

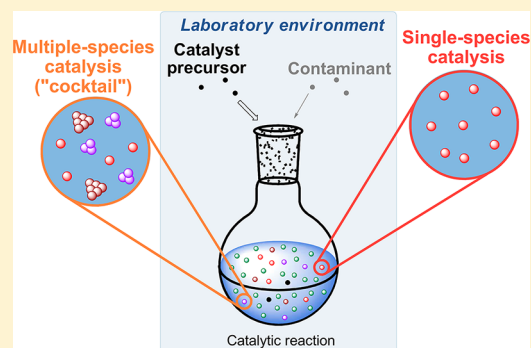
Catalytic C–C and C–Heteroatom Bond Formation Reactions: In Situ Generated or Preformed Catalysts? Complicated Mechanistic Picture Behind Well-Known Experimental Procedures

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ABSTRACT: In situ generated catalysts and preformed catalysts are two practical strategies widely used in cross-coupling methodology that have long been considered to involve the same active species in the catalytic cycle. Recent mechanistic studies have revealed two fundamentally different pictures of catalytic reactions in solution. Preformed catalysts with strongly bound ligands initiate transformations mainly involving single type of metal species. In contrast, in situ generated catalysts give rise to cocktail-type systems with different metal species presented in solution. The role of catalyst precursor, interconversions of catalytic species during reaction, stability and recycling of catalyst, catalysis by autocatalyst exhaust and plausible sources of metal-containing contaminants are the key points discussed in this review.



1. INTRODUCTION

In recent decades, transition-metal-catalyzed carbon–carbon and carbon–heteroatom bond formation reactions have made an outstanding contribution to the production of fine chemicals, pharmaceutical substances, natural products, smart materials, and synthetic building blocks.^{1–5} Catalytic cross-coupling and Heck reactions provided a fascinating opportunity for the incorporation of various aryl, alkenyl, dienyl, and alkynyl substituents into organic molecules (Scheme 1A). Exceptional functional group tolerance further extended the scope and application of these practical approaches. The milestone methodology development was to achieve catalytic cross-coupling reactions involving heteroatomic functional groups in order to form carbon–heteroatom bonds.^{6–9}

Catalytic addition to alkynes is another useful methodology for incorporation of carbon–heteroatom bonds in dienyl and alkenyl units. Addition reactions are atom-economic and do not produce waste; thus, they comply with green chemistry approaches by intrinsic design. These reactions were successfully used for the construction of C–N, C–O, C–P, C–S, C–Se, and C–I bonds (Scheme 1B).^{10,11}

For practical synthetic procedures and industrial scale applications, catalyst amounts as small as possible should be used to reach cost-efficiency criterion. A continuous search for highly efficient catalytic systems led to development of the reactions with extremely low loadings of the catalyst. As a result, the catalytic reactions can now be carried out using ppm or ppb catalyst loadings.^{12,13} Such extraordinary activity of the catalysts undoubtedly indicates that thorough control over the reaction conditions and understanding of the mechanism are needed in order to eliminate plausible influence of various factors on the reaction outcome.^{14–17}

In spite of massive efforts, many questions still remain about the mechanistic nature of the catalytic systems. Myriad publications on cross-coupling reactions, often with controversial observations, further complicate convergence into a consistent overall picture. The key problems include stability/interconversion of catalytic species during the reaction and the role of catalyst precursor.

On one hand, it was reported that catalytic reactions can be initiated with virtually any source of the metal (metal salt, metal complex, nanoparticle, colloid system, supported metal particles, etc.).^{18–23} It is interesting to point out that the variety of catalyst precursors was proposed to generate similar type of reactivity. Moreover, the same catalytic cycles are typically proposed in vast majority of the studies.

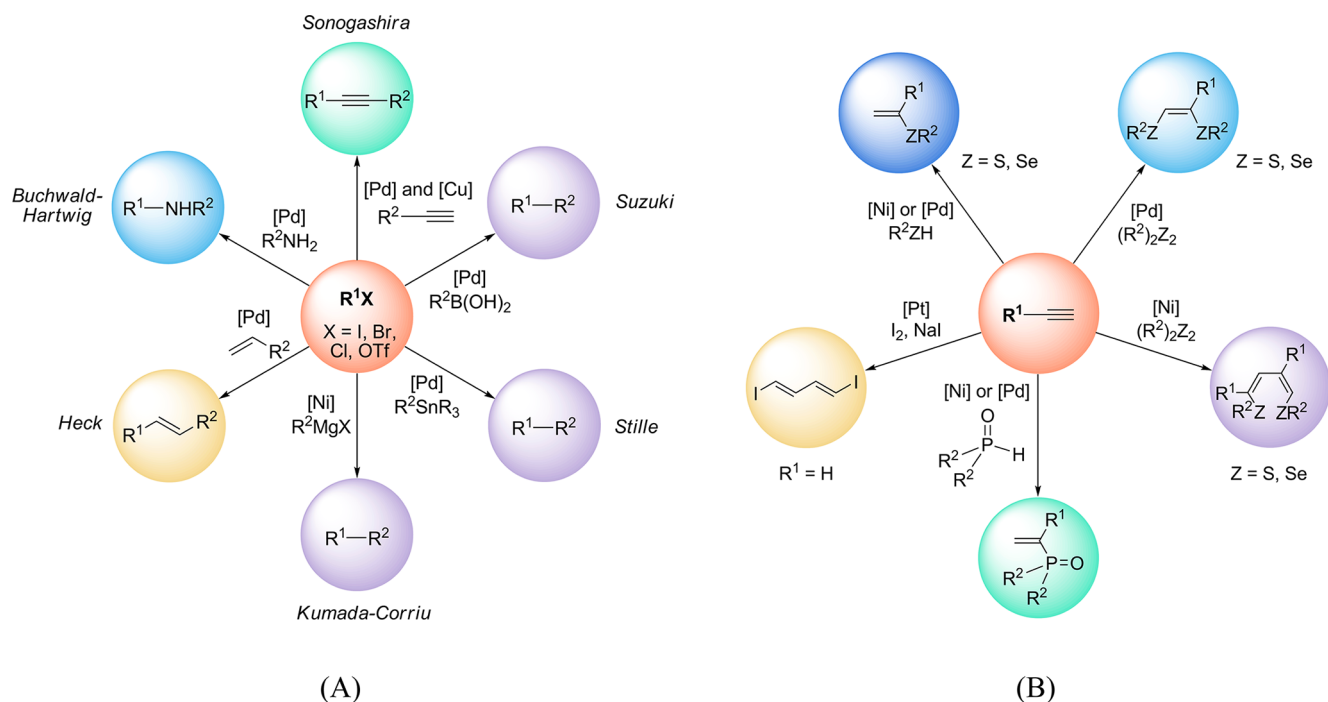
On the other hand, there is a noticeable difference between preformed and in situ generated catalysts that cannot be explained on the bases of such simplified picture. Another important question concerns recycling: if the reaction can be initiated with a variety of initial metal forms, then reactivation and reuse of the catalyst should be an easy option. That is obviously not the case, and catalyst recycling is still a challenge. Gaining an insight into this topic is of principal importance to make progress toward recyclable metal catalysts suitable for reuse without the loss of catalytic activity.^{24,25}

In the present short review, we consider catalytic cross-coupling reactions (Scheme 1A) and addition reactions (Scheme 1B) since independent mechanistic studies of both systems have revealed similar mechanistic trends involving participation of various types of active centers in catalysis. We

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Scheme 1. C–C and C–Heteroatom Bond Formation via Cross-Coupling and Heck Reactions (A) and a Few Selected Examples of Catalytic Addition to Alkynes (B)



highlight important mechanistic findings dealing with the nature of the catalytic active centers and analyze the possibility to clarify mechanistic picture with precise experimental measurements.

2. FORMATION AND INTERCONVERSION OF CATALYTIC SPECIES DURING THE REACTION

Depending on the type of catalyst precursor and on the nature of catalytic system two boundary cases may be expected for reactions in solution:

- “Single-type” metal species catalysis: a well-defined metal complex with strongly bound ligands is introduced as precursor followed by minor chemical modifications prior entering the catalytic cycle. Initially designed metal–ligand(s) core is preserved during the catalytic cycle, whereas formation of other metal species is not facilitated, unless decomposition of the metal complex occurs.
- “Cocktail-type” metal species catalysis: a variety of metal-containing centers are accessible including metal complexes, clusters and nanoparticles.²⁶ Dynamic behavior is not uncommon and involves interconversion of metal centers during the catalytic reaction. In situ generated catalysts or usage of nanoparticles as catalyst precursors are feasible ways to initiate such systems.

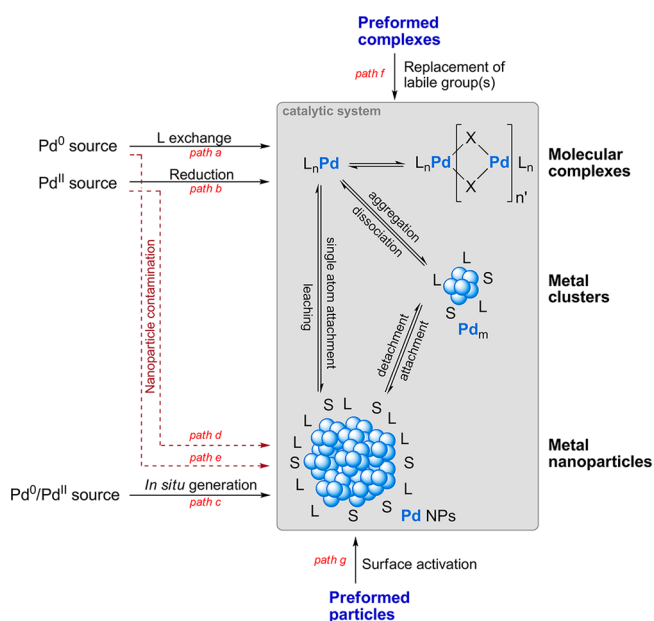
Here we briefly mention possible pathways of catalyst evolution in solution (sections 2.1), followed by concise discussion of both types of catalytic systems (sections 2.1 and 2.3) and important practical considerations in order to correctly reveal the nature of the catalytic system (sections 2.4–2.8)

2.1. Plausible Pathways of Catalyst Evolution in Solution: Single Metal Atom Transfer vs Oriented Attachment/Detachment. Recent mechanistic investigations have clearly pointed out the complexity of catalytic active sites interconversions in solution and the diversity of metal-

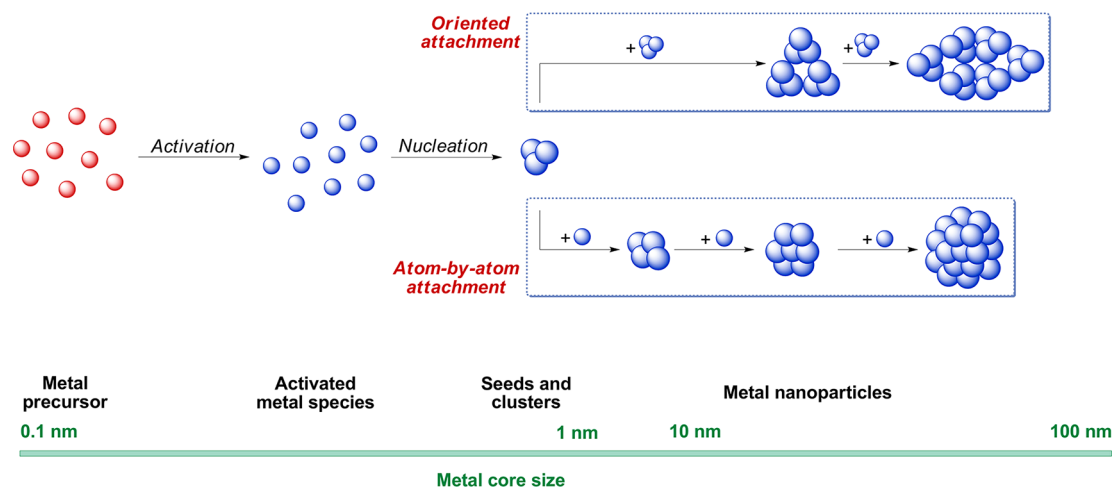
containing species in catalytic systems (Scheme 2).^{22,26–29} Such processes typically take place in the case of in situ generated catalysts and in the case of application of nanoparticles as catalyst precursors.

Mononuclear metal complexes L_nPd are readily involved in the equilibrium with dinuclear $L_nPd_2X_2$ and polynuclear species, wherein dinuclear metal species can represent catalytically active form^{7,30,31} or a resting state.^{22,32,33}

Scheme 2. Plausible Pathways of the Palladium Species Transformation during the Catalytic Reaction (L, Ligand; S, Solvent; X, Heteroatom)



Scheme 3. Plausible Pathways of the Nanoparticle Growth in Solution



Aggregation of molecular complexes leads to the formation of metal clusters and nanoparticles. Several studies revealed in situ generation of metal nanoparticles in the course of catalytic transformations.^{22,27,34–36} The first pathway of nanoparticle formation would involve atom-by-atom growth process (Scheme 3). The process should result in the formation of nanoparticles of different shapes and a variety of size distributions. Consumption of the metal from solution in nonordered way at the end generates amorphous metal forms (like Pd black, etc.). The second pathway involves formation of metal clusters, followed by nanoparticles assembly via oriented attachment of these clusters (Scheme 3).^{37–39} In such a case, the particles of specific uniform shape with a narrow size distribution may be formed. Prolongation of ordered growth facilitates formation of microcrystals and crystalline phases (coexistence of both growth pathways or a pathway switch may be observed as metal concentration dependent process).

Under catalytic conditions, after activation of the metal precursor (e.g., replacement of ligands for zerovalent complexes or reduction of metal salts), nucleation and the initial growth lead to the formation of small metal seeds and clusters (about 1 nm in diameter). Self-assembled aggregation and coalescence of these primary particles result in formation of nanoparticles via oriented attachment. Another possibility for the formation of nanoparticles is growth caused by sequential attachment of the activated metal atoms to the metal clusters (Scheme 3).

Oriented attachment was shown to play an important role in the crystal growth process. Recently, milestone findings describing transmission electron microscopy (TEM) studies of the nanoparticles formation have been reported.^{40,41} High-resolution TEM observation of metal species in the fluid cell showed that their aggregation into the single crystal proceeded through the oriented attachment, which occurred only when the particle shape perfectly matched the crystal lattice of the growing crystal.⁴⁰

Under catalytic conditions, neither nanoparticles nor their aggregates represent the final static point in the interconversion of metal species. The presence of reactive organic compounds in reaction mixture facilitates reverse process of the catalyst leaching (Scheme 2). Accordingly, there are two different approaches explaining the nature and mechanism of leaching process. The first pathway suggests coordination of strong metal binding reagent (organic halide, ligand, solvent) to the surface of the nanoparticle followed by the metal complex

dissociation and, if further repeated, atom-by-atom metal particle degradation. The key step of the second leaching pathway is the detachment of small metal clusters (instead of mononuclear complexes), the process called oriented detachment.

Taking into account feasible interconversions of metal species in solution, the main pathways of generation of catalyst active species are summarized in Scheme 2 (paths a–f). A typical approach is to utilize Pd⁰ source and directly involve the species in catalytic transformation with/without ligand exchange (path a). Various Pd^{II} sources are equally well suitable but require preliminary activation *via* reduction by phosphine ligands, reagents, etc. (path b). In situ generation of metal nanoparticles, either as active centers or as reservoir of metal species, is another useful opportunity (path c). Nanoparticle contamination in molecular Pd⁰ and Pd^{II} sources may significantly influence the mechanism of the active sites formation (paths d, e).^{42,43} Leaching process is blurring the border between different types of catalysts and makes their behavior more complicated. In overall, the dynamic nature of the catalytic systems provides a valuable practical advantage, since reaction may be initiated with virtually any source of palladium from various precursors.

More sophisticated approach is to use specially designed preformed catalysts (path f). Generation of active species in such a case involves minimal changes, like replacement of labile ligands. Preformed metal nanoparticles are usually obtained by the reduction of palladium salts or decomposition of zerovalent palladium compounds in the presence of specific stabilizers and such nanoparticles can be used in catalysis after surface activation (path g).

Determination of correct nature of catalytic system in the homogeneous-cluster-nanoparticle-heterogeneous metal species continuum in some cases is rather difficult question.⁴⁴ A series of simple and more sophisticated tests were developed to reveal the role of active species and distinguish different mechanistic pathways.⁴⁴

2.2. Preformed Metal Catalysts with Strongly Bound Ligands ("Single-Type" Catalytic Centers). In spite of their simplicity, in situ formed catalytic systems have some disadvantages and their application in organic synthesis may require time-consuming optimization for particular reaction conditions. For the laboratory use there are several widely known sources of palladium such as Pd₂dba₃, Pd(OAc)₂, PdCl₂,

etc. These compounds are not directly involved in the reaction, so they have to be chemically modified before entering catalytic cycle. The presence of the reagents with different functional groups in the same vessel with such palladium precatalyst leads to complicated transformations and interconversions of metal species and, as a result, may cause a decrease in the reaction yield and selectivity. Due to rather sensitive dynamic nature of catalytic systems, reoptimization of reaction conditions may be required even after a subtle change in substituents and structure of reagents. Not surprisingly, a huge number of publications were reported to optimize reaction conditions for particular combination of coupling substrates.^{1–5,18–23} Apart from that, partial decomposition of palladium precursors during the storage may cause significant changes in the resulting catalyst behavior.^{42,43}

In order to overcome these difficulties preformed catalysts can be used as an efficient strategy. Preformed catalysts are constructed based on transition metal compounds stabilized by strongly bound ligands such as N-heterocyclic carbenes,⁴⁵ biaryl phosphines,^{9,45–47} ferrocenyl phosphines,^{12d,45} cyclodextrin-based ligands,^{12e} functionalized calixarenes,^{12f} and other systems.⁴⁵ These catalysts are more stable than in situ formed catalytic systems and in many cases could be more active and selective. A number of fascinating examples of high catalytic activity of preformed palladium complexes have been described.⁴⁵ As a representative example, the comparison of various types of phosphine ligands and palladium precursors in the reaction between poorly reactive aryl chloride with electron donating substituents and difluoro phenylboronic acid can be considered.⁴⁷ Several biaryl phosphines (XPhos, SPhos, RuPhos) with various combinations of the metal precursor were evaluated (Figure 1). Palladium acetate, Pd₂(dba)₃, and three dinuclear palladium complexes containing 2-amino-

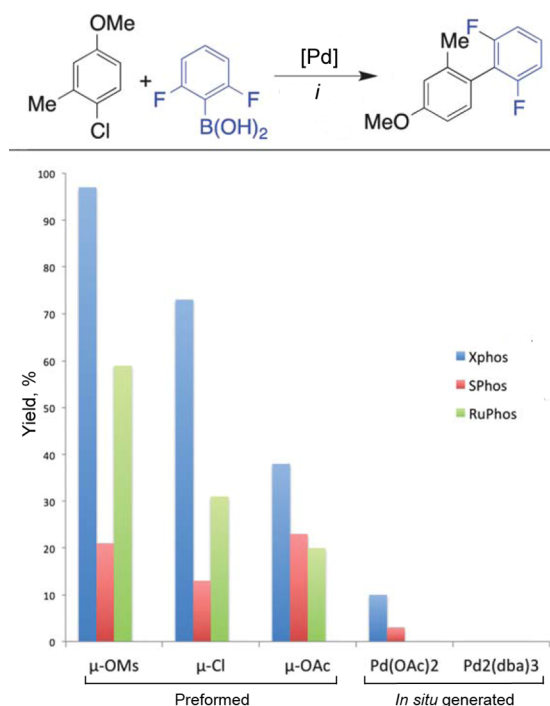


Figure 1. Comparison of the product yields for the catalytic systems involving various phosphine ligands and palladium precursors. Conditions: (i) 2% Pd/L, K₃PO₄ (0.5 M)/THF, rt, 30 min (adapted from ref 47.).

biphenyl chelating ligands and different bridging groups (mesylate, chloride, and acetate bridges) served as the catalyst precursors. It was found that the use of bulky phosphine ligand in the preformed palladium catalyst gives highly reactive catalytic system which is suitable for the transformation involving inactive aryl chloride. The yield decreased from 95% to 10% (and even lower) upon changing from preformed to in situ generated catalyst.

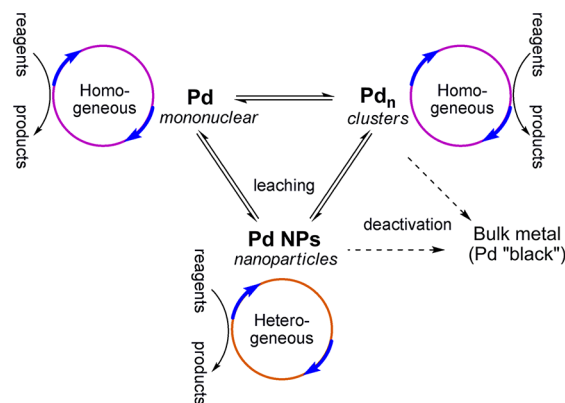
The superiority of preformed palladium complexes with biaryl phosphine ligands was demonstrated for the Suzuki reaction involving nitrogen-rich heteroaryl halides⁴⁸ and for the catalytic cyanation of aryl chlorides and bromides.⁴⁹

Well-designed preformed catalyst is a good strategy to maintain “single-type” catalytic system with noticeable advantages including the use of stoichiometric amount of ligand, easy catalyst generation and higher efficiency as compared to a combination of separate metal source and ligand employed for in situ catalyst generation.

2.3. “Cocktail” of Catalysts and Adaptive Pd Catalysis.

In the absence of a preformed stabilizing metal–ligand framework, various transition-metal-containing species are accessible once the catalyst precursor is introduced into the reaction. The resulting catalytic system can be better described as a “cocktail” of catalysts rather than single-type metal species catalysis.²⁶ Different mechanisms are realized in the “cocktail”-like reaction media: homogeneous catalysis by molecular complexes or metal clusters, and heterogeneous catalysis by metal particles (Scheme 4). Catalysis with mononuclear

Scheme 4. Catalytic Cycles Involving Different Types of Catalysts and Possible Pathways for Interconversion between Metallic Species²⁶



complexes and nanoparticles is well-known for broad scope of reactions,^{18–23,45} while synthetic application of catalysis by metal clusters is comparatively less developed area. An important study supporting the possibility of bimetallic mechanism of C–C coupling reaction was reported involving Pd^I–Pd^I species even in the absence of phosphine ligands.^{50,51}

Depending on the reagents and conditions, each cycle can contribute to the overall product formation to a greater or lesser extent (Scheme 4). From a certain point of view, the “cocktail-type” catalyst can be considered as a self-tuning system, which can be adjusted in situ for the particular set of substrates. Self-tuning nature is an important prerequisite toward achievement of challenging aim of construction of highly efficient all-purpose catalyst.

However, several factors require particular attention. The performance of the catalyst may strongly depend on various

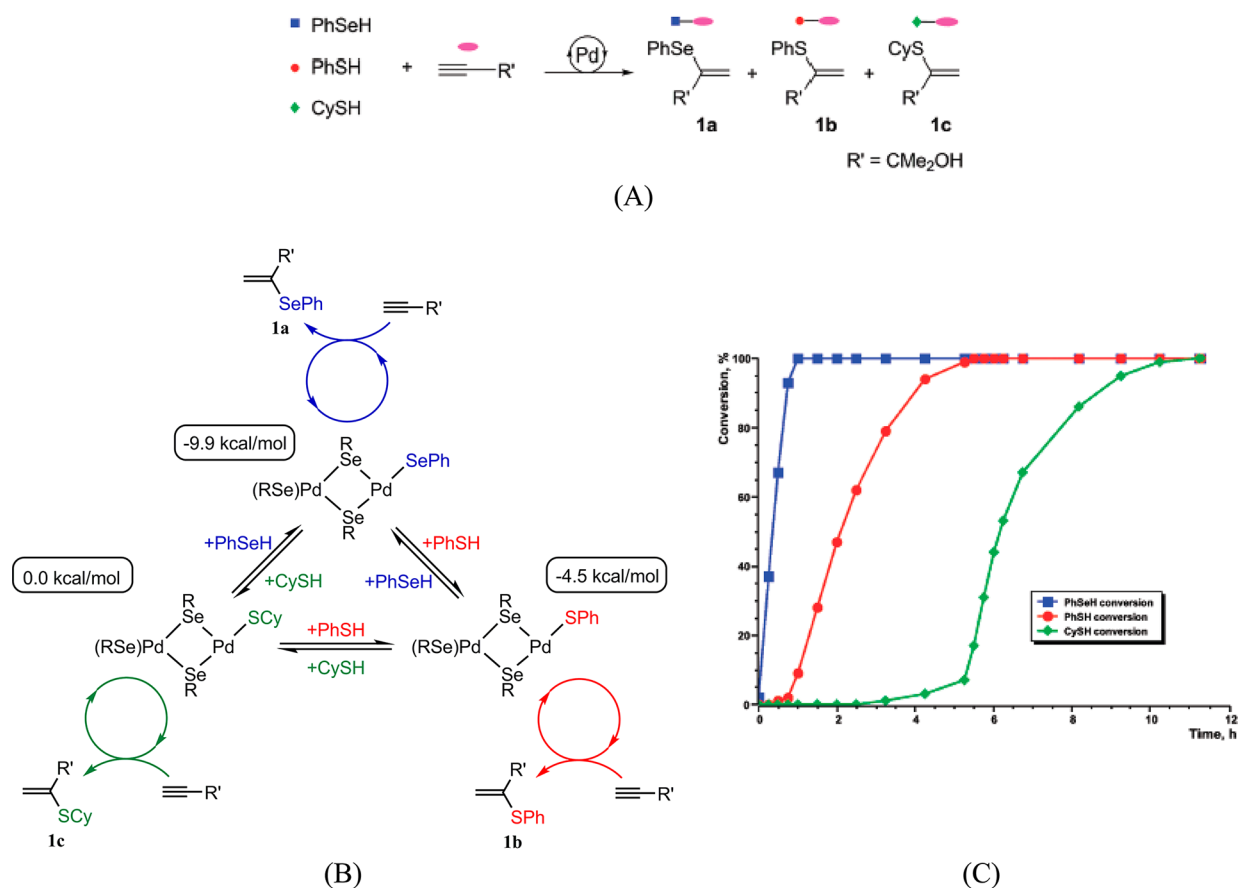


Figure 2. (A) Reaction between 2-methyl-3-butyn-2-ol and three-component mixture of organochalcogen compounds. (B) Scheme of adaptive tuning of the catalyst, calculated ΔG values, and corresponding catalytic cycles for the each form of catalyst. (C) Kinetic curves obtained by NMR monitoring.⁵²

factors and even slight changes in the reaction conditions or in the substrate structure may have a significant impact on the catalyst nature. The problems with the catalyst recycling and contamination of products with the traces of metal are other disadvantages of “cocktail-type” catalytic systems.

The proof of concept of adaptive catalytic system was demonstrated recently for the carbon-chalcogen bond formation via addition reaction.⁵² This system was similar to “cocktail” of catalyst discussed above because of its dynamic nature; however, catalyst operation was performed in a controlled manner. Nanoparticles of insoluble coordination polymer $[\text{Pd}(\text{ZR})_2]_n$ served as the catalyst ($\text{Z} = \text{S}, \text{Se}$). High oxidation state of the palladium centers, stabilization of the polymeric structure by μ_2 -ZR ligands, and relative mobility of the terminal μ_1 -ZR groups made this catalyst highly efficient, easily tunable, and stable. Besides that, unprecedented selectivity of the catalyst was achieved in the reaction of alkynes with thiols and selenols. NMR monitoring of the reaction between the alkyne and three-component mixture of organochalcogen compounds clearly demonstrated superior selectivity of the catalytic system (Figure 2), where only one reaction at a time took place.

The observed high selectivity of the catalytic system may be explained by ability of the palladium catalyst for adaptive tuning. Difference in the Pd–Z bond energies leads to the formation of the palladium catalyst with only one type of reactive μ_1 -chalcogenide groups on the surface which facilitate addition of the corresponding chalcogen-containing compound.

Therefore, only one catalytic transformation is mediated at a time (Figure 2C). After completion of a preceding reaction the active site of catalyst rebuilds and the next transformation starts. High mobility of the palladium catalyst and the absence of noticeable induction delays (Figure 2C) are conditioned by small energy barriers of the chalcogen-exchange process in the active centers.⁵²

On one hand, entangled mechanistic picture for the catalytic transformations in the dynamic systems significantly complicates rational catalyst design, but on the other hand, controlled self-regulation and self-tuning processes can provide extraordinary tools to achieve high efficiency and selectivity, as well as to access new functionality.

It is important to mention that formation of dynamic catalytic systems with varying contributions of different metal species to the product formation was described in the ligand-accelerated catalysis approach.⁵³ In the presence of tartrate ligand, titanium alkoxides formed multicomponent mixture, which contained several Ti_nL_m species in solution. Although several metal species have shown desired catalytic activity, for efficient titanium-catalyzed asymmetric epoxidation it was enough if a single metal complex has exhibited good activity and high enantioselectivity.⁵³

2.4. Pd Contamination of the Environment. The leaching phenomenon, which was described in the previous sections, attracts much attention in biology and ecology since palladium-containing catalysts are widely used in the human’s life. Automobile catalysts are the major sources of so-called

traffic-related elements.^{54,55} In addition, it has been shown that metallic species can be released from automotive brakes and organometallic fuel additives.⁵⁶ Using a number of analytical methods, it has been established that the concentration of palladium in airborne particulate matter (PM₁₀) can vary within a wide range from 0.1 pg/m³ to more than 650 pg/m³.⁵⁷ The measured palladium content in the road dusts reaches 250–300 μg/kg.⁵⁸

Obviously, palladium leaching takes place even in the gas-phase processes like conversion of exhaust of an internal combustion engine. A related study of the mechanism and kinetics of Pd and Pt leaching from the automobile catalyst in solution has been performed.⁵⁹ Natural complexing agents such as citric acid, sodium pyrophosphate, sodium chloride, and fulvic acid were used as a model compounds for the kinetic measurements. It was established that the leaching in solution was a pH-dependent process. Citric acid and alkaline sodium pyrophosphate were the most active complexing agents. Both Pd and Pt were released into solution as hydroxide complexes M(OH)⁺ and M(OH)₂. The mechanism of gas-phase leaching seems to be more complex because of the different nature of the coordinating molecules which are present in the combustion chamber exhaust.

Pd and Pt contamination of the environment is regarded as an eco-important topic requiring particular attention due to high toxicity of platinum-group elements. Strong toxic effect is attributed to the induction of the programmed cell death.⁶⁰ The possible catalytic activity of the metal salts or nanoparticles dispersed in soil, air and water makes their negative impact more significant (including indirect effects and after effects).

2.5. Cross-Coupling by Autocatalyst Exhaust. Autocatalyst exhaust may contain relatively large amount of palladium and other platinum-group metals which can be accumulated in the soil, road dust and airborne particles. The quantity and concentration of palladium dispersed into the environment are sufficient for the catalytic reactions to occur.

The results of the elegant study of the spent automotive catalyst and airborne matter activity in the carbon–carbon bond formation reaction were recently described.⁶¹ Three model reactions were chosen for the evaluation of the catalytic activity: Heck, Suzuki, and hydroformylation reactions. Airborne matter collected on the PM₁₀ filters and containing from 0.08 to 8 ppm of palladium showed high activity toward Heck reaction between iodobenzene and *n*-butyl acrylate. The yield of cinnamate product reached 98%. In case of Suzuki coupling the catalyst activity was lower.

For the samples of the spent automotive catalysts, the content of platinum-group metals varied from 1.6 to 3200 ppm for Pd, from 2.6 to 65 ppm for Pt, and from 0.22 to 100 ppm for Rh. Palladium-catalyzed Heck and Suzuki reactions resulted in the product formation up to high yields. In case of Heck reaction between iodobenzene and 2-butene-1-ol the product yield was about 50% for the 7.6 ppm catalyst loading. Rhodium-catalyzed hydroformylation reaction was carried out using relatively high Rh loading (200–250 ppm), and in this case, conversion of starting material reached 80%.

Thus, spent automotive catalysts and airborne matter are able to show moderate to high catalytic activity in the carbon–carbon bond formation reactions. High catalytic activity of the airborne matter should be noted because this type of metal-containing pollutant is presented in the air and can be easily transferred to a regular laboratory environment.

2.6. “Magnetic-Stirrer-Bar-Catalyzed” Transformation.

The contamination of chemicals, glassware, and laboratory equipment with metals is an important problem in terms of the reliable characterization of highly active catalysts at low metal loadings and metal-free systems. In many cases, this question is of principal importance for correct determination of the nature of catalytic system.

The fascinating example of magnetic stirrer bar “catalyzed” transformation was recently published.⁶² Rhodium nanoparticles were disposed onto the surface of regular PTFE-coated stirring bar using microwave-assisted decomposition of Rh₆(CO)₁₆ in ionic liquid (Figure 3).

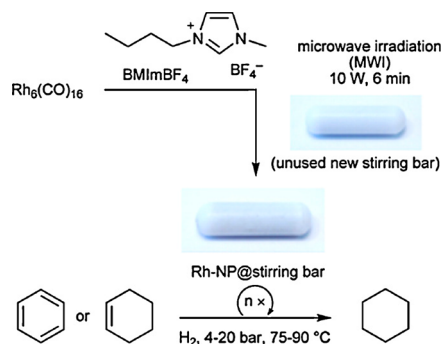


Figure 3. Deposition of rhodium nanoparticles onto the surface of stirring bar and model rhodium-catalyzed hydrogenation reaction.⁶²

Rhodium-catalyzed hydrogenation of benzene and cyclohexene was employed as a model reaction (Figure 3). The amount of rhodium on the surface of stirring bar was enough to mediate catalytic transformation. Cyclohexene was successfully converted into cyclohexane using about 50 ppm of catalyst. Several simple tests demonstrated that the catalyst leaching in solution and even metal deposition onto the reaction vessel surface caused by abrasion of stirring bar occur in this system.⁶²

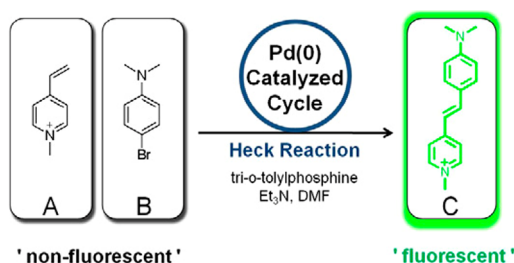
The study suggests that magnetic stirrer bars should be a single use only (or the surface should be carefully controlled and cleaned), otherwise a ppm level amount of metal may remain and penetrate to the next reaction studied. It can be clearly seen that the rational design of highly active catalytic systems becomes a difficult task because the presence of undesired metal impurities makes system behavior unpredictable. Significant attention should be paid to critically assess laboratory equipment and environment.

2.7. Heck Reaction as a Sensor for Pd. The question about possible effect of the trace impurities on the reaction outcome arises in the case of metal-free analogues of the cross-coupling and other transition-metal-catalyzed reactions. The impurities that are contained in the metal-free additives can serve as an actual catalyst.⁶³ Recently, highly sensitive fluorescence method for the identification and quantification of palladium species at ppb and ppt levels has been described.⁶⁴ This method was successfully used for the palladium traces detection in the Suzuki reaction mixture which was prepared without addition of any transition-metal compounds. It was shown that palladium catalyst can be efficient even at a concentration less than 1 ppb.

It is interesting to mention that catalytic carbon–carbon bond formation itself can be utilized as a sensor for palladium.⁶⁵ Palladium-catalyzed Heck reaction between *N*-methylvinylpyridinium iodide and 4-bromo-*N,N*-dimethylaniline results in

formation of a fluorescent compound that can be easily detected (Scheme 5). The detection limit for this sensor is 5.45×10^{-6} M of palladium.

Scheme 5. Heck Reaction As a Sensor for Palladium⁶⁵



A large number of examples of the Pd metal traces' impact on the reaction outcome have been reviewed.^{14,44} For example, it has been shown that Sonogashira coupling of tolylacetylene with 4-iodoacetophenone did not occur in the presence of AuI/dppe, but the addition of 12 ppm of palladium as $\text{Pd}_2(\text{dba})_3 \cdot \text{CHCl}_3$ complex led to the 16% conversion of the initial compounds.¹⁶ Complete conversion of the reactants was gained using 1200 ppm of palladium.

2.8. Clean Room Technology. Clean room is a special research technology with the controlled level of contaminants and dust in the laboratory space.⁶⁶ Permanent laminar or turbulent air flow with continuous filtration maintains a constant level of purity. Clean room requirements are defined within a specific range, particularly, the number of particles per cubic meter of air should not exceed 10 for the high-class ISO 1 clean rooms (ISO 14644-1 clean room standard). This technology is commonly used in semiconductor manufacturing, microelectronics, biology, and life sciences where even a small amount of airborne matter is unacceptable.⁶⁷ Several fascinating problems were solved in these fields using clean rooms. Nanotechnology and nanomaterial science in many cases require clean room conditions for the devices and materials fabrication because even small defects caused by dust or other pollutants can lead to crucial changes in the properties of the resulting product. The use of clean room conditions is in great demand for the electronic devices manufacturing even in the laboratory practice.^{68,69} The strong necessity of the clean environment for the preparation of microporous silica membranes was demonstrated.⁷⁰ The number and size of defects in membrane had a strong impact on its transport properties toward various gases and, as a result, on the efficiency of membrane for the gas separation. The use of clean room technology minimized the number of defects and improved performance of the membrane.

In the field of catalysis, clean rooms can be useful for correct determination of catalytic activity at ppm/ppb (and below) level, as well as for the detection of fine effect of the impurities on the catalytic activity. As an example, the impact of sodium impurities at ppm-level on the structure and phase composition of the supported molybdenum catalyst was studied using clean room and clean bench technologies.⁷¹

The high cost of maintenance⁷² makes clean room technology difficult to access for regular chemical applications; nevertheless, transition-metal-catalyzed transformations have clearly reached a certain level where precise control of laboratory conditions is urgently needed. Carrying out reactions under clean room environment also implies rigorous control of

elemental composition and trace level contamination of all chemicals and apparatus (glassware, stirrers, etc.) used in the reaction.

3. FUTURE AND OUTLOOK

The "cocktail"-type nature of catalytic systems is an important factor that predetermined successful application of cross-coupling and Heck reactions. Simple combinations, like $\text{Pd}(\text{OAc})_2/\text{L}$ or $\text{Pd}_2\text{dba}_3/\text{L}$, may initiate a number of transformations and generate a variety of metal species in solution. Dynamic nature allowed formation of catalytically active species and facilitation of thermodynamically favorable chemical reactions to yield the desired product. As an illustrative example, a common molecular catalyst precursor, Pd_2dba_3 , may have a varying content of Pd species with nanoparticle contamination up to 40%.⁴³ Nevertheless, it was the widely used compound that successfully mediated a large number of catalytic transformations. In the absence of active centers interconversion in solution, the catalytic reaction would be much more sensitive to the type and purity of catalyst precursor. In fact, the dynamic "cocktail"-type behavior of catalytic systems was practically utilized for a long time, while the fact has been rationalized only recently.

Further development of dynamic catalytic systems contributes to the concept of adaptive catalysis. In adaptive systems, the nature of catalyst active centers is changed in the controlled manner to achieve desired reactivity and selectivity. To highlight the difference, in a simple dynamic system (Scheme 4) several types of metal species are formed (in hardly controlled manner) and catalyze formation of the same products. In adaptive catalytic systems, the properties of the catalyst may be changed even to such extend that sequential formation of different products is possible while retaining high selectivity at each stage (Figure 2).

A fundamentally different approach for catalyst development is to get better control over the nature of the catalyst by avoiding formation of "cocktail" of metal species in solution. Well-designed precatalysts with strongly bound ligands lead to preferential involvement of single-type species catalysis. The presence of only one type of metal complex in solution simplifies optimization and rationalization of relationship between structure and activity. The use of sterically hindered and bulky ligands is important not only to influence particular elementary steps of the catalytic cycle (i.e., oxidative addition, reductive elimination, etc.) but also to shield the metal center and avoid formation of dinuclear and polynuclear metal complexes and clusters (thus, avoid cocktail of species).

State-of-the-art mechanistic understanding of catalytic C–C and C–heteroatom bond formation reactions showed that catalysis may be initiated with various sources of metal species, whereas dynamic nature of the catalytic system may generate a diversity of complexes and particles. Reaction mechanism becomes extremely complex matter at ppm/ppb catalyst loadings, where regular analytic tools reach their sensitivity limits. Taking into account the level of contamination all around, penetration of platinum-group metal particles into regular laboratory environment is unavoidable. Catalysis has accomplished a remarkable point recalling for special research environment standards, like those previously approved for nanotechnology and pharmacology. Continuation of development of highly efficient ppm/ppb level catalysts under routine laboratory conditions would unlikely gain further insight, rather could produce controversial or difficult to reproduce results.

Outstanding research endeavors are anticipated in near future to clarify the nature of transition-metal-catalyzed reactions.

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Valentine P. Ananikov is a Professor and Laboratory Head of the ND Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, where he is inspired by mechanistic studies of catalytic reactions and applications in organic synthesis.

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