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**Palladium Catalysis**

# Water-Stabilized Three- and Four-Atom Palladium Clusters as Highly Active Catalytic Species in Ligand-Free C–C Cross-Coupling Reactions**

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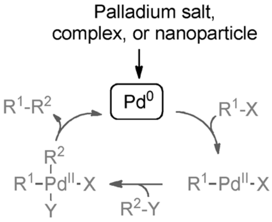
Palladium-catalyzed cross-coupling reactions are recognized as fundamental transformations in chemistry.[1] The general mechanism for these reactions under ligand-free conditions (Scheme 1) involves an oxidative addition–reductive elimination cycle of a palladium(0) species generated in situ.[2] Despite considerable effort during last three decades, the exact nature of the $Pd^0$ catalytic species still remains unveiled.



***Scheme 1.*** General mechanism for palladium-catalyzed cross-coupling reactions under ligand-free conditions.

It is accepted that the oxidative-addition step controls the overall rate of the coupling, and catalyst optimization has been a key point of research, since the reactivity of the organic halide ($I > Br \gg Cl$) is inversely proportional to its availability ($Cl > Br \gg I$) and cost.[3] Although successful catalytic systems have also been developed with palladium salts,[4,5] very small amounts of phosphine palladium complexes[6–9] enable the coupling of iodo-, bromo-, and chloroarenes under mild conditions. The implementation of these catalysts in advanced organic synthesis has been satisfactory, and many intermediates en route to pharmaceutical, agrochemical, polymer, and materials-science products have been synthesized according to these protocols.[10] However, industry still relies in many cases on bromo rather than chloro derivatives, since the former present a good cost/reactivity relationship that allows the use of simpler palladium catalysts. For example, the most common UV-B sunscreen on the market, 2-ethylhexyl-*p*-methoxycinnamate, is manufactured worldwide in multiton quantities by Heck coupling[11] of the corresponding bromoderivative with palladium nanoparticles on carbon as a catalyst at 180 °C and without additional ligands,[12] despite the fact that highly active and selective palladium complexes can operate at lower reaction temperatures.

Different palladium compounds, such as salts,[4,5] complexes in oxidized or reduced form,[13,14] and nanoparticles,[15–18] are able to catalyze the coupling of bromo compounds. Although palladium complexes catalyze the coupling at mild temperatures without an induction period, a reaction-induction time is observed for any palladium catalyst under heating conditions (> 130 °C), as explained by the mechanism in Scheme 1.[2,19] Another experimental observation is the degradation of palladium salts and complexes to form nanoparticles in few minutes under coupling conditions,[6] and some authors have proposed that the starting $Pd^0$ active species are these nanoparticles or some entities leached from them.[4,6,20–28]

Herein, we show that regardless of the starting palladium source, that is, whether it is a salt, a complex, or nanoparticles, C–C bond-forming reactions, such as Heck, Sonogashira, Suzuki, and Stille coupling reactions, of iodo and bromo derivatives do not proceed at the higher rates until small palladium clusters of three and four atoms are formed[16,28,29] in *N*-methylpyrrolidone (NMP) under heating: common experimental reaction conditions for Heck coupling.[2,4–6,12] After identifying the exact active species, we found that the three- and four-palladium-atom clusters can be stabilized by water and stored for at least one month for later use, when turnover frequencies between $10^5$ and $10^6$ molecules of product per atom of palladium per hour were observed: the highest values reported to date for some of the reactions studied. We also show that not only water but also other nucleophiles dislodge palladium clusters from nanoparticles, and how the nature of the nucleophile and the nanoparticle size both affect cluster formation. Although the palladium clusters presented herein function at temperatures about 70 °C higher than those used with the best palladium complexes, and although they are not active with less activated chloro derivatives, they are nevertheless useful for the synthesis of a large number of compounds that are accessible by palladium catalysis under these ligand-free conditions, including industrially important products, such as 2-ethylhexyl-*p*-methoxycinnamate.

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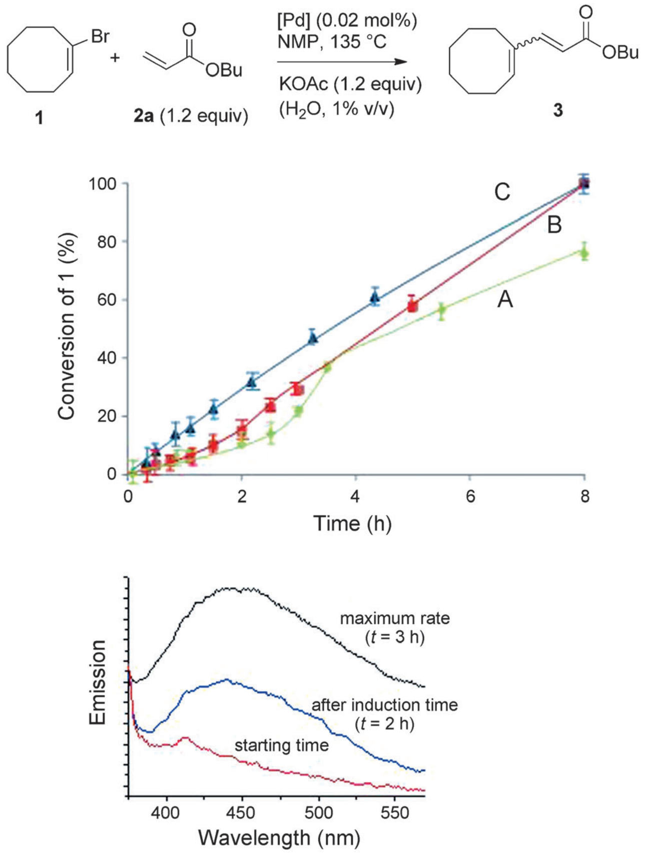
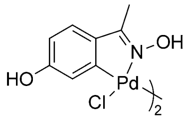


***Figure 1.*** Top graph: Conversion–time plot for the Heck coupling between **1** and **2a** with different palladium catalysts in anhydrous media and in the presence of water: A) $Pd(OAc)_2$, no water; B) Pd nanoparticles, no water; C) Pd nanoparticles with added water. Bottom graph: Corresponding UV/Vis fluorescence emission spectra (irradiation wavelength: 370 nm) for the anhydrous samples (curves A and B) at different time intervals. Aqueous samples (curve C) gave a similar emission spectrum to that at the maximum rate.

Figure 1 shows the kinetic results for the cross-coupling reaction between the vinyl bromide **1**[30] and the butyl acrylate **2a** under the catalysis of palladium acetate or monodisperse palladium nanoparticles of approximately 3.9 nm in diameter in solution (see Figure S1 in the Supporting Information). The two palladium catalysts gave a typical sigmoidal curve under anhydrous conditions. Other palladium precursors, including $[Pd_2dba_3]$ (dba = dibenzylideneacetone), an oxime palladacycle complex **4**,[31–33] and a phosphine palladium complex **5**,[34,35] and Pd/C (1 wt %) showed a similar sigmoidal curve under anhydrous conditions (see Figure S2). The turnover frequencies (TOFs), measured after the induction period, differed slightly depending on the starting palladium source. High-resolution transmission electron microscopy (HRTEM) together with dynamic light scattering (DLS) measurements revealed that the palladium salts and complexes decomposed to form 2–10 nm palladium nanoparticles in a few minutes when the reaction was carried out under anhydrous conditions (see Figure S3), in agreement with previous reports.[7,36] However, the reaction-induction period continues for approximately two additional hours after the formation in situ of the palladium nanoparticles; a similar induction period was observed when palladium was incorporated as preformed nanoparticles. The results clearly indicate that the palladium nanoparticles generated in situ are not the catalytically active species.



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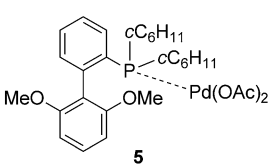

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To find out which were the catalytically active palladium species, we analyzed reaction samples before and after the induction time by electrospray ionization mass spectrometry (ESIMS) and matrix-assisted laser desorption/ionization coupled to time-of-flight (MALDI-TOF) mass spectrometry (see Figure S3). The results indicated that the reaction started only when palladium clusters with a mass below 500 Da appear, and not before. The evolution of the catalytic system was also studied by UV/Vis spectroscopy. According to the jellium model,[37] metal particles in the subnanometer regime present a typical wavelength absorption in the visible region as a function of their size, and the corresponding fluorescence signal when irradiated at that wavelength. In contrast, palladium nanoparticles present only a weak, broad, nonfluorescence signal in the UV/Vis region.[38]

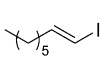
When the cyclic vinyl bromide **1** in the presence of palladium nanoparticles (3.9 nm) was submitted to anhydrous coupling conditions and the reaction was followed by gas chromatography–mass spectrometry (GC–MS) and absorption and emission UV/Vis spectroscopy, only the nonfluorescence plasmon band corresponding to the palladium nanoparticles at approximately 420 nm was observed during the induction time. However, as soon as a new band at about 300–350 nm appeared, and clear fluorescence bands appeared at 450 nm upon irradiation, the reaction started, and conversion was observed. Interestingly, the same absorption and emission bands (450 nm) appeared immediately after irradiation at approximately 350 nm appeared immediately when water (1 % v/v) was introduced into the reaction medium at reaction time zero, and the induction period disappeared (see curve C in Figure 1). The induction period also disappeared when water was introduced and $[Pd_2dba_3]$, complexes **4**[31] and **5**,[35] and Pd/C (1 wt %) were used as catalysts. The addition of the free oxime of complex **4** to the water-treated nanoparticles did not produce any change in the reaction kinetics; this result discards the possibility of any role of the ligand on the active species (see Figure S4). The addition of more water and acidification or basification did not change the kinetic profile observed, which discards the possibility that the effect of water is derived from the better dissolution of potassium acetate (see Figure S4). Therefore, we can assume, in a first approximation, that water promotes the formation of palladium active sites from palladium nanoparticles in solution. In control experiments without added palladium, no significant conversion occurred.

From the results obtained up to this point, we could conclude that: a) palladium nanoparticles are not the active species in the Heck reaction, but rather small palladium clusters, which are responsible for the UV/Vis signal at 450 nm; b) contact of the palladium nanoparticles with water instantaneously generates palladium species that absorb at 450 nm. Thus, if water is introduced into the reaction media, the palladium clusters described above are formed instantaneously, and the induction period disappears.

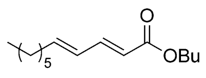
To estimate the size of the palladium species whose formation was promoted by water, we irradiated palladium nanoparticles in aqueous solution at different wavelengths from 296 to 548 nm, which correspond to palladium clusters of 2–13 atoms according to the jellium model. Significant emission signals (450 nm) were only observed in the range 336–370 nm, which corresponds to small clusters with three and four metal atoms. We isolated the mixture of products **3** and confirmed that they did not absorb or emit in the blue region and therefore did not interfere with the UV/Vis measurements. The possibility that the adsorption of synthetic ligands, solvent, or reactants, or changes in particle shape or metal-surface roughness could produce the fluorescence emission was discarded on the basis of control experiments and a literature search. Indeed, we cannot talk of surface area in molecular entities such as subnanometric metal clusters.

Treatment of the palladium nanoparticles with any other reagent of the coupling reaction, including the vinyl bromide, did not produce the UV/Vis-active species at room temperature. However, if the vinyl bromide or the alkene was introduced into a reactor that already contained the nanoparticles and water, the reaction started without an induction period. These results strongly suggest that water promotes the formation of subnanometric palladium clusters with three and four atoms from nanoparticles and stabilizes these clusters, and that these species catalyze the Heck coupling reaction between **1** and **2a** at the highest rate, either in the presence of water or under anhydrous conditions. We cannot distinguish whether the minimal catalytic activity found during the induction time, before the boost in the reaction rate, is due to palladium nanoparticles or minor amounts of three- and four-atom palladium clusters that have already formed.

If we accept that water is able to promote the formation of and stabilize the active sub-nanoclusters, then it should be possible to prepare and store separately the three- and four-atom-cluster catalytic species, to be used later on demand. To check this possibility, we added Pd(OAc)$_2$ or palladium nanoparticles (3.9 nm) to an aqueous solution of NMP (water/Pd molar ratio: 3000) and kept the mixture a flask for 1 month. After this period of time, part of the solution was added as a catalyst to a mixture of vinyl bromide **1** and butyl acrylate **2a**. No induction period was observed, and the initial reaction rate per palladium atom was the same as when the clusters were freshly generated in situ by performing the reaction in the presence of water (see Figure S5). Therefore, we can conclude that a) clusters with three and four palladium atoms are active species for the Heck C–C bond-forming reaction studied; b) water generates these active species from palladium nanoparticles formed in situ from palladium complexes, salts, or nanoparticles; c) it is possible to form and stabilize ex situ these palladium aggregates with three and four atoms in aqueous media and to store them for a long time for used on demand. These subnanometric palladium clusters not only catalyze the Heck coupling of vinyl bromide **1** but also that of the vinyl iodide **6** (see Figure S6). However, the conversion of **6** into **7** was not higher than 50% even after prolonged reaction times. The addition of BuN$^+$I$^-$ (20 mol%) inhibited the reaction, which suggests that the catalyst is poisoned after the release of iodide. Similar results were obtained with Pd(OAc)$_2$, [Pd$_2$dba$_3$], and complexes **4** and **5**. To estimate the relative rate of conversion of aryl iodides and bromides without the interference of poisoning, we tested *p*-bromoiodobenzene (**8c**) as a substrate for the coupling reaction. The results clearly indicate that iodides are activated much faster than bromides (see Figure S7), in accordance with the more facile oxidative addition of the former.



**6**



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To study the formation of the palladium clusters under anhydrous conditions, we prepared different palladium-on-carbon solids with particle sizes ranging from 2.5 to 5.7 nm and tested them in the Heck reaction of *p*-bromoanisole (**8l**) under anhydrous or aqueous conditions (see Figure S8). The results show that the amount of palladium that is leached into solution without water is significantly lower, as measured by inductively coupled plasma atomic emission spectroscopy (ICP-AES) analysis of the reaction at different reaction times, and that the reaction starts and proceeds only after 2 h. When **8l** was absent, no palladium leached into solution. These results indicate that the mechanism of palladium leaching in the absence of water involves the oxidative addition of the bromoarene to the outer shell of palladium atoms on the nanoparticle. If this hypothesis is correct, the induction time should correspond to the amount of palladium exposed on the solid, as indeed is the case (see Figure S8). HRTEM and DLS measurements have shown that palladium salts and complexes decompose rapidly to nanoparticles with different sizes under reaction conditions. The formation of nanoparticles with different sizes explains the different TOF values found for the homogeneous catalysts under anhydrous conditions after the induction time. When water is present, the dislodging of palladium atoms from the nanoparticles is far more efficient and also proportional to the amount of palladium atoms exposed. These results together suggest that the limiting step in the initiation of the reaction is the efficient removal of palladium atoms from the nanoparticle surface, either by water or the aryl bromide, and the subsequent formation of the atomic clusters. They nicely fit the mechanisms proposed by de Vries[22] and Reetz,[4] Amatore and Jutand,[21] Ananikov and Beletskaya,[28] and others.[2,6] We also found that the addition of water once the reaction had stopped conferred new catalytic activity to the deactivated palladium catalyst. It is accepted that deactivation of palladium mainly occurs after agglomeration. If this hypothesis is correct, the addition of water to commercially available palladium black should improve the reaction. Indeed, we observed just such an effect (see Figure S9).

Although the chemical basis for the formation of these subnanometric palladium clusters is not clear at this stage, a likely explanation is a disruption of the nanoparticle Stern shell upon the addition of water. The relatively unhindered nucleophilic oxygen atom would remove and somewhat stabilize the subnanometric palladium clusters. The enhancement of the reaction rate by minor amounts of water during palladium-catalyzed reactions under the reaction conditions used in this study is a widely observed effect that has not been explained satisfactorily to date.[39–42] Thus, the stabilization of the three- and four-atom active palladium clusters by water provides a plausible explanation for the positive effect of water on the rate of these reactions. If this hypothesis is correct, other relatively unhindered nucleophiles, such as amines, might give the same effect. Indeed, cyclohexylamine promoted the formation of the palladium clusters more efficiently than water, as assessed by fluorescence measurements; consequently, the Heck coupling of bromobenzene (**8h**) with **2a** proceeded faster (see Figure S10). The reaction mixture with water was darker than that with cyclohexylamine, and the reaction mixture under anhydrous conditions without cyclohexylamine was darker still (see Figure S10). The catalytic activity decreased with the degree of substitution at the nitrogen atom of the amine, and for the same degree of substitution, the more nucleophilic the amine was, the higher the activity was (see also Figure S10). In other words, both steric and electronic factors control the formation of palladium clusters, and an optimum combination is found in the relatively unhindered, hard nucleophile cyclohexylamine. In accordance, extremely basic nucleophiles, such as first-generation phosphazenes, promoted the coupling efficiently. The use of secondary aliphatic amines also led to an improvement in the reaction rate as compared to that with water, but tertiary amines and cyclic amines performed less well. Furthermore, the use of different alcohols only led to a decrease in the reaction rate and the final conversion with respect to the results with water, since their steric hindrance is higher.

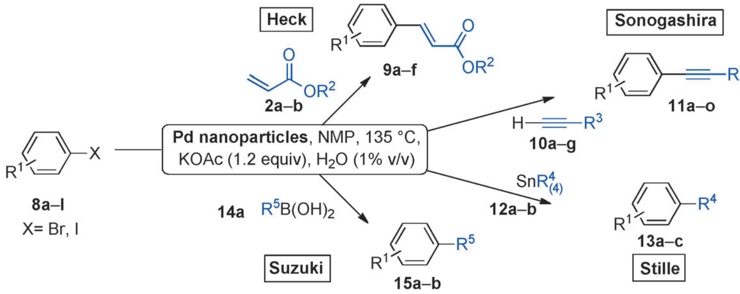
The extension of our study to other substrates for palladium-catalyzed C–C cross-coupling reactions was then envisaged. If the oxidative addition to the palladium clusters is the rate-limiting step of the coupling reaction and the formation of the clusters only depends on the presence of water (or other nucleophiles) under the general reaction conditions described above, other C–C coupling reactions should in principle also be feasible with excellent catalytic turnovers. Different iodo- and bromoarenes were coupled with acrylates (Heck), alkynes (Sonogashira), organotin compounds (Stille), and phenylboronic acids (Suzuki) in the presence of the palladium clusters described above with excellent initial catalytic activities and in good final yields (Table 1; see Figure S11 for a complete list of results with the relevant structures). Note that the catalytic activity is calculated with respect to the total amount of palladium and not with respect to the amount of catalytically active species, which according to the experiments with Pd/C may account for less than 10% of the total palladium present.

The Heck reaction proceeded with different iodo- and bromoarenes and acrylates in high yields, and the multiton UV-B sunscreen 2-ethylhexyl-*p*-methoxycinnamate was synthesized in high yield with a quantity of palladium of only 3 ppm. Remarkably, a variety of iodo and bromo derivatives underwent Sonogashira coupling with an array of alkynes with TOF values of up to $10^5$ molecules of product per atom of palladium per hour. As far as we know, this catalytic system is the most active reported for such a reaction.[43–45] ICP-AES analysis of the reaction mixture showed that copper was introduced by the reagents into the reaction mixture in a quantity of less than 0.2 ppm, and no change in the catalytic activity was found when CuI (300 ppm) was added. These results confirm that the reaction is truly copper-free. When vinyl bromide **1** was used as a substrate and kinetic experiments were combined with UV/Vis spectroscopic measurements of the reaction solution, we again found that palladium clusters of three and four atoms were formed under anhydrous conditions at the time at which the reaction started and products were formed (see Figure S12). As observed for the Heck reaction, the clusters were formed rapidly, and the induction time was suppressed if water was added. The stability of the palladium clusters in solution over time was also evaluated for the Sonogashira reaction (see Figure S13). The results were similar to those obtained for the Heck reaction and indicated unchanged catalytic activity for at least 1 month.

The Stille coupling was also evaluated under the reaction conditions with the stabilized three- and four-atom palladium clusters. A $\mathrm{TOF}_0$ value of 200000 molecules of product per atom of palladium per hour was observed for the coupling between bromoderivative **8g** and tetrabutyltin (**12a**). This level of catalytic activity is, to our knowledge, the highest ever reported for the Stille reaction.[46] Again, catalyst activity was only observed when palladium aggregates of three and four metal atoms were formed (see Figure S14). Control experiments without added palladium did not show any significant conversion. The Suzuki coupling of phenylboronic acid with different aryl halides proceeded under typical conditions and with less palladium by one order of magnitude than the amount required for Heck, Sonogashira, and Stille coupling reactions (Table 1).[47] As observed for the other reaction types, when a palladium salt ($Pd(OAc)_2$), a palladium complex ($[Pd_2dba_3]$, palladacyles, phosphine complexes), or palladium nanoparticles were used as catalysts, an induction period was observed that disappeared when water was added.

Palladium nanoparticles, whether they had been treated with water or not, were inactive as catalysts for the intramolecular amination of *ortho*-alkynyl anilines and for the "click" reaction, two well-known reactions catalyzed by small amounts of Lewis acids, including palladium salts (see Figure S15). These results indicate that the palladium clusters are not positively charged, which is in agreement with the expectation that catalysts with high electron density on the palladium site should show superior reactivity in the oxidative addition step. Measurement of the $\zeta$ potential of the reaction mixture when the atomic palladium clusters were generated with cyclohexylamine showed negative values, which infer that the palladium clusters are anionic in nature. In any case, the three- and four-atom palladium clusters seem to present an electronic density suitable for the highly efficient oxidative

*Table 1:* Results of the Heck, Sonogashira, Stille, and Suzuki cross-coupling reactions of different iodo- and bromoarenes under palladium-cluster catalysis in the presence of water.



| X | R$^1$ | R$^2$/R$^3$/R$^4$/R$^5$ | Product | Pd [ppm] | TOF$_0$ [h$^{-1}$][a] | Yield [%][b] |
|---|---|---|---|---|---|---|
| I | *p*-COMe (**8a**) | R$^2$ = *n*Bu (**2a**) | **9a** | 3 | $2.3\times10^{5}$ | 99 |
| I | H (**8b**) | R$^2$ = *n*Bu (**2a**) | **9b** | 30 | $1.2\times10^{4}$ | 99 |
| I | H (**8b**) | R$^3$ = *n*Oct (**10a**) | **11a** | 300 | $2.0\times10^{3}$ | 73 |
| I | H (**8b**) | R$^3$ = Ph (**10b**) | **11b** | 300 | $7.2\times10^{3}$ | 83 |
| I | H (**8b**) | R$^5$ = Ph (**14a**) | **15a** | 30 | $3.2\times10^{3}$ | 68 |
| I | *p*-Br (**8c**) | R$^2$ = *n*Bu (**2a**) | **9c** | 300 | $3.6\times10^{3}$ | 99 |
| I | *p*-Br (**8c**) | R$^3$ = *n*Oct (**10a**) | **11c** | 300 | $3.1\times10^{3}$ | 99 |
| I | *p*-OMe (**8d**) | R$^2$ = *n*Bu (**2a**) | **9d** | 300 | $3.2\times10^{3}$ | 99 |
| I | *p*-OMe (**8d**) | R$^2$ = 2-ethylhexyl (**2b**) | **9e** | 3 | $8.8\times10^{4}$ | 99 |
| Br | *p*-COH (**8e**) | R$^3$ = *n*Oct (**10a**) | **11d** | 3 | $2.0\times10^{5}$ | 99 |
| Br | *p*-COH (**8e**) | R$^3$ = Ph (**10b**) | **11e** | 300 | $8.4\times10^{3}$ | 99 |
| Br | *o*-COH (**8f**) | R$^4_{(4)}$ = ($n$Bu)$_4$ (**12a**) | **13a** | 30 | $8.2\times10^{3}$ | 91 |
| Br | *p*-COMe (**8g**) | R$^2$ = *n*Bu (**2a**) | **9a** | 300 | $3.1\times10^{4}$ | 99 |
| Br | *p*-COMe (**8g**) | R$^3$ = Ph (**10b**) | **11f** | 300 | $1.8\times10^{4}$ | 99 |
| Br | *p*-COMe (**8g**) | R$^3$ = *n*Oct (**10a**) | **11g** | 300 | $2.1\times10^{3}$ | 99 |
| Br | *p*-COMe (**8g**) | R$^3$ = *n*Oct (**10a**) | **11g** | 0 | – | < 5 |
| Br | *p*-COMe (**8g**) | R$^4_{(4)}$ = ($n$Bu)$_4$ (**12a**) | **13b** | 3 | $2.0\times10^{5}$ | 70[c] |
| Br | *p*-COMe (**8g**) | R$^4_{(4)}$ = ($n$Bu)$_4$ (**12a**) | **13b** | 0 | – | < 5 |
| Br | *p*-COMe (**8g**) | R$^4_{(4)}$ = Ph, Me$_3$ (**12b**) | **13c** | 3 | $7.9\times10^{4}$ | 44 |
| Br | *p*-COMe (**8g**) | R$^5$ = Ph (**14a**) | **15b** | 0.3 | $1.0\times10^{5}$ | 61[c] |
| Br | H (**8h**) | R$^2$ = *n*Bu (**2a**) | **9b** | 300 | $8.8\times10^{2}$ | 64 |
| Br | H (**8h**) | R$^3$ = *n*Oct (**10a**) | **11a** | 300 | $5.2\times10^{3}$ | 99 |
| Br | H (**8h**) | R$^3$ = *m*-tolyl (**10c**) | **11h** | 300 | $6.6\times10^{3}$ | 99 |
| Br | H (**8h**) | R$^3$ = *o*-tolyl (**10d**) | **11i** | 300 | $1.2\times10^{3}$ | 96 |
| Br | H (**8h**) | R$^3$ = *p*-MeOC$_6$H$_4$ (**10e**) | **11j** | 300 | $2.4\times10^{3}$ | 99 |
| Br | H (**8h**) | R$^3$ = *o*-MeOC$_6$H$_4$ (**10f**) | **11k** | 300 | $2.0\times10^{3}$ | 94 |
| Br | H (**8h**) | R$^3$ = *n*-dodecyl (**10g**) | **11l** | 300 | $8.0\times10^{2}$ | 97 |
| Br | H (**8h**) | R$^5$ = Ph (**14a**) | **15a** | 30 | $7.6\times10^{3}$ | 87 |
| Br | H (**8h**) | R$^5$ = Ph (**14a**) | **15a** | 0 | – | < 5 |
| Br | *p*-Me (**8i**) | R$^3$ = *n*Oct (**10a**) | **11m** | 300 | $2.0\times10^{3}$ | 83 |
| Br | *o*-OMe,*p*-naphthyl (**8j**) | R$^3$ = *n*Oct (**10a**) | **11n** | 300 | $4.9\times10^{3}$ | 99 |
| Br | *o*,*o*,*p*-*i*Pr$_3$ (**8k**) | R$^2$ = 2-ethylhexyl (**2b**) | **9f** | 300 | $1.1\times10^{4}$ | 35[c] |
| Br | *p*-OMe (**8l**) | R$^2$ = *n*Bu (**2a**) | **9d** | 300 | $4.7\times10^{2}$ | 40 |
| Br | *p*-OMe (**8l**) | R$^2$ = *n*Bu (**2a**) | **9d** | 0 | – | < 5 |
| Br | *p*-OMe (**8l**) | R$^3$ = Ph (**10b**) | **11j** | 300 | $2.8\times10^{2}$ | 50 |

[a] The initial turnover frequency (TOF$_0$) was calculated on the basis of the total amount of palladium. [b] Product yields after 24 h. [c] Reaction temperature: 160 °C.

addition of aryl iodides and bromides, and if the oxidative addition is the rate-limiting step of the reaction, the rate of the coupling depends only on the aryl halide and is independent of the second reaction partner. This mechanistic hypothesis is corroborated by a comparison of the initial reaction rates of different aryl halides. For example, with iodobenzene (**8b**), a TOF$_0$ value of around 5000 h$^{-1}$ was observed for the Heck, Sonogashira, and Suzuki coupling, around half the value (2000 h$^{-1}$) was observed for bromobenzene (**8h**) under the same reaction conditions, and with *p*-bromoacetophenone (**8g**) a value of around 20000 h$^{-1}$ was observed for the four different coupling reactions. Furthermore, chloro derivatives did not react at all under these reaction conditions, regardless of the coupling partner and the amount of catalyst used. This result indicates that the palladium clusters are not able to promote the oxidative addition to start the catalytic cycle.

In conclusion, three- and four-atom palladium clusters are formed from palladium nanoparticles and are responsible for the catalytic activity of palladium salts, complexes, and nanoparticles in NMP under heating conditions. These clusters can be stored in aqueous solution to be used on demand and catalyze the Heck, Sonogashira, Stille, and Suzuki coupling reactions of different iodo and bromo derivatives under ligand-free, industrially viable conditions in high yields and with unprecedented turnover frequencies in some cases. The activation of chloro derivatives is not possible with this catalytic system. The results presented herein connect with those found for gold catalysts and point to the potential of metallic clusters as highly active catalysts for organic reactions.[48,49] Our results do not contradict those found for poly(vinylpyrrolidone) (PVP) palladium-supported solids,[50,51] in which case it is thought that unsaturated palladium atoms, such as those present at the edges and corners of crystals, are the active species. Indeed, the smaller the palladium crystallites, the larger the number of unsaturated atoms will be. In our case, the fact that three- and four-palladium-atom clusters are present makes the number of such unsaturated sites very large, and the corresponding TOF values very high.

## Experimental Section

General procedure: Potassium acetate (58 mg, 0.6 mmol) was placed in a 1.5 mL vial equipped with a magnetic stir bar, and anhydrous NMP (1 mL) was added. The desired volume of the palladium catalyst solution, water (0.5 mmol), the corresponding halide (0.5 mmol), and the coupling counterpart (acrylate or boronic acid: 0.6 mmol, 1.2 equiv; alkyne or stannane: 1 mmol) were then added, and the vial was sealed and placed in a preheated oil bath at 135 °C. The reaction mixture was stirred, and aliquots of 0.05 mL were taken periodically and diluted in diethyl ether (1.5 mL) for GC analysis with nitrobenzene as an external standard. The same aliquots without nitrobenzene were used for UV/Vis spectroscopic measurements.

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