Desperately Seeking For The Catalytic Species In Suzuki-Miyaura Reaction

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Desperately Seeking For The Catalytic Species In Suzuki-Miyaura Reaction

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“I remember my friend Johnny von Neumann used to say, with four parameters I can fit an elephant, and with five I can make him wiggle his trunk.”

Enrico Fermi

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Depuis tout petit, j'ai rêvé de ce moment où je deviendrais docteur. Réaliser ce doctorat était une aventure très enrichissante tant dans le domaine scientifique qu'humain.

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Résumé

L’état de l’art montre que l’utilisation de Pd supporté sans ligand est une idée séduisante car elle permet d’éviter les problèmes liés à la présence des ligands potentiellement coûteux et toxiques, et également de récupérer plus facilement le catalyseur en fin de réaction. Ainsi, il est plus aisé de respecter la réglementation fixant la teneur maximale de Pd dans les principes actifs pharmaceutiques (IPA) à une concentration inférieure à 10 ppm. Cependant, la présence des espèces (moléculaires ou nanoparticules) de Pd en solution lors de l’utilisation de catalyseurs solides a créé un débat important dans la bibliographie sur la vraie nature de la catalyse, hétérogène à la surface du Pd supporté ou homogène par l’intermédiaire d'espèces en solution.

Dans ce travail la réaction de Suzuki-Miyaura (SM) a été choisie comme réaction cible. En absence d’étude cinétique globale dans la bibliographie une étude cinétique a été effectuée avec un catalyseur moléculaire afin d’obtenir une loi mécanistique qui représente la partie homogène de la réaction.

Un test innovant a été proposé afin de bien distinguer entre les contributions homogène et hétérogène et de déterminer par la suite la nature des espèces qui catalysent la réaction. Ce test a été appliqué dans la réaction de différents iodo, bromo, et chloro aryles en utilisant plusieurs catalyseurs supportés tout en variant la nature du support et l’état d’oxydation du Pd (Pd(0) et Pd(II)) dans le précurseur initial.

Enfin, un modèle de réacteur a permis de démontrer que pour le même iodoaryle, peu importe la nature du solide, le Pd supporté semble relarguer les mêmes espèces actives en solution qui catalysent la réaction SM avec des activités initiales de l’ordre de 500 000 h^{-1}. Le « split flow reactor » est un nouveau test très simple à utiliser qui, accompagné de techniques d’analyses en ligne, peut permettre de suivre l’évolution des espèces catalytiques en temps réel, et d’étudier d’autres systèmes chimiques.

Mots clés : Suzuki-Miyaura, Catalyse hétérogène, Catalyse homogène, Pd Leaching.

Summary

The use of ligand-free supported Pd is an attractive idea because it avoids problems related to the presence of the ligands (cost and toxicity). Also the catalyst is easily recovered at the end of the reaction by conventional methods such as filtration or decantation. Thus, it is easier to meet regulations in Active Pharmaceutical Ingredients (<10 ppm). However, the presence of molecular or atomic Pd species in solution when using solid catalysts has created an important discussion on the true nature of catalysis. This last could be heterogeneous on the surface of the supported Pd or homogeneous via species in solution.

In this work the Suzuki-Miyaura (SM) reaction was chosen as the target reaction. In the absence of an overall kinetic study in the literature, a kinetic study was carried out with a molecular catalyst. It provided a mechanistic law that represents the homogeneous part of the reaction.

Furthermore, an innovative test ("split flow reactor") has been proposed. It permits to distinguish between the homogeneous and heterogeneous contributions and to determine the nature of the species that catalyze the reaction. It was used in the reaction of different iodo, bromo, and chloro aryls. Several supported catalysts were used by varying the nature of the support and the oxidation state of Pd (Pd (0) and Pd (II)) in the initial precursor.

Finally, a reactor model has shown that for the same iodoaryl, whatever the nature of the solid, the supported Pd seems to release the same active species in solution. These species catalyze the SM reaction with initial activities of the order of 500 000 h^{-1}. The split flow reactor is a new, easy-to-use test. Accompanied with online analysis techniques, it can be used to track the evolution of catalytic species in real time and to study other chemical systems.

Keywords: Suzuki-Miyaura, Heterogeneous catalysis, homogeneous catalysis, Pd leaching

Introduction

Carbon-carbon (C-C) cross-coupling reactions are the key of biaryl synthesis which represents an important step in the generation of complex molecules in different fields, pharmaceuticals, agrochemicals, and new products. They have been the subject of numerous and prolific research in organometallic chemistry and catalysis [1] crowned by the 2010 Nobel Prize for Chemistry [2, 3, 4, 5], awarded to Richard Heck, Ei-ichi Negishi and Akira Suzuki. As pointed out in a recent paper reporting the use of intelligent search algorithms, Suzuki-Miyaura (SM) reaction represents up to 10 % of a 1 million patents database in the field of pharmaceuticals [1].

Historically, most of the SM catalysts are molecular palladium complexes, either free in solutions or supported on solids. Thus ligands are required to stabilize these complexes.

SM reaction is most of the time catalyzed by palladium (Pd), depending on the initial state of the pre-catalyst, the catalysis could be homogeneous when soluble Pd molecular species are used or heterogeneous when the Pd species are supported. Moreover, molecular Pd is usually accompanied by ligands [6, 7] in order to increase their activity and inhibit the deactivation processes. However, these ligands are generally toxic and/or expensive, which increases the cost of production by the catalyst cost or the required separations and purification to remove all ligands and lower the Pd concentration to the accepted limits. Therefore, scientists have recourse the use of “ligands-free catalysis”, which are for some authors true molecular species, the ligands being the reagents, or Pd-colloids generated by the reduction of palladium salts ($PdCl_2$, $Pd(OAc)_2$, $Pd(NO_3)_2$) [7, 8, 9, 10].

The use of ligands-free catalysis solves a part of the problem, i.e. the cost and toxicity of added ligands, but does not solve the issue of Pd removal from the final products. Thus two possible solutions could be selected, increase the activity of these soluble species in order to reduce the concentration to ppb level, or support them on a heterogeneous support.

From an industrial viewpoint, the idea to catalyze the Suzuki-Miyaura reaction (SMR) 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 [11].

These solids could distributed in 10 categories [12]; (1) metallic Pd, (2) Pd oxide, (3) Pd deposed on transition metals or rare earth, (4) Pd deposed on S- or P-block metal oxide, (5) Pd/C, (6) Pd(II) complexes anchored on inorganic materials, (7) Pd(II) complexes grafted on organic polymers, (8) Pd-containing hybrid materials (MOFs), (9) gold/Pd core/shell Nps and (10) Pd alloys, as classified by Zotto et al.

However, when these solid catalysts are used in SM reaction, leaching of Pd into the solution was frequently found [13, 14]. This leaching phenomenon was largely analyzed in the last decades by many authors [14,15,16] opening a controversial discussion about the “heterogeneous” vs. the “homogeneous” nature of the catalysis. In fact, the reaction could occur at the surface of the supported palladium (Pd) giving a heterogeneous mechanism or it could be catalyzed by the soluble leached Pd species giving a homogeneous molecular mechanism.

Several reviews are published yearly with tentative explanations of this behavior. Interestingly, while most of these reviews discuss this behavior, only few depict the different approaches and techniques used to distinguish between homogeneous and heterogeneous Suzuki catalysis. Protocols such as the correlation of Pd content in solution with the reaction yield [16], the hot filtration tests [13], the Three-Phase test [17], poisoning tests [13, 18] or the “Nanoparticle-Exclusion Experiments” [19] can be used. More sophisticated methods have been also used such as X-ray absorption spectroscopy (XAS) to monitor the structure of Pd nanoparticles (NPs) during the Suzuki reaction [20], and Pd NPs coated AFM tip [21]. Detailed discussions of the advantages and drawbacks of these methods have been published and the general conclusion emphasized that there is no single definitive experiment for making this distinction [22, 23]. While everybody will agree with this general statement and would use a combination of methods before arriving at a compelling conclusion, it prompted us in this thesis to re-investigate ligand-free Pd SM coupling and answer at least three fundamental questions:

- Could more and more general evidences be gathered to prove that the leached Pd species are active for the SM reaction?
- Are the catalytic properties, i.e. activity, selectivity, of the leached Pd species independent from the solid precursor?

- Does the leaching process depend on the nature of the solid precursors?

This thesis is structured in 4 chapters:

The 1st chapter will propose a state of the art on the bibliography of published works with catalysts introduced at the solid dry state (powder) in the reactor, either to be used in batch or continuous operation. Then, it will distinguish catalytic species supposed to act 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 NPs (<100 nm). Turnover frequencies were calculated hypothesizing that only the leached species are responsible for the catalytic reaction. At the end of this chapter we will analyze the existent technics to discriminate between homogeneous/heterogeneous systems and a tentative methodology will be proposed to help researchers reaching some conclusions about the location of the reaction (in Liquid or on Solid).

In order to have at hands a robust kinetic model describing the behavior of a typical homogeneous catalyst, a complete kinetic study of the Suzuki-Miyaura reaction catalyzed by the Herrmann-Beller palladacycle, with microkinetics and analytic approaches is presented in the 2nd chapter.

The 3rd chapter is divided into two parts, a presentation of the “split flow reactor”, a new tool to discriminate between homogeneous/heterogeneous systems, followed by several experimental tests with a variety of seven very different Pd/supported catalyst in the SM reaction of different aryl halides.

The last chapter will focus on the reactor and reaction modeling to interpret the different experimental results obtained in chapter 3. Initially a reactor model based on the experimental data will be developed using the kinetic law obtained in chapter 2. After that, the model will be applied and validated on the SM reaction of 4-iodoacetophenone with the solid precursors studied in chapter 3. Then a series of simulations will be performed to explain the behavior of Chloro and Bromo aryls.

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Chapter 1

About solid phase vs. liquid phase in Suzuki-Miyaura reaction

This chapter was adapted from the publication:

A. Bourouina, V. Meille, and C. de Bellefon, “About Solid Phase vs. Liquid Phase in Suzuki-Miyaura Reaction,” *Catalysts*, vol. 9, no. 1, p. 60, Jan. 2019.

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

1.1 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 reactions from 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.

1.2 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 cannot 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).

The turnover number (TON) describes the work the catalytic site has performed. It is defined as the number of moles of aryl halide 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 aryl halide 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.

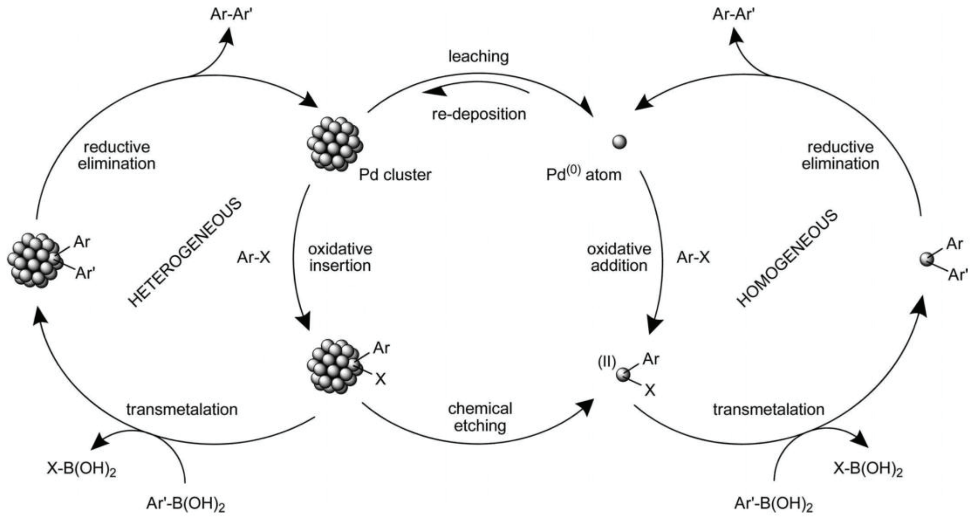

Figure 1 Proposed mechanism for the PdNP-catalyzed Suzuki cross-coupling involving both homogeneous and "heterogeneous" pathway, reprinted with permission from [14]. Copyright (2012) American Chemical Society. Please note that both act in the liquid phase.

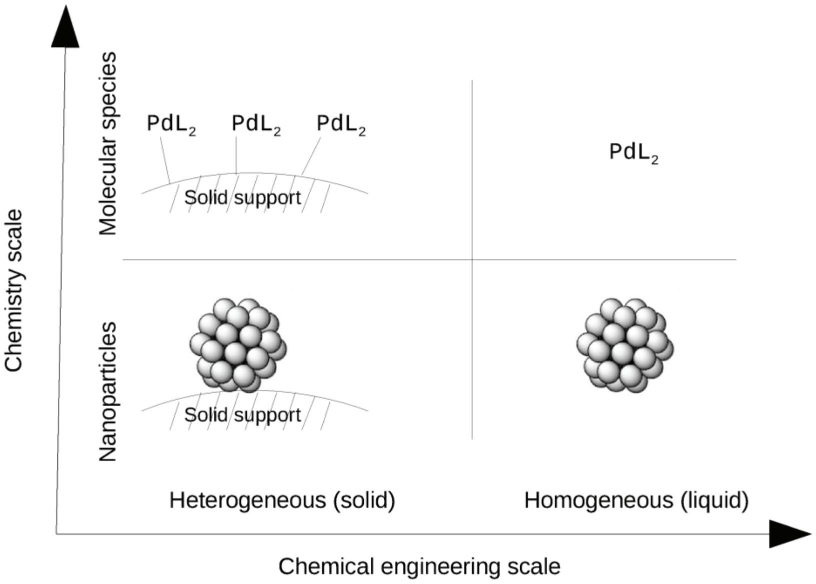

Figure 2 Definition of homogeneous and heterogeneous systems in this review.

1.3 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 *p*-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].

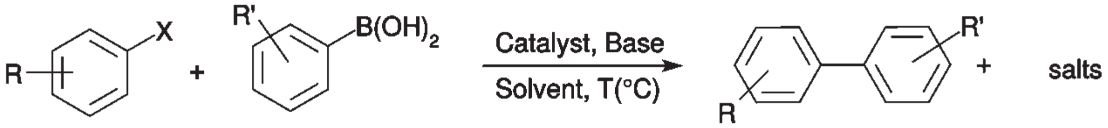

Figure 3 Schematic representation of the Suzuki coupling - R'= H (otherwise specified).

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 has 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 catalyzed 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 PdCl2-2,6-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]

1.4 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 $\mathrm{TOF}_{\mathrm{leach}}$), 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 $\mathrm{TOF}_{\mathrm{leach}}$ 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. $\mathrm{TOF}_{\mathrm{tot}}$ 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 TOFleach 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} (mol %)	TON mol/mol	TOF (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.

1.5 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 (93h^{-1}) and the leached one 5810 (1160h^{-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 than 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 hundred 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/ZrO2) 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 TOFtot 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 TOFleach 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 than 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 TOFleach 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 correspond 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 cannot 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. Recently, only 0.001 mol% of Pd (0.5 ppm of Pd) was used in the reaction of bromotoluene (93% of conversion) [94]. 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, 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]

1.6 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.

1.6.1 Concepts/Principles

1.6.1.1 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.

1.6.1.2 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.

1.6.1.3 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.

1.6.1.4 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 downstream 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.

1.6.1.5 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 result 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.

1.6.1.6 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].

1.6.1.7 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].

1.6.2 Measurements and Analyses

1.6.2.1 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.

1.6.2.2 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.

1.6.2.3 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.

1.6.3 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.

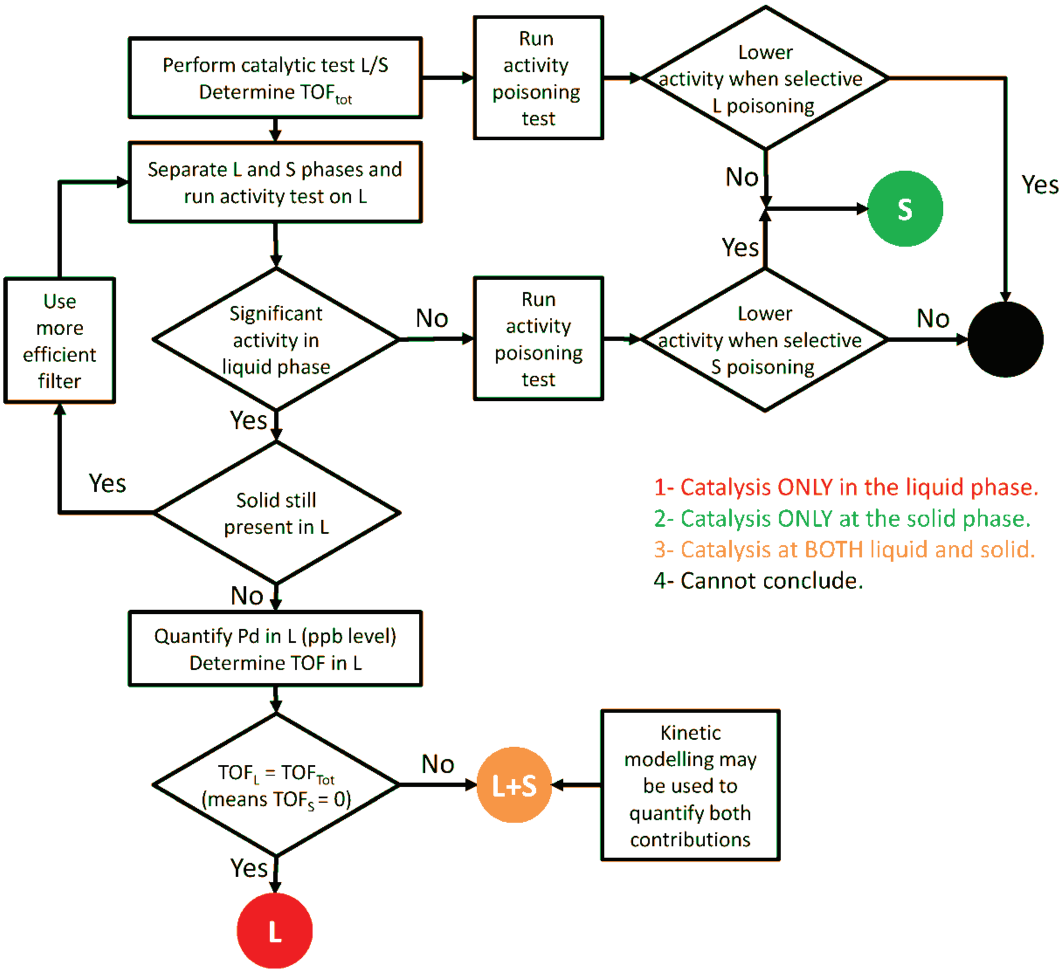

Figure 4 Possible decision tree to try to discriminate homogeneous (L) and heterogeneous (S) mechanisms.

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 $(\mathrm{TOF}_{tot}-\mathrm{TOF}_{L})/\mathrm{TOF}_{tot} < 5\%$. 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.

1.7 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.

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APPENDICES

A.1 Hot filtration test (Split test)

<table>
<tr><td colspan="2">Description: Separation between Solid (S) and Liquid (L) phases & verification of activity (conversion) inside the homogeneous phase.</td></tr>
<tr><td colspan="2">Main hypothesis: Liquid phase contains homogeneous active species that catalyze the reaction.</td></tr>
<tr><th>Possible Results</th><th>Possible conclusions</th></tr>
<tr><td>Change of activity after separation</td><td>Homogeneous catalysis</td></tr>
<tr><td>Homogeneous activity is higher than zero</td><td>Both mechanisms (need further verification)</td></tr>
<tr><td>No activity</td><td>Possible heterogeneous (need further verification).</td></tr>
<tr><td colspan="2">Side hypothesis: No homogeneous activity because of lost (or deactivation) of homogeneous active species.</td></tr>
<tr><td colspan="2">Complimentary methods & analysis:
- ICP analysis (at ppb level) for homogeneous phase before & after separation.
- ICP analysis for possible adsorption of Pd at filter.
- Poisoning method to check if there is homogeneous active species before separation.
- Solid phase analysis (TEM) for any changes of the catalyst surface.</td></tr>
<tr><th>Advantages</th><th>Drawbacks</th></tr>
<tr><td>Easy and rapid to perform.
Clear conclusion if the result is positive.
No need for specific tools.</td><td>Many possible interpretations for negative results.</td></tr>
</table>

A.2 Pd trace-analysis

<table>
<tr><td colspan="2">Description: Analyze of homogeneous phase for Pd species (ICP, AAA)</td></tr>
<tr><td colspan="2">Main hypothesis: Leaching of homogeneous species into the solution.</td></tr>
<tr><th>Possible Results</th><th>Possible conclusions</th></tr>
<tr><td>Detection of Pd species</td><td>Leaching of Pd into the solution</td></tr>
<tr><td>No Pd inside solution</td><td>Need further verification</td></tr>
<tr><td colspan="2">Side hypothesis:
- Pd concentration lower than the detection limit of analysis method.
- Pd readsorbed into the support.</td></tr>
<tr><td colspan="2">Complimentary methods & analysis:
- Use of ICP-MS (ppb level).
- Always use the ICP as a complimentary method with other tests.
- Make analysis at different conversions (lower than 100%).
- Solid analysis before and after reaction.</td></tr>
<tr><th>Advantages</th><th>Drawbacks</th></tr>
<tr><td>Give the quantity of Pd inside solution.</td><td>Need specific tools.
No information about the homogeneous or heterogeneous activity of Pd. Leached species may be inactive.</td></tr>
</table>

A.3 Reusability test

Description: Make several runs with same solid catalyst at the same experimental conditions.

Main hypothesis: Constant activity If the catalysis is heterogeneous.

Possible Results	Possible conclusions
Constant (or fluctuating) activity.	Possibly heterogeneous (further analysis required (F.A.R.))
Continual decrease of activity	Possibly homogeneous (F.A.R.)

Side hypothesis:

- Catalyst worked for small TON.
- Pd redeposit at the end of reaction.
- Loss of solid.

Complimentary methods & analysis:

- Check the higher possible value of TON.
- Make run at conversion lower than 100% (50% for example).
- Continually check the mass of solid catalyst.
- Analyze solid phase at the end (TEM, ICP).
- Analyze homogeneous phase (ICP).

Advantages	Drawbacks
Easy to perform. No specific tools.	Many possible conclusions. Need further methods & analysis to conclude.

A.4 Compartmented reactor with membrane

<table>
<tr><td colspan="2">Description: Two reactors (one with catalyst & other without) separated with nanoporous membrane.</td></tr>
<tr><td colspan="2">Main hypothesis: Homogeneous mechanism if activity inside the second reactor without solid catalyst</td></tr>
<tr><th>Possible Results</th><th>Possible conclusions</th></tr>
<tr><td>Same activity (conversion) in both reactors.</td><td>Homogeneous mechanism</td></tr>
<tr><td>No activity inside the second reactor</td><td>Possibly heterogeneous (F.A.R.)</td></tr>
<tr><td>Lower activity inside second reactor</td><td>Possibly both (F.A.R.)</td></tr>
<tr><td colspan="2">Side hypothesis:
- Catalyst adsorption on membrane.
- Pd redeposition on the initial support.
- Deactivation of homogeneous Pd species.</td></tr>
<tr><td colspan="2">Complimentary methods & analysis:
- Membrane analysis for any possible Pd deposit.
- Homogeneous poisoning method for any homogeneous activity.
- ICP-MS analysis for any Pd inside second reactor.</td></tr>
<tr><th>Advantages</th><th>Drawbacks</th></tr>
<tr><td>Qualitative conclusion</td><td>Difficult to perform & need specific tools.</td></tr>
</table>

A.5 Continuous compartmented operation (Split flow test)

Description: Two reactors (first with catalyst & second without) separated by filter.

Main hypothesis: Homogeneous contribution if conversion increases inside the second reactor

Possible Results	**Possible conclusions**
Same activity inside both reactors.	Homogeneous mechanism
No activity inside the second reactor	Possibly heterogeneous (F.A.R.)
Lower activity inside second reactor	Possibly both (F.A.R.)

Side hypothesis:

- Possible catalyst rapid deactivation or readsorption inside the first reactor.

Complimentary methods & analysis:

- Check for possible catalyst deactivation (add active species stabilizers)
- ICP analysis for solid & liquid phases.
- Use of mathematical models.

Advantages	**Drawbacks**
Easy to perform. Work on steady state. Possible distinction of homogeneous & heterogeneous contributions using model.	Difficult to conclude if there is no activity inside the empty (second) reactor.

A.6 3-Phase-test

<table>
<tr><td colspan="2">Description: Bond of a reagent to a support & see its conversion with solid precursor.</td></tr>
<tr><td colspan="2">Main hypothesis: Homogeneous mechanism if the desired product was detected.</td></tr>
<tr><th>Possible Results</th><th>Possible conclusions</th></tr>
<tr><td>Complete activity</td><td>Homogeneous mechanism</td></tr>
<tr><td>No activity</td><td>Possible heterogeneous (F.A.R.)</td></tr>
<tr><td>Small activity</td><td>Possible both (F.A.R.)</td></tr>
<tr><td colspan="2">Side hypothesis:
- Side reaction (reagent conversion to undesired products).
- Short lifetime of active species.</td></tr>
<tr><td colspan="2">Complimentary methods & analysis:
- Check for possible catalyst deactivation (add of active species stabilizers)
- ICP analysis for solid & liquid phases.
- Use excess of base and boronic acid.</td></tr>
<tr><th>Advantages</th><th>Drawbacks</th></tr>
<tr><td>Clear conclusion if result is positive</td><td>Competition with side reaction.
No conclusion for negative results.</td></tr>
</table>

A.7 Poisoning tests

<table>
<tr><td colspan="2">Description: Use of poison that deactivate the catalyst at a desired form.</td></tr>
<tr><td colspan="2">Main hypothesis: clear conclusion if the poison doesn’t stop the reaction</td></tr>
<tr><th>Possible Results</th><th>Possible conclusions</th></tr>
<tr><td>No effect after adding the poison</td><td>Homogeneous (if Hg for example) mechanism.</td></tr>
<tr><td>No activity</td><td>Cannot conclude (F.A.R.)</td></tr>
<tr><td>Small activity</td><td>Possible both (F.A.R.)</td></tr>
<tr><td colspan="2">Side hypothesis:
- The poison can change the reaction conditions (viscosity, T (°C)).
- The poison is not selective.</td></tr>
<tr><td colspan="2">Complimentary methods & analysis:
- Always use the poisoning test as a complimentary method with other tests.</td></tr>
<tr><th>Advantages</th><th>Drawbacks</th></tr>
<tr><td>Clear conclusion if result is negative
Easy to perform.</td><td>Many possible interpretations if the poison stops the reaction.</td></tr>
</table>

A.8 Microscopy (TEM)

<table>
<tr><td colspan="2">Description: Take images of catalyst before & after the reaction</td></tr>
<tr><td colspan="2">Main hypothesis: If there are no variation of the catalyst surface (distribution & sizes) the catalysis is heterogeneous</td></tr>
<tr><th>Possible Results</th><th>Possible conclusions</th></tr>
<tr><td>No variation of catalyst surface</td><td>Possible Heterogeneous mechanism (F.A.R).</td></tr>
<tr><td>Variation of catalyst surface</td><td>Possible Homogeneous mechanism (F.A.R.)</td></tr>
<tr><td colspan="2">Side hypothesis:
- If there are no variations the catalyst did not work enough (small TON).
- Change of surface can be due to some physical phenomenon.</td></tr>
<tr><td colspan="2">Complimentary methods & analysis:
- Always use the TEM test as a complimentary method with other tests.
- Check the TON value.</td></tr>
<tr><th>Advantages</th><th>Drawbacks</th></tr>
<tr><td>Easy to perform.</td><td>There is no clear conclusion about the nature of the mechanism.
Not very sensible.</td></tr>
</table>

Chapter 2

Homogeneous kinetic study of Suzuki-Miyaura reaction of 4-Iodoacetophenone catalyzed by palladacycle

Abstract:

This chapter presents a kinetic study of the Suzuki-miyaura reaction catalyzed by Herrmann-Beller palladacycle. Initially, the experimental conditions were verified and optimized to avoid any mass transfer or mixing limitations. Then, the initial experimental effects were determined for the catalyst and reagents. A reaction mechanism was chosen depending on the experimental observations, and then validated by using both a microkinetic and an analytic approach. The latter permits to obtain a simplified law that adequately represents the experimental results for specific conditions.

Keywords: Kinetic, microkinetic, homogeneous catalysis, Suzuki-Miyaura, Herrmann-Beller palladacycle.

2.1 Introduction

Suzuki-Miyaura (SM) reaction and more generally Pd carbon-carbon (C-C) cross-coupling reactions, have been the subject of numerous and prolific researches in organic chemistry and catalysis [1] crowned by the 2010 Nobel Prize for Chemistry [2, 3, 4, 5], awarded to Richard Heck, Ei-ichi Negishi and Akira Suzuki.

In the last decades, many authors have shown interest in the mechanism [6, 7, 8, 9, 10, 11, 12, 13, 14] proposing different scenario, all displaying the same basic elementary steps, but with detailed discussions about several mechanistic key points such as the nature of the active catalytic species [15, 12, 7], the role of the base [16, 17, 18], the missing links in the transmetallation step [19] and the solvent effect [14]. Thus, the mechanism and, more generally, to the reaction [1], very few publications provide global kinetic data and/or rate laws, are related to the full kinetic study of the Suzuki-Miyaura coupling. Thus, the quantitative impacts of the different protagonists - catalyst, arylhalide, boronic acid and base - are seldom available in a single rate law albeit such impacts would be highly valuables for the design of production processes.

Concerning the base, some in-depth mechanistic studies have detailed their antagonistic impact, showing that a simple reaction order cannot describe its role [17, 16]. However, a first order with respect to NaOH was published years ago [20] .

The reaction order with respect to palladium is also a matter of controversy. In the study of the reaction between bromobenzene and phenylboronic acid using $PdCl_2$ as a catalyst, it was shown that the catalysis reaction and deactivation are only first order depending on the catalyst concentration [21]. Recently, the coupling of 1-bromo-4-nitrobenzene with phenylboronic acids was tested using a new Pd(0) silica supported catalyst in the SM reaction [22]. The rate law was shown to be 1st order with respect to Pd, irrespectively of the Pd concentration. Last, a half reaction order with respect to the palladium concentration was evidenced in Heck coupling of iodobenzene with styrene using a palladium dimer complex as the catalyst precursor [23].

Concerning the reaction order with respect to the arylhalide, some consensus seems to be reached. For example, a zero-reaction order with respect to arylbromide at 65 °C was published [20] for the SM reaction, in spite of this a first order for arylhalide was recently published [24].

In addition to the complexity of the mechanism and the lack of complete kinetics studies, other challenges relate to the difficulties to solubilize all reactants in the same solvent (organohalide, organometallic, inorganic bases, and catalyst) that needs specific experimental conditions to avoid mass transfer limitations and mixing issues.

In this work, the SM coupling of 4-iodoacetophenone with phenylboronic acid was chosen as the model reaction. Firstly, the reaction conditions were optimized using different bases, solvents and catalysts. Then the initial order of the reaction depending on the initial concentration of each reactant was determined. Finally, all experimental data were fitted by taking into account a single mechanism using both a micro-kinetic approach and the analytical rate law derived from the mechanism.

2.2 Experimental section

2.2.1 Chemical products

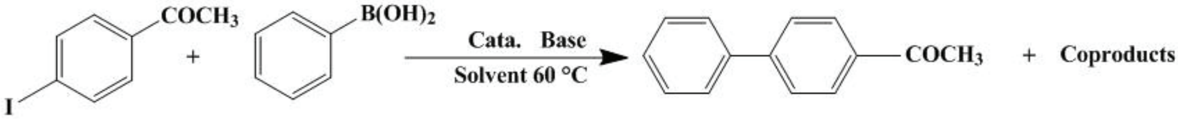
The experiments were carried out in anhydrous ethanol (CARLO ERBA). Reagents were 4-iodoacetophenone (Acros Organics), phenylboronic acid (Acros Organics), and seven Sigma-Aldrich bases (MeONa, NaOH, CH_3COONa, NEt_3, K_2CO_3, K_3PO_4 and K_2HPO_3). All solvents and reagents were used without purification. Four homogeneous palladium complexes were used (Sigma-Aldrich): Herrmann-Beller palladacycle, PEPPSI™-IPr catalyst, 1,2-bis(phenylsulfinyl)ethane palladium(II) acetate and Salicylaldehyde thiosemicarbazone palladium(II) chloride (Appendix 1).

2.2.2 Gas chromatography analysis (GC)

GC-FID chromatography (Agilent Technologies 6890N, column OPTIMA 5 (10 m x 100 µm x 0.1 µm), Split 1/250 volume injected 1 µL (300 °C), Flow H2: 0.4 mL / min, Program oven: 150 °C (30 s) then 50 °C/min up to 340 °C (42 s), FID Detector). N-tetradecane (Acros Organics) was used as an internal standard.

2.2.3 General procedure for the Suzuki coupling of 4-iodoacetophenone and phenylboronic acid in a batch reactor

Initially a solution of Herrmann-Beller palladacycle (4.7 mg, 0.005 mmol) in toluene (20 ml) was prepared. Then 4-iodoacetophenone (0.264 g, 1 mmol), phenyl boronic acid (0.145 g, 1.2 mmol), sodium methoxide (0.08 g, 1.5 mmol), n-tetradecane (0.3 mass equivalent) as a GC internal standard and anhydrous ethanol (20 ml) were added to a three-neck round-bottom flask equipped with a stirring bar. The dissolution was improved in an ultrasonic bath at room temperature (Elmasonic S30H) for 30 min, after that the flask was preheated at 60 °C inside an oil bath under agitation for 30 min, when this temperature was reached, a blank sample of 0.5 ml was syringed out for GC analysis and an aliquot (0.2 ml) of Herrmann-Beller palladacycle previously prepared (0.094 mg, 0.0001 mmol) was added. The samples were withdrawn at different times during the course of the reaction (1 h). Immediately after sampling, all samples were quenched in a mixture of deionized water (2 ml) and dichloromethane (VWR) (1 ml). The heavier organic phase was collected, dried over $MgSO_4$, filtered through a cotton wool and analyzed using GC-FID.



Scheme 1 Suzuki-Miyaura coupling of 4-iodoacetophenone with phenylboronic acid

2.2.4 General procedure for the Suzuki coupling of 4-iodoacetophenone and phenylboronic acid in the flow reactor

A typical reactant solution was prepared by dissolution of 4-iodoacetophenone (2.46 g, 0.01 mol, 1 eq.), phenylboronic acid (1.45 g, 0.012 mole, 1.2 eq.), MeONa (0.81 g, 0.015 mole, 1.5 eq.) and n-dodecane (0.5 g, 0.003 mole, 0.3 eq.) in ethanol (400 ml). An ultrasonic bath (Elmasonic S30H) was used to help dissolution (ultrasound for 30 min at room temperature).

Another solution was prepared by dissolution of Herrmann-Beller palladacycle (I) (0.0047 g, 0.005 mmol) in 20 ml of toluene (VWR).

The reagent solution was pumped (Shimadzu LC-20AP), and the catalyst solution (Programmable Syringe Pump Harvard PHD 4400 Hpsi) was added through the preheated (60 °C ± 2 °C) empty stainless steel tube (8.8 mm i.d SWAGELOK fittings); both solutions were mixed with a micromixer (SSIMM-IMM) or a T mixer (SWAGELOK) (Figure 5). Note that the residence time was controlled by both the flow rate and by the reactor length.

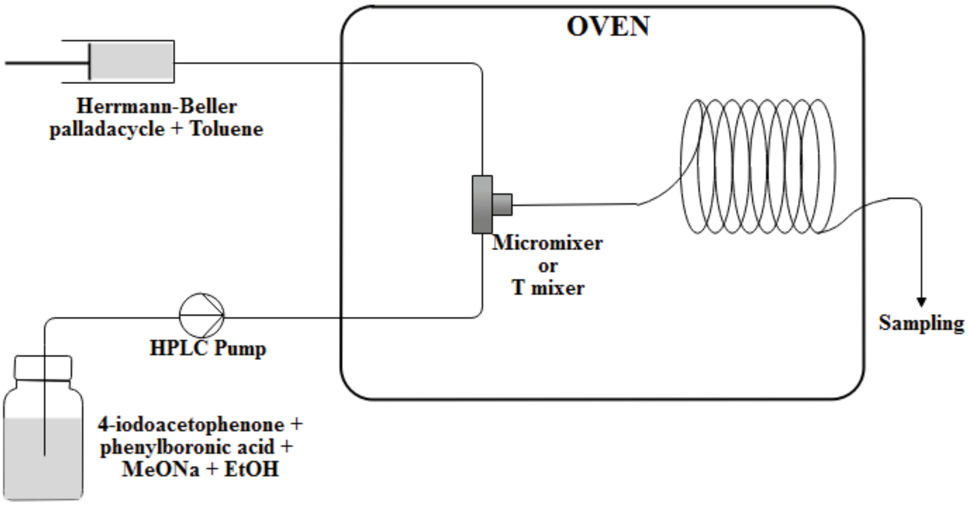


Figure 5 Flow test experimental set-up

2.2.5 Method of initial rate determination

The first order derivative at t=0 of a fitted five-order polynomial to the concentration profile normalized by the Pd concentration was chosen for the initial rate determination (see the example in (Appendix 2).

2.3 Results and discussions

2.3.1 Optimization of the reaction conditions

2.3.1.1 Palladium test

In order to study the kinetics of the homogeneous reaction, the catalyst should be soluble, active, stable without the formation of Pd black, and selective for the SM reaction.

Four homogeneous catalysts were tested in the SM coupling of 4-iodoacetophenone and phenylboronic acid (Table 4). PEPPSI (**II**) was active and selective giving 100% yield in bi-aryl in 1 hour transformed into Pd black very quickly which indicates that it was unstable at its molecular state. The same result was obtained for 1,2-bis(phenylsulfinyl)ethane palladium(II) acetate (**III**): it was active, selective but it formed Pd black during the course of the reaction. The salicylaldehyde thiosemicarbazone palladium (II) chloride (**IV**) was inactive even at 100 °C for 1 h. Finally, Herrmann-Beller palladacycle (**I**), showed the highest activity and selectivity without the formation of Pd black. Thus, **I** was selected to perform the kinetic study in this work.

Table 4 Catalyst selection for the Suzuki-Miyaura coupling of 4-iodoacetophenone with phenylboronic acid

Type of homogeneous catalysts	Pd black	Activity	% yield	Solubility
Herrmann-Beller palladacycle (I)	None	+++	100	+
PEPPSI™-IPr catalyst (II)	++	++	100	+
1,2-Bis(phenylsulfinyl)ethane palladium(II) acetate (III)	++	+	100	+
Salicylaldehyde thiosemicarbazone palladium(II) chloride (IV)	None	-	0 (<1)[a]	+

Conditions: 4-iodoacetophenone (1 mmol, 1eq.), phenylboronic acid (1.2 mmol, 1.2 eq.), K_2CO_3 (2 mmol, 2 eq.), ethanol 20 ml, 60 °C and 1 h. **I** (0.005 mmol, 0.005 eq.), **II**, **III** and **IV** (0.01 mmol). [a]: yield at 100°C.

2.3.1.2 Choice of the base

Seven bases were evaluated (Figure 6). Firstly, their solubility was tested. Three bases (K_2CO_3, K_3PO_4, and K_2HPO_3) were not soluble in ethanol at 0.1 M (2 eq.). In order to improve their solubility a 1:1 mixture of ethanol:water was used, but in such mixture, which was not sufficient to solubilize the reagents and products. Thus, the quantity of water was changed to reach a 9:1 ethanol:water mixture in which the reacting solution was soluble whatever the conversion. K_2CO_3, K_3PO_4 allowed to reach high conversions, in contrast with K_2HPO_3.

The activity of soluble bases in ethanol (MeONa, NaOH, CH_3COONa and NEt_3) was tested in the same reaction at 60 °C for 1 h. Besides, only sodium methoxide and sodium hydroxide showed a good activity (Figure 6).

Finally, ethanol and MeONa were chosen because they showed the highest activity, and the mixture was homogeneous at room temperature, in contrast to sodium hydroxide that was active but required more mixing to be dissolved.

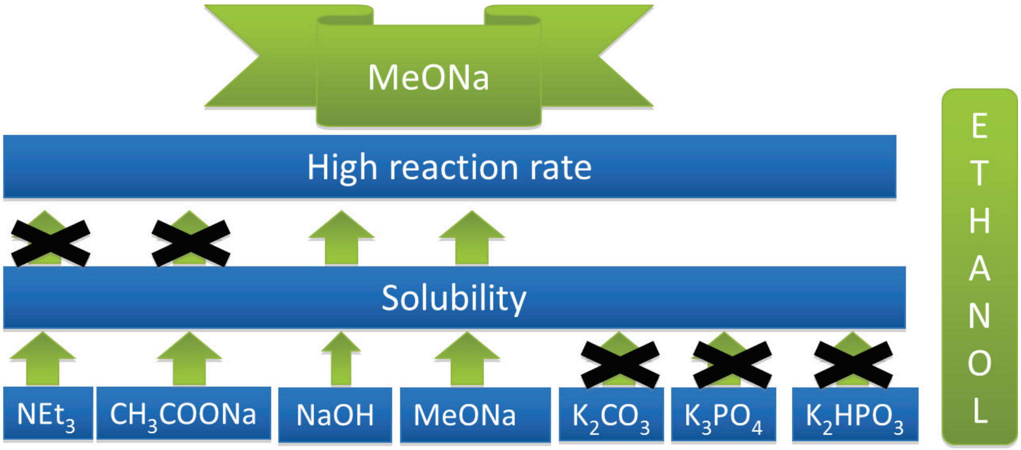


Figure 6 Choice of the base

To conclude, the kinetic study of SM coupling of 4-iodoacetophenone and phenylboronic acid will be performed using Herrmann-Beller palladacycle (**I**), ethanol as solvent and sodium methoxide as a base.

2.3.2 Kinetic study

2.3.2.1 Preliminary observations

The commercially available Herrmann-Beller palladacycle (**I**) has a crystalline form with quite large crystals. Dissolution in ethanol is rather slow and one must be cautious in order to avoid catalyst dissolution coupled to reaction kinetics. Thus **I** should initially be dissolved in toluene in which it dissolves easily, without forming Pd black for several days [25]. Such issue is well illustrated by comparing conversion vs. time profiles of experiments where the catalyst is pre-dissolved and other where it is used as received, i.e. as crystals (Figure 7).

Thus, the catalyst initially dissolved in toluene with 5.80 10^{-5} mol_{Pd}/l gave the same kinetic profile as the directly used catalyst with a concentration ten times higher than the other one (4.48 10^{-4} mol_{Pd}/l) demonstrating that the dissolution kinetics may limit the apparent rate of reaction.

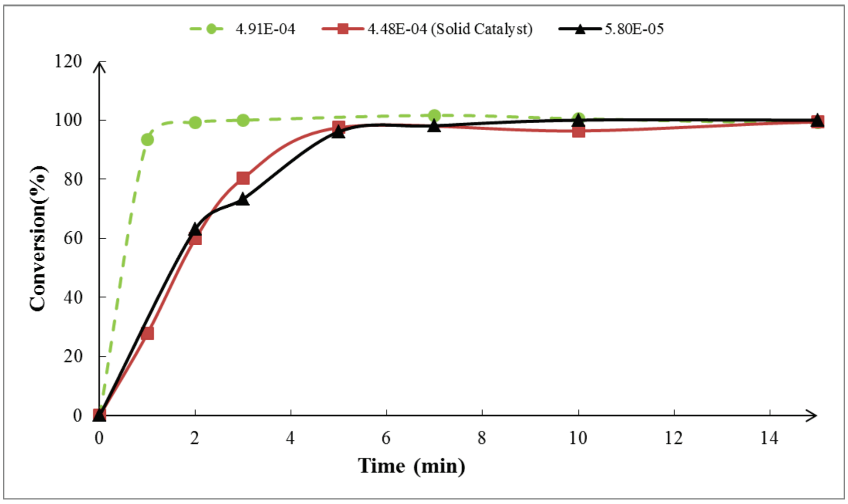


Figure 7 Effect of palladacycle pre-dissolution in toluene. (a) brown squares: use of crystalline catalyst directly (2.5 10^{-4} mol_I/l); (b) green circles pre-dissolution of the catalyst in toluene (2.5 10^{-4} mol_I/l) and the (c) black triangles with pre-dissolution of the catalyst in toluene (2.5 10^{-5} mol_I/l). **Conditions:** 4-iodoacetophenone (0.05 M, 1 eq.), phenylboronic acid (0.06 M, 1.2 eq.), MeONa (0.075 M, 1.5 eq.), **I** (2.5 10^{-5} mol_I/l, 0.0005 eq.) or **I** (2.5 10^{-4} mol_I/l, 0.005 eq.), T=60 °C, 20 ml of ethanol.

The use of toluene as the solvent for the catalyst dissolution could however lead to a micro-mixing problem between liquid phases (ethanol and toluene). Hence the measured kinetics can be limited by mass transfer between these phases. In order to check for micro-mixing issues, three tests were carried out: the first one using a batch reactor (20 ml), the second one using a flow reactor with a T-mixer and the last one using flow reactor with a commercial micromixer (IMM).

The yield vs. time profiles for three different reactors reveal negligible differences (Figure 8), which indicates the absence of mixing limitations. Therefore, it is confirmed that using these experimental conditions, the true reaction kinetics is measured.

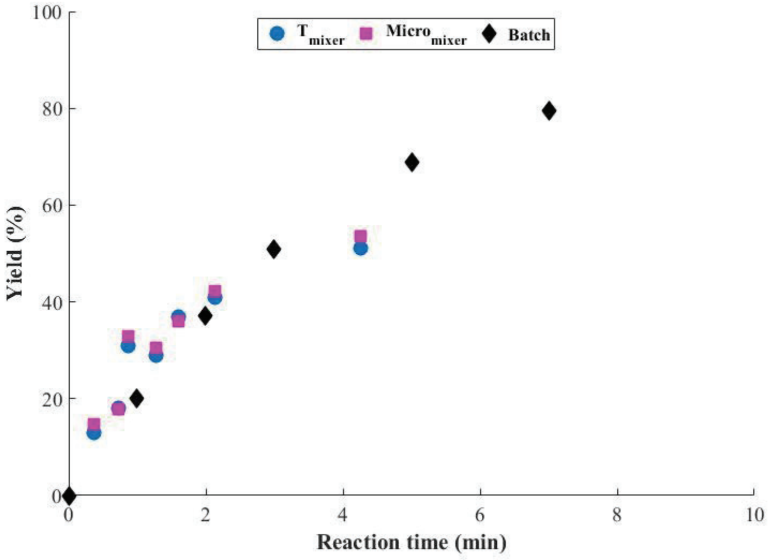


Figure 8 Verification that the reaction is not limited by micro-mixing or mass transfer

Conditions: 4-iodoacetophenone (0.025 M, 1 eq.), phenylboronic acid (0.03 M, 1.2 eq.), MeONa (0.038 M, 1.5 eq.), **I** (2.5 10^{-6} M, 0.0001 eq.) and 60 °C. **Flow conditions:** flow rate from 0.3 ml/min to 1 ml/min, reactor length from 40 cm to 290 cm.

2.3.2.2 Temperature effect and activation energy

The effect of temperature on the SMR was studied by varying the temperature from 19 °C to 80 °C using two different concentrations of palladium ($5 \cdot 10^{-6}$ mol/l and $5 \cdot 10^{-5}$ mol/l), The other reaction parameters were constant. As expected, the increase of temperature increased the reaction rate, for both concentrations of Pd, the catalyst was very active reaching 167 000 h^{-1} at 80 °C.

The Arrhenius plot of the reaction initial rate for two different concentration of Pd. gave a similar value for the global activation energy, with an average value of 59 kJ/mol. Such value is in the range of those determined for many homogeneous catalytic reactions in which metal-to-carbon bonds making/breaking is involved such as hydrogenations, hydroformylations etc [26,27].

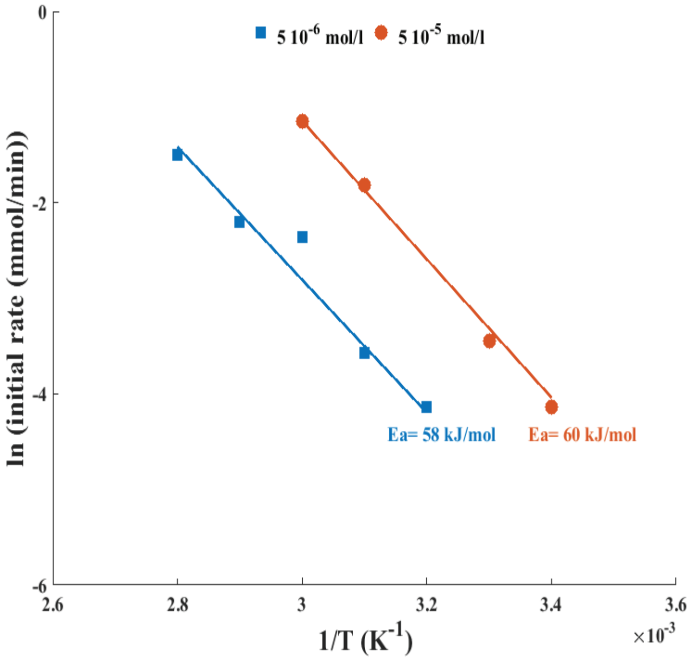
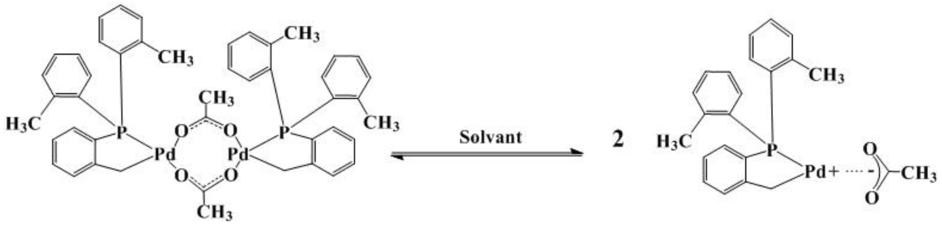


Figure 9 Effect of temperature on Suzuki-coupling of 4-iodoacetophenone and phenylboronic acid using two different concentrations of Pd (Arrhenius Plot).

Conditions: 4-iodoacetophenone (0.05 M, 1 eq.), phenylboronic acid (0.06 M, 1.2 eq.), MeONa (0.075 M, 1.5 eq.), I (2.5 10^{-5} M or 2.5 10^{-6} M), 20 ml of ethanol and 60 °C

2.3.2.3 Effect of the catalyst concentration

The concentration of palladium was varied between 5 10^{-6} and 5 10^{-4} mol/l, but only the experiments with Pd concentrations lower than 22 10^{-6} mol/l were used for the determination of the initial rate of the reaction because for higher Pd concentrations the reaction is so fast that conversions higher than 50 % are reached after only 1 min. The initial reaction rate is first order with respect to initial Pd concentration (Figure 10).This first order can be explained by an instantaneous transformation of the dimeric Pd precursor into monomeric Pd species.



Scheme 2 Dimer/monomer equilibrium of **I**

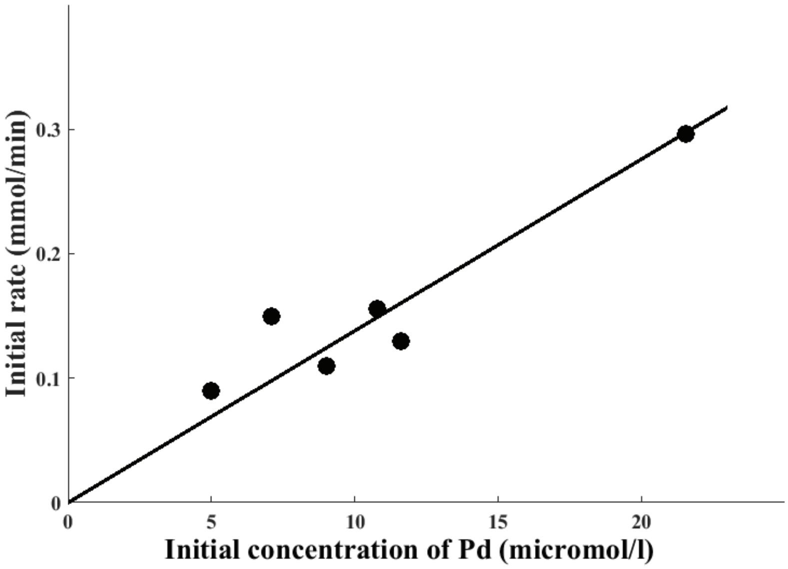


Figure 10 Effect of the initial concentration of Pd on the reaction rate. Conditions: 4-iodoacetophenone (0.05 M, 1 eq.), phenylboronic acid (0.06 M, 1.2 eq.), MeONa (0.075 M, 1.5 eq.), **I** from 2.5 10^{-6} M to 2.5 10^{-4} M, 20 ml of ethanol and 60 °C.

2.3.2.4 Effect of aryl halide concentration

The aryl halide plays an important role in the oxidative addition elementary step producing Pd(II) complex from zero-valent Pd. This Pd(0)/Pd(II) mechanism was largely studied in the literature [28, 29, 30], and it is known to be a very fast step in SM reaction [16, 17].

In order to determine the effect of aryl halide concentration, the initial concentration of 4-iodoacetophenone was varied between 25 mmol/l and 100 mmol/l (Figure 11). The initial rates increase linearly with the concentration which indicates an apparent first order with respect to 4-iodoacetophenone.

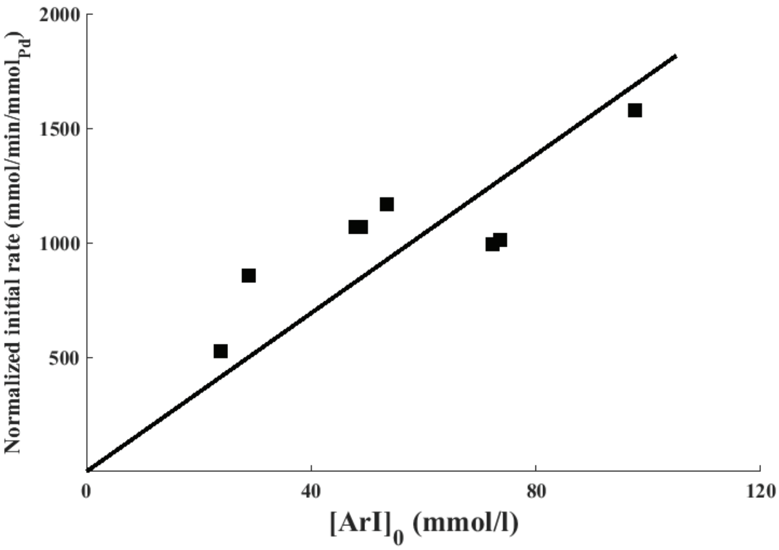


Figure 11 Effect of the initial concentration of 4-iodoacetophenone

Conditions: 4-iodoacetophenone from 0.025 to 0.15 M, phenylboronic acid (0.06 M, 1.2 eq.), MeONa (0.075 M, 1.5 eq.), I (2.5 10^{-6} M), 20 ml of ethanol and 60 °C.

2.3.2.5 Effect of base and phenylboronic acid concentration

The effect of the base was largely discussed in many publications [31, 18, 16, 17, 19, 32], it has been demonstrated that the base plays an important role in the transmetallation elementary step through two possible pathways as it will be discussed in the discussion section. Figure Appendix 3 shows the variation of the product concentration using different initial equivalents of sodium methoxide and phenylboronic acid. Indeed when one of them is the limiting reagent the product concentration respects the stoichiometry of the reaction.

The initial concentration effect of phenylboronic acid and sodium methylate was studied by varying the concentration of each one (Figure 12) between 0.03 M and 0.15 M. Surprisingly, both reagents gave a straight line that has a slope equal to zero, which indicates a zero order with respect to their initial concentration.

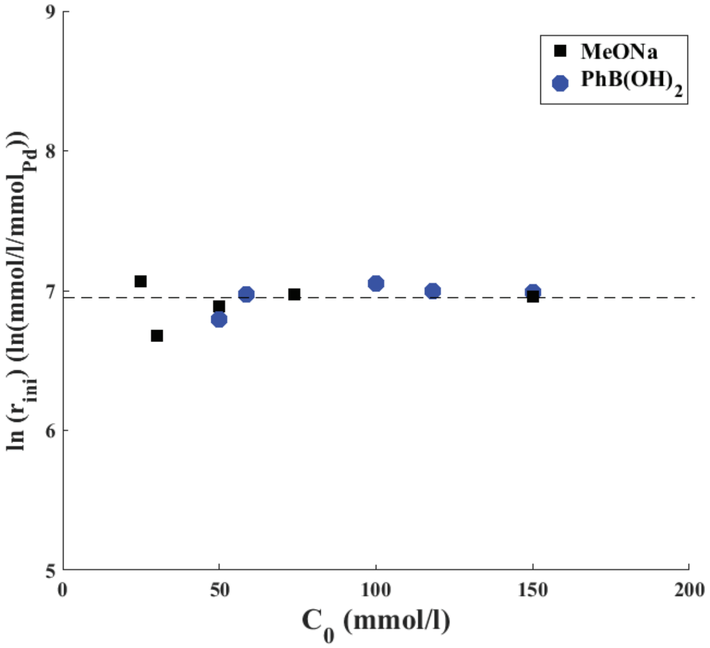


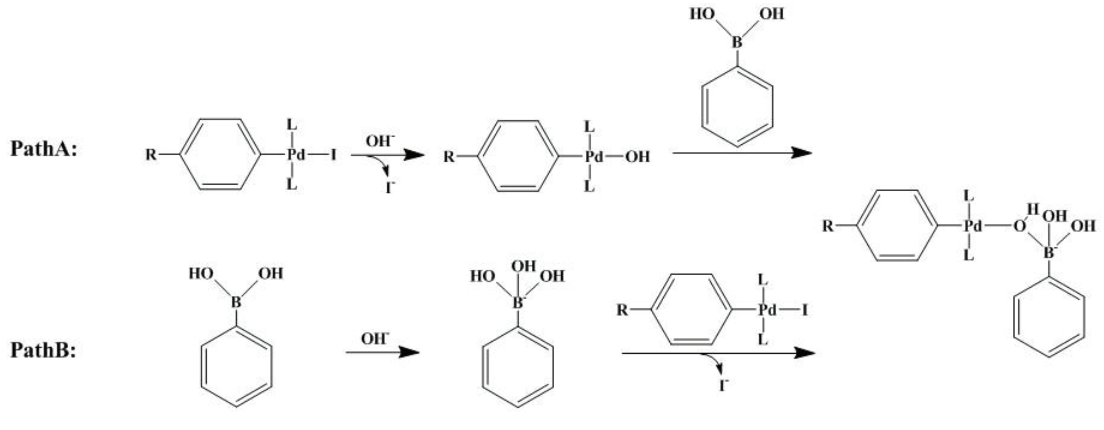
Figure 12 Phenylboronic acid and sodium methylate effect on SM initial reaction rate

Conditions varying PhB(OH)$_2$: 4-iodoacetophenone (0.05 M, 1 eq.), phenylboronic acid from 0.03 to 0.15 M, MeONa from 0.035 to 0.15 M, **I** (2.5 10^{-6} M), 20 ml of ethanol and 60 °C. **Conditions varying MeONa:** 4-iodoacetophenone (0.05 M, 1 eq.), phenylboronic acid (0.06 M, 1.2 eq.), MeONa from 0.035 to 0.15 M), **I** from (2.5 10^{-6} M), 20 ml of ethanol and 60 °C. The solid line is a trend line.

2.4 Kinetic modeling

The mechanism of Suzuki-Miyaura (SM) reaction was largely analyzed in the literature [33, 7, 16, 17, 34, 35], all authors have agreed that SM reaction proceeds through four different elementary steps, oxidative addition, halide ligand exchange, transmetallation and reductive elimination.

The oxidative addition is well known [28, 29, 30] and is suggested to be a very fast step [17]. In the case of the transmetallation step, authors said that there are two possible pathways (Scheme 3) that are distinguished by the role of the base [36, 28, 29, 30], with the question whether the base reacts first with the palladium complex or with the phenylboronic acid. Moreover, Amatore et al. [17] said that there are some possible negative effects of the base by forming inactive $PhB(OH)_3^-$ and inactive Pd(II) complex with Na^+. The last step is the reductive elimination, that generates the coupling product and the zero-valent Pd from the trans-$[Pd(Ar)\text{-}(Ar^{'})(L)_2]$.



Scheme 3 Base effect in the transmetalation elementary step

Regarding the experimental results obtained above, the use of a strong base [37] and the deficiency of ligands [31] path B (**Scheme 3**) was selected, with the base reacting with the phenylboronic acid as a very fast irreversible reaction [33].

2.4.1 Reaction mechanism and modeling

As discussed above, a mechanism with reaction between base and phenylboronic acid has been chosen (Figure 13). This is the generally accepted mechanism for SM reaction [7, 37] where the transmetallation step passes through the formation of a boronate [$PhB(OH)_3]^-$ intermediate via a fast equilibrium.

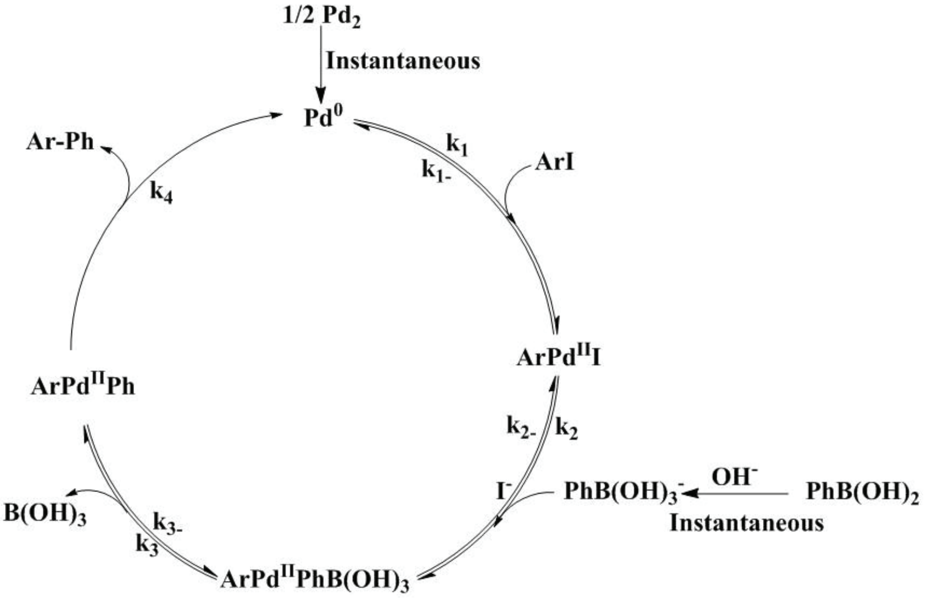


Figure 13 Suzuki-Miyaura coupling mechanism chosen

2.4.2 Simplifications

2.4.2.1 Reduction of Pd_2^{2+} into Pd^0

The fact that Pd(II) palladacycles are reduced to Pd(0) is well documented in the literature [7], albeit with no detailed mechanism and most often with a significant induction period. The formation of Pd(0) from a palladacycle precursor with Me_3SnPh [39], and the X ligand substitution by $PhB(OH)_3^-$ proposed recently [40] has inspired our proposal.

Overall, since no induction period was evidenced experimentally, we considered the formation of Pd(0) from the dimmer as an instantaneous step. Note that the H. Beller palladacycle (II) is known to display no induction period for Heck coupling which support our hypothesis [41, 42].

$$\frac{1}{2}Pd_2 \xrightarrow{Instantaneous} Pd^0 \qquad (1)$$

2.4.2.2 Generation of boronate [PhB(OH)$_3$]$^-$

The reaction between phenylboronic acid and the hydroxide ion was supposed to be instantaneous and completely shifted to the right:

$$OH^- + PhB(OH)_2 \xrightarrow{Instantaneous} PhB(OH)_3^- \tag{2}$$

2.4.2.3 Catalyst deactivation

The mechanisms with possible deactivation processes (c, d) were also tested but the optimization always shown no impact of their kinetic constant (k_6 and k_{6-}) in the estimating process (see Appendix 11). Thus the catalyst deactivation was neglected in the kinetic model.

2.4.2.4 Side reactions

Only the homocoupling side reaction was detected in some experiments with a biphenyl yield lower than 1 %. Thus it was neglected in the kinetic model.

2.4.3 Experimental results used for kinetic modeling

In order to get good simulation results and validate the mechanism the selected experimental results should respect some criteria (Chapter 3 Basic Concepts in Chemical Kinetics from [43]):

- Experiments should be reproducible.
- Only experiments without anomalies were used (induction period, catalyst deactivation).
- Good mass balance between reactants and products.

From 38 experiments in the batch reactor, only 29 respect the proposed criteria. All the 14 experiments carried out in the flow reactor have been selected for the optimization process.

2.4.4 Reactor model

An ideal batch reactor model was used because all experiments were carried out in a three-neck round-bottom flask equipped with a stirring bar. The continuous experiment was modeled like two unique batch experiments by using conversion as function of residence time.

2.5 The microkinetic approach

2.5.1 Elementary equations

From previous remarks and simplifications, and using the mechanism Figure 13, the obtained microkinetic system is:

Oxidative addition

$$Pd + ArI \xrightarrow[k_1]{} ArPdI \tag{3}$$

$$ArPdI \xrightarrow[k_{1-}]{} Pd + ArI \tag{4}$$

halide ligand exchange

$$PhB(OH)_3^- + ArPdI \xrightarrow[k_2]{} ArPdPhB(OH)_3 \tag{5}$$

$$ArPdPhB(OH)_3 \xrightarrow[k_{2-}]{} PhB(OH)_3^- + ArPdI \tag{6}$$

Transmetalation

$$ArPdPhB(OH)_3 \xrightarrow[k_3]{} ArPdPh + B(OH)_3 \tag{7}$$

$$ArPdPh + B(OH)_3 \xrightarrow[k_{3-}]{} ArPdPhB(OH)_3 \tag{8}$$

Reductive elimination

$$ArPdPh \xrightarrow[k_4]{} ArPh + Pd \tag{9}$$

2.5.2 Mass Balance equation

Pd
$$\frac{d[Pd]}{dt} = -r_1 + r_{1-} + r_4 \tag{10}$$

ArI
$$\frac{d[ArI]}{dt} = -r_1 + r_{1-} \tag{11}$$

ArPdI
$$\frac{d[ArPdI]}{dt} = r_1 - r_{1-} - r_2 + r_{2-} \tag{12}$$

$PhB(OH)_3^-$
$$\frac{d[PhB(OH)_3^-]}{dt} = -r_2 + r_{2-} \tag{13}$$

$ArPdPhB(OH)_3$
$$\frac{d[ArPdPhB(OH)_3\,]}{dt} = r_2 - r_{2-} - r_3 + r_{3-} \tag{14}$$

ArPdPh
$$\frac{d[ArPdPh]}{dt} = r_3 - r_{3-} - r_4 \tag{15}$$

$B(OH)_3$
$$\frac{d[B(OH)_3]}{dt} = r_3 - r_{3-} \tag{16}$$

I^-
$$\frac{d[I^-]}{dt} = r_2 - r_{2-} \tag{17}$$

ArPh
$$\frac{d[ArPh]}{dt} = r_4 \tag{18}$$

2.5.3 Rate laws for the elementary steps

$$r_1 = k_1 \cdot [Pd] \cdot [ArI] \tag{19}$$

$$r_{1-} = k_{1-} \cdot [ArPdI] \tag{20}$$

$$r_2 = k_2 \cdot [ArPdI] \cdot [PhB(OH)_3^-] \tag{21}$$

$$r_{2-} = k_{2-} \cdot [ArPdPhB(OH)_3\,] \cdot [I^-] \tag{22}$$

$$r_3 = k_3 \cdot [ArPdPhB(OH)_3\,] \tag{23}$$

$$r_{3-} = k_{3-} \cdot [ArPdPh] \cdot [B(OH)_3] \tag{24}$$

$$r_4 = k_4 \cdot [ArPdPh] \tag{25}$$

Mass action laws were considered for each of the elementary steps.

2.5.4 Kinetic constants

$$k_1 = k_{01} \cdot e^{\frac{-E_{a1}}{RT}} \tag{26}$$

$$k_{1-} = k_{01-} \cdot e^{\frac{-E_{a1-}}{RT}} \tag{27}$$

$$k_2 = k_{02} \cdot e^{\frac{-E_{a2}}{RT}} \tag{28}$$

$$k_{2-} = k_{02} \cdot e^{\frac{-E_{a2-}}{RT}} \tag{29}$$

$$k_3 = k_{03} \cdot e^{\frac{-E_{a3}}{RT}} \tag{30}$$

$$k_{3-} = k_{03-} \cdot e^{\frac{-E_{a3-}}{RT}} \tag{31}$$

$$k_4 = k_{04} \cdot e^{\frac{-E_{a4}}{RT}} \tag{32}$$

2.5.5 Initial conditions

$Pd(t=0) =[Pd]_0$ (33)

$ArI(t=0) =[ArI]_0$ (34)

$ArPdI(t=0) =[ArPdI]_0$ (35)

$OH^-(t=0) =[OH^-]_0$ (36)

$PhB(OH)_3^-(t=0) =[PhB(OH)_3^-]_0$ (37)

$ArPdPhB(OH)_3(t=0) =[ArPdPhB(OH)_3]_0$ (38)

$ArPdPh(t=0) =[ArPdPh]_0$ (39)

$B(OH)_3(t=0) =[B(OH)_3]_0$ (40)

$$ArPh(t=0) = [ArPh]_0 \quad (41)$$

2.5.6 The simulation and optimization methods

The kinetic model is a system of ordinary differential equations (ODE). It was simulated on a computer program using Matlab© and optimized using the "lsqcurvefit" function with a trust-region-reflective algorithm. Besides, lsqcurvefit function has the residual sum of squares as predetermined objective function.

The experimental data used for the fitting are the measured concentration of 4-iodoacetophenone, 4-acetylbiphenyl, and the stoichiometric concentrations of $B(OH)_3$ and NaI. All the concentrations were normalized by the initial concentration of 4-iodoacetophenone (0.05 M). Furthermore, only the first 7 points for each experiment were used, i.e the points at full conversion are neglected.

The described micro kinetic approach involves a mechanism featuring 4 elementary steps with 4 kinetic constants and unknown concentrations for at least 3 catalytic species (since all the 4 catalytic species are related by the mass balance on total Pd which is known). For a full determination driving to a unique mathematical solution, it requires to have experimental data on the intermediates concentrations. In the absence of such information, multiple solutions for the parameters estimation are possible. In the following, the work was achieved without information on the catalytic species and one possible set of numerical values for the parameters is provided as an illustration. In the future, a single solution will be obtained with more experimental work such as for example starting from intermediate pallacycle-ArPdI which would be synthesized from reacting the palladacycle precursor with ArI in a similar way as described in the literature [16, 17]. Such work involving heavy synthesis of organometallic compounds of palladium is far behind the scope of this thesis work. Thus, our purpose is to build a full kinetic model that would be fed with more experimental results in the future.

2.5.7 Simulation results and discussions

In order to estimate the kinetic parameters the program was launched with a multi-start function, until it converged to the lower value of the objective function (the residual sum of squares) between the experimental results and the estimated ones. The impact of the reversible parameters **k_{1-}, k_{2-}** and **k_{3-}** was tested at the end of the estimation process and they have no impact; hence the corresponding steps were neglected in the final estimation (Figure 14).

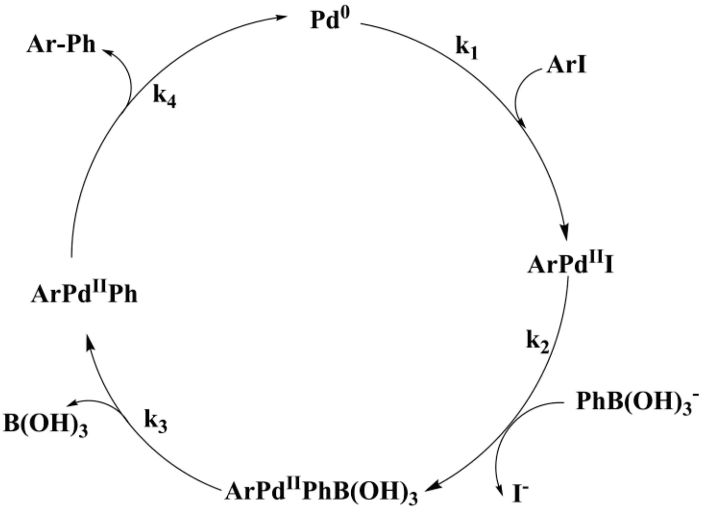


Figure 14 The final mechanism used for the simulation process

Table 5 shows the estimated parameters using the mechanism (Figure 14). They show a satisfying confidence interval (for the values of estimated constants with confidence interval and activation energies see Appendix 4).

Table 5 Estimated parameters at 60 °C using the mechanism (**Figure 14**)

Kinetic parameters	**Estimated value**
$k_1(mol^{-1}l\ min^{-1})$	1.93×10^4
$k_2(mol^{-1}l\ min^{-1})$	2.21×10^5
$k_3(min^{-1})$	3.03×10^6
$k_4(min^{-1})$	4.74×10^3

The parity plot curve (Figure 15) shows a good fit between the model and experimental concentration of the product, with only 15 % of dispersion for 41 experiments (27 in batch reactor and 14 in continuous reactor), with only 2 experiments were out of the 15 %

without any explanation. An example of appropriate representation of the experiments by the estimated parameters is presented in Appendix 5.

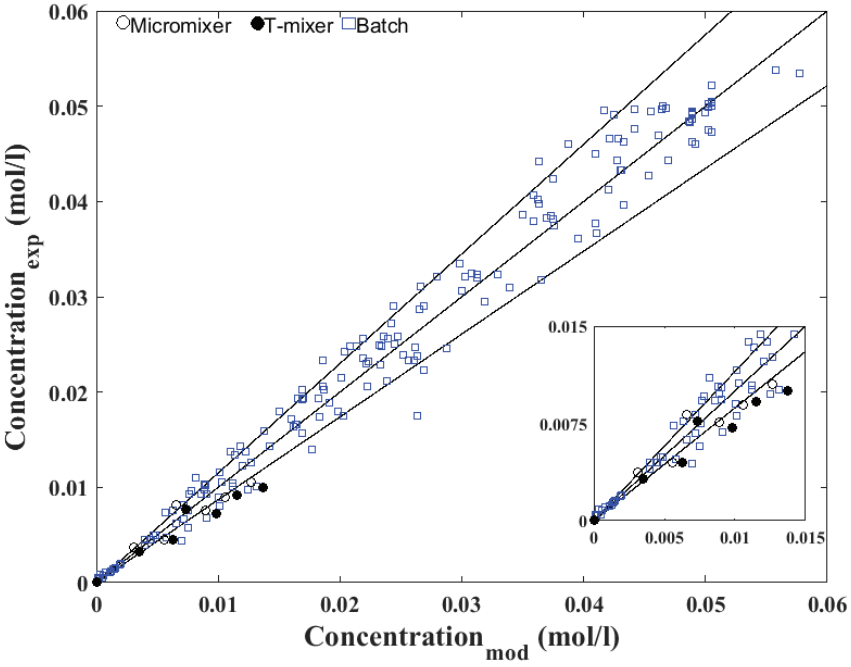


Figure 15 parity plot between experimental and modeled concentrations

Batch reactor: 27 experiments with 7 points per experiment. **Flow reactor:** 14 experiments with 1 point per experiment.

2.6 Analytical approach

A microkinetic approach was previously used to estimate the kinetic parameters and validate the chosen model. In this part an analytical approach will be studied in order to derive a kinetic law from the previously validated mechanism (Figure 16).

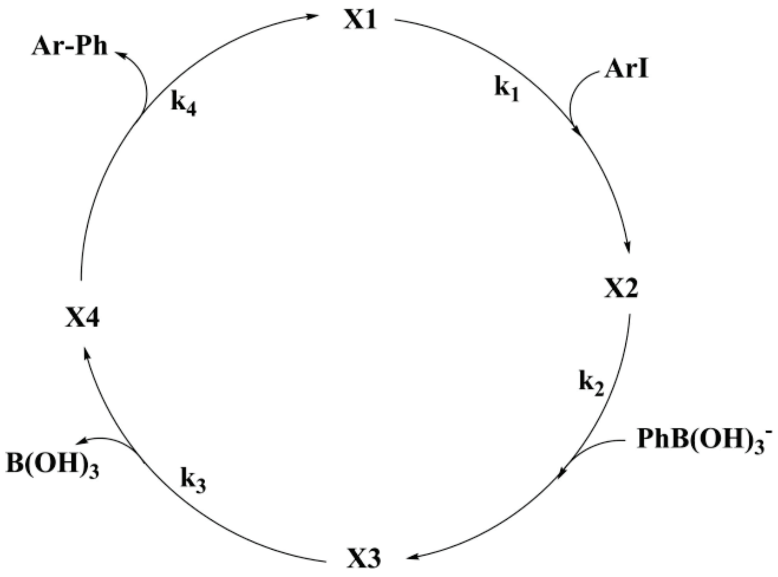


Figure 16 Homogeneous mechanism for Suzuki-Miyaura reaction

In the following for the sake of clarity: **A**: ArX, **B**: $PhB(OH)_3^-$, **C**: $B(OH)_3^-$, **P**: coupling product (Ar-Ph), X1, X2, X3, and X4 are intermediate species of palladium with:

$$X1 + X2 + X3 + X4 = Pd_0 \tag{42}$$

The mechanism Figure 16 is represented by using the equations of elementary steps (43)-(46).

$$X1 + A \underset{k_1}{\rightarrow} X2 \tag{43}$$

$$\mathrm{B} + X2 \underset{k_2}{\rightarrow} X3 + I \tag{44}$$

$$X3 \underset{k_3}{\rightarrow} X4 + \mathrm{C} \tag{45}$$

$$X4 \underset{k_4}{\rightarrow} P + X1 \tag{46}$$

By using system of equations (42) - (46) the partial differential equation (PDE) of Pd intermediate species are written as follows:

$$X1: \qquad \frac{dX1}{dt} = -k_1 \cdot A \cdot X1 + k_4 X4 \tag{47}$$

$$X2: \qquad \frac{dX2}{dt} = k_1 \cdot A \cdot X1 - k_2 \cdot B \cdot X2 \tag{48}$$

$$X3: \qquad \frac{dX3}{dt} = k_2 \cdot B \cdot X2 - k_3 \cdot X3 \tag{49}$$

$$X4: \qquad \frac{dX4}{dt} = k_3 \cdot X3 - k_4 \cdot X4 \tag{50}$$

From (47) - (50) the equations for intermediate species can be written:

$$\frac{dXi}{dt} = M \cdot \begin{bmatrix} X1 \\ \vdots \\ X4 \end{bmatrix} \tag{51}$$

Where M is:

$$M = \begin{bmatrix} -k_1 A & 0 & 0 & k_4 \\ k_1 A & -k_2 B & 0 & 0 \\ 0 & k_2 B & -k_3 & 0 \\ 0 & 0 & k_3 & -k_4 \end{bmatrix}$$

Moreover, the system (42) and by using the quasi stationary state approximation (QSSA), (51) became:

$$\frac{dXi}{dt} = M' \cdot \begin{bmatrix} X1 \\ \vdots \\ X4 \end{bmatrix} = (0,0,0,0,Pd_0) \tag{52}$$

With $M'\ is$:

$$M' = \begin{bmatrix} -k_1 A & 0 & 0 & k_4 \\ k_1 A & -k_2 B & 0 & 0 \\ 0 & k_2 B & -k_3 & 0 \\ 0 & 0 & k_3 & -k_4 \\ 1 & 1 & 1 & 1 \end{bmatrix}$$

Furthermore, according to the mechanism (Figure 16) and the evolution of reactant A with time, the reaction rate is given by:

$$r = -\frac{dA}{dt} = k1 \cdot A \cdot X1 \tag{53}$$

After simplifications, rearrangements and substituting the solution of system (52) inside the equation (53), X1 is expressed according to equation 54 and the reaction rate according to equation 55:

$$X1 = \frac{k_2 k_3 k_4\, Pd_0\, B}{(k_2 k_3 k_4\, B + k_1 k_3 k_4\, A + k_1 k_2\, A\, B(k_4 + k_3)} \tag{54}$$

$$r = \frac{k_1 k_2 k_3 k_4\, Pd_0\, A\, B}{(k_2 k_3 k_4\, B + k_1 k_3 k_4\, A + k_1 k_2\, A\, B(k_4 + k_3)} \tag{55}$$

2.6.1 Mass Balance equations

A: $$\frac{dA}{dt} = -\mathrm{r} \tag{56}$$

B: $$\frac{d\mathrm{B}}{dt} = -\mathrm{r} \tag{57}$$

C: $$\frac{dC}{dt} = \mathrm{r} \tag{58}$$

I: $$\frac{d\mathrm{I}}{dt} = \mathrm{r} \tag{59}$$

P: $$\frac{dP}{dt} = \mathrm{r} \tag{60}$$

2.6.2 Initial conditions

A: $$A(\mathrm{t}=0)=A_0 \tag{61}$$

B: $$B(\mathrm{t}=0)=B_0 \tag{62}$$

C: $$C(\mathrm{t}=0)=C_0=0 \tag{63}$$

I: $$I(\mathrm{t}=0)=I_0=0 \tag{64}$$

P: $$P(\mathrm{t}=0)=P_0=0 \tag{65}$$

2.6.3 Simulation results and discussions

In order to compare the microkinetic and the analytical approaches, the estimated parameters by the microkinetic approach (Table 5) were used in the analytical law (55) in a simulation by Matlab© to reproduce the experimental results. As expected both methods gave exactly the same parity plot of best fit between the calculated concentration and the experimental one (see Appendix 8 for an example with one experiment).

Moreover in order to compare the experimental remarks previously obtained for the effect of the initial reagents concentration on the initial reaction rate, equation (55) was rewritten in function of the conversion (X) and the initial concentrations A_0, B_0 and Pd_0.

$$r=\frac{k_1k_2k_3k_4\;(Pd_0A_0^2\,X^2-(Pd_0A_0^2+Pd_0A_0B_0)\,X+Pd_0A_0B_0)}{\alpha X^2+\beta X+\gamma} \tag{66}$$

With:

$$\alpha=k_1k_2k_4A_0^2+k_1k_2k_3A_0^2$$

$$\beta=-k_2k_3k_4*A0-k_1k_2A_0(k_4A_0-k_4B_0-\frac{k_3}{k_2}k_4-k_3A_0-k_3B_0)$$

$$\gamma=k_2k_3k_4B_0+k_1k_3k_4A_0+k_1k_2k_3A_0B_0+k_1k_2k_4A_0B_0$$

Initially at t=0 the conversion X=0 and r(t=0) = r_0:

$$r_0 = \frac{k_1\, Pd_0 A_0}{1 + \frac{k_1 A_0}{k_2 B_0} + A_0\left(\frac{k_1}{k_3} + \frac{k_1}{k_4}\right)} \qquad (67)$$

From (67) a first order dependance on Pd concentration is easily noticeable, which is in total agreement with the experiments (Figure 10). Furthermore, the initial reaction rate was determined from (67) by varying the initial concentration (A_0) in an interval between 0.005 M and 0.1 M with keeping all the other concentrations constants (the same thing was done with B_0) (Figure 17). Hence, at a concentration lower than 0.03 M, a first order can be found for A_0, while for concentrations higher than 0.03 M, the initial concentration A_0 shows a complicated positive order. In the other hand, the concentration of B_0 gave a positive order for very small concentration and a zero order at concentrations higher than 0.05 M; these remarks can be mathematically seen from equation (67):

When $B_0 \rightarrow 0$, r0 $\rightarrow 0$ and when $B_0 \rightarrow \infty$, r0 $\rightarrow$constant independent from B_0 (Constant= $\frac{k_1\, Pd_0 A_0}{1+KA_0}$). These results are in agreement with the kinetic orders estimated from the experimental initial rates.

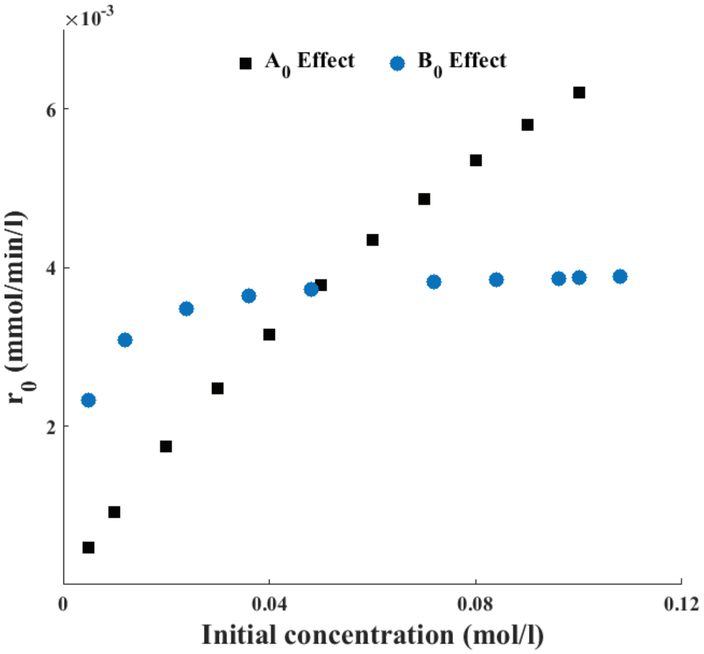


Figure 17 Effect of A_0 and B_0 on the reaction initial rate

2.6.4 Simplified analytical reaction rate

After rearrangement the reaction rate equation (55) can be written as follows:

$$r = \frac{k_1\, Pd_0 A}{1 + k_{12}\frac{A}{B} + A(k_{13} + k_{14})} \tag{68}$$

With: $\boldsymbol{k_{12}} = \frac{k_1}{k_2}, \boldsymbol{k_{13}} = \frac{k_1}{k_3}, \boldsymbol{k_{14}} = \frac{k_1}{k_4}$. Note that this equation is correct for all B>0.

Table 6 Values of reaction rate parameters calculated using the estimated values of k_1, k_2, k_3 and k_4 at 60 °C (Table 5).

$\boldsymbol{k_{12}}(-)$	$\boldsymbol{k_{13}(mol^{-1}l)}$	$\boldsymbol{k_{14}(mol^{-1}l)}$
0.09	**0.006**	**4.07**

In Suzuki-Miyaura reaction, the concentrations of base and phenylboronic acids are always higher or equal than those of the aryl halides [44], [45], 43, 44, 24], which means that B is always higher or equal to A, from this point and by taking in consideration the value of

Table **6**, k_{13} is always insignificant compared to k_{14} ,and the reaction rate can be simplified as presented in Equation 69, with only 5 % of relative error compared to the microkinetic results (Figure 14):

$$r = \frac{k_1\, Pd_0 A}{1 + k_{14}\, A} \tag{69}$$

If the concentration of A is lower or equal to 0.02 M; $\boldsymbol{k_{14}\, A}$ became insignificant compared to **1** and the reaction rate equation can be written as:

$$r = k_1\, Pd_0 A \tag{70}$$

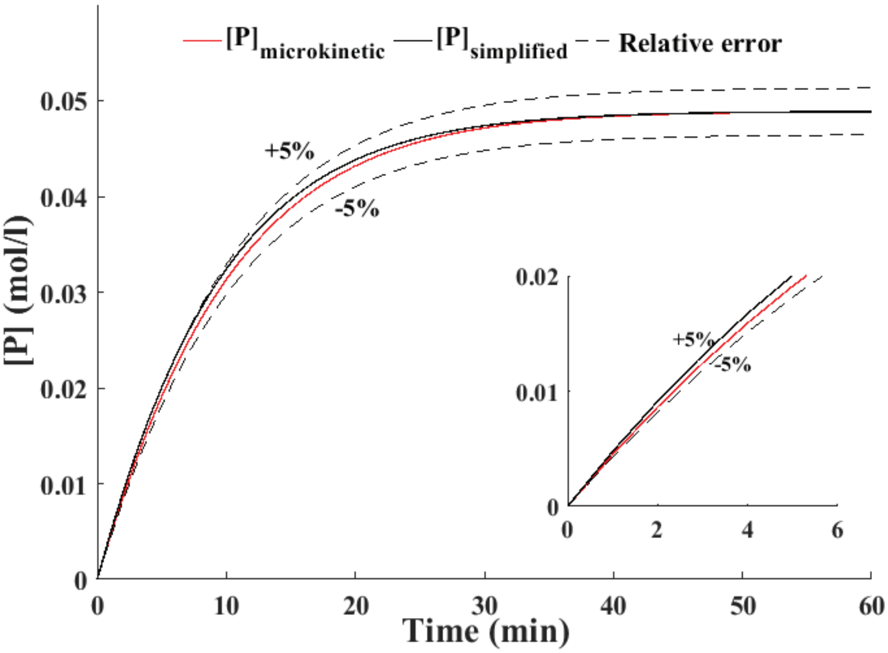


Figure 14 Microkinetic vs. simplified kinetic law **(69)**

Conditions: A (0.05 M, 1 eq.), Pd$_0$ (5 10-^{6} M), and 64 °C.

2.7 Conclusion

In this chapter the experimental conditions of Suzuki-Miyaura reaction of 4-iodoacetophenone with phenylboronic acid have been optimized to avoid all mass transfer limitations, by initially choosing a stable active and selective homogeneous catalyst. Then, from a variety of bases, sodium methylate has been selected for its activity and solubility in ethanol.

Furthermore, a kinetic study was carried out by initially checking the effect of the initial concentration of each reagent on the initial reaction rate. In fact a quasi-first order was found for the 4-iodoacetophenone with a first order dependance on the initial concentration of palladium. Surprisingly, a zero order was found for higher concentrations of the base and the phenyl boronic acid. After that, these results and remarks have been used to choose a corresponding mechanism that was tested and confirmed by modeling with both a microkinetic and analytic approach.

Finally a simplified kinetic law was obtained, and this last will be used in the reactor modeling (chapter 4).

For the first time a global activation energy, with an average value equal to 59 kJ/mol was determined for the SM reaction catalyzed by a homogeneous catalyst.

Moreover the micro-kinetic analysis showed that the more difficult step is the oxidative addition with Ea= 61 kJ/mol.

A global rate law was derived and validated for the SM reaction. This study needs to be completed by future works, with the bromide and the chloride derivatives, and also with weaker bases in order to define their effects on the rate limiting step, the nature of the mechanism, and the form of the kinetic rate law.

2.8 List of abbreviations

$[Pd_2]$	Concentration of palladacycle (mol l^{-1})
$[Pd]$	Concentration of atomic (mol l^{-1}) or X1
$[ArI]$	Concentration of 4-iodoacetophenone (mol l^{-1}) or A
$[ArPdI]$	Concentration of Pd(Ar)-(I)(L)$_2$ (mol l^{-1} min^{-1}) or X2
$[PhB(OH)_3^-]$	Concentration of boronate (mol l^{-1}) or B
$[ArPdPhB(OH)_3\,]$	Or X3 (mol l^{-1})
$[ArPdPh]$	Or X4 (mol l^{-1})
$[B(OH)_3]$	Concentration of the broric product (mol l^{-1}) Or C
$[I^-]$	Concentration of NaI (mol l^{-1}) Or I
$[ArPh]$	Concentration of the reaction product or P (mol l^{-1})
$E_{a\mathrm{i}}$	Activation energy for each elementary step (J/mol)
k_i	Kinetic constants of the reaction elementary steps
R	Ideal gas constant (J mol^{-1}K^{-1})
r_i	Reaction rates of elementary steps (mol l^{-1} min^{-1})
r_0	Initial reaction rates of elementary steps (mol l^{-1} min^{-1})
∞	infinity symbol

2.9 References

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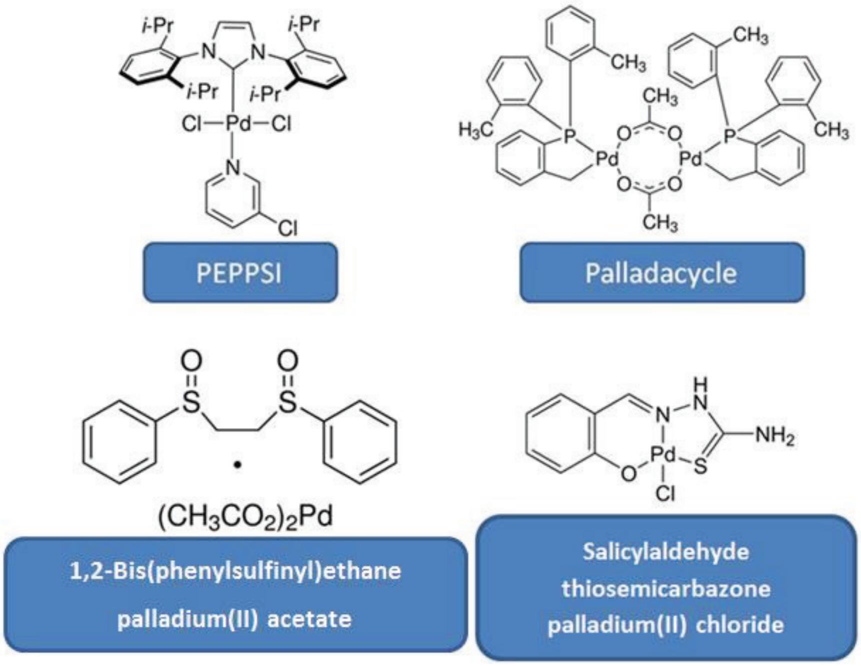
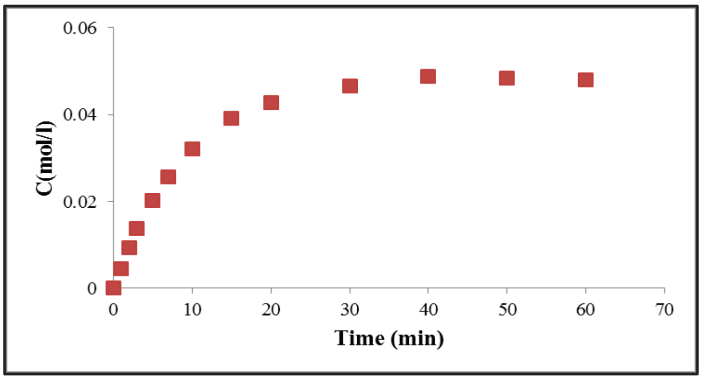
APPENDICES

A.1 List of the tested homogeneous catalysts



Appendix 1 List of the tested homogeneous catalysts

A.2 Example of reaction initial rate determination



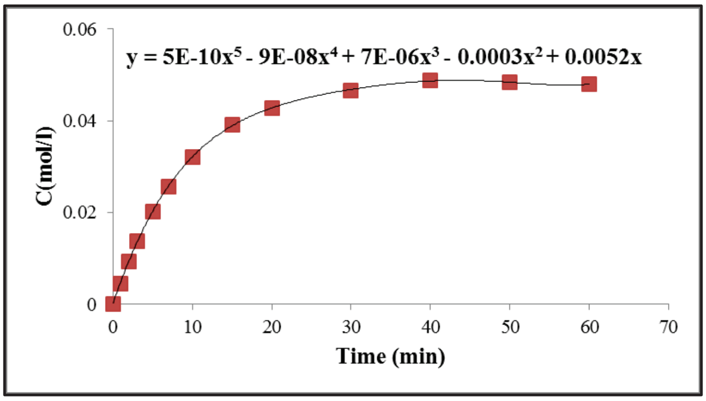
Plot [P] = f(t)

Fit the concentration profile to a five-order polynomial.

$\frac{d(C)}{dt}_{t=0}$

r_0=5.2 mmol/l/min

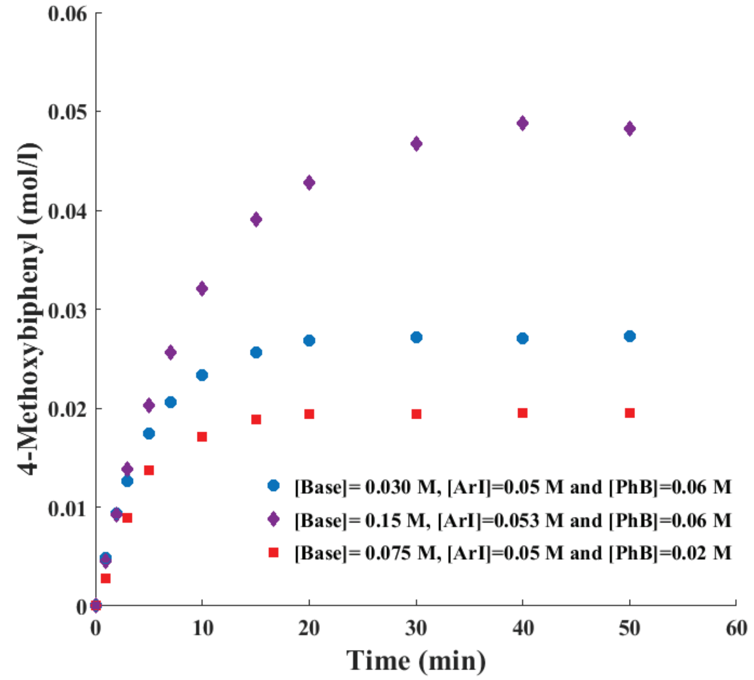
r_0=1070 mmol/min/mmol$_{Pd}$



Conditions: 4-iodoacetophenone (0.05 M, 1 eq.), phenylboronic acid (0.06 M), MeONa (0.075 M, 1.5 eq.), I (2.5 10-^{6} M), 20 ml of ethanol and 64 °C.

Appendix 2 method of initial rate determination

A.3 Stoichiometry of the reaction depending on the base concentration



Appendix 3 Stoichiometry of the reaction depending on the base concentration

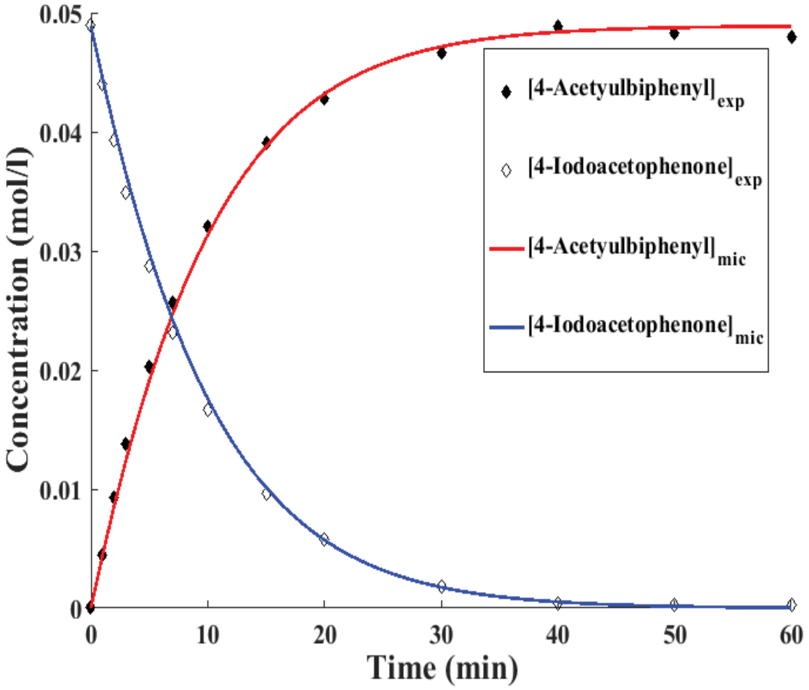
Conditions: T=60°C, ethanol volume =20 ml.

A.4 **Estimated parameters by microkinetic approach**

Appendix 4 Estimated parameters for microkinetic model

Kinetic parameters	**Estimated value**
$k_{01}(mol^{-1}l\ min^{-1})$	$(7.80 \pm 0.5) \times 10^{13}$
$k_{02}(mol^{-1}l\ min^{-1})$	$(4.72 \pm 0.9) \times 10^{13}$
$k_{03}(min^{-1})$	$(6.00 \pm 2) \times 10^{12}$
$k_{04}(min^{-1})$	$(7.12 \pm 1.1) \times 10^{12}$
$E_{\mathrm{a1}}(J\ mol^{-1})$	$(6.12 \pm 0.03) \times 10^{4}$
$E_{\mathrm{a2}}(J\ mol^{-1})$	$(5.31 \pm 0.05) \times 10^{4}$
$E_{\mathrm{a3}}(J\ mol^{-1})$	$(4.02 \pm 0.5) \times 10^{4}$
$E_{\mathrm{a4}}(J\ mol^{-1})$	$(5.85 \pm 0.05) \times 10^{4}$

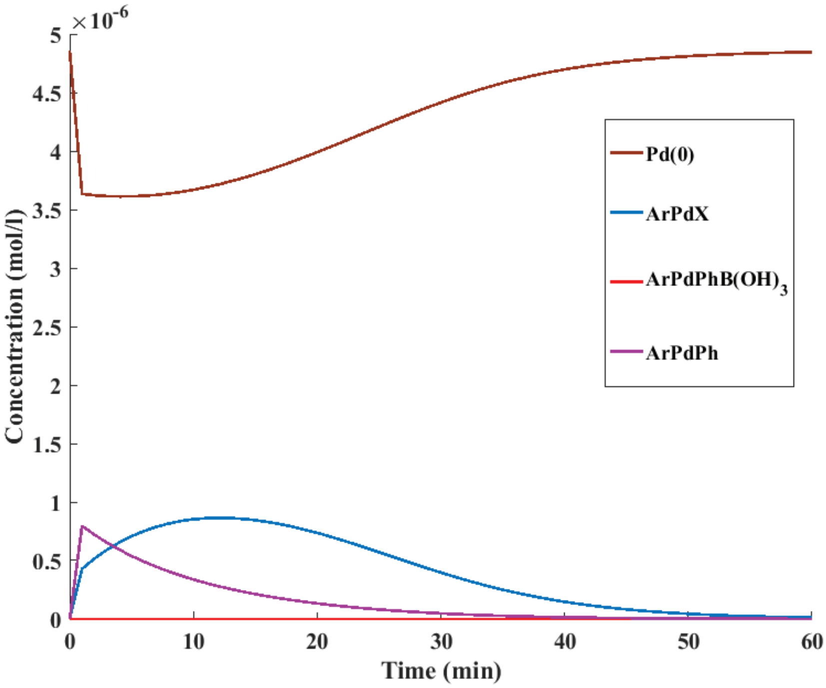
A.5 Example of accurate representation of the experiments by the estimated parameters (microkinetic approach)



Appendix 5 Model versus experimental results for one experiment

Experimental conditions: 4-iodoacetophenone (0.05 M, 1 eq.), phenylboronic acid (0.06 M), MeONa (0.075 M, 1.5 eq.), I (2.5 10-^{6} M), 20 ml of ethanol and 60 °C.

A.6 **Variation of the concentration of Pd intermediate species (microkinetic approach)**

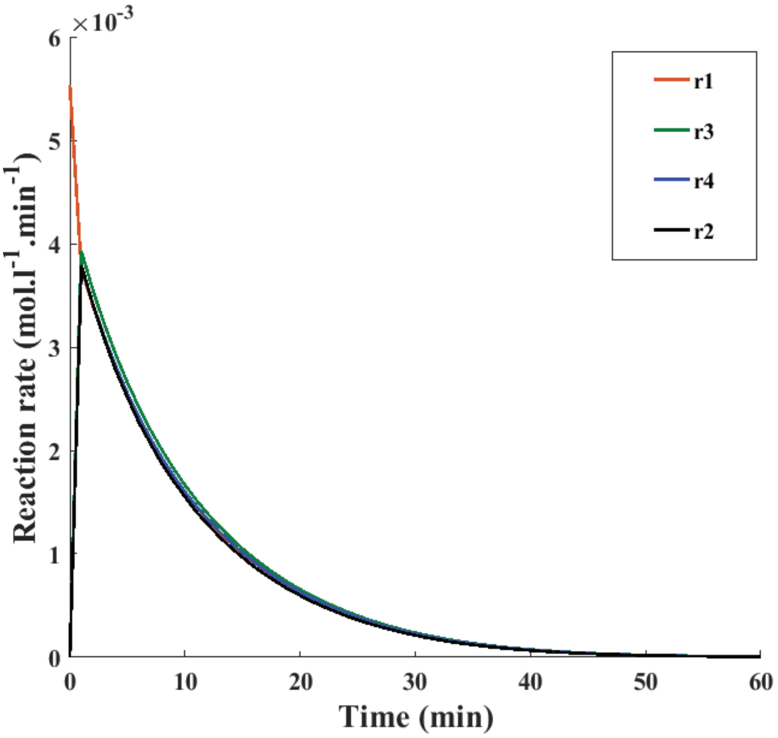


Appendix 6 Calculated intermediate species of Pd

Experimental conditions: 4-iodoacetophenone (0.05 M, 1 eq.), phenylboronic acid (0.06 M), MeONa (0.075 M, 1.5 eq.), I (2.5 $10-^{6}$ M), 20 ml of ethanol and 60 °C.

Appendix 6 shows the variation of the concentration of Pd intermediate species, the concentration of dimer palladium is initially transformed to monomer palladium. The resting state is an equilibrium between three species Pd(0), ArPdX and ArPdPh.

A.7 **Calculated elementary rates vs. time ((microkinetic approach)**



Appendix 7 Calculated elementary rates

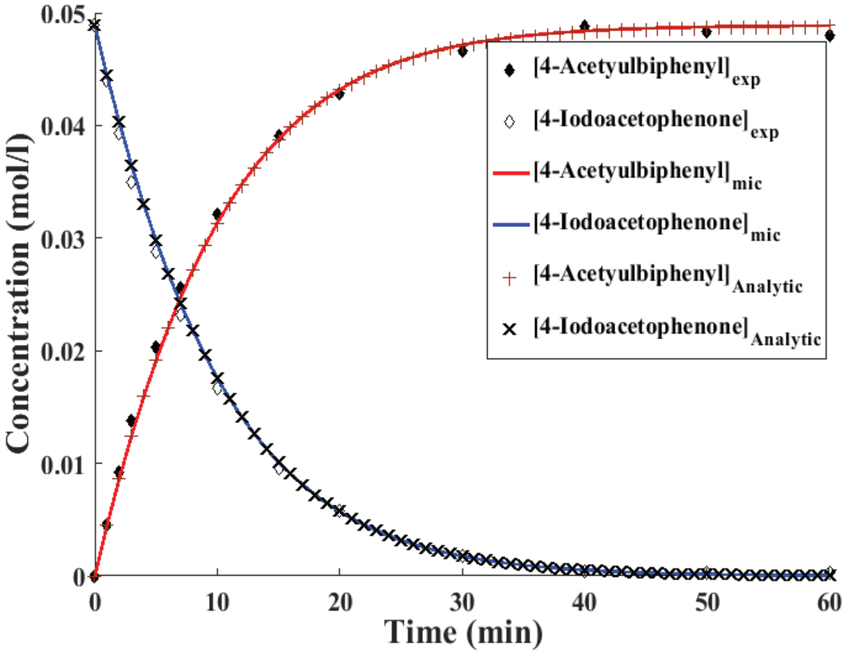
Experiment conditions: 4-iodoacetophenone (0.05 M, 1 eq.), phenylboronic acid (0.06 M), MeONa (0.075 M, 1.5 eq.), I (2.5 10-6 M), 20 ml of ethanol and 60 °C.

A.8 **Correlation Matrix for the microkinetic approach**

	k_{01}	k_{02}	k_{03}	k_{04}	Ea_1	Ea_2	Ea_3	Ea_4
k_{01}	1.00	-0.02	0.19	-0.16	-0.76	0.42	-0.50	-0.15
k_{02}	-0.02	1.00	0.36	-0.70	0.04	-0.68	0.06	-0.22
k_{03}	0.19	0.36	1.00	-0.60	-0.56	0.13	0.61	0.10
k_{04}	-0.16	-0.70	-0.60	1.00	0.18	-0.26	-0.16	0.73
Ea_1	-0.76	0.04	-0.56	0.18	1.00	-0.29	-0.10	-0.19
Ea_2	0.42	-0.68	0.13	-0.26	-0.29	1.00	-0.43	-0.26
Ea_3	-0.50	0.06	0.61	-0.16	-0.10	-0.43	1.00	-0.06
Ea_4	-0.15	-0.22	0.10	0.73	-0.19	-0.26	-0.06	1.00

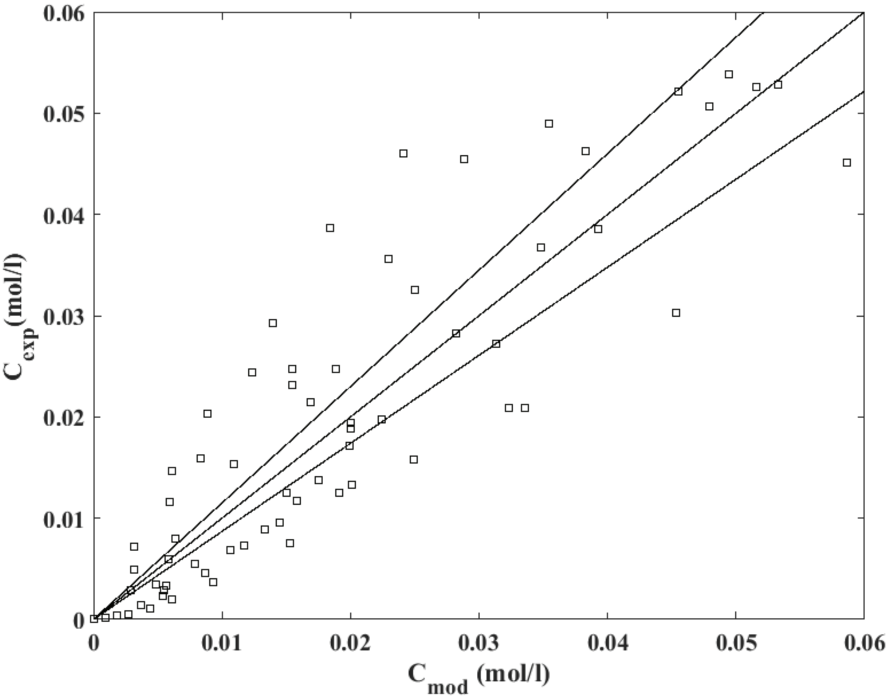
The correlation matrix shows no correlation between the estimated parameters.

A.9 Concentration profile for one experiment by using microkinetic and analytical approaches



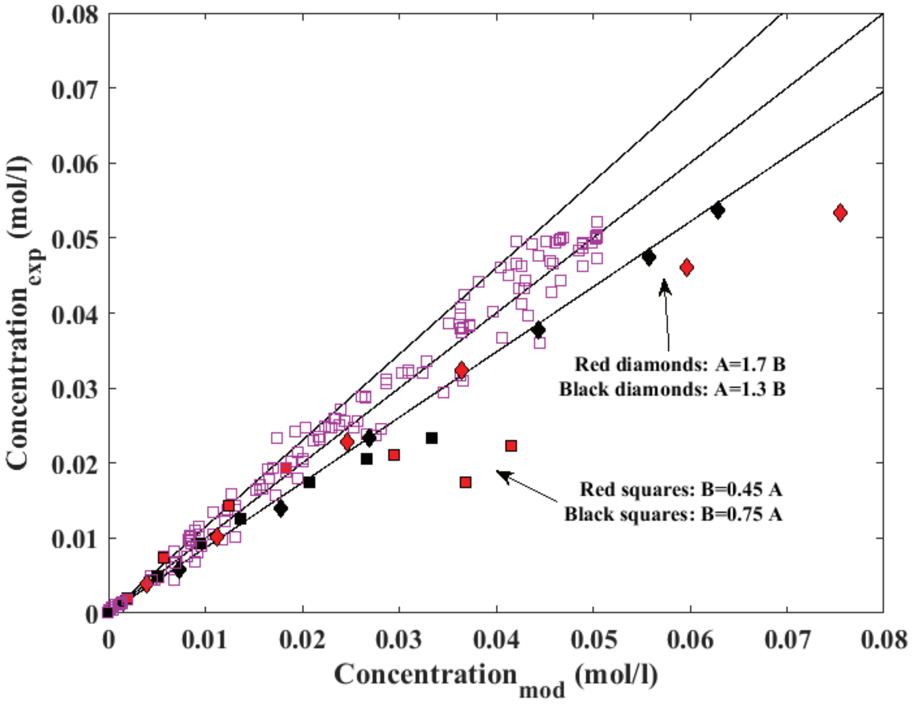
Appendix 8 model versus experimental results for one experiment by using microkinetic and analytical approaches. Conditions: see **Appendix 5**

A.10 Parity plot for non selected experiments



Appendix 9 Experimental concentration of the product vs. calculated one for the nine (9) non-selected experiments with anomalies (induction period, catalyst deactivation, bad mass balance).

A.11 Parity plot of best fit for simplified law:

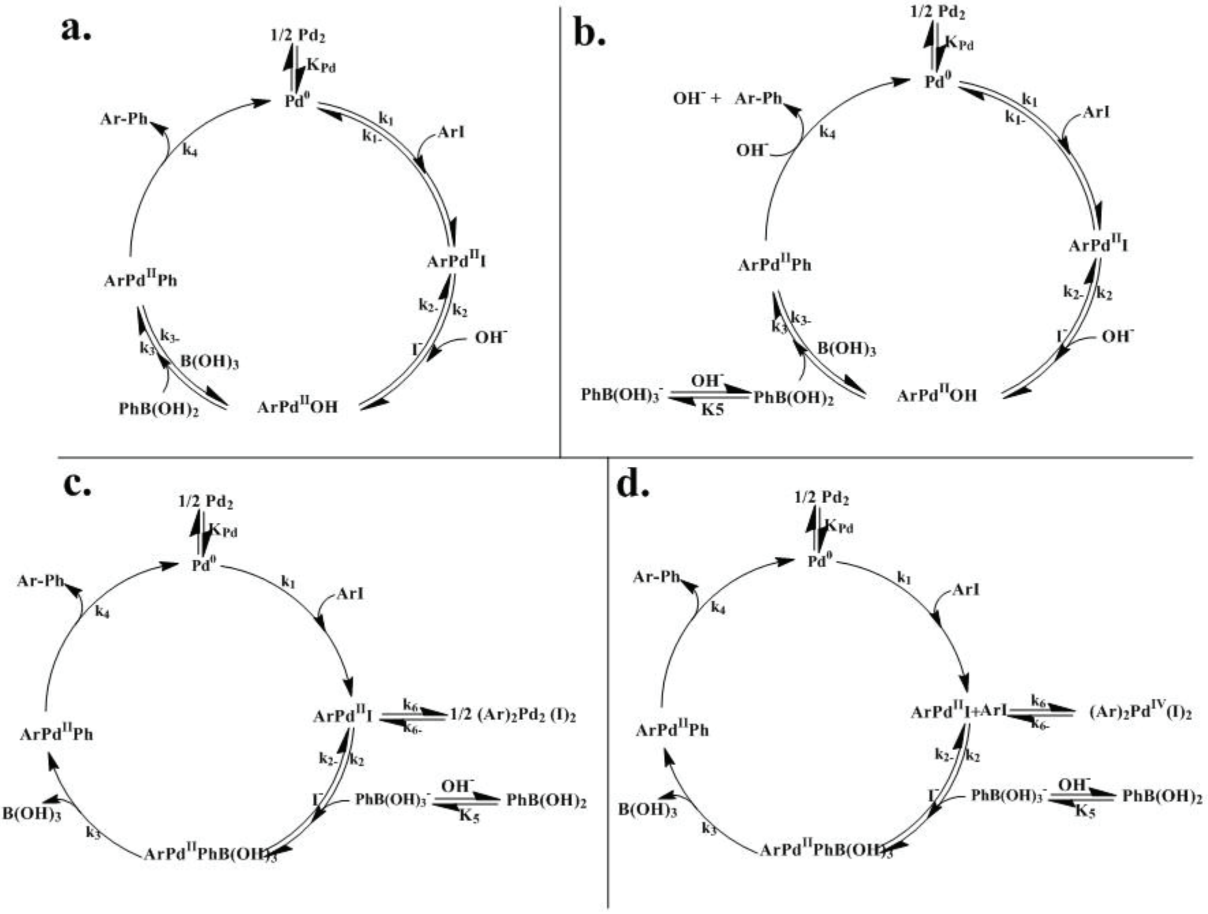


Appendix 10 Parity plot of best fit by using the simplified analytic law

As mentioned before the simplified law have a good presentation of the experimental results except those where A is higher than B.

A.12 Comments on the mechanism:

In addition to the chosen mechanism, other mechanisms have been initially tested (**Appendix 11**), without convergence to good result.



Appendix 11 Possible mechanisms for Suzuki-Miyaura reaction

Chapter 3

Innovative flow split test to discriminating between heterogeneous and homogeneous contributions in Suzuki coupling

This chapter was adapted with modification and addition from the publication:

A. Bourouina, V. Meille, and C. de Bellefon, “A flow split test to discriminating between heterogeneous and homogeneous contributions in Suzuki coupling,” *J. Flow Chem.*, vol. 8, no. 3, pp. 117–121, Dec. 2018.

Abstract:

The homogeneous vs heterogeneous contributions when using solid catalysts for the Suzuki-Miyaura coupling is still disputed. Leaching is often observed and quantified albeit with unclear conclusions about contributions of the leached species and of the solid catalyst to the global catalytic activity. In this work, a new flow reactor designed to discriminate both contributions is proposed. This last demonstrates the presence of a homogeneous contribution for the reaction of a variety of iodoaryls with Pd supported catalysts. Chloro and bromo derivatives behave differently. This reactor is simple to build and could be of general use to reveal actual heterogeneous vs homogeneous catalysis for many reactions.

Keywords: Suzuki-Miyaura · Heterogeneous · Leaching · Palladium

3.1 Introduction

The knowledge of the reaction location is of prime importance both to design efficient industrial processes and to understand the underlying fundamental mechanisms. For example, many catalytic processes are operated with heterogeneous (solid) catalysts for easier separation and downstream treatments thus to lower operating costs. However, when the fluid phase is a liquid, it appears that the knowledge of the reaction location is not straightforward. Indeed, active catalytic species may leach from the solid, which is then a simple catalyst precursor, and solubilizes in the liquid phase in which it catalyzes the reaction. Several papers including recent reviews have analyzed such situations for different type of catalytic processes[1, 2, 3, 4]. One must realize that the design of a catalytic reactor is largely based on the assumption of the reaction location simply because the reaction time, i.e. the contact time between the reagents and the catalyst, hence the reactor efficiency depends on that knowledge. Other characteristics of the reactor are also based on that assumption such as mass and heat transfer performances and mixing. Last, downstream treatments also depend on this knowledge, a simple distillation could be transformed into a catalytic reactor producing side products when catalytic species are transported. Among the very large diversity of catalytic reactions, some are well known to be heterogeneous, i.e. processes in which the reaction takes place at the solid, but other are more questionable. C-C coupling such as the Heck and Suzuki- Miyaura reactions are striking examples of this situation and have been the matter of extensive investigations since 20 years to actually demonstrate the heterogeneous (solid) vs homogeneous (liquid phase) catalysis [5, 1]. With the wider use of continuous processes (Flow Chemistry), this issue has gained more interest since soluble catalytic species will be transported out of the reactor (C-C coupling [6, 7], olefin metathesis [8, 9], hydroformylation [10]). Indeed, whereas it is clear that the Heck reaction proceeds through a homogeneous mechanism in the liquid phase (even when starting from a solid catalyst precursor), the situation is much more complex for the Suzuki-Miyaura reaction. A review depicts the different approaches and techniques used to distinguish between homogeneous and heterogeneous Suzuki catalysis [11]. Protocols such as the correlation of Pd content in solution with the reaction yield [12], the hot filtration tests [3], the Three-Phase test [13], poisoning tests [3, 14] or the “Nanoparticle-Exclusion Experiments” [15] can be used. Heavier methods have been used also such as X-ray absorption spectroscopy (XAS) to monitor the structure of Pd NPs during the Suzuki reaction [16], and Pd NP coated AFM tip

[17]. Detailed discussions of the advantages and drawbacks of these methods have been published and the general conclusion emphasized that there is no single definitive experiment for making this distinction [4, 17]. While everybody will agree with this general statement and would use a combination of methods before arriving at a compelling conclusion, it prompted us to reinvestigate ligand-free Pd SM coupling catalytic species with a new reactor design able to discriminate between homogeneous and heterogeneous catalysis. This new design is based on a continuous operation and avoids all the difficulties linked to the hot-filtration and the ambiguous exploitation of poisoning tests. At this point, we would like to mention that this method has been recently proposed by Barreiro et al. with the name "Tandem flow reactor". It was used for the Heck coupling [19] which is already known to proceed by homogeneous catalysis. As mentioned, this new method is based on the time-length analogy between closed (batch) reactors and open (continuous) reactors [19, 20] and simply adapts the well-practiced "Batch Split Test" (generally called "hot-filtration test" to a "Flow Split Test" (Figure 18). Doing so, this new method avoids the main drawback of the split test by ensuring a non-disruptive process between the heterogeneous liquid-solid reactor and the homogeneous "split" test.

Zotto et al [1] have classified the solid catalyst employed in Pd C-C coupling reaction in 10 categories; (1) metallic Pd, (2) Pd oxide, (3) Pd deposed on transition metals or rare earth, (4) Pd deposed on S- or P-block metal oxide, (5) Pd/C, (6) Pd(II) complexes anchored on inorganic materials, (7) Pd(II) complexes grafted on organic polymers, (8) Pd-containing hybrid materials (MOFs), (9) gold/Pd core/shell Nps and (10) Pd alloys. In this work we will use heterogeneous precursors of type (1), (3), (4), (5) and (6) with different aryl halides in order to check the homogeneous vs. heterogeneous activities with a large diversity of solid precursors containing Pd.

3.2 Experimental section

3.2.1 Chemicals and analysis

Experiments were carried out at 60 °C in anhydrous ethanol (CARLO ERBA). The reagents were 4-iodoacetophenone (Acros Organics), 3-iodoacetophenone (Aldrich), 4-iodoanisole (Acros Organics), 4-bromoacetophenone (Aldrich), 4-chloroacetophenone (Sigma Aldrich), phenylboronic acid (Acros Organics), and sodium methylate (Acros Organics). Different commercial catalytic precursors known for their heterogeneous activity were bought; Siliacat

Pd(0) (SILICYCLE R815-100), Siliacat Pd(II)-DPP (SILICYCLE R390-100), Strem Pd(0) /Silica (STREM CHEMICALS 46-2090), Pd(0) /Alumina (5 % of Pd, Strem), Pd/C (5 % of Pd, Strem), $Ce_{0.2}Sn_{0.79}Pd_{0.01}O_{2-\delta}$(synthetized by Heidrun Gruber-Woelfler [22]) and Pd@ALG-XG (synthetized by N. Tanchoux team, MACS, ICGM) were used without purification or treatments. Reactants were stored in closed reservoirs and used under ambient atmosphere except special mention. The catalysts samples were withdrawn and quenched in a mixture of deionized water (2 ml) and dichloromethane (VWR) or ethyl acetate (Sigma Aldrich) (1 ml). The heavier organic phase was collected then, dried over MgSO4, filtered through a cotton wool section and analyzed using GC-FID chromatography (Agilent Technologies 6890N, column OPTIMA 5 (10m x 100µm x 0.1µm), Split 1/250 volume injected 1µL (300 ° C), H_2 flowrate: 0.4 mL / min, Oven program: 150 ° C (30s) then 50 ° C/min up to 340 ° C (42s), FID Detector). N-tetradecane (Acros Organics) or naphtalene (Acros Organics) were used as an internal standard. Stainless steel tubes (SWAGELOK SS-T4-S-035-6ME) and PFA tubes (SWAGELOK PFA-T2-030-100) were used for the catalytic column and tubular reactor respectively. Calibration curves are made for the main reagents and products (ArI, $PhB(OH)_2$, Ar-Ph, Ph-Ph, Ar-Ar, ArH) ensuring quantitative mass balance.

3.2.2 Packed bed preparation

The catalytic columns were prepared using stainless steel tubes (4.6 mm i.d.) of different lengths (5-20 cm depending on the catalyst amount). The solids were packed inside the tubes manually in a similar fashion than HPLC columns. Both ends of the column were fitted with appropriate Swagelok fittings, including filters (RESTEK). The empty tube section was made from PFA tube (1.7 mm i.d., 1m length). Note here that each column could be used for several experiments, i.e. several flow rates. The void volume of the packed beds may depend on the nature and the shape of the different solid used. A residence time distribution analysis has been performed with a typical solid (SiO_2, 20-100 µm) showing a void volume equal to 0.5. The indication of the total work achieved by the solid catalyst precursor is featured as the TON.

$$TON = \frac{quantity\ of\ converted\ aryl\ halide}{total\ quantity\ of\ Pd\ inside\ the\ column\ (or\ leached\ Pd)}$$

$$TOF = \frac{quantity\ of\ converted\ aryl\ halide}{total\ quantity\ of\ Pd\ inside\ the\ column\ (or\ leached\ Pd) \times residence\ time}$$

3.2.3 Batch catalytic test with solid catalyst

Initially, 4-iodoacetophenone (0.264 g, 1 mmol), phenyl boronic acid (0.145 g, 1.2 mmol), sodium methylate (0.08 g, 1.5 mmol), n-tetradecane (0.3 mass equivalent) as a GC internal standard and anhydrous ethanol (20 ml) were added to a three-neck round-bottom flask equipped with a stirring bar. The dissolution was improved by using an ultrasonic bath at room temperature (Elmasonic S30H) for 30 min, after that the flask was preheated at 60 °C inside an oil bath under agitation for 30 min, when this temperature was reached, a blank sample of 0.5 ml was syringed, then 0.01 g of Pd(0) Siliacat (0.8 μmol of Pd) was added. The samples were withdrawn at different times for 1 hour and filtered through a syringe filter (0.25 μm) then quenched in a mixture of deionized water (2 ml) and ethyl acetate (ref) (1 ml). The organic phase was collected then, dried over $MgSO_4$, filtered through a cotton wool section and analyzed using GC-FID.

3.2.4 Continuous Catalytic Tests

A typical reagent solution was prepared by dissolution of 4-iodoacetophenone (2.46 g, 0.01 mole, 1eq), phenylboronic acid (1.45 g, 0.012 mole, 1.2 eq.), MeONa (0.81 g, 0.015 mole, 1.5 eq.) and n-tetradecane (0.5 g, 0.003 mole, 0.3 eq.) in ethanol (400 ml). An ultrasonic bath was used to help dissolution (ultrasound for 30 min at room temperature). The solution was pumped (Shimadzu LC-20AP) through the preheated (60 °C ± 2 °C) catalytic column and passed through the empty tube (Figure 18). Generally, valve 2 is closed and valve 1 is open, allowing sampling at the outlet of the set-up. For sampling at the column outlet, valve 2 is open and valve 1 is closed, allowing all the liquid flow to be collected. Sampling for GC analysis was performed after washing the sampling tube and valve for 2 min. The residence time was controlled by the liquid flow rate. Sampling was performed at steady state conversion. Steady state is reached since the time elapsed between starting the experiment and sampling is long compared to the total residence time.

3.2.5 Measurement of Pd leaching

Many samples (20 ml) of the cumulated liquid were collected at the tube outlet for experiments 1-5 ($P_{dleaching}$ for Siliacat Pd(0), Table 8), 6-9 ($P_{dleaching}$ for Strem Pd(0), Table 8) and 10-11 ($P_{dleaching}$ for Siliacat -Pd(II), Table 8) and analyzed by ICP-MS.

Pd analysis was performed outside our laboratory by ICP-MS (Mikroanalytisches Labor Pascher, Germany). The general method is to prepare the solution samples and send them to

Pascher Labor, in this method samples take few days to arrive and the sample solution is handled in unknown conditions, which can result in Pd deposition in the vial walls. In order to check this, 50 ml of a solution (**A**) were collected at the tube outlet, and then it was divided to 3 samples:

1. 12 ml of the solution **A** were mixed with 0.12 g of a Pd scavenger (QS-TA, QuadraSil), agitated at room temperature (rt.) for 10 h to catch all the Pd inside solution, then evaporated and dried at 100 °C.
2. 26 ml the solution **A** were mixed with 0.1 ml of HCl solution (35%) inside a PFA vial.
3. 12 ml of the solution **A** were stored in glass vial without any operation.

Then, the samples 1, 2 and 3 were sent to Mikroanalytisches Labor. Table 7 shows the ICP-MS analysis for the 3 samples, the Pd concentration is almost the same whatever the method of sample preparation, which indicates that we can directly send our samples in glass vials without further treatments.

Table 7 ICP-MS analysis for different samples

Sample	1 (with scavenger)	2 (with HCl)	3 (nothing)
Pd concentration (ppm)	0.06	0.07	0.07

Conditions: Q_L=1 ml/min, 4-iodoacetophenone 25 mM, $PhB(OH)_2$ 30 mM, and MeONa 37.8 mM. Column of Pd(0) Siliacat : m_{Pd}= 19.3 mg.

3.3 The principle of split flow reactor

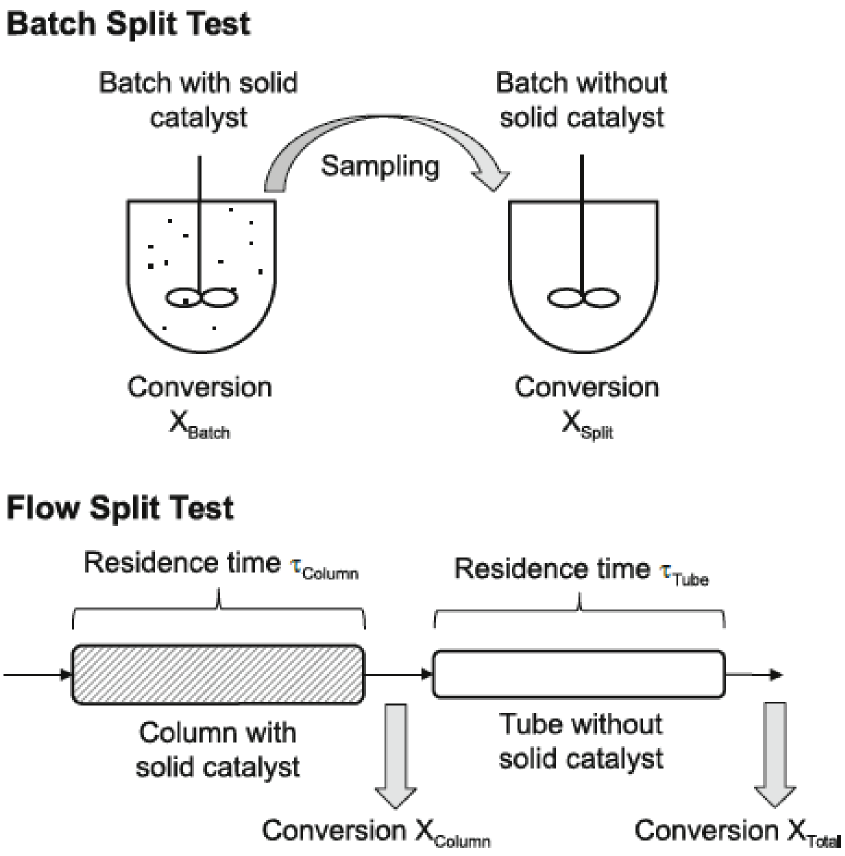


Figure 18 Principle of split tests

In the batch split test, at a given reaction time t, the reaction mixture is sampled (filtered) with caution to minimize or, better, avoid any solid catalyst in the sample. Then the sample is maintained under the same operating conditions than the original reaction mixture. The conversions (yields) are then measured in both reactors and compared. Three types of behavior could be observed:

- The conversion in the split reactor is unchanged compared to that at the time of sampling. In such case it is concluded that the reaction is occurring at the solid. The catalysis is probably heterogeneous.

- The conversion in the split reactor is increasing at comparable rate than the original batch reactor. In that case, it is concluded that the catalysis occurred in the liquid phase, albeit with no conclusion about the exact nature of the catalyst which could be nanoparticles or molecular species or both.

- Any in-between situation for which it is difficult to assess the location of the catalytic reaction.

In the flow split test, the liquid mixture is pumped in a first reactor containing the putative solid catalyst for a given contact time then, it is circulated in an empty tube. While the three types of behavior could be observed very much like for the batch split test, this set-up presents many interesting features to help distinguishing between solid or liquid phase catalysis that cannot be achieved in the Batch mode. Some of these features are detailed below:

- The “split” between the solid containing reactor and the empty section is performed with no risk of exposition of the reaction mixture to air, moisture, etc. and without temperature variations that could impact the reaction.
- The amount of solid (putative) catalyst in the reactor is very high so that even in the situation where a small amount of solid would be entrained, the amount of conversion due to that solid in the empty tube section would be negligible.
- The flow split test is most often operated in the steady-state regime thus revealing unambiguously any unsteady-state processes such as catalyst deactivation that could lead to false conclusions in the batch mode.
- The reaction time in the solid containing section and that in the empty tube section can be varied independently, precisely and easily by changing the liquid flow rate and/or the length of the tube/column.
- Simple reactor modelling could provide the potential activity of the solid and that of liquid phase species. Thus the flow split test is a promising concept that has a very broad scope for application and which, when coupled to simple reactor modelling, has the potential to build in depth and unambiguous conclusions concerning the homogeneous vs heterogeneous nature of catalysis.

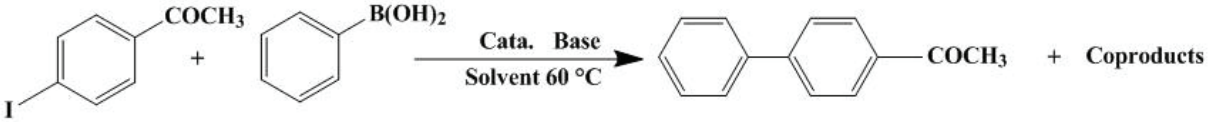
3.4 Reactor dimensioning

The reactor is composed of two parts, a catalytic column and an empty tube, the volume of the tube can be easily varied, but the choice of the packed bed (column) volume is very important to get good results, because the conversion at the column outlet should be lower than 100 % to allow the reaction to continue inside the empty tube.

The volume of the column was designed based on an experimental batch test, followed by a quick preliminary test with different flow rates to choose the best experimental conditions.

3.5 Demonstrate the efficiency of the flow split test concept

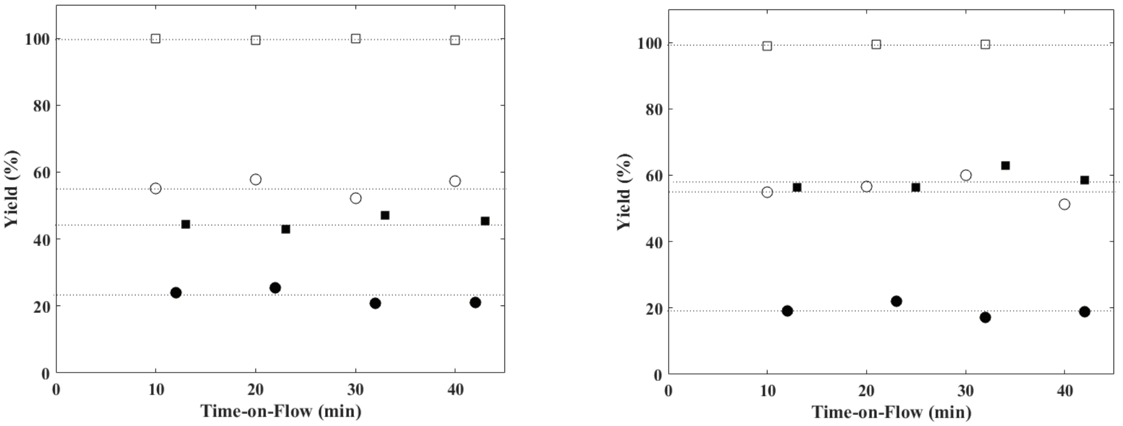
In order to demonstrate the efficiency of the flow split test concept, the Suzuki-Miyaura (SM) reaction of 4-iodoacetophenone with phenylboronic acid in ethanol in the presence of Pd containing solids and sodium methylate was selected as the target reaction (**Scheme 4**).



Scheme 4 Suzuki-Miyaura reaction

Initially, four heterogeneous palladium (Pd) solids precursors were used, Pd Nps encaged inside silica matrix (Pd(0) Siliacat), crystals of Pd supported on silica (Pd(0) Strem), a Pd(II complex supported on silica (Pd(II) Siliacat), and a Pd(0) supported on alumina (Pd(0)/ Alumina). All the tests were made using two different flow rates (Figure 19). Note that the absence of any possible deposition of active Pd inside the empty tube was verified, by flowing reagents directly through the preheated tube at the end of each test with a catalyst. The empty symbols show the conversion measured at the end of the empty tube, representing the total conversion reached in both successive zones (filled column + empty tube).

The conversion increase during residence in the empty tube is thus due to palladium that has leached from the column with a homogeneous mechanism. Furthermore a longer test (6 h) was carried out with two different catalysts (Figure 20) to inform about the stability of the conversion. If Pd leaching was due to badly anchored Pd species on the solid surface, a rapid decrease of the activity would have been expected, which is not the case.

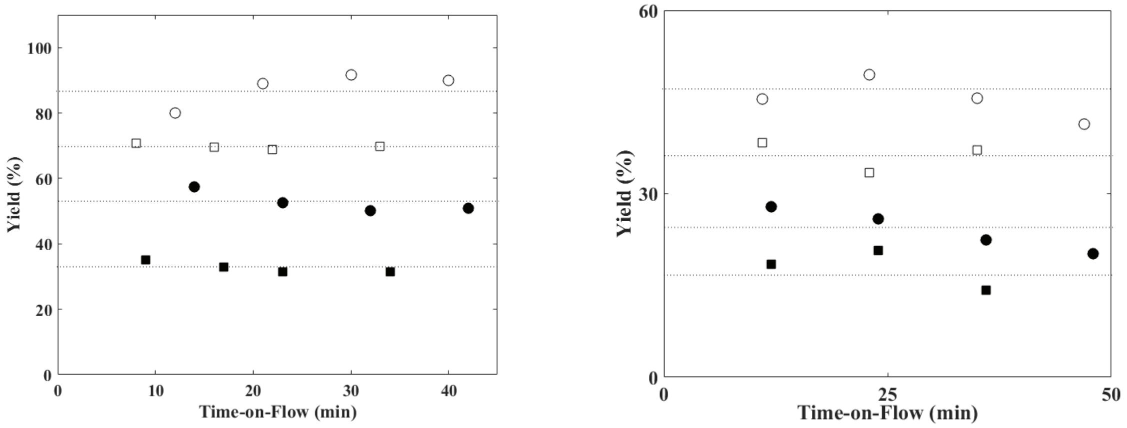


Pd(0) Siliacat

Circles: Q_1= 0.6 ml/min, squares: Q_2= 0.2 ml/min

Pd (0) Strem

Circles: Q_1= 0.6 ml/min, squares: Q_2= 0.2 ml/min



Pd(II) Siliacat

Circles: Q_1= 0.4 ml/min, squares: Q_2= 1 ml/min

Pd/Alumina

Circles: Q_1= 2 ml/min, squares: Q_2= 3 ml/min

Figure 19 Conversion of 4-iodoacetophenone at the outlet of the column (filled symbols) and at the outlet of the tube (empty symbols).

Conditions: The dotted lines represent the mean value for each series. 0.025 M of 4-iodoacetophenone, MeONa (1.5 eq, 0.038 M), phenylboronic acid (1.2 eq, 0.03 M). Pd(0) Siliacat m_{Pd}= 8.73 mg, Pd(0) Strem m_{Pd}= 17.20 mg, Pd(II) Siliacat m_{Pd}= 0.60 mg,), Pd(0)/Alumina m_{Pd}= 31.2 mg.

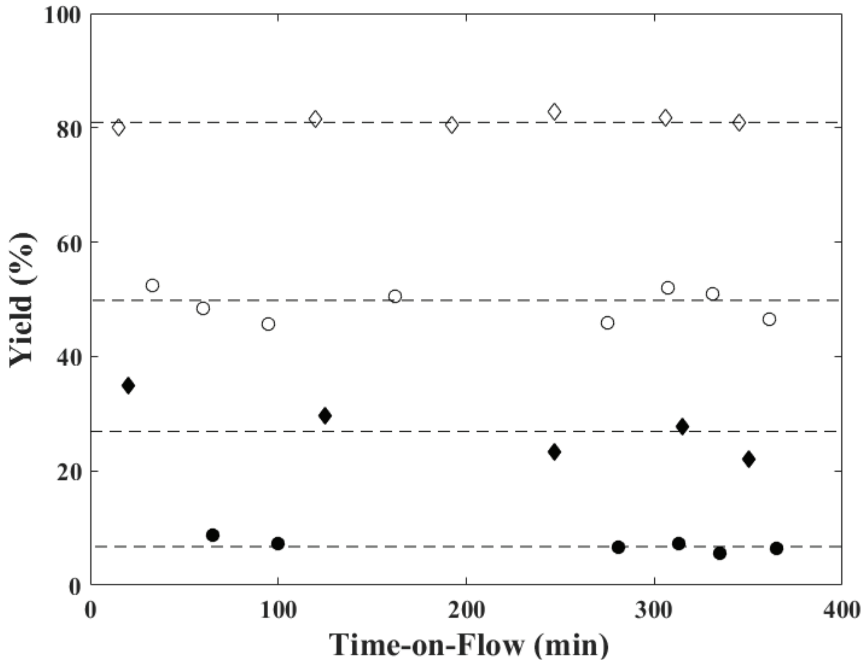


Figure 20 Conversion of 4-iodoacetophenone at the column outlet (filled symbols) and at the tube outlet (empty symbols) for 2 catalysts.

Conditions: The dotted lines represent the average value for each series. 1.8 mg Pd for Siliacat Pd(0) (Circles), and 15 mg Pd for Strem Pd(0) (Diamonds); Temperature of 60 °C and liquid flow rate of 0.3 mL/min for both catalysts in both sections.

Other experiments with 4-iodoacetophenone are presented in Table 8 for five heterogeneous precursors. The table presents the conversion and yield after the column section and at the end of the tube section (see Figure 1), and the corresponding residence times and conditions. The rows present different tests performed at various flow rates with a variety of catalysts. All results show a conversion increase in the tube section, which can be explained by palladium leaching with a homogeneous mechanism. ICP/MS analysis of the reaction products (last column of Table 8), performed in a mixture of collected products at different flow rates, indeed, showed a mean Pd concentration of 100 ppb for both Pd(0) catalysts supported on silica (entries 1-9, Table 8) and 500 ppb in the case of the immobilized complex (Pd(II) Siliacat) (entries 10-11, Table 8). The palladium supported on alginate (entry 12, Table 8) showed a leaching of 110 ppb while the $Ce_{0.2}Sn_{0.79}Pd_{0.01}O_{2-\delta}$ showed only 70 ppb (entry 13, Table 8).

Table 8 Flow split tests in the SMR of 4-iodoacetophenone using different catalysts with Pd leaching concentration

Entry	Catalyst	m_{Pd} (mg)	Q (ml/min)	$t_{on\text{-}flow}$ (min)	$Conv_{col}$ (Yield)	$Conv_{tub}$ (Yield)	τ_{Column} (min)	τ_{tube} (min)	Pd leach. (ppm)	TON_{Column}	TON_{tube}	TOF_{Column} (h^{-1})	TOF_{tube} (h^{-1})
1	Pd(0)/SiO$_2$ Siliacat	8.7	0.2	43	50(50)	100(100)	2.1	10.7	0.12^a	11000	11000	315500^c	62000^c
2			0.4	46	21(21)	58(58)	1.1	5.4		4600	8200	253000^c	90800^c
3			0.6	42	10(10)	43(43)	0.7	3.6		2200	7300	189300^c	121500^c
4			1	34	5(5)	23(23)	0.4	2.2		1100	4000	165600^c	108400^c
5			1.4	30	3(3)	13(13)	0.3	1.5		700	2200	132500^c	88300^c
6	Strem Pd(0)/SiO$_2$	15	0.2	49	58(58)	100(100)	2.1	10.7	0.1^a	15400	11100	439100^c	62400^c
7			0.6	40	24(24)	56(56)	0.7	3.6		6400	8500	545100^c	141300^c
8			1	30	12(12)	46(46)	0.4	2.2		3200	9000	477000^c	245700^c
9			1.4	25	15(15)	38(38)	0.3	1.5		4000	6100	795000^c	243800^c
10	Siliacat Pd(II)-DPP/SiO$_2$	0.6	0.4	25	56(54)^d	95(88)	0.05	5.4	0.53^a	2700	2050	3240000^c	22800^c
11			1	30	37(32)^d	75(70)	0.02	2.14		1600	2200	4800000^c	60300^c
12	Pd@ALG-XG	58.7	1.5	96	4(4)	63(63)	0.4	15.7*	0.11^b	1000	14200	144600	54300
13	$Ce_{0.2}Sn_{0.79}Pd_{0.01}O_{2-\delta}$	9.83	1	160	9(9)	69(69)	0.8	23.6*	0.07^b	3400	22700	255500	57800
14	Pd(0)/Alumina	31.2	2	48	24(24)	87(87)	0.4	11.8*	NA	NA	NA	NA	NA

Conditions: 4-iodoacetophenone 25 mM, PhB(OH)$_2$ 30 mM, MeONa 37.5 mM, T= 60 °C. Tube volume= 2.14 ml.

*: tube volume: 23.55 ml. ^{a}: Leached Pd was measured for an accumulated solution using different flow rates. ^{b}: Leached Pd for one flow rate. ^{c}: Calculated using the mean value of leached Pd. ^{d}: Homocoupling biphenyl side product TON and TOF value are rounded with 2 significant digits for the sake of clarity.

ND: not analyzed.

Turnover frequencies (TOF_{liq}) were determined with the concentration of the leached Pd in solution. For the Pd(0) supported catalysts (entries 1-5,6-9 and 12-13, Table 8) the activity inside the column was between 133,000 and 800,000 h^{-1}. Where it was between 55,000 and 250,000 h^{-1} inside the tube. While the Pd(II) supported complexes showed an activity of 4 million h^{-1} inside the column and only several hundred thousand h^{-1} inside the tube (entries 10-11, Table 8). Mean activities inside the column are always higher than those inside the empty tube. This would be too rapidly explained by the presence of catalytic species of different natures. Indeed, the TOFs in Table 8 are determined by using the average conversion, thus representing mean activities whose value depends on the reached conversion (see Figure 21).

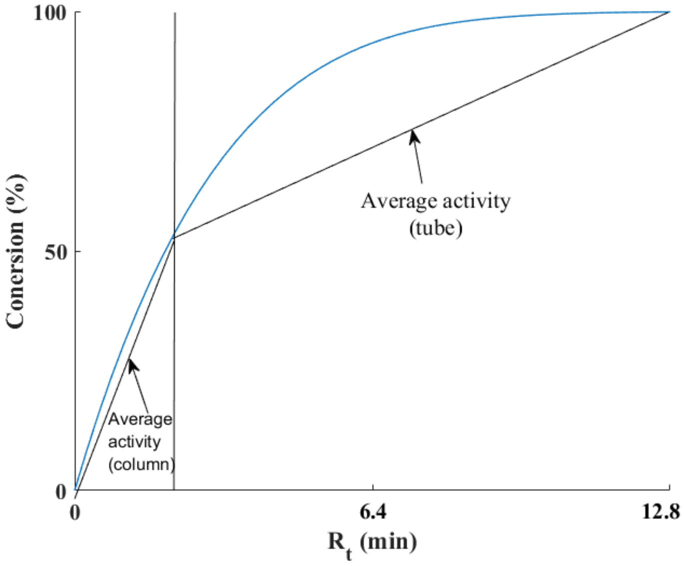


Figure 21 Average activity inside column and tube with conversion

3.6 Leaching vs. flowrate

In order to find the relationship between the leaching and the contact time of reagents with the catalyst, a test was performed at different flow rates, using the reaction of 4-iodoacetophenone with phenylboronic acid through a column packed by Pd(0) Siliacat. Figure 22 represents the variation of leached Pd concentration at the column outlet as a function of liquid flow rate (a); it increases linearly by increasing the residence time generating an increase of SMR product yield. The nonlinear behavior observed in Figure 22,b is well in line with previous reports made in batch reactors [22, 11]. Advanced modeling would explain quantitatively such behavior (see next chapter).

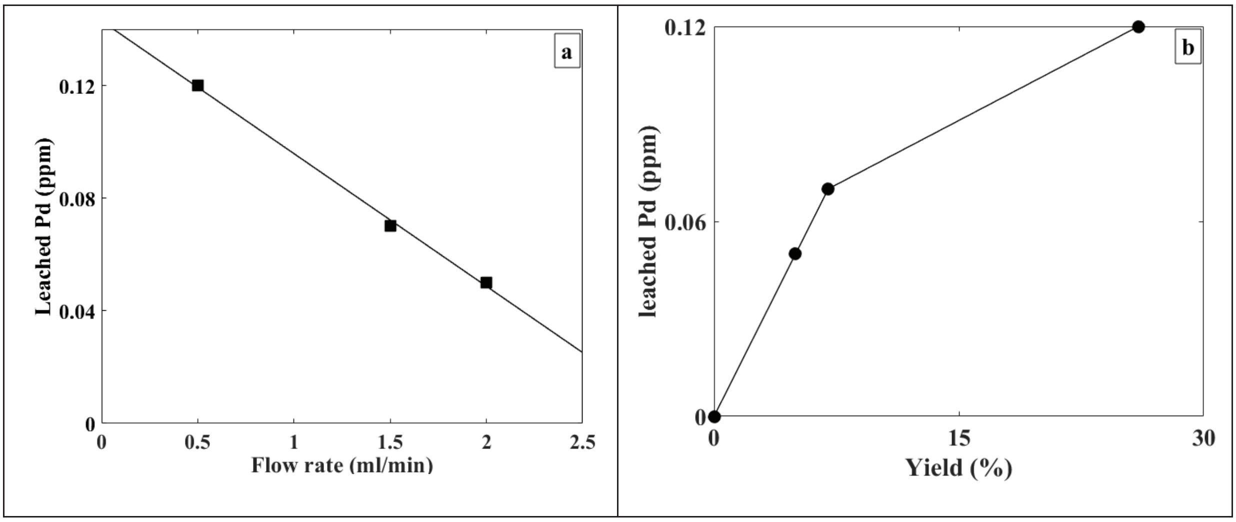


Figure 22 Pd leaching vs. flow rate (a) and Pd leaching vs. yield (b).

Conditions: 4-iodoacetophenone 25 mM, $PhB(OH)_2$ 30 mM, MeONa 37.5 mM, T= 60 °C. Pd(0) Siliacat: m_{Pd}= 19.3 mg. Tube volume= 2.14 ml.

3.7 Reagent responsible for leaching

In order to check whose reagents are responsible for leaching, it was decided to let the solid precursor in contact with each reagent separately. Hence the set-up was modified as shown in Figure 23. Considering the diversity of solvents (5) and the number of reagents (3), the number of possible combinations is 30 tests. However, our goal in this study is to only check the effect of each reagent separately.

3.7.1 Experimental section

For this test, a catalytic column was prepared using stainless steel tubes (4.6 mm i.d., 10 cm length) and filled with 0.624 g of Pd(0)/Alumina (5% of Pd 31.2 mg). Both ends of the column were fitted with appropriate Swagelok fittings, including filters (RESTEK). The empty tube section was made from PFA tube (1.7 mm i.d., 11 m length). The same flow rate was used in both HPLC pumps (Q_1=Q_2=0.5 ml/min) (Figure 23). Different experiments, described below, were designed to discriminate the role of each chemical compound in the leaching mechanism.

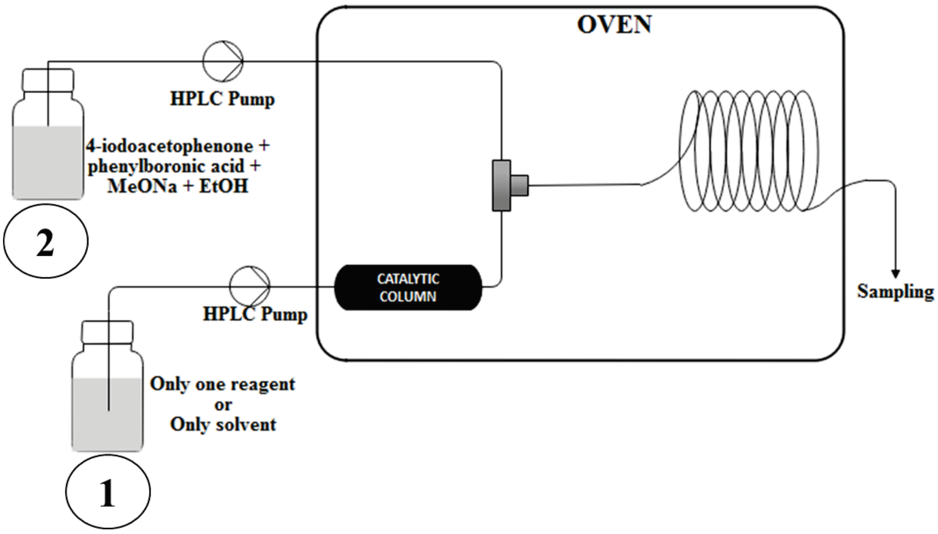


Figure 23 Experimental set-up to identify the reactant responsible for leaching

Role of the solvent: 40 ml of five (5) solvents were prepared (EtOH, water, THF, 1,4-dioxane, and acetonitrile), and a mixture of 4-iodoacetophenone (1.538 g, 6.25 mmol, 1 eq.), phenylboronic acid (0.908 g, 7.5 mmol, 1.2 eq.), sodium methylate (0.506 g, 9.38 mmol, 1.5 eq.) and naphthalene as a GC-FID internal standard (0.264 g, 2.06 mmol, 0.33 eq.) in ethanol (250 ml). Solvents were injected one by one using the HPLC pump (1) and the reagent solution was introduced using the HPLC pump (2), the conversion was followed at the outlet of the empty tube at different times (30, 40, 50 and 60 min).

Role of iodoacetophenone: A solution of 4-iodoacetophenone (0.246 g, 1 mmol) and naphthalene (0.042 g, 0.33 mmol) as GC internal standard, in 40 ml of ethanol was pumped by the HPLC pump (1). Another solution of phenylboronic acid (0.145 g, 1.2 mmol) and MeONa (0.081, 1.5 mmol) in 40 ml of ethanol was pumped by the HPLC pump (2). Then the conversion was followed at the outlet of the tube at different times (30, 40, 50 and 60 min).

Role of phenylboronic acid: A solution of phenylboronic acid (0.145 g, 1.2 mmol) in 40 ml of ethanol was pumped by the HPLC pump (1). Another solution of 4-iodoacetophenone (0.246 g, 1 mmol), MeONa (0.081, 1.5 mmol) and naphthalene (0.042 g, 0.33 mmol) as GC internal standard, in 40 ml of ethanol was pumped by the HPLC pump (2). Then the conversion was followed at the outlet of the tube at different times (30, 40, 50 and 60 min).

Role of sodium methylate: A solution of MeONa (0.081, 1.5 mmol) in 40 ml of ethanol was pumped by the HPLC pump (1). Another solution of 4-iodoacetophenone (0.246 g, 1 mmol), phenylboronic acid (0.145 g, 1.2 mmol) and naphthalene (0.042 g, 0.33 mmol) as GC internal standard, in 40 ml of ethanol was pumped by the HPLC pump (2). Then the conversion was followed at the outlet of the tube at different times (30, 40, 50 and 60 min).

Table 9 Reagent responsible for leaching using Pd(0)/ Alumina

Entry	1	2	Catalyst	Yield (%)*
1	EtOH	Solution of Reagents (a)	Pd(0) /Alumina	0
2	Water			0
3	Tetrahydrofuran			0
4	1,4-Dioxane			0
5	Acetonitrile			0
6	4-Iodoacetophenone	Solution of Reagents (b)		32.7
7	$PhB(OH)_2$	Solution of Reagents (c)		2
8	MeONa	Solution of Reagents (d)		0

Conditions : Q_1=Q_2= 0.5 ml/min. (a) : 0.025 M of 4-iodoacetophenone, 0.03 M of phenylboronic acid, 0.038 M of MeONa, 250 ml of absolute ethanol. (b): 0.03 M of phenylboronic acid, 0.038 M of MeONa in 40 ml of of absolute ethanol. (c): 0.025 M of 4-iodoacetophenone, 0.038 M of MeONa, 40 ml of absolute ethanol. (d): 0.025 M of 4-iodoacetophenone, 0.03 M of phenylboronic acid, 40 ml of absolute ethanol. T=60°C. Pd(0)/alumina : m_{Pd}=31.2mgV_{tube}=23.6ml. * conversion= yield here.

3.7.2 Results and discussions

The results obtained in Table 9 from the test presented in Figure 23 in order to identify the reagent or reagents responsible for Pd leaching; the columns represent the mixtures of solutions used and the product yield, and lines represents the reagents used. First of all, a series of solvents; ethanol, water, THF, 1,4-dioxane and acetonitrile were respectively pumped through the Pd(0)/ alumina column, in the same time a mixture of SMR reagents (4-iodoacetophenone, $PhB(OH)_2$ and sodium methylate in ethanol) was introduced after the catalytic column (Figure 23). Active Pd leaching was then indirectly identified by following the yield of 4-methoxybiphenyl coupling product at the outlet of the empty tube. After that, SMR reagents were pumped one by one respecting the same protocol described above.

At the end of these tests, the conversion of reactants when the solvent was injected alone through the column was always equal to zero with a variety of solvents, which means that the solvent is not responsible for the generation of homogeneous active Pd. On the other hand, when the base and the phenylboronic acid were injected in the column the SMR yield was equal to zero and 2 %, respectively, indicating the absence of active species for the base with a small amount of leaching for phenylboronic acid. As expected, a significant yield (33 %) was found when the 4-iodoacetophenone was injected through the column indicating an important leaching of active Pd species, which corresponds to the leaching mechanism proposed for SM reaction in the bibliography were the iodo-aryls react with the surface of the catalyst to generate soluble Pd(II) complexes [23, 3, 24]. However, our set-up allows for more quantitative analysis of the leaching process. Indeed, only 33% conversion is observed when the only leaching reagent is ArI. It was more (63%) when all reagents were injected (entry14, Table 8). This could be explained by the possible deactivation of leached Pd species in the absence of other reagents. More tests are required by using the other possible combination and quantify the amount of leached Pd.

3.8 Open cell foam reactor as a solution for pressure drop issue

Open Cell Foams (OCF) are attractive materials for liquid-solid catalytic processes, since they offer a very high porosity and quite large opening. This allows possible insoluble particles generated during the reaction to be transported out of the reactor avoiding a too high pressure drop.

Since active charcoal is a material which is subject to mechanical attrition hence to product some very fine particles, resulting in an increase of the pressure drop. Thus, it was decided to use OCF coated with a thin layer of Pd/C to check for Pd leaching when using Pd/C precursors. For the sake of comparison Pd(0)/Silica and Pd(II)/silica precursors were also used.

3.8.1 Experimental section

3.8.2 Foam properties

The foam properties (**Table 10**) have been determined by the nondestructive Computed X-ray tomography technique followed by image analysis and 3D reconstruction. X-ray tomography was performed in the MATEIS laboratory at INSA-Lyon, on v|tome|x s apparatus manufactured by Phoenix X-ray, a GE company (Wunstorf, Germany). After 3D volume reconstruction, we obtain a 3D volume of 900x600x500 voxels with a voxel size of 16 μm. Image processing analysis was performed using Imorph (http://imorph.sourceforge.net/) by M.-L. Zanota (Research engineer, CPE Lyon).

Table 10 Open cell metallic foam properties

Material	Commercial references	Porosity ε (-)	Cell size (μm)	Mean windows diameter (μm)	Specific surface area (m^2/m^3)
FeCrAl	Hollomet Foamet ID03142	0.9	800	12	2700

3.8.3 Catalytic foam column preparation

3.8.3.1 Preparation of catalyst suspension for Pd/C coating on foams

Initially, 20 ml of deionized water was mixed with 20 ml of Triton X-100 (ACROS) inside a Planetary Ball Mills (Retsch PM100), and then the mixture was agitated for 3 min at 250 rpm (rotation per minutes). After that, 800 mg of Dextrin (from corn type I, Sigma Aldrich) was introduced and the mixture was agitated at 250 rpm for 5 min.Then, 10 g of the catalyst Pd/C (5% Pd, Johnson Matthey) was added slowly to the mixture which was crushed for 5 min at 500 rpm in a planetary ball mill.

To confirm that the viscosity of the suspension was appropriate, the bowl was then opened, and the suspension was inspected using a spatula; as it was very liquid, 2.5 mg of catalyst was added (Pd/C 5%), and the new suspension was agitated inside the planetary ball mills for 40 min at 500 rpm.

3.8.3.2 Coating of the catalyst on the metallic foam

The metallic foam was previously cut into small cylinders of 1 cm of length and 0.45 cm of diameter by electroerosion. The small cylinders were calcined at 900 °C for 10 hours with a ramp of 2 °C and were weighed before the coating.

After 40 min inside the planetary mill the catalyst suspension was restored inside a beaker, and the cylinders were immersed in the suspension. Note that one should remove the excess of catalyst suspension at the foam surface using a flow of air. After that, the foam cylinders were dried at 120 °C under oven all the night, then treated for 2 h under nitrogen flow inside a horizontal oven at 300 °C and reduced in the same oven under a flow of H_2/N_2 (20/80 %) for 2 h at 300 °C with a ramp of 3 °C/min. The resulting coated foam is presented in Figure 24.

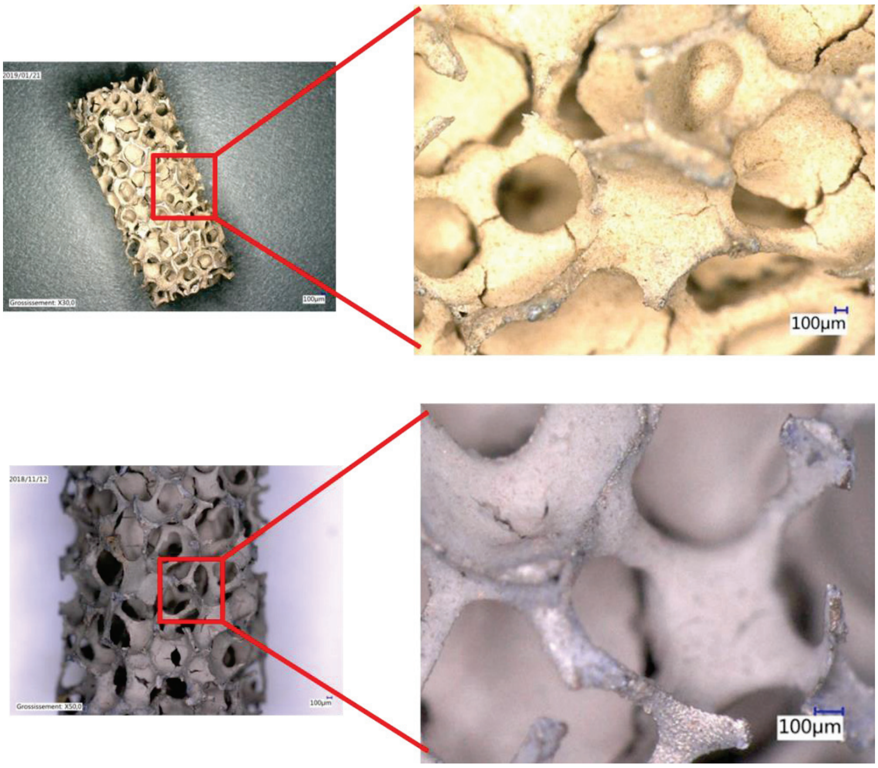


Figure 24 Optical microscopy for two different open cell foams before calcination

Table 11 presents all the parameters and conditions that have been used for the preparation of different catalytic foam cylinders. Furthermore, for each catalyst, 10 cylinders were used, and put inside a 10 cm stainless steel tube (4.6 mm i.d.).The amount of Pd in the column was determined by subtracting the mass of the filled column from the previous mass of the empty tube and the uncoated cylinders.

Table 11 Conditions for the preparation of catalytic open cells foam

Catalyst	Suspension Preparation	Quant.	calcination	Deposited Pd (mg)
Pd/C	Deionized water	20 ml	120 °C at night. 300 °C, 2 h (N2) 300 °C, 2h, 3 °C/min (H_2/N_2 20/80 %)	3.47
	Triton	20 ml		
	Dextrin	800 mg		
	Pd/C	12.5 g		
Pd(0) Siliacat or (Pd(II) Siliacat)	Ludox (HS40)	0.11 (0.09) g	120 °C at night. 4 h at 400 °C, 2 °C/min	2.25 (4.3)
	Deionized water	20 (20) ml		
	HEC (1% in H_2O)	5 (5) ml		
	Catalyst	4.84 (5.31) g		

3.8.4 Pressure drop in packed bed reactor vs. metallic open cell foam

For all the previous tests the split flow reactor was composed of a catalytic column directly packed with the solid catalysts which create some pressure drop problems. For all the tested catalysts except Pd/C, the pressure drop increase is slow enough to get some data points. The column filled by the Pd/C (5%) cannot be tested because the pressure increased drastically within a few minutes it exceeds the maximum pressure limits of HPLC pump (for safety it was fixed at 220 bar). Therefore, we decided to support the Pd/C catalyst on metallic open cell foam. Figure 25 represents the pressure variation inside the column for a packed with Pd(0) Siliacat and Pd/C deposed on a metallic foam. In fact, for the packed bed the pressure increases as a function of time until it reaches 200 bar after 350 min. This pressure increase is caused by the formation of salts which are not soluble in ethanol, and this is why the packed bed column should be cleaned by a 1:1 mixture of water: ethanol after each test. In the case of Pd/C it was impossible to make a test with a classically packed column, but when the catalyst was supported on a metallic open cell foam, the pressure remained still below 20 bar after 6 hours of test, and the concentration of leached Pd at the outlet of the column was equal to 0.36 ppm, which indicates that the catalyst was very well attached to the foam.

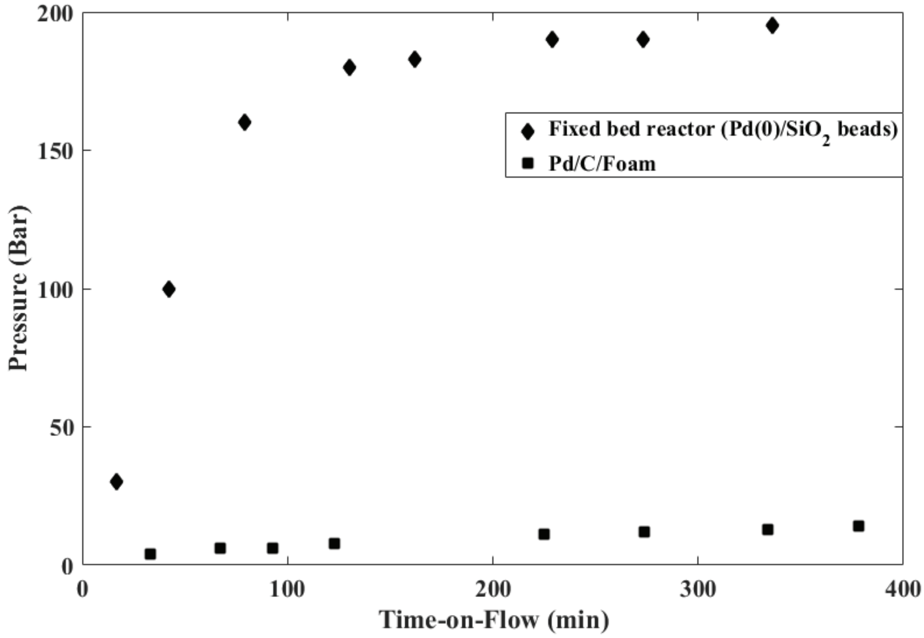


Figure 25 pressure variation inside the column for fixed bed and foam reactor.

Conditions: Q=1 ml/min. T=60 °C, 0.025 M of 4-iodoacetophenone, 0.030 M of phenylboronic acid and 0.038 M of MeONa. **Fixed bed:** Pd(0) Siliacat (10 cm), m_{Pd}= 19.3 mg. **OCF reactor:** Pd/C/Foam (10 cm), m_{Pd}= 3.4 mg.

3.8.5 Results with OCF reactor

In order to check if the Pd/C supported on foam shows a homogenous contribution or not, it was tested with 3 different aryl iodides (4-iodoacetophenone, 4-iodoanisole and 3-iodoacetophenone) using two different solvents (ethanol and a 1:9 mixture of water and ethanol) (Table 12). 4-Iodoacetophenone showed an important homogeneous contribution inside the empty tube for different flow rates and with both solvents, the Pd leaching for this catalyst was analyzed for (Q= 1 ml/min) and it was equal to 1 % of the total Pd after 100 min of work. The conversion inside the Pd/C/Foam was stable for more than 16 hours of discontinued tests with different flow rates, which corresponds to a total TON higher than 100. Pd(0) Siliacat and Pd(II) Siliacat were also deposited on the same metallic foam with the experimental process (Table 11), the homogeneous contribution inside the tube was important for both catalysts (Table 12), and the pressure drope was lower than 10 bar during the whole test.

Table 12 Tests with catalytic open cell foams

Entry	Reagents	Catalyst	Solvent	m_{Pd} (mg)	Q(ml/min)	X_{col} (Y_{col})	X_{tub} (Yield)	$TOF_{col.tot}$ (h^{-1})
1	4-Iodoacetophenone	Pd/C/Foam	EtOH	3.47	0.3	79(79)	93(93)	11
2					0.6	62(62)	82(82)	17
3					1	26(26)	46(46)	12
4	4-Iodoanisole		EtOH/ H_2O (9:1)		0.5	14(1.7)	18(4.4)	0.4
5					0.2	24(5)	29(10)	0.5
6	3-Iodoacetophenone				0.6	9(8.5)	14(13)	2
7					0.2	32(31)	54(53)	3
8	4-Iodoacetophenone				1	14(12)	27(25)	5
9					0.6	26(23)	48(46)	6
10		Pd(0) Siliacat /Foam	EtOH	2.25	1	13(13)	23(23)	9
11		Pd(II) Siliacat / Foam	EtOH	4.3	2	24(24)	44(44)	18

Conditions: T=60 °C, 0.025 M of 4-iodoacetophenone, 0.030 M of phenylboronic acid and 0.038 M of MeONa. OCFs: 1.5 ml. Empty tube: 2.14 ml. $TOF_{col.tot} = \frac{Converted\ quantity\ in\ column}{total\ quantity\ of\ Pd \cdot R_t}$.

The effect of solvent was studied with Pd/C/Foam for the same reagent (4-iodoacetophenone). It showed that adding water (1:9) into ethanol lowers the activity and generates the homocoupling subproduct (entry 3 vs 8, Table 12). Moreover, the activities of iodo aryls could be classified as follows 4-iodoacetophenone> 3-iodoacetophenone>4-iodoanisole. Also Pd(II)/SiO_2/Foam was more active than Pd(0)/SiO_2/Foam and Pd(0)/C/Foam (entries 3,10, 11, Table 12). Both Pd(0) precursors have shown almost the same activity despite a different Pd loading (entries 3, 10, Table 12). Last, 4-iodoanisole reveals poor selectivity in the SM coupling product, Ullmann coupling prevailing.

3.9 Use of scavengers

Beyond the homogeneous (i.e. in solution) vs. heterogeneous (i.e. on the solid) nature of the active species that catalyze SM reaction, when a homogeneous mechanism is identified, a new debate raises about the true nature of active species: they can be Pd nanoparticles [25, 26], mononuclear Pd [22, 11, 27, 28, 29, 30] or a mixture of both which is called “cocktail catalysis” [31, 32, 2, 33, 34].

The identification of the true nature of active species shows an important challenge, because of the low stability and lower concentration of mononuclear Pd, making its identification with sample techniques very difficult. In our work we propose an indirect method to determine the molecular or colloidal nature of true active species, by using a Pd scavenger that captures the catalyst under the reaction conditions.

3.9.1 Experimental section

3.9.1.1 Chemicals and analysis

Batch tests were carried out using two catalysts, palladium Nps (Figure 26) synthesized in the C2P2 Laboratory (CPE Lyon, France) and Herrmann-Beller palladacycle (Sigma Aldrich), while the continuous test were performed with a column packed with Siliacat Pd(0) (SILICYCLE R815-100). Four commercial scavengers (Figure 27) were used, Smopex®-111 (S11), Smopex®-112 (S112), Smopex®-234 (S234), and QuadraSil® TA (QS-TA). Analyses were made by GC-FID chromatography (Agilent Technologies 6890N, column OPTIMA 5 (10m x 100µm x 0.1µm), split 1/250 volume injected 1µL (300 ° C), H_2 flow rate: 0.4 mL / min, oven program: 150 ° C (30s) then 50 ° C / min up to 340 ° C (42s), FID Detector).

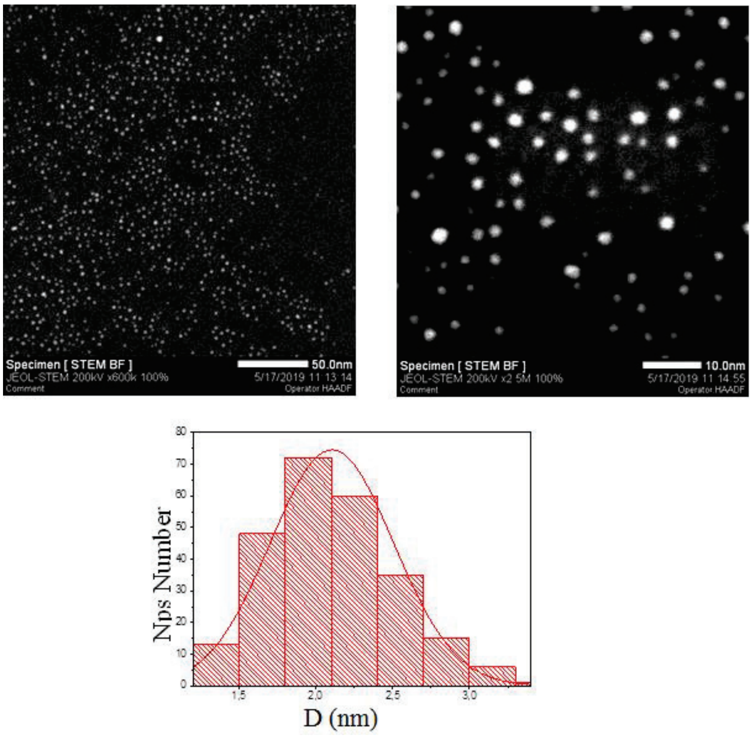


Figure 26 Pd Nps STEM images with the histogram of size distribution (C2P2 images)

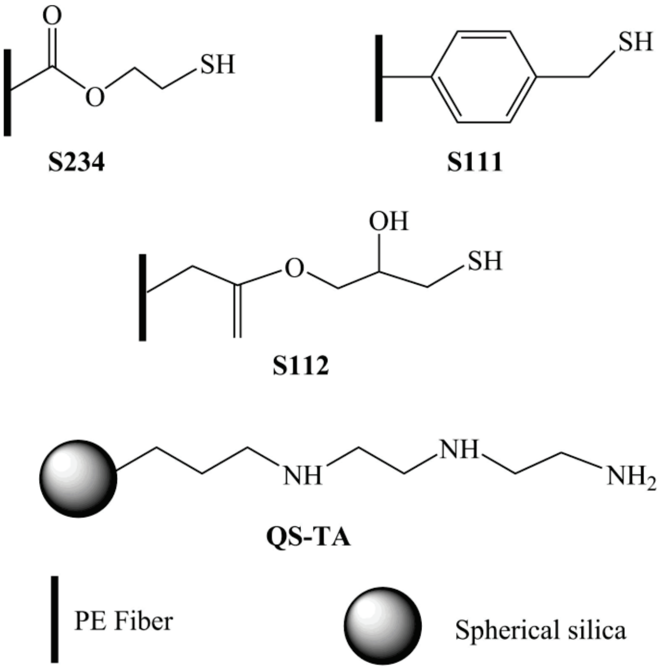


Figure 27 Pd scavengers used (molecules from [35, 36])

3.9.1.2 Scavenger batch test 1:

In a typical test, a solution was prepared by dissolution of 4-iodoacetophenone (0.492 g, 2 mmol, 1 eq.), phenylboronic acid (0.290 g, 2.4 mmol, 1.2 eq.), MeONa (0.162 g, 3 mmol, 1.5 eq.) and naphthalene (0.084 g, 0.6 mmol, 0.3 eq.) in ethanol (40 ml). An ultrasonic bath was used to help dissolution (ultrasound for 30 min at room temperature). The solution was added to a three-neck round-bottom flask equipped with a stirring bar and preheated at 60 °C in an oil bath under agitation for 30 min. The scavenger QS-TA (20 mg) was preheated in the same oil bath in another three-neck round-bottom flask equipped with a stirring bar. Then a catalytic solution (4 ml, 0.4 mM of palladacycle in toluene or Pd Nps in toluene) was added to the first solution. After 10 min half of the first solution was syringed and mixed with the scavenger (Figure 28).

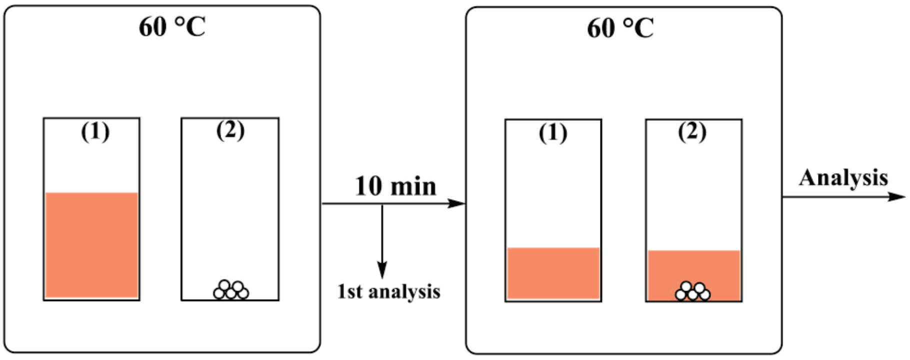


Figure 28 Scavenger batch test 1

3.9.1.3 Scavenger batch test 2

A first solution of Pd Nps in toluene (0.4 mM_{Pd}, 1 ml) was mixed under agitation at room temperature with the scavenger (QS-TA, 0.040 g). A second catalytic solution of Pd Nps in toluene (0.4 mM_{Pd}, 1 ml) was agitated to be used as a blank. Two other solutions were prepared by dissolution of 4-iodoacetophenone (0.037 g, 0.15 mmol, 1 eq.), phenylboronic acid (0.0033 g, 0.027 mmol, 1.2 eq.), MeONa (0.012 g, 0.0225 mmol, 1.5 eq.) and naphthalene (0.042 g, 0.3 mole, 0.3 eq.) in ethanol (3 ml). Then 0.03 ml of the first solution was syringed, filtered through a PTFE syringe filter (0.25 µm) then added to the first preheated batch, after that, 0.03 ml of the blank solution was added to the second batch, and the conversion was followed at different times for 1 hour (Figure 29). Note that the same process was used with palladacycle.

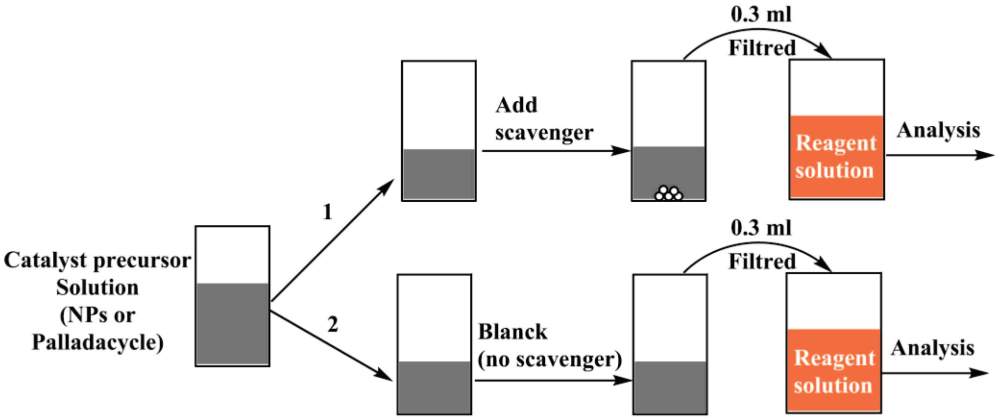


Figure 29 Scavenger test batch 2 example for Nps (the same test was used for Palladacycle)

3.9.1.4 Continuous test with scavengers

Reagents solution has been prepared by dissolution of 4-iodoacetophenone (3.69 g, 15 mmol, 1 eq.), phenylboronic acid (2.18 g, 18 mmol, 1.2 eq.), MeONa (1.22 g, 22.5 mmol, 1.5 eq.) and naphthalene (0.645 g, 5 mmol, 0.3 eq.) in ethanol (600 ml). 0.003 g of a scavenger (QS-TA) was diluted with 1.52 g of silica C18 with the same particle size (20-100 µm), then agitated by spatula to make good dispersion. After that, 0.524 g of the prepared solid mixture was packed inside a stainless steel tubes (4.6 mm i.d., 5 cm). Reagents were then pumped through the preheated catalytic column followed by the preheated scavenger column, and the conversion was measured before and after the scavenger column as shown in Figure 30.

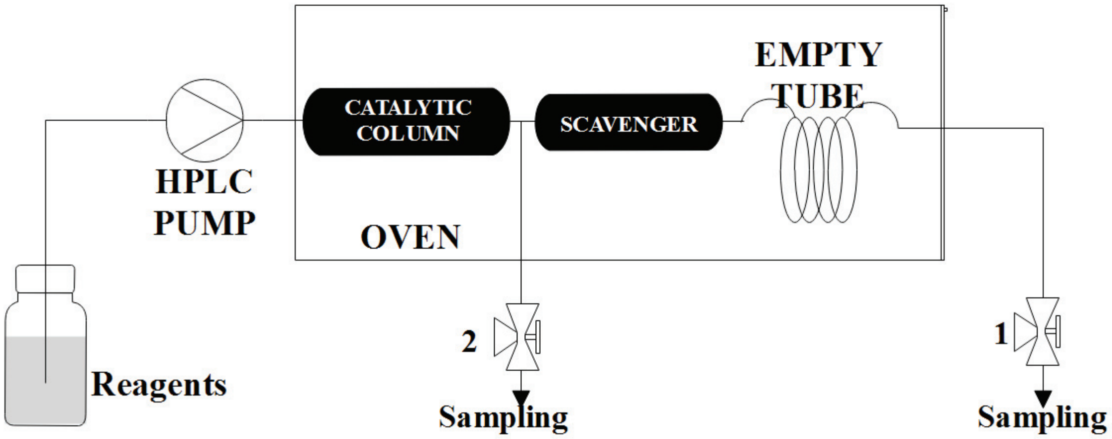


Figure 30 Continuous scavenger test

Conditions: L_{tube}= 11 cm (3.18 mm id.), $L_{Scavenger}$ column = 5 cm (4.6 mm id.), $L_{Catalytic}$ column= 10 cm (4.6 mm id.). T= 60 °C.

3.9.2 Results and discussion

3.9.2.1 Batch tests

The aim of these tests with different solids is to check if one solid could catch the Pd from the solution in molecular and/or colloidal form. Therefore, 4 solid scavengers were used in SM reaction catalyzed by Pd Nps or Hermann Beller palladacycle in order to check if one of them can selectively catch Pd complexes or Pd Nps. Table 8 represents the obtained results for different solids supposed to stop the reaction. In test 1 (Figure 28) the solids were added after the beginning of the reaction at 20% of conversion, and only 2 of them (S234 and QS-TA) stopped the reaction for both catalysts. In test 2 (Figure 29), the solids were initially added to the catalyst solution, then a volume of the mixture (scavenger + catalyst) was syringed, filtered, then added to the preheated reagents, this second test was made to confirm that the scavenger could capture the molecular catalyst at its initial form , and not in its leached active form. Indeed, adding the scavenger after the beginning of the reaction could result in the capturing of Pd(0) species involved in the Pd(0)/Pd(II) mechanism [37]. Batch test 2 showed also that S234 and QS-TA are scavenging Pd Nps and molecular catalyst.

Table 13 Scavenger tests with Pd Nps and palladacycle

Catalyst	Batch test 1				Batch test 2			
	S_{111}	S_{112}	S_{234}	QS-TA	S_{111}	S_{112}	S_{234}	QS-TA
Palladacycle	no	no	yes	yes	no	no	yes	yes
Pd Nps	no	no	yes	yes	no	no	yes	yes
Pd/Scavenger (% mol)	0.36	0.32	0.4	0.92	0.36	0.32	0.4	0.92

Conditions: T=60 °C, 0.025 M of 4-iodoacetophenone, 0.030 M of phenylboronic acid and 0.038 M of MeONa. $m_{scavenger}$= 0.001 g for all the solids. n_{Pd}= 1.2 10^{-5} mmol. **No:** the reaction is not stopped until it reached 100% of conversion after 1h. **Yes:** the reaction is stopped with 0% of conversion after 1h.

3.9.2.2 Continuous test

After the batch tests, QS-TA scavenger has been selected to perform the continuous test.

3.9.2.2.1 Functionalized C18 Silica

Initially a “blank test” was performed using functionalized C18 silica (Sigma Aldrich 40-63 μm) to check that silica is not able to catch the active palladium. The leached species were still active, with the same activity with or without C18 column. In fact, 10% of yield was obtained at the column outlet whith 25% after the C18 bed, meaning that the C18 silica has no impact on the active species in the stationary state.

3.9.2.2.2 Excess of scavenger

When the scavenger column was filled by 680 mg of QS-TA tri-amine functionalized silica, a comparison of the conversion after the catalytic bed and after the scavenger + empty tube was also performed, in the same operating conditions as the blank test. A conversion of 11 % was obtained both after the catalytic bed and after the scavenger + tube, which means that the leached catalyst was catched or deactivated by the scavenger.

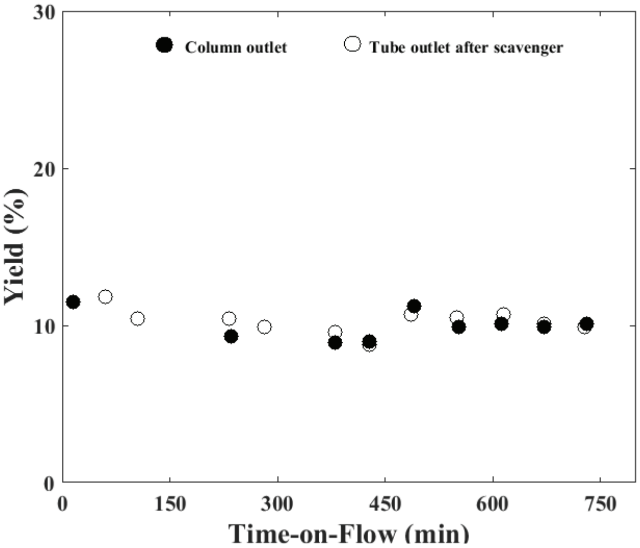


Figure 31 Continuous scavenger test with QS-TA scavenger

Conditions: Q= 1ml/min, T=60°C, 25 mM of 4-iodoacetophenone, 30 mM phenylboronic acid and 37.5 mM of MeONa in ethanol. Pd(0) Siliacat column: 19.27 mg of Pd, Scavenger QS-TA column: 0.68 g.

At the end of this test, the reagents were introduced directly through the scavenger column, and no conversion was detected which means that the captured Pd species are inactive.

The scavenger column was then dried in the oven (100 °C) and emptied to recover the spent scavenger. It presents a yellow color with few small black points (Figure 32). The yellow color could indicate the presence of a Pd(II) complexes [38], and the black points indicate Pd Nps. A Scanning transmission electron microscopy (STEM) analysis was carried out to try to determine the size of Pd Nps at the surface of the scavenger, but nothing was found because the concentration of adsorbed Pd was too low.

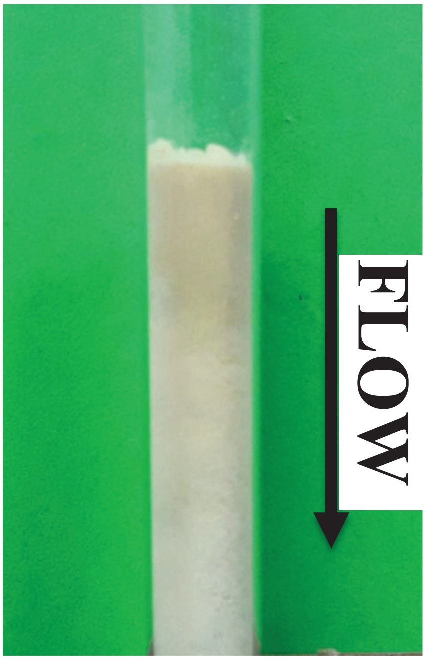


Figure 32 The color of QS-TA scavenger after a catalytic test

3.9.2.2.3 Dilution with C18

In the previous test there was no conversion after the scavenger column because of the scavenger excess, here the QS-TA scavenger was diluted with C18 functionalized silica to obtain a homogeneous mixture inside a 5 cm column (4.6 mm id.), with only 1.03 mg of QS-TA scavenger and 0.40 g of C18 silica. This column was used in the same conditions as the previous test; but the conversion continues to increase after the scavenger column until it reached a stationary state with 58 % of yield (Figure 33). This result is very important because it means that the scavenger column can be saturated like a chromatographic column.

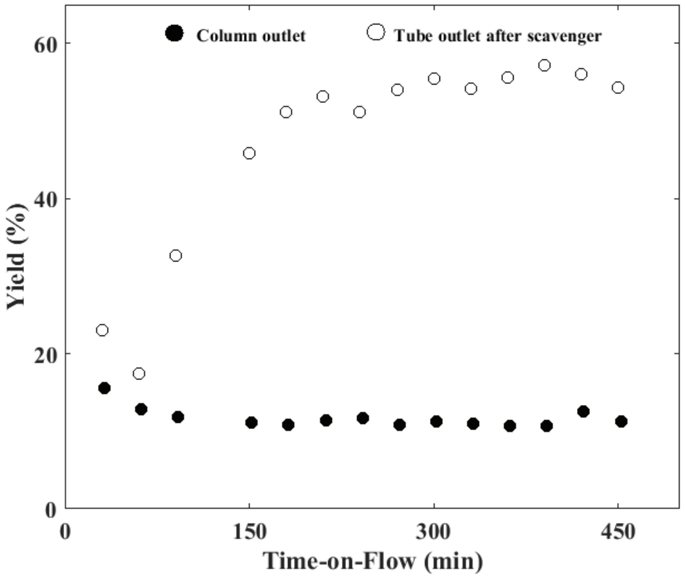


Figure 33 Variation of 4-methoxybiphenyl yield before and after a scavenger column filled by QS-TA and C18 functionalized silica.

Conditions: see **Figure 31**, $m_{QS\text{-}TA}$= 1.03 mg, m_{C18}= 0.397 g, Q=1 ml/min

To conclude this part, from a variety of 4 scavengers only two capture the active species. They are selective for both Pd complexes and Nps. Thus it was difficult to use them as a tool to determine the nature (NPs, or complexes) of active species. More analysis should be done to determine the reason why the tested scavenger S111 and S112 were not scavenging.

3.10 Comments with other reagents (Other aryl iodides, bromides and chlorides)

The presence of a homogeneous mechanism in Suzuki-Miyaura reaction of 4-iodoacetophenone has been proved in this work, with different heterogeneous type Pd precursors, the same remark was found for two other aryl iodides; 4-iodoanisole and 3-iodoacetophenone using Pd/C/foam (Table 12). Herein more tests have been carried out with inactive aryls and other catalysts.

3-Iodoacetophenone has been used in the split flow test using Pd(0) Siliacat as a catalyst (Table 14), with 19 % of conversion increase inside the empty tube which indicates the presence of an important homogeneous mechanism. Furthermore, using the same catalyst 44 % of conversion was found at the tube outlet which is higher than the conversion measured at the column outlet (24%) indicating that the transformation of 4-iodoanisole also presents an important homogeneous contribution, which is found by other authors for aryl iodides [38, 31, 27, 40, 34]

In order to understand the SM reaction of bromides, 4-bromoacetophenone was tested with two catalysts (Table 14), Pd(0) Siliacat and Pd(II) Siliacat , both catalysts showed a homogeneous contribution inside the empty tube [40, 41, 28, 33, 42], but it was lower than the one obtained with the 4-iodoacetophenone homologue. Furthermore, Pd leaching was equal to 0.23 ppm which is the same order of concentration found for iodide; note that the selectivity of both catalysts for SMR was lower than their selectivity with 4-iodoacetophenone (>99%), showing the presence of dehalogenation side-reaction inside the column.

The 4-chloroacetophenone was almost inactive (Table 14) with only 1 % of yield increase inside the empty tube. This result can indicate a heterogeneous nature of active species with chlorides, but 0.17 ppm of leached Pd has been measured when Pd(II) Siliacat was used as a catalyst. This leached Pd could indicate the presence of a homogeneous mechanism [12] with unstable homogeneous Pd that deactivates quickly via the generation of bigger NPs via Oswald ripening and/or the generation of inactive Pd complexes. This remark was cited by the team of Beletskaya [29]; they found that the bigger Pd Nps (10-20 nm) were only active with iodide (iodobenzene) and inactive with the other halide (bromobenzene), which can explain the lower homogeneous activity of aryls bromide and chloride.

Table 14: Flow split tests other reactants with different catalysts with Pd leaching concentration

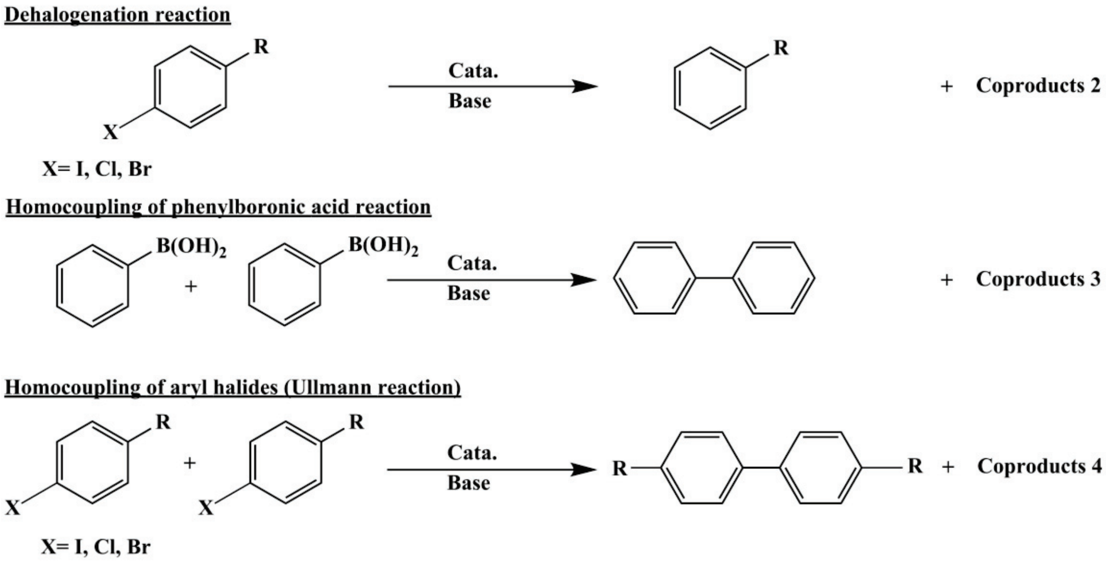
Reagents	Catalyst	m_{Pd} (mg)	X_{col} (Yield)	X_{tube} (Yield)	Q (ml/min)	τ_{column} (min)	$\tau_{col+tube}$ (min)	Pd leach. (ppm)
3-Iodoacetophenone	Pd(0) Siliacat	19.7	31(31)	50(50)	1	0.94	3.1	NA
4-Iodoanisole			24(24)	44(44)	1	0.94	3.1	NA
4-Bromoacetophenone	Pd(II) Siliacat	0.6	12(5)	16(9)	0.3	0.08	7.2	0.23
		2.5	60(52)	68(60)	0.5	0.2	4.5	NA
	Pd(0) Siliacat	9.1	50(8)^a	96(54)^a	0.6	0.7	15*	NA
4-Chloroacetophenone	Pd(0) Siliacat	17.5	100(41)	100(41)	1	0.83	3	NA
			87(36)	87 (37)^b	1.5^b	0.55	2	NA
	Siliacat Pd(II)-DPP	11	47(33)	48(34)^b	1^b	0.42	2.6	0.17
			35(21)	35(22)	1.3	0.32	2	

Conditions : 4-iodoacetophenone 25 mM, phenylboronic acid 30 mM, MeONa 37.5 mM, 60 °C for iodides and bromides, 67 °C for chlorides. Empty tube volume: 2.14 ml, *: 8.58. NA: not analyzed.

[a] : under N_2 and TBAB.

[b]: under N_2.

3.11 Split flow reactor for production (selective for homogeneous reaction)



Scheme 5 Possible side reactions with Pd catalysts in the reaction of aryl halides with phenylboronic acid

Many side reactions could be involved in the reaction of some inactive aryl halides under specific reaction conditions [43]. Scheme 4 represents the different possible side reactions with SMR: dehalogenation of the aryl halide, homocoupling of the phenyl boronic acid and the Ullmann reaction.

For example, in the reaction 4-bromoacetophenone with phenylboronic acid catalyzed by Pd(0) Siliacat (60 °C and EtOH as solvent), the SMR product yield at the column outlet was equal to 8 % and the dehalogenation yield was equal to 25 %, surprisingly at the tube outlet only the SMR product yield increased until it reached 54 %, while the dehalogenation yield was stagnant at 25 %, the same remark was obtained with Pd(II) Siliacat where the SMR product yield increased from 52 % to 60 % and the dehalogenation yield was stable at 5 %. Furthermore, when the 4-iodoanisole was tested through Pd/C/Foam column using a mixture of 9:1 (ethanol:water) as solvent, it showed 8% of the Ullmann homocoupling product inside the column, but this yield did not increase inside the empty tube, while Suzuki-Miyaura product yield increased from 5 % at the column outlet to 10 % at the tube outlet.

These observations mean that the split flow reactor can not only be used as a test to study the homogeneous vs. heterogeneous mechanistic nature of the reaction, but it can also be used as a very selective reactor to the homogeneous reactions. In these cases the column is only used as a reservoir for the generation of true homogeneous hyper active species. These species will continue the selective SM reaction inside the homogeneous empty tube.

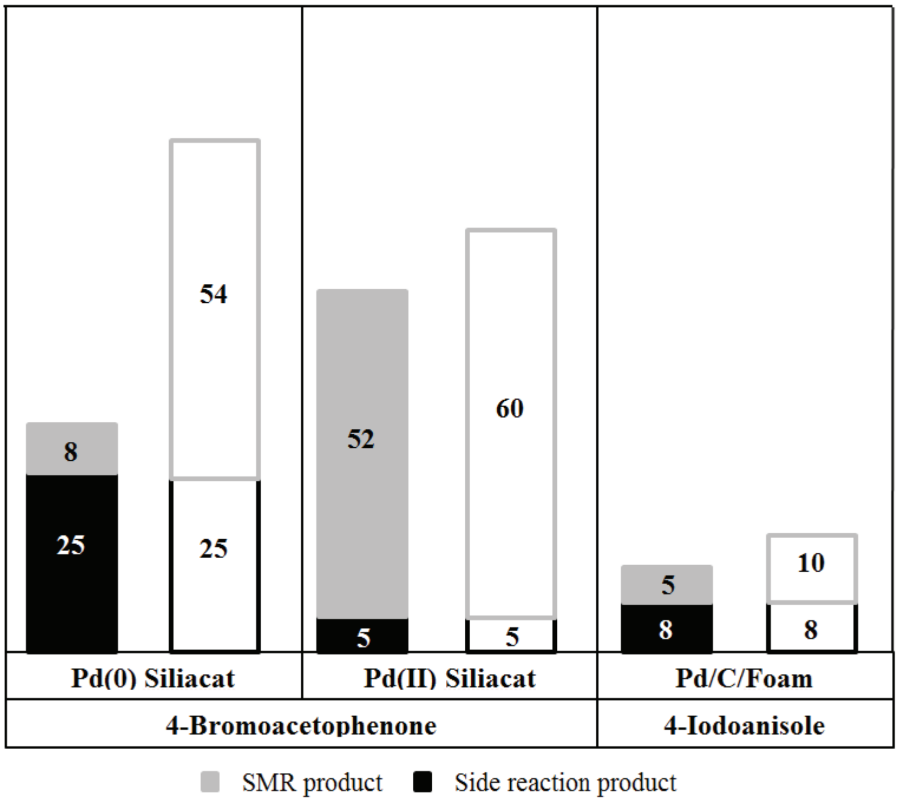


Figure 34 Variation of the SMR and side products yield for 4-bromoacetophenone and 4-iodoanisole, at column outlet (filled bars) and tube outlet (empty bars)

Conditions: see **Table 12** for 4-iodoanisole and **Table 14** for 4-bromoacetophenone

3.12 Conclusion

In this chapter a new tool “Split Flow Reactor” to discriminate between the homogeneous and the heterogeneous nature of active species that catalyze Suzuki-Miyaura reaction was described, and tested with different reactant and catalysts.

The 4-iodoacetophenone was initially tested with a variety of heterogeneous catalyst precursors of different nature (Pd(0)/Silica, Pd(0)/Alumina, Pd(0)/C, Pd(II)/Silica, Pd(0)/Alginate and $Ce_{0.2}Sn_{0.79}Pd_{0.01}O_{2-\delta}$), all of them showed an important homogeneous contribution inside the empty tube, with small amount of Pd leaching below ppm level (70-500 ppb). 4-iodoacetophenone was found to be the only responsible for Pd leaching, with a linear relation between the leached amount of Pd and the residence time in the column of precursor. Furthermore, the use of open cell foams coated with solid catalyst, reduce the pressure drop problems from 200 bars (after 6 h with classic fixed bed) to a stable pressure below 20 bars.

At the end, the existence of a homogeneous mechanism for aryl bromides and chlorides was inspected, showing a small homogeneous contribution of bromide with almost a zero contribution of the chloride with 23 ppb and 17 ppb Pd leaching, respectively.

The split flow reactor is a great tool to show the presence of homogeneous contribution inside the empty tube, but inside the column the homogeneous and heterogeneous mechanisms are coupled, and in order to separate them and understand if there is a dominant mechanism a reactor model based on Pd leaching and the activities inside the empty tube and the column should be used.

3.13 List of abbreviations

i.d	Internal diameter (m)
m_{Pd}	Palladium mass (mg)
$m_{scavenger}$	Scavenger mass (mg)
Nps	Nano-particles
n_{Pd}	number of moles of palladium (mol)
Q	Liquid flow rate (ml/min)
τ	Residence time (min)
T	Temperature (°C)
TBAB	Tetrabutylammonium bromide
TON	Turn over number ($mol_{product}$/ mol_{Pd})
TOF	Turn over frequency ($mol_{product}$ $mol_{Pd}^{-1}h^{-1}$)

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Chapter 4

Modeling of the heterogeneous and homogeneous contributions in Suzuki coupling by using the flow split test

Abstract:

This work aims at developing a simplified model that permits to distinguish between the homogeneous and the heterogeneous contributions inside the split flow reactor. In fact 4-iodoacetophenone shows a pure homogeneous nature for all the Pd(0) supported catalysts, whereas a dominant heterogeneous mechanism was present with a Pd(II) complex supported on silica. However, both supported Pd(0) and Pd(II) catalysts generate the same very active species with initial activity as high as 500,000 h^{-1} mol_{prod}/mol_{Pd}. The different behavior of chloro and bromo derivatives could be explained by both pure heterogeneous or pure homogeneous mechanism.

Keywords: Homogeneous mechanism, heterogeneous mechanism, Suzuki-Miyaura, very active Pd species.

4.1 Introduction

In the previous chapter, a simple and rather inexpensive setup (Split Flow Reactor) was used in the SMR of different aryl halides by using a variety of Pd supported catalysts. All of them showed an important activity inside the empty tube for 4-iodoacetophenone, a lower activity in the case of 4-bromoacetophenone and absence of activity for 4-chloroacetophenone while detecting the same level of very low leached Pd concentration for all derivatives (0.1-0.5 ppm). In order to quantify and identify the homogeneous or heterogeneous nature of the catalysis, a reactor model is used in this chapter.

4.2 Reactor modeling

In order to identify the homogeneous or heterogeneous behavior of the catalysts a reactor model was built. The following assumptions were verified and used:

4.2.1 Isothermal behavior

The reactor is composed of a packed bed column followed by an empty tube, both of them are placed in a closed oven. The reactor is always preheated for 30 min at 60 °C before pumping the reagent solution, and this last is preheated inside a stainless steel coil tube before being injected through the column. The average molar enthalpy of SMR is $\Delta H=$ -224 KJ/mol [1], this value was used in a steady state energy and molar balance of a PFA tubular reactor (Appendix 13) and showed a negligible effect of temperature variation inside the reactor, thus considering all these information the reactor is considered as an isothermal reactor.

4.2.2 Reaction kinetic rate law

In the chapter number 2 a complete kinetic study was carried out by using 4-iodoacetophenone, phenylboronic acid and sodium methylate as a base, catalyzed by a homogeneous catalyst. This study was validated by both a microkinetic and an analytic approach. This last was led to a simplified kinetic law well describing the experiments where the concentration of the base and the phenylboronic acid are higher than the aryl halide concentration. The kinetic law of equation (1) will be used to represent the reaction kinetic for both homogeneous and heterogeneous part:

$$r = \frac{k_1\, C_{Pda}^{L}\, C_A}{1 + k_2 C_A}\ (mol \cdot m_L^{-3} \cdot s^{-1}) \tag{71}$$

We have postulated that, if a heterogeneous mechanism could occur, the kinetic law would have the same form (with different values of parameters) than the homogeneous reaction.

4.2.3 Leaching of catalytic species

In the 3rd chapter, it was demonstrated that the concentration of leached Pd in the solution increased with the residence time (Rt). Moreover, the test aiming at finding the reactant responsible for leaching showed that only aryl iodide results into leaching of active Pd species. Thus a first order dependence towards the supported Pd and the concentration of aryl halide law was selected:

$$r_{leaching} = k_{leach}\, C_{Pda}^{S} C_A\ (mol_{Pd} \cdot m_L^{-3} \cdot s^{-1}) \tag{72}$$

4.2.4 Catalyst deactivation

Catalyst deactivation represents an important issue in Pd catalyzed reactions, due to the catalyst poisoning by impurities, agglomeration, generation of inactive Pd complexes, irreversible adsorption of soluble Pd active species, [2, 3, 4]. Hence, the possible catalyst deactivation processes were lumped in one kinetic constant except for the column where it is represented by two kinetic constants, one for deactivation and the second one for the possible readsorption of homogeneous Pd. Note that a linear law was used for adsorption because of very low concentration of homogeneous Pd.

$$r_{deact} = k_{deact}\, C_{Pda}^{L} (mol_{Pd} \cdot m_L^{-3} \cdot s^{-1}) \tag{73}$$

$$r_{ads} = k_{ads}\, C_{Pd}^{L}\ (mol_{Pd} \cdot m_L^{-3} \cdot s^{-1}) \tag{74}$$

4.2.5 Axial dispersion

4.2.5.1 Inside the column (packed bed reactor)

In order to determine the value of axial dispersion coefficient and the liquid hold-up in the prepared columns, a residence time distribution (RTD) was performed (Appendix 12). The obtained results showed a liquid hold-up of 0.52 with a value of axial dispersion equal to $5 \cdot 10^{-9}$ m^2/s, that matches a Péclet number ($Pe = \frac{u \cdot l}{D_{ax}}$) higher than 800, allowing to neglect the axial distribution effect in the column [5, 6].

4.2.5.2 Inside the empty tube

The mixing effect inside the empty tube was checked by comparing the conversion at its outlet to the conversion obtained at the outlet of a packed tube reactor filled by inert glass beads (50-150 µm). Hence, the same catalytic column was used at two different flow rates followed by the tubular reactor in the first case and by the packed tube reactor in the second case (Table 15). Both reactors show negligible variation in the conversion thus, the axial dispersion can be neglected for our reactor modeling.

Table 15 Variation of the conversion at tube outlet by using the same catalyst

Flow rates (ml/min)	0.3	0.6
X_{column} (Y_{column}) (%)	7 (7)	2 (2)
X_{tube} (Y_{tube}) (%)	(47.9) 47.9	(28.2) 28.2
$X_{packed\ bed}$ ($Y_{packed\ bed}$) (%)	(48.1) 48.1	(28.1) 28.1

Conditions: 25 mM 4-iodoacetophenone, 30 mM $PhB(OH)_2$ and 37.5 mM MeONa. Pd(0)-Siliacat: m_{Pd}=1.82 mg. Tube volume: 2.14 ml.

4.2.6 Mass transfer limitations

4.2.6.1 External mass transfer limitations

In order to check the effect of external diffusion an experiment was performed by varying the length of the column and the flow rate while keeping the same residence time constant. Note that if there would be mass transfer limitations the conversion varies because extern mass transfer is proportional to Reynolds.

Table 16 Effet of external limitation on the reaction yield

			Residence time (s)		
			33	50	100
l(cm)	5	Yields (Re)	23.8 (2.3)	52.9 (1.5)	58.2 (0.8)
	15	Yields (Re)	24.2 (6.8)	51.5 (4.6)	59.5 (2.3)
	20	Yields (Re)	24.4 (9.1)	52.0 (6.1)	60 (3)

Conditions: 0.025 M of 4-iodoacetophenone, 0.030 M of phenylboronic acid and 0.038 M of MeONa. **Columns:** Pd(0) Siliacat: m_{Pd5cm} = 7.9 mg, m_{Pd15cm} = 26.3 mg, m_{Pd20cm} = 35.4 mg. Reynold(Re)=$\frac{u\ D_t}{\vartheta}$.

For a given residence time, the variation of the Re number has no impact on the yield, which permits to neglect the effect of the external diffusion.

4.2.6.2 Internal mass transfer limitations

For the estimation of the internal diffusion limitations, Weisz-Prater Criterion (75) between the observed reaction rate and the diffusion rates was used. A very low diffusion coefficient of 10^{-10} m^2/s was used and gave an effective diffusivity of 10^{-11} m^2/s. Moreover, a numerical application with an exemple from entry (1) table2 (chapter 3) gave CW<<1 (particle size 60 µm, robs=0.1 $mol/m^3/s$ and CW=0.04), which means that there is a negligible concentration gradient within the particle. Except for Pd@ALG-XG that have a bigger particles diameter (1 mm) giving CW=10, thus they will not considered in this part.

$$C_W = \frac{r_{obs} \cdot L^2}{D_e \cdot C_{As}} \tag{75}$$

The final diagram from all previous assumptions is presented as follow:

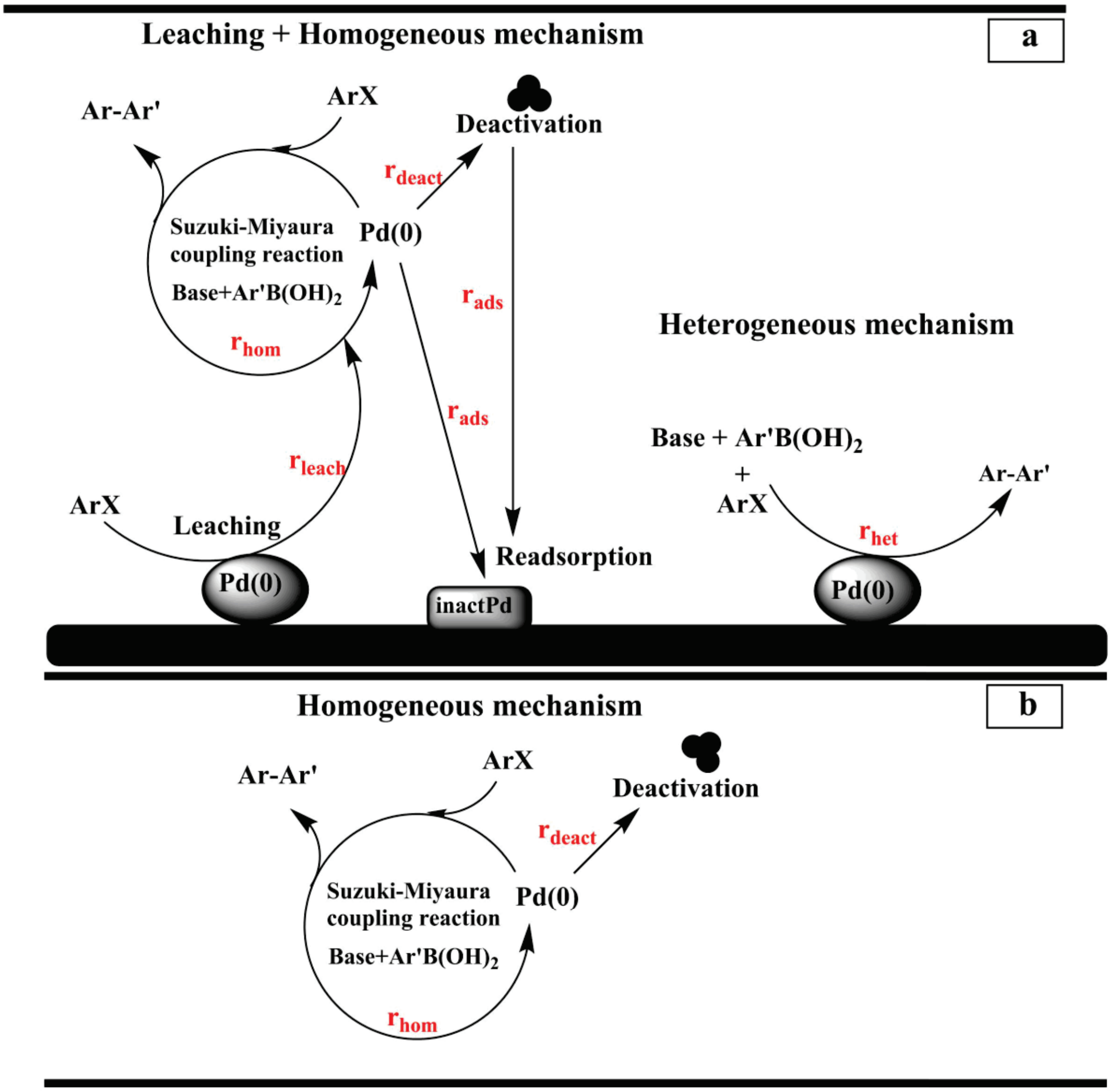


Figure 35 Homogeneous vs. heterogeneous catalysis a): inside column and b): inside tube

4.2.7 Mass balance equations

Material Balance on homogeneous Pd (column)	$\frac{\partial C_{Pd}^{L}}{\partial t} = -Q\frac{\partial C_{Pd}^{L}}{\partial V} + r_{leaching} - k_{ads}\, C_{Pd}^{L}$	(76)
Material Balance on homogeneous Pd (tube)	$\frac{\partial C_{Pd}^{L}}{\partial t} = -Q\frac{\partial C_{Pd}^{L}}{\partial V}$	(77)
Material Balance on homogeneous active Pd (column)	$\frac{\partial C_{Pda}^{L}}{\partial t} = -Q\frac{\partial C_{Pda}^{L}}{\partial V} + r_{leaching} - k_{ads}\, C_{Pda}^{L} - k_{deact}\, C_{Pda}^{L}$	(78)
Material Balance on heterogeneous active Pd	$\frac{\partial C_{Pda}^{S}}{\partial t} = -r_{leaching}$	(79)
Material Balance on reagent A (column)	$\frac{\partial C_{A}}{\partial t} = -Q\frac{\partial C_{A}}{\partial V} - r_{hom} - r_{het}$	(80)
Material Balance on reagent A (tube)	$\frac{\partial C_{A}}{\partial t} = -Q\frac{\partial C_{A}}{\partial V} - r_{hom}$	(81)
Leaching rate (mol/m^3 /s)	$r_{leaching} = k_{leach}\, C_{Pda}^{S} C_{A}$	(82)
Homogeneous rate (mol/m^3 /s)	$r_{hom} = \frac{k_{hom1}\, C_{Pda}^{L} C_{A}}{1 + k_{hom2} C_{A}}$	(83)
Heterogeneous rate (mol/m^3 /s)	$r_{het} = \frac{k_{het1}\, C_{Pda}^{S}\, C_{A}}{1 + k_{het2} C_{A}}$	(84)
Catalyst deactivation (column) (mol/m^3/s)	$r_{deact-column} = k_{deact}\, C_{Pda}^{L}\ and$ $r_{ads} = k_{ads}\, C_{Pd}^{L}$	(85)
Catalyst deactivation rate (tube) (mol/m^3/s)	$r_{deact-tube} = k_{deact}\, C_{Pda}^{L}$	(86)

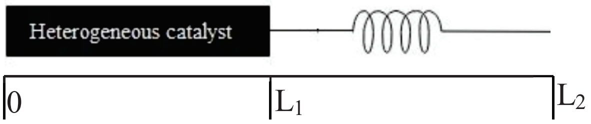
The material balance for other species (B, C) is not written since they are not independents because the chemical system differ only one reaction.

4.2.8 Initial conditions

Initially all concentrations inside tube and column are equal to zero (0), except the concentration of solid Pd that is equal to the total concentration of Pd initially loaded.

4.2.9 Boundary conditions

Boundary conditions type of Dirichlet and Neumann were used:



$C_A(t,L=0)=25\ \text{mol}\cdot\text{m}^{-3}$, $C_B(t,L=0)=30\ \text{mol}\cdot\text{m}^{-3}$, $C_C(t,L=0)= C_{Pd}^{L}(t,L=0)= C_{Pd}^{s}(t,L=0)=0$ mol/l

$C_A(t,\ L_1^-)= C_A(t,\ L_1^+)$, $C_B(t,\ L_1^-)= C_B(t,\ L_1^+)$,$C_C(t,\ L_1^-)= C_C(t,\ L_1^+)$, $C_{Pd}(t,\ L_1^-)= C_{Pd}(t,\ L_1^+)$,

$$\frac{\partial C_{Pdsolid}(t,L_1)}{\partial t} = 0$$

$$\frac{\partial C_A(t,L_2),}{\partial t} = \frac{\partial C_B(t,L_2)}{\partial t} = \frac{\partial C_C(t,L_2)}{\partial t} = \frac{\partial C_{Pd}(t,L_2)}{\partial t} = 0$$

4.2.10 Simulation and optimization method

For solving the system of equations, initially the partial differential equations (PDE) were transformed into ordinary differential equations (ODE) by using the method of lines with an implicit scheme, and 100 nodes. Then MATLAB © solver "ode15s" was used to solve the ODE system.

The experimental data used are the concentrations of coupling product, arylhalide, and leached Pd that was multiplied by 10^5 factor to have more impact in the estimation objective function (the residual sum of squares). The optimization and curve fitting on the experimental data were carried out using "lsqcurvefit" function on MATLAB ©.

4.3 Simulation results

4.3.1 Model validation with 4-iodoacetophenone experiments

4.3.1.1 Pd(0) supported catalysts

Initially, the experimental results obtained by using Pd(0)-Siliacat, Pd(0)-Strem and Pd(0)/Alumina in the reaction of 4-iodoacetophenone were used in the parameters estimation (Table 17). The impact of each parameter was inspected and only k_{hom1}, k_{het1} and k_{leach} were found to have an impact on the objective function (the residual sum of squares). Identical values were obtained for all three Pd(0) catalysts. The heterogeneous contribution appears to be negligible for all the solid catalysts tested, even for Siliacat Pd(0) which is reported not to leach [7, 8].

Table 17 kinetic parameters for 4-iodoacetophenone with different catalysts[a]

Parameters	**Estimated value**
$k_{hom1}(mol^{-1}m_L^3\,s^{-1})$	5.48±0.2
$k_{hom2}(mol^{-1}m_L^3)$	$6.91\cdot10^{-9}$(no impact)
$k_{het1}(mol^{-1}m_L^3s^{-1})$	$(1.02\pm0.9)\cdot10^{-7}$ (slight impact)
$k_{het2}(mol^{-1}m_L^3)$	$5.67\cdot10^{-9}$(no impact)
$k_{leach}(mol^{-1}m_L^3s^{-1})$	$(4.56\pm0.5)\cdot10^{-9}$
$k_{deact}(s^{-1})$	$1.00\cdot10^{-5}$(no impact)
$k_{ads}(s^{-1})$	$1.00\cdot10^{-8}$(no impact)

[a]: estimated by using the experimental results of Pd(0)-Siliacat, Pd(0)-Strem and Pd(0)/Alumina.

The validity of the model and the parameters obtained is demonstrated by the parity plot by using the retained parameters, showing a good agreement between the computed and the experimental 4-iodoacetophenone concentrations for the 3 different catalysts at different flow rates (Figure 36, Figure 37).

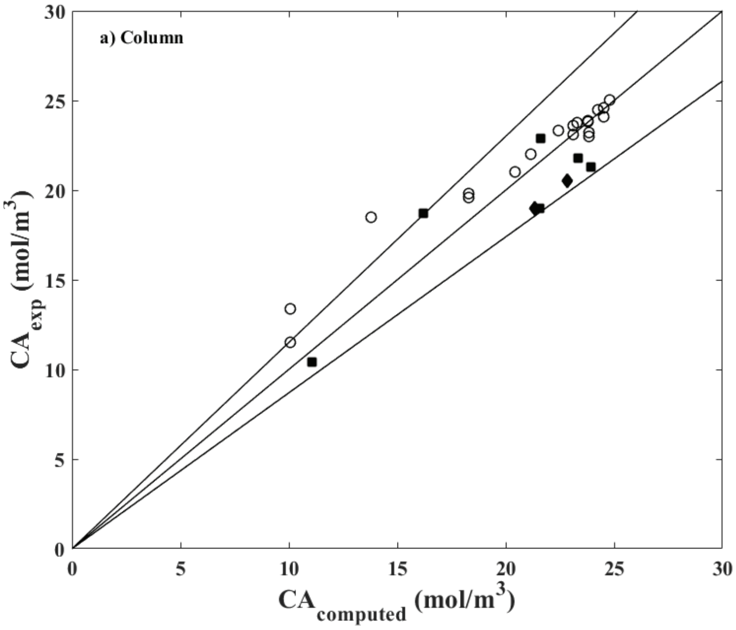


Figure 36 Parity plot of best fit for 4-iodoacetophenone and leached Pd concentrations at column outlet for different Pd(0) catalysts (Pd(0)-Siliacat(empty circles), Pd(0)-Strem (black squares), Pd(0)/alumina (diamonds)).

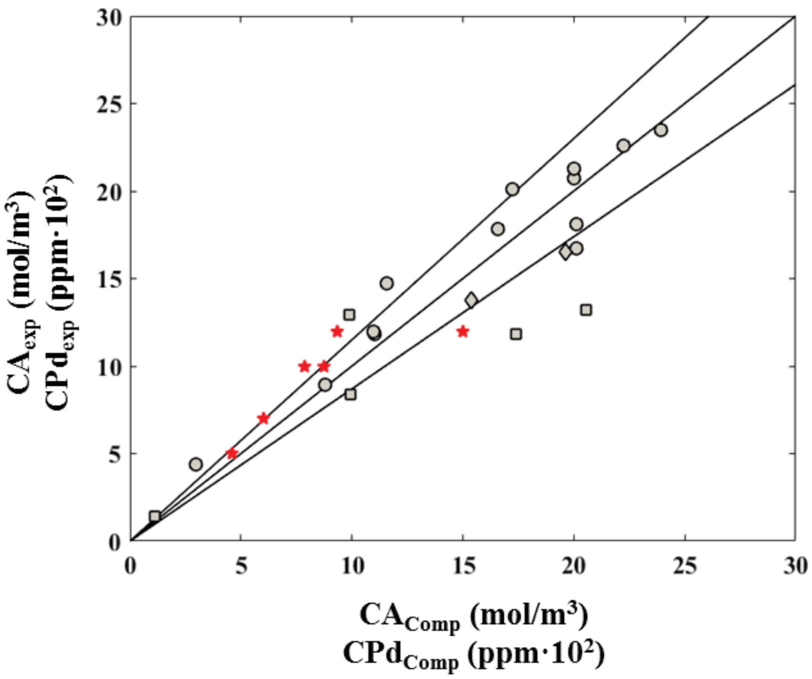


Figure 37 Parity plot of best fit for 4-iodoacetophenone and leached Pd concentrations at tube outlet for different Pd(0) catalysts (Pd(0)-Siliacat(black circles), Pd(0)-Strem (black squares), Pd(0)/alumina (diamonds), $Pd_{leaching}$ (red stars))

The variation of reaction rates inside the column (continuous lines) and the empty tube (dashed lines) (Figure 38) are determined by using the estimated kinetic constants (Table 17). The homogeneous rate is dominant compared to the other rates, confirming the homogeneous nature of active species, which follows the same conclusions published by other authors for aryl iodide [9, 10, 11, 12]. The decrease of the homogeneous rate in absence of deactivation is due to the decrease of the reagents concentration by conversion (right axis).

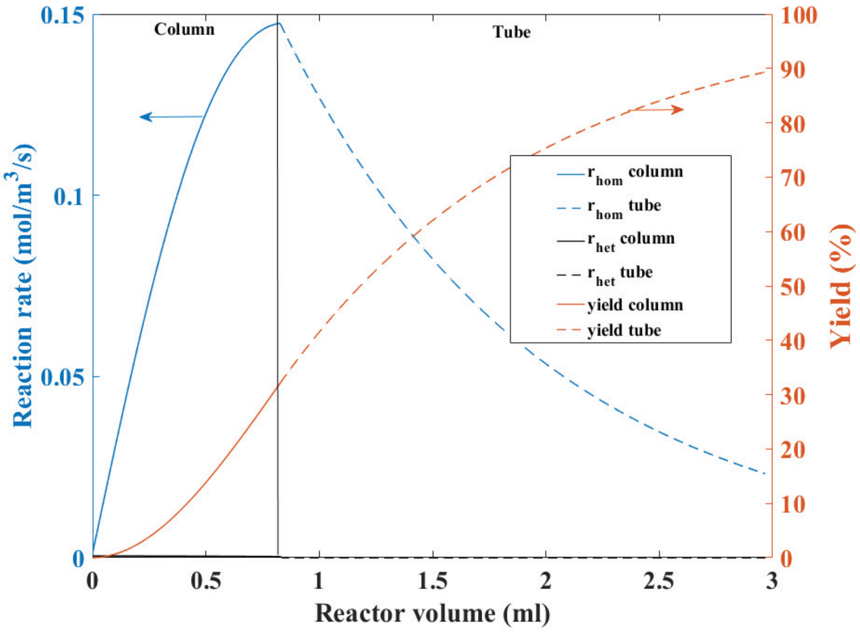


Figure 38 Simulated homogeneous vs. heterogeneous reaction rates and conversion inside the reactor for 4-iodoacetophenone. Continuous line (column), dashed line (tube).

Conditions: Pd(0)-Siliacat, m_{Pd0}= 16.7 mg, $V_{Lcolumn}$= 8.31 ml, V_{Ltube}=2.14 ml, Q=0.6 ml/min, $t_{on\text{-}flow}$= 50 min. For Pd leaching see (Appendix 14).

4.3.1.2 Tests with other catalysts

The previously obtained kinetic parameters (Table 17) were tested with other catalysts ($Ce_{0.2}Sn_{0.79}Pd_{0.01}O_{2-\delta}$, Pd/C/foam and Pd(II)-DPP-Siliacatat) without any fit, in order to check their predisposition to leaching. Figure 39 shows the parity plot between the computed concentrations and the experimental ones. The $Ce_{0.2}Sn_{0.79}Pd_{0.01}O_{2-\delta}$ catalyst shows a good predicted conversion at column and tube outlet with a predicted Pd leaching value of 0.065 ppm near to the experimental one 0.07 ppm. Furthermore, Pd/C/Foam and Pd(II)-Siliacat show a predicted conversion lower than the experimental one, with a lower predicted Pd leaching, respectively 0.07 ppm vs. 0.36 for Pd/C/Foam and 0.004 ppm vs. 0.53 ppm for Pd(II) -DPP-Siliacat. In order to understand this different behavior, each catalyst will be analyzed separately by following the method:

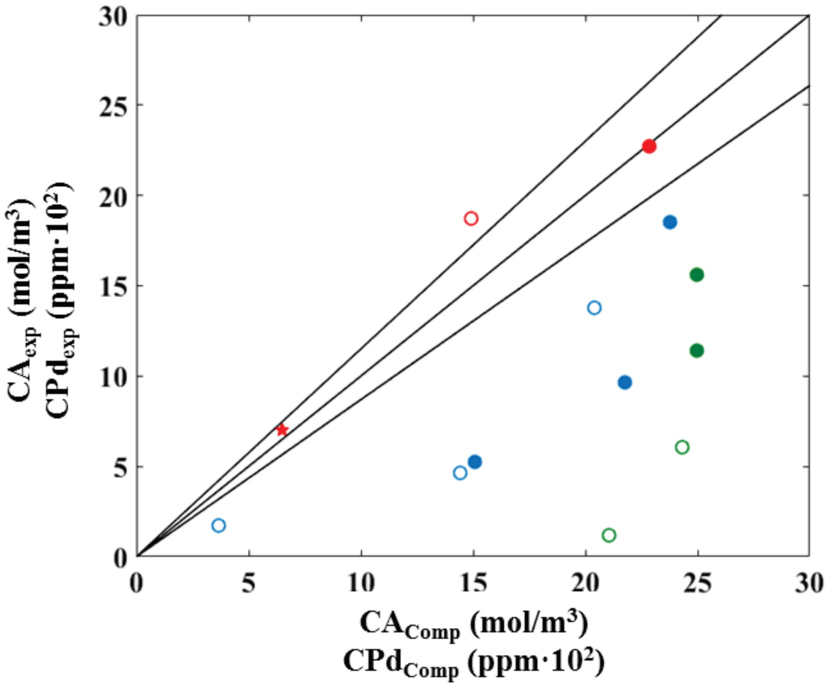


Figure 39 Parity plot of best fit for 4-iodoacetophenone at column and tube outlet for other Pd(0) catalysts ($Ce_{0.2}Sn_{0.79}Pd_{0.01}O_{2-\delta}$ (red circles), Pd/C/Foam (blue circles), Pd(II)-Siliacat/Foam (green circles) and $Pd_{leaching}$ (stars)). Filled circles (column), empty circles (tube).

4.3.1.2.1 Method used for the parameter estimation with other catalysts

Step 1: the previously obtained kinetic parameters (Table 17) are firstly used without fit.

Step 2: If the results obtained in step 1 are not good, the homogeneous kinetic parameter (k_{hom}) is fixed, by assuming that the same homogeneous species are present, and a new parameter estimation is performed for the other parameters (k_{het}, k_{leach}, k_{deact} and k_{ads}).

Step 3: If the previous steps did not show a good prediction of the experimental results, then all parameters are used for a new estimation.

4.3.1.2.2 Pd/C foam catalysts

For Pd/C/Foam the quantity of experimental leaching was higher than the mean leaching obtained for other Pd(0) catalysts (0.07 ppm vs 0.36 ppm), thus a new estimation was made for Pd/C/Foam and the obtained leaching constant was higher than other catalysts (k_{leach} = $(4.07\pm0.4)\cdot10^{-8}$), by just changing the leaching constant the new parity plot confirms the homogeneous nature of mechanism (Figure 40). This homogeneous nature was studied and confirmed in details by Jeng-Shiou et al. for Suzuki-Miyaura reaction [1] and by other authors for Heck reaction [13].

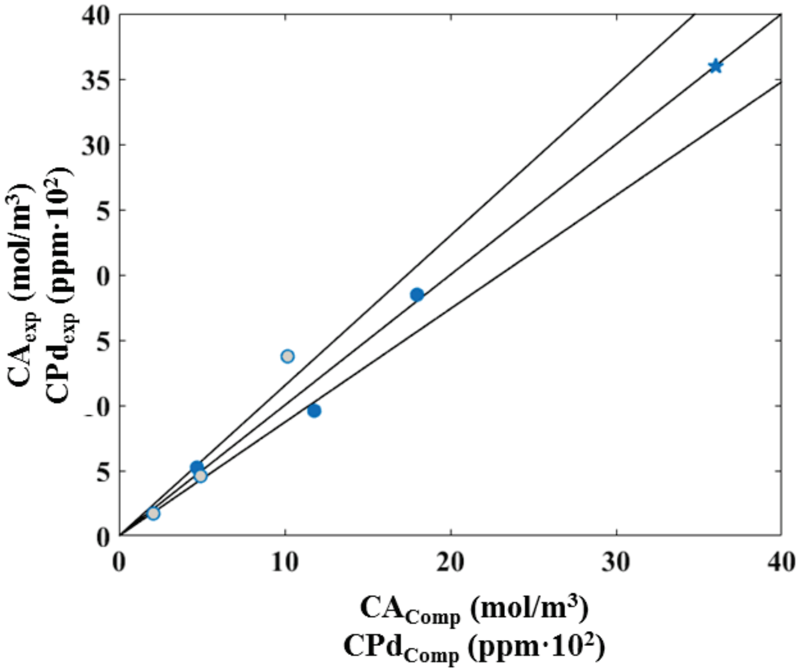


Figure 40 Parity plot of best fit for 4-odoacetophenone concentration at column and tube outlet and leached Pd concentration for Pd/C/Foam. Filled circles (column), empty circles (tube), $Pd_{leaching}$ (blue star) (ppm10^2)

As obtained with the other Pd(0) catalysts, the heterogeneous rate was negligible compared to the homogeneous one. However a deactivation process of the leached Pd was found (k_{deact} =(7±0.5)10^{-3}) (Figure 42).

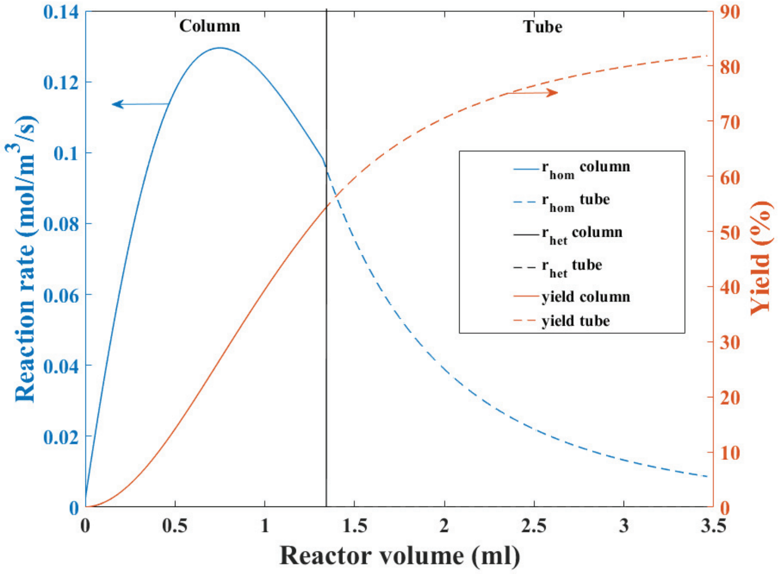


Figure 41 Simulated homogeneous vs. heterogeneous reaction rates and conversion inside the reactor for 4-iodoacetophenone. Continuous line (column), dashed line (tube).

Conditions: Pd/C/Foam, m_{Pd0}= 3.47 mg, $V_{Lcolumn}$= 1.33 ml, V_{Ltube}=2.14 ml, Q=0.6 ml/min, $t_{on-flow}$= 80 min.

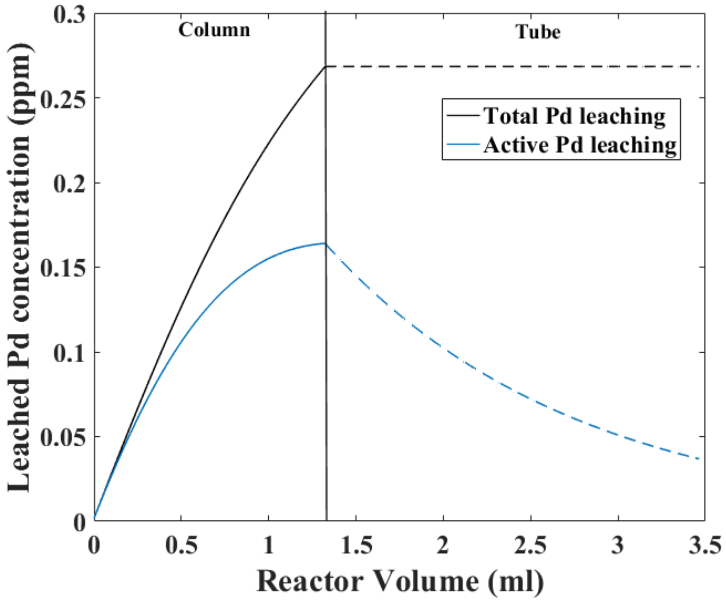


Figure 42 total and avtive leached Pd for Pd/C/Foam. **Conditions:** see **Figure 41**

4.3.1.2.3 Pd(II) supported complex

In the case of the Pd(II)-DPP supported on silica (Pd(II)-DPP-Siliacat), the experimental Pd leaching was remarkably higher than the one obtained for Pd(0) supported catalysts (0.53 ppm), thus a new estimation (Figure 43) was done with this catalyst, leading to parameters with the same homogeneous activity and more leaching. An important total heterogeneous activity (Table 18) was found inside the column compared to the homogeneous one (Figure 44), but the initial heterogeneous TOF was largely lower than the homogeneous one (89.1 mol/mol$_{Pda}{}^{S}$/h vs. 500,000 mol/mol$_{Pda}{}^{L}$/h).

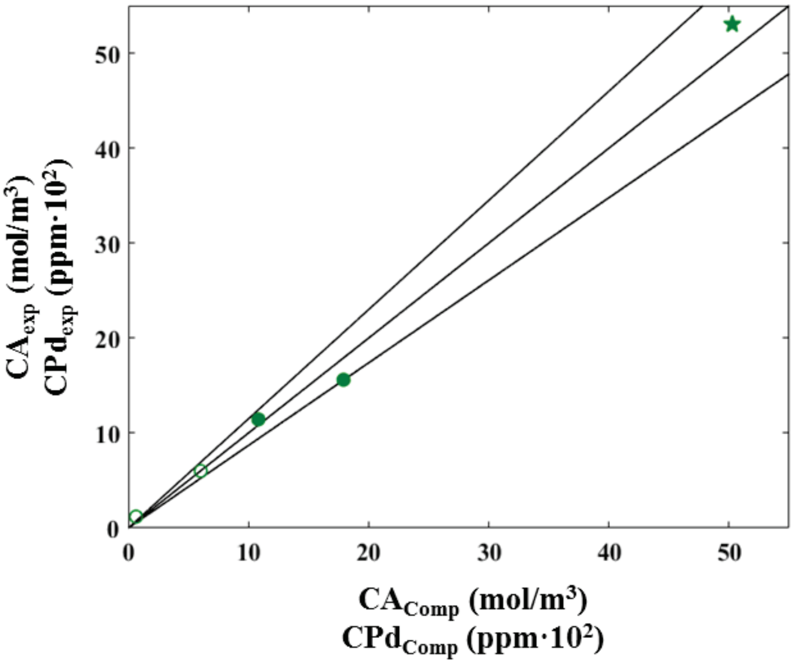


Figure 43 Parity plot of best fit for 4-iodoacetophenone concentration at column and tube outlet for Pd(II)-DPP-Siliacat. Filled circles (column), empty circles (tube), Pd$_{leaching}$ (green star) (ppm10^2)

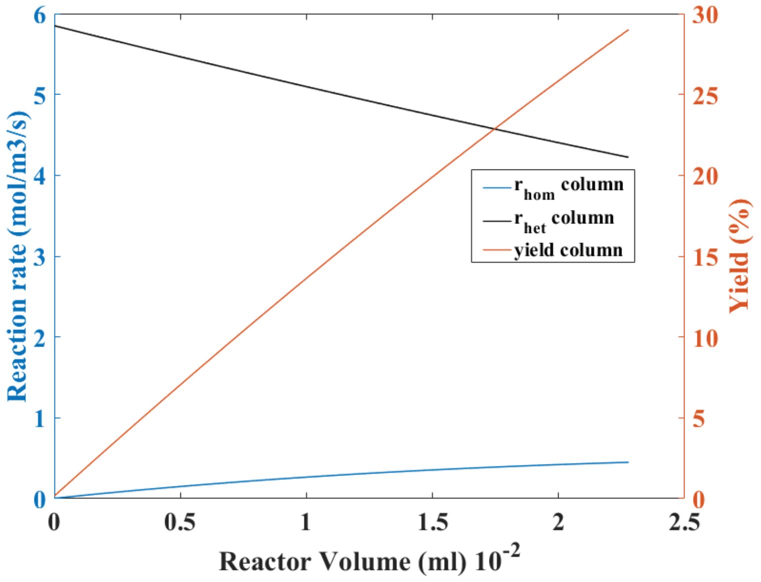


Figure 44 Homogeneous vs. heterogeneous reaction rates and conversion inside the column for 4-iodoacetophenone with Pd(II)-DPP-Siliacat. Continuous line (column), dashed line (tube).

Conditions: Pd(II)-Siliacat, m_{Pd0}= 0.6 mg, $V_{Lcolumn}$= 0.023 ml, Q=1 ml/min, $t_{on\text{-}flow}$= 40 min.

Table 18 Final estimated kinetic parameters for all catalyst with 4-iodoacetophenone

	k_{hom} $(mol^{-1}m^3\ s^{-1})$	k_{het} $(mol^{-1}m^3\ s^{-1})$	k_{leach} $(mol^{-1}m^3\ s^{-1})$	k_{des} (s^{-1})	k_{ads} (s^{-1})
Pd(0)/SiO_2 Siliacat	5.48±0.2	$(1.02\pm0.9)\cdot10^{-7}$	$(4.56\pm0.5)\cdot10^{-9}$	0	0
Pd(0)/SiO_2 Strem					
Pd(0)/Alumina					
$Ce_{0.2}Sn_{0.79}Pd_{0.01}O_{2-\delta}$					
Pd/C/Foam			$(4.07\pm0.4)\cdot10^{-8}$	$(7\pm0.3)\cdot10^{-3}$	0
Pd(II)-DPP/SiO_2 Siliacat		$(9.90\pm0.2)\cdot10^{-4}$	$(6.75\pm0.7)\cdot10^{-7}$	$(2\pm0.1)\cdot10^{-2}$	0

To conclude this part, it is possible to describe the behavior of very different catalysts by the same homogeneous Pd activity and different heterogeneous, leaching and deactivation constants, indicating that the homogeneous reaction seems to be controlled by the same active species at concentration of Pd in solution as low as 100 ppb, with a negligible heterogeneous contribution for Pd(0) supported catalysts. The distinct leaching and deactivation kinetic constants for some catalysts seem to depend on the nature of the support or the use of a ligand, however more analyzes are required to confirm these dependencies (TEM, SAXS/WAXS,…).

One should mention that more complex models involving several homogeneous species (mononuclear Pd species, Nps Pd species, etc.), as advocated by other research teams [14], could be developed. Without performing the work, the results could be given: more complex models will work as well! Simply, because more parameters are used. As Johnny von Neumann was used to say:" with four parameters I can fit an elephant, and with five I can make him wiggle his trunk." [15]. In such a situation, the simpler model is the best. Furthermore, a "cocktail catalyst" model would likely give the same proportion of more active species and less active species for all catalyst precursors. Last with more results tomorrow (EXAFS, SAXS/WAXS, etc.) we might be able one day to reach a better understanding of these mechanisms, closest to the truth.

4.4 Application to Chloro and Bromo derivatives

Previously, the homogeneous nature of the coupling mechanism for 4-iodoacetophenone was confirmed by using a variety of Pd supported precursors. The experimental results in the previous chapter (Chapter 3) with the chloro and bromo homologues (4-chloroacetophenone and 4-bromoacetophenone) showed a different behavior inside the empty tube. In the tube no conversion for the aryl chloride and a lower homogeneous contribution for the aryl bromide were observed, with relatively high Pd leaching. Thus, this different behavior was analyzed in this section, by using two possible explanations:

- chloro and bromo derivatives react via a dominant heterogeneous mechanism.
- chloro and bromo derivatives react via a homogeneous mechanism like the iodo counterpart but with a higher deactivation.

The model that was built and validated with 4-iodoacetophenone was used to simulate these possible mechanisms with the operating conditions (Table 19). Note that the aim of this section is not to quantify the experimental results, but to open a qualitative discussion about the possible mechanisms for such experimental behavior.

Table 19 General operating conditions used for simulations

Simulation parameters	**values**
Column volume (ml)	0.83
Tube volume (ml)	2.14
$m_{\text{Solide Pd}}$ (mg)	16.73
Liquid flow rate (ml/min)	1
Reaction time on flow (min)	50

4.4.1 First hypothesis: dominant heterogeneous mechanism with leaching of inactive Pd species

4.4.1.1 Case1: negligible activity in the empty tube for the chloro compound

When the 4-chloroacetophenone was used in SMR, no activity inside the empty tube was detected, despite a Pd leaching as high as 0.2 ppm. Thus only a heterogeneous constant and a leaching constant were used in this simulation (Table 20).

Table 20 simulation parameters for pure heterogeneous mechanism with inactive Pd leaching

$k_{hom}\ (mol^{-1}m^{3}\ s^{-1})$	0
$k_{het}\ (mol^{-1}m^{3}\ s^{-1})$	$1.72\cdot10^{-5}$
$k_{leach}\ (mol^{-1}m^{3}\ s^{-1})$	$9.71\cdot10^{-9}$
$k_{des}\ (s^{-1})$	0
$k_{ads}\ (s^{-1})$	0

As mentioned in Figure 45, a pure heterogeneous mechanism (dark line in right axes) gave only conversion inside the column (continuous line) without any conversion inside the empty tube (dashed lines). Furthermore inactive Pd leaching in the solution (Figure 45 (b)) can be a result of support solubilization by the base, or generation of thermodynamically stable inactive Pd complexes [15].

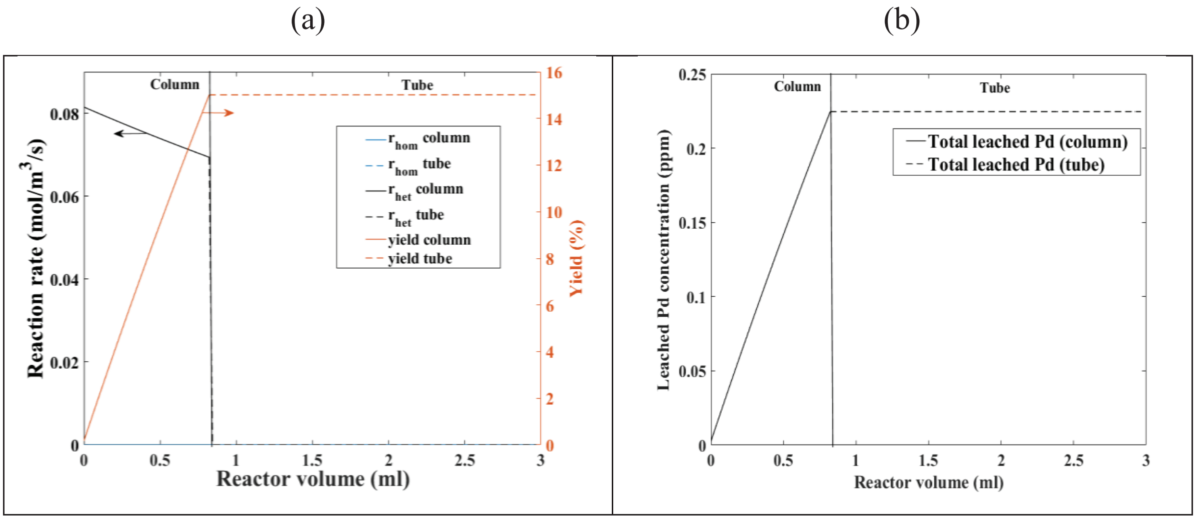


Figure 45 a) homogeneous vs. heterogeneous reaction rates and conversion inside the reactor for pure heterogeneous mechanism. b) homogeneous Pd concentration profiles inside column and empty tube continuous line (column), dashed line (tube).

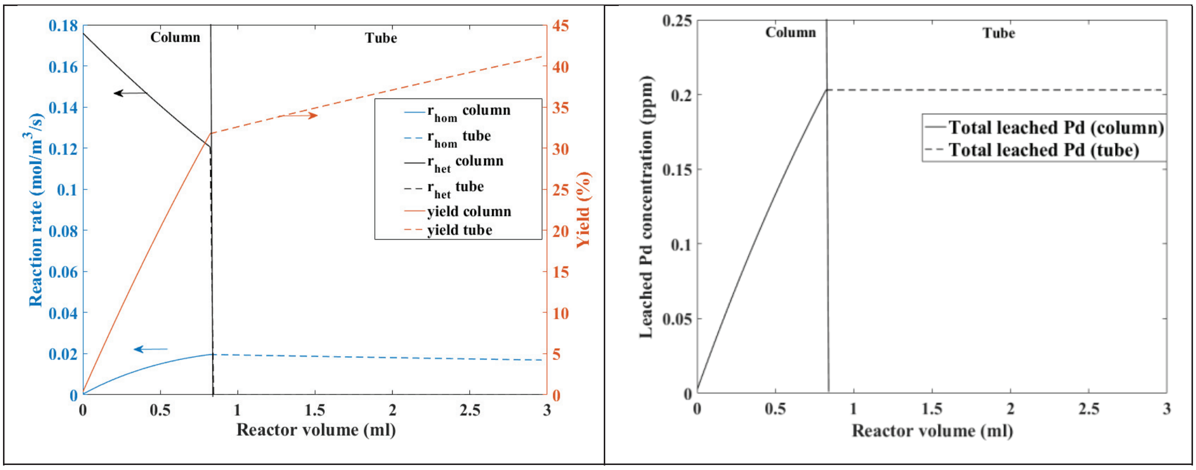
4.4.1.2 Case2: slight activity inside the empty tube for bromo derivative

In the case of 4-bromoacetophenone, a slight homogeneous conversion was found inside the empty tube, with concomitant Pd leaching (0.2 ppm). This suggests the presence of possible homogeneous and heterogeneous mechanisms in the same time. Simulation parameters used are presented in Table 21.

Table 21 simulation parameters for dominant heterogeneous mechanism with inactive Pd leaching

$k_{hom}\ (mol^{-1}m^3\ s^{-1})$	0.6
$k_{het}\ (mol^{-1}m^3\ s^{-1})$	$3.72{\cdot}10^{-5}$
$k_{leach}\ (mol^{-1}m^3\ s^{-1})$	$9.71{\cdot}10^{-9}$
$k_{des}\ (s^{-1})$	0
$k_{ads}\ (s^{-1})$	0

This time the homogeneous reaction rate is not negligible compared to the heterogeneous one (Figure 46 (a)), because it’s the origin of the conversion inside the empty tube, the same Pd leaching level (0.2 ppm) was obtained (Figure 46 (b)).



(a) (b)

Figure 46 (a) homogeneous vs. heterogeneous reaction rates and conversion inside the reactor for dominant heterogeneous mechanism. (b) homogeneous Pd concentration profiles inside column and empty tube.

4.4.2 Second hypothesis: homogeneous mechanism with important catalyst deactivation

The heterogeneous dominant mechanism seems to explain very well the behavior of chloro and bromo, however this time the second hypothesis was simulated taking in account an important catalyst deactivation, and a possible redeposition of the Pd in solution [16], 9].

4.4.2.1 Case1: negligible activity in the empty tube for the chloro compound

The parameters used for this simulation are regrouped in Table 22, the obtained results (Figure 47 (a)) shows that the conversion continuously increases inside the column without any conversion inside the empty tube. Furthermore, the leached Pd quickly deactivate when it leaves the reservoir of Pd (column). It is thus supposed that two types of Pd in solution can be found, active and inactive Pd in the solution (Figure 47 (b)).

Table 22 simulation parameters for homogeneous mechanism with high deactivation

$k_{hom}\ (mol^{-1}m^3\ s^{-1})$	5.45
$k_{het}\ (mol^{-1}m^3\ s^{-1})$	0
$k_{leach}\ (mol^{-1}m^3\ s^{-1})$	$9.71 \cdot 10^{-8}$
$k_{des}\ (s^{-1})$	0.1
$k_{ads}\ (s^{-1})$	0.13

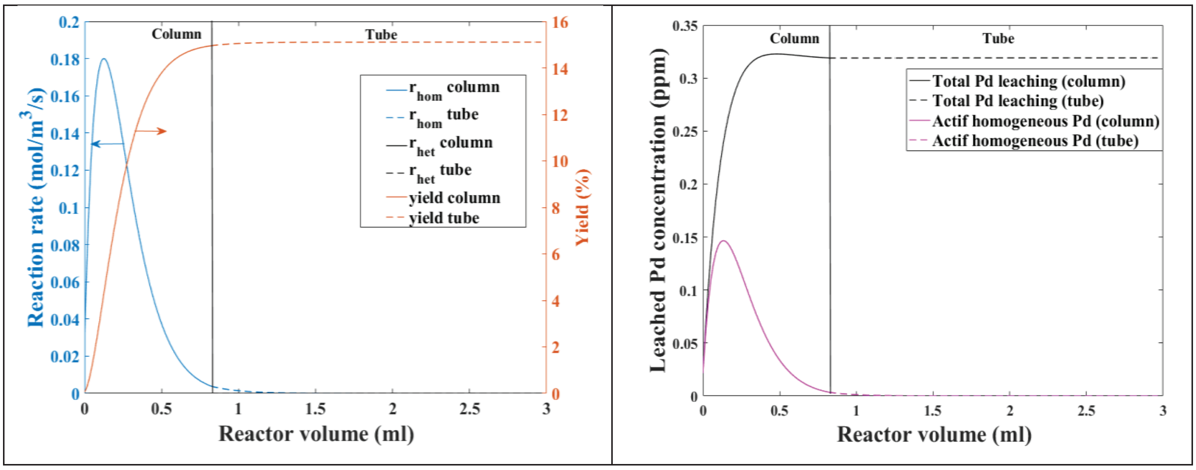


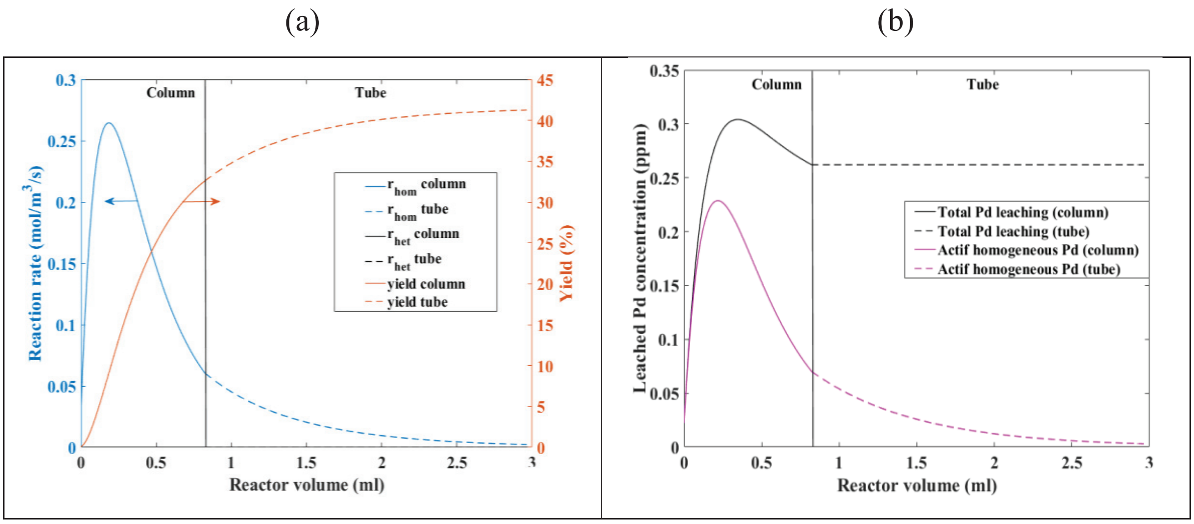
Figure 47 (a) homogeneous vs. heterogeneous reaction rates and conversion inside the reactor for homogeneous mechanism with deactivation. (b) homogeneous total and inactive Pd concentration profiles inside column and empty tube.

4.4.2.2 Case2: slight activity inside the empty tube for bromo derivative

When the same parameters are used as in Table 22, and only the deactivation kinetics was decreased indicating a lower deactivation process (Table 23), a homogeneous contribution could be found inside the empty tube (Figure 48 (a)), because the active Pd species are not instantaneously deactivated after leaving the column, a continuous decrease of active species inside the tube was found (Figure 48 (b)).

Table 23 simulation parameters for homogeneous mechanism with high deactivation

$k_{hom}\ (mol^{-1}m^3\ s^{-1})$	5.45
$k_{het}\ (mol^{-1}m^3\ s^{-1})$	0
$k_{leach}\ (mol^{-1}m^3\ s^{-1})$	$9.71\cdot10^{-8}$
$k_{des}\ (s^{-1})$	0.025
$k_{ads}\ (s^{-1})$	0.13


(a)

(b)

Figure 48 (a) homogeneous vs. heterogeneous reaction rates and conversion inside the reactor for homogeneous mechanism with slight deactivation. (b) homogeneous total and inactive Pd concentration profiles inside column and empty tube.

4.4.3 Comments on the two possible mechanisms

It was found that both mechanisms could be used to account for the behavior of chloro and bromo derivatives (when the split flow test was used, with only the concentration of leached Pd in the solution (ICP-MS) and the conversion at tube and column outlet as available information).

It means that when a catalytic system is investigated using the split-reactor, the absence of conversion in the empty tube does not rule out the presence of the homogeneous mechanism.

In order to get a clearer vision and to give a justified conclusion, other analysis are required to identify and quantify the presence of the Pd readsorption before and after the reaction (TEM) but also under the reaction conditions in situ to check if the adsorbed Pd is active or not. Furthermore, the characterization of Pd species in solution at reaction condition to determine their nature, size, and morphology is also required; techniques like SAXS/WAXS are suggested for this.

When all, the information are collected, kinetic parameters became decoupled and a more general model can be used by taking in account the Pd dispersion and the size variation of supported Pd and/or possible leached Pd Nps.

4.5 Conclusion

In this chapter, a reactor model was proposed based on justified hypothesis and experimental remarks. It was firstly tested and validated by an estimation with the experimental results of Suzuki-Miyaura reaction of 4-iodoacetophenone with three different Pd(0) supported catalysts (Pd(0)/SiO_2 Siliacat, Pd(0)/SiO_2 Strem and Pd(0)/Alumina). Moreover, the obtained parameters were used without any fit to predict the behavior of $Ce_{0.2}Sn_{0.79}Pd_{0.01}O_{2-\delta}$. However, other fits were required with Pd(0)/C/Foam and Pd(II)-DPP/SiO_2 Siliacat, that showed a deactivation process of Pd in solution with an important heterogeneous contribution with the Pd(II) supported catalyst. The final results showed that the homogeneous contribution of all tested catalysts could be represented by the same kinetic constant, indicating the same nature of the catalytic species with an initial TOF in the range 500,000 $mol_{product}/mol_{leachedPd}/h$. Interestingly, the initial TOF measured for the homogeneous Herrmann-Beller catalyst in chapter 2 was 100,000 $mol_{product}/mol_{Pd}/h$ meaning that the leached species are more active than the palladacycle.

In a second part, the same model was used to explain the different behavior of chloro and bromo homologues. Two approaches were used, a pure heterogeneous and a pure homogeneous with Pd deactivation. Both approaches could be used with success to explain this behavior and more experimental analysis are suggested to characterize the leached and supported Pd species in order in-situ and ex-situ in order to get clear information about the nature of true catalysis.

4.6 List of abbreviations

C_A	Concentration of 4-iodoacetophenone in liquid phase (mol m^{-3})
C_{As}	Concentration of 4-iodoacetophenone on the surface of the catalyst (mol m^{-3})
C_{Pd}^{L}	Total Pd concentration in the liquid pahse (mol m^{-3})
C_{Pda}^{L}	Active Pd concentration in the liquid pahse (mol m^{-3})
C_{Pd}^{s}	Concentration of total supported Pd on the solid (mol m^{-3})
C_{Pda}^{s}	Concentration of active supported Pd on the solid (mol m^{-3})
D_{ax}	Axial dispercion (m^2 s^{-1})
D_e	Effective diffusivity (m^2 s^{-1})
D_t	Internal diameter of the reactor
k_{ads}	Kinetic constant of Pd adsorption (s^{-1})
k_{deact}	Kinetic constant of Pd deactivation (s^{-1})
k_{leach}	Kinetic constant of Pd leaching (mol^{-1}m^{3}s^{-1})
k_{het}	Heterogeneous kinetic constant $(mol^{-1}m^{3}\ s^{-1})$
k_{hom}	Homogeneous kinetic constant $(mol^{-1}m^{3}\ s^{-1})$
l	Column length (m)
L	Characteristic length (m)
m$_{Pd}$	Pd mass inside the column (mg)
ppm	part per million (mg$_{Pd}$/Kg$_{solution)}$
Q	Liquid flow rate (ml min^{-1})
$r_{deact-Column}$	Rate of liquid Pd deactivation inside the column (mol^{1}m^{-3}s^{-1})
$r_{deact-tube}$	Rate of liquid Pd deactivation inside the tube (mol^{1}m^{-3}s^{-1})
$r_{leaching}$	Pd leaching reaction rate (mol m^{-3} s^{-1})
r_{hom}	Homogeneous reaction rate (mol^{1}m^{-3}s^{-1})
r_{het}	Heterogeneous reaction rate (mol^{1}m^{-3}s^{-1})
r_{obs}	Observed reaction rate (mol^{1}m^{-3}s^{-1})
R$_t$	Residence time (s)
t$_{on-flow}$	Time on flow (min)

u	Liquid velocity (m s^{-1})
$V_{Lcolumn}$	Liquid volume of the column (ml)
V_{Ltube}	Liquid volume of the tube (ml)
ΔH	Reaction enthalpy (kJ mol^{-1})
C_W	Weisz-Prater Criterion ($C_W = \frac{r_{obs}\cdot L^2}{D_e\cdot C_{As}}$)
Re	Reynold number ($Re = \frac{u\,D_t}{\vartheta}$)

4.7 Bibliographie

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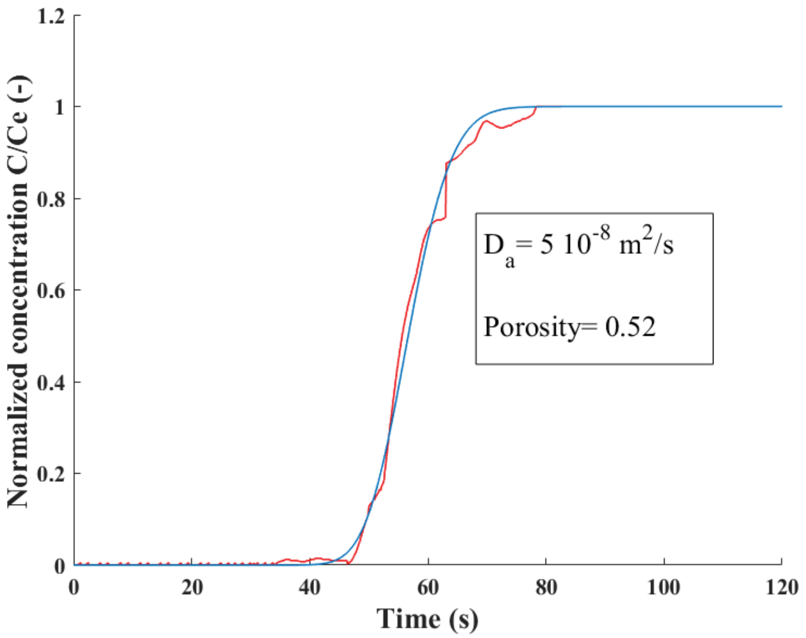
APPENDICES

A.1 **Residence time distribution for column**

In order to determine the value of axial dispersion coefficient and the liquid volume in the prepared columns, a typical column was filled by C18 functionalized silica with the same particle size distribution as the used catalysts (20-100 μm). Then a residence time distribution test was performed by using a step tracer experiment (uracil (Sigma Aldrich) as a tracer that is not adsorbed by the functionalized C18 Silica), then a dispersive packed bed reactor model was used to estimate the porosity and the axial dispersion [1].



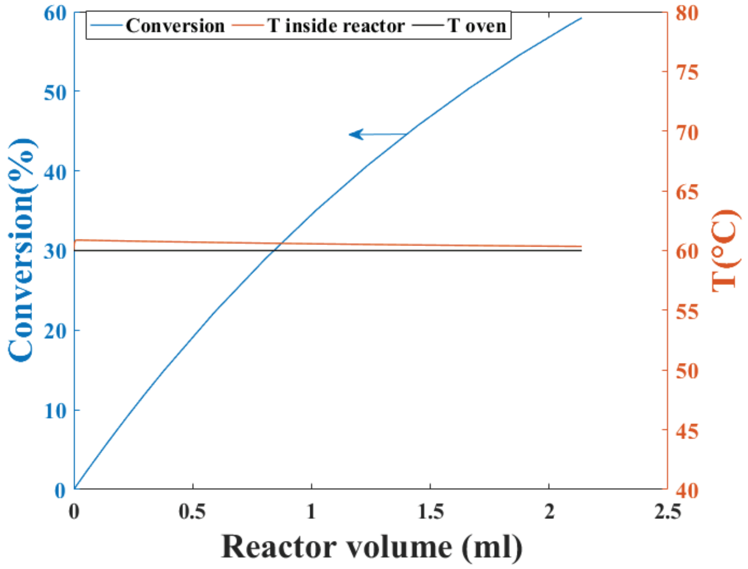
Appendix 12 Experimental vs. Optimized step response profile of normalized concentration at column outlet

Conditions: Q_L=0.46 ml/min, Column: length 5 cm, diameter: 0.46 cm.

[1] Levenspiel, Chemical Reaction Engineering, 3rd ed. Wiley, 1999.

A.2 Isothermal behavior

Reaction rate (mol/m3/s)	$r = k_0 \cdot C_{Pd} \cdot \exp(\frac{-E_a}{RT}) \cdot (1 - X) \cdot C_A$
Energy balance	$\frac{dT}{dV} = \frac{U \cdot a \cdot (T_a - T) - r \cdot \Delta H}{F_{A0}(C_{PA} + X\Delta C_P)}$
Molar balance	$\frac{dX}{dV} = \frac{-r}{F_{A0}}$
with: k_0: homogeneous kinetic constants ($m^3 mol^{-1} s^{-1}$), T: temperature inside the reactor (°C) a: specicif area (m^{-1}) , Ta: Oven temperature (°K), ΔH_{RX}: Reaction enthalpy ($J\ mol^{-1}$), Cp_i: specific heat of reactants ($J\ mol^{-1}K^{-1}$), θ_i: molar fraction, U: overall heat transfer coefficient ($J\ m^{-2}K^{-1}s^{-1}$), X: conversion, F_{A0}: inlet flow rates ($mol\ s^{-1}$).	

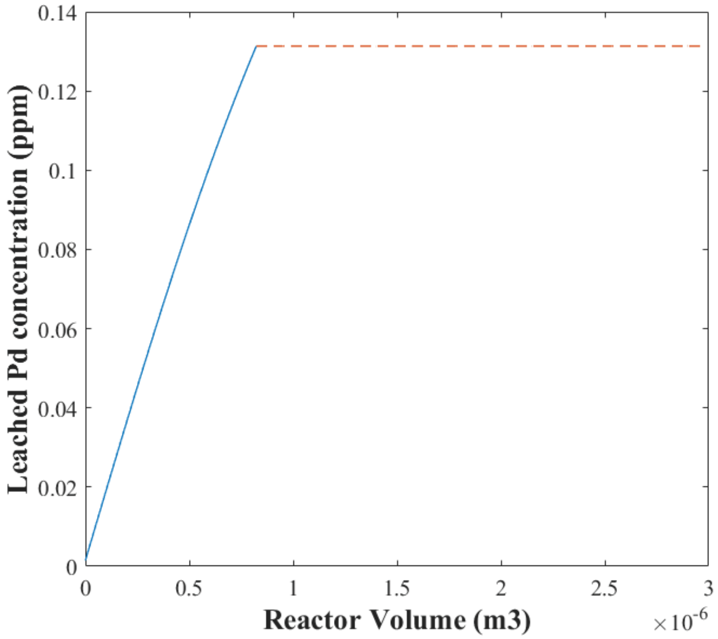


Appendix 13 Isothermal behavior of the reactor

A.3 Matrix correlation for parameter estimation (Table 17)

	k_{hom1}	k_{hom2}	k_{het1}	k_{het2}	k_{leach}	k_{deact}	k_{ads}
k_{hom1}	1.00	-0.86	0.00	0.00	0.56	-0.69	0.30
k_{hom2}	-0.86	1.00	0.01	0.01	-0.57	0.59	-0.01
k_{het1}	0.00	0.01	1.00	0.89	-0.27	-0.07	0.00
k_{het2}	0.00	0.01	0.89	1.00	-0.27	-0.07	0.00
k_{leach}	0.56	-0.57	-0.27	-0.27	1.00	-0.84	-0.01
k_{deact}	-0.69	0.59	-0.07	-0.07	-0.84	1.00	-0.02
k_{ads}	0.30	-0.01	0.00	0.00	-0.01	-0.02	1.00

A.4 Homogeneous Pd concentration profiles inside column and empty tube



Appendix 14 homogeneous Pd concentration inside column and empty tube continuous line (column), dashed line (tube). **Conditions:** see **Figure 38**

Conclusions and Outlooks

The main objective of this thesis was to re-investigate ligand-free Pd SM coupling and answer at least three fundamental questions:

- Could more and more general evidences be gathered to prove that the leached Pd species are active for the SM reaction?
- Are the catalytic properties, i.e. activity, selectivity, of the leached Pd species independent from the solid precursor?
- Does the leaching process depend on the nature of the solid precursors?

In this context, a new approach (chapter 1) was used to analyze the bibliography reporting on three types of catalysts: homogeneous molecular complexes, heterogeneous supported molecular complexes, and heterogeneous supported Pd crystallites or nanoparticles (NPs). This last class of catalysts was analyzed by supposing that a homogeneous activity could explain the published results. That analysis was coupled with a balanced state of the art review of the known methods to determine the homogeneous vs heterogeneous nature of catalysis. The main two conclusions were: (i) not just a single method but a combination of methods is generally proposed and required to determine the nature of the catalysis and (ii) the catalytic activity of the leached Pd species – when analyzed – is generally either underestimated or overlooked. Following this literature survey, a strategy was proposed to prove that the leached Pd species are active for the SM reaction.

First of all (chapter 2), a kinetic study was performed to assess the detailed catalytic activity of a reference molecular catalyst, i.e. the Herrmann-Beller palladacycle. Both microkinetics and analytic models based on the well accepted SM mechanism were used.

Albeit the active species could not be the same, it was anticipated that the mathematical form of the rate law obtained for the palladacycle would be the same for other homogeneous Pd species and, if they exist, of homogeneous active species.

New perspectives are drawn on the effect of the reagents and co-reagents (the base and the phenylboronic acid). Thus, it has been demonstrated that the phenylboronic acid reacts instantaneously with the base, the resulting boronic salt being the active reagent in the catalytic cycle. Such results enlighten the literature controversy on the effect of these reagents. Last, a simple but robust kinetic law is proposed to account for homogeneous catalytic activity.

Second, a new experimental tool “Split Flow Reactor” was described in chapter 3. It allows to identify and quantify the homogeneous and the heterogeneous contribution in catalyzed SM reaction. The reactor was developed and used to investigate a variety of 7 heterogeneous precursors and aryl halides (iodo, chloro and bromo) in chapter 3. For the aryl iodide, an important homogeneous catalysis is evidenced in the empty tube, whatever the nature or the initial oxidation state of the solid precursor Pd (Pd(0) or Pd(II)) or the support (SiO_2, Alginate, Charcoal,..). On the other hand, the chloro derivative was converted only in the presence of the catalytic solid and the bromo homologues showed a homogeneous activity between the iodo and chloro. Furthermore, Pd leaching was surprisingly at the same level for the three derivatives, in the range 0.1 to 0.5 ppm. These results demonstrates that the “Split Flow Reactor” is an inexpensive and valuable test to evaluate the contribution of a homogeneous mechanism. It could also be easily used to investigate other chemical systems. The main conclusion of this chapter is the proof that leached Pd species are indeed involved in the SM reaction, at least for iodo and bromo derivatives.

Third, a reactor model was built in chapter 4, which allows to quantitatively assessing the homogeneous and heterogeneous contributions. For that goal, the kinetic law determined in chapter 2 and the experimental results with 4-iodoacetophenone with 3 catalyst precursors from chapter 3 were used to implement and validate a reactor model that was used in chapter 4. The model was then tested with success for the other catalysts precursors. Remarkably, all the catalytic systems display the same value for the kinetic parameters which seems to indicate that the same homogenous active species are involved which also means that the catalytic properties, i.e. activity, selectivity, of the leached Pd species independent from the solid precursor. Also, all heterogeneous solid Pd precursors exhibit a negligible heterogeneous contribution, except for Pd(II)-DPP-Siliacat, but the supported Pd, in this last, presents a lower initial TOF compared to the homogeneous one (89.1 mol/mol$_{Pdas}$/h vs. 500,000 mol/mol$_{PdaL}$/h). The leaching mechanism has been approached albeit not in details. It is shown that the iodo-aryl reagent is mainly responsible for the leaching and depends on the nature of the solid Pd precursor. Finally, the behavior of chloro and bromo homologues could successfully be explained by using either a dominant heterogeneous mechanism or a pure homogeneous mechanism. More knowledge about the actual mechanism for chloro and bromo derivatives should involve more sophisticated analysis to characterize the nature of the Pd species at the surface of the support or inside the solution before and after the reaction.