Chapter 1

General Introduction

"Functionalization of Indoles and Related N-Heterocycles"

1.1 Heterocyclic Compounds

Heterocycles constitute the largest and most diverse classical division of organic compounds. Being referred in the Encyclopaedia Britannica as – "A class of organic compounds characterized by the presence of at least one atom of an element (heteroatom) other than carbon in its cyclic ring structure" [1]. The most common heteroatoms encountered are nitrogen, oxygen, and sulphur confined in the aromatic or non-aromatic ring structures. The presence of heteroatoms in organic core offers a high degree of structural diversity within this class of molecules with greater implications in chemical and biological domain [2,3]. In chemical abstracts, more than half of the known organic compounds are recorded as heterocycles. Thus, the chemistry of heterocyclic compounds is considered as one of the most intriguing and ever-expanding branches of organic chemistry.

Literature studies reveal the records of heterocyclic chemistry started back in the 1800s, as a foundation step towards improvement of organic chemistry. Some of the initial advances include, isolation of alloxan from uric acid achieved by Brugnatelli in 1818, synthesis of furfural by reacting sulphuric acid and starch by Dobereiner in 1832, and isolation of pyrrole from dry distillation of bones in 1834 by Runge [4]. In 1951, Chargaff spotted the role of heterocycle pyrimidines and purines in genetic coding in living organisms [4]. Since then, these molecules have sustained the interest of researchers through decades of historical developments in organic synthesis and biomedical science.

1.2 *N*-Heterocycles: The Molecules of Diverse Biological Functions

Within the vast library of available heterocyclic compounds, those containing at least one nitrogen atom in the ring skeleton are of particular interest. These *N*-heterocycles are inherently braided into most of the basic biochemical processes of life, controlling the foundation of existence. *N*-heterocyclic scaffolds are present in base pairs of purines (guanine and adenine) and pyrimidines (thymine, cytosine, and uracil), found in DNA and RNA [5]. These *N*-heterocycles are incorporated as background skeletons of various biological macromolecules including nucleic acids, amino acids, hormones, enzymes, vitamins, and various natural products [6-8]. Thus, the fundamental languages of life processes, encompassing cell metabolism and

functioning, heredity and evolution, prominently feature a great variety of *N*-heterocyclic moieties that are essential for their manifold properties. Figure **1.1** features some of the commonly encountered five- or six-membered *N*-heterocyclic cores present in natural and synthetic compounds.

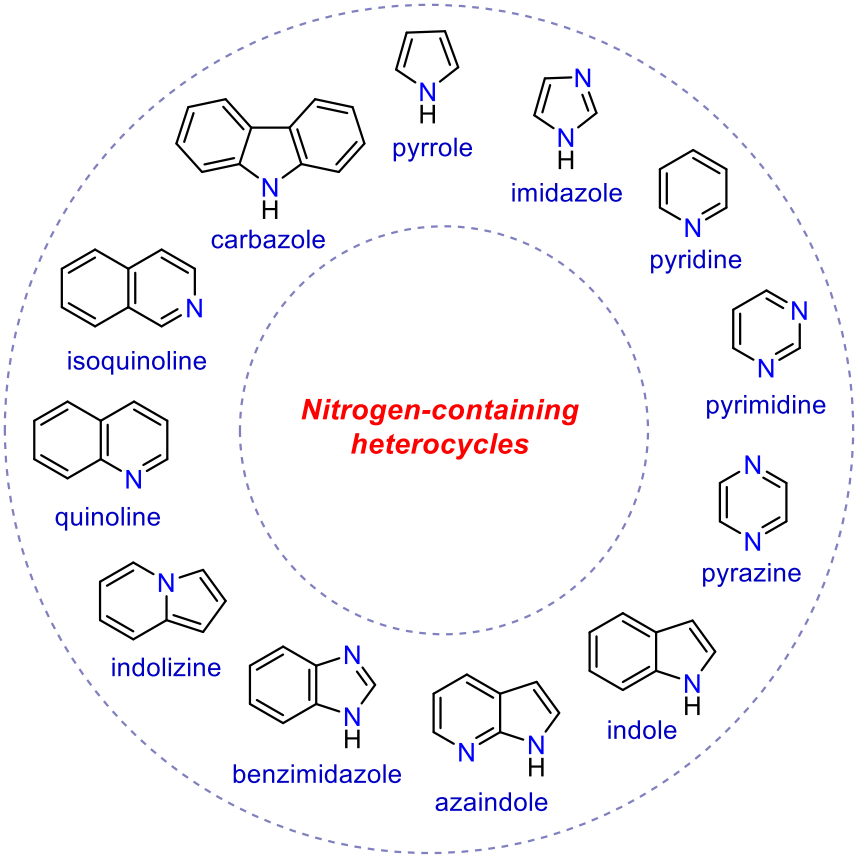


Figure 1.1 Representative examples of parent *N*-heterocyclic compounds

Most of the *N*-heterocyclic compounds distributed in nature shows exceptional spectrum of physiological and pharmacological activities including antimicrobial, anticancer, anti-inflammatory, antiviral, insecticidal, antidepressant and analgesic behaviour [7,9]. These properties impact these molecules as prime candidates in pharmaceutical domain. A glance at the US Food and Drug Administration (FDA) databases reveals presence of *N*-heterocycle in more than 60% of approved drugs [10], underlining the structural significance of these heterocycles in engineering of clinically-significant molecules. The interest in these molecules cumulates from their capacity to establish diverse molecular interactions, such as ionic bonding, H-bonding formation, dipole-dipole interactions, van der Waals forces, hydrophobic interactions, and π-stacking interactions of nitrogen compounds, allowing them to

bind to a variety of enzymes and receptors in biological targets with high affinity [11]. These interactions also assist as a powerful tool to manipulate the physicochemical properties such as polarity, solubility, lipophilicity, pharmacokinetics, and toxicological properties of drug molecules [7]. Thus, the control over nature of substituents and their positions around a heterocyclic module can induce infinite diversity among this class of molecules. Certainly, these natural products continue to be the greatest inspiration for chemists to devise imaginative ways to mimic and synthesize such incredible heterocyclic architectures.

1.3 Indole-Based Heterocyclic Compounds

Indole, also known as benzo[*b*]pyrrole is one of the well-known scaffolds in chemical biology and natural product domain. The discovery of indole is linked with the development of dye indigo. Adolf von Baeyer in 1866 investigated the conversion of indigo into various products and in the process of structural determination of indigo, he discovered the compound indole. Later in 1869 its molecular structure was proposed [12]. In 1883, Fischer indole synthesis was reported for the first time, which is considered as an efficient and one of the finest methods of indole synthesis [13,14].

The indole is prominently an active moiety in naturally occurring alkaloids, which are nitrogen containing secondary metabolites in plants and animals [15,16]. Alkaloids such as tryptophan is well known for its nutritional importance to animals and human beings [17], Serotonin is an important neurotransmitter in animals [17], and reserpine is used for lowering of blood pressure and as a tranquilizer [18].

Marine natural products often display broader diversity and novelty relative to terrestrial source ones, emerging from unique marine environments with high pressure, high salt content and low temperature conditions [19,20]. Marine organisms are one of the richest producers of bioactive natural products, and various indole metabolites have been identified and reported with diverse physiological activities.

Studies by Qiu and co-workers on metabolites of a deep-sea sediment, isolated brominated bis-indole metabolites from the 25D7 clone derived *E. coli* fermentation broth, *via* addition of 5-bromoindole into the culture medium [26]. The 5-

bromometagenediindole B (**1**) demonstrated cytotoxic activity against breast (MCF-7), skin (B-16), hepatocellular (BEL-7402), and fibrosarcoma (HT-1080) tumor cell lines *in vitro* [21]. Similarly, 3,3′-bisindole (**2**) and 3,3-(2,3-dihydroxypropyl)diindole (**3**) were isolated from marine-derived *Nocardiopsis* species which exhibited antimicrobial activity against several strains of Gram-positive and Gram-negative bacteria, and yeast *Candida albicans*. Compound **2** also produced a weak inhibition against human epithelial carcinoma (KB) and lung (LU-1) cancer cell lines [22]. Figure **1.2** illustrates few marine-derived indole containing heterocyclic compounds with biological prominence.

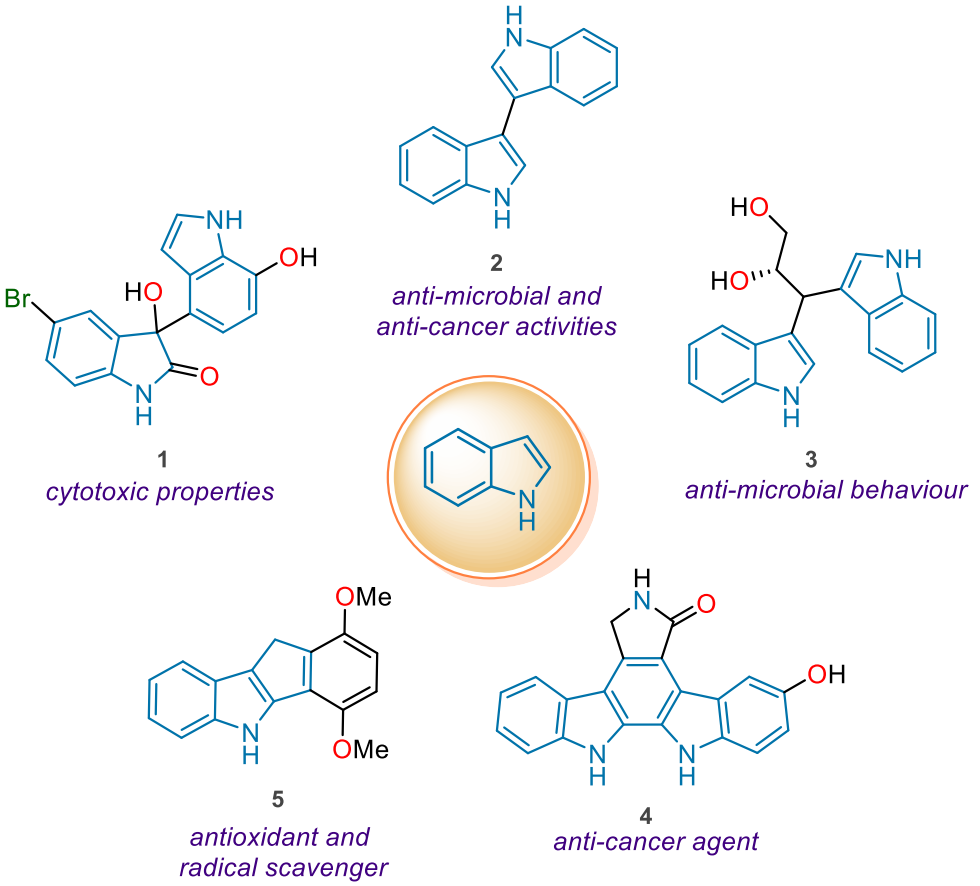
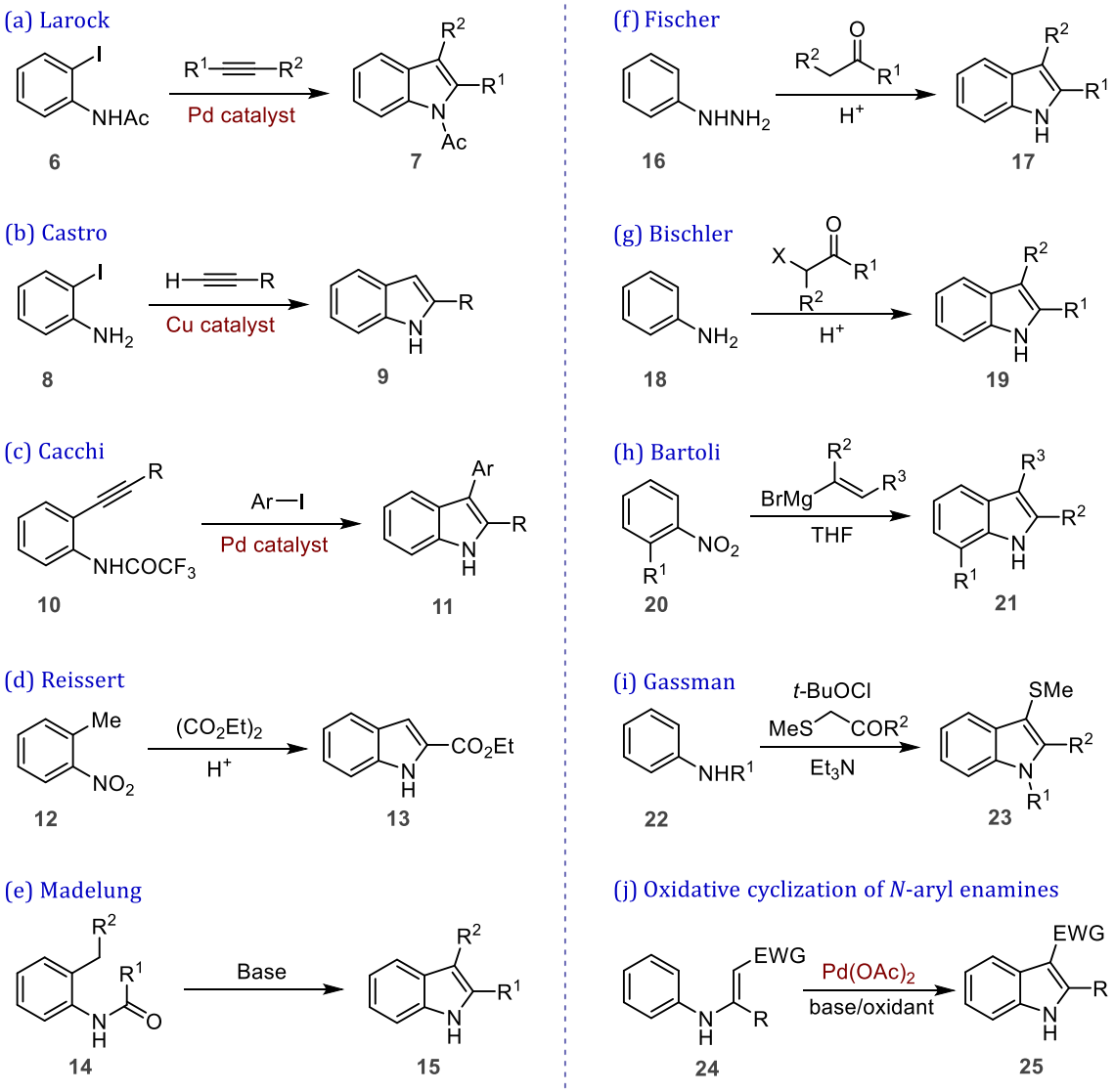


Figure 1.2 Indole-based heterocyclic compounds with biological significance

Ma and co-workers showed successful isolation of natural indolocarbazole alkaloids from marine-derived *Streptomyces* species DT-A61 [23]. The compound (**4**) exhibited significant cytotoxic activity against human prostate (PC-3) cancer cells and also displayed potent enzyme inhibitory activity on protein kinases. Similar indole fused-ring structures were synthesized by Saracoglu and co-workers where compound **5** showed powerful antioxidant and H_2O_2 scavenging activity [24].

1.4 Synthetic Approaches to Indoles

Owing to the structural significance of the core, indole has been termed a "privileged structure" [25]. Hence, development of strategies for the convergent synthesis of indole and related heterocycle derivatives have been an active area of research for centuries. With a few exceptions, indole synthesis mostly involves annulation of the five-membered ring to an existing benzene ring bearing appropriate functionality. This is usually achieved by employing disubstituted arene precursors where the two substituents are connected in *ortho*-relationship with each other or monosubstituted precursors in which a single substituent is cyclized directly onto the aromatic ring (Scheme **1.1**) [26].



Scheme 1.1 Classical methods of synthesis of indole from (a-e) *ortho*-disubstituted arene precursor, and (f-j) monosubstituted precursors

Most of the approaches to indole synthesis, including many of the modern catalytic methods mainly involved *ortho*-disubstituted arene precursors utilizing transition-metal catalysis or non-catalytic pathways. Some of the classical examples include the cyclization by Larock, Cacchi, Castro, Reissert, Madelung, etc (Scheme **1.1a-e**) [26,27]. Use of such bifunctional precursors appear advantageous as it allows regiospecific closure of the indole ring as compared to using monosubstituted precursors where the possibility of ring closure in two different directions might give mixture of isomeric products. However, preparation of starting materials with two specific substituents at adjacent positions show synthetic complexity in terms of lengthy preparation steps required to make the precursor. In contrast, monosubstituted precursors are usually accessed much more readily. One example being the Fischer indole synthesis, which shows coupling of mono-functionalized arene with a readily available aldehyde or ketone (Scheme **1.1f**) [28]. Although first reported in 1883, but remains the pre-eminent method for the synthesis of indoles till date. Similar synthesis was reported by Bischler involving alkylation of an aniline with an α-haloketone, followed by acid-catalyzed ring closure (Scheme **1.1g**) [29], and Bartoli synthesis where *ortho*-substituted nitroarenes react with excess of Grignard reagent for synthesis of indoles (Scheme **1.1h**) [30].

Among the numerous developments that have emerged for the synthesis of indoles in recent years, transition metal mediated oxidative cyclization of *N*-aryl enamines has emerged as a considerable approach (Scheme **1.1j**) [31]. *N*-aryl enamines generated from anilines and electron-poor alkynes were further treated with stoichiometric Pd(II) salt in presence of additional oxidant. The reaction proceeds *via* successive electrophilic palladation of the enamine and arene, followed by reductive elimination, and many variants of the approach have emerged in recent times. But the scope of these reactions is mostly limited by the requirement for an electron-withdrawing group to stabilize the enamine intermediate.

Despite significant advances in construction of indole ring system from pre-designed starting molecules, the prime difficulties associated with the methods are the inaccessibility and toxicity of the precursors used, harsh reaction conditions and poor substrate scope of the reactions. Hence, there has been considerable effort to find safer and more reliable alternatives.

Another strategy for synthesis of substituted indole derivatives appears from the concept of functionalization of available indole framework, which can be manifested either through halogenation and subsequent C–C cross-coupling methodology, or through direct C–H bond activation [32]. The concept and detailed overview of the process will be discussed in the upcoming sections to follow.

1.5 Introduction to C–H Activation and Functionalization

C–H bonds, the most fundamental linkage in organic compounds are generally inert and thermodynamically stable (bond dissociation energies ≥ 90–110 kcal mol^{-1}). In synthetic chemistry, C–H bond activation refers to an organic transformation involving cleavage of a C–H bond, which is further functionalized to a new C–R bond, where R can be C, O, or N atom (Figure **1.3**) [33].

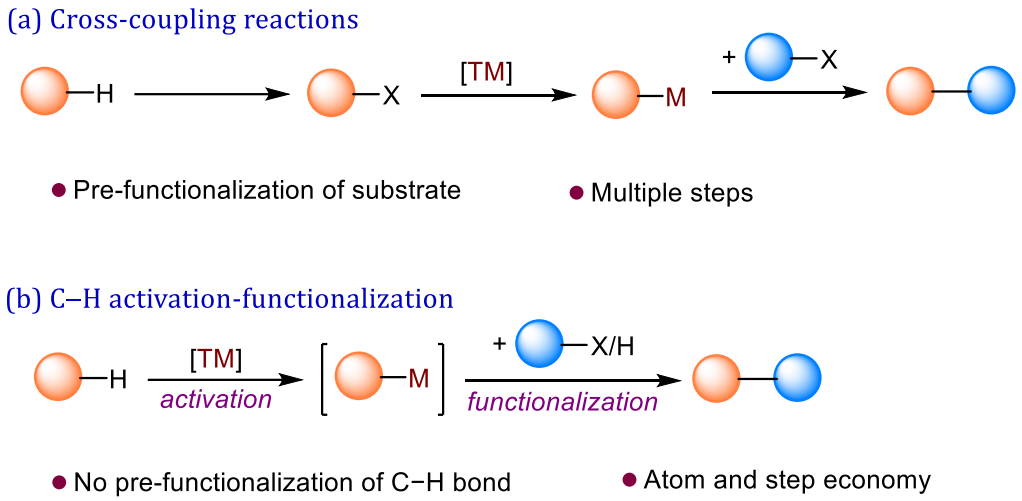
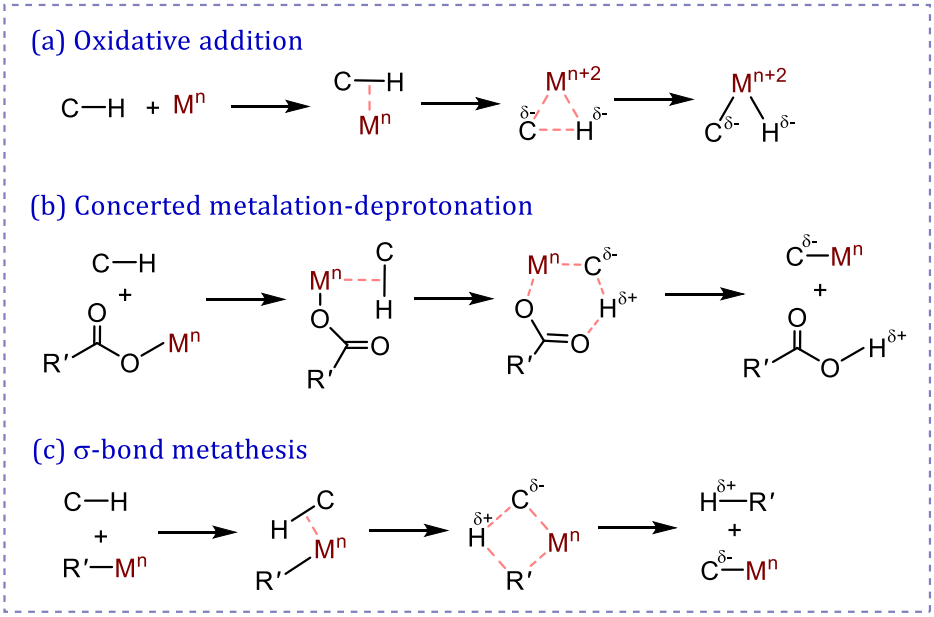


Figure 1.3 C–H bond activation and functionalization

In comparison to the established cross-coupling methodologies for the formation of C–R bonds, direct C–H activation and functionalization removes the requirement for pre-functionalization of coupling partners, also avoiding intermediate functional group manipulations and formation of undesired stoichiometric by-products. Direct functionalization of non-activated C–H bonds represents an attractive class of transformation which maximizes atom- and step- economy, evolving as an environmentally attractive synthetic paradigm [34]. The process enables the direct use of the most abundant feedstock of C–H bonds for the explorations of more complex and functionalized organic molecules. Thus, C–H activation has advanced as an attractive and powerful tool for the functionalization of organic molecules.

However, an intrinsic challenge to this chemistry lies in controlling positional-selectivity, as a single organic molecule can incorporate several types of unique C–H bonds in its structure [35]. Similarly, low reactivity of C–H bonds often entails harsh reaction conditions to achieve the desired selectivity in synthetically useful yields. Thus, site-selective activation of one C–H bond in presence of multiple C–H bonds is a long-standing challenge. Conceptually, two different ways of site-selection can be addressed: substrate control and reagent control [36,37]. The former relies on the inherent preference of the substrate to react at one specific site, while the latter depends on special features of the reagent that can overcome the intrinsic biasness of the substrate.

Transition metals (TM) play a pivotal role in C–H bond activation-functionalization chemistry. Mechanistically, C–H activation process involves coordination of the C–H bond to the metal-center to form an organometallic carbon–metal (C–M) bond (Scheme **1.2**) [36,38].



Scheme 1.2 Different modes of transition metal-catalyzed C–H activation

The activation process can be initiated by the following three pathways-

(a) **Oxidative addition**, where a low-valent electron-rich transition metal center is inserted into a C–H bond;

(b) **Concerted metalation-deprotonation** (**CMD**), which is a type of electrophilic activation mechanism followed by intramolecular deprotonation by acetate or

carboxylate ligands, typically occur for electropositive late transition metal complexes; or

(c) **σ-bond metathesis**, which is a concerted four-centered mechanism for early transition metal complexes in higher oxidation state involving bond breaking and formation in one step.

The former require a change in oxidation state, which is contrasted with the latter two mechanisms that maintained the metal oxidation state. Thus, the type of inner sphere C–H bond cleavage mechanism depends on the nature and the oxidation state of the metal in the particular complex.

1.6 Site-Selective Functionalization of Indole C–H Bonds

After the advent of Pd-catalyzed cross-coupling reactions and transition metal-catalyzed C–H activation process, direct modification of the indole nucleus has emerged as a diverse and practical synthetic approach. Some pioneering examples of C–H activation of indoles have been reported as early as the 1980s, however until the 2000s this methodology was not fully evolved. Since then, development of methodologies concerning indole synthesis and selective functionalization has become one of the most attractive goals in organic chemistry.

Structurally, there are six C–H bonds in the indole motif available for direct C–H activation and functionalization: positions C2 and C3 in the pyrrole core, and C4-C7 in the benzene core (Figure **1.4**).

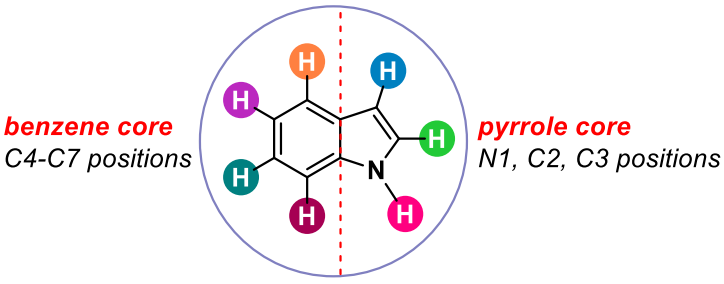


Figure 1.4 Structure of indole motif

However, all these C–H bonds are non-equivalent in terms of reactivity and electronic properties. The C3 position of indole is the most reactive site followed by C2 in terms of their nucleophilic reactivities [39]. The intrinsic reduced nucleophilicity of the *N*–H functionality permits *N*-substitution only when the *N*–H proton is removed to

generate a strongly charged nucleophile [40]. Consequently, majority of the attention has been paid on the functionalization of indoles in the C2 and C3 positions, employing divergent methods based on transition metal catalysis and using metal-free protocols [41-43]. In contrast, regioselective C–H functionalization at the C4-C7 positions in indole are more difficult to achieve because of their lowered reactivities. Yet exciting developments have been achieved to access the remote regioselectivities by careful installation of appropriate directing groups [44-47].

In the following sections, a detailed overview of the major advances on direct C–H functionalization of indole at C2 and C3 positions has been provided driven by various transition metal-catalyzed and metal-free activation processes using appropriate directing groups or directing group-free strategies (Figure **1.5**).

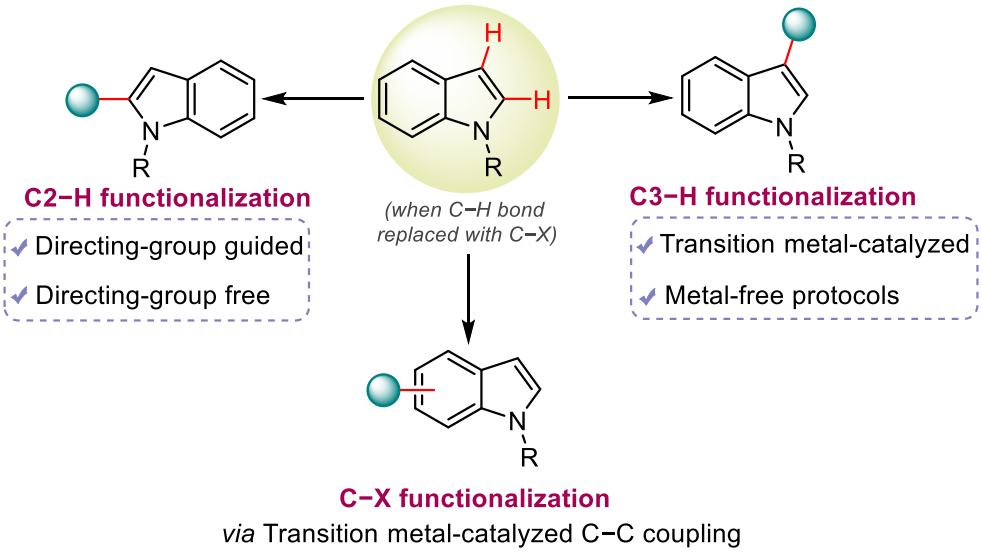


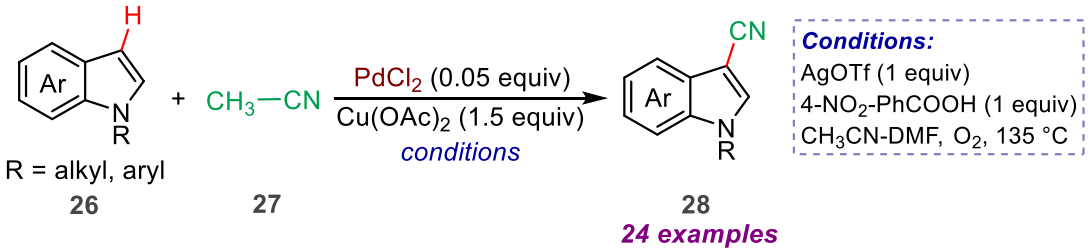
Figure 1.5 Scope of the literature review of the thesis

1.7 Functionalization at the C3 Position of Indoles

Being the most reactive position of indole nucleus, one of the most classic reactions of indoles involve electrophilic functionalization at the C3 position. The high reactivity of the 3-position can be predicted on the basis of significant delocalization of electron density from nitrogen to the C3 atom of the ring, and also from the frontier electron density information obtained from molecular orbital calculations [48]. Thus, functionalization at C3 position of indoles is still one of the thriving areas of research and a range of metal-catalyzed and metal-free approaches have been established for the process. Some of the seminal works are highlighted in the section below.

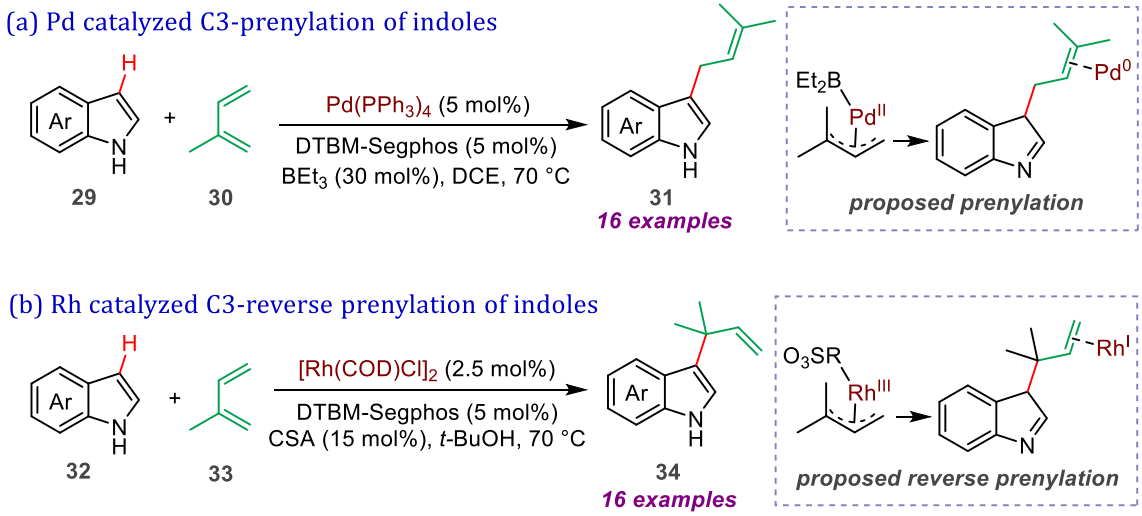
1.7.1 Transition Metal-Catalyzed C3-Functionalization of Indoles

Palladium metal catalysis have been highly appreciated in the field of direct C–H functionalization reactions. Zhou and co-workers designed a $PdCl_2$ catalyzed methodology for C3-cyanation of *N*-substituted indoles (**26**) *via* C–H bond activation [49]. CH_3CN (**27**) is utilized as a green and environmentally friendly cyanide source in presence of $Cu(OAc)_2$ under O_2 atmosphere (Scheme **1.3**). AgOTf was used as a co-oxidant in the process. Mechanistic outlook is provided by initial C3–H activation of indole with Pd(II) catalyst, followed by transition metal-catalyzed C–CN bond cleavage of acetonitrile, thus subsequently leading to the desired 3-cyanoindole derivatives (**28**).



Scheme 1.3 $PdCl_2$ catalyzed C3-cyanation of *N*-substituted indoles

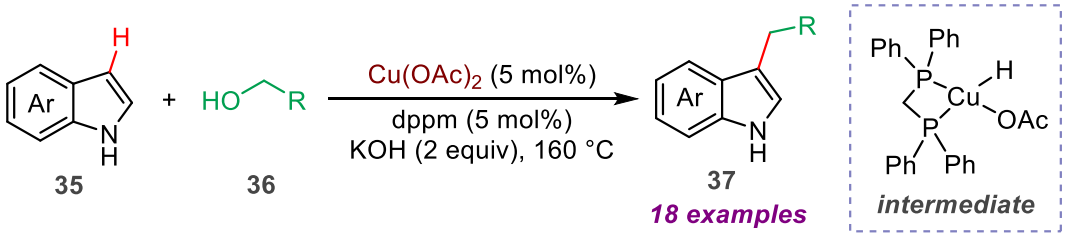
Chen and co-workers reported their findings on regio-divergent C3-prenylation and reverse prenylation of indoles with isoprene *via* C–H functionalization [50]. Manipulation of the regioselectivity was controlled by the choice of metal-hydrides (M–H): Pd–H facilitates prenylation (Scheme **1.4a**) whereas Rh–H facilitates reverse prenylation (Scheme **1.4b**).



Scheme 1.4 Regio-divergent Pd and Rh catalyzed C3-functionalization of indoles

Excellent selectivity is achieved for C3-prenylated indoles (**31**) using $Pd(PPh_3)_4$ as catalyst in combination with DTBM-Segphos and BEt_3, while $[Rh(COD)Cl]_2$ in combination with DTBM-Segphos and CSA worked for C3-reverse prenylated indoles (**34**). Mechanism for this divergent selectivity followed a similar pathway with initial oxidative addition of metal-center to respective BEt_3 or CSA, followed by migratory insertion of isoprene into M–H bond, further being attacked by the C3 position of indoles. The differences in regiochemical preference are decided from the respective stabilities of the olefin-metal complexes formed in the process.

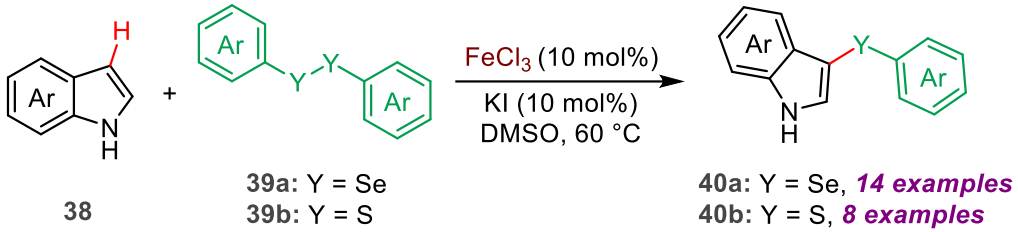
In contrast to the expensive metal catalysts, catalysis by non-precious, earth-abundant 3d metals such as iron, nickel, copper, cobalt, and others are gaining importance in C–H activation reactions due to the economic benefits of these metals. Dang and co-workers have developed a methodology for C3-alkylation of indoles (**35**) with alcohols (**36**) catalyzed by copper *via* borrowing hydrogen strategy [51]. $Cu(OAc)_2$ in used as the catalyst in combination with dppm ligand for the study (Scheme **1.5**). Hydrogen borrowing methodology has recently emerged as an alternative approach to the classical alkylation processes as non-toxic and easily available alcohols are used as alkylating reagents. Experimental evidences reveal formation of a copper hydride (Cu–H) complex and *in situ* generation of aldehyde species. Subsequent attack of aldehyde at C3 position of indole and following hydride transfer step from copper hydride to indole gives the C3-alkylated indoles (**37**). Similar methodologies presenting C3-alkylation of indoles *via* borrowing hydrogen catalysis have been achieved with Co [52] and Ni [53] containing catalytic systems.



Scheme 1.5 $Cu(OAc)_2$ catalyzed C3-alkylation of indoles

Being one of the most abundant elements on earth, iron represents an obvious choice for catalyst development. Rampon and co-workers devised an iron catalyzed methodology for C3-chalcogenylation of indoles (Scheme **1.6**) [54]. $FeCl_3$ was used as the catalyst in presence of KI for the rapid synthesis of 3-selenylindoles (**40a**) and

3-sulfenylindoles (**40b**) from diphenyl diselenides (**39a**) and diphenyl disulfides (**39b**) respectively. Mechanistic investigations reveal reduction of Fe(III) to Fe(II) and formation of I_2 in the process, which effectively conducts the reaction further. The formation of electrophilic intermediate in the form Ar–Y–I (Y = S, Se) attacks through the C3 position of indole generating the desired regioselectivity.



Scheme 1.6 $FeCl_3$ catalyzed C3-selenylation/sulfenylation of indoles

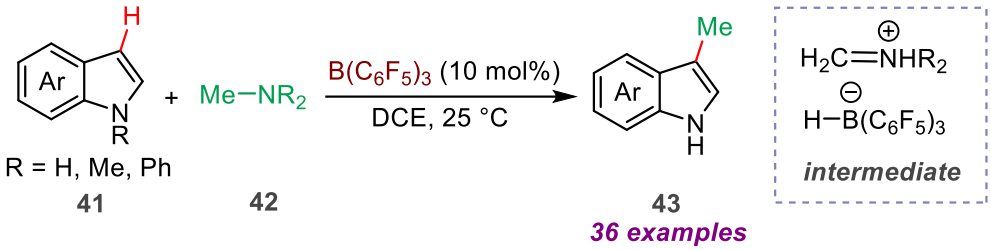
Despite successful and innovative advances towards metal-mediated functionalization approaches, the dependence of the methods on expensive metal catalysts marks serious complications, as they are highly moisture and air-sensitive, and their preparation process needs complex handling and harsh conditions. Additionally, the protocols come with an associated difficulty of removal of metal impurities from the products, which restricts their practical utility. Thus, from the green chemistry perspectives, metal-free processes emerge as a beneficial alternative to transition metal catalysis.

1.7.2 Metal-Free Protocols for C3-Functionalization of Indoles

In the contemporary world of ample metal mediated transformations, there is a unique space for metal-free functionalization techniques. Being less toxic and cost-effective, it becomes a prerequisite for medicinal and pharmaceutical industry. Therefore, there is rising demand for the development of metal-free catalytic systems for C–H functionalization approaches. Some of the notable approaches for direct C3-functionalization of indoles have been highlighted in this section.

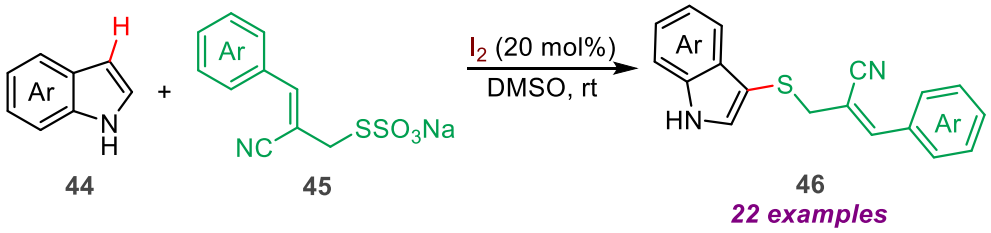
Pulis and co-workers described a triaryl borane catalyst $B(C_6F_5)_3$ towards direct C3-alkylation of indoles with amine-derived alkylating agents (Scheme **1.7**) [55]. The borane catalyst was shown to mediate heterolytic cleavage of the *α*-nitrogen C(sp^3)–H bonds in the amine-based alkylating agents (**42**) *via* hydride abstraction, generating iminium-borohydride ion pairs. The electrophilic iminium species attacks

through the C3 position of indoles, further eliminating an amine molecule produces the C3-alkylated indoles (**43**) in the process.



Scheme 1.7 $B(C_6F_5)_3$ catalyzed C3-methylation of indoles

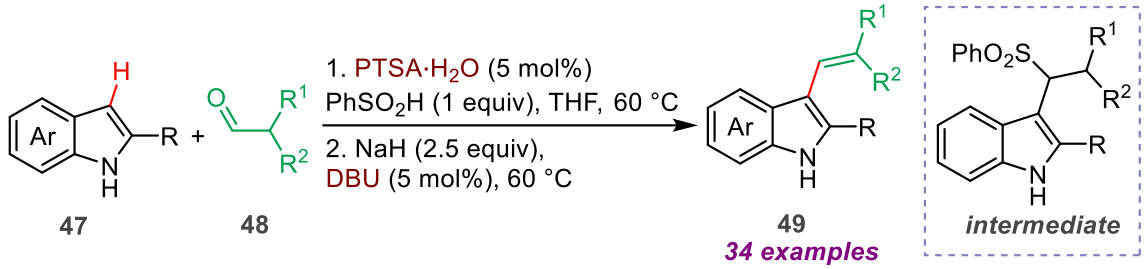
"Molecular iodine catalysis" has emerged as a green and environmentally versatile approach in conducting essential organic transformations. Being naturally abundant, inexpensive, non-toxic, and its mild Lewis acidic behaviour makes it a popular choice of catalyst in metal-free processes. Singh and co-workers described a molecular-iodine catalyzed regioselective C3-thioallylation of indoles using Bunte salts derived from Baylis–Hillman bromides [56]. Bunte salt ($RSSO_3Na$) (**45**) are used as the sulphur source, easily obtained from functionalized α, β-unsaturated olefin Baylis–Hillman (BH) bromides (Scheme **1.8**). The reaction of Bunte salts with molecular iodine generates the electrophilic sulfenyl iodide species, which undergoes regioselective Friedel–Crafts reaction at the most reactive C3 position of indole finally leading to the C3-thioallylated indole (**46**) derivatives.



Scheme 1.8 I_2 catalyzed C3-thioallylation of indoles

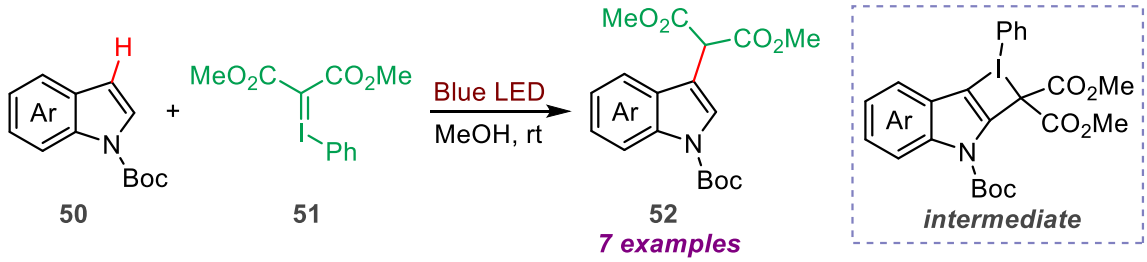
Similar to the Lewis acid catalysis, Brønsted acids have also been commonly encountered as catalysts in the topic concerned. Maji and co-workers designed a transition metal-free C3-alkenylation of indoles (**47**) with aliphatic aldehydes (**48**) as alkenylating agents (Scheme **1.9**) [57]. Several 2-substituted 3-alkenylindoles (**49**) were synthesized *via* one-pot sequential Brønsted acid-base catalysis. $PTSA{\cdot}H_2O$ was used as the Brønsted acid and DBU as Brønsted base catalysts for the transformation.

To maintain the desired regioselectivity, phenylsulfonyl group is installed under acidic conditions, which can be subsequently removed under basic conditions, finally leading to the 3-alkenylindoles.



Scheme 1.9 PTSA·H_2O-DBU catalyzed C3-alkenylation of indoles

Recently, several green initiatives have been implemented towards C–H functionalization process. Visible light is gaining interest as one of the clean and sustainable energy sources used in various organic transformations *via* photocatalysis. Sen and co-workers disclosed a procedure for alkylation of indoles with dimethyl malonate derived phenyl iodonium ylides (**51**) under a blue LED light (435–445 nm) source (Scheme **1.10**) [58]. Mechanistic observations suggested the involvement of a radical pathway in the blue LED mediated C–H functionalization reaction, with the formation of an iodocyclobutane intermediate, which subsequently leads to the formation of 3-alkylated indoles (**52**). However, this method suffered serious issues of regioselectivity. Only the *N*-Boc indole derivatives could afford exclusive C3-alkylated products while free *N*–H indoles provided mixtures of C2 and C3 substituted products.

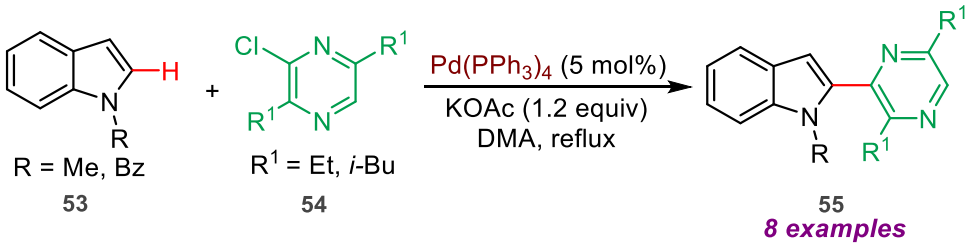


Scheme 1.10 C3-alkylation of *N*-Boc indoles under blue LED

1.8 Transition Metal-Catalyzed C2-Functionalization of Indoles

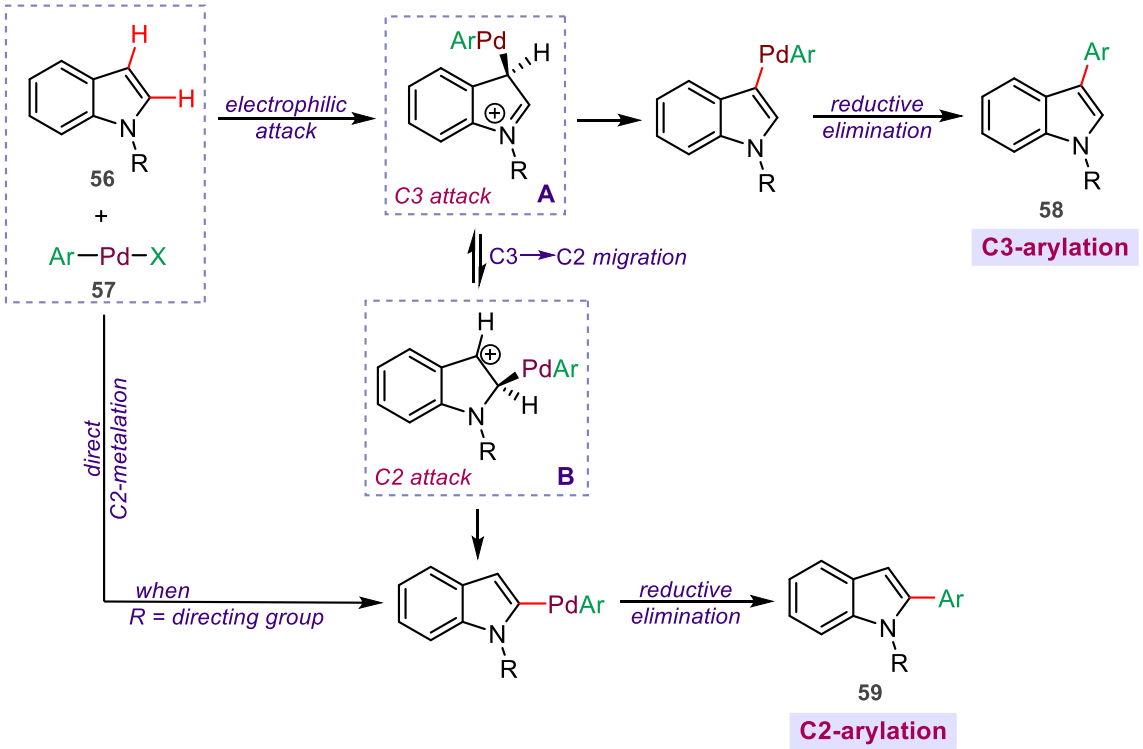
The first Pd catalyzed direct C2-arylation of indoles was reported by Shimizu and co-workers in 1985, where chloropyrazines (**54**) were coupled at 2-position of indoles

(**53**) in the presence of $Pd(PPh_3)_4$ and KOAc (Scheme **1.11**) [59]. This C2 selectivity seemed surprising at that time, being contradicting to the well-established electrophilic aromatic substitution predominantly occurring at the C3 position. Although the mechanism in action was not clear but the result opened new dimensions for organic chemists to explore this new regioselectivity.



Scheme 1.11 $Pd(Ph_3)_4$ catalyzed C2-arylation of indoles with chloropyrazines

Mechanistic rationale to the regioselective preferences of C2 versus C3 positions was interpreted in a $Pd(OAc)_2$ catalyzed arylation of indoles (**56**) by Sames and co-workers [60]. It was proposed that the most probable mechanism for both C2- and C3-arylation pathways initiated *via* electrophilic addition of Pd(II) at the more activated C3 position (Scheme **1.12**).



Scheme 1.12 Proposed mechanism for C2- and C3-arylation of indoles

This C3-palladated indole species (**A**) can either undergo deprotonation and reductive elimination to give the C3-arylated indole (**58**), or experience a C3→C2 migration (1,2-migration) of Pd metal (**B**) leading to the C2-arylated indole (**59**). The driving force for this C3→C2 migration is related to stabilization of the C–Pd bond provided by the nitrogen atom adjacent to C2 position.

Alternately, the direct C2-palladation of indole is possible *via* a non-electrophilic pathway. However, the presence of a strong directing group is often necessitated [60]. Several directed and non-directed transformations that have been appraised for achieving the C2 site selectivity have been outlined in the following sections.

1.8.1 Directing Group Guided C2-Functionalization of Indoles

Owing to the C3 versus C2 selectivity, functionalization at C2 position have been possible through regiocontrol directing group approach (Figure **1.6**). This can be mainly achieved by positional blocking of reactive C3 position or *via* pre-installation of appropriate directing groups at *N*1 position of indoles [47]. The nature of the directing groups (DG) play a crucial role in the activation of inactivated C–H bonds.

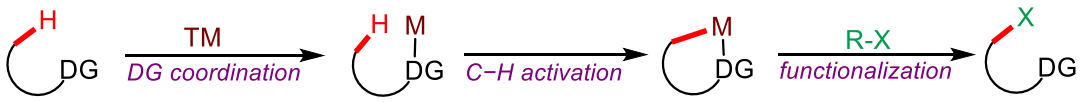
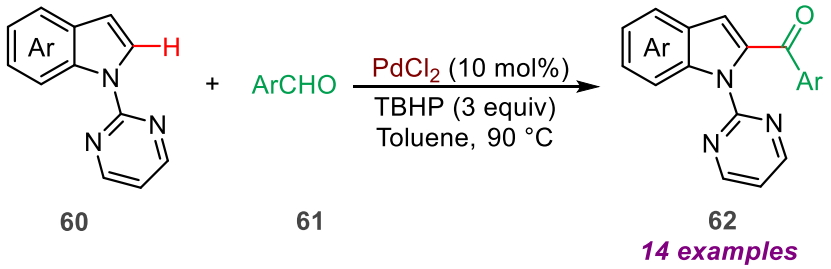


Figure 1.6 Directing group mode of action

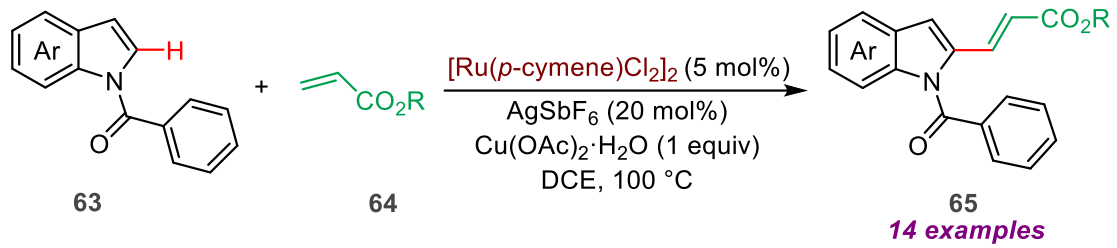
Transition metal catalytic systems including palladium, rhodium, ruthenium, and iridium have been used for demonstrating regioselective C2-functionalization of indoles. Palladium, being commonly used, occupies a pivotal role as a catalyst for C–H bond functionalization reactions. Sekar and co-workers devised a strategy for C2-acylation of indoles (**60**) directed by *N*-pyrimidine directing groups in presence of $PdCl_2$ catalyst and an external oxidant TBHP (Scheme **1.13**) [61].



Scheme 1.13 $PdCl_2$ catalyzed C2-acylation of *N*-(2-pyrymidyl)indoles

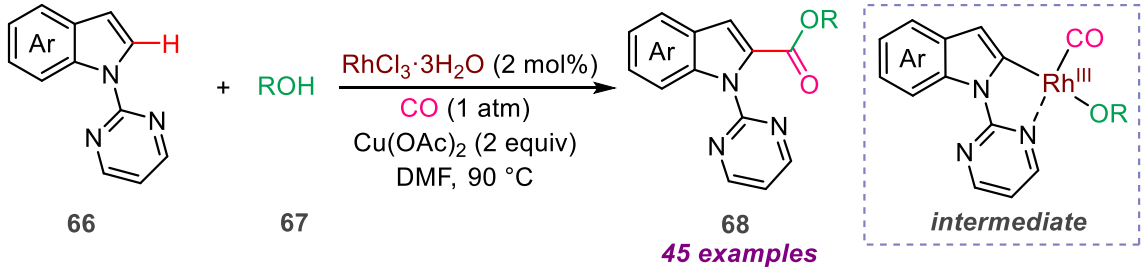
Aldehyde (**61**) was used as the acyl source in the reaction and addition of excess aldehyde is found to produce C2,C7-diacylated indoles through double C–H functionalization reaction. Initial coordination of Pd metal with pyrimidine nitrogen is predicted to give the desired regioselectivity.

Ruthenium metal has also been highly appreciated for C–H functionalization reactions. Prabhu and co-workers have designed Ru(II) catalyzed alkenylation of indoles (**63**) at the C2-position directed by benzoyl directing groups [62]. [Ru(*p*-cymene)Cl_2]$_2$ is employed as the catalyst, in presence of $AgSbF_6$ as activator, and $Cu(OAc)_2{\cdot}H_2O$ as oxidant (Scheme **1.14**). A range of alkyl acrylates (**64**) furnished the desired oxidative Heck-type coupled product (**65**) with high regioselectivity. C2-directing ability of Ru(II) is triggered by its tendency to form five-membered cyclic intermediates.



Scheme 1.14 [Ru(*p*-cymene)Cl_2]$_2$ catalyzed C2-alkenylation of *N*-benzoylindoles

Use of CO in transition metal-catalyzed intermolecular C–H carbonylation reaction of indoles with different nucleophiles provides great scientific interest. Yang and co-workers reported a rhodium catalyzed system for a unique alkoxycarbonylation of indoles (**66**) with alcohols (**67**) and CO catalyzed by $RhCl_3{\cdot}3H_2O$ (Scheme **1.15**) [63].

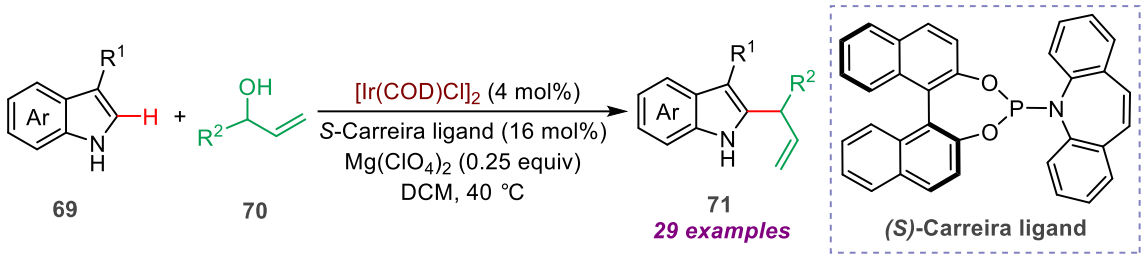


Scheme 1.15 $RhCl_3{\cdot}3H_2O$ catalyzed C2-alkoxycarbonylation of *N*-(2-pyrymidyl)indoles

The method offers convenient access to diverse indole-2-carboxylic esters (**68**), at low catalyst loading (2 mol%) in the presence of $Cu(OAc)_2$ as a stoichiometric oxidant

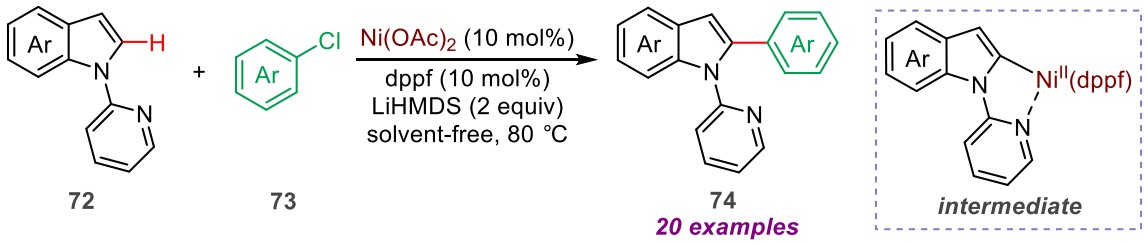
and *N*-pyrimidyl or *N*-pyridyl directing groups. Mechanistic investigations revealed initial coordination of the nitrogen directing group to Rh(III) catalyst forming a five-membered rhodacycle species, which is followed by 1,1-migratory insertion of CO into the Rh–C bond.

In a similar trend, iridium metal catalysis was also explored for C–H functionalization of indoles. You and co-workers designed an intermolecular C2-allylation of indoles (**69**) with allylic alcohols (**70**) catalyzed by iridium (Scheme **1.16**) [64]. This directing group-free approach relies on a $[Ir(COD)Cl]_2$ complex, in presence of Lewis acid $Mg(ClO_4)_2$ to activate the allylic alcohol. Mechanistically, the reaction proceeds *via* direct C2-attack rather than C3-allylation followed by *in situ* migration. The proposed pathway highlights a necessary positional blocking of C3 position of indole to achieve selective C2-allylation (**71**). However, in the absence of C3 substituent, allylation takes places exclusively at the C3 position.



Scheme 1.16 $[Ir(COD)Cl]_2$ catalyzed C2-allylation of 3-substituted indoles

In recent years, there is a substantial shift towards the development of C–H bond functionalization protocols employing naturally abundant and inexpensive 3d metals. In that matter, nickel catalysis has been recognized as an increasingly attractive platform. Punji and co-workers developed a nickel-based methodology for the *N*-pyridine directed C2-functionalization of indoles (**72**) with aryl chlorides (**73**) using $Ni(OAc)_2$/dppf catalyst system at 80 °C (Scheme **1.17**) [65].



Scheme 1.17 $Ni(OAc)_2$ catalyzed C2-arylation of *N*-(2-pyridyl)indoles

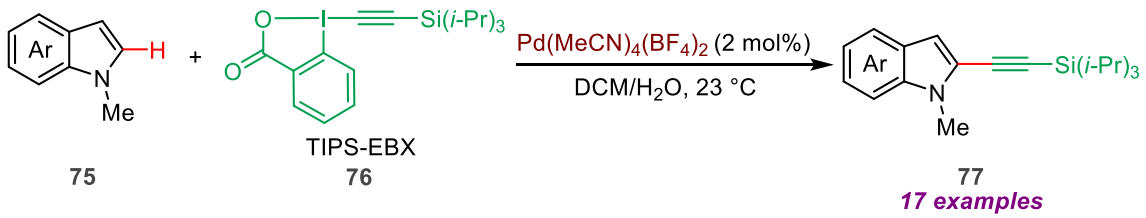
Mechanistic investigations reveal initial coordination of Ni to pyridine-*N* necessary for achieving the C2 selectivity followed by one-electron oxidative addition of aryl chlorides. Similarly, development of iron and cobalt catalysis for C–H activation reactions have been highly appreciated from its economic perspectives [66].

Thus, *N*-directing group mediated C2-functionalization of indoles proceed in appreciable yields maintaining the desired C2 regioselectivity. However, dependency on directing groups is an obvious drawback, requiring additional installation and removal steps, which leads to generation of by-products, thus questions their practicality.

1.8.2 Directing Group-Free C2-Functionalization of Indoles

Apart from the methodologies discussed in section **1.8.1**, development of new catalytic methodologies for direct arylation of indoles without pre-installed directing groups hold significant synthetic potential as it eliminates the need for introducing protecting groups and reactive functionalities prior to C–C bond formation. The methods rely on selective targeting of C–H bonds at C2 position in presence of reactive C3 position and *N*–H functionality.

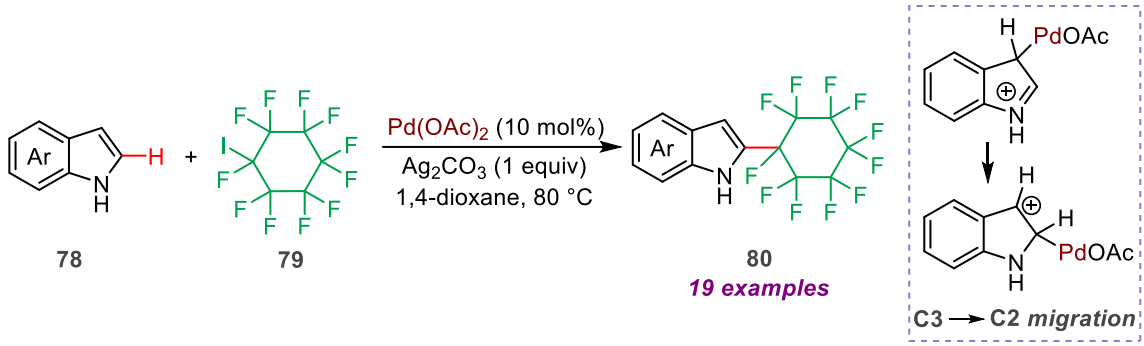
Waser and co-workers designed a directing group-free strategy for C2-alkynylation of indoles (**75**) with a hypervalent iodine reagent triisopropylsilylethynyl-1,2-benziodoxol-3(1*H*)-one (TIPS-EBX) (**76**) using $Pd(MeCN)_4(BF_4)_2$ as catalyst (Scheme **1.18**) [67]. The reaction was expected to follow a Pd(II)/(IV) cycle initiated either *via* direct C2-palladation or electrophilic C3-palladation followed by migration. Further oxidative alkynylation of TIPS-EBX gives Pd(IV), which after reaction regenerates Pd(II) by reductive elimination.



Scheme 1.18 $Pd(MeCN)_4(BF_4)_2$ catalyzed C2-alkynylation of *N*-methylindoles

Incorporation of fluorine atoms or fluoroalkyl groups into biologically active molecules is a well-established strategy to improve the pharmacological and

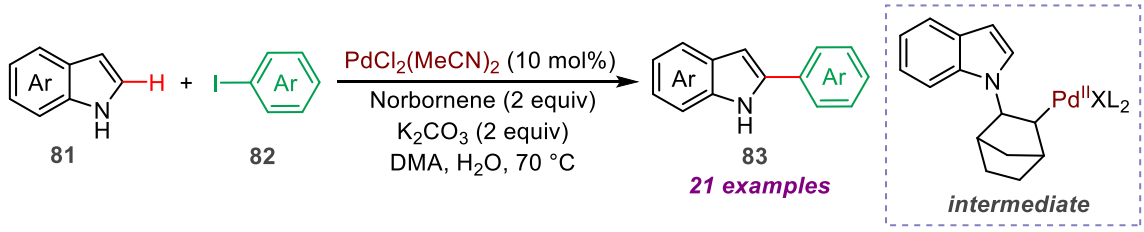
physicochemical characteristics of the molecules. Guo and co-workers developed a method for perfluoroalkylation in C2-position of indoles catalyzed by $Pd(OAc)_2$ (Scheme **1.19**) [68].



Scheme 1.19 $Pd(OAc)_2$ catalyzed C2-perfluoroalkylation of free (*N*–H) indoles

The protocol employed iodofluoroalkanes (**79**) as practical perfluoroalkyl source in presence of Ag_2CO_3 as oxidant. Investigations on reaction mechanism proved feasible involvement of radicals in this reaction. The reaction is expected to take the initial C3-palladation route followed by migration of the C3–Pd bond to activated C2 position. The fluoroalkyl radicals then undergo oxidative addition and subsequent reductive elimination generates the 2-fluoroalkylated indoles (**80**). The role of Ag oxidants in Pd catalyzed C–H functionalization process lies in regenerating back the active Pd(II) catalyst species from Pd(0) after the reaction.

In another method of Pd-catalyzed direct C2-arylation reaction of free (*N*–H) indoles, Jiang and co-workers devised a norbornene mediated regioselective C–H activation strategy [69]. Iodobenzene (**82**) was used as the arylating reagent in presence of $PdCl_2(MeCN)_2$ catalyst and K_2CO_3 as base (Scheme **1.20**).

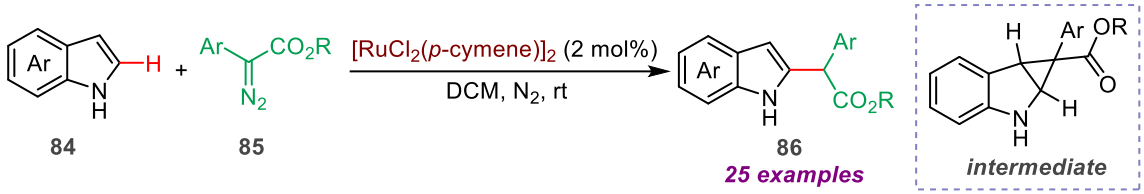


Scheme 1.20 $PdCl_2(MeCN)_2$ catalyzed C2-arylation of free (*N*–H) indoles

Presence of norbornene as a transient mediator displayed high C2 selectivity for the arylation process. The mechanistic pathway was shown to involve an initial *N*-palladation of indoles and aminopalladation of norbornene to form a Pd(II)

intermediate which will undergo *ortho*-C–H activation and final norbornene extrusion generates the C2-arylated indoles (**83**).

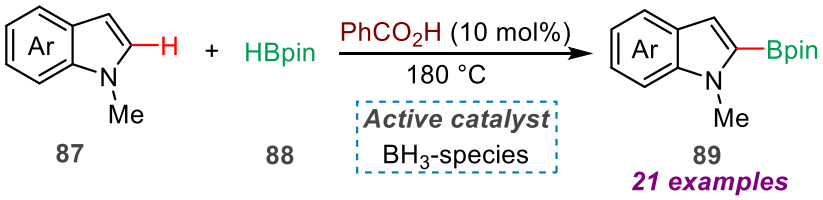
Yu and co-workers presented a methodology for ruthenium catalyzed directing group-free C2-alkylation of free (*N*–H) indoles (**84**) [70]. $[RuCl_2(p\text{-cymene})]_2$ was used as the catalyst and α-aryldiazoesters (**85**) as the carbenoid source, displaying complete C2-selectivity at room temperature conditions (Scheme **1.21**).



Scheme 1.21 $[RuCl_2(p\text{-cymene})]_2$ catalyzed C2-alkylation of free (*N*–H) indoles

Mechanistically, this Ru-catalyzed indole C–H functionalization was predicted to occur *via* a cyclopropylindoline intermediate, and its subsequent ring-opening at the C3 position afforded the C2-alkylated products (**86**). Moreover, this cyclopropanation also accounts for the poor reactivity of indoles bearing the *N*- and C3-substituents due to steric interference.

Although the field of C2-functionalization have been dominated by transition metal catalysis, some metal-free approaches have also been embraced to address the regioselectivity. Zhang and co-workers designed a benzoic acid-promoted C–H borylation of indoles (**87**) with pinacolborane (HBpin) (**88**) (Scheme **1.22**) [71].



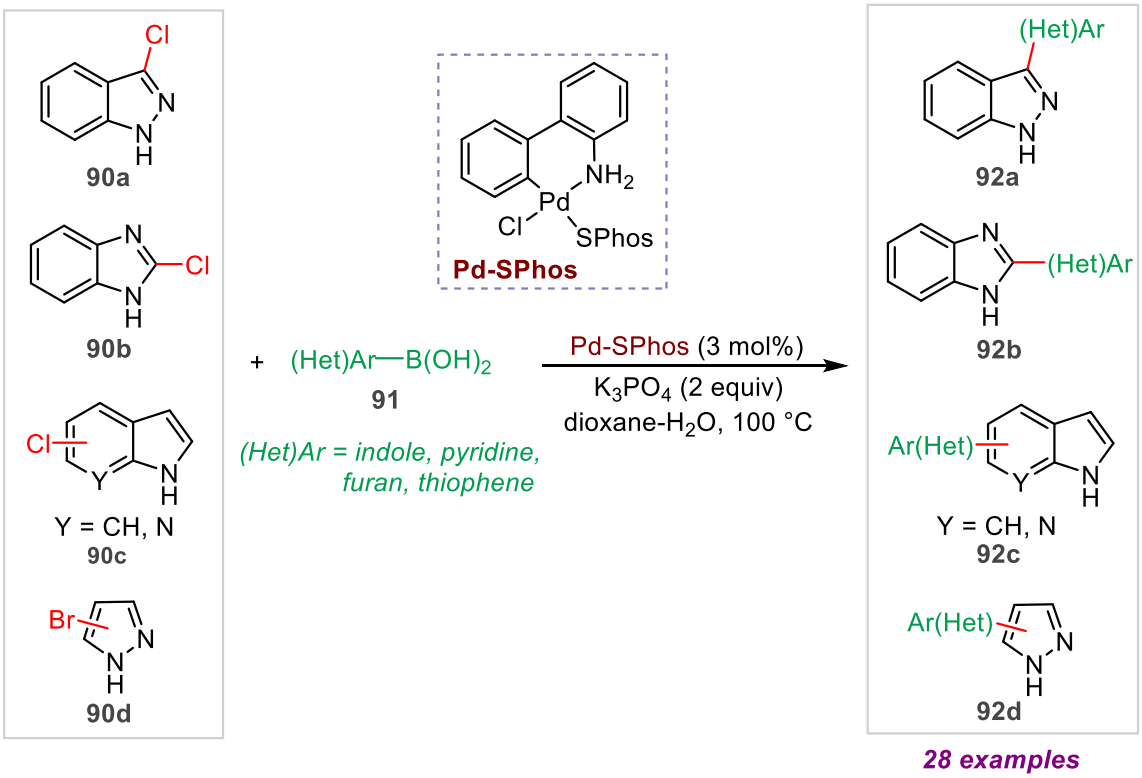
Scheme 1.22 Benzoic acid promoted C2-borylation of *N*-methylindoles

Investigations on reaction pathway reveal BH_3-related borane species to be the active catalyst in this C–H borylation, which might be formed by the decomposition of HBpin in the presence of promoter. The method displayed high C2 regioselectivity without the aid of any transition metal and this unique C2 selectivity can be explained from the possibility of rapid protodeboronation of the C3 isomers, which results in the formation of thermodynamically more stable C2 isomers.

1.9 C–C Coupling of Pre-Functionalized Positions of *N*-Heterocycles

Apart from the direct activation of C–H bonds, functionalization of pre-activated positions of heterocyclic molecules is commonly highlighted in the literature. The idea stemmed from the use of pre-functionalized substrates and their selective functionalization *via* transition metal-catalyzed classical C–C cross-coupling reactions [72,73]. The halogenated organic moiety is functionalized with regioselectivity at the C–X (*X = halogen*) bond with the corresponding coupling partner. Contemporary developments in metal catalyzed C–C bond-formation methodologies have shown valuable and practical applications in conventional arylated substrates. However, the methods suffer constraints when more challenging nitrogen-containing heterocycles are employed as one or both of the coupling partners. Suzuki-Miyaura cross-coupling reaction is one of the most promising and powerful tools for functionalization of organic compounds, even facilitating the C–C coupling of tricky substrate combinations.

Buchwald and co-workers described a methodology for Suzuki-Miyaura cross-coupling of azole halides (**90a-d**) with heteroaryl boronic acids (**91**) (Scheme **1.23**).



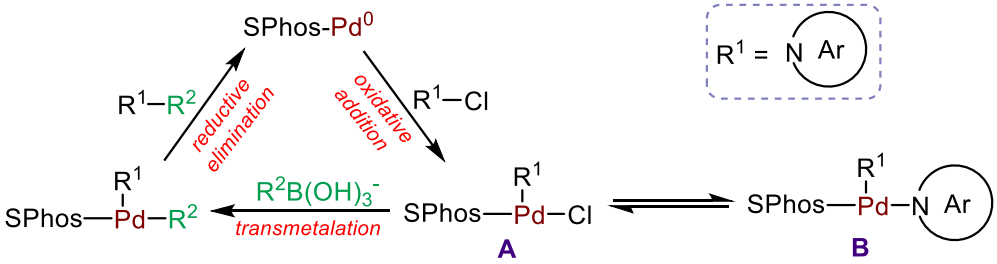
Scheme 1.23 Pd-SPhos catalyzed Suzuki-Miyaura coupling reaction of *N*-heterocyclic halides with heteroarylboronic acids

The reaction was catalyzed by SPhos-Pd precatalyst in presence of K_3PO_4 as base. The method provides access to a wide range of *N*-containing biaryls (**92a-d**) comprising indazole, benzimidazole, pyrazole, indole, oxindole, and azaindole core. Despite successful applications, the process often suffers limitation with respect to substrate scope and high reaction temperature.

The study also accounted for a general understanding of the lowered reactivity of these substrates under classical cross-coupling conditions. The probable mechanism behind the inhibitory effects of acidic *N*–H groups on Pd-catalyzed cross-coupling reactions can be explained as-

1. Complexation of the metal center to the nitrogen atom leading to deactivation of the catalyst;
2. A high energy barrier for oxidative addition of *N*-heterocyclic halides; or
3. A high energy barrier for reductive elimination to form the product.

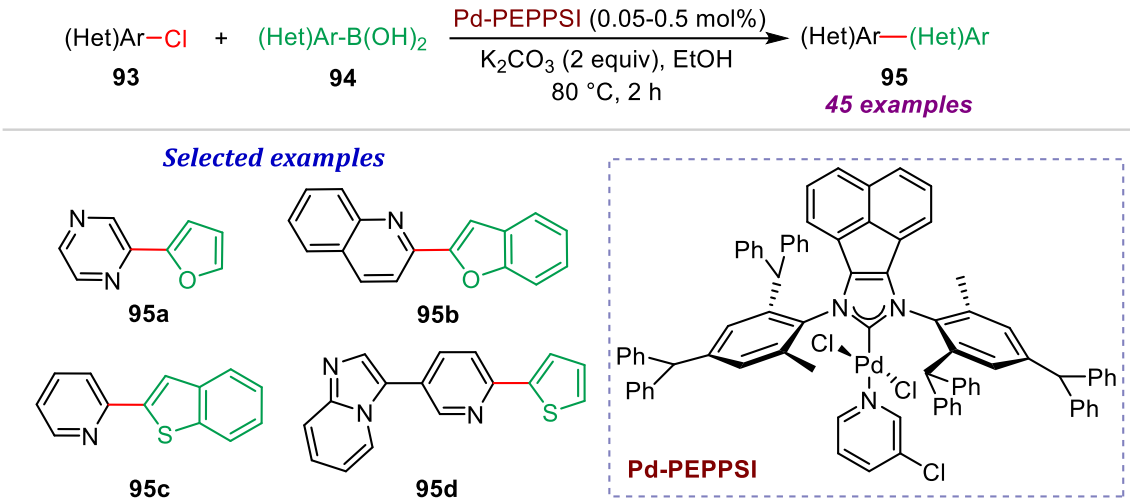
Experimental examinations encountered a [Pd–N] intermediate in the process which was proposed to be the catalytic resting state in the cross-coupling reaction of nitrogen-rich heterocycles [74]. A plausible mechanism has been proposed (Scheme **1.24**) which shows the existence of an equilibrium between [Pd–Cl] (**A**) and [Pd–N] (**B**) species. The presence of additional boronic acid helps reverse the inhibitory effect by shifting the equilibrium back in favour of [Pd–Cl] species, asserting transmetalation to be the rate-determining step. The existence of such equilibrium additionally demands elevated temperatures and extended reaction times.



Scheme 1.24 Mechanism of Suzuki-Miyaura coupling reaction of *N*-rich heterocyclic substrates

Ouyang and co-workers designed a series of Pd-PEPPSI complexes bearing "bulky-yet-flexible" substitutions to translate their catalytic performance towards Suzuki-

Miyaura coupling of various heteroaryl chlorides (**93**) with heteroaryl arylboronic acids (**94**) (Scheme **1.25**) [75].



Scheme 1.25 Pd-PEPPSI catalyzed Suzuki-Miyaura cross-coupling reaction of *N*-heterocycles

This work represents an example for utilization of C–C coupling reaction for synthesis of (hetero)biaryl derivatives. They revealed that the flexible, steric and bulky environment provided by the acenaphthyl backbone in the complex proved to be highly efficient precatalyst for explorations in *N*-containing polyheteroarenes (**95**) containing pyridine, pyrazine, quinolone, thiazole, and imidazole core at low metal loading. Additionally, the π-stacking interactions between the *para*-benzhydryl groups of the complex and the (hetero)aryl chloride substrates, aids in promoting the oxidative addition step in the cross-coupling reaction.

Thus, the appropriate modifications of traditional C–C cross-coupling methodologies provides a facile and flexible link to generation of functionalized heterocyclic compounds by selective functionalization of C–X bond.

1.10 Towards Sustainability of Synthetic Developments

In recent years, the ideals of green chemistry and sustainability have emerged as a dominant theme in organic chemistry, contributing to the broader scope of global sustainable future. The "*12 Principles of Green Chemistry*" introduced by Anastas and Warner in 1998 has been formulated as "design rules" to make chemical processes environmentally benign [76]. Recently, enormous efforts have been made for

designing innovative strategies in accordance with the fundamental principles which contribute to minimal waste generation, lesser toxicity, energy efficient, employing natural sources, thus being safe and harmless to the human kind [77]. Also, the concept of green chemistry matrices has aided to quantify the efficiency and environmental performance of chemical processes on the basis of parameters such as atom economy, E-factor, process mass intensity, reaction mass efficiency and many others [78]. Thus, keeping in mind the fundamental concept of sustainability, while developing catalytic methodologies is crucial. Although an absolute green synthesis does not exist, however designing an unconventional synthesis which can represent an advance in sustainability can be categorized as greener synthesis (Figure **1.7**).

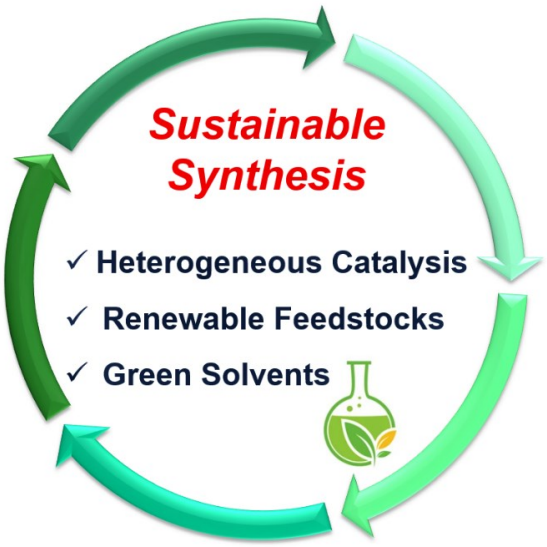


Figure 1.7 Sustainable organic synthesis

1.10.1 Heterogeneous Catalysis

Catalysis have been ever-growing as a prominent field of science as it represents a convenient route to meet the challenges of energy and sustainability [34]. However homogeneous forms of expensive metal catalysts pose environmental and economic demerits. Thus, to address a more compatible path apart from wasteful homogeneous transition metal chemistry, innovations are now focused on developing alternative recoverable, heterogeneous catalysts [79]. Provided sufficiently low metal leaching, heterogenization on solid supports with high surface area can render the use of expensive transition metals more sustainable. Hence, driving a necessary shift from conventional catalysis to nano-catalysis in the quest

for an improved and advanced catalytic pathway. The chemistry of metal particles at nanoscale level (1-100 nm) has materialized as an interesting field with increasing applications in industrial and chemical synthesis [80]. A wide range of support materials have been used for the adsorption of nanoparticles (NPs). The supports necessarily do not exhibit any catalytic activity of its own, however cooperates with the NPs to assist in promoting a particular transformation. Hence, the choice of appropriate supports is a topic of great importance [81].

1.10.2 Choosing Greener Solvents

Traditional organic synthesis relies heavily on organic solvents for a multitude of tasks, including dissolution of the components and facilitating chemical reactions. Consequently, the environmental impact of organic solvents has been the topic of extensive deliberation as they are used in vast quantities and thus contributing to a substantial amount of the waste generated. Solvent selection guides adopted by different research organizations ranked the solvents based on certain parameters such as, waste disposal, environmental impact, health, and safety [82]. Assessment of the commonly used solvents revealed alcohols and esters to be reasonably greener than structurally similar solvents from other classes. In contrast, most of the hydrocarbons, chlorinated hydrocarbons and ethers are classified as hazardous having toxic and flammability issues. Reactions in polar aprotic solvents such as DMSO and DMF with high boiling points are identified to have safety concerns, which also involve aqueous work-up with challenging solvent recovery and waste disposal issues.

Significant move towards sustainability has been achieved with catalytic reactions in aqueous media. Water having so much to offer; being inherently safe, non-flammable, abundantly available, cost-efficient and poses no health threat, can be used in catalytic processes by employing water-compatible catalysts [83]. Provided organic compounds are generally immiscible in water, simple extractive workup can readily separate a water-soluble homogeneous catalyst as an aqueous phase from reactants and products present in separate organic phase. The process allows easy recovery and reusability of the catalyst and also opening new directions towards aqueous biphasic catalysis [82]. Thus, water is indisputably considered as an ideal solvent and use of water is always sustainable.

1.10.3 Biomass-Based Renewable Materials

Use of chemicals and reagents from renewable resources is a topic of intensive discussion driven by the depletion of petroleum resources together with environmental concerns. Biomass, the only source of abundant renewable carbon, can be used as a sustainable raw-material. Taking advantage of the structural diversity of different biomass resources, it offers a platform for the production of wide variety materials and compounds [84]. Among the available biomass resources, the by-products of agricultural activities such as crop residues, gain significant attention. This organic matter of the horticultural wastes is a storehouse of valuable phytochemicals and are potential lignocellulosic feedstocks [85]. The quantities of organic waste generated from natural sources are extremely large, which is causing global concern in the form of environmental pollution and waste management issues. Therefore, the utilization of natural waste materials in the synthesis of products having applications in various sectors frames the foundation for a sustainable future.

1.11 Thesis Outline and Objectives

Based on the extensive literature survey on the functionalization of *N*-heterocyclic compounds, and realizing the opportunity for further developments, the thesis delivers a methodical study on the development of catalytic protocols for site-selective functionalization of indoles and related *N*-heterocycles according to the following research objectives-

(a) Development of metal-free catalytic pathway for C3-functionalization of indoles- with special focus on "molecular iodine catalysis".

(b) Development of heterogeneous Pd-based catalytic strategies for C2-functionalization of indoles.

(c) Designing of heterogeneous Pd/Ag-based bimetallic system for C–X bond functionalization of *N*-rich heterocyclic compounds *via* Suzuki-Miyaura cross-coupling reaction.

The rational design, scope and limitations, synthetic applications, and mechanistic pathways of the developed methodologies have been detailed in the following chapters.

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