catalysts

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Review

About Solid Phase vs. Liquid Phase in Suzuki-Miyaura Reaction

Amine Bourouina †, Valérie Meille *,† and Claude de Bellefon *,†

Laboratoire de Génie des Procédés Catalytiques, Institut de Chimie de Lyon, Université de Lyon,
UMR 5285-CNRS-CPE Lyon-UCBL, 69100 Villeurbanne, France; abo@lgpc.cpe.fr
* Correspondence: vme@lgpc.cpe.fr (V.M.); cdb@lgpc.cpe.fr (C.d.B.); Tel.: +33-4-72-43-1755 (V.M.)
† These authors contributed equally to this work.

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Abstract: A critical review of conclusions about the putative heterogeneous mechanism in the Suzuki-Miyaura coupling by supported Pd solids is reported. In the first section, the turnover frequencies (TOF) of 20 well-established homogeneous catalysts are shown to be in the range 200 to 1,000,000,000 h^{-1}. The evidences used to prove a heterogeneous mechanism are discussed and another interpretation is proposed, hypothesizing that only the leached species are responsible for the catalytic reaction, even at ppb levels. Considering more than 40 published catalytic systems for which liquid phase Pd content have been reported, activities have been computed based on leached Pd concentrations and are shown to be in the range TOF 150 to 70,000,000 h^{-1}. Such values are compatible with those found for the well-established homogeneous catalysts which questions the validity of the conclusions raised by many papers about the heterogeneous (solid) nature of Suzuki-Miyaura catalysis. Last, a tentative methodology is proposed which involves the rational use of well-known tests (hot-filtration test, mercury test…) to help to discriminate between homogeneous and heterogeneous mechanisms.

Keywords: C-C coupling; Suzuki-Miyaura; homogeneous; heterogeneous; leaching

1. Introduction

Many recent reviews are dedicated to the Suzuki-Miyaura (SM) reaction, one of the most important catalytic reactions for the pharmaceutical industry [1–4]. It represents up to 10% of a 1 million patents database in the field of pharmaceuticals as pointed out in a recent paper reporting the use of intelligent search algorithms [5]. From an industrial viewpoint, the idea to catalyze the SM reaction with insoluble Pd catalysts is very attractive since the solid catalysts are easily separated from the reaction mixture by conventional processes such as filtration or decantation for example. Furthermore, continuous reactors, where the solid catalyst is maintained while the process fluid is circulated, couple the two functionalities, i.e., reaction and separation of the catalyst, are now common practice in industry. Such processes better known as Flow Chemistry are targeted by many companies and research teams. The solid catalysts could be palladium nanoparticles (NPs) containing solids (Pd/alumina, Pd/silica, …) or anchored palladium transition metal complexes on solids. Consequently, a huge effort has been made to prepare, characterize and test such catalysts with very probing results [6–11]. Meanwhile, it has also generated a controversial debate since in many instances, soluble Pd species were identified thus calling for less robust conclusion about "true" heterogeneous catalysis [12,13]. Last, many reports point Pd leaching from the solid. Leaching of Pd does address not just the technological issue of downstream processing to comply with regulations but more strikingly, the issue of the reaction location. The design of the flow reactor will certainly be different if the reaction takes place at the solid or in the liquid phase, with the leached Pd species as the catalyst. Thus, in Flow Chemistry, the knowledge of the reaction location is of prime importance both to design efficient industrial processes and to understand the underlying fundamental mechanisms. It is not our goal to present an umpteenth review on that subject or an update of the recent reviews but to propose an alternative interpretation of the data obtained by the different researchers. Using solid catalytic precursors, it appears clearly from several publications that leached species, either as a complex or as nanoparticles in solution are wholly or partially responsible for the catalytic activity (e.g., [13,14]). The nature of these species in solution is still a debate, as it is also in the case of homogeneous precursors. Some believe that nanoparticles in solution are inevitably formed and are only responsible for the catalytic activity [15], other think that a true homogeneous (complex-catalyzed) mechanism can occur [16]. Apart from that debate, some authors support the idea of real heterogeneous catalysts that do not release any (or sufficient) traces of Pd to contribute to the catalytic activity [17,18]. It appears from these publications that often, trace amounts of Pd are measured in the solution. First, this concentration may be under-estimated because it is measured at high conversion while redeposition may have occurred. Moreover, even considering these low values, an exercise can consist in the calculation of a turnover frequency (TOF) that would be obtained considering the only contribution of (traces) leached species. Calculated values in general reach 10^5 h^{-1}, with some examples going to values that seem incredibly high (10^7 h^{-1}, e.g., [18]). Please note that using Pd complexes as catalysts, TOFs up to 10^7 h^{-1} have also been measured using micro-wave heating [19], making realistic the view that the leached species are the only active in the above cited examples. Such very high activities, obtained with a very low Pd total concentration of 50 ppb [19], are strong arguments to systematically look for what should be called hyperactive species.

A recent publication of Del Zotto et al. [2] mentions: “the solid (pre)catalyst acts as a reservoir of soluble catalytically active palladium species”. Starting from this postulate, we have tried to reinterpret the data published by the authors in favor of true heterogeneous mechanism. For that purpose, we have considered the amount of leached palladium, either measured or corresponding to the detection limit of the analytical methods (generally Inductively Coupled Plasma Mass Spectrometry (ICP-MS)). The methodology for this review is thus simply to check whether the measured activity of solid Pd catalysts could actually be explained by the activity of the leached Pd species. For that, the activities of well identified molecular Pd complexes, of recognized leached Pd species, and last of putative solid Pd catalysts are reviewed. A discussion balancing these activities with typical homogeneous vs. heterogeneous discrimination tests will then be presented.

2. Definitions

This review will only consider the published works with catalysts introduced at the solid dry state (powder) in the reactor, either to be used in batch or continuous operation. Then, we will distinguish catalytic species acting in the solid state, called “real heterogeneous catalysts” and those acting in the liquid phase, because of leaching and formation of molecular species and/or detachment of some nanoparticles. The limit between both systems must be defined, as nanoparticles are seen as a heterogeneous catalyst by some authors [20–23]. In the present work, the limit will be set at 100 nm. Particles smaller than 100 nm will be considered as part of the liquid phase, because they can not be easily separated. For example, the mechanism proposed by Perez-Lorenzo [14] which proposes the role of leached species from Pd nanoparticles indicates a homogeneous contribution and a heterogeneous (surface) contribution (see Figure 1). To our point of view, as both systems react in the liquid phase and not on a solid support, they will be considered as homogeneous (see our definitions in Figure 2).

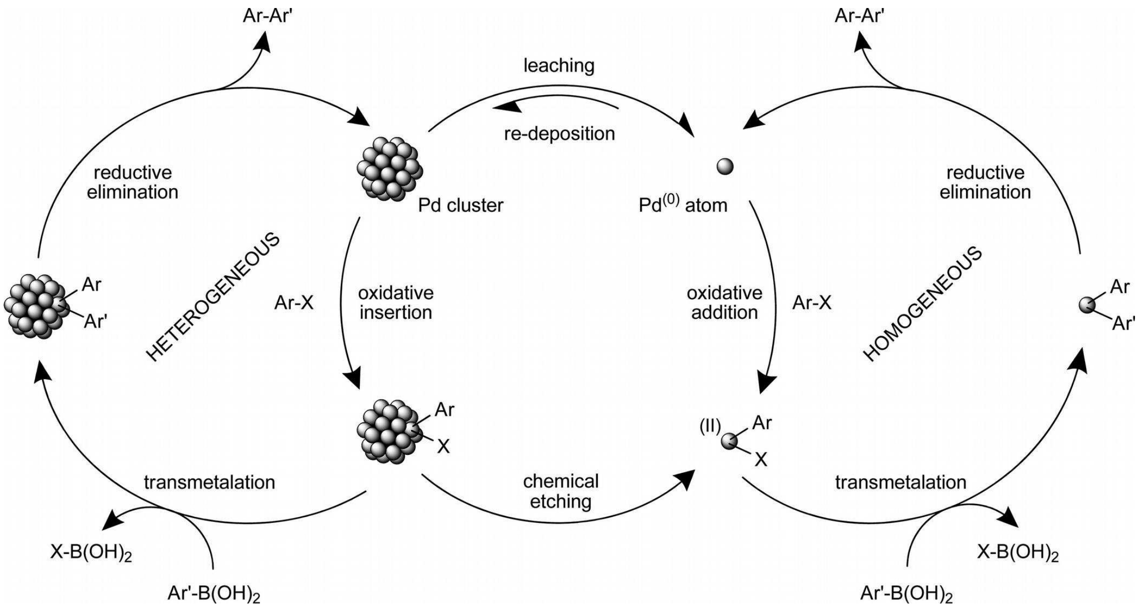

Figure 1. Proposed mechanism for the PdNP-catalyzed Suzuki cross-coupling involving both homogeneous and "heterogeneous" pathway, reprinted with permission from [14]. Copyright (2012) American Chemical Society. Please note that both act in the liquid phase.

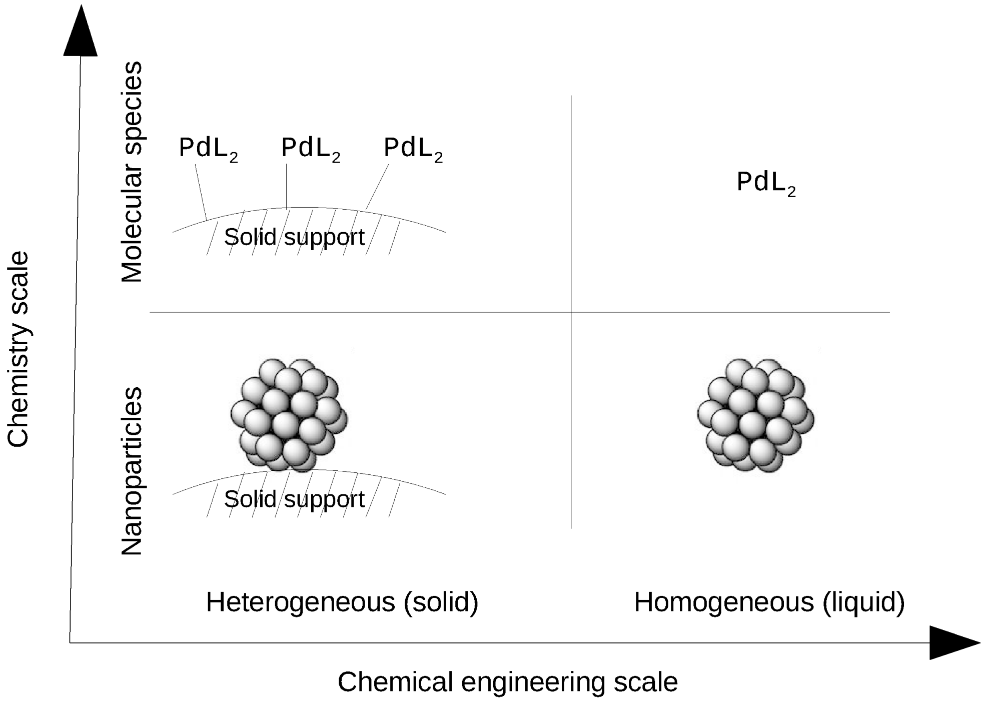

Figure 2. Definition of homogeneous and heterogenous systems in this review.

The turnover number (TON) describes the work the catalytic site has performed. It is defined as the number of moles of arylhalide transformed per mole of palladium during one single experiment or cumulative tests (“recycling”). The TOF in h^{-1} describes the intrinsic activity of the catalytic site. It is defined as the number of moles of arylhalide transformed per mole of palladium for a given contact time between the catalyst and the reagents. Depending on the reference contact time chosen, the TOF can be computed at different conversions. For example, TOF_{init} represents the initial activity of the catalyst and corresponds to the slope at the origin of the curve TON vs. time. Generally, the average

TOF is provided, the reference time being the time required to reach "quantitative conversion" or the total duration of the test. For an in depth discussion of the TOF, see [24]. Also, depending on the definition of the catalytic site, the value of TOF could be very different. In the present study and since two very different definitions of the catalytic sites will be used, i.e., heterogeneous and homogeneous catalysis, two different values of TOF will be presented. Thus, TOF_{tot} refers to the total quantity of Pd engaged in the test whereas TOF_{leach} refers to the quantity of Pd which has leached in solution, from the solid.

3. Recognized Homogeneous Catalysts

Very high activities and TONs have been obtained for molecular palladium complexes and can serve as references for high level performances. The values of TON and TOF reached in the transformation of aryl halides and phenylboronic acid (see Figure 3) are reported in Table 1 where the symbols X and R refers to the halide and the aryl substituent. Starting first with the transformation of chloroaryls, very few TONs exceeding 1 million were reported in the literature. Nevertheless, the strategies followed to reach high TONs were either to use stabilizers to prevent the agglomeration of formed nanoparticles from the pre-catalyst, or to synthesize ligands able to stabilize the catalytic homogeneous species over a very long time via multiple binding to the metal. Concerning the first idea, Zhou et al. used tetrabutylammonium bromide (TBAB) to stabilize NPs formed from $PdCl_2$ and an imidazole ammonium chloride ligand, allowing the reaching of respectable TONs of 66,000 with a TOF of 22,000 h^{-1} (Table 1, entry 5) [25]. The last strategy was used by Wang et al. with air-stable tetraphosphine. In the transformation of 4-chloroacetophenone, it only allows the reaching of a TON of 10,000 (Table 1, entry 1) [26]. However, the very activated substrate 2-chloro-5-(trifluoromethyl)nitrobenzene could be coupled with phenylboronic acid at low Pd concentration, reaching a TON of 680,000 at 130 °C (Table 1, entry 4) [26]. Similarly, TONs of 2 millions were obtained for the coupling of 4-chloroacetophenone, 4-chloronitrobenzene or 4-chlorotoluene with phenylboronic acid at 100 °C, using a phosphite ligand [27]. There was no spectacular increase in rate by using such ligand, but a greater catalyst longevity which is conferred by the π-acidic nature of the phosphite ligand. Mean TOFs near 100,000 h^{-1} were observed (Table 1, entry 6). Again using stable complexes, Feuerstein et al. obtained TOFs reaching several hundred thousands h^{-1} for particular chloroaryls (Table 1, entry 7) [28].

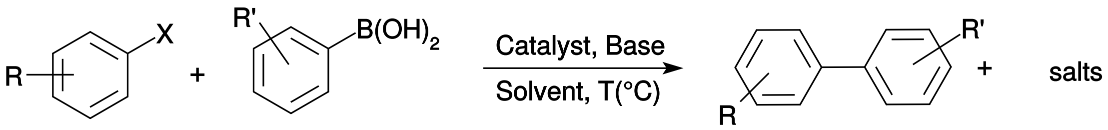

Figure 3. Schematic representation of the Suzuki coupling - R'= H (otherwise specified).

In their review about extremely low Pd-levels used in C-C coupling reactions, Deraedt and Astruc [29] reported many catalytic systems able to be used at traces in the reacting solution. The reached levels depend on the stability of the active species in solution, which reveals to be much higher for bromo and iodoaryls than for chloro ones. Whereas activities usually follow the trend ArI > ArBr > ArCl, some examples exist with a more efficient coupling of a bromo compound than a iodo one and have recently been discussed in the recent article of Ho et al. [30]. Concerning iodoaryls, high TONs (540,000) were obtained while using dendrimer-stabilized nanoparticles [31] in the transformation of iodobenzene with phenylboronic acid at RT (Table 1, entry 8). The activity was nevertheless not very high (maximum TOF = 6000 h^{-1}). TONs close to 1 million were also reported by Li et al. [32] for the transformation of 1-iodo-4-nitrobenzene at RT in water with a complex prepared from $Pd(OAc)_2$ and 1,1,3,3-tetramethyl-2-n-butylguanidine. In that case, it corresponds to a mean TOF of 42,000 h^{-1} (Table 1, entry 9).

More examples were reported for the transformation of bromoaryls, and very low Pd concentrations have been used by some authors. Even higher TON than with iodoaryls have been obtained. For the reaction of 4-bromoacetophenone with phenylboronic acid, at RT and using tetranuclear palladium(II) complexes in NMP/water, a TON of 530,000 and a TOF of 23,000 h^{-1} were obtained (Table 1, entry 10) [33]. The same reaction was also performed during a very short experiment of 5 min with a temperature increase from RT to 150 °C using a micro-wave heating source [19]. Only 250 ppb Pd were needed, using an acid stabilized stock solution of palladium acetate, to reach 99% product yield (Table 1, entry 18, TON = 212,000, mean TOF = 1.5 million h^{-1}). Again for the same reaction, Wolfe et al. developed a phosphane ligand, which, associated with palladium acetate, allows to reach a TON of 91 million and a mean TOF of 3.8 million h^{-1} at 100 °C (Table 1, entry 19) [34]. For the transformation of 4-bromotoluene with a similar complex, high TON (ca. 15 million) and TOF (202,000 h^{-1}) were also reported for a conversion of 29% (Table 1, entry 13) [35]. Very high TON (97 million) and activities (4.8 million h^{-1}) were reported by Doucet et al. and Feuerstein et al. for the coupling of 4-bromoacetophenone at 130 °C catalysed by a tetraphosphine Pd complex (Table 1, entry 20) [36,37]. Further in the development of tetraphosphines, incredibly high TON (340 billion) and TOF (1 billion h^{-1}) were reached by Zaborova et al. [38] at 120 °C with a cyclodextrin-tetraphosphine hybrid which was proposed to prevent the agglomeration of Pd(0) into inactive species (Table 1, entry 21). This article thus demonstrates that very low Pd concentrations can catalyze the Suzuki coupling. The same authors also studied the coupling of more electron-rich aryl bromides at 120 °C. 4-bromoanisole and 4-bromotoluene were coupled with TONs of 60 and 130 million respectively and TOFs of 380,000 and 670,000 h^{-1} (Table 1, entries 14 and 15) [38]. Using a palladium-aminocarbene, Luzyanin et al. obtained a TON of 1.4 million for the coupling of 4-bromoanisole with phenylboronic acid at 80 °C. TOFs close to 1 million h^{-1} were obtained (Table 1, entry 17) [39]. Similar TONs (1 million) and activities (1 million h^{-1}) were recorded for the transformation of 2-bromotoluene at 110 °C using Pd(II) dimers with N-heterocyclic carbene (NHC) ligands [40]. In the transformation of 4-bromobenzotrifluoride, a TON of 58 million was observed with $PdCl_2$-2,6-bis(1,5-diphenyl-1H-pyrazol-3-yl)pyridine catalyst (Table 1, entry 12) [41]. In the case of a solution of nanoparticles stabilized by dendrimers, high performances have also been obtained by the group of Astruc [21]. At 80 °C, a TON of 2.7 million was reached for 1-bromo-4-nitro-benzene with a TOF of 45,000 h^{-1} (Table 1, entry 11).

While this review is far from being exhaustive, it reveals that TONs and TOFs exceeding millions (million h^{-1} respectively) can be reached with homogeneous catalysts, especially for the transformation of bromoaryls for which an example with values of TON/TOF of several billions (billion h^{-1}). In the case of chloroaryls, reported values are at least one order of magnitude lower. Note here that there is no needs for showing all examples of very active homogeneous catalysts for the SM reaction since only selected examples suffice to demonstrate that very active homogeneous Pd species could exist.

Table 1. TONs and TOFs obtained for SM coupling with Pd complexes of NPs in solution.

Entry	**X**	**R**	**Solvent**	**Catalyst**	**T (°C)**	**Pd_{tot} (mol %)**	**TON mol/mol**	**TOF (h^{-1})**	**Ref.**
1	4-Cl	$COCH_3$	DMAc	Pd tetraphosphine	130	0.01	10,000	170	[26]
2	4-Cl	$COCH_3$	Toluene	$Pd(OAc)_2$+phosphane	100	0.02	4600	200	[34]
3	2-Cl	CN	Xylene	Pd tetraphosphine	130	0.002	29,000	1450	[28]
4	2-Cl	1-NO_2+5-CF_3	DMAc	Pd tetraphosphine	130	10^{-4}	680,000	5000	[26]
5	4-Cl	NO_2	H_2O	TBAB stab. NPs	120	0.001	66,000	22,000	[25]
6	4-Cl	$COCH_3$ - H - NO_2	Dioxane	Pd phosphite	100	5×10^{-5}	2,000,000	100,000	[27]
7	2-Cl	1-NO_2+5-CF_3	Xylene	Pd tetraphosphine	130	10^{-5}	6,800,000	340,000	[28]
8	I	H	$CHCl_3$-MeOH	Dendrimer stab. NPs	25	10^{-4}	540,000	6000	[31]
9	4-I	NO_2	H_2O	$Pd(OAc)_2$+guanidine	RT	10^{-4}	850,000	42,000	[32]
10	4-Br	$COCH_3$	NMP-H_2O	tetranuclear Pd(II)	RT	1.8×10^{-4}	530,000	23,000	[33]
11	4-Br	NO_2	EtOH-H_2O	Dendrimer stab. NPs	80	3×10^{-5}	2,700,000	45,000	[21]
12	4-Br	CF_3	EtOH	$PdCl_2$ pyridine	70	10^{-6}	58,000,000	72,000	[41]
13	4-Br	CH_3	Dioxane	$Pd(OAc)_2$ - monophosphane	100	2×10^{-6}	14,550,000	202,000	[35]
14	4-Br	OCH_3	Xylene	Pd cyclodextrin-tetraphosphine	120	3×10^{-7}	60,000,000	380,000	[38]
15	4-Br	CH_3	Xylene	Pd cyclodextrin-tetraphosphine	120	3×10^{-7}	130,000,000	670,000	[38]
16	2-Br	CH_3	Ethylene glycol	Pd(II)NHC dimer	110	10^{-4}	900,000	900,000	[40]
17	4-Br	OCH_3	EtOH	Pd aminocarbene	80	10^{-5}	1,400,000	1,000,000	[39]
18	4-Br	$COCH_3$	EtOH-H_2O	Stab. $Pd(OAC)_2$	150	250 ppb	212,000	1,500,000	[19]
19	4-Br	$COCH_3$	Toluene	$Pd(OAc)_2$+phosphane	100	10^{-6}	91,000,000	3,800,000	[34]
20	4-Br	CF_3 or $COCH_3$	Xylene	Pd tetraphosphine	130	10^{-6}	96,000,000	4,800,000	[36]
21	4-Br	$COCH_3$	Xylene	Pd cyclodextrin-tetraphosphine	120	10^{-10}	340,000,000,000	1,000,000,000	[38]

4. Solid Pre-Catalysts Providing Active Species in Solution

The fact that some species in solution can be the true catalyst in the SM reaction is a well-known phenomenon that was recently reviewed [2,42,43]. Our objective is thus not to provide a new inventory of the corresponding articles, but to extract some quantitative information about the reaction rates and TONs. Supposing that the analyzed Pd concentration in the liquid medium is totally responsible for the catalytic activity, we have calculated TOFs based on this only contribution (noted TOF_{leach}), to check whether the reached values were in the range of the TOFs published with homogeneous Pd catalysts. A series of authors suspect that the leached Pd during the reaction may totally or partly explain the activity of their solid pre-catalysts. However, when Inductively Coupled Plasma - Atomic Emission Spectroscopy (ICP-AES) analyses are performed, the concentration is often below the limit of detection. This can be related either to a lower value of palladium concentration (<1 ppm) or to redeposition of the Pd at high conversion. Please note that knowing the contribution of the leached species is not straightforward since the Pd concentration in the solution varies with the conversion. This was observed by several authors, with a concentration varying by one order of magnitude between 50 and 100% conversion [44–46]. The values given in Table 2 have thus to be considered as orders of magnitude since the values of leached concentrations were not always associated with the conversions at which they have been measured.

In the team of Holmes and McGlacken, it was found that the morphology of Pd nanoparticles impacted the conversion of 4-bromoanisole with phenylboronic acid. This was explained by the leaching susceptibility of the nanocrystals, Pd being more easily leached from [100] facets than from [111] ones [47]. The concentration of Pd found in reacting solutions (0.32 to 1.1 ppm) leads to mean TOF_{leach} of a few hundreds h^{-1} (Table 2, entries 1 and 3).

Using Pd nanoparticles supported on hydrotalcite for the coupling of iodobenzene with phenylboronic acid, Vaerenbergh et al. [46] observed by ICP-AES a leaching of a few percent of Pd, with a concentration varying with the conversion (maximum of 2.6% Pd at 88% conversion). Redeposition of Pd on the surface occurred at full conversion. TOF_{tot} is low (<10 h^{-1}). By considering the only fraction of leached Pd, TOF_{leach} can reach some hundreds h^{-1} (Table 2, entry 2). Similarly, the team of Kohler, Soomro et al. observed that the Pd concentration in solution during the reaction correlates with the progress of the reaction. This made them conclude that dissolved molecular palladium is the catalytically active species. Thanks to redeposition, the Pd concentration in the product may be brought to a minimum value, lower than 1 ppm [44,45]. In the case of aryl bromides, up to 50% of the initial Pd atoms were found to leach in the reacting solution at partial conversion (<80%) and the Pd was shown to redeposit on the surface at full conversion. Switching to chlorides, in the case of the coupling of 4-chloroacetophenone with phenylboronic acid, the Pd leaching reached lower values and the redeposition was not effective. This was explained by the presence of TBAB which was mandatory to obtain a conversion, but prevented the redeposition process. TOF_{leach} reached 1070 h^{-1} for this last reaction at 65 °C (Table 2, entry 4). The same leaching/redeposition principle was also used by Ohtaka et al. who showed that polystyrene was adapted for Pd redeposition and allowed to perform several consecutive runs [48].

The use of a Pd foil in the coupling of 4-iodo-nitrobenzene with phenylboronic acid at 100 °C showed a considerable pitting of the surface, proving the leaching of Pd [49]. Consistent with this, the authors observed about 100 ppb of Pd in solution, which corresponds to a mean TOF_{leach} of ca. 2000 h^{-1} supposing that the leached species are the only responsible for the 45% conversion in 24 h (Table 2, entry 5). The value is rather low, because the reaction is probably mass transfer limited due to the absence of stirring due to the use of a Pd foil.

Other evidences of Pd leaching was found by Mieczynska et al., using $Pd(OAc)_2$ supported on siloxane co-polymers. 18% of the initial Pd content was analysed in the solution after 5 consecutive reactions of 2-bromotoluene with phenylboronic acid. The addition of Hg only slows the reaction but does not prevent it. The authors thus propose a cocktail catalysis in which species in solution and supported Pd(0) can catalyze the reaction, according to the concept proposed by Ananikov et al. [50,51].

Considering the leached species as the only active catalyst, this would correspond to a mean TOF$_{leach}$ during these 5 runs of 2400 h^{-1}, which is still a modest value (Table 2, entry 6) [52].

During the coupling of 4-iodoanisole with phenylboronic acid catalysed by supported Pd NPs, Niu et al. measured a Pd leaching by ICP-MS. The leached Pd species were proposed to be responsible for the cross-coupling products. 60 ppb Pd in the solution correspond to a mean TOF$_{leach}$ of 14,000 h^{-1} (Table 2, entry 7). After reaction, the newly reduced Pd(0) atoms nucleate and grow into fresh crystalline-NPs. Due to the absence of surfactants, the size and shape of these new NPs changed [53]. The same phenomenon was observed for the bromide but no activity was recorded for the chloride.

In another example, using multi-walled carbon nanotube/dimethylaminopyridine (DMAP) stabilised Pd nanoparticle composites in the coupling of 4-iodobenzoic acid with phenylboronic acid, the Pd concentration in the solution was below the limit of detection of atomic adsorption spectroscopy (AAS), reported to be 10 ppb (Table 2, entry 8). Nevertheless, the authors performed a hot filtration test at 18% conversion and obtained an increase of activity in the filtrate (free from solid). The nanoparticles were thus susceptible to leaching (either as colloids or Pd complex) in very low amount but sufficient to participate partly or fully to the catalytic activity [54]. Considering 10 ppb of Pd in the solution, a TOF$_{leach}$ of 23,000 h^{-1} can be estimated by the increase of 18 to 31% conversion during the hot filtration test. It is thus reasonable to admit that the leached species are fully responsible of the conversion.

Other teams have tried to use the hot filtration test to prove that leached species can participate to the reaction, but did not obtain a further conversion of the reacting mixture after removal of the solid pre-catalyst [52,55]. However, both teams nevertheless concluded that their reactions were running in the liquid phase since poisoning tests and ICP-MS analysis showed the role of leached species. Thus, in the coupling reaction between various bromoarenes and phenylboronic acid, using palladium doped CeO_2, SnO_2 or their mixed oxides as the pre-catalyst, Lichtenegger et al. were totally aware of the fact that the reaction proceeded via dissolved Pd species in a homogeneous mechanism [55]. Thus, with concentrations of Pd going from 0.06 to 0.14 mg$_{Pd}$/L, the TOF$_{leach}$ reached values of 50,000 h^{-1} (Table 2, entries 10 and 11). Due to Pd redeposition on the support, the use of the catalyst for successive runs or in continuous operation is presented as a good option [56]. A membrane reactor was also used to demonstrate that Pd(0) atoms or Pd(II) ions can leach from Pd nanoparticles during the reaction of 4-iodotoluene with phenylboronic acid at 100 °C [57]. The leaching of small clusters was conversely not observed.

A good control of the leached species was attained by several authors, using Au-Pd bimetallic catalytic precursors. For Fang et al., the reactivity of leached Pd can be tuned by the number of Pd shells around the Au core [58]. In the case of Niu et al., Pd-Au was used and analyzed by XRD to get some information about the structural changes of the catalysts due to Pd-leaching (Table 2, entry 9) [53]. Bimetallic AuPd catalysts were also used by Al-Amin et al. [59], using Sulfur-modified Au-supported Pd material under a microwave irradiation to generate a controlled amount of leached Pd (<1 ppm), declared to be the active species in the coupling of a variety of arylhalides and boronic acids. Such low controlled leaching allows to reach high TONs. The TOF$_{leach}$ exceeded 1,000,000 h^{-1} for the reaction of iodobenzene with 4-chlorophenylboronic acid but still reached more than 100,000 h^{-1} for the coupling of bromobenzene with the same boronic compound (Table 2, entries 12 and 13). Note that the TOF values are mean values obtained after 1 h of reaction where full conversion is observed. Thus, initial TOF$_{leach}$ may be much higher, but still in the range of Pd complexes' activity. The authors really support the idea of releasing controlled weak amounts of Pd from a reservoir (20 ppb for the iodoaryls, 200 ppb for the bromoaryls). Thus, after 10 reuses of the same Pd precursor, they didn't reach a noticeable Pd depletion of the solid surface, despite the non-redeposition of Pd that micro-wave irradiation prevents.

Palladium supported on a highly cross-linked imidazolium-based materials (10 wt-%) was used in the reaction of 4-bromotoluene at 50 °C for 36 h, using a new experimental device that permits to reduce the E-factor compared to a classic batch operation (Table 2, entry 14). The same catalyst was used for 4 consecutive tests with 95% yield, which corresponds to a TON of 3800 and a TOF$_{tot}$ of 26 h^{-1}. Only 0.015 wt-% of Pd leaching was found in the isolated product for a single test giving a TOF$_{leach}$ of 176,000 h^{-1}, authors said that this Pd was a result of a release and catch mechanism. Furthermore, the same team [60,61] used Pd NPs supported on zirconium phosphate glycine diphosphonate nanosheets (Pd/ZPGly-15) in the reaction of 4-bromoanisole for 3 runs using the same experimental device. Pd leaching was near 3 ppm in the isolated product giving a TOF$_{leach}$ 200 times higher than the TOF$_{tot}$ obtained for total Pd (Table 2, entry 15). After the hot filtration test the authors concluded that the reaction is working on a release and catch mechanism, and that the ZPGly system is able to catch efficiently the released Pd.

Table 2. Calculation of TOF that could be due to leached Pd from solid catalysts. ^{a} R′ = pinacol phenylboronate ^{b} R′ = 4-Cl (see Figure 3).

Entry	X	R	Solvent	Catalyst	T (°C)	Pd$_{tot}$ (mol %)	Pd Leach. (ppm)	TOF$_{tot}$ (h^{-1})	TOF$_{Leach}$ (h^{-1})	Ref.
1	4-Br	OCH_3	EtOH-H_2O	Pd cubic NC	RT	0.5	1.1	<10	230	[47]
2	I	H	DMF-H_2O	Pd (NP) /hydrotalcite	40	2	<2% Pd$_{tot}$	10	430	[46]
3	4-Br	OCH_3	EtOH-H_2O	Pd octahedric NC	RT	0.5	0.32	<10	770	[47]
4	4-Cl	$COCH_3$	NMP-H_2O	Pd/Al_2O_3 + TBAB	65	0.1	25% Pd$_{tot}$	270	1070	[45]
5	4-I	NO_2	DMF-H_2O	Pd foil	100	-	0.1	-	2000 ^{a}	[49]
6	2-Br	CH_3	iPrOH-H_2O	Pd$(OAc)_2$/siloxane	60	0.23	18% Pd$_{tot}$	430	2400	[52]
7	4-I	OCH_3	THF	Pd/C	80	0.8	0.06	<10	14,000	[53]
8	4-I	COOH	H_2O	NPs Pd-DMAP/MWCNT	100	0.05	<0.01	1000	22,700	[54]
9	4-I	OCH_3	THF	Pd-Au/SBA-15	80	0.8	0.02	<10	27,000	[53]
10	4-Br	CH_3	EtOH-H_2O	$Ce_{0.99}$-$Pd_{0.01}O_{2-x}$	75	0.5	0.06	200	31,000	[55]
11	4-Br	CH_3	EtOH-H_2O	$Sn_{0.99}$-$Pd_{0.01}O_{2-x}$	75	0.5	0.14	1200	53,000	[55]
12	Br	H	DMF	S-modified-Au-Pd	90	-	0.2	-	130,000 ^{b}	[59]
13	I	H	EtOH	S-modified-Au-Pd	80	-	0.02	-	1,300,000 ^{b}	[59]
14	4-Br	CH_3	EtOH	Pd cross-linked imidazolium	50	0.1	0.015%	26	176,000	[62]
15	4-Br	OCH_3	EtOH 96%	Pd/ZPGly-15	70	0.1	3	98	19,200	[61]

Defining where the reaction occurs, in the liquid phase or at the solid surface, is not a simple question, and many authors keep on wondering the role of each contribution. After having thought that their resin-supported palladium was not subject to leaching during the Suzuki coupling of chloroarenes and arylboronic acids [63], the group of Monguchi and Sajiki realized that Pd actually leached during the course of the reaction but was redeposited on the support at reaction completion [64]. As the solid surface is modified with time, an unsolved question is whether the loss of activity is due to the surface rearrangement or to Pd depletion. The authors think that the decrease of Pd species on the resin surface (and migration inside the resin) caused the decrease of the catalytic activity due to the difficult uptake of substrates inside the support. This still supposes that a heterogeneous contribution exists. Similarly, the team of Zou and Martin-Matute present different contributions where the role of leached species is not easy to establish. Using Pd nanoparticles immobilized into an amino-functionalized metal–organic framework, they observed some leaching, but still a very good recyclability of their catalyst. After 10 runs, less than 1% of the initial Pd content was lost [65]. They concluded in favor of a heterogeneous catalysis mechanism with their material. The same conclusion of robust heterogeneous catalyst arises from their continuous experiments despite leaching till 1.2 ppm in the produced solution [66]. In another work from the same team, it is said that leached Pd species can be responsible for the Suzuki reaction. The small Pd NPs in the Metal Organic Framework (MOF) can "act as a reservoir of Pd atoms or ions, which subsequently form larger Pd NPs on the MOF surface" [67]. The same analysis can apply to a very recent work concerning hybrid hydrogels able to act as Pd scavengers. A homogeneous contribution during the reaction was established, but the authors still supposed a dominant contribution of the immobilized Pd [68]. We will see in the next section that even if clear or sufficient evidences were not found by many other authors, the proposal that leached species are the active catalyst seems to be an alternative interpretation of results in most of the cases.

5. Putative Heterogeneous Catalysts

Despite a lot of articles claiming that heterogeneous catalysts are just a reservoir of active species as depicted above, some authors, even very recently [69,70], consider that the solid material is the only true catalyst for the reaction. Their conclusions are supported by different analyses, either of the Pd content in the solution or by split-tests, poisoning tests or other ways to try to identify the active species. Other interpretations of the data acquired by these groups are nevertheless possible, (a) because the limits of Pd detection are not low enough, (b) because the analyses are not always performed in the optimal conditions (conversion, reaction temperature), (c) because the TON reached is very low. The applicability of the different analyses and methods to discriminate homogeneous and heterogeneous contributions will be further discussed in the next section. In the present paragraph, considering that traditional tests to discriminate between a heterogeneous process and a homogeneous one are not unambiguous, we have re-interpreted the data obtained with solid catalysts, assuming that the performances are the only fate of leached species. Table 3 gathers the results after new interpretation. In the table, for the calculation of the TOF reached by leached species, it is proposed to consider that 1 ppm is the limit of detection of ICP-AES (otherwise specified) and that this amount can be present in the solution if no other analysis is done. Note that Pd may have been redeposited on the support at the reaction completion and that the value of 1 ppm is just to propose an order of magnitude for a TOF due to potentially leached species.

The team of Sureshbabu et al. [71] synthesized a Pd(0)/polyvinyl cloride (PVC) (13 wt-% Pd) from $PdCl_2$ inside a PVC suspension. This precursor was used in the reaction of iodobenzene (Entry 2, Table 3), in a batch reactor at 25 °C, with a yield that goes from 99% at the first run to 96% and 90% at the 4th and 5th runs respectively. Besides, the amount of palladium was decreased from 13% to 12.7% and then 11.81 wt-% in the last two cycles respectively, which was considered negligible by the authors, although it represents 2.3% and 9% of the initial mass of Pd. Based on the amounts of Pd released inside the solution the TON (TOF) increases from 480 (48 h^{-1}) to 5300 (533 h^{-1}).

Pd-NHC supported on macroporous polystyrene (Pd-NHC-MPS) was tested for 5 runs in the reaction of 4-bromoacetophenone (Entry 3, Table 3) [72]. The yield was stable at 94% with a Pd leaching equal to 3%, 1.1%, 1.2%, 1.4% et 1.3% for each run respectively, which represents 8% of the total Pd used. However, no attempt was made by the authors to quantify the association between the Pd in solution and the yield, considering that the activity was largely related to the supported Pd because of the stable yield. While comparing the TON (TOF) of the total Pd 465 (93 h^{-1}) and the leached one 5810 (1160 h^{-1}), the values obtained due to the leached species only are still modest.

Veisi et al. [70] used a Pd supported on NPs of magnetic iron (Fe_3O_4), in 7 successive runs with 4-bromoanisole. Only 5% of Pd was leached at the last run giving a homogeneous activity 20 times more then the heterogeneous one and the same results were obtained with 4-bromoacetophenone [73] giving a TOF_{leach} one order of magnitude higher than TOF_{tot} (Entry 4, Table 3).

Yuan et al [8] used 0.9 mol% of a Pd supported on metal-organic frameworks (Pd-MIL-101 (MOFs)), in the reaction of several chloro-aryls (e.g., chloroanisole entry 5, Table 3), leaching was less than 0.2 mol%, giving a TOF_{leach} of 2800 h^{-1} that was 500 times more than the TOF_{tot} (6 h^{-1}).

Two bases (Cs_2CO_3 and iPr_2NH) were used by Pascanu et al. [65] with a Pd supported on MOF (8 wt-% Pd@MIL-101Cr-NH_2) as a catalyst in the reaction of 4-bromoanisole with pinacol phenylboronate (Entries 1 and 7, Table 3), 0.17 ppm and 5.64 ppm Pd were analyzed in solution for Cs_2CO_3 and iPr_2NH respectively. These amounts of Pd correspond to a TON (TOF_{leach}) of 30,900 (5140 h^{-1}) and 930 (155 h^{-1}) respectively. A reusability test was carried out for 10 runs with p-bromotoluene (Entry 9, Table 3) giving a stable conversion of 100%, but the 10 cycles correspond only to a TON (TOF_{tot}) about 330 (66 h^{-1}). Whereas 0.96% of Pd was lost after the last run, this amount of Pd gives a TON (TOF_{leach}) equal to 34,400 (6880 h^{-1}).

Sometimes the TOF calculated for the leached Pd is more logical and much more interesting than the one obtained for the total mass, which is the case of Sahu et al. [74] who tested well dispersed Pd NPs on silica (Pd(NP)-NMe_2/SiO_2 (4 wt-%)) in the reaction of p-bromoanisole (Entry 12, Table 3) for

6 runs. Meanwhile, the yield decreased from 98% to 90%, with a TOF_{tot} of 250 h^{-1}. Only 2% of the Pd was leached giving a TOF_{leach} of 12,500 h^{-1}. Furthermore, different heterogeneous precursors have been tested in the reaction of iodoaryls (Entries 16, 11, 10, 13, 8, Table 3) and in all the tests the TOF obtained for total Pd was in the order of several hundreds h^{-1}, but when it was calculated using the amount of leached Pd, it increases to several tens of thousands h^{-1} [69,75–78].

Palladium nanoparticles supported on zirconium oxide (Pd NPs/ZrO_2) were used in several runs in the reaction of 5 iodoaryls and 5 bromoaryls with phenylboronic acids (R'=H, OCH_3 or CH_3) (Entry 17, Table 3) [79], the average yield obtained was 79%, which corresponds to a total TON (TOF_{tot}) of 7900 (57 h^{-1}). Moreover, ICP-MS analysis showed that 67 ppb of Pd passed to the solution which represents a TOF_{leach} of 56,500 h^{-1}.

Suzuki-reaction for 3-iodophenol (Entry 18, Table 3) was carried out inside a fixed bed reactor filled with Pd/C (10% Pd) for 18 h, which gave a TOF_{tot} equal to 239 h^{-1}. This value increases to 71,550 h^{-1} considering the leached Pd (40 ppm) [80].

The SiliCycle Inc. company has commercialized several silica supported Pd catalysts, which were evaluated in several works. In 2011 [81], 0.1 mol% of a Pd encaged inside the silica matrix (Siliacat Pd(0)) was used with iodonitrobenzene (Entry 29, Table 3) during 7 runs. The conversion was maximum at 100% with a TON_{tot} (TOF_{tot}) equal to 7000 (1000 h^{-1}), calculated for the total amount of Pd. The ICP-AES analysis showed an average leaching of 0.02 ppm (except for the first run 0.18 ppm which can be a result of residual Pd from the synthesis of the catalyst), this leaching value corresponds to a TOF_{leach} of 424,000 h^{-1}. Furthermore, the same catalyst was tested in the reaction of bromoacetophenone (Entry 22, Table 3), the total TON and TOF_{tot} obtained were near to 1000 and 12,500 h^{-1} respectively. 2 ppm of Pd were transferred into solution giving a TOF_{leach} of 127,200 h^{-1}.

The coupling of 4-bromoanisole (Entry 30, Table 3) and 4-bromobenzonitrile with phenylboronic acid (Entry 36, Table 3) were tested in flow at 70 °C through a reactor filled with a Pd(II) complex supported on silica (SiliaCat Pd-DPP) [82]. The obtained yield was 48% for the bromoanisole with 26.75 ppm Pd in the isolated product and 95% for the bromobenzonitrile with 1.26 ppm in the isolated product. The two Pd values in solution give TOF_{leach} of 453,000 h^{-1} and 9,614,000 h^{-1} respectively. Kappe's team used the coupling of 4-iodobenzonitrile with phenylboronic acid [83] in flow with SiliaCat Pd-DPP (Entries 14 and 19, Table 3). Only 1% of the total quantity of Pd was leached for the THF/EtOH/H_2O/K_2CO_3 system, which corresponds to a TOF_{leach} of 88,800 h^{-1}.

Back to non-commercial catalysts, Crudden et al. used a Pd on a functionalized silica (Pd-SBA-15-SH) in the coupling of a bromoaryl (Entries 20 and 32, Table 3) at two different temperatures, 80 °C for 5 h and 100 °C for 2 h, giving yields of 98% (TOF_{tot}= 20 h^{-1}) and 97% (TOF_{tot} = 50 h^{-1}) respectively [84]. 3 ppb and 90 ppb of Pd are leached in the first and second tests, these values correspond to TOF_{leach} equal to 1,390,000 h^{-1} and 114,000 h^{-1}. The hot filtration and the three phase tests were made to check the heterogeneous behavior of the catalyst, which gave 7% of conversion (max.) for 8 h and 13 h respectively.

Using 0.4 mol% of Holmium(III) metal–organic framework (Ho-MOF) supported Pd in the reaction of iodobenzene with phenylboronic acid at 100 °C (Entry 21, Table 3) during 5 successive tests at 99% conversion without leaching measurement, a TON (TOF_{tot}) of 1240 (248 h^{-1}) was observed [85]. In similar operating conditions, the authors measured 86 ppb Pd leaching during Heck coupling. Assuming that this value could also be measured during the SM reaction, TOF_{leach} would reach 122,000 h^{-1}.

Zhong et al. [86] have studied the coupling of a bromoaryl (Entry 23, Table 3) using NPs of Pd supported on mesoporous carbon. Only less than 0.1 ppm of Pd was leached, which gives a TOF_{leach} of 132,500 h^{-1}, thousands time higher than the one measured for total Pd (50 h^{-1}).

Pd NPs synthesized from [$PdCl_2$(COD)] were used in an ionic liquid to catalyze the reaction of bromobenzene with phenylboronic acid under argon (Ar) at 100 °C (Entry 24, Table 3) [87]. The yield ranges between 92% and 77% for 10 consecutive runs, with 3–5 ppm of Pd in the isolated product, this value results to a TOF_{leach} of 138,000 h^{-1}.

The reaction of 4-iodoanisole with phenylboronic acid catalysed by a Pd-NHC complex supported on silica coated magnetic nanoparticles (Pd-NHC-MNP) was performed for 6 successive runs at 80 °C (Entry 31, Table 3). The yield decreased continuously from 97% to 88% in the last run, which gives a TON (TOF_{tot}) equal to 4633 (908 h^{-1}) [88]. Considering the ICP-AES analysis showing 0.15% of Pd leaching, corresponds values for TON (TOF_{leach}) are 539,000 (634,000 h^{-1}).

Indra et al. have prepared a solid precursor by supporting [Pd(COD)Cl_2] on hydroxyapatite. This solid has been used in the reaction of several iodo, bromo and chloroaryls [89] with 4-methylphenylboronic acid. In the case of iodoaryls, 10 runs at 0.034 mol% of Pd gave a TON (TOF_{tot}) equal to 30,000 (125 h^{-1}). The ICP-AES analysis did not detect Pd in solution (<1 ppb), but calculating an hypothetic TOF corresponding to this small level of Pd (1 ppb), the TOF is still not very high (442,000 h^{-1}) and can be considered as plausible (Entry 28, Table 3).

Siga et al. [10] tested a polymer-anchored palladium(II) precursor in the reaction of three different aryl halides (iodo, bromo, chloro-benzene) (Entries 40, 35 and 26 Table 3). In order to show the stability of the catalyst, 15 consecutive runs were performed with p-bromoacetophenone (Entry 37, Table 3) the conversion was between 99% and 97% (TOF_{tot} = 29,440 h^{-1}), with Pd leaching less than 0.3%, which gives a TOF_{leach} of 9,810,000 h^{-1}. This very high value is still in the range of what was observed for very active Pd complexes in the transformation of bromoaryls.

A self-assembled heterogeneous precursor inspired from metalloenzyme proteins was used in the reaction of chloro- (Entry 27, Table 3), bromo- (Entry 34) and iodotoluene (Entry 25) with phenylboronic acid at 100 °C, giving TOF_{tot} between 12,500 h^{-1} and 119,000 h^{-1}. The ICP-AES analysis did not show any Pd in solution for a detection limit at 5 ppb. A calculation of TOF_{leach} with this very low Pd level gives till 2.7 million h^{-1} for the bromoaryl. This high value due to the non-measurable concentration Pd in solution can be explained by the possibility of readsorption during cooling at the end of the reaction [11].

A stable yield of 92% (TOF_{tot} = 20 h^{-1}) was obtained with a mesoporous LTA zeolite-supported palladium (Pd-MP-LTA) for 10 runs in the reaction of chloroanisole with phenylboronic acid (Entry 33, Table 3) [90]. Besides, the ICP-AES showed a leaching of 0.0009% of Pd into the solution giving a TOF_{leach} of 2,270,000 h^{-1}. Note that this high value may be over-estimated due to a leaching measurement at the end of the reaction, where a possible readsorption of Pd may have occurred.

The reaction of 4-iodotoluene (Entry 41, Table 3) was conducted inside a flow microreactor filled by Pd supported on micro-particles of poly-hydromethylsiloxane (PHMS) at 65 °C, giving 55% of yield after 30 min of reaction time. Under the same conditions, the maximum TON that would be obtained during a year of operation was estimated to 4000 with a very small mean TOF_{tot} less than 0.5 h^{-1}. Considering 0.3 ppb of Pd at the reactor outlet, the calculation of TOF_{leach} leads to a value of 65 million h^{-1}. This very high value is of course related to the very low level of leached Pd measured. Nevertheless, it is not excluded that, due to the high retention times in the packed bed reactor, leaching/redeposition may have occurred before the reactor exit.

Microwave (MW) assisted reaction of several aryl halides showed good results with TOF_{tot} higher then 200,000 h^{-1} [18]. For example the reaction of 4-bromoanisole without solvent under micro-wave irradiation (400 W) using a chitosan-pyridil-base Pd(II) gave a TOF_{tot} of 240,000 h^{-1}. Moreover, the conversion decreased from 99% to 75% when the catalyst was used for 7 runs (Entry 38, Table 3), this decrease can be explained by the fact that the catalyst was deactivated or lost via leaching. However, ICP-AES test showed that only 2% of the initial Pd was lost after the 7th run. The calculated TOF_{leach} thus reaches 10,500,000 h^{-1}. The same team [91] tested Pd supported on silicagel with the same reactants (Entry 42, Table 3) under MW at 50 °C without solvent, the obtained results showed a TOF_{tot} near to one million h^{-1}, with 99% yield. In the same work, Pd leaching was as less as 1% after 10 runs which corresponds to a TOF_{leach} two orders of magnitude higher than TOF_{tot}. Such very high values of TOF_{leach} ar far beyond the values that are classically obtained with Pd complexes. However, it must be noticed that the values of TOF_{tot} without micro-wave heating are 2 to 3 orders of magnitude lower than those reported above (Entries 39 and 43, Table 3). A much higher local temperature than expected can perhaps explain the very high values observed with micro-wave irradiation.

To conclude this part, TOFs have been recalculated considering some leaching in the solution, giving values that may be very high, but still in the range of what was observed for homogeneous catalysts (Section 3). Furthermore, when leaching of Pd species into solution is as small as few ppb (or can not be detected by ICP tests) there is no clue about the heterogeneous nature of the mechanism, especially for tests with complete conversion (100%) because of possible readsorption of Pd leached at the end of the reaction [45,49,64,92]. Moreover, in many recent publications the concentration of Pd used for reaction was already at the ppb level, making the detection of leached species inevitably challenging, e.g., Yamada et al. [11] with ca. 10 ppb of Pd for the reaction of 4-iodotoluene (Entry 25, Table 3) which is only 2 times higher than their limit of detection (5 ppb). Another example comes from the work of Chtchigrovsky et al. [93] who used 0.0001 mol% of Pd, which represents only 10 ppb of Pd. Other examples, even at ppm levels are also ambiguous (e.g., [73,91], . . .) when the analytical tool does not allow to go below 1 ppm, like very recently, in the work of Abdellah et al. [94] who worked with 0.5 ppm of Pd in the reaction of bromotoluene (93% of conversion). It thus appears that heterogeneous precatalysts may be the source of very active catalytic species in solution, acting as a reservoir of these species. By the controlled release of a few ppb of Pd in solution, the reactions products do not require a further purification.

Table 3. Literature data stating for putative heterogeneous catalysis. [a] in isolated product; [b] average value for several runs; R′ = H (see Figure 3) except [c]: see text; R_1 = CH_3, H or $COCH_3$; NA: not available.

Entry	X	R	Solvent	Catalyst	T (°C)	Pd_{tot} (mol %)	Pd Leach. (ppm)	TOF_{tot} (h^{-1})	TOF_{leach} (h^{-1})	Ref.
1	4-Br	OCH_3	H_2O	Pd-MIL-101Cr-NH_2	RT	3	5.64	6	155	[65]
2	I	H	EtOH:H_2O	Pd(0)/PVC	25	1	2.4	48 [b]	533 [b]	[71]
3	4-Br	$COCH_3$	DMF:H_2O	Pd-NHC-MPS	50	1	7.07	93 [b]	1160 [b]	[72]
4	4-Br	CH_3	EtOH:H_2O	Pd(0/II)/magnetic Fe_3O_4 NPs	25	0.2	3.53	133 [b]	2650 [b]	[70]
5	4-Cl	OCH_3	H_2O	Pd-MIL-101 (MOF)	80	0.9	<0.2% Pd_{tot}	6	2800	[8]
6	2-Br	CH_3	iPrOH:H_2O	Pd/Copolymer	60	0.23	5.85	400 [b]	3600 [b]	[52]
7	4-Br	OCH_3	H_2O	Pd-MIL-101Cr-NH_2	RT	3	0.17	6	5140	[65]
8	I	H	EtOH:H_2O	SBA-15/di-urea/Pd	70	0.26	2.55	322 [b]	5800 [b]	[78]
9	p-Br	CH_3	EtOH:H_2O	Pd-MIL-101Cr-NH_2	RT	3	1.5	66 [b]	6880 [b]	[65]
10	I	H	H_2O:iPrOH	Pd/AlO(OH) NPs	25	0.12	1.1	394 [b]	11,800 [b]	[77]
11	I	H	EtOH:H_2O	Pd/Fe_3O_4-PC	60	0.02	<1	1891 [b]	11,900 [b]	[76]
12	p-Br	OCH_3	H_2O	Pd (NP)-NMe_2/SiO_2	50	0.1	<2% Pd_{tot}	250	12,500	[74]
13	I	H	EtOH:H_2O	3D rGO/Pd	80	0.5	0.658	471 [b]	15,200 [b]	[69]
14	4-I	CN	MeOH:H_2O	Siliacat Pd-DPP	70	5 mg_{Pd}	0.1% Pd_{tot}	2	21,000	[83]
15	4-Br	$COCH_3$	H_2O	C60-TEGS/$PdCl_2$	80	0.0087	0.231	2700 [b]	27,000 [b]	[73]
16	4-I	OCH_3	EtOH:H_2O	Pd(0)-AMP-SMC	90	0.24	<0.1	111	47,100	[75]
17	5-I and 5-Br	R_1	H_2O	Pd NPs/ZrO_2	90	0.1	0.067	57 [b]	56,500 [b;c]	[79]
18	3-I	OH	H_2O:iPrOH	Pd/C	150	12 mg_{Pd}	40	239	71,550	[80]
19	4-I	CN	THF:EtOH:H_2O	Siliacat Pd-DPP	80	3.9 mg_{Pd}	1% Pd_{tot}	81	88,800	[83]
20	4-Br	$COCH_3$	H_2O	Pd-SBA-15-SH	100	1	0.09	50	114,000	[84]
21	I	H	DMF	Pd HoMOF	100	0.4	0.086	248 [b]	122,000 [b]	[85]
22	4-Br	$COCH_3$	MeOH	Siliacat Pd(0)	75	0.1	2	12,500	127,200	[95]
23	4-Br	$COCH_3$	EtOH:H_2O	Pd (NP)/mesop carbon	80	2	<0.1	50	132,500	[86]
24	Br	H	H_2O	Pd-NPs-IL	100	0.25	5 [a]	368 [b]	138,000 [b]	[87]
25	4-I	CH_3	H_2O	MEPI-Pd	100	2.8×10^{-5}	<0.005	119,000	233,000	[11]
26	Cl	H	H_2O	Polymer anchored Pd(II)	100	0.001	<0.3	840	280,000	[10]

Table 3. *Cont.*

Entry	X	R	Solvent	Catalyst	T (°C)	Pd$_{tot}$ (mol %)	Pd Leach. (ppm)	TOF$_{tot}$ (h^{-1})	TOF$_{leach}$ (h^{-1})	Ref.
27	4-Cl	CH_3	H_2O	MEPI-Pd	100	0.0066	<0.005	15,000	308,000	[11]
28	I	H	H_2O	$[Pd(COD)Cl_2]$/hydroxyapatite	80	0.034	<0.001	125 [b]	422,000 [b;c]	[89]
29	4-I	NO_2	MeOH	Siliacat Pd(0)	65	0.1	0.02	1000 [b]	424,000 [b]	[81]
30	p-Br	OCH_3	THF:EtOH:H_2O	Siliacat Pd-DPP	70	46.64 mg$_{Pd}$	26.76	12	453,000	[82]
31	4-I	OCH_3	DMF:H_2O	Pd-NHC-MNP	80	0.12	0.064	908 [b]	634,000 [b]	[88]
32	4-Br	$COCH_3$	H_2O	Pd-SBA-15-SH	80	1	0.003	20	1,390,000	[84]
33	4-Cl	OCH_3	EtOH:H_2O	Pd-MP-LTA	50	1	0.0048	20 [b]	2,270,000 [b]	[90]
34	4-Br	CH_3	H_2O	MEPI-Pd	100	0.004	<0.005	12,500	2,770,000	[11]
35	Br	H	H_2O	Polymer anchored Pd(II)	100	0.001	<0.3	28,800	9,600,000	[10]
36	p-Br	CN	THF:EtOH:H_2O	Siliacat Pd-DPP	70	46.64 mg$_{Pd}$	1.26	295	9,610,000	[82]
37	p-Br	$COCH_3$	H_2O	Polymer anchored Pd(II)	100	0.001	<0.3	29,440 [b]	9,810,000 [b]	[10]
38	4-Br	OCH_3	Neat	Chitosan-pyridil-base Pd(II)	50	0.005	2% Pd$_{tot}$	210,000 [b]	10,500,000 [b]	[18]
39	4-Br	OCH_3	Toluene	Chitosan-pyridil-base Pd(II)	100	0.005	NA	440	NA	[18]
40	I	H	H_2O	Polymer anchored Pd(II)	100	0.001	<0.3	57,600	19,200,000	[10]
41	4-I	CH_3	EtOH:H_2O	Pd-PHMS (0.06-0.12mm)	65	20 mg$_{Pd}$	0.0003[a]	1	64,600,000	[96]
42	4-Br	OCH_3	Neat	Silicagel-Pd	50	0.0015	1% Pd$_{tot}$	724,000 [b]	72,400,000 [b]	[91]
43	4-Br	OCH_3	Toluene	Silicagel-Pd	100	0.0015	NA	1500	NA	[91]

6. Guidelines to Try to Discriminate Homogeneous/Heterogeneous Systems

The diversity of methods and evidences that were used by the authors to conclude about a heterogeneous or a homogeneous mechanism deserves to be discussed. The objective is to draw some guidelines to help researchers in their concluding remarks. Authors should not conclude too rapidly that a catalyst acts heterogeneously. A list of methods for distinguishing heterogeneous and homogeneous mechanisms has already been published [14,97–100]. We will try to discuss hereafter the advantages and limitations of each method. Note that a detailed analysis of their advantages and drawbacks is provided in the supplementary material. As a matter of fact, a test is generally composed of three main components: (i) a concept or principle, (ii) one or several methods to get quantitative metrics, which could be measurements and analysis and last (iii) the assumption of one main hypothesis as well as some side hypotheses.

6.1. Concepts/Principles

Hot-Filtration

First, the hot-filtration test is one of the most used methods to indicate whether leached species may be responsible for a part of the conversion. It consists in removing the solid at the reaction temperature and check whether the reaction goes on or not in the liquid. For example, in the cross-coupling between 4-iodoanisole and phenylboronic acid, a removal of the Pd supported on silica magnetite composite 10 min after the beginning of the reaction stopped the conversion. It was concluded that the reaction behaves heterogeneously [75]. The difficulties and possible mis-interpretation of the hot-filtration test lies on the temperature holding during the solid filtration because redeposition can occur when the temperature decreases. The result of the test also depends on the conversion at which the solid removal was done. When the test is positive, there is no doubt that the homogeneous species can catalyze partly or totally the reaction but when the test is negative, it is not safe to conclude. It may that during the filtration, the active species died and render the test false.

Reusability Test

Also sometimes called "recycling test", it consists in reusing the solid catalyst in one new batch (or several successive ones) with fresh reactants. This is a very simple and thus extensively used method to check whether some active species are still present on the solid surface from one batch to another. Many difficulties are associated to this method. Most of the authors go to 100% conversion before reusing the solid. First, it does not allow to measure a change in the catalyst activity; moreover, it is known that if release-and-capture occurs, most of the leached species during the course of the reaction will be readsorbed on the surface at full conversion. The test can still be very informative if the objective is to check that the re-capture (if exists) is effective and allows to go to very high TON by successive batch operations. Nevertheless, reusing a solid several times does not prove that the mechanism is heterogeneous. Thus, better than going to 100% conversion and, in association to the hot-filtration test, the hot solid removed during the course of the reaction (between 30 and 70% conversion) can be reused in new batches. The comparison between run 1 and 2 can thus be informative. If the conversion is not the same between these 2 runs, this shows that the catalyst was modified, either because some active species leached or because it was deactivated. If the conversion is the same, it is dangerous to conclude that the catalyst was not modified since it may be a huge reservoir, progressively leaching some reacting species. In that case, an ICP-MS analysis must be performed to bring supplementary information.

Compartmented Reactor with Membrane

A method based on the use of a membrane was proposed in the case of Heck cross-coupling but can also be used for Suzuki reaction [101]. It consists of using 2 reacting compartments separated by a nanoporous membrane (5 nm) that allows the passage of Pd atoms and ions but not of Pd nanoclusters. The reactants are present in both compartments but at the initial state, Pd clusters (15 nm) are only present in one of them and the base in the second one. The fact that the reaction products are observed in the second compartment was found as a proof that some Pd small species leached from the clusters. The use of this test can thus provide a proof that leached species are active; however, it is not possible to conclude if no activity is observed in the second compartment.

Continuous Compartmented Operation or Split-Flow Test

Recently, a method was proposed for the Heck and Suzuki reactions [102,103] to characterize the activity of putative leached species for Pd catalyzed C-C couplings. The set-up consists in a packed-bed column filled with a solid catalyst (e.g., Pd/silica, Pd/C, supported Pd complexes . . .), followed dowstream by an empty tube fed continuously by a reacting solution, the measurement of the conversion after the solid section is compared to the conversion after the empty section. Whereas an increase of conversion in the second compartment is a clear indication that some species have leached, a negative test is not sufficient to demonstrate that the catalyst acts heterogeneously. Some Pd may also have leached but may have lost its activity.

3-Phase-Test

The 3-phase-test was first introduced by Davies et al. for the study of C-C coupling reactions [92]. The substrate is attached to a resin thanks to an amide bond. The method does not allow to elucidate whether all of the reactivity is associated with the homogeneous catalyst. However, it was demonstrated that the resin may serve as a convenient catalyst precursor for the release of catalytic species in solution and acts as a scavenger for Pd at the end of reactions. This test was thus used by Budroni et al. [104] during the coupling of 4-bromoanisole and phenylboronic acid using Pd nanoparticles on silica as a catalyst with bromoanisole grafted on silica as a third phase. After the reaction and NaOH hydrolysis, 4-carboxybiphenyl and large amounts of benzoic acid were obtained. This results demonstrates that leached Pd was active, but also more selective for dehalogenation than for cross-coupling. Note that the authors observed a negative hot-filtration test. The short lifetime of the active species in solution is an open question and can explain both a negative hot-filtration test and a positive 3-phase-test. The 3-phase-test has to be carefully carried out, e.g., it is important to add a soluble aryl halide, since it is believed that oxidative addition with this soluble reagent is necessary to Pd into solution [92]. Moreover, to ensure that the reaction is not starved of boronic acid, Webb et al performed the three-phase test with a large excess of boronic acid [105]. They observed an increase of the conversion, showing a competition between the soluble aryl halide and the supported aryl halide. The reaction in solution is favored at the expense of reaction on support. They insist on the importance to probe the three-phase test with an appropriate homogeneous or with a heterogeneous catalyst known to leach Pd.

Mercury-Drop-Test

Complimentary tests comprise the mercury drop test. It consists in adding an excess of mercury in the reacting solution and observing whether the reaction is stopped or not. The test is based on the ability of Hg(0) to form an inactive amalgam with Pd(0) or to adsorb on the metal surface. Mercury is expected not to react with complexes. For example, the test has been used to assess the molecular nature of the catalytic system resulting from the combination of Pd_2dba_3-$CHCl_3$ and hexacationic triarylphosphine-based dendriphos ligands [106]. Furthermore, it was used to check that Pd–NHC dimeric complexes are the actual active species in the Suzuki coupling of 2-bromotoluene with phenylboronic acid and that Pd black observed during the course of the reaction is not the active form of the catalyst [40]. Conversely, during the coupling of 4-bromoacetophenone and phenylboronic acid in water at 120 °C, the addition of a drop of mercury to the mixture containing the Pd chelating complex stopped the reaction, indicating that Pd(0) species were involved in catalysis [25]. Another example shows the contribution of both the Pd complex and Pd(0) NPs. It concerns the use of a zwitteronic Pd complex in water [107]. Very recently, a paper was published about the limit of use of the mercury-drop-test. Mercury can indeed react with some Pd complexes, e.g., palladacycles [108]. A discussion of the limit of this test can be found in [97].

Other Poisoning Methods

A review of commercial grafted polymeric fibers used as Pd scavengers has been published by Johnson-Matthey [109]. Among them, thiol-based scavengers are said to be the most suitable. According to Huang et al., in the case of Heck couplings, silica-bound thiols are more efficient than resin-bound thiols in residual palladium removal from reaction solution [110]. All of these scavengers effectively poison the dissolved catalytic species but hardly scavenge Pd clusters. In all cases, it must be reminded that the kinetics of scavenging may be slow, and that the scavenging efficiency is not total. Moreover, thiols can also leach in the solution thus poisoning Pd species instead of scavenging them. In several publications, a mercaptopropyl-modified silica has been used as a tethered ligand for palladium scavenging. Bare SH-silica is indeed able to selectively poison soluble active Pd species [111]. For example, Sahu et al. added SH-SiO_2 to the mixture of bromotoluene, phenylboronic acid and Pd NPs/silica with a ratio S:Pd equal to 1200. No poisoning of the reaction was noticed, allowing the authors to conclude for true heterogeneous catalysis, despite the observation of 2% Pd in the solution [74]. To our point of view, as some Pd supported on thiolated silica show some activity in Suzuki coupling [84], the SH poisoning test has to be examined thoroughly. Note that the use of this test is highly disputed in the article of Webb et al. [105].

6.2. Measurements and Analyses

Pd Trace-Analysis

Associated to the solid hot-filtration, the Pd trace-analysis in the solution is often an inescapable tool to evaluate the level of leaching. As the leached concentration may be very low, ICP-MS should be preferred to ICP-AES, allowing to reach ppb levels. Measuring Pd in solution is a proof that some Pd has leached but it is not a proof that the leached species are the active ones. Measuring no Pd in solution is not a sufficient proof that Pd has not leached. It is known from several authors that the concentration of leached Pd varies with the conversion and/or the temperature [44–46,49]. Adsorption of the leached species on the solid at full conversion or when the temperature gets lower has to be kept in mind. It is thus important to measure the concentration of Pd at different conversions and to make sure that the Pd will not be adsorbed on the vial walls during cooling. Adding some hydrochloric acid is a possible solution, and it can also be advised to voluntarily adsorb the Pd on charcoal and analyze the resulting solid after drying. The analysis of the solid pre-catalyst, before and after test is also an appropriate complimentary analysis to check the fraction of Pd that was lost [52,55]. The limitations of this method are first linked to the limit of detection of the apparatus. Even if ICP-MS allows to go down to ppb levels, it must be reminded that ppb levels are sufficient to catalyse the Suzuki coupling. A positive test allows to conclude that some species have leached, but it does not allow to conclude that these species are the active ones. A negative test does not allow to conclude, because some redeposition of the leached Pd may have occurred in the reaction vessel before sampling or on the walls of the sample vial.

Microscopy

Transmission electron microscopy (TEM) is an illustrative method used by many authors to compare images of the surface before and after the reaction and try to get an information about the absence of leaching or aggregation. Several authors have used this technique without finding any variation between the fresh and the used catalyst, for TONs between 300 and 1200 [8,52,65,69,88]. Other authors have been able to see a variation of the particle size for TONs between 1300 and 6000 [74,75,85]. Therefore the TEM can be used as a complimentary technique when Pd atoms have sufficiently worked. The technique has also allowed to visualize Pd clusters captured on activated carbon after reaction filtration [112] and to observe the Pd NPs growing [25,113]. Note that amongst the microscopy techniques, AFM can also be used [114] but the method is not standard and will not be discussed here.

X-ray Absorption Spectroscopy (XAS)

XAS analysis can be used to observe the fate of the catalytic species during the reaction. It is of course not a routine analysis but can bring useful information. It allowed Lee et al. to follow the becoming of Pd NPs during the coupling of iodoanisole and phenylboronic acid [115,116] and to conclude that the catalytic activity is associated with the presence of stable surface defect atoms on the NPs. They found no evidence for the contribution of molecular Pd species. More recently, using a flow reactor in a XAS beam line, the leaching and speciation of Pd along the catalyst bed was observed [117]. The concentration of Pd(0) was found to increase from the entrance to the exit of the reactor. XANES spectra showed the promotion of Pd reduction by hot ethanol [117]. Whereas the method is useful to observe the oxidation state change during the reaction, its access is limited.

6.3. Guidelines

Attributing heterogeneous vs. homogeneous catalysis in SM reaction is a type of binary classification. In binary classification, a false negative is an error in which a result (from a test) improperly indicates no presence of a condition (the result is negative), when in reality it is present. Adapting this idea to the presence of Pd, the result of ICP analysis could be yes or no, that being the detection limit. Thus the statement of heterogeneous catalysis based on ICP analysis of leached Pd is a false negative in the sense that Pd is indeed present in the solution, at levels that could not be detected.

We should always remember the scientific methodology: a failure of an experiment does not necessarily mean the hypothesis is false. Experiments always depend on several hypotheses, e.g., that the test equipment is working properly, and a failure may be a failure of one of the auxiliary hypotheses. Conversely, agreement does not assure that the hypothesis is true; future experiments may reveal problems.

Since not one test could answer the question of liquid vs. solid phase location for the catalysis [118], a methodology based on the rational combination of several tests is proposed to answer this issue (Figure 4).

In the decision tree, note that conclusions 3 and 4 are different. Indeed, in conclusion 3, it is proven—and possibly quantified—that the reaction is taking place at both sites while in conclusion 4, no statement could be made. Among all the published tests, a choice has been made to keep those tests that are easier to perform without the need of adapting the chemistry to the test. Too specific tests such as the 3 phase test that required special functionalization of the reagents or the Pd size variation technique, which calls for mastering Pd NPs size growth. Thus it is believed that the proposed tests involved in this methodology can be generally applied to any chemical/catalyst system. Concerning analysis, too heavy tools such as XAS are discarded since the availability is restricted and it provides few conclusive results on that debate concerning the location of the reaction but rather concerns the nature of liquid phase catalysts, i.e., molecular complexes vs nanoparticles.

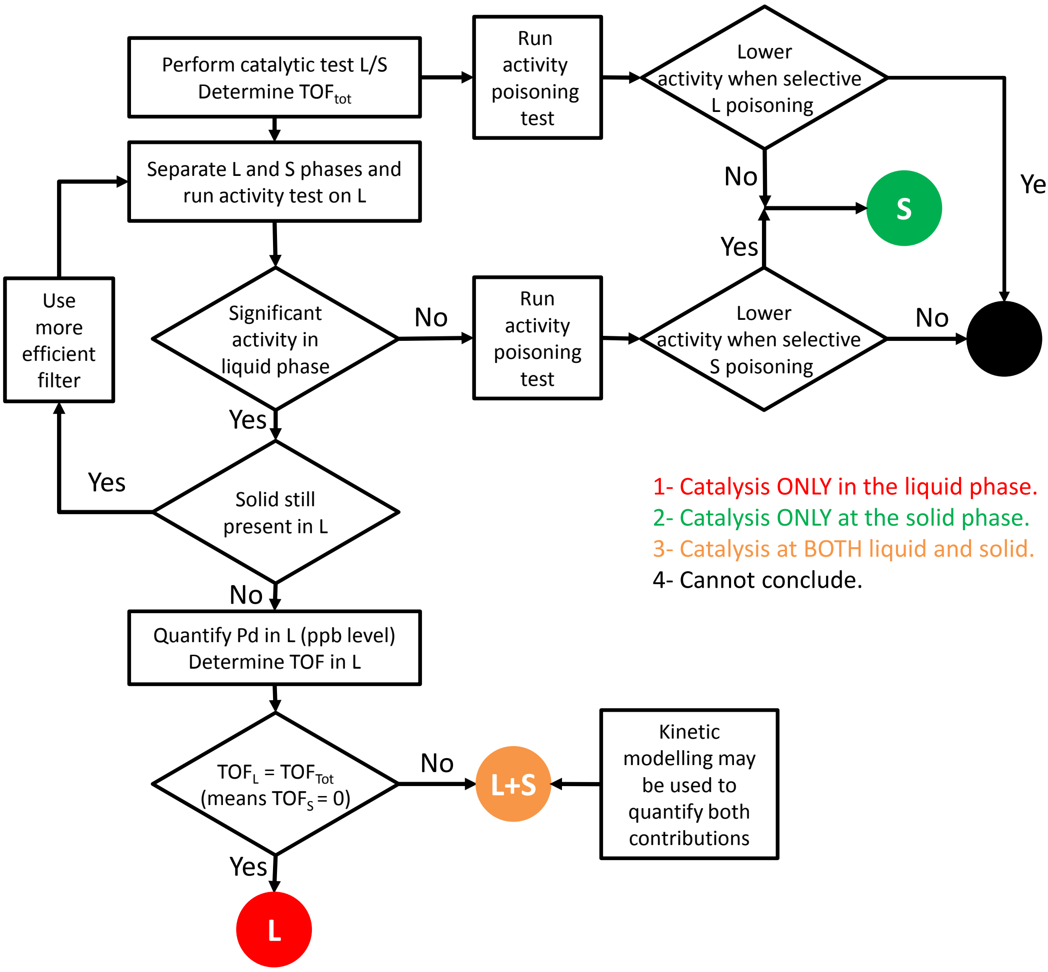

Figure 4. Possible decision tree to try to discriminate homogeneous (L) and heterogeneous (S) mechanisms.

The proposed methodology starts with performing a simple catalytic test to obtain a global activity (TOF$_{tot}$) (at this point, it is important to determine the complete conversion vs. time profile to check for the absence of catalyst deactivation). Then, the activity of the liquid phase alone (TOF$_L$) could be determined using any liquid/solid separation method as long as the separation is thoroughly performed, allowing a quantitative separation of the liquid sample. Such liquid/solid separation could be performed using the hot filtration test or the flow split test since they require equipments that are generally available in any chemistry laboratory. At this point, a simple comparison of the global activity and the liquid phase activity could drive to the conclusion that catalysis is occurring only in the liquid phase if TOF$_L$ = TOF$_{tot}$ which means that the contribution of the solid to the global activity is negligible. The main issue here is to define a threshold level for comparison of the activities. A criteria could be (TOF$_{tot}$-TOF$_L$)/TOF$_{tot}$ < 5%. When that condition is not fulfilled, i.e., when TOF$_L$ is significantly lower than TOF$_{tot}$, the solid contribution is significant and a simple reactor model with simple kinetic models can help to quantitatively assess the contributions of the solid and liquid catalysis. If negligible activity is detected in the liquid phase, tests must be applied to the solid. A negative selective poisoning of the solid will not allow to conclude. On the other hand, a positive solid poisoning, strengthened by a negative liquid poisoning, could allow to propose a heterogeneous (solid) mechanism.

7. Conclusions

In this review, we have proposed to reinterpret published data considering the hypothesis that true heterogeneous catalysis (supported catalysis) does not exist in the Suzuki-Miyaura coupling.

We have calculated TOFs that would be obtained considering the contribution of leached Pd only. Values obtained were still in the range of what is measured for very active Pd complexes, making the hypothesis tenable. The consequence is that heterogeneous precursors can actually be the source of very active homogeneous (molecular or NP) species that are able to catalyse Suzuki-Miyaura reaction. Favouring the formation of few amounts of such hyperactive species would allow to avoid Pd contamination in the reaction products. In a last part of the review, the methods used to try to discriminate between homogeneous and heterogeneous mechanisms have been recalled. A tentative methodology has been proposed to help researchers reaching some conclusions about the location of the reaction (in Liquid or on Solid). It is also advised not to give too peremptory assertions because many tests lead to an ambiguous conclusion.

Supplementary Materials: The following are available online at http://www.mdpi.com/2073-4344/9/1/60/s1, Table S1: Hot filtration test (Split test), Table S2: Pd trace-analysis, Table S3: Reusability test, Table S4: Compartmented reactor with membrane, Table S5: Continuous compartmented operation (Split flow test), Table S6: 3-Phase-test, Table S7: Poisoning tests, Table S8: Microscopy (TEM).

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