



## Review

# Catalyst Recycling in the Suzuki Coupling Reaction: Toward a Greener Synthesis in the Pharmaceutical Industry

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**Abstract:** The Suzuki coupling is a transition metal-catalyzed, cross-coupling carbon–carbon (C–C) bond forming reaction between organic boron compounds and organic halides. As an operationally simple and versatily applicable procedure, the Suzuki coupling reaction has found immense applications in drug discovery and development in the pharmaceutical industry. Recently, the topic of catalyst recycling has undergone intensive investigations with ever-growing interest in eco-friendly and sustainable synthesis. To recapitulate the latest progress in catalyst recycling in the Suzuki coupling reaction, this invited paper reviews key principles, benefits, challenges, and cutting-edge applications of recyclable catalysts for green synthesis of industrially valuable bioactive molecules. This review paper also discusses how artificial intelligence (AI) could further advance green synthesis of pharmaceutical products.

**Keywords:** Suzuki reaction; transition metal catalyst; catalyst recycling; green chemistry; artificial intelligence; machine learning



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## 1. Introduction

The Suzuki coupling reaction, also known as the Suzuki–Miyaura cross-coupling reaction, is one of the most versatile reactions to form carbon–carbon (C–C) bonds and involves a cross-coupling of organoboranes with an aryl halide in the presence of a transition metal catalyst, a ligand, and an aqueous base. The air- and moisture-stabilities, flexibility of substrates, and excellent reaction yields have led this reaction into the eminent position in synthetic organic chemistry.

The Suzuki coupling reaction has been extensively utilized in the synthesis of various industrially important compounds, such as olefins, styrenes, and substituted biphenyls [1]. For instance, Frederick et al. recently reported a total synthesis of abemaciclib using the Suzuki coupling reaction [2]. Abemaciclib is a compound that blocks the growth of malignant cells by inhibiting cell cycle progression and hence, has a consequential application as a bioactive anti-cancer drug in the pharmaceutical industry [3,4]. The Suzuki coupling reaction successfully introduced a C–C bond between boronic ester and pyrimidine to form a building block of abemaciclib. The Suzuki coupling reaction played a pivotal role for the synthesis of many other drugs and late-stage drug candidates, such as rucaparib, merestinib, and lapatinib [5].

While the Suzuki coupling reaction has been an irreplaceable part of pharmaceutical synthesis, the process heavily relies on harsh reaction conditions, toxic reagents, and copious amounts of solvents, which could cause health- and environment-related concerns and problems [6,7]. To address these issues, the concept of green chemistry was introduced to the industry in the 1990s [8]. Green chemistry is the design of chemical products or processes that maximize the product yield while reducing the use or generation of hazardous substances and hence, navigate the industry toward sustainable manufacturing. From the business point of view, green chemistry has also brought manufacturers considerable

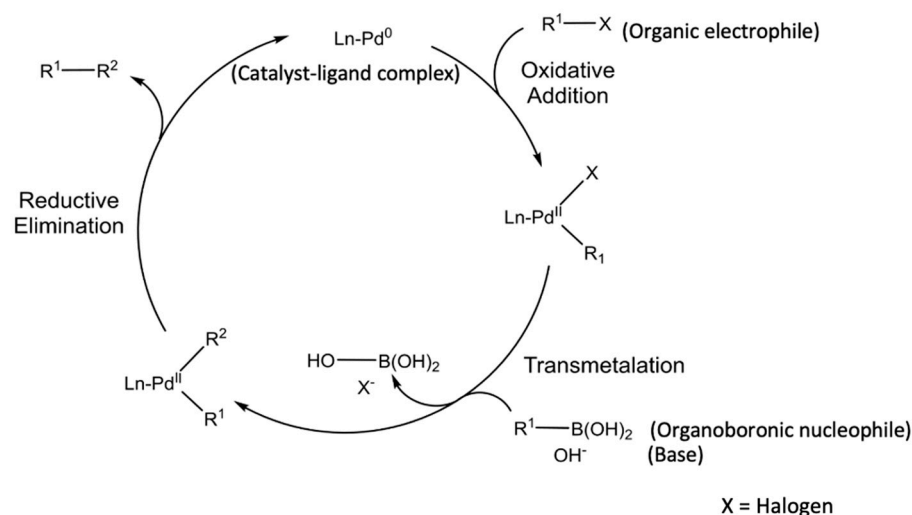
advantages, such as reduction in production cost, faster manufacturing, capacity increase, and energy savings, ultimately leading to more profitable outcomes [8]. To date, a myriad of studies has been conducted to develop sustainable synthetic processes by renovating the feedstocks, reaction conditions, and purification and isolation methods for the Suzuki coupling reaction [8–10].

One propitious approach for sustainable synthesis is to develop a recyclable transition metal catalyst that can be completely removed from the reaction mixture and is reusable in consecutive runs without a significant loss of catalytic performance. In the conventional Suzuki coupling process, the costly metal catalyst is not only discarded as it loses activity during the first run but may also be incorporated into the final product as a contaminant since complete removal is hardly achievable. Therefore, it has been evident that the development of a novel recyclable catalytic system is of great importance to minimize health- and environment-related concerns as well as the production cost.

To recapitulate the unmistakable recent progress in catalyst recycling in the Suzuki coupling reaction, this paper will review the key advancements in principles, benefits, challenges, and cutting-edge applications of recyclable catalysts for green synthesis of various industrially valuable substances. This review paper will also discuss how artificial intelligence (AI) could further advance green synthesis of pharmaceutical chemicals. It is among the purposes of this paper to develop a practical signpost on this rapidly growing field of research.

## 2. Principles of the Suzuki Coupling Reaction

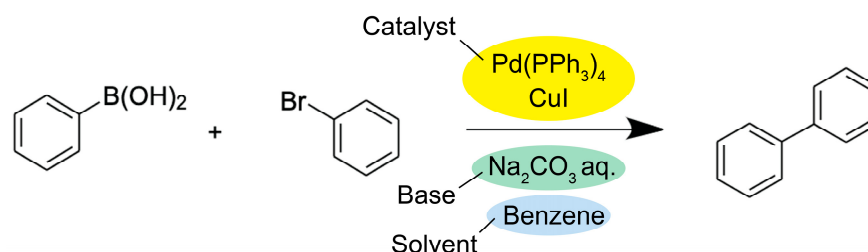
The Suzuki coupling reaction is a versatile method to form a C–C bond between an organoboronic nucleophile and an organic electrophile under basic conditions in the presence of a metal catalyst and ligand [11]. As illustrated in Figure 1, the Suzuki coupling reaction begins with the formation of a catalyst–ligand complex. The organic electrophile is then introduced into the complex via oxidative addition, followed by transmetalation during which the organoboronic nucleophile is introduced into the complex. Lastly, the palladium–ligand complex is separated from the coupling product via reductive elimination.



**Figure 1.** Catalytic cycle of the Suzuki coupling reaction [12].

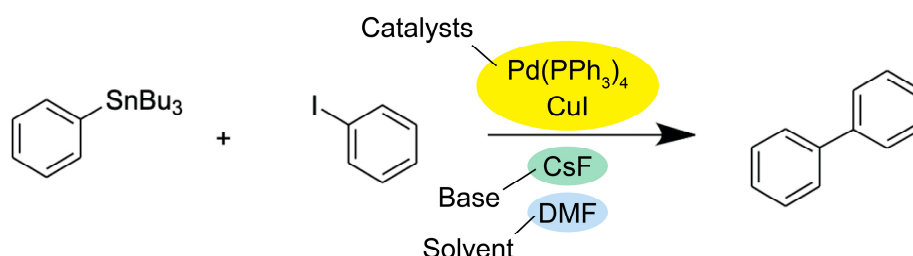
A typical Suzuki coupling reaction is illustrated in Figure 2. The metal catalyst undergoes a two-electron transfer and thus, changes its oxidation state. For instance, the commonly used palladium catalyst is oxidized from Pd(0) to Pd(II) during oxidative addition to receive the organic electrophile, while Pd(II) is reduced back to Pd(0) during reductive elimination of a coupling product. The alternative Pd(II)/Pd(IV) mechanism, where Pd(IV) forms from Pd(II), has also been proposed in recent literature [13]. For either pathway, the aqueous base is essential in the reaction to convert the boronic acid to a more

reactive organoborate that can be efficiently coupled with the organic electrophile [14]. The ligand joins the catalytic cycle by forming a complex with the metal catalyst and combines with the organic electrophile [15].

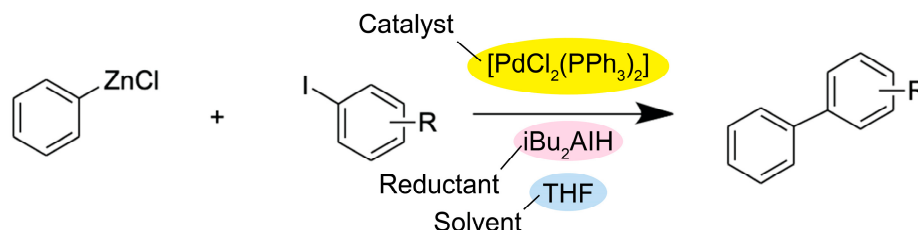


**Figure 2.** General reaction scheme for the Suzuki coupling reaction [16].

There are various other cross-coupling reactions that enable organic transformations via similar mechanisms, such as the Stille coupling and the Negishi coupling (Figures 3 and 4). However, the Stille coupling reaction relies on organotin reagents, which are mostly toxic and expensive and have a low tolerance to functional groups [17]. As for the Negishi coupling, it suffers from low yields and low tolerance to functional groups because zinc is normally strongly bonded to carbon atoms and is less reactive toward halides [18,19]. On the other hand, the Suzuki coupling reaction offers various advantages over other coupling reactions. For instance, organoboron compounds are readily available on the market, less toxic, and highly stable to heat, oxygen, and water. In addition, a wide range of reagents can react under mild conditions. Moreover, by-products can be easily isolated from the product by extraction and/or chromatography [20–22]. Thus, the Suzuki coupling reaction has been widely used in the synthesis of a variety of fine chemicals and pharmaceuticals in industrial research over several decades [23,24].



**Figure 3.** General reaction scheme for the Stille coupling reaction [25].



**Figure 4.** General reaction scheme for the Negishi coupling, where  $i\text{Bu}_2\text{AlH}$  is diisobutylaluminium hydride [23].

Before Suzuki and Miyaura discovered the palladium-catalyzed cross-coupling reaction of organoboronic acids, the cross-coupling reactions were limited to the use of magnesium-, manganese-, iron-, and nickel-based Grignard reagents as nucleophiles [26,27]. In 1976, Negishi demonstrated the efficacy of organonickel reagents as nucleophiles, while Heck observed the coupling reaction of boronic acid with an alkene in the presence of stoichiometric quantities of palladium [23]. It was in 1979, when Suzuki and Miyaura integrated Heck's and Negishi's discoveries and reported the well-known palladium-catalyzed

cross-coupling reaction between 1-alkenylboranes and aryl halides, using a palladium(0) catalyst. Since then, an enormous number of studies, including the use of nickel and copper catalysts instead of palladium catalysts, have been undertaken on the Suzuki coupling reaction to synthesize various industrially important substances.

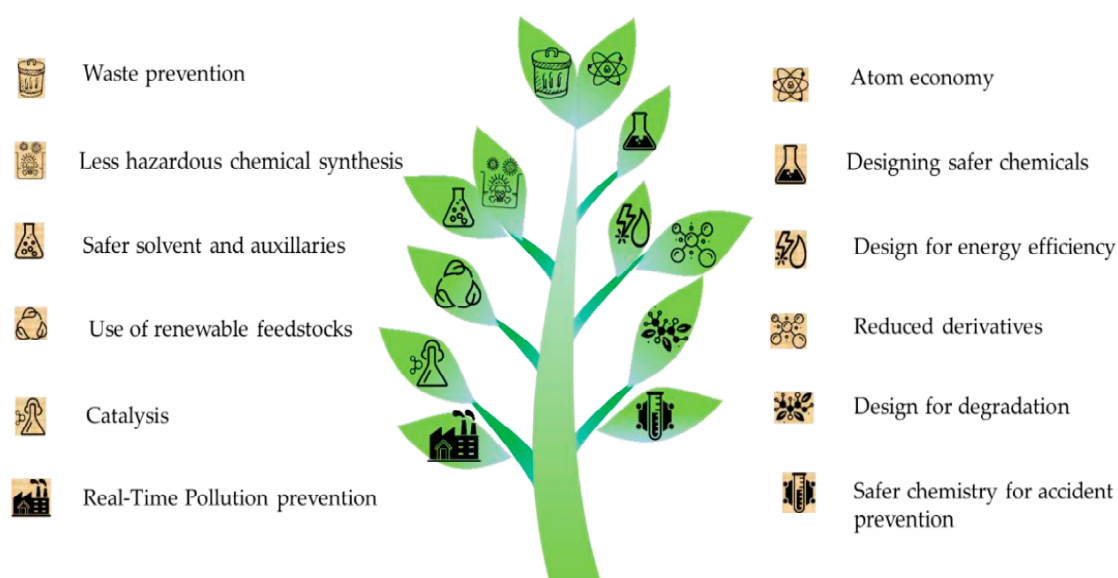
Most of these cross-coupling reactions have long relied on the use of palladium compounds as catalysts due to the superior catalytic performance and the high stability in various reaction conditions [28]. More recently, however, other transition metal catalysts, such as copper and nickel catalysts, have also been explored to develop more environmentally benign synthetic processes [29].

### 3. Sustainable Synthesis and Catalyst Recycling

#### 3.1. Green Chemistry

Despite its contribution to various organic syntheses, there are several health- and environment-related concerns associated with the Suzuki coupling reaction. One major problem is the conventional metal catalysts used in the reaction cannot be completely removed from the final pharmaceutical products, thus potentially causing health risks from the residual metals in pharmaceutical drugs. Although the residual metal content is strictly regulated by the U.S. Food and Drug Administration (FDA) and is minimized by a range of synthetic techniques and instruments that have been rapidly developed, long-term exposure to toxic metals even at low concentrations could result in physiological and neurological disfunctions [30]. In addition, the metal catalysts that can be successfully removed from the reaction media are discarded as a hazardous waste, which could cause environmental problems [31].

To resolve these issues, recent research has focused on environmentally friendly synthetic processes by encompassing the idea of green chemistry [32]. Green chemistry, as defined by the U.S. Environmental Protection Agency (EPA), is “the design of chemical products and processes that reduce or eliminate the use or generation of hazardous substances” [33]. Green chemistry comprises 12 principles (Figure 5) by following the use and generation of hazardous substances, such as toxic catalysts, that can be reduced while maximizing the product yield. Therefore, the concept of green chemistry not only navigates the industry toward more sustainable and safe manufacturing but could also bring manufacturers considerable advantages, such as reduction in production cost, faster manufacturing, production capacity increase, and energy savings [8].



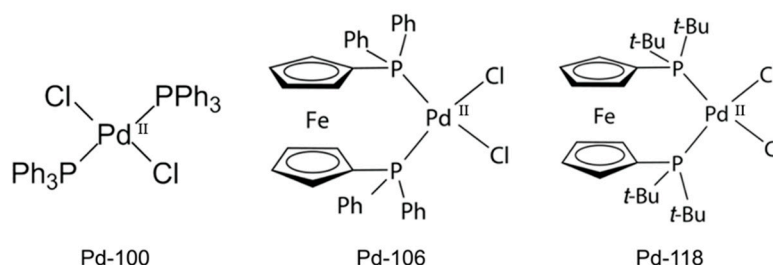
**Figure 5.** The 12 principles of green chemistry, adapted under a Creative Commons Attribution 4.0 License from [34] (p. 2) © 2019 Swaraj Rashmi Pradhan, Ramón Fernando Colmenares-Quintero and Juan Carlos Colmenares Quintero.

An example of green chemistry was demonstrated by Miyamoto et al., who developed a polychelated resin scavenger that quickly binds to residual metal particles from the Suzuki coupling reaction and separates them from pharmaceutical products [35]. The use of resin-based scavengers has paved a way to increase the purity of pharmaceutical products by almost completely removing the metal catalysts. Currently, green chemistry is considered as an essential part of pharmaceutical production, and this trend is expected to grow even further.

### 3.2. Recyclable Palladium Catalysts

A palladium catalyst is one of the most commonly used catalysts in the pharmaceutical industry [36]. However, the palladium catalyst is costly compared to other transition metal catalysts, such as nickel and copper [37]. Indeed, the price of palladium metal is EUR 1925 (approx. USD 2000.00) per mol while the price of nickel and copper metal is EUR 12.18 and EUR 4.92, respectively (approx. USD 12.00 and USD 5.00, respectively). Therefore, over the last few decades, catalyst recycling has been a key research theme to attain economical production in the pharmaceutical industry. In catalyst recycling, metal catalysts are not only removed from the reaction mixture but can also be reused in consecutive runs. Thus, catalyst recycling also offers an additional advantage in pharmaceutical production by reducing the amount of metal wastes generated during the processes.

The commonly employed catalytic systems in the Suzuki coupling reaction are based on homogeneous catalysts [38]. Homogeneous catalysts, such as a Pd-100, Pd-106, and Pd-118 (Figure 6), are the types of catalysts that are in the same phase as reactants and typically exhibit high catalytic activities because of the high degree of interaction between catalysts and reactants [29]. In practice, however, homogeneous catalysts are hardly retrievable from the reaction mixture as they are thermally sensitive and decompose at temperatures above 150 °C [39]. As such, the catalysts cannot be separable, for instance, by distillation, and catalyst recycling is usually not viable [39]. Heterogeneous catalysts, on the other hand, are in a different phase from reactants and hence, offer great benefits, such as higher thermal stability, reusability in several consequent reactions with little loss of catalytic activity, and easy separation from the reaction mixture [40]. Consequently, recyclable catalysts used in the Suzuki coupling reaction are predominantly heterogeneous catalysts.



**Figure 6.** Homogeneous catalysts: Pd-100, Pd-106 and Pd-118 [41].

There is, however, a notable challenge with heterogeneous catalysts—the leaching problem. Leaching is a phenomenon in which metal ions are released from the central core of the catalyst and results in the deactivation of the catalyst [42]. In consecutive reaction cycles, the catalysts gradually lose metal ions, which eventually leads to a total loss of catalytic activity. Leaching also causes a metal contamination in reaction products as leached metal ions are integrated into the products. As such, additional purification steps are required to remove the contaminants but could significantly increase the production cost. Therefore, the leaching problem is an immense issue in economical production and in achieving high recyclability of heterogeneous catalysts.

There are currently two major strategies to minimize metal leaching [43]. The first approach is to modify the reaction conditions, including the change of solvent types and reaction temperatures. However, this method is not practical in industrial settings because it requires the modification of reaction conditions for each run.



The second method is to employ a supporting material to stabilize palladium catalysts (Table 1). This strategy could be more viable for a large-scale production as reaction conditions can be kept unchanged in consecutive runs [44,45]. In this method, palladium particles are immobilized by supporting materials to prevent separating from the framework. A myriad of studies has been conducted to evaluate the effectiveness of supporting materials, and it is well-documented the choice of supporting materials is crucial for successful realization of a stable and reusable metal catalyst [39].

**Table 1.** Supporting materials and their recyclability.

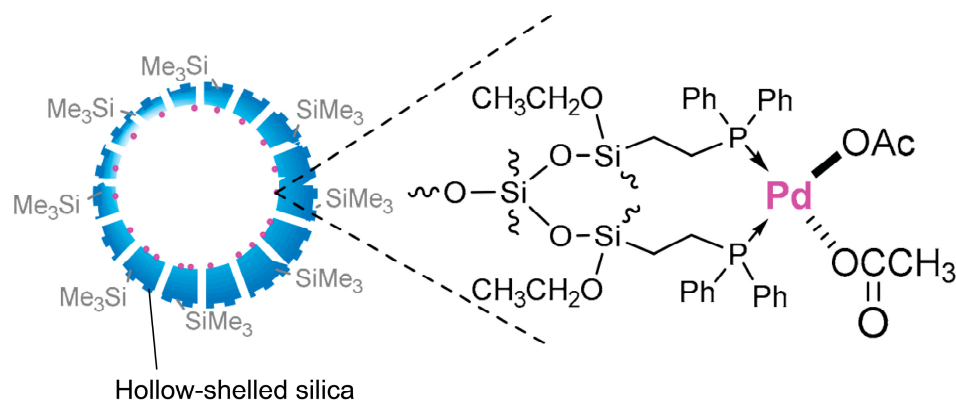
Product	Reactants		Catalyst	Recyclability	Yield (%)	Turnover Frequency * (h <sup>-1</sup> )	Turnover Number †	Reference
	Aryl Halide	Organo Borate						
4-Methoxybiphenyl	4-Iodoanisole	Phenylboronic acid	Hollow-shell-structured silica-supported Pd	≥5 runs	94% (Fresh) 90% (5th run)	93	93	[46]
4-Methoxybiphenyl	4-Iodoanisole	Phenylboronic acid	Pd/H-MOR	≥10 runs	95% (Fresh) 90% (10th run)	617	308	[47]
4-Methoxybiphenyl	4-Iodoanisole	Phenylboronic acid	TiO <sub>2</sub> supported Pd	≥5 runs	89% (Fresh) 87% (5th run)	31	124	[48]
4-Acetylbiphenyl	4'-Bromoacetophenone	Phenylboronic acid	Dioxime-functionalized Fe <sub>3</sub> O <sub>4</sub> supported Pd	≥5 runs	98% (Fresh) 93% (5th run)	50,336	839	[49]
Biphenyl	4-Iodobenzene	Phenylboronic acid	Carbon nanotube supported Pd	≥6 runs	94% (Fresh) 96% (7th run)	450	337	[50]
Biphenyl	Iodobenzene	Phenylboronic acid	Zr-UiO-66 MOF supported Pd	≥9 runs	98% (Fresh) 86% (9th run)	11,276	1879	[51]
4-Hydroxybiphenyl	4-Hydroxyiodobenzene	Phenylboronic acid	Dendrimer supported Pd	≥8 runs	98% (Fresh) 94% (8th run)	76	1523	[52]
4-Methylbiphenyl	4-Bromotoluene	Phenylboronic acid	Phytochemical supported Pd	≥7 runs	—	—	—	[53]
4-Methylbiphenyl	4-Iodotoluene	Phenylboronic acid	Silica Supported Ni	≤4 runs	76% (Fresh) 37% (5th run)	16	375	[29]
4-Methylbiphenyl	Iodobenzene	Phenylboronic acid	Carbon nanotube supported Cu	≥5 runs	90% (Fresh) 84% (5th run)	244	223	[54]

\* Calculated using the expression:  $\left(\frac{\text{Moles of product}}{\text{Moles of catalyst}}\right) \left(\frac{1}{\text{Reaction time in hour}}\right)$ . † Calculated using the expression:  $\left(\frac{\text{Moles of product}}{\text{Moles of catalyst}}\right)$ .

Silica is an inorganic porous material with high stability and accessibility as well as robust bindings to the surface of catalysts [55,56]. However, because of hindered access between catalytic sites and substrates, silica-supported catalysts have relatively poor catalytic activity [57]. To improve the affinity of catalytic sites and substrates, Mohammed et al. investigated a hollow-shell-structured silica with a homogenous space, which was isolated by a permeable shell (Figure 7) [46]. By modifying the inner wall with silane groups and cross-linking with palladium acetate, a highly effective catalytic system was realized with catalytic sites located in the inner shell. It was demonstrated this silica-based catalyst can be reused at least five times with a 90% yield in the Suzuki coupling reaction of 1-iodo-4-methoxybenzene with phenylboronic acid.

A mordenite (MOR)-supported palladium catalyst was presented by Zhou et al. [47]. MOR is one of the most versatile inorganic zeolites with high mechanical strength and is used in catalytic processes of various reactions, such as ethanol production from natural gas [58]. Due to the high surface area of palladium nanoparticle–MOR complex, MOR-supported palladium catalysts were proven to possess excellent catalytic activity and enable high yield without the presence of toxic or expensive ligands. The authors demonstrated a robust performance of the catalyst in the synthesis of crizotinib, a kinase inhibiting molecule used to treat lung cancer. Additionally, MOR-supported palladium catalysts could be prepared simply by soaking the reaction mixture (ethanol, palladium chloride, H-mordenite, and potassium hydroxide) in an ultrasonic bath for 1 hour. The reusability of the palladium nanoparticle–MOR complex was studied for the Suzuki coupling reaction of phenylboronic acid with 4-iodoanisole, where the catalyst was easily retrieved by centrifugation after the reaction and was reused up to ten times with only

a total decrease of 5% yield. The palladium nanoparticle–MOR catalyst also possesses exceedingly high catalytic performance with the turnover frequency (TOF) being more than 600 on average.

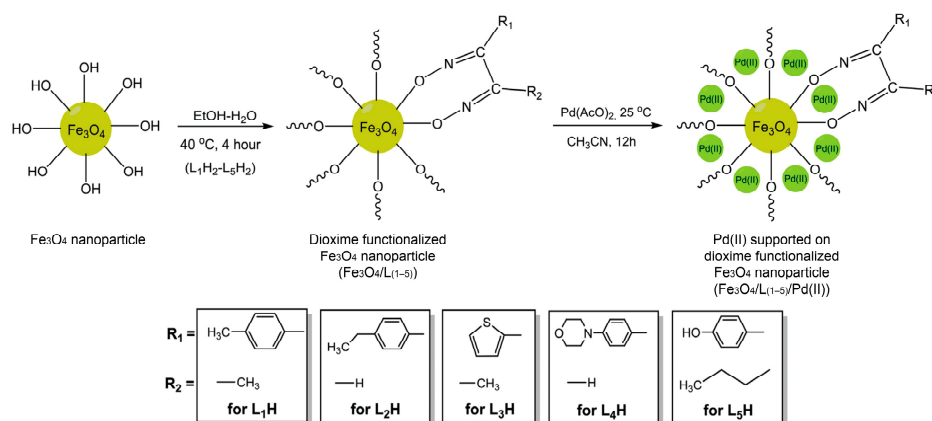


**Figure 7.** Hollow-shelled silica-supported palladium catalyst adapted under a Creative Commons Attribution 4.0 License from [46] (p. 3) © 2021 Abdulelah Taher Ali Mohammed, Lijian Wang, Ronghua Jin, Guohua Liu, and Chunxia Tan.

Koohgard et al. reported palladium nanoparticles anchored to titanium dioxide could serve as a robust catalyst for Suzuki coupling reaction [48]. Titanium dioxide is an inexpensive photocatalyst with high stability, but its ability to absorb visible light is limited. By incorporating noble metals, such as palladium, which is known to absorb visible light, they developed a light-harvesting catalytic system. Another study showed a catalyst that absorbs visible light produces energetic electrons on its surface which are then transferred to reactant molecules, resulting in a photocatalytic activation of the reaction [59]. Indeed, Koohgard's catalyst performed excellently in the Suzuki coupling reaction under visible light. Because of the high performance of the catalyst in photo-induced reactions, it is of great interest to utilize it in organic transformation reactions, such as photoredox reactions with only the catalyst and a light source, thus leading to eco-friendly synthesis. The reusability of this type of catalyst was studied for the Suzuki coupling reaction of 4-methoxyiodobenzene and phenyl boronic acid under visible light. The efficiency of photocatalytic activity was maintained at an 87% yield even after five consecutive runs, and only 0.01 wt% of palladium was leached out from the surface. Bhat et al. also developed a recyclable Pd/TiO<sub>2</sub> catalyst using cordierite monolith [60]. They first synthesized a stoichiometric ion compound, Ti<sub>1-x</sub>Pd<sub>x</sub>O<sub>2-x</sub>, ( $x = 0.01\text{--}0.03$ ), in which the Pd<sup>2+</sup> ion was dispersed into TiO<sub>2</sub>, which increased the surface area of catalytic sites. They demonstrated the high catalytic activity of the Pd/TiO<sub>2</sub> compound and proposed its industrial application by stabilizing it with a cordierite monolith framework. They coated Pd/TiO<sub>2</sub> onto a cordierite monolith and enabled its easy separation from reaction solutions in addition to the enhanced recyclability. This catalytic system showed a high recyclability upon just a few steps and little loss of catalytic activity even after seven consecutive runs.

Iron oxide metal nanoparticles are another common supporting material of palladium catalysts. Many studies have demonstrated the high catalytic activity of palladium catalysts supported on iron oxides (Fe<sub>3</sub>O<sub>4</sub> and Fe<sub>2</sub>O<sub>3</sub>) and an easy separation from the reaction mixture by utilizing external magnets [61–66]. However, because of a leaching problem, iron dioxides in their original forms cannot be recycled for another run [67]. To resolve the leaching problem, Kilic et al. modified the surface of Fe<sub>3</sub>O<sub>4</sub> with strong donor dioxime ligands (Figure 8) [49]. Multiple Suzuki coupling reactions were carried out under the presence of the palladium catalyst supported on dioxime-functionalized Fe<sub>3</sub>O<sub>4</sub> nanoparticles. The catalyst enabled the extremely short reaction time, approximately 1 minute for the reaction to complete, and hence, demonstrated its excellent catalytic performance with TOF being more than 50,000. In addition, dioxime ligands were turned out to minimize the

agglomeration of nanometals and preserve the  $\text{Fe}_3\text{O}_4$  magnetic core from over-oxidation. This results in the high recyclability of the catalyst, and a decrease of only 5% yield and the turnover number (TON) of more than 800 were observed during the five consecutive runs.



**Figure 8.** Synthesis of Pd(II) supported on dioxime functionalized  $\text{Fe}_3\text{O}_4$  nanoparticle, adapted with permission from [49] (p. 132) © 2019 Elsevier.

Carbon materials have also been studied extensively as potential candidates for supporting materials of palladium catalysts. Yet, conventional carbon materials [68] tend to suffer from drawbacks, such as a difficulty to characterize the structure by spectroscopy and various types of contaminations frequently present in carbon materials [69]. As a potential solution to overcome these drawbacks, carbon nanotubes have attracted considerable interests since they have high thermal and chemical stabilities and little contaminants. Furthermore, its exceptionally small size enables carbon nanotubes to be efficiently distributed in a solution and to have greater interactions with reagents, making it an effective catalyst supporting material for organic reactions.

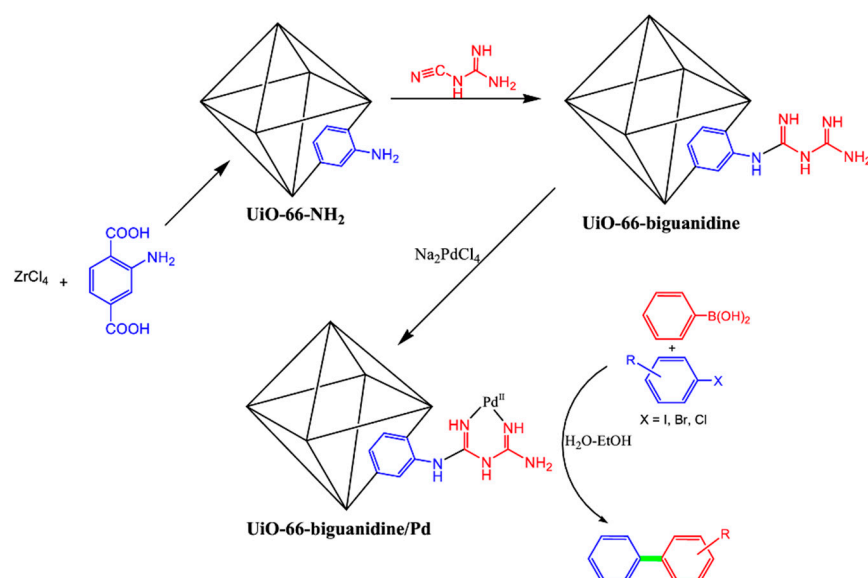
Pan et al. demonstrated the potency of the carbon nanotube by preparing carbon nanotube-supported palladium catalyst that could be easily characterized by transmission electron microscopy [50]. The authors utilized the catalyst in the Suzuki coupling reaction and demonstrated the high catalytic performance with the reaction yield being 94% and TOF being more than 400 on average. The recyclability was also confirmed that almost no decrease of yield was experimentally observed even after the sixth run, although the significant metal leaching was observed after the sixth run.

However, many of the carbon nanotube-supported metal catalysts require an isolation from the reaction mixture through particular nanofilters, which results in a costly operation [69]. To solve this challenge, Desmecht et al. introduced magnetic iron oxide nanoparticles onto the surface of the catalyst complex which enabled facile separation upon magnetic treatments. Although further experiments are expected, the authors predicted this catalytic system could be reused for multiple runs similar to carbon nanotube-supported metal catalysts.

Metal organic frameworks (MOFs) have also been examined for immobilization of palladium nanoparticles. MOF is a coordination network with organic ligands containing potential voids, where active catalytic sites can be immobilized [70]. Furthermore, MOF is a highly stable compound at a high temperature, and its physical properties are easily modifiable by changing the metal species [71]. Thus, the use of MOF as a supporting material of metal catalysts has recently been spotlighted in catalyst recycling.

Veisi et al. have utilized Zr-Uio-66 MOF bearing a high chemical stability to prepare a MOF supported Pd catalyst, Uio-66-biguanidine/Pd (Figure 9) [51]. The prepared catalyst was tested in the Suzuki coupling reaction, and it showed a reaction time as short as 10 min. This led to high TOF being more than 10,000 on average in the reaction. The reusability was also demonstrated to be prominent in the Suzuki coupling reaction, and the catalyst could be used for nine runs without considerable decreases in reaction yields.





**Figure 9.** Sequential synthesis of UiO-66-biguanidine/Pd nanocomposite catalyst, adapted under a Creative Commons Attribution 4.0 License from [51] (p. 2) © 2021 Hojat Veisi, Mozhddeh Abrifam, Sheida Ahany Kamangar, Mozghan Pirhayati, Shokoufeh Ghahri Saremi, Mohammad Noroozi, Taiebeh Tamoradi, and Bikash Karmakar.

Peng et al. recently incorporated ethylenediaminetetraacetic acid (EDTA) into MOF to develop a tightly bound catalytic system benefited with an additional stabilization [72]. EDTA is a strong chelating compound with six binding sites and can encapsulate a variety of metal species due to its large coordination number. The EDTA-metal complex was thus grafted in the MOF network to create a robust catalytic system that performed competently with more than 20 different metal ions. The catalyst also exhibited excellent catalytic activity for the Suzuki coupling reaction, with the reaction yield being up to 99% and excellent efficiency in catalyst removal.

Dendrimers are highly branched macromolecules with an ability to encapsulate metal nanoparticles and hence, can stabilize metal nanoparticles for recycling. The dendrimer's branches are also used to physically control the access of reagents and to achieve chemoselectivity in organometallic reactions [73]. Furthermore, the terminal groups of dendrimers can be easily manipulated to have desired solubility in organic or aqueous solvent systems [74], which makes them prominent in separation and recycling in multiple reaction cycles. Wu et al. utilized phosphine ligands to further stabilize and activate the dendrimer-palladium catalysts and successfully catalyzed Suzuki coupling reactions with only 4% of decrease in yield for eight cycles and with little metal leaching [52,75]. However, the reactions were slightly sluggish and required 20–48 h of reflux, which resulted in comparably low TOFs.

Palladium nanoparticle catalysts are typically prepared using toxic and expensive chemicals under high pressure and temperature in opposition to the recent trend in green chemistry [76]. To incorporate the idea of green chemistry into the synthesis of recyclable palladium nanoparticle catalysts, Veisi et al. developed a novel palladium catalyst, using naturally derived phytochemicals [53]. Phytochemicals, such as *Argemone mexicana* leaf extracts, are compounds produced by plants and are known to mediate the reduction of metal ions into nanoparticles through green pathways [77,78].

Phytochemicals can also stabilize metal nanoparticles by modifying the physicochemical properties of metal nanoparticle clusters, highlighted as an excellent supporting material of palladium nanoparticles. For instance, Veisi et al. utilized *R. canina* fruit extract as a reducing and stabilizing agent to prepare the palladium catalyst under mild reaction conditions in the absence of toxic ligands [53]. Furthermore, the prepared catalyst was used

for the Suzuki coupling reaction for seven cycles and was shown to be highly stable and efficient in catalytic reactions.

### 3.3. Recyclable Nickel Catalysts

Although palladium is the most common metal catalyst in the Suzuki coupling reaction, recent studies also spotlighted the use of nickel as a sustainable alternative to palladium. Nickel is not only more affordable and earth-abundant than palladium [37,79], but equally importantly, it has unique oxidation states (i.e., Ni(0)/Ni(II) or Ni(I)/Ni(III)) that inherit distinctive catalytic properties [80]. Yet, similar to palladium catalysts, leaching is also a major concern for nickel catalysts, and therefore, supporting materials, such as those introduced for palladium catalysts, are required to stabilize nickel catalysts for recycling [29,52,75,81,82].

There are several drawbacks with the nickel catalysts for the Suzuki coupling reaction. Firstly, a high catalyst loading is typically required to achieve a high yield due to lower catalytic activity of nickel [29]. The reaction normally requires 5–10 mol% of nickel catalyst loadings [29], while the reaction can be achieved with 0.5–2 mol% of palladium catalyst loadings [83]. Thus, the drawback could not only offset the inexpensive aspect but also lead to an unwanted nickel contamination in reaction products if the high catalyst loading is employed [29,84]. In addition, the nickel catalyst cannot catalyze the reactions that produce hetero-biaryl molecules, and consequently, applicability in the pharmaceutical industry is largely limited [79]. Moreover, the catalytic performance significantly decreases when certain supporting materials are used. For instance, Key et al. reported a nickel catalyst supported onto silica lost its yield in half only after the fourth consecutive run of the Suzuki coupling reaction [29]. This phenomenon occurred presumably because nickel catalysts are prone to undergo a more significant leaching than those based on palladium when particular porous materials, such as silica, are used. Because of this susceptibility to the choice of supporting materials, nickel catalysts are less preferred than palladium-based catalysts in current industrial practices.

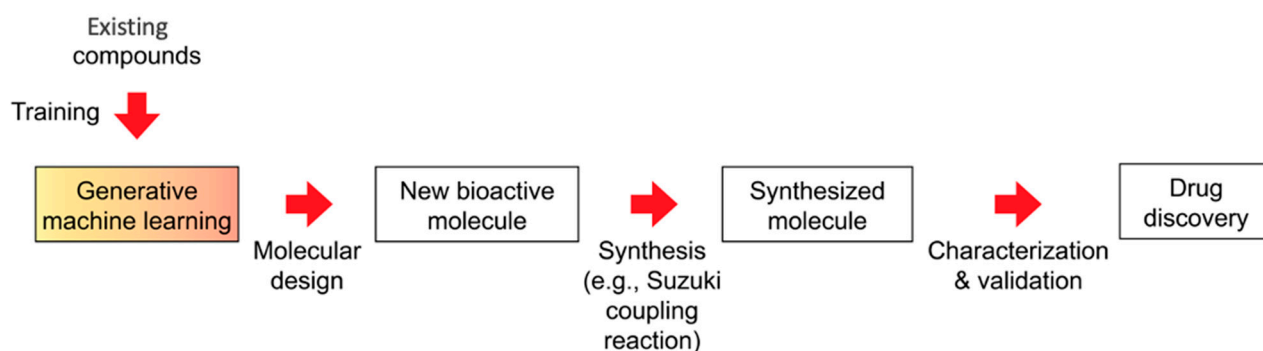
### 3.4. Recyclable Copper Catalysts

Copper is another low-cost alternative metal catalyst and could have a lower toxicity than palladium [85]. Copper exhibits a unique reactivity in organic reactions; numerous copper-catalyzed cross-coupling reactions were reported to proceed even in the absence of a ligand [86,87]. Although the recyclability of copper catalysts is still under development, Akbarzadeh et al. demonstrated a copper catalyst supported onto carbon nanotube to exhibit excellent recyclability in the Suzuki coupling reaction [54]. Magnetic carbon nanotubes were utilized as a supporting material of copper to add stabilization as well as magneticity and hence, was easily separable from the reaction solution by an external magnet. In the study, the copper catalyst was tested for recyclability in the Suzuki coupling reaction and evidenced to catalyze the reaction for five consecutive cycles with only a 6% decrease in reaction yields, where an elemental analysis confirmed negligible metal leaching even after the fifth cycle.

## 4. Suzuki Coupling and AI: Toward a Greener Synthesis in the Pharmaceutical Industry

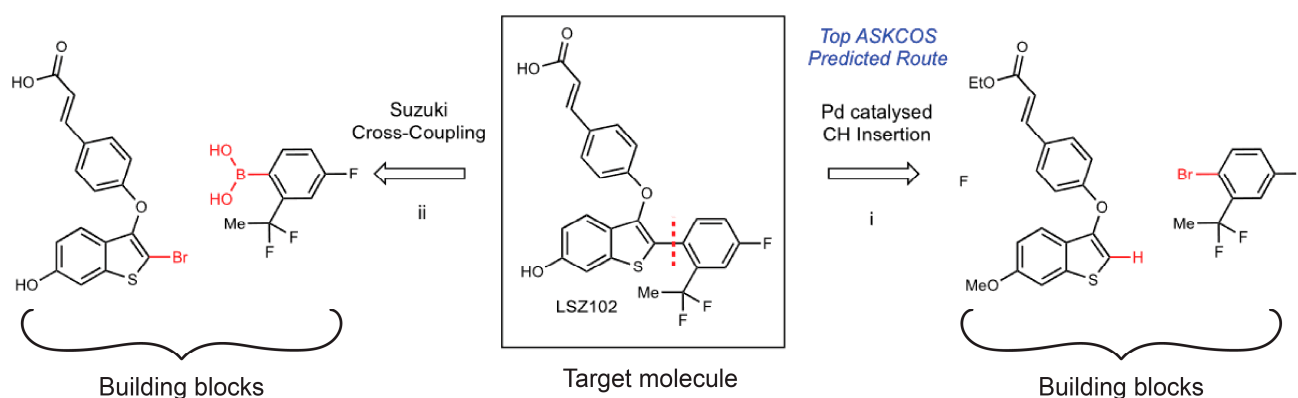
Artificial intelligence (AI) is a field of study that aims at developing machines capable of performing challenging tasks with little or no human intervention [88]. This can be realized, for instance, by engrafting the machine with an ability to learn on its own—by directly looking at the data, computers automatically identify the useful rules [89]. This specific subset of artificial intelligence is termed machine learning and has been extensively applied for a variety of purposes in the pharmaceutical industry. For instance, new compounds with desired properties can be designed by machine learning of datasets of existing materials. As shown in Figure 10, such a technique, called generative machine learning, is

expected to assist drug discovery to a large extent [90] but could also lead to discovery of a novel recyclable catalyst for the Suzuki coupling reaction.



**Figure 10.** Concept of generative machine learning for drug discovery proposed by Merk et al. in 2018, redrawn from [90] (p. 1).

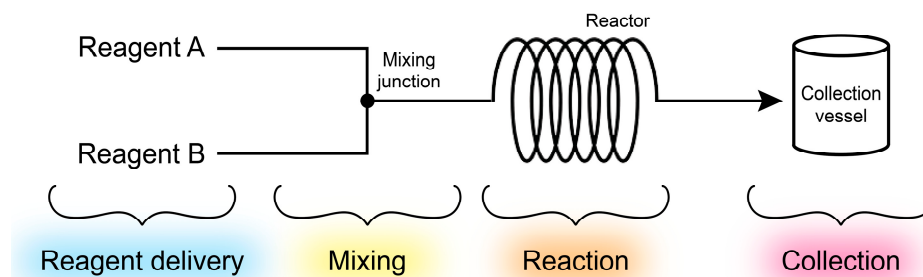
Machine learning can also be applied for retrosynthesis and synthesis planning of various bioactive molecules. For instance, Struble et al. investigated machine learning-based prediction of building blocks of a selective estrogen receptor degrader (LSZ102) and successfully determined valid synthetic routes, as shown in Figure 11 [91]. Optimization of reaction conditions, including the reaction temperature and catalyst loading, was examined by Fu et al. for the Suzuki coupling reaction of various molecules, and it was reported the machine-learning technique successfully identified the optimal reaction conditions for both modeled and unseen reactions [92].



**Figure 11.** Retrosynthetic predictions for a bioactive molecule (LSZ102) by machine learning: (i) C–H insertion and (ii) C–H insertion, adapted under a Creative Commons Attribution 4.0 License from [91] (p. 8674) © 2020 American Chemical Society.

Another vital application of machine learning lies in the domain of continuous flow systems. A continuous flow system is defined as an array of chemical processes performed in a continuously flowing stream [93]. A typical continuous flow system consists of pumps that send reagents, a mixing junction to blend the reagents, a reaction coil (reactor) with an appropriate length for the reaction to complete, and a vessel for collection (Figure 12) [94]. In contrast to conventional static batch systems, continuous flow reactors have advantages, such as better reaction control and easy scalability. For instance, because solutions of reagents are fed by pumps, various parameters, such as reaction pressure and residence time, can be easily controlled by a computer to maximize the yield [95]. In addition, inherent scalability is another notable merit for the industry—the continuous flow technology does not require re-optimization of critical reaction parameters and allows multistep reactions to be combined into a telescoped one-flow sequence [95,96]. From the viewpoint of green chemistry, continuous flow systems could also be a preferred choice over the conventional

static reactors as toxic and corrosive reagents and intermediates remain inside a closed system [97]. Moreover, because of significantly less purification and work-up issues, continuous flow systems could generate less waste.



**Figure 12.** Key elements of a continuous flow system, redrawn from [94] (p. 11).

There are, however, notable challenges with the current continuous flow technology. For instance, optimization of chemical reactions for continuous flow systems is laborious as there are many simultaneous objective functions, such as reaction yield, process cost, impurity levels, and environmental impact [98]. To circumvent these hurdles, Schweidtmann et al. examined a multi-objective machine-learning technique [98]. By employing exemplar chemical reactions, self-optimization of chemical reactions was successfully demonstrated with good compromise between multiple performance criteria.

Another considerable challenge with continuous flow systems is on the catalyst recyclability. In a continuous flow system, a heterogeneous catalyst is placed in a packed-bed reactor, and the reaction solution is pumped through the reactor [99]. Thus, the reaction and the separation of the catalyst take place simultaneously. To continuously operate the system without retrieval of deactivated catalysts, the use of reusable catalysts, such as those discussed in Sections 3.2–3.4, is crucial. However, because catalysts are continuously exposed to the reaction solution, metal components gradually separate from the catalytic framework, eventually leading to deactivation. This problem could become even more significant in large-scale manufacturing with a higher flow rate. Therefore, development of exceptionally durable (recyclable) catalysts is imperative to achieve a more efficient continuous flow process and its application in the pharmaceutical industry.

## 5. Future Perspectives

Over the last few decades, a tremendous number of studies have been conducted to explore highly effective and reusable catalytic systems for the Suzuki coupling reaction. The catalytic systems reviewed in this paper were a handful of highlights in the recent progress, and there are more new catalysts developed daily.

Many of the reviewed catalysts were reported to exhibit excellent catalytic activity, easy removal upon a simple separation technique, and high recyclability. However, one common drawback is a high concentration (e.g., 0.5–10 mol%) of metal catalyst was typically required to complete a conversion in most of the reactions outlined in this review. This contradicts with industrial requirements where low catalyst loading is essential to reduce the production cost, waste generation, and health- and environment-related risks. In this respect, future work is recommended to develop a recyclable catalyst with enhanced catalytic activity to lower the catalyst loading.

In the context of continuous flow synthesis, further improvement of durability of recyclable catalysts is another crucial future research topic. As reviewed in Section 4, catalysts are ceaselessly exposed to reaction solution in a continuous flow reactor, and therefore, improvement of catalyst durability is of paramount importance for uninterrupted production.

With respect to AI and machine-learning techniques, which have demonstrated a potential role in predictive chemistry and synthesis planning, one latent challenge is the currently available data sets are severely biased toward factors, such as individual ex-

periences of researchers and immediate availability of reagents [100,101]. In addition, reaction databases contain reactions with high yields, but only a handful of negative examples of low-yielded or failed reactions are available [100,102]. In view of these biasing factors, electronic laboratory notebooks, which contain innumerable unproductive but invaluable reactions were proposed to lift the bias from databases [100,103]. However, because electronic laboratory notebooks are not readily available in public or even commercial databases, the limitation of data sets have largely precluded the versatility of machine-learning techniques until now [100]. Therefore, it is recommended to develop a data augmentation strategy, whereby databases are, for instance, supplemented with chemically plausible, negative, and unbiased examples [100,101].

## 6. Conclusions

Suzuki coupling reaction is an industrially indispensable, transition metal-catalyzed C–C forming reaction that has played a central role in the synthesis of various bioactive molecules. However, in the conventional Suzuki coupling process, the costly metal catalyst is not only discarded after a single use as it loses catalytic activity but may also be incorporated into the final product as complete removal is hardly achievable. Hence, it has been evident the development of a novel recyclable catalytic system is of great importance to minimize health and environmental risks as well as to lower the production cost. One of the most promising approaches to develop such catalysts is with supporting materials that prevent metal leaching. In this paper, various types of supporting materials were reviewed, including silica, MOR, titanium dioxide, iron oxides, carbon nanotubes, MOFs, dendrimers, and phytochemicals along with their recyclability. Benefits, challenges, and recent applications of nickel and copper catalysts were also reviewed as sustainable and low-cost alternatives to palladium catalysts. This paper then discussed how AI could expedite green synthesis of pharmaceutical products, followed by challenges of ongoing progress and future directions.

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