

## Mizoroki-Heck Cross-Coupling: Mechanism, Catalysis with Transition Metals and Graphene Synergistic Catalysts and Applications

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### ABSTRACT

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Upon examining the progression of organic chemistry and comprehending its fundamental nature, it becomes evident that carbon-carbon bond-forming processes hold unparalleled significance in creating this field of scientific inquiry. The Diels-Alder, Grignard, and Wittig reactions are three notable examples of chemical processes that have played significant roles in the development of modern chemical synthesis throughout the past century. During the last quarter of the 20th century, a novel category of carbon-carbon bond-forming reactions emerged, relying on transition-metal catalysts and substantiated to be exceedingly effective instruments in the field of synthesis. One of the most researched cross-coupling reactions is the Mizoroki-Heck reaction, which has garnered significant attention and was conferred the Nobel Prize in Chemistry. This review focuses on the examination of various catalysts employed in Mizoroki-Heck cross coupling processes, namely those composed of transition metals and reduced graphene oxide (rGO). The selected examples serve as compelling illustrations of the significant efficiency of these catalysts in the realm of complete synthesis, hence emphasizing their prospective utility in the field of chemical synthesis.

**Keywords:** Mizoroki-Heck Reaction, Mechanism, Catalysis, Applications.

## 1. INTRODUCTION

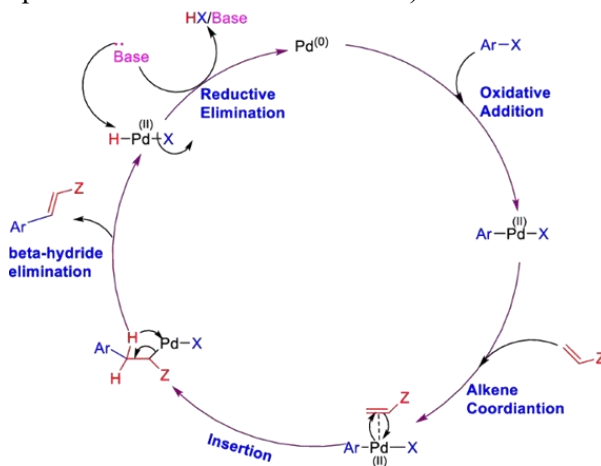
Since the initial laboratory synthesis of acetic acid by Kolbe in 1845, wherein a carbon-carbon bond was first constructed, carbon-carbon bond-forming processes have significantly influenced and shaped the field of chemical synthesis. Grignard-type and Aldol- reactions, the Wittig and related reactions, and the Diels Alder and related pericyclic processes, are among the various examples of such chemical transformations that have significantly enhanced our capacity to build progressively intricate carbon frameworks. Consequently, these advancements have facilitated the synthesis of a wide range of organic compounds. During the latter part of the 20th century, a novel framework to produce carbon-carbon bonds has evolved, significantly augmenting the capabilities of synthetic organic chemists in constructing intricate molecular structures. This development has also brought about a shift in our perception of synthesis methodologies. The ability to form carbon-carbon bonds between or within functionalized and sensitive substrates, facilitated by transition-metal catalysis, has opened new possibilities in various fields. These include total synthesis, medicinal and process chemistry, chemical biology, and nanotechnology.

One of the notable processes in this category is the carbon-carbon bond-forming reactions catalyzed by palladium. This coupling results in the formation of products that can be considered as the outcome of substituting an atom of hydrogen in the alkene coupling partner. The initial instances of this reaction, in its present-day recognizable form, were independently documented by Mizoroki in 1971<sup>1</sup> and, in an amended

form, by Heck (1972)<sup>2</sup>. Nevertheless, it took over ten years for the synthetic organic community to start exploring the wider applicability of this transition. The emergence of asymmetric catalytic Heck reactions throughout latter part of the 1980s sparked a renewed wave of enthusiasm within the scientific community, thereby reigniting scholarly attention towards this particular area of study<sup>3</sup>. The Heck reaction is currently recognized as a very reliable and effective approach for creating carbon-carbon bonds, with a particular emphasis on the production of tertiary and quaternary stereocenters and the synthesis of intramolecular rings. This field of study continues to thrive and attract significant scientific attention. Notably, it has served as a significant source of inspiration for crucial modifications that, over time, have developed distinct designations, characteristics, and significance within the realm of total synthesis.

### 1.1 MIZOROKI-HECK C-C COUPLING MECHANISM

The reaction mechanism of Mizoroki-Heck in homogeneous catalytic systems was initially proposed by Dieck and Heck in 1974<sup>4</sup>. This assertion is widely acknowledged, albeit with certain constraints, even in contemporary discourse. The Mizoroki-Heck reaction mechanism is facilitated by the usage of palladium acetate as a homogeneous catalyst, in conjunction with the existence of ligands (such as  $\text{PdCl}_2\text{L}_2$ , where L represents a ligand like  $\text{P}(\text{o-tolyl})_3$  or  $\text{PPh}_3$ ). This reaction occurs between a vinyl or aryl halide ( $\text{R-X}$ , where X represents either iodine or bromine).



**Figure 1.** Mechanism of Heck Coupling

The image illustrates the representation of either olefin or acrylate. The catalytic process involves four crucial steps, resulting in the shift of palladium's oxidation state from 0 to 2, specifically from Pd (0) to Pd (II).

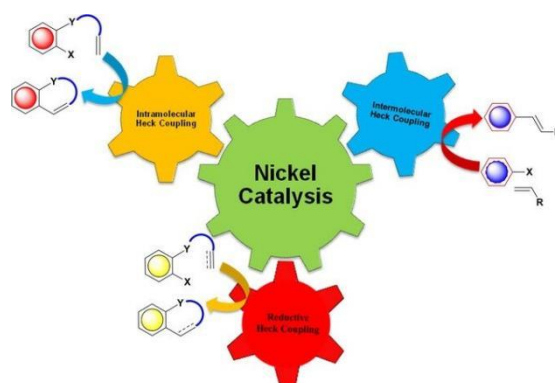
- i. Initially, an aryl halide undergoes oxidative addition to the Pd (0) complex, resulting in the formation of an arylpalladium (II) halide.
- ii. In order to produce a  $\sigma$ -alkylpalladium (II) halide, an oxygen atom is introduced into a  $\sigma$ -aryl-palladium (II) halide compound. This process subsequently facilitates the rearrangement of the alkene molecule by liberating one of the phosphine ligands.
- iii. A hybrid palladium (II) halide, which is synchronized to the arylated alkene, is formed via the elimination and dissociation of a hydride.
- iv. The rejuvenation of the active Pd (0) complex is facilitated via reduction, which effectively eliminates the hydridopalladium(II) species<sup>5-6</sup>

The composition and reactivity of the Pd(0) and Pd(II) intermediates in the Heck catalytic reaction can be influenced by various experimental conditions, including the choice of catalytic precursors such as Pd(0) complexes, Pd(OAc)<sub>2</sub>, or palladacycles, as well as the categories of ligands employed, such as carbenes, mono- or bisphosphines, and bulky monophosphines<sup>5</sup>. Although the overall mechanism of the Heck reaction has been well-established, there remains ongoing debate on the specific role of heterogeneous catalysts in this process. Indeed, the aforementioned statements hold validity, as they have been deduced from investigations concerning the operational principles of Heck reactions facilitated by fortified heterogeneous catalysts based on palladium (Pd). Firstly, it has been observed that the leaching phenomenon occurs in supported-Pd catalysts, leading to the creation of soluble palladium species that possess catalytic activity. Secondly, these species actively partake in the reactions. Lastly, it is worth noting that the catalytic capabilities of these species, along with their subsequent reattachment onto the solid substrate, play a substantial role in shaping the overall rates of the reactions<sup>7</sup>. However, it is widely acknowledged that the coordination sphere approach, which is suggested for the catalytic reactions using homogeneous catalysts, accurately describes the majority of important aspects in the catalytic phase of heterogeneous-catalyzed Heck reactions<sup>8</sup>.

## 1.2. CATALYSTS

### 1.2.1 Nickel based catalysts

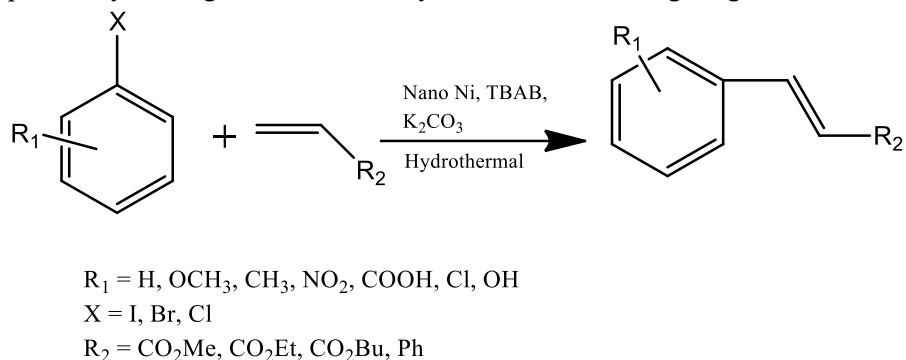
In recent years, the utilization of nickel catalysts in Heck-coupling reactions has emerged as a significant advancement in the field of chemical synthesis. Compared to other catalysts composed of transition metals, this particular catalyst has garnered significant interest due to its unique features, rendering it highly advantageous in numerous synthetic applications. Nickel catalysts exhibit several notable advantages owing to their cost-effectiveness, widespread availability, and environmentally benign nature. Nickel plays a crucial role in a diverse collection of Heck practices, including intra-molecular Heck reactions, intermolecular Heck reactions, and reductive Heck reactions. These processes lead to the formation of biologically significant carbocycles and heterocycles.



**Figure 2.** Uses of Nickel Catalyst in different reactions

A multitude of structural constituents seen in naturally occurring chemicals were synthesized by carbocyclization or hetero-cyclization reactions, employing reaction conditions that were optimized for maximum efficiency. The cyclization method of reductive Heck has been employed to construct hetero- or carbo-cyclic systems with a high number of members. These large rings serve by way of crucial building blocks in the production of pharmaceuticals and the manufacture of bioactive compounds. In contrast, the investigation of intermolecular Heck-type reactions has made more significant advancements. The

intermolecular Heck reaction, catalyzed by nickel, encompasses a range of reactions including carbonyl-Heck, silyl-Heck, and other diverse reaction types. Additionally, there have been documented instances of asymmetric Heck-coupling reactions occurring with unactivated alkenes. These reactions yield compounds that possess a quaternary stereogenic core that may be accessed with high regio- and enantioselectivity <sup>9</sup>.

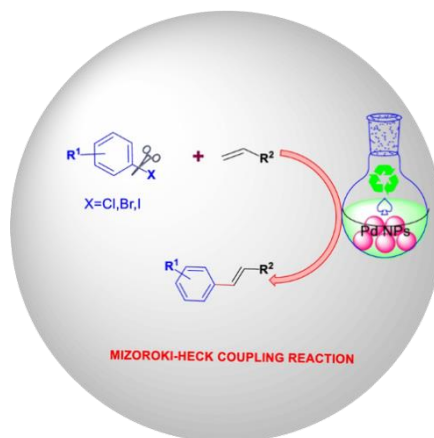


**Figure 3.** Nickel Catalyzed Cross Coupling Reaction

### 1.2.2 Palladium based catalysts

The Heck, Suzuki, Stille, Buchwald-Hartwig and Sonogashira reactions represent a subset of the several coupling reactions that have experienced significant advancements through the utilization of homogeneous palladium catalysis. This methodology possesses the capacity to facilitate the initial or enhanced synthesis of several products. This kind of catalysis offers several advantages, including high reaction rates, high turnover numbers (TON), and often exceptional yields and selectivities.

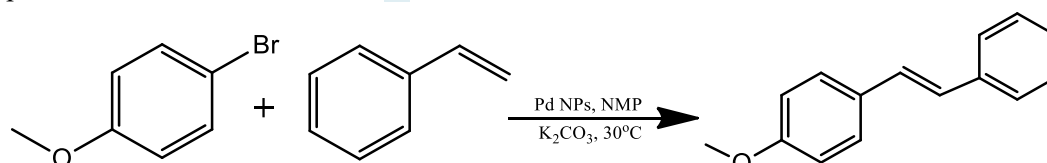
The properties of these palladium catalysts can be altered through the introduction of various ligands such as amines, phosphines, dibenzylideneacetone (dba), carbenes, and other similar compounds. Due to meticulous ligand design, catalysts have been engineered to exhibit enhanced tolerance towards weak leaving groups such as chloride.



**Figure 4.** Palladium Catalysis

These catalysts demonstrate improved turnover numbers (TON) and reaction rates, possess prolonged durability, and exhibit sufficient stability to enable reactions to be conducted under ambient conditions in the occurrence of water and air. In numerous illustrations, the structural composition of the catalytic species is discernible, hence enabling the establishment of connections between structure and activity. In recent years, there has been a notable emergence of Pd catalysts free of ligand as a promising and essentially advantageous alternative to conventional methodologies that are ligand-assisted. Nevertheless, there exist

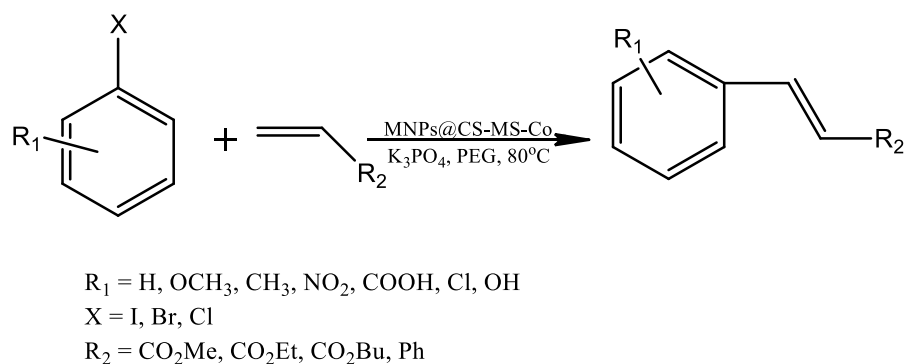
certain drawbacks associated with homogeneous catalysis, with the primary concern being the lack of feasibility in terms of catalyst recycling or reutilization. As a consequence, the loss of valuable metals and ligands occurs, leading to impurities in the final products, necessitating the filtration of surplus metals<sup>10</sup>. There remain significant barriers impeding the general adoption of homogeneous Pd-catalyzed coupling procedures in industrial applications<sup>11</sup>. The utilisation of heterogeneous Pd catalysis shows potential as a viable approach to address these challenges. Here, Palladium is securely fastened with a support<sup>12-13</sup> like activated carbon<sup>14-16</sup> zeolites and molecular sieve<sup>13, 17-21</sup> metal oxides<sup>13, 22-23</sup> (mainly alumina or silica but also ZnO, ZrO<sub>2</sub>, TiO<sub>2</sub>, MgO), clays<sup>24</sup>, alkaline earth and alkali salts (BaSO<sub>4</sub>, CaCO<sub>3</sub>, SrCO<sub>3</sub>, BaCO<sub>3</sub>), porous glass<sup>25</sup>, organic polymers<sup>13</sup>, or polymers embedded in porous glass<sup>26</sup>. Nevertheless, it is worth noting that complexes in which the ligands are attached to the support through covalent or ionic interactions can also facilitate the covalent attachment of palladium to a solid support. The recyclability of the heterogeneous catalyst can be achieved using either method, provided that it has not undergone excessive deactivation. The presence of oxygen in a wet environment has been seen by Mahmoud et al. to result in the existence of distinct catalysts for the Heck coupling processes. The methodology provides significant quantities with minimal or negligible toxicity and is characterized by its simplicity of implementation. Despite multiple applications, the catalytic efficiency remains unaltered. In the course of conducting stability tests on the substance, it was observed that the Au/Pd bimetallic nanoparticles did not exhibit any discernible release of active species into the reaction mixture<sup>27</sup>.



**Figure 5.** Palladium Catalyzed Cross Coupling Reaction

### 1.2.3 Cobalt based catalysts

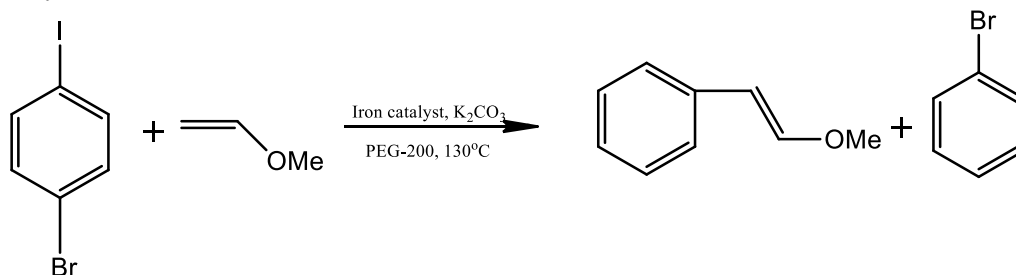
Chitosan (CS) exhibits efficient metal transportation capabilities due to its composition of porous, self-supporting nanofibrillar microspheres. The ability to modulate coordination of cobalt by using a benign chemical ligand, specifically methyl salicylate, is assisted by the occurrence of amino-groups on CS. The catalyst exhibits high efficiency in facilitating the Mizoroki-Heck cross-coupling reaction among diverse functional substrates, employing moderate and sustainable reaction conditions. Specifically, the reaction is conducted in polyethylene glycol as the solvent, at a temperature of 80 degrees Celsius, and within a relatively short reaction period of 1 hour. The Sonogashira cross-coupling methodology employed a cobalt complex as a heterogeneous catalyst, which demonstrated efficacy, cost-effectiveness, and environmental safety. The interactions between various aryl halides and phenylacetylene resulted in product yields ranging from fair to good. The catalyst exhibits a high recyclability potential, as it may be reused for up to five sequential cycles without an obvious decline in the catalytic activity when regenerated using an external magnet. Moreover, the catalyst does not necessitate the presence of phosphine, copper, or palladium<sup>28</sup>.



**Figure 6.** Cobalt Catalyzed cross Coupling Reaction

#### 1.2.4 Iron based catalysts

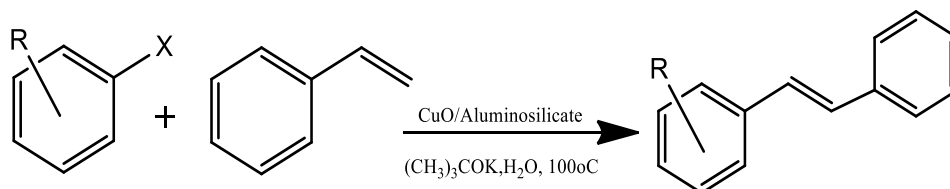
The catalysis of the Heck reaction between olefins and aryl iodides has been effectively achieved by employing an acac-functionalized silica substrate that supports green Fe-based catalysts. Our catalytic system exhibited activity comparable to those of palladium catalysts. Following each iteration of the reaction, the catalyst was subjected to filtration in order to facilitate its reuse. The reaction was also carried out using the green solvent polyethylene glycol. The catalyst facilitated the selective olefination of aryl iodides over aryl bromides<sup>29</sup>



**Figure 7.** Iron Catalyzed Cross Coupling Reaction

#### 1.2.5 Copper based catalysts

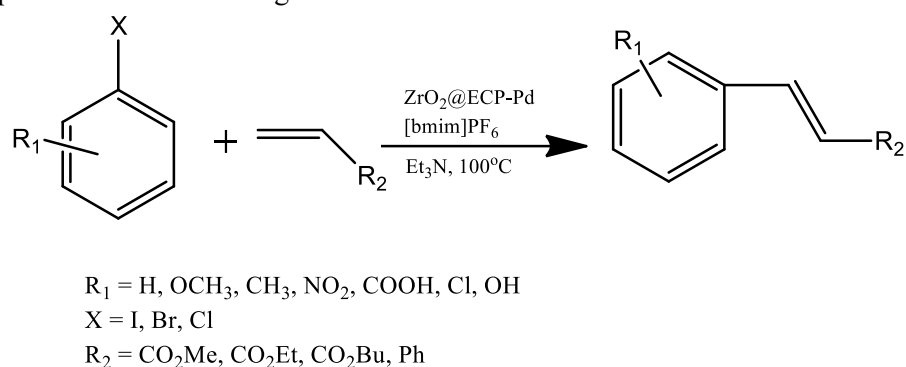
The catalytic efficacy of CuO/aluminosilicate has been demonstrated in the Heck coupling reaction of styrene with aromatic halides in an aqueous medium. The catalyst (Copper oxide/aluminosilicate) synthesized from copper chloride hexa-hydrate, aluminium nitrate, and tetraethyl orthosilicate (TEOS) was subjected to analysis using SEM-EDX, XPS, TEM-HR, and XRD techniques. The investigation involved the utilization of styrene and 4-chlorobenzonitrile as a representative system to ascertain the most favorable reaction conditions. This was achieved by the systematic exploration of diverse solvents, bases, catalyst concentrations, and temperatures. The reach of the reaction was successively expanded to comprise substituted aryl halides. A series of experiments were conducted to investigate the selection of regimes, the presence of heterogeneity, and the potential for recyclability<sup>30</sup>



**Figure 8.** Copper Catalyzed Cross Coupling Reaction

### 1.2.6 Zirconium based catalysts

The utilization of phosphine-functionalized  $\text{ZrO}_2$  nanoparticles as a support for palladium represents a fresh and highly proficient nanocatalyst for the Mizoroki-Heck and Suzuki-Miyaura reactions. The nanocatalyst is referred to as  $\text{ZrO}_2@\text{ECP-Pd}$ . To synthesize the new catalyst, the compound  $\text{Pd}(\text{OAc})_2$  was mixed with  $\text{PPh}_2$ -functionalized  $\text{ZrO}_2$  nanoparticles. The catalyst underwent evaluation by several analytical techniques counting Fourier transform infrared (FTIR), X-ray diffraction (XRD), transmission electron microscopy (TEM), scanning electron microscopy (SEM), inductively coupled plasma (ICP) and thermal gravimetric analysis examination after its synthesis. The synthesized catalyst in the aforementioned studies was characterized by the presence of spherical particles with a standard deviation of less than 1040 nm. The utilization of the  $\text{ZrO}_2@\text{ECP-Pd}$  nanocatalyst was seen to significantly enhance the Suzuki Miyaura and Mizoroki Heck cross-coupling reactions involving diverse aromatic halides. These reactions, which involve electron-sufficient and electron-deficient aromatic iodides/bromides and heteroaryl iodides, can result in yields of relevant end products that range from superior to outstanding. Furthermore, these reactions can be completed in a shorter period of time. The present methodology utilizes environmentally sustainable solvents such as water and  $[\text{bmim}]\text{PF}_6$ , hence eliminating the need for the utilization of detrimental sol emissions. Furthermore, the nanocatalyst exhibits advantageous characteristics and can be effectively reused in subsequent reactions following its retrieval <sup>31</sup>.



**Figure 9.** Zirconium Catalyzed Cross Coupling Reaction

### 1.2.7 Nanocatalysis

Recent advancements in the utilization of noble metal nanoparticles have been noted by Narayanan in the catalysis of Heck and Suzuki reactions <sup>32</sup>. Because of their high surface-to-volume ratio and the existence of highly reactive surface atoms, nanoparticles of metal in colloidal fluids and adsorbates on bulk substrates have garnered significant interest as catalysts for a broad range of inorganic and organic chemical reactions. This paper presents a comprehensive analysis of the influence of nanoparticle shape on the catalytic presentation of nanotechnology catalysts in Suzuki and Heck cross-coupling reactions. Additionally, it explores the utilization of bi-metallic, tri-metallic, and multi-metallic nanoparticles in these catalytic activities. Cai et al. <sup>33</sup> conducted a comprehensive review on the utilization of bimetallic nanomaterials as catalysts for organic transformations. The review highpoints the potential broad range of reactions that can be facilitated by palladium-based catalysts, such as magnetically separable "quasi-homogeneous" gold-palladium nanoalloys, palladium-nickel particles immobilized in silica nano rattles, and carbon-supported bimetallic palladium-metal nanoparticles (where the metal can be silver, nickel, or copper). Bimetallic nanoparticles consisting of Pd-Cu/C were synthesized by irradiation at room temperature and were observed to have remarkable catalytic activity in Heck- and Suzuki-type coupling reactions. Baboo et al. have conducted investigations on catalysis for several processes, including hydrogenation, oxidation, Heck, Sonogoshira, Suzuki, reductive amination, hydrodechlorination, hydrogenolysis and amidation. The

emphasis of researchers has shifted towards the use of multimetallic nanocatalysts that exhibit exceptional performance, as opposed to their monometallic counterparts. This preference persists, despite the fact that nanocatalysts derived from nanomaterials can be conveniently retrieved for further use without compromising their catalytic efficacy. The utilisation of bimetallic nanostructures in oxidation, hydrogenation, and coupling reactions has been extensively examined in the literature. Nevertheless, their untapped potential in the realm of complex molecule synthesis has to be completely explored. The review examines the potential of bimetallic nanoparticles composed of palladium and nickel, which can be separated using magnetic properties, as catalysts for coupling reactions. Labulo et al. have conducted a review on the efficacy of Carbon Nano Tubes as catalyst supports for C-C cross-couplings mediated by palladium processes<sup>34</sup>. The utilization of palladium catalysts in these processes has demonstrated their superiority in terms of catalytic performance and recycling efficiency, owing to the stability they offer.

### **1.2.8 Graphene based metal catalysts**

Graphene refers to the sp<sup>2</sup>-hybridized carbon atoms arranged in a two-dimensional structure. Graphene has been the focus of extensive theoretical and experimental research due to its exceptional electrical, mechanical, and chemical properties<sup>35</sup>. Graphene exhibits great potential as a highly effective catalyst support material in various applications owing to its exceptional surface area and remarkable thermal, chemical, and mechanical durability<sup>36</sup>. Furthermore, due to their exceptional capabilities, metal nanoparticles find widespread use in fields such as catalysis, electronics, and optics<sup>37</sup>. Because of this, there has been a lot of interest recently in metal NPs (nano-particles) supported on graphene, which unite the benefits of both metal NPs and graphene<sup>37</sup>. Gas phase reduction, chemical reduction, microwave-assisted reduction, plasma reduction, and hydrothermal approach provide a limited selection of the methodologies available for the synthesis of hybrid materials comprising metal nanoparticles and graphene<sup>38-39</sup>. The gas-liquid interfacial plasma (GLIP) approach is considered as one of the viable procedures, exhibiting certain advantages that distinguish it from alternative methods. The advantages encompassed in this context encompass a heightened level of reactivity, an exceptionally high density, the ability to produce nanomaterials on a large scale, a rapid rate of processing, the ability to continuously synthesize, the avoidance of toxic preservatives and antioxidants, the ability to conduct reactions at ambient temperatures, and the absence of the necessity for agitation during the nanoparticle formation process<sup>40</sup>. From being discovered in 2004, graphene, a carbon compound known for its extraordinary qualities, has been the subject of intensive research due to its distinctive chemical and physical characteristics, as well as its significant specific surface area<sup>41</sup>. Graphene-based materials exhibit considerable potential as viable candidates for implementation in catalysis and as catalyst support<sup>42</sup>. The demand for graphene and its derivatives is substantial due to their considerable contribution to a novel category of carbocatalysts<sup>43</sup>. There is a scarcity of published literature pertaining to the application of graphene or graphene oxide as a reliable substrate for a Palladium catalyst in Carbon-Carbon cross coupling reactions<sup>44</sup>. The catalytic activity of Pd<sup>2+</sup>-graphene oxide and Pd<sup>2+</sup>-graphene gradually diminished during prolonged utilisation. Consequently, the localization of Pd nanoparticles is limited to the material's surface, suggesting a lack of strong interactions between palladium and the supporting material<sup>44</sup>. Consequently, our attention has been drawn towards the exploration of enhanced catalysts in order to expedite the catalytic performance of heterogeneous Pd micro catalysts<sup>45</sup>

### **1.2.9 rGO based metal catalysts**

In recent years, there has been a significant amount of research conducted on the application of reduced graphene oxide (rGO) as carbon nanomaterials in the field of catalysis<sup>46</sup>. Emerging prospects for the



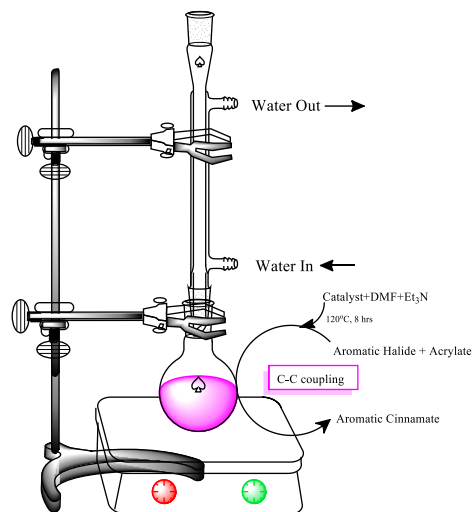
utilization of reduced graphene oxide (rGO) As a catalyst or catalyst support of the future generation are enabled <sup>47-49</sup> by its electronic properties <sup>36</sup> and high surface area <sup>50</sup>. The potential for utilizing reduced graphene oxide as catalytic supports exhibits a higher degree of promise <sup>49</sup>. Nanomaterials have the capability to be integrated with other nanomaterials, resulting in the formation of nanocomposites. Furthermore, they possess the ability to produce consistent dispersions in both aqueous and organic environments <sup>51</sup>. Researchers have incorporated several metal nanoparticles (NPs) into a two-dimensional catalytic support known as reduced graphene oxide (rGO) in order to generate potential catalysts for diverse processes. In recent scholarly articles, catalysts such as Palladium, gold, and Platinum supported on Reduced Graphene oxide have been utilized for organic reactions <sup>52</sup>. The majority of the publications analyzed utilized noble metals assisted by reduced graphene oxide (rGO) in their catalytic processes. Despite the potential usefulness of low-cost first-row transition metals assisted by reduced graphene oxide (rGO) as catalysts in many organic processes, there is a noticeable scarcity of published literature on this topic <sup>52-54</sup>. In recent years, the utilisation of reduced graphene oxide (rGO) as a catalytic support has exhibited significant benefits in the field of cross-coupling chemistry. Zero-valent homogeneous complexes stabilized by organic ligands are commonly employed as catalysts for cross-coupling reactions <sup>55-58</sup>. The researchers were able to address the difficulties associated with the recovery and reusability of a homogeneous catalyst by employing ligand-free heterogeneous catalysts supported by reduced graphene oxide (rGO). Numerous investigations have provided evidence that the use of composite materials consisting of palladium (Pd) and reduced graphene oxide (rGO), characterized by their heterogeneous composition, showcases exceptional catalytic efficacy in Carbon-Carbon cross coupling events, including the Mizoroki-Heck, Sonogashira, and Suzuki-Miyaura reactions.

## **2 EVALUATION OF CATALYSIS IN HECK COUPLING**

### **2.1 General procedure**

A solution containing an aromatic halide compound (1 mmol), alkene (2 mmol), and triethylamine (Et<sub>3</sub>N) (4 mmol) in dimethylformamide (DMF) (4 ml) as a solvent was supplemented with a catalyst (0.01 mmol). Prior to conducting gas chromatographic analysis, the solution in question was subjected to an eight-hour reaction period at a temperature of 120 degrees Celsius. The catalyst was isolated using the process of centrifugation, followed by ethanol washing and subsequent vacuum drying, in order to preserve it for future utilization. The organic solution was subjected to three extractions using a volume of twenty milliliters of ethyl acetate each time, followed by dehydration using MgSO<sub>4</sub>. The solvent was let to undergo

evaporation, and subsequently, the contaminated mixture was subjected to purification using column chromatography employing a hexane/ethyl acetate mixture in an 8:2 ratio.

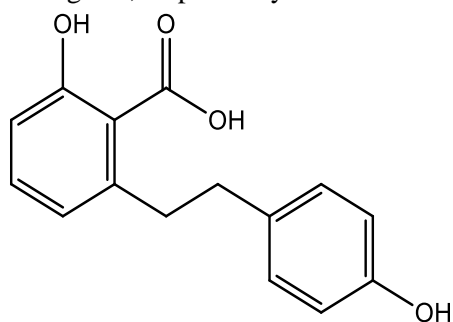


**Figure 10.** Reaction Setup for Heck Cross Coupling Reaction

### 3 APPLICATIONS

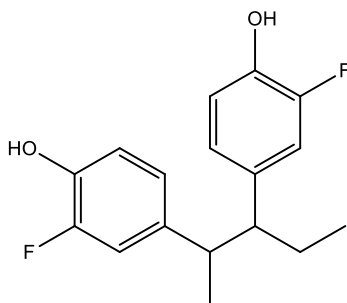
The Heck coupling reaction is employed for the formation of carbon-carbon bonds. The process necessitates the utilisation of a palladium catalyst in conjunction with a coupling reaction involving an alkene or alkyne and an aromatic or vinyl halide. The objective of Heck coupling is to accomplish:

1. Heck coupling is a highly important approach in the synthesis of complex chemical molecules. The approach described herein enables the dependable and efficient construction of carbon-carbon bonds, a crucial step in the synthesis of various medicines and natural compounds<sup>59</sup>. Lakshmi and colleagues have developed a novel methodology for the efficient synthesis of dibenzyls and alkyl phenyl esters. The methodology employs a singular catalyst that is capable of being reused, with settings that are notably mild. The present methodology exhibits promising prospects for application in the synthesis of commercially significant chemicals, including lunularic acid and bifluranol. These compounds find utility as antifungal and anti-androgen pharmaceutical agents, respectively.



Lunularic acid

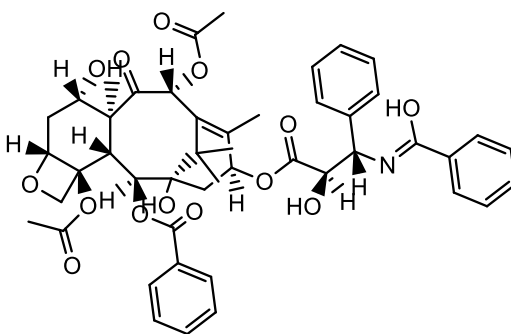
**Figure 11.** Structure of Lunularic acid



Bifluranol

**Figure 12.** Structure of Bifluranol

- The implementation of a solitary catalyst and a unified reaction process can provide significant benefits for the industrial utilization of these compounds, as it enables time and cost efficiencies<sup>60</sup>. Amy and her colleagues engage in a scholarly discourse over the application of the asymmetric intra-molecular Heck reaction in the context of accomplishing the whole synthesis of naturally occurring chemicals. This research has the potential to provide valuable insights for the pharmaceutical sector about the synthesis and utilization of natural compounds and their derivatives. Possible candidates for therapeutic interventions can be generated by employing complex chemical structures and the asymmetric intramolecular Heck reaction<sup>61</sup>
2. The utilization of Heck coupling can be employed to modify compounds with biological activity by introducing supplementary functional groups to the molecule. Modifying this particular characteristic of the chemical compound has the potential to enhance its efficacy and specificity, hence facilitating the development of more effective pharmacological agents. In their study, Wendy and her colleagues presented the findings of their investigation into the synthesis of taxol analogues. Taxol is obtained from natural sources, but the analogues synthesized in this work are exclusively the result of human innovation. The utilization of these analogues in the advancement of novel cancer therapies may perhaps yield advantageous outcomes<sup>62</sup>



Paclitaxel

**Figure 13.** Structure of Paclitaxel

3. Heck coupling is utilized in a variety of electrical and optoelectronic applications, including the fabrication of organic light-emitting diodes (OLEDs) and solar cells. Consequently, the formation of conjugated systems is crucial for facilitating the efficient transport of charge and

energy. The primary focus of Zhuhao et al.'s research and development endeavors revolved around the creation of nonfullerene acceptors intended for utilisation in polymer solar cells. The manufacturing procedures employed for the production of acceptors BDDEH-4F and BDDBO-4F involved the utilisation of ligand-free direct heteroarylation and ligand-free organostannanes, respectively. These acceptors exhibit remarkable potential as suitable candidates for incorporation into low-cost nonfullerene solar cells due to their notable efficiency and advantageous structural characteristics <sup>63</sup>.

4. The examination of reaction processes has extensively examined Heck coupling as a model reaction. Numerous theoretical and experimental methodologies have been employed to investigate the process behind Heck coupling, thereby enhancing our comprehension of the operational principles governing transition metal catalysts <sup>64</sup>.

Currently, there is ongoing research focused on the development of enhanced palladium catalysts to facilitate Heck coupling reactions. The utilisation of innovative catalysts in synthetic processes has the potential to enhance reaction efficiency, selectivity, and scope, hence improving overall effectiveness <sup>65</sup>.

#### 4 SUMMARY

The Heck reaction has demonstrated significant resilience and efficacy as a means of facilitating formation of carbon–carbon bond and continues to be a thriving field of study. The researchers' passion and reasonable optimism contribute to the advancement of scientific knowledge, leading to the development of improved and more efficient catalyst production methods. Additionally, their efforts help to address longstanding issues by offering viable answers. The employment of these reactions has the potential to decrease the need for several protection-deprotection protocols in organic synthesis, resulting in a discount in the overall number of steps prerequisite when systematically developed. Additionally, these reactions offer additional reactivities, which can enhance product selectivity and minimize the consumption of volatile organic compounds. The remarkable capacity of palladium to accommodate a broad range of functional groups enables the feasibility of Heck reactions on substrates that are very susceptible to chemical reactivity. Furthermore, the intramolecular Heck reaction is a highly potent technique utilized for the synthesis of several compounds with quaternary and/or asymmetric carbon centers. The widely accepted mechanism for the Heck reaction is predicated on the involvement of intermediate species containing Pd in 0 (zero) and 2+ oxidation state. Nevertheless, the plausibility of the Pd<sup>2+</sup>/Pd<sup>4+</sup> mechanism is not dismissed by a significant number of researchers. The occurrence of the Pd<sup>2+</sup>/Pd<sup>4+</sup> mechanism is postulated in cases where a direct conversion from Pd<sup>0</sup> to Pd<sup>2+</sup> is not readily observable or when the Pd(II) species is unable to complete hydride transfer or reductive elimination reactions with ease. The potential for utilizing the Heck reaction in many transformations appears promising, as evidenced by its successful application in heterogeneous, homogeneous, and even heterogenized catalysis employing organometallic complexes. Several of these have already been implemented on an industrial basis. Paradoxically, while numerous metal-based catalysts have been documented in the literature for facilitating the Heck reaction in the production of bulk chemicals, it is noteworthy that when these reactions are employed for the synthesis of intricate molecules such as agrochemicals, pharmaceuticals, or fragrances, catalysts such as Pd<sub>2</sub>(dba)<sub>3</sub>, Pd(OAc)<sub>2</sub>, PdCl<sub>2</sub>L<sub>2</sub>, Pd/C, PdCl<sub>2</sub>(dppf)<sub>2</sub> and Pd(PPh<sub>3</sub>)<sub>4</sub> continue to be the preferred choices. Extensive research has been conducted, however, there is still a significant amount of work that has to be undertaken.

- There exist numerous encounters and outlooks within the research communal that must be addressed in order to establish an industrial process that is economically viable, resilient, and dependable. One such challenge involves the pursuit of catalyst precursors and ligands that enable

high turnover numbers (TON) and turnover frequencies (TOF), thereby rendering the process parsimoniously appealing.

- The successful transition from laboratory-scale to production-scale necessitates the utilisation of a catalytic precursors and ligands that are both more efficient and cost-effective.
- The preparation of a catalyst that is stable in the occurrence of air and moisture is crucial due to the susceptibility of reactions to molecular oxygen poisoning. Indeed, the development of a catalyst that exhibits enhanced performance in watery environments is a significant advancement.
- The objective is to provide standardized reaction conditions that are characterized by mildness and enable the use of lower catalyst loadings.
- The current research focuses on the advancement of a novel class of palladacycles, which have great potential for future use in various industrial processes.
- The comprehension of the mechanism underlying heterogeneous catalysis remains a topic of ongoing discourse.
- The utilization of more affordable and readily accessible initial substances, particularly chloroarenes and chloroalkenes, is a specialized area that requires further exploration in terms of discovering novel methodologies, as well as developing catalysts and ligands.
- Gaining insight into the underlying factors and effectively preventing the occurrence of metal precipitation.
- The utilization of more cost-effective first-row transition elements in the development of catalysts would significantly contribute to the advancement of practical research.
- Enhancements in catalyst efficiency, coupled with catalyst recycling, have been particularly significant in the context of pharmaceutical and other precise chemical synthesis procedures.
- The resolution of the problem pertaining to the contagion of the final product with palladium necessitates additional purifying procedures.

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