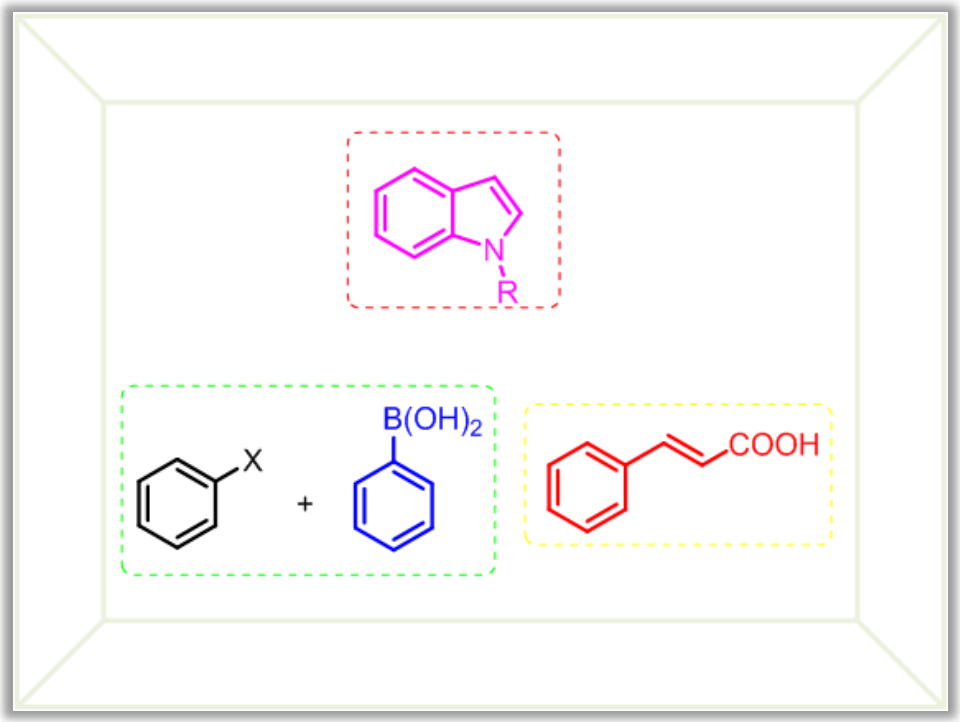
Chapter 1

Introduction

Functionalization of Indoles and Oxidative Coupling Reactions



1.1 General Introduction

In synthetic chemistry, the selective formation of bonds between carbon-carbon (C-C) and carbon-heteroatom (C-X, X = O, N, S, P, Se, etc.) is the major challenge to obtain value-added molecules. The wide range of economically and scientifically important functional materials, natural products, pharmaceutical agents, fine chemicals, and agrochemicals contain C-C and C-X bonds, and hence the construction of such linkages is a key process in organic synthesis. The development of new synthetic protocols for the direct and selective functionalization of C-H bonds is a prime and longstanding target in chemistry. Before the involvement of transition metal catalysis, the development of C-C and C-X bonds was very stagnant and limited. Nucleophilic addition, substitution, and Friedel-Craft-type reactions are the classical methods for regio- and stereospecific C-C and C-X bond formation. The transition metal-catalyzed cross-coupling reactions have emerged as a versatile tool for the formation of chemical bonds during the 1960s and made remarkable advancements in the last three decades [1,2]. Transition metal-based reactions are not only studied in academia but also extensively employed in synthetic technologies and chemical industries [2].

In a molecule, an isolated C-H bond is very less reactive due to the non-polar nature and high kinetic barrier related to the C-H bond cleavage. The earliest example of functionalization of isolated alkyl C-H bond was reported by Hoffman in 1883 where functionalization was done by the creation of extremely reactive nitrogen or oxygen based-radicals under highly acidic conditions [3]. In 1892, Volhard reported the first example of transition metal-assisted C-H bond functionalization that involved the formation of chloromercurythiophene by the reaction between mercury(II) chloride and thiophene [3]. With the aid of a transition metal catalyst, the activation of specific and remote C-H bonds can be done and functionalized to form C-C and C-X bonds with no requirement of prior oxidation [3]. C-H bond activation and functionalization offer a greener solution through high efficiency, selectivity, step, and atom economy and help in the construction of valuable advanced materials [4].

Additionally transitional metal-free and catalyst-free reaction strategies for C-C and C-X bond formation reactions have also gained momentum in recent years. The contemporary research efforts focused on addressing the environmental issues to meet the sustainable developmental goals. In this regard functionalization of indoles *via* C-C bond formation

reactions and methodology development for oxidative coupling reactions is very important from the modern synthetic chemistry point of view.

1.1.1 Indole-based functionalization reactions

In nature, a large number of heterocyclic compounds are widely distributed due to their importance in various life processes. Among them, indole moiety is one of the most important heterocyclic compounds having excessive π-electron density and a nitrogen atom (*N*-heterocycle) along with other carbon atoms [5]. After the first preparation of indole in 1866 by Adolf von Baeyer through the reduction of oxindole with zinc dust, it has become a privileged structural motif in the research area of organic synthesis [6]. The name "indole" came from its isolation from the natural dye "indigo" in 1869 [7]. In the last few decades, the chemistry of indole has fascinated researchers, owing to its far-ranging applications in agrochemicals, pharmaceuticals, and material chemistry (Figure **1.1** and **1.2**) [6,7]. The significance of indole ring was brought to light in the mid of 1950s through the discovery of alkaloid reserpine, one of the first drugs used in the treatment of anxiety and mental disorder [8]. Another important indole-based highly efficient antitumor agent vincristine was discovered in the 1960s and in a later stage, other indolyl alkaloids were developed with varied physiological properties including antihypertensive, anti-inflammatory, antimitotic, and tranquilizing activities [9]. It is found in the literature that 24 currently marketed drugs contain indole ring, nailing it as the fourth most prevalent heterocyclic molecule [10]. Indole is an electron-rich heterocyclic compound and it shows much higher reactivity in electrophilic aromatic substitution reactions as compared to benzene [9]. Due to the high nucleophilicity of the C-3 position of indole ring, functionalization takes place through electrophilic substitution at that position and these types of reactions are 10^3 times more reactive than benzene positions [11].

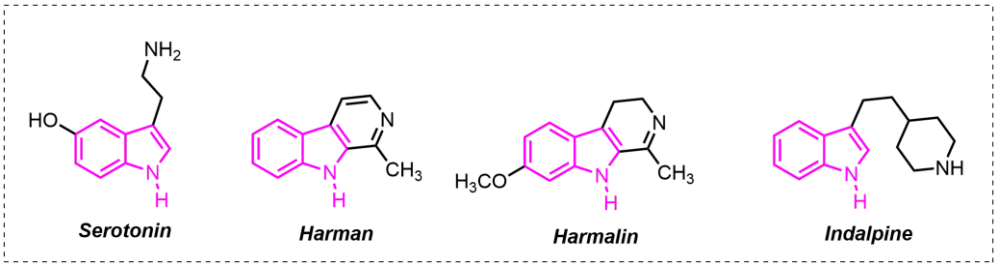


Figure **1.1**. Representative structures of indole-based alkaloids

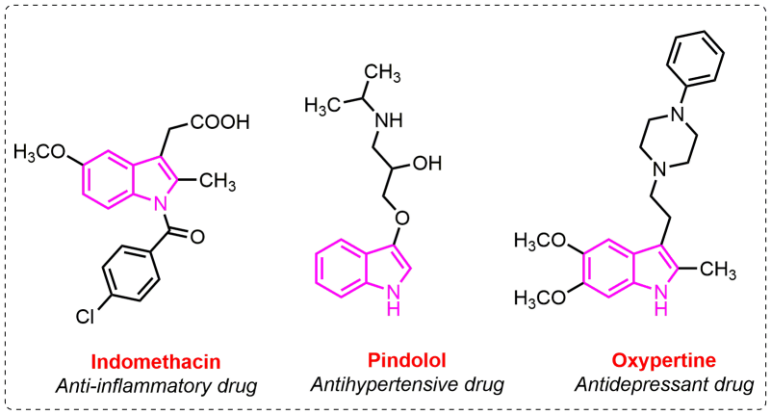
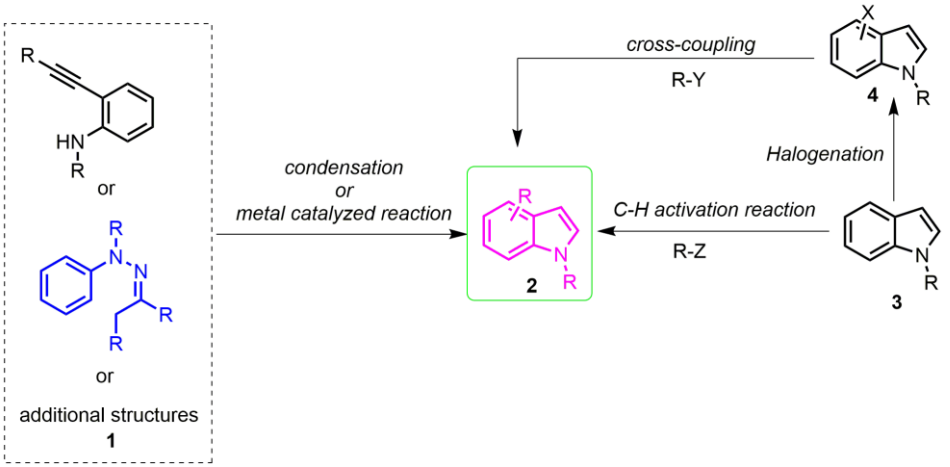


Figure **1.2**. Representative examples of pharmaceutically active indole derivatives

A variety of well-known classical methods including the Fisher indole synthesis [12], Bischler indole synthesis [13], Gassman indole synthesis [14], Larock indole synthesis [15], etc. along with new modified methodologies are extensively employed to synthesize indole moiety. The related works of indole functionalization in the early stage are mainly focused on the Friedel-Crafts-type reactions [7a]. Functionalized indoles (**2**) can be synthesized by employing three main strategies [16] (Scheme **1.1**). The first method involves cyclization reaction in which indole and embedded functionalities are made from benzoid precursors or additional structures (**1**) *via* metal-catalyzed or condensation reactions [17]. In the second strategy, functionalization occurs through halogenations (**4**) and successive cross-coupling of the indole scaffold itself [18]. The third approach involves direct C-H bond activation [16]. Initially, the condensation strategy attracted the scientific community to get functionalized indole, but in the later stage advent of transition metal-catalyzed cross-coupling and C-H activation methodologies were found to be the more viable and direct approach. With different appealing features like high step and atom economy, synthetic realism, C-H bond activation has become an attractive approach in synthetic organic chemistry. Although C-H bond activation is a multifaceted platform for functionalization reactions, there are two major challenges, including low reactivity of C-H bond and regioselectivity of similar C-H bond in the same molecule. To overcome these challenges, sometimes harsh reaction conditions are provided to obtain the desired product in synthetically useful yield [19].



Scheme **1.1**. Three major strategies for the synthesis of functionalized indole

Pioneering work of C-H functionalization of indole was reported in 1980s but it was not fully advanced until 2000s [20]. With the increasing demand of indole based pharmaceutically active compounds and complicated natural products, tremendous progress has been made in the field of C-H bond functionalization in recent years. There are six C-H bonds in indole scaffold, out of which C-2, and C-3 are in the pyrrole core and C-4 to C-7 are in the benzene core (Figure **1.3**). There is a little bit of difference in the electronic properties and the reactivity of these bonds [21]. The high reactivity of the C-3 position offers Friedel-Crafts-type reactions and in recent times transition metal-catalyzed functionalization is also expanded at that position [22]. For C-2 selective functionalization of indole, directing groups (DGs) (attached to nitrogen atom) assisted as well as directing group-free methodologies has been reported successfully. Typically, for C-4 to C-7 functionalization, pre-installation of directing groups and auxiliaries in the indole ring is required to achieve the goal by using transition metal catalyst [16,23]. Our main focus is to discuss both transition metal-catalyzed (specifically Pd metal) and transition metal-free C-2 and C-3 functionalization reactions of indole.

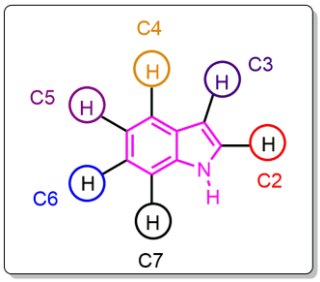


Figure **1.3**. Indole scaffold representing C-2 to C-7 C-H bonds

1.1.1.1 Palladium (Pd) catalyzed C-2 functionalization of indole

With the invention of industrial production of acetaldehyde from ethylene catalyzed by Pd salt, this noble metal occupies the synthetic domain of transition metal catalyst for diverse organic transformations. Generally, Pd-catalyzed reactions are well-tolerable to a broad range of functionalities and hence, applicable to the synthesis of complex organic structures [24]. The chemistry behind the Pd-catalyzed reactions is strongly dependent on different factors like the nature of ligands, additives, bases, temperature, and solvent. The combination of all these factors provides a platform for adjustable reaction conditions to bring flexibility to Pd chemistry.

The functionalization reactions of indole employ both Pd(II) salts and Pd(0) complexes. $Pd(OAc)_2$, $PdCl_2$, $Pd(TFA)_2$, and $Pd(PPh_3)_4$ are some examples of commercially available most commonly utilized Pd(II) and Pd(0) species, respectively. The electrophilic nature of Pd(II) salts tends to interact with electron-rich species such as arenes, alkenes, alkynes, etc. Pd(II) salts attack alkenes or alkynes to form π-complexes and as a result, the electron density around the C-C multiple bonds decreases, thereby enhancing intramolecular or intermolecular nucleophilic attack across the coordinated olefinic or acetylenic moiety (**A** and **B**) (Figure **1.4**). On the other hand, Pd(II) salts react with arenes by electrophilic substitution reaction (**C**). Pd(0) complexes undergo oxidative addition (**D**) with aryl, vinyl, heteroaryl halides, or triflates to form Pd(II) at the initial step of the catalytic cycle which is then further attacked by the nucleophiles. Allylic esters like carbonates and acetates can form π-allylic Pd-complex (**E**) on reaction with Pd(0) and then nucleophiles can attack at one of the allylic positions to furnish the allylated product [24].

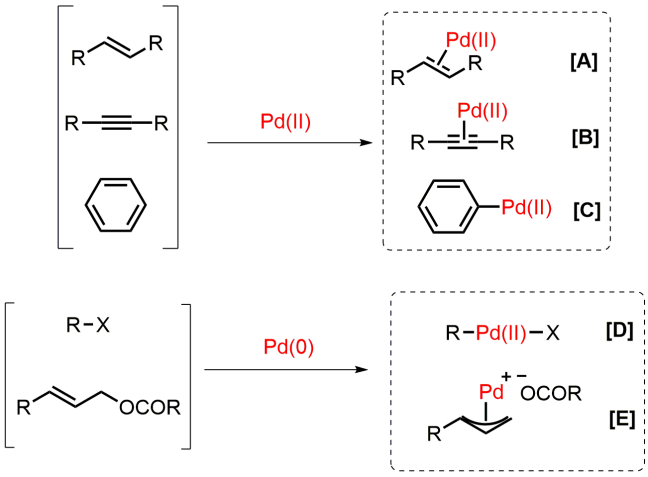


Figure **1.4**. Representative interactions of Pd(II) salts and Pd(0) complexes

From the literature, it is seen that in lots of Pd(II) salt-catalyzed reactions, generation of Pd(0) species occurs at the end of reactions which is *in situ* re-oxidized to Pd(II) by using different oxidants such as copper salts [$CuCl_2$, $Cu(OAc)_2$, etc.], MnO_2, *tert*-butylhydroperoxide (TBHP), benzoquinone, etc. [24]. Pd(0) complexes have filled d-orbitals (d^{10}) and are nucleophilic. In most of the catalytic cycles, this Pd(0) reacts with polar or non-polar covalent bonds X-Y, such as O-H, N-H, C-O, C-halogen, C-H, H-H, etc. through oxidative addition, resulting in the formation of X-Pd(II)-Y complex. The oxidative addition generates an electrophilic Pd(II) center that undergoes various synthetic transformations depending on reaction conditions. The σ-donor ligands coordinated to the Pd center favour the oxidative addition. The addition of monodentate ligands most likely forms a cis complex in the oxidative addition step which then isomerizes to a thermodynamically more stable trans complex. The functionalization reactions of indole most commonly prefer phosphine ligands to form soluble Pd catalysts and to modulate the reactivity of Pd complexes [24]. In addition to ligands, other reagents like alcohols, carbon monoxide, amines, terminal alkynes, alkenes, and metal hydrides can also reduce Pd(II) to Pd(0) *in situ*. Alternatively, ligand-free approaches are also available in the literature for the functionalization of indole. Pd on charcoal, or other solid-supported Pd nanocatalysts have been also utilized as Pd(0) sources in reactions. Generally, phosphine ligands are not employed in the case of Pd on charcoal or other heterogeneous Pd catalysts to avoid leaching.

Additives, particularly halide additives, play an important role in controlling the reaction result of Pd-catalyzed reactions [25]. The stability of five-coordinate Pd complexes as well as dimeric Pd complexes is greatly influenced by the nature of halide ions [26]. Also, in the isomerization of π-allyl Pd complexes chloride ion plays a significant role. These halide additives have been employed broadly in various synthetic protocols of indole derivatives. However, the behaviour of ligands and additives are not similar in all the reactions as the catalytic cycles for different reactions involve several steps, therefore the chemical nature and reactivity of different intermediates vary depending upon the applied reaction conditions. Thus the electronic and steric nature of both ligands and additives or the presence of either ligands or additives in the reaction affects getting synthetically useful yield.

By using Pd catalysts a wide range of organic transformation have been carried out to afford C-2 selective products with different coupling partners (Figure **1.5**). C-2 selective

products can be achieved by using different means like positional blocking (mostly at C-3), adding directing groups, modifying reaction conditions, and developing new catalytic systems [27]. A few examples of Pd-catalyzed C-2 functionalization reactions are discussed below:

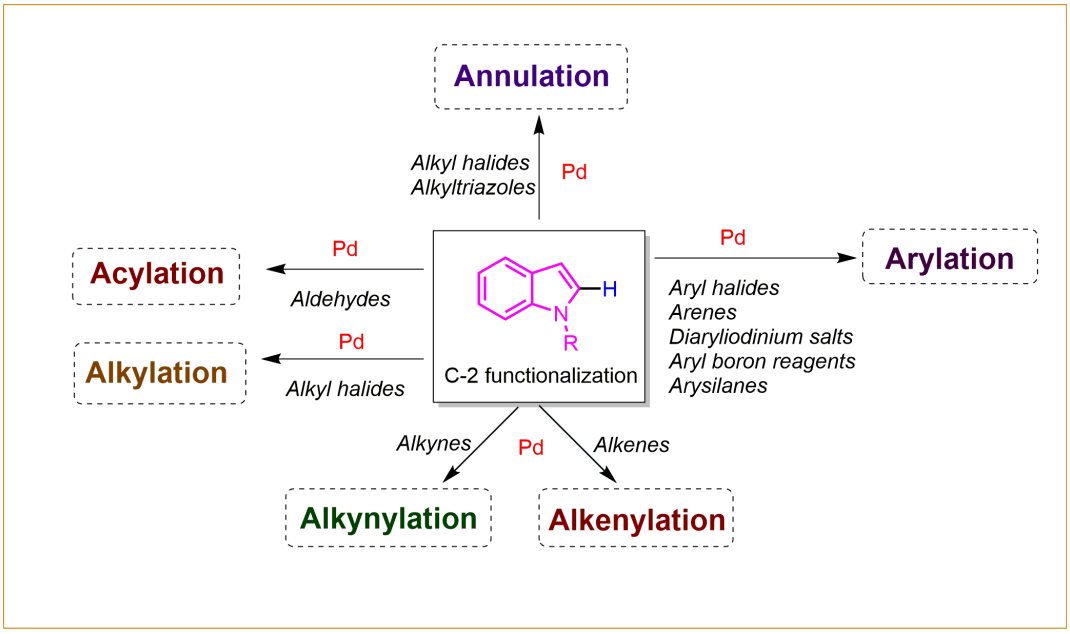
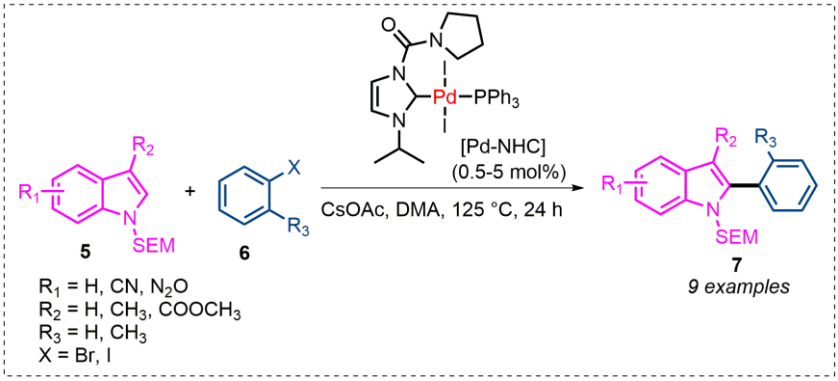
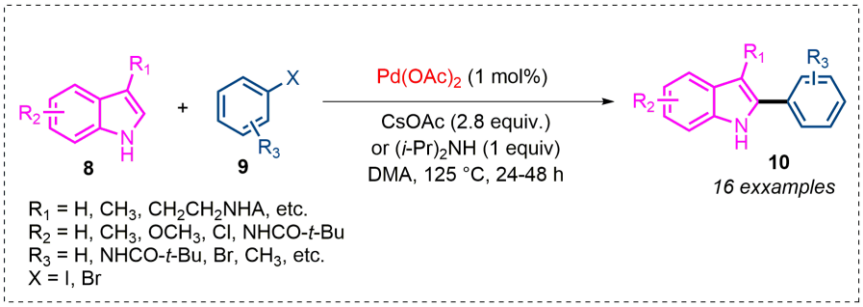


Figure **1.5**. C-2 functionalization of indole using different coupling partners

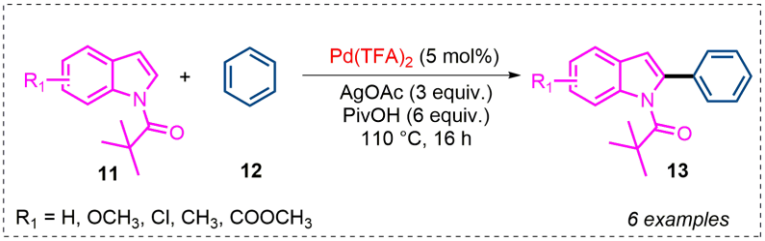
Using [2-(trimethylsilyl)ethoxymethyl] (SEM) as directing group, Sames and co-workers reported the C-2 arylation of indole (**7**) [28]. Both iodo and bromoarenes (**6**) successfully arylate the indole at C-2 in presence of the Pd-NHC complex (Scheme **1.2**). From their study they found that iodoarenes were better substrates to obtain higher yields with low catalyst loading. Sames group developed another methodology for C-2 arylation, catalyzed by $Pd(OAc)_2$ without using any ligand and directing groups (Scheme **1.3**) [29]. By thorough study, they discovered that the nature of halide ions affected the selectivity and efficiency of the C-2 arylation. Between iodo and bromoarenes, iodoarenes substantially preferred C-2 products rather than C-3. To develop a very high atom economic process, Fagnou and co-workers reported the C-2 arylation of indoles with arenes (**13**) by using $Pd(TFA)_2$ catalyst and AgOAc oxidant (Scheme **1.4**) [30]. Depending on the nature of oxidants, the regioselectivity of the reaction was controlled. AgOAc favoured the C-2 arylation whereas $Cu(OAc)_2$ favoured the C-3 arylation. The reaction was more efficient in the case of benzene rather than disubstituted benzene.



Scheme **1.2**. Pd-NHC complex catalyzed C-2 arylation of indoles

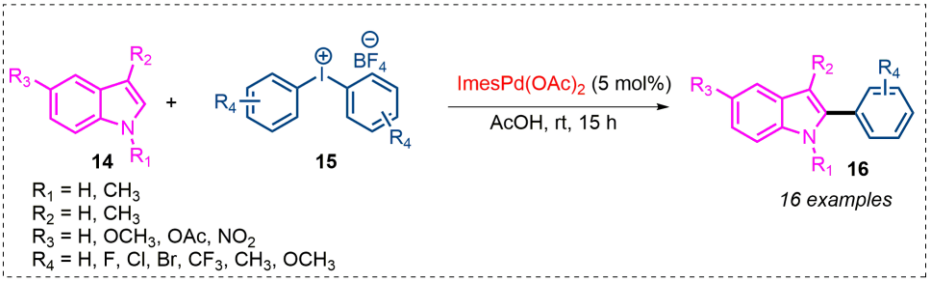


Scheme **1.3**. $Pd(OAc)_2$ catalyzed ligand and directing group-free C-2 arylation



Scheme **1.4**. $Pd(TFA)_2$ catalyzed direct arylation of indoles

Diaryliodonium salt (**15**) is another coupling partner for C-2 arylation of indole and one such strategy was reported by Sanford group where they used Pd-NHC complex as catalyst and the reaction was carried out at room temperature (Scheme **1.5**) [31]. The viability of the reaction was due to involvement of Pd(II)/(IV) mechanism. In their methodology, electrophilic palladation was favourable for electron-deficient system.



Scheme **1.5**. Diaryliodonium salt as arylating agent for C-2 functionalization of indoles

An important strategy for obtaining site-selective functionalization or alkenylation indole is to employ nitrogen-containing auxiliaries to direct the catalyst at the required position [32]. Some of these auxiliaries (Figure **1.6**) are pyridine [33], pyrimidine [34], 2-pyridylsulfonyl group [35], 2-pyrimidylmethyl [36], *N*,*N*-dimethylcarbamoyl [37], and *o*-aminophenyl [38] groups.

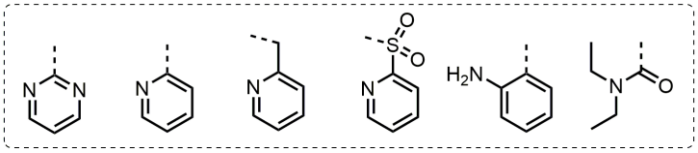
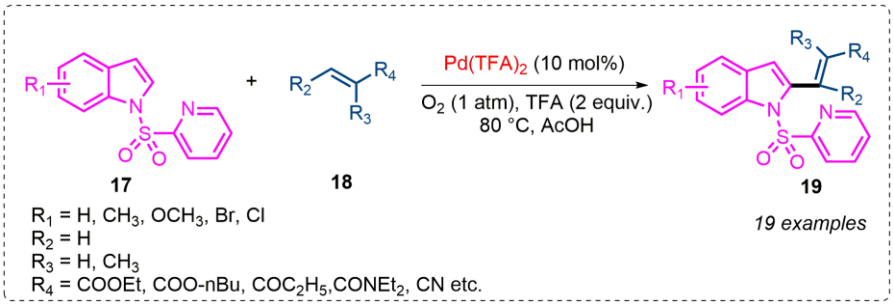


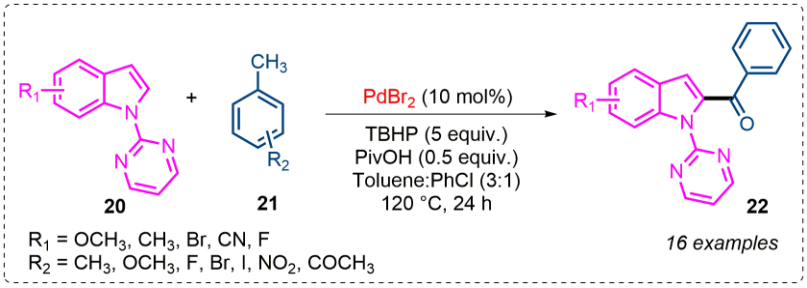
Figure **1.6**. Representative examples of nitrogen-containing auxiliaries

Wang and co-workers reported the 2-pyridylsulfonyl auxiliary assisted C-2 alkenylation of indoles using $Pd(TFA)_2$ as the catalyst and molecular oxygen as oxidant (Scheme **1.6**) [39]. Complete regio- and stereoselectivity were maintained throughout the reaction and only *E*-isomers (**19**) were obtained.



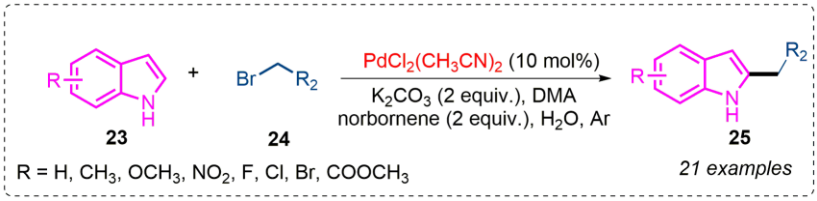
Scheme **1.6**. Auxiliary assisted C-2 alkenylation of indoles

Another example of auxiliary-assisted C-2 functionalization was developed by Eycken and co-workers where they carried out the acylation of indoles (**22**) in presence of $PdBr_2$ catalyst and TBHP oxidant (Scheme **1.7**) [40]. Using toluene (**21**) as the acyl source, the mechanism involved either Pd(II) or dimeric Pd(III) species.



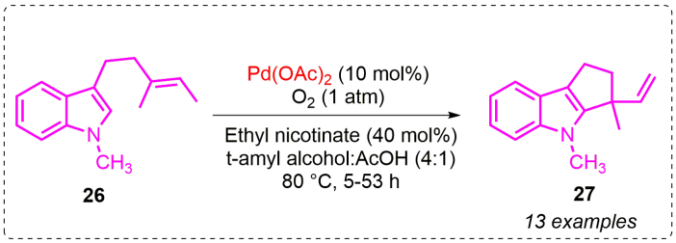
Scheme **1.7**. C-acylation of indoles using pyrimidine auxiliary

Alkyl bromides (**24**) are an active coupling partner for C-2 alkylation of indole and this alkylation was introduced by Bach group and their methodology followed norbornene-mediated Pd-catalyzed cascade reaction (Scheme **1.8**) [41]. Their protocol showed good tolerance to diverse functional groups.

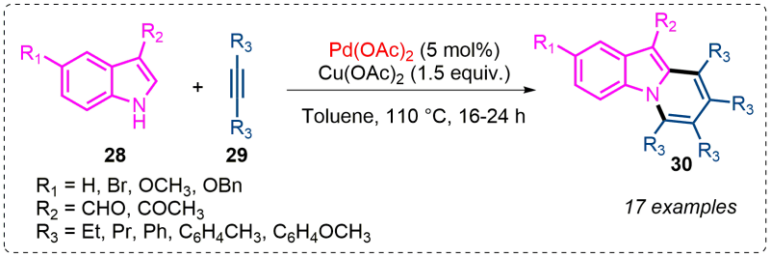


Scheme **1.8**. C-2 alkylation of indoles

In the Pd-catalyzed C-2 functionalization of indoles, there are examples of the construction of fused rings through intramolecular or intermolecular annulation reactions. The early example of intramolecular annulation was reported by Stoltz and co-workers (Scheme **1.9**) [42]. In their reaction they utilized indoles having alkenyl groups at the C-3 and in presence of ethyl nicotinate under oxygen atmosphere; both five (**27**) and six-membered fused rings were synthesized in good yields. An example of intermolecular annulation was reported by Kundu group to synthesize pyrido[1,2-*a*]indoles (**30**) from 3-substituted indoles and internal alkynes (**29**) (Scheme **1.10**) [43]. Pyrido[1,2-*a*]indoles are fluorescent compounds and their methodology involved sequential C-H and N-H functionalization.

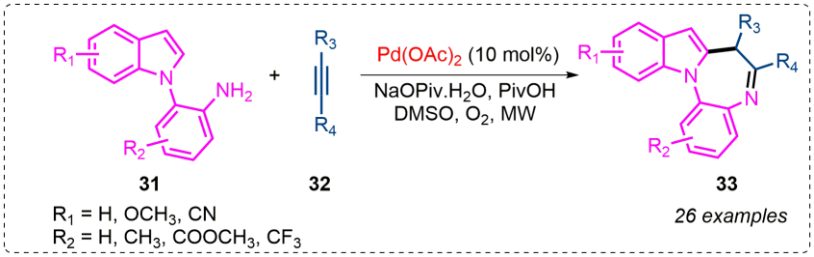


Scheme **1.9**. Pd-catalyzed intramolecular annulation of indoles



Scheme **1.10**. Pd-catalyzed intermolecular annulation of indoles

Microwave irradiation is an alternative methodology for annulation of indoles. Sun and co-workers developed a strategy to synthesize indole[1,7-*a*]diazepines (**33**) by using *o*-indolo anilines (**31**) and internal alkynes (**32**) (Scheme **1.11**) [44]. This regioselective Pd-catalyzed [5+2] cyclization was achieved by using pivalic acid additive and molecular oxygen, which were the key components for the regeneration of electrophilic Pd species in the catalytic cycle.



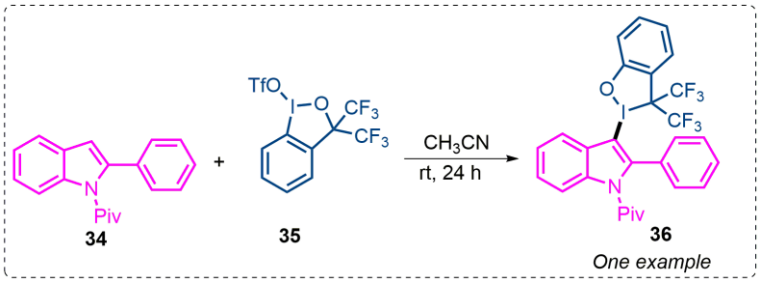
Scheme **1.11**. Microwave assisted intermolecular annulation of indoles

C-2 selective functionalization of indoles has received extensive interest from the synthetic community and further modifications to afford more efficient and sustainable protocols in this area are still going on.

1.1.1.2 Transition metal-free C-3 functionalization of indole

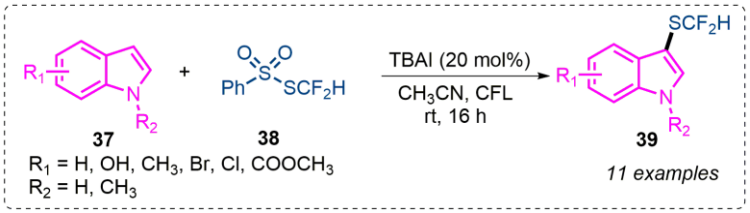
Although transition metal-catalyzed indole functionalization covers a vast area of organic synthesis and innovative developments are still going on, there are many transition metal-free approaches have been reported. The significant advances regarding transition metal-free protocols incorporate, (a) searching new electrophiles for C-3 functionalization, (b) utilizing chiral phosphoric acid for enantioselective functionalization, and (c) finding new ligand-enabled transition metal-free functionalization. Concerning this, we will discuss a few selected examples of transition metal-free C-3 functionalization of indoles.

The strategy for C-3 selective λ^3 iodination of indole was developed by Yoshikai group where benziodoxole triflate (BXT) (**35**) was used as an electrophile (Scheme **1.12**) [45]. The synthesized product (**36**) was comprised of benziodoxole group, which can act as a good leaving group, and hence their desired product can be used as a precursor for further conversions. This reaction was also feasible in mechanochemical ball-milling under solvent-free conditions.



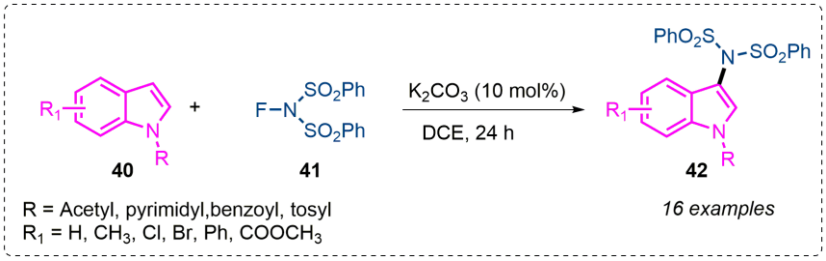
Scheme **1.12**. C-3 functionalization of indole using BXT

Visible light mediated transition metal-free C-3 difluoromethylthiolation of indoles (**39**) was reported by Li group and this approach discovers that $PhSO_2$-SCF_2H (**38**) is an easily available, stable reagent for direct functionalization (Scheme **1.13**) [46]. Homolytic cleavage of S-S bond due to irradiation in visible light enhanced by *tetra*-butylammonium iodide (TBAI) and thereby producing the difluoromethylthiyl radical in the mechanistic route.



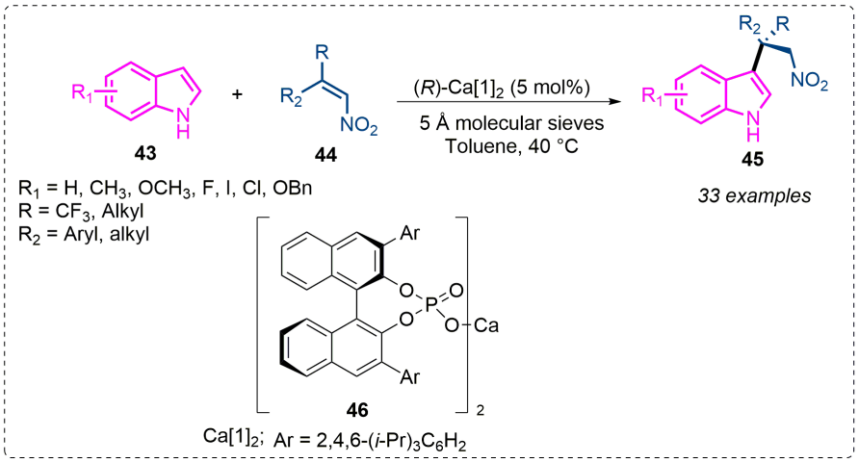
Scheme **1.13**. Visible light mediated difluoromethylthiolation of indoles

Adding a catalytic amount of base, C-3 amidation of indoles (**42**) with *N*-fluorobenzenesulfonimide (NFSI) (**41**) was developed by Yang group (Scheme **1.14**) [47]. Without using an external oxidant, this amidation exhibited good tolerance to diverse functionalities. A free radical mechanism was addressed for this transformation.



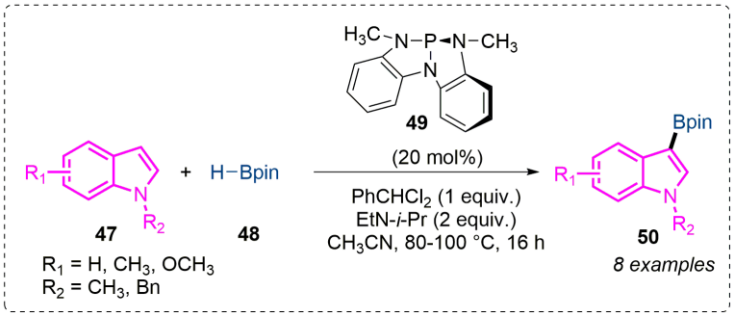
Scheme **1.14**. C-3 amidation of indoles

Akiyama and co-workers reported the enantioselective C-3 functionalization of indole by using a calcium-chiral BINOL phosphate (**46**) metal-ligand system (Scheme **1.15**) [48]. With β-nitrostyrenes (**44**) as coupling partner, a Friedel-Craft-type alkylation was occurred; exhibiting excellent enantioselectivity. For the success of the reaction N-H of indole was necessary to interact with phosphoryl oxygen. Moreover, nitrostyrenes with *Z*-isomer showed higher enantioselectivity through this protocol.



Scheme **1.15**. Enantioselective C-3 functionalization of indole with nitrostyrene

Phosphorous triamide [P{N(*o*-N-Me-C_6H_4)$_2$}] (**49**) is another phosphorous-based catalyst which was utilized by Radosevich and co-workers to carry out the electrophilic aromatic borylation of indoles (**50**) in presence of HBpin (**48**) as coupling partner (Scheme **1.16**) [49]. Benzyl chloride was employed as additive in order to generate Cl-Bpin through relay oxidation of phosphorous hydrido-diazaphospholene.



Scheme **1.16**. C-3 borylation of indoles using phosphorous triamide

1.1.2 Oxidative coupling reactions

Transition metal-catalyzed coupling reactions can be categorized into three types: traditional, reductive, and oxidative coupling depending upon the nature of the coupling partners (Figure **1.7**) [50]. Among these three couplings, oxidative coupling has proved to be one of the most straightforward strategies for C-C and C-X bond formation reactions. This coupling occurs between two nucleophiles in the presence of an oxidant [50]. Although the bond formation between two nucleophiles seems incredible, the involvement of transition metal catalysts along with oxidants has allowed the reaction feasible. Depending upon the nucleophiles, various oxidants such as, hydrogen peroxide (H_2O_2), molecular oxygen (O_2), *tert*-butylhydroperoxide (TBHP), high valent metal salts (copper, iron, vanadium, etc.), and halides (iodine oxidants) are used to carry out reactions [51]. Two types of oxidative coupling reactions are focused on in our work: (i) Heterogeneous catalyst-based Suzuki-Miyaura cross-coupling reaction, (ii) Decarboxylative coupling of cinnamic acids.

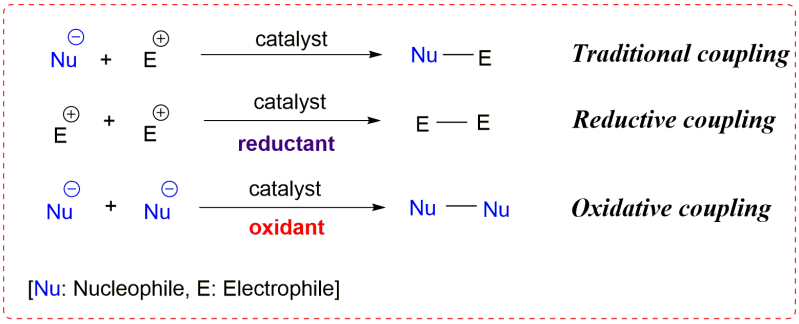
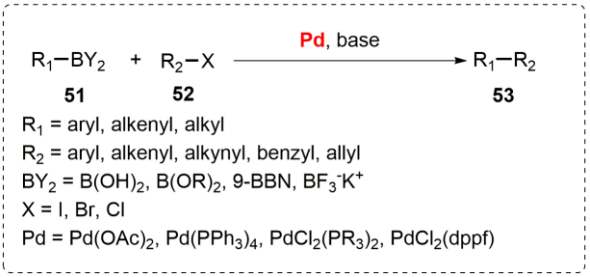


Figure **1.7**. Cross-coupling through traditional, reductive, and oxidative coupling

1.1.2.1 Heterogeneous catalyst-based Suzuki-Miyaura cross-coupling reaction

Professor Akira Suzuki from Hokkaido University, Japan made a significant contribution to the field of transition metal-catalyzed cross-coupling reactions in 1979 [52]. Suzuki and Miyaura developed a Pd-catalyzed cross-coupling reaction between aryl halides and organoboron compounds (mainly boronic acid and its ester), the most valuable transformation for the C-C bond formation in modern-day synthetic organic chemistry. Since then, various research groups have done vast improvements to Suzuki-Miyaura cross-coupling reaction (Scheme **1.17**). This coupling reaction is one of the most commanding reactions to synthesize biaryl compounds, which occupy a vast area in medicinal, polymer, and material chemistry [53].



Scheme **1.17**. Pd-catalyzed Suzuki-Miyaura cross-coupling reaction

The two important reasons behind this influential synthetic method include: (a) the reaction is well-tolerable to diverse functional groups under mild reaction conditions and therefore valuable for the total synthesis of pharmaceutical compounds, (b) the "greenness" of organoborons, in comparison to other known organometallic coupling agents, is not only due to its bench-stability, easy accessibility, and non-toxicity but also because the inorganic by-product; boric acid which is generated from the organoboron counterpart during the reaction can be easily removed after reaction completion [54]. Neutral boron exhibits three sp^2 hybridized orbital in a trigonal planar geometry and one non-bonding empty p-orbital orthogonal to the plane. This vacant p-orbital control the reactivity pattern and offers susceptibility for electron acceptance from Lewis bases. Upon binding with the base, this boron forms a tetrahedral borate complex that exhibits different properties from the neutral planar precursor [55]. The main role of the base in Suzuki coupling reaction is to convert boronic acid to more reactive organoborate complex, thereby facilitating the transmetalation with Pd-halide intermediate.

Till date, researchers have developed numerous homogeneous and heterogeneous catalysts for Suzuki-Miyaura cross-coupling reaction [56]. But, the use of Pd metal in homogeneous form causes difficulties in separation and recovery from the reaction media. Alternatively, heterogeneous catalysis offers easy recovery and reusability of the catalyst which is cost-effective and signifies a sustainable development for any catalytic methods. The solid-supported Pd catalysts for Suzuki-Miyaura cross-coupling reaction have gained immense attention in recent years [57]. The materials used as support should have distinctive features like air and moisture stability, affordable, high chemical and thermal stability, ease of chemical alteration, etc. [57d]. Therefore, solid-supported highly efficient Pd nanocatalysts are considered as the key objective for Suzuki-Miyaura cross-coupling reaction from green chemistry viewpoint. In this section we will discuss examples of solid-supported Pd nanocatalysts and their applications in Suzuki-Miyaura cross-coupling reaction.

1.1.2.2 Advantages of nanocatalyst

Nanocatalysts have received extensive interest in recent years owing to their wide range of applications in the field of heterogeneous catalysis. By altering their sizes, shapes, and morphologies, one can design highly active, stable, and selective catalysts for different catalytic processes [58]. The reasons for the higher activity of nanocatalysts are:

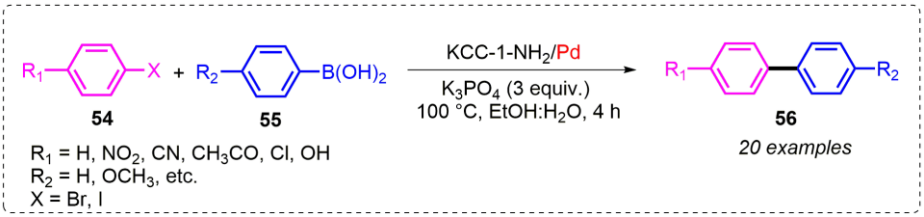
(a) Since the nanoparticles (NPs) are smaller in size, therefore their surface-to-volume ratio is very high.
(b) The high surface area of the nanocatalysts increases the contact between reactants and the catalyst and thereby facilitating the reaction rate.
(c) The size, shape, and morphology of the nanocatalyst can be controlled easily during the catalyst designing which brings flexibility to catalytic processes.
(d) In specific cases, synthesis and application of magnetic nanoparticles are beneficial for easy and efficient recovery from the reaction mixture with the help of an external magnet.

1.1.2.3 Solid-Supported Pd-nanocatalyst

1.1.2.3.1 Pd-catalyst supported on silica

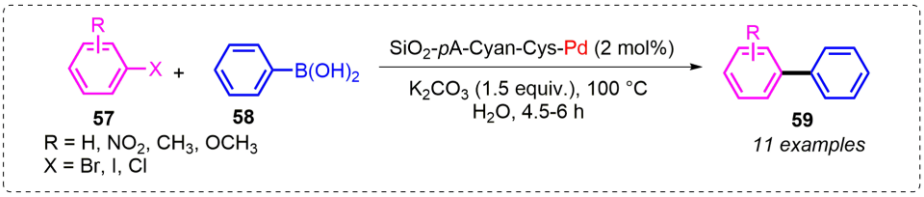
Owing to excellent stability, easy availability, porosity, and inertness for transition metal particles immobilization, silica is a good example of solid support [59]. The deposition

of Pd NPs on silica can be done by chemical vapour infiltration, ion exchange, *in situ* reduction, and wetness impregnation [60]. Polshettiwer group reported a strategy for Pd NPs supported on fibrous nano-silica KCC-1 (Scheme **1.18**) [61]. They functionalized the silica with aminopropyl groups and the deposition of Pd NPs was done by hydrogen reduction method. From TEM images the authors stated that Pd NPs (1-5 nm) were completely loaded in the KCC-1 fibers. The synthesized nanocatalyst (KCC-1-NH_2/Pd) was reusable up to seven catalytic cycles.



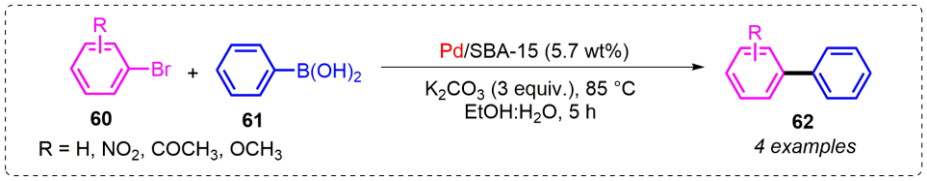
Scheme **1.18**. KCC-1-NH_2/Pd-catalyzed Suzuki coupling

Pd NPs supported on silica-bonded propylamine-cyanuric-cysteine (SiO_2-*p*A-Cyan-Cys-Pd) was synthesized by Khojastehenezhad and co-workers and studied its behaviour in Suzuki-Miyaura cross-coupling reaction (Scheme **1.19**) [62]. The Pd NPs were attached through thiol groups of the support and the average size of nanoparticles was less than 30 nm in diameter. The developed catalyst was recyclable for up to five consecutive cycles.



Scheme **1.19**. SiO_2-*p*A-Cyan-Cys-Pd-catalyzed Suzuki coupling

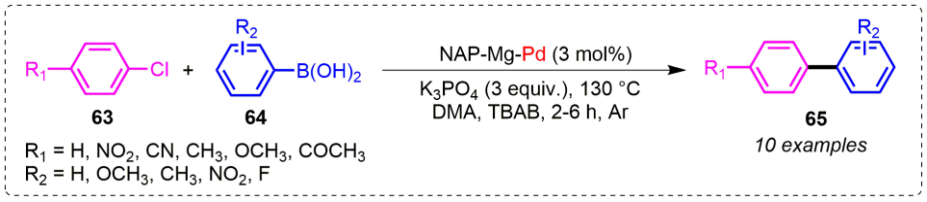
Gao group developed Pd NPs supported on mesoporous SBA-15 SiO_2 through sol-gel pathway under H_2 atmosphere (Scheme **1.20**) [63]. TEM analysis indicated the well dispersion of Pd NPs in SBA-15 channels with approximate diameter in the range of 5-10 nm. They reported that loading of Pd NPs on the support could be controlled by varying the amount of added Pd salt. This nanocomposite was reused for five cycles.



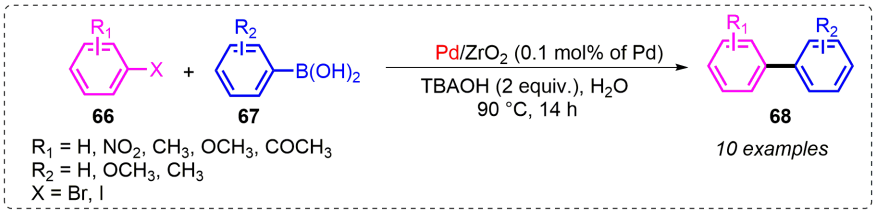
Scheme **1.20**. Pd/SBA-15 catalyzed Suzuki coupling

1.1.2.3.2 Pd-catalyst supported on metal oxides and layered double hydroxides

Similar to silica, metal oxides, and double hydroxides are used as the solid support for loading Pd NPs. Choudary group reported the synthesis of magnesium oxide (MgO)-stabilized Pd NPs and employed this nanocatalyst for Suzuki coupling (Scheme **1.21**) [64]. The nanocatalyst was prepared by counter-ion stabilization of $PdCl_4^{2-}$ with nanocrystalline MgO followed by reduction. The coupling of boronic acids with aryl bromides or iodides was done at room temperature in water in the presence of K_2CO_3. For aryl chlorides, reactions were done at 130 °C in DMA with K_3PO_4 and *tetra*-butyl ammonium bromide (TBAB). The catalyst was reusable for up to four cycles with the retention of catalytic activity. Similar to MgO, Pd NPs supported on tetragonal zirconium oxide (ZrO_2) nanopowder was synthesized by Cioffi group by using the electrochemical impregnation method (Scheme **1.22**) [65]. The efficiency of the catalyst, Pd/ZrO_2 was due to its stabilization by *tetra*-butyl ammonium hydroxide (TBAOH) that played the role of both base and phase-transfer agent. The spherical NPs were evenly dispersed on the ZrO_2 support and the synthesized catalyst was reused ten times without significant loss of its activity.

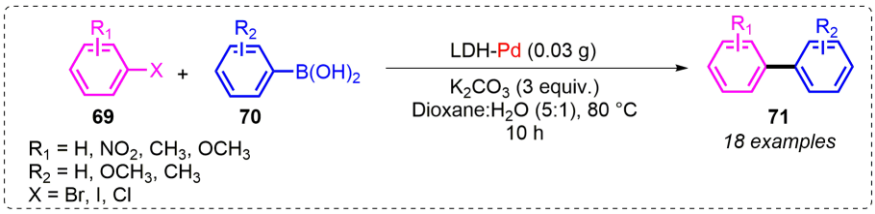


Scheme **1.21**. NAP-Mg-Pd-catalyzed Suzuki coupling

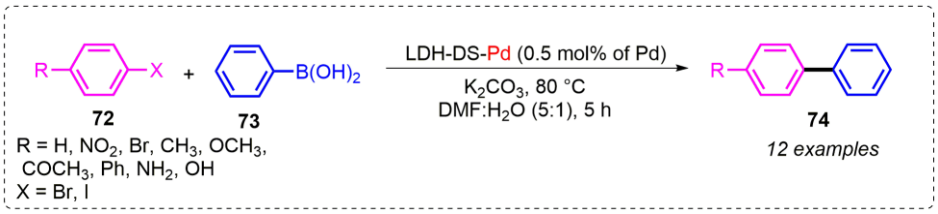


Scheme **1.22**. Pd/ZrO_2 catalyzed Suzuki coupling

Layered double hydroxides (LDH) are anionic clays or hydrotalcite-like materials, containing intercalated anions comprised of oxometalates or metal complexes [60]. These materials have been used as solid support for transition metals in recent years. Parida and co-workers reported the synthesis of Pd NPs supported on amine-functionalized LDH and applied this nanocatalyst in Suzuki coupling (Scheme **1.23**) [66]. The amine group of *N*-[3-(trimethoxysilyl)-propyl]ethylenediamine (TPED) stabilized the Pd NPs. The average diameter of the NPs was in the range of 2-5 nm which was obtained from TEM images. The catalyst was reusable for up to four cycles without significant loss of its catalytic activity. Similarly, Jiang group developed a strategy for the synthesis of Pd NPs supported on dodecylsulfate anion-embedded LDH (Scheme **1.24**) [67]. The intercalation of the anions within the layers of LDH changed the interlayer spacing from micro to meso-size range, thereby favouring the diffusion of organic molecules. The deposition of Pd NPs on the support was done by reduction and this lipophilic catalyst was reused for five catalytic cycles.



Scheme **1.23**. LDH-Pd-catalyzed Suzuki coupling

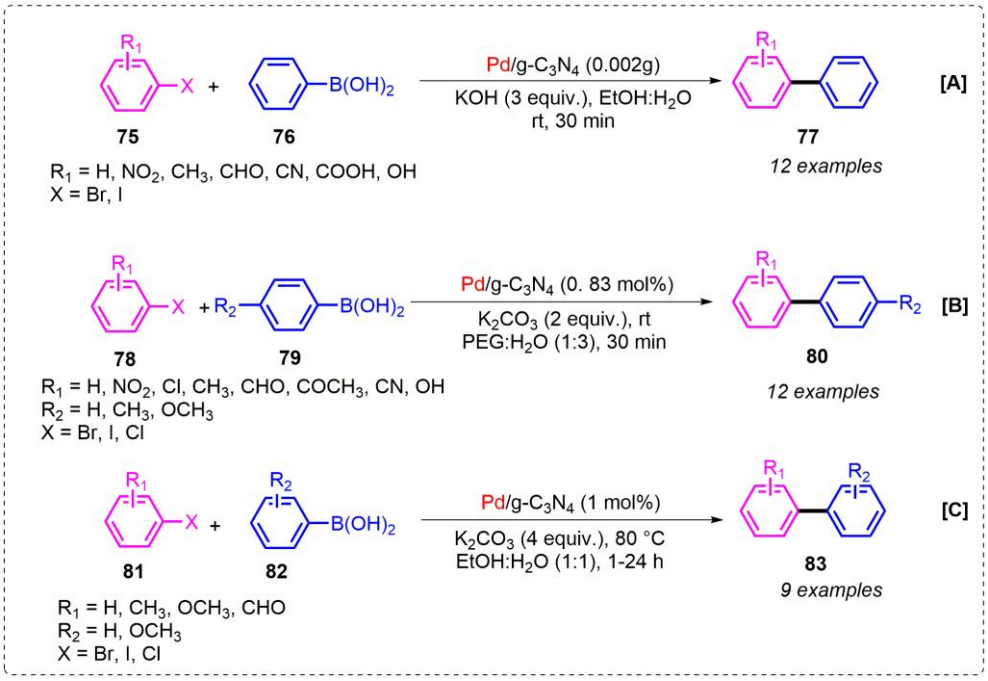


Scheme **1.24**. LDH-DS-Pd-catalyzed Suzuki coupling

1.1.2.3.3 Pd-catalyst supported on graphitic carbon nitride (g-C_3N_4)

Researches in recent years have shown that graphitic carbon nitride (g-C_3N_4) is a unique support for metal NPs. It is a two-dimensional graphite-like layered structure having sp^2 bonded carbon and nitrogen atoms [68]. Triazine (C_3N_3) and heptazine (or tri-*s*-triazine; C_6H_7) are the two basic units of g-C_3N_4. Heptazine-based g-C_3N_4 is the most stable and favoured phase, which is also known as melem and is the building block of the graphitic

sheet [69]. Wang group reported the synthesis of Pd NPs supported on g-C_3N_4 surface and studied its behaviour in Suzuki coupling (Scheme **1.25A**) [70]. They synthesized g-C_3N_4 surface by heating cyanamide. Pd NPs were distributed uniformly on the surface and the average diameter of the NPs was around 2.75 nm. The nitrogen functionalities of the surface acted as anchoring sites for homogeneous dispersion and stabilization of NPs. This nanocatalyst was reused for five cycles. Another example of g-C_3N_4 supported Pd NPs was established by Huang and co-workers (Scheme **1.25B**) [71]. In their methodology, thermal polymerization of melamine was done to obtain g-C_3N_4. TEM images indicated that the average diameter of Pd NPs was around 3.25 nm. The platelet-like nanocatalyst was reusable up to five cycles with the retention of catalytic activity. In a similar way, Zhong and co-workers reported the deposition of Pd NPs on g-C_3N_4 by ultrasonic-assisted solution method (Scheme **1.25C**) [72]. In this methodology, urea was the precursor for g-C_3N_4, and SiO_2 was employed as a hard template. The prepared NPs were of about 4 nm in size and this nanocatalyst was reused for five times with good catalytic efficiency.

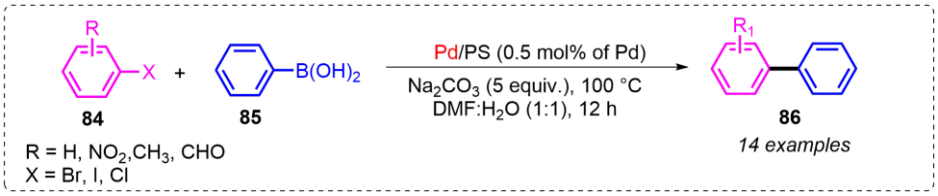


Scheme **1.25**. Pd/g-C_3N_4 catalyzed Suzuki coupling

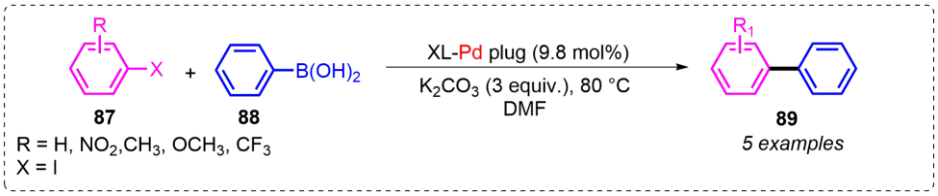
1.1.2.3.4 Pd-catalyst supported on polymer

Functionalized polymers act as the support for transition metals and the supported metal catalysts are employed in different synthetic processes. Naeini group developed a

strategy for the deposition of Pd NPs on cross-linked polystyrene surface (Scheme **1.26**) [73]. They prepared the cross-linked polystyrene by free-radical polymerization between divinylbenzene and styrene monomer in the presence of AIBN as the initiator. The average size of the deposited NPs was around 50 nm. This nanocatalyst was recycled five times without considerable loss of its activity. In another study, Bradley and co-workers reported the immobilization of Pd NPs within aminomethylstyrene resin plugs in the presence of succinyl chloride cross-linkers and employed this nanocatalyst in Suzuki coupling (Scheme **1.27**) [74]. TEM images indicated that at the edge of the resin plug Pd NPs were about 7 nm in size and the size increased to approximately 25-70 nm near the middle of the plug. The synthesized NPs were of different shapes like cubic, diamond, triangular, pentagon, rhomboidal, and trapezium. This nanocatalyst was reused for four catalytic cycles. Similarly, water-soluble Pd NPs were synthesized by Khokhlov group, supported on polystyrene-polyethylene oxide (PS-PEO) copolymer in the presence of *N*-cetylpyridinium chloride surfactant [75]. Other polymer support such as poly(*N*-isopropylacrylamide) [76], polyvinylpyrrolidone (PVP) [77], and polyion complex composed of poly(acrylic acid) and poly{4-chloromethylstyrene-co-(4-vinylbenzyl)tributylammonium chloride} [78] are usually employed for immobilization and stabilization of Pd NPs.



Scheme **1.26**. Pd/PS catalyzed Suzuki coupling

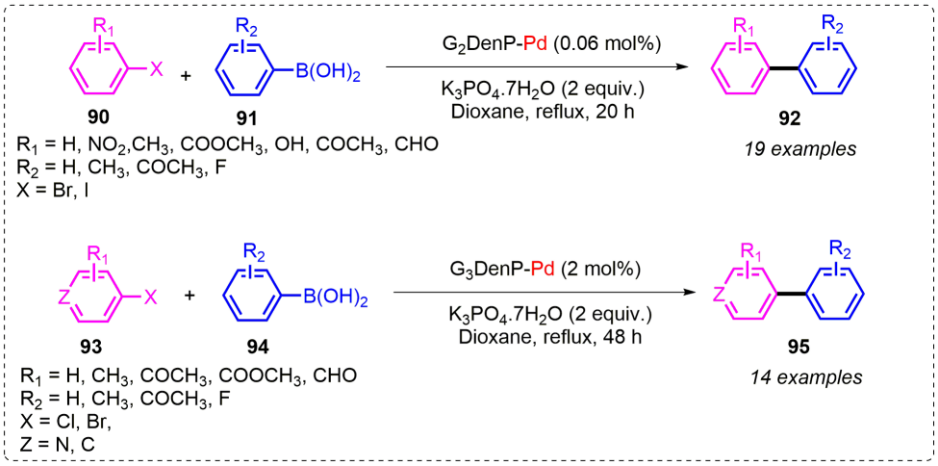


Scheme **1.27**. XL-Pd plug catalyzed Suzuki coupling

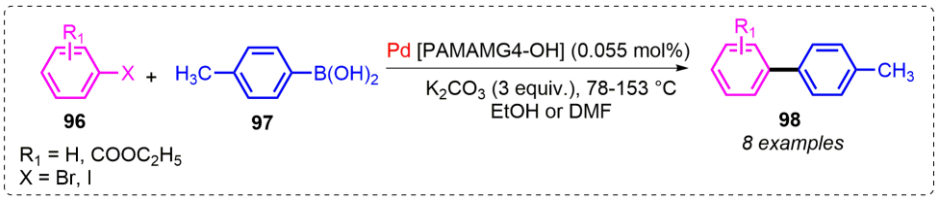
1.1.2.3.5 Pd-catalyst supported on dendrimer

Dendrimers are highly ordered, branched, three-dimensional macromolecules having a typical symmetric core with an inner and an outer shell [79]. NPs can be deposited either

inside the dendrimers or in their periphery. As a support, dendrimers help the metal NPs in two ways: firstly, they stabilize the NPs by preventing agglomeration, and secondly, branches of dendrimers act as selective gates by controlling the access of small molecules to the interior of NPs. Encapsulation of metal NPs inside dendrimers was first introduced by the groups of Tomalia, Crooks, and Esumi [80]. Fan and co-workers developed a strategy for the synthesis of phosphine dendrimer stabilized Pd NPs and utilized this nanocatalyst in Suzuki coupling (Scheme **1.28**) [81]. In their work, Fréchet-type polyaryl ether dendrons were employed owing to their chemical inertness and inability to coordinate with Pd. The reaction of corresponding dendritic bromides with $KPPh_2$ resulted in the formation of three different generations of phosphine ligands G_nDenP (n = 1-3). The size of the Pd NPs decreased with the increasing size of the dendritic ligand. The synthesized nanocatalyst was recyclable nine times without considerable loss of its activity. A similar type of work was reported by Fox group where they prepared third-generation dendrimer-supported Pd NPs (Pd-G3) by using Fréchet-type polyaryl ether disulfide dendron and showed that the stability of the catalyst was very high for several months both in powder and solution form [82]. Christensen group synthesized Pd NPs encapsulated in hydroxyl-terminated poly(amidoamine) (PAMAM G4-OH) dendrimers and studied their behaviour in Suzuki coupling (Scheme **1.29**) [83]. The average size of the NPs was around 3.2 nm. The nanocatalyst was highly stable for more than six months. Another dendrimer-based synthesis was reported by Astruc group [84]. They utilized five generations of diaminobutane dendrimers (DAB). The lower-generation dendrimer-supported Pd catalysts (DAB-G1, DAB-G2, and DAB-G3) exhibited higher catalytic activity as compared to higher-generation dendrimers (DAB-G4, and DAB-G5). They believed that the change in the catalytic activity might be lower accessibility of the substrates to the catalytic sites in entering the dendrimer.



Scheme **1.28**. G_nDenP-Pd-catalyzed Suzuki coupling

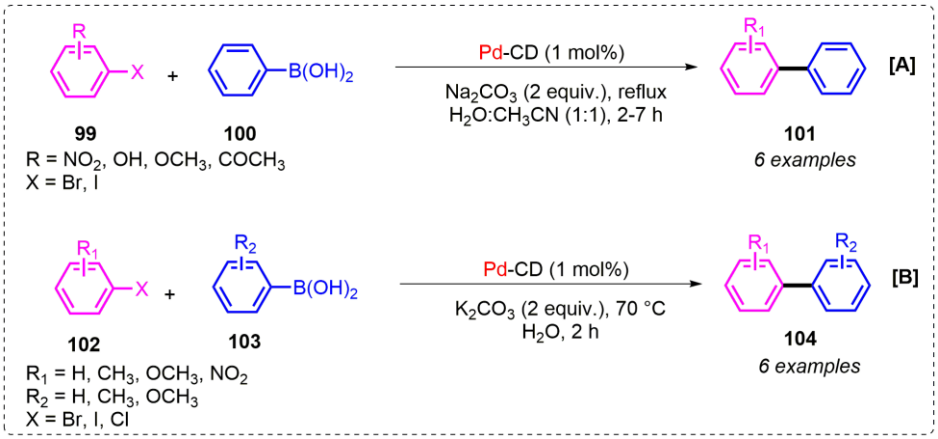


Scheme **1.29**. Pd [PAMAM G4-OH] catalyzed Suzuki coupling

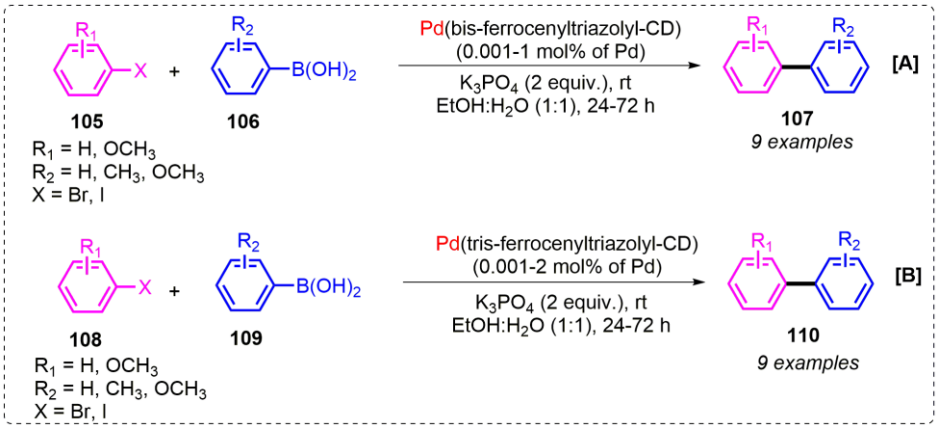
1.1.2.3.6 Pd-catalyst supported on cyclodextrin

Cyclodextrins (CDs) are cyclic oligosaccharides in which D-glucopyranoside units are linked by α-1,4-glycosidic bond [85]. These are promising molecular receptors in supramolecular chemistry. The existence of a hydrophobic cavity makes cyclodextrin an attractive supramolecular receptor. In particular, β-cyclodextrin has a hydrophobic inner surface and a hydrophilic outer surface [85]. Owing to its nature, it can be utilized as an environmentally benign medium for catalytic processes and has drawn the attention of synthetic organic chemists. Kaifer group reported the CD-capped Pd NPs catalyzed Suzuki coupling reaction (Scheme **1.30A**) [86]. They used perthiolated-β-cyclodextrin to cap the NPs. The synthesized nanocatalyst was highly soluble in water. For a better understanding of the advantages of employing CD, they carried out an experiment between iodoferrocene, an excellent guest for β-cyclodextrin receptor, and phenylboronic acid and found improved yield compared to homogeneous reaction conditions. Similarly, Bazgir and co-workers reported the synthesis of β-cyclodextrin decorated with Pd NPs and employed this nanocatalyst in Suzuki coupling in an aqueous medium (Scheme **1.30B**) [87]. The hydroxyl group in the outer surface of β-cyclodextrin offered sufficient

coordination sites to bind with Pd NPs. The average diameter of the NPs was in the range of 12-15 nm which was bigger than the cavity of β-cyclodextrin, indicating that Pd NPs were located outside the cavity. This nanocatalyst was reused for six catalytic cycles without a significant loss of activity. Another strategy to immobilize and stabilize Pd NPs supported on bis- and tris(ferrocenyltriazolylmethyl)arene-β-cyclodextrin was established by Astruc group (Scheme **1.31**, **A** and **B**) [88]. Bis- and tris(ferrocenyltriazolylmethyl)arenes were prepared by Click chemistry. The approximate size of the NPs was around 5-6 nm. The branches of CD encapsulated NPs and reactants and therefore the catalytic reaction occurred between β-cyclodextrin termini and the support framework.



Scheme **1.30**. Pd-CD catalyzed Suzuki coupling



Scheme **1.31**. **[A]** Pd(bis-ferrocenyltriazolyl-CD) and **[B]** Pd(tris-ferrocenyltriazolyl-CD)-catalyzed Suzuki coupling

1.1.2.4 General mechanism for nanocatalyst-based Suzuki-Miyaura cross-coupling reaction

In the case of nanocatalyst-based reaction, initially Pd(0) forms Pd(II) complex (**A**) by oxidative addition with aryl halide and then form species **B** by reaction with the base (Figure **1.8**). The base activates the boronic acid by forming borate anion which then undergoes transmetallation to form the intermediate **C**. This intermediate finally furnishes the biaryl product (**D**) and Pd(0) after reductive elimination.

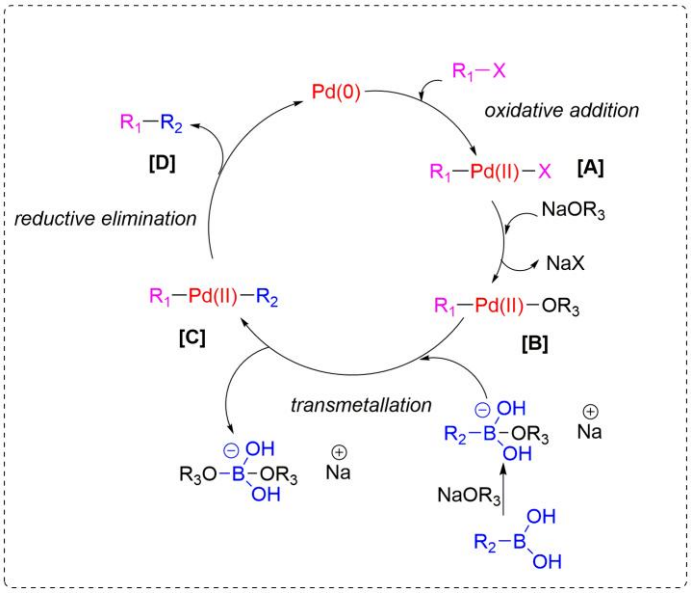


Figure **1.8**. Mechanism of nanocatalyst-based Suzuki-Miyaura coupling reaction

1.1.2.5 Decarboxylative coupling of cinnamic acids

Decarboxylation is one of the vital processes for different metabolic pathways like citric acid cycle and glycolysis. Direct decarboxylative functionalization is one of the most significant transformations in organic synthesis due to regiospecificity, step and atom economic nature. These types of coupling reactions have very convenient synthetic strategies that can be easily operated and generates less toxic by-products [89]. Decarboxylative couplings represent a beneficial alternative to classical cross-coupling or addition reactions of organometallic reagents [90]. Unlike organometallic reagents, carboxylic acids are air and moisture stable, non-toxic, cheap, easy to handle and highly abundant in nature with great structural diversity; turning into an interesting coupling partner for cross-coupling reactions [91]. In the past few decades, an abundance of catalytic transformations for decarboxylative functionalization provide an easy access to

various valuable classes of products and synthetic intermediates for different reaction pathways [90]. Depending upon the nature of the catalyst system and reaction conditions utilized, carboxylic acids can serve as radical, nucleophilic, or electrophilic synthetic equivalents of acyl, alkyl or aryl units or organometallic reagents (Figure **1.9**) [91a].

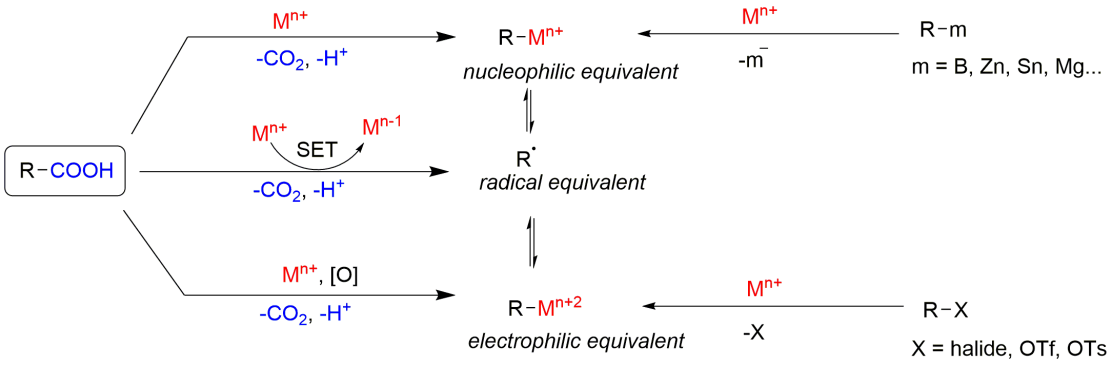


Figure **1.9**. Multifaceted pathways for generation of coupling intermediates from carboxylic acid

Arene carboxylic acids, particularly cinnamic acids have broad spectrum applications in the decarboxylative coupling reactions owing to their stability, easy handling, and structural diversity, and can be easily synthesized from aromatic aldehydes by Perkin reaction, which results in the construction of C-C, C-N, C-S, and C-P bonds [90]. The general mechanism (Figure **1.10**) of transition metal-catalyzed decarboxylative coupling involves the formation of an organometallic species (**B**) after the elimination of CO_2 from the metal-carboxylate (**A**). This organometallic species then undergo coupling reactions with another molecule either through oxidative or redox-neutral coupling depending upon the applied reaction conditions [92].

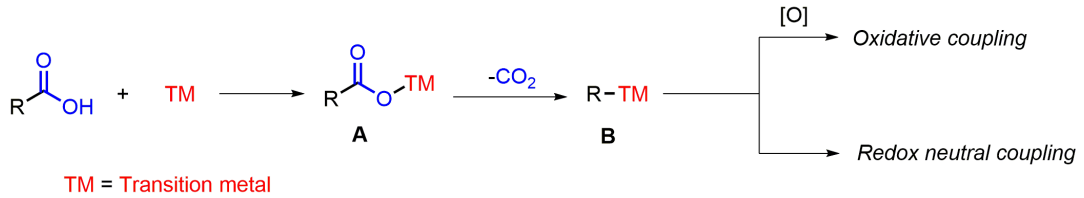


Figure **1.10**. Mechanistic pathway for transition metal-catalyzed decarboxylative coupling

To eliminate CO_2 from metal carboxylates of simple carboxylic acids require harsh reaction conditions and the addition of a mediator (silver or copper salts) to the reaction protonated the organometallic species (**B**) (Figure **1.10**) rather than forming the coupling

product [93]. Hence to improve the decarboxylative functionalization, another pathway i.e. radical addition-elimination process (Figure **1.11**) is found to be fruitful to carry out the reaction in relatively mild conditions.

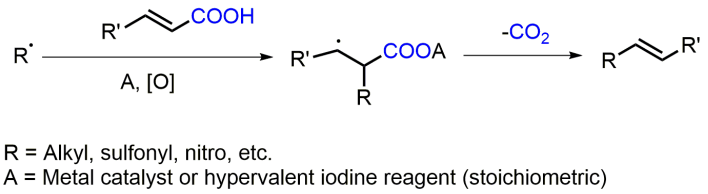


Figure **1.11**. Radical addition-elimination mechanism for decarboxylative functionalization

The reactivity of cinnamic acid is mainly due to the polarized alkenyl moiety and the carboxylic acid group [94]. Cinnamic acids have broad-spectrum applications in the pharmaceutical industries owing to their physiological properties like antioxidant [95], antimicrobial [96], anticancer [97], antimalarial [96], and antidiabetic [95], etc. In addition to transition metal-catalyzed decarboxylative coupling, metal-free approaches; particularly hypervalent iodine reagents are utilized in recent years [92]. The decarboxylative coupling of cinnamic acid can be categorized into five groups: (a) radical addition, (b) electrophilic addition, (c) Michael addition, (d) acids as nucleophiles, and (e) electrophilic acids. Here, we will discuss the decarboxylative coupling of cinnamic acids involving a radical addition pathway.

The decarboxylative cross-coupling of cinnamic acids through a radical pathway is mainly utilized for the construction of C-C, C-P, C-N, C-S, and C-Si bonds. To maintain the stereoselectivity (predominantly *E* configuration) [**A**] (Figure **1.12**) in the desired product, generally, a high temperature is required in this radical mechanism [98]. Moreover, this decarboxylative cascade can undergo cyclization or oxidative cross-coupling (Figure **1.12**) to afford epoxides [**B**] [99], ketones [**C**] [100], and furans [**D**] [101]. The most commonly used oxidants in decarboxylative coupling are Ag_2O, $K_2S_2O_8$, TBHP, DTBP, H_2O_2, and dicumyl peroxide. In radical addition, carbon, nitrogen, phosphorus, sulfur, and silicon radicals are generated throughout the process depending on the applied reaction conditions.

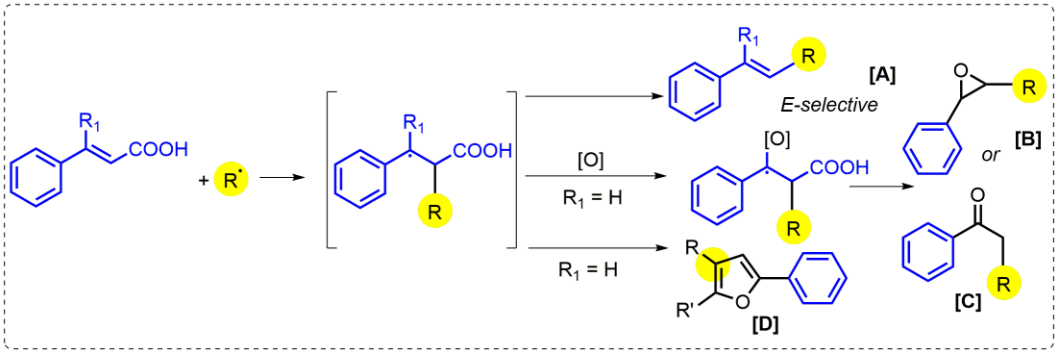
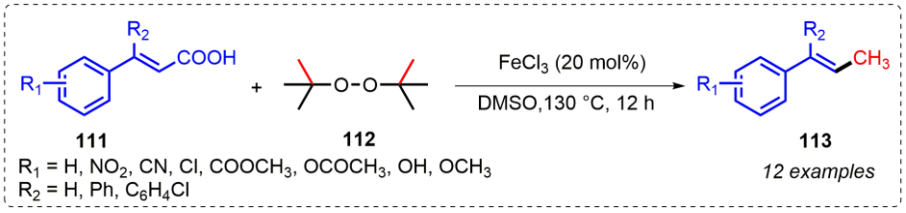


Figure **1.12**. Radical couplings of cinnamic acids

1.1.2.5.1 Decarboxylative coupling incorporating carbon radical

Precursors of carbon radicals like acyl, methyl, trifluoromethyl, acids, aldehydes, ketones, amide, alcohols, ethers, nitriles, epoxides, etc. are subjected to go through addition decarboxylation process [94].

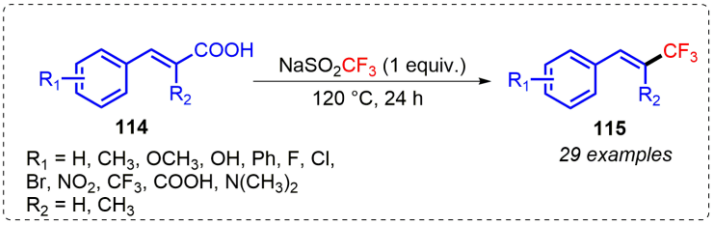
A strategy for decarboxylative methylation of cinnamic acids (**113**) was described by Mao group, utilizing DTBP (**112**) both as the oxidant and the methyl source (Scheme **1.32**) [102]. This $FeCl_3$-catalyzed decarboxylative methylation involved a radical mechanism where the stereochemistry of the alkene was retained throughout the reaction.



Scheme **1.32**. $FeCl_3$ catalyzed decarboxylative methylation of cinnamic acids

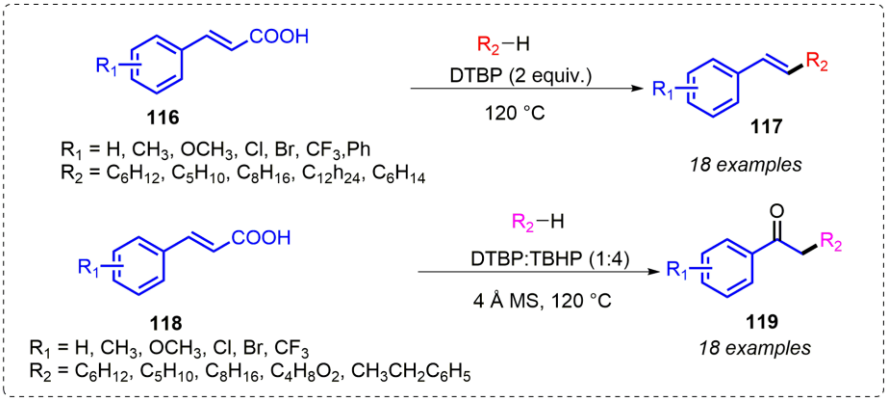
Trifluoromethylated organic compounds have a wide range of applications in medicinal chemistry [103]. The compounds containing C_{vinyl}-CF_3 groups like cyhalothrin, and panomifene are used in medicinal chemistry. In recent years, Togni reagent ($NaSO_2CF_3$) has received considerable attention as the source for CF_3 group owing to its air and moisture stability [104]. Cai and co-workers reported the synthesis of C_{vinyl}-CF_3 bond *via* decarboxylative coupling of cinnamic acids with Togni reagent (Scheme **1.33**) [98]. With good functional group tolerance, their methodology furnished *E* alkene (**115**) through a

free radical pathway. Both Togni and Togni-type (CF_2SO_2R) reagents are well-suited for decarboxylative coupling with cinnamic acids [105].



Scheme **1.33**. Construction of C_{vinyl}-CF_3 bond using Togni reagent

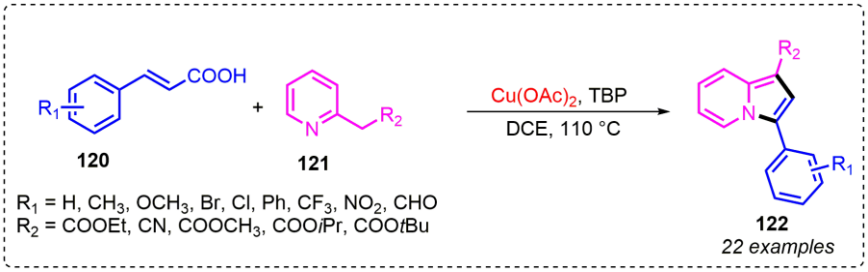
Alkanes are effective coupling partners for the decarboxylative alkylation of cinnamic acids promoted by peroxides in transition metal-free conditions. Sun and co-workers developed a strategy to obtain alkenes and ketones from cycloalkanes by tuning the oxidant (Scheme **1.34**) [106]. The addition of DTBP formed alkenes with *E* selectivity (**117**) while DTBP and TBHP in the ratio of 1:4 offered ketones (**119**). The hydroxyl radical from TBHP generated the intermediate β-hydroxy acid which on further reaction converted into ketones. Alkyl acids [107], alkyl aldehydes [108], halogenoalkanes [109], and *N*-(acyloxy)phthalimide [110], alkyl iodides (ICH_2X, where X = CHF_2, CF_3, CH_2F, CH_2CF_3, CN) [111] generate alkyl radicals which undergoes the radical addition-decarboxylation process.



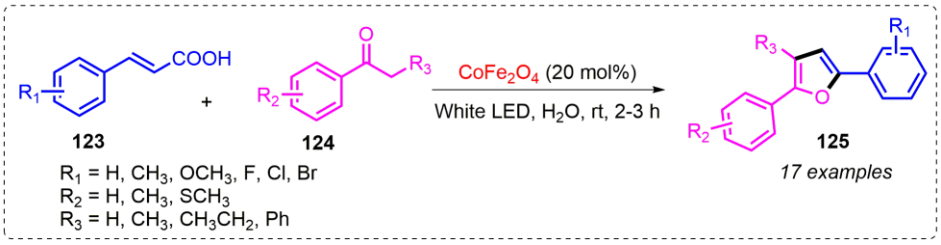
Scheme **1.34**. Decarboxylative alkylation of cinnamic acids

Cai group developed the decarboxylative annulation to synthesize indolizines (**122**) by using a copper catalyst and TBP oxidant (Scheme **1.35**) [112]. The benzyl radical generated during the reaction went through cyclization and oxidative aromatization to furnish indolizines. The presence of copper salt and oxidant was necessary for the success of the reaction. Different sources of benzyl radicals such as arenes [113], boron

reagents [114], and benzaldehydes [115] are utilized for radical addition-decarboxylation strategy. Another type of decarboxylative annulation to synthesize furan (**125**) was reported by Rai group (Scheme **1.36**) [116]. A cooperative effect of $CoFe_2O_4$ nanoparticles and visible light proceeded this [3+2] cycloaddition in an aqueous medium at room temperature. The nanoparticles not only accelerated the conversion but also increased the reaction yield. By forming carbonyl radicals, cyclic ketones also undergo decarboxylative annulation through the radical addition process [117]. By using transition metals and oxidants, keto acids [118], toluenes [119], and amides [120] can generate acyl radicals that undergo decarboxylative coupling with cinnamic acids.

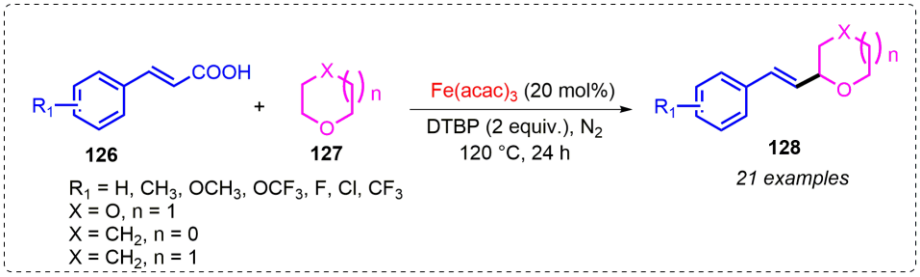


Scheme **1.35**. Synthesis of indolizines *via* decarboxylative annulation

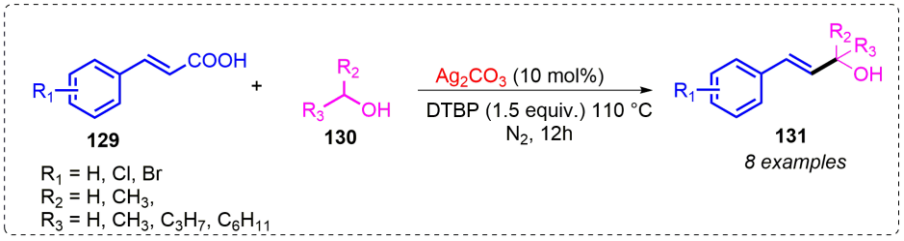


Scheme **1.36**. Synthesis of furan through decarboxylative annulation

Cyclic ethers and alcohols are mostly studied as decarboxylative coupling partners with cinnamic acids. These transformations can be achieved either by using transition metals or oxidants or both in the reactions [121]. Pan and co-workers established iron-catalyzed alkenylation of cyclic ethers (**128**) in presence of DTBP (Scheme **1.37**) [122]. This radical addition-decarboxylation process was carried out in a nitrogen atmosphere. A strategy for Ag_2CO_3-catalyzed decarboxylative coupling of cinnamic acids with alcohols (**131**) was developed by Fang group (Scheme **1.38**) [121d]. Their methodology was favourable for all three alcohols (primary, secondary, and tertiary).



Scheme **1.37**. $Fe(acac)_3$ catalyzed alkenylation of cyclic ethers



Scheme **1.38**. Ag_2CO_3 catalyzed alkenylation of alcohol

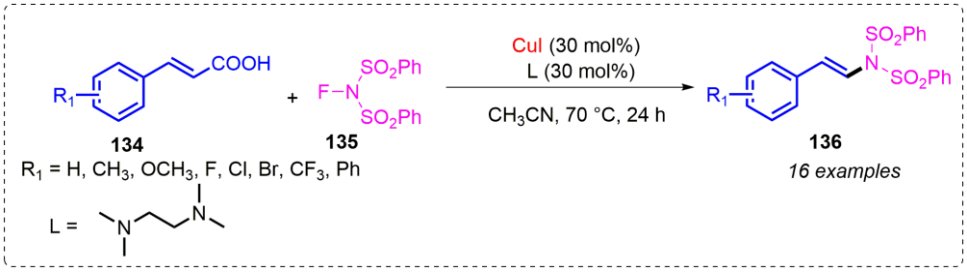
1.1.2.5.2 Decarboxylative coupling incorporating nitrogen radical

The addition of nitrogen radicals to cinnamic acids results in the formation of nitro-olefins. The classical method for nitro-olefin synthesis employed the Henry reaction, a condensation reaction between nitroalkanes and carbonyl compounds in presence of a base [123]. This radical addition-decarboxylation strategy is an alternative approach for nitro-olefins synthesis by employing $NaNO_2$ [124], *tert*-butylnitrite (TBN) [123], NO_2BF_4 [125], $Bi(NO_3)_3.5H_2O$ [126], etc. as the NO_2 radical precursor. Maiti group reported the metal-free synthesis of nitro-olefins (**133**) by using TBN and TEMPO (Scheme **1.39**) [123]. Under the air atmosphere, the NO radical offered by TBN forms the NO_2 radical which on further reactions furnished nitro-olefins. The addition of TEMPO maintained the *E*-selectivity in products.

Scheme **1.39**. Synthesis of nitro-olefins from cinnamic acids

The construction of the C-N bond using cinnamic acids is closely confined to the nitro-olefins synthesis. Decarboxylative imidation is another prospect for C-N bond formation

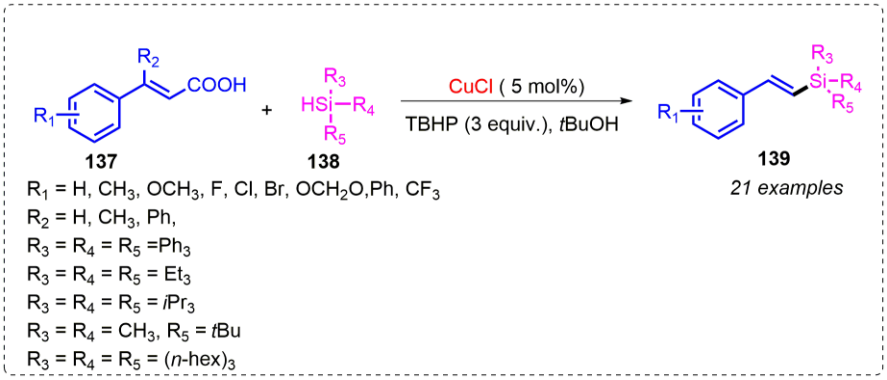
by incorporating cinnamic acids. Tang and co-workers developed a strategy for decarboxylative imidation (**136**) by using *N*-fluorobenzenesulfonimide (**135**), catalyzed by copper salts (Scheme **1.40**) [127]. This imidation was a ligand-assisted intermolecular radical addition process.



Scheme **1.40**. CuI catalyzed decarboxylative imidation of cinnamic acids

1.1.2.5.3 Decarboxylative coupling incorporating silicon, phosphorus, and sulfur radicals

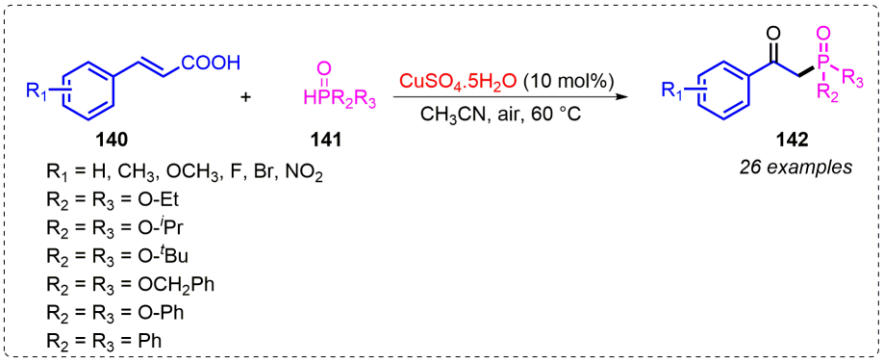
C-Si bond formation through the radical decarboxylative process is limited in the literature. Liu group developed decarboxylative silylation of cinnamic acids, catalyzed by copper salt in presence of TBHP oxidant (Scheme **1.41**) [128]. This stereospecific (*E*-isomer) silylation (**139**) involved a radical addition-decarboxylation mechanism.



Scheme **1.41**. CuCl catalyzed decarboxylative silylation of cinnamic acids

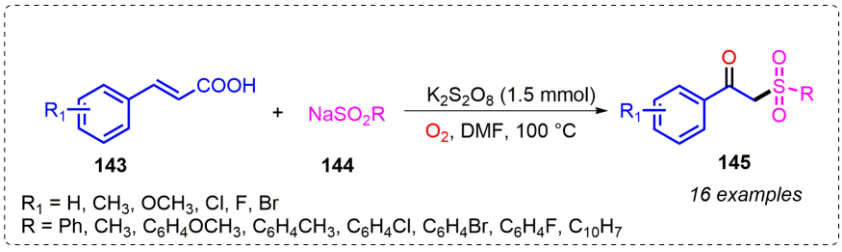
The formation of the C-P bond (**142**) through decarboxylative phosphorylation of cinnamic acids was reported by Zhao and co-workers using copper salt in CH_3CN (Scheme **1.42**) [129]. CH_3CN promoted the formation of $[(CH_3CN)_nCu^{II}\text{-O-O}]$ radical intermediate that played a significant role in the mechanism. Furthermore, copper [130],

and nickel [131]-catalyzed and transition metal-free [132] approaches are found in the literature for phosphorylation of cinnamic acids.

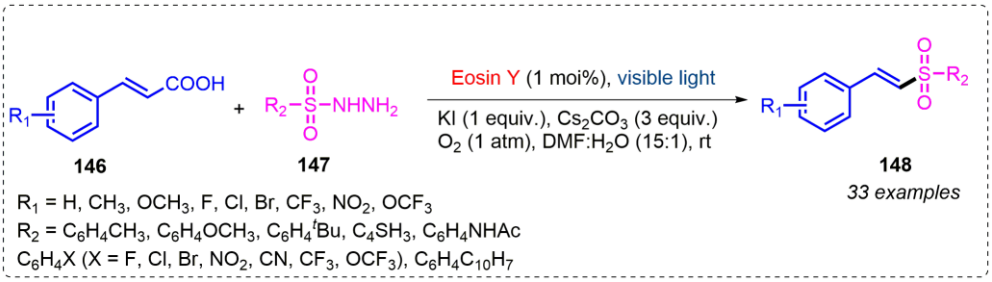


Scheme **1.42**. $CuSO_4.5H_2O$ catalyzed decarboxylative phosphorylation of cinnamic acids

Similar to carbon, nitrogen, silicon, and phosphorus radicals, sulfur radicals also exhibit a radical addition-decarboxylation process with cinnamic acids. Through this process vinyl sulfones can be synthesized by using disulfides [133], sodium sulfinates [134], TosMIC [135], and aryl sulfonate phenol esters [136] as the radical sulfur source. Among these sources, sodium sulfinates are widely employed. Yadav and co-workers developed a strategy for oxidative decarboxylative functionalization of cinnamic acids with sodium sulfinate salts (Scheme **1.43**) [137]. This transition metal-free transformation was mediated by $K_2S_2O_8$ to afford β-keto sulfones (**145**) under aerobic conditions. The keto source of β-keto sulfones was obtained from atmospheric oxygen. Sulfonylhydrazides (**147**) are also an alternating radical source and this was reported by Weng group (Scheme **1.44**) [138]. By using eosin Y as the photocatalyst, irradiated by visible light, this transition metal-free approach was carried out in presence of oxygen. Moreover, $AgSCF_3$ [139], and NH_4SCN [140] can also be used as the radical sulfur sources.



Scheme **1.43**. $K_2S_2O_8$ mediated decarboxylative oxysulfonylation of cinnamic acids



Scheme **1.44**. Visible light irradiated decarboxylative sulfonylation of cinnamic acids

Despite remarkable development, direct C-H functionalization through decarboxylation remains elusive. Therefore, the exploration and development of simple and sustainable methodologies for the decarboxylative functionalization of cinnamic acids are highly desirable.

1.2 The Thesis

The thesis comprises seven chapters, out of which one chapter is for general introduction; the experimental works have been included in five chapters and one chapter combines the concluding remarks of whole work with future scope. Among the five chapters, chapters 2, 3, and 4 describe the methodologies for functionalization of indoles and related molecules. Chapters 5 and 6 are focused on heterogeneous catalysis for C-C bond formations *via* Suzuki-Miyaura coupling and decarboxylative alkenylation reaction. Detailed studies of work are discussed in the corresponding chapters.

1.3 Objectives of the present work

The main objectives of my research work are:

(a) Development of reaction strategies for site specific functionalization of indoles and related molecules.

(b) Design of newer heterogeneous Pd-based catalytic system for minimizing base-stoichiometry in Suzuki-Miyaura cross-coupling reaction.

(c) Development of Cu-based catalyst system for decarboxylative alkenylation of cyclic ethers with cinnamic acids.

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