1H), 4.49 (dd, J = 8.8, 4.4 Hz, 1H), 3.27 (dd, J = 18.0, 9.6 Hz, 1H), 2.99 (s, 3H), 2.90 – 2.83 (m, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 184.1, 181.1, 153.3, 141.4, 139.1, 139.9, 139.7, 138.4, 135.8, 130.9, 128.0, 127.9, 125.1, 123.4, 117.3, 113.8, 42.5, 41.1, 29.1; HRMS (ESI) *m/z*: [M + H]$^+$ Calcd for $C_{19}H_{16}N3O_4^+$ 350.1135; Found 350.1134.



1-Methyl-3-(2-(3-(trifluoromethyl)phenyl)-1*H*-indol-3-yl)pyrrolidine-2,5-dione (27ha): The title compound was purified by column chromatography on silica gel using EtOAc/ hexanes (1: 3, *v/v*) as an eluent; off white solid (64 mg, 46%); mp = 152-154 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.66 (s, 1H), 7.96 (d, J = 12.4 Hz, 2H), 7.83 – 7.77 (m, 2H), 7.45 (d, J = 8.0 Hz, 1H), 7.20 – 7.15 (m, 2H), 7.03 (t, J = 7.8 Hz, 1H), 4.45 (dd, J = 9.2, 4.8 Hz, 1H), 3.26 (dd, J = 18.4, 10.0 Hz, 1H), 2.98 (s, 3H), 2.89 – 2.83 (m, 1H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 179.3, 177.0, 136.8, 136.6, 135.9, 135.7, 135.0, 133.3 (d, $^4J_{C\text{-}F}$ = 5.4 Hz), 133.0, 130.5, 130.1 (q, $^2J_{C\text{-}F}$ = 31.5 Hz), 126.3 (d, $^4J_{C\text{-}F}$ = 4.0 Hz), 125.3 (q, $^2J_{C\text{-}F}$ = 20.2 Hz), 124.5 (q, $^1J_{C\text{-}F}$ = 270.9 Hz), 122.8, 120.1, 118.7, 112.4 (d, $^4J_{C\text{-}F}$ = 5.2 Hz), 108.8 (d, $^4J_{C\text{-}F}$ = 2.8 Hz), 37.8, 36.5, 25; HRMS (ESI) *m/z*: [M + H]$^+$ Calcd for $C_{20}H_{16}F_3N_2O_2^+$ 373.1158; Found 373.1126.

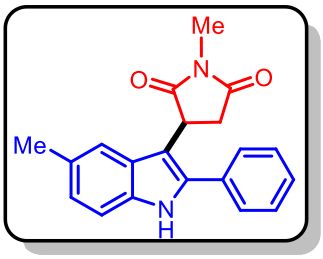


3-(2-(2-Hydroxyphenyl)-1*H*-indol-3-yl)-1-methylpyrrolidine-2,5-dione (27ja): The title



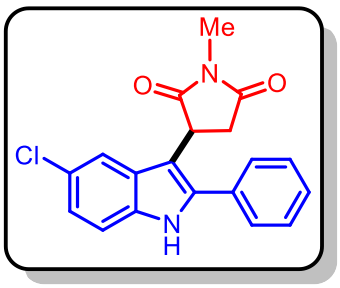
compound was purified by column chromatography on silica gel using EtOAc/ hexanes (1: 3, *v/v*) as an eluent; off white solid (32 mg, 41%); mp = 216-218 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.19 (s, 1H), 7.48 – 7.41 (m, 2H), 7.25 (t, *J* = 7.8 Hz, 1H), 7.14 (t, *J* = 7.4 Hz, 2H), 7.04 – 7.01 (m, 2H), 6.93 (t, *J* = 7.6 Hz, 1H), 4.32 (dd, *J* = 9.6, 5.2 Hz, 1H), 3.15 (dd, *J* = 18.4, 9.6 Hz, 1H), 3.07 (s, 3H), 3.04 – 2.99 (m, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 184.0, 181.7, 160.0, 141.0, 139.0, 136.3, 134.7, 130.6, 126.5, 124.4, 124.2, 123.7, 122.2, 121.2, 116.6, 112.9, 43.0, 40.9, 29.7; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{19}H_{17}N_2O_3^+$ 321.1234; Found 321.1233.

1-Methyl-3-(5-methyl-2-phenyl-1*H*-indol-3-yl)pyrrolidine-2,5-dione (27ka): The title



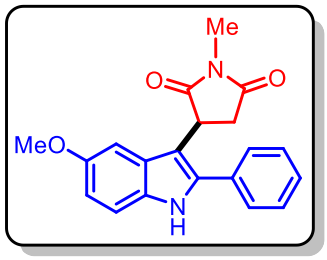
compound was purified by column chromatography on silica gel using EtOAc/ hexanes (1: 4, *v/v*) as an eluent; off white solid (45 mg, 58%); mp = 216-218 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (s, 1H), 7.61 (d, *J* = 6.8 Hz, 2H), 7.50 – 7.43 (m, 3H), 7.27 (d, *J* = 8.4 Hz, 1H), 7.05 (d, *J* = 8.0 Hz, 1H), 6.94 (s, 1H), 4.39 (t, *J* = 7.6 Hz, 1H), 3.16 (s, 3H), 3.11 (d, *J* = 7.2 Hz, 2H), 2.43 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 179.0, 176.8, 137.7, 134.4, 132.1, 129.8, 129.0, 128.8, 128.6, 126.4, 124.4, 117.8, 111.3, 107.2, 37.9, 36.1, 25.2, 21.7; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{20}H_{19}N_2O_2^+$ 319.1441; Found 319.1426.

3-(5-Chloro-2-phenyl-1*H*-indol-3-yl)-1-methylpyrrolidine-2,5-dione (27pa): The title

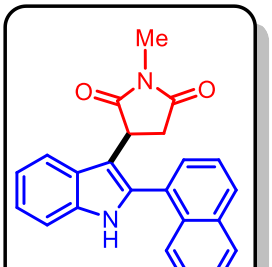


compound was purified by column chromatography on silica gel using EtOAc/ hexanes (1: 3, *v/v*) as an eluent; off white solid (55 mg, 37%); mp = 182-184 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32 (s, 1H), 7.60 (d, *J* = 6.8 Hz, 2H), 7.53 – 7.47 (m, 3H), 7.33 (d, *J* = 8.4 Hz, 1H), 7.19 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.14 (d, *J* = 1.6 Hz, 1H), 4.39 (dd, *J* = 9.6, 5.6 Hz, 1H), 3.17 (s, 3H), 3.12 (dd, *J* = 18.4, 9.6 Hz, 1H), 3.07 – 3.01 (m, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 178.5, 176.2, 139.0, 134.3, 131.4, 129.1, 129.0, 128.8, 127.3, 126.2, 123.2, 117.7, 112.6, 107.5, 37.7, 36.0, 25.3; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{19}H_{16}ClN_2O_2^+$, 339.0895; Found 339.0834.

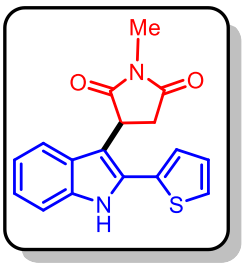
3-(5-Methoxy-2-phenyl-1*H*-indol-3-yl)-1-methylpyrrolidine-2,5-dione (27ma): The title compound was purified by column chromatography on silica gel using EtOAc/ hexanes (1: 3, *v/v*) as an eluent; off white solid (70 mg, 78%); mp = 174-176 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (s, 1H), 7.63 – 7.61 (m, 2H), 7.53 – 7.49 (m, 2H), 7.47 – 7.45 (m, 1H), 7.32 (d, *J* = 8.8 Hz, 1H), 6.90 (dd, *J* = 8.8, 2.4 Hz, 1H), 6.62 (d, *J* = 2.4 Hz, 1H), 4.40 (dd, *J* = 9.0, 5.8 Hz, 1H), 3.82 (s, 3H), 3.16 (s, 3H), 3.13 – 3.10 (m, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 178.8, 176.7, 154.5, 138.3, 131.1, 131.2, 129.04, 128.7, 128.7, 126.7, 112.3, 107.6, 100.8, 55.9, 37.8, 36.0, 25.1; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{20}H_{19}N_2O_3^+$ 335.1390; Found 335.1333.



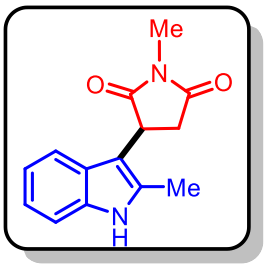
1-Methyl-3-(2-(naphthalen-1-yl)-1*H*-indol-3-yl)pyrrolidine-2,5-dione (27na): The title compound was purified by column chromatography on silica gel using EtOAc/ hexanes (1: 4, *v/v*) as an eluent; off white solid (94 mg, 65%); mp = 146-148 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.12 (s, 1H), 8.06 (d, *J* = 8.8 Hz, 1H), 7.99 (q, *J* = 8.8, 4.8 Hz, 2H), 7.75 (d, *J* = 8.4 Hz, 1H), 7.58 – 7.56 (m, 2H), 7.47 (d, *J* = 8.0 Hz, 1H), 7.16 (dd, *J* = 15.6, 7.6 Hz, 2H), 7.02 (t, *J* = 7.4 Hz, 1H), 4.56 (dd, *J* = 9.2, 4.8 Hz, 1H), 3.31 (dd, *J* = 18.4, 9.6 Hz, 1H), 2.95 (s, 3H), 2.85 – 2.80 (m, 1H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 179.6, 177.4, 137.2, 136.5, 133.3, 132.8, 129.8, 128.9, 128.6, 128.1, 127.7, 127.2, 127.1, 126.8, 126.5, 122.5, 120.0, 118.3, 112.3, 108.1, 37.9, 36.6, 25.2. HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{23}H_{19}N_2O_2^+$ 355.1441; Found 355.1409.



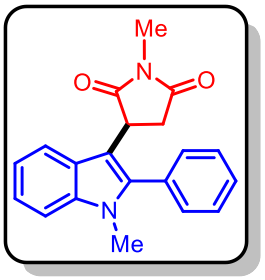
1-Methyl-3-(2-(thiophen-2-yl)-1*H*-indol-3-yl)pyrrolidine-2,5-dione (27oa): The title compound was purified by column chromatography on silica gel using EtOAc/ hexanes (1: 4, *v/v*) as an eluent; off white solid (53 mg, 68%); mp = 180-182 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.52 (s, 1H), 7.72 (dd, *J* = 5.2, 1.2 Hz, 1H), 7.44 – 7.40 (m, 2H), 7.24 (dd, *J* = 5.2, 3.6 Hz, 1H), 7.15 (t, *J* = 7.6 Hz, 1H), 7.11 (d, *J* = 7.6 Hz, 1H), 7.00 (t, *J* = 7.2 Hz, 1H), 4.62 (dd, *J* = 9.6, 5.2 Hz, 1H), 3.27 (dd, *J* = 18.0, 9.6 Hz, 1H), 2.98 (s, 3H), 2.78 (dd, *J* = 18.0, 5.2 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 178.9, 177.0, 136.6, 133.5, 130.8, 128.4, 127.5, 127.1, 126.5, 122.7, 120.1, 118.5, 112.2, 108.5, 38.0, 36.6, 25.2; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{17}H_{15}N_2O_2S^+$, 311.0849; Found 311.0828.



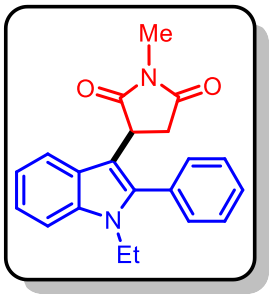
1-Methyl-3-(2-methyl-1*H*-indol-3-yl)pyrrolidine-2,5-dione (27qa): The title compound was purified by column chromatography on silica gel using EtOAc/ hexanes (1: 1, *v/v*) as an eluent; off white solid (65 mg, 71%); mp = 164-166 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (s, 1H), 7.27 (d, *J* = 8.2 Hz, 1H), 7.15 – 7.11 (m, 1H), 7.10 – 7.03 (m, 2H), 4.21 (dd, *J* = 9.6, 5.2 Hz, 1H), 3.22 (dd, *J* = 18.4, 9.6 Hz, 1H), 3.19 (s, 3H), 2.96 (dd, *J* = 18.8, 5.2 Hz, 1H), 2.26 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 178.9, 176.8, 135.5, 133.1, 126.0, 121.6, 119.9, 117.0, 110.9, 106.9, 37.7, 36.2, 25.2, 11.6; HRMS (ESI) *m/z*: $[M + H]^+$Calcd for $C_{14}H_{15}N_2O_2^+$ 243.1128; Found 243.1080.



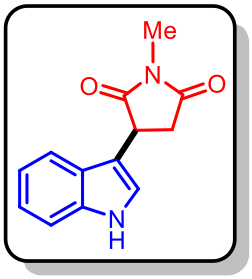
1-Methyl-3-(1-methyl-2-phenyl-1*H*-indol-3-yl)pyrrolidine-2,5-dione (27ra): The title compound was purified by column chromatography on silica gel using EtOAc/ hexanes (1: 4, *v/v*) as an eluent; off white solid (45 mg, 59%); mp = 174-176 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 – 7.49 (m, 5H), 7.41 (d, *J* = 8.4 Hz, 1H), 7.33 – 7.31 (m, 1H), 7.26 (d, *J* = 8.0 Hz, 1H), 7.16 (t, *J* = 7.8 Hz, 1H), 4.19 (dd, *J* = 9.2, 6.0 Hz, 1H), 3.63 (s, 3H), 3.09 (s, 3H), 3.07 – 3.03 (m, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 178.9, 176.7, 140.0, 137.3, 130.9, 130.7, 128.9, 128.7, 125.2, 122.3, 120.2, 118.0, 110.1, 108.2, 38.0, 36.6, 30.9, 25.1; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{20}H_{19}N_2O_2^+$ 319.1441; Found 319.1405.



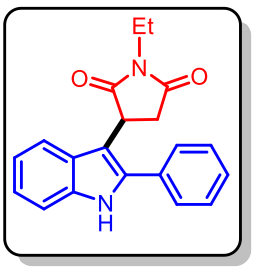
3-(1-Ethyl-2-phenyl-1*H*-indol-3-yl)-1-methylpyrrolidine-2,5-dione (27sa): The title compound was purified by column chromatography on silica gel using EtOAc/ hexanes (1: 3, *v/v*) as an eluent; Off white solid (46 mg, 61%); mp = 148-150 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (d, *J* = 6.0 Hz, 4H), 7.43 (d, *J* = 8.0 Hz, 2H), 7.31 – 7.29 (m, 1H), 7.27 – 7.26 (m, 1H), 7.17 – 7.13 (m, 1H), 4.13 (dd, *J* = 9.2, 5.6 Hz, 1H), 4.07 (qd, *J* = 7.2, 1.6 Hz, 2H), 3.11 – 3.06 (m, 1H), 3.05 (s, 3H), 3.03 – 3.00 (m, 1H), 1.29 (t, *J* = 8.0 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 178.9, 176.7, 139.4, 136.0, 131.0, 130.8, 128.9, 128.7, 125.5, 122.2, 120.0, 118.1, 110.2, 108.4, 38.8, 37.9, 36.6, 25.0, 15.4; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{21}H_{21}N_2O_2^+$ 333.1598; Found 333.1557.



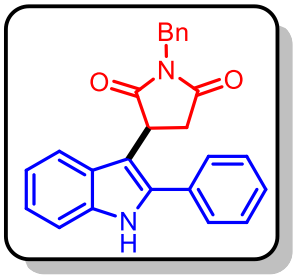
3-(1*H*-Indol-3-yl)-1-methylpyrrolidine-2,5-dione (27ta): The title compound was purified by column chromatography on silica gel using EtOAc/ hexanes (1: 1, *v/v*) as an eluent; off white solid (58 mg, 60%); mp = 170-172 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (s, 1H), 7.45 (d, *J* = 8.0 Hz, 1H), 7.39 (d, *J* = 8.4 Hz, 1H), 7.25 (t, *J* = 7.6 Hz, 1H), 7.17 (d, *J* = 7.8 Hz, 1H), 7.13 (d, *J* = 2.4 Hz, 1H), 4.33 (dd, *J* = 9.6, 4.8 Hz, 1H), 3.30 (dd, *J* = 18.2, 9.4 Hz, 1H), 3.14 (s, 3H), 2.96 (dd, *J* = 18.4, 4.8 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 178.3, 176.5, 136.6, 125.7, 122.7, 122.2, 120.1, 118.5, 111.6, 111.5, 38.2, 36.5, 25.1; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{13}H_{13}N_2O_2^+$, 229.0972; Found 229.0921.



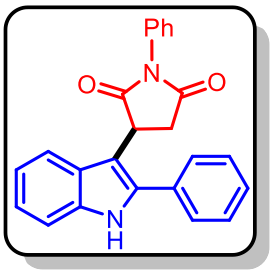
1-Ethyl-3-(2-phenyl-1*H*-indol-3-yl)pyrrolidine-2,5-dione (27ab): The title compound was purified by column chromatography on silica gel using EtOAc/ hexanes (1: 4, *v/v*) as an eluent; off white solid (60 mg, 73%); mp = 198-200 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 (s, 1H), 7.67 – 7.65 (m, 2H), 7.52 (t, *J* = 7.2 Hz, 2H), 7.47 (d, *J* = 7.2 Hz, 1H), 7.43 (d, *J* = 8.0 Hz, 1H), 7.26 – 7.21 (m, 2H), 7.12 (t, *J* = 7.4 Hz, 1H), 4.40 (t, *J* = 7.6 Hz, 1H), 3.74 (q, *J* = 6.0 Hz, 2H), 3.13 – 3.11 (m, 2H), 1.31 (t, *J* = 6.0 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 178.5, 176.5, 137.6, 136.0, 131.9, 129.1, 128.8, 128.7, 126.2, 122.8, 120.5, 118.3, 111.6, 108.0, 37.8, 36.1, 34.2, 13.1; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{20}H_{19}N_2O_2^+$ 319.1441; Found 319.1438.



1-Benzyl-3-(2-phenyl-1*H*-indol-3-yl)pyrrolidine-2,5-dione (27ac): The title compound was purified by column chromatography on silica gel using EtOAc/ hexanes (1: 4, *v/v*) as an eluent; off white solid (128 mg, 65%); mp = 124-126 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.60 (d, *J* = 6.8 Hz, 2H), 7.50 (t, *J* = 7.6 Hz, 2H), 7.42 (dd, *J* = 15.2, 6.8 Hz, 2H), 7.34 – 7.29 (m, 5H), 7.09 (t, *J* = 7.3 Hz, 1H), 6.84 – 6.78 (m, 2H),4.68 (s, 2H), 4.50 (dd, *J* = 10.0, 5.2 Hz, 1H), 3.32 (dd, *J* = 18.4, 10.0 Hz, 1H), 2.81 (dd, *J* = 18.4, 4.8 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 179.3, 177.0, 137.4, 136.4, 136.3, 132.2, 129.4, 128.1, 128.9, 128.7, 128.5, 128.2, 126.2, 122.3, 119.7, 118.3, 112.3, 107.5, 42.4, 37.8, 36.4; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{25}H_{21}N_2O_2^+$ 381.1598; Found 381.1572.

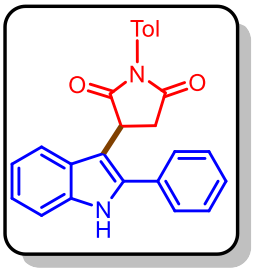


1-Phenyl-3-(2-phenyl-1*H*-indol-3-yl)pyrrolidine-2,5-dione (27ad): The title compound was



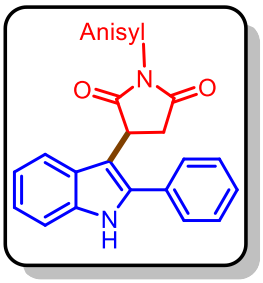
purified by column chromatography on silica gel using EtOAc/ hexanes (1: 4, *v/v*) as an eluent; off white solid (71 mg, 75%); mp = 216-218 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (s, 1H), 7.71 – 7.69 (m, 2H), 7.56 – 7.55 (m, 1H), 7.54 – 7.53 (m, 1H), 7.52 – 7.51 (m, 1H), 7.50 – 7.48 (m, 1H), 7.46 (d, *J* = 7.6 Hz, 2H), 7.42 – 7.41 (m, 1H), 7.40 – 7.39 (m, 1H), 7.30 – 7.26 (m, 2H), 7.20 – 7.16 (m, 2H), 4.60 (dd, *J* = 8.8, 6.4 Hz, 1H), 3.33 (d, *J* = 3.6 Hz, 1H), 3.31 (d, *J* = 1.2 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 177.8, 175.6, 137.7, 136.1, 132.2, 131.9, 129.2, 129.1, 128.9, 128.8, 128.7, 126.5, 126.2, 122.8, 120.6, 118.2, 111.7, 107.9, 38.0, 36.3; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{24}H_{19}N_2O_2^+$ 367.1441; Found 367.1402.

3-(2-Phenyl-1*H*-indol-3-yl)-1-(*p*-tolyl)pyrrolidine-2,5-dione (27ae): The title compound was



purified by column chromatography on silica gel using EtOAc/ hexanes (1: 4, *v/v*) as an eluent; off white solid (77 mg, 78%); mp = 204-206 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (s, 1H), 7.68 (d, *J* = 6.8 Hz, 2H), 7.54 (t, *J* = 6.8 Hz, 2H), 7.48 (d, *J* = 7.6 Hz, 1H), 7.43 (d, *J* = 8.0 Hz, 1H), 7.48 (d, *J* = 8.4 Hz, 1H), 7.34 (d, *J* = 8.0 Hz, 3H), 7.25 (d, *J* = 7.2 Hz, 2H), 7.17 (t, *J* = 7.6 Hz, 1H), 4.56 (dd, *J* = 8.8, 6.4 Hz, 1H), 3.30 (d, *J* = 3.6 Hz, 1H), 3.28 (d, *J* = 1.2 Hz, 1H) 2.42 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 177.8, 175.7, 138.7, 137.7, 136.1, 131.9, 129.9, 129.6, 129.4, 129.1, 128.9, 128.7, 126.3, 122.8, 120.6, 118.2, 111.6, 108.1, 38.0, 36.3, 21.2; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{25}H_{21}N_2O_2^+$ 381.1598; Found 381.1557.

1-(4-Methoxyphenyl)-3-(2-phenyl-1*H*-indol-3-yl)pyrrolidine-2,5-dione (27af): The title



compound was purified by column chromatography on silica gel using EtOAc/ hexanes (1: 4, *v/v*) as an eluent; off white solid (90 mg, 87%); mp = 192-194 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.51 (s, 1H), 7.69 (d, *J* = 7.6 Hz, 2H), 7.58 (t, *J* = 7.4 Hz, 2H), 7.49 (d, *J* = 7.2 Hz, 1H), 7.45 (d, *J* = 8.4 Hz, 1H), 7.34 (d, *J* = 8.8 Hz, 1H), 7.27 (d, *J* = 8.0 Hz, 2H), 7.18 (t, *J* = 7.6 Hz, 1H), 7.08 (d, *J* = 8.4 Hz, 3H), 4.65 (dd, *J* = 9.6, 5.2 Hz, 1H), 3.81 (s, 3H), 3.43 (dd, *J* = 18.2, 9.8 Hz, 1H) 3.01 (dd, *J* = 18.0, 5.2 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 178.7, 176.3, 159.5, 137.7, 136.6, 132.5, 129.4, 129.1, 128.7, 128.7, 126.5, 125.8, 122.3, 120.0, 118.4, 114.7, 112.3, 107.8, 55.9, 38.2, 36.8; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{25}H_{21}N_2O_3^+$ 397.1547; Found 397.1546.

3-(2-Phenyl-1*H*-indol-3-yl)pyrrolidine-2,5-dione (27ag): The title compound was purified by column chromatography on silica gel using EtOAc/ hexanes (1: 1, *v/v*) as an eluent; off white solid (50 mg, 66%); mp = 282-284 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.94 (s, 1H), 10.42 (s, 1H), 7.43 (d, J = 7.6 Hz, 3H), 7.25 – 7.18 (m, 3H), 7.08 (d, J = 7.6 Hz, 1H), 6.93 – 6.90 (m, 1H), 6.82 (d, J = 8.4 Hz, 1H), 4.20 – 4.16 (m, 1H), 2.84 – 2.83 (m, 2H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 180.3, 177.9, 137.8, 136.5, 1 32.3, 128.9, 128.7, 128.1, 126.0, 121.9, 119.6, 118.1, 112.0, 107.0, 39.2, 37.4; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{18}H_{15}N_2O_2^+$ 291.1128; Found 291.1113.

4.4A.4.4 X-ray Crystallographic Analysis of 28aa

Single crystals of **28aa** [$C_{19}H_{16}N_2O_2$] were obtained as yellow blocks from chloroform-hexane solvent mixture. The crystal data collection and data reduction were performed using CrysAlis PRO on a single crystal Rigaku Oxford XtaLab Pro diffractometer. The crystals were kept at 93(2) K during data collection using CuKα (λ = 1.54184) radiation. Using Olex2,[52] the structure was solved with the ShelXT [53] structure solution program using Intrinsic Phasing and refined with the ShelXL [53] refinement package using Least Squares minimization.

Table 4.4A.4: Crystal data and structure refinement for **28aa**.

Identification code	**28aa**
Empirical formula	$C_{19}H_{16}N_2O_2$
Formula weight	304.34
Temperature/K	93(2)
Crystal system	monoclinic
Space group	$P2_1$
a/Å	12.4146(6)
b/Å	9.1711(5)
c/Å	13.5882(8)
α/°	90

β/°	105.086(5)
γ/°	90
Volume/Å^3	1493.77(14)
Z	4
ρ_{calc}g/cm^3	1.353
μ/mm^{-1}	0.716
F(000)	640.0
Crystal size/mm^3	0.15 × 0.1 × 0.04
Radiation	Cu Kα (λ = 1.54184)
2Θ range for data collection/°	6.738 to 159.198
Index ranges	-15 ≤ h ≤ 14, -11 ≤ k ≤ 6, -16 ≤ l ≤ 17
Reflections collected	8879
Independent reflections	4340 [R_{int} = 0.0685, R_{sigma} = 0.0914]
Data/restraints/parameters	4340/1/417
Goodness-of-fit on F^2	1.094
Final R indexes [I>=2σ (I)]	R_1 = 0.0862, wR_2 = 0.2693
Final R indexes [all data]	R_1 = 0.0903, wR_2 = 0.2721

4.4A.5 REFERENCES

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Chapter 4B

Manganese(I)-Catalyzed *ortho*-Hydroalkylation of Aryl Substituted *N*-Heteroaromatic Compounds with Maleimides

4.4B.1 INTRODUCTION

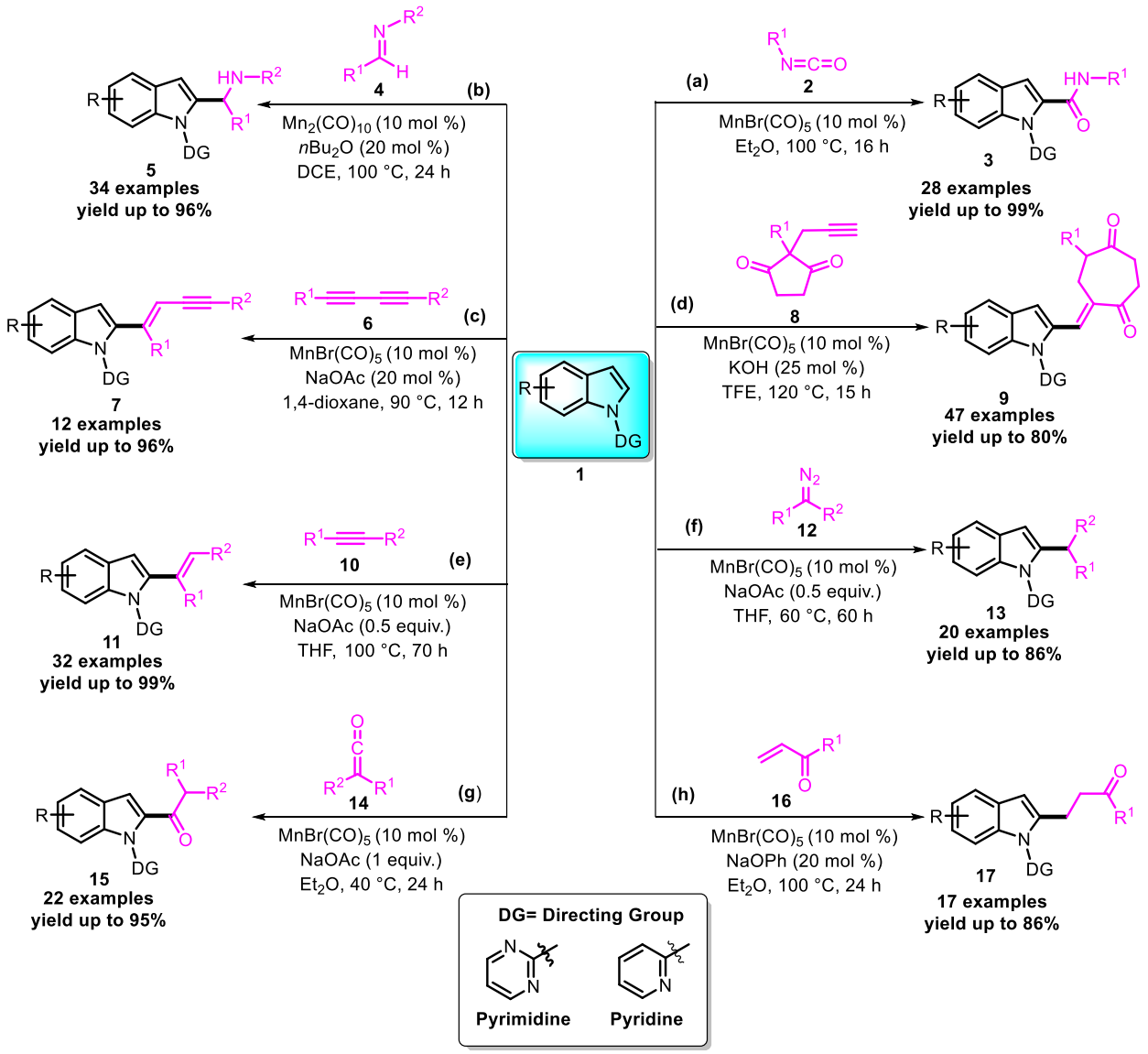
Aryl-substituted *N*-heteroaromatic scaffold is widely present in synthetic molecules, natural products, and π-conjugated functional materials of immense biological as well as industrial importance. With their widespread applications, regioselective functionalization of aryl-substituted *N*-heteroaromatics has been a highly intriguing topic of research in the past two decades. Among various approaches, transition-metal catalyzed direct C–H bond functionalization has been recognized as a reliable approach as it avoids pre-functionalization of substrates and exhibits high atom- and step-economy. 1-4

Succinimide is a prominent structural motif frequently encountered in a variety of natural products and biologically active compounds.[5-9] Succinimides also serve as an important precursor for the preparation of bioactive molecules such as pyrrolidines and γ-lactams. In recent years, readily accessible maleimides have been extensively utilized as coupling partners in chelation-assisted transition-metal catalyzed C–H bond functionalization reactions for late-stage introduction of succinimide or maleimide moiety in a variety of (hetero)arenes through hydroalkylation or alkenylation.[10, 11] Most of these transformations rely on second-row transition metal (ruthenium,[12-18] and rhodium[19-35]) based catalysts. However, the use of more earth-abundant cobalt catalysts has started to gain importance in recent years.[36-39] Despite significant progress in this area, the development of synthetic methods using inexpensive and environmentally benign catalysts is still desirable.

Manganese has emerged as a significant catalyst in C–H activation. It ranks as the twelfth most abundant element in the Earth's crust and is the third most abundant transition metal.[40] Additionally, enzymes containing manganese have been discovered to play essential roles in metabolizing cholesterols, carbohydrates, and amino acids.[41] The cost-effectiveness and lower toxicity of manganese make it a more desirable alternative to the transition metal catalysts typically derived from platinum, palladium, ruthenium, rhodium, and iridium.[42, 43] Numerous manganese-catalyzed C-H activation/ functionalization strategies have been reported to date, with ongoing extensive research in this field.[44, 45]

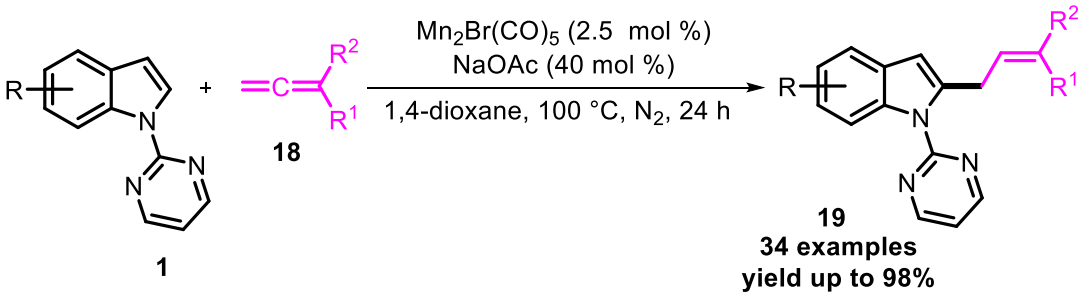
Considering the privilege of indole scaffold in medicinal chemistry and natural products, there's a significant research focus on enhancing methods for activating and functionalizing C(sp^2)–H bonds in indole skeleton. Starting from different coupling partners, manganese(I)-catalyzed

strategies have been developed for the functionalization of indole nuclei over them in recent years. In this regard, in 2015, the Ackermann group established a C-H aminocarbonylation strategy for the coupling between heteroarenes (**1**) with aryl, alkyl isocyanates (**2**) by utilizing a removable directing group under Mn(I) catalysis, yielding C-2 functionalized indole derivative (**3**) in good yields (**Scheme 4.4B.1a**).[46] Subsequently, the same research group describe convenient C–H activation/ hydroarylation of imines (**4**) with 1-(pyridin-2-yl)-1*H*-indole (**1**) using an Mn(I) catalyst to deliver C-2 substituted amine derivatives (**5**) (**Scheme 4.4B.1b**).[47] Glorius group described a novel and efficient Mn(I)-catalyzed C-H functionalization of heteroarenes (**1**) with 1,3-diynes (**6**) (**Scheme 4.4B.1c**).[48] The developed protocol showed a high stereo-, chemo-, and regioselectivity with good to excellent yields. Li and co-workers developed the facile and ideal protocol for the synthesis of seven-membered carbocycles (**9**) by the C-H activation of heteroarenes (**1**) with alkyne-functionalized 1,3-cyclopentadiones (**8**) by utilization of Mn(I) catalyst (**Scheme 4.4B.1d**).[49] The developed protocol proceeds *via* C-H alkenylation, and carbonyl addition, followed by retro-Aldol cyclization. Rueping and group developed an efficient and regioselective protocol for the synthesis of C2-alkenylated indole derivatives (**11**) by using Mn(I)-catalyzed C-H activation of *N*-(2-pyrimidinyl)indoles (**1**) with substituted alkynes (**10**) (**Scheme 4.4B.1e**).[50] Remarkably, good functional group compatibility, removable directing groups, and highly regio-and stereoselectives are the advantages of this synthetic strategy. Wang *et al*. demonstrated an Mn(I)-catalyzed C-H functionalization of *N*-pyrimidinyl indole (**1**) with 2-diazomalonate (**12**) as a coupling partner for the synthesis of C2-alkylated indole frameworks (**Scheme 4.4B.1f**).[51] In 2022, the Zang group reported an effective method for the synthesis of C2-acylated indoles (**15**) through Mn(I)-catalyzed C-H activation of indoles (**1**) with ketene (**14**) which was used as an acylating reagent (**Scheme 4.4B.1g**).[52] Wang group demonstrated an efficient approach to access C2-alkylated indoles (**17**) by the simple conjugate addition of indole (**1**) with α,β-unsaturated carbonyls compounds (**16**) *via* Mn(I)-catalyzed C-H activation(**Scheme 4.4B.1h**).[53] The significant features exhibited protocol, broad substrate scope with good functional group tolerance, and high atom economy.



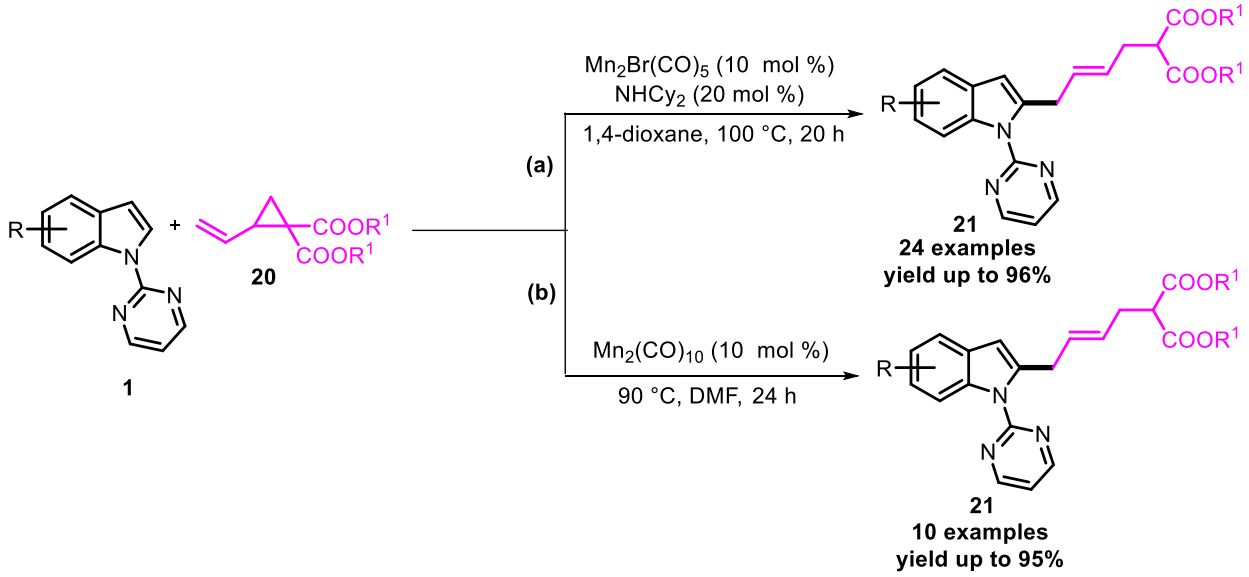
Scheme 4.4B.1: Mn(I)-catalyzed C-H functionalization of indoles with different coupling partner

Wang *et al*. developed the facile and ideal protocol for the site-selective C-H functionalization of *N*-pyrimidinyl indole by utilization of Mn(I)-catalyst (**Scheme 4.4B.2**).[54] Allylation takes place between *N*-pyrimidinyl indoles (**1**) and allenes (**18**) in the presence of $Mn_2Br(CO)5$, and NaOAc to afford the allylated arene derivatives (**19**) in good to excellent yields. The synthetic potential of the developed protocol has been demonstrated by a gram-scale experiment with lower catalyst loading. In addition broad functional group compatibility resulting the effectiveness of the method.



Scheme 4.4B.2: Mn(I)-catalyzed C-H functionalization of *N*-pyrimidinyl indole with allenes

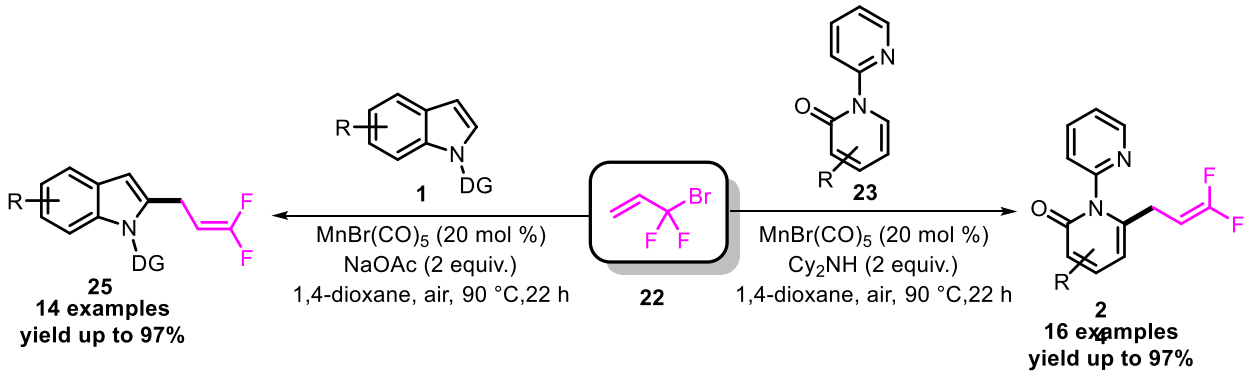
In 2017, the Ackermann group reported the Mn(I)-catalyzed C-H activation of *N*-pyrimidinyl indoles (**1**) and vinylcyclopropane-1,1-dicarboxylate (**20**) for the synthesis of allylated arenes (**21**) (**Scheme 4.4B.3a**).[55] The notable features of the protocol are broad substrate scope, high distereo-, chemo-, and side selectivities. Kinetic isotopic studies and DFT studies revealed that the reaction involves facile C-H activation in an organometallic fashion. In the same year, the Glorius group also reported Mn(I)-catalyzed C-H activation of *N*-pyrimidinyl indoles (**1**) with vinylcyclopropane-1,1-dicarboxylate (**20**) (**Scheme 4.4B.3b**).[56]



Scheme 4.4B.3: Mn(I)-catalyzed C-H functionalization of *N*-pyrimidinyl indole with 2-vinylcyclopropane-1,1-dicarboxylate

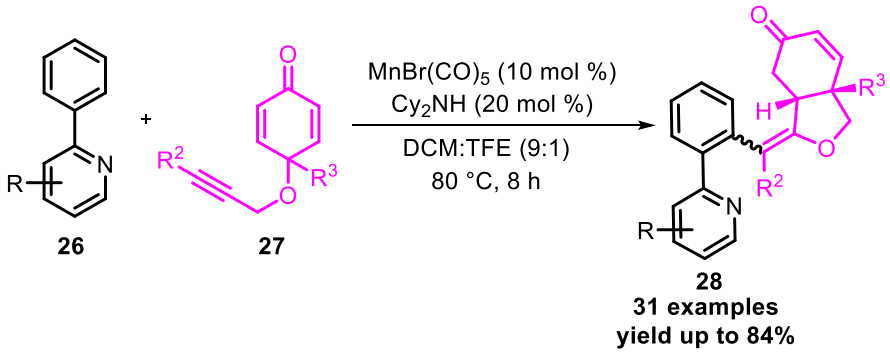
Zang and co-workers developed manganese(I)-catalyzed difluoroallylation of 2-pyridone (**23**) and indole (**1**) derivatives by utilizing 3-bromo-3,3-difluoropropen (**22**) through C-H activation (**Scheme 4.4B.4**).[57] The developed methodology shows extensive applicability across various

substrates, demonstrating robust compatibility with various functional groups. Moreover, this methodology was successfully applied to late-stage diversification, enabling 3,3-difluoroallylation of bioactive molecules, including tryptophan and melatonin analogs.



Scheme 4.4B.4: Mn(I)-catalyzed C-H functionalization of 2-pyridone and indole with 3-bromo-3,3-difluoropropen

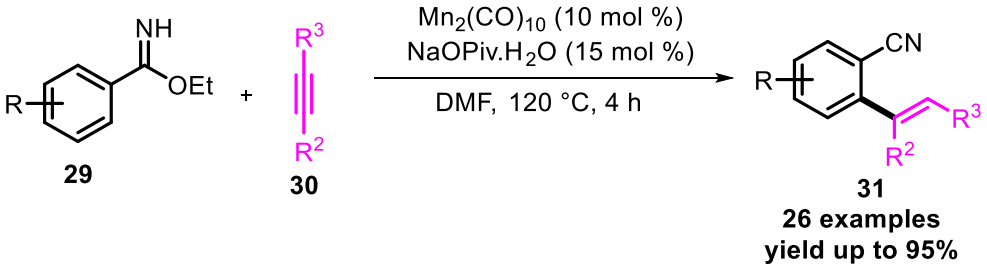
In 2019, Lin *et al*. reported a manganese(I)-catalyzed novel and efficient strategy for arylation by using a coupling reaction between 2-arylpyridin (**26**) with 1,6-enynes (**27**) *via* C−H bond activation (**Scheme 4.4B.5**).[58] The promising advantages of the protocol are high chemoselectivity and atom economy, good functional group compatibility, with moderate to good yields. Moreover, mechanistic investigations indicated that the cleavage of the C−H bond was involved in the rate-determining step.



Scheme 4.4B.5: Mn(I)-catalyzed C-H functionalization of 2-arylpyridin with 1,6-enynes

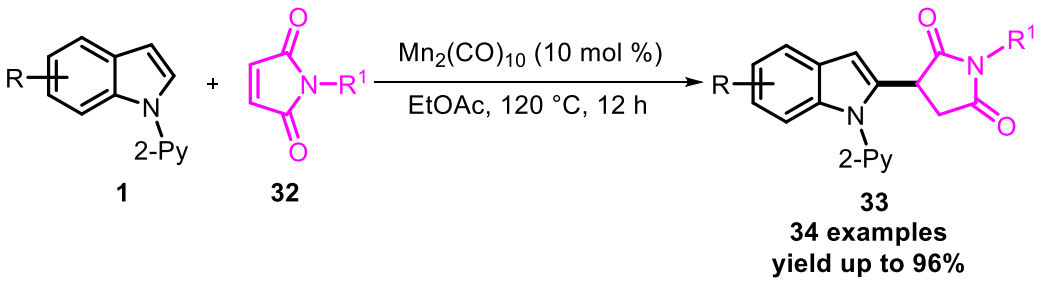
Wang group reported the Mn(I)-catalyzed C-H bond activation using benzimidates (**29**) with alkynes (**30**) to afford the monoalkenylated aromatic nitriles derivatives (**31**) (**Scheme 4.4B.6**).[59]

The method exhibited a simple catalytical system, broad functional group tolerance, and high monoalkenylation selectivity as well as *E/Z* stereoselectivity.



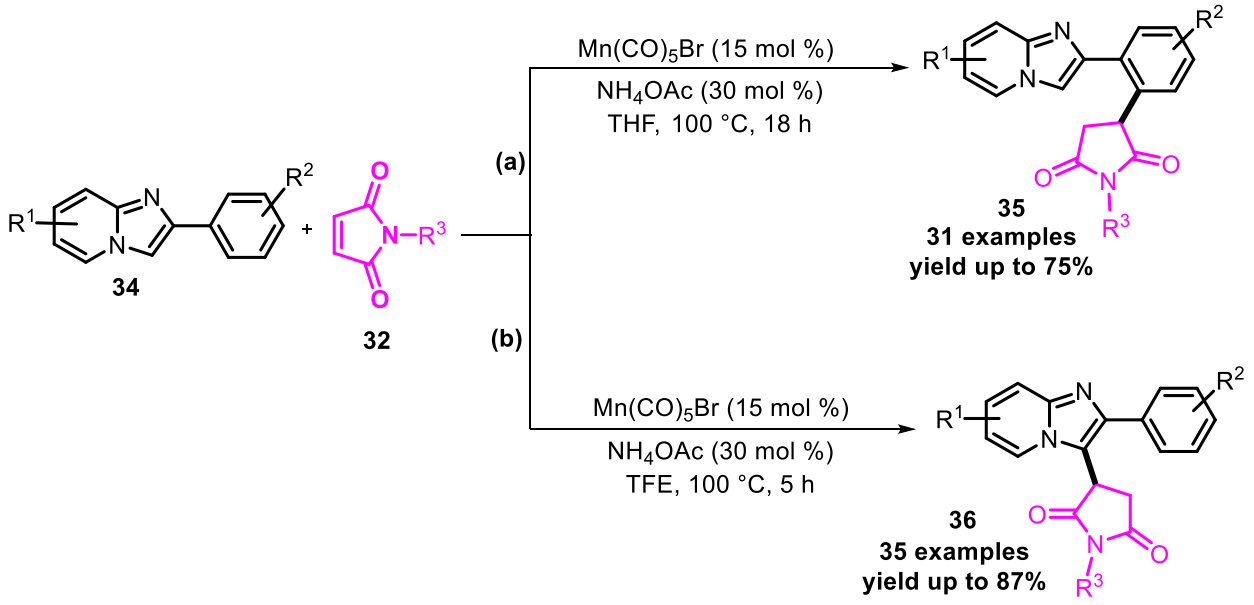
Scheme 4.4B.6: Mn(I)-catalyzed *ortho*-C-H alkenylation of aromatic N-H imidates with alkynes

In 2017, Song *et al.* reported Mn(I)-catalyzed novel and efficient strategy for C2-alkylation of *N*-pyrimidinyl indoles (**1**) with maleimides (**32**) to access a variety of 3-(indol-2-yl)succinimide derivatives (**33**) good to excellent yields (**Scheme 4.4B.7**).[60] The versatility of the protocol is interestingly described for various substrates, such as ethyl acrylate, maleates, and pyrroles, as well as 1,4-dihydro-1,4-epoxynaphthalene.



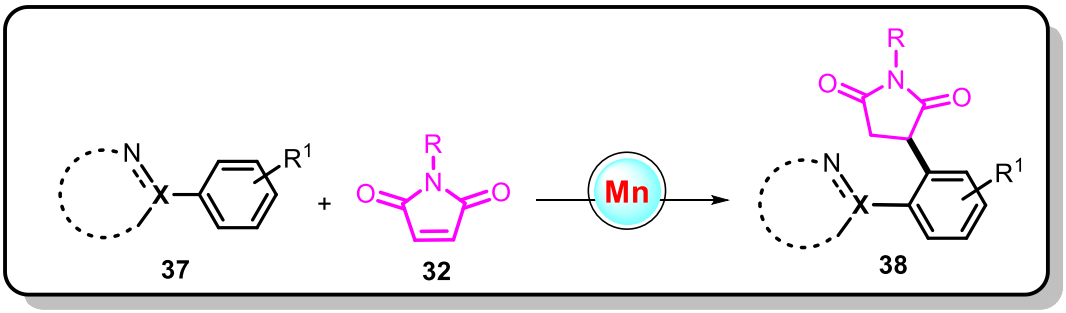
Scheme 4.4B.7: Mn(I)-catalyzed C-H activation of alkenylation of indoles with maleimides

In 2021, Patel and co-workers demonstrated the Mn(I)-catalyzed solvent switched functionalization of imidazopyridine **(34)** with maleimide **(32)** for the construction of imidazo[1,2-*a*]pyridin-2-yl)phenyl) pyrrolidine-2,5-dione **(35)** and (2-phenylimidazo[1,2-*a*]pyridin-3-yl)pyrrolidine-2,5-dione **(36)** (**Scheme 4.4B.8**).[61] The selectivity of the C-3 or *ortho*-alkylated products has been achieved by switching the polar protic solvent (TFE) and polar aprotic solvent (THF). Additionally, this protocol was effectively investigated for the alkylation of the drug Zolimidine.



Scheme 4.4B.8: Mn(I)-catalyzed solvent-driven strategies to access functionalization of imidazopyridine with maleimides

Inspired by work on manganese-catalyzed C2-hydroalkylation of indoles, we envisioned that selective *ortho*-hydroalkylation of aryl substituted *N*-heteroaromatic compounds with maleimides could be accomplished using a cheaper environmentally benign manganese(I)-catalyst. In continuation of our interest in transition-metal catalyzed C–H functionalization of heterocycles, herein, we disclose a manganese-catalyzed *ortho*-hydroalkylation of aryl substituted *N*-heteroaromatic (**37**) compounds with maleimides (**32**) to produce 3-(2-(*N*-heteroaryl)aryl)pyrrolidine-2,5-diones (**38**) (**Scheme 4.4B.9**).



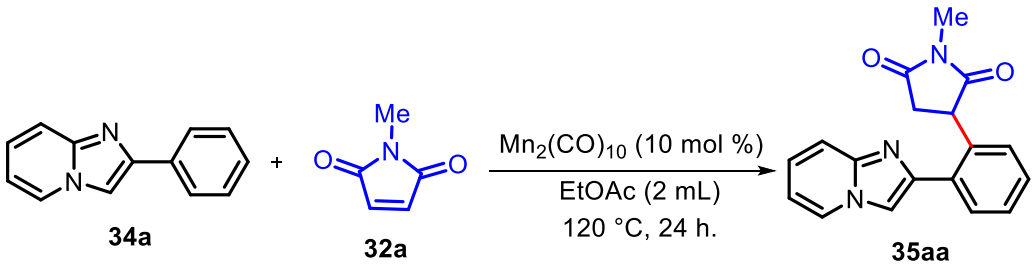
Scheme 4.4B.9: Mn(I) Catalyzed *ortho*-alkylation of aryl-substituted *N*-heteroaromatic compounds with maleimides

4.4B.2 RESULTS AND DISCUSSION

We commenced our study by investigating the model reaction of 2-phenylimidazo[1,2-*a*]pyridine (**34a**) with *N*-methylmaleimide (**32a**). When a mixture of **34a** and **32a** was heated in the presence of $Mn_2(CO)_{10}$ (10 mol %) in ethyl acetate at 120 °C (**Table 4.4B.1**, entry 1), the reaction occurred solely at the *ortho*-position of 2-phenyl ring giving hydroalkylated product, 3-(2-(imidazo[1,2-*a*]pyridin-2-yl)phenyl)-1-methylpyrrolidine-2,5-dione (**35aa**), in 77% yield (**Table 4.4B.1**, entry 1). The structure of the alkylated product **35ba** was ascertained by ^{1}H NMR, ^{13}C {^{1}H} NMR and HRMS analysis. In the ^{1}H NMR of **35ba**, the methyl peak of C19-H of *N*-methyl maleimide appeared at 3.0 ppm, and another aliphatic proton of malemide C15-H and C16-H appaired 4.7 ppm, 3.3-2.9 ppm respectively, rest of the aromatic proton well match with the structure (**Figure 4.4B.1**). In ^{13}C{^{1}H}NMR of **35ba**, carbonyl carbon of *N*-methyl maleimide appeared at 179.2 ppm and 177.3 ppm along with other carbons (**Figure 4.4B.2**). A peak at *m/z* 320.1394 in the HRMS corresponding to molecular formula $C_{19}H_{18}N_3O_2$ [M+H] ion confirmed the structure of **35ba**.

Different organic and inorganic bases were tried to improve efficiency (**Table 4.4B.1**, entries 2–9). Unfortunately, the use of base did not improve the yield of **35aa**, only NaOAc, CsOAc, KOAc, DIPEA, and Et_3N were effective providing **35aa** in 32-63% yields. Next, we evaluated the solvent effect, model reaction was performed in various solvents such as ethyl acetate, THF, hexane, dioxane, DCE, diethyl ether, acetone, and DMF (**Table 4.4B.1**, entries 1, 10-16). Among them, ethyl acetate was found to be the most effective providing **35aa** in 77% yield. The reaction temperature had a significant effect on the outcome of the reaction; the yield of **35aa** was reduced by decreasing (80 °C) as well as increasing (150 °C) the reaction temperature (**Table 4.4B.1**, entries 17 and 18). Moreover, altering the other Mn salts like $Mn(OAc)_2{\cdot}4H_2O$ and $Mn(acac)_2$ were also not found to be effective (**Table 4.4B.1**, entries 19-20). The $MnBr(CO)_5$ was reacted smoothly to afford the desired product in 61% yield (**Table 4.4B.1**, entry 21). The product **35aa** was not formed in the absence of a catalyst, signifying the indispensable role of the catalyst (**Table 4.4B.1**, entry 22).

Table 4.4B.1: Selected optimization results for *ortho*-hydroalkylation of **34a** with **32a**.[a]



34a **32a** **35aa**

entry	deviation from standard conditions	% yield of **35aa**[b]
1	**none**	**77**
2	NaOAc as base	32
3	CsOAc as base	35
4	KOAc as base	39
5	DIPEA as base	63
6	Et_3N as base	52
7	DBU as base	nr
8	Piperidine as base	trace
9	KO^{t}Bu as base	15
10	THF as solvent	32
11	Hexane as solvent	trace
12	1,4-Dioxane as solvent	27
13	DCE as solvent	nr
14	Ether as solvent	10
15	Acetone as solvent	33
16	DMF as solvent	6
17	at 80 °C	19
18	at 150 °C	46
19	$Mn(acac)_2$ as catalyst	trace
20	$Mn(OAc)_2{\cdot}4H_2O$ as catalyst	trace
21	$MnBr(CO)_5$ as catalyst	61
22	no catalyst	nr

[a]Reaction condition: **34a** (0.26 mmol, 1.0 equiv.), 3**2a** (0.31 mmol, 1.2 equiv.), catalyst (10 mol %), base (20 mol %), solvent (2 mL), heated in oil bath for 24 h. [b]Isolated yield. nr = No reaction

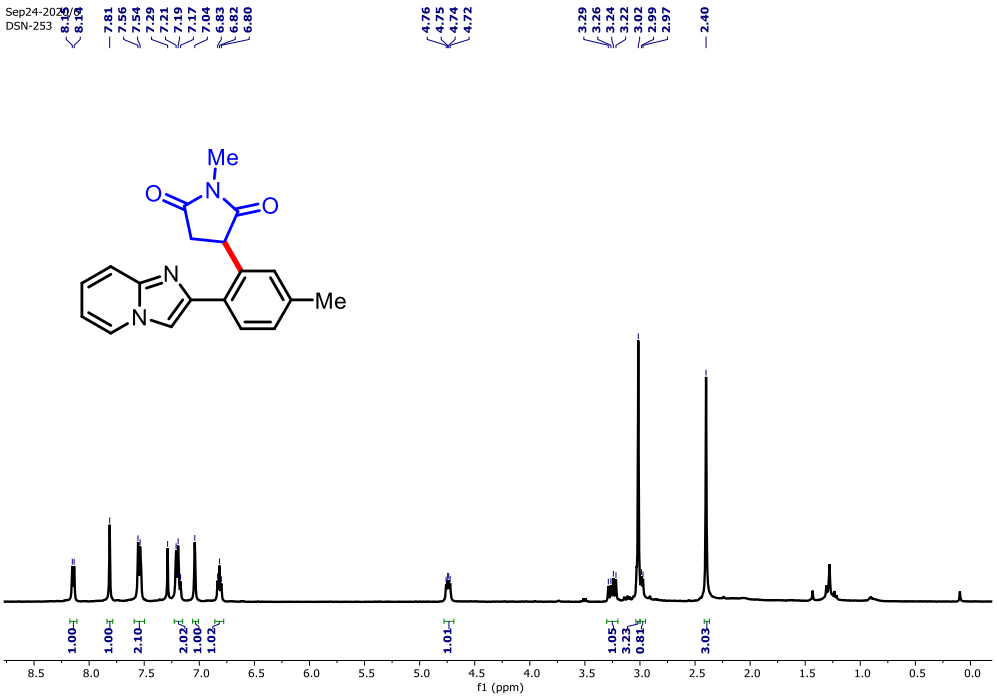


Figure 4.4B.1: ^{1}H NMR spectra of 3-(2-(imidazo[1,2-*a*]pyridin-2-yl)-5-methylphenyl)-1-methylpyrrolidine-2,5-dione (**35ba**) recorded in $CDCl_3$

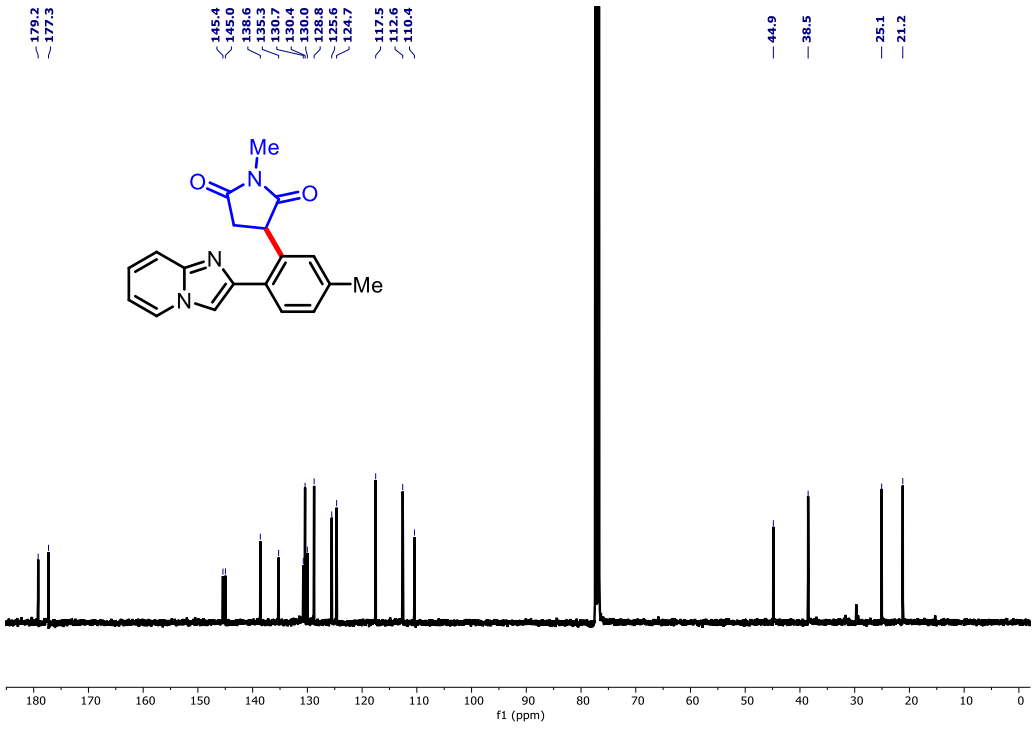
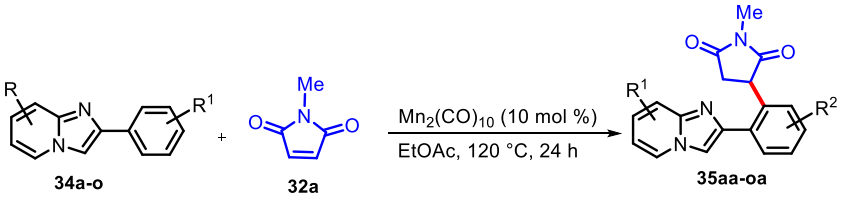
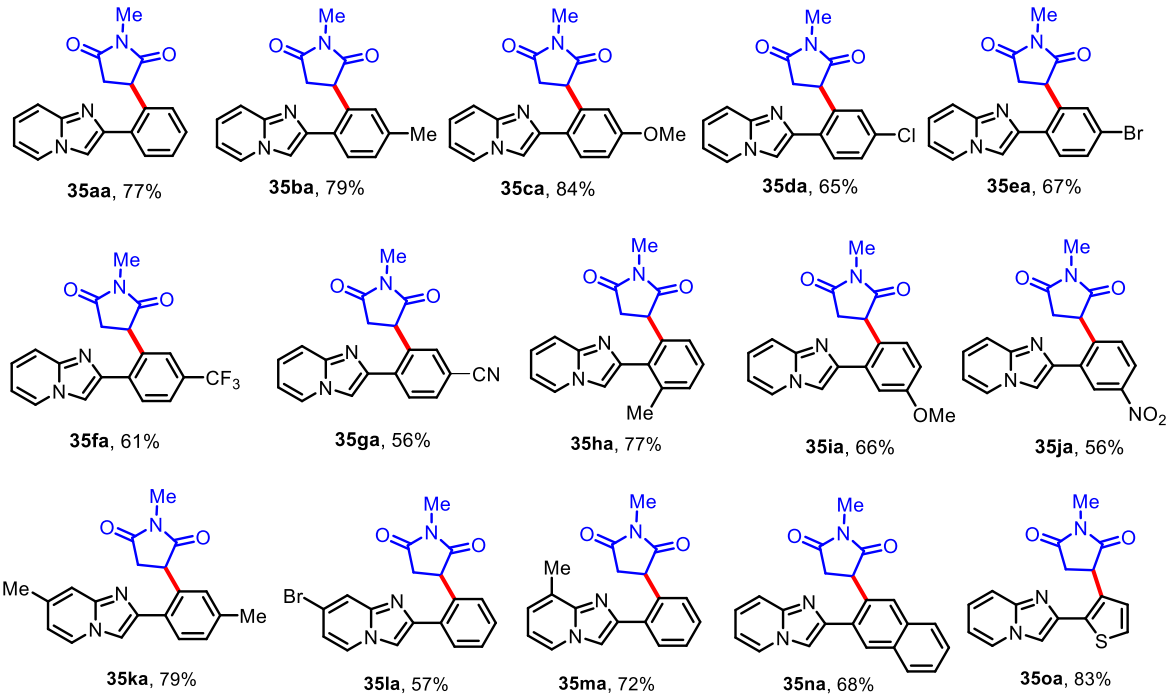


Figure 4.4B.2: $^{13}C\{^{1}H\}$ NMR spectra of 3-(2-(imidazo[1,2-*a*]pyridin-2-yl)-5-methylphenyl)-1-methylpyrrolidine-2,5-dione (**35ba**) in $CDCl_3$

With the optimized reaction conditions in hand, the scope and generality of the designed protocol for the hydroalkylation reactions was explored (**Table 4.4B.2**). A variety of 2-arylimidazo[1,2-*a*]pyridines bearing electron-donating (Me and OMe) as well as electron-withdrawing (Cl, Br, CN and CF_3) substituents at *para*-position of the C2-phenyl ring reacted smoothly with **32a** to afford corresponding *ortho*-hydroalkylated products (**35aa-ga**) in moderate to very good (56-84%) yields. Substrates with electron-donating groups at the C2-phenyl ring gave slightly higher yields than those with electron-withdrawing groups (compare **35ba** and **35ca** with **35fa** and **35ga**). *Ortho*-substituted 2-(*o*-tolyl)imidazo[1,2-*a*]pyridine (**34h**) also reacted smoothly with **32a** to furnish the desired hydroalkylated product **35ha** in 77% yields. Interestingly, reaction of *meta*-substituted 2-(*m*-methoxyphenyl)imidazo[1,2-*a*]pyridine (**34i**) and 2-(*m*-nitrophenyl)imidazo[1,2-*a*]pyridine (**34j**) with **32a** took place with high regioselectivity to afford hydroalkylated product **35ia** and **35ja** in 66% and 56% yields, respectively. 2-Phenylimidazo[1,2-*a*]pyridines bearing substituent on imidazopyridine nucleus (**34k-m**) were also suitable substrates for this process and offered corresponding hydroalkylated products (**35ka-35ma**) in moderate to good yields. Furthermore, 2-(napthyl-2-yl)imidazo[1,2-*a*]pyridine (**34n**) and 2-(thiophene-2-yl)imidazo[1,2-*a*]pyridine (**34o**) were also found to be good partners under these conditions, affording corresponding hydroalkylated products **35na** and **35oa** in 68% and 83% yields, respectively. The method tolerated various functional groups including halogens which are useful for late-stage functionalization to more complex molecules. Further, the structure of compound **35ca** was unambiguously ascertained by single crystal X-ray analysis **(Figure 4.4B.3**, CCDC 2107805).

Table 4.4B.2: Substrate scope for 2-arylimidazo[1,2-*a*]pyridines.[a,b]





[a]Reaction condition: **34** (0.26 mmol), **32a** (0.31 mmol, 1.2 equiv.), $Mn_2(CO)_{10}$ (10 mol %), EtOAc (2 mL), 120 °C, 24 h. [b]Isolated yield.

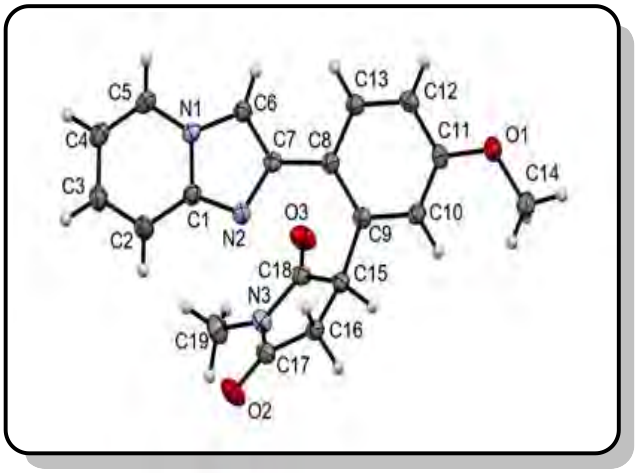
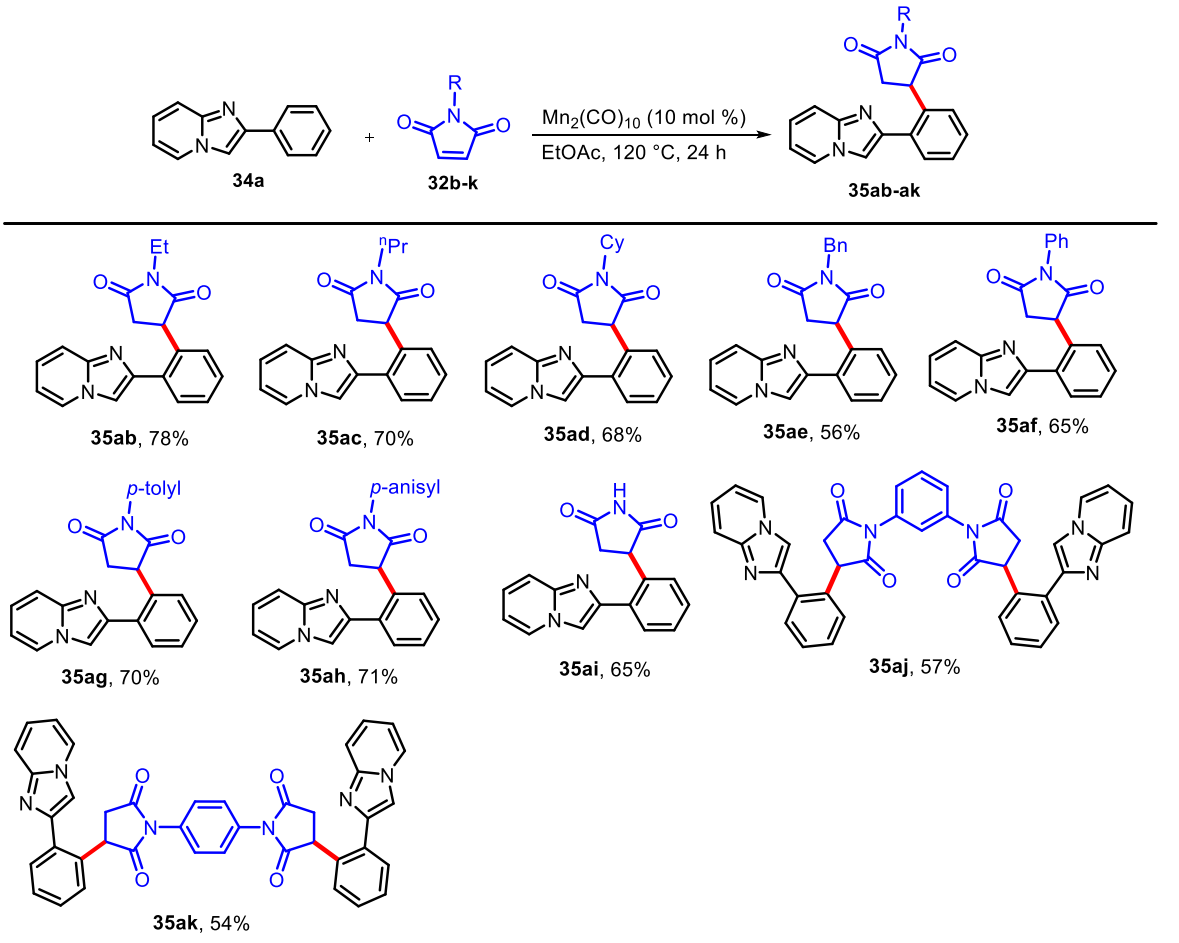


Figure 4.4B.3: Single crystal ORTEP diagram of compound **35aa**. The thermal ellipsoids are drawn to a 50 % probability level (**CCDC No** 2107805)

Next, we investigated the substrate scope with respect to maleimides (**Table 4.4B.3**). The reaction of *N*-alkylmaleimides (**32b-d**), *N*-benzylmaleimide (**32e**) and *N*-arylmaleimides (3**2f-h**) with **34a** readily afforded corresponding hydroalkylated products (**35ab-35ah)** in good to high (56-78%) yields. Unsubstituted maleimide (3**2i**) also reacted with **34a** under standard reaction conditions to furnish corresponding hydroalkylated **35ai** in 65% yield. Interestingly, 1,3-phenylenedimaleimide (3**2j**) and 1,4-phenylenedimaleimide (3**2k**) on reaction with **34a** furnished corresponding *bis*-hydroalkylated products **35aj** and **35ak** in 57% and 54% yields, respectively. No significant effect of the *N*-substituent of maleimide was observed with regard to their reactivity.

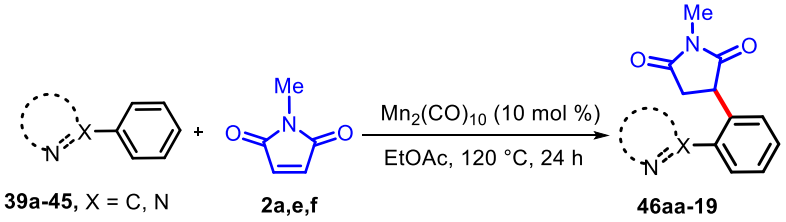
Table 4.4B.3: Substrate scope for maleimides.[a,b]

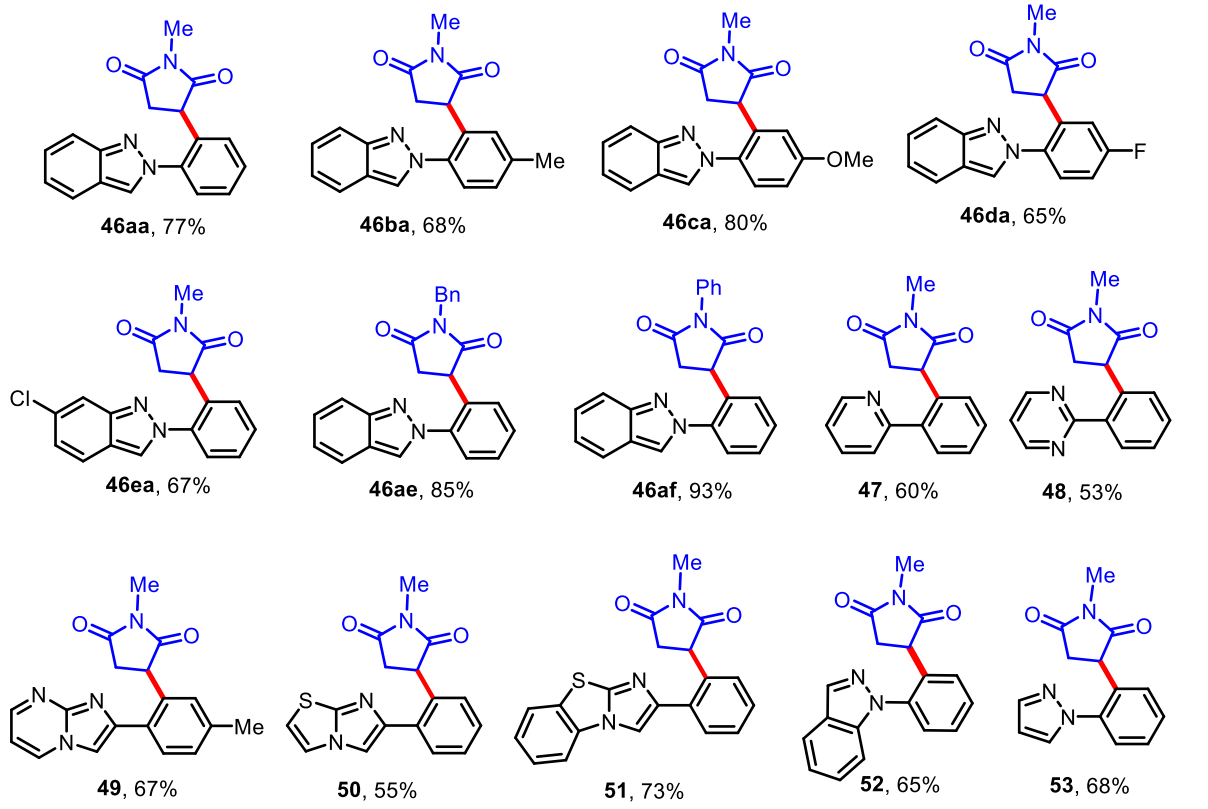


[a]Reaction condition: **34** (0.26 mmol), **32** (0.31 mmol, 1.2 equiv.), $Mn_2(CO)_{10}$ (10 mol %), EtOAc (2 mL), 120 °C, 24 h. [b]Isolated yield.

The scope of the transformation was next examined for other aryl substituted *N*-heteroaromatic compounds and the results are shown in **Table 4.4B.4**. A wide range of aryl substituted *N*-heteroaromatics such as 2-arylindazoles (**39a-f**), 2-phenylpyridine (**26**), 2-phenylpyrimidine (**40**), 2-phenylimidazo[1,2-*a*]pyrimidine (**41**), 2-phenylimidazo[2,1-*b*]thiazole (**42**), 2-phenylbenzo[*d*]-imidazo[2,1-*b*]thiazole (**43**), 1-phenylindazole (**44**) and 1-phenylpyrazole (**45**) could be used and provided the corresponding *ortho*-hydroalkylated products (**46a-53**) in moderate to excellent yields (53−93%). Both electron-donating and electron-withdrawing groups on the aryl ring of 2-arylindazole were well tolerated. Interestingly, halogens (F, Cl) which are potentially susceptible to further functionalization were also tolerated.

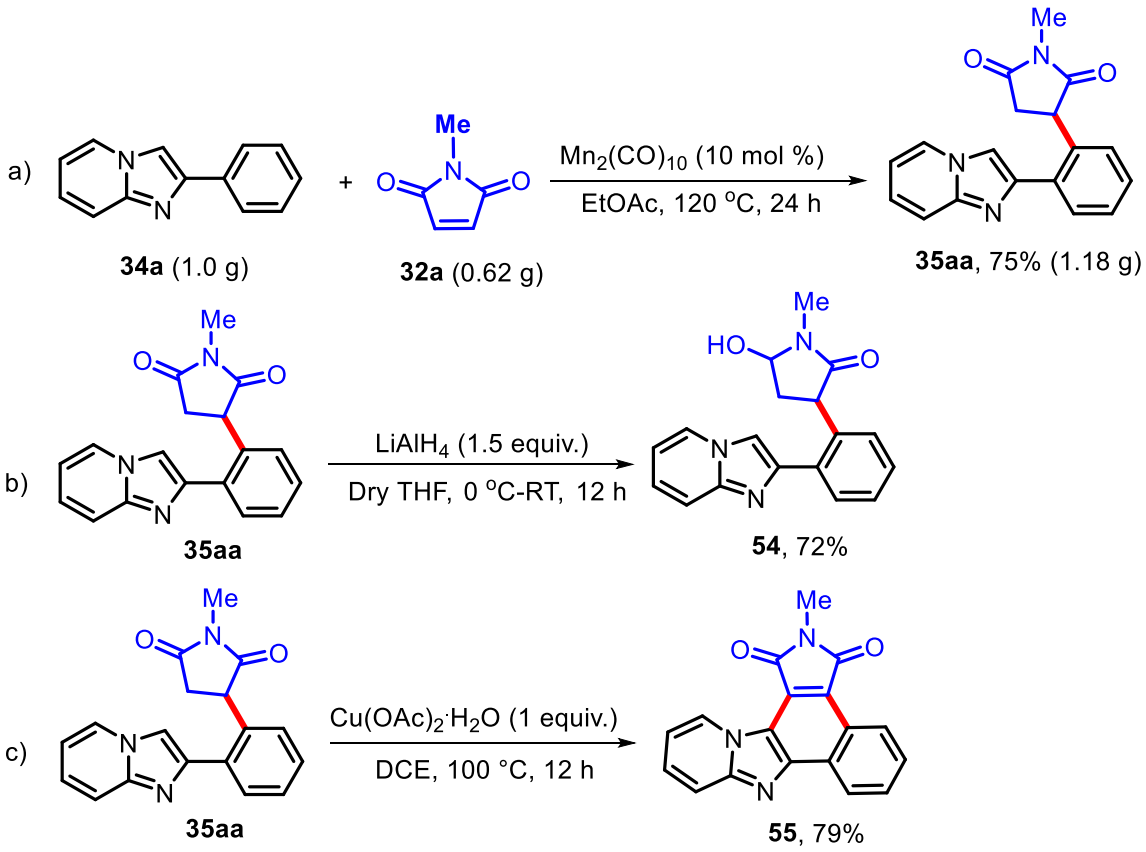
Table 4.4B.4: Substrate scope for other aryl substituted *N*-heteroaromatic compounds.[a,b]





[a]Reaction condition: **39-45** (0.26 mmol), **32** (0.31 mmol, 1.2 equiv.), $Mn_2(CO)_{10}$ (10 mol %), EtOAc (2 mL), 120 °C, 24 h. [b]Isolated yield.

The synthetic potential of the developed protocol was further highlighted through gram-scale experiment and reduction of succinimide motif (**Scheme 4.4B.10**). The gram-scale reaction of **34a** (1.0 g, 5.16 mmol) with 3**2a** (0.62 g, 5.68 mmol) produced corresponding hydroalkylated product **35aa** in 75% (1.18 g) (**Scheme 4.4B.10a**). Reduction of **35aa** by $LiAlH_4$ in dry tetrahydrofuran produced 5-hydroxy-3-(2-(imidazo[1,2-*a*]pyridin-2-yl)phenyl)-1-methylpyrrolidin-2-one (**54**) in 72% yield (**Scheme 4.4B.10b**). Further, oxidative cyclization of **35aa** using $Cu(OAc)\cdot H_2O$ in dichloroethane at 100 °C for 12 h produced corresponding maleimide annulated product **55** in 79% yield (**Scheme 4.4B.10c**).

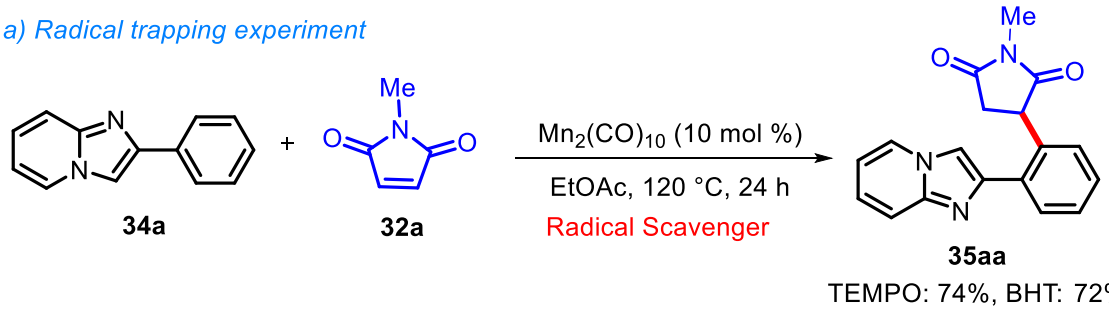


Scheme 4.4B.10: Gram-scale synthesis and synthetic utility of **35aa**

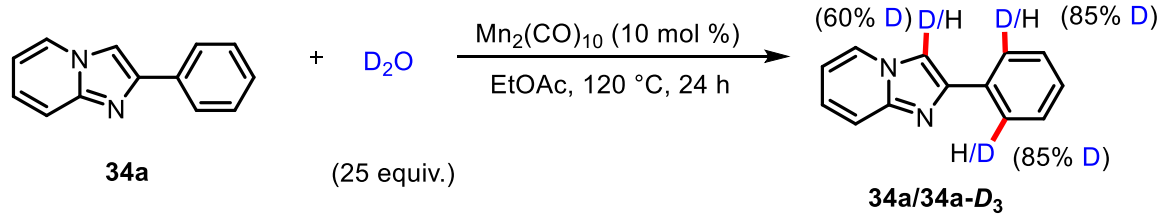
To shed more light on the reaction mechanism, some control experiments were performed (**Scheme 4.4B.11**). At first, reaction of **35a** with **32a** was performed under the optimized reaction conditions in the presence of radical scavengers TEMPO (2,2,6,6-tetramethylpiperidine-1-oxyl) and BHT (2,6-di-*tert*-butyl-4-methyl phenol) which afforded **35aa** in 74% and 72% yields, respectively (**Scheme 4.4B.11a**). The results revealed that the reaction does not involve the radical

process. When **34a** was subjected to standard conditions in the absence of 3**2a** using D_2O (25 equiv.) as co-solvent, 85% H/D exchange at the *ortho*-position of the phenyl ring and 60% H/D exchange at the C3-position of **34a** was observed suggesting that the Mn-catalyzed C–H bond activation at the *ortho*-positions is reversible (**Scheme 4.4B.11b**). Next, kinetic isotopic effect (KIE) was investigated by intermolecular competitive and parallel experiment using **34a** and **34a-*d*$_5$** with 3**2a** under standard reaction conditions (**Scheme 4.4B.11c**). As a result *KIE* value of 2.0-2.1 (based on ^{1}H-NMR analysis) was obtained which indicated that the C–H bond cleavage is relatively fast and it might not be involved in the turnover-limiting step. Further, an intermolecular competition experiment using 2-(4-methoxyphenyl)-imidazo[1,2-*a*]pyridine (**34c**) and 2-(4-cyanophenyl)imidazo[1,2-*a*]pyridine (**34g**) with **32a** produced corresponding hydroalkylated products **35ca** and **35ga** in a ratio of 3: 1 (**Scheme 4.4B.11d**), indicated that substrates with electron-rich C2-arene ring reacted more preferentially.

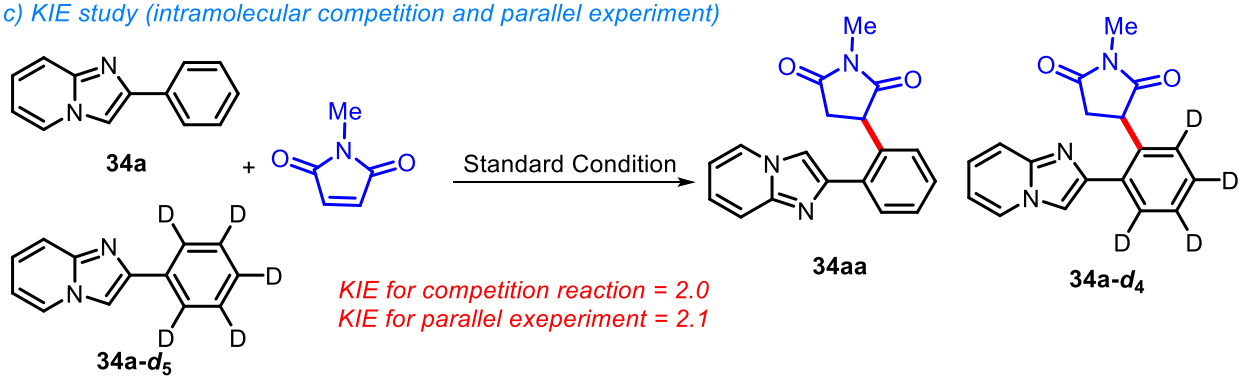
a) Radical trapping experiment

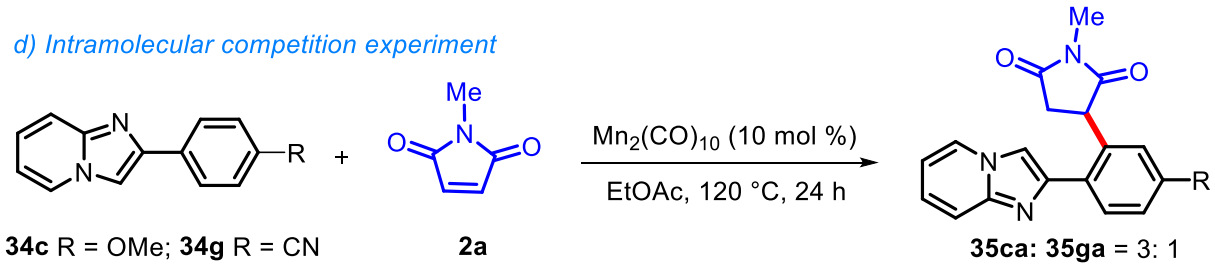


b) Deuterium exchange experiment



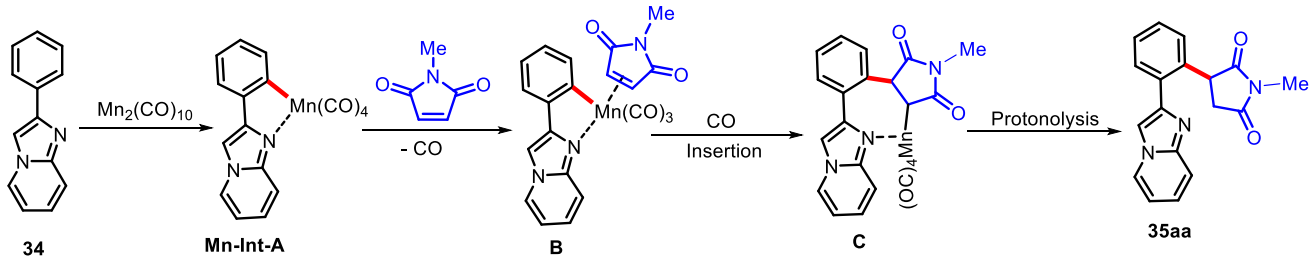
c) KIE study (intramolecular competition and parallel experiment)





Scheme 4.4B.11: Control experiments

On the basis of previous reports[62] and control experiments a plausible mechanism for the hydroalkylation is depicted in **Scheme 4.4B.12**. The C–H activation of the imidazo[1,2-a]pyridine **34a** gives metallacycle Mn-Int-**A** (detected in LC-HRMS). Next, coordination of **32a** and release of CO produces manganacycle **B** (detected in LC-HRMS). Regioselective migratory insertion of the Mn–C bond into the maleimide gives intermediate **C**, which might be protonolyzed to produce the desired product **35aa**.



Scheme 4.4B.12: Plausible mechanism

4.4B.3 CONCLUSION

In summary, a manganese-catalyzed method for the regioselective *ortho*-hydroalkylation of aryl substituted *N*-heteroaromatic compounds with maleimides is described. The reaction produced moderate to good yields of hydroalkylated products from a wide range of aryl substituted *N*-heteroaromatic compounds and maleimides. Broad substrate scope with high functional group tolerance, additive-free mild reaction conditions and excellent regioselectivity are the silent feature of the developed protocol. The developed protocol is amenable for a gram-scale reaction. Control experiments indicated that the C–H bond breaking is not involved in rate limiting step.

4.4B.4 EXPERIMENTAL SECTION

4.4B.4.1 General Information

All reagents and solvents were commercially available and were used without further purification unless otherwise noted. ^{1}H NMR and ^{13}C NMR spectra of isolated compounds were recorded on a Bruker 400 MHz spectrometers using tetramethylsilane (TMS) as an internal reference and $CDCl_3$ as a solvent. The *J* values and δ values of spectral data are given in Hz and ppm. The ^{1}H and ^{13}C shifts were referenced at 7.28 ppm and 77.1 ppm, respectively. The splitting pattern of the proton illustrated as: singlet (s), doublet (d), triplet (t), quartet (q), quintet (quint), sextet (sext), septet (sept) and multiplet (m) and their combinations as well. Purification of compound was performed on column chromatography using silica (100-200 mesh size) as stationary phase and mixture of hexane/ethyl acetate as eluent. Commercially available 0.25 mm silica gel 60-F254 plate were utilized for thin-layer chromatography (TLC). Melting point were measured on Stanford Research Systems EZ-Melt automated apparatus and uncorrected. HRMS were tested by using electrospray ionization (ESI) method on an Agilent Q-TOF LC-MS spectrometer.

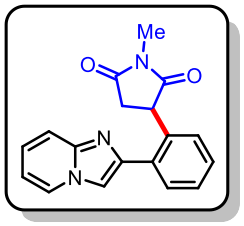
4.4B.4.2 Representative Experimental Procedure for Hydroalkylation

An oven dried 10 mL pressure tube was charged with 2-phenylimidazo[1.2-*a*]pyridine (**34**) (50 mg, 0.26 mmol) and *N*-methylmaleimide (**32**) (32 mg, 0.29 mmol), $Mn_2(CO)_{10}$ (10 mol %), and EtOAc (2 mL). The reaction vial was tightly capped and stirred at 120 °C for 24 h in an oil bath. After completion of the reaction, reaction mixture was cooled to room temperature. The ethyl acetate was evaporated under reduced pressure to obtain crude product. The crude product was purified by column chromatography on silica gel (100-200 mesh size) using EtOAc/hexane as eluent to give **35**.

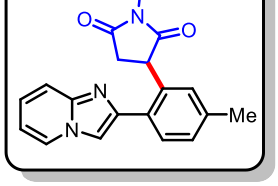
4.4B.4.3 Representative Experimental Procedure for the Synthesis of 46

An oven dried 10 mL pressure tube was charged with 2-phenylindazole (**39**) (50 mg, 0.26 mmol) and *N*-methylmaleimide (**32**) (32 mg, 0.29 mmol), $Mn_2(CO)_{10}$ (10 mol %), and EtOAc (2 mL). The reaction vial was tightly capped and stirred at 120 °C for 24 h in an oil bath. After completion of the reaction, reaction mixture was cooled to room temperature. The ethyl acetate was evaporated under reduced pressure to obtain crude product. The crude product was purified by column chromatography on size silica gel (100-200 mesh size) using EtOAc/hexane as eluent to give **46**.

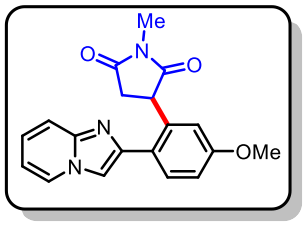
3-(2-(Imidazo[1,2-*a*]pyridin-2-yl)phenyl)-1-methylpyrrolidine-2,5-dione (35aa): The title compound was purified by column chromatography on silica gel using EtOAc/ hexanes (2: 1, *v/v*) as an eluent; off white solid (60 mg, 77%); mp = 156-158 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (d, *J* = 6.8 Hz, 1H), 7.83 (s, 1H), 7.65 – 7.63 (m, 1H), 7.53 (d, *J* = 8.8 Hz, 1H), 7.38 (s, 2H), 7.25 – 7.17 (m, 2H), 6.81 (t, *J* = 6.8 Hz, 1H), 4.76 (q, *J* = 9.6, 5.4 Hz, 1H), 3.25 (dd, *J* = 18.4, 9.6 Hz, 1H), 3.00 (dd, *J* = 18.4, 5.4 Hz, 1H), 2.99 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 179.0, 177.2, 145.4, 145.0, 135.5, 133.7, 130.5, 129.4, 128.7, 127.9, 125.6, 124.7, 117.6, 112.6, 110.6, 45.0, 38.5, 25.0; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{18}H_{16}N_3O_2^+$ 306.1237; Found 306.1262.



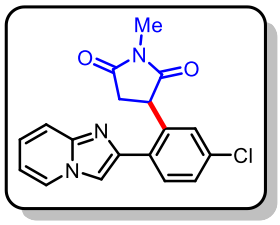
3-(2-(Imidazo[1,2-*a*]pyridin-2-yl)-5-methylphenyl)-1-methylpyrrolidine-2,5-dione (35ba): The title compound was purified by column chromatography on silica gel using EtOAc/ hexanes (3: 1, *v/v*) as an eluent; off white solid (60 mg, 78%); mp = 202-204 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (d, *J* = 6.8 Hz, 1H), 7.81 (s, 1H), 7.58 – 7.53 (m, 2H), 7.19 (t, *J* = 8.2 Hz, 2H), 7.04 (s, 1H), 6.82 (t, *J* = 6.8 Hz, 1H), 4.74 (dd, *J* = 9.6, 5.6 Hz, 1H), 3.25 (dd, *J* = 18.2, 9.4 Hz, 1H), 3.02 (s, 3H), 2.98 (dd, *J* = 18.0, 5.6 Hz, 1H), 2.40 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 179.2, 177.3, 145.4, 145.0, 138.6, 135.3, 130.8, 130.4, 130.0, 128.8, 125.6, 124.7, 117.5, 112.6, 110.4, 44.9, 38.5, 25.1, 21.2; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{19}H_{18}N_3O_2^+$ 320.1394; Found 320.1404.



3-(2-(Imidazo[1,2-*a*]pyridin-2-yl)-5-methoxyphenyl)-1-methylpyrrolidine-2,5-dione (35ca): The title compound was purified by column chromatography on silica gel using EtOAc/ hexanes (3: 1, *v/v*) as an eluent; off white solid (62 mg, 84%); mp = 174-176 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (dt, *J* = 6.8, 1.2 Hz, 1H), 7.76 (s, 1H), 7.57 (d, *J* = 8.4 Hz, 1H), 7.51 (d, *J* = 8.8 Hz, 1H), 7.19 – 7.14 (m, 1H), 6.92 (dd, *J* = 8.4, 2.4 Hz, 1H), 6.81 – 6.76 (m, 2H), 4.72 (dd, *J* = 9.4, 5.4 Hz, 1H), 3.85 (s, 3H), 3.24 (dd, *J* = 18.2, 9.4 Hz, 1H), 3.03 – 3.02 (m, 1H), 2.99 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 178.8, 177.1, 159.7, 145.3, 145.0, 136.8, 131.8, 126.3, 125.5, 124.5, 117.4, 115.3, 113.0, 112.5, 110.1, 55.4, 45.1, 38.4, 25.1; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{19}H_{18}N_3O_3^+$ 336.1343; Found 336.1347.

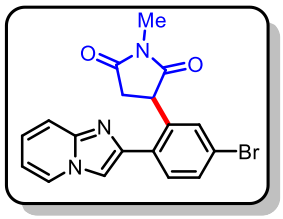


3-(5-Chloro-2-(imidazo[1,2-*a*]pyridin-2-yl)phenyl)-1-methylpyrrolidine-2,5-dione (35da):



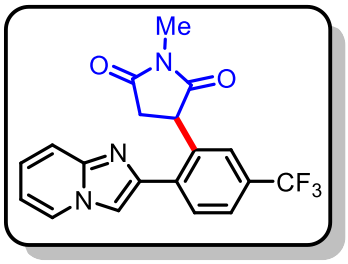
The title compound was purified by column chromatography on silica gel using EtOAc/ hexanes (3: 1, *v/v*) as an eluent; off white solid (48 mg, 65%); mp = 165-167 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (dt, *J* = 6.8, 1.2 Hz, 1H), 7.82 (s, 1H), 7.59 (d, *J* = 8.4 Hz, 1H), 7.53 (d, *J* = 9.2 Hz, 1H), 7.37 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.25 (d, *J* = 2.4 Hz, 1H), 7.21 (dd, *J* = 9.2, 6.8 Hz, 1H), 6.83 (dt, *J* = 6.8, 1.2 Hz, 1H), 4.75 (dd, *J* = 9.6, 5.6 Hz, 1H), 3.27 (dd, *J* = 18.0, 9.6 Hz, 1H), 3.00 (dd, *J* = 18.0, 6.0 Hz, 1H), 3.00 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 178.3, 176.7, 145.1, 144.4, 137.1, 134.3, 132.3, 131.6, 129.7, 128.1, 125.6, 125.0, 117.6, 112.8, 110.7, 44.9, 38.3, 25.1; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{18}H_{15}ClN_3O_2^+$ 340.0847; Found 340.0837.

3-(5-Bromo-2-(imidazo[1,2-*a*]pyridin-2-yl)phenyl)-1-methylpyrrolidine-2,5-dione (35ea):



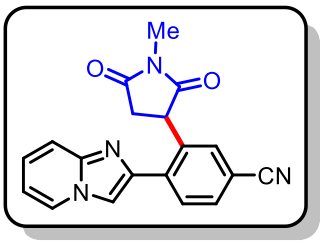
The title compound was purified by column chromatography on silica gel using EtOAc/ hexanes (3: 1, *v/v*) as an eluent; off white solid (47 mg, 67%); mp = 134-140 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (dt, *J* = 6.8, 1.2 Hz, 1H), 7.82 (s, 1H), 7.53 – 7.50 (m, 3H), 7.39 (t, *J* = 1.2 Hz, 1H), 7.20 (dd, *J* = 9.2, 6.8 Hz, 1H), 6.83 (dt, *J* = 6.8, 1.2 Hz, 1H), 4.73 (dd, *J* = 9.6 5.6 Hz, 1H), 3.26 (dd, *J* = 18.2, 9.6 Hz, 1H), 3.00 (dd, *J* = 18.0, 5.6 Hz, 1H), 3.00 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 178.3, 176.7, 145.1, 144.4, 137.4, 132.7, 132.6, 131.8, 131.1, 125.6, 125.0, 122.4, 117.6, 112.8, 110.7, 44.8, 38.3, 25.1; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{18}H_{15}BrN_3O_2^+$ 384.0342; Found 384.0340.-

3-(2-(Imidazo[1,2-*a*]pyridin-2-yl)-5-(trifluoromethyl)phenyl)-1-methylpyrrolidine-2,5-dione



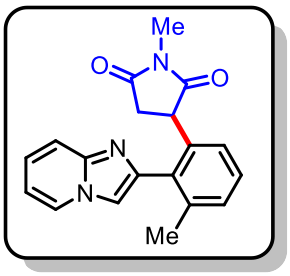
(**35fa**): The title compound was purified by column chromatography on silica gel using EtOAc/ hexanes (3: 1, *v/v*) as an eluent; off white solid (43 mg, 61%); mp = 172-174 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (dt, *J* = 6.8, 1.2 Hz, 1H), 7.88 (s, 1H), 7.78 (d, *J* = 8.0 Hz, 1H), 7.64 (d, *J* = 8.0 Hz, 1H), 7.54 – 7.51 (m, 2H), 7.22 (dd, *J* = 9.2, 6.8, 1.3 Hz, 1H), 6.85 (dt, *J* = 6.8, 1.2 Hz, 1H), 4.78 (dd, *J* = 9.6, 6.0 Hz, 1H), 3.30 (dd, *J* = 18.0, 9.6 Hz, 1H), 3.07 (dd, *J* = 18.0, 6.0 Hz, 1H), 3.00 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 178.2, 176.70, 145.2, 144.2, 137.2, 136.0, 130.7, 130.4 (d, $^{2}J_{C\text{-}F}$ = 32.7 Hz), 127.2 (d, $^{3}J_{C\text{-}F}$ = 4.0 Hz), 125.7, 125.2, 124.8 (q, $^{3}J_{C\text{-}F}$ = 3.7 Hz), 123.8 (q, $^{1}J_{C\text{-}F}$ = 270.3 Hz), 117.8, 113.0, 111.1, 45.5, 38.3, 25.2; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{19}H_{15}F_3N_3O_2^+$ 374.1111; Found 374.1103.

4-(Imidazo[1,2-*a*]pyridin-2-yl)-3-(1-methyl-2,5-dioxopyrrolidin-3-yl)benzonitrile (35ga):



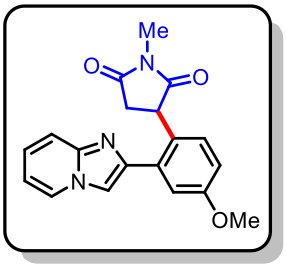
The title compound was purified by column chromatography on silica gel using EtOAc/ hexanes (3: 1, *v/v*) as an eluent; off white solid (42 mg, 56%); mp = 228-230 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (d, *J* = 6.8 Hz, 1H), 7.90 (s, 1H), 7.77 (d, *J* = 8.0 Hz, 1H), 7.67 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.58 (d, *J* = 1.6 Hz, 1H), 7.52 (d, *J* = 9.2 Hz, 1H), 7.26 – 7.22 (m, 1H), 6.80 (t, *J* = 6.8 Hz, 1H), 4.82 (dd, *J* = 9.6, 5.6 Hz, 1H), 3.31 (dd, *J* = 18.0, 9.6 Hz, 1H), 3.02 (s, 3H), 3.01 (dd, *J* = 18.0, 6.0 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 177.9, 176.4, 145.3, 143.7, 138.2, 136.5, 134.0, 131.3, 130.8, 125.8, 125.5, 118.3, 117.8, 113.3, 112.1, 111.4, 45.2, 38.2, 25.2; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{19}H_{15}N_4O_2^+$ 331.1190; Found 331.1176.

3-(2-(Imidazo[1,2-*a*]pyridin-2-yl)-3-methylphenyl)-1-methylpyrrolidine-2,5-dione (35ha):



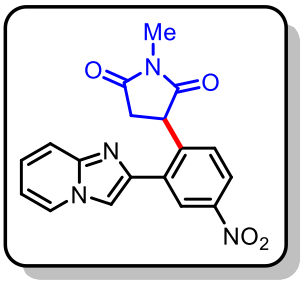
The title compound was purified by column chromatography on silica gel using EtOAc/ hexanes (2: 1, *v/v*) as an eluent; off white solid (58 mg, 77%); mp = 169-171 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (d, *J* = 6.8 Hz, 1H), 7.67 – 7.64 (m, 2H), 7.34 – 7.23 (m, 3H), 7.04 (d, *J* = 7.6 Hz, 1H), 6.87 (t, *J* = 6.8 Hz, 1H), 4.07 (dd, *J* = 9.4, 5.4 Hz, 1H), 3.06 (dd, *J* = 18.2, 9.6 Hz, 1H), 3.06 (dd, *J* = 18.4, 5.2 Hz, 1H), 2.85 (s, 3H), 2.22 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 178.7, 176.6, 144.9, 142.8, 138.9, 137.5, 134.0, 129.5, 129.0, 125.6, 124.9, 124.8, 117.7, 112.8, 112.4, 44.7, 38.4, 24.8, 21.0; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{19}H_{18}N_3O_2^+$ 320.1394; Found 320.1404.

3-(2-(Imidazo[1,2-*a*]pyridin-2-yl)-6-methoxyphenyl)-1-methylpyrrolidine-2,5-dione (35ia):



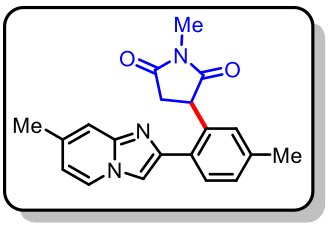
The title compound was purified by column chromatography on silica gel using EtOAc/ hexanes (3: 1, *v/v*) as an eluent; off white solid (49 mg, 66%); mp = 160-162 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (dt, *J* = 6.8, 1.2 Hz, 1H), 7.85 (s, 1H), 7.55 (d, *J* = 9.2 Hz, 1H), 7.22 – 7.18 (m, 2H), 7.16 (d, *J* = 8.4 Hz, 1H), 6.93 (dd, *J* = 8.4, 2.8 Hz, 1H), 6.83 (dt, *J* = 6.8, 1.2 Hz, 1H), 4.64 (dd, *J* = 9.6, 5.6 Hz, 1H), 3.86 (s, 3H), 3.21 (dd, *J* = 18.3, 9.6 Hz, 1H), 2.99 (s, 3H), 2.97 – 2.94 (m, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 179.3, 177.2, 158.9, 145.2, 145.0, 134.8, 130.5, 127.6, 125.6, 124.9, 117.6, 115.7, 114.4, 112.7, 110.7, 55.5, 44.2, 38.5, 25.0; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{19}H_{18}N_3O_3^+$ 336.1343; Found 336.1306.

3-(2-(Imidazo[1,2-*a*]pyridin-2-yl)-6-nitrophenyl)-1-methylpyrrolidine-2,5-dione (35ja): The



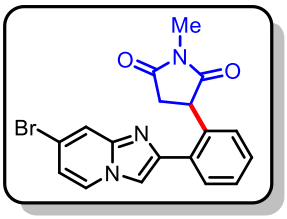
title compound was purified by column chromatography on silica gel using EtOAc/ hexanes (3: 1, *v/v*) as an eluent; off white solid (41 mg, 56%); mp = 92-94 °C; Pale yellow solid (41 mg, 56%); R_f = 0.3 (EtOAc/Hexane = 3: 1, *v/v*); mp = 92-94 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.51 (d, *J* = 2.4 Hz, 1H), 8.22 – 8.19 (m, 2H), 7.96 (s, 1H), 7.55 (d, *J* = 9.2 Hz, 1H), 7.45 (d, *J* = 8.4 Hz, 1H), 7.26 (t, *J* = 8.0 Hz, 1H), 6.89 (t, *J* = 6.8 Hz, 1H), 4.95 (dd, *J* = 9.6, 5.6 Hz, 1H), 3.34 (dd, *J* = 18.2, 9.6 Hz, 1H), 3.05 – 2.99 (m, 1H), 3.02 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 177.8, 176.4, 147.4, 145.3, 143.4, 142.3, 135.3, 131.1, 125.8, 125.6, 125.0, 122.9, 117.8, 113.3, 111.3, 45.2, 38.1, 25.2; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{18}H_{15}N_4O_4^+$ 351.1088; Found 351.1026.

1-Methyl-3-(5-methyl-2-(7-methylimidazo[1,2-*a*]pyridin-2-yl)phenyl)pyrrolidine-2,5-dione



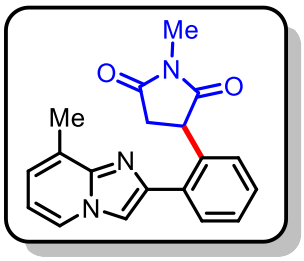
(35ka): The title compound was purified by column chromatography on silica gel using EtOAc/ hexanes (3: 1, *v/v*) as an eluent; off white solid (59 mg, 79%); mp = 177-179 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (d, *J* = 6.8 Hz, 1H), 7.72 (s, 1H), 7.53 (d, *J* = 7.6 Hz, 1H), 7.27 (s, 1H), 7.18 (d, *J* = 8.4 Hz, 1H), 7.03 (s, 1H), 6.64 (dd, *J* = 7.2, 1.6 Hz, 1H), 4.73 (dd, *J* = 9.6, 5.6 Hz, 1H), 3.23 (dd, *J* = 18.2, 9.4 Hz, 1H), 3.01 (s, 3H), 3.23 (dd, *J* = 18.0, 5.6 Hz, 1H), 2.41 (s, 3H), 2.39 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 179.2, 177.3, 145.5, 145.2, 138.4, 135.5, 135.2, 131.0, 130.3, 130.0, 128.7, 124.7, 115.8, 115.2, 109.8, 45.0, 38.5, 25.1, 21.3, 21.2; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{20}H_{20}N_3O_2^+$ 334.1550; Found 334.1539.

3-(2-(7-Bromoimidazo[1,2-*a*]pyridin-2-yl)phenyl)-1-methylpyrrolidine-2,5-dione (35la): The



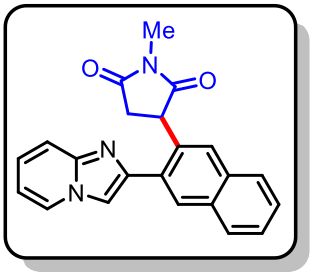
title compound was purified by column chromatography on silica gel using EtOAc/ hexanes (3: 1, *v/v*) as an eluent; off white solid (40 mg, 57%); mp = 147-149 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 (s, 1H), 7.82 (s, 1H), 7.62 – 7.61 (m, 1H), 7.43 – 7.38 (m, 3H), 7.25 (d, *J* = 8.4 Hz, 2H), 4.73 (dd, *J* = 9.4, 5.4 Hz, 1H), 3.26 (dd, *J* = 18.2, 9.4 Hz, 1H), 3.01 (dd, *J* = 18.4, 5.6 Hz, 1H), 3.00 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 178.9, 177.1, 146.3, 143.4, 135.5, 133.1, 130.4, 129.6, 128.9, 128.2, 128.0, 125.6, 118.2, 110.8, 107.3, 45.0, 38.5, 25.1; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{18}H_{15}BrN_3O_2^+$ 384.0342; Found 384.0340.

1-Methyl-3-(2-(8-methylimidazo[1,2-*a*]pyridin-2-yl)phenyl)pyrrolidine-2,5-dione (35ma):



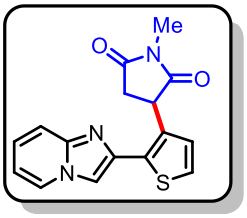
The title compound was purified by column chromatography on silica gel using EtOAc/ hexanes (3: 1, *v/v*) as an eluent; off white solid (55 mg, 72%); mp = 165-167 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, *J* = 6.8 Hz, 1H), 7.82 (s, 1H), 7.63 (dd, *J* = 5.8, 3.4 Hz, 1H), 7.39 (dd, *J* = 5.6, 3.6 Hz, 2H), 7.23 (dd, *J* = 5.6, 3.2 Hz, 1H), 7.03 (d, *J* = 6.8 Hz, 1H), 6.77 (t, *J* = 6.8 Hz, 1H), 4.76 (dd, *J* = 9.2, 5.6 Hz, 1H), 3.12 (dd, *J* = 18.4, 9.4 Hz, 1H), 3.12 (dd, *J* = 18.4, 5.6 Hz, 1H), 2.95 (s, 3H), 2.62 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 178.9, 177.0, 145.1, 144.2, 135.9, 133.5, 131.0, 129.3, 128.9, 128.6, 127.9, 124.2, 123.5, 113.1, 111.5, 44.7, 38.9, 24.9, 17.1; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{19}H_{18}N_3O_2^+$ 320.1394; Found 320.1404.

3-(3-(Imidazo[1,2-*a*]pyridin-2-yl)naphthalen-2-yl)-1-methylpyrrolidine-2,5-dione (35na):



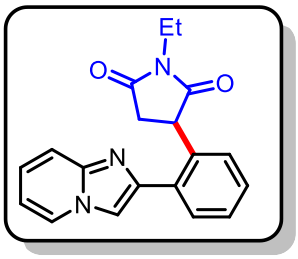
The title compound was purified by column chromatography on silica gel using EtOAc/ hexanes (3: 1, *v/v*) as an eluent; off white solid (49 mg, 68%); mp = 198-200 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (d, *J* = 6.8 Hz, 1H), 8.13 (s, 1H), 7.92 (s, 1H), 7.89 – 7.83 (m, 2H), 7.76 (s, 1H), 7.57 – 7.49 (m, 3H), 7.22 (t, *J* = 8.0 Hz, 1H), 6.85 (t, *J* = 6.8 Hz, 1H), 4.89 (dd, *J* = 9.6, 5.6 Hz, 1H), 3.05 (dd, *J* = 18.8, 9.6 Hz, 1H), 3.01 (s, 3H), 2.94 (dd, *J* = 20.0, 6 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 179.0, 177.2, 145.7, 145.1, 133.6, 133.0, 132.7, 131.4, 129.9, 129.0, 127.7, 127.5, 126.7, 126.6, 125.6, 124.8, 117.6, 112.7, 110.9, 45.4, 38.7, 25.0; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{22}H_{18}N_3O_2^+$ 356.1394; Found 356.1427.

3-(2-(Imidazo[1,2-*a*]pyridin-2-yl)thiophen-3-yl)-1-methylpyrrolidine-2,5-dione (35oa): The



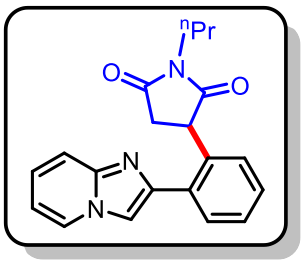
title compound was purified by column chromatography on silica gel using EtOAc/ hexanes (3: 1, *v/v*) as an eluent; off white solid (64 mg, 83%); mp = 166-168 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (d, *J* = 6.8 Hz, 1H), 7.77 (s, 1H), 7.43 (d, *J* = 9.2 Hz, 1H), 7.33 (d, *J* = 5.2 Hz, 1H), 7.27 (t, *J* = 6.4 Hz, 1H), 7.15 (t, *J* = 7.8 Hz, 1H), 6.77 (t, *J* = 6.8 Hz, 1H), 4.90 (dd, *J* = 9.4, 5.8 Hz, 1H), 3.28 (dd, *J* = 18.0, 9.2 Hz, 1H), 3.11 (dd, *J* = 18.0, 6.0 Hz, 1H), 3.10 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 177.8, 176.8, 145.1, 141.4, 134.0, 132.2, 128.1, 125.5, 124.7, 123.9, 117.4, 112.5, 109.3, 41.0, 38.1, 25.3; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{16}H_{14}N_3O_2S^+$ 312.0801; Found 312.0815.

1-Ethyl-3-(2-(imidazo[1,2-*a*]pyridin-2-yl)phenyl)pyrrolidine-2,5-dione (35ab): The title



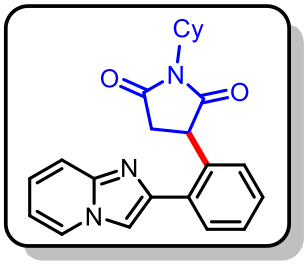
compound was purified by column chromatography on silica gel using EtOAc/ hexanes (3: 1, *v/v*) as an eluent; off white solid (64 mg, 78%); mp = 187-189 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (d, *J* = 6.8 Hz, 1H), 7.85 (s, 1H), 7.66 – 7.62 (m, 1H), 7.57 (d, *J* = 9.2 Hz, 1H), 7.41 – 7.37 (m, 1H), 7.23 – 7.18 (m, 2H), 6.83 (t, *J* = 6.8 Hz, 1H), 4.82 (dd, *J* = 9.6, 5.2 Hz, 1H), 3.66 – 3.49 (m, 2H), 3.27 (dd, *J* = 18.4, 9.2 Hz, 1H), 2.97 (dd, *J* = 18.4, 5.2 Hz, 1H), 1.18 (t, *J* = 7.2 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 178.7, 176.9, 145.4, 145.1, 135.9, 134.0, 130.6, 128.8, 128.5, 127.8, 125.6, 124.7, 117.7, 112.6, 110.8, 44.4, 38.7, 33.9, 13.1; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{19}H_{18}N_3O_2^+$ 320.1394; Found 320.1404.

3-(2-(Imidazo[1,2-*a*]pyridin-2-yl)phenyl)-1-propylpyrrolidine-2,5-dione (35ac): The title



compound was purified by column chromatography on silica gel using EtOAc/ hexanes (3: 1, *v/v*) as an eluent; off white solid (60 mg, 70%); mp = 160-162 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (d, *J* = 6.8 Hz, 1H), 7.86 (s, 1H), 7.65 – 7.63 (m, 1H), 7.58 (d, *J* = 9.2 Hz, 1H), 7.40 – 7.38 (m, 2H), 7.22 – 7.19 (m, 2H), 6.83 (t, *J* = 6.8 Hz, 1H), 4.83 (dd, *J* = 9.6, 5.6 Hz, 1H), 3.56 – 3.43 (m, 2H), 3.27 (dd, *J* = 18.4, 9.6 Hz, 1H), 2.95 (dd, *J* = 18.4, 5.6 Hz, 1H), 1.62 (h, *J* = 7.6 Hz, 2H), 0.92 (t, *J* = 7.6 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 178.9, 177.1, 145.3, 145.1, 136.0, 133.9, 130.6, 128.8, 128.3, 127.8, 125.6, 124.8, 117.6, 112.6, 110.9, 44.2, 40.6, 38.6, 21.1, 11.4; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{20}H_{20}N_3O_2^+$ 334.1550; Found 334.1528.

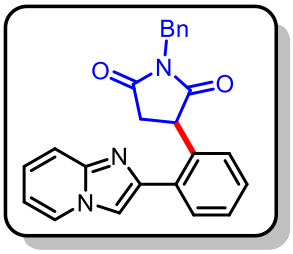
1-Cyclohexyl-3-(2-(imidazo[1,2-a]pyridin-2-yl)phenyl)pyrrolidine-2,5-dione (35ad): The title



compound was purified by column chromatography on silica gel using EtOAc/ hexanes (3: 1, *v/v*) as an eluent; off white solid (65 mg, 68%); mp = 145-147 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (d, *J* = 6.8 Hz, 1H), 7.89 (s, 1H), 7.66 – 7.60 (m, 2H), 7.41 – 7.37 (m, 2H), 7.24 – 7.16 (m, 2H), 6.84 (t, *J* = 6.8 Hz, 1H), 4.83 (dd, *J* = 9.6, 5.2 Hz, 1H), 4.06 – 4.00 (m, 1H), 3.23 (dd, *J* = 18.4, 9.6 Hz, 1H), 2.90 (dd, *J* = 18.4, 5.0 Hz, 1H), 2.21 – 2.15 (m, 2H), 1.85 – 1.81 (m, 2H), 1.68 – 1.61 (m, 3H), 1.35 – 1.23 (m, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 179.0, 177.1, 145.1, 136.5, 134.2, 130.8, 128.8, 127.7, 127.5, 125.6, 124.7, 117.8, 112.6, 111.0,

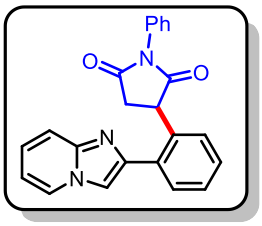
51.9, 43.4, 38.6, 28.9, 28.7, 25.9, 25.1; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{23}H_{24}N_3O_2^+$, 374.1863; Found 374.1852.

1-Benzyl-3-(2-(imidazo[1,2-*a*]pyridin-2-yl)phenyl)pyrrolidine-2,5-dione (35ae): The title



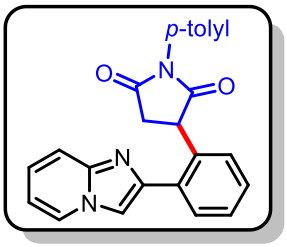
compound was purified by column chromatography on silica gel using EtOAc/ hexanes (2: 1, *v/v*) as an eluent; off white solid (54 mg, 56%); mp = 160-162 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (d, *J* = 6.8 Hz, 1H), 7.85 (s, 1H), 7.65 (d, *J* = 6.8 Hz, 1H), 7.51 (d, *J* = 9.2 Hz, 1H), 7.45 – 7.30 (m, 7H), 7.21 – 7.15 (m, 2H), 6.82 (t, *J* = 6.8 Hz, 1H), 4.84 (dd, *J* = 9.6, 5.6 Hz, 1H), 4.77 – 4.62 (m, 2H), 3.28 (dd, *J* = 18.4, 9.6 Hz, 1H), 2.95 (dd, *J* = 18.4, 5.6 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 178.6, 176.6, 145.4, 145.1, 136.1, 135.7, 133.8, 130.5, 128.9, 128.7, 128.7, 128.6, 127.9, 127.8, 125.6, 124.7, 117.6, 112.6, 110.7, 44.5, 42.6, 38.6; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{24}H_{20}N_3O_2^+$ 382.1550; Found 382.1534.

3-(2-(Imidazo[1,2-*a*]pyridin-2-yl)phenyl)-1-phenylpyrrolidine-2,5-dione (35af): The title



compound was purified by column chromatography on silica gel using EtOAc/ hexanes (3: 1, *v/v*) as an eluent; off white solid (62 mg, 65%); mp = 210-212 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (d, *J* = 6.8 Hz, 1H), 7.87 (s, 1H), 7.70 – 7.68 (m, 1H), 7.48 – 7.36 (m, 8H), 7.27 (d, *J* = 6.8 Hz, 1H), 7.15 (t, *J* = 8.0 Hz, 1H), 6.82 (t, *J* = 6.8 Hz, 1H), 4.85 (dd, *J* = 9.8, 5.8 Hz, 1H), 3.39 (dd, *J* = 18.2, 9.8 Hz, 1H), 3.21 (dd, *J* = 18.2, 6.0 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 177.6, 176.0, 145.5, 145.1, 135.2, 133.6, 132.4, 130.6, 130.2, 129.3, 128.9, 128.7, 128.2, 128.1, 126.5, 126.4, 125.6, 124.7, 117.8, 112.7, 110.6, 45.7, 38.2; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{23}H_{18}N_3O_2^+$ 368.1394; Found 368.1382.

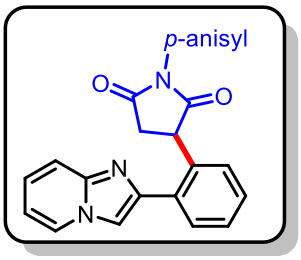
3-(2-(Imidazo[1,2-*a*]pyridin-2-yl)phenyl)-1-(*p*-tolyl)pyrrolidine-2,5-dione (35ag): The title



compound was purified by column chromatography on silica gel using EtOAc/ hexanes (2: 1, *v/v*) as an eluent; off white solid (69 mg, 70%); mp = 198-120 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (dt, *J* = 6.8, 1.2 Hz, 1H), 7.86 (s, 1H), 7.70 – 7.66 (m, 1H), 7.49 (d, *J* = 9.2 Hz, 1H), 7.44 – 7.40 (m, 2H), 7.39 – 7.36 (m, 1H), 7.25 (d, *J* = 8.0 Hz, 2H), 7.18 – 7.13 (m, 3H), 6.81 (dt, *J* = 6.8, 1.2 Hz, 1H), 4.85 (dd, *J* = 9.8, 5.8 Hz, 1H), 3.38 (dd, *J* = 18.2, 9.8 Hz, 1H), 3.19 (dd, *J* = 18.3, 6.0 Hz, 1H), 2.39 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 177.7,

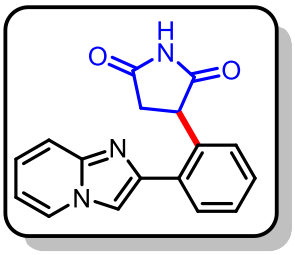
176.2, 145.5, 145.1, 138.3, 135.3, 133.7, 130.6, 130.1, 129.9, 129.8, 129.6, 128.7, 128.0, 126.3, 126.2, 125.6, 124.7, 117.8, 112.7, 110.7, 45.6, 38.3, 21.2; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{24}H_{20}N_3O_2^+$ 382.1550; Found 382.1572.

3-(2-(Imidazo[1,2-*a*]pyridin-2-yl)phenyl)-1-(4-methoxyphenyl)pyrrolidine-2,5-dione (35ah):



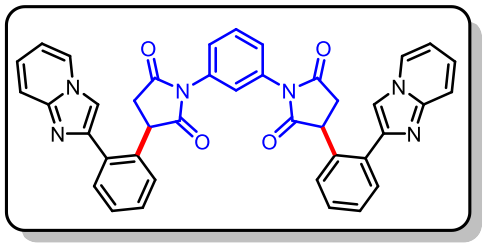
The title compound was purified by column chromatography on silica gel using EtOAc/ hexanes (2: 1, *v/v*) as an eluent; off white solid (72 mg, 70%); mp = 197-199 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (dt, *J* = 6.8, 1.2 Hz, 1H), 7.87 (s, 1H), 7.69 (dd, *J* = 5.6, 3.2 Hz, 1H), 7.49 (d, *J* = 9.2 Hz, 1H), 7.44 – 7.40 (m, 2H), 7.39 – 7.36 (m, 1H), 7.21 – 7.14 (m, 3H), 6.98 – 6.94 (m, 2H), 6.82 (td, *J* = 6.8, 1.2 Hz, 1H), 4.84 (dd, *J* = 9.6, 5.6 Hz, 1H), 3.84 (s, 3H), 3.38 (dd, *J* = 18.4, 9.6 Hz, 1H), 3.18 (dd, *J* = 18.4, 5.6 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 177.9, 176.3, 159.2, 145.4, 145.1, 135.3, 133.6, 130.6, 130.1, 128.7, 128.1, 127.6, 125.6, 125.1, 124.8, 117.8, 114.3, 112.7, 110.7, 55.5, 45.5, 38.2; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{24}H_{20}N_3O_3^+$ 398.1499; Found 398.1477.

3-(2-(Imidazo[1,2-*a*]pyridin-2-yl)phenyl)pyrrolidine-2,5-dione (35ai): The title compound was



purified by column chromatography on silica gel using EtOAc/ hexanes (2: 1, *v/v*) as an eluent; off white solid (49 mg, 65%); mp = 137-139 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.67 (s, 1H), 8.17– 8.15 (m, 1H), 7.84 (s, 1H), 7.67 – 7.64 (m, 1H), 7.62 (d, *J* = 9.2 Hz, 1H), 8.42– 8.38 (m, 2H), 7.32 – 7.28 (m, 1H), 7.23 – 7.19 (m, 1H), 6.83 (td, *J* = 6.8, 1.2 Hz, 1H), 4.87 (dd, *J* = 9.6, 6.0 Hz, 1H), 3.28 (dd, *J* = 18.4, 9.6 Hz, 1H), 3.02 (dd, *J* = 18.4, 5.6 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 179.4, 177.2, 145.1, 145.0, 135.2, 133.7, 130.5, 128.9, 128.8, 128.0, 125.7, 125.0, 117.6, 112.8, 110.8, 45.9, 39.6; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{17}H_{14}N_3O_2^+$ 292.1081; Found 292.1082.

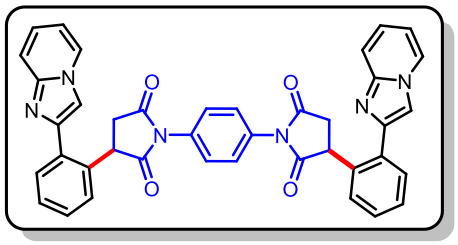
1,1'-(1,3-Phenylene)bis(3-(2-(imidazo[1,2-*a*]pyridin-2-yl)phenyl)pyrrolidine-2,5-dione)



(35aj): The title compound was purified by column chromatography on silica gel using EtOAc/ hexanes (4: 0, *v/v*) as an eluent; off white solid (97 mg, 57%); mp = 189-191 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (d, *J* = 6.8 Hz, 2H), 7.85 (s, 2H), 7.71 – 7.67 (m, 2H), 7.57 – 7.54 (m,

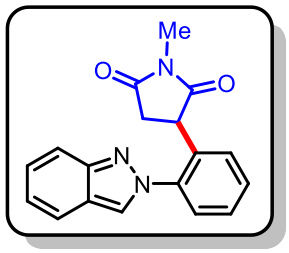
1H), 7.51 – 7.49 (m, 1H), 7.48 – 7.46 (m, 1H), 7.44 – 7.32 (m, 9H), 7.13 (t, *J* = 8.0 Hz, 2H), 6.78 (t, *J* = 6.8 Hz, 2H), 4.83 – 4.74 (m, 2H), 3.36 – 3.26 (m, 2H), 3.15 – 3.06 (m, 2H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 177.2, 177.1, 175.5, 175.4, 149.8, 145.2, 134.8, 134.6, 133.5, 133.4, 133.0, 132.9, 130.5, 130.4, 130.0, 129.6, 129.2, 129.1, 128.9, 128.7, 128.7, 128.7, 128.1, 125.9, 125.8, 125.7, 125.6, 125.5, 125.0, 124.2, 124.0, 123.9, 117.9, 112.8, 110.6, 110.5, 45.9, 45.7, 37.9, 37.7; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{40}H_{29}N_6O_4^+$ 657.2245; Found 657.2203.

1,1'-(1,4-Phenylene)bis(3-(2-(imidazo[1,2-*a*]pyridin-2-yl)phenyl)pyrrolidine-2,5-dione)

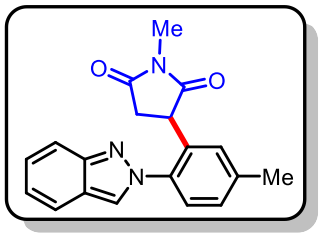


(35ak): The title compound was purified by column chromatography on silica gel using EtOAc/ hexanes (4: 0, *v/v*) as an eluent; off white solid (91 mg, 54%); mp = 174-176 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (dd, *J* = 6.4, 2.5 Hz, 2H), 7.86 (s, 2H), 7.71 – 7.67 (m, 2H), 7.57 – 7.54 (m, 2H), 7.50 – 7.46 (m, 2H), 7.45 – 7.41 (m, 6H), 7.39 – 7.37 (m, 2H), 7.17 – 7.12 (m, 2H), 6.83 – 6.79 (m, 2H), 4.82 – 4.75 (m, 2H), 3.36 (dd, *J* = 18.3, 9.7 Hz, 2H), 3.21 (dd, *J* = 18.3, 6.2 Hz, 2H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 177.3, 177.2, 175.7, 175.7, 149.8, 145.3, 145.1, 138.4, 135.2, 134.9, 134.8, 133.4, 133.4, 132.0, 132.0, 130.6, 130.5, 130.0, 129.6, 128.7, 128.7, 128.2, 128.2, 126.8, 126.7, 126.6, 126.6, 125.6, 125.5, 124.9, 124.9, 117.8, 112.8, 112.8, 110.6, 110.5, 46.0, 45.9, 38.1, 38.0; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{40}H_{29}N_6O_4^+$ 657.2245; Found 657.2195.

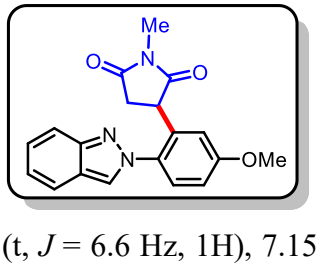
3-(2-(2*H*-Indazol-2-yl)phenyl)-1-methylpyrrolidine-2,5-dione (46aa): The title compound was purified by column chromatography on silica gel using EtOAc/ hexanes (1: 3, *v/v*) as an eluent; off white solid (55 mg, 71%); mp = 93-95 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (s, 1H), 7.74 (d, *J* = 8.4 Hz, 1H), 7.69 (d, *J* = 8.8 Hz, 1H), 7.56 – 7.51 (m, 3H), 7.38 – 7.33 (m, 2H), 7.16 (t, *J* = 7.6 Hz, 1H), 4.10 (dd, *J* = 8.8, 6.0 Hz, 1H), 3.17 – 3.11 (m, 2H), 2.71 (s, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 177.1, 176.1, 149.5, 139.9, 133.4, 130.4, 129.8, 128.9, 127.0, 125.2, 122.6, 122.3, 120.5, 117.7, 43.6, 38.1, 24.9; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{18}H_{16}N_3O_2^+$ 306.1237; Found 306.1193.



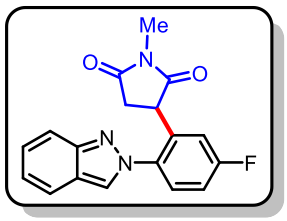
3-(2-(2*H*-Indazol-2-yl)-5-methylphenyl)-1-methylpyrrolidine-2,5-dione (46ba): The title compound was purified by column chromatography on silica gel using EtOAc/ hexanes (2: 1, *v/v*) as an eluent; off white solid (52 mg, 68%); mp = 131-133 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (s, 1H), 7.74 (d, *J* = 8.5 Hz, 1H), 7.69 (d, *J* = 8.8 Hz, 1H), 7.39 (d, *J* = 8.0 Hz, 1H), 7.36 – 7.31 (m, 2H), 7.16 (t, *J* = 7.6 Hz, 2H), 4.05 (dd, 9.6, 5.6 Hz 1H), 3.18 – 3.06 (m, 2H), 2.73 (s, 3H), 2.47 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 177.4, 176.2, 149.4, 140.1, 137.5, 133.1, 130.8, 129.4, 126.9, 125.2, 122.5, 122.2, 120.5, 120.4, 117.7, 43.4, 38.1, 24.9, 21.2; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{19}H_{18}N_3O_2^+$ 320.1394; Found 320.1302.



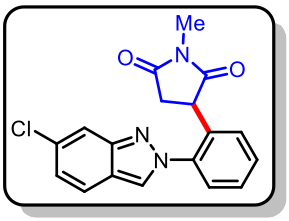
3-(2-(2*H*-Indazol-2-yl)-5-methoxyphenyl)-1-methylpyrrolidine-2,5-dione (46ca): The title compound was purified by column chromatography on silica gel using EtOAc/ hexanes (3: 1, *v/v*) as an eluent; off white solid (59 mg, 80%); mp = 167-169 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (s, 1H), 7.73 (d, *J* = 8.5 Hz, 1H), 7.69 (d, *J* = 8.7 Hz, 1H), 7.43 (d, *J* = 8.7 Hz, 1H), 7.34 (t, *J* = 6.6 Hz, 1H), 7.15 (t, *J* = 7.7 Hz, 1H), 6.99 (dd, *J* = 8.6, 1.8 Hz, 1H), 6.86 (d, *J* = 2.8 Hz, 1H), 4.01 (t, *J* = 7.6 Hz, 1H), 3.90 (s, 3H), 3.10 (d, *J* = 7.6 Hz, 2H), 2.68 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 177.0, 176.0, 160.3, 149.4, 134.9, 133.1, 128.4, 126.8, 125.5, 122.5, 122.2, 120.4, 117.6, 115.9, 113.3, 55.7, 43.6, 37.9, 24.9; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{19}H_{18}N_3O_3^+$ 336.1343; Found 336.1267.



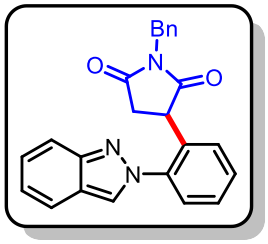
3-(5-Fluoro-2-(2*H*-indazol-2-yl)phenyl)-1-methylpyrrolidine-2,5-dione (46da): The title compound was purified by column chromatography on silica gel using EtOAc/ hexanes (2: 1, *v/v*) as an eluent; off white solid (50 mg, 65%); mp = 147-149 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (d, *J* = 0.8 Hz, 1H), 7.74 (dt, *J* = 8.5, 1.1 Hz, 1H), 7.70 – 7.67 (m, 1H), 7.50 (dd, *J* = 8.8, 5.2 Hz, 1H), 7.36 (dd, *J* = 8.8, 6.6 Hz, 1H), 7.23 – 7.14 (m, 2H), 7.11 (dd, *J* = 8.8, 2.8 Hz, 1H), 4.06 (dd, *J* = 9.2, 6.2 Hz, 1H), 3.17 – 3.05 (m, 2H), 2.70 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 176.4, 175.6, 162.2 (d, $^{1}J_{C\text{-}F}$ = 250.0 Hz), 149.6, 136.2 (d, $^{4}J_{C\text{-}F}$ = 3.0 Hz), 135.8, (d, $^{3}J_{C\text{-}F}$ = 8.0 Hz), 134.2, 128.9 (d, $^{3}J_{C\text{-}F}$ = 8.0 Hz), 127.2, 125.4, 122.8, 122.3, 120.4, 117.8, 117.3 (d, $^{2}J_{C\text{-}F}$ = 24.0 Hz), 115.8 (d, $^{2}J_{C\text{-}F}$ = 24.0 Hz), 43.4, 37.8, 25.0; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{18}H_{15}FN_3O_2^+$ 324.1143; Found 324.1059.



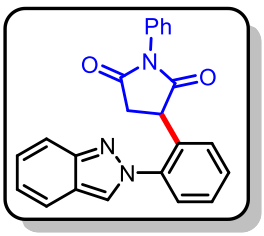
3-(2-(6-Chloro-2*H*-indazol-2-yl)phenyl)-1-methylpyrrolidine-2,5-dione (46ea): The title compound was purified by column chromatography on silica gel using EtOAc/ hexanes (2: 1, *v/v*) as an eluent; off white solid (50 mg, 67%); mp = 136-138 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (s, 1H), 7.73 (d, *J* = 1.9 Hz, 1H), 7.64 (d, *J* = 9.2 Hz, 1H), 7.56 – 7.51 (m, 3H), 7.40 – 7.38 (m, 1H), 7.30 – 7.27 (m, 1H), 4.10 (dd, *J* = 9.2, 6.0 Hz, 1H), 3.18 – 3.08 (m, 2H), 2.74 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDDCl_3$) δ 177.0, 176.0, 147.8, 139.6, 133.2, 130.6, 130.0, 129.0, 128.5, 128.3, 126.9, 124.8, 122.6, 119.3, 119.2, 43.6, 38.0, 25.0; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{18}H_{15}ClN_3O_2^+$ 340.0847; Found 340.0770.



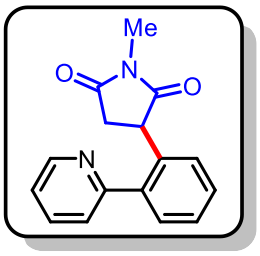
3-(2-(2*H*-Indazol-2-yl)phenyl)-1-benzylpyrrolidine-2,5-dione (46ae): The title compound was purified by column chromatography on silica gel using EtOAc/ hexanes (3: 1, *v/v*) as an eluent; off white solid (83 mg, 85%); mp = 121-123 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (s, 1H), 7.76 (dt, *J* = 8.4, 1.2 Hz, 1H), 7.71 – 7.69 (m, 1H), 7.54 – 7.48 (m, 3H), 7.43 – 7.25 (m, 7H), 7.19 – 7.15 (m, 1H), 4.52 – 4.33 (m, 2H), 4.10 (dd, *J* = 9.6, 5.5 Hz, 1H), 3.16 (dd, *J* = 18.4, 9.6 Hz, 1H), 2.99 (dd, *J* = 18.4, 5.5 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 176.9, 175.6, 149.6, 140.0, 135.7, 133.6, 129.9, 129.6, 128.9, 128.8, 128.6, 127.9, 127.0, 127.0, 125.2, 122.6, 122.3, 120.5, 117.7, 42.9, 42.6, 38.1; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{24}H_{20}N_3O_2^+$ 382.1550; Found 382.1458.



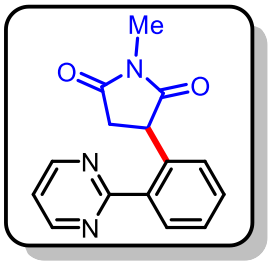
3-(2-(2*H*-Indazol-2-yl)phenyl)-1-phenylpyrrolidine-2,5-dione (46af): The title compound was purified by column chromatography on silica gel using EtOAc/ hexanes (3: 1, *v/v*) as an eluent; off white solid (88 mg, 93%); mp = 129-131 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 (d, *J* = 1.0 Hz, 1H), 7.76 – 7.68 (m, 2H), 7.60 – 7.53 (m, 3H), 7.50 – 7.48 (m, 1H), 7.38 – 7.30 (m, 4H), 7.19 – 7.15 (m, 1H), 6.95 – 6.92 (m, 2H), 4.31 (t, *J* = 8.0 Hz, 1H), 3.32 (d, *J* = 8.0 Hz, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 175.9, 175.0, 149.8, 140.0, 133.0, 131.7, 130.7, 129.8, 129.0, 128.9, 128.4, 127.2, 127.1, 126.3, 125.2, 122.7, 122.4, 120.6, 117.9, 44.0, 38.0; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{23}H_{18}N_3O_2^+$ 368.1394; Found 368.1306.



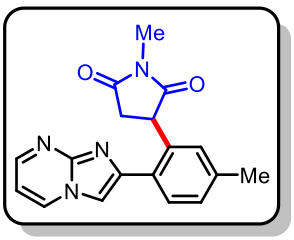
1-Methyl-3-(2-(pyridin-2-yl)phenyl)pyrrolidine-2,5-dione (47): The title compound was purified by column chromatography on silica gel using EtOAc/ hexanes (3: 1, *v/v*) as an eluent; off white solid (51 mg, 60%); mp = 118-120 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57 (d, *J* = 4.0 Hz, 1H), 7.80 (dt, *J* = 7.7, 2.0 Hz, 1H), 7.59 (d, *J* = 7.6 Hz, 1H), 7.51 – 7.49 (m, 1H), 7.44 – 7.42 (m, 2H), 7.27 – 7.24 (m, 2H), 4.39 (dd, *J* = 9.5, 5.6 Hz, 1H), 3.19 (dd, *J* = 18.4, 9.6 Hz, 1H), 2.97 (s, 3H), 2.92 (dd, *J* = 18.6, 5.6 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 178.6, 176.7, 159.1, 148.6, 140.2, 136.9, 135.6, 130.6, 129.4, 129.2, 128.0, 124.2, 122.1, 44.9, 38.7, 25.0; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{16}H_{15}N_2O_2^+$ 267.1128; Found 267.1141.



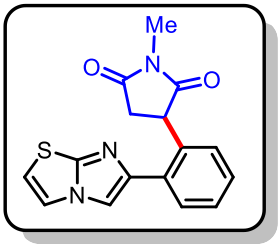
1-Methyl-3-(2-(pyrimidin-2-yl)phenyl)pyrrolidine-2,5-dione (48): The title compound was purified by column chromatography on silica gel using EtOAc/ hexanes (3: 1, *v/v*) as an eluent; off white solid (45 mg, 53%); mp = 152-154 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.76 (d, *J* = 4.8 Hz, 2H), 8.26 – 8.13 (m, 1H), 7.51 – 7.47 (m, 2H), 7.30 – 7.21 (m, 2H), 4.70 (dd, *J* = 9.6, 5.6 Hz, 1H), 3.25 (dd, *J* = 18.4, 9.6 Hz, 1H), 3.06 (s, 3H), 2.88 (dd, *J* = 18.4, 5.6 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 178.6, 176.8, 165.7, 156.8, 136.9, 136.1, 132.0, 130.9, 130.6, 128.2, 119.0, 46.1, 38.3, 25.0; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{15}H_{14}N_3O_2^+$ 268.1081; Found 268.1055.



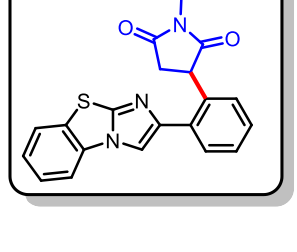
3-(2-(Imidazo[1,2-a]pyrimidin-2-yl)-5-methylphenyl)-1-methylpyrrolidine-2,5-dione (49): The title compound was purified by column chromatography on silica gel using EtOAc/ hexanes (2: 1, *v/v*) as an eluent; off white solid (51 mg, 67%); mp = 139-141 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.54 (dd, *J* = 4.0, 2.0 Hz, 1H), 8.47 (dd, *J* = 6.8, 2.0 Hz, 1H), 7.80 (s, 1H), 7.55 (d, *J* = 8.0 Hz, 1H), 7.20 (d, *J* = 7.6 Hz, 1H), 7.03 (s, 1H), 6.90 (dd, *J* = 6.8, 4.2 Hz, 1H), 5.06 (dd, *J* = 9.6, 5.6 Hz, 1H), 3.37 (dd, *J* = 18.4, 9.6 Hz, 1H), 3.08 (s, 3H), 2.90 (dd, *J* = 18.4, 5.6 Hz, 1H), 2.40 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 179.2, 177.1, 149.8, 148.0, 147.4, 139.3, 135.8, 133.0, 130.1, 130.0, 129.6, 128.8, 108.9, 108.5, 44.3, 38.5, 25.1, 21.2; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{18}H_{17}N_4O_2^+$ 321.1346; Found 321.1357.



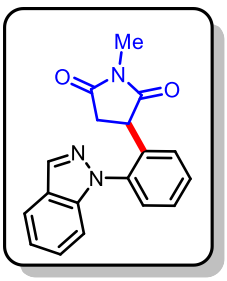
3-(2-(Imidazo[2,1-*b*]thiazol-6-yl)phenyl)-1-methylpyrrolidine-2,5-dione (50): The title compound was purified by column chromatography on silica gel using EtOAc/ hexanes (2: 1, *v/v*) as an eluent; off white solid (42 mg, 54%); mp = 132-134 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (s, 1H), 7.58 – 7.56 (m, 1H), 7.48 (d, *J* = 4.4 Hz, 1H), 7.38 – 7.33 (m, 2H), 7.21 – 7.18 (m, 1H), 6.88 (d, *J* = 4.8 Hz, 1H), 4.79 (dd, *J* = 9.6, 5.6 Hz, 1H), 3.26 (dd, *J* = 18.4, 9.6 Hz, 1H), 3.05 (s, 3H), 2.91 (dd, *J* = 18.4, 5.6 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 179.1, 177.0, 149.6, 147.0, 135.4, 133.9, 130.1, 128.8, 128.5, 127.9, 118.5, 112.8, 110.7, 44.5, 38.5, 25.1; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{16}H_{14}N_3O_2S^+$ 312.0801; Found 312.0788.



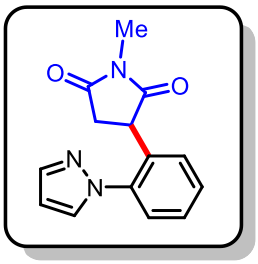
3-(2-(Benzo[d]imidazo[2,1-*b*]thiazol-2-yl)phenyl)-1-methylpyrrolidine-2,5-dione (51): The title compound was purified by column chromatography on silica gel using EtOAc/ hexanes (3: 1, *v/v*) as an eluent; off white solid (49 mg, 73%); mp = 160-162 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (s, 1H), 7.75 (d, *J* = 7.9 Hz, 1H), 7.67 (d, *J* = 8.0 Hz, 1H), 7.65 – 7.63 (m, 1H), 7.50 (dt, *J* = 7.7, 1.2 Hz, 1H), 7.42 – 7.38 (m, 3H), 7.24 – 7.22 (m, 1H), 4.83 (dd, *J* = 9.5, 5.2 Hz, 1H), 3.30 (dd, *J* = 18.4, 9.5 Hz, 1H), 3.07 (s, 3H), 2.94 (dd, *J* = 18.4, 5.2 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 179.1, 177.0, 147.5, 146.0, 135.4, 133.7, 132.1, 130.2, 130.1, 128.9, 128.6, 127.9, 126.3, 125.2, 124.5, 112.9, 109.7, 44.6, 38.5, 25.1; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{20}H_{16}N_3O_2S^+$ 362.0958; Found 362.0885.



3-(2-(1*H*-Indazol-1-yl)phenyl)-1-methylpyrrolidine-2,5-dione (52): The title compound was purified by column chromatography on silica gel using EtOAc/ hexanes (1: 3, *v/v*) as an eluent; off white solid (51 mg, 65%); mp = 226-228 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (s, 1H), 7.80 (d, *J* = 8.4 Hz, 1H), 7.53 – 7.38 (m, 6H), 7.28 – 7.24 (m, 1H), 4.10 (dd, *J* = 9.6, 5.6 Hz, 1H), 3.03 (dd, *J* = 18.4, 9.6 Hz, 1H), 2.89 (dd, *J* = 18.4, 5.6 Hz, 1H), 2.76 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 177.3, 176.2, 140.6, 138.1, 135.4, 135.2, 130.3, 129.5, 128.9, 128.1, 127.4, 124.2, 121.8, 121.0, 110.4, 43.4, 37.8, 24.9; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{18}H_{16}N_3O_2^+$ 306.1237; Found 306.1175.

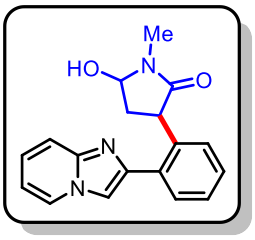


3-(2-(1*H*-Pyrazol-1-yl)phenyl)-1-methylpyrrolidine-2,5-dione (53): The title compound was



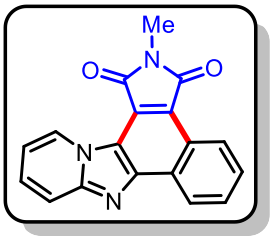
purified by column chromatography on silica gel using EtOAc/ hexanes (2: 1, *v/v*) as an eluent; off white solid (60 mg, 68%); mp = 112-114 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, *J* = 2.4 Hz, 1H), 7.65 (d, *J* = 2.0 Hz, 1H), 7.45 – 7.42 (m, 2H), 7.38 – 7.35 (m, 1H), 7.32 – 7.28 (m, 1H), 6.46 – 6.45 (m, 1H), 4.17 (dd, *J* = 9.6, 5.6 Hz, 1H), 3.12 (dd, *J* = 18.4, 9.6 Hz, 1H), 2.97 (s, 3H), 2.86 (dd, *J* = 18.4, 5.6 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 177.6, 176.2, 140.8, 139.6, 133.1, 131.2, 130.0, 129.1, 128.8, 126.6, 107.2, 43.4, 37.8, 25.2; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{14}H_{14}N_3O_2^+$ 256.1081; Found 256.1094.

3-(2-(Imidazo[1,2-*a*]pyridin-2-yl)phenyl)-1-methyl-1,3-dihydro-2*H*-pyrrol-2-one (54): The



title compound was purified by column chromatography on silica gel using EtOAc/ hexanes (2: 1, *v/v*) as an eluent; off white solid (36 mg, 72%); mp = 192-194 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (dt, *J* = 6.8, 1.2 Hz, 1H), 7.79 (s, 1H), 7.65 (d, *J* = 9.2 Hz, 1H), 7.55 (dt, *J* = 7.6, 0.8 Hz, 1H), 7.48 – 7.46 (m, 2H), 7.40 – 7.34 (m, 1H), 7.32 – 7.28 (m, 1H), 6.92 (td, *J* = 6.8, 1.2 Hz, 1H), 5.11 (d, *J* = 5.2 Hz, 1H), 4.10 (dt, *J* = 9.2, 5.2 Hz, 1H), 3.00 (s, 3H), 2.77 (d, *J* = 9.2 Hz, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 172.6, 145.12, 144.4, 138.5, 133.2, 130.5, 129.1, 127.1, 126.7, 125.7, 125.7, 117.1, 113.2, 110.7, 91.5, 42.5, 37.1, 26.8; HRMS (ESI) *m/z*: $[M + H - H_2O]^+$ Calcd for $C_{18}H_{16}N_3O^+$ 290.1288; Found 290.1286.

2-Methyl-1*H*-benzo[*e*]pyrido[1',2':1,2]imidazo[4,5-*g*]isoindole-1,3(2*H*)-dione (55): The title



compound was purified by column chromatography on silica gel using EtOAc/ hexanes (1: 4, *v/v*) as an eluent; yellow solid (39 mg, 79%); mp = 297-299 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.01 (d, *J* = 6.9 Hz, 1H), 9.07 – 9.04 (m, 1H), 8.82 (d, *J* = 7.6 Hz, 1H), 7.89 (d, *J* = 9.2 Hz, 1H), 7.79 – 7.76 (m, 2H), 7.63 (t, *J* = 7.9 Hz, 1H), 7.10 (t, *J* = 6.8 Hz, 1H), 3.29 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 169.7, 168.4, 149.8, 130.6, 130.4, 128.7, 128.7, 128.6, 126.2, 125.5, 123.6, 123.6, 120.3, 118.8, 117.5, 112.7, 112.6, 23.9; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{18}H_{12}N_3O_2^+$ 302.0924; Found 302.0936.

4.4B.4.4 X-ray crystallographic analysis of compound 35ca

The single crystal of the compound **35ca** ($C_{19}H_{17}N_3O_3$) was obtained from slow evaporation of chloroform: hexane solutions. A suitable crystal was selected and mounted on a XtaLAB AFC12 (RINC): Kappa dual home/near diffractometer. The crystal was kept at 93(2) K during data collection. Using Olex2 [63], the structure was solved with the ShelXT [64] structure solution program using Intrinsic Phasing and refined with the ShelXL [65] refinement package using Least Squares minimisation.

Table 4.4B.4.4: Crystal data and structure refinement for **35ca**

Identification code	**35ca**
Empirical formula	$C_{19}H_{17}N_3O_3$
Formula weight	335.35
Temperature/K	93(2)
Crystal system	monoclinic
Space group	$P2_1/n$
a/Å	7.9667(2)
b/Å	8.8920(2)
c/Å	22.4932(5)
α/°	90
β/°	93.666(2)
γ/°	90
Volume/Å^3	1590.16(6)
Z	4
ρ_{calc}g/cm^3	1.401
μ/mm^{-1}	0.792
F(000)	704.0

Crystal size/mm^3	0.2 × 0.05 × 0.03
Radiation	Cu Kα (λ = 1.54184)
2Θ range for data collection/°	7.878 to 160.006
Index ranges	-9 ≤ h ≤ 7, -10 ≤ k ≤ 6, -28 ≤ l ≤ 28
Reflections collected	8226
Independent reflections	3315 [R_{int} = 0.0268, R_{sigma} = 0.0396]
Data/restraints/parameters	3315/0/228
Goodness-of-fit on F^2	1.068
Final R indexes [I>=2σ (I)]	R_1 = 0.0384, wR_2 = 0.0955
Final R indexes [all data]	R_1 = 0.0441, wR_2 = 0.0984
Largest diff. peak/hole / e Å^{-3}	0.25/-0.20

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Chapter 5

Conclusions and Future Scope

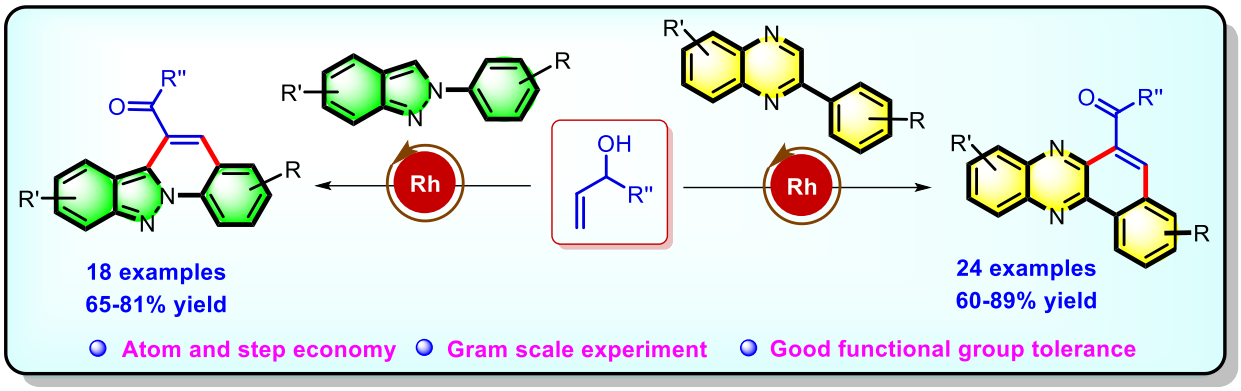
5.1 General conclusions

Worldwide, synthetic chemists play a pivotal role in constructing biologically potent fused heterocyclic molecules crucial in agrochemicals, pharmaceuticals, and natural products. The focus is on efficiently producing complex bioactive compounds with minimal synthetic steps, high atom economy, and readily available starting materials. Notably, there's a growing emphasis on synthesizing complex heterocyclic structures in a single step. The transition-metal catalyzed C-H activation method has emerged as a powerful tool in organic synthesis, gaining considerable attention for its effectiveness in constructing complex heterocyclic moieties without the need for pre-functionalization of starting materials.

In recent years, there has been a notable focus on metal-catalyzed C–H functionalization reactions, gaining attention for their efficacy in forming C–C and C–X (X = N, O, S, halogen, etc.) bonds. These methods offer the advantages of constructing complex molecular structures, demonstrating excellent regioselectivity, and good functional tolerance. In the thesis entitled "**Transition Metal Catalyzed Synthesis of Aza-fused Heterocycles and Hydroalkylation of Aryl-Substituted *N*-Heterocycles"** The synthesis of aza-fused heterocycle and alkylation of aryl-substituted *N*-heterocycles has been achieved through rhodium, copper, ruthenium and manganese catalyzed oxidative annulation reactions.

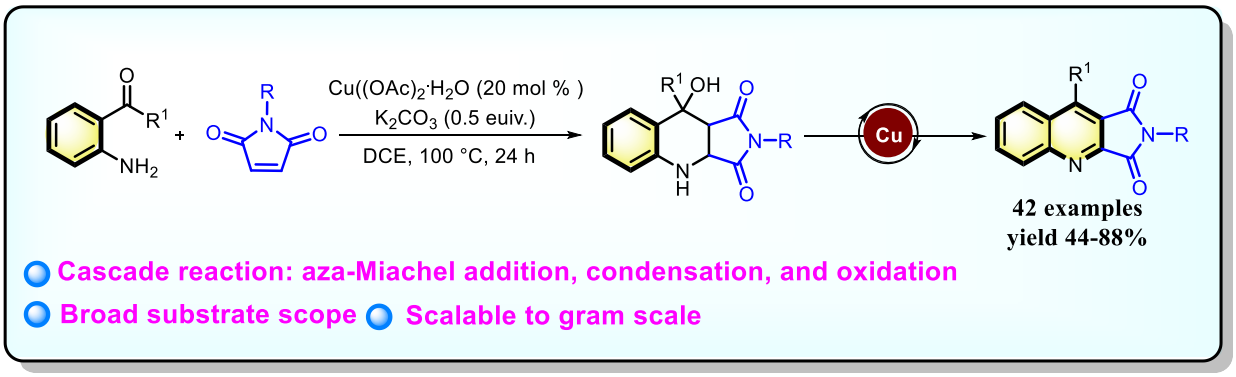
Chapter 1 The thesis provides a brief summary of literature reports focusing on C-H functionalization and oxidative C-H/C-H coupling reactions. Numerous studies on C-H activation present a significant opportunity for synthetic chemists. This opportunity allows them to synthesize aza-fused heterocycles with a wide range of functionalities.

Furthermore, one spot synthesis of polyheterocycles such as benzo[*a*]phenazines and indazolo[2,3-*a*]quinolones derivatives *via* an Rh(III)-catalyzed oxidative [4+2] annulation of 2-arylquinoxalines and 2-aryl-2*H*-indazoles with allyl alcohols respectively (**Scheme 5.1)**. All synthesized compounds were characterized by ^{1}H NMR, ^{13}C{^{1}H} NMR, and HRMS spectroscopy, and one of the compounds was unambiguously characterized by single-crystal X-ray diffraction analysis. The method features a broad substrate scope, excellent functional group tolerance, and scaled-up synthesis capability, thus providing easy access to medicinally valuable fused polyheterocyclic compounds. A tentative mechanism of the annulation reaction has been proposed based on a preliminary mechanistic investigation.



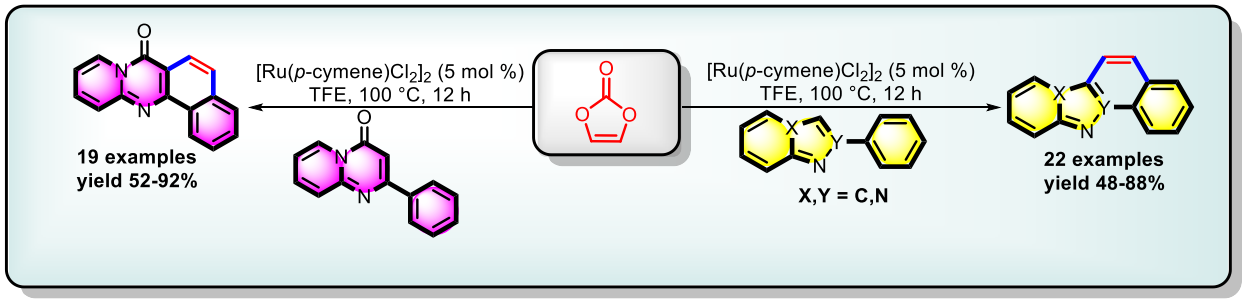
Scheme 5.1: Rhodium(III)-catalyzed oxidative annulation of 2-arylquinoxalines and 2-aryl-2*H*-indazoles with allyl alcohols

Chapter 2 deals with the Cu(II)-catalyzed cascade synthesis of 1*H*-pyrrolo[3,4-*b*]quinoline-1,3(2*H*)-diones has been achieved from readily available *o*-amino carbonyl compounds and maleimides (**Scheme 5.2)**. This one-pot cascade strategy involves a copper-catalyzed aza Michael addition followed by condensation and oxidation to deliver the target molecules. The structure of all products was confirmed by spectral data such as ^{1}H, $^{13}C\{^{1}H\}$, HRMS, and single crystal X-ray analysis. This simple one-pot approach exhibited a broad substrate scope and high functional group tolerance and yielded 1*H*-pyrrolo[3,4-*b*]quinoline-1,3(2*H*)-diones in moderate to good (44−88%) yields under mild conditions. To gain insight into the mechanism, we could also isolate the intermediate of this transformation, which was confirmed ^{1}H, $^{13}C\{^{1}H\}$, HRMS, and spectroscopic data. A notable feature of the developed methods is that it can afford biologically active pyrrolo[3,4-*b*]quinolinediones in a single synthesis step from easily accessible starting materials.



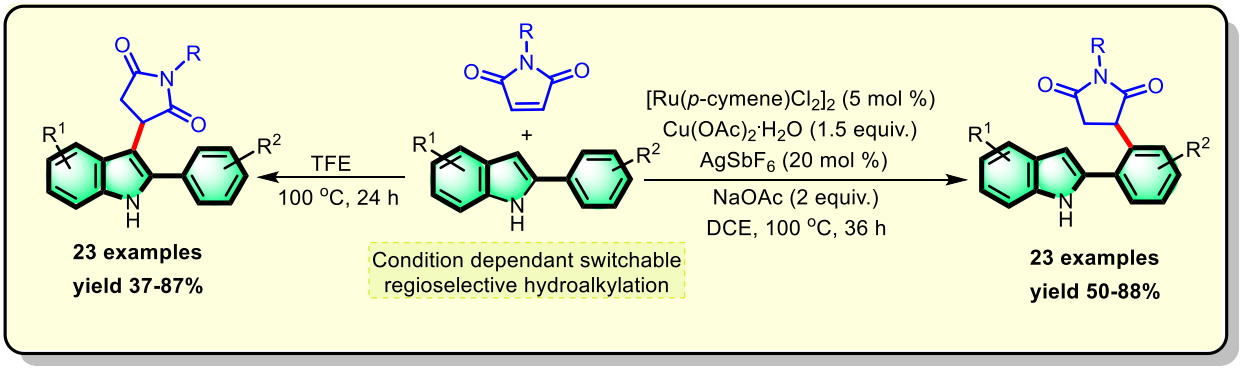
Scheme 5.2: Copper(II)-catalyzed synthesis of pyrrolo[3,4-*b*]quinolinediones from *ortho*-Amino carbonyl compounds and maleimides

Chapter 3 describes Ru(II)-catalyzed direct C-H/C-H annulation 2-phenyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one with vinylene carbonate as an acetylene surrogate for the construction of 7*H*-benzo[*H*]pyrido[2,1-*b*]quinazolin-7-one (**Scheme 5.3)**. This protocol is also applicable for 2-phenyl-2*H*-indazole and 2-phenylimidazo[1,2-*a*]pyridine for the direct synthesis of polyaromatic compounds. The synthesized polyaromatic compound derivatives were well characterized by ^{1}H, $^{13}C\{^{1}H\}$ NMR and HRMS analysis, as well as one of the compounds characterized by single X-ray crystal analysis. A series of polyaromatic compounds were synthesized in moderate to excellent yields with a tolerance of various functional groups, and the gram-scaled reaction also went smoothly without any problem. To gain insight into the mechanism, ruthenacycle I intermediate was successfully isolated and analyzed by ^{1}H and $^{13}C\{^{1}H\}$ NMR. So, based on previous literature reports and control experiments, a tentative mechanism has been described.



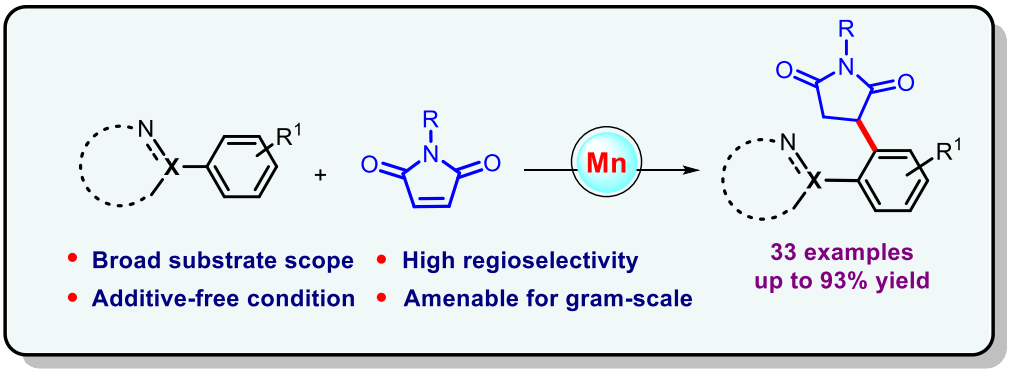
Scheme 5.3: Ru(II)-catalyzed [4 + 2] annulation of 2-arylheteroaryl with vinylene carbonate

Chapter 4A elaborates on condition-based switchable regioselective hydroalkylation of 2-arylindoles with maleimides has been developed. The reaction in the presence of a Ru(II)-catalyst resulted in hydroalkylation at the *ortho*-position of the C2-aryl ring via C–H activation, whereas the reaction in the absence of the catalyst in TFE resulted in C3-hydroalkylation (**Scheme 5.4a)**. The functionalized indole derivatives were well characterized by ^{1}H NMR, $^{13}C\{^{1}H\}$ NMR, and HRMS analysis, as well as single X-ray crystal analysis. Various functional groups, both on the indole ring and on the 2-phenyl ring, were tolerated, and a wide range of hydroalkylated products were obtained in moderate to high (37–88%) yields. The mechanism of the developed protocol was proposed based on some control experiments and previous literature reports.



Scheme 5.4a: Ru(II)-catalyzed regioselective hydroalkylation of 2-arylindoles with maleimides

Chapter 4B a regioselective manganese-catalyzed ortho-hydroalkylation of aryl-substituted *N*-heteroaromatic compounds with a range of maleimides, is described. The developed C–H bond functionalization protocol allowed introduction of succinimide motif at the *ortho*-position of aryl ring of N-heteroaromatic compounds, such as 2-arylimidazo[1,2-*a*]pyridines, 2-arylindazoles, 2-phenylpyridine, 2-phenylpyrimidine, 2-phenylimidazo[1,2-*a*]pyrimidine, 2-phenylimidazo[2,1-*b*]thiazole, 2-phenylbenzo[*d*]imidazo[2,1-*b*]thiazole, 1-phenylindazole and 1-phenylpyrazole to produce 3-(2-(*N*-heteroaryl)aryl)-pyrrolidine-2,5-diones in good yield (**Scheme 5.4a)**. The *ortho*-functionalized aryl substituted *N*-heteroaromatic derivatives were well characterized by ^{1}H NMR, ^{13}C{^{1}H} NMR, and HRMS analysis, as well as single X-ray crystal analysis. Broad substrate scope with high functional group tolerance, additive-free mild reaction conditions, and excellent regioselectivity are the silent features of the developed protocol. The developed protocol is amenable to a gram-scale reaction. Control experiments indicated that the C–H bond breaking is not involved in the rate-limiting step.



Scheme 5.4b: Manganese(I)-catalyzed *ortho*-hydroalkylation of aryl-substituted *N*-heteroaromatic compounds with maleimides

Future Scope of the Research Work

Nitrogen-containing fused heterocyclic compounds play a crucial role in organic synthesis, finding applications in natural products, pharmaceuticals, medicinal chemistry, and material science. The challenge lies in the need for pre-functionalized starting materials, leading to multistep syntheses with low atom and step economy. To address this, there has been a notable focus on transition metal-catalyzed C–H functionalization and oxidative annulation in chemical transformations. These methods have garnered attention for enabling the efficient synthesis of *N*-fused heterocycles in a single step, utilizing readily available substrates.

While the primary emphasis of the thesis revolves around C–H functionalization and annulation reactions, there exists a wide-ranging scope for the synthesis of fused aza-heterocycles and their subsequent C–H activation. This suggests a broader application and significance beyond the specific focus on the mentioned reactions. In particular, biologically important 2-phenylquinoxaline, 2-phenyl-2*H*-indazole, 2-phenyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one, 2-phenylimidazo[1,2-*a*]pyridine, and 2-phenyl-1*H*-indole were exclusively explored and used for further C-H functionalization. Some target molecules are demonstrated below, which can be prepared by minor modification of the reaction condition developed for the C-H functionalization and annulation reactions. Furthermore, exploring the synthesis of target molecules using cost-effective 3d-transition metal catalysts would be highly interesting.

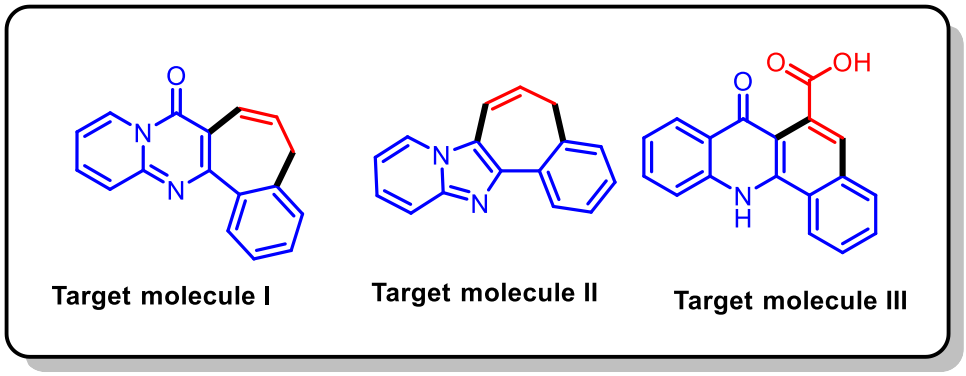


Figure 5.1: Transition metal-catalyzed synthesis of fused heterocycles

Appendices

List of Publications *[A-1]*

1. Sonam, Vikki N. Shinde, Neha Meena, **Dhananjay S. Nipate**, Krishnan Rangan, Anil Kumar, Metal-free benzoylation of imidazoheterocycles by oxidative decarboxylation of arylglyoxylic acids. *Org. Biomol. Chem.*, **2020**, *18*, 9072-9080.
2. Vikki N. Shinde, Tapta Kumar Roy, Sonam, **Dhananjay S. Nipate**, Neha Meena, Krishnan Rangan, Anil Kumar, Rhodium(III)-catalyzed annulation of 2-arylimidazo[1,2-*a*]pyridines with maleimides: synthesis of 1*H*-benzo[*e*]pyrido[1',2':1,2]imidazo[4,5-*g*]isoindole-1,3(2*H*)-diones and their photophysical studies. *Adv. Synth. Catal.,* **2020**, *362*, 5751-5764.
3. **Dhananjay S. Nipate**, Sonam Jaspal, Vikki N. Shinde, Krishnan Rangan, Anil Kumar "TEMPO-mediated cross-dehydrogenative coupling of indoles and imidazo[1,2-*a*]pyridines with fluorinated alcohols" *Org. Lett*. **2021**, *23*, 1373-1377.
4. **Dhananjay S. Nipate**, Vikki N. Shinde, Krishnan Rangan, Anil Kumar "Switchable regioselective hydroalkylation of 2-arylindoles with maleimides" *Org. Biomol. Chem*., **2021**, *19*, 4910-4921.
5. **Dhananjay S. Nipate**, Sonam Jaspal, Vikki N. Shinde, Krishnan Rangan, Anil Kumar "TEMPO-Mediated synthesis of indolyl/Imidazo[1,2-*a*]pyridinyl-substituted para-Quinone methides from butylated hydroxytoluene" *J. Org. Chem.*, **2021**, *86*, 17090-17100.
6. Vikki N. Shinde., Bhawani, **Dhananjay S. Nipate**, Sonam, Neha Meena, Krishnan Rangan, Anil Kumar, Manganese-Catalyzed ortho-Hydroalkylation of Aryl-Substituted N-Heteroaromatic Compounds with Maleimides. *Synthesis*, **2023**, *55*, 3632-3643.
7. **Dhananjay S. Nipate**, Krishnan Rangan, Anil Kumar "Copper (II)-Catalyzed Synthesis of Pyrrolo [3, 4-*b*] quinolinediones from *o*-Amino Carbonyl Compounds and Maleimides" *Org. Lett*. **2023**, *25*, 1315-1319.
8. Neha Meena, **Dhananjay S. Nipate**, Prakash N. Swami, Krishnan Rangan, and Anil Kumar, Ru(II)-catalyzed [4+2]-annulation of 2-alkenyl/2-aryl-imidazoles with maleimides and 1,4-naphthoquinones: Access to imidazo-fused polyheterocycles. *J. Org. Chem.* **2024**, 89, 2272–2282.
9. **Dhananjay S. Nipate**, Neha Meena, Prakash N. Swami, Krishnan Rangan, and Anil Kumar, Rh(III)-catalyzed oxidative [4+2] annulation of 2-arylquinoxalines and 2-aryl-2*H*-indazoles with allyl alcohols. *Chem. Commun*., **2024**, *60*, 344-347.
10. **Dhananjay S. Nipate**, Prakash N. Swami, Amol B. Gadekar, Tarun jangir, Krishnan Rangan and Anil Kumar· Synthesis of polyheterocycles by Ru(II)-catalyzed [4+2] annulation of 2-arylheteroarenes with vinylene carbonate *Chem. Asian. J. **2024*** (Manuscript under revision).

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Ru(II)-Catalyzed [4 + 2]-Annulation of 2-Alkenyl/Arylimidazoles with *N*-Substituted Maleimides and 1,4-Naphthoquinones: Access to Imidazo-Fused Polyheterocycles

Neha Meena, Dhananjay S. Nipate, Prakash N. Swami, Krishnan Rangan, and Anil Kumar*

Cite This: https://doi.org/10.1021/acs.joc.3c02229 Read Online

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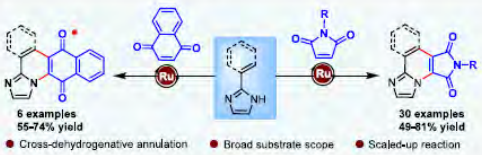
ABSTRACT: Synthesis of imidazo-fused polyheterocyclic molecular frameworks, viz. imidazo[1,2-*a*]pyrrolo[3,4-*e*]pyridines, imidazo[2,1-*a*]pyrrolo[3,4-*c*]isoquinolines, and benzo[*g*]imidazo[1,2-*a*]quinoline-6,11-diones, has been achieved by the ruthenium(II)-catalyzed [4 + 2] C−H/N−H annulation of 2-alkenyl/2-arylimidazoles with *N*-substituted maleimides and 1,4-naphthoquinones. The developed protocol is operationally simple, exhibits broad substrate scope with excellent functional group tolerance, and provides the desired products in moderate to good yields. The mechanistic studies suggest that the reaction involves the formation of a C−C bond through Ru-catalyzed C(sp^2)−H bond activation followed by intramolecular cyclization.



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Rh(III)-catalyzed oxidative [4+2] annulation of 2-arylquinoxalines and 2-aryl-2*H*-indazoles with allyl alcohols†

Dhananjay S. Nipate,[a] Neha Meena,[a] Prakash N. Swami,[a] Krishnan Rangan[b] and Anil Kumar*[a]

Synthesis of functionalized benzo[a]phenazines and indazolo[2,3-a]quinolines has been developed through Rh(III)-catalyzed oxidative annulation of 2-arylquinoxalines and 2-aryl-2*H*-indazoles with allyl alcohols, respectively. The method features a broad substrate scope, excellent functional group tolerance, good to high yields of annulated products, and scaled-up synthesis capability. Based on a preliminary mechanistic investigation, a tentative mechanism of annulation reaction has been proposed.

diverse, and atom-economical method for the synthesis of these important fused heterocycles.

In recent years, transition metal-catalyzed C–H/C–H and C–H/N–H annulation with different coupling partners has become a powerful and attractive method with high atom- and step-economy in organic synthesis to construct diverse carbo- and heterocycles.[7] Among various coupling partners, allyl alcohols have been widely used as alkene partners, equivalent to α,β-

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Copper(II)-Catalyzed Synthesis of Pyrrolo[3,4-*b*]quinolinediones from *o*-Amino Carbonyl Compounds and Maleimides

Dhananjay S. Nipate, Krishnan Rangan, and Anil Kumar*

Cite This: *Org. Lett.* 2023, 25, 1315−1319 Read Online

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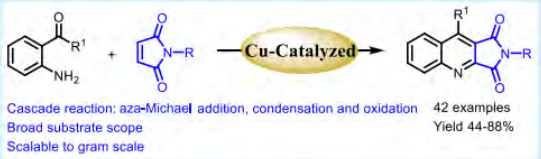
ABSTRACT: A copper(II)-catalyzed cascade synthesis of 1*H*-pyrrolo[3,4-*b*]quinoline-1,3(2*H*)-diones has been achieved from readily available *o*-amino carbonyl compounds and maleimides. This one-pot cascade strategy involves a copper-catalyzed aza-Michael addition followed by condensation and oxidation to deliver the target molecules. The protocol features a broad substrate scope and excellent functional group tolerance and affords products in moderate to good (44−88%) yields.



Synthesis V. N. Shinde et al. Special Topic

Manganese-Catalyzed *ortho*-Hydroalkylation of Aryl-Substituted *N*-Heteroaromatic Compounds with Maleimides

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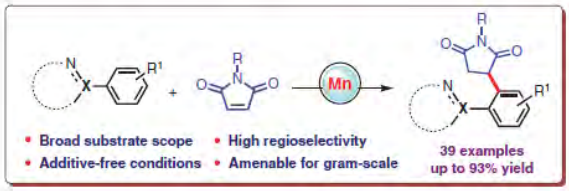
Bhawani Bhawani◊[a]
Dhanajay S. Nipate[a]
Sonam Sonam[a]
Neha Meena[a]
Krishnan Rangan[b]
Dalip Kumar[a]
Anil Kumar*[a]



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■■*A) New reference 15 (CCDC information; journal style); old refs 15/16 now 16/17; B) Experimental procedures for* **5aa-5ga** *deleted (duplication of compounds* **13-19***)*■■

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Switchable regioselective hydroalkylation of 2-arylindoles with maleimides†

Dhananjay S. Nipate,‡[a] Vikki N. Shinde,‡[a] Krishnan Rangan[b] and Anil Kumar *[a]

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Accepted 4th May 2021

DOI: 10.1039/d1ob00690h

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A condition-based switchable regioselective hydroalkylation of 2-arylindoles with maleimides has been developed. The reaction in the presence of a Ru(II)-catalyst resulted in hydroalkylation at the *ortho*-position of the C2-aryl ring *via* C–H activation whereas the reaction in the absence of the catalyst in TFE resulted in C3-hydroalkylation. Various functional groups both on the indole ring and on the 2-phenyl ring were tolerated and a wide range of hydroalkylated products were obtained in moderate to high (37–88%) yields.

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TEMPO-Mediated Synthesis of Indolyl/Imidazo[1,2-*a*]pyridinyl-Substituted *para*-Quinone Methides from Butylated Hydroxytoluene

Dhananjay S. Nipate,§ Sonam,§ Vikki N. Shinde, Krishnan Rangan, and Anil Kumar*

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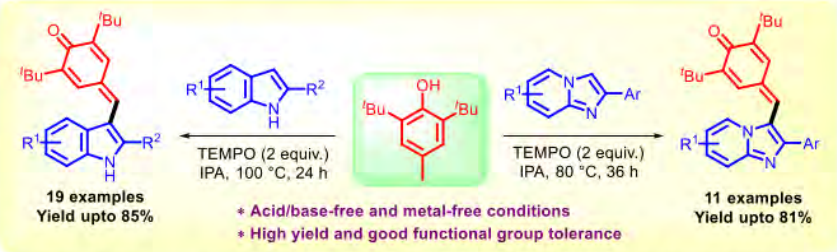

ABSTRACT: A series of indolyl or imidazo[1,2-*a*]pyridinyl-substituted *para*-quinone methides (*p*-QMs) is prepared by a metal-free, TEMPO-mediated cross-dehydrogenative coupling of butylated hydroxytoluene (BHT) with indoles or imidazo[1,2-*a*]pyridines in good to high yields. Broad substrate scope with respect to indoles and imidazo[1,2-*a*]pyridines, good functional group tolerance, and acid/base-free conditions are advantageous feature of the developed protocol. The method was amenable for scale-up on the gram scale. Based on control experiments, a reaction mechanism is proposed to describe this transformation.

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TEMPO-Mediated Cross-Dehydrogenative Coupling of Indoles and Imidazo[1,2-*a*]pyridines with Fluorinated Alcohols

Dhananjay S. Nipate,[§] Sonam Jaspal,[§] Vikki N. Shinde, Krishnan Rangan, and Anil Kumar*

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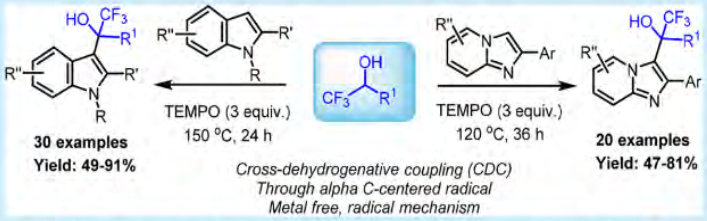

ABSTRACT: A simple and highly efficient metal-free method has been developed for hydroxyfluoroalkylation of indoles and imidazo[1,2-*a*]pyridines via TEMPO-mediated C(sp^3)−H and C(sp^2)−H bond cross-dehydrogenative coupling of fluorinated alcohols and indoles. The protocol showed broad substrate scope, afforded good yields of hydroxyfluoroalkylated products, and was amenable for scale-up. Mechanistic investigation indicated involvement of the radical pathway.

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Metal-free benzoylation of imidazoheterocycles by oxidative decarboxylation of arylglyoxylic acids†

Sonam Jaspal,[a] Vikki N. Shinde,[a] Neha Meena,[a] Dhananjay S. Nipate,[a] Krishnan Rangan[b] and Anil Kumar *[a]

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A simple and straightforward approach has been realized for the direct benzoylation of imidazoheterocycles by oxidative decarboxylation of arylglyoxylic acids in the presence of $K_2S_2O_8$ as an oxidant. Various functional groups were tolerated on both imidazoheterocycles and arylglyoxylic acids and a wide range of C5-benzoyl-imidazoheterocycles were obtained in good to high yields (50−84%). Radical trapping experiments confirmed the involvement of the radical pathway. The developed protocol is amenable for a scale-up reaction.

Advanced Synthesis & Catalysis 10.1002/adsc.202000960

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FULL PAPER

Rhodium(III)-Catalyzed Annulation of 2-Arylimidazo[1,2-*a*]pyridines with Maleimides: Synthesis of 1*H*-Benzo[e]pyrido[1',2':1,2]imidazo[4,5-*g*]isoindole-1,3(2*H*)-diones and their Photophysical Studies

Vikki N. Shinde,[a] Tapta Kanchan Roy,[b] Sonam Jaspal,[a] Dhananjay S. Nipate,[a] Neha Meena,[a] Krishnan Rangan,[c] Dalip Kumar[a] and Anil Kumar*[a]

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ChCl:2ZnCl2 Catalyzed Efficient Synthesis of New Sulfonyl Decahydroacridine-1,8-Diones via One-Pot Multicomponent Reactions to Discover Potent Antimicrobial Agents

Manisha R. Bhosle[a], Moseen A. Shaikh[a], Dhananjay Nipate[a], Lalit D. Khillare[a], Giribala M. Bondle[a], and Jaiprakash N. Sangshetti[b]

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ABSTRACT

A library of new sulfonyl decahydroacridine-1,8-diones has been efficiently synthesized by the one-pot three-component reactions of 4-(*p*-tolyl sulfonoxy) benzaldehyde, dimedone, and amines in choline chloride-based deep eutectic mixture. Pure target compounds are obtained in very good to excellent yields over short reaction times using straightforward work-up procedure. The synthesized heterocyclic decahydroacridine-1,8-diones were investigated for their *in vitro* antimicrobial activity. The minimum inhibitory concentration was determined for the test compounds as well as for reference standards. Compounds **4f**, **4m**, **4n**, and **4o** have shown good antibacterial activity whereas compounds **4a**, **4c**, **4g**, **4j**, and **4r** have displayed better antifungal activity.

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ChCl:2ZnCl2; deep eutectic solvent; multicomponent reactions; decahydroacridine-1,8-diones; antimicrobial agents

List of Presentations in Conferences *[A-3]*

1. **Dhananjay S. Nipate**, Krishnan Rangan, and Anil Kumar, Rh(III)-catalyzed oxidative [4+2] annulation of 2-arylquinoxalines with allyl alcohols. Oral Presentation at 27th ISCB international conference (ISCBC-2022), Biral Institute of Technology, Mesra, Ranchi, 16th-19th November 2022
2. **Dhananjay S. Nipate**, Krishnan Rangan, Anil Kumar, Copper (II)-Catalyzed Synthesis of Pyrrolo [3, 4-b] quinolinediones from o-Amino Carbonyl Compounds and Maleimides. I have received the RSC (Royal Society of Chemistry) (**Best Poster Award**) at "Frontiers at The Chemistry- Allied Sciences Interface" (FCASI)-2023, Jaipur, 20-21 April 2023.
3. **Dhananjay S. Nipate**, Neha Meena, Prakash N. Swami, Krishnan Rangan, and Anil Kumar, Rh(III)-catalyzed oxidative [4+2] annulation of 2-arylquinoxalines and 2-aryl-2H-indazoles with allyl alcohols. I received the RSC (Royal Society of Chemistry) (**Best Poster Award**) at the 32th CRSI National Symposium in Chemistry, 1st – 4th July 2024, BITS Pilani, Pilani Campus.

Brief Biography of the Candidate *[A-4]*

Nipate Dhananjay Shrinivas, born in Oct 1994 in Beed (Maharashtra), India, holds a B.Sc (April 2015) and MSc in chemistry (April 2017) from Dr. Babasaheb Ambedkar Marathwada University, Aurangabad, Maharashtra, India. In June 2019, he was awarded the State Eligibility Test Lectureship (SET) and Graduate Aptitude Test in Engineering (GATE)-in March 2019.

He received a CSIR project fellowship by clearing joint as a research fellow under the guidance of Prof. Anil Kumar at the Department of Chemistry, BITS Pilani, Pilani Campus, Rajasthan. In August 2019, he enrolled in the Ph.D. program at BITS Pilani. His research revolves around the C-H bond functionalization of selected azaheterocycles employing transition metal-catalyzed reactions.

Throughout his academic journey, he has published nine research articles in peer-reviewed international journals, with 5 of them being the first author. He has also actively participated in three international/national conferences, presenting his work as poster presentations. He received the two best poster awards at Frontiers at The Chemistry- Allied Sciences Interface" (FCASI)-2023, Jaipur, 20-21 April 2023 and 32nd CRSI National Symposium in Chemistry, 1 – 4 July 2024, BITS Pilani, Pilani Campus respectively.

Brief Biography of the Supervisor [*A-5]*

Dr. Anil Kumar is a professor of chemistry at Birla Institute of Technology and Science (BITS), Pilani, Pilani campus. He completed his PhD from the department of chemistry, University of Delhi, under the esteemed guidance of Professor SMS Chauhan in 2004. During his doctoral research, Dr. Kumar focused on developing heterogeneous catalysts for organic synthesis, with a strong emphasis on green chemistry principles. Following his doctoral studies, Dr. Kumar pursued his postdoctoral research at the department of biomedical and pharmaceutical sciences, University of Rhode Island, Kingston, USA, under the mentorship of Prof. Keykavous Parang. His postdoctoral work involved the synthesis of novel Src kinase inhibitory agents and solid-phase synthesis.

In 2006, Dr. Kumar joined the department of chemistry at BITS Pilani as Assistant Professor, and through his dedication and exceptional contributions, he was promoted to Associate Professor in February 2013 and later to Professor in August 2018. Throughout his career, he has displayed outstanding leadership, serving as the Associate Dean for Work Integrated Learning Programmes (WILP) from May 2014 to August 2018 and as the Head of the Department of Chemistry, BITS Pilani, Pilani Campus, from September 2014 to August 2016. Dr. Kumar is highly regarded for his remarkable achievements and has earned several accolades, including the CRSI Bronze Medal (2020) from CRSI Bangalore, Prof. S. Venkateswaran Faculty Excellence Award (2017) from BITS Alumni Association, Dr. Arvind Kumar Memorial Award (2014) from Indian Council of Chemists, ISCB Young Scientist Award in Chemical Sciences (2013) from ISCB Lucknow, and Harrison McCain Foundation Award (2012) from Acadia University, Canada. He is currently serving as a council member (2023-2026) of CRSI Bangalore.

With over 23 years of extensive research experience and more than 17 years of teaching experience, Dr. Kumar's expertise lies in developing novel reaction methodologies using transition metal-catalyzed C-C, N, S, and O coupling reactions, green chemistry, ionic liquids, and medicinal chemistry. He has an impressive publication record, with over 181 research papers published in reputed international journals and four book chapters covering the areas of synthetic organic chemistry, green chemistry, and medicinal chemistry. He has also co-edited a two-volume book on Transition–metal catalyzed C-H functionalization of heterocycles

published by Wiley VCH. Prof. Kumar has delivered more than 45 invited lectures at national and international symposiums/conferences.

Dr. Kumar is an accomplished mentor, having supervised thirteen PhD students as a supervisor and two as co-supervised. Currently, he supervises six PhD students. He has successfully executed six research projects as Principal Investigator (PI), sponsored by SERB, DST, CSIR, and UGC, and three projects as Co-PI, sponsored by SERB, DST, and Ranbaxy.

A respected member of various professional organizations, Dr. Kumar is a life member of the Chemical Research Society of India, Bangalore; the Indian Society of Chemists and Biologists, Lucknow; and the Indian Council of Chemists, Agra. He serves as a valuable member of the editorial advisory board for The Open Catalysis Journal and actively contributes as a reviewer for several international journals in organic chemistry.

Dr. Anil Kumar's relentless pursuit of excellence in research and his dedication to imparting knowledge to the next generation of scientists have made him a prominent figure in the field of chemistry, earning him admiration and respect from peers and students alike. His passion for exploring novel chemical transformations and fostering sustainable practices in chemistry continues to inspire and shape the future of the discipline.