Organoiodine-Promoted Strategies for the Construction of Selected Bioactive Heterocycles

THESIS

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by

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Dedicated to My

Father G. Velladurai, Mother V. Balasundari,

Wife A. Baggyalakshmi, Friend Jenison

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V. ARUN

ABSTRACT

Organoiodine reagents have been extensively used in plethora of organic transformations to assemble medicinally important azaheterocycles because of their safety profile, mild reaction conditions and high yields of pure products. The recent surge of organoiodine-based reactions as potential alternatives to transition metal-catalyzed reactions led to the development of many novel synthetic protocols by devoiding the usage of ligands, additives and excess reagents. In view of economic and environmental consideration, new and improved catalytic methods involving organoiodine reagents should become an area of major focus to facilitates the synthesis of bioactive heterocycles in more sustainable fashion. This thesis deals with the utility of organoiodine reagents in the development of new synthetic routes to construct medicinally important azaheterocycles *via* C-C and C-X bond formations.

The first chapter highlights the recent advancement of organoiodine reagents in the construction of biologically important azaheterocycles and natural products. Especially synthesis, reactivity and applications of diaryliodonium salts in the carbon-carbon and carbon-heteroatom bond formations for the constructions of valuable heterocyclic frameworks under metal and metal-free conditions are briefly explained in this chapter. Additionally, significance of natural and synthetic bisindole analogues and azaheterocylces in cancer drug discovery are also elaborated.

The second chapter illustrates the synthesis of novel 2,5-bis(indolyl)-1,3,4-oxadiazoles by iodobenzene diacetate-mediated oxidative cyclization of easily accessible bis(indolyl)hydrazide-hydrazones involving relatively benign reaction conditions. All of the synthesized oxadiazoles showed improved cytotoxicity over previously reported bis(indolyl)heterocycles. Bromo-substituted bis(indolyl)1,3,4-oxadiazole was the most active compound in the series with IC_{50} value of 20 nm against prostate (DU145) and cervical (HeLa) cancer cell lines. The structure–activity relationship study revealed that a bromo substituent is crucial for imparting potent cytotoxic activity and N-alkylation is beneficial for improving the selectivity of the compound towards a particular cancer type. Preliminary mechanism of action studies of bis(indolyl)-1,3,4-oxadiazoles indicated apoptotic induced cell death in breast cancer cells (MDA-MB-231)

The third chapter demonstrates the synthesis of diaryl sulfones and biaryls using diaryliodonium salts. Part A describes an efficient and general protocol for the synthesis of diaryl sulfones *via* the metal-free coupling of readily available diaryliodonium salts and arenesulfinates in PEG-400 under microwave irradiation has been developed. Utilizing this metal-free and eco-friendly protocol, various diaryl sulfones were prepared in high yields and shorter reaction times under mild reaction conditions. Furthermore, the coupling of diaryliodonium with arenesulfinate salts with and without copper iodide provided convenient access to various diaryl sulfones with high selectivity. Part B exemplified a ligand- and base-free Pd-catalyzed synthesis of useful biaryls from easily accessible and stable diaryliodonium salts. The highlights of the present protocol include operational simplicity, mild reaction conditions, broad substrate scope for symmetrical and unsymmetrical biaryls, scalability, and the use of a recyclable Pd catalyst. The potential utility of the developed method was demonstrated by preparing valuable heterocycles such as 5-aryluracils, carbazoles, chromenones, fluorenones, phenanthiridines, and boscalid analogues.

The fourth chapter illustrates the synthesis of 2-arylindoles and heteroaryl carboxylates under ligand and base-free conditions. Part A elaborates on successful utilization of carboxylic acid as a traceless directing group to arylate C2-position of indole in a regioselective fashion by using easily accessible heteroaryl carboxylic acids and diaryliodonium salts. The C2-arylation of indole derivatives proceed *via* decarboxylative coupling using only catalytic amount of $Pd(OAc)_2$ (1.0 mol%) in water. The developed protocol was successfully progressed without any ligand, oxidant, base and acid to prepare a range of 2-arylindoles in good to excellent yields. The protocol was equally compatabile with indole-3-acetic acid, indole-3-butyic acid and tryptamine The synthetic utility of the developed procedure was proved by preparing CDK inhibitor, Paullone in good yield. Part B deals with a new eco-friendly synthetic protocol to prepare heteroaryl carboxylates from heteroaryl carboxylic acids and diaryliodonium salts under neat DMF heating without any acid, base or coupling reagents. This strategy was compatible to variety of heterocyclic acids such as indole, pyrrole, furan and pyridine. Interestingly, indole-3-acetic acid also afforded the corresponding carboxylates in good yields. In all cases C-O arylated products were exclusively formed.

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LIST OF ABBREVATIONS AND SYMBOLS

Abbreviation/Symbol	Description
α	Alpha
β	Beta
Δ	Delta
°C	Degree centigrade
Å	Angstrom
Ac	Acetyl
Ac_2O	Acetic anhydride
ACN	Acetonitrile
Ar	Aryl
Bn	Benzyl
BTI	[Bis(trifluoroacetoxy)iodo]benzene
Bu	Butyl
t-BuOK	Potassium *tert*-butoxide
Calcd.	Calculated
^{13}C	Carbon-13
CA-4	Combretastatin A-4
Cat.	Catalyst
CAN	Ceric ammonium nitrate
$CDCl_3$	Deuterated chloroform
Chalcones	1,3-Diarylprop-2-en-1-ones
Conc	Concentration
CuAAC	Copper catalyzed Azide-Alkyne Cycloaddition

CDK	Cyclin-dependent kinase
d	Doublet
DABCO	1,4-Diazabicyclo[2.2.2]octane
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
dd	Doublet of doublet
DCE	Dichloroethane
DCM	Dichloromethane
DG	Directing group
DIB	(Diacetoxy)iodobenzene
DMA	*N,N*-Dimethylacetamide
DMP	Dess-Martin periodinane
DMF	*N,N*-Dimethylformamide
DMF-DMA	*N,N*-Dimethylformamide dimethyl acetal
DMSO-d_6	Deuterated dimethylsulfoxide
EC_{50}	Maximal effective concentration
ED_{50}	Effective dose 50%
EDTA	Ethylenediaminetetraacetic acid
EGFR	Epidermal growth factor receptor
EI	Electron ionization
ESI	Electrospray ionization
EtOAc	Ethyl acetate
EtOH	Ethanol
Equiv	Equivalent
g	Gram
GPCR	G-protein coupled receptors

h	Hours
HCN	Hydrogen cyanide
HFIP	*1,1,1,3,3,3*-Hexafluoroisopropanol
HRMS	High resolution mass spectra
HTIB	(Hydroxy(tosyloxy)iodo)benzene
IBX	2-Iodoxybenzoic acid
IC_{50}	Half maximal inhibitory concentration
IR	Infrared
Hz	Hertz
J	Coupling constant
Lit.	Literature
m-CPBA	*m*-Choroperbenzoic acid
MCR	Multi component reaction
Me	Methyl
MS	Mass spectrometry
mp	Melting point
m	Multiplet
MeOH	Methanol
mg	Milligram
MHz	Mega Hertz
MIC	Minimum inhibitory concentration
min	Minutes
mL	Milliliter
mmol	Millimole

MTT	(3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide)
MW	Microwave
NCI	National Cancer Institute
NH_3	Ammonia
N_2	Nitrogen gas
NMP	*N*-Methyl pyrrolidine
NMR	Nuclear magnetic resonance
O_2	Oxygen gas
PIFA	Bis(trifluoroacetoxy)iodobenzen
PPA	Polyphosphoric acid
PPAR	Peroxisome proliferator-activated receptor
PEG	Polyethylene glycol
PIDA	Phenyl iodonium diacetate
Ph	Phenyl
ppm	Parts per million
PS	Polymer supported
%	Percentage
psi	Per square inch
PTK	Protein tyrosine kinase
PTP1B	Protein tyrosine phosphatase 1B
p-TsOH	*p*-Toluenesulfonic acid
R	Hydrocarbon
rt	Room temperature

s	Singlet
NBS	*N*-Bromosuccinimide
NIS	*N*-Iodosuccinimide
NIPA	N-(2-iodophenyl)acylamide
nM	Nano molar
SAR	Structure-activity relationship
t	Triplet
t-Bu	Tertiary butyl
T3P	Propylphosphonic anyhydride
TCPTP	T-Cell protein tyrosine phosphatase
TBAI	Tetrabutylammonium iodide
TBHP	*tert*-Butyl hydroperoxide
TDA-1	Tris(3,6-dioxaheptyl)amine
TFA	Trifluoroacetic acid
TFAA	Trifluoroacetic anhydride
TfOH	Trifluoromethanesulfonic acid
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMS	Tetramethylsilane
TMSCl	Trimethylsilyl chloride
δ	Parts per million
UV	Ultraviolet
w	Watt
μM	Micromolar

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Chapter I

Introduction

1.1 Introduction

Organoiodine compounds have emerged as versatile and environmentally benign reagents for organic chemistry.[1-3] It received noteworthy reputation in recent years as reagents of choice for synthetically useful oxidative transformations.[4] These reagents have been effectively utilized to carry out many organic transformations leading to various useful molecules.[5] For environmentally benign synthesis of useful molecules, organoiodine reagents have been increasingly utilized as very versatile and mild oxidants providing alternate to toxic and metal-based (lead, mercury and thallium) reagents, but with fewer toxicity effects.[1] In particular, trivalent and pentavalent organoiodine reagents with their strong electrophilic character and good leaving group ability of phenyliodino moiety renders as reagents of choice in synthetic chemistry. Organoiodine reagents bearing more than eight electrons in their valence shell are called as hypervalent organoiodine reagents. Iodine in iodine(III) reagents has a total of ten electrons and the overall geometry is distorted trigonal bipyramidal with two heteroatoms ligands X occupying the apical positions and with the least electronegative carbon ligand and both electron pairs residing in equatorial position.[6] The most common structural types of iodine (V) have a distorted octahedral structure with the organic group and the electron pair in apical position and four heteroatoms in the basal positions.[7] Two orthogonal (**3c**-**4e**) bonds accommodate all ligands while the apical moiety is bonded covalently to iodine.[2] Trivalent organoiodine reagents, for example, diaryliodonium salts **1**[5], iodobenzene diacetate (IBD, **2**)[9], bis(trifluoroacetoxy)iodobenzene (PIFA, **3**)[10], [hydroxy(tosyloxy)iodo]benzene (HTIB, Koser's reagent, **4**), iodosylbenzene **5** and iodobenzene dichloride **6**[8] have been more frequently utilized in the oxidative transformations of unsaturated substrates to various natural

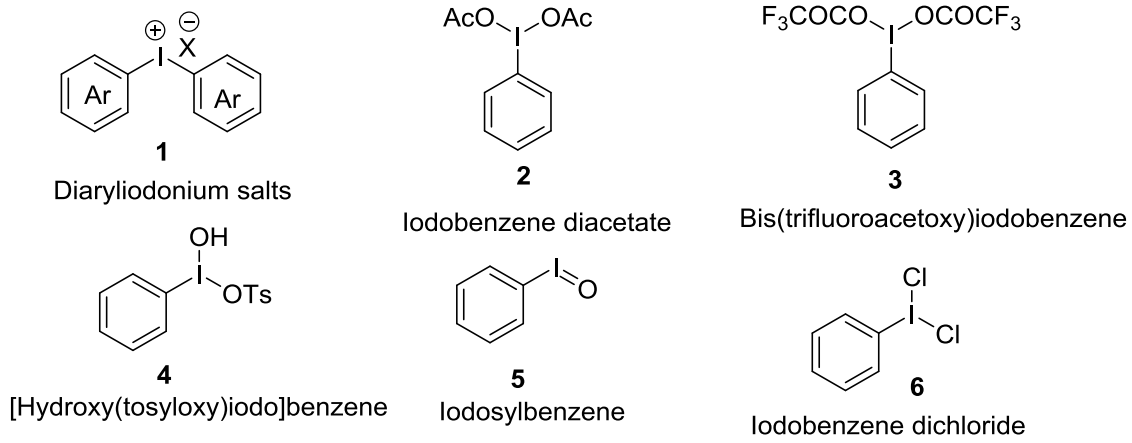


Figure 1.1 Some commonly used iodine(III) reagents

and synthetic compounds with interesting biological properties. Structures of some commonly used iodine(III) reagents are shown in Figure 1.1 Because of their strong electrophilic character, organoiodine reagents with iodine(V) including Dess-Martin periodinane (DMP, **7**)[11] and 2-iodoxybenzoic acid (IBX, **8**)[12] have been widely used in oxidative transformations leading to useful compounds.[4] They are well known as mild, highly selective and environmentally benign oxidants for performing many useful organic transformations. Togni's reagent **9**[13], iodosodilactone **10**[14] and TMS-EBX **11**[15] are among the recently identified cyclic organoiodine (III) reagents which have been widely used in a plethora of organic transformations. Structures of some commonly used organoiodine (V) reagents and cyclic iodine (III) reagents are depicted in Figure 1.2.

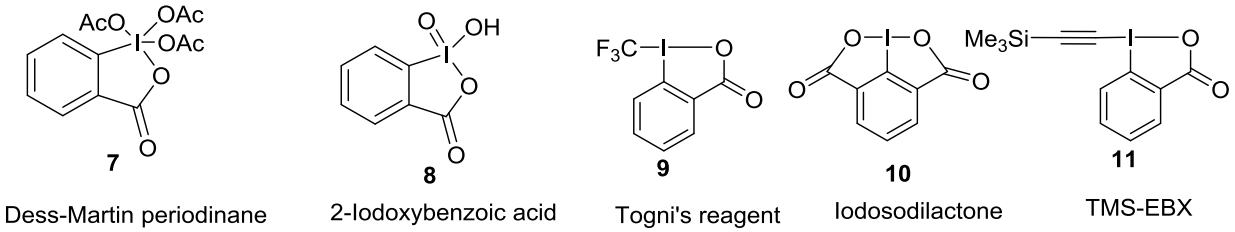


Figure 1.2 Some commonly used iodine(V) and cyclic iodine(III) reagents

To make organoiodine-induced protocols, more economical and effective polymer-supported organoiodine reagents were prepared (Figure 1.3).[16] Ley et al. prepared various polymer-supported organoiodine reagents **12-15** and demonstrated their synthetic potential in a range of useful compounds in high yield with high purity.[17] These supported reagents were found to be equally efficient and reactive in addition to their recyclability and reusability features. After the reaction polymer-supported (PS) with monovalent iodine could be recovered in quantitative yield by simple filtration, regenerated and reused which makes them to be very useful, effective and eco-friendly reagents in modern organic synthesis (Figure 1.4).

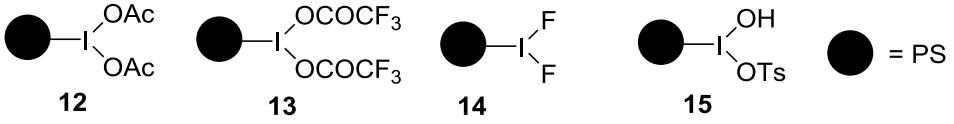


Figure 1.3 Polymer-supported iodine(III) reagents

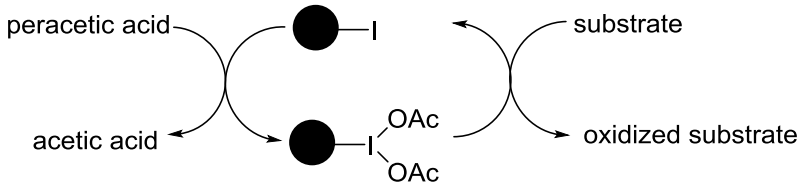


Figure 1.4 Catalytic cycle of polymer-supported iodine(III) reagent

The explosive nature and low solubility of IBX in standard organic solvents and susceptibility of DMP to moisture and prolonged storage restricts the synthetic utility of I(V) reagents.[18] To circumvent this problem, various non-explosive and soluble derivatives (**16-18)** of IBX have been synthesized (Figure 1.5). Mulbaier and Giannis synthesized a polymer-supported-IBX **16** and used for the oxidation of alcohols.[19] After the oxidation reaction generated reduced form of polymer-support can be easily separated by simple filtration to reuse the reagent by employing oxone as a terminal oxidant. Zhdankin et al. synthesized a polymer-supported N-(2-iodophenyl)acylamide (NIPA, **17**) which was effectively applied for the oxidation of a wide range of alcohols.[20] Zhang et al. prepared 5-trimethylammonio-1,3-dioxo-1,3-dihydro-λ^5–benzo[*d*][1,2]iodoxol-1-ol anion (AIBX, **18)**, a water soluble *o*-iodoxybenzoic acid derivative with a trimethylammonium moiety and successfully performed dehydrogenation of various β-keto esters. AIBX was easily regenerated and reused in the oxidation of β-keto esters.

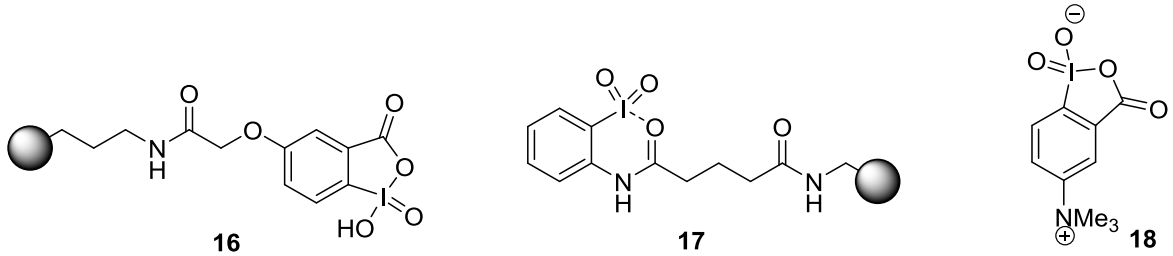
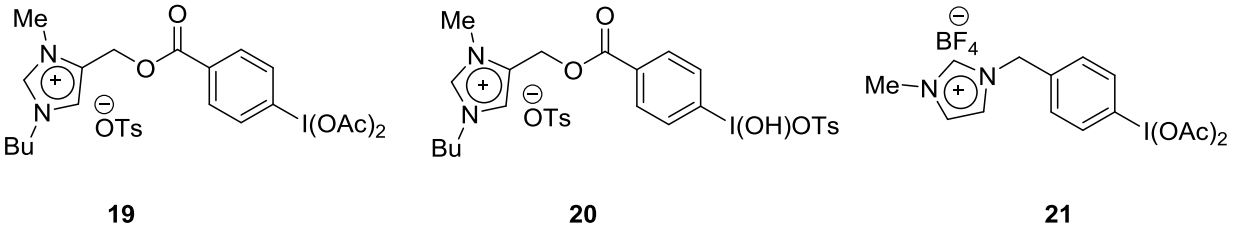


Figure 1.5 Structures of some representative iodine(V) reagents

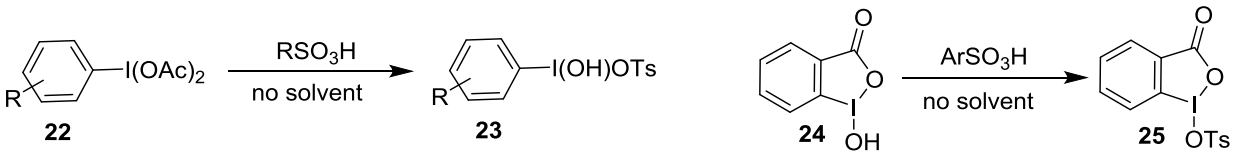
Handy and Okello prepared ionic liquid-supported stable and recyclable organoiodine(III) reagents **19** and **20** (Figure 1.6) and used in the preparation of α-functionalized ketones.[21] The by-product supported monovalent iodine could be easily separated from the product and recycled without compromising the product yield. In 2006, Zhang et al. reported an environmentally benign ionic liquid-supported iodine(III) reagent **21** (Figure 1.6) which was found to be quite effective in the selective oxidation of primary alcohols.[22]



19 **20** **21**

Figure 1.6 Representative ionic liquid-supported iodine(III) reagents

Prospects of organoiodine(V) reagents as environmentally benign oxidants were further strengthened by the success of I(V) promoted reactions in benign and recyclable reaction media such as water and ionic liquids. For example, IBX or DMP in [bmim]BF4 and [bmim]PF6 were utilized for the smooth oxidation of alcohols to the corresponding carbonyl compounds in excellent yields with high product selectivity. IBX or DMP promoted oxidative transformations were faster in ionic liquids when compared to conventional solvents (DMF, DMSO, water and EtOAc).[23] Chen et al. also developed an efficient and eco-friendly protocol for the oxidation of alcohols to carbonyl compounds by employing IBX in [bmim]Cl and water at room temperature. Further, by-product iodosobenzoic acid and reaction medium could be easily recycled without effecting the product yield.[24] Formation and successful reactions of organo iodine reagents in absence of organic solvent further widen their synthetic potential in modern organic synthesis. Yusubov and Wirth prepared trivalent and pentavalent iodine reagents (**22-25**) under solvent-free condition[25] and utilized in the preparation of useful precursors, α-tosyloxyketones with improved yield (Scheme 1.1).



22 **23** **24** **25**

Scheme 1.1 Solvent-free synthesis of organoiodine reagents

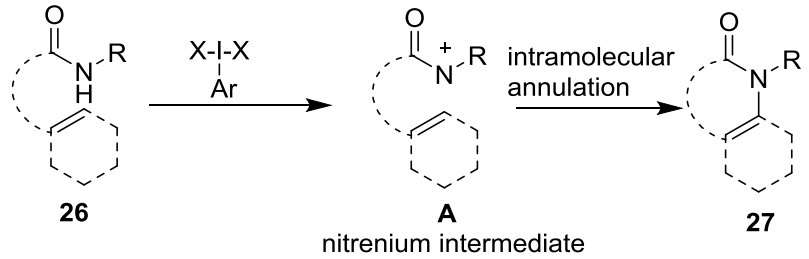
Organoiodine reagents are conventionally used as stoichiometric oxidants. In view of economic and environmental considerations, the recycling and catalytic applications of organoiodine reagents have been explored. In order to make organoiodine reagents cost effective and eco-friendly *in situ* oxidation of I(I) to I(III) or I(III) to I(V) in presence of an oxidant has been achieved. The successful *in situ* generation of these reagents enabled to perform several organic transformations under catalytic condition leading to smooth formation of various heterocycles.

Generally, a catalytic amount (5-20 mol%) of iodobenzene in presence of stoichiometric amount of oxidants such as *m*-CPBA, hydrogen peroxide or oxone was used for the *in situ* formation of active catalytic organoiodine reagents. Ochiai et al demonstrated iodobenzene catalyzed acetoxylation of ketones by *in situ* formation of IBD from the reaction of catalytic iodobenzene with stoichiometric amount of *m*-chloroperbenzoic acid.[26] Similarly, iodoarene-catalyzed cyclization of phenols was reported by Kita et al. using hydrogen peroxide/acid anhydride system. Similar to I(III) reagents, iodine(V) reagents were also effectively generated *in situ* using stoichiometric amounts of oxone and successfully explored their catalytic applications in the oxidation of alcohols.[27] Aiming to develop eco-friendly protocols using environmentally safe reagents, Vinod et al. developed a catalytic organoiodine(V) reagent using oxone as a co-oxidant and applied for the oxidation of various alcohols.[28]

1.2 Organoiodine reagents in the construction of azaheterocycles

Organoiodine reagents are rapidly prepared from easily accessible starting materials. In recent years, resurgent of interest in organoiodine led to discover many new organoiodine compounds with numerous synthetic utilities in modern organic synthesis for the construction of various bioactive heterocycles.[29] These organoiodine reagents offers many advantages such as reduced toxicity, high reactivity, stability, ready availability and easy handling and they have been successfully utilized to accomplish plethora of organic transformations such as oxidations, oxidative cyclizations, oxidative halogenations, oxidative functionalization of alkenes, oxidation of phenols, α-functionalization of carbonyl compounds. Especially, nitrogen-containing heterocylces are recognized as privileged structures in drug discovery. Thus, preparation of azaheterocycles is of great importance due to their various biological activities such as antimalarial, anti-HIV, antiviral, anti-cancer and antifungal. Organoiodine(III) mediated/catalyzed intramolecular oxidative C–H bond functionalization of heteroarenes and alkenes has been widely applied in the synthesis of several biologically active heterocyclic scaffolds.[30] This intramolecular oxidative C–H bond functionalization reaction leads to the formation of carbon–carbon and carbon–heteroatom bonds in an efficient manner. Of all bond formation reactions, C–N bond annulations have been exploited most and are of immense importance because of the wide occurrence of nitrogen-containing compounds as natural products, bioactive molecules, and functional materials. The common reactive intermediate formed during intramolecular C-N bond formation is depicted in Scheme 1.2. Experimental evidence disclosed that these reactions proceed *via* an ionic mechanism, involving initial

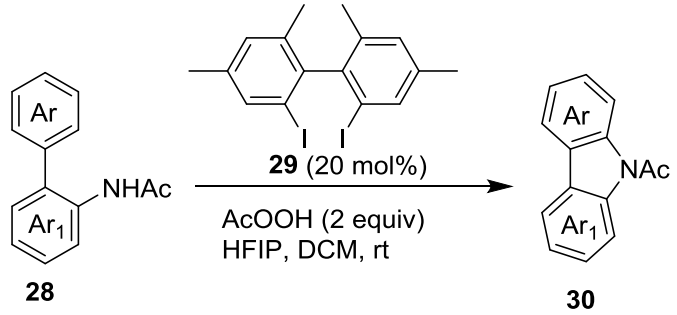
generation of N-acylnitrenium intermediate **A** from the reaction of the amide **26** with iodine(III) reagent, followed by intramolecular nucleophilic attack by a heteroarenes or alkenes led to cyclized products **27**.



Scheme 1.2 General reactivity pattern for oxidative amidation protocol

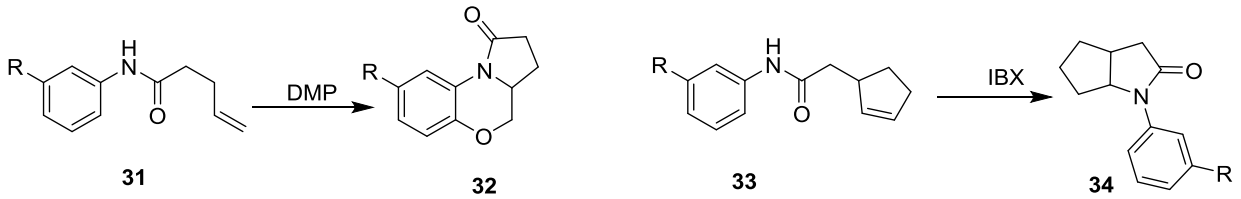
Some of the recent applications of organoiodine reagents for the construction of azaheterocycles are given below.

1.2.1 Carbazoles: By employing the aryl iodide **29** as a catalyst in the presence of peroxyacetic acid, Antonchick et al.[31] demonstrated an organocatalytic approach to synthesize carbazoles **30** through intramolecular C–H amination of amide precursors **28** (Scheme 1.3).



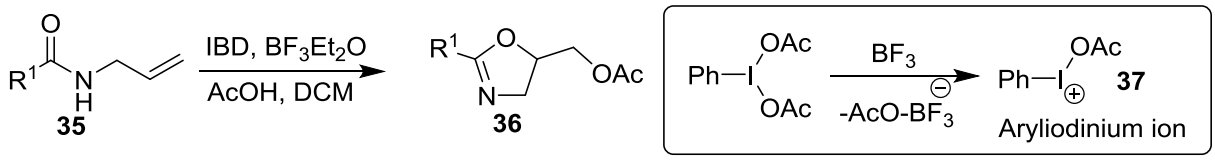
Scheme 1.3 Synthesis of carbazoles

1.2.2 Pyrrolidinones and oxazolidinones: The treatment of *N*-arylpentamides **31** with DMP (Dess-Martin periodinane), initiates an oxidation-cyclization sequence afforded tricyclic oxazine derivatives **32** (Scheme 1.4).[32] The IBX (2-iodoxybenzoicacid) promoted oxidation of unsaturated *N*-arylamides and urethanes **33** proceed efficiently to provide a variety of pyrrolidinones **34** (Scheme 1.4).[33]



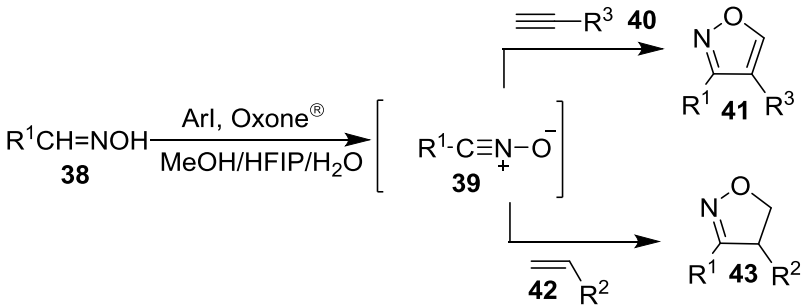
Scheme 1.4 Synthesis of oxazines **32** and pyrrolidinones **34**

1.2.3 Oxazolines: A new methodology for oxazolines was developed based on the unique property of iodine(III) reagents. Iodine(III) reagents based approach is a better alternative for the traditional methods to enantioselectively synthesize an oxazoline scaffold **36**. In this reaction, the electrophilicity of iodine(III) reagent, IBD was enhanced by the addition of a Lewis acid ($BF_3.Et_2O$). The possible mechanistic pathway suggested that an initial conversion of IBD into more electrophilic aryliodonium ion **37** which reacted with *N*-allylamides **35** to produce the functionalized oxazolines in good yields (Scheme 1.5).[34]



Scheme 1.5 Enantioselective synthesis of oxazolines

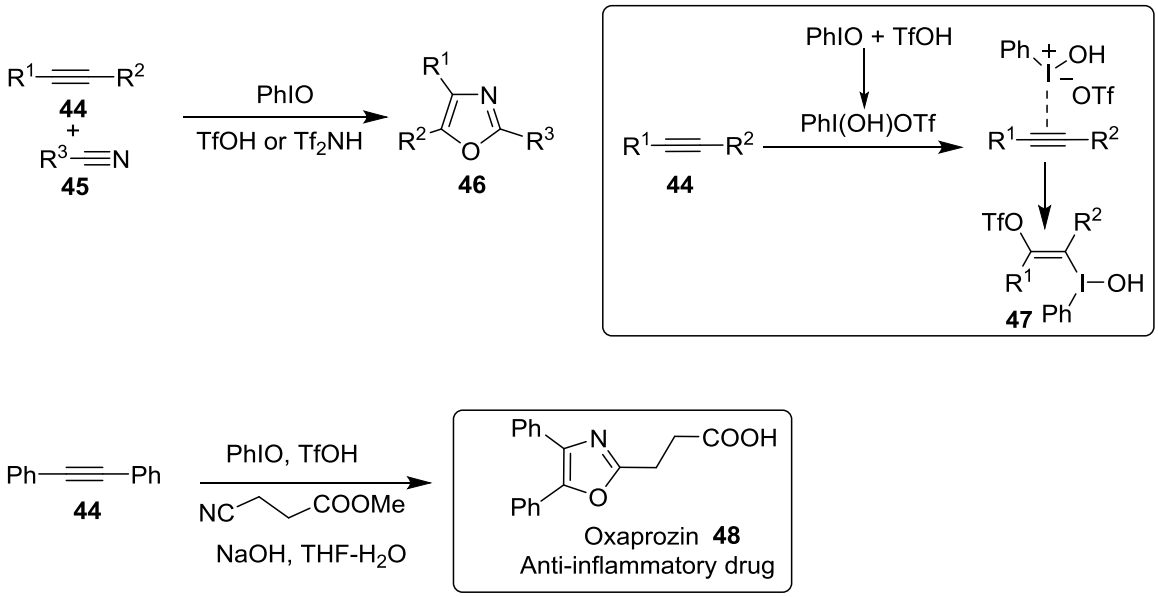
1.2.4 Isoxazoles: Zhdankin et al. reported the iodine(III) catalyzed oxidative cycloaddition of aldoximes **38** with alkenes and alkynes to prepare isoxazoles and isoxazolines. The active organoiodine(III) species was generated *in situ* by the oxidation of catalytic 3,5-dimethyliodo-benzene using oxone as an inexpensive and environmentally safe terminal oxidant in aqueous 1,1,1,3,3,3-hexafluoroisopropanol (HFIP). This activated iodine(III) promoted oxidation of corresponding aldoximes efficiently produced nitrile oxides **39** which upon cycloaddition reaction with various alkynes **40** and alkenes **42** resulted in isoxazoles **41** and isoxazolines **43** respectively in moderate to excellent yields (up to 92 %). In this oxidative conversion, HFIP is believed to increase the electrophilicity of I (III) reagent (Scheme 1.6) [35].



Scheme 1.6 Synthesis of substituted isoxazoles and isoxazolines

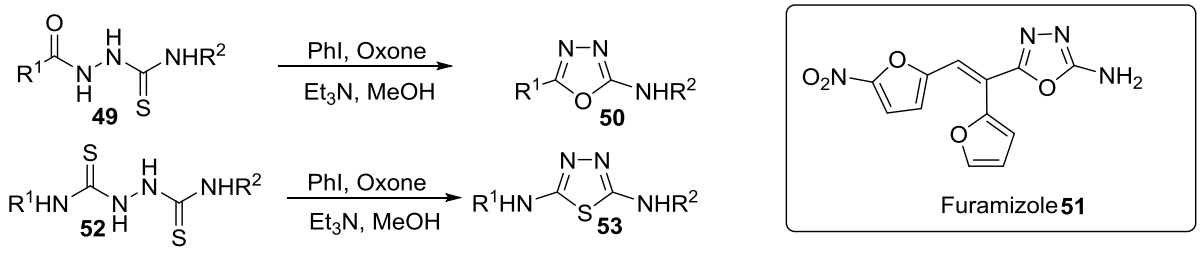
1.2.5 Oxazoles: A regioselective synthesis of 2,4-disubstituted and 2,4,5-trisubstituted oxazoles was developed by Saito et al. The reaction was fruitfully carried out by the activation of alkynes

44 using mild iodine(III) reagent, PhI(OH)OTf. Alkyne activating reagent PhI(OH)OTf was generated *in situ* by the combination of iodosobenzene and triflic acid. The activated alkynes **47** were reacted with various nitriles **45** by Ritter-type addition and subsequent cyclization with oxygen atom in an [2+2+1] annulation fashion to deliver the useful oxazole derivatives **46** in good yields. The mechanistic investigation of the initial activation step revealed that PhI(OH)OTf and alkynes combination likely to form alkenyliodonium intermediates. The developed method allowed to prepare an anti-inflammatory drug Oxaprozin **48** (Scheme 1.7).[36]



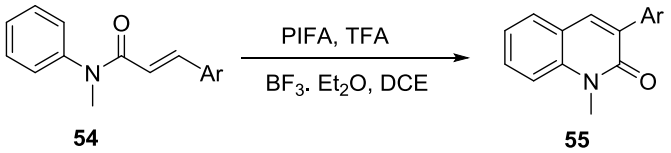
Scheme 1.7 Regioselective synthesis of substituted oxazoles

1.2.6 Oxadiazoles and Thiadiazoles: Oxidative desulfurization of acylthiosemicarbazides **49** and bisdiarylthioureas **52** involving hydroxy(phenyl)iodonium ion was effectively applied by Telvekar et al. to achieve the corresponding oxadiazoles **50** and thiadiazoles **53** in good to excellent yields. This active iodine species, hydroxy(phenyl)iodonium ion was generated by the oxidation of iodobenzene using inexpensive and readily available oxone as a co-oxidant at room temperature. (Scheme 1.8).[37]



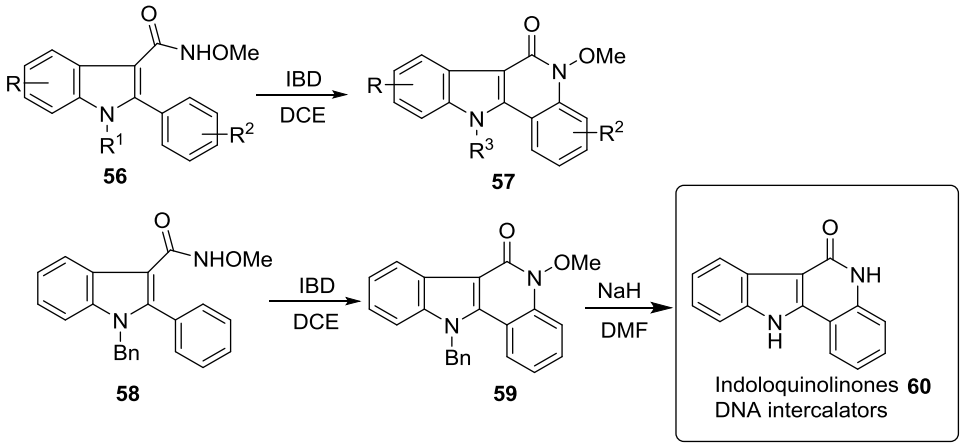
Scheme 1.8 Catalytic iodine(III)-mediated synthesis of oxadiazoles and thiadiazoles

1.2.7 Quinolinones: Zhao et al. utilized the remarkable oxidative property of PIFA in C-C bond formation to prepare an array of 3-arylquinolin-2-ones **55** (Scheme 1.9). PIFA-promoted oxidation of *N*-methyl-*N*-phenylcinnamamides **54** in presence of a Lewis acid afforded 3-arylquinolin-2-ones in good yields. Formation of 3-arylquinolin-2-ones was realised through the PIFA-promoted simultaneously C-C bond formation and 1,2-aryl migration. This simple and metal-free PIFA-mediated green approach for the biologically important 3-arylquinolin-2-ones also widen the synthetic utility of organoiodine reagents.[38]



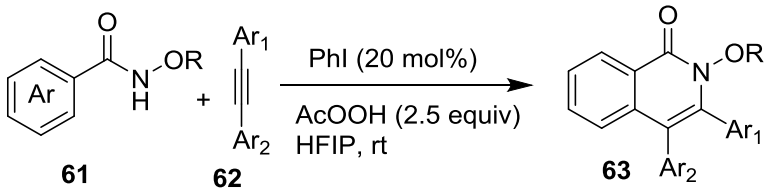
Scheme 1.9 PIFA-promoted synthesis of arylquinolinones from phenylcinnamamides

1.2.8 Indoloquinolinones: Indoloquinolinones **60** are widely present in numerous bioactive natural products endowed with potent cytotoxic properties. Zhang et al. effectively utilized I(III)-promoted intramolecular oxidative C-N bond formation reaction to prepare a series of naturally occurring bioactive indoloquinolinones. This metal-free, IBD-mediated protocol can be extended to achieve various natural occurring indoloquinolinones **60** (Scheme 1.10) [39].



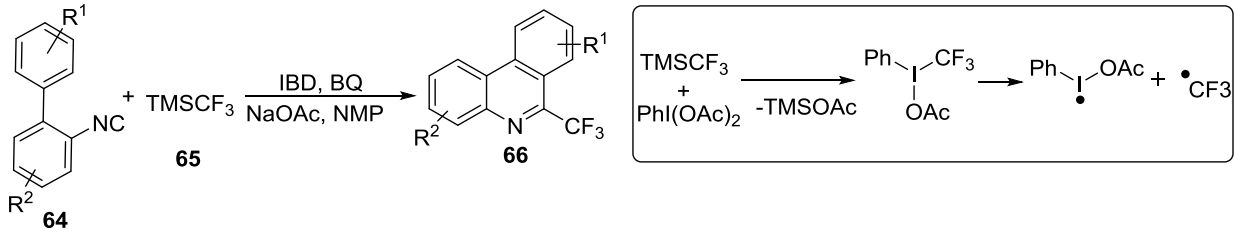
Scheme 1.10 Synthesis of indoloquinolinones

1.2.9 Isoquinolones: A novel transition metal-free highly regioselective synthesis of diverse isoquinolone derivatives **63** was developed as shown in Scheme 1.11. In this mild iodobenzene-catalyzed annulation process, a series of readily available symmetrical and non-symmetrical internal alkynes **62** were coupled with N-alkoxybenzamide derivatives **61** in the presence of peracetic acid as an oxidant.[40]



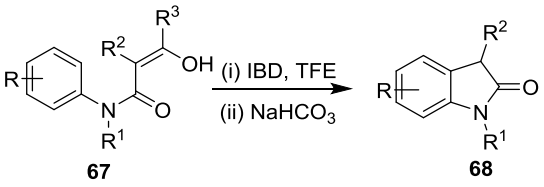
Scheme 1.11 Synthesis of isoquinolones

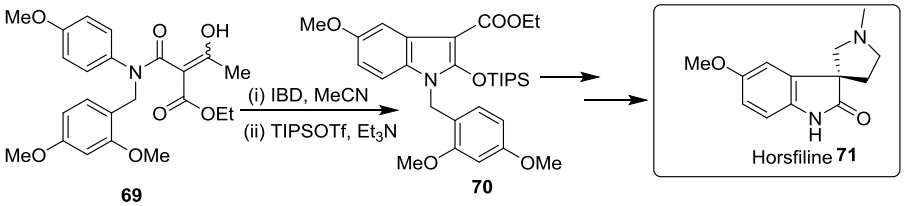
1.2.10 Phenanthridines: Introduction of a trifluoromethyl group is very important and challenging task in medicinal chemistry. Most frequently, trifluoromethyl group is introduced to modulate the physicochemical properties and to increase binding affinity of drug molecules. Through oxidative cyclization of 2-isocyanobiphenyls **64** by employing a combination of IBD and $TMSCF_3$ **65** led to the various 6-(trifluoromethyl) phenanthridines **66** (Scheme 1.12). This metal-free process probably occurs through the direct C-CF_3 bond formation in a successive oxidative cyclization afforded 6-(trifluoromethyl)phenanthridines in good yields.[41]



Scheme 1.12 IBD-mediated synthesis of 6-(trifluoromethyl) phenanthridines

1.2.11 Oxindoles: Very recently, Zhao et al. showed that the 3-functionalized oxindoles **68** can be easily synthesized from the IBD-promoted cyclization of readily available anilides **67**. The I (III) promoted transformation was proposed to occur *via* initial C-C bond formation followed by

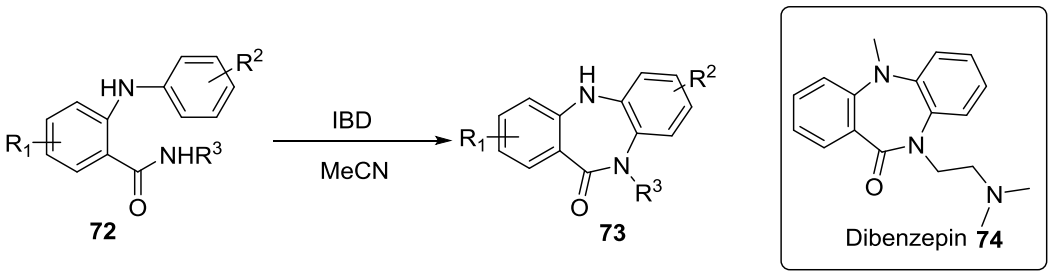




Scheme 1.13 I(III)-mediated synthesis of 2-oxindoles

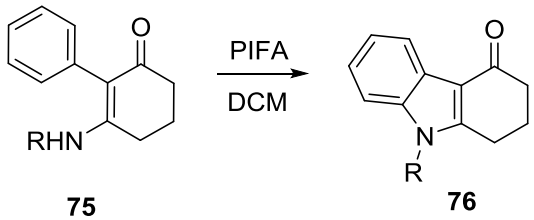
a deacetylation reaction to furnish the monofunctionlized 2-oxoindoles **68.** The developed method provided direct access to an important indole precursor **70** to prepare naturally occurring Horsfiline **71** (Scheme 1.13).[42]

1.2.12 Benzodiazepines: Benzodiazepine is a privileged scaffold present in various medicinally important molecules for example, an antidepressant drug, Dibenzepin **74**. Very recently, a good approach for the synthesis of 1,4,-benzodiazepines **73** have been developed by Zhao et al. (Scheme 1.14). The preparation of 1,4,-benzodiazepines involved the IBD-promoted oxidation of easily accessible 2-arylaminobenzamides **72** through C-N bond formation. This new methodology delivered a series of 1,4,-benzodiazepines in good yields. Moreover, this method can facilitates the synthesis of valuable benzodiazepine containing drug molecules. [43]



Scheme 1.14 I(III)-mediated synthesis of 1,4,-benzodiazepines

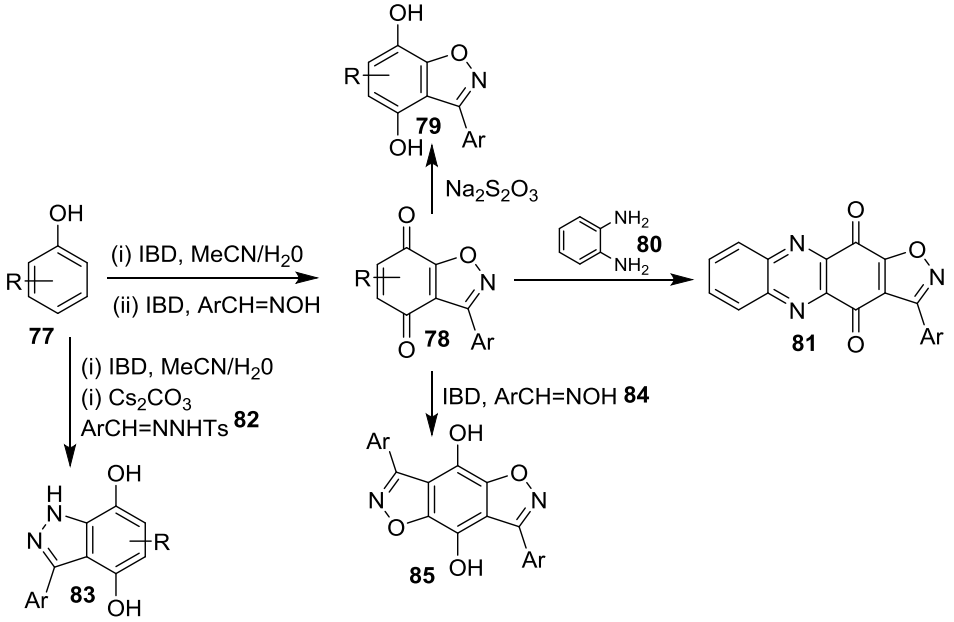
1.2.13 Carbazolones: The oxidative property of PIFA used in the construction of interesting carbazolone analogues **76**. Carbazolone unit associated with various alkaloids is frequently utilized in the drug discovery research. PIFA-induced C-N bond formation in various 2-aryl enaminones **75** afforded carbazolone derivatives in good yields (Scheme 1.15). This mild and easily available PIFA-mediated synthesis of carbazolone can be extended to prepare various biologically useful fused analogues.[44]



Scheme 1.15 PIFA-mediated synthesis of carbazolone derivatives

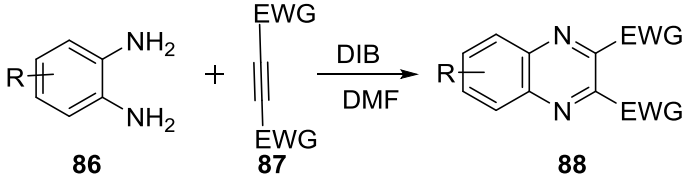
1.2.14 Benzo[*d*]isoxazoles: Very recently Liu et al. prepared diversely substituted benzo[*d*]isoxazoles **81** through a versatile one-pot [3+2] cycloaddition between nitrile oxides and benzoquinone intermediates **78**. The reactive intermediates were smoothly prepared from IBD-mediated oxidation of the corresponding nitriles and phenols **77** to deliver benzoquinone adducts **79** which were reduced to benzo[*d*]isoxazole-4,7-diols **80** by employing $Na_2S_2O_3$.

When the adduct **78** was treated with 1,2-diaminobenzene it afforded isoxazolo[5.4-a]phenazines **81**. Similarly, the cycloaddition of the adduct **78** with nitrile oxide, generated from IBD-mediated oxidation of the corresponding oxime afforded benzodiisoxazole-4,8-diols **85**. The scope of the reaction was further extended by preparing another interesting heterocycle indazole-4,7-diol **83** *via* IBD-mediated [3+2] cycloaddition from phenol and tosylhydrazone (Scheme 1.16).[45]



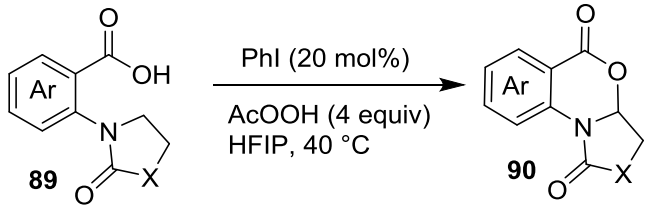
Scheme 1.16 One-pot **s**ynthesis of benzo[d]isoxazoles

1.2.15 Quinoxalines: A practical and high yielding application of IBD-induced oxidative [4+2] annulations of *o*-phenylenediamines **86** and electron-deficient alkynes **87** was described in the construction of quinoxaline derivatives **88** (Scheme 1.17). The oxidative annulation was successfully mediated by I(III) reagent between diaminobenzene ($4e^-$ center) and electron-poor alkynes ($2e^-$ center). Formation of quinoxalines was proposed to involve an initial generation of enamine which likely to undergo IBD-mediated oxidative annulation and aromatization. This metal-free and green protocol is very useful for the preparation of diverse bioactive quinoxalines (Scheme 1.23).[46]



Scheme 1.17 Synthesis of bioactive quinoxalines

1.2.16 Benzoxazinones: Martin and co-workers[47] have recently developed an organocatalytic C(sp^3)–H bond functionalization/C–O bond forming reaction to access benzoxazinone derivatives **90**. Here, the authors used 20 mol% of iodobenzene as an organocatalyst in combination with 4.0 equiv. of AcOOH as a terminal oxidant in this intramolecular oxidative coupling of **89** (Scheme 1.18).

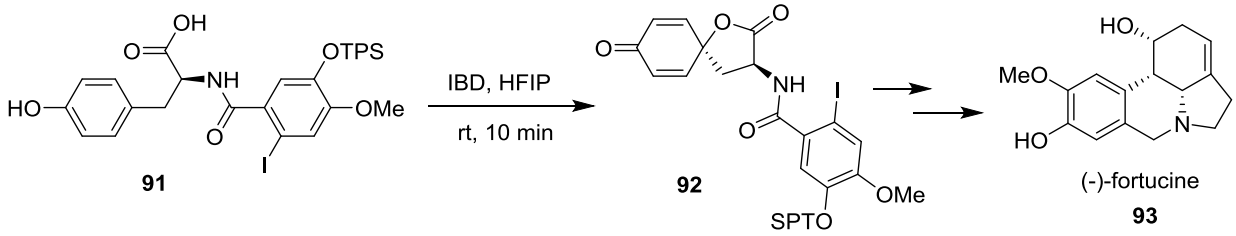


Scheme 1.18 Synthesis of bioactive benzoxazinones

1.3 Key intermediates in natural products constructions

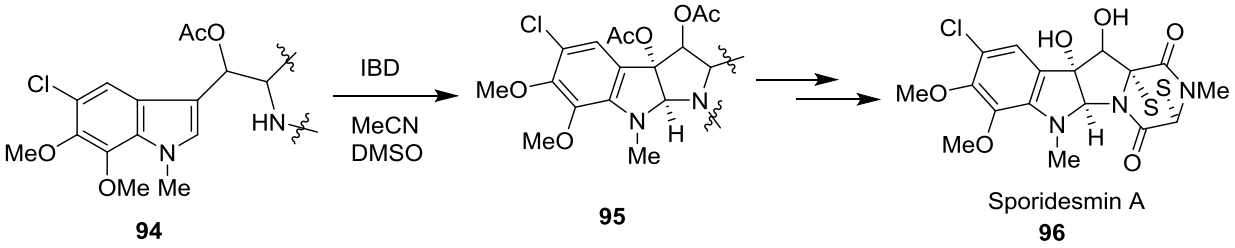
Total synthesis of stereochemically enriched molecules is one of the challenging areas in modern organic synthesis. Particularly organoiodine compounds have been used extensively in the construction of complex natural products with high selectivity.[48]

1.3.1 Fortucine: Canesi co-workers developed an asymmetric synthesis of the Amaryllidaceae alkaloid fortucine **93**. The L-tyrosine derived phenol **91** was reacted with IBD in HFIP to induce an oxo-spirocyclization which transformed **91** into the *p*-quinolic lactone **92**, The resulting **92** intermediate was then converted in 11 steps into (–)fortucine (Scheme 1.19).[49]



Scheme 1.19 Synthesis of para-quinolic lactone

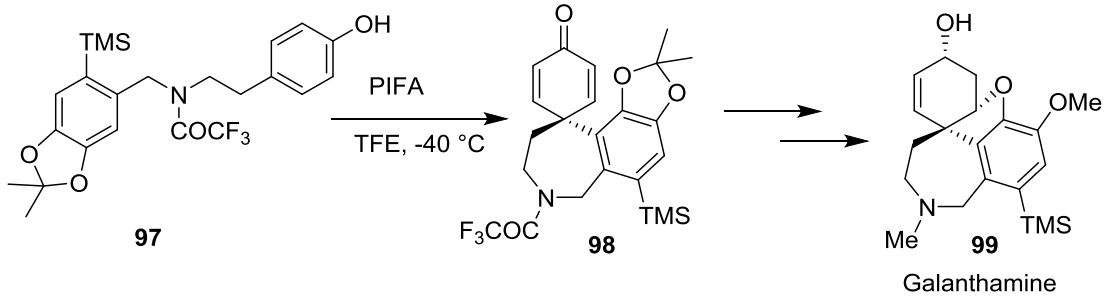
1.3.2 Sporidesmin A: Kishi and co-workers utilized IBD-mediated oxidative cyclization strategy in the stereospecific synthesis of fused indoline precursor **95** which is a key precursor for the preparation of toxic metabolite Sporidesmin A (Scheme 1.20).[50]



94 95 96

Scheme 1.20 Synthesis of indoline intermediate

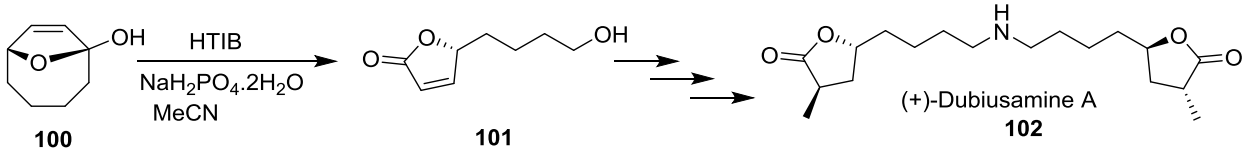
1.3.3 Galanthamine: PIFA-promoted intramolecular C-C bond forming strategy was employed for the preparation of Amaryllidaceae alkaloids Galanthamine **99**. This mild protocol produce stereoselective seven-membered spiro quinone molecule **98** from **97** in good yields (Scheme 1.21).[51]



97 98 99

Scheme 1.21 Preparation of spiro intermediate

1.3.4 (+)-Dubiusamine A: Total synthesis of stereochemically enriched molecules is one of the challenging areas in modern organic synthesis. Yoshiharu et al. successfully utilized HTIB in the total synthesis of natural occurring (+)-Dubiusamine A **102** (Scheme 1.22). The key-step in this synthesis was oxidative fragmentation of 9-oxa-bicylco[4.2.1] non-7-en-1-ol **100** to useful building block butenolide **101** with high enanatiomeric excess. The obtained butenolide was subjected to various transformations to produce (+)-Dubiusamine A (Scheme 1.22).[52]

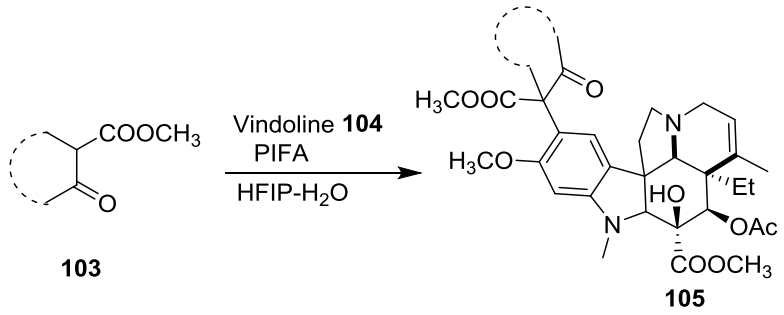


100 101 102

Scheme 1.22 Synthesis of 5-(4-hydroxybutyl)-2(5*H*)furanone

1.3.5 Vinblastine: Bis(indole) alkaloids, vinodline and vinblastine are well-known antimitotic agents. Synthesis of vinblastine analogues is difficult due to their structural complexity. To circumvent this problem, Boger et al prepared various vinblastine analogues **105** through

PIFA-mediated intermolecular C-C coupling of vinodline **104** with *β*-ketoesters, *β*-diketones, *β*–ketonitriles, *β*–ketoaldehydes, malononitriles and *β*–cycanoesters **103** (Scheme 1.23). The formation of vinblastine analogues was postulated to arise from the selective C-H activation and direct formation of sp^3-sp^2 bond. The developed method paved way to synthesize various vinblastine analogues using PIFA a mild eco-friendly reagent.[53]



Scheme 1.23 Synthesis of vinblastine analogues

1.4 Diaryliodonium Salts

Diaryliodonium salts are well renowned electrophilic aryl sources employed in various arylation reactions.[54-56] Owing to the several promising features like easy to synthesize, non-toxic, benign safety profile, air and moisture stability. Diaryliodonium salts have been used as an excellent aryl coupling partners for diverse range of alkenes, alkynes and heterocycles under metal and metal-free reaction conditions.[57-59] In current scenario diaryliodonium salts are frequently used as arylating agents besides their interesting applications in the construction of valuable heterocycles with five- and six-membered ring systems.[60]

1.4.1 Structure and geometry

Diaryliodonium salts **106** (Ar_2IX) are a class of iodine(III) reagents with two aryl moieties and an anionic part (X) with ten electrons. The geometry of Ar_2IX is pseudo trigonal bipyramidal with the weakly bonded anionic part at apical position, two aryl groups at apical and equatorial and two lone pairs occupied at equatorial position. X-ray studies showed diaryliodonium salts are T-shaped geometry (Figure 1.7) with the bond angle of Ar-I-Ar is 90°. The I-X bond in **106** is longer than the average covalent bond length. The high reactivity of iodonium salts **106** is illustrated by the leaving group ability of iodobenzene (106 times > triflate) released from the corresponding diaryliodonium salt. Given the superior solubility and non-nucleophilic

character, diaryliodonium salts **106** with triflate and tetrafluoroborate anions are most frequently employed in synthetic transformations.[60]

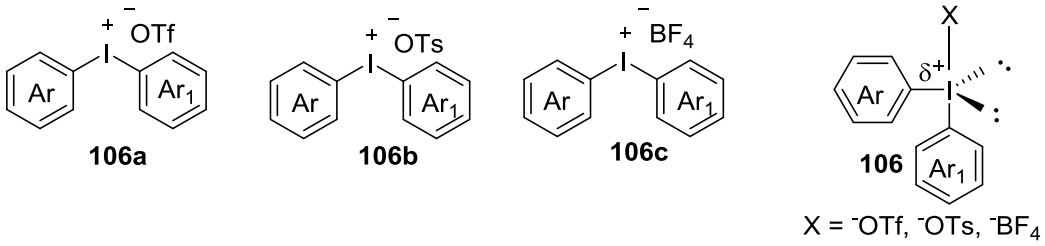
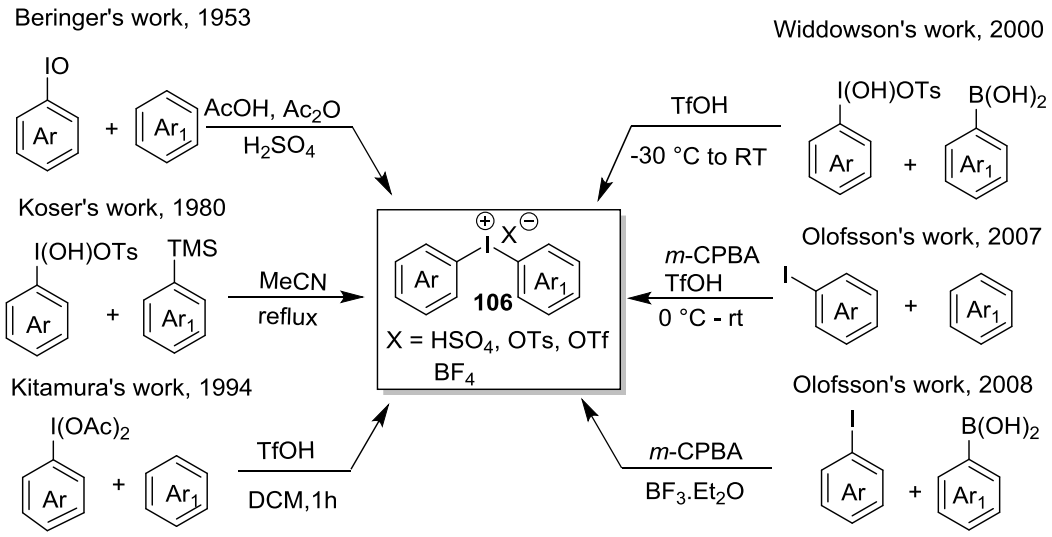


Figure 1.7 Structures and geometry of commonly used diaryliodonium salts

1.4.2 Preparation of diaryliodonium salts

In general, preparation of diaryliodonium salts involves two steps, first oxidation of an aryl iodide(I) to iodine(III) species and next ligand exchange with arenes or organometallic reagents. Diaryliodonium salts **106** were first prepared by Meyer and Hartmann in 1894.[4a] Nevertheless, the synthetic procedure was time-consuming with less yield. In 20th century this reagent was rediscovered with the myriad of synthetic transformations. In 1950, Beringer reported the synthesis of symmetrical and unsymmetrical diaryliodonium salts using organoiodine(III) compounds namely, iodosylarenes (ArI=O), iodobenzene diacetate (IBD), iodoxyarenes ($ArIO_2$) and electron-rich arenes in the presence of sulphuric acid.[61] Later, in 1980 Koser and co-workers prepared diaryliodonium tosylates by employing hydroxy(tosyloxy)-iodobenzene and arylsilanes.[62] Afterwards, Kitamura et al.[63] disclosed an improved procedure to access diaryliodonium salts by involving the reaction of (diacetoxyiodo)arenes and electron-rich arenes in triflic acid. Notably, triflic acid was found to be an effective alternative to sulfuric acid, acetic acid and *p*-toluenesulfonic acid in the terms of reactivity and isolation of diaryliodonium triflate salts. Next, Widdowson and co-workers prepared diaryliodonium salts by employing IBD and arylboronic acids in triflic acid.[64] Recently, Olofsson's group developed an operationally simple, one-pot general protocol to achieve diaryliodonium triflates in good to excellent yields.[65] This convenient method uses the reaction of aryl iodides and arenes in the presence of *m*-chloroperbenzoic acid (*m*-CPBA) and triflic acid. Use of mild oxidant *m*-CPBA is advantageous due to its less solubility in organic solvents which facilitates its removal from the reaction



Scheme 1.24 Methods to prepare diaryliodonium salts

mixture. The protocol is applicable to a range of iodoarenes and arenes. In an alternative route, the same research group[66] prepared various symmetrical and unsymmetrical diaryliodonium salts from iodoarenes and arylboronic acids as outlined in Scheme 1.24.

1.4.3 General reactivity

The general mechanism for metal-free reactions with Ar_2IX **106** involves two steps, where the nucleophile first attacks the electrophilic iodine to give a T-shaped intermediate in a ligand exchange (Figure 1.8). This process occurs rapidly for iodine(III) species, and can be either associative or dissociative. In the subsequent step, the nucleophile and the equatorial aryl moiety are reductively eliminated in a ligand coupling. The ligand coupling step is concerted and depends on the incoming nucleophiles

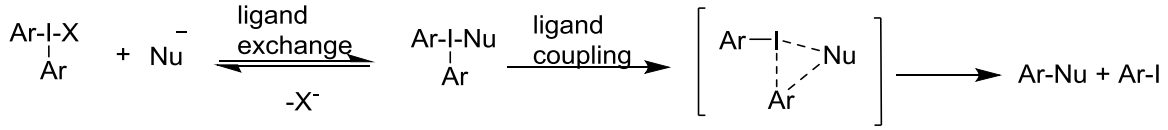


Figure 1.8 Reactivity of metal-free reactions

Arylations under metal-catalyzed conditions are usually suggested to proceed by transfer of one aryl group to the metal to create a high oxidation state ArM complex, followed by reductive elimination with the nucleophile (Figure 1.9).

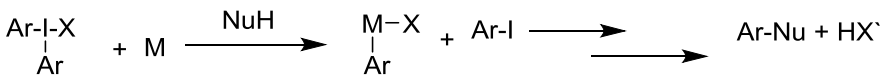


Figure 1.9 Reactivity of metal-catalyzed arylations

1.4.4 Plausible catalytic cycle

The reactivity of diaryliodonium salts could be enhanced in the presence of copper and palladium catalysts. Research groups of Gaunt and Sanford disclosed the metal-catalyzed (Cu and Pd) arylation of indoles using diaryliodonium salts, and investigated the mechanistic pathways. In 2008, Gaunt et al. proposed an elegant hypothesis that Cu(I) reduce the iodonium salt with the release of highly electrophilic aryl copper(III) species and iodoarenes.[67] This *in situ* generated reactive species could rapidly undergo functionalization with the nucleophile under fairly mild reaction conditions (Figure 1.10a).

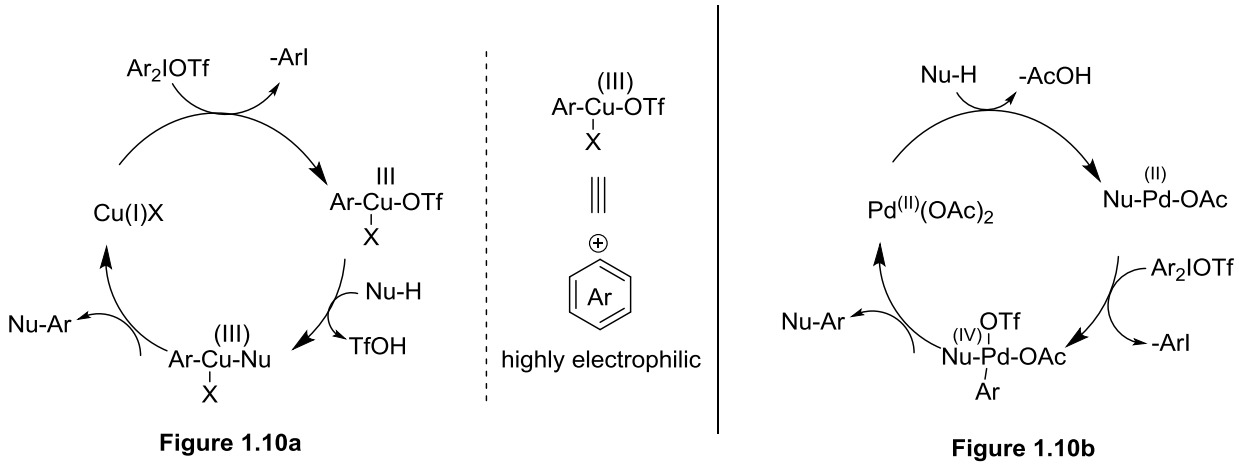


Figure 1.10a

Figure 1.10b

Figure 1.10 Plausible catalytic pathways involving Cu and Pd

In 2006, Sanford and co-workers described a Pd(II)-catalyzed C-H arylation of indoles and proposed a persuasive $Pd^{II/IV}$ catalytic pathway for the formation of 2-arylindoles (Figure 10b).[68, 69]

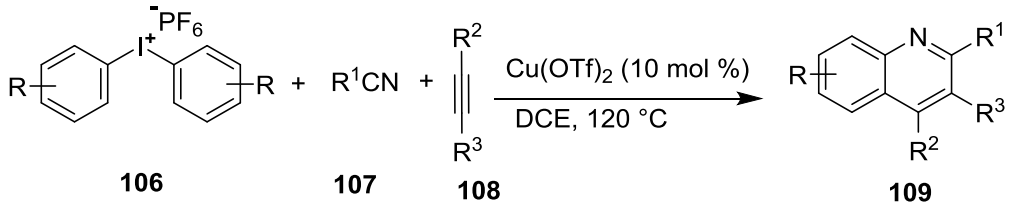
1.4.5 Heterocycles synthesis

Heterocyclic compounds are extensively distributed in many natural products, life saving drugs and organic materials. Owing to the high significance and applications in drug discovery research construction of heterocycles is a long-standing interest. Assembly of heterocyclic compounds particularly, five- and six-membered ring systems and arylated heterocycles with interesting biological properties and for being important building blocks which are frequently encountered in natural products and various therapeutic agents. Though there are plethora of protocols to construct useful five and six-membered heterocycles but still straightforward and eco-friendly methods to access these heterocycles are highly desirable. In view of significant advantages, diaryliodonium salts have been widely utilized in the direct arylation and preparation of bio-active heterocycles. We have summarized the recent applications of

diaryliodonium salts in the arylation of heterocycles and construction of quinolines, phenanthridines, oxindoles, arylcoumarins, acridines, and acridones.

1.4.5.1 Quinolines

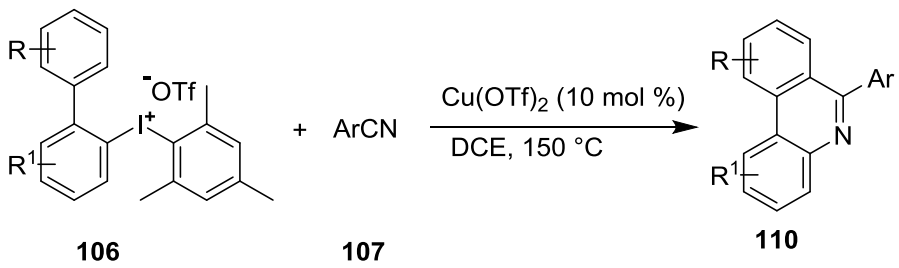
Chen's group[70] developed a general and elegant pathway for the synthesis of quinolines **109** using multicomponent approach by employing diaryliodonium salts **106**, nitriles **107** and alkynes **108**. The reaction proceeded *via* [2+2+2] regioselective cascade annulation strategy to generate quinoline derivatives in good to excellent yields. Iodonium salts **106** bearing non-coordinating anion PF_6 gave better yields than the salts with $^-$OTf, Br^- and $^-$OTs counter ions. Use of electron deficient nitriles like ethyl cyanoformate and diethyl cyanophosphate failed to deliver the annulated products. Identified reaction conditions covers variety of internal alkynes, asymmetric alkynes and diaryliodonium salts to prepare various quinolines (Scheme 1.31).



Scheme 1.31 Synthesis of quinolines and representative examples

1.4.5.2 Phenanthridines

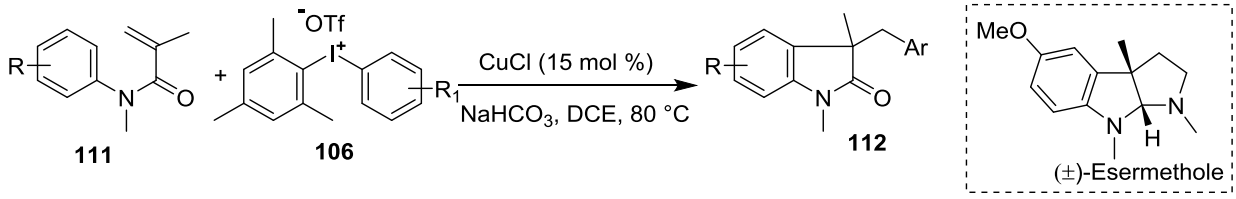
Li et al.[71] reported a copper-catalyzed cascade coupling strategy for the synthesis of phenanthridine derivatives **110** using diaryliodonium salts as an aryl source. The reaction was smoothly proceeded in the presence of $Cu(OTf)_2$ and dichloroethane at 150 °C to produce **110** in good yields. Mechanistically, *in situ* generated copper(I) species from $Cu(OTf)_2$ underwent oxidative insertion with diaryliodonium salt to furnish a highly electrophilic Ar-Cu(III) species. Consecutive nucleophilic addition of nitriles and annulation led to the corresponding phenanthridines in moderate to excellent yields (Scheme 1.32).



Scheme 1.32 Synthesis of phenanthridine derivatives

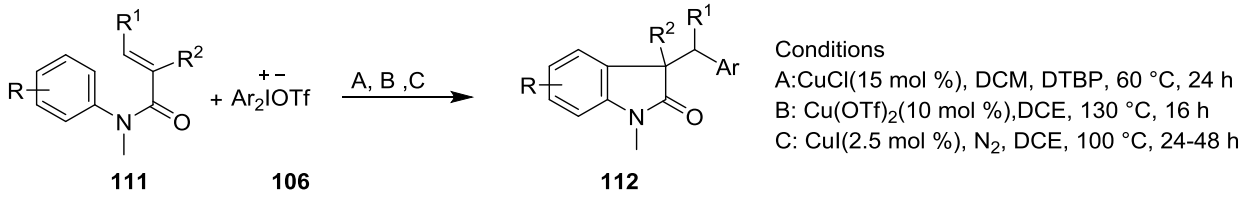
1.4.5.3 Oxindoles

Zhou co-workers described the copper-catalyzed arylation/vinylation of electron-deficient alkenes **111** to furnish highly substituted oxindoles **112** using diaryliodonium salts **106** as coupling partners.[72] After exploring various parameters, cuprous chloride in the presence of sodium bicarbonate found to be the best catalytic conditions. Formation of C-C bond proceeded with electrophilic addition of Cu(III)-aryl intermediate, followed by aromatization and reductive elimination to produce oxindoles **112** in good yields. The obtained oxindoles **112** were utilized to prepare complex bio-active natural product (±)-Esermethole (Scheme 1.33).



Scheme 1.33 Synthesis of oxindoles

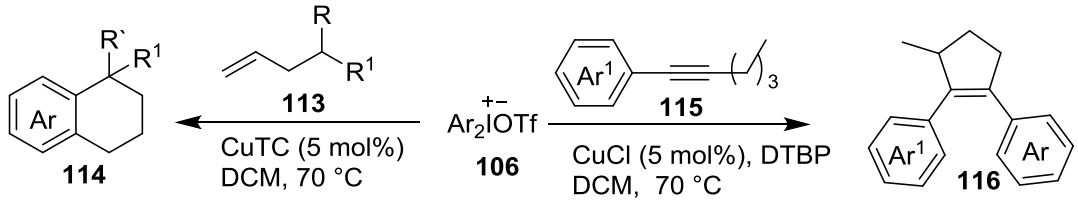
Likewise, Tang et al.[73] explored the synthesis of oxindoles **112** using diaryliodonium salts **106** and 2,6-ditertbutylpyidine (DTBP) as a base. Later, two different research groups[74, 75] have independently reported the synthesis of oxindoles **112** under base-free conditions in the presence of a copper catalyst and diaryliodonium salts **106** (Scheme .134).



Scheme 1.34 Synthesis of oxindoles

1.4.5.4 Carbocyclization

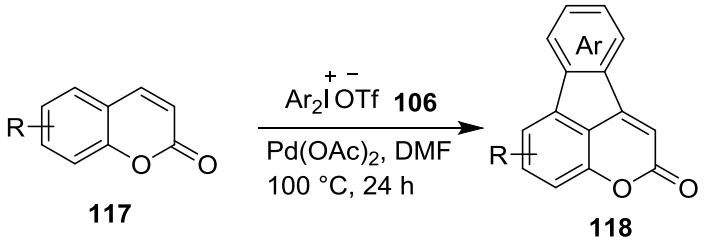
Interestingly, Gaunt and co-workers[76] described the efficient transformation of easily available alkenes and alkynes into substituted tetralins and cyclopentenes in good yields. Air-stable, copper(I) thiophene-2-carboxylate (CuTC), copper(I) chloride and sterically-hindered 2,6-ditertbutylpyidine (DTBP) are the suitable catalysts and base for the carbocyclization of **113** and **115**. Detailed mechanistic investigations revealed that concerted 1,2-hydride and 1,5-hydride shifts led to the desired products **114** and **116** in good yields (Scheme 1.35).



Scheme 1.35 Synthesis of substituted tetralins and cyclopentenes

1.4.5.5 Benzocoumarins

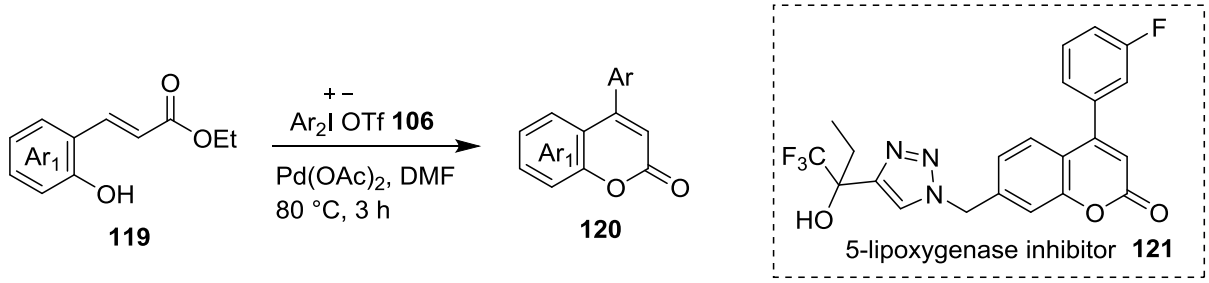
An unprecedented, Pd-catalyzed two consecutive C-C bonds forming strategy was employed between diaryliodonium salts **106** and coumarins **117** to construct π-expanded 4,5-dibenzo-coumarins **118**. Formation of dibenzocoumarins **118** was smoothly proceeded without any external oxidant, ligand or directing groups. Interestingly, coumarins with hydroxyl group produced **118** without any *O*-arylation. However, sterically-hindered bis(2,4,6,-trimethyl-phenyl)iodonium triflate failed to afford the desired fused product. The proposed diarylation proceeded *via* Pd(II/IV) catalytic cycles with the synergistic activations of C-I and vicinal C-H bonds in diaryliodonium salts (Scheme 1.36).[77]



Scheme 1.36 Synthesis of 4,5-dibenzocoumarins and their representative examples

1.4.5.6 4-Arylcoumarins

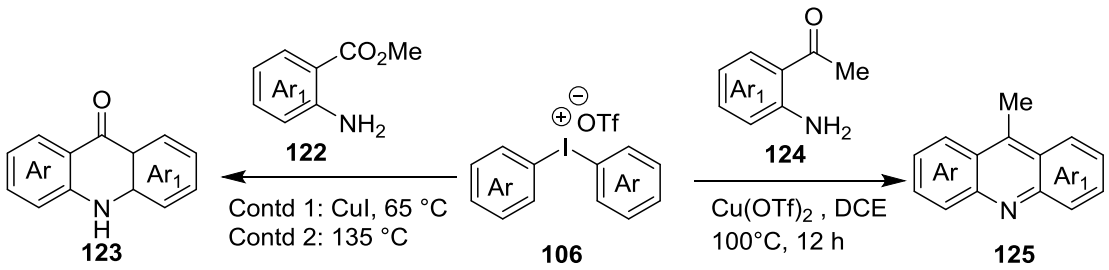
Yang et al.[78] extended the synthetic utility of diaryliodonium salts in the construction of 4-arylcoumarins **120** *via* Pd-catalyzed arylations and cyclizations of hydroxylcinnamates **119**. In the presence of CuI and $Cu(OTf)_2$ arylcinnamates were obtained rather than expected arylcoumarins **120**. By changing the catalyst from copper to palladium the reaction progressed in anticipated manner to afford 4-arylcoumarins **120** in better yields. This ligand and base-free approach is well-suited for diverse diaryliodonium salts and *o*-hydroxyl cinnamates and provided an alternative convenient route for 5-lipoxygenase inhibitor **121** (Scheme 1.37).



Scheme 1.37 Synthesis and selected examples of 4-arylcoumarins

1.4.5.7 Acridines and Acridones

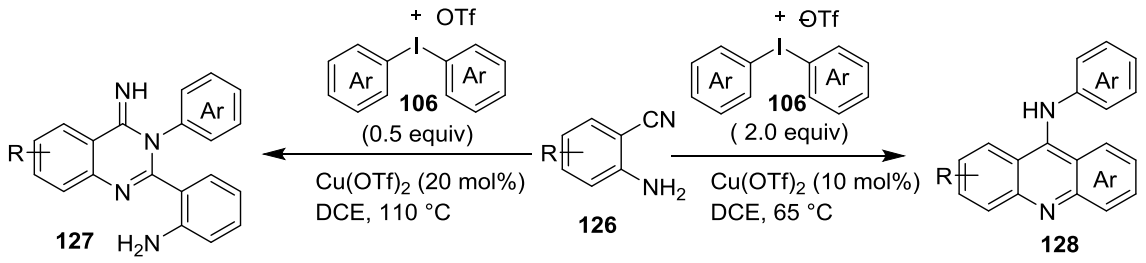
Recently, Pang et al.[79] reported a domino arylation and Friedel-Crafts acylation between *o*-acylanilines **124** and diaryliodonium salts **106** to achieve valuable acridine derivatives **125.** Interestingly, this reaction proceeded effectively either under copper-catalyzed or metal-free conditions at an elevated temperature (130-135 °C). The reaction of *o*-aminobenzoates **122** with diaryliodonium salts **106** generated acridone framework **123** in high yields (Scheme 1.38).



Scheme 1.38 Some selected examples of prepared acridines and acridones

1.4.5.8 Quinazolinimines

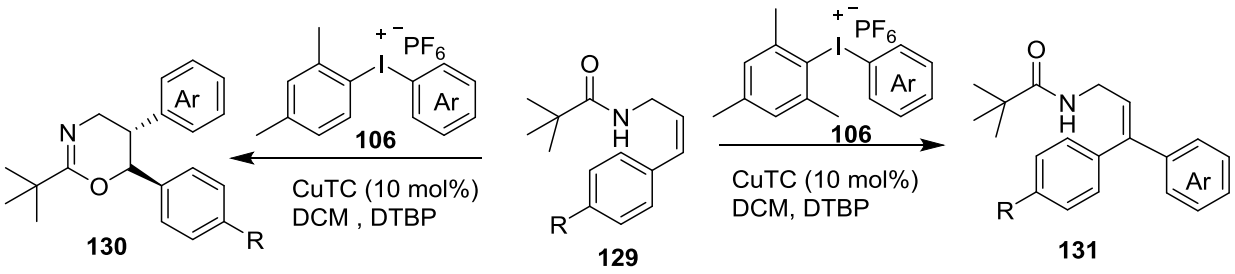
Recently, a new tandem approach was developed by Chen and co-workers[80] for the synthesis of quinazolinimines **127** and acridines **128** from easily accessible *o*-cyanoanilines **126** and diaryliodonium salts **106**. This protocol is well-suited for 1-amino-2-cynaocyclopentene and cyclohexene to afford pyrimidine analogues. Detailed optimization reaction conditions and mechanistic experiments disclosed that 0.5 equivalent of **106** afforded quinazolinones **127**, whereas**,** its excess quantity (2.0 equiv) led to acridines **128** in good yields (Scheme 1.39).



Scheme 1.39 Synthesis of quinazolinimines and acridines

1.4.5.9 Diaryloxazines

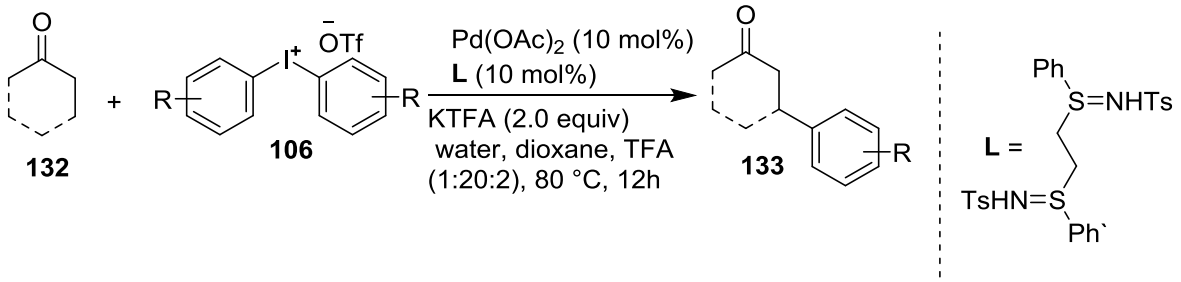
A chiral copper(II)bisoxazoline-catalyzed reaction of readily available allylic amides **129** and diaryliodonium salts **106** led to enantioselective synthesis of 1,3-oxazines **130** and *β,β′*-diaryl enamides **131**. Sterically-hindered base 2,6-ditertbutylpyidine (DTBP) was used in order to avoid the decomposition of chiral catalyst by the release of HPF_6. The electronic nature of diaryliodonium salts was found to be crucial for the enantioselective synthesis of **130** and **131** (Scheme 1.40).[81]



Scheme 1.40 Synthesis of various 1,3-oxazines and *β,β′*-diaryl enamides

1.4.5.10 β-arylation of ketones

Huang and co-workers illustrated the application of diaryliodonium salts **106** in the selective *β*-arylation of ketones **132** using Pd-catalyst.[82] This method enabled to arylate various cyclic and linear ketones in excellent yields under oxidant free conditions. Under the reaction conditions, potassium trifluoroacetate (KTFA) and trifluoroacetic acid (TFA) behaved as buffer pair to maintain the required acidity of reaction medium. From the detailed mechanistic investigation and control experiments, involvement of Pd nanoparticles was suggested in the present catalytic system (Scheme 1.41).

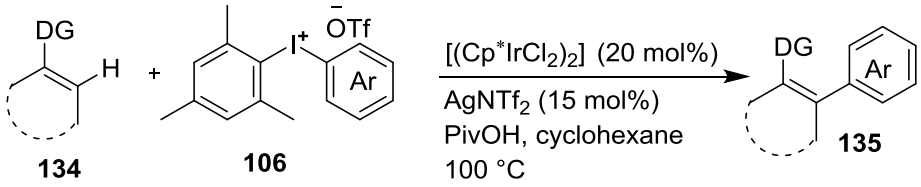


Scheme 1.41 Synthesis of *β*-arylated ketones and their representative examples

1.4.5.11 Arylheterocyles

First example of Ir(III)-catalyzed *β*-arylation of aliphatic sp^3 C-H bonds present in oximes and nitrogen-containing heterocycles like pyrazines, pyrazoles, quinolines, isoxazole, pyridine

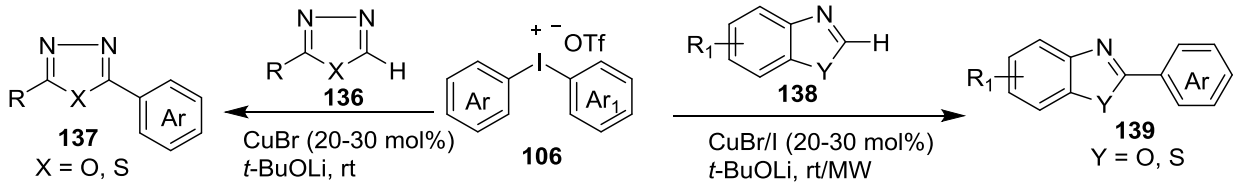
derivatives, substituted enamides and carboxylic acids, have been discovered. This protocol displayed high functional groups tolerance and also proved an effective synthetic tool for late-stage regioselective C-H arylation of complex triterpenoid molecules, for example, Lanosterol and Oleanolic acid. Outcome of the detailed mechanistic studies and density functional theory calculations suggested that sp^3 C-H bond present in the substrates **134** were activated by the concerted metallation–deprotonation process and oxidation of Ir(III) to Ir(IV) (Scheme 1.42).[83]



Scheme 1.42 Synthesis of arylheterocycles

1.4.5.12 2-Arylazoles

Kumar and co-workers[84] developed a general and high-yielding protocol for the C-H arylation of various azaheterocycles such as oxadiazoles, thiadiazoles, benzoxazoles and benzothiazoles using diaryliodonium salts **106** at room temperature. The C-H arylation required simple catalytic system (CuBr/*t*-BuOLi) with reduced reaction time (15 min) to produce arylated azoles **137** in fairly good yields. The reactivity order of different heterocycles **138** was rationalized by the variable acidity of C_2-H (oxadiazoles = benzoxazoles (pKa = 24.8) > thiadiazoles >benzothiazoles (pKa = 27.3). Under the optimized conditions, C_2-H arylation of benzothiazole could not be achieved. Modified reaction conditions involving the use of MW successfully afforded 2-arylbenzothiazoles in good yields. The synthetic utility of developed protocol was extended to prepare a Tafamidis analogue which is a well known drug for neurodegenerative diseases (Scheme 1.43).

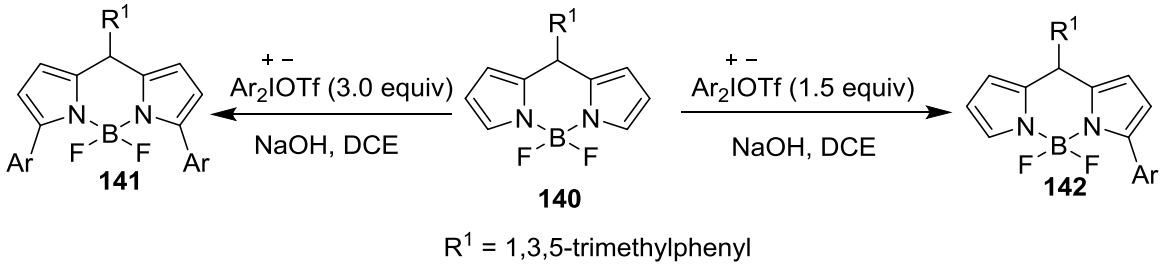


Scheme 1.43 Synthesis of various 2-arylazoles

1.4.5.13 Arylation of boron dipyrromethenes

Jiao et al.[85] developed a metal-free, *α*-selective C-H arylation of boron dipyrromethenes **140** by employing mild coupling partners, diaryliodonium salts **106**. The developed protocol furnished an array of mono **142** and diarylated **141** boron dipyrromethenes in moderate to good yields. No

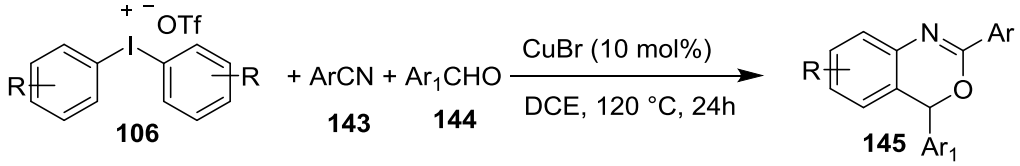
product was formed upon addition of radical inhibitor (BHT) 2,6-di-*tert*-butyl-4-methylphenol suggested the involvement of an aryl radical. The arylated compounds **141** and **142** displayed promising photophysical properties (Scheme 1.44).



Scheme 1.44 Synthesis of α-arylated boron dipyrromethenes

1.4.5.14 Benzoxazines

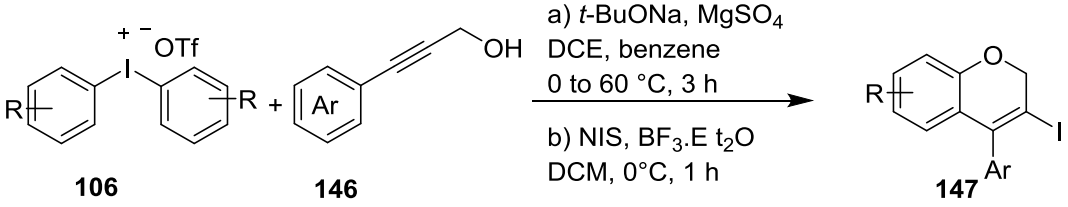
Very recently, an interesting Cu-catalyzed one-pot [2+2+2] cascade annulation of nitriles **143**, aldehydes **144** and diaryliodonium salts **106** has been developed by Jinhu et al. to construct benzoxazines **145** frameworks.[86] Iodonium salts **106** bearing functional groups such as aldehyde, halogens, alkyl and naphthyl were tolerated to afford **145** under the optimized reaction conditions. When two aldehyde groups were present in *p*-phthalaldehyde, then selectively one of –CHO underwent cyclization to give corresponding product (Scheme 1.45).



Scheme 1.45 Synthesis of benzoxazines and their representative examples**.**

1.4.5.15 3-Iodochromenes

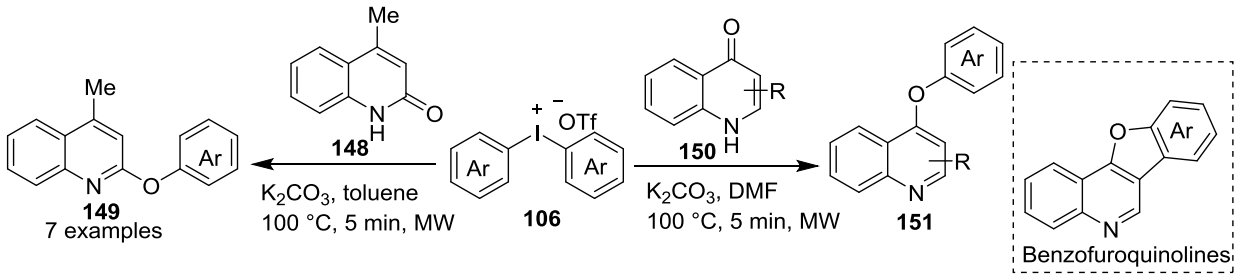
Togo and co-workers[87] developed an efficient metal-free synthesis of 3-iodochromenes **147** from easily accessible diaryliodonium salts and aryl/alkly-propyn-1-ols **146**. This elegant transformation proceeded *via* one-pot *O*-arylation of aryl/alkly-propyn-1-ols in the presence of base *t*-BuONa and subsequent iodocyclization using *N*-iodosuccinimide and Lewis acid $BF_3.Et_2O$. Iodochromenes **147** could be converted into beneficial molecules using metal-catalyzed C-C bond forming strategies (Scheme 1.46).



Scheme 1.46 Synthesis of iodochromenes

1.4.5.16 2/4-Aryloxyquinolines

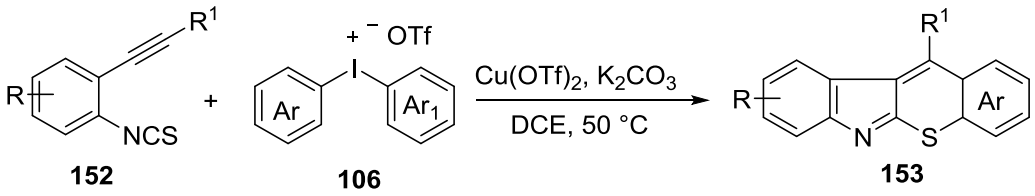
Kumar et al.[88] disclosed a metal- and ligand-free approach for the synthesis of aryloxyquinolines **149** and **151** by the direct *O*-arylation of readily accessible quinolones **148/150** using diaryliodonium salts **106** as aryl source. The reaction conditions were compatible with 2-/4-quinolones **148/150** and diaryliodonium salts **106** bearing sterically congested and sensitive functional substituents such as mesityl and halides. Moreover, use of microwave energy, mild reaction conditions, good product yields (55-80%) and short reaction time (5 min) are significant features of the protocol. Prepared 4-aryloxyquinolines **151** were utilized in the construction of biologically important benzofuro[3,2-*c*]quinolines (Scheme 1.47).



Scheme 1.47 Synthesis of 2-and 4-aryloxyquinolines

1.4.5.17 Thiochromeno[2,3-*b*]indoles

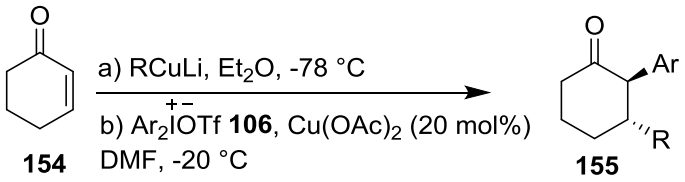
An efficient $Cu(OTf)_2$-promoted synthesis of thiochromeno[2,3-*b*]indoles **153** was developed from alkynylaryl isothiocyanates **152** and diaryliodonium salts **106.** The reaction involves successive *S*-arylation and cyclization to furnish fused heterocycles **153.** Under the optimized conditions both electron-rich and electron-poor iodonium salts were smoothly coupled with isothiocyanates **152** to afford the corresponding fused heterocycles **153** in 35-70% yields. Addition of a radical inhibitor led to **153** in excepted yield which suggested the involvement of carbocation mechanism (Scheme 1.48).[89]



Scheme 1.48 Synthesis of thiochromeno[2,3-*b*]indoles

1.4.5.18 *α*-Aryl-*β*-substituted cyclic ketones

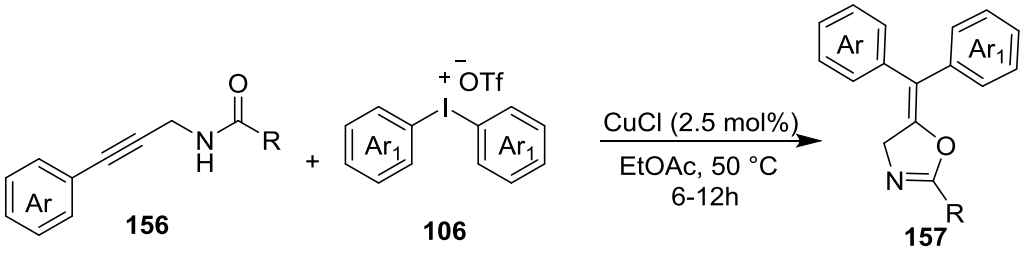
Pan et al.[90] reported an efficient method for the construction of *α*-aryl-*β*-substituted cyclic ketones **155** using diaryliodonium salts **106**. The current transformation involved Cu-promoted one-pot Michael addition followed by stereoselective arylation of cyclohexene-1-one and cyclohepten-1-one using alkyl, aryl and sterically challenging lithium reagents as Michael donors and different diaryliodonium salts **106** as aryl partner. Proposed mechanistic pathway involves reaction of Cu(I) species and diaryliodonium salts to generate an highly electrophilic Cu(III)-aryl species, which believed to react with enolate to produce the desired substituted cyclic ketones **155** in excellent yields (Scheme 1.49).



Scheme 1.49 Synthesis of *α*-aryl-*β*-substituted cyclic ketones

1.4.5.19 Oxazolines

Adam et al.[91] demonstrated a novel copper-catalyzed ring closure-carboarylation strategy for the construction of oxazoline derivatives **157** using easily accessible alkylpropargylamides **156** and diaryliodonium salts **106**. Iodonium salts **106** having *ortho* and *para* substitutents delivered **157** in relatively better yields. This one-pot method provides access to novel oxazolines heterocyclic core with highly substituted exo double bond (Scheme 1.50).

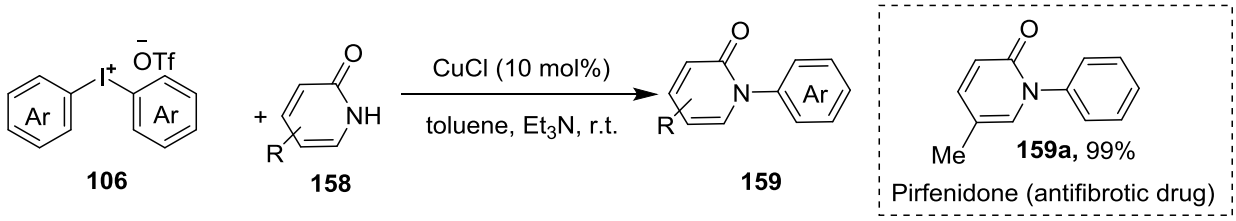


Scheme 1.50 Synthesis of oxazolines and their representative examples

1.4.5.20 Pyridones

Recently, Kim and co-workers reported the copper-catalyzed *N*-arylation of 2-pyridones **158** using solid aryl coupling partner diaryliodonium salts **106** at room temperature. Various symmetrical and unsymmetrical diaryliodonium salts have been employed with 2-pyridones, to furnish the desired products **159** in excellent yields. Further investigation of counter ion effect

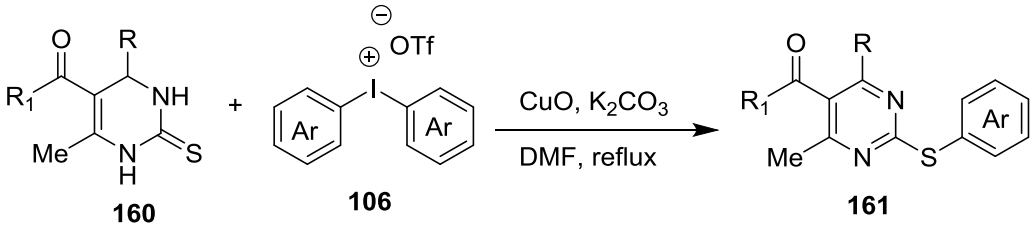
in diaryliodonium salts revealed that OTf, BF_4 and PF_6 ions yielded the desired products in **159** good yields in shorter time, while OTs, Cl, and Br showed the negative impact on the reaction and delivered the desired products in low yields with longer reaction times. Next, the developed protocol was effectively utilized to prepare an antifibrotic drug, Pirfenidone (**159a**) which is used in the treatment of idiopathic pulmonary fibrosis (Scheme 1.51).[92]



Scheme 1.51 *N*-arylation of 2-pyridones using diaryliodonium salts

1.4.5.21 2-(Phenylthio)pyrimidine

In 2013, Karade et al.[93] reported the synthesis of biologically important scaffold 2-(phenylthio)pyrimidine (**161**) *via* C-S coupling of 4-aryl-3,4-dihydropyrimidine-2(1*H*)-thione **160** using diaryliodonium salts **106** in the presence of catalytic amount of CuO nanoparticles. This protocol showed good compatibility towards various functional groups and furnished **161** in good to excellent yields. In the case of unsymmetrical iodonium salts, mixture of S-arylated products were obtained. The CuO nanoparticles was recycled and reused for three times without any loss of catalytic activity (Scheme 1.52).

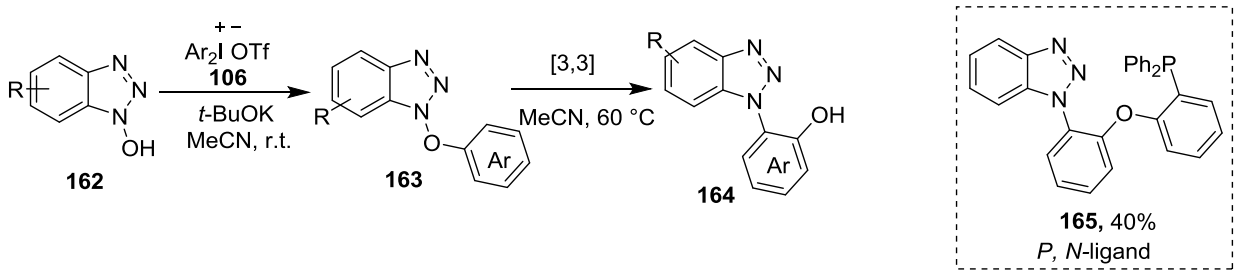


Scheme 1.52 Synthesis of 4-aryl-3,4-dihydropyrimidine-2(*1H*)-thiones

1.4.5.22 *N*-(2-Hydroxyaryl)benzotriazoles

Very recently, Dong-Liang Mo and co-workers developed a metal-free approach for the synthesis of *N*-(2-hydroxyaryl)benzotriazoles **164** using *N*-hydroxybenzotriazoles **162** and diaryliodonium salts **106**.[94] Initially, reaction of *N*-hydroxybenzotriazoles **162** with **106** at room temperature delivered the *O*-arylated product **163**, which underwent [3,3] sigmatropic rearrangement at 60 °C to provide *N*-(2-hydroxyaryl)benzotriazoles **164** in good yields. A variety of diaryliodonium salts and *N*-hydroxybenzotriazoles were examined to show the

generality of developed protocol. Authors also showed practical utility of the method by the synthesis of novel *P*, *N*-type ligands **165** in two steps (Scheme 1.53).



Scheme 1.53 Synthesis of ***N***- (2-hydroxyaryl)benzotriazoles

1.5 Importance of bis(indole) compounds

Bis(indole) alkaloids isolated from the plants and marine organisms have been widely recognized for their application as pharmaceuticals.[95] Most of the bis(indole) alkaloids exhibit remarkable cytotoxic activity. These classes of molecules contain a five or six-membered heterocyclic ring or linear chain linker in between two indole nuclei.[96] Natural bis(indolyl) compounds with different heterocylic spacers are reported to display different biological

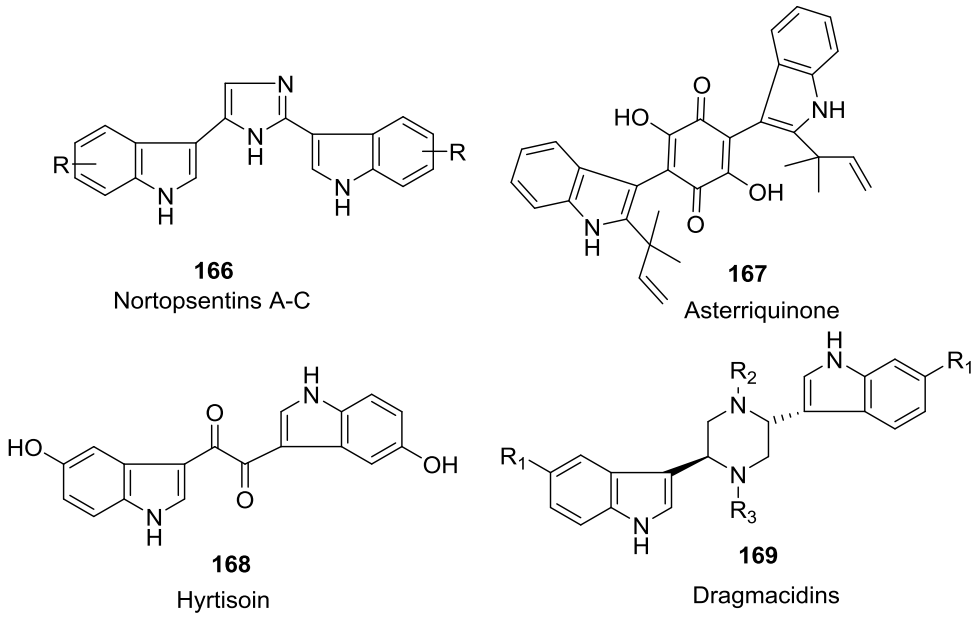


Figure 1.11 Some of the naturally occurring bis(indolyl) compounds **166-169**

properties. For example (Figure 1.11), Nortopsentins A-C **166** are interesting bis(indole) alkaloids, with its bis(indolyl)imidazole skeleton exhibited *in-vitro* cytotoxicity against P388 cells (IC_{50} = 4.5-20.7μM).[97] Their *N*-methylated derivatives showed significant improved cytotoxicity against pancreatic (IC_{50} = 0.8-2.1μM). Asterriquinone, a bis(indolyl)dihyroxy-

quinones **167** inhibited the binding of Grb2 receptor protein (IC_{50} = 1.2 μM).[98] Hyrtiosins B

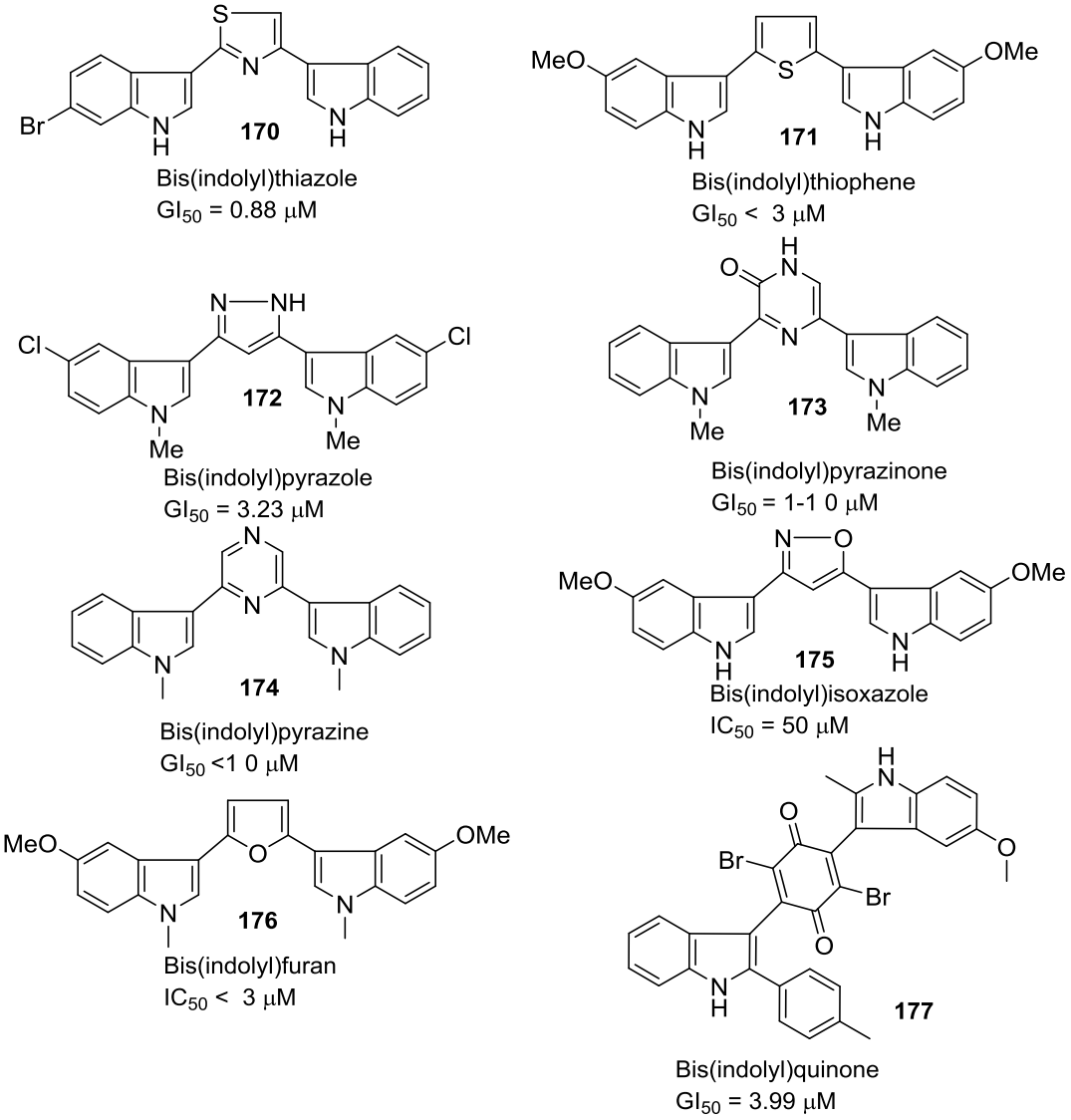
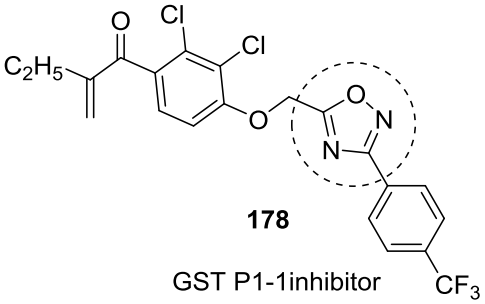


Figure 1.12: Some of the synthetic bis(indolyl) heterocycles as cytotoxic agents **170-177**

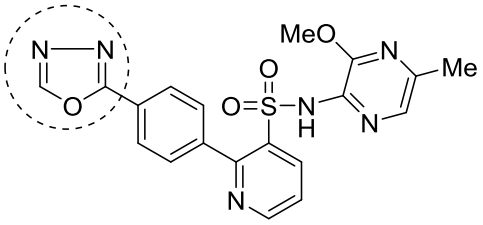
168 is a linear bis(indole) compound with dicarbonyl skeleton as a linker between two indole moieties. It showed significant cytotoxic activity against human epidermoid carcinoma KB cells (IC_{50} = 4.3 μM). Dragamcadins **169**, which were isolated from deep water marine sponge with good *in-vitro* cytotoxicity against pancreatic, lung, colon and mammary cancer cell lines (IC_{50} = 1-15 μM).[99] In view of interesting biological activities of natural and synthetic bis(indoles), nortopsentins have been considered as important lead compounds to identify indole-based novel bioactive heterocycles. In the recent past, various analogues of nortopsentins **170-177** have been reported to exhibit significant cytotoxicity against human cancer cell lines with IC_{50} values in

low micro-molar concentration range.[100-102] Some of the potent nortopsentin analogues are listed in Figure 1.12

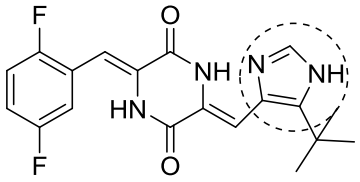
1.6 Importance of azaheterocycles: Azaheterocycles such as oxadiazoles, thiadiazoles, imidazoles, and quinoxalines are widely present in bio-active natural products.[103,104] Some examples of biologically active azaheterocycles (**178-183**) are shown in Figure 1.13. Oxadiazoles are an unique class of five-membered heterocyclic compounds that are probably most prevalent heterocyclic scaffold occurring in most of the bioactive compounds. Oxadiazoles are used as a bioisosteric replacement for amide and ester functionalities. The 1,2,4-oxadiazole **178** exhibited good anti-proliferative activity against GST P1-enzyme.[105]



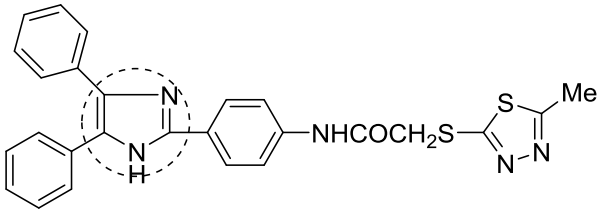
178
GST P1-1inhibitor
IC_{50} = 0.7μM



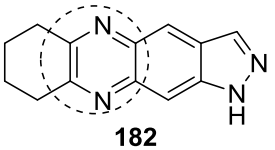
179
Zibotentan
Anti-cancer agent



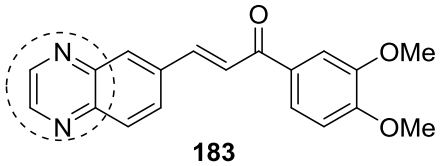
180
Plinabulin
IC_{50} = 2.6 nM



181
Anticancer agent
IC_{50} = 3.2 μM



182
Pim Kinase inhibitor
IC_{50} = 10 μM



183
Anti- cancer agent
IC_{50} = 2.29 μM

Figure 1.13: Some of the synthetic cytotoxic azaheterocycles **178-183**

Zibotentan **179**, containing a 1,3,4-oxadiazole scaffold showed potent cytotoxicity against various cancer cell lines.[106]. For instance, Plinabulin **180** is a potent microtubule targeting agent

derived from the natural product phenylstatin.[107] It is now under phase II clinical trial as an anticancer agent. Imidazole is another important five-membered nitrogen heterocycle with significant biological properties.[108] Diphenyl(imidiazole) derivative **181** has been reported to display good cytotoxicity against breast cancer cell line.[109] Furthermore, quinoxaline is a six-membered heterocycle which is among the privileged structures in drug discovery and widely present in many bio-active natural products.[110] For example, a series of pyrazolo (quinoxaline) **182** has been reported as a potent Pim kinases inhibitor with IC_{50} values in micro-molar range.[111] Quinoxaline derived chalcones **183** exhibited significant anti-proliferative activity against glioma cell lines.[112]

1.7 Conclusions and present work

With interesting selectivity and electrophilic properties of organoiodine reagents, it is of great interest to investigate their synthetic utilities. Organoiodine reagents are non-metallic oxidants which are devoid of toxicity and require simple experimentation and mild reaction conditions. With available catalytic strategy to perform many I(III) and I(V)-mediated oxidative transformations together with suitable oxidants, could encourage design and use of organo iodine reagents to develop eco-friendly synthesis of diverse bioactive heterocycles under mild conditions.[16] There has been a continuous surge of interest in the construction of bioactive heterocyclic compounds. Particularly, five- and six-membered ring systems with interesting biological activities and for being important building blocks frequently found in natural products. Taking into cognizance, the ubiquitous presence of heterocycles in natural products and pharmaceutical agents, the development of rapid and efficient preparative protocols for these heterocycles remain an urgent task in medicinal chemistry. There has been numerous innovative research efforts are ongoing under the awareness of environment issues towards minimization of toxic chemicals and waste production. Sustainability has become one of the greatest scientific challenges nowadays, due to environmental and health issues. Thus, there is need for developing facile, efficient and non-polluting synthetic strategies that utilize benign and catalytic amounts of reagents, avoids the use of toxic reagents and organic solvents.

The present study is mainly focusing on the synthetic utilities of organoiodine(III) reagents, for example, iodobenzene diacetate and diaryliodonium salts, in the construction of bioactive heterocycles. Particularly, we developed a benign synthetic route to access Nortopsentin analogues bis(indole)-1,3,4-oxadiazoles and evaluated their anticancer activity against human

tumour cell lines. Next, using diaryliodonium salts we prepared medicinally important diaryl sulfones under ligand and metal-free conditions. Then, by employing polyethylene glycol and palladium acetate combination on diaryliodonium salts we successfully prepared useful biaryls and heteroaryls. Finally, by applying C-H functionalization and selective O-arylation strategy involving diaryliodonium salts, we developed an eco-friendly and high yielding procedure to obtain diversely substituted 2-arylindoles and heteroaryl carboxylates.

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Chapter II

Design and synthesis of bis(indolyl)-1,3,4-oxadiazoles as anticancer agents

2. Bis(indolyl)-1,3,4-oxadiazoles as anticancer agents

2.1 Introduction

Marine organisms are cornucopia sources of structurally diverse natural products acquired with potential biological activities.[1-4] Among the various marine compounds, bis(indole) based alkaloids are unique class of compounds possessing a heterocyclic or linear linker between two indole rings.[5] These isolated bis(indole) alkaloids (Figure 2.1) are termed as 'secondary metabolites' because marine organisms generate these toxic chemicals for their defense mechanism to protect themselves from the external threat.[6] Nortopsentin **A** bis(indolyl)imidazole alkaloids (**1**) isolated from the deep sea sponge *Spongosorites ruetzleri*,

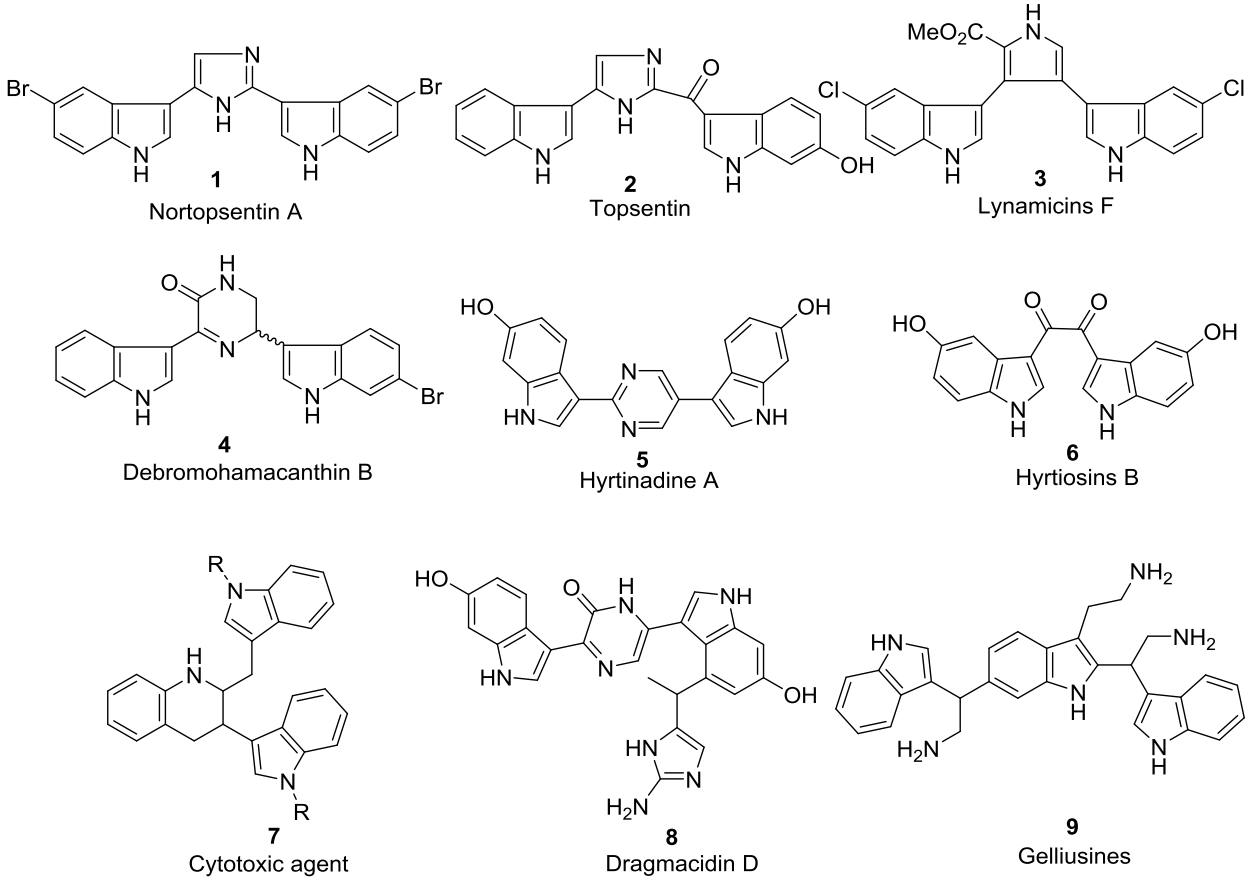


Figure 2.1 Natural bis(indole) alkaloids as anticancer agents

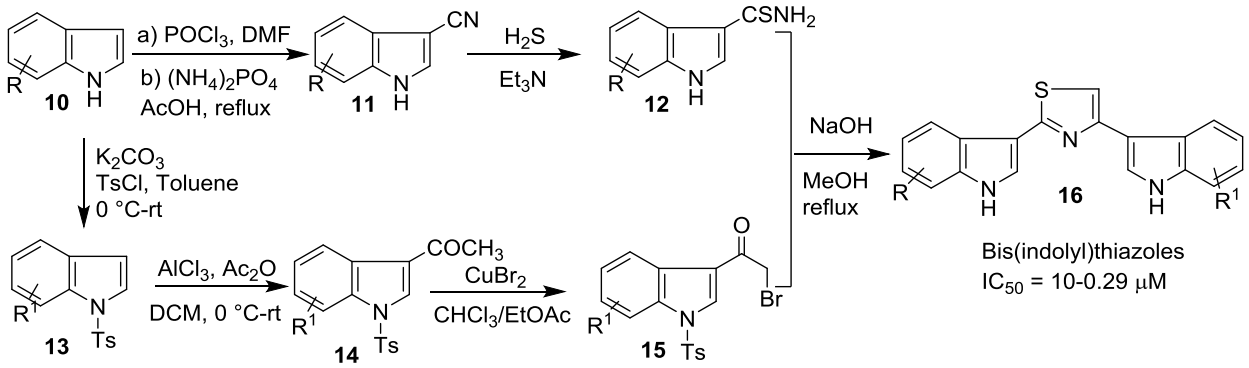
displayed potent and diverse medicinal properties such as anticancer, anti-inflammatory and antiviral.[7] Later, Topsentin (**2**) was identified from sponge *Spongosorites genitrix* exhibits significant cytotoxicity against human leukemia cell-line K-562 (0.6 µg/mL).[8] Recently, a new bis(indole) alkaloid named Lynamicins F (**3**) extracted from deep sea-derived actinomycete

Streptomyces species.[9] It bears a pyrrole unit with moderate anticancer activity against MCF-7 cell line. Debromohamacanthin B (**4**) consists of six-membered heterocyclic ring dihydro-pyrazinone as a linker between two indoles displayed cytotoxicity against a panel of cancer cell lines.[10] Kobayashi et al. identified a new bis(indole) alkaloid Hyrtinadine A (**5**) isolated from Okinawan marine sponge *Hyrtios* species.[10] It is known to exhibit *in vitro* cytotoxicity against murine leukemia L-1210 and human epidermis carcinoma KB cells. Hyrtiosin B (**6**) a symmetrical diketone molecule isolated from the marine sponge *Smenospongia* species displayed an moderate antiproliferative activities towards various tumor cell lines.[11] Compound **7** showed reasonable anticancer property on L1210 leukemia cells with IC_{50} = 2.7 μM.[12] Dragmacidin D (**8**) is a potent inhibitor of serine-theronine phosphates isolated from Caribbean marine sponges.[13,14] Gelliusines (**9**) extracted from Caledonian marine sponges possessing an indole nucleus as a spacer exhibits cytotoxicity against KB cell lines.[15] Owing to the significant anticancer property of bis(indole) alkaloids, they received much attention in the drug discovery research. Many medicinal chemists have treated bis(indole) alkaloids as lead compounds to develop new anticancer agents by modifying the central heterocyclic ring with various bio-active heterocycles to improve the cytotoxicity against specific cancer cell lines and minimize the toxicity.[16]

2.2 Synthetic bis(indole) analogues

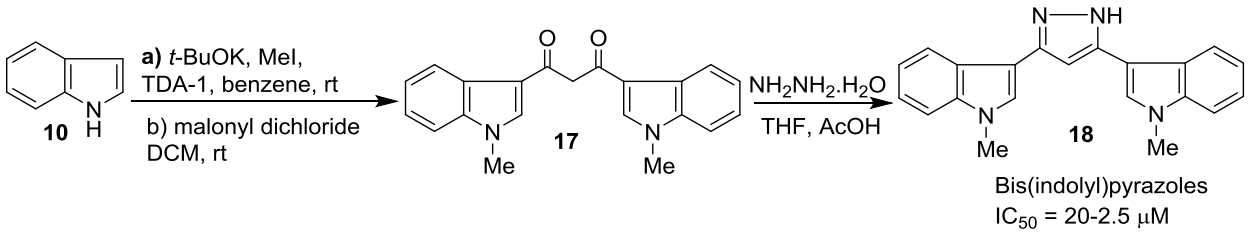
Jiang and Gu[17] synthesized three new Nortopsentin analogues namely, bis(indolyl)thiazoles, bis(indolyl)pyrazinones and bis(indolyl)pyrazines and evaluated their cytotoxicity against a variety of human tumor cell lines. General synthetic route to construct bis(indolyl)thiazoles **16** is depicted in Scheme 2.1. Initially, indole-3-carbonitriles **11** were prepared from the corresponding indoles **10** *via* Vilsmeier-Haack formylation followed by the treatment of ammonium phosphate in acetic acid. Addition of hydrogen sulphide to nitriles **11** yielded indole-3-carbothioamides **12** in good yields. *α*-Bromoketones **15** were accomplished from the appropriate indoles through Friedel-Crafts acylation of *N*-protected indoles **13.** Acylated indoles **14** were subjected with copper bromide in chloroform:ethylacetate (1:1) mixture to afford α-bromoketones **15** in excellent yield. Finally, the two intermediates **12** and **15** were refluxed in ethanol to produce the cyclized product *N*-protected bis(indolyl)thiazoles which were

deprotected under basic conditions and afforded the desired bis(indolyl)thiazoles **16** in good to excellent yields.



Scheme 2.1 Synthesis of bis(indolyl)thiazoles

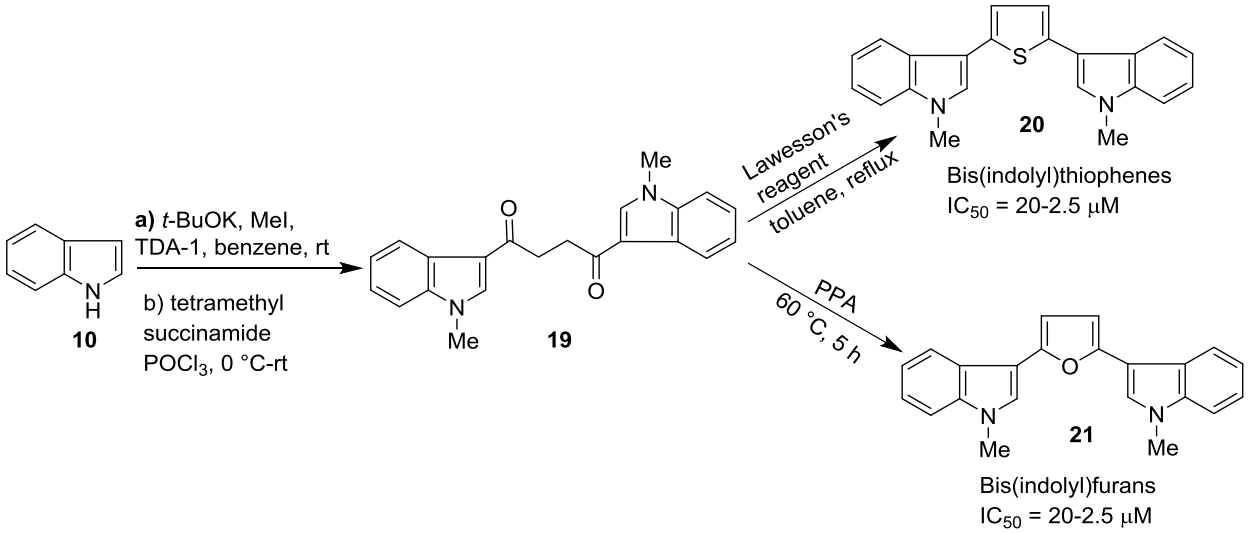
Diana and co-workers reported the synthesis of bis(indolyl)pyrazoles **18** by replacing the central imidazole ring of Nortopsentin with pyrazole moiety and examined the anticancer activity against different cancer cell lines (Scheme 2.2). The synthetic approach of bis(indolyl)pyazoles is commenced with the *N*-methylation of indoles in the presence of methyl iodide, potassium *t*-butoxide and catalyst tris(3,6-dioxaheptyl)amine (TDA-1) as illustrated in Scheme 2.2. Next, reaction between malonyl dichloride and *N*-methylated indoles afforded the valuable intermediate bis(indolyl)-1,3-diketones **17** which upon reaction with hydrazine monohydrate produced **18**.



Scheme 2.2 Synthesis of bis(indolyl)pyrazoles

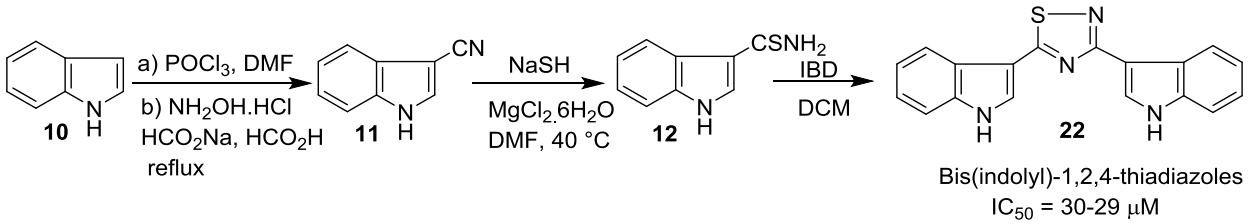
In continuation to the promising anticancer results of bis(indolyl)pyrazoles, Diana research group explored the synthesis and biological evaluation of bis(indolyl)thiophenes **20**[18] and bis(indolyl)furans **21**[19] as Nortopsentin analogues. The synthesis of **20** and **21** are illustrated in Scheme 2.3. The versatile intermediate bis(indolyl)-1,4-diketones **19** prepared from the reaction between *N*-methylated indole and tetramethyl succinamide. Next, treatment of Lawesson's reagent to **19** yielded the cyclized product bis(indolyl)thiophenes **20** in good yields. Conversely

the same intermediate **19** undergo intramolecular cyclization in the presence of polyphosphoric acid and led to bis(indolyl)furans **21** in excellent yields.



Scheme 2.3 Synthesis of bis(indolyl)thiophenes and furans

In 2011, Kumar et al.[20] synthesized a series of novel bis(indolyl)-1,2,4-thiadiazoles **22** by substituting the central ring of Nortopsentin with thiadiazole ring and evaluated their anticancer activity against a panel of cancer cell lines. Synthesis of bis(indolyl)-1,2,4-thiadiazoles is carried out as shown in Scheme 2.4. Initial formylation of indole was accomplished with $POCl_3$ and DMF to produce indole-3-carboxyaldehydes in excellent yields. Subsequently, indole-3-carboxyaldehydes were transformed into the corresponding indole-3-carbonitriles **11** by treatment with hydroxylamine hydrochloride, sodium formate and formic acid. Treatment of carbonitriles **11** with sodium hydrogen sulphide and magnesium chloride yielded indole-3-carboxamides **12** in moderate yields. Finally, iodobenzene diacetate (IBD) was employed to achieve bis(indolyl)-1,2,4-thiadiazoles **22** in good to excellent yields.



Scheme 2.4 Synthesis of bis(indolyl)-1,2,4-thiadiazoles

2.3 Significance of 1,3,4-oxadiazole in drug discovery

Heterocycles are certainly a vital backbone for most of the marketed drugs and bioactive molecules.[21-23] Among the various heterocycles, 1,3,4-oxadiazole is a potential five-membered heterocyclic ring having a broad range of biological activities including antitumor[24], antibacterial[25], anti-inflammatory[26], antitubercular[27], anti-anxiety[28], antiviral[29] and antifungal[30] properties. Considering the medicinal chemistry point of view, 1,3,4-oxadiazole exhibits impressive medicinal properties metabolic stability and excellent pharmacokinetic property.[24]

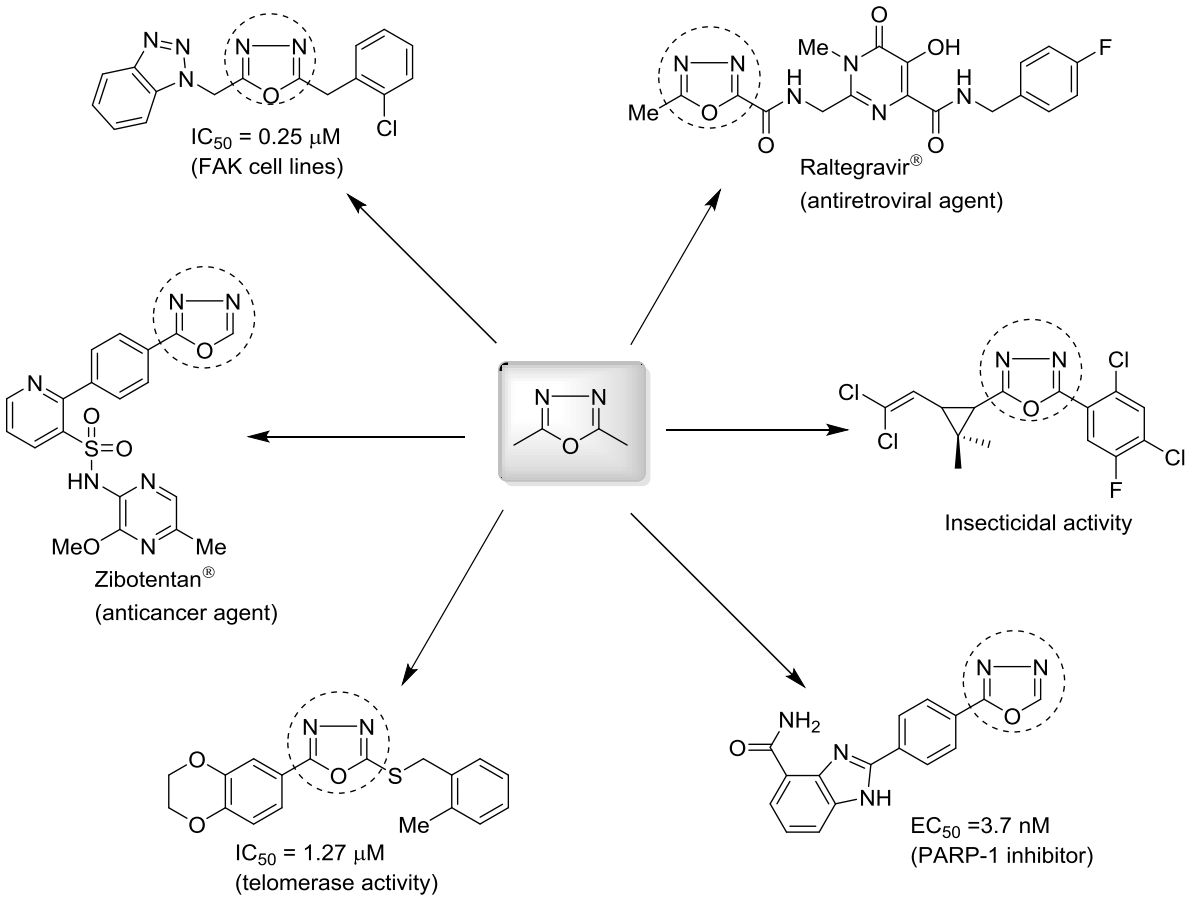


Figure 2.2 Bioactive heterocycles with 1,3,4-oxadiazole moiety

Therefore, it acts as suitable bioisosteres for carboxylic acids, esters and amides. It is a flat five-membered ring system which can be properly orients towards the target proteins. The presence of azole (-N=C-O-) group in oxadiazole ring, enhances the lipophilicity that facilitate the drug to reach the target by transmembrane diffusion. In recent years, medicinal chemists have used 1,3,4-oxadiazole as an important pharmacophore to develop new anticancer entities against different cancer cell lines.[31-33] For example, marketed anticancer drug Zibotentan® contain 1,3,4-oxadiazole

nucleus (Figure 2.2). Very recently, Shalini et al.[34] reviewed the anticancer properties of 1,3,4-oxadiazole core by targeting various growth factors, enzymes and kinase inhibitors.

2.4 Construction of 1,3,4-oxadiazole nucleus

Besides the immense biological significance, syntheses of 1,3,4-oxadiazoles have fascinated to medicinal chemists. There are many synthetic procedures available to construct 1,3,4-oxadiazole system **24** (Figure 2.3). Mostly utilizes oxidative cyclization of acylhydrazones **23** involving ceric ammonium nitrate (CAN)[35], $KMnO_4$[36], I_2/K_2CO_3[37], Br_2,[38] and $Cu(OTf)_2$[39].

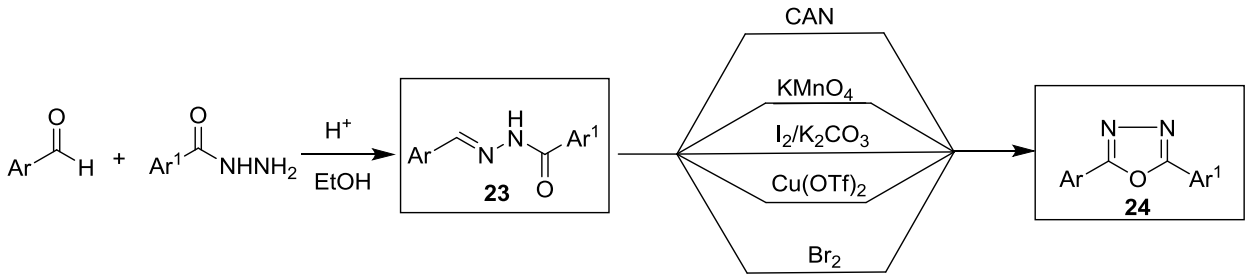


Figure 2.3 Synthesis of 1,3,4-oxadiazoles

Very recently, Aravind and Yadav[40] developed a visible-light-promoted synthesis of 1,3,4-oxadiazoles from acylhydrazones at room temperature using eosin Y as an organophotoredox catalyst. However, most of these procedures involve the use of corrosive solvents, toxic and lachrymatory reagents and mostly results in moderate product yields. Recently organic transformation using organoiodine reagents gained wide popularity among the synthetic chemists due to their many practical advantages associated with enhanced reaction rates, high yields, improved selectivity and relatively less toxic reaction conditions.[41-43]

2.5 Rationale design

Based on the biological importance of natural bis(indole) alkaloids and their synthetic analogues heterocyclic spacers such as imidazole, thiazole, furan, thiophene between the two indole rings were found to be crucial role for tuning their anticancer properties. Likewise, 1,3,4-oxadiazole also known to be an unambiguous cytotoxic pharmacophore studied for their antiproliferative activity against various human tumor cell lines. To develop new anticancer entity by employing the medicinal significance of bis(indole) alkaloids and 1,3,4-oxadiazoles, we designed bis(indolyl)-1,3,4-oxadiazoles **25** by incorporating 1,3,4-oxadiazole as linker between two indoles as depicted in Figure 2.4.

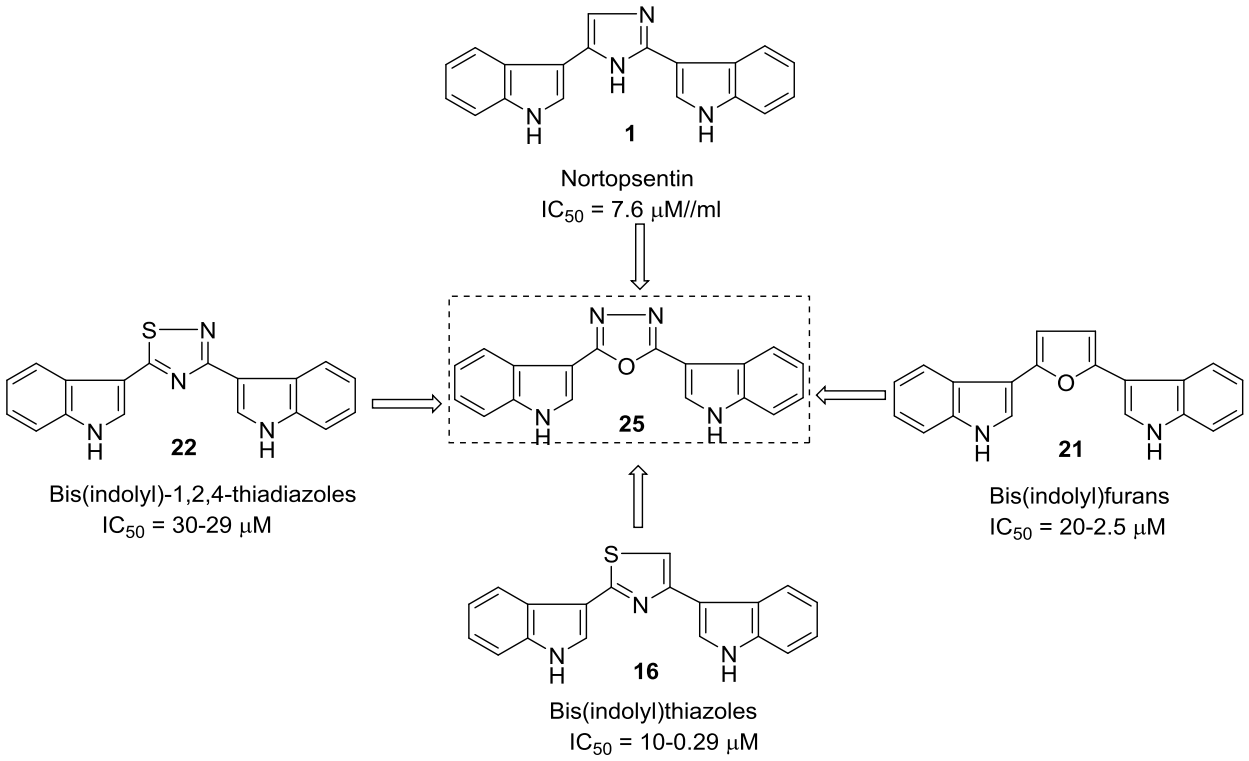


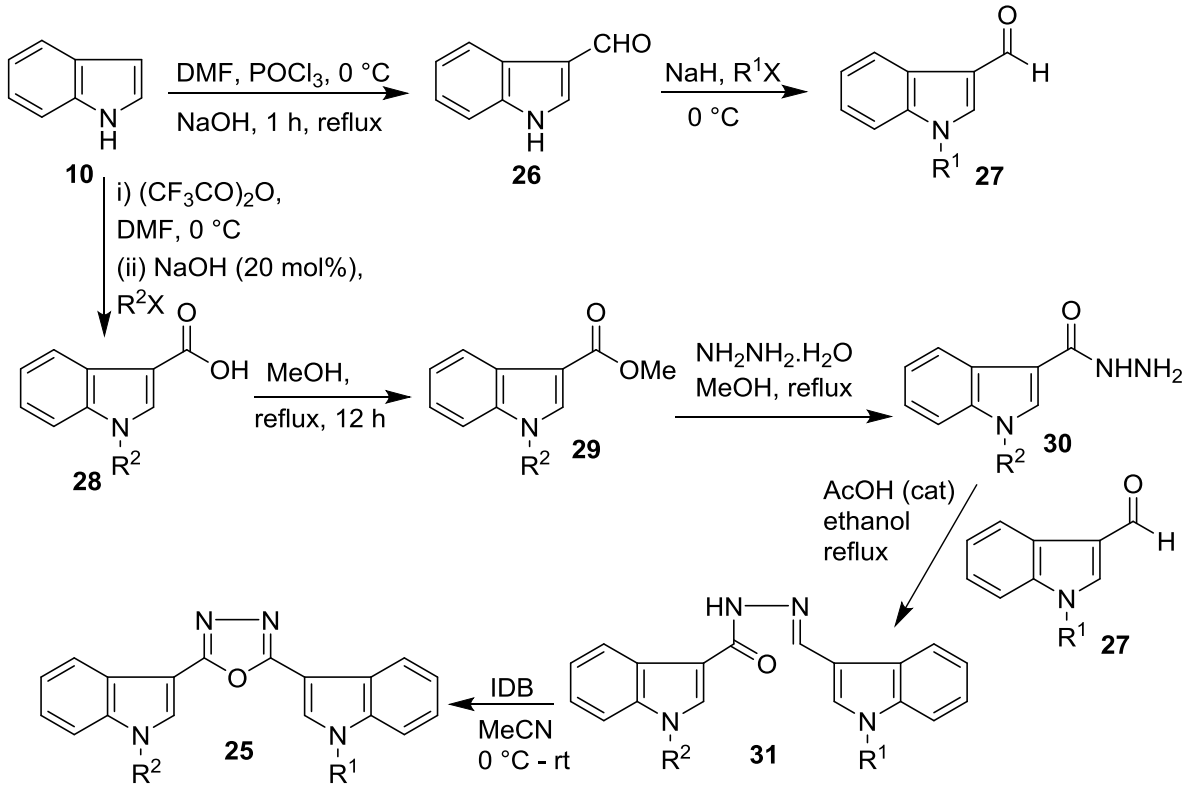
Figure 2.4 Rationale design for the synthesis of 1,3,4-oxadiazole

2.6 Results and discussion

2.6.1 Chemistry

Synthesis of bis(indolyl)-1,3,4-oxadiazoles was achieved as described in Scheme 2.5. Indole-3-carboxyaldehydes **26** were prepared from corresponding indoles **10** by Vilsmeier-Haack formylation, which were then followed by *N*-alkylation afforded **27** in good yields. On the other side, indole-3-hydrazides **30** were synthesized in three steps. Initially, indoles **10** were converted into the corresponding indole-3-carboxylic acid **28**, which were then esterified to **29** and treated with hydrazine hydrate to obtain desired indole-3-carbohydrazides **30**. Intermediate bis(indolyl)hydrazide-hydrazones **31** were synthesized in good yields from reaction of indole-3-carboxaldehydes **27** and indole-3-carbohydrazides **30** in presence of acetic acid in ethanol. Our initial attempts to cyclize intermediate bis(indolyl)hydrazide-hydrazones **31** using [bis(trifluoroacetoxy)iodo]benzene (BTI) and Dess-Martin Periodinate (DMP) resulted in poor yields of the desired bis(indolyl)-1,3,4-oxadiazoles **25**. However, the oxidative-cyclization of bis(indolyl)hydrazide-hydrazones **31** was successful with iodobenzene diacetate (IBD) at room

temperature in acetonitrile to produce bis(indolyl)-1,3,4-oxadiazoles **25** in good yields (Scheme 2.5).



Scheme 2.5 Synthesis of bis(indolyl)-1,3,4-oxadiazoles

From IR spectra of compounds **25a**-**m**, it was observed that the carbonyl streching bands observed at (1680-1660 cm^{-1}) in precursor hydrazide-hydrazones disappeared. Moreover, in ^{1}H NMR spectra of compounds **25a**-**m**, diapperance of characteristic singlets observed in intermediate hydrazie-hydrazones **31** at about 8.5 ppm and 11.00 ppm (broad) due to the azomethine (–CH=N-) and hydrazide (-CO-NH=N-) protons, confirms the oxidative-cyclization of **31** to give 1,3,4-oxadiazole ring. Optimized protocol was used to synthesize a series of bis(indolyl)-1,3,4-oxadiazoles **25a**-**m**

Copies of NMR (^{1}H and^{13}C) and mass spectra of compound **25b** are shown in Figures 2.5-2.7

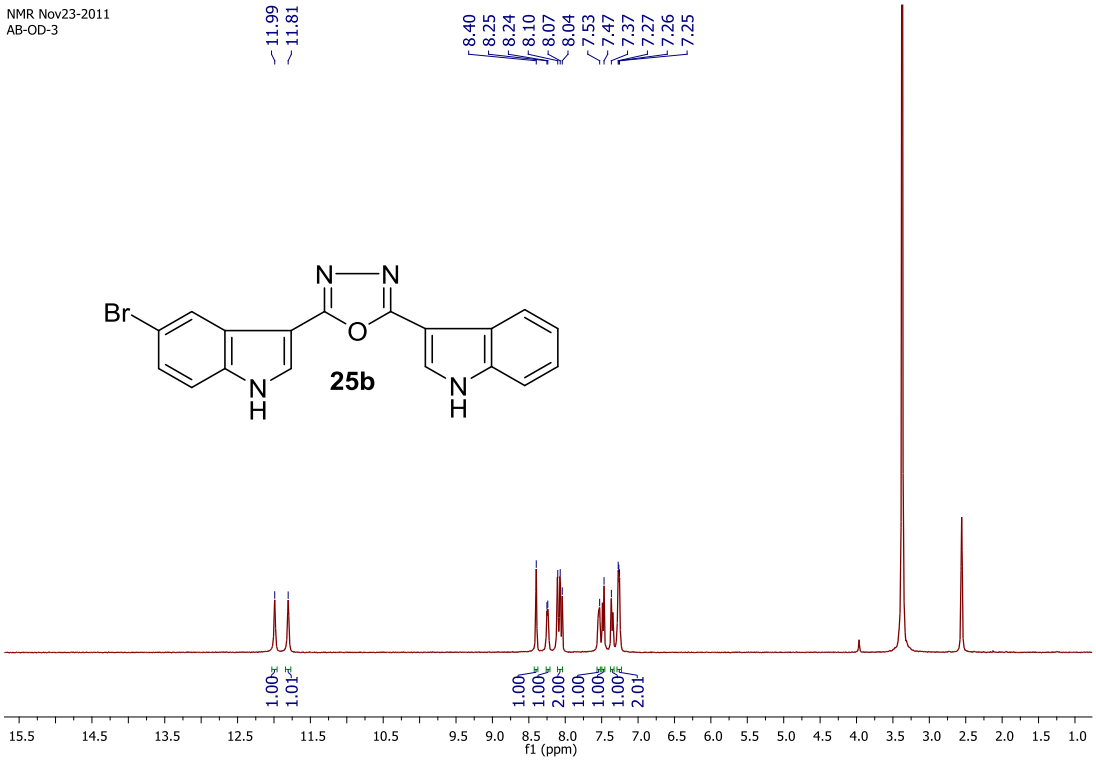


Figure 2.5 ^{1}H NMR spectrum of compound **25b**

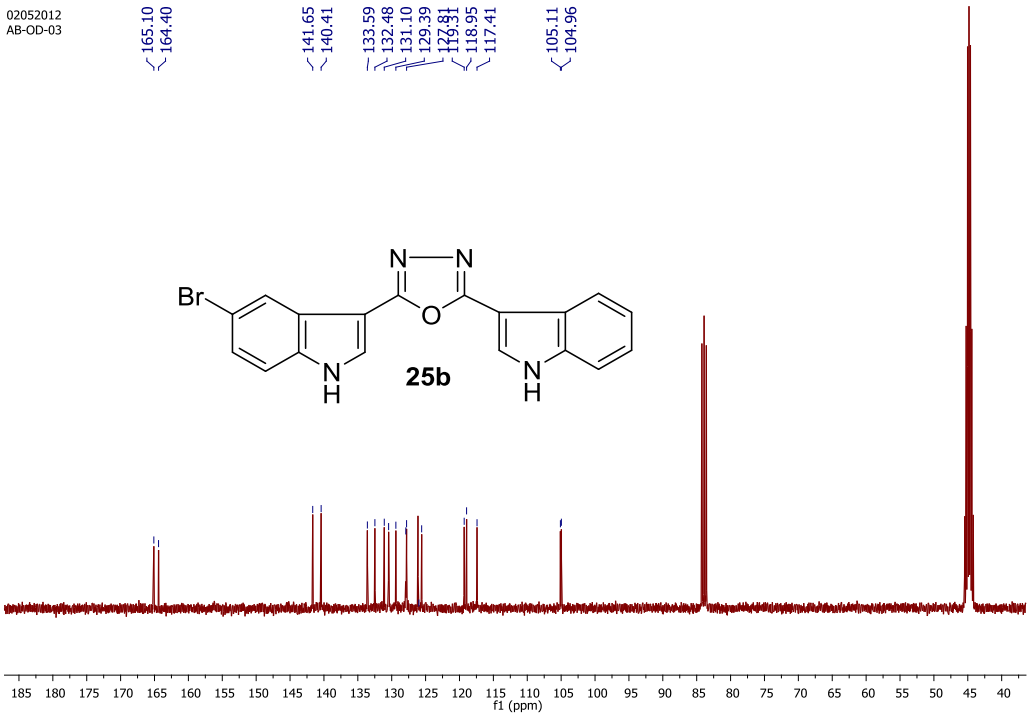


Figure 2.6 ^{13}C NMR spectrum of compound **25b**

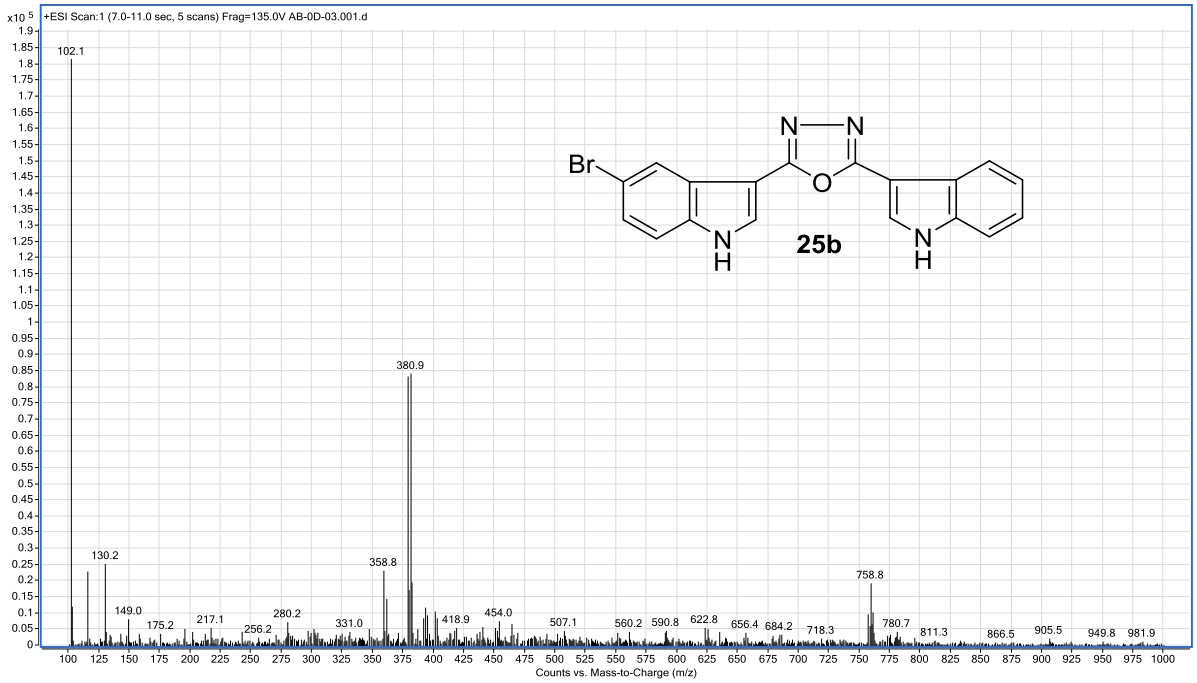
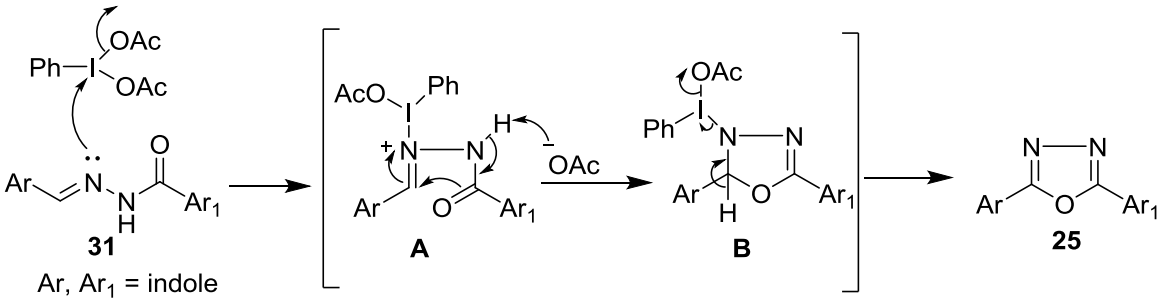


Figure 2.7 Mass spectrum of compound **25b**

2.6.2 Plausible Mechanism

The plausible mechanism for the formation of product bis(indolyl)-1,3,4-oxadiazole **25** is depicted in Scheme 2.6. Initially, the treatment of iodobenzene diacetate with hydrazine-hydrazone **31** results in an intermediate **A**, which undergoes internal nucleophilic attack to produce **B**. Finally, elimination of iodobenzene and acetic acid afforded the desired product **25**.

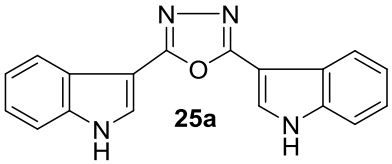
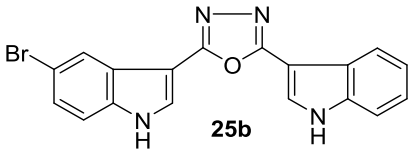
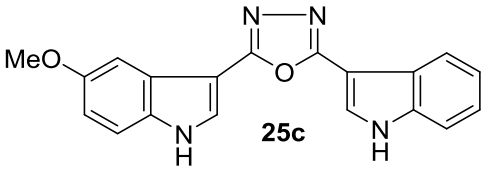
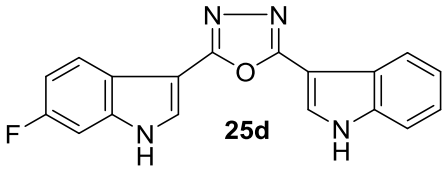
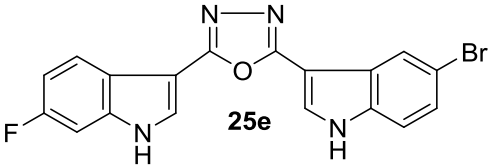
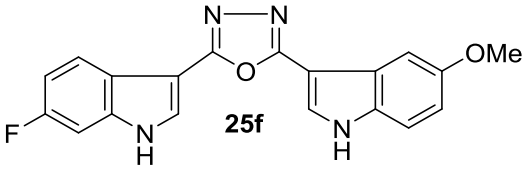
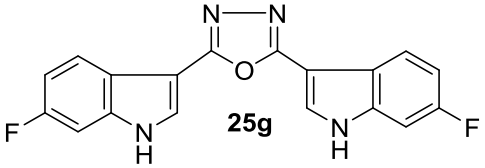


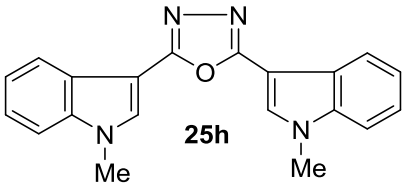
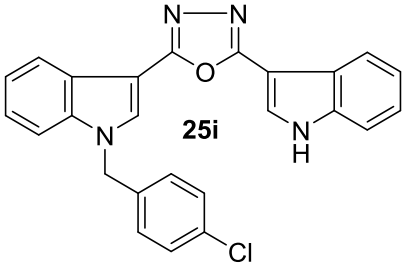
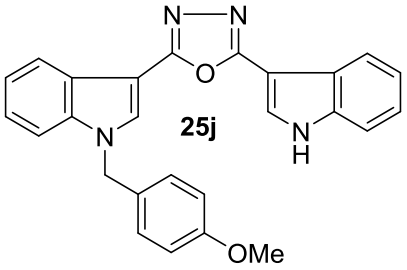
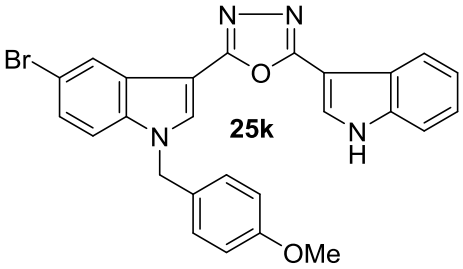
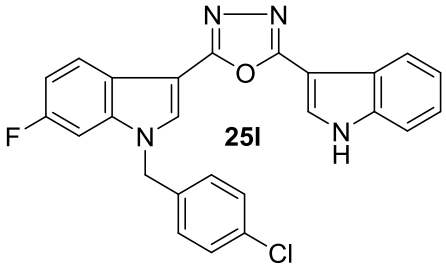
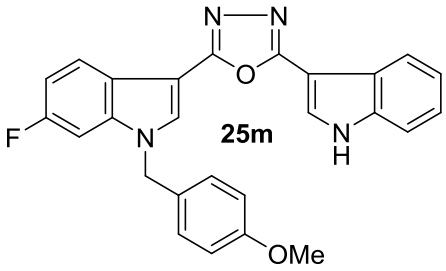
Scheme 2.6 Plausible mechanism for the formation of bis(indolyl)-1,3,4-oxadiazole **25**

2.6.3 *In-vitro* anticancer activity

All the synthesized bis(indolyl)-1,3,4-oxadiazoles **25a-m** were studied for their anticancer activity against six various human cancer cell lines: pancreas (ASPC1), prostate (DU145 and PC3), cervical (HeLa), breast (MDA-MB231) and ovarian (OVCAR). Anticancer activity of bis(indolyl)-1,3,4-oxadiazole **25a-m** are expressed in terms of IC_{50} values as shown in Table 2.1.

Table 2.1 Anticancer activity of bis(indolyl)-2,3,4-oxadiazoles **25a**-**m** (IC_{50} values in μM)

Bis(indolyl)-1,3,4-oxadizoles	ASPC1	DU145	HeLa	MDA-MB-231	OVCAR	PC3
 **25a**	0.46	0.23	0.53	0.09	0.10	8.43
 **25b**	0.20	**0.02**	**0.02**	0.24	0.15	0.25
 **25c**	0.06	0.72	66.8	0.90	0.38	0.11
 **25d**	0.31	9.79	6.86	4.34	0.38	0.11
 **25e**	0.45	**0.08**	**0.06**	0.20	0.23	4.55
 **25f**	1.68	0.42	52.9	6.44	2.91	0.10
 **25g**	0.20	0.15	**0.06**	0.21	0.15	1.09

 **25h**	0.10	0.52	4.55	15.71	0.97	0.12
 **25i**	2.47	0.37	0.73	126.3	0.16	7.11
 **25j**	**0.05**	0.54	5.94	168.9	0.10	3.33
 **25k**	0.43	0.11	8.10	0.86	0.27	0.24
 **25l**	1.60	0.14	0.96	2.58	0.24	0.05
 **25m**	**0.07**	0.10	1.20	17.22	0.11	0.14
Doxorubicin	1.69	11.59	12.9	1.55	1.05	9.27

Most of the compounds **25a-m** were exhibited significant anticancer activity, IC_{50} ranging from 20 nM to 100 nM. The cytotoxic effects of various substituents on indole ring were evaluated. Structure-activity relationship study revealed that substituents at C-5 position of indole ring favour the anticancer activity and selectivity. The compound **25a** showed good cytotoxicity against multiple cancer cell lines with IC_{50} values less than 0.1 µM and the highest activity was observed against breast (MDA-MB-231, IC_{50} = 0.09 µM) and ovarian cancer cells (OVCAR, IC_{50} = 0.10 µM). We observed that the anticancer activity of **25a** having 1,3,4-oxadiazole spacer was improved several folds when compared with previously reported bis(indolyl)heterocycles with different five/six-membered spacers. The substituents at C-5 position of indole ring plays a vital role in improving anticancer activity. Bromo and methoxy groups at C-5 of indole led to compounds **25b** and **25c,** respectively. The compound **25b** was found to be most active in the series having good cytotoxicity profile against all the tested cancer cell lines (IC_{50} > 0.3 µM) and showed highest cytotoxicity against prostate and cervical cancer cells (IC_{50} = 20 nM each). However, the compound **25c** showed selective anticancer activity against pancreas cancer cells (ASPC1, EC_{50} = 60 nM). Introduction of fluorine at C-6 position of indole (compound **25d)** did not show any improvement in activity but activity against pancreas, prostate and ovarian cancer cell cells (IC_{50} ~ 0.3 µM). With fluorine atom at C-6 position of indole ring, compounds **25e-g** were prepared. This change in case of compounds **25e** and **25f** anticancer activity was reduced. However, the compound **25g** exhibited improved cytotoxicity against multiple cancer cell lines with 100-folds selective cytotoxicity against Hela cancer cells (IC_{50} = 60 nM) when compared to **25d** (IC_{50} = 6.86 µM). *N*-Alkylation of compounds **25a**, **25b** and **25d** led to compounds **25h** (N-methyl) and **25h-m (***N*-chloro/methoxybenzyl) without any significant improvement in anticancer activity. Introduction of *p*-methoxybenzyl substituent at *N*-1 of **25a** led to compound **25j** with improved selective cytotoxicity against pancreas cancer cells (ASPC1, IC_{50} = 50 nM). Compounds **25l** and **25m** were obtained by incorporating *p*-chlorobenzyl and *p*-methoxybenzyl groups to compound **25d** with improved anticancer activity against multiple cancer cell lines. It was also observed that compounds **25l** and **25m** were selectively cytotoxic against prostate (PC3, IC_{50} = 50 nM) and pancreas (ASPC1, IC_{50} = 70 nM) respectively. Overall, synthesized series of bis(indolyl)-1,3,4-oxadiazoles **25a-m** were found to be superior over the reference compound Doxorubicin (Table 2.1). Introduction of 1,3,4-oxadiazole as spacer in bis(indolyl)heterocycles is

beneficial for the anticancer activity and selectivity towards tested prostate and breast cancer cell lines.

2.6.4 Apoptosis Study

Apoptosis is a programmed cell-death, which naturally occurs during the development and aging process in the body in order to maintain cell population in tissues.[44-46] Apoptosis is identitfed by cell shrinakge, blebbing of plasma membrane, condensation and fragmentation of DNA as depicted in Figure 2.8.

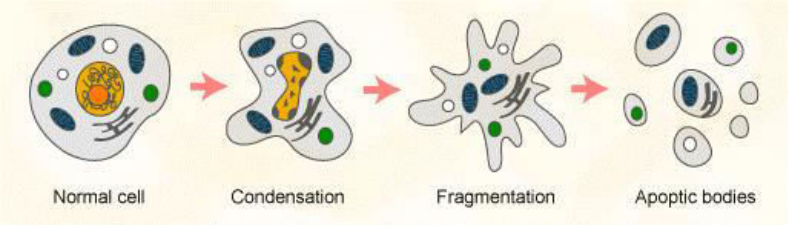


Figure 2.8 Representation of normal apoptosis

Due to the significance of apoptosis indudced cell death, we investigated the mechanism of cell death in MDA-MB-231 cells using three potent compounds **25c**, **25g** and **25h**. While **25c** and **25g** were highly potent (IC_{50} = 0.9 and 0.21 µM respectively), **25h** was moderate (IC_{50} = 15.71 µM). After incubating for 48 h, MDA-MB-231 cells were fixed and stained with propidium iodide and nuclear morphology analyzed using fluorescence microscopy. While DMSO-treated control cells revealed normal healthy nuclei, inhibitor-treated cells showed apoptotic nuclei (Figure 2.9). Thus, these results demonstrated that apoptosis is the major mechanism by which bis(indolyl)-1,3,4-oxadiazoles promote cell death.

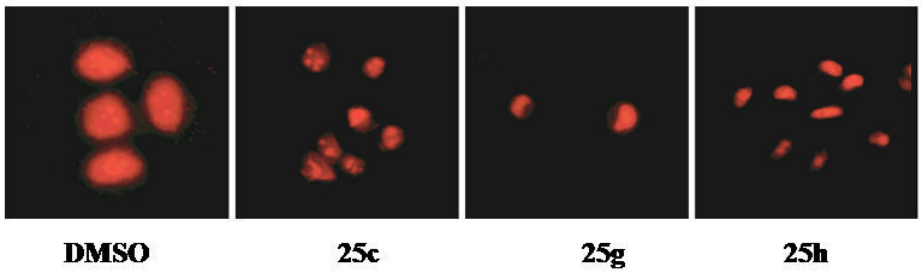
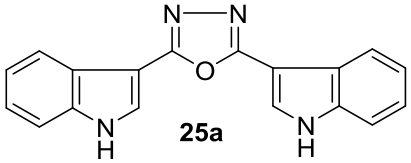
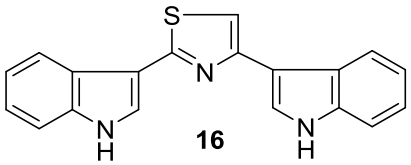
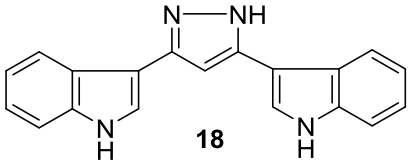
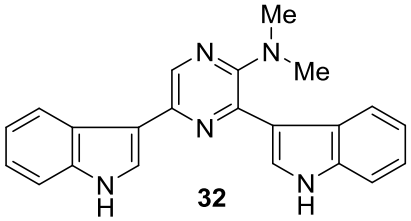
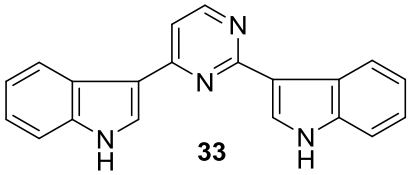
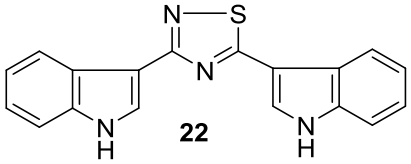
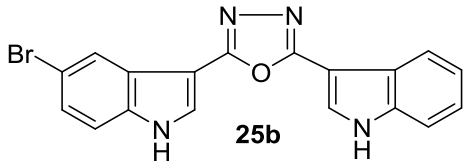
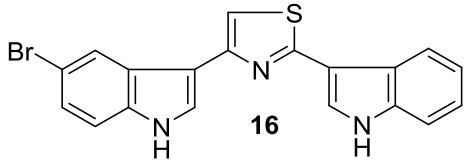
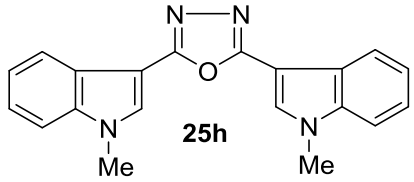
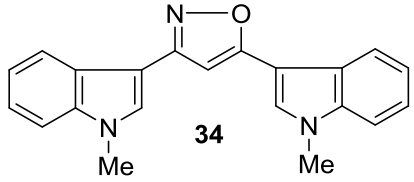


Figure 2.9 Propidium iodide staining of MDA-MB-231 cells treated with either DMSO, **25c, 25g-25h**

Moreover, we have noticed that present series of bis(indolyl)-1,3,4-oxadiazoles **25a-m** were several folds more potent than previously reported bis(indoles) with various five/six-membered heterocyclic moiety as a spacer (Table 2.2).

Table 2.2 Comparison of cytotoxicity data of bis(indole) analogues synthesized in present study and reported in literature.

Compounds	MDA	OVCAR	PC3	DU145
 **25a**	0.09	0.10	8.43	0.23
 **16**	83.0	>100	>100	>100
 **18**	8.06	>100	8.11	1.56
 **32**	____	4.68	3.69	____
 **33**	4.52	>100	2.72	____
 **22**	70.15	____	>100	>100

 **25b**	0.24	0.15	0.25	0.02
 **16**	3.77	2.35	2.81	2.03
 **25h**	15.71	0.97	0.12	0.52
 **34**	____	11.1	28.	18.3

2.6.5 Conclusions

In summary, we have synthesized a series of novel 2,5-bis(indolyl)-1,3,4-oxadiazoles **25a**-**m** by using relatively iodobenzene diacetate mediated oxidative cyclization of easily accessible bis(indolyl)hydrazide-hydrazones **31**. All the synthesized 2,5-bis(indolyl)-1,3,4-oxadiazoles showed improved cytotoxicity over previously reported bis(indoles)heterocycles. Bis(indolyl)-1,3,4-oxadiazole **25b** with bromo substituent was found to be most active in the series having IC_{50} value 20 nM against prostate (DU145) and cervical (HeLa) cancer cells. The present structure-activity relationship (SAR) studies revealed that bromo substituent is a crucial role in imparting the anticancer activity and *N*-alkylation is beneficial for improving the selectivity against particular cancer cells. Preliminary mechanism of action studies in MDA-MB-231 breast cancer cells indicate that bis(indolyl)-1,3,4-oxadiazoles **25a**–**m** induce apoptosis and promote cell death.

2.7 Experimental Details

2.7.1 General remarks: All the laboratory grade reagents were obtained commercially either from Aldrich or Spectrochem. The reactions were monitored by thin layer chromatography, which were performed on commercially available Merck precoated plates (silicagel. $60F_{254}$, 0.25 mm). The solvents were evaporated using Büchi rotary evaporator. Melting points were determined by *E-Z* melting apparatus. NMR (^{1}H and ^{13}C) spectra were recorded on a Bruker advance II (400Mz) spectrophotometer. The coupling constants *J* are given in Hz. Mass spectra of the synthesized compounds were recorded using 'Hewlett-Packard' HP GS/MS 5890/5972.

2.7.2 General Experimental Procedures

(a) Indole-3-carboxyaldehydes 26

To an oven dried round-bottomed flask freshly distilled dimethylformamide (14 mL, 18.8 mmol) was added. The flask content was cooled at 0 °C for 30 min. To this cooled DMF freshly distilled phosphorous oxychloride (4.4 mL, 4.7 mmol) was added dropwise over a period of 0.5 hour. The mixture became pinkish colour this indicated that formylation complex was has formed. Subsequently, a solution of indole (5g, 4.2 mmol) in DMF (5 mL) was added slowly to the reaction mixture for an hour, the temperature should be below 10 °C. After addition, the temperature was raised to 35°C and stirred until it became yellow paste. Later, 10g crushed ice was added, the yellow paste turned to clear cherry-red solution. To this 60 mL sodium hydroxide (18 g, 11.0 mol) solution was dropped wise and the resulted solution was heated rapidly at 90 °C and cooled to room temperature. Finally, it was stored at refrigerator for overnight and product was filtered under vacuum. The solid was washed with water, dried and afforded pure indole-3-carboxyaldehydes **26**.[47]

(b) Alkylation of indole-3-carboxyaldehydes 27

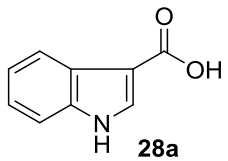
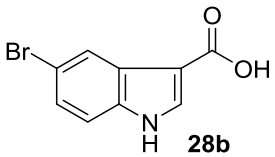
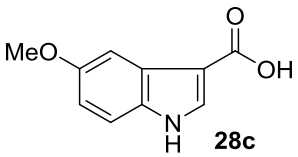
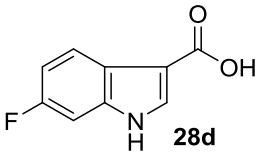
To a stirred mixture of indole-3-carboxaldehyde (**26**, 34 mmol) in 50% aqueous NaOH (40 mL), water (60 mL) and tetrabutylammonium bromide (0.1 g, 3.4 mmol) was added methyl iodide/4-chlorobenzylchloride/4-methoxybenzylchloride (34 mmol) in toluene (30 mL). After the compl-etion of reaction, organic layer was washed twice with aqueous $NaHCO_3$ (50 mL), water and saturated brine solution (100 mL), and then dried over anhydrous Na_2SO_4. The solvent was

evaporated under vacuum and the residue was washed with diethyl ether to afford crude alkylated product which upon recrystallization with ethyl acetate and hexane led to pure alkylated 3-carboxaldehydes **27**.[48]

(c) Indole-3-carboxylic acid 28

To a cooled solution (0 °C) of indole in DMF mixture, appropriate amount of trifluoroacetic anhydride was added dropwise. The reaction mixture was allowed to stir at 0 °C for 3 h. After, it was poured into ice, and the solid obtained was filtered and washed with water. Next the crude product was dissolved in 20% NaOH and refluxed for 6 h. The contents were allowed to cool and washed with dichloromethane. The aqueous layer was acidified with dil. HCl and precipitated the required indole-3-carboxylic acids. It was filtered and dried in vacuum to afford pure indole-3-carboxylic acids. Similarly, indole-3-carboxyxlic acids **28b-d** were prepared.[49-52]

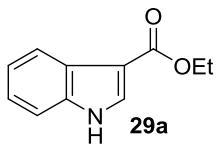
Synthesized indole-3-carboxylic acids 28a-d

 **28a**	 **28b**	 **28c**	 **28d**
mp 230-232 °C (lit[43] 229-234 °C)	mp 234-236 °C (lit[44] 238-240 °C)	mp 172-173 °C (lit[45] 172-175 °C)	mp 242-243 °C (lit[46] 242-244 °C)

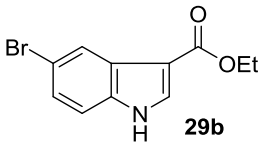
(d) Synthesis of ethyl-1*H*-indole-3-carboxylate 29a-d

To a suspension of indole-3-carboxylic acids (2 g) in 20 mL ethanol was added con.H_2SO_4 (0.1 mL). The reaction mixture was refluxed until the completion of reaction (20 h). After completion of the reaction, ethanol was evaporated and the residue so obtained was extracted using ethyl acetate (10 mL × 2). The organic layer was dried and evaporated under reduced pressure to afford the pure ethyl-1*H*-indole-3-carboxylate **29a** in good yields. Likewise, substituted ethyl-1H-indole-3-carboxylates **29b**-**d** were synthesized.[53-55]

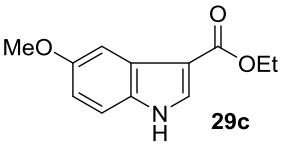
Synthesized ethyl-1*H*-indole-3-carboxylates 29a-d



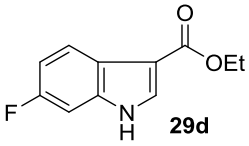
mp 121-122 °C
(lit[53]120-124 °C)



mp 191-192 °C
(lit[54]192-1943 °C)



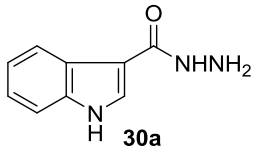
mp 145-146 °C
(lit[55] 143-144 °C)



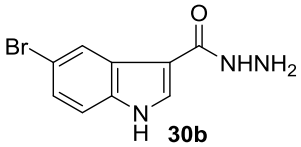
mp 142-122 °C

(e) Synthesis of indole-3-carboxyhydrazides 30: To an oven dried 50 mL round bottomed flask indole-3-carboxylate (1 g), hydrazine hydrate (5 equiv), ethanol (10 mL) were charged and heated at 80 °C for 6 h. After completion of the reaction solvent was evaoprated under reduced pressure. The obtained crude solid was filtered and recrystallized from ethanol to furnish the desired indole-3-carboxyhydrazides **30a** in good to excellent yields. Similarly, indole-3-carboxy-hydrazides **30b-d** were prepared.[53-55]

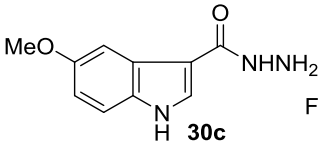
Synthesized indole-3-carboxyhydrazides 30a-d



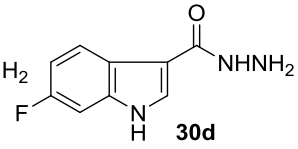
mp 232-234 °C
(lit[53] 230-232 °C)



mp 255-257 °C
(lit[54] 255-256 °C)

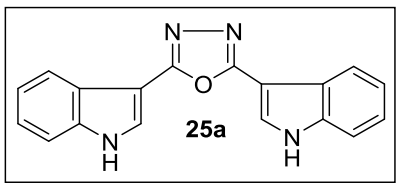


mp 177-179 °C
(lit[55] 178-179 °C)

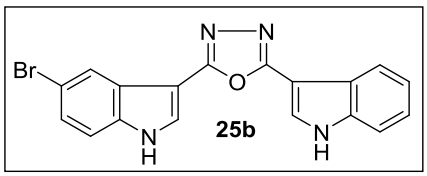


mp 202-204°C

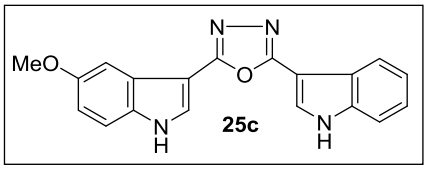
(f) Synthesis of bis(indolyl)-1,3,4-oxadiazoles 25a-m: To a stirred solution of bis(indolyl)-hydrazide-hydrazones **31** (1 mmol) in acetonitrile (5 mL), iodobenzene diacetate (1 mmol) was added and stirred for 30 min at 25 °C temperature. After completion of the reaction, the product was filtered and the crude solid so obtained was washed with hexane and saturated sodium bicarbonate solution (20 mL) to get pure bis(indolyl)-1,3,4-oxadiazoles **25a-m**.



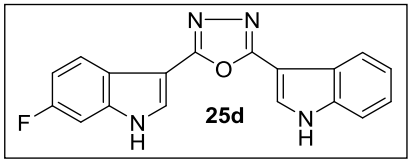
2,5-Bis(3′-indolyl)-1,3,4-oxadiazole (25a): Pale-white solid, 100 mg, Yield 84%, mp 248-250 °C, IR (KBr, υ cm^{-1}) 3400, 1600, 1270. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.66 (s, 2H), 8.29-8.21 (m, 2H), 8.03-7.81 (m, 2H), 7.54-7.52 (m, 2H), 7.28-7.26 (m, 4H). MS (ESI) *m/z* calcd for $C_{18}H_{13}N_4O$ $[M+H]^+$ 301.1, found 301.1.



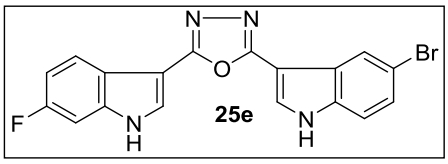
2-[3′-(5′-Bromoindolyl)]-5-(3′-indolyl)-1,3,4-oxadiazole (**25b**): Off-white solid, 95 mg, Yield 79%, mp > 280 °C, IR (KBr, υ cm^{-1}) 3400, 1600, 1172. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.99 (s, 1H), 11.81 (s, 1H), 8.40 (s, 1H), 8.25 (d, *J* = 4.8 Hz, 1H), 8.10-8.04 (m, 2H), 7.54-7.47 (m, 2H), 7.37 (d, *J* = 8.4Hz, 1H), 7.29-7.24 (m, 2H). MS (ESI) *m/z* calcd for $C_{18}H_{12}BrN_4O$ $[M+H]^+$ 379.0, found 379.0.



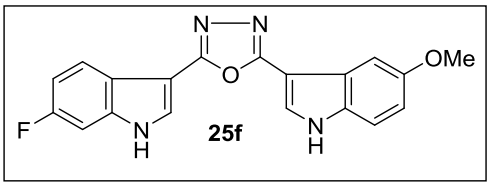
2-[3′-(5′-Methoxyindolyl)-5-(3′-indolyl)-1,3,4-oxadiazole - (**25c**): Brown solid, 100 mg, Yield 81%, mp 155-157 °C, IR (KBr, υ cm^{-1}) 3250, 1580, 1219. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.72 (s, 1H), 11.61 (s, 1H), 8.27 (d, *J* = 7.0 Hz, 1H), 8.04-7.94 (m, 2H), 7.75 (s, 1H), 7.53 (d, *J* = 8.0 Hz, 1H), 7.42 (d, *J* = 8.0 Hz, 1H), 7.27-7.25 (m, 2H), 6.90 (d, *J* = 8.8 Hz, 1H), 3.92 (s, 3H). MS (ESI) *m/z* calcd for $C_{19}H_{15}N_4O_2$ $[M+H]^+$ 331.1, found 331.0.



2-[3′-(6′-Fluoroindolyl)]-5-(3′-indolyl)-1,3,4-oxadiazole (**25d)** Off-white solid, 90 mg, Yield 75%, mp: 238-240 °C. IR (KBr, υ cm^{-1}) 3300, 1600, 1180. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.82 (s, 1H), 11.78 (s, 1H), 8.25-8.19 (m, 2H), 8.06-8.05 (m, 2H), 7.54-7.52 (m, 1H), 7.27-7.23 (m, 3H), 7.06-7.01 (m, 1H). MS (ESI) *m/z* calcd for $C_{18}H_{12}FN_4O$ $[M+H]^+$ 319.1, found 319.1.

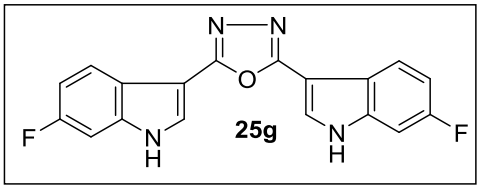


2-[3′-(5′-Fluoroindolyl)]-5-[3′-(6′-bromoindolyl)]-1,3,4-oxadiazole (**25e**) Off-white solid, 105 mg, Yield 70%, mp > 280 °C, IR (KBr, υ cm^{-1}) 3460, 1600, 1236. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.06 (s, 2H), 8.35 (s, 1H), 8.19-8.14 (m, 3H), 7.51 (d, *J* = 8.6 Hz, 1H), 7.30-7.25 (m, 2H), 7.08-6.95 (m, 1H). MS (ESI) *m/z* calcd for $C_{18}H_{11}BrFN_4O$ $[M+H]^+$ 397.0, found 397.0.

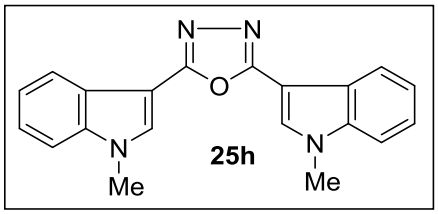


2-[3′-(6′-Fluoroindolyl)]-5-3′-(5′-methoxyindolyl)-1,3,4-oxadiazole (**25f**) Off-white solid, 98 mg, Yield 76%, mp 276-279 °C, IR (KBr, υ cm^{-1}) 3327, 3188, 1600, 1209, ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.91(s, 1H), 11.76 (s,

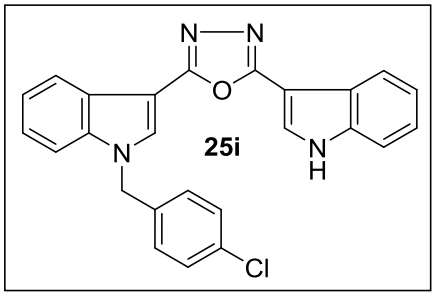
1H), 8.17 (m, 3H), 7.70 (d, *J* = 8Hz, 1H), 7.43 (d, *J* = 8.2 Hz, 1H), 7.28 (dd, 1H), 7.08-7.06 (m, 1H), 6.90-6.88 (m, 1H), 3.90 (s, 3H). MS (ESI) *m/z* calcd for $C_{19}H_{14}FN_4O_2$ $[M+H]^+$ 349.1, found 349.1.



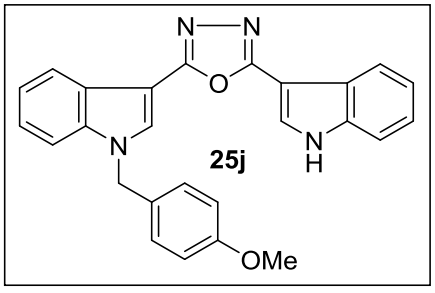
2,5-Bis(6′-fluoro-1*H*-indol-3-yl)-1,3,4-oxadiazole (**25g**). Off-white solid, 100 mg, Yield 75%, mp > 280 °C, IR (KBr, υ cm^{-1}) 3225, 1600, 1180. ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.03 (s, 2H), 8.25-8.16 (m, 4H), 7.32 (dd, *J* = 9.6, 2.0 Hz, 2H), 7.13-7.08 (m, 2H). MS (ESI) *m/z* calcd for $C_{18}H_{11}F_2N_4O$ $[M+H]^+$ 337.1, found 337.1.



2,5-Bis-[3′-(*N*-methylindolyl)]-1,3,4-oxadizole(25h). White solid, 110 mg, Yield 79%, mp 239-241 °C, IR (KBr, υ cm^{-1}) 1595, 1155. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.26 (d, *J*=7.3 Hz, 2H), 8.07 (s, 2H), 7.51 (d, *J* = 7.8 Hz, 2H), 7.36-7.28 (m, 4H), 3.96 (s, 6H). ^{13}C NMR (100 MHz, DMSO-d_6): 159.41, 136.89, 130.84, 124.51,122.65, 121.11, 120.57, 110.31, 99.05, 33.00. MS (ESI) *m/z* calcd for $C_{20}H_{16}N_4O$ $[M+H]^+$ 329.1, found 329.1.

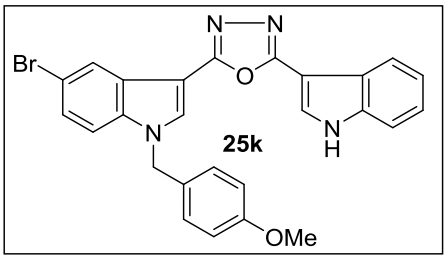


2-[3′-(1′-(*p*-Chlorobenzyl))-indolyl]-5-(3′-indolyl)-1,3,4-oxadiazole (**25i**) Off-white solid, 100 mg, Yield 80%, mp > 280 °C, IR (KBr, υ cm^{-1}) 3223, 1622, 1250. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.69 (s, 1H), 8.33-8.26 (m, 2H), 8.14 (s, 1H), 8.03-7.97 (m, 1H), 7.55-7.52 (m, 1H), 7.44-7.42 (m, 1H), 7.33-7.22 (m, 8H), 5.51 (s, 2H). MS (ESI) *m/z* calcd for $C_{25}H_{18}ClN_4O$ $[M+H]^+$425.1, found 425.0 .

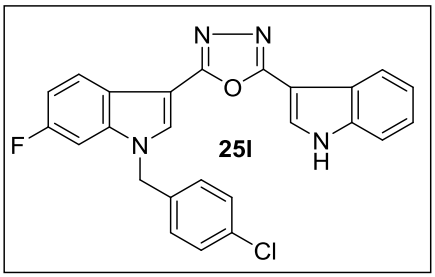


2-[3′-(*N*-*p*-Methoxybenzyl)-indolyl)]-5-(3′-indolyl)-1,3,4-oxadiazole (**25j**) Reddish brown solid, 102 mg, Yield 78%, mp 210-212 °C, IR (KBr, υ cm^{-1}) 3223, 1610, 1250. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.88 (s, 1H), 8.28-8.22 (m, 3H), 8.13-8.11 (m, 1H), 7.57-7.52 (m, 2H), 7.30-7.24 (m, 6H), 6.87 (d, *J* = 8.7 Hz, 2H), 5.48 (s, 2H), 3.74 (s, 3H). MS (ESI) *m/z*

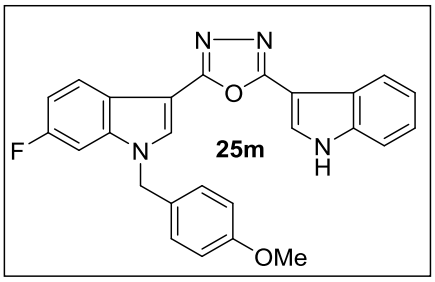
calcd for $C_{26}H_{21}N_4O_2$ $[M+H]^+$421.2, found 421.2.



2-[3′-(*N*-*p*-Chlorobenzyl)-5′-bromoindolyl)]-5-(3′-indol-yl)-1,3,4-oxadiazole (**25k**) Off-white solid, 95 mg, Yield 80%, mp > 280 °C, IR (KBr, υ cm^{-1}) 3208, 1600, 1182. ^{1}H NMR (400 MHz, DMSO-d_6) 11.80 (s, 1H), 8.44 (d, *J* = 1.7 Hz, 1H), 8.29 (s, 1H), 8.26-8.22 (m, 1H), 8.06 (d, *J* = 2.8 Hz, 1H), 8.03 (s, 1H), 7.55-7.52 (m, 1H), 7.44 (d, *J* = 8.7 Hz, 1H), 7.39-7.31 (m, 3H), 7.28-7.25 (m, 3H), 5.55 (s, 2H), 3.76 (s, 3H). MS (ESI) *m/z* calcd for $C_{26}H_{20}BrN_4O_2$ $[M+H]^+$ 499.1, found 499.1.



2-[3′-(N-*p*-Chlorobenzyl)-6′-fluoroindolyl)]-5-(3′-indol-yl)-1,3,4-oxadiazole (**25l**). Off-white solid, 100 mg, Yield 81%, mp 264-266 °C, IR (KBr, υ cm^{-1}) 3319, 1600, 1176. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.83 (s, 1H), 8.28-8.22 (m, 3H), 8.07 (d, *J* = 10.1 Hz, 1H), 7.54 (d, *J* = 8.4 Hz, 1H), 7.35-7.22 (m, 7H), 7.09 (t, *J* = 8.2 Hz, 1H), 5.52 (s, 2H). MS (ESI) *m/z* calcd for $C_{25}H_{17}ClFN_4O$ $[M+H]^+$ 443.1, found: 443.1.



2-[3′-(N-*p*-Methoxybenzyl)-6′-fluoroindolyl)]-5-(3′-indolyl)-1,3,4-oxadiazole (**25m**). Off-white solid, 95 mg, Yield 82%, mp 220-222 °C, IR (KBr, υ cm^{-1}) 3225, 1600, 1250. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.81 (s, 1H), 8.24-8.19 (m, 3H), 8.09-8.03 (m, 1H), 7.54-7.52 (m, 1H), 7.33-7.25 (m, 5H), 7.07 (t, *J* = 8.3 Hz, 1H), 6.88 (d, *J* = 8.4 Hz, 2H), 5.42 (s, 2H), 3.76 (s, 3H). MS (ESI) *m/z* calcd for $C_{26}H_{20}FN_4O_2$ $[M+H]^+$ 439.1, found: 439.1.

2.8 Biological Assays

2.8.1 MTT Assay: Six human cancer cell lines: pancreas (AsPC1), prostate (DU145 and PC3), cervical (HeLa), breast (MDA-MB231) and ovarian (OVCAR) were cultured in RPMI-1640 media supplemented with 10% heat inactivated fetal bovine serum and 1%

penicillin/streptomycin. They were seeded in 96-well plates at a density of 4 x 10^3 cells per well for 12 h. Cells were incubated with various concentrations of the compounds ranging from 10 nM–1 mM. After 48 h, MTT (3-(4,5-dimethyldiazol-2-yl)-2,5-diphenyltetra-zoliumbromide) was added to the final concentration of 0.2 mg/mL and incubated for 30 min. The cells were washed twice with PBS and lysed in 100 μL dimethylsulfoxide, and the absorbance was measured at 570 nm using Tecan Spectrafluor Plus.

2.8.2 Nuclear Staining Using Propidium Iodide

MDA-MB-231 cells plated on coverslips were treated either with 0.01% DMSO (control), or 10 μM 25c, 25g and 25h. After the treatment, cells were fixed with cold methanol for 5 min, followed by rehydration in PBS and and permeabilization using 0.1% Triton X-100 in PBS plus 2% BSA. Cells were treated with 0.1 μg/ml RNase A in PBS for 1 h, rinsed, and stained with 2.5 μg/ml propidium iodide in PBS for 1 h. Before mounting with Mowiol, coverslips were washed twice with PBS and once with H_2O.

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Chapter III

Formation of C-S and C-C bonds

Part A: Metal-free synthesis of diaryl sulfones

Part B: Ligand and base-free access to biaryls

3.1 Part A: Diaryl sulfones

3.1.1 Introduction

Aryl sulfones are an important class of compounds which are widely utilized in industry and many organic transformations.[1-5] Especially, diaryl sulfones are employed in the biological field as antibacterial **1-2**[6], antimicrobial[7], antitumor **3**[8], 11β HSDI inhibitor **4**[9], selective 5-HT_{2A} inhibitor **5**[10]**,** antifungal **6**[11], antimigraine **7**[12], agrochemical **8**[13, 14] and polymer product **9**[15] (Figure 3.1.1).

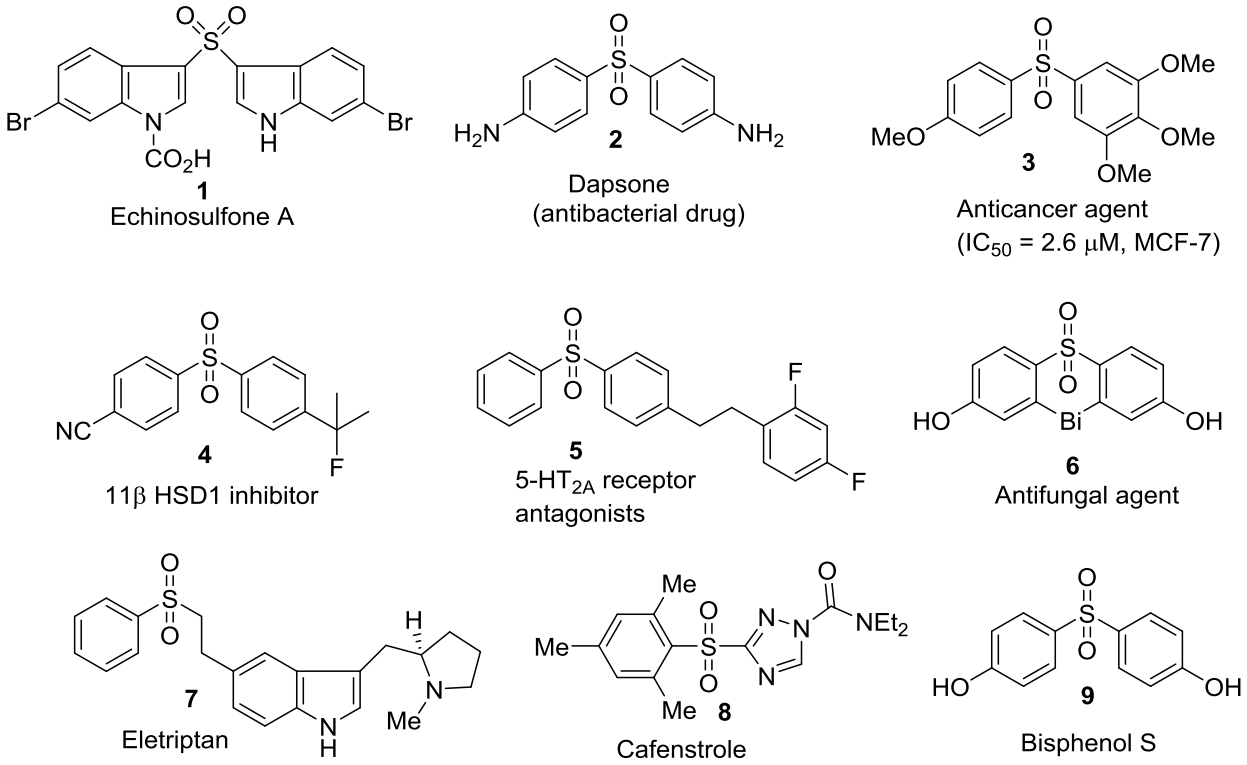


Figure 3.1.1 Examples of bio-active molecules containing aryl sulfone moiety

Moreover, they are useful intermediates for the preparation of various fine chemicals and biologically active molecules. Because of their emerging biological and synthetic applications, constructions of diaryl sulfones have attracted much attention and a number of strategies have been developed. According to classical methods, sulfones are prepared by the oxidation of sulfides and sulfoxides,[16] Friedel-Crafts electrophilic aromatic substitution of arenes with either arenesulphonic acids or corresponding halides in the presence of strong acids.[17] Afterwards,

organometallic approach was discovered, where the coupling between organaomagnesium halides or organolithium compounds with sulphonate esters were utilized to synthesize sulfone derivatives.[16, 18] In recent years, palladium and copper chemistry have overtaken the traditional approaches because they required less-functionalized starting materials and obviating moisture – sensitive reagents.[19-21] Recently, diarylsulfones were prepared by the oxidative coupling of arylboronic acid and arylsulfonyl chlorides using metal-catalysts.[22, 23] Very recently, C-H functionalization strategy has been developed to achieve diaryl sulfones from unactivated

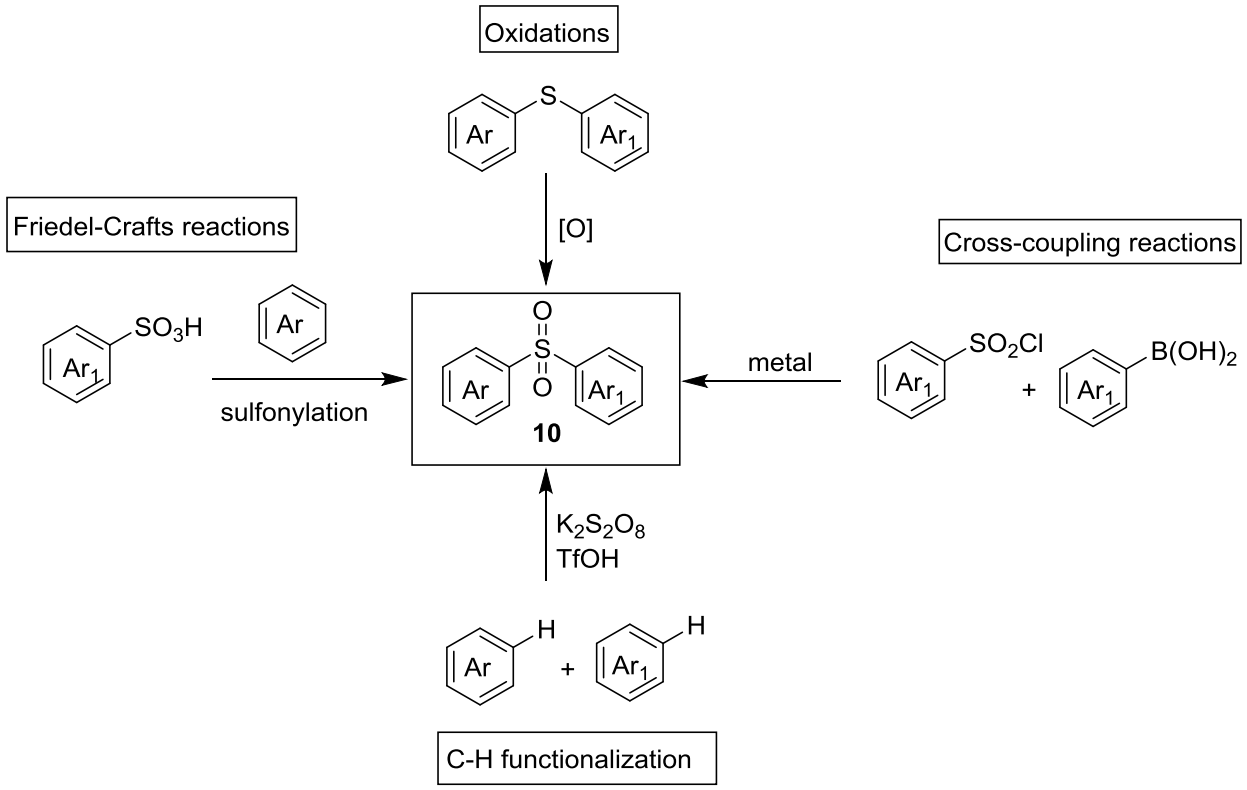


Figure 3.1.2 Existing methods to construct diaryl sulfones

arenes in the presence of oxidants and strong acids.[24] Moreover, the synthesis of diaryl sulfones from diaryliodonium salts and sulfinate salt was reported by utilizing expensive palladium catalyst.[25] The disadvantages found in using metal catalysts are longer reaction time, expensive and moisture-sensitive reactants. To overcome these drawbacks and to study the chemistry of diverse diaryliodonium salts, we developed a new greener synthetic protocol to achieve diaryl sulfones by using cheaper, easily available and eco-friendly solvent polyethylene glycol (PEG-400) under microwave irradiation.[26] Microwave (MW) reactions are popular in recent decades,

due to their advantages such as efficient heating, less energy consumption compared to conventional heating, reduced reaction time, and also termed to be a greener approach in synthetic chemistry.[27] Microwave irradiation has also been widely used in organic synthesis for the formation of a variety of carbon–carbon and carbon–heteroatom bonds.[28-30]

3.1.2 Significance of diaryliodonium salts

Diaryliodonium salts have proved to be versatile electrophiles in organic synthesis, they are stable and easy to handle.[31] In recent years, diaryliodonium salts have been used extensively in the arylation of various nucleophiles involving oxygen,[32] sulfur,[33] nitrogen,[34] fluorine[35], arenes[36] and other heterocycles.[37] Very recently, Yu and co-workers reported the metal-free arylation of various nitrogen heterocycles using diaryliodonium salts.[38] Gaunt et al. reported the copper-catalyzed alkene arylation using diaryliodonium salts,[39] whereas Rodriguez and co-workers reported the metal-free C–H direct arylation of unbiased arenes.[40] Varma and co-workers achieved the Heck type arylation of alkenes using diaryliodonium salts.[41] To develop new Src kinase inhibitors, kumar et al. disclosed a facile one-pot synthesis of 1,2,3-triazoles utilizing diaryliodonium salts, sodium azide, and terminal acetylenes.[42] In recent years, there has been surge of interest in the chemistry of diaryliodonium salts and metal-free arylation reactions. In continuation of our ongoing research efforts directed towards the synthetic utilities of organoiodine reagents, we have developed an efficient, rapid, high-yielding, and metal-free protocol for the preparation of various diaryl sulfones.

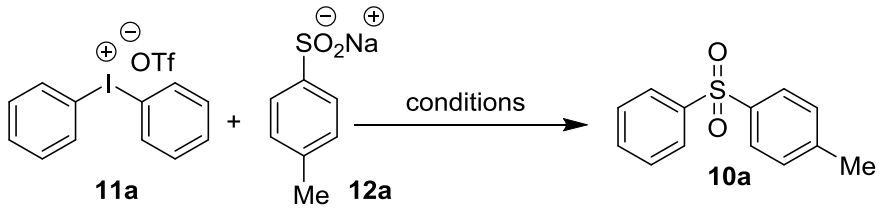
3.1.3 Results and Discussion

3.1.3.1 Chemistry

To begin our investigation, we carried out the model reaction between diphenyliodonium triflate (**11a**) and sodium *p*-toluenesulfinate salt (**12a**) under various conditions. The reaction of diphenyliodonium triflate (**11a**) with sodium *p*-toluenesulfinate (**12a**) at room temperature in PEG-400 did not proceed even after stirring for 24 h. Next, we investigated this coupling reaction under microwave irradiation and found that the formation of phenyltolyl sulfone **10a** was excellent in PEG-400 (Table 3.1.1, entry 4). Reaction solvents such as ethanol, dimethylformamide, and acetonitrile afforded the desired product in poor yields (20–37%). Attempts to conduct the coupling reaction in water and tetrahydrofuran failed to afford any product probably due to the poor solubility of the reactants. Among the diaryliodonium salts

having different counteranions (OTf, OTs, and Br) we found that diaryliodonium triflate is the best to obtain diaryl sulfones in excellent yields.

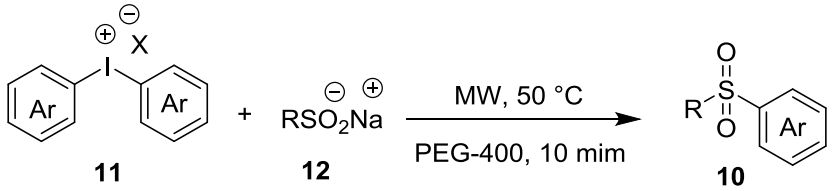
Table 3.1.1 Optimization of reaction conditions[a]



Entry	Solvent	Time (min)	Yields (%)[b]
1	MeCN	30	20
2	DMF	30	10
3	Ethanol	30	37
4	**PEG-400**	**10**	**97**
5	THF	30	NR
6	Water	30	NR
7	___	30	NR

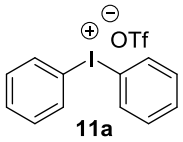
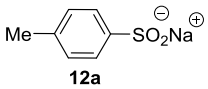
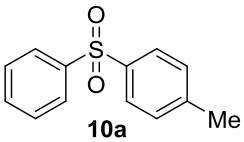
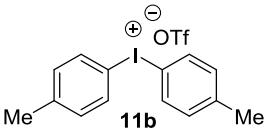
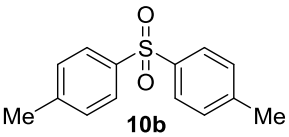
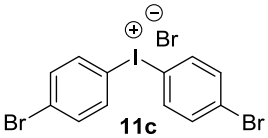
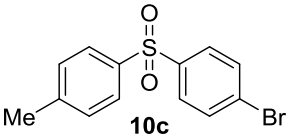
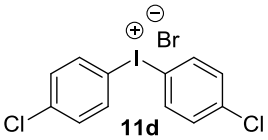
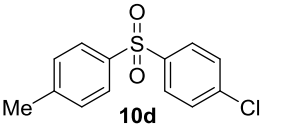
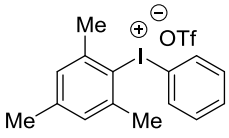
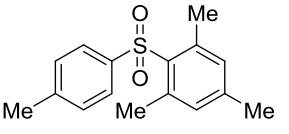
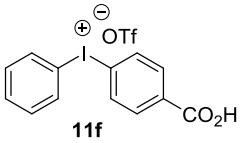
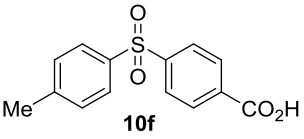
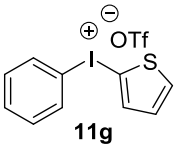
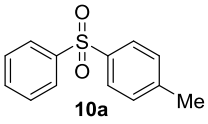
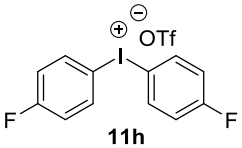
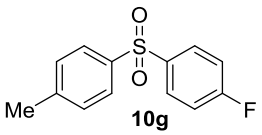
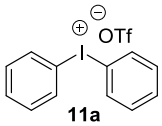
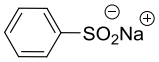
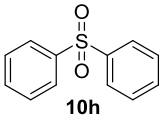
[a]MW irradiation at 50 °C, [b]Isolated yields, NR = no reaction

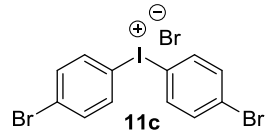
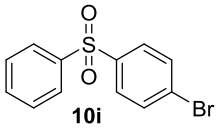
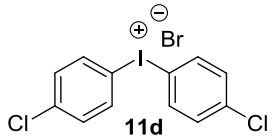
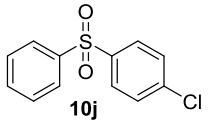
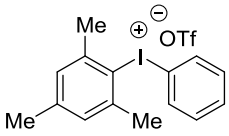
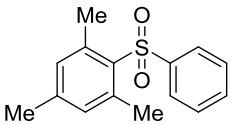
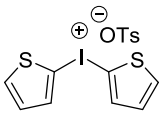
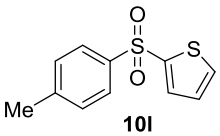
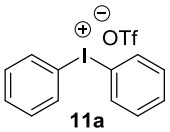
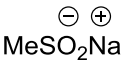
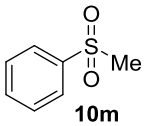
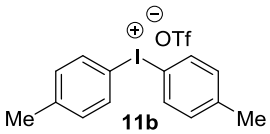
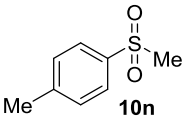
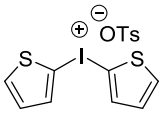
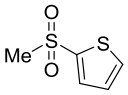
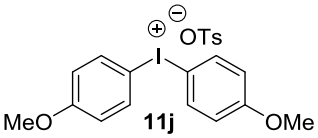
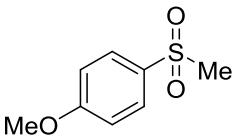
The optimized conditions were applied to other symmetrical and unsymmetrical diaryliodonium salts and sulfinate salts, and the results are summarized in Table 3.1.2. Identified reaction conditions were well tolerated by various diaryliodonium salts containing electron-withdrawing (bromo, chloro, fluoro & carboxylic acid), electron-donating (methyl), heterocyclic arene (thienyl) and bulkier (mesityl) substituents diaryliodonium salts **11** afforded the desired diarylsulfones **10a-p** in excellent yields (82-96%). The arenesulfinate salts **12a-b** were found to



Scheme 3.1.1 Synthesis of diaryl sulfones **10** from diaryliodonium salts **11**and sulfinate salts **12**

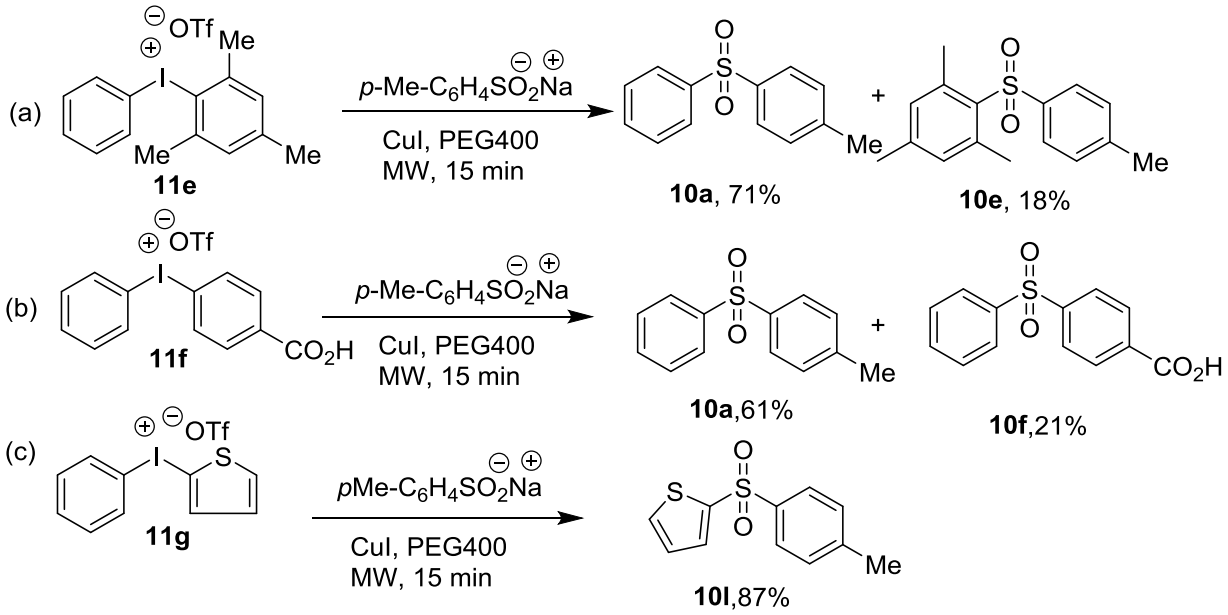
Table 3.1.2 Synthesized diaryl sulfones **10a-p**[a]

Diaryliodonium salts	Sulfinate salts	Diaryl sulfones	Yield (%)	Mp (°C)
 **11a**	 **12a**	 **10a**	96	119-121 (lit[23] 119-122)
 **11b**	**12a**	 **10b**	92	157-159 (lit[21] 158-159)
 **11c**	**12a**	 **10c**	82	131-133 (lit[21] 132-134)
 **11d**	**12a**	 **10d**	83	116-118 (lit[21] 119-120)
 **11e**	**12a**	 **10e**	89	116-117 (lit[43] 115-117)
 **11f**	**12a**	 **10f**	91	120-121
 **11g**	**12a**	 **10a**	86	119-121 (lit[23] 119-122)
 **11h**	**12a**	 **10g**	88	85-87 (lit[21] 85-86)
 **11a**	 **12b**	 **10h**	94	128-130 (lit[23] 127-129)

 **11c**	**12b**	 **10i**	86	91-92 (lit[44] 92-94)
 **11d**	**12b**	 **10j**	82	77-79 (lit[44] 77-78)
 **11e**	**12b**	 **10k**	91	79-80 (lit[44] 79-81)
 **11i**	**12a**	 **10l**	82	116-118 (lit[23] 118-120)
 **11a**	 **12c**	 **10m**	83	145-146 (lit[22] 144-145)
 **11b**	**12c**	 **10n**	83	84–86 (lit[19] 85–87)
 **11i**	**12c**	 **10o**	73	47-48 (lit[19] 45-47)
 **11j**	**12c**	 **10p**	84	119–120 (lit [19]118–120)

[a]Reaction conditions: 50 °C, MW, (**10a–l**: 10 min; **10m–p**: 30 min).

be relatively more reactive (10 min) than the corresponding sodium methanesulfinate **12c** (30 min). After preparing various diaryl sulfones in excellent yields, we explored the coupling reaction of diaryliodonium salts **11e–g** and sodium *p*-toluenesulfinate (**12a**) in the presence of a catalytic amount of CuI (Scheme 3.1.2). Interestingly, in the case of **11e** diaryl sulfone **10a** in

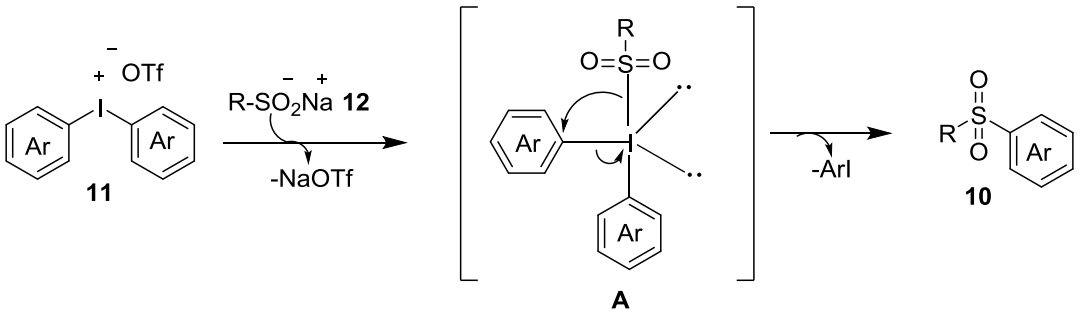


Scheme 3.1.2 Copper iodide-catalyzed formation of diaryl sulfones **10**

71% yield as a major product along with a small amount of diaryl sulfone **10e** (18% yield) in contrast, **10a** was the exclusive product of the coupling reaction in the absence of CuI. When unsymmetrical diaryliodonium salt **11f** was treated with sodium p-toluenesulfinate (**12a**) under the similar reaction conditions, diaryl sulfone **10a** was obtained as a major product (61% yield) along with a minor amount of **10f** (21%); whereas **10f** was exclusively formed under copper-free conditions. Further, coupling of heteroaryl iodonium salt **10g** in the presence of CuI gave exclusively thienyl tolyl sulfone **10l** in 81% yield, whereas the corresponding copper-free coupling reaction delivers diaryl sulfone **10a** in 86% yield. This different selectivity of unsymmetrical diaryliodonium salt with and without CuI as a catalyst could be utilized to prepare diversely substituted diaryl sulfones.

3.1.3.2 Plausible Mechanism

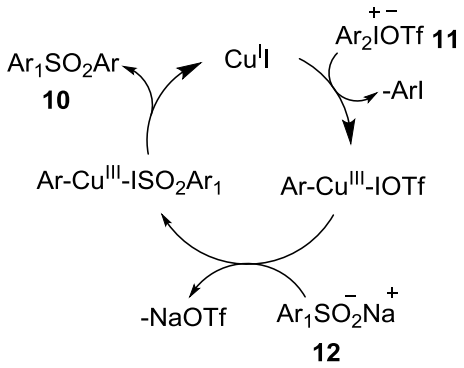
A possible mechanistic pathway for the coupling of diaryliodonium salts **11** and arene/alkyl sulfinates **12** is depicted in Scheme 3.1.3. Initially, nucleophilic sulfinate species attack the electron- deficient iodine centre forms a tricoordinated intermediate **A** which likely underwent reductive elimination with the release of desired diaryl sulfones **10** and iodobenzene.[32]



Scheme 3.1.3 Plausible mechanism for the formation of diaryl sulfones

3.1.3.3 Plausible mechanism for the Cu(I)-catalyzed formation of diaryl sulfones

The difference in reactivity in the presence of copper could be rationalized *via* the initial oxidative insertion of copper(I) to the diaryliodonium salt **11** to form an organo Cu(III)–aryl species I (stabilized by electron-rich aryl moiety) by the loss of an aryl iodide with a relatively electron-deficient aryl ring. The highly electrophilic species I is then attacked by sodium arenesulfinate **12** to generate the aryl–Cu(III)–arenesulfinate species II, which upon reductive elimination results in diaryl sulfone **10** (Scheme 3.1.4). Generally, the most electron-rich aryl moiety was transferred to arenesulfinates when unsymmetrical diaryliodonium salts were employed.[39] However, the exact mechanism for the formation of diaryl sulfones remains unclear at this stage.



Scheme 3.1.4 Plausible mechanism for the Cu-catalyzed formation of diaryl sulfones

The NMR (^{1}H & ^{13}C) copies of **10f** are shown in Figures 3.1.3 and 3.1.4

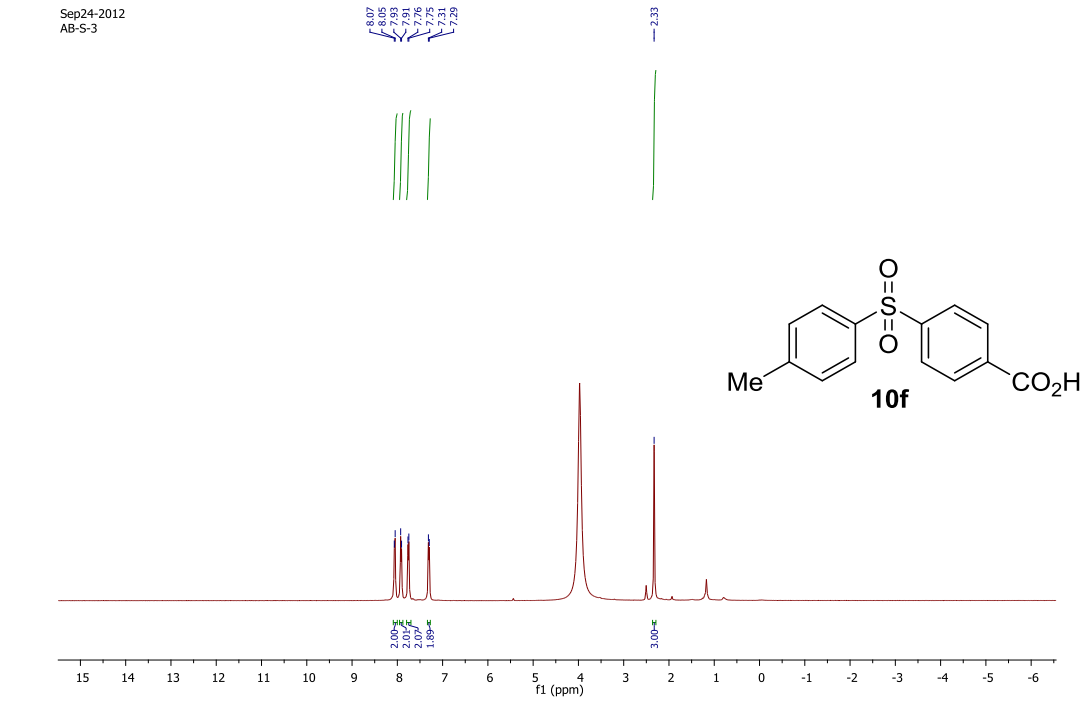


Figure 3.1.3 ^{1}H NMR spectrum of *p*-tolylsulfonyl benzoic acid **10f**

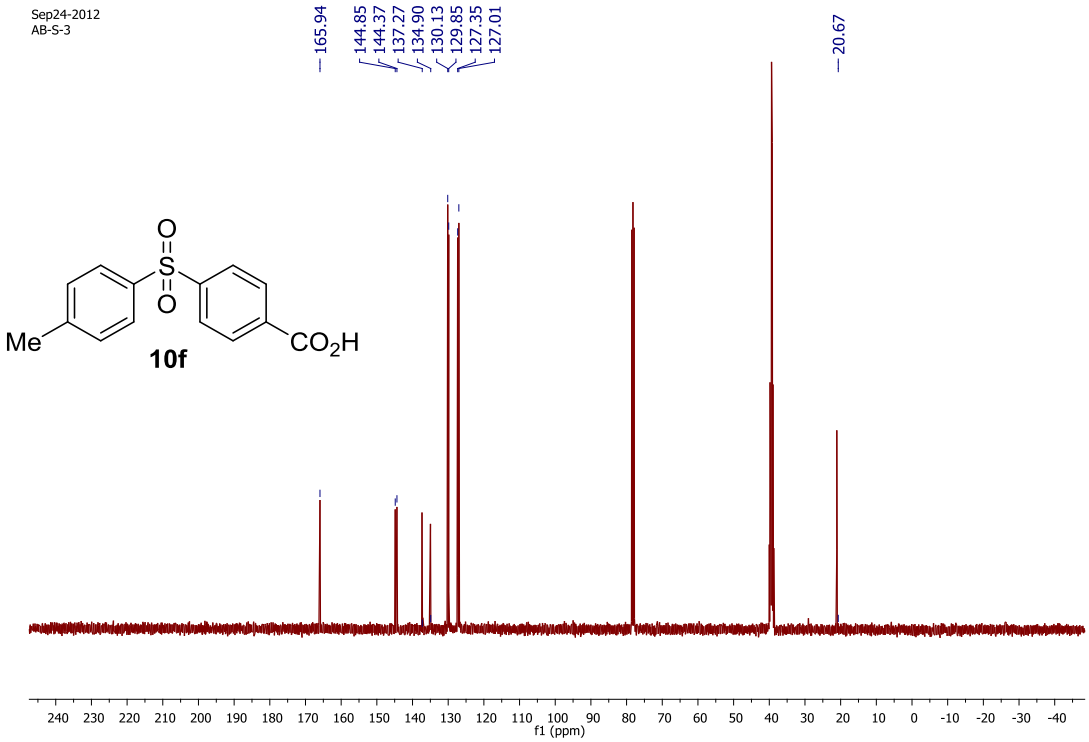


Figure 3.1.4 ^{13}C NMR spectrum of *p*-tolylsulfonyl benzoic acid **10f**

3.1.4 Conclusions

We have developed a novel and metal-free synthetic method to prepare various diaryl sulfones in high yields from readily available diaryliodonium salts and arenesulfinates using the green solvent PEG-400 in a short reaction time. The copper iodide catalyzed coupling of diaryliodonium salts and arenesulfinate salts resulted in different selectivity to afford diverse diaryl sulfones.

3.1.5 Experimental Details

3.1.5.1 General Information: All the laboratory reagents were obtained commercially. The reactions were monitored by thin layer chromatography and performed on Merck pre-coated plates (silica gel 60 F_{254}, 0.2mm). Column chromatography was performed using 100-200 mesh silica gel and ethyl acetate/hexane mixture used for elution. Melting points were determined by E-Z melting point apparatus. NMR spectra were recorded in (DMSO-d_6) Bruker Advance II (400 MHz) spectrometer using TMS as internal standard. The coupling constant (*J*) are in Hz. Mass spectra were recorded using 'Hewlett-Packard' HP GS⁄MS 5890⁄5972.

3.1.5.2 General Experimental Procedures

(a) Diaryliodonium triflates 11

To a stirred solution of iodoarene (0.5 g, 2.5 mmol) in dichloromethane (8 mL) was added *m*-chloroperbenzoic acid (0.455 g, 2.6 mmol) and followed by arene (0.22 mL, 2.5 mmol) at room temperature. Reaction contents were cooled to 0 °C and then trifluoromethanesulfonic acid (0.23 mL, 2.6 mmol) was added dropwise while maintaining the same temperature. The mixture was allowed to stir at room temperature for additional 30 min. The solvent was evaporated under vaccum and diethyl ether (3 mL) was added to the residue under cooling (0°C) conditions. The solid so obtained was washed twice with diethyl ether and dried to afford diaryliodonium triflates **11** as white solids in 50-88% yields.[98]

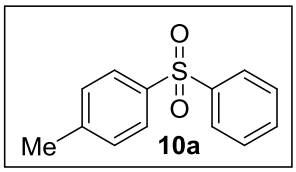
(b) Diaryl sulfones

To a mixture of diaryliodonium salt (0.2 mmol) and arenesulfinate salt (0.2 mmol) in PEG-400 (0.1 mL) was placed in a sealed microwave vial and irradiated in MW (power 200 W) at 50 °C

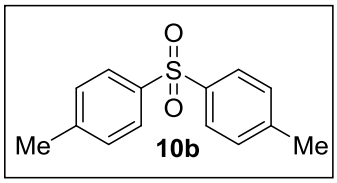
for 10 min. After completion, water (1 mL) was added and the reaction mixture was extracted with EtOAc (3 × 5 mL). The combined organic extract was washed with water (4 mL) and dried over anhydrous sodium sulfate. The solvents were evaporated *in vacuo*, the solid thus obtained was washed with hexane to remove aryl iodide, filtered the desired diaryl sulfones **10**.

(c) Copper-catalyzed preparation of diaryl sulfones

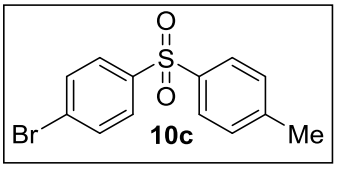
A mixture of diaryliodonium salts (0.2 mmol) and sodium *p*-toluenesulfinate (0.2 mmol) in PEG-400 (0.1 mL) were charged in sealed microwave vial. A catalytic amount of CuI (10 mol %) was added to the reaction mixture and the vial was irradiated in MW (power 200 W) at 50°C for 10 min. After completion of the reaction, 20% sodium carbonate solution (2 mL) was added. The aqueous layer was extracted with EtOAc (3 × 5 mL), washed with water (7 mL) and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure and the residue so obtained was purified by column chromatography over silica gel (100-120 mesh) using hexane-EtOAc (4:1) as eluent to afford the desired diaryl sulfones.



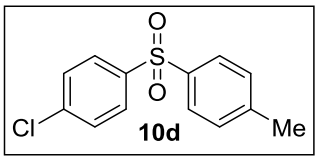
Phenyltolyl sulfone (10a): White solid, Yield 96%, mp 119-121°C (lit[23]119-122 °C), IR (KBr, υ cm^{-1}) 1303, 1149. ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.36 (s, 3H), 7.33 (d, 2H, *J* = 8.0 Hz), 7.58-7.50 (m, 3H), 7.77 (d, 2H, *J* = 8.1 Hz), 7.87 (d, 2H, *J* = 7.3 Hz). MS (ESI) *m/z* calcd for $C_{13}H_{13}O_2S$ $[M+H]^+$ 233.1, found 233.1.



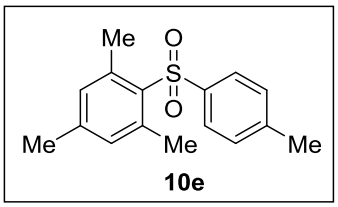
Bistolyl sulfone (10b): White solid, Yield 92%, mp 157-159 °C (lit[21] 158-159 °C). IR (KBr, υ cm^{-1}) 1288, 1149. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 2.35 (s, 6H,), 7.30 (d, 4H, *J* = 8 Hz), 7.73 (d, 4H, *J* = 7.73 Hz). MS (ESI) *m/z* calcd for $C_{14}H_{15}O_2S$ $[M+H]^+$ 247.1, found 247.1.



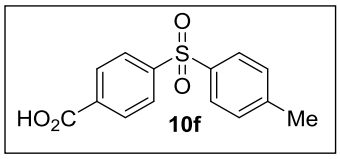
***p*-Bromophenyltolyl sulfone (10c):** White solid, Yield 82%, mp 131-133 °C (lit[21] 132-134 °C). IR (KBr, υ cm^{-1}) 1319, 1149. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.36 (s, 3H) 7.38 (d, 2H, *J* = 8.1 Hz), 7.62 (d, 2H, *J* = 8.6 Hz), 7.83-7.74 (m, 4H). MS (ESI) *m/z* calcd for $C_{13}H_{12}BrO_2S$ $[M+1]^+$ 311.0, found 311.0.



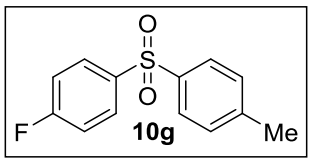
***p*-Chlorophenyltolyl sulfone (10d):** White solid, Yield 83%, mp 116-118 °C (lit[21]119-120 °C). IR (KBr, υ cm^{-1}) 1319, 1149 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ = 2.36 (s, 3H) 7.38 (d, 2H, *J* = 8.1 Hz), 7.62 (d, 2H, *J* = 8.6 Hz), 7.83-7.74 (m, 4H)MS (ESI) *m/z* calcd for $C_{13}H_{12}ClO_2S$ $[M+H]^+$ 267.0, found 267.1.



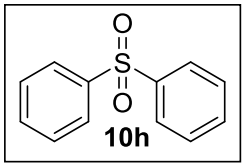
2,4,6-Trimethylphenyltolyl sulfone (10e): White solid, Yield 89% mp 116-117 °C (lit[42] 115-117 °C). ^1H NMR (400 MHz, DMSO-d_6) δ 2.32 (s, 3H), 2.36 (s, 3H), 2.56 (s, 6H), 7.10 (s, 2H), 7.33 (d, 2H, *J* = 8.0 Hz), 7.77 (d, 2H, *J* = 8.1 Hz), ^{13}C NMR (100 MHz, DMSO-d_6)143.18, 142.89, 139.90, 139.07, 133.60, 131.84, 129.25, 125.67, 22.18, 21.03, 20.42. MS (ESI) *m/z* calcd for $C_{16}H_{19}O_2S$ $[M+H]^+$ 275.1 found 275.1.



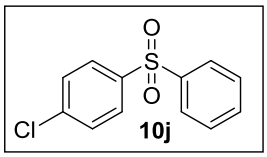
***p*-Tolylsulfonyl benzoic acid (10f):** White solid, Yield 91%, mp 119-121 °C. ^1H NMR (400 MHz, DMSO-d_6) δ 2.33 (s, 3H), 7.31 (d, 2H, *J* = 7.5 Hz), 7.76(d, 2H, *J* = 7.5 Hz), 7.93 (d, 2H, *J* = 7.9 Hz), 8.07 (d, 2H, *J* = 7.7 Hz). ^{13}C NMR (100 MHz, DMSO-d_6) δ 165.94, 144.85, 144.37, 137.27, 134.90, 130.13, 129.85, 127.35, 127.01, 20.67. MS (ESI) *m/z* calcd for $C_{14}H_{13}O_4S$ $[M+H]^+$ 277.0 found 277.0.



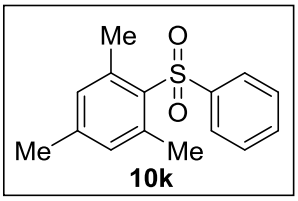
***p*-Fluorophenyltolyl sulfone (10g):** White solid, Yield 88%, mp 85- 87 °C (lit[21] 85-86 °C). ^1H NMR (400 MHz, DMSO-d_6) δ 2.36 (s, 3H), 7.47-7.45 (m, 4H,), 7.85 (d, 2H, *J* = 6.6 Hz), 8.05 (dd, 2H, *J* = 9.0, 5.1Hz). MS (ESI) *m/z* calcd for $C_{13}H_{12}FO_2S$ $[M+H]^+$ 251.0 found 251.0.



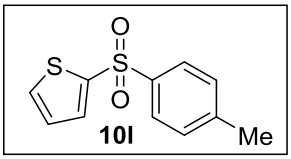
Diphenyl sulfone (10h): White solid, Yield 88%, mp 128-130 °C (lit[23] 127-129 °C). IR (KBr, υ cm^{-1}) 1303, 1149 cm^{-1}.^1H NMR (400 MHz, DMSO-d_6) δ 7.61-7.50 (m, 6H), 7.85 (d, 4H, *J* = 8.6 Hz). MS (ESI) *m/z* calcd for $C_{12}H_{11}O_2S$ $[M+H]^+$ 219.0 found 219.0.



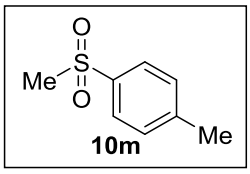
***p*-Chlorophenylphenyl sulfone (10j):** White solid, Yield 96%, mp 77-79 °C (lit[43] 77-78 °C). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.65 (d, 2H, J = 7.8 Hz). 7.71 (d, 3H, J = 8.6 Hz).) 7.98 (d, 4H, J = 8.2 Hz). MS (ESI) *m/z* calcd for $C_{12}H_{10}ClO_2S$ $[M+H]^+$ 253.0 found 253.0.



2,4,6-Trimethylphenylphenyl sulfone (10k): White solid, Yield 91%, mp 78-80 °C (lit[43] 79-81°C). ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.30 (s, 3H), 2.56 (s, 6H), 7.11 (s, 2H), 7.42 (t, 2H, J = 7.8 Hz), 7.53 (t, 1H, J = 7.4 Hz), 7.72 (d, 2H, J = 7.7 Hz). ^{13}C NMR (100 MHz, DMSO-d_6) 143.33, 141.25, 133.16, 131.58, 131.30, 129.72, 121.68, 113.42, 26.45, 20.21. MS (ESI) *m/z* calcd for $C_{15}H_{17}O_2S$ $[M+H]^+$ 261.1 found 261.1.



(2-Thienyl)tolyl sulfone (10l): White solid, Yield 82%, mp 116-118 °C (lit[23] 118-120°C). ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.34 (s, 3H), 7.29 (d, 2H, J = 8.0 Hz), 7.55-7.46 (m, 2H, J = 7.4 Hz), 7.74 (d, 2H, J = 8.0 Hz), 7.83 (d, 1H, J = 7.5 Hz). MS (ESI) *m/z* calcd for $C_{11}H_{11}O_2S_2$ $[M+H]^+$ 239.0 found 239.0.



Methyltolyl sulfone (10m): White solid, Yield 83%, mp 84-86 °C (lit[19] 85-87 °C). ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.12 (s, 3H), 7.63 (t, 2H, J = 8.17 Hz), 7.71 (t, 1H, J = 5.4 Hz), 7.94 (d, 2H, J = 7.2 Hz). MS (ESI) *m/z* calcd for $C_8H_{11}O_2S$ $[M+H]^+$ 171.0 found 171.0.

3.2 Part B: Synthesis of Biaryls

3.2.1 Introduction

Biaryls and heterobiaryls **1**-**9** are ubiquitous motifs present in natural products, medicinal agents, ligands and organic materials (Figure 3.2.1). Therefore, the construction of these scaffolds has been a topic of great significacne in chemistry. Most common approaches to prepare biaryls **20**

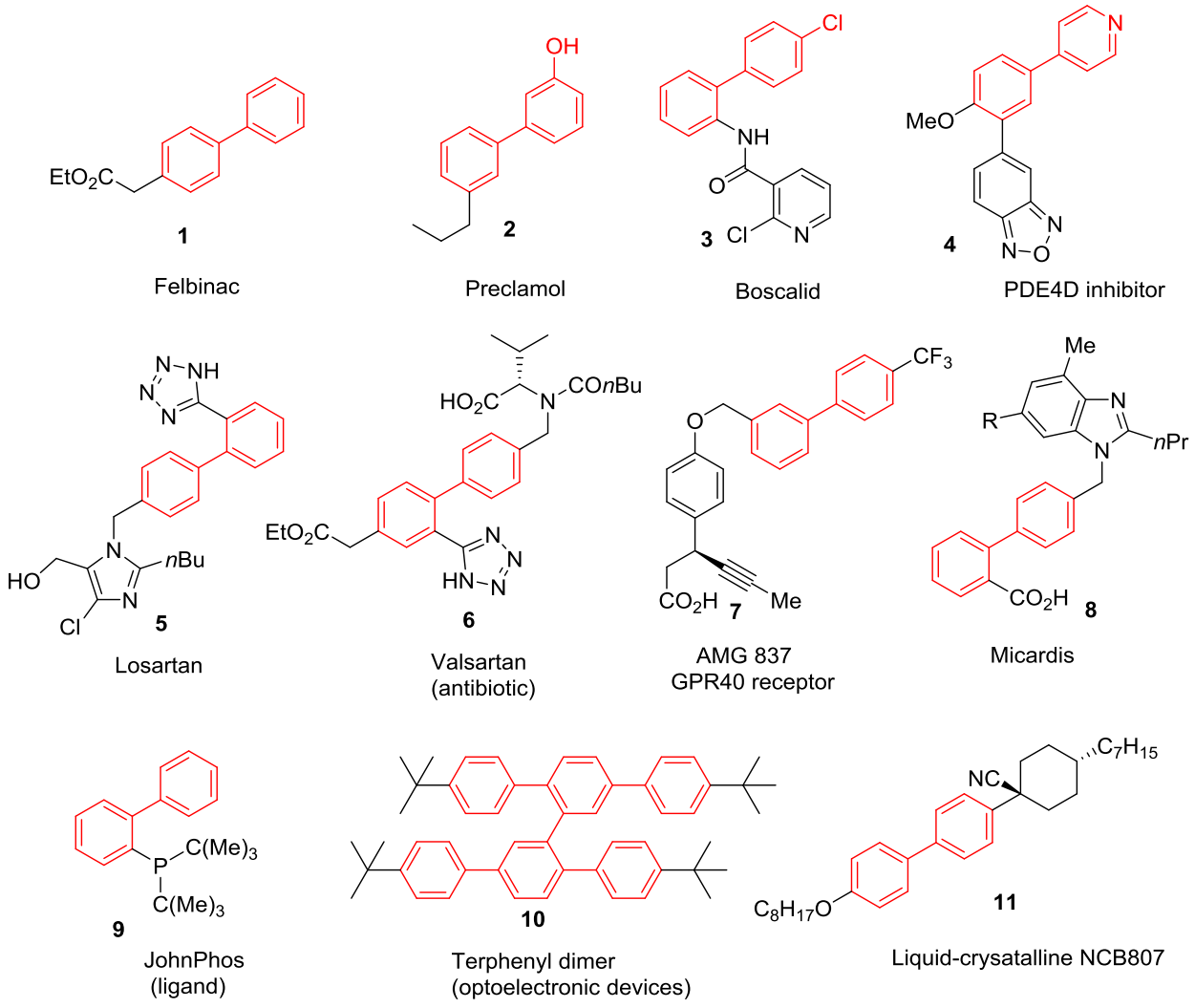
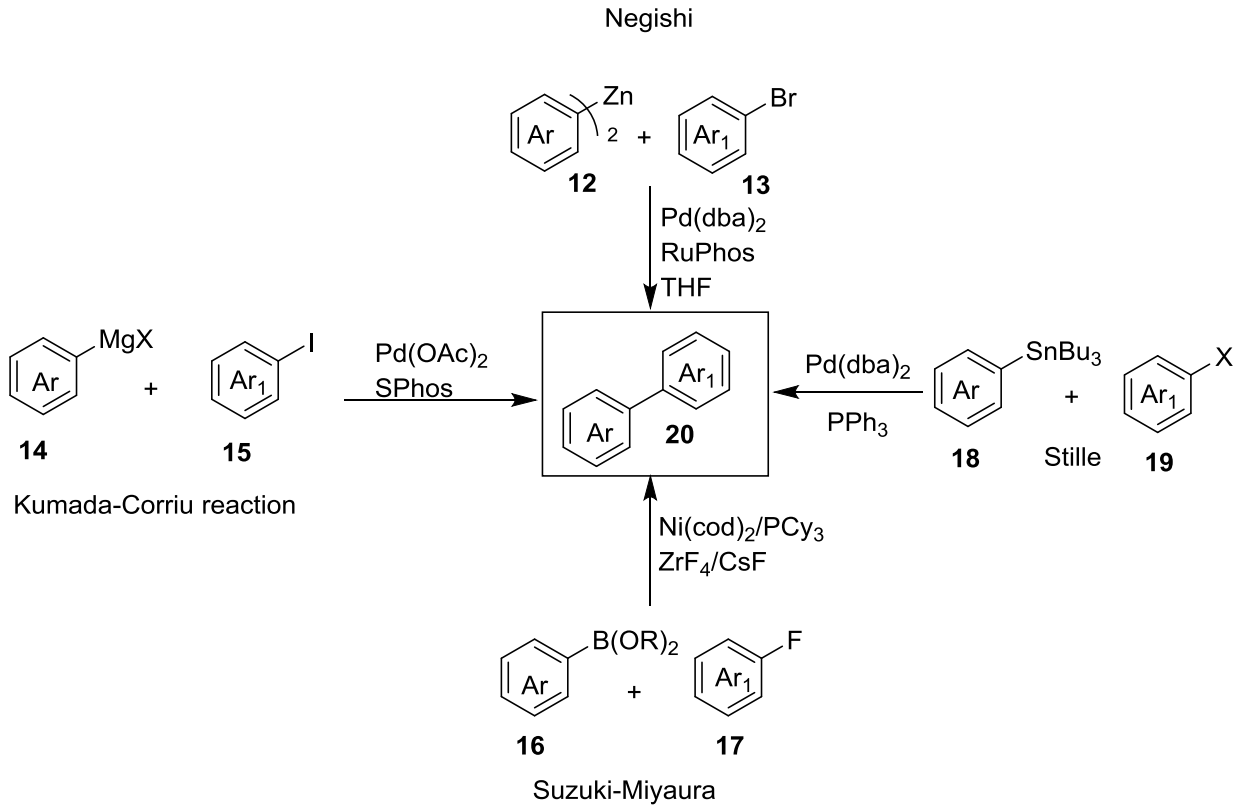


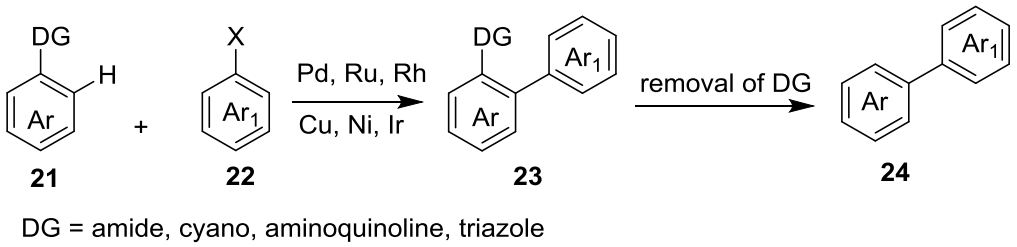
Figure 3.2.1 Some important molecules containing biaryl motif

are traditional cross-coupling (Scheme 3.2.1) reactions which involve the pre-activated precursors namely aryl pseudohalides and aryl metal reagents (e.g. Stille, Kumada, Suzuki and Negishi reactions).[45-48]



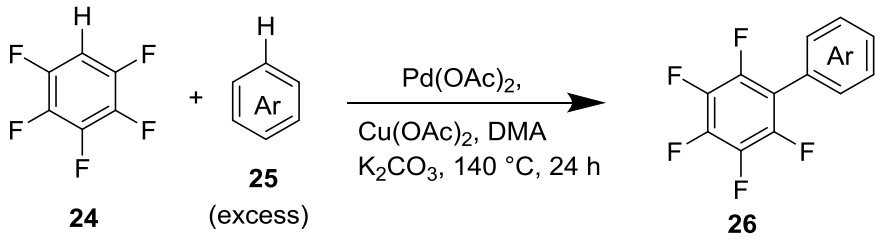
Scheme 3.2.1 Classical cross-coupling reactions to prepare biaryls

Kienle and Knochel demonstrated the Negishi reaction between organozinc reagents **12** and aryl bromides **13** in the presence of $Pd(dba)_2$ and RuPhos at room temperature. Recently, an efficient Pd-catalyzed synthesis of biaryls from Grignard reagent **14** and aryliodides **15** is reported.[49] Itami et al.[50] developed a nickel-catalyzed Suzuki-Miyaura cross-coupling reaction between aryl boronic esters **16** and aryl fluorides **17**. Finally, Pd-catalyzed Stille reaction between arylstannanes **18** and arylhalides **19** to accomplish biaryls **20** (Scheme 3.2.1). The metal reagents required for these classical couplings are prepared from laborious synthetic procedures involving multi-steps, column chromatography, expensive metal-catalysts, ligands, bases, cryogenic conditions and inert atmosphere. In recent past, these methods have been supplanted by emerging and attractive C-H functionalization strategies namely directing group (DG)-assisted arylation,[51, 52] cross-dehydrogenative coupling,[53-55] and transition-metal (TM)-free cross-coupling reactions.[56, 57] In directing group-assisted arylation regioselectively ortho position of the substrates **21** is selectively get functionalized with the help of transition-metal catalysts.



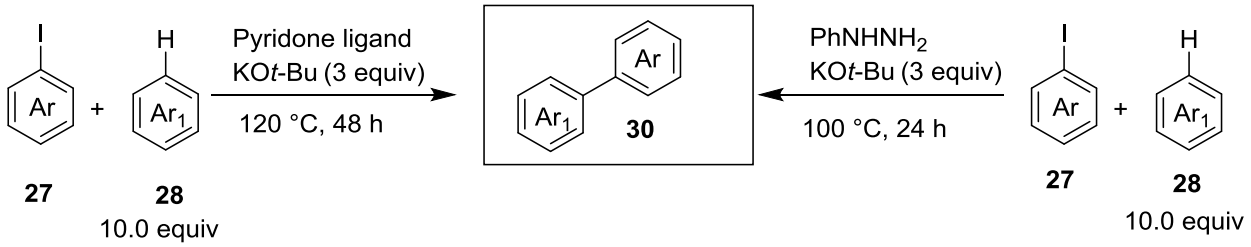
Scheme 3.2.2 Directing group-assisted arylation

Cross-dehydrogenative coupling reaction is a dual C-H activation strategy in which there is no requirement of pre-activated metal reagents, directing groups and aryl halides. Ye and Weiping disclosed the effective cross-dehydrogenative coupling between pentafluoroarenes **24** and arenes **25** for the synthesis of fluorinated biaryls **26** in good yields.[52]



Scheme 3.2.3 Cross-dehydrogenative coupling reaction

Nevertheless, excess of arenes (as solvent), limited to fluorinated aryl substrates and poor regioselective C-H arylations are the major obstacles associated with cross-dehydrogenative coupling reactions. In recent years, transition-metal free coupling reactions got much interest because expensive metals are not involved in the C-H functionalizations. Most of the TM-free cross-couplings employ aryl halides (**27**, 1.0 equiv), excess of arenes (**28**, 10.0 equiv), radical initiator (2-3 equiv), base, elevated temperatures (>140°C) and long reaction times (24-72 h).



Scheme 3.2.4 Transition-metal-free coupling reaction

Therefore, simple and atom economy protocol to prepare valuable biaryls from easily available starting materials are highly desirable.

In the recent years, tremendous efforts have been directed towards the chemistry of diaryliodonium salts due to their highly intrinsic electrophilic nature compared to the corresponding arylhalides.[31] They are stable solids, inert to air and moisture and also proved to be mild non-toxic arylating agents that are easily prepared from commercially available starting materials.[58-60] Owing to the increasing significance, diaryliodonium salts have been extensively studied for various TM-catalyzed and metal-free arylations and also in the construction of heterocycles.[61-71] Research originating from the groups of Sanford, Macmilian and Gaunt demonstrate the synthetic utilities of diaryliodonium salts *via* copper or palladium-mediated carbon-carbon bond formation.[72-74] To the best of our knowledge, reports involving the reductive- couplings of diaryliodonium salts to access biaryls involved the use of stoichiometric amounts of methylmagnesium iodide and anhydrous nickel chloride under inert atmosphere [75-77] activated Zn in the presence of a palladium catalyst, combination of diethylzinc and $Pd(OAc)_2$ [10c] and indium with $Pd(OAc)_2$ under N_2 environment. Besides limited substrate scope and formation of a mixture of biaryls in some cases, these reaction conditions involves the use of stoichiometric amounts of ligands, metals and sensitive reagents. Subsequently, sodium tetraarylborates, organoboranes, organostannanes and arenes have also been coupled with diaryliodonium salts using $PdCl_2$, $Pd(PPh_3)_4$, CuI, and Pd-complex to prepare diverse biaryls.[78-81]

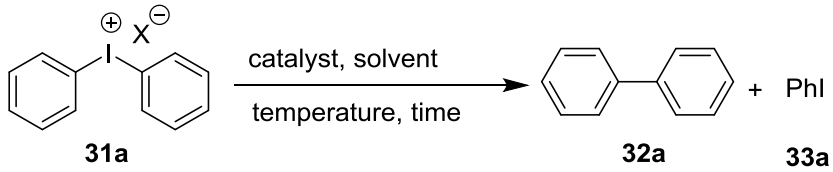
3.2.2 Results and Discussion

3.2.2.1 Chemistry

As a result of our ongoing research directed towards the synthetic utilities of hypervalent iodine reagents,[37, 82-84] we envisioned an operationally simple $Pd(OAc)_2$-PEG-400 catalytic system to prepare biaryls by harnessing the two aryl moieties from easily accessible and stable diaryliodonium salts. This protocol proceeded under neutral conditions without the use of any activating metal reagent, ligand, and base, to generate an array of biaryls in good to excellent yields. Despite additional synthetic step required to obtain the diaryliodonium salts, the present protocol provides a convenient route to prepare biaryls in view of the associated drawbacks of

the direct coupling of aryl halides and arenes in C–H functionalization strategies. At the outset of this study, we chosen diphenyliodonium triflate **31a** as a model substrate to identify the optimum

Table 3.2.1 Optimization of reaction conditions



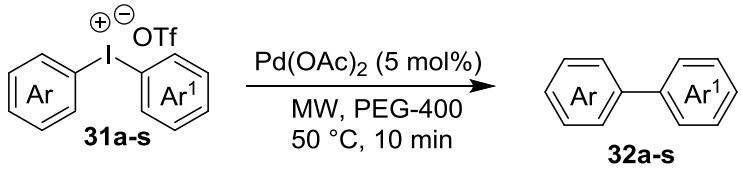
31a **32a** **33a**

Entry	Catalyst (mol%)	X	Solvent	Temp (°C)	Time	Yield(%)[c]	
						32a	**33a**
1[a]	CuI (50)	OTf	DMF	140	24 h	-	-
2[a]	CuI (50)	OTf	dioxane	80	12 h	-	-
3[a]	$Cu(OTf)_2$ (50)	OTf	DCE	80	12 h	-	-
4[a]	CuCl (50)	OTf	dioxane	80	12 h	-	70
5[a]	CuBr(50)	OTf	dioxane	80	12 h	-	10
6[a]	$CuBr_2$ (50)	OTf	dioxane	80	12 h	-	70
7	$Cu(OAc)_2$ (50)	OTf	dioxane	80	30 min	-	60
8	$Pd(OAc)_2$(10)	OTf	DCE	50	30 min	-	-
9	$Pd(OAc)_2$(10)	OTf	DMF	50	30 min	-	-
10	$Pd(OAc)_2$ (10)	OTf	water	50	30 min	-	-
11	$Pd(OAc)_2$ (10)	OTf	dioxane	50	30 min	60	10
12	$Pd(OAc)_2$ (10)	OTf	PEG-400	50	10 min	90	-
13[b]	$Pd(OAc)_2$ (5)	OTf	PEG-400	50	10 min	90	-
14[a]	$Pd(OAc)_2$ (5)	OTf	PEG-400	50	10 min	NR	
15[a]	$Pd(OAc)_2$ (5)	OTf	PEG-400	100	2 h	75	
16[b]	$Pd(OAc)_2$(5)	OTs	PEG-400	50	10 min	-	90
17[b]	$Pd(OAc)_2$ (5)	Br	PEG-400	50	10 min	-	90
18[b]	$Pd(OAc)_2$(5)	BF_4	PEG-400	50	10 min	40	50

[a] Conventional heating. [b] MW (50 W). [c] Isolated yield, NR = no reaction

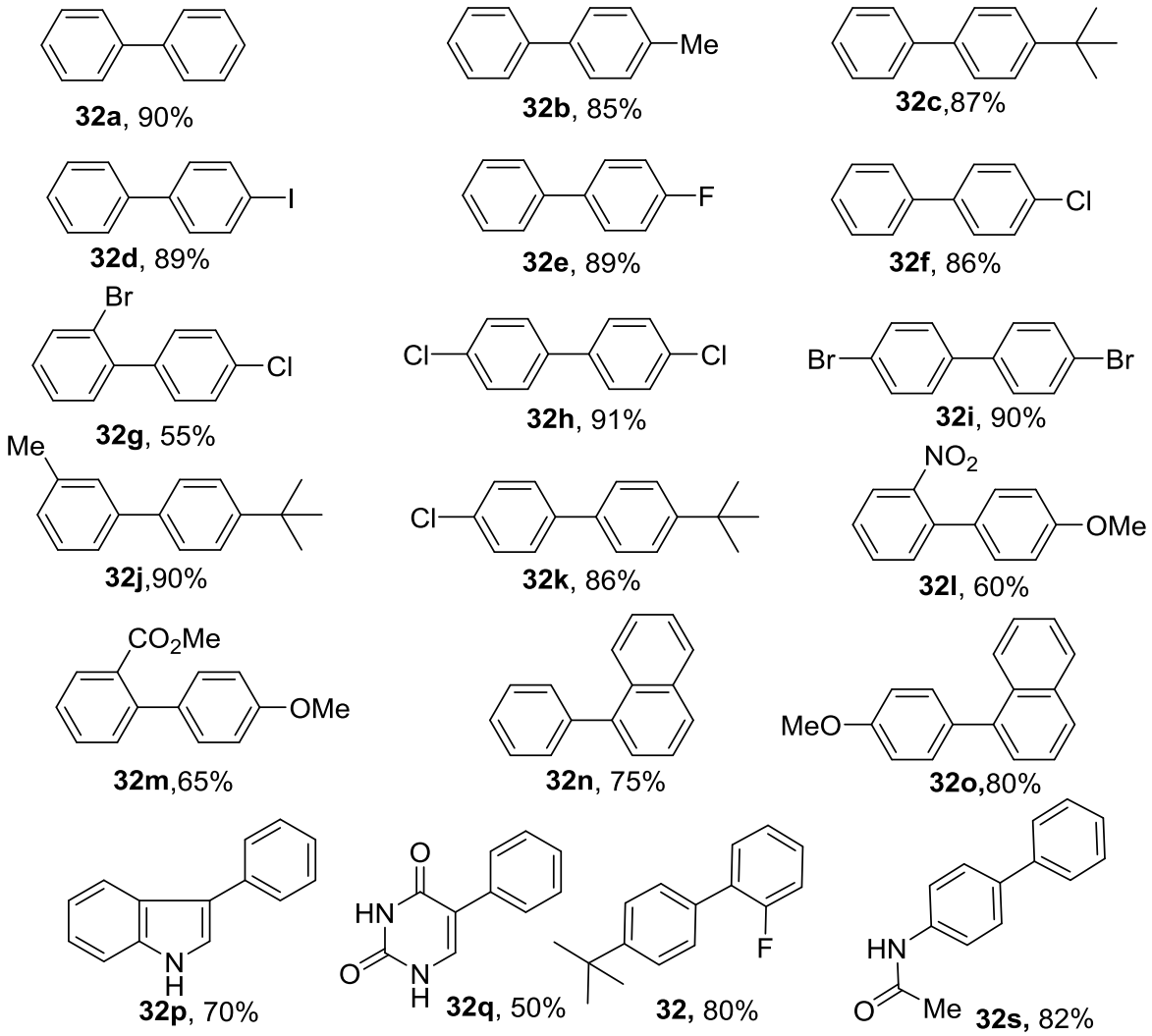
reaction conditions. Initially, the coupling reaction was performed in the presence of CuI (0.5 equiv) at 140 °C for 24 h but no desired biphenyl (**32a**) was obtained (Table 3.2.1, entry 1). Consecutive reaction trials with various copper catalysts including CuI, $Cu(OTf)_2$, CuCl, CuBr, $Cu(OAc)_2$ and $CuBr_2$ in DCE or dioxane at 80 °C for 12 h were also unsuccessful (Table 3.2.1, entries 2-7). We further explored the reaction of **31a** in the presence of Pd catalyst using microwave (MW) irradiation. MW is a greener methodology to activate the reaction, because it drives the chemical transformations very rapidly than conventional heating along with the desired products in high yields.[27, 85] Reaction of **31a** in the presence of $Pd(OAc)_2$ (10 mol%) in DCE and DMF under MW irradiation at 50 °C for 30 min also failed to deliver **32a**. Surprisingly, under the similar reaction conditions when we changed the solvent from DMF to dioxane, the anticipated product **32a** was obtained in 60% yield (Table 3.2.1, entry 11). Notably, when the reaction of 3**1a** was conducted in polyethylene glycol-400 (PEG-400), **3a** was formed in 90% yield within 10 min. PEG-400 as a reaction medium has received greater attention due to its appealing and eco-friendly features.[26] No change in the yield was observed upon reducing the loading of $Pd(OAc)_2$ from 10 to 5 mol%. Under conventional heating (50 °C) conditions Pd-catalyzed reductive coupling of **31a** failed to produce **32a** (Table 3.2.1, entry 14) however, upon raising the reaction temperature to 100 °C, **32a** was obtained in 75 % yield (Table 1, entry 15). During the optimization of reaction conditions, we also screened diphenyliodonium salts bearing different counter ions ($^-$OTf, $^-BF_4$, Br^- and $^-$OTs) and found that the diphenyliodonium triflate (**31a)** to be the most suitable salt to obtain biaryls **2** in high yields. Diphenyliodonium tetrafluoroborate was relatively better than the salts bearing bromide and tosylate counterions (Table 3.2.1, entries 16-18). The scope of the protocol was investigated by treating various symmetrical and unsymmetrical diaryliodonium salts under the catalytic system. All the diaryliodonium salts **31a-z** were prepared by known protocols involving easily available arenes and iodoarenes.[99] Iodonium salts containing electron-donating groups like methyl (**31b)** and *t*-butyl (**31c, 31j, 3lk** and **31r)** were successfully coupled to afford the corresponding biaryls **32b-c** and **32j** in good to excellent yields (85-90%, Table 2). Iodonium salts **31d-i** possessing halogens (F, Cl, Br and I) were well tolerated under the optimal reaction conditions and delivered the corresponding biaryls **32d-i** in good yields (55-90%). These halogen bearing biaryls **32d, 32g** and **32i** could serve as useful precursors for various cross-coupling reactions leading to useful molecules in addition to their interesting organic luminogen properties.[86]

Gratifyingly, fused ring naphthyl derivatives **32n** and **32o** were prepared in 75% and 80% yields, respectively. Diaryliodonium salts possessing nitro (**31l),** ester (**3lm)** and amide **(31s)** functional groups were successfully prepared and converted into the corresponding biaryls **32l-m** and **32s** in good yields (60-82%).



Scheme 3.2.5 Synthesis of unsymmetrical biaryls

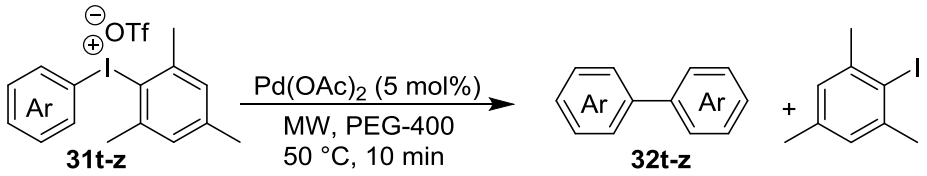
Table 3.2.2 Synthesized biaryls



To our delight, indolyl(phenyl)iodonium salt **31p** gave the anticipated 3-phenylindole (**32p**) in 70% yield. The developed strategy was successfully extended to prepare arylated pyrimidine base by using 5-phenyluracil iodonium salt (**31q)** and afforded 5-phenyluracil (**32q)** in 50 % yield. Arylated uracils are well known for their interesting medicinal properties.[87]

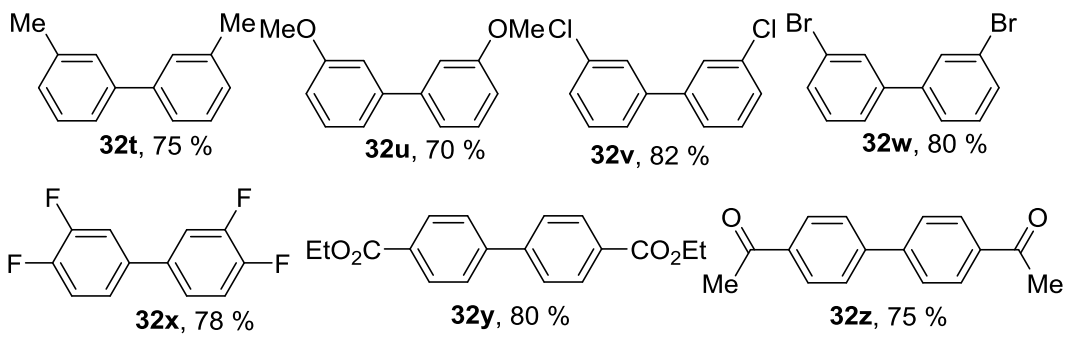
3.2.2.2 Reductive coupling of aryl(mesityl)iodonium triflate

Phenyl(mesityl)iodonium triflate with bulky mesityl moiety led to biphenyl **32a** rather than expected phenyl-mesityl coupled product. This interesting observation motivated us to prepare various symmetrical biaryls **32t-z** (Table 3.2.3). In these reactions iodomesitylene (**33b**) was behaving as a leaving group and another aryl partner underwent self coupling to deliver the symmetrical biaryls **32t-z**. The released **33b** was easily recovered from the reaction mixture by hexane wash and the resulted **33b** was successfully reused to prepare diaryliodonium salts **31t-z**. Notably, various aryl(mesityl) iodonium salts bearing methyl (**31t**), methoxy (**31u**), halogens (**31v-x),** ester (**31y**) and acetyl (**31z**) substituents were well tolerated under the reaction conditions to produce various symmetrical biaryls **32t-z** in good to excellent yields (70-82 %). Though the protocol is fairly general, however, it may not be suitable to prepare highly oxygenated or amino substituted biphenyls due to inaccessibility of the corresponding diaryliodonium salts.



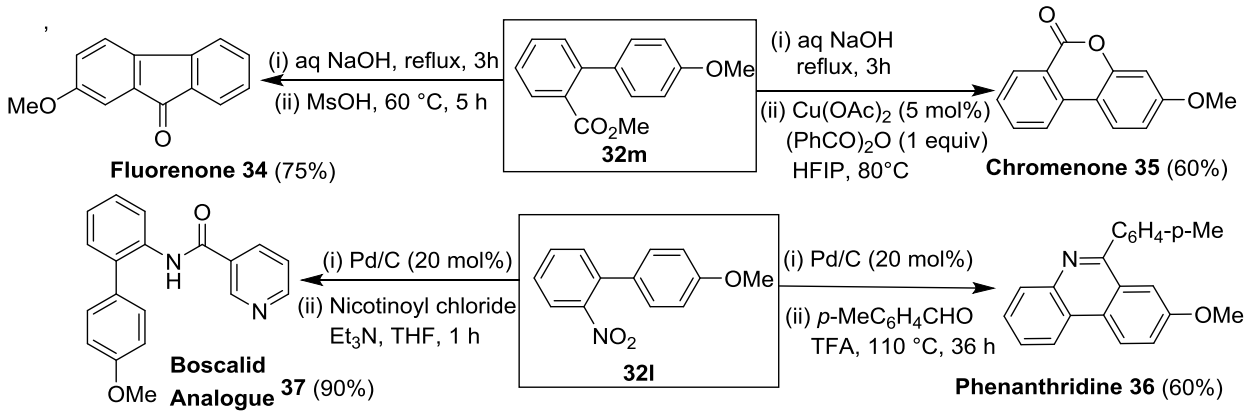
Scheme 3.2.6 Synthesis of symmetrical biaryls

Table 3.2.3 Synthesized symmetrical biaryls



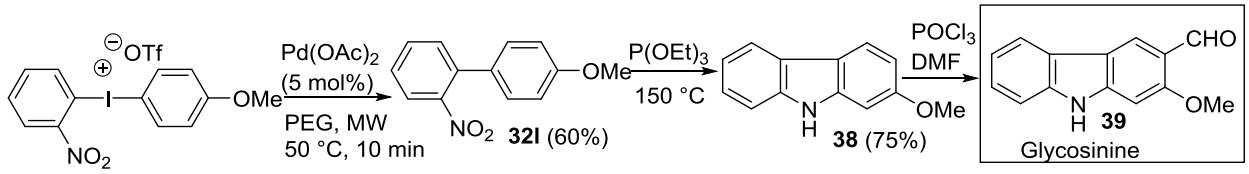
3.2.2.3 Synthetic applications

The synthetic usefulness and prowess of the methodology was obvious by the successful preparation of *o*-functionalized biaryls **32l-m** from the corresponding iodonium salt **31l-m** within 10 min (Scheme 3.2.7). Biaryl **32m** was utilized to obtain fluorenone **34** (75%) and chromenone **35** (60%). Similarly, a useful precursor, *o*-nitro biaryl **32l** was smoothly converted into phenanthiridine **36** (60%) and Boscalid analogue **37** (90%) in good to excellent yields.[88-91]



Scheme 3.2.7 Synthesis of drug-like molecules

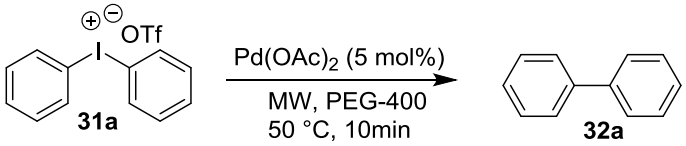
Interestingly, biaryl **32l** also provides a simple and efficient route to carbazole alkaloid glycosinine **39** (Scheme 3).[92, 93] To demonstrate scalability (1 gram) of the developed protocol, we have prepared **32a** in 88% yield from **31a** under the optimized reaction conditions



Scheme 3.2.8 Synthesis of Glycosinine precursor

3.2.2.3 Recyclability of Pd-PEG catalytic system

The recyclability of Pd-PEG catalytic system was demonstrated by the reaction of **31a** under the optimized conditions. After the first cycle, the reaction mixture was extracted with diethyl ether and the obtained Pd-PEG residue was subjected to next cycle by using same substrate **31a** without any addition of $Pd(OAc)_2$. Gratifyingly, the Pd-PEG catalytic system was successfully



Scheme 3.2.9 Synthesis of biphenyl (**32a**)

recovered and reused six times without any loss of catalytic activity to produce **32a** in 90%, 89%, 87%, 87%, 85%, and 85% yields, respectively.[94-97]

3.2.2.4 Mechanistic studies

(i) Reaction between $Pd(OAc)_2$ + PEG-400

a) Catalytic amount of $Pd(OAc)_2$ (2 mg, 5 mol%) and PEG-400 (2 mL) was taken into a 10 mL MW vial and kept the contents at room temperature for 10 min. Subsequently ^{1}H NMR spectrum of the resulting solution was recorded as depicted in Figure. 3.2.2.

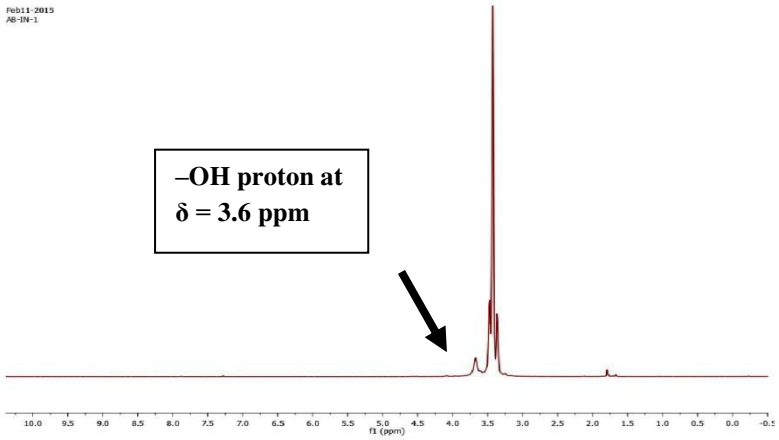


Figure 3.2.2 ^{1}H NMR of PEG-400 + $Pd(OAc)_2$ (5 mol%) before MW irradiation.

b) A mixture of $Pd(OAc)_2$ (2 mg, 5 mol%) and PEG-400 (2 mL) was taken in a MW vial (10 mL) and the contents were exposed to MW irradiation for 10 min. Subsequently, ^{1}H NMR spectrum of the resulting solution was recorded as illustrated in Figure 3.2.3.

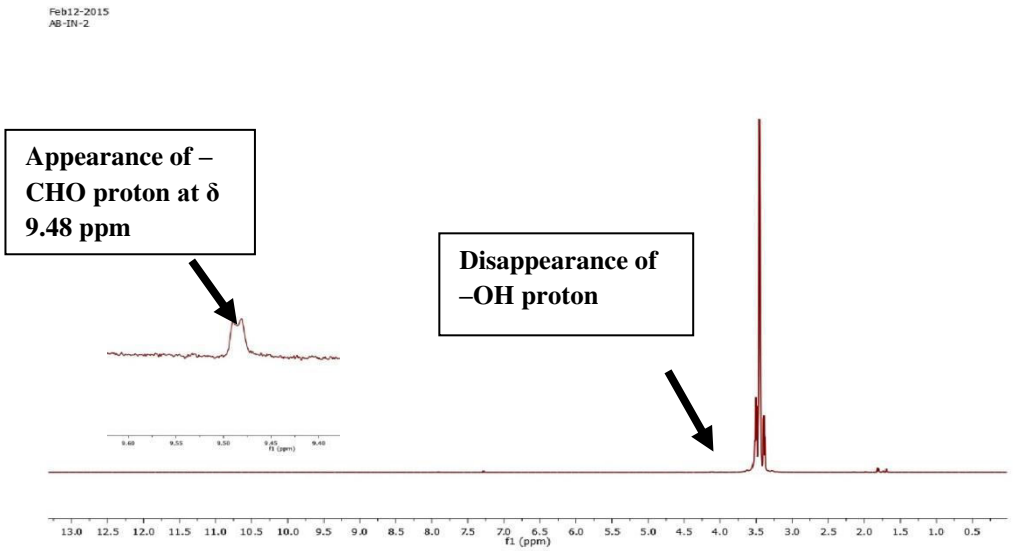
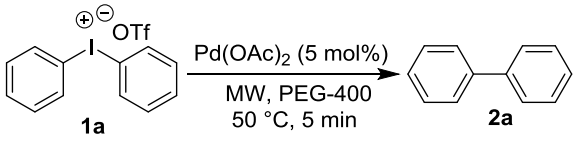


Figure 3.2.3 ^{1}H NMR of PEG-400 + $Pd(OAc)_2$ (5 mol%) solution after MW irradiation for 10 min

By comparing the above two NMR spectra given in figures 3.2.2 and 3.2.3, it is believed that initially Pd(0) species was generated from $Pd(OAc)_2$ by the concomitant oxidation of PEG-OH into PEG-CHO.

(ii) HPLC experiments

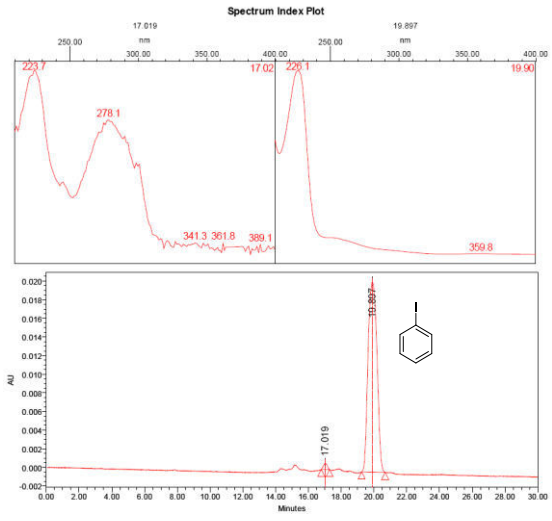
We have performed HPLC analysis of the reaction mixture obtained after irradiating in MW for 5 min. No peak corresponds to iodobenzene was observed. HPLC traces for standard samples of iodobenzene and biphenyl, and reaction mixture are appended below (Figure 3.2.4)



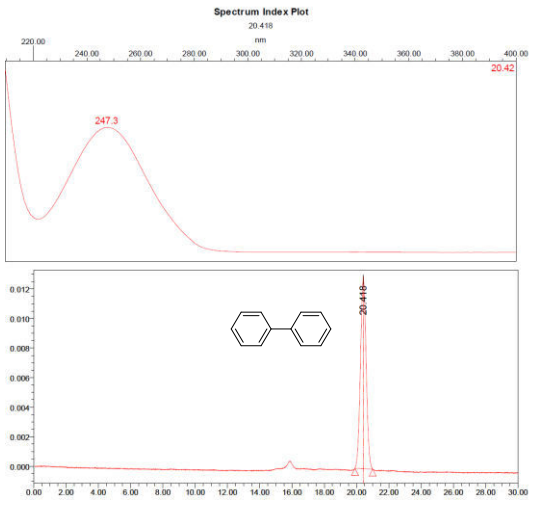
Scheme 3.2.10 Reductive coupling of **31a** under the optimized reaction conditions

HPLC analysis rules out the involvement of iodobenzene during the reductive coupling of diaryliodonium salt **31a** to biphenyl.

HPLC chromatogram of standard iodobenzene



HPLC chromatogram of standard biphenyl



HPLC Chromatogram of the reaction mixture

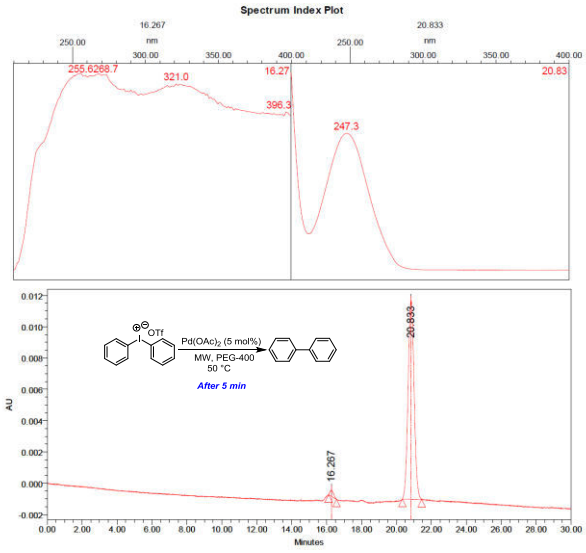
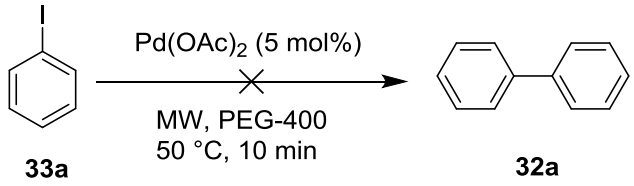


Figure 3.2.4 HPLC chromatograms

To get mechanistic insight, we treated iodobenzene (**33a)** under the optimized reaction conditions (Scheme 3.2.11).



Scheme 3.2.11 Reaction of iodobenzene under the optimized conditions

No bipheyl **32a** was formed under these conditions. In HPLC analysis of the reaction mixture, no peak corrseponds to biphenyl was observed.

HPLC Chromatogram of the reaction mixture

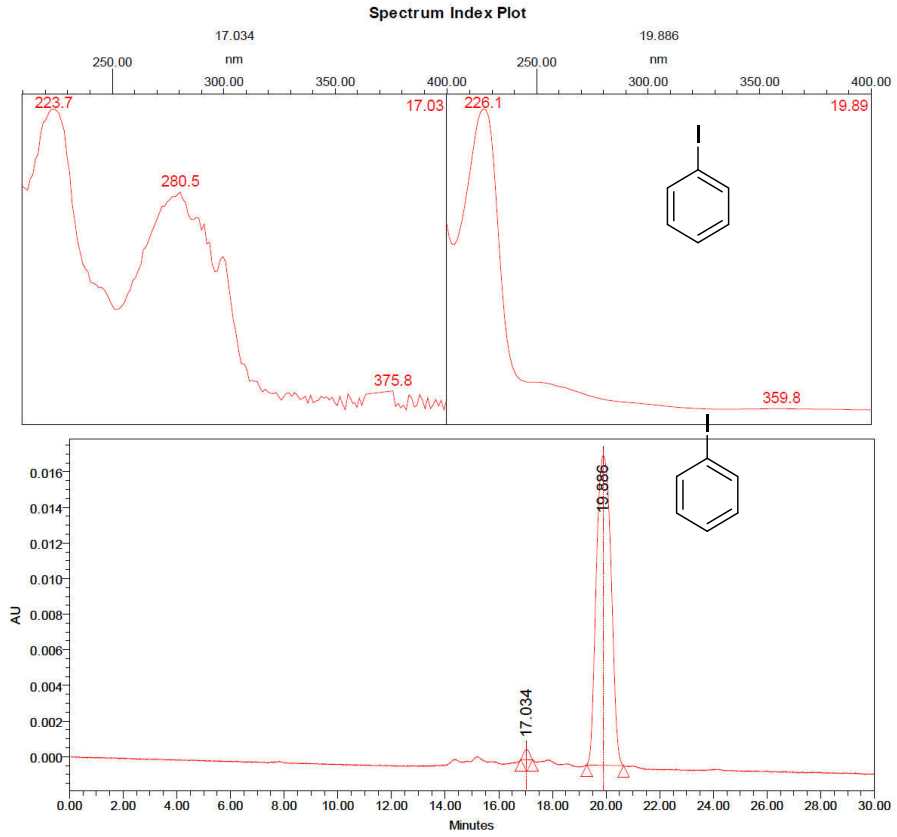


Figure 3.2.5 HPLC Chromatogram of the reaction mixture

(iii) TEM analysis of the reaction mixture ($Pd(OAc)_2$+PEG-400+diphenyliodonium salt)

To ascertain the formation Pd-nanoparticles[94, 96-98] under the optimized experimental reaction conditions, we have independently examined the reaction mixture using transmission electron

microscopy (TEM). The TEM results showed the formation of palladium nanoparticles in the range of 3.69-7.12 nm.

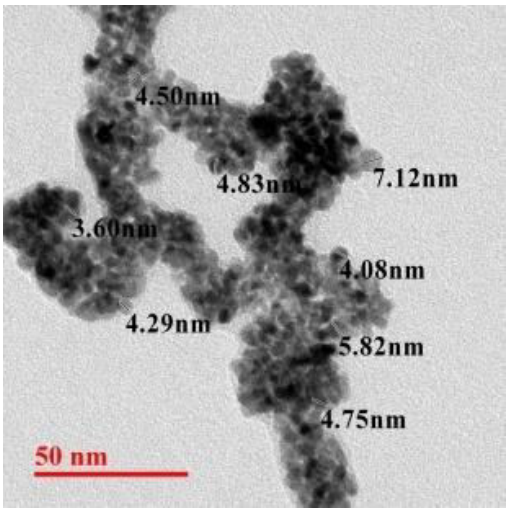


Figure 3.2.6 TEM image of Pd nanoparticles

(iv) UV-Visible absorption studies of $Pd(OAc)_2$+PEG-400 solution before and after MW irradiation

UV-Vis absorption spectra were recorded before and after MW irradiation of solutions containing 5 mol% of $Pd(OAc)_2$ in PEG-400. A peak was observed around 400 nm corresponds to Pd(II) (black coloured curve, Figure 3.2.7), which completely disappeared after MW irradiation of the same solution (red coloured curve, Figure. 3.2.7) suggesting the conversion of Pd(II) to Pd(0).[98]

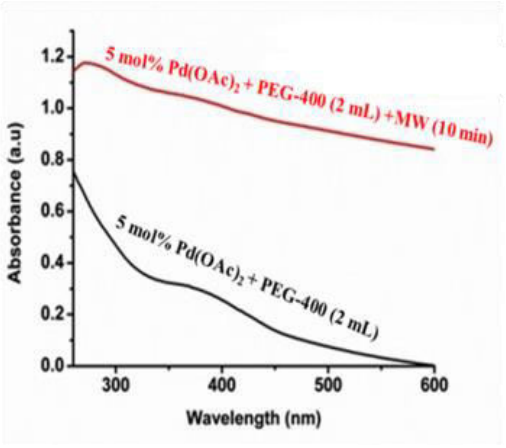


Figure 3.2.7 UV-Vis absorption spectra of 5 mol% $Pd(OAc)_2$ in PEG-400

3.2.2.4 Plausible Mechanism

Based on our results and literature reports,[98] a plausible mechanism for the formation of biaryls is depicted in Scheme 4. It is believed that initial MW irradiation of a solution of palladium acetate in PEG-400 (reducing species) generates Pd(0) species **A** which upon oxidative addition to diaryliodonium salt is believed to give arylpalladium species **B**, which likely to rearrange Pd(II) species **C.** Subsequently, reductive elimination of **C** generates biaryls and Pd(0).[64]

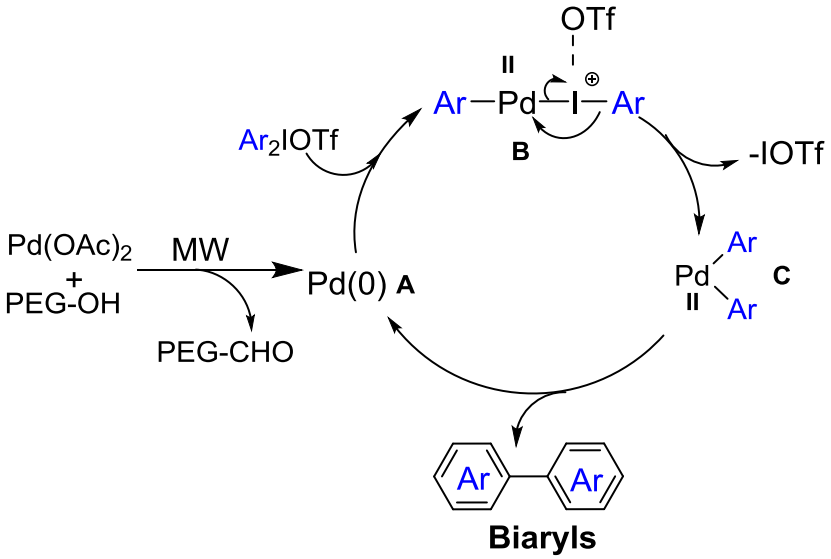


Figure 3.2.8 Plausible mechanism for the synthesis of biaryls

Under the optimized reaction conditions neither iodobenzene (**33a**) led to biphenyl (Scheme 5) nor it was produced upon reductive coupling of **31a**. These observations suggest that aryliodide may not be involved at any stage in the reductive coupling of diaryliodonium salts to biaryls **2**. However, formation of symmetrical biaryls **32t-z** *via* the reductive couplings of aryl(mesityl)iodonium triflates **31t-z** needs further mechanistic investigation.

All the newly synthesized iodonium salts and biaryls were were well characterized by using IR, NMR (^{1}H and ^{13}C) and mass spectral data. The NMR copies (^{1}H and ^{13}C) of compounds **31o** and **32l** are given below.

4-Anisyl-1-naphthyliodonium triflate (31o)

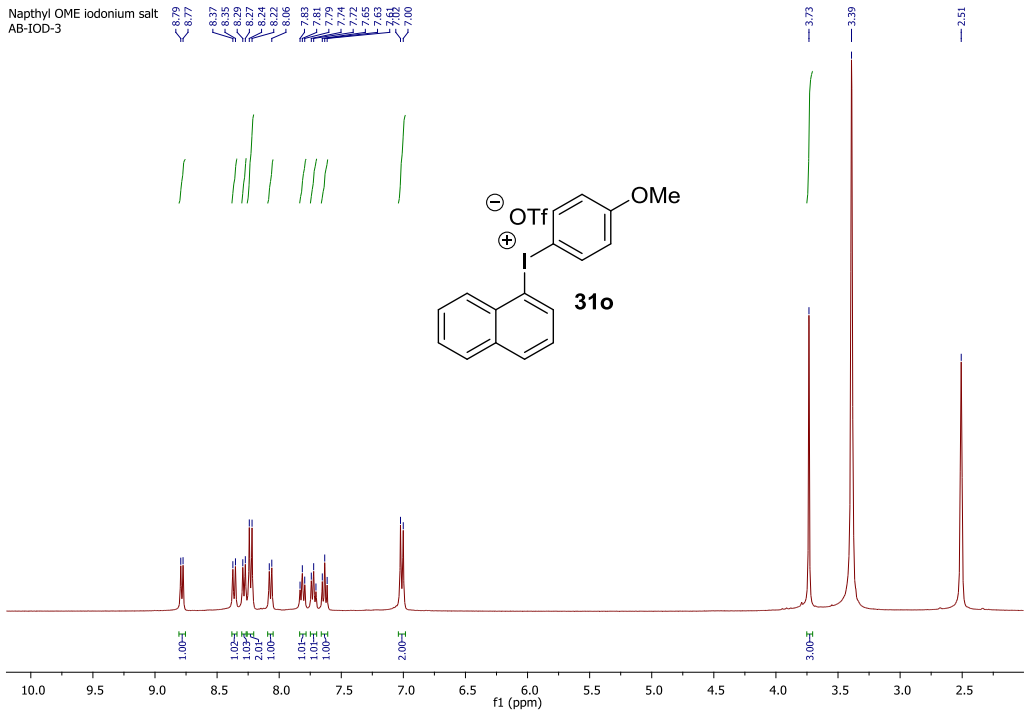


Figure 3.2.10 ^{1}H NMR spectrum of the 4-anisyl-1-naphthyliodonium triflate **31o**

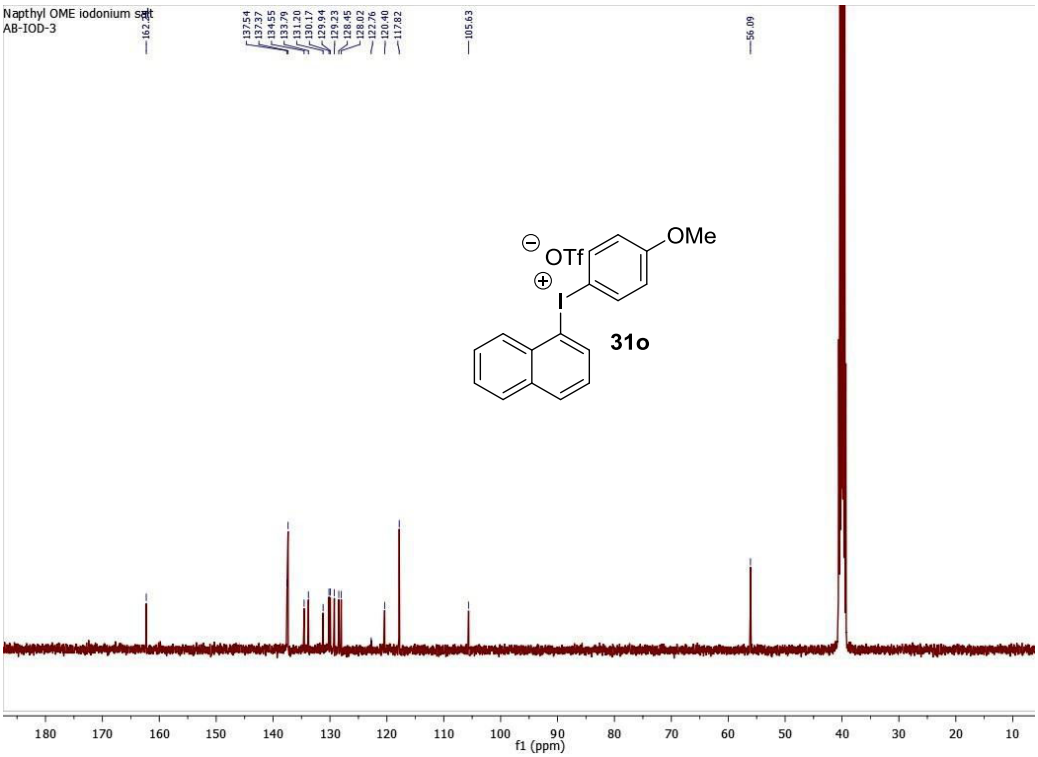


Figure 3.2.11 ^{13}C NMR spectrum of the 4-anisyl-1-naphthyliodonium triflate **31o**

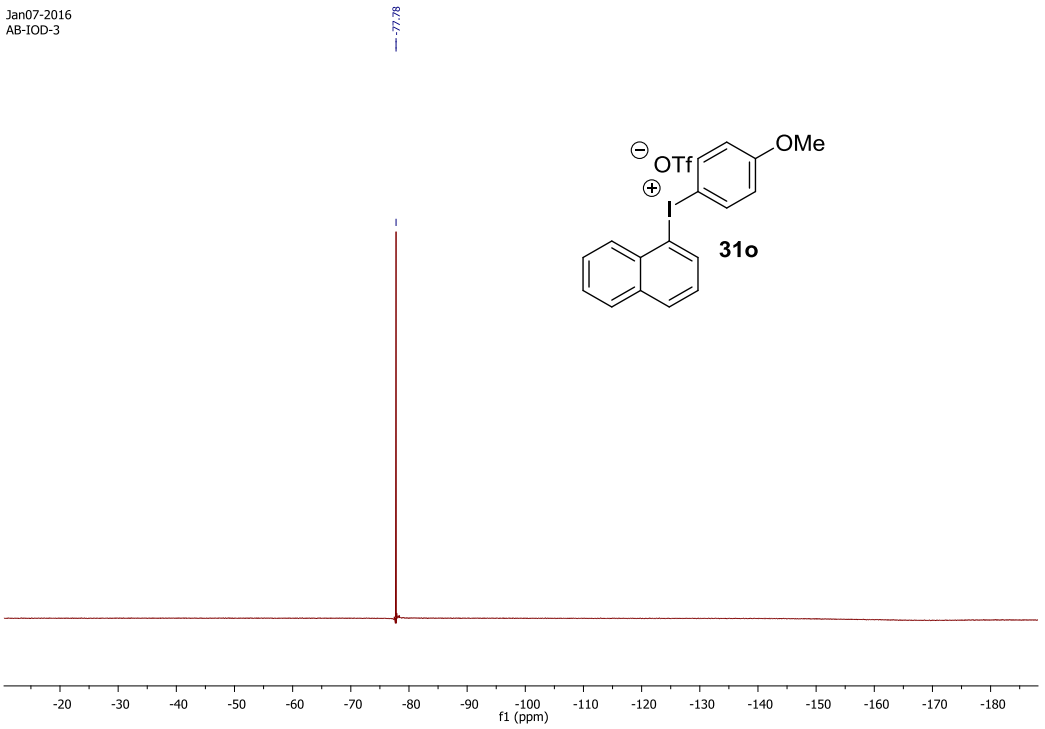


Figure 3.2.12 ^{19}F NMR spectrum of the 4-anisyl-1-naphthyliodonium triflate **31o**

4-Methoxy-2'-nitro-biphenyl

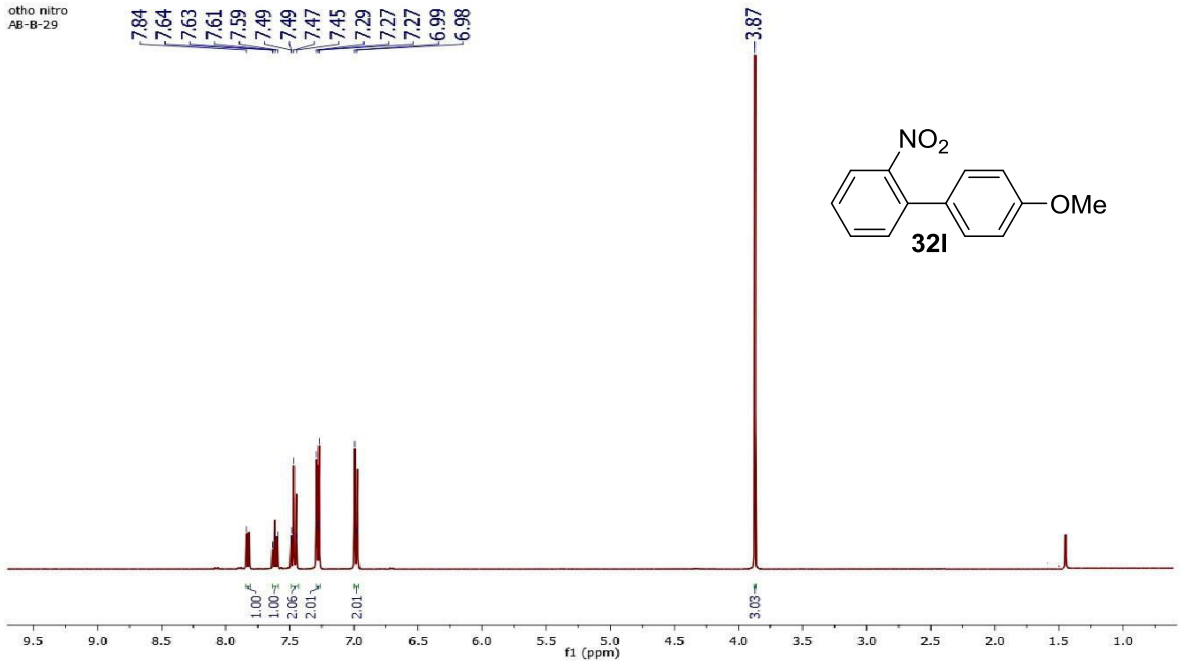


Figure 3.2.13 ^{1}H NMR spectrum of the 4-methoxy-2'-nitro-biphenyl **32l**

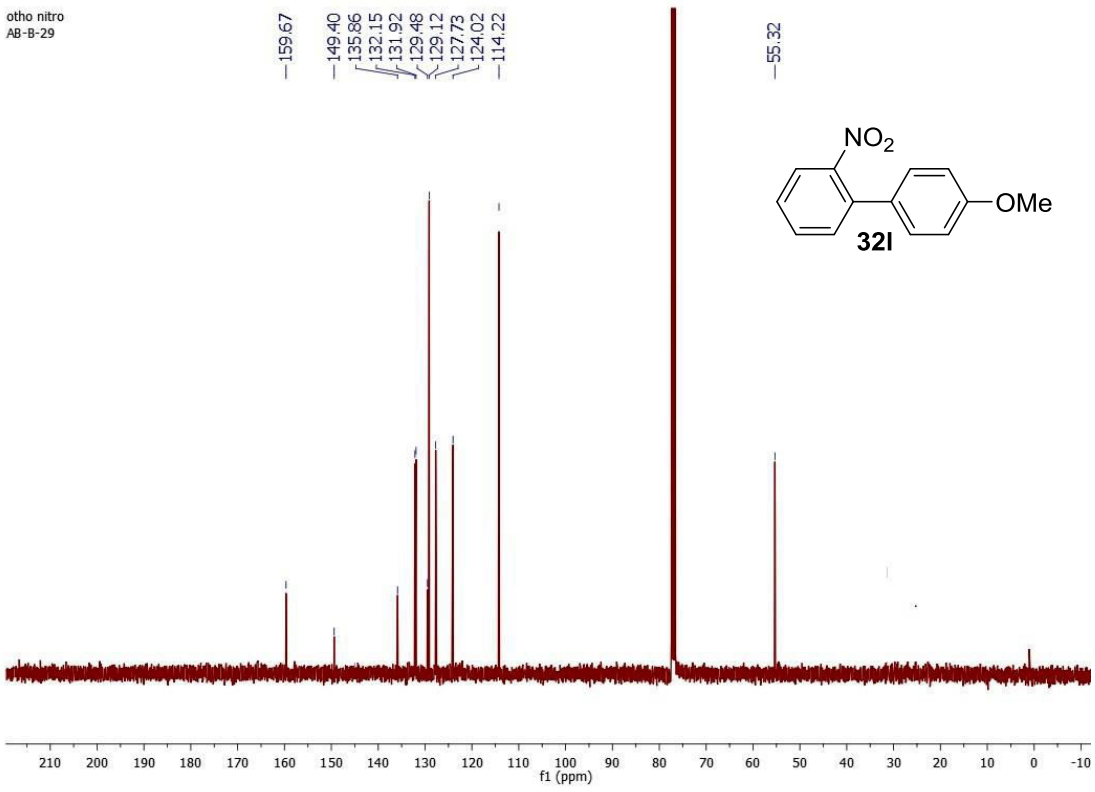


Figure 3.2.14 ^{13}C NMR spectrum of the 4-methoxy-2'-nitro-biphenyl **32l**

3.2.2.5 Conclusions

In summary, we have successfully developed a ligand and base-free Pd-catalyzed synthesis of useful biaryls from easily accessible and stable diaryliodonium salts. The highlights of the present protocol are operationally simple, mild reaction conditions, broad substrate scope for symmetrical and unsymmetrical biaryls, scalable and use of recyclable Pd catalyst. The potential utility of the developed method was demonstrated by preparing valuable heterocycles such as 5-aryluracils, carbazoles, chromenones, fluorenones, phenanthiridines and Boscalid analogues.

3.2.3 Experimental Section

3.2.3.1 General materials and methods: Chemicals and solvents were purchased from Aldrich, Alfa Aesar, Merck and Spectrochem. Thin layer chromatography (TLC) technique was used to monitor the progress of the reactions. It was conducted on Merck pre-coated plates (silica gel 60, F_{254}, 0.25mm). Hand UV lamp was used to visualize the TLC plates. All the synthesized

compounds were purified by column chromatography which was performed on silica gel (mesh size 100-200). The solvents were distilled-off using Buchi rotary evaporator. Microwave (MW) reactions were carried out in CEM DISCOVER instrument (power = 50 watt, pressure = 50 psi). Melting points were determined using E-Z melting point apparatus and were uncorrected. The NMR (^{1}H, ^{13}C and ^{19}F) spectra were recorded using Bruker-Avance II (400, 100 and 376 MHz) spectrometer. Chemical shift (δ) are reported in parts per million (ppm) relative to tetramethylsilane (TMS) which act as an internal standard. The coupling constants (*J*) were given in Hz. The multiplicities were expressed as: s= singlet, d= doublet, t= triplet, q= quartet and m= multiplet. Mass spectra were obtained from WATERS XEVO TQD mass spectrometer. Analytical RP-HPLC was conducted on WATERS 515 HPLC system with a Sunfire C18 column (5 µm, 4.6 × 250 mm), PDA detector, flow rate 0.2 mL/min and a solvent (acetonitrile)

3.2.3.2 General Experimental Procedures

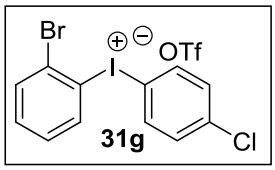
(a) Diaryliodonium salts 31a-m and 31p-z

To a stirred solution of iodoarene (0.5 g, 2.5 mmol) in dichloromethane (8 mL) was added *m*-chloroperbenzoic acid (0.455 g, 2.6 mmol) and followed by arene (0.22 mL, 2.5 mmol) at room temperature. Reaction contents were cooled to 0 °C and then trifluoromethanesulfonic acid (0.23 mL, 2.6 mmol) was added dropwise while maintaining the same temperature. The mixture was allowed to stir at room temperature for additional 30 min. The solvent was evaporated under vaccum and diethyl ether (3 mL) was added to the residue under cooling (0°C) conditions. The solid so obtained was washed twice with diethyl ether and dried to afford diaryliodonium triflates **31** as white solids in 50-88% yields.[99]

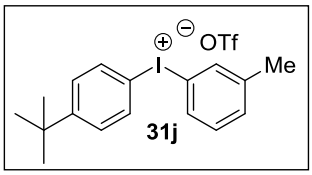
(b) 1-Naphthylphenyliodonium triflate (31n)

To a stirred solution of 1-iodonaphthalene (0.5 g, 1.96 mmol) in dichloromethane (8 mL) was added *m*-chloroperbenzoic acid (0.365 g, 2.12 mmol) followed by benzene (0.35 mL, 3.92 mmol) at room temperature. After stirring the mixture at same temperature for 10 min, trifluoromethanesulfonic acid (0.35 mL, 3.93 mmol) was added dropwise at room temperature and continued stiring for additional 30 min. Solvent was evaporated under vaccum and diethyl ether (3 mL) was added to the residue at 0°C. The solid so obtained was washed twice with

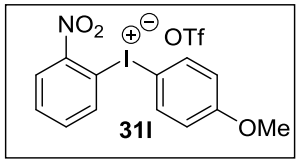
diethyl ether and dried to afford 1-naphthylphenyliodonium triflate (**31n**) as a light brown solid in 75% yield (0.77 g). Similarly other diaryliodonium salt **31o** was prepared.



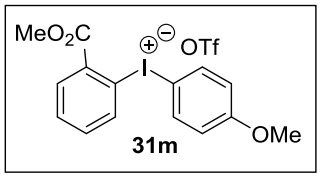
(2-Bromophenyl)(4-chlorophenyl)iodonium triflate (31g) Off-white solid, 380 mg, Yield 65%, mp 175-176 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.15 (d, J = 8.0 Hz, 2H), 7.76-7.71 (m, 1H), 7.61-7.54 (m, 2H), 7.41 (t, J = 7.0 Hz, 1H), 7.27 (d, J = 8.0 Hz, 2H), ^{13}C NMR (101 MHz, DMSO-d_6) δ 139.1, 137.9, 135.0, 133.3, 131.0, 129.2, 127.6, 122.7, 118.6, 110.3.



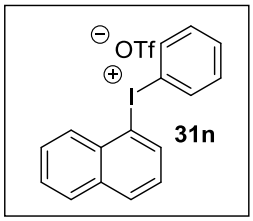
(4-(*t*-Butylphenyl)(*m*-tolyl)iodonium triflate (31j) White solid, 550 mg, Yield 78%, mp 151-152 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.60 (d, J = 8.0 Hz, 2H), 7.53– 7.50 (m, 2H), 7.45 (d, J = 8.0 Hz, 2H), 7.39 (d, J = 7.1 Hz, 1H), 7.22 – 7.19 (m, 1H), 2.29 (s, 3H), 1.42 (s, 9H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 156.9, 140.3, 138.4, 128.6, 128.0, 127.7, 126.7, 125.6, 114.2, 112.0, 34.0, 31.4, 21.3.



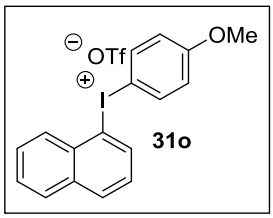
(4-Methoxyphenyl)(2-nitrophenyl)iodonium triflate (31l) Light-brown solid, 450 mg, Yield 70%, mp 160 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.49 (d, J = 9.4 Hz, 1H), 8.27 (d, J = 8.6 Hz, 2H), 7.94 – 7.79 (m, 3H), 7.24 (d, J = 8.6 Hz, 2H), 3.88 (s, 3H).^{13}C NMR (101 MHz, DMSO-d_6) δ 163.3, 146.7, 139.1, 137.9, 135.1, 133.3, 127.6, 118.6, 110.3, 104.2, 56.3.



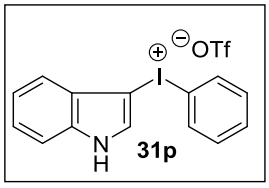
2-(Methoxycarbonyl)phenyl)(4-methoxyphenyl)iodonium triflate (**31m**) Light brown solid, 493 mg, Yield 71%, mp 165-166 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.35 (d, J = 8.2 Hz, 1H), 8.33 (d, J = 8.0 Hz, 2H), 8.26 (d, J = 8.0 Hz, 2H), 7.78-7.74 (m, 2H), 6.9 (s, 1H), 4.0 (s, 3H), 3.88 (s, 3H).^{13}C NMR (101 MHz, DMSO-d_6) δ 168.4, 151.4, 143.8, 137.9, 133.5, 131.9, 130.5, 129.1, 128.0, 118.4, 114.1, 54.9, 53.2.



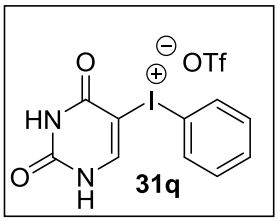
1-Naphthylphenyliodonium triflate (31n). Brown solid, 770 mg, Yield 75%, mp 210 °C (lit[61] 210-212 °C). ^{1}H NMR (400 MHz, DMSO-d_6) 8.81 (d, J = 7.5 Hz, 1 H), 8.41-8.32 (m, 4 H), 8.10 (d, J = 8.1 Hz, 1 H), 7.85 (t, J = 8.2 Hz, 1 H), 7.85 -7.56 (m, 3 H), 7.51 (t, J = 7.6 Hz, 2 H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 137.3, 134.7, 134.1, 133.7, 131.2, 130.1, 130.0, 129.2, 129.0, 128.8, 128.2, 127.6, 119.4, 116.6. ^{19}F NMR (376 MHz, DMSO-d_6) δ -78.78.



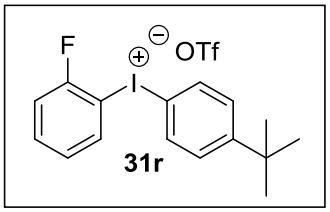
4-Anisyl-1-naphthyliodonium triflate (31o). Light brown solid, 700 mg, Yield 70%, mp 180-182 °C (lit[61] 178-180 °C). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.78 (d, J = 7.4 Hz, 1H), 8.36 (d, J = 8.4 Hz, 1H), 8.28 (d, J = 8.2 Hz, 1H), 8.23 (d, J = 8.9 Hz, 2H), 8.07 (d, J = 8.1 Hz, 1H), 7.81 (t, J = 7.6 Hz, 1H), 7.72 (t, J = 7.5 Hz, 1H), 7.63 (t, J = 7.8 Hz, 1H), 7.01 (d, J = 8.9 Hz, 2H), 3.73 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 162.2, 137.5, 137.3, 134.5, 133.7, 131.2, 130.1, 129.9, 129.2, 128.4, 128.0, 122.7, 120.4, 117.8, 105.6, 56.0. ^{19}F NMR (376 MHz, DMSO-d_6) δ -77.78.



(1*H*-indol-3-yl)(phenyl)iodonium triflate (31p). Off-white solid, 375 mg, Yield 66%, mp 183-185 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.40 (s, 1H), 8.42 (s, 1H), 7.72 (dd, J = 6.9, 1.5 Hz, 1H), 7.59-7.54 (m, 2H), 7.47 (t, J = 7.2 Hz, 4H), 7.31-7.24 (m, 2H).^{13}C NMR (101 MHz, DMSO-d_6) δ 138.1, 136.2, 135.6, 134.5, 131.9, 128.5, 127.5, 125.9, 124.0, 122.3, 119.2, 117.8, 113.4.



Uracil(phenyl)iodonium triflate (31q). White solid, 783 mg, Yield 85%, mp 250 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11. 04 (s, 1H), 10.85 (s, 1H). 7.65 (s, 1H), 7.42-7.38 (m, 2H), 7.30 (d, J = 7.2 Hz, 1H), 7.19 (2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 164.7, 151.9, 143.2, 142.6, 142.3, 130.7, 119.3, 100.6.

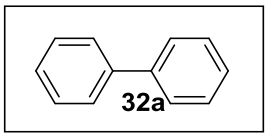


(4-(*t*-Butyl)phenyl)(2-fluorophenyl)iodonium triflate (31r). White solid, 312 mg, Yield 66%, mp 167-169 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.47 – 8.42 (m, 1H), 8.14 (d, J = 8.6 Hz, 2H), 7.76 –

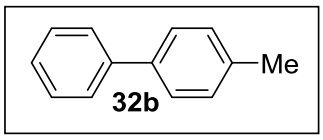
7.71 (m, 1H), 7.61 – 7.54 (m, 3H), 7.39 (t, J = 7.1 Hz, 1H), 1.25 (s, 9H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 160.8, 158.4 (d, ^1J = 247 Hz), 137.6, 136.0 (d, ^3J = 8 Hz,), 135.4, 129.5, 128.1, 117.4 (d, ^2J = 22 Hz), 113.7, 104.3 (d, ^4J = 4 Hz), 35.4, 31.1.

(c) Preparation of Biaryls

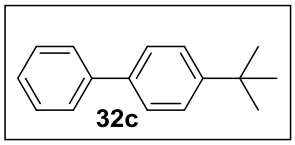
To a 10 mL MW vial with magnetic stir bar diphenyliodonium triflate **31a** (0.1 g, 0.232 mmol), catalytic amount of $Pd(OAc)_2$ (2.6 mg, 5 mol%) and PEG-400 (2 mL) were added. The reaction vial was kept under MW irradiation for 10 min at 50 °C (power = 50 watt and pressure =50 psi). Completion of the reaction was confirmed by TLC (hexane as an eluent) and the resulting contents were taken into water, extracted with ethyl acetate (3 × 3 mL) and dried the combined organic layer over anhydrous sodium sulfate. After removal of the organic solvent, the residue so obtained was purified by column chromatography (hexane as an eluent) and afforded the desired product **32a** in 90% yield (32 mg)



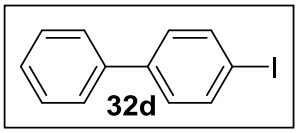
Biphenyl (32a). White solid, 32 mg, Yield 90%, mp 67-68 °C (lit[100] 67-69 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (d, J = 7.8 Hz, 4H), 7.48 (t, J = 7.6 Hz, 4H), 7.38 (t, J = 7.3 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 141.3, 128.8, 127.3, 127.2. MS (ESI) *m/z* calcd for $C_{12}H_{11}$ $(M+H)^+$ 155.0, found 155.0.



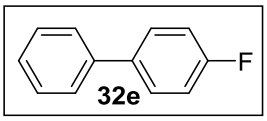
4-Methyl-biphenyl (**32b**). White solid, 32 mg, Yield 85%, mp 46-47 °C (lit[101-103] 47-49 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, J = 8.2 Hz, 2H), 7.53 (d, J = 8.1 Hz, 2H), 7.45 (t, J = 7.7 Hz, 2H), 7.37 (t, J = 8.0 Hz, 1H), 7.28 (d, J = 7.8 Hz, 2H), 2.43 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 141.1, 138.3, 137.0, 129.5, 128.7, 127.03, 127.01, 21.1. MS (ESI) *m/z* calcd for $C_{13}H_{13}$ $(M+H)^+$ 169.0, found 169.0.



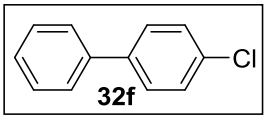
4-*tert*-butyl-biphenyl (32c). White solid, 37 mg, Yield 87%, mp 47-48 °C (lit[104-106] 48-49 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (d, J = 7.8 Hz, 2H), 7.59 (d, J = 8.0 Hz, 2H), 7.51-7.44 (m, 4H), 7.35 (t, J = 8.0 Hz, 1H), 1.39 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 149.9, 141.0, 138.1, 128.6, 127.0, 126.7, 126.6, 125.6, 34.5, 31.2. MS (ESI) *m/z* calcd for $C_{16}H_{19}$ $(M+H)^+$ 211.1, found 211.0.



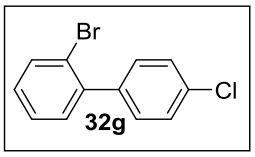
4-Iodo-biphenyl (32d). White solid, 44 mg, Yield 89%, mp 108-109 °C (lit [107]107-108 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 7.78 (m, 2H), 7.59 – 7.57 (m, 2H), 7.48-7.45 (m, 2H), 7.39-7.28 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 140.7, 140.0, 137.8, 129.0, 128.9, 127.8, 126.9, 93.0. MS (ESI) *m/z* calcd for $C_{12}H_{10}I$ $(M+H)^+$ 281.0, found 281.0.



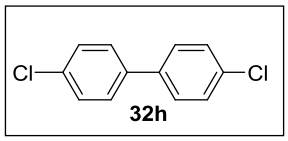
4-Fluoro-biphenyl (**32e**). White solid, 34 mg, Yield 89%, mp 68-69 °C (lit[108, 109] 69-70 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 – 7.52 (m, 4H), 7.49 – 7.45 (m, 2H), 7.40 – 7.38 (m, 1H), 7.19 – 7.13(m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.6 (d, ^{1}J = 245 Hz), 140.2, 137.3 (d, ^{4}J = 3.2 Hz), 128.8, 128.7 (d, ^{3}J = 8.7 Hz), 127.2, 127.1, 115.5 (d, ^{2}J = 21.5 Hz). MS (ESI) *m/z* calcd for $C_{12}H_{10}F$ $(M+H)^+$ 173.1, found 173.0.



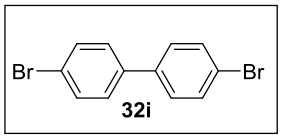
4-Chloro-biphenyl (32f). White solid, 32 mg, Yield 86%, mp 76-78 °C (lit[110] 77- 78 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 – 7.53 (m, 4H), 7.50 – 7.44 (m, 5H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 140.0, 138.4, 133.7, 129.0, 128.8, 128.2, 127.5, 126.9. MS (ESI) *m/z* calcd for $C_{12}H_{10}Cl$ $(M+H)^+$ 189.0, found 189.0.



2-Bromo-4'-chloro-biphenyl (32g).[111] Colourless liquid, 27 mg, Yield 55%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (d, *J* = 8.0 Hz, 1H), 7.49 – 7.42 (m, 4H), 7.39 – 7.36 (m, 2H), 7.27 – 7.23 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 141.3, 139.4, 133.7, 133.2, 131.1, 130.7, 129.0, 128.2, 127.5, 122.5. MS (ESI) *m/z* calcd for $C_{12}H_9BrCl$ $(M+H)^+$ 266.9, found 266.9

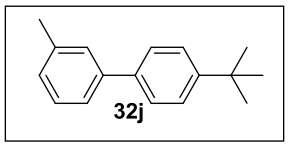


4,4'-Dichloro-biphenyl (32h). Colourless solid, 40 mg, Yield 91%, mp 146-147 °C (lit[112] 147-149 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, *J* = 8.7 Hz, 4H), 7.43 (d, *J* = 8.7 Hz, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.4, 133.7, 129.0, 128.2. MS (ESI) *m/z* calcd for $C_{12}H_9Cl_2$ $(M+H)^+$ 223.0, found 223.0.

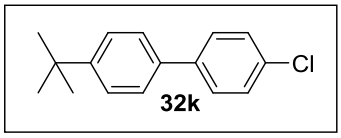


4,4'-Dibromo-biphenyl (32i). White solid, 47mg, Yield 90%, mp 166-168 °C (lit[113] 168-169 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, *J* =

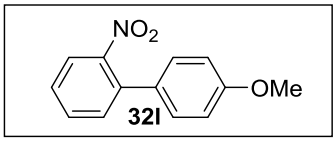
8.6 Hz, 4H), 7.44 (d, *J* = 8.6 Hz, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.9, 132.0, 128.5, 121.9. MS (ESI) *m/z* calcd for $C_{12}H_9Br_2$ $(M+H)^+$ 311.0, found 311.0.



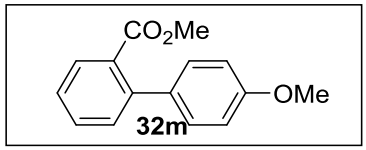
3-Methyl-4'-*t*-butyl-biphenyl (32j). Light brown solid, 40 mg, Yield 90%, mp 75-76 °C (lit[114] 77-78 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, *J* = 8.6 Hz, 2H), 7.54 – 7.49 (m, 2H), 7.45 (d, *J* = 8.6 Hz, 2H), 7.39 (d, *J* = 7.3 Hz, 1H), 7.23 – 7.19 (m, 1H), 2.48 (s, 3H), 1.42 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 149.9, 141.1, 138.4, 137.1, 128.6, 127.8, 127.7, 126.7, 125.6, 124.1, 34.4, 31.4, 21.6. MS (ESI) *m/z* calcd for $C_{17}H_{21}$ $(M+H)^+$ 225.2, found 225.1.



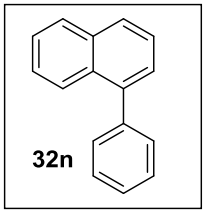
4-Chloro-4'-*t*-butyl-biphenyl (32k). White solid, 40 mg, Yield 86%, mp 124-126 °C (lit[115] 123-124 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 – 7.49 (m, 4H), 7.45 – 7.41 (m, 4H), 1.39 (s, 9H).^{13}C NMR (101 MHz, $CDCl_3$) δ 150.7, 138.4, 133.7, 129.0, 128.8, 128.2, 126.6, 125.8, 34.5, 31.3. MS (ESI) *m/z* calcd for $C_{16}H_{18}Cl$ $(M+H)^+$ 245.1, found 245.1.



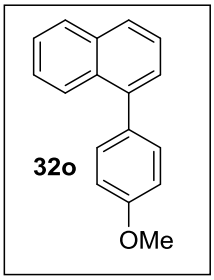
4-Methoxy-2'-nitro-biphenyl (32l). Yellow solid, 27 mg, Yield 60%, mp 60 °C (lit[93] 61-62 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (d, *J* = 8.1 Hz, 1H), 7.64 – 7.59 (m, 1H), 7.47 (t, *J* = 8.1 Hz, 2H), 7.27 (d, *J* = 8.1 Hz, 2H), 6.98 (d, *J* = 8.1 Hz, 2H), 3.87 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.6, 149.4, 135.8, 132.1, 131.9, 129.4, 129.1, 127.7, 124.0, 114.2, 55.3. MS (ESI) *m/z* calcd for $C_{13}H_{12}NO_3$ $(M+H)^+$ 230.1, found 230.1.



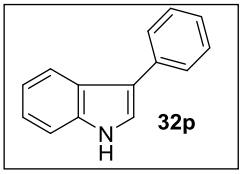
Methyl-4'-methoxy(1,1'-biphenyl)-2-carboxylate (32m).[116] Colourless oil, 30 mg, Yield 65%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, *J* = 7.5 Hz, 1H), 7.53 (d, *J* = 7.6 Hz, 1H), 7.42-7.37 (m, 2H), 7.26 (d, *J* = 8.8 Hz 2H), 6.96 (d, *J* = 8.8 Hz, 2H), 3.87 (s, 3H), 3.69 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.4, 158.9, 142.0, 131.2, 130.8, 130.7, 129.7, 129.4, 126.8, 113.4, 55.2, 52.0. MS (ESI) *m/z* calcd for $C_{15}H_{15}O_3$ $(M+H)^+$ 243.1, found 243.1



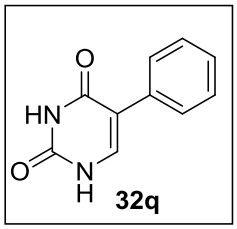
1-Phenyl-naphthalene (32n).[101] Colourless oil, 36 mg, Yield 75%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, *J* = 8.2 Hz, 2H), 7.93 (d, *J* = 8.2 Hz, 1H), 7.61 – 7.54 (m, 6H), 7.52 – 7.48 (m, 3H).^{13}C NMR (101 MHz, $CDCl_3$) δ 140.8, 140.3, 133.8, 131.6, 130.1, 128.8, 128.3, 127.6, 127.2, 126.9, 126.0, 125.8, 125.4. MS (ESI) *m/z* calcd for $C_{16}H_{13}$ $(M+H)^+$ 205.1, found 205.1.



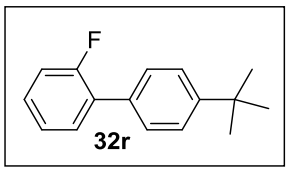
1-(4-Methoxyphenyl)naphthalene (32o). White solid, 27 mg, Yield 80%, mp 115-116 °C (lit[113] 116-117 °C). ^{1}H NMR (400 MHz, CDCl3) δ 7.99 – 7.92 (m, 2H), 7.88 (d, *J* = 8.2 Hz, 1H), 7.57 – 7.44 (m, 6H), 7.08 (d, *J* = 8.8 Hz, 2H), 3.93 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.9, 139.9, 133.8, 133.1, 131.8, 131.1, 128.2, 127.3, 126.9, 126.0, 125.9, 125.7, 125.4, 113.7, 55.3.



3-Phenylindole (32p). White solid, 27 mg, Yield 70%, mp 86 °C (lit[117a] 85-87 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (s, 1H), 8.04 (d, *J* = 7.8 Hz, 1H), 7.77 – 7.71 (m, 2H), 7.56 – 7.50 (m, 2H), 7.46 (d, *J* = 7.7 Hz, 1H), 7.38 (dd, *J* = 5.0, 2.4 Hz, 2H), 7.29 – 7.26 (m, 2H).^{13}C NMR (101 MHz, $CDCl_3$) δ 136.6, 135.5, 129.7, 128.8, 126.0, 122.4, 121.9, 120.3, 119.8, 118.3, 115.2, 111.5. MS (ESI) *m/z* calcd for $C_{14}H_{12}N$ $(M+H)^+$ 194.1, found 194.1.

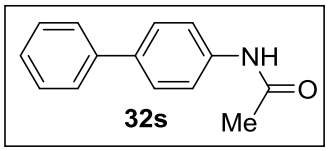


5-Phenyluracil (32q). White solid, 25 mg, Yield 50%, mp 250 °C (lit[118a] 250 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ ^{1}H NMR (400 MHz, $CDCl_3$) δ 11. 28 (s, 1H), 11.18 (s, 1H). 7.62 (s, 1H), 7.55 (d, *J* = 7.4 Hz, 2H), 7.38 (t, *J* = 7.2 Hz 2H), 7.29 (t, *J* = 7.2 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.8, 151.1, 140.1, 133.7, 128.4, 128.4, 127.4, 112.8.

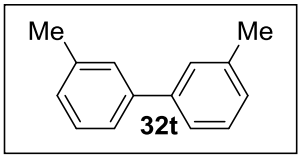


2-Fluoro-4'-*t*-butyl-biphenyl (32r). White solid, 35 mg, Yield 80%, mp 71 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 – 7.53 (m, 4H), 7.52 – 7.48 (m, 4H), 1.40 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.0 (d, ^1J

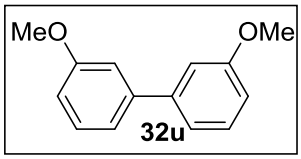
= 240 Hz), 150.6, 149.9, 138.2, 130.7 (d, ^4J = 4 Hz), 128.6 (d, ^3J = 6 Hz,), 126.6, 125.6, 125.4, 124.3, 116.1(d, ^2J = 23 Hz), 34.5, 31.4. HRMS (ESI) *m/z* calcd for $C_{16}H_{18}F$ $(M+H)^+$ 229.1314, found 229.1317



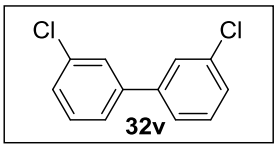
***N*-biphenyl-4-yl-aceatmide (32s)**. Light brown solid, 30 mg, Yield 82%, mp 158 °C (lit[119] 158-159 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (s, 1H), 7.63 – 7.54 (m, 6H), 7.45 (t, *J* = 7.6 Hz, 2H), 7.35 (t, *J* = 7.3 Hz, 1H), 2.22 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.7, 140.4, 137.2, 132.1, 128.8, 127.5, 127.1, 126.8, 120.3, 24.6.



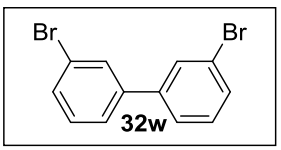
3,3'-Dimethylbiphenyl (32t).[120] Colourless oil, 28 mg, Yield 75%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (d, *J* = 8.4 Hz, 4H), 7.40 – 7.33 (m, 2H), 7.20 (d, *J* = 7.4 Hz, 2H), 2.46 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 141.3, 138.2, 128.6, 128.0, 127.9, 124.3, 21.5. MS (ESI) *m/z* calcd for $C_{14}H_{15}$ $(M+H)^+$ 183.1, found 183.1.



3,3'-Dimethoxybiphenyl (32u).[100] Colourless oil, 30 mg, Yield 70%. 1H NMR (400 MHz, $CDCl_3$) δ 7.39 (t, *J* = 7.9 Hz, 2H), 7.22 (dd, *J* = 7.6, 1.6 Hz, 2H), 7.15-7.13 (m, 2H), 6.95 (dd, *J* = 8.0, 1.4 Hz, 2H), 3.89 (s, 6H).^{13}C NMR (101 MHz, $CDCl_3$) δ 159.8, 142.6, 129.7, 119.7, 112.9, 112.8, 55.3. MS (ESI) *m/z* calcd for $C_{14}H_{15}O_2$ $(M+H)^+$ 215.1, found 215.1.

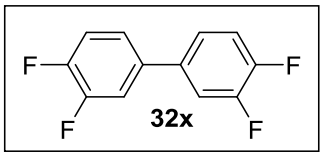


3,3'-Dichloro-biphenyl (32v). Colourless solid, 36 mg, Yield 82%, mp 30-31 °C (lit[121] 30-32 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, *J* = 4 Hz, 2H), 7.48 – 7.45 (m, 2H), 7.42 – 7.35 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 141.6, 134.8, 130.1, 127.8, 127.2, 125.2. MS (ESI) *m/z* calcd for $C_{12}H_9Cl_2$ $(M+H)^+$ 222.0, found 222.0

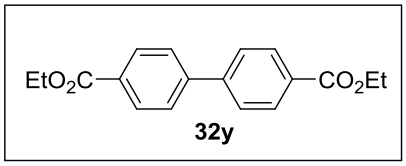


3,3'-Dibromo-biphenyl (32w).[122] Yellow oil, 40 mg, Yield 80%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (t, *J* = 1.8 Hz, 2H), 7.54 – 7.48 (m, 4H), 7.34 (t, *J* = 7.8 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 141.7, 130.8,

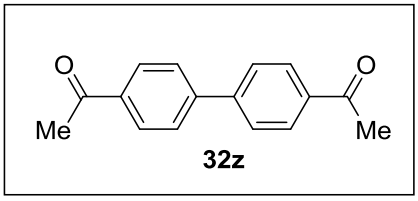
130.4, 130.1, 125.7, 123.0. MS (ESI) *m/z* calcd for $C_{12}H_9Br_2$ $(M+H)^+$ 310.9, found 310.9.



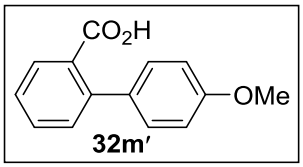
3,3',4,4'-Tetrafluoro-1,1'-biphenyl (32x). Colourless solid, 34 mg, Yield 78%, mp 80-82 °C (lit[123] 80-82 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.31 (m, 2H), 7.28 – 7.24 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.0, 151.7, 151.6, 151.3, 149.6, 149.5, 149.2, 149.0, 136.5, 122.97, 122.95, 122.91, 117.8, 117.7, 116.09, 116.02. MS (ESI) *m/z* calcd for $C_{12}H_7F_4$ $(M+H)^+$ 227.0, found 227.0.



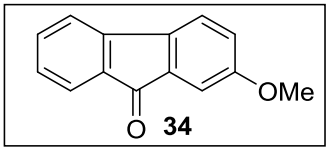
4,4'-Dicarbethoxybiphenyl (32y). White solid, 43 mg, Yield 80%, mp 221-223 °C (lit[100] 223-224 °C). IR (KBr, υ cm^{-1}) 3001, 2947, 1718, 1582. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (d, *J* = 8.5 Hz, 4H), 7.71 (d, *J* = 8.5 Hz, 4H), 4.44 (q, *J* = 7.1 Hz, 4H), 1.44 (t, *J* = 7.1 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.3, 144.3, 130.1, 130.0, 127.2, 61.1, 14.3. MS (ESI) *m/z* calcd for $C_{18}H_{19}O_4$ $(M+H)^+$ 299.1, found 299.1.



4-4'-Diacetylbiphenyl (32z). White solid, 28 mg, Yield 75%, mp 193-194 °C (lit[124] 194-195 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (d, *J* = 8.4 Hz, 4H), 7.75 (d, *J* = 8.4 Hz, 4H), 2.68 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 197.6, 144.3, 136.5, 129.0, 127.4, 26.7.

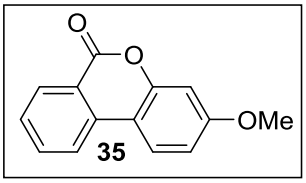


4-Methoxy-2'-biphenylcarboxylic acid (32m'). Light brown solid, 50 mg**,** Yield 90%, mp 141-142 °C (lit[125] 140-142 °C); IR (KBr, υ cm^{-1}) 3780, 2950, 1715, 1607.^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, *J* = 8.8 Hz, 1H), 7.59-7.55 (m, 1H), 7.44 – 7.37 (m, 2H), 7.30 (d, *J* = 8.7 Hz, 2H), 6.95 (d, *J* = 8.7 Hz, 2H), 3.87 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.5, 159.1, 142.8, 133.3, 132.0, 131.1, 130.6, 129.6, 129.3, 126.8, 113.6, 55.2. MS (ESI) *m/z* calcd for $C_{14}H_{13}O_3$ $(M+H)^+$ 229.1, found 229.1.

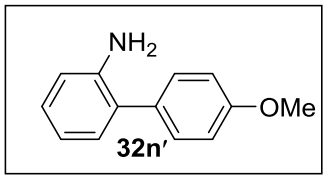


2-Methoxy-9-fluorenone (34). Yellow solid, 35 mg, Yield 75%, mp 73-74 °C (lit[126] 72-74 °C); IR (KBr, υ cm^{-1}) 2924, 1713, 1605, 1466,

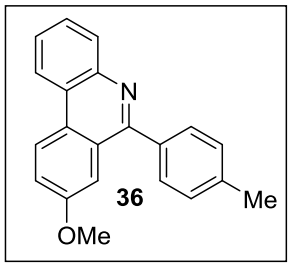
1203, 1080**.** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (d, *J* = 8.1 Hz, 1H), 7.47 – 7.41 (m, 3H), 7.24 – 7.20 (m, 2H), 7.01 (dd, *J* = 8.2, 2.5 Hz, 1H), 3.88 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 193.9, 160.8, 144.8, 137.0, 135.9, 134.8, 134.3, 127.8, 124.3, 121.3, 120.3, 119.5, 109.3, 55.7. MS (ESI) *m/z* calcd for $C_{14}H_{11}O_2$ $(M+H)^+$ 211.1, found 211.1.



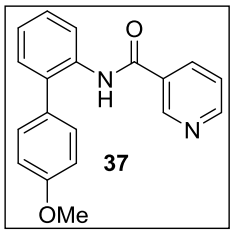
3-Methoxy-6H-benzo[*c*]chromen-6-one (35).[127] Brown solid, 20 mg, Yield 60%, mp 124-125 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.39 (d, *J* = 8.0 Hz, 1H), 8.04 (d, *J* = 8.2 Hz, 1H), 7.98 (d, *J* = 8.3 Hz, 1H), 7.85 – 7.79 (m, 1H), 7.54 (t, *J* = 7.6 Hz, 1H), 6.97 – 6.88 (m, 2H), 3.92 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.1, 160.1, 153.4, 135.6, 134.9, 130.3, 127.6, 123.6, 121.1,119.6, 112.5, 111.3, 101.3, 55.7. MS (ESI) *m/z* calcd for $C_{14}H_{11}O_3$ $(M+H)^+$ 227.1, found 227.1.



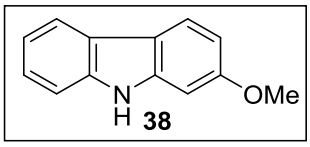
4-Methoxy-2'-amino-biphenyl (32n').[128] Yellow liquid, 45 mg, Yield 89%, IR (KBr, υ cm^{-1}) 3418, 2924, 2854. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (d, *J* = 8.8 Hz, 2H), 7.23 – 7.17 (m, 2H), 7.05 (d, *J* = 8.8 Hz, 2H), 6.89 (dd, *J* = 11.7, 4.3 Hz, 1H), 6.81 (d, *J* = 7.9 Hz, 1H), 3.91 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.8, 143.7, 131.83, 130.5, 130.2, 128.2, 127.4, 118.6, 115.5, 114.2, 55.3. HRMS (ESI) *m/z* calcd for $C_{13}H_{14}NO$ $(M+H)^+$ 200.0997, found 200.0998.



8-Methoxy-6-(tolyl)phenanthiridine (36). Yellow solid 25 mg, Yield 60%, mp 120-122 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.65 (s, 1H), 8.55 (d, *J* = 7.8 Hz, 1H), 8.23 (d, *J* = 9.0 Hz, 1H), 7.68 (d, *J* = 8.1 Hz, 3H), 7.53 (d, *J* = 4.3 Hz, 1H), 7.40 – 7.38 (m, 2H), 7.31 (d, *J* = 8.6 Hz, 2H), 3.87 (s, 3H), 2.50 (s, 3H).^{13}C NMR (101 MHz, $CDCl_3$) δ 160.3, 158.0, 144.9, 138.5, 137.0, 130.2, 130.1, 129.4, 129.1, 128.4, 127.7, 126.8, 123.8, 121.4, 120.9, 114.8, 109.0, 55.5, 21.4. HRMS (ESI) *m/z* calcd for $C_{21}H_{18}NO$ $(M+H)^+$ 300.1310, found 300.1311.



***N*-(4'-Methoxybiphenyl-2-yl)nicotinamide (37)**. Yellow solid, 30 mg, Yield 90%, mp 111 °C. IR (KBr, υ cm^{-1}) 3418, 3063, 2962, 1659, 1589, 1520. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.80 – 8.71 (m, 2H), 8.45 (s, 1H), 8.08 (d, *J* = 8.5 Hz, 2H), 7.31 – 7.22 (m, 6H), 7.04 (d, *J* = 8.5 Hz, 2H), 3.88 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.1, 159.5, 152.3, 147.5, 135.2, 134.5, 132.4, 130.4, 130.3, 129.7, 128.3, 124.8, 123.7, 121.3, 114.7, 55.3. HRMS (ESI) *m/z* calcd for $C_{19}H_{17}N_2O_2$ $(M+H)^+$ 305.1212, found 305.1211.



2-Methoxy-9*H*-carbazole (38). White solid, 25 mg, Yield 75%, mp 232-234 °C (lit[129] 233-235 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.28 (s, 1H), 7.90 – 7.80 (m, 2H), 7.34 (d, *J* = 8.1 Hz, 1H), 7.27 (dd, *J* = 8.8, 5.0 Hz, 1H), 7.08 (d, *J* = 4.5 Hz, 1H), 6.87 (d, *J* = 5.3 Hz, 1H), 6.77 – 6.72 (m, 1H), 3.83 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.8, 141.0, 139.7, 124.2, 123.2, 120.7, 119.2, 118.9, 116.9, 110.4, 107.7, 94.6, 55.5. MS (ESI) *m/z* calcd for $C_{13}H_{12}NO$ $(M+H)^+$ 198.1, found 198.1.

3.3 References

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Chapter IV

Formation of C-C and C-O bonds

Part A: Decarboxylative C2-arylation of indoles

Part B: Preparation of heteroaryl carboxylates

4.1 Part A: Decarboxylative C2-arylation of indoles

4.1.1 Introduction

Carboxylic acid is an ubiquitous functional group present in amino acids, drug molecules and organic materials.[1] It has been recognized as a versatile building block for various functional group transformations. They are stable, commercially available and do not require any precautions to handle. In recent years, carboxylic acids have been converted into various valuable products by using metal-catalyzed approaches.[2] In 2006, Goossen[3] co-workers performed a pioneering work on metal-catalyzed decarboxylative approach to construct new C-C bond between *o*-nitrobenzoic acid and aryl bromides. The reaction involved palladium/copper catalytic system to produce biaryls. In this reaction copper salt was used to decarboxylate the acid and palladium catalyst to promote the cross-coupling reaction. The key step in decarboxylative strategy is the reaction of carboxylic acid with suitable metal to produce reactive carbometallated species **2** with the expulsion of carbon dioxide, which acts like organometallic species.[4] So it can be a better alternative to the expensive traditional organometallic reagents like boronic acids, Grignard and tin reagents.

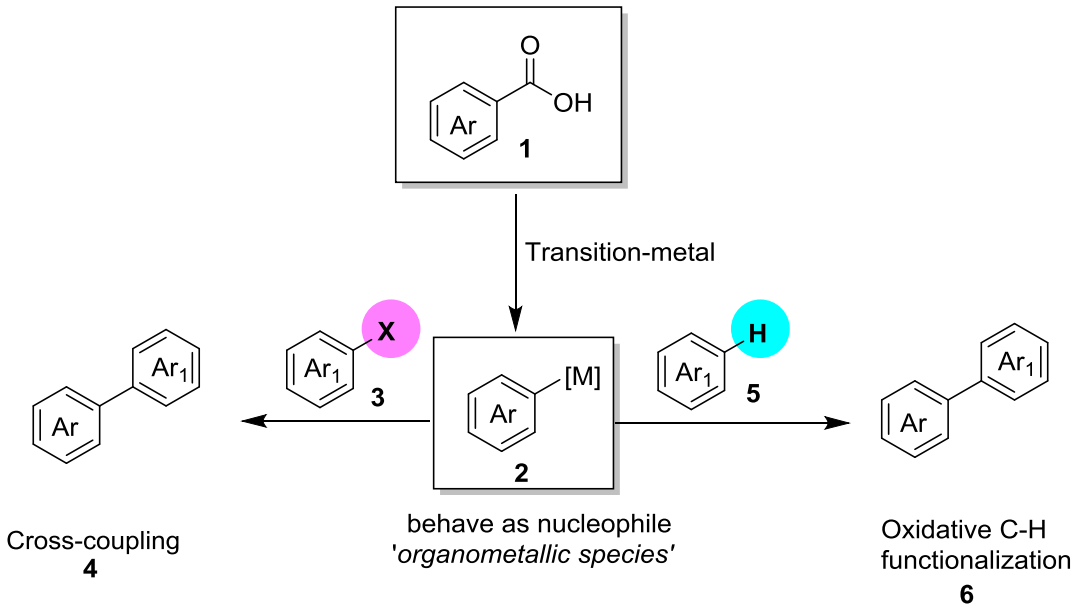


Figure 4.1.1 General reactivity patterns of decarboxylative couplings

Another prime advantage of decarboxylative coupling is release of innocuous carbon dioxide as the only byproduct that minimizes the waste generated during the reaction. Generally, decarboxylative reactions are proceeded *via* either decarboxylative cross-coupling reactions **4** and oxidative C-H functionalizations **6** where the reactive species **2** react with aryl halides **3** and in later case it is coupled with arenes **5** (Figure 4.1.1).[5]

In most of the decarboxylative approaches palladium catalyst is paired with stoichiometric amount of copper or silver salt to promote decarboxylation. Based on the catalyst system carboxylic acid behaves as synthetic equivalents of aryl, acyl or aryl halides or organometallic reagents.[6] Owing to high significance of metal-catalyzed decarboxylative strategies, enormous progress has been achieved to assemble variety of C-C, C-O, C-S, C-P and C-N bonds.[7-9] As a result, a variety of innovative catalytic combinations are evolved to achieve the desired products using decarboxylative coupling strategy and many impressive reaction pathways are proposed to understand the new catalytic transformations

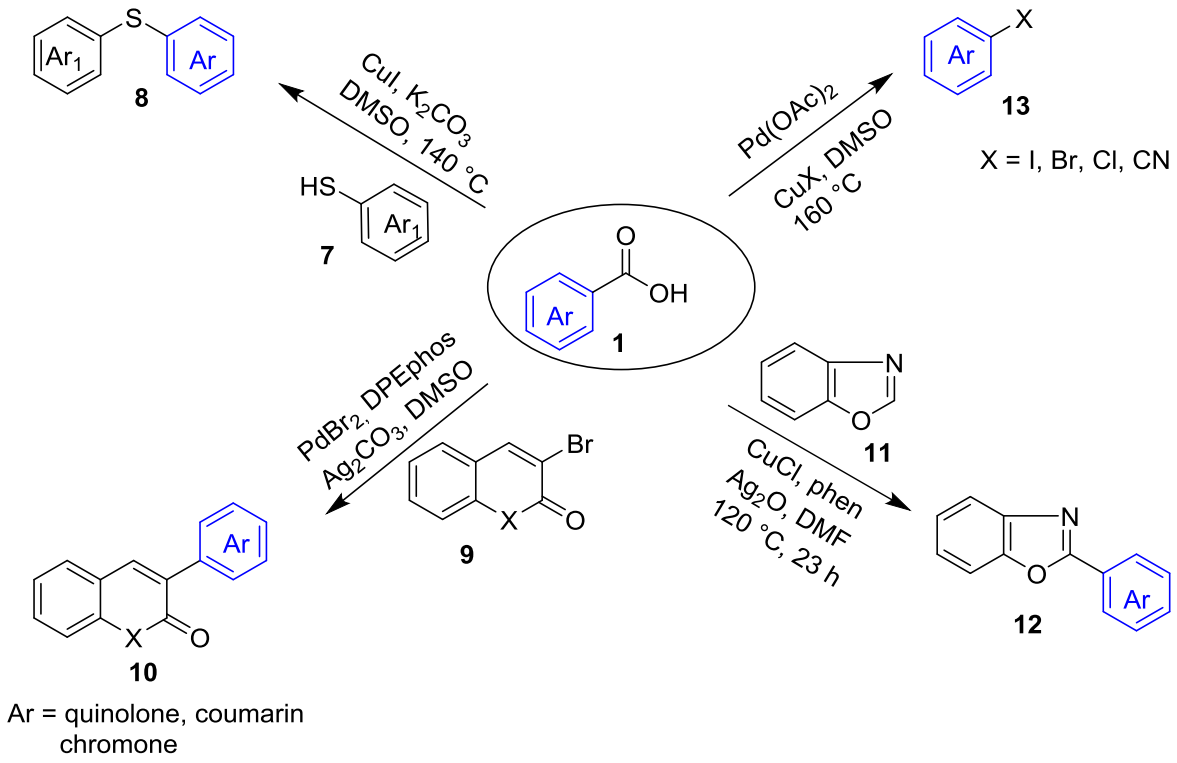


Figure 4.1.2 Some recent examples of decarboxylative arylation reactions

In 2016, Li and Hoover[10] disclosed a copper-catalyzed decarboxylative coupling strategy between thiols **7** and aromatic carboxylic acids **1** to furnish diaryl sulfides **8** in good yields. Alami and his group[11] demonstrated an efficient decarboxylative cross-coupling reaction between heterocyclic carboxylic acid **1** and heteroaryl halides **9** using $PdBr_2$/DPEphos catalytic system. This protocol furnished bis(heterocycles) **10** based on coumarins, chromones, quinolin-4-ones and quinolin-2-ones in good yields. An efficient copper-catalyzed decarboxylative C-H arylation of benzoxazoles **11** was established by Hoover and his co-workers.[12] This transformations was well tolerated by diverse electron-rich benzoxazoles and electron-deficient acids and afforded 2-arylbenzoxazoles **12** in good to excellent yields. Cai et al.[13] described an operationally simple procedure to access haloarenes **13** by employing easily available aryl carboxylic acids, $Pd(OAc)_2$ and copper halides. Here, copper halides behaved as halide sources for the reaction (Figure 4.1.2).

4.1.2 Carboxylic acid as traceless directing group

Nowadays, directing group-assisted C-H functionalization is one of the promising organic tools for the chemists to assemble heterocyclic frameworks, molecular materials, polymers and pharmaceutical targets in fewer steps.[14-16] The catalytic functionalization of unreactive C-H bonds into C-C and C-heteroatom bonds are challenging due to selective C-H bond activation over the other C-H bonds in the molecule. For example, in benzene (**14**) it is difficult to discriminate the reactivity between the C-H bonds (Figure 4.1.3).

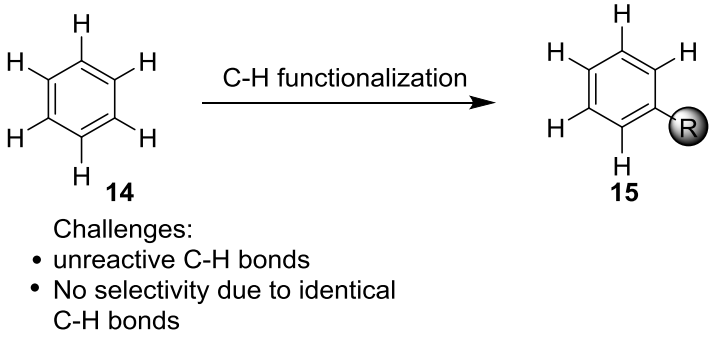


Figure 4.1.3 C-H functionalization

In order to accomplish the selective C-H functionalization in a molecule **15**, incorporate a directing group (functional group or atom) that is talented to coordinate with the metal center and deliver the

catalyst to a proximal C-H bond (Figure 4.1.4).[17] Usually this occurs *via* the formation of thermodynamically favored five or six-membered metallacyclic intermediate. High site-selectivity is due to the accumulation of metal-catalyst at the reaction site. These strategies are generally referred to as directed C-H bond functionalization or directing group-assisted C-H functionalization.[18] In literature there are many directing groups available for the myriad of C-H transformations.

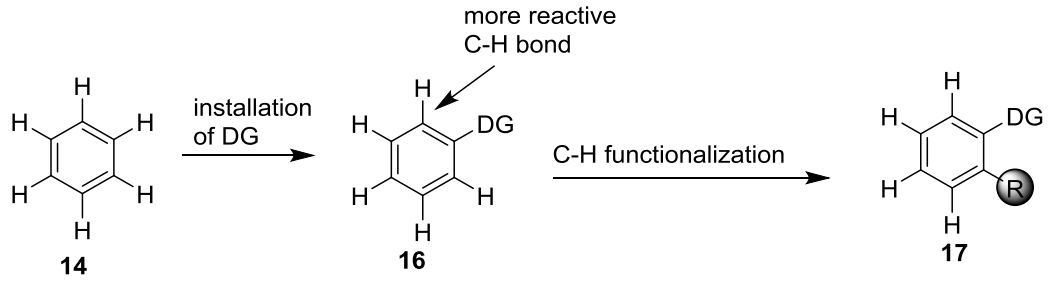


Figure 4.1.4 Incorporation of directing group and C-H functionalization

Amide,[19] pyridine,[20] pyrimidine,[21] aminoquinoline,[22] triazole,[23] and azobenzene,[24] are promising and well studied directing groups. Nevertheless, after C-H functionalization of the substrates **17** using the aforementioned directing groups, next it is mandatory and laborious to remove the directing group from the final products **18**. However, in some cases directing groups are utilized for various synthetic manipulations. In recent years, carboxylic acid **19** is identified as a traceless directing group[25] which means tandem C-H functionalizations and removal of carboxylic acid as

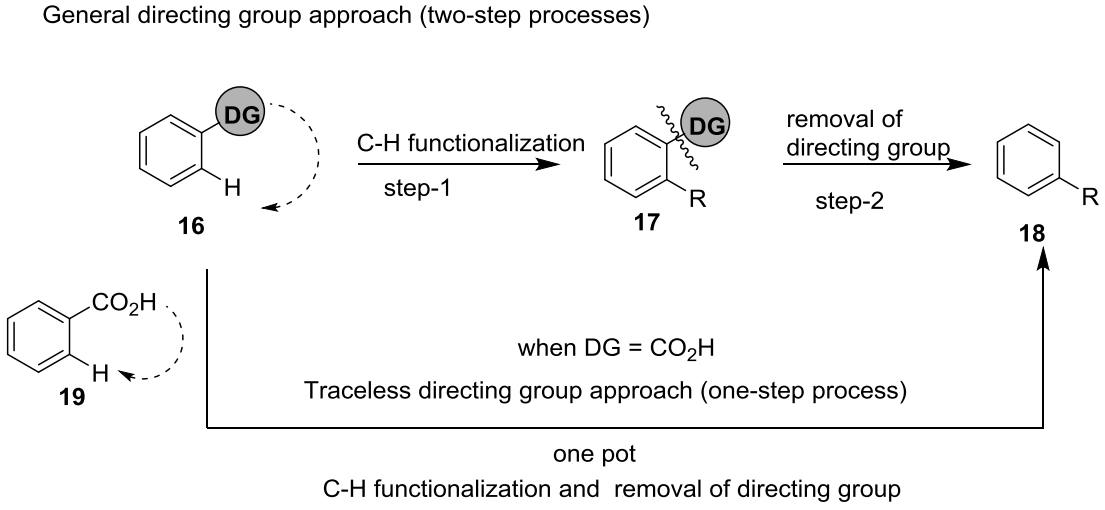


Figure 4.1.5 Difference between general and traceless directing group

carbon dioxide to produce desired ortho functionalized products (Figure 4.1.5). Remarkably this carboxylic acid approach reduces the directing group removal step so that usage and waste generated by the organic reagents and solvents are considerable minimized.

4.1.3 Synthesis of 2-arylindoles using diaryliodonium salts

2-Arylindoles are frequently encountered in many medicinally important molecules, natural products, therapeutic agents, ligands and functional materials (Figure 4.1.6). 3-Formyl-2-arylindole **20** showed promising anticancer activity through tubulin inhibition. Compound **21** which bearing ortho-methoxy substitutent used as a ligand in coupling reactions.[26] 5-Nitro-2-phenylindole (**22)** displayed NorA efflux pump inhibitor property.[27] Bazedoxifene (**23**) is a marketed drug having 2-arylindole as an important pharmacophoric unit.[28] Diamidino-2-phenylindole **24** is a fluorescent molecule which is used in fluorescent microscopy to visualize DNA.[29] GPCR ligand **25** and MDR

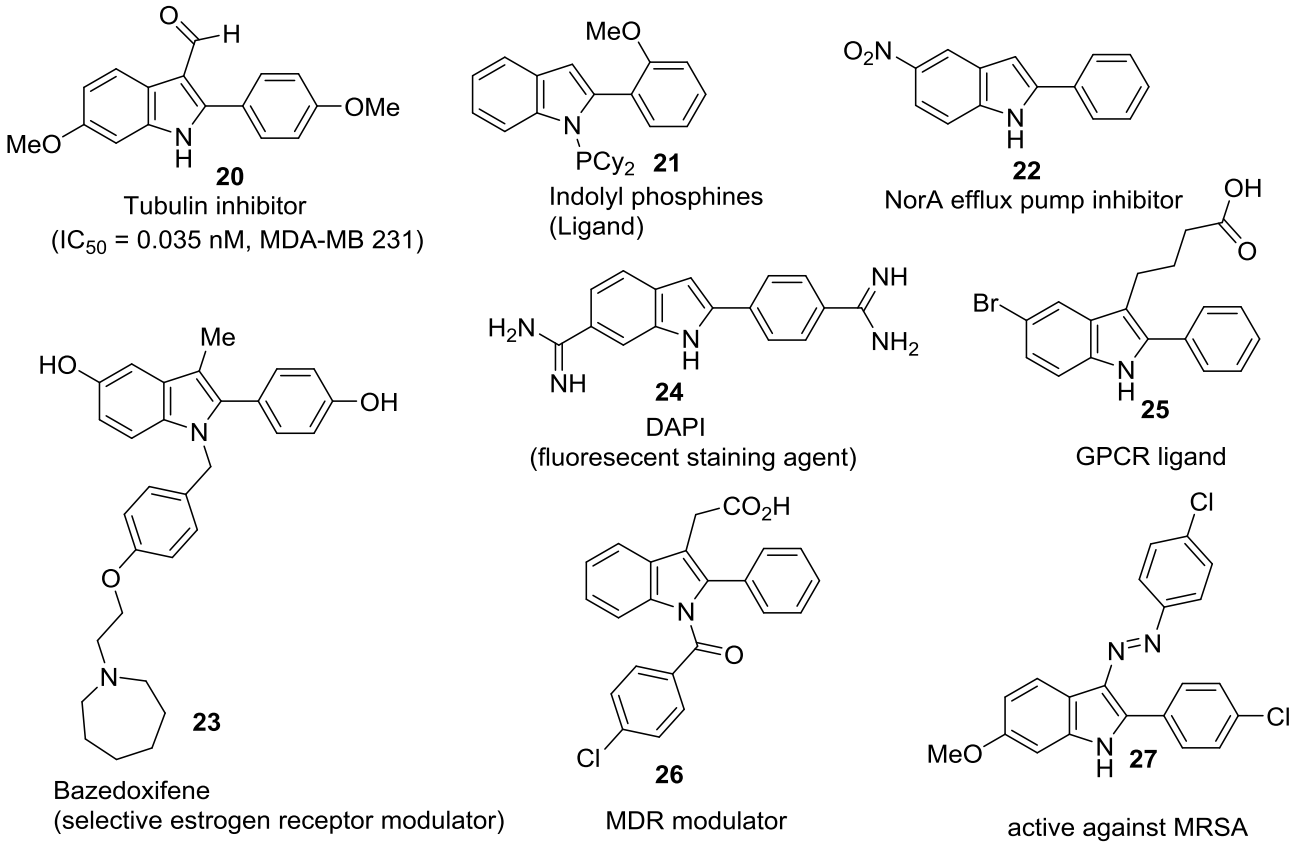
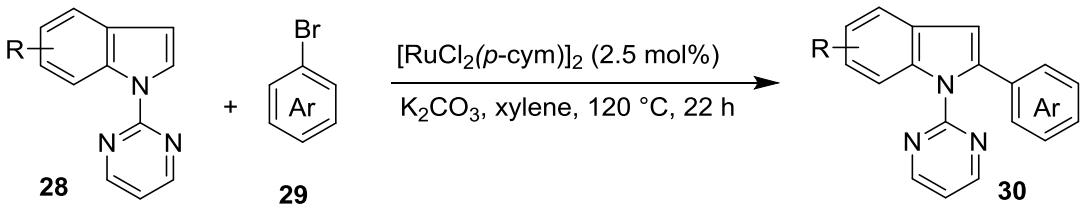


Figure 4.1.6 Examples of medicinally important molecules bearing 2-arylindole skeleton

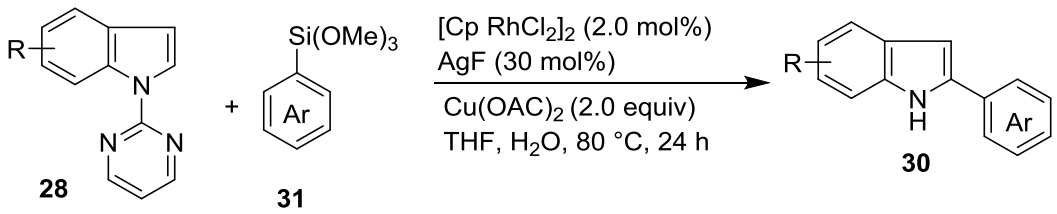
modulator **26** are having C3-carboxylic acid and C2-aryl ring. Compound **26** is an analogue of familiar antiproliferative agent, Indomethacin. Arylazoindole **27** showed potent anti-MRSA activity.[30] Preparation of 2-arylindole and related analogues received considerable attention among the synthetic chemists due to their immense significance in drug discovery. In recent years, metal-catalyzed C-H functionalization strategy provides a feasible and appreciable synthetic routes to access 2-arylindoles. Significant features of the C-H functionalization approaches are to produce the desired molecules in fewer steps, high atom-economy, selective removal of C-H bond and the reaction conditions are well-tolerated by the sensitive functional groups present in the substrates.

In 2011, Ackermann and Login[31] disclosed a ruthenium-catalyzed C2-arylation of indole **30** by employing aryl bromides **29** and a pyrimidine **28** as a removal directing group. The developed reaction condition was suitable to arylate pyrroles and thiophenes (Scheme 4.1.1).



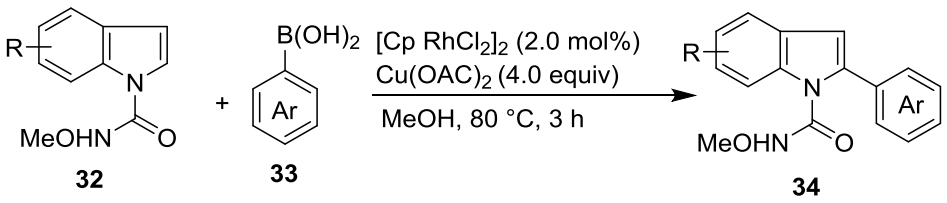
Scheme 4.1.1 Ruthenium-promoted synthesis of 2-arylindoles

A facile rhodium-catalyzed direct C2-arylation of *N*-pyrimidyl(indoles) using arylsilanes **31** as a coupling reagent in aqueous media was developed by Loh et al.[32] Under the identified catalytic conditions, heterocyclic silanes and various substituted indoles were successfully coupled to afford the desired 2-arylindoles **30** in good to excellent yields (Scheme 4.1.2).



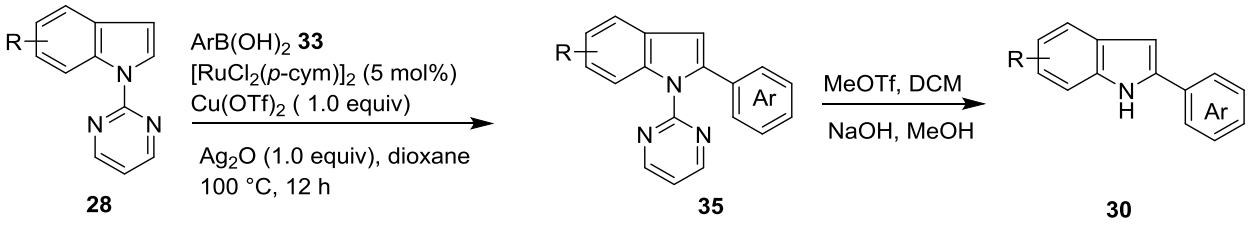
Scheme 4.1.2 Synthesis of 2-arylindoles using arylsilanes

Cui et al.[33] developed an efficient Rh(III)-catalyzed selective coupling reaction of *N*-methoxy-1*H*-indole-1-carboxamide **32** with arylboronic acids **33** to prepare *N*-substituted-2-arylindoles **34** in high yields. The key feature of this protocol is C2-arylation of indoles using carboxamide as a directing group in the presence of rhodium and copper catalysts (Scheme 4.1.3).



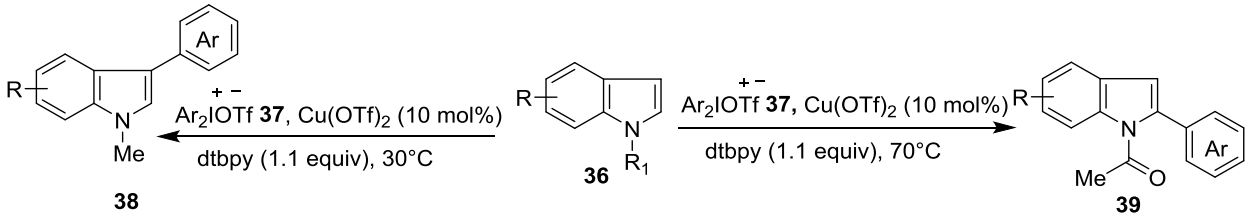
Scheme 4.1.3 Rhodium-catalyzed preparation of 2-arylindoles

Recently, Kapur et al.[34] reported a ruthenium-catalyzed C2- arylation of indoles using aryl boronic acid **33** as an aryl coupling agent and pyrimidine **28** as a removable directing group.Substituted boronic acids (halogens, trifluoromethyl, and nitro) and indoles were well-tolerated under the optimized reaction conditions to produce 2-arylindoles **30** in good-excellent yields (Scheme 4.1.4).



Scheme 4.1.4 Arylation of *N*-pyrimidylindoles

Gaunt and co-workers[35] developed a mild copper-catalyzed regioselective arylations of *N*-protected indoles using diaryliodonium salts. The noteworthy part of this transformation is the formation of C3 arylated indoles in case of indole with free–NH. Conversely, –NH protected indoles directed the incoming aryl group to C2-position and results in 2-arylindoles in good yields (Scheme 4.1.5).



Scheme 4.1.5 Copper-catalyzed regioselective synthesis of 3/2-arylindoles

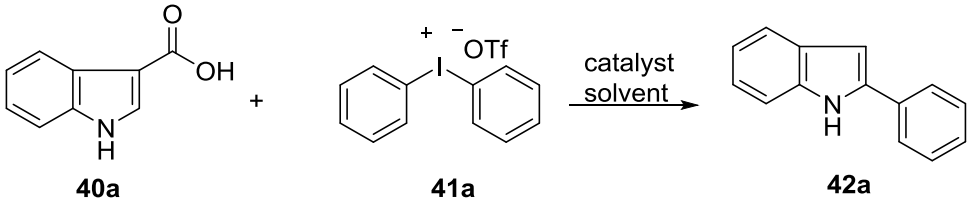
Though there are elegant approaches to prepare 2-arylindoles using directing groups. Incorporation and removal of directing groups are required arduous procedures. In order to improve the reaction conditions by averting ligand, base and oxidant and remove the directing group in one-pot fashion. We envisaged to prepare 2-arylindoles using Pd-catalyzed decarboxylative approach involving diaryliodonium salts as aryl sources. Diaryliodonium salts for being inherently stable solids and easy to access, are frequently used in organic synthesis as highly electrophilic arylating agents to prepare useful natural and bioactive heterocycles.[36-38] Hence, utilities of diaryliodonium salts got groundbreaking advancement for the arylation and assembly of heterocyclic frameworks.[39-48]

4.1.4 Results and discussion

4.1.4.1 Chemistry

We initiated our investigation by indole-3-carboxylic acid (**40a)** and using diphenyliodonium triflate (**41a)** as model substrates (Table 4.1.1). All indole-3-carboxylic acids **40** are prepared from the basic hydrolysis of 3-trifluoroactetyl indole. Diaryliodonium salts **41** are synthesized from the commercially available iodoarenes and arenes in the presence of oxidant *m*CPBA. The decarboxylative arylation of **40a** with **41a** in the presence of 1.0 mol% $Pd(OAc)_2$ in acetic acid generated anticipated 2-phenylindole (**42a)** in 80% yield. To improve the yield of **42a**, different solvents were screened. No product was formed in DMF, whereas, other solvents including 1,4-dioxane, toluene and 1,2-dichloroethane resulted in inferior yield. Gratifyingly, the use of water as a solvent led to **42a** in excellent yield (91%). Water is a superior solvent with satisfactory properties such as non-combustible, non-toxic, cheap and can be handled without any precaution.[49] Moreover, after completion of the reaction, crude product **42a** was easily separated out from the reaction medium (water) as thick oil. Having the optimized reaction conditions in hand (Scheme 4.1.6), scope of diaryliodonium salts and heteroaromatic carboxylic acids was explored. All the diaryliodonium salts were synthesized from the corresponding arenes and iodoarenes.[50] Unsymmetrical iodonium salts possessing electron-withdrawing groups such as ester and nitro, produced the corresponding 2-arylindoles **42b** and **42d** in 85 and 81% yields, respectively (Table 4.1.2). Halogen (chloro) bearing iodonium salt **41c** successfully produced **42c** in 88% yield. Similarly, sterically hindered ortho substituted (OMe, CO_2Me and NO_2) iodonium salts **41e-f**, **2h** also delivered

Table 4.1.1 Optimization of reaction conditions[a]

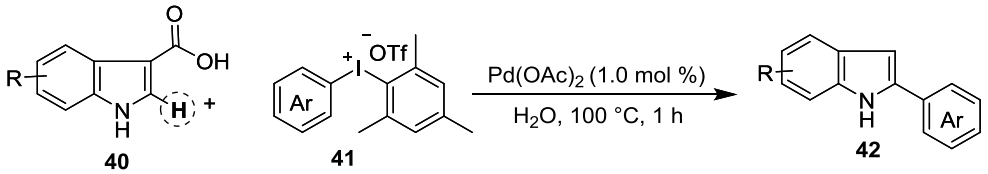


40a **41a** **42a**

Entry	Catalyst (mol %)	Solvent	Time (h)	Yields (%)[c]
1	$Pd(OAc)_2$ (1.0)	AcOH	2	80
2	$Pd(OAc)_2$ (1.0)	1,4-dioxane	2	64
3	$Pd(OAc)_2$ (1.0)	DMF	12	NR
4	$Pd(OAc)_2$ (1.0)	toluene	2	45
5	$Pd(OAc)_2$ (1.0)	DCE	2	66
6	$Pd(OAc)_2$ (1.0)	water	1	91
7[b]	$Pd(OAc)_2$ (1.0)	water	1	91

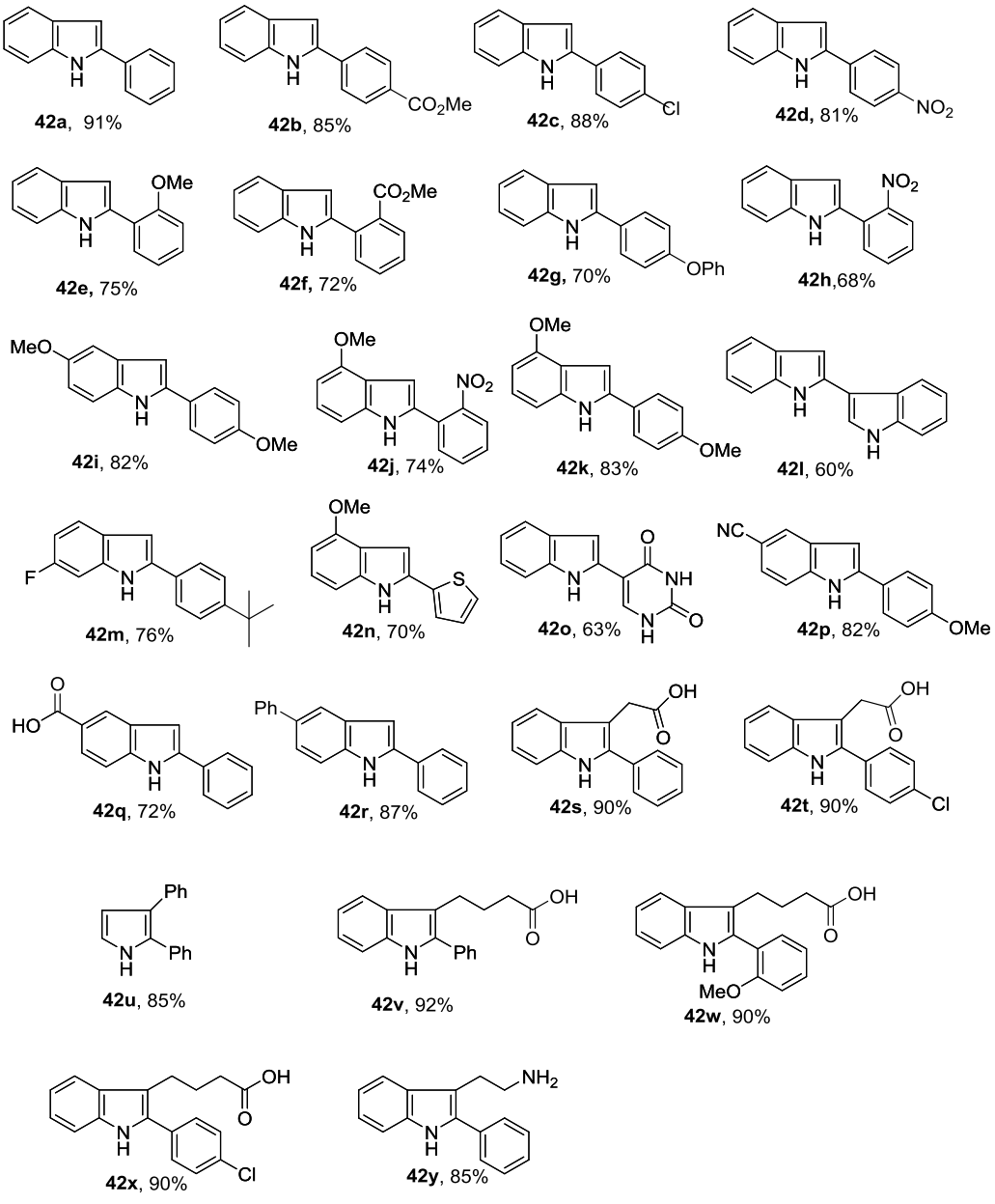
[a]Reaction conditions: **40a** (100 mg, 0.62 mmol), **41a** (267 mg, 0.62 mmol), $Pd(OAc)_2$ (1.0 mol%), 100 °C, [b] used mesityl(phenyl)iodonium salt (0.62 mmol), [c]isolated yields, NR = no reaction.

the anticipated products **42e-f, 42h** and **42j** in high yields (68-75%). Heterocyclic iodonium salts, indole(phenyl)iodonium tosylate (**41j**) and mesityl(thienyl)iodonium triflate (**41k**) also worked well to afford C2-heteroarene motifs **42l** (60%) and **42n** (70%) in good yields. Medicinally important candidate, 2-indolyluracil **42o** was easily obtained from **40a** and mesityl(uracil)iodonium triflate in 63% yield. Biologically important 4/5-methoxy indoles were also successfully arylated to prepare the corresponding 2-aryl-4/5-methoxyindoles **42i** and **42k** in better yields (82%). 4/5-Methoxyindoles are known to display interesting anticancer properties through the inhibition of tubulin. To further widen the scope of this decarboxylative C2-arylation strategy, indole-3,5-dicarboxylic acid **40g** was subjected to optimized reaction conditions. Interestingly, C-5 carboxylic acid remained unreactive and selectively afforded C2-arylated product **42q** in 72% yield. Formation of **42q** suggests activation of C2-position *via* co-ordination of C3-carboxylic acid with palladium.



Scheme 4.1.6 Regioselective synthesis of 2-arylindoles **42a-y**

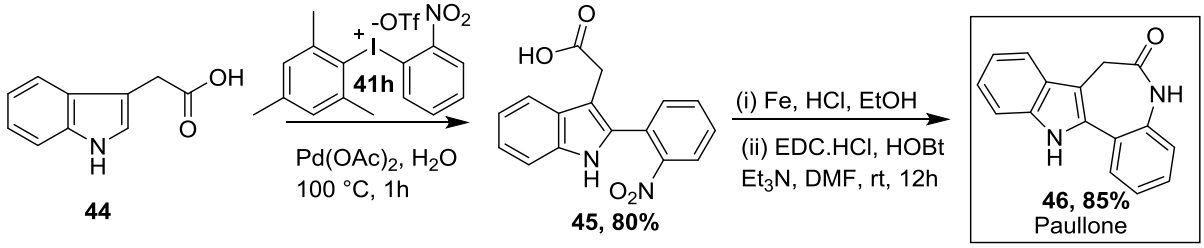
Table 4.1.2 Library of synthesized 2-arylindoles **42a-y**



.In case of pyrrole-3-carboxylic acid, we attained diarylated **42u** rather than monoarylated product. Diarylation of pyrrole-3-carboxylic acid is likely to proceed *via ortho*-arylation followed by *ipso*-arylation. Encouraged by the successful arylation of indole-3-carboxylic acids and diarylation of pyrrole, next analogue indole systems, indole-3-acetic acid, indole-3-butyric acid and tryptamine were examined. Interestingly, carboxylic acid and amine functionalities were successfully directed the incoming iodonium salts to furnish C2-arylated products **42s**-**t** and **42v**-**y** in excellent yields (85-90%). Compounds **42s**-**t** and **42v**-**y** with carboxylic acid and amine moieties could be used for further synthetic manipulation to generate complex bioactive molecules.

4.1.4.2 Synthesis of Paullone

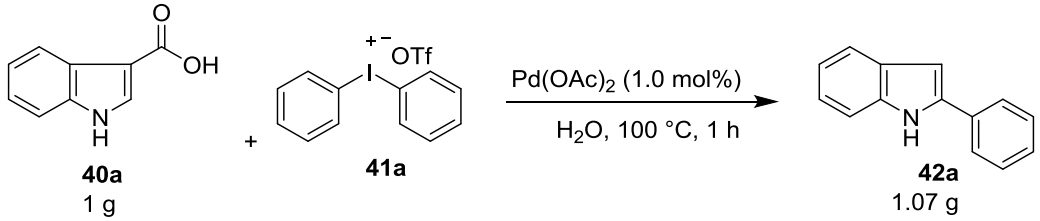
To prove the synthetic utility of identified protocol, we prepared Paullone (**46**), a well-known cyclin-dependent kinase (CDK) inhibitor,[51] in 85% yield from the reaction of indole-3-acetic acid (**44**) and iodonium salt 2h. Aryl intermediate **45** was converted into Paullone (**46**) by reducing the nitro group and followed by amide coupling as depicted in Scheme 4.1.7.



Scheme 4.1.7 Synthesis of CDK-Inhibitor, Paullone

4.1.4.3 Gram-scale synthesis of 2-phenylindole

To demonstrate the scalability of the reaction (Scheme 4.1.8), we successfully isolated **42a** (1.07g) in 90 % yield from the reaction of indole-3-carboxylic acid (**40a**, 1g) with mesityl(phenyl)iodonium salt (**41b)**



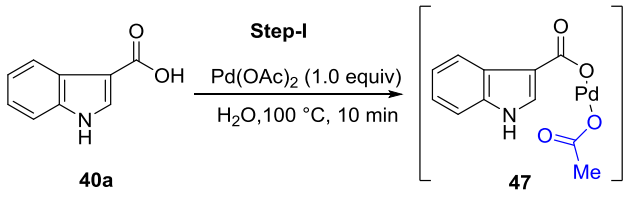
Scheme 4.1.8 Gram-scale synthesis of 2-phenylindole

Generated iodomesitylene during the reaction, was recovered and reused for the synthesis of mesityl(phenyl)iodonium salt (41b) indicating that the developed protocol is highly economical.

4.1.4.4 Mechanistic studies for the formation of 42a

(a) *In situ* generation of Pd(II)carboxylate 47

A suspension of $Pd(OAc)_2$ (69 mg, 0.31 mmol) and indole-3-carboxylic acid (**40a**, 50 mg, 0.31 mmol) in water (5 mL) was refluxed for 10 min, and evaporated the water under reduced pressure (Scheme 4.1.9). The black color solid so obtained was analyzed by obtaining ^{1}H NMR (^{1}H & ^{13}C), IR and Mass spectra as depicted in Figures 4.1.7-4.1.11. Appearance of characteristic peaks at δ 1.91 ppm (–CH_3) in ^{1}H NMR and at δ 172.6 ppm (>C=O) in ^{13}C NMR indicates the formation of Pd(II)carboxylate **47**.



Scheme 4.1.9 Synthesis of Pd(II)carboxylate **47**

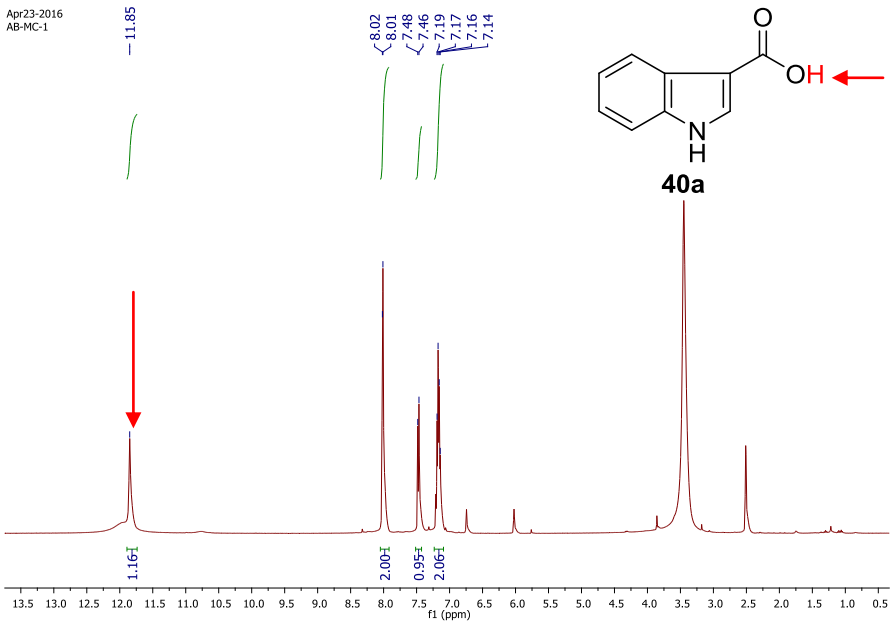


Figure 4.1.7 ^{1}H NMR spectrum of indole-3-carboxylic acid **40a**

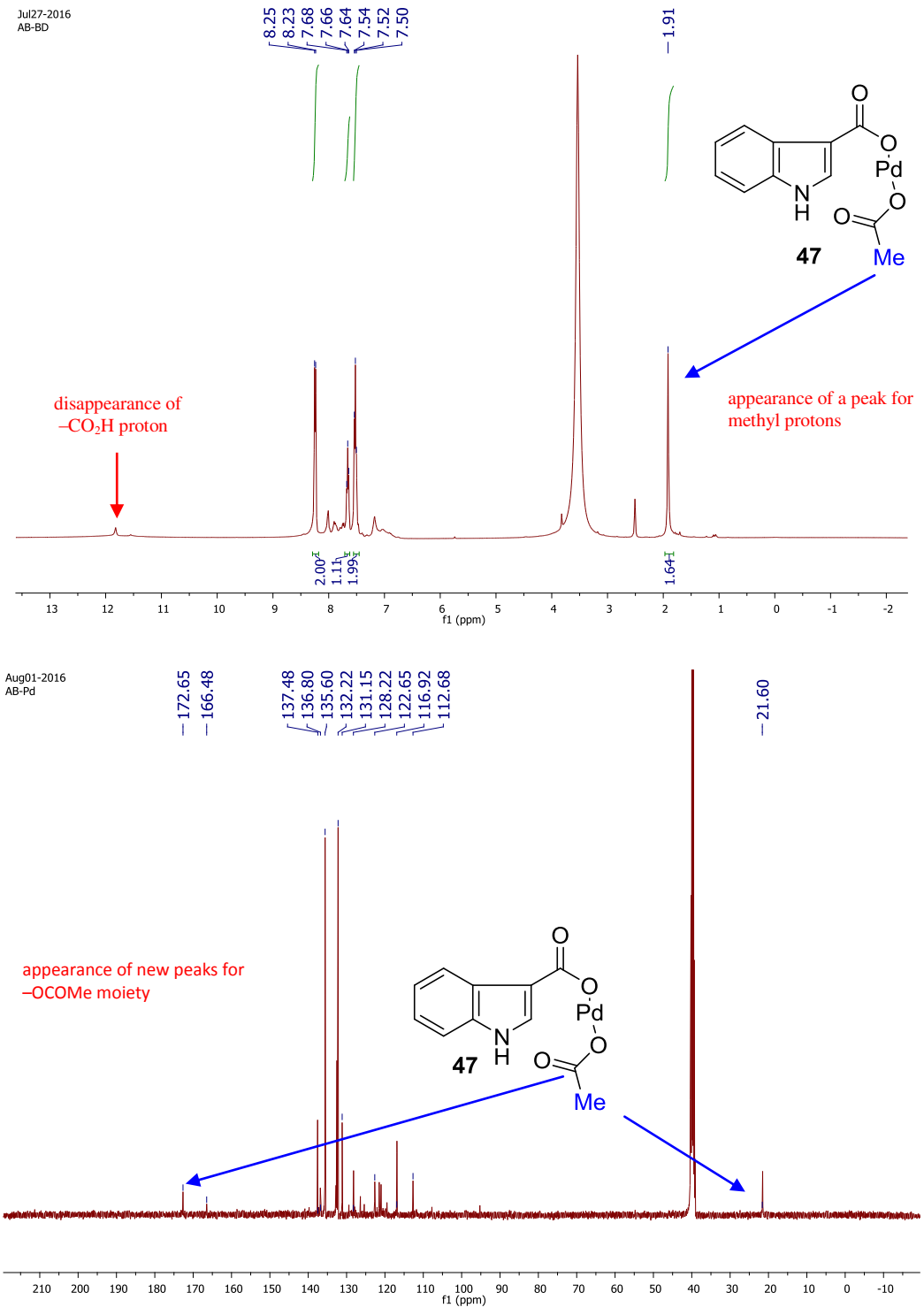


Figure 4.1.8 ^{1}H and ^{13} C NMR spectra of Pd(II)carboxylate **47**

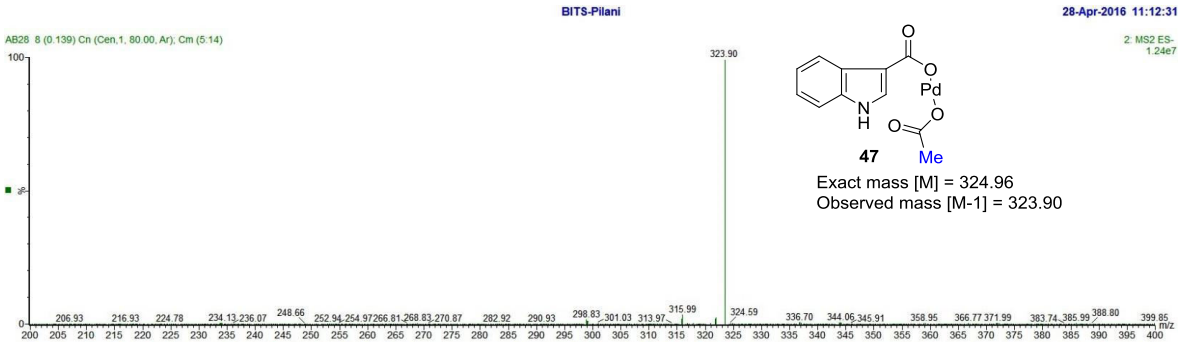


Figure 4.1.9 Mass spectrum of the Pd(II)carboxylate **47**

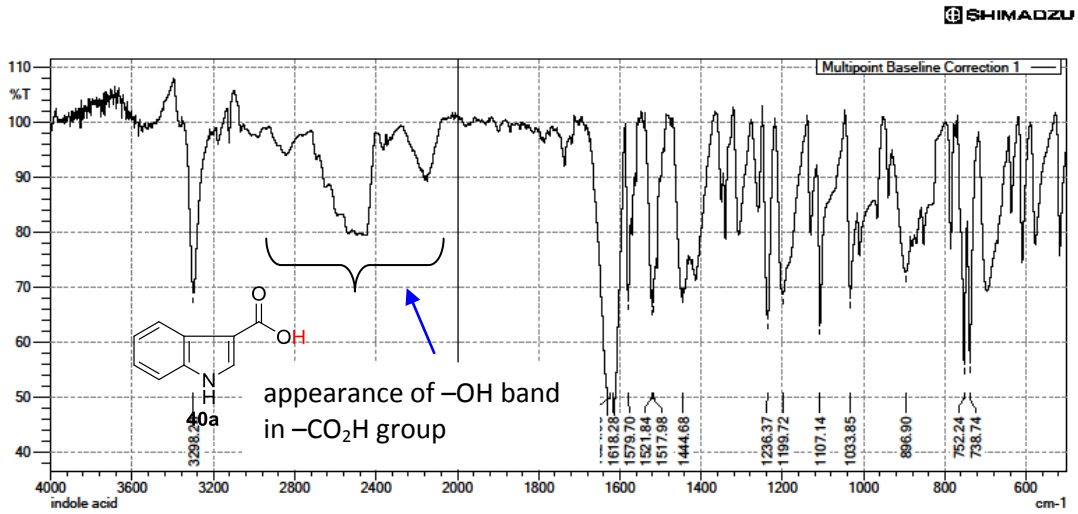


Figure 4.1.10 IR spectrum of indole-3-carboxylic acid

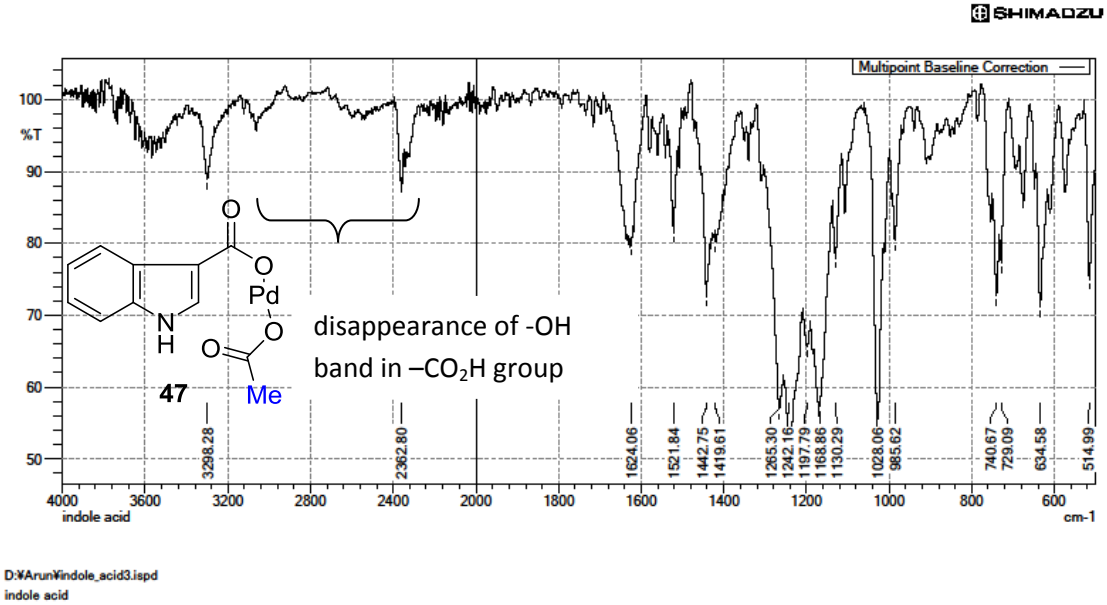
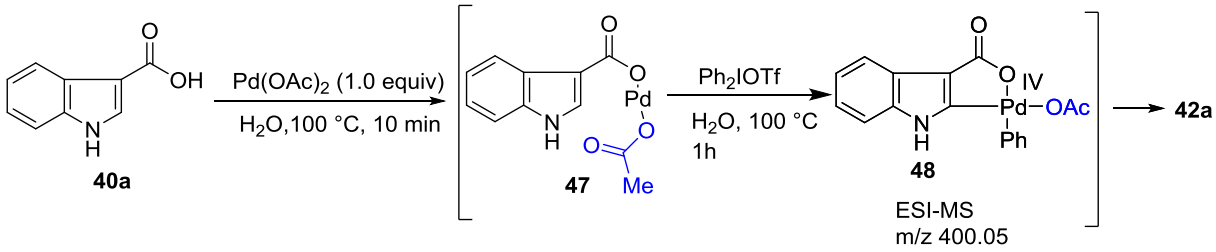


Figure 4.1.11 IR spectrum of Pd(II)carboxylate **47**

(b) *In situ* generation of Pd(IV) complex 10 and formation of 42a

A mixture of black colored solid residue **47** obtained in step I and diaryliodonium salt **41a** (0.31 mmol) was heated at 100 °C in water for 10 min (Scheme 4.1.10). The crude reaction mixture was subjected to mass spectrometry analysis which showed a peak at m/z 400.05 (Figure 4.1.12). Appearance of a peak at m/z 400.05, suggests the involvement of proposed Pd(IV) complex **48** in the formation of **42a**. Interestingly, when the same reaction mixture was heated for 1 h instead of 10 min, exclusive formation of **42a** was observed (90 % yield). This experimental observation points out that the C2-arylation is likely to proceed *via* palladium species **47** and **48**.



Scheme 4.1.10 Synthesis of Pd(IV) complex **48**

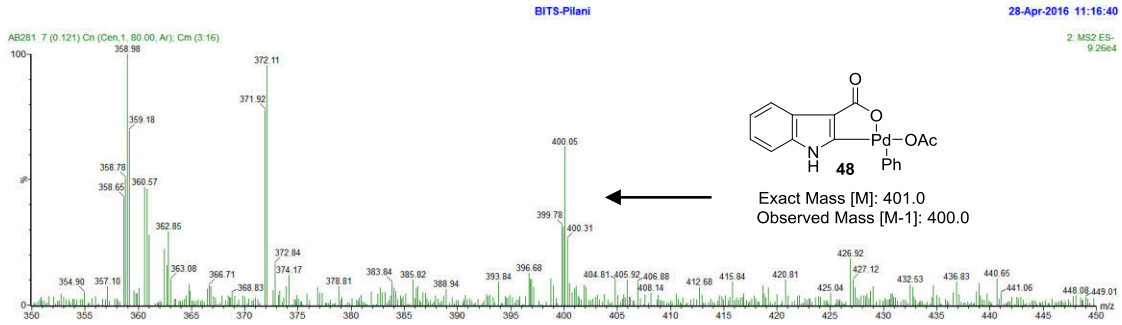
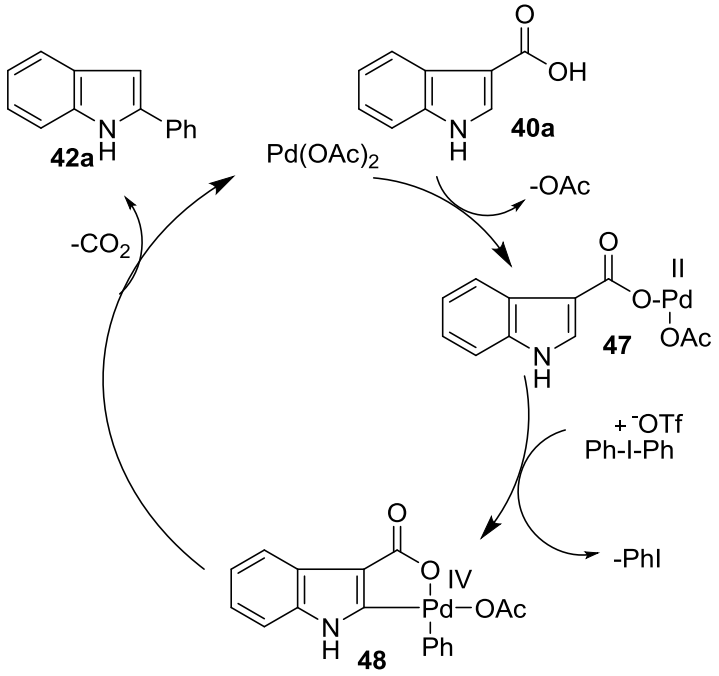


Figure 4.1.12 Mass spectrum of the Pd(IV) complex **48**

4.1.4.5 Plausible Reaction Mechanism

Literature reports[52-55] and our findings (Schemes 4.1.11) in the formation of **42**, suggest that the initial reaction of indole-3-carboxylic acid (**40a**) with $Pd(OAc)_2$ provides Pd(II) carboxylate **47** with the concomitant release of acetic acid. Next, oxidative addition of complex **47** with diphenyliodonium triflate likely to furnish Pd(IV) **48** which upon reductive elimination and decarboxylation believed to produce the desired C2-arylated product **42a** along with regeneration of the catalyst



Scheme 4.1.11 Plausible reaction pathway

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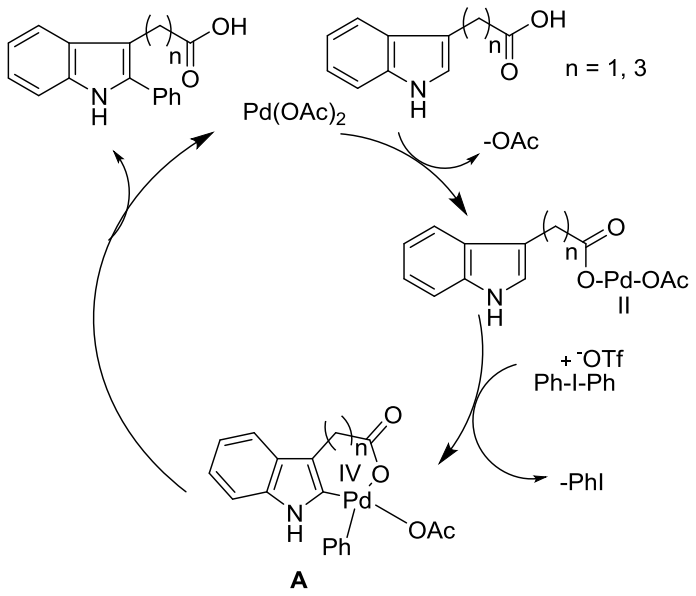
4.1.4.6 Plausible mechanism for indole-3-acetic acid and indole-3-butyric acid

Based on the literature precedents, the possible mechanism for the C2-arylation of indole-3-acetic acid and indole-3-butyric acid is depicted in Scheme 4.1.12. The intramolecular coordination of carboxylic acid and palladium is believed to generate the palladacycle (**A**) which upon reductive elimination likely to generate the corresponding 2-arylindoles.



Scheme 4.1.12 Plausible mechanism for the C2-arylation of indole-3-acetic acid and indole-3-butyric acid

4.1.4.7 Identification of particle size

To check whether the Pd-catalyzed decarboxylative coupling proceeded through Pd nanoparticles, we refluxed the mixture of indole-3-carboxylic acid (**40a**, 0.62 mmol), diphenyliodonium salt (**41a,** 0.62 mmol) and $Pd(OAc)_2$ (0.0062 mmol) in water for 1 h. After completion of the reaction, the contents were analyzed by dynamic light scattering experiment using Zetasizer Malvern instrument. The obtained graph given below (Figure 4.1.13) indicates that the particles size is greater than > 1000 nm.

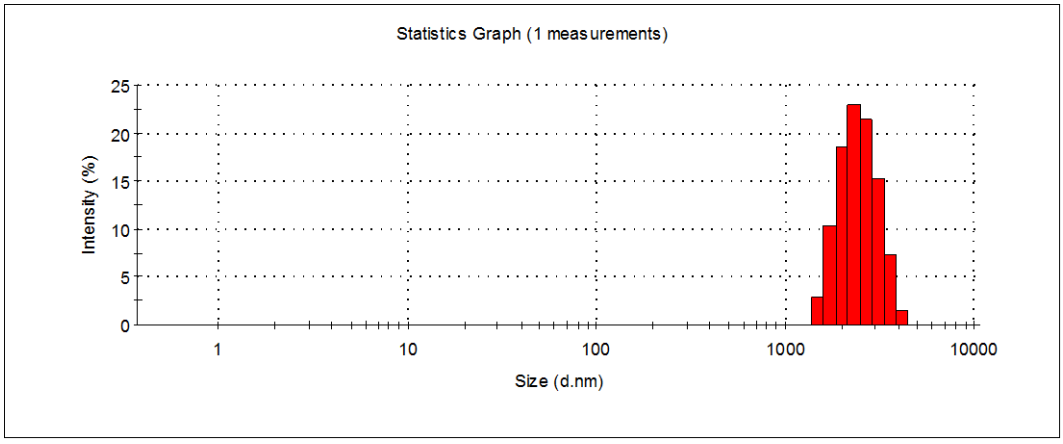


Figure 4.1.13 Particles size distribution in the reaction mixture

The NMR (^{1}H and ^{13}C) copies of compound **42f** is given below.

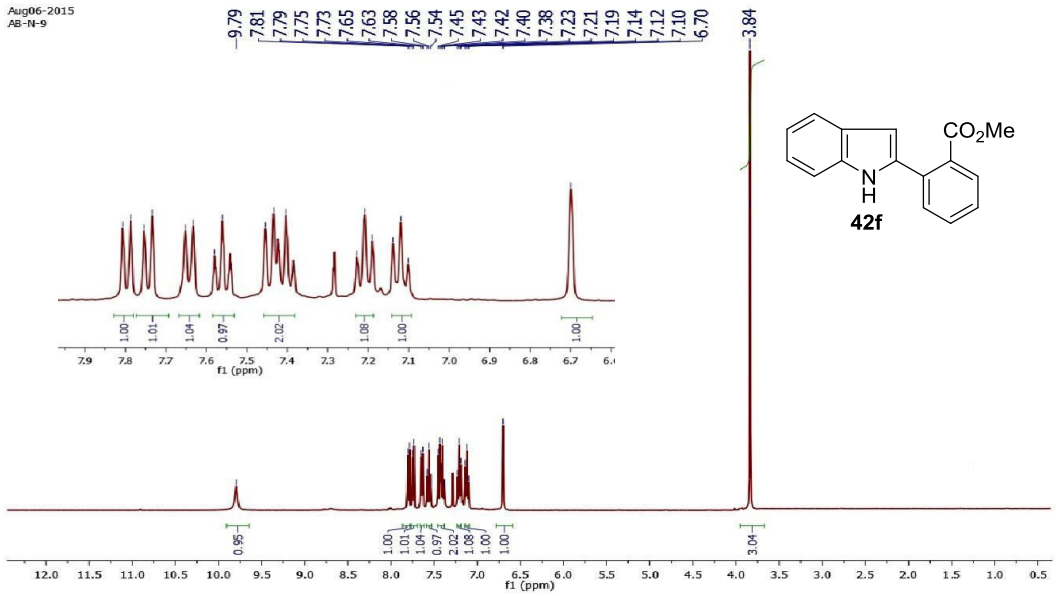


Figure 4.1.14 ^{1}H NMR spectrum of methyl-2-(1*H*-indol-2-yl)benzoate (**42f**)

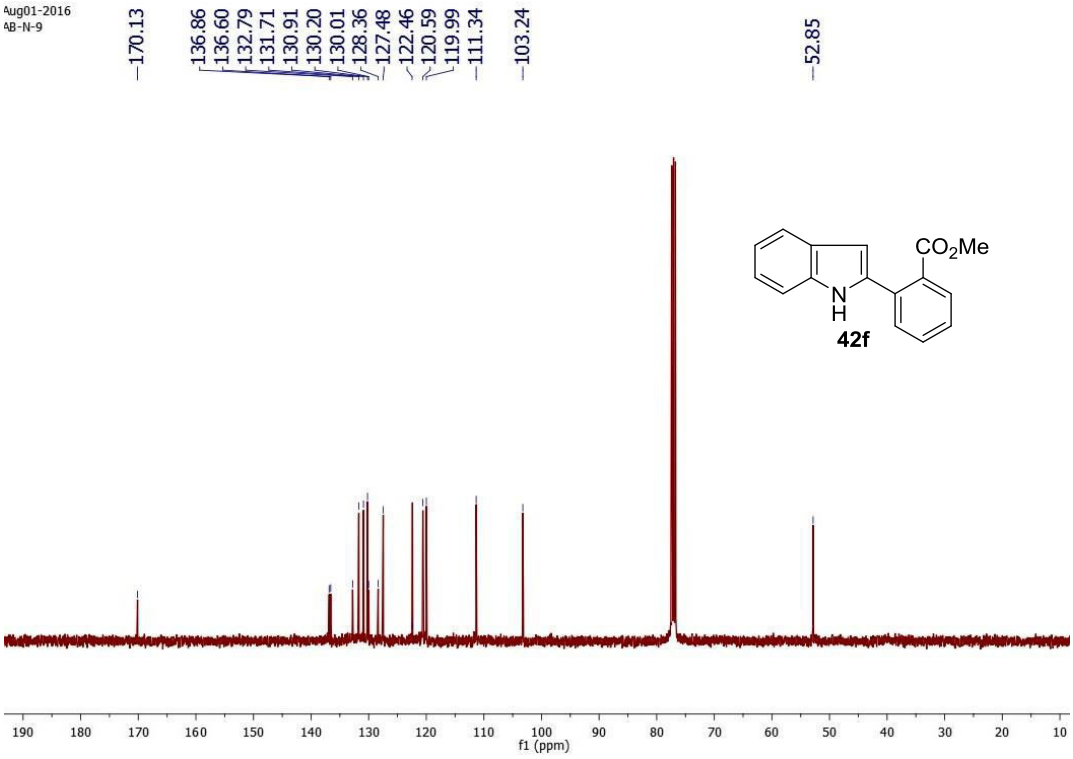


Figure 4.1.15 ^{13}C NMR spectrum of methyl-2-(1*H*-indol-2-yl)benzoate (**42f**)

4.1.4.8 Conclusions

In summary, we have successfully utilized carboxylic acid as a traceless directing group to arylate C2-position of indole in a regioselective fashion using easily accessible heteroaryl carboxylic acids and diaryliodonium salts. The C2-arylation of indole derivatives proceed *via* decarboxylative coupling using only catalytic amount of $Pd(OAc)_2$ (1.0 mol%) in water. The developed protocol was successfully progressed without any ligand, oxidant, base and acid to prepare a range of 2-arylindoles in good to excellent yields. The protocol was equally compatabile with indole-3-acetic acid, indole-3-butyic acid and tryptamine The synthetic utility of the developed procedure was proved by preparing CDK inhibitor, Paullone in good yield.

4.1.5 Experimental Details

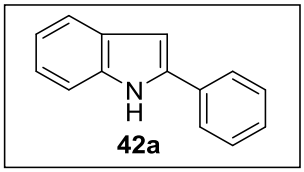
4.1.5.1 General Information: All the laboratory reagents were obtained commercially. The reactions were monitored by thin layer chromatography and performed on Merck pre-coated plates (silica gel 60 F_{254}, 0.2mm). Column chromatography was performed using 100-200 mesh silica gel and ethyl acetate/hexane mixture used for elution. Melting points were determined by E-Z melting point apparatus. NMR spectra were recorded in (DMSO-d_6) Bruker Advance II (400 MHz) spectrometer using TMS as internal standard. The coupling constant (*J*) are in Hz. Mass spectra were recorded using 'Hewlett-Packard' HP GS⁄MS 5890⁄5972.

4.1.5.2 Typical Experimental Procedure

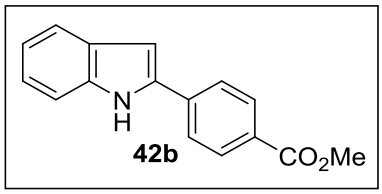
(a) Preparation of 2-phenylindole (42a)

In an oven dried round bottomed flask (10 mL), indole-3-carboxylic acid (**40a**, 100 mg, 0.62 mmol) mesityl(phenyl)iodonium salt (**41b**, 293 mg, 0.62 mmol), $Pd(OAc)_2$ (1.4 mg, 0.0062 mmol) and water (1 mL) were added sequentially. The mixture was stirred at 100 °C for 1h. After the completion of reaction, contents were allowed to cool at room temperature. The reaction mixture was extracted with ethyl acetate and dried over anhydrous Na_2SO_4. After removal of the organic solvent, the residue so obtained was purified by silica gel column chromatography (hexane/ethyl acetate 8:2) and obtained the desired 2-phenylindole **42a** in 91% (102 mg) yield.

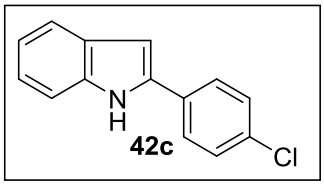
Spectral data of 2-arylindoles (42a-y)



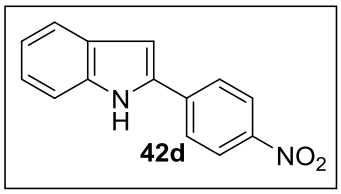
2-Phenyl-1*H*-indole (42a). White solid, 102 mg, Yield 91%, mp 188-189 °C (lit.[56, 57] 186-187 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.37 (s, 1H), 7.71 – 7.66 (m, 3H), 7.49 – 7.43 (m, 3H), 7.36 (t, *J* = 7.4 Hz, 1H), 7.25 – 7.21 (m, 1H), 7.18 – 7.13 (m, 1H), 6.87 (d, *J* = 1.3 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 137.8, 136.8, 132.3, 129.2, 129.0, 127.7, 125.1, 122.3, 120.6, 120.2, 110.9, 100.0. MS (ESI) *m/z* calcd for $C_{14}H_{12}N$ $(M+H)^+$ 194.1, found 194.1



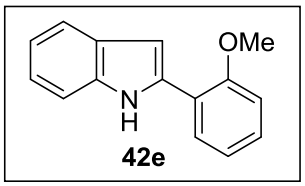
Methyl-4-(1*H*-indol-2-yl)benzoate (42b). Off-white solid, 133 mg, Yield 85%, mp 200-202 °C (lit[58] 201-202 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.87 (s, 1H), 8.07 (d, *J* = 7.0 Hz, 2H), 7.80 (d, *J* = 8.2 Hz, 2H), 7.62 (d, *J* = 7.9 Hz, 1H), 7.43 (d, *J* = 8.1 Hz, 1H), 7.22 – 7.16 (m, 1H), 7.09 (t, *J* = 7.5 Hz, 1H), 6.93 (s, 1H), 3.92 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.8, 137.5, 136.8, 136.7 130.2, 128.9, 128.5, 124.8, 122.7, 120.8, 120.1, 111.3, 101.2, 52.1. MS (ESI) *m/z* calcd for $C_{16}H_{14}NO_2$ $(M+H)^+$ 252.1, found 252.1.



2-(4-Chlorophenyl)-1*H*-indole (42c). White solid, 124 mg, Yield 88%, mp 204-205 °C (lit[57] 205-207 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.82 (s, 1H), 7.68 – 7.59 (m, 3H), 7.44 – 7.36 (m, 3H), 7.19 – 7.14 (m, 1H), 7.08 (dd, *J* = 10.9, 4.0 Hz, 1H), 6.78 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 137.2, 136.8, 133.0, 131.1, 128.9, 126.5, 122.2, 120.5, 120.1, 111.2, 99.7. MS (ESI) *m/z* calcd for $C_{14}H_{11}ClN$ $(M+H)^+$ 228.1, found 228.1.

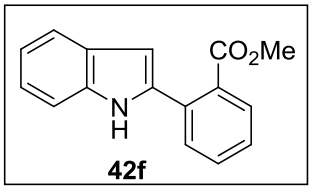


2-(4-Nitrophenyl)-1*H*-indole (42d). Yellow solid, 119 mg, Yield 81%, mp 249-250 °C (lit[58] 248-250 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.87 (s, 1H), 8.15 (d, *J* = 8.7 Hz, 2H), 7.85 (d, *J* = 8.7 Hz, 2H), 7.52 (d, *J* = 7.9 Hz, 1H), 7.35 (d, *J* = 8.2 Hz, 1H), 7.11 (t, *J* = 7.6 Hz, 1H), 6.99 (t, *J* = 7.5 Hz, 1H), 6.90 (s, 1H).^{13}C NMR (101 MHz, $CDCl_3$) δ 146.0, 138.9, 138.09, 135.4, 128.6, 125.3, 124.1, 123.2, 120.9, 120.1, 111.6, 102.3. MS (ESI) *m/z* calcd for $C_{14}H_{11}N_2O_2$ $(M+H)^+$ 239.1, found 239.1.



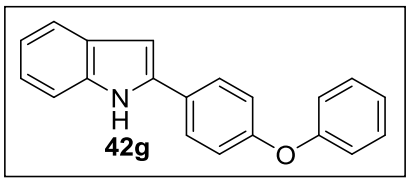
42e

2-(2'-Methoxyphenyl)-1*H*-indole (42e). White solid, 103 mg, Yield 75%, mp 76-78 °C (lit[58] 75-77 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.71 (s, 1H), 7.88 (dd, *J* = 7.7, 1.7 Hz, 1H), 7.67 (d, *J* = 8.8 Hz, 1H), 7.45 (d, *J* = 8.0 Hz, 1H), 7.35 – 7.29 (m, 1H), 7.23 – 7.19 (m, 1H), 7.16 – 7.05 (m, 3H), 6.94 (d, *J* = 3.0 Hz, 1H), 4.05 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.7, 136.1, 135.9, 128.5, 128.3, 128.1, 121.8, 121.5, 120.6, 120.2, 119.8, 111.9, 110.9, 99.8, 55.9. MS (ESI) *m/z* calcd for $C_{15}H_{14}NO$ $(M+H)^+$ 224.1, found 224.1.



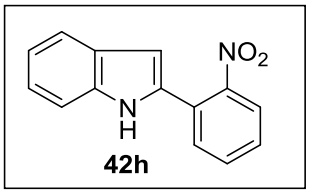
42f

Methyl-2-(1*H*-indol-2-yl)benzoate (42f). White solid, 112 mg, Yield 72%, mp 136-137 °C (lit[59] 135 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.79 (s, 1H), 7.80 (d, *J* = 7.8 Hz, 1H), 7.74 (d, *J* = 7.9 Hz, 1H), 7.64 (d, *J* = 7.9 Hz, 1H), 7.56 (t, *J* = 8.3 Hz, 1H), 7.46 – 7.38 (m, 2H), 7.21 (t, *J* = 7.6 Hz, 1H), 7.12 (t, *J* = 7.5 Hz, 1H), 6.70 (s, 1H), 3.84 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.1, 136.8, 136.6, 132.7, 131.7, 130.9, 130.2, 128.3, 127.4, 122.4, 120.5, 119.9, 111.3, 103.2, 52.8. MS (ESI) *m/z* calcd for $C_{16}H_{14}NO_2$ $(M+H)^+$ 252.1, found 252.1.



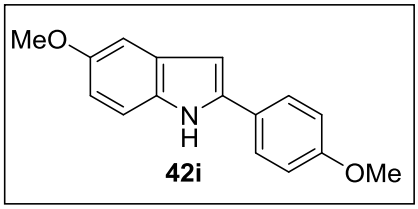
42g

2-(4-Phenoxyphenyl)-1*H*-indole (42g). Colourless oil, 123 mg, Yield 70%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32 (s, 1H), 7.65 (d, *J* = 8.6 Hz, 3H), 7.44 – 7.38 (m, 3H), 7.24 – 7.15 (m, 3H), 7.14 – 7.05 (m, 4H), 6.79 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.1, 156.8, 138.6, 137.5, 136.7, 129.8, 129.3, 127.5, 126.6, 123.6, 122.2, 120.5, 120.2, 119.2, 119.1, 110.8, 99.5. HRMS (ESI) *m/z* calcd for $C_{20}H_{16}NO$ $(M+H)^+$ 286.1154, found 286.1181.



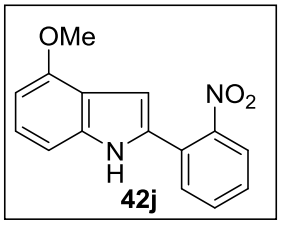
42h

2-(2-Nitrophenyl)-1*H*-indole (42h). Orange solid, 100 mg, Yield 68%, mp 136-138 °C (lit[57] 136-140 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.54 (s, 1H), 7.84 (d, *J* = 8.7 Hz, 1H), 7.67 (d, *J* = 7.8 Hz, 2H), 7.53 (d, *J* = 7.6 Hz, 2H), 7.45 (t, *J* = 8.4 Hz, 2H), 7.18 (d, *J* = 7.3 Hz, 1H), 6.75 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 132.5, 132.3, 131.7, 128.6, 127.1, 124.2, 123.1, 122.7, 121.0, 120.4, 118.8, 111.6, 111.2, 104.5. MS (ESI) *m/z* calcd for $C_{14}H_{11}N_2O_2$ $(M+H)^+$ 239.1, found 239.1.



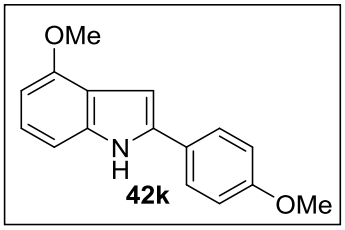
42i

5-Methoxy-2-(4-methoxyphenyl)-1*H*-indole (42i). White solid, 108 mg, Yield 82%, mp 216-218 °C (lit[56] 218-219 °C) ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (s, 1H), 7.61 – 7.56 (m, 2H), 7.31 (s, 1H), 7.10 (s, 1H), 7.02 – 6.98 (m, 2H), 6.87 – 6.83 (m, 1H), 6.67 (s, 1H), 3.89 (s, 3H), 3.88 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.3, 154.4, 138.7, 131.8, 129.9, 126.4, 125.2, 114.5, 112.0, 111.4, 102.1, 98.7, 55.8, 55.4. MS (ESI) *m/z* calcd for $C_{16}H_{16}NO_2$ $(M+H)^+$ 254.1, found 254.1



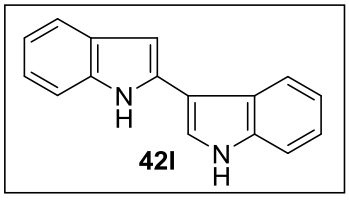
42j

4-Methoxy-2-(2-nitrophenyl)-1*H*-indole (42j). Orange solid, 103 mg, Yield 74%, mp 180-182 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57 (s, 1H), 7.82 (dd, *J* = 8.1, 1.0 Hz, 1H), 7.70 (dd, *J* = 7.8, 1.3 Hz, 1H), 7.64-7.60 (m, 1H), 7.50 – 7.45 (m, 1H), 7.19 (t, *J* = 8.0 Hz, 1H), 7.04 (d, *J* = 8.2 Hz, 1H), 6.86 (d, *J* = 1.8 Hz, 1H), 6.57 (d, *J* = 7.8 Hz, 1H), 3.99 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 153, 148.7, 138.3, 132.4, 131.7, 130.9, 128.4, 126.9, 124.3, 124.1, 119.2, 104.5, 101.9, 99.9, 55.3. HRMS (ESI) *m/z* calcd for $C_{15}H_{13}N_2O_3$ $(M+H)^+$ 269.0848, found 269.0850



42k

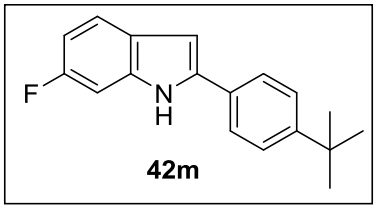
4-Methoxy-2-(4-methoxyphenyl)-1*H*-indole (42k). White solid, 109 mg, Yield 83%, mp 130-132 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 (s, 1H), 7.60 (d, *J* = 8.8 Hz, 2H), 7.13 (t, *J* = 7.9 Hz, 1H), 7.04 (d, *J* = 8.1 Hz, 1H), 7.00 (d, *J* = 8.8 Hz, 2H), 6.85 (s, 1H), 6.57 (d, *J* = 7.7 Hz, 1H), 4.01 (s, 3H), 3.88 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.1, 153.1, 137.9, 136.5, 126.3, 125.2, 122.7, 120.0, 114.4, 104.2, 99.9, 96.0, 55.4. 55.3. HRMS (ESI) *m/z* calcd for $C_{16}H_{16}NO_2$ $(M+H)^+$ 254.1103, found 254.1112



42l

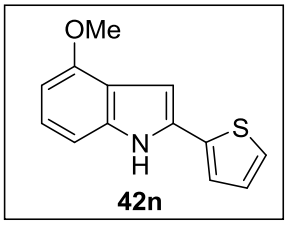
1*H*,1'*H*-2,3'-biindole (42l). White solid, 86 mg, Yield 60%, mp 200 - 201 °C (lit[60] 201°C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.73 (s, 1H), 8.54 (s, 1H), 8.29 – 8.21 (m, 1H), 8.13-8.09 (m, 2H), 7.65 (d, *J* = 8.1 Hz, 1H), 7.52 – 7.35 (m, 5H), 6.98 (d, *J* = 8.6 Hz, 1H).^{13}C NMR (101 MHz,

$CDCl_3$) δ 138.8, 137.3, 133.8, 131.7, 126.3, 123.1, 122.1, 121.1, 120.0, 119.7, 119.4,119.3, 112.4, 111.1, 110.8, 98.9. MS (ESI) *m/z* calcd for $C_{16}H_{13}N_2$ $(M+H)^+$ 233.1, found 233.1



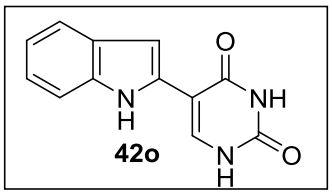
42m

2-(4-(*tert*-Butyl)phenyl)-6-fluoro-1*H*-indole (42m). Colorless liquid, 32 mg, Yield 76%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.38 (s, 1H), 7.60 (d, *J* = 8.5 Hz, 2H), 7.55 – 7.52 (m, 1H), 7.49 (d, *J* = 8.5 Hz, 2H), 7.11 (dd, *J* = 7.6, 2.1 Hz, 1H), 6.93 – 6.88 (m, 1H), 6.78 (d, *J* = 1.3 Hz, 1H), 1.38 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.1, 158.7, 138.5, 136.7, 129.3, 126.0, 125.9, 124.7, 121.2, 121.1, 108.9, 108.7, 99.3, 97.4, 97.1, 34.6, 31.3. HRMS (ESI) *m/z* calcd for $C_{18}H_{19}FN$ $(M+H)^+$ 268.1423 found 268.1431



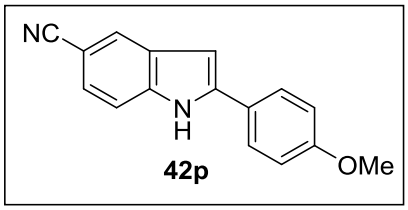
42n

4-Methoxy-2-(thiophen-2-yl)-1H-indole (42n). Colourless liquid, 83 mg, Yield 70%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (s, 1H), 7.19 (t, *J* = 8.0 Hz, 2H), 7.13 (s, 1H), 7.06 (d, *J* = 8.2 Hz, 2H), 6.72 (s, 1H), 6.61 (s, 1H), 4.02 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.7, 136.1, 128.5, 128.3, 121.8, 121.5, 120.6, 120.2, 119.8, 111.9, 110.9, 99.8, 55.9. HRMS (ESI) *m/z* calcd for $C_{13}H_{12}NOS$ $(M+H)^+$ 230.0561, found 230.0570



42o

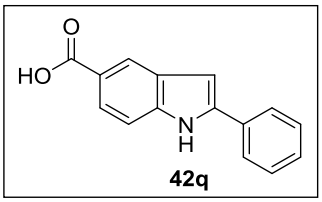
5-(1*H*-indol-2-yl)pyrimidine-2,4(1*H*,3*H*)-dione (42o).[61] White solid, 88 mg, Yield 63%, mp > 250 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.25 (s, 1H), 11.17 (s, 1H), 8.46 (s, 1H), 7.71 (d, *J* = 8.5 Hz, 2H), 7.59 (s, 1H), 7.25 – 7.21 (m, 1H), 7.18 – 7.14 (m, 1H), 6.86 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.6, 157.6, 140.0, 137.8, 136.6, 132.3, 127.7, 122.3, 120.7, 120.2, 110.9, 100.0. HRMS (ESI) *m/z* calcd for $C_{12}H_{10}N_3O_2$ $(M+H)^+$ 228.0695, found 228.0613.



42p

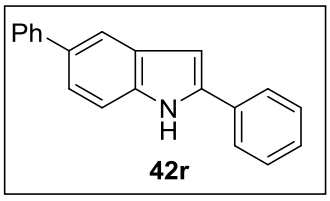
2-(4'-Methoxyphenyl)-1*H*-indole-5-carbonitrile (42p). Colourless oil, 109 mg, Yield 82%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (d, *J* = 6.9 Hz, 1H), 7.89 (d, *J* = 8.1 Hz, 2H), 7.68 – 7.66 (m, 1H), 7.60 (d, *J* = 8.0 Hz, 2H), 7.40 (d, *J* = 7.6 Hz, 1H), 6.70 (d, *J* = 8.6 Hz,

1H), 3.70 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.8, 141.9, 138.4, 137.8, 133.4, 133.2, 129.0, 128.5, 127.6, 125.4, 124.0, 112.8, 55.3. HRMS (ESI) *m/z* calcd for $C_{16}H_{13}N_2O$ $(M+H)^+$ 249.0950, found 249.0989.



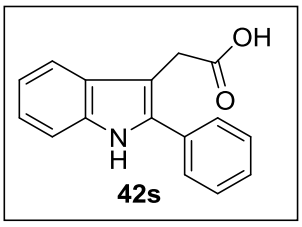
42q

2-Phenyl-1*H*-indole-5-carboxylic acid (42q). Colourless oil, 83 mg, Yield 72%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.76 (s, 1H), 7.88 (d, *J* = 7.8 Hz, 2H), 7.61 (s, 1H), 7.50 – 7.41(m, 3H), 7.34 (t, *J* = 7.4 Hz, 1H), 7.17 (dd, *J* = 8.3, 1.6 Hz, 1H), 6.98 (d, *J* = 1.4 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.6, 144.0, 142.6, 137.0, 134.1, 133.0, 132.9, 132.7, 130.2, 126.3, 124.6, 116.0, 104.4. HRMS (ESI) *m/z* calcd for $C_{15}H_{12}NO_2$ $(M+H)^+$ 238.0790, found 238.0750.



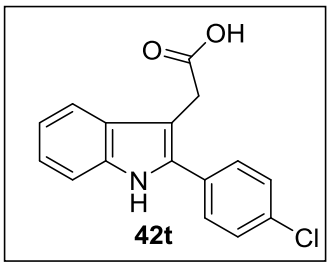
42r

2,5-Diphenyl-1*H*-indole (42r). Colorless oil, 98 mg, Yield 87%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.37 (d, *J* = 7.7 Hz, 1H), 7.87 (d, *J* = 6.4 Hz, 1H), 7.80 (d, *J* = 8.5 Hz, 1H), 7.72 – 7.66 (m, 3H), 7.51 – 7.46 (m, 5H), 7.43 (d, *J* = 8.5 Hz, 1H), 7.37 (d, *J* = 7.0 Hz, 2H), 6.92 (d, *J* = 2.1 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 139.3, 138.1, 129.0, 128.6, 127.8, 127.3, 126.7, 126.4, 125.1, 122.6, 122.2, 119.2, 119.1, 111.1, 100.8, 100.2. HRMS (ESI) *m/z* calcd for $C_{20}H_{16}N$ $(M+H)^+$ 270.1204, found 270.1264.



42s

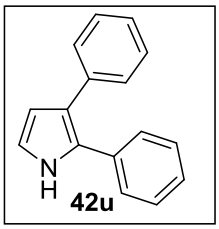
.**2-(2-Phenyl-1*H*-indol-3-yl)acetic acid (42s)**.[62] Colourless oil, 129 mg, Yield 90%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.36 (s, 1H), δ 7.71 (d, *J* = 7.4 Hz, 2H), 7.58 – 7.52 (m, 3H), 7.41 (t, *J* = 7.5 Hz, 2H), 7.14 (t, *J* = 7.3 Hz, 1H), 7.04 (t, *J* = 7.3 Hz, 1H), 3.75 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.6, 136.4, 132.2, 129.1, 128.8, 128.2, 128.2, 122.7, 120.2, 119.2, 110.9, 104.9, 30.7. MS (ESI) *m/z* calcd for $C_{16}H_{14}NO_2$ $(M+H)^+$ 252.1, found 252.1



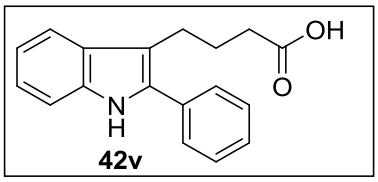
42t

2-(2-(4-Chlorophenyl)-1*H*-indol-3-yl)acetic acid (42t). Colorless oil, 146 mg, Yield 90%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.43 (s, 1H), 7.75 (d, *J* = 8.6 Hz, 2H), 7.62 (d, *J* = 8.6 Hz, 2H), 7.58 (s, 1H), 7.42 (d, *J* = 8.1 Hz, 1H), 7.15 (d, *J* = 7.1 Hz, 1H), 7.06 (t, *J* = 7.8 Hz, 1H), 3.76 (s,

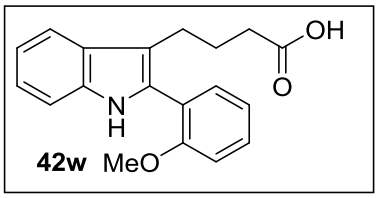
2H). ^{13}C NMR (101 MHz, DMSO- d_6) δ 173.7, 136.4, 134.7, 132.8, 131.7, 129.9, 129.2, 129.1, 122.4, 119.4, 111.7, 106.1, 31.1. HRMS (ESI) *m/z* calcd for $C_{16}H_{13}ClNO_2$ $(M+H)^+$ 286.0557, found 286.0568



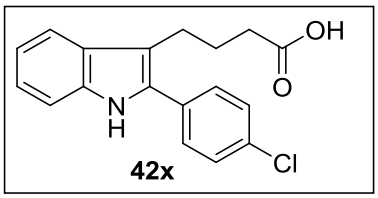
2,3-Diphenyl-1*H*-pyrrole (42u).[63] White solid, 167 mg, Yield 85%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (s, 1H), 7.37 – 7.32 (m, 2H), 7.29 – 7.14 (m, 8H), 6.76 (t, *J* = 2.7 Hz, 1H), 6.38 (t, *J* = 2.8 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 136.2, 133.1, 128.9, 128.7, 128.3, 128.1, 127.6, 126.4, 125.0, 121.7, 118.3, 110.5. MS (ESI) *m/z* calcd for $C_{16}H_{14}N$ $(M+H)^+$ 220.1, found 220.1



4-(2-Phenyl-1*H*-indol-3-yl)butanoic acid (42v).[62] Colorless oil, 126 mg, Yield 92%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.17 (s, 1H), 11.20 (s, 1H), 7.68 (d, *J* = 7.2 Hz, 2H), 7.61 (d, *J* = 7.9 Hz, 1H), 7.52 (t, *J* = 7.7 Hz, 2H), 7.38 (t, *J* = 8.5 Hz, 2H), 7.16 – 7.10 (m, 1H), 7.04 (dd, *J* = 8.4, 4.4 Hz, 1H), 2.94 – 2.83 (m, 2H), 2.34 (t, *J* = 7.2 Hz, 2H), 1.97 – 1.86 (m, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 174.9, 136.4, 134.3, 133.4, 129.2, 128.5, 128.1, 127.6, 121.9, 119.1, 111.9, 111.6, 34.0, 26.4, 24.2. MS (ESI) *m/z* calcd for $C_{18}H_{18}NO_2$ $(M+H)^+$ 280.1, found 280.1

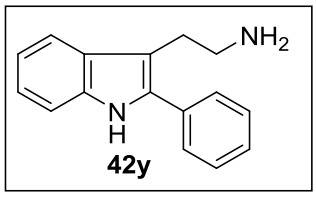


4-(2-(2-Methoxyphenyl)-1*H*-indol-3'-yl)butanoic acid (42w). Colorless oil, 136 mg, Yield 90%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56 (s, 1H), 7.69 (d, *J* = 7.8 Hz, 1H), 7.51 (d, *J* = 7.5 Hz, 1H), 7.40 (t, *J* = 7.0 Hz, 2H), 7.22 (d, *J* = 7.9 Hz, 1H), 7.17 (d, *J* = 7.8 Hz, 1H), 7.09 (t, *J* = 7.5 Hz, 1H), 7.04 (d, *J* = 8.3 Hz, 1H), 3.88 (s, 3H), 3.01 – 2.89 (m, 2H), 2.41 (t, *J* = 7.3 Hz, 2H), 2.10 – 2.05 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 179.9, 156.9, 135.6, 131.3, 129.3, 128.3, 121.9, 121.4, 120.9, 119.1, 118.9, 113.0, 111.4, 111.1, 110.7, 55.6, 33.5, 25.3, 24.1. HRMS (ESI) *m/z* calcd for $C_{19}H_{20}NO_3$ $(M+H)^+$ 310.1365, found 310.1370



4-(2-(4-Chlorophenyl)-1*H*-indol-3-yl)butanoic acid (42x). Colorless oil, 138 mg, Yield 90%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (s, 1H), 7.68 (d, *J* = 7.8 Hz, 1H), 7.50 (d, *J* = 8.4 Hz, 2H), 7.45

(d, *J* = 8.4 Hz, 2H), 7.39 (d, *J* = 8.0 Hz, 1H), 7.27 (d, *J* = 7.1 Hz, 1H), 7.19 (t, *J* = 7.4 Hz, 1H), 2.99 – 2.93 (m, 2H), 2.44 (t, *J* = 7.1 Hz, 2H), 2.11 – 2.06 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 180.1, 135.9, 133.6, 133.4, 131.5, 129.2, 129.1, 128.9, 122.6, 119.8, 119.2, 112.9, 110.8, 33.5, 25.4, 23.7. HRMS (ESI) *m/z* calcd for $C_{18}H_{17}ClNO_2$ $(M+H)^+$ 314.0870, found 314.0876



42y

2-(2-phenyl-1*H*-indol-3-yl)ethan-1-amine (**42y**).[62] Colorless oil, 125 mg, Yield 85%. ^{1}H NMR (400 MHz, DMSO- d_6) δ 11.35 (s, 1H), 7.82 (s, 2H), 7.63 (dd, *J* = 7.5, 2.7 Hz, 3H), 7.54 (t, *J* = 7.6 Hz, 2H), 7.44 – 7.36 (m, 2H), 7.17 – 7.12 (m, 1H), 7.07 (t, *J* = 7.8 Hz, 1H), 3.15 (dd, *J* = 8.0, 6.5 Hz, 2H), 3.07 (s, 2H). ^{13}C NMR (101 MHz, DMSO- d_6) δ 136.4, 135.5, 132.8, 129.3, 128.7, 128.4, 128.1, 122.6, 119.4, 118.7, 111.8, 106.9, 34.7, 29.6. MS (ESI) *m/z* calcd for $C_{16}H_{17}N_2$ $(M+H)^+$ 237.1, found 237.1

4.2 Part B: Preparation of heteroaryl carboxylates

4.2.1 Introduction

Heteroaryl carboxylates are a paramount class of molecules present in natural products, therapeutic agents and also they are prevalent building blocks to access several bioactive compounds, organic materials and complex natural products.[64, 65] For examples, synthetic cannabinoids (Figure 1) are an interesting class of recreational designer drugs, which are used to understand the mechanism of phychoactive substances. Especially, indole nucleus **1** bearing arylcarboxylates and fluorine fragments is well-known synthetic cannabinoid, beacuse it exhibit improved cannabinoid type 1 receptor binding affinity.[66] An interesting CD38 inhibitor **2** with IC_{50} 4.7 μM was identified.[67] CD38 is a glycoprotein regulates Ca^{2+} signalling and also responsible for diseases like diabetets and leukemia. Compound **3** displayed encourgarging antiplatelet property by inhibiting P2Y12 receptor.[68] Herdmanines D (**4**) is a marine natural product exhibits mRNA inhibiting property.[69] Tropisetron (**5**) is a serotonin 5-HT_3 receptor antagonist used in the treatement for cancer chemotherapy-induced emesis.[70]. Thiophene arylcarboxylates **6** showed potent hyperglycemic activity.[71] Owing to the substantial importance of heteroaryl carboxylates in medicinal field their syntheses have been pursued with considerable interests by the organic chemists.

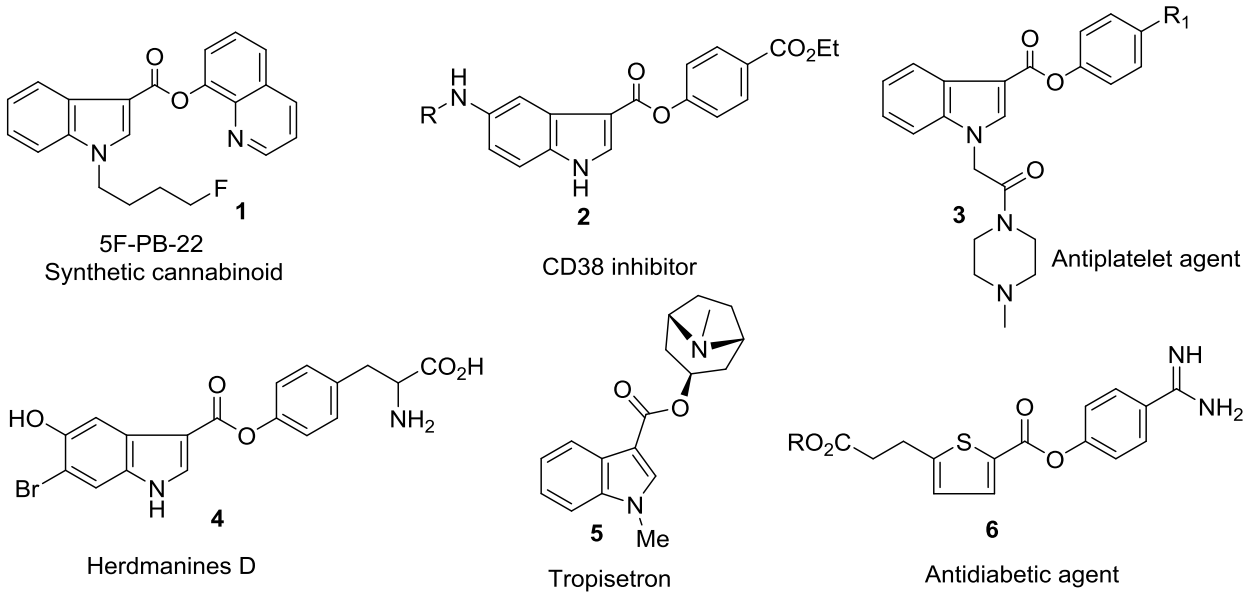
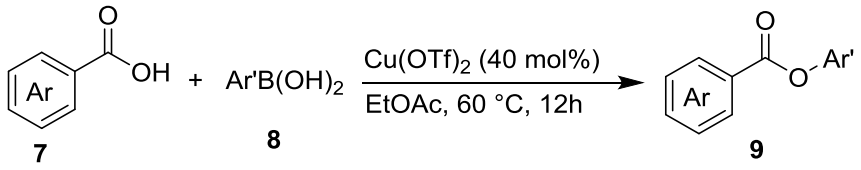


Figure 4.2.1 Examples of some biologically important heteroaryl carboxylates

In general, heteroaryl carboxylates are routinely achieved *via* esterification of appropriate carboxylic acids with alcohols in the presence of acid, base or coupling reagents. In recent years, there has been a significant improvement in the metal-catalyzed C-H functionalization strategies to assemble heteroaryl carboxylate frameworks. The improved protocols can withstand various carboxylic acids and sensitive-functional groups. The aryl partners under metal-catalyzed and metal-free reaction conditions are either boronic acids or arenes.

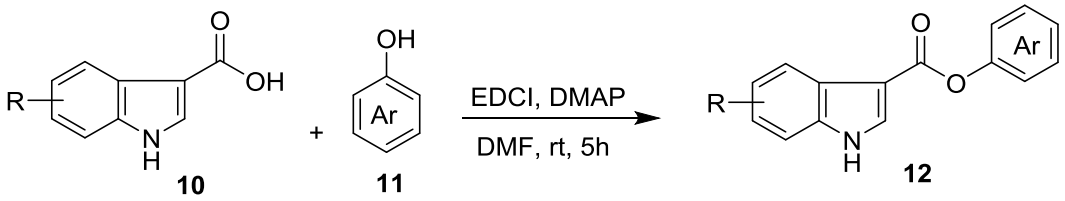
4.2.2 Synthesis of heteroaryl carboxylates

Cheng and co-workers[72] reported an expeditious synthesis of heteroaryl carboxylates **9** by employing arylcarboxylic acids **7** and boronic acids **8** in the presence of a copper catalyst . The methodology showed excellent functional group tolerance under ambient conditions (Scheme 4.2.1).



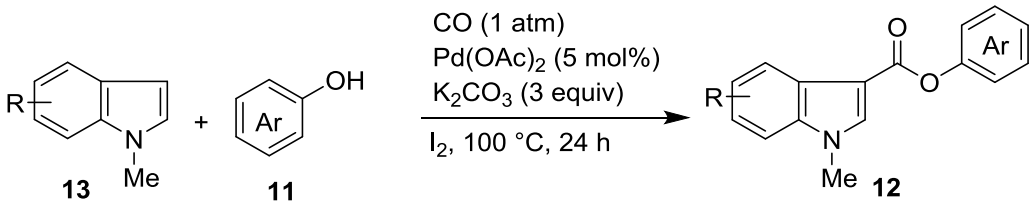
Scheme 4.2.1 Copper-catalyzed synthesis of heteroaryl carboxylates

Biologically important indolearyl carboxylates **12** were achieved *via* the activation of indole-3-carboxylic acid **10** involving EDCI and DMAP and coupling with various phenols **11** (Scheme 4.2.2).[73]



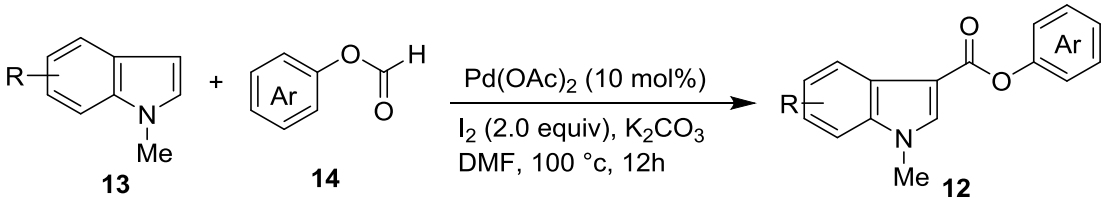
Scheme 4.2.2 Esterification of indole-3-carboxylic acid using phenols

A novel Pd-catalyzed direct carbonylation of indoles with different phenols **11** to access indolearyl carboxylates **12** was developed. This reaction regioselectively afforded indole-3-carboxylates and it has been applied to prepare natural product tropisetron (Scheme 4.2.3).[74]



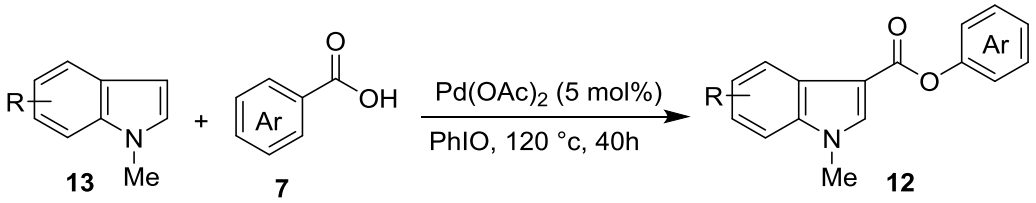
Scheme 4.2.3 Pd-catalyzed carbonylation of indoles

Lan et al.[75] developed an efficient cross-dehydrogenative coupling reaction between *N*-protected indoles **13** and aryl formates **14** to assemble indolearyl esters **12** in high yields. The reaction involved a catalytic amount of $Pd(OAc)_2$, K_2CO_3 and molecular iodine as an oxidant. Various substituted indoles and aryl formates **14** coupled smoothly to produce **12** (Scheme 4.2.4).



Scheme 4.2.4 Cross-dehydrogenative coupling between indoles and arylformates

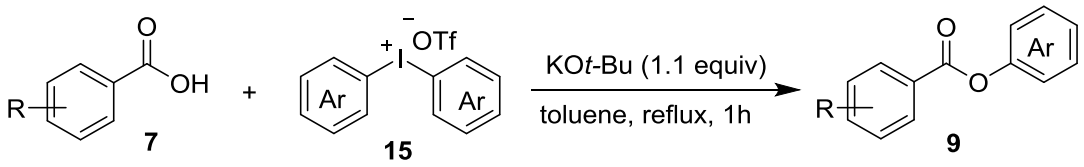
Very recently, indoles **13** and arylcarboxylic acids **7** were successfully converted into indolearyl carboxylates **12** with the aid of palladium acetate and iodosobenzene. This simple oxidative-coupling approach was compatible to various substituted carboxylic acids and indoles (Scheme 4.2.5).[76]



Scheme 4.2.5 Pd-catalyzed reaction between *N*-substituted indoles and heteroaryl acids

In last decade, diaryliodonium salts have rapidly progressed in C-C and C-heteroatom bond forming reactions.[36] Due to high electrophilic character, diaryliodonium salts can be coupled with various nucleophiles under mild reaction conditions.[38] Using diaryliodonium salts, Olofsson *et al.*[77] reported the arylation of carboxylic acids in the presence of KO*t*-Bu in toluene at 70 °C. The protocol

proceeds under mild conditions and found to be useful to make sterically hindered carboxylates in good yields (Scheme 4.2.6).



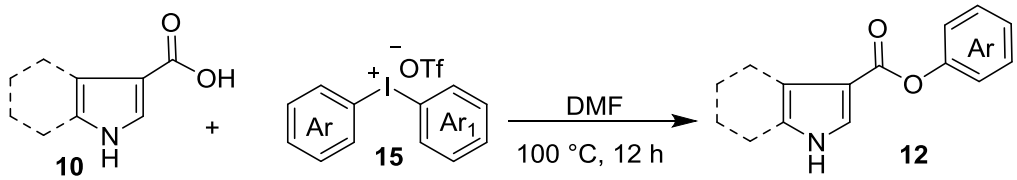
Scheme 4.2.6 Base- catalyzed reaction between diaryliodonium salts and substituted benzoic acids

Later, Nagorny et al. reported copper-catalyzed arylation of carboxylic acids using and diaryliodonium salts as aryl source in the presence of co-catalyst thiophosphoramides.[78] However, arylation of heteroaryl carboxylic acids using diaryliodonium salts under base-free conditions is largely unexplored.

4.2.3 Results and Discussion

4.2.3.1 Chemistry

We commenced our investigation by using indole-3-carboxylic acid **10a** and diphenyliodonium triflate **15a** as a coupling partners. Initally we attempted to form C-O bond between **10a** and **15a** in various solvets like THF, DCE, methanol and DMSO under feflux conditions. The reaction was failed in most of the solvents but in DMSO it afforded only 20% of the desired product.

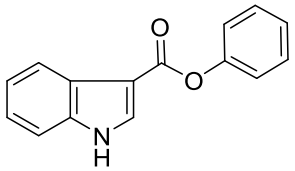


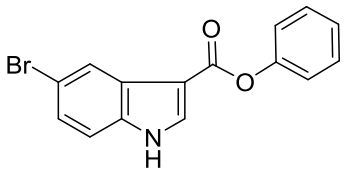
Scheme 4.2.7 Synthesis of heteroaryl carboxylates **12**

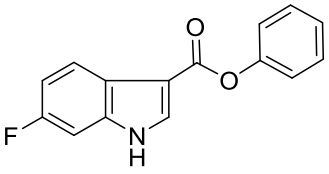
.Next the C-O coupling was tried in DMF, is noteworthy to mention that, under DMF reflux without any base and metals the anticipated indole-3-phenylcarboxylate (**12a**) was isolated in 80% yield (Scheme 4.2.7). Under the optimized reaction conditions, O-arylated products were obtained without any trace of N-arylated heteroaryl acids despite the indole moiety having free -NH. Remarkably, our simple protocol showed excellent control over regioselectivity by C2 and O-arylations. Compared to unsubstituted indole, electron rich (4 and 5-methoxy) substituted indoles

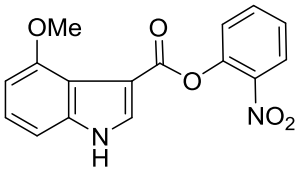
10d-e showed better reactivity towards diversely substituted diaryliodonium salts (NO_2, dimethyl, *t*-butyl & tolyl) to afford **12d**-**g** in 75-85% yields. To improve the significance of the developed strategy, we turned our attention to arylate pyrrole and furan carboxylic acids. We observed excellent reactivity of pyrrole-3-carboxyxlic acid and furan-2-carboxylic acid towards chloro (**15c**) and *o*-methoxy substituted iodonium salts **15e** to access the corresponding esters **12j** and **12l** in 85-92% yields within 3h. Gratifyingly, the developed esterification procedure was also amenable to

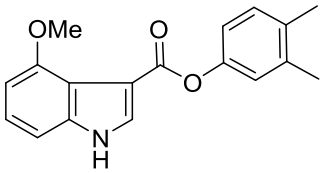
Table 4.2.1 Prepared heteroaryl carboxylates

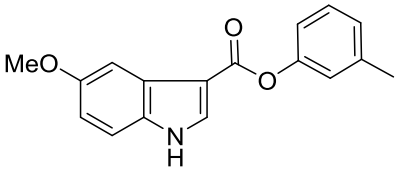

12a, 80%

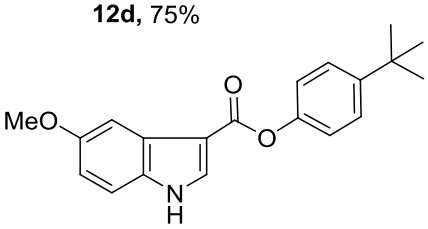

12b, 85%

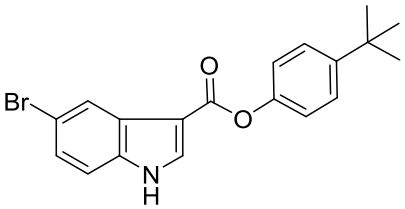

12c, 78%

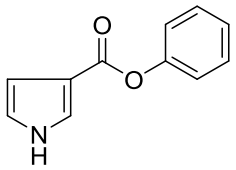

12d, 75%

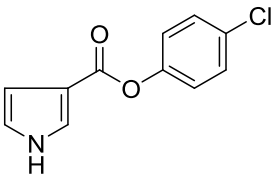

12e, 80%

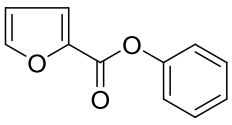

12f, 85%

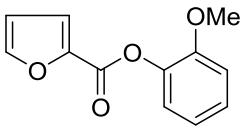

12g, 78%

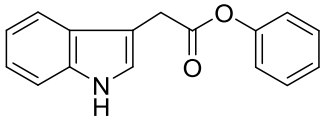

12h, 82%

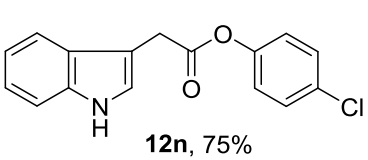

12i, 85%

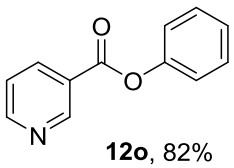

12j, 88%

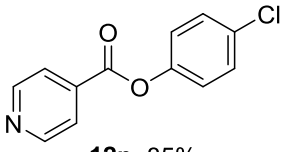

12k, 90%

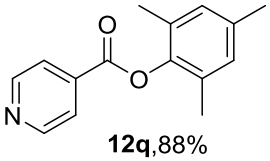

12l, 92%


12m, 90%


12n, 75%


12o, 82%


12p, 85%


12q,88%

six -membered pyridyl carboxylic acids to produce nicotinic (**12o**) and isonicotinic acids (**12p**-**q**) in 82-88 % yields (Table 4.2.1).

The NMR (^{1}H and ^{13}C) copies of compounds **12h** is given below.

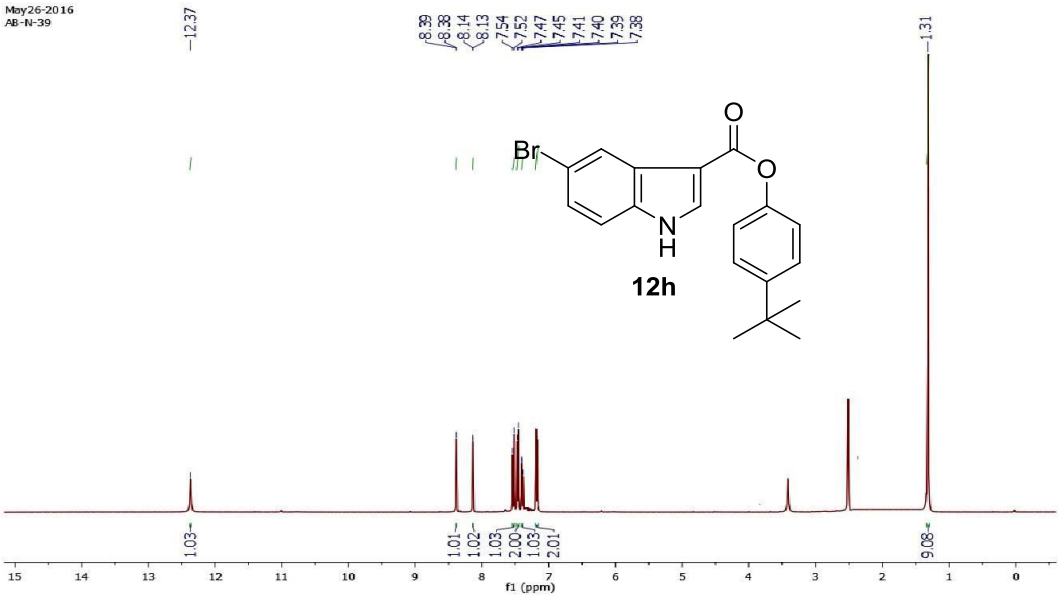


Figure 4.2.2 ^{1}H NMR spectra of 4-(*t*-butyl)phenyl 5-bromo-1*H*-indole-3-carboxylate (**12h**)

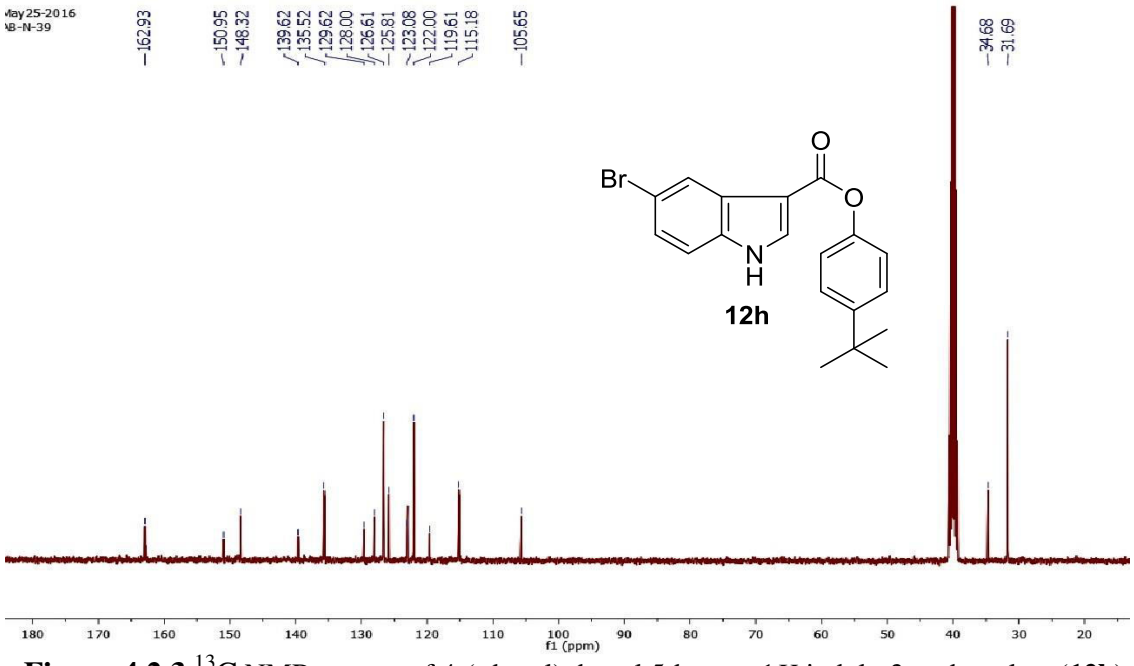
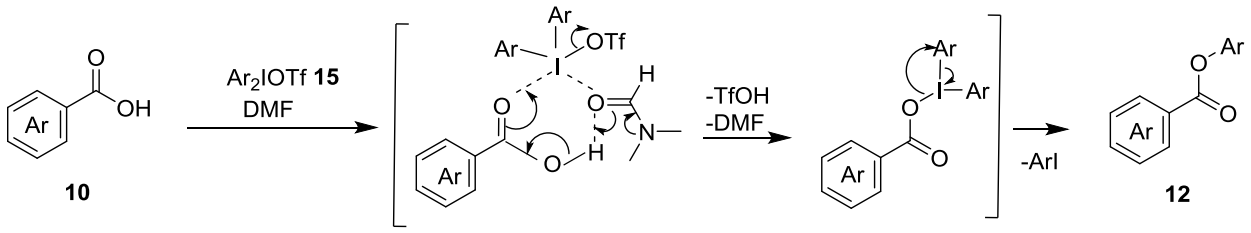


Figure 4.2.3 ^{13}C NMR spectra of 4-(*t*-butyl)phenyl 5-bromo-1*H*-indole-3-carboxylate (**12h**)

4.2.3.2 Possible mechanism

Regrading the meachanistic pathway for the O-arylation of carboxylic acid **10**, it is believed that carboxylic acid **10** and iodonium salt **15** in DMF may form six-membered transition state A which undergoes migration and reductive elimination[79] as depicted in Scheme **4.2.8** to afford the anticipated product **12**.



Scheme 4.2.8 Plausible mechanism for the O-arylation of heteroaryl carboxylic acid

4.2.3.3 Conclusions

We have developed a new eco-friendly synthetic protocol to prepare heteroaryl carboxylates from heteroaryl carboxylic acids and diaryliodonium salts under neat DMF heating (100 °C) without any acid, base and coupling reagents. This strategy was compatible to variety of heterocyclic acids such as indole, pyrrole, furan and pyridine. Interestingly, indole-3-acetic acid also afforded the corresponding carboxylates in good yields. In all cases C-O arylated products were exclusively formed.

4.2.4 Experimental Details

4.2.4.1 General Information: All reagents and solvents were purchased form Aldrich, Alfa Aesar, Merck, and Spectrochem. Progress of the reaction was monitored by thin-layer chromatography (TLC) technique and it was visualized with the help of hand held UV lamp. Column chromatography was carried out by using silica gel (100-200 mesh). Melting points of the purified compounds were measured in E-Z melting point instrument and the values are uncorrected. NMR (^{1}H & ^{13}C) spectra were recorded on Bruker-Avance II (400 and 100 MHz) spectrometer in deuterated DMSO-d_6 and $CDCl_3$. Chemical shifts (δ) are represented in parts per million (ppm) relative to tetramethylsilane (TMS) which was used as an internal standard. The coupling constants (*J*) were given in Hz. The multiplicities are expressed as: s= singlet, d= doublet, t= triplet, q= quartet and m= multiplet. Mass

spectra were obtained from WATERS XEVO TQD mass spectrometer. Nicotonic acid, isonicotonic acid and furan-2-carboxylic acid are directly purchased from the commercial sources

4.2.4.2 General Experimental Procedures

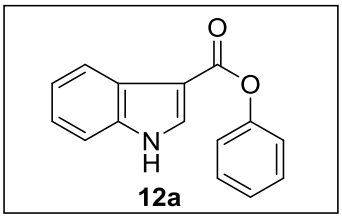
(a) Indole-3-carboxylic acid 10

To a stirred solution of indole (1g, 1.0 equiv) in dimethylformamide (5 mL), trifluoroacetic anhydride (1.16 equiv) was added dropwise at 0 °C. After 3 h the content were poured into icewater (20 mL) and the product was isolated by filtration.[80] The residue was washed with water (10 mL). The crude so obtained was suspended in 20% aqueous NaOH (20 mL) and refluxed for 6 h. The mixture was cooled, washed with CH_2Cl_2 (2 × 100 mL) and acidified. The precipitate was isolated by filtration and dried to afford pure indole-3carboxylic acid **10**.

(b) Heteroaryl carboxylates 12a-q

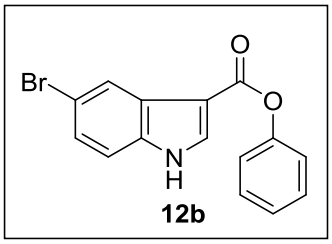
In an oven dried 10 mL round bottomed flask, indole-3-carboxylic acid **10** (100 mg, 1.0 equiv) and diaryliodonium salt (**15**, 1.0 equiv) were taken in DMF (0.5 mL). The mixture was stirred at 100 °C for 12h. Progress of the reaction was monitored by TLC. Once the reaction got completed, the contents were poured into ice and extracted with ethyl acetate. The organic layer was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The obtained residue was purified through column chromatography (hexane/ethyl acetate 7:3) to afford the desired heteroaryl carboxylates **12a-q** in 75- 80% yields.

Spectral data of heteroaryl carboxylates 12a-q



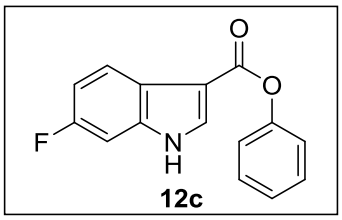
12a

Phenyl-1*H*-indole-3-carboxylate (12a). White solid, 112 mg, Yield 80%, mp 175-176 °C (lit[75] 176-178 °C), IR (KBr, υ cm^{-1}) 3315, 1701. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.95 (s, 1H), 8.13 (d, *J* = 3.0 Hz, 1H), 8.01 (d, *J* = 2.9 Hz, 1H), 7.41 (d, *J* = 5.6 Hz, 1H), 7.36 (t, *J* = 7.9 Hz, 2H), 7.22 – 7.14 (m, 5H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.6, 151.1, 136.0, 132.5, 129.1, 126.5, 125.3, 123.4, 122.5, 122.3, 120.8, 111.6, 108. MS (ESI) *m/z* calcd for $C_{15}H_{12}NO_2$ $(M+H)^+$ 238.1, found 238.1



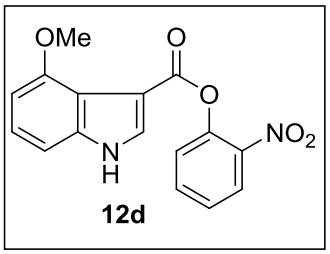
12b

Phenyl-5-bromo-1*H*-indole-3-carboxylate (12b). Thick brown oil, 112 mg, Yield 85%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.44 (s, 1H), 8.06 (s, 1H), 7.85 (s, 1H), 7.29 – 6.98 (m, 7H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.8, 150.7, 135.3, 133.6, 129.1, 127.6, 125.5, 125.3, 123.4, 121.8, 115.0, 113.7, 106.1. HRMS (ESI) *m/z* calcd for $C_{15}H_{11}BrNO_2$ $(M+H)^+$ 315.9895, found 315.9855.



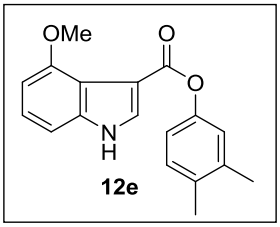
12c

Phenyl-6-fluoro-1*H*-indole-3-carboxylate (12c). Colorless oil, 111 mg, Yield 78%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.98 (s, 1H), 8.19 (d, J = 3.4 Hz, 1H), 8.06 (s, 1H), 7.46 (t, J = 7.9 Hz, 2H), 7.32 – 7.27 (m, 3H), 7.16 (s, 1H), 7.08 (d, J = 7.2 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.2, 161.6 (d, $^{1}J_{C\text{-}F}$ = 240 Hz), 150.7, 136.3 (d, $^{3}J_{C\text{-}F}$ = 15 Hz), 132.3, 129.4, 125.7, 122.6 (d, $^{3}J_{C\text{-}F}$ = 10 Hz), 122.4, 122.0, 111.2 (d, $^{2}J_{C\text{-}F}$ = 24 Hz), 108.3, 98.3(d, $^{2}J_{C\text{-}F}$ = 26 Hz). HRMS (ESI) *m/z* calcd for $C_{15}H_{11}FNO_2$ $(M+H)^+$ 256.0696, found 256.0641.



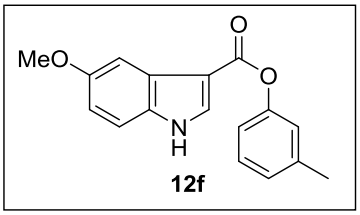
12d

2-Nitrophenyl-4-methoxy-1*H*-indole-3-carboxylate (12d). Yellow oil, 122 mg, Yield 75%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.98 (s, 1H), 8.29 (d, J = 3.0 Hz, 1H), 7.85 (s, 1H), 7.75 (d, J = 7.0 Hz, 1H), 7.67(d, J = 7.7 Hz, 1H), 7.63 (s, 1H), 7.65 – 7.59 (m, 1H), 7.04 (d, J = 6.5 Hz, 1H), 6.56 (d, J = 5.1 Hz, 1H), 3.99 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.6, 153.6, 149.6, 148.8, 138.5, 132.4, 131.8, 128.4, 127.0, 124.3, 124.2, 119.2, 104.5, 102.0, 99.9, 55.3. HRMS (ESI) *m/z* calcd for $C_{16}H_{13}N_2O_5$ $(M+H)^+$ 313.0746, found 313.0785



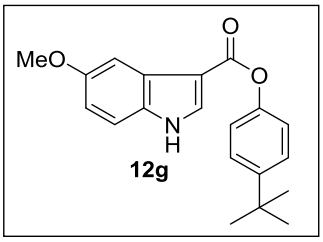
12e

3,4-Dimethylphenyl 4-methoxy-1*H*-indole-3-carboxylate (12e). Colourless oil, 123 mg, Yield 80%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.3 (s, 1H), 8.36 (s, 1H), 7.47 (s, 1H), 7.42 (d, J = 7.6 Hz, 1H), 7.22 (d, J = 7.8 Hz, 1H), 7.13 (s, 1H), 7.06 (s, 1H), 6.92 (s, 1H), 4.01 (s, 3H), 2.35 (s, 3H), 2.33 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.6, 153.2, 150.5, 149.0, 137.9, 137.1, 136.1, 130.2, 126.2, 122.8, 122.3, 120.0, 104.2, 99.9, 96.4, 55.3, 19.9, 19.5. HRMS (ESI) *m/z* calcd for $C_{18}H_{18}NO_3$ $(M+H)^+$ 296.1208, found 296.1257.



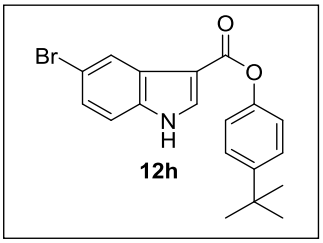
12f

***m*-Tolyl-5-methoxy-1*H*-indole-3-carboxylate (12f).** Colorless oil, 125 mg, Yield 85%, ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.04 (s, 1H), 8.25 (d, *J* = 3.0 Hz, 1H), 7.49 (s, 1H), 7.44 (d, *J* = 8.8 Hz, 1H), 7.34 (d, *J* = 7.7 Hz, 1H), 7.13-7.06 (3H), 6.89 (dd, *J* = 8.8, 2.0 Hz, 1H), 3.78 (s, 3H), 2.36 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 163.1, 155.6, 151.1, 139.5, 134.2, 131.8, 129.5, 127.2, 126.4, 123.1, 119.6, 113.8, 113.1, 105.5, 102.4, 55.6, 21.3. HRMS (ESI) *m/z* calcd for $C_{17}H_{16}NO_3$ $(M+H)^+$ 282.1052, found 282.1087



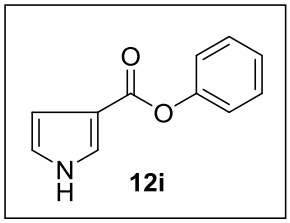
12g

4-(*t*-Butyl)phenyl-5-methoxy-1*H*-indole-3-carboxylate (12g). Brown thick liquid, 131 mg, Yield 78%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.05 (s, 1H), 8.25 (d, *J* = 2.9 Hz, 1H), 7.52 – 7.44 (m, 4H), 7.17 (d, *J* = 8.6 Hz, 2H), 6.89 (dd, *J* = 8.8, 2.4 Hz, 1H), 3.78 (s, 3H), 1.31 (s, 9H).^{13}C NMR (101 MHz, DMSO-d_6) δ 163.3, 155.6, 148.8, 148.1, 134.2, 131.8, 127.1, 126.5, 122.0, 113.8, 113.0, 105.5, 102.5, 55.6, 34.6, 31.7. HRMS (ESI) *m/z* calcd for $C_{20}H_{22}NO_3$ $(M+H)^+$ 324.1521, found 324.1586.



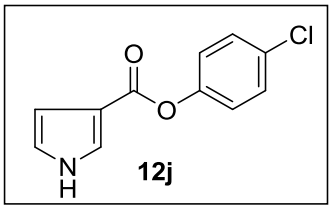
12h

4-(tert-butyl)phenyl 5-bromo-1*H*-indole-3-carboxylate (12h). Pale brown oil, 131 mg, Yield 82%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.37 (s, 1H), 8.38 (d, *J* = 3.0 Hz, 1H), 8.13 (d, *J* = 1.7 Hz, 1H), 7.53 (d, *J* = 8.6 Hz, 1H), 7.46 (d, *J* = 8.7 Hz, 2H), 7.41 – 7.38 (m, 1H), 7.18 (d, *J* = 8.6 Hz, 2H), 1.31 (s, 9H). ^{13}C NMR (101 MHz, DMSO- d_6) δ 162.9, 150.9, 148.3, 139.6, 135.5, 129.6, 128.0, 126.6, 125.8, 123.0, 122.0, 119.6, 115.1, 105.6, 34.6, 31.6. HRMS (ESI) *m/z* calcd for $C_{19}H_{19}BrNO_2$ $(M+H)^+$ 372.0521, found 372.0578.

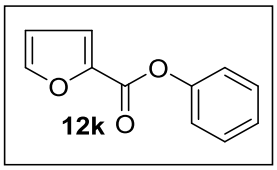


12i

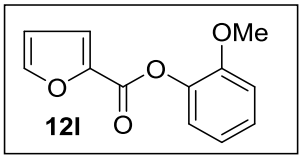
Phenyl-1*H*-pyrrole-3-carboxylate (12i). Colorless oil, 143 mg, Yield 85%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.80 (s, 1H), 7.48 (t, *J* = 7.9 Hz, 2H), 7.32 (t, *J* = 7.4 Hz, 1H), 7.26 (d, *J* = 7.5 Hz, 2H), 7.21 (s, 1H), 6.99 (s, 1H), 6.38 (d, *J* = 3.7 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.8, 150.6, 129.5, 125.8, 124.4, 121.88, 121.82, 117.0, 110.8. HRMS (ESI) *m/z* calcd for $C_{11}H_{10}NO_2$ $(M+H)^+$188.0633, found 188.0637.



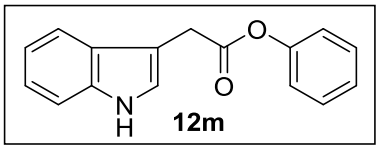
4-Chlorophenyl 1*H*-pyrrole-3-carboxylate (12j) Off-white solid, 175 mg, Yield 88%, mp 112-114 °C. ^{1}H NMR (400 MHz, $CDCl_3$) ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.91 (s, 1H), 7.47 (d, *J* = 8.2 Hz, 2H), 7.26 (d, *J* = 8.2 Hz, 2H), 7.21 (s, 1H), 6.99 (s, 1H), 6.38 (d, *J* = 3.7 Hz, 1H) ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.8, 150.6, 132.4, 129.4, 124.4, 121.8, 117.0, 110.8, 109.1. HRMS (ESI) *m/z* calcd for $C_{11}H_9ClNO_2$ $(M+H)^+$222.0244, found 222.0249.



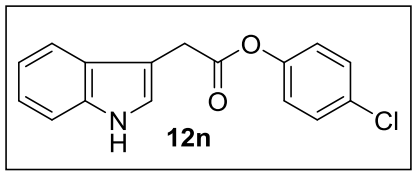
Phenylfuran-2-carboxylate (12k).[72] White solid, 151 mg, Yield 90%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (s, 1H), 7.48 – 7.41 (m, 3H), 7.31 (d, *J* = 7.4 Hz, 1H), 7.25 (d, *J* = 8.4 Hz, 2H), 6.61 (dd, *J* = 3.4, 1.7 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.0, 150.2, 147.2, 143.9, 129.5, 126.1, 121.6, 119.5, 112.2. MS (ESI) *m/z* calcd for $C_{11}H_9O_3$ $(M+H)^+$189.0, found 189.0



2-(Methoxyphenyl)furan-2-carboxylate (12l). Colorless oil, 179 mg, Yield 92%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (s, 1H), 7.42 (d, *J* = 3.5 Hz, 1H), 7.26 (d, *J* = 7.5 Hz, 1H), 7.18 (d, *J* = 7.8 Hz, 1H), 7.02 (dd, *J* = 14.3, 8.0 Hz, 2H), 6.61 (s, 1H), 3.85 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.5, 151.3, 147.0, 143.9, 139.1, 127.2, 122.9, 120.8, 119.4, 112.5, 112.1, 55.91. HRMS (ESI) *m/z* calcd for $C_{12}H_{11}O_4$ $(M+H)^+$ 219.0579, found 219.0514.

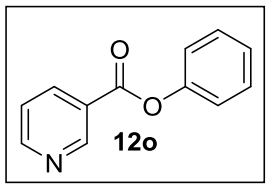


Phenyl 2-(1*H*-indol-3-yl)acetate (12m). Colourless liquid, 179 mg, Yield 90%, ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.06 (s, 1H), 7.63 (d, *J* = 7.7 Hz, 1H), 7.45 – 7.36 (m, 4H), 7.25 (t, *J* = 7.3 Hz, 1H), 7.12 (t, *J* = 9.1 Hz, 3H), 7.05 (t, *J* = 7.2 Hz, 1H), 4.05 (s, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 170.9, 151.1, 136.6, 129.9, 127.5, 126.2, 124.8, 122.1, 121.6, 119.0, 118.9, 112.0, 106.9, 31.3. HRMS (ESI) *m/z* calcd for $C_{16}H_{14}NO_2$ $(M+H)^+$ 252.0946, found 252.0911.

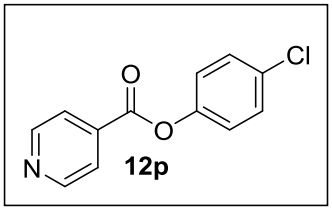


4-Chlorophenyl 2-(1*H*-indol-3-yl)acetate (12n). Colorless liquid, 150 mg, Yield 75%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.06 (s, 1H), 7.63 (s, 1H), 7.56 (d, *J* = 8.0 Hz, 2H), 7.43 – 7.33

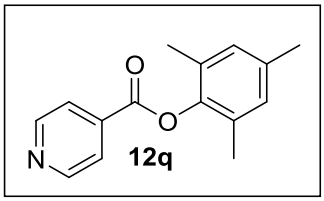
(m, 3H), 7.12 (d, *J* = 8.0 Hz, 2H), 7.05 (t, *J* = 7.2 Hz, 1H), 4.12 (s, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 163.1, 152.1, 136.4, 134.7, 132.8, 131.7, 129.2, 129.1, 122.4, 119.5, 119.3, 11.7, 106.1, 31.1. HRMS (ESI) *m/z* calcd for $C_{16}H_{13}ClNO_2$ $(M+H)^+$ 286.0557, found 286.0524.



Phenyl nicotinate (12o).[76] Colorless liquid, 150 mg, Yield 82%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.43 (s, 1H), 8.89 (d, *J* = 4.3 Hz, 1H), 8.50 – 8.47 (m, 1H), 7.52 – 7.46 (m, 3H), 7.33 (t, *J* = 7.0 Hz, 1H), 7.27 (d, *J* = 7.1 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.4, 153.8, 151.3, 150.6, 137.7, 129.7, 126.8, 125.6, 123.6, 121.1. MS (ESI) *m/z* calcd for $C_{12}H_{10}NO_2$ $(M+H)^+$ 200.1, found 200.1.



4-Chlorophenylisonicotinate (**12p**). Colorless liquid, 161 mg, Yield 85%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.91 (d, *J* = 6.0 Hz, 2H), 8.07 (d, *J* = 6.0 Hz, 2H), 7.80 (d, *J* = 8.0 Hz, 2H), 7.24 (d, *J* = 8.0 Hz, 2H).^{13}C NMR (101 MHz, $CDCl_3$) δ 163.4, 153.7, 150.6, 145.6, 136.6, 129.4, 122.2, 114.0. HRMS (ESI) *m/z* calcd for $C_{12}H_9ClNO_2$ $(M+H)^+$ 234.0244, found 234.0294.



Mesityl isonicotinate (**12q**). Colorless liquid, 172 mg, Yield 88%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.90 (d, *J* = 6.0 Hz, 2H), 8.07 (d, *J* = 6.0 Hz, 2H), 6.96 (s, 2H), 2.33 (s, 3H), 2.16 (s, 6H).^{13}C NMR (101 MHz, $CDCl_3$) δ 163.1, 153.9, 150.8, 145.6, 135.8, 129.4, 123.3, 20.8, 16.2. HRMS (ESI) *m/z* calcd for $C_{15}H_{16}NO_2$ $(M+H)^+$ 242.1103, found 242.1182.

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Chapter V

Conclusions

5.1 Conclusions

This thesis focused on applications of organoiodine reagents in the development of new synthetic protocols to construct 1,3,4-bis(indolyl)-1,3,4-oxadiazoles, diaryl sulfones, biaryls, heteroaryls, 2-arylindoles and heteroaryl carboxylates. During this study we developed new eco-friendly catalytic system and mild reaction conditions to assemble medicinally important molecules like 1,3,4-bis(indolyl)-1,3,4-oxadiazoles, diaryl sulfones and 2-arylindoles and versatile synthetic intermediates such as biaryls and heteroaryl carboxylates . Moreover, using our new developed protocols highly valuable therapeutic molecules Boscalid analogue, a marketed antifungal drug, carbazole alkaloid Glycosinine and Paullone a naturally occurring cyclin dependent kinase inhibitor were prepared.

First chapter briefly explains the structure, properties, sustainable features and recent applications of organoiodine reagents in various organic transformations.

In second chapter, we described the facile synthesis and cytotoxicity studies of novel bis (indolyl)-1,3,4-oxadiazoles. In detail, a series of thirteen novel 2,5-bis(indolyl)-1,3,4-oxadiazoles synthesized by relatively iodobenzene diacetate mediated oxidative cyclization of easily accessible bis(indolyl)hydrazide-hydrazones. All the synthesized 2,5-bis(indolyl)-1,3,4-oxadiazoles were evaluated for in vitro cytotoxicity against six various human cancer cell lines such as pancreas (ASPC1), prostate (DU145 and PC3), cervical (HeLa), breast (MDA-MB231) and ovarian (OVCAR). Most of the compounds were exhibited significant anticancer activity, IC_{50} ranging from 20 nm to 100 nm. Bis(indolyl)-1,3,4-oxadiazole with bromo substituent was found to be most active in the series having IC_{50} value 20 nM against prostate (DU145) and cervical (HeLa) cancer cells. The present structure-activity relationship (SAR) studies revealed that bromo substituent is a crucial role in imparting the anticancer activity and *N*-alkylation is beneficial for improving the selectivity against particular cancer cells. Further studies to identify the exact mechanism of action of bis(indolyl)-1,3,4-oxadiazoles and identification of cellular target is in progress.

The third chapter of the thesis deals the synthesis of two series of novel biaryls using diaryliodonium salts. This chapter is combined of two individual parts. In part A, An efficient and general protocol has been developed for the synthesis of diaryl sulfones via the metal-free coupling of readily available diaryliodonium and arenesulfinate salts in PEG-400 under microwave irradiation. Utilizing this metal-free and eco-friendly protocol, we have prepared

various diaryl sulfones in high yields and shorter reaction time under mild reaction conditions. The copper iodide-catalyzed coupling of diaryliodonium salts and arenesulfinate salts resulted in different regioselectivity to afford diverse diaryl sulfones. In part B, developed a ligand- and base-free, Pd-catalyzed protocol to access a wide range of symmetrical and unsymmetrical biaryls from stable diaryliodonium salts. The reaction involved the use of an effective and recyclable Pd/polyethylene glycol-400 catalyst systems to harness the aryl moieties of two diaryliodonium salts. The highlights of the present protocol include operational simplicity, mild reaction conditions, and broad substrate scope for symmetrical and unsymmetrical biaryls, scalability, and the use of a recyclable Pd catalyst. The potential utility of the developed method was demonstrated by preparing valuable heterocycles such as 5-aryluracils, carbazoles, chromenones, fluorenones, phenanthiridines, and boscalid analogues.

Chapter four of the thesis highlights the synthesis 2-arylindoles *via* decarboxylative c-c coupling in aqueous medium and heteroaryl carboxylates under base-free conditions using diaryliodonium salts. In this, we observed the utility of easily accessible heteroaromatic carboxylic acids and diaryliodonium salts to construct valuable 2-arylindoles and heteroaryl carboxylates in a regioselective fashion. The C2-arylation of indole derivatives proceed *via* decarboxylative coupling using only catalytic amount of $Pd(OAc)_2$ (1.0 mol%) in water. Base-free O-arylation of heteroaryl carboxylic acids occurred in neat DMF. The developed protocol was successfully progressed without any ligand, oxidant, base and acid to prepare a range of heteroaryl carboxylic carboxylates in good to excellent yields. The synthetic utility of the developed procedure was proved by preparing CDK inhibitor, Paullone in good yield.

5.2 Future scope of the work

Due to the significant achievements of organoiodine reagents in the constructions of various C-C, C-N, C-S and C-O bonds enabling to access valuable heterocycles under mild reaction conditions. The impressive features of organoiodine reagents are enhanced electrophilicity, stable solid compounds, no special precaution to handle, easy to prepare and recyclability of released iodoarenes during the reaction. These unique properties are highly favourable for today sustainable chemistry. In line with this, the developed protocols in the thesis will further widened its synthetic applications by constructing manifold novel transformations for the drug like molecules, bioactive natural products and organic materials.

List of Publications

1. **V.Arun**, Meenakshi Pilania, Dalip Kumar, An access to 2-arylindoles via decarboxylative C-C coupling in aqueous medium Ligand and base-free access to diverse biaryls by the reductive coupling of diaryliodonium salts, ***Chemistry-An Asian Journal, 2016****, 11, 3345.*
2. **V.Arun**, P.O.Venkataramana reddy, Meenakshi Pilania, Dalip Kumar, Ligand and base-free access to diverse biaryls by the reductive coupling of diaryliodonium salts, ***European Journal Organic Chemistry, 2016,*** *2096.*
3. Dalip Kumar, **V.Arun**, Meenakshi Pilania, K. P. Chandra Shekar, A metal-free and microwave-assisted efficient synthesis of diaryl sulfones, ***Synlett, 2013****, 831*.
4. Dalip Kumar, **V.Arun**, N. Maruthi Kumar, G. Acosta, B. Noel, K. Shah, A facile synthesis of novel bis-(indolyl)-1,3,4-oxadiazoles as potent cytotoxic agents, ***ChemMedChem, 2012****, 7, 1915*.
5. Dalip Kumar, **V.Arun**, Meenakshi Pilania, N. Maruthi Kumar, Organohypervalent iodine reagents in the synthesis of bioactive heterocycles, ***(Chapter 14), Elsevier, 2014*** *(book chapter).*
6. Dalip Kumar, **V.Arun**, Meenakshi Pilania, Manish K Mehra and Santosh B Khandagale, Diaryliodonium salts: Emerging reagents for arylations and heterocycles synthesis, ***Chemistry Biology Interface***, ***2016***, 6, 270 (*review).*
7. Meenakshi Pilania, **V. Arun**, M. P. Tantak, Dalip Kumar, Cu-catalyzed Expeditious Synthesis of *N*-Benzylaminoheterocycles using *N*-Tosylhydrazones and Aminohete-roarenes, ***Chemistry Select, 2016****, 1, 6368.*
8. M. P. Tantak, V. Gupta, K. Nikhil, **V. Arun**, R. P. Singh, P. N. Jha, K. Shah, Dalip Kumar, Sequential one-pot synthesis of bis(indolyl)glyoxylamides: Evaluation of antibacterial and anticancer activities, ***Bioorganic Medicinal Chemistry Letters, 2016****, 26*, 3167.
9. Dalip Kumar, Meenakshi Pilania, **V.Arun**, Bhupendra Mishra, A Facile and Expeditious One-Pot Synthesis of α-keto-1,3,4-oxadiazoles, ***Synlett, 2014,*** *1137.*
10. Dalip Kumar, Meenakshi Pilania, **V. Arun**, Savita Pooniya, C-H arylation of azaheterocycles: A direct ligand-free and Cu-catalyzed approach using diaryliodonium salts, ***Organic and Biomolecular Chemistry, 2014,*** *12, 6340.*

APPENDICES

List of Oral/Poster presented in Conferences

1. **V. Arun** and Dalip Kumar presented a poster on "An access to 2-arylindoles via decarboxylative C-C coupling in aqueous medium Ligand and base-free access to diverse biaryls by the reductive coupling of diaryliodonium salts" at national conference on **Organic Chemistry in Sustainable Development** organized by BITS PILANI during, **August 29-30, 2016**.

2. **V. Arun** delivered an oral presentation on "Direct synthesis of diverse biaryls *via* microwave-promoted palladium catalyzed reductive couplings of diaryliodonium salts" at **52nd ACC Symposium by Indian Chemical Society** held at JECRC University, Jaipur during **December 28-30, 2015.**

3. **V. Arun** and Dalip Kumar presented a poster on "Palladium catalyzed greener and direct synthesis of diverse biaryls *via* microwave-promoted reductive couplings of diaryliodonium salts" at international conference on **Nascent Developments in Chemical Sciences** organized by BITS PILANI during **October 23-25, 2015**

4. **V. Arun** and Dalip Kumar presented a poster on "Rapid synthesis of diarylsulfones from diaryliodonium salts" at **National conference on Frontiers at the Chemistry-Allied Science Interface** organized by University of Rajasthan during **March 13-14, 2015**.

5. **V. Arun** and Dalip Kumar presented a poster on "A facile Synthesis and Anticancer Evaluation of Novel Bis(indolyl)-1,3,4-oxadiazoles" **National Symposium on Transcending Frontiers in Organic Chemistry, CSIR-NIIS**T, Thiruvanathapuram, Kerala, **October 09-11, 2014**.

6. **V. Arun** and Dalip Kumar presented a poster on "A Rapid Synthesis of Diaryl Sulfones'' **20th International ISCB Conference on Chemistry and Medicinal Plants in Translational Medicine for Healthcare**: University of Delhi, New Delhi, **March 01-04, 2014**.

7. **V. Arun** and Dalip Kumar delivered an oral presentation on "Synthesis And Anticancer Evaluation Of Novel Bis(indolyl)-1,3,4-oxadiazoles'' **National Conference On Recent Developments In Chemical Sciences NCRDCS-14**, Guru Jambheshwar University, Hisar, Haryana, February **26-27, 2014**.

8. **V. Arun** and Dalip Kumar presented a poster on "Design, Synthesis and Anticancer Activity of Novel Bis(indolyl)-1,3,4-oxadiazoles" **19th International ISCB Conference on Recent advances and current trends in Chemical and Biological Science**s, Mohanlal Sukhadia University, Udaipur, Rajasthan, **March 02-05, 2013**.

BRIEF BIOGRAPHY OF THE CANDIDATE

V. Arun born in Tuticorin, Tamil Nadu, India. He attained his Bachelor degree in Chemistry from V.O.Chidambaram College, Tuticorin with first class distinction. Then did his Master degree (Medicinal Chemistry) from Sri Ramachandra University, Chennai, India from 2007 to 2009. In December 2009, he qualified CSIR-NET (LS) and then he cleared GATE exam in 2010 February. In March 2011, he joined the Department of Chemistry, BITS Pilani as junior research fellow in CSIR sponsored Project under the supervision of Prof. Dalip Kumar. Subsequently, in 2011 August, he registered for Ph.D program under the guidance of Prof. Dalip Kumar with the financial assistance from the CSIR sponsored Project. In October 2014, he received CSIR-SRF fellowship. During the Ph.D tenure, he has presented (oral/poster) his research work in various national and international conferences. He has published research articles in well renowned international journals.

BRIEF BIOGRAPHY OF THE SUPERVISOR

Dr. Dalip Kumar is a Professor of Chemistry at Department of Chemistry, Birla Institute of Technology and Science, Pilani. He received his Ph.D degree from Kurukshetra University, Kurukshetra, Haryana in 1997. For his doctoral degree, he worked with Prof. Shiv P. Singh in the research area of heterocyclic chemistry. After his doctorate, he worked as a post-doctoral fellow (1997-1999) with Prof. Rajender S. Varma at Sam Houston State University, TX, USA. He was also associated with Prof. Sean M. Kerwin as a post-doctoral fellow (1999-2000), College of Pharmacy, University of Texas at Austin, TX, USA. He joined BITS Pilani, Pilani campus, as a lecturer during 2000-2002. Later, in December 2002, he moved to University of Maryland, College Park, MD, USA as a Research Associate. In 2004, Prof. Kumar rejoined BITS Pilani, Pilani campus, as an Assistant Professor, at Department of Chemistry and since then he is continuing there. He was promoted to professor in year 2012. He has been involved in research for the last 20 years and in teaching for 13 years. As a result of his research accomplishment, he has around 120 international publications in peer reviewed journals. Prof. Kumar has guided six Ph.D students and currently he is supervising six Ph.D. students. He has one US patent, one Indian patent and handled several projects from DST, DRDO, UGC, CSIR and DBT. Currently, he has one DST-JSPS Indo-Japan project and a collaborative industrial project from Ranbaxy Research Laboratory Ltd.

Prof. Kumar is a recipient of prestigious CRSI Bronze Medal from Chemical Research Society of India in 2016, Honorary Diploma for Scientific Achievements and International Scientific Collaboration by Russian International Charitable Foundation “Scientific Partnership”, Moscow, Russia (March 2013). He received the Prof. R. D. Desai 80th Birthday Commemoration Medal and Prize from Indian Chemical Society for year 2015. He is an Associate Editor of Chemistry & Biology Interface Journal published by Indian Society of Chemists and Biologists, Lucknow. Prof. Kumar is life members of Indian Chemical Society, Indian Society of Chemists and Biologists, and Indian Council of Chemists. His current research pursuit is focused on synthesis of indole and porphyrin derived potential anticancer agents by employing transition-metals and organoiodine reagents.