
Nitrogen-containing heterocycles (***N*-heterocycles**), are wide-extended in nature with pronounced biological activities and important constituents of active biomolecular targets. US Food and Drug Administration (FDA) database reveals the presence of *N*-heterocycle in more than 60% of approved drugs available in the market today. Their immense bio-potency and importance in modern science, has captivated the scientific minds towards synthesis and selective functionalization of *N*-based heterocycles. The indole core, an important *N*-heterocyclic module in the drug and pharmaceutical world and prevailing to its larger manifestation in natural and synthetic compounds, has been recognized as a “*privileged structure*”. Since the first isolation and initial studies by von Baeyer in 1866, the chemistry of indole has engrossed central attention among organic chemists, and extensive efforts have been devoted for the construction and modification of these molecular structures. The earlier studies focused on the synthesis of indoles, developed several classical methods, including reactions by Fischer, Larock, Bischler, Nenitzescu, Madelung, Bartoli, among others. However, much of recent progress has been directed towards selective C–H bond activation and functionalization of indole frameworks, empowering previously inaccessible selectivity, step-economical and environmentally friendly synthetic process.

Structurally, there are six C–H bonds in the indole motif available for direct C–H activation and functionalization. However, all these C–H bonds are non-equivalent in terms of reactivity and electronic properties. The C3 position is inherently the reactive position followed by C2 in terms of their nucleophilic reactivities. C3 position was traditionally known for Friedel–Crafts reactions, though recent developments have expanded the reaction types at this position. However, most of the methods relied on expensive and complex metal catalyst systems containing, Pd, Ir, Au, Rh, or Ru, which are moisture- and air-sensitive, and requirement of complex handling and harsh reaction parameters, limits their practical utility. In the present context, a metal-free C3-functionalization approach appears more attractive, being less toxic, cost-effective, and offering beneficial alternatives to transition-metal catalysis.

Recent emergence of transition-metal catalyzed C–H activation has advanced as an influential means for accessing the less activated C2 position selectively. However,

achieving the regio-selectivity often suffers from installation of directing groups at *N*-position, high reaction temperature, possibility of side reactions and an expensive metal catalyst (mostly Pd) in homogeneous forms. Heterogeneous catalysts alternatively can provide an economic avenue with ease of separation and the possibility of catalyst recyclability. Thus, a methodology involving heterogeneous catalytic pathway without the obligation of directing groups or ligands is a more convenient approach for the C2-functionalization process. Accessing the benzene core regioselectivities in indole remains a scientific challenge owing to the dominant reactivity of the pyrrole core and requisites design of properly functionalized synthons to achieve the remote selectivity. Another breakthrough in functionalization of *N*-heterocyclic molecules entails catalytic C–C bond formation *via* selective C–X ($X = \textit{halogen}$) bond functionalization. The method can provide a facile and flexible access to promising target heterocyclic nitrogen scaffolds with chemical and biomedical significance.

The Thesis

The thesis delivers a methodical study on the development of catalytic protocols for site-selective functionalization of indoles and related *N*-heterocycles. The main text of the thesis has been organized into six chapters, including introduction (**Chapter 1**), four experimental chapters (**Chapter 2-5**), followed by conclusion and future scopes (**Chapter 6**). Chapter 2-5 covers the rational design, scope and limitations, synthetic applications, and mechanistic pathways of the developed reactions.

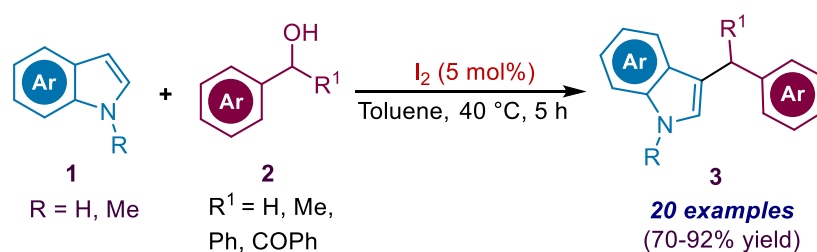
Chapter 1: General Introduction

Chapter 1 provides a brief outline of the thesis delivering a comprehensive account on the background concepts and literature survey, fundamental to the research works described in the thesis. It begins with an introduction on heterocyclic compounds and their importance- with a special relevance to nitrogen-rich heterocycles such as indoles. This is followed by a general discussion on C–H activation and functionalization as important tools in organic transformation reactions. Subsequently, a concise overview on the recent developments in the functionalization of indole and related heterocycles have been summarized, considering- (i) direct C–H bond activation of C2 and C3 positions of indole; and (ii)

C–C bond formation *via* C–X bond functionalization in *N*-heterocycles (Suzuki–Miyaura cross-coupling reaction).

Chapter 2: Molecular Iodine Catalyzed Selective C3-Benzylation of Indoles with Benzyl Alcohols

This chapter describes a metal-free protocol for selective C3-benzylation of indoles with benzyl alcohols (Scheme 2.1).



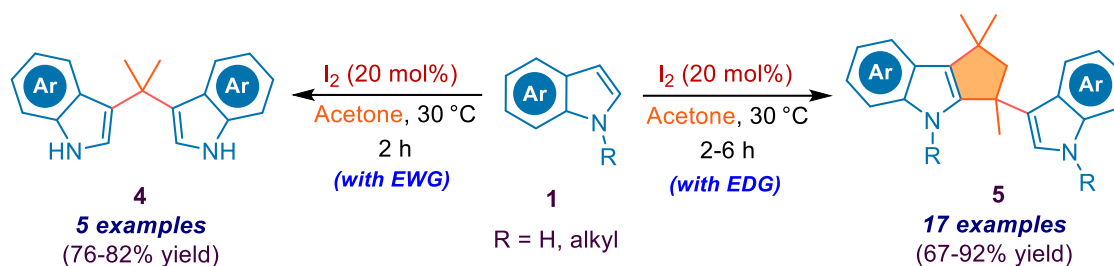
Scheme 2.1 C3-benzylation of indoles using molecular-iodine catalyst

The reaction proceeds with molecular iodine (I₂) as the catalyst under ligand- and base-free conditions. Benzyl alcohols are selected as green alkylating agents, as the only by-product generated is water, hence producing an environmentally benign and clean process. Wide functionality tolerance was observed under the reaction condition with electronically diverse indole (**1**) and benzyl alcohol (**2**) derivatives. Interesting influence of the solvent on the rate of reaction was encountered. Aprotic solvents such as toluene, dichloromethane, acetonitrile resulted in suitable yields of the reaction whereas protic media such as water, methanol, and ethanol showed no reaction progress. In the presence of protic solvents, iodine is known to decompose slowly to form Brønsted acid HI. Observation of no reaction in protic media clearly rules out the contribution of Brønsted acid mode of catalysis by I₂, and accounts for the halogen-bond activation mechanistic pathway of I₂.

Chapter 3: Molecular Iodine Catalyzed Selective Construction of Cyclopenta[*b*]indoles from Indoles and Acetone

Cyclopentannulated indoles are privileged nitrogen-heterocycles due to their prevalence in natural products and active pharmaceutical ingredients. Exploring further on the line of “Iodine catalysis,” this chapter emphasize on the synthesis of

cyclopenta[*b*]indoles from readily available 2,3-unfunctionalized indoles and acetone, employing molecular iodine (I₂) as catalyst (Scheme 3.1).

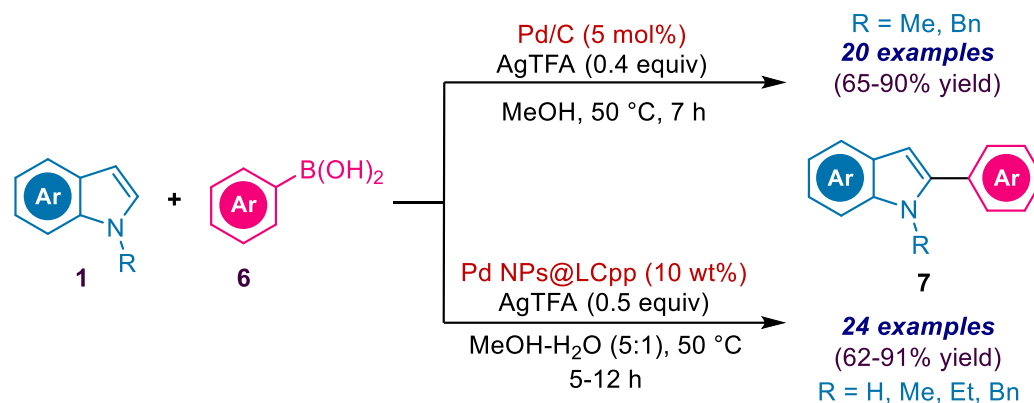


Scheme 3.1 Substrate-controlled synthesis of cyclopenta[*b*]indole using I₂ catalyst

The synthesis proceeds at ambient temperature (30 °C) without the requirement of any additives, inert or anhydrous reaction conditions. Explorations on diverse substitution pattern revealed an essential substrate-control in the reaction. High-density electronic core of indole favours the formation of indolyl-cyclopenta[*b*]indole derivatives (**5**), whereas electron deficiency of the core hindered the cyclization process, hence directing the reaction to bis(indolyl)propane derivatives (**4**). Further, mechanistic investigations *via* isolation and structure elucidation by ¹H and ¹³C NMR analysis, proved bis(indolyl)alkane to be the key intermediate for the cascade addition-intramolecular cyclization process. The mechanism also rationalizes the distinct reactivity differences between the two electronically varied classes of indole. The findings greatly contribute to enrich the greener synthesis of ring-fused indoles.

Chapter 4: *Studies on Heterogeneous Pd-Based Catalytic System for C–H Bond Functionalization at C2 Position of Indoles*

Transition-metal catalyzed C–H activation has emerged as an influential means for the direct functionalization of unactivated C(sp²)–H bonds forming new C(sp²)–C(sp²) bonds in an atom- and step-economic way. Realizing the importance of the method, this chapter is further classified into two sections deliberating two different heterogeneous Pd-based catalytic strategies for directing-group-free C2-arylation of indoles (**1**) with arylboronic acids (**6**) (Scheme 4.1). Section 4.1 explores the catalytic feasibility of commercial Pd supported on carbon (Pd/C) towards the arylation, whereas Section 4.2 highlights the application of a synthesized Pd-lignocellulose nanomaterials (Pd NPs@LC_{pp}) prepared in an environmentally-sustainable approach for achieving the regioselective arylation.



Scheme 4.1 C2-arylation of indoles using two heterogeneous Pd catalyzed methodologies

Section A: *Palladium-on-Carbon as a Reusable Heterogeneous Catalyst for C2-Arylation of N-Alkylated Indoles with Arylboronic Acids*

This section demonstrates C2-functionalization of indoles using 10% Pd/C as a heterogeneous catalyst in presence of a silver trifluoroacetate oxidant. Pd/C offers beneficial alternative to conventional homogeneous catalysis of expensive and air-sensitive Pd catalysts. Pd/C gains attention being relatively cheap, its ease of handling, availability, easy recovery, and reusability. The methodology exhibits better reactivity with electron-rich substituents on indole compared to the electron-deficient ones. This provides a direct correlation to the initial electrophilic palladation at the most nucleophilic C3 position of the indole ring followed by a C3→C2 migration for achieving the desired site-selectivity. The protocol offers substantial benefits such as achieving high C2 selectivity without the aid of ligands or directing groups, reduced oxidant stoichiometry and reusability of catalyst. X-ray photoelectron spectroscopic (XPS) studies of the recycled catalyst identifies reduced Ag(0) species in the reused heterogeneous sample, specifying the role of air as co-oxidant in allowing re-oxidation of reduced Ag(0) to active Ag(I) species for achieving maximum performance with reduced oxidant amount.

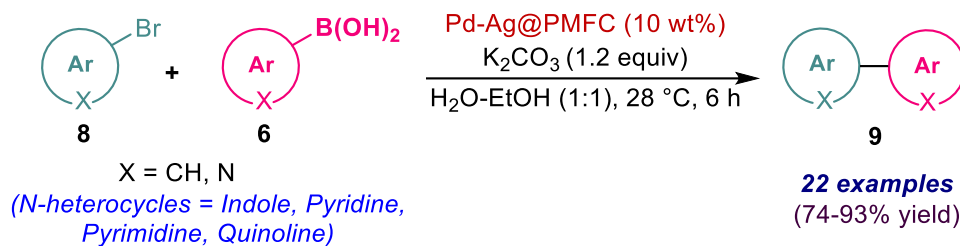
Section B: *Pd(0)-Embedded-Lignocellulosic Nanomaterials: A Bio-Tailored Reusable Catalyst for Selective C2-Arylation of Free N-H Indoles*

With the intention of extending further on the study of C2-arylation of indoles, this section focus on sustainable development of Pd nanoparticles (NPs) supported on lignocellulose bio-support (Pd NPs@LC_{pp}). Lignocellulose- a carbon-neutral

renewable source, is derived from non-food biomass feedstocks of waste pomegranate peels, using a simple chemical-free extraction process in aqueous medium. The formation of Pd NPs@LC_{pp} has been characterized by standard spectroscopic techniques including TEM, SEM-EDX, PXRD studies, FT-IR spectroscopy, XPS and BET surface area analysis. The newly developed features of Pd bio-nanomaterials were translated towards directing-group-free catalytic C2-arylation of indoles with arylboronic acids. Compared to the methodology developed in Section A, the bio-derived catalyst showed admirable functionality tolerance towards free N-H indoles. Further application of the protocol was noted for selective double-functionalization of indole frameworks *via* sequential C2-functionalization/Suzuki-Miyaura coupling reaction in a one-pot system.

Chapter 5: *Bimetallic Pd-Ag Nanoclusters Decorated Micro-Cellulose Bio-Template for Catalytic Suzuki-Miyaura Coupling Reaction of N-Rich Heterocycles*

This chapter highlights development of a bimetallic strategy for interpreting the importance of Suzuki-Miyaura coupling reaction to N-rich heterocyclic systems. Cellulose-the most prominent green materials have been extracted from the waste feedstock of pomegranate fruit peels in a simple ethanol-water filtration approach. The micro-fibrous network of cellulose (PMFC) functions as a true bio-template for Pd-Ag bimetallic nanoclusters (Pd-Ag@PMFC), whose formation, morphological characters, and elemental information have been evidenced by standard analytical techniques including TEM, SEM-EDX, ICP-OES, PXRD studies, FT-IR spectroscopy, XPS and BET surface area analysis. UV-Vis spectroscopic identification of Pd-Ag@PMFC material shows surface plasmon absorption of Ag NPs implying the presence of photoexcited electrons of Ag on the metal surface. The interfacial electron transfer from the plasmonic metal Ag to Pd makes the heterogeneous catalyst suitable for room temperature Suzuki-Miyaura coupling of diverse N-heteroaryl bromides (**8**) with N-heteroarylboronic acids (**6**) *via* visible light mediated localized surface plasmon resonance (LSPR) (Scheme 5.1). The methodology offers new-dimensions towards heterogeneous photocatalysis as a promising “green” technology and a renewable energy source.



Scheme 5.1 Suzuki-Miyaura coupling of *N*-heterocycles using Pd-Ag@PMFC catalyst

Chapter 6: Conclusion and Future Scopes

This chapter summarizes all the significant findings from the experiments performed to meet the objectives of the thesis and providing a glimpse of the future prospect to extend the current methodologies and explore new dimensions in the field of *N*-heterocyclic chemistry.

Keywords

Heterocyclic compounds, Nitrogen-heterocycles, Indole, C-H functionalization, Suzuki-Miyaura coupling reaction, Molecular iodine, Halogen-bond activation, Pd nanoparticles, Pd-Ag bimetallic nanoclusters, Biomass-support, Heterogeneous catalysis, Photocatalyst, Sustainable synthesis.