High-Turnover Palladium Catalysts in Cross-Coupling and Heck Chemistry: A Critical Overview

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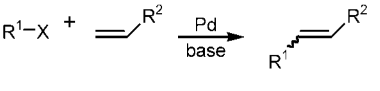
Abstract: This review discusses the problems associated with developing high-turnover catalysts for the cross-coupling and Heck reactions. New developments in the area, principally constituted by palladacycles and coordinatively unsaturated Pd catalysts featuring bulky phosphanes of high donicity, are reviewed from a mechanistic and synthetic standpoint, and compared with more traditional catalysts obtained from conventional mono- and polydentate N- and P-based ligands, as well as Pd catalysts without strong ligands, such as Pd colloids or heterogeneous catalysts. Carbene ligands are also briefly presented. Whereas a single, most promising approach to high-turnover Pd catalysis cannot presently be defined, it is clear that the new "PdL$_1$" catalysts (where L$_1$ is a monodentate bulky P ligand of high donicity) represent the latest, most important development in Pd research, certainly from the standpoint of scope and probably also from the standpoint of efficiency. High turnovers with these catalysts have been described and their use will certainly increase in the next few years. The review ends with a brief discussion containing practical considerations on how to choose a high TON catalyst for a given Heck or cross-coupling reaction of interest.

Keywords: amination; bidentate ligands; carbene ligands; colloids; cross-coupling reaction; Heck reaction; heterogeneous catalysis; ligandless; nanoparticles; palladacycles; palladium; phosphane ligands; turnover frequency (TOF); turnover number (TON)

1 Introduction

As attested to by the many contributions contained in this Special Issue, the Heck reaction [Eq. (1)][1–3] and the cross-coupling reaction [Eq. (2)],[4] two catalytic processes of exceptional scope, comprise a synthetic tool that has reached a high level of maturity.



(1)

$$R^1\text{–}X + R^2\text{–}M \xrightarrow{Pd} R^1\text{–}R^2 \qquad (2)$$

M = MgX, ZnX, BX$_2$,SnR$_3$, SiX$_3$ etc.

During the first two decades since its inception in the late 1960s and early 1970s, the main aim of this research area has been to examine the scope of the new synthetic tool. In the last ten years, on the other hand, considerable attention has also been devoted to mechanistic investigations, as well as to the extension of these methods to carbon-heteroatom bond-forming reactions.[5] However, with the final frontiers, i.e., the catalytic activation of aryl chlorides[6] and the cross-coupling between *sp*^{3}-based partners,[7] beginning to yield under the systematic attacks of Buchwald, Fu, Hartwig and others, some of the interest is shifting toward making these reactions more economical and practical, in order to move them from the academic laboratory to the industrial plant, where they are still rarely utilized.[8–10]

One reason for this state of affairs is the high cost of Pd catalysts, coupled with the fact that the classical catalysts apparently require loads of 1–5% mol to induce effective coupling, and this makes modern homogeneous catalysts clearly unattractive with respect to heterogeneous

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Vittorio Farina was born on June 8, 1953 in Pisa, Italy, and received his B. S./M. S. degree from the University of Pisa, Italy, with Prof. Francesco Pietra (1977). After obtaining a Ph. D. degree from the University of Alberta (1982) with Prof. D. L. J. Clive and a 2-year postdoctoral stay at Cornell University with Prof. J. E. McMurry, Dr. Farina joined the Chemical Process Development group of Bristol-Myers in Syracuse, NY. In 1987, he joined the Antitumor Chemistry Group of Bristol-Myers (later BMS) in Wallingford, CT, where he worked in the areas of drug delivery, prodrugs, and the chemistry of new taxol analogues. In 1993, he moved to Boehringer Ingelheim where, over the next 10 years, he built the department of Chemical Development. In 2003, he became Highly Distinguished Scientist in the same department. His research interests are primarily process development and the scale-up of chemical processes, and also catalysis, asymmetric synthesis and palladium chemistry.

ones, which are readily recovered by filtration and recycled.[11,12] The latter, however, have not quite enjoyed the scope and the versatility associated with their modern homogeneous counterparts.

If the catalytic load of these soluble Pd catalysts could be reduced to a significantly smaller level, homogeneous catalysis would be much more practical and may completely supplant heterogeneous catalysis. Although many techniques for attaining high turnover number (TON) using heterogeneous catalysts coupled with recycling strategies have been described, this review focuses on high-turnover catalysts (HTC), i.e., catalysts that possess such longevity and can operate at such low levels that, in principle, they *may not have to be recovered and recycled*.

Practically speaking, any catalyst displaying $>10^3$ turnover number, i.e., a catalyst that can lead to quantitative conversion of starting materials at a load of 0.1% mol, will be defined here as an HTC. Both homogeneous and heterogeneous catalysts (and some borderline cases) will be described, as long as high TONs can be achieved in a batch mode, i.e., without recycling. The issue of recycles will be briefly addressed only as it pertains to the mechanism with which some heterogeneous catalysts operate.

In addition to cost, a second problem associated with organometallic catalysis is contamination of the product by the metal, and this, at least in the case of pharmaceuticals, has to be tightly controlled, usually to levels below 10 ppm. It is easy to see that both problems (cost and contamination) will be automatically eliminated with catalysts that display TONs of 10^5 or higher. Any Pd-based methodology with TONs of 10^5-10^6 and adequate turnover frequency (TOF) will be very practical for pharmaceutical and fine chemical applications. Beyond this level it is rather meaningless, from a practical standpoint, to venture.

It is easy to convince ourselves that this is the case by creating a hypothetical example of an active pharmaceutical ingredient (API) produced at an output of 10 tons/year at a total production cost of \$ 1,000/kg. Assuming a similar MW for API and catalyst (which is not unreasonable given the complexity of modern ligands), one will need only 10 g of the catalyst per year if the TON is 10^6. Even at a high assumed price (e.g., \$ 100,000/kg), the cost associated with the catalyst will be \$ 1,000/year, i.e., 0.01% of the total cost of the API. Likewise, the contamination problem will be non-existent even if the whole catalytic load ends up in the API.

On the other hand, Pd catalysts with these very high TONs are unknown for practical industrial applications. With a more reasonable goal of 10^3 TONs, the same analysis shows that the catalyst, at the above price, would contribute \$ 100/kg to the cost of the API, i.e., 10%, which is unacceptably high. Catalysts operating at these TONs will have to contain inexpensive ligands (i.e., cost \$ 10,000/kg or less) and/or be easily recycled, in such a way as to reduce the total cost contribution by the catalyst to $<1\%$. Strategies to recover the spent metal will also have to be generated, in order to contain costs.

In 1995, Herrmann, Beller and co-workers announced what was then considered to be a "new principle" in palladium catalysis: the use of palladacycle **1** (the Herrmann–Beller palladacycle, or HBP) afforded unprecedented TONs. For example, in the Heck coupling of *p*-formylbromobenzene with acrylates, TONs of about 2×10^5 were achieved.[13]

Very quickly, palladacycle research became a hot field, with many groups entering the stage and introducing their own variants of the HBP prototype. Higher and higher TONs were reported for some very simple Heck and Suzuki couplings.[14–17]

These early studies must be credited with focusing the attention of the organometallic community on the search for high TONs. Very soon, other paradigms began to emerge which also yielded high TONs. In fact, some simple, well-known catalysts even exceeded the performance of the typical palladacycle in some cases. The purpose of this review is to examine critically the field of high-TON palladium research, to present the reader with an overview of the variety of approaches at one's disposal in the development of efficient Pd catalysts, and, whenever possible, to make constructive recommendations on how to use the available literature in order to develop a high-TON catalyst for a specific Pd-catalyzed coupling. The material in this review, which covers the most significant developments in the field until the end of 2003 and some key studies thereafter, is organized according to catalyst type and not according to reaction, because this makes the discussion of the high TON problem simpler and more organized.

2 Different Paradigms in High-TON Research

The study of TONs in palladium-mediated C–C bond formation processes is a very important area of research. The factors that affect overall rates and robustness of the catalysts are, unfortunately, not well understood. Recent literature has been preoccupied mostly with tabulating TONs in a limited set of reactions using a large variety of ligands and catalysts, and also with reaching higher and higher TONs in a number of very simple model systems. Unfortunately, it is not possible to extract a few general rules from this ample body of literature. Although many decomposition modes of Pd catalysts have been elucidated,[18] their role in limiting TON in many specific organic reactions described in this review has not been clearly examined. Without a full knowledge of catalyst decomposition pathways, it is difficult to predict maximum TONs. In the future, any quantitative kinetic work aimed at balancing knowledge of catalytic parameters *vs.* catalyst decomposition kinetics will help substantially in reaching the goal of designing high-TON catalysts for every application.

The recent flurry of TON measurements has certainly highlighted a previously under-appreciated fact: for "easy" reactions, such as the Heck and Suzuki coupling of aryl iodides and activated aryl bromides with acrylates and phenylboronic acid, respectively, virtually any Pd source is capable of reaching extremely high TONs. This is quite interesting, but it helps very little in the way of designing a high-TON catalyst for a very specific, more complex application.

In order to develop a Pd-catalyzed reaction of practical utility, the industrial chemist must start with a clear cost target. If an approximate cost scenario for the final target molecule is known, it is much easier to set a target TON, because the cost of Pd is a given. For most pharmaceuticals, a TON of 10^2 or so may be satisfactory during the early development phase, when the cost of the API is relatively high, but when approaching commercialization a TON of 10^3 or better will be invariably desirable. In the fine chemical industry, even higher TONs may be indispensable.

Upon reading about the fantastic TONs reported in this review (*vide infra*), some readers may believe this target to be within easy reach. Unfortunately, this is not so: in complex synthetic situations, few catalysts achieve TONs of 10^3 in Heck or cross-coupling reactions.[9,10,19–21]

Here are some of the major challenges associated with the development of a catalytic step:

1) *Scope:* The choice of the electrophile may be affected by cost factors. For example, an aryl chloride may be a necessary substrate, thus restricting the field of catalysts to those which can provide C–Cl activation.[6] Alternatively, the desired synthetic pathway may point to a single specific electrophile type (i.e., a cheap sulfonate like tosylate, if the key intermediate is a phenol; triflates are often too expensive to use). In general, the chemist may have little or no leeway in choosing the type of electrophile, thus limiting the field of useful catalysts.
2) *Purity:* Very often a crude electrophile or a crude nucleophile (or both, for a convergent synthesis) are used for obvious cost-related reasons. The development chemist must manage his purification schemes with the goal of attaining a high-yielding, high-TON catalytic step. Very often the TON increases when highly purified coupling substrates are used, but this is usually not practical to do in a manufacturing process that seeks to control costs.
3) *Impurity profile:* Pd-catalyzed reactions that are of industrial utility must minimize side-product formation and yield impurity profiles that can be successfully and reproducibly managed (i.e., reduced) in the subsequent chemical steps or in a purification step. For example, simple lab strategies like using an excess of one of the two reacting partners may not be an option in the plant, and yet driving the reaction to completion may be an absolute necessity if unreacted starting materials cannot be removed by purification.
4) *Throughput:* Reactions on an industrial scale tend to be run under high concentration conditions and in a short time frame. In the pharmaceutical industry, reaction times over 10–12 h are deemed impractical, because in this case the reaction itself may become the bottleneck operation in the production train. In a catalytic reaction, this translates into the necessity of having a catalyst with high TOF. Shorter reaction times can be usually achieved by increasing the catalyst load, but this is undesirable as it increases costs. Therefore, balancing TOFs with TONs can be a tricky enterprise.
5) *Time:* In the pharmaceutical setting, there is a limited amount of time to develop a process, because development strategies often demand a synthesis lock rather early on. To displace a stoichiometric process with a catalytic one, the chemist has to solve the high TON/high TOF problem in a matter of months, not years. Obviously, if the situation looks promising, the catalytic process may be implemented with the expectation of further improvements later on. But if the data are not promising, the catalytic process will be abandoned. Often companies develop "second-generation processes"

> once drug approval is reasonably certain. At this stage, there is usually more time to develop the catalytic process, and once drug dosage and cost are clearly defined, it is much easier to deal with the economic scenario. Nevertheless, even under this scenario there is tremendous urgency: the company must try to register the new process as soon as possible, for obvious financial reasons.

In order to deal with all these problems, many companies have established dedicated catalysis groups. In order to cope with the narrow time frame for catalyst development, high-throughput screening methods are becoming more and more popular.[21]

One of the first academic groups to focus the attention of the chemical community on the importance of developing catalysts with high TONs for palladium-based couplings was the one led by Herrmann. To explain the high TONs observed with the HBP (**1**), Herrmann and co-workers speculated that a novel Pd(II)–Pd(IV) mechanism may be operative.[13] This claim captured the attention of many investigators, and from then on, measuring TONs for Pd-catalyzed coupling reactions, especially using palladacycles, became popular.

Suddenly, new and more effective palladacycles were described, primarily by Bedford,[22] Najera[23] and Milstein,[24] among the many.

Some authors, primarily Santelli,[25] took quite a different approach. Santelli postulated that the Pd center had to be strongly stabilized (by up to 4 phosphine equivalents): regardless of the resting state of the catalyst, decomposition from a Pd(0) species may be involved in limiting the lifetime of the catalyst. Such decomposition, probably due to precipitation of inactive Pd particles (Pd black), may be retarded if the Pd center could be kept highly coordinated. This idea, whatever its merits may be, has yielded TONs of $>10^8$ in some simple couplings and has shown a very broad scope, in fact one of the broadest ones in the field of Pd HTC.

Another very successful approach, which is based on quite a different assumption, utilizes under-ligated Pd catalysts as a compromise between the desire for stability and the need for activity. This approach has been utilized, in conjunction with bulky and/or highly donating phosphorus ligands, in the activation and coupling of aryl chlorides.[26] Its great potential toward a general solution to the problem of high TON is evident, provided the narrow steric windows necessary for effective catalysis can be adequately controlled.[27,28]

Palladium catalysts based on nucleophilic carbene systems are relatively new on the scene, but have already displayed an interesting level of catalytic effectiveness, both in terms of scope and TONs.[29]

Other workers have claimed that, since phosphanes and other ligands all retard catalysis and may be a major cause of catalyst decomposition, we should avoid them completely, and "ligandless" catalysts or colloids should be used. The ligandless approach has been championed for over two decades by Beletskaya [30,31] and Jeffery,[32] and it is extremely successful in a number of cases. Whereas in these early cases the role of colloids remained unrecognized, many workers have been quite successful at creating and stabilizing Pd colloidal nanoparticles, which in some cases achieve high TONs.[33,34] The attractiveness of the "ligandless approach", which is based on *in situ*-generated colloids, is enhanced by the fact that, in those cases where TONs are not quite so spectacular, recovery of the catalyst as Pd black, if necessary, is much easier than when soluble ligands are present.[35]

Finally, some workers have begun to ask the question whether the "traditional" catalytic systems, i.e., $Pd(OAc)_2$ plus PPh_3 or $(o\text{-Tol})_3P$, are really catalytically so inefficient because of their notorious thermal instability. While there is no question that phosphorus ligands can be labile under some coupling conditions,[18] the relationship of this instability to catalysis has not been thoroughly investigated.[36]. Indeed, some cases are known where ligand decomposition produces more active catalysts. An intriguing example is provided by Hartwig's Q-phos ligand.[37] Unfortunately, recovering ligands at the end of the reaction in the search for catalyst decomposition pathways is not always practical and is rarely done.

In any case, literature evidence, which is over 20-years old, suggesting that the classical Heck conditions are conducive to high TONs ($>10^5$),[38] has received insufficient attention. As a consequence, classical palladium-phosphane systems have not been tested systematically for maximum TONs.

Lately, palladacycles immobilized on polymer supports have appeared in the literature. This seems at odds with the discovery that these catalysts are not directly active, but function as "pre-catalysts"; palladium leaches out into the solution to become activated.[39]

Finally, some heterogenized classical systems, i.e., N,N-bidentate ligands, display very high TONs in palladium catalysis even without recycle.[40] Analogously, simple heterogeneous Pd/C catalysts can display very high TONs, even though slow leaching limits their recyclability.[41]

Some of the catalysts and ligands that have been proposed as solutions to the high-TON problem and are discussed in this review are synoptically represented in Figure 1.

3 Palladacycle Pre-Catalysts[14–16]

3.1 Mechanistic Considerations

It is instructive to discuss recent mechanistic work at the outset, in order to develop a working model of pallada-

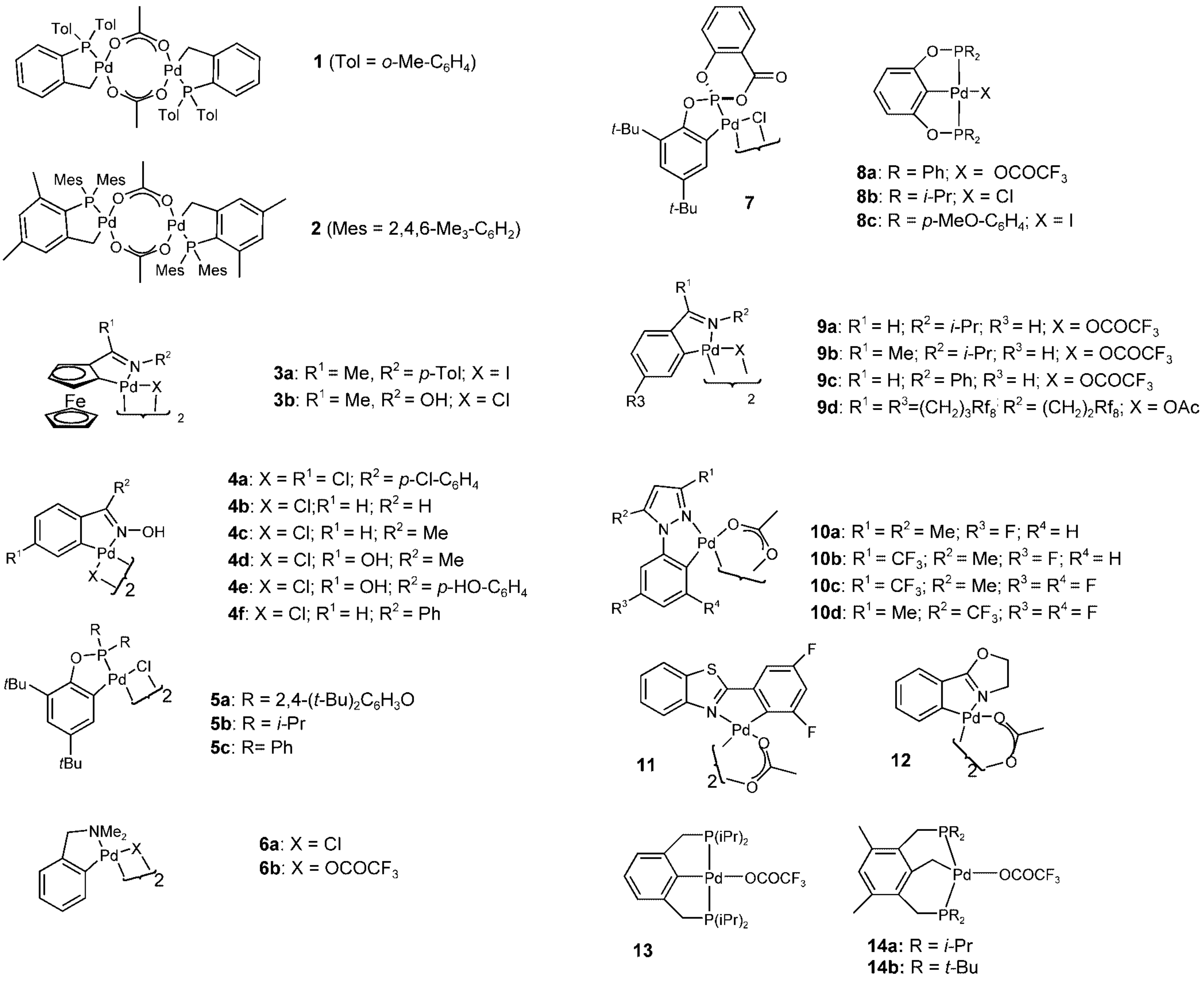


Figure 1.

cycle catalysis. This will aid comprehension and will facilitate the discussion of the high TONs observed and the limitations of this new class of Pd catalysts.

The original paper by Herrmann et al. described species **1** and **2** as very active catalysts,[13] and made the intriguing suggestion that, because the catalyst could be recovered unchanged in good yield at the end of the reaction, the active species had to be a Pd(II) catalyst, which had to operate through a Pd(II)/Pd(IV) cycle, i.e., *a new mechanism in Heck chemistry.* Under this paradigm, the accelerating effect displayed by (o-Tol)$_3$P in many Pd-catalyzed reactions is due to the *in situ* formation of this highly active palladacycle, and not to steric effects, i.e., its large Tolman cone angle.

Following Herrmann's suggestions, Shaw entertained speculations as to how the Pd(II)/Pd(IV) cycle may operate in a Heck reaction,[42,43] and this was compounded later on by a computational study mapping the presumed new mechanistic cycle.[44] Independently, Jensen et al. proposed, without experimental support, a new peculiar "reverse mechanism" for some new pincer complexes that was centered on a very unusual C–H activation of the alkene acceptor during a typical Heck reaction.[45]

However, after these initial speculations, all experimental evidence available to date speaks against such Pd(II)/Pd(IV) cycle. Soon after Herrmann's first disclosure, Hartwig provided, in a probing study, two general pathways whereby palladacycles such as **1** do readily lead, as expected, to Pd(0) species (Schemes 1 and 2).[46]

Thus, **1** reacts stoichiometrically with diethylamine with breakage of the acetate bridge, leading to monomeric species **3.1**. This, when treated with base and additional free ligand, brings about reaction and formation of the "traditional catalyst" Pd[(o-Tol)$_3$P]$_2$, **3.4**. In the case of a cross-coupling reaction (e.g., Stille coupling),

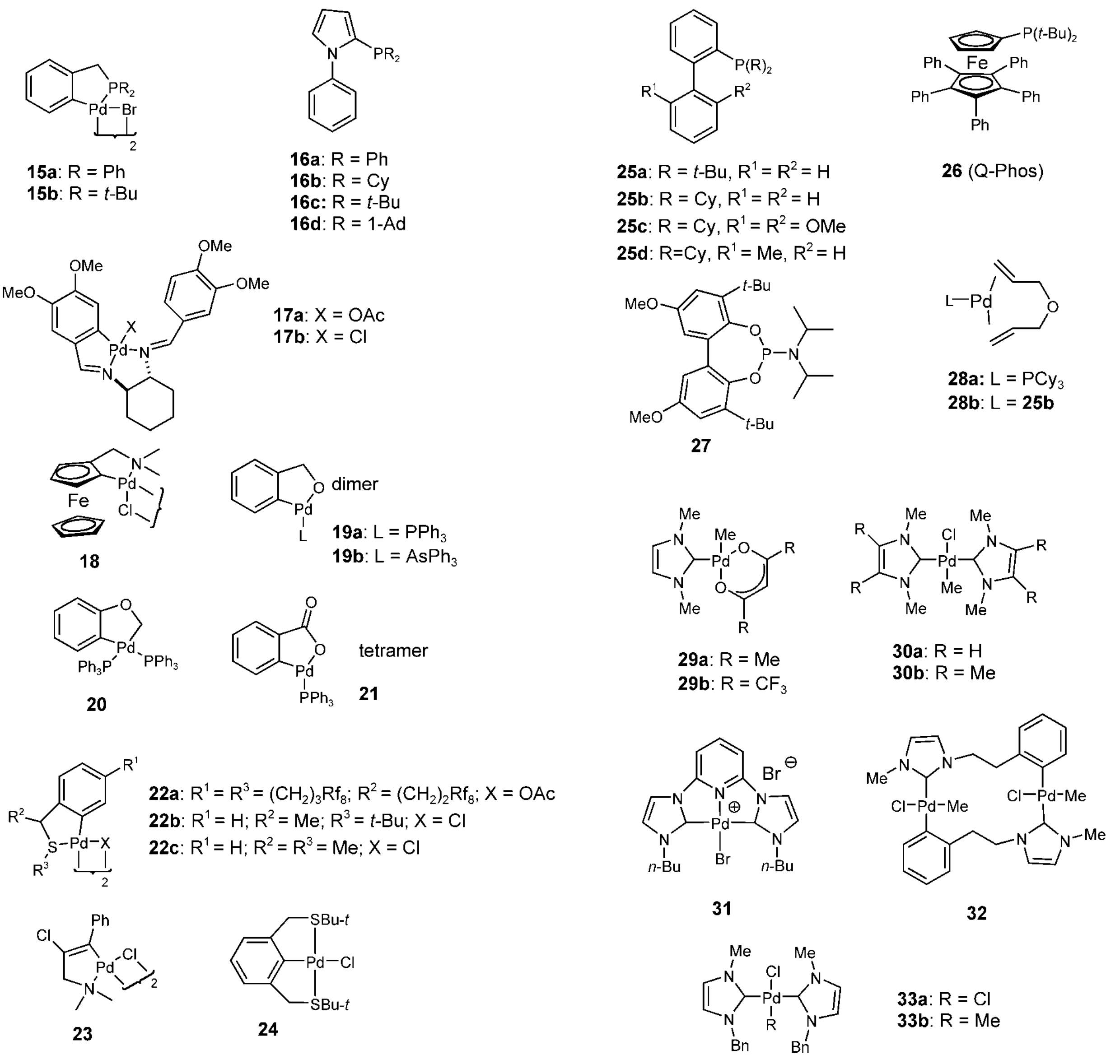


Figure 1. (cont.)

transmetalation of **1** with aryltin **3.5** readily produces an underligated Pd(0) species **3.6**, which is rather unstable in the absence of extra ligand, disproportionating to elemental Pd and, presumably, the catalytically active PdL_2 species.

With these results in hand, it is hard to escape the conclusion that, contrary to what had previously been assumed, palladacycles like **1** are only bystanders or "dormant species", i.e., they are not involved in the real catalytic cycle. If this is true, **1** may be a source of coordinatively unsaturated "PdL_1" species, and the relative success of tri-*o*-tolylphosphane as a ligand would indeed be due, as traditionally thought, to its large cone angle and ready dissociability.

Hartwig's experiments (Scheme 2) would also suggest that species like **1** may lead, upon activation, to considerable amounts of colloidal Pd(0) which, contrary to the early assumptions, must also be considered as a potential source of catalysis. Finally, activation of **1** by transmetalation produces a new ligand (see **3.6**), and this suggests that the active catalyst in cross-couplings employing **1** *is actually different in each case*, depending on the activating species used in the particular experiment. This may potentially complicate the mechanistic picture and also the interpretation of the TON data reported in the literature. In the light of this observation, such TONs must be interpreted with caution, and certainly not generalized.

Although no mechanism for the activation of **1** during a Heck coupling has been provided, it is rather easy to imagine olefin insertion in the C–Pd bond as the activating step. Such C–Pd stoichiometric insertions across

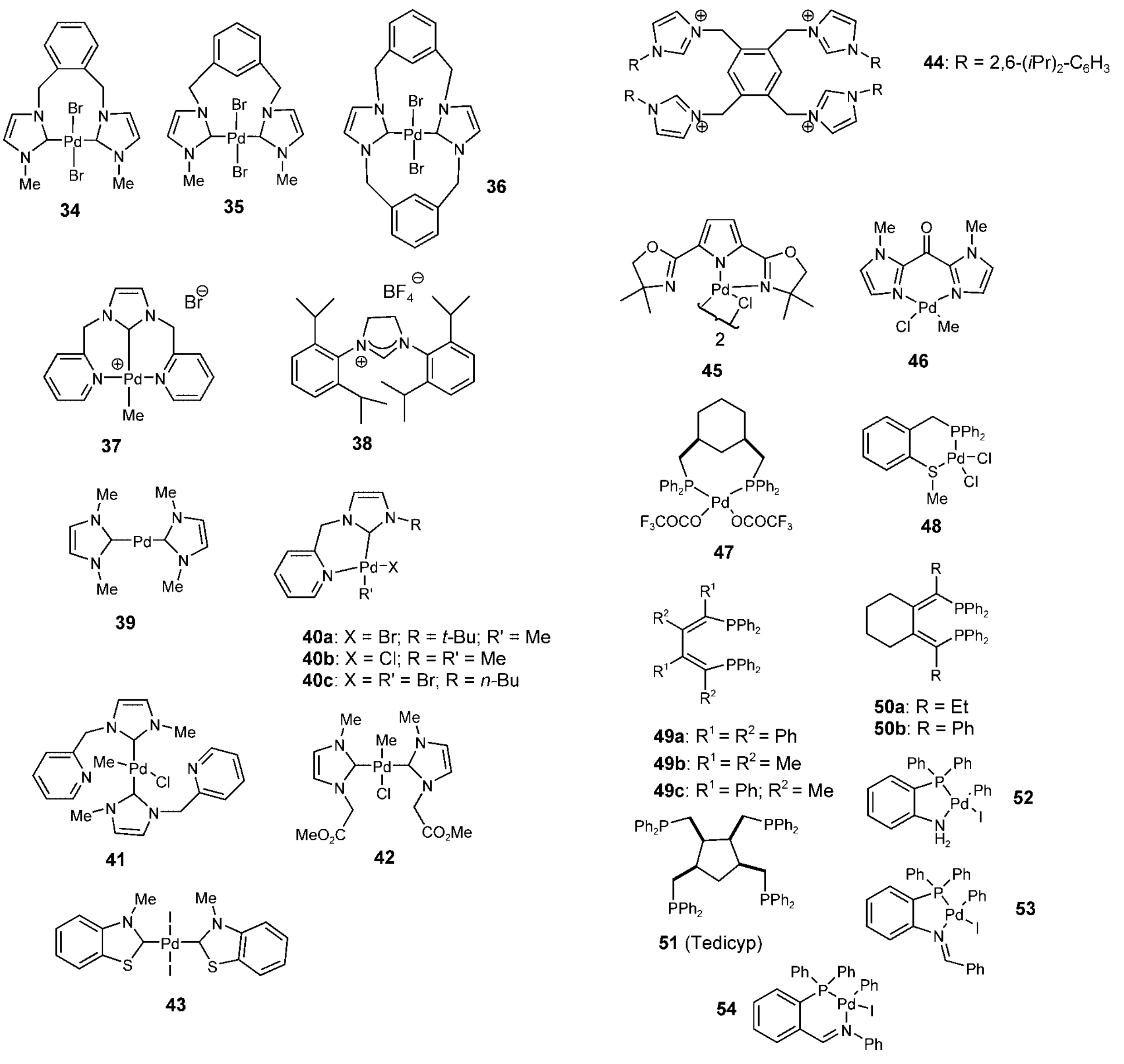


Figure 1. (cont.)

multiple bonds are well precedented in palladacycle research.[47] On the other hand, oxidative addition of the aryl halide to **1**, which would be an essential first step of the Pd(II)/Pd(IV) cycle, has never been clearly documented.

After Hartwig's study, the first kinetic data with **1** were reported by Beller et al., and in most cases an induction period was detected.[48] Later, Nowotny et al. provided conclusive evidence that polymer-supported palladacycle **3.7** (Scheme 3) is labile under typical Heck conditions, and that the active catalyst is soon transferred into solution. When the reaction is run at 140 °C, the kinetics are sigmoidal, showing that the active species slowly builds up in solution, then decomposes. In addition, on a second recycle all the activity is in solution, probably as colloidal Pd(0) stabilized by the large excess of the amine hydroiodide formed, and no activity is left with the polymer support. These observation are quite consistent with **3.7** (in this case a C,N palladacycle) being a slow source of active colloidal Pd particles.[39]

Not surprisingly, when palladacycles incorporating chiral centers were used in an attempt to perform a Heck reaction enantioselectively, the products obtained were totally racemic.[49]

More recently, Blackmond, Pfaltz and co-workers have developed a detailed kinetic model of a Heck reaction catalyzed by dimeric palladacycles such as **1**.[50,51] Although the steps leading from **1** to the active Pd(0) species are ill-defined, from a kinetic standpoint the activation steps can be lumped together into a single parameter (k_{diss}). The model explains the experimental ob-

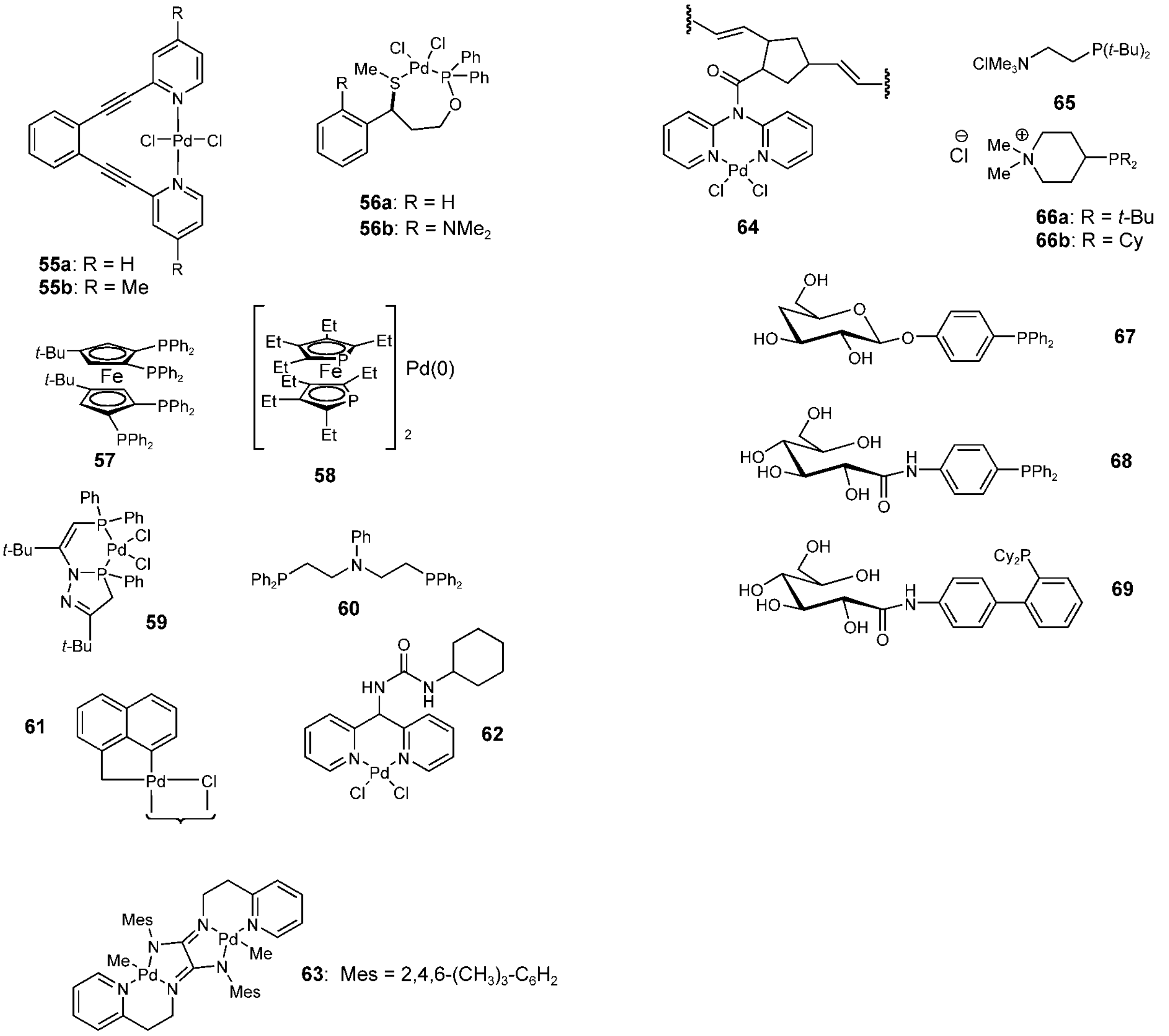
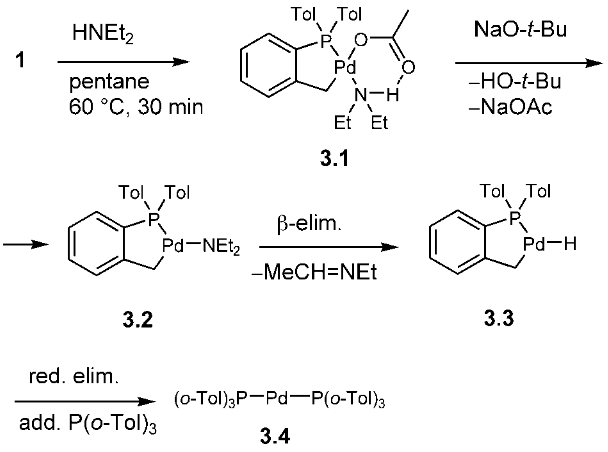


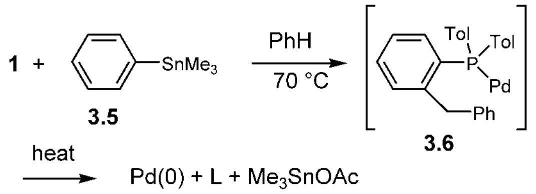
Figure 1. (cont.)

servations and is consistent with an *active species being slowly metered out into the reaction.* Thus, the rate-determining step is outside the true catalytic cycle, and this has important consequences for the use of these catalysts. As the authors comment, the TOFs and TONs with dimers such as **1** would appear even more impressive if based on the actual amount of Pd present in the catalytic cycle itself. In addition, due to the dimeric nature of the pre-catalyst, the relative catalytic efficiency is higher at lower concentrations. An important point made by the authors is the following: studies that employ similar initial Pd concentrations but widely different concentrations of *catalytically active Pd species* must be compared with great caution, especially if TONs and TOFs are the focus of the discussion. This point was recently expanded by de Vries et al., who noted a better TON for Pd(OAc)$_2$ the lower the concentration. The reason for this behavior is the formation of Pd(0) black at higher Pd concentrations, a simple kinetic consequence of the mechanism of Pd(0) aggregation in solution.[52] The study also showed that the active species derived from **1** is a monomeric ligand-free Pd(0) species. *TOFs and TONs that are essentially identical to those displayed by palladacycle **1** can indeed be obtained simply by using low concentrations of Pd(OAc)$_2$.* These studies finally clarify why pre-catalysts such as **1** have been reported as having higher TONs than the more classical catalysts: the catalyst concentrations were kept identical in the comparisons. The problem with this deceptively sound approach is that, whereas Pd(OAc)$_2$ pre-catalyst usually *enters the catalytic cycle quickly*, **1** *releases the active species at a rate that is inferior to the catalytic rate,* and this is equivalent to a slow metering in of the active catalyst, thus making such comparison incorrect. When these comparisons are made under the kinetically appropriate conditions, de Vries showed that **1** behaves as a typical "ligand-less" Pd(0) catalyst.[52]

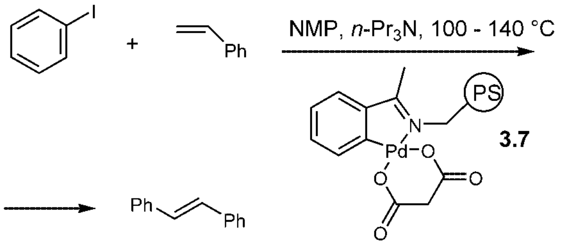
A more recent thorough study by Herrmann and Böhm has confirmed that **1** and Pd(0) plus (*o*-Tol$_3$)P lead to the same active species under similar conditions.



Scheme 1.

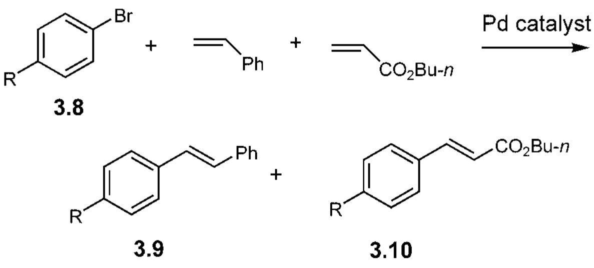


Scheme 2.



TON (1st cycle): 15,625
TON (2nd cycle): filtrate, 17,000; rec. **3.7**, 0
PS = polystyrene

Scheme 3.



Pd catalyst	Ratio **3.9/3.10** (R = COMe)
1	4:96
Pd[(*o*-Tol)$_3$P]$_2$	3:97
[ArPdBr(*o*-Tol$_3$)P]$_2$	2:98

Scheme 4.

This was shown through an interesting series of competition experiments, isotope effect measurements and Hammett studies. For example, in the Heck coupling of a number of *p*-substituted aryl bromides **3.8** under pseudo-first order conditions (excess of aryl halides), using styrene and *n*-butyl acrylate as acceptors in a competitive experiment, the same ratio of products was obtained regardless of the pre-catalyst employed (Scheme 4).[53] The fact that the product ratio does not depend on the catalyst used seems to point to the presence of the same catalytic species, i.e., a Pd(0) catalyst.

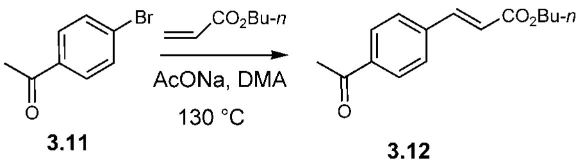
To conclude this section, all available evidence so far points to the view that palladacycles are catalytically inactive species, but can function as sources of Pd(0), which is usually released at a rate that is generally slower than that of the catalytic reaction. The release rate will depend on the reagents used, the reaction conditions and the structure of the reactants (the activating species).

3.2 Scope and Synthetic Applications

The synthetic use of palladacycles has been reviewed.[14–16] From the recent mechanistic work, it is clear that use of these pre-catalysts cannot ignore the rather arduous activation process. Although it is true that most palladacycles are thermally very stable, stability *per se* does not make a catalyst useful. Actually, it is often a drawback. Thus, the reader will notice that, under most modern conditions, Heck and cross-coupling chemistry can be usually run in the thermal range 20–80 °C, whereas most palladacycles are used at 120–180 °C. This temperature range is clearly not attractive for synthetic applications beyond couplings with simple unfunctionalized systems. This must be kept in mind when trying to apply palladacycles in synthesis: *they will need high temperatures to become activated.*

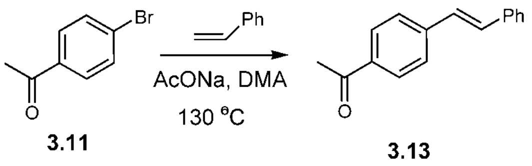
The activation temperature and rate are basically unpredictable and are not constant for a given palladacycle; rather, they depend on the specific activating agent. The ligand itself is modified by the event and, if no further coordinating species is added, *the actual catalyst is therefore a different species for each entry.* This complicates any generalization one may want to try to carry out on the various TONs listed.

In addition, when catalysts are used at very low loadings, the issue of reproducibility must be addressed, as it is likely that even traces of impurities in the solvent or reagents will affect the maximum TON. Only in some footnotes can one find hints that reproducibility has indeed been an issue.[46]



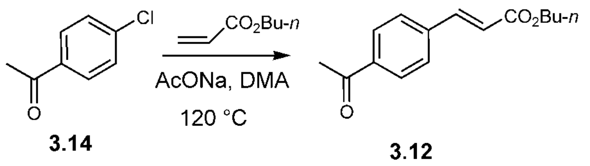
Pd catalyst	TON
1, TBAB	10^6
$Pd(OAc)_2 + PPh_3$, TBAB	10^6
$Pd(OAc)_2 + (o\text{-}Tol)_3P$, TBAB	10^6

Scheme 5.



Pd catalyst	TON
1	4.9×10^5
$Pd(OAc)_2$	5.6×10^5
$Pd(OAc)_2 + PPh_3$	9.4×10^5

Scheme 6.



Pd catalyst	TON
1, TBAB	4.0×10^4
$Pd(OAc)_2 + PPh_3$, TBAB	1.9×10^4

Scheme 7.

Finally, high TONs have been reported mostly for very simple systems, where virtually any Pd-containing catalyst displays high activity, e.g., the Heck reaction of iodobenzene or activated aryl bromides with acrylates or styrene, or the Suzuki coupling of these halides with phenylboronic acid. When palladacycles have been tested in synthetically complex substrates, they have in no case enjoyed such high TONs (*vide infra*).

In spite of all these caveats, it is clear that TONs reported for palladacycles sometimes exceed the TONs observed with traditional catalysts, often in significant ways. In the light of the above mechanistic discussion, this can be due either to the slow activation of the precatalyst or to the *in situ* formation of ligands that are stabilizing in nature to some or all the intermediates in the catalytic cycle.

Early palladacycles did not dramatically outperform traditional catalysts. For example (Scheme 5), *p*-bromoacetophenone couples with butyl acrylate in the presence of **1** or classical Pd(II) species plus phosphane with identical TONs.[54]

The situation is analogous in the Heck reactions of styrene (Scheme 6). Here classical catalysts are slightly better than these early palladacycles.

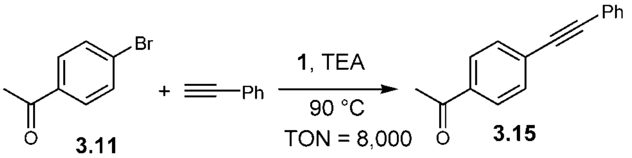
Palladacycle **1** was also found to be active in the Heck reaction of activated aryl chlorides.[54] Here also, however, palladium acetate and simple phosphanes produce very active catalysts, displaying only slightly lower TONs. With both catalysts, the addition of tetrabutylammonium bromide (TBAB) is necessary to achieve high TONs (Scheme 7). In the light of recent work (*vide infra*), it is likely that the observed effect is actually due to the ability of TBAB to stabilize Pd(0) nanoparticles against further aggregation and deactivation.[55]

With regard to cross-coupling reactions, a preliminary study found that **1** displays TONs of up to 7.4×10^4 in the Suzuki coupling using **3.11** and phenylboronic acid. Under similar conditions, classical phosphane-based catalysts are less effective. Even activated aryl chlorides undergo Suzuki coupling in the presence of **1** with fairly high TONs (up to 2,100).[56]

Herrmann et al. have also reported the use of palladacycle **1** in Heck reactions using "environmentally-friendly" non-aqueous ionic liquids (NAILs) as solvents, e.g., TBAB at 130 °C. A very high TON in the reaction of **3.11** with styrene was observed (*ca.* 10^6).[57]

Under these conditions, operating at higher catalyst concentrations (1% load) is also possible, and this can be followed by recycling of the catalyst by removal of the product and subsequent addition of fresh reagents to the NAIL solution containing the unspent catalyst.[58] However, catalytic activity is progressively lost, in agreement with our mechanistic understanding. As active Pd(0) is slowly leached out, TOF decreases. After 8 recycles, only 23% of the original **1** is left in solution. Thus, less than 10^3 TON are possible with this recycling protocol, which is clearly inferior to a *single use* of 1 ppm catalyst.

Applications of **1** to the Sonogashira reaction have also been briefly reported. TONs of up to 8,000 were obtained [Eq. (3)]. No Cu(I) co-catalyst was necessary.[59]



(3)

The HBP species is the only palladacycle that has been tested in several demanding synthetic operations, and it is worth briefly reviewing here the reported synthetic scope. A brief technical report provides a comprehensive list of applications up to 1998.[60]

A complex Stille biaryl coupling, in the synthesis of biphenomycin, was said to proceed more efficiently (73% yield) with 5% **1** instead of some previously reported conditions, i.e., $(dppf)_2PdCl_2/CuBr$ (49% yield).[61]

Tietze et al. have utilized palladacycle **1** rather extensively in the total synthesis of steroids and cephalotaxine alkaloids, at catalytic loads in the 1–10% range.[62–69] In one case where a 2.5% load was employed, comment was made about the inability to recover, at the end of the reaction, more than 30% unreacted **1**.[70]

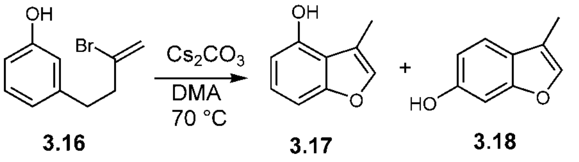
Use of **1** in solid phase Stille couplings gave better results than more conventional conditions (i.e., no deposition of Pd mirrors using **1**).[71] Catalyst **1** was also found useful in biaryl synthesis by direct intramolecular aryl palladation (10% load)[72,73] and domino sequences using allylic alkylation/Heck couplings.[74]

Rawal et al. have described a novel anion-accelerated intramolecular cyclization of alkenyl bromides onto phenols using **1**. The palladacycle gives better yields than its classical Pd(0)/phosphane counterparts. However, it displays no *ortho vs. para* selectivity, whereas modest preference for producing **3.18** is demonstrated using a classical Heck system (Scheme 8).[75]

These small selectivity differences between catalysts are not easily explainable. In a related paper, Rawal et al. remark that **1** performs identically to the classical Heck systems, and that this observation differs from Herrmann's.[76]

On the other hand, there are many examples where the use of **1** as pre-catalyst was found unsatisfactory. In the application of the intramolecular Heck reaction to the synthesis of galanthamine, **1** performed poorly.[77] In the application of the intramolecular Heck reaction to the synthesis of cardenolides,[78] **1** is totally ineffective, whereas, interestingly, $Pd(OAc)_2/(o\text{-}Tol)_3P$ mixtures provide high yields at 45–75 °C. Other examples where **1** is inferior to standard catalysts in the Stille,[79] tandem Suzuki/Heck[80] and Heck couplings[81] have been reported. Unexpected reactions with **1** have also been described.[82]

Interestingly, in none of the synthetically relevant cases reported to date was a TON better than 100 observed. Thus, it is possible that the huge TONs enjoyed by this particular catalyst in simple model systems may not be easily translatable to more complex substrates, or it is also possible that **1** was not properly challenged in terms of maximum TON in many of the above studies.



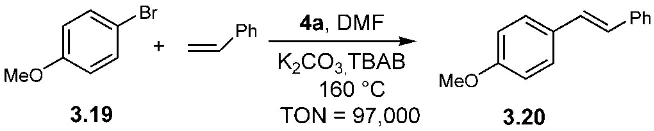
Pd catalyst	Yield	Ratio **3:17/3.18**
1 (5%)	82%	1:1
$Pd(OAc)_2$ + (*o*-Tol)$_3$P	43%	2:3
$Pd(PPh_3)_4$	32%	3:5

Scheme 8.

Major improvements from these early catalysts, both in scope and in TONs, have been reported during the last 8 years. Imine- and oxime-derived palladacycles have been introduced as the most effective phosphane-free catalytic systems in Heck and cross-coupling chemistry. For example, ferrocenylimine palladacycles **3a, b** have shown TONs approaching 10^7 for simple Heck reactions,[83,84] and they have been shown to work well even in water, provided TBAB is added (PhI with ethyl acrylate at 80 °C, 2.8×10^5 TON).[85] Milstein et al. have reported somewhat lower TONs for the Heck reaction (10^5–10^6) using imine-palladacycle precatalyst **9b**.[86] Application of **9a–c** to the Suzuki coupling of bromoarenes has also yielded TONs around 10^5.[87]

Attempts at creating a highly recyclable imine-palladacycle by attaching fluorous tails to these imine precatalysts (e.g., **9d**) have been unsuccessful, mainly due to the formation of Pd(0) nanoparticles as the active species, as demonstrated by TEM.[88,89] These experiments confirm that imine-palladacycles are catalytically inactive and are a slow source of active Pd(0) nanoparticles.[39,90]

Oxime-palladacycles **4a–f** are even more impressive than imine-palladacycles, and reach TONs of 10^{10} in classical Heck reactions with iodobenzene. In addition, they display unusually high activity even with deactivated aryl bromides [Eq. (4)], but rather low TONs with aryl chlorides (around 100).[23,91]



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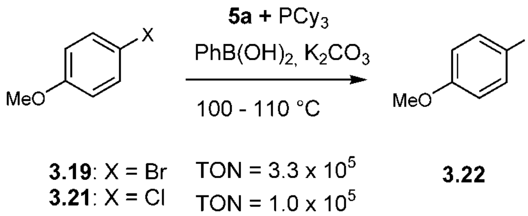


Scheme 9.

Nájera et al. report that, when used at higher loads, these catalysts exhibit an induction period. On recycling the catalyst, this induction stage disappears, which is consistent with the slow formation (at 110–160 °C) of active Pd(0) colloids, as discussed in Section 3.1. Interestingly, these authors report that **4a** reacts with methyl acrylate at high temperatures to form Pd(0) black. This shows for the first time how palladacycles can be activated during Heck coupling, i.e., probably by insertion of the olefin in the C–Pd bond of the palladacycle, followed by reduction to Pd(0). Other authors have independently studied oxime-palladacycles and reported also very high TON.[92,93]

Oxime-palladacycles afford high TONs in the Sonogashira reaction of aryl iodides (up to 72,000), without the need for copper additives.[94,95]

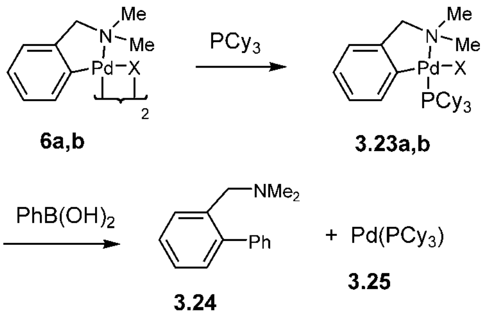
Application of an oxime-palladacycle to the Suzuki reaction was also very successful. High TONs were obtained with activated aryl bromides, and even, albeit to a lesser extent, with activated chlorides.[96] These couplings can be carried out in water provided that TBAB is employed, probably because of its properties of colloid stabilizer.[97,98]

In general, the aryl phosphate-palladacycles described by Bedford are the most active ones (highest TONs) ever reported. In Heck[99] and Suzuki[22] reactions using simple, activated aryl bromides, **5a** reaches TONs > of 5×10^6.

More importantly, electron-rich analogues like **5b** and **5c** were shown to produce TONs > 10^6 for the coupling of deactivated aryl bromides with phenylboronic acid, and TONs > 10^8 for the same reaction with activated aryl bromides, in the presence of extra phosphite ligand.[100,101]

A very important mechanistic observation was reported recently, also by Bedford et al., who reported that catalyst longevity for **5a–c** increases appreciably in the presence of added phosphanes. For example, **5a–c** plus added tri(cyclohexyl)phosphane (PCy_3) afford the largest TONs ever reported for the cross-coupling of deactivated aryl bromides, and allow even the coupling of *deactivated aryl chlorides with excellent TON* (Scheme 9).[102]

These high TON may be related to the formation of Pd(0) complexes with phosphanes of high donicity (see Section 4), perhaps as mixed complexes with the phosphite that is released *in situ*.[103] More research is needed to clarify the exact nature of the catalytic species in these high-TON couplings.[104]



Scheme 10.

A modification of catalysts **5a–c** is constituted by the related phosphate-palladacycle **7**, which reaches a new TON record in the Suzuki coupling of *deactivated aryl chlorides* such as **3.21** (*ca.* 1.3×10^5).[105]

Recently, Bedford et al. have reported on the hydrolytic instability of these complexes under typical Suzuki conditions, although the mechanistic consequences of this observation are still unclear.[106]

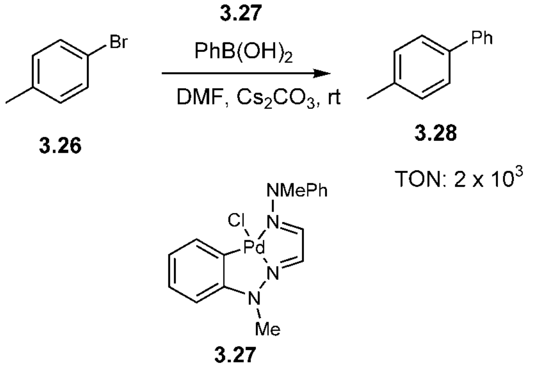
Arylamine-palladacycles[107,108] such as **6a, b** have been studied also by Bedford and co-workers. In this case as well, the addition of bulky trialkylphosphanes allows the activation of aryl chlorides toward the Suzuki reaction. The activation mechanism was also elucidated. Thus, **6b** reacts with PCy_3 to yield first intermediate **3.23b** which, upon reaction with the arylboronate, slowly releases free amine **3.24** and the active "PdL_1" **3.25** (Scheme 10), whereas the released amine probably plays no coordinative role through the catalytic cycle.[109]

Preliminary work using $Pd(OAc)_2$ plus L, e.g. P(*t*-Bu)$_3$ and PCy_2(*o*-biphenyl), in comparison with palladacycles **6a, b** and added ligand,[110] fails to show equivalence and demonstrates the superiority of palladacycles in some cases. The picture is clearly very complex.

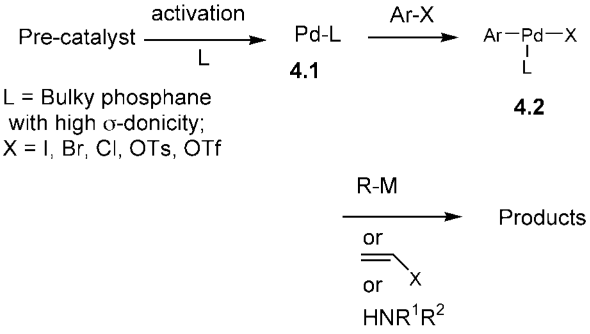
Other types of C,N-palladacycles have been described, often achieving the usual TONs of > 10^6 in simple Heck reactions, e.g., **10a–d**,[111] **11** and analogues,[111,112] **12**[86] and **61**.[113] Activation of aryl chlorides with C,N-palladacycles is possible, as usual, upon addition of bulky trialkylphosphanes.[114] Catalysts derived from propargylamines as ligands afford high TONs in standard Heck reaction, presumably *via* Pd(0) colloids.[115]

Another type of palladacycles that has received much attention are the so-called "pincer phosphite complexes", exemplified by **8a–c**. These pre-catalysts, due to the double intramolecular coordination, are even more stable that the Herrmann palladacycles. Thus, their reactions are usually performed at very high temperatures.[116] Relatively high TONs can be achieved in a number of standard couplings.[117] Deactivation of these catalysts by 1,4-dienes has been reported.[118]

In the class of P,C-palladacycles, isosteres of Herrmann's palladacycle **1** can be obtained from benzylphos-



Scheme 11.



Scheme 12.

phanes,[119] whereas dibenzylphosphanes yield novel pincer complexes.[24] Other P,C-palladacycles have been described,[43,120,121] as well as the novel C,S-palladacycles,[122,123] and even C,N,N-palladacycles.[124] These catalysts perform relatively well in simple systems, and it is not worth discussing them in further detail here, as their behavior resembles that of the many other palladacycles already discussed.

Most interesting and unusual are C,N,N catalysts such as **3.27** (Scheme 11). These are known to couple unactivated aryl bromides with phenylboronic acid at room temperature![125]

Although TONs with **3.27** (prepared *in situ* or preformed) do not qualify as very high (at best around 10^3), such activity under unprecedentedly mild conditions is unexpected and intriguing among palladacycles, and may be promising for synthetic applications. The activation mode of these novel palladacycles deserves detailed elucidation.

From the above discussion, it seems likely that all palladacycles that have been studied to date function as "by-standers", slowly releasing underligated or ligandless Pd(0), which is the catalytically active species. The difficulty in understanding the rates of release of the active catalyst, which strongly depend on the coupling partners and other reagents, may hinder the rational application of these palladacycles in organic catalysis.

4 Highly Coordinatively Unsaturated Palladium Catalysts

4.1 Mechanistic Considerations

It has been widely appreciated for many years that coordinative unsaturation at Pd(II) is a necessary condition at least for some, if not all, cross-couplings[126] and Heck insertions.[127] The reluctance of 16e-Pd(II) intermediates bearing two phosphane ligands to undergo direct transmetalation has been clearly documented, and pre-dissociation of these complexes to yield a 14e-Pd(II) intermediate, where one of the phosphanes has been replaced by solvent or an agostic interaction, has been convincingly demonstrated to be a low free-energy pathway to transmetalation.[128]

As a consequence of these studies, a useful paradigm in much cross-coupling chemistry has been to use ligands that have low σ-donicity toward Pd(II), in such a way as to promote this pre-dissociation.[126] It was therefore surprising, at least initially, to find that bulky trialkylphosphanes behaved as useful ligands in C–C and C–N bond-forming processes, because trialkylphosphanes are strong donors, and therefore would not be expected to dissociate readily, but rather would be assumed to be powerful inhibitors of any kind of transmetalation at Pd(II).[129]

However, this initially puzzling observation has given rise to what is, without doubt, the most important paradigm to emerge in Pd(0) catalysis in the last 10 years: the use of bulky phosphanes of high σ-donicity. This new principle has widely expanded the scope of Pd(0) catalysis, making the activation of aryl chlorides and simple sulfonates possible, as well as allowing the use of sp^3-based electrophiles in cross-coupling chemistry. The success of this approach lies apparently in the ability of bulky phosphanes to promote coordinative unsaturation at Pd by *sterically-driven dissociation*. In addition, their high donicity is able to stabilize mono-ligated Pd(0) species, which function as highly reactive yet relatively stable catalytic intermediates.

Our current mechanistic understanding of their role as ligands is therefore in agreement with the earlier ideas about transmetalation: coordinative unsaturation at Pd is really the key to high reactivity.[28] The bulky phosphanes achieve this by steric bulk (large cone angle) instead of low σ-donicity.[130] From a series of recent investigations, the picture that is emerging is shown in Scheme 12.

Pre-catalyst activation, achieved by a variety of means,[131] gives rise to 12e–species **4.1**, a species that may be further coordinated by solvent molecules, but which owes its high reactivity toward oxidative addition to the fact that it has only one strong donor in its coordination sphere. Obviously, a second trialkylphosphane of high donicity in the coordination sphere of Pd(0) (which may be the case when using high concentrations of L or simply a trialkylphosphane of insufficient steric bulk) would dramatically slow down reactivity. Oxidative addition leads to T-shaped complex **4.2**, which may or may not be further stabilized by solvent molecules or agostic interactions.

T-shaped species such as **4.2**, having no solvent in the fourth coordination site of Pd(II), have been recently isolated and characterized by Hartwig et al. and shown to be highly reactive catalytic intermediates.[27,103] Any type of metathesis reaction with such an unsaturated species is relatively fast, and therefore these bulky ligands allow many catalytic reactions to proceed under really mild conditions, even at room temperature.[26,132]

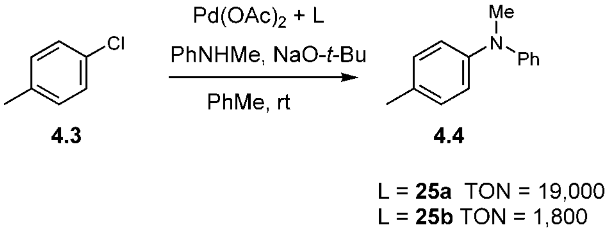
These already exciting developments would be even more important if, for some reasons, these new catalysts were able to display high TONs in synthetically important reactions. Some early indications suggest that this may be the case, and it is even possible to begin to speculate about a rationale for the high robustness of some of these catalysts: in a recent study, Buchwald et al. have noted, in the Pd(0) species obtained from Pd/dba complexes and bulky ligand **25c**, a stabilizing π-interaction of the Pd atom with the *ipso*-carbon of the lateral aromatic ring. This is suggested to play a role in the stability of the Pd(0) species. Such an interaction is not present in related Pd(II) complexes.[133]

Whereas the exact structural basis for the success of ligands such as **25a–d** is not yet clear, some kind of interaction of the Pd center with the ancillary aryl rings must be responsible for some of the properties of the derived catalysts.[26] An interesting rationale proposed to account for the superior performance of ligand **25c** *vs.* **25a, b,d** is based on the inability of this new ligand to form palladacycles.[133] As we have seen above, palladacycles are difficult to activate and any pathway leading to their formation may result in decreased catalytic activity. This suggestion, which awaits experimental support, seems to contradict the hypothesis that palladacycles are superior catalysts.

4.2 Scope and Synthetic Applications

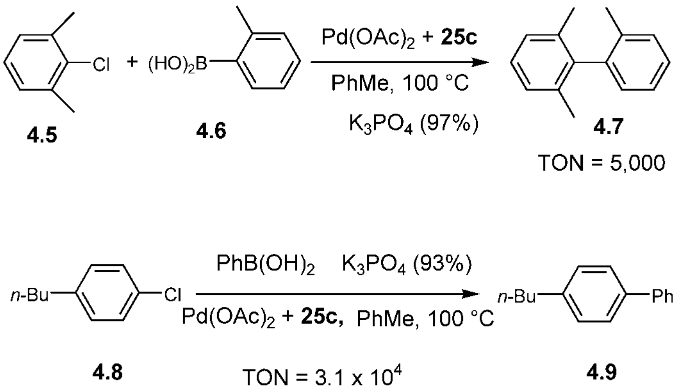
The new paradigm, which can be conveniently designated as the "PdL$_1$" approach, has led Buchwald and coworkers to develop a series of (biaryl)dialkylphosphanes of which **25a, b** are the most extensively studied.

Their initial application was in the amination of aryl chlorides. In addition to providing a general entry into arylamines from aryl chlorides, these ligands display high TONs in the few cases where they were tested (Scheme 13).[134] It must be stressed that these high TONs are observed under very mild thermal conditions, which points to a position of prominence for these ligands in synthetic methodology.[132]



L = **25a** TON = 19,000
L = **25b** TON = 1,800

Scheme 13.



TON = 5,000

TON = 3.1 x 10^4

Scheme 14.

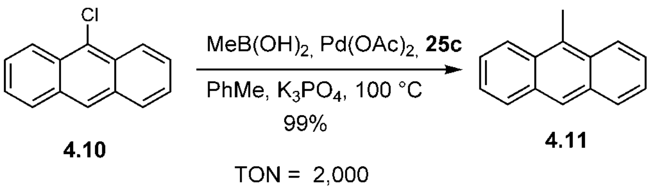
These ligands are also useful in Suzuki cross-coupling reactions.[26] With activated aryl bromides, TONs of *ca.* 10^8 are observed. However, the authors remark that even $Pd(OAc)_2$ achieves TONs $> 10^5$ in these systems, and therefore they are hardly a meaningful benchmark.

In the Suzuki coupling of aryl chlorides, TONs of *ca.* 10^3 were reported with **25a**, which is encouraging but not yet as high as those obtained using the Bedford palladacycle and added PCy_3 (see Scheme 9). However, the catalysts introduced by Buchwald do not need high-temperature activation and are likely to be active under much milder conditions.

More recently, Buchwald et al. have reported on the expanded scope of ligand **25c** in the Suzuki coupling.[133] Such a ligand promotes the coupling of unactivated aryl chlorides with high TONs. Significantly, hindered substrates also couple, for the first time, with very practical TONs and in almost quantitative yields (Scheme 14).

The scope of the coupling extends to a variety of heteroaryl chlorides and hindered aryl boronates. Thus, this ligand is one of the most useful ones ever developed in terms of scope and efficiency in cross-coupling reactions.

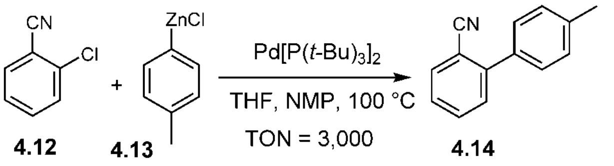
In addition, alkylboronic acids also couple with aryl chlorides under these conditions. Preliminary data show that this reaction proceeds with a respectable TON [Eq. (5)].



(5)

Fu et al. have shown that $Pd[P(t\text{-}Bu)_3]_2$ is a very powerful catalyst in a variety of cross-coupling [6,135] and Heck reactions,[136] and has the ability to couple aryl chlorides. Although the initial focus has been scope and not high TON, this catalyst has been shown to perform in the Heck reaction of activated aryl bromides with a TON $> 10^4$,[137] and in the Suzuki coupling of aryl chlorides and deactivated bromides also with a TON $> 10^4$,[135] suggesting that such catalysts may also have excellent potential for application in industrial synthesis.

Interestingly, this catalyst also displays high TONs in Negishi couplings: for example, biaryl **4.14**, a key intermediate in the synthesis of marketed angiotensin II receptor antagonists, can be obtained as shown in Eq. (6), with a rather high TON.



(6)

Hartwig et al. have used extensively the new bulky ligand Q-phos, **26**.[37] This ligand displays high TONs ($> 10^5$) in standard Suzuki couplings, and moderately high TONs in the amination of aryl chlorides ($> 10^3$). Its synthetic scope was shown to be broad.

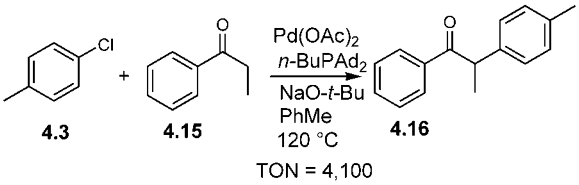
A new ligand type that was kinetically shown to react *via* "PdL_1" species is the phosphoramidite **27**.[130] This showed high TONs (5×10^5) in the Heck reaction of iodobenzene and styrene under rather mild conditions (65–80 °C). Interestingly, palladacycle **1** was not active under these conditions, highlighting the need for high-temperature activation with these pre-catalysts. Ligands such as **27**, which are modular in nature, seem to offer considerable promise in the development of electronically and sterically tunable ligands.

Palladium-monophosphane complexes have also been obtained from pre-catalysts that are weakly coordinated by acyclic dienes, as in **28a, b**.[138]

Water-soluble versions of these strong phosphane donors were recently reported by Shaughnessy et al. Thus, Suzuki coupling of unactivated aryl bromides and phenylboronic acid in the presence of ligands **66a, b** proceeds in water under mild conditions (80 °C) and excellent TONs (*ca.* 7×10^5).[139]

Beller et al. have reported careful fine-tuning of the steric properties of trialkylphosphane ligands, and shown that bis(adamantyl)(*n*-butyl)phosphane ($BuPAd_2$) in conjunction with $Pd(OAc)_2$, catalyzes the Suzuki coupling of aryl chlorides (unactivated and deactivated) with good TONs ($> 10^4$).[140]

This ligand has also been applied to the efficient coupling of aryl chlorides with enolates [Eq. (7)].[141] This reaction has recently enjoyed a tremendous expansion in scope,[142,143] but trails behind the more entrenched counterparts like the Suzuki and Heck reactions in terms of high TON research. Thus, such high efficiency is synthetically important and promising for the future of this reaction.



(7)

In conclusion, "PdL_1" catalysts are emerging as a powerful paradigm in the activation of previously unreactive electrophiles. Some of the catalysts in this category have also shown impressive TONs in a few test systems. Given our improving mechanistic understanding of how these species perform their catalytic function, it is likely that this class of palladium catalysts will play a leading role in the study of HTC in the next few years.

5 Carbene Ligands

5.1 Mechanistic Considerations

Carbene ligands are relatively new actors on the stage of palladium-catalyzed cross-coupling chemistry, yet they have already given rise to a host of interesting applications.[29]

Introduced also by Herrmann et al. as new, high-TON ligands in Pd-based cross-coupling chemistry,[144] carbenes have been little studied mechanistically. Heterocyclic carbenes bind Pd(II) much more strongly that phosphanes,[29] and therefore L-dissociative processes are probably less important here, as discussed by Cavell et al.[145] The Heck olefin insertion is therefore postulated to occur through pentacoordinated intermediates.[146,147] When chelating ligands (as in **31)** were used, the kinetic behavior was sigmoidal, implying slow conversion to an active species.

The mercury test (negative) suggests that these reactions are homogeneous. On the other hand, the enhancement of TONs by tetraalkylammonium salts suggests the presence of active colloids. A variety of chelated catalysts was explored by Cavell et al. and compared with monocarbene complexes. Surprisingly, chelated bis(carbene) complexes such as **35** displayed similar TONs and TOFs as simple, non-chelated bis(carbene)complexes like **33a, b** (10^5–10^6).[148]

More work is needed before the reasons for the success of these ligands can be mechanistically understood.

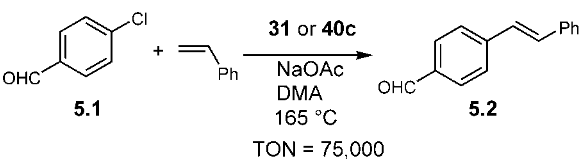
5.2 Scope and Synthetic Applications

From the structural standpoint, the catalysts used range from the monoligated Pd complexes such as **29**, to the bis-ligated counterparts, like **30, 33, 39, 42, 43**, to the "hemilabile" systems such as **32**, **37**, **40**, **41**, to systems where bis-ligation is enforced through intramolecular chelation, such as **31**, **34**, **35**, **36**, **44**. All these various systems have been shown to achieve high TONs in simple coupling reactions.

For example, monoligated **29a, b** catalyzed the Heck reaction of *p*-bromoacetophenone with *n*-butyl acrylate (DMA, NaOAc, 120 °C) with TONs of 7.4×10^4 and 1.1×10^5, respectively, and bis-ligated **30a** behaves similarly (TON of 10^5). The Pd(0) catalyst **39** also displays a similar TON, but without an activation period.[144] In addition to similar TONs, mono- and bis-ligated catalysts also show similar TOFs.[146]

Monocarbene complexes with coordinating labile ligands, such as **40** and its dimer **32**, also show high TONs in simple test systems: thus, in the Suzuki coupling of phenylboronic acid with *p*-bromoacetophenone, hemilabile monocarbene complex **40b** and bis(carbene) complex **41** achieve almost identical TON (1.1–1.2×10^5). In the Heck reaction of the same substrate with acrylates, conventional bis(carbene) complexes like **42** displays similar TONs (7×10^5) as the more complex bis(carbene) species **41** (9.5×10^5) and mono(carbene)-complexes like **40b** (6×10^5).[145] Addition of tetrapropylammonium bromide to the catalytic system allows the TONs to surpass 10^6. Additional work with hemilabile systems such as **40a** has shown even higher TONs ($> 10^6$) for the very simple Heck reaction of iodobenzene with methyl acrylate.[149]

Chelating bis(carbene) complexes were first reported by Herrmann and co-workers.[150] In this class, the most studied ones are pincer complexes such as **31**.[151,152] Their activity was tested in standard Heck and Suzuki couplings. Interestingly, in the model reaction [Eq. (8)], the pincer complex **31** required very high temperatures in order to be activated, just as the mono(carbene) analogue **40c**, and the two had similar TOFs and TONs.



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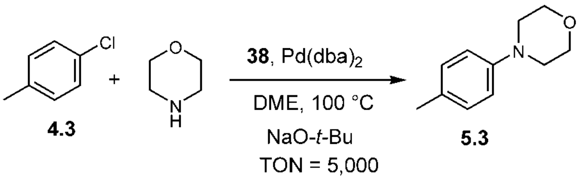
Recyclability of **31** was studied, with mixed results: whereas with *p*-bromoanisole up to six recycles were possible (at 0.1% load), with *p*-chlorobenzaldehyde recycle was unsuccessful.

Tetradentate carbene complexes (e.g., utilizing ligand **44**) have shown excellent TONs in a Suzuki reaction in water.[153] Novel mixed Pd catalysts bearing both a heterocyclic carbene and a phosphane as ligands have been used in the Suzuki coupling with aryl chlorides,[154] whereas new carbene-containing palladacycles have found use in the amination of aryl chlorides,[155] in both cases without reaching high TON.

Very bulky carbene ligands, in conjunction with Pd(0) species, have found use in the amination of aryl chloride, with good TONs [Eq. (9)].[156] The reaction can also be carried out at room temperature with a number of substrates. The TON depends on the particular amine used.



(9)

Finally, benzothiazolecarbenes have been also used as ligands (e.g., in catalyst **43**), with TONs in the range 10^5–10^6 in the usual simple Heck model systems like iodobenzene plus acrylates.[157]

From the above discussion, it is clear that heterocyclic carbenes play a useful role as Pd ligands in cross-coupling and Heck chemistry. On the other hand, their catalytic performance seems constant regardless of the ligation state of the catalyst, and this is unusual. More kinetic work needs to be carried out in order to begin to understand how these ligands operate in Pd catalysis. As far as scope is concerned, these ligands have displayed high TONs only in a small number of synthetically simple operations, and their utility can only be judged after they have been tested against more demanding benchmark reactions.

6 Bi- or Multidentate P- or N-Based Ligands

6.1 Mechanistic Considerations

To the extent that coordinative unsaturation is necessary for all the catalytic steps at Pd to proceed smoothly, it would seem detrimental to use bi- or multidentate ligands, which lead to higher coordination states that are enforced by chelation. However low their TOFs may be, these complexes often display high TONs, presumably because chelation ensures that the Pd(0) intermediates in the cycle do not become underligated and therefore aggregate to inactive clusters. Whether or not this simple reasoning has any merit, multidentate ligands do often lead to catalysts with high TONs.

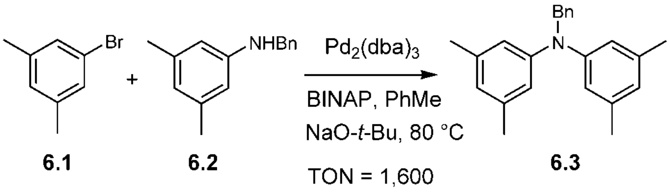
6.2 Scope and Synthetic Applications

Although both P,P- and N,N-bidentate ligands have been used often in Heck reactions, their turnover numbers have been determined only rarely. Recently, the maximum TONs for classical P,P Pd bidentate complexes have been determined in connection with a standard Heck reaction (*p*-bromoacetophenone plus methyl acrylate). Here typical bidentate ligands, such as dppe, dppf and dppp all achieve similar turnover numbers (almost 10^4).[158] The purpose of this study was to demonstrate the higher durability of new P,P,N-tridentate ligands such as **60** which, however, achieve TONs that are not significantly better than those of the more traditional chelating ligands.[159]

The situation is even more unusual in the Heck reaction of iodobenzene, where all Pd catalysts tried, from $Pd(OAc)_2$ to ligated Pd(II) (with PPh_3 or dppp or **59**, **60**) achieve basically the same TON (about 10^5). These data were confirmed by Shaw et al. under slightly different conditions.[160] Hartwig's $(t\text{-Bu})_2PFc$ also achieved $> 10^5$ TON in simple Heck couplings, [137] and $> 10^4$ in standard ketone enolate arylation, which are among the best ever observed.[161] These results perhaps only demonstrate that some of these model reactions are unsuitable as systems on which to study TON values and rank different catalysts.

Typical P,P-bidentate ligands are also excellent at catalyzing the Suzuki reaction, again only for activated electrophiles, like *p*-bromoacetophenone. Indeed, BINAP and dppf achieve TONs of about 10^5, as do the novel bidentate ligands **49a–c** and **50a, b**.[162] Even the TOFs are almost identical for all systems studied. This refutes the general statement, often found in the literature, that Pd/phosphane complexes are thermally unstable and lead to premature catalyst destruction and consequently low TONs.

BINAP, as thoroughly documented by Buchwald et al., is also an excellent ligand for the Pd-catalyzed amination of aryl bromides.[163] This is a much more difficult model reaction in terms of TON than the above simple Heck couplings, and the TON of *ca.* 10^3 observed in a model amination is among the highest in this class of reactions [Eq. (10)].



(10)

A recent study with a new bidentate P,P-ligand (see complex **47**) shows TONs $> 10^6$ for the Heck reactions of iodobenzene.[164] Unfortunately, no direct comparison is made with other bidentate ligands. To make matters more complicated, complexes such as **47**, upon heating, lead to the formation of P,P,C-pincer complexes, which were studied separately as catalysts. Their TONs, however, are lower than with the parent **47**.[165]

Another bidentate ligand that has achieved high TONs (*ca.* 10^6) in simple Suzuki couplings with *p*-bromoacetophenone is diphosphaferrocene **58**,[166] but the catalytic properties of this interesting ligand have not been fully tested, especially with synthetically more challenging substrates.

When examining the area of *multidentate* P-based ligands, worthy of note is the tetradentate ligand Tedicyp (**51**), which was introduced by Santelli and co-workers.[167] Its catalytic performance is impressive and has been quite extensively explored. Therefore, this ligand warrants a close examination. The central idea of its design is that intermediate Pd(0) species have to be protected by internal ligation against possible decomposition pathways through under-ligation and subsequent colloid formation. Whether this is actually the reason for the high TONs observed with **51**, it is not at all clear. The authors have carried out no mechanistic work, and it seems unlikely that the Pd center could be tetra-ligated at any stage of the catalytic cycle. It is possible that Tedicyp functions simply as yet another bidentate catalyst, but its efficiency is clearly superior to that of the more conventional P,P-bidentate ligands discussed above.

Santelli et al. pushed the efficiency of the Tedicyp-based catalysts to TONs $> 10^8$ in Suzuki couplings of activated aryl bromides. Especially impressive are the numbers (TON $> 10^6$) with deactivated systems like 4-bromoanisole: this matches the efficiency of the most active palladacycles (i.e., Bedford's phosphinites **5**).

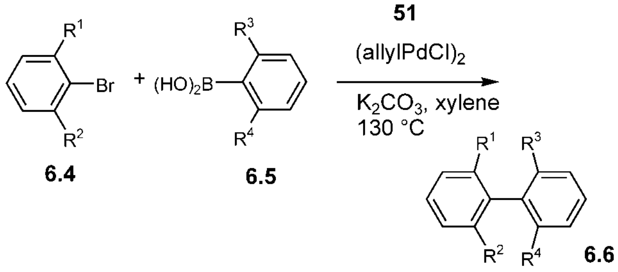
Tedicyp is one of the few systems where scope *vs.* TON has been thoroughly examined. In the Suzuki reaction with heretoaryl bromides, for example, it is clear that the maximum TON depends very intimately on the electrophile.[168,169] Thus (Scheme 15), in the bromopyridine series the TON decreases in the order 3-Br > 4-Br > 2-Br, and in the bromothiophene series it decreases in the order 3-Br > 2-Br. A possible interaction between Pd and the heteroatom was invoked, but caution is in order when explaining maximum TONs.[170]

Another study by Santelli and co-workers concerns the role of steric effects in both coupling partners on maximum TON.[171] In the synthesis of hindered biaryls **6.6**, it was found that TONs drop with steric hindrance around the reacting carbon atoms, i.e., they drop in the same way as TOF would be expected to drop (Scheme 16). One *ortho* alkyl group on the aryl halide (**6.4**) has little effect, but two of them lower the TON by a factor of ten. The same is true for the arylboronate (**6.5**): one alkyl group in the *ortho* position has little ef-

$$\mathrm{ArBr} + \mathrm{PhB(OH)_2} \xrightarrow[\mathrm{K_2CO_3,\ xylene}\ 130\ °\mathrm{C}]{\mathbf{51}\ \mathrm{(allylPdCl)_2}} \mathrm{Ar\text{-}Ph}$$

ArBr	TON
2-Bromopyridine	6.2×10^4
3-Bromopyridine	2.5×10^6
4-Bromopyridine	8.1×10^5
2-Bromothiophene	5.8×10^5
3-Bromothiophene	8.0×10^7

Scheme 15.

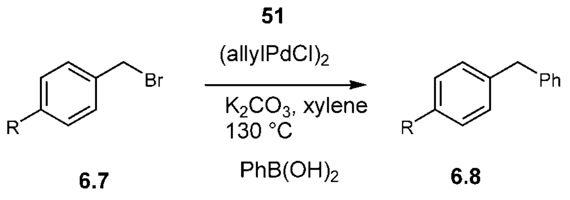


R^1	R^2	R^3	R^4	TON
H	H	H	H	7.5×10^6
Me	H	H	H	8.8×10^6
Me	Me	H	H	8.8×10^5
H	H	Me	H	4.3×10^6
H	H	Me	Me	4.3×10^4
Me	H	Me	Me	830
Me	Me	Me	Me	0

Scheme 16.

fect, but two drastically lower the maximum TON achievable. Finally, *ortho* alkyl groups on both electrophile and nucleophile combine to dramatically depress TON.

In another thorough study on electronic effects both on the aryl bromides and the arylboronic acid, Santelli et al. demonstrated that TON decreases, as expected, with the introduction of electron-releasing groups on the aryl bromide, as this holds the catalyst in the labile Pd(0) state for a longer time.[172] Unexpectedly, a variety of *p*-substituted aryl boronates gave widely different TONs. This was explained with the possible presence of Pd poisons in the boronic acid, and the hypothesis was actually demonstrated by using two batches of boronate of different purities. The TONs achieved were 8×10^3 and 10^5, respectively, in the same reaction under the same conditions. This highlights a problem that has been neglected by other workers: the purity of the reagents (and solvents) may dramatically affect TONs, especially when measuring ultra-high TONs ($>10^6$). This issue must always be taken very seriously in any study that attempts to correlate structure and TON.



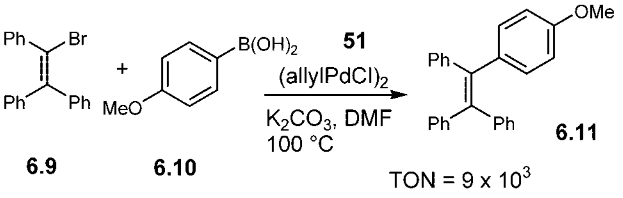
a) R = H TON = 5.8×10^5
b) R = NO_2 TON = 8.7×10^5
c) R = CF_3 TON = 9.4×10^4

Scheme 17.

Benzyl bromides can also be coupled with arylboronic acids in good yields and TONs of often $>10^5$, although the structure/TON relationship was complex both with respect to halide and with respect to boronates (Scheme 17). Benzyl bromides with electron-releasing *para* substituents were not studied, but electron-withdrawing substituents (**6.7a–c**) generally led to products **6.8a–c** in high TONs.[173] Benzyl chlorides gave much lower TONs (generally $<10^3$).

The Tedicyp-based catalysts even promote Suzuki couplings of aryl chlorides, although only in activated cases and with very modest TONs (usually around 10^3, but up to 10^6 in isolated cases).[174]

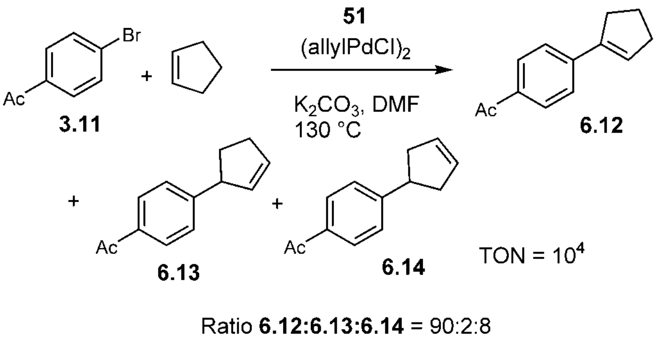
A more recent study extended the Suzuki coupling with Tedicyp to alkenyl bromides.[175] Polysubstituted alkenyl bromides couple with a variety of arylboronic acids in rather high TONs (up to *ca.* 10^4). Even trisubstituted substrates like **6.9** couple in good TON to yield tetrasubstituted alkenes (**6.11**) [Eq. (11)].



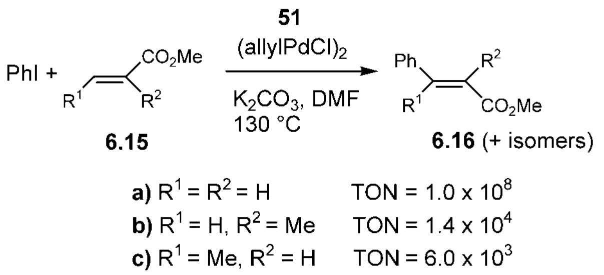
(11)

As one would expect, Tedicyp is also highly active in the Heck reaction. With reactive substrates, such as activated aryl bromides and iodobenzene, TONs up to 10^8 were observed in reactions with acrylates.[176] Styrene gave TONs around 10^5 and *n*-butyl vinyl ether of around 10^4.[177] Heteroaryl halides (mostly bromides, some iodides) can also be coupled with styrene and acrylates, but the resulting TONs vary widely (from 20 to *ca.* 10^6) and no clear trend can be defined.[178]

ortho-Substituted aryl bromides were also studied; as in the Suzuki reaction, it was found that in the Heck re-



Scheme 18.



Scheme 19.

action with acrylates, *o*-Me substitution still yielded a TON around 10^4, but *o, o*-disubstitution led to a TON of only 200.[179]

The Heck reaction with a number of non-activated olefins (i.e., linear alkenes, cycloalkenes) was also studied.[180] Generally, mixtures of double bond isomers are obtained, and this cannot be avoided with Tedicyp. On the other hand, high TONs were obtained even with these less active reaction partners (Scheme 18).

Interestingly, even 1,1- and 1,2-disubstituted olefins (mostly acrylates) can be coupled in good yield and medium TON using iodobenzene as the electrophile (Scheme 19), although double bond substitution even with a methyl group (as in **6.15b, c**) leads to a huge decrease in TON *vs.* the very reactive methyl acrylate. The TONs drop rapidly when using less activated electrophiles.[181]

Other applications of **51** concern the Heck coupling of β-bromostyrene (TONs $> 10^4$ with acrylates),[182] and the Sonogashira coupling using Cu as co-catalyst (TON $>$ 10^6 in the coupling of iodobenzene with phenylacetylene).[183]

Another new tetradentate P-based ligand is ferrocenyl-tetraphosphane **57**. Structural studies show that this species behaves as a bidentate ligand toward Pd, but species containing two Pd atoms per molecule of ligand were also observed. These ligands display fairly high TONs in classical Heck and Suzuki reactions with activated substrates (up to 10^6 for iodobenzene plus *n*-butyl acrylate).[184] It is not clear, nor was it addressed in the above papers, whether the catalytic activities observed with **51** and **57** are due to monometallic species or there is contribution from a more active bimetallic species. Such a phenomenon may contribute to the much higher TONs observed for **51** *vs.* conventional bidentate ligands. Recently James et al. have proposed a "Cooperativity Index" in tetra- and hexadentate ligands and shown it to be rather small (up to 1.17) in a model system. It would be interesting to apply such an approach to highly effective ligands such as **51** and **57**.[185]

Multidentate N ligands, although much less studied than the above P-based species, have also been shown to yield high-TON palladium catalysts in simple Heck and Suzuki reactions.

Thus, bis-imidazole ligands, featured in **46**, led to TONs of *ca.* 10^5 in the Heck reaction of activated aryl bromides with acrylates,[186] and the same is true for catalyst **62**, bearing a bis-pyridine ligand,[187] which achieved such TONs also in the Suzuki coupling of activated substrates. Even a *trans*-chelating N,N ligand (**55**) was used in the Heck reaction of iodobenzene with acrylates (the TON was up to 7.9×10^4).[188]

In addition, catalysts based on tridentate N,N,N ligands have been studied (see **45** and **63**) and have shown TON $> 10^5$ in standard Heck and Suzuki couplings.[189–191]

P,N-bidentate ligands have also been used successfully. Thus catalysts **52**, **53** and **54** achieve high TONs ($>$ 10^6) in the Heck coupling of iodobenzene with acrylates.[192]

Finally, P,S-bidentate ligands have also been described and, perhaps surprisingly, they show some of the highest TONs ever described for simple Heck reactions. Thus, catalyst **48** is the most active of all catalysts ever reported in the Heck coupling of deactivated aryl bromides (i.e., *p*-methoxybromobenzene) and styrene, with TONs $> 10^6$,[193] whereas **56a, b** are much less robust (TON in the same reaction: 5.7×10^3).[194]

As we have just discussed, conventional bidentate and some novel multidentate ligands can offer some of the highest TONs ever observed in simple Heck and Suzuki couplings. Even deactivated aryl bromides have been coupled with exceptionally high TONs. In addition, the scope of ligands such as **51** is very impressive, offering high TONs in a number of synthetically more interesting situations *vs.* the usual standard high-TON benchmarks. Thus, the claim that phosphanes, in combination with Pd(0), lead to intrinsically unstable catalytic systems and therefore do not allow high TONs, a statement often found in the palladium literature, has no general validity.

7 "Ligandless Catalysts"

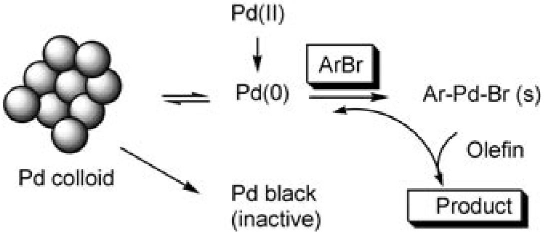
7.1 Mechanistic Considerations

The field of "ligandless" palladium catalysis is over two decades old. Championed by Beletskaya for the cross-coupling reaction[30] and by Jeffery for the Heck reaction,[32] "naked" palladium, i.e., a Pd atom not surrounded by strong, donating ligands such as phosphanes, is known to yield very high TOFs, but supposedly also short lifetimes, due to the lack of stabilizing ligands. Palladium black is known to deposit rather quickly in these reactions, and it is likely that active nanoparticles of Pd, on the road to complete deactivation, play a significant role in catalysis.

Mechanistic work in this area is lacking, but indirect evidence for the role of colloids is constituted by the beneficial effect of tetraalkylammonium halide salts, known colloid stabilizers, in most of these reactions.

In any case, little systematic work has been carried out with the aim at evaluating and understanding TONs with ligandless catalysts. These are, of course, among the most attractive catalysts, because they employ no expensive ligands and are associated with easy recovery of spent Pd (as Pd black, without ligands complicating the separation).

De Vries et al. have addressed the practical problem of carrying out a variety of Heck reactions using $Pd(OAc)_2$ without ligands or additives, for better recovery and lower cost. They found that at low catalyst/substrate ratio, i.e., at low concentration of Pd(0), the aggregation of the catalyst to form inactive Pd black is slowed down markedly, whereas catalysis still occurs at reasonable rates, provided the Pd load is at 0.01–0.1% (10^3–10^4 TONs). This provides a practical solution to the Heck reaction of aryl bromides (including deactivated ones) with a variety of acceptors, e.g., vinyl ethers, *N*-vinylacetamide and 3-buten-2-ol.[52] Recovery of the Pd and recycle by oxidation, if desired, is also facile upon deposition onto silica or Celite.[35]



Scheme 20.

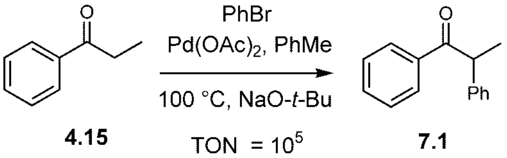
In Scheme 20 a possible rationale for the observed effect is illustrated. Active monomeric Pd(0) is in dynamic equilibrium with soluble clusters, which eventually aggregate to inactive Pd. At the same time, it can also react with the aryl halide to enter the cycle. As the Pd(0) concentration is kept low, the oxidative addition is favored over Pd aggregation (by the law of mass action), thereby prolonging catalyst life. The higher the Pd(0) concentration, the faster the deactivation relative to catalytic performance.

7.2 Scope and Synthetic Applications

There are early indications that, in some cases, fairly high TONs are possible with inorganic Pd(II) salts. For example, coupling of iodobenzene with phenylmagnesium bromide can be catalyzed by $PdCl_2$ with a TON of about 10^4.[195] Likewise, $Pd(OAc)_2$ has been shown to catalyze the Heck reaction of *m*-iodobenzoic acid with acrylic acid in refluxing water, with a TON of 2×10^5.[196]

Novak et al. have shown that, in the Suzuki coupling of *p*-nitroiodobenzene, "ligandless palladium" achieves much better TOF that Pd/PPh_3 catalysts, and also a much higher TON (5×10^3 *vs.* 500, respectively).[197] Bumagin et al., using sodium tetraphenylborate as the Suzuki coupling partner in water, have achieved a TON of $> 10^5$.[198] A similar TON using just $Pd(OAc)_2$ and phenylboronic acid was observed by Buchwald et al.[26] While these numbers do not match the more active Pd species discussed in the previous sections, they are high enough to warrant more scrutiny.

In many cases, "ligandless palladium" is used as a control experiment in studies involving the exploration of new ligands. For example, Buchwald et al., while exploring ligand effects in the palladium-catalyzed enolate arylation reaction, found that simple ketone enolates, like the one derived from propiophenone, couple with bromobenzene under the catalysis of $Pd(OAc)_2$ without added ligands, to yield **7.1** with a high TON [Eq. (12)].[199]



(12)

Dupont et al. have reported on the use of $PdCl_2(SEt_2)_2$ in Heck reactions of iodobenzene or activated aryl bromides.[200] Here also high TONs (up to 5×10^5) were reported, provided tetrabutylammonium bromide (TBAB) was added, presumably as a stabilizer of Pd colloids. Slightly lower TONs were observed in the Suzuki reaction catalyzed by this new "ligandless species".[201] $Pd(OAc)_2$ behaved analogously. Even activated aryl chlorides can be coupled using $Pd(OAc)_2$/TBAB in water (TON up to 3.2×10^3).[202] The authors assume the catalytic species is a colloidal system.

A recent disclosure by Yao et al. highlights the large TON increase in the Heck reaction of bromobenzene with styrene catalyzed by $Pd(OAc)_2$ when K_3PO_4 is used as a base (TON of 3.8×10^4 *vs.* 720 with the classical NaOAc). The authors speculate on a mechanism based on a Pd(II)/Pd(IV) cycle, which is highly unlikely.[203]

Clearly, in spite of their tendency to rapidly form colloids and eventually inactive Pd, "ligandless catalysts" are quite useful in cross-coupling and Heck chemistry and, most of all, are very economical and practical to use. If the colloids hypothesized in Scheme 20 are indeed in equilibrium with soluble, catalytically active Pd(0), and deactivation is due to further aggregation of these unstable colloids, one may wonder whether it is possible to stabilize them against deactivation, thereby creating more robust "ligandless" catalysts. Indeed, the use of TBAB achieves exactly this goal.[55] More systematic attempts at stabilizing palladium colloids are briefly discussed in the next section.

8 Stable Colloids and Nanoparticles

8.1 Mechanistic Considerations

Colloid research in catalysis is a complex subject which is mostly outside the scope of this article. Some relevant reviews have recently appeared and the reader interested in the field is referred to these more authoritative accounts.[33,34]

The area of Pd colloids as catalysts for C–C bond formation has been advanced mostly by Reetz and coworkers. Reetz et al. showed that nanostructured Pd clusters can be stabilized by propylene carbonate and do not precipitate Pd black up to 140–155 °C.[204] TEM showed the presence of remarkably uniform nanoparticles with a diameter of 8–10 nm.

A mechanistic study by Reetz et al. has shed some light on the role of colloids in many phosphane-free Pd-catalyzed processes. While studying the Heck reaction of iodobenzene with ethyl acrylate under typical Jeffery conditions, these authors noticed an induction period of *ca.* 1 h. After this period both catalysis and formation of Pd colloids (by TEM analysis, average size: 1.6 nm) was noticed. A proof of the catalytic role of the colloids was provided by their stoichiometric reaction with iodobenzene. A clear oxidative addition which solubilized the Pd colloid took place, and the product, probably a $[PhPdX_3]^{2-}$ species, was characterized by ^{13}C NMR spectroscopy. This species was able to complete the Heck cycle. In cases where no catalysis took place, no colloid activation by the aryl halide took place either.[55]

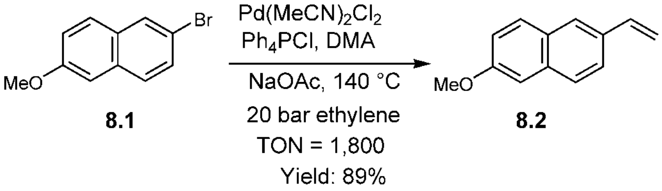
Interestingly, a similar reaction using palladacycle **1** or Pd/PPh_3 traditional catalysts showed no formation of colloids at any stage, but simple $Pd(OAc)_2$ led, as expected, to small, unstable colloids (average diameter: 1.2 nm). This seminal paper points to the important role of Pd nanoparticles in many catalytic reactions where strongly coordinating Pd ligands are not employed.

8.2 Scope and Synthetic Applications

Reetz's early colloids had some catalytic activity in simple reactions, but only at high temperatures and with low TON. For example, colloids stabilized by a surrounding layer of tetrabutylammonium halide were shown to catalyze standard Suzuki reactions with low TONs.[205] Similar systems using tetraoctylammonium bromide were described by Beller et al., and achieved fairly good TONs (around 10^3) in the Heck reaction of activated aryl bromides and acrylates.[206]

The particle size of Pd colloids can be smoothly controlled by redox-based fabrication.[207]

In their continuing studies on new colloidal systems, Reetz et al. described the novel tetraphenylphosphonium chloride/dimethylglycine (DMG) stabilizing combination. With this system, even chlorobenzene couples with styrene, albeit with low TON, while bromobenzene achieves rather high TONs with acrylates (*ca.* 10^4).[208] An interesting practical application of the new colloid is shown in the difficult olefination of **8.1** with ethylene [Eq. (13)].[208] In a related paper, the performance of these new colloids was extended to TONs > 10^5 in Heck reactions of bromobenzene.[209]



(13)

A rather high TON was reported in the Heck reaction of highly activated aryl bromides with styrene using colloids derived from *in situ*-reduced Pd(0) and polystyrene/poly-4-vinylpyridine co-polymers. The size of the particles was approximately controlled by the rate of reduction of the pre-catalyst, i.e., $Pd(OAc)_2$. TONs in the best cases were up to 5×10^4.[210]

Further elucidation of the reactivity of these small palladium clusters came from the work of Bradley, Blackmond et al.[211] These workers used homopolymers of PVP and produced the colloids by hydrogenating the ligand of $Pd(dba)_2$, thereby forming uncoordinated Pd(0). The diameter of the cluster could be controlled rather well by varying the H_2 pressure in the hydrogenation. In the Heck reaction of *p*-bromobenzaldehyde and acrylates, TONs up to 10^5 could be achieved, thereby underscoring the potential of nanoclusters of controlled size in high-TON palladium research. Kinetic data suggest that Pd "defect" sites, i.e., Pd centers with low metal-metal coordination, are the active centers for catalysis, and that the species that reacts with the aryl halide is not Pd(0) that has left the nanoparticle and has become solubilized, as shown in Scheme 20, but, rather, a Pd(0) atom from the cluster, followed by solubilization of the Pd(II) intermediate. This conclusion is in agreement with the work of Reetz, which was already discussed.[55] Various other polymer-stabilized Pd nanoparticles in Suzuki couplings have also been reported.[212,213]

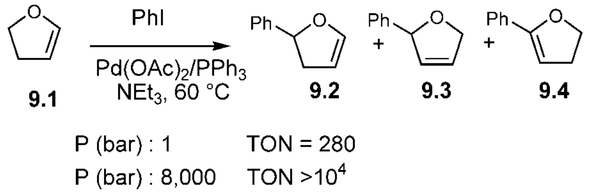
It seems clear that Pd nanoparticle research is still in its infancy, and that the prospects of obtaining high TONs in cross-coupling and Heck chemistry using Pd colloids stabilized by novel means are quite good. Obviously, there is a high degree of overlap between the use of "ligandless" catalysts and stabilized nanoparticles, as most likely in both cases soluble Pd clusters are responsible for the catalytic activity, or at least part of it. It is not clear, however, whether the more challenging substrates, like deactivated aryl bromides and simple aryl chlorides, can be subjected to effective catalysis using Pd colloids, i.e., without the use of strong donor ligands. This may turn out to be a general limitation of "ligandless" Pd in catalysis.

9 Traditional Catalytic Systems

As discussed in the introduction, traditional Pd(0)/triarylphosphane catalysts have been used in much of the early Pd literature and have served admirably to scope out the new synthetic tool. Whereas interest has shifted to TON lately, it is fair to say that the early catalysts, although much maligned in relation to their thermal instability, have not been carefully scrutinized when it comes to their potential for high TONs. On the other hand, the few careful studies that have been carried out suggest the maximum TON achievable with these systems is fairly good. For example, Spencer in 1983 published a thorough study on the TON of typical Heck reactions of aryl bromides with styrene, acrylates and acrylonitrile. The TONs achieved with $Pd(OAc)_2/P(o\text{-Tol})_3$ (the original Heck system) were uniformly $>10^3$ and reached, in one case, 1.3×10^5.[38] The full study on palladacycle **1** by Herrmann et al. also reported that, in the presence of TBAB, both Pd/PPh_3 and $Pd/(o\text{-Tol})_3P$ catalysts achieved TONs that were, surprisingly, as high as those displayed by **1** or by "ligandless Pd" (i.e., *ca.* 10^6).[54]

Another thorough study on maximum TONs achieved by the classical Heck catalyst was reported by DeVries et al. in their study of the Heck reaction of *o*- and *p*-bromotoluene with ethylene. Under the best conditions, styrenes were obtained in fairly high TONs (*ca.* 3×10^3).[214]

Recently, water-soluble triarylphosphanes bearing a carbohydrate moiety were shown to achieve TONs of $10^4 - 10^5$ in Suzuki and Heck couplings of activated systems, and this appears to be much better than the performance of the traditional Pd(0)/TPPTS ligands.[215–217] An unusual triarylphosphane, i.e., bis-(*o*-chlorophenyl)phenylphosphane, affords TONs of up to 7×10^3 in activated Suzuki couplings.[218]



Scheme 21.

The traditional phosphites were also examined as high TON ligands. For standard Heck reactions and Suzuki couplings, TONs of $>10^4$ and $>10^5$ were observed, respectively, but this approach is made unattractive by the extremely large L:Pd ratio that had to be used.[219,220]

Interestingly, pressure can dramatically increase maximum TON, as demonstrated by Reiser et al.[221] This interesting observation has not been followed up with more studies of TON *vs.* pressure, but it is intriguing enough to warrant extension to other catalytic systems (Scheme 21).

Overall, it seems possible, at least for activated electrophiles, to achieve high TONs even with traditional Pd/triarylphosphane systems. Surprisingly, there are very few studies on the TON potential of these relatively old catalytic systems. Although their relative thermal instability is documented, their potential for achieving practical catalysis in industrial systems should not be hastily dismissed.

10 Polymer-Supported Catalysts

10.1 Mechanistic Considerations

Only when mechanistic knowledge of a catalytic system is fairly extensive, does it make sense to immobilize such system on a solid support, in such a way as to probe its recyclability. Often knowledge of the mechanism suggests the best location of such support within the ligand sphere of the Pd. Unfortunately, catalyst immobilization is often carried out without mechanistic considerations, and this results in poorly useful catalytic systems. The main mechanistic problem in this area is whether catalysis is truly heterogeneous (i.e., the whole catalytic cycle takes place on the supported catalyst) or it operates in solution, through leaching of highly active Pd(0) particles. Criteria for differentiating heterogeneous from homogeneous catalysis have been presented in the literature,[222] and further discussion is outside the scope of this review. Suffice it to say that, as noted below, many workers have employed tests that are regarded as inconclusive (i.e., primarily catalyst filtration techniques) for their mechanistic inferences.

10.2 Scope and Synthetic Applications

Polymer-supported catalysis can be a useful means to separate a spent catalyst from the reaction mixture, but it is traditionally carried out with the intent of recycling the (still active) catalyst at the end of each batch. Because this is an alternative strategy to the use of small amounts of high-TON catalysts, it is basically outside the scope of this review. However, insofar as it pertains to the immobilization of some catalysts that have previously been shown to display high TONs, it will be briefly discussed here.

The key challenge in catalyst heterogenization is the ability to create highly active surfaces, i.e., use a support that does not restrict diffusion in and out of the catalytic sites. In general, this is difficult, and the catalytic performance of a Pd system will usually decrease on immobilization, sometimes drastically. For this reason, catalyst heterogenization is a very specialized field that requires a lot of skill.

Several palladacycles have been immobilized on polymeric supports. For example, Bergbreiter and co-workers have immobilized a S,C,S Pd(II) pincer complex, using a PEG support. Depending on the linker, some catalysts clearly lost activity after one cycle, whereas one of the catalysts could be recycled three times without (apparent) loss of activity. Given the rather high catalyst load (0.1%) and the intrinsically high efficiency of palladacycles in solution, it is most likely that slow release of Pd(0) particles is responsible for the catalysis, without this translating into a major loss of Pd from the polymer.[223] Immobilization of these pincer complexes on polyacrylamides allowed reaction under thermomorphic conditions.[224] P,C,P Pd(II) pincer complexes were also immobilized on silica, and achieved TONs of *ca.* 3,000 in the Heck coupling of iodobenzene with acrylates, with some recyclability. As the corresponding soluble catalysts achieve TONs $> 10^5$, it is clear that > 100 recycles would be necessary for the polymer-supported catalyst to match its soluble counterpart in terms of efficiency. On the other hand, the catalyst was only recycled three times, reportedly "with high activity".[225]

Imine-based palladacycles have also been immobilized, and have been shown to release rather readily soluble Pd(0), rendering a recycle impossible. These catalysts are more interesting as mechanistic probes than as practical synthetic tools.[39,226]

The Herrmann catalyst **1** was also immobilized on a polystyrene support and, not surprisingly, it was found to lose activity after each recycle. The catalyst is active at loads down to 0.2%, but even after several recycles the overall TONs do not approach those obtained by using lower levels of **1** in a batch mode.[227]

Recently, a silica-based immobilized oxime-palladacycle was developed for the Suzuki coupling of activated aryl bromides (load : 0.65% Pd). At this level, $> 1,000$ recycles would be needed to match the effectiveness of the soluble counterpart.[228] The authors claim the immobilized catalyst is recyclable without loss of activity and it is a genuine heterogeneous catalyst, as filtration of the reaction mixture produced a catalytically active solid and an inactive filtrate. On the other hand, it has already been commented often in the literature that this test is insufficient to distinguish homogeneous from heterogeneous catalysis, as deactivation of soluble species is often triggered by the filtration process.[12] In general, given what we know about the mechanism by which palladacycles act, it appears very unlikely that these catalysts can operate in a truly heterogeneous fashion. In general, there does not seem to be a solid rationale for the immobilization of palladacycles.

Rather, there is a good rationale for *not immobilizing* palladacycles: this follows from De Vries' studies.[52] Low concentrations of Pd(0) in solution will aggregate and deactivate much more slowly than at high concentrations. This high dilution (achieved by slow release) is probably the secret behind the apparent success of the palladacycles. If one removes this "homeopathic" condition, e.g., by immobilization on a polymer and releasing Pd(0) in higher concentrations, the advantage of palladacycles is lost and the overall maximum TON will drop considerably.

Chelating Pd-carbene complexes have been immobilized on polystyrene, with $\mathrm{TON} > 10^3$ per cycle and with at least ten cycles possible (total TON up to 3.5×10^4) in the Heck reaction of *p*-bromoacetophenone and acrylates. The TOFs are depressed *vs.* the homogeneous counterpart by a factor of ten.[229] Pincer carbene complex **31** has also been immobilized on clays like MK-10, again with TON of *ca.* 10^3 per run, TOFs that are equal to the ones with soluble **31**, and reasonably good recyclability (for the coupling of iodobenzene and styrene).[230] In both cases, which are clearly different from the case of palladacycles, no activity was found in the solution under optimized conditions, suggesting that catalysis may be heterogeneous.

Polymer-supported, phosphane-free Pd catalysts were constructed with β-ketoester ligands. These catalysts can operate at a level of 10^3 TONs per cycle in the coupling of iodobenzene with styrene or acrylates. DMG, a known colloid stabilizer, improves catalyst performance and a few recycles were possible. Given that the Pd here is essentially "ligandless" as soon as it is reduced to Pd(0) and given the role of DMG, it is apparent that this cannot be true heterogeneous catalysis, but rather a complex way to slowly meter Pd(0) nanoparticles into a solution.[231]

All the catalysts described above are apparently successful, but their use has been limited to very active systems, i.e., systems in which ppm (or even ppb) levels of homogeneous Pd have been shown to be effective at triggering coupling. Thus, it is hard to conclude that these catalysts truly represent new practical solutions to catalysis and even harder to make the case that they operate by truly heterogeneous mechanisms.

The most impressive heterogenized catalysts are those described by Buchmeiser et al. and are exemplified by **64**. They are apparently robust N,N-bidentate ligands supported on a polyolefin scaffold and activated by binding with Pd(II) salts. With these catalysts, TONs of $> 10^5$ are achieved in the Heck reactions of iodobenzene, and TONs $> 10^4$ can be obtained even with bromobenzene and chlorobenzene, provided TBAB is added.[232] The authors remark that TONs are actually higher than those observed for the soluble catalyst counterpart. This may be due, in the latter case, to the slow formation of colloids, which would then aggregate and lead to catalyst deactivation. The polymeric support is rich with uncoordinated bis-pyridine ligands, which may scavenge any free Pd(0) in solution and therefore retard the formation and growth of colloids. Recyclability of the catalyst was not addressed, but these TONs are competitive with the best solution TONs, and an advantage of using these systems, even without recycle, would be the ready separation of the product from the catalytic system. With these catalysts, TONs of *ca*. 10^3 can be obtained in the amination of bromobenzene.

On the other hand, the related mixed pyridyl/quinolyl ligand-based catalysts were less stable and leached Pd into the solution.[40] A remedy seems to be the introduction of bis-pyrimidyl ligands. These led to catalysts that achieved higher TOFs than the parent pyridyl-based catalysts and exhibit good TONs (10^3–10^4) in the Heck and Suzuki couplings of bromoarenes, including deactivated ones, as well as some activated chloroarenes.[233]

In conclusion, immobilization of Pd on a polymer is an established, alternative approach to the use of high-TON catalysts in a batch mode. An in-depth discussion of the general problems encountered in heterogeneous catalysis is outside the scope of this review. We must stress again that mechanistic considerations should go into the design of these catalysts; in particular, when in the homogeneous reaction the active Pd species is known (or suspected) to become detached from his carrier ligands during the catalytic cycle, immobilization of the Pd through such ligands cannot possibly be successful, although some level of catalysis will probably be observed, at least in simple systems.

11 Heterogeneous Catalysts

11.1 Mechanistic Considerations

Several papers have addressed the problem of Pd leaching from the support when dealing with heterogeneous catalysts.[234–237] This is indeed the key mechanistic issue when using heterogeneous catalysts. Since the problem is often ambiguously presented and may give rise to confusion, it is necessary to comment here on the possible mechanisms by which elemental Pd on a solid support (or on a colloid, for example), may catalyze complex multistep reactions like a cross-coupling.

The frequent and unfortunate statements found in the literature claiming that these reactions may occur on the heterogeneous Pd surface may have led some readers to believe that the entire catalytic cycle could take place with the Pd species mediating the coupling firmly anchored to the solid support. This is highly unlikely. As aptly remarked in a recent review,[12] it is clear that the activity of heterogeneous catalysts is related to the ability of the reacting aryl halide to undergo oxidative addition with an atom of Pd on the surface of the catalyst, and extract it into the solution. The rest of the catalytic cycle will then occur in solution.[55] The main feature of the solid support that affects TON is its ability to recapture the spent Pd at the end of each cycle in a form that will make it active again for another cycle of catalysis. This shuttling of Pd atoms from the surface to solution is probably an obligatory step in all "heterogeneous" situations. Filtration techniques cannot really distinguish between a "shuttling" and a "surface" mechanism, because the poorly ligated "ArPdX" solution species may be present in undetectably small amounts, and is also known to be very unstable toward disproportionation to Ar–Ar and $PdBr_2$.[28]

Thus, the secret to high TON and recyclability of heterogeneous catalysts may lie in the ability of the solid support to "recapture" each Pd atom at the end of each cycle in an "activated form",[237] as opposed to allowing Pd to form colloids and then inactive aggregates. When more conclusive experiments were carried out, e.g., the "three-phase test", this shuttling effect of Pd (from the solid to the solution and back to the solid) was proven without doubt.[238]

11.2 Scope and Synthetic Applications

A rigorous discussion of heterogeneous palladium catalysis is outside the scope of this review. The clear advantage of heterogeneous catalysis is the easy separation of product from catalyst, and perhaps recyclability (which is, however, not a given). The problems associated with heterogeneous catalysts in palladium chemistry are mainly the difficulty of tuning the Pd, the often low TOFs (*vs.* the homogeneous counterparts), and the loss of metal due to leaching into the solution, followed by reprecipitation in a less active form, as already discussed.

A few reports have described highly active heterogeneous catalysts which have yielded high TONs ($> 10^3$) in a single batch mode, and therefore fall to some extent within the scope of the review. For a more general survey, the reader is referred to a recent, thorough account.[12]

Pd on MgO was reported as early as in 1990 to catalyze the Heck reaction of chlorobenzene with styrene at 150 °C, with a TON of 1.6×10^3. This was much better than the TON observed with other supports, like silica, alumina, carbon and sepiolite.[239] Other workers have taken a systematic look at different metal oxide supports and have concluded that titanium oxides are superior to MgO, but no TONs were provided.[240]

Palladium on porous glass can also achieve high TONs (up to 4×10^3) in the Heck reactions of 4-bromoacetophenone at 180 °C. The authors remark that the TON improves when lowering the catalyst load.[241] This is suggestive of slow leaching of Pd(0) into the solution.[52]

Similarly, Pd grafted on mesoporous MCM-41 achieves good TONs (5×10^3), but only with activated aryl bromides and acrylates.[242] A thorough study of the new surface shows a highly dispersed Pd load. The mercury poisoning test and filtration experiments suggest that the reaction is heterogeneous.[243]

Palladium-modified zeolites yielded heterogeneous catalysts endowed with excellent TOF, and TONs around 10^3 for the Heck reactions of aryl bromides (including deactivated ones). Even aryl chlorides can be coupled at 170 °C, although with lower TONs. The authors detect some Pd leaching, but conclude it is not enough to explain the observed catalytic activity.[244] Others found these catalysts are not directly recyclable, but needing reactivation.[245]

Palladium on carbon is a group of rather popular heterogeneous catalysts for C–C bond formation. A thorough study by Köhler et al. provided evidence that, under some reaction conditions, Pd(0) leaching from the metal is responsible for most of the catalysis observed in Heck and Suzuki couplings of aryl halides. Therefore, recycling is problematic.

However, Pd redeposition on the solid support can be achieved by careful fine-tuning of the reaction protocol, therefore ensuring almost complete removal of Pd from the reaction mixture upon filtration.[41,246] The TONs are quite high, up to 3.6×10^4 for the reaction of bromobenzene with styrene, and up to 7.2×10^3 for the analogous reaction of *p*-methoxybromobenzene. Analogously, Suzuki coupling with phenylboronic acid proceeds with TONs of *ca.* 2×10^4 for both unactivated and deactivated aryl bromides. Activated chlorides also couple with TONs $> 10^3$. These constitute reasonable activity and scope for a catalyst as cheap and easy to use as Pd/C.[247]

A more extensive study of the Suzuki coupling of aryl chlorides using Pd/C was recently published, although maximum TONs were not addressed.[248]

Some of the highest TONs observed in Suzuki couplings were reported by Shimizu et al. using Pd supported on sepiolite. TONs of $5-6 \times 10^4$ were observed for deactivated and unactivated aryl bromides, respectively, and TONs for activated substrates reached 10^5. These figures are quite remarkable, because the catalyst could be recycled and no activity was found in the solution phase upon filtration.[249] Good TONs were also found with Pd supported on hydroxyapatite, the TONs being essentially identical to the ones above with a variety of aryl bromides in Heck and Suzuki coupling.[250] Recyclability was reported to be good. In this paper, filtration was also used to assess and reject the possibility of leaching, and the reaction was said to "proceed on the PdHAP-1 surface". The lack of validity of the filtration test has been amply commented upon in the literature.[12,222] A Hammett study as well as Heck competition experiments between two olefins were used to support a Pd(II)/Pd(IV) mechanism. Unfortunately, this type of information is of little value in pinpointing where the reaction occurs and how. A Hammett constant that is different from the one observed with $Pd(PPh_3)_4$ is not at all surprising, given that highly ligated and electron-rich Pd will most likely undergo oxidative addition with different selectivities than a Pd colloid or a heterogeneous surface. Indeed, reaction selectivity difference is one of the criteria proposed by Laine in order to distinguish between cluster and mononuclear catalysis.[222]

In spite of the confusing elements contained in some of these studies, heterogeneous catalysis can be useful in Pd-catalyzed C–C bond forming reactions, provided the surface is highly active toward oxidative addition. Although the scope of the reaction is not quite as broad as for the homogeneous reaction, in cases where activated electrophiles were used very large TONs were observed. Regardless of recyclability of the catalyst, this feature alone makes the use of heterogeneous Pd attractive, due to the ease of its separation from the products.

12 Practical Considerations and Conclusion

The search for the optimum catalyst must of course begin with an examination of the reaction to be catalyzed, a literature analysis, and an understanding of the type of catalyst that may be successful in a given application. This will restrict the field somewhat.

In general, scope permitting, it is always advisable to begin by screening "ligandless" [251] or heterogeneous conditions (e.g., Pd/C or other supported catalysts commercially available). An automated screen or a rapid manual study can easily go through some of the ligandless conditions developed in the literature. It is important to test both Pd(0) and Pd(II) species: although often identical in behavior, it is however possible that the activation rate of Pd(II) to Pd(0) may play a role, or that "innocent" ligands like dba may affect catalyst performance. Avoiding the use of ligands will make the Pd easier to separate from the products and recovered, if necessary. In addition, special ligands add substantially to the cost of the catalyst. Therefore, if some product is observed under these conditions, it makes sense to try to optimize the reaction for high TOF, TON and product purity.

Unfortunately, ligands are often needed in order to modulate the rate of some or all of the catalytic steps, like oxidative addition, insertion, transmetalation and reductive elimination. In this case, perusal of the literature will provide some hints. In general, it is wise to start by screening commercially available and inexpensive ligands, both monodentate and bidentate ones. From this screen, a certain picture will emerge that will allow further experimentation to be planned. For example, all polydentate catalysts may be ineffective, allowing one to focus on the monodentate ones, or *vice versa*.

It is desirable to elucidate first the type of catalyst that will yield the desired product in good yield and acceptable purity before trying to optimize for TON. Obviously, a high-TON catalyst which does not achieve the desired yield or purity is not a practical tool.

In terms of scope and TON, the most promising catalysts are clearly the "PdL_1" catalysts introduced by Buchwald, Fu, Hartwig, Beller and others, which have been amply discussed in this review.

It is likely that most synthetic transformations of the type described here can be successfully carried out with these catalysts, and many of the reported TONs are relatively high. When using electrophiles that are poorly activated, this new class of sterically tunable ligands in conjunction with Pd(0) or Pd(II) sources is the most promising one to start with.

Less well documented are the heterocyclic carbene ligands. Their scope is slowly expanding and, although their TONs have not been tested in complex systems, these ligands are clearly more robust than most phosphanes and therefore their use in high-TON research has considerable synthetic potential.

The early enthusiasm created by palladacycles as new catalysts must now be tempered by our growing understanding of the origins of their activity. Although they constitute an interesting new principle in catalysis, their performance may be simply mimicked, at least in some cases, by dilute $Pd(OAc)_2$. Therefore, future applications of palladacycles in industrial processes may not be as promising as originally thought.

The recent flurry of publications dealing with high-TON catalysis in organopalladium chemistry is just scratching the surface of this complex and important problem. If the industrial use of these reactions is to increase beyond the handful of examples that are currently being practiced, our understanding of how the new Pd catalysts operate and our quantitative appreciation of their decomposition pathways must dramatically increase. One of the aims of this short review is to stimulate further work in these directions.

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