Synthesis of Azaheterocycles *via* Copper/Palladium-Catalyzed Intramolecular Arylation Reactions

THESIS

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by

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Dedicated to

My beloved mother and father

BIRLA INSTITUTE OF TECHNOLOGY AND SCIENCE
PILANI (RAJASTHAN)

CERTIFICATE

This is to certify that the thesis entitled **"Synthesis of Azaheterocycles *via* Copper/Palladium-Catalyzed Intramolecular Arylation Reactions"** submitted by **Mr. Hitesh Kumar Saini**, ID No **2012PHXF0428P** for the award of Ph. D. Degree of the Institute embodies the original work done by him under my supervision.

Date:

Signature in full of the Supervisor:

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ABSTRACT

The arylation reactions have greatly enhanced our ability to create complex and functionalized molecules for several applications in medicinal and materials science. The thesis mainly focuses on Cu/Pd-catalyzed arylation reactions which comprises the synthesis of some selected fused aza-heterocycles. The whole thesis has been divided in six chapters.

The first chapter of thesis describes the brief literature overview on intramolecular arylations. The Cu/Pd catalyzed step economic arylation delivers different heterocycles via direct C-H functionalization. Different approached for the synthesis of heterocycles through palladium/copper-catalyzed arylation with detailed mechanisms of C-H functionlzation have been discussed in this chapter.

The second chapter of thesis reports a simple and convenient approach for the synthesis of imidazo[1,2-*f*]phenanthridines *via* post functionalization of imidazoles obtained through four component reaction of 1,2-dicarbonyl compounds, anilines, aldehyde and NH_4OAc. Synthesized imidazo[1,2-*f*]phenanthridine derivatives were obtained in good to excellent (58-94%) yields. The developed methodology is highly compatible with electron releasing as well as withdrawing groups. The methods involves palladium catalyzed direct arylation involving sp^2 C−H functionalization.

The third chapter of thesis describes the sequential copper and palladium-catalyzed one-pot reaction using 2-bromo-*N*-(2-bromophenyl)benzamides and phenyl acetylenes. The developed method afforded novel azepino-fused isoindolinone derivatives in good to high yields (22-90%). The protocol involves copper-catalyzed Sonogashira coupling, intramolecular hydroamidation and palladium-catalyzed intramolecular direct arylation. Various functional groups were tolerated under these conditions and two carbon-carbon bonds and one carbon-nitrogen bond were formed in this one-pot method.

The fourth chapter of thesis describes synthesis of isoindolo[2,1-*b*]isoquinolin-7(5*H*)-one framework *via* copper-catalyzed Sonogashira coupling, intramolecular hydroamidation and palladium-catalyzed intramolecular arylation. The structure of the novel heterocyclic framework has been elucidated with the help of NMR, HRMS and single X-ray crystal analysis. This unified approach provided the number of isoindolo[2,1-*b*]isoquinolin-7(5*H*)-ones derivatives in moderate to excellent yields with broad substrate scope and functional group compatibility.

The fifth chapter of thesis describes the synthesis of π-extended naphtho-fused imidazo[1,2-*a*]pyridines. The reaction of 2-(2-bromophenyl)imidazo[1,2-*a*]pyridine-3-carbaldehydes with different active methylene containing compounds easily provided naphtho[1',2':4,5]imidazo[1,2-*a*]pyridines in moderate to excellent (35-91%) yields. The cascade reaction involved Knoevenagel condensation followed by copper-catalyzed alkene arylation. Three new carbon-carbon bonds with retention of nitrile/ ketone/ ester functionality make this method advantageous for further synthetic manipulations. These π-extended naphtho-fused structures have been studied to explore their photophysical properties. Absorption and emission maxima of naphtho-fused imidazo[1,2-*a*]pyridines is shifted bathochromically and emit the high fluorescence quantum yield. Thus, synthesized and relevant π-extended polyheterocyclic compounds can be of interest of material chemist.

The sixth chapter of the thesis describes overall summary of the thesis work along with the future scope of the research work.

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LIST OF ABBREVIATIONS/SYMBOLS

Abbreviation/Symbol	Description
α	Alpha
β	Beta
Δ	Delta
δ	Parts per million
°C	Degree centigrade
Å	Angstrom
AcOH	Acetic acid
ACN	Acetonitrile
Ar	Aryl
Aq	Aqueous
Bn	Benzyl
Bu	Butyl
t-BuOK	Potassium *tert*-butoxide
t-BuONO	*tert*-Butyl nitrite
Calcd.	Calculated
^{13}C	Carbon-13
CAN	Ceric ammonium nitrate
$CDCl_3$	Deuterated chloroform
CHDA	*E*-1,2-Diaminocyclohexane
Conc	Concentration
COSY	Correlation spectroscopy
CuAAC	Copper catalyzed azide-alkyne cycloaddition

d	Doublet
dd	Doublet of doublet
DABCO	1,4-Diazabicyclo[2.2.2]octane
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCE	Dichloroethane
DCM	Dichloromethane
DMA	*N*,*N*-Dimethylacetamide
DMAD	Dimethyl acetylene dicarboxylate
DMF	*N*,*N*-Dimethylformamide
DMSO-d_6	Deuterated dimethylsulfoxide
DNA	Deoxyribonucleic acid
EI	Electron ionization
ESI-MS	Electron spray ionization mass spectrometry
ESI-TOF	Electron spray ionization-time of flight
ESIPT	Excited state intramolecular proton transfer
EtOAc	Ethyl acetate
Et	Ethyl
EtOH	Ethanol
Equiv	Equivalent
G	Gram
h	Hours
HRMS	High resolution mass spectrometry
HTIB	(Hydroxy(tosyloxy)iodo)benzene
IR	Infrared
Hz	Hertz

J	Coupling constant
Lit.	Literature
MCR	Multi component reaction
Me	Methyl
MS	Mass spectrometry
mp	Melting point
m	Multiplet
mg	Milligram
MHz	Mega hertz
min	Minutes
mL	Milliliter
mmol	Millimole
MW	Microwave
N_2	Nitrogen gas
NMR	Nuclear magnetic resonance
NOE	Nuclear overhauser effect
NOESY	Nuclear overhauser effect spectroscopy
NBS	*N*-bromosuccinimide
NIS	*N*-iodosuccinimide
O_2	Oxygen gas
PEG	Polyethylene glycol
PivOH	Pivalic acid
PIDA	Phenyl iodonium diacetate
Ph	Phenyl
Phen	1,10-Phenanthroline

ppm	Parts per million
Pr	Propyl
%	Percentage
p-TsOH	*p*-Toluenesulfonic acid
rt	Room temperature
s	Singlet
SET	Single electron transfer
t	Triplet
TBAI	Tetrabutylammonium iodide
TBHP	*tert*-Butyl hydroperoxide
TEA	Triethyl amine
TEMPO	*2,2,6,6*-tetramethylpiperidine-1-oxyl
TFA	Trifluoroacetic acid
TfOH	Trifluoromethanesulfonic acid
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMS	Tetramethylsilane
TMSCl	Trimethylsilyl chloride
OTf	Triflouromethanesulfonate

Chapter 1

Recent Advances in the Synthesis of Fused Heterocycles *via* Copper/ Palldium-Catalyzed Arylation Reactions

1.1 Introduction

Nature is always a good example for a chemist to get inspired for the advancement through its vast diversity. In this aspect, organic synthesis has been exploited too much by the creation of new molecules and discovery of complex building blocks. Over the centuries, chemists have learnt how to prepare new molecules, basically by the interconversion of functional groups. Numerous type of organic scaffolds are designed, and achieved at a level of sophistication where reactions and reagents are available to synthesize any complex target molecule.[1] For continuous developments in organic synthesis towards drug discovery, heterocycles have been studied and applied majorly.[2] Universal occurrence of diverse alkaloids, antibiotics, amino acids, vitamins, and hormones in nature made researchers more prone to develop new heterocyclic compounds in laboratory.[3-7]

Heterocyclic compounds are those where carbocyclic ring contains at least one carbon, which is replaced by hetero atoms *i.e.* Nitrogen, Oxygen, Sulfur and others.[8-9] Intrinsic biological importance of these heterocyclic compounds occupies a unique place in daily life. Hence, synthetic incorporation of hetero atoms to the basic unit of cyclic organic molecules through different chemical transformation provides an excellent alternative in order to facilitate diverse heterocycles.[10-12]

Among heterocycles, so far spurring study has been developed regarding nitrogen heterocycles because of their significant occurrence in nature as well as pharmaceuticals.[13] In particular, aza-fused heteroaromatics comprise a family of biological agents with pharmacological properties. In view of these applications, their DNA-chain intercalating ability makes them suitable for mutagenic and anti-neoplastic applications.[14-16] Creation of new functionality on these aza-heteroaromatics has immensely fascinated scientific community for the late-stage diversification of various kinds of organic scaffolds.[17] In this aspect, C-H functionalization has been witnessed to lead extended conjugation system and emerged truly as a revolutionary trend in organic synthesis.[17-19]

1.2 Role of transition metal to functionalize C-H bond

Owing to importance of diverse substituted molecules, the chemists have always been curious to functionalize C-H bond. In this respect, several traditional methods have been described where Friedel Craft reaction is one of the earliest example.[20] In recent years, the direct cleavage of inert C-H bond could be possible by using transition metals over multistep functional group interconversions (**Figure 1.1**).

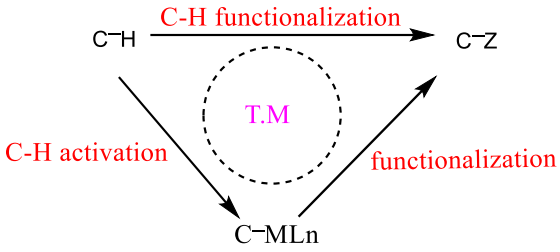
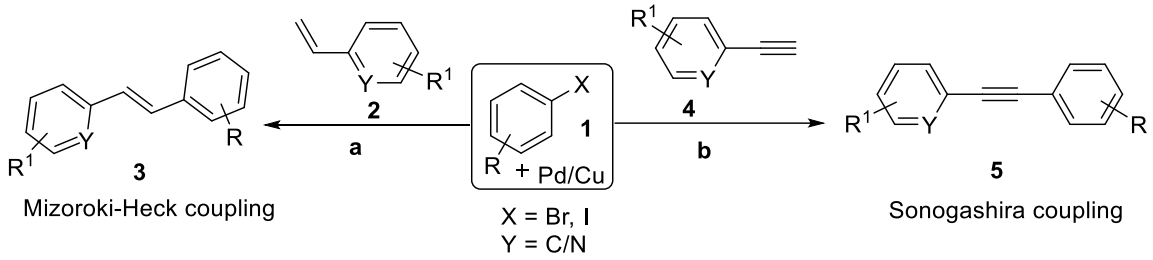


Figure 1.1 Transition metal catalyzed C-H functionalization

A detailed study of the C-H bond cleavage has been addressed in this context regarding the process by which it can be directly functionalized. The reaction of inert C-H bond with transition metals gives C-M bond which is more reactive than its C-H counterpart.[21] The resulting C-M bond leads to the C-C bond formation easily and efficiently which resolves step economy issue over multistep synthesis. Prior to this, a supportive idea for metal catalyzed C-H functionalization, concerning the oxidation of carbon chain by employing palladium (II) catalyst, cropped up which led to the formation of carbonyl compounds.[22] This oxidation of olefins involves the synthesis of acetaldehyde from ethylene (Wacker process). This has been an inspiration for further developments, especially for **Richard Heck**, who worked in 1960's and developed several coupling reactions with a catalytic amount of palladium (II) or stoichiometric amount of mercury.[23-27] The reaction of ethylene with phenylmercuric acetate and lithium tetrachloropalladate gives styrene (80%) and *trans*-stilbene (10%). Later on, the employed consecutive approaches motivated him for further improvement, and consequently described a palladium catalyzed simple protocol for the coupling of iodobenzene with styrene (known as the Heck reaction).[28] Mizoroki had also developed similar reaction in order to access new C-C bond.[29-30] However, further applications of this reaction could not be followed up due to his sudden demise from cancer at a young age. The developed cross-coupling between alkenes (**2**) and aryl halides (**1**) under palladium catalysis is known as Mizoroki-Heck coupling (**Scheme**

1.1a). This pioneer work has brought a paradigm shift in organic synthesis and eventually recognized with the Nobel Prize to R. Heck for chemistry in the year of 2010. One of related reactions which increase the carbon chain *via* direct C-H functionalization reaction is the Sonogashira coupling; the so-called coupling allows the reaction between aryl halide (**1**) with aryl/hetero alkynes (**4**) in presence of catalytic amount of palladium and copper salts (**Scheme 1.1b**). Thus, functionalization of C-H bond under palladium and copper metals has been convenient approach for the synthesis of variety of complex molecules.[31]



Scheme 1.1 Mizoroki-Heck and Sonogashira coupling reactions

1.3 Significance of Arylation

All heterocycles are generally adorned with C-H bonds, found in living organisms as well as in materials. The decoration of these heterocycles can further be transformed to other privileged molecules through C-H arylation and have become more convenient approach to access extended conjugated heterocycles (**Figure 1.2**).[19, 32]Owing to conversion into new heterocycle, arylation lie at the heart of the organic chemistry, especially in the synthesis of extended π-conjugated aromatic systems.[33-35] The extended conjugated system shows distinct fluorescent properties which make the chemist's interest special in the field of material science. For example, HPPCO (4-hydroxy-5-phenylpyrido[3,2,1-*jk*]carbazol-6-one) display an attractive optical applications since it possess long π-conjugated systems.[36] Benzimidazo[1,2-*f*]phenanthridine used as electronic devices and organic light emitting diodes (OLEDs).[37-39] Apart from this, the enriched π-electrons *N*-heterocycles containing aryl-aryl bonds are frequently encountered in biological systems (**Figure 1.2**). Many natural products and drug candidates comprise these arylated fused *N*-heterocycles. For example, an alkaloid Narciprimine is a cytotoxic agent.[40] Luotonin A,an alkloid containing quinazoline core exibits variety of intriguing biological properties such as anti-abscesses, anti-inflammation, and topoisomerase I inhibitor.[41-42] Trispheridine and Nitidine

are phenanthridine based natural products with antitumor, antibacterial, antifungal and cytotoxic activites.[43]

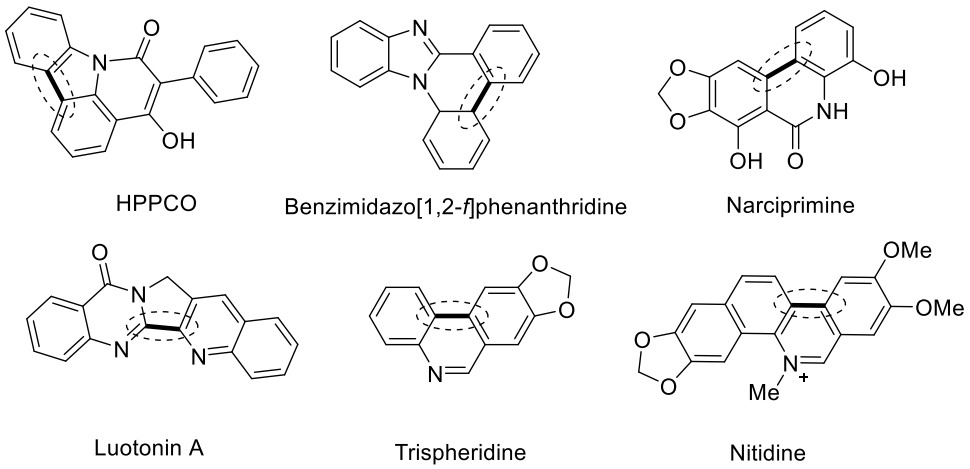


Figure 1.2 Aryl-aryl bond containing representative structures

1.4 Transition metal catalyzed arylation

The history of arylation reactions is long and rich.[44-45]From the first report of the Ullmann coupling over a century ago,[46]to the recent transition metal-catalyzed cross-coupling reactions of present era,[47-48] there has been an over whelming development in researchers ability to create these challenging bonds. Presently, arylation reactions can be furnished in high yields under mild conditions with catalysts that exhibit broad functional group tolerance.

An arsenal of the catalytic methods including the Stille,[49] Suzuki-Miyaura,[50] Negishi,[51] and Hiyama[52] couplings has been developed to provide the shortcuts compared with classical organic synthesis. These developed couplings have earned significant attention of organic researcher which rendered arylations with more efficient and straightforward manner. The arylation reactions using abovementioned coupling require both coupling partner to be prefunctionlized where one must be organometallics using B, Sn, Mg, Si etc. These functionalized substrates lead coupled product along with the elimination of stoichiometric amount of wastage which greatly violate the principle of green chemistry with poor atom economy (**Figure 1.3a**).[53] Thus, the focus has been turn to develop new reactions where unfunctionalized C-H bond is activated to achieve arylation for desired C-C/C-heteroatom bond formation` (**Figure 1.3b**).[54] In recent era, further a fascinating strategy emerged as cross dehydrogenative coupling (CDC) or oxidative coupling where both of the coupling site does not have prior functionalization to lead new structures (**Figure 1.3c**).[55] This advance technique

provides an excellent alternative where two inert C-H bonds without prior activation give coupled product.

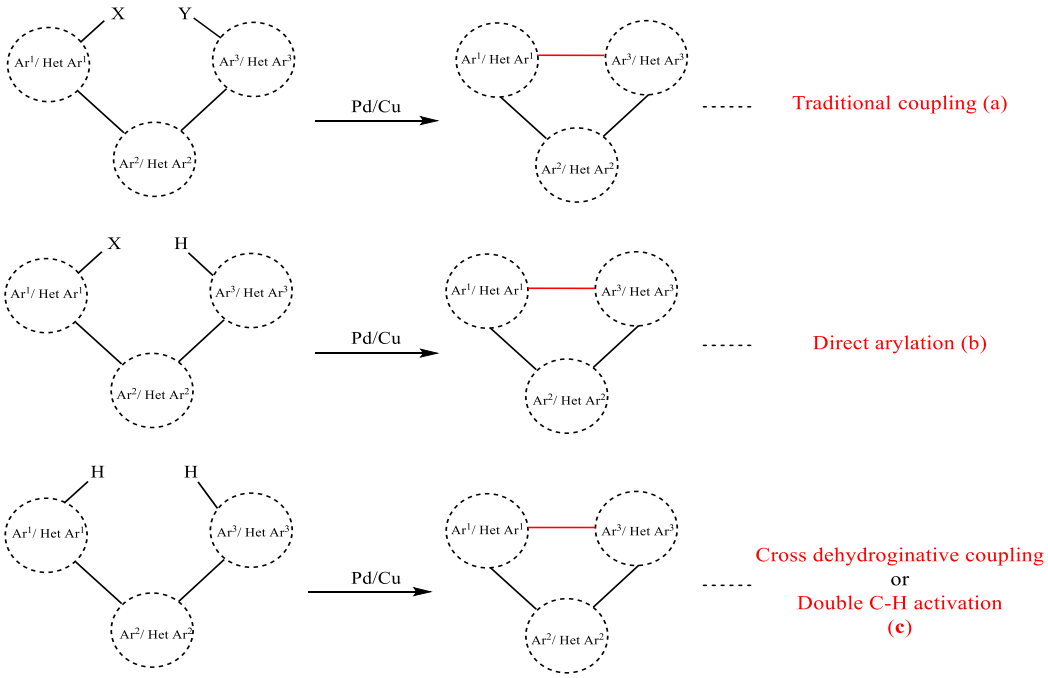


Figure 1.3 Different approaches for C-H arylations

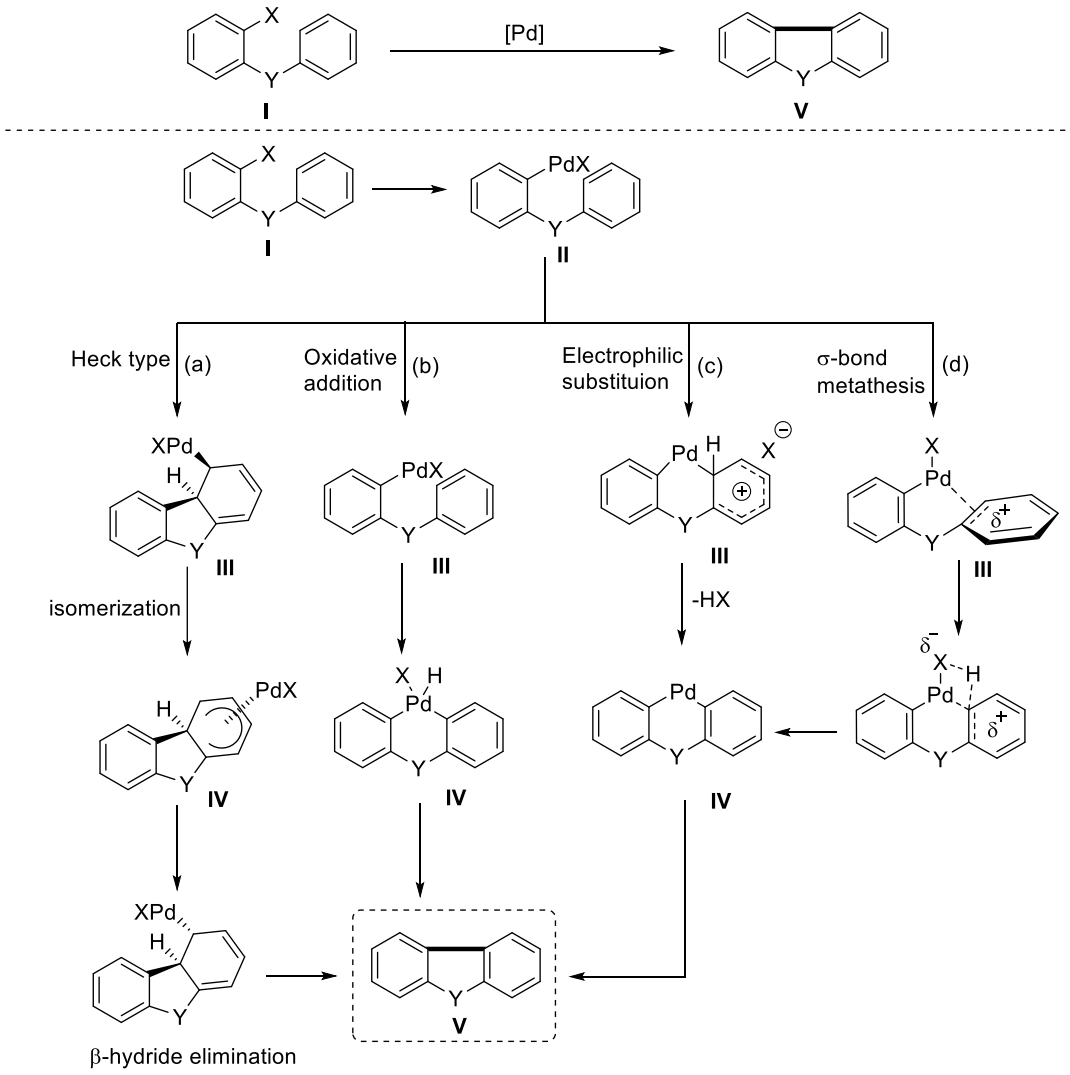
1.4A Mechanistic aspects of direct arylation under palladium catalysis

Basically, there are four ways to describe C-H functionalization/arylation as shown in **Scheme 1.4**: **a**) Heck type **b**) Oxidative addition **c**) Electrophillic aromatic substitution **d**) σ-Bond metathesis.

a) **Heck type**: This type of addition was first time reported by Heck in 1968. First palladium salt inserts into carbon-halogen bond of substrate **I** to give palladium complex. Subsequently, the migration of palladium complex to neighboring aryl ring *via* syn addition to gives a new aryl palladium complex which further undergoes β-hydride elimination to afford cross-coupled product **V** (**Scheme 1.4a**).

b) **Oxidative addition**: The organo palladium complex (**II**) insert into C-H bond of neighboring aryl ring and gives tetra-coordinated palladium complex (**IV**) which subsequently leads to fused molecule (**V**) *via* direct arylation (**Scheme 1.4b**).

c) **Electrophilic aromatic substitution**: Direct arylation occurs *via* electrophillic palladation in formed organometallic complex **II** which involve the cyclic transition state *i.e.* arenium ion along with sp^3 hybridized carbon (**Scheme 1.4c**).



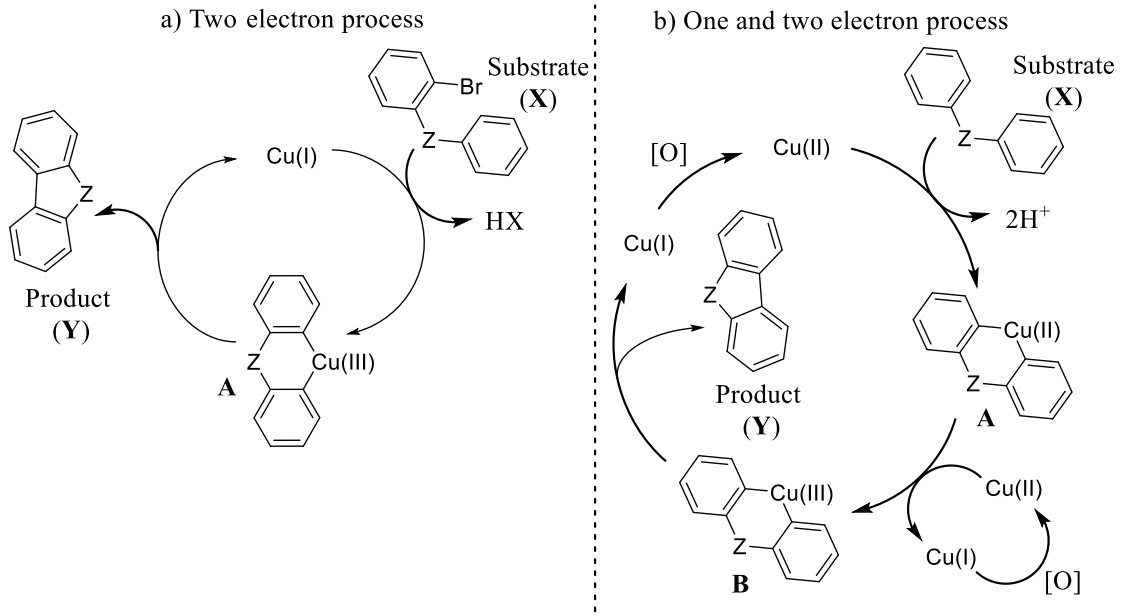
Scheme 1.4 Different possibilities for Palladium catalyzed C-H arylation

d) ***σ*-Bond metathesis**: C-H functionalization proceeds through concerted mechanism where four membred cyclic transition state forms from intermediate **III** to afford arylated product **V** (**Scheme 1.4d**).

Among the mentioned possible pathways, the nature of exact mechanism in a particular reaction depends on the substrate, base, ligand and solvent used.

1.4B Mechanistic aspects of direct arylation under copper catalysis

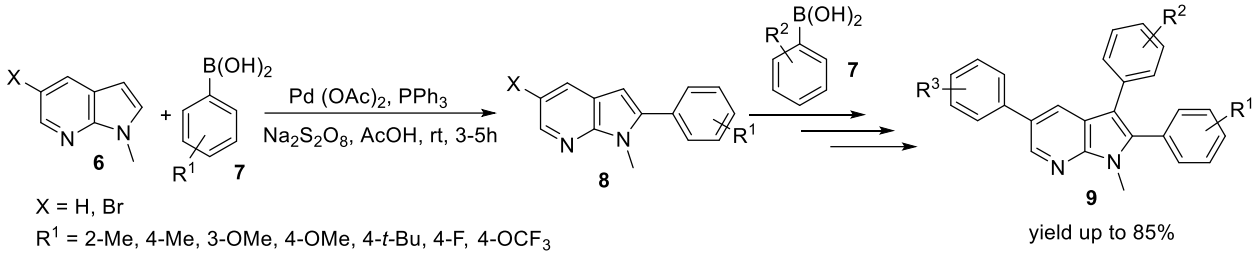
The mechanism of the C-H functionalization/arylation under copper catalysis is quite complex because different oxidation states of copper (Cu^0, Cu^I, Cu^{II}, and Cu^{III}) are found to occur in different reactions. The two electron process in copper catalyzed C-H functionalizations has gained much attention. A common mechanism using Cu^I/Cu^{III} catalytic cycle has been proposed (**Scheme 1.5a**). In this, first Cu^I form an organocopper^{III} intermediate **A** with substrate (**X**) through oxidative addition step followed by reductive elimination of organocopper^{III} offers the coupled cyclized product (**Y**) and catalytic cycle is completed by releasing Cu^I species. Another process involves one- and two- electrons of copper to functionalize C-H bond (**Scheme 1.5b**). In this process different $Cu^I/Cu^{II}/Cu^{III}$ catalytic cycles are involved where formation of an organocopper^{III} intermediate (**B**) is the key step. First, Cu^{II} reacts with substrate (**X**) to form organometallic Cu^{II} intermediate (**A**) using C-H functionalization reaction. Then, disproportionation of Cu^{II} intermediate (**A**) results in formation of organocopper^{III} intermediate (**B**) which subsequently affords C-C coupled product (**Y**) *via* reductive elimination and releasesCu^I species which is then oxidized into Cu^{II} to take part in the next catalytic cycle.



Scheme 1.5 Possible mechanism for copper catalyzed C-H arylation

The arylation reaction has been categorized in two types: i) intermolecular arylation and ii) intramloecular arylation.

1.4.1 Intermolecular arylation: In recent years, intermolecular arylation reactions have been extensively reviewed in review articles and book chapters.[56-60] As a typical example, therapeutically important azaindoles (**6**) were functionalized with phenyl boronic acids (**7**) to give arylated azaindoles (**8**) by Sames[61] and Fagnou,[62] independently through palladium catalyzed intermolecular reactions. Das and group[63] developed a method for the synthesis of poly substituted azaindoles (**9**) *via* multiple intermolecular arylation reactions (**Scheme 1.2**).

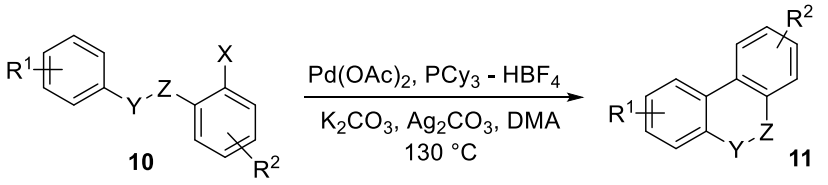


X = H, Br
R^1 = 2-Me, 4-Me, 3-OMe, 4-OMe, 4-*t*-Bu, 4-F, 4-OCF_3
R^2 = 4-Me, 4-Cl, 4-F, 4-CF_3, 4-CN
R^2 = 4-OMe, 4-Cl, 2,4 di-F, 2-Napthyl

Scheme 1.2 Pd-catalyzed multiple C-H arylations on azaindole skeleton

1.4.2 Intramolecular arylation: In last two decades, palladium/copper catalyzed intramolecular direct arylation of various heterocyclic substrates has been described by several groups.

Fagnou and colleagues demonstrated an Pd-catalyzed intramolecular direct arylation approach using designed precursor **10** for the synthesis of targeted fused molecule (**11**) (**Scheme 1.3**).[64] The pre-functionalized aryl ring (substituted with chloro, bromo, iodo) reacted under palladium catalysis to facilitate the desired arylated product **11**in good to excellent yield.



X = Cl, Br, I
Y = CH_2, NBz, O, C=O
Z = CH_2, NMe, C=O
R^1 = aryl, heteroaryl
R^2 = aryl

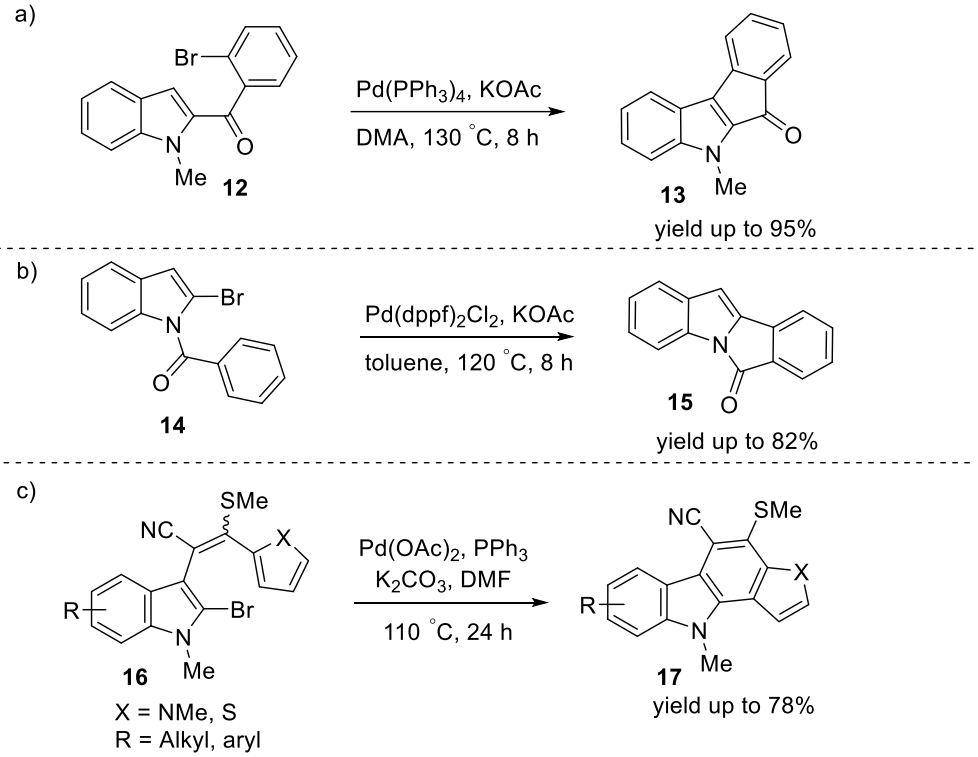
Scheme 1.3 Pd-catalyzed intramolecular direct arylation

1.4.2.1 Pyrroles and Indoles

An early example appeared in 1991 by Ma and colleague which involves intramolecular direct arylationof 2-bromobezoyl-*N*-methylindole (**12**) to give desired cyclized molecule **13** in the

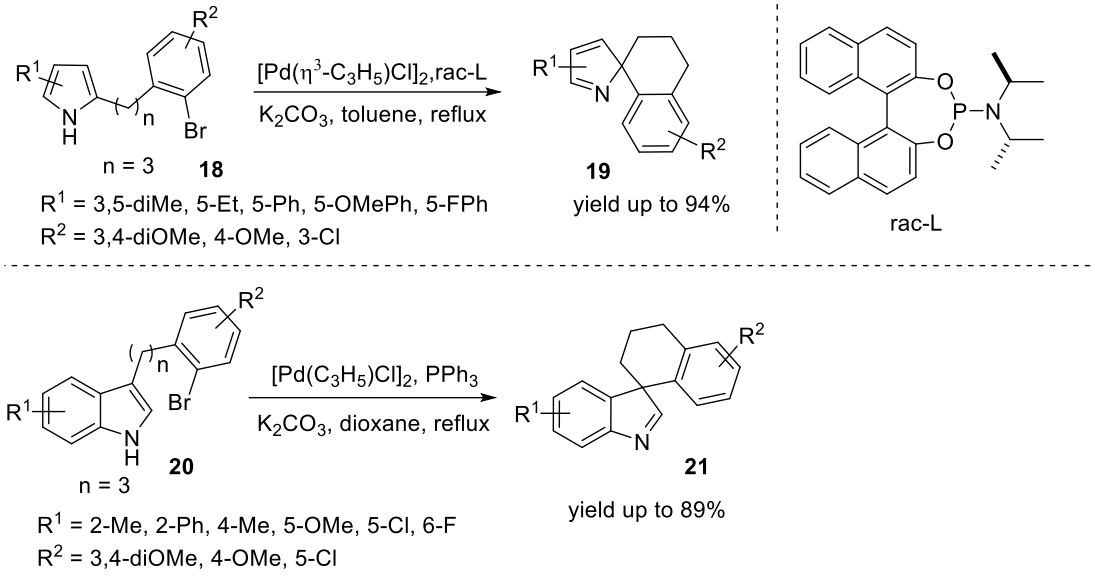
presence of $Pd(PPh_3)_4$, and KOAc in DMA(**Scheme 1.6a**).[65] Later, Bao and team have applied same palladium catalyzed direct arylation strategy *via* C-H activation on substituted indoles (**14**) to generate isoindolinone fused indoles (**15**). A variety of substituents on indole precursor were well tolerated under the optimized reaction conditions and offered fifteen different analogues of 6H-isoindolo[2,1-*a*]indol-6-ones(**15**) in moderate to high yields (**Scheme 1.6b**).[66]

In extension, Ila and group have also described polycyclic heteroarenes from activated indoles (**16**) by Pd-catalyzed intramolecular heteroarylation reaction (**Scheme 1.6c**).[67] The efficient synthesis led to diverse array of novel indole-fused aryl/heteroaryl analogues(**17**) in good yields.



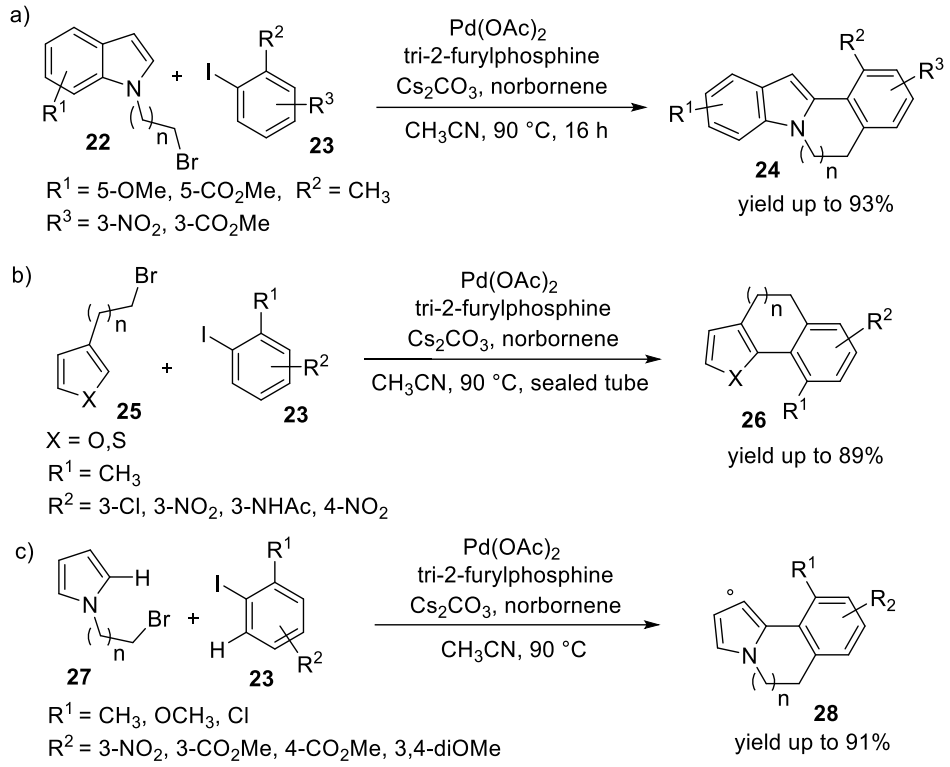
Scheme 1.6 Synthesis of indole-fused polycyclic derivatives

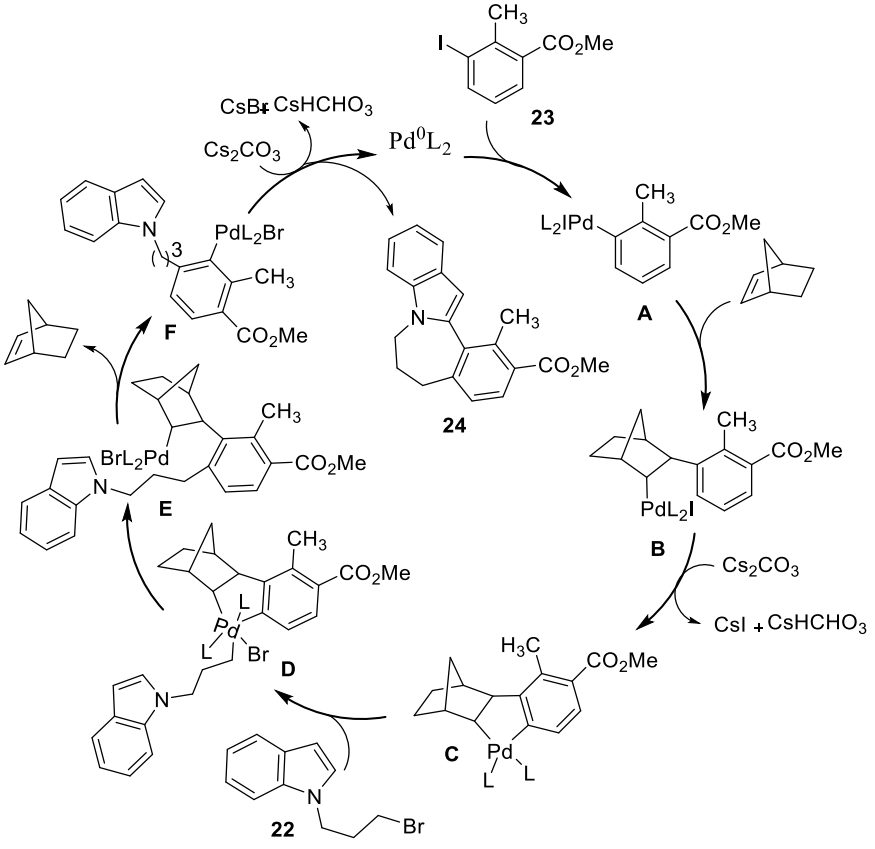
You group employed two consecutive Pd-catalyzed intramolecular dearomative arylation for the synthesis of spironaphthalenepyrrole(**19**) and spiroindolenine(**21**) derivatives through functionalization at C-2, C-3 position of pyrrole(**18**) and indoles (**20**), respectively (**Scheme 1.7**).[68-69] Synthesized molecules obtained in good to excellent yields under optimized reaction condition. The generation of quaternary center at C-2 and C-3 position of theses heterocycles makes this methodology of special interest for further study.



Scheme 1.7 Pd-catalyzed dearomative arylation of pyrroles and indoles

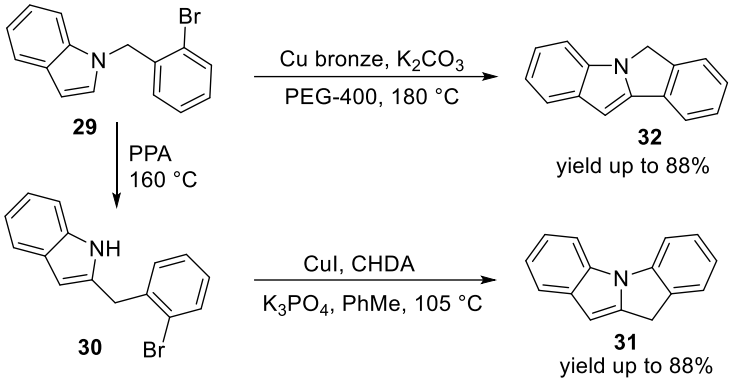
Lautens and group described the synthesis of six-or seven- membred ring annulated indoles (**24**) from alkylated indoles (**22**) and 2-iodotoluenes (**23**) that involve Pd-catalyzed, norbornene mediated cascade aromatic alkylation followed by intramolecular direct arylation reaction (**Scheme 1.8a**).[70] Similarly, polycyclic furans and thiophenes derivatives (**26**) were synthesized in one pot ortho alkylation/direct heteroarylation (**Scheme 1.8b**).[71] Subsequently, the same group further developed a method for the synthesis of annulated pyrrole-heterocycles (**28**) through Pd-catalyzed/norbornene mediated sequential coupling in one pot (**Scheme 1.8c**).[72]The developed methodology involves alkylation followed by arylation. The new aryl-heteroaryl bond formation occurs from the reaction of C-H bond of C-2 position of the indole with Pd-complex of aryl ring(intermediate **F**) and regeneration of active palladium complex makes the catalytic cycle complete (Shown in proposed mechanism of **scheme 1.8**).





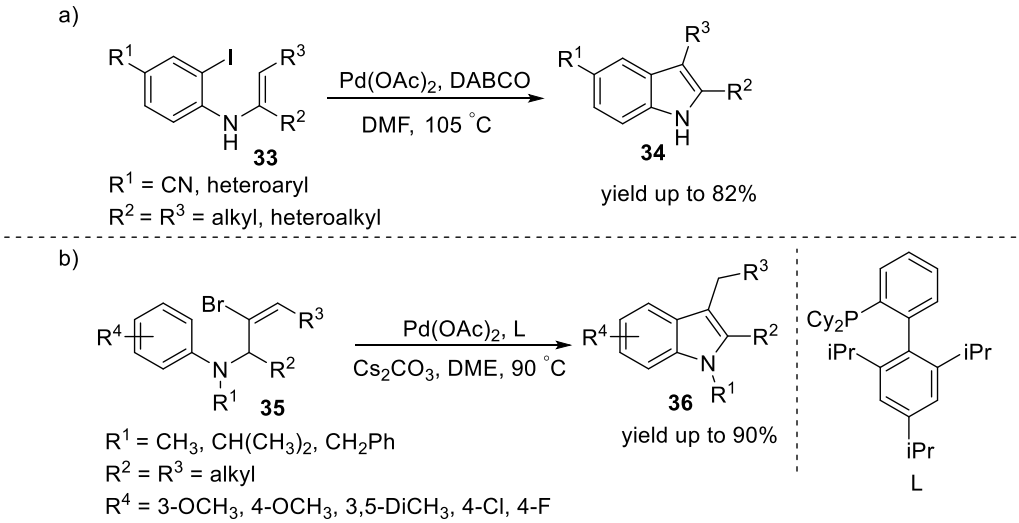
Scheme 1.8 Synthesis of annulated *N*-heterocycles and proposed mechanism

SanMartin and co-workers described copper catalyzed C-H arylation approach using functnalized indoles (**29**, **30**). The developed route led to isoindolo[2,1-*a*]indole (**32**) and its structural isomer indolo[1,2-*a*]indole (**31**) from corresponding indoles in high yields (**Scheme 1.9**).[73]



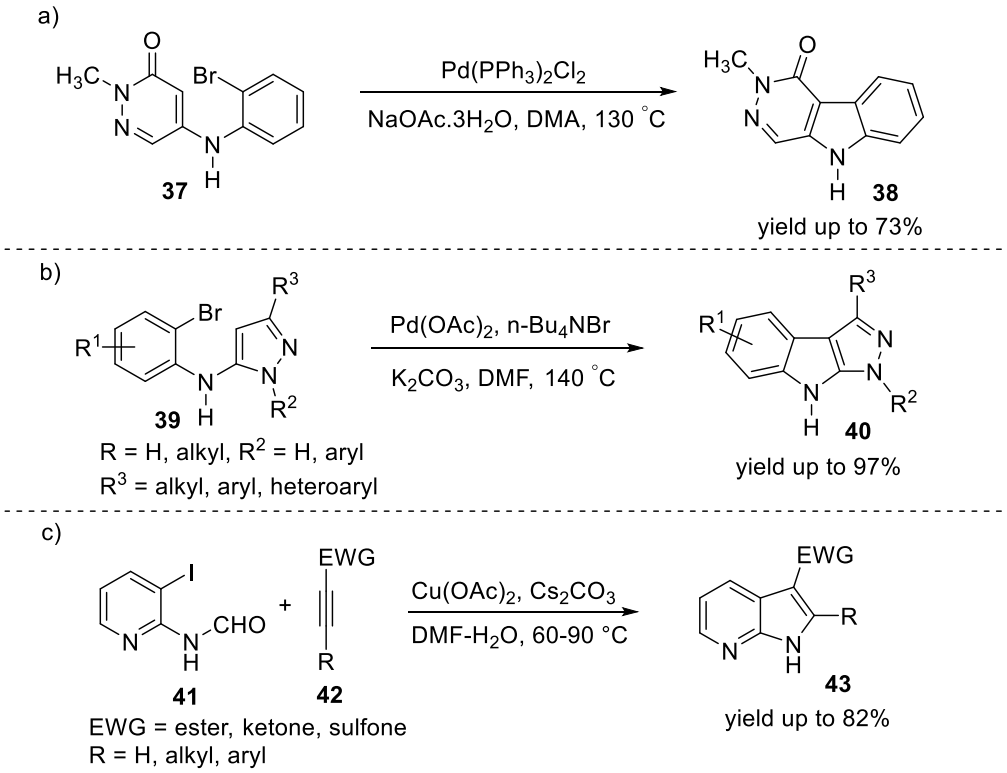
Scheme 1.9 Cu-catalyzed direct arylation of indoles

Chen *et al.* demonstrated a simple method for the synthesis of diversely substituted indoles from enamines (**33**) which involves palladium catalyzed alkene arylation and facilitates the desired products (**34**)in moderate to good yields (**Scheme 1.10a**).[74] The generality of reaction was investigated by varying different electron releasing and withdrawing groups containing enamines. Furthermore, a cascade palladium catalyzed arylation reaction has been developed using differently designed enamines (**35**) by Yagoubi and group which delivered a wide range of functionalized indoles (**36**) in poor to excellent yields (**Scheme 1.10b**).[75]



Scheme 1.10 Synthesis of functionalized indoles via Pd-catalyzed intramolecular arylation

Halasz*et al.* described synthesis of pyridazinoindole system from functionalized pyridazinones (**37**) through intramolecular heteroarylation where palladium catalyzed C-H arylation was carried out under the $Pd(PPh_3)Cl_2$, $NaOAc{\cdot}3H_2O$ in DMA at 130 ˚C to afford the desired product pyridazinone fused indole (**38**) (**Scheme 1.11a**).[76] Similarly, Illa and co-workers have developedpyrazolo fused indoles (**40**) *via* palladium catalyzed intramolecular heteroarylation using 2-bromoaniline substituted pyrazole derivatives (**39**) (**Scheme 1.11b**).[77] The described approach is compatible with a range of electron withdrawing and donating substituents to achieve moderate to good yield of fused indoles. Back and group prepared azaindole derivatives (**43**) through conjugate addition of *N*-formyl 3-iodopyridines (**41**) to activated acetylenes (**42**) followed by copper catalyzed intramolecular arylation (**Scheme 1.11c**).[78] Different electron releasing and withdrawing groups were examined to explore various azaindoles and gave moderate to high yield of the target products.

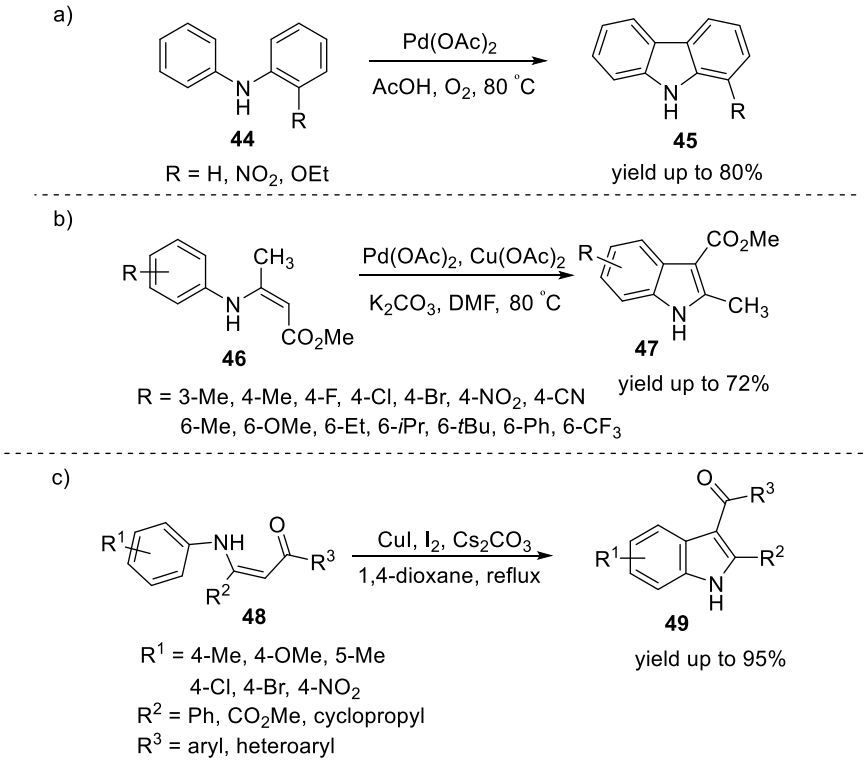


Scheme 1.11 Synthesis of functionalized indoles *via* Pd/Cu-catalyzed intramolecular heteroarylation

1.4.2.1.1 Synthesis of indoles through oxidative coupling

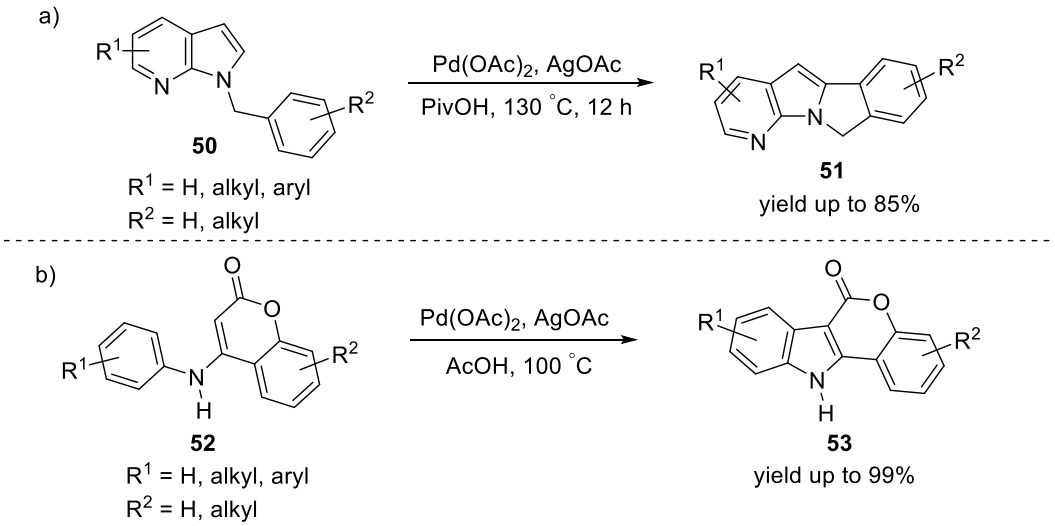
In past years, there has been major concern how atom economic path could be employed in chemical synthesis. Therefore, the direct use of two arenes or alkenes (without pre-functionalization) has been fascinating for recent years.[79-80] Several groups directed their efforts to develop new methodologies for indole synthesis using the cross dehydrogenative coupling approach.[81-82]In light of this, Akermark and group described facile palladium catalyzed intramolecular direct arylation to give new benzo-fused indole derivatives(**45**) from *N*-phenyl anilines (**44**) (**Scheme 1.12a**).[83] Later on, Glorius and team achieved functionalized indoles **47**using enamines**46** under $Pd(OAc)_2$ as catalyst, $Cu(OAc)_2$ as oxidant and K_2CO_3as base in DMF at 80 ˚C (**Scheme 1.12b**).[84-85] This broadly applicable indole synthesis afforded different indole analogues in moderate to high yields.

Liu *et al.* disclosed the formation of oxidative C-C bond under copper catalyzed iodine mediated C-H functionalization to synthesize various indoles (**49**) from *N*-aryl enamines (**48**) (**Scheme 1.12c**).[86] Versatility of this approach was described with electron releasing as well as electron withdrawing substrates which offered excellent yield of the functionalized indoles. The developed methodology has future scope as further functionalization onto accessed indoles.



Scheme 1.12 Synthesis of indoles *via* Pd/Cu-catalyzed cross-dehydroginative couplings

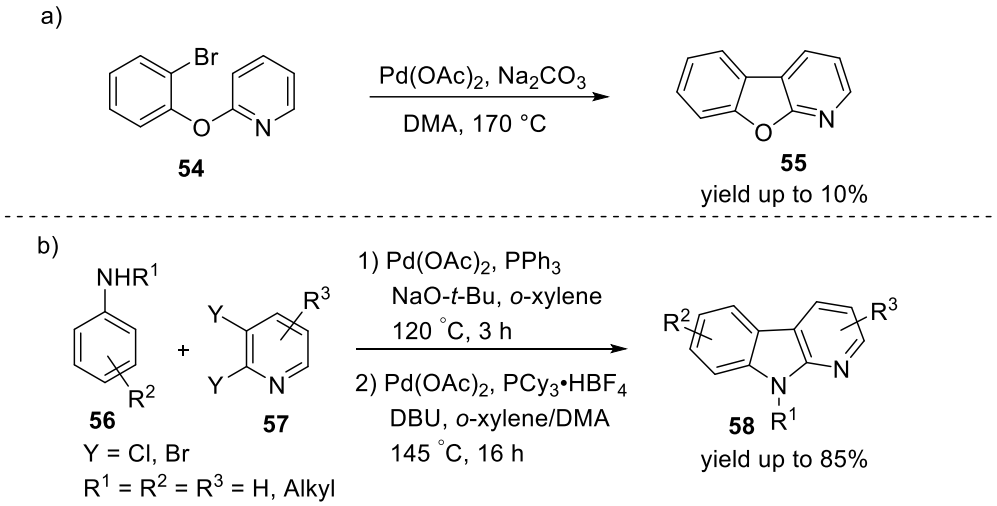
Recently, Laha *et al*. reported the synthesis of fused 7-azaindoles (**51**) from alkylated azaindole using palladium catalyzed intramolecular dehydroginative cross-coupling (**Scheme 1.13a**).[87] This novel approach delivered thirteen fused 7-azaindole analogues in moderate to good yields. Also, Xu and group disclosed an atom economic practical palladium catalyzed intramolecular oxidative arylation using *N*-aryl substituted coumarins (**52**) (**Scheme 1.13b**).[88] Using this approach a variety of biologically valuable substituted indolo[3,2-*c*]coumarins (**53**) could be achieved.



Scheme 1.13 Pd-catalyzed synthesis of indole fused heterocycles *via* oxidative intramolecular arylation

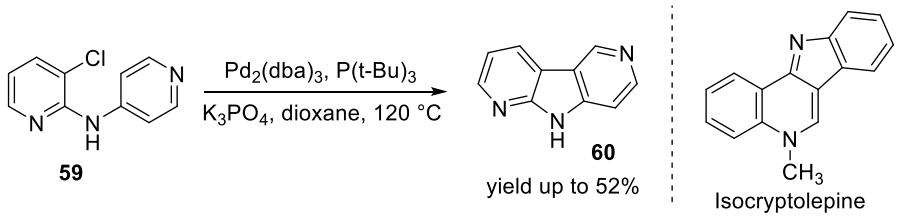
1.4.2.2 Pyridines and Quinolines

The first intramolecular direct arylation on pyridine had been reported by Ames. In this early report, benzofuro[2,3-*b*]pyridine (**55**) was prepared in low yield (10%) from 2-(2-bromophenoxy)pyridine (**54**) through palladium catalyzed intramolecular cyclization which ledto one new C-C bond between aryl and pyridyl ring (**Scheme 1.14a**).[89] Thereafter, Cuny and group reported one pot synthesis of substituted α-carbolines (**58**) from different anilines (**56**) and 2,3-dihalo substituted pyridines (**57**) ring which involve $Pd(OAc)_2$ catalyzed aryl amination followed by intramolecular direct arylation (**Scheme 1.14b**).[90] This sequential approach provided an array of α-carbolines in moderate to excellent yields.



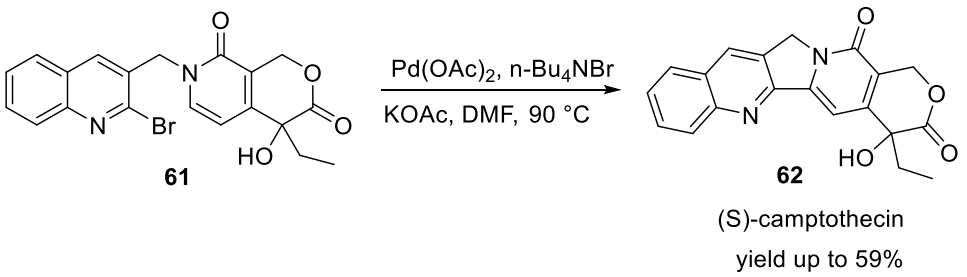
Scheme 1.14 Direct arylation on pyridine

Jonckers *et al.*developed a methodology for 9*H*-pyrrolo[2,3-*b*:4,5-*c*′]dipyridine(**60**) *via* palladium catalyzed arylation approach by treating 3-chloro-2-(4-pyridylamino)pyridine (**59**) with $Pd_2(dba)_3$, P(*t*-Bu)$_3$ and K_3PO_4 in dioxane at 120 ˚C (**Scheme 1.15**).[91] As synthetic utility, Isocryptolepine alkaloid was also successfully synthesized using this method in three synthetic steps.



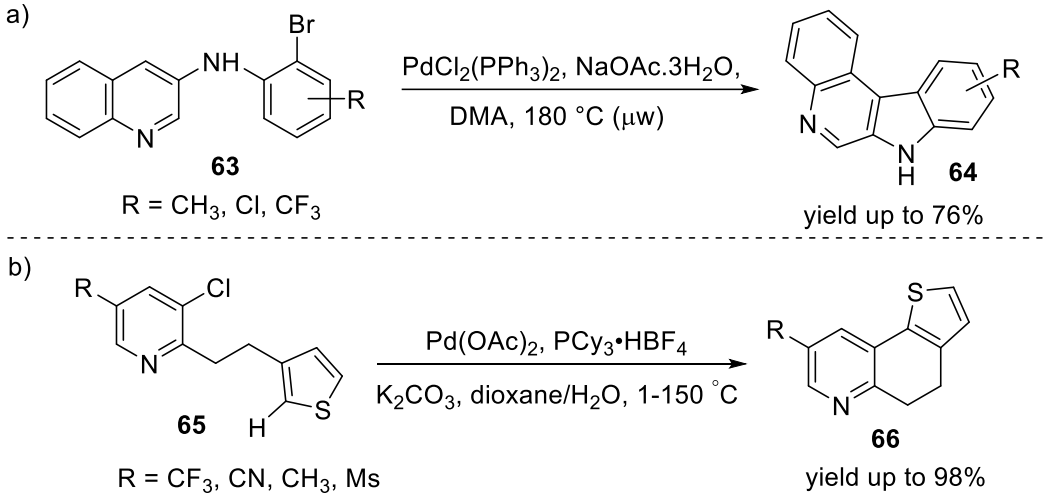
Scheme 1.15 Pd-catalyzed synthesis of hetero-aryl fused pyridines

Among pyridine containing heterocycles, quinoline and its mimic are found in many pharmaceuticals and natural products.[92-94] Therefore, various groups have been motivated to take up functionalization of the quinoline moiety.An early example appeared by Comins and group who described synthesis of alkaloid (S)-Camptothecin (**62**) by using $Pd(OAc)_2$ catalyzed direct arylation (**Scheme 1.16**).[95-96] This developed methodology was also utilized for the synthesis of other natural products like Luotonin A and B,[97] Mappicine[98] and Rutaecarpine[99] by other groups.



Scheme 1.16 Synthesis of Camptothecin using Pd-catalyzed intramolecular direct arylation

Similarly, microwave assisted synthesisof 7*H*-indolo[2,3-*c*]quinolines(**64**) could be achieved through Pd-catalyzed intramolecular direct arylation using optimized reaction condition at higher temperature from *N*-(2-bromophenyl)quinolin-3-amine(**63**) (**Scheme 1.17a**).[100-101] Recently, Lautens and team described a one pot synthesis of 4,5-dihydrothieno[2,3-*f*]quinolines (**66**) from substituted pyridine derivatives (**65**) by employing palladium catalyzedC-H arylation (**Scheme 1.17b**).[102] The developed step-economic protocol was applied for rapid construction of 6-alkylsubstituted dihydrobenzoquinolines.

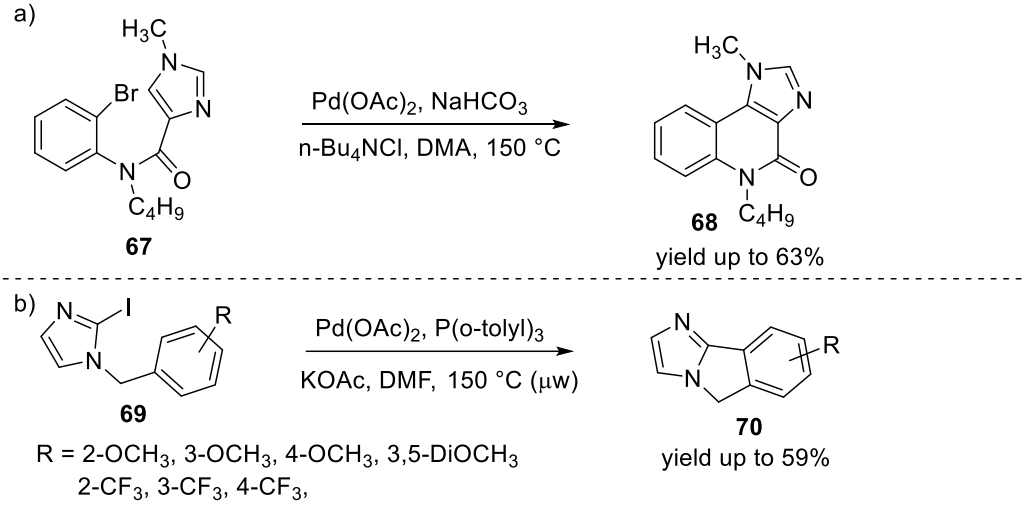


Scheme 1.17 Pd-catalyzed intramolecular arylation/heteroarylationon substituted quinolines and pyridines

1.4.2.3 Imidazoles and pyrimidines

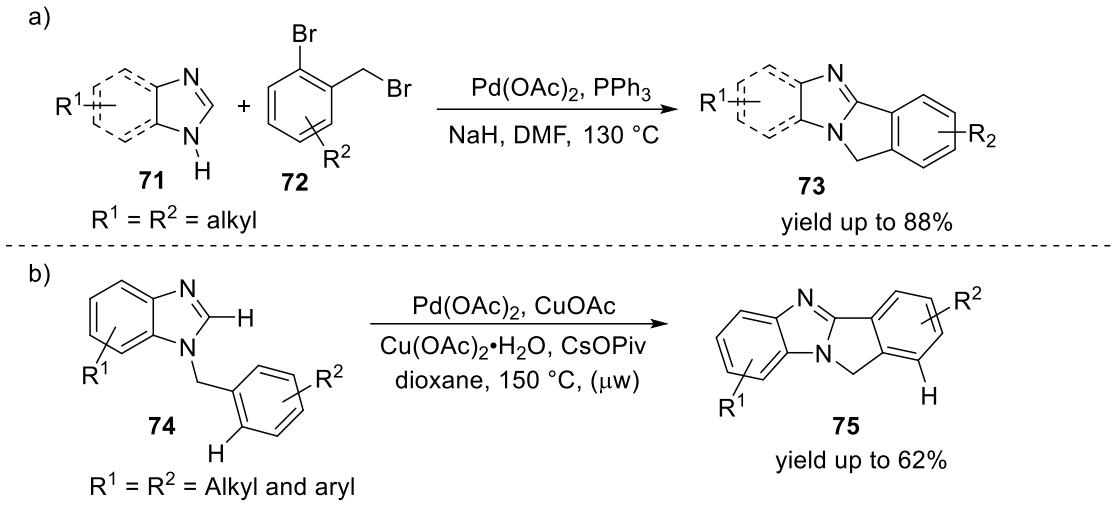
Imidazo fused quinoline derivatives exhibit potent biological activities such as contraceptive, hypertensive, antiallergic, and antiasthmatic.[103-105] Thus, stimulated efforts have been directed to make such kind of fused heterocycles. Suzuki and colleague reported a route to afford 5-butyl-1-methyl-1,5-dihydro-4H-imidazo[4,5-c]quinolin-4-one (**68**) from *N*-(2-bromophenyl)-*N*-butyl-

1-methyl-1H-imidazole-4-carboxamide (**67**) by using Pd-catalyzed intramolecular direct arylation (**Scheme 1.18a**).[106] Subsequently, Dubois and group disclosed a rapid microwave assisted intramolecular direct arylation involving C2-position of the imidazole ring (**69**) under optimized reaction condition as $Pd(OAc)_2$, P(*o*-tolyl)$_3$ and KOAc in DMF for 15 minutes at 150 ˚C (**Scheme 1.18b**).[107] The developed methodology was generalized by having various electron donating as well as electron withdrawing substituents on aryl ring and produced imidazole fused cyclized products **70**in moderate yields.



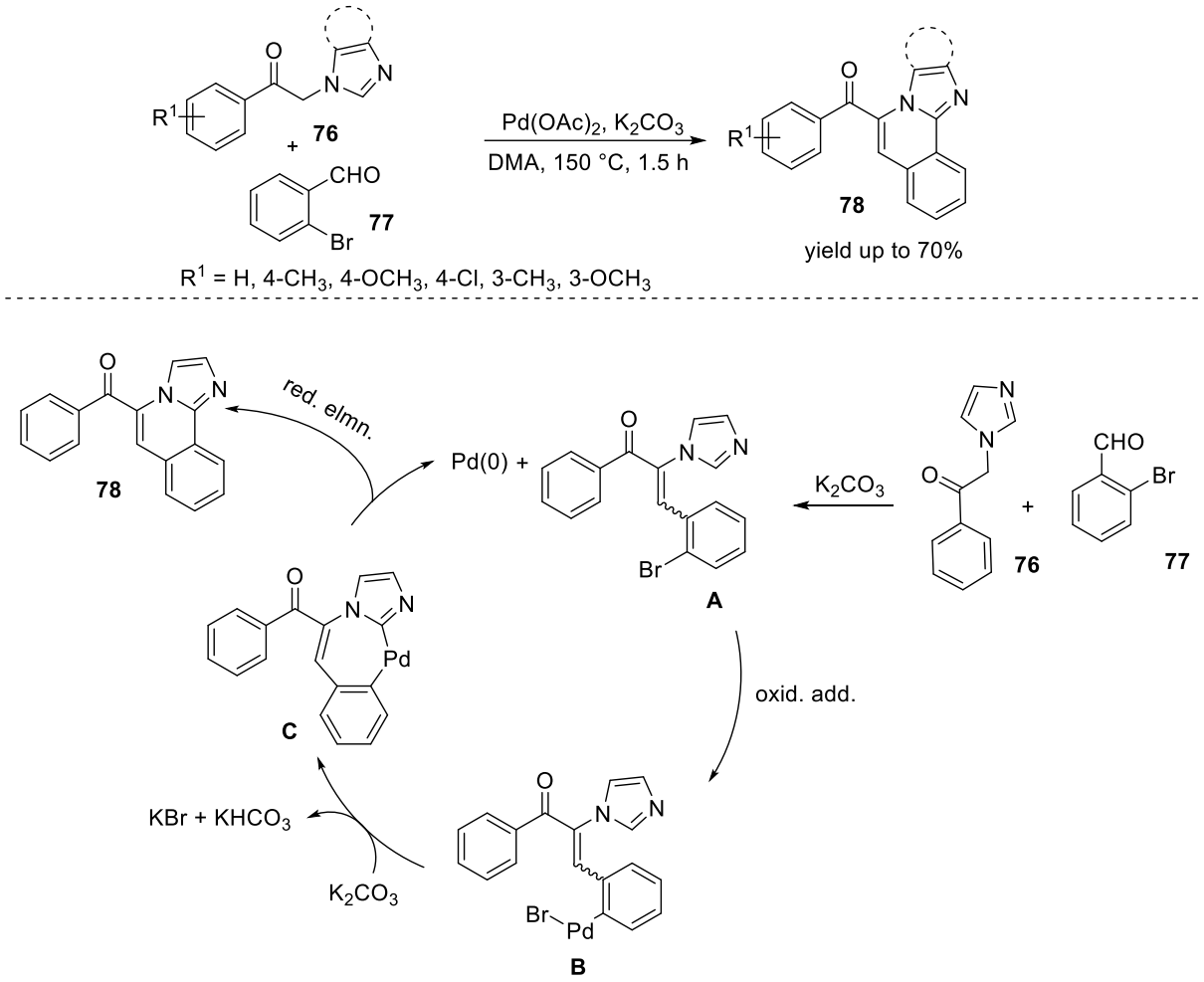
Scheme 1.18 Pd-catalyzed C-2 arylation on functionalized imidazole

A regio- and chemo- selective domino reaction has been described by Laha*et al.* which involves *N*-benzylation followed by palladium catalyzed intramolecular C-H arylation to lead annulated imidazole fused heterocycles (**73**) in moderate to good yields(41-88%) (**Scheme 1.19a**).[108]Further, an improved synthesis has been described by DeBoef group where substituted imidazole (**74**) were employed without any prefunctionalization (**Scheme 1.19b**).[109] The desired benzimidazo-fused isoindoleproducts (**75**) were obtained in moderate yields under dual Pd^{II}/Cu^{I} catalysis *via* intramolecular cross-dehydrogenative coupling.



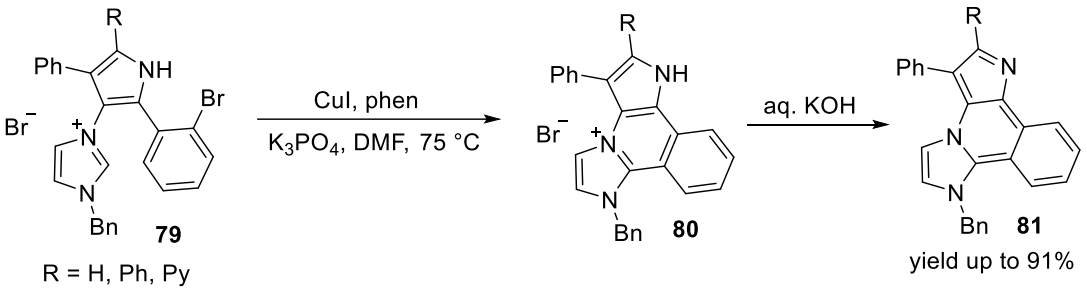
Scheme 1.19 Synthesis of benzimidazo fused isoindole via Pd-catalyzed intramolecular direct arylation and cross dehydrogenative coupling

In the series of direct arylations *via* Pd-catalyzed C-H functionalization of imidazoles, our group has also reported a cascade protocol using diversely substituted imidazoles (**76**) and 2-bromobenzaldehyde (**77**) which proceeded through cross aldol condensation followed by palladium catalyzed intramolecular direct arylation and offered the expected imidazo/benzimidazo fused isoquinolines(**78**) in moderate to good yields (**Scheme 1.20**).[110]



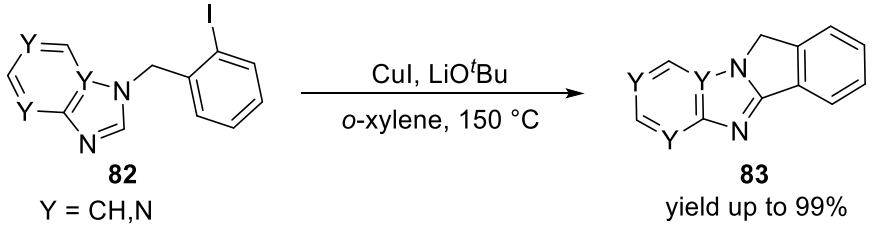
Scheme 1.20 Synthesis of imidazo fused isoquinolines and its proposed mechanism

A recent approach appeared by Khlebnikov and group used pyrrolylimidazolium bromides (**79**) as stating precursor for the synthesis of imidazo-fused isoquinolines*via* palladium catalyzed direct arylation. The designed substrate **79** undergoes intramolecular direct arylation catalyzed by CuI under the controlled tautomeric form of imidazoliumylpyrrolide-imidazole-*N*-heterocyclic carbine (NHC). Synthesized substituted imidazo[2,1-*a*]-pyrrolo[3,2-*c*]isoquinolin-4-ium bromides (**80**) were obtained in good yields which was further treated with aq. KOH to deliver non-ionic substituted imidazo[2,1-*a*]pyrrolo[3,2-*c*]isoquinolines (**81**) (**Scheme 1.21**).[111]



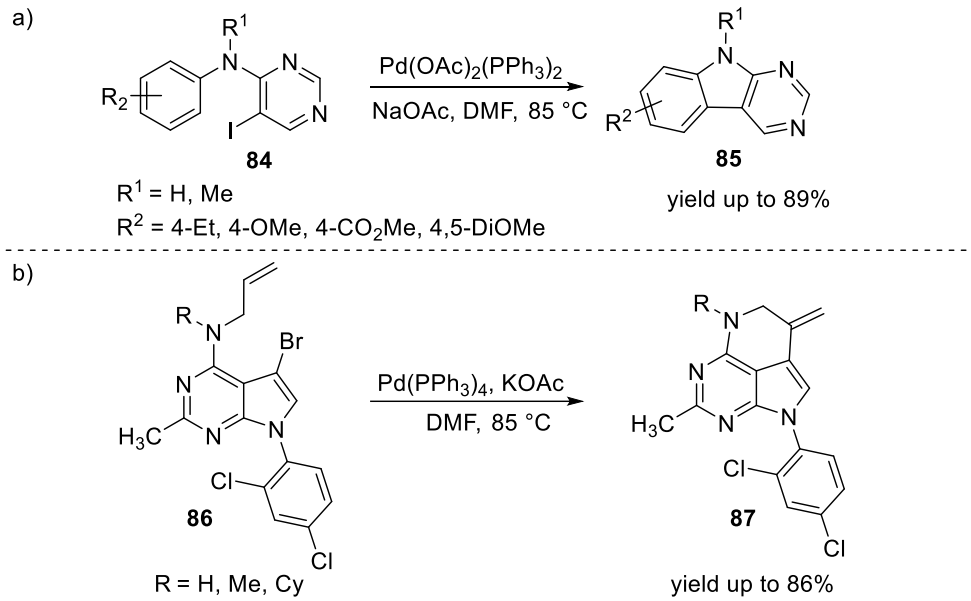
Scheme 1.21 Cu-catalyzed C-H arylation of pyrrolylimidazolium bromides

Dominguez and colleagues functionalized both 9*H*-purine and 4-azabenzimidazole heterocycles (**82**) under CuI and LiO^{t}Bu in *o*-xylene at 150 ˚C (**Scheme 1.22**).[112] The developed ligand free protocol led to biologically relevant tri- and tetracyclic compounds **83** in excellent yield.



Scheme 1.22 Cu-catalyzed direct arylation of indoles and imidazoles

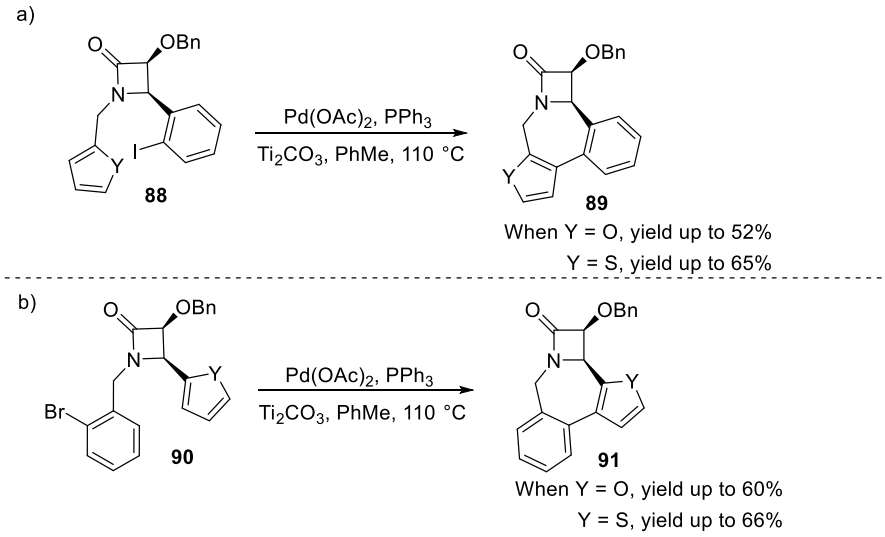
Pyrimidine based structure occupies an exclusive place in organic synthesis due to its structure similarity to biogenic purines. As a result, synthetic methodologies where pyrimidine based analogues employed to get pyrimidine fused heterocycles have attracted attention of chemists. In this addition, Zhang and team developed a method to obtain pyrimido fused indoles(**85**) from activated pyrimidine derivatives (**84**) under optimized reaction condition as $Pd(OAc)_2(PPh_3)_2$ and NaOAc in DMF at 85 ˚C. The aryl ring of all substrates tolerated electron releasing and withdrawing substitution well to afford desired product in moderate to excellent yield (**Scheme 1.23a**).[113] Another different approach that involves intramolecular Heck cyclization to construct new six membred ring as fused molecule on bicyclic pyrrolopyrimidine derivatives (**86**). The reported method provides pharmaceutically important scoffold pyrimidine fused tricyclic products (**87**) up to 86% yield (**Scheme 1.23b**).[114]



Scheme 1.23 Pd-catalyzed pyrrolo fused pyrimidines through direct arylation

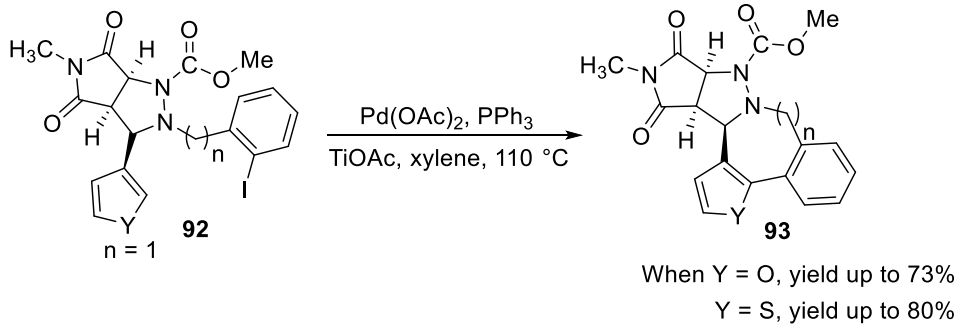
1.4.2.4 Furans and Thiophenes

Grigg reported intramolecular arylation on furan and thiophene (**88, 90**) for the preparation of polycyclic *β*-lactams (**89**, **91**). Cyclic amide tethered different substituted furan and thiopene proceeded under $Pd(OAc)_2$, PPh_3, and Ti_2CO_3 in toluene at 110 ˚C *via* intramolecular direct arylation and offered the fused cyclized products (**89**, **91**) in moderate yields (**Scheme 1.24 a,b**).[115]



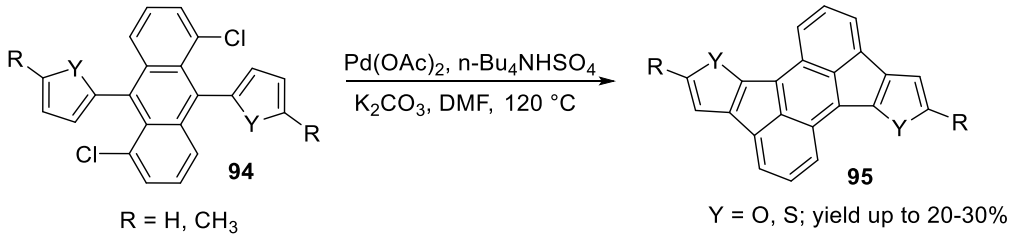
Scheme 1.24C-H functionalization of aryl/heteroaryl to cyclic *β*-lactams

Later, similar approach has been employed by the same authors using heteroaryl substituted designed substrate (**92**) under palladium catalysis. Developed direct arylation accessed large number of interesting fused six to eight membred furan and thiophene structures (**93**) in good yields (**Scheme 1.25**).[116]



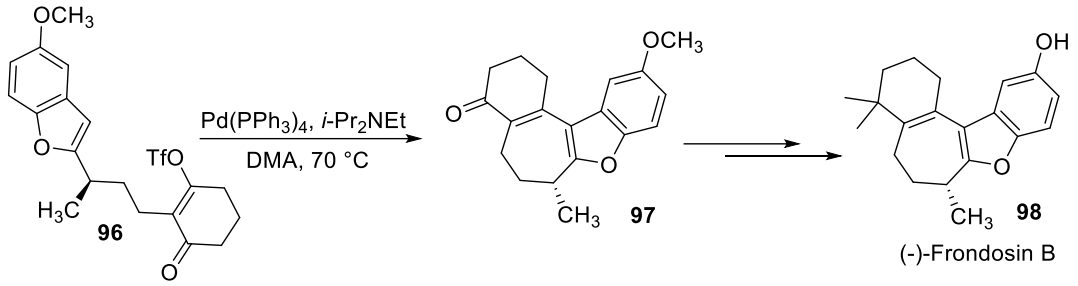
Scheme 1.25 Pd-catalyzed direct arylation of furan and thiophene

Multiple C-H functionalization involving direct arylation reactions has been explained by Dehaen and group under $Pd(OAc)_2$, n-Bu_4NHSO_4, and K_2CO_3 in DMF at 120 ˚C. The palladium catalyzed transformation delivered symmetrically fused novel heterocyclic analogues of rubicene(**95**) in low yields (**Scheme 1.26**).[117]



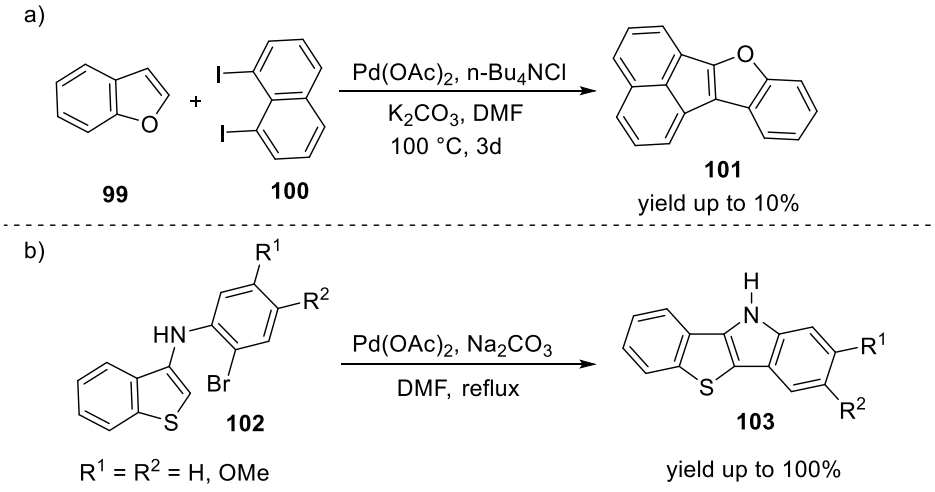
Scheme 1.26 Synthesis of novel symmetrical rubicene analogues

Trauner described the total synthesis of (-)-Frondosin B using a novel palladium catalyzed cyclization. This asymmetric total synthesis has undergone macrocyclization step *via* intramolecular C-H cross-coupling reaction to lead targeted (-)-Frondosin B (**98**) with 22% of the overall yield (**Scheme 1.27**).[118-119]



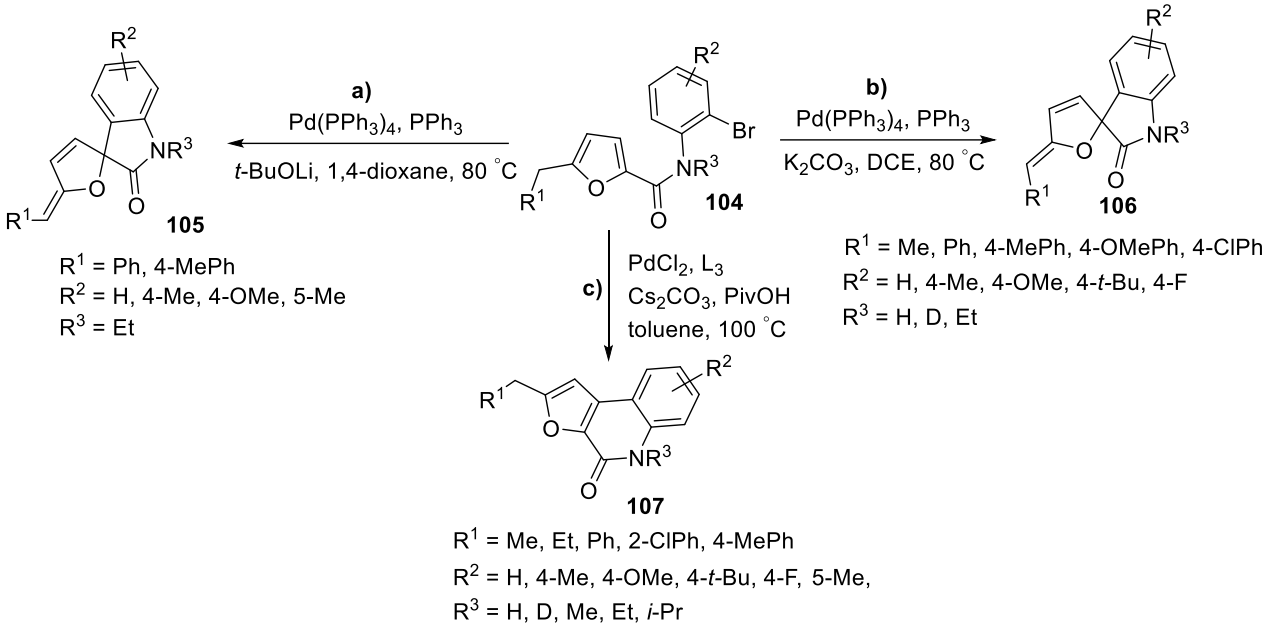
Scheme 1.27 Total synthesis of (-)-Frondosin B*via* Pd-catalyzed intramolecular direct arylation

Dyker described that 1,8-Diiodonaphthalene (**100**) could be used for annulations reaction with benzofuran (**99**) under palladium catalysis using dual C-H functionalization reaction. However, poor reactivity of benzofuran offered desired pentacyclic product **101**in very low yield (**Scheme 1.28a**).[120] In subsequent year, Queiroz and co-workers developed palladium catalyzed cyclization to give indolo-fused thiophenes (**103**) from designed prefunctionalied benzothiophenes (**102**) substrate. The novel synthetic route successfully generalized using different substitution at aryl ring and shown excellent reactivity which delivered target compound yield up to 100% (**Scheme 1.28b**).[121-122]



Scheme 1.28 C-H arylation of benzo-fused furan and thiophenes

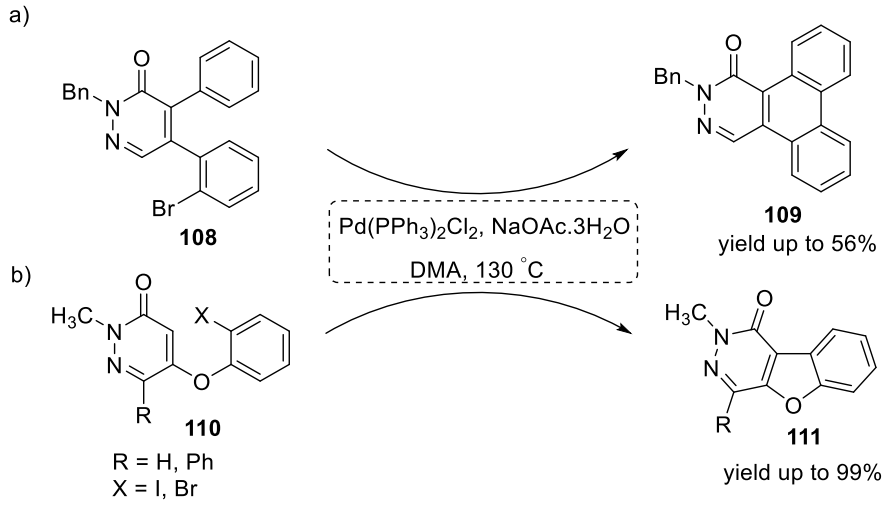
Very recently, regio- and stereo- selective approach appeared to access different spirooxindoles and 5*H*-furo[2,3-c]quinolin-4-ones (**107**) from *N*-(2-bromophenyl)-2-furancarboxamides (**104**) (**Scheme 1.29**).Three possible pathways **a**, **b**, **c** proposed to lead different structures under palladium catalysis.[123] Path **a** and**b** described the *E* isomer (**105**) and *Z* isomer (**106**) of alkenes in spirooxindoles *via* electrophillic palladation and Heck insertion, respectively. Path **c** undergoes *via* concerted metalation-deprotonation process and offers various furan fused quinolin-4-one derivatives (**107**) (**Scheme 1.29**).



Scheme 1.29 Pd-catalyzedregio- and stereo- selective approach using N-(2-bromophenyl)-2-furancarboxamides

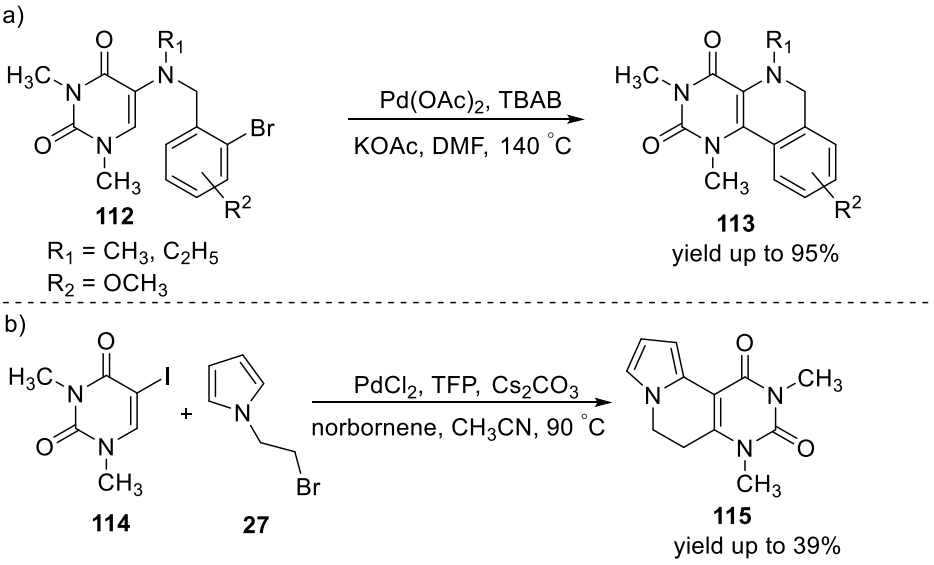
1.4.2.5 Pyridazin-3-one and pyrimidine-2,4-dione

Carbon-carbon bond formation through C-H arylation has also been reported on pyridazinone system. Matyus and colleagues reported the synthesis of 2-benzyldibenzo[*f*,*h*]phthalazin-1(2*H*)-one (**109**) and 2-methylbenzofuro[2,3-*d*]pyridazin-1(2*H*)-one (**111**) from corresponding pyridazin-3(2H)-ones (**108**) *via* direct arylation under $Pd(PPh_3)_2$, $NaOAc{\cdot}3H_2O$ in DMA at 130 ˚C (**Scheme 1.30a,b**).[76, 124] Desired cyclic products **109**, **111**could be obtained in good to excellent yield and well compatible with phenoxy substituted pyridazin-3(2*H*)-one (**110**).



Scheme 1.30 Direct arylation on pyridazinone system

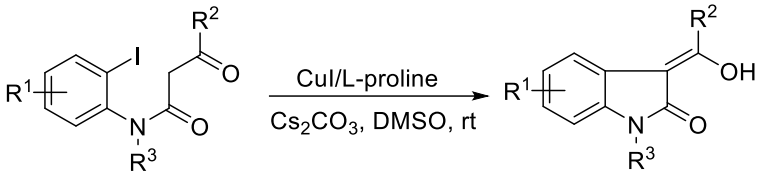
Majumdar reported an efficient protocol for the synthesis benzannulated pyrido-fused pyrimidinediones (**113**) under $Pd(OAc)_2$, TBAB, KOAc in DMF at 140 ˚C (**Scheme 1.31a**).[125] Synthesizedpyrido-fused uracil analogues could be achived up to 95% yield with different electron releasing substitutents. In addition, Lautens and team has also used iodo-uracil analogues (**114**) and treated under palladium catalyzed/norbornene mediated sequential coupling for the development of pyrrolo-fused pyrimidinediones (**115**) in moderate yield (**Scheme 1.31b**).[72]



Scheme 1.31 Palladium catalyzed arylationon uracil analogues

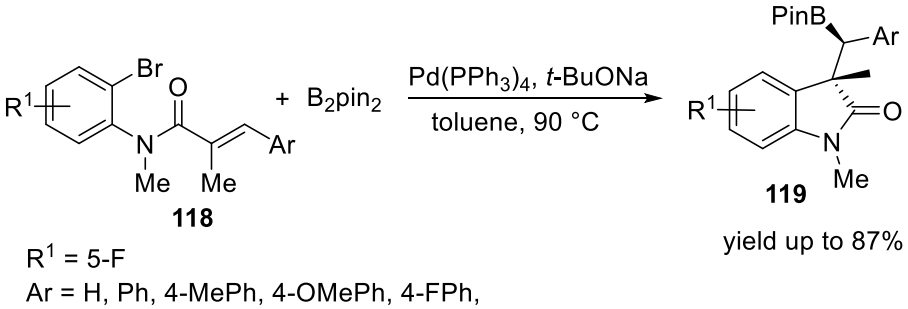
1.4.3Miscellaneous methods for Intramolecular C-H arylation

Ma and his colleague reported an intramolecular coupling using 2-iodoanilides (**116**) for the synthesis of 3-acyloxindoles (**117**) under the combination of CuI/L-proline with Cs_2CO_3 in DMSO at room temperature (**Scheme 1.32**).[126] Different substituents were employed on aromatic ring to check reactivity of substrates and functional group tolerance. The desired cyclized product obtained up to 83% yield under optimized reaction condition.



Scheme 1.32 Synthesis of oxindoles analogues through intramolecular arylation

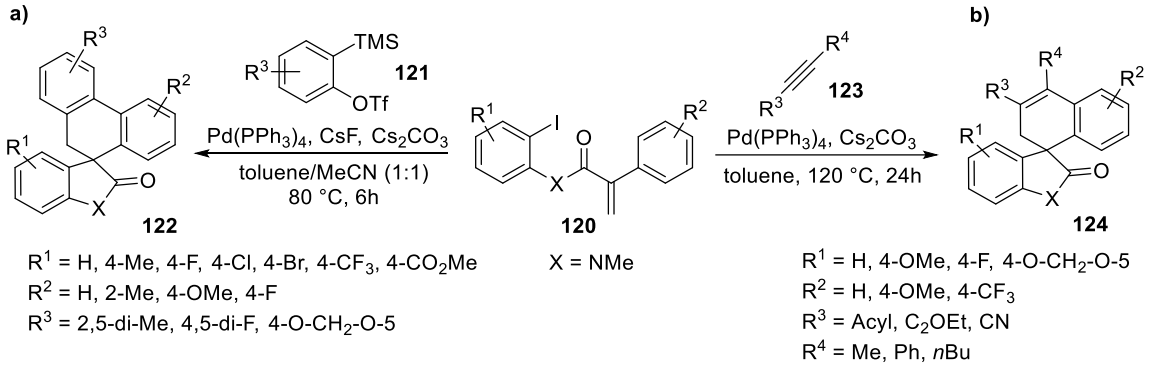
In the same context to oxindoles synthesis, 3,3-disubstituted oxindoles (**119**) were achived by Pd-catalyzed intramolecular arylation subsquent by borylation reaction from unsaturated amides (**118**). Electron releasing and withdrawing group containing derivatives were prepared for the successful generalization and the yield given is up to 87% (**Scheme 1.33**).[127] The Methodolgy involves oxidative addition, transmetallation and reductive elimination and afforded targeted products in good yields.



Scheme 1.33 Pd-catalyzed arylation and borylation from unsaturated amides

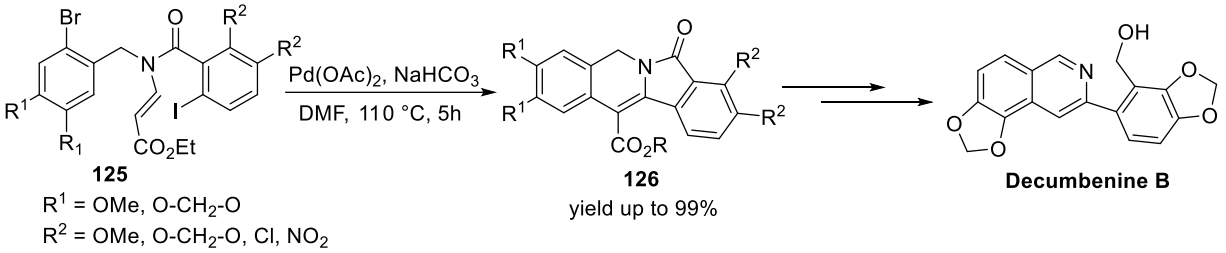
Apart from this, two consecutive reports *via* spiro cyclization appeared again by pioneer scientist Lautensas mentioned below in **Scheme 1.34**. The palladium catalyzed C-H activation followed by benzyne and alkyne insertion to *N*-(2-iodophenyl)-N-methyl-2-phenylacrylamide (**120**) under optimal condition lead to varieties of spirooxindoles (**122, 124**). Transparent mechanistic

evidence (X-ray) suggests that the reactions undergo through sequential carbopalladation, C-H activation followed by insertion to afford desired product in average to high yields (**Scheme 1.34**).[128-129]



Scheme 1.34 Pd-catalyzed spirocyclization using functionalized acrylamides

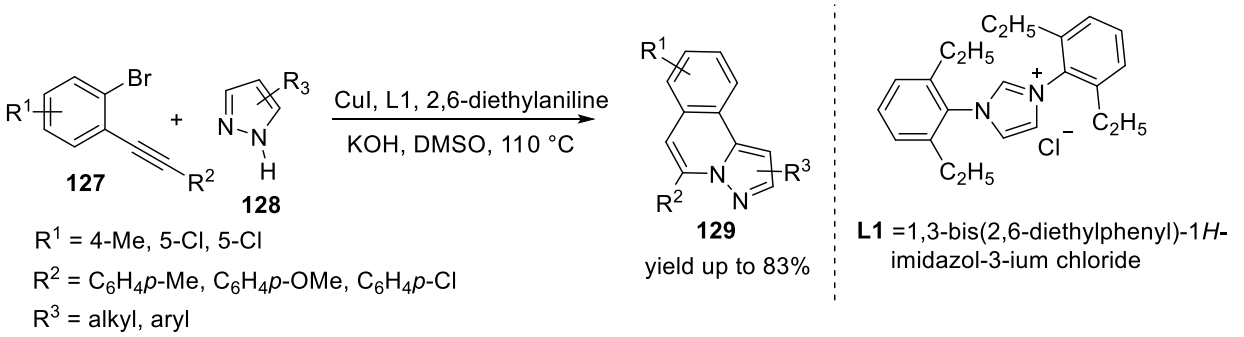
Kim reported sequential Heck reaction using substituted benzamidoacrylates (**125**) under $Pd(OAc)_2$, and $NaHCO_3$ in DMF at 110 ˚C for 5h. First Heck coupling provided five membred ring *via* carbon-carbon bond which subsequently follow another Heck cyclization to give six membred ring and furnished diversely substituted dibenz[*a,f*]indolizines(**126**) (**Scheme 1.35**).[130] Further conversion of one of its analogues to decumbenine B (natural alkaloid) demonstrates the synthetic utility of this transformation in natural product synthesis.



Scheme 1.35 Pd-catalyzed double cyclization using acryl tethered functionalized amides

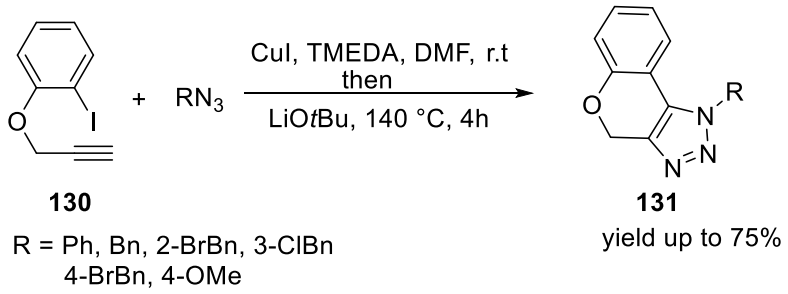
Wu and group developed a route to pyrazolo fused isoquinolines (**129**) from 2-alkynyl bromobenzenes (**127**) with pyrazoles (**128**) under CuI, *N*-heterocyclic carbene L1, 2,4-diethylaniline and strong base KOH in DMSO at 110 ˚C conditions and involves Cu-catalyzed hydroamination followed by C-H activation process (**Scheme 1.36**).[131] Aryl and heteroaryl rings were employed having different electron donating and withdrawing substituents. The better

result in the form of good product yields was obtained when alkyne aryl ring is branched with electron withdrawing group.



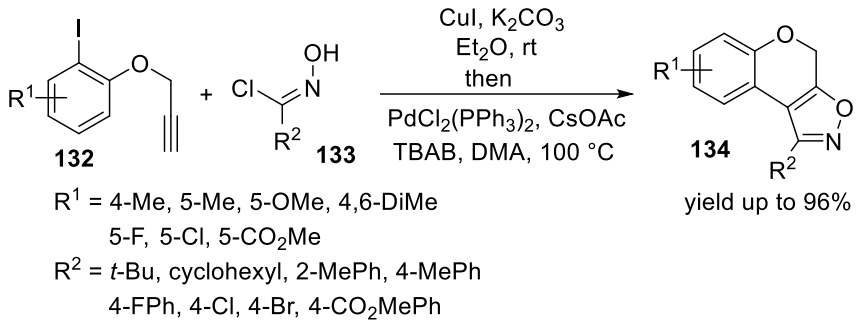
Scheme 1.36 Cu-catalyzed tandem reaction of 2-alkynylbromobenzenes and pyrazoles

A sequential copper-catalyzed click reaction followed by direct arylation in one pot fashion was demonstrated by Swamy and group using 1-iodo-2-(prop-2-yn-1-yloxy)benzene (**130**) with arylazides for the synthesis of dihydrochromeno-fused triazoles derivatives (**131**) (**Scheme 1.37**).[132] The atom economical click reaction underwent in presence of CuI, TMEDA in DMF at room temperature then cross coupling reaction occurred between aryl iodide and trizole ring in same pot under LiO^{t}Bu at 140 ˚C.



Scheme 1.37 Synthesis of dihydrochromeno-fused trizoles*via* Cu-catalyzed sequential click and direct arylation

In extension, another sequential synthesis was reported by Guo*et. al.* using copper and palladium catalysisfor C-C and C-N bonds formation which facilitates tricyclic isoxazole derivatives (**134**). First, copper catalyzed 1,3-dipolar cycloaddition between 1-iodo-2-(prop-2-yn-1-yloxy)benzenes (**132**) and *N*-hydroxy-4-methylbenzimidoylchlorides (**133**) give 5-[(2-iodophenoxy)methyl]-3-phenylisoxazoles which further undergo *via* palladium catalyzed arylation to give 1-phenyl-4*H*-chromeno[4,3-*d*]isoxazoles derivatives in higher to excellent yields (**134**) (**Scheme 1.38**).[133]



Scheme 1.38 Synthesis of chromeno-fused isoxazolesusing Cu/Pd-catalyzed cycloaddition and direct arylation

1.5 Conclusion

In last 20 years, copper and palladium catalyzed C-H arylation/functionalization has been exploited too much because it directly cleaves the inert C-H bond and led to new aryl-aryl, aryl-heteroaryl, heteroaryl-heteroaryl bonds for the synthesis and functionalization of *N*-heterocycles. The step economy process of this advance techniques used in shortening the lengthy synthetic routes of many natural products, pharmaceuticals and also reduce waste by-products as well as human labor. In addition, nowadays some recent studies is being more focused towards milder or metal free reaction condition to achieve direct arylation/functionalization at the level of industrialization with inexpensive process.

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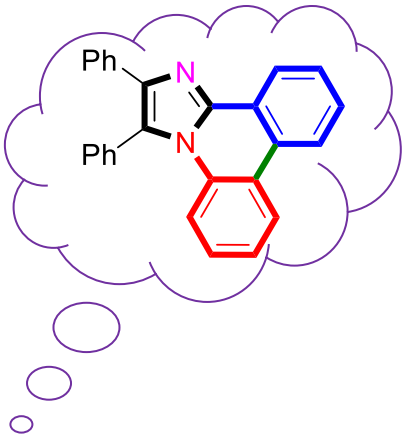
Chapter 2

Synthesis of Imidazo[1,2-*f*]phenanthridines through Palladium-Catalyzed Intramolecular Direct Arylation



2.1 Introduction

Phenanthridine is a tricyclic heterocycle which stands in a class of *aza*-polycyclic aromatic compounds, have their occurrence in natural products, and clinical pharmaceuticals.[1-3] Their versatile applications in material science and biological science make them as privilege core among heterocycles.[4-6] Trispherine, Decarine, and Nitidine are few examples of nature derived products which contain phenanthridine as core structure.[7-9] Phenanthriplatin have bifunctional site such as cisplatin and has promising anticancer activity.[10] Ehtidium bromide is used as fluorescence staining agent.[11] Deep red emitting iridium complex $(TP\text{-}BQ)_2Ir(acac)$ shows electrophosphorescent properties in material science (**Figure 2.1**).[12] Thus, the discovery of phenanthridine based alkaloids and in parallel new studies of biological properties of phenanthridine derivatives has resulted in increased scientific interest in past few decades.

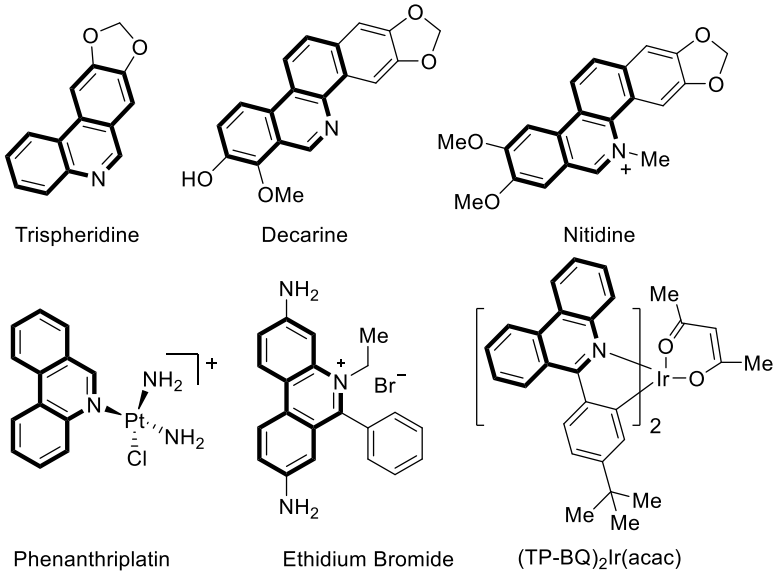


Figure 2.1 Selected phenanthridine based natural products and synthetic compounds

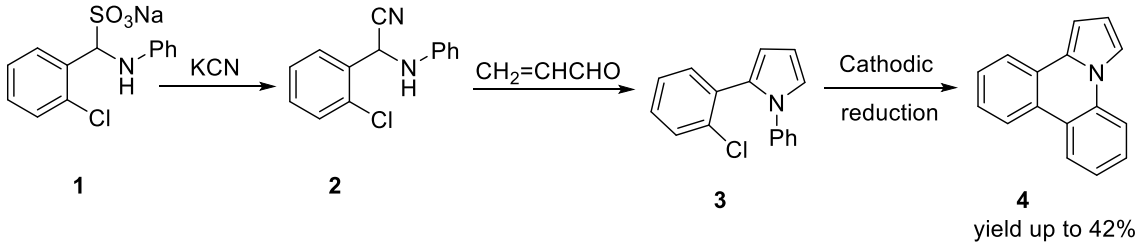
Owing to their biological activites and materials properties, synthesis of phenanthridines and its derivatives were motivated by variety of routes.

2.1.1 Traditional synthesis

a. From aniline derivatives

In aprotic solvents, the electrochemical reduction of heterocycles bearing phenyl and 2-halophenyl leads to a cyclization reaction. The process generally involves the generation of a

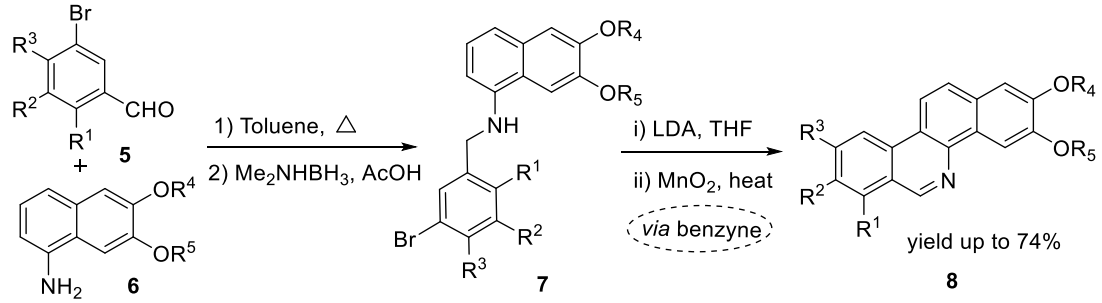
phenyl radical through carbon halogen bond cleavage. Grimshaw and group have developed phenanthridines synthesis (**4**) using an electrochemical cyclization process (**Scheme 2.1**).[13-15]



Scheme 2.1 Synthesis of pyrrolo-fused phenanthridine

b. **Cyclization of *N*-(halobenzyl)arylamines**

Kessar *et. al.* described a synthetic route to access phenanthridines derivatives (**8**) through benzyne mediated cyclization from *N*-(2-halobenzyl)-1-naphthylamines (**7**).[16] Alkaloids like chelerythrine, and decarine have been accessed in multisteps by this synthetic protocol. Nakanishi *et. al.* also developed similar strategy (**Scheme 2.2**).[17] Though, a key difference in benzaldehyde precursors of both aforementioned protocol which contain halo substitution at 2 and 5 positions, respectively. These reactions undergo through reactive benzyne intermediate. Barluenga and co-workers demonstrated synthesis of benzo-fused heterocyclic derivatives through anionic benzyne cyclization.[18]

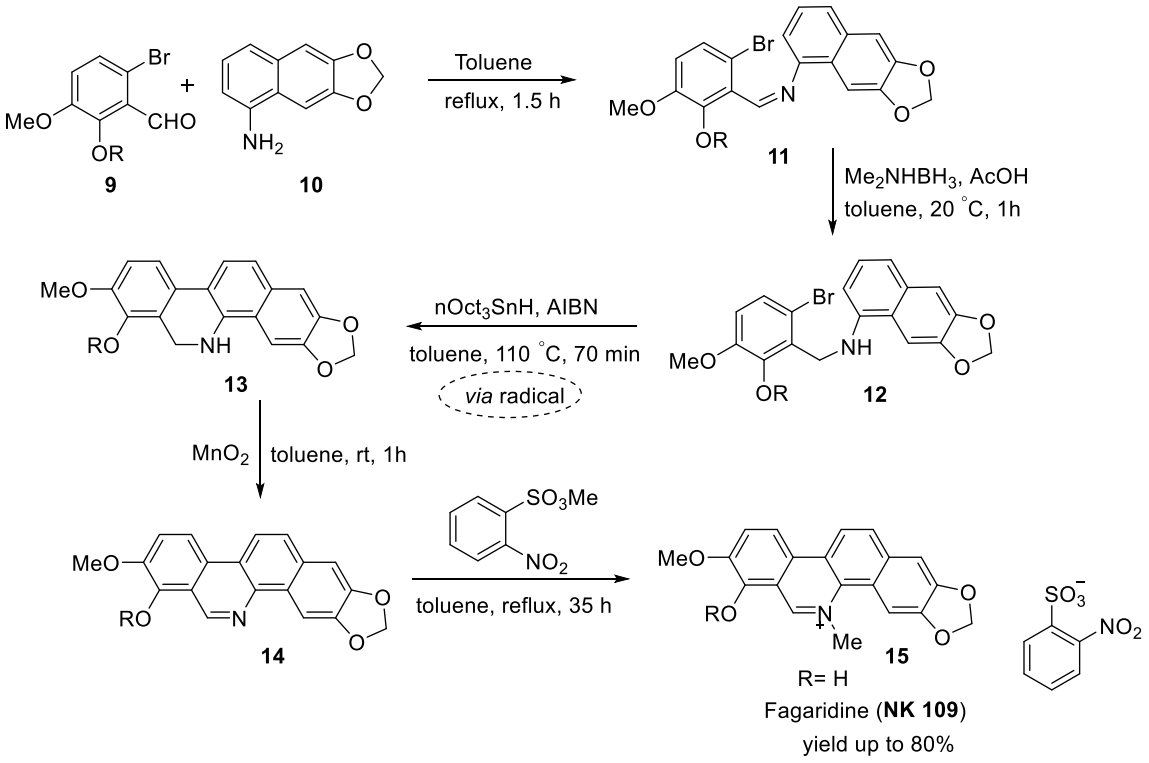


Scheme 2.2 Synthesis of benzo[c]phenanthridines from *N*-(halobenzyl)arylamines

c. **Intramolecular radical cyclizations of *N*-(*o*-halobenzyl)arylamines**

Nakanishi *et al.* has reported synthesis of phenanthridines (**14**) from *N*-(*o*-halobenzyl)anilines (**12**) using *n*Oct$_3$SnH-AIBN and MnO_2 *via* the intramolecular cyclization followed by oxidation. The required substrate *N*-(*o*-halobenzyl)anilines (**12**) was prepared by the reductive amination reaction in between precursors **9** and **10** followed by reduction under Me_2NHBH_3/ AcOH in

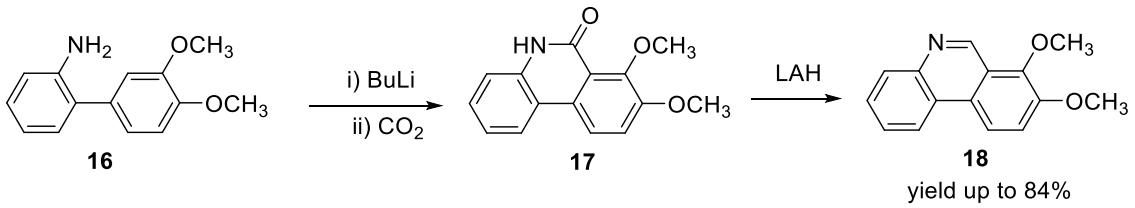
toluene. The developed synthetic approach led to the synthesis of Fagaridine (NK 109) (**15**), an anticancer benzo[*c*]phenanthridine alkaloid (**Scheme 2.3**).[19]



Scheme 2.3 Total synthesis of alkaloid Fagaridine NK 109

d. Reduction of phenanthridones

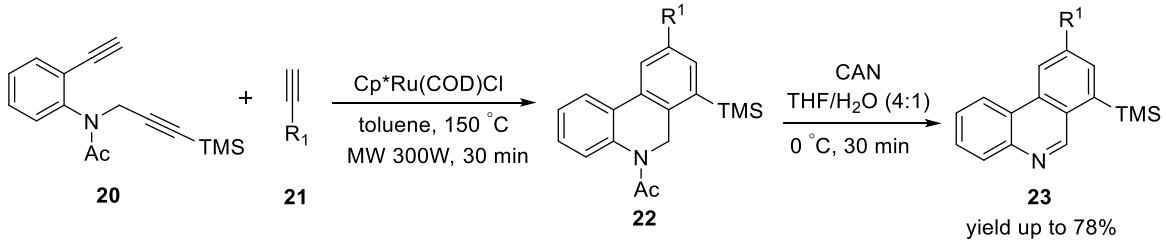
Phenanthridines can be accessed from phenanthridone by using zinc dust or lithium aluminium hydride as reducing agent.[20] Narasimhan and group reported a multistep synthesis of phenanthridines (**18**) by treatment of phenanthridone (**17)** with reducing agent $LiAlH_4$ (**Scheme 2.4**).[21] The substrate **17** was prepared by lithiation followed by carbonylation of substituted aniline derivative (**16**).



Scheme 2.4 Synthesis of substituted phenanthridines

e. **Microwave-mediated cyclotrimerization**

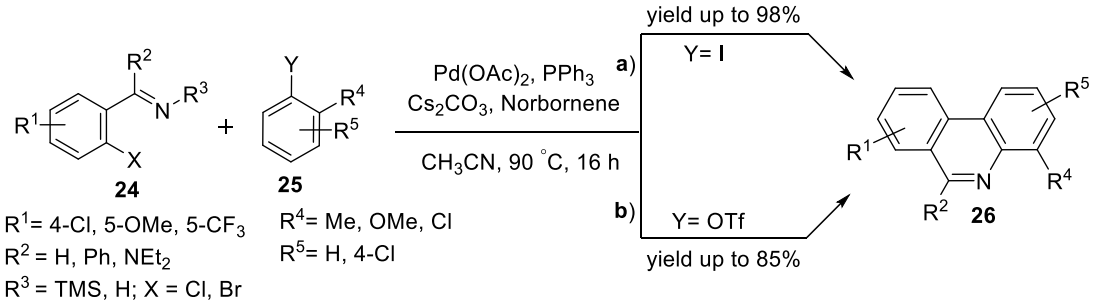
Synthesis of functionalized phenanthridines (**23**) *via* Ru catalyzed [2+2+2] cyclotrimerization of diynes **20** and **21** has been reported by Sripada and group (**Scheme 2.5**).[22] This facile approach resolves regioselectivity issues through the choice of a sterically demanding regio-directing group as TMS and delivered the tricyclic products (**23**) in good yields.



Scheme 2.5 Synthesis of phenanthridines *via* Ru-catalyzed [2+2+2] cyclotrimerization

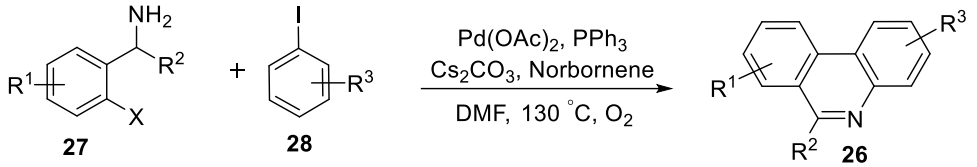
2.1.2 An overview of some selected palladium catalyzed phenanthridines

Among the transition metals, palladium catalyzed cross coupling reactions has been much efficient due to its reactivity and selectivity towards particular site in the molecule. Various efforts have been directed in past to explore routes for efficient synthesis of phenanthridines. In light of different methods, Lautens *et al.* developed synthesis of diversely substituted phenanthridines (**26**) from imines (**24**) and aryl iodides (**25**) that undergo *via* ortho arylation and subsequent *N*-arylation under palladium catalysis (**Scheme 2.6a**).[23] Another similar approach developed by the same group where substituted aryl triflates were used as one of precursor rather than substituted aryl iodide with functionalized imines (**24**) in palladium-catalyzed domino direct arylation/*N*-arylation reaction (**Scheme 2.6b**).[24] This method directly accessed phenanthridine alkaloids like as Nitidine and NK109 which demonstrated new opportunity for biological studies.



Scheme 2.6 Synthesis of phenanthridines using functionalized imines

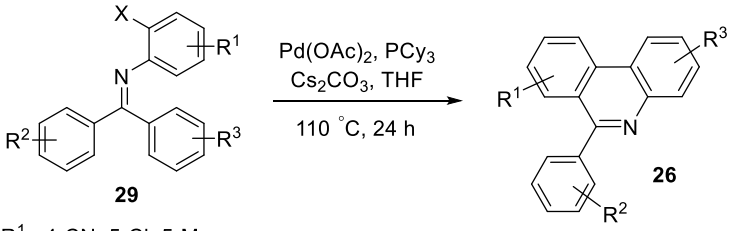
An expeditious synthesis of phenanthridines was developed by Malacria and team from benzylamines (**27**) and aryl iodides (**28**) by using palladium/norbornene co-catalyzed domino approach (**Scheme 2.7**).[25] Diversely 6-substituted phenanthridines (**26**) were achieved with excellent yields under optimized reaction conditions. The developed method involves intramolecular amination with an oxidative dehydrogenation.



R^1 = 4,5-OCH_2O-, 5-F
R^2 = H, Me, Ph
R^3 = 2-Me, 2-Et, 2-Cl, 2-CF_3
3-Me, 3-OMe, 4-Me, 4-OMe

Scheme 2.7 Access of phenanthridines from benzyl amines and aryl iodides

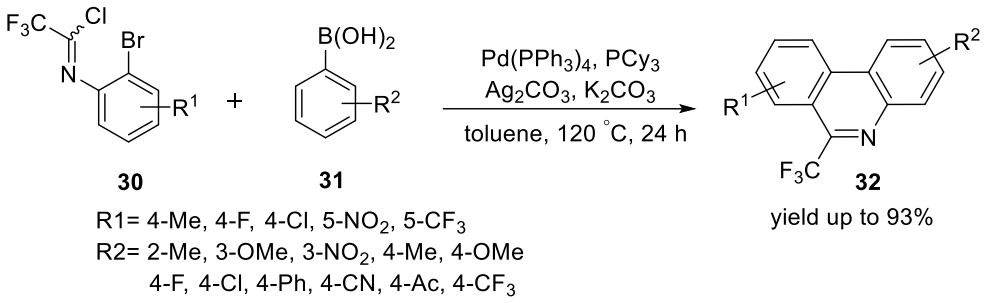
In extension of aforementioned Lautens work, Li and co-workers also demonstrated a straightforward palladium-catalyzed intramolecular C-H activation using N-(2-bromophenyl)-1,1-diphenylmethanimine (**29**) to afford corresponding phenanthridines (**26**) *via* direct arylation (**Scheme 2.8**).[26] This developed protocol was applied to make a small library of phenanthridine derivatives in good yields.



R^1= 4-CN, 5-Cl, 5-Me,
R^2 = R^3 = 2-Me, 4-Me, 4-OMe, 4-Cl
X = Cl, Br, I

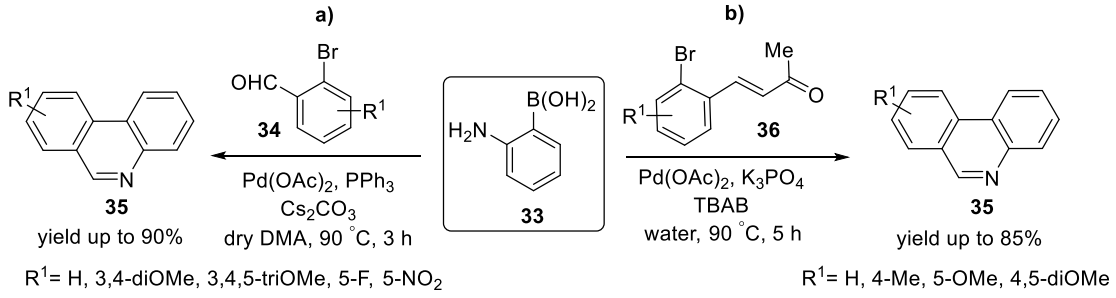
Scheme 2.8 Palladium catalyzed phenanthridines *via* direct arylation

Wang *et. al.* reported a palladium catalyzed synthesis from N-aryltrifluoroacetimidoyl chlorides (**30**) with arylboronic acids (**31**) *via* Suzuki/C-H arylation to afford 6-(trifluoromethyl) substituted phenanthridines (**32**) (**Scheme 2.9**).[27] Various analogues containing electron releasing and withdrawing substituents were prepared in moderate to excellent yields. This new optional route could be useful to access trifluoromethyl tethered phenanthridine building blocks.



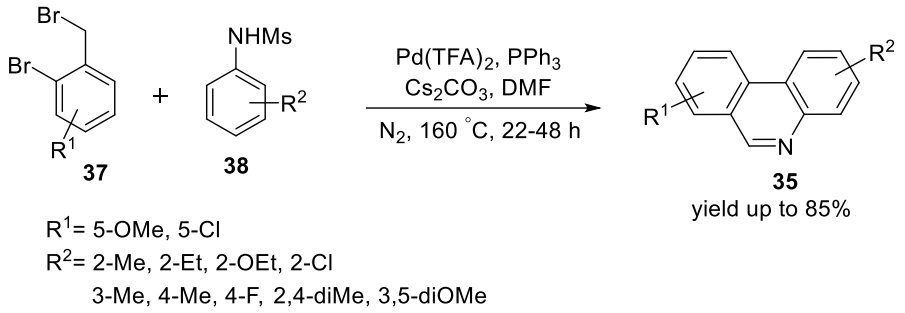
Scheme 2.9 Synthesis of trifluoromethyl substituted phenanthridines

In this same year, two more consecutive reports were appeared by Ray and co-workers where *o*-aminobenzeneboronic acids (**33**) were treated with *o*-bromobenzaldehydes (**34**) and β-(2-bromoaryl)-α,β-unsaturated carbonyl compounds (**36**), separately (**Scheme 2.10**). *o*-Aminobenzeneboronic acids (**33**) with *o*-bromobenzaldehydes (**34**) have undergone through palladium catalyzed Suzuki followed by condensation reaction to give substituted phenanthridines (**35**) (**Scheme 2.10a**).[28] Similarly, *o*-aminobenzeneboronic acids (**33**) with β-(2-bromoaryl)-α,β-unsaturated carbonyl compounds (**36**) led to the corresponding phenanthridine (**35**) derivatives *via* Suzuki coupling–Michael addition reaction in the presence of $Pd(OAc)_2$ and K_3PO_4 as a catalytic system (**Scheme 2.10b**).[29]



Scheme 2.10 Route to access phenanthridines by using *o*-aminobenzeneboronic acids

Chen and team also reported a facile and practical approach to access 6-unsubstituted phenanthridines (**35**) from 2-bromobenzylbromides (**37**) and N-Ms arylamines (**38**). A series of phenanthridine analogues were prepared under optimized reaction condition (**Scheme 2.11**). The developed methodology involves palladium catalyzed nucleophillic substitution followed by C-H activation/aromatization.[8] Also, an expeditious synthesis of the natural alkaloid trisphaeridine using this described strategy made it as useful method for scientific community.



Scheme 2.11 Direct access of phenanthridines via C-H activation

Structural studies of phenanthridines system are mostly based on its widespread use as DNA and RNA intercalator. Therefore, to enlarge the structural diversity associated with its intercalation properties, imidazo-fused phenanthridines have stimulated interest towards their synthesis (**Figure 2.2**).[30-34]

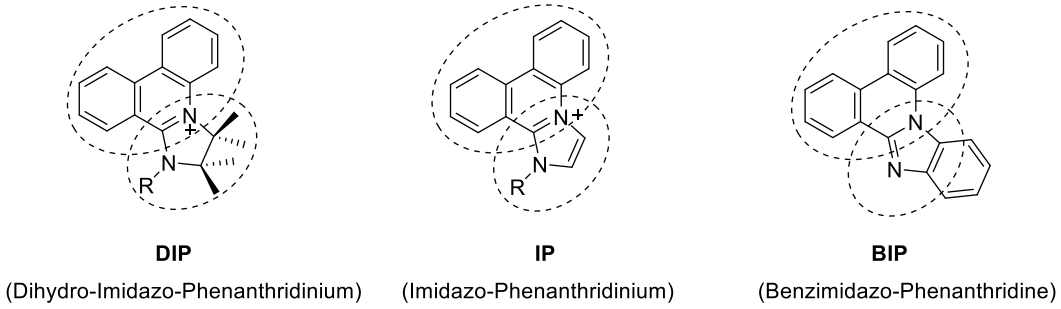
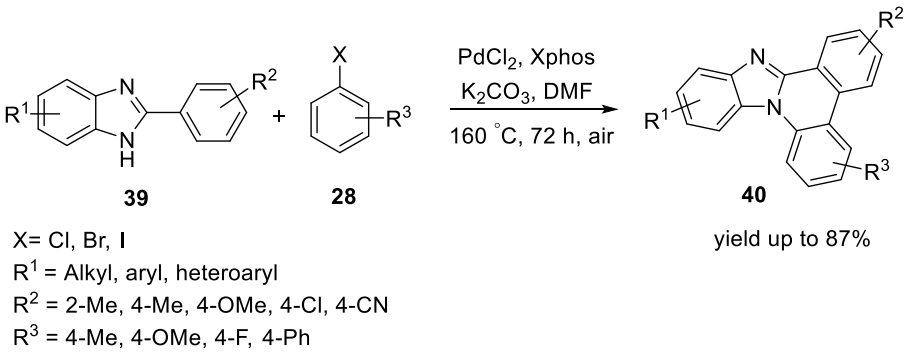


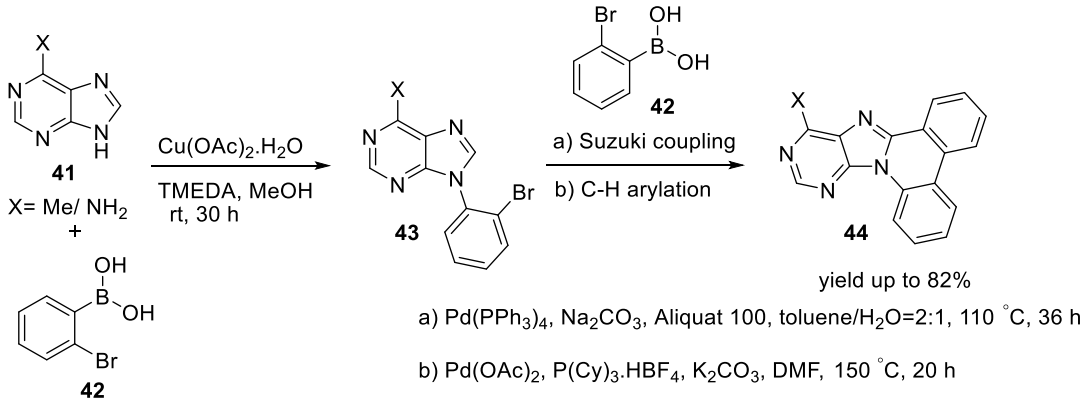
Figure 2.2 Imidazo-fused phenanthridines

Also, imidazo[1,2-*f*]phenanthridine (**40**) based compounds have received significant importance in material chemistry for electronic devices and organic light emitting diodes (OLEDs).[35-38] Moreover, compounds containing these motifs have been studied for various pharmaceutical activities.[39] Grimshaw group achieved synthesis of imidazo[1,2-*f*]phenanthridine skeleton through reductive cyclization of 2-(2-chlorophenyl)-1-phenyl-1*H*-benzo[*d*]imidazole using mercury reduction cathode[40] and Pipe's group synthesized these molecules *via* intramolecular rearrangement reactions.[41] In recent years, palladium catalyzed coupling reactions have been successfully employed for the synthesis of hetero-aromatic ring fused-phenanthridines.[42-45] Zhao and group developed a tandem one pot protocol for benzimidazole-fused phenanthridines (**40**) from 2-phenylbenzimadzoles (**39**) and aryl iodides (**28**) which comprises C-H arylation followed by aerobic oxidative C-H amination to access C-C and C-N bond formation (**Scheme 2.12**).[46]



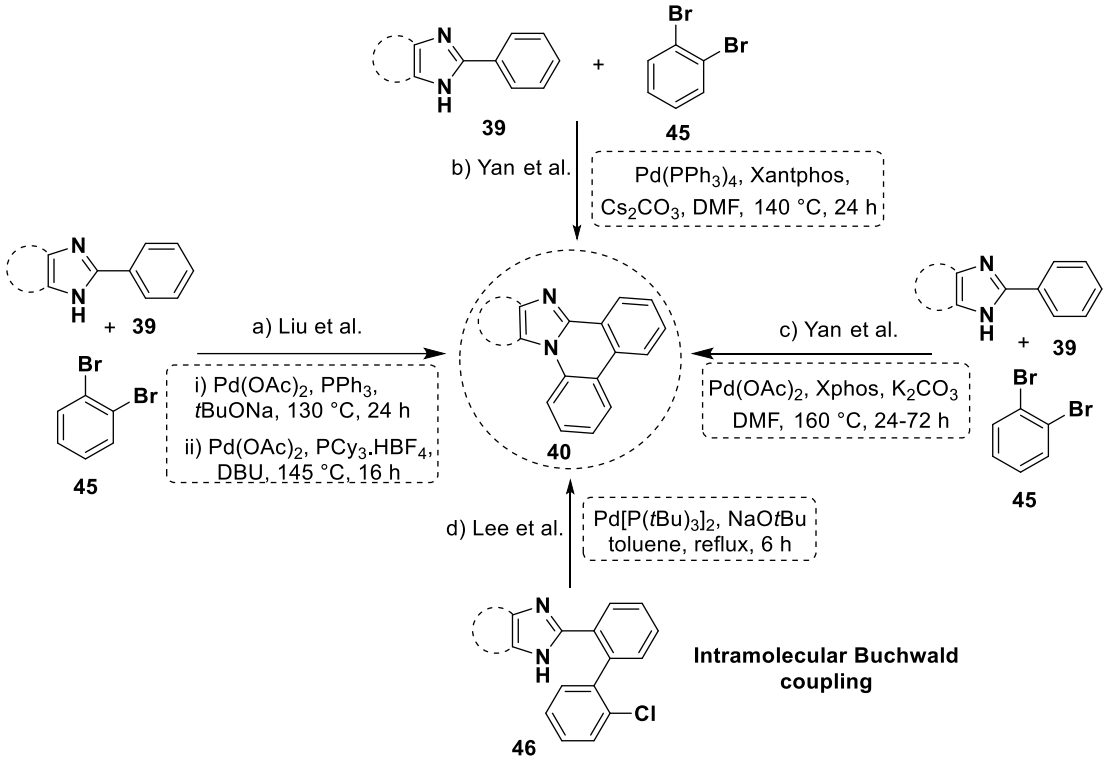
Scheme 2.12 Palladium catalyzed synthesis of benzimidazole-fused phenanthridines

Similarly, Synthesis of purino fused phenanthridines (**44**) has been achieved from purines (**43**). The developed approach involves double Suzuki reaction followed by intramolecular direct arylation reaction (**Scheme 2.13**).[47]



Scheme 2.13 Synthesis of purino[8,9-*f*]phenanthridines from purines

Synthesis of imidazo-fused phenanthridines (**40**) has also been achieved by palladium catalyzed cascade reaction of dihalobenzenes (**45**) with 2-phenylimidazoles (**39**) through N−H/C−H bonding (**Scheme 2.14**).[35, 37, 39, 48] Synthesis of substituted imidazo[1,2-*f*]phenanthridines (**40**) has also been achieved through intramolecular Buchwald coupling by using 2-(2'-chloro-[1,1'-biphenyl]-2-yl)-1H-imidazole (**46**) (**Scheme 2.14d**).[38]

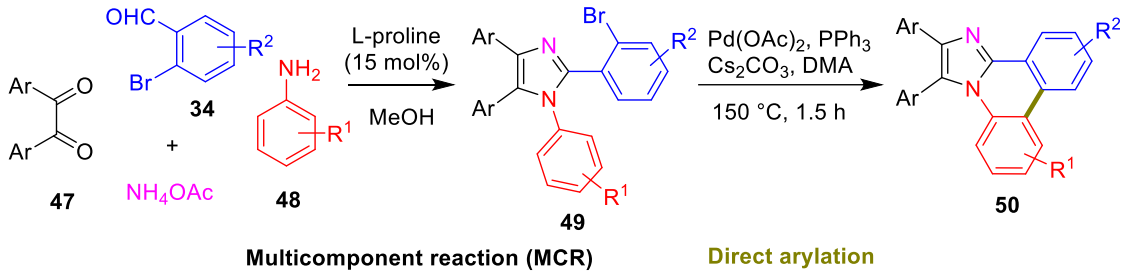


Scheme 2.14 Synthesis of imidazo[1,2-*f*]phenanthridines

It is worth to mention that the synthetic precursors, for this process have been achieved in two-steps where palladium catalyzed Suzuki-Miura reaction was involved as one of the key reactions. The synthetic methods developed for heteroaryl-fused phenanthridines are not comprehensive and suffer with limitations such as prolonged reaction time, multistep protocols for the synthesis of precursors, inconvenient procedures for the scale-up reactions, and limited substrate scope. Therefore, there is still a substantial room for the development of modular methods with simplified substrates to construct heteroaryl-fused phenanthridines.

Post functionalization of the molecules obtained through multi component reactions can offer complex structures in simpler and lower number of steps.[49] Several fused heterocycles of biological importance have been synthesized from simple and readily available raw materials following this approach in recent years.[50-51] The basic concepts of disconnections are generally overruled for the synthesis of molecules with increased skeleton diversity following combination of MCRs with tandem reactions or C-H functionalization reactions.[50, 52-59] With our continuing interest in the synthesis of novel azole-fused polyheterocycles using C–H functionalizations[60-63] and increasing interest of synthetic chemists in exploiting nitrogen based chelating groups for

transition metal-catalyzed C–H functionalization,[64-65] we envisaged that 2,3-diarylimidazo[1,2-*f*]phenanthridines (**50**) can be easily attained by palladium catalyzed direct intramolecular C-H arylation[42, 63, 66-70] of 2-(2-bromophenyl)-1,4,5-triaryl-1H-imidazoles (**49**) which in turn can be achieved by well recognized four-component imidazole synthesis (**Scheme 2.15**).[71-78]

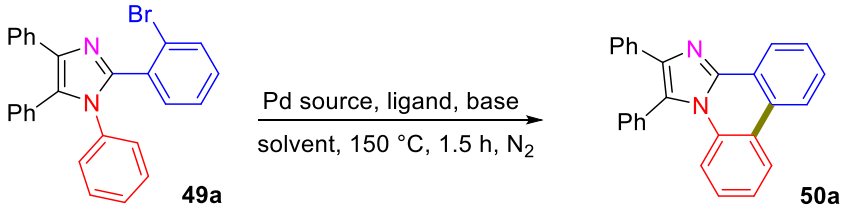


Scheme 2.15 Synthesis of 2,3-diarylimidazo[1,2-f]phenanthridines

2.2 Results and discussion

Our investigation commenced with the synthesis of 2-(2-bromoaryl)-1,4,5-triaryl-1*H*-imidazoles (**49a**) by one-pot reaction of benzil (**47a**), 2-bromobenzaldehyde (**34a**), aniline (**48a**) and ammonium acetate using L-proline (15 mol%) as a catalyst in methanol at 60 °C for 8 h.[15a] Next, synthesis of 2,3-diphenylimidazo[1,2-*f*]phenanthridines (**50a**) was initiated by reacting **49a** with $Pd(OAc)_2$ (5 mol %), PPh_3 (10 mol %), and Cs_2CO_3 (2 equiv.) in *N*,*N*-dimethylacetamide (DMA) at 150 °C under nitrogen atmosphere *via* direct intramolecular arylation involving sp^2 C–H activation. To our delight, complete consumption of **49a** was observed in 1.5 h and **50a** was obtained in 88% yield (**entry 1**, Table 1).

Table 2.1: Optimization of direct arylation conditions[a]



Entry	Catalyst	Ligand	Base	Solvent	Yield (%)[b]
1	$Pd(OAc)_2$	PPh_3	Cs_2CO_3	DMA	88
2	$Pd(PPh_3)_4$	PPh_3	Cs_2CO_3	DMA	26

3	**$Pd(PCy_3)_2Cl_2$**	**PPh_3**	**Cs_2CO_3**	**DMA**	**94**
4	$Pd(PCy_3)_2Cl_2$	PPh_3	K_2CO_3	DMA	42
5	$Pd(PCy_3)_2Cl_2$	PPh_3	KO*t*Bu	DMA	83
6	$Pd(PCy_3)_2Cl_2$	P(*o*-tolyl)$_3$	Cs_2CO_3	DMA	69
7	$Pd(PCy_3)_2Cl_2$	P(Cy)$_3$	Cs_2CO_3	DMA	74
8	$Pd(PCy_3)_2Cl_2$	-	Cs_2CO_3	DMA	40
9	$Pd(PCy_3)_2Cl_2$	PPh_3	Cs_2CO_3	toluene	12
10	$Pd(PCy_3)_2Cl_2$	PPh_3	Cs_2CO_3	DMSO	85
11	$Pd(PCy_3)_2Cl_2$	PPh_3	Cs_2CO_3	DMF	86
12	-	PPh_3	Cs_2CO_3	DMA	NR[c]

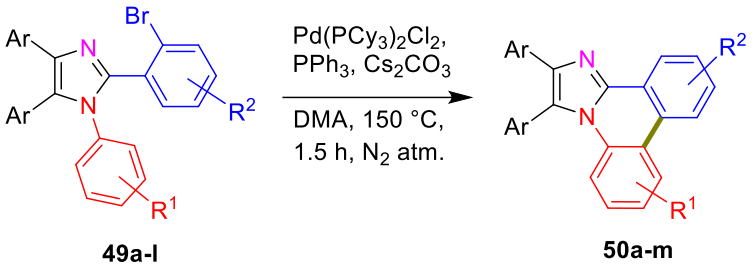
[a]Reagents and conditions: **49a** (0.3 mmol), [Pd] (5 mol %), ligand (10 mol %), base (0.6 mmol), solvent (4 mL), temp, 1.5 h, N_2. [b]Isolated yields. [c]No reaction

Encouraged by this result, we further attempted to optimize the reaction conditions by varying the catalyst, ligand, base and solvent to improve the yields of **50a**. Higher yields of **50a** were obtained using $Pd(PCy_3)_2Cl_2$ among all the palladium catalysts screened (**entry 3**, Table 2.1). Subsequent examination of various bases and ligands showed that Cs_2CO_3 and PPh_3 are the base and ligand of the choice for this direct intramolecular arylation involving C−H functionalization (**entries 3-7**, Table 2.1). Poor yields of **50a** were obtained when the reaction was performed in the absence of ligand (**entry 8**, Table 2.1). Further screening of solvents suggested that polar aprotic solvents such as DMA, DMSO and DMF are favourable whereas non-polar aprotic solvents like toluene are not suitable for this reaction (**entries 9-11**, Table 2.1). As expected, formation of **50a** was not observed when the reaction was performed in the absence of palladium catalyst (**entry 12,** Table 2.1).

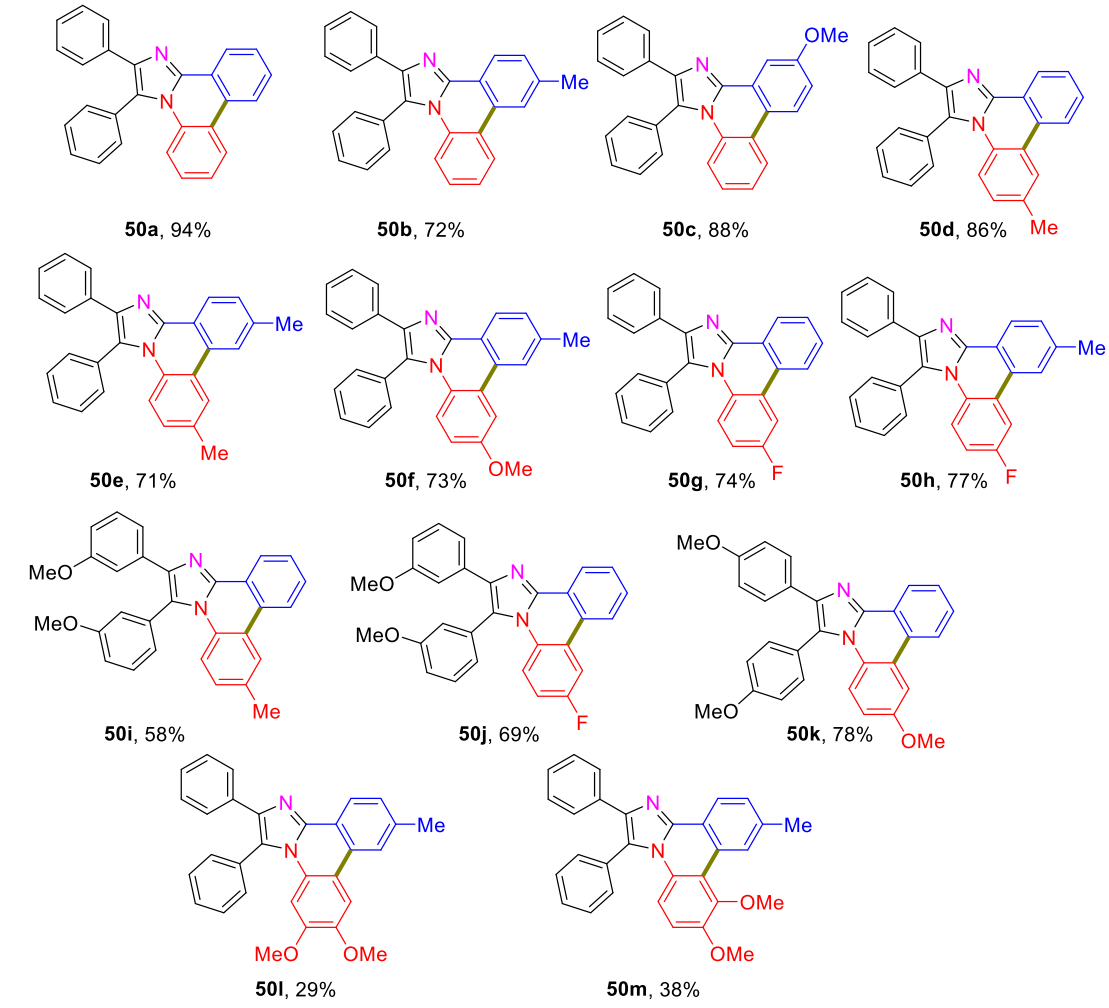
Having established the optimal reaction conditions (**entry 3**, Table 2.1), we then focussed our attention towards the scope of this reaction to synthesize library of 2,3-diarylimidazo[1,2-*f*]phenanthridines (**Table 2.1**). The substituted 2-(2-bromoaryl)-1,4,5-triaryl-1*H*-imidazoles (**50a-**

l) were prepared by varying benzils, 2-bromobenzaldehyde and anilines in the four component synthesis of imidazole[15a] and then subsequent palladium-catalyzed direct intramolecular arylation was investigated. The results are summarized in Table 2.2. As can be seen from table 2.2, N_1-aryl and C-2 aryl substituted imidazoles with electrons releasing -Me and -OMe groups (**49b-f**) gave desired products in good to excellent yields (72-88%). Electron withdrawing (fluoro) substituents on diversely substituted N_1-aryl imidazoles (**49g-h**) could also undergo to the direct intramolecular arylation and afforded good yields of corresponding fused phenanthridines (**50g-h**). Substitutions on C-4/C-5 aryl rings of imidazoles have also slightly influenced the yields of fused phenanthridines. For example, imidazoles with *m*-methoxyphenyl at C-4 and C-5 position offered lower yield of corresponding imidazo[1,2-*f*]phenanthridines (**50j**, Table 2) in comparison to phenyl ring (**50g**, Table 2.2), whereas, imidazoles with *p*-methoxyphenyl at C-4 and C-5 position offered higher yield of corresponding imidazo[1,2-*f*]phenanthridines (**50k**, Table 2.2) in comparison to phenyl ring (**50f**, Table 2). When, imidazole with 2,3-dimethoxyphenyl substituent at N_1-position (**49l**) was subjected to the direct intramolecular arylation procedure, two regioisomers (**50l** and **50m**) were produced in approx. 3: 4 ratio. Interestingly, a sterically more hindered isomer **50m** was produced preferentially. It is believed that the palladium catalyzed direct intramolecular arylation happens through σ-H bond metathesis. Formation of sterically more hindered isomer **50m** preferentially over **50l** also supports this mechanism where success of direct intramolecular arylation procedure depends on the acidity of C-H bond to be activated rather than electronic effects.

Table 2.2. Substrate scope for synthesis of imidazo fuzed phenantheridines [a]



49a-l **50a-m**



[a]Reagents and conditions: **49** (0.3 mmol), $Pd(PCy_3)_2Cl_2$ (5 mol %), PPh_3 (10 mol %), Cs_2CO_3 (0.6 mmol), DMA (4 mL), 150 °C, 1.5 h, N_2. Yields were reported after isolation through column chromatography.

The structure of all synthesized imidazo[1,2-*f*]phenanthridines was characterized by NMR spectroscopy and mass spectrometry. Among their characterized structures, NMR spectra of **50b** have been shown in **Figure 2.3**.

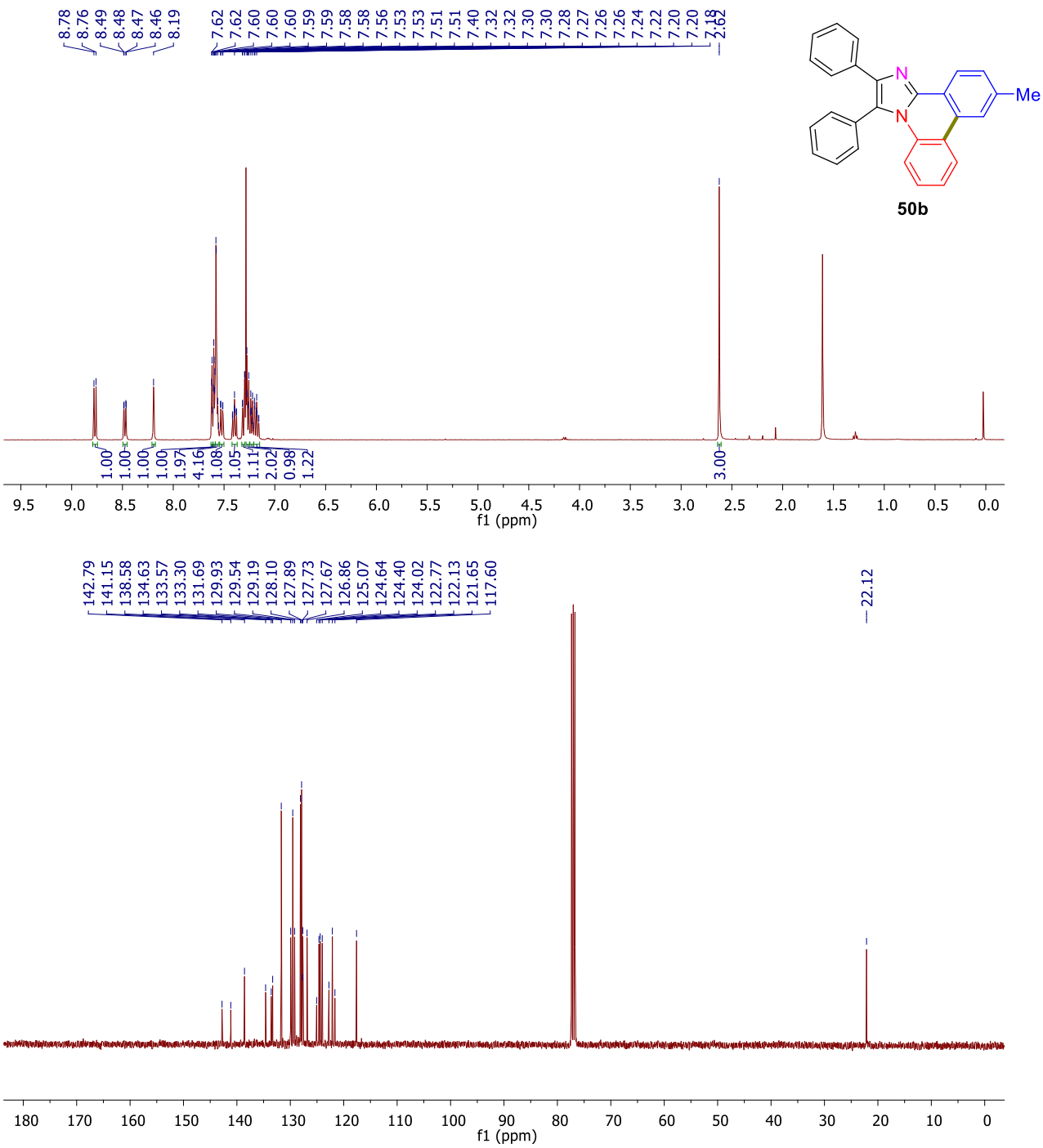


Figure 2.3 The ^{1}H and ^{13}C NMR spectra of **50b**

In description of aforementioned spectral data, ^{1}HNMR of compound **50b** exhibited 17 protons in aromatic region which appeared in range of δ 7.16-8.78, along with one clear characteristic singlet at 8.19 ppm. Aliphatic three methyl protons appeared as singlet at 2.62 ppm to satisfy the

obtained structure. ^{13}C NMR spectrum comprised the total 24 carbons peak where one methyl appeared at 22.12 ppm and remaining all carbons turned up in aromatic region.

2.3 Conclusion

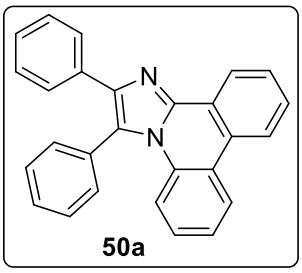
A simple and convenient approach has been developed for the synthesis of imidazo[1,2-*f*]phenanthridine framework *via* post functionalization of imidazoles obtained through four component reaction of 1,2-dicarbonyl compounds, anilines, aldehyde and NH_4OAc. The methodology involves palladium catalyzed direct arylation involving sp^2 C–H functionalization. The reported method delivered good to high yields of imidazo[1,2-*f*]phenanthridine derivatives (**58**-**94**%) starting from readily available precursors.

2.4 Experimental

General information: The chemical structure of the compounds was determined NMR (^1H and ^{13}C NMR) and mass spectra. The NMR spectra were recorded on Bruker Avance III 400 spectrometer and chemical shifts are reported in parts per million (ppm) using deuterated solvent peak or tetramethylsilane as an internal standard. Melting points were determined in open capillary tubes on EZ-Melt automated melting point apparatus and are uncorrected. All the reactions were monitored using thin layer chromatography (TLC) on 0.2 mm silica gel F254 plates (Merck). All chemicals were obtained from the commercial suppliers and used without further purification.

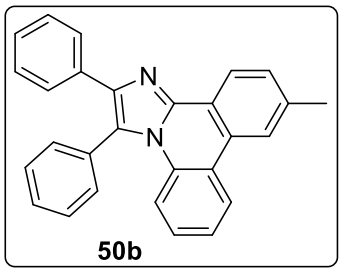
General procedure for the synthesis of 2,3-diarylimidazo[1,2-*f*]phenanthridine: An oven-dried 10 mL round bottom flask was charged with 2-(2-bromophenyl)-1,4,5-triphenyl-1H-imidazole (**49a**) (135 mg, 0.3 mmol), PPh_3 (8 mg, 0.03 mmol), Cs_2CO_3 (196 mg, 0.6 mmol) and DMA (4 mL) then purged with N_2 for 5-10 min. $Pd(PCy_3)_2Cl_2$ (11 mg, 0.015 mmol) was added and the resulting solution was stirred at 150 ˚C for 1.5 h under N_2 atmosphere. On completion, the reaction mass was cooled to ambient temperature, diluted with water 10 mL and extracted into EtOAc (2 × 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and evaporated to dryness. The crude residue so obtained was purified by column chromatography (EtOAc-hexanes) to afford **50a** in 94% (104 mg) yield.

2,3-Diphenylimidazo[1,2-*f*]phenanthridine (50a)



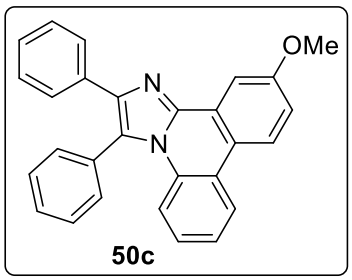
Yield 94%; White solid; mp 175-177 °C, ^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.68 (d, *J* = 7.2 Hz, 2H), 8.64 – 8.61(m, 1H), 7.90 – 7.38 (m, 10H), 7.34 – 7.08 (m, 5H); ^{13}C NMR (100 MHz, DMSO-d_6) δ = 141.9, 140.6, 134.6, 133.2, 133.1, 131.9, 130.30, 130.2, 129.5, 129.3, 128.7, 128.6, 127.7, 127.6, 127.5, 125.8, 125.5, 125.3, 124.2, 123.5, 123.4, 122.6, 117.1. HRMS-ESI: *m/z* [M + H]$^{+}$ calcd for $C_{27}H_{19}N_2$: 371.1543; found: 371.1548.

10-Methyl-2,3-diphenylimidazo[1,2-*f*]phenanthridine (50b)



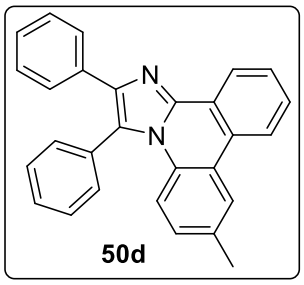
Yield 72%; White solid; mp 221-223 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.77 (d, *J* = 8.1 Hz, 1H), 8.48 (dd, *J* = 8.2, 1.3 Hz, 1H), 8.19 (s, 1H), 7.64 – 7.55 (m, 7H), 7.52 (dd, *J* = 8.1, 0.9 Hz, 1H), 7.43 – 7.37 (m, 1H), 7.33 – 7.29 (m, 1H), 7.28 – 7.15 (m, 4H), 2.62 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 142.8, 141.1, 138.6, 134.6, 133.6, 133.3, 131.7, 129.9, 129.5, 129.2, 128.1, 127.9, 127.7, 127.7, 126.9, 125.1, 124.6, 124.4, 124.0, 122.8, 122.1, 121.6, 117.6, 22.1. HRMS-ESI: *m/z* [M + H]$^{+}$ calcd for $C_{28}H_{21}N_2$: 385.1699; found: 385.1695.

11-Methoxy-2,3-diphenylimidazo[1,2-*f*]phenanthridine (50c)



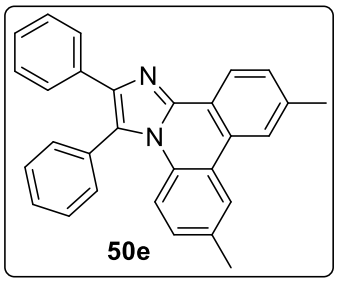
Yield 88%; White solid; mp 220-222 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.36 (d, *J* = 8.1 Hz, 1H), 8.32 – 8.24 (m, 2H), 7.68 – 7.53 (m, 7H), 7.37 (t, *J* = 7.6 Hz, 1H), 7.34 – 7.20 (m, 5H), 7.13 (t, *J* = 7.8 Hz, 1H), 4.09 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 159.9, 142.4, 141.3, 134.5, 133.2, 132.5, 131.7, 129.6, 129.3, 128.2, 127.9, 126.9, 126.7, 125.5, 125.2, 124.6, 123.9, 123.5, 122.9, 121.4, 118.8, 117.5, 105.1, 55.8. HRMS-ESI: *m/z* [M + H]$^{+}$ calcd for $C_{28}H_{21}N_2O$: 401.1648; found: 401.1647.

7-Methyl-2,3-diphenylimidazo[1,2-*f*]phenanthridine (50d)



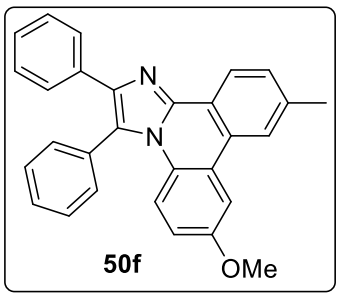
Yield 86%; White solid; mp 196-198 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.91 – 8.86 (m, 1H), 8.40 (dd, *J* = 7.3, 2.0 Hz, 1H), 8.28 – 8.26 (m, 1H), 7.72 – 7.64 (m, 2H), 7.64 – 7.60 (m, 2H), 7.60 – 7.54 (m, 5H), 7.34 – 7.20 (m, 3H), 7.17 (s, 1H), 7.02 (dd, *J* = 8.7, 1.5 Hz, 1H), 2.49 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 142.4, 141.1, 134.6, 134.1, 133.2, 131.7, 131.4, 129.5, 129.2, 128.9, 128.5, 128.3, 128.1, 127.9, 127.6, 126.9, 125.2, 124.7, 124.1, 123.9, 122.7, 122.1, 117.4, 21.2. HRMS-ESI: *m/z* $[M + H]^+$ calcd for $C_{28}H_{21}N_2$: 385.1699; found: 385.1696.

7,10-Dimethyl-2,3-diphenylimidazo[1,2-*f*]phenanthridine (50e)



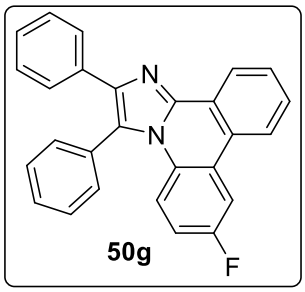
Yield 71%; White solid; mp 229-231 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.76 (d, *J* = 8.1 Hz, 1H), 8.26 (s, 1H), 8.19 (s, 1H), 7.63 – 7.61 (m, 1H), 7.60 – 7.59 (m, 1H), 7.58 – 7.54 (m, 5H), 7.51 (dd, *J* = 8.2, 1.0 Hz, 1H), 7.28 – 7.24 (m, 2H), 7.24 – 7.20 (m, 1H), 7.17 (d, *J* = 8.7 Hz, 1H), 7.00 (dd, *J* = 8.7, 1.5 Hz, 1H), 2.62 (s, 3H), 2.48 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 142.6, 140.9, 138.4, 134.7, 133.9, 133.3, 131.7, 131.5, 129.8, 129.5, 129.1, 128.8, 128.1, 127.9, 127.7, 126.8, 124.9, 124.6, 124.0, 122.6, 122.1, 121.7, 117.4, 22.1, 21.2. HRMS-ESI: *m/z* $[M + H]^+$ calcd for $C_{29}H_{23}N_2$: 399.1856; found: 399.1852.

7-Methoxy-10-methyl-2,3-diphenylimidazo[1,2-*f*]phenanthridine (50f)



Yield 73%; white solid; mp 178-180 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.76 (d, *J* = 8.1 Hz, 1H), 8.11 (s, 1H), 7.89 (d, *J* = 2.8 Hz, 1H), 7.62 – 7.50 (m, 8H), 7.28 – 7.19 (m, 4H), 6.78 (dd, *J* = 9.3, 2.9 Hz, 1H), 3.93 (s, 3H), 2.62 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 156.2, 142.2, 140.8, 138.4, 134.7, 133.2, 131.7, 130.0, 129.5, 129.2, 128.1, 127.8, 127.4, 126.8, 124.8, 124.7, 124.1, 122.2, 121.8, 118.7, 114.6, 114.2, 107.5, 55.6, 22.1. HRMS-ESI: *m/z* $[M + H]^+$ calcd for $C_{29}H_{23}N_2O$: 415.1805; found: 415.1802.

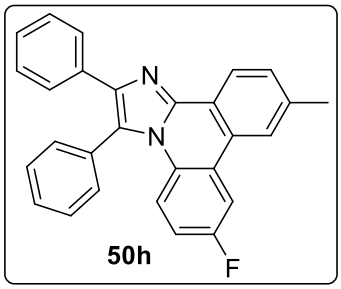
7-Fluoro-2,3-diphenylimidazo[1,2-*f*]phenanthridine (50g)



50g

Yield 74%; white solid; mp 192-194 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.91 – 8.87 (m, 1H), 8.30 – 8.25 (m, 1H), 8.11 (dd, *J* = 10.1, 2.9 Hz, 1H), 7.77 – 7.65 (m, 2H), 7.66 – 7.52 (m, 7H), 7.34 – 7.28 (m, 1H), 7.28 – 7.20 (m, 3H), 6.97 – 6.87 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 159.4 (d, *J* = 244.2 Hz), 142.2, 141.3, 134.4, 132.9, 131.6, 131.2, 129.7, 129.5, 129.1, 128.7, 128.5, 128.2, 127.9, 127.4, 127.0, 125.3, 124.7, 124.2, 122.3, 119.2 (d, *J* = 8.1 Hz), 115.3 (d, *J* = 23.3 Hz), 109.9 (d, *J* = 24.0 Hz). HRMS-ESI: *m/z* $[M + H]^+$ calcd for $C_{27}H_{18}FN_2$: 389.1449; found 389.1444.

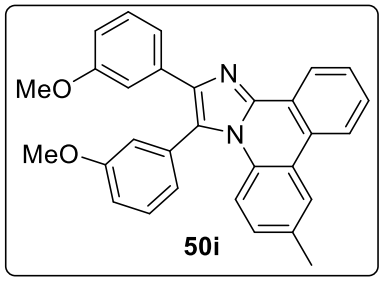
7-Fluoro-10-methyl-2,3-diphenylimidazo[1,2-*f*]phenanthridine (50h)



50h

Yield 77%; white solid; mp 215-217 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.77 (d, *J* = 8.1 Hz, 1H), 8.10 (dd, *J* = 10.2, 2.8 Hz, 1H), 8.07 (s, 1H), 7.63 – 7.53 (m, 8H), 7.29 (d, *J* = 1.5 Hz, 1H), 7.28 – 7.20 (m, 3H), 6.94 – 6.85 (m, 1H), 2.62 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 159.4 (d, *J* = 237.6 Hz), 142.4, 141.2, 138.8, 134.4, 133.0, 131.6, 130.6, 129.9, 129.7, 129.4, 128.1, 127.8, 126.9, 126.9, 124.9, 124.8 (d, *J* = 7.8 Hz), 124.7, 122.3, 121.9, 119.2 (d, *J* = 8.2 Hz), 115.2 (d, *J* = 23.3 Hz), 109.8 (d, *J* = 23.6 Hz), 22.1. HRMS-ESI: *m/z* $[M + H]^+$ calcd for $C_{28}H_{20}FN_2$: 403.1605; found: 403.1601.

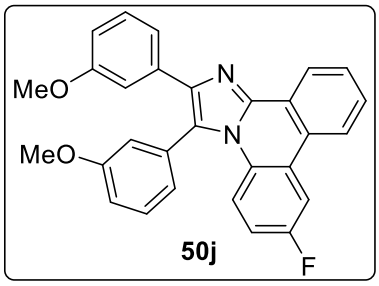
2,3-Bis(3-methoxyphenyl)-7-methylimidazo[1,2-*f*]phenanthridine (50i)



50i

Yield 58%; off-white solid; mp 145-147 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.93 – 8.83 (m, 1H), 8.42 – 8.34 (m, 1H), 8.25 (s, 1H), 7.67 (dd, *J* = 6.5, 2.5 Hz, 2H), 7.51 (t, *J* = 7.9 Hz, 1H), 7.27 – 7.03 (m, 8H), 6.80 (d, *J* = 8.0 Hz, 1H), 3.83 (s, 3H), 3.71 (s, 3H), 2.49 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 160.4, 159.3, 142.2, 140.7, 135.8, 134.5, 134.2, 131.3, 130.6, 129.2, 129.1, 128.4, 128.1, 127.7, 125.1, 124.7, 124.06, 124.0, 123.8, 122.6, 122.1, 120.3, 117.5, 116.5, 115.3, 113.6, 112.3, 55.4, 55.0, 21.2. HRMS-ESI: *m/z* $[M + H]^+$ calcd for $C_{30}H_{25}N_2O_2$: 445.1911; found: 445.1912.

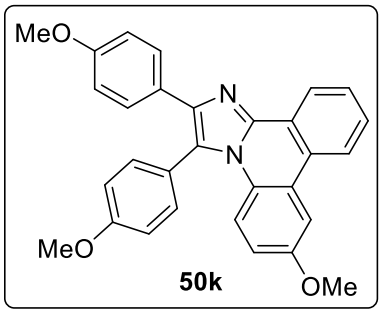
7-Fluoro-2,3-bis(3-methoxyphenyl)imidazo[1,2-f]phenanthridine (50j)



50j

Yield 69%; pale yellow solid; mp 150-152 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ = 8.71 – 8.59 (m, 2H), 8.54 (d, *J* = 10.4 Hz, 1H), 7.82 – 7.69 (m, 2H), 7.60 (t, *J* = 8.0 Hz, 1H), 7.29 – 7.17 (m, 7H), 7.07 (s, 1H), 6.83 – 6.76 (m, 1H), 3.80 (s, 3H), 3.61 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ = 161.2, 160.8, 159.4, 157.9, 141.4, 140.1, 135.8, 134.1, 131.6, 129.9, 129.8 (d, *J* = 2.2 Hz), 129.6, 129.5, 127.1, 125.6, 124.82 (d, *J* = 8.4 Hz), 124.2, 123.9, 123.7, 119.9, 119.2, 119.1, 117.0, 116.4, 116.1, 113.3, 112.7, 111.2 (d, *J* = 24.0 Hz), 55.9, 55.1. HRMS-ESI: *m/z* [M + H]$^{+}$ calcd for $C_{29}H_{22}FN_2O_2$: 449.1660; found: 449.1665.

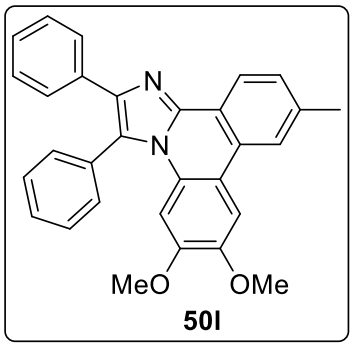
7-Methoxy-2,3-bis(4-methoxyphenyl)imidazo[1,2-f]phenanthridine (50k)



50k

Yield 78%; off-white solid; mp 191-193 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.88 – 8.84 (m, 1H), 8.34 – 8.30 (m, 1H), 7.90 (d, *J* = 2.9 Hz, 1H), 7.71 – 7.62 (m, 2H), 7.59 – 7.54 (m, 2H), 7.48 – 7.44 (m, 2H), 7.31 (d, *J* = 9.3 Hz, 1H), 7.14 – 7.09 (m, 2H), 6.86 – 6.80 (m, 3H), 3.97 (s, 3H), 3.93 (s, 3H), 3.81 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 160.2, 158.6, 156.1, 141.7, 140.9, 132.9, 132.4, 128.9, 128.3, 127.9, 127.3, 125.3, 124.6, 124.2, 124.1, 122.1, 118.6, 115.0, 114.8, 114.2, 113.8, 113.6, 107.6, 55.6, 55.4, 55.2. HRMS-ESI: *m/z* [M + H]$^{+}$ calcd for $C_{30}H_{25}N_2O_3$: 461.1860; found: 461.1862.

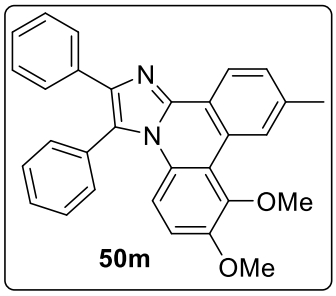
6,7-Dimethoxy-10-methyl-2,3-diphenylimidazo[1,2-f]phenanthridine (50l)



50l

Yield 29%; off-white solid; mp 242-244 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.77 (d, *J* = 8.1 Hz, 1H), 8.01 (s, 1H), 7.78 (s, 1H), 7.67 – 7.53 (m, 7H), 7.47 (dd, *J* = 8.1, 0.9 Hz, 1H), 7.28 – 7.19 (m, 3H), 6.96 (s, 1H), 4.06 (s, 3H), 3.31 (s, 3H), 2.63 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 148.9, 146.3, 142.6, 140.8, 138.4, 134.6, 133.8, 132.4, 129.5, 129.1, 128.9, 128.1, 127.8, 127.6, 126.8, 124.7, 124.2, 121.45, 120.80, 115.7, 105.2, 100.9, 56.2, 55.0, 22.1. HRMS-ESI: *m/z* [M + H]$^{+}$ calcd for $C_{30}H_{25}N_2O_2$: 445.1911; found: 445.1915.

7,8-Dimethoxy-10-methyl-2,3-diphenylimidazo[1,2-f]phenanthridine (50m)



Yield 38%; off-white solid; mp 218-220 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.19 (s, 1H), 8.80 (d, *J* = 8.1 Hz, 1H), 7.61 – 7.49 (m, 9H), 7.30 – 7.17 (m, 3H), 7.13 (d, *J* = 9.4 Hz, 1H), 6.81 (d, *J* = 9.4 Hz, 1H), 3.95 (s, 3H), 3.91 (s, 3H), 2.61 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 150.0, 148.1, 142.8, 141.2, 138.5, 134.7, 133.5, 131.6, 129.6, 129.5, 129.0, 128.6, 128.1, 127.9, 127.6, 127.2, 126.8, 124.9, 124.3, 122.2, 118.2, 113.5, 111.9, 59.9, 56.3, 22.4. HRMS-ESI: *m/z* $[M + H]^+$ calcd for $C_{30}H_{25}N_2O_2$: 445.1911; found: 445.1917.

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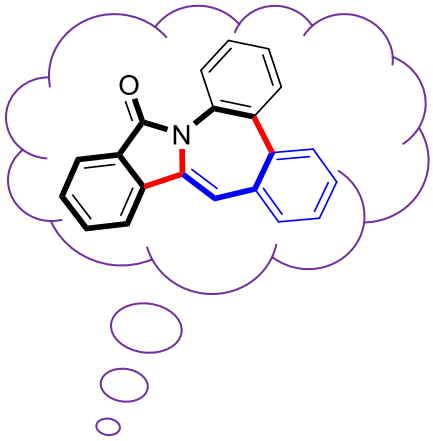
Chapter 3

Route to Access Azepino-fused Isoindolinones by Sequential Copper-Catalyzed Sonogashira Coupling, Hydroamidation and Palladium-Catalyzed Intramolecular Direct Arylation



3.1 Introduction

Isoindolinone is a nitrogen containing bicyclic heterocycle which is ubiquitously found in variety of natural products and synthetic compounds with wide range of bioactivities.[1-6] Indoprofen[7], Chlortalidone[8] and Pestalachloride A[2] are the few selected examples which contain this valuable isoindolinone scaffold (**Figure 3.1**). Similarly, azepine framework is also widely encountered in many naturally occurring alkaloids such as marine hymenialdisine and marketed drugs such as amezepine,[9] anafranil,[10] carbamazepine (**Figure 3.1**).[11-12] Owing to their applications, several synthetic routes have been developed for long back. Specially, the last decade has witnessed admirable advancement in the synthesis of these privilege heterocycles.

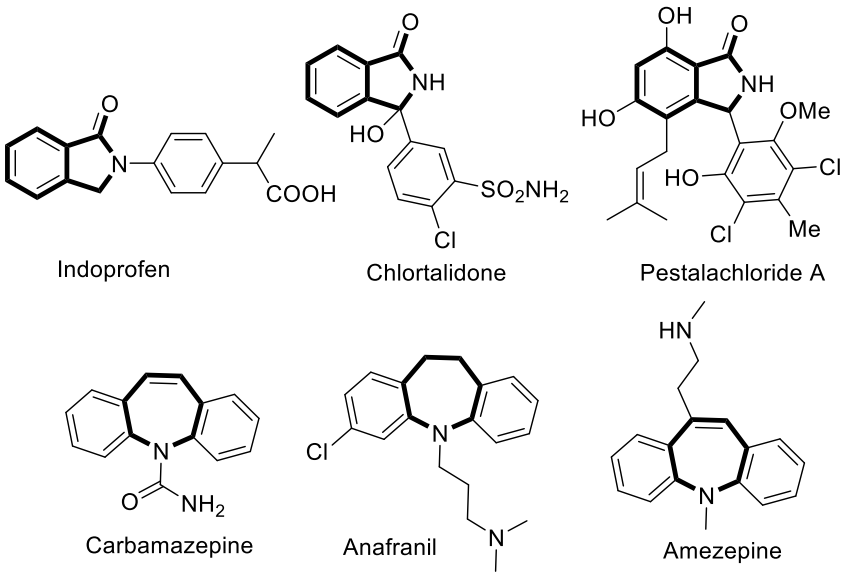
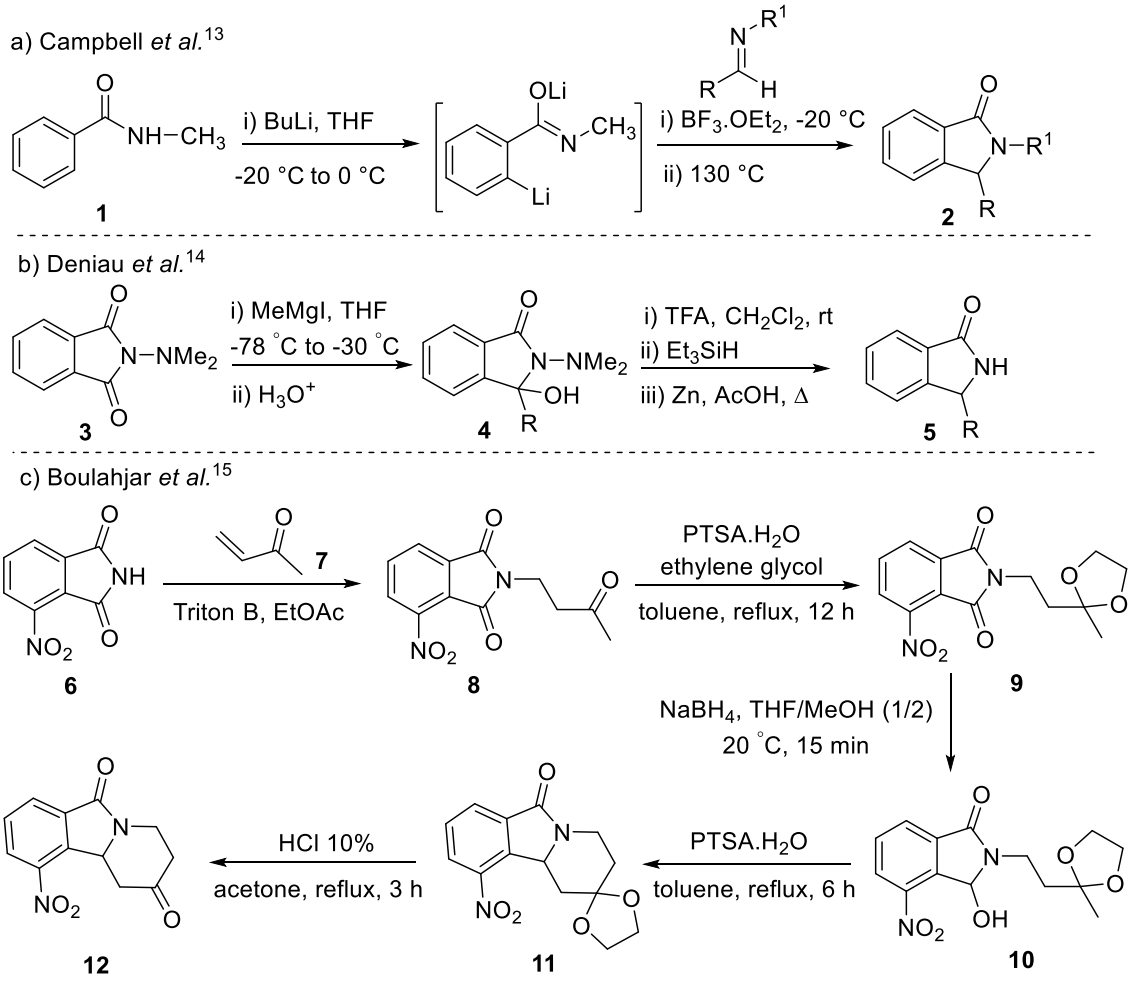


Figure 3.1 Representative compounds containing isoindolinone and azepine scaffolds

3.1.1 Multi step synthesis of isoindolinones

Isoindolones derivatives can be prepaired by multisteps synthesis using classical approaches. Campbell and group demonstrated a method for isoindolinones (**2**) from *N*-methylbenzamide (**1**).[13] Lithation reaction of **1** followed by reaction with imine under $BF_3.OEt_2$ delivered expected products in good to high yields (**Scheme 3.1a**). Synthesis of 3-substituted pthalimidines (**5**) was achieved from *N*-dimethylamino phthalimide (**3**).[14] The *N*-dimethylamino phthalimide reacted readily with a stoichiometric amount of Grignard reagents (MeMgI) at low temperature to give the *N,O*-hemiacetals (**4**). The hydroxy functionality in *N,O*-hemiacetals can be removed

by treating with excess of trifluoroacetic acid to give iminium salt. The formed iminium salt was smoothly reduced with triethylsilane to furnish *N*-protected bicyclic compounds. Finally deprotection of *N*-dimethylamino group was achived with excess amount of zinc in refluxing acetic acid to get the targeted 3-substituted phthalimidines (**5**) in good yields. Similarly, Boulahjar and his colleagues have disclosed synthesis of substituted tetrahydropyrido[1,2-*a*]isoindolone derivatives (valmerins) (**12**).[15] The multiple steps synthesis involve, first Michael addition, ketalation, reduction followed by acid catalyzed cyclization to afford desired products (**Scheme 3.1c**).



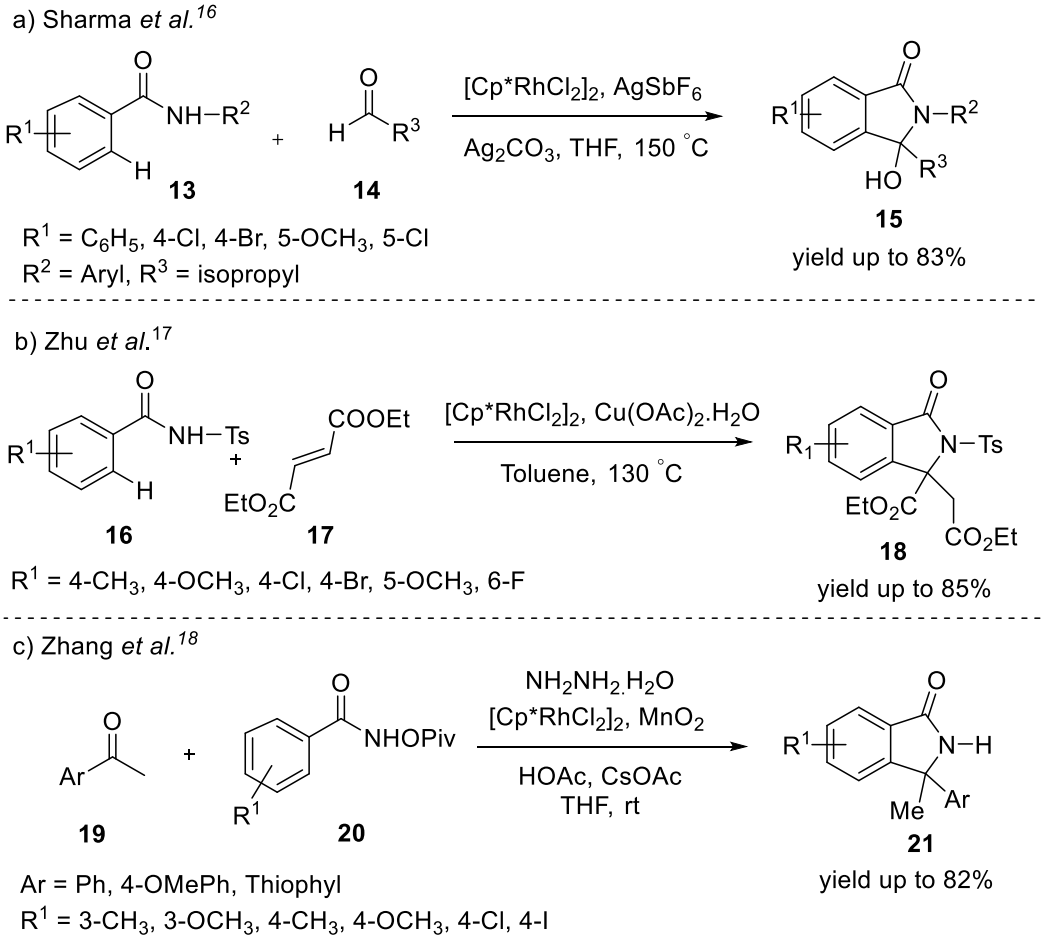
Scheme 3.1 Classical approaches for isoindolones synthesis

These aforementioned synthetic approaches used regents which are quite difficult to handle like BuLi, RMgX, HCl and also involved multiple steps. Thus, there is need to develop relatively

safer methods. In this perspective, transition metal catalysed couplings greatly had been effective to provide these molecules in single step under comparitively mild conditions.

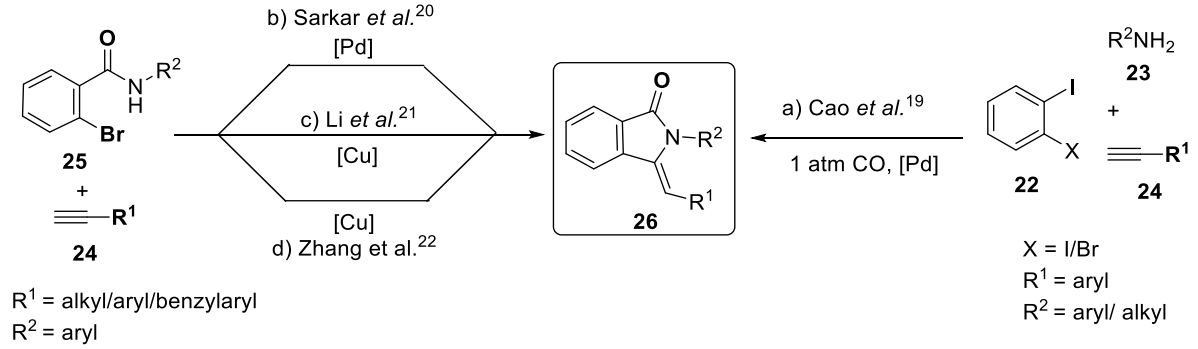
3.1.2 Transition metal catalyzed synthesis of isoindolinone

There are reports by different research group to access isoindolinones by Rh-catalyzed one pot reaction (**Scheme 3.2**). In substituted benzamides direct functionalization of C-H bond easily undergo cyclization to afford medicianally important isoindolinones. Sharma *et al*. developed the rhodium catalyzed oxidative acylation between aldehyde (**14**) and *N*-substituted benzamides (**13**) to yield 3-hydroxyisoindolin-1-ones (**15**) (**Scheme 3.2a**).[16] Zhu *et al*. described rhodium calatyzed C-H olefination of N-benzoylsulfonamides (**16**) with activated internal alkenes (**17**) to afford 3,3-disubstituted isoindolinones (**18**) (**Scheme 3.2b**).[17] In 2015, Zhang and co-workers also developed a facile synthesis of isoindolinones (**21**) by rhodium catalyzed C-H activation benzamides (**20**) (**Scheme 3.2c**).[18]



Scheme 3.2 Rh-catalyzed functionalized isoindolones

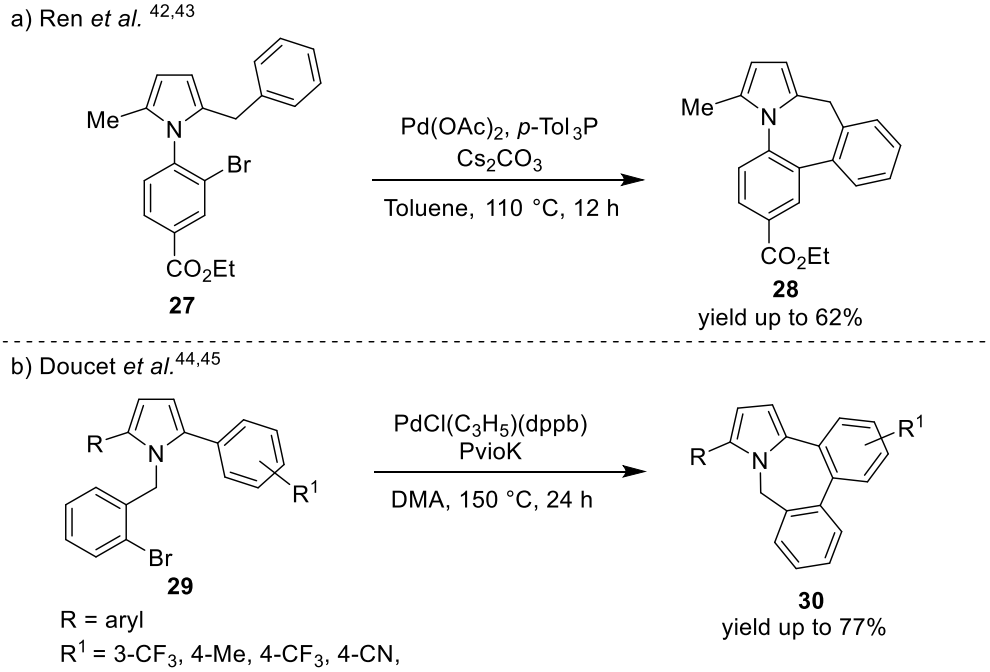
Synthesis of isoindolinones have also been achieved by using copper and palladium catalysts which are relatively cheaper than rhodium catalysts (**Scheme 3.3**). Cao and group developed a palladium catalyzed synthesis that features carbonylation-hydroamination reaction to access different isoindolinone analogues (**26**) (**Scheme 3.3a**).[19] Similarly, an operationally simple green methodology was developed for 3-substituted isoindolinones (**26**) in aqueous micellar medium by palladium catalyzed reaction of various halo-substituted benzamides (**25**) with different alkynes (**24**) (**Scheme 3.3b**)[20]. Li and Zhang group have independently developed a copper catalyzed annulation of benzamides (**25**) with alkynes (**24**) to give corresponding isoindolinones (**Scheme 3.3c and d**).[21-22] These reaction involved copper catalyzed sonogashira followed by hydroamidation reactions. The regio- and stereoselective synthesis of (*Z*)-3-methyleneisoindolin-1-one (**26**) derivatives were prepared through copper catalyzed two consecutive C-C and C-N couplings. Variation of *N*-substituents such as different alkyls, aryls, and heteroaryls makes these methods more versatile to deliver different types of isoindolinones.



Scheme 3.3 Copper/palladium catalyzed synthesis of isoindolinones

Reactions that involve palladium-catalyzed intramolecular direct arylation are of special interest as they lead to polycyclic heterocycles and preclude the presence of additional functional group in the substrate.[23-29] These reaction sequences have been elegantly investigated by several groups to synthesize complex heterocyclic compounds.[30-41] However, only a few examples of such intramolecular direct arylation leading to azepino-fused heterocycles have been described revealing the fact that their access is quite challenging. For example, Ren *et al.* reported few example of azepino-fused pyrroles (**28**) *via* intramolecular direct arylation in their work on synthesis of condensed *N*-heterocycles by benzylic C-H activation (**Scheme 3.4a**).[42-43] Doucet and team has also prepared dibenz[*c*,*e*]pyrazolo[1,5-*a*]azepine derivatives (**30**) by the intramolecular Pd-catalyzed direct arylation of C5-arylated 1-(2-bromobenzyl)-2-phenyl-1*H*-

pyrrole (**29**) *via* the formation of a seven-membred ring (**Scheme 3.4b**).[44-45] Wallace *et al.* synthesized dibenz[c,e]azepines via intramolecular direct arylation of *N*-(2-bromobenzyl)-1-phenylmethanamines.[46]



Scheme 3.4 Access of dibenzo[*c*,*e*]pyrazolo[1,5-*a*]azepines

3.1.3 Importance of hybrid *N*-fused heterocycles

The hybrid structure of isoindolinone and azepine derivatives have drawn substantial attention due to their occurance in natural and synthetic compounds with potential biological properties. Lennoxamine[47] and chilenine[48] are the natural alkloids which are isolated from Chilean Berberidaceae species. Azepino[2,1-*a*]isoindol-5-ones[49] a synthetic compound have been found to show urotensin-II receptor antagonist activity (**Figure 3.2**). Only very few methods are available for the synthesis of azepino-isoindolinones.[50] Therefore, development of facile and straightforward synthesis for azepino-isoindolinones will expedite evaluation of their biological activities.

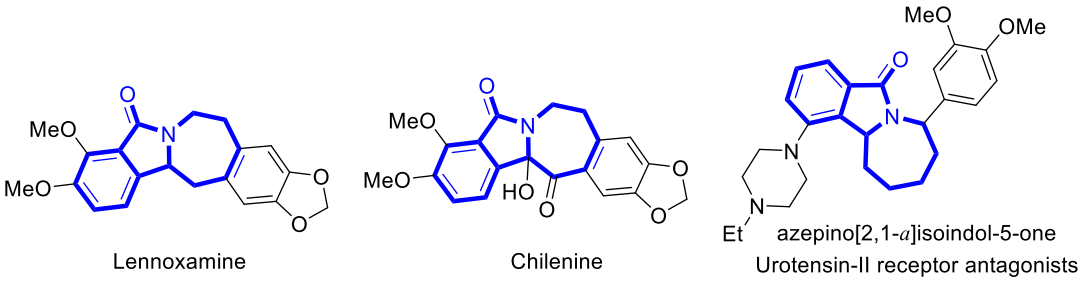
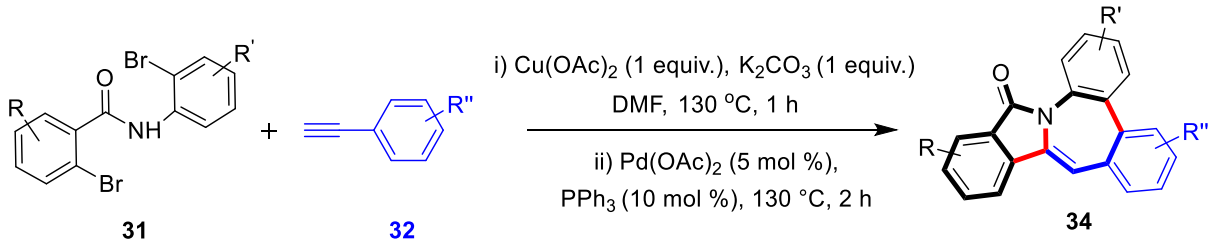


Figure 3.2 Selected biologically active compounds containing azepino-fused isoindolinone skeleton.

To synthesize these hybrid *N*-heterocycles *via* cascade or tandem reactions coupled with metal catalyzed C-H functionalization and sequential reactions have become one of the most attractive approach.[51-53] Development of synthetic routes for the construction of bioactive heterocyclic scaffolds in less number of synthetic steps with high structural complexity and diversity is an everlasting demand in organic chemistry. Thus, we herein report a new method for the synthesis of azepino-fused isoindolinone derivatives by sequential copper-catalyzed Sonogashira coupling, intramolecular hydroamidation and palladium-catalyzed intramolecular direct arylation (**Scheme 3.5**).



Scheme 3.5 Synthesis of Azepino-fused isoindolinone derivatives

3.2 Results and discussion

We selected reaction of 2-bromo-*N*-(2-bromophenyl)benzamide (**31a**) and phenyl acetylene (**32a**) as model reaction to optimize reaction conditions. Initially, 14*H*-dibenzo[4,5:6,7]azepino[2,1-*a*]isoindol-14-one (**34aa**) was obtained in 41% yield when **31a** and **32a** were allowed to react in the presence of CuI (30 mol %), K_2CO_3 (2 equiv), in DMF (4 mL) at 130 °C for 1 h followed by addition of $Pd(OAc)_2$ (5 mol %) and PPh_3 (10 mol %) to the reaction mixture and continued heating for 2 h (Table 3.1, entry 1). The structure of **34aa** was characterized by different spectroscopic techniques (IR, MS and NMR). In the ^1H NMR

spectrum of **34aa**, a singlet peak was observed at 6.62 ppm for the C_9-proton along with remaining protons and in the ^{13}C NMR amidic carbon appeared at 164 ppm along with all other expected carbons (**Figure 3.3**). In the IR spectrum of **34aa**, a characteristic peak was obtained at 1689 cm^{-1} for amidic C=O stretching (**Figure 3.4**). Finally, appearance of a peak at *m/z* 296.1066 corresponding to $C_{21}H_{14}NO^+$ $[M + H]^+$ ion in the HRMS spectrum of **34aa** further confirmed its structure (**Figure 3.4**).

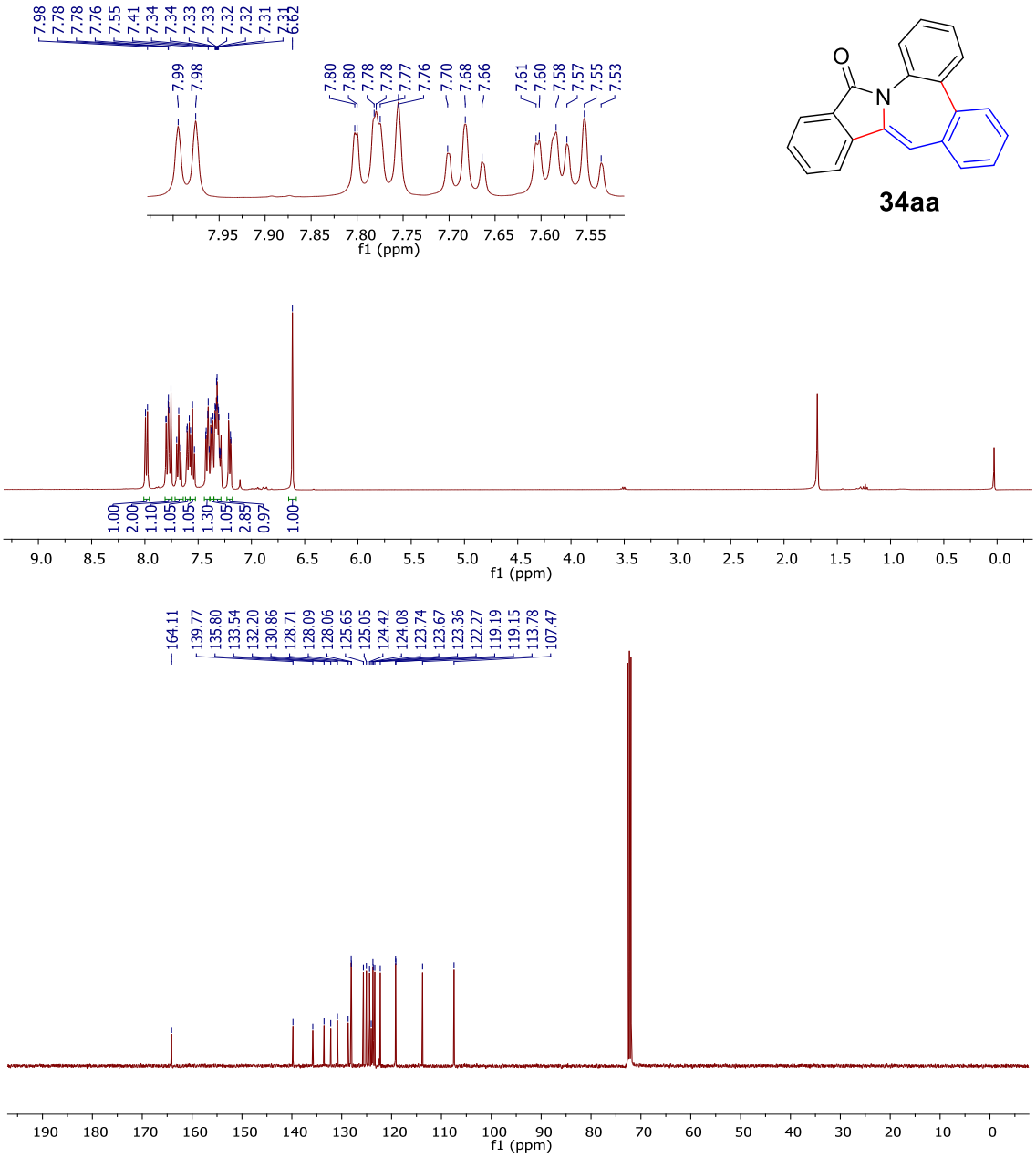


Figure 3.3 ^1H and ^{13}CNMR spectra of **34aa**

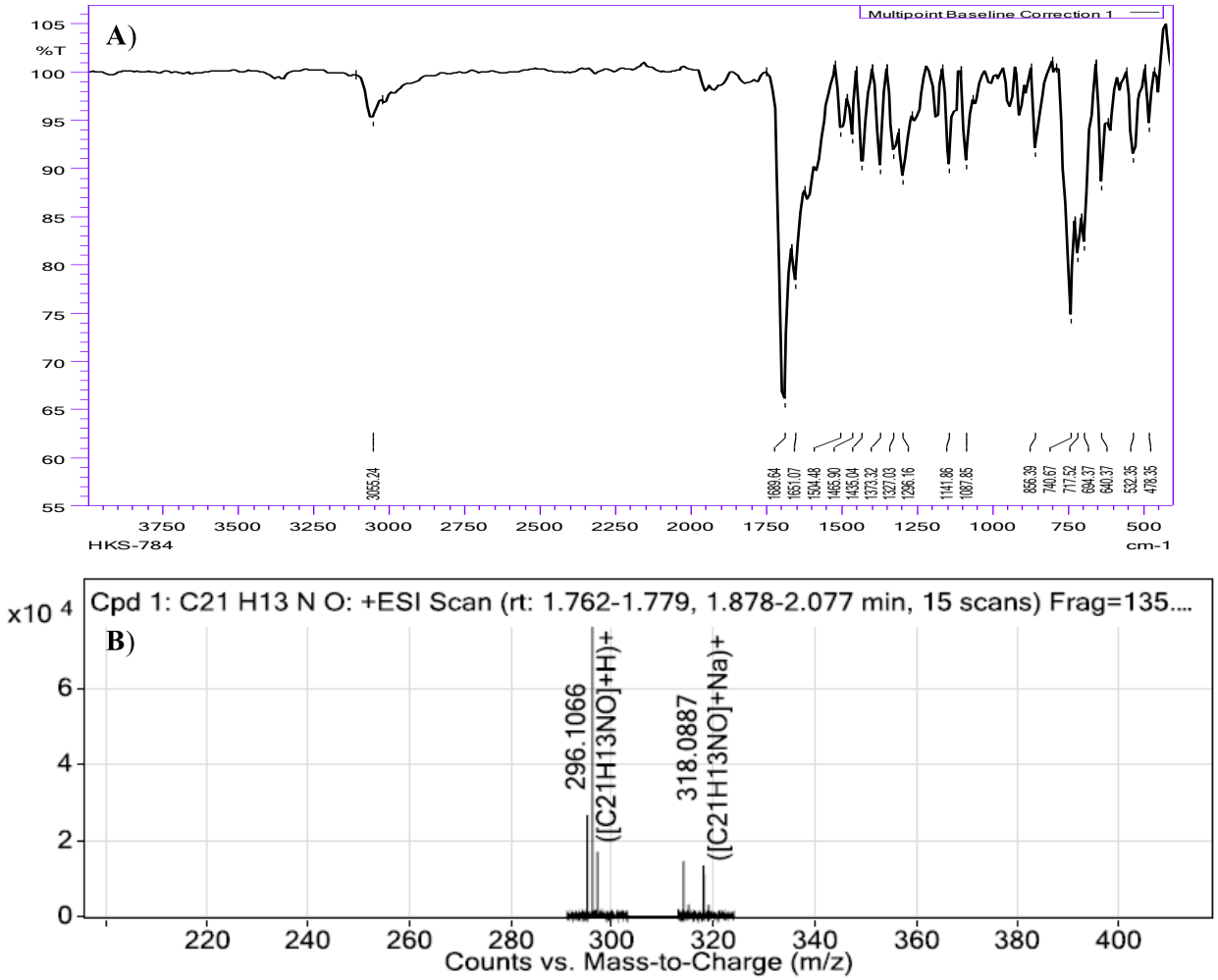
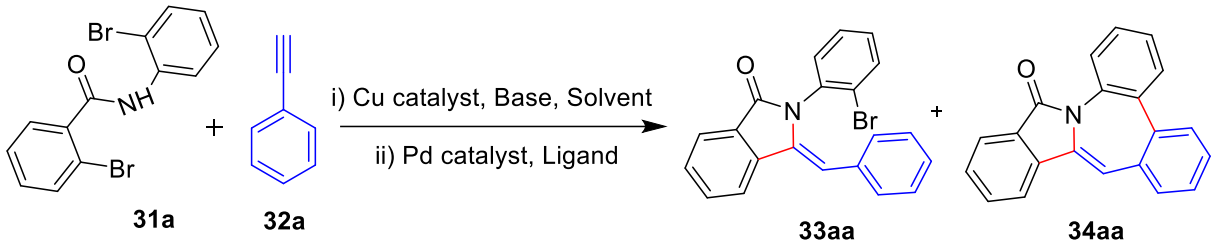


Figure 3.4 A) IR spectra of **34aa** and B) HRMS spectra of **34aa**

We then went on to screen reaction conditions by varying different catalysts, bases and solvents to improve the yield of **34aa** (Table 3.1). The best yield of **34aa** (73%) was obtained by performing model reaction in the presence of $Cu(OAc)_2 \cdot H_2O$ (30 mol %), K_2CO_3 (2 equiv.) in DMF at 130 °C for 1 h followed by addition of $Pd(OAc)_2$ (5 mol %) and PPh_3 (10 mol %) and continuing reaction for additional 2 h at 130 °C (Table 3.1, entry 5). It is worth to mention that when reaction of **31a** and **32a** was performed in the presence of CuI/L-proline, cyclized intermediate, 3-benzylidene-2-(2-bromophenyl)isoindolin-1-one (**33aa**) was obtained in 71% yield, however, continuing reaction further by adding $Pd(OAc)_2$ (5 mol %) and PPh_3 (10 mol %) resulted in only 20% yield of **34aa** (Table 3.1, entry 2).

Table 3.1. Optimization of the reaction conditions[a]



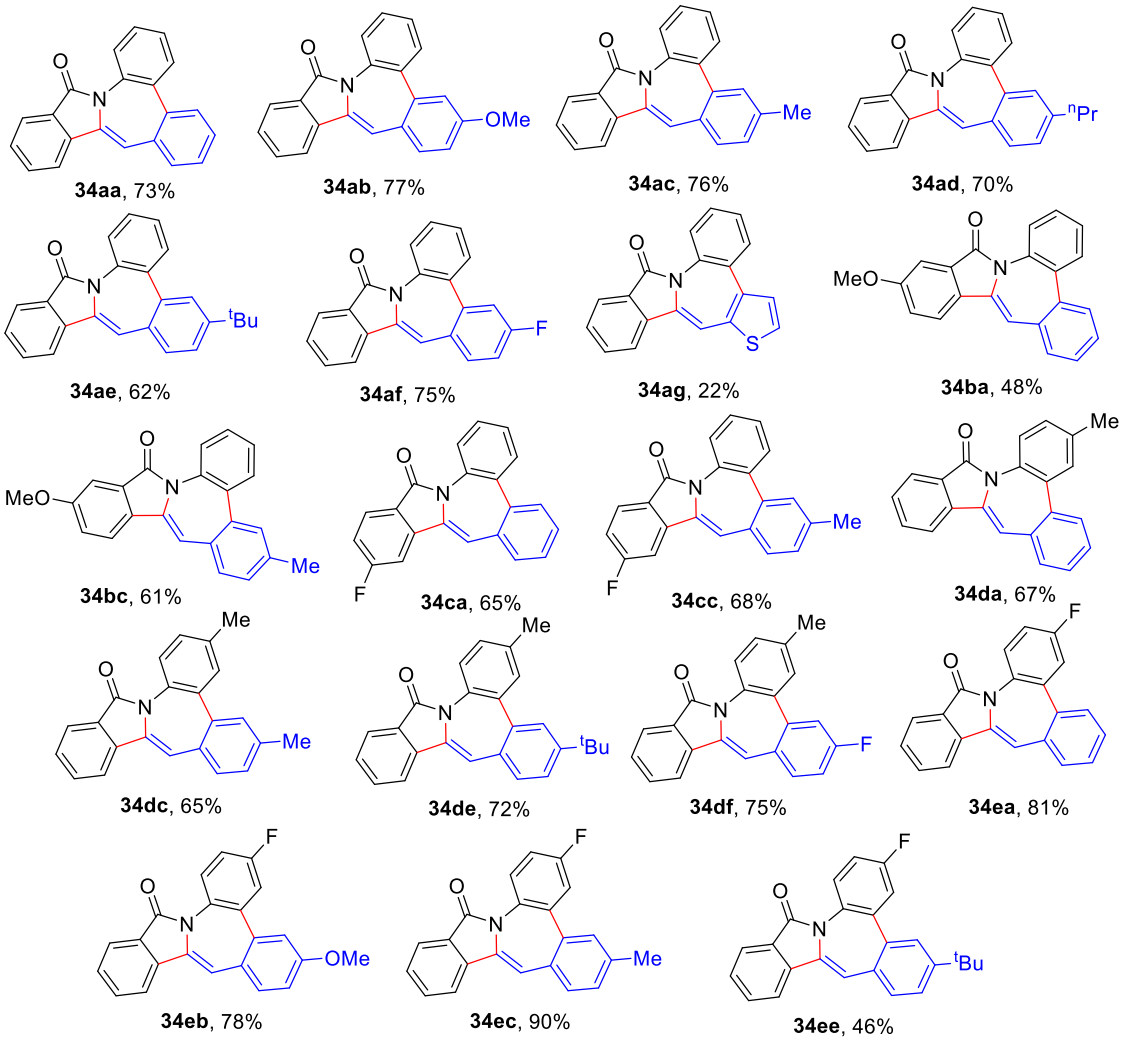
Sr. No.	Cu catalyst	Base	Pd catalyst/ Ligand	Solvent	% yield[b]	
					33aa	**34aa**
1	CuI	K_2CO_3	$Pd(OAc)_2/PPh_3$	DMF	5	41
2	CuI/L-proline	K_2CO_3	$Pd(OAc)_2/PPh_3$	DMF	71	20
3	CuBr	K_2CO_3	$Pd(OAc)_2/PPh_3$	DMF	trace	38
4	$CuCl_2$	K_2CO_3	$Pd(OAc)_2/PPh_3$	DMF	trace	33
5	**$Cu(OAc)_2$**	**K_2CO_3**	**$Pd(OAc)_2/PPh_3$**	**DMF**	-	**73**
6	-	K_2CO_3	$Pd(OAc)_2/PPh_3$	DMF	-	-
7	$Cu(OAc)_2$	K_2CO_3	$PdCl_2/PPh_3$	DMF	7	39
8	$Cu(OAc)_2$	K_2CO_3	$Pd(PPh_3)_4$	DMF	trace	44
9	$Cu(OAc)_2$	K_2CO_3	$Pd(PPh_3)_4/PPh_3$	DMF	trace	51
10	$Cu(OAc)_2$	K_2CO_3	-	DMF	87	-
11	$Cu(OAc)_2$	K_2CO_3	$Pd(OAc)_2$	DMF	4	38
12	$Cu(OAc)_2$	K_2CO_3	$Pd(OAc)_2/PPh_3$	DMSO	trace	62
13	$Cu(OAc)_2$	K_2CO_3	$Pd(OAc)_2/PPh_3$	PEG-400	-	69
14	$Cu(OAc)_2$	K_2CO_3	$Pd(OAc)_2/PPh_3$	Dioxane	-	-

15	$Cu(OAc)_2$	K_3PO_4	$Pd(OAc)_2/PPh_3$	DMF	-	61
16	$Cu(OAc)_2$	^tBuOK	$Pd(OAc)_2/PPh_3$	DMF	trace	49
17	$Cu(OAc)_2$	Cs_2CO_3	$Pd(OAc)_2/PPh_3$	DMF	15	trace
18	$Cu(OAc)_2$	$N(Et)_3$	$Pd(OAc)_2/PPh_3$	DMF	20	-
19	$Cu(OAc)_2$	DIPEA[c]	$Pd(OAc)_2/PPh_3$	DMF	18	-
20	$Cu(OAc)_2$	DBU[c]	$Pd(OAc)_2/PPh_3$	DMF	22	trace
21	$Cu(OAc)_2$	-	$Pd(OAc)_2/PPh_3$	DMF	-	-

[a]Reagents and conditions: i) **31a** (0.5 mmol), **32a** (1.0 mmol), Cu-catalyst (30 mol %), base (1.0 mmol), solvent (4 mL), 130 °C; 1 h; ii) Pd catalyst (5 mol %), PPh_3 (10 mol %), 130 °C, 2 h. [b]Isolated yields. [c]DIPEA = *N*,*N*-Diisopropylethylamine, DBU = 1,8-Diazabicyclo[5.4.0]undec-7-ene.

After having optimized reaction conditions, we investigated the substrate scope of the developed sequential reaction for the synthesis of azepino-fused isoindolinones. As shown in table 3.2, various 2-bromo-*N*-(2-bromophenyl)benzamides (**31**) reacted with different aryl acetylene (**32a-g**) to give corresponding products (**34aa**–**34ag**). Aryl acetylene with electron releasing groups (**32ab-d**) gave good yields (70-77%). However, sterically hindered *tert*-butyl group on aryl acetylene (3**2e**) produced slightly lower yield of 34ae (62%). Aryl acetylene with fluoro substitution (**2f**) yielded the respective product **34af** in 75% yield. 2-ethynylthiophene (**31g**) could not react efficiently and led to desired product **34ag** in 22%. Further, variation on functionalized amide was investigated to see the effect on reaction yield. When aryl rings of amide, substituted with electron donating/withdrawing groups (**31ba-ea**) reacted smoothly to give respective products in moderate to good yields (48%-81%).

Table 3.2. Substrate scope for synthesis of azepino-fused isoindolinones[a,b]



[a]Reaction conditions: **31** (0.5 mmol), **32** (1.0 mmol), $Cu(OAc)_2 \cdot H_2O$ (30 mol %), K_2CO_3 (1.0 mmol), DMF (4 mL), 130 °C, 1 h; ii) $Pd(OAc)_2$ (5 mol %), PPh_3 (10 mol %), 130 °C, 2 h.

Variation on 2-bromo-*N*-(2-bromoaryl)benzamides (**31b-e**) as well as aryl acetylenes (32b-f) has also been checked and gave corresponding azepino-fused isoindolinones in good to excellent yields (46-90%). Benzamide (**31e**) with *N*-(2-bromo-4-fluoro)phenyl group gave corresponding cyclized product (**34ec**) in highest yield (90%). It is worth mentioning that desired product was not obtained from the reaction of 4-nitrophenyl acetylene (**32h**) and 4-pyridyl acetylene (**32i**) with **31a**. In case of **32h**, debrominated intermediate 3-(4-nitrobenzylidene)-2-phenylisoindolin-1-one (**35ah**) was obtained in 14% yield, while 2-(2-bromophenyl)-3-(pyridin-2-ylmethylene)-isoindolin-1-one (**33ai**) was obtained in 24% from **32i**.

Structures of the intermediate **33ac** and the product **34ab** were confirmed by single crystal XRD analysis. The intermediate compound **33ac** ($C_{22}H_{16}BrNO$) and the product **34ab** ($C_{22}H_{15}NO_2$) were crystallized from MeOH:CH_3CN (1:1) mixed solvent medium and ethanol solvent, respectively. The **33ac** and **34ab** crystals were obtained as colorless and yellow color blocks respectively. The single crystal XRD data were collected on suitable crystals at 93 K using MoKα (λ = 0.71073) X-ray source with Rigaku Oxford XtaLab Pro diffractometer. The **33ac** and **34ab** are crystalized in triclinic space group P-1 (no. 2) and monoclinic space group $P2_1/c$ (no. 14), respectively. Crystallographic data are submitted to Cambridge Crystallographic Data Center and corresponding CCDC numbers for the **33ac** and **34ab** are 1562652 and 1562241, respectively. The ORTEP diagram of **33ac** and **34ab** are given in figure 3.5 and their unit cell parameters are given in Table 3.3.

Table 3.3: Crystal data and structure refinement for **33ac**

Identification code	exp_125-HKS875	ρ_{calc}g/cm^3	1.499
Empirical formula	$C_{22}H_{16}BrNO$	μ/mm^{-1}	2.385
Formula weight	390.27	F(000)	396.0
Temperature/K	93(2)	Crystal size/mm^3	0.3 × 0.2 × 0.2
Crystal system	triclinic	Radiation	MoKα (λ = 0.71073)
Space group	P-1	2Θ range for data collection/°	9.784 to 49.998
a/Å	8.4605(4)	Index ranges	-10 ≤ h ≤ 8, -11 ≤ k ≤ 12, -12 ≤ l ≤ 13
b/Å	10.4327(4)	Reflections collected	9960
c/Å	10.9453(4)	Independent reflections	3013 [R_{int} = 0.0245, R_{sigma} = 0.0172]
α/°	71.307(4)	Data/restraints/parameters	3013/0/227
β/°	73.812(4)	Goodness-of-fit on F^2	1.077
γ/°	75.455(4)	Final R indexes [I>=2σ (I)]	R_1 = 0.0359, wR_2 = 0.0875
Volume/Å^3	864.84(7)	Final R indexes [all data]	R_1 = 0.0371, wR_2 = 0.0880
Z	2	Largest diff. peak/hole / e Å^{-3}	2.42/-0.39

Table 3.4: Crystal data and structure refinement for 3**4ab.**

Identification code	exp_121-HKS792R	ρ_{calc}g/cm^3	1.374
Empirical formula	$C_{22}H_{15}NO_2$	μ/mm^{-1}	0.088
Formula weight	325.35	F(000)	680.0
Temperature/K	93(2)	Crystal size/mm^3	0.5 × 0.2 × 0.15
Crystal system	monoclinic	Radiation	MoKα (λ = 0.71073)
Space group	$P2_1/c$	2Θ range for data collection/°	9.866 to 49.982
a/Å	11.7661(8)	Index ranges	-13 ≤ h ≤ 13, -20 ≤ k ≤ 23, -8 ≤ l ≤ 7
b/Å	19.4015(12)	Reflections collected	10592
c/Å	7.0848(5)	Independent reflections	2748 [R_{int} = 0.0348, R_{sigma} = 0.0320]
α/°	90	Data/restraints/parameters	2748/0/227
β/°	103.517(7)	Goodness-of-fit on F^2	1.032
γ/°	90	Final R indexes [I>=2σ (I)]	R_1 = 0.0352, wR_2 = 0.0784
Volume/Å^3	1572.52(19)	Final R indexes [all data]	R_1 = 0.0493, wR_2 = 0.0861
Z	4	Largest diff. peak/hole / e Å^{-3}	0.28/-0.28

For **33ac**, the C1=O1 and C18-Br1 and C8=C9 bond lengths are 1.217(3) Å, 1.887(3) Å and 1.344(4) Å, respectively. The *N*-bromophenyl ring deviated from the planarity with isoindolinone ring with C1-N1-C17-C18 torsion angle 73.12°. The distance between the centroids of the two phenyl groups substituted to the isoindolinone ring is 3.781 Å. The distance between the Br1 and H11, possibly involving in C-H activation in forming seven-member ring, is 3.218 Å. In crystal structure of **34ab**, the C1=O1 and C8=C9 bond lengths are 1.2252(19) Å and 1.339(2) Å. The bond length C15-C16 connecting the two phenyl group is 1.491(2) Å, which is slightly longer than the carbon-carbon bond lengths in the phenyl rings (1.371 Å – 1.413 Å). The two phenyl rings are deviated from the planarity of each rings with torsion angle of C10-C15-C16-C21 = 38.29°. The bond angles C8-N1-C21, C8-N1-C1, C1-N1-C21, C15-C16-C21, C15-C16-C17, C10-C15-C16 and C14-C15-C16 are 102.51(21), 110.45(12), 122.68(12), 125.26(13), 117.69(13), 122.56(13) and 118.20(13) degrees, respectively.

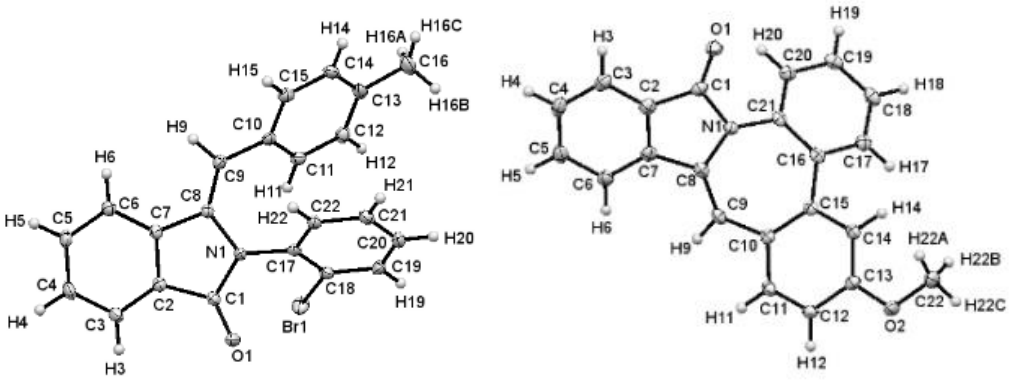


Figure 3.5 ORTEP diagram and atomic numbering of **33ac** (CCDC 1562652) and **34ab** (CCDC 1562241). The displacement ellipsoids are drawn at 50% probability level.

2D COSY (Figure 3.6) and 1D NOE (Figure 3.7) experiments allowed the identification of configuration at the C=C double bond of **33ac** as *Z*. Irradiating C_4-proton at δ 7.89 resulted enhanced singlet signal at δ 6.86 and *vice versa*. Interestingly, NOE was not observed between tolyl ring protons and vinylic proton. This is consistence with the non-planarity of the two aryl rings in **33ac** as observed in the X-ray crystallographic analysis (Figure 3.5, CCDC 1562652).

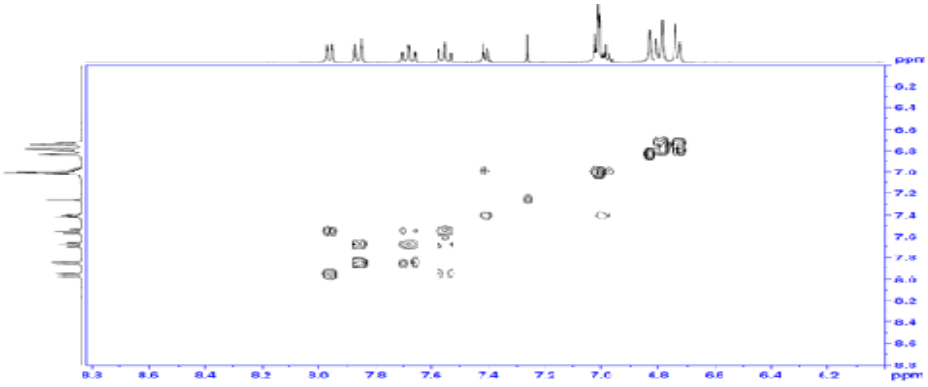


Figure 3.6 2D COSY spectrum of 33ac

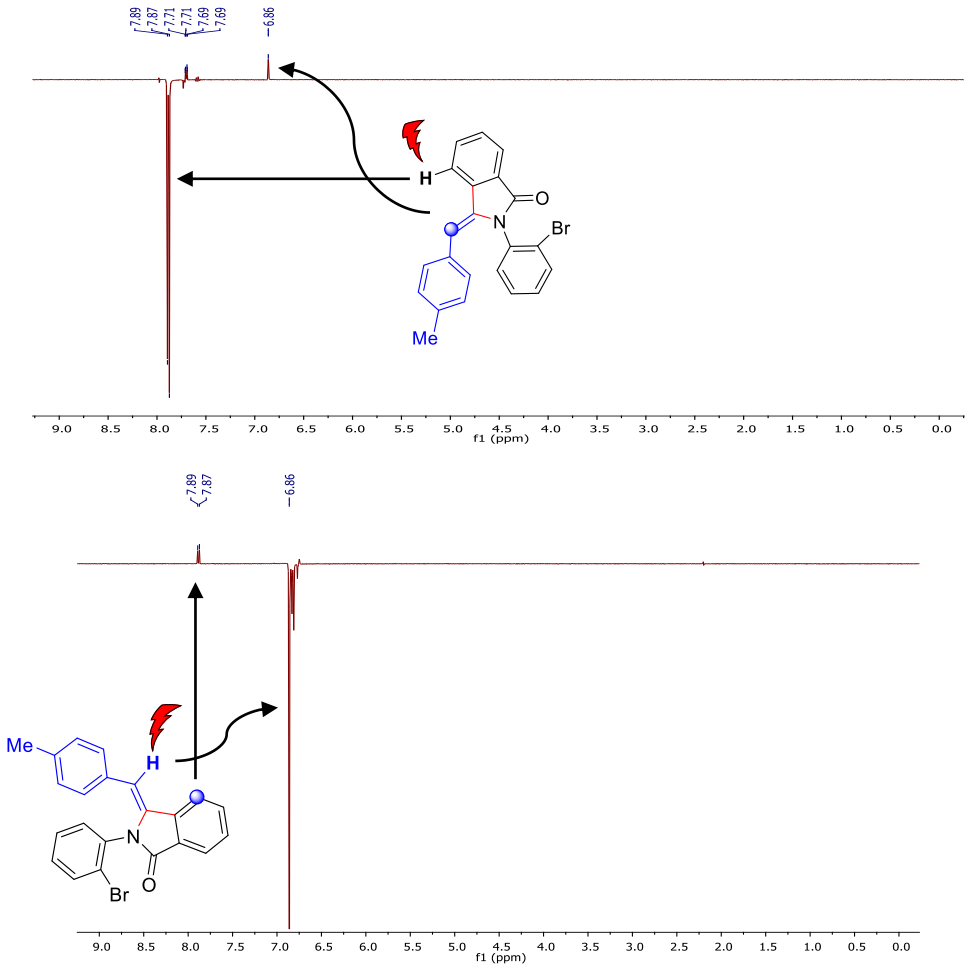
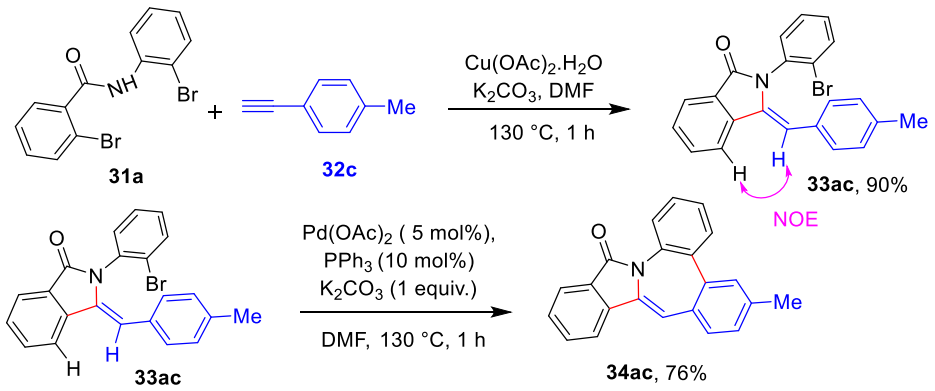


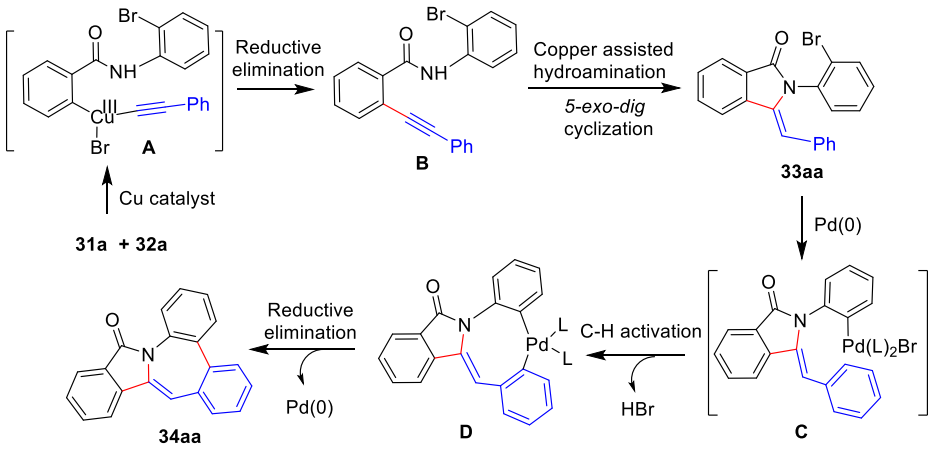
Figure 3.7 1D NOE spectra of 33ac

Finally, some control experiments were performed to explore the reaction mechanism of the developed methodology. In this series, reaction of 2-bromo-*N*-(2-bromophenyl)benzamide (**31a**) with 1-ethynyl-4-methylbenzene (**32c**) in the presence of $Cu(OAc)_2 \cdot H_2O$ (30 mol %) and K_2CO_3 (2 equiv.) in DMF at 130 °C for 1 h resulted in the formation of isoindolinone intermediate **32ac** in 90% yield (**Scheme 3.6**). Next, reaction of **33ac** with $Pd(OAc)_2$ (5 mol %), PPh_3 (10 mol %) and K_2CO_3 (2 equiv.) in DMF at 130 °C for 1 h gave **34ac** in 76% yield indicating that the reaction proceeds *via* isoindolinone intermediate.



Scheme 3.6 Control experiments

On the basis of experimental observations, isolated intermediate and the literature evidence it is expected that in this one-pot protocol, Cu(II) initially interacts with alkyne to give copper acetylide as starting point of the catalytic cycle[54] which then on oxidative addition reaction with **31a** gives intermediate **A** (**Scheme 3.7**). Following reductive elimination with assistance of base intermediate **A** leads to the formation of Sonogashira product **B**. Finally, intermediate **B** undergoes 5-*exo-dig* cyclization to give isoindolinone intermediate 33**aa**.[21-22] In second step, oxidative addition of **33aa** under the palladium catalysis[55-56] gives intermediate **C** which then forms eight-membered palladacycle (**D**) *via* C-H activation. Reductive elimination of **D** leads to the target product **34aa**.



Scheme 3.7 Proposed mechanism

3.3 Conclusion

In summary, a sequential copper and palladium-catalyzed one-pot method has been developed for the synthesis of azepino-fused isoindolinone derivatives in good to high yields (22-90%). The

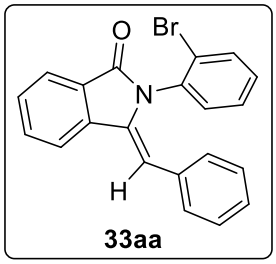
developed protocol involves copper-catalyzed Sonogashira coupling, intramolecular hydroamination and palladium-catalyzed intramolecular direct arylation. The developed protocol tolerated various functional groups and involved formation of two carbon-carbon bonds and one carbon-nitrogen bond in one-pot fashion.

3.4 Experimental

General information: Melting points were determined in open capillary tubes on a EZ-Melt automated melting point apparatus and are uncorrected. Reactions were monitored by using thin layer chromatography (TLC) on 0.2 mm silica gel F254 plates (Merck). The chemical structures of final products were determined by NMR spectra (^{1}H and ^{13}C NMR). The NMR spectra were recorded on Bruker Avance III 400 spectrometer. Chemical shifts were reported in parts per million (ppm) using deuterated solvent peak or tetramethylsilane (TMS) as internal standard. HRMS were recorded using Agilent technologies 6545 Q-TOF LC/MS. The crystal data collection and data reduction were performed using CrysAlis PRO on a single crystal Rigaku Oxford XtaLab Pro diffractometer. All chemicals were obtained from the commercial suppliers and used without further purification. All reactions were performed on 0.5 mmol scale.

Representative procedure for the synthesis of azepino-fused isoindolinones: A clean, oven-dried 10 mL round bottom flask was charged with 2-bromo-*N*-(2-bromophenyl)benzamide (**31a**) (178 mg, 0.5 mmol), phenyl acetylene (**32a**) (102 mg, 1.0 mmol), $Cu(OAc)_2 \cdot H_2O$ (30 mg, 30 mol %), K_2CO_3 (138 mg, 1.0 mmol) and DMF (4 mL). Resulting solution was stirred at 130 °C for 1 h, then $Pd(OAc)_2$ (6 mg, 5 mol %) and PPh_3(13 mg, 10 mol %) were added to the reaction mixture at ambient temperature and continued stirring with heating at 130 °C. After 2 h, the reaction mass was cooled to room temperature, diluted with water (10 mL) and extracted into EtOAc (2 × 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and evaporated to dryness. The crude residue was purified by column chromatography (EtOAc/hexanes 1:5 *v/v*) to give **34aa** in 73% (108 mg) yield.

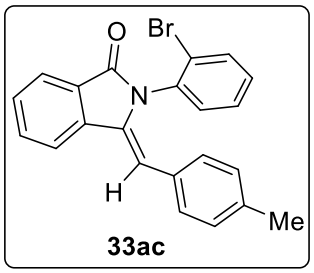
(Z)-3-Benzylidene-2-(2-bromophenyl)isoindolin-1-one (33aa)



33aa

Yield 87%; white solid, mp 151-153 °C; IR (nujol): ν 3055, 1705, 1655, 1470, 1134, 760, 694 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.99 (d, J = 7.5 Hz, 1H), 7.89 (d, J = 7.7 Hz, 1H), 7.72 (t, J = 7.5 Hz, 1H), 7.60 (t, J = 7.5 Hz, 1H), 7.42 (d, J = 7.1 Hz, 1H), 7.09 – 6.91 (m, 8H), 6.88 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.2, 138.4, 135.7, 134.1, 133.2, 132.9, 132.6, 130.6, 129.4, 129.3, 128.8, 127.7, 127.5, 127.2, 126.6, 124.0, 123.4, 119.6, 107.8; HRMS (ESI/Q-TOF) calcd for $C_{21}H_{15}BrNO$ 376.0332, found 376.0332 $[M+H]^+$.

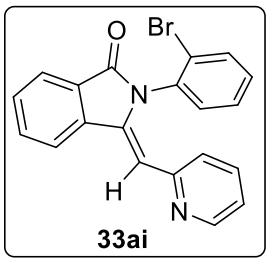
(Z)-2-(2-Bromophenyl)-3-(4-methylbenzylidene)isoindolin-1-one (33ac)



33ac

Yield 90%; brown solid, mp 143-145 °C; IR (nujol): ν 2916, 1705, 1647, 1470, 1123, 752, 691 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.99 (d, J = 7.6 Hz, 1H), 7.88 (d, J = 7.8 Hz, 1H), 7.71 (td, J = 7.6, 1.1 Hz, 1H), 7.58 (td, J = 7.5, 0.8 Hz, 1H), 7.47 – 7.39 (m, 1H), 7.07 – 6.97 (m, 3H), 6.86 (s, 1H), 6.83 – 6.75 (m, 4H), 2.20 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.2, 138.5, 136.4, 135.9, 133.7, 132.9, 132.5, 130.6, 130.2, 129.1, 129.1, 128.7, 127.9, 127.6, 127.5, 124.0, 123.4, 119.5, 108.1, 21.1; HRMS (ESI/Q-TOF) calcd for $C_{22}H_{17}BrNO$ 390.0488, found 390.0488 $[M+H]^+$.

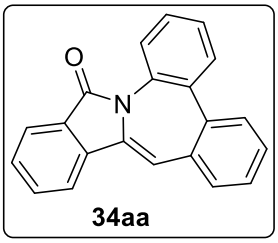
(Z)-2-(2-Bromophenyl)-3-(pyridin-2-ylmethylene)isoindolin-1-one (33ai)



33ai

Yield 24%; brown solid, mp 172-174°C; IR (nujol): ν 3078, 1701, 1651, 1427, 1219, 764, 694 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.75 (d, J = 1.3 Hz, 1H), 8.64 – 8.60 (m, 1H), 8.04 – 7.96 (m, 1H), 7.82 (dd, J = 8.0, 1.1 Hz, 1H), 7.69 (td, J = 7.7, 1.5 Hz, 1H), 7.65 – 7.57 (m, 2H), 7.55 - 7.47 (m, 2H), 7.41 (td, J = 8.0, 1.8 Hz, 1H), 7.33 (d, J = 7.8 Hz, 1H), 7.26 – 7.20 (m, 1H), 5.99 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.1, 154.3, 149.4, 139.4, 136.4, 134.8, 134.2, 133.9, 132.5, 131.9, 130.8, 130.2, 130.1, 128.7, 125.8, 125.5, 124.5, 123.7, 122.1, 111.7; HRMS (ESI/Q-TOF) calcd for $C_{20}H_{14}BrN_2O$ 377.0284, found 377.0313 $[M+H]^+$.

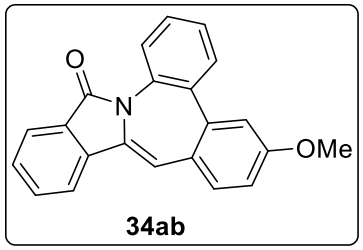
14*H*-Dibenzo[4,5:6,7]azepino[2,1-*a*]isoindol-14-one (34aa)



34aa

Yield 73%; yellow solid, mp 133-135°C; IR (nujol): ν 3055, 1690, 1651, 1373, 1296, 741 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.99 (d, J = 7.6 Hz, 1H), 7.83 – 7.74 (m, 2H), 7.68 (t, J = 7.3 Hz, 1H), 7.62 – 7.58 (m, 1H), 7.55 (t, J = 7.6 Hz, 1H), 7.43 – 7.40 (m, 1H), 7.39 – 7.35 (m, 1H), 7.35 – 7.29 (m, 3H), 7.22 – 7.18 (m, 1H), 6.62 (s, 1H);^{13}C NMR (100 MHz, $CDCl_3$) δ164.1, 139.8, 135.8, 133.5, 132.2, 130.9, 128.7, 128.1, 128.1, 125.6, 125.0, 124.4, 124.1, 123.7, 123.7, 123.4, 122.3, 119.2, 119.1, 113.8, 107.5; HRMS (ESI/Q-TOF) calcd for $C_{21}H_{14}NO$ 296.1076, found 296.1066 $[M+H]^+$.

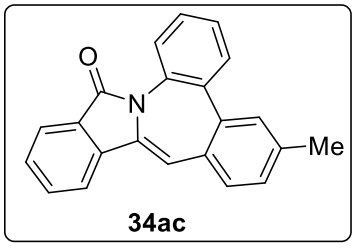
6-Methoxy-14*H*-dibenzo[4,5:6,7]azepino[2,1-*a*]isoindol-14-one (34ab)



34ab

Yield 77%; yellow solid, mp 163-165 °C; IR (nujol): ν 3051, 1690, 1651, 1597, 1493, 1312, 1022, 853 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, J = 7.6 Hz, 1H), 7.81 (d, J = 8.2 Hz, 1H), 7.74 (d, J = 7.7 Hz, 1H), 7.67 (t, J = 7.5 Hz, 1H), 7.56 – 7.50 (m, 2H), 7.44 (d, J = 7.6 Hz, 1H), 7.39 (t, J = 7.5 Hz, 1H), 7.32 (d, J = 7.4 Hz, 1H), 7.17 – 7.14 (m, 1H), 6.86 (dd, J = 8.5, 2.4 Hz, 1H), 6.59 (s, 1H), 3.90 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.9, 159.6, 142.2, 140.5, 139.9, 137.0, 133.2, 132.7, 132.6, 131.4, 128.8, 128.7, 128.6, 128.5, 126.9, 124.0, 123.9, 118.3, 116.1, 113.4, 112.3, 55.5; HRMS (ESI/Q-TOF) calcd for $C_{22}H_{16}NO_2$ 326.1176, found 326.1178 $[M+H]^+$.

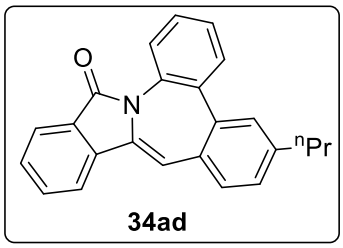
6-Methyl-14*H*-dibenzo[4,5:6,7]azepino[2,1-*a*]isoindol-14-one (34ac)



34ac

Yield 76%; yellow solid, mp 189-191 °C; IR (nujol): ν 3032, 1697, 1647, 1493, 1304, 853, 748, 725 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, J = 7.6 Hz, 1H), 7.79 (dd, J = 8.2, 1.0 Hz, 1H), 7.77 – 7.73(m, 1H), 7.67 (t, J = 7.2 Hz, 1H), 7.54 (t, J = 7.4 Hz, 1H), 7.47 – 7.40 (m, 2H), 7.40 – 7.34 (m, 1H), 7.32 (dd, J = 7.5, 1.1 Hz, 1H), 7.16 – 7.08 (m, 2H), 6.60 (s, 1H), 2.43 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.8, 143.6, 140.5, 138.5, 138.2, 137.0, 133.5, 132.9, 132.7, 132.7, 131.1, 129.9, 128.9, 128.8, 128.8, 128.4, 126.9, 123.9, 123.9, 118.4, 112.3, 21.4; HRMS (ESI/Q-TOF) calcd for $C_{22}H_{16}NO$ 310.1226, found 310.1226$[M+H]^+$.

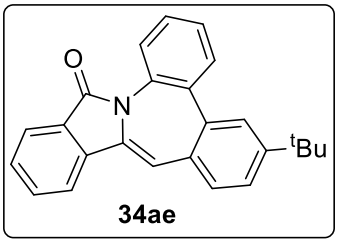
6-Propyl-14*H*-dibenzo[4,5:6,7]azepino[2,1-*a*]isoindol-14-one (34ad)



34ad

Yield 70%; viscous yellow; IR (nujol): ν 2959, 1701, 1651, 1373, 748, 694 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, J = 7.6 Hz, 1H), 7.80 (dd, J = 8.2, 1.3 Hz, 1H), 7.76 (d, J = 7.8 Hz, 1H), 7.68 (td, J = 7.4, 1.0 Hz, 1H), 7.57 – 7.51 (m, 1H), 7.45 – 7.40 (m, 2H), 7.40 – 7.35 (m, 1H), 7.34 – 7.29 (m, 1H), 7.14 – 7.12 (m, 2H), 6.62 (s, 1H), 2.67 (t, J = 7.6 Hz, 2H), 1.68 – 1.74 (m, 2H), 1.00 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.9, 143.6, 143.3, 140.5, 138.1, 137.0, 133.6, 133.1, 132.7, 132.7, 130.6, 129.9, 128.9, 128.7, 128.4, 128.3, 128.1, 126.9, 123.9, 118.4, 112.4, 37.9, 24.4, 13.8; HRMS (ESI/Q-TOF) calcd for $C_{24}H_{20}NO$ 338.1539, found 338.1591 $[M+H]^+$.

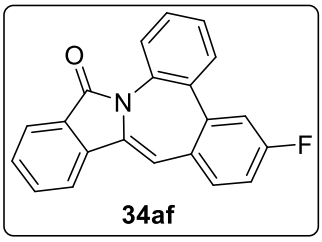
6-(*tert*-Butyl)-14*H*-dibenzo[4,5:6,7]azepino[2,1-*a*]isoindol-14-one (34ae)



34ae

Yield 62%; pale yellow solid, mp 120-122 °C; IR (nujol): ν 2959, 1701, 1651, 1474, 1300, 1138, 748, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, J = 7.6 Hz, 1H), 7.80 (d, J = 8.2 Hz, 1H), 7.76 (d, J = 7.8 Hz, 1H), 7.68 (t, J = 7.2 Hz, 1H), 7.63 – 7.60 (m, 1H), 7.54 (t, J = 7.5 Hz, 1H), 7.45 – 7.40 (m, 1H), 7.39 – 7.30 (m, 3H), 7.16 (d, J = 8.1 Hz, 1H), 6.63 (s, 1H), 1.40 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.8, 151.7, 143.8, 140.6, 137.9, 137.0, 134.0, 133.0, 132.7, 132.7, 129.6, 129.0, 128.8, 128.4, 127.7, 126.9, 125.1, 123.9, 123.9, 118.4, 112.2, 34.9, 31.2; HRMS (ESI/Q-TOF) calcd for $C_{25}H_{22}NO$ 352.1696, found 352.1727 $[M+H]^+$.

6-Fluoro-14*H*-dibenzo[4,5:6,7]azepino[2,1-*a*]isoindol-14-one (34af)

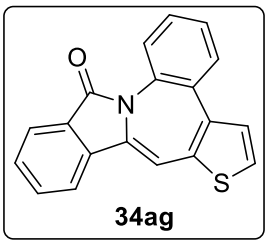


34af

Yield 75%; pale yellow solid, mp 199-201 °C; IR (nujol): ν 3059, 1697, 1659, 1285, 1096, 718, 694 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.01 – 7.95 (m, 1H), 7.82 – 7.77 (m, 1H), 7.74 (d, J = 7.8 Hz, 1H), 7.68 (td, J = 7.5, 1.1 Hz, 1H), 7.56 (td, J = 7.6, 1.0 Hz, 1H), 7.44 – 7.36 (m, 2H), 7.35 – 7.27 (m, 2H), 7.19 – 7.15 (m, 1H), 7.04 – 6.96 (m, 1H), 6.57 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.9, 162.3 (d, J = 248.7 Hz), 143.9, 143.9, 140.6, 140.5, 136.9, 132.9, 132.6, 131.9 (d, J = 3.2 Hz), 131.6, 131.5, 129.2 (d, J = 7.8

Hz), 128.7, 127.1, 124.0, 124.0, 118.5, 117.1 (d, J = 23.1 Hz), 115.0 (d, J = 21.7 Hz), 111.2; HRMS (ESI/Q-TOF) calcd for $C_{21}H_{13}FNO$ 314.0976, found 314.1030 $[M+H]^+$.

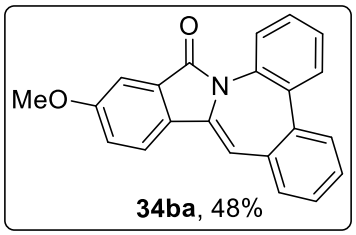
13*H*-Benzo[6,7]thieno[2',3':4,5]azepino[2,1-*a*]isoindol-13-one (34ag)



34ag

Yield 22%; brown solid, mp 210-212 °C; IR (nujol): ν 3055, 1701, 1639, 1504, 1296, 1134, 829, 737, 710 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, J = 7.6 Hz, 1H), 7.73 – 7.67 (m, 3H), 7.60 – 7.56 (m, 1H), 7.49 (dd, J = 7.7, 1.6 Hz, 1H), 7.40 – 7.33 (m, 2H), 7.33 – 7.29 (m, 1H), 7.28 – 7.23 (m, 1H), 6.65 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.8, 143.0, 138.4, 138.0, 136.1, 135.6, 132.7, 130.2, 129.5, 129.2, 129.0, 128.6, 128.3, 126.9, 125.4, 125.4, 123.8, 118.2, 105.3; HRMS (ESI/Q-TOF) calcd for $C_{19}H_{12}NOS$ 302.0634, found 302.0622 $[M+H]^+$.

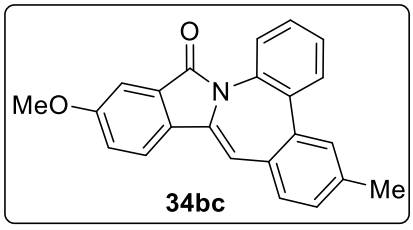
12-Methoxy-14*H*-dibenzo[4,5:6,7]azepino[2,1-*a*]isoindol-14-one (34ba)



34ba, 48%

Yield 48%; yellow solid, mp 161-163 °C; IR (nujol): ν 3055, 1713, 1647, 1489, 1312, 822, 748 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.79 (dd, J = 8.2, 1.1 Hz, 1H), 7.65 (d, J = 8.5 Hz, 1H), 7.61 – 7.57 (m, 1H), 7.45 – 7.40 (m, 2H), 7.40 – 7.35 (m, 1H), 7.35 – 7.29 (m, 3H), 7.24 (dd, J = 8.5, 2.4 Hz, 1H), 7.21 – 7.16 (m, 1H), 6.50 (s, 1H), 3.93 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.9, 161.0, 144.5, 140.4, 137.9, 135.7, 133.4, 132.8, 130.5, 130.3, 130.1, 129.5, 128.4, 128.1, 128.0, 126.9, 123.7, 122.0, 120.0, 110.8, 105.7, 55.9; HRMS (ESI/Q-TOF) calcd for $C_{22}H_{16}NO_2$ 326.1176, found 326.1211$[M+H]^+$.

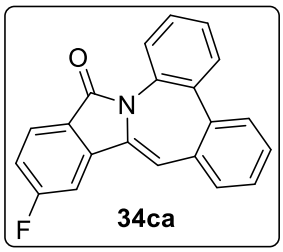
12-Methoxy-6-methyl-14*H*-dibenzo[4,5:6,7]azepino[2,1-*a*]isoindol-14-one (34bc)



34bc

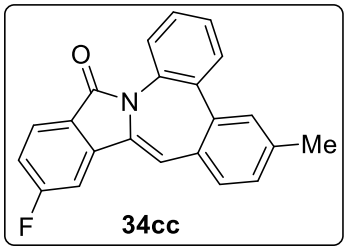
Yield 61%; yellow solid, mp 151-153 °C; IR (nujol): ν 3024, 1705, 1651, 1489, 1343, 1018, 748 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.79 (dd, J = 8.2, 1.2 Hz, 1H), 7.65 (d, J = 8.5 Hz, 1H), 7.47 – 7.40 (m, 3H), 7.40 – 7.34 (m, 1H), 7.31 (dd, J = 7.6, 1.3 Hz, 1H), 7.24 (dd, J = 8.5, 2.4 Hz, 1H), 7.14 – 7.09 (m, 2H), 6.49 (s, 1H), 3.93 (s, 3H), 2.42 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.9, 160.8, 143.5, 140.4, 138.0, 137.8, 133.4, 133.0, 132.7, 131.0, 130.3, 130.2, 129.6, 128.8, 128.4, 126.8, 123.7, 122.0, 119.9, 110.9, 105.6, 55.8, 21.3; HRMS (ESI/Q-TOF) calcd for $C_{23}H_{18}NO_2$ 340.1332, found 340.1330 $[M+H]^+$.

11-Fluoro-14*H*-dibenzo[4,5:6,7]azepino[2,1-*a*]isoindol-14-one (34ca)



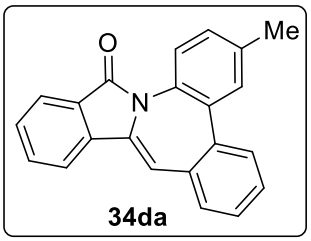
Yield 65%; yellow solid, mp 196-198 °C; IR (nujol): ν 3063, 1697, 1647, 1477, 1146, 880, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.97 (dd, J = 8.4, 4.9 Hz, 1H), 7.76 (dd, J = 8.2, 1.2 Hz, 1H), 7.60 (dd, J = 7.5, 1.3 Hz, 1H), 7.43 – 7.39 (m, 2H), 7.39 – 7.29 (m, 4H), 7.27 – 7.22 (m, 1H), 7.22 – 7.18 (m, 1H), 6.57 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.8, 165.9 (d, J = 253.0 Hz), 143.4 (d, J = 3.8 Hz), 140.5, 139.2 (d, J = 10.5 Hz), 138.5, 135.2, 133.4, 132.8, 130.5, 130.0, 128.8, 128.6, 128.2, 127.1, 126.3 (d, J = 10.1 Hz), 125.0, 123.8, 117.2 (d, J = 24.2 Hz), 113.3, 105.4 (d, J = 24.7 Hz); HRMS (ESI/Q-TOF) calcd for $C_{21}H_{13}FNO$ 314.0976, found 314.0970 $[M+H]^+$.

11-Fluoro-6-methyl-14*H*-dibenzo[4,5:6,7]azepino[2,1-*a*]isoindol-14-one (34cc)



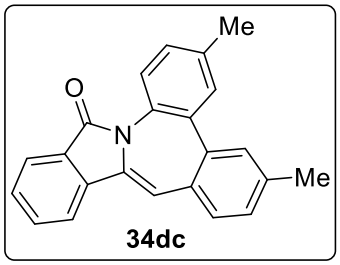
Yield 68%; yellow solid, mp 178-180 °C; IR (nujol): ν 3067, 1697, 1651, 1474, 1327, 880, 748 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.96 (dd, J = 8.4, 4.9 Hz, 1H), 7.76 (dd, J = 8.2, 1.3 Hz, 1H), 7.44 – 7.29 (m, 5H), 7.23 (td, J = 8.7, 2.2 Hz, 1H), 7.15 – 7.12 (m, 1H), 7.11 – 7.09 (m, 1H), 6.55 (s, 1H), 2.43 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.8, 165.9 (d, J = 252.7 Hz), 142.5 (d, J = 3.8 Hz), 140.4, 139.2 (d, J = 10.5 Hz), 138.9, 138.4, 133.4, 132.8, 132.5, 131.2, 130.1, 128.9, 128.5, 127.0, 126.2 (d, J = 10.1 Hz), 124.9, 123.8, 116.9 (d, J = 24.2 Hz), 113.5, 105.3 (d, J = 24.7 Hz), 21.4; HRMS (ESI/Q-TOF) calcd for $C_{22}H_{15}FNO$ 328.1132, found 328.1125 $[M+H]^+$.

3-Methyl-14*H*-dibenzo[4,5:6,7]azepino[2,1-*a*]isoindol-14-one (34da)



Yield 67%; yellow solid, mp 179-181 °C; IR (nujol): ν 3055, 1701, 1655, 1296, 1099, 845, 760 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, J = 7.6 Hz, 1H), 7.75 (d, J = 7.7 Hz, 1H), 7.70 – 7.63 (m, 2H), 7.60 (d, J = 7.2 Hz, 1H), 7.54 (t, J = 7.4 Hz, 1H), 7.35 – 7.28 (m, 2H), 7.23 – 7.15 (m, 3H), 6.59 (s, 1H), 2.39 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.7, 144.5, 138.3, 137.9, 136.9, 136.6, 135.7, 133.2, 133.1, 132.7, 130.3, 129.8, 129.2, 129.1, 128.9, 128.3, 128.0, 123.8, 123.7, 118.5, 112.0, 20.9; HRMS (ESI/Q-TOF) calcd for $C_{22}H_{16}NO$ 310.1226, found 310.1274 $[M+H]^+$.

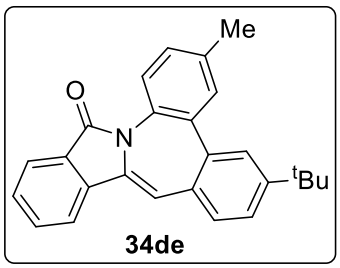
3,6-Dimethyl-14*H*-dibenzo[4,5:6,7]azepino[2,1-*a*]isoindol-14-one (34dc)



34dc

Yield 65%; yellow solid, mp 156-158 °C; IR (nujol): ν 3032, 1701, 1655, 1504, 1296, 1096, 903, 841 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, J = 7.6 Hz, 1H), 7.74 (d, J = 7.8 Hz, 1H), 7.70 – 7.62 (m, 2H), 7.53 (t, J = 7.1 Hz, 1H), 7.41 (s, 1H), 7.22 (s, 1H), 7.20 – 7.15 (m, 1H), 7.14 – 7.06 (m, 2H), 6.57 (s, 1H), 2.43 (s, 3H), 2.40 (s, 3H);^{13}C NMR (100 MHz, $CDCl_3$) δ 168.7, 143.6, 138.3, 138.2, 137.9, 136.9, 136.5, 133.2, 133.1, 132.9, 132.6, 131.0, 129.9, 129.1, 128.9, 128.8, 128.8, 123.8, 123.7, 118.4, 112.2, 21.4, 20.9; HRMS (ESI/Q-TOF) calcd for $C_{23}H_{18}NO$ 324.1383, found 324.1415 $[M+H]^+$.

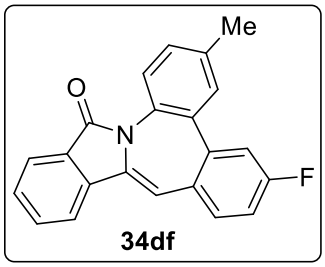
6-(*tert*-Butyl)-3-methyl-14H-dibenzo[4,5:6,7]azepino[2,1-*a*]isoindol-14-one (34de)



34de

Yield 72%; viscous yellow; IR (nujol): ν 2959, 1701, 1651, 1508, 1099, 756, 698 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, J = 7.6 Hz, 1H), 7.76 (d, J = 7.8 Hz, 1H), 7.70 – 7.64 (m, 2H), 7.61 (d, J = 1.9 Hz, 1H), 7.54 (t, J = 7.5 Hz, 1H), 7.34 (dd, J = 8.1, 2.0 Hz, 1H), 7.21 – 7.17 (m, 2H), 7.15 (d, J = 8.1 Hz, 1H), 6.61 (s, 1H), 2.42 (s, 3H), 1.41 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.7, 151.6, 143.9, 138.0, 137.9, 136.9, 136.5, 133.7, 133.0, 133.0, 132.6, 129.6, 129.1, 128.9, 128.9, 127.5, 125.1, 123.8, 123.8, 118.4, 112.0, 34.9, 31.2, 21.0; HRMS (ESI/Q-TOF) calcd for $C_{26}H_{24}NO$ 366.1852, found 366.1887 $[M+H]^+$.

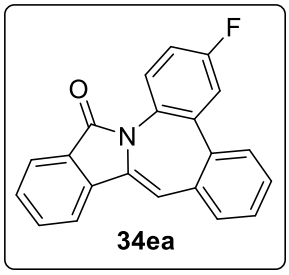
6-Fluoro-3-methyl-14*H*-dibenzo[4,5:6,7]azepino[2,1-*a*]isoindol-14-one (34df)



34df

Yield 75%; yellow solid, mp 222-224 °C; IR (nujol): ν 3043, 1701, 1658, 1604, 1184, 867, 748, 690 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, J = 7.6 Hz, 1H), 7.74 (d, J = 7.8 Hz, 1H), 7.67 (m, 2H), 7.59 – 7.50 (m, 1H), 7.31 (dd, J = 10.2, 2.6 Hz, 1H), 7.23 – 7.13 (m, 3H), 6.99 (td, J = 8.1, 2.6 Hz, 1H), 6.55 (s, 1H), 2.40 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.7, 162.3 (d, J = 248.6 Hz), 143.9 (d, J = 1.8 Hz), 140.6 (d, J = 7.7 Hz), 138.0, 136.8, 136.8, 133.0, 132.8, 132.0, 131.9 (d, J = 1.2 Hz), 131.8, 131.5 (d, J = 8.3 Hz), 129.8, 129.1, 128.8, 123.9 (d, J = 1.7 Hz), 118.4, 117.0 (d, J = 23.1 Hz), 114.9 (d, J = 21.7 Hz), 111.0, 20.9; HRMS (ESI/Q-TOF) calcd for $C_{22}H_{15}FNO$ 328.1132, found 328.1137$[M+H]^+$.

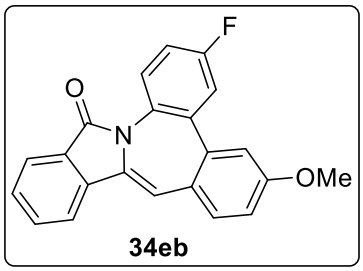
3-Fluoro-14*H*-dibenzo[4,5:6,7]azepino[2,1-*a*]isoindol-14-one (34ea)



34ea

Yield 81%; yellow solid, mp 197-199 °C; IR (nujol): ν 3071, 1705, 1655, 1489, 1296, 1192, 802, 748 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.01 – 7.94 (m, 1H), 7.80 – 7.73 (m, 2H), 7.69 (td, J = 7.3, 1.1 Hz, 1H), 7.58 – 7.54 (m, 2H), 7.38 – 7.30 (m, 2H), 7.24 – 7.17 (m, 1H), 7.15 – 7.03 (m, 2H), 6.60 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.8, 160.8 (d, J = 245.7 Hz), 144.6, 137.0, 136.8, 136.4, 136.3, 135.7, 135.6, 132.9, 130.3, 130.0, 129.3, 128.7, 128.6, 125.5 (d, J = 8.5 Hz), 124.0, 118.6 (d, J = 23.5 Hz), 118.6, 115.2 (d, J = 22.3 Hz), 112.0; HRMS (ESI/Q-TOF) calcd for $C_{21}H_{13}FNO$ 314.0976, found 314.0987 $[M+H]^+$.

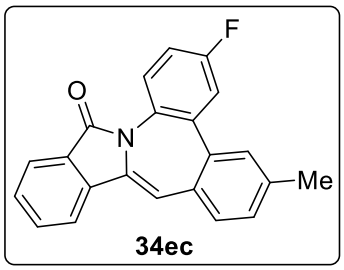
3-Fluoro-6-methoxy-14*H*-dibenzo[4,5:6,7]azepino[2,1-*a*]isoindol-14-one (34eb)



34eb

Yield 78%; yellow solid, mp 157-159 °C; IR (nujol): ν 2924, 1697, 1600, 1500, 1296, 852, 694 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, J = 7.6 Hz, 1H), 7.82 – 7.72 (m, 2H), 7.68 (t, J = 7.5 Hz, 1H), 7.54 (t, J = 7.4 Hz, 1H), 7.19 – 7.04 (m, 4H), 6.88 (dd, J = 8.5, 2.6 Hz, 1H), 6.58 (s, 1H), 3.91 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.8, 160.7 (d, J = 245.6 Hz), 159.7, 142.3, 138.6, 136.9, 136.3 (d, J = 2.9 Hz), 135.4 (d, J = 7.5 Hz), 132.8, 131.6, 128.9, 128.5, 128.4, 125.7 (d, J = 8.4 Hz), 123.9, 118.5 (d, J = 23.6 Hz), 118.3, 116.0, 115.5 (d, J = 22.3 Hz), 114.0, 112.1, 55.6; HRMS (ESI/Q-TOF) calcd for $C_{22}H_{15}FNO_2$ 344.1081, found 328.1080$[M+H]^+$.

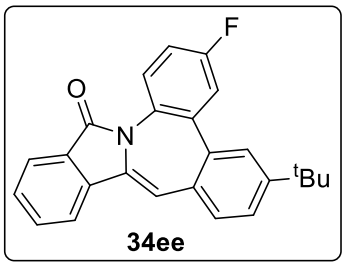
3-Fluoro-6-methyl-14*H*-dibenzo[4,5:6,7]azepino[2,1-*a*]isoindol-14-one (34ec)



34ec

Yield 90%; yellow solid, mp 193-195 °C; IR (nujol): ν 3020, 1693, 1666, 1589, 864, 752, 694 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, J = 7.6 Hz, 1H), 7.81 – 7.70 (m, 2H), 7.69 – 7.62 (m, 1H), 7.54 (t, J = 7.2 Hz, 1H), 7.36 (s, 1H), 7.17 – 7.01 (m, 4H), 6.56 (s, 1H), 2.42 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.7, 160.8 (d, J = 245.6 Hz), 143.6, 138.7, 136.9 (d, J = 1.4 Hz), 136.8, 136.3 (d, J = 2.9 Hz), 135.7 (d, J = 7.5 Hz), 132.9, 132.8, 131.0, 130.1, 129.4, 129.1, 128.6, 125.5 (d, J = 8.5 Hz), 123.9, 118.5 (d, J = 23.5 Hz), 118.5, 115.1 (d, J = 22.3 Hz), 112.2, 21.3; HRMS (ESI/Q-TOF) calcd for $C_{22}H_{15}FNO$ 328.1132, found 328.1137$[M+H]^+$.

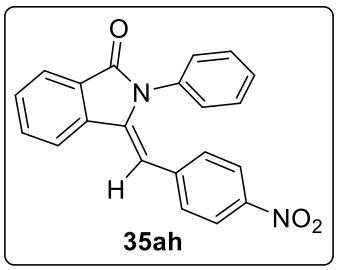
6-(Tert-butyl)-3-fluoro-14*H*-dibenzo[4,5:6,7]azepino[2,1-*a*]isoindol-14-one (34ee)



34ee

Yield 46%; viscous yellow; IR (nujol): ν 2959, 1701, 1501, 1474, 1300, 860, 732, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, J = 7.6 Hz, 1H), 7.81 – 7.73 (m, 2H), 7.71 – 7.65 (m, 1H), 7.59 – 7.52 (m, 2H), 7.37 (dd, J = 8.1, 2.0 Hz, 1H), 7.16 (d, J = 8.1 Hz, 1H), 7.13 – 7.04 (m, 2H), 6.61 (s, 1H), 1.40 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.7, δ 160.8 (d, J = 245.4 Hz), 151.9, 143.9, 136.9, 136.6 (d, J = 1.4 Hz), 136.3 (d, J = 2.9 Hz), 136.2 (d, J = 7.5 Hz), 132.9, 132.8, 129.9, 129.1, 128.6, 127.5, 125.7, 125.6 (d, J = 8.5 Hz), 123.9, 118.5 (d, J = 23.4 Hz), 118.5, 115.1 (d, J = 22.3 Hz), 112.0, 34.9, 31.2; HRMS (ESI/Q-TOF) calcd for $C_{25}H_{21}FNO$ 370.1602, found 370.1596$[M+H]^+$.

(Z)-3-(4-Nitrobenzylidene)-2-phenylisoindolin-1-one (35ah)



35ah

Yield 14%; yellow solid, mp 290-292 °C; IR (nujol): ν 3071, 1701, 1651, 1508, 1339, 745, 694 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.44 (d, J = 2.3 Hz, 1H), 8.13 (dd, J = 8.5, 2.3 Hz, 1H), 8.02 (d, J = 7.6 Hz, 1H), 7.82 – 7.77 (m, 2H), 7.75 (t, J = 7.5 Hz, 1H), 7.64 (t, J = 7.4 Hz, 1H), 7.49 – 7.37 (m, 3H), 7.32 (d, J = 8.6 Hz, 1H), 7.12 – 7.00 (m, 1H), 6.63 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.6, 147.9, 146.9, 142.3, 139.5, 133.3, 132.9, 131.4, 130.3, 130.3, 129.6, 127.7, 125.3, 124.5, 124.3, 124.3, 122.9, 119.0, 109.5; HRMS (ESI/Q-TOF) calcd for $C_{21}H_{15}N_2O_3$ 343.1077, found 343.1077 $[M+H]^+$.

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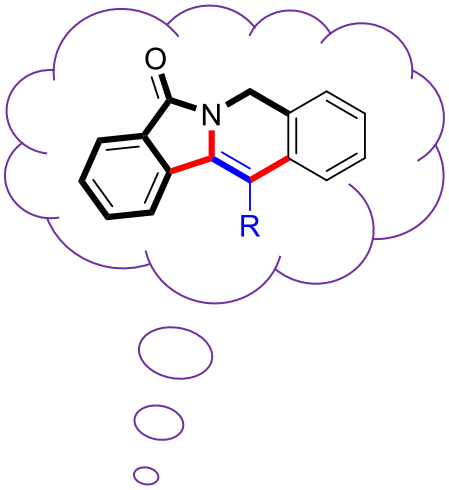
Chapter 4

Copper Catalyzed Sonogashira Coupling, Intramolecular Hydroamidation and Palladium Catalyzed Heck Reaction toward One-pot Synthesis of Isoindolo[2,1-*b*]isoquinolin-7(5H)-ones



4.1 Introduction

As described in chapter 1, palladium and copper are the significant metal catalysts to cleave inert C-H bond that facilitate C-C and C-N bonds formation to offer functionalized molecule with diverse substitution *via* distinctive approach such as hydroamination,[1] hydroamidation and direct arylation. Inspired by these approaches and previous work, naturally occurring fused *N*-heterocycles *i.e.* Magallanesine and like structures have been conceived to construct in this chapter. The aforementioned natural product contains isoindolinone framework which is also an integral part of numerous naturally occurring biologically active compounds such as Lenalidomide,[2-3] Aristoyagonine, Aristolactam E, Piperolactam E, Nuevamine,[4-5] Lennoxamine,[6] and Rosettacin[7] (**Figure 4.1**) as well as synthetic compound isoindolo[2,1-*b*]isoquinolin5(7*H*)-one (topoisomerase I inhibitor)[8-9] (**Figure 4.1**). These isoindolinone based compounds have demonstrated fascinating biological properties.

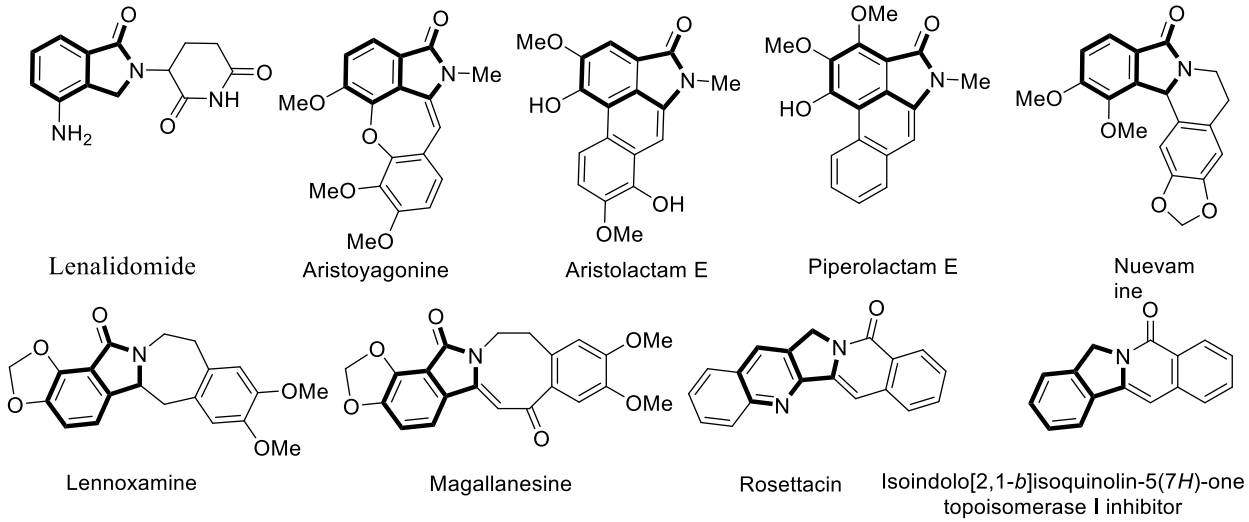


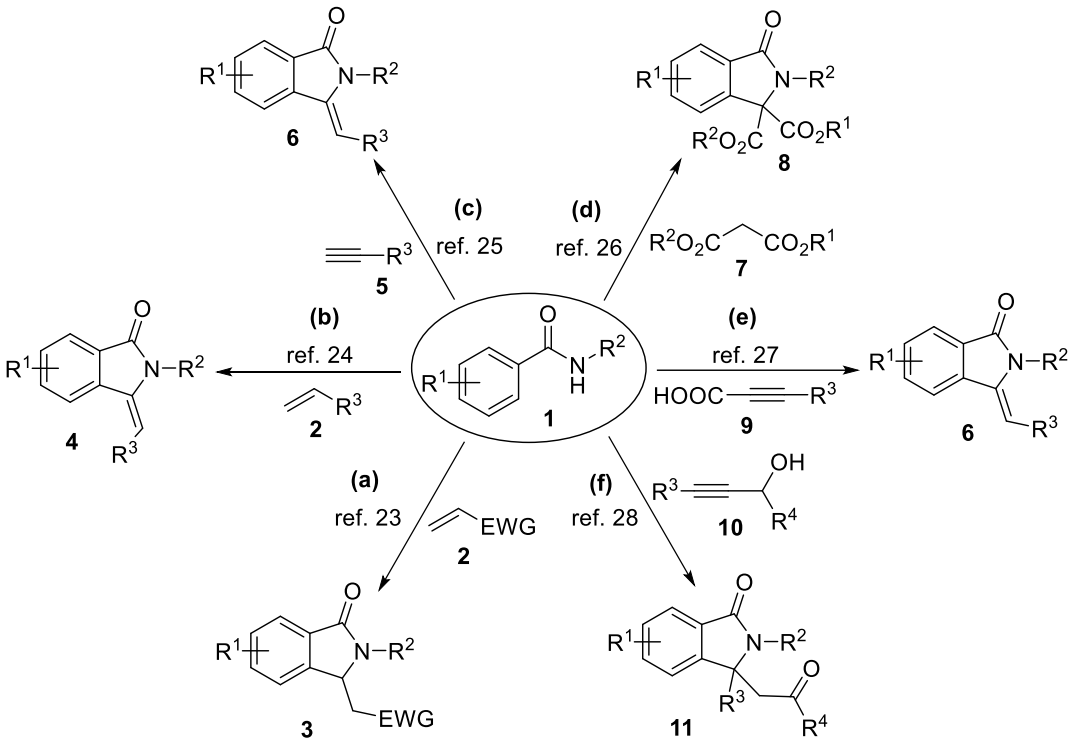
Figure 4.1 Selected natural products and bioactive compounds containing isoindolinone scaffold.

4.1.1 Synthesis of isoindolinones

In view of the diverse biological spectrum and unique structural features of isoindolinones, much effort has been devoted to synthesize isoindolinone core and its derivatives by several research groups.[10-13] Copper catalyzed Sonogashira coupling followed by intramolecular hydroamidation from pre-functionalized amide is an efficient pathway for the construction of isoindolinones. Ma and Zhang group have independently synthesized isoindolinones by copper catalyzed consecutive Sonogashira coupling and hydroamidation cyclization.[14-16] Further improved

synthetic methodology demonstrated that application of C-H activation to access isoindolinones derivatives.[17-22] Atom economic C-H activation precludes prior functionalization in the designed substrates. In this perspective, Zhu group described Pd-catalyzed methodology for the synthesis of diversely substituted isoindolinones (**3**) from *N*-tosylbenzamide (**1**) and activated alkenes (**2**) (**Figure 4.2a**).[23] The methodology is compatible with aliphatic as well as conjugated alkenes. Milburn described the direct access of alkylidene isoindolinones (**4**) from corresponding *N*-alkoxybenzamides (**1**) and alkenes (**2**) which proceeds through Pd-catalyzed *E*-selective C-H activation (**Figure 4.2b**).[24] Developed protocol found to tolerate broad range of functionality to access isoindolinones analogues. You and group disclosed a copper mediated oxidative coupling followed by hydroamidation to obtain 3-substituted isoindolinone (**6**) derivatives (**Figure 4.2c**).[25] The key features of this protocol are broad substrate scope containing different corresponding amides as well as alkynes. The exclusive chemo-, regio-, and stereoselectivity have made this method more attractive compared to the previous methods. Similarly, In subsequent year, another copper catalyzed oxidative coupling has been developed to access functionalized isoindolinone (**8**) under $Cu(OAc)_2$, Li_2CO_3 and Ag_2CO_3 in DMSO for 12 h at 80 °C (**Figure 4.2d**).[26] The reaction proceeds through C(sp^2)-H of respective *N*-arylbenzamidamide (**1**) and C(sp^3)-H of dimethyl malonates (**7**) C-C coupling followed by intramolecular oxidative C-N bond formation to lead cyclized isoindolinone derivatives.

In addition to the palladium and copper catalyzed synthesis, some other transition metals like cobalt and rhodium were used to make isoindolinone structures. Decarboxylative C-H activation of benzamides (**1**) and alkynyl carboxylic acid (**9**) under cobalt catalysis was reported by Hao *et. al.* (**Figure 4.2e**).[27] Initial cobalt complex coordinates with benzamide to undergo C(sp^2)-H activation and alkynyl carboxylic acid to produce alkyne radical *via* protodecarboxylation. Reaction of these active species gives corresponding six coordinated Co(IV) intermediate which facilitate isoindolinones (**6**) in average to good yields. Different electron releasing and withdrawing substitution containing isoindolinone analogues were prepared to generalize this transformation. Liu and team showcased rhodium catalyzed tranformation using different benzamides (**1**) and propargyl alcohols (**10**) which includes C-H activation followed by [4 + 1] cyclization reactions and offered a series of isoindolinones (**11**) containing quaternary carbon (**Figure 4.2f**).[28]

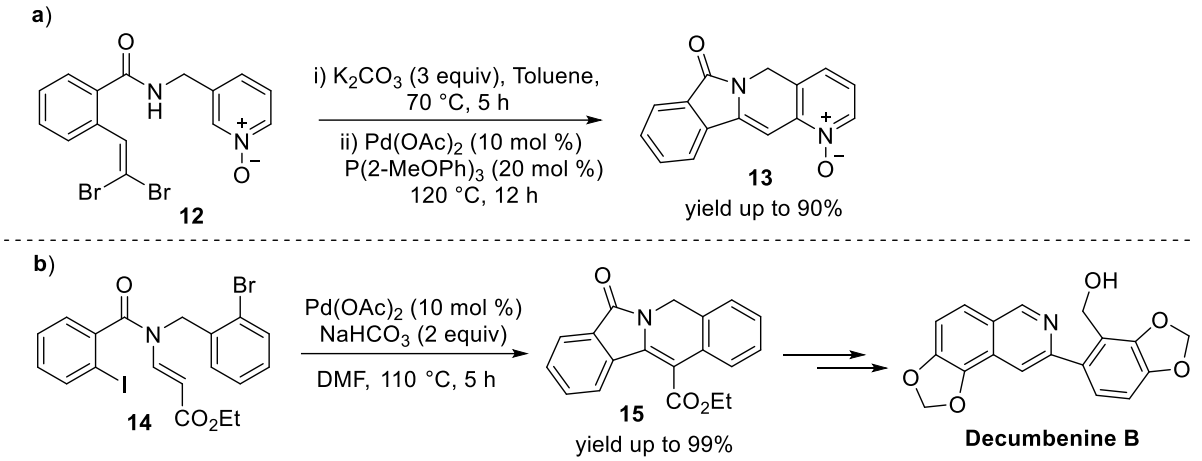


a) $Pd(OAc)_2$ / O_2, bathophenanthroline, DMF, 110 °C, 24h; **b)** $Pd(OAc)_2$ / O_2, benzoquinone, AcOH, 110 °C, 24 h
c) $Cu(OAc)_2$, t-amylOH, 120 °C, 24 h; **d)** $Cu(OAc)_2$, Li_2CO_3, Ag_2CO_3, DMSO, 80 °C, air, 12 h
e) $Co(OAc)_2{\cdot}4H_2O$, Ag_2O, Na_2CO_3, DMF, 100 °C, air, 12 h; **f)** $[Cp^*RhCl_2]_2$, CsOAc, DCE, 80 °C, 12 h

Figure 4.2 Various routes to access functionalize isoindolinones

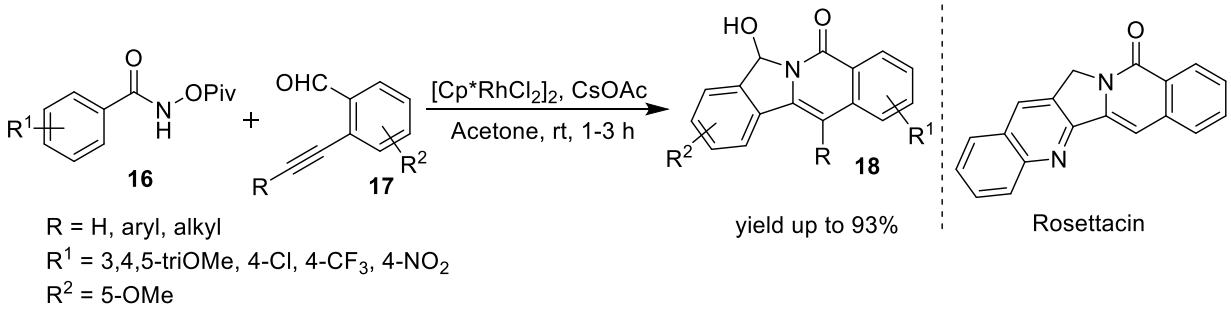
4.1.2 *N*-Heterocyclic-fused isoindolinone

Chatti and co-workers prepared fused tricyclic isoindolinone derivatives through one pot cascade multicomponent reaction. The formation of multiple bonds (C-C, C-N, C-O) from 5-amino-2-furaldehyde, diethyl maleate, and phenylglycinol in toluene at reflux gave a series of enantiopure heteroaryl fused isoindolinone analogues in good yields.[29] Similarly, sequential reactions have proven to be a powerful tool to synthesize complex molecular scaffolds.[30-32] Regard to this, Zhang group developed an efficient method for the synthesis of indolizinones (**13**) using *gem*-dibromoolefins (**12**) through palladium-catalyzed reaction that involves sequential one-pot intramolecular C–N bond formation and direct C–H arylation (**Scheme 4.1a**).[33] Kim group prepared isoindolo[2,1-*b*]isoquinoline derivatives (**15**) by palladium catalyzed sequential intramolecular double Heck reactions from corresponding functionalized amide (**14**) and further applied to access a natural alkaloid Decumbenine B (**Scheme 4.1b**).[34] Prior to this, Kim group reported synthesis of alkaloid Magallanesine containing isoindolinone core by employing sequential intramolecular Heck reaction and Friedel–Crafts acylation reactions.[35]



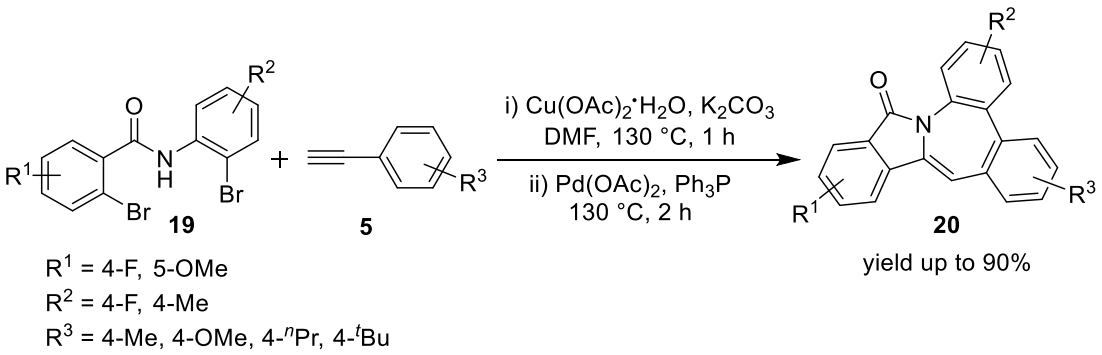
Scheme 4.1 Synthesis of polycyclic isoindolinones using Pd-catalyzed sequential reactions

Reddy group prepared 7-hydroxyisoindolo[2,1-*b*]isoquinolin-5(7H)-ones (**18**) by Rh(III)-catalyzed reaction of 2-alkynyl aldehydes (**17**) and *N*-(pivaloyloxy)benzamides (**16**) that involves cascade alkyne insertion/intramolecular amide nitrogen addition to aldehydes (**Scheme 4.2**).[36] Different aryl/hetero aryl substitutions here employed to generalize this methodology under optimal conditions to get corresponding products in high yields. Further utility of this developed approach was illustrated by synthesizing Rosettacin alkaloid in two step process.



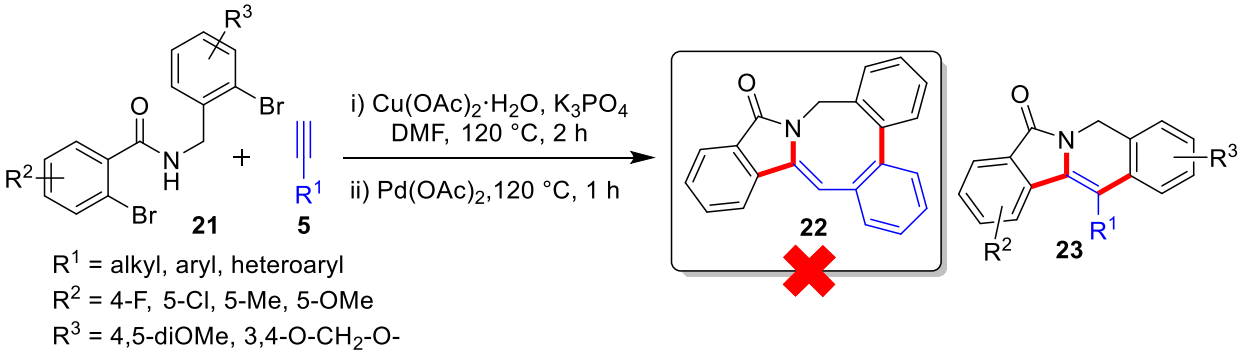
Scheme 4.2 Rh-catalyzed synthesis of functionalized isoindolo-fused isoquinolin-5(7H)-ones

Our group reported an efficient one-pot method for the synthesis of azepino-fused isoindolinones (**20**) from functionalized amide **19** and aromatic alkynes **5** *via* sequential copper-catalyzed Sonogashira coupling/intramolecular hydroamidation and palladium-catalyzed intramolecular direct arylation reaction (**Scheme 4.3**).[37] This modular approach was applied to make nineteen analogues in moderate to high yields containing both electron releasing and electron withdrawing group.



Scheme 4.3 Cu/Pd-catalyzed synthesis of azepino-fused isoindolinones

With this advent of interest, we planned to construct eight membred ring containing fused isoindolinone (**22**) scaffolds which has close structure to alkaloid Magallanesine. However, our designed rationale led to the formation of isoindolo[2,1-*b*]isoquinolin-7(5H)-one (**23**). In this chapter, we herein report an efficient method accessing isoindolo[2,1-*b*]isoquinolin-7(5H)-one (**23**) through copper-catalyzed Sonogashira coupling, intramolecular hydroamidation and subsequent palladium(II)-catalyzed ligand free Heck reaction (**Scheme 4.4**).



Scheme 4.4 Cu/Pd-catalyzed synthesis of heterocycle-fused isoindolinones

4.2 Results and discussion

Our studies commenced with the reaction of 2-bromo-*N*-(2-bromobenzyl)benzamide (**21a**) and phenyl acetylene (**5a**) under our previously reported condition for sequential reactions. The reaction of **21a** and **5a** in the presence of $Cu(OAc)_2{\cdot}2H_2O$ (30 mol %), K_2CO_3 (2 equiv.) in DMF for 1 h at 130 °C followed by addition of $Pd(OAc)_2$ (5 mol %) and PPh_3 (10 mol %) to the cooled reaction mixture and heating for additional 2 h at 130 °C resulted in one major product along with two minor products (Table 4.1, entry 1). Description of spectral analysis of major product, IR indicated about the presence of amidic functionality with a characteristic peak at 1689 cm^{-1}.

In the ^{1}H NMR spectrum, appearing of a singlet peak at 5.26 ppm for two protons and missing of expected singlet for vinylic proton indicated that the product structure do not match with the expected compound **22aa**. Further in the ^{13}C NMR spectrum the number of signals were less than the expected compound **22aa** (**Figure 4.3**). In HRMS analysis a peak appeared at *m/z* 310.1219 corresponding to $C_{22}H_{16}NO$ $[M + H]^+$ ion (**Figure 4.4**). Careful analysis of the all spectral data revealed that the major product is 12-phenylisoindolo[2,1-*b*]isoquinolin-7(5*H*)-one (**23aa**) instead of the expected product **22aa**. Finally, the single X-ray crystallography confirms its structure as **23aa** (CCDC No 1853630) (**Figure 4.4**). Also, the two other minor products could be identified as 3-benzylidene-2-(2-bromobenzyl)isoindolin-1-one (**24aa**) and 3-benzylidene-2-(2-(phenylethynyl)benzyl)-isoindolin-1-one (**25aa**).

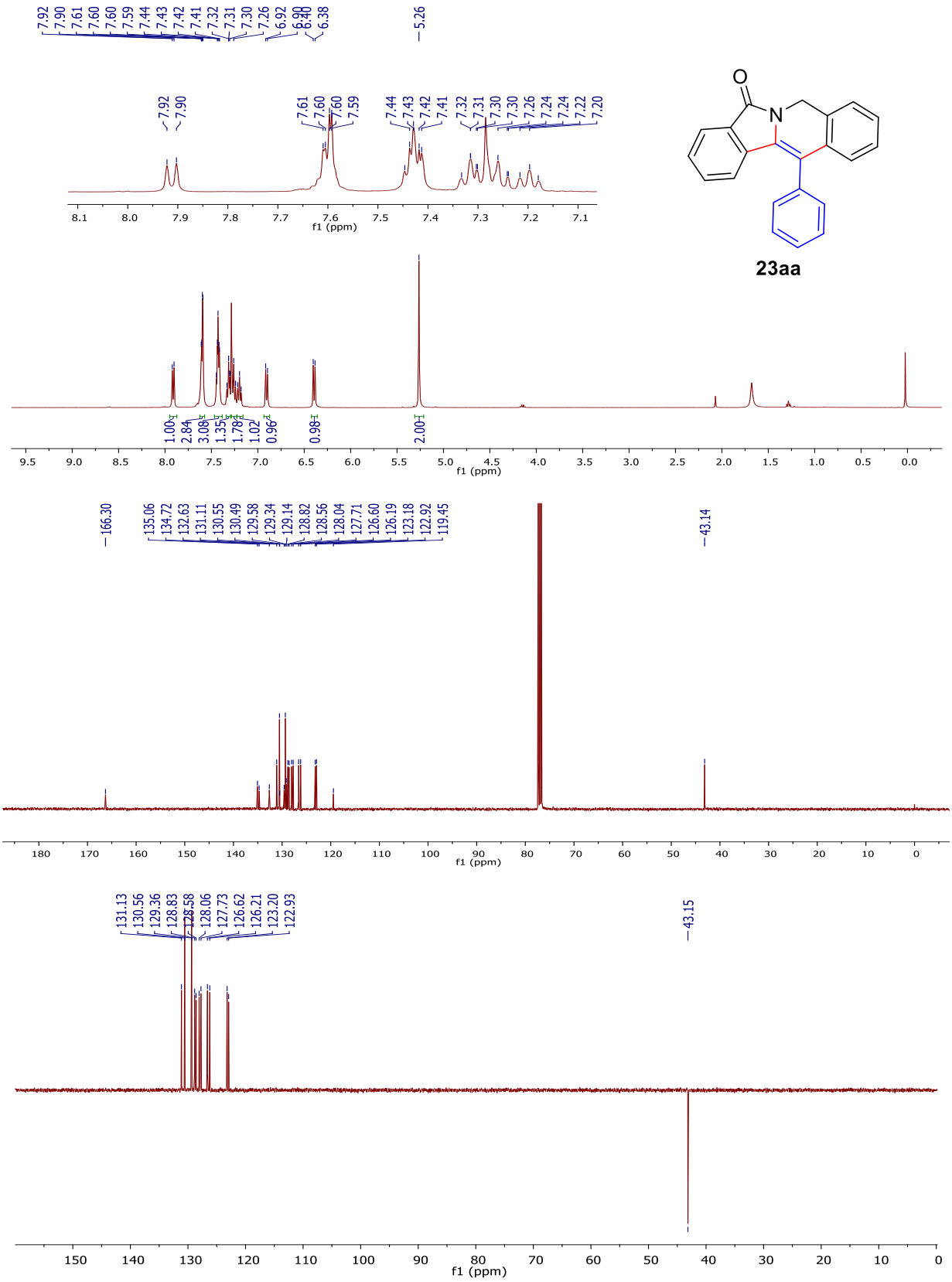


Figure 4.3 The ^{1}H NMR, ^{13}C NMR and DEPT-135 spectra of **23aa**

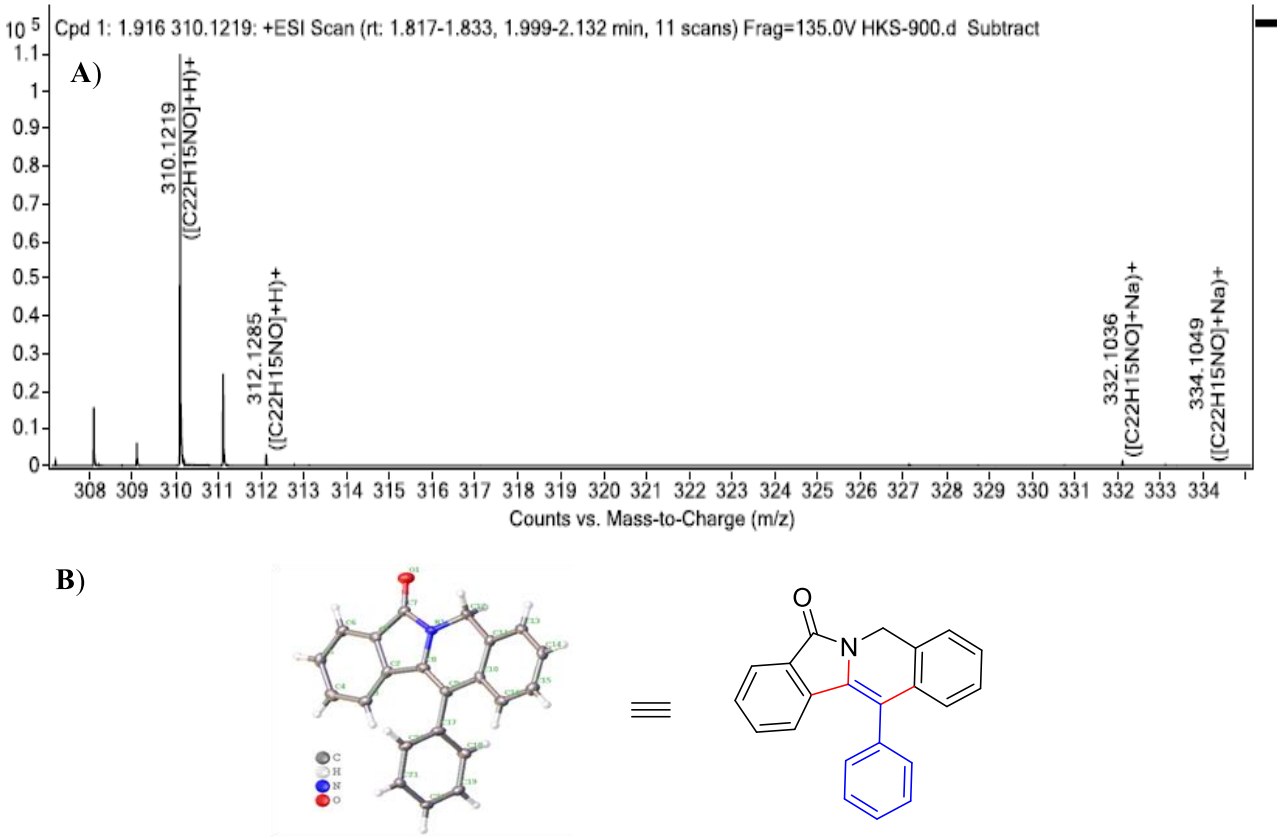
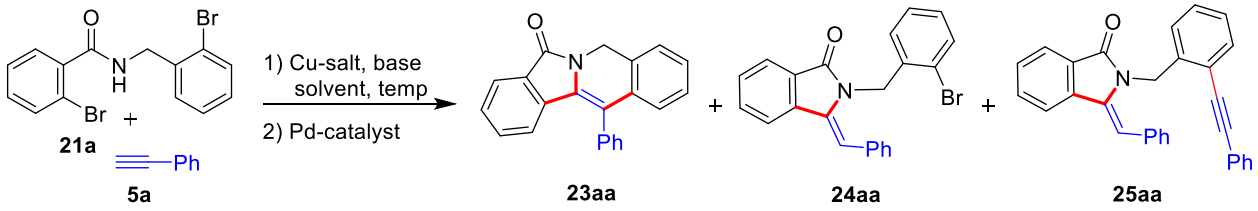


Figure 4.4 A) HRMS spectrum and **B**) single crystal X-ray of **23aa**

Encouraged by initial results, we decided to optimize the reaction conditions for the synthesis of **23aa** by varying the catalyst, solvent, and base. The results are summarized in **Table 4.1**.

Table 4.1. Optimization of the reaction conditions for the synthesis of **23aa**.[a]



Entry	Cu-catalyst	Pd-catalyst	Base	Solvent	% Yield[b]		
					23aa	**24aa**	**25aa**
1.	$Cu(OAc)_2.H_2O$ [c]	$Pd(OAc)_2/PPh_3$	K_2CO_3	DMF	54	3	15
2.	$Cu(OAc)_2.H_2O$[d]	$Pd(OAc)_2/PPh_3$	K_2CO_3	DMF	63	5	11
3.	$Cu(OAc)_2.H_2O$[e]	$Pd(OAc)_2/PPh_3$	K_2CO_3	DMF	68	7	05

4.	$Cu(OAc)_2.H_2O$	$Pd(OAc)_2$	K_2CO_3	DMF	71	8	04
5.	CuBr	$Pd(OAc)_2$	K_2CO_3	DMF	44	9	7
6.	$CuCl_2$	$Pd(OAc)_2$	K_2CO_3	DMF	40	11	5
7.	CuI	$Pd(OAc)_2$	K_2CO_3	DMF	41	8	12
8.	$Cu(OAc)_2.H_2O$	$PdCl_2$	K_2CO_3	DMF	52	7	5
9.	$Cu(OAc)_2.H_2O$	$PdCl_2(PPh_3)_2$	K_2CO_3	DMF	49	4	7
10.	$Cu(OAc)_2.H_2O$	$Pd(PPh_3)_4$	K_2CO_3	DMF	46	8	4
11.	$Cu(OAc)_2.H_2O$	$Pd(OAc)_2$	K_2CO_3	DMA	70	8	6
12.	$Cu(OAc)_2.H_2O$	$Pd(OAc)_2$	K_2CO_3	Toluene[f]		NR	
13.	$Cu(OAc)_2.H_2O$	$Pd(OAc)_2$	K_2CO_3	MeCN[f]		NR	
14.	**$Cu(OAc)_2.H_2O$**	**$Pd(OAc)_2$**	**K_3PO_4**	**DMF**	**76**	**4**	**0**
15.	$Cu(OAc)_2.H_2O$	$Pd(OAc)_2$	^tBuOK	DMF	8	0	41
16.	$Cu(OAc)_2.H_2O$	$Pd(OAc)_2$	Cs_2CO_3	DMF	0	6	5
17.	$Cu(OAc)_2.H_2O$[g]	$Pd(OAc)_2$	K_3PO_4	DMF	32	39	00

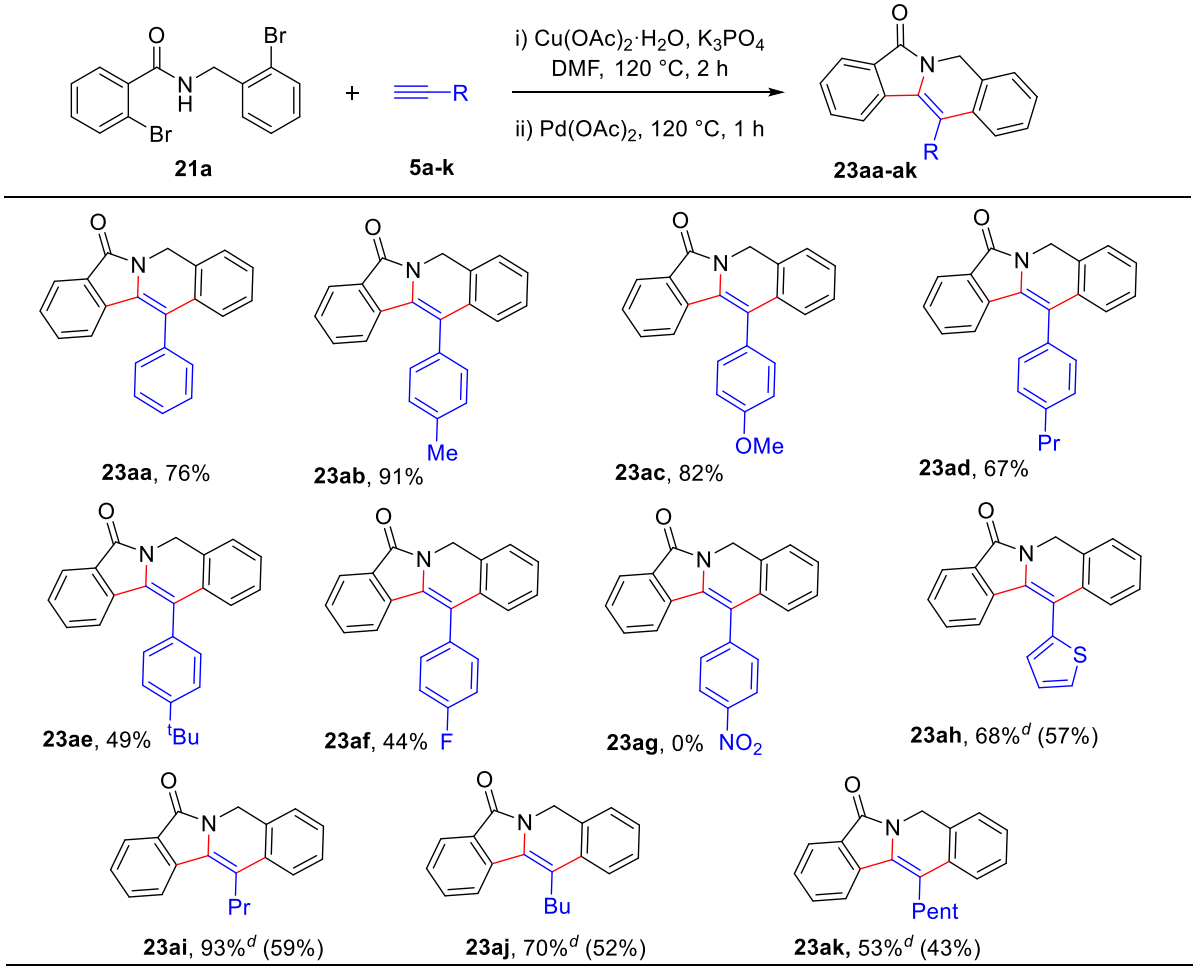
[a]Reaction conditions: **21a** (0.5 mmol), **5a** (1.0 mmol), Cu-catalyst (10 mol %), base (1.0 mmol), solvent (4 mL) at 120 °C, 2 h followed by Pd-catalyst (5 mol %), 120 °C, 1 h. [b]Isolated yields. [c]Reaction was performed at 130 °C with 30 mol % $Cu(OAc)_2.H_2O$. [d]20 mol % $Cu(OAc)_2.H_2O$ was used. [e]10 mol % $Cu(OAc)_2.H_2O$ was used. [f]Reaction was performed at reflux. [g]Reaction was performed at 90 °C. NR = No reaction.

Decreasing amount of copper catalyst in the first step resulted increased yield of **23aa** with slightly increased yield of **24aa** (Table 4.1, entries 2 and 3). When, $Pd(OAc)_2$ was added without external PPh_3 ligand further a slight increment in the yield of **23aa** was observed (Table 4.1, entry 4). This result indicates that the palladium catalyzed Heck coupling may be proceeding through Pd(II) and not through Pd(0). Screening of different copper catalysts revealed $Cu(OAc)_2 \cdot H_2O$ to be ideal, providing **23aa** in 71% yield (Table 4.1, entry 4). The use of other copper salts such as $CuCl_2$, CuBr, and CuI failed to afford the desired product **23aa** in satisfactory yields (Table 4.1, entries 5-7). We then investigated other palladium sources including $PdCl_2$, $PdCl_2(PPh_3)_2$ and $Pd(PPh_3)_4$ and identified $Pd(OAc)_2$ as the most efficient catalyst (Table 4.1, compare entry 4 with entries 8-10). Among the different solvents were screened, toluene and acetonitrile were failed to produce **23aa** where DMF and DMA afforded desired compound **23aa** almost in the similar yield with other two by-products (Table 4.1, compare entry 4 with entries 11-13). From screening of different bases such as K_2CO_3, K_3PO_4,

^{t}BuOK, and Cs_2CO_3 (Table 4.1, entries 4, 14-16), K_3PO_4 was found the most suitable base for this transformation which is in agreement with the first report on ligand free $Pd(OAc)_2$ catalyzed Heck reaction.[38] Further temperature study revealed that optimized 120 °C temperature is the best for present transformation (Table 4.1, compare entries 14 and 17).

With the optimized condition in hand, the scope of the sequential reaction was investigated by using 2-bromo-*N*-(2-bromobenzyl)benzamide (**21a**) and a variety of terminal alkynes (**5a-k**) (**Table 4.2**). The results listed in table 4.2 indicated that ethynylbenzenes (**5a-d**) with activating groups such as methyl, methoxy and *n*-propyl on the phenyl ring reacted smoothly to give corresponding products **23ab-ad** in reasonably good (67-91%) yields.

Table 4.2: Scope of alkynes for the synthesis of isoindolo[2,1-*b*]isoquinolin-7(5*H*)-ones.[a,b]

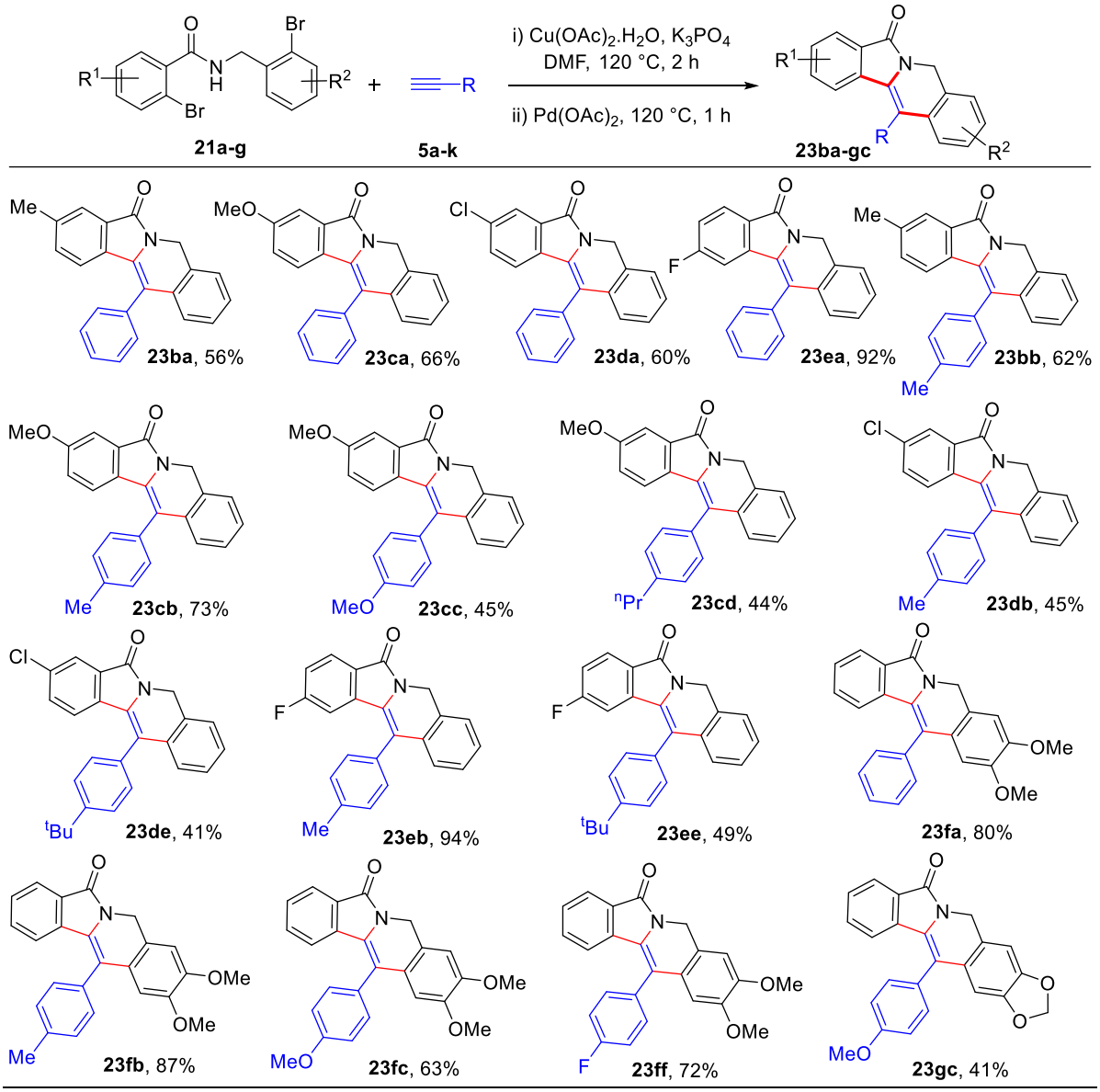


[a]Reaction conditions: **21** (0.5 mmol), **5** (1.0 mmol), $Cu(OAc)_2.H_2O$ (10 mol %), K_3PO_4 (1.0 mmol), DMF (4 mL), 120 °C, 2 h followed by addition of $Pd(OAc)_2$ (5 mol %) at rt, 120 °C, 1 h. [b]Isolated yields. [d]Isolated yields in two steps. The yield in parentheses refers to isolated intermediate.

Ethynylbenzenes with sterically hindered *tert*-butyl group (**5e**) and fluoro group (**5f**) also yielded the respective product **23ae-af** in 49% and 44% yields, respectively. Unfortunately, reaction of ethynylbenzene with highly deactivating groups on the phenyl ring such as 1-ethynyl-4-nitrobenzene (**5g**) was unsuccessful under similar reaction conditions. 2-Ethynylthiophene (**5h**) also participated in this reaction to give the corresponding product **23ah** in 68% yield. Interestingly, in addition to ethynylbenzenes, aliphatic alkynes such as pent-1-yne (**5i**), hex-1-yne (**5j**) and hept-1-yne (**5k**) also reacted with **21a** to afford the corresponding compounds (**23ai-ak**) in moderate to excellent (53-93%) yields.

Next, scope of diversely substituted 2-bromo-*N*-(2-bromobenzyl)benzamides (**21b-g**) was explored (**Table 4.3**). Benzamides (**21b-e**) with either electron donating or electron withdrawing substituents on amide ring reacted smoothly with phenyl acetylene (**5a**) to give corresponding products **23ba-ea** in good yields (56-92%). benzamides (**21b-e**) with substituent on amide ring were treated with differently substituted alkynes (**5a-e**) to give corresponding isoindolo[2,1-*b*]isoquinolin-7(5*H*)-ones(**23bb-ee**) in moderate to excellent (41-94%) yields. No obvious electronic effect was observed for substitution at C-3 position of benzamide, however benzamide with 4-fluoro substituent on amide ring (**5e**) resulted in highest yield. Good yield from fluoro-substituted substrate provides an opportunity for the further functionalization.[39] Finally, benzamide **21f** and **21g** bearing 3,4-dimethoxy and 3,4-dioxomethylene groups, respectively, in the benzyl ring reacted well with different alkynes (**5a-f**) to give corresponding products (**23fa-gc**) in moderate to good yield.

Table 4.3: Scope of 2-bromo-*N*-(2-bromobenzyl)benzamides for the synthesis of isoindolo[2,1-*b*]isoquinolin-7(5*H*)-ones.[a,b]

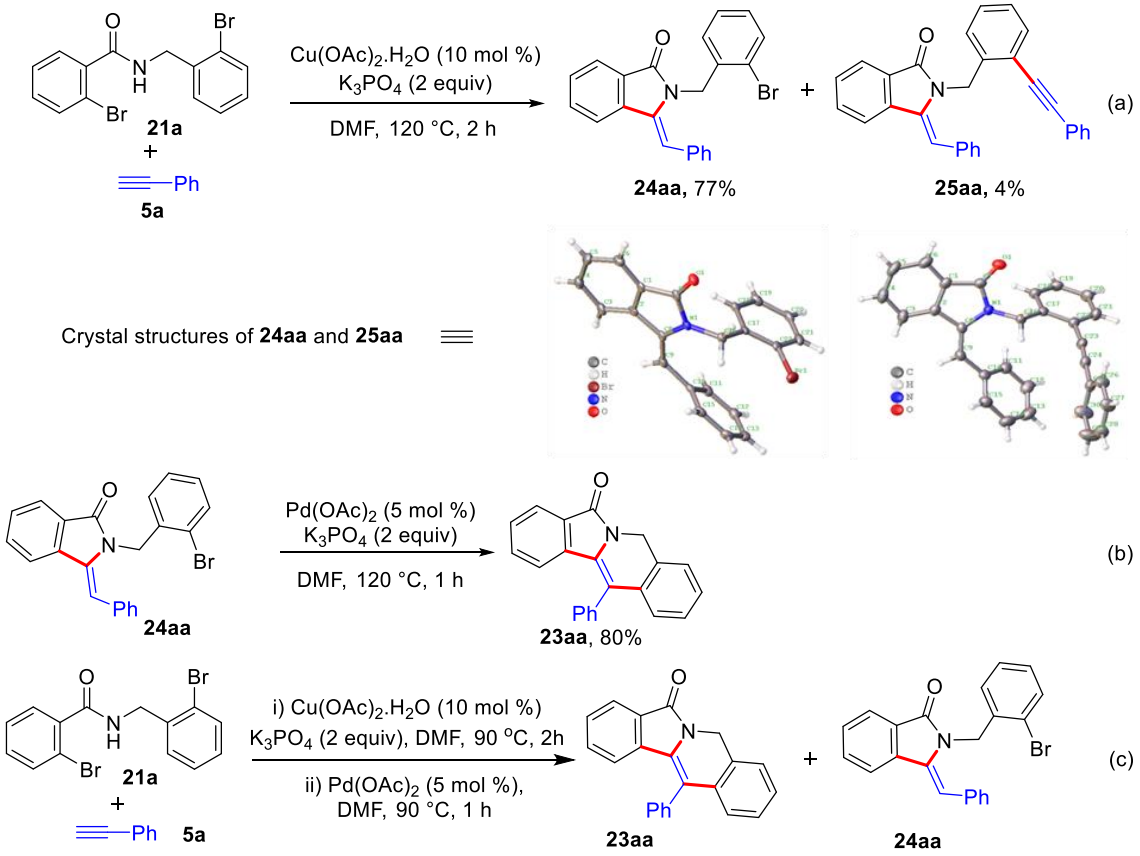


[a]Reaction conditions: **21** (0.5 mmol), **5** (1.0 mmol), $Cu(OAc)_2.H_2O$ (10 mol %), K_3PO_4 (1.0 mmol), DMF (4 mL), 120 °C, 2 h followed by addition of $Pd(OAc)_2$ (5 mol %) at rt, 120 °C, 1 h. [b]Isolated yields.

In order to check the feasibility of the developed method for scale up, a gram scale reaction of **21a** (2.7 mmol, 1.01 g) and **5a** (5.5 mmol, 0.56 g) was performed. The reaction proceeded smoothly to give **23aa** in 69% isolated yield.

A set of control experiments were performed to elucidate the mechanism for the sequential reaction (**Scheme 4.5**). Firstly, the reaction of **21a** and **5a** under optimized conditions in the

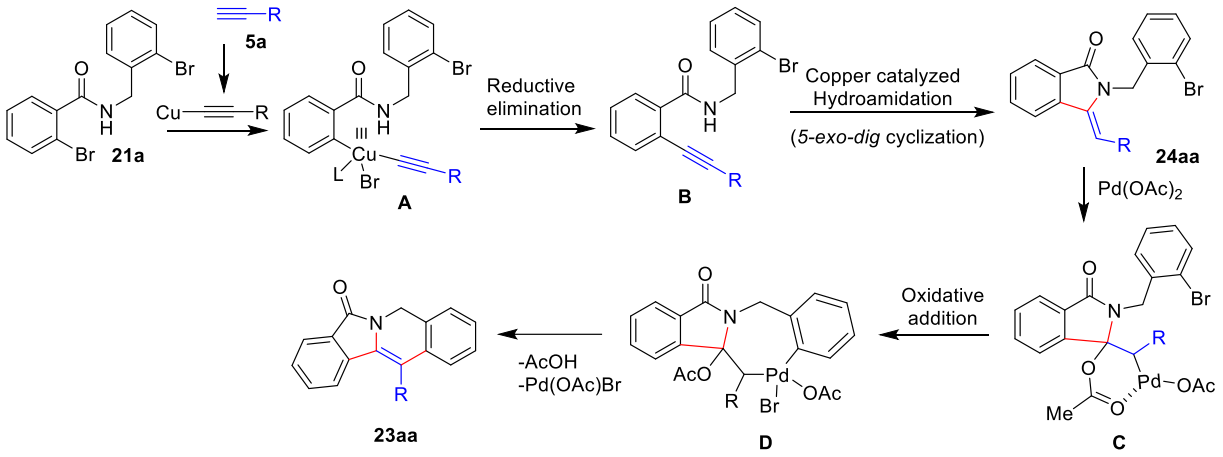
absence of $Pd(OAc)_2$ gave **24aa** and **25aa** in 77% and 4%, respectively (**Scheme 4.5a**). The structures of both **24aa** (CCDC No 1853080) and **25aa** (CCDC No 1853081) were also unambiguously confirmed by single crystal X-ray analysis. Further, when isolated **24aa** was treated with $Pd(OAc)_2$ in the presence of K_3PO_4 in DMF for 1h at 120 °C, cyclized product **23aa** was obtained in 80% yield (**Scheme 4.5b**). These results indicate that the reaction proceeds through **24aa** and $Pd(OAc)_2$ is essential for the Heck coupling. Lowering temperature for the reaction of **21a** and **5a** to 90 °C resulted decrease in the yield of **23aa** but increase in the yield of **24aa** (**Scheme 4.5c**), suggested that intramolecular arylation is difficult to facilitates target product **23aa** in good yield.



Scheme 4.5 Control experiments

Based on the experimental evidences and literature reports, a plausible mechanism of the sequential copper and palladium catalyzed reaction has been proposed in **Scheme 4.6**. It is believed that Cu(II) initially interacts with alkyne **5a** to give copper acetylide as starting point of the catalytic cycle[40] which then on oxidative addition reaction with **21a** gives intermediate **A** (**Scheme 4.6**). Following reductive elimination with assistance of base intermediate **A** leads to

the formation of Sonogashira product **B**. Finally, intermediate **B** undergoes 5-*exo*-*dig* cyclization to give isoindolinone intermediate **24aa.**[14-16, 41] The mechanism for the second step is not clear. It is expected that the reaction proceeds via Pd(II)/Pd(IV) cycle, however involvement of Pd(0)/Pd(II) cycle cannot be ruled out at this stage. It is proposed that the intermediate **24aa** on reaction with $Pd(OAc)_2$ leads to the formation of a transient palladacycle **C**[38] which then undergoes intramolecular oxidative addition to generate the Pd(IV) species **D**. Base-promoted elimination of the acetate ion from **D** followed by reductive elimination leads to the product **23aa** with regeneration of Pd (II) species.



Scheme 4.6 Proposed mechanism

4.3 Conclusion

In summary, we have developed a novel and efficient one-pot sequential process involving copper-catalyzed Sonogashira coupling, hydroamidation and Pd(II)-catalyzed Heck reaction for the preparation of isoindolo[2,1-*b*]isoquinolin-7(5*H*)-ones derivatives (**23aa-gk)**. This unified approach provided isoindolo[2,1-*b*]isoquinolin-7(5*H*)-ones in moderate to excellent yields with broad substrate scope and functional group compatibility.

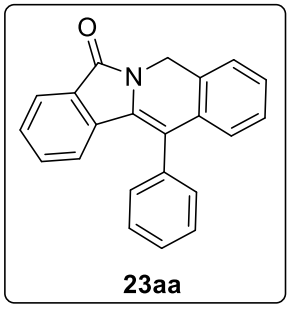
4.4 Experimental

General information: All reagents and solvents were purchased from commercial sources and used without further purification. Melting points were measured using an automatic capillary point apparatus and are uncorrected. The thin layer chromatography (TLC) was performed on 0.25 mm silica gel 60-F_{254} and a UV-lamp was used as visualizing agent. Column chromatography was performed using silica gel (100-200 mesh) and hexane and ethyl acetate

were used as eluents. The ^{1}H and ^{13}C NMR spectra were obtained on 400 MHz and 100 MHz spectrometer. Coupling constant and chemical shifts were reported in hertz (Hz) and parts per million (ppm) respectively, relative to the internal standard of tetramethylsilane (TMS). IR spectroscopy was performed as a neat sample on a FT-IR instrument and values are expressed in cm^{-1}. The HRMS were analyzed by electrospray ionization (ESI) method on a Q-TOF LC-MS spectrometer.

Representativeprocedure for the synthesis of isoindolo[2,1-*b*]isoquinolin-7(5*H*)-one (23aa): A clean, oven-dried 10 mL round bottom flask was charged with 2-bromo-*N*-(2-bromobenzyl)benzamide (**21a**) (185 mg, 0.5 mmol), phenyl acetylene (**5a**) (102 mg, 1.0 mmol), $Cu(OAc)_2.H_2O$ (10 mg, 10 mol %) and K_3PO_4 (212 mg, 1.0 mmol) in DMF (4 mL). Resulting solution was stirred at 120 °C for 2 h then $Pd(OAc)_2$ (6 mg, 5 mol %) was added at ambient temperature in one pot fashion and continued the reaction mixture for another 1 h at 120 °C. On completion, the reaction mass was cooled to room temperature, diluted with water 30 mL and extracted into EtOAc (2 × 30 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and evaporated to dryness. The crude residue was purified by column chromatography (EtOAc/hexanes = 2:3 *v/v*) to obtain **23aa** in 76% (118 mg) yield.

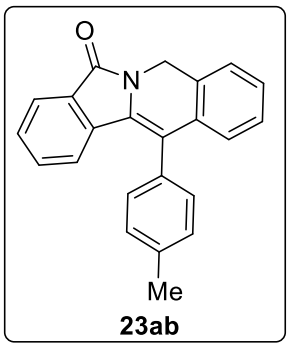
12-Phenylisoindolo[2,1-*b*]isoquinolin-7(5*H*)-one (23aa)



23aa

Yield 76%; Yellow solid, mp 245-247 °C; IR (nujol): ν 1689, 1450, 1396, 1355, 756, 694 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, J = 7.6 Hz, 1H), 7.61 – 7.59 (m, 3H), 7.45 – 7.41 (m, 3H), 7.33 – 7.30 (m, 1H), 7.26 – 7.24 (m, 2H), 7.20 (t, J = 7.3 Hz, 1H), 6.91 (d, J = 7.7 Hz, 1H), 6.39 (d, J = 7.9 Hz, 1H), 5.26 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.3, 135.1, 134.7, 132.6, 131.1, 130.5, 130.5, 129.6, 129.3, 129.1, 128.8, 128.6, 128.0, 127.7, 126.6, 126.2, 123.2, 122.9, 119.4, 43.1; DEPT-135 (100 MHz, $CDCl_3$) δ 131.1, 130.6, 129.4, 128.8, 128.6, 128.1, 127.7, 126.6, 126.2, 123.2, 122.9, -43.1; HRMS (ESI/Q-TOF) calcd for $C_{22}H_{16}NO$ 310.1226, found 310.1219 $[M+H]^+$.

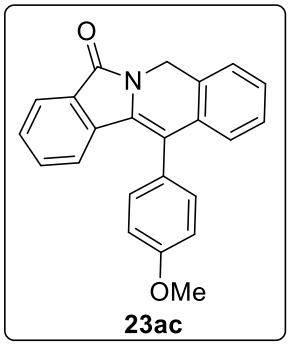
12-(p-Tolyl)isoindolo[2,1-*b*]isoquinolin-7(5*H*)-one (23ab)



23ab

Yield 91%; Yellow solid, mp 231-233 °C; IR (nujol): ν 1697, 1458, 1365, 1355, 756, 694 cm^{-1}; ^1H NMR (400 MHz, DMSO) δ 7.81 (d, *J* = 7.5 Hz, 1H), 7.50 (td, *J* = 7.5, 0.7 Hz, 1H), 7.44 (t, *J* = 6.4 Hz, 1H), 7.40 (td, *J* = 7.8, 1.0 Hz, 1H), 7.33 – 7.29 (m, 3H), 7.23 (t, *J* = 7.5 Hz, 1H), 6.77 (d, *J* = 7.7 Hz, 1H), 6.39 (d, *J* = 7.8 Hz, 1H), 5.16 (s, 2H), 2.48 (s, 3H); ^{13}C NMR (100 MHz, DMSO) δ 165.5, 138.5, 134.7, 132.6, 132.0, 131.9, 130.5, 130.3, 129.7, 129.7, 129.6, 129.4, 128.5, 128.2, 127.4, 125.9, 123.1, 123.1, 119.3, 43.1, 21.5; HRMS (ESI/Q-TOF) calcd for $C_{23}H_{18}NO$ 324.1383, found 324.1379 $[M+H]^+$.

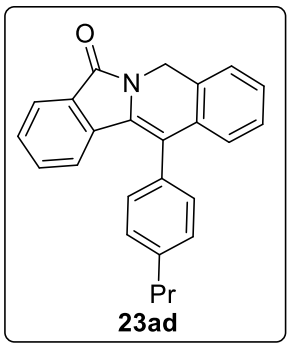
12-(4-Methoxyphenyl)isoindolo[2,1-*b*]isoquinolin-7(5*H*)-one (23ac)



23ac

Yield 82%; Yellow solid, mp 229-231 °C; IR (nujol): ν 1689, 1512, 1365, 1242, 763, 694 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, *J* = 7.6 Hz, 1H), 7.42 (td, *J* = 7.5, 0.6 Hz, 1H), 7.33 – 7.27 (m, 5H), 7.20 (td, *J* = 7.8, 1.8 Hz, 1H), 7.14 – 7.11 (m, 2H), 6.95 (d, *J* = 7.6 Hz, 1H), 6.51 (d, *J* = 7.9 Hz, 1H), 5.23 (s, 2H), 3.96 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.3, 159.7, 134.8, 132.9, 131.7, 131.1, 130.7, 129.5, 129.2, 128.7, 128.0, 127.7, 126.9, 126.6, 126.2, 123.2, 122.9, 119.2, 114.7, 55.4, 43.1; HRMS (ESI/Q-TOF) calcd for $C_{23}H_{18}NO_2$ 340.1332, found 340.1326 $[M+H]^+$.

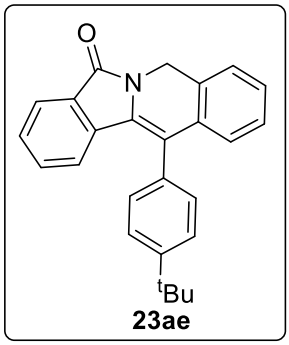
12-(4-Propylphenyl)isoindolo[2,1-*b*]isoquinolin-7(5*H*)-one (23ad)



23ad

Yield 67%; Yellow solid, mp 146-148 °C; IR (nujol): ν 1689, 1519, 1458, 1072, 694 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, *J* = 7.6 Hz, 1H), 7.44 – 7.39 (m, 3H), 7.32 – 7.29 (m, 3H), 7.28 – 7.24 (m, 2H), 7.20 (t, *J* = 7.4 Hz, 1H), 6.94 (d, *J* = 7.6 Hz, 1H), 6.42 (d, *J* = 7.9 Hz, 1H), 5.26 (s, 2H), 2.77 (t, *J* = 7.8 Hz, 2H), 1.87 – 1.74 (m, 2H), 1.06 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.3, 143.1, 134.8, 132.8, 132.1, 131.0, 130.4, 130.3, 129.5, 129.4, 129.2, 128.7, 128.0, 127.7, 126.5, 126.3, 123.2, 122.9, 119.6, 43.1, 37.9, 24.5, 13.8; HRMS (ESI/Q-TOF) calcd for $C_{25}H_{22}NO$ 352.1696, found 352.1691 $[M+H]^+$.

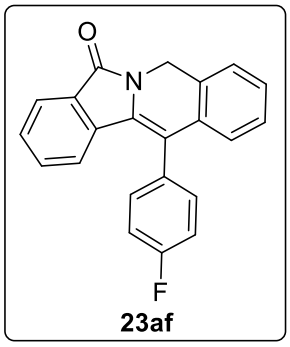
12-(4-(*t*-Butyl)phenyl)isoindolo[2,1-*b*]isoquinolin-7(5*H*)-one (23ae)



23ae

Yield 49%; Off-white solid, mp 258-260 °C; IR (nujol): ν 1689, 1519, 1458, 1111, 756, 694 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, *J* = 7.6 Hz, 1H), 7.60 (d, *J* = 8.3 Hz, 2H), 7.42 (td, *J* = 7.5, 0.7 Hz, 1H), 7.34 – 7.29 (m, 3H), 7.28 – 7.24 (m, 2H), 7.20 (td, *J* = 7.8, 1.5 Hz, 1H), 6.94 (d, *J* = 7.6 Hz, 1H), 6.40 (d, *J* = 7.9 Hz, 1H), 5.25 (s, 2H), 1.47 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.3, 151.7, 134.8, 132.8, 131.8, 131.1, 130.4, 130.1, 129.5, 129.1, 128.7, 128.0, 127.7, 126.5, 126.3, 126.1, 123.2, 122.8, 119.6, 43.1, 34.8, 31.5; HRMS (ESI/Q-TOF) calcd for $C_{26}H_{24}NO$ 366.1852, found 366.1848 $[M+H]^+$.

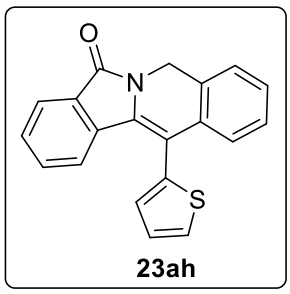
12-(4-Fluorophenyl)isoindolo[2,1-*b*]isoquinolin-7(5*H*)-one (23af)



23af

Yield 44%; Yellow solid, mp 202-204 °C; IR (nujol): ν 1689, 1512, 840, 779, 694 cm^{-1}; ^1H NMR (400 MHz, CDCl3) δ 7.92 (d, J = 7.6 Hz, 1H), 7.45 (td, J = 7.5, 0.8 Hz, 1H), 7.42 – 7.38 (m, 2H), 7.33 – 7.29 (m, 5H), 7.21 (td, J = 7.8, 1.8 Hz, 1H), 6.87 (d, J = 7.7 Hz, 1H), 6.43 (d, J = 7.9 Hz, 1H), 5.25 (s, 2H); 13C NMR (100 MHz, CDCl3) δ 166.3, 162.9 (d, *J* = 248.1 Hz), 134.6, 132.5, 132.4 (d, *J* = 8.0 Hz), 131.2, 130.9, 130.9, 129.6, 129.1, 129.0, 128.2, 127.8, 127.0, 126.7, 126.0, 123.0 (d, *J* = 3.6 Hz), 118.2, 116.5 (d, *J* = 21.4 Hz), 43.1; HRMS (ESI/Q-TOF) calcd for $C_{22}H_{15}FNO$ 328.1132, found 328.1128 $[M+H]^+$.

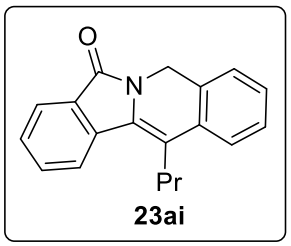
12-(Thiophen-2-yl)isoindolo[2,1-*b*]isoquinolin-7(5*H*)-one (23ah)



23ah

Yield 68%; Yellow solid, mp 251-253 °C; IR (nujol): ν 1689, 1519, 1458, 1111, 779, 694 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, *J* = 7.5 Hz, 1H), 7.63 (dd, *J* = 5.2, 1.0 Hz, 1H), 7.47 (t, *J* = 7.2 Hz, 1H), 7.36 (t, *J* = 7.6 Hz, 1H), 7.31 – 7.22 (m, 4H), 7.15 (dd, *J* = 3.4, 1.0 Hz, 1H), 7.10 (d, *J* = 7.4 Hz, 1H), 6.57 (d, *J* = 7.8 Hz, 1H), 5.23 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.4, 135.4, 134.4, 133.0, 132.8, 131.4, 129.5, 129.3, 129.2, 128.7, 128.1, 127.9, 127.8, 127.6, 126.5, 125.8, 123.4, 123.0, 111.3, 43.0; HRMS (ESI/Q-TOF) calcd for $C_{20}H_{14}NOS$ 316.0791, found 316.0787 $[M+H]^+$

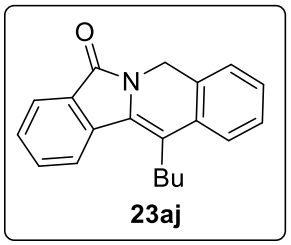
12-Propylisoindolo[2,1-*b*]isoquinolin-7(5*H*)-one (23ai)



23ai

Yield 93%; Yellow solid, mp 142-144 °C; IR (nujol): ν 1681, 1519, 1458, 1087, 817, 756, 694 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.99 (d, *J* = 7.5 Hz, 1H), 7.92 (d, *J* = 7.9 Hz, 1H), 7.66 (t, *J* = 7.5 Hz, 1H), 7.56 – 7.52 (m, 2H), 7.36 (t, *J* = 7.3 Hz, 1H), 7.32 – 7.26 (m, 2H), 5.11 (s, 2H), 3.02 (t, *J* = 8.12 Hz, 2H), 1.83 –1.74 (m, 2H), 1.19 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.8, 134.7, 131.7, 131.5, 130.1, 129.9, 129.9, 128.5, 128.0, 127.8, 126.8, 123.7, 123.4, 123.2, 119.5, 43.0, 28.8, 22.5, 14.4; HRMS (ESI/Q-TOF) calcd for $C_{19}H_{18}NO$ 276.1383, found 276. 1379 $[M+H]^+$.

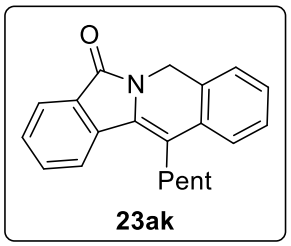
12-Butylisoindolo[2,1-*b*]isoquinolin-7(5*H*)-one (23aj)



23aj

Yield 70%; Yellow solid, mp 163-165 °C; IR (nujol): ν 1681, 1519, 1458, 1095, 763, 694 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.99 (d, *J* = 7.5 Hz, 1H), 7.95 (d, *J* = 7.9 Hz, 1H), 7.67 (t, *J* = 7.6 Hz, 1H), 7.57 – 7.53 (m, 2H), 7.39 – 7.29 (m, 3H), 5.12 (s, 2H), 3.06 (t, *J* = 8 Hz, 2H), 1.63 (m, 4H), 1.07 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.8, 134.7, 131.7, 131.5, 130.0, 129.9, 129.9, 128.5, 128.0, 127.8, 126.8, 123.7, 123.4, 123.2, 119.7, 43.0, 31.3, 26.6, 23.2, 14.0; HRMS (ESI/Q-TOF) calcd for $C_{20}H_{20}NO$ 290.1539, found 290.1535 $[M+H]^+$.

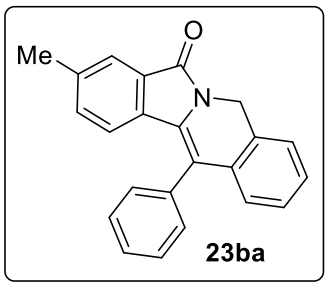
12-Pentylisoindolo[2,1-*b*]isoquinolin-7(5*H*)-one (23ak)



23ak

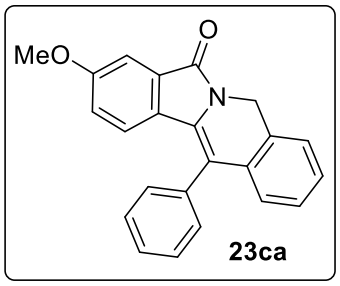
Yield 53%; Yellow solid, mp 91-93 °C; IR (nujol): ν 1681, 1519, 1465, 1288, 765, 694 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.99 (d, *J* = 7.5 Hz, 1H), 7.93 (d, *J* = 7.9 Hz, 1H), 7.66 (td, *J* = 7.8, 1.1 Hz, 1H), 7.57 – 7.52 (m, 2H), 7.37 (td, *J* = 7.9, 1.9 Hz, 1H), 7.33 – 7.29 (m, 2H), 5.12 (s, 2H), 3.04 (t, *J* = 8.2 Hz, 2H), 1.79 – 1.71 (m, 2H), 1.62 – 1.55 (m, 2H), 1.52 – 1.43 (m, 2H), 0.99 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.8, 134.7, 131.7, 131.6, 129.9, 129.9, 129.9, 128.5, 128.0, 127.8, 126.8, 123.7, 123.4, 123.2, 119.8, 43.0, 32.3, 28.9, 26.9, 22.6, 14.1; HRMS (ESI/Q-TOF) calcd for $C_{21}H_{22}NO$ 304.1696, found 304.1692 $[M+H]^+$.

9-Methyl-12-phenylisoindolo[2,1-*b*]isoquinolin-7(5*H*)-one (23ba)



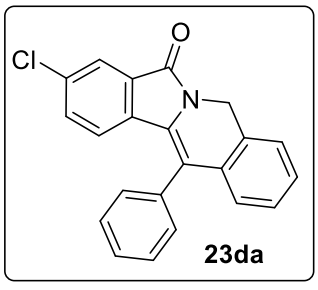
Yield 56%; Yellow solid, mp 242-244 °C; IR (nujol): ν 1689, 1519, 1489, 1365, 763, 702 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.70 (s, 1H), 7.60 – 7.56 (m, 3H), 7.42 – 7.39 (m, 2H), 7.31 – 7.24 (m, 2H), 7.18 (td, *J* = 7.8, 1.4 Hz, 1H), 7.07 (d, *J* = 8.8 Hz, 1H), 6.89 (d, *J* = 7.7 Hz, 1H), 6.27 (d, *J* = 8.0 Hz, 1H), 5.23 (s, 2H), 2.41 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.4, 139.3, 135.2, 132.7, 132.2, 130.6, 129.8, 129.3, 129.1, 128.5, 127.8, 127.7, 126.6, 126.0, 123.1, 123.0, 118.6, 43.1, 21.6; HRMS (ESI/Q-TOF) calcd for $C_{23}H_{18}NO$ 324.1383, found 324.1379 $[M+H]^+$.

9-Methoxy-12-phenylisoindolo[2,1-*b*]isoquinolin-7(5*H*)-one (23ca)



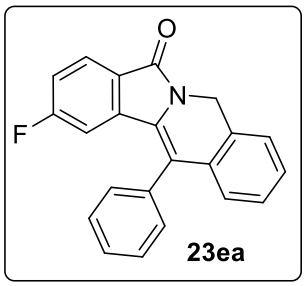
Yield 66%; Brown solid, mp 201-203 °C; IR (nujol): ν 1689, 1519, 1489, 1080, 833, 702 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.62 – 7.57 (m, 3H), 7.43 – 7.40 (m, 2H), 7.38 (d, *J* = 2.4 Hz, 1H), 7.31 (d, *J* = 6.8 Hz, 1H), 7.26 (dd, *J* = 7.4, 1.1 Hz, 1H), 7.19 (t, *J* = 7.5 Hz, 1H), 6.89 (d, *J* = 7.6 Hz, 1H), 6.81 (dd, *J* = 8.6, 2.5 Hz, 1H), 6.29 (d, *J* = 8.6 Hz, 1H), 5.24 (s, 2H), 3.87 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.2, 160.6, 135.2, 132.7, 131.3, 130.7, 130.3, 129.3, 128.9, 128.5, 127.7, 127.5, 126.5, 125.9, 124.4, 119.4, 118.1, 105.7, 55.7, 43.2; HRMS (ESI/Q-TOF) calcd for $C_{23}H_{18}NO_2$ 340.1332, found 340.1324 $[M+H]^+$.

9-Chloro-12-phenylisoindolo[2,1-*b*]isoquinolin-7(5*H*)-one (23da)



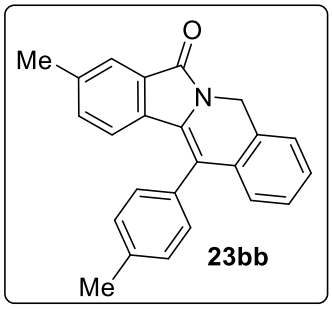
Yield 60%; Yellow solid, mp 254-256 °C; IR (nujol): ν 1697, 1543, 1519, 1365, 825, 725, 702 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, *J* = 1.7 Hz, 1H), 7.60 – 7.59 (m, 3H), 7.41 – 7.39 (m, 2H), 7.32 – 7.29 (m, 2H), 7.22 – 7.18 (m, 2H), 6.91 (d, *J* = 7.7 Hz, 1H), 6.28 (d, *J* = 8.4 Hz, 1H), 5.25 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.9, 135.0, 134.7, 132.8, 132.3, 131.3, 131.0, 130.4, 129.6, 129.4, 129.0, 128.8, 128.3, 127.8, 126.6, 126.4, 124.3, 123.0, 120.2, 43.2; HRMS (ESI/Q-TOF) calcd for $C_{22}H_{15}ClNO$ 344.0837, found 344.0831 $[M+H]^+$.

10-Fluoro-12-phenylisoindolo[2,1-*b*]isoquinolin-7(5*H*)-one (23ea)



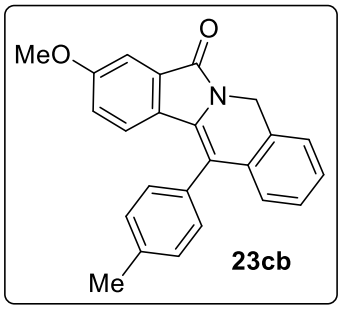
Yield 92%; Yellow solid, mp 228-230 °C; IR (nujol): ν 1689, 1519, 1458, 1365, 1157, 702, 648 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.88 (dd, *J* = 8.4, 5.1 Hz, 1H), 7.62 – 7.60 (m, 3H), 7.40 (dd, *J* = 6.5, 3.1 Hz, 2H), 7.32 – 7.29 (m, 2H), 7.22 – 7.18 (m, 1H), 7.12 (td, *J* = 8.7, 2.2 Hz, 1H), 6.91 (d, *J* = 7.7 Hz, 1H), 6.01 (dd, *J* = 9.3, 2.1 Hz, 1H), 5.25 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.3, 164.5 (d, *J* = 249.7 Hz), 136.8 (d, *J* = 11.0 Hz), 134.4, 132.3, 130.3, 129.7 (d, *J* = 3.9 Hz), 129.5, 129.2, 128.9, 128.4, 127.8, 126.5 (d, *J* = 21.9 Hz), 125.7 (d, *J* = 1.9 Hz), 124.8 (d, *J* = 10.0 Hz), 120.5, 116.5 (d, *J* = 24.2 Hz), 110.4, 110.1, 43.2; HRMS (ESI/Q-TOF) calcd for $C_{22}H_{15}FNO$ 328.1132, found 328.1126 $[M+H]^+$.

9-Methyl-12-(p-tolyl)isoindolo[2,1-*b*]isoquinolin-7(5*H*)-one (23bb)



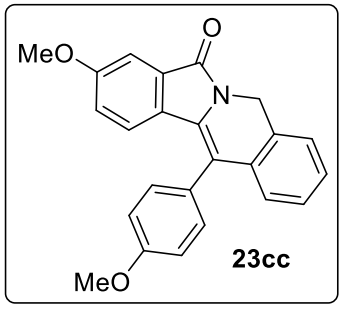
Yield 62%; Yellow solid, mp 253-255 °C; IR (nujol): ν 1689, 1519, 817, 763, 709 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.71 (s, 1H), 7.39 (d, *J* = 7.8 Hz, 2H), 7.30 – 7.28 (m, 3H), 7.26 – 7.24 (m, 1H), 7.18 (t, *J* = 7.5 Hz, 1H), 7.09 (d, *J* = 8.0 Hz, 1H), 6.92 (d, *J* = 7.7 Hz, 1H), 6.36 (d, *J* = 8.0 Hz, 1H), 5.23 (s, 2H), 2.54 (s, 3H), 2.42 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.4, 139.2, 138.2, 132.9, 132.3, 132.2, 132.0, 130.6, 130.4, 130.0, 129.8, 129.1, 127.7, 127.6, 126.5, 126.0, 123.1, 123.0, 118.7, 43.1, 21.6, 21.5; HRMS (ESI/Q-TOF) calcd for $C_{24}H_{20}NO$ 338.1539, found 338.1531 $[M+H]^+$.

9-Methoxy-12-(p-tolyl)isoindolo[2,1-*b*]isoquinolin-7(5*H*)-one (23cb)



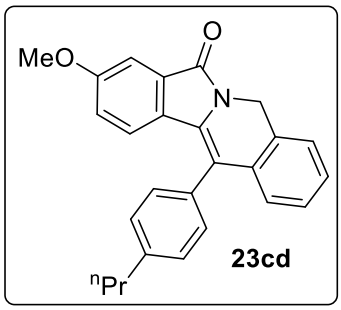
Yield 73%; Yellow solid, mp 212-214 °C; IR (nujol): ν 1689, 1489, 1365, 825, 771 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.37 (m, 3H), 7.30 – 7.28 (m, 3H), 7.25 (td, *J* = 7.4, 1.3 Hz, 1H), 7.18 (td, *J* = 7.9, 1.1 Hz, 1H), 6.91 (d, *J* = 7.7 Hz, 1H), 6.83 (dd, *J* = 8.6, 2.5 Hz, 1H), 6.37 (d, *J* = 8.7 Hz, 1H), 5.23 (s, 2H), 3.87 (s, 3H), 2.53 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.2, 160.6, 138.2, 132.9, 132.0, 131.3, 130.5, 130.3, 130.0, 128.9, 127.6, 127.6, 126.5, 125.9, 124.5, 119.3, 118.1, 105.6, 55.7, 43.2, 21.5; HRMS (ESI/Q-TOF) calcd for $C_{24}H_{20}NO_2$ 354.1489, found 354.1481 $[M+H]^+$.

9-Methoxy-12-(4-methoxyphenyl)isoindolo[2,1-*b*]isoquinolin-7(5*H*)-one (23cc) Yield 45%;



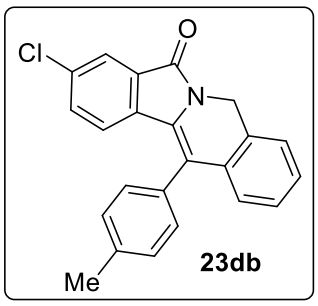
Yellow solid, mp 197-199 °C; IR (nujol): ν 1681, 1512, 1489, 1242, 1026, 771, 725 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.38 (d, *J* = 2.4 Hz, 1H), 7.33 – 7.30 (m, 2H), 7.25 (td, *J* = 7.3, 1.2 Hz, 1H), 7.19 (t, *J* = 7.8 Hz, 1H), 7.13 – 7.10 (m, 2H), 6.93 (d, *J* = 7.5 Hz, 1H), 6.84 (dd, *J* = 8.6, 2.5 Hz, 1H), 6.40 (d, *J* = 8.6 Hz, 1H), 5.22 (s, 2H), 3.96 (s, 3H), 3.87 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.2, 160.6, 159.7, 133.0, 131.8, 131.3, 130.5, 128.9, 127.6, 127.6, 127.1, 126.5, 125.9, 124.5, 119.4, 117.8, 114.7, 105.6, 55.7, 55.4, 43.2; HRMS (ESI/Q-TOF) calcd for $C_{24}H_{20}NO_3$ 370.1438, found 370.1431 $[M+H]^+$.

9-Methoxy-12-(4-propylphenyl)isoindolo[2,1-*b*]isoquinolin-7(5*H*)-one (23cd)



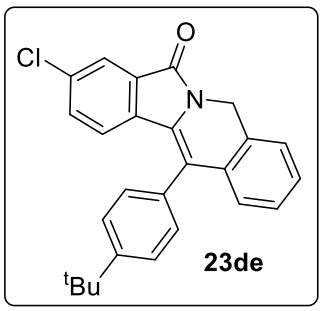
Yield 44%; Yellow solid, mp 147-149 °C; IR (nujol): ν 1705, 1519, 1489, 1080, 825, 771 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.40 (s, 1H), 7.38 – 7.37 (m, 2H), 7.30 (d, *J* = 8.1 Hz, 3H), 7.25 (td, *J* = 7.4, 1.2 Hz, 1H), 7.19 (t, *J* = 7.5 Hz, 1H), 6.93 (d, *J* = 7.6 Hz, 1H), 6.81 (dd, *J* = 8.6, 2.5 Hz, 1H), 6.32 (d, *J* = 8.6 Hz, 1H), 5.23 (s, 2H), 3.86 (s, 3H), 2.78 – 2.75 (m, 2H), 1.85 – 1.75 (m, 2H), 1.06 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.2, 160.6, 143.0, 132.9, 132.3, 131.3, 130.4, 130.3, 129.3, 128.9, 127.6, 127.6, 126.5, 126.0, 124.4, 119.3, 118.2, 105.6, 55.7, 43.2, 37.9, 24.5, 13.8; HRMS (ESI/Q-TOF) calcd for $C_{26}H_{24}NO_2$ 382.1802, found 382.1792 $[M+H]^+$.

9-Chloro-12-(p-tolyl)isoindolo[2,1-*b*]isoquinolin-7(5*H*)-one (23db)



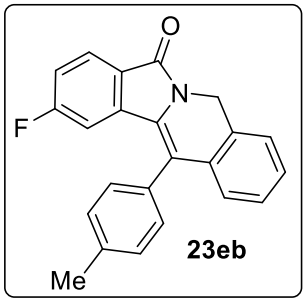
Yield 45%; Yellow solid, mp 236-238 °C; IR (nujol): ν 1697, 1519, 1458, 1365, 825, 709 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, *J* = 1.7 Hz, 1H), 7.40 (d, *J* = 7.8 Hz, 2H), 7.30 – 7.28 (m, 4H), 7.24 – 7.17 (m, 2H), 6.93 (d, *J* = 7.7 Hz, 1H), 6.37 (d, *J* = 8.4 Hz, 1H), 5.24 (s, 2H), 2.54 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.9, 138.6, 134.9, 132.9, 132.4, 131.5, 131.2, 131.0, 130.2, 130.1, 129.6, 129.1, 128.3, 127.8, 126.6, 126.4, 124.4, 123.0, 120.3, 43.2, 21.5; HRMS (ESI/Q-TOF) calcd for $C_{23}H_{17}ClNO$ 358.0993, found 358.0985 $[M+H]^+$.

12-(4-(*t*-Butyl)phenyl)-9-chloroisoindolo[2,1-*b*]isoquinolin-7(5*H*)-one (23de)



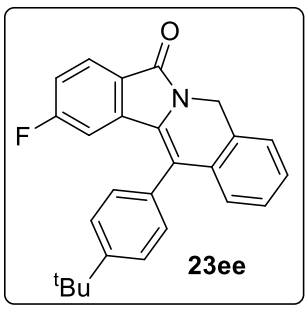
Yield 41%; Yellow solid, mp 252-254 °C; IR (nujol): ν 1697, 1543, 1519, 1458, 1064, 825, 771, 725 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, *J* = 1.7 Hz, 1H), 7.61 – 7.59 (m, 2H), 7.33 – 7.29 (m, 4H), 7.24 – 7.21 (m, 2H), 6.96 (d, *J* = 7.6 Hz, 1H), 6.29 (d, *J* = 8.4 Hz, 1H), 5.25 (s, 2H), 1.47 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.9, 151.9, 134.9, 132.9, 132.4, 131.5, 131.3, 131.0, 130.0, 129.6, 129.1, 128.3, 127.8, 126.6, 126.5, 126.2, 124.3, 122.9, 120.3, 43.2, 34.9, 31.5; HRMS (ESI/Q-TOF) calcd for $C_{26}H_{23}ClNO$ 400.1463, found 400.1448 $[M+H]^+$.

10-Fluoro-12-(*p*-Tolyl)isoindolo[2,1-*b*]isoquinolin-7(5*H*)-one (23eb)



Yield 94%; Yellow solid, mp 287-289 °C; IR (nujol): ν 1689, 1512, 1458, 1265, 1072, 763, 702, 640 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.87 (dd, *J* = 8.3, 5.1 Hz, 1H), 7.42 (d, *J* = 7.8 Hz, 2H), 7.32 – 7.29 (m, 4H), 7.22 – 7.18 (m, 1H), 7.11 (td, *J* = 8.8, 2.2 Hz, 1H), 6.93 (d, *J* = 7.7 Hz, 1H), 6.11 (dd, *J* = 9.3, 2.1 Hz, 1H), 5.23 (s, 2H), 2.54 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.3, 164.5 (d, *J* = 249.4 Hz), 138.7, 136.8 (d, *J* = 11.0 Hz), 132.4, 131.3, 130.2, 130.1, 129.6 (d, *J* = 3.9 Hz), 129.2, 128.3, 127.8, 126.6, 126.5, 125.7 (d, *J* = 1.8 Hz), 124.8 (d, *J* = 10.1 Hz), 120.6, 116.4 (d, *J* = 24.2 Hz), 110.3 (d, *J* = 26.0 Hz), 43.2, 21.5; HRMS (ESI/Q-TOF) calcd for $C_{23}H_{17}FNO$ 342.1289, found 342.1282 $[M+H]^+$.

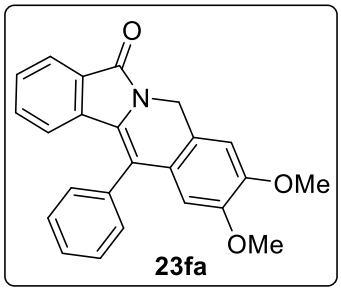
12-(4-(*t*-Butyl)phenyl)-10-fluoroisoindolo[2,1-*b*]isoquinolin-7(5*H*)-one (23ee)



Yield 49%; Yellow solid, mp 269-271 °C; IR (nujol): ν 1689, 1458, 1396, 1157, 763, 725, 702 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.87 (dd, *J* = 8.4, 5.1 Hz, 1H), 7.62 (d, *J* = 8.3 Hz, 2H), 7.33 – 7.29 (m, 4H), 7.23 – 7.19 (m, 1H), 7.11 (td, *J* = 8.7, 2.2 Hz, 1H), 6.97 (d, *J* = 7.6 Hz, 1H), 5.96 (dd, *J* = 9.4, 2.2 Hz, 1H), 5.24 (s, 2H), 1.47 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.4, 164.4 (d, *J* = 249.5 Hz), 152.1, 136.8 (d, *J* = 11.1 Hz), 132.4, 131.9, 129.9, 129.7 (d, *J* = 3.9 Hz), 129.2, 128.3, 127.8, 126.6,

126.5, 126.3, 125.6 (d, J = 1.8 Hz), 124.7 (d, J = 10.0 Hz), 120.7, 116.4 (d, J = 24.2 Hz), 110.3 (d, J = 26.3 Hz), 43.2, 34.9, 31.4; HRMS (ESI/Q-TOF) calcd for C26H23FNO 384.1758, found 384.1744 $[M+H]^+$.

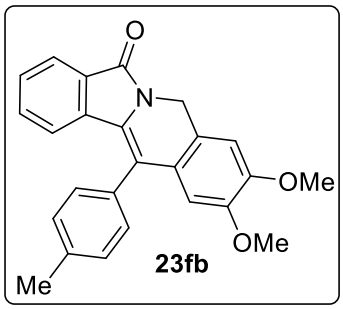
2,3-Dimethoxy-12-phenylisoindolo[2,1-*b*]isoquinolin-7(5*H*)-one (23fa)



23fa

Yield 80%; Yellow solid, mp 225-227 °C; IR (nujol): ν 1631, 1512, 1458, 1342, 732, 702 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, J = 7.6 Hz, 1H), 7.61 – 7.59 (m, 3H), 7.44 – 7.38 (m, 3H), 7.24 (t, J = 7.08 Hz, 1H), 6.83 (s, 1H), 6.41 (s, 1H), 6.38 (d, J = 7.9 Hz, 1H), 5.20 (s, 2H), 3.96 (s, 3H), 3.66 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.3, 149.2, 148.2, 135.2, 134.7, 131.0, 130.5, 129.3, 129.2, 128.9, 128.6, 128.4, 125.4, 122.8, 122.8, 122.2, 119.6, 109.7, 109.5, 56.2, 55.9, 43.0; HRMS (ESI/Q-TOF) calcd for $C_{24}H_{20}NO_3$ 370.1438, found 370.1429 $[M+H]^+$.

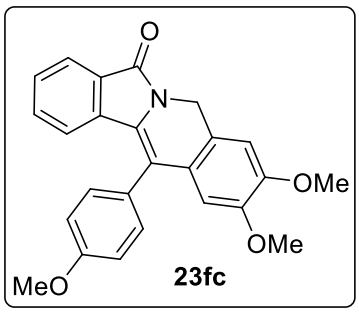
2,3-Dimethoxy-12-(*p*-tolyl)isoindolo[2,1-*b*]isoquinolin-7(5*H*)-one (23fb)



23fb

Yield 87%; Yellow solid, mp 209-211 °C; IR (nujol): ν 1681, 1512, 1458, 1342, 1103, 763, 696 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, J = 7.6 Hz, 1H), 7.41 – 7.38 (m, 3H), 7.30 (d, J = 8.0 Hz, 2H), 7.28 – 7.24 (m, 1H), 6.82 (s, 1H), 6.47 – 6.44 (m, 2H), 5.18 (s, 2H), 3.95 (s, 3H), 3.68 (s, 3H), 2.54 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.2, 149.1, 148.2, 138.3, 134.8, 132.0, 130.9, 130.2, 130.0, 129.2, 128.9, 128.3, 125.6, 122.9, 122.8, 122.3, 119.6, 109.7, 109.7, 56.2, 56.0, 43.0, 21.5; HRMS (ESI/Q-TOF) calcd for $C_{25}H_{22}NO_3$ 384.1594, found 384.1585 $[M+H]^+$.

2,3-Dimethoxy-12-(4-methoxyphenyl)isoindolo[2,1-*b*]isoquinolin-7(5*H*)-one (23fc)

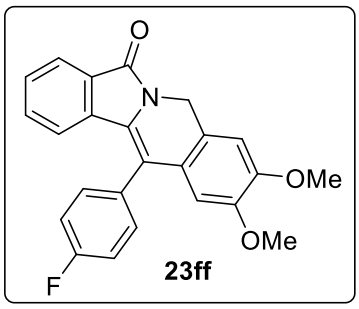


23fc

Yield 63%; Yellow solid, mp 216-218 °C; IR (nujol): ν 1681, 1512, 1450, 1350, 1103, 771, 725, 696 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, J = 7.5 Hz, 1H), 7.40 (t, J = 7.3 Hz, 1H), 7.34 (d, J = 8.6 Hz, 2H), 7.29 – 7.25 (m, 1H), 7.13 (d, J = 8.6 Hz, 2H), 6.82 (s, 1H), 6.48 (d, J = 7.9 Hz, 1H), 6.46 (s, 1H), 5.18 (s, 2H), 3.97 (s, 3H), 3.95 (s, 3H), 3.69 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ

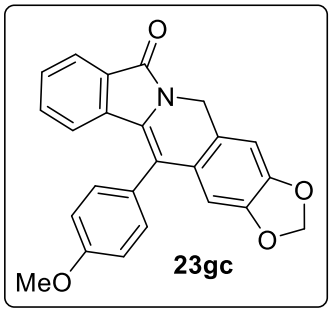
166.2, 159.7, 149.1, 148.2, 134.8, 131.6, 130.9, 129.2, 129.1, 128.3, 127.1, 125.7, 122.9, 122.8, 122.2, 119.3, 114.7, 109.7, 109.6, 56.2, 56.0, 55.4, 43.0; HRMS (ESI/Q-TOF) calcd for C25H22NO4 400.1543, found 400.1531 $[M+H]^+$.

12-(4-Fluorophenyl)-2,3-dimethoxyisoindolo[2,1-*b*]isoquinolin-7(5*H*)-one (23ff)



Yield 72%; Yellow solid, mp 229-231 °C; IR (nujol): ν 1681, 1512, 1458, 1350, 1219, 1103, 763, 696 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, *J* = 7.6 Hz, 1H), 7.44 – 7.40 (m, 3H), 7.34 – 7.28 (m, 3H), 6.83 (s, 1H), 6.41 (d, *J* = 7.9 Hz, 1H), 6.36 (s, 1H), 5.19 (s, 2H), 3.96 (s, 3H), 3.68 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.2, δ 162.9 (d, *J* = 248.3 Hz), 149.3, 148.3, 134.5, δ 132.3 (d, *J* = 8.0 Hz), 131.13, 131.10, 131.0, 129.3, 128.6, 125.3, 123.0, 122.6, 122.2, 118.3, 116.51 (d, *J* = 21.4 Hz), 109.8, 109.3, 56.2, 55.9, 43.0; HRMS (ESI/Q-TOF) calcd for C24H19FNO3 388.1343, found 388.1330 $[M+H]^+$.

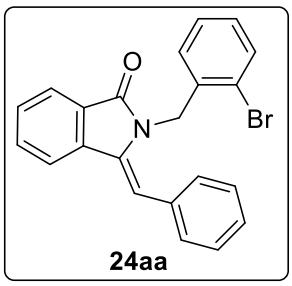
12-(4-Methoxyphenyl)-[1,3]dioxolo[4,5-*g*]isoindolo[2,1-*b*]isoquinolin-7(5*H*)-one (23gc)



Yield 41%; Brown solid, mp 114-116 °C; IR (nujol): ν 1689, 1504, 1458, 1242, 1026, 833, 725 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, *J* = 7.4 Hz, 1H), 7.41 (t, *J* = 7.5 Hz, 1H), 7.30 (d, *J* = 8.8 Hz, 3H), 7.12 (d, *J* = 8.4 Hz, 2H), 6.81 (s, 1H), 6.47 (d, *J* = 7.9 Hz, 1H), 6.43 (s, 1H), 5.97 (s, 2H), 5.16 (s, 2H), 3.97 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.2, 159.8, 147.5, 147.2, 134.7, 131.6, 131.0, 129.3, 129.2, 128.4, 127.2, 127.1, 123.6, 122.9, 122.8, 119.3, 114.8, 107.1, 106.5, 101.5, 55.4, 43.3; HRMS (ESI/Q-TOF) calcd for $C_{24}H_{18}NO_4$ 384.1230, found 384.1219 $[M+H]^+$.

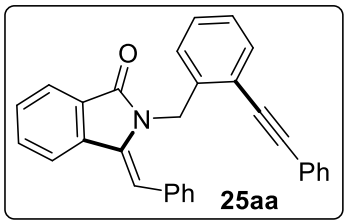
Intermediates

(Z)-3-Benzylidene-2-(2-bromobenzyl)isoindolin-1-one (24aa)



Yield 77%; White solid, mp 158-160 °C; IR (nujol): ν 1705, 1342, 1111, 948, 748, 694, 624 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, *J* = 7.6 Hz, 1H), 7.83 (d, *J* = 7.8 Hz, 1H), 7.70 (td, *J* = 7.6, 1.1 Hz, 1H), 7.59 (td, *J* = 7.5, 0.8 Hz, 1H), 7.36 (dd, *J* = 7.9, 1.1 Hz, 1H), 7.24 – 7.20 (m, 1H), 7.17 (td, *J* = 7.6, 1.1 Hz, 1H), 7.12 (t, *J* = 7.6 Hz, 2H), 7.05 (td, *J* = 7.9, 1.6 Hz, 1H), 6.93 (dd, *J* = 8.1, 1.0 Hz, 2H), 6.83 (s, 1H), 6.77 – 6.75 (m, 1H), 4.84 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.6, 138.2, 135.6, 134.3, 133.7, 132.3, 132.2, 129.2, 128.7, 128.1, 128.0, 127.9, 127.5, 127.1, 126.5, 123.6, 122.2, 119.6, 107.8, 45.8; HRMS (ESI/Q-TOF) calcd for C22H17BrNO 390.0488, found 390.0487 $[M+H]^+$.

(Z)-3-benzylidene-2-(2-(phenylethynyl)benzyl)isoindolin-1-one (25aa)



Yield 4%; Off-white solid, mp 109-111 °C; IR (nujol): ν 1697, 1489, 1334, 1103, 956, 756, 694 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, *J* = 7.5 Hz, 1H), 7.82 (d, *J* = 7.8 Hz, 1H), 7.68 (td, *J* = 7.6, 1.1 Hz, 1H), 7.56 (td, *J* = 7.5, 0.8 Hz, 1H), 7.42 – 7.39 (m, 2H), 7.38 – 7.34 (m, 3H), 7.34 – 7.30 (m, 1H), 7.19 – 7.14 (m, 3H), 7.09 (t, *J* = 7.4 Hz, 2H), 6.97 – 6.93 (m, 2H), 6.81 (s, 1H), 6.74 – 6.70 (m, 1H), 5.10 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.8, 138.4, 138.2, 134.4, 134.0, 132.1, 131.8, 131.4, 129.1, 128.8, 128.2, 128.2, 128.1, 128.1, 127.9, 127.4, 126.4, 124.9, 123.6, 123.3, 121.0, 119.5, 107.8, 94.6, 86.5, 44.3; HRMS (ESI/Q-TOF) calcd for $C_{30}H_{22}NO$ 412.1696, found 412.1698 $[M+H]^+$.

X-ray crystallographic data of compound **23aa, 24aa and 25aa** is as follows

Table 4.4 Crystal data and structure refinement for 23aa, 24aa and 25aa

Empirical formula	$C_{22}H_{15}NO$	$C_{22}H_{16}BrNO$	$C_{30}H_{21}NO$
Formula weight	309.35	390.27	411.48
Temperature/K	93(2)	93(2)	93(2)
Crystal system	monoclinic	triclinic	monoclinic
Space group	$P2_1/c$	P-1	$P2_1/c$
a/Å	10.6454(10)	8.7437(4)	14.9969(4)
b/Å	15.8564(11)	9.0981(5)	14.8584(3)
c/Å	9.6081(10)	11.3532(6)	10.6249(3)

α/°	90	89.931(4)	90
β/°	112.912(12)	69.876(5)	110.575(3)
γ/°	90	83.515(4)	90
Volume/Å^3	1493.9(3)	841.91(8)	2216.53(11)
Z	4	2	4
ρ_{calc}g/cm^3	1.375	1.539	1.233
μ/mm^{-1}	0.084	2.450	0.575
F(000)	648.0	396.0	864.0
Crystal size/mm^3	0.5 × 0.5 × 0.3	0.11 × 0.08 × 0.06	0.1 × 0.1 × 0.06
Radiation	MoKα (λ = 0.71073)	MoKα (λ = 0.71073)	CuKα (λ = 1.54184)
2Θ range for data collection/°	10.05 to 57.916	7.124 to 59.814	8.664 to 148.818
Index ranges	-11 ≤ h ≤ 14, -18 ≤ k ≤ 21, -12 ≤ l ≤ 12	-12 ≤ h ≤ 10, -12 ≤ k ≤ 11, -15 ≤ l ≤ 15	-13 ≤ h ≤ 18, -12 ≤ k ≤ 18, -12 ≤ l ≤ 12
Reflections collected	10300	12080	7754
Independent reflections	3477 [R_{int} = 0.0492, R_{sigma} = 0.0255]	4229 [R_{int} = 0.0664, R_{sigma} = 0.0706]	3961 [R_{int} = 0.0186, R_{sigma} = 0.0195]
Data/restraints/parameters	3477/0/217	4229/0/226	3961/0/290
Goodness-of-fit on F^2	1.058	0.989	1.024
Final R indexes [I>=2σ (I)]	R_1 = 0.0855, wR_2 = 0.2156	R_1 = 0.0469, wR_2 = 0.0969	R_1 = 0.0379, wR_2 = 0.0994
Final R indexes [all data]	R_1 = 0.0885, wR_2 = 0.2174	R_1 = 0.0723, wR_2 = 0.1055	R_1 = 0.0395, wR_2 = 0.1006
Largest diff. peak/hole / e Å^{-3}	1.60/-0.40	0.91/-0.56	0.43/-0.17

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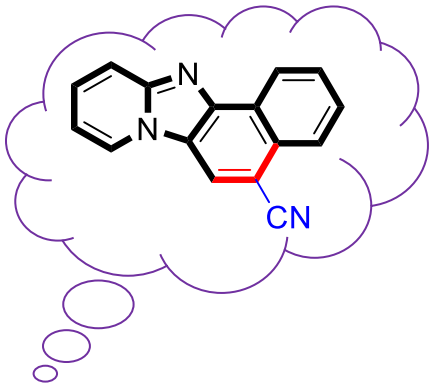
Chapter 5

Synthesis of Naphtho-Fused Imidazo[1,2-*a*]pyridines *via* Copper Catalyzed Alkene Arylation



5.1 Introduction

Imidazo[1,2-*a*]pyridine is an important heterocyclic motif that became widespread in various fields of science including medicinal chemistry and material science.[1-4] Molecules with this moiety have shown wide range of biological properties such as antimicrobial, anticancer, analgesic, antiepileptic, antiulcer and antituberculosis.[5-16] Several marketed drug formulations such as zolpidem (used to treat insomnia & brain disorders), saripidem, alpidem and necopidem (possessing sedative and anxiolytic effects), zolimidine (used for treatment of peptic ulcers), miroprofen (analgesic), and optically active GSK812397 (a candidate for treatment of HIV infection) possess this structural moiety (**Figure 5.1**). Imidazo[1,2-*a*]pyridines are also of interest in the field of optoelectronics. Compounds with imidazo[1,2-*a*]pyridine moiety are reported to exhibit excited state intramolecular proton transfer (ESIPT) (**Figure 5.1**).[17-19] The utility of imidazo[1,2-*a*]pyridines in different areas has motivated significant research efforts towards synthesis and functionalization of these scaffolds in the last one decade.[20-23]

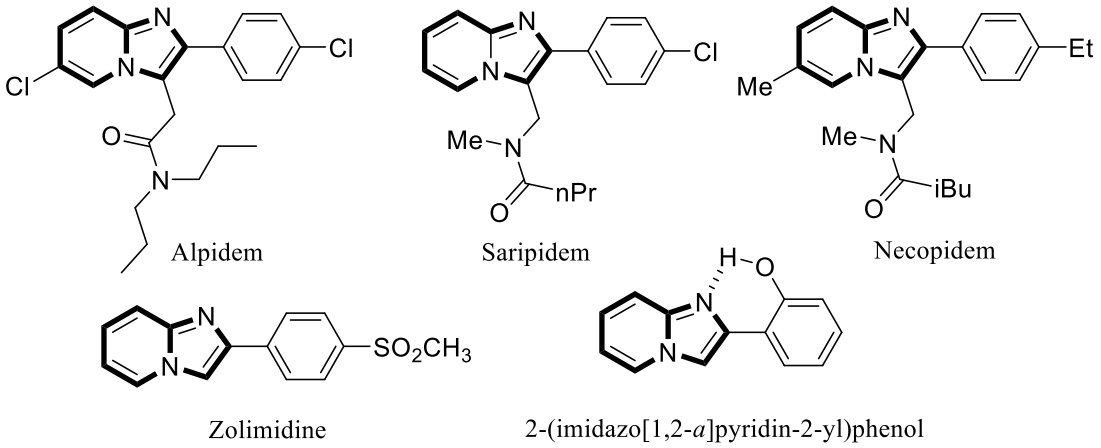
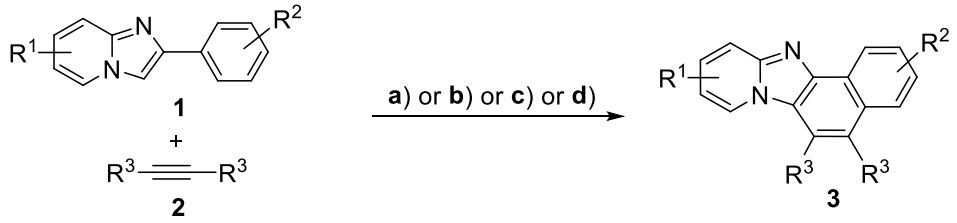


Figure 5.1 Representative Imidazo[1,2-*a*]pyridines based structures

In recent years, synthesis of extended π-conjugated systems has received considerable attention owing to their potential applications as organic electronic and optical materials.[24] Transition metal catalyzed arylation reactions have received increasing attention as a powerful strategy to construct these extended π-systems.[25-27] In 2015, four conseutive reports appeared *via* Rh-catalyzed oxidative annulation of 2-arylimidazo[1,2-*a*]pyridines (**1**) with alkynes (**2**) to give naphtho-fused imidazo[1,2-*a*]pyridines (**3**) (**Scheme 5.1**).[28-31] The disclosed Rh-catalyzed 2-fold C-H activation occured successfully under oxidizing condition where first Rh (III)-activates C-H bond *via* chelation through nitrogen followed by rollover C-H activation. These approaches

provide straightforward route to functionalized polycyclic imidazopyridines in good to excellent yields.

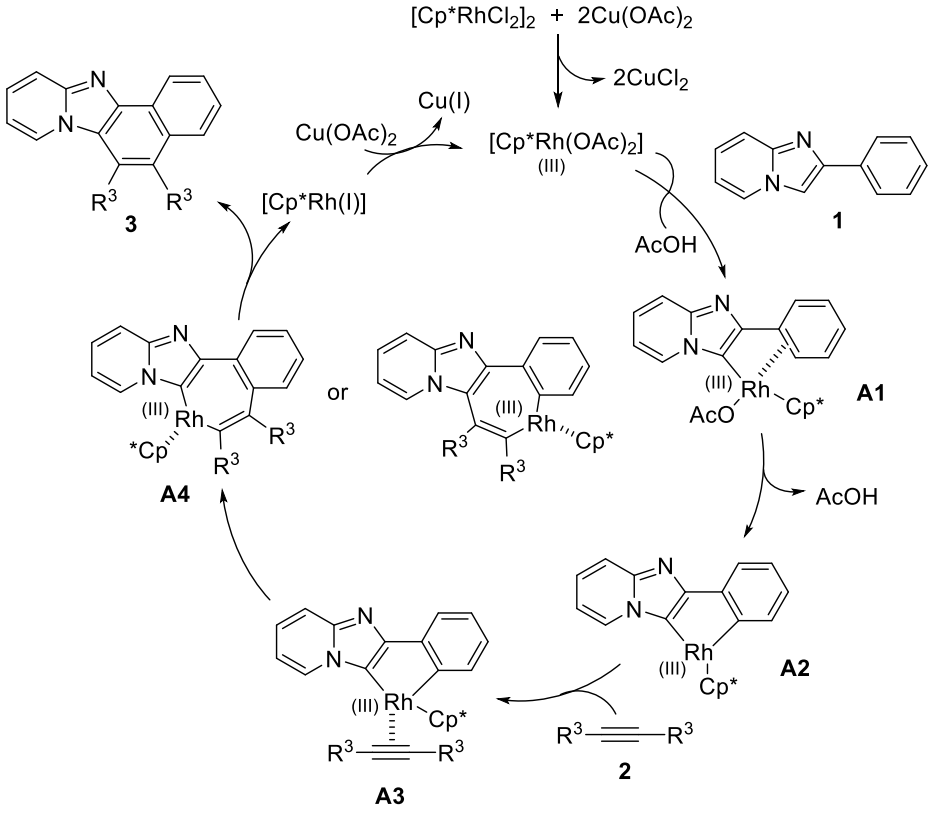


$R^1 = R^2$ = Alkyl, -F, -Cl, -Br, $-NO_2$

R^3 = Aryl

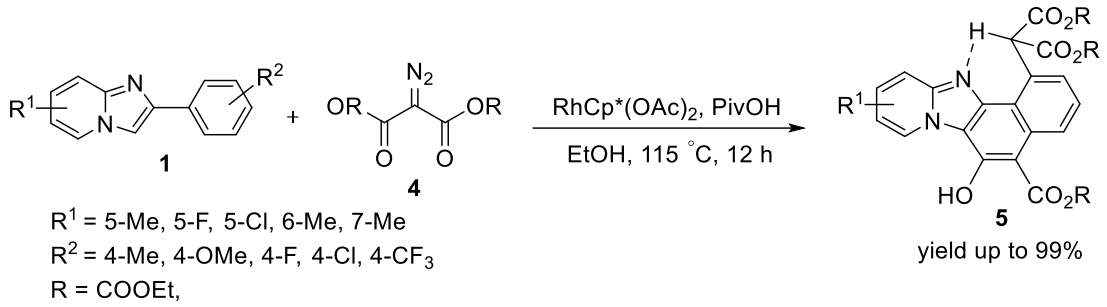
a) $[RhCp^*Cl_2]_2/AgSbF_6$, AgOAc, DCE, 100 °C; **b**) $[Cp^*Rh(CH_3CN)_3]$-$(SbF_6)_2$,$Cu(OAc)_2$, toluene,110 °C

c) $[RhCp^*Cl_2]_2/Co(OAc)_2.4H_2O$, DMF,110 °C, Air; **d**) $[RhCp^*Cl_2]_2$,Cs_2CO_3, $Cu(OAc)_2.H_2O$,toluene, 125 °C



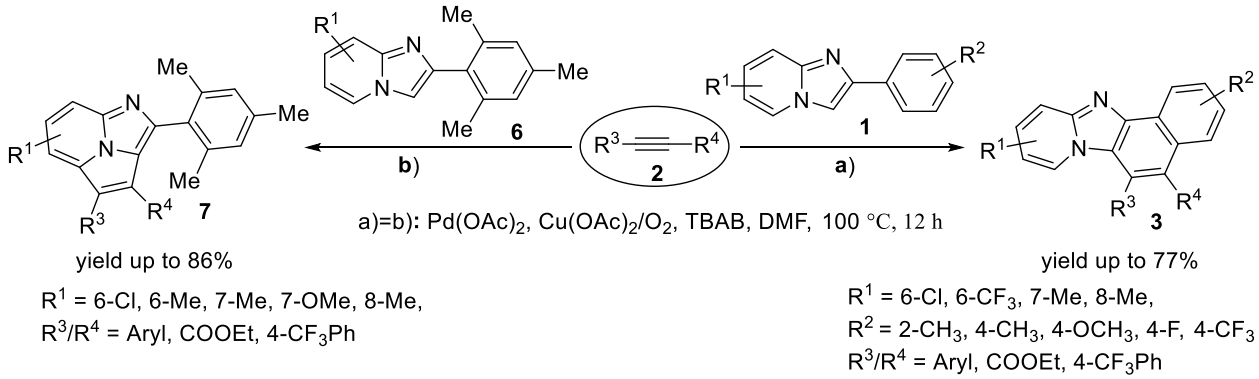
Scheme 5.1 Rh-catalysed synthesis of naphtho-fused imidazo[1,2-*a*]pyridines

The method was further improved by Yunyun Li and co-workers who described the reaction between 2-phenylimidazo[1,2-*a*]pyridines (**1**) and activated α-diazo esters (**4**) *via* rhodium (III) catalyzed carbocyclization process. The reaction involved C-H activation and dialkylation of arene followed by intramolecular nucleophilic substitution to afford polycyclic imidazopyridines (**5**) (**Scheme 5.2**).[32]



Scheme 5.2 Synthesis of functionalized naphtho-fused imidazo[1,2-*a*]pyridines using 2-phenylimidazo [1,2-*a*]pyridine and α-diazo esters

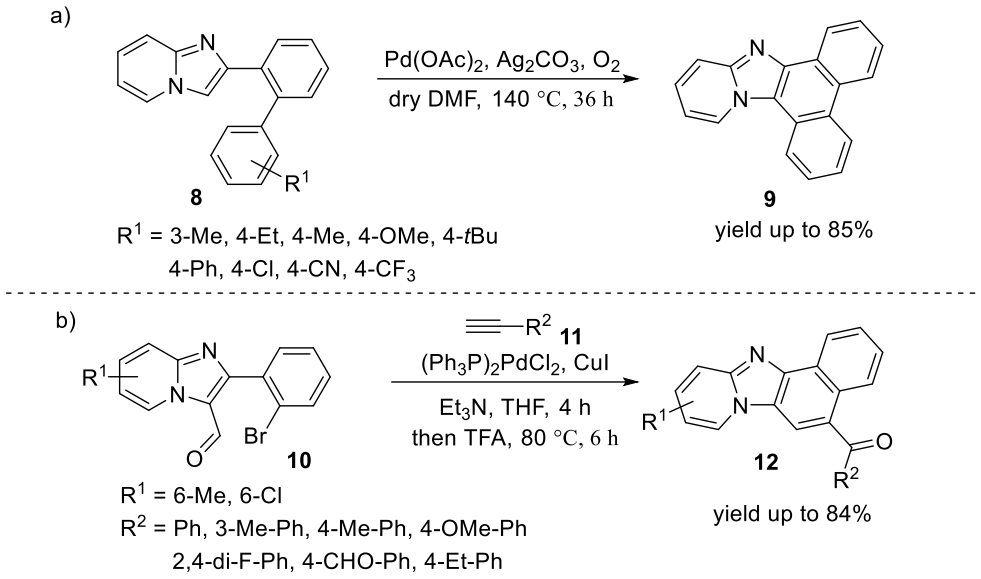
It has always been challenge how existing methods could be improved by comparatively mild reaction condition. In this regard, Pd-catalyzed synthesis of polycyclic imidzopyridines have been disclosed by different research groups through C-H bond functionalization. Li and group described a palladium catalyzed oxidative cycloaromatization to improve abovementioned Rh-catalyzed synthesis (**Scheme 5.3**).[33-34] Interestingly, naphtho[1′,2′:4,5]imidazo[1,2-a]-pyridines (**3**) in **path a** were obtained from 2-phenylimidazo [1,2-*a*]pyridine (**1**) with alkynes (**2**) whereas imidazo[5,1,2-*cd*]indolizine (**7**) **path b** were obtained from 2-mesitylimidazo[1,2-*a*]pyridine (**6**) with alkynes (**2**) using Pd-catalyzed dehydroginative annulations with diarylalkynes *via* cleavage of C-H bonds.



Scheme 5.3 Pd-Catalyzed synthesis of polycyclic imidzopyridines

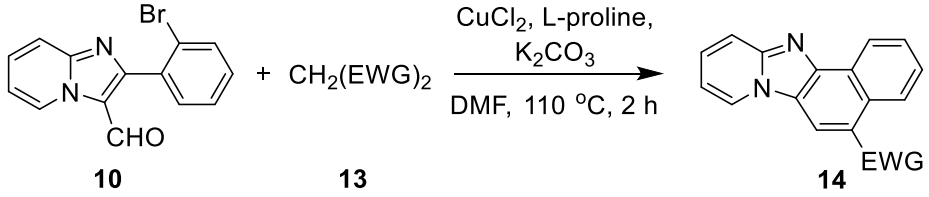
Later on, several other Pd-catalyzed approaches appeared on imidazo[1,2-*a*]pyridines which comprising direct arylation[35] (**Scheme 5.4a**), sequential Sonogashira coupling followed by trifluoroacetic acid promoted alkyne-carbonyl metathesis[36] (ACM) to achive imidazo[1,2-*a*]pyridines-fused heteropolynuclear framework (**Scheme 5.4b**). Access of these *N*-fused

heterocyles through above mentioned distinct approach (Direct arylation, ACM) has been easy and convenient and compatible with wide range of functional group tolerance.



Scheme 5.4 Routes to access polycyclic imidzo-pyridines via direct arylation and alkyne-carbonyl metathesis

Apart from these synthetic analogues, Several π-expanded heterocycles have been synthesized using Rh[37] and Pd-catalyzed[38] reactions. However, there is much interest in the development of Cu-catalyzed cascade reactions for the synthesis of structurally diversified π-expanded heterocycles in one pot because of the convenience, low cost, and high efficiency.[39-43] With the advent of interest in π-expanded heterocyclic compounds, we, therefore envisioned in this chapter a simple and straightforward synthesis of naphtho-fused imidazo[1,2-*a*]pyridines (**14**) (**Scheme 5.5**) which can offer new opportunities to develop materials for future optoelectronic applications.



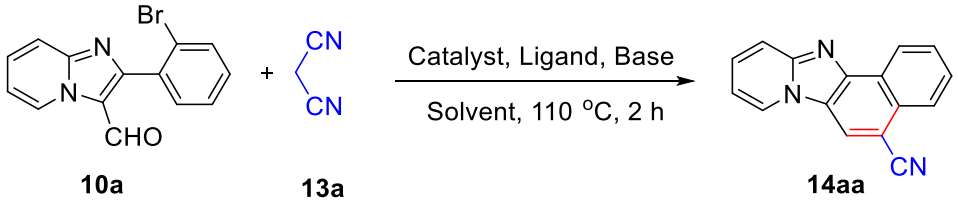
Scheme 5.5 Synthesis of naphtho-fused imidazo[1,2-*a*]pyridines

5.2 Results and discussion

Our initial study commenced with the reaction of 2-(2-bromophenyl)imidazo[1,2-*a*]pyridine-3-carbaldehydes (**10a**) with malononitrile (**13a**) in the presence of CuI (10 mol %), L-proline (20 mol %) and K_2CO_3 (2 eq.) in DMF at 110 °C. After continuing the reaction for 2 h, a new product was observed which was isolated in a 80% yield and characterized as 5-cyanonaphtho[1',2':4,5]imidazo[1,2-*a*]pyridines (**14aa**).

Encouraged by this result, we further attempted to optimize the reaction conditions for the synthesis of **14aa** by varying the catalyst, ligand, base and solvent. The results for the optimization reactions are summarized in table 5.1. Among different copper catalysts screened, $CuCl_2$ was found to be the most effective for this tandem reaction to give **14aa** in a 91% yield (entries 1-4, table 5.1). Among inorganic bases, KOH, *t*-BuOK, K_2CO_3 and Cs_2CO_3 were tested at 110 °C in DMF, K_2CO_3 provided the highest yield of **14aa** (entry 4, table 5.1). Organic bases such as DBU, DABCO and Et_3N were not effective (entries 11-13, table 5.1). It is worth mentioning that **14aa** was not obtained when reaction was performed in the absence of base (entry 7, table 5.1). This suggests that base has a crucial role in this transformation. Screening of different solvents such as DMSO, DMF, CH_3CN and toluene revealed that the reaction is favoured in polar aprotic solvents. Maximum yield of **14aa** was obtained in DMF, whereas good to moderate yield was obtained in DMSO and CH_3CN (entries 14-15, table 5.1). In toluene no product was obtained (entry 16, table 5.1).

Table 5.1 Optimization of the reaction conditions[a]



10a **13a** **14aa**

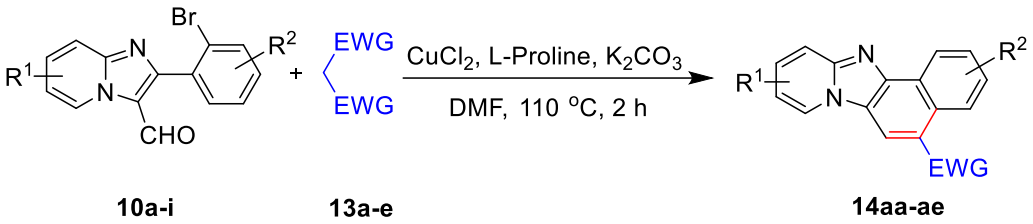
Entry	Catalyst	Ligand	Base	Solvent	Yield (%)[b]
1	CuI	*L*-proline	K_2CO_3	DMF	80
2	CuBr	*L*-proline	K_2CO_3	DMF	82
3	$Cu(OTf)_2$	*L*-proline	K_2CO_3	DMF	65
4	$CuCl_2$	*L*-proline	K_2CO_3	DMF	91
5	$CuCl_2$	-[c]	K_2CO_3	DMF	38

6	$CuCl_2$	1,10-Phen	K_2CO_3	DMF	25
7	$CuCl_2$	*L*-proline	-[d]	DMF	-[e]
8	$CuCl_2$	*L*-proline	KOH	DMF	84
9	$CuCl_2$	*L*-proline	KOBu-*t*	DMF	70
10	$CuCl_2$	*L*-proline	Cs_2CO_3	DMF	65
11	$CuCl_2$	*L*-proline	DBU	DMF	-[e]
12	$CuCl_2$	*L*-proline	DABCO	DMF	-[e]
13	$CuCl_2$	*L*-proline	$N(C_2H_5)_3$	DMF	-[e]
14	$CuCl_2$	*L*-proline	K_2CO_3	DMSO	83
15	$CuCl_2$	*L*-proline	K_2CO_3	CH_3CN	48
16	$CuCl_2$	*L*-proline	K_2CO_3	Toluene	-[e]

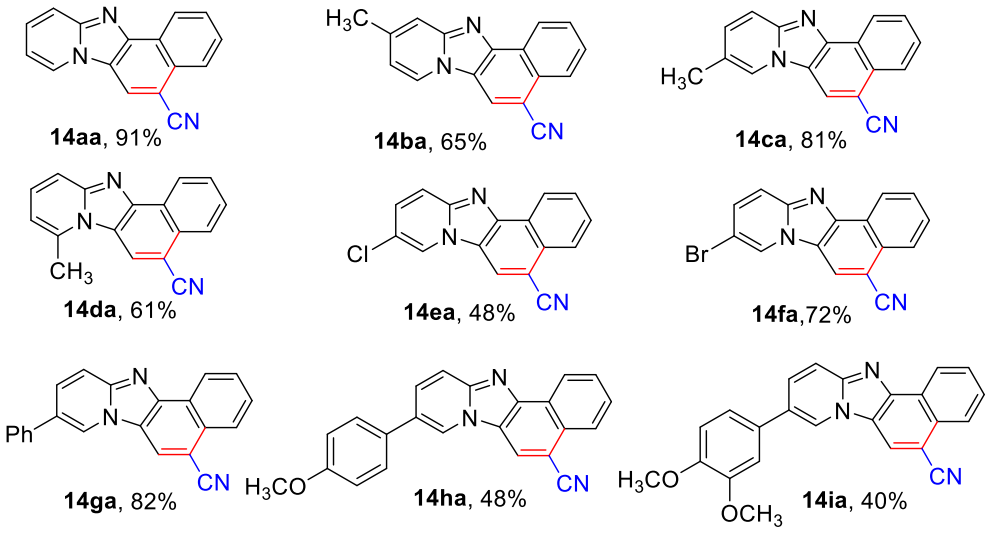
[a]Reagents and conditions**: 10a** (1.0 mmol), **13a** (4.0 mmol), catalyst (10 mol %), ligand (20 mol %), base (2.0 mmol), solvent (4 ml), 110 °C, 2 h. [b]Isolated yield of **14aa**. [c]No ligand. [d]No base. [e]Formation of **14aa** was not observed.

With the optimized reaction conditions in hand, we then focused our attention towards the scope of this cascade protocol for the synthesis of library of naphtho-fused imidazo[1,2-*a*]pyridines. As shown in table 5.2, reaction of diversely substituted 2-(2-bromophenyl)imidazo[1,2-*a*]pyridine-3-carbaldehydes (**10a-j**) and malononitrile (**13a**) produced corresponding 5-cyanonaphtho-fused imidazo[1,2-*a*]pyridines (**14aa-ja**) in moderate to excellent (**40-91**%) yields. There was no much effect observed of different substitution present on aryl/heteroaryl rings of 2-phenylimidazo[1,2-*a*]pyridine. Also, a varity of functional groups were tolerated including halogen substitutions on aryl/heteroaryl rings. For example, tolerance of bromo group at C-6 of imidazo[1,2-*a*]pyridine provides scope for further functionaliztion of the product **14fa** *via* transition metal catalyzed coupling reactions. Reaction of other active methylene compounds *viz.* methyl acetoacetate (**13b**), ethyl acetoacetate (**13c**), diethyl malonate (**13d**) and pentane-2,4-dione (**13e**) was also performed with 2-(2-bromoaryl)imidazo[1,2-*a*]pyridine-3-carbaldehydes, **10a-d**, **10f** and **10j** to give coressponding naphtho-fused imidazo[1,2-*a*]pyridines (**14ab-ae**) in moderate yield (Table 5.2).

Table 5.2 Naphtho-fuzed imidazo[1,2-*a*]pyridines[a]



10a-i **13a-e** **14aa-ae**



[a]Reaction was performed using **13c** in methanol. [b]Using diethyl malonate **13d** as active methylene substrate.

The structures of all the synthesized compounds were elucidated by IR, NMR and mass spectrometry. A representative spectral data for compound **14ha** is provided in **figure 5.2**. In IR spectrum of **14ha**, a characteristic peak was observed at 2214 cm^{-1} for CN group. The two charecteristics singlet at 3.92 ppm and 8.46 ppm for C_6-proton and aliphatic 4-methoxyphenyl protons at C_9 position appeared in the ^1H NMR spectrum. Similarily, a prominent nitrile carbon peak was observed in the ^{13}C NMR spectrum at 102 ppm along with all other expected carbons.

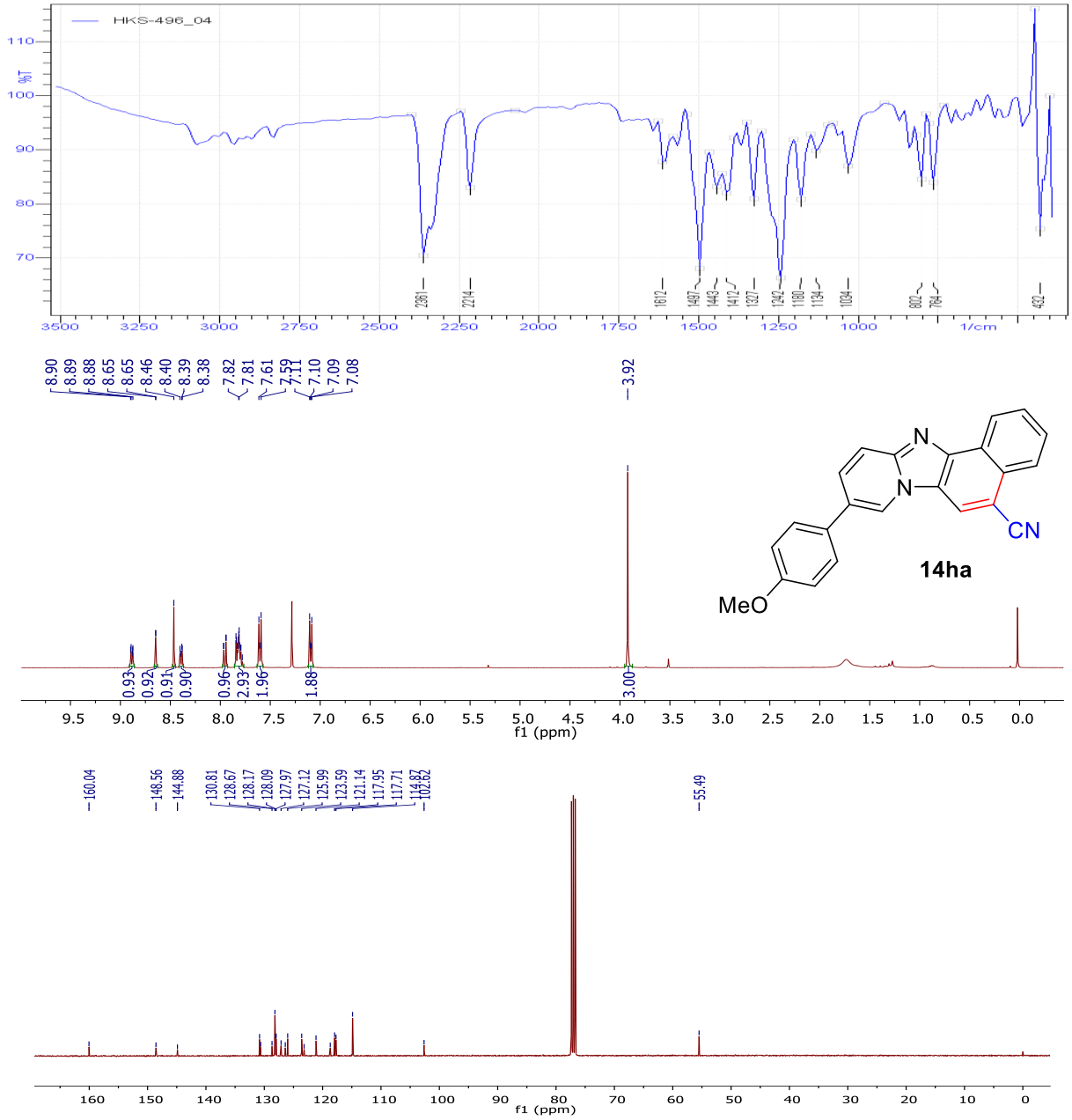
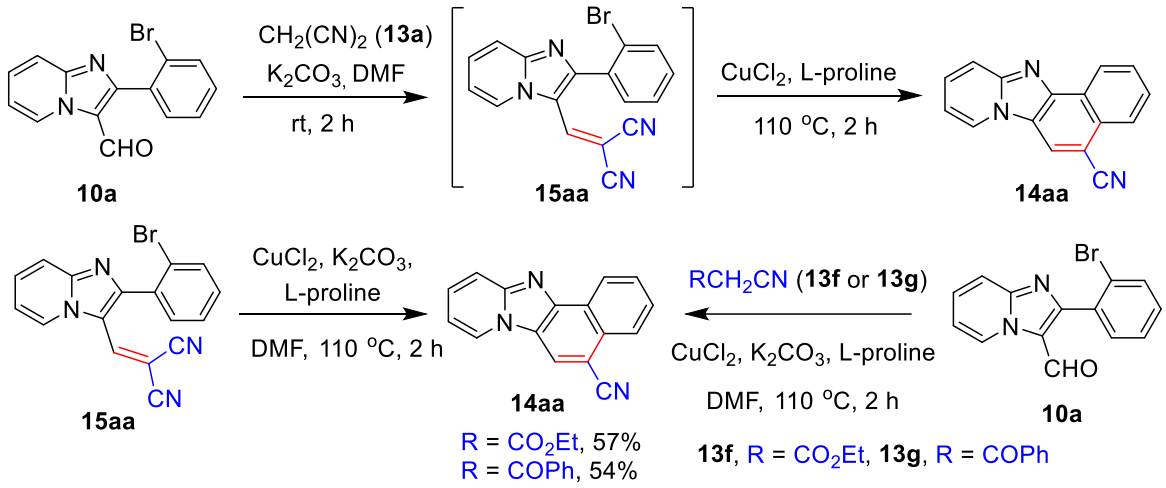


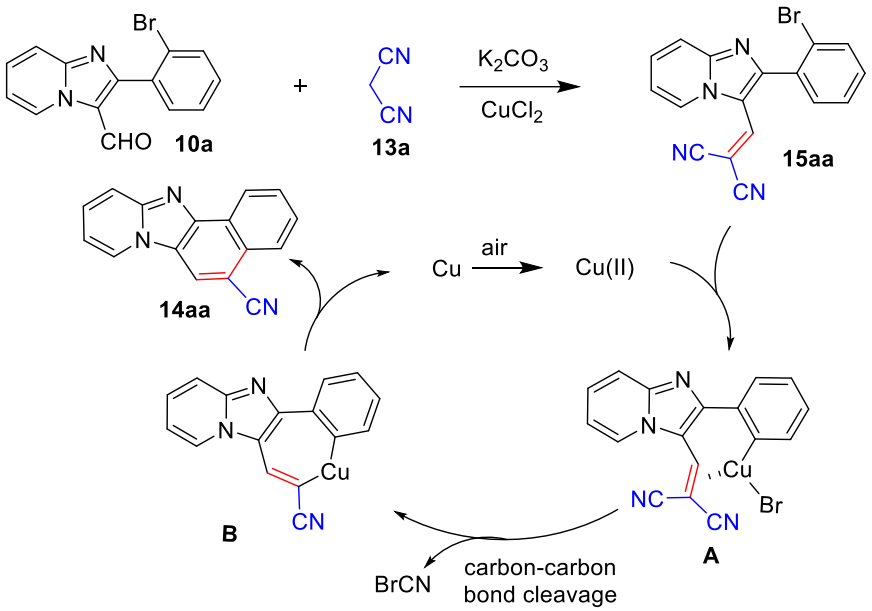
Figure 5.2 IR, ^1H and ^{13}C spectra of **14ha**

After with all successful characterization, we wanted to investigate synthetic pathway of the cascade sequences. For this few control experiments were performed (**Scheme 5.6**). Reaction of **10a** and **13a** in the presence of K_2CO_3 produced intermediate **15aa** which on further reaction with $CuCl_2$ (10 mol %) and L-proline (20 mol %) for 2 h at 110 °C led to formation of **14aa**. To further validate this pathway, isolated **15aa** was treated under standard reaction conditions to afford **14aa** in 74% yield. Further, reaction of ethyl-2-cyanoacetate (**13f**) and 3-oxo-3-phenylproanenitrile (**13g**) with **10a** under similar reaction condition gave **14aa** in 57% and 54% yield, respectively. This may be due to the cleavage of more stable 1-oxoethan-1-ylium and oxo(phenyl)methylium ion in the reaction, respectively.



Scheme 5.6 Control experiments

Exact mechanistic details are not clear for this copper-catalyzed cascade reaction at present, but based upon the above results and literature reports[44-46] a plausible mechanism of the reaction is shown in **Scheme 5.7**. Initially, Knoevenagel condensation product **15aa** is formed which reacts under copper catalysis to produce intermediate **A**. Subsequently, rearrangement of intermediate **A** produces intermediate **B** through carbon–carbon (C−C) bond cleavage[47-48] with release of BrCN as a byproduct. Finally, intermediate **B** undergoes reductive elimination to give product **14aa**.



Scheme 5.7 Proposed mechanism

5.3 Photophysical study

Imidazo[1,2-*a*]pyridines display very good luminescent properties and they emit in blue-light region with high fluorescence quantum yields. However, limited amount of photophysical data are available for fused imidazo[1,2-*a*]pyridines,[49-52] which prompted us to study photophysical properties of novel π-expanded naphtho-fused imidazo[1,2-*a*]pyridines. Figure 5.3 shows absorption and emission spectrum of unsubstituted imidazo[1,2-*a*]pyridine (**IP**) and naphtho-fused imidazo[1,2-*a*]pyridines (**14aa**). The absorption and emission data along with Stokes shift and quantum yield for **14aa-14jc** are shown in Table 5.3. The absorption and emission maxima of **14aa-14jc** were bathochromically shifted by 33-44 nm and 26-57 nm, respectively in comparison with IP.

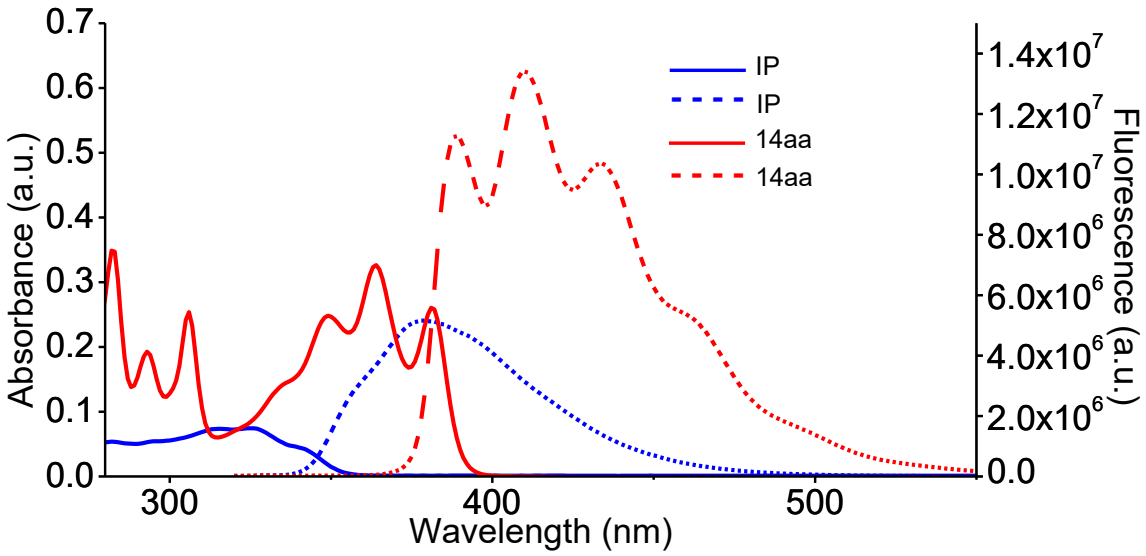


Figure 5.3 Absorption and emission spectra of **IP** and **14aa** in CH_3CN (1.0×10^{-5} M) at 25 °C.

The fluorescence quantum yield for naphtho-fused imidazo[1,2-*a*]pyridine was found to be in the range of 0.7−60% and were higher in comparison to **IP**. The naphtho-fused imidazo[1,2-*a*]pyridines (**14fa** & **14fb**) with bromo substituent at C-5 position of imidazo[1,2-*a*]pyridine showed fluorescence quenching and gave very low quantum yield (**Table 3**). On the other hand, naphtho-fused imidazo[1,2-*a*]pyridines with electron rich substituents at C-5 position of imidazo[1,2-*a*]pyridine were found to be strong emissive and gave high quantum yield. Further, it was observed that fluorescence intensity of **14ha** decreased with increasing concentration.

Table 5.3 Photophysical data for imidazo[1,2-*a*]pyridine and naphtho[1',2':4,5]imidazo[1,2-*a*]pyridines[a]

Compd.	Absorbance (λ_{max}) (nm)	Emission[b] (λ_{max}) (nm)	Stokes shift (cm^{-1})	Φ_f[c]
[d]IP	326	380	4359	0.46
14aa	348, 363, 380	410	1926	0.54
14ba	349, 363, 380	413	2103	0.59
14ca	351, 366, 385	414	1819	0.6
14da	345, 360, 376	406	1965	0.54

14ea	352, 369, 387	423	2199	0.41
14fa	353, 369, 387	424	2255	0.008
14ga	353, 368, 387	417	1859	0.46
14ha	355, 370, 389	421	1954	0.37
14ia	353, 370, 389	437	2665	0.33
14ab	349, 363, 381	415	2150	0.6
14bb	350, 363, 379	418	2462	0.57
14fb	354, 369, 388	430	2517	0.007
14ac	348, 363, 380	415	2219	0.54
14cc	352, 366, 383	419	2243	0.58
14dc	346, 359, 376	411	2265	0.53
14ae	351, 366, 383	420	2300	0.01
14ja	350, 365, 383	404	1357	0.58
14jc	351, 365, 382	407	1608	0.50

[a]Measured in acetonitrile (1.0×10^{-5} M) at 25 °C. [b]Excited at 300 nm. [c]Measured with quinine sulphate in 0.1N H_2SO_4, as standard. [d]IP = unsubstituted 2-phenylimidazo[1,2-*a*]pyridine.

5.4 Conclusion

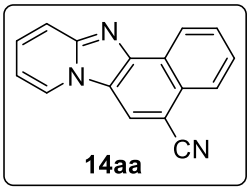
In conclusion, library of π-extended naphtho-fused imidazo[1,2-*a*]pyridines could be rapidly assembled from simple starting materials by copper catalyzed cascade reactions under mild conditions. The strategy provides functnalized naphtho[1',2':4,5]imidazo[1,2-*a*]pyridine analogues in moderate to excellent (**35-91**%) yields. The cascade reaction involves Knoevenagel condensation followed by copper-catalyzed chemoselective cross-coupling reactions *via* carbon-carbon bond cleavage. Reaction has high functional group tolerance. The absorption and emission maxima of naphtho-fused imidazo[1,2-*a*]pyridines is bathochromically shifted and they emitted with high fluorescence quantum yield. The developed methodology can be a useful tool for the synthesis of relevant π-extended polyheterocyclic compounds of interest in materials and medicinal chemistry.

5.5 Experimental

Melting points were determined in open capillary tubes on a EZ-Melt automated melting point apparatus and are uncorrected. Reactions were monitored by thin layer chromatography (TLC) on 0.2 mm silica gel F254 plates (Merck). The NMR spectra (^{1}H and ^{13}C NMR) were recorded on Bruker Avance III 400 spectrometer and chemical shifts are reported in parts per million (ppm) using deuterated solvent peak or tetramethylsilane as an internal standard. HRMS were recorded using Agilent technologies 6545 Q-TOF LC/MS. IR spectra were recorded on a FTIR spectrophotometer, and the ν_{max} values are expressed in cm^{-1}. All the chemicals were obtained from commercial suppliers and used without further purification.

Representative procedure for the preparation of Naphtho-fused imidazo[1,2-*a*]pyridines: A clean, oven dried 10 mL RB flask was charged with 2-(2-bromophenyl)imidazo[1,2-*a*]pyridine-3-carbaldehydes (**10a**) (301 mg, 1.0 mmol), malononitrile (**13a**) (264 mg, 4.0 mmol), $CuCl_2$ (13 mg, 10 mol %), *L*-proline (23 mg, 20 mol %) and K_2CO_3 (276 mg, 2.0 mmol) in DMF (4.0 mL). The resulting solution was stirred at 110 °C for 2 h. After completion of the reaction, reaction mass was cooled to room temperature. Ethyl acetate was added to the crude residue and washed with water. The organic layer was collected and dried over anhydrous Na_2SO_4 then evaporated under reduced pressure. Crude residue was purified by column chromatography (EtOAc: hexanes, 2: 3, *v/v*) to obtain naphtho[1',2':4,5]imidazo[1,2-*a*]pyridines (**14aa**) in 91% yield (222 mg).

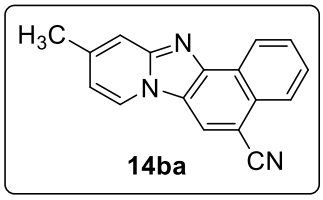
Naphtho[1',2':4,5]imidazo[1,2-*a*]pyridine-5-carbonitrile (14aa)



14aa

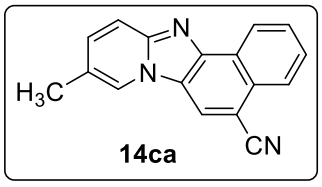
Yield 91%; off-white solid; mp 269-271 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.88 (d, *J* = 4.8 Hz, 1H), 8.58 (d, *J* = 5.4 Hz, 1H), 8.41 (s, 2H), 7.92 (d, *J* = 8.7 Hz, 1H), 7.81 (d, *J* = 0.5 Hz, 2H), 7.61 (s, 1H), 7.11 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.5, 144.6, 130.6, 130.0, 128.1, 127.9, 126.3, 126.0, 124.8, 123.6, 122.9, 118.7, 118.3, 117.6, 112.7, 102.7; IR (KBr) *ν*: 3078, 3024, 2214 (CN_{str}), 1589, 1497, 1450, 1366, 1265, 879 cm^{-1}; HRMS calcd for $C_{16}H_{10}N_3$ 244.0869; found 244.0871 $[M + H]^+$.

10-Methylnaphtho[1',2':4,5]imidazo[1,2-*a*]pyridine-5-carbonitrile (14ba)



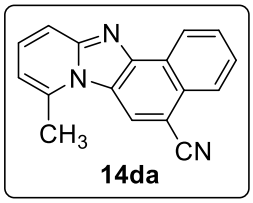
Yield 65%; off-white solid; mp 289-291 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.88 – 8.82 (m, 1H), 8.42 (d, *J* = 6.9 Hz, 1H), 8.39 – 8.36 (m, 1H), 8.36 (s, 1H), 7.83 – 7.74 (m, 2H), 7.64 (s, 1H), 6.91 (dd, *J* = 6.9, 1.3 Hz, 1H), 2.55 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.0, 144.9, 141.8, 130.6, 127.9, 127.7, 126.3, 125.9, 123.9, 123.6, 122.8, 118.8, 117.4, 116.5, 115.4, 101.9, 22.0; IR (KBr) ν 2214 (CN_{str}), 1589, 1497, 1450, 1412, 1366, 1257, 872 cm^{-1}; HRMS calcd for $C_{17}H_{12}N_3$ 258.1026; found 258.1021 $[M + H]^+$.

9-Methylnaphtho[1',2':4,5]imidazo[1,2-*a*]pyridine-5-carbonitrile (14ca)



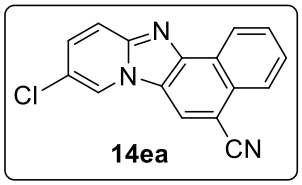
Yield 81%; white solid; mp 269-271 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.87 (d, *J* = 6.8 Hz, 1H), 8.46 – 8.34 (m, 3H), 7.88 – 7.74 (m, 3H), 7.46 (d, *J* = 9.2 Hz, 1H), 2.51 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.6, 133.3, 130.5, 128.0, 127.9, 126.4, 126.0, 123.5, 122.8, 122.7, 122.4, 118.8, 117.7, 117.6, 102.4, 18.3; IR (KBr) ν 3765, 3441, 2214 (CN_{str}), 1638, 1412, 758 cm^{-1}; HRMS calcd for $C_{17}H_{12}N_3$ 258.1026; found 258.1022 $[M + H]^+$.

8-Methylnaphtho[1',2':4,5]imidazo[1,2-*a*]pyridine-5-carbonitrile (14da)



Yield 61%; off-white solid; mp 197-198 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.90 (dd, *J* = 6.5, 2.8 Hz, 1H), 8.60 (s, 1H), 8.34 (dd, *J* = 6.6, 2.8 Hz, 1H), 7.87 – 7.77 (m, 3H), 7.59 – 7.50 (m, 1H), 6.84 (d, *J* = 6.8 Hz, 1H), 3.10 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.6, 145.2, 138.5, 130.1, 130.0, 128.2, 127.6, 126.0, 125.4, 123.9, 123.7, 121.6, 119.1, 115.7, 113.4, 101.8, 21.5; IR (KBr) ν 2847, 2214 (CN_{str}), 1420, 1285, 766, 417 cm^{-1}; HRMS calcd for $C_{17}H_{12}N_3$ 258.1026 found 258.1021 $[M + H]^+$.

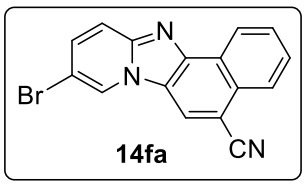
9-Chloronaphtho[1',2':4,5]imidazo[1,2-*a*]pyridine-5-carbonitrile (14ea)



14ea

Yield 48%; off-white solid; mp above 300 °C; ^{1}H NMR (400 MHz, CD_3OD in $CDCl_3$) δ 8.86 – 8.81 (m, 1H), 8.78 (dd, *J* = 1.9, 0.8 Hz, 1H), 8.50 (s, 1H), 8.41 – 8.36 (m, 1H), 7.89 – 7.81 (m, 3H), 7.60 (dd, *J* = 9.7, 2.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$ and CH_3OH-d_4, ratio 4:1) δ 147.46, 144.4, 131.7, 130.6, 128.5, 128.4, 126.1, 126.0, 123.5, 123.2, 122.9, 121.1, 118.3, 118.2, 117.9, 103.6; IR (KBr) ν 2361, 2214 (CN_{str}), 1497, 1420, 1319, 810, 758 cm^{-1}; HRMS calcd for $C_{16}H_9ClN_3$ 278.0480 found 278.0485 $[M + H]^+$.

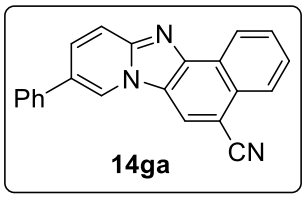
9-Bromonaphtho[1',2':4,5]imidazo[1,2-*a*]pyridine-5-carbonitrile (14fa)



14fa

Yield 72%; white solid; mp above 300 °C; ^{1}H NMR (400 MHz, CD_3OD in $CDCl_3$) δ 8.94 – 8.81 (m, 1H), 8.73 (d, *J* = 0.9 Hz, 1H), 8.46 – 8.35 (m, 2H), 7.87 – 7.78 (m, 3H), 7.66 (dd, *J* = 9.6, 1.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.6, 144.7, 133.2, 130.6, 128.4, 128.3, 126.4, 126.1, 125.1, 123.6, 122.7, 119.0, 118.3, 117.4, 107.1, 103.8; IR (KBr) ν 3796, 2206 (CN_{str}), 1497, 1134, 810 cm^{-1}; HRMS calcd for $C_{16}H_9BrN_3$ 321.9974; found 321.9978 $[M + H]^+$ and 323.9964 $[M + H + 2]^+$

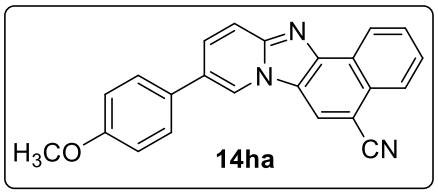
9-Phenylnaphtho[1',2':4,5]imidazo[1,2-*a*]pyridine-5-carbonitrile (14ga)



14ga

Yield 82%; white solid; mp 254-256 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.91 – 8.86 (m, 1H), 8.71 (dd, *J* = 1.5, 0.9 Hz, 1H), 8.48 (s, 1H), 8.41 – 8.37 (m, 1H), 7.98 (dd, *J* = 9.4, 0.8 Hz, 1H), 7.88 – 7.83 (m, 1H), 7.83 – 7.77 (m, 2H), 7.68 (t, *J* = 1.6 Hz, 1H), 7.66 (s, 1H), 7.56 (t, *J* = 7.5 Hz, 2H), 7.51 – 7.45 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.7, 145.0, 136.4, 130.8, 130.7, 129.4, 128.5, 128.2, 128.0, 127.4, 127.1, 126.4, 126.0, 123.6, 123.2, 121.9, 118.6, 118.1, 117.7, 102.8; IR (KBr) ν 2361, 2214 (CN_{str}), 1589, 1489, 1450, 1412, 1335, 1265, 756 cm^{-1}; HRMS calcd for $C_{22}H_{14}N_3$ 320.1182; found 320.1177 $[M + H]^+$.

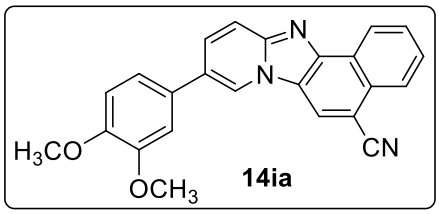
9-(4-methoxyphenyl)naphtho[1',2':4,5]imidazo[1,2-*a*]pyridine-5-carbonitrile (14ha)



14ha

Yield 48%; pale-yellow solid; mp 264-266 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.92 – 8.86 (m, 1H), 8.65 (d, *J* = 0.4 Hz, 1H), 8.46 (s, 1H), 8.39 (dd, *J* = 6.8, 2.1 Hz, 1H), 7.95 (dd, *J* = 9.4, 0.7 Hz, 1H), 7.86 – 7.76 (m, 3H), 7.64 – 7.57 (m, 2H), 7.13 – 7.06 (m, 2H), 3.92 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.0, 148.6, 144.9, 130.8, 130.6, 128.7, 128.2, 128.1, 128.0, 127.1, 126.4, 126.0, 123.6, 123.2, 121.1, 118.7, 118.0, 117.7, 114.9, 102.6, 55.5; IR (KBr) ν 2361, 2214 (CN_{str}), 1497, 1412, 1327, 1242, 1180, 802, 764 cm^{-1}; HRMS calcd for $C_{23}H_{16}N_3O$ 350.1288; found 350.1291 $[M + H]^+$.

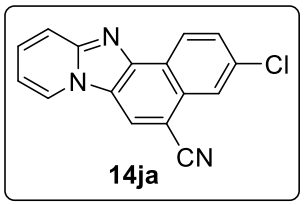
9-(3,4-dimethoxyphenyl)naphtho[1',2':4,5]imidazo[1,2-*a*]pyridine-5-carbonitrile (14ia)



14ia

Yield 40%; pale-yellow solid; mp 242-244°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.91 – 8.87 (m, 1H), 8.67 (s, 1H), 8.50 (s, 1H), 8.40 (dd, *J* = 6.8, 2.3 Hz, 1H), 7.97 (dd, *J* = 9.4, 0.8 Hz, 1H), 7.85 (d, *J* = 1.7 Hz, 1H), 7.83 – 7.77 (m, 2H), 7.21 (dd, *J* = 8.3, 2.1 Hz, 1H), 7.14 (d, *J* = 2.1 Hz, 1H), 7.04 (d, *J* = 8.3 Hz, 1H), 4.02 (s, 3H), 3.98 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.7, 149.6, 148.6, 144.9, 130.9, 130.7, 129.2, 128.1, 128.0, 127.4, 126.4, 126.0, 123.6, 123.2, 121.3, 119.7, 118.7, 118.0, 117.8, 111.9, 110.2, 102.7, 56.2, 56.1; IR (KBr) ν 2361, 2214 (CN_{str}), 1497, 1450, 1257, 764 cm^{-1}; HRMS calcd for $C_{24}H_{18}N_3O_2$ 380.1394; found 380.1387 $[M + H]^+$.

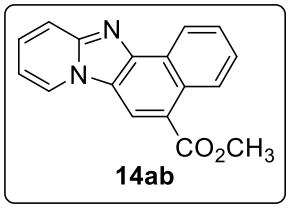
3-Chloronaphtho[1',2':4,5]imidazo[1,2-a]pyridine-5-carbonitrile (14ja)



14ja

Yield 59%; yellowish solid; mp >300 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.84 (d, *J* = 8.7 Hz, 1H), 8.62 (d, *J* = 6.9 Hz, 1H), 8.49 (s, 1H), 8.41 (d, *J* = 1.8 Hz, 1H), 7.95 (d, *J* = 9.2 Hz, 1H), 7.79 (dd, *J* = 8.7, 2.0 Hz, 1H), 7.69 – 7.64 (m, 1H), 7.17 (t, *J* = 6.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$ and CH_3OH-d_4, ratio 4:1) δ 149.6, 134.6, 131.5, 131.0, 128.8, 125.3, 125.1, 125.0, 124.2, 122.7, 119.0, 117.7, 116.0, 113.3, 104.3, 101.5; IR (KBr) ν 3425, 3078, 2214 (CN_{str}), 1582, 1558, 1497, 1435, 1358, 1265, 1095, 756 cm^{-1}; HRMS calcd for $C_{16}H_9ClN_3$ 278.0480; found 278.0483 $[M + H]^+$.

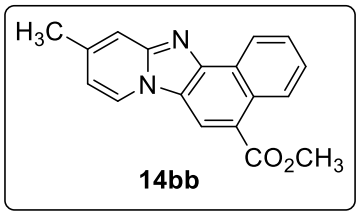
Methylnaphtho[1',2':4,5]imidazo[1,2-*a*]pyridine-5-carboxylate (14ab)



14ab

Yield 35% (70% when **13c** was used in methanol); off-white solid; mp 183-185 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.20 – 9.14 (m, 1H), 8.91 – 8.85 (m, 1H), 8.72 (s, 1H), 8.54 (dd, *J* = 5.8, 1.0 Hz, 1H), 7.86 (d, *J* = 9.2 Hz, 1H), 7.77 – 7.69 (m, 2H), 7.54 – 7.48 (m, 1H), 6.99 (td, *J* = 6.8, 1.0 Hz, 1H), 4.06 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.8, 149.2, 144.6, 130.2, 129.3, 127.4, 126.9, 126.8, 126.7, 124.8, 123.3, 122.8, 120.2, 118.1, 115.7, 112.0, 52.2; IR (KBr) *ν* 3063, 3032, 1713 ($C=O_{str}$), 1589, 1497, 1443, 1373, 1273, 1227, 756 cm^{-1}; HRMS calcd for $C_{17}H_{13}N_2O_2$ 277.0972; found 277.0968 $[M + H]^+$.

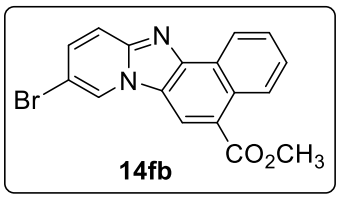
Methyl-10-methylnaphtho[1',2':4,5]imidazo[1,2-*a*]pyridine-5-carboxylate (14bb)



14bb

Yield 35%; off-white solid; mp 153-155 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.21 – 9.15 (m, 1H), 8.89 – 8.84 (m, 1H), 8.73 (s, 1H), 8.44 (d, *J* = 6.9 Hz, 1H), 7.77 – 7.71 (m, 2H), 7.69 (s, 1H), 6.84 (dd, *J* = 6.9, 1.5 Hz, 1H), 4.07 (s, 3H), 2.53 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.8, 149.5, 144.2, 141.4, 130.2, 127.4, 126.8, 126.6, 126.4, 123.9, 123.4, 122.6, 119.8, 116.2, 115.6, 115.0, 52.2, 22.0; IR (KBr) *ν* 3032, 2947, 2361, 1705 ($C=O_{str}$), 1589, 1497, 1435, 1366, 1265, 1227, 787 cm^{-1}; HRMS calcd for $C_{18}H_{15}N_2O_2$ 291.1128; found 291.1133 $[M + H]^+$.

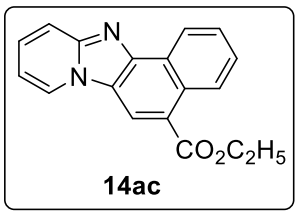
Methyl-9-bromonaphtho[1',2':4,5]imidazo[1,2-*a*]pyridine-5-carboxylate (14fb)



14fb

Yield 36%; off-white solid; mp 225-227 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.15 (d, *J* = 5.1 Hz, 1H), 8.82 (d, *J* = 4.6 Hz, 1H), 8.65 (s, 2H), 7.74 (d, *J* = 8.6 Hz, 3H), 7.55 (d, *J* = 9.3 Hz, 1H), 4.07 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.5, 147.3, 144.6, 132.4, 130.1, 127.7, 127.0, 126.9, 126.7, 125.0, 123.2, 122.6, 121.1, 118.7, 115.4, 106.4, 52.3; IR (KBr) *ν* 3441, 1682 ($C=O_{str}$), 1582, 1412, 1234, 764 cm^{-1}; HRMS calcd for $C_{17}H_{12}BrN_2O_2$ 355.0077; found 355.0069 $[M + H]^+$ and 357.0057 $[M + H + 2]^+$.

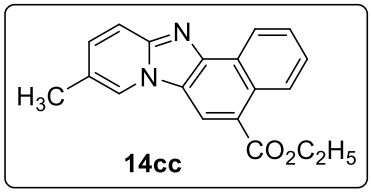
Ethyl naphtho[1',2':4,5]imidazo[1,2-*a*]pyridine-5-carboxylate (14ac)



14ac

Yield 44% (38% using **13d**); off-white solid; mp 140-142 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.17 (dd, *J* = 6.6, 2.9 Hz, 1H), 8.94 – 8.86 (m, 1H), 8.77 (s, 1H), 8.62 (d, *J* = 6.8 Hz, 1H), 7.89 (d, *J* = 9.2 Hz, 1H), 7.78 – 7.69 (m, 2H), 7.56 – 7.49 (m, 1H), 7.02 (t, *J* = 6.7 Hz, 1H), 4.54 (q, *J* = 7.1 Hz, 2H), 1.52 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.5, 149.2, 144.6, 130.2, 129.2, 127.4, 126.9, 126.7, 124.9, 123.3, 122.9, 120.8, 118.2, 115.5, 112.0, 61.2, 14.6; IR (KBr) ν 3024, 2978, 2361, 1697 ($C{=}O_{str}$), 1589, 1504, 1443, 1360, 1265, 1219, 787, 741 cm^{-1}; HRMS calcd for $C_{18}H_{15}N_2O_2$ 291.1128; found 291.1131 $[M + H]^+$.

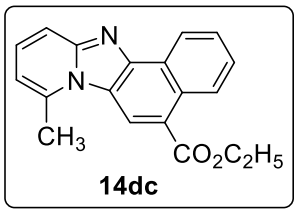
Ethyl-9-methylnaphtho[1',2':4,5]imidazo[1,2-*a*]pyridine-5-carboxylate (14cc)



14cc

Yield 45%; white solid; mp 192-193 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.22 – 9.12 (m, 1H), 8.93 – 8.86 (m, 1H), 8.75 (s, 1H), 8.39 (d, *J* = 0.7 Hz, 1H), 7.79 (d, *J* = 9.3 Hz, 1H), 7.77 – 7.68 (m, 2H), 7.38 (dd, *J* = 9.3, 1.6 Hz, 1H), 4.56 (q, *J* = 7.1 Hz, 2H), 2.48 (s, 3H), 1.55 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.5, 148.3, 144.6, 132.4, 130.1, 127.2, 126.9, 126.6, 123.2, 122.8, 122.5, 121.8, 120.4, 117.4, 115.6, 61.1, 18.3, 14.6; IR (KBr) ν 3433, 2986, 1705 ($C{=}O_{str}$), 1643, 1420, 1257, 766 cm^{-1}; HRMS calcd for $C_{19}H_{17}N_2O_2$ 305.1285; found 305.1291 $[M + H]^+$.

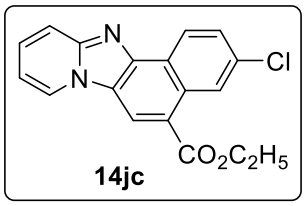
Ethyl-8-methylnaphtho[1',2':4,5]imidazo[1,2-*a*]pyridine-5-carboxylate (14dc)



14dc

Yield 38%; off-white solid; mp 151-153 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.18 – 9.08 (m, 1H), 9.04 (s, 1H), 8.97 (s, 1H), 7.84 (d, *J* = 8.9 Hz, 1H), 7.79 – 7.69 (m, 2H), 7.57 – 7.39 (m, 1H), 6.82 (d, *J* = 6.5 Hz, 1H), 4.56 (q, *J* = 7.0 Hz, 2H), 3.16 (s, 3H), 1.54 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.8, 150.2, 145.0, 138.7, 129.6, 129.5, 127.6, 126.5, 124.1, 123.5, 120.2, 119.7, 115.5, 113.0, 61.1, 21.4, 14.5; IR (KBr) ν 3734, 2888, 1705 ($C{=}O_{str}$), 1643, 1257, 756 cm^{-1}; HRMS calcd for $C_{19}H_{17}N_2O_2$ 305.1285; found 305.1289 $[M + H]^+$.

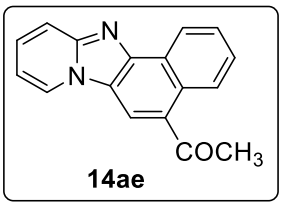
Ethyl 3-chloronaphtho[1',2':4,5]imidazo[1,2-*a*]pyridine-5-carboxylate (14jc)



14jc

Yield 36%; brownish solid; mp 202-204 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.25 (d, *J* = 1.7 Hz, 1H), 8.79 (s, 1H), 8.76 (s, 1H), 8.59 (d, *J* = 6.8 Hz, 1H), 7.87 (d, *J* = 9.2 Hz, 1H), 7.66 (dd, *J* = 8.7, 1.8 Hz, 1H), 7.61 – 7.52 (m, 1H), 7.06 (t, *J* = 6.6 Hz, 1H), 4.54 (q, *J* = 7.1 Hz, 2H), 1.54 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.9, 149.5, 144.4, 133.7, 131.0, 129.7, 127.3, 126.3, 125.0, 124.96, 124.7, 122.9, 119.3, 118.1, 116.7, 112.2, 61.3, 14.5; IR (KBr) *ν* 3425, 2933, 1705 ($C=O_{str}$), 1638, 1558, 1497, 1435, 1265, 1227, 748 cm^{-1}; HRMS calcd for $C_{18}H_{14}ClN_2O_2$ 325.0738; found 325.0736 $[M + H]^+$.

1-(Naphtho[1',2':4,5]imidazo[1,2-*a*]pyridin-5-yl)ethanone (14ae)



14ae

Yield 48%; brownish solid; mp 188-190 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.97 (dd, *J* = 7.3, 2.1 Hz, 1H), 8.88 – 8.83 (m, 1H), 8.58 (d, *J* = 6.8 Hz, 1H), 8.42 (s, 1H), 7.88 (d, *J* = 9.2 Hz, 1H), 7.76 – 7.66 (m, 2H), 7.56 ─7.52 (m, 1H), 7.04 (t, *J* = 6.8 Hz, 1H), 2.86 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.3, 149.3, 144.3, 129.4, 129.3, 127.8, 127.2, 127.0, 126.9, 124.7, 123.2, 122.5, 118.2, 114.3, 112.2, 29.9; IR (KBr) *ν* 3425, 1643 ($C=O_{str}$), 1566, 1497, 1443, 1366, 1342, 1257, 879, 756 cm^{-1}; HRMS calcd for $C_{17}H_{13}N_2O$ 261.1022; found 261.1027 $[M + H]^+$.

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Chapter 6

Conclusions

6.1 General conclusions

Nowadays, there has been a major concern in organic synthesis regarding how to access the complex bioactive organic molecules with maximum atom involvement of reactants in minimum synthetic steps. In this respect, the evolution of copper- and palladium- catalyzed reactions represents a paradigm shift from traditional organic synthesis. The atom and step economy features of these reactions have witnessed a revolutionary trend to achieve molecular complexity and emerged as the '**renaissance**' in organic synthesis.

In this context, copper and palladium catalyzed direct arylation has been employed as one of the advanced approaches to access *N*-fused heterocycles. The development of new routes offers multiple new C-C and C-N bonds with good functional group tolerance and excellent regioselectivity using the arylation approach in one pot process.

The present thesis entitled "**Synthesis of Azaheterocycles *via* Copper/Palladium-Catalyzed Intramolecular Arylation Reactions**" deals with the synthesis of some selected azaheterocycles which obeys the term atom and step economy. Particularity, we have focused on imidazole- and isoindolinone- fused *N*-heterocycles that have close proximity to related naturally occurring heterocycles and pharmaceuticals. The thesis consists of the total of six chapters.

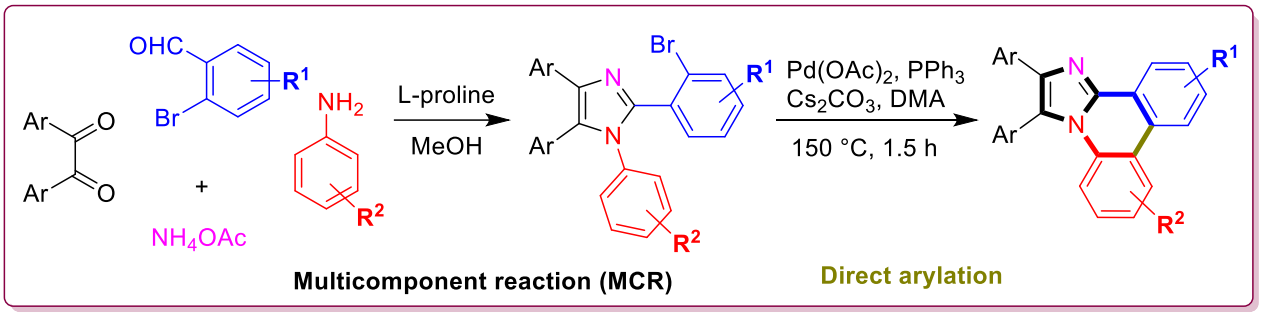
6.2 Specific conclusions

A brief overview of the first five chapters is discussed herewith in sixth as conclusion chapter.

The first chapter of the thesis describes a concise literature overview of the chemistry of arylation of different heterocycles. In this chapter, described synthetic approaches majorly deal with the five, six, and seven membered heterocyclic rings that involve Cu/Pd catalyzed intramolecular arylation reactions. A few of the reported methods directly accesses natural products *via* distinct C-H arylation. Also, the detailed mechanisms of Cu/Pd catalyzed arylations have been explained which describes the direct functionalization of chemically inert C-H bond and led to complex fused heterocycles. Overall, this chapter provides a brief history of intramolecular arylations and delivered the new synthetic protocols to accessing diverse heterocycles.

The second chapter of the thesis describes the synthesis of imidazo-fused phenanthridines. In past years, various synthetic routes have been explored to access phenanthridine analogues since these planar extended conjugated systems intensively studied for efficient DNA binding

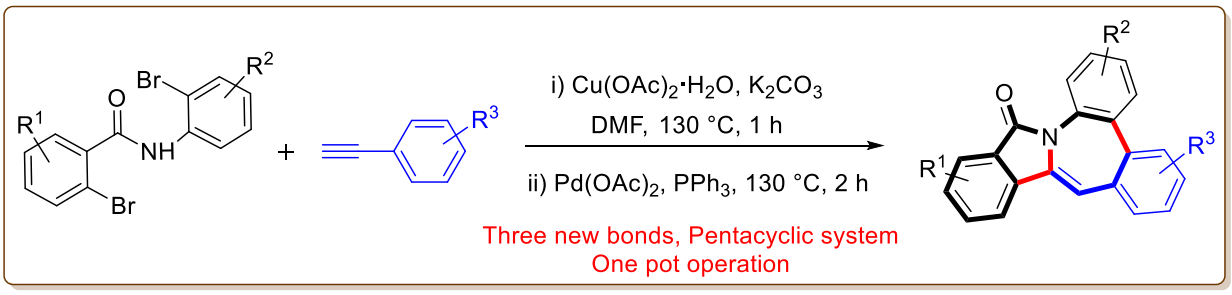
capability. Addition to this, fused-phenanthridines has been received as attractive attention after DNA discovery and recognized as a symbol of potential DNA intercalators. Thus, our valuable efforts designed and succeeded to discover a novel route for imidazo-fused phenanthridines involving palladium-catalyzed intramolecular C-C bond formation (**Scheme 6.1**). Prior to this, four component reactions of 1,2-dicarbonyl compounds, anilines, aldehydes, and ammonium acetate offer different imidazole derivatives.



Scheme 6.1 Synthesis of 2,3-diarylimidazo[1,2-f]phenanthridines

The functionalized imidazoles facilitate efficiently direct arylation and comprise thirteen of the privilege imidazo-fused phenanthridines derivatives in good to excellent (58-94%) yields. All the derivatives are highly compatible with electron releasing as well as withdrawing groups.

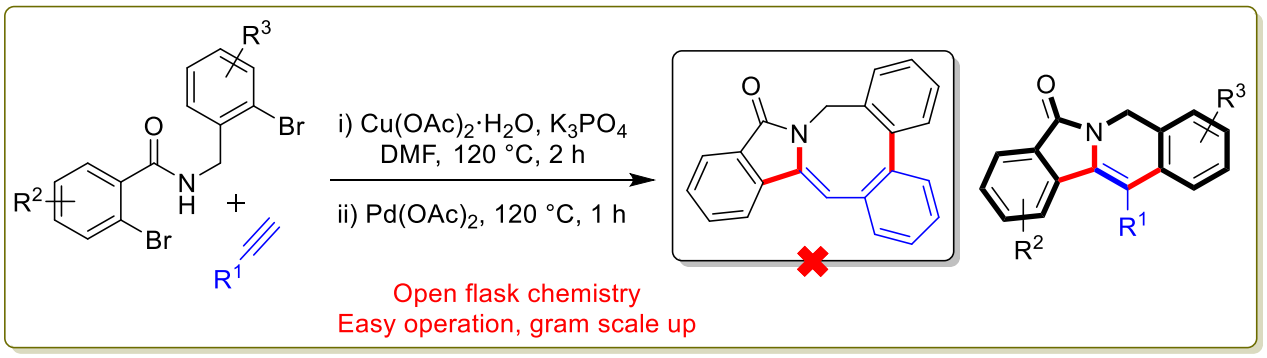
The third chapter of thesis commences how the Cu/Pd catalyzed sequential reactions are significant to access novel *N*-fused heterocycles. In this prospect, azepino-fused isoindolinones have been targeted since a few natural products like chilenine, lennoxamine, and cephalotaxine contain the similar skeleton. Desired target molecule (14*H*-dibenzo[4,5:6,7]azepino[2,1-*a*]isoindol-14-one) has been realized successfully under a sequential copper-catalyzed Sonogashira coupling followed by intramolecular hydroamidation and palladium-catalyzed intramolecular direct arylation reaction (**Scheme 6.2**).



Scheme 6.2 Synthesis of azepino-fused isoindolinone derivatives

This convenient and modular approach further employed for various azepino-fused isoindolinone analogues containing electron releasing and withdrawing group and found to show moderate to high (22-90%) yields under optimized reaction conditions.

The fourth chapter of the thesis comprises the same strategy of the previous chapter and facilitates different *N*-fused heterocycles. With this advent of the reported strategy, naturally occurring Magallanesine and similar structures were conceived to construct in this chapter. However, our designed rationale led to the formation of isoindolo[2,1-*b*]isoquinolin-7(5*H*)-one as a different heterocyclic framework. Serendipitous synthesis led us close to the related natural products *i.e* Nuevamine, Camptothecin, and Rosettacin which exhibit diverse medicinal properties. Further, the reaction of different 2-bromo-*N*-(2-bromobenzyl)benzamides and phenyl acetylenes under one-pot sequential process gives diversely substituted isoindolo-fused isoquinolin-7(5*H*)-ones in moderate to excellent yields with high functional group compatibility (**Scheme 6.3**).

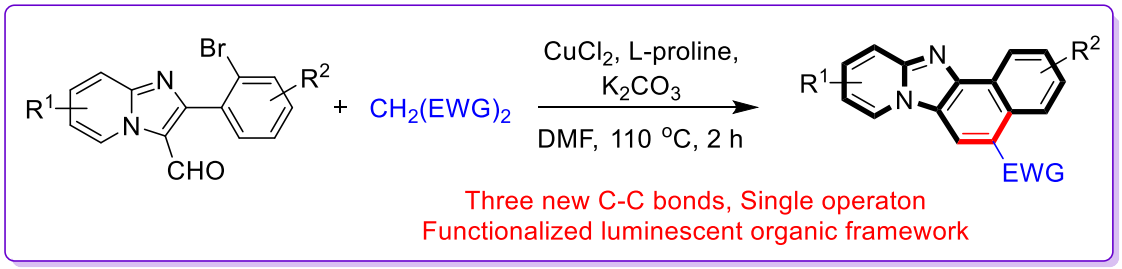


Scheme 6.3 Synthesis of isoindolo fused isoquinolin-7(5H)-ones

This unified Cu/Pd catalyzed approach involves the formation of two carbon-carbon bonds and one carbon-nitrogen bond and represents a rapid practical strategy to access bioactive isoindolo[2,1-*b*]isoquinolin-7(5*H*)-ones.

The fifth chapter of the thesis reports the synthesis of naphtho-fused imidazo[1,2-a]pyridines (NIP) and their photophysical studies. Over the years, the presence of imidazo[1,2-a]pyridine (IP) skeleton has fetched lots of attention in medical science, especially its derivatives. The slight structural changes in its derivatives comprise different biologically active compounds with interesting pharmacological properties. Zolpidem, Saripidem, Alpidem, Necopidem and Miroprofen are the few examples of commercially available marketed drugs containing different

functionalization on imidazo[1,2-a]pyridine core. Thus, there has been an interest to achieve fused functionalize molecule containing imidazo[1,2-a]pyridine motif. In this direction, we have designed a precursor 2-(2-bromophenyl)imidazo[1,2-*a*]pyridine-3-carbaldehydes and commenced our study with the reaction of 2-(2-bromophenyl)imidazo[1,2-*a*]pyridine-3-carbaldehydes and malononitrile. The reaction has been proposed to undergo *via* Knoevenagel condensation followed by the copper-catalyzed alkene arylation. The new product has been isolated in 80% yield and characterized from different spectroscopic techniques (IR, NMR, HRMS) as our desired 5-cyanonaphtho [1',2':4,5]imidazo[1,2-*a*]pyridine. Further improvement in reaction yield was observed by optimization of different reaction conditions using copper catalysts, ligands and bases. With the best reaction condition, the generalization of the developed approach provides diversly substituted naphtho[1',2':4,5]imidazo[1,2-*a*]pyridines in moderate to excellent (35-91%) yields (**Scheme 6.4**).



Scheme 6.4 Synthesis of naphtho-fused imidazo[1,2-*a*]pyridines

The formation of three new carbon-carbon bonds with retaining nitrile, ketone and ester functionality under copper-catalyzed one-pot tandem protocol makes this method advantageous. In recent years, synthesis of extended π-conjugated systems has also received much attention in material science. Therefore, as further applications, photophysical properties were studied of these π-extended conjugated naphtho-fused imidazo[1,2-*a*]pyridines.

The absorption and emission maxima of the naphtho-fused imidazo[1,2-a]pyridines are bathochromically shifted (**Figure 6.1**) and emit with high fluorescence quantum yields.

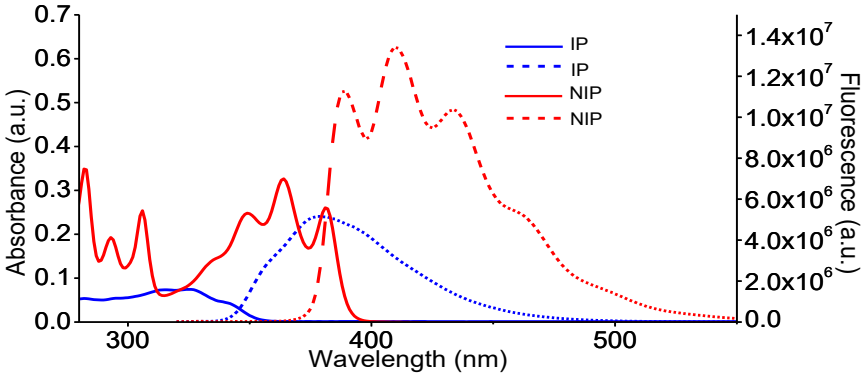


Figure 6.1 Absorption and emission spectra of **IP** and **NIP** in CH_3CN (1.0×10^{-5} M) at 25 °C.

6.2 Future scope of the research work

Cu/Pd catalyzed arylation meet the present requirement of modern chemistry by involving atom and step economic path. Utilizing the distinct approach, this thesis mainly focuses on N-heterocycles syntheses which are the most significant components of pharmaceuticals. Despite this, many challenging *N*-heterocycles and others exist for discovery and further exploitation. Many natural products and close structures containing fused *N*-heterocycles as their central framework can be accessed *via* developed aforementioned approaches. All synthesized compounds whichever already exist in literature follow improved synthetic methodologies over previously reported methods. These value-added routes would be desirable for future synthesis and may reach to the challenging leftover. Also, the reported methodologies could be the potential alternates to traditional linear synthesis for accessing other fused hybrid bio-active *N*-heterocycles.

The present thesis comprises most of the novel structures which are containing azepino-fused isoindolinones, isoindolo-fused isoquinolin-7(5*H*)-ones, and naphtho-fused imidazo[1,2-*a*]pyridines frameworks. These novel structures have close proximity to a few natural products and pharmaceuticals. Hence, there will be the excellent opportunities for the researcher in applied chemistry to explore further numerous applications of all synthesized novel compounds. Apart from this, literature evidence strongly suggests that novel designing and accessing of fused *N*-heterocycles would be helpful to reach expected targets which are being needed for human

welfare. In this respect, few novel target structures have been designed to partial fulfillment of present demand and may be expected to show diverse potential applications (**Figure 6.2**).

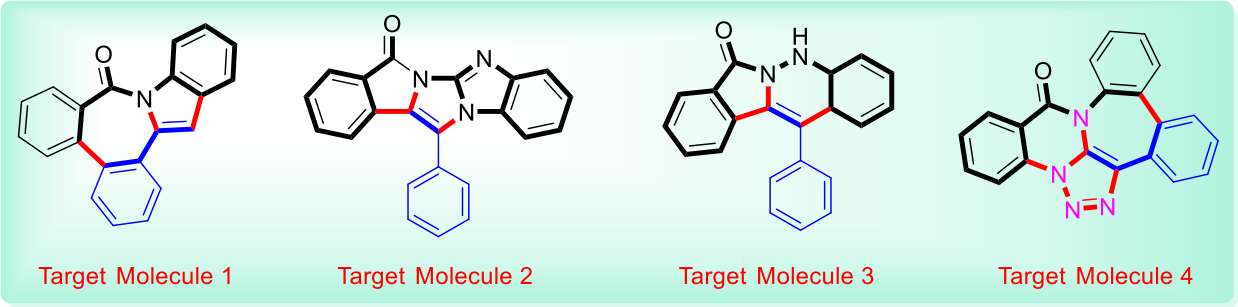


Figure 6.2 Some designed fused *N*-heterocycles

Appendices

Appendices

LIST of PUBLICATIONS *[A-1]*

1. **Hitesh Kumar Saini**, Shiv Dhiman, Nitesh Kumar Nandwana, Krishnan Rangan and Anil Kumar, Copper Catalyzed Sonogashira Coupling, Intramolecular Hydroamidation and Palladium Catalyzed Heck Reaction toward One-pot Synthesis of Isoindolo[2,1-*b*]isoquinolin-7(5*H*)-ones, *Org. Biomol. Chem.* **2019**, *17*, 4281-4290
2. Nitesh Kumar Nandwana, Rajnish Prakash Singh, Om P. S. Patel, Shiv Dhiman, **Hitesh Kumar Saini**, Prabhat N. Jha, and Anil Kumar, Design and Synthesis of Imidazo/Benzimidazo[1,2-*c*]quinazoline Derivatives and Evaluation of their Antimicrobial Activity, *ACS Omega* **2018**, *3*, 16338-16346
3. Shiv Dhiman, Nitesh Kumar Nandwana, **Hitesh Kumar Saini**, Dalip Kumar, Krishnan Rangan, Katherine N. Robertson, Mukund Jha and Anil Kumar, Nickel-Catalyzed Tandem Knoevenagel Condensation and Intramolecular Direct Arylation: Synthesis of Pyrazolo[5,1-*a*]isoquinoline Derivatives, *Adv. Synth. Catal.* **2018**, *360*, 1973-1983
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5. Nitesh Kumar Nandwana, Vikki N Shinde, **Hitesh Kumar Saini** and Anil Kumar, Copper-Catalysed One-pot Tandem Reaction for the Synthesis of Imidazo[1,2-*c*][1,2,3]triazolo[1,5-*a*]quinazolines, *Eur. J. Org. Chem.* **2017**, 6445-6449.
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7. Nitesh Kumar Nandwana, Shiv Dhiman, **Hitesh Kumar Saini**, Indresh Kumar and Anil Kumar, Synthesis of Quinazolinones, Imidazo[1,2-*c*]quinazolines and Imidazo[4,5-*c*]quinolines through Tandem Reductive Amination of Aryl Halides and Oxidative Amination of C(sp^3)-H Bonds, *Eur. J. Org. Chem.* **2017**, 514-522.

8. Shiv Dhiman, **Hitesh Kumar Saini**, Nitesh Kumar Nandwana, and Anil Kumar, Copper Catalyzed Synthesis of Quinoline Derivatives *via* Tandem Knoevenagel Condensation, Amination and Cyclization, *RSC Adv.* **2016**, *6*, 23987-23994.
9. **Hitesh Kumar Saini**, PinkuKaswan, KasiviswanadharajuPericherla,and Anil Kumar, Synthesis of Naphtho-Fused Imidazo[1,2-*a*]pyridines through Copper Catalyzed Cascade Reactions, *Asian J. Org. Chem*. **2015**, *4*, 1380-1385.
10. **Hitesh Kumar Saini**, Shiv Dhiman, KasiviswanadharajuPericherla, and Anil Kumar, Synthesis of Imidazo[1,2-*f*]phenanthridines through Palladium Catalyzed Intramolecular Direct Arylation, *Synthesis* **2015**, *47*, 3727-3732.
11. PinkuKaswan, KasiviswanadharajuPericherla, **Hitesh Kumar Saini** and Anil Kumar, One-pot, Three Component Tandem Reaction of 2-Aminopyridines, Acetophenones and Aldehydes: Synthesis of 3-Aroylimidazo[1,2-*a*]pyridines, *RSC Adv*. **2015**, *5*, 3670-3677.

CONFERENCE PRESENTATIONS

Oral Presentations

1. **Hitesh Kumar Saini**, Nitesh Kumar Nandwana, Shiv Dhiman, and Anil Kumar "Sequential Sonogashira Coupling, Hydroamination and Direct Arylation: A New Route to Azepino-fused Isoindolinones" National Symposium on Contemporary Facets in Organic Synthesis (CFOS)-2017, Department of Chemistry, **IIT Roorkee**, India, December 22-24, 2017.
2. **Hitesh Kumar Saini**, Nitesh Kumar Nandwana, Shiv Dhiman, and Anil Kumar "Copper, and Palladium Catalyzed Consecutive-Operation: Direct Synthesis of Functionalized Azepino Fused Isoindol-14-ones" National Conference on New Vistas in Chemical Research (NVCR)-2017, Department of Chemistry, **The IIS University Jaipur**, India, January 18-19, 2017.
3. **Hitesh Kumar Saini**, PinkuKaswan, KasiviswanadharajuPericherla,and Anil Kumar "Synthesis of Naphtho-Fused Imidazo[1,2-*a*]pyridines *via* Copper Catalyzed Cascade Reactions and Study of their Photophysical Properties" International Conference on Current Challenges in Drug Discovery Research (CCDDR)-2015, Department of Chemistry, **MNIT Jaipur**, India, November 23-25, 2015.

Poster Presentations

1. **Hitesh Kumar Saini**, and Anil Kumar "A New Strategy to Access Azepino-Fused Isoindol-14-ones" 23th ISCB International Conference (ISCBC-2017) on Interface of Chemical Biology in Drug Research, **SRM University**, Chennai, India, February 8-10, 2017.
2. **Hitesh Kumar Saini**, PinkuKaswan, Shiv Dhiman, Nitesh Kumar Nandwana, and Anil Kumar "A Copper-Catalyzed Cyanation on Substituted Imidazoles with Malononitrile and Study of their Photophysical Properties" National Conference on Organic Chemistry in Sustainable Development: Recent Advances and Future Challenges (OCSD)-2016, Department of Chemistry, **BITS Pilani-Pilani Campus**, Rajasthan, India, August 29-30, 2016.
3. **Hitesh Kumar Saini**, PinkuKaswan, KasiviswanadharajuPericherla,and Anil Kumar "A New Route to Naphtho-Fused Imidazo[1,2-*a*]pyridines *via* Copper Catalyzed Cascade Reactions and Study of their Photophysical Properties"International conference on Nascent Developments in Chemical Sciences: Opportunities for Academia-Industry Collaboration (NDCS)-2015, Department of Chemistry, **BITS Pilani-Pilani Campus**, Rajasthan, India, October 16-18, 2015.
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5. **Hitesh Kumar Saini**, Shiv Dhiman, KasiviswanadharajuPericherla, and Anil Kumar "Facile Synthesis of Imidazo[1,2-*f*]phenanthridines through Palladium Catalyzed Intramolecular Direct Arylation" National Conference on Advanced Scientific Developments in Chemical Sciences (ASDCS)-2014, Department of Chemistry, **DeenbandhuChhotu Ram University of Science and Technology**, Murthal, India, March 14, 2014.
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WORKSHOP

1. Workshop on Analytical Instruments for Chemical and Environmental Engineers (WAICEE), March 22-23rd, 2013 at Department of Chemical Engineering, BITS Pilani, Pilani Campus, Rajasthan, India.

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Copper and palladium-catalyzed sequential reactions: one-pot synthesis of isoindolo[2,1-*b*]isoquinolin-7(5*H*)-ones†

Hitesh Kumar Saini,‡[a] Shiv Dhiman,‡[a] Nitesh Kumar Nandwana,[a] Rangan Krishnan[b] and Anil Kumar *[a]

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A highly efficient protocol has been developed for the synthesis of diversely substituted isoindolo[2,1-*b*]isoquinolin-7(5*H*)-ones through sequential Cu(II)-catalyzed Sonogashira coupling, intramolecular hydroamidation followed by palladium-catalyzed ligand-free Heck reaction. Good to excellent yields (41–94%) were observed with excellent substrate scope and functional group tolerance. The developed method represents a practical strategy for the construction of bioactive isoindolo[2,1-*b*]isoquinolin-7(5*H*)-ones.

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Article

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Design and Synthesis of Imidazo/Benzimidazo[1,2-*c*]quinazoline Derivatives and Evaluation of Their Antimicrobial Activity

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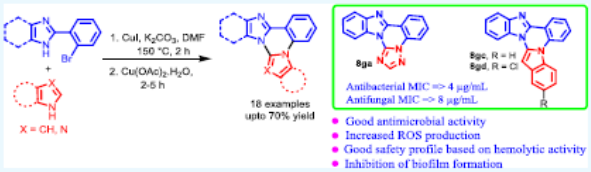
Supporting Information

ABSTRACT: A new class of fused quinazolines has been designed and synthesized via copper-catalyzed Ullmann type C−N coupling followed by intramolecular cross-dehydrogenative coupling reaction in moderate to good yields. The synthesized compounds were tested for in vitro antibacterial activity against three Gram negative (*Escherichia coli*, *Pseudomonas putida*, and *Salmonella typhi*) and two Gram positive (*Bacillus subtilis*, and *Staphylococcus aureus*) bacteria. Among all tested compounds, 8ga, 8gc, and 8gd exhibited promising minimum inhibitory concentration (MIC) values (4−8 μg/mL) for all bacterial strains tested as compared to the positive control ciprofloxacin. The synthesized compounds were also evaluated for their in vitro antifungal activity against *Aspergillus niger* and *Candida albicans* and compounds 8ga, 8gc, and 8gd having potential antibacterial activity also showed pronounced antifungal activity (MIC values 8−16 μg/mL) against both strains. The bactericidal assay by propidium iodide and live−dead bacterial cell screening using a mixture of acridine orange/ethidium bromide (AO/Et·Br) showed considerable changes in the bacterial cell membrane, which might be the cause or consequence of cell death. Moreover, the hemolytic activity for most potent compounds (8ga, 8gc, and 8gd) showed their safety profile toward human blood cells.



FULL PAPER DOI: 10.1002/adsc.201701519 Advanced Synthesis & Catalysis

Nickel-Catalyzed Tandem Knoevenagel Condensation and Intramolecular Direct Arylation: Synthesis of Pyrazolo[5,1-*a*]-isoquinoline Derivatives

Shiv Dhiman,[a] Nitesh Kumar Nandwana,[a] Hitesh Kumar Saini,[a] Dalip Kumar,[a] Krishnan Rangan,[b] Katherine N. Robertson,[c] Mukund Jha,[d] and Anil Kumar[a,*]

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Sequential Reaction

Sequential Copper-Catalyzed Sonogashira Coupling, Hydroamination and Palladium-Catalyzed Intramolecular Direct Arylation: Synthesis of Azepino-Fused Isoindolinones

Hitesh Kumar Saini,[a] Nitesh Kumar Nandwana,[a] Shiv Dhiman,[a] Krishnan Rangan,[b] and Anil Kumar*[a]

Abstract: A sequential copper-catalyzed Sonogashira coupling followed by an intramolecular hydroamination and palladium-catalyzed intramolecular direct arylation reaction was developed to provide a convenient and modular approach for the synthesis of useful azepino-fused isoindolinones. Nineteen azepino-fused isoindolinones were prepared in moderate to high (22–90 %) yields. The developed protocol tolerated various functional groups and involved the formation of one carbon–nitrogen and two carbon–carbon bonds in a one-pot fashion. The palladium-catalyzed intramolecular direct arylation step involved formation of an unusual eight-membered palladacycle.

ChemPubSoc Europe
DOI: 10.1002/ejoc.201701221
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Communication

Domino Reactions

Copper-Catalyzed One-Pot Tandem Reaction for the Synthesis of Imidazo[1,2-*c*][1,2,3]triazolo[1,5-*a*]quinazolines

Nitesh K. Nandwana,[a] Vikki N. Shinde,[a] Hitesh K. Saini,[a] and Anil Kumar*[a]

Abstract: A copper-catalyzed tandem reaction of 2-(2-bromoaryl)imidazoles/2-(2-bromoaryl)benzimidazoles, alkynes, and sodium azide was developed for the synthesis of imidazo-[1,2-*c*][1,2,3]triazolo[1,5-*a*]quinazolines in moderate to excellent yields (50–85 %). The one-pot method involves copper-catalyzed azide–alkyne cycloaddition (CuAAC), intramolecular cross-dehydrogenative C–N bond formation, and Ullmann-type C–N coupling. This protocol involves the use of air as the oxidant under mild and ligand-free reaction conditions, and the reaction can be performed with a broad range of substrates with high efficiency.

ChemPubSoc Europe
DOI: 10.1002/slct.201701778
Chemistry SELECT Full Papers

Organic & Supramolecular Chemistry

A Facile Synthesis of Quinazolin-4(3*H*)-ones via Copper-Catalyzed One-Pot, Three-Component Tandem Reaction

Shiv Dhiman, Nitesh K. Nandwana, Shreemala Dhayal, Hitesh K. Saini, Dalip Kumar, and Anil Kumar*[a]

A simple and convenient one-pot, three-component tandem reaction has been developed for the synthesis of substituted quinazolin-4(3H)-ones using CuI/L-proline as catalytic system. A series of 35 quinazolin-4(3H)-ones was synthesized in good to high yield. The method involves copper-catalyzed double C—N coupling, reductive amination, condensation, cyclization and aerobic oxidation. Good functional group tolerance, mild reaction condition, readily available starting materials and user friendly procedure makes this protocol practically good and attractive method for the synthesis of quinazolin-4(3H)-ones.

ChemPubSoc Europe

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EurJOC European Journal of Organic Chemistry

Full Paper

Nitrogen Heterocycles

Synthesis of Quinazolinones, Imidazo[1,2-*c*]quinazolines and Imidazo[4,5-*c*]quinolines through Tandem Reductive Amination of Aryl Halides and Oxidative Amination of C(sp^3)–H Bonds

Nitesh Kumar Nandwana,[a] Shiv Dhiman,[a] Hitesh Kumar Saini,[a] Indresh Kumar,[a] and Anil Kumar*[a]

Abstract: A tandem multicomponent approach has been described for the synthesis of quinazolinones, imidazo[1,2-*c*]quinazolines and imidazo[4,5-*c*]quinolines. The reaction involves a copper-catalyzed reductive amination through azidation followed by reduction and oxidative amination of C(sp^3)–H bonds of *N*,*N*-dimethylacetamide in the presence of TBHP (*tert*-butyl-hydroperoxide) as oxidant. The method uses the easily available sodium azide as a nitrogen source and DMA (*N*,*N*-dimethylacetamide) as a one-carbon source for the synthesis of these *N*-fused heterocycles in good to excellent yields. The reaction can also be used for gram-scale synthesis.

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Copper-catalyzed synthesis of quinoline derivatives *via* tandem Knoevenagel condensation, amination and cyclization†‡

Shiv Dhiman, Hitesh Kumar Saini, Nitesh Kumar Nandwana, Dalip Kumar and Anil Kumar*

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A novel regioselective synthesis of 2-aminoquinolines and 2-arylquinoline-3-carbonitriles is described *via* copper-mediated tandem reaction. Formation of substituted quinolines involves Knoevenagel condensation of *ortho*-bromobenzaldehyde with active methylene nitriles followed by copper-catalyzed reductive amination and intramolecular cyclization.

ACES

DOI: 10.1002/ajoc.201500297

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Full Paper

Nitrogen Heterocycles

Synthesis of Naphtho-Fused Imidazo[1,2-*a*]pyridines through Copper-Catalyzed Cascade Reactions

Hitesh Kumar Saini, Pinku Kaswan, Kasiviswanadharaju Pericherla, and Anil Kumar*[a]

Dedicated to Professor S. M. S. Chauhan on the occasion of his 64th birthday

Abstract: A highly efficient copper-catalyzed one-pot tandem protocol has been developed for the synthesis of naphtho-fused imidazo[1,2-*a*]pyridines. The transformation involves a Knoevenagel condensation followed by a chemoselective cross-coupling reaction along with a carbon-carbon bond cleavage. This protocol can tolerate a variety of functional groups and provided naphtho[1′,2′:4,5]imidazo[1,2-*a*]pyridines in moderate to excellent (35–91 %) yields. The photophysical studies of the naphtho-fused imidazo[1,2-*a*]pyridines show a bathochromic shift between the band maxima of the absorption and emission spectra. These compounds emit with high fluorescence quantum yields.

A

Synthesis of Imidazo[1,2-*f*]phenanthridines through Palladium-Catalyzed Intramolecular C–C Bond Formation

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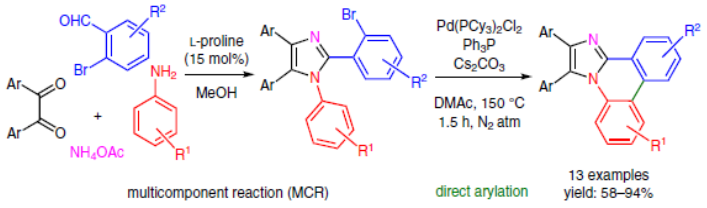

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One-pot, three component tandem reaction of 2-aminopyridines, acetophenones and aldehydes: synthesis of 3-aroylimidazo[1,2-*a*]pyridines†

Pinku Kaswan, Kasiviswanadharaju Pericherla, Hitesh Kumar Saini and Anil Kumar*

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Accepted 4th December 2014

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A facile synthesis of 3-aroylimidazo[1,2-*a*]pyridine derivatives has been achieved through the one-pot, three-component tandem reaction of acetophenones, arylaldehydes and 2-aminopyridines in the presence of a catalytic amount of copper(II) chloride and air as the sole oxidant. The developed one-pot method is atom-economical and utilizes readily available precursors to offer highly functionalized N-fused imidazoles in moderate to good yields (26–82%). The presented tandem process is expected to proceed *via* crossed aldol condensation, Michael addition, copper catalyzed oxidative cyclization and subsequent aromatization.

Brief Biography of the candidate *[A-3]*

Hitesh Kumar Saini was born in August 1990 at village Jeewa wali dhani of Jhunjhunu district in Rajasthan, India. He completed his BSc and MSc degrees from University of Rajasthan, Jaipur in the year 2009 and 2011, respectively. After clearing CSIR-UGC (JRF) with AIR 69th he joined for the PhD programme at Department of Chemistry, BITS Pilani, Pilani Campus in January 2013 under the supervision of Prof. Anil Kumar. He has also cleared GATE-2012. Mr. Hitesh was upgraded to senior research fellowship (SRF) in January 2015. During the doctoral research, he has published eleven research articles in peer reviewed international journals. He has also participated in various national/international conferences and symposiums and presented his research work in the form of oral and poster presentations.

Mr. Saini's research mainly focuses on the development of new synthetic methodologies for the synthesis of fused aza-heterocycles through copper and palladium-catalyzed direct arylation reactions.

Brief Biography of the Advisor *[A-4]*

Dr. Anil Kumar is Professor of Chemistry at the Birla Institute of Technology and Science, Pilani. He obtained his PhD degree from Department of Chemistry, University of Delhi, Delhi, India under the guidance of Professor SMS Chauhan in 2004. During his doctoral studies Dr. Kumar worked on development of heterogeneous catalyst for organic synthesis with emphasis on green chemistry. He was postdoctoral fellow at Department of Biomedical and Pharmaceutical Sciences, University of Rhode Island, Kingston, USA in Prof. KeykavousParang group during May 2004 to April 2006. In his postdoctoral studies he has worked on synthesis of novel Src kinase inhibitory agents and solid phase synthesis. He joined Department of Chemistry, Birla Institute of Technology and Science, Pilani, India as Assistant Professor in 2006 and was promoted to Associate Professor on February 2013 and Professor on August 2018. Dr. Kumarhas also served as Associate Dean, Work Integrated Learning Programmes (WILP) during May 2014 – August 2018 and Head of Department of Chemistry, BITS Pilani, Pilani Campusduring September 2014 – August 2016. He has visited University of Rhode Island, Kingston, USA and Chapman University, Irvine, USA as visiting scientist, and Acadia University, Wolfville, Canada as Harrison McCain visiting Professor.

Dr. Kumar is recipient of Prof. S. Vankateswaran Faculty Excellence Award from BITSAA for 2017, Dr. Arvind Kumar Memorial Award from Indian Council of Chemists for 2014, ISCB Young Scientist award in Chemical Sciences for 2013, and Harrison McCain Foundation award from Acadia University, Canada for 2012. He has 19 year of research experience and over 12 year of teaching experience. His research interest lies in development of reaction methodologies using transition metal catalyzed C-C coupling reactions, green chemistry, ionic liquids and medicinal chemistry. He has published 150 research papers in international journals of repute in the area of synthetic organic chemistry, green chemistry and medicinal chemistry and contributed two book chapters. He has participated in several national and international symposiums/ conferences and delivered more than 40 invited lectures. He has guided eight PhD students as supervisor and two as co-supervisor. Currently he is supervising seven PhD students as supervisor and one student as co-supervisor. He has completed four research project as PI sponsored by DST, CSIR and UGC, and one as Co-PI sponsored by DST. Currently, he has one major projects from SERB. He is editor for Canadian Chemical Transactions and member of editorial advisory board for The Open Catalysis Journal and also served as a reviewer for several journals. He is life member of Chemical Research Society of India, Bangalore; Indian Society of Chemists and Biologists, Lucknow; and Indian Council of Chemists, Agra.