

A unifying mechanism for all high-temperature Heck reactions. The role of palladium colloids and anionic species

Johannes G. de Vries*

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The Heck reaction has been the subject of intense investigation in the past decade. Many new types of catalysts have been developed in addition to the existing palladium/phosphine complexes. Prominent among these are palladacycles, pincers, several types of heterogeneous palladium catalysts, colloids and ligand-free palladium, usually in the form of $\text{Pd}(\text{OAc})_2$. Most of the newer types function only at higher temperatures, typically between 120 and 160 °C. It has been shown that irrespective of the catalyst precursor, none of these catalysts are stable at these high temperatures. They all have a tendency to form soluble palladium(0) colloids or nanoparticles, certainly with less reactive substrates such as aryl bromides or chlorides. The Heck reaction takes place by attack of the arylating agent on the palladium atoms in the outer rim of the nanoparticles. This leads to formation of monomeric or dimeric anionic palladium complexes that undergo the usual steps of the Heck mechanism as described by Amatore and Jutand.

DSM Pharma Chemicals—Advanced Synthesis, Catalysis & Development, P.O. Box 18, 6160, MD Geleen, The Netherlands

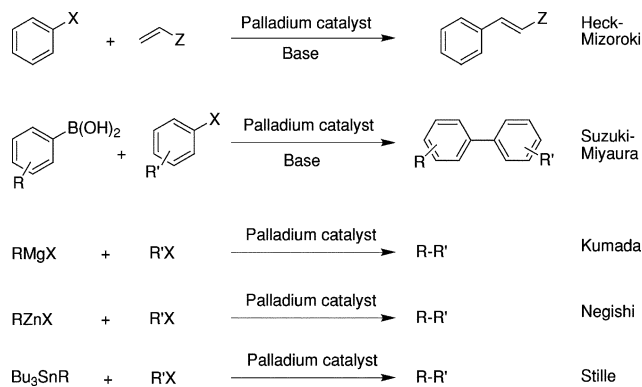
Johannes (Hans) G. de Vries (1951) received his PhD degree at the University of Groningen under the guidance of R. M. Kellogg, working on a bio-organic subject. After a post-doc at Brandeis University, Waltham, USA with J. B. Hendrickson and R. H. Abeles he returned to Europe to take up employment with 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 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 chemicals and vitamin branches. His main research topics are asymmetric catalysis and catalysed C–C bond formation. He works very much at the interface with academia. 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. He is married and has three children. He is (co-)author of 20 patents and 85 publications.



Johannes G. de Vries

1 Introduction

Palladium catalysed C–C bond formations, such as the Heck–Mizoroki reaction,¹ the Suzuki–Miyaura reaction,² the Kumada reaction, the Negishi reaction³ and the Stille⁴ reaction had its origin in the seventies of the previous century (Scheme 1).



Scheme 1 Palladium catalysed C–C bond formation.

After the initial discoveries and some scope determination, the chemistry did not play a major role in organic synthesis as simple stoichiometric chemistry was available as an alternative for quite a few of these methods and less accessible structures such as biaryls had not found any major applications. In the nineties, interest in this type of chemistry suddenly surged, driven by a number of different developments.

A major one was the revolution taking place in medicinal chemistry, where better insight in the underlying mechanism of disease had led to the development of new drugs based on the natural substrates for enzymes or receptors. Often these new drugs are complex molecules that are constructed in lengthy total syntheses of 20 or more synthetic steps. For the assembly of the carbon skeleton C–C bond formation using strong bases is often used.

This in turn necessitates extensive use of protection/deprotection schemes. Interestingly, many palladium catalysed C–C bond-forming methods can be performed under neutral or mildly basic conditions, obviating the need for protection/deprotection. Not surprisingly, many medicinal chemists enthusiastically embraced the use of palladium catalysis as a means to make their syntheses more efficient. Several processes based on the use of palladium catalysed C–C bond formation are now actually carried out on ton-scale.^{1h,5}

Symmetrical and unsymmetrical biaryl compounds were a rare commodity in the seventies, but in the last few decades important applications have been found for biaryl compounds in liquid crystals, in polymers, in drugs such as the Sartan class of blood pressure lowering agents and as chiral ligands.^{1h}

A third development emerged from the Central Research Laboratories of Hoechst, where Beller together with Herrmann from the Technical University of Munich, driven by the desire to extend the Heck reaction to the cheaper and more readily available aryl chlorides had developed a new type of catalyst based on a palladacycle (Fig. 1).⁶

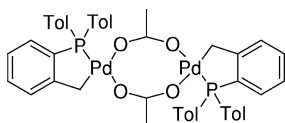


Fig. 1 Palladacycle.

This new direction in catalysis galvanised the academic research and led to the development of a great number of palladacycle and pincer catalysts that found application in the Heck and Suzuki reactions at high temperatures.⁷ It also spurred an exciting debate about the mechanism of the Heck reaction catalysed by palladacycle catalysts. Initially, Beller, Herrmann and co-workers proposed that the reaction proceeds through a Pd(II)/Pd(IV) cycle and on first sight this appeared a reasonable mechanism, in spite of the known lability of Pd(IV) species.^{6a} However, when Louie and Hartwig showed that palladacycles are easily transformed into Pd(0) species, albeit under slightly different conditions as during the Heck reaction, a Pd(0)/Pd(II) cycle again became more likely.⁸ We will come back later to this mechanistic discussion.

Other catalytic systems have been developed for the Heck reaction, such as the heterogeneous palladium catalysts, which are highly preferred in industry because of their easy separation.⁹ However, the much lower rate obtained with Pd/C led to the development of several new classes of catalysts with palladium in zeolites, or as part of inorganic lattices.⁹ Many of these catalysts seemed to lead to higher rates than the conventional palladium on carbon.

The use of stabilised palladium colloids† as catalysts for the Heck reaction was developed independently by Reetz *et al.*¹⁰ and by Hermann, Beller and co-workers.¹¹ Reetz *et al.* also pioneered the use of additives such as tetraphenylphosphonium salts¹² and

† In this article the words colloids and nanoparticles will be used to describe the same phenomenon: a large agglomeration of metal atoms in the zero oxidation state, with sizes in the nanometer range (usually 1.5–7 nm in this context), that nevertheless remains in solution. They are usually stabilized by salts or ligands. Clusters are smaller organometallic compounds containing more than one metal atom with a well-defined structure.

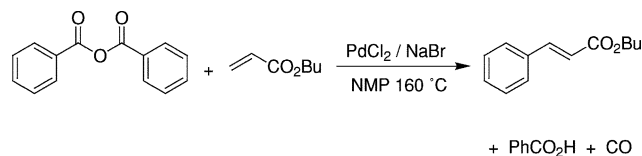
dimethyl glycine¹³ that can be used in combination with palladium salts leading to catalysts that can be used with activated aryl chlorides. The activation of aryl chlorides can also be achieved with palladium complexes with bulky basic trialkyl ligands as pioneered by Littke and Fu,¹⁴ Hartwig and co-workers¹⁵ and Beller and co-workers¹⁶ or with carbene ligands.¹⁷

And finally, the use of ligand-free palladium has become increasingly important. Heck had demonstrated that Pd(OAc)₂ without additional ligands can be used as catalyst in the Heck reaction on aryl iodides.^{1a} Jeffery showed that this works particularly well in the presence of tetralkylammonium halide salts.¹⁸ We have recently extended this reaction to aryl bromides.¹⁹ The key finding here was the necessity to increase the substrate/catalyst ratio in order to suppress formation of palladium nanoparticles. This work has highlighted the importance of palladium colloids and the role they play in ligand-free Heck reactions.²⁰ It has now become apparent that colloids are present also in Heck reactions at high temperatures with palladacycles, with heterogeneous palladium catalysts²¹ and probably also in reactions catalysed by conventional palladium/phosphine complexes.²² In Heck reactions at lower temperature the conventional palladium phosphine complexes seem to remain intact and functional as testified by the existence of many asymmetric Heck reactions.^{23,24}

In this Perspective we will concentrate on the pivotal role played by palladium nanoparticles in all Heck reactions performed at higher temperatures and we will propose a mechanism for ligand-free Heck reactions that takes into account all the known data.

2 Ligand-free palladium catalysis in the Heck reaction

Our own work in this area started from an entirely different vantage point. We were interested in reducing the waste load common to the production of fine chemicals. As inorganic salts are a major part of this waste and unlike the organic waste it cannot be rendered harmless *via* wastewater treatment we decided to focus on halide free C–C bond formation. This eventually led to the finding that benzoic anhydride can be used as arylating agent in the Heck reaction (Scheme 2).²⁵ Use of other derivatives of aromatic carboxylic acids has been developed by Goossen *et al.*²⁶



Scheme 2 Waste-free Heck reaction with aromatic carboxylic anhydrides.

One of the many surprising elements regarding this reaction is the fact that it does not proceed in the presence of ligands, such as PPh₃. Later it was found that the presence of ligands prevents the decarbonylation reaction, which is a necessary step in the catalytic cycle.²⁷ Also, this catalyst needs about 4 equivalents of bromide or chloride with respect to palladium. In the absence of halide the reaction proceeds at a much lower rate. Spectroscopic research using EXAFS led to the conclusion that at the onset of reaction rapid formation of Pd(0) occurs; even after filtration of the reaction mixture most of the palladium is present in the form of soluble

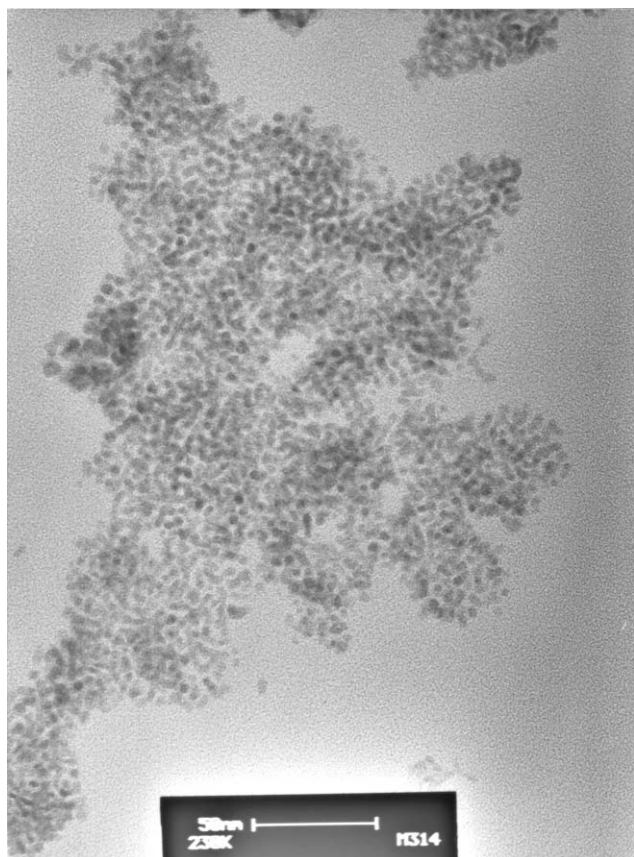


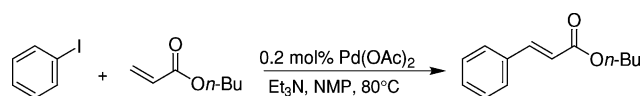
Fig. 2 TEM of palladium nanoparticles in the Heck reaction of benzoic anhydride.

$\text{Pd}(0)$.²⁸ In addition to this evidence, TEM pictures clearly show the presence of palladium nanoparticles (Fig. 2).

Interestingly, ES–MS analysis of this reaction showed the presence of a number of anionic monomeric and dimeric palladium species. One of these was PhPdCl_2^- (in this reaction NaCl was used as additive). It is quite possible that this compound is present in

solution as a dimeric species. These findings suggest that although a very large amount of the palladium is actually in the form of soluble nanoparticles, the actual catalysis proceeds *via* monomeric, or possibly dimeric anionic species. The role of the halide salt may be twofold: it stabilises the colloids, thus preventing their further growth to palladium black and they function as ligand for palladium in the actual catalytic cycle, which proceeds through anionic intermediates, in analogy with the proposals of Amatore and Jutand for the catalysis by palladium–phosphine complexes.²⁹

Ligand-free catalysis has many advantages; properly used, the catalysis may be faster, the work-up is easier and costs are reduced. For this reason we continued our study of ligand-free systems using iodobenzene as the substrate (Scheme 3).

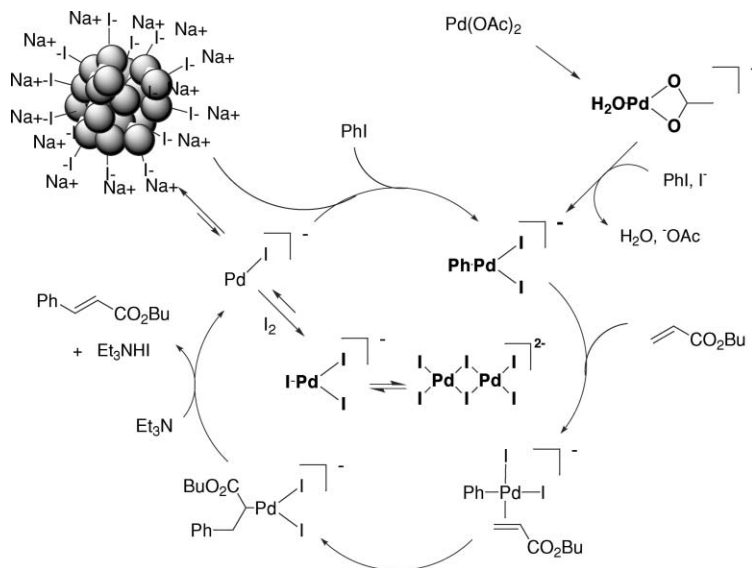


Scheme 3 Ligand-free Heck reaction on iodobenzene.

Using ES–MS we detected the presence of PhPdI_2^- in the Heck reaction of iodobenzene. In addition to that, a large peak attributable to PdI_3^- is visible.³⁰ Independent work performed by Evans *et al.* using EXAFS showed the presence of large amounts of the dimeric species Pd_2I_6^- in this reaction.³¹

We have summarised the above findings in the mechanistic proposal depicted in Scheme 4.

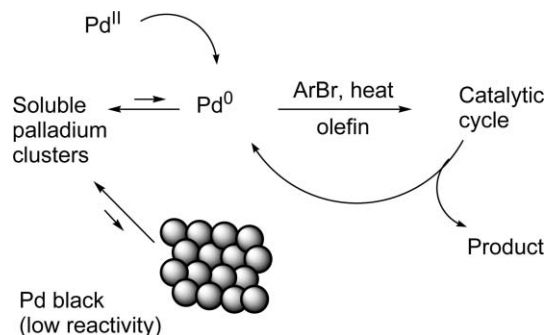
In the first phase of the reaction $\text{Pd}(\text{II})$ is reduced to $\text{Pd}(0)$.³² In the initial 5 min of the ArI reaction we observe $(\text{H}_2\text{O})\text{PdOAc}^-$, which is a rare example of an anionic palladium (0) complex. This complex may undergo oxidative addition of aryl iodide to form ArPdI_2^- . This species and all other underligated species may well have a molecule of solvent (NMP, DMF) coordinated or they may be present as dimers.³¹ The rest of the catalytic cycle proceeds along conventional lines *via* olefin complex formation, olefin insertion and β -hydride elimination. After β -hydride elimination, the anionic palladium species left is highly underligated. At this stage three pathways are possible: (a) reaction with I_2 to form PdI_3^-



Scheme 4 Mechanistic proposal for ligand-free Heck reaction on aryl iodide (intermediates in bold have been observed by ES–MS or by EXAFS).

or more likely its dimer; (b) formation of soluble nanoparticles; (c) reaction with ArI. Since oxidative addition is fast with ArI, we would expect that in this case during the reaction hardly any palladium colloids will be formed, depending on the substrate to catalyst ratio. This is in agreement with the findings from Evans. At this point it is unclear where the I_2 comes from, although traces of oxygen seem the most likely explanation. At the end of the reaction the nanoparticles will form rapidly, leading eventually to the formation of palladium black. Using ICP-MS we were able to show that >99% of the palladium originally present in solution precipitates. This formed the basis of an attractive catalyst recycle in which the palladium was precipitated on a carrier material such as decalite and subsequently reactivated by addition of I_2 , which rapidly reoxidises Pd(0) to Pd(II).³⁰

The picture changes dramatically upon attempted use of aryl bromides. The oxidative addition of aryl bromides is slower than that of aryl iodides and this now becomes the rate-determining step. As a consequence, most of the palladium will be in the form of Pd(0). It is highly likely that under these circumstances colloid formation will be the faster reaction. If the nanoparticles grow beyond a certain size, palladium black formation will occur and the Heck reaction stops (Scheme 5).



Scheme 5 Competing pathways for palladium in the Heck reaction on aryl bromides.

This is a well-known phenomenon in homogeneous palladium-catalysed reactions. Although the Heck reaction itself is fast enough, catalysis is thwarted by the precipitation of the catalyst. And although Pd/C is a known catalyst for the Heck reaction, reaction can now take place only at the surface of the catalyst, presumably at kinks and steps, and it thus needs higher temperatures up to 190 °C for useful reaction rates.³³ The challenge is thus to prevent the formation of palladium black by stabilising the colloids or by slowing down their growth. A number of approaches to achieve this have been reported; most of these are based on stabilisation of the colloids by weakly binding ligands,³⁴ polymers,³⁵ dendrimers³⁶ polymeric micelles³⁷ or reverse micelles.³⁸ Although these solutions certainly work and allow the Heck reactions to be performed on aryl bromides without the use of phosphorus ligands, they have lost the attraction of the simple ligand-free catalyst system that was so easy to separate and recover at the end of the reaction. A much better solution becomes apparent upon closer examination of Scheme 4. It would seem that colloid formation is higher order in palladium, whereas the Heck reaction is first order, or even half-order if dimeric species are involved. Thus, we expected that lowering the palladium concentration with respect to the substrate would allow the Heck reaction to

compete against colloid formation. This theory was borne out in practice. Fig. 3 shows the effect of the substrate/catalyst ratio on the rate of the Heck reaction between bromobenzene and *n*-butyl acrylate. It is clear from this picture that higher substrate catalyst ratios lead to the rapid precipitation of palladium black and the reaction stalls. At very low concentrations the reaction becomes too slow to be practical, although it will go to completion after much longer reaction times or higher reaction temperatures. If the substrate/catalyst ratio is kept somewhere between 0.1 and 0.01 mol% the reaction proceeds smoothly and is finished within a reasonable time span. We have examined the scope of this reaction and found that at $S/C = 0.05$ mol% all substrates tested were completely converted in 1–15 h. We have dubbed this low-loading Heck reaction “homeopathic palladium”.

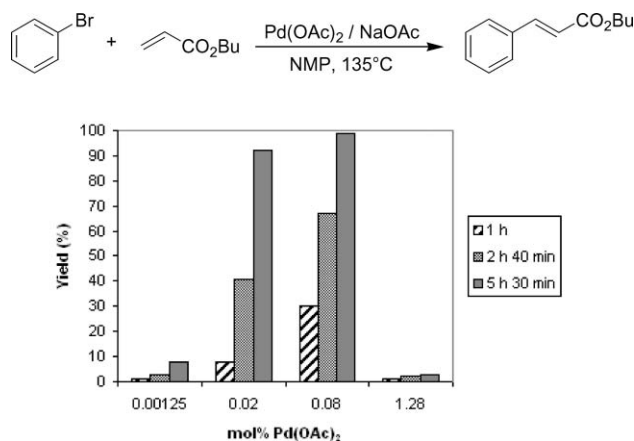


Fig. 3 Effect of the substrate/catalyst ratio on the rate of the Heck reaction between PhBr and *n*-butyl acrylate.

Earlier, Reetz, Westermann *et al.* had observed that in Heck reactions of ArBr and activated ArCl catalysed by Pd(OAc)₂ and *N,N*-dimethylglycine the effect of the additive disappeared at very low palladium concentrations.¹³ This can be explained by assuming that *N,N*-dimethylglycine stabilises the colloids and prevents their agglomeration to palladium black. At the lower concentrations this is no longer necessary, as the size of the colloids remains small either because of the kinetic reasons outlined above or possibly because of le Chatelier's principle.³⁹

Mechanistically, the picture may well be similar to the reaction on iodobenzene as depicted in Scheme 4, with one important difference: the oxidative addition of bromobenzene is the rate-determining step. As the palladium is now mostly present in the zero oxidation state it will take the form of soluble nanoparticles. These nanoparticles have been observed by Dupont during the Heck reaction on aryl bromides, by performing the reaction in ionic liquids, which allows TEM analysis without evaporation of solvent which could possibly disturb the system.⁴⁰ The question can also be raised if the colloids are involved at all in the catalysis as it would be possible that the small amount of palladium that takes part in the catalytic cycle actually stays there till all substrate has been used up. This question has been answered by two studies. In a ¹³C NMR study, Reetz was able to show that upon reaction of the preformed colloids with a stoichiometric amount of ArI a species forms in which most likely a carbon atom is bound to palladium.⁴¹ He presumed that in this case PhPdI, PhPdI₃²⁻

or the dimer of PhPdI_2^- had formed. Upon addition of styrene, stilbene formation occurred. We presume that the picture is similar for reaction with ArBr . In another study Dupont and co-workers showed that the size of the nanoparticles at the beginning and the end of the reaction is dramatically different.⁴² This seems to support the presumption that oxidative addition of bromoarene takes place continuously at the outer rim of the nanoparticles and is followed by detachment of the anionic complex from the colloid. It is not clear at what stage the palladium becomes detached from the colloid. It is possible that ArPdBr_2^- or its dimer is the leaving species, but maybe the detachment is assisted by the reaction with the olefin. It also seems very unlikely that the entire catalytic cycle takes place on the surface of the colloids, as not enough coordination sites would be available to complete the catalytic cycle. An ES-MS study performed by us revealed only the presence of minor amounts of PdBr_3^- in solution. This is expected, as most of the palladium will be locked up in the colloids.

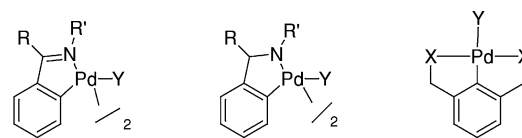
One tell-tale sign of the involvement of colloids is the dependency of the turnover frequency on the S/C ratio. This is already apparent from Fig. 3. A calculation of the turnover frequencies of these reactions reveals the following values after 2 h 40 min: 309 (0.08 mol%), 787 (0.02 mol%), 900 (0.00125 mol%) h^{-1} . This increase can be easily explained because at higher S/C ratios the size of the nanoparticles is reduced and the ratio between available palladium at the surface *vs.* total palladium increases.

Thus, for the Heck reaction with most arylating agents with the exception of aryl chlorides, ligand-free palladium in the form of $\text{Pd}(\text{OAc})_2$ is more than adequate as long as the substrate/catalyst ratio is kept low, between 0.01–0.1 mol%. For aryl chlorides this system does not work and here additives such as tetraphenylphosphonium bromide¹² or *N,N*-dimethylglycine¹³ are necessary to prevent formation of palladium black. Better still is the use of palladium catalysts base on bulky alkylphosphines.^{14–16}

Recently, Ley, Holmes and co-workers reported the use of polyurea encapsulated $\text{Pd}(\text{OAc})_2$ as catalyst (2.5 mol%) for the Heck reaction of aryl iodides and bromides at 90 °C.⁴³ The TOF is thus about 50-fold lower than the TOF reported by us for the use of $\text{Pd}(\text{OAc})_2$. However, the temperature is also 40 °C lower, making a comparison difficult. The authors report leaching to the extent of 60–79 ppm, it is thus by no means certain that reaction takes place in the microcapsules. No recycling was reported.

3 Palladacycles and pincer complexes

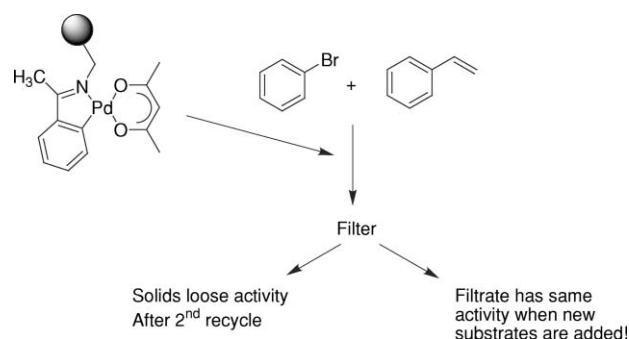
After the first publication of Hermann, Beller and co-workers⁶ many publications have appeared on the synthesis of novel palladacycle structures based on cyclometallated complexes of palladium with aromatic compounds containing a side chain with heteroatoms such as P, N, S and O.⁷ Also pincer complexes with cyclometallated ligands of the type PCP, SCS and NCN were developed (Fig. 4).⁷ All these compounds are active catalysts in Heck and Suzuki reactions at high temperatures. Several proposals have been advanced for the mechanism of these reactions. In the case of palladacycles these involved $\text{Pd}(\text{II})/\text{Pd}(\text{IV})$ cycles,⁴⁴ monoligated palladium in a $\text{Pd}(\text{0})/\text{Pd}(\text{II})$ cycle,⁴⁵ anionic $\text{Pd}(\text{0})$ species⁴⁶ and involvement of dimeric species. Although none of these mechanisms have been sufficiently proven nor disproven, the following experiment shed an entirely different light on the matter. When Nowotny and co-workers immobilised the imine-based



R = alkyl, aryl; R' = alkyl aryl, Oalkyl; Y = Cl, Br, I, OTf, OAc;
X = NR_2 , PR_2 , $\text{OP}(\text{OR})_2$, SR

Fig. 4 Generic structures of palladacycles and pincers.

palladacycle developed by Milstein and co-workers⁴⁷ the recycling experiment did not deliver the expected results. The catalyst was duly filtered off and reused, but the solid lost its activity after the second use.⁴⁸ On the other hand, when bromobenzene and styrene were added to the filtrate the reaction proceeded at the same rate (Scheme 6).



Scheme 6 Loss of activity of immobilised palladacycle is indicative of ligand-free palladium.

This clearly shows that the catalyst becomes detached from its ligand, presumably by reduction. Although this experiment does not exclude residual activity of the ligand bound metal, it certainly shows that soluble palladium is present. Beletskaya *et al.* in their work on nitrogen-containing palladacycles already commented that these were only the precursors of a $\text{Pd}(\text{0})$ species, based on the observation of induction periods and sigmoidal kinetic curves.⁴⁹

In many reports on catalytic activity of palladacycles in the Heck reaction turnover frequencies have been measured at different S/C ratios. In all these papers the TOF increases with increasing S/C. In most papers no explanation is given for this phenomenon. Pfaltz, Blackmond and co-workers explain the effect by a dimer–monomer pre-equilibrium of the catalyst.⁵⁰ We believe the effect is caused by the fact that part of the palladium is present in the form of soluble nanoparticles.^{19,20} At higher substrate/catalyst ratios more palladium will be in the catalytic cycle for the kinetic and/or thermodynamic reasons described above. In addition, the size of the colloids will be smaller at higher S/C ratios making the ratio between palladium on the outer rim and palladium on the inside of the colloids more favourable.

We have compared the rate of the Hermann–Beller palladacycle with our own homeopathic palladium method at the same S/C ratio. In these experiments the catalysts were added to the hot solution containing all other ingredients. Under these circumstances there hardly is any induction period in both reactions. This would seem to dispel the notion that palladacycles act as a slow release reservoir for $\text{Pd}(\text{0})$. Comparing the rates, it is obvious that these

are very similar (Fig. 5). It would seem that the residual Tol₃P retards the catalysis with the HB catalyst somewhat.

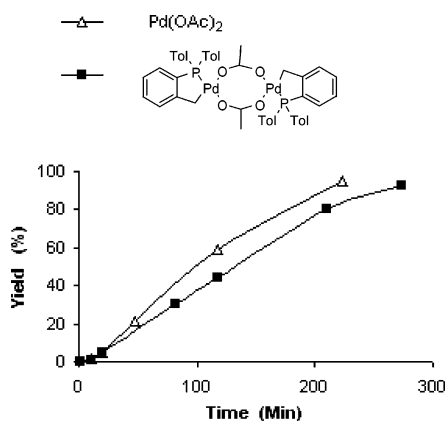


Fig. 5 Rate comparison between Pd(OAc)₂ and the HB catalyst in the Heck reaction between PhBr and *n*-butyl acrylate in NMP with NaOAc as base at 140 °C.

An ES–MS comparison of both reactions was most revealing. Whereas initially the HB palladacycle was clearly visible in the positive mode, a few minutes into the reaction, this signal had disappeared and in both reactions only a weak signal of PdBr₃[−] was obtained with no signals in the positive mode. This again seems to support the fact that both reactions proceed *via* the same mechanism.

In the past two years many publications have appeared that all provide evidence that palladacycles and pincers are not stable under the conditions of the Heck reaction at high temperatures. Two recent reviews have summarised and critically evaluated these data.^{7d,51}

Attempts to create recyclable catalysts have been most revealing. Thus, Gladysz in an attempt to recycle an imine based palladacycle carrying fluoros ponytails also found activity transferred to the non-fluorous phase and was able to prove the presence of Pd-colloids using TEM.⁵²

Several studies have appeared that show beyond doubt that PCP and SCS pincer complexes also decompose during the Heck reaction and lead to the formation of colloidal palladium.⁵³ Evidence was based on immobilisation studies and on the application of the extensive Hg poisoning protocol developed by Widegren and Finke, which proved the presence of palladium colloids.⁵⁴

Thus, the conclusion seems justified that all palladacycles and pincers decompose during the Heck reaction at high temperatures to form palladium colloids. The mechanism of these reactions proceeds *via* anionic palladium species as proposed by us, although in the case of more reluctant substrates the bulk of the palladium will be present as colloids.

4 Heterogeneous palladium catalysts

The use of heterogeneous palladium on solid carriers such as Pd/C, Pd/SiO₂ and Pd/Al₂O₃ as catalyst for the Heck reaction on aryl iodides and bromides has been reported.⁵⁵ In general these reactions proceed much more slowly than those catalysed by soluble metal catalysts. This is understandable as the catalysis can only take place at the surface of the catalyst.⁵⁶ Many groups have

tried to develop more active palladium catalysts by changing the nature of the carrier material. Strauss and co-workers described the use of palladium on porous glass as catalyst for the Heck reaction of aryl iodides and activated bromides with turnover numbers up to 4000.⁵⁷ Many examples have been described in which the palladium was “encapsulated” in a zeolite framework such as MCM-41,⁵⁸ zeolite NaY⁵⁹ and SAPO-31.⁶⁰ Shi and co-workers reported the use of palladium deposited inside the channels of SBA-15 mesoporous silica.⁶¹ Jacobs, de Vos and co-workers used Mordenite treated with Pd(NH₃)₄²⁺.⁶² Kaneda and co-workers treated hydroxyapatite (Ca₁₀(PO₄)₆(OH)₂ with PdCl₂(PhCN)₂.⁶³ This resulted in an extremely active catalyst for the Heck reaction of aryl bromides at 0.2 mol% of palladium. In almost all of these studies some degree of leaching of palladium was observed during the reaction, although all palladium would be deposited on the carrier at the end of the reaction. When all these reports are compared there is an obvious cross-correlation, which has escaped most authors: the rate in all of these reactions is highly dependent on the substrate/catalyst ratio (S/C).⁶⁴ Thus, the higher the S/C, the higher the rate. This effect is of course very similar to that observed when using soluble Pd(OAc)₂. Arai and co-workers were the first to propose that it is indeed the leached palladium species that is responsible for the reaction in his work on the use of supported palladium catalysts in the Heck reaction of iodobenzene and methyl acrylate.⁶⁵

By using a three phase test with an aryl iodide attached to a solid support, Davies *et al.* were able to show that the Pd/C becomes active in the Heck reaction on butyl acrylate only after addition of a soluble monomeric aryl iodide or bromide.⁶⁶ Interestingly, he also found that the rate increased with increasing amounts of NaOAc. This suggests that the heterogeneous catalyst is solubilised by oxidative addition of the aryl halide and enters the catalytic cycle in the form of a soluble anionic species such as [ArPd(OAc)Br][−] or [ArPd(OAc)_n][−]. Biffis reported more or less similar findings in the Heck reaction with Pd/Al₂O₃ (AO–Pd) and Pd deposited on an ion-exchange resin containing sulfonate groups (PS–Pd).^{21c} Aryl bromide alone was sufficient to solubilise the palladium when AO–Pd was used, but ArBr and NaOAc where necessary with PS–Pd. A review on the use of heterogeneous catalysts in the Heck reaction in which Biffis, Zecca and Basato describe the importance of leaching is highly recommended reading.⁶⁷

Köhler and co-workers performed extensive studies on a range of Pd/C catalysts that differed in Pd dispersion, Pd distribution and oxidation state.^{21a} He found that most active systems were obtained with catalysts that had high dispersion, low degree of reduction and uniform Pd impregnation. In addition, sufficient water content was also found to be important. It was also concluded that palladium leaching correlates significantly with the reaction parameters. In a later paper he found that Pd deposited on the zeolite NaY can even be used for the Heck reaction on aryl chlorides in the presence of tetrabutylammonium bromide.^{21b} Here again a good correlation was found between palladium in solution and the conversion of aryl bromide (Fig. 6). During the reaction about one third of the palladium goes into solution, but after the reaction is finished, less than 1 ppm of palladium is found in solution.

Thus, there is extensive evidence that all heterogeneous palladium catalysts are functioning as homogeneous catalysts in the

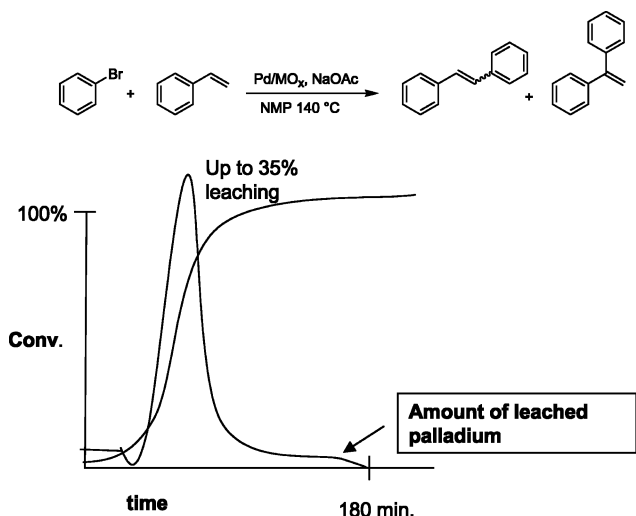
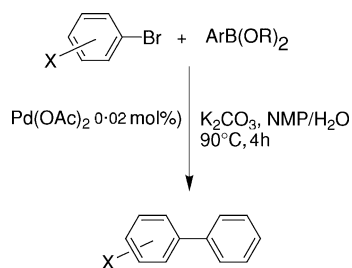


Fig. 6 Correlation between palladium leaching and rate of the Heck reaction.

Heck reaction. They may be partly present as colloids, but in the catalytic cycle the palladium is present in monomeric or dimeric form as anionic species.

Ligand-free palladium in other C–C bond forming reactions

Several papers have been published describing the use of ligand-free palladium in the Suzuki reaction. Interestingly, the reaction seems to work even at the relatively high C/S ratio of 0.5–2 mol%, although Bu_4NBr was needed for good activity.⁶⁸ Indeed, the observation has been made before that aromatic boronic acids stabilise palladium colloids. Nevertheless, it is possible to lower the C/S ratio further. We found the reaction works well with aryl bromides and some activated aryl chlorides in the presence of 0.02–0.0005 mol% of $\text{Pd}(\text{OAc})_2$ (Scheme 7).⁶⁹



Scheme 7 Homeopathic palladium in the Suzuki coupling.

Interestingly, Leadbeater and Marco initially reported a metal-free Suzuki to take place under microwave irradiation at temperatures of about 180 °C.⁷⁰ Initially, the solution was screened for the presence of palladium in ppm quantities which were found to be absent. However, in view of the demonstrated ability of homeopathic amounts of palladium in the Suzuki reaction we felt that this was not sufficient proof for a metal-free mechanism.⁷¹ Indeed, upon further analysis Arvela and Leadbeater found PPT amounts of palladium in the inorganic base to be the culprit.⁷²

Use of ligand-free palladium in the Negishi reaction met with limited success and gave very poor results in the Kumada reaction.⁶⁸

Fairlamb *et al.* have studied the use of a bimetallic palladacycle as catalyst in the Sonogashira reaction.⁷³ They made the surprising discovery that also in this reaction the TOF increases with lower catalyst loadings. This is presumably also due to the formation of palladium colloids in this reaction. Use of palladium colloids as catalyst for the Sonogashira reaction has been reported.⁷⁴ In one case, use of sonication led to enhanced reaction rates, allowing the Sonogashira reaction to proceed at room temperature.^{74a}

5 Conclusions

In view of the extensive evidence based on TEM, MS, EXAFS, filtration tests of immobilised catalysts and Finke inhibition tests we conclude that in all Heck reactions at high temperatures, certainly above 120 °C, the palladium catalyst, irrespective of the nature of its precursor, is rapidly reduced to $\text{Pd}(0)$ which has a strong tendency to form soluble colloids. The arylating agent continuously attacks the palladium atoms at the rim of the nanoparticles leading to the formation of soluble anionic complexes. After completion of a Heck cycle in solution, the palladium may fall back on the colloids or engage in the next oxidative addition. There is no advantage in the application of palladacycles, palladium complexes or heterogeneous palladium catalysts as compared to palladium acetate. However, palladium acetate is not a good catalyst for the Heck reaction of unactivated aryl chlorides. In this case the heterogeneous catalysts or the palladium catalysts based on basic bulky phosphines seem to perform better.

Immobilisation of palladium catalysts for use at high-temperature Heck reactions is also not recommended for the same reasons.

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