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Recent advances in palladium-catalysed organic synthesis using water as solvent

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ABSTRACT

Palladium catalysis is regarded as a significant tool for the construction of carbon-carbon and carbon-heteroatom bond in organic synthesis. Thus the sustainable development of this type of transformations, especially designing properly, clean chemical technology, is of great importance. Recently, water as a reaction medium has been developed in both academic laboratories and in the industry, improving the reaction activity and selectivity of the organic reaction through its own properties (such as polarity, high dielectric constant). This review focuses on palladium-catalysed organic synthesis using water as solvent, summarizing relevant articles published from 2015 to 2025. Meanwhile, mechanistic studies, supported by experimental investigations, are thoroughly reviewed to elucidate the interplay between water and palladium species in facilitating bond-forming processes. Furthermore, practical applications of these aqueous-phase methodologies in the synthesis of complex natural products and pharmaceutical intermediates are showcased, underscoring their potential for scalable and sustainable chemical manufacturing.

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1. Introduction

Over the past several decades, the construction of carbon-carbon and carbon-heteroatom bonds through the application of green and sustainable strategies has emerged as a potent and indispensable approach within both academic research laboratories and industrial settings. Among various reaction media, water has evolved into a highly effective medium owing to its cost-effectiveness, safety, and environmental friendliness. water possesses inherent properties, such as polarity and a high dielectric constant, which can enhance the reaction rates by facilitating the interaction between the reactants and the palladium catalyst [1–4]. Furthermore, water can form hydrogen bonds with reactants, intermediates, and the catalyst itself. This can stabilize transition states and intermediates, potentially lowering activation energies and increasing reaction rates. In addition, water can hydrate the palladium catalyst, forming a hydration shell around the metal center. This can stabilize the catalyst and prevent it from aggregating or deactivating. Since the 1980s [5], significant advancements have been made in utilizing water as a reaction medium. Notably, transition metal-catalysed organic synthesis in the aqueous phase has become one of the most efficacious and pivotal strategies for synthesizing a wide array of agrochemicals, natural products, pharmaceuticals, and polymers. Undoubtedly, the adoption of water as a reaction medium plays a pivotal role in the development of green and sustainable chemistry, promoting the transition towards more environmentally benign synthetic methodologies.

However, a key limitation of aqueous media in organic reactions is the poor solubility of organic substrates and reagents. To overcome this challenge, surfactants such as polyoxyethanyl-α-tocopheryl sebacate (PTS) or TPGS-750-M are employed. These amphiphilic compounds spontaneously assemble into micelles driven by the hydrophobic effect. In this configuration, the hydrophobic moieties are shielded from the polar aqueous environment, while the polar head groups of the surfactants interact with water, thereby minimizing unfavorable interactions. Additionally, a common strategy reported in the literature for aqueous-phase catalytic systems involves the use of phase-transfer catalysts, amphiphilic molecular additives, or the modification of catalysts to locally aggregate organic substances (fragments) in the aqueous phase, creating a hydrophobic microreactive environment. For reactions involving non-activated organic substrates, the acidity strength of the catalyst often dictates whether the reaction can proceed smoothly. Therefore, it is of significant importance to stabilize and "protect" strong acid sites in water by leveraging the hydrophobic effect of organic fragments.

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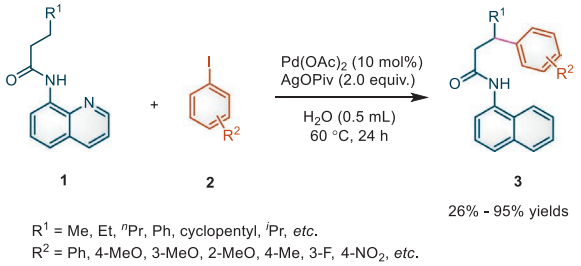
Palladium-catalysed organic synthesis represents one of the most crucial synthetic tools developed in recent decades, attributed to its excellent tolerance of functional groups and compatibility with polar protic solvents. Within this context, water, which was first employed as a reaction medium for synthesizing indigo in 1866 [6] and subsequently utilized to accelerate the Diels-Alder reaction and enhance selectivity in 1980, has been widely recognized as an efficient and environmentally benign solvent in palladium catalysis. To date, palladium-catalysed aqueous reactions have been extensively applied in cross-coupling, amination, C–H activation, cyclization, among others, demonstrating, in some instances, superior reaction activity and selectivity compared to organic solvents [7–10]. Moreover, palladium-catalysed aqueous reactions are also extensively employed for the green and efficient construction of bioactive compounds (*e.g.*, indoles, nucleobases, and their non-natural analogs) [11,12].

Against this backdrop, this review summarizes the most recent significant advances in Pd-catalysed aqueous reactions from 2015 to late 2025. To facilitate a comprehensive understanding and future development of novel reactions, this review is organized by reaction types, encompassing C–H activations, cross-coupling reactions, annulation reactions, amination reactions, hydrocarboxylation reactions, Tsuji-Trost reactions, alkylation reactions, cyanation, and asymmetric catalysis. To our knowledge, few reviews have systematically summarized these advancements, despite the existence of reviews focusing solely on palladium-catalysed cross-coupling reactions and organic synthesis in the aqueous phase [7–12]. Thus, a timely review is urgently needed given the current vigorous development of palladium-catalysed aqueous organic chemistry. The comprehensive information presented in this review is expected to inspire chemists from both academia and industry to design novel, efficient, and sustainable synthetic processes. By leveraging the unique properties of water as a reaction medium and the versatility of palladium catalysis, future research endeavors hold the promise of further advancing the field of green and sustainable chemistry.

2. Palladium-catalysed C–H activations in aqueous phase

Palladium-catalysed C–H activation has emerged as a formidable and versatile tool for enhancing molecular complexity in organic synthesis, offering improved efficiency and selectivity [13–16]. Despite the notable progress in Pd-catalysed C–H bond functionalization, the majority of these reactions continue to rely on organic solvents. In recent decades, the advent of the "green chemistry" paradigm has underscored the necessity for conducting chemical reactions under conditions characterized by low energy consumption (*e.g.*, avoiding high temperatures) and minimal environmental pollution (*e.g.*, reducing the utilization of toxic reagents). Consequently, palladium-catalysed C–H functionalizations in aqueous media have garnered increasing attention from organic chemists. Several strategies for the direct functionalization of aromatic and heteroaromatic rings in pure aqueous phase have been sequentially reported, showcasing the potential of water as a sustainable reaction medium.

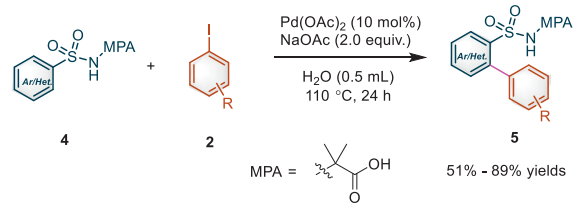
In 2005, Sharpless [17] and his colleagues introduced the "on-water" concept, highlighting two critical parameters: reaction rate and the insolubility of substrates in water. This innovative approach has since sparked heightened interest in exploiting water as a reaction medium for the synthesis of both simple and complex molecules. Subsequently, the research groups of Lipshutz [18] and Larrosa [19] independently reported the direct arylation of amides and indole rings, respectively, utilizing aryl iodides as the aryl source in aqueous phase catalysed by $Pd(OAc)_2$. These pioneering studies underscored the feasibility and efficiency of palladium-catalysed C–H functionalizations using water as solvent.



Scheme 1. Palladium-catalysed arylation of C(sp^3)-H bonds of carbonyl β-position in water.

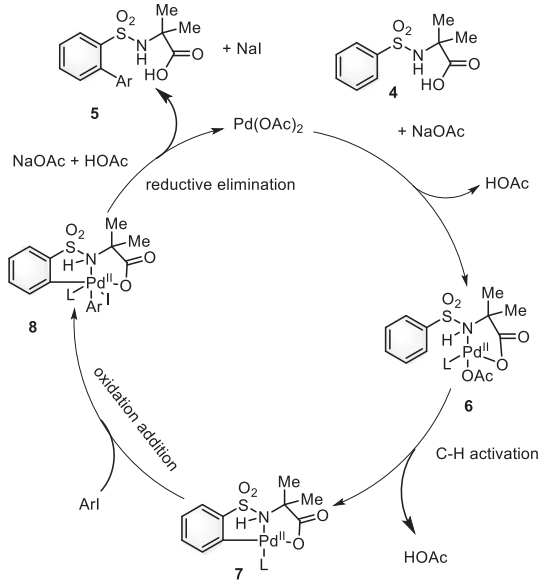
Compared to the extensive research on C(sp^2)-H activation reactions in aqueous media, reports on aqueous β-C(sp^3)-H arylation reactions under mild conditions remain scarce. In 2014, Chen and coworkers reported a palladium-catalysed direct C(sp^3)-H arylation of the terminal methyl group of amino acids, employing a tetrachloroethane/water mixed solvent system [20]. This study represented a significant step forward in expanding the scope of C–H functionalization to sp^3-hybridized carbon centers. In 2016, Zhou and colleagues further advanced this field by utilizing N-protected 8-aminoquinoline and aryl iodides as reactive substrates, $Pd(OAc)_2$ as the catalyst, and AgOPiv as an iodine quencher in water at 60 °C. This protocol successfully afforded the desired β-arylation products with yields ranging from 26% to 95% [21]. Detailed condition optimization revealed that the choice of silver salt, reaction temperature, and $Pd(OAc)_2$ loading significantly influenced the reaction yield. However, the inability to obtain the desired product using aryl bromides indicated that this system was primarily limited to aryl iodides (Scheme 1). In conclusion, the exploration of palladium-catalysed C–H functionalizations in aqueous media represents a promising avenue for the development of green and sustainable organic synthesis. While significant strides have been made in C(sp^2)-H activation, further research is warranted to expand the scope and efficiency of aqueous β-C(sp^3)-H arylation reactions. The continued refinement of reaction conditions and the discovery of novel catalytic systems hold the potential to unlock new synthetic pathways and enhance the sustainability of organic chemistry.

Almost concurrently, Chen and his research team documented a palladium-catalysed mono-selective *ortho* C–H arylation of aryl sulfonamides in an aqueous environment [22]. In this seminal work, the authors elucidated that the sulfonamide moiety could effectively serve as a directing group, facilitating the activation of C–H bonds within aromatic systems. It was particularly noteworthy that, although these reactions proceed efficiently in organic solvents, the methodology demonstrated markedly enhanced efficiency when conducted in water, outperforming its organic solvent counterparts. The reaction exhibited excellent tolerance to various functional groups and proceeded with high regioselectivity, specifically targeting the *ortho* position relative to the sulfonamide sulfur atom in arenes. An added advantage of this approach was the ease with which the auxiliary sulfonamide group could be removed post-reaction, either through acidic hydrolysis or converted into primary biaryl sulfonamides employing 30 mol% CuO as a catalyst. This versatility enhanced the synthetic utility of the method, allowing for straightforward modification of the product. Mechanistic investigations revealed that the bidentate nature of the sulfonamide directing group plays a pivotal role in promoting *ortho* C–H bond activation in arenes linked to sulfonamide sulfur atoms. The chelating effect of the sulfonamide group with the palladium catalyst stabilizes the transition state, thereby lowering the activation energy and enhancing the reaction rate (Scheme 2). This finding underscores the importance of directing group design in facilitating selective C–H functionalization reactions.



Ar/Het. = Ph, 4-MeOC$_6$H$_4$, 2-thiethyl, 4-NO$_2$C$_6$H$_4$, 4-CF$_3$C$_6$H$_4$, 3-MeC$_6$H$_4$, 2-ClC$_6$H$_4$ *etc.*
R^2 = 4-Me, 4-MeO, 4-CF$_3$, Ph, 4-Br, 4-Cl, 3-F, 3-Me, 4-CN, 4-NO$_2$, *etc.*

Scheme 2. Palladium-catalysed mono-selective *ortho* C–H arylation of aryl sulfonamides in water.

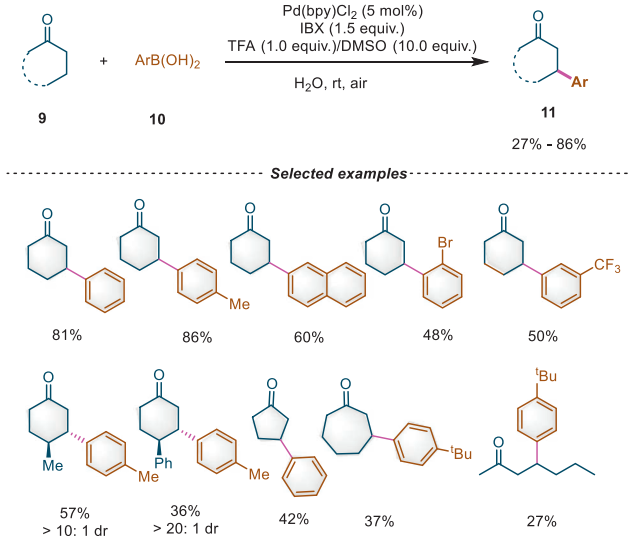


Scheme 3. A possible mechanism for palladium-catalysed mono-selective *ortho* C–H arylation of aryl sulfonamides.

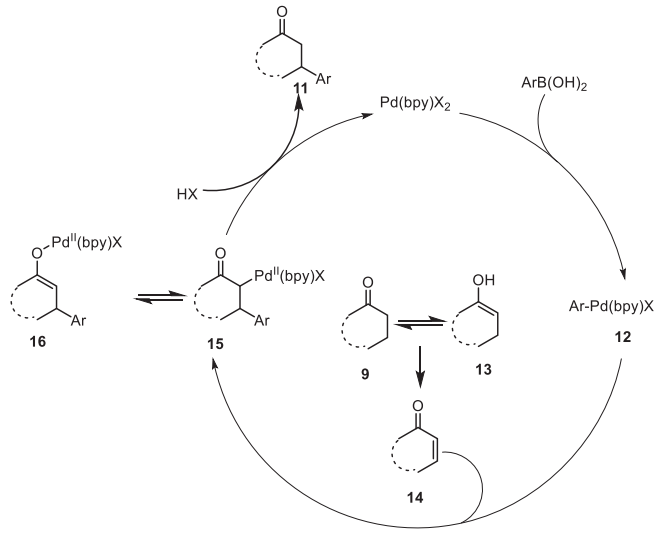
The control experiment observed low KIE value (KIE value of 1.2), which suggested that the C–H bond cleavage step was not involved in the turn-over-limiting step. Based on these, the authors proposed a plausible reaction mechanism. As outlined as Scheme 3, substrate **4** coordinated to Pd(OAc)$_2$, then underwent ligand exchange to form palladium complex **6**. This complex underwent cyclopalladation *via* C–H cleavage to produce Pd^{II} intermediate **7**. Intermediate **7** reacted with an aryl iodide through oxidative addition, followed by reductive elimination to yield the arylation product **5** and regenerate the palladium catalyst.

Carbonyl groups and their adjacent α-hydrogens are highly susceptible to functionalization owing to their inherent electrophilicity and acidity. However, the direct β-functionalization of carbonyl compounds has long posed a significant challenge in organic synthesis due to the relatively inert nature of β-C-H bonds and the lack of effective directing groups or activation strategies. In 2017, Li and coworkers made a breakthrough by developing a direct β-C-H arylation of ketones under exceptionally mild conditions in aqueous solution [23]. This innovative methodology leverages the synergistic action of readily available *o*-iodoxybenzoic acid (IBX) as an oxidant and arylboronic acids as nucleophilic reagents. The reaction proceeds smoothly in water, eliminating the need for harsh conditions or toxic organic solvents, and provides a concise and efficient route to access β-arylated ketones in good to excellent yields (Scheme 4).

The authors proposed a tentative mechanism [24]: Initially, enolization of ketones catalysed by acids occurred, and the enol reacts with IBX to form α,β-unsaturated ketones [25]. Subsequently, Ar-[Pd] was generated through transmetalation of the aryl group from arylboronic acids to palladium, which then reacts with the C=C bond of the α,β-unsaturated ketones to produce palladium enolate **13**. Finally, protonolysis of **13** yielded the desired β-arylated ketone and regenerates the Pd catalyst (Scheme 5). The key to the success of this method lies in the careful selection of reaction components and conditions. IBX serves as a mild yet effective oxidant, facilitating the *in-situ* generation of a reactive intermediate that enables β-C-H bond activation. Arylboronic acids, on the other hand, act as nucleophilic partners, undergoing transmetalation with palladium and subsequent reductive elimination to form the desired β-arylated products. The aqueous environment not only enhances the reaction efficiency but also simplifies the workup procedure, making the process more environmentally friendly.

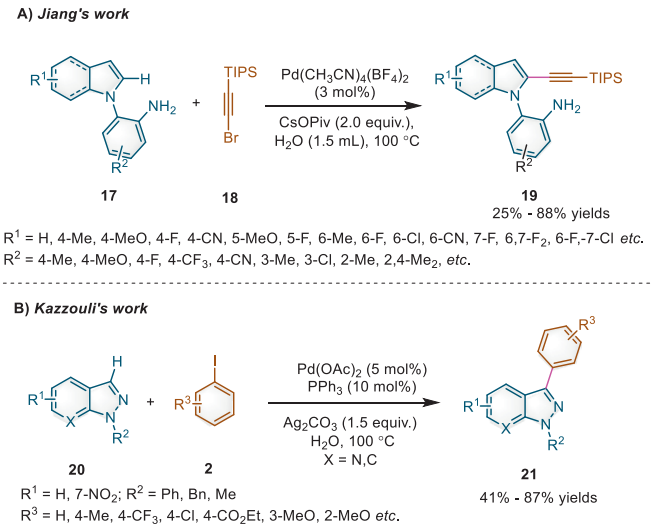


Scheme 4. A direct β-C-H arylation of ketones under very mild conditions in aqueous solution.

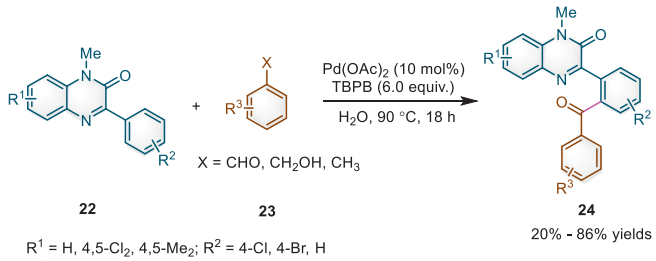


Scheme 5. A possible mechanism for palladium-catalysed β-C-H arylation of ketones.

Indoles, a class of heterocyclic compounds with profound bioactivity, have garnered extensive attention in organic synthesis due to their diverse potential applications in pharmaceuticals, agrochemicals, and materials science. The derivatization of indoles, particularly through selective C–H bond functionalization, remains a



Scheme 6. Pd(II)-catalysed C–H activation of indoles.



Scheme 7. Regioselective C–H acylation of quinoxalin-2(1*H*)-one derivatives.

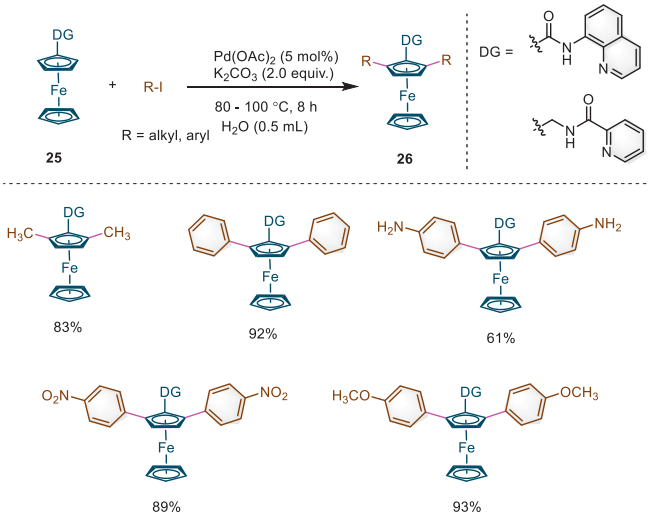
pivotal area of research aimed at enhancing their structural complexity and biological properties.

In 2019, Jiang and coworkers achieved a significant breakthrough by developing a highly regioselective Pd(II)-catalysed C–H activation/alkynylation reaction at the C2 position of indoles using bromoalkynes in water [26]. This methodology capitalized on the directing ability of a primary amine group appended to the indole scaffold, which guided the palladium catalyst to selectively activate the C2-H bond. The reaction proceeded with excellent regioselectivity, favoring the C2 position over other potentially reactive sites. Moreover, it exhibited broad substrate compatibility, accommodating a variety of indole derivatives with different substituents. The scalability of this protocol was demonstrated by its successful application to gram-scale synthesis, highlighting its potential for industrial-scale production. Further transformations of the alkynylated products underscored the synthetic utility of this approach, enabling the straightforward synthesis of four distinct derivative products. Notably, the transformation achieved high chemoselectivity, favoring C–C bond formation over competing C–N bond formation pathways. The presence of a free amine group in the product also facilitated subsequent structural modifications and diversification, expanding the scope of possible derivatives. Importantly, water served as the sole reaction medium, aligning with the principles of green chemistry by providing an environmentally benign, sustainable, and safe solvent alternative (Scheme 6A).

In a parallel advancement, Kazzouli and coworkers in 2020 reported an efficient method for the synthesis of a series of C3-arylated 1*H*-indazoles and C3-arylated 1*H*-7-azaindazoles in good yields, utilizing water as the solvent for the C3 direct arylation reaction [27]. This work further expanded the repertoire of C–H functionalization reactions in aqueous media, demonstrating the versatility of water as a reaction solvent for diverse heterocyclic systems. The methodology leveraged the inherent reactivity of the indazole and azaindazole scaffolds, enabling the selective introduction of aryl groups at the C3 position. The use of water as the solvent not only simplified the reaction workup but also contributed to the overall sustainability of the process (Scheme 6B). Simultaneously, Wu and coworkers reported an efficient palladium-catalysed direct Hiyama coupling reaction of quinoxalin-2(1*H*)-ones with aryl siloxanes [28]. Although not directly related to indole derivatization, this work exemplified the growing trend of developing palladium-catalysed C–C bond-forming reactions in aqueous media. The Hiyama coupling, a variant of cross-coupling reactions, provided an alternative route to access aryl-substituted heterocycles, complementing existing methodologies. The use of aryl siloxanes as coupling partners offered advantages in terms of stability and handling compared to traditional organometallic reagents.

Compared to the traditional Friedel-Crafts acylation, which often necessitates harsh acidic conditions, pre-functionalization of substrates, and generates significant amounts of waste, transition metal-catalysed direct C–H acylation has emerged as a highly attractive and sustainable alternative in contemporary organic synthesis. This approach is particularly valued for its superior atom economy, streamlined synthetic pathways (fewer steps), precise control over regioselectivity, and compatibility with readily available and inexpensive aroyl surrogates, thereby reducing reliance on costly or hazardous reagents [29–32]. In 2022, Singh and coworkers made a significant contribution to this field by developing an eco-friendly and sustainable method for the regioselective C–H acylation of quinoxalin-2(1*H*)-one derivatives [33]. Their innovative protocol utilized water as the reaction solvent and $Pd(OAc)_2$ as the catalyst, aligning perfectly with the principles of green chemistry. The reaction proceeded smoothly with a variety of commercially available aroyl surrogates, including aldehydes, toluenes, and benzyl alcohols, affording the desired monoacylated products in moderate to good yields (20%–86%). This methodology boasts several key advantages. Firstly, it exhibits a broad substrate scope, demonstrating compatibility with a diverse range of quinoxalin-2(1*H*)-one derivatives. Secondly, the reaction achieves excellent regioselectivity, selectively targeting the C–H bond adjacent to the nitrogen atom in the quinoxalinone ring, ensuring the formation of the desired monoacylated products. Thirdly, it displays high functional group tolerance, with the presence of various functional groups on the substrate not interfering with the reaction, thereby highlighting its robustness. Lastly, the reaction is readily scalable to the gram level in an aqueous medium without compromising yield or selectivity, making it highly suitable for industrial applications. Mechanistically, the reaction is believed to proceed *via* a free radical pathway. Palladium acetate plays a dual role, acting as both a catalyst and a source of palladium species capable of activating the C–H bond. The radical initiator TBPB generates aryl radicals from the aroyl surrogates, which then undergo addition to the palladium-activated C–H bond of the quinoxalinone. Subsequent reductive elimination releases the monoacylated product and regenerates the palladium catalyst, thus completing the catalytic cycle (Scheme 7). The use of water as the solvent not only simplifies the reaction workup but also significantly enhances the sustainability of the process. Water is non-toxic, inexpensive, and readily available, making it an ideal medium for large-scale synthesis. Moreover, the absence of organic solvents reduces the environmental impact and health hazards associated with traditional synthetic methods.

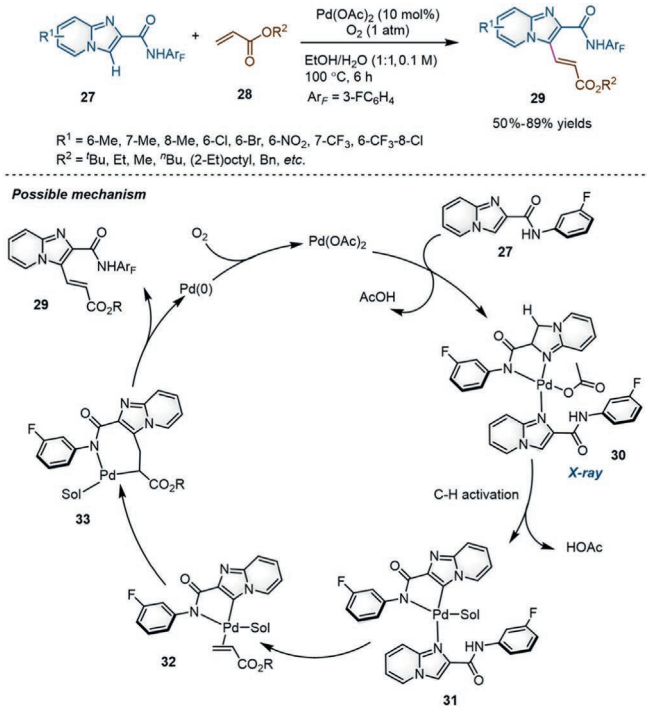
Almost concurrently, Elias and coworkers reported a pioneering study on the bis C–H bond functionalization of ferrocene derivatives, leveraging the power of palladium catalysis in an aqueous environment [34]. Their work demonstrated the feasibility of



Scheme 8. Bis C–H bond functionalization of ferrocene derivatives in water.

achieving double C–H activation and subsequent functionalization under relatively mild reaction conditions, marking a significant advancement in the field of organometallic chemistry. In their approach, Elias and coworkers utilized 5 mol% of $Pd(OAc)_2$ as the catalyst, with water serving as the reaction solvent. This choice of solvent not only aligns with the principles of green chemistry but also offers several practical advantages, including ease of handling, low toxicity, and environmental benignity. The substrates employed in this study were ferrocene derivatives bearing an 8-aminoquinoline directing group, which played a crucial role in guiding the palladium catalyst to the desired C–H bonds. Additionally, alkyl iodides or various iodobenzene derivatives were used as the coupling partners, providing a diverse range of functional groups that could be introduced onto the ferrocene scaffold. The reactions were carried out in an aqueous medium under air at 80 °C for 8 h. The use of air as the oxidant simplifies the reaction setup and eliminates the need for specialized equipment or inert gas atmospheres. The addition of 2.0 equiv. of K_2CO_3 as the base facilitated the deprotonation steps necessary for C–H activation and subsequent coupling reactions. Under these optimized conditions, the desired bis C–H bond functionalized ferrocene derivatives were obtained in good to excellent yields, showcasing the efficiency and robustness of the protocol (Scheme 8).

In 2024, Karpoormath and coworkers reported a palladium-catalysed C–H olefination of imidazo[1,2-*a*]pyridine carboxamides with various acrylates in aqueous ethanol (H_2O/EtOH; 1/1) using green O_2 as the oxidant [35]. The experiments suggested that the C–H activation exhibited user-friendly conditions, excellent yields, and broad substrate scope, and was applicable for the C–H deuteriation of corresponding heteroarenes using D_2O. The authors proposed a reasonable mechanism as outlined in Scheme 8. The reaction began with the formation of a tetra-coordinated square-planar Pd(II) intermediate (complex **30**) *via* complexation between $Pd(OAc)_2$ and imidazo[1,2-*a*]pyridine carboxamide **26**. Releasing 1 equiv. of AcOH to generate intermediate **30**, which then coordinated with the solvent to form the reactive intermediate **31** through a C–H activation step. Coordination of the olefin to led to the formation of intermediate **32** [28], accompanied by the release of 1 equiv. of substrate **26**. Subsequent 1,2-migratory insertion, β-hydride elimination, and reductive elimination from intermediate **33** afforded the desired product **29**. Finally, oxidation of the Pd(0) species with oxygen regenerated Pd(II), completing the catalytic cycle. The authors proposed that the C–H activation step



Scheme 9. Palladium-catalysed C–H olefination of imidazo[1,2-*a*]pyridine carboxamides with various acrylates in aqueous ethanol.

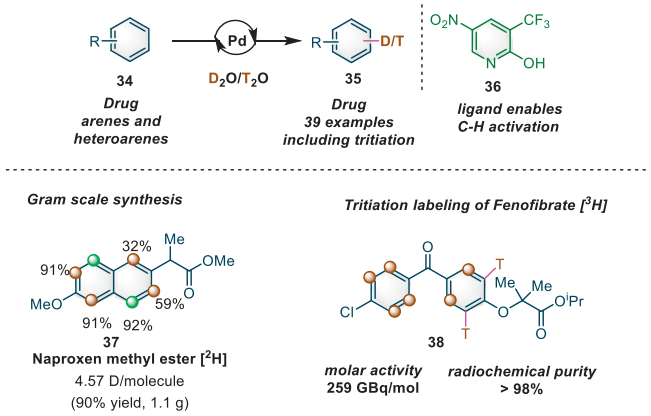
occurred after the formation of a tetra-coordinated square-planar Pd-substrate adduct **30** (Scheme 9).

In Karpoormath's report, the authors described the method of deuterium incorporation to imidazo[1,2-*a*]pyridine carboxamides. Deuterium oxide (D_2O) was employed as both the deuterium source and solvent for heteroarene substrates bearing electron-donating and electron-withdrawing substituents under modified reaction conditions. Later, Maiti and coworkers reported a non-directed homogeneous Pd-catalysed hydrogen isotope exchange reaction by C–H activation strategy [36]. In this study, the authors used D_2O, the most convenient and cost-effective deuterium source, as the sole solvent to avoid fluorinated solvents, and employed 10 mol% $Pd(OAc)_2$ as the catalyst. As a result, 39 pharmaceuticals were labeled with clean reaction profiles and high deuterium uptake. The authors subjected [D]−1,2-dimethoxybenzene to the optimized reaction conditions using H_2O as the solvent. A significant amount of [H] incorporation was observed, which illustrates that the C–H activation step was reversible. In addition, the authors reported the first use of non-directed homogeneous Pd-catalysis for H/T exchange on three pharmaceuticals using T_2O as the isotopic source, demonstrating its potential for radiotracer synthesis. It is worth noting that the described method involving the synthesis of tritiated analogues of APIs, might offer an interesting alternative to established tritiation protocols, particularly in terms of radioisotope incorporation regioselectivity (Scheme 10).

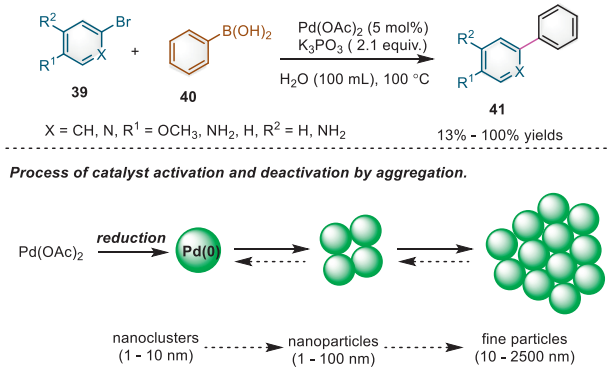
3. Palladium-catalysed cross-coupling in aqueous phase

3.1. Palladium-catalysed Suzuki-Miyaura cross-coupling reactions

The Suzuki-Miyaura coupling reaction, which is catalysed by palladium, has attracted considerable research interest and has been widely applied in both academic and industrial contexts [37–40]. However, with the increasing demand for environmentally friendly and sustainable processes in the contemporary chemical industry, modifications to the Suzuki coupling reaction condi-



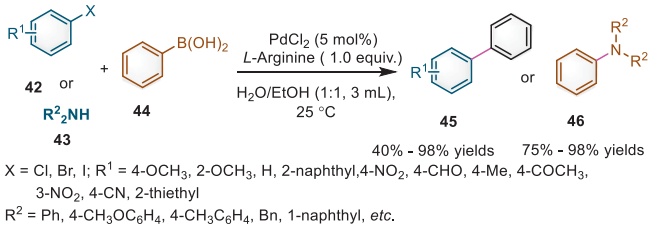
Scheme 10. Palladium-catalysed deuterium incorporation to imidazo[1,2-*a*]pyridine carboxamides.



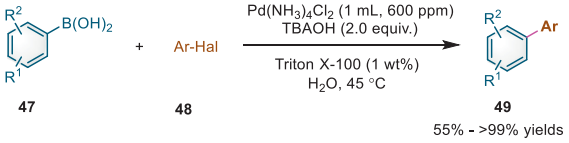
Scheme 11. Palladium-catalysed Suzuki coupling involving aryl bromides and phenylboronic acid in water.

tions have become imperative. In 2016, Liotta and coworkers [41] reported a palladium-catalysed Suzuki coupling reaction utilizing model aryl bromides (namely, 4-bromoanisole, 4-bromoaniline, 4-amino-2-bromopyridine, and 2-bromopyridine) and phenylboronic acid in an aqueous medium. This reaction was carried out on a 100 mL scale with 20–40 mmol of aryl bromide, without the need for additional ligands. The authors conducted a thorough optimization of the yields for four model substrates and identified the pivotal reaction parameters that influenced these yields. The findings unequivocally demonstrated that the parameters essential for achieving high yields are substrate-specific. Furthermore, the results revealed that Suzuki reactions involving basic nitrogen-containing substrates in water, without the addition of external ligands, could attain quantitative yields of the desired products. It was plausible that the basic nitrogen atoms function as *in situ* ligands, thereby stabilizing the active Pd(0) species and preventing deactivation processes such as aggregation (Scheme 11).

In 2017, Veisi and coworkers demonstrated the dual role of L-arginine (2-amino-5-guanidinopentanoic acid) as both a base and a ligand, enabling palladium-catalysed C–C and C–N cross-coupling reactions to proceed efficiently in aqueous media [42]. By employing a diverse range of aryl halides (including iodides, bromides, and chlorides), they successfully synthesized the corresponding Suzuki coupling products with yields ranging from good to excellent. Moreover, under identical reaction conditions, the cross-coupling reactions between arylboronic acids and various amines in an aqueous environment also proceeded smoothly, affording products with similarly high yields. Notably, the palladium catalyst utilized in this study exhibited excellent recyclability. It could be readily separated from the reaction mixture and reused mul-



Scheme 12. Palladium-catalysed C–C and C–N cross-coupling reactions in aqueous media.



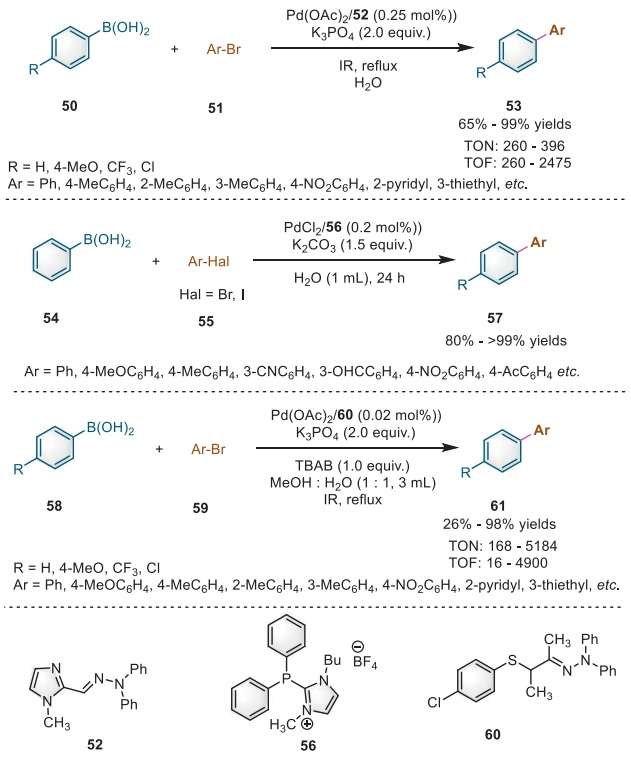
Scheme 13. Ligand-free, ppm-level Pd-catalysed Suzuki-Miyaura cross-coupling in aqueous solution.

tiple times without significant degradation in catalytic activity, thereby enhancing the practicality and sustainability of the process (Scheme 12).

In the context of Suzuki-type C–C coupling reactions, the base plays an indispensable role, and its specific nature is pivotal to the success of the catalytic process, albeit the precise mechanism of its action remains somewhat ambiguous. It is widely recognized that the base accelerates the rate-determining transmetalation and reductive elimination steps, which are crucial for the efficient progression of the reaction.

In 2019, Gao and coworkers introduced an innovative protocol for conducting ligand-free, ppm-level palladium-catalysed Suzuki-Miyaura cross-coupling reactions in aqueous solutions, wherein bases serve to stabilize the active catalytic species [43]. To facilitate the solubilization of organic substrates in water, the commercially available surfactant Triton X-100 was utilized as an emulsifier. This method boasted several advantages, including high catalytic activity, a strong potential for green chemical development, short reaction times, broad substrate applicability, yields ranging from good to excellent, operational simplicity, and exceptional recyclability of the palladium catalyst. To delve deeper into the role of the base in palladium catalysis, the authors employed a combination of electrochemical techniques, transmission electron microscopy (TEM), ultraviolet-visible (UV) spectroscopy, and X-ray photoelectron spectroscopy (XPS). Their findings revealed that, in this particular reaction system, bases not only stabilized the active palladium species but also exhibited anti-reduction properties in strongly basic environments. This stabilization prevented the aggregation and subsequent deactivation of palladium, thereby ensuring the sustained activity of the catalyst throughout the reaction (Scheme 13).

Simultaneously, Ortega-Jiménez and coworkers used an imidazole-hydrazone ligand, realizing a palladium-catalysed Suzukie-Miyaura reaction in water using IR irradiation as the energy source [44]. The system tolerated various functionalized arylboronic acids, aryl halides, and hetero-aryl bromides, giving the desired products in good yields. The authors demonstrated that an air-stable, phosphine-free hydrazone ligand containing a heterocycle moiety was effective for palladium-catalysed Mizoroki-Heck and Suzuki-Miyaura cross-couplings under IR irradiation. Later, Gholinejad and coworkers developed a new 1–butyl–3-methyl-2-(diphenylphosphino)imidazalolium exafluoro-phosphate as the water-soluble ligand, finishing the palladium-catalysed Suzuki-Miyaura reaction [45]. Obviously, the Suzuki coupling



Scheme 14. Ligand-enabled palladium-catalysed coupling reaction in water.

reactions of aryl iodides and bromides, including those with electron-donating and -withdrawing groups, were performed with various arylboronic acids. The catalyst was recycled and reused for six runs with only slight loss of activity (Scheme 14). In 2023, Ortega-Jiménez and coworkers synthesized arylhydrazone derivatives containing the thioether moiety and use them as ligands for palladium-catalysed Suzuki-Miyaura cross-coupling reactions in aqueous medium and under IR irradiation [46].

Recently, heterogeneous palladium catalysts featuring tailored structural designs have emerged as highly promising candidates for efficient and stable catalytic processes. In 2020, Yamada and coworkers reported the utilization of a dual-mode catalyst system composed of linear poly(4-vinylpyridine) and tetrachloropalladate for facilitating various cross-coupling reactions. Notably, this system exhibited the ability to generate both palladium nanoparticles and palladium complex catalysts under distinct reaction conditions [47]. Specifically, the Suzuki-Miyaura coupling and C–H arylation reactions involving aryl chlorides and bromides with arylboronic acids, thiophenes, furans, benzene, and anisole proceeded with remarkable efficiency in the presence of a palladium catalyst loading ranging from 0.004 mol% (40 mol ppm) to 1 mol%, yielding the desired products in excellent quantities (Scheme 15).

Subsequently, the same research group developed a novel polymeric palladium catalyst through a self-assembly strategy, employing palladium species and copolymers of 4-vinylpyridine and 4–*tert*-butylstyrene [48]. Experimental investigations revealed that the incorporation of tertiary butyl groups into the polymer backbone significantly enhanced the catalytic activity and stability of the catalyst under continuous-flow Suzuki-Miyaura coupling conditions. In 2023, Lin and coworkers further advanced the field by developing a high-efficiency *N*-heterocyclic carbene (NHC)-palladium catalyst, which successfully catalysed a palladium-mediated coupling reaction [49]. The authors posited that the homogeneous dispersion of *N*-heterocyclic carbene palladium (Pd) within the polymer network played a pivotal role in substantially boosting the catalytic performance of the Pd-NHC catalyst. This enhancement translated into exceptional activity, stability, and reusability for the Suzuki-Miyaura coupling reaction conducted in an aqueous medium (Scheme 15).

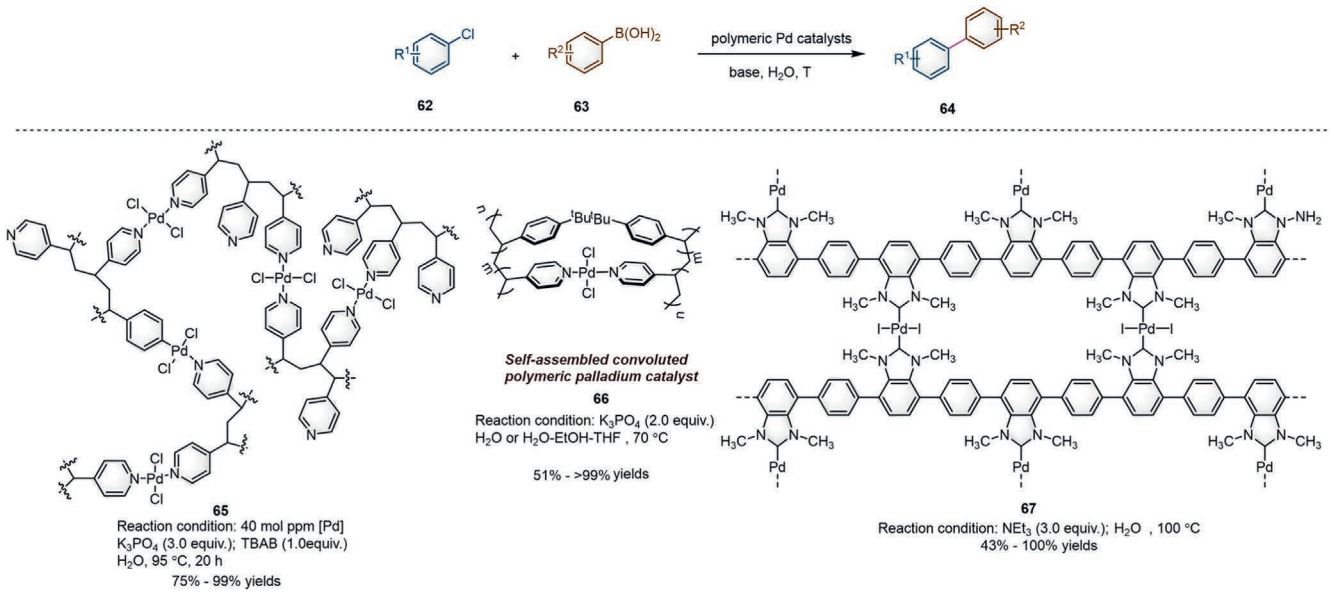
3.2. Palladium-catalysed Mizoroki-Heck cross-coupling reactions

Palladium-catalysed Mizoroki-Heck-type reactions have firmly established themselves as a highly dependable approach for the construction of complex carbocyclic and heterocyclic molecular frameworks [50]. Considering the myriad benefits associated with the utilization of water as a reaction solvent, substantial research endeavors have been dedicated to the development of Pd-catalysed aqueous Mizoroki-Heck reactions. These efforts are primarily aimed at enhancing the efficiency, sustainability, and practical applicability of these synthetic methodologies, while simultaneously broadening their utility in the synthesis of a diverse array of complex organic compounds.

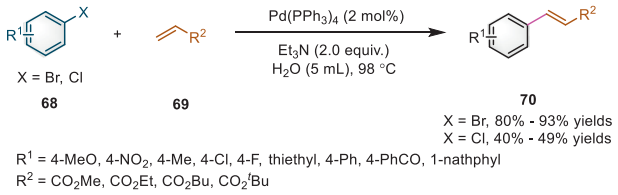
In 2017, Rode and coworkers reported a pioneering study on a palladium-catalysed Mizoroki-Heck coupling reaction conducted in water under reflux conditions, without the need for any additional additives [51]. Utilizing a catalyst system comprising $Pd(PPh_3)_4$, Et_3N, and H_2O at 98 °C, the reaction proceeded seamlessly, yielding the desired Mizoroki-Heck coupling products in excellent quantities from a wide spectrum of electron-withdrawing and electron-donating aryl bromides and chlorides within a notably short reaction timeframe. Through meticulous condition optimization, it was discerned that triethylamine exhibited the highest catalytic efficiency. This is likely attributable to its dual functionality as both a base and a ligand in the Heck reaction, as previously documented in the literature. Triethylamine demonstrated a strong propensity to coordinate with palladium, thereby forming an active Pd complex. Furthermore, the formation of ammonium salts contributed to the stabilization of the Pd-active species in the aqueous environment. It is noteworthy that the authors incorporated calcined PdO into the catalytic cycle for the model reaction involving 4-bromoanisole and *t*–butyl acrylate in the presence of PPh_3. The Pd catalyst displayed exceptional activity over ten consecutive runs, with no discernible decline in product yield (Scheme 16).

Almost concurrently, Zhang and coworkers achieved a significant breakthrough by developing a water-soluble salicylaldoxime-functionalized PEG-1000-grafted dicationic ionic liquid as a highly efficient ligand for palladium-catalysed Mizoroki-Heck reactions in aqueous media [52]. This innovative ligand design enabled the smooth progression of the reactions, yielding the corresponding coupling products in good to excellent quantities. The reactions demonstrated broad substrate applicability, successfully coupling a diverse range of aryl bromides-including those bearing both electron-deficient and electron-rich substituents-with various olefins. The excellent compatibility with different substrates highlights the versatility and robustness of this catalytic system. The use of a water-soluble, PEG-1000-grafted dicationic ionic liquid ligand not only facilitated efficient catalysis in an aqueous environment but also contributed to the sustainability and green chemistry aspects of the process. The reactions proceeded under mild conditions, further enhancing their practical utility (Scheme 17). This work represents an important advancement in the development of environmentally friendly and efficient catalytic systems for Mizoroki-Heck reactions.

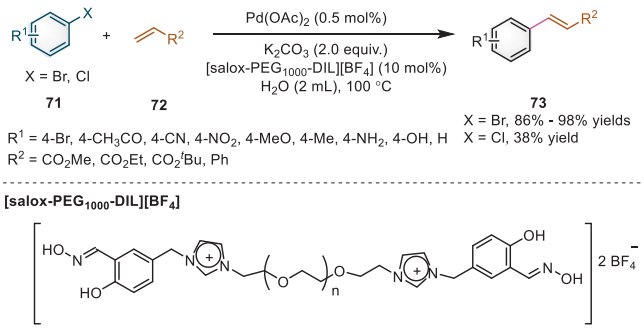
In 2020, Kumbhar and coworkers reported a significant advancement in Mizoroki-Heck reaction methodology by developing a ligand-free palladium-catalysed system that utilized *in situ* generated palladium nanoparticles (PdNPs, sized 5–10 nm) in an aqueous solution containing a bio-surfactant [53]. This approach facilitated the efficient coupling of various aryl bromides with different olefins, yielding the desired products in good to excellent



Scheme 15. Heterogeneous palladium-catalysed coupling reaction.

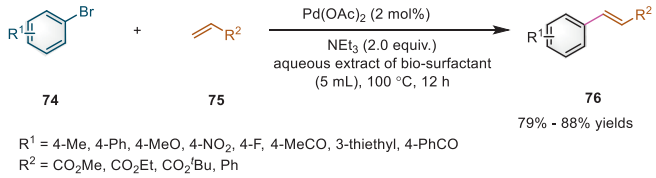


Scheme 16. Mizoroki-Heck coupling of aryl bromides and chlorides and *t*–butyl acrylate.



Scheme 17. Dicationic ionic liquid as a water-soluble and recyclable ligand for palladium-catalysed Mizoroki-Heck reactions.

quantities. A notable achievement of this study was the successful demonstration of gram-scale synthesis of the target product while maintaining excellent yields, highlighting its practical viability for industrial-scale applications. The protocol stood out for its adherence to green chemistry principles, featuring ligand-free conditions that simplified the catalytic system and reduced potential toxicity and cost. Conducting the reaction in an aqueous medium minimized the use of organic solvents, enhancing environmental sustainability. Furthermore, the utilization of a bio-surfactant derived from renewable natural resources contributed to the eco-friendly nature of the process. The *in-situ* generation of PdNPs provided an economical and straightforward route for catalyst preparation, making the overall approach both sustainable and cost-effective. This work thus presented a scalable and environmentally benign



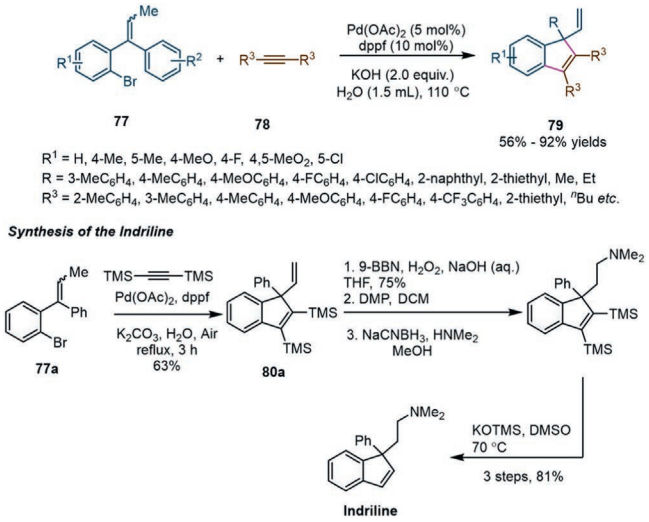
Scheme 18. Ligand-free palladium-catalysed Mizoroki-Heck coupling reaction.

strategy for Pd-catalysed Mizoroki-Heck reactions with significant potential for large-scale organic synthesis (Scheme 18).

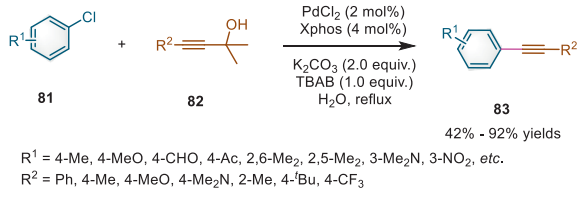
In 2023, Liu and coworkers achieved a notable breakthrough by developing an intermolecular consecutive double Mizoroki-Heck reaction that efficiently coupled tri-substituted alkenes with internal alkynes to produce substituted indene derivatives in pure water [54]. This innovative approach operated under air, showcasing remarkable tolerance to a wide range of functional groups and demonstrating excellent scalability. Interestingly, the introduction of surfactants such as SDS (sodium dodecyl sulfate) and TPGS-750 M led to a significant decrease in yields, presumably due to the oxidation of the metal catalysts by these additives. The practical utility of this protocol was further underscored by its successful application in the efficient synthesis of biologically significant indene derivatives, including indriline. This work not only expands the scope of Mizoroki-Heck reactions but also highlights the potential for environmentally friendly and scalable synthetic routes to valuable organic compounds (Scheme 19).

3.3. Palladium-catalysed Sonogashira cross-coupling reactions

In 2017, Liu and coworkers unveiled a highly efficient and environmentally sustainable palladium-catalysed deacetonative coupling reaction, which facilitated the direct coupling of aryl propargylic alcohols with aryl chlorides in an aqueous medium [55]. This innovative method demonstrated remarkable tolerance to a diverse array of functional groups, including ethers, aldehydes, ketones, and heterocycles, while consistently delivering the desired products in good yields. A notable feature of this protocol was its ability to promote consecutive reactions between 2-methyl-3-butyn-2-ols and electron-rich aryl chlorides under standard reaction conditions, successfully yielding the corresponding symmetric alkynes in good



Scheme 19. Palladium-catalysed double Mizoroki-Heck reaction.



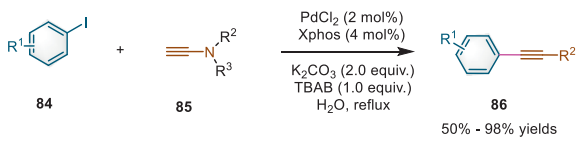
Scheme 20. Palladium-catalysed deacetonative Sonogashira cross-coupling reactions.

quantities. This work not only advanced the field of palladium-catalysed cross-coupling reactions but also underscored the potential for developing green and sustainable synthetic methodologies in organic chemistry (Scheme 20).

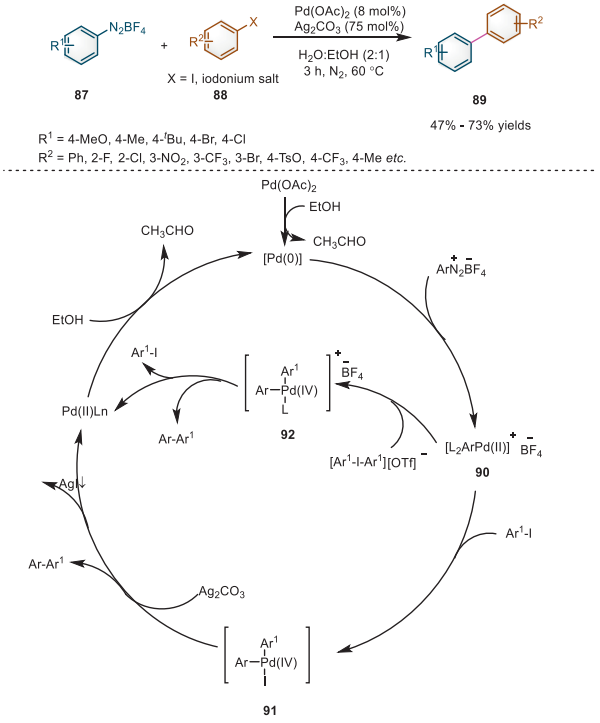
Ynamides [56–59], a unique class of alkynes featuring an electron-donating amide nitrogen adjacent to the alkyne moiety, have emerged as highly versatile building blocks for the synthesis of nitrogen-containing organic compounds. However, their practical application has been hindered by their inherent moisture sensitivity, which often leads to decomposition or unwanted hydration reactions under heating, acidic conditions, or in the presence of transition-metal catalysts. This necessitates the use of dry organic solvents in their preparation, posing challenges for sustainable and environmentally friendly synthetic methodologies. In a significant breakthrough in 2021, Wu and coworkers addressed this limitation by developing a palladium-catalysed Sonogashira coupling reaction conducted in water, leveraging a readily available quaternary ammonium salt as a surfactant to stabilize the reaction system [60]. Sulfonamide-based ynamides, chosen for their enhanced stability, were employed as model substrates. The reactions proceeded smoothly, coupling sulfonamide-based ynamides with aryl ynamines to yield the desired products in good to excellent yields. This aqueous-phase protocol not only overcame the moisture sensitivity issue but also offered a greener and more sustainable alternative to traditional methods, expanding the scope of ynamide chemistry in organic synthesis (Scheme 21).

3.4. Other types of palladium-catalysed cross-coupling reactions

Aryldiazonium salts have proven to be highly valuable cross-coupling partners in palladium-catalysed reactions, including the Heck-Matsuda and Suzuki processes, as well as serving as electrophiles in C–H arylation reactions. In 2023, Jana and coworkers made a significant advancement by employing readily avail-



Scheme 21. Palladium-catalysed Sonogashira coupling reaction of sulfonamide-based ynamides.



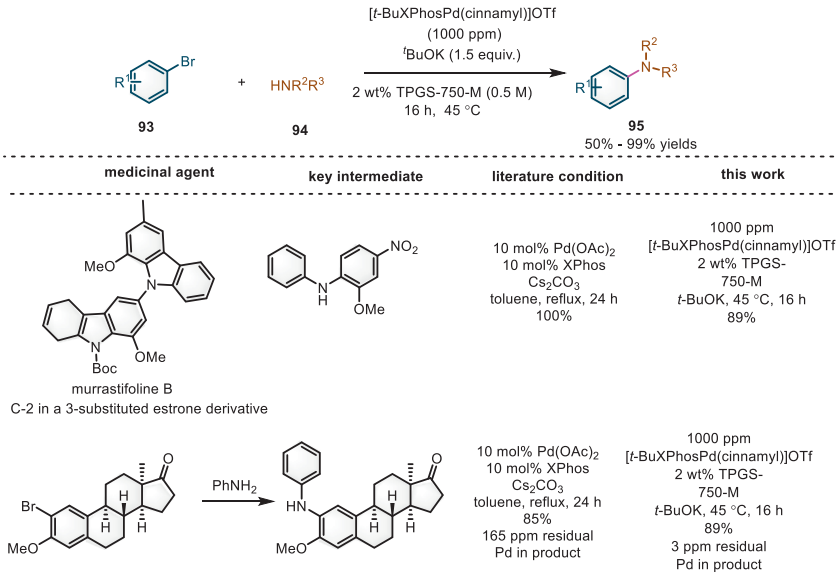
Scheme 22. Palladium-catalysed cross-electrophile coupling reaction of aromatic diazonium salt.

able aromatic diazonium salts alongside aryl iodides or diaryliodonium salts as reactive substrates in a palladium-catalysed, highly chemoselective cross-electrophile coupling reaction [61]. This reaction was conducted in a water-ethanol (2:1) mixed solvent system, which offered both environmental friendliness and enhanced reaction efficiency.

Mechanistically, the oxidative addition of the aryldiazonium salt to the palladium catalyst generated a cationic palladium species. This intermediate played a crucial role in accelerating the subsequent oxidative addition of the aryl iodide, thereby facilitating the selective formation of cross-coupling products in good yields. The authors proposed that the reaction proceeded through a Pd(0)-Pd(II)-Pd(IV) catalytic cycle. In this cycle, the active Pd(0) species was generated *in situ* by the reduction of Pd(II) with ethanol, which served as both a solvent and a reducing agent. This innovative approach not only expanded the scope of palladium-catalysed cross-coupling reactions but also provided a sustainable and efficient method for the synthesis of complex aromatic compounds (Scheme 22).

4. Palladium-catalysed amination in aqueous phase

Palladium-catalysed amination has emerged as a cornerstone in the synthesis of pharmaceuticals, agrochemicals, and fine chemicals due to its unparalleled ability to forge C–N bonds-a structural

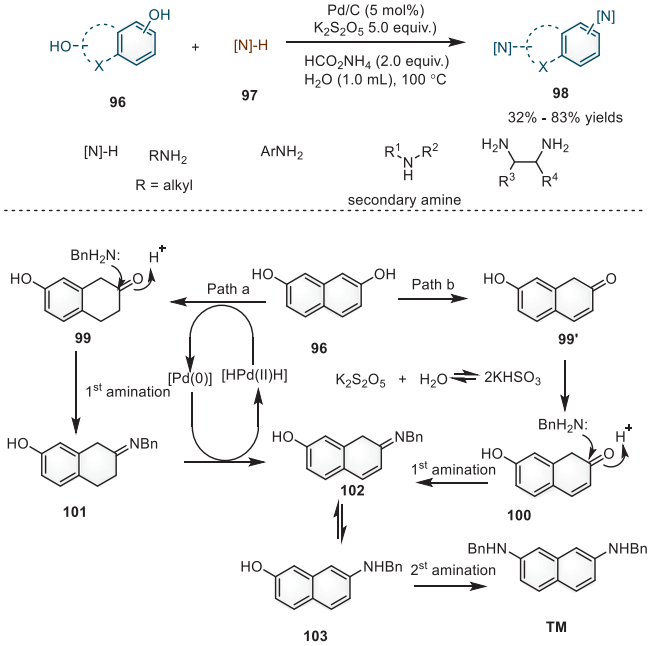


Scheme 23. [*t*-BuXPhos(Pd-π-cinnamyl)]OTf catalysed amination reactions.

motif ubiquitous in bioactive molecules [62–64]. The quest for greener and more sustainable amination protocols has driven significant innovation, with aqueous-phase reactions gaining prominence for their reduced environmental impact.

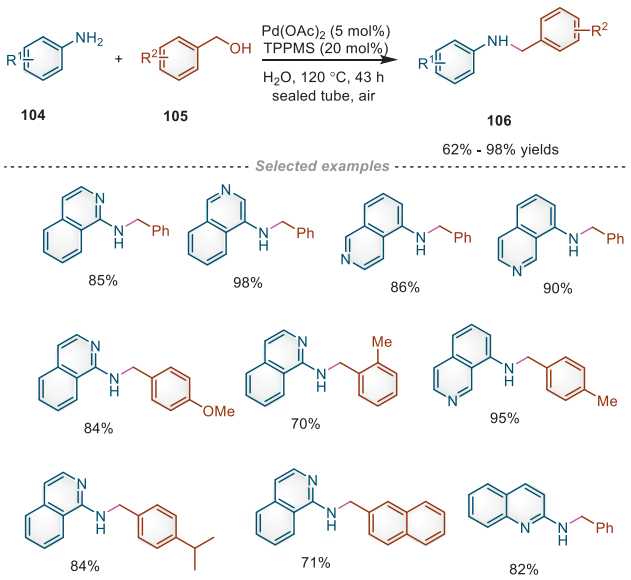
In 2019, Lipshutz and coworkers introduced a breakthrough precatalyst system, [*t*-BuXPhos(Pd-π-cinnamyl)]OTf, which enabled highly efficient amination reactions in water [65]. This robust 1:1 Pd-ligand complex operated at remarkably low catalyst loadings (typically 1000 ppm Pd) and mild temperatures (room temperature to 45 °C), delivering amination products in exceptional yields (50 %–99 %). The protocol's practicality was demonstrated through the synthesis of six key intermediates for medicinally relevant natural products or active pharmaceutical ingredients (APIs). Notably, this aqueous method outperformed traditional organic-solvent-based aminations by enabling ppm-level pre-catalyst loadings, lower reaction temperatures, and faster kinetics. For instance, amination of a 3-substituted estrone derivative at C-2 achieved a 40-fold reduction in Pd and ligand loadings (10 mol% = 100,000 ppm), a decreased temperature (45 °C *vs.* 110 °C), and a shorter reaction time (16 h *vs.* 24 h). Moreover, residual Pd contamination was drastically lower in water (3 ppm) compared to toluene (165 ppm), highlighting the method's superior purity profile (Scheme 23). Subsequent advancements further expanded the scope of aqueous Pd-catalysed amination. Friis and coworkers reported a biphasic MeTHF/water system for C–N cross-coupling of aryl amines and aryl halides, leveraging phase separation to simplify product isolation [66]. Building on this, Lipshutz and coworkers in 2024 pioneered a continuous-flow approach for Pd-catalysed C–N cross-couplings on water, merging the benefits of aqueous chemistry with the efficiency of flow systems [67]. This evolution underscores the growing momentum toward sustainable, scalable, and high-performance amination methodologies in modern synthetic chemistry.

In 2020, Chen and coworkers [68] reported a Pd-catalysed *N*-arylation of phenols with amines *via* aqueous hydrogen-transfer coupling. Using HCO_2NH_4 as the hydrogen source, Pd/C as catalyst, and $K_2S_2O_5$ as additive in water at 120 °C under N_2, the reaction smoothly afforded products in 32 %–83 % yield. The authors proposed a possible reaction pathway for this hydrogen transfer amination. Initially, HCO_2NH_4 reacted with the Pd catalyst to form an active HPd(II)H species, which hydrogenated 2-naphthol to ketone **99**, regenerating the catalyst. In the presence of $K_2S_2O_5$, **99** underwent the first amination with benzylamine (**97**) to afford intermediate **101**. Subsequent dehydrogenation of **101** yielded **102** and released HPd(II)H (path a). Finally, tautomer **103** underwent a second amination to form product **98**. The authors thought that $K_2S_2O_5$ was essential (path b), as its sole use afforded only trace product. Together with H_2O, it enabled cyclohexenone formation from naphthol under these conditions (Scheme 24).



Scheme 24. Pd-catalysed *N*-arylation of phenols with amines *via* aqueous hydrogen-transfer coupling.

Borrowing-hydrogen coupling has emerged as a powerful strategy for atom-economical and environmentally benign synthesis, enabling the direct dehydrative union of amines with alcohols without relying on stoichiometric reagents or pre-formed intermediates. In 2008, Milstein and coworkers set a precedent by developing a pincer-type ruthenium complex-catalysed amination of alcohols using aqueous ammonia under base-free conditions, offering a markedly greener route to primary amines [69]. This sem-



Scheme 25. Pd-catalysed borrowing-hydrogen protocol that couples aminoisoquinolines with benzylic alcohols.

inal work highlighted the potential of transition-metal-catalysed borrowing-hydrogen reactions in sustainable synthesis.

Building on this foundation, Azumaya and coworkers (2020) advanced the field by introducing a palladium-catalysed borrowing-hydrogen protocol that efficiently coupled aminoisoquinolines with benzylic alcohols in pure water [70]. Leveraging a π-benzylpalladium system, the reaction proceeded smoothly without the need for bases or additional additives, delivering *N*-benzylated aminoisoquinolines in moderate to excellent yields while generating water as the sole byproduct. Mechanistic insights were gleaned from crossover experiments using [D_7]benzyl alcohol and 4-methoxybenzyl alcohol, which revealed H/D scrambling in the products. Kinetic isotope effect (KIE) studies (KIE = 4.4) implicated benzylic C–H bond cleavage of the alcohol as the turnover-limiting step, supporting a borrowing-hydrogen pathway in aqueous media. Critically, the use of a water-soluble Pd^0/TPPMS (triphenylphosphine monosulfonate) catalyst system enabled the challenging benzylic amination of aminoisoquinolines without deactivation of Pd^{II} intermediates, a common issue in aqueous environments. This protocol not only expanded the scope of borrowing-hydrogen reactions to heterocyclic amines but also demonstrated the feasibility of performing such transformations in water-a solvent of choice for green chemistry-while maintaining high activity and selectivity (Scheme 25).

In 2024, Lipshutz and coworkers reported a groundbreaking sustainable palladium-catalysed C–N coupling protocol for aliphatic amines, leveraging a catalytic system composed of ppm-level recyclable palladium, a commercial ligand, and recycled water-or even seawater-as the reaction medium [71]. This environmentally benign approach not only demonstrated exceptional versatility but also efficiently tolerated challenging reaction partners, enabling late-stage functionalization of complex molecules. The method provided a concise and efficient synthesis of naftopidil [72], a selective α_1-adrenergic receptor antagonist, in 67 % isolated yield over three steps, while also delivering highly functionalized pharmaceuticals such as Duloxetine (Cymbalta), Paroxetine (Paxil), and Fluoxetine (Prozac) in good-to-excellent yields. A key advantage of this aqueous system was its exceptional purity, with ICP-MS analysis detecting no residual palladium (<1 ppb) in the final products-well below the FDA's daily limit of 10 ppm per dose. This eliminated the need for costly metal scavengers or extensive purification, further enhancing the method's sustainability and cost-effectiveness. By combining ultra-low catalyst loadings, recycled solvents, and compatibility with seawater, this work establishes a new paradigm for green chemistry in pharmaceutical synthesis, offering a scalable and eco-friendly alternative to traditional C–N coupling methods (Scheme 26).

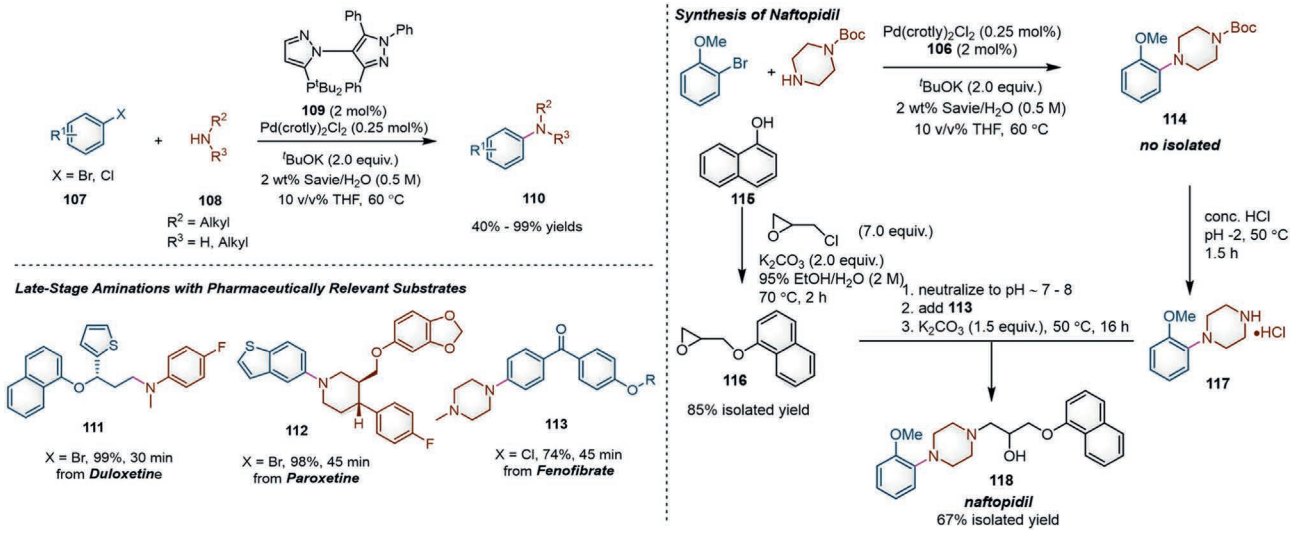
5. Palladium-catalysed carboxylation in aqueous phase

Catalytic carbonylations utilizing carbon monoxide (CO) occupy a central position in green chemistry and industrial synthesis, enabling the efficient construction of carbonyl-containing compounds. While Pd-catalysed carbonylative couplings in homogeneous media are renowned for their high activity and selectivity, they face significant drawbacks, including the challenge of catalyst separation and recycling. In 2015, Jiang and coworkers [73] introduced an innovative solution by proposing thermoregulated phase-transfer catalysis (TRPTC), a strategy rooted in the cloud point (Cp) behavior of non-ionic alkylpolyoxyethylene surfactants. This TRPTC system was ingeniously applied as a recyclable catalytic medium for the palladium-catalysed carbonylative Sonogashira coupling of aryl iodides with terminal alkynes and CO in water.

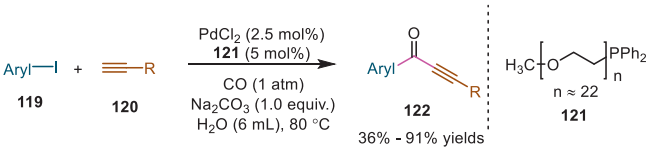
Operating under mild CO pressure in an aqueous environment, the reaction proceeded smoothly, delivering the desired alkynones in moderate to good yields. Notably, the TRPTC system addressed the catalyst recovery issue by exploiting temperature-induced phase separation: at lower temperatures, the catalyst remained dissolved in the aqueous phase, while heating above the cloud point triggered its transfer into a separate organic phase, enabling facile separation. Rigorous evaluation of catalyst reusability and palladium leaching revealed that the system could be recycled up to four times without significant loss of activity, demonstrating both practicality and sustainability (Scheme 27). This work not only advanced the field of carbonylative couplings by merging aqueous compatibility with efficient catalyst recycling but also highlighted the potential of TRPTC as a versatile platform for green chemistry applications, where thermal regulation serves as a simple yet powerful tool for catalyst management.

The hydroxycarbonylation of alkenes, as elucidated by van Leeuwen, proceeds *via* a Pd(II)-hydride pathway where efficiency and selectivity are modulated by Brønsted/Lewis acid additives and the electronic/steric properties of supporting phosphine ligands [74]. In 2019, Liu and coworkers advanced this field by designing a tri-functional ligand (**124**) integrating a phosphino fragment, a Lewis acidic phosphonium cation, and a hydrophilic sulfonate (SO_3^-) anion for co-catalysed hydroxycarbonylation [75]. This integrated ligand outperformed simple mixtures of individual functional groups, with *in situ* FT-IR and crystallographic studies revealing a cooperative H_2O activation mechanism: The phosphonium center withdraws electron density from the O–H bond ($H_2O \rightarrow P(V)^{++}$), while the sulfonate engages the same water molecule *via* hydrogen bonding ($SO_3^- \cdots H_2O$). This dual interaction facilitates the reversible formation of mono- and dinuclear Pd-H species (A/B), gated by dynamic SO_3^- coordination. In 2023, Chen and coworkers introduced a picolinamide-derived diphosphine ligand bearing a hydrophilic sulfonate group, enabling Pd-catalysed hydrocarboxylation of alkynes at room temperature in water [76]. The reaction exhibited broad substrate scope, delivering products with high yields and excellent branched selectivity (b/l > 95:5). Mechanistic studies highlighted ligand-metal cooperativity between the basic pyridine and hydrophilic sulfonate, which accelerated key catalytic steps (Scheme 28).

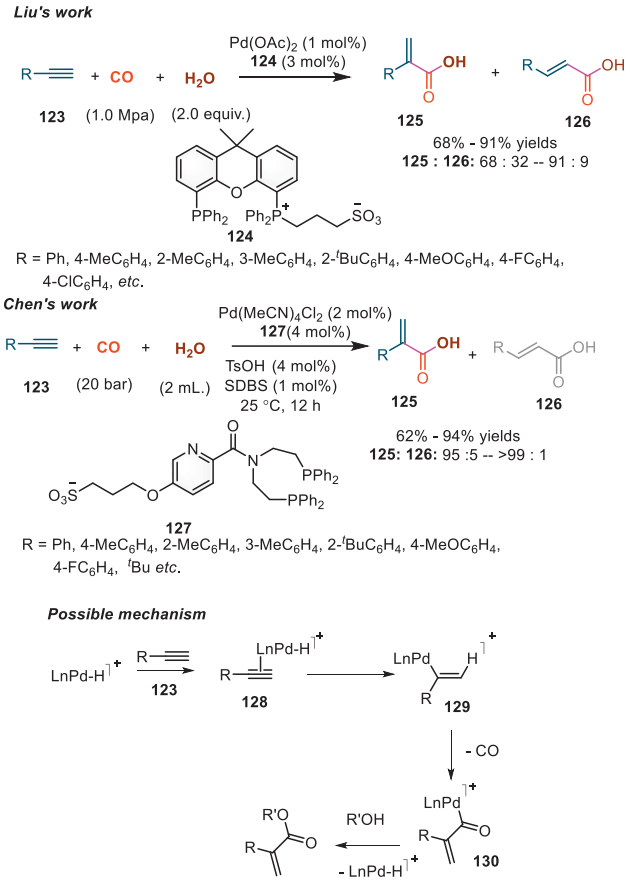
Also in 2023, Zhu and coworkers reported a palladium-catalysed four-component carbonylation in water, using aryl iodides and alkyl halides as coupling partners to synthesize esters and diesters in moderate to good yields [77]. Control experiments



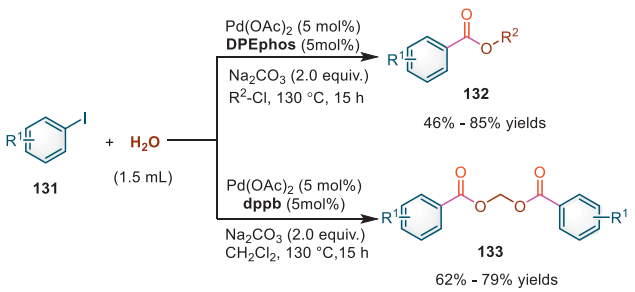
Scheme 26. Pd-catalysed C–N coupling of aliphatic amines.



Scheme 27. Ligand-palladium-catalysed carbonylative Sonogashira coupling of aryl iodides.



Scheme 28. The co-catalysis of hydroxycarbonylation.

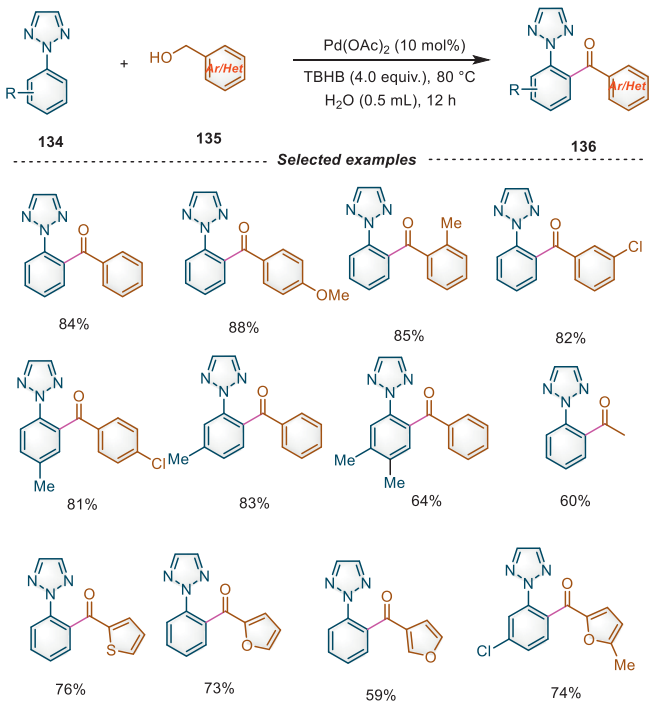


Scheme 29. Palladium-catalysed four-component carbonylation.

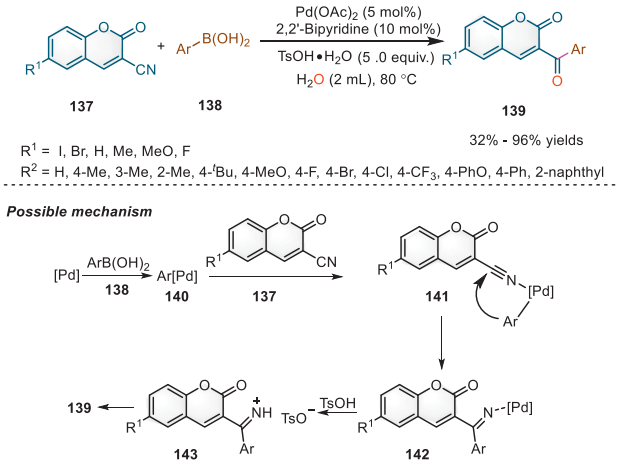
confirmed carboxylic acid formation precedes nucleophilic attack by the carboxylate on the alkyl halide. Notably, symmetric anhydrides formed when water volume was below 1.5 mL, suggesting water's dual role as solvent and reactant (Scheme 29).

Pd-catalysed acylations with directing groups represent a powerful strategy for regiocontrol. Among these, the 1,2,3-triazole ring system has emerged as a versatile motif for regioselective acylation [78,79]. In 2016, Jain and coworkers disclosed a Pd-catalysed *ortho*-acylation of *N*-aryl-1,2,3-triazoles using benzylic, heterocyclic, and aliphatic alcohols as acyl donors and TBHP as the oxidant [80]. The reaction proceeded in aqueous media without phase-transfer catalysts or surfactants, enabling straightforward product isolation *via* minimal organic solvent extraction. This eco-friendly protocol also facilitated the synthesis of triazole-substituted fluorenone, a core structure in bioactive molecules (Scheme 30). Collectively, these advances underscore the synergy between ligand design, solvent engineering, and mechanistic insights in driving Pd-catalysed carbonylations toward sustainability, efficiency, and broad applicability.

The nitrile functional group has proven to be a highly versatile synthetic intermediate, enabling efficient and modular access to a wide range of valuable compounds, including carboxylic acid derivatives, amides, heterocycles, ketones, and aldehydes. In 2019, Wenig and coworkers capitalized on this versatility by employing nitriles as a carbonyl source and arylboronic acids as the aryl donor in a palladium-catalysed carbonylation strategy for the synthesis of 3-aroyl coumarins [81]. This method operated in an environmentally benign and non-toxic aqueous medium, demonstrating broad



Scheme 30. Palladium-catalysed regioselective *ortho*-acylation of *N*-aryl-1,2,3-triazoles.



Scheme 31. Palladium-catalysed carbonylation for the synthesis of 3-aroyl coumarins.

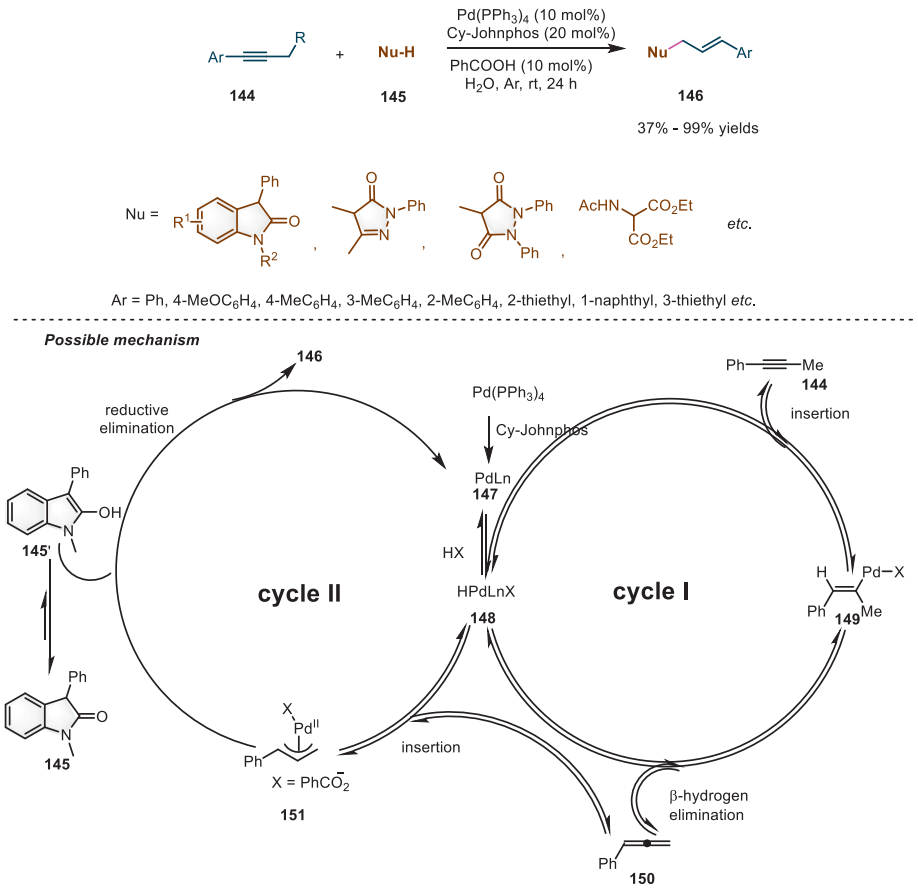
substrate compatibility and delivering the target 3-aroyl coumarins in moderate to excellent yields. Notably, 3-cyanocoumarins bearing bromo– and iodo-substituents reacted efficiently with arylboronic acids, yielding the desired products in 51%–95% yields (Scheme 31).

Mechanistic investigations, including labeling experiments, revealed that the carbonyl oxygen in the products originated from water [82]. The proposed catalytic cycle (Scheme 31) begins with transmetalation between the Pd(II) precatalyst and arylboronic acid, generating aryl-Pd(II) species **140**. This species undergoes regioselective carbopalladation of the nitrile group, forming the ketimine-Pd(II) complex **141**. A critical C–C bond-forming event occurs *via* intramolecular migratory insertion of the aryl group into the C≡N bond, yielding ketimine-Pd(II) intermediate **142**. Finally, hydrolysis of this intermediate by water releases the 3-aroylcoumarin product **139** and regenerates the active Pd(II) catalyst, completing the cycle. This approach not only highlights the utility of nitriles as carbonyl surrogates but also underscores the potential of aqueous Pd-catalysed systems for sustainable and atom-economic synthesis of complex heterocycles. The combination of mild reaction conditions, green solvent, and high functional group tolerance makes this method particularly attractive for pharmaceutical and fine chemical applications.

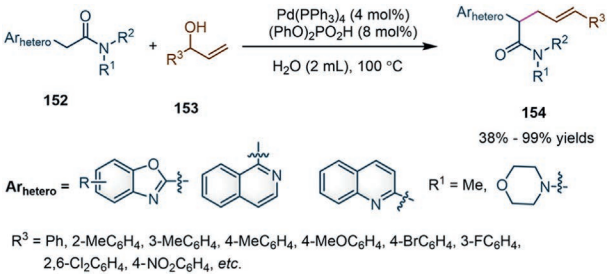
6. Palladium-catalysed Tsuji-Trost type alkylation in aqueous phase

The Tsuji-Trost reaction constitutes a powerful platform for forging diverse C–C and C-X bonds, enabling concise syntheses of bioactive natural products and pharmaceutical agents. In 2003, Kobayash and Manabe reported an allylic substitution of allyl alcohols in water as a suspension medium under a cooperative palladium- and carboxylic acid catalysis [83]. In 2017, Lin and coworkers applied various nucleophiles with internal alkynes as reactive substrates, describing a palladium-catalysed allylic alkylation in water [84]. The protocol demonstrates broad functional-group tolerance, scalability, and exceptional regiocontrol, affording lots of allylic compounds with indolinones, ketones, amines as well as electron rich aromatic compounds as nucleophiles. It was worth noting that generating the requisite arylallene *in situ* directly from alkynes obviates both external oxidants and stoichiometric leaving groups, affording exceptional atom economy. The protocol's versatility was further demonstrated by straightforward deuterium incorporation upon substituting D_2O for H_2O. The authors proposed a possible mechanism. As outlined in Scheme 32. The transformation included two satalytic cycles. Catalytic cycle I: Ligand exchange of $Pd(PPh_3)_4$ with Cy-JohnPhos generated the active species **147**; subsequent protonation by benzoic acid affords the hydridopalladium(II) complex **148**. *syn*-migratory insertion of **147** into alkyne **144** gives adduct **149**, whose β-hydride elimination released phenylallene **150** and regenerates **148**. Catalytic cycle II: *Re*-insertion of **148** into the newly formed allene **150** furnishes the η^3-allylpalladium(II) intermediate **151**. Nucleophilic capture of **151** by **145′** delivered product **146** and restores the active catalyst **147** for the next turnover (Scheme 32).

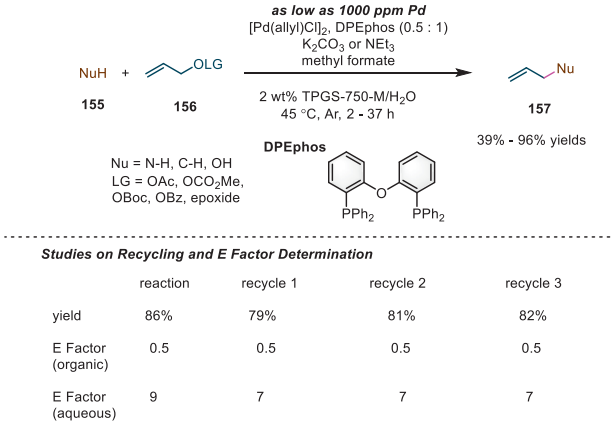
In 2019, Zhong and coworkers developed a highly efficient palladium-catalysed allylic substitution reaction between benzothiazole acetic amides and allylic alcohols, using water as the sole solvent [85]. This method employed a catalytic system consisting of 4 mol% $Pd(PPh_3)_4$ and 8 mol% $(PhO)_2PO_2H$ under thermal conditions (100 °C), delivering the desired allylated products in good to excellent yields (up to 99%) with high regioselectivity favoring branched isomers. Notably, the reaction demonstrated excellent scalability, as evidenced by its successful execution on a gram scale (5.0 mmol of benzothiazolylacetamide), yielding the product in 88% efficiency. The resulting allylated benzothiazolylacetamide derivatives proved to be versatile intermediates, undergoing diverse post-functionalization reactions such as epoxidation, dihydroxylation, and Suzuki coupling (Scheme 33), thereby enabling rapid access to structurally complex heterocycles with potential biological activity. Mechanistically, the reaction likely proceeds *via* a Pd(0)/Pd(II) catalytic cycle, where oxidative addition of Pd(0) to the allylic alcohol forms a π-allyl-Pd(II) intermediate, which was subsequently attacked by the benzothiazole nucleophile. The $(PhO)_2PO_2H$ ligand not only facilitates catalyst regeneration but may also assist in proton transfer steps. This aqueous protocol aligns with green chemistry principles by avoiding organic solvents, while its high yields, scalability, and functional group tolerance make it highly practical for both academic research and pharmaceutical applications, particularly in the synthesis of benzothiazole-based bioactive molecules.



Scheme 32. Palladium-catalysed allylic alkylation using various nucleophiles with internal alkynes.



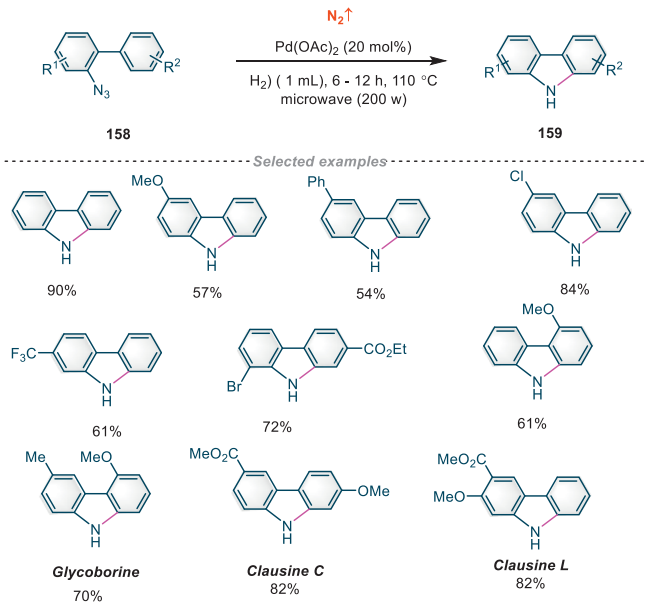
Scheme 33. Palladium-catalysed allylic substitution reaction involving benzathiazole acetic amides and allylic alcohols.



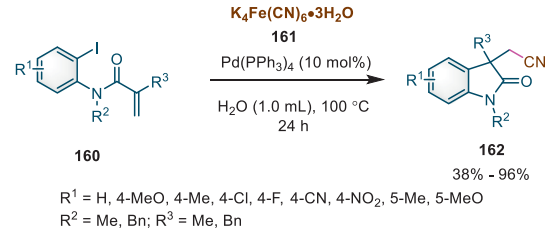
	reaction	recycle 1	recycle 2	recycle 3
yield	86%	79%	81%	82%
E Factor (organic)	0.5	0.5	0.5	0.5
E Factor (aqueous)	9	7	7	7

Scheme 34. Palladium-catalysed Tsuji–Trost reactions enabled by aqueous micellar catalysis.

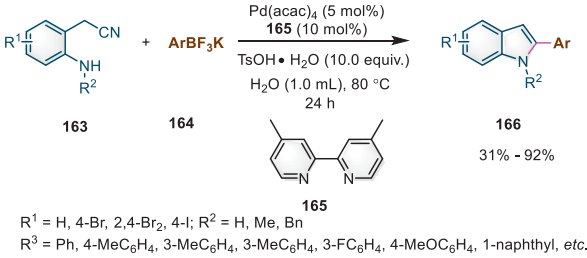
In 2020, Lipshutz and coworkers pioneered a sustainable palladium-catalysed Tsuji-Trost reaction under micellar catalysis conditions in water, marking a significant advancement in green chemistry [86]. This method operated with an exceptionally low palladium loading (1000 ppm, or 0.1 mol%) and leveraged designed surfactant technology to create a stable micellar environment in recyclable water. The reaction accommodated a wide range of substrates, including those previously unreported in aqueous micellar systems, and proceeded under mild conditions with high yields. Notably, the protocol demonstrated excellent scalability to multigram levels, with the reaction medium retaining its efficiency even after multiple recycling cycles, thereby minimizing waste generation. The low *E*-factor (a measure of environmental impact) underscored the method's sustainability, offering a practical and eco-friendly alternative to traditional organic solvents for complex molecule synthesis. Almost simultaneously, Suzuka and coworkers reported an amphiphilic PS-PEG resin-supported phenanthroline-palladium complex for catalyzing Friedel-Crafts-type alkylations of indoles in water under aerobic conditions [87]. This heterogeneous system combined the benefits of water as a solvent with the ease of catalyst recovery, delivering good-to-high yields of the desired products. The resin-supported catalyst exhibited stability and reusability, further enhancing the method's green credentials. Together, these studies highlighted the growing potential of aqueous micellar and heterogeneous catalysis in enabling sustainable, low-catalyst-loading transformations for the synthesis of bioactive molecules, with broad implications for pharmaceutical and fine chemical industries (Scheme 34).



Scheme 35. C–H amination reaction in water by palladium-based metallonitrene chemistry.



Scheme 36. Palladium-catalysed dmino Heck/cynation raction in water.



Scheme 37. Palladium-catalysed tandem addition/cyclization reaction of 2-(2-aminoaryl)acetonitriles.

7. Palladium-catalysed cyclization in aqueous phase

7.1. Palladium-catalysed intramolecular cyclization in aqueous phase

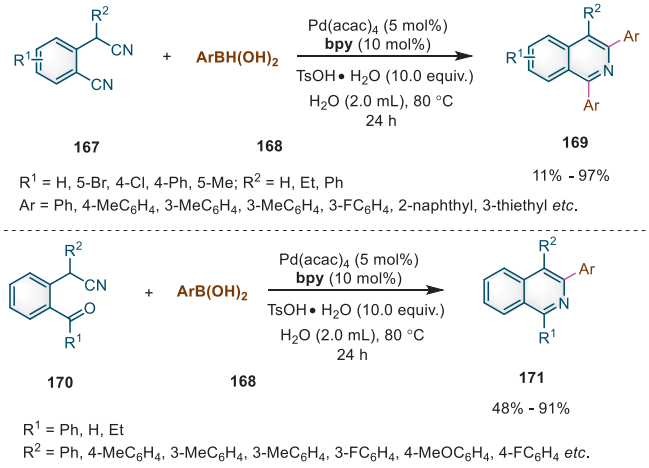
Cyclization reactions have proven to be a powerful and concise strategy for constructing complex molecular architectures by streamlining synthetic routes [88–91]. Among these, metal-catalysed cyclizations in aqueous media have garnered significant attention due to their compatibility with green chemistry principles. In 2016, Lu and coworkers demonstrated an intramolecular C–H amination reaction *via* palladium-catalysed metallonitrene chemistry in water, efficiently yielding carbazole derivatives with good to high yields [92]. Notably, while organic solvents alone yielded poor results, the addition of water significantly enhanced product formation, highlighting the critical role of the aqueous environment. Mechanistic investigations revealed that the electronic properties of the azidophenyl substituent profoundly influenced the rate-determining step, offering insights into substrate design. This method exhibited excellent functional group tolerance, enabling the straightforward synthesis of natural carbazole alkaloids such as glycoborine and clausines C, L, and H (Scheme 35). The use of water as a solvent not only improved reaction efficiency but also aligned with sustainable practices by avoiding hazardous organic solvents. Collectively, this work underscores the potential of aqueous metal-catalysed cyclizations as a versatile and environmentally benign platform for accessing structurally diverse and biologically relevant heterocycles.

In 2016, Wang and coworkers developed a palladium-catalysed domino Heck/cyanation reaction in water, enabling the efficient synthesis of 3-cyanomethyl oxoindoles with yields ranging from 38% to 96% [93]. This method distinguished itself by utilizing water as a green solvent, replacing conventional organic solvents, and eliminating the need for an external base to scavenge acids generated during the reaction. The domino process seamlessly combined Heck coupling with subsequent cyanation, streamlining the synthesis of 3-cyanomethylindolinone derivatives. Compared to existing literature protocols, this approach offered significant environmental and operational advantages, including reduced waste, enhanced safety, and simplified reaction conditions. Mechanistically, the aqueous environment likely facilitated proton transfer and stabilized reactive intermediates, contributing to the reaction's efficiency. The protocol's broad substrate scope and high functional group tolerance further underscored its practicality for accessing structurally diverse oxoindoles, which are valuable scaffolds in medicinal chemistry. Collectively, this work exemplified the integration of sustainable chemistry principles with catalytic innovation, providing a versatile and eco-friendly route to biologically relevant heterocycles (Scheme 36).

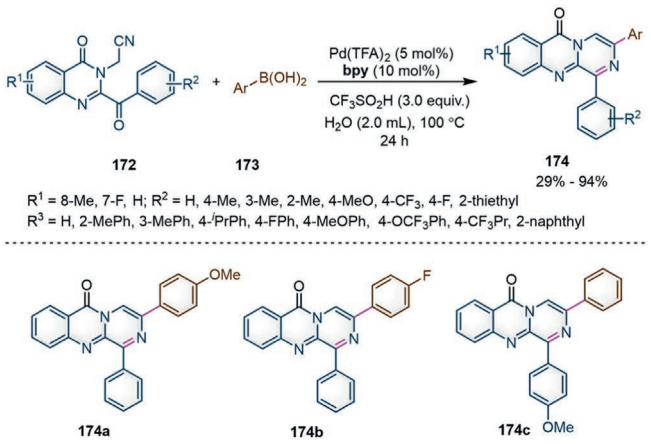
2-Arylindoles and their derivatives constitute a highly valuable class of heterocyclic compounds with widespread applications in medicinal chemistry and pharmaceutical development [94,95]. Given their biological significance, the pursuit of efficient, sustainable synthetic methodologies for their preparation has remained a vibrant area of research. In 2017, Chen and coworkers introduced an innovative palladium-catalysed tandem addition/cyclization strategy utilizing potassium aryltrifluoroborates as aryl donors—a choice motivated by their low toxicity, air stability, and moisture compatibility [96].

The reaction proceeded in an aqueous medium, where 2-(2-aminoaryl)acetonitriles reacted with potassium aryltrifluoroborates to afford 2-arylindoles in moderate to excellent yields. Notably, the protocol was amenable to laboratory-scale preparation, demonstrating its practicality for larger-scale synthesis. Beyond the primary cyclization, the researchers explored further transformations of the synthesized 2-arylindoles. For instance, substrate **162** underwent Baeyer-Villiger oxidation to yield 2-phenylbenzoxazinone, while sequential Baeyer-Villiger oxidation/amination furnished 2-phenylquinazolinone [97,98]. Additionally, sulfenylation reactions delivered 2-phenyl-3-(phenylthio)-1*H*-indole in good yields [99]. Collectively, this work provided a sustainable and scalable route to 2-arylindoles, offering access to structurally diverse derivatives with potential therapeutic applications. By leveraging stable, user-friendly reagents and an eco-friendly solvent, the study set a benchmark for environmentally conscious heterocycle synthesis (Scheme 37).

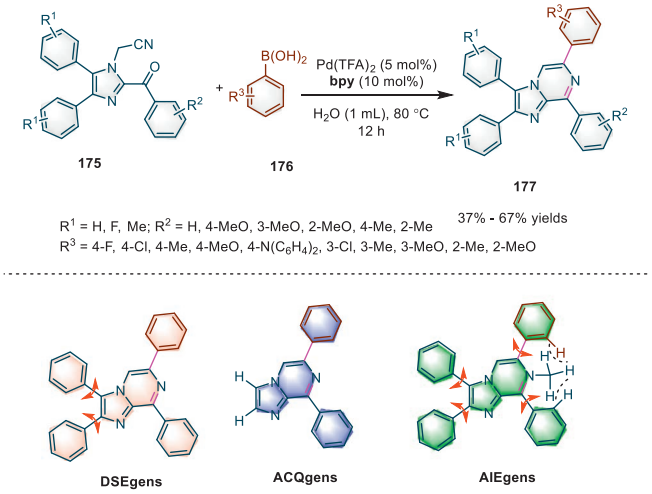
Building on their earlier work, Chen and coworkers further expanded the scope of palladium-catalysed aqueous cyclization reactions by employing 2-(cyanomethyl)benzonitriles or 2-(2-carbonylphenyl)acetonitriles with arylboronic acids as coupling partners [100]. This tandem cyclization protocol, conducted in water, demonstrated remarkable versatility, accommodating arylboronic acids bearing electron-donating (*e.g.*, *para*-methyl, 97%



Scheme 38. Palladium-catalysed tandem cyclization reaction of 2-substituted benzonitriles.



Scheme 39. Palladium-catalysed cascade C–C coupling/cyclization/aromatization of 2-(4-oxoquinazolin-3(4*H*)-yl)acetonitriles.

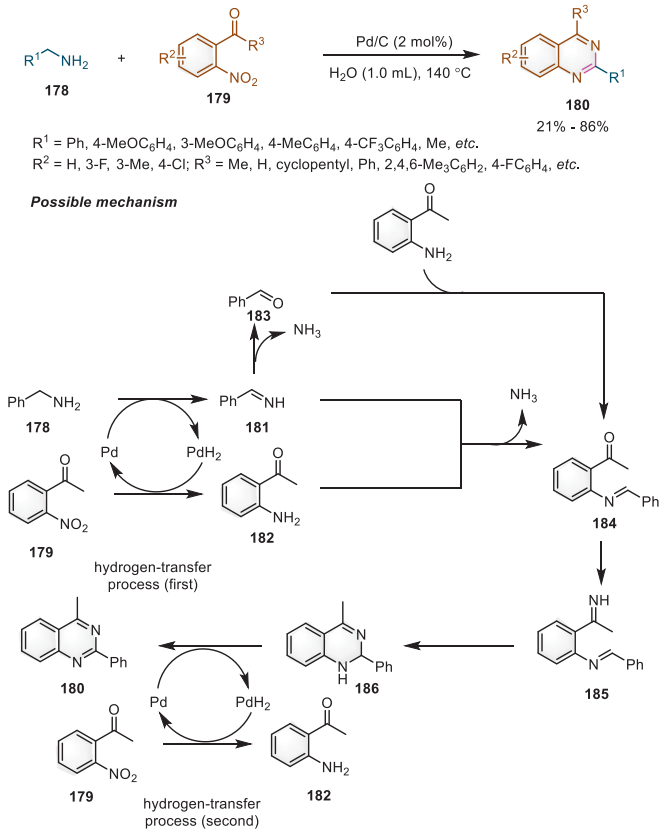


Scheme 40. Palladium-catalysed cyclization for the synthesis of multi-substituted imidazo[1,2-*a*]pyridazine.

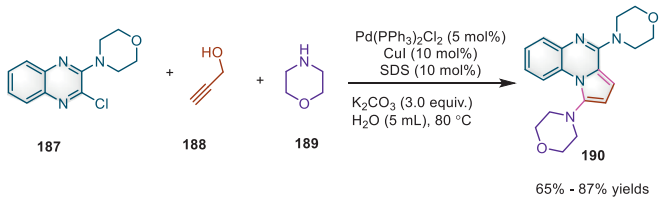
yield) and electron-withdrawing groups (*e.g.*, *para*-fluoro, 85% yield), as well as nitriles substituted with diverse functional groups. The method efficiently yielded a range of isoquinoline derivatives (36%–92% yields) featuring methoxy, trifluoromethyl, and other substituents, highlighting its functional group tolerance. Mechanistic studies, including control experiments and DFT calculations, revealed a pathway involving carbopalladation of the C(sp^3)-cyano group followed by intramolecular cyclization (Scheme 38). In 2020, the same group advanced the field by developing a palladium-catalysed cyclization of 2-(arylamino)benzonitriles with arylboronic acids, enabling the synthesis of 9-arylacridines, a class of heterocycles with potential optoelectronic and biological applications [101]. This aqueous-phase reaction leveraged the stability of arylboronic acids and the nucleophilicity of arylamino nitriles, proceeding through a similar Pd(0)/Pd(II) catalytic cycle with high regioselectivity. Parallelly, in 2019, Yu and coworkers reported a Pd-catalysed domino cyclization of benzonitriles with arylboronic acids to construct 4-arylquinazoline scaffolds [102]. This method utilized a sequential C–N bond formation and cyclization process, demonstrating compatibility with substituted arylboronic acids and delivering quinazolines in moderate to good yields. The reaction's efficiency was attributed to the *in situ* generation of a palladacycle intermediate, which facilitated rapid cyclization under mild conditions.

In 2021, Chen and coworkers reported a palladium-catalysed cascade C–C coupling/cyclization/aromatization of 2-(4-oxoquinazolin-3(4*H*)-yl)acetonitrile derivatives with arylboronic acids in water [103]. This method was not only carried out in a green solvent (water), but also exhibited good functional tolerance, enabling the synthesis of a variety of pyrazino-fused quinazolinones in 29%–94% yields. The authors also investigated the fluorescence-structure relationship of certain molecules, and found that all compounds emitted intense green light near 500 nm, accompanied by significant Stokes shifts exceeding 100 nm. Such substantial Stokes shifts help to mitigate fluorescence self-quenching, a feature that is advantageous for applications in optoelectronics and biology. Notably, compounds **174a** and **174c** exhibited higher quantum yields, suggesting that the incorporation of electron-donating groups can boost the luminescent efficiency of quinazolinone derivatives. In addition, compound **174b** exhibits aggregation-induced emission characteristics along with a substantial Stokes shift (Scheme 39).

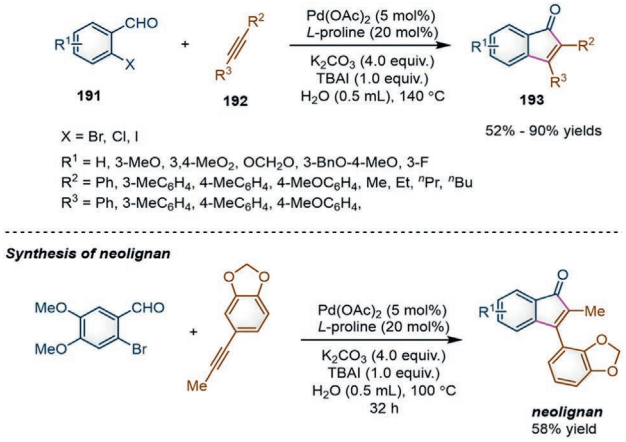
In 2022, Zou and coworkers reported a tandem reaction in water promoted by palladium catalysis for the synthesis of multi-substituted imidazo[1,2-*a*]pyridazine derivatives with dual-state emission (DSE) properties [104]. The authors used 2-(2-benzoyl-4,5-diphenyl-1*H*-imidazol-1-yl)acetonitrile (**175a**) and phenylboronic acid (**176a**) as model substrates, optimizing the reaction parameters. The experiment results suggested that the desired product could be efficiently synthesized under the following conditions: Water as the solvent, $Pd(TFA)_2$ as the catalyst, 2,2′-bipyridine (bpy) as the ligand, no additives, and a reaction temperature of 80 °C for 12 h. On this basis, the authors investigated the scope of the substrates and found that a variety of *N*-substituted 2-acylimidazoles and boronic acid substrates were well tolerated, affording the desired multi-substituted imidazo[1,2-*a*]pyridazine **177** in 37%–67% yields. Through fluorescence and mechanistic studies, the authors thought the crucial role of the neighboring benzene rings in maintaining the aggregated or solid-state emission of the DSE molecules. Moreover, the introduction of additional methyl groups in DSEgens disrupted the coplanarity, thereby generating corresponding AIEgens. Further live-cell imaging studies highlighted that the novel DSEgens could serve as specific lipid droplet (LD) probes across a range of concentrations. This work not only provided an environmentally friendly and cost-effective method for the synthesis of DSE molecules but also offered an effective strategy for the design, synthesis, and discovery of new DSE molecules with potential practical applications (Scheme 40).



Scheme 41. Palladium-ctalyzed hdrogen-tansfer cclization of ntroacetophenones.



Scheme 42. Palladium-catalysed multi-component cyclization reaction in water.



Scheme 43. Palladium-catalysed cyclization strategy of *ortho*-halobenzaldehydes with internal alkynes.

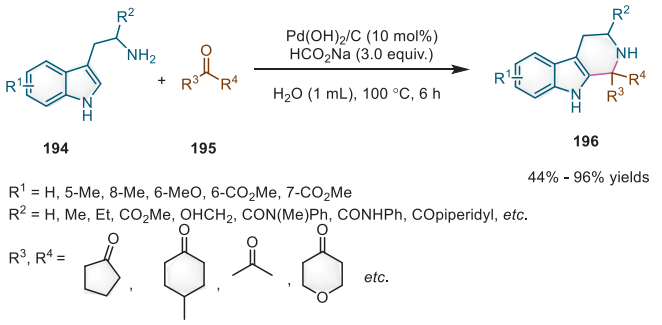
7.2. Palladium-catalysed intermolecular cyclization in aqueous phase

In 2016, Wan and coworkers disclosed an efficient, sustainable, palladium-catalysed hydrogen-transfer cyclization reaction for the synthesis of quinazoline compounds containing C–N bonds [105]. The authors used a commercial Pd/C catalyst to achieve the oxidative amination of C(sp^3)-H bonds in *o*-nitroacetophenone with benzyl amines or amino acids in water, constructing C–N bonds through a C–N bond cleavage-formation sequence. This method featured broad substrate scope, good recyclability of the catalyst, and excellent tolerance to air, Notably, additional oxidants, ligands, or bases did not require, thus offering a new and practical approach for the formation of complex C–N bonds. Based on control experiments and literature reports, the authors proposed a plausible mechanism. Initially, the dehydrogenation of benzylamine generated an imine and a palladium-hydride species (PdH_2), with the latter reducing the nitroarene to the corresponding amine. Subsequently, the imine underwent C–N bond cleavage to form an intermediate, which was then converted to the final product through cyclization and a second hydrogen-transfer process (Scheme 41).

Later, Keivanloo and coworkers disclosed a palladium-catalysed *multi*-component cyclization reaction in water for the synthesis of 1,4-disubstituted pyrrolo[1,2-*a*]quinoxaline derivatives [106]. The reaction owned well tolerated, using 3-substituted-2-chloroquinoxaline, propargyl alcohol, and secondary amines as starting materials, the method could efficiently synthesize the desired products under mild conditions *via* a one-pot reaction, with simple and controllable reaction conditions. In addition, this method had high atom economy, with no need for complex protection and deprotection steps during the reaction, short reaction time, and no complicated post-treatment process, resulting in good yields of the products (Scheme 42).

In 2018, Satyanarayana and colleagues developed a palladium-catalysed cyclization protocol for *ortho*-halobenzaldehydes with internal alkynes, employing water as the reaction solvent [107]. This synthetic strategy proceeds *via* sequential acylation and intramolecular aldol condensation reactions, and exhibits excellent regioselectivity-an attribute that is particularly pronounced when unsymmetrical alkylarylacetylenes are used as substrates. Notably, the method features high atom economy, obviating the need for intricate protection and deprotection steps throughout the reaction process. Additionally, it offered the advantages of a short reaction duration and simple post-reaction workup procedures, enabling the formation of target products in good yields. By leveraging this protocol, the authors successfully synthesized a series of indenone derivatives bearing diverse substituents, thereby verifying the broad substrate scope of the method. Of further significance, this cyclization strategy also demonstrates high efficacy in natural product synthesis, as exemplified by its successful application in the preparation of neolignane (Scheme 43).

Transition-metal-catalysed C–H functionalization has emerged as a powerful strategy for constructing C–C bonds, with directing groups (DGs), including removable DGs, traceless DGs, and transient directing groups (TDGs), being successfully leveraged to enhance the efficiency of such reactions. In 2019, Li and colleagues developed a palladium-catalysed "two-in-one" protocol for C–H bond functionalization in aqueous media [108]. The core innovation of this method resides in the employment of a transient directing group (TDG) as a reactive component: this TDG not only guides the C–H bond functionalization process but is also ultimately incorporated into the target product, eliminating the need for post-reaction removal of the directing group. Notably, this strategy enabled the synthesis of a series of tetrahydro-β-carboline derivatives in good yields, with successful access to natural products such as Komavine and Spiroindolone, findings that underscore the broad substrate scope of the method. Of further significance, this approach is not limited to the construction of tetrahydro-β-carboline scaffolds; it can also be extended to



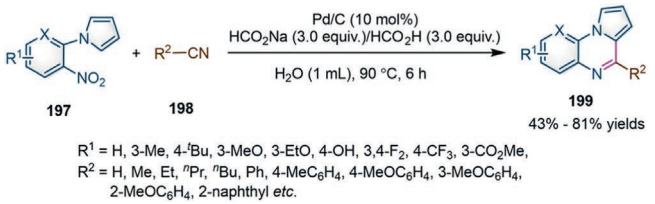
Scheme 44. Palladium-catalysed "two-in-one" method in water for the functionalization of C–H bonds.

other electron-deficient aromatic systems, as exemplified by its application in the C2 functionalization of pyridine. Deuterium-labeling experiments provided mechanistic insights, confirming that the transient directing group (specifically the imine moiety) plays a pivotal role in accelerating C–H bond activation, thereby facilitating the overall reaction (Scheme 44). Subsequently, the same research group reported a palladium-catalysed transformation that converts phenols into tetrahydro-β-carboline derivatives bearing a spirocyclic moiety at the C-1 position [109]. This reaction proceeds through a sequential cascade of key steps: Cleavage of the C(Ar)-O bond in phenols, activation of the C–H bond in tryptamines, and subsequent formation of C–N and C–C bonds. A wide range of substituted phenols were found to react with diverse tryptamine derivatives under the optimized conditions, consistently affording the desired spirocyclic tetrahydro-β-carboline products in good yields-further demonstrating the versatility and synthetic utility of this palladium-catalysed strategy.

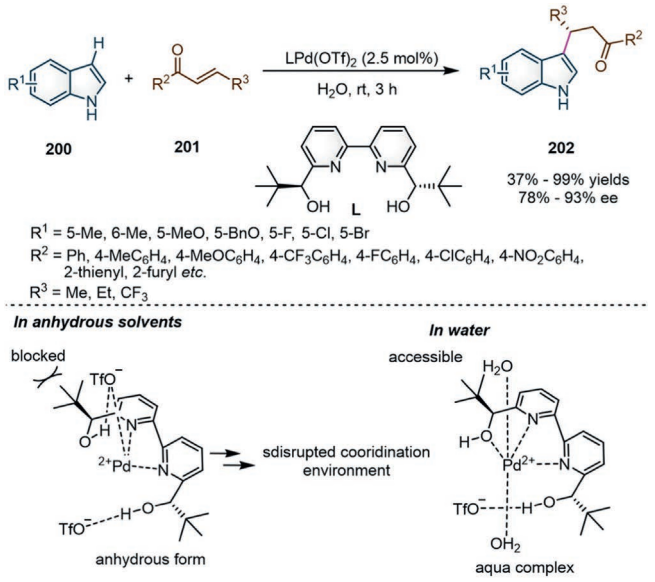
In 2023, Xie and colleagues reported a palladium-catalysed transfer hydrogenation protocol for the synthesis of tetrahydro-β-carbolines, which enables C–H bond functionalization under aqueous conditions by employing nitriles as carbon synthons [110]. A key feature of this reaction lies in the use of low-cost sodium formate/formic acid (HCOONa/HCOOH) as hydrogen donors; this design obviates the requirement for high-pressure hydrogen gas, a common hazard in traditional hydrogenation processes, and thus substantially enhances operational safety. Notably, the C–H bond functionalization step exhibits excellent regioselectivity, ensuring the precise formation of the target tetrahydro-β-carboline scaffold. Moreover, the reaction system demonstrates broad tolerance toward a diverse array of functional groups, including electron-donating substituents (*e.g.*, -Me, -OMe, -$N(CH_3)_2$, -naphthyl), electron-withdrawing substituents (*e.g.*, -F, -CF_3), and ester groups (-$COOCH_3$), a characteristic that expands its applicability in the synthesis of structurally varied tetrahydro-β-carboline derivatives. In addition to its synthetic versatility and safety advantages, this method also features practical sustainability: the palladium catalyst can be easily recovered *via* simple filtration following the reaction. Importantly, the recovered catalyst maintains catalytic activity even after at least five cycles of reuse, with no significant deactivation observed (Scheme 45). This recyclability not only reduces the cost associated with precious metal catalysts but also minimizes environmental impact, further highlighting the utility of this protocol.

8. Palladium-catalysed asymmetric reaction in aqueous phase

Chiral aqua or hydroxo complexes of transition metals have attracted considerable attention owing to their substantial potential for application in catalytic processes involving carbon-carbon bond formation, a capability that surpasses that of their corresponding anhydrous counterparts. The coordinating water molecules in aqua



Scheme 45. Palladium-catalysed transfer hydrogenation method for the synthesis of tetrahydro-β-carbolines.



Scheme 46. Palladium-catalysed enantioselective catalytic functionalization of indole C–H bonds in aqueous systems.

complexes engage in significantly stronger hydrogen bonding interactions than free water molecules, enabling them to participate in intramolecular hydrogen bonding within the first hydration shell and, in certain cases, conferring pronounced Brønsted acidity.

In 2020, Yang and coworkers demonstrated a palladium-catalysed asymmetric ring-opening (ARO) reaction of oxabenzonorbornadienes with a diverse array of alkoxysilanes, employing a mixed solvent system of dichloroethane (DCE) and water (3:1) [111]. This catalytic system exhibited notable advantages, including air stability, water insensitivity, and reduced catalyst loadings, while achieving moderate enantioselectivities across most substrates. Subsequently, Kobayashi and coworkers developed a robust yet highly Lewis acidic chiral aqua complex by utilizing a chiral 2,2′-bipyridine ligand that simultaneously functioned as a hydrogen-bond donor. This complex enabled the efficient and highly enantioselective catalytic functionalization of indole C–H bonds in aqueous media [112].

The cationic aqua palladium(II) complex demonstrated excellent stability in aqueous systems, resisting hydrolysis and deactivation even during extended reaction periods, thereby enhancing the practical feasibility and cost-effectiveness of the method. Through experimental and density functional theory (DFT) calculations, the authors elucidated a unique reaction mechanism wherein the aqua palladium(II) complex augmented its Lewis acidity *via* hydrogen bonding interactions with the trifluoromethanesulfonate anion. This interaction facilitated the electrophilic palladation of indole. Notably, enantioselectivity was unattainable in organic solvents or under solvent-free conditions but was exceptionally high in aqueous environments (Scheme 46).

9. Conclusion

Water has increasingly been recognized as an ideal green and sustainable reaction medium for organic synthesis, owing to its low cost, inherent safety, environmental benignity, and unique physicochemical properties, including high polarity and dielectric constant. Palladium-catalysed reactions occupy a central position in the construction of carbon-carbon and carbon-heteroatom bonds, with their execution in aqueous systems offering notable advantages, such as enhanced reactivity and selectivity coupled with a significant reduction in organic solvent consumption, a paradigm that aligns seamlessly with the principles of green chemistry. This review systematically summarizes recent advances (2015–2025) in palladium-catalysed organic transformations conducted in aqueous media, encompassing key reaction classes such as C–H activation, cross-coupling (*e.g.*, Suzuki-Miyaura, Mizoroki-Heck, Sonogashira), amination, carbonylation, Tsuji-Trost-type alkylation, cyclization, and asymmetric synthesis.

In this context, water as a green solvent significantly enhances reaction activity and selectivity while reducing dependence on organic solvents, due to its low cost, safety, environmental friendliness, and unique physicochemical properties, such as high polarity and dielectric constant. Chemists have made substantial progress in developing efficient and recyclable palladium catalysts, including Pd/C, palladium nanoparticles, and *N*-heterocyclic carbene (NHC)-Pd complexes, which enable catalyst loadings at the ppm level and support multiple reuse cycles. To address solubility challenges of organic substrates in water, surfactants (*e.g.*, Triton X-100) and amphiphilic ligands have been introduced, creating microreactive environments that facilitate reaction progress. The versatility of aqueous-phase systems extends beyond traditional coupling reactions to include C–H functionalization, multi-component cyclization, and asymmetric synthesis, providing efficient pathways for constructing complex molecules, such as natural products and pharmaceutical intermediates. Furthermore, mechanistic insights gained through density functional theory (DFT) calculations and experimental validation have elucidated the pivotal role of water molecules in forming hydrogen-bond networks, facilitating proton transfer, and stabilizing active intermediates, thereby offering a rational basis for catalyst design.

CRediT authorship contribution statement

Kai Wang: Writing – original draft. **Zhongwei Ye:** Writing – review & editing. **Er-Qing Li:** Project administration. **Linlin Shi:** Project administration.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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