



## Review

## Palladacycles in catalysis – a critical survey

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**Abstract**

The application of palladacycles as catalysts for cross-coupling and similar reactions is reviewed. In the majority of cases palladacycles are likely to serve as a source of highly active but unstable zero-valent palladium species. In this respect the palladacycles resemble the so-called phosphine-free catalysts. The advantages and limitations of palladacycle catalysts are discussed.

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**1. Introduction**

The introduction of the cyclopalladated tri-*o*-tolylphosphine by Herrmann et al. [1] to palladium catalyzed Heck and cross-coupling reactions excited high expectations about this class of palladium catalysts. The palladacycles appeared as long-sought structurally defined catalysts promising: (a) new mechanisms of well-known reactions expectedly involving Pd(II)/Pd(IV) oxidation states; (b) conservation of coordination shell during the catalytic action; (c) thus a very likely high enantioselectivity with chiral palladacycles; (d) design of recyclable catalysts with palladacycles supported on solid carriers, etc. However, already the first data obtained with these systems invoked serious doubts on these subjects. In 2000 we have tentatively hypothesized [2] that palladacycles actually are not structurally robust catalysts, but are disassembled during the pre-activation stage and release either mono-phosphine or phosphine-free low-ligated Pd(0) complexes. If this is so, the palladacycles are likely to be a representative of a large class of Pd catalyst precursors, which lose their structural identity in the catalytic cycle, being unsuitable for any appli-

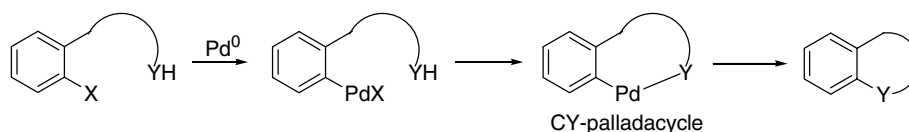
cations requiring the conservation of the coordination shell. Since then this hypothesis has found numerous confirmations, while the opposite point of view, though not altogether discarded, is so far unsupported by solid evidence.

Nevertheless, the palladacycles in catalysis is an exciting area of research. Though the investigation of palladacycles has failed to substantiate the initial promises, it brilliantly served to reveal and highlight the principles of operation of low-ligated and phosphine free catalysts, helped to evaluate the real potential of these systems. It could hardly be so if the initial promises of these systems would have not appeared so bright and so fruitful.

Palladacycles are ubiquitous in catalytic transformations. Palladacyclic intermediates play important role in cascade transformations leading to complex molecular architectures ([3,4]), and proximally (*ortho* or *peri*) directed arylation reactions (cf. e.g. [5–10]). Intramolecular cross-coupling reactions, powerful tools for the synthesis of various heterocycles and carbocycles should by default involve the palladacycle intermediates (Scheme 1).

Stable palladacycles contain five-membered Pd-containing rings, from which the reductive elimination is hardly possible. Larger palladacycles are often transient readily giving heterocycles after reductive elimination (cf. e.g. [11]).

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Scheme 1.

Palladacycles are often referred to as highly thermally stable compounds. It should be clearly understood that this refers only to the stability in solid state, which actually has little to do with catalysis. Many palladacycles can indeed be heated without decomposition to 200 °C or above. However, in the solutions in reaction mixtures, containing solvents, reagents, bases, this is not generally true. On the contrary, lot of data clearly shows that palladacycles are highly labile compounds, undergoing ready transformations with and without fission of palladacycle ring under rather mild conditions. Dimeric palladacycles undergo dissociation to monomeric forms in highly dilute solutions in coordinating solvents already at room temperature [12]. Thus, it could be tentatively assumed that at elevated temperatures normally used for cross-coupling reactions dimer–monomer equilibrium is fully shifted to monomeric state.

The goal of the present review is to discuss the application of palladacyclic complexes in catalysis. Recently, a number of excellent authoritative reviews appeared on this subject, coming from leading researchers in this area [13,14], thus inevitably being highly personalized accounts. Our goal was to present a more detached, and therefore a more skeptical, discussion of these phenomena. We think that this area already matured enough, so that a critical analysis could not be harmful, but may help to highlight problems and achievements.

## 2. General considerations

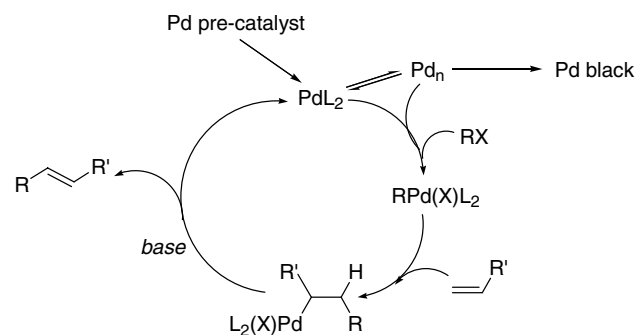
Among classical reactions of Pd catalyzed chemistry, to mention only the most prolific – Heck reaction, cross-coupling, allylic substitution, there is a certain inequality in what concerns the catalysts used. Some, as the Heck reaction and cross-coupling with arylboronic acids are largely indifferent to the nature of catalyst, allowing well for simplest sources of palladium to serve as effective catalysts, not depending on specific ancillary ligands. In parallel, both allow for almost infinite decrease of catalyst loading, thus showing incredible turnover numbers (TONs). All this, however, is true only for reactive substrates – aryl iodides and activated bromides, standard olefins (in Heck reaction) and arylboronic acids (in Suzuki reaction). All other reactions (including Heck and Suzuki reactions with less reactive substrates) show much more discriminative behavior towards catalysts to require more or less narrow scope of specific ligands. Besides, such reactions usually do not allow for considera-

ble decrease of catalyst loading showing TON values of  $10^2$ – $10^3$  orders of magnitude at best. The most probable source of this disparity is associated with essential difference in the operation of the respective catalytic cycles. For Heck and Suzuki reactions the rate-limiting step is the oxidative addition, all other steps taking place readily without the help from ancillary ligands.

First, let us consider the Heck reaction (Scheme 2). The insertion and reductive elimination steps are commonly very facile not to require any ancillary ligands to take place. However, specific ligands may be required for the cases when the control over the selectivity should be imposed, e.g. when side reactions may compete with reductive elimination. This often happens when olefin possesses allylic H atoms providing alternative path for PdH elimination to lead to the double bond migration.

Oxidative addition is commonly believed to be very facile for aryl iodides and activated aryl bromides. With such substrates any form of Pd(0) is supposed to add to C–X bond under mild conditions, the ligand effects being minimal to be easily masked off by other factors.

Oxidative insertion competes with the processes of Pd deactivation, which supposedly proceed through small Pd clusters, nanoparticles, further growing to large inactive metal particles (the palladium black). Nucleation and growth of palladium metal is a sophisticated process with complex kinetics and complex dependence on many factors (temperature, concentration of Pd, coordination state of Pd, concentration of ligands and other supporting species in solution, solvent, viscosity, etc.), so there is no chance ever to make any quantitative predictions on the course of this process. The competition between inactivation and oxidative addition defines the overall characteristics of a given catalytic system, in the first



Scheme 2. Approximate catalytic cycle for the Heck reaction.

place its longevity (commonly measured by the net number of catalytic cycles, TON) and catalytic activity (measured by TOF, either average or, if kinetic monitoring is performed, the peak value). Unfortunately, average TOF values, reported in the vast majority of publications, are of little use for comparisons between catalytic systems, because both the induction period and leveling-off at maximum conversions, if not measured, arbitrarily change the values of TOF. Any comparisons made with such TOF values should be misleading [15]. Therefore, we are not using this parameter in this text.

A due care should be given also for longevity parameter, TON. In many publications, enormous TON values are reported, which implies using submicrogram amounts of palladium catalyst. However, these values are often measured for low conversions and yields, and the reaction rate levels off at such low conversions, which obviously means that the catalyst is deactivated. With tiny amounts of catalyst there is no chance to observe the usual inactivation product, the Pd black, and Pd should be transformed into some other unknown inactive form. In our opinion, huge TON values for low conversion runs are practically useless, as soon as such data clearly shows that a given catalyst under such conditions and at such initial concentration is unable to deliver practically useful performance. We shall therefore not include such record-making but synthetically inept results in the discussion, but instead shall cite only those TON values obtained with synthetically useful conversions/yields.

In the case of aryl iodides and activated aryl bromides [16] oxidative addition is so fast that no appreciable concentration of Pd(0) can build up, and Pd black cannot form unless the initial concentration of Pd pre-catalyst is unreasonably high. Moreover, Pd nanoparticles, if formed, are dissolved under such conditions, so that the sedimentation of Pd black is reversible and does not lead to full inactivation of the catalyst. Biffis et al. [17] in studying supported catalysts, such as Pd/Al<sub>2</sub>O<sub>3</sub> or Pd nanoparticles immobilized on polystyrene resin, have shown that catalytic activity is associated with leached Pd dissolved from the solid phase. Re-dissolution occurred only in the presence of reactive halides. It should be noted that leaching from solid state is the reverse process to nucleation and growth of Pd metal particles. Both processes are kinetically too complex, so if Pd black or Pd nanoparticles are involved, the behavior of such catalytic system should be very irregular, very sensitive to various factors, and thus highly irreproducible. The formation of Pd nanoparticles is a common feature of phosphine-free catalytic systems, and is very often noted in palladacycle-driven catalytic reactions.

In the case of less reactive substrates, including unactivated aryl bromides and activated aryl chlorides, the

picture is even less clear. Until recently it was believed that such reactions do require phosphine complexes of palladium, because the oxidative addition can occur only with Pd(0) phosphine complexes, in which the ligand activates Pd towards this reaction. However, more and more data show that such substrates can be made to react successfully in phosphine free systems. These data show that at elevated temperatures, roughly estimated to be above 120 °C the oxidative addition to all aromatic C–Br bonds and activated C–Cl bonds can take place effectively without the need to activate Pd(0) by special ligands (some modulation of activity by fortuitous ligands, such as halides or acetate, can take place [18], but so far this effect has not been unambiguously quantified in preparatively relevant cases).

In 1998 Reetz et al. have shown that simple Pd complexes are effective catalysts for Heck reaction of bromobenzene with styrene in the presence of *N,N*-dimethylglycine (NaOAc, NMP 130 °C) giving high TONs of up to 10<sup>5</sup> order of magnitude. Moreover, it has been shown that with low loadings of Pd catalyst the effect of *N,N*-dimethylglycine is actually very small, and practically the same yields/TON can be obtained with mere Pd(OAc)<sub>2</sub> as catalyst. The effect of this additive was essential only in the presence of high loadings of Pd salt (1–0.01 mol%) [19]. Thus, it is obvious that the competition between oxidative addition and Pd inactivation takes place here also, at higher concentrations of Pd when the nucleation of metal particles is more probable, the agents preventing this process help to keep Pd in solution. Thus, there is a paradoxical situation: phosphine-free catalytic system should perform better at lower concentrations, as the rate of inactivation reaction (second or higher catalytic order in Pd) decays faster than the rate of oxidative addition (first order in Pd). We have observed such behavior when studying phosphine-free Heck reaction in aqueous microemulsions [20] (cf. also the discussion in [2]).

Further studies fully confirmed the ability of simple Pd salts to serve as catalysts in standard Heck reactions with unactivated aryl bromides, provided that the optimization of concentration and conditions is undertaken. Thus, de Vries et al. have shown that phosphine-free catalytic system can be very effective if an optimal concentration of Pd(OAc)<sub>2</sub> is taken (around 0.05 mol% or rather 0.001 mmol per 5 ml roughly equal to 0.2 mM). At lower concentrations (order of magnitude 0.02 mM) reaction is too slow. At higher concentrations a fast deactivation occurs due to aggregation. With optimal concentration of Pd aryl bromides, both activated and unactivated, react with various alkenes (acrylates, styrene, vinyl ether, vinylacetamide, 3-buten-2-ol) giving Heck products in high, near to quantitative, yields, with TONs around 2000 (NMP, NaOAc, 135–140 °C). The activity of Pd(OAc)<sub>2</sub> under these conditions is practically identical to the activity of Herrmann–Beller's palladacycle [21]. Palladium

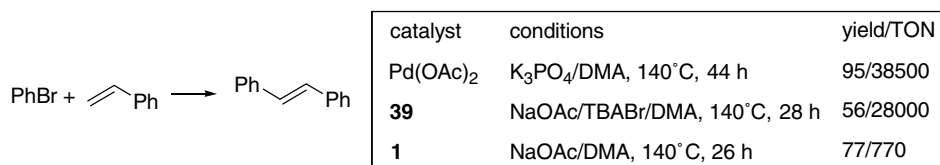
halides can also be used as catalysts [22]. Similar results have been obtained by Dupont and co-workers [23] with both  $\text{Pd}(\text{OAc})_2$  and mercaptide complex  $\text{PdCl}_2(\text{SEt})_2$ . For optimal results with phosphine-free catalysts the choice of base is also very essential. Sodium acetate often gives good results. However, a particularly active system applicable for inactivated aryl bromides is formed if  $\text{Pd}(\text{OAc})_2$  is used in DMA solution in the presence of  $\text{K}_3\text{PO}_4$  as base. In the case of reaction of  $\text{PhBr}$  with styrene this “artless” system by far outperforms (Scheme 3) such notable Heck performers as Herrmann–Beller’s and Dupont’s palladacycles [24]. This system is reactive enough to give high yields of styrene even with deactivated *p*-bromoanisole (17 h, 71%, TON 1420). With other standard Heck olefin methyl acrylate the system gave poorer yields, though this might be due not to lower reactivity towards this substrate, but rather due to competitive oligomerization of acrylate at high temperature in the presence of stronger base  $\text{K}_3\text{PO}_4$ .

Besides simple salts an immense variety of non-phosphine complexes has been revealed to possess high activity in the standard Heck reactions (cf. e.g. [25] and references therein). Many chelating NN, NO and other such, complexes were successfully tried. Even *Pd salen* complex, which is commonly regarded as a “dead” molecule, in which Pd is hidden inside a robust coordination shell, showed reasonable activity. General trends observed in the reactions catalyzed by such complexes are readily recognizable to be essentially the same for all phosphine-free systems: (i) high TONs observed for reactions of aryl iodides and activated aryl bromides; (ii) possibility to apply the catalysts to unactivated bromides and activated chlorides at high temperatures (usually in the range 130–180 °C), often in the presence of additional reagents supposedly helping to sustain Pd(0) in solution by stabilizing small clusters and not permitting them to further agglomerate to inactive particles. The most popular of such stabilizing reagents are quaternary ammonium halides (the so-called Jeffery’s approach [26–30]).

For reactions requiring harsh heating it is very essential to use such Pd-containing compounds which are not decomposed easily to release inactive Pd black. The immersion of less robust compounds, to which most simple Pd salts and complexes belong, into a hot reaction mixture would lead to immediate death of such

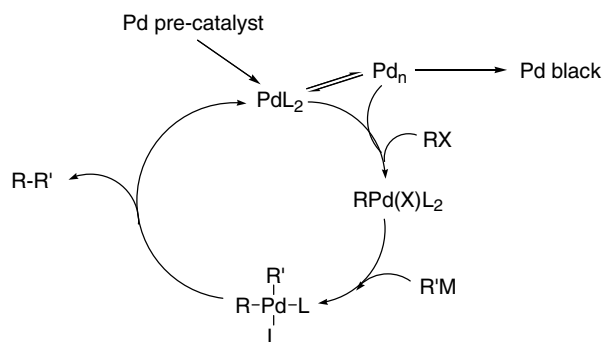
“catalyst”. This trivial factor is often neglected, though it is often critical, making the results obtained with phosphine-free systems poorly reproducible. With due care and optimal concentrations even the simplest Pd salts, as is shown above, behave well. It takes, however, a lot of labor, experience and luck to adjust such methods to practically useful reactions. In this respect the use of palladium complexes, which survive harsh temperatures and release Pd slowly due to more or less controllable reactions with the components of reaction media, is of particular interest. Palladacycles obviously are the best known examples of such complexes, though many other choices exist, including non-palladacycle chelated complexes and supported palladium catalysts (we give no references here, as a representative list would be unreasonably long).

Unactivated aryl chlorides deserve a special mention. “Unligated” Pd(0) is definitely capable of oxidative insertion into such bonds at high temperatures – actually under the same conditions as are used for unactivated bromides and activated chlorides, if only with an additional increase of temperature. However, the conversions and yields are poor or, at best, modest. It is nevertheless possible by careful optimization of Pd source to obtain good results. Thus, the use of Pd supported in the zeolite cage has been shown to be capable to catalyze the reaction of  $\text{PhCl}$  with styrene ( $\text{Ca}(\text{OH})_2$ , TBABr, NMP, 160 °C, 6 h) to give 85% yield and TON 1400 [31], apparently the best result ever obtained with unactivated aryl chloride and Pd catalyst without special ligands (electron-rich bulky phosphines or heterocyclic carbenes). However, the same system gives usual poor 19–39% yields for 4-chlorotoluene, clearly revealing the inborn problem of such catalytic systems – the lack of scope and generality, as the conditions optimized for any substrate would fail even for its closest relatives. High temperature is also a limiting factor for application of the method for more complex applications than the standard reactions of simple haloarenes with styrene or acrylates. Therefore, the use of special phosphine and carbene ligands, which are expensive, required in large amounts, but applicable to a wide scope of substrates using a reliable general preparative method operating at room or slightly above temperature, is so far a preferred laboratory practice. Phosphine-free methods can be, however, quite useful for industry, in which careful optimization of procedures is always done at the



Scheme 3.





Scheme 4. Approximate catalytic cycle for cross-coupling reactions.

development stage and is not an obstacle, if the overall cost of production is stimulating.

Palladium-catalyzed cross-coupling reactions are considered within a similar catalytic cycle (Scheme 4).

The considerations given above for the Heck reaction are valid for cross-coupling reaction with arylboronic acids, the Suzuki reaction. In it, the oxidative addition step is believed to be rate limiting, while two following steps (transmetallation and reductive elimination) are fast, at least for common arylboronic acids.

Moreover, this reaction is even less sensitive to the presence of special ligands, and simple phosphine-free catalysts are, in general, more active than in the standard Heck reaction. This is most likely accounted for by the presence of olefinic reagent in the latter, which, being a good  $\pi$ -ligand for Pd, exerts a certain deactivating effect on the Pd catalysts lacking strong ligands in the coordination shell.

Efficient cross-coupling reaction of aryl chlorides with Ph<sub>4</sub>BNa has been reported to run in aqueous media in the presence of simple Pd salts [32]. Aryl bromides, both activated and unactivated, readily take place in phosphine-free cross-coupling reactions with arylboronic acids in aqueous media in high yields and with impressive TONs [33].

There is, however, a paradox. While the activity of simple phosphine-free catalysts is apparently higher in Suzuki reactions, the longevity of catalyst in Heck reaction is apparently better. The best TON values for Heck reactions are several orders of magnitude higher than the respective records in Suzuki reaction. The key to this paradox is likely to be the same – the olefin in Heck reaction acts as a stabilizing ligand increasing the lifetime of catalytic system.

Other cross-coupling reactions (such as Stille's cross-coupling with organotin or Sonogashira's cross-coupling with terminal acetylenes, as well as C-heteroatom cross-coupling reactions) are essentially different. Reactions with rate-limiting transmetallation steps (such as Stille or Sonogashira reactions) do allow for phosphine-free protocols, but are generally reluctant to run in the presence of low concentrations of catalyst, most

likely due to kinetic reasons. Such reactions as amination, arylation of CH-acids, allylic substitution require specific ancillary ligands and are not indifferent to the coordination shell of palladium. All these reactions are not easy targets for the application of palladacyclic catalysts.

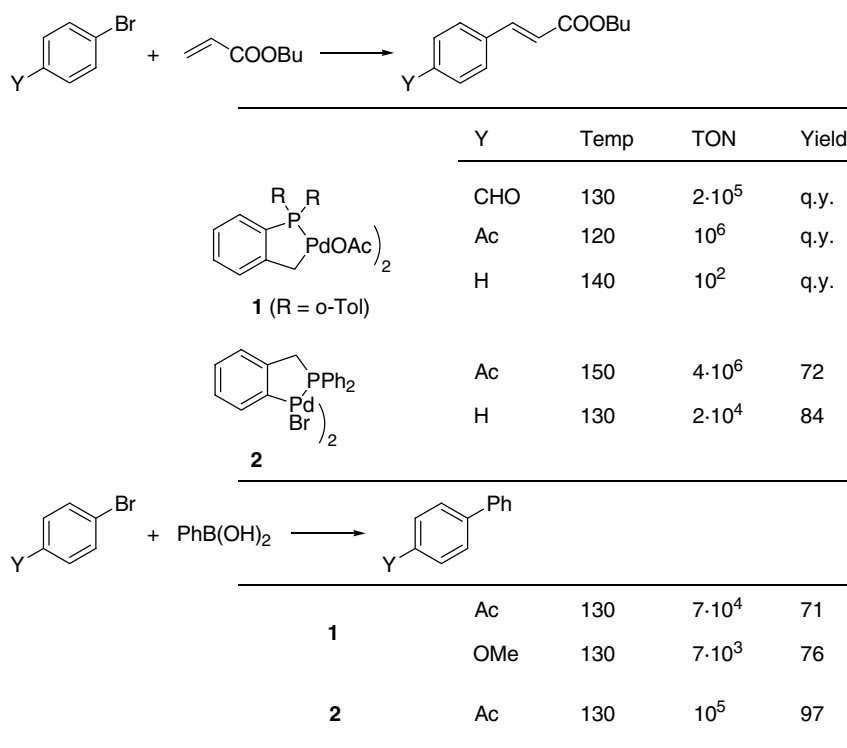
### 3. Phosphine-derived palladacycles

The tide of palladacycles began in 1995 by a pioneering work by Herrmann et al., who discovered that a well-known complex (**1**, R,R' = *o*-Tol) (Scheme 5), readily formed by heating Pd(OAc)<sub>2</sub> with (*o*-tol)<sub>3</sub>P, shows an outstanding catalytic activity, far surpassing the activity of classical Pd(OAc)<sub>2</sub>-(*o*-tol)<sub>3</sub>P catalytic system.

In the Heck reaction of activated bromoarene (*p*-bromobenzaldehyde) with butyl acrylate the amount of catalyst could be reduced down to  $5 \times 10^{-4}$  mol%, thus giving TON of 200,000 (NaOAc, DMA, 135 °C), an amazing number for those days. With less active bromoarenes, such as PhBr itself, and electron-rich bromobenzenes the results were much less spectacular, with good yields obtained with as much as 1–0.5 mol% Pd, thus giving TONs of about 100–200. The addition of soluble bromides (TBABr, LiBr) improved the situation, and made possible to obtain TON 810 at 81% yield with activated chloroarene *p*-chlorobenzaldehyde [34]. With this complex an induction period has been usually observed whenever kinetic studies were undertaken. However, high temperatures over 110 °C and induction period are not a general rule in the reactions catalyzed by this complex. Depending on conditions and co-reagents, the activity can be invoked under milder conditions. In the reaction of iodoarenes the palladacycle is active already at 85 °C (0.1 mol% Pd, Bu<sub>3</sub>N, DMA), and under these conditions no induction period is observed [15].

Further activation of the Herrmann–Beller catalyst **1** can be done by the application of ionic liquids as solvents. Thus, in the reaction of *p*-bromoacetophenone with styrene huge TON of 1,000,000 is observed and quantitative yields of *p*-acetylstyrene can be achieved (120 °C, 0.0001 mol% Pd) [35]. In this system a low conversion of chlorobenzene could be even observed. TON can further be increased by addition of fresh portions of substrates to reaction mixture, though after about four such reinitializations the activity decreases.

A very thorough study has been undertaken to elucidate differences between the catalysis by palladacycle **1** and standard catalysts Pd(*o*-Tol<sub>3</sub>P)<sub>2</sub> and [PhPd(*o*-Tol<sub>3</sub>P)Br] in standard Heck reaction [36]. The statistically meaningful differences (in regioselectivity, substrate selectivity, isotope effect, Hammett reaction constant) were indeed discovered, but the magnitude of discrepancies was so small that conclusions about possible changeover of mechanism from Pd(0)/Pd(II)



Scheme 5. Representative performance of PC-palladacycles (more detailed figures and conditions, see text).

to Pd(II)/Pd(IV) could hardly be justified. It should be emphasized that the common Pd(0)/Pd(II) catalytic is actually a generalized scheme allowing for numerous variations, e.g. in the nature of catalytically active species, which should result in the variation of measurable characteristics of reactivity without the need to resort to essentially different mechanism. And, vice versa, if the characteristics of two reactions are so close that precise measurements are required to differentiate between them, why should different mechanisms be introduced?

The Hammett reaction constants  $\rho$ , measured for palladacycle-driven reaction is rather small (1.58), though still higher than that measured for reaction catalyzed by standard catalysts (1.00) [36]. This seems to contradict with the well-known fact that Heck reaction is considerably, often dramatically, more facile for electron-deficient “activated” haloarenes. Thus, a due care should be paid to the application of data measured in kinetic experiments carried out at higher dilutions with low conversion of starting materials to interpretation of preparative scale runs.

Though since the discovery in 1995 of palladacyclic catalysts, the number of such complexes have been increasing as a geometrical progression, the palladacycle **1** appears to remain the only palladacycle which found application in organic synthesis, and is commercially offered by major reagent companies.

Palladacycle **1** is useful in the Heck reaction with *gem*-disubstituted olefins, such as metacrylate (Bu<sub>3</sub>N,

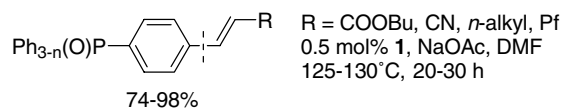


Fig. 1.

DMA, 140 °C, 4–24 h) [37,38]. Catalyst **1** was also used to perform the olefination of *p*-bromophenyl substituted triarylphosphine oxides (Fig. 1) [39].

Tietze et. al. has used the the Herrmann–Beller palladacycle in a number of intramolecular Heck reactions within complex syntheses of steroid analogues (e.g. [40–42]). Reactions are usually carried out in aqueous polar solvents (DMF or MeCN) under conventional or microwave heating, as e.g. in the following examples (Scheme 6).

The outstanding results observed for the first palladacyclic catalyst inspired hopes that the modification of this molecule can open a route to a vast family of catalysts with enhanced activity, enantioselectivity, etc. However, it soon have been established that all close analogues of **1**, bearing bulky alkyls at phosphorus atom (**3**, Fig. 2), invariably gave inferior catalytic systems [43].

However, an immobilized version of this palladacycle **4** showed activity in standard Heck reactions of bromoarenes, including deactivated ones with methyl acrylate (0.002–0.5 mol% Pd, NaOAc, DMA, 130 °C), as well as in cross-coupling of *p*-bromoacetophenone with

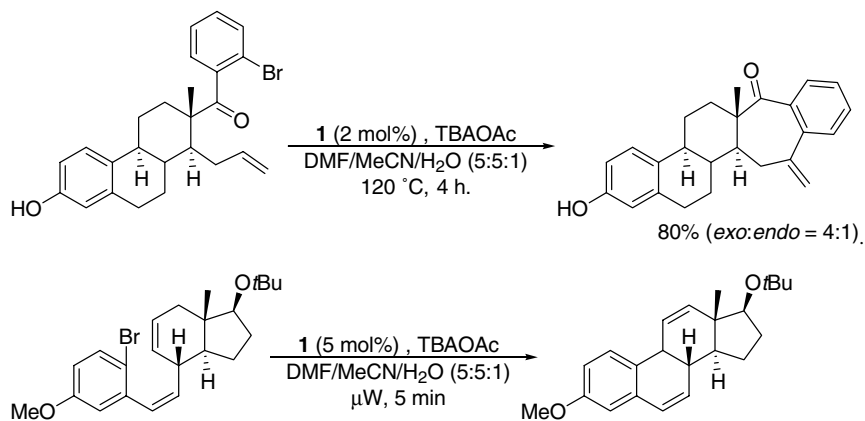
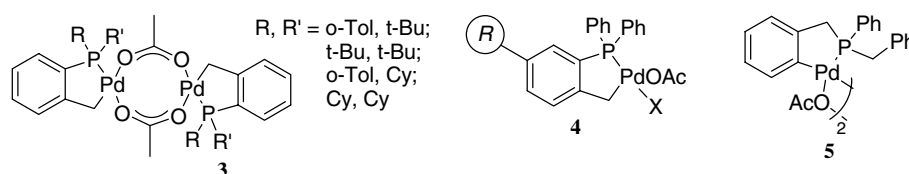
Scheme 6. The application of **1** in intramolecular Heck reactions.

Fig. 2.

$\text{PhB(OH)}_2$  (0.2 mol% Pd,  $\text{K}_2\text{CO}_3$ , xylene, 130 °C) or phenylacetylene (0.2 mol% Pd,  $\text{Et}_3\text{N}$ , 90 °C) to give high yields of target products [44]. Using initially 2 mol% Pd the catalyst can be recycled up to 6 times in Heck reaction of activated bromoarene. Given high initial loading this reaction cannot be regarded as a critical test for demonstrating longevity of supported palladacycle, as soon as with such substrate any residual Pd content, practically in any form, can show catalytic activity.

Palladacycles derived from benzyldiphenylphosphine **2** give catalytic system with activity similar to **1** in Heck reactions of bromoarenes with butyl acrylate (NaOAc, DMA, 130 °C) to give cinnamates in high yields with 0.02–0.002 mol% Pd (*p*-BrC<sub>6</sub>H<sub>4</sub>Ac: 24 h, 98%, TON 4900; PhBr: 175 h, 84%, TON 21,100, etc.). Yields are lower for electron-rich bromoarenes. Huge TONs were obtained for *p*-BrC<sub>6</sub>H<sub>4</sub>Ac at higher temperatures 150–170 °C, the best being 3,590,000 TON/72% yield (0.00002 mol% Pd, 150 °C, 144 h). Unlike **1** this system is reported to be insensitive towards the addition of TBABr [45].

However, a very similar palladacycle derived from dibenzylphosphine (**5**) showed modest activity for the Heck reaction of *p*-bromobenzaldehyde with standard olefins (acrylate, styrene, etc., system: NaOAc, DMF, 120 °C). This system has been applied for modification of tetrakis(*p*-bromophenyl)porphyrin, though with inferior results as compared with the standard catalytic system (Pd(OAc)<sub>2</sub>-PPh<sub>3</sub>) [46].

Shaw's palladacycles based on tri- $\alpha$ -naphthylphosphine (**6**, **7**, Fig. 3) represent an example of different

structural class of phosphine-based palladacycles, in which Pd is bonded to triarylphosphine phosphorus and  $\text{sp}^2$ -carbon. It is not surprising then that in solid state these palladacycles are showing even higher thermal stability than the Herrmann–Beller palladacycle **1**. However, this complex can be made to operate at the same or even lower temperatures than HB, which illustrates the thesis that the conditions at which the catalytic action of a given palladacycle-based system is triggered is not directly associated with thermal stability in pure state. This palladacycle has been tested in standard Heck reactions. Unfortunately, most of the results were obtained for highly reactive iodoarenes, making it impossible to elucidate the real activity of catalytic systems based on these palladacycles. Huge TONs of 650,000 has been obtained for the reaction of PhI with styrene at 120 °C (yield 65%, 5 days, 0.0001 mol% Pd), and 1,120,000 in the reaction of PhI with methyl acrylate at as low as 95 °C (yield 56%, 13 days, 0.00005 mol% Pd). Better yields can be obtained with

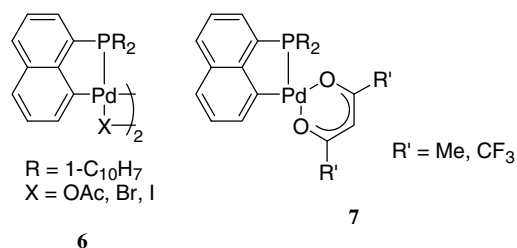


Fig. 3.

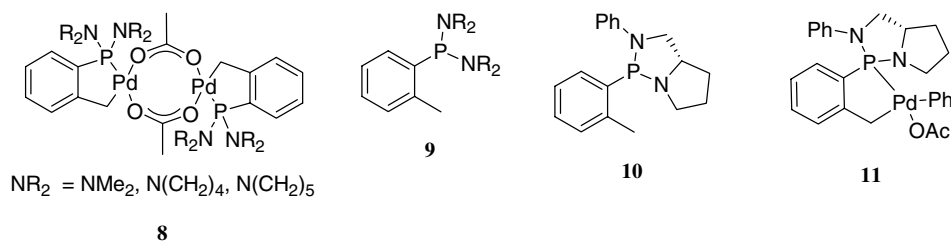


Fig. 4.

more conservative loadings (88%, 5 days, 0.001 mol% Pd). The complexes show modest activity for the reaction of PhBr with styrene (115 °C, 77%, TON 770, 0.01 mol% Pd) [47].

Aminophosphine analogues **8** (Fig. 4) of the Herrmann–Beller palladacycle has been prepared and announced as highly effective catalysts for Heck reaction of norbornene terminated by hydride reduction of stable intermediate (Scheme 7) [48].

High TON values were obtained for PhBr and PhOTf (0.0005 mol% Pd, 98–99%, TON  $2 \times 10^5$ ). PhCl reacted in quantitative yield, though at lower though still very decent TON (0.5 mol% Pd, 99%, TON 190). Iodobenzene was processed with incredible catalytic efficiency, with quantitative yields being obtained with loadings of Pd down to  $10^{-7}$  mol%. An apparently unbeatable record was established with catalyst loading of  $5 \times 10^{-9}$  mol% giving 79% yield and 16 billion turns of the catalytic cycle! Unfortunately, it is not possible to evaluate the place of this catalytic system in the row of palladacycle pre-catalysts as: (i) the system has not been tested in more conventional Heck or cross-coupling reactions; (ii) as can be deduced from experimental procedures actually not preformed palladacycles, but an equimolar mixture of Pd(OAc)<sub>2</sub> and aminophosphine ligand **9** has been put into reaction mixtures. It is not evident that palladacycle is indeed formed under the conditions and with high dilutions used in the experiments. The attempt to use chiral version of phosphine **10** has met with limited success: enantioselectivity was indeed observed but *ee* was rather low (2–14% with PhI, 14–25% for PhOTf) [49].

A very important finding in this work is the isolation of Pd(IV) complex **11**, formally being the product of oxidative addition of PhX to palladacycle. This fact can be interpreted in favor of the elusive Pd(II)/Pd(IV) mechanism. However, as no more evidence has been published, at least on whether this complex may or may not react

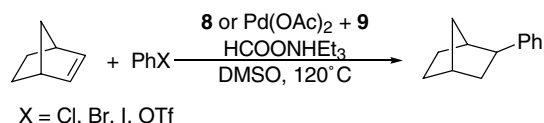
with norbornene, it is not clear that this complex has indeed anything to do with the catalytic cycle, and is not simply an unreactive by-product. Still, up to now it is possibly the only direct evidence on the formation of Pd(IV) complexes retaining palladacycle fragment in the reactions catalyzed by a palladacycle, and as such this evidence is precious. It should be noted that Pd-catalyzed reactions of norbornene were shown by Catellani et al. [3,50–57] to often involve the formation of palladacycles.

In the Suzuki reaction first results were obtained also with the Herrmann–Beller palladacycle **1**. High TONs were recorded for reaction of PhB(OH)<sub>2</sub> with aryl bromides, both activated (*p*-BrC<sub>6</sub>H<sub>4</sub>Ac) and unactivated (*p*-MeOC<sub>6</sub>H<sub>4</sub>Br) (xylene, 130 °C, K<sub>2</sub>CO<sub>3</sub>) [34]. Similar TONs obtained with so different substrates, apparently different from what is observed in Heck reaction catalyzed by **1**, were interpreted in favor of oxidative addition not being rate-limiting step. It may well be possible that in this system it is the rate of Pd(0) release from palladacycle that is the bottleneck. The system is effective even with deactivated aryl chloride (*p*-ClC<sub>6</sub>H<sub>4</sub>OMe) giving 82% yield with Pd loading of 0.1 mol%. Higher TON can be obtained with lower Pd loading (0.01 mol%) though in this case the yield is low (21%). Direct comparison with the system Pd(OAc)<sub>2</sub>–(*o*-tol)<sub>3</sub>P has shown that this commonly used system is inferior in yields, and Pd black sediments during the reaction, while **1** has been visually stable.

Similar results were obtained with **2**, the analogue of the Herrmann–Beller palladacycle. High TONs of up to  $10^5$  were obtained for *p*-BrC<sub>6</sub>H<sub>4</sub>Ac in full conversion runs (yield 97%) with 0.001 mol% Pd (K<sub>2</sub>CO<sub>3</sub>, 130 °C, xylene 20 h), and though the system gave poor results with aryl chlorides, even activated [45].

In the Stille reaction HB palladacycle has been occasionally used as pre-catalyst in special synthetic applications. Thus, the use of this complex for the synthesis of half-products on the route to biphenomycin antibiotics has been reported to give better results than the conventional systems used for Stille coupling (e.g. Pd<sub>2</sub>dba<sub>3</sub>, AsPh<sub>3</sub>, CuI or LiCl, NMP) (Scheme 8) [58].

Similarly, superior results were used with the Herrmann–Beller palladacycle **1** in cross-coupling of resin-bound stannane with aryl bromides as compared with



Scheme 7.



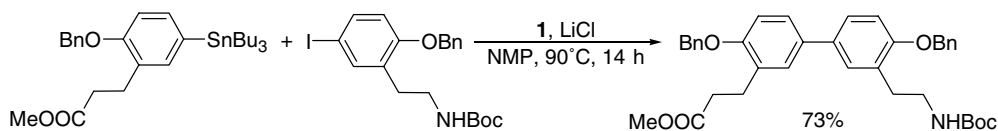
standard catalytic system used for homogeneous Stille reactions, including  $\text{AsPh}_3$  complex of palladium. The catalytic system showed excellent tolerance to sensitive functionality in the coupling partners, including epoxide, azide, carbamate, etc., though the system completely failed for substrate containing unprotected aminoalcohol residue (Scheme 9). When applied to the same bromoarenes with non-supported stannane, **1** gave no advantages over conventional catalysts [59].

Homocoupling of aryl iodides can be performed in the system containing Pd catalyst and hydroquinone as stoichiometric reducing agent (2.5–5 mol% Pd,  $\text{Cs}_2\text{CO}_3$ , hydroquinone, DMA, 50–75 °C). Either **1** or a mixture of  $\text{Pd}(\text{OAc})_2$  with (*o*-tol) $_3\text{P}$  can be used with equal success. Palladacycle is fully operative already at 50 °C (Scheme 10). This simple reaction again reveals that Pd(0) can be released from a palladacycle under unexpectedly mild conditions. Moreover, hydroquinone is a standard free radical inhibitor, which is always present in olefins used for Heck reactions – styrene, acrylates, etc., and which is often not removed before the reaction or even specially added to suppress polymerization. Thus, this compound may as well influence the outcome of Heck reactions, thus being a likely factor of high discrepancies in the results obtained with similar pre-catalysts. Whether this is true or not is has never been tested [60].

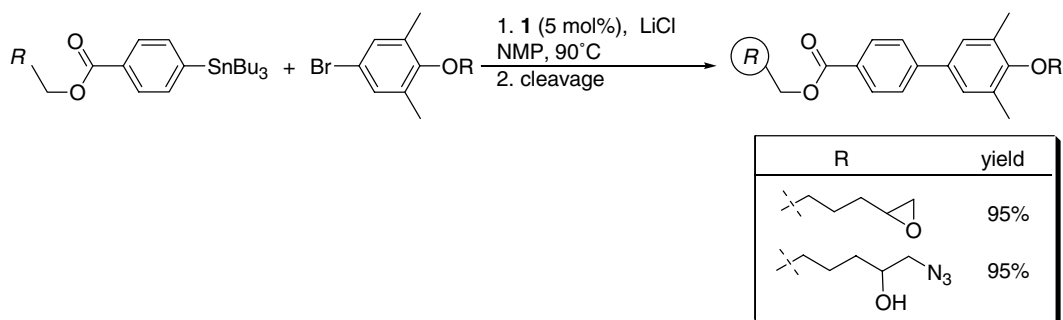
#### 4. Phosphite palladacycles

The discovery that phosphite-based palladacycle can be at least as effective catalysts as phosphine-based palladacycle (Scheme 11) is an achievement the significance of which for palladium catalysis cannot be overestimated. Indeed, phosphine-based palladacycle could be considered as precursors of Pd(0) complexes stabilized by phosphine ligand(s). Phosphites are well known to be unable to effectively stabilize zero-valent palladium, a huge 10–100-fold excess of phosphite is required to make catalytic system capable of processing deactivated substrates [61]. Thus, the phosphite-based system should be regarded as an instantiation of phosphine-free methodology – a bridge to catalytic system altogether lacking phosphorus compounds in any form.

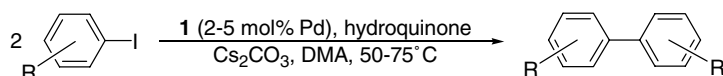
The first phosphite-derived palladacycle **12** were proposed for catalytic applications by Bedford et. al [62]. In Heck reaction, this catalyst awakes above 110 °C, performs well at 140 °C, and shows huge efficiency at 180 °C in the reactions of bromoarenes with methyl acrylate or styrene (NaOAc, DMA). At 140 °C TONs are around  $10^2$ – $10^3$  with good to quantitative conversions (e.g. PhBr: 0.2 mol% Pd, 18 h, 51%, TON 255). Electron-rich *p*-bromoanisole can be reacted with acrylate in the presence of  $\text{K}_2\text{CO}_3$  as base in high yield, though rather slow (160 °C, 65 h, 98%, TON 9800). Reactive bromoarenes,



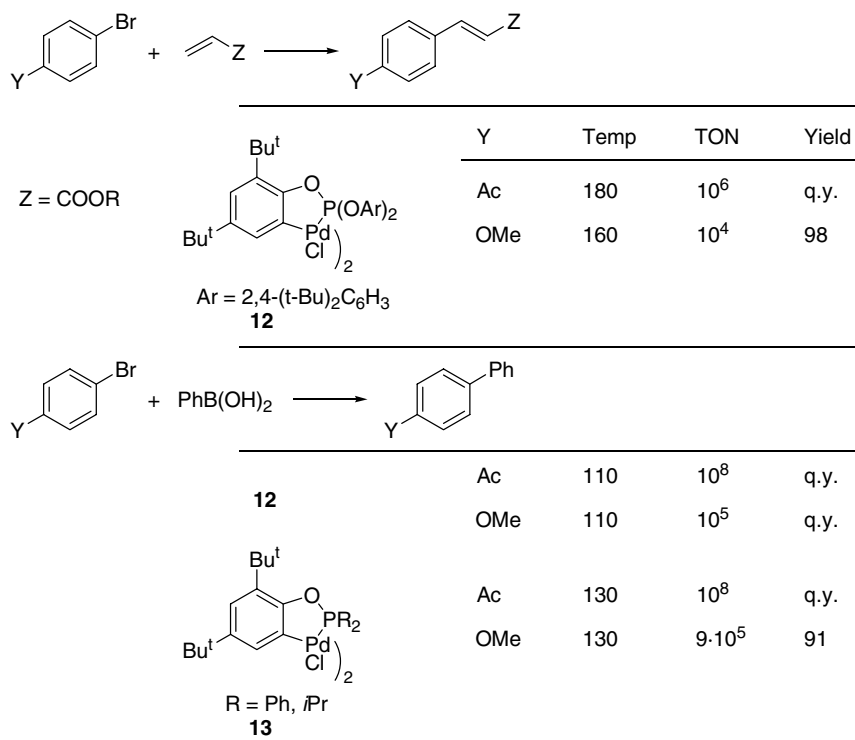
Scheme 8.



Scheme 9.



Scheme 10.



Scheme 11. Representative performance of phosphite-derived palladacycles.

such as *p*-BrC<sub>6</sub>H<sub>4</sub>Ac processed at 180 °C at very high rate, e.g. in the reaction with butyl acrylate TON 1,000,000 and quantitative conversion (0.0001 mol% Pd, 6 h). Styrene gives lower yields as under harsh conditions polymerization competes with Heck reaction.

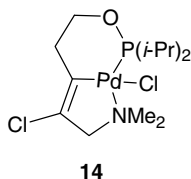
In Suzuki reaction, phosphite palladacycle **12**, as in the case of Heck reaction, afforded higher TON values. Thus, using *p*-BrC<sub>6</sub>H<sub>4</sub>Ac and 0.000001–0.00001 mol% Pd (toluene, K<sub>2</sub>CO<sub>3</sub>, 110 °C) huge TONs reaching 100,000,000 was obtained, and the overall reaction rate also was very high (87% yield after 1 h with 0.0001 mol%, 100% after 18 h with 0.00001 mol% Pd). Unactivated bromides (bromobenzene, bromoanisoles, bromotoluenes) can be processed with ease, and very high yields can be reached using 0.01–0.001 mol% Pd after 18 h [63,64]. A direct comparison of orthometalated complex with mixture of Pd<sub>2</sub>(dba)<sub>3</sub> and triarylphosphite gave almost identical results under the same conditions and same loadings of Pd (0.0001 mol%, 24–30% yield, 240,000–300,000 TON after 18 h). The mixture of Pd(OAc)<sub>2</sub> and triarylphosphite is capable of catalyzing cross-coupling of aryl bromides with PhB(OH)<sub>2</sub> at room temperature [65]. At the same time, the use of preformed bis-phosphite complex PdL<sub>2</sub>Cl<sub>2</sub> gave poorer results (64% vs. 100% with 0.001 mol% Pd), though this difference is not so great to allow for any meaningful conclusions. No induction period has been noted.

The palladacycle **12** is also capable of catalyzing the reaction between bromoarenes, both activated (*p*-BrC<sub>6</sub>H<sub>4</sub>Ac, with 0.1–0.01 mol% Pd) and deactivated (*p*-bromoanisole, 0.5 mol% Pd was required for high conversions), with butylboronic acid, and again practically the same results were obtained with palladacycle and with mixtures of Pd<sub>2</sub>(dba)<sub>3</sub> or Pd(OAc)<sub>2</sub> with triarylphosphite, as well as the system Pd(OAc)<sub>2</sub>–PCy<sub>3</sub>.

Phosphinite palladacycles **13** are devised apparently to combine in one molecule the advantages of palladacycle and modulation of catalyst properties by phosphine ligand. The complexes indeed show high catalytic activity in Suzuki reaction of aryl bromides with PhB(OH)<sub>2</sub>, though not much different from the activity of parent phosphite palladacycle (cf. Scheme 9). High yield and huge TON can be obtained with deactivated substrate *p*-bromoanisole, with little difference observed between the complexes with PPh<sub>2</sub> and P(*i*-Pr)<sub>2</sub> groups (toluene, K<sub>2</sub>CO<sub>3</sub>, 0.0001 mol% Pd, 130 °C, 18 h, R = *i*-Pr: 91%, TON 910,000; R = Ph: 85%, TON 850,000). Further decreasing Pd concentration leads to decrease of yield to ca. 20%, though TON grows to an impressive value of 2–2.6 millions. With activated substrate *p*-BrC<sub>6</sub>H<sub>4</sub>Ac Pd loading can be decreased to 10<sup>–6</sup>–10<sup>–7</sup> mol% to give TONs of the order of hundred millions. The system, however, failed in the case of deactivated chloroarene. The system Pd<sub>2</sub>(dba)<sub>3</sub> – ligand is able to catalyze the reaction, but

with apparently worse yields (36 vs. 85%, under identical conditions) [66].

Phopshinite palladacycle with aliphatic backbone **14** gives a nice hint that a highly active catalytic system can indeed employ this structural feature. The complex is capable to perform the cross-coupling of aryl chlorides with arylboronic acids. Reactions performed with relatively high catalyst loadings (0.5–1 mol% Pd, CsF, dioxane, 130 °C – reaction performed in a closed vessel, 27 h) consistently give high yields of cross-coupling products with a broad selection of aryl chlorides and arylboronic acids [67]. Though Pd in this palladacycle is doubly chelated, the structure can hardly be regarded among pincer complexes (vide infra), as two arms are likely to be bonded with essentially different strength, so that partial dechelation should be greatly facilitated. Indeed, PC-cycle is six-membered – a rare example in palladacycle catalysis dominated by more stable five-membered rings.



It should be noted that the simplest palladacycle of this sort, orthopalladated triphenylphosphite, was tested in the hydrogenation of olefins as early as in 1986 [68]. The reactions were performed under harsh conditions (toluene, 190 °C). Under these conditions the non-palladacyclic bis-phosphite complex rapidly decomposes to give Pd mirror, and is not active. However, no other advantages were discovered, and we failed to find any other attempts to use palladacycles for hydrogenation since then.

## 5. CN-palladacycles

The available variety of CN-palladacycles is remarkable. So far, possibly all major types have been tested in Heck and cross-coupling reactions to show performance ranging from high through excellent to extraordinary. Currently it seems impossible to find a nitrogen-containing palladacycle with low or no activity in standard Heck or Suzuki reactions. Such an indifference of catalytic activity to the ligand part of complex is of no precedence in catalysis. Apparently the ligand serves as mere packaging for palladium, a sort of disposable wrapper. So, it hardly makes sense to design sophisticated ligands for the construction of palladacycles, and trival nitrogen-containing compounds (Schiff bases, oximes, benzylamines, etc.) should be the best

choice. Is there any difference between various CN-palladacycles?

### 5.1. Imine palladacycles

The pioneering work in this area belongs to Milstein et al. who introduced a vast class of imine-based palladacycles. *Ortho*-palladated imines, such as **15** or **16** (Fig. 5) are highly reactive in the reaction of PhI and PhBr with methyl acrylate to afford quantitative yields (NMP, 140 °C, Na<sub>2</sub>CO<sub>3</sub> or Et<sub>3</sub>N), and very high TONs (PhI: 3.5 × 10<sup>-6</sup> mol% Pd, 18 h, 100%, TON 1429000; PhBr: 7 × 10<sup>-5</sup> mol% Pd, 130 h, 96%, TON 132,900). Iodobenzene can be reacted with styrene and several other olefins less common in Heck reaction, such as indene, cyclohexene, dihydrofuran, though with less spectacular results (lower TONs and moderate yields) [69].

Kinetic measurements accomplished by precision calorimetry showed that Milstein's imine palladacycles are indeed much more active than the Herrmann–Beller palladacycle **1**. Curiously, the complex of PdBr<sub>2</sub> with the simplest Schiff base **17** (Fig. 6) has been shown to possess roughly the same activity as Milstein's palladacycles [70] (later [71] a palladacyclic structure **18** was attributed for the complex formed by Pd(OAc)<sub>2</sub> with this imine). The reactions with both catalyst precursors have a distinct induction period [70,72,73].

Imine based palladacycles were further investigated by Nowotny et al. [74], who discovered several essential phenomena. The complexes started to show activity in the reaction of PhI with styrene at 100 °C, but the reaction was slow and suffered from a long induction period. Full activity comparable to this measured by Milstein et al. has been reached at 140 °C (Pr<sub>3</sub>N, NMP), unfortunately under conditions different from those used by Milstein et al., so only approximate comparison can be made. The complexes are unstable under heating in

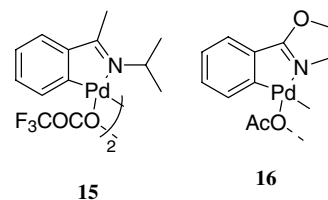


Fig. 5.

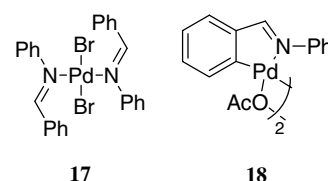


Fig. 6.

solution in the absence of any additives to decompose into black colloid solutions of Pd. The complex immobilized on polystyrene resin loses its activity after withdrawal from reaction mixture, while the solution retains catalytic activity and can be recharged with substrates. Initially the reaction showed an induction period, more lengthy at 100 °C, shorter at 140 °C. Nowotny et al. came to a conclusion that it is not cyclopalladate, but actually Pd nanoparticles which are true catalysts in this case.

In further studies a number of analogues of original Milstein's imine palladacycles were introduced. Thus, imine palladacycles built over ferrocene scaffold **19** (Fig. 7) showed high activity towards PhI already at 100 °C in the presence of Et<sub>3</sub>N in dioxane solvent. Quantitative yields and very high TONs were recorded for the reaction with acrylate, the highest TON amounting to 7,360,000 (92% yield, 338 h). In the reaction with styrene yields and TONs were markedly lower (the best yield/TON: 71%/260,800, 70 h). Among bromoarenes only the reaction of *p*-nitrobromobenzene was described to require higher temperature (140 °C) and DMF as solvent and giving either quantitative yields at modest TON (100%/3660) or modest yield at huge TON (64/2,340,000, 55 h) [75].

Fluorous analogues **20** of Milstein's palladacycle **15** were used for Heck reaction of PhI and *p*-BrPhAc with methyl acrylate or styrene. Huge TONs were recorded at 140 °C (DMF, Et<sub>3</sub>N, 10<sup>-4</sup> mol% Pd). The reaction with PhI can be run at reasonable rate yet at 80–100 °C with TONs about 10,000 and high yields of Heck products, and the catalyst under such conditions can be recycled by extraction with perfluoroorganic solvent. The activity

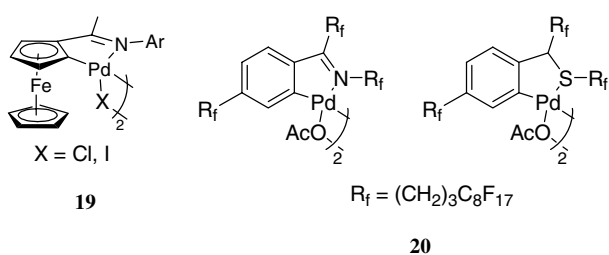


Fig. 7.

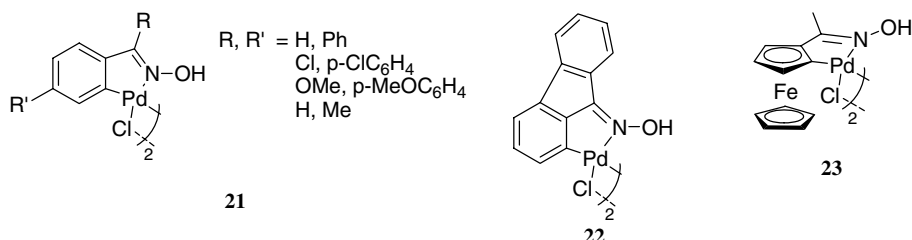


Fig. 8.

of catalyst solution, however, degrades with each recycling, and some palladium is leached into DMF layer, so that no more than four reuses are possible. In the first runs the induction period was evident. Palladium nanoparticles were suggested to play the major role in the observed catalytic activity [71,76]. Practically identical activity and overall behavior has been observed for sulfur-containing palladacycle [71].

In Suzuki reaction, CN-palladacycles show impressive efficiency. Milstein's imine palladacycle **15** is used for cross-coupling of PhB(OH)<sub>2</sub> with bromoarenes (0.0005 mol% Pd, K<sub>2</sub>CO<sub>3</sub>, xylene, 130 °C). High TONs of the order of 100,000 were obtained both for activated and deactivated bromoarenes, though the yields with the latter were in general not exceeding 60–80% [77]. The difference between activated and deactivated substrates, measured by competitive reactions, was revealed to be quite small ( $\rho$  close to 1), which has been interpreted as a token of other than Pd(II)/Pd(0) mechanism of the catalytic cycle. The same phenomenon, as we have seen above, has been observed for phosphine-derived palladacycles in Suzuki reaction

### 5.2. Oxime palladacycles

Soon after the introduction of imine palladacycles it became known that possibly the simplest of palladacycles, the well-known cyclopalladated *N,N*-dimethylbenzylamine, benzaldoxime, and benzophenone oxime are no losers in this race. Either of the three can be used in Heck reactions of iodoarenes (PhI and *p*-MeOC<sub>6</sub>H<sub>4</sub>I) and bromobenzene with acrylate or styrene (0.0001 mol% Pd, K<sub>2</sub>CO<sub>3</sub>, NMP, 150 °C). High TON values were recorded in the reactions of PhI with ethyl acrylate (7 h, 96%, TON 145,454), PhBr with styrene (29 h, 87%, 86,666). Electron-deficient chloroarenes (*p*-nitro, *p*-cyanochlorobenzene) can also be reacted with reasonable results (30–42 h, 51–78%, TONs up to 70,000) [78]. Electron-rich chloroarene *p*-chlorotoluene reacted in the presence of either AlCl<sub>3</sub> or TBAI in low yield (12–28%).

An extended study of oxime derived palladacycles **21**, **22** (Fig. 8) has been undertaken by Najera et al. In their first article, all complexes were shown to possess compa-

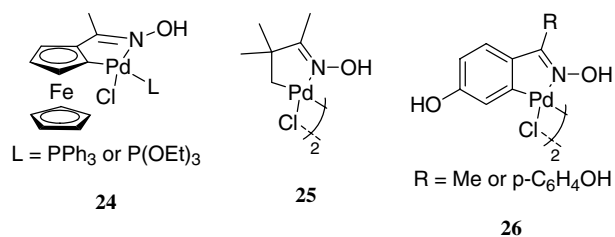


Fig. 9.

rable activity in the reaction of PhI or *p*-BrPhAc with methyl acrylate in the presence of such bases as  $\text{Et}_3\text{N}$ , CsF,  $\text{K}_2\text{CO}_3$ , NaOAc to give quantitative yields of cinnamates and TONs up to 10,000, though apparently establishing records has not been the goal of the researchers (140 °C, DMF or NMP, 0.5–0.001 mol% Pd, 1.5–12 h). Positive influence of TBABr additive on the reaction with *p*-bromoacetophenone was noted [79].

Similar activity has been demonstrated by Iyer et al. for cyclopalladated oxime of acetylferrocene (0.01 mol% Pd, NaOAc, NMP, 140–150 °C). Both dimeric **23** and monomeric **24** complexes (Fig. 9) were included into the study. Expectedly, at high reaction temperature there should no be essential difference between monomer and dimer. Monomeric complexes **24** included one extra ligand, phosphine or phosphite, which could have helped to stabilize zero-valent palladium and increase the stability of the catalytic system, particularly important for less reactive substrates. The results obtained, however, gave no clue to this problem, as all three complexes showed comparable reactivity without any discernible trends. This is not surprising as equimolar amounts of neither  $\text{PPh}_3$  nor phosphite are able to effectively stabilize Pd(0). In order to modulate the activity of catalyst more potent phosphines should be taken [80].

In further studies Najera et. al involved the whole series of oxime palladacycles derived from acetophenones, benzophenones, acetylferrocene, and even the aliphatic palladacycle formed from pinacolone oxime **25**. In the test reaction of methyl acrylate with PhI (110 °C,  $\text{Et}_3\text{N}$ , DMF, 0.01 mol% Pd) all complexes gave near to quantitative yields, though the complexes bearing electron-withdrawing substituents afforded high yields in less time. Thus, for preparative purposes the most convenient and effective pre-catalyst is cyclopalladated *p,p'*-dichlorobenzophenone oxime. The reaction carried out with  $\text{Li}_2\text{PdCl}_4$  and *p,p'*-dichlorobenzophenone oxime gave lower yield than the reaction in the presence of preformed palladacycle (62% after 6 h vs. 99% after 1.5 h), though direct comparison is not possible as the first reaction was performed with different base ( $\text{K}_2\text{CO}_3$ ). Reaction catalyzed by  $\text{Li}_2\text{PdCl}_4$  was slower (90% after 3.5 h), though the difference is not dramatic.

In order to lower palladium loading the temperature should be elevated, all record-making results were ob-

tained at 160 °C at which temperature TONs up to amazing value  $10^{10}$  were obtained (72 h,  $10^{-8}$  mol% Pd, 99% yield) for Heck reaction with iodobenzene, the level of efficiency which reminds of enzymatic catalysis.

Induction period was evident in the reactions. Pre-heated solution of palladacycle initiated the reaction without induction period. No induction period was observed if the reaction mixture was re-charged with fresh reactants. Heating with acrylate led to precipitation of Pd black, and lower conversions were observed with such catalyst.

Preparative scope of this reaction is typical for the best palladacyclic systems. In the reaction with acrylate iodoarenes reacted in quantitative yields at 110 °C (0.01 mol% Pd). Bromoarenes required  $\text{K}_2\text{CO}_3$  base, addition of TBABr and temperature of 130 °C. High yields were obtained with activated bromoarenes (*p*-acetyl-, *p*-nitro-, *p*-phenylbromobenzene, 2-bromonaphthalene). PhBr gave 49% (24 h), electron-rich bromoarenes gave low to modest yields (24–57%). Chloroarenes also were reactive though at 160 °C, and while *p*-nitrochlorobenzene gave high yield (92%), *p*-chloroanisole gave only 23% after 24 h under different conditions ( $\text{LiBr}$ ,  $\text{Cs}_2\text{CO}_3$ , dioxane, 160 °C).

Heck reaction with styrene gave high yields with iodoarenes (0.1–0.01 mol% Pd, 110 °C), bromoarenes (activated substrates were used at 130 °C, unactivated at 160 °C, with as low as 0.001 mol% Pd), chloroarenes. PhCl (60% yield, 24 h, 0.5 mol% Pd) and *p*-chloroanisole (22%, 24 h,  $\text{LiBr}$ , 0.2 mol% Pd) required NMP as solvent. Other olefins (substituted styrenes, ethyl vinyl ether, acrylonitrile) can also be used with iodoarenes and activated bromo- and chloroarenes giving modest to high yields [81].

In Suzuki reactions, oxime palladacycles **21** were shown to catalyze the reaction of *p*- $\text{BrC}_6\text{H}_4\text{Ac}$  with  $\text{PhB}(\text{OH})_2$  (0.1 mol% Pd,  $\text{K}_2\text{CO}_3$ , toluene, 110 °C, 0.5 h) in near to quantitative yields [79]. In further studies these complexes have been shown to be of general utility for cross-coupling of a broad range of aryl chlorides and bromides. With aryl bromides, both activated and deactivated, the reaction is run at 110 °C (0.001 mol% Pd for activated bromides, 0.01 mol% Pd for electron-rich bromides,  $\text{K}_2\text{CO}_3$ , toluene) to consistently give high yields of cross-coupling products in fast reactions usually not requiring more than 2 h for completion. TONs of ca. 200,000 were reached for *p*- $\text{BrC}_6\text{H}_4\text{Ac}$ , while for *p*- $\text{MeOC}_6\text{H}_4\text{Br}$  TONs were lower not exceeding 10,000 in the high yield runs (as usual, higher TONs could be reached in reactions with incomplete conversions). Remarkably, with higher Pd loading (0.2 mol%) and activated bromide, the reaction can be run at room temperature in quantitative yield after 5 h. High efficiency of the system observed with activated bromoarene has been further illustrated by using initial loading of 0.01 mol%



Pd, but 5 times recharging the system with fresh reagents, with only a small deterioration towards the final run. The whole series of palladacycles worked well, with the best results being obtained for cyclopalladated *p,p'*-dichlorobenzophenoxime, which is consistent both with the results on Heck reaction, and with the observations made by other authors (vide infra) that electron-withdrawing substituents in palladacycles, where ver the comparative data are available, usually improve the activity. It should be noted that in this system, a ligand-free palladium salt  $\text{Li}_2\text{PdCl}_4$  is also capable of catalyzing the reaction, but is only half as active as palladacycles.

Palladacycles **21** catalyses the cross-coupling of aryl chlorides with  $\text{PhB(OH)}_2$ , though reasonable results can be obtained only in the presence of TBABr additive, the best solvent being aqueous DMF ( $\text{K}_2\text{CO}_3$ , 5 vol% water, 130–160 °C, 0.5–6 h). Activated chloroarene *p*- $\text{ClC}_6\text{H}_4\text{Ac}$  gave high yields and good TONs (up to 1000 with 0.1 mol% Pd, 160 °C, 0.5 h), and deactivated chloroarenes gave only modest yields and TONs even at 160 °C [82].

Both parent palladacycles **21** and their water-soluble analogues **26** have been shown to be able to perform cross-coupling reactions in water and aqueous solvents with aryl chlorides and bromides. Reactions of aryl chlorides can be run in neat water (0.01–1 mol% Pd,  $\text{K}_2\text{CO}_3$ , TBABr, water, 100 °C), thus actually in a heterogeneous media, as the substrates investigated are generally water-insoluble in the amounts specified (2 mmol, that is several hundreds of milligrams per 7 ml water), and TBABr in this case should perform as phase-transfer catalyst – the role well known in the Suzuki reactions in aqueous systems [33]. The reaction takes from 1 h (0.1 mol% Pd) for *p*-chloroacetophenone to 6 h (1 mol% Pd) for *p*-chloroanisole or *p*-chloroaniline to give good yields of cross-coupling products. Even more remarkable is the fact that the reaction of *p*- $\text{ClPhAc}$  can be run at room temperature in which case aqueous methanol should be taken as solvent. Though the yields are only modest (40–50% after 18 h), particularly for deactivated electron-rich chloroarenes, the overall possibility to perform phosphine-free reaction with chloroarene under so mild conditions is an important message telling essential news about the boundaries of activity in palladium catalyzed systems. Simple palladium salts like  $\text{Pd(OAc)}_2$  or  $\text{Li}_2\text{PdCl}_4$  gave poor results.

Excellent performance has been noted for cross-coupling with aryl bromides. High yields were obtained

both in refluxing water and in aqueous methanol at r.t. with 0.01–0.001 mol% Pd for a wide scope of substrates including activated and deactivated aromatic and heteroaromatic aryl bromides. However, in this case, as has been shown by control runs using *p*- $\text{BrC}_6\text{H}_4\text{Ac}$ , simple Pd salts show equal (in boiling water) or slightly inferior performance in these reactions. The latter result is not surprising as high activity of phosphine-free systems in aqueous solvents has been extensively documented earlier [33]. Besides  $\text{PhB(OH)}_2$  the method is applicable to the cross-coupling with alkylboronic acids, as well as cross-coupling of  $\text{PhB(OH)}_2$  with benzyl or allyl chlorides (Scheme 12) [83,84].

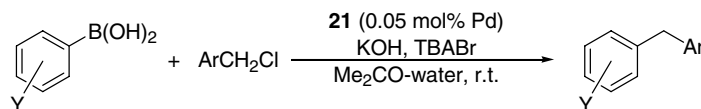
Oxime palladacycles can be immobilized on silica surface through an appropriate trialkoxysilane linker. Such catalyst is useful for performing cross-coupling of *p*-chloro or *p*-bromoacetophenone with  $\text{PhB(OH)}_2$  in Najera's aqueous system (0.6 mol% Pd,  $\text{K}_2\text{CO}_3$ ,  $\text{H}_2\text{O}$ , 100 °C) to give high yields even after eight recyclings of solid phase. No leaching of active Pd to liquid phase has been noted. This is thus a unique case when a supported palladacyclic catalyst seems to be reluctant to release Pd [85,86].

Cyclopalladated benzophenoxime has been found to be effective in alkoxy carbonylation of aryl iodides to give the respective alkyl benzoates in high yield [87]. Convenience of palladacycle is in its high stability towards CO atmosphere, no palladium black deposition occurs even at elevated temperatures. It should be noted that fast deactivation of catalyst due to formation of Pd black is a common cause of poor yields in alkoxy carbonylation catalyzed by less stable phosphine free complexes.

Thus, it should be concluded that oxime derived palladacycles show unusually high performance (remarkable activity with aryl chlorides, enhanced recyclability of supported catalyst) which cannot be fully rationalized within the paradigm, in which palladacycles are regarded as a source of low-ligated Pd(0). Further examination of these systems is thus highly desirable.

### 5.3. Miscellaneous CN-palladacycles

A number of CN-palladacycles have been proposed for standard Heck reactions with iodoarenes. As soon as iodoarenes can be readily processed using the simplest Pd salts, the use of more sophisticated catalyst for this purpose is of no clear practical perspective, and should



Scheme 12.

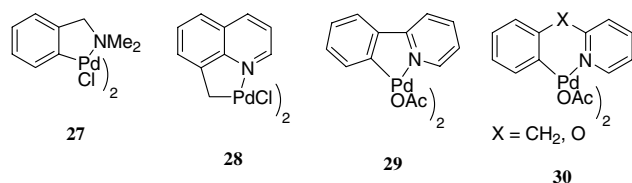


Fig. 10.

be regarded only to provide some clues about functioning of Pd catalysts.

When a wide selection of palladacycles including cyclopalladated benzylamines, pyridine and quinoline derivatives (e.g. **27–30**, Fig. 10), were tested in Heck reaction of iodobenzene and ethyl acrylate or styrene (0.1 mol% Pd, Bu<sub>3</sub>N, DMA, 85 °C), all gave similarly high, nearly quantitative yields. Activated bromoarene can be processed at 140 °C, bromobenzene is also reactive though high yields were not reached for it. High TON values (10<sup>5</sup> at 85 °C, 2 × 10<sup>6</sup> at 140 °C for iodobenzene, 4 × 10<sup>4</sup> for *p*-bromoacetophenone) were observed [15].

Cyclopalladated benzylamines were later studied in more detail and wider assortment including ferrocene derivatives (e.g. **32**, Fig. 11) in the reaction of PhI with methyl acrylate, though under more harsh conditions (140 °C, DMA, Et<sub>3</sub>N). Quantitative yields and high TONs were recorded for all complexes (0.001 mol% Pd, 99–100%, TON 100,000). However, with very low loadings of palladacycles (0.00001 mol%) an apparent difference between dimeric complexes and monomeric complexes (e.g. **27** vs. **31**) has been noted, the latter being markedly more active (yields 31–34% vs. 91–96%, TONs 3 × 10<sup>6</sup> vs. 9 × 10<sup>6</sup>, 11 h). This difference is most likely to be attributed not to monomeric/dimeric nature, but to the presence of extra ligand PPh<sub>3</sub> that might have played an important role in the stabilization of active zero-valent form of Pd at low concentrations. Electron rich iodoarenes (*p*-iodophenol and *p*-iodotoluene) can also be processed in high yields and TONs up to 10<sup>4</sup>–10<sup>5</sup>. Bromobenzene was not reactive (<1% conversion), other bromides were not studied [88].

A wide series of palladacycles derived from 1-arylpyrazoles **33** or 2-arylbenzothiazoles **34** (Fig. 12) were shown to possess high catalytic activity at yet lower temperatures in the reaction of butyl acrylate with iodobenzene. With 1 mol% of palladacycle in DMF the reaction

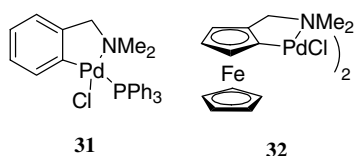


Fig. 11.

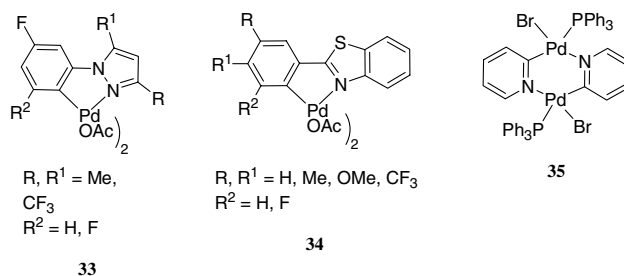
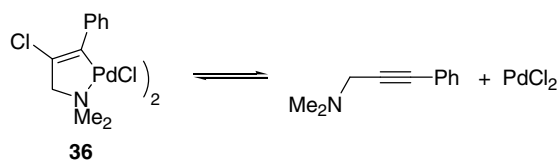


Fig. 12.

gave high yields already at 70 °C, provided that potassium or sodium formates be used as bases. K<sub>2</sub>CO<sub>3</sub> can also be used though the reactions were slower, and NaOAc being a poor base. Under such differentiating conditions palladacycles exhibited markedly different activity, with those bearing electron-withdrawing F or CF<sub>3</sub>-substituents in the ring bonded to Pd, giving better results. This substituent effect has been attributed to the weakening of C–Pd bond, thus facilitating the release of catalytically active species. Favorable effect of formates along with this observation could be interpreted in favor of Pd(0) species, possibly nano-particles, as active pre-catalysts. High TONs of 2,000,000 were obtained at 100–110 °C (5 × 10<sup>-5</sup> mol% Pd), further confirming that the complexes effectively work as pre-catalysts at lower temperatures than the majority of other palladacycles.

2-Bromopyridine readily gives binuclear palladacycle **35** with two palladium atoms per cycle in the reaction with Pd(PPh<sub>3</sub>)<sub>4</sub> (toluene, 90 °C, 4 h). Such complexes are known since early 80s, and already then were used as catalyst precursors for the cross-coupling of Grignard reagents with chloropyridines, possibly the earliest mention of the use of palladacycles in cross-coupling chemistry [89]. This complex later has been shown to be formed in the cross-coupling reaction of 2-bromopyridine with PhB(OH)<sub>2</sub> catalyzed by Pd(PPh<sub>3</sub>)<sub>4</sub>. The complex was employed for cross-coupling reactions of various aryl bromides including deactivated and sterically hindered ones (2-bromoanisole, 2-bromo-*m*-xylene) under remarkably mild conditions (0.2 mol% Pd, Na<sub>2</sub>CO<sub>3</sub>, aq. THF, 60 °C) to give good yields of the respective biphenyls, and modest TONs of 10<sup>2</sup> order of magnitude in anaerobic atmosphere. The addition of extra amounts of PPh<sub>3</sub> inhibited the reaction. Pre-activation mechanism has been proposed involving the release of monophosphine Pd(0) complex from the palladacycle [90]. Given the strictly anaerobic conditions, such complex indeed may survive during several hundred catalytic cycles, and deliver enhanced activity. Common triphenylphosphine complexes of Pd (e.g. Pd(PPh<sub>3</sub>)<sub>4</sub>, PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub>) are unable to perform Suzuki reaction with such substrates under so mild conditions.

Essential lowering temperature of reaction depends on the possibility of palladacycle to readily release Pd.

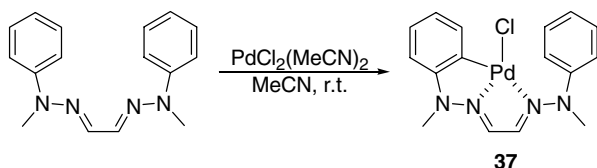


Scheme 13.

An interesting example of such labile palladacycles is aliphatic system derived from aminoalkynes by the addition of  $\text{PdCl}_2$ . In DMSO solution the formation of palladacycle is reversible (Scheme 13). This complex (**36**) catalyzes the standard reaction of  $\text{ArI}$  with butyl acrylate or styrene (DMA, NaOAc, TBABr). The complex is operative even at room temperature, though with much higher Pd loadings (1 mol%). The best result is 76% after 48 h. At 50 °C near to quantitative yield can be obtained with 0.1 mol% Pd. Activated bromoarenes are as well reactive, giving modest to good yields with 1 mol% Pd at r.t. Impressive TONs ( $10^6$ ) and high yields are obtained at 150 °C, showing that high stability of palladacycle is not an absolute requirement for achieving high TONs [91].

The most unusual results were published on the application of glyoxal bis-hydrazone ligands for Suzuki reaction. Both the mixture of Pd salt ( $\text{PdCl}_2$  or  $\text{Pd}(\text{OAc})_2$ ) with the ligand, or preformed palladacycle **37** (Scheme 14) effectively catalyze cross-coupling reaction of aryl bromides, including deactivated ones, with  $\text{PhB}(\text{OH})_2$  and other boronic acids at room temperature in aqueous DMF with  $\text{Cs}_2\text{CO}_3$  base. The palladacycle is formed by room temperature reaction, which is not surprising, as the palladation of electron-rich phenyl ring in hydrazone should be very facile. With 2 mol% Pd the reactions give high, usually near to quantitative yields of cross-coupling products even with *p*-bromotoluene and *p*-bromoanisole, and the reactions took only 3 h (30 min in the case of *p*-bromotoluene). Pd loading can be reduced to 0.05 mol% at the expense of reaction time. TON optimization has not been undertaken [92].

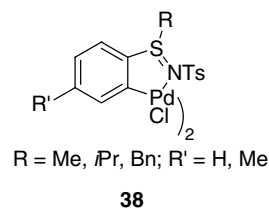
The ability to process unactivated bromoarenes at room temperature at practically relevant rate (1 mmol is quantitatively processed within 15 min to 3 h) places this system among the most potent catalytic systems for Suzuki reaction published up to now, including both phosphine-free and phosphine-assisted catalysts. In the domain of palladacyclic catalysts, this catalyst shares



Scheme 14.

the top row with Najera's oxime palladacycle system treated above. It draws attention that both systems are aqueous, performed either in neat water, or in solvent with high water content (DMF–water = 2:1 v/v), thus linking this chemistry to well-known phosphine-free aqueous catalytic systems for Suzuki reaction [33].

A series of sulfur-containing NC-palladacycles **38** obtained from sulfilimines are capable of catalyzing cross-coupling of unactivated aryl bromides with  $\text{PhB}(\text{OH})_2$  (NaOAc, toluene, 110 °C). Surprisingly, the reaction is reported to take place also in water, though bromotoluene is insoluble in it and no phase-transfer or amphiphilic agent is present. This system resembles that reported by Najera et al. using oxime-derived palladacycles (vide infra), which, however, required TBABr for operation. With PhCl only low yields (20–30%) were recorded [93]. The same palladacycles catalyze cross-coupling of iodoarenes with phenylacetylene or propargylic alcohol in copper-free system (0.25 mol% Pd,  $\text{Et}_3\text{N}$  as solvent, 80 °C, 12 h, yields 84–88%). Low yields were obtained from PhCl or PhBr [93]. The homocoupling reaction can as well be catalyzed by sulfilimine palladacycles in the presence of hydroquinone as reductant ( $\text{K}_2\text{CO}_3$ , hydroquinone, NMP, 125 °C, 24 h) in modest yields (35–48%) [93].

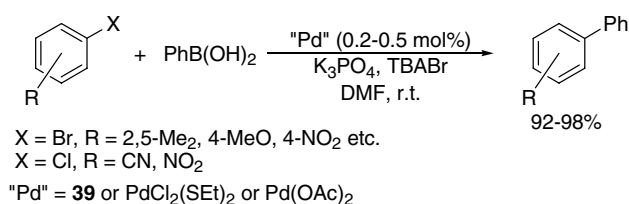


## 6. CS- and CO-palladacycles

Benzylsulfide palladacycles **39** showed modest activity (in comparison with best CP and CN-palladacycles) capable to catalyze Heck reaction of iodoarenes with styrene or acrylates at 140 °C ( $\text{Et}_3\text{N}$ , DMA) with TONs up to  $5 \times 10^4$ . Higher TONs of  $10^6$  order of magnitude can be obtained at the expense of yield. Bromoarenes, both activated and unactivated, as well as activated chloroarene *p*-nitrochlorobenzene require the addition of TBABr, higher temperatures up to 170 °C, and NaOAc as base to give yields not exceeding 60–70% and TONs up to  $3 \times 10^4$  [94]. These palladacycles are, however, more active in Suzuki reaction. High yields of cross-coupling products are formed with activated and unactivated bromoarenes with 0.002–1 mol% Pd, with TONs up to  $4 \times 10^4$  at 130 °C. Preparatively useful procedure applicable to a wide scope of iodo- and bromoarenes (including electron-rich and sterically

demanding ones) and activated chloroarenes requires 0.2–0.5 mol% Pd and 0.2 equiv. of TBABr to give near to quantitative yields after 2–4 h at 130 °C – among the best results (not in the sense of records, but in the sense of fullness of scope and consistency of yields obtained for different substrates) obtained for palladacycle pre-catalysts in Suzuki reaction. Even unactivated aryl chlorides react under these conditions, though the yields are only modest. Most interestingly, the same catalytic system works at room temperature for the same scope of substrates, only with extension of reaction time to 38 h [95]. Soon it was shown that in the describes system ( $K_3PO_4$  as base, TBABr additive, DMF) similar or even identical results can be obtained with simpler palladium sources,  $PdCl_2(SEt)_2$  or  $Pd(OAc)_2$  [96]. Both give a fast reaction at 130 °C or slower, but still giving high yields of cross-coupling products, reaction at room temperature. While at 130 °C all three sources of Pd work without noticeable differences, at room temperature palladacycle furnishes quantitative yields in 2–3 times less time (Scheme 15). Such results surely call for more extended evaluation of preparative potential of this system. What causes a simple Pd salt to effectively perform as catalyst in cross-coupling of unactivated substrates? Is it  $K_3PO_4$  which was later shown to be particularly effective in a phosphine-free protocol of Heck reaction [24], the addition of TBABr or DMF solvent, or a lucky combination of all these? So far, there are no answers.

The mechanism of action of SC-palladacycles is most likely to be the same as of other palladacyclic systems – release of zero-valent palladium. Thus, the use of S-chiral version of palladacycle **39** (Fig. 13) for reaction of aryl bromides or iodides with dihydropyrene, a standard model for enantioselective Heck reaction, gave racemic product [97].



Scheme 15.

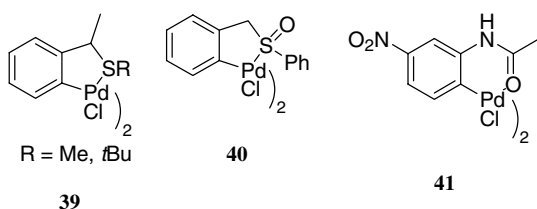


Fig. 13.

Among other SC-palladacycles, sulfoxide-derived complex **40** showed modest activity in the reaction of  $PhB(OH)_2$  with *p*-bromotoluene (0.1 mol% Pd,  $K_2CO_3$ , toluene, 110 °C, 3 h, yield 54%) [93].

CO-palladacycles so far attracted little attention. Some simple ones, e.g. cyclopalladated acetanilide **41**, were shown to behave similarly to common CN-palladacycles in standard Heck reactions [15].

## 7. Pincer palladacycles

Bis-chelated palladacycles of XCX (X = P, N, S) type, usually referred to as "pincer" [98–100] should be treated separately, as due to their exceptional stability, such complexes are likely candidates for observing unusual catalytic chemistry with pincer structure being retained. If there is Pd(II)/Pd(IV) mechanism for Heck reaction or cross-coupling anywhere, then pincer complexes are the right place to look at.

The first pincer palladacycles **42**, **44** (Fig. 14) which were studied in such reactions were PCP-complexes, which were shown to catalyze Heck reaction of aryl bromides and iodides with styrene or acrylates in near to quantitative yields and high TONs of the order of  $10^5$  for both iodoarenes, activated bromoarenes and PhBr itself ( $3.5\text{--}9 \times 10^{-5}$  mol% Pd,  $Na_2CO_3$ , DMA, 140 °C) [101]. Competitive runs with a series of aryl halides showed the accelerating effect of electron-withdrawing substituents, with a low value of reaction constant  $\rho = 1.39$ . This, as is evident from comparison with non-pincer palladacycles (see above), is a normal reactivity profile not requiring new mechanisms. The palladacycle, however, according to NMR, remains unchanged after the reaction, which would have been essential evidence in favor of palladacycle-retaining mechanism. This evidence, unfortunately, remains the sole one, and thus cannot be treated as decisive. No details on how NMR monitoring was performed has been given, and it is very likely that modest sensitivity of NMR dictated that this test has been accomplished with a rather high initial loading of catalyst making probable that 5–10% of it decomposed to release catalytic species.

The other anomaly observed for Heck reactions catalyzed by PCP-palladacycles is the inhibition of reaction by 1,4-dienes, or inability to perform intramolecular Heck reaction onto 1,4-diene moiety (Scheme 16) [102]. It, however, stops attention that the comparison was made to standard phosphine-assisted intramolecular Heck protocol, which: (a) requires high loading of Pd catalyst (5 mol% vs. 0.5 mol% used in palladacycle-driven experiment); (b) standard procedure uses 3 equiv. of phosphine ligand, while in the palladacycle-driven experiment the ratio Pd:phosphine is dramatically lower. In the well-established protocols for intramolecular Heck reactions phosphine ligands are essential to block



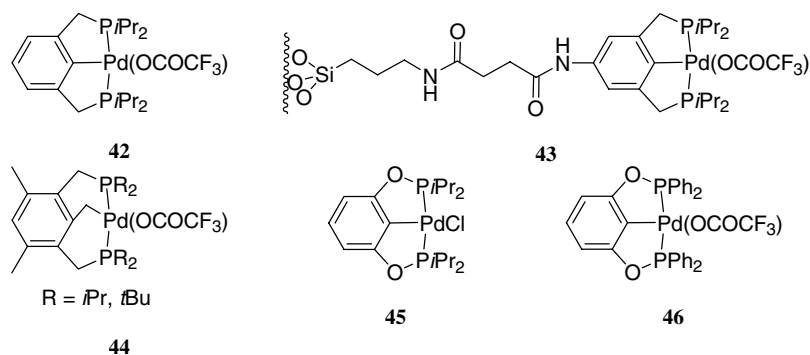
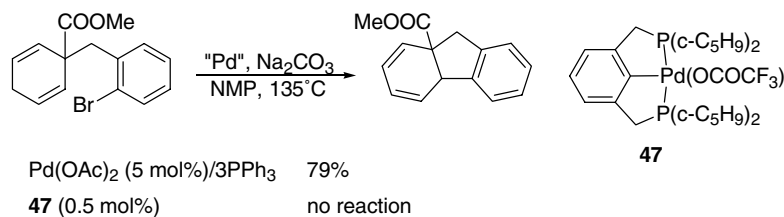


Fig. 14.



Scheme 16.

unwanted pathways and coordination to substrate. The same is true for intermolecular Heck reactions with complex olefins (1,4-diene is likely to belong to such). Thus, this test should also hardly be regarded as decisive to reveal unusual reactivity in pincer-complex catalysis.

More complex bi- and trinuclear pincer complexes were obtained and showed moderate level of activity in standard Heck reactions [103].

PCP-pincer has been immobilized on silica (**43**). The supported complex catalyzed the reaction of iodoarenes, activated and unactivated bromoarenes with acrylates or styrene in high yields (Na<sub>2</sub>CO<sub>3</sub>, NMP, 140 °C) [104]. This work provides important evidence on the difference of pincer palladacycles from monocyclic ones. Indeed, the reactions required rather high loading of Pd (of the order of 0.1–1 mol%) and showed that the supported catalyst suffered partial leaching of Pd. Still, the catalyst can be successfully reused from 2 to 5 times, with each run taking 24 h of heating at 140 °C. This should mean that pincer complex is indeed robust enough to endure harsh conditions with only partial decomposition. Thus, most probably, pincer complexes release catalytically active Pd much more slowly than

simple palladacycles, and immobilization of pincers with careful optimization of conditions to ensure acceptable level of leaching and reaction rate, can indeed bring forward practical catalysts.

PCP-pincer built over fully aliphatic backbone **48** (Fig. 15) showed only standard activity in Heck reactions of aryl iodides and bromides with acrylates or styrene. High yields and TONs reaching  $5 \times 10^5$  require prolonged heating at 140–160 °C (Na<sub>2</sub>CO<sub>3</sub>, NMP) [105].

Phosphite-derived pincer PCP-palladacycles are, similarly to PC-monopalladacycles, less expensive than their bis-phosphine counterparts. Such pincer complex **49** has been described by Shibasaki and co-workers [106] and exploited in Heck reaction of iodoarenes with butyl acrylate (Na<sub>2</sub>CO<sub>3</sub>, NMP, 140 °C) giving near to quantitative yields and very high TONs of 10<sup>6</sup> order of magnitude. At 180 °C further increase of TON to 10<sup>7</sup> order of magnitude can be reached. It is interesting that the presence of hydroquinone is required for effective functioning of this system. The role of this additive is likely to help palladacycle to release active Pd(0) species acting as a reducing agent, similarly to homocoupling procedures [60] (vide infra).

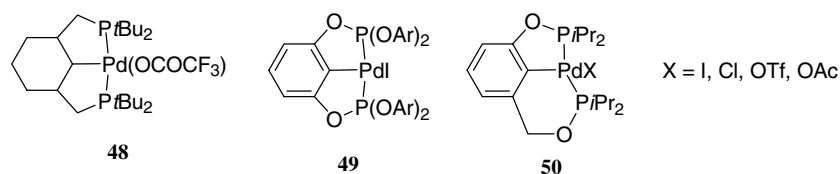


Fig. 15.

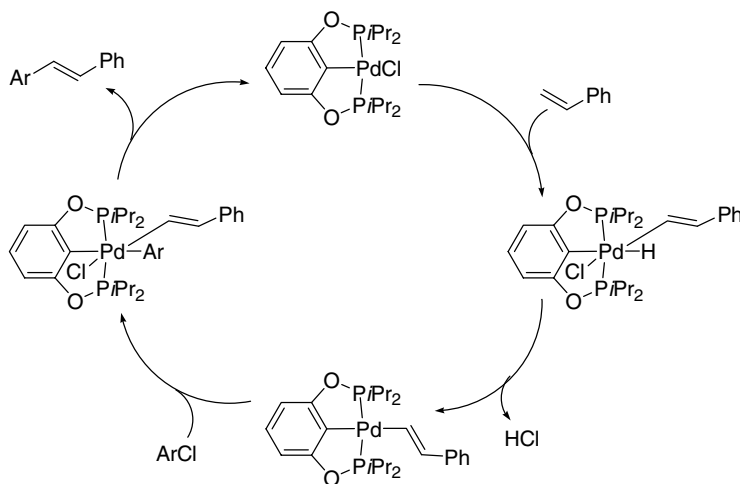


Pincer complex **45** belongs to phosphinite palladacycles, similar to monopalladacycle **13**. It can be used for arylation of disubstituted olefins, such as methacrylate or  $\alpha$ -methylstyrene by bromo or iodoarenes ( $\text{Na}_2\text{CO}_3$ , DMF, 180 °C). The reactions were run under very harsh conditions, and are often accompanied by diarylation [107]. This palladacycle showed a remarkable activity for the arylation of styrene by aryl chlorides, both activated and unactivated. Under harsh conditions (0.67 mol% Pd, CsOAc or  $\text{Cs}_2\text{CO}_3$  or  $\text{Na}_2\text{CO}_3$ , dioxane, 180 °C) full conversion took one day. The reaction took place even at 120 °C, though took 5 times more time [108]. Therefore, this system should be regarded as one of the most reactive among palladacycle-based catalysts for the processing of chloroarenes. Milstein's pincer palladacycle **42** was reported to be unable to perform this task effectively. A Pd(IV)/Pd(II) mechanism rooted in the well-known Shaw's catalytic cycle [47] has been proposed (Scheme 17). This unusual mechanism, however, remains to be substantiated by experimental evidence.

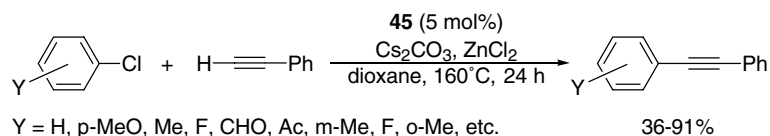
Palladacycle **45** proved to be capable of catalyzing cross-coupling of phenylacetylene with aryl chlorides, among the first examples of successful involvement of unreactive chloroarenes into Sonogashira reaction. The addition of 10 mol% of  $\text{ZnCl}_2$  is required to achieve good yields. The reaction requires prolonged heating at high temperature, and high loading of palladacyclic catalyst (Scheme 18) [109].

Another phosphinite palladacycle **46** was tested in cross-coupling of aryl bromides with  $\text{PhB(OH)}_2$  (0.01–0.0001 mol% Pd,  $\text{K}_2\text{CO}_3$ , toluene, 130 °C) to give high yields and TONs of the order of  $10^5$  for activated bromoarene [110]. With unactivated bromoarene the yields are, however, modest to good, and high TON values can be obtained only for incomplete conversion runs. Chloroarenes are either unreactive or give poor yields. Thus, the performance of this pincer catalyst should be considered to be inferior to simpler Bedford's phosphite monopalladacycle **13**: though the former have shown higher TONs for *p*-bromoanisole, the latter consistently gives high yields with all sorts of bromoarenes.

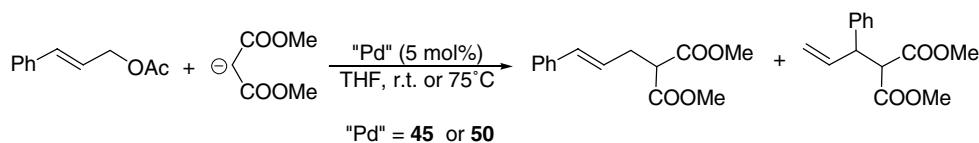
Phosphinite pincer palladacycles were found to be effective in the alkylation of malonate anion by allylic acetates (Scheme 19). The reaction takes place under mild conditions and gives high yields of substituted malonates with “non-rearranged” product prevailing [111]. Unlike Heck and cross-coupling reactions in which there is only a marginal dependence of reaction outcome on variations of palladacyclic catalyst structure, here an apparent sensitivity to catalyst was observed. Non-symmetrical palladacycle **50** was much more active than symmetrical ones, such as **45** (the former operated at room temperature, the latter – at 75 °C). Moreover, weaker anionic ligands gave strong acceleration ( $\text{OTf} > \text{Cl} > \text{I}$ ), and the addition of silver salts to palladacycles with  $\text{X} = \text{Cl}$  was also beneficial.



Scheme 17. The tentative Pd(IV)/Pd(II) mechanism of pincer palladacycle catalyzed Heck arylation.



Scheme 18.



Scheme 19.

Might it be Pd(IV)/Pd(II) mechanism with intact palladacycle as catalyst that is operating in this case? There is a strong temptation to believe so – if it were not for that most likely there possibly is no such mechanism for allylic substitution. Indeed, the allylic substitution is commonly believed to be initiated by oxidative insertion of Pd(0) to allylic substrates to give  $\eta^3$ -allylic Pd(II) complex. As far as we know there is no evidence that Pd(II) can take part in oxidative addition to allylic compounds to give  $\eta^3$ -allylic Pd(IV) complexes. Moreover, there is a useful analogy in Pt chemistry, which is much more liable than Pd to form +4 oxidation state. Allylic substitution can be catalyzed by Pt complexes, but – only through the same standard mechanism as is operating in palladium catalyzed reaction, that is via Pt(0)/Pt(II) species ([112] and references therein). Certainly, such indirect evidence cannot altogether rule out Pd(IV)/Pd(II) mechanism, but certainly makes it not the first option to be considered. If so, this reaction proceeds through a common Pd(II)/Pd(0) mechanism, which shows that pincer palladacycles may be subject to partial or full cleavage under very mild conditions, in this case, possibly by the action of malonate, which is taken in excess. We can suggest the following mechanism of how Pd(0) forms, taking into consideration the influence of the complex structure and ligand properties of anionic ligand (Scheme 20).

Pincer NCN-palladacycles were not so far well studied in palladium catalyzed chemistry. The simplest bis-benzylamine pincer **51** (Fig. 16) catalyzes Heck reaction of iodoarenes with methyl acrylate ( $\text{Et}_3\text{N}$ , DMF, 110 °C), though is ineffective with bromo and chloroarenes, even activated. A more complex molecule **52** showed somewhat higher activity being able to involve activated bromoarenes with as high as 0.01 mol% Pd catalyst loading. It is interesting to note that for this complex a dynamic behavior has been established in NMR spectra, associated with the exchange of two nitrogens [113]. Thus, at moderate temperatures (below 90 °C) a sponta-

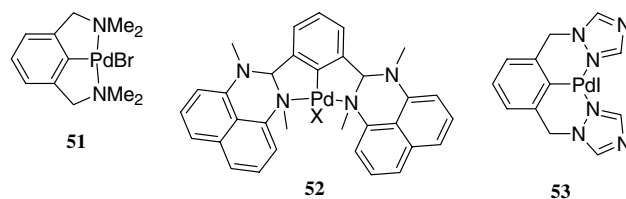


Fig. 16.

neous rupture of Pd–N bond and re-coordination with other nitrogen atom take place, once again showing that the stability of palladacyclic and even pincer structures should not be overestimated.

Bis-triazole compound **53** has been shown to catalyze Heck reactions of acrylate with activated aryl bromides and chlorides (1 mol% Pd, NaOAc, DMA, 125–140 °C). The addition of TBABr or 18-crown-6 considerably improve the yields [114].

Pincer SCS-palladacycles **54** (Fig. 17) were shown to catalyze Heck reactions of iodoarenes with acrylates, acrylonitrile, styrene or 4-vinylpyridine (0.1 mol% Pd,  $\text{Na}_2\text{CO}_3$  or  $\text{Et}_3\text{N}$ , NMP, 110 °C) in high yields. By attaching this various polymeric supports (PEG, poly(*N*-isopropylacrylamide), polyisobutylene) gave recyclable catalysts **55** useful for the same Heck reactions. At least 3 recyclings were possible, with interesting trend of steady increase of reaction yield with each next recycling. The catalysts failed to catalyze the reactions with aryl bromides, even at 140 °C, though only unactivated ones were tried. Besides Heck reaction, cross-coupling of the

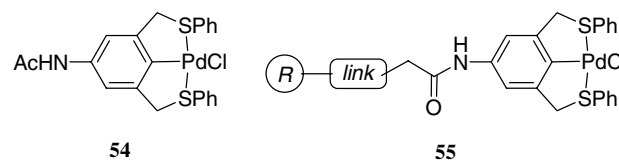
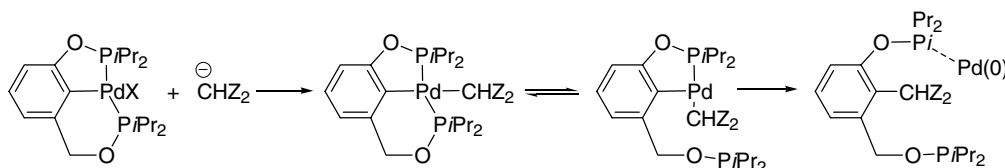


Fig. 17.

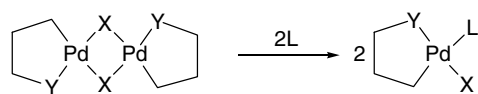


Scheme 20.

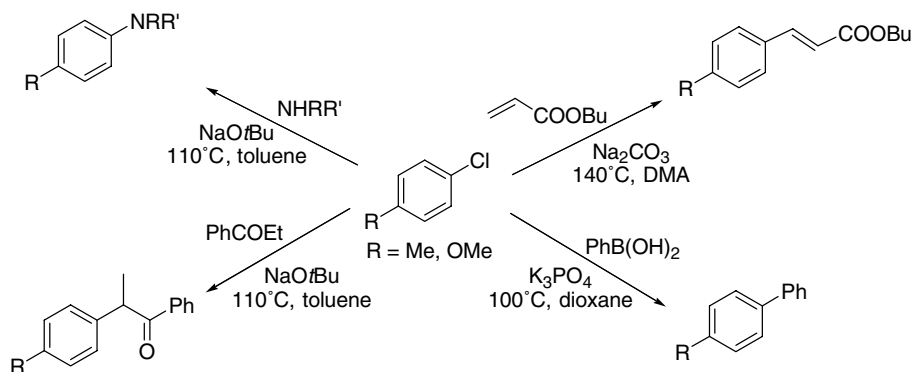
same aryl iodides with  $\text{PhB(OH)}_2$  can be similarly realized [115–117].

## 8. Hybrid palladacyclic catalysts

Huge base of experimental data gained so far, thus, rather clearly show that the scope of catalytic activity of palladacycles in Heck and cross-coupling reactions is roughly equivalent to the scope of the so-called phosphine-free chemistry. It involves in the first place aryl iodides and activated aryl bromides. Unactivated aryl bromides and activated aryl chlorides also belong to this scope, though in this case elevated temperatures and careful optimization of reaction conditions are required to find the optimal regime of reaction. However, apparently palladacyclic catalysts alone are helpless if the modulation of activity of Pd catalyst is required, e.g. in the case of unactivated aryl chlorides, as well as the reactions of aryl bromides at lower temperatures. In such cases special bulky and electron-rich phosphine ligands are indispensable. An interesting approach is to combine palladacycles as convenient Pd sources and special ligands in catalytic system. Particularly interesting is to use preformed 1:1 complex – a hybrid of palladacyclic Pd source and potent monodentate ligand (Scheme 21). The advantages are: (i) the economy on expensive ligand, as in this case the exactly 1:1 Pd:L stoichiometry is furnished by the structure of hybrid complex, while preformed non-palladacyclic complexes usually possess  $\text{PdL}_2$  stoichiometry; (ii) free phosphines usually require special handling techniques, while hybrid complexes are air and moisture insensitive compounds which can be stored without rigorous precautions.



Scheme 21.



Scheme 22. Cross-coupling reactions catalyzed by complexes **56** and **57**.

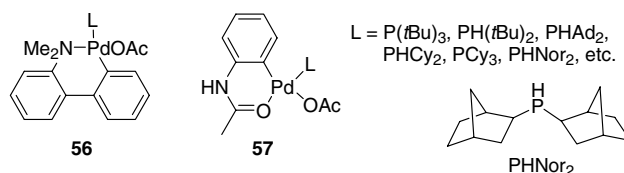


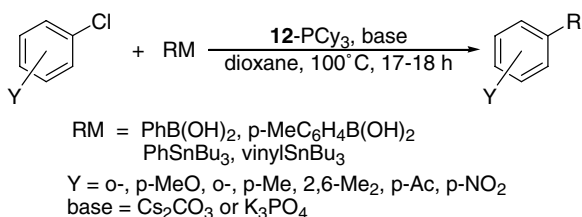
Fig. 18.

The following work illustrates this nicely. Thus, Heck reaction with chloroarenes (*p*-chlorotoluene or *p*-chloroanisole) can be successfully carried out in the system consisting of Pd source (either palladacycles or Pd salts) and secondary phosphine in DMA (140 °C, NaOAc, 20 h). Palladacycles alone failed to catalyze the reaction with chloroarenes. It should be noted that in all cases the system palladacycle-phosphine were, at best, equivalent or inferior to the catalyst formed by the same phosphine and  $\text{PdCl}_2$ . Thus, e.g. the reaction using di-*tert*-butylphosphine gave 77% yield with  $\text{PdCl}_2$ , versus 46–77% obtained with various palladacycles. Reaction using *Pt*-Bu<sub>3</sub> gave quantitative yield with  $\text{PdCl}_2$ , and no more than 71% with palladacycles. Convenience of palladacycles becomes more evident when monomeric monophosphine palladacyclic complexes **56**, **57** (Fig. 18) are obtained and used.

These complexes are air stable, and thus are more convenient in handling than toxic pyrophoric volatile phosphines. The results obtained with such complexes are remarkable, as high to quantitative yields of Heck reaction with butyl acrylate, cross-coupling with  $\text{PhB(OH)}_2$ , arylation of morpholine, *N*-methylaniline or propiophenone were reported (Scheme 22) [118].

A remarkable system of this sort has been described by Bedford et al. Aryl chlorides can be made to react with  $\text{PhB(OH)}_2$  in the presence of Bedford's phosphite palladacycle **12** and  $\text{PCy}_3$  (Scheme 23).

Deactivated chlorides, such as *p*-chloroanisole give quantitative yields of cross-coupling product in the presence of as low as 0.01 mol% Pd ( $\text{Cs}_2\text{CO}_3$ , dioxane, 100 °C, 17 h) and TONs up to 34,000 (with 0.001–0.002



Scheme 23.

mol% Pd). In this case the mixture of Pd(OAc)<sub>2</sub> and phosphite/PCy<sub>3</sub> is apparently inferior furnishing meager 12% yield. Also, the use of such ligands as *Pt*-Bu<sub>3</sub> or PCy<sub>2</sub>(*o*-biphenyl) is ineffective. Reactive chloroarenes can be quantitatively processed with as low as 0.0001 mol% Pd with amazing TONs of up to 1,000,000. The 1:1 ratio of Pd:PCy<sub>3</sub> should be maintained, as with higher amounts of phosphine the reaction is inhibited. Excellent performance of this system has been explained by an optimal combination of high catalyst longevity and high activity, PCy<sub>3</sub> ligand accounts for the latter, while  $\pi$ -acidic ligand phosphite stabilizes the zero-valent Pd without suppressing its reactivity [64].

Partial hydrolysis of phosphite ligands as such or in the coordination shell of Pd can lead to the formation of new ligands P(H)(O)(OR)<sub>2</sub>. However, a careful study of possible influence of such ligands on the catalytic activity of palladacycle-based systems revealed no unambiguous trends [119].

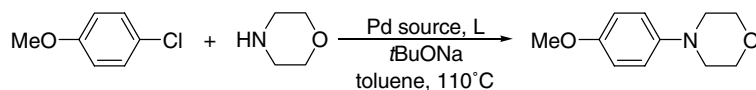
Benzylamine CN-palladacycles, such as **27**, can be adjusted to cross-coupling of aryl chlorides exactly as phosphite-based palladacycles, by coordination of PCy<sub>3</sub> ligand to monomeric complex (0.001–1 mol% Pd, Cs<sub>2</sub>CO<sub>3</sub>, dioxane, 100 °C). With low Pd loading (0.01 mol%) palladacycle gave much better results than Pd(OAc)<sub>2</sub> taken as Pd source in this system [120]. Deactivated substrate *p*-chloroanisole gives quantitative yields of cross-coupling product with 0.1 mol% Pd, with TONs reaching 8000. The reaction can be run at 60 °C with 1 mol% Pd (97% yield, 17 h). Interestingly, 2-chloroanisole and 2-chlorotoluene give even better results, with near to quantitative conversions already with 0.01

mol% Pd. Activated substrate *p*-chloroacetophenone is quantitatively processed with 0.001 mol% Pd, thus showing impressive TON of 99,000. Addition of extra amount of PCy<sub>3</sub> inhibits the reaction [121].

Benzylamine palladacycles has also been used for amination of deactivated chloroarene (Scheme 24). In this case *Pt*-Bu<sub>3</sub> should be used as “working” ligand to obtain high yield (92% after 17 h) and selectivity, using 0.1 mol% Pd as palladacycle. Again, the use of Pd(OAc)<sub>2</sub> as Pd source with all other conditions taken the same, gave dramatically worse results (1% conversion) [120].

Monophosphine cyclopalladate complexes are also more effective in the reactions of deactivated aryl bromides than the respective dimeric complexes. A number of such hybriide complexes of CN-palladacycles with PPh<sub>3</sub>, PCy<sub>3</sub>, AsPh<sub>3</sub>, and other phosphines has been studied in the reaction of *p*-bromoanisole with PhB(OH)<sub>2</sub> (K<sub>2</sub>CO<sub>3</sub>, toluene, 110 °C, 17 h), all showing TONs of 10<sup>5</sup> order of magnitude measured for 0.0001 mol% Pd loading and constant reaction time across all reactions [120]. The activity of phosphine-containing complexes was usually higher than that of dimeric palladacycles, though the difference was not large enough to allow for sound conclusions. Deactivated bromoarene and relatively mild reaction conditions imply the use of effective supporting ligand, and phosphine-free catalysis in such case is not efficient. However, the data show that the trends of catalytic activity are actually very uneven and unpredictable. For example, the effect of anionic ligand may be much greater than the effect of the change of phosphine or monomer/dimer, as the data of Fig. 19 show (yields of cross-coupling product is given, catalyst loading 0.0001 mol% Pd).

Moreover, the behavior of this system is strongly dependent of initial catalyst loading (Scheme 25). Thus, with 0.0001 mol% Pd and at 110 °C the complex **A** with PPh<sub>3</sub> ligand showed better performance than the complexes with substituted phosphines. On the other hand, with 0.1 mol% Pd at 80 °C complex **B** with less basic phosphine outperformed both **A** and **C** by more than 2 times, being the only catalyst giving high conversion



Scheme 24.

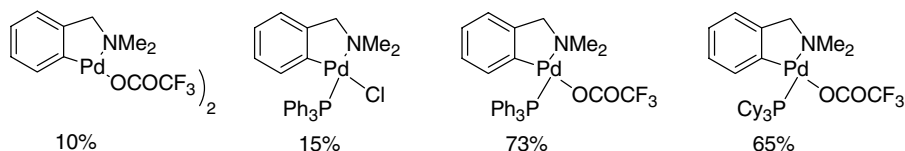
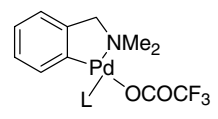


Fig. 19. Comparison of yields of cross-coupling products obtained with different benzylamine palladacycles.

Conditions	catalyst		
	A	B	C
$10^{-4}$ mol% Pd, 110 °C	73	35	51
$10^{-1}$ mol% Pd, 80 °C	40	85	25


  
 L = PPh<sub>3</sub>, **A**  
 P(C<sub>6</sub>H<sub>4</sub>CF<sub>3</sub>)<sub>3</sub>, **B**  
 P(C<sub>6</sub>H<sub>4</sub>OMe)<sub>3</sub>, **C**

Scheme 25. Yields of cross-coupling products in the reactions catalyzed by different palladacycle-triarylphosphine complexes.

and yields, while the other two suffered full deactivation at less than 40% conversion.

Such irregular behavior betrays the systems involving multi-step reactions with very complex interplay of kinetic parameters. Comparison between such systems hardly can be helpful, unless a very rigorous standardization of all involved parameters is undertaken.

Carbene ligands are advertised as a substitute for electron-rich bulky phosphines owing to their capability to drive the reactions with unactivated aryl chlorides and bromides (cf. e.g. [13,122–124]). Not surprising then that these ligands have been successfully introduced into hybrid palladacycle-carbene catalysts. Such complexes were used for Heck reaction between bromoarenes and acrylate or styrene (0.0016 mol% Pd, K<sub>2</sub>CO<sub>3</sub>, TBABr, NMP, 130–150 °C) giving high yields with both activated and deactivated substrates, and TONs of 10<sup>4</sup> order of magnitude. The same system with higher catalyst loading (0.01 mol% Pd) can be applied to activated aryl chlorides giving Heck products in good yields

and TONs of 10<sup>3</sup> order of magnitude [125]. Oxime **58** and benzylamine **59** palladacycles (Fig. 20) gave different yields/TONs, though the difference was not high, not systematic to allow for meaningful speculations. In several cases comparative runs with hybrid complexes of oxime palladacycle with PPh<sub>3</sub> and P(OEt)<sub>3</sub> gave similar results (variations of yields in the range 65.7–93.2% in one example and 73.2–92.6 in the other example). Hybrid palladacycle-carbene complexes **58**, **59** were also tested in the reaction of aryl halides (iodides, bromides, activated chlorides) with PhB(OH)<sub>2</sub> (0.01–0.1 mol% Pd, K<sub>3</sub>PO<sub>4</sub>, DMF, 120 °C) to give modest to good yields [125].

Hybrid complexes with bulky carbene ligands **60** were shown by Nolan et al. to catalyze the cross-coupling of arylboronic acids with aryl chlorides at room temperature. Unactivated and sterically hindered aryl chlorides react readily to give near to quantitative yields of biaryls (2 mol% Pd, *t*-BuONa, *i*-PrOH, r.t., 0.75–2 h). The palladacycle thus release Pd(0) under very mild conditions.

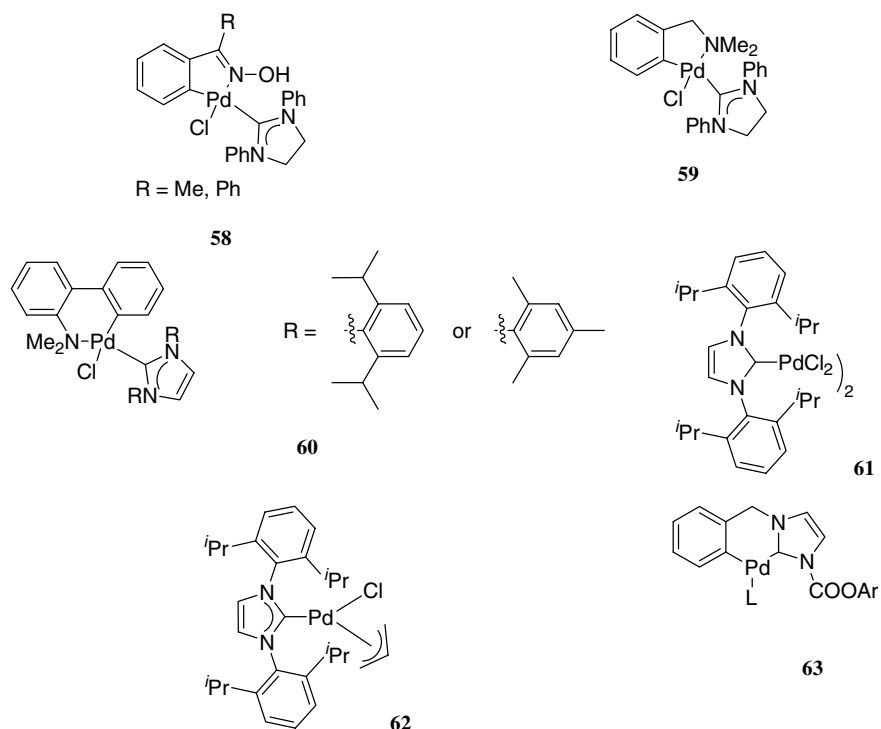
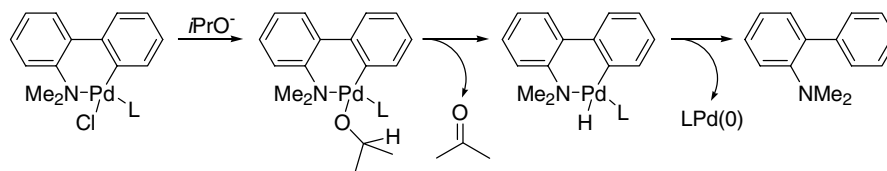


Fig. 20.



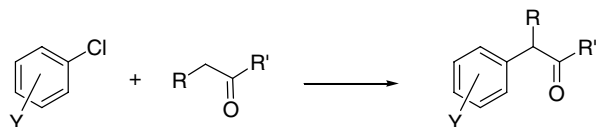


Scheme 26.

The following mechanism is postulated involving  $\beta$ -hydride elimination from isopropoxide complex (Scheme 26) [123].

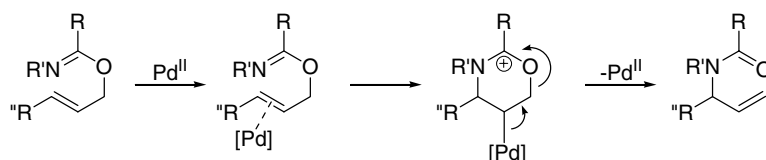
The same complexes are capable to readily catalyze the arylation of amines and ketones by a wide range of aryl chlorides and triflates under mild conditions. The complex **60** with more bulky *N,N'*-bis((2,6-diisopropylphenyl)-imidazol)-2-ylidene ligand was more active than its counterpart with mesityl groups. A wide scope of amines, including primary and secondary aliphatic, cyclic, and aromatic ones, could be arylated in high yields (1 mol% Pd, *t*-BuONa, dioxane, 70 °C) [126]. However, a simple dimeric complex **61** of the same carbene [Pd(L)Cl<sub>2</sub>]<sub>2</sub> is equally effective in these reactions under practically identical conditions (1 mol% Pd, *t*-AmOK, DME, 80 °C) [127,128]. Similar situation has been reported for arylation of ketones. Both palladacyclic complex **60** and  $\pi$ -allyl complex **62** without palladacyclic part [129] were active in arylation of ketones by aryl chlorides. (Scheme 27).

The generation of interesting palladacycles **63** incorporating carbene residue and their use in Suzuki cross-coupling reactions of iodoarenes and activated bromoarenes has been described recently, but no evidence in favor of proposed structure has been given [130].



**Method A:** **62** (1 mol%), *t*BuONa, THF, 50–70 °C  
**Method B:** **60** (1 mol%), *t*BuONa, dioxane, 70 °C

Scheme 27.



Scheme 28.

## 9. Palladacycles as structurally defined catalysts

The discussion would be incomplete if examples of essentially different behavior, when palladacycles indeed behave as structurally defined species in catalysis, not be given. There are a few reactions catalyzed by palladacycles, which present a sharp contrast to those treated above, particularly in what concerns high sensitivity to structural features. Palladium in paladacyclic environment possess Lewis acidity, and thus can behave as mild acidic catalysts. Thus, Overman et al. discovered a highly effective and enantioselective rearrangement of allylic amidates (Scheme 28), catalyzed by cationic palladacycle catalysts derived from ferrocenyloxazolines **64** (Fig. 21).

Trifluoroacetate ligand is essential for conversion, and the respective iodide is not reactive. Stereoselectivity is determined by full stereochemical configuration of ligand, with R<sub>3</sub>Si substituent at ferrocene being essential for high enantioselectivity (*ee* up to 96% were reached) [131]. Bis-palladacycles **65** gave similar results [132].

Palladacycle built over cobalt sandwich **66** showed outstanding performance in the rearrangement of allylic trichloroacetamides, for which all other Pd catalysts failed. Practically quantitative yields and *ee* (up to 96%) of trichloroacetamides of allylamines were received (5 mol% Pd, CH<sub>2</sub>Cl<sub>2</sub>, r.t. – 38 °C, 18 h), thus giving an effective general route to chiral allylamines (Scheme 29) [133]. The same catalyst is useful for the rearrangement of allylic *N*-aryltrifluoroacetamides. In both cases the catalyst was highly reactive even without prior exchange of chloride for better nucleofuge (trifluoroacetate or triflate) [134].

Lewis acid catalysis by cationic palladacycles has been also employed in carbanionic condensations. cationic pincer palladacycles effectively catalyze Michael addition at room temperature (Scheme 30) [135], including enantioselective version [135b]. Globular macromo-



phosphine-free systems, both what these catalysts can do, and what they can not do. From phosphine-derived palladacycles to phosphite-derived ones, then to palladacycles altogether lacking phosphorus, further on – to chelated complexes without C–Pd bonds, the road run gradually revealing that all these compounds have more in common. This is the capability to catalyze common C(sp<sup>2</sup>)–C(sp<sup>2</sup>) and C(sp)–C(sp<sup>2</sup>) bond forming reactions very efficiently (in high yields and enormous TONs) – with aryl iodides and electron-poor aryl bromides, less efficiently and under harsh conditions – with all other aryl bromides and electron-poor aryl chlorides. The reactions, particularly with more challenging substrates, are very sensitive to conditions, solvent, base, even concentrations, which means that if optimal conditions were not established in a given work, the reported performance of a given system might be heavily underestimated. The reactions are very sensitive to such components of reaction mixture which may help to support Pd(0) in the absence of good ligands. Polar coordinating solvents (DMF, DMA, NMP, etc.), hard bases (acetate, phosphate, preferably in soluble form, as e.g. Cs salts or anhydrous K<sub>3</sub>PO<sub>4</sub>), special additives (quaternary ammonium halides are the most popular) all may play the role of transient Pd(0) stabilizers.

Palladacyclic catalysts are thus a subclass of phosphine-free catalysts. This remains true even if palladacycle itself is formed from phosphine precursor. There is no reliable data showing that the behavior of such palladacycles is essentially different from non-phosphine palladacycles. This may be associated with two factors: (i) phosphines used for the construction of palladacycles are rarely effective ligands themselves, particularly in 1:1 ratio; (ii) palladacycle-catalyzed reactions are very often carried out in air atmosphere, in which phosphines should be rapidly oxidized to the oxides and thus withdrawn from catalytic cycle.

The role of palladacycle is to feed Pd(0) to the reaction mixture. The release of Pd(0) from palladacycle is effected not by thermal destruction, as was commonly believed at early stages of palladacycle catalysis, but by reactions with components of reaction mixture. This process is often rather slow, that accounts for one of main advantages of palladacycles. The ability of palladacycles to release Pd(0) not instantaneously but slowly helps to suppress unwanted inactivation processes, the nucleation and growth of large inactive Pd metal particles.

Phosphine-free chemistry is of limited scope. Special ligands (bulky electron-rich phosphines or heterocyclic carbenes) are essential and should be used if: (i) a control of selectivity (regio- or enantioselectivity) is desired; (ii) reactions with aryl bromides or chlorides are to be performed reliably and under mild conditions; (iii) C-heteroatom or C(sp<sup>3</sup>)–C bond forming reactions are to be performed.

Special ligands can be combined with palladacycles into hybrid catalysts, which retain the advantages of both. Such complexes are usually not more active than non-palladacyclic complexes with the same ligands, but may be useful because of: (i) convenience of handling (insensitivity to air or moisture); (ii) economy on expensive phosphine or carbene ligands. Hybrid catalysts are likely to deliver the most active mono-ligated Pd(0)L complexes to the reaction mixture.

At last, it should be noted that though the predominate majority of data gained on palladacycle catalysts can be interpreted within a common approach implying full disassembly of palladacyclic structure at the catalyst pre-activation stage, the other approaches should not be discarded. Special attention should be given to those instances of the behavior of palladacyclic complexes, which fall outside of the common paradigm, e.g. when a given complex retains activity under milder conditions, lower temperatures, or delivers good yields with unactivated aryl chlorides, or is applied to less common reactions.

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