Shielding Effect of Nanomicelles: Stable and Catalytically Active Oxidizable Pd(0) Nanoparticle Catalyst Compatible for Cross-Couplings of Water-Sensitive Acid Chlorides in Water

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ABSTRACT: Under the shielding effect of nanomicelles, a sustainable micellar technology for the design and convenient synthesis of ligand-free oxidizable ultrasmall Pd(0) nanoparticles (NPs) and their subsequent catalytic exploration for couplings of water-sensitive acid chlorides in water is reported. A proline-derived amphiphile, PS-750-M, plays a crucial role in stabilizing these NPs, preventing their aggregation and oxidation state changes. These NPs were characterized using 13C nuclear magnetic resonance (NMR), infrared (IR), and surface-enhanced Raman scattering (SERS) spectroscopy to evaluate the carbonyl interactions of PS-750-M with Pd. High-resolution transmission electron microscopy (HRTEM) and energy-dispersive X-ray spectroscopy (EDX) studies were performed to reveal the morphology, particle size distribution, and chemical composition, whereas X-ray photoelectron spectroscopy (XPS) measurements unveiled the oxidation state of the metal. In the cross-couplings of water-sensitive acid chlorides with boronic acids, the micelle’s shielding effect and boronic acids plays a vital role in preventing unwanted side reactions, including the hydrolysis of acid chlorides under basic pH. This approach is scalable and the applications are showcased in multigram scale reactions.

KEYWORDS: micellar catalysis, chemistry in water, acid chloride, nanoparticle, sustainability

INTRODUCTION

Palladium (Pd) serves as the preferred metal for catalysis in modern organic synthesis,1−3 as evidenced by its applications in several industrial processes4−6 and the 2010 Nobel Prize in chemistry.1,7,8 Its exceptional catalytic activity in constructing bonds between highly functionalized molecules stems from its ability to readily switch between oxidation states for achieving the desired reaction pathway.9,10 In general, most Pd-mediated catalytic processes operate under Pd(0) to Pd(II) or Pd(II) to Pd(IV) cycles.1,11 The latter two-electron catalytic cycle’s scope and sustainability are often limited by the requirement of stronger oxidants and/or directing groups in the substrate,12,13 whereas the Pd(0)/Pd(II) cycle can be attained using a broad range of electrophiles and nucleophiles under mild conditions.2,14 Many significant advancements have been reported demonstrating the efficient carbon−carbon and carbon−heteroatom bond construction,2,14−16 often relying on new catalyst designs to generate and stabilize the catalytically essential Pd(0) species. These generally focus on fine-tuning the steric and electronic parameters associated with the ligand bound to the Pd atom.16−18

especially in heterogeneous and quasi-homogeneous forms, also plays a critical role in catalyst efficiency.

Recently, nanocatalysis (quasi-homogeneous) has emerged as a powerful tool to enable cross-couplings under mild conditions.19−22 Because of their improved surface to volume ratio, nanoparticle (NP) catalysts exhibit enhanced activity,20,21,23,24 selectivity,25,26 and recyclability20,21 compared to their homogeneous organometallic counterparts. These properties rely significantly on the NP’s morphology, size, and oxidation state. The nature of the ligand/capping agent and the kind of nucleation determine the size, shape, and morphology of resulting NPs.28−30 Generally, phosphines or nitrogen-based ligands are required for the desired properties.20,21,27,28 Often, such ligands adversely affect the sustainability parameters.20,21,27,31 In the absence of such ligands, Pd(0) readily
NMP,36 where the solvent
Suzuki
(Figure 1). We likewise demonstrate their utility in traditional applications in cross-couplings of water-sensitive acid chlorides
NPs from Pd(II) salt in an aqueous micellar solution and their report a phosphine ligand-free synthesis of ultrasmall Pd(0)
oxidative cross-couplings under mild conditions. Herein, we and their accommodation in the micellar interface enabled
consequence of uniformly distributed ultrasmall NPs stabilized
of organic synthesis. The broad utility of these catalysts are a
interest from a sustainability perspective as water serves as the
green and preferred solvent.37

Our study began with the synthesis of Pd(0) NPs, achieved by suspending Pd(OAc)2 as the NP precursor in an aqueous
• phosphine-free ultrasmall Pd(0) nanoparticles

Figure 1. Phosphine ligand-free Pd(0) NPs for sustainable C−C couplings.

oxidizes to Pd(II), causing agglomeration of NPs. Removing
these ligands without compromising the catalytic activity and
aforementioned physical nature of NPs is always highly
desirable, especially for large-scale applications where cost,
sustainability, and ease of product purification are critical. Hence, solvent-stabilized Pd(0) NPs have recently emerged as a viable alternative.32−34 Traditionally, the synthesis of such
NPs relies on toxic organic solvents, such as DMF34,35 and
NMP,38 where the solvent’s tertiary amide group plays a vital role in stabilizing the NP.

Designing an amphiphile possessing structural features similar to DMF and NMP could enable the synthesis, stabilization, and applications of phosphine-free Pd(0) NPs under aqueous conditions. This synthetic approach could be of interest from a sustainability perspective as water serves as the
green and preferred solvent.37−39 Realizing the aforementioned
needs while advancing chemistry in water, our laboratory has
developed a proline-based amphiphile PS-750-M that mimics
dipolar−aprotic solvents, such as DMF, NMP, and
DMAc.40−44 Incorporating a tertiary amide group into the
amphiphile helps stabilize the NPs and facilitate their delivery
into the micellar interior or polar−nonpolar interface.45−47

Our group recently leveraged this amphiphile’s ability to
stabilize Pd(II) NPs and employed it in efficient oxidative
Mizoroki−Heck type couplings.48 Stabilization of Pd(II) NPs and their accommodation in the micellar interface enabled oxidative cross-couplings under mild conditions. Herein, we report a phosphine ligand-free synthesis of ultrasmall Pd(0) NPs from Pd(II) salt in an aqueous micellar solution and their applications in cross-couplings of water-sensitive acid chlorides
(Figure 1). We likewise demonstrate their utility in traditional
Suzuki−Miyaura couplings, which are established workhorses of organic synthesis. The broad utility of these catalysts are a
consequence of uniformly distributed ultrasmall NPs stabilized by PS-750-M.

## RESULTS AND DISCUSSION

Our study began with the synthesis of Pd(0) NPs, achieved by suspending Pd(OAc)2 as the NP precursor in an aqueous
solution of PS-750-M and reducing it with phenylboronic acid under basic pH. The base activates the phenylboronic acid,
causing transmetalation on Pd(II) by phenyl nucleophiles. The fast reductive elimination of biphenyl, rapid nucleation, and in situ capping of resulting NPs with PS-750-M provide ultrasmall
and highly active Pd(0) NPs (Scheme 1; for details, see page S2 in the Supporting Information). This mild synthetic route is scalable and completely avoids harsh reductants (MeMgBr,
LAH, or NaBH4) and toxic organic solvents (CH2Cl2,
THF).20,21,47,49 The NPs obtained by this mild technology were characterized using a variety of analytical techniques. Infrared (IR) and 13C nuclear magnetic resonance (NMR)
spectroscopy, and surface-enhanced Raman scattering (SERS)
were used for probing the interaction between Pd and the
carbonyls of PS-750-M, whereas high-resolution transmission electron microscopy (HRTEM) was employed to examine morphology and particle size distribution. Energy-dispersive X-
ray spectroscopy (EDX) mapping allows for the determination of the chemical composition, and X-ray photoelectron spectroscopy (XPS) allows for studying the metal’s oxidation state.

13C NMR studies were performed to probe the interaction of the carbonyl functional groups of PS-750-M with Pd (Figure
2A; also see, page S6 of the Supporting Information). The ester and amide carbonyls of the free amphiphile appeared at
173.4 and 173.1 ppm, respectively, whereas the acetate
ester carbonyl of Pd(OAc)2 appeared at 172.8 ppm. The

Scheme 1. Nanoparticle Synthesis

![Scheme 1. Nanoparticle Synthesis](https://doi.org/10.1021/jacsau.1c00236)

The multiplicity of 13C signals from the carbonyls of PS-750-M are due to the
presence of different sized micelles. To con
firm metal-amphiphile interactions, infrared spectroscopic (IR) studies were also
performed (see page S5 of the Supporting Information). In the IR spectrum of the metal-free PS-750-M, the stretching frequency of carbonyl functional groups appears at 1711 and
1640 cm−1. The ester carbonyl of the Pd(OAc)2 shows a

[Image 170x702 to 214x745]

[Image 253x640 to 393x737]

[Image 505x454 to 541x491]
However, the IR spectrum of the NPs was distinct from PS-750-M and Pd(OAc)$_2$. A new set of signals appeared at 1736, 1644, and 1567 cm$^{-1}$ suggesting binding of the amphiphile’s carbonyls with the metal NP (Figure 2B).

To further confirm the Pd-PS-750-M interaction and probe the functional groups responsible for interaction, we performed SERS analysis of PS-750-M-bound Pd NPs, neat PS-750-M, and Pd(OAc)$_2$. Figure 3 shows a SERS spectrum of Pd NPs encapsulated by micelles of PS-750-M (red curve). Vibrational modes with peaks at 1615 and 1762 cm$^{-1}$ are assigned to the carbonyl vibrations from the amide and ester, respectively. The SERS spectrum from neat PS-750-M without Pd (blue curve) shows an amide carbonyl vibration at 1629 cm$^{-1}$ and an ester carbonyl vibration at 1771 cm$^{-1}$. The decrease in Raman shift of the carbonyl vibrational modes with Pd present indicates binding of the carbonyls with the Pd, which weakens the C=O bond and causes the shift in peak frequency. Peaks at 1475, 1316, and 987 cm$^{-1}$ in the neat PS-750-M also shift to 1423, 1311, and 949 cm$^{-1}$ when Pd NPs are present. These vibrational modes are likely associated with the carbonyl carbon and amide/ester nitrogen/oxygen atoms (e.g., OCN, CCN, OCO, CCO) supporting the assertion that the carbonyl is physisorbed to Pd. A Raman spectrum from a precursor Pd(OAc)$_2$ crystal is shown for comparison (black curve). Therefore, based on SERS, IR, and NMR analysis, the ester and amide functional groups of PS-750-M are responsible for metal-micelle binding.

HRTEM analysis indicated the formation of ultrasmall Pd NPs with an average size of 2.41 nm (Figure 4A–C). Likewise, scanning transmission electron microscopy-high-angle annular dark-field imaging (STEM–HAADF) reveals the NPs formation. However, these particles tend to aggregate easily under high-energy electron beam exposure limiting the acquisition of STEM–HAADF imaging (Figure 4D; see pages S3 and S4 in the Supporting Information). EDX mapping reveals the presence of the nitrogen from the amphiphile and Pd in the NPs (Figure 4E). These combined techniques confirmed the formation of ultrasmall Pd NPs. Further, the XPS analysis of the anhydrous NPs confirms the presence of both the Pd(II) and Pd(0) based on their distinct binding energies in the peak deconvolution spectrum of Pd 3d$/2$ (Figure 4F; see page S7 in the Supporting Information). Most likely, the presence of Pd(II) arises from the aerobic oxidation of surface Pd(0) to Pd(II) during the drying process.

Because of the facile transmetalation of arylboronic acids to PS-750-M-stabilized Pd NPs, our evaluation on the catalytic activity of these Pd(0) NPs started with the cross-couplings of acid chlorides and boronic acids, providing access to functionalized ketones under mild aqueous conditions.$^{50–52}$ Recognizing the widespread distribution of these compounds in pharmaceuticals, agrochemicals, and fine chemicals,$^{53–55}$ this transformation could be a greener alternative compared to the traditional multistep route involving Grignard addition to an aldehyde followed by oxidation of the resulting alcohol.$^{56,57}$ Therefore, we investigated the possibility of such a C–C coupling reaction catalyzed by phosphine-free Pd(0) NPs using benzoyl chloride (1) and 4-(trifluoromethyl)-phenylboronic acid (2) as benchmark substrates under aqueous micellar conditions.

Optimization studies revealed the dependence of the choice of the reaction medium, catalyst, base, and global concentration on the reaction outcome (Table 1; see pages S10–S12 in the Supporting Information). Optimal conditions involve 3
Replacing the base Na2CO3 with Et3N or KOH earth-abundant metals, such as Ni or Cu, results in traces of yield of the desired product concentration, providing 94% conversion and 90% isolated aq. PS-750-M as reaction medium with a 0.25 M global internal standard.  

Table 1. Optimization Studies

| entry | deviations from std. conditions | 3 (%) |  
|-------|-------------------------------|-------|
| 1     | none                          | 94 (90) |
| 2     | Ni NPs instead of Pd          | traces |
| 3     | Cu NPs instead of Pd          | traces |
| 4     | Et3N instead of Na2CO3        | 32    |
| 5     | KOH instead of Na2CO3         | 40    |
| 6     | H2O instead of PS-750-M       | 53    |
| 7     | THF instead of PS-750-M       | 66    |
| 8     | 0.5 mol % of Pd(0) NPs       | 52    |

*Conditions: 1 (0.25 mmol), 2 (0.275 mmol), NP catalyst (3 mol %), Na2CO3 (0.5 mmol), 1 mL of 3 wt % aq. PS-750-M, 23 °C, 3 h.  

mol % Pd(0) NPs, 2.0 equiv. of Na2CO3 as base, and 3 wt % aq. PS-750-M as reaction medium with a 0.25 M global concentration, providing 94% conversion and 90% isolated yield of the desired product 3 (entry 1). Replacing Pd with earth-abundant metals, such as Ni or Cu, results in traces of 3 (entries 2, 3). Replacing the base Na2CO3 with Et3N or KOH drops the reaction conversion to 32 and 40%, respectively (entries 4, 5). Considerable homocoupling of boronic acid 2 was observed (27%) when KOH base was used. The poor catalytic activity observed may be due to the competitive binding of Et3N with Pd occupying the catalytic sites. Likewise, the use of KOH may cause faster hydrolysis of benzyol chloride or disintegration of Pd-amphiphile binding. The importance of the amphiphile as a reaction medium in this catalytic reaction is evident as its removal provides only 53% conversion to 3 (entry 6); most likely, the acid chloride’s simultaneous reactivity with water is responsible for low conversion. Switching the reaction medium to THF is also detrimental, forming only 66% 3 (entry 7) along with the homocoupling of 2 and unreacted acid chloride, indicating the importance of aqueous micellar conditions for the desired reactivity. Deviation from optimal catalyst loading to 5000 ppm (0.5 mol %) provides 52% of the desired product in GC-MS analysis (entry 8; for details on catalyst loading, see page S10 in the Supporting Information). Furthermore, increasing the temperature to 45 °C with this low catalyst loading affords only 37% GC-MS conversion to 3 along with hydrolysis of the acid chloride (for details, see page S10 in the Supporting Information). Most notably, the reaction’s outcome significantly depends on the order of addition; the acid chloride must be added after cooling the mixture to 0 °C (for details, see pages S21 and S22 in the Supporting Information).

With the optimal reaction conditions established, the substrate scope was explored using combinations of various acid chlorides and aryl and heteroarylboronic acids (Table 2, 3–30). These studies indicated that the reaction outcome most likely does not rely on the coupling partner’s steric and electronic factors. The scope study showed excellent functional group tolerance. Fluoro (4, 6, 7, 13, 17, 27–29), nitro (5), ester (8), chloro (4, 8), and trifluoromethyl (3, 16, 21, 23, 28) groups were well tolerated. Notably, in these examples, fluoro functional groups may be susceptible to the S8Ar side reaction remained intact. Electron-deficient boronic acids with o-difluoro substituent showed good reactivity (6). Furthermore, arylboronic acids containing a terminal vinyl substituent cleanly reacted without undesired side reactions such as Heck-type coupling or polymerization, thus providing access to functionalized styrenes (11, 14, 20). Arylboronic acids possessing o-methyl (13, 17) or o-methoxy (15) substituents displayed good-to-excellent reactivity. Notably, the technology is amenable to cross-couplings of alkyl acid chloride, which are problematic considering their higher reactivity toward hydrolysis or ketene formation, under basic aqueous conditions (19, 20). For example, lauroyl chloride displayed good-to-excellent reactivity with various arylboronic acids, including terminal vinyl (20) and thiophenyl (19) groups. Other sulfur-containing heterocycles also exhibit excellent reactivity under these mild catalytic conditions (9, 10, 12–14, 19, 21, 22, 24, 27, 30). However, pyridyl-containing substrates completely inhibited the reaction, which may be due to the disruption of Pd-amphiphile binding due to competitive Pd-pyridine binding (for details see page S25 in the Supporting Information).

To evaluate the stability of acid chloride 1, three parallel reactions were conducted by dispersing benzoyl chloride in the basic micellar solution using standard reaction conditions as illustrated in Table 3. A nitrogen nucleophile morpholine was introduced to individual reactions at 0, 30, and 60 min, respectively. The amount of amide formation (1a) was monitored by GC-MS analysis. The % conversions to 1a

Figure 4. (A–C) HRTEM images and histogram of the NPs. (D) STEM-HAADF image. (E) EDX mapping analysis. (F) Peak deconvoluted XPS spectra of Pd.
provide an indirect idea of stability of acid chloride under these conditions (Table 3, entries 1−3; for details, see page S24 in the Supporting Information). On the basis of conversion to 1a, approximately half of 1 was hydrolyzed but the remaining still existed after 1 h. This indicates that the boronic acid may further play a role in determining the stability of acid chlorides by lowering the overall pH of the reaction mixture. Therefore, we determined the pH of a standard reaction mixture before and after the addition of boronic acid 2. The reaction mixture’s pH changed from 9.33 to 8.76. (for details, see page S23 in the Supporting Information). On the basis of these results, both the aqueous nanomicelles and arylboronic acid possibly play a significant role in determining the stability of acid chloride in aqueous medium.

Next, the activity of these NPs were evaluated for the ligand-free Suzuki−Miyaura (SM) couplings under mild micellar conditions. Considering this reaction’s broad importance,58−60 the ability to carry out this transformation without using any phosphine ligands under micellar conditions would be of great significance. Similar to the NP activity toward cross-couplings of acid chlorides, good-to-excellent catalytic activity was observed for SM couplings of functionalized aryl and heteroaryl halides and aryl- and heteroarylboronic acids (Table 4, 31−50). Excellent functional group tolerance was also observed in this transformation. Functional groups such as formyl (35, 42, 43, 45), chloro (34, 40, 47, 48, 50), cyano (33, 38, 39, 42, 44), fluoro (33, 35, 37, 38, 42−44, 47), nitro (34, 41, 49), ketone (37, 48, 49), trifluoromethyl (32), and amide (47) were all well-tolerated. Various heterocyclic boronic acids possessing benzodioxane (40, 44), benzothiophene (38, 39), and thiophene (32, 46) residues showed good-to-excellent reactivity. Notably, substrates susceptible to α-arylation were well tolerated, and no such side-product was observed (37, 48, 49).

Table 2. Substrate Scope for Ketone Synthesis

| Reaction | Yield (%) | Reaction | Yield (%) |
|----------|-----------|----------|-----------|
| 1        | 89        | 2        | 89        |
| 2        | 63        | 3        | 48        |

“Conditions: acid chloride (0.25 mmol), arylboronic acid (0.275 mmol), NP catalyst (3 mol %), Na2CO3 (0.5 mmol), 1 mL of 3 wt % aq. PS-750-M, 23 °C; all yields are isolated.

Table 3. Stability Analysis of Acid Chloride

| Entry | Time (min) | 1a (GC-MS conversion) (%) |
|-------|------------|--------------------------|
| 1     | 0          | 89                       |
| 2     | 30         | 63                       |
| 3     | 60         | 48                       |

“Conditions: Step 1, 1 (0.5 mmol), Na2CO3 (1.0 mmol), 2 mL 3 wt % aq. PS-750-M, 23 °C, 1 min; step 2, morpholine (2.5 mmol), 0−23 °C, 1 h; conversions based on GC-MS using mesitylene (0.5 mmol) as an internal standard.

Table 4. Substrate Scope for Suzuki−Miyaura Coupling

| Reaction | Yield (%) | Reaction | Yield (%) |
|----------|-----------|----------|-----------|
| 1        | 85%       | 2        | 86%       |
| 2        | 85%       | 3        | 90%       |
| 3        | 82%       | 4        | 90%       |

“Conditions: aryl halide (0.25 mmol), arylboronic acid (0.275 mmol), NP catalyst (3 mol %), K3PO4·H2O (0.75 mmol), 1 mL of 3 wt % aq. PS-750-M, 60 °C; all yields are isolated. bReaction temperature is 45 °C instead of 60 °C.
49). Even though these NPs are compatible for the coupling of a broad range of electrophiles and nucleophiles, these NPs are non-recyclable in nature.

To demonstrate the scalability of these transformations, we performed several reactions on a preparative scale. For example, benzoylation of 4-trifluoromethyl phenylboronic acid 2 was performed at the 20 mmol scale to obtain the desired ketone 3 in 86% isolated yield (Scheme 2A; see pages S17 and 18 in the Supporting Information). Likewise, these Pd(0) NPs were also employed on multigram scale (25 mmol) synthesis of intermediate 34, a boscalid synthon (Scheme 2B). The coupling of 1-bromo-2-nitrobenzene (51) with 4-chlorophenyl boronic acid (52) under mild micellar conditions provides 34 in 90% isolated yield. The yields in these large-scale reactions are similar to those obtained in small-scale reactions depicted in Tables 2 and 3.

Further, this technology’s application was evaluated on a compound from Merck’s informer library (Scheme 3A; for details, see page S19 in the Supporting Information). The Suzuki–Miyaura coupling of a highly functionalized triazole-containing oxazolidine derivative 53 with boronic acid 52 afforded the desired product 54 in 63% isolated yield. Another exciting feature of aqueous micellar nanocatalysis is the ability to enable sequential reactions without isolation of intermediates. Hydrogenation reactions under micellar conditions are often selective and do not demand high hydrogen pressure because of the enhanced solubility of hydrogen in the nanomicelles.25 Anticipating that our Pd(0) NPs would also perform selective hydrogenation, we extended our nanocatalysis scope to one-pot reactions involving cross-coupling and selective carbonyl reduction (Scheme 3B; see page S20 in the Supporting Information). After the SM coupling of 5-bromo-2-fluorobenzonitrile (55) with 4-formyl phenylboronic acid (56), the aldehyde group of the resultant biaryl 42 was selectively reduced in the presence of the sensitive fluoro and cyano groups to the corresponding benzyl alcohol 57 with excellent isolated yield (74%). Notably, the same NPs sequentially enabled both transformations in a single pot, simply by introducing hydrogen.

**CONCLUSION**

In conclusion, by harnessing the synergy between Pd(0) and PS-750-M, phosphine ligand-free Pd(0) NPs are developed for sustainable Suzuki–Miyaura couplings of acid chlorides and aryl halides. The synthetic protocols for NP formation and subsequent catalytic reactions are green and do not require organic solvents or harsh reductants. In these NPs, PS-750-M plays a vital role in stabilizing the Pd(0), circumventing the need for phosphine ligands. The NPs are active for high-valued transformations with broad substrate scope and excellent functional group tolerance. These NPs provide a convenient and scalable new nanotechnology that is benign by design, eco-friendly, and affordable.

**ASSOCIATED CONTENT**

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacsau.1c00236. Materials and methods, supplementary figures, supplementary tables, supplementary schemes, and analytical data (PDF)

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The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes
The authors declare no competing financial interest.

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REFERENCES
(1) Johansson Seechurn, C. C. C.; Kitching, M. O.; Colacot, T. J.; Snieckus, V. Palladium-Catalyzed Cross-Coupling: A Historical Contextual Perspective to the 2010 Nobel Prize. Angew. Chem., Int. Ed. 2012, 51, 5062–5085.
(2) Nicolou, K. C.; Bulger, P. G.; Sarlah, D. Palladium-Catalyzed Cross-Coupling Reactions in Total Synthesis. Angew. Chem., Int. Ed. 2005, 44, 4442–4489.
(3) Li, H.; Johansson Seechurn, C. C. C.; Colacot, T. J. Development of Preformed Pd Catalysts for Cross-Coupling Reactions, beyond the 2010 Nobel Prize. ACS Catal. 2012, 2, 1147–1164.
(4) Gardner, B. M.; Seechurn, C. C. C. J.; Colacot, T. J. Industrial Milestones in Organometallic Chemistry. Organometallic Chemistry in Industry. 2020, 1–22.
(5) Colacot, T. J. C. C. J. S. Organometallic Chemistry in Industry: A Practical Approach. In Focus on Catalysts; Colacot, T., Ed.; Wiley, 2020; Vol. 2020, pp 336.
(6) Buchwald, S. L.; Mauger, C.; Mignani, G.; Scholz, U. Industrial-Scale Palladium-Catalyzed Coupling of Aryl Halides and Amines - A Personal Account. Adv. Synth. Catal. 2006, 348, 23–39.
(7) Suzuki, A. Cross-Coupling Reactions Of Organoboranes: An Easy Way To Construct C-C Bonds (Nobel Lecture). Angew. Chem., Int. Ed. 2011, 50, 6722–6737.
(8) Negishi, E. Magical Power of Transition Metals: Past, Present, and Future (Nobel Lecture). Angew. Chem., Int. Ed. 2011, 50, 6738–6764.
(9) Beletskaya, I. P.; Cheprakov, A. V. The Heck Reaction as a Sharpening Stone of Palladium Catalysis. Chem. Rev. 2000, 100, 3009–3066.
(10) Hartwig, J. F. Carbon-Heteroatom Bond Formation Catalysed by Organometallic Complexes. Nature 2008, 455, 314–322.
(11) Kalyani, D.; Deprez, N. R.; Desai, L. V.; Sanford, M. S. Oxidative C-H Activation/C-C Bond Forming Reactions: Synthetic Scope and Mechanistic Insights. J. Am. Chem. Soc. 2005, 127, 7330–7331.
(12) Neufeldt, S. R.; Sanford, M. S. Controlling Site Selectivity in Palladium-Catalyzed C-H Bond Functionalization. Acc. Chem. Res. 2012, 45, 936–946.
(13) Ackermann, L. Carboxylate-Assisted Transition-Metal-Catalyzed C-H Bond Functionalizations: Mechanism and Scope. Chem. Rev. 2011, 111, 1315–1345.
(14) Ruiz-Castillo, P.; Buchwald, S. L. Applications of Palladium-Catalyzed C-N Cross-Coupling Reactions. Chem. Rev. 2016, 116, 12564–12649.
(15) Rayadurgam, J.; Sana, S.; Sasikumar, M.; Gu, Q. Palladium Catalyzed C-C and C-N Bond Forming Reactions: An Update on the Synthesis of Pharmaceuticals from 2015–2020. Org. Chem. Front. 2021, 8, 384–414.
(16) Hartwig, J. F. Evolution of a Fourth Generation Catalyst for the Amination and Thioetherification of Aryl Halides. Acc. Chem. Res. 2008, 41, 1534–1544.
(17) Deangelis, A. J.; Gildner, P. G.; Chow, R.; Colacot, T. J. Generating Active L-Pd(0) via Neutral or Cationic π-Allylpalladium Complexes Featuring Biaryl/Bipyrazolylphosphines: Synthetic, Mechanistic, and Structure-Activity Studies in Challenging Cross-Coupling Reactions. J. Org. Chem. 2015, 80, 6794–6813.
(18) Sury, D. S.; Buchwald, S. L. Dialkyaryl Phosphines in Pd-Catalyzed Amination: A User’s Guide. Chem. Sci. 2011, 2, 27–50.
(19) Favier, I.; Pla, D.; Gómez, M. Palladium Nanoparticles in Polyols: Synthesis, Catalytic Couplings, and Hydrogenations. Chem. Rev. 2020, 120, 1146–1183.
(20) Handa, S.; Wang, Y.; Gallou, F.; Lipshutz, B. H. Sustainable Fe-Pd Pd Nanoparticle Catalysis of Suzuki-Miyaura Cross-Couplings in Water. Science 2015, 349 (6252), 1087–1091.
(21) Handa, S.; Jin, B.; Bora, P. P.; Wang, Y.; Zhang, X.; Gallou, F.; Reilly, J.; Lipshutz, B. H. Sonogashira Couplings Catalyzed by Fe Nanoparticles Containing ppm Levels of Reusable Pd, under Mild Aqueous Micellar Conditions. ACS Catal. 2019, 9, 2423–2431.
(22) Cortes-Clerget, M.; Akporji, N.; Takale, B. S.; Wood, A.; Landstrom, E.; Lipshutz, B. H. Earth-Abundant and Precious Metal Nanoparticle Catalysis. In Nanoparticles in Catalysis; Kobayashi, S., Ed.; Topics in Organometallic Chemistry; Springer, 2020; Vol. 66, pp 77–129. DOI: 10.1007/3418_2020_36
(23) Farina, V. High-Turnover Palladium Catalysts in Cross-Coupling and Heck Chemistry: A Critical Overview. Adv. Synth. Catal. 2004, 346, 1533–1582.
(24) Hamasaka, G.; Roy, D.; Tazawa, A.; Uozumi, Y. Arylation of Terminal Alkynes by Aryl Iodides Catalyzed by a Parts-per-Million Loading of Palladium Acetate. ACS Catal. 2019, 9, 11640–11646.
(25) Bihani, M.; Bora, P. P.; Nachtegaal, M.; Jasinski, J. B.; Plummer, S.; Gallou, F.; Handa, S. Microballs Containing Ni(0)Pd(0) Nanoparticles for Highly Selective Micellar Catalysis in Water. ACS Catal. 2019, 9, 7520–7526.
(26) Somorjai, G. A.; Li, Y. Selective Nanocatalysis of Organic Transformation by Metals: Concepts, Model Systems, and Instruments. Top. Catal. 2010, 53, 832–847.
(27) Ansari, T. N.; Taussat, A.; Clark, A. H.; Nachtegaal, M.; Plummer, S.; Gallou, F.; Handa, S. Insights on Bimetallic Micellar Nanocatalysis for Buchwald-Hartwig Aminations. ACS Catal. 2019, 9, 10389–10397.
(28) Da Silva, F. P.; Fiorio, J. L.; Rossi, L. M. Tuning the Catalytic Activity and Selectivity of Pd Nanoparticles Using Ligand-Modified Supports and Surfaces. ACS Omega 2017, 2, 6014–6022.
(29) Chen, J.; Zhang, Q.; Wang, Y.; Wan, H. Size-Dependent Catalytic Activity of Supported Palladium Nanoparticles for Aerobic Oxidation of Alcohols. Adv. Synth. Catal. 2008, 350, 453–464.
(30) Ozkar, S.; Finke, R. G. Palladium(0) Nanoparticle Formation, Stabilization, and Mechanistic Studies: Pd(acac)_2 as a Preferred Precursor, [Bu_4N]_2HPO_4 Stabilizer, plus the Stoichiometry, Kinetics, and Minimal, Four-Step Mechanism of the Palladium Nanoparticle Formation and Subsequent Oxidation. Langmuir 2016, 32, 3699–3716.
(31) Handa, S.; Andersson, M. P.; Gallou, F.; Reilly, J.; Lipshutz, B. H.; Handa Pd: A General Ligand Enabling Sustainable Ppm Levels of Palladium-Catalyzed Cross-Couplings in Water at Room Temperature. Angew. Chem., Int. Ed. 2016, 55, 4914–4918.
(32) Doherty, S.; Knight, J. G.; Backhouse, T.; Abood, E.; Al-Shaikh, H.; Clemmet, A. R.; Ellison, J. R.; Bourne, R. A.; Chamberlain, T. W.;
Pd Nanoparticles as Catalyst for Formic Acid Electro-Oxidation. Zhang, X. One-Pot Synthesis of Graphene-Supported 2015 1790.
Amide Couplings in Water: Extraction, Column Chromatography, Shielding Effect of Micelle for Highly Effective and Selective 3037 4enes in Water under Mild Conditions.
Micelle-Enabled Clean and Selective Sulfonylation of Polyfluoroar-016

Ibrahim, F.; Liang, S.; Hammond, G. B.; Gallou, F.; Handa, S. 2018 ACS Catal. Enantioselective Palladium Catalysis for Convenient sp2-sp3 Coupling of 10970. Bihani, M.; Ansari, T. N.; Finck, L.; Bora, P. P.; Jasinski, J. B.; 10963 103. Klingler, F. D. Asymmetric Hydrogenation of Prochiral Amino Ketones to Amino Alcohols for Pharmaceutical Use. Acc. Chem. Res. 2007, 40, 1367–1376.

(50) Xin, B.; Zhang, Y.; Cheng, K. Phosphine-Free Cross-Coupling Reaction of Arylboronic Acids with Carboxylic Anhydrides or Acyl Chlorides in Aqueous Media. J. Org. Chem. 2006, 71, 5725–5731.

(51) Blangetti, M.; Rosso, H.; Prandi, C.; Degostino, A.; Venturrello, P. Suzuki-Miyaura Cross-Coupling in Acylation Reactions, Scope and Recent Developments. Molecules 2013, 18, 1188–1213.

(52) Buchspies, J.; Soostak, M. Recent Advances in Acyl Suzuki Cross-Coupling. Catalysts 2019, 9, 53–76.

(53) Sawai, K.; Tatumi, R.; Nakahodo, T.; Fujihara, H. Asymmetric Suzuki-Miyaura Coupling Reactions Catalyzed by Chiral Palladium Nanoparticles at Room Temperature. Angew. Chem., Int. Ed. 2008, 47, 6917–6919.