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Forum

Genesis of Coordinatively Unsaturated Palladium Complexes Dissolved from Solid Precursors during Heck Coupling Reactions and Their Role as Catalytically Active Species

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The Forum Article critically summarizes investigations and discussions on the nature and role of potential active species in C–C coupling reactions of the Heck type using catalyst systems with "ligand-free" inorganic salts, simple inorganic complexes, and supported and nonsupported (colloidal) Pd particles. From a series of experiments and reports, it can be concluded that the "active species" is generated in situ in catalytic systems at higher temperature conditions (>100 °C). In all heterogeneous systems with solid Pd catalysts, Pd is dissolved from the solid catalyst surface under reaction conditions by a chemical reaction (complex formation and/or oxidative addition of the aryl halide), forming extremely active coordinatively unsaturated Pd species. Pd is partially or completely redeposited onto the support at the end of the reaction when the aryl halide is used up. The Pd dissolution–redeposition processes correlate with the reaction rate and are strongly influenced by the reaction conditions. Skilled preparation of the catalyst and careful adjustment of the reaction conditions allowed the development of highly active heterogeneous catalysts (Pd/C, Pd/metal oxide, and Pd/zeolite), converting aryl bromides and aryl chlorides in high yields and short reaction times. Reaction conditions have been developed allowing the conversion of bromobenzene with turnover numbers (TONs) of 10^7 and even of unreactive aryl chlorides (chlorobenzene and chlorotoluene) in high yields with simple "ligand-free" Pd catalyst systems like $PdCl_2$ or $Pd(OH)_2$ in the absence of any organic ligand. Simple coordinatively unsaturated anionic palladium halide (in particular, bromo) complexes $[PdX_n]^{m-}$ play a crucial role as precursor and active species in all ligand-free and heterogeneous catalyst systems and possibly in Heck reactions at all.

1. Introduction

Pd represents one of the most interesting transition metals applied to organic synthesis. Because of the unique combination of various properties relevant for catalytic cycles, its compounds are the catalyst of choice for a variety of rather different reactions such as hydrogenation, oxidation, and C−C coupling reactions.[1] An enormous number of new Pd complexes, organometallic compounds, and supported Pd catalysts for C−C coupling reactions in particular of the Heck type have been reported in the last 10 years.[2] The motivation was to demonstrate useful applications of the presented new organic ligands or organometallic compounds in the majority of papers. However, there were also an increasing number of papers regarding in situ transformations that Pd catalysts undergo before and during the catalytic cycle and focusing on the nature of the true catalytically active species. For C−C coupling reactions, practically every form of Pd used has

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(2) For reviews, see: (a) Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev.* **2000**, *100*, 3009−3066. (b) Whitcombe, N. J.; Hii, K. K.; Gibson, S. E. *Tetrahedron* **2001**, *57*, 7449−7476. (c) Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 4176−4211. (d) Hillier, A.; Nolan, P. *Plat. Met. Rev.* **2002**, *46*, 50−64. (e) Ferré-Filmon, K.; Delaude, L.; Demonceau, A.; Noels, A. F. *Coord. Chem. Rev.* **2004**, *248*, 2323−2336.

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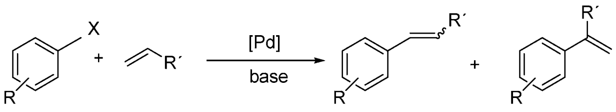
Scheme 1. General Scheme of the Heck Reaction Including Chosen Substrates



X = Cl, Br, I
R = CH_3CO, NO_2, H, CH_3, OCH_3
R´= Aryl, COOAlkyl

been proposed as the catalytically active species in the past decade. Recent reports on the high activity of so-called "ligand-free" Pd systems with very low Pd amounts (ppm or ppb levels) and on the temporary dissolution of Pd atoms from supported Pd nanoparticles in heterogeneous catalyst systems renewed once again this discussion about the specific active species in C−C coupling reactions. This Forum Article takes up these investigations and discussions on the role of highly coordinatively unsaturated Pd species in simple systems with inorganic salts or (halo and acetato) complexes generated in situ under chosen reaction conditions (at higher temperatures) in particular from solid Pd particles in the catalytic cycle. In fact, investigations with heterogeneous, i.e., more complex, systems brought more light into the reaction mechanism of the Heck reaction in general in the past few years.[3]

After a short summary of the relevant aspects of Heck reactions and catalysts, the present knowledge about so-called "ligand-free" catalyst systems (Pd salts and colloids) will be shortly summarized and solid (supported) Pd catalysts will be introduced. The main focus will be on the formation, reactions, and reprecipitation of highly coordinatively unsaturated Pd complexes in heterogeneous solid−liquid systems at higher temperatures. A more detailed understanding of the numerous (partially reversible) processes within an extended catalytic Heck cycle and of the crucial reaction parameters led to the development of very simple but highly active and selective heterogeneous systems. Corresponding conclusions allowed the conversion even of unreactive aryl chlorides with ligand-free Pd salts described herein for the first time.

2. The Heck Reaction: A Short Introduction

About 30 years ago, Heck and Nolley[4] and Mizoroki et al.[5] developed independently a simple reaction for the arylation of olefins. This "Heck reaction" (Scheme 1) soon became an important tool for fine chemical synthesis and industrial applications. Originally, the coupling of an aryl halide and an olefin was performed using a homogeneous Pd^0 complex in the presence of a base. In the following years, many efforts have been made to extend the scope of the Heck reaction. Various classes of compounds, such as aryl triflates, aromatic anhydrides, carboxylic acids, aryl diazonium salts (Matsuda−Heck reaction), benzyl halides, halides of benzoic acids (Blaser−Heck reaction), alkyl halides, and boronic acids, have been utilized besides aryl halides, which still play an outstanding role.[2]

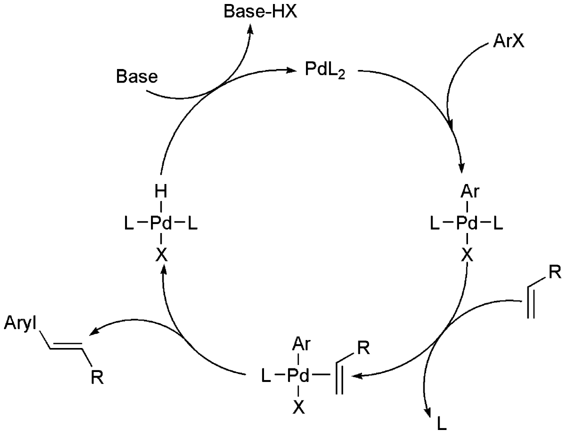


Figure 1. General catalytic cycle for the homogeneously catalyzed Heck reaction. According to the generally accepted modified catalytic cycle by Amatore and Jutand,[7] Pd complexes are anionic because of the coordination of halide ions; i.e., "PdL_2" should be understood as $[PdL_2X]^-$, etc.

The reactivity of the different aryl halides decreases from iodides to bromides and chlorides because of the different strengths of the aryl−X bond (C−I < C−Br < C−Cl). Activated aryl halides have an electron-withdrawing group in the para position, so the aromatic system is electron-deficient and can be activated more easily. Styrene and acrylic esters are the most common olefin compounds applied. The number of suitable Pd complexes increased rapidly; new types of sterically hindered, chelating, or chiral phosphine ligands as well as carbene complexes or palladacycles have been designed. Besides Pd^0 complexes, also Pd^{II}-containing systems, which are reduced in situ, can be employed. The catalytic cycle proposed originally by Heck (Figure 1), which is widely accepted, starts with an oxidative addition of aryl halide to a 14-electron Pd^0 complex PdL_2. This results in the formation of *cis*-$ArPdXL_2$, which isomerizes to the thermodynamically favored trans complex. A free coordination site is generated by losing one of the ligands, and subsequently the alkene is coordinated to form a π complex. A new C−C bond is formed in the following migratory insertion step. The formed alkene is released from the complex via β-H elimination after rotation. PdL_2 is regenerated by removal of HX, which is quenched by the base.[6] This cycle has been modified by Amatore and Jutand focusing on the anionic nature of the Pd complexes (see the comment in the caption of Figure 1).[7]

A careful view into the literature shows that the reaction conditions have a dramatic influence on the yield of the reaction. Several solvents are widely applied in Heck reactions. In most cases, polar aprotic solvents [e.g., 1-methyl-2-pyrrolidone (NMP), *N*,*N*-dimethylacetamide, *N*,*N*-di-

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(7) (a) Amatore, C.; Jutand, A. *J. Organomet. Chem.* **1999**, *576*, 254−278. (b) Amatore, C.; Jutand, A. *Acc. Chem. Res.* **2000**, *33*, 314−321.

methylformamide, dioxane] are utilized; however, also water, other common organic solvents (e.g., toluene, hexane, and ethanol), or very special solvents (e.g., supercritical CO_2 and ionic liquids) have been applied. A comparable large variety of different bases turned out to be suitable. Tertiary amines (NEt_3 and NBu_3) and alkali salts like carbonates, acetates, or phosphates play the most important role among them. Besides, also hydroxides and fluorides have been employed. The most promising combination of solvent and base depends strongly on the catalytic system. Solubility of the base and its basicity in the respective solvent must also be taken into account. Many optimized catalyst systems that have been reported up to now require the addition of special agents for stabilization of the active Pd species. Especially, tetraalkylammonium halides are suitable to affect the activity and agglomeration of Pd.[8]

3. Ligand-Free and Colloidal Pd Systems as Heck Catalysts

Besides organometallic compounds or mixtures of Pd with stabilizing ligands, it is well-known that simple (pure) inorganic Pd complexes or simple Pd salts can also catalyze the Heck reaction. Very early after the discovery of the reaction by Heck and Mizoroki, Pd black was identified as an active catalyst for the conversion of (however exclusively) iodobenzene.[9] Already Mizoroki concluded from the experimental results that Pd black was not the actual catalyst but only some kind of precursor or reservoir for the active Pd species. Mizoroki described the use of $PdCl_2$ (1 mol %) in the presence of sodium acetate as the base in methanol (120 °C).[5] The original procedure reported by Heck uses 1 mol % of $Pd(OAc)_2$ as the precatalyst, tributylamine as the base, and NMP as the solvent at 100 °C.[4] According to the general view in the literature, both reactions are “ligand-free”, although the large excess (100 times) of acetate or amine as ligands plays a substantial role in the reaction cycle. In both cases, aryl iodides and various olefins served as the substrates.

By introduction of additional ligands and complexes like phospine, palladacycle, or carbene complexes of Pd, also aryl bromides and even the unreactive aryl chlorides could be converted.[2] Also, the activity of ligand-free catalysts could be further increased by the introduction of tetraalkylammonium salts by Jeffery.[8] The accelerating effect of the tetraalkylammonium halides is probably due to several reasons. Again, additional ligands — the halides — are introduced to the reaction mixture in excess amounts (relative to Pd). The possible importance of anionic Pd complexes in the Heck cycle has been reported.[7] The tetraalkylammonium halides are known to stabilize nanosized Pd colloids against agglomeration, representing the major path to deactivation. Finally, the solubility of the anionic Pd complexes will be increased by the tetraalkylammonium counterion.

It had been shown later that Pd colloids can be stabilized also by a number of polymers under Heck reaction conditions.[10] It was suggested that Pd colloids are involved in ligand-free Heck reactions.[11] The question of whether the observed Pd colloids are the actual catalysts functioning at surface sites similar to heterogeneous catalysis or whether they serve only as a reservoir or donor of smaller and more reactive fragments was not decided.

Ligand-free Heck reactions with (nonactivated) aryl bromides under Jeffery conditions (1 mol % of Pd, without additional stabilizing agents) generally fail due to precipitation of Pd. Precipitation of Pd (black) is a well-known phenomenon in Pd-catalyzed reactions, even with Pd catalysts containing an excess of P ligands. A way to prevent the formation of Pd black is to reduce the amount of Pd in the reaction system, i.e., to increase the substrate/catalyst ratio. This approach has been successfully demonstrated by Beletskaya and Cheprakov,[2a] Reetz et al.,[12] and de Vries et al.[13] and introduced as the so-called “homeopathic” Pd to the literature. The ligand-free Pd catalyst becomes more active at lower concentrations. At values between 0.1 and 0.01 mol %, the catalyst remains in solution because the size of the clusters does not increase (the rate of the oxidative addition is sufficiently high to prevent agglomeration).[14] Other groups have independently reported similar homeopathic ligand-free Pd-catalyzed reactions of aryl bromides. Schmidt et al. increased the amount of aryl bromide, relative to the olefin, and noted a beneficial effect of the addition of formate.[15] Leadbeater reported a ligand-free Heck reaction of bromoarenes in water in the presence of NBu_4Br using microwaves as the heating source.[16] It should be mentioned here that for typical supported Pd catalysts, e.g., Pd on activated carbon or on metal oxides, the substrate/catalyst ratio does not play a significant role in the activity of the catalyst. For example, bromobenzene is converted with the same efficiency to Heck products for catalyst amounts of 0.005 mol % as well as 2 mol % Pd by Pd/C, indicating a particular way of stabilizing Pd against agglomeration different from the “homeopathic” approach (for dissolution−reprecipitation processes, see below).[17]

All so-called “ligand-free” Pd systems reported failed in the activation of aryl chlorides.

4. Heck Coupling by Solid (Heterogeneous) Catalysts: A General Consideration

In the past decade, a large number of heterogeneous Pd catalysts for C−C coupling reactions in particular of Heck

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type were reported. Generally, Pd in various forms was supported on solid inorganic, C, or polymer materials. The main driving forces for the development of these Pd catalyst systems were recovery, recycling, and reuse of the catalyst. In principle, such systems can also be regarded as ("organic ligand-free") Pd colloids that are stabilized by interaction with the support. One of the most important differences between reported homogeneous organometallic and supported systems (including colloidal systems) is the clearly lower activity of the latter catalysts (often by orders of magnitude). This is reflected by the model systems investigated. Typical reports of heterogeneous catalysts focus on aryl iodides and activated aryl bromides as substrates. This is in good agreement with the activity observed for Pd black or Pd colloids discussed before.

Most heterogeneous catalysts that are suitable for reactions of aryl iodides and activated bromides (like bromoacetophenone or bromonitrobenzene) failed in reactions of the nonactivated bromobenzene and of aryl chlorides. However, in the past few years, an increasing number of heterogeneous catalyst systems have been developed that allow conversion of bromobenzene and even of unreactive aryl chlorides. The common properties of these catalysts are summarized and discussed in the next chapters.

A specific problem in heterogeneous Heck systems is possible Pd leaching from the solid phase into the liquid phase. In fact, most papers of the past few years that investigated this subject report a more or less significant metal loss in heterogeneous Heck reactions. Often, however, Pd concentrations in liquid solution were very small at the end of the reaction, leading to the conclusion that these traces are not significant for the catalytic reaction. This question seems to be a crucial point and is discussed in detail in the next chapter.

5. Mechanism Involving Solid Pd: Generation of Dissolved Active Pd Species from Solid Precursors under Reaction Conditions

Although there were still several articles in the last years claiming a true heterogeneous (surface) mechanism for the Heck reaction, a careful interpretation of the literature gives clear evidence for a quasi-homogeneous one. This can also be derived from recent reviews exactly on this subject.[3,18] The actual active species is Pd in solution (molecularly) dissolved by leaching from the solid precatalyst. Consequently, the Heck cycle would be analogous to the homogeneous one (Figure 1), where the solid catalyst serves only as a reservoir for active Pd species in solution, as was already proposed by Mizoroki. Probably the first clear indications were reported by Schmidt and Mametova by kinetic investigations on the reaction mechanism with aryl iodides.[19] The leaching process itself with typical supported Pd catalysts was first studied in detail by Arai et al. and reported in a series of papers for the reaction of iodobenzene and methyl acrylate.[20] Biffis et al. and several other groups confirmed these results for different catalysts used for the reaction of aryl iodides and bromides.[3,15,17,21] The pseudo-homogeneous mechanism can be concluded and has been proposed for practically all types of heterogeneous catalysts: for typical metal oxide supported Pd, for activated C catalysts, for different kinds of polymer supports, and for Pd colloids. In cases where the authors propose a heterogeneous (surface-based) mechanism, all effects and observations can be explained also by the leaching model.

Some of the (probably) wrong conclusions in the literature during this period are due to the fact that measurable amounts of Pd are often observed in solution only during the reaction. Because of redeposition, the Pd concentration in the solution is very small or not detectable at the end of the reaction. In addition, several experimental tests on the "heterogeneity" of the reaction were obviously not suitable for the Heck reaction. Also very important, the majority of the mechanistic investigations were performed with aryl iodides (or activated aryl bromides) only. It has been described before that an extremely low amount of Pd on the ppm or sub-ppm level is able to convert these substrates easily.[22] The nature and role of the various Pd species in Heck reactions with heterogeneous catalysts have been conclusively discussed and illustrated in the reviews on heterogeneous Heck catalysis by Biffis et al., Jones et al., and ourselves.[3]

One of the most obvious and suitable experimental approaches to investigating in situ transformations in heterogeneous systems is the determination of the Pd content dissolved in solution dependent on the progress of the reaction (conversion of substrates and formation of products). Such experiments have been performed and reported with a series of supported catalysts (Pd on metal oxides, activated C, and zeolites) for Heck reactions of bromobenzene and of aryl chlorides in the past few years.[23] The results show clearly and reproducibly that Pd is dissolved from the catalyst surface during the reaction and partially or completely reprecipitated onto the support at the end of the reaction.

Figure 2 illustrates an experiment correlating the Pd concentration in the solution with conversion during a typical Heck reaction. In such an experiment, samples were taken continuously from the reaction mixture and Pd trace analyses were performed [atomic absorption spectroscopy/inductively coupled plasma (ICP) optical emission spectroscopy]. An

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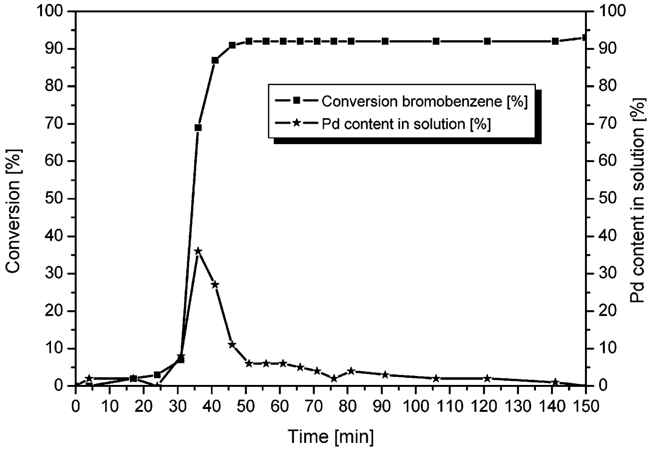

Figure 2. Time-dependent correlation of conversion and Pd leaching (percentage of the total Pd amount) in the Heck reaction of bromobenzene and styrene in the presence of Pd/TiO_2 (reaction conditions: 180 mmol of bromobenzene, 270 mmol of styrene, 216 mmol of NaOAc, 0.2 mol % Pd catalyst, 180 mL of NMP, 140 °C).

original experiment using bromobenzene and styrene as reactants shows that, during the first 25 min, while the temperature is raised, there is only little (or no) leaching and no conversion. After a temperature of 140 °C is reached, about one-third of the Pd is leached from the surface of the support (strictly speaking, the rate of dissolution of surface Pd atoms by complex formation reached a “visible” value). Simultaneously, the majority of the aryl halide is converted within a few minutes. After the reaction is finished (the aryl halide is used up), Pd is (nearly) completely redeposited onto the support. Please note that such a heterogeneous system would be truly ligand-free (provided that the base does not coordinate and NBu_4Br is not added) until the very first aryl halide molecules have been converted (oxidative addition). When the reaction continues, the species in solution are halide complexes of palladium $[PdX_n]^{m-}$ (Pd^{II} or Pd^0).

The same qualitative behavior has been observed for corresponding experiments with aryl chlorides (chlorobenzene and chloroacetophenone). The time schedule, total Pd concentration in the solution, and reaction conditions were, however, different. The dissolution of Pd in aryl chloride systems is slower compared to aryl bromides. The amount of Pd leached into the solution must be higher in aryl chloride systems in order to achieve high conversion within reasonable reaction times. This is illustrated in Figure 3 as a schematic drawing. It visualizes the results of a number of corresponding experiments now being available for reactions of bromobenzene, chloroacetophenone, chlorobenzene, and chlorotoluene and Pd on various supports (metal oxides, activated C, and zeolites).[23]

The reaction of aryl halides and styrene (point A → point C) is complete within a few minutes at 140 °C (for aryl bromides) or 160 °C (aryl chlorides), respectively, with the best optimized supported Pd catalysts (e.g., Pd on C, on metal oxides, or on zeolites). The dissolution of Pd from the support (point A) becomes significant at the temperature where high conversions are observed. The onset and shape of the dissolution curve depend on a variety of parameters (substrate, catalyst, solvent, temperature, base, additives, atmosphere; see later). The maximum Pd concentration in the solution correlates well with the highest reaction rate (turning point B of the conversion curve). The Pd concentration in the solution decreases with continued conversion (point C; decrease of the aryl halide concentration), leading to (nearly) complete reprecipitation (point D) of the originally dissolved Pd (fortunately) onto the support. Increased temperature and/or excess of a reducing agent (e.g., sodium formate) added at the end of the reaction reduces the Pd concentration in the solution to traces (1 ppm or sub-ppm level). This can be of relevance for practical applications in the pharmaceutical industry, where Pd contamination of the organic product must be prevented very strictly. This approach represents a very simple, convenient, and cheap workup procedure. The disadvantage is that the high Pd dispersion on the support can be reduced (particle agglomeration) by this drastic procedure, as demonstrated by transmission electron microscopic investigations of fresh and spent Pd/activated C catalysts. As a result, the activity of the recycled/reused catalysts is reduced. On the other hand, workup procedures (partial reoxidation of Pd^0 by I_2 or Br_2) have been reported that open other opportunities for reactivation of the solid catalyst. (This procedure works, however, only with aryl iodides and activated aryl bromides.)[24] Careful control of the reaction conditions and catalyst properties has been demonstrated to be another successful approach to developing catalysts that are reusable several times without a significant loss in activity.[23] Such reaction conditions were found empirically (by screening) and involve, e.g., the nature of the base and application of oxidizing or reducing conditions during the reaction and can be understood as parameters that control the temporary Pd concentration and oxidation state during the reaction. Probably continuous dissolution and redeposition processes of Pd during the reaction not only keep the Pd particle size small (and in the right oxidation state) in solution but also on the surface of a support.

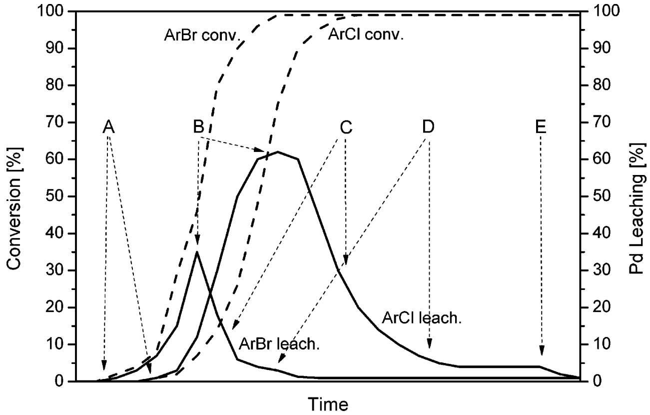

Figure 3. Schematic drawing of the time-dependent correlation of conversion and dissolved Pd amount in a typical Heck reaction with solid (supported) Pd catalysts. Heck reactions of aryl bromide and aryl chloride are compared. Arrows A, B, etc., mark typical events during comparable experiments reported up to now (A, Pd dissolution starting at the reaction temperature; B, maximum amount of Pd in solution/highest reaction rate; C, substantial redeposition of Pd onto the support with increasing conversion; D, (far-reaching) completion of Pd redeposition; E, complete redeposition of even Pd traces by increased temperature/reducing agents).

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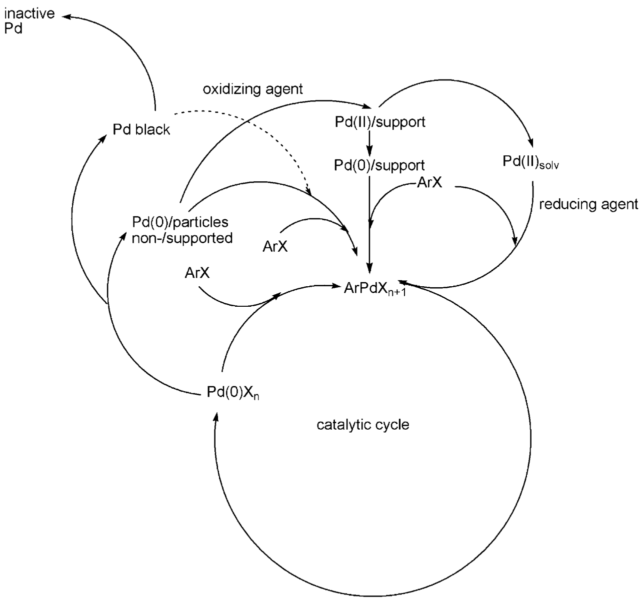

Figure 4. Extended catalytic cycle of Heck reactions including solid Pd species: possible reaction pathways, processes, and species. Charges of the intermediate species have been omitted for simplification. Species like "Pd^0X_n" and "$ArPdX_{n+1}$" within the catalytic cycle are assumed to be negatively charged.

6. How Do the Nature and Properties of a Solid Catalyst and the Reaction Conditions Influence Pd Dissolution and Thus the Activity and Selectivity of the Reaction?

Several approaches allowed an efficient activation of bromobenzene and of aryl chlorides. For Pd supported on C and on metal oxides, the best catalyst performances were achieved for the following catalyst properties: (i) Pd should be highly dispersed on the support surface. (ii) It should be present as palladium(II) (oxide or hydroxide). The classical prereduction in H at elevated temperature decreases the activity in general significantly. The low activity of several reported Pd/C catalysts can be explained in this manner. (iii) The catalysts should not be dried before use. Some water content is found to be advantageous.[25]

Taking this into account, the influence of the support is of minor importance for reactions of all aryl bromides. Similar good results can be obtained with activated C, MgO, TiO_2, SiO_2, Al_2O_3, AlF_3, etc. Differences found in the literature are probably due to different Pd dispersions, Pd reduction degrees, or water contents. For the activation of nonactivated aryl chlorides, a "fine-tuning" of the support and the reaction conditions can be necessary.

Pd complexes immobilized in zeolite cages turned out to belong to the very best catalysts for Heck reactions. Originally, it was assumed that the isolation of molecular Pd in zeolite pores was responsible for its stabilization against agglomeration and that the reaction took place within the zeolite cages. Recent investigations have shown, however, that the cycle shown in Figure 4 is also valid for these highly active catalyst systems. The reaction takes place outside of the zeolite pores; Pd is leached into the bulk solution, catalyzes the Heck reaction, and diffuses back into the pores. Obviously, the zeolite pore system allows a particularly efficient equilibration of all processes and cycles given in Figure 4. Highly active palladium halide complexes are delivered continuously, and agglomeration is effectively prevented.[23]

The complex mechanism and the various processes (Figure 4) are responsible for the strong influence of the reaction conditions and parameters. Additives play an important role. Thus, the performance of different catalysts can be improved by (defined) small amounts of oxidizing as well as reducing agents and by a variety of additives (in particular, by alkyl ammonium halides) and is strongly influenced by the nature of the solvent and base. Note that these parameters also influence Pd leaching in an analogous manner. This provides various possibilities to improving the catalytic performance simply by varying these parameters. In particular, for the activation of aryl chlorides, a very careful choice of not only solvent, base, additives, and temperature but also catalyst is necessary. Some of the thus optimized parameters are different from those considered to be the best for the same reaction with bromobenzene. The choice of reaction parameters may be less critical for very good organometallic Pd catalysts and, in particular, for lower reaction temperatures ($<$100 °C).

7. Extended Catalytic Cycle of Heck Reactions: A Complex System Offering a Number of Ways To Intervene and To Control

A proposal for an extended reaction cycle for Heck catalysis with solid (supported) Pd catalysts is illustrated in Figure 4. It reflects that a considerable number of processes involving metallic Pd (particles, colloids, or clusters) on the support or in solution, molecular Pd^0 and Pd^{II} species supported or in solution, and aryl halides complete the classical Heck cycle (Figure 1). Although the dissolution and redeposition of Pd has been proven by a number of authors and experiments, some of the single steps such as, e.g., the immediate dissolution "reaction" are still under discussion. Several experiments indicate that a chemical reaction (rather than a physical dissolution) is responsible for Pd leaching. The oxidative addition of aryl halide to a surface Pd^0 atom could represent the actual dissolution step in the absence of potential ligands (NBu_4Br). In these cases, Pd dissolved into solution can be detected significantly at temperatures as high as the reaction temperature (140 °C for aryl bromides and 160 °C for aryl chlorides) only. Leaching at lower temperatures is not observed or, better, the Pd concentration in the solution is small due to slow dissolution. The sequence of oxidative addition and Pd dissolution by complex formation can be modified in the presence of additional ligands like bromide or acetate ions (from the base or NBu_4Br additives).

Before oxidative addition of aryl halide is possible, the metal (ions) must be present as Pd^0. The best heterogeneous Pd catalysts contain, however, Pd^{II} species on the support surface (or, alternatively, Pd^{II} complexes in zeolite cages) in their initial state. Possibly the oxidative addition/dissolu-

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(25) (a) Heidenreich, R. G.; Köhler, K.; Krauter, J. G. E.; Pietsch, J. *Synlett* **2002**, *7*, 1118−1122. (b) Heidenreich, R. G.; Krauter, J. G. E.; Pietsch, J.; Köhler, K. *J. Mol. Catal. A: Chem.* **2002**, *182−183*, 499−509.

Table 1. Heck Reactions of Bromobenzene and Aryl Chlorides in the Presence of Ligand-Free Pd Catalysts under Optimized Reaction Conditions

entry	catalyst	catalyst amount (mol %)	X	R	base	atm.	*t* (h)	*T* (°C)	convn (%)	yield (%)
1[a]	$Pd(OAc)_2$	0.01	Cl	$COCH_3$	$Ca(OH)_2$	O_2	6	160	100	94
2[a]	$Pd(OAc)_2$	0.01	Cl	H	$Ca(OH)_2$	O_2	6	160	71	38
3[a]	$Pd(OAc)_2$	0.01	Cl	CH_3	$Ca(OH)_2$	O_2	6	160	9	3
4	$Pd(OH)_2$	0.1	Br	H	NaOAc	Ar	4	140	99	89
5	$PdO*H_2O$	0.1	Br	H	NaOAc	Ar	4	140	100	92
6	$PdCl_2$	0.1	Br	H	NaOAc	Ar	4	140	98	88
7	$Pd(OAc)_2$	10^{-5}	Br	H	NaOAc	Ar	4	140	99	90
8	$Pd(OAc)_2$	3×10^{-7}	Br	H	NaOAc	Ar	4	140	15	14
9[a]	none[b]		Br	H	NaHCOO	Ar	17	140	45	42

[a] Addition of 6 mmol of NBu_4Br as an additive. [b] Traces of Pd found in the base by ICP-MS.

tion step is easier when a single Pd^0 surface atom is bound to a palladium(II) oxide or hydroxide surface compared to metallic Pd^0. Prereduction of Pd^{II} by reactants or additives understandably occurs only on the outermost surface of a Pd particle. Alternatively, Pd^{II} species can be dissolved by formation of anionic Pd^{II} complexes with ligands present in the reaction system. Pd reduction and oxidative addition of aryl halide would occur in this case with dissolved Pd complexes (immediately after the leaching step). Such a system containing a higher Pd^{II} concentration in comparison to Pd^0 is assumed to be more stable against Pd agglomeration and Pd black formation and thus against deactivation. The latter interpretation would also explain why working under (moderate) oxidative conditions (air or oxygen instead of an inert atmosphere) increases the catalytic performance of Pd/metal oxide or zeolite catalysts. Both steps, reduction of Pd^{II} to Pd^0 as well as oxidative addition, can be the rate-limiting step of this first phase of the cycle. Accordingly, also reducing agents (accelerating the reduction step) can increase the reaction rate in Heck reactions.

The dissolution of Pd atoms from supported catalysts probably generates coordinatively unsaturated Pd species (anionic complexes) being extremely active in the classic Heck cycle. The intrinsic nature of these species is still unknown. For aryl bromides (and to some extent for activated aryl chlorides), these systems represent ligand-free catalysts. The reaction is fast enough to be finished before Pd agglomeration or deactivation occurs to a significant extent. For aryl chlorides, additional halide ligands (preferentially Br^-) are necessary in order to achieve a comparable situation. Conversions of chlorobenzene and chlorotoluene were possible accordingly with the addition of NBu_4Br only. The situation becomes more similar to homogeneous Pd complex catalysis. It also demonstrates the particular role and extremely high activity of the simple Pd complex $[PdBr_n]^{n-}$ as active species.

Pd colloids as active species can be excluded according to a series of experiments. They themselves act as a reservoir for molecular Pd species in solution.[26] In addition, we do not see any reason why the surface of small Pd (nano)-particles ("nanoclusters") in solution should be active but the surface of Pd particles of the same size supported on a solid carrier, however, should not. In other words, the investigations and results obtained for simple supported Pd particles deliver, in principle, information that is valid also for Heck reactions catalyzed by Pd nanoparticles. Even more, such studies can be of particular interest because additional ligands for the stabilization of the colloids are not necessary in the case of supported systems.

An important additional argument for a common mechanism of homogeneous and heterogeneous catalysts is that all Heck reactions with aryl halides using colloids or solid supported or homogeneous catalysts have the same product selectivity to Heck products. One could expect rather significant differences between a reaction on a solid surface and that on a single metal complex in solution. The only difference found is the varying contribution of dehalogenation of aryl halide (besides aryl−aryl coupling). Dehalogenation is found at increased temperature (e.g., with aryl chlorides) and under reducing conditions. In both cases, agglomeration (and precipitation) of Pd is strongly promoted. For the latter case, detailed experimental results are available: an excess of reducing agent in the reaction mixture suppresses Pd leaching nearly completely.[25b] However, conversion of aryl bromide is observed (completed after 4 h). The main product found is benzene. Accordingly, it seems reasonable to assume that dehalogenation of aryl halides occurs over Pd metal particles and via a truly heterogeneous surface mechanism.

8. Simple Pd Salts Achieve Huge Turnover Numbers (TONs; 10^7 with Bromobenzene) and Activate Aryl Chlorides: The Importance of Reaction Conditions

The question arises as to whether new insights into the reaction mechanism, the structure−activity relationships, and, in particular, the influence of various reaction parameters could allow the development of more active "ligand-free" catalysts. Up to now, ligand-free systems were believed to be unable to convert aryl chlorides at all. Table 1 demonstrates, however, that the careful choice of reaction conditions combined with the use of NBu_4Br as an additive (formation of $[PdBr_n]^{m-}$ complexes) allows the conversion of aryl chlorides by simple homogeneously dissolved palladium acetate in the absence of additional organic ligands (entries 1−3). In addition, Table 1 shows that the same simple catalyst system converts bromobenzene with TONs of 10 million (10^7; entries 7 and 8). Comparable results could be achieved up to now only for aryl iodides. Also, inorganic Pd compounds, like $PdCl_2$, $Pd(OH)_2$, and PdO, exhibit

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(26) Thathagar, M. B.; ten Elshof, J. E.; Rothenberg, G. *Angew. Chem., Int. Ed.* **2006**, *45*, 2886−2890.

remarkable activity (entries 4−6). Furthermore, conversion of bromobenzene to Heck products could apparently be performed without the addition of Pd (entry 9). Traces of Pd were introduced by the inorganic base as proven by ICP-MS analysis of all reactants and additives. Similar observations have been made by the group of Leadbeater for Suzuki couplings of aryl bromides.[27]

In conclusion, each new Pd catalyst system called "highly active" in Heck reactions should be compared to the simple ligand-free systems described in the literature and in Table 1. Also, each interpretation of the experiments aimed at the true "active" species or at the reaction mechanism should take these orders of magnitude into account.

9. Conclusions and Perspectives

The crucial active species in heterogeneous Heck catalysis with Pd supported on solids, Pd colloids, and Pd black and also with ligand-free systems and probably generally in homogeneous Heck catalysis in the higher temperature region (>100 °C) are the same (or at least very similar) coordinatively unsaturated Pd atoms or, more exactly, anionic halide complexes in liquid solution. In heterogeneous systems, Pd is dissolved from the solid catalyst surface during the reaction by a chemical reaction (complex formation and/or oxidative addition), forming these extremely active species, and partially or completely redeposited onto the support at the end of the reaction (when aryl halide is used up). The Pd dissolution−redeposition processes correlate with the reaction rate and are strongly influenced by the reaction conditions, which must be adjusted carefully. Pd leaching is a prerequisite for the high activity and selectivity of heterogeneous catalysts in Heck reactions.

New insights into the extended catalytic cycle of Heck reactions and proof of in situ transformations of the catalysts also remind us of a more correct view on catalysis: Catalysis cannot be described by one single specific "active species" but only by a rather complex reaction pathway. It is a cycle of several partial reactions including deactivation steps (Pd particle formation, ripening, and precipitation) and several "active" species or intermediates. They proceed with different reaction rates and have different lifetimes and altogether determine and explain the catalytic activity and function. The slowest, i.e., rate-limiting step, and also the rate of competing deactivation steps can vary in dependence on (i) the substrate (aryl halide, alkene, and their concentration), (ii) the nature of the catalyst or precursor (Pd^{II} or Pd^0, solid or dissolved, with ligands or ligand-free), and (iii) reaction conditions (solvent, temperature, base, additives, and atmosphere). Thus, we can intervene the catalytic cycle and control the whole reaction.

If carefully done, it is even possible to achieve the highest activity and selectivity with the simplest forms of Pd, e.g., simple compounds like $PdCl_2$ or $Pd(OH)_2$ converting even unreactive aryl chlorides without any organic ligand. In comparison to special highly active organometallic complexes, the window of reaction conditions (solvent, base, and additives) tolerated by the catalytic system is probably narrower. We propose, however, that the continued understanding of single steps of the catalytic cycle like oxidation, reduction, and solubility of simple palladium halide species and of deactivation processes under reaction conditions is as important and promising for the development of new efficient Pd catalysts as the synthesis of new organic ligands.

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(27) Arvela, R. K.; Leadbeater, N. E.; Sangi, M. S.; Williams, V. A.; Granados, P.; Singer, R. D. *J. Org. Chem.* **2005**, *70*, 161−168.