Chapter 1

General Introduction

Palladium and Copper Catalysed Synthesis of Functionalised Carbocycles and Heterocycles

Chapter 1

General Introduction

1.1. Transition metal catalysis

Catalysis plays a pivotal role in modern science, transforming the construction of complex molecular structures with exceptional selectivity and efficiency. Its advancements have significantly influenced science and technology, leading to the development of synthetic methods that are environmentally friendly, cost-effective, time-efficient, high-yielding, and labor-saving. Synthetic organic chemistry has been shaped by two key strategies: transition-metal catalysis and organocatalysis, both of which have earned Nobel Prizes: in 2001 (Knowles, Noyori, and Sharpless for stereoselective catalysis), 2005 (Chauvin, Grubbs, and Schrock for olefin metathesis), 2010 (Heck, Negishi, and Suzuki for palladium-catalysed cross-coupling reactions), and 2021 (List and MacMillan for asymmetric organocatalysis) [1].

The study of coordination bonds by Warner and Jørgensen, which earned a Nobel Prize in 1913, sparked a surge of interest in transition metals and their complexes [2]. Transition metals are vital in catalysis due to their ability to exist in multiple oxidation states, facilitating electron transfer and the formation of intermediates that drive reactions. For example, in the Haber-Bosch process, iron (Fe) catalyses the reaction between nitrogen (N_2) and hydrogen (H_2) to produce ammonia (NH_3) under high pressure (150–200 atm) and moderate temperature (400–500 °C) [3]. In the Contact method, V_2O_5 accelerates SO_2 oxidation to SO_3 at around 450 °C, with an equilibrium constant favoring SO_3 production [4]. Catalysts such as Wilkinson's rhodium compound [$(PPh_3)_3RhCl$] and palladium in the Heck reaction, where complexes of Pd(0) or Pd(II) enable the coupling of alkenes and organo halides, have transformed organic chemistry [5, 6]. The Wacker process, using palladium (II) chloride ($PdCl_2$) and copper (II) chloride ($CuCl_2$), oxidises ethylene (C_2H_4) to acetaldehyde (CH_3CHO) under aqueous conditions [7]. Ruthenium-based Grubbs catalysts, such as [$RuCl_2(PCy_3)_2(=CHPh)$], enable efficient olefin metathesis by rearranging carbon-carbon double bonds [8].

Biological systems also rely heavily on transition metals to carry out essential and diverse biochemical processes. Iron, in the form of Fe^{2+}/Fe^{3+}, plays a central role in haemoglobin by binding reversibly to molecular oxygen (O_2), enabling efficient oxygen transport throughout the bloodstream and its release in oxygen-deprived tissues. Molybdenum (Mo), found in nitrogenase enzymes, is crucial for the biological fixation of atmospheric nitrogen (N_2) into ammonia (NH_3), a process that involves complex multi-electron transfers coupled with ATP hydrolysis and assisted by iron–sulfur clusters. Copper (Cu^+/Cu^{2+}) is another vital metal involved in redox reactions within enzymes like cytochrome c oxidase, which is central to the mitochondrial electron transport chain and cellular respiration. Zinc (Zn^{2+}), though redox-inactive, is indispensable for the structural integrity and catalytic activity of numerous enzymes, including carbonic anhydrase and DNA-binding zinc finger proteins. Cobalt (Co^{3+}), present in vitamin B_{12} (cobalamin), plays a key role in methyl group transfer and the metabolism of fatty acids and amino acids. Manganese (Mn^{2+}), found in the oxygen-evolving complex of photosystem II, is essential for the water-splitting reaction in photosynthesis. [9].

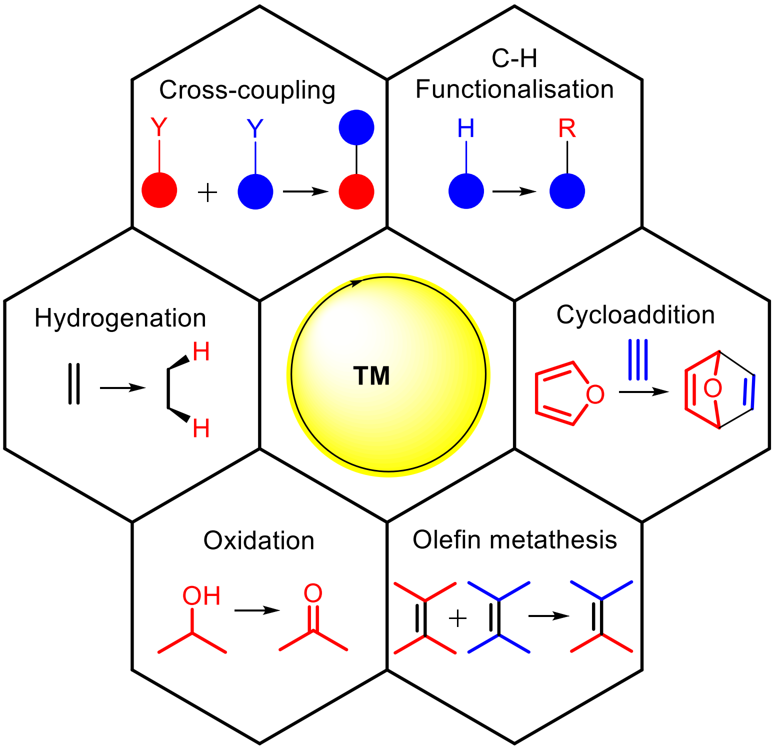


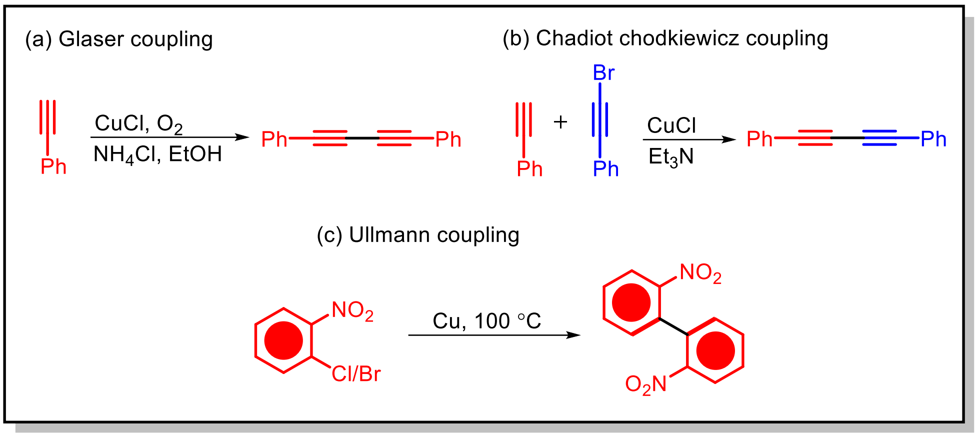
Figure 1.1. Utility of transition metals in organic synthesis

Transition metals play a vital part in synthesis, for their unique electronic, variable oxidation states, and ability to form coordination complexes that enable a wide range of reactions. In redox processes, metals such as ruthenium, chromium, and manganese are particularly significant. For example, ruthenium tetroxide efficiently oxidises alkenes to ketones or aldehydes, while chromium-based reagents like PCC selectively oxidise primary alcohols to aldehydes. In reduction reactions, catalysts such as palladium and platinum are widely used for hydrogenation, facilitating the addition of hydrogen to alkenes, alkynes, or carbonyl compounds under mild conditions, which is essential for functional group transformations. Transition metals also enhance cycloaddition reactions, including [2+2] and [4+2] (Diels-Alder) cycloadditions, by lowering activation energies and providing precise regio- and stereochemical control. For instance, rhodium-catalysed asymmetric cycloadditions are pivotal in synthesising pharmaceuticals. Olefin metathesis, catalysed by molybdenum or ruthenium complexes such as Grubbs catalysts, enables the redistribution of alkene fragments *via* metal-carbene intermediates. This reaction is widely used for synthesising polymers, macrocycles, and complex molecules under mild conditions, with excellent functional group tolerance. Transition metals also play a key role in activating small molecules and breaking strong bonds, such as molecular hydrogen in hydrogenation or carbon monoxide in hydroformylation. For example, cobalt or rhodium catalysts activate CO and H_2 to convert alkenes into aldehydes. Additionally, metals like palladium, rhodium, and iridium facilitate C-H activation, breaking inert C-H bonds and enabling direct functionalisation of hydrocarbons without pre-functionalisation steps. Cross-coupling reactions, such as Suzuki, Heck, Chan-Lam and Stille couplings, depend on palladium catalysts to form bonds through oxidative addition, transmetallation, and reductive elimination [1, 10].

The utilisation of transition metals, complexes as well as their nanoparticles is therefore essential in the construction of linkages useful in making functionalised carbocycles and heterocycles.

1.2. Transition metal catalysed cross-coupling reactions

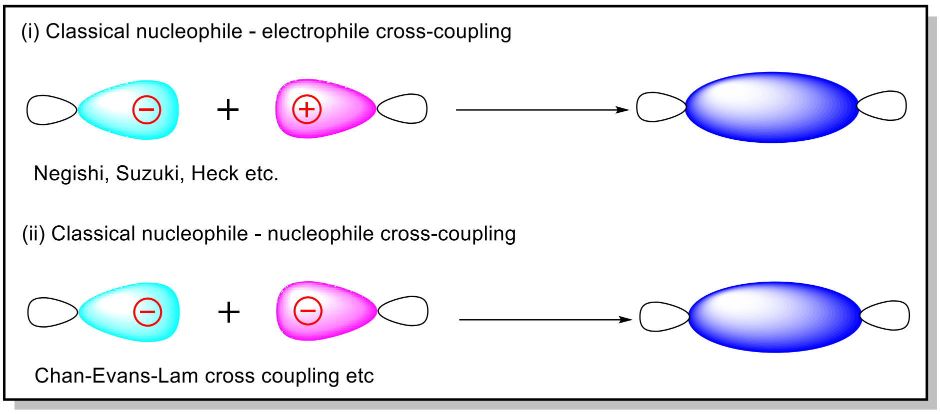
The cross-coupling reactions involve two different reactants, each possessing one or more activating groups, reacting in the presence of a transition metal catalyst. These processes eliminate the activating groups and form new bonds between the remaining molecular fragments. The first metal-mediated carbon-carbon (C-C) coupling reaction was documented by Glaser in 1869 (**Scheme 1.1 (a)**) [11], utilizing copper (I) salts for the homocoupling of phenylacetylene, which produced diphenyldiacetylene. In 1901, Ullman reported the homocoupling of aryl halides, employing a stoichiometric amount of copper metal to synthesise symmetrical biaryls (**Scheme 1.1 (b)**) [12]. Subsequently, in 1957, Cadiot and Chodkiewicz introduced a selective cross-coupling method between alkynes and bromoalkynes using a catalytic amount of copper salts, achieving a high yield of 1,3-diynes (**Scheme 1.1 (c)**) [13]. The 1960s and 1970s marked significant advancements in C-C cross-coupling reactions, revolutionising organic synthesis.



Scheme 1.1. Unprecedented cross-couplings under palladium and copper catalysis

Cross-coupling reactions can generally be divided into two main types. The first type involves the interaction between an electrophile and a nucleophile, often referred to as traditional or classical cross-coupling [14]. In this type, the electrophilic component is typically an organohalide, while the nucleophilic component is an organometallic reagent. Examples of such reactions include the Suzuki-Miyaura, Heck, and Stille couplings, which are primarily used for the formation of carbon-carbon bonds. The second class of cross-couplings, being oxidative cross-coupling, involves the formation of a new carbon-carbon or carbon-heteroatom bond between two organic molecules, facilitated by a metal catalyst and an oxidation step [15]. In this process, one or both reactants are oxidised to increase their reactivity, allowing them to couple effectively. The reaction typically involves aryl or vinyl groups, with an oxidizing agent playing a key role in activating the reactants. Oxidative cross-coupling reactions are advantageous for synthesising complex organic compounds, as they often require milder conditions and can handle a broader range of substrates compared to traditional cross-coupling methods. A notable example is the Chan-Lam coupling, where copper catalyses the reaction between aryl boronic acids and amines (**Scheme 1.2**) [16].

The classical electrophile-nucleophile cross-couplings [15 ,16] show a catalytic cycle consisting of three steps. First, oxidative addition occurs, where the R_1-X bond (X being a heteroatom) in the electrophile adds to the transition metal catalyst (M), forming the intermediate R_1-M-X.



Scheme 1.2. Classical and oxidative cross-couplings

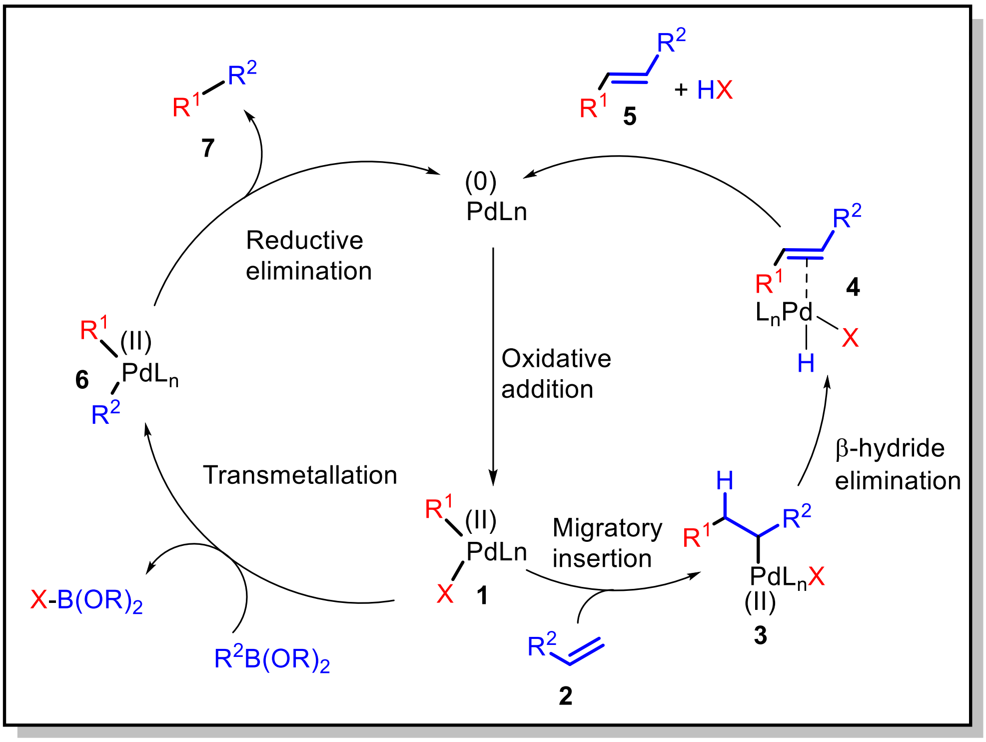
Next, transmetallation takes place, in which the nucleophile R_2-M' reacts with R_1-M-X to produce R_1-M-R_2. In Suzuki-Miyaura couplings, this step may include migratory insertion and β-hydride elimination, as seen in Heck coupling. Finally, reductive elimination of R_1-M-R_2 yields the coupled product R_1-R_2, or base-assisted H-X elimination forms the product while regenerating the catalyst. Notably, the cycle does not require an external oxidant, as the oxidizing role is generally fulfilled by the electrophile itself.

Oxidative cross-coupling is a flexible method for forming bonds between two nucleophilic centers, such as C-H/C-H or C-H/H-X (X = heteroatom such as N). The nucleophiles involved include organometallic reagents (C(sp)-M, C(sp^2)-M, and C(sp^3)-M), hydrocarbons (C-H), salts (M-X), and heterocyclic compounds. Although it is based on the principles of traditional cross-coupling reactions, oxidative cross-coupling requires an additional oxidant. A major limitation is the reliance on external oxidants, though some processes use air as the oxidant. Other challenges include issues with chemo-selectivity and regioselectivity, though recent research has yielded promising results. Critical considerations for these reactions include selecting an appropriate oxidant and catalyst combination, understanding the role of the oxidant, and identifying the active catalyst within the system [17].

1.3. Palladium in C-C and C-heteroatom cross-couplings

Palladium is a crucial metal in organic synthesis, particularly for forming C-C and C-heteroatom bonds [18]. Its unique chemical properties and flexible redox behavior make it invaluable in catalytic processes. Palladium can exist in multiple oxidation states—0, +2, and +4 – enabling its role as a catalyst in diverse reactions. The standard reduction potentials for its common redox pairs are $E_{Pd^{2+}/Pd}{}^{o}$ = +0.951 V, $E_{Pd^{4+}/Pd^{2+}}{}^{o}$= +0.62 V and $E_{Pd^{2+}/PdH_2}{}^{o}$ = -0.13 V, highlighting its versatility in redox and catalytic transformations [19]. One of palladium's defining features is its ability to undergo oxidative addition, where a Pd(0) complex reacts with a molecule like a halide or organic compound to form a Pd(II) complex. This step is essential in catalytic cycles as it raises palladium's oxidation state and activates the substrate for further transformations. This property is fundamental to cross-coupling and other catalytic reactions. Palladium’s affinity for soft π- and N-donor ligands supports the concerted steps required for these cycles, making it ideal for facilitating both oxidative and reductive transformations. Cross-coupling reactions, where palladium is a preferred metal, follow a consistent mechanism. Typically, the process begins with the *in-situ* Pd(II) reduction of a pre-catalyst to a Pd(0) species, although direct Pd(0) sources can also be used. The Pd(0) species then undergoes oxidative addition with an aryl halide or pseudohalide, forming an arylpalladium (II) complex. Two catalytic pathways may follow in the palladium-catalysed cycle. The first is 1,2-insertion and β-hydride elimination, where a new Pd(II) complex is formed, and an unsaturated product is released, as exemplified in the Heck reaction. The second pathway involves transmetallation and reductive elimination, in which the halogen is replaced by another ligand, such as an aryl or heteroaryl fragment, resulting in cross-coupling (**Scheme 1.3**).

The palladium-catalysed oxidative bond formation has been recognised since the Wacker process, which was used to produce acetaldehyde. This marked the first industrial-scale use of homogeneous catalysis for ethylene oxidation. The process was found to follow a pathway in which a palladium-π-complex with the alkene is formed. After deprotonation and elimination of β-hydride, this results in the creation of an enol and a Pd(0) complex. Cu(II) oxidises Pd(0) and revives the Pd(II) species. Reduced Cu(II) is then re-oxidised to Cu(II) by molecular oxygen, completing the catalytic cycle. A similar transformation using an acidic solution of $PdCl_2$ as the catalyst and $CuCl_2$ in stoichiometric amounts, with oxygen present. Olefin-palladium interaction was utilised by Fujiwara in 1968 for substitution reactions involving aromatic compounds [20a]. 1968, Richard Heck published his work on the coupling of organomercuric compounds with alkenes with lithium tetrachloropalladate (II) catalyst. Heck and Mizoroki later expanded on this research by replacing the toxic aryl mercury compounds with an aryl halide and by means of palladium (II) acetate catalyst [20b].



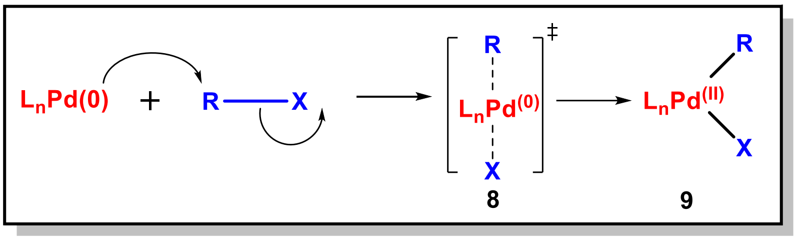
Scheme 1.3. Palladium catalysed cross-coupling: the general mechanisms

In 1975, Sonogashira, devised a method for forming C(sp2)-C(sp) linkages by combining unsaturated organo halides with alkynes with a palladium catalyst, copper (I) co-catalyst, and a basic environment (**Scheme 1.4**) [21]. In 1977, Negishi introduced a metal-mediated process involving organic halides or triflates and organozinc reagents, favouring palladium over nickel to maintain stereochemical integrity (**Scheme 1.4**) [22].

1.3.1. Oxidative addition to Palladium (0)

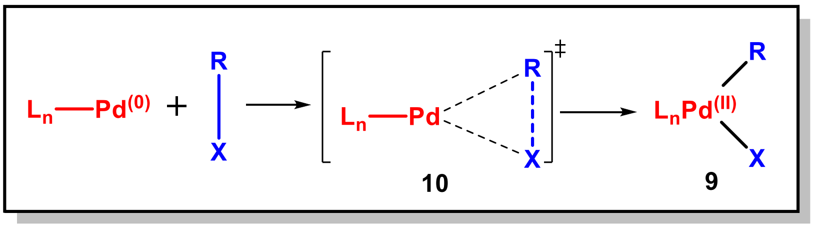
The addition of the C-X bond to the Pd(0) center leads to the creation of C-Pd(II)-X species where Pd inserts to the C-X bond [23]. The speed of oxidative addition among the halides increases down the group with the C-I bond undergoing oxidative addition most easily. Any increase in the electron density on the palladium center is seen to increase the rate of oxidative addition with strong σ-donating groups facilitating faster oxidative addition. The oxidative addition step can take place *via* two pathways, namely the nucleophilic displacement S_N2 pathway and concerted pathway *via* a three membered ring intermediate [24].

In the nucleophilic displacement S_N2 pathway, the Pd(0) center interacts with the carbon of the electrophile (C-X), leading to the removal of the halide and cationic intermediate generation, which is swiftly trailed by the association of the charged species with Pd, resulting the formation of desired complex (**Scheme 1.4**). Such a mechanism for oxidative addition is normally shown by activated molecules such as alkyl, allyl and benzyl halides.



Scheme 1.4. Oxidative addition *via* nucleophilic displacement

The other mechanism, concerted addition, shown by aryl halides, proceeds through a 3-center transition state, to form a *cis*-$[PdL_nRX]$ complex. The *cis*-complex then rapidly isomerises into the more stable *trans*-$[PdL_nRX]$ complex (**Scheme 1.5**).



Scheme 1.5. Concerted mechanism for oxidative addition

The oxidative addition step is generally followed by either transmetallation or by insertion which can lead to different reactivities.

1.3.2. The Suzuki-Miyaura cross-coupling reaction

In the mid-1970s, while searching for a mild procedure to synthesise internal aryl alkenes, Suzuki and co-workers observed the easy formation of the desired product *via* joining of alkenyl boranes with alkenyl halides in the presence of palladium salt catalyst and stoichiometric base [25]. The reaction was then seen to be highly feasible with aryl boronic acids/boronates and aryl halides/pseudohalides to synthesise the privileged biphenyl system. Contrary to the previously reported cross-coupling processes, organoboron compounds employed in this reaction are bench stable and are readily available. This reaction speeded up C-C bond formation research and has been utilised in the synthesis of several active pharmaceutical ingredients (APIs), pharmaceuticals, functional materials and agrochemicals (**Figure 1.2**) [26].

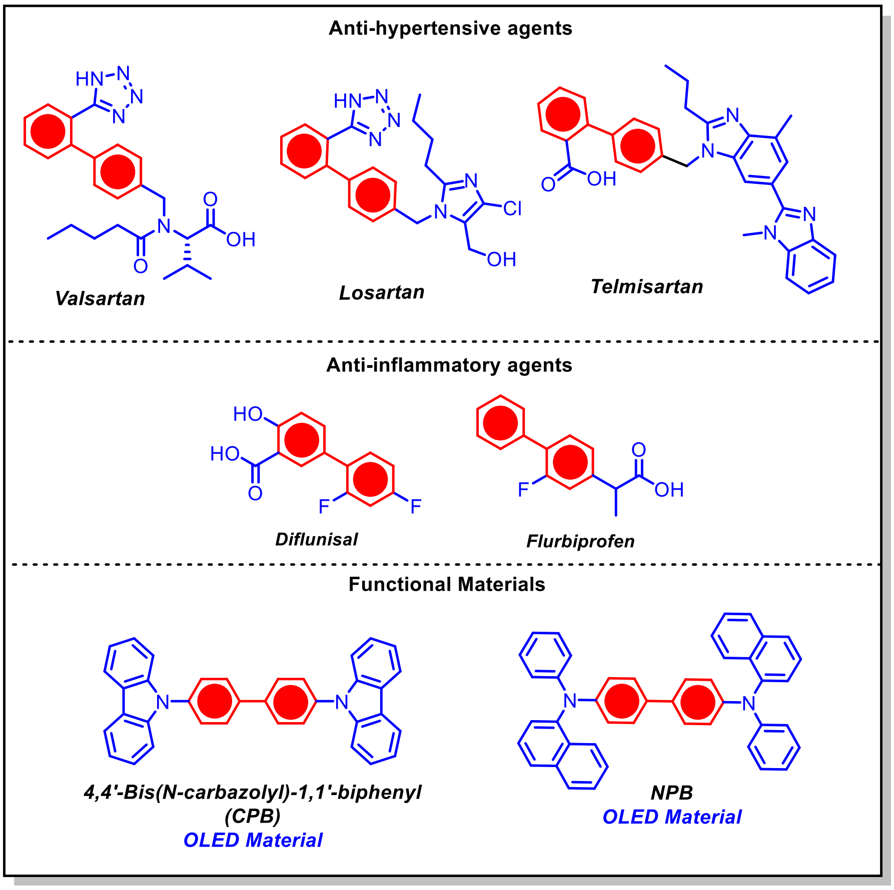
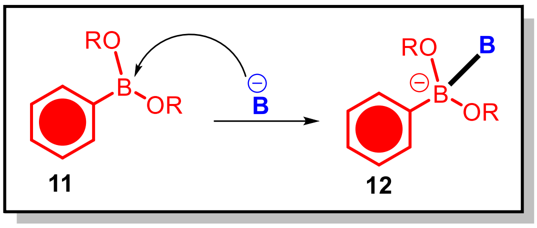


Figure 1.2. Essential materials synthesised using Suzuki-Miyaura cross-coupling as key step

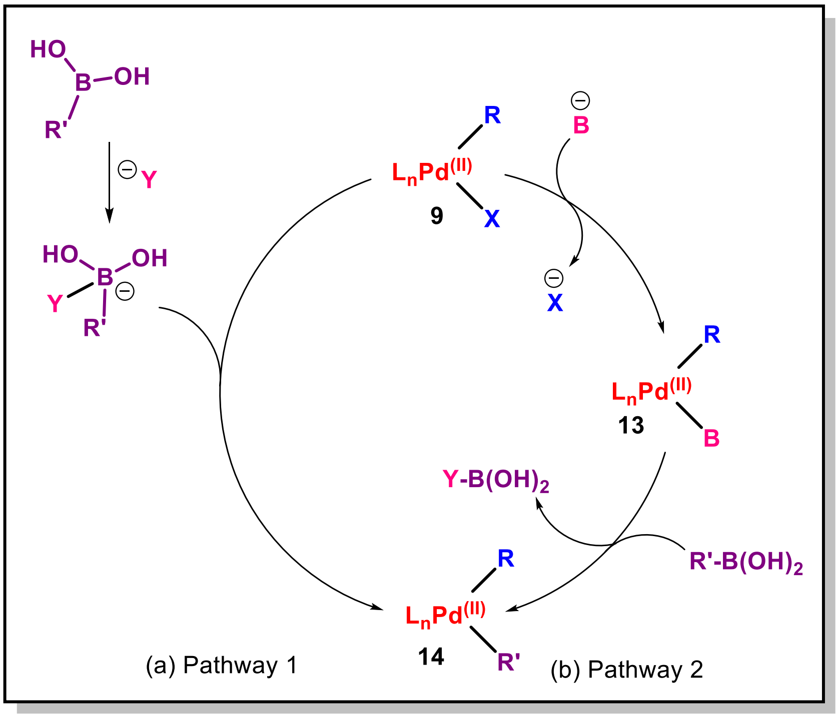
In the Suzuki reaction, the base plays a crucial role in facilitating the process. It activates the boronic acid (or boronate ester) by converting it into a more nucleophilic boronate anion, which is essential for the transmetallation step (**Scheme 1.6**). Additionally, the base helps stabilise the palladium-halide species formed during the oxidative addition step by neutralising the displaced halide or pseudohalide

It also neutralises acidic byproducts, such as boric acid, that can form during the reaction, maintaining optimal reaction conditions. By increasing the reactivity of the boron species, the base accelerates the transmetallation step, making the overall reaction more efficient. Common bases used include inorganic bases like NaOH, KOH, K_2CO_3, and Cs_2CO_3, as well as organic bases such as triethylamine (Et_3N).



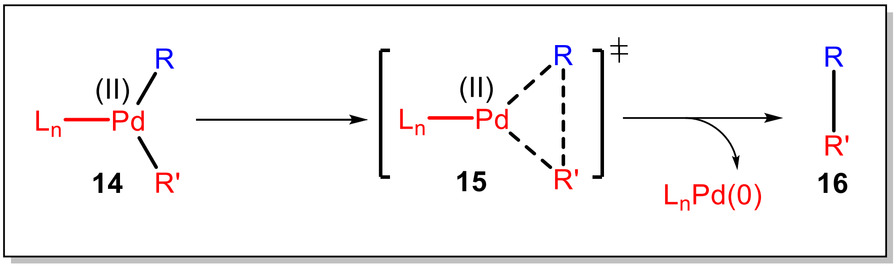
Scheme 1.6. Boronic acid/boronate activation by the base

The reaction starts with the oxidative addition of the organo halide to the palladium center, to form the Pd(II) intermediate (**13**). This is followed by the transmetallation step. Transmetallation is the phase in which the organic group is relocated from one metal to another, resembling an exchange of ligands between two metals. Although the primary step (oxidative addition) of the Suzuki-Miyaura reaction is well understood, the mechanism of transmetallation remains unclear [27]. It is widely recognised that organoboron moiety actively partakes at this stage and a base is essential. The involvement of a base has led to the proposal of dual possible trails [24, 28]. In one pathway (**Scheme 1.7**(**a**)), the base reacts with the organoboron to form an anionic "ate complex" which attacks the palladium halide complex. In the other pathway (**Scheme 1.7** (**b**)), the process happens in binary steps: first, a ligand substitution takes place where the base replaces the halogen to form a palladium base complex, which subsequently reacts with the neutral organoborane. Computational studies by Maseras and co-workers [29] have suggested the first way, to be the most authentic. Nevertheless, this has been a subject of debate. Kinetic studies conducted by the Hartwig group [30] indicate that in the presence of a weak base, transmetallation proceeds *via* second pathway, involving complex involving palladium coordinated to the base residue and a neutral organoboron species. Additional investigational studies by Amatore and co-workers [31] further support pathway 2, showing that in the presence of surplus halide, the boronate pathway is subdued, suggesting that the second mechanism is more likely. The transmetallation step in Suzuki coupling is followed by the reductive elimination step which outcomes the formation of C-C bond (product) along with the regeneration of the Pd(0) center. Reductive elimination can take place over several mechanisms; but, in monodentate Pd(II) complexes, it predominantly follows a concerted mechanism. This trail encompasses the formation of a sole C–C bond *via* a three-membered transition state like the three-membered transition state in oxidative addition.



Scheme 1.7. Transmetallation pathways post oxidative addition to Pd(0)

The transmetallation step in Suzuki coupling is followed by the reductive elimination step which results in the formation of C-C bond (product) along with the regeneration of the Pd(0) center. Reductive elimination can take place through various mechanisms; however, in monodentate Pd(II) complexes, it predominantly follows a concerted mechanism (**Scheme 1.8**). This pathway involves the formation of a single C–C bond *via* a three-membered transition state like the three-membered transition state in oxidative addition.



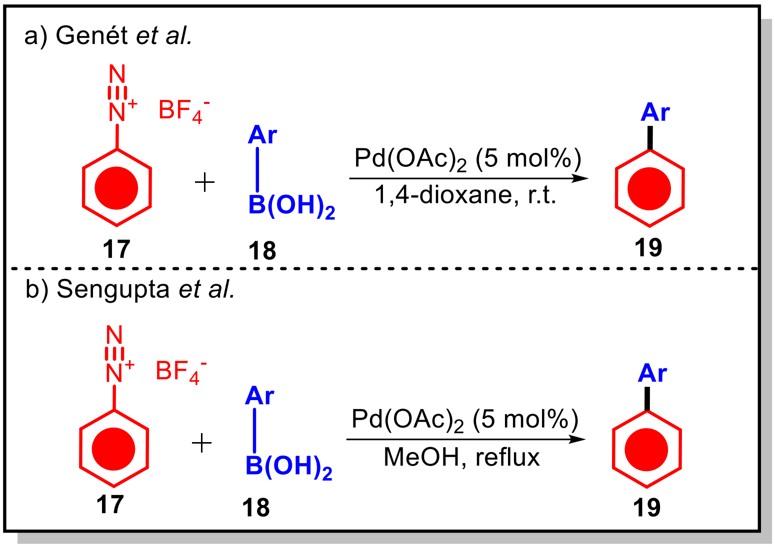
Scheme 1.8. Three-membered transition state pathway for reductive elimination

The palladium (0) center is also seen to catalyse the Suzuki reaction with coupling partners other than aryl halides. These range from acyl halides, esters, amides to diazoniums and nitroarenes. The mechanisms for each coupling partner distinct from the other.

1.3.2.1. Suzuki-Miyaura cross-coupling of aryldiazonium salts

Aryldiazoniums have been utilised as substrates for palladium catalysed reactions since their first utilisation with palladium by Matsuda and co-workers in the preparation of the herbicide Prosulfuron in a protocol involving Matsuda-Heck reaction as a key step. Arylboronic acids are seen to undergo cross-couplings with aryldiazoniums to form chemically essential biphenyls. The application of arenediazonium salts in Suzuki-Miyaura cross-couplings was achieved 20 years after their initial use in palladium-catalysed reactions. This discovery was made independently by Genêt *et al.* [32] and Sengupta *et al.* [33] (**Scheme 1.9 (a)** and **(b)**), and modest to respectable yields of biaryl products were attained. Arenediazonium tetrafluoroborates and arylboronic acids were coupled using Pd(OAc)$_2$, without the addition of bases or ligands. The importance of solvent and temperature was highlighted, with the best results being achieved in 1,4-dioxane at room temperature or refluxing ethanol/methanol. Minimal effects on reaction rates were observed for different substituents on the diazonium salts, demonstrating that oxidative addition was unlikely the rate determining step (r.d.s). However, yields were significantly hindered by *ortho* substitution on boronic acids.

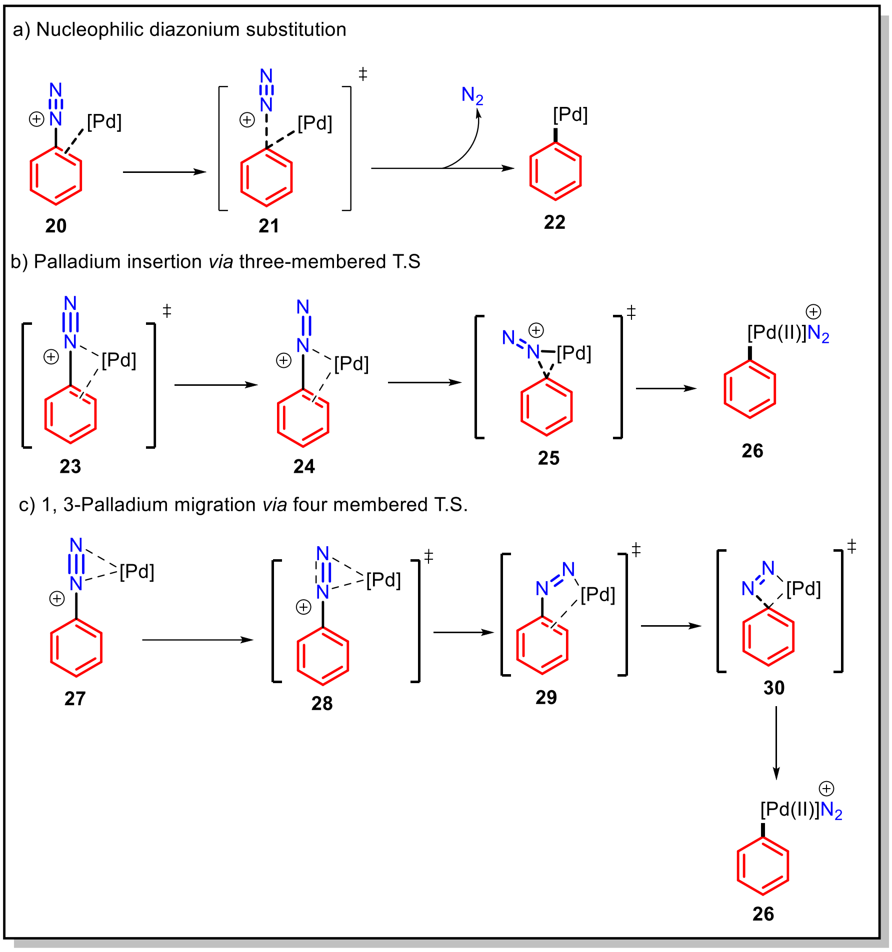
Aryl diazonium coupling with boronic acids, can have three mechanisms for oxidative addition of the diazo moiety to the Pd(0) center as studied by Braga and co-workers [34].



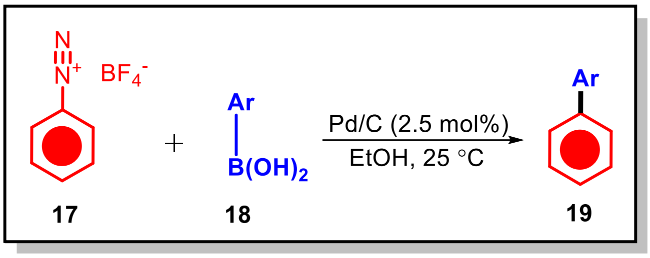
Scheme 1.9. Palladium (II) acetate catalysed cross-coupling of aryl diazonium salts with arylboronic acids

The first plausible mechanism is the nucleophilic substitution of the diazonium by the Pd(0) complex (**Scheme 1.10 (a)**), second one involving palladium insertion into the C-N bond of aryl diazonium *via* three membered T.S (**Scheme 1.10 (b)**) and the third one being a multistep 1, 3-palladium migration process involving a four membered T.S (**Scheme 1.10 (c)**). Computational studies reveal the irreversible nature of oxidative addition, with the formation of Pd(II) aryl bond serving as the trigger for the reaction. The lower energy pathway followed by the third mechanism involving 1,3-migration is the energetically most favourable pathway [34].

Colleville team reported the first ever Suzuki-Miyaura cross-coupling of aryldiazonium salts with aryl boronic acids under heterogeneous conditions. A mere 0.25 mol% of palladium on carbon (Pd/C) was able to catalyse the arylation of aryldiazonium salts with aryl boronic acids at 25 °C in ethanol (**Scheme 1.11**) [35].



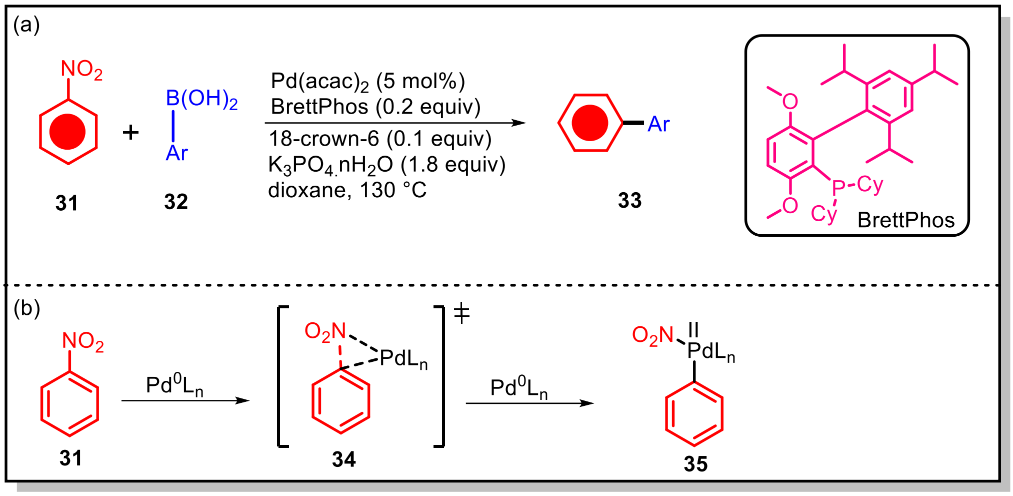
Scheme 1.10. Oxidative addition of diazonium to palladium center



Scheme 1.11. Cross-coupling of aryldiazonium salts with arylboronic acids in the presence of Pd/C as catalyst

1.3.2.2. Nitroarenes as coupling partners under palladium catalysis

Nitroarenes are another class of molecules that rely on the initial oxidative addition with palladium (0) centers to undergo cross-coupling reactions with partners such as arylboronic acids and phenols [36]. Nakao and co-workers described the cross-coupling of arylboronic acids with nitroarenes for the first time with the catalytic Pd(acac)$_2$. However, owing to the higher bond energy of the C-N bond of nitroarene, the reaction, the reaction requires the utilisation of strong sigma donor ligands such as BrettPhos. Computational studies by the same research group showed nitroarene oxidative addition to the Pd(0) center to take place like that of aryl halide in a path involving a three membered cyclic transition state. The remaining of the mechanism being the same as that of aryl halide, post oxidative addition (**Scheme 1.12**).

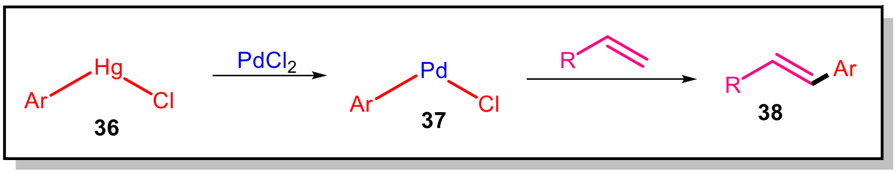


Scheme 1.12. (a)First ever palladium catalysed cross-coupling of nitroarenes with arylboronic acids; (b) Oxidative addition *via* three membered transition state

Nitroarenes have also been successfully coupled with aryl halides under palladium catalysis.

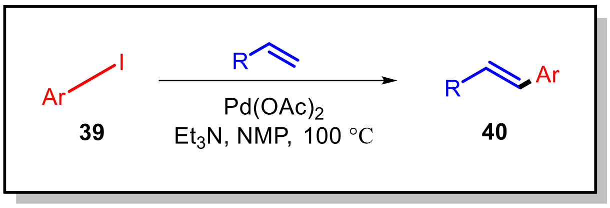
1.3.3. The Heck reaction

The Heck reaction involves the vinylation or arylation of olefins, accommodating a varied array of substrates such as styrene derivatives, acrylates, and intramolecular double bonds. In the late 1960s, Heck demonstrated that arylated alkenes could be synthesised by reacting alkenes with a stoichiometric amount of [Ar–Pd–Cl] or [Ar–Pd–OAc], generated *in-situ* by combining ArHgCl with $PdCl_2$ or ArHgOAc with $Pd(OAc)_2$, respectively (**Scheme 1.13**). These pioneering studies by Heck paved the way for a new reaction, later named the Mizoroki–Heck reaction (**Scheme 1.14**).



Scheme 1.13. Heck's pioneering synthesis of internal alkene

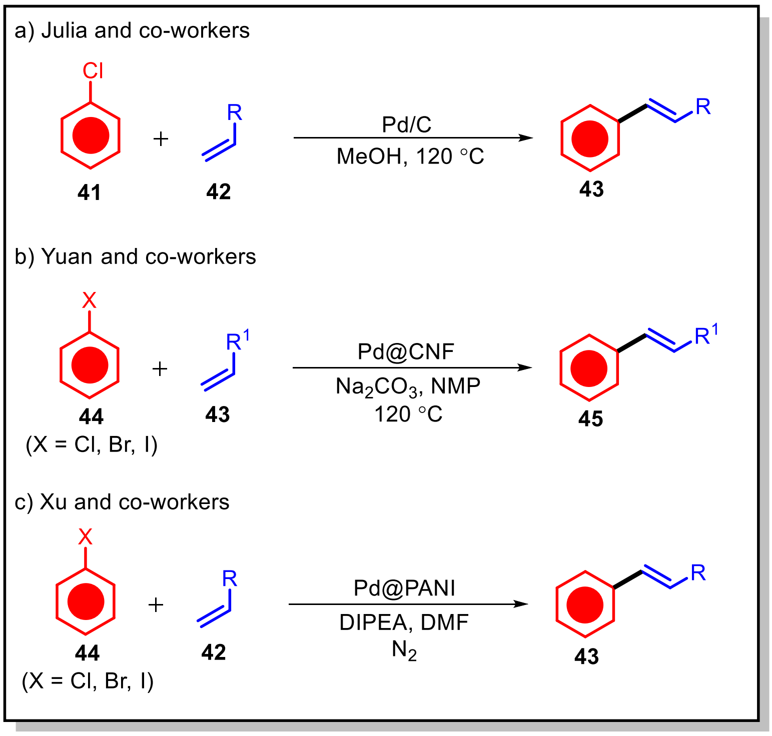
In 1972, Heck and Nolley [37] observed the formation of arylated alkene with aryl iodide in the presence of palladium (II) acetate catalyst, tributylamine base in *N*-methylpyrrolidone (NMP) at 100 °C. The same reaction was seen to proceed even in the absence of solvents. In 1973, Mizoroki and coworkers [38] expanded their earlier work to include aryl bromides, which were found to be significantly less reactive than aryl iodides, following the reactivity trend PhI > PhBr > PhCl. Palladium black was identified as more efficient than $PdCl_2$, and the use of a phosphine ligand (PPh_3) was noted to provide slight benefits (**Scheme 1.14**).



Scheme 1.14. Mizoroki–Heck reaction with aryl iodides

Since then, the reaction has been studied by several research groups across the globe. As such the reaction has been successfully conducted under several reaction conditions that includes the utilisation of a variety of palladium complexes, ligand systems, green solvents as well as palladium-based nanomaterials [39]. Green solvents, environmentally friendly solvents that are non-toxic, sustainable, and minimise ecological and health impacts, for instance have been utilised successfully for Heck reactions along with palladium catalysts. Additionally, palladium nanomaterials in sync with green solvents have also been used for Heck reaction. Palladium nanoparticles (PdNPs) are integral to the Heck reaction and can be employed either as pre-synthesised catalysts or generated *in-situ* during the reaction, each offering unique advantages. Pre-synthesised PdNPs are carefully engineered for specific size, shape, and catalytic properties, ensuring consistent and efficient performance. Their nanoscale dimensions and large surface area facilitate enhanced interaction with reactants, reducing activation energy and accelerating reaction rates. Functionalisation with ligands, polymers, or supports further improves their stability, selectivity, and control over reaction conditions, making them highly effective in complex transformations. Additionally, their recyclability aligns with green chemistry principles, reducing waste and operational costs.

The first ever heterogeneous Heck reaction between aryl halides (chlorides) and olefins was reported by Julia *et al.*, which apparently required a temperature of 120 °C [40]. Wang *et al.* reported the first synthesis and characterisation of carbon nanofibre-reinforced Pd catalysts. The palladium was presented as sphere-like particles smaller than 7 nm in width, with their size controllable by varying the reduction and calcination temperatures. These well-dispersed Pd/CNF catalysts demonstrated excellent activity for Heck reactions between olefins and aryl halides. Additionally, they offered real advantages, including high thermal steadiness, oxygen insensitivity, easy separation from reaction products, and reusability [41]. Xu and co-workers reported a practical and ligand-free Heck reaction with a relatively broad application scope, catalysed by the recyclable heterogeneous Pd@PANI catalyst. During the catalyst fabrication, air was used as the oxidant, enabling the controlled nucleation and slow growth of Pd nanoparticles with high stability during the *in-situ* polymerisation of PANI, without requiring additional chemical reagents. This process produced ultrasmall, uniform Pd@PANI particles with remarkable catalytic activity. The study demonstrates that Pd@PANI is a practical, stable, and accessible catalyst, presenting a viable alternative to conventional palladium complexes [42].



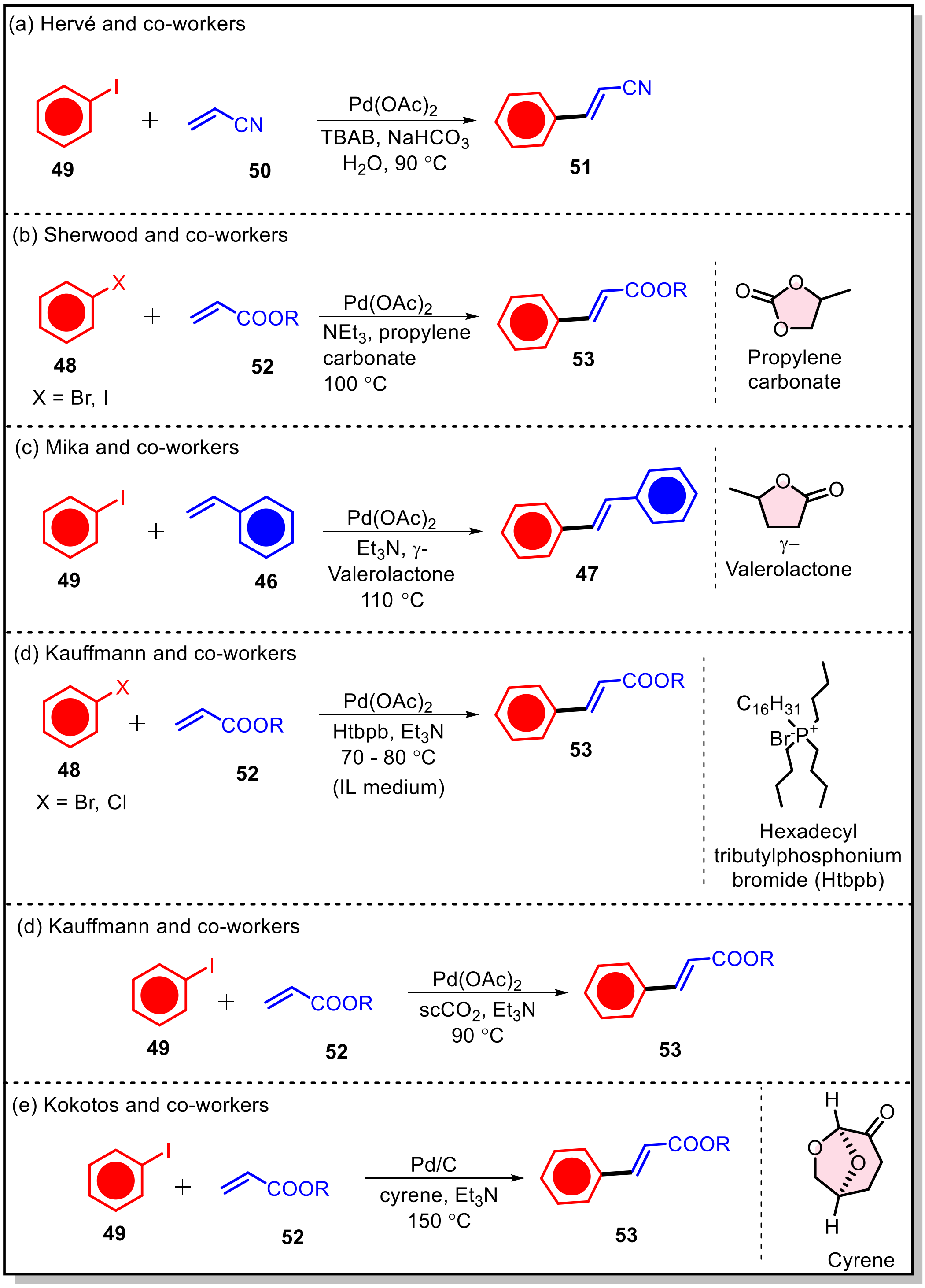
Scheme 1.15. Pd nanomaterials in Heck reaction

The heck reaction has also been successfully carried out by researchers across the globe in the presence of green solvents as reaction medium. These include the universal solvent, water [43], cyclic carbonates [44], valerolactone [45], ionic liquids [46], supercritical carbon dioxide [47], cyrene [48] etc. Another solvent, PEG (Polyethylene Glycol), is highly valuable in cross-coupling reactions, including Heck reactions, due to its unique properties. It serves as a green, environmentally friendly alternative to traditional organic solvents, aligning with sustainable chemistry principles. PEG enhances the solubility of both polar and non-polar reactants, facilitating better interaction and improving reaction efficiency. Moreover, it stabilises transition metal catalysts, such as palladium complexes, preventing their degradation and ensuring higher yields [49] (**Scheme 1.16**).

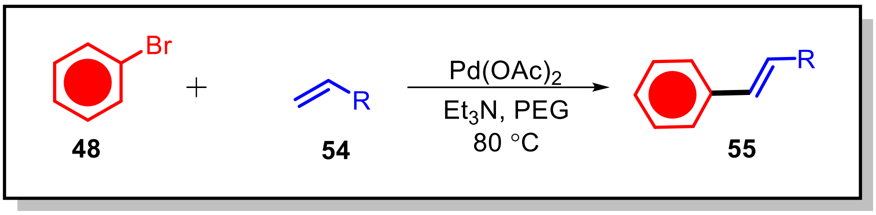
An alternative method for forming C-C bonds in Heck reactions involves the use of nanoparticles generated directly within the reaction mixture (*in-situ* generation), a process referred to as Nanoparticle-Catalysed Organic Synthesis Enhancement (NOSE) [50, 51]. This method utilises solvents such as water, ethanol, ionic liquids etc which aid in stabilising and dispersing palladium nanoparticles. These nanoparticles, produced from palladium compounds under specific conditions such as heating or reduction, function as highly efficient catalysts, enhancing both the speed and precision of the reaction. Since the nanoparticles are formed *in-situ*, there is no need for prior preparation or stabilisation, simplifying the setup. Newly formed nanoparticles are particularly effective due to their ability to adapt to the reaction conditions. By employing environmentally friendly solvents and stabilisers, the NOSE method minimises the required catalyst amount, facilitates the recovery and reuse of materials, and aligns with green chemistry principles.

Another greener solvent is a greener solvent frequently used in Heck reactions is poly(ethylene glycol) (PEG) which is extensively studied as a replacement in various cross-coupling processes. PEG is a benign, cost-effective, thermally stable, and reusable polymer, available in a wide range of molecular weights, usually between 200 and 4000. It can function as a medium or a phase transfer catalyst, making it an eco-friendly and safer option compared to traditional volatile and hazardous organic solvents. The use of PEG as a solvent for the Heck reaction was first reported by Chandrasekhar and colleagues (**Scheme 1.17**) [52]. PEG with a molecular weight of

2000 or less was found to be an efficient medium for the regioselective reaction of aryl bromides with olefins. It also offered easy recyclability of both the solvent and Pd catalyst. Since then, several protocols have emerged utilising PEG solvent for Heck reaction [53].



Scheme 1.16. Heck reactions in green solvents.



Scheme 1.17. Heck reaction in PEG-400

1.3.3.1. The intramolecular Heck reaction

The intramolecular Heck reaction is a palladium-catalysed process where an aryl or vinyl halide reacts with an alkene within the same molecule to form cyclic structures. It is widely utilised in synthesising natural products, pharmaceuticals, and complex organic compounds (**Figure 1.3**), enabling the efficient formation of five- to seven-membered rings and fused systems with excellent regio- and stereoselectivity.

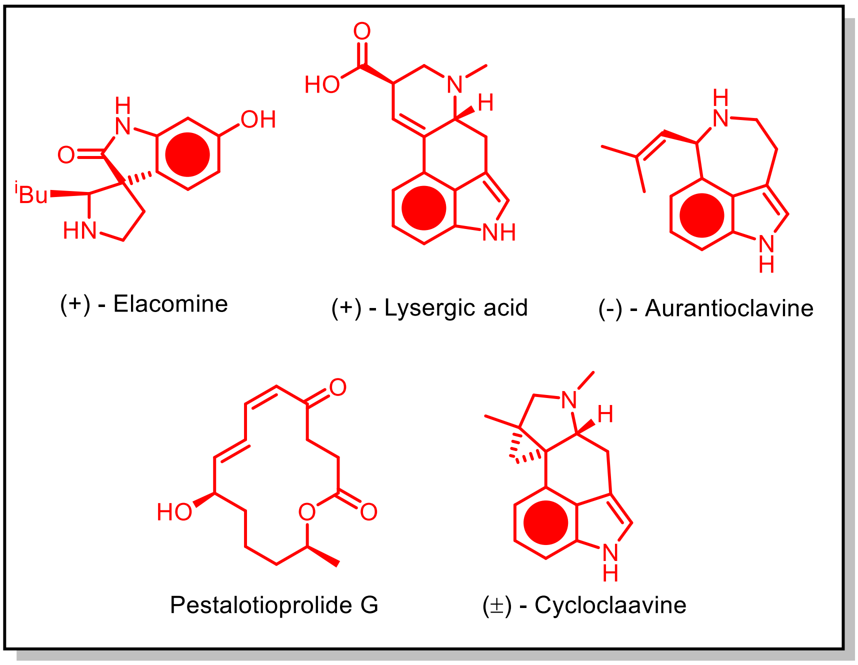
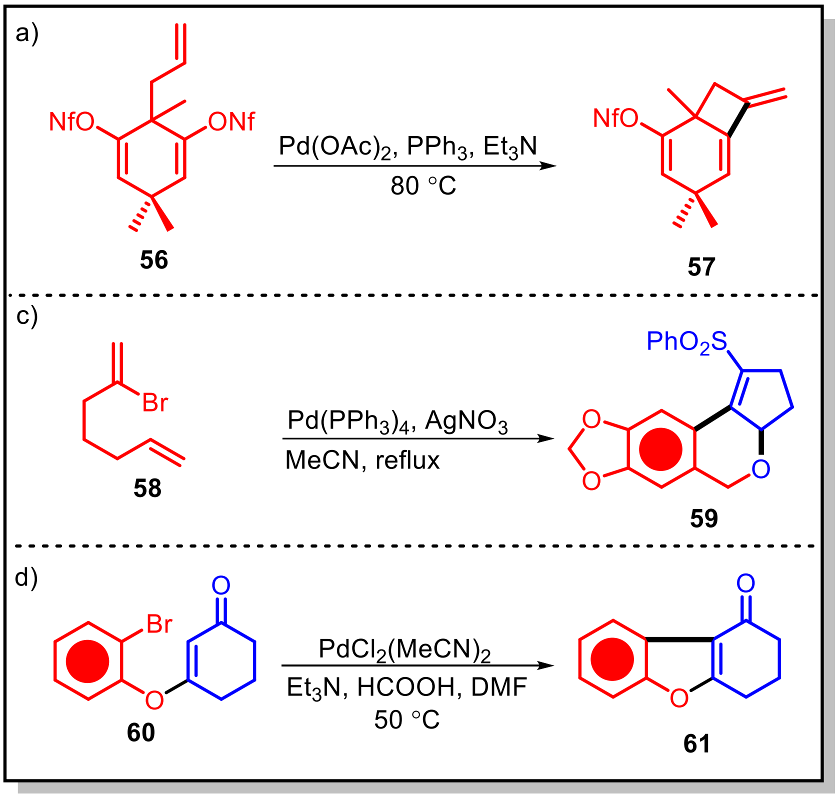


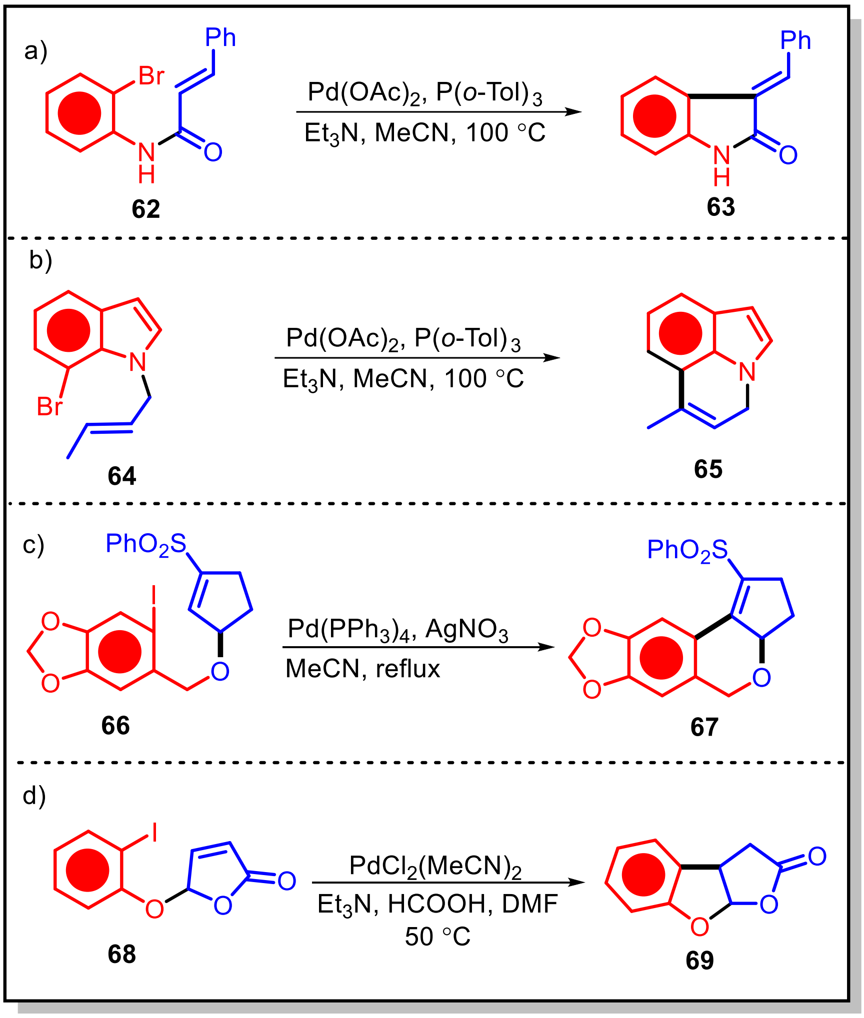
Figure 1.3. Natural products synthesised with intramolecular Heck reaction as a key step

The synthesis of carbocycles and heterocycles *via* intramolecular Heck cyclisation can result in the formation of both endocyclic and exocyclic double bonds to construct rings with sizes as high as twenty-seven atoms. The cyclisation can involve vinyl, allyl groups or longer tethers. Pd-catalysed intramolecular cyclisation of 2- haloalkadienes and associated compounds enables the synthesis of ring sizes ranging from three to nine members. This is accomplished *via exo–trig* cyclisations to get three- to nine-membered rings or *endo–trig* cyclisations get upto nine-membered rings (**Scheme 1.18**) [54].



Scheme 1.18. Intramolecular Heck cyclisation for the synthesis of four, five and six membered carbocycles

In a similar fashion, the reaction has been utilised for heterocycle formation. This includes the nitrogen, oxygen heterocycles and more. To create a heterocycle through an intramolecular Heck-type reaction, the starting material must satisfy certain key requirements. It must possess a halide or triflate group to enable oxidative addition to the palladium catalyst, along with a side chain such as an alkyne or alkene located at appropriate distances, and a heteroatom within. Structures with an allylic side chain can be readily synthesised by modifying 2-bromo- or 2-iodo anilines, phenols, or thiophenols. These structures serve as precursors for a variety of heterocycles which are closely associated with many natural products and biologically active compounds (**Scheme 1.19**) [55].

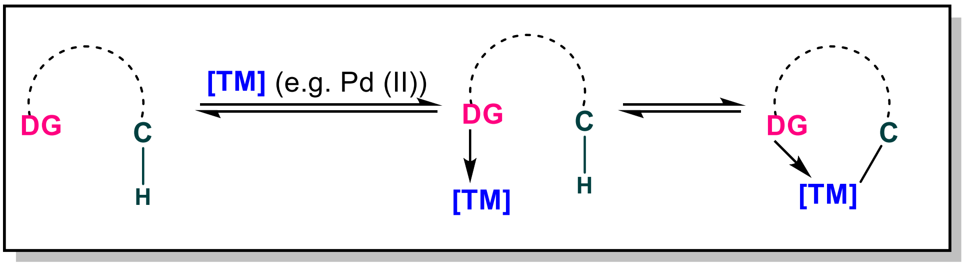


Scheme 1.19. Intramolecular Heck cyclisation for the synthesis of five and six membered nitrogen and oxygen heterocycles

1.4. Palladium in C-H functionalisation

A key feature of palladium-catalysed carbon-carbon bond formation is the generation of aryl or alkyl palladium (II) species, which undergo further transformations to form new bonds. Simplifying and optimising the methods for producing these intermediates in a cost-effective manner would significantly enhance the efficiency of such reactions. Unactivated carbon-hydrogen (C–H) bonds offer nearly endless possibilities as reaction partners, as they can be cleaved by palladium (II) catalysts. From a synthetic standpoint, these reactions not only expand reactivity options but also provide new synthetic strategies [56].

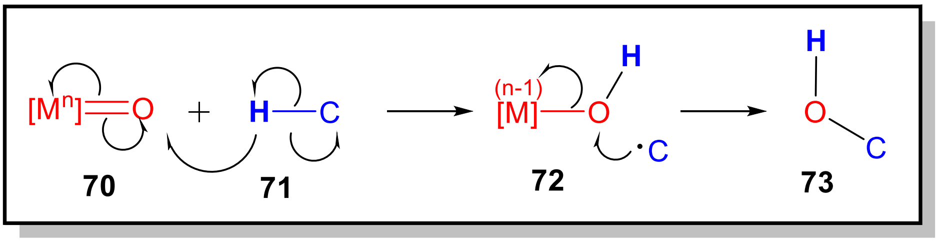
Functional group-assisted C-H bond cleavage holds significant potential in this context. The site selectivity is influenced by the closeness of the C-H bond to the palladium center, and the necessary interactions between the substrate and the catalyst are notably enhanced through the heteroatom coordination of with the metal center. As a result, palladium-directing group coordination is often regarded as a crucial aspect in catalytic C-H bond functionalisation methods (**Scheme 1.20**) [57].



Scheme 1.20. Site selectivity control in C-H activation

The processes of C-H activation and functionalisation can be categorised into two primary pathways. The first mechanism is known as the outer-sphere mechanism. It involves inserting a C-H bond into the ligand of a transition metal (TM) complex. The second mechanism involves the coordination of the C-H bond to the metal center. This results in the formation of an organometallic complex, where the organo species stays in the inner sphere during C-H bond breaking. Although "C-H activation" and "C-H functionalisation" terms are frequently used synonymously, there is increasing agreement to reserve "C-H activation" term specifically for inner-sphere pathway

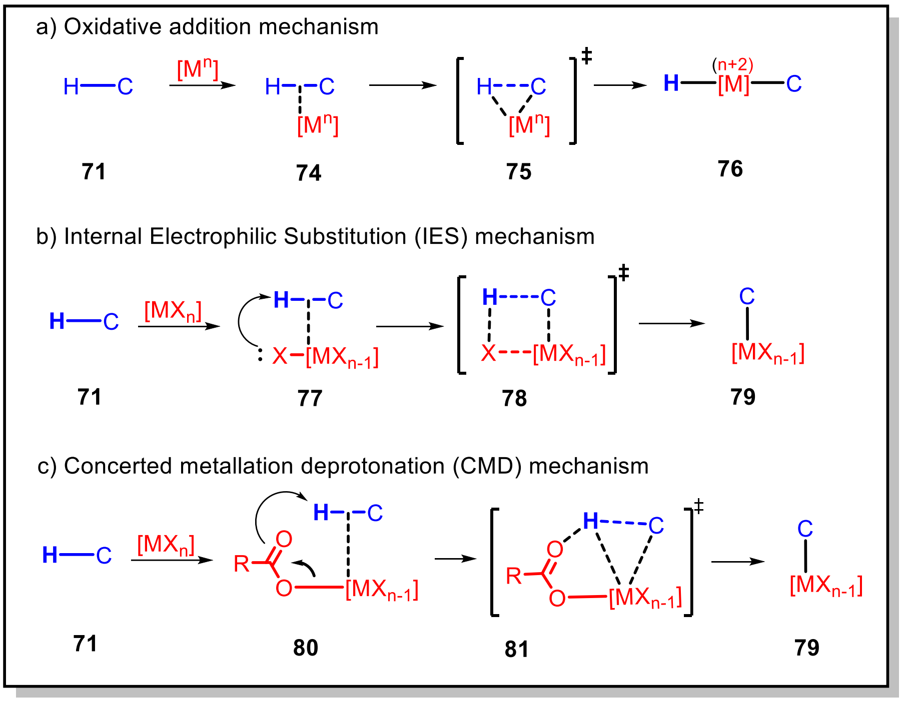
Outer sphere pathways do not involve the direct interaction of the metal center to the C-H bond to be activated. For example, in oxidation of alkane, enzyme-based metal-oxo species, or counterparts, facilitate activation of C-H group over a metalloradical pathway known as the rebound mechanism. This mechanism involves the oxo species abstracting a hydrogen radical from the alkane, followed by the rapid reattachment to the hydroxo metal intermediate (**Scheme 1.21**).



Scheme 1.21. Outer sphere C-H activation

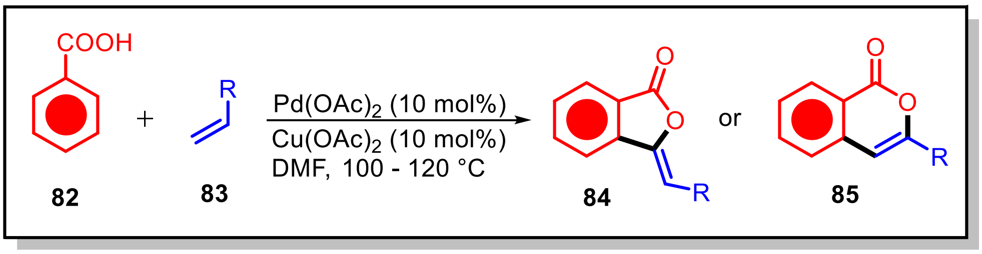
In contrast, inner-sphere mechanisms are classified into three types. The first is oxidative addition (OA), which occurs in low-valent, transition metal complexes that are electron-rich. The second is σ-bond metathesis (σ-BM), commonly found in electrophilic transition metal complexes. The third is electrophilic activation (EA), which takes place in late transition metals with electron-diminishing ligands.

Late transition metals with electron deficiency, such as Pd(II) can undergo reactions *via* electrophilic activation (EA) mechanisms. In these cases, the initial coordination of the C-H bond to the metal involves strong σ-donation. The π-back-donation is weak. This is typically followed by heterolytic cleavage (deprotonation). The process is facilitated by an external anion. A typical variation of this mechanism comprises intramolecular deprotonation facilitated by a ligand based on a heteroatom, such as an alkoxide or halide. This process can also occur through a cyclic and concerted pathway with the aid of a bridging ligand like acyloxy or carbonate anions. These processes are called by several terms, including concerted metalation-deprotonation (CMD), ambiphilic metal-ligand activation (AMLA), 1,2-addition and internal electrophilic substitution (IES). The basicity of the ligand is increased by hydrogen bonding between the lone-pair-bearing ligand, often oxygen-based, and the H-C proton. As a result, C-H bond breaking is facilitated. This, in turn, increases the electron density of the C-H bond and strengthens the agostic interaction (**Scheme 1.22**) [58].



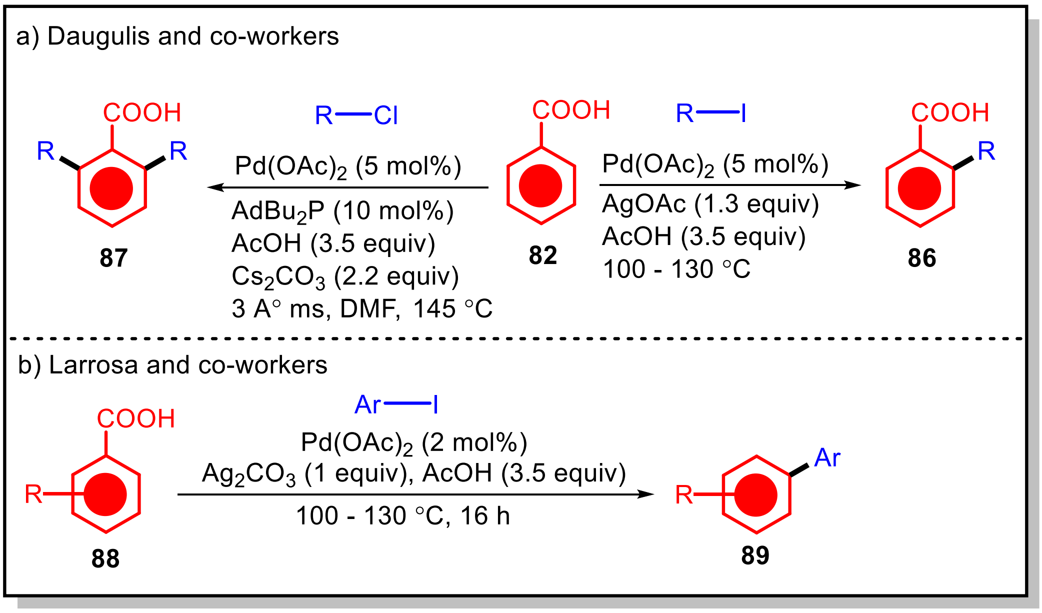
Scheme 1.22. Directing group assisted C-H activation mechanisms

Researchers worldwide have explored various directing groups in regioselective transformations under palladium catalysis, with the carboxylic acid group being one of them. Carboxylic acids are abundant and exhibit extensive physical variety, originating from both artificial and natural sources. Their weak aptitude of coordination with Pd(II) catalysts makes them versatile directing groups for C-H bond functionalisation reactions. Additionally, carboxylic acids are capable of being easily detached or transformed into other functional groups through well-established reactions. In 1998, the Miura group pioneered research on palladium-catalysed C-H olefination directed by carboxylate groups. They demonstrated that naphthoic acids and benzoic acids have the potential to react with alkenes to yield phthalide or isocoumarin derivatives in modest to good yields (**Scheme 1.23**) [59]. Since then, carboxylic acids have been used for several *ortho*- functionalisations under Pd(II) catalysis, that include alkylations, arylations, cyclisations etc.



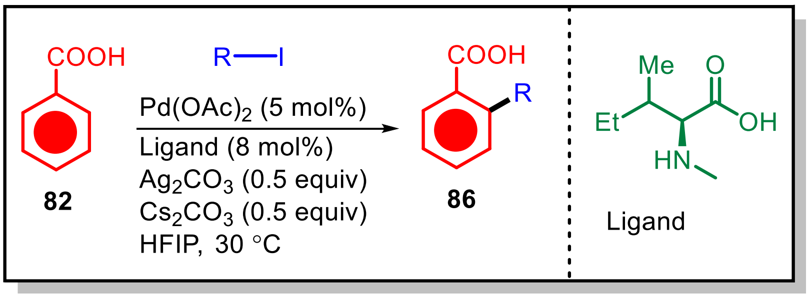
Scheme 1.23. Carboxylic acid directed cyclisation involving terminal alkene under Pd(II) catalysis

Of the essential transformations of benzoic acids involving C-H activation, *ortho*-arylation is a major process. The arylating agents used can be aryl halides, pseudohalides etc. Daugulis and his team presented the initial instance of benzoic acid *ortho*-arylation, achieving the generation of biarylcarboxylates through a Pd(II) acetate-catalysed reaction between haloarenes and benzoic acids. They proposed two strategies: one involving iodoarenes with silver (I) acetate and another using chloroarenes in the presence of a bulky phosphine ligand. The aryl iodide pathway is suggested to follow a catalytic cycle involving Pd(II)–Pd(IV), with silver (I) acetate helping in revival of the catalyst. The aryl chloride pathway, on the other hand, is likely to function *via* a catalytic cycle involving Pd(0)–Pd(II). A ligand is necessitated to support in the oxidative addition of ArCl to Pd(0). [60]. In 2011, the preparation of *meta*-substituted biaryls using *ortho*-substituted aryl acids *via ortho*-C-H arylation coupled with carboxyl removal was established by Larrosa and his team. This represented unprecedented example of a phenylation process where the -COOH group was removed *in-situ* [61]. A key challenge in this reaction was arylation of the solvent, which required the use of an excess amount of the arylating agent. Both these protocols require high temperature (**Scheme 1.24 (a)** and **(b)**).



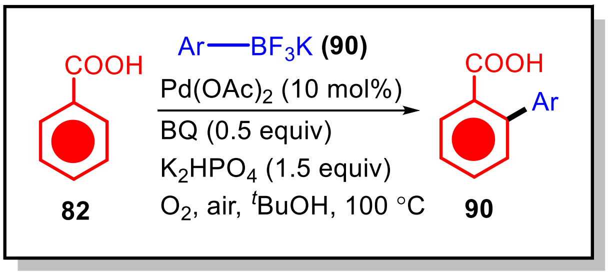
Scheme 1.24. *Ortho*- arylations of benzoic acids under Pd(II) catalysis

Su and colleagues reported a room-temperature *ortho*-arylation of benzoic acids with iodoarenes, catalysed by $Pd(OAc)_2$ using HFIP as the solvent. They attributed the triumph of this process to the use of singly protected amino acid ligands. (**Scheme 1.25**) [62].



Scheme 1.25. HFIP mediated *ortho*-arylation of benzoic acid at room temperature

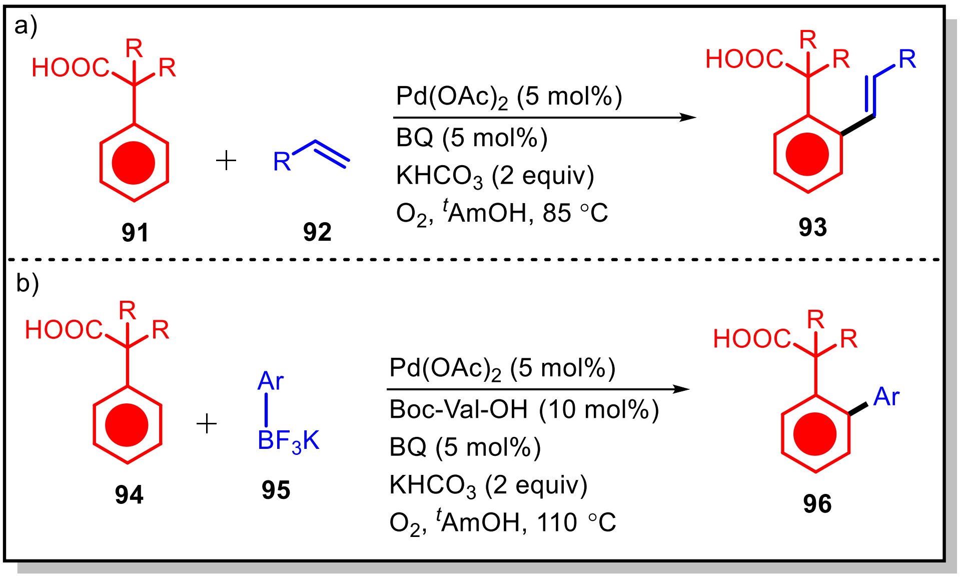
Boronates have also been utilised as arylation partners aromatic acid *ortho*-arylation. Yu and his team showed that benzoic acids can undergo $Pd(OAc)_2$-mediated coupling with aromatic boronates *via* a Pd(0)–Pd(II) cycle of catalysis. The initial protocols required oxidants namely silver(I) carbonate and benzoquinone, which resulted in small yields of the product aryl acids. However, in 2008, the same group developed an improved, silver-free method through aromatic trifluoroborates along with a O_2/benzoquinone system as the oxidising agent (**Scheme 1.26**) [63, 64].



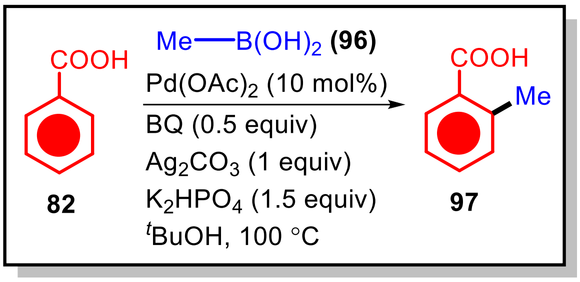
Scheme 1.26. Aryl trifluoroborate salts as arylating agents

In addition to benzoic acid and heteroarene carboxylic acids, phenylacetic acids and 3-phenylpropionic acids, which are more valuable in synthetic applications, can also act as effective reactants in palladium-catalysed C-H functionalisation processes. In 2010, the Yu group presented a simple, atom-efficient palladium mediated C-H alkenation of benzylic acids, applying molecular oxygen as the final oxidant. A range of benzylic acids were used in this catalytic scheme where decent yields of the desired products were isolated. α-Chiral substrates required the presence of lithium (I) carbonate as the base that helped avoid racemisation and resulted product with a higher enantiomeric excess. The *ortho*-arylation of such systems however, takes place with aromatic trifluoroborate salts with an amino acid ligand (**Scheme 1.27 (a)** and **(b)**) [65, 66].

The coordinating nature of the carboxylic acid group was effectively utilised in *ortho*-alkylation reactions. Yu's group demonstrated Pd-catalysed methylation of benzoic acids at *ortho*-position with the use of methylboronate, necessitating presence of benzoquinone and Ag_2CO_3 (**Scheme 1.28**). However, attempts to extend this methodology to other alkylboron reagents were hindered by the potential for *β*-hydride elimination. In 2013, Yu and colleagues successfully circumvented this limitation by employing a ligand-enhanced approach. This strategy, utilising mono-N-protected amino acids as ligands, facilitated efficient Pd-catalysed C-H alkylation of phenylacetic and benzoic acids. The added catalytic function of the *α*-amino acid ligands was ascribed to the observed enhancement in C-H bond cleavage activity. [66].

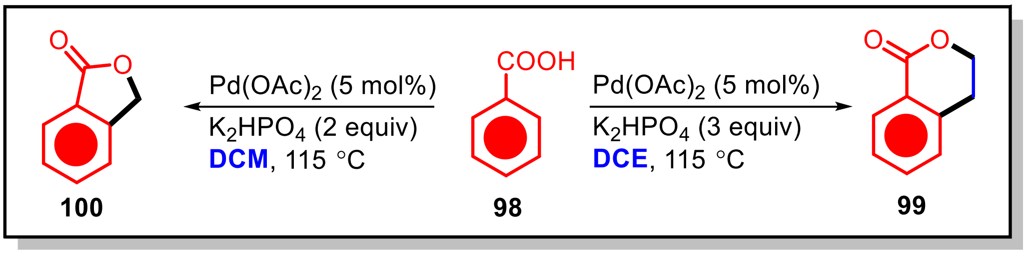


Scheme 1.27. (a) and (b) alkenylation and arylation of benzylic acids under Pd(II) catalysis



Scheme 1.28. C2 methylation of benzoic acid under carboxylic acid assistance

The cyclisation of aryl carboxylic acids was extended to encompass reactions with dichloromethane (DCM) and dibromomethane (DBM), resulting in the production of five- and six-membered benzolactones as depicted in **Scheme 1.29**.



Scheme 1.29. Dual alkylation *via* C-H activation for the synthesis of five and six membered lactones

All these examples reflect the directing ability of carboxylic acid group with Pd(II) center, the activation step being a concerted metalation deprotonation (CMD) pathway.

1.5. Copper in cross-coupling reactions

Copper (Cu), a widely used and versatile metal, occupies group 11 and period 4 of the periodic table. Its symbol, "Cu," derives from the Latin term "Cuprum," signifying its historical significance. In its natural state, copper is frequently encountered in combination with iron and sulfur, forming the mineral chalcopyrite. Characterised by its distinctive reddish hue, pure copper exhibits remarkable physical properties, including high malleability, ductility, and exceptional thermal and electrical conductivity [68].

This versatility extends to its chemical behaviour, primarily attributed to its ability to exist in multiple oxidation states, including Cu^+ (copper (I)), Cu^{2+} (copper (II)), and the less common Cu^{3+} (copper (III)) [69]. This diverse range of oxidation states significantly influences its unique chemical reactivity. Moreover, copper's high boiling point renders it exceptionally suitable for high-temperature and high-pressure applications, enabling its utilisation in specialised chemical reactions.

The catalytic potential of copper was first recognised by pioneering researchers like Ullmann and Goldberg, who demonstrated its effectiveness in biaryl synthesis and *N*- and *O*-arylations, respectively [70, 71]. Initially, copper was employed in stoichiometric amounts in organic synthesis, a practice that was deemed acceptable due to its affordability. However, with the growing emphasis on sustainability and economic efficiency in modern research, the focus shifted towards developing more efficient catalytic systems. Subsequently, groundbreaking research by scientists like Buchwald and Hartwig [72, 73] demonstrated the remarkable catalytic capabilities of copper, even when used in minute quantities. This led to the development of both homogeneous and heterogeneous Cu-catalysed systems for sustainable organic synthesis. Copper's inherent advantages, including its low cost, low toxicity, abundant natural reserves, and remarkable tolerance towards diverse functional groups, established it as a compelling alternative to more expensive transition metals such as palladium. While copper exhibits significant catalytic potential, a deeper understanding of its organometallic chemistry is crucial for further advancements. Compared to the well-established field of palladium chemistry, the reactivity of organo-cuprates in the Cu(I) and Cu(III) oxidation states remains relatively unexplored. However, a notable observation is the successful implementation of numerous "ligand-free" [74] Cu-catalysed syntheses, highlighting the potential for efficient copper catalysis even without the need for additional supporting ligands. Furthermore, the concept of "synergistic Pd/Cu catalysis" is gaining significant attraction. In reactions such as the Sonogashira cross-coupling, copper acts as a co-catalyst, activating the terminal alkyne by forming a Cu acetylide complex, while palladium shows a vital role in the organometallic sequence [75].

1.5.1. Copper catalysed C-N bond formations and the Chan-Lam reaction

The strategic formation of carbon-nitrogen bonds is crucial in synthetic organic chemistry [76, 77]. Transition metal-catalysed methods, particularly for creating aryl ethers, amines, and thioethers, are vital tools in drug discovery and development [78]. Key examples include the Buchwald-Hartwig [79, 80], Ullmann-Goldberg, and Chan-

Lam cross-coupling reactions. The Cu-catalysed Ullmann-Goldberg and Pd-catalysed Buchwald-Hartwig reactions are established methods for coupling nucleophiles with aryl halides. However, traditional Ullmann-Goldberg reactions often require harsh conditions, while Buchwald-Hartwig reactions can necessitate high temperatures and expensive reagents. Inspired by the success of the Suzuki-Miyaura reaction in carbon-carbon bond formation, milder and more efficient methods for creating carbon-heteroatom bonds (C-X, where X = O, N, S) have been developed, expanding the options available to synthetic chemists.

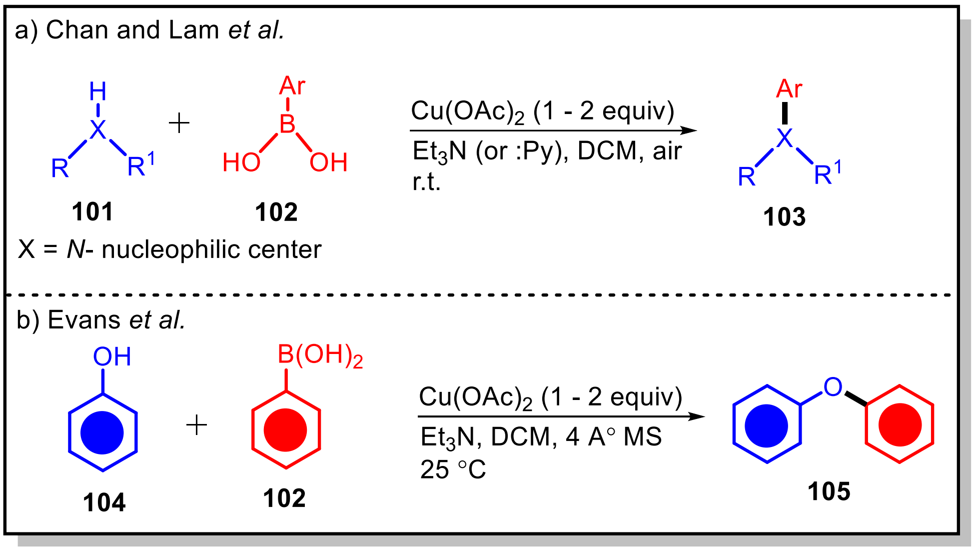
The growth of copper-catalysed C–N cross-coupling processes began with Dodonov's group, which reported the arylation of alcohols, phenols, amines, and water using triphenylbismuth diacetate [81]. Barton's group later demonstrated the use of triarylbismuth diacylates [82] and phenyllead triacetate [83] for *N*-arylations, further expanding their work to include the *N*-arylation of amino acids [84] and heterocyclic amines [85] using triphenylbismuth and aryllead triacetate, respectively. While both organobismuth and organolead reagents showed similar chemical behavior and facilitated efficient C–N cross-couplings, aryllead reagents required higher temperatures and produced toxic byproducts. Arylbismuth reagents, though promising, were limited to arylating indole-like heteroarenes and faced challenges with accessibility and potential toxicity. A breakthrough came when Chan, in his research on triarylbismuth arylations, successfully used arylboronic acids [86] marking an important step forward in carbon-nitrogen cross-coupling processes.

Table 1.1. Arylation of nucleophilic centers, historical context.

Group	Arylation
1986–Dodonov and co-workers	Arylation of Alcohols, Phenols, Amines and water with $Ph_3Bi(OAc)_2$
1986–Barton and co-workers	Arylation of amines with $Ph_3Bi(OCOR)_2$
1987, 1989–Barton and co-workers	Arylation of aliphatic, aromatic and heterocyclic amines with $Ph_3Bi(OAc)_3$
1989–Barton and co-workers	Arylation of aliphatic, aromatic and heterocyclic amines with $PhPb(OAc)_3$

1996–Barton and co-workers	Arylation of hydrazines and derivatives with diethylaluminium chloride
1996–Barton and co-workers	Arylation of amides, carbamates, urethanes, sulfonamides etc with triarylbismuth

The discovery of *Cu*(II)-promoted nucleophile-nucleophile or oxidative Cu-catalysed cross-coupling with aryl organoborons, known as the Chan-Evans-Lam (CEL) crosscoupling, represented a breakthrough (**Scheme 1.29**). Chan and his team were the first to use arylboronic acids for arylation of an extensive variety of reactants under similar settings used for arylations with triarylbismuth [87]. At the same time, Lam and his colleagues at DuPont Merck Pharmaceutical Company independently reported using arylboronic acids for synthesising biologically active *N*-arylated heterocycles [88]. Evans and his group also developed a similar Cu-based method for arylating various phenols and tyrosine derivatives with arylboronic acids [89], which was later applied to the efficient synthesis of a precursor to *L*-thyroxine. CEL cross-coupling reactions, despite requiring stoichiometric amounts of Cu-metal/oxidant and excess arylboronic acids, offer several advantages over other high-temperature, stoichiometric metal-catalysed reactions. These include the use of inexpensive and readily available Cu catalysts without complex ligand design, the ability to run reactions under "open-flask" conditions at ambient temperature with a mild base and in air, and the use of easily accessible, stable, and bench-stable arylboronic acids that allow reactions in aqueous media. Additionally, the reactions are compatible with a wide range of nucleophiles and substrates with sensitive functional groups. Apart from arylboronic acids, organoboron counterparts such as boronate esters, boroxines, aryl trifluoroborate salts, and triolborates are also used for the reaction, though most of these derivatives are less compatible in the reaction. Arylboronic acids, the key reagents in Chan-Lam cross-coupling, are boron compounds with one carbon substituent and two hydroxyl groups in a trigonal planar geometry. They are mild Lewis acids, non-toxic, moisture-stable, and considered "green" compounds because they degrade to boric acid [90]. Their mild Lewis acidity and hydrogen bonding ability make them polar and easy to prepare, either through a two-step oxidation of boranes or directly from arenes and indoles [91, 92].



Scheme 1.30. Chan-Evans-Lam arylation, the breakthrough processes

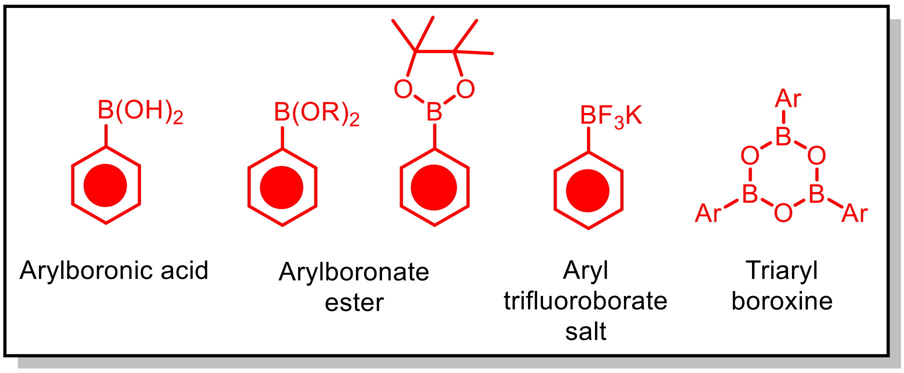


Figure 1.4. Arylating agents in Chan-Lam coupling

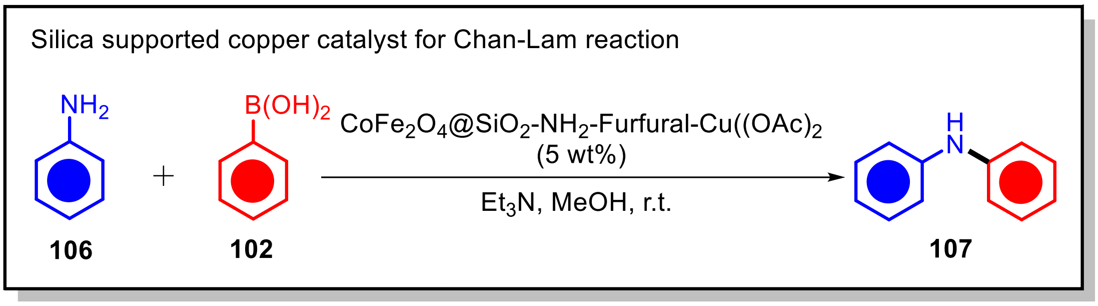
Amines are the primary nucleophiles targeted in Chan–Lam cross-coupling reactions, but this method can form a variety of C–heteroatom bonds, with about twelve different types possible. The range of nucleophiles that can be arylated using the Chan–Lam strategy [94, 95, 96, 97], the use of *N*-nucleophiles remains the most widespread in Chan–Lam cross-couplings. The CEL reaction is highly versatile, accommodating a broad spectrum of functional groups. These include nitrogen-containing compounds like amines, amides, and heterocycles; oxygen-containing species such as phenols and alcohols; sulfur-based nucleophiles like thiols and sulfonamides; as well as phosphorus, selenium, and tellurium derivatives. Remarkably, even carbon-centered nucleophiles, along with biologically relevant molecules such as amino acids and peptides, can be employed in CEL reactions, underscoring the wide applicability and synthetic value of this powerful methodology.

1.5.1.1. Heterogeneous Cham-Lam cross-coupling

The C-N bond formation under Chan-Lam conditions have also been successfully reported with heterogeneous catalytic systems. This enhances reaction efficiency, simplifies catalyst recovery, and enables more sustainable synthetic processes [98].

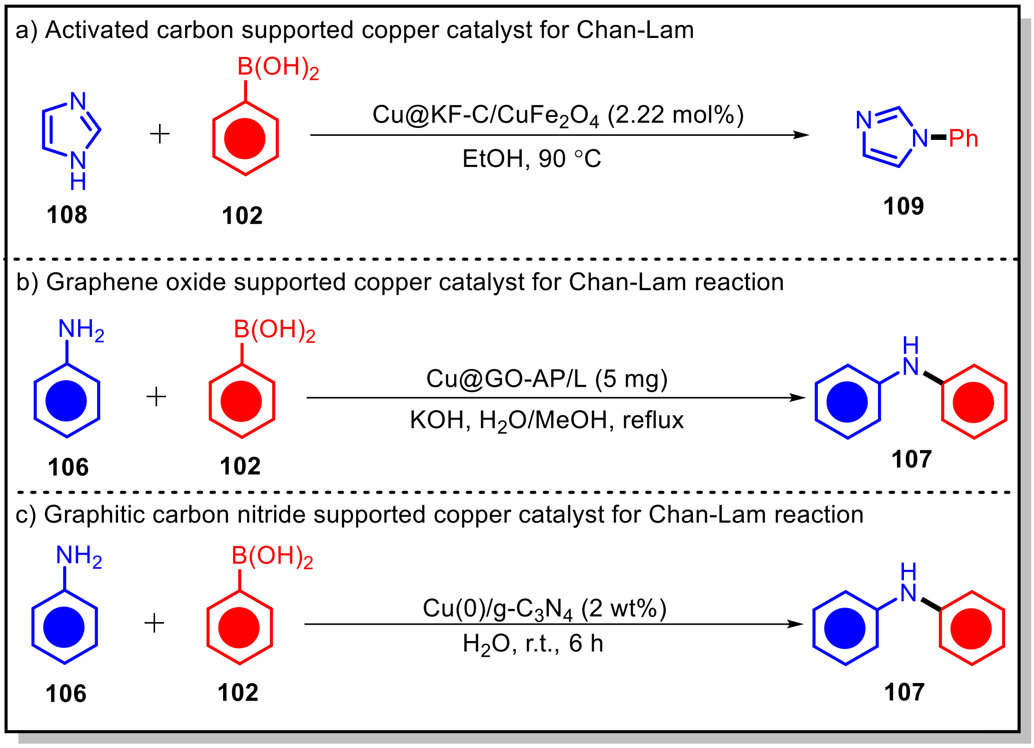
This approach involves immobilizing copper catalysts on solid supports, such as silica, alumina, or polymeric materials, facilitating easier catalyst separation from reaction mixture after the reaction is complete. One of the primary advantages of using heterogeneous catalysts in Chan-Lam reactions is the ease of catalyst retrieval and reusability, which is invaluable in large-scale reactions or those requiring multiple cycles. Immobilizing copper on solid supports allows the catalyst to be recovered through simple filtration, centrifugation, or other separation techniques, eliminating the need for expensive and time-consuming purification processes and making the reaction more cost-effective and environmentally sustainable. Additionally, the enhanced stability of copper catalysts on solid supports protects the copper species from degradation or aggregation, resulting in more robust catalysts that can withstand harsher reaction conditions, reduce deactivation issues, and enable longer reaction times and higher turnovers—beneficial for large-scale or industrial applications. Heterogeneous systems also offer environmental benefits by minimizing copper leaching, reducing toxic contamination, and allowing reactions to be conducted in environmentally friendly solvents like water or alcohols. This approach aligns with green chemistry principles and reduces the need for toxic or expensive ligands, further enhancing sustainability and cost-effectiveness [99].

Several types of heterogeneous systems have been developed for use in Chan-Lam reactions, each offering unique advantages. One of the most used supports is silica, which provides a high surface area and stability under various reaction conditions. Copper nanoparticles or copper salts can be immobilised on silica through methods like impregnation or sol-gel techniques. These systems have been successfully employed in Chan-Lam reactions (**Scheme 1.31**), often providing good catalytic activity and reusability [99].



Scheme 1.31. Silica – supported copper material for Chan-Lam reaction

Carbon-based materials, such as activated carbon (**Scheme 1.32 (a)**) [100], graphene oxide (**Scheme 1.32 (b)**) [101], graphitic carbon nitrides (**Scheme 1.32 (c)**) [102], etc have also been explored as supports for copper catalysts in Chan-Lam reactions. These materials offer high surface areas and excellent conductivity, which can enhance the catalytic activity of copper species. Carbon-based supports have also been shown to be highly reusable, making them attractive for sustainable synthetic processes. Additionally, materials such as metal organic frameworks (MOFs) [103] and covalent organic frameworks (COFs) [104] are another class of materials that have been studied as supports for copper catalysts. These supports have a unique structure that allows for the stabilisation of copper species, providing a stable environment for the catalyst. These systems have been shown to exhibit good catalytic activity and can be easily regenerated for repeated use.

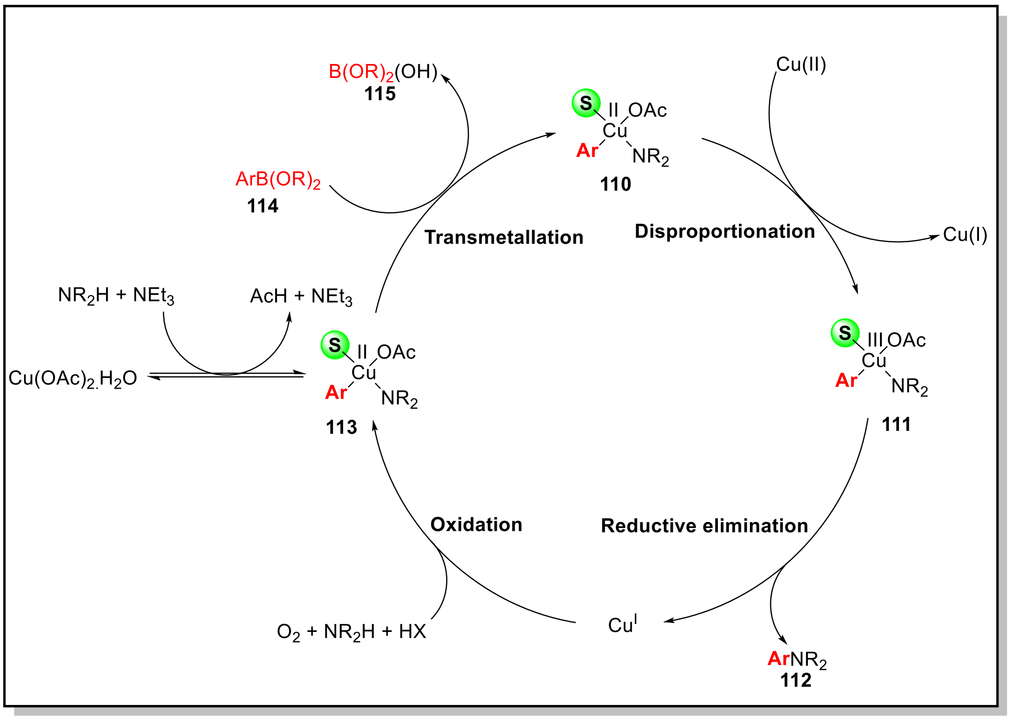


Scheme 1.32. Carbon support-based copper catalysts for Chan-Lam cross-couplings

1.6. Mechanistic pathway for Chan-Lam coupling

The CEL cross-coupling reaction, catalysed by *Cu*(II), has been extensively studied by Stahl and Watson. Watson's group, through spectroscopic analysis, proposed a general mechanism for this reaction under classical conditions. This involves $Cu(OAc)_2·H_2O$ catalyst, molecular oxygen as the oxidant, Et_3N as the base, and acetonitrile as the solvent at room temperature. However, variations in these parameters can significantly impact the reaction's kinetics and pathway.

In acetonitrile, $Cu(OAc)_2·H_2O$ exists as a dimer. Amine coordination weakens the metal-metal bonds in this dimer, facilitating its conversion into the catalytically active monomeric form. Ligation of arylboronic acid to this active catalyst triggers transmetallation, forming a Cu(II)–aryl complex. A crucial and rate-determining stage is the disproportionation of this Cu(II)-aryl complex into a Cu(III) complex. Subsequent reductive elimination from the Cu(III) species releases the anticipated product and generates a Cu(I) intermediate. The catalytic cycle is completed by the re-oxidation of Cu(I) to Cu(II) by O_2. Excess boronic acid, while often necessary, can lead to side products such as phenols, ethers, protodeboronated products, and reductive homocoupling products. While minimizing some of these side products is possible, the mechanisms underlying protodeboronation and reductive homocoupling remain less understood. Slower disproportionation steps can contribute to the buildup of aryl-Cu(II) species, which may further promote side product formation. A thorough understanding of these by-products is crucial for optimizing reaction conditions and developing more efficient catalytic systems.



Scheme 1.33. General catalytic pathway for Chan-Lam coupling

1.7. Thesis overview and objectives

This thesis explores the developing effective catalytic approaches for C-C, C-O and C-N bond formation reactions, leading to the formation of functionalised carbocycles and heterocycles. The research encompasses a diverse range of catalytic systems, including homogeneous palladium catalysis, heterogeneous supported palladium catalysis, and copper nanocatalysis. Key areas of investigation include the development of a robust and efficient C-H arylation protocol using Pd(II) and carboxylic acid as a directing group, the exploration of heterogeneous palladium catalysts for efficient C-C and C-O bond formation reactions, the utilisation of Pd(II) catalysis to facilitate intramolecular variant of Heck reactions for the synthesis of indole derivatives, and the investigation of copper nanocatalysts in C-N bond construction reactions, specifically focusing on the Chan-Lam cross-coupling strategy. Keeping these in mind, the objectives of the thesis are as follows:

- Utilisation of Pd(II) salt in the directing group (-COOH) assisted *ortho*-C-H arylation reaction. Ligand directing group assisted C-H arylation helps in arylation at positions that are conventionally hard to achieve.
- Utilisation of supported palladium catalysis in C-C and C-O bond formation reactions. Supported catalysis involving palladium centers provides efficient ways to form C-C and C-O bonds and gives heterogeneity.
- Utilisation of Pd(II) salt in intramolecular Heck cyclisation for the synthesis of indoles. Intramolecular Heck reaction is a powerful tool for making C-C bonds and synthesising molecular systems under Pd(II) catalysis due to its wide functional group tolerance.
- Utilisation of copper nanocatalysis for the formation of C-N bonds. Among the various C-N bond formation reactions, Chan-Lam cross-coupling strategy is the most sought-after process on account of its versatility and wide tolerance of functional groups.

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