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# Ligand-free Heck reactions using low Pd-loading

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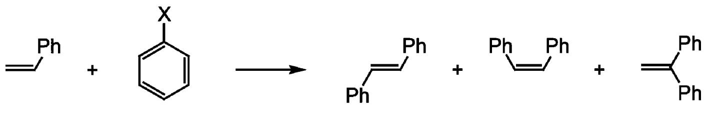
Activated and non-activated aryl bromides undergo smooth ligand-less Heck reactions, provided low amounts of palladium salts such as $Pd(OAc)_2$ are used (ideally 0.01–0.1 mol%). This industrially viable process appears to involve palladium nanoparticles.

## Introduction

The palladium-catalysed coupling of olefins with aryl- or vinyl halides, known as the Heck reaction, is a standard method for carbon–carbon bond formation in organic synthesis.[1] Academic and industrial interest in this reaction has increased in recent years, fueled by the development of more active catalyst systems, the discovery of waste-free versions,[2] and the desire to put the vast empirical data on a sound mechanistic basis.[3] Very often the arylation of styrene (**1**) with a phenyl halide (**2**) is used as the model reaction.

The first protocol published by Mizoroki describes the use of $PdCl_2$ (1 mol%) in the presence of sodium acetate



**1** **2 a** X = I
**b** X = Br
**c** X = Cl
**3** **4** **5**

Manfred T. Reetz was born in Germany in 1943 and obtained a B.S. degree from Washington University (St. Louis) in 1965 and an M.S. degree in chemistry from the University of Michigan in 1967. In 1969 he received his Ph.D. degree from the University of Göttingen (Germany) under the direction of U. Schöllkopf. Following postdoctoral training under R. W. Hoffmann at the University of Marburg, he obtained his Habilitation there in 1976, spent two years as Associate Professor at the University of Bonn before becoming Full Professor in Marburg in 1980. In 1991 he moved to Mülheim/Ruhr and became director at the Max-Planck-Institut für Kohlenforschung. His current interests include homogeneous transition metal catalysis, nanostructured transition metal clusters and directed evolution of enantioselective enzymes.

Johannes (Hans) G. de Vries received his Ph.D. degree at the University of Groningen in 1979. After a post-doc at Brandeis University he returned to Europe to take up employment with Sandoz as a medicinal chemist, first in Vienna, afterwards in London. More interested in developing new chemistry rather than drugs he took up employment with DSM in Geleen, The Netherlands, where he still works today as a principal scientist in homogeneous catalysis for fine chemicals. His main task is to introduce homogeneous catalysis in the plants of DSM's fine chemical branch. He also pioneered the use of HTE at DSM. In 1999 he was appointed part-time professor at the University of Groningen. In 2001 he was appointed visiting industrial professor at the University of Bristol. Recent research subjects are asymmetric hydrogenation (MonoPhos), aromatic substitution, CO chemistry, combined bio- and homogeneous catalysis, chiral recognition and process intensification.

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as the base in methanol in a closed vessel (120 °C).[4] The original procedure reported by Heck is also ligand-free, employing 1 mol% of $Pd(OAc)_2$ as the pre-catalyst, tributylamine as the base and *N*-methylpyrrolidinone (NMP) as the solvent in an open vessel at 100 °C (or no solvent).[5] In both cases aryl iodides and various olefins served as the substrates. Inspired by Fitton, *et al.*, who had reported that in stoichiometric reactions Pd(0) in the form of $Pd(PPh_3)_4$ undergoes oxidative addition to phenyl halides (**2**) with formation of isolable complexes of the type $PhPdX(PPh_3)_2$,[6] Heck extended the coupling reaction to the cheaper but less reactive aryl bromides by introducing phosphines as ligands (1 mol% $[Pd(OAc)_2(PPh_3)_2]$).[7] Since then, an overwhelming number of other catalysts,[1] in particular palladacycles,[8] carbene complexes[9] and complexes based on bulky tertiary phosphines[1c] have been described, the latter allowing the smooth reaction of traditionally sluggish aryl chlorides. Prior to this development, Jeffery had introduced the use of tetraalkylammonium salts originally meant as phase transfer catalysts in ligand-free Heck reactions of aryl iodides (1–5% $Pd(OAc)_2$).[10] In a synthetically significant development, Beletskaya demonstrated the ligand-free use of $Pd(OAc)_2$ in aqueous medium, certain water-soluble aryl iodides and bromides serving as substrates.[1b] Pd-loadings as low as 0.0005 mol% sufficed with 3-iodobenzoic acid, which led to the term “homeopathic” doses.[1b]

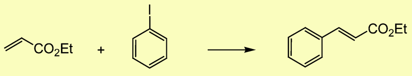
Although P-ligands stabilise palladium and influence its catalytic activity, the simplest and cheapest Pd-catalysts are of course ligand-free systems, specifically when used in such low amounts that the term homeopathic is justified. Such an experimental protocol would constitute a significant advancement, especially if generally applicable. Recently, such ligand-free Heck reactions in organic solvents at extremely low Pd-loadings have been described.[11,12] They work astonishingly well with aryl bromides, as in the reaction of styrene (**1**) with bromobenzene (**2b**). Here we focus on this synthetically important development and also address mechanistic questions.

## Formation and catalytic activity of Pd-colloids

Our interest in two seemingly unrelated projects carried out in Mülheim, namely Heck reactions and Pd-colloids† led to the realization that the two areas are related. It had been known for a long time that tetraalkylammonium halides stabilize nano-sized transition metal colloids.[13] The surfactants prevent undesired agglomeration by forming a monomolecular layer around the metal core, as demonstrated for Pd-colloids using transmission electron microscopy (TEM) and scanning tunnel microscopy (STM).[14] Pd-colloids of this kind can be prepared size-selectively in the range of 1–5 nm in organic solvents or in water by reducing $PdCl_2$ chemically or electrochemically in the presence of a tetraalkyl ammonium salt.[14] In an extension of this work it was discovered that an external reducing agent is not necessary if a palladium salt such as $PdCl_2$, $Pd(OAc)_2$ or $Pd(NO_3)_2$ is gently warmed in THF in the presence of excess tetraalkylammonium *carboxylates* ($R_4N^+R'CO_2^-$) which function as a reducing *and* stabilizing agent (Fig. 1).[15]

We suspected that similar Pd-colloids are formed during Heck reactions under Jeffery conditions. Indeed, preformed Pd-colloids of this kind were shown to be Heck catalysts.[16] Moreover, we demonstrated that $Pd(OAc)_2$ (which in pure form is known to decompose at 100 °C with formation of Pd-black) can be used as a precursor for solvent-stabilized Pd-colloids simply by heating in a polar solvent such as propylene carbonate,[17] the 8–10 nm sized Pd(0)-nanoparticles showing no tendency to agglomerate (no undesired Pd-black) even at 120 °C for days! Other polar solvents such as NMP are also capable of stabilizing Pd-colloids in the absence of surfactants, polymers or ligands,[17] which normally need to be added as stabilizers. The exact nature of the stabilizing effect of polar solvents (complexation?) is currently unknown. These nanomaterials also display catalytic activity in Heck reactions, although the conditions and amount of catalyst used were not optimized.[17]

These observations suggest, but do not prove, that phosphine-free Heck reactions involve nano-sized Pd-colloids. In order to put these speculations on a more sound basis we applied *in situ* transmission electron microscopy (TEM) to the Heck reaction of ethyl acrylate (**6**) (10 mmol) and iodobenzene (**2a**) (5 mmol) under Jeffery conditions (12.5 mmol NaOAc; 5 mmol $n$-$Bu_4N^+Br^-$; 0.25 mmol Pd(OAc); 5 mL dimethylacetamide (DMA); 50 °C for 1 h; >95% conversion).[18] The reaction was also monitored by GC. The immediate formation of 1.3–1.6 nm sized Pd-colloids was visualized by TEM and shown to persist during the entire reaction (Fig. 2a). In further experiments preformed $R_4N^+X^-$-stabilized Pd-colloids[16] were shown to interact with iodobenzene (**2a**) in a stoichiometric reaction with formation of Ph–PdX species, possibly in anionic form as indicated by UV/Vis and NMR analysis.[18]



6 2a 7

Another example of the presence of palladium colloids is in the Heck reaction using benzoic anhydride as the arylating agent.[2a] In this reaction, which is catalysed by 0.1 mol% $PdCl_2$ activated with a small amount of NaCl or NaBr, nanoclusters (4–5 nm) were observed by TEM analysis (Fig. 2b). Use of energy dispersive X-ray analysis (EDX) confirmed the palladium core, probably stabilised by halide salts (in this case NaCl) and/or polar solvent.

In other work Ley reported the incorporation of $Pd(OAc)_2$ in polyurea microcapsules, affording materials which contain Pd-nanoparticles capable of catalysing Suzuki and Heck reactions.[19] Moreover, several other publications deal with ligand-less Pd-catalysed Heck reactions,[1] although the authors do not explicitly consider the possible role of Pd-colloids. Finally, there are now four different reports that show that certain palladacycles are in fact not stable under the conditions of the Heck reaction at higher temperatures and merely serve as a source of ligand-free palladium.[12,20]

Taken together, these observations strongly suggest that Pd-colloids are involved in many ligand-free Heck reactions. However, they say nothing about the question whether the observed Pd colloids are the actual catalysts, possibly functioning at defect sites, steps

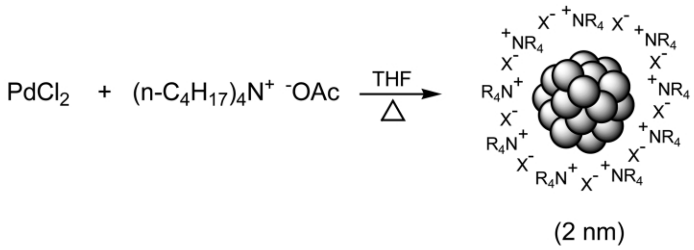


**Fig. 1** Mild thermal preparation of Pd-colloids stabilized by ammonium salts.[15]

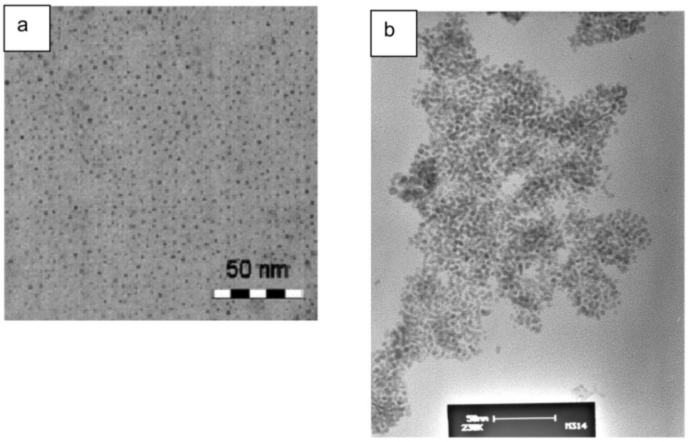


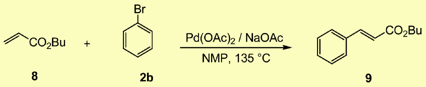
**Fig. 2** (a) TEM image of Pd-nanoparticles (1.6 nm) formed in the Heck reaction of **6** with **2a** under Jeffery conditions.[18] (b) TEM image of Pd-nanoparticles (4–5 nm) in Heck reaction employing benzoic anhydride as the arylating agent.[2a]

and kinks similar to heterogeneous catalysis, or whether they serve as a reservoir or donor of smaller and more reactive fragments.

## Ligand-free Heck reactions of aryl bromides with low palladium doses

It was previously shown in Mülheim that phosphine-free Heck reactions of aryl bromides occur smoothly using 1.5 mol% of $PdCl_2(PhCN)_2$ or $Pd(OAc)_2$ in the presence of NaOAc as base and *N*,*N*-dimethylglycine (DMG) as an additive.[11] Although the role of DMG remained unclear, we did observe that its use becomes superfluous upon reducing the amount of Pd-catalyst to very low values. For example, in the reaction of styrene (**1**) with bromobenzene (**2b**) using only 0.0009 mol% of $Pd(OAc)_2$ and NaOAc as base in NMP as solvent (130 °C) in the absence of any additional ligand, conversion turned out to be 85% (**3** : **4** : **5** = 93.0 : 0.7 : 6.3) after 96 h. Thus, the ligand-free catalyst seems to "improve" upon lowering the Pd-loading.[11] This system was also studied by *in situ* TEM analysis, which again demonstrated the existence of Pd-colloids averaging 1.6 nm in size, in this case as solvent-stabilised nanoparticles.[18]

In the absence of stabilizers, such as tetraalkylammonium salts, the ligand-free systems are stable in the Heck reaction of aryl iodides because of the fast oxidative addition step and because part of the palladium is stored as bridged $[Pd_2I_6]^{2-}$ anions.[21] However, in the case of the less reactive aryl bromides as substrates, use of ligand-free $Pd(OAc)_2$ has hitherto not been very successful. This can be explained by the fact that unlike with the aryl iodides oxidative addition of the aryl bromide is the rate-determining step. A large part of the palladium is now in the form of Pd(0), which is stored in palladium clusters that are stabilised only by NaBr and/or the polar solvent. These clusters are relatively unstable and further aggregate to form palladium black, which leads to the termination of the reaction (or nearly so). As the clustering is probably higher order in palladium and the Heck reaction first[3] or half-order,[22] lowering the palladium concentration might effectively suppress cluster formation or reduce their size. The DSM work has shown that this is indeed true as long as the palladium concentration is kept below 0.1 mol%. A practical range is between 0.01–0.1 mol% (Fig. 3).[12] It is possible to work at considerably lower ratios, as shown earlier by the Mülheim work,[11] but here the duration of the reaction becomes impractically long; whereas at higher catalyst concentrations the reaction clearly stalls and formation of palladium black is visible.



The Heck reaction using such low amounts of palladium has a broad scope in substrates.[12] Using robotic equipment a wide range of substituted aryl bromides were screened, including 3-bromopyridine. Olefins included butyl acrylate, styrene, cyclohexyl vinylether, *N*-vinyl-acetamide, methyl 2-acetamido-acrylate and 3-buten-2-ol. Using only 0.05 mol% of $Pd(OAc)_2$ with NaOAc as base in NMP at 135 °C, practically all substrates were fully converted within 1–15 h (Fig. 4). In a recent publication Yao and coworkers report that $Et_3N$ does not work well under comparable circumstances, the best results being obtained with $K_3PO_4$ as base.[23] It is not clear why the expected presence of small amounts of regioisomers was not mentioned in this report.

The method has also been used by DSM for the preparation of a range of enantiopure substituted *N*-acetyl-phenylalanines. This was accomplished by the Heck reaction of methyl *N*-acetamidoacrylate with differently substituted bromarenes at very low $Pd(OAc)_2$-loading in the absence of any ligands, followed by Rh/MonoPhos hydrogenation.[24]

The use of unusually low Pd-loading in the Suzuki reaction on aryl bromides such as **10** is also possible and leads to a very fast reaction with turnover frequencies up to 30 000.[25]

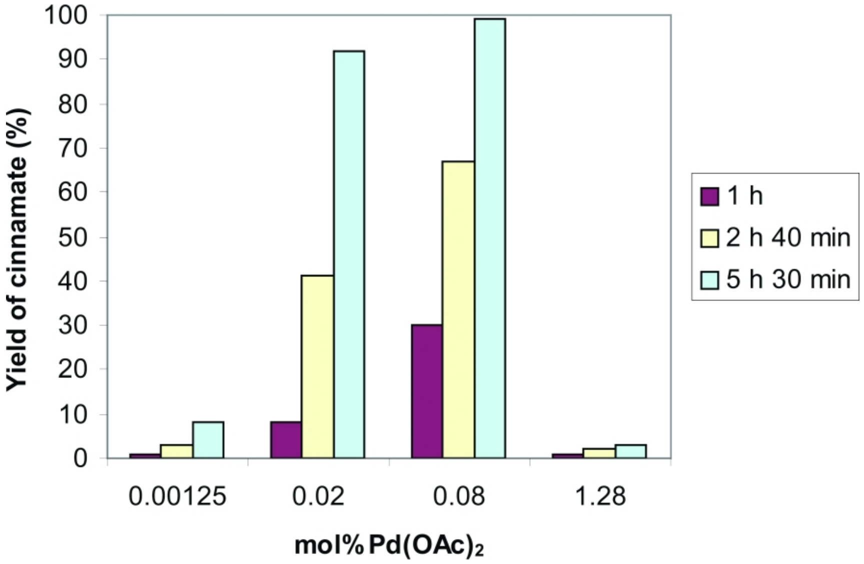


**Fig. 3** Optimal catalyst loading in the ligand-less Heck reaction of **8** with **2b**.[12]

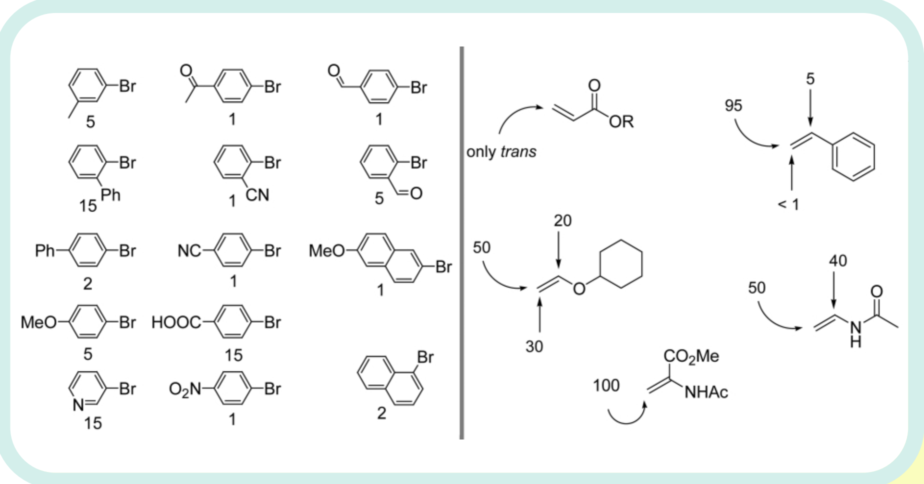
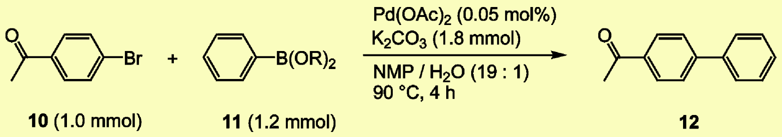


**Fig. 4** Scope of the ligand-less Heck reaction between aryl bromides and butyl acrylate **8** (left: numbers are hours needed for 100% conversion) and between various aryl bromides and olefins (right: numbers indicate isomeric product ratios). Conditions: 0.05 mol% $Pd(OAc)_2$, NaOAc, NMP, 130 °C, 2 mmol scale.[12]



**10** (1.0 mmol) **11** (1.2 mmol) **12**

## Mechanistic aspects

Although palladium clusters were found to be present in many ligand-free Heck reactions, it is not entirely clear if and how they are involved in the catalysis. There is a clear pointer however: in all ligand-free Heck reactions on aryl bromides, including those in which certain palladacycles are the catalyst precursor, the turnover frequency increases with decreasing catalyst concentration.[26] This points in the direction of an equilibrium between a higher order palladium species, *i.e.* the palladium cluster and a lower-order species, such as the monomeric or dimeric catalyst species. According to Le Chatelier, the equilibrium shifts towards the lower order species at lower concentrations. Low Pd concentrations suppress the formation of Pd-black and keep all the metal available for catalysis. Thus, a general scheme for the reaction can be postulated as shown in Fig. 5. A detailed discussion concerning the possible nature of the lower order species in the complex catalytic cycle is beyond the scope of the present review. Little exact information is available, although proposals have been made for the ligand-free Heck reaction with aryl iodides.[21,27]

## Conclusion and outlook

Ligand-free Heck reactions of aryl bromides can be performed conveniently on a wide range of substrates provided that the palladium concentration is kept between 0.01–0.1 mol%. At lower palladium concentrations the reaction will be too slow; whereas at higher concentrations palladium black will rapidly form. Mechanistically, colloidal palladium clusters are involved which serve as a reservoir for the actual catalytically active species.[12,17,28] Protocols employing extremely low amounts of Pd-salts in the absence of ligands are of considerable practical and therefore of industrial significance. Indeed, the method has been scaled up by DSM to kg size to prepare a drug intermediate.[12]

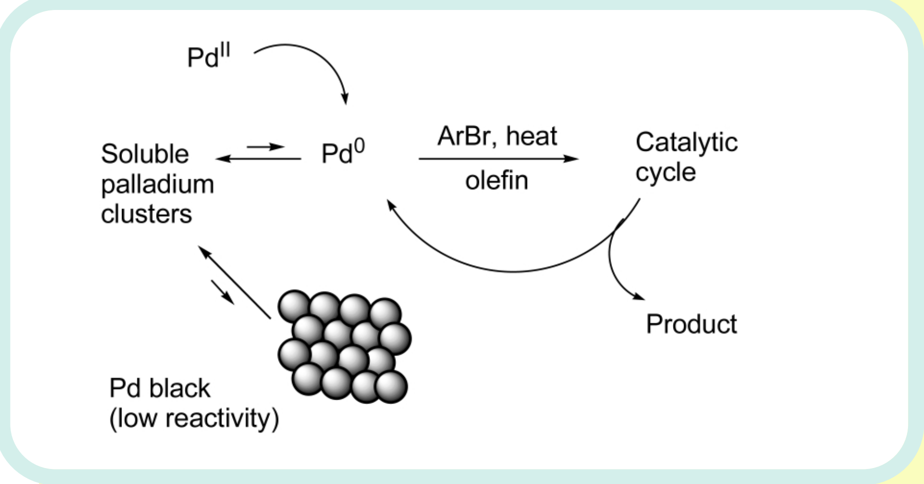


**Fig. 5** General scheme for ligand-less Heck reactions at low Pd-loading.[12]

The presence of transition metal clusters in both homogeneous and heterogeneous catalysis seems to be a much more general phenomenon than most researchers have assumed so far. In this respect Köhler's work on Heck reactions using Pd on activated carbon deserves particular attention.[29] A recent report by Lipshutz and Tesche has highlighted the presence of homogeneous species in reactions catalysed by heterogeneous nickel.[30] In these systems it may also be possible to work in the absence of ligands at low concentrations. Other well-documented examples include platinum catalysed hydrosilylations[31] and ruthenium catalysed hydrogenation reactions[32] where the catalyst precursors are transition metal complexes. A future challenge will be to develop reaction conditions that keep the size of the clusters as low as possible as this will increase the percentage of transition metal actually working in the catalytic cycle. Another conclusion that can be drawn is that since most of the palladium is locked up in the cluster the true rate of the catalytic reaction must be extremely high. Finally, more work is necessary in order to unravel the precise nature of the reactive species in the catalytic cycle.

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