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Individuation and study of supported catalytic systems suitable for practically useful C-C cross-coupling reactions performed in batch and/or flow conditions

By

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Abstract

In the context of organic chemistry, and in particular in the C-C cross-coupling reactions catalyzed by transition metals such as nickel or palladium, the use of green and environmental friendly synthetic methodologies is of growing interest for both Academy and Industry. In this context, the replacement of homogeneous metal catalysts with heterogeneous systems and the replacement of classical batch-type reactors with continuous flow systems is today considered of primary importance.

In fact, the supported catalysts can offer numerous advantages compared to those homogeneous, resulting much more attractive from both scientific and applied point of view: in general, they are more practical, versatile, and stable are often they can be handled and used in the presence of air and/or moisture; moreover, they can simplify the isolation operation and make possible to separate and recover the catalyst by simple filtrations or centrifugations, as well as to obtain products containing negligible amounts of metals. Furthermore, in many cases the supported catalyst can be reused several times. However, it should be noted that, in general, supported systems are less active than corresponding homogeneous systems, but this lower catalytic activity can be compensated by increasing reaction temperature and catalytic load.

On the other hand, continuous flow systems have several advantages compared to conventional batch reactors: better mass and heat transfer, greater safety when working with explosive or toxic reagents, more accurate control of reaction times, easier manipulation of air and moisture sensitive reaction mixtures, high surface/volume ratio, and, above all, a much greater ease of scale-up (for example, by connecting several reactors in parallel). Furthermore, flow reactors facilitate the integration of multi-step process, allowing to gain time compared to usual batch procedures. All these features are in agreement with the principles of green chemistry, but also with industrial needs and demands.

Therefore, the possibility to combine the favourable features of continuous-flow systems with those of supported catalysts within the same fluidic device (Continuous-Flow Reactor, CFR), can represent a significant strategic advantage.

However, as regards the C-C cross-coupling reactions, on the basis of literature data it is possible to affirm that the supported catalysts, and in particular their use in continuous flow reactors, present problems and difficulties not yet actually overcome: costs, difficult

availability, need for high catalytic loads, inadequate performance (compared to the homogeneous catalysis) are the main limitations of most of the supported catalysts studied for these cross-couplings; also, the continuous flow reactors so far used for these reactions have similar limits, that make them not really useful from an applied and industrial point of view.

Bearing in mind all these considerations, we put forward the idea to verify if cheap, simple, practical, easily available and industrially acceptable supported catalysts ("purpose-build" and/or commercial), and continuous-flow packed-bed systems, could be conveniently applied in C-C cross-coupling reactions carried out in rather green and industrially acceptable conditions.

In particular, we decided to explore, both in batch and continuous-flow mode, four commercial catalysts easily available, very different in nature and quite cheap (PdEnCat-40, Fibrecat-1007, $PdCl_2(PPh_3)_2$-PS and $Pd(PPh_3)_4$-PS) and three new "home-made" catalysts, prepared "via" Metal Vapour Synthesis (Pd/PVPy, Pd/MCM-41 and Pd-Cu/PVPy), testing them in C-C bond forming reactions of particular interest, such as Mizoroki-Heck alkenylations, Sonogashira-type alkynylations and Suzuki-Miyaura reactions.

Our investigations demonstrated that under rather simple and convenient conditions (a moderate excess of bases, a moderate amount of organic solvents, or in some cases, in only water or in absence of solvents, under aerobic atmosphere and with very low metals loading (0.10-0.15 mol% of Pd), these systems are really efficient in promoting C-C cross-coupling reaction of several iodoarenes and bromoarenes.

In fact, as regards Sonogashira-type cross-coupling, it was thus established that the reaction conditions more satisfactory, taking account of efficiency, generality and applicability in flow reactors, involve the use of DMF/H_2O as solvent and pyrrolidine as base, at 95 °C and in aerobic atmosphere. In these conditions, low doses (0.1 mol% of Pd) of all the catalysts studied showed a fairly good and similar efficiency with several aryl iodides; however some specific features of each catalyst have been identified, thanks to a suitable series of reactions carried out with a limited, but significant, variety of 1-arylalkyne and aryl iodides (electron-rich or electron-neutral). Unfortunately, in these conditions none of the catalysts tested was able to significantly promote the alkynylation of 4-iodophenol (**8ab**, a highly electron-rich compound). But it was also pointed out a more serious limitation of these systems: all were unable, under the employed reaction conditions, to catalyze efficient reactions between aryl halides and aliphatic 1-alkynes.

It was also carried out a first series of pilot trials on the possibility to use these catalysts in Sonogashira-type alkynilations of bromoarenes. It has thus been established, that only the Fibrecat 1007 (**2**) and the Pd-Cu/PVPy (**7**) are able to efficiently promote the alkynilation of bromobenzene, thanks to the use of a "one-pot" domino Halex-Sonogashira process, carried out by the addition of KI in the reaction mixture under suitable conditions, carefully developed. However, even these conditions require low metals loads and are not affected by the presence of air.

As regards the Suzuki-Miyaura cross-coupling, it was established that the reaction conditions more satisfactory, taking account of efficiency and generality, involve the use of DMF/H_2O or EtOH/H_2O as solvents, and potassium phosphate as base, at 125 °C and in aerobic atmosphere. In these conditions, low doses (0.15 mol% of Pd) of all the catalysts studied showed a fairly good and similar efficiency with several aryl and alkenyl bromides or aryl iodides; however some specific features of each catalyst have been identified, thanks to a suitable series of reactions carried out with a limited, but significant, variety of aryl boronic acids and aryl bromides (electron-rich, electron-neutral or electron-poor). Unfortunately, in these conditions none of the catalysts tested was able to significantly promote the reaction with 3-bromothiophene (**8j**).

It was also carried out a first series of pilot trials on the possibility to use these catalysts in Suzuki reaction of chloroarenes. It has thus been established that only the Fibrecat 1007 (**2**) and Pd/MCM-41 (**6**) are able to efficiently promote the reactions of aryl chlorides electron-neutral (**8m**) and electron-poor (**8o** and **8l**), thanks to the use of potassium carbonate (rather than K_3PO_4) as base for **2**, and using only water (rather than DMF/H_2O or EtOH/H_2O) as solvent for **6**.

As regards the Mizoroki-Heck cross-coupling, it was established that the reaction conditions more satisfactory, taking account of efficiency, generality and applicability in flow, involve the classic use of NMP as solvent and tripropylamine as base, at 125-150 °C in anaerobic atmosphere. In these conditions, low doses (0.10 mol% of Pd) of all the catalysts studied showed excellent and similar efficiency; however some specific features of each catalyst have been identified, thanks to a suitable series of reactions carried out with a limited, but significant, variety of aryl iodides (electron-rich or electron-neutral), affording very good yields with low leaching (0.12-1.50 % of the total Pd load) at 125°C with Pd/PVPy and Pd-MCM-41. The reaction with aryl bromides were efficiently promote affording good yields with moderate leaching (1.55-1.90 % of Pd) at 150 °C with the above home-made catalysts; it is worth of note that, in these conditions none of the commercial catalysts tested was able to significantly promote the reaction with aryl bromides, and that all give rise to an extremely high leaching of Pd (9-10 % of Pd).

However, to allow efficient Heck-type reactions with these commercial catalysts, they have been developed suitable *Jeffery-type* conditions, thanks to the addition of TBAB in the reaction mixture. However, even these conditions require low metals loads and are not affected by the presence of air. Under these new conditions the alkenylation of bromobenzene (**8b**) with butyl acrylate (**24**) gave moderate or good yields (30-70 %), depending on the catalyst, but with different bromoarenes, such ethyl-4-bromobenzoate (**8i**) and 4-bromo-nitrobenzene (**8d**), much better results were obtained. Moreover, in our optimized conditions the leaching of Pd is moderate (less than 2.0 % of Pd).

Given the good results obtained in batch processes, after that, we focused our attention on the development and study of original packed-bed mini-reactors of design and construction extremely simple and cheap, using as filling the four commercial catalysts; only for the Mizoroki-Heck reactions we user also Pd/PVPy (**5**) and Pd/MCM-41 (**6**) catalysts.

Our packed-bed flow mini-reactors are made with simple PTFE tubes (an inexpensive, versatile, chemically resistant, easily available and manipulable material) filled with supported catalysts.

In general, our reactors (columns) are prepared with 0.2 cm internal diameter (outside diameter 0.3 cm) Teflon tubes; their length varies from case to case, but usually is between 2 and 8 cm. The catalyst, pure or mixed with glass beads (150-200 μm), is introduced into the reactors as a *slurry* or *dry*. Then the catalyst is compressed (2-10 bar) and conditioned with about 5 mL of the reaction solvent.

We tested our simple packed-bed mini-reactors in the above mentioned C-C cross-coupling reactions, initially using the conditions optimized in batch. In these conditions, all the catalysts packed in our reactors showed a fairly good efficiency in a model reaction, allowed high conversions within several minutes of residence time; the productivities were comparable to those obtained in batch and the leaching was contained (even if dependent on the type of reaction, catalyst and packing-type).

In fact, in the Sonogashira reaction the best performances were achieved packing the reactors with the commercial catalysts mixed with an approximately equal volume of the above mentioned glass beads. These reactors allowed high conversions within 25-30 minutes, with a low total catalytic load and a limited leaching of Pd. However also in this case have been highlighted some differences in behavior and specificity of the catalysts under examination.

For regard the catalyst, the best performances were obtained packing the reactors with $PdCl_2(PPh_3)_2$-PS (**3**): these results may already be classified among the best so far reported in the literature.

As regards the Suzuki-Miyaura reaction, the best results were obtained packing the reactors with the commercial catalysts mixed with a volume beads approximately 10 times greater of the above mentioned catalysts. These reactors allowed high conversions within 30-40 minutes, and keep them for long time (18-23 hours); the better results were obtained with Fibrecat 1007 (**2**) and $PdCl_2(PPh_3)_2$-PS (**3**) showing an efficiency comparable to that obtained in batch (about 600 in flow, respect to 660 in batch mode) with a similarly low total catalytic load and a limited leaching of Pd.

On the other hand, under the conditions optimized in batch mode, all the catalysts packed in our reactors showed a fairly good efficiency with iodobenzene in Mizoroki-Heck reactions, allowed high conversions within 20-30 minutes of residence time, with productivities comparable to those obtained in batch and a limited leaching of Pd.

However, the best performances in this reaction were achieved packing the reactors with the laboratory-prepared catalysts Pd/MCM-41 (pure) and Pd/PVPy (pure or mixed with an approximately equal volume of glass beads). In fact, these reactors afforded high conversions for 60-100 hours, with a residence time of 22-25 minutes, high productivity, and a very low leaching of Pd, with various aryl iodides; to TEM studies of the spent catalysts showed an increase in mean particle size respect that observed in a fresh sample. This phenomenon can be attributed to the Ostwald ripening process which may occur under the reaction conditions used.

Moreover, the Pd/MCM-41 (**6**) catalyst, was the only one able to promote the reaction with aryl bromides in continuous-flow condition.

Finally, in the final part of this Thesis work we focused our attention on the synthesis of several natural and/or bioactive compounds such as some cinnamic acids **27g-i** and the cinnamide **28c**, the natural pterostilbene (**13n**) and two new natural derivatives **13o** and **13p**.

In particular, given the good results obtained in the study on Mizoroki-Heck reactions, both in batch and flow conditions we envisioned to build the cinnamic acids **27g-i** and the cinnamide **28c** from the corresponding butyl cinnamates **25**, obtained by Mizoroki-Heck coupling of commercially available precursors (carried out with the better catalysts previously observed, Pd/PVPy (**5**) and Pd-MCM-41 (**6**)).

So our strategy focused on cinnamic acids and cinamides formation involving *i)* a Mizoroki-Heck coupling to form the C-C bond (performed in batch and flow mode), *ii)* an ester hydrolysis reaction to form the cinnamic acids **27** (performed always in batch mode) and *iii)* a classic amidation to form the corresponding cinamides **28** (performed always in batch mode).

Thanks to this procedure, we obtain the desired three interesting cinnamic acids **27g**, **27h**, **27i** in two step, and the cinnamide derivative **28c** in three step, , with good total yields, using in the key step (Mizoroki-Heck coupling) simple and cheap supported catalysts under batch and flow mode.

Furthermore, taking into account the synthetic procedures used in literature to obtain **13n** and **13o**, as well as the good results obtained in our study on the Suzuki reaction with (E)-β-bromostyrenes (paragraph 2.3.4) and those obtained in the synthesis of (E)-β-bromostyrenes starting from corresponding cinnamic acids (paragraph 2.6.), we decided to base our synthetic approach to the preparation of pterostilbene (**13n**) on a key step corresponding of a Suzuki-Miyaura reaction between 4-hydroxy-(E)-β-bromostyrene (**12e**), or 4-t-butyldimethylsilyloxy-(E)-β-bromostyrene (**12f**) and 3,5-dimethoxyphenylboronic acid (**9d**); it is be noted that 13n is a starting material to prepare the two new natural and bioactive compounds **13o** and **13p** by suitable literature procedures of etherification and next migration.

Unfortunately, in this case, the flow process has not provided the same good results obtained in the synthesis carried out in batch mode. In fact during the flow process we observed the complete desilylation of the starting material **12f**, with consequent loss of reactivity in the Suzuki reaction.

The studies summarized above have been the subject of the following communications:

Oral and Poster communications:

I. *XVII National Congress of Catalysis GIC 2013 and XI National Congress of Zeolites Science and Technology, 15-18 September **2013**, Riccione; Poster,* C. Evangelisti, G. Fusini, A. Carpita, R. Psaro; *"Continuous flow Heck coupling reaction using MVS-derived palladium nanoparticles deposited on polyvinylpyridine"*

II. *FineCat 2014- Symposium on heterogeneous catalysis for fine chemicals, 2-3 April **2014**, Palermo; Oral Comunication,* C. Evangelisti, G. Fusini, A. Carpita, R. P. Jumde, A. Mandoli, R. Psaro; *"Palladium particles on polyvinylpyridine supports: Applications in continuous-flow Mizoroki-Heck reactions"*

III. XXV National Congress of SCI, 7-12 September ***2014****, Arcavacata di Rende; Poster,* G. Fusini, A. Carpita, C. Evangelisti, A. Mandoli, R. Psaro; *"Palladium nanoparticles supported on mesoporous silica: applications in continuous-flow Mizoroki-Heck reactions"*

IV. XXXVI National Congress of Organic Chemistry Division of the SCI, 13-17 September ***2015****, Bologna; Poster,* G. Fusini, A. Carpita, F. Gallo, C. Boldrini; *"Catalytic Hunsdiecker reaction in continuous-flow"*

1. Introduction

1.1 Transition metal-catalyzed carbon-carbon cross-coupling reactions: a brief overview

At the dawn of the 21st century, transition metal-catalyzed coupling reactions play a vital role in the production of many industrially important chemicals; in fact, transition metals have a unique ability to activate various organic compounds and through this activation they can catalyze the formation of a wide range of new C-C, C-H, C-N, C-O, C-S, C-P or C-M bonds.**[1]**
However, metal-catalyzed C-C bond formations are undoubtedly one of the most important and useful class of reactions in synthetic organic chemistry: they are of great strategic importance for the chemo-, regio- and stereoselective preparation, from simple and readily accessible reactants, of many complex organic molecules such as pharmaceuticals, agrochemicals and other fine chemicals.**[2]**
This fact was recognized by the award of the 2005 Nobel Prize in Chemistry to Y. Chauvin, R. H. Grubbs, and R. R. Schrock for the formation of carbon-carbon double bonds,**[3]** and of the 2010 Nobel Prize in Chemistry to Richard F. Heck, Ei-Ichi Negishi and Akira Suzuki for the metal-catalyzed formation of carbon-carbon single bonds.**[4]**

Currently all types of cross-coupling reactions promoted by transition metals are the subject of extensive studies aimed to make them more efficient and convenient. However, in recent years both academic and industrial research has devoted a remarkable attention to Heck-type alkenylations**[5]**, Sonogashira-type alkynylations**[6]** and Suzuki-Miyaura reactions**[7]** (see **Figure 1.1.1**), due to their characteristics of generality, efficiency and selectivity, as well as to the applied interest of the compounds that they allow to obtain; moreover these cross-coupling reactions are particularly attractive even for their intrinsic practicality, simplicity and greeness.**[8, 5-7]** These properties result mainly from the fact that such reactions do not require stoichiometric organometallic reagents, or employ non-hazardous and stable organometallics.

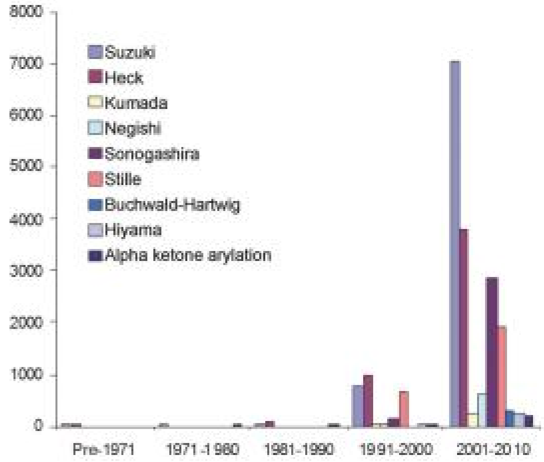


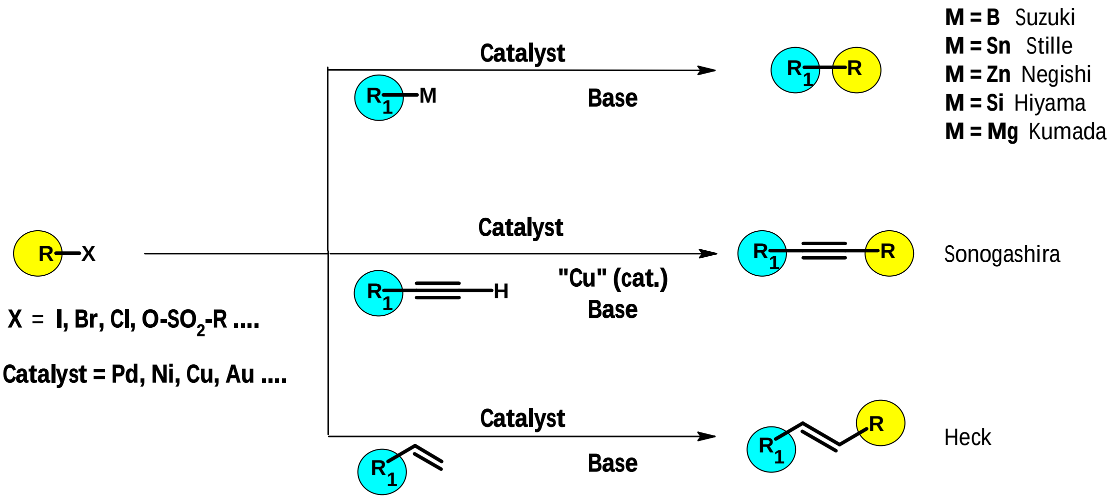
Figure 1.1.1: Growth in the number of publications and patents on named metal-catalyzed cross-coupling reactions.

On the other hand, the development of green synthetic methodologies is of growing interest for both Academy and Industry, not only for their lower environmental impact, but also because they allow a more sustainable chemistry and reduce pollution at the source; resulting in lower costs and increase the feasibility of the processes. In this context, the replacement of homogeneous metal catalysts with heterogeneous systems is today considered of primary importance.**[9]** But in the context of the C-C cross-coupling reactions promoted by transition metals, it is considered very important even the replacement of the classical batch-type reactors with continuous flow systems.

Supported catalysts can offer numerous advantages compared to those homogeneous, and therefore are much more attractive from both scientific and applied point of view. In fact, usually they are more practical, versatile, and stable: often they can be handled and used in the presence of air and/or moisture. But, above all, they can simplify the isolation procedures, being separable and recoverable by filtration or centrifugation; thus they can afford to obtain products containing negligible amounts of metals. Furthermore, in many cases the supported catalyst can be reused several times.**[9h-I, 10]** However, it should be noted that, in general, supported systems are less active than corresponding homogeneous systems, but this lower catalytic activity can be compensated by increasing reaction temperature and/or catalytic load.**[9h-I, 10]**

1.1.1 General characteristics of the C-C Cross-Coupling

All type of C-C cross-coupling reactions are characterized by the metal-catalyzed coupling of an organic electrophile (typically an organic halide or sulphonate) with an organic nucleophile (**Scheme 1.1.1**). The organic halide can be an sp-, sp^2-, or sp^3- hybridized carbon with any halogen or pseudohalogen leaving group. The majority of research has focused on sp^2 carbon–halogen bonds.

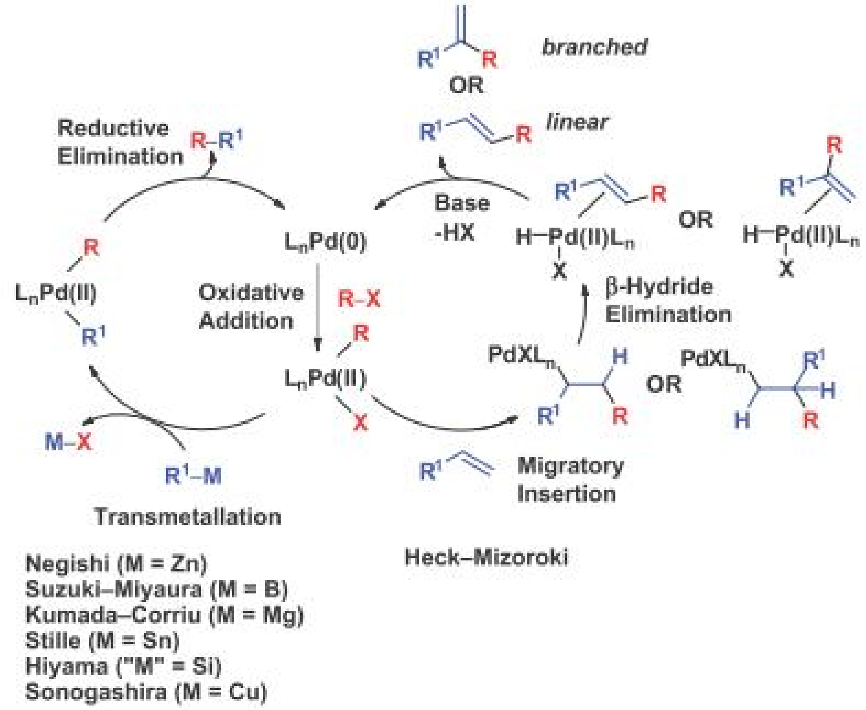


Scheme 1.1.1 : General scheme for C-C cross-coupling reactions

As results from **scheme 1.1.1**, a variety of name reactions have been developed using organometallic carbon nucleophiles, stoichiometric or catalytically generated *in situ*; the Heck coupling of aryl halides and alkenes also falls into this class of reactions, although it involves a different mechanism.**[1d, 2]**

Generally the most widely used metal catalyst are transition metal complexes from group 8-10, especially nickel and palladium.**[11]** The reason for which these metals are the most common ones originates from their Ni(II)/Ni(0) and Pd(II)/Pd(0) ease of redox exchange, which is an indispensable condition for the catalytic cycle to be completed. Between these two metals, however, Pd catalysts have been demonstrated to have more advantages for cross-coupling reactions than those of Ni. **[12]** For example, they tend to be less sensitive to oxygen and are believed to be less toxic. Moreover, unlike Ni catalysts, Pd complexes tend to react without the intervention of radical intermediates, which can eventually lead to side products such as those from homocoupling. Consequently, Pd-catalyzed cross-coupling reactions have been the most developed ones.

The generally accepted mechanisms for these palladium-catalyzed cross-coupling reactions are depicted in **Scheme 1.1.2.[1d, 13]** Common to all types of these coupling reactions is the *oxidative addition* of the organic halide (or pseudohalide) to the catalytically active Pd(0) species (directly introduced or preformed in *situ*), which initiates the catalytic cycle. At this stage the processes diverge (**Scheme 1.1.2**).



Scheme 1.1.2: General catalytic cycle for C-C cross-coupling reactions

In all couplings involving stoichiometric organometallics (Suzuki, Negishi, Kumada, Stille and Hiyama) or organometallic species catalytically generated *in situ* (Pd/Cu co-catalyzed Sonogashira), the reaction progresses by *transmetallation* of the organometallic species to generate a Pd(II) intermediate bearing the two organic coupling partner fragments. Subsequent *reductive elimination* results in C-C bond formation with the regeneration of Pd(0) species to re-enter into the catalytic cycle (**Scheme 1.1.2)**. However, in the case of copper-free Sonogashira-type reactions the terminal alkyne coordinates to the Pd-center and subsequently undergoes a base assisted deprotonation, thus forming directly the species that give raise to the *transmetallation* (see paragraph 2.4).

Alternatively, In the Mizoroki–Heck coupling (with not require the use of stechiometric or catalytic organometallic compounds), the oxidative addition is followed by co-ordination of an alkene to the Pd(II) species, followed by its *syn migratory insertion*. The regioselectivity of this insertion depends on the nature of the alkene, the catalyst, and the reaction conditions employed. The newly generated organopalladium species then undergoes *syn β-hydride elimination* to form the alkene product. Subsequently, base-assisted elimination of HX from [L$_n$Pd(H)(X)] occurs to regenerate the Pd(0) catalyst to re-enter into the cycle.**[14]**

The success of all these reactions depends on how many challenging coupling partners are successfully coupled without any deleterious incidents, within a reasonable time frame. This is related to the **TON** (defined as the absolute number of passes through the catalytic cycle before the catalyst become deactivated) and **TOF** (defined as the number of passes through the catalytic cycle per unit time) of the catalyst.**[15]**

Although the catalytic cycles involve a Pd(0) complex, many simple and cheap Pd(II) and Pd(0) complexes can be generally used as catalyst precursors; a lot of these (the most used ones) are commercially available, for example $Pd(OAc)_2$, $PdCl_2(PPh_3)_2$, $Pd(PPh_3)_4$, $PdCl_2(dppf)$, $Pd_2(dba)_3$ and (η^3-allyl-$PdCl)_2$. While moderate success can be achieved in coupling activated, electronically poor aryl iodide substrates with these commercial Pd complexes, they are not particularly useful for a wide range of difficult substrates or less active organohalides. **[1d, 16**]
In fact, the oxidative addition of organohalides or pseudo-halides to Pd(0) (most frequently observed is the oxidative addition of organic halides of sp2 carbons), show a relative reactivity rate that decreases in the following order; C-I > C-OTf /C-OTs > C-Br >>> C-Cl, and fluorides are almost inert. **[17]**.
Therefore, a variety of auxiliary ligands and Pd complexes have been used/developed to improve conditions, substrate scope and catalytic activity (**Figure 1.1.2**). **[13, 14c, 16, 18]**
Classically, addition of tri-substituted phosphine ligands has given favorable improvements, with PPh_3 being the most commonly employed.**[16]** Moreover, as the electron density of the phosphine ligand increases, the oxidative addition of the organohalide becomes more facile, which was first demonstrated with use of $P(^tBu)_3$ in Pd-catalyzed amination reactions.**[16, 19]**
This ligand not only improved oxidative addition enough to use aryl chlorides as reagents, but its steric bulk also enhanced product elimination from the Pd center.**[19b, 20]** Although many examples of coupling reaction enhancement via bulky, electron-rich phosphines have been published, catalytic coupling with deactivated aryl chlorides and alkyl-halides remains a challenge.
More recently, same excellent results, have also been obtained by developing new and more efficient Pd(II) and/or Pd(0) complexes phosphine-free, such as palladacycles (introduced into cross-coupling reaction by Hermann and Beller in 1995),**[21]** palladium-N-heterocyclic carbene ligands (Pd-NHC) complex (developed by Nolan and coworkers),**[22]** and other complexes systems. These systems, that generally are less toxic and, more robust, have shown a higher thermal stability and a superior catalytic performance, even when replacing the most active phosphine ligands.[**21,22**]

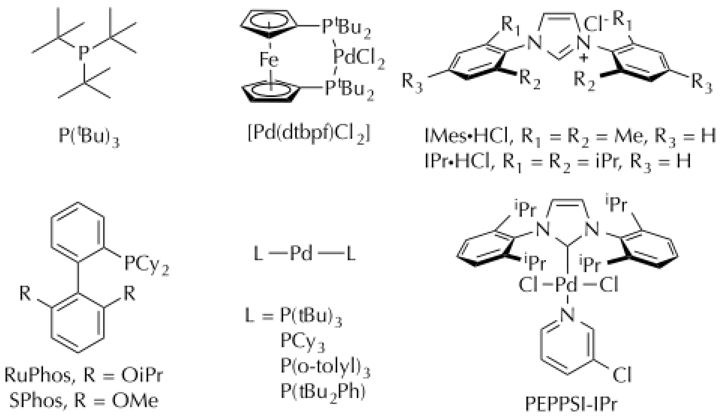


Figure 1.1.2: Phosphines, NHC ligands and their Pd complex developed and used

For example, palladacycles show high activity in Heck reactions with aryl chlorides (up to a TOF of 200000),**[23],** and the combination of palladacycles with NHC ligands has enabled the reaction of substituted aryl chlorides in Suzuki-type reaction at room temperature within 1h.**[24]**

Unfortunately, usually these systems are not satisfactory from the point of view of their industrially application. The principal drawbacks are the availability, stability, and cost of the palladium complexes and ligands; furthermore, homogeneous palladium catalysts are usually not reusable and the products are frequently contaminated by residual palladium and ligands, which can be difficult to separate from the end product.**[25]**

1.1.2 Heterogeneous catalysts in C-C cross-coupling[9a-d, 26]

Classically, homogeneous palladium catalysis has gained enormous relevance in various coupling reactions such as Heck, Stille, Suzuki, Sonogashira, and Buchwald-Hartwig reactions. Many products could be synthesized by this methodology for the first time or in a much more efficient way than before. This type of catalysis provides high reaction rate and high turnover numbers (**TON**) and often affords high selectivities and yields. The properties of such Pd catalysts can be tuned by ligands, such as phosphines, amines, carbenes, dibenzylideneacetone (dba), etc. Proper ligand design has led to catalysts that tolerate weak leaving groups such as chloride, exhibit higher TON and reaction rates, have improved lifetimes, and are suitably stable to run the reactions without the exclusion of water or air and at lower temperatures. The structure of the catalytic species is often known, and structure-activity relations could be established.

Unfortunately, one key point for the industrial development and practical use of homogeneous ligands/catalysts is the contamination of products by palladium and/or ligands (principally phosphines that are toxic and difficult to remove) and separation of products from the catalytic media. These problems have to be overcome in the application of homogeneous Pd-catalyzed coupling reactions in industry and are still a challenge.**[10b, 27]** In fact, from an industrial as well as an economic standpoint, a process free from soluble ligands and/or metals, and a simple removal of the catalyst would provide much needed impetus to the development of improved catalyst systems.

Recent developments of ligand-free Pd catalysts (with excellent TON and/or TOF) have provided interesting and practically important alternatives to ligand-assisted methodologies**.[5b, 28]** For example, the introduction of quaternary ammonium salts by Jeffery**[28a]**; applied as additives in Heck reaction with ligand-free Pd(II) catalysts, they provided excellent results under mild reaction conditions even in aqueous medium. Ammonium halides do not only serve as phase-transfer agent, but the anions also stabilize the catalytically active form of Pd; however the palladium is of course never really “ligand-free” (it is always coordinated by substrates). On the other hand, as already indicated above, homogeneous catalysis has a number of drawbacks, in particular, the lack of reuse of the catalyst or at least the problem of recycling of the catalyst. This leads to a loss of expensive metal and ligands and to impurities in the products and the need to remove residual metals.**[25b, 29]**

Thus, it is not surprising that the heterogenization of homogeneous catalytic reactions has attracted great attention from a wide range of organic chemists over the last few decades.**[30]** In fact, immobilizations of homogeneous catalysts into insoluble solid supports by covalent bonding, complexation and/or encapsulation enables the easy recovery by filtration or centrifugation and reuse of catalysts following appropriate workup processes.**[27e, 31]**

In supported Pd catalysts, Pd is fixed to a solid support, such as activated carbon (charcoal, for a recent review of application in C-C coupling reactions, see Seki, ref 32a),**[32]** zeolites,**[31b,33]** molecular sieves,**[31b,33]** metal oxides (mainly silica or alumina but also MgO, ZnO, TiO_2, ZrO_2),**[31b, 34]** clays,**[35]** alkali and alkaline earth salts ($CaCO_3$, $BaSO_4$, $BaCO_3$, $SrCO_3$), porous glass,**[36]** organic polymers (polystyrene cross-linked is one of the most widely employed macromolecular supports),**[31b]** or polymers embedded in porous glass.**[37]** Practically all imaginable support materials have also been proposed and applied.

On the other hand, Pd can also be fixed to a solid support as a complex; that is, the ligands are covalently bound to the support. Both techniques allow one to separate the heterogeneous catalyst after the reaction or to reuse it as long as it is not too deactivated or both.**[10b, 37, 38]**

All these supported materials offer several advantageous features in heterogeneous catalysis, such as thermal and moisture stability,**[10a]** selectivity, recyclability and ease of separation from the reaction products (also leading to operational flexibility).

The application of supported Pd was introduced into Pd-catalyzed coupling reactions relatively late (early 1970s) but has been increasingly used up to now, although normally these systems require more drastic reaction conditions than homogeneous catalysts, due to somewhat lower activities. However, this is not a problem as far as the stability of the catalysts is concerned, because they often are relatively stable, In this way, the somewhat lower activities can be compensated to some extent by using higher temperatures and catalyst loadings. For example, Pd/C is one of the earliest forms of heterogeneous catalysts developed. Although it has a long history in hydrogenation and hydrogenolysis catalysis, only recently has it been explored as a catalyst for cross-coupling reactions: under suitable reaction conditions it showed high activity and selectivity even converting aryl chlorides with rates comparable to highly active homogeneous Pd complexes.**[39]** Some industrial applications have already been developed.**[40]**

Currently, a large number of supported catalysts have been successfully applied in a variety of coupling reactions.**[41]** Palladium complexes and Pd nanoparticles involved in dendritic structures have been reported, too **[42]**. For example, Pd/C (in different load, 0.05-5.00 mol% Pd) has been described as an effective catalyst for Suzuki, Heck, Sonogashira and Stille couplings**[9]**, but also Pd nanoparticles supported on microporous and mesoporous supports showed highly catalytic activity in Hech and Sonogashira coupling. More special applications include the use of Pd complexes and (supported) nanoparticles in biphasic systems of immiscible solvents and in ionic liquids**[43]**. In the case of ionic liquids, recycling can be achieved by recharging the ionic liquid phase containing the catalyst with new educts and base after product extraction, washing, and drying**[43,44]**.

At current, a high number of solid-supported Pd catalysts are commercially available (in addition to the classic Pd/C, Pd/SiO_2 and Pd/Al_2O_3, there are, for example, the new Pd EnCat™**[45]**, Pd-Fibrecat®**[46]** and Pd-SiliaCat**[47]** lines of catalysts, as well as other Pd/polymer species)**[48]**. However, they often differ in structure (support and Pd), composition, and activity depending on the supplier.

Catalytical processes in the production of fine and intermediate chemicals have found great interest in industry which is well aware of commercial as well as environmentally sustainable aspects. The individuation of general methods for the transformation of major homogeneous catalysts to give recyclable heterogeneous catalysts is a reasonable idea, combining the positive effects of catalytical performance and practical use.

Generally applicable methods for the transformation of major homogeneous catalysts to give recyclable heterogeneous catalysts are:

- Steric hindrance - occlusion in porous systems**[49]**

The "ship-in-a-bottle" catalyst's main feature is the host-guest interaction which is neither covalent nor ionic. The guest is retained in the zeolite matrix by restrictive pore openings and will, in principle, keep all properties of the homogeneous complex in addition to the advantages offered by the heterogeneous system.

- Impregnation**[49a, 50]**

Most of the heterogeneous catalyst which are in practical use consist of one or more catalytically active compounds which are impregnated on supporting carrier materials. This method can be chosen to immobilise acids and bases as well as salts, oxides or complexes. The major drawback is leaching of one or more component which leads to irreversible deactivation of the catalyst. Physisorption can be enhanced by choosing the appropriate porous, chemical and electronical properties. This leads to catalysts with sufficient long term stability due to, e.g., ionic linkages.

- Grafting**[33b, 49a, 51]**

The immobilisation of organic molecules on inorganic or organic supports by the creation of a covalent bond is called grafting. This stable bond prevents leaching of the grafted moiety. Established homogeneous catalysts have to be chemically modified by the introduction of a suitable linker for the immobilisation by this method. This can also affect the catalytic properties of the active component.

The preferred mode of deposition depends also on the type of support. With oxides and carbon supports, wet or dry impregnation, deposition-precipitation, deposition-reduction, and ion-exchange methods can be applied using most often an aqueous solution of a suitable Pd(II) precursor, such as $PdCl_2$, $Pd(NH_3)_4]Cl_2$, $Pd(NO_3)_2$, H_2PdCl_4, or $[Pd(NH_3)_4](NO_3)_2$. On the other hand, organic solutions of Pd(0) complexes, are also sometimes used.**[33a]** The surface of the support can be covalently functionalized by ligands, such as phosphines, pyridines, or mercaptanes, which form complexes with dissolved Pd salts (grafting technique). This methodology is widely used in polymer-**[41]** and silica-supported**[52]** palladium catalysts and is another method to prepare solid-supported Pd catalysts.**[53]** Finally, solid supported Pd catalysts are prepared by Sol-gel processes, mainly for silica- and alumina-supported Pd catalysts. The support is generated from a monomer, such as tetraethoxysilane or aluminum isopropoxide in the presence of a soluble Pd compound, and eventually a linker. In this way, usually amorphous materials are obtained, where a part of the Pd is encapsulated.

Although the active species in Pd-catalyzed cross-coupling reactions is Pd(0), the metal can generally be used as Pd(0) or Pd(II)**[10a]** on the solid support. In the latter case, in situ reduction to Pd(0) occurs during the application in cross-coupling reactions without the addition of extra reducing reagents, but the generation of the Pd(0) from Pd(II) at the solid support can often be advantageous because species are generated, which exhibit a higher catalytic activity.**[33a, 41, 52, 53]**

The support should provide a mean of easy and rapid recycling of the catalyst and usually has an impact on the activity of the catalytic system. Functional groups, particle size, surface area, pore structure, and acid-base properties are important parameters of the support.**[27e]** The support can affect the catalyst activity either by creating reactive spots at the Pd metal crystallites**[54]** or by improved release of Pd(0) into the solution by leaching.**[32a-d, 55]**

Due to their controlled pore size, microporous and mesoporous materials, such as zeolites, can be advantageous over simple metal oxides. Pd(0) clusters can be encapsulated in these pores: the pore size and structure of such supports can have an important impact on the reactivity and selectivity of those catalysts.**[56]** In particular, the robust nature of the supports and their abilities in stabilizing reactive centers are crucial requirements for durable applications.

1.1.3 Advantages and Drawbacks [57]

Homogeneous and heterogeneous catalysts offer their own distinct advantages.**[58]** On the other hand, from an industrial and environmental standpoint a key question is how to minimize the catalyst cost (economics of the process) and metal contamination of the product (strict requirement for active pharmaceutical product).

These cost and purification demands have spurred significant research in two distinct areas: (i) immobilization of palladium so that it can be recovered and reused and (ii) development of highly active catalysts that are active at low metal concentrations.

Supported catalysts have the inherent advantage of easy separation by simple filtration and very often also of better handling properties. In principle the product is un-contaminated with a transition metal or ligand and allows the catalyst to be recycled into the next reaction. But this is always true?

While the distinction between homogeneous and heterogeneous catalysis seems well-defined, in many cases there may be leaching of the transition metal into solution.

The nature of the active catalyst species in solid support palladium catalyst of the cross-coupling reactions is debatable. There are two extremes either i) the reaction is catalyzed directly by heterogeneous palladium catalysis (Pd/support, Pd clusters, Pd surface) or ii) the palladium leaches from the solid support and catalyzes the reaction homogeneously.

Studies of catalytic activity of heterogenized Pd catalysts in Heck reactions have demonstrated the existence of significant Pd-leaching and important contribution of a soluble catalyst in the main reaction course.**[59]** However, in some cases, the nature of the true catalyst is still ambiguous. In particular for Suzuki reactions, claims exist in the literature supporting both “soluble molecular catalysts” as well as “truly heterogeneous”, insoluble Pd catalysts.**[59a]** One of the main problems exists in the fact that in general, truly active species is only generated in situ whereas the “initial catalyst” can just be regarded as a “precursor”. While experimentally proven ideas of this in situ generation of catalytically active species have been developed in homogeneous catalysis (e.g. pre-reduction of the active metal or ligand dissociation), the situation is by far more complex in heterogeneous catalysis. In fact, identifying the true active catalytic species is critically important for future advances in the rational design of coupling catalysts, and in their applicability in flow systems.

In these instances the question that always remains is whether the catalytic activity resides with the leached metal. In other situations, it is unclear whether a “release and capture” of the transition metal catalyst has occurred.**[60]**

In fact, several study have shown that in many cases the concentration of palladium species in solution commonly increases during the reaction; upon completion, the concentration decreases dramatically due to re-adsorption (re-precipitation) of palladium on the solid support.**[61]** Thus, the solid support probably acts as a “reservoir” of soluble, catalytically active metal species. However, the actual nature of the catalytically active species may depend on the specific properties of the support material (surface area, morphology, porosity) and active centers (dispersion, metal-support interactions, mobility on the surface, oxidation state), all parameters to be considered when using palladium catalysts heterogenized.**[62]**

Unfortunately, in the case of systems with “release and capture” of the metal, the recovered supported catalysts are often inactive, and consequently not recyclable, because the metal particles are increased during the “*release-capture”* process. For example, a TEM investigation of an highly active Pd/C catalyst tested for the Heck coupling of bromobenzene and styrene at

140°C before and after a 20 h reaction shows that the uniform distribution of the Pd nanoparticles in the fresh catalyst is lost after the reaction, while the Pd crystallites average size increases from 2.4 nm to 23 nm (one order of magnitude) and the same crystallites agglomerate into larger particles.**[63]**

General leaching of palladium is responsible for most catalytic processes observed for most "heterogeneous" Pd catalysts developed thus far. This does not necessarily limit the practical synthetic advantages of these materials, although the cases for which the catalyst is recyclable and leaching is limited must be distinguished from options for which the catalyst is strongly modified and the original activity is dramatically reduced after one run.

1.2 Continuous-Flow Chemistry (A short introduction)

The petrochemical industry relies on large-scale continuous chemical processes which display high-level efficiency for many years.**[64]** In contrast, the synthesis of fine chemicals and pharmaceuticals is traditionally performed in well-defined batches both in laboratory practice and on an industrial production-scale.

In recent years, the continuous-flow organic synthesis has developed into an established tool both for academic and industrial chemists. The growing interest in this new technology has been highlighted by a dramatic increase in the number of publications that describe the application of micro/meso flow reactors in various field of organic chemistry, and their application to process development and production.[**65**]

More recently, thanks to the advent of commercially available micro/meso flow reactors, pharmaceutical companies are embracing flow methodology in drug discovery programs, attracted by its potential advantages over the existing batch techniques. Theoretical and practical benefits associated with performing reaction under micro/meso continuous flow have been demonstrated for a number of common organic transformations, ranging from liquid-liquid to solid-liquid-gas systems. In particular for pharma companies, a very attractive feature of continuous-flow processes is the elimination of the risks associated with failing to scale up a process because the reaction conditions set-up on microreactor can be directly transferred to production scale without the need of re-optimization, either by running the flow-reactor for an extended time or by employing multi-channel parallel reactors (numbering-up process).

In addition, the growing importance of continuous processes is well in accordance with the principles of green chemistry,. In particular, the aim of green chemistry is to perform clean organic reactions under conditions which require less energy, less materials and less solvents.**[66]** In effect the heat exchange in flow is better than in batch reactions, and therefore reactions can run in a more precise and steady manner which may improve yield and selectivity: whereas batch processes involve a continuous variation of temperature, pressure and other parameters. In addition, the smaller reaction volumes, compared to batch processes, can be conducted in a safer way and some processes are only possible as continuous processes.[**67**]

Therefore, flow chemistry represents an important opportunity for contributing towards the identification of an efficient and modern strategy to develop the necessary synthetic tools and towards greening chemical production.

1.2.1 General characteristics of the continuous-flow process

Continuous-flow systems are generally composed of the following basic components: one or more fluid control devices which load the solutions of different reactants to the reactor section, the actual reactor (that usually can be heated or cooled), in which reactions can occur under a precise control of temperature and/or pressure and suitable reservoirs to collect the resulting mixture (**Figure 1.2.1**).

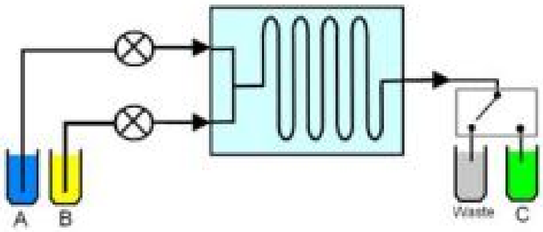


Figure 1.2.1. General scheme of Continuous-flow systems

Usually, flow reactors consist of narrow channels (maximum internal volume in the range of mL) formed from materials such as silicon, glass, stainless steel, ceramics or polymers.[**68]** For synthetic applications these channels are interconnected to a series of reservoirs containing reagents and/or solvents. These regents are pumped together in a specific sequence (by suitable pump systems capable of operating accurately over a range of flow rates),with laminar flow dominating and mixing occurring principally via diffusion, but not always (to see in paragraph 1.2.2).[**69]** The reagents are then allowed to react under controlled conditions for specified reaction times, thus minimising side reactions.[**70]**

Laboratory scale flow reactors can generally be divided into two broad classes on the basis of channels size and volume: micro- and meso/mini-flow reactors. In general, but the distinction is not so sharp and well defined, micro-flow reactors present channel having diameter from 10 to 1000 μm, whereas meso or mini-flow reactors are characterized by larger channels with diameter up to 5mm.[**71**]

Both these two types of reactors have unique advantages and disadvantages, principally related to the dimensions of the channels, but also with the shape and the fabrication techniques of the reactors themselves (**Scheme 1.2.1**).

Micro-flow reactors are designed and produced with expensive and sophisticated methods, coming from the field of semiconductor microelectronics, such as photolithography and micro-patterning, and they are usually planar object with size of small plate, the "chip" (**Figure 1.2.2**).**[72]**

Figure 1.2.2: a) polymer, b) metallic and c) glass Micro-flow reactors

Meso or Mini-flow reactors are instead constructed of simple polymer, glass or metal tubing with linear, T, Y or arrowhead shaped junctions, generally used in chromatography (**Figure 1.2.3**).

Figure 1.2.3: a) polymer, b) metallic and c) glass Mini-flow reactors

In this case the construction is a much more simple process that can be easily performed in a laboratory.**[73]** Furthermore, also for this reason, these mini/meso systems are more economically acceptable from an industrial point of view.

Micro flow reactor
Channel diameter: 50-500 μm

Advantages

- high heat transfer surface to product volume ratios
- good heat transfer capabilities

Disadvantages

- micro channels suffer from restricted flow capacity
- high pressure drop
- tendency to block

Mini flow reactor
Channel diameter: 500-2000 μm

Advantages

- improved flow capacity
- lower pressure drop
- no blocking of channels

Disadvantages

- lower heat transfer surface restricted flow capacity
- poor heat transfer capabilities
- limited capabilities foe a given diameter and length

Scheme 1.2.1: Comparation of Advantage and Disadvantage of Micro and Mini reactor

1.2.2 Fluid dynamics[74] and notes on the mixing

In synthetic applications, reagents and/or solvents are pumped together into the flow reactor, in a specific sequence, by suitable pump systems (pressure driven flow); generally, but not always, the flow is laminar, and mixing occurs via diffusion.

The motion of a fluid within a channel is described by the Navier-Stokes equations system. In brief, two types of forces act on any element of the fluid: the inertia forces, which express the tendency of a body to maintain its initial motion, and viscous forces, which are responsible for the friction phenomena internal to the fluid and the transport of momentum in its interior. Ina fluid system of very small dimensions, in particular of the order of micrometers, viscous forces prevail over the inertial ones.

The relationship between the two types of forces is represented by adimensionless parameter, the Reynolds number (Re):

$$\mathrm{Re} \qquad \overline{}$$

Where ρ is the density, ν the linear velocity of an element of the fluid, η the viscosity, and L a characteristic dimension of the system(in the case of a fluid in a cylindrical channel it is represented by the hydrodynamic diameter of the channel). This dimensionless parameter is used to discriminate between two flow regimes: the turbulent flow and the laminar flow. With values between 1 and 2300, the flow is dominated by viscous forces and it is defined as laminar (ensure efficient mixing). With values greater then 3000, inertial forces dominate and the flow is defined as turbulent (**Figure 1.2.4**). When the Reynolds number is between 2.300 and 3000, the flow is neither laminar nor turbulent: it is the “transition zone”.**[65]**

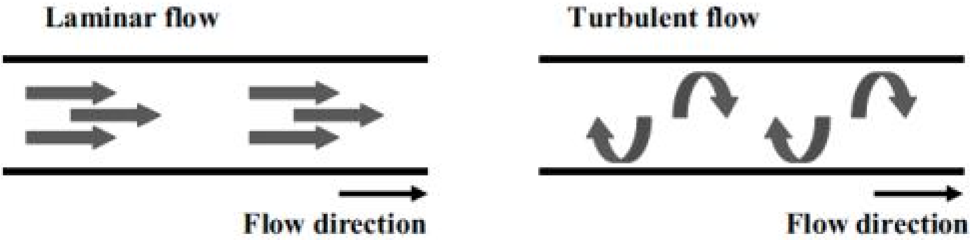


Figure 1.2.4. Laminar and Turbulent flow motion

Moreover, the Re number is an index also important to describe the mixing. In fact, the effective and fast mixing of reactive or non-reactive fluids is an essential and critical issue to achieve complete reaction for many fluidic devices. While a turbulent flow consists of elements in chaotic motion, which results in a contribution to the convective mixing, a purely diffusive mixing is present in a laminar flow, typical of micro/minifluidic systems.**[75]**

A further dimensionless index, useful to understand the relative importance of diffusion and convective bulk flow for transporting solute and solvent molecules, is given by the Peclet number (Pe):

$$\mathrm{Pe} = \frac{\nu \cdot \mathrm{L}}{D}$$

Where v is the linear velocity of an element of the fluid, L is the channel width and D is the mass or thermal diffusion coefficient of the solute in question.

This dimensionless parameter is defined to be the ratio of the rate of advection of a physical quantity by the flow to the rate of diffusion of the same quantity driven by an appropriate gradient, and it depends on the heat capacity, density, velocity, characteristic length and heat or mass transfer coefficient.

In conclusion, the Peclet number provides an indication of the relative importance of diffusion and convection, the diffusion being the random thermal motion of molecules within their surrounding environment, and convection the transport as a result of bulk motion of a fluid; it can be readily adjusted through the choice of flow velocity and the dimensions of the system used.

The dynamics of mixing is easily predictable, thanks to the fact that the diffusion in the steady state is described by Fick’s first law.

The competition between convection and diffusion, embodied in the Péclet number, forms the basis for a number of techniques for sensing and separating flow ingredients. The most devices are designed to operate at intermediate Pe, where differences in solute diffusion rates play the key role.**[74]**
Unfortunately, the Peclet number is not always optimal for fluidic systems; there are cases in which the mixing is negligible because, for example, the diffusion time is too long compared to the length of the channel.
To overcome this problem it may be necessary to use suitable mixing systems (micromixers) able to generate turbulent motion inside the channels (see **Figure 1.2.5**).**[76]**

In general, micromixers are classified into passive and active, depending on whether or not mixing is assisted by an external stirring mechanism or external field **[76b, 77]**.
Passive mixers do not require external energy; mixing relies on molecular diffusion aided by geometrical manipulations such as generation of chaotic advection**[78]**. T- and Y- and arrowhead shaped passive micromixers are most used to study the fundamentals of mixing processes **[79]**. In these geometries, mixing can be enhanced by roughening the channel walls and introducing obstacles in the flow path, both of which generate vortices and chaotic advection.
An active micromixer requires an external power source input, such as thermal disturbances, pressure disturbances**[80]**, acoustic disturbances **[81]**, piezoelectric vibrating membranes, electrohydrodynamic**[82]** and magnetohydrodynamic action among others.

Unfortunately, some of the micromixers mentioned above are complicated to implement or difficult to integrate in real applications. A number of numerical and/or experimental studies **[83]** have been carried out to search for simplicity, ease of integration and efficiency in microfluidic devices. For example, in one of these studies four intersection geometries for the inlet channels were taken in consideration: a 90° inlet channel (right angle intersection), a ‘‘Y’’ intersection, a ‘‘T’’ intersection, and an arrowhead intersection respectively (**Figure 1.2.5**); the authors claim that the best mixing occurs in the T and arrowhead intersections (such as those used in present work), i.e., where the fluid paths are forced to go around a sharp bend. The worst mixing occurs in the single-right angle intersection, where one of the inlet fluids does not travel around any bend or obstacle at the intersection.

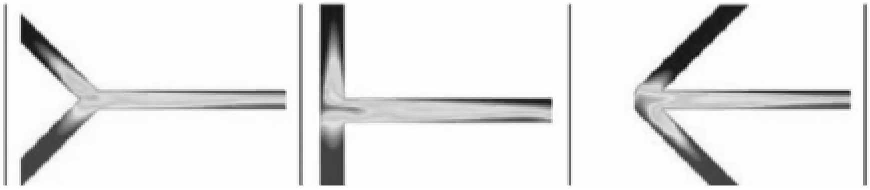


Figure 1.2.5: Micromixeres at "Y" intersection, "T" intersection, and arrowhead intersection

Correlated at the different flow type (laminar or turbulent) and at diffusion efficiency, is the velocity profile into the reactor channel. Theoretically, under true laminar flow conditions, the flow velocity at the fluid boundary layer next to the channel wall is zero, and at the centre of the channel is twice the average bulk velocity (parabolic flow); this can lead to non-homogeneous residence times into the reactor. Under conditions where some degree of turbulent flow exists, the effect of radial diffusion within the channel creates movement at the wall interface and slows the central channelwith consequent most homogeneous residence times (**Figure 1.2.6**).

In practical terms the implications of parabolic flow are that different components within the system can experience different conditions. The length of time each remain in the reactor and the parameters (e.g. temperature) they are exposed to during that time will vary, and it should be remembered that quoted experimental conditions, for a chemical synthesis for example, are generally referring to average conditions.**[84]**

Figure 1.2.6. Velocity profiles for laminar and turbulent flow

Currently, these effect of the different flow velocity of the fluids into the reactors (parabolic flow effect) is solved using the electroosmotic flow**[85]**: application of a potential difference at the ends of the system, with the direct movement of ions in solution toward the electrode of opposite charge.In this case the velocity is linearly proportional to the applied voltage, allowing precise fluid handling; the velocity profile is nearly flat across the channel, leading to greatly reduced dispersion of reagents if compared to pressure driven flow.

Unfortunately, the use of electroosmotic flow is restricted to polar solvents such as water, methanol, acetonitrile, dimethylformamide and tetrahydrofuran and to device materials that develop surface charges such as glass, silicon and treated PDMS (polydimethylsiloxane).

1.2.3 Batch versus Continuous-flow processes

There are numerous fundamental differences between classical batch experiments and continuous-flow reaction technology.**[64-65]**

First of all, in standard segmentally operated reaction vessels the conversion depends only on the reaction time, whereas in a continuous-flow apparatus, in which a continuous stream of reactants flows through the reactor channels where the transformations take place, the conversion to the products becomes a function both of the time and the distance covered in the reactor.**[86]** In other words, the chemical process becomes also space-resolved (**Figure 1.2.7**).

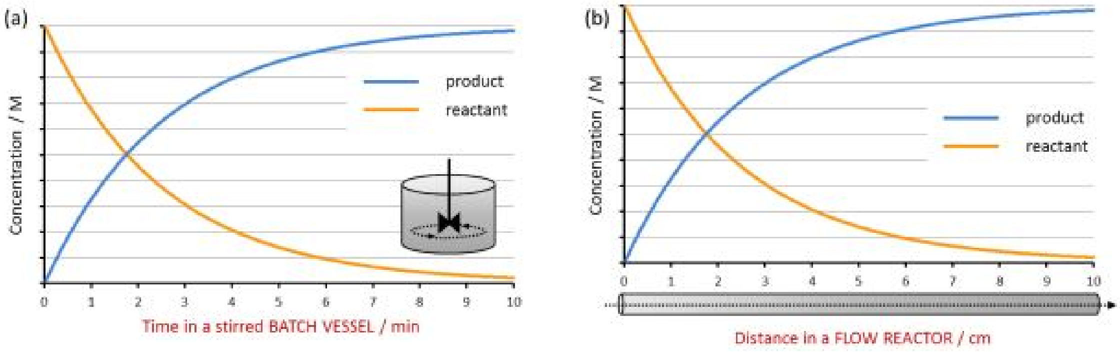


Figure 1.2.7 : Batch vs. Continuous flow conversion profiles

In batch processes the reaction stoichiometry is defined as the ratio among the moles of reactants while, in flow process, it depends both from the ratio of the reactant concentration and from their flow rate. For this reason the flow system is quite more flexible as concentrations and flow rates of the reactants can vary in an independent way to find the optimal conditions.**[86, 87]**

For these reason in a continuous process, the reaction time is assigned as the interval spent by a given molecule in the active reactor zone, best defined as the "Residence Time" (RT) and is determined by the ratio between the reactor volume and the total flow rate.[**87**]

RT (min) = Reactor Volume (mL) / Total Flow Rate (mL/min)

The amount of synthesized product per hour, called "Output", is not related to the classical concept of batch scale, but it is instead defined by a relation among the flow rate, concentration, molecular weight of the product and the reaction yield.

$$OUTPUT\ (g/h) = Flow\ Rate\ (mL/min) \times Conc\ (mmol/mL) \times MW\ (g/mol) \times Yield\ (\%) \times 0.0006$$

Moreover, the yield is instead space-time resolved (to compare among them different fluidic systems, or to compare classical batch experiments and continuous-flow reaction), and it is expressed as the ratio between the mass of the obtained compound and the product of the reactor volume and the total time spent in the reactor, (therefore this “spice time yield” can’t be compared with the classical yields).**[88]**

$$Spice\ Time\ Yield\ (Kg/m^3\ s) = product\ mass\ /\ (reactor\ volume \times time)$$

Beyond the introduction of these parameters, flow systems present several advantages with respect to batch systems. Many of these are associated with the *small dimensions of the channels*, and include the precise control of the reaction conditions, the efficient mass and heat transfer, the possibility of working under superheating conditions. Other advantages are associated with the *continuous nature of the process*, and include the simplicity in reaction scale-up, the possibility of performing sequential synthetic step with different control of reaction conditions, the possibility of introducing in-line purification by means of supported scavengers or sorbents and the possibility of interfacing the reactor with in-line analysis device for real time monitoring.

1.2.3.1 Advantages related to the small dimensions of the channels

1.2.3.1.1 Heat and mass transfer control

In the classical batch reactors, such as round-bottom flasks, the control of heat and mass distribution is generally achieved by mechanical stirring through turbulence at high Reynolds numbers.**[89]** In most cases, however, mass transfer is a key element of many chemical transformations and clearly inertial forces often provide insufficient mixing quality; this also implies that not homogeneous temperatures can be obtained, with the formation (in connection with the reactor geometry) of concentration gradients and hot spots that can lead to poor yields and low reaction selectivity.

On the other hand micro/mini reactors assure a rapid and efficient mixing of reagents because of the continuous and controlled addition of small volumes of reagents, reducing up to milliseconds the time required to obtain a homogeneous solution, avoiding the formation of hot spots and concentration gradients (**Figure 1.2.8a-b**).**[90]**

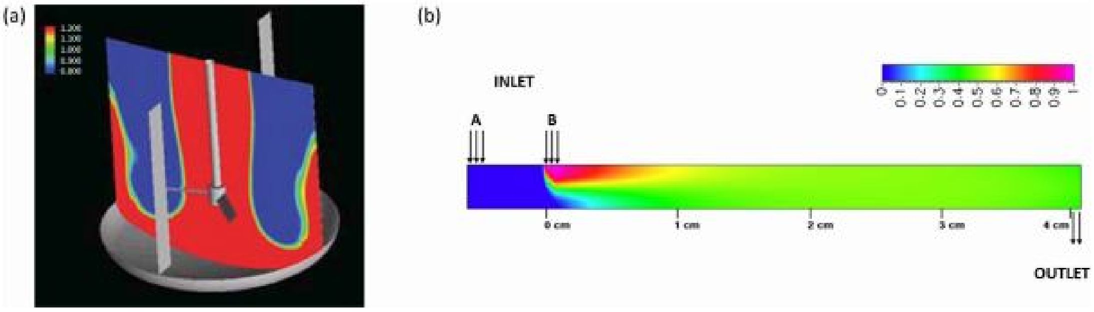


Figure 1.2.8a: Simulated Concentration profiles in a batch (a) and a Continuous-flow reactor (b)

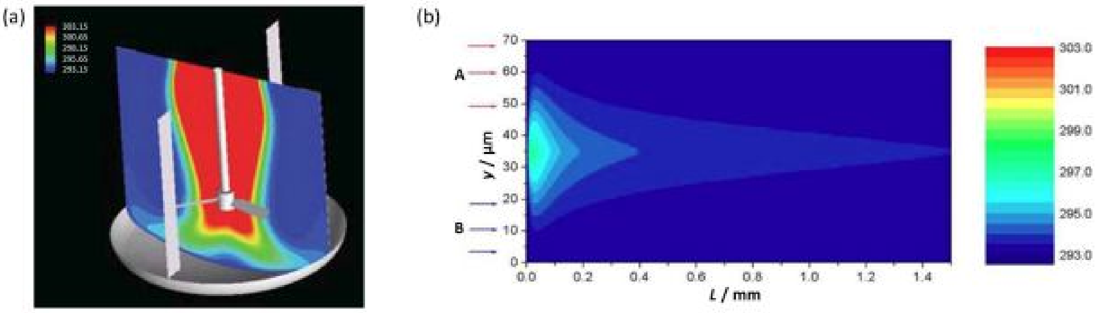


Figure1.2.8b: Simulated Temperature profiles in a batch (a) and a Continuous-flow reactor (b)

Moreover, in the course of a chemical reaction, heat is exchanged via the reactor surface, and the surface area-to-volume ratio is therefore a critical factor in efficient reactor design. Compact flow devices have specific surface areas several orders of magnitude larger than those of conventional batch equipment.**[87, 91]** For example, a 10-mL tubular reactor with a channel diameter of 1 mm has a surface-to-volume ratio around 50 times higher than that of a standard 250-mL round-bottomed flask.**[92]**

Heat exchange is driven similarly by a steep temperature gradient. At every point along the flow channel concentration and temperature gradients are stable. These stable gradients provide better control of reaction conditions compared to conventional synthesis, and aid the maintenance of isothermal conditions with improved production safety.**[93]** Even explosive reactants**[94]** or highly unstable intermediates can be handled readily.**[95]** The higher heat transfer capacity of the flowreactor is able to avoid that the process temperature moves away from the set one. On the contrary, in a classical reactor, the range of temperature around the set parameter is broader, mainly because of the lower specific surface area and mixing issue. This different distribution may influence the route of the synthetic process. In fact, batch reactors often provide wide temperature profiles, leading to undesired byproduct formation (**Figure 1.2.9**).**[96]** In contrast, the efficient temperature control in flow results in a narrow temperature distribution and does not permit the formation of hot spots or the accumulation of heat in the reaction mixture, and undesired side-reactions are suppressed, resulting in higher selectivity (**Figure 1.2.9**).**[96, 97]**

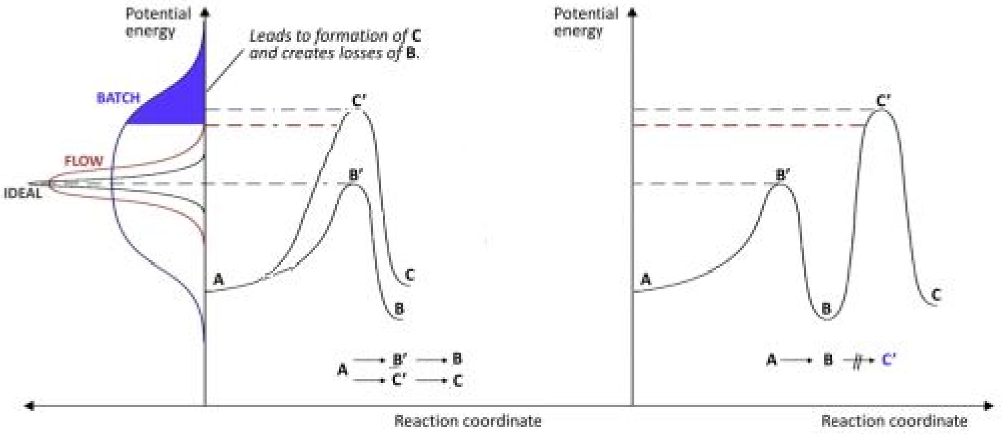


Figure 1.2.9: Effect of the heat control on the reaction selectivity

Thanks to the effective heat and mass transfer control, an additional advantage is the much better yield and reproducibility of the flow reactions as compared with those in a conventional apparatus.**[96]**

Furthermore, thanks to the small dimensions of channels and the precise control of reaction conditions, the flow device can allows superheating conditions and high safety. When conducting reactions on a laboratory-scale that may one day be scaled to production, the safety of a transformation is one of the most important considerations to make.

Looking at the issue from both a safety perspective and one of cost, industry finds it is desirable to scale reactions that do not require large amounts of heat management and/or flammable and pyrophoric compounds, as well as hazardous chemistry or, extreme conditions (**Figure 1.2.10**).**[98]** Consequently, there are lists of reactions that are not used when transferring synthetic routes from the research laboratory through to process scale-up. In continuous flow, syntheses that were previously “forbidden” for safety reasons (or even reactions simply not possible in batch) thanks to the efficient heat management, and the fact that only a small amount of material is

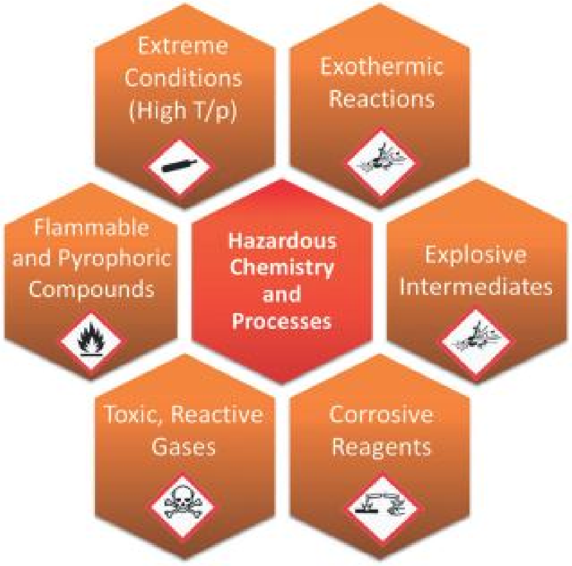


Figure 1.2.10: Hazardous Chemistry and Processes

committed to the reaction, can become less hazardous and therefore more acceptable (**Figure 1.2.11**).**[99]**

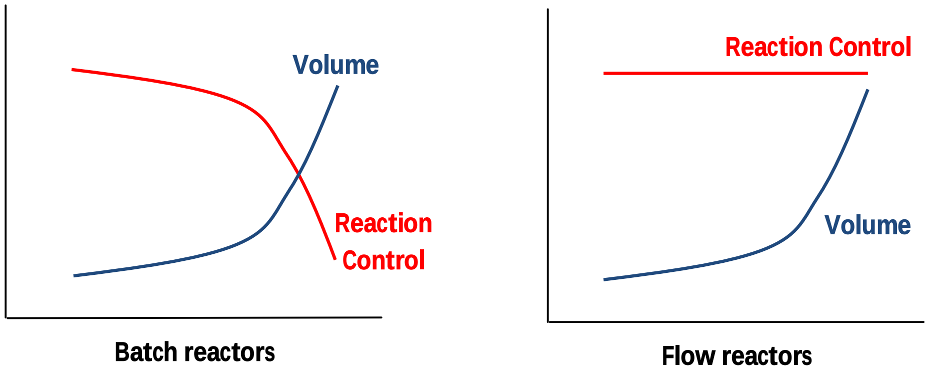


Figure 1.2.11: Dependence of the safety by the reaction volume in Batch and Continuous-flow reactor

Besides, in flow device sunstable or otherwise hazardous synthetic intermediates can be generated *in situ* inside a closed, pressurized system and converted directly into a more advanced, non-hazardous intermediate or product by combining multiple reagent streams. **[64, 65, 93a, 100]** Similarly, the reaction temperature can be changed rapidly along the reactor channel. This allows uninterrupted, continuous multi-step processes to be performed, and eliminates the need to handle or store excessive amounts of potentially toxic, reactive, or explosive intermediates.**[101]** Since the actual reaction volumes in a flow device are very small, safety concerns associated with hazardous reagents are further minimized. Moreover, the fraction of gas volume in a pressurized liquid-filled system is significantly reduced. This is crucial to avoid evaporation of low-boiling reagents or formation of explosive gas mixtures. The miniaturization, furthermore, has an immediate effect on radical chain reactions, and the propagation of explosions is suppressed.**[90]** The application of flow reactors can thus drastically expand the safe operation range of current processes.**[93b, 102]**

Similarly, in batch chemistry the highest reaction temperature depends on the boiling point of the used solvent, while flow reactors working under pressure control allow to perform reactions at temperature higher than the solvent boiling point; in addition, the application of high pressure in chemical reactions is favourable, as indicated by Le Chatelier’s principle, because increase the miscibility of liquids and the solubility of solid or gases, enhancing synthetic efficiency.

Through suitable back-pressure valves regulators, high-pressure conditions are widely employed in flow reactors: it is thus possible to ensure simpler access to harsh conditions than do conventional high-pressure autoclaves or the use of high boiling solvents,**[102a, 103]** simplifying the reaction work-up. The contained environment and the ease of pressurizing in flow device remove the boiling point barrier and allow the superheating of solvent in a safe and simple manner, thereby providing novel process windows in an increased space for chemical synthesis.**[104]**

1.2.3.2 Advantages related to the continuous nature of the process

To the continuous nature of the flow chemistry technique are associated some benefits such as:

- **Ease of scale-up** without alteration of the reactor engineering, by extending the run time (to hours or even a whole day) and/or employing multiple identical parallel reactors (numbering-up process), as well as by simple extension of the reactor dimensions (length and/or inner diameter) (**Figure 1.2.12**).**[105]**

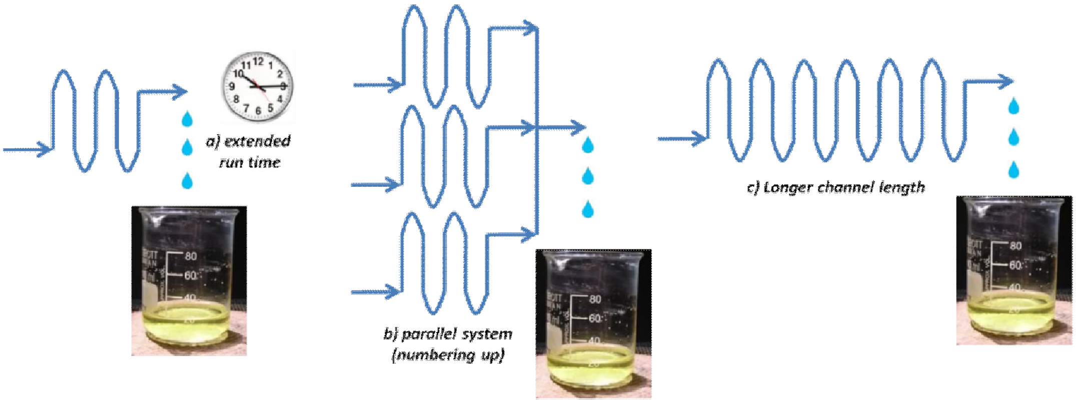


Figure 1.2.12: Scale-up in Continuous-flow chemistry

  Only if the reactor size is increased above a certain level (switch from micro at mini or from mini at macro reactor), a re-optimization of the most important reaction parameters may be necessary. On the contrary, traditional batch scale-up often requires heavy modifications of laboratory protocolsand optimization of reactor parameters,frequently accompanied by non-negligible variation of yields, purities and safety (see paragraph 1.2.3.1).

- **Possibility to carry out continuous sequential step** of two or more reactions, without breaking the sequence with workup and purification. The sequence of reactions can occur directly through a series of connected reactors, which parameters are accurately set for the specific synthetic step (**Figure 1.2.13**). Flow technique permits the linking of individual reactions into multi-step sequences, allowing for one reaction to flow seamlessly into another and creating a rapid route to the desired more complex product by combining multiple synthetic steps into a continuous operation. Between each step may be present, when necessary, a system for trapping and eliminating possible by-products, without interrupting the flow.**[106]**

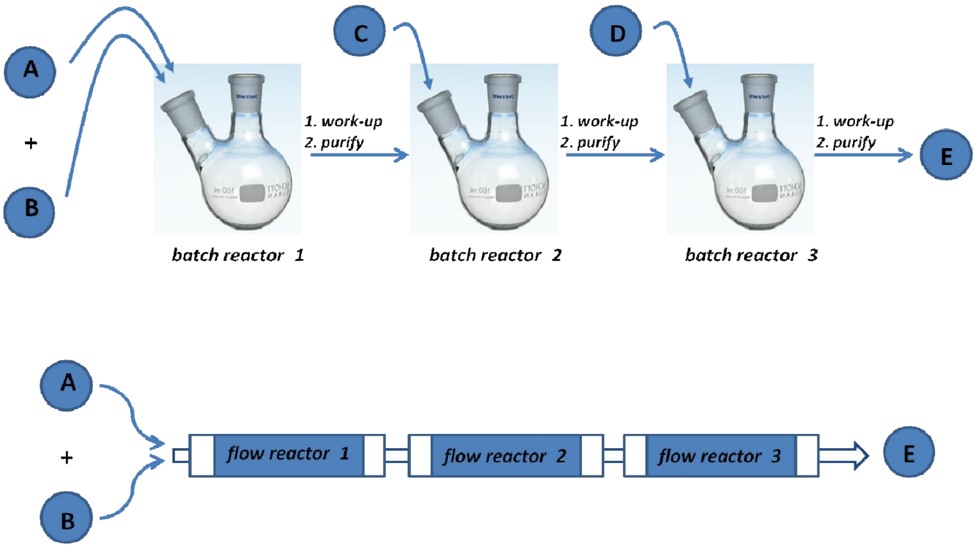


Figure 1.2.13: Possible sequential step in batch and flow

Furthermore, the continuous nature of these systems makes possible the use of solid supported reagents, catalysts and scavengers, permitting rapid access to target molecules without the isolation of any intermediates.

1.2.3.3 Drawbacks of continuous-flow systems

Unfortunately, together with the many advantages, the continuous-flow technology has some drawbacks, also related to the continuous nature of the process and/or to the small dimensions of the channels. These drawbacks can reduce both academic and industrial interest towards this technique.

The small dimensions of the channels, associated with the continuous nature of the process, can represent a problem when reaction mixtures involving solid particles are used in continuous process. Many useful transformations take advantage of solid starting materials, form insoluble byproducts, or generate products near saturation.**[107]** In fact, an analysis performed on 86 different reactions (in 2005, by D. M. Roberge et al)**[108]**, concluded that 50% of the reactions would have cost benefits by switching to a continuous flow mode.**[108]**

Unfortunately, the 63% of this reaction involved the use of solids, can result in the flow-induced deposition, bridging, or random detachment of deposits constraining the production; with consequently severe impact on a chemical process, including the shutdown time (**Figure 1.2.14**).**[108]**

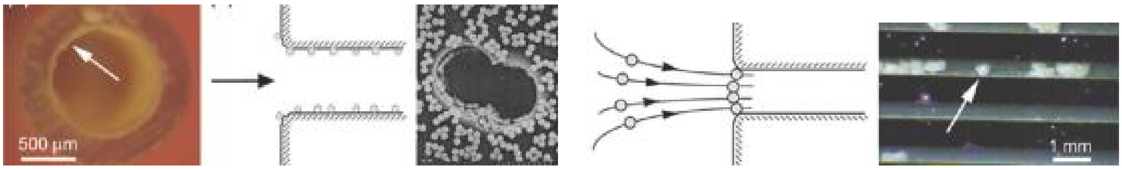


Figure 1.2.14: Possible sequential step in batch and flow

Therefore, in recent years the issue of solids handling in continuous reactor systems has gained considerable attention as the evolution from traditional batch processing to continuous flow mode to impact in the fine-chemicals industry.

Some problems of homogeneity associated at the small dimensions of the channels may be due of the presence/production of bubbles that not dissolve in the reaction mixture: this phenomenon can lower the mixing efficiency, and prevent the full conversion of the starting material..**[109]**

Some drawbacks are also associated to the continuous nature of the flow chemistry technology.**[109]** The continuous, sequential steps of two or more reactions are possible if reaction times are similar; otherwise switching and recycling valves are required for guaranteeing the full conversion of the starting material in any step.

Other limitations of the flow technology concern the generality of applications. In fact, currently the flow process has a limited flexibility to change products, being useful only for relatively fast reaction.

Finally, these systems appear much more fragile, with an high receptiveness to malfunctions, since a single fault can stop the entire course of the production.

1.3 Combined technologies

Organic synthesis seems to have become so very advanced that basically every molecular target, how structurally complex it may be, can be addressed. However, these advances are not fully reflected in the industrial context.**[9h, 110]** Many developments from the research laboratories lack practicability as far as scale-up, easy and rapid workup and product isolation as well as recyclability of catalysts.**[111]**

Nowadays, very good results in the rapid incorporation into industrial processes can often be obtained with the combination of the advantages of two or more new synthetic methods and/or new techniques termed 'enabling technologies for organic synthesis', thus further improving and enhancing the efficacy of each approach.**[9e, 112]**

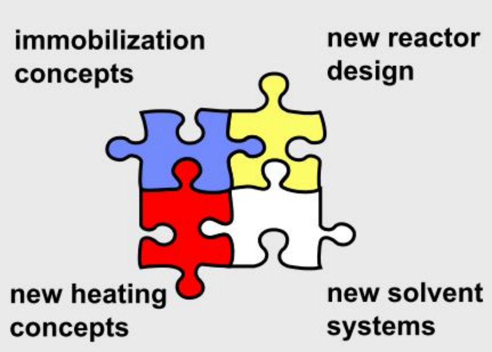


Figure 1.3.1: Enabling technologies

Enabling technologies can briefly be summarised as (a) solid phase assistance such as hetereogenised homogeneous catalysts,**[9e, 113]** (b) new solvent systems like ionic liquids,**[114]** (c) new heating devices such as microwave (μw) irradiation**[6m, 115]** and (d) new reactor designs such as continuous-flow and micro reactors (**Figure 1.3.1**), but the list can be complemented with additional techniques).**[109b, 116]**. Especially, flow systems provide an additional benefit because they close the gap between bench chemistry and chemical engineering by mimicking large-scale production on the laboratory scale.

Various successful examples of combining two or more of these techniques in order to achieve faster synthesis or improved work-up have recently appeared in the literature, particularly in the field of catalysis. **[112]**

For example, some groups combined microwave-assisted procedures with solid phase technique, and applied this association in C–C cross couplings reactions**[117]**, as well as in the synthesis of several heterocycles**[118]** and natural product derivatives**[119]**. However, publications concerning the use of insoluble Pd-catalysts under microwave irradiating conditions are scarce.**[120]** The combination of immobilized homogeneous catalysts and microwave assistance is particularly appealing in order to overcome the less favourable kinetics of biphasic systems. Instead, more recently some groups combined successfully heterogeneous catalysis and new solvent systems; however, studies in which the solvent system becomes part of the immobilization concept are still rare.**[121]** These combined techniques were applied in gas-phase hydrogenations of alkenes**[122]** and C-C cross coupling reactions**[114g, 120, 123]**.

1.3.1 Heterogeneous catalysis under continuous flow conditions[124]

Only recently, the concepts of fluidic devices and continuous-flow reactor technology have become new key issues as part of enabling techniques. Most micro/mini fluidic devices for laboratory scale are based on homogeneous systems;**[125]** however, an ideal continuous flow process combines novel reactor design with heterogenized reagents,**[126]** or heterogeneous (as well as immobilized homogeneous) catalysts.**[127]** This can represent a strategic advantage as regards the progressive intensification and the future sustainability of production processes of fine organic chemicals and pharmaceutical compounds.**[91a, 116c, 128]**

Heterogeneous catalysis provides a useful addition to microreactor technology allowing expansion in the use of catalysis under flow conditions. In many cases small amounts of catalyst can be employed, and potentially recycled over numerous runs.

The potential advantages of heterogeneous catalysis in conjunction with continuous-flow reactor technology include: (a) continuous product formation, (b) simple product/catalyst separation and re-use of catalyst, (c) increased reaction rates, (d) improved heat transfer and precise temperature control, (e) Improved mass transfer of a mass transfer limited reaction, (f) safer synthesis due to the continuous generation/consumption of unstable or toxic intermediates, (g) easier scale-up, (h) operation at more severe reaction conditions, (i) more efficient use of resources and generation of less waste, (l) integration of reaction monitoring and processing steps and (m) low cost reactors.

Although this idea has recently attracted a great deal of interest, its actual use for the preparation of high added-value products is, however, extremely limited.**[128a]**

Moreover, before this technology can be said to be mature for use in an industrial environment, several scientific problems are still awaiting a satisfactory solution:

- In the case of supported metal systems, the high costs and often the difficult availability of the supported metal system, together with the need to increase the catalytic activity and lower the metal leaching (in order to reduce the product contamination and to make the system longer lasting under flow conditions) are the main problems of most of the supported catalysts. In this respect, of particular interests it could be the use of nanostructured metal catalysts,**[129]** for which just a few examples (limited to monometallic systems) exist for microfluidic devices.**[130]**

- As regards the flow reactor technology, most of the continuous flow processes so far described utilize four principal reactors type: packed-bed, monolithic, wall-coated and membrane reactors..

Packed bed catalytic reactors are very versatile, and most of the continuous flow processes so far described utilize these reactors, due to their ease preparation and regeneration (by introducing/removing the supported catalyst in the tube reactor). Unfortunately, these systems commonly show uncontrolled fluid dynamics, which result in stagnation zones and hot-spot formation, broad residence time distribution and low selectivity; in essence, low process efficiency.

Wall-coated reactors (principally microreactors) substantially minimize the mass transfer resistance and ensure smooth inflow of reagents without leading to any adverse pressure drop or blockage of microchannels.**[131]** In addition, well defined flow geometries are observed, which enable one to predict the fluid dynamics, and the heat and mass transfer properties inside the reactor.**[132]** In the literature, significant advances in the immobilization of different kinds of catalysts on the interior of the micro-channel walls, and studies of their catalytic applicability for a variety of reactions, are described. In spite of good flow-through properties observed in this method, in general, the catalyst loading is lower compared to the other two approaches, owing to a mono-layer/thin film of the catalyst supported on the inner walls of a microreactor. In order to overcome this shortfall, different methodologies, such as tethering of polymer brushes **[133]** and deposition of inorganic porous material on the microchannel surface to increase the catalyst loading, have been used.

Monolithics, and membranes reactors have a high void volume and a large geometric surface area. This results in a low pressure drop during the passage of a gas or a fluid and a large contact area of the reagent or the catalyst with the fluid.**[134]** Nevertheless, usually these systems are of complex preparation/regeneration (for monolithic systems): it is not easy to generate uniform monolithic phase and/or membrane framework with defined pore size.

The membranes are often mechanically instable, and for this reason the most prominent applications of membrane reactors are gas–liquid reactions, while liquid–liquid or liquid–solid reactions have seen limited use.

Monolithic reactors with regular or irregular channels based on polymeric phases are commonly prepared by not easy copolymerization of different monomers in the presence of porogens, or polymerization of a monolithic polymeric phase wedged inside the microchannel pore system of an inert support (such as glass and other preformed inorganic materials), or via photografting of the cross linker acrylate and the reactive monomer.

Another problem of monolithic reactors is the availability of methods for the immobilization in the reactor of transition-metal catalysts with high efficiency and broad scope. In fact, packed-bed reactors are easily filled with pre-prepared, covalently or coordinatively immobilized, supported catalyst (already studied and developed for the use in batch reactors); on the contrary, monolithic reactors require *ad hoc* procedures, not yet simple, for the noncovalent immobilization of ligands, metals and/or catalysts; these procedures, could guarantee, also for the smallest sized devices, a stable support material, high ligand/catalyst loadings, and suitable fluidodynamic properties, at the same time.

As regards monolithic systems, the major disadvantage of a covalent attachment of a precious ligand is the limited lifetime of these catalytic complexes, being incorporated inside the reactor. In fact, it was impossible to regenerate the solid phase after the catalyst had lost its activity, or to easily implement new monolithic material inside the column. For this reason currently several groups have envisaged other modes of attachment, such as a) physisorption,**[37]** b) immobilization by ionic interactions (ion exchange)**[130c]** and c) immobilization by coordination to metal centers**[130d]**.

However, In view of industrial up-scaling and economical considerations, the use of packed and monolithic flow reactors containing functionalized polymeric resins or inorganic materials has some important differences compared to that of supported catalysts in batch reactors.

In fact, when immobilized palladium is used as catalyst in a typical batch cross-coupling reaction, the concentration of palladium species in solution increases during the process; upon completion the concentration decreases dramatically due to re-adsorption (re-precipitation) of palladium on the solid support. Thus the catalyst probably acts as a "reservoir" of soluble, catalytically active metal species which, however, are not lost and do not contaminate the products (so the catalyst can be effectively recycled).**[61]**

But when working in continuous flow the situation may be quite different. In a continuous flow process employing packed-bed or monolithic reactors the reaction stream may transport the palladium "through" the support owing to continuous metal leaching/re-adsorption contaminating the reaction product (**Figure 1.3.2**).

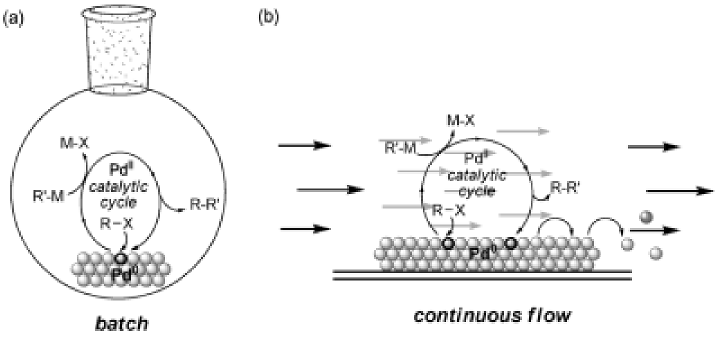


Figure 1.3.2: Comparison of metal leaching phenomena under a) batch, and b) continuous flow conditions

To solve this problem, most frequently continuous-flow processes require the presence of a scavenging cartridge in line to the catalytic reactor (**Figure 1.3.3**), to efficiently capture palladium residues, affording reaction products in high purity.**[135]**

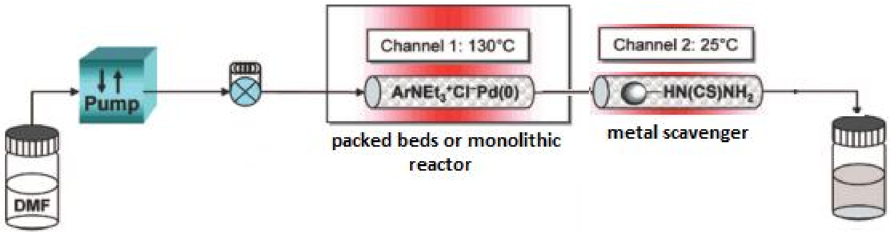


Figure 1.3.3: Typical metal-scavenger in-line to the catalytic continuous flow reactors

However, these systems quickly lose their catalytic activity, with consequent expensive removal or regeneration of the old, inactive catalyst.

Based on all these considerations, the concept of immobilizing transition metals as catalysts for cross-coupling reactions executed in continuous flow—where the reaction mechanism may in fact be "homogeneous"—remains currently somewhat questionable. Furthermore, swelling of the polymer supports, deposition of products/by-products and the need to periodically replace/regenerate the "catalytic filling" actually complicate the use of flow reactors in an industrial environment.

1.4 Scopes of this thesis – Our Research Objectives and Working Plan

Summarising the above paragraphs, currently the academic and industrial research is devoting considerable attention to the use in C-C cross-coupling reactions of heterogeneous metal catalysts and/or continuous flow systems. In fact, supported catalysts can offer numerous advantages compared to those homogeneous, resulting much more attractive from both scientific and applied point of view: in general, they are more practical, versatile and stable, and often they can be handled and used in the presence of air and/or moisture; further, they can simplify the isolation procedures, be recovered and recycled easily, and allow to obtain products containing negligible amounts of metals.**[9h-i,10]**

However, it should be noted that, usually, supported systems are less active than corresponding homogeneous systems, but this lower catalytic activity can be compensated by increasing reaction temperature and catalytic load.**[9h-i,11]**

Moreover, today it is considered very important even the replacement of the classical batch-type reactors with continuous flow systems.**[65]** In fact, the continuous flow systems can offer several advantages compared to conventional batch reactors, resulting much more attractive from both scientific and applied point of view: in general, they have a better mass and heat transfer, a greater safety when working with explosive or toxic reagents, a more accurate control of the reaction times, an easier manipulation of air sensitive reaction mixtures, an high surface/volume ratio, and, above all, a much greater ease of scale-up (simply connecting several reactors in parallel or increasing the reactor dimension).**[90-106]**

However, it should be noted that, usually, continuous flow systems suffer from inhomogeneous reaction mixtures (presence/production of solids and/or bubbles that not dissolve in the reaction mixture), but these drawbacks can be compensated choosing suitable reaction conditions.**[107-109]**

In this context, the industrial and scientific world has devoted a remarkable attention to Heck-type alkenylations**[5]**, Sonogashira-type alkynylations**[6]** (recently, copper-free procedures have been also developed)**[136]** and Suzuki-Miyaura reactions**[7]**, due to their characteristics of generality, efficiency and selectivity, as well as to the strategic importance of the compounds that they allow to obtain. Moreover, these cross-coupling reactions are particularly attractive even for their intrinsic practicality, simplicity and greenness.**[8,5-7]** (More detailed informations about these reactions will be furnished in the introduction of paragraph 2.3, 2.4 and 2.5, respectively). All these features play an important role from an industrial and environmental standpoint.

Unfortunately, to date, the majority of the supported catalysts and/or continuous flow systems applied in the above mentioned C-C cross-coupling (but not only), are complex and not easily available; besides, they generally require reaction conditions little practical and green.

Moreover, in the literature are very few studies applied to the synthesis of bioactive compounds of applied interest which use supported catalysts and/or continuous flow systems, especially combined. (More detailed information will be furnished in the introductions of sections 2.3.1, 2.3.3, 2.4.1. 2.4.3, 2.5.1 and 2.5.3 respectively).

On these bases, the ultimate goal of this Doctorate project, (first phase of a wider series of studies), was the identification and exploitation of the actual application possibilities of practical, economic, easily accessible and industrially acceptable supported catalysts in C-C bond forming reactions of particular interest, such as Heck-type alkenylation, Sonogashira-type alkynylation and Suzuki-Miyaura reactions.

In other words, with this PhD thesis we intended to begin to answer the following questions:

1) *By using cheap, practical, easily available and simple supported catalysts, it is possible to promote with sufficient efficiency batch C-C cross-coupling reactions, even in rather green and industrially acceptable conditions?*
2) *It is possible to do this even in continuous flow mode, with simple, versatile and low-cost packed-bed mini-reactors?*
3) *These new methods are really suitable for the convenient synthesis of bioactive and/or natural compounds of applicative and industrial interest?*

Consequently, our project aimed to identify and test the behaviour, in cross-coupling reactions carried out in batch and/or flow reactors, of some heterogeneous catalysts both commercially available and purpose-built (in collaboration with the ISTM-CNR Institute of Milan), as well as to determine efficient and feasible, but also quite green and industrially acceptable, reaction conditions in which these catalysts are able to promote efficiently the reactions.

The commercial catalysts were chosen among the most innovative but also cheap and easily available although still not extensively investigated for the use in C-C cross-coupling reactions. As regards the laboratory-prepared catalysts, these are made from palladium nanoparticles and readily available, cheap supports, by using Metal Vapour Synthesis (MVS) and/or adsorbition-reduction techniques.

As regards instead the reaction conditions, these had to be identified among the most practical, convenient and green, but also taking into account their applicability in flow systems. In fact, as already described and explained (paragraph 1.3.1), the academic and industrial research has devoted a remarkable attention to the development and use in C-C cross-coupling reactions of continuous-flow systems, and in particular to the possibility to merge heterogeneous catalysis with continuous-flow reactors.

The potential advantages of heterogeneous catalysis in conjunction with continuous-flow reactor technology are several (see paragraph 1.3.1), but mainly include: (a) continuous product formation, (b) simple product/catalyst separation and re-use of catalyst, (c) more safer synthesis, (d) easier scale-up, (e) more efficient use of resources and generation of less waste, (f) integration of reaction monitoring and processing steps and (g) low cost reactors.

Consequently, our project planned to develop simple and versatile packed-bed flow systems, filled with the same chosen o prepared catalysts, and test the behaviour and the applicability of these reactors in C-C bonds formations.

We decided to develop packed-bed reactors simply because reactors of this type *i*) are more versatile, *ii*) are easily obtainable from simple, cheap and available materials, *iii*) allow a direct comparison between batch and continuous-flow mode under identical reaction conditions.

The greater versatility of these reactors is very important: they can be readily prepared introducing the catalyst (pure or mixed with inert materials, dry or as a slurry with a suitable solvent) into the reactor. This can then be used to make different types of cross-coupling reactions; once the catalytic activity is exhausted, the filling can be easily and cheaply replaced.

As regards the materials of the reactors, we decided to use simple PTFE tubes: they are inexpensive, versatile, thermally and chemically resistant, easily available and manipulable.**[137]**

However, our intention was to compare all selected catalytic systems (under batch and flow mode) in term of catalytic activity, productivity and palladium leaching in the reaction mixture, as well as to verify their recyclability in batch and their life-time in flow. In addition, we intended to perform and compare Transmission Electron Microscopy (TEM) analyses of the catalysts, both freshly prepared (or bought) and recovered after the use (in batch or flow).

Finally, the project included to outline, under batch and flow conditions, scope, limits and actual possibilities of the selected supported catalysts, as well as, on the basis of the obtained results, the use of some of the best catalysts (and flow reactors) in the synthesis of bioactive substances of applicative interest.

In summary, the working plan of this Doctorate Thesis was:

1) to select cheap, convenient and easily available supported palladium catalysts able to efficiently promote the three strategically important cross-coupling reactions chosen (Suzuki, Sonogashira and Heck);
2) to identify, for these reactions and these catalysts, green, convenient and efficient conditions, by using suitable model substrates;
3) to verify if these reaction conditions were general and could be extended to other substrates (in particular, aryl, but also alkenyl, halides of different type); .
4) to develop simple and versatile packed-bed continuous-flow reactors, using as filling the same catalysts;
5) to verify the generality, convenience and efficiency in cross-coupling reaction of our continuous-flow reactors, and compare batch and flow results;
6) to evaluate, both in batch and flow reactors, the palladium leaching and the recyclability of catalysts under the developed reaction conditions;
7) to prepare, using the new procedures developed, potentially useful bioactive compounds, also of industrial interest.

2. Result and Discussion

2.1 Synthesis and choice of simple and cheap heterogeneous catalysts

As already shown in paragraph 1.4, our main objective was to investigate the practical use of simple and cheap supported palladium catalysts in Suzuki-, Sonogashira- and Heck-type cross-coupling reactions carried out in batch and/or flow reactors under reaction conditions as feasible, green and convenient as possible. Therefore, the choice of suitable catalysts (in addition to that of proper conditions) was a very critical stage.

Our selection of the catalysts was based on criteria of easy availability, cost effectiveness and efficiency, as well as on the state of the art of the use of these catalysts in cross-coupling reactions (as regards commercial catalysts).

2.1.1 Choice of the commercial supported catalysts

2.1.1.1 Commercially available palladium heterogeneous catalysts

Currently, several type of heterogeneous palladium systems are commercially available. These systems range from classical Pd/C and Pd/γ-Al_2O_3 to the most innovative and new Fibrecat™ and SiliaCat®; they mainly differ in *i)* chemical nature of the solid support entrapping the Pd catalyst (organic, inorganic, or hybrid organic-inorganic), *ii)* the nature of the catalyst attachment (chemical or physical entrapment) and *iii)* the nature of the entrapped palladium catalyst (Pd organometallic complex or Pd nanoparticles).

What we needed were efficient, cheap and easily available heterogeneous catalysts, which were also robust, air and moisture-stable and effective in promoting cross-coupling reactions in batch and flow mode, but not yet extensively studied. An analysis of the recent literature allowed us to identify a group of heterogeneous Pd catalysts that respected our selection parameters.

Palladium on charcoal (also called activated carbon) (Pd/C) remains the main commercial catalyst employed in heterogeneously catalyzed cross-coupling reactions (the first report in Heck reaction was published in the pioneering work of Julia et al. early as in 1973)**[138]**.**[9d]**

It can be purchased from various laboratory suppliers, such as Acros, Sigma-Aldrich, Lancaster, or Alfa Aesar, or from the manufacturers Degussa or Johnson Matthey in various qualities with a Pd content ranging from 1% to 20%. The materials can contain water up to 50%. Pd/C is used with or without additional ligands.**[9d]**

However, it is a highly pyrophoric material and when used in batch on large scale the filtration operations are especially hazardous, where ignition can occur if not cautiously performed (when dry). Because of this, the operations are typically carried out under inert atmospheres, thus adding further complexity. Moreover, owing to dissolution and re-precipitation of Pd during reaction, this system showed activity reduction**[25b, 139]** by more than 50% when the catalyst is reused, thus impacting the overall economy of the process both in batch and in flow. For example, Kappe and co-workers reported the use of Pd/C, immobilized in the replaceable, pre-packed stainless steel cartridge of a high pressure flow reactor (X-Cube),**[140]** as a catalyst for Mizoroki–Heck reactions performed under continuous-flow conditions. The authors describe that the reactions proceed efficiently, but with a high loss of Pd from catalyst (ICP-MS analysis showed that 89% of the palladium had leached into the solution).**[140]**

In a similar way, other commercially available classical supported palladium catalysts based on supports such as SiO_2, γ-Al_2O_3, MgO, $BaSO_4$, $CaCO_3$, TiO_2, etc., can be purchased from various laboratory suppliers; they also have been used to promote cross-coupling reactions, but far less than Pd/C, with excellent results only in Heck reaction. The first report about a heterogeneous Heck catalyzed by Pd supported on metal oxides (Pd/MgO) was published by Kaneda et al. in 1990,**[141]**. Later, several other metal oxides have been employed as supports for Pd catalysts (currently commercially available) to be used in Heck reactions (Biffis and co-workers reviewed palladium metal catalysts in Heck reactions in 2001).**[31]** Most applications were performed under ligand-free conditions, but in general these systems showed a lower activity of the previously cited Pd/C.**[34b-c]**

Moreover, in cross-coupling reactions these systems showed a decrease of the catalytic activity during the recycling experiments; instead, all these catalysts are commonly and successfully used in hydrogenation processes carried out both in batch and flow mode.**[142]**

These “classical” catalysts, although widely studied in cross-coupling reactions carried out both in batch and in flow, taking into account the limitations described above appeared not suitable for our purposes and our study.

In the past decade, several innovative catalyst series have been commercialized; for example, NanoSelect (BASF), Noblyst (Evonik), Fibrecat® (Johnson Matthey), LaPCat^{TM} (Reaxa), EnCats^{TM} (Reaxa; today's S. Amit) and some Pd complex polymer-bound (Biotage); more recently, several silica-based catalysts have been commercialized by the PhoshonicS (2009) and the SiliCycle (SiliaCat®, 2010).

Nanoselect and Noblyst are quite expensive heterogeneous catalysts for hydrogenations; they are not yet simply available and rarely used in cross-coupling reactions. Therefore they also were not suitable to our purpose.

The LaPCat^{TM} (a trademark of Reaxa) are copper- and palladium-containing perovskites, commercially available from 2005. These perovskites containing Pd have been used in Suzuki-Miyaura cross-coupling reactions (and, to a lesser extent, in Ullmann and Sonogashira-type reactions).**[143]** Reaxa (and recently Sigma-Aldrich also) provides a kit of 6x100mg LaPCat^{TM} perovskites containing Pd and/or copper (**Table 2.1.1**)**[144]**

Catalyst	Formulation	Formula Weight	Pd (wt%)	Cu (wt%)	Surface Area (m2/g)	Mean Particle Size (μm)
FP2	$LaFe_{0.95}Pd_{0.05}O_3$	245.29	2.169	-	5.5	41.1
FP8	$LaFe_{0.80}Pd_{0.20}O_3$	252.87	8.417	-	5.7	3.3
CoP	$LaFe_{0.57}Co_{0.38}Pd_{0.05}O_3$	246.46	2.159	-	3.4	4.0
CuP	$LaFe_{0.57}Cu_{0.38}Pd_{0.05}O_3$	248.21	2.144	8.20	12	3.7
CoCu	$La0.9Ce_{0.1}Co_{0.60}Cu_{0.40}O_3$	247.81	-	8.64	7.9	5.4
YBCu	$YBa_2Cu_3O_7$	666.22	-	24.1	0.3	10.6

Table 2.1.1: Series of heterogeneous Perovskites Reaxa catalysts containing Pd or Cu (LaPCat^{TM})

Pd-containing LapCat catalysts were successfully used in Suzuki-Miyaura reactions between several aryl halides (bromides, iodides and chlorides) and boronic acids or esters. Screening of solvents and reaction conditions demonstrated that a wide range of aqueous mixtures of solvents (nonaqueous solvent mixtures were unsuccessful) at 80-100 °C and in the presence of low loads of Pd (0.05-0.1 mol% Pd) can be employed, affording the desired biaryls in high yields.**[145]**

In 2005 Ley's group published a study on the use in Sonogashira coupling of commercially available copper- and palladium-containing perovskites.**[143]** They reported that catalysts like LaPdCu*, LaPd* and NdPdCu* efficiently promoted Sonogashira couplings under both microwave and conventional heating. Notably, rather low Pd loadings (0.125 mol %) were employed.

More recently, in 2014 (after the starting of this project) Ley and co-workers published a study on the use of these perovskite catalysts in Sonogashira and Heck coupling reactions performed in flow reactors. The system was applied to a wide range of functionalized substrates, allowing clean and fast delivery of the products within a few minutes (10–30 min), but inline scavenging of Pd with thiourea polymer (QPTU) and sulfonic acid resin (QP-SA) is required.

In general, these systems have shown very high turnover numbers (up to 400,000) and products made with LaPCat™ catalysts have low residual metal contamination compared to conventional homogeneous catalyst systems. However, these catalysts operate with a mechanism that involves the generation of a soluble catalytically active Pd species, which is desorbed from the bulky inorganic phase and probably re-adsorbed/re-precipitated on a modified solid phase after the reaction is complete. Whereas the surface of the catalyst is relatively uniform and appears amorphous, the post-reaction catalyst has undergone a profound morphological change and seems to consist essentially in a new crystalline phase. This phenomenon clearly limits the reusability of these catalysts both in batch and flow mode, with a low industrial appeal (also due to their high cost: 700 € for the 6 x 100 mg LaPCat^{TM} kit).

Also the PdEnCat® are marketed by Reaxa (and world-wide distributed by Sigma-Aldrich from 2002). In this catalyst family the palladium is microencapsulated in a cross-linked polyurea matrix, prepared by in situ interfacial polymerization. These matrices can have different porosity, and consequently a different accessibility to substrates, increasing from PdEnCat^{TM} 40 to 30 (the numbers relate to the percentage matrix content). The PdEnCat® are air-stable, highly active, and easily recoverable catalysts; they are available in a without ligands, with co-encapsulated ligands and as nanoparticles (see **Table 2.1.2**).

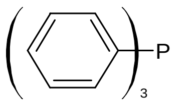
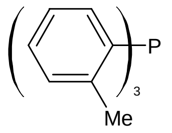
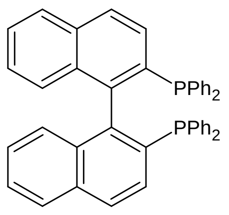
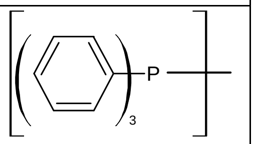
Product	Pd content % w/w	Co-encapsulated ligand
Pd(II) EnCat^{TM} 30	3.9-4.3	-
Pd(II) EnCat^{TM} 40	3.9-4.6	-
Pd(0) EnCat 30NP	3.9-4.6	
Pd(II) EnCat^{TM} TPP30	3.9-4.7	
Pd(II) EnCat^{TM} TOTP30	3.9-4.7	
Pd(II) EnCat^{TM} BINAP30	3.9-4.7	
Pd(II) EnCat^{TM} polyTPP30	3.9-4.6	

Table 2.1.2: Series of heterogeneous PdEnCat Reaxa catalysts

These Pd-encapsulated catalyst have been used in several C-C cross-coupling reactions, mostly Suzuki, Heck, Sonogashira, Kumada and Stille reactions;**[45b, 49c, 146]** for this purpose, several types of conditions have been successfully employed, including the microwave heating, and the use of $scCO_2$ as solvent.

Palladium EnCats were used for the first time in Suzuki-type reactions; **[45b]** in particular, the Pd EnCat 40 catalyst was successfully tested in the coupling of simple aryl bromides and boronic acids, affording the desired crude products containing only 13 ppm of palladium (detected by ICP analysis). EnCat-catalyzed Suzuki and Heck reactions have also been achieved using water as reaction media, obtaining good yields, comparable to those achieved using EnCats in organic solvents.**[146m]** and supercritical carbon dioxide**[49c, 147]** EnCats have been applied also in microwave-assisted Suzuki reaction.**[146h]** The conditions were optimized for a wide range of substrates, using ethanol as solvent and tetrabutylammonium acetate as homogeneous base.

The use of supercritical carbon dioxide as a solvent for EnCat-mediated Suzuki-type reactions has been extended to a continuous flow process, initially on a laboratory scale,**[147a]** then on a commercial scale apparatus.**[146f]** The coupling of 4-tolylboronic acid and iodobenzene was achieved at laboratory scale in 85% conversion in three passes at 55 °C and quantitative conversion from a single pass at 70 °C. On scale-up, an 81% conversion was realized at 100°C, 166 bar and flow rates between 6 and 10 mL/min. Quantitative conversions could also be attained using a mixture of toluene and methanol. It was noted that the catalyst bed had stable activity for over 1 h and that palladium contamination of the product was < 0.8 ppm.

Likewise, Pd(II) EnCat 30 catalyzed, microwave-assisted Suzuki cross-couplings were also applied to a simple flow system placed in the microwave cavity; microwave energy was pulsed and cooling applied to the tube so as to avoid overheating of the catalyst. Despite a short residency time of approximately 1 min at a flow rate of 0.1 mL min^{-1}, complete reaction was seen in all cases.**[146h, 148]** Only recently our research group first described Sonogashira type, alkynes-aryl halide cross-coupling reactions promoted by Pd EnCat catalysts, readily carried out under solvent less, copper-free conditions (with and without microwave-heating).**[146a, 146i, 146m-n, 149]**

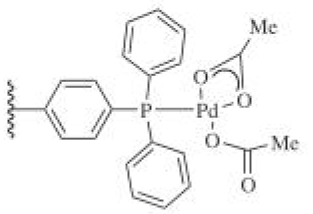
In conclusion, Pd EnCat™ catalysts appeared particularly attractive, because they are quite cheap, easily available, and not yet extensively studied in C-C cross-coupling reactions. particularly with regard to the use in flow reactors.

Johnson Matthey in 2010 commercializes a new generation of catalysts, which combine the selectivity of homogeneous catalysts with the ease of handling and separation of heterogeneous catalysts: the FibreCat® series.**[150]** FibreCats® are new heterogeneous catalysts with polymer-supported ligands; they consist of a polymer fiber, that is inert and insoluble in all solvents, to which functional groups, ligands and the precious metal can be added. The polymer support is a polyethylene or polypropylene fiber functionalized with vinyl monomers through electron beam irradiation. The initially reported system included a triphenylphosphine-modified fiber to which various palladium precursors could be coordinated.

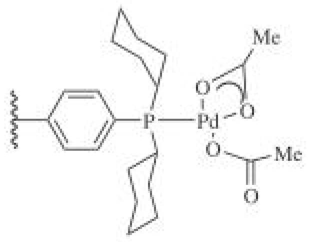
These polymers are fibers instead of beads, which may facilitate the contact between the catalyst and the reagents without the swelling required for some of the polystyrene materials. In fact, the catalytic centers are located at the exterior of the fiber, where they are easily accessible, while the resulting mechanically and chemically robust catalytic fibers alleviate the swelling problem typical of traditional polymeric beads. The range of products is suitable for many catalytic reactions: up to now, four series of these catalysts are commercially available.

The FibreCat 1000 series consists of palladium catalysts for coupling reactions, whereas the 2000 series covers rhodium catalysts for hydrogenation reactions. The 3000 series consists of oxidation catalysts, one ruthenium catalyst for selective oxidations and two osmium catalysts for dihydroxylations. The 4000 series includes one platinum catalyst for hydrosilylation reactions.

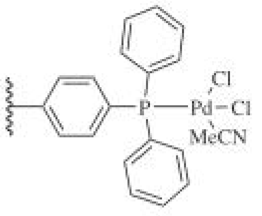
The Fibrecat 1000 series for carbon-carbon coupling reactions include a first generation of FibreCat catalysts consisting of Ph_3P-based systems with various Pd precursors; the most common are the FibreCat® 1001, FibreCat® 1007 and FibreCat® 1026 (**Figure 2.1.1**), designed for the conversion of aryl bromides and aryl iodides only. Subsequently, a second generation of FibreCats was introduced for the coupling of deactivated aryl chlorides. These materials incorporate an additional electron-rich and bulky monodentate ligand, such as Q-Phos, $^tBu_3P$, $(Me_2NC_6H_4)P(^tBu)_2$ (Ata-Phos), and IPr-carbene, as well as bidentate ligands such as BINAP, dppf, and dippf, bound to the heterogenized Pd center.



FibreCat® 1001
PPh_2-fibre/$Pd(OAc)_2$



FibreCat® 1007
PCy_2-fibre/$Pd(OAc)_2$

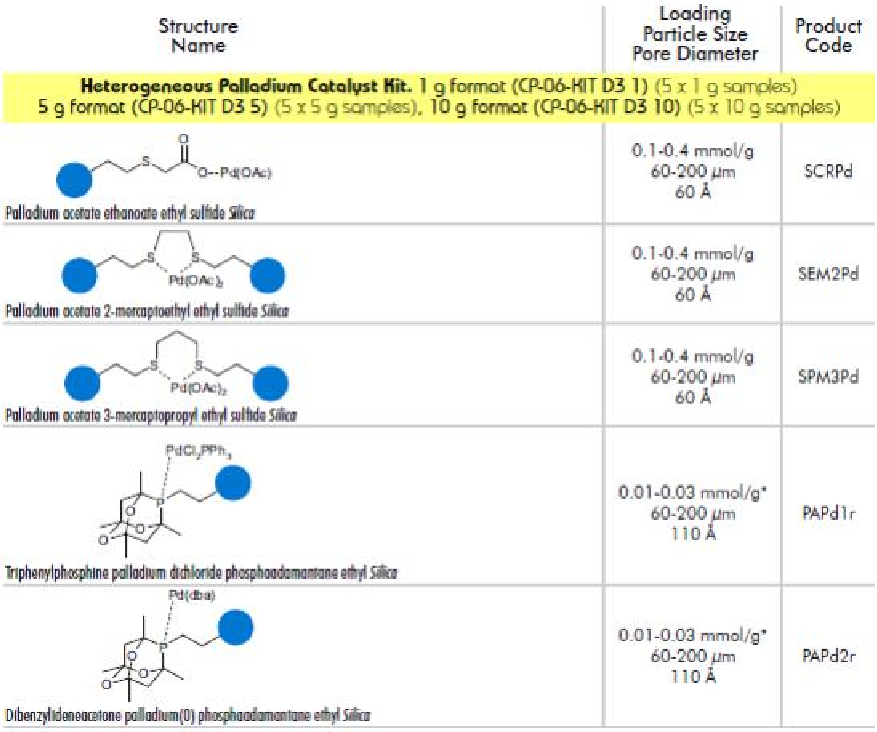


FibreCat® 1026
PPh_2-fibre/$PdCl_2$/MeCN

Figure 2.1.1: Fibrecat series for C-C cross-coupling

Even these cheap and easily available systems. not yet accurately studied in C-C cross-coupling reactions, , especially as regards the simple and affordable Fibrecat 1007.

Since 2009, the British company PhosphonicS commercializes a portfolio of heterogeneous functionalized silica-based catalysts (**Table 2.1.3**).**[151]**



Structure Name	Loading Particle Size Pore Diameter	Product Code
Heterogeneous Palladium Catalyst Kit. 1 g format (CP-06-KIT D3 1) (5 x 1 g samples) 5 g format (CP-06-KIT D3 5) (5 x 5 g samples), 10 g format (CP-06-KIT D3 10) (5 x 10 g samples)		
Palladium acetate ethanoate ethyl sulfide Silica	0.1-0.4 mmol/g 60-200 μm 60 Å	SCRPd
Palladium acetate 2-mercaptoethyl ethyl sulfide Silica	0.1-0.4 mmol/g 60-200 μm 60 Å	SEM2Pd
Palladium acetate 3-mercaptopropyl ethyl sulfide Silica	0.1-0.4 mmol/g 60-200 μm 60 Å	SPM3Pd
Triphenylphosphine palladium dichloride phosphaadamantane ethyl Silica	0.01-0.03 mmol/g* 60-200 μm 110 Å	PAPd1r
Dibenzylideneacetone palladium(0) phosphaadamantane ethyl Silica	0.01-0.03 mmol/g* 60-200 μm 110 Å	PAPd2r

Table 2.1.3: PhosphonicS heterogeneous palladium catalyst kit sample series

The most active catalyst of this series is made of silicaethylphosphatrioxaadamantane palladium; when it has been applied in low catalytic amounts (0.1 mol% in xylene at 120°C or under microwave irradiation of EtOH:H_2O:DME solutions) to a broad range of Suzuki substrate pairs, this Pd catalyst was found effective, reusable, and resistant to leaching, even if the hot filtration test was performed after only 2 min, a time frame that may be too short to observe accumulation of leached Pd in solution.**[152]** Unfortunately, these palladium catalysts on phosphine ligand-functionalized silica are commercially available but rather expensive.**[153]**

In 2010, a new series (trade named SiliaCat®) of Organically Modified Silicates (ORMOSIL) entrapped palladium catalysts for cross-coupling reactions was introduced by Canada's company SiliCycle (**Table 2.1.4**).

SiliaCatDPP-Pd and SiliaCatS-Pd are, respectively, diphenylphosphine and thiol based palladium(II) heterogeneous catalysts synthesized from a mercapto and diphenylphosphine functionalized organosilica matrix.**[154]** These economics catalysts can effectively catalyze Mizoroki-Heck, Sonogashira, Suzuki–Miyaura, Stille, Buchwald, and Kumada cross-coupling reactions with low leaching and good selectivity.**[155]**

More recently (since 2012), the new nanostructured Pd(0) catalyst SiliaCatPd(0), able to catalyze a number of C-C bond formation reactions, was introduced.**[156]**

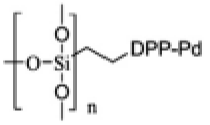
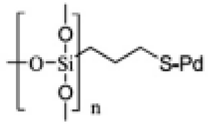
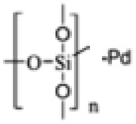
Product	**Pd loading mmol/g**	**Silica size µm**	**Structure**
SiliaCatDPP-Pd(II)	0.3-0.4	63-150	
SiliaCatS-Pd(II)	3.9-4.7	63-150	
SiliaCat-Pd(0)	0.03-0.17	60-125	

Table 2.1.4: SiliaCat heterogeneous palladium catalyst sample series

All SiliaCat® palladium catalysts (SiliaCatDPP-Pd, SiliaCatS-Pd, and SiliaCatPd(0)) were recently applied to the conversion of widely different substrates in Suzuki, Sonogashira, and Heck coupling reactions run in a parallel synthesizer.**[157]** The method enables quick screening with identification of the best reaction conditions and rapid library generation. Leaching tests for all catalysts employed show, invariably, that minimal leaching values are obtained with the SiliaCatPd(0) catalyst. However, in general the leaching increases with decreasing reactivity, and the highest release levels were afforded with nitrogen-coordinating substrates such as pyridines and quinoline.

Moreover, SiliaCatDPP-Pd and SiliaCatS-Pd were recently applied in Suzuki and Negishi cross-coupling reactions under continuous-flow conditions with low leaching and good yields and selectivity.**[153, 158]** In general, these systems seem very interesting for our purposes, but, at least until the start of this doctoral work, they were still difficult to find world-wide.

Finally, as regards the polymer-supported palladium, the polystyrene (cross-linked with divinylbenzene) beads doped with palladium catalysts are stable to heat and air and can be reused several times with minor decrease in activity in many cross coupling reactions.**[159]** Sigma-Aldrich, for instance, offers a wide variety of resins made of polystyrene-supported (PS) Pd species, and to be used for cross-coupling reactions (**Table 2.1.5**).**[160]**

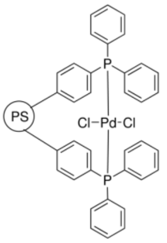
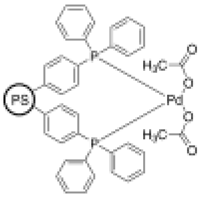
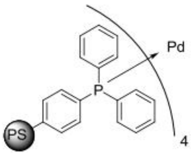
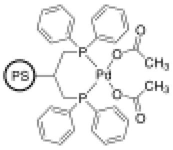
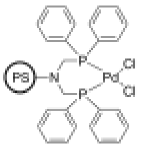
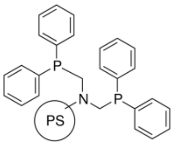
Product	Catalog Sigma-Aldrich code	Pd loading mmol/g	size mesh	Structure
$PdCl_2(PPh_3)_2$-PS polymer-bound	596930	1.0-2.0	200-400	
$Pd(OAc)_2$-PS polymer-bound	654167	1.0-1.5	200-400	
$Pd(PPh_3)_4$-PS polymer-bound	511579	0.5-0.9	200-400	
Bis[(diphenylphosphanyl)methyl]amine palladium(II) acetate, polymer-bound	654159	0.5-1.0	70-90	
Bis[(diphenylphosphanyl)methyl]amine palladium(II) dichloride, polymer-bound	646555	0.5-1.0	70-90	
N-Methylimidazolium palladium(II), polymer-bound	650927	1.0-2.0	70-90	

Table 2.1.5: Polymer-bound heterogeneous palladium catalyst sample of the Sigma-Aldrich

In many cases these resins leach palladium in several organic solvents (such as DMF, dioxane, toluene, etc.) and are broken by vigorous, long-lasting stirring. For example, the PS-Pd catalyst developed by Park and co-workers**[161]** rapidly loses the original activity in the Suzuki–Miyaura reaction, owing to palladium leaching and Pd nanoparticle aggregation, with yield in the third reuse lowered to only 38% from the original 98%.

In water the performance of polystyrene-supported catalysts improves, with decreased leaching. Wang and co-workers for instance reported that sodium tetraphenylborate rapidly reacts with aryl bromides in water at 120°C, under microwave irradiation, in the presence of a PS palladium catalyst to afford polyfunctional biaryls in good yields over 10 consecutive reaction runs without noticeable decrease in activity.**[162]** However, the scope of these materials is often limited to one specific reaction, and leaching is almost invariably responsible for the observed catalysis.

2.1.1.2 Commercial palladium supported catalysts selected

On the basis of our purposes and selection criteria, listed in paragraph 1.5, we have chosen four simple, readily available, easy to handle, economic and not yet thoroughly studied commercial catalysts characterized by very different property and structures: PdEnCat-40 (**1**), Fibrecat 1007 (**2**), $PdCl_2(PPh_2)$-PS (**3**) and $Pd(PPh_3)_4$-PS (**4**).

2.1.1.2.1 Pd EnCat-40™

The Pd EnCat™ 40 (**1**, catalog Sigma-Aldrich 644714), consist of Pd(II) acetate microencapsulated in a polyurea matrix in content of 40 %; the commercial product contain 0.37-0.44 mmol of Pd per gram of catalyst (**Figure 2.1.2**).

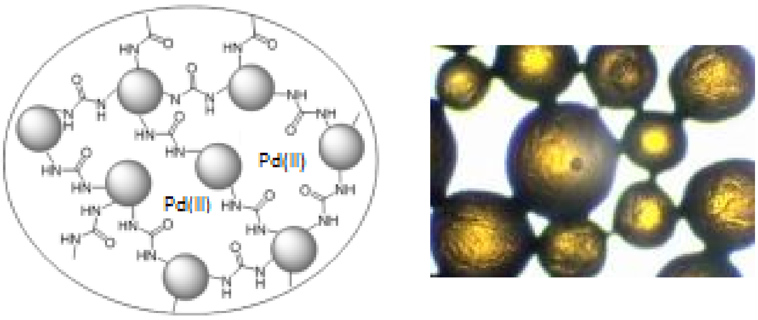


Figure 2.1.2: Pd EnCat-40

In literature there are some studies on the use of this catalyst in cross-coupling reactions performed under batch and/or flow conditions, but its actual potential and limits are yet to be verified.

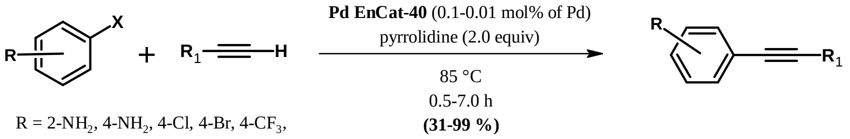
In batch mode this catalyst was used/studied in Heck, Suzuki and Sonogashira reactions.

In Heck reaction this catalyst was used only by Richardson and Jones, which carried out the coupling of iodobenzene or iodopyridine and butyl acrylate in either isopropyl alcohol (IPA) at 90°C, toluene at 110°C, or DMF at 110°C. In all experiments with Pd-EnCat 40, a 40:1 ratio of aryl halide to palladium was used.

The authors reported that, among the three solvents selected for this study, DMF has the greatest percentage of polymer swelling (110%) and gives the most palladium in solution (7 ppm). IPA and toluene cause significantly less swelling (5% and 0%, respectively), and both have < 1 ppm of palladium detected in solution.**[163]** Other studies on the Heck alkenylation have been performed using Pd EnCat-30, conceptually similar, but with improved kinetics while maintaining the mechanically robust nature.**[164]**

As regards Sonogashira-type coupling reactions, the first specific study about its use in these reactions is due to our research group in late 2009.

In particular, it was found that low loading of Pd EnCat 40 (corresponding to 0.01 mol % of Pd) gave good to excellent yields with iodo and bromo arenes under copper- and solvent-free conditions (**Scheme 2.1.1**).**[146g]**



R = 2-NH$_2$, 4-NH$_2$, 4-Cl, 4-Br, 4-CF$_3$,
4-MeCO, 2-COOMe, 4-Me, 2-Me
R1 = C$_6$H$_5$, 2-MeOC$_6$H$_4$, i-Pr$_3$Si
X = I, Br

Scheme 2.1.1: Pd EnCat-40 in Sonogashira Cu-free coupling[186]

In these conditions the catalyst is recyclable at least 3 times without significant loss of effectiveness. Moreover, in this study the authors report some tests with microwave heating:, also in this case the effect on yields and reaction times was dramatic.

Later, other studies on Sonogashira coupling have been performed using Pd EnCat-30 and/or Pd EnCat TPP30, by Ley's group **[149a]** and Kuang's group**[149b]**. However, it must be said, the loading of palladium required to obtain satisfying yields was much higher (1.0-3.5 mol %).

As regards the use in Suzuki coupling reactions, the Pd EnCat 40 was studied by Ley's group and other in both conventional solvents and scCO$_2$.**[45b, 49c, 146d, 147]**

This specie has proven to be effective as recyclable catalyst for use in Suzuki-type cross-coupling reactions, and do not require expensive phosphines as co-ligands; but, in general, these studies do not contain further details.

In continuous-flow mode, this catalyst has been used/studied in Suzuki reactions performed in conventional solvents or scCO$_2$,**[146d, 147]** as well as under microwave heating,**[146f]**, obtaining in all cases good yields after single or three passes through the reactor. The reactions are rather efficient (in one case authors report exploratory commercial-scale continuous flow using a 14.5 cm x 25.4 mm i.d. ModCol column with toluene/methanol as solvent and, most significantly, continuous flow using a 48.5 cm x 25.4 mm i.d. high-pressure column), but sometimes an additional purification step was required to remove residual palladium. Noteworthy, later other authors demonstrated that PdEnCat is only a solid reservoir for soluble, catalytically active Pd particles**[164a]**. Moreover, as it was demonstrated under microwave irradiation, prolonged heating of the reactor was detrimental for the polymer support, causing it to collapse, melt and eventually clog the tube.**[146f]**

2.1.1.2.2 FibreCat 1007®

The FibreCat® 1007 (**2**, cat. Aldrich 590231) is one of the most easily available and cheap palladium-based FibreCats: it consist of Pd(II) acetate anchored on fiber polyethylene support by dicyclohexylphenylphosphine ligand. The commercial product contain 0.40-0.60 mmol of Pd per gram of catalyst (**Figure 2.1.3**).

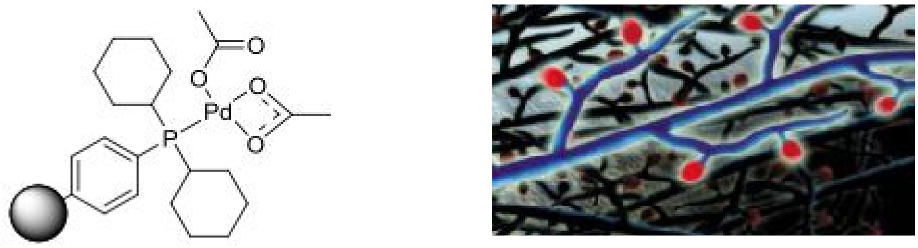


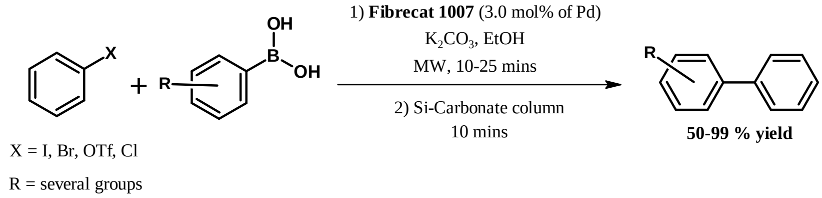
Figure 2.1.3: Fibrecat 1007

In literature are reported some examples of its use and study in cross-coupling reactions under batch and/or flow conditions, but, as in the case of Pd Encat 40, its actual potential and limits are yet to be verified.

In batch mode this commercial catalyst has been used/studied in Buchwald–Hartwig Amination,**[165]** α-Arylation**[166]** and Suzuki reactions; but it had not yet been tested in Heck and Sonogashira reactions. However, similar alkenylations or alkynylations were carried out with a certain success using a particular Fibrecat hardly available.**[167]**

The first study reported in the literature on Suzuki reactions promoted by fibreCat 1007 is due to Colacot and collaborators, in 2002; authors claim that, in a model Suzuki screen of p-bromoacetophenone with phenylboronic acid, results obtained with some types of FibreCat were slightly superior to the corresponding homogeneous systems in terms of selectivity and leaching.**[46]**

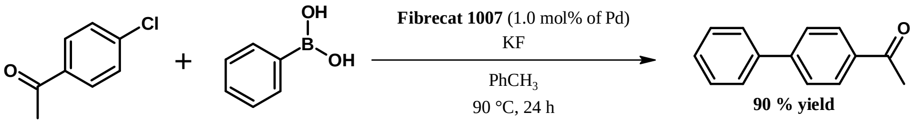
In 2004, Sauer a Wang, using Fibrecat 1007 and other two Fibrecat (1001 and 1032), successfully coupled several aromatic halides and/or triflates under microwave-promoted conditions (**Scheme 2.1.2**).**[168]**



Scheme 2.1.2: Fibrecat 1007 in Suzuki coupling under MW heating

In this case the authors obtained good results in terms of yields and reaction times using a high catalyst load (3.0 mol % of Pd). Nevertheless, under these conditions moderate yields were achieved with inactivated aryl chlorides.

However, Nishida and Tagata claim that, under conventional heating, this system is able to promote the Suzuki coupling of low-reactive aryl chlorides in toluene and KF as base, to give the desired products in high yields (**Scheme 2.1.3**)**[169]**



Scheme 2.1.3: Fibrect 1007 in Suzuki coupling with aryl chlorides[199]

In general, FibreCat 1007 provides good filterability, which is industrially advantageous over conventional polymer bead-supported catalysts.

In 2006, Tye et collaborators reported a study on the minimization of palladium content in Suzuki cross-coupling reactions, carried out with several catalyst among which the Fibrecat 1007; in preliminary screens these authors verified that the use of this catalyst lead to the efficient synthesis of a range of functionally diverse biaryls in good yield (for most cases) and with low levels of Pd contamination (70 ppm, that the authors reduced at < 10 ppm for a wide variety of building blocks using a Pd-scavenger).**[170]**

As regards flow reactors, until 2012 (when this doctorate work was started), this catalyst was used/studied only in one paper on Sonogashira-type Cu-free coupling reactions.**[171]** In this work the authors reported the screening of 4 commercial heterogeneous catalysts over six Sonogashira coupling reactions together with longevity estimation. The Fibrecat 1007 and 1001 showed the highest performance with 4-iodo-anisole, if both the conversion and the selectivity were taken into consideration, while when 4-bromo-anisole was applied as an aromatic halide these systems gave very low results.

Later, in 2014, Gordon and co-workers reported an efficient continuous flow approach to obtain furan-based biaryls. They screened different palladium catalysts, including the Fibrecat

1007; this catalyst giver rise to the desired Suzuki reactions with relatively high efficiencies.**[172]**

However, more recently other Fibrecat (principally 1001) were applied with a certain success in Suzuki and Heck coupling under flow conditions.**[173]**

2.1.1.2.3 $PdCl_2(PPh_3)_2$-PS

The $PdCl_2(PPh_3)_2$-PS (**3**, Catalog Sigma-Aldrich 596930), consists of $PdCl_2$ anchored to a diphenylphosphinated divinylbenzene cross-linked polystyrene matrix (PS).

The commercial product contain 0.90-1.10 mmol of Pd per gram of catalyst; the particle size is of 100-200 mesh (**Figure 2.1.4**).

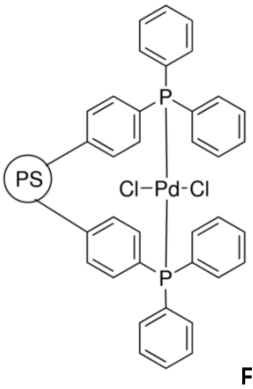


Figure 2.1.4: $PdCl_2(PPh_3)_2$-PS

Although this supported catalyst is commercially available for several years, there are not many papers on its catalytic abilities in cross-coupling reactions performed in batch reactors.

The first example of its applicability in Suzuki reactions is found in the work of Fenger and Le Drian (1998),**[174]** where this system was compared with other polymer supported catalysts; in the model reaction between phenylboronic acid and 4-bromopyridine it gave a yield of only 72% with a very high level of catalyst (13.5 mol % of Pd).

Other uses are reported in ChemFiles "Polymer-Supported Catalysts and Reagents" of the Aldrich, with just one example of cross-coupling reactions.**[160a]**

However, in literature there are several very similar systems that are used in C-C cross-couplings.**[113b, 175]** For example, Bai and Wang applied palladium chloride attached to polymer-supported diphenylphosphine in the coupling between sodium tetraphenylborate and various aryl bromides, using water as the solvent in conjunction with focused microwave irradiation.**[162]**

In flow mode, until 2012 (when this doctorate work was started), this catalyst was used/studied in only one article about Sonogashira-type, Cu-free coupling reactions.**[171]** In this work the authors reported a screening of four commercial heterogeneous catalysts over six Sonogashira coupling reactions, together with longevity estimation. The $PdCl_2(PPh_3)_2$-PS showed the good performances with 4-iodo-anisole as halide, and provided the best results in terms of the selectivity and yield with the deactivated 4-bromo-anisole.

2.1.1.2.4 $Pd(PPh_3)_4$-PS

The $Pd(PPh_3)_4$-PS (**4**, catalog Sigma-Aldrich 511579), developed by Fenger and Le Drian in 1998,**[174]** consists of a diphenylphosphinated divinylbenzene (2 %) cross-linked polystyrene matrix (PS) treated with a solution of $Pd(PPh_3)_4$. The commercial product contain 0.50-0.90 mmol of Pd per gram of catalyst; the particle size is of 100-200 mesh (**Figure 2.1.5)**.

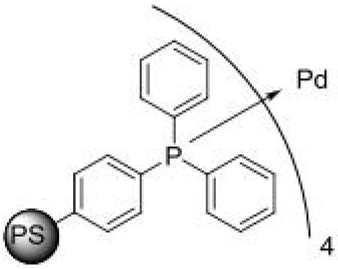


Figure 2.1.5: $Pd(PPh_3)_4$-PS

In the original work the catalyst was tested in the Suzuki–Miyaura reaction between 4-bromopyridine with phenylboronic acid, carried out in batch mode. Excellent yields, analogous to those obtained when $Pd(PPh_3)_4$ was used as homogeneous catalyst, were obtained, with the advantage that the heterogeneous catalyst could be easily separated from the reaction mixture and reused more than five times without any activity decrease.**[174]**

However, in literature there are several very similar systems that have been used in cross-coupling reactions.**[113, 175]** For example, Jang in 1997**[176]** reported the use of a polymer-bound $Pd(PPh_3)_4$ catalyst in the Suzuki coupling of a number of organoboranes with alkenyl bromides, iodobenzene, and aryl triflates; the polymer-supported catalyst was been prepared from Merrifield resin. In this case the authors obtained good isolated yields in the range 78-96%; the catalytic activity was at least comparable to that of homogeneous $Pd(PPh_3)_4$, and in some cases was significantly improved. The catalyst was reused more than 10 times with no decrease in activity, showing the huge utility of these supported catalysts.

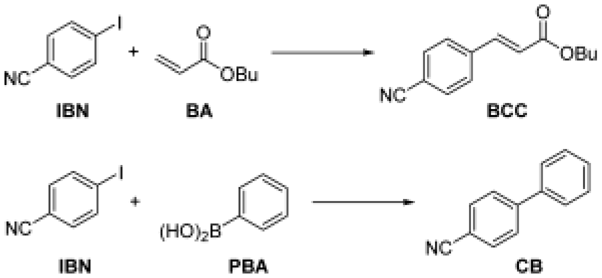
In 2000 Miyaura**[159a]** investigated the use of PS-bound Pd in cross-coupling reactions and successfully extended the range of applicable substrates. Tolylboronic acid was thus coupled to a number of chloropyridines, activated chloroarenes, and chloroquinoline. Yields were generally in the region of 90%, and the catalyst was reused six times without loss of activity, although the appearance of the polymer was reported to change from yellow to gray.

In 2007 Becht and co-workers **[177]** reported the use in Sonogashira-type reactions of polymer-bound palladium catalysts with different aryl substituted phosphines ligands. These systems afforded good yields with several electron-rich aryl iodides and low catalytic loading of Pd (0.5-0.05 mol %), but in presence of high amounts of CuI as co-catalyst (5.0 mol %). The catalysts were reused more than 4 times with no decrease in activity, although these systems showed a leaching in the range 1.0-2.0 %.

In flow mode, until 2012 (when this doctorate work was started) this type of catalyst was not used/studied in cross-coupling reactions.

In 2014, it has been shown by Gordon and co-workers that this catalyst can be applied for continuous-flow Suzuki–Miyaura reactions involving furylboronic acids,**[172]** although a detailed investigation on the stability of this particular catalyst was not carried out.

Most recently, in 2015, Kappe and co-workers reported the screening of 4 commercial supported catalysts over two cross-coupling reaction models (the Mizoroki–Heck reaction of 4-iodobenzonitrile with n-butyl acrylate and the Suzuki–Miyaura reaction of the same halide with phenylboronic acid, **Scheme 2.1.4**).**[173]**



Scheme 2.1.4: Cross-Coupling Reactions Selected as Models in the Kappe's group Study[216]

In the case of the Heck reaction an essentially constant reaction profile was obtained under steady-state conditions. Full conversion was obtained within the relatively short contact time of the reaction mixture with the catalyst bed, although with a quite low selectivity (formation of ca. 25% dehalogenation product and ca. 15% homocoupling).

As regards the Suzuki reaction, the situation looks completely different. In this case the substrate was fully consumed during the first 40 min of reaction, but then dropped dramatically to a conversion of <10%. Moreover, the catalyst was rapidly degraded during this reactions, and significant amounts of metal were most likely leached from the support, contaminating the products.**[173]**

2.1.2 “Home-made” palladium nanoparticle catalysts

As already mentioned in paragraph 1.4, in addition to suitable commercial catalysts, we wanted to test also some *“purpose-build”* systems prepared and studied in collaboration with the ISTM-CNR Institute of Milan.

These *home-made* catalysts have been developed taking account of the simplicity and cost of the method as well as the availability and cheapness of the solid supports.

Supported Palladium catalysts were prepared by many methods (see paragraph 1.1.2), which allow to obtain supported Pd-complexes**[178]**, supported Pd-nanoparticles and encapsulated Pd-complexes **[179]**

The nature of the metal and the support can lead to different results as regards the characteristics, and therefore properties, of a catalyst. Similarly, the preparation techniques used can affect the delicate balance among high activity, high selectivity, and lifetime of the obtained catalyst system. Typically, the different approaches envisage an improved stabilization and an improved reusability, but a proper comparison between them is difficult to establish due to the lack of a model reaction as well as a proper kinetic study of the catalytic effect.**[180]**

In this contest, transition metal nanoparticles (NPs) have gained a lot of interest over the last decade for a variety of applications, with catalysis exerting a central role.**[181]** These nanometer species are considered ideal candidates for improving the sustainability of catalytic processes, blending together the advantages of homogeneous and heterogeneous catalysts.**[182]** The reduction of metal particles size to the nanoscale lead to an increase of the surface-to-volume ratio and thus the number of active sites, maximizing the use of noble metals. However, the catalytic activity is not dependent only on the particle size, and maximum activity at a certain optimal intermediate size has been reported,**[183]** which suggests that both the number of surface metal atoms (active sites) and the electronic properties at nanoscale can have a profound impact on catalytic activities.

In this respect, Pd nanoparticles are widely utilized, directly as catalysts or as precursors of supported catalyst, to promote C-C cross-coupling reactions, as witnessed by the numerous reviews present in the literature.**[9a, 26e, 184]** Metal NPs have low stability against agglomeration, since the bulk metal is the thermodynamic minimum, however NPs highly dispersed on solid supports exhibit higher stability and catalytic activities than the same NPs stabilized in liquid phase and applied in biphasic reactions.**[185]**

Supported metal NPs can be prepared by means of deposition methodologies of nanoparticle solutions, where the particle size and size distribution are finely controlled, generally resulting highly homogeneous and extremely small (< 10 nm), widely distributed and already in catalytically active form Pd(0).These differences in the size and distribution of the particles result in a different catalytic activity; in fact usually the catalytic activity decreases with the increase of average particle diameter,**[186]** as it has recently been observed in hydrogenation**[187]** and hydrosilylation**[188]** reactions, as well as in Heck-type alkenilations**[189]**

On the basis of the literature, stable heterogeneous catalytic systems making use of supported Pd NPs can undoubtedly allow effective cross-coupling reactions carried out in batch mode.**[189c-e]** For example, Pd nanoparticles supported on polymers like polyvinylpyridine**[189c,d]** and/or polyidimethilphosphazene,**[189e]** (particle size = 2.0 nm) showed a catalytic activity superior to that of various commercial (homogeneous and heterogeneous) catalytic systems in Heck reaction, with low leaching phenomenon.

Stable supported catalytic systems making use of supported Pd NPs can also be effectively used to promote cross-coupling reactions performed in continuous flow systems.**[190]** In this way, the high local concentration of catalyst, together with the absence of reagent diffusion limitation, can allow conversion rates higher than in batch mode.**[66b-c, 86, 191]** However, the use of continuous flow microreactors, necessitates stable NPs which can be reused for many cycles. Therefore, the leaching of metal species associated with the use of Pd NPs for C-C cross-couplings under flow conditions represents an important issue.

2.1.2.1 Preparation of nanoparticle-supported catalysts - Metal Vapour Synthesis

For the reasons discussed in the previous paragraph, the use of supported palladium nanoparticles looked particularly attractive for our purposes. Moreover, the application of these systems could offer advantages in terms of catalytic activity, efficiency, low palladium leaching and even of recycling. Obviously, all this depends on the method of nanoparticle preparation and the nature of the support used.**[192]**

The various methods for synthesizing metal NPs were extensively reviewed by Bönnemann,**[193]** Schmid,**[194]** Aiken and Finke,**[195]** Roucoux,**[196]** Wilcoxon**[197]**, Philippot and Chaudret**[198]** and Cushing**[199].** In general, there are four main categories.

- **Reduction of transition metal salt precursors[200]**

In this approach,a reducing agent (e.g.hydrogen, alcohol, hydrazine or borohydride) is mixed with the metal precursor salt in the presence of stabilizing agents(ligands, polymers or surfactants) to prevent the undesired agglomeration and formation of metal powders. The chemical reduction route is simple, low cost and not time consuming, but the actual size of the NPs depends on many factors, including the type of reducing agent, metal precursor, solvent, concentration, temperature and reaction time.

Generally, the nanoparticles aggregates made by this method were 3.0 – 10.0 nm in diameter. This method proved to be inconvenient for scale up and, even after being washed, the nanoparticles still contained measurable levels of carbon, oxygen, and chlorine.**[201]** Other problems are the difficulty to obtaina full reduction of metal ions to zero-valent state, and sintering, which can take place during the treatment at high temperature.

- **Decomposition of organometallic precursors[196, 202]**

This approach is based on thermal, ultrasound and/or catalytic decomposition of organometallics in the presence of a surface passivation agent for particle protection and stabilization. More particularly, suitable organometallic compounds dissolved in a solvent or brought in the vapor state are adsorbed on a support; once adsorbed, the controlled thermolysis leads to loss of binders and to the growth of the metal nanoparticles.

Generally, the nanoparticles aggregates made by this method were 5.0 – 15.0 nm in diameter. This method proved to be inconvenient for scale up due to sintering, during the treatment at high temperature.

- **Electrochemical synthesis[194-196, 203]**

This method was developed by Reetz in the 1990s;**[204]** the overall process includes five steps 1)oxidative dissolution of the sacrificial metal bulk anode; 2) migration of metal ions to the cathode; 3)reductive formation of zero-valent metal atoms at the cathode; 4) nucleation and growth of metal particles and 5)arresting the growth process and stabilizing the NPs with protecting agents (e.g. tetraalkylammonium ions).

The electrochemical pathway avoids contamination with by-products resulting from chemical reducing agents, and the products are easily isolated from the precipitate. Further, it allows size-selective particle formation by tuning the current density (high current densities lead to small NPs, and vice versa). The particle size can also be controlled by adjusting the distance between the electrodes, the reaction time and temperature, or the solvent polarity.

This method was successfully applied in the preparation of vary monometallic NP organosols and hydrosols, including Pd, Ni, Co, Fe, Ti, Ag and Au. Bimetallic alloys (e.g. Pd–Ni, Fe–Co and Fe–Ni) are accessible if two sacrificial metal anodes aroused simultaneously.**[205]**

- **Metal vapour synthesis (MVS) [206]**

The method consists in the simple co-condensation of the atomic vapour of a metal (generated by heating throughthe Joule effect, or by electron-impact) with those of one or more weakly coordinating organic solvents (toluene, tetrahydrofuran, n-pentane, etc.) under high vacuum (generally 10^{-4}-10^{-6} mbar) at low temperature (-196 °C), giving a solid matrix.**[207]**

Subsequently, upon warming, the dissolved solid matrix forms stable (at suitable temperature) zero-valent nanoparticles solutions with very low particle size (usually < 5.0 nm of diameter).

This method was successfully applied in the preparation of monometallic NPs, including Pd, Ni, Pt, Rh, Cu, Co, Fe, Ti, Ag and Au. Hetero bimetallic NPs (e.g. Pd–Ni, Au–Pd etc.) can be prepared by the Full-SMAD technique (Solvated Metal Atom Dispersion), that allows the simultaneous vaporization of two different bulk metals, or the Half-SMAD technique, that involves the simple mixing of two different zero-valent metal nanoparticle solutions.

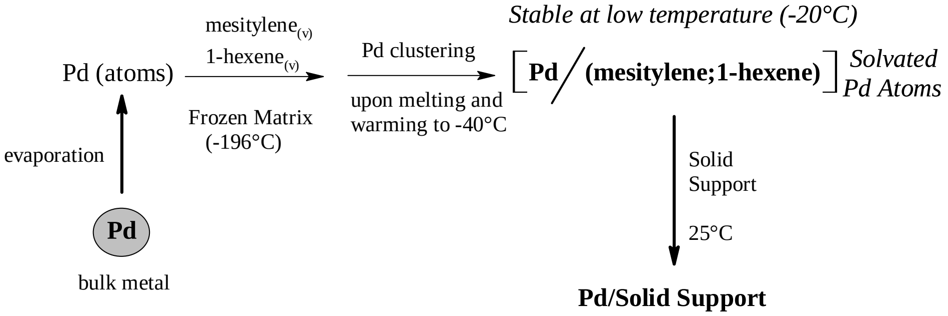
This last method appears to be particularlyinteresting for our purposes; in fact, it allows the preparation of Pd(0) nanoparticles without contamination of ligands or other (which is also attractive from a "green" point of view)**[208]** by using common metal turnings or powder, and a simple and currently commercial apparatus (**Figure 2.1.6**).

Moreover, this technique can allows to obtain bi- or multi-metal catalytic systems that show characteristic and property similar to a metal alloy, but very different from that obtained by simple mixing of different metal nanoparticles solutions.**[209]**

Figure 2.1.6: a) MVS apparatus for the synthesis of mono- and bimetallic nanoparticles (Pd, Au, Pt, Ni, Rh, Co, Cu) b) Glass reactor equipped with joule effect heating for vaporization one or two metals simultaneously

For these reasons, we decided (in collaboration with the ISTM-CNR Institute of Milan, and in particular with Dr. Claudio Evangelisti) to make our *"purpose-build"* catalysts *via* Metal Vapour Synthesis, by using the apparatus reported in **Figure 2.1.6**.

Following a well established procedure**[30c, 189d]** the palladium atoms were co-condensed, at liquid nitrogen temperature (-196°C) and under vacuum (10^{-4}torr), with a 1:1 (v/v) mixture of 1-hexene and mesitylene, forming a solid matrix on the glass reactor walls. A brown solution was then obtained by heating the reactor until the solid matrix melts (ca. -40°C); this solution contains palladium nanoclusters, which are soluble and stabilized by the excess of the organic solvents (Palladium Solvated Metal Atoms, Pd-SMA). The Pd-SMA solution be haves as a source of metal nanoparticles in a content. When the solution is warmed to room temperature in the presence of the selected support, the nanoclusters are easily deposited leading Pd nanoparticles highly dispersed on the support with a very narrow particle size distribution (mean diameter between 1.0 and 3.0 nm) (**Scheme 2.1.5**).**[30c]** The MVS approach to obtain size-controlled metal particles has generally the following advantages over traditional metal particle synthesis which foresees a reduction step of the oxidized metal precursor: (i) The final metal content can be sterred by the concentration of the solvated metal particles in solution; (ii) Metal particles of comparable size are accessible, regardless of the support employed; (iii) The supported NPs contain only metal in its reduced form.



Scheme 2.1.5: General scheme of Preparation of supported metal nanoparticles by Metal Vapour Synthesis

2.1.2.2 Solid Supports selection

Therefore, taking into account the statements reported in the paragraph 1.4, to prepare our *"home-made"* catalysts we select two different type of solid supports.

Many kind of solid supports have been commercialized and used (directly or functionalized) to prepare palladium catalysts (carbon, zeolites, silica, polymers, etc.). Unfortunately, in many cases, the supported systems leach palladium under the reaction conditions leading to highly active soluble palladium species. Only a few examples of leach-free heterogeneous palladium systems have been reported; they include palladium salts on zeolites (whose behaviour depends on the catalyst pre-treatment and on the base and solvent used)**[210]** and palladium nanoparticles deposited on i) a particular layered double hydroxide,**[211]** ii) suitable functionalized zeolites containing primary amino groups,**[212]** and -SH **[52]** or iii) suitable functionalized silica containing -NH_2 and -SH groups.**[156]**
Moreover, the presence of protective organic capping ligands, or their decomposition products, is considered to have a detrimental effect on catalytic activity; in fact they can block the catalytically active sites on the supported nanoparticle surface.**[213]** That is why the organic ligands are suggested to be carefully selected (weakly bound ligands are preferred) or even removed to recover activity. Nevertheless, the capping ligands can also act as spacers between the metal NPs and the support in such a way that beneficial metal–support interactions can be obtained, tuned and optimized in order to increase the activity of supported metal catalysts.**[214]** Therefore organic ligands, surfactants, polymers or inorganic coatings are employed to stop the particle growth process, control the size of NPs and keep them stable by steric or electrostatic stabilization.**[215]**

On the basis of the literature and our selection criteria (see paragraph 1.4), we chose two simple, commercially available and cheap solid supports with different property and characteristics: a functionalized polymer and a mesostructured material.

The first (the functionalized polymer) is the PVPy [poly(4-vinylpyridine) cross-linked with 2% divinylbenzene] of the Sigma-Aldrich (**Figure 2.1.7**) mainly used as metal scavenger**[189b]** or support of oxidizing and reducing agent.**[216]**

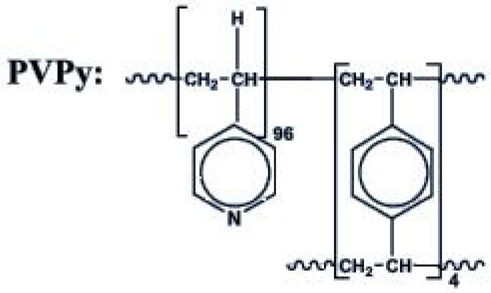


Figure 2.1.7: poly(4-vinylpyridine) cross-linked with 2% divinylbenzene

This polymer, insoluble in water and common organic solvents, has attracted much attention because of its commercial availability, stability, reasonable high loading capacity, good swelling characteristics, and good physicochemical structure. The high presence of pyridine groups allows fixing oxidizing and reducing agents, as well as metals, on PVPy via electrostatic force, which may be of an ion-exchange or chelation type.**[216]**

Although PVPy has a low cross-linking degree (2%), it is poorly swellable in most common solvents, and particularly in mesitylene (the swelling degree expressed as specific absorbed volume of mesitylene per gram of dry PVPy is as low as 0.2 cm^3/g)**[217]**

Generally, swelling has an adverse effect on the mechanical properties of lightly cross-linked resins. Normally, the larger the swelling degree, the weaker the swollen material.

Moreover, the low cross-linked PVPy is most flexible and stable during handling and use, while more highly cross-linked PVPy is more rigid, and the polymer chains are susceptible to degradative scission during physical handling.

Our choice of PVPy as support is also derived from our previous experience with several resin-supported palladium catalysts prepared via MVS;**[30c, 189d]** In particular, just the Pd/PVPy obtained via MVS had been already prepared, studied and applied(in Heck and Suzuki coupling reactions performed in batch) from our group, with good to excellent results.**[30c, 218]** This system was particularly stable in the Heck-type alkenylation of alkyl acrylates with iodo- and bromoarenes, ensuring a very low Pd. The corresponding trans-cinnamates were obtained with yields in the range 35-95% at 100-175°C, depending on the substituent present on the aromatic ring of the aryl halide. In addition, the catalyst can be recovered and reused without loss of catalytic activity.**[30c]**

When used in the Suzuki-Miyaura reactions, low loads of this system allow efficient cross-couplings between several arylboronic acids and activated or deactivated aryl bromides, carried-out in aerobic conditions. Our Pd/PVPy also showed good recyclability, with coupling yields maintained over five catalytic cycles, and a low Pd leaching.**[218]**

Seen such preliminary good results it looked very interesting and useful to a study of the catalyst system in the continuous-flow.

The other solid support chosen (the mesostructured material) is a commercial mesopourous silica MCM-41 (Sigma-Aldrich, **Figure 2.1.8**).

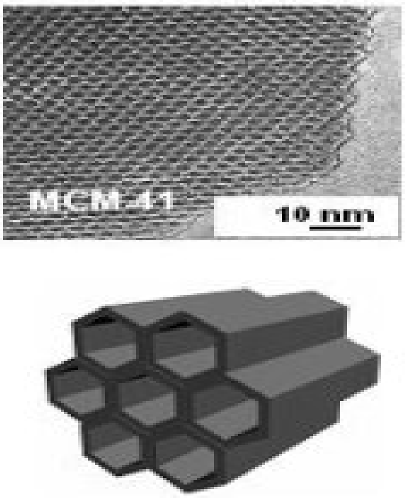


Figure 2.1.8: Mesopourous silica MCM-41

It's a mesoporous silicate molecular sieve, that was first developed by researchers at Mobil Oil Corporation in 1990s.**[219]** The MCM-41 consists of a regular hexagonal arrangement of cylindrical mesopores that form

a one-dimensional pore system (with diameters ranging from 2.0 to 10 nm).**[220]** It is characterized by an independently adjustable pore diameter, an array of nonintersecting hexagonal channels, a sharp pore distribution, a large surface area (≈1000 m^2/g) and a large pore volume. The pores are larger than with zeolites, and, contrary to zeolites, the framework of MCM-41 has no bronsted acid centers because there is no aluminium contained in the lattice. In general, the pure silica MCM-41 materials are very few hydrothermally stabile (mainly in boiling water).**[221]** Indeed, when subjected to refluxing in water for short periods of time, conventional pure silica MCM-41 materials are readily rendered amorphous.**[221a]** The hydrothermal stability of pure silica MCM-41 materials can, however, be improved by adding various salts to their synthesis gels**[222]** or via post synthesis modifications which either increase the pore wall thickness**[223]** or render the walls hydrophobic.**[224]**

Up to now, due to its unique properties such as homogeneity of the pores, high surface area, narrow pore size distribution, tunable and accessible pores and good thermal stability, MCM-41 has been a focus for several research areas like nanoscience,**[225]** catalysis,**[226]** environmental purification,**[227]** adsorption **[228]** and drug delivery**[229].** In fact, the MCM-41 (mainly functionalized) is widely used as support of palladium(0) or (II) complexes to be used as catalysts for cross-coupling reactions.**[230]**

Jana et al. reported Pd(0) immobilized into a silica-based mesoporous material to develop the catalyst Pd(0)-MCM-41, which washighly active in C-C coupling reactions. $[Pd(NH_3)_4]_2^+$ ions have been incorporated into the mesoporous material during synthesis of MCM-41 and subsequently upon treatment with hydrazine hydrate. Pd(0)-MCM-41 showed high catalytic activity toward C-C bond formation reactions like Heck and Sonogashira coupling, with high TONs. This catalyst was also efficient in the activation of arylchloride to give impressive conversion in cross-coupling reactions under mild conditions.**[231]** Clark et al. have also reported C-C coupling of iodobenzene using pyridinium–Pd complexes immobilized on MCM-41 with a minimal level of Pd leaching and TONs of around 2000 mmol of methylcinnamate/mmol Pd in the fifth cycle.**[232]**

Cai and co-workers have recently developed a novel MCM-41-supported sulfur Pd(0) complex and explored its catalytic properties in Sonogashira coupling reaction. This mesoporous material (MCM-41) was conveniently synthesized from commercially available mercaptopropyltriethoxysilane via immobilization on MCM-41, followed by reacting with Pd chloride.**[233]** Using piperidine as both the solvent and the base and in the presence of CuI as the co-catalyst, this novel MCM-41-supported sulfurPd(0) provided a very efficient system for Sonogashira coupling reaction of activated and unactivated aryl iodides with terminal alkynes.

Kosslick and co-workers prepared the Al-MCM-41-supported Pd. The alkylsulfonated support is prepared by bi- or tridentate anchoring of mercaptopropyltriethoxysilane on the wallsof Al-MCM-41. This system was successfully used in Suzuki coupling reaction; remarkably, the recycled catalysts showed an enhanced activity.**[234]**

The imidazolium-tagged carbapalladacycle electrostatically bound to Al/MCM-41 was used as a catalyst for the Suzuki coupling in toluene and DMF as solvent. Better results were obtained inthe latter aprotic polar solvent, in good agreement with the general behavior of the catalytic activity of the soluble parent carbapalladacycle.**[235]** Instead Corma and co-workers established that an oxime-carbapalladacycle complex covalently anchored onto mercaptopropyl-modified MCM-41 catalyzed cross-couplings of halobenzenes with phenylboronic acid in aqueous media.**[236]**

Considering the above-mentioned good results reported in the literature on functionalized MCM-41-based catalysts, as well as the unique properties and enormous advantage of the large pore size of theMCM-41 material (which, both in batch and flow mode, can facilitate the flow of reactant and product molecules in and out of the pore system), we decided to attempt touse the simple and commercially available pure MCM-41 (pore size 2.1-2.7 nm) as a support for MVS-derived palladium nanoparticles.

2.1.2.3Preparation and characterization of our supported catalysts

The Pd/PVPy (**5**) and Pd/MCM-41 (**6**) species were prepared using the Palladium Solvated Metal Atoms (Pd-SMA) obtained via MVS by applying the procedure outlined above (paragraph 2.1.2.1). A 2.8-3.0 mg/mL solution of Pd-SMA in a 1-hexene/mesitylene mixture was added drop by drop to a suspension of solid support (PVPy or MCM-41) in 1-hexene/mesitylene. The mixture so obtained was stirred for 16-24 h at room temperature until the solution was colourless. The solvent was removed and the light-brown solid was washed with n-pentane and dried under reduced pressure, to obtain **5** and **6** with a nominal Pd loading of 1 % wt. The metal content of the samples was determined and confirmed by ICP-OES analysis.

2.1.2.3.1 Pd/PVPy, (5)

The polyvinylpyridine-supported palladium catalyst, Pd/PVPy (**5**), was prepared by means of MVS technique, as previously described**[237].**The palladium content, measured by ICP-OES analysis, was 1.0 wt. % (0.094 mmol g^{-1}).

TEM micrographs of the Pd/PVPy system (**Figure 2.1.9**) show a representative microstructure of the system. PVPy polymer appeared homogeneously populated by nanometric metal particles distributed in a narrow range (1.0 nm-6.0 nm) with a mean diameter of 2.7 nm. Moreover, high resolution TEM analysis (Figure 1, upper right) suggest metal particles included into the polymeric resin, in agreement with previously reported data**[30c, 189d]** on the strong affinity of metal nanoparticles with the pyridine moiety of the support.

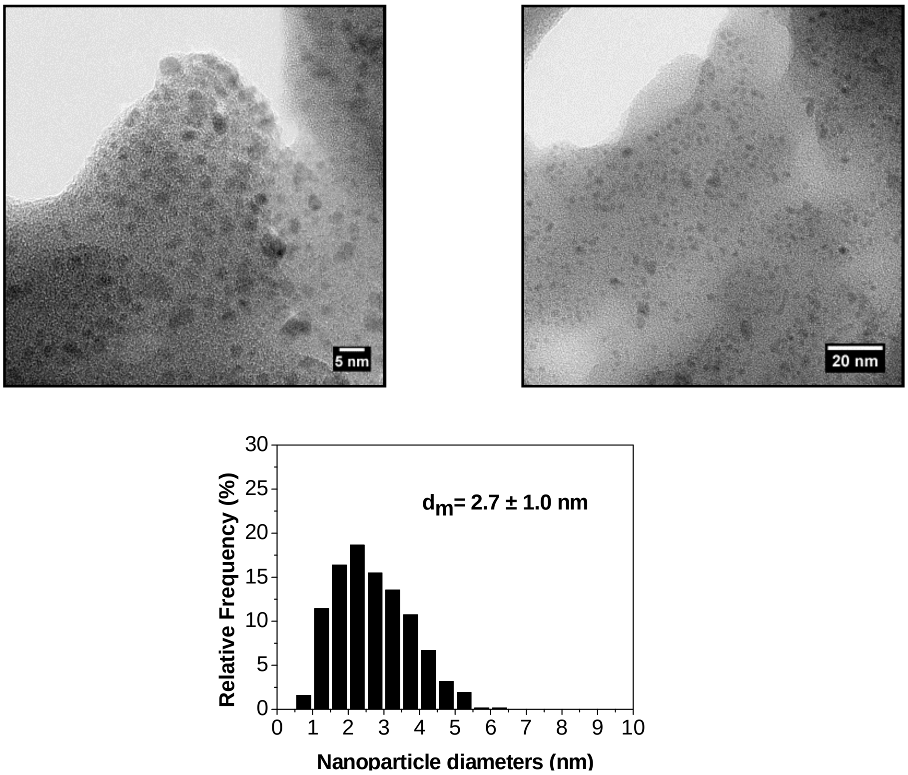


Figure 2.1.9.TEM microphotograph and metal particle size distribution of MVS-Pd/PVPy: whole bead.

Structural and morphological characterization by XAS analysis of the pristine Pd/PVPy system (**Figure 2.1.10**) confirm that there may be an electrostatic interaction between the Pd atoms and the nitrogen atoms of the pyridine rings, as already reported in the literature.**[30c, 189d]**

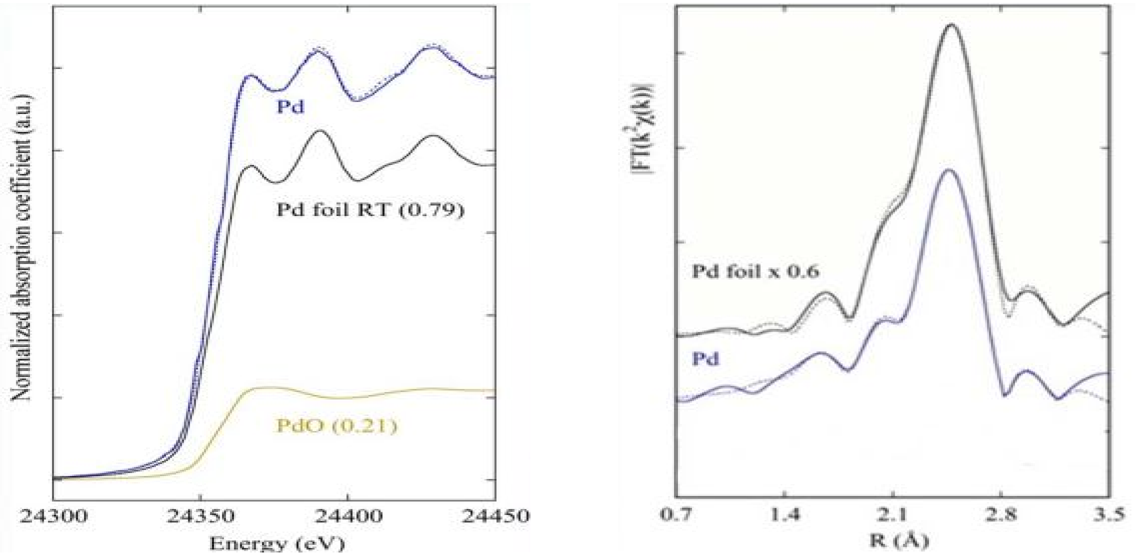


Figure 2.1.10: XANES AND EXAFS spectra of pristine MVS-Pd/PVPy

2.1.2.3.2 Pd/MCM-41 (6)

The mesoporous silica-supported palladium catalyst, Pd/MCM-41 (**6**), was prepared by means of the same,above described,MVS technique.**[237]** The palladium content, measured by ICP-OES analysis, was 1.0 wt. % (0.096mmol g^{-1}) and 2.0 wt. % (0.188 mmol g^{-1}).

TEM micrographs analysis and particle size distributionof the Pd on MCM-41 support (**Figure2.1.11**) show a representative microstructure of the system. Metal particles ranging mainly from 1 to 6 nm, and are homogeneously and symmetrically distributed around a mean size of about 2.9 nm. The standard deviation also showed that the nanoparticles are relatively monodisperse in the solution.

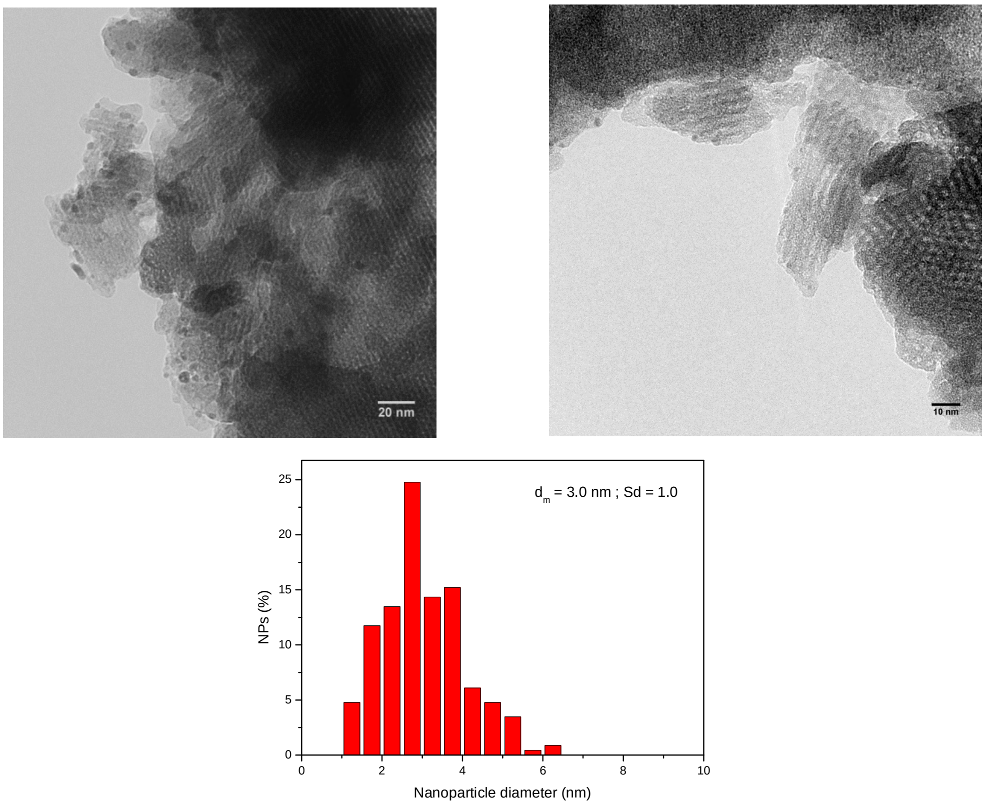


Figure 2.1.11.TEM microphotograph and metal particle size distribution of MVS-Pd/PVPy: whole bead.

2.1.2.4 Preparation and characterization of bimetallic Pd-Cu supported catalyst

In addition to the above described monometallic catalysts (Pd/PVPy and Pd/MCM-41), we also planned to develop a simple and inexpensive bimetallic system (mainly thought for Sonogashira-type cross-couplings).

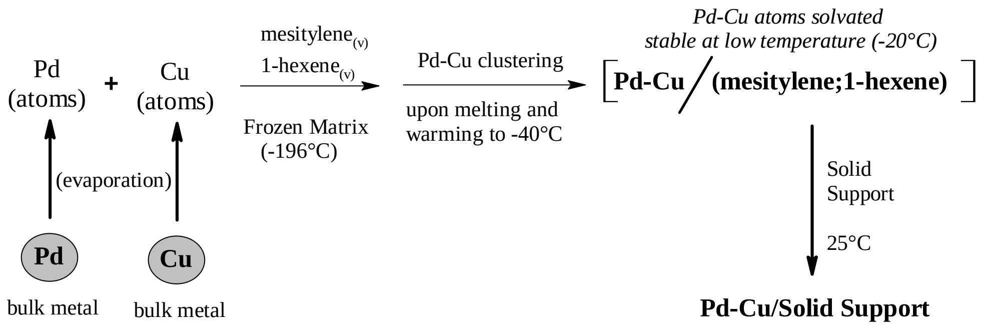
Recently, a variety of Pd NPs were reported to be highly active and reusable catalysts in the Sonogashira coupling reactions, as already outlined in paragraph 2.1.2.**[9a]** Although some of these Pd NPs showed high efficiencies in the absence of a CuX co-catalyst, others provided low efficiencies even in the presence of amine additives.**[238]** The bimetallic alloy NPs comprising a noble metal and a first-row transition metal such as iron, cobalt, nickel, and copper show an enhancement in the catalytic properties owing to the synergistic effects between the two distinct metals.**[239]** Therefore, the use of a bimetallic alloy NP catalyst comprising both Pd and Cu metals on its surface could be beneficial for the Sonogashira couplings to obtain high yields. Besides this advantage, CuPd alloy NPs are cost-effective catalysts compared to monometallic Pd NPs due to Pd metal being used less. In recent years, several bimetallic Pd NPs have been tested as catalysts in the Sonogashira couplings including Ni/Pd core/shell NPs,**[240]** Pd–Co bimetallic nanospheres,**[241]** and, after the start of this Doctoral work, PdCo alloy NPs,**[242]** Pd–Cu mixed NPs,**[243]** and nano-Pd/PdO/Cu system.**[244]** In a very recent study, Gao et al. reported Pd/Cu nanoalloys supported on montmorillonite as the catalysts for the Sonogashira couplings of aryl iodide and various alkynes;**[245]** Furthermore, in 2015, Metin et coll. reported that monodisperse CuPd alloy NPs supported on reduced graphene oxide (rGO) can successfully be employed as catalysts in Sonogashira-type cross-coupling reactions carried out under mild/aerobic conditions with various aryl iodide and bromide.**[246]**

2.1.2.4.1 Pd-Cu/PVPy (7)

The supported palladium-copper bimetallic systems, were prepared depositing Pd-Cu bimetallic solvated metal atoms (SMA) on a commercially available polyvynilpyridine cross-linked with divinylbenzene resin (PVPy), according to MVS technique**[203a, 247]**.

Palladium and copper atoms, produced by resistive heating of the metal under high vacuum, were co-condensed at liquid nitrogen temperature with a mixture of 1-hexene and mesitylene solvents on the cooled wall of the reactor. On warming until the solid matrix melted, a brown solution, Pd-Cu SMA, was obtained. The deposition of the bimetallic nanoparticles was quantitatively carried out warming up to room temperature under stirring the Pd-Cu SMA in the presence of the solid support (**Scheme 2.1.6**).

As previously observed for monometallic Pd SMA**[30c]**, the high thermal stability of the Pd-Cu/(mesitylene;1-hexene) SMA allows a more controlled deposition of the metal particles on the resin support.



Scheme 2.1.6: General scheme of Preparation of supported bimetal nanoparticles by Metal Vapour Synthesis

The morphology and metal particle size distribution of the new bimetallic system so obtained, Pd-Cu/PVPy, were investigated by high resolution transmission electron microscopy (HRTEM). X-ray absorption fine structure (XAFS) spectroscopy at the Pd K-edge was used to determine the structural features of the samples. Both techniques were also used to study the bimetallic system recovered after bein used.

TEM micrograph and particle size distribution of the MVS-derived Pd-Cu/PVPy system are reported in **Figure 2.1.12**. The bimetallic system appeared homogeneously populated by nanostructured metal particles distributed in a narrow range (1.0 nm - 6.0 nm) with a mean diameter of 2.5 nm. The micrographs show the presence metal particles covered by the polymeric resin, in agreement with previously reported data**[30c]** on the strong affinity of metal nanoparticles with the pyridine moiety of the support.

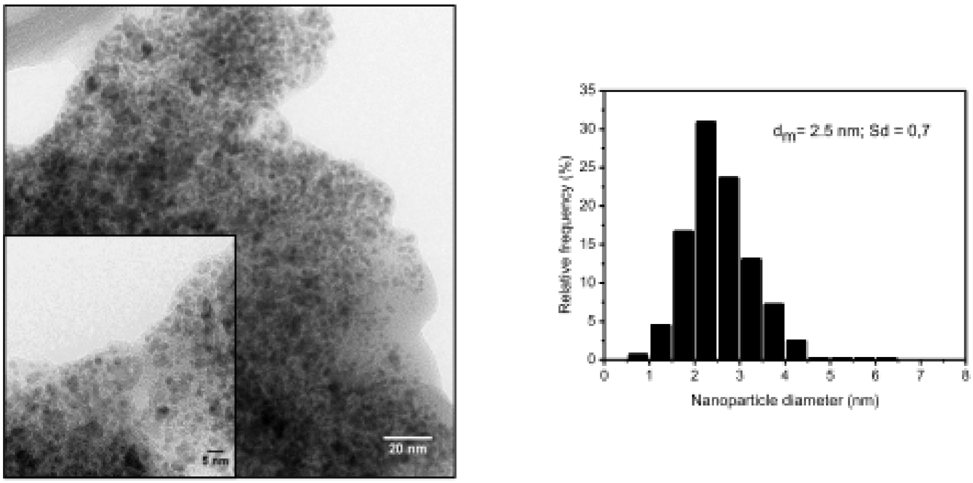


Figure 2.1.12. TEM micrographs and metal particle size distribution of Pd-Cu/PVPy system.

XAFS analysis, reported in **Figure 2.1.13**, indicates the probable presence of small Pd-rich cores, some Pd-Cu heterometallic bonds shell and a relevant oxide layer.

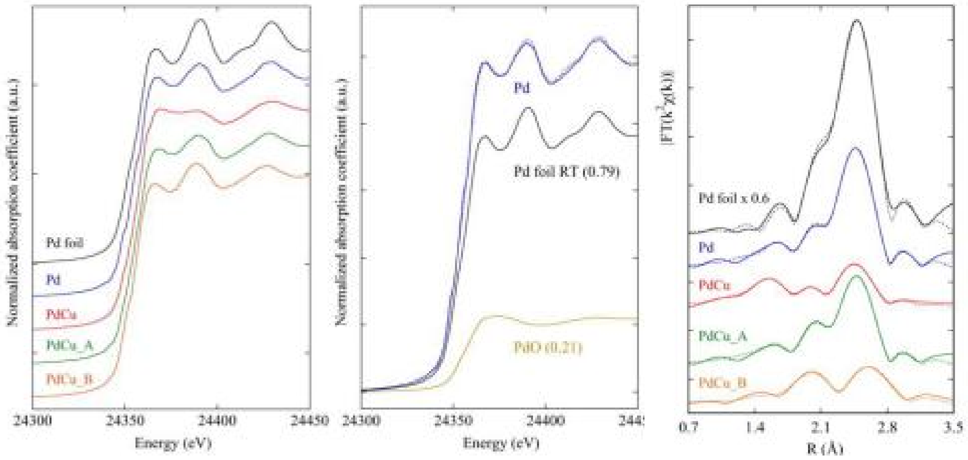


Figure 2.1.13: XANES spectra (left) and Fourier Transforms of the experimental EXAFS signals (right) at the Pd K-edge of the catalysts supported on PVPy

The EXAFS data analysis shows the presence of three different contributions: Pd-O, Pd-Pd and Pd-Cu. A small amount of hetero- atomic Pd-Cu bonds and a shortening of the Pd-Pd distance probably due to the smaller Pd nanoparticles dimension**[248]** were observed. A possible explanation could be that, in the bimetallic sample, the presence of Cu has an effect on the dimension of the nanoparticles formed (as seen also by TEM analysis) and on some alloying that is probably present only in the immediate subsurface layers. Compared to the monometallic sample, the Pd-O contribution in the bimetallic catalyst is higher as clearly visible in the XANES region (**Figure 2.1.13**): the EXAFS data analysis is compatible with the presence of small Pd-rich cores surrounded by a thin and not uniform Pd-Cu alloyed shell and an oxide layer.

2.1.3 Reproducibility effect of nanoparticles size in Pd/MCM-41 catalyst

As mentioned in paragraph 2.1.2, one reason for the popularity of nanoparticle catalysts for various reactions is due to its high surface area to volume ratio, which makes it catalyze the reaction faster than the other ligand bound catalysts. The ratio of surface area to volume determines the activity of these catalysts. As a result, the size of nanoparticles itself determines the activity of the catalyst.
Generally, the NPs size depend of the stabilization property of solid support, and of the preparation/deposition method (see paragraph 2.1.2).

In the Metal Vapour Synthesis, the solvated nanoparticles were obtained with very small dimension, and using opportune solid supports the nanoparticles size were maintained.

In fact in our case, previously study proved that MVS-prepared catalysts supported on the poly(4-vinylpyridine) cross-linked with divinylbenzene, but too other coordinating supports as polyvinylpyrrolidone (PVP), showed highly reproducibility in the palladium nanoparticles size anchored into the solid support.**[30c, 189d, 249]**

The same results we have obtain on the Pd-Cu/PVPy; in fact, in this case the presence of the pyridine group in the solid support stabilized the metal nanoparticles, obtaining highly reproducibility in the nanoparticles size, depositing nanoparticle solvated metal atoms of several concentration.

Given this, for regard the Pd/MCM-41, the reproducibility of the NPs size were not granted. In fact the MCM-41 showed cylindrical mesopores (diameter of 2-6.5 nm) that form a one-dimensional pore system; but the silica generally provides an inert environment for the immobilization of the nanoparticles.**[250]**

In the preparation of several lots of Pd/MCM-41 (**6**) starting with several palladium solvates concentration, we observed an interesting variation of the nanoparticles size.

The Figure 2.1.3.1 showed the representative TEM image of palladium nanoparticle supported on the MCM-41 matrix seeds and their size distribution histogram with the average size of the nanoparticles, obtained using a 1.3 mg/mL solution of the Palladium Solvated Metal Atoms (Pd-SMA). The size distributions that were determined by using ImageTool software were plotted into a size distribution histogram. Gaussian fit of the histogram showed an average size of (1.53 ± 0.66) nm. The small standard deviation showed that the nanoparticles were monodisperse on the support, and in this case the several nanoparticles were encapsulated into the porous of the MCM-41.

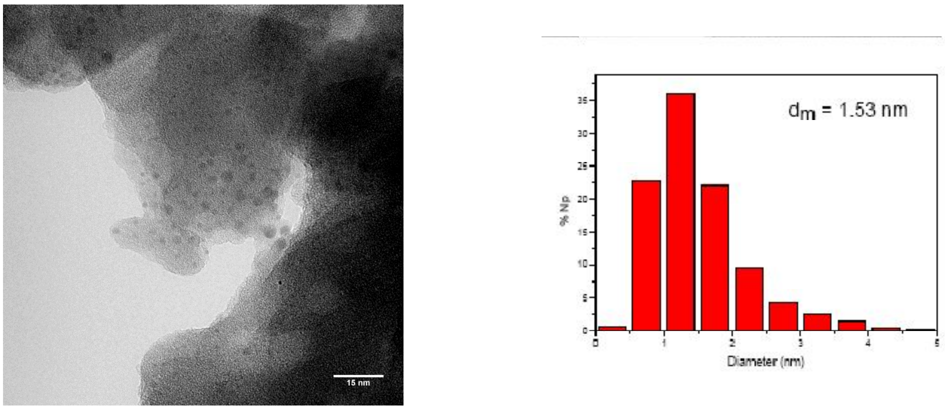


Figure 2.1.3.1: TEM image of Pd nanoparticles seed (a) and size distribution histogram of the nanoparticles (b)

The Figure 2.1.3.2 showed the representative TEM image of the second lot of palladium nanoparticles supported on MCM-41 (obtained using a 3.6 mg/mL solution of the Pd-SMA) and their histogram. The Gaussian fit of the histogram showed the average size of (3.40 ± 1.64) nm. The standard deviation also showed that the nanoparticles are relatively monodisperse in the support, and in this case not observed nanoparticles in the porous.

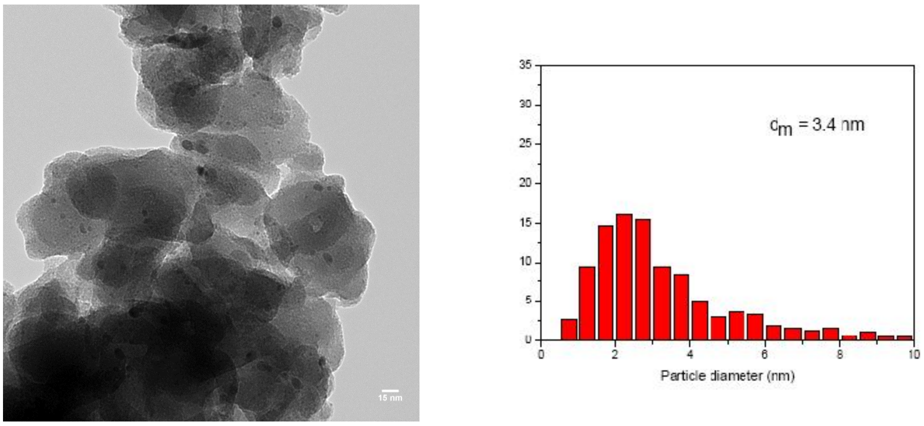


Figure 2.1.3.2: TEM image of Pd nanoparticles seed (a) and size distribution histogram of the nanoparticles (b)

The Figure 2.1.3.3 showed the TEM representative image of the third lot of Pd nanoparticles supported on the MCM-41 (obtained using a 3.2 mg/mL solution of the Pd-SMA) and their histogram. The Gaussian fit of the histogram showed the average size of (3.00 ± 1.01) nm. The standard deviation also showed that the nanoparticles are relatively monodisperse in the support, and none of the nanoparticles were observed in the porous of the MCM-41.

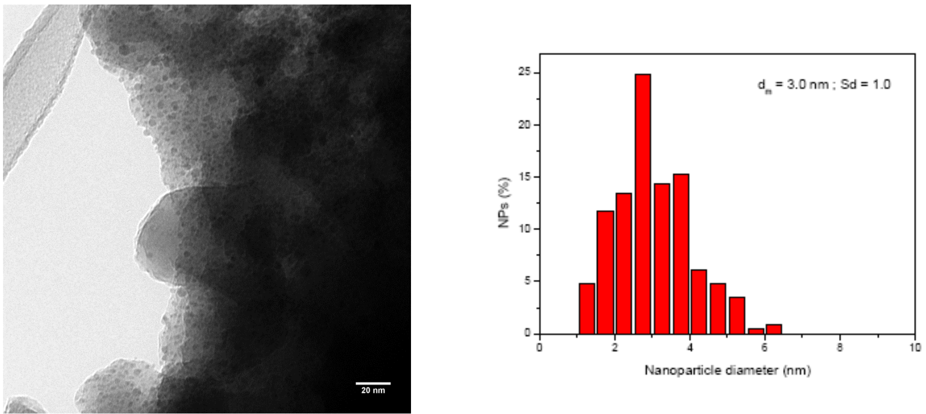


Figure 2.1.3.3: TEM image of Pd nanoparticles seed (a) and size distribution histogram of the nanoparticles (b)

Finally, the Figure 2.1.3.4 showed the TEM representative image of the fourth lot of Pd nanoparticles supported on the MCM-41 (obtained using a 2.1 mg/mL solution of the Pd-SMA) and their histogram. The Gaussian fit of the histogram showed the average size of (2.90 ±

1.30) nm. The standard deviation also showed that the nanoparticles are relatively monodisperse in the support.

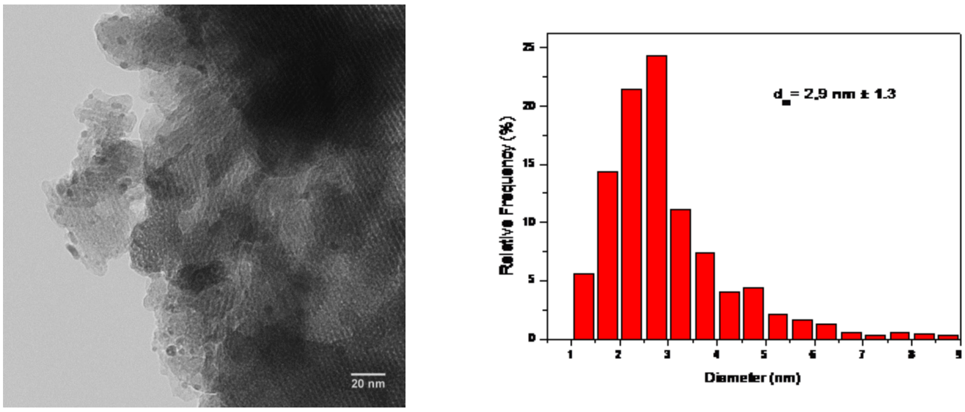


Figure 2.1.3.4: TEM image of Pd nanoparticles seed (a) and size distribution histogram of the nanoparticles (b)

The representative TEM images and size distribution histograms above reported, showed how in the preparation of a system inert environment for the immobilization of the nanoparticles, without -NH_2 or -SH groups, it has a high dependence of the particles size from the Palladium Solvated Metal Atoms (Pd-SMA) concentration obtained via MVS.

Moreover, only in the case of nanoparticles of 1.53-2.90 nm size we observed the 80-90 % of the nanoparticles into the porous of the mesopourous support.

At the light of this effect, we decided to examine the catalytic activity of these several batch of the Pd/MCM-41 (**6**) in the Suzuki reaction (because of its high activity and selectivity) between 1-bromo-2-anisole (**8a**) and phenylboronic acid (**9a**).

In this experiment, the effect of different sizes of nanoparticles was investigated, and compared with a Pd/MCM-41 (**6**) obtained by classical impregnation/reduction technique using $Pd(OAc)_2$ solution (4-5 nm of Pd particles size).

The activity was measured by measuring the conversion of product formed over time using GC and GC-MS

Figure 2.1.3.5 showed the 2-methoxybiphenyl conversion versus time up to two hours of the Suzuki reaction with different sizes of Pd nanoparticles loaded into the same size of mesoporous silica MCM-41. Overall it showed that the smaller the size of nanoparticle was, the higher activity it had. The higher catalytic activity was indicated by the higher 2-methoxybiphenyl conversion over time.

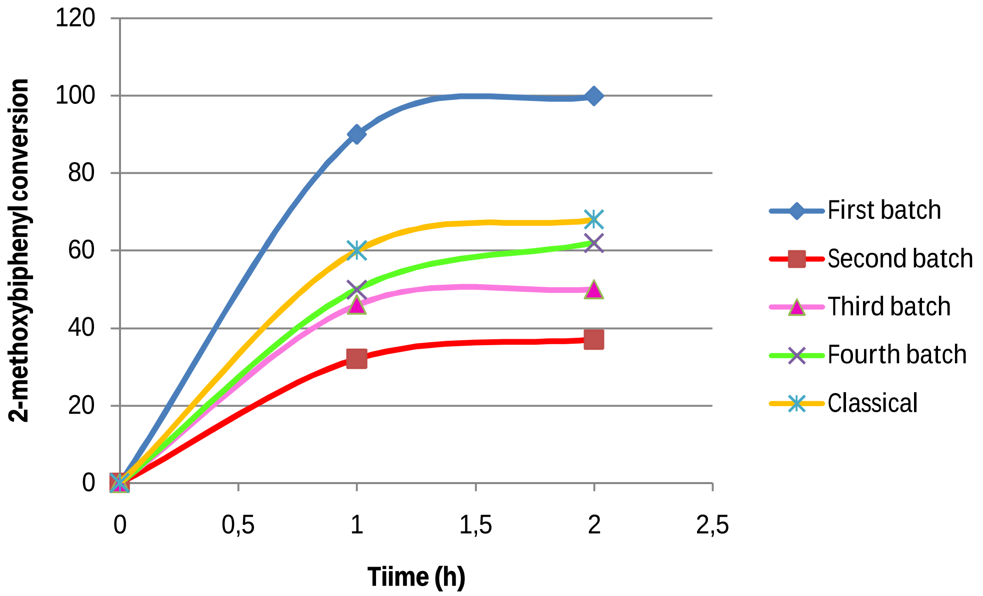


Figure 2.1.3.5: Graphic of Suzuki reaction of different Pd/MCM-41 catalysts batch for 2 h reaction

The first batch (1.53 nm of nanoparticles dimension) showed very highly activity with low leaching data (< 0.20 %), obtaining complete conversion in 2 h. The other catalysts batch showed respectively an inferior activity, generally corresponding at the size variation of the nanoparticles; in fact, the third batch (3.00 nm of nanoparticles size) showed an halve activity respect at the first.

However, the majority of the catalysts batch tested showed a drastic loss of the activity after 1 h, except the fourth batch, probably for an increase in mean particle size with respect that observed in a fresh sample that can be attributed to the Ostwald ripening process in reaction conditions, given by TEM studies.

The fourth batch, and specially the classical-prepared catalyst showed more particular activity data.

The classical-prepared catalyst, (generally between 4-5 nm of size) showed an better activity of the several MVS-prepared catalyst that have inferior nanoparticles size, but probably this effect has attributed at the highly leaching data (5.00 %).

For regard the fourth batch, this showed a nanoparticles size of 2.90 nm, most similar at the size of the third batch (3.00 nm), but the activity profile appear most particular. In fact until the 1 h the two catalysts batch showed a similar activity (compare violet and green line), but after this time the profile changed, despite the leaching date appear similar. The third batch showed a drastic/complete loss of the activity, while the fourth batch showed only a light loss of the activity.

Probably this effect was connected to the presence of the several nanoparticles in the MCM-41 cavity, that in the fourth batch was superior at 80 %; and after the 1 h result yet active and not increased in size.

2.2 Preparation of simple and cheap continuous-flow reactors

For regard the application in flow of the previously selected/prepared catalysts in Suzuki-, Sonogashira- and Heck-type cross-coupling reactions under reaction conditions as feasible, green and convenient as possible; we necessity of buy or mad packed bed reactors.

2.2.1 Packed bed reactors

Currently, several type of continuous-flow reactor filled with heterogeneous palladium catalysts are commercially available (**Figure 2.2.1**).

Figure 2.2.1: Commercial continuous flow reactors (a) CatCart® of Thalesnano; (b) PASSFlow of CHELONA

These systems range from packed bed CatCarts® (filled with several heterogeneous catalysts range from Pd/C and $Pd/\gamma\text{-}Al_2O_3$ to the most innovative and new Fibrecat™) of the Thalesnano (**Figure 2.2.1a**)**[251]**; to the most innovative monolithic reactors PASSFlow of the CHELONA GmbH (**Figure 2.2.2b**)**[252]**.

Unfortunately, these systems are still quite expensive,**[253]** and necessity of expensive opportune flow systems (X-Cube™, Phoenix Flow Reactor™ and Synthesizer) reported in **Figure 2.2.2**.

Uniqsis FlowSyn
Vapourtec R-Series
Vapourtec E-Series
FutureChemistry FlowStart Evo
Chemtrix Labtrix
Syrris Asia
Accendo Propel
Advion NanoTek
ThalesNano H-Cube Pro
Sigma-Aldrich Microreactor Explorer

Figure 2.2.2: Commercial continuous flow systems

Taking into account what the statements reported said in the paragraph 1.4. We prepared original packed-bed mini-reactors of design and construction extremely simple and cheap. Generally, the mini-reactors in literature are mad with several materials (as mentioned in paragraph 1.2.1). However, we opted to prepare our packed-bed flow mini-reactors with simple PTFE tubes, because it's an inexpensive, versatile, chemically resistant, easily available and manipulable material (**Figure 2.2.3**)**[137]**.

Figure 2.2.3: PTFE tubes

In general, our mini-reactors (columns) were prepared with 0.2 cm internal diameter (outside diameter 0.3 cm) Teflon tubing; their length varies from case to case, but usually is between 2.0 and 8.0 cm. An end of every reactor was stopped with about 0.5 cm of silanized glass wool (20 mg) locked with a opportune PEEK fitting, then using the other side the catalyst, pure or mixed with glass beads (150-200 µm) or other material, is introduced into the reactors as a slurry or dry (**Figure 2.2.4**).

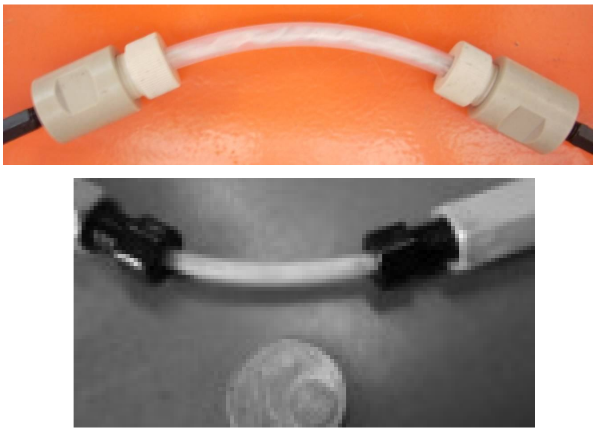


Figure 2.2.4: PTFE reactors

So each end (input and output) are made out by means of fitting PEEK 1/4"-28, respectively to a reservoir of the reaction mixture at the entrance, and to a collection reservoir exit. Finally, the catalyst was compressed and conditioned with 5-10 mL of the reaction solvent to about 2-3 bar. The elution of the reaction mixtures through these systems as was done by means of suitable syringe pump (**Figure 2.2.5**), as better specified in the various cases.

Figure 2.2.5: Our simple and cheap continuous flow system

2.3 Suzuki reaction and classical catalyst used

Suzuki-Miyaura reaction is characterised by a metal catalyzed (principally palladium) cross-coupling of two sub-units, one from an organoboron compounds (boronic acid or its derivative) and the other from an organohalide or triflate (aryl, alkenyl, and alkynyl halides) to give a conjugated 1,3-diene or biaryl motif, in the presence of a base (**Scheme 2.3.1**).**[7c, 11b, 22, 110c, 254]**

R = 1-alkenyl, (hetero)aryl, 1-alkynil, benzyl

R_1 = 1-alkenyl, (hetero)aryl, 1-alkynil, alkyl

X = I, Br, Cl, OTf

Y = OR, OH, R

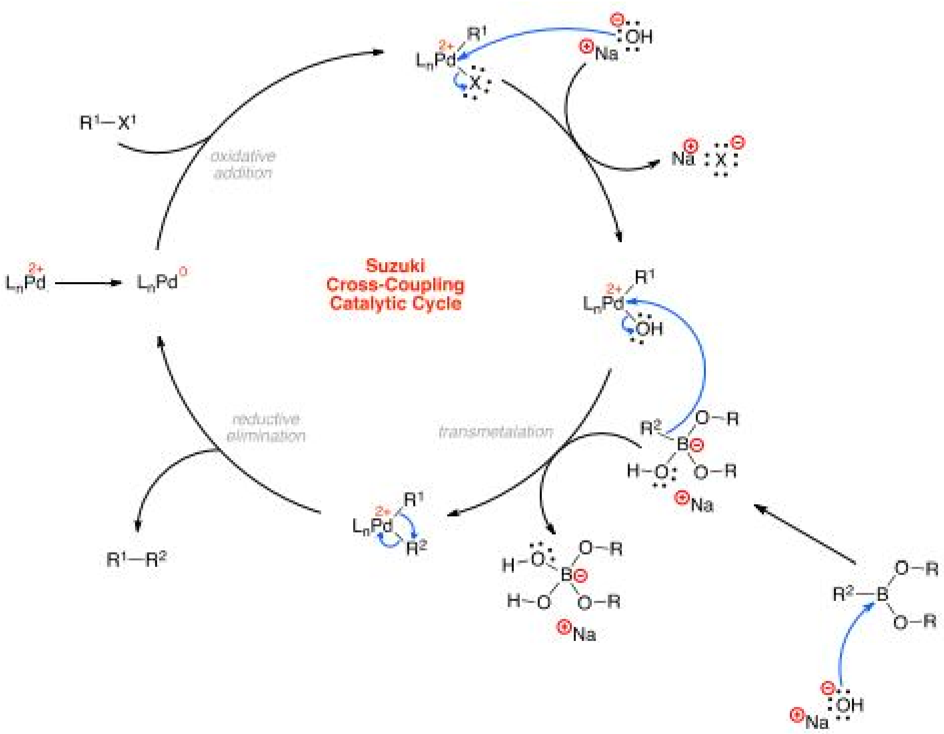
Scheme 2.3.1. Generic scheme of Suzuki-Miyaura cross-coupling reaction

This reaction becomes one of the most important carbon-carbon bond formation reaction for the expansion of the carbon framework in organic molecules since its discovery in 1979.**[255]** Amongst its wide applicability; Suzuki-Miyaura reaction is particularly useful as a way for the assembly of conjugated diene and higher polyene systems of high stereoisomeric purity as well as of biaryl and related systems, which have a diverse spectrum of applications, ranging from pharmaceuticals to advanced materials.**[1d, 256]**

The popularity of Suzuki reaction is due to its versatility, efficiency and most important of all, high regio- and stereo selectivity in the synthesis of C(sp^2)-C(sp^2) bonds.**[184a]**

A variety of substrates and functional groups can be used under the reaction conditions, which is ideal to synthesize many intermediates in constructing the complex drug molecules.

Besides that, the non-toxicity and simplicity related to the preparation of organoboron compounds (e.g. aryl, vinyl, alkyl);**[254h, 257]** their relative stability to air and water, combined with the relatively mild conditions for the reaction as well as the formation of nontoxic by-products, makes Suzuki-Miyaura reaction an important method for enlarging carbon skeleton. Unfortunately, the organoboron compounds have a low nucleophilicity date from the small electronegativity difference between the boron and the carbon atom. To reduce this problem requires the addition of negatively charged species that complexing the boron atom, make the organoboron compound more nucleophilic.



Scheme 2.3.2. General catalytic cycle of Suzuki Reaction

The general mechanism of the Suzuki reaction can be seen on **Scheme 2.3.2**. The first step of the catalytic cycle is attachment of palladium (Pd) catalyst to the halides by oxidative addition, which increases the oxidation state of Pd catalyst from 0 to 2. This step is the rate determining step of the reaction. After oxidative addition, the boronic acid is activated by the base present in the solution which enhances the polarization of the ligand and facilitates transmetalation. The base has been suggested to have a role of increasing the nucleophilicity of the organic group of boron atom and forming alkoxy palladate from aryl palladium halide.**[258]**

The last step of the cycle is reductive elimination, releasing the product and regenerating Pd catalyst back to its original oxidation state so that it can participate in the catalytic cycle again.

As base, historically they have been used alkali hydroxides and alkoxides, both anhydrous and in aqueous environment; then the range of the base stock used has expanded to other oxygenated bases (carbonates and phosphates), amines and fluorides.**[7, 255c]**

Organoboron species used for this purpose are normally boranes or acids or boronic esters. However, especially recently, have been reported various uses of organoboron different species, such as, for example organotrifluoroborate or tetraorganoborates, as well as the use as acceptors ipervalent iodine compounds. **[7, 255c]**

2.3.1 State of art of Suzuki reaction with aryl and alkenyl halides in batch mode

As mentioned in general for all cross-coupling in paragraph 1.1, classic and/or modern Pd complexes with phosphine ligands and not only (Pd-NHC,**[259]** palladacycles,**[23, 260]** Pd-XPHOS,**[261]** etc.) are intensively employed as homogeneous catalysts in reactions of Suzuki-Miyaura of vinyl and aryl halides,**[7, 255c]** where the systems most commonly used are precisely species triarylphosphine/Pd (II) or Pd (0).

Despite their success (high catalytic activity and selectivity), such systems may lead to problems related to the difficult availability of the catalyst, to the precarious stability, to the difficult handling and ultimately high cost of the system itself. As already mentioned in the paragraph 1.1, all these difficulties with the inability to recycle the catalyst in a simple way, as well as the frequent contamination of the product of synthesis or the use of catalytic systems efficient but very expensive, have resulted in a continuous increase, as regards the reaction of Suzuki-Miyaura, and the study of the use of supported catalytic systems, at low release of palladium and easily recyclable.**[262]**

The supported catalyst most studied and used in the reaction of Suzuki-Miyaura is the Pd/C because its availability, easy handling, and reusability;**[263]** it can further be used in coupling of various organic moieties different from aryl compounds, such as alkenes, alkynes, or alkanes. The first example of Pd/C-catalyzed Suzuki reaction was reported by Marck and co-workers in 1994.**[264]** Subsequently, Pd/C is used with or without additional phosphine ligands, and often the application of aqueous solvents is advantageous.**[164, 265]**

In general, the Pd/C-catalyzed Suzuki reaction using a palladium load between 1.0 at 5.0 mol % with or without additional phospine ligands**[40b, 265f, 265h]** in the presence of more than stoichiometric quantities of inorganic (Na_2CO_3, K_2CO_3, $NaHCO_3$, NaOH, K_3PO_4) or amines bases; in organic solvents (alcohols, DME, NMP, DMF, DMA) dry or aqueous under inert atmosphere and at temperatures up to 120 °C, obtaining excellent results even with deactivated aryl bromides.**[40b, 265f, 265h]**

Recently new protocols have been developed to use Pd/C in water alone as a solvent,**[265b, 265g, 266]** adding some additives, such as quaternary ammonium salts (tetrabutylammonium bromide (TBAB) or hexadecyltrimethylammonium bromide (CTAB)), and/or the application of microwave irradiation, and pressure are required for effective reaction progress.**[265b,c,f,g, 266]**

Despite the large amount of examples reported in the literature on the use of Pd/C, the information regarding its effective leaching and the tendency to recycled it is most limited.

In general, regarding the recyclability of the catalyst, the Pd/C can be reusable for 4-5 cycles without drastic decreases efficiency, but the quantities involved are quite high, in order of 1.5-3.5 mol %.**[2d, 62, 267]** The leaching dates of the catalyst are low and approximate; in some examples the Pd/C leaching is very low (< 1.0 %)**[61a, 267a]**, but in other examples the leaching is superior at 3.0 **%.[2d, 62]**

In fact, the Pd/C is a system where the particles of palladium are finely distributed, but weakly anchored to the surface; therefore the leaching of Pd may depend heavily on different reaction conditions (temperature, base and solvent type and/or quantity).**[268]**

In addition to the Pd/C, in Suzuki-Miyaura reaction have been employed other supported catalysts consisting of palladium supported on metal oxides;**[9d, 250b, 262f, 269]** such as Pd/Al_2O_3,**[269a-c]** Pd/MgO e Pd/SiO_2,**[269d-e]** Pd/Al_2O_3-ZrO_2, Pd/Al_2O_3-ZrO_2-Eu_2O_3 and Pd/MgO-La_2O_3,**[269f]** Pd-containing perovskites (in particular $LaFe_{0.57}Co_{0.38}Pd_{0.05}O_3$)**[145a, 270]**, Pd/$TiO_2$**[269m, 271]** and Pd-doped mixed oxides**[272]**; as well as systems of Pd on modified silica**[250b, 262f, 269i-o]** and nano-crystal oxides**[269g-h]** are the only examples in this field reported in the literature. Each of these catalysts, of course, has the characteristics and activities different, but in general, all require a dose range between 0.5 and 3.0 mol%, although there are cases in which they have been used a larger amount; normally they are employed in the presence of bases such as carbonates or fluorides (very efficient in systems based on Al_2O_3), using solvents such as DMF or aqueous solutions of alcohols, xylene, dioxane or simply H_2O, under mild temperatures (50-100 ° C) and inert atmosphere.**[2d]** These systems formed by Pd simply deposited and/or adsorbed directly on oxides and/or zeolites, are very catalytically active in the reaction of Suzuki-Miyaura, but regarding they're effective leaching and the tendency to recycled it is most limited. In fact, in some cases palladium leaching during catalysis was evidenced. Although no noble metal leaching was observed using vary mixed oxides, but these systems in the recycling the activity slightly decreased (after 1 h the yield dropped from 99 to 95%).**[269a, 273]** The Pd-containing perovskite catalyst was recycled four times without apparent loss of activity**[145a]**, and a further detailed study revealed that the effective catalytic species was present in solution phase**[270]**. While the systems supported on zeolites and/or functionalized oxides show low leaching; however, the recyclability of the catalyst is possible only after appropriate regeneration with oxygen and/or hydrogen, while allowing for a certain reduction of catalytic activity in the reuse.**[250b, 269g-l, 274]**

In last decades, were to be published an increased number of articles that used a palladium catalysts supported onto organic polymers: metal anchored on the polymer matrix, or incapsulated in to the matrix.**[273, 275]**

These systems are both commercial systems, such as FibreCat**[46]** and PdEnCat^{TM} (Pd is encapsulated in a tioureic resin)**[45b, 49c, 164a, 276]**, that non-commercial polystyrene systems, with coordinating groups to the metal**[277]** and other polymer systems such as polyvinylpyrrolidone (PVP)**[278]** and polyanilina (PANI)**[279]** that already have the coordinating groups.

For these species are described good and efficient reactions with both aryl bromides that with aryl chlorides, under biphasic and/or three-phase conditions. In any cases, these systems were are used in reaction with alkenyl halides obtaining good/excellent yields with highly stereo-specificity.

Finally, have been described some, for now limited, examples of nano-particles of palladium prepared in various ways and supported on polyvinylpyridine (nanospheres),**[189c]** polyvinylpyrrolidone (PVP),**[275a]** and PEG,**[275b-d]** as well as other organic polymers of various types.**[275e-g]** Usually they are very efficient in Suzuki reactions even in aqueous environments and are efficiently recyclable with low levels of leaching.

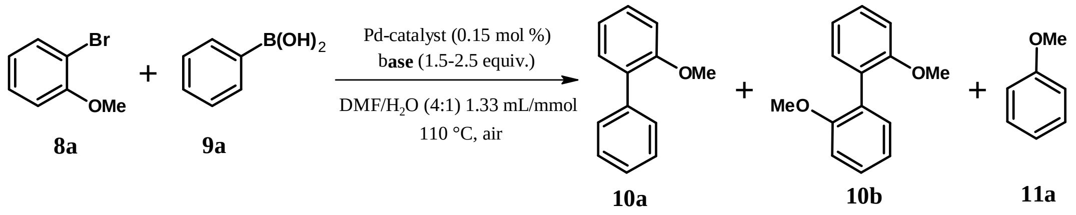
2.3.2 Development of batch conditions for Suzuki-Miyaura reactions

As outline in paragraph 1.4, our studies focused on three different cross-coupling between Suzuki-Miyaura coupling and seven different catalysts: three prepared “via” MVS with the collaboration of Dr Claudio Evangelisti (previously see above in paragraph 2.1.4) and four commercially available (previously see above in paragraph 2.1.3).

In Suzuki-Miyaura reaction we investigated only six different catalysts: all four commercially available catalysts previously selected in paragraph 2.1.3 and the two mono-metal MVS-prepared catalysts previously prepared in paragraph 2.1.4.

In this study we determine the most efficient and feasible reaction conditions in which these catalysts are able to promote the Suzuki reaction, taking into account their applicability in flow.

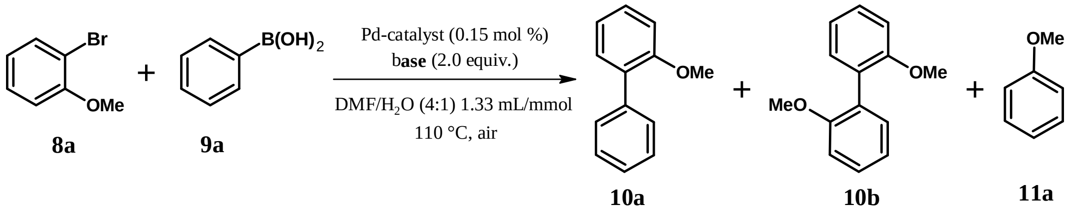
The reaction conditions were optimised by screening a number of solvents and bases for the reaction of 2-bromoanisole (**8a**) with phenylboronic acid (**9a**) (model reaction, **Scheme 2.3.2.1**); evaluating, from point of view of the yield and reaction time, the effects of different solvents, bases, optimum temperature and suitable reaction atmosphere; taking account of efficiency, generality and possibility in flow reactors (**Tables 2.3.2.1-2**). Initially, the catalytic trials were run in DMF/H_2O (4:1, v/v) at 110°C, according to our previous studies that demonstrated the beneficial effect of this condition on the rate of Pd-catalyzed Suzuki reactions using Pd/PVPy as catalyst**[218]**.



Scheme 2.3.2.1: Model reaction used for optimization of Suzuki cross-coupling

Initially, we examined the effect of the kind of base in the presence of 0.15 mol% of Pd-catalysts in DMF/H_2O (4:1 $^v/_v$) at 110 °C. For regard the mono-metallic MVS-prepared catalyst, the use of organic bases, such as pyrrolidine gave disappointing results (**Table 2.3.2.1**, entry 5). Inorganic bases, such as Na_2CO_3, $NaHCO_3$ and NaOH gave disappointing results (**Table 2.3.2.1**, entries 1-3 and 7-9) despite which were commonly used for the Suzuki–Miyaura coupling reaction. KF also gave mostly dehalogenation with Pd/PVPy and disappointing result with Pd/MCM-41; whereas in the presence of K_3PO_4, the cross-coupling product was obtained in moderate yield (40 %) in conjunction with the product of homocoupling with Pd/PVPy (**Table 2.3.2.1**, entry 6) and in good-excellent yield without homocoupling product with Pd/MCM-41, though the Pd/MCM-41 respect at Pd/PVPy result low and/or difficultly reproducible as showed in paragraph 2.1.6.

Table 2.3.2.1: Effect of the type of base on the Suzuki-Miyaura coupling reaction catalyzed by MVS Pd systems.[a]

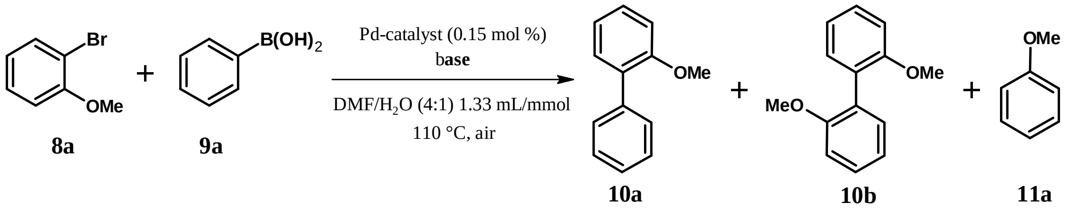


Entry	*Catalyst*	*Base*	*Reaction time (h)*	*Conversion of 8*[b] *(%)*	*Selectivity*[b] ***10a** / [**10b**+**11a**]*	*Yield of **10a***[c] *(%)*
1	*Pd/PVPy*	*Na_2CO_3*	*6*	*18*	*28 / 72*	*2*
2		*K_2CO_3*	*24*	*nr*[d]	*-*	*-*
3		*NaOH*	*6*	*60*	*11 / 89*	*5*
4		*KF*	*6*	*99*	*1 / 99*	*-*
5		*Pyrrolidine*	*24*	*nr*[d]	*-*	*-*
6		*K_3PO_4*	*72*	*99*	*60 / 40*	*42*
7	*Pd/MCM-41*	*K_2CO_3*	*2*	*66*	*90 / 10*	*50*
8		*Cs_2CO_3*	*2*	*59*	*95 / 5*	*65*
9		*$NaHPO_4$*	*24*	*nr*[d]	*-*	*-*
10		*KF*	*2*	*55*	*50/50*	*-*
11		*Pyrrolidine*	*24*	*nr*[d]	*-*	*-*
12		*DABCO*	*24*	*nr*[d]	*-*	*-*
13[d]		*K_3PO_4*	*3*	*99*	*95 / 5*	*96*

a) Reaction conditions: 1.0 equivalent of aryl halide (**8**), 1.25 equivalent of boronic acid (**9**), 0.15 mol % of Pd as catalyst, base, DMF/H_2O 4:1 (1.33 mL/mmol), 110°C, air atmosphere; b) Evaluated by GC analyses; c) Isolated Yield by MPLC; d) using 1.5 equivalent of base

For regard the commercial catalysts previously selected, a complete conversion of 2-bromoanisole (**8a**) and phenylboronic acid (**9a**) into 2-methoxy-1,1'-biphenyl (**10a**) (model reaction, **Scheme 2.3.2.1**) was achieved in 0.5 h by using K_3PO_4 as the base and 0.15 mol% amount of Pd with respect to **8a**. Other inorganic bases have been screened, thus also KF and KOAc have shown to be effective. The reaction run with KF as base in DMF/H_2O (4:1, v/v) was faster, as complete formation of **10a** was obtained in 0.5-1.5 h; while the use of KOAc as base to take complete formation of product only with 1.0 mol% amount of Pd and especially using Pd-EnCat-40 (**1**).

Table 2.3.2.2: Effect of the type of base on the Suzuki-Miyaura coupling reaction catalyzed by commercial Pd systems.[a]



Entry	*Catalyst*	*Base (equiv.)*	*Reaction time (h)*	*Conversion of* ***8***[b] *(%)*
1	*PdEnCat-40*	*KOAc (1.5)*	*6*	*99*
2		K_3PO_4 *(1.5)*	*0.5*	*99*
3		*KF (2.5)*	*1.5*	*90*
4	*Fibrecat 1007*	*KOAc (1.5)*	*2*	-
5		*KF (2.5)*	*0.5*	*95*
6		K_3PO_4 *(1.5)*	*0.5*	*95*
7	$PdCl_2(PPh_3)_2$*-PS*	K_3PO_4 *(1.5)*	*0.5*	*95*
8		*KF (2.5)*	*0.5*	*86*
9		*KOAc (1.5)*	*2*	-
10	$Pd(PPh_3)_4$*-PS*	*KF (2.5)*	*1.5*	*95*
11		K_3PO_4 *(1.5)*	*0.5*	*99*
12		*KOAc (1.5)*	*2*	-

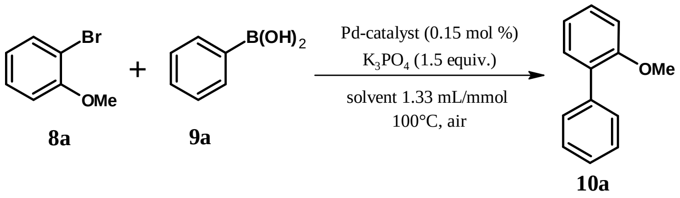
a) Reaction conditions: 1.0 equivalent of aryl halide (**8**), 1.25 equivalent of boronic acid (**9**), 0.15 mol % of Pd as catalyst, base, DMF/H_2O 4:1 (1.33 mL/mmol), 100°C, air atmosphere; b) Evaluated by GC analyses; c) Isolated Yield by MPLC.

On the light of these preliminary results, phosphate is apparent the more general base of all; then K_3PO_4 was chosen as bases for further optimization.

Then, we tested all supported catalysts using K_3PO_4 as base, to examine the effect of the kind of solvent in the presence of 0.15 mol% of Pd-catalysts.

Taking into account the literature dates we examined the supported catalysts in EtOH/H_2O (1:1) and only H_2O as solvent at reflux temperature, which are commonly used in Pd-catalyzed coupling reactions; to test the versatility of all catalysts, object of our study (**Table 2.3.2.3**).

Table 2.3.2.3: Effect of the solvent on the Suzuki-Miyaura coupling reaction catalyzed by our supported Pd systems.^{a}



Entry	Catalyst	Solvent	Reaction time (h)	Conversion of **8**^{b} (%)	Yield of **10**^{c} (%)	Leaching^d (%)	Catalytic activity^e
1^f	*PdEnCat-40*	*EtOH/H_2O (1:1 v/v)*	*4*	*95*	*86*	*-*	*158*
2		*H_2O*	*3*	*99*	*90*	*1.7*	*220*
3^f	*Fibrecat 1007*	*EtOH/H_2O (1:1 v/v)*	*1*	*95*	*85*	*< 1.0*	*633*
4		*H_2O*	*3*	*96*	*86*	*3.5*	*213*
5^f	*$PdCl_2(PPh_3)_2$-PS*	*EtOH/H_2O (1:1 v/v)*	*1.5*	*98*	*87*	*< 1.0*	*440*
6		*H_2O*	*3*	*96*	*85*	*1.4*	*213*
7^f	*$Pd(PPh_3)_4$-PS*	*EtOH/H_2O (1:1 v/v)*	*2*	*90*	*82*	*-*	*300*
8		*H_2O*	*2*	*90*	*88*	*2.7*	*300*
9^f	*Pd/PVPy*	*EtOH/H_2O (1:1 v/v)*	*30*	*25*	*19*	*-*	*5*
10		*H_2O*	*24*	*50*	*34*	*1.0*	*14*
11^f	*Pd/MCM-41*	*EtOH/H_2O (1:1 v/v)*	*4*	*40*	*22*	*1.7-3.4*	*67*
12		*H_2O*	*2.5*	*96*	*82*	*0.7-3.1*	*256*

a) Reaction conditions: 1.0 equivalent of aryl halide (**8**), 1.25 equivalent of boronic acid (**9**), 1.5 equivalent of K_3PO_4, 0.15 mol % of Pd as catalyst, solvent (1.33 mL/mmol), 100°C, air atmosphere; b) Evaluated by GC analyses; c) Isolated Yield by MPLC; d) Evaluated by ICP-OES after microfiltration (0.45 mm) and reported as Pd leached wt.% of the total available metal; e) Calculated as moles of aryl halide converted/moles of metal per hour; f) solvent concentration 3.00 mL/mmol.

These conditions showed substantially higher selectivity of the desired product **10a**, and the catalysts showed good yields (except for Pd/PVPy) in short time (1-4 h). However, with pure water condition, all commercial catalysts have a loss catalytic activity compared with DMF/H_2O condition; while the Pd/MCM-41 showed higher reactivity compared with DMF/H_2O condition. Most interesting result the leaching of the catalysts in water, in fact all catalysts showed similar or higher leaching date compared with DMF/H_2O date, except the commercial $PdCl_2(PPh_3)_2$-PS that showed a loss leaching date.

In alcoholic/aqueous solvent, which are commonly used in Fibrecat-catalyzed coupling reactions, but not only; the two “home-made” catalysts showed a loss catalytic activity compared with other conditions (DMF/H_2O and H_2O); while all commercial catalysts showed a good catalytic activity, and in particular, the Fibrecat 1007 (**2**) and $PdCl_2(PPh_3)_2$-PS (**3**) showed a similar activity that obtained in DMF/H_2O at 110°C.

Unfortunately, these conditions (most green respect to DMF/H_2O) appears not applicable in flow, because completely not homogeneous at cold and at hot. In fact, we need reaction mixtures the most homogeneous possible (excluding the catalyst) for the its application in flow mode.

In particular, the EtOH/H_2O reaction mixture result separate in three different phases (exclude the catalyst) that appears unlikely manage.

The water reaction mixture not result generally efficient with the majority of the our selected/studied catalysts, and showed most limitations in the use of the reagent, see that solid organic compounds were not dissolved in only water; therefore this condition were able only when at least an organic compound (halide and/or boronic acid) and the product of the coupling are liquid at room temperature.

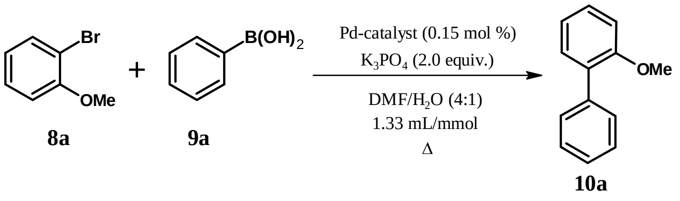
On the light of these results, we were decided to identify conditions that would allow the homogeneity of the cold reaction mixture. It was then made to a wide range of solubility tests using a number of base-solvent pairs that had been used in the literature, even sporadically, with good success in Suzuki cross-coupling. We tested most bases and pure or mixed solvent, but unfortunately the majority of the pairs result not completely homogeneous at cold, and the unique base-solvent pairs completely homogeneous, like as: Tetrabutylammonium acetate in EtOH or EtOH/H_2O (1:1) or DMF/H_2O or Toluene/H_2O (9:1); are totally inefficient in Suzuki cross-coupling with our selected/studied catalysts.

In general, after these results, K_3PO_4 in DMF/H_2O is apparent the more general condition of all catalysts both of in batch that in flow mode resulting completely homogeneous at hot (over 85°C), showing high catalytic activity with the majority of the our selected/studied catalysts.

Previously to explore the scope and generality of the catalysts in DMF/H_2O with K_3PO_4 as base, we examined other interesting parameters such as temperature, reaction atmosphere and amount of the catalyst.

For regard the temperature (**Table 2.3.2.4**) we showed that reducing the temperature to 100°C the reaction time and yield for the majority of the catalysts does not undergo drastic variation. Reducing further the temperature at 90°C, the all commercial catalysts showed an extension of the reaction time and lowered the yield, while Pd/MCM-41 (**6**) does not. Drastically effect on the extension of the reaction time and lowered the yield for all catalysts will have as the temperature is below 85°C.

Table 2.3.2.4: Effect of the temperature on the Suzuki-Miyaura coupling reaction catalyzed by supported Pd systems.[a]



Entry	*Catalyst*	*Temperature*	*Reaction time (h)*	*Conversion of **8**[b] (%)*	*Leaching[d] (%)*
1	*PdEnCat-40 (**1**)*	*100*	*0.5*	*99*	-
2		*90*	*2*	*99*	*1.7*
3		*85*	*2*	*90*	*< 1.0*
4	*Fibrecat 1007 (**2**)*	*100*	*1.5*	*96*	*3.5*
5		*90*	*2.0*	*98*	*< 1.0*
6	*$PdCl_2(PPh_3)_2$-PS (**3**)*	*85*	*3*	*94*	*1.4*
7		*100*	*2*	*95*	-
8	*$Pd(PPh_3)_4$-PS (**4**)*	*90*	*1*	*97*	*2.7*
9		*85*	*3*	*65*	-
10	*Pd/MCM-41 (**6**)*	*85*	*24*	*50*	*1.0*
11		*90*	*4*	*40*	*1.7-3.4*
12		*100*	*2.5*	*96*	*0.7-3.1*

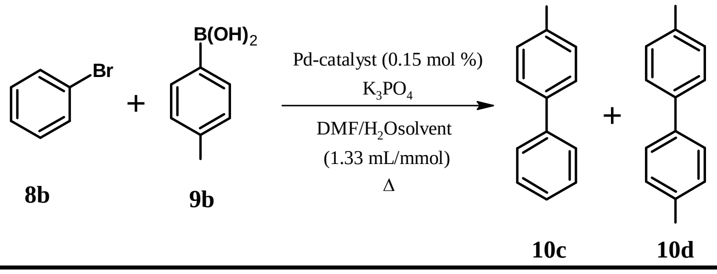
a) Reaction conditions: 1.0 equivalent of aryl halide (**8**), 1.25 equivalent of boronic acid (**9**), 1.5 equivalent of K_3PO_4, 0.15 mol % of Pd as catalyst, DMF/H_2O (1.33 mL/mmol), air atmosphere; b) Evaluated by GC analyses; c) Isolated Yield by MPLC; d) Evaluated by ICP-OES after microfiltration (0.45 mm) and reported as Pd leached wt.% of the total available metal; e) Calculated as moles of aryl halide converted/moles of metal per hour.

Among the catalysts, what less affected from the temperature is the Pd/MCM-41 (**6**), which requires 8 h lead to complete the reaction only when the temperature is lowered to 85°C. Between the four commercial catalysts what seems to be affected more than the temperature, at least under the conditions used, is the FibreCat 1007 (**2**), which requires 3 h lead to complete the reaction when the temperature is lowered to 90°C.

For regard the amount of the catalyst, in the case of the conditions hitherto optimized, consisting to DMF/H_2O (4:1) as solvent and K_3PO_4 as base at 110 °C, the optimal and general amount of Pd catalysts is 0.15 mol%, in fact, only the Pd/MCM-41 could be decreased to 0.05 mol% without significant loss of reactivity.

Finally, but not for this less important, we examined the necessity to perform the coupling under aerobic or anaerobic conditions (**Table 2.3.2.5**). In fact, the possibility to perform the coupling under aerobic conditions, it can greatly simplify the procedures for preparation and use of the catalytic reactors and of the reaction mixtures for continuous-flow process. Moreover, the use of aerobic conditions is even performed to evaluate the stability of the catalytic systems in this reaction process.

Table 2.3.2.5: Effect of the atmosphere on the Suzuki-Miyaura coupling reaction catalyzed by supported Pd systems.[a]



Entry	*Catalyst*	*Atmosphere*	*Reaction time (h)*	*Conversion of **8**[b] (%)*	*Leaching[d] (%)*	*Catalytic activity[e] (h^{-1})*
1	*PdEnCat-40*	*air*	*3*	*95*	*-*	*211*
2		*Ar*	*3*	*99*	*1.7*	*220*
3	*Fibrecat 1007*	*air*	*1.5*	*96*	*3.5*	*427*
4		*Ar*	*1.5*	*98*	*< 1.0*	*436*
5	*$PdCl_2(PPh_3)_2$-PS*	*air*	*2.5*	*96*	*1.4*	*256*
6		*Ar*	*2.5*	*90*	*-*	*240*
7	*$Pd(PPh_3)_4$-PS*	*air*	*2*	*90*	*2.7*	*300*
8		*Ar*	*2*	*25*	*-*	*83*
9	*Pd/MCM-41*	*air*	*4*	*99*	*1.0*	*165*
10		*Ar*	*4*	*99*	*1.7-3.4*	*165*
11	*Pd/PVPy*	*air*	*15*	*96*	*0.7-3.1*	*43*
12		*Ar*	*30*	*52*	*1.5*	*12*

a) Reaction conditions: 1.0 equivalent of aryl halide (**8**), 1.25 equivalent of boronic acid (**9**), 1.5 equivalent of K_3PO_4, 0.15 mol % of Pd as catalyst, DMF/H_2O (1.33 mL/mmol); b) Evaluated by GC analyses; c) Isolated Yield by MPLC; d) Evaluated by ICP-OES after microfiltration (0.45 mm) and reported as Pd leached wt.% of the total available metal; e) Calculated as moles of aryl halide converted/moles of metal per hour.

Generally, the use of aerobic conditions has not evident effects on the efficiency of the various systems in terms of reaction time, conversion and leaching; at exception of the Pd/PVPy.

Surprisingly, Pd/PVPy catalyzed the Suzuki–Miyaura coupling reaction under aerobic conditions leading to an increase of activity, without production of by-products, and with a comparable Pd leaching respect the corresponding reaction carried out under argon atmosphere (**Table 2.3.2.5**, compare entries 11 to 12). This result is rather particular, but already noticed in the study of other catalytic systems, both homogeneous and heterogeneous.**[343]** The authors report that Suzuki reactions carried out in polyethylene glycol or aqueous media and promoted by the zero-valent palladium nanoparticles formed "*in situ*" for the reduction of $Pd(OAc)_2$ or directly of Pd/C, progressing better and much faster in aerobic atmosphere in that atmosphere of N_2. They supposed that palladium nanoparticles could adsorb molecular oxygen on their surfaces in the presence of pure oxygen or air. As a result, the oxygen-adsorbed palladium nanoparticles (peroxo–palladium complex)**[344]** were more stable against aggregation and maintained high catalytic activity which could accelerate the oxidative addition step in the catalytic cycle due to the enhanced electron density of palladium.

At the light of all these optimized study results, taking into account the our necessity of most generally and efficient conditions easily translated in flow mode, The conditions that we use subsequently are 1.5 equivalent of K_3PO_4 as base, 1.33 mL/mmol of DMF/H_2O (4:1) as solvent, at 100°C using 0.15 mol% of the palladium under aerobic atmosphere.

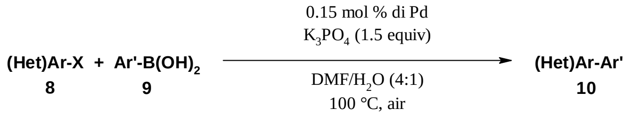
2.3.2.1 Performance of the catalysts in Suzuki coupling reaction with aryl iodides and bromides in batch

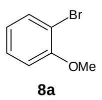
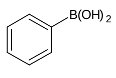
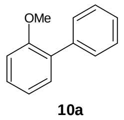
To explore the scope and generality of the catalysts, the optimized aerobic protocol was applied for reactions of a variety of differently substituted aryl halides and arylboronic acids. Therefore, a study was set up by selecting aryl iodides bearing electron withdrawing and donating groups and a few examples of aryl bromides. The outcomes are summarized in **Table 2.3.2.6**.

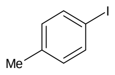
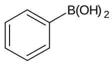
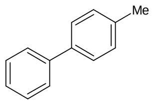
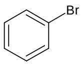
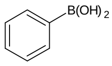
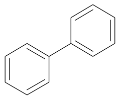
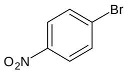
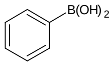
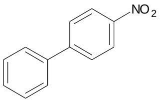
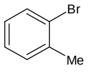
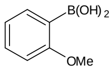
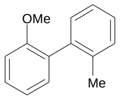
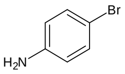
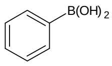
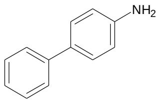
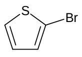
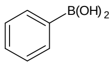
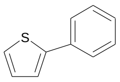
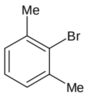
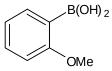
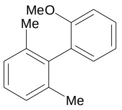
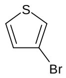
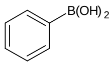
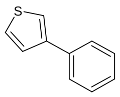
Generally, deactivated aryl iodides and both activated and deactivated aryl bromides were completely converted into the corresponding products in 41–99% yields within 0.5 h–72 h (**Table 2.3.2.6**). The reactions showed good diversity in the presence of both electron withdrawing and donating groups. For the deactivated aryl bromides sterically hindered, a satisfactory yield could be obtained in short time with the majority of the catalysts, while the Pd/PVPy require to increasing of the reaction time at 72 h (**Table 2.3.2.6**, entries 6, 30, 48). It was interesting to note that both protic free groups (-NH_2) were good tolerated in the reaction conditions with all catalysts (**Table 2.3.2.6**, entries 31-36).

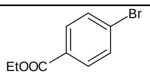
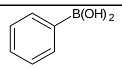
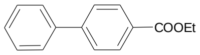
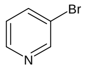
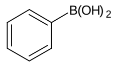
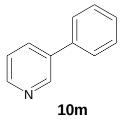
Regarding aryl boronic acids, the coupling reaction of electron-rich, but sterically hindered such as 2-methoxyphenylboronic acid (**9c**) led to the corresponding product in moderate yield (32-79 %) in conjunction with the product of homocoupling (**Table 2.3.2.6**, entry 25-30).

Table 2.3.2.6: Scope and generality of our supported catalysts in Suzuki-Miyaura coupling reaction with aryl halides.[a]



Entry	*R-X* **(8)**	*Ar'-B(OH)$_2$* **(9)**	*Catalyst*	*Time (h)*	*Product* **(10)**	*Yield of 10*[b] *(%)*	*Leaching*[c] *(%)*
1	 **8a**	 **9a**	***PdEnCat-40***	***0.5***	 **10a**	***93***	***1.5***
2			***Fibrecat 1007***	***2.0***		***95***	***2.8***
3			***PdCl$_2$(PPh$_3$)$_2$-PS***	***2.0***		***94***	***3.0***
4			***Pd(PPh$_3$)$_4$-PS***	***1.0***		***92***	***1.3***
5			***Pd/MCM-41***	***1.0***		***93***	
6			***Pd/PVPy***	***72***		***62***	

7	 **8c**	 **9a**	PdEnCat-40	0.5	 **10c**	96	
8			Fibrecat 1007	0.5		97	
9			PdCl$_2$(PPh$_3$)$_2$-PS	0.5		96	
10			Pd(PPh$_3$)$_4$-PS	0.5		96	
11			Pd/MCM-41	0.5		97	
12			Pd/PVPy	1.0		94	
13	 **8b**	 **9a**	PdEnCat-40	0.5	 **10e**	99	
14			Fibrecat 1007	1.0		99	
15			PdCl$_2$(PPh$_3$)$_2$-PS	1.0		99	
16			Pd(PPh$_3$)$_4$-PS	0.5		99	
17			Pd/MCM-41	1.0		99	
18			Pd/PVPy	15		99	
19	 **8d**	 **9a**	PdEnCat-40	0.5	 **10f**	97	
20			Fibrecat 1007	0.5		98	
21			PdCl$_2$(PPh$_3$)$_2$-PS	0.5		96	
22			Pd(PPh$_3$)$_4$-PS	0.5		97	
23			Pd/MCM-41	1.0		98	
24			Pd/PVPy	1.5		98	
25	 **8e**	 **9c**	PdEnCat-40	1.5	 **10g**	41	
26			Fibrecat 1007	1.5		57	
27			PdCl$_2$(PPh$_3$)$_2$-PS	1.5		71	
28			Pd(PPh$_3$)$_4$-PS	1.5		61	
29			Pd/MCM-41	3.5		79	
30			Pd/PVPy	72		32	
31	 **8f**	 **9a**	PdEnCat-40	1	 **10h**	91	3.9
32			Fibrecat 1007	4		90	3.9
33			PdCl$_2$(PPh$_3$)$_2$-PS	1		84	11.6
34			Pd(PPh$_3$)$_4$-PS	1		86	9.8
35			Pd/MCM-41	-		-	
36			Pd/PVPy	24		58	
37	 **8g**	 **9a**	PdEnCat-40	24	 **10i**	n.r.	
38			Fibrecat 1007	24		n.r.	
39			PdCl$_2$(PPh$_3$)$_2$-PS	24		n.r.	
40			Pd(PPh$_3$)$_4$-PS	24		n.r.	
41			Pd/MCM-41	3.0		72	
42			Pd/PVPy	21.5		83	
43	 **8h**	 **9c**	PdEnCat-40	24	 **10j**	10	
44			Fibrecat 1007	24		12	
45			PdCl$_2$(PPh$_3$)$_2$-PS	24		15	
46			Pd(PPh$_3$)$_4$-PS	24		8	
47			Pd/MCM-41	27		18	
48			Pd/PVPy	72		32	
49	 **8j**	 **9a**	PdEnCat-40	24	 **10l**	n.r.	
50			Fibrecat 1007	24		n.r	
51			PdCl$_2$(PPh$_3$)$_2$-PS	24		n.r	
52			Pd(PPh$_3$)$_4$-PS	24		n.r	
53			Pd/MCM-41	22		73	

54	 **8i**	 **9a**	***Pd/MCM-41***	***1.0***	 **10k**	***98***
55			***Pd/PVPy***	***2.5***		***87***
56	 **8k**	 **9a**	***PdEnCat-40***	***1.0***	 **10m**	***85***
57			***Fibrecat 1007***	***1.0***		***96***
58			***$PdCl_2(PPh_3)_2$-PS***	***1.0***		***86***
59			***$Pd(PPh_3)_4$-PS***	***1.0***		***79***
60			***Pd/MCM-41***	***1.0***		***92***

a) Reaction conditions: 1.0 equivalent of aryl halide (**8**), 1.25 equivalent of boronic acid (**9**), 1.5 equivalent of K_3PO_4, 0.15 mol % of Pd as catalyst, DMF/H_2O 4:1 (1.33 mL/mmol), air atmosphere; b) Isolated Yield by MPLC; c) Evaluated by ICP-OES after microfiltration (0.45 mm) and reported as Pd leached wt.% of the total available metal

In detail, the results obtained with the two "home-made" catalysts, consist in a Pd nanoparticles deposited on two different supports, are very interesting. More in particular, from a long series of tests, carried out on various compounds (phenylboronic acid and 2-methoxyphenylboronic acid as boronic species and 2-bomo or 4-bromoarenes electron-poor and electron-rich as halides), allowed to establish that the Pd/MCM-41 (**6**) is the most efficient to promoting the reaction under the previously optimized conditions. In fact, the Pd/PVPy (**5**) showed fairly good yields with aryl bromides in long times (10-24 h) under rather simple and convenient optimized conditions. These optimized conditions were used to react a wide range of bromo-(hetero)arenas (both electron-rich and electron-poor, or sterically hindered) affording good yields with moderate leaching (1.2 % of the total Pd load) in long reaction times. Significantly lower yield (32 %) were obtained between 2-methoxyphenylboronic acid and 2-bromoanisole.

While, the Pd/MCM-41 (**6**) showed a good oven excellent yields with bromo-(hetero)arenas (both electron-rich and electron-poor, or sterically hindered) with moderate leaching (% of the total Pd load) under more satisfactory, taking account of efficiency, generality and possibility in flow reactors conditions. The above mentioned optimized reactions conditions were used to react a wide range of bromo-(hetero)arenes (both electron-rich and electron-poor, or sterically hindered). With various aromatic boronic acids, affording good to excellent yields of the desired biaryls in short times. Significantly lower efficiency (73 % of yield in 22 h) were obtained with hetero-aryl 3-bromothiophene (**8j**) and 2-bromothiophene (**8g**).

As regard the four commercial catalysts investigated in the Suzuki-Miyaura cross-coupling of aryl bromides, under above mentioned optimized conditions (K_3PO_4 as base, DMF/H_2O as solvent, at 100 °C in aerobic atmosphere), low doses (0.15 mol% Pd) of all the catalysts studied showed a fairly good and similar efficiency in short times (0.5-4 h); however some specific features of each catalyst that have been identified, thanks to a suitable series of reactions carried out with a limited, but significant, variety of aryl boronic acids and aryl bromides (electron-rich or electron-neutral and sterically hindered).

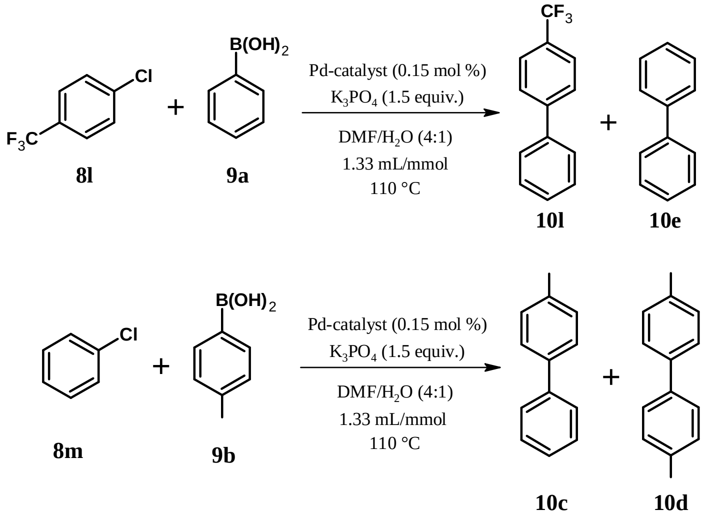
These systems affording good to excellent yields in short times with 4-bromoaniline (**8f**, to present a protic free groups -NH_2 on the aromatic ring), but with evident leaching (4.0-12 % of the total Pd load). Therefore, in these conditions the four commercial systems affording good yield with (hetero)aryl bromides electron-poor like 3-bromopyridine (**8k**); but unfortunately, in these conditions none of the catalysts tested was able to significantly promote the reaction with 3-bromothiophene (**8j**) both as 100°C to 125°C.

2.3.2.2 Performance of the catalysts in Suzuki coupling reaction with aryl chlorides in batch

From an industrial point of view, aryl chlorides, despite their lack of reactivity, are more interesting substrates as they are cheaper and readily accessible raw materials. Only few examples of palladium catalysts on silica supports capable of activating chloroarenes towards C-C bonds formation reactions have been described in the literature.**[178b, 236, 281]**

For this reason we have also evaluated the coupling ability of aryl chlorides (generally little reactive to their reluctance to oxidatively add to Pd) using the previously mentioned catalysts. Unfortunately, under the above optimized conditions (a moderate excess of potassium phosphate as base, in DMF/H_2O (4:1) as solvent, aerobic atmosphere and 0.15 mol% of metals loads) none of the studied catalysts result able to significantly promote the reaction between aryl chlorides and boronic acids.

In detail, we examined the catalysts in the reaction of 4-chlorobenzotrifluoride (**8l**) with phenylboronic acid (**9a**) and chlorobenzene (**8m**) with toluilboronic acid (**9b**), evaluating the conversions and yields (**Scheme 2.3.2.2**).



Catalyst	conversion	10o/10d	time
PdEnCat-40	41 %	99/1	19h
Fibrecat 1007	51 %	99/1	19h
$PdCl_2(PPh_3)_2$-PS	10 %	50/50	96h
$Pd(PPh_3)_4$-PS	37 %	99/1	24h
Pd/MCM-41	48 %	99/1	24h
Pd/PVPy	90 %	20/80	96h

Catalyst	conversion	10c/13	time
PdEnCat-40	61 %	18/57	19h
Fibrecat 1007	74 %	24/50	19h
$PdCl_2(PPh_3)_2$-PS	0 %	-	96h
$Pd(PPh_3)_4$-PS	75 %	18/57	24h
Pd/MCM-41	80 %	29/51	24h
Pd/PVPy	90 %	20/80	96h

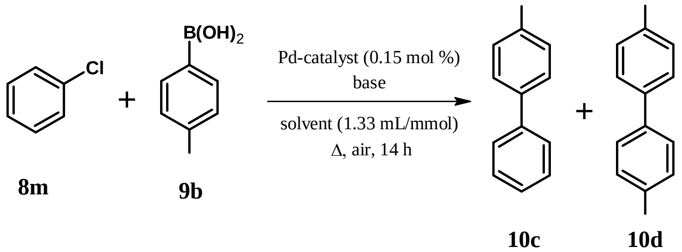
Scheme 2.3.2.2: Efficiency of previously optimized condition with aryl chlorides in Suzuki-Miyaura reaction

The four commercial catalysts and the two “home-made” catalysts under this condition showed very low efficiency after long reaction times. $PdCl_2(PPh_3)_2$-PS (**3**) and Pd/PVPy (**5**) appear completely inactive under this conditions to promote preferentially the oxidative homocoupling of boronic acids. While, the Fibrecat 1007 (**2**) and Pd/MCM-41 (**6**) appear to be the best catalysts under this conditions.

However, given the high industrial interest for aryl chlorides, we decided to determine the most efficient and feasible reaction conditions in which any our catalysts are able to promote the Suzuki reaction between aryl chlorides and aryl boronic acids, taking into account (if possible) their applicability in flow.

Taking into account the literature dates in the supported Pd-catalyzed reaction with aryl chlorides and at the light of previously optimized study with aryl bromides, we examined the supported catalysts (except $PdCl_2(PPh_3)_2$-PS (**3**) and Pd/PVPy (**5**)) in most solvent mixture like DMF, H_2O, EtOH/H_2O (1:1), DMF/H_2O (4:1) and toluene/EtOH/H_2O (3:2:2) using many bases like KF, K_3PO_4 and K_2CO_3 in vary excess with the addition of surfactant additive when necessary (**Table 2.3.2.7**).

Table 2.3.2.7: Effect of the solvent and base on the Suzuki-Miyaura coupling reaction with aryl chlorides.[a]



Entry	Solvent	Base (equiv.)	TBAB (equiv.)	temperature	Catalyst	Conversion of **8m**[b]	selectivity **10c/10d**[b]
1	DMF	K_2CO_3 (1.2)	0.1	125	PdEnCat-40	40	35/65
2					Fibrecat 1007	60	53/47
3					Pd(PPh3)4-PS	60	21/79
4					Pd/MCM-41	-	-
5	H_2O	K_3PO_4 (2.0)	0.5	100	PdEnCat-40	34	70/30
6					Fibrecat 1007	36	91/9
7					Pd(PPh3)4-PS	55	70/30
8					Pd/MCM-41	68	100/0
9	DMF/H_2O (4:1)	K_3PO_4 (2.0)	0.5	125	PdEnCat-40	64	13/87
10					Fibrecat 1007	68	79/21
11					Pd(PPh3)4-PS	70	14/86
12					Pd/MCM-41	72	14/86
13	DMF/H_2O (4:1)	K_2CO_3 (2.0)		125	PdEnCat-40	32	90/10
14					Fibrecat 1007	75	100/0
15					Pd(PPh3)4-PS	41	75/25
16					Pd/MCM-41	35	90/10

17	***DMF/H$_2$O (4:1)***	***KF (2.0)***	***125***	***PdEnCat-40***	34	***80/20***
18				***Fibrecat 1007***	69	***85/15***
19				***Pd(PPh3)4-PS***	55	***52/48***
20				***Pd/MCM-41***	-	-
21	***EtOH/H2O (1:1)***	***K$_3$PO$_4$ (2.0)***	***90***	***PdEnCat-40***	40	***89/11***
22				***Fibrecat 1007***	67	***92/8***
23				***Pd(PPh3)4-PS***	25	***80/20***
24				***Pd/MCM-41***	30	***90/10***
25	***EtOH/H2O (1:1)***	***KF (2.0)***	***90***	***PdEnCat-40***	-	-
26				***Fibrecat 1007***	11	***0/100***
27				***Pd(PPh3)4-PS***	-	-
28				***Pd/MCM-41***	-	-
29	***Tol/EtOH/H$_2$O (3:2:2)***	***K$_2$CO$_3$ (2.0)***	***95***	***PdEnCat-40***	-	-
30				***Fibrecat 1007***	12	***17/83***
31				***Pd(PPh3)4-PS***	-	-
32				***Pd/MCM-41***	-	-

a) Reaction conditions: 1.0 equivalent of aryl halide (**8m**), 1.25 equivalent of boronic acid (**9b**), 1.2 or 2.0 equivalent of base, 0.15 mol % of Pd as catalyst, solvent (1.33 mL/mmol), air atmosphere; b) Evaluated by GC analyses

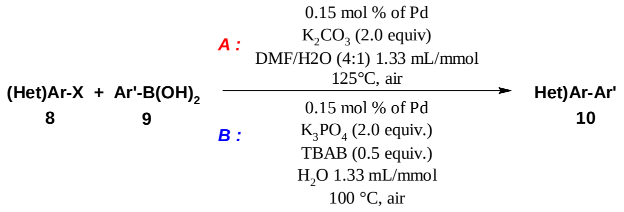
On the light of these preliminary results carried out a first series of pilot trials on the possibility to use these catalysts, in Suzuki reaction of chloro-arenes. It has thus been established, that only the Fibrecat 1007 (**2**) and Pd/MCM-41 (**6**) are able to efficiently promote the reactions of aryl chlorides electron-neutral (chlorobenzene), thanks to the use of a potassium carbonate as base in DMF/H_2O with Fibrecat 1007 (**2**); while, it was necessary to find different conditions with Pd/MCM-41 (**6**); in particular, it has been developed a process in only water, thanks to the addition of TBAB in the reaction mixture (carried out under suitable conditions, carefully developed).

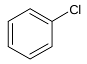
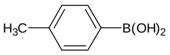
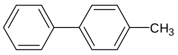
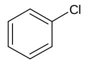
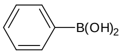
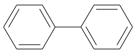
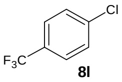
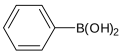
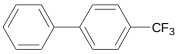
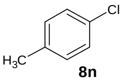
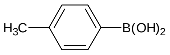
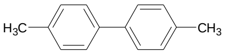
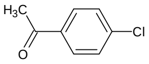
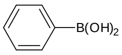
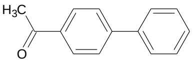
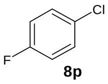
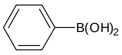
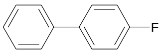
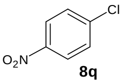
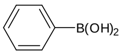
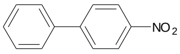
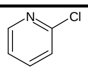
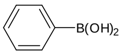
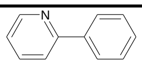
Identified two catalysts that are able to promote the reactions with aryl chlorides, even if under reaction conditions not applicable in flow, but however, even these conditions require low metals loads and are not affected by the presence of air. For **2** is necessary use an excess of K_2CO_3 (2.0 equiv.) as base in DMF/H_2O (4:1) at 125°C directaly in aerobic atmosphere; while for **6** is necessary the use of an excess of K_3PO_4 (2.0 equiv.) as base in only water as solvent, with addition of moderate amount (0.5 equiv.) of the additive tetrabutylammonium bromide (TBAB).

We proceeded to explore the scope and generality of these catalysts, applied the optimized aerobic protocol for reactions of a variety of differently substituted aryl chlorides and arylboronic acids.

Therefore, a study was set up by selecting a few examples of aryl chlorides bearing electron withdrawing and donating groups. The outcomes are summarized in **Table 2.3.2.8**.

Table 2.3.2.8: Scope and generality of our supported catalysts in Suzuki-Miyaura coupling reaction with aryl chlorides.[a]



Entry	*R-X* ***(8)***	*Ar'-B(OH)$_2$* ***(9)***	*Catalyst*	*condition*	*Time (h)*	*Product* ***(10)***	*Yield of **10**^{b} (%)*	*Leaching^c (%)*
1	 **8m**	 **9b**	***Fibrecat 1007***	***A***	***24***	 **10c**	***60***	***0.50***
2			***Pd/MCM-41***	***B***	***24***		***63***	***0.70***
3	 **8m**	 **9a**	***Fibrecat 1007***	***A***	***28***	 **10e**	***49***	**-**
4			***Pd/MCM-41***	***B***	***27***		***41***	**-**
5	 **8l**	 **9a**	***Fibrecat 1007***	***A***	***4***	 **10n**	***54***	**-**
6			***Pd/MCM-41***	***B***	***24***		***47***	**-**
7	 **8n**	 **9b**	***Fibrecat 1007***	***A***	***65***	 **10d**	***31***	**-**
8	 **8o**	 **9a**	***Fibrecat 1007***	***A***	***5***	 **10o**	***67***	**-**
9			***Pd/MCM-41***	***B***	***27***		***98***	**-**
10	 **8p**	 **9a**	***Pd/MCM-41***	***B***	***27***	 **10p**	***51***	**-**
11	 **8q**	 **9a**	***Pd/MCM-41***	***B***	***2***	 **10f**	***98***	**-**
12	 **8r**	 **9a**	***Pd/MCM-41***	***B***	***76***	 **10q**	***36***	**-**

a) Reaction conditions: ***A*** = 1.0 equivalent of aryl halide (**8**), 1.25 equivalent of boronic acid (**9**), 2.0 equivalent of K_2CO_3, 0.15 mol % of Pd as catalyst, DMF/H_2O 4:1 (1.33 mL/mmol), 125°C, air atmosphere; ***B*** **=** 1.0 equivalent of aryl halide (**8**), 1.25 equivalent of boronic acid (**9**), 2.0 equivalent of K_3PO_4, 0.15 mol % of Pd as catalyst, 0.5 equivalent of TBAB, H_2O (1.33 mL/mmol), 100°C, air atmosphere; b) Isolated Yield by MPLC; c) Evaluated by ICP-OES after microfiltration (0.45 mm) and reported as Pd leached wt.% of the total available metal

Under these new conditions the reactions of chlorobenzene with phenylboronic acid gave a moderate yield (41-49 %), but with different boronic acid much better results were obtained (**Table 2.3.2.8**; entry 1-2).

Therefore, these catalysts are able to promote (under the new conditions) the reaction with vary chloro-arenes (both electron-rich and electron-poor) to obtain much better results. In particular, the Pd/MCM-41 (**6**) is very efficient to promote the reactions with 4-chloro-nitrobenzene (**8q**) and 4-chloro-acetophenone (**8o**) (quantitative reactions), while the Fibrecat

1007 are able to promote the reaction with electron-rich aryl chloride like 4-chlorotoluene (**8n**) in acceptable reaction time. Moreover, in these our optimized conditions the leaching of Pd is extremely low (less than 0.50 % with Fibrecat-1007 (**2**) and less than 0.70 % with Pd/MCM-41 (**6**)). Unfortunately, despite these low values of leaching, it was not possible to recycle the catalyst more than once without decreasing drastically its efficiency (both in terms of yield and reaction times). Furthermore, Pd/MCM-41 (**6**) has the problem of reproducibility (in preparation phase), which can greatly influence the efficiency and leaching as observed/studied on bromides in paragraph 2.1.3.

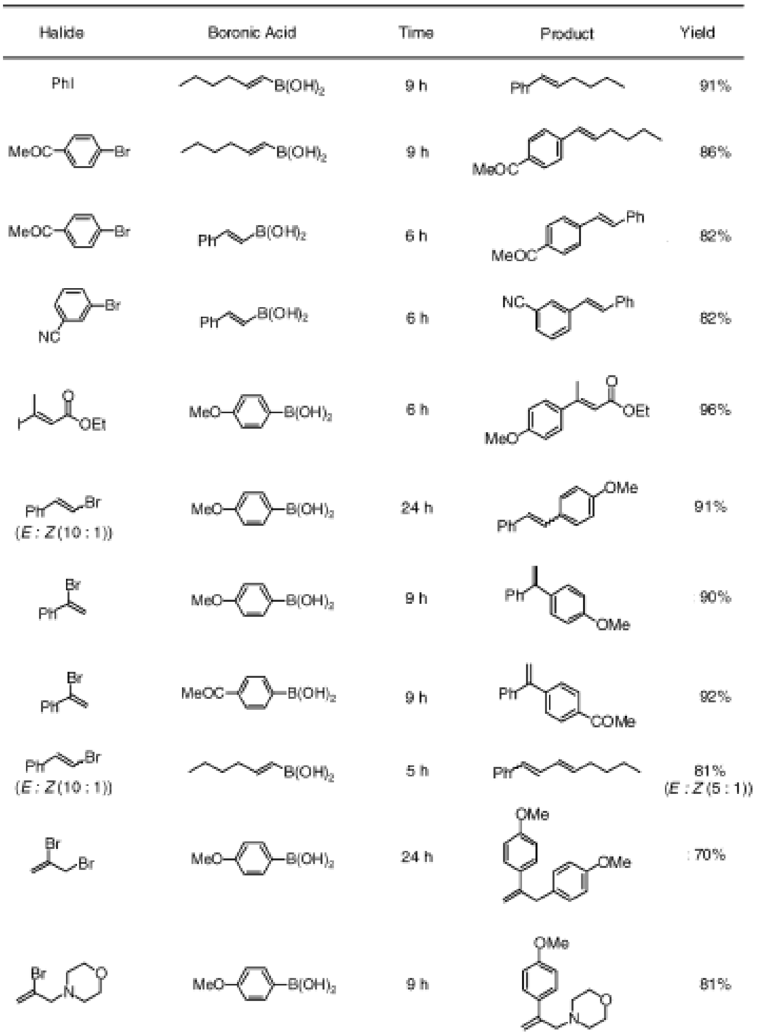
2.3.2.3 Performance of the catalysts in Suzuki coupling reaction with alkenyl halides in batch

Given the excellent results obtained with aryl halides, it was considered appropriate to test our catalysts and conditions previously optimized/studied, on alkenyl halides; since in the literature there are few data on the real-reactivity of these systems in supported catalysis, moreover the alkenyl halides were intensively applied to the synthesis of compounds of biological, pharmacological and/or agrarian interest, also to industrial level, in homogeneous catalysis.**[256b]**

In literature, the studies and applications that analyze the reactivity of olefin halides in Suzuki-Miyaura reactions, promoted by supported catalysts have a fairly small number. In fact in the majority of cases the Pd-supported catalysts are used with aryl halides, always considered less reactive compared to corresponding olefin, often reclining on the equation "a good reactivity with the aryl precursor same excellent reactivity with the olefin precursor".**[282]**

The first work that describes the use of a supported catalyst in the Suzuki reaction with some alkenyl halides was reported by Jang and co-workers in 1997.**[176]** In this work the authors compare a polystyrene-supported catalyst with the homogeneous $Pd(PPh_3)_4$ in the reaction between vary alkenyl bromides and alkenyldialkilboranes. Surprisingly this work showed a better reactivity of the supported system regard the homogeneous in term of TONs and yields. Unfortunately, the authors do not report Pd-leaching data, but state that the catalyst is recyclable (if used in 1 mol % of Pd load) repeatedly, without loss of activity.**[176]**

In 2003 Yamada et co-workers describe the heterogeneous Suzuki-Miyaura reaction of aryl and alkenyl halides with arylboronic and alkenylboronic acids catalyzed by low doses (8 × 10-7 to 5 × 10-4 mol % of Pd) of an assembled insoluble catalyst (PdAS), prepared from $(NH_4)_2PdCl_4$ and a non-cross-linked amphiphilic polymer with phosphine ligands (poly(N-isopropylacrylamide-co-4-diphenylstyrylphosphine).**[283]** This catalyst is highly efficiently to catalyze the Suzuki-Miyaura reaction of aryl and alkenyl halides and benzylic chlorides with arylboronic and alkenylboronic acids and alkyl-9-BBNs in term of yield and TONs (It should be noted that the highest TON reached over one million) (**Scheme 2.3.2.3**).**[283]**

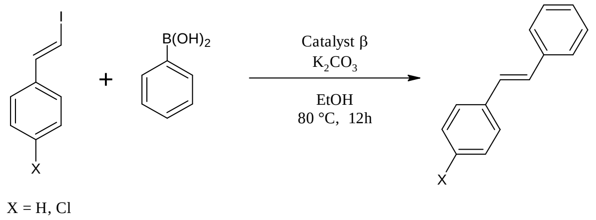


Scheme 2.3.2.3: Heterogeneous Suzuki-Miyaura reaction of aryl and alkenyl halides catalyzed by low doses of PdAS

However, from a comparison between the results obtained with alkenyl halides and those reported, in the same work with the same conditions, of aryl halides, one can derive that, in general, the reactivity of olefinic halides appears to be lower (in terms of yield and TON) to that of the aryl halides.

Unfortunately, the authors do not report Pd-leaching data, and the catalyst is recyclable 10 times without loss of activity, but exclusively for the reaction between iodobenzene and phenylboronic acid.**[283]**

Most recently (in 2009) the Hoshiya group report only two examples of the heterogeneous Suzuki-Miyaura reaction of alkenyl halides with arylboronic acids catalyzed by an palladium catalyst supported on gallium arsenide, {Pd}-S-GaAs(001).**[284]** In this work the authors report a careful study of the recyclability of the catalyst in the Suzuki-Miyaura reaction of aryl and alkenyl halides with boronic acids. The catalyst is easily recyclable without loss of activity and low leaching with aryl halides, while with two alkenyl halides (trans-β-iodostyrene and 2-bromo-1-(4-chlorophenyl)ethylene) during the recycle the yields of corresponding stilbenes gradually decreased (**Scheme 2.3.2.4**).**[284]**



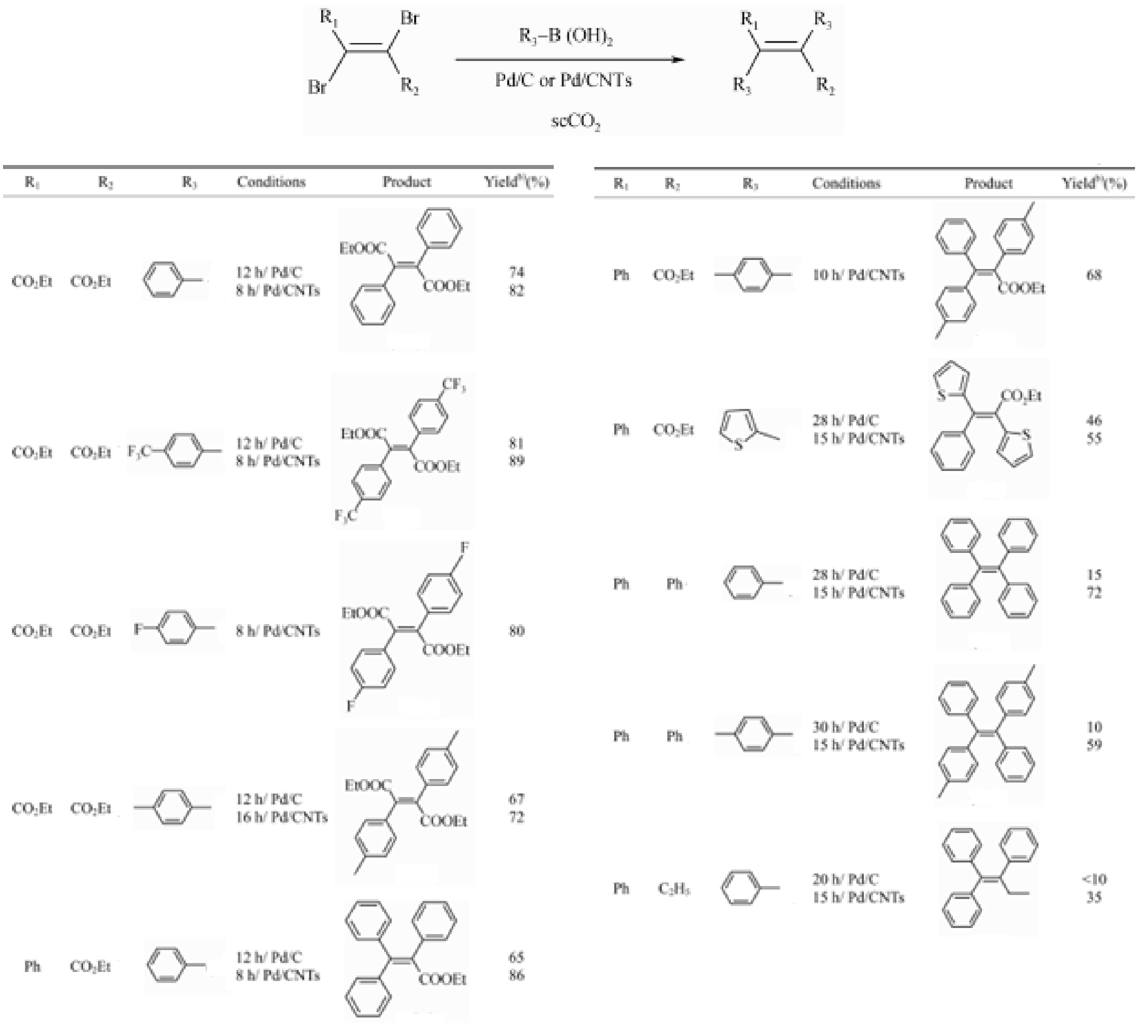
Iodide	Yield										
	1st	2nd	3rd	4th	5th	6th	7th	8th	9th	10th	ave.
X = H	95	78	88	71	91	87	84	54	26	22	70
X = Cl	89	91	87	78	58	46	69	44	26	31	62

Scheme 2.3.2.4: **Heterogeneous Suzuki-Miyaura reaction of trans-β-iodostyrenes catalyzed by {Pd}-S-GaAs(001).**

Finally, in 2008 Zhou and co-works have described a facile and efficient method for the synthesis of tetrasubstituted olefins in supercritical carbon dioxide through the Suzuki-Miyaura reaction of dibromo-substituted olefins with boronic acids catalyzed by carbon nanotubes-supported palladium nanoparticles (Pd/CNTs).**[284]**

The Pd/CNTs could more effectively catalyze the reaction of dibromo-substituted olefins with boronic acids, affording the corresponding tetrasubstituted olefins with moderate to good yields (**Scheme 2.3.2.5**).

The results have been compared, in the same conditions, with Pd/C; resulting more efficient the same Pd/C.



R$_1$	R$_2$	R$_3$	Conditions	Product	Yield$^{b)}$(%)
CO$_2$Et	CO$_2$Et		12 h/ Pd/C 8 h/ Pd/CNTs		74 82
CO$_2$Et	CO$_2$Et		12 h/ Pd/C 8 h/ Pd/CNTs		81 89
CO$_2$Et	CO$_2$Et		8 h/ Pd/CNTs		80
CO$_2$Et	CO$_2$Et		12 h/ Pd/C 16 h/ Pd/CNTs		67 72
Ph	CO$_2$Et		12 h/ Pd/C 8 h/ Pd/CNTs		65 86

R$_1$	R$_2$	R$_3$	Conditions	Product	Yield$^{b)}$(%)
Ph	CO$_2$Et		10 h/ Pd/CNTs		68
Ph	CO$_2$Et		28 h/ Pd/C 15 h/ Pd/CNTs		46 55
Ph	Ph		28 h/ Pd/C 15 h/ Pd/CNTs		15 72
Ph	Ph		30 h/ Pd/C 15 h/ Pd/CNTs		10 59
Ph	C$_2$H$_5$		20 h/ Pd/C 15 h/ Pd/CNTs		<10 35

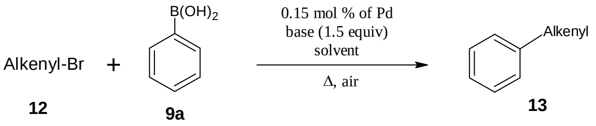
Scheme 2.3.2.5: Heterogeneous Suzuki-Miyaura reaction of dibromo-substituted olefins catalyzed by Pd/CNTs and Pd/C.

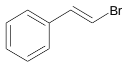
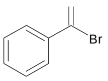
At the light of these limited literature data, and to consider the synthetic importance of this Suzuki-Miyaura reaction; we decided to investigate the coupling ability of our supported catalysts with alkenyl halides (generally considered more reactive of the corresponding aryl halides, but not completely confirm from the literature data above mentioned).

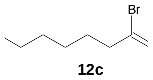
Initially, taking account the optimization study with aryl bromides (see paragraph 2.3.2.1) and the presume more reactivity of alkenyl systems regards at aryl halides; we decided to examine the our supported catalysts in the best conditions previously individuated on aryl bromides like K_3PO_4 or KF as base in DMF/H_2O and EtOH/H_2O as solvent using low doses of catalyst (0.15 mol % of Pd) in aerobic atmosphere at the same temperature used with aryl halides.
Obviously in these tests we not use the only water as solvent resulting completely unhomogeneous with all type of reagents and at any temperature.

In detail we examined the coupling ability of our supported catalysts with alkenyl halides, and consequently evaluate the true more reactivity of these halides, by screening the previously mentioned conditions for the reaction of three different alkenyl halides such as the commercials (E)-β-bromostyrene (**12a**), α-bromostyrene (**12b**) and the synthetized, but disponible in our laboratory, 2-bromo-1-octene (**12c**) with phenylboronic acid (**9a**); evaluating from point of view of the yield, reaction time and leaching data (**Table 2.3.2.9**).

Table 2.3.2.9: Efficiency of aryl halides conditions in Suzuki-Miyaura reaction with alkenyl halides[a]



Entry	Alkenyl bromide	Solvent	Base (equiv)	temperature	Catalyst	time (h)	Conversion of **12**[b] (%)	Yield of **13**[c] (%)	Leaching[d] (%)
1		DMF/H_2O (4:1)	KF (1.2)	100	PdEnCat-40	16	trace	-	-
2					Fibrecat 1007	16	trace	-	-
3					$Pd(PPh_3)_4$-PS	16	trace	-	-
4					$PdCl_2(PPh_3)_2$-PS	16	trace	-	-
5					Pd/MCM-41	16	trace	-	-
6		DMF/H_2O (4:1)	K_3PO_4 (1.5)	100	PdEnCat-40	1	99	91	0.50
7					Fibrecat 1007	1	99	91	2.60
8	 **12a**				$Pd(PPh_3)_4$-PS	1	99	90	-
9					$PdCl_2(PPh_3)_2$-PS	1.5	99	86	6.20
10					Pd/MCM-41	1	99	90	-
11		EtOH/H_2O[e] (1:1)	K_3PO_4 (1.5)	90	PdEnCat-40	5	99	97	0.02
12					Fibrecat 1007	1	98	55	0.15
13					$Pd(PPh_3)_4$-PS	3	98	-	-
14					$PdCl_2(PPh_3)_2$-PS	6	99	98	0.31
15					Pd/MCM-41	5	97	-	-
16		DMF/H_2O (4:1)	KF (1.2)	100	PdEnCat-40	16	trace	-	-
17					Fibrecat 1007	16	trace	-	-
18					$Pd(PPh_3)_4$-PS	16	trace	-	-
19					$PdCl_2(PPh_3)_2$-PS	16	trace	-	-
20					Pd/MCM-41	16	trace	-	-
21		DMF/H_2O (4:1)	K_3PO_4 (1.5)	100	PdEnCat-40	0.5	99	80	2.10
22					Fibrecat 1007	1	96	76	0.69
23	 **12b**				$Pd(PPh_3)_4$-PS	1	96	74	2.00
24					$PdCl_2(PPh_3)_2$-PS	1	99	82	0.38
25					Pd/MCM-41	1	99	80	-
26		EtOH/H_2O[e] (1:1)	K_3PO_4 (1.5)	90	PdEnCat-40	2.5	99	88	0.21
27					Fibrecat 1007	0.5	99	95	0.61
28					$Pd(PPh_3)_4$-PS	1	99	66	0.49
29					$PdCl_2(PPh_3)_2$-PS	5	99	98	0.10
30					Pd/MCM-41	3	99	80	-

31	 **12c**	*DMF/H_2O (4:1)*	*KF (1.2)*	*100*	*PdEnCat-40*	24	n.r.	-	-
32					*Fibrecat 1007*	24	n.r.	-	-
33					*$Pd(PPh_3)_4$-PS*	24	n.r.	-	-
34					*$PdCl_2(PPh_3)_2$-PS*	24	n.r.	-	-
35					*Pd/MCM-41*	24	n.r.	-	-
36		*DMF/H_2O (4:1)*	*K_3PO_4 (1.5)*	*100*	*PdEnCat-40*	2	86	*29*	-
37					*Fibrecat 1007*	1	88	*34*	-
38					*$Pd(PPh_3)_4$-PS*	1.5	85	*30*	-
39					*$PdCl_2(PPh_3)_2$-PS*	3	91	*32*	-
40					*Pd/MCM-41*	4	67	-	-
41		*EtOH/H_2O^e (1:1)*	*K_3PO_4 (1.5)*	*90*	*PdEnCat-40*	2.0	88	*26*	-
42					*Fibrecat 1007*	1.5	83	*21*	-
43					*$Pd(PPh_3)_4$-PS*	2.0	81	*32*	-
44					*$PdCl_2(PPh_3)_2$-PS*	3.0	90	*35*	-
45					*Pd/MCM-41*	6.0	70	-	-

a) Reaction conditions: 1.0 equivalent of alkenyl halide (**12**), 1.25 equivalent of phenylboronic acid (**9a**), 1.2-1.5 equivalent of base, 0.15 mol % of Pd as catalyst, solvent (1.33 mL/mmol), air atmosphere; b) Evaluated by GC analyses; c) Isolated Yield by MPLC; d) Evaluated by ICP-OES after microfiltration (0.45 mm) and reported as Pd leached wt.% of the total available metal; e) 3.00 mL/mmol

These preliminary tests showed interesting but discordant result. Using the KF as base none of the catalysts tested are able to promote these reaction (despite in this condition the our commercial catalysts promote efficiently the reaction with 2-bromoanisole (**8a**) in short time, see Table 2.3.2.2 paragraph 2.3.2). While using the K_3PO_4 both in DMF/H_2O that in EtOH/H_2O, the catalysts are able to promote the reaction with complete conversion in acceptable short time (< 5 h); but only with the bromostyrenes these reactions are obtained with good and excellent yields (60-98 %).

The 2-bromo-1-octene (**12c**) in these conditions are completely converted, but unfortunately the yields of the desiderate product are most moderate (21-35 %). These results are probably have to dimerization/polymerization phenomena of the start material in these conditions.

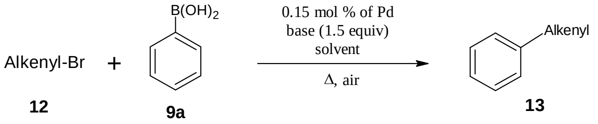
For regard the leaching data, generally the leaching in EtOH/H_2O are similar between the bromostyrenes and most low (< 0.60 %), while in DMF/H_2O the leaching are generally more superior (> 1.00 %) and much depend from the bromostyrenes used.

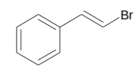
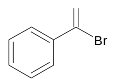
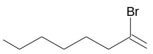
At the light of these results, we decided to research reaction conditions most efficient with 2-bromo-1-octene (**12c**); For this we decide to apply the reaction condition previously optimized with aryl chlorides in paragraph 2.3.5 (principally K_2CO_3 as base in DMF/H_2O as solvent).

Moreover, given the excellent results obtained with the bromostyrenes, both in DMF/H_2O that in EtOH/H_2O respectively at 100°C and 90°C; we decided to investigate the efficiency performance reducing the reaction temperature, could evaluated the real difference in reactivity between aryl and alkenyl halides.

In detail the tests of reduction of temperature were/are performed only on bromostyrenes using the commercial catalysts. While the conditions to use the K_2CO_3 as base in DMF/H_2O were/are performed with all three alkenyl bromides to better evaluated the effect (positive or negative) using for simplicity and rapidity only the commercial Fibrecat 1007 as catalyst. Moreover, the K_2CO_3 as base with Fibrecat 1007 as catalyst was used too in EtOH/H_2O (**Table 2.3.2.10**)

Table 2.3.2.10: Efficiency of aryl chlorides optimized condition, and effect of the temperature in Suzuki-Miyaura reaction with alkenyl halides[a]



Entry	*Alkenyl bromide*	***Solvent***	*Base (equiv.)*	*temperature*	*Catalyst*	*time (h)*	*Conversion of **12**[b] (%)*	*Yield of **13**[c] (%)*	*Leaching[d] (%)*
1	 **12a**	DMF/H2O (4:1)	K_3PO_4 (1.5)	80	PdEnCat-40	4.0	99	56	0.06
2					Fibrecat 1007	3.0	98	56	1.61
3					$Pd(PPh_3)_4$-PS	-	-	-	-
4					$PdCl_2(PPh_3)_2$-PS	2.0	99	46	-
5			K_2CO_3 (2.0)	100	Fibrecat 1007	4.0	90	56	4.14
6		$EtOH/H_2O$[e] (1:1)	K_3PO_4 (1.5)	70	PdEnCat-40	6.0	25	-	-
7					Fibrecat 1007	5.0	35	-	-
8					$Pd(PPh_3)_4$-PS	-	-	-	-
9					$PdCl_2(PPh_3)_2$-PS	10.0	36	-	-
10			K_2CO_3 (2.0)	95	Fibrecat 1007	6.0	66	28	-
11	 **12b**	DMF/H2O (4:1)	K_3PO_4 (1.5)	80	PdEnCat-40	1.0	98	70	1.41
12					Fibrecat 1007	2.0	98	65	0.36
13					$Pd(PPh_3)_4$-PS	2.0	90	63	0.13
14					$PdCl_2(PPh_3)_2$-PS	1.5	99	71	1.02
15			K_2CO_3 (2.0)	100	Fibrecat 1007	1.0	99	58	0.21
16		$EtOH/H_2O$[e] (1:1)	K_3PO_4 (1.5)	70	PdEnCat-40	4.0	99	70	0.12
17					Fibrecat 1007	1.0	99	76	0.56
18					$Pd(PPh_3)_4$-PS	2.0	99	53	0.45
19					$PdCl_2(PPh_3)_2$-PS	7.0	80	74	0.09
20			K_2CO_3 (2.0)	95	Fibrecat 1007	0.5	99	53	0.19
21	 **12c**	DMF/H2O (4:1)	K_2CO_3 (2.0)	100	Fibrecat 1007	3.0	86	29	-
22		$EtOH/H_2O$[e] (1:1)	K_2CO_3 (2.0)	90	Fibrecat 1007	2.0	83	21	-

a) Reaction conditions: 1.0 equivalent of alkenyl halide (**12**), 1.25 equivalent of phenylboronic acid (**9a**), 1.5 or 2.0 equivalent of base, 0.15 mol % of Pd as catalyst, solvent (1.33 mL/mmol), air atmosphere; b) Evaluated by GC analyses; c) Isolated Yield by MPLC; d) Evaluated by ICP-OES after microfiltration (0.45 mm) and reported as Pd leached wt.% of the total available metal; e) 3.00 mL/mmol

These conditions tests showed interesting results from point of view of the reactivity of the alkenyl halides.

Principally, neither these conditions using the K_2CO_3 (most efficient with aryl chlorides catalyzed by Fibrecat 1007) appears able to promote selectively the coupling with aliphatic alkenyl halides like 2-bromo-1-octene (**12c**); and the same conditions reducing the efficiency of the coupling also to bromostyrenes (compare **Table 2.3.2.10** with **Table 2.3.2.9**).

For regard the reduction of the temperature, we showed that reducing the temperature the catalytic activity for the majority of the catalysts does undergo reduction. In detail reducing the temperature to 80°C in the DMF/H_2O conditions, the complete conversion of the reaction with α–bromostyrene (**12b**) and (E)-β-bromostyrene (**12a**) suffered light variation but with evident loss of yield (more evident with **12a**).

The reduction of the temperature in EtOH/H_2O to 70°C showed different result between the two bromostyrenes. In the test with **12b** the reaction times and yields are light varied, but always acceptable (reaction times lower 10 h and yields over the 70 %); while with **12a** none of the catalysts are able to promote efficiently the reaction (conversions were stopped at low values).

In conclusion, at the light of all these results (resumed in **Table 2.3.2.9** and **Table 2.3.2.10**) we identified two principally efficient, practical and green conditions that use 1.5 equiv. of K_3PO_4 as base, low doses of catalyst (0.15 mol % of Pd), aerobic atmosphere and as solvent respectively DMF/H_2O at 100°C or EtOH/H_2O at 80°C.

However, taking into account the leaching and yield data, generally the better reaction condition are K_3PO_4 in EtOH/H_2O, given that showed excellent yields with very low leaching (**Table 2.3.2.9**).

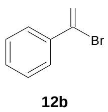
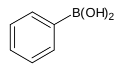
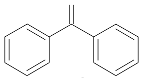
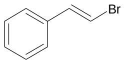
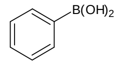
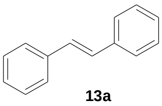
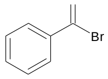
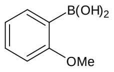
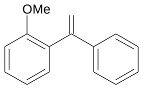
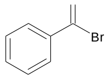
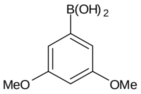
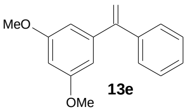
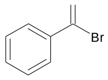
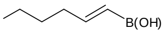
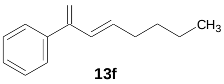
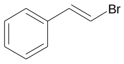
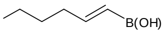
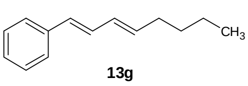
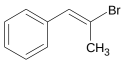
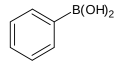
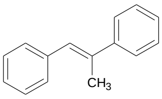
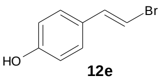
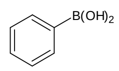
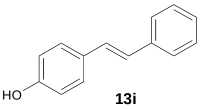
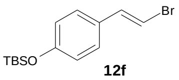
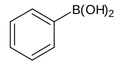
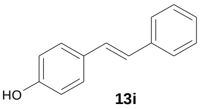
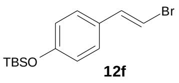
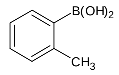
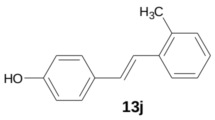
Identified and selected one practical, efficient, green and if possible applicable in flow; reaction condition where our commercial catalysts are able to promote the reactions with bromostyrenes.

We proceeded to explore the scope and generality of these catalysts, applied the optimized aerobic protocol for reactions of a variety of differently substituted bromostyrenes and arylboronic acids. β-Bromostyrenes were synthetized by opportune and selective procedure of catalytic halo-decarboxylation, better illustrated in paragraph 2.6 taking account its application in a possible continuous-flow sequential process.

Therefore, the study was set up by selecting a few examples of β-bromostyrenes bearing electron withdrawing and donating groups. The outcomes are summarized in **Table 2.3.2.11**.

Table 2.3.2.11: Scope and generality of our supported catalysts in Suzuki-Miyaura coupling reaction with bromostyrenes.[a]

$$\underset{\textbf{12}}{\text{Alkenyl-Br}} + \underset{\textbf{9}}{\text{Ar'-B(OH)}_2} \xrightarrow[\text{EtOH/H}_2\text{O (1:1) 3.0 mL/mmol, 80 °C, air}]{\text{0.15 mol \% di Pd, K}_3\text{PO}_4\text{ (1.5 equiv)}} \underset{\textbf{13}}{\text{Alkenyl-Ar'}}$$

Entry	*(Het)Ar-X* **(14)**	*Ar'-B(OH)$_2$* **(9)**	*Catalyst*	*Time (h)*	*Product* **(15)**	*Yield of 3[a] (%)*	*Leaching[b] (%)*
1	 **12b**	 **9a**	PdEnCat-40	2.5	 **13b**	88	0.21
2			Fibrecat 1007	0.5		95	0.61
3			PdCl$_2$(PPh$_3$)$_2$-PS	1.5		99	0.10
4			Pd(PPh$_3$)$_4$-PS	2		66	0.49
5	 **12a**	 **9a**	PdEnCat-40	5	 **13a**	97	0.02
6			Fibrecat 1007	1		55	0.15
7			PdCl$_2$(PPh$_3$)$_2$-PS	6		98	0.31
8	 **12b**	 **9c**	PdEnCat-40	2	 **13d**	78	
9			Fibrecat 1007	24		-	
10			PdCl$_2$(PPh$_3$)$_2$-PS	3		94	
11	 **12b**	 **9d**	PdEnCat-40	7	 **13e**	59	
12			Fibrecat 1007	7		52	
13			PdCl$_2$(PPh$_3$)$_2$-PS	7		60	
14	 **12b**	 **9e**	PdEnCat-40	2.5	 **13f**	42	0.05
15			Fibrecat 1007	1.5		25	0.22
16			PdCl$_2$(PPh$_3$)$_2$-PS	4		34	0.13
17	 **12a**	 **9e**	PdEnCat-40	6	 **13g**	32	0.17
18			Fibrecat 1007	1.5		87	2.48
19			PdCl$_2$(PPh$_3$)$_2$-PS	5		61	0.86
20	 **12d**	 **9a**	PdEnCat-40	8	 **13h**	-	
21			Fibrecat 1007	8		-	
22			PdCl$_2$(PPh$_3$)$_2$-PS	8		-	
23	 **12e**	 **9a**	PdEnCat-40	24	 **13i**	n.r.	
24			Fibrecat 1007	24		trace	
25			PdCl$_2$(PPh$_3$)$_2$-PS	24		n.r.	
26			Pd(PPh$_3$)$_4$-PS	24		n.r.	
27	 **12f**	 **9a**	PdEnCat-40	10	 **13i**	n.r.	
28			Fibrecat 1007	6		67	
29			PdCl$_2$(PPh$_3$)$_2$-PS	10		n.r	
30	 **12f**	 **9f**	PdEnCat-40	10	 **13j**	n.r.	
31			Fibrecat 1007	8		45	
32			PdCl$_2$(PPh$_3$)$_2$-PS	10		n.r.	
33			Pd(PPh$_3$)$_4$-PS	10		n.r.	

Reaction conditions: 1.0 equivalent of alkenyl halide (**12**), 1.25 equivalent of boronic acid (**9**), 1.5 equivalent of K_3PO_4, 0.15 mol % of Pd as catalyst, EtOH/H_2O (3.00 mL/mmol), air atmosphere

a) Isolated Yield by MPLC; b) Evaluated by ICP-OES after microfiltration (0.45 mm) and reported as Pd leached wt.% of the total available metal.

The results obtained with the selected commercial catalysts, to consist in a Pd(0) and Pd(II) deposited or incapsulated on polymer supports, are very interesting. More in particular, from a long series of tests, carried out on various compounds (phenylboronic acid (**9a**), 2-methoxyphenylboronic acid (**9c**), 3,5-dimethoxyphenylboronic acid (**9d**) and 1-exenylboronic acid (**9e**) as boronic species and α-bomo- or (E)-β-bromostyrenes electron-poor and electron-rich as halides), allowed to establish that the catalysts studied showed a fairly good efficiency in short times (0.5-7 h); however some specific features of each catalyst that have been identified.

These systems affording similar good to excellent yields in short times with α-bromostyrene (**12b**), except when used with a sterically hindered boronic acid such as 2-methoxyboronic acid (**9c**). In fact in this case the Fibreacat 1007 (**2**) is not able to promote the reaction.

Sterically hindered is very important effect, in fact none of the catalysts result able to promote the reaction with [(1*E*)-2-bromoprop-1-en-1-yl]benzene (**12d**, an β-bromostyrene sterically hindered).

Moreover, the presence of a protic free groups -OH on the aromatic ring **12e** is very dramatic (compared with the effect given on aryl halides) and only the Fibrecat 1007 (**2**) showed trace of the desiderated product after 24 h.

In the reaction with protect protic group **12f** again the Fibrecat 1007 (**2**) is the only catalyst able to promote the reactions, but in these reaction conditions (K_3PO_4 in $EtOH/H_2O$) during the reaction, the protecting group is eliminate, and the product at the end reaction show a protic free group. Unfortunately, this concomitance of the coupling and the protect group elimination cause a moderate yields of the desiderate products with many amount of the protic free group start materials.

Regarding the boronic acids, the coupling reaction of aryl boronic acid, such as phenylboronic acid (**9a**), 2-methoxyphenylboronic acids (**9c**) and 3,5-dimethoxyphenylboronic acid (**9d**), proceeded quite efficiently. However, it is interesting to note that the reaction with alkenyl boronic acid affording good yields in the coupling with (E)-β-bromostyrene (**12a**) catalyzed by **2** (87 %) and **3** (61 %); while in the coupling with α-bromostyrenes (**12b**) the complete conversion is obtain in low time, but the yields are very low (< 40).

Finally for regard the leaching, its generally very low whether we use aryl or alkenyl boronic acid in the coupling with vary bromostyrenes.

2.3.2.4 Conclusions

In conclusion we have individuated and optimized simple, efficient and environmentally friendly Suzuki-Miyaura conditions based on K_3PO_4 as the base and DMF/H_2O, or EtOH/H_2O, or only water as the solvent, that can allow the use of four commercially available and cheap palladium supported catalysts.
Moreover, we have developed a new supported catalyst MVS-prepared that appear very efficient in the same above mentioned conditions (Pd/MCM-41), and we have extended the knowledge on Pd/PVPy (MVS-prepared), which precedently have been used only in Heck-type reactions.

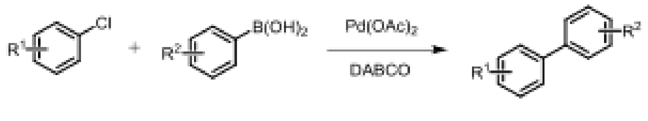
Generally the studied catalysts are able to furnish high catalytic activity in Suzuki cross-coupling reaction in batch mode, both with aryl and vinyl halides, but the results depend strongly from the specific halide and boronic acid used.

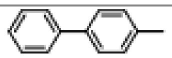
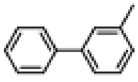
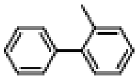
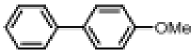
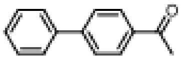
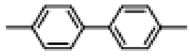
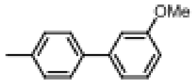
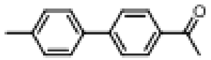
As aryl chlorides reaction, it was necessary to find different conditions; in particular, it has been developed a process for a commercial catalysts (Fibrecat 1007), thanks to the use of K_2CO_3 as base in the reaction mixture (carried out under suitable conditions, carefully developed), or using the only water as solvent for regard the laboratory-prepared catalyst (Pd/MCM-41). However, even these conditions require low metals loads and are not affected by the presence of air. Under these new conditions the reaction of chlorobenzene with phenylboronic acid gave a moderate yield, but with different chloro-arenes much better results were obtained.

Most particular appear the vinyl halides arylation; in fact these systems react in conditions and time similar at aryl iodides, but the yields of the corresponding product are many lower particularly in the reaction with vinyl iodides.
Probable the vinyl halides result most sensible and little stable in these reaction conditions, but unfortunately the our supported catalysts, but in general all supported catalyst, require many drastic condition (respect at homogeneous catalysts) to promote the cross-coupling; and this makes no exceptions.

2.3.3 Suzuki-Miyaura coupling reaction in flow

Suzuki couplings have become a routine transformation in synthetic chemistry and as such there has been much interest in translating their use into continuous flow processing. A demonstration of the efficiency of flow *vs* batch for Suzuki couplings was undertaken by Li and co-workers.**[286]** They reported Suzuki coupling of both electron-rich and electron-poor aryl chlorides with phenyl boronic acid, catalyzed by a non-phosphane ligand catalyst system Pd(OAc)$_2$/DABCO, in a capillary microreactor at 50 °C (**Scheme 2.3.3.1**).

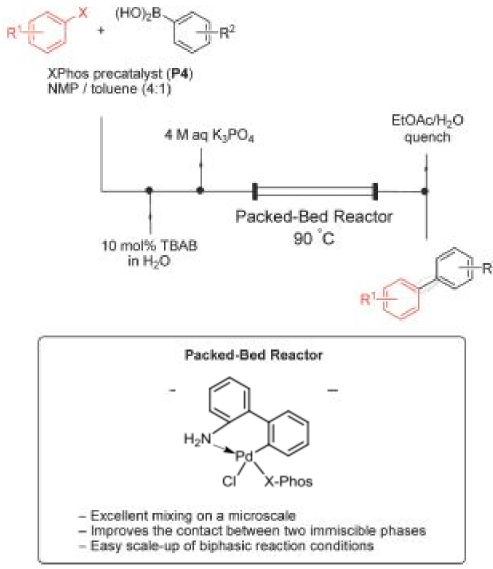


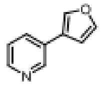
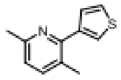
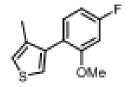
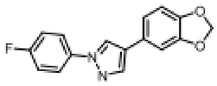
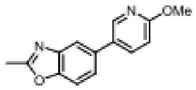
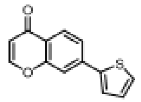
Product	Conversion (%)[b]		
	Flow (4 h)	Batch (4 h)	Batch (24 h)
	98	61	98
	99	56	99
	99	52	86
	99	35	57
	99	68	99
	99	65	99
	97	54	95
	99	69	99

Scheme 2.3.3.1: Comparison of batch *vs* flow for Suzuki coupling

Quantitative yields were obtained for most substrates with a relatively long residence time of four hours. However, conversions of only 12-69% were achieved under the corresponding batch conditions, which required 24 h to achieve full conversion. The drive for achieving low catalyst loadings and high turnover frequencies (TOF) is as prevalent in continuous processing as it is in batch. The lowest catalyst loading reported to date using a flow protocol is 0.05 mol%. Noel and Musacchio have reported the Suzuki coupling of heteroaryl halides with aryl and heteroarylboronic acids, using X-Phos Pd precatalyst (0.05-1.5 mol%) and phase transfer catalyst (TBAB) in the presence of aq. K$_3$PO$_4$.**[287]** In this case an efficient packed bed system was exploited to ensure good mixing of the biphasic medium consisting of

NMP/toluene/H2O (4:1:5); and excellent yields were obtained at 90 °C in a residence time of 3 min, for the vast majority of heteroaryl substrates examined (**Scheme 2.3.3.2**).



Product	X	Pd (mol%)	Yield (%)
	Cl	1.5	92
	Cl	1.0	87
	Cl	0.5	98
	Br	0.5	88
	Br	1.5	89
	Cl	0.5	96
	OTf	0.2	84

Scheme 2.3.3.2 : Schematic microreactor setup for continuous-flow Pd-catalyzed Suzuki-Miyaura cross-coupling

Flow processing also offers advantages to high throughout synthesis and compound library preparation due to the uniformity of reaction environment and ability to be fully automated. Ley and Baxendale demonstrated the possibility of utilising microreactors for the synthesis of a library of biaryls via Suzuki coupling.**[146f]** The use of Pd EnCat in conjunction with microwave irradiation provided a platform from which to screen an extensive variety of coupling partners. A total of 341 Suzuki couplings were conducted including an automated sequence of 10 in succession with short wash periods in between.

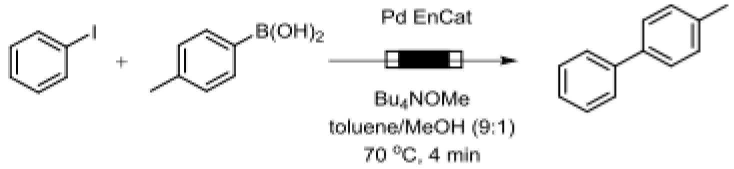
2.3.3.1 State of art of Suzuki reaction with aryl and alkenyl halides in flow mode

As previously mentioned in paragraph 1.3.1; in general for all cross-coupling there are a wide variety of different catalytic technologies available for conducting cross-couplings in continuous flow. Traditionally heterogeneous systems were favoured due to their ease of separation, recycling and high surface areas making for more efficient processing. **[124, 190b]**

However, with issues surrounding leaching of Pd into solution and subsequent loss of activity making their use problematic over extended periods of time.

For regard the Suzuki-Miyaura cross-coupling reaction a broad range of solid supports were developed and applied in continuous-flow chemistry, such as, silica,**[153, 288]** monolithic supports,**[37, 130c-d, 289]** polymer beads**[290]** and PdEnCats**[146d, 147a]**.
However, strong evidence indicates that these solid supports function as "palladium reservoir" and gradually leach the catalytically active Pd species into solution.**[53, 60, 164a, 291]**
Furthermore, swelling of the polymer supports, deposition of products/by-products and the necessity to periodically replace the cartridges can complicate their use in continuous-flow chemistry.

Ley and co-workers investigated the use of a polyurea-encapsulated palladium(II) acetate (PdEnCats) precatalyst in the Suzuki coupling of iodobenzene and p-tolylboronic acid (**Scheme 2.3.3.3**) under continuous flow conditions.**[147a]** The authors using an HPLC column packed with the [PdEnCat] catalyst obtain the desired biaryl in 70-85% yields with nBu_4NOH and nBu_4NOMe as bases at 70°C, after just three passes through the column reactor with a residence time of 4 min. They investigated several bases, but Bu_4NOMe gave the best results as it afforded a homogeneous reaction mixture which maximised the interaction between reagents and catalyst.



Scheme 2.3.3.3: Pd EnCat catalysed Suzuki coupling in flow.

The same authors also investigated the effect of microwave heating in Suzuki-Miyaura under flow conditions.**[146f]** In this work the author using an reactor design is based upon a simple continuous glass U-tube that may be packed with the heterogeneous catalyst and inserted into the microwave cavity (**Figure 2.3.3.1**).

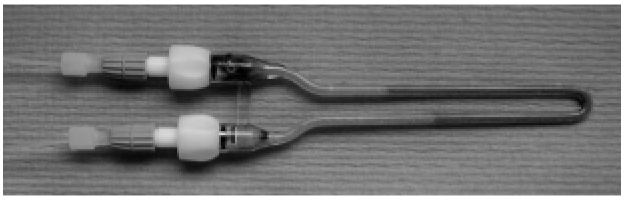
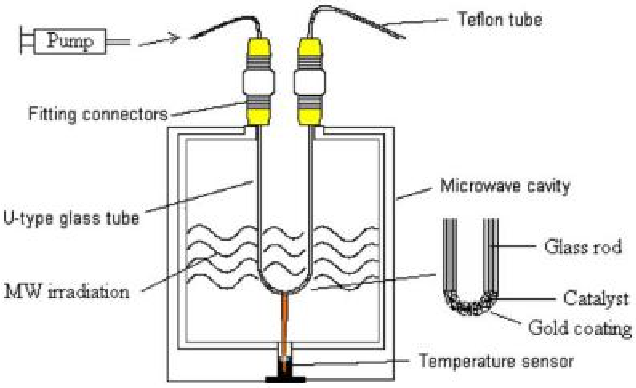


Figure 2.3.3.1: Glass U-tube flow reactor microwave insert.

The reactions are much more efficient provided a platform from which to screen an extensive variety of coupling partners, but sometimes an additional purification was required to remove residual palladium by passing the reaction mixture through a metal-scavenging Quadrapuret TU (thiourea) column (later other authors demonstrated that PdEnCat is reservoir of soluble palladium)**[164a]**, and it was demonstrated that prolonged heating of the reactor at a constant power level of 50 W was detrimental for the polymer support, causing it to collapse, melt and eventually clog the tube.

This was bypassed by applying a modified heating protocol in which the microwave-heating phase (30 s, 50 W) was followed by a cooling phase (18 s, no power application).

The same glass U-tube flow reactor microwave insert are used by Haswell and co-works in microwave-assisted Suzuki coupling between a range of aryl halides and phenylboronic acid; evaluating many catalysts and bases.**[292]** This method involved coating of the reactor with a gold film, which led to a more efficient absorption of the microwaves and enabled the microwave power to be reduced to less than 100 W. The necessity to employ a gold-coated reactor indicates that the microwave irradiation heated the reactor and not directly the solvent (**Scheme 2.3.3.4**).



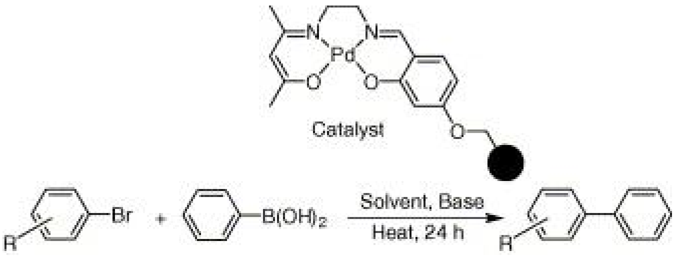
Scheme 2.3.3.4: Schematic diagram of the setup for microwave-assisted coupling reactions

This system show good result using Pd/SiO2, but after constant microwave irradiation at 100 W the catalyst particles are aggregate which in turn deactivates the catalyst.

Leeke et al. further investigated the Suzuki coupling of iodobenzene and toluilboronic acid with Pd EnCat in flow, this time on an exploratory commercial scale, utilising both traditional organic solvents and $scCO_2$.**[146d]** They observed that, in a conventional solvent system (toluene/methanol 9:1), both reaction temperature and flow rate were significant factors in the conversion. In general higher temperatures afforded higher conversions up to 100 °C, after which this effect was less prominent.

The optimum flow rate was found to be 6.4 mL/min, which afforded a 74% conversion to desired biaryl. Any attempt to lower the flow rate and thus increase residence time, afforded lower conversions. This was attributed to poorer mixing due to a lower solid/liquid ratio. At all temperatures and flow rates, homocoupling to the undesirable biphenyl byproduct did not exceed 1.8%. To improve conversion further the reagent solution was passed three times over the column, but this only afforded a slight increase in conversion. It was found that the pH of the reaction mixture dropped from pH 13.4 initially to 7.3 after the first pass. Addition of a further portion of Bu_4NOMe after the first pass returned the pH to 13.4 and afforded complete conversion on the second pass. The same reaction was examined under $scCO_2$ conditions, with MeOH as a co-solvent to increase the solubility of the Bu_4NOMe. An optimum conversion of 81% was achieved under supercritical conditions at 166 bar and 100 °C, with a reagent flow rate of 5.5 g/min. Raising the pressure showed a decrease in conversion and lowering the pressure afforded satisfactory conversion, although this resulted in a two-phase liquid-vapour reaction system (effectively utilising a $scCO_2$ expanded solvent system).**[293]**
Operating at lower pressures could provide advantages in process economics upon scale up. Initially it was thought that palladium leaching from Pd EnCat under continuous flow conditions was negligible, with ICP-MS analysis indicating palladium levels of 10 ppm (0.025% metal loss) in the filtered reagent solution.**[294]**

Styring and co-workers performed continuous flow Suzuki–Miyaura reactions in a pressure driven mini flow reactor packed with polystyrene–DVB crosslinked Merrifield resin beads supported salen-type palladium(II) complex (**Scheme 2.3.3.5**).**[290, 295]** The supported Pd complex was loaded into an Omnifit columns**[296]** (25 mm x 3 mm) for low pressure liquid chromatography, supplied by a standard syringe pump by PTFE tubing (i.d. 0.8 mm). The column was heated via immersion in a water bath. Care was taken to ensure homogeneity of the reaction mixture throughout the process.



Scheme 2.3.3.5: Pd(II) salen complex supported on Merrifield resin beads catalysed Suzuki coupling in flow.

The system shown good catalytic activity in Suzuki cross-coupling reactions, carried out with various aryl and heteroaryl bromides with a slight excess of phenylboronic acid were found to be 100 °C with a residence time of 10.5 min using DIPEA as the base in a solvent mixture of DMF/Water (1:1). Unfortunately, the Merrifield resin exhibits significant swelling in the reaction solvent, resulting in complete blockage of the microreactor; moreover, in an attempt to improve the conversion the authors employed the so-called "stopped flow technique" previously demonstrated by Wiles et al.**[297]** in which a 10 min period of flow was alternated with a fixed period in which flow was stopped, before restarting flow for another 10 min. This has the effect of increasing the apparent residence time without lowering the flow rate. Using an initial stopped flow period of 5 min improved the conversion slightly to 76% and increasing the time gave a linear increase in conversion up to 86% for 20 min, with no by-products observed in any of the runs.

Kirschning and co-workers developed monolithic continuous flow reactors (PASSFlow) containing palladium, consisting of a monolithic block based on a highly porous polymer/glass composite material.**[37, 126b, 289f-g]** Those reactors were employed to perform fast Heck reactions, copper-free Sonogashira-type reactions and Suzuki-Miyaura reactions in excellent yield with residence times ranging from 30 min-3 h, but show, however, not unexpectedly, the authors ascertained a significant loss of Pd from the reactors.

The same authors further expanded the use of monoliths by incorporating them inside Raschig rings.**[298]** The Raschig ring reactor has the advantage over a rod-type reactor as it can be easily unscrewed and the spent rings removed and replaced with newly functionalised rings.**[130d]** The **Figure 2.3.3.2** illustrates the separate components of the Raschig ring reactor.

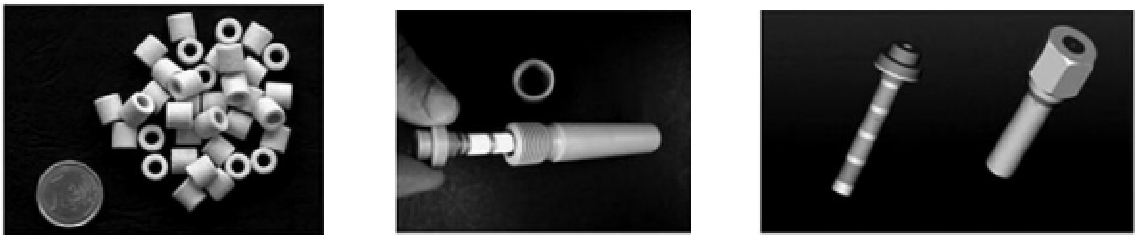


Figure 2.3.3.2: Raschig rings aligned on a perforated tube, within a PEEK polymer casing.

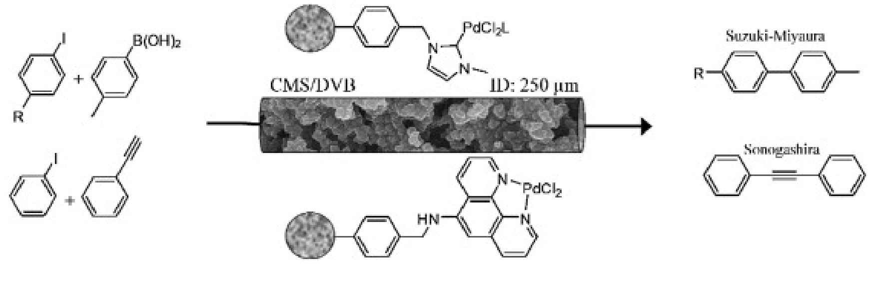
These reactors are adaptable being utilised for small scale reactions (only one ring) as well as larger scales. The rings can be prepared in large quantities, making them more economically viable than rod shaped reactors.**[299]**

This system was then utilised in both the Suzuki and Heck cross coupling reactions. It was found that the catalyst showed excellent stability without loss of activity even after the tenth run. For each run the palladium leaching was determined to be in the region of 0.7 ppm.

In 2011, Haswell has been demonstrated that the combination of Pd-functionalized silica monolithic reactors with microwave heating results in a high percentage yield of the desired reaction products for Suzuki–Miyaura reactions under flow conditions.**[105]**

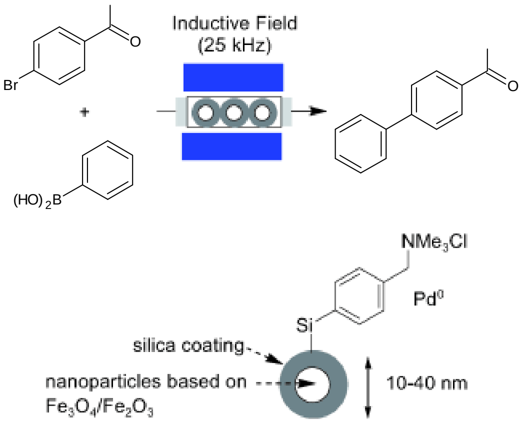
In this work the authors report a scaled-up by increasing the diameter of the catalytic monolith used. However, as microwave penetration is necessary to obtain reliable heating characteristics, there will come a point at which the monolith diameter will become larger than the penetration depth of the microwaves (estimated to be 4 cm), which will lead to an unheated, cold “core”. Moreover, this approach is related to the pressure drop required to produce the required flow rate, which will increase proportionally with the length. Hence, the mechanical strength of the monolith structure, i.e., the strength to resist collapse of the pores and/or the monolith casing material, ultimately limits the maximum length achievable.

Guijt et al. have also utilised phenanthroline functionalised poly(glycidyl methacrylate-co-ethylene dimethacrylate) (GMA-co-EDMA) as a solid macroporous monolith to support palladium, which was used as a catalyst for Suzuki reactions in microfluidic device (**Scheme 2.3.3.6**).**[289a]**



Scheme 2.3.3.6: Palladium phenanthroline functionalised monolithic reactor in Suzuki coupling.

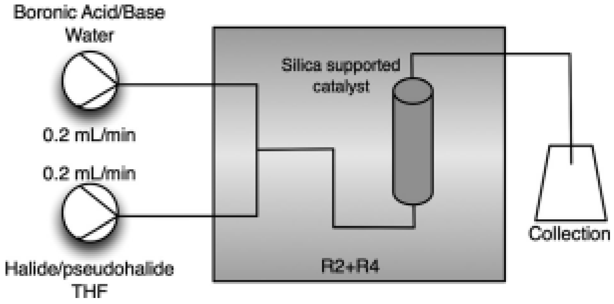
Kirschning et al. in 2008 prepared Pd functionalised, silica coated Fe3O4/Fe2O3 nanoparticles (10-40 nm), which were used for Suzuki and Heck couplings under flow conditions (**Scheme 2.3.3.7**).**[300]** An added advantage of these particles is their superparamagnetic behaviour, which allows them to be heated via magnetic induction when subjected to an electromagnetic field. This was exploited as a way of heating the flow reactor remotely and allowing heat to be generated directly at the reaction site inside the reactor. The silica coating on the surface of the magnetic nanoparticles prevents oxidation of the highly reactive metallic surface in air and also allows for easy functionalisation and transition metal loading.



Scheme 2.3.3.7: Palladium supported on magnetic nanoparticles inside microreactors in Suzuki coupling

The catalyst (2.8 mol% loading) was utilised in both the Suzuki and Heck coupling reactions. The Suzuki coupling of p-bromoacetophenone and phenyl boronic acid, in the presence of CsF in DMF:H_2O afforded a 77% isolated yield of the desired product with a residence time of 1 h at 100 °C. The ICP-MS analysis revealed only low levels of palladium leaching was occurring (34 ppm) and the catalyst could be reused for more than three runs with no loss of activity.

Most recently, but after the starting of this PhD work, Muñoz and co-works at the end of 2012 reported our investigation in the reaction of bromobenzene and (4-methoxyphenyl)boronic acid using SiliaCat®DPP-Pd as the supported catalyst in continuous flow.**[153]** A solution of the aryl halide in THF was combined with a solution of the boronic acid and the base in water using the Vapourtec R2+R4 system.**[301]** The biphasic solvent system was used to ensure complete dissolution of any solid, thus avoiding any subsequent clogging. The mixture was then passed through a 6.6 mm (i.d.) Omnifit column containing 1 g of supported catalyst (**Scheme 2.3.3.8**).



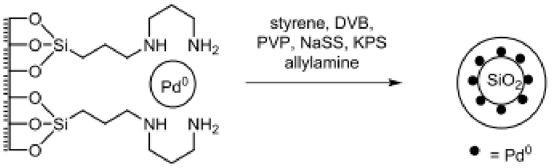
Scheme 2.3.3.8: General experimental set-up of the flow system

The system gave good to excellent yields for both electron rich and electron poor aryl bromides. The same cartridge could be employed for more than 30 consecutive reactions without a decrease in activity with calculated TON was higher than 100, but with a Pd/halide ratio of 0.4 mol %. The use of this flow procedure allowed up to 1.71 mmol/h of product to be produced without a decrease in the activity of the catalyst. Moreover, this system could be used later for other reactions. Leaching of palladium was determined for the coupling reaction both in the organic and aqueous layers. In the organic phase less than 10 ppb of Pd were determined. In the aqueous phase only 20 ppb were detected.

In the same period Pagliaro and co-works report the Suzuki–Miyaura coupling reaction using different aryl halide substrates under flow using SiliaCat DPP-Pd and SiliaCat S-Pd as catalysts.**[158b]** The reaction mixture are divided in two solution, the “solvent 1” (0.020 M solution of aryl halide in 20 vol % methanol/water) and “solvent 2” (0.022/0.030 M solution of phenyl boronic acid/potassium carbonate in 20 vol % methanol/water) and the two solutions was combined using modular flow reaction microreactor (ASIA)**[302]**

The substrates were rapidly converted into coupled products in good to excellent yields for iodo and bromoarenes, while showing the known low reactivity of chloroarene substrates with flow-rate range 50-500 µL/min.

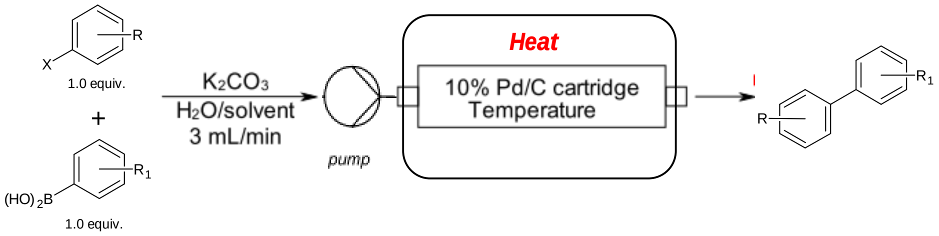
Frost and co-work described in 2014 the preparation and use of a novel silica-supported polymer-encapsulated Pd catalyst for both Suzuki and Heck couplings in flow.**[303]** Pd was supported onto surface functionalized amorphous silica, before being subjected to a polymerisation of styrene, divinylbenzene (DVB) and allyl amine to form spherical particles with a porous copolymer coating (**Scheme 2.3.3.9**).



Scheme 2.3.3.9: Preparation of silica-supported polymer-encapsulated Pd catalyst

The reagent solutions were pumped over an Omnifit column, packed with a mixture of the supported Pd catalyst and sand (100 x 6 mm, ca. 200 mg catalyst, 1.5 g sand). Suzuki couplings of aryl iodides and phenylboronic acid in the presence of DIPEA, were conducted at 120 °C with residence times of 20-50 min. This gave good to excellent conversions for both electron rich and electron poor aryl iodides.

Same in 2014, Mateos et collaborators report a green and scalable procedure for extremely fast ligandless Suzuki–Miyaura cross-coupling reactions in aqueous 2-propanol using Pd/C in continuous flow.**[304]** The authors using a ThalesNano H-Cube MIDI®, to work at high pressures and temperatures. The reactants were injected using integrated HPLC-type pump, and flowed into a MIDI Cart catalyst packed bed reactor at the desired temperature, controlled accurately by the system (**Scheme 2.3.3.10**).**[305]**

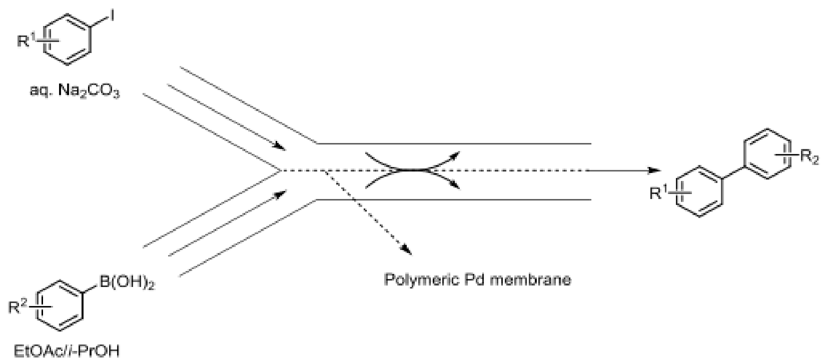


Scheme 2.3.3.10: General continuous-flow setup for Suzuki cross-coupling using Pd/C cartridge.

All experiments are performed at 150°C with a flow-rate of 3 mL/min on a halide scale of 0.5 g. Under these conditions the authors obtained a good yields with vary aryl iodides and bromides using Pd/C as cartridge. Unfortunately, this system showed a not indifferent palladium releasing, with a residual palladium content in the desired product of range 30-50 ppm.

In 2015, same using Pd/C cartridge (0.3 mL internal volume), Sajiki and co-works report the Suzuki-Miyaura coupling in flow with more aryl iodides using Na_2CO_3 as base in EtOH/H_2O as solvent; obtaining good yields in a single pass at flow-rate of 1.0 mL/min.**[306]** The tests were performed on a scale of 1.0 mmol of aryl halides using the reactor packing with 100 mg of the catalyst at 10 % $^{W}/_{W}$ (corresponding to use 0.09 mmol of Pd). This system showed a very low palladium releasing, with a residual palladium content in the organic and aqueous phase of < 1.0 ppm.

Finally, it is interesting to mention even a system to in contrast to the packed bed and monolithic approach, Uozumi et co-works prepared a polymeric Pd membrane inside a microreactor channel and showcased its use in catalysing Suzuki couplings.**[307]** Using a microreactor with a Y-shaped dual inlet, they flowed opposing solutions of the polymer (poly(N-isopropylacrylamide)$_5$-co-(4-diphenylstyrylphosphine)) in EtOAc and the Pd source ($PdCl_4(NH_4)_2$) in water, into the microchannel at 25 °C with a flow rate of 25 mL/min. This formed a two-phase laminar flow, at the interface of which the Pd polymer membrane was precipitated. Suzuki couplings were conducted in a biphasic fashion with solutions of aryl iodide in ethyl acetate/isopropyl alcohol (2:5) and arylboronic acid in aqueous Na_2CO_3 introduced into the two channels, once again with laminar flow, separated by the catalytic membrane at which the reaction took place (**Figure 2.3.3.3**).



Scheme 2.3.3.3: Y-junction microchannel reactor with polymeric Pd membrane in Suzuki coupling

This afforded good to excellent yields for the synthesis of biaryls. Quantitative conversion was achieved for a variety of aryl iodides and boronic acids with short residence times of 4-5 s at 50 °C. ICP-AES analysis showed minimal Pd leaching from the membrane into the reagent streams.

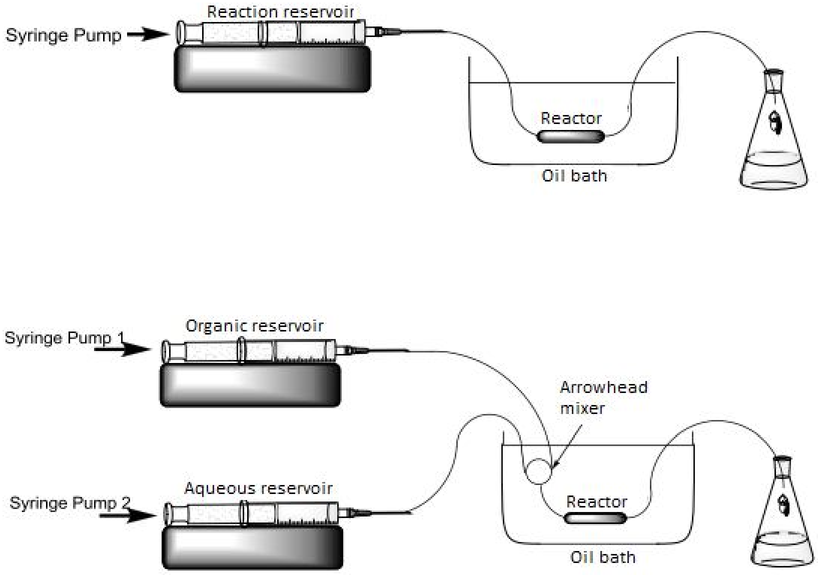
2.3.4 Study and application of packed-bed reactors in Suzuki-Miyaura reactions under continuou-flow

As outline in paragraph 1.4, our studies focused also on applicability of supported catalysts under most efficient and feasible reaction condition in continuous-flow process. In fact, for regards the C-C and C-Heteroatoms cross-coupling reactions, and in particular for Suzuki-Miyaura coupling; it is possible to affirm on the basis of literature data, that the application of the supported catalysis, in continuous-flow reactors is limited, and to present problems and difficulties not yet actually overcome such as: difficult availability, need for high catalytic loads, inadequate performance, inadequate productivity and elevated leaching; that more them not really useful from applicative and industrial point of view (see above paragraph 2.3.3.1).

Given the good results obtained in batch mode (paragraph 2.3.2), we have been started the planned study and development of original packed-bed mini-reactors of design and construction extremely simple and cheap (see paragraph 2.2).

As the light of the results obtained in paragraph 2.3.2 and taking account the necessity of the reaction conditions most homogeneous possible for optimal application in flow.

For regard the application of the mini-reactors in Suzuki coupling, we test the model reaction between 2-bromoanisole (**8a**) with phenylboronic acid (**9a**) (**Scheme 2.3.2.1**, paragraph 2.3.2) applied the more efficient, previously described in paragraph 2.3.2, reaction condition in batch mode like 1,2 equivalents of boronic acid, 1,5 equivalents of K_3PO_4 as base, 1,33 mL/mmol of DMF/H_2O 4:1 as solvent, at 110 °C; using, in the tests, reactors packed with the four commercial catalysts pure or mixed at sand or glass beads in different volume ratio (as subsequently better describe case to case) connected directly to one reservoir or using a new system formed to two reservoirs (one for organic phase and one for aqueous phase) connected to reactor by an opportune arrowhead shaped junctions mixer, commercially available (as subsequently better describe case to case) (**Scheme 2.3.4.1**).



Scheme 2.3.4.1 : Generel experimental set-up of the flow systems used in our tests

Initially, we examined one reactor packing with 50 mg of the pure commercial catalyst Pd(PPh_3)$_4$-PS (**4**, length of 3.5 cm). The reaction mixture prepared directly at air was eluted in the reactor with a residence time equal at the reaction time in bath mode (0.5 h) corresponding at 0.22 mL/h of flow-rate.

Unfortunately, in this test we observed several problems of fluidic mixing already in the reaction reservoir and during the elution. In fact, our batch-mode optimized conditions (K_3PO_4 in DMF/H_2O) result lightly inhomogeneous, at cold, but in the reservoir of the reaction mixture at pressure superior at 1 atm the effect is amplified.

To resolve this problem we could opted to: ***a)*** heating the reaction reservoir (over 80°C the reaction mixture is completely homogeneous) ***b)*** diluting the reaction mixture over 1.33 mL/mmol) and ***c)*** developing a new system formed to two reservoirs (one for organic phase and one for aqueous phase) connected to reactor by an opportune mixer.

Heat the reaction reservoir required the use of the opportune heating systems and reservoir materials that permitted a simple heating via induction, but this is again our principle to develop simple and versatile packed-bed continuous-flow systems.

The dilution of the reaction mixture was simple and possible, in fact the reaction mixture was completely homogeneous over 6.60 mL/mmol, but unfortunately at this dilution none of the supported catalysts (object of this PhD work) were able to promote the Suzuki-Miyaura reaction.

The develop of a new system formed to two reservoirs (one for organic phase and one for aqueous phase) connected to reactor by an opportune mixer, commercially available or laboratory prepared, appeared the most efficient method to solve the problem.

The organic phase reservoir consisting of aryl halide and boronic acid in DMF, while the aqueous phase reservoir consisting of potassium phosphate in water. For regard the connector between the two reservoirs and the reactor, taking into account the literature dates (see paragraph 1.2.2), the best mixing occurs in the T and arrowhead intersections, where the fluid paths are forced to go around a sharp bend. The worst mixing occurs in the single-right angle intersection, where one of the inlet fluids does not travel around any bend or obstacle at the intersection. We were opted to arrowhead mixer, that other act of junction it promote the fluid dynamic mixing, commercially available (Cheminert mixing tee in PEEK, **Figure 2.3.4.1**)**[308]** and laboratory prepared in PTFE. Both the mixer that the reactor are heated to the reaction temperature to improve the mixing.

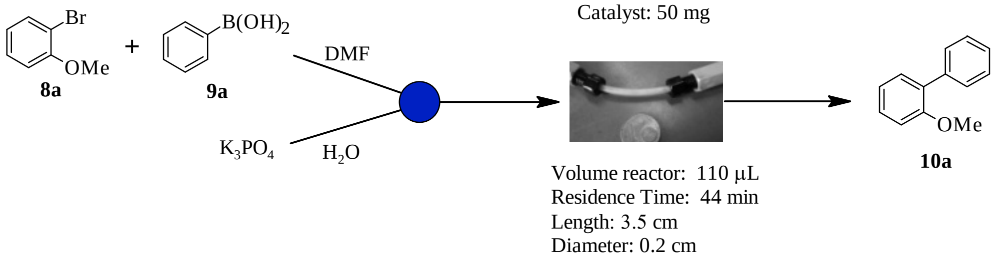
Figure 2.3.4.1: Arrowhead shaped Cheminert mixing tee in PEEK

In the explorative test (with reactor packing with 50 mg of Pd$(PPh_3)_4$-PS (**4**)) the two reaction mixture (organic and aqueous) were eluted in the arrowhead mixer at different flow-rate, corresponding to ratio of the single solvent component of the reaction mixture generally used in batch DMF/H_2O (4:1). In detail the organic mixture are eluted at 0.12 mL/h and the aqueous mixture are eluted at 0.03 mL/h with total flow-rate in the reactor to 0.15 mL/h corresponding at residence time of 46 min.

Unfortunately, in this test we observed a new problem correlated at counter-pressure and at different flow-rate of the single syringe pumps in entry to the reactor. The organic solution (eluted at major flow-rate) block the elution of the aqueous solution (eluted at ¼ flow-rate), and a portion of the organic solution entered itself in the aqueous reservoir; with consequent low conversion (≈ 20 %).

To solve this new problem we decided to apply at the two mixture (organic and aqueous) the same flow-rate, corresponding to half of the output stream from the reactor. To do this we modified the ratio between DMF and H_2O, passing from 4:1 at 1:1, maintaining unchanged the global concentration of the reagents (1.33 mL/mmol of the global solvent mixture) (**Table 2.3.4.1**). In fact, the only variation of the solvent mixture component ratio does not involve obvious variations of efficiency in batch mode.

Table 2.3.4.1: Variation of solvent mixture component ratio[a]



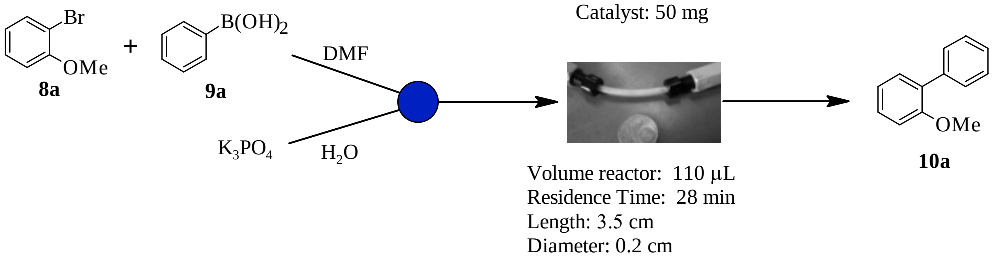
Fraction	Conc. Org. Phase (mmol/mL)	Flow-rate Org. Phase (mL/h)	Conc. Aq. Phase (mmol/mL)	Flow-rate. Aq. Phase (mL/h)	Flow-rate Total (mL/h)	Volume Total (mL)	Conversion in **10a**[b] (%)
1	0.934	0.12	5.56	0.03	0.15	1.0	20
2	0.934	0.24	5.56	0.06	0.30	1.0	20
3	1.49	0.12	2.22	0.12	0.24	0.8	86
4	1.49	0.12	2.22	0.12	0.24	0.6	20

a) Reaction condition: Org. Phase 1.0 equivalent of **8a**, 1.25 equivalent of **9a**, DMF; Aq. Phase 1.50 equivalent of K_3PO_4, H_2O; Reactor 50 mg of Catalyst; b) Evaluated by GC.

Effectively, using these modification in the model reaction with the reactor packing with 50 mg of the pure $Pd(PPh_3)_4$-PS (**4**) (length of 3.5 cm); in the firstly 0.8 mL (corresponding at 0.45 mmol of **8a**) eluted outlet of the system we have obtained a conversion of 86 % with a global flow-rate of 0.24 mL/h corresponding at 29 min of the residence time in the reactor. Unfortunately, after other 0.6 mL (0.34 mmol) the conversion drops drastically at 20 % and the reactor becomes blocked.

At the light of these results, we decided to varied also the concentration of the organic and aqueous mixture, passing form a global 1.33 mL/mmol at 2.14 mL/mmol reported at **8a** (**Table 2.3.4.2**).

Table 2.3.4.2: Variation of the concentration of the organic and aqueous mixture[a]



Fraction	Volume (mL)	**8a** eluted (mmol)	Washing	Conversion in 10a[b] (%)
1	0.8	0.374	-	98
2	0.6	0.28	-	98

3	0.6	0.28	-	95
4	0.4	0.186	Yes	68
5	0.8	0.374	-	86
6	1.6	0.746	-	68
7	1.1	0.513	Yes	56
8	0.8	0.374	-	96
9	0.7	0.326	-	86
10	0.5	0.234	Yes	50

a) Reaction condition: Org. Phase 1.0 equivalent of **8a**, 1.25 equivalent of **9a**, DMF; Aq. Phase 1.50 equivalent of K_3PO_4, H_2O; Reactor 50 mg of Catalyst; b) Evaluated by GC.

This variation showed a several effect, obtaining complete conversion for consecutive 1.4 mL (corresponding at 0.66 mmol) and subsequently light drops of the conversion. Unfortunately, during the drops of the conversion, the reactor becomes blocked, but washing with solvent mixture alone appears to restore efficiency to the system. In general by a flow/wash process we obtain a medium conversion of 78 % of 4.4 mmol of **8a** using 50 mg of catalyst, corresponding at Pd load of 0.8 mol%.

Individuated the optimum parameters of volume ratio, concentrations and flow-rates between organic and aqueous mixture we examined the effect of different packing typology on all commercial catalysts. For this we tested reactors packing with commercial catalysts pure and mixed with glass beads in 1:1 or 1:10 volume ratio.

We select the glass beads to dilute the catalysts because these are inert not functionalized materials with similar size (150-200 μm) of the commercial catalysts object of this work.

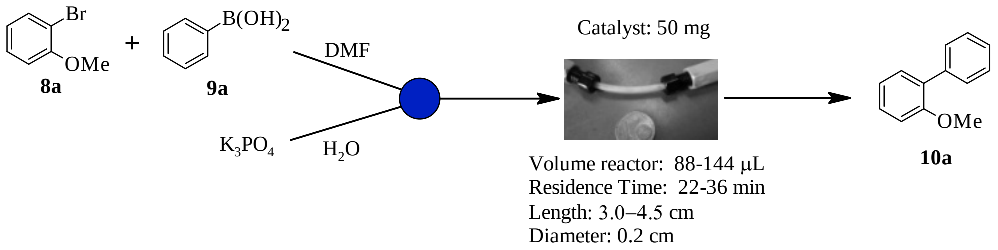
Initially we tested the other Pd catalysts (Fibrecat 1007 (**2**), PdEnCat-40 (**1**) and $PdCl_2(PPh_3)_2$-PS (**3**)) pure, under previously optimized conditions.

The reactors were prepared introducing the catalyst into the reactors as slurry or dry. Then the catalyst is compressed (2-4 bar) and conditioned with about 5 mL of the DMF/H_2O (1:1); their length varies from case to case, but usually is between 3.0 and 4.5 cm.

The organic phase, aryl halide and boronic acid in DMF (1.07 mL/mmol of **8a**); and the aqueous phase, potassium phosphate in H_2O (0.71 mL/mmol of K_3PO_4), were eluted in the system at the same flow-rate of 0.12 mL/h (half of the output stream from the reactor, 0.24 mL/h) with a general residence time usually range to 22-36 min.

Under these conditions the catalysts showed highly conversion (> 98 %) except the PdEnCat-40 that showed an initial conversion of 40 % (**Table 2.3.4.3**).

Table 2.3.4.3: Suzuki-Miyaura coupling using reactors packing with pure catalysts[a]



Fraction	Catalyst (mmol of Pd)	Volume (mL)	**8a** eluted (mmol)	Washing	Conversion in **10a**[b] (%)
1	Fibrecat (0.036)	4.0	1.868		99
2		5.6	2.615	Yes	98
3		3.5	1.635		98
4		6.1	2.849	Yes	96
5		1.1	0.514		93
6		0.9	0.420		79
TOT.		**21.2**	**9.900**		**97**
1	$PdCl_2(PPh_3)_2$-PS (0.051)	2.0	0.934	-	99
2		2.8	1.301	Yes	98
3		1.0	0.467		99
4		3.8	1.775	Yes	98
5		1.8	0.841		98
6		5.6	2.615	Yes	95
7		1.8	0.841		85
8		5.6	2.615		50
TOT		**24.4**	**11.395**		**86**
1	Pd EnCat-40 (0.055)	2.0	0.934		40
2		1.0	0.467	Yes	10
3		1.0	0.167		0
TOT		**4.0**	**1.568**		**22.5**

a) Reaction condition: Org. Phase 1.0 equivalent of **8a**, 1.25 equivalent of **9a**, DMF; Aq. Phase 1.50 equivalent of K_3PO_4, H_2O; Reactor 50 mg of Catalyst; b) Evaluated by GC.

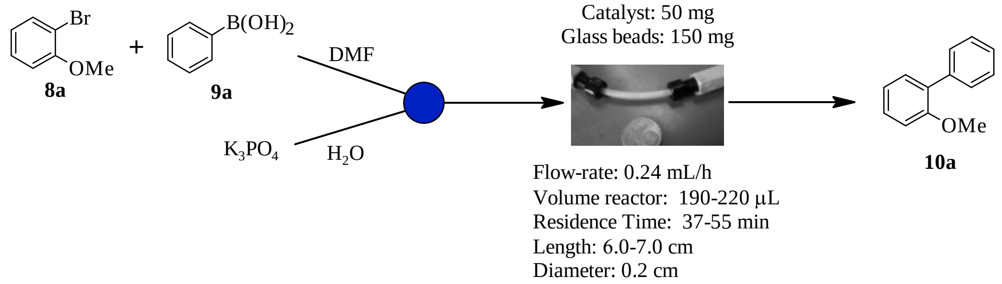
Unfortunately, the use of these reactors (packing with pure catalysts) does not permit to evaluated the efficiency of these systems, because in the major of the systems were showed pressure increasing with consequent blocking of the reactors; despite we washed the reactors with DMF/H_2O (1:1).

To research the better performances in Suzuki-Miyaura coupling with these catalysts, we prepared the reactors introducing as dry the commercial catalysts (50 mg) mixed with an approximately 1:1 volume ratio of the above mentioned glass beads (150 mg). The obtained reactors had lengths varies from case to case, but usually is between 6.0 and 7.0 cm corresponding at internal volume of 190-220 μL.

These reactors were examined in the same model reaction maintaining unchanged the parameters (concentration, flow-rate, etc.) of the above mentioned tests that use the pure catalysts.

Under these conditions the catalysts showed highly medium conversions (> 70 %), except the PdEnCat-40 that showed an initial conversion of 50 %, within 55 minutes of the residence times and keep them for long time (too 100 hours), with a good efficiency**[309]** (**Table 2.3.4.4**).

Table 2.3.4.4: Suzuki coupling using reactors packing with catalysts mixed glass beads in 1:1 volume ratio^{a}



Fraction	Catalyst (mmol of Pd)	Vol. Fractions (mL)	**8a** eluted (mmol)	Conversion of **8a**^{b} (%)	Pd release^{c} (%)
1	$Pd(PPh_3)_4$-PS (0.035)	1.10	0.51	92	
2		1.80	0.84	90	
3		1.10	0.51	88	
4		0.70	0.33	70	
5		0.40	0.19	60	
6		0.70	0.33	50	
		1.10	0.51	45	
Total		**6.90**	**3.22**	**75.0**	**-**
1	Pd EnCat-40 (0.055)	1.28	0.60	50	
2		1.28	0.60	0	
Total		**2.56**	**0.40**	**25.0**	**-**
1	Fibrecat 1007 (0.036)	4.00	1.87	99.0	
2		5.60	2.62	98.0	
3		3.50	1.64	98.0	
4		6.10	2.85	96.0	
5		1.10	0.51	93.0	
6		0.90	0.42	79.0	
Total		**21.20**	**9.91**	**96.6**	**0.40**
1	$PdCl_2(PPh_3)_2$-PS (0.051)	2.00	0.93	99.0	
2		2.80	1.30	98.0	
3		1.00	0.47	99.0	
4		3.80	1.78	98.0	
5		1.80	0.84	98.0	
6		5.60	2.62	95.0	
7		1.80	0.84	85.0	
8		5.60	2.62	50.0	
Total		**21.20**	**11.40**	**85.4**	**0.26**

a) Reaction condition: Org. Phase 1.0 equivalent of **8a**, 1.25 equivalent of **9a**, DMF; Aq. Phase 1.50 equivalent of K_3PO_4, H_2O; Reactor 50 mg of Catalyst; b) Evaluated by GC; c) Evaluated by ICP-OES

In detail, the results obtained are very interesting. The reactor packing with Pd(PPh3)4-PS mixed at glass beads showed a similar result obtained using the reactor with pure catalyst (75 % of medium conversion) eluted 3.22 mmol of **1a** with global efficiency of 92 (corresponding at

1.0 mol% of Pd load in batch), but in this case the intermediate wash were not necessary, and the pressure increasing with consequent blocking of the reactors phenomena were many limited.

The PdEnCat-40 result the only system none able to promote the coupling in flow under these conditions, in fact this system showed a low initial conversion (50 % in the first 0.6 mmol of eluted **8a**). Conversion that drops drastically at zero after other 0.6 mmol of **8a** eluted. However, the phenomena of blocking the reactor were not observed.

The better performances in this reaction were achieved by packing the reactors with the Fibrecat-1007 and $PdCl_2(PPh_3)_2$-PS mixed with glass beads, that showed a high conversions within 50 minutes and keep them for long time (100 hours), with a efficiency of 300, respect at 660 of the batch mode. However, these result were inferior respect at the data obtained with the same catalysts in batch mode.

Most interesting result the Pd release of the reactors (analysed directly the contents of the palladium in the solution out from the reactors without microfiltration); in fact, despite the activity of the catalysts drops after many eluted **8a** (varied from case to case), the data of Pd released were very low (< 0.40 % of the Pd packing into the reactors).

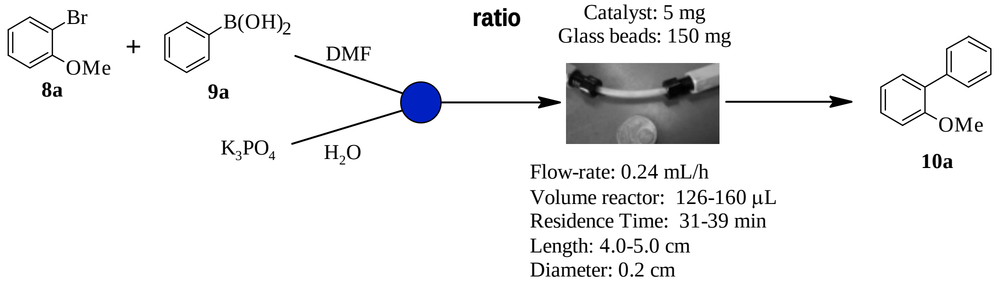
These results were deduce that the loss of activity were must at passivation of the palladium or structural modification of the supported catalysts.

At the light of these positive results, to better the performances in the Suzuki-Miyaura coupling with these catalysts, we decided to prepare the reactors most diluted introducing as dry the commercial catalysts (5.0 mg) mixed with an approximately 1:10 volume ratio of the above mentioned glass beads (150 mg). The obtained reactors had lengths varies from case to case, but usually is between 4.0 and 5.0 cm corresponding at internal volume of 126-160 μL.

These reactors were examined in the same model reaction maintaining unchanged the parameters (concentration, flow-rate, etc.) of the above mentioned tests that use the pure and 1:1 mixed catalysts.

Under these conditions the systems showed similar medium conversions (> 70 %) respect at the data obtained with reactors 1:1 mixed, within 30-40 minutes of the residence times and keep them for long time (18-23 hours), showed, for the best catalytic systems, a batch similarly efficiency and a limited leaching of Pd (**Table 2.3.4.5**).

Table 2.3.4.5: Suzuki-Miyaura coupling using reactors packing with catalysts mixed glass beads in 1:10 volume ratio



Fraction	Catalyst (mmol of Pd)	Vol. Fractions (mL)	**8a** eluted (mmol)	Conversion of **8a** (%)	Pd release (%)
1		0.21	0.10	99	
2		0.21	0.10	99	
3	Pd(PPh$_3$)$_4$-PS (0.0039)	0.21	0.10	90	
4		0.21	0.10	75	
5		0.42	0.20	54	
6		0.42	0.20	35	
Total		**1.68**	**0.80**	**68.0**	**0.40**
1		0.21	0.10	60	
2	Pd EnCat-40 (0.0055)	0.21	0.10	50	
3		0.21	0.10	30	
4		0.21	0.10	10	
Total		**0.84**	**0.40**	**23.3**	**-**
1		0.21	0.10	99.9	
2		0.25	0.12	99.9	
3		0.21	0.10	99.0	
4		0.21	0.10	98.0	
5		0.42	0.20	90.0	
6	Fibrecat 1007 (0.0051)	0.42	0.20	86.0	
7		0.42	0.20	82.0	
8		0.46	0.22	75.0	
9		0.42	0.20	70.0	
10		0.42	0.20	70.0	
11		0.46	0.22	54.0	
12		0.42	0.20	43.0	
Total		**4.32**	**2.06**	**76.7**	**0.30**
1		0.31	0.15	92.0	
2		0.25	0.12	85.0	
3		0.46	0.22	82.0	
4		0.46	0.22	82.0	
5		0.52	0.25	82.0	
6		0.46	0.22	80.0	
7	PdCl$_2$(PPh$_3$)$_2$-PS (0.0055)	0.52	0.25	79.0	
8		0.48	0.23	79.0	
9		0.48	0.23	78.0	
10		0.46	0.22	77.0	
11		0.46	0.22	68.0	
12		0.52	0.25	58.0	
13		0.42	0.20	50.0	
14		0.42	0.20	35.0	
Total		**6.22**	**2.98**	**73.0**	**0.30**

a) Reaction condition: Org. Phase 1.0 equivalent of **8a**, 1.25 equivalent of **9a**, DMF; Aq. Phase 1.50 equivalent of K_3PO_4, H_2O; Reactor 5 mg of Catalyst; b) Evaluated by GC; c) Evaluated by ICP-OES

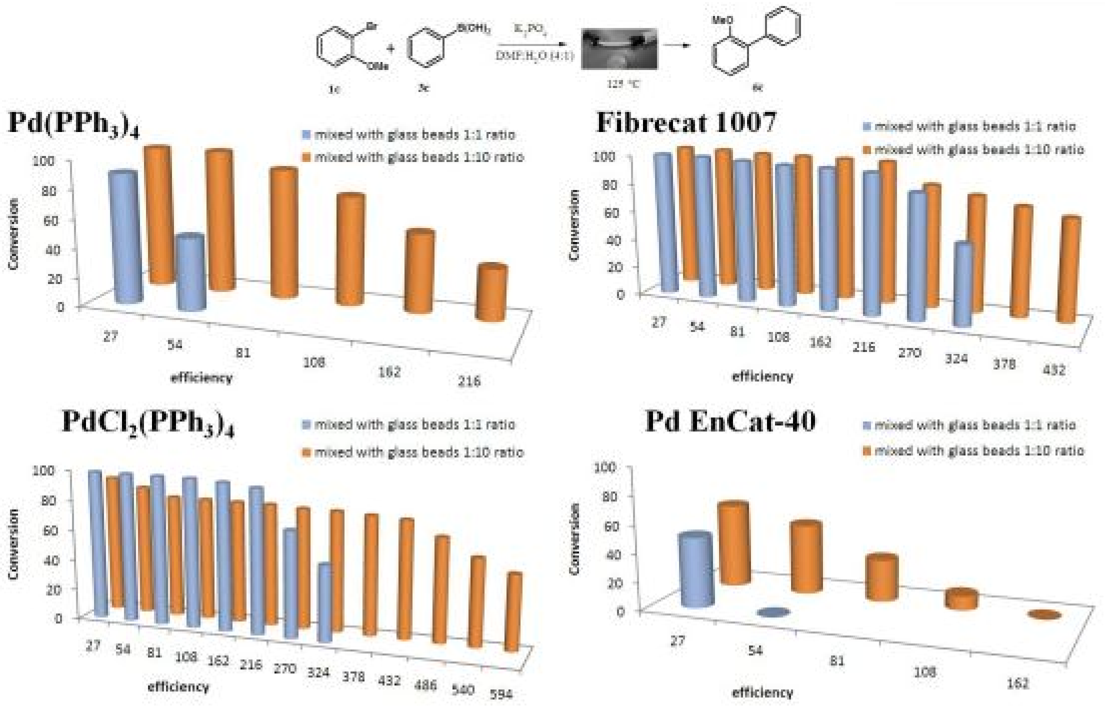
The results obtained are very interesting. In fact, the reactors packing with commercial catalysts mixed at glass beads in 1:10 ratio showed bigger efficiency respect at 1:1 ratio (**Scheme 2.3.4.2**). In detail, Pd(PPh$_3$)$_4$-PS (**4**) mixed at glass beads showed a similar result obtained using the reactor with 1:1 mixed ratio (68 % of medium conversion) eluted 0.80 mmol of **8a** with global efficiency of 205 (corresponding at 0.50 mol% of Pd load in batch) with low Pd release (0.40 %).

The PdEnCat-40 (**1**) result once more the only system none perfectly able to promote the coupling in flow under these conditions, however in this test showed its better initial conversion (60 % in the first 0.1 mmol of eluted **8a;** corresponding at 0.5 mmol using 50 mg of catalyst). Conversion that drops drastically at 10% after other 0.3 mmol of **8a** eluted.

The better performances in this reaction were achieved once more by packing the reactors with the Fibrecat-1007 (**2**) and PdCl$_2$(PPh$_3$)$_2$-PS (**3**) mixed with glass beads in 1:10 ratio; that showed a low Pd release (0.25-0.30 %).

The Fibrecat 1007 (**2**) showed high conversions within 35 minutes and keep them for 18 h (conversion medium of 76 %), with an efficiency of 500, corresponding to use 0.20 mol% of the Pd load in batch mode.

While the PdCl$_2$(PPh$_3$)$_2$-PS (**3**) showed conversions within 40 minutes and keep them for 28 h (conversion medium of 73 %), with an efficiency of 600 respect at 660 in batch mode, corresponding to use 0.16 mol% of the Pd load in batch mode.



Scheme 2.3.4.2: Efficiency comparison between reactors packing with catalysts mixed with glass beads in 1:1 and 1:10 ratio

Given these results we decide to examine under this conditions and flow system also the Pd/MCM-41. In this case the catalyst (30 mg) was introduced in the reactor as pure, because the Pd load of the catalyst is very low (1 % $^{W}/_{W}$), and 30 mg of this catalyst correspond at 0.0028 mmol of palladium.

The obtained reactors had lengths of 3.5 cm corresponding at internal volume of 110 μL. These reactors were examined in the same model reaction maintaining unchanged the parameters (concentration, flow-rate, etc.) of the above mentioned tests with commercial catalysts.

Unfortunately, under these conditions the system result none able to promote the reaction, showing only trace of the desiderate product also lowering the flow rate to 0.10 mL/h.

Finally, given the optimum results in the model reaction with an aryl halide; we decide to examine the possible application of the our packed-bed reactors in the reaction with alkenyl halides.

For this test we examined the reaction of α-bromostyrene (**12b**) and (E)-β-bromostyrene (**12a**) with phenyl boronic acid (**9a**).

As the light of the results obtained in paragraphs 2.3.2.3, initially we applied the more efficient, previously described reaction condition in batch mode like 1,2 equivalents of boronic acid, 1,5 equivalents of K_3PO_4 as base, 3.00 mL/mmol of EtOH/H_2O 1:1 as solvent, at 100 °C; using, in the tests, the reactor packed with the Fibrecat 1007 (**2**) mixed with glass beads in 1:10 volume ratio, using the new system formed to two reservoirs (one for organic phase and one for aqueous phase) connected to reactor by an opportune arrowhead shaped junctions mixer, commercially available.

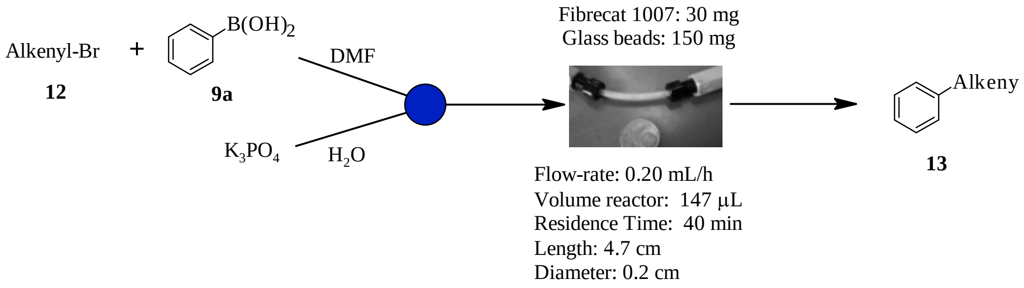
Unfortunately, under this condition (EtOH/H_2O 1:1) the conversion was very low (< 40 %) and the reactor becomes blocked, at cause of the low solubility of the coupling products in this solvent mixture.

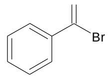
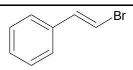
At the light of these results, and tacking account the result obtained in batch mode with alkenyl halides (see paragraph 2.3.2.3) and in flow mode with aryl halides; we decide to apply the coupling in DMF/H_2O 1:1 using yet the system formed to two reservoirs (one for organic phase and one for aqueous phase) connected to reactor (Fibrecat 1007 mixed with glass beads) by an opportune arrowhead shaped junctions mixer.

The organic phase, bromostyrene and boronic acid in DMF (1.07 mL/mmol of **12**); and the aqueous phase, potassium phosphate in H_2O (0.71 mL/mmol of K_3PO_4), were eluted in the system at the flow-rate of 0.10 mL/h (half of the output stream from the reactor, 0.20 mL/h) with a general residence time usually range to 40 min.

Under these conditions the α-bromostyrene showed high conversion (96 %) within 40 minutes and keep them for long time (> 31 hours), while the (E)-β-bromostyrene showed initially a good conversion (88 %), but drops dramatically almost immediately and you still have problems of clogging (**Table 2.3.4.6**).

Table 2.3.4.6: Suzuki-Miyaura coupling under continuou-flow with bromostyrenes[a]



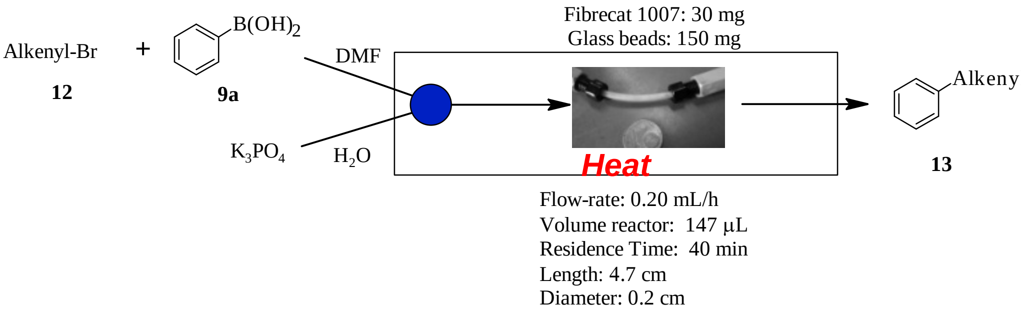
Fraction	Alkenyl halide (**12**)	Vol. Fractions (mL)	**12** eluted (mmol)	Conversion of **12**[b] (%)
1	 **12b**	1.10	0.21	96.0
2		1.00	0.19	96.0
3		1.00	0.19	96.0
4		1.10	0.21	96.0
5		2.00	0.37	96.0
Total		**6.20**	**1.17**	**96.0**
1	 **12a**	0.80	0.30	88.0
2		1.40	0.53	46.0
3		0.40	0.15	32.0
Total		**2.60**	**0.98**	**56.7**

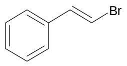
a) Reaction condition: Org. Phase 1.0 equivalent of **12**, 1.25 equivalent of **9a**, DMF; Aq. Phase 1.50 equivalent of K_3PO_4, H_2O; Reactor 5 mg of Catalyst; b) Evaluated by GC

In detail, the results obtained are very interesting. The reactor packing with Fibrecat-1007 mixed at glass beads showed high conversions within 40 minutes and keep them for long time (> 31 hours) with α-bromostyrene, while with (E)-β-bromostyrene the result was slightly better than the test in EtOH/H_2O (1: 1), but the problem of clogging was still present, even if only in the cold collection tube. In fact, in DMF/H_2O the reaction product appear completely soluble at hot.

To solve this problem of solidification at cold in the collection tube, it was decided to minimize the amount/length of cold-tube, keeping it as possible immersed in the oil bath. Opportune measures have enabled us to reduce this area a few millimetres. So we re-applied with (E)-β-bromostyrene the same conditions using these devices (**Table 2.3.4.7**)

Table 2.3.4.7: Suzuki-Miyaura coupling using new flow device for (E)-β-bromostyrene[a]



Fraction	Alkenyl halide	Vol. Fractions (mL)	**12** eluted (mmol)	Conversion of **12**[b] (%)	Yield of **13** (%)
1		0.80	0.15	99.0	
2		1.20	0.23	78.0	
3		1.10	0.22	65.0	
4	**12a**	2.00	0.38	46.0	
5		0.80	0.15	26.0	
Total		**5.90**	**1.13**	**59.0**	**36.2**

a) Reaction condition: Org. Phase 1.0 equivalent of **12a**, 1.25 equivalent of **9a**, DMF; Aq. Phase 1.50 equivalent of K_3PO_4, H_2O; Reactor 5 mg of Catalyst; b) Evaluated by GC

In this case the phenomena of blocking the reactor were not observed, and the catalytic system showed complete conversion in the elution of 0.15 mmol of halide. Subsequently the conversion of single fractions decreases up to 26 %, with a medium conversion of 60 %; with a total yield of 36 %.

2.3.4.1 Conclusions

In conclusion, at the light of these results (resumed in **Table 2.3.4.4-2.3.4.5**) we could affirm that with our packed-bed reactors (at least when filled with Fibrecat 1007 and $PdCl_2(PPh_3)_2$-PS), may allow to achieve the same performance obtained in the batch with the same catalyst (used in similar conditions).

In addition, the performances of the reactors so filled, appear almost comparable to the best obtained in the literature works mentioned in paragraph 2.3.3.1.

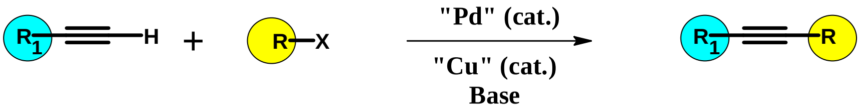
In fact, the great majority of Suzuki-Miyaura reactions carried out with packed bed reactors prepared with supported catalysts require an actual catalytic loading which may range from 1.0 up to even more than 20 mol%; only in a few cases are reported examples where the real ratio between catalyst inside the reactor and halide actually eluted is ≤ 0.002, as obtained with our better reactors; thus demonstrating that this can be done without expensive and complicated systems.

Moreover, with Fibrecat 1007 it was possible to achieve good performances also with alkenyl bromides (α- and β-bromostyrenes), even if in presence of same problems correlated at the product of the process (see **Table 2.3.4.6-2.3.4.7**).

However, the performance achieved with these alkenyl halides are very interesting. In fact, not resulting to today, literature works concerning the use of alkenyl halides in Suzuki-Miyaura reaction in flow mode (see paragraph 2.3.3.1).

2.4 Sonogashira reaction and classical catalyst used

Sonogashira-Hagihara reaction is characterised by a metal catalyzed (principally palladium) cross-coupling of terminal alkynes with vinyl or aryl halides or sulphonates to form conjugated enynes or aryl alkynes motif, in the presence of an amine base (but it is also possible to use oxygen bases**[6i-m]** or fluorides**[6n-p]**) and in co-catalysis of Cu(I) (**Scheme 2.4.1**) even if currently this reaction could are promoted of only Pd or Cu.**[6a-h]**



R = 1-alkenyl, (hetero)aryl

R_1 = 1-alkenyl, (hetero)aryl, alkyl

X = I, Br, Cl, O-SO_2-R

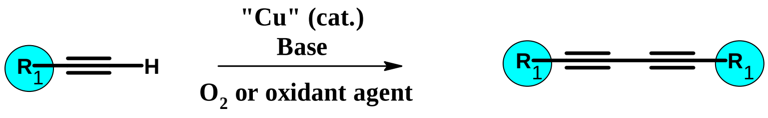
Scheme 2.4.1. Generic scheme of Sonogashira-Hagihara cross-coupling reaction

This cross-coupling reaction is well-known as being one of the most powerful methods for the straightforward construction of sp^2-sp carbon-carbon bonds, in particular for the formation of alkynes since its discovery in 1975.**[6h, 310]**

Amongst its wide applicability; Sonogashira-Hagihara reaction is particularly useful as a way for the assembly of conjugated enynes systems as well as of internal alkynes and related systems, which have a diverse spectrum of synthetic applications, ranging from biologically-active molecules**[311]**, natural products**[312]**, conducting polymers/engineering materials**[313]**, and macrocycles with acetylene links**[314]**.

The popularity of Sonogashira reaction is due to its versatility, efficiency and most important of all, its intrinsic practicality, easily and greeness.**[6a-h]** Such qualities result mainly from the fact that this reaction do not require the use of stoichiometric organometallic compounds.

In the classical procedure (co-catalyzed of Cu(I)) A variety of substrates and functional groups can be used under the reaction conditions, which is ideal to synthesize many intermediates in constructing the complex drug molecules. Besides that, compared to Stephen-Castro coupling**[315]**, that use stechiometric copper acetylides, in this Cu(I) co-catalyzed procedure, the organometallic copper compound is present only in catalytic amount as intermediates the reaction, resulting many practical, simply and green. Unfortunately, the presence of Cu(I) also has drawbacks, apart from including in the reacting mixture another difficult to recover reagent. Thus, can result in the formation of some Cu(I) acetylides in situ that can undergo oxidative homocoupling reactions of alkynes in presence of air or other oxidative agents (the so-called Glaser coupling) (**Scheme 2.4.2**) thereby reducing yields and increasing unwanted side products.**[316]** Buchwald and Gelman have also found that CuI had a deleterious effect on the Sonogashira cross-coupling reaction.**[317]**

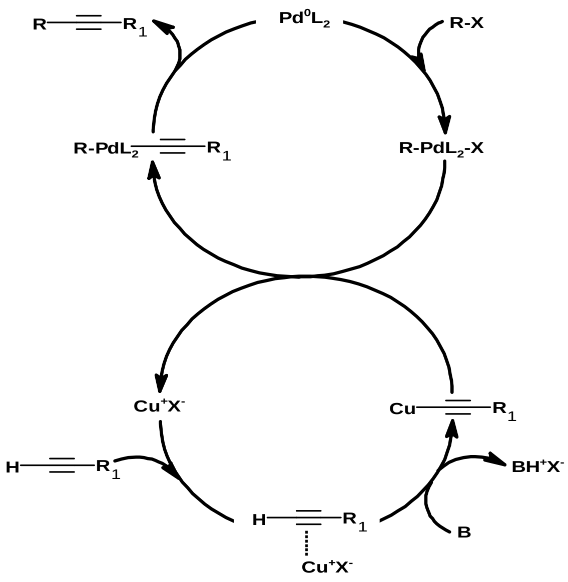


R_1 = 1-alkenyl, (hetero)aryl, alkyl

Scheme 2.4.2: Generic scheme of oxidative homocoupling

To reduce this problem, significant efforts have being dedicated to develop coupling procedures working in the absence of copper salts. These procedures generally aim to increase the reactivity of the catalytic system, thus making the presence of copper unnecessary and the reaction better sustainable and selective **[318]** In fact, in this “Cu-free” procedure is not formed organometallic intermediate (as better described later).

Other important problem to address when dealing with this type of alkynylation procedure is the applicability of the reaction to different substrates. Thus, the general reactivity order of the sp^2 species is vinyl iodide ≥ vinyl triflate > vinyl bromide > vinyl chloride > aryl iodide > aryl triflate ≥ aryl bromide >> aryl chloride; therefore, the Sonogashira process usually runs smoothly when the more expensive and unstable aryl or vinyl iodides are used. Moreover, if the organic halide system is “*activated*”, that is, electron-poor, the situation is even more favorable. Thus, deactivated aryl bromides are difficult starting materials for coupling reactions, whereas the cheapest aryl chlorides, if not strongly activated, represent a real challenge for any cross-coupling methodology.**[256c]**



L = phospene, base, solvent or alkyne

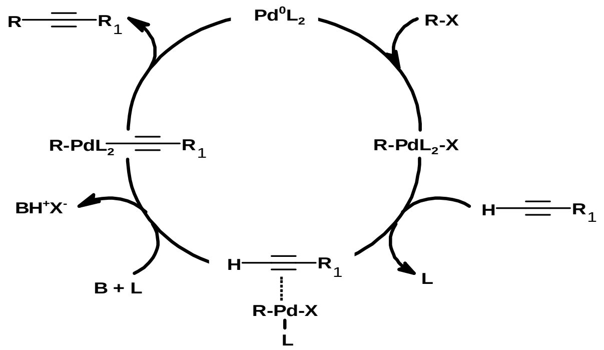
Scheme 2.4.3. General catalytic cycle of Sonogashira Cu co-catalyzed

The complete mechanism for the Sonogashira reaction is not completely understood because of the difficulty of isolating and analyzing the organometallic compounds that are present only as intermediates in the reaction. Moreover the classical procedure (Cu co-catalyzed) and the more modern "*Cu-free*" procedure show vary difference. However, the more acceptable mechanism in the classical procedure involves two independent catalytic cycles, the palladium and the copper cycle (**Scheme 2.4.3**).**[6g, 319]**

The generally accepted catalytic cycle for the palladium catalysis (the Pd-cycle) is based on a usually attachment of palladium (Pd) catalyst to the halides by oxidative addition, which increases the oxidation state of Pd catalyst from 0 to 2. This step is the rate determining step of the reaction; given the characteristics of the halides substrate are crucial, with this step being facilitated if X= I or OTf and if the electronic density is reduced on the C-X bond by the presence of electron-withdrawing groups. The next step in the Pd-cycle would connect with the cycle of the copper co-catalyst (the Cu-cycle). Thus, a usually rate-determining transmetalation from the copper acetylide formed in the Cu-cycle would generate a Pd(II)L_2 species and CuX, which gives the final coupled alkyne after *trans*/*cis* isomerisation and reductive elimination with regeneration of the catalyst.

For regard the Cu-cycle is still poorly understood. In fact, the base (generally an amine) is supposed to abstract the acetylenic proton of the terminal alkyne, thus forming a copper acetylide in the presence of the copper(I) salt. But, it should be pointed out that the generally employed amines are usually not basic enough to deprotonate the alkyne in order to generate the anionic nucleophile that should form the copper acetylide. Therefore, a π-alkyne-Cu complex could be involved in the cycle,**[320]** thus making the alkyne proton more acidic for easier abstraction.

The mechanism of the copper-free Sonogashira reaction is also not well-known. However, the first step would be the oxidative addition of halide to the Pd(0) complex (**Scheme 2.4.4**).



L = phospene, base, solvent or alkyne

Scheme 2.4.4: General catalytic cycle of Sonogashira Cu-free

The second step is under debate. As previously mentioned, the amines generally employed are usually not able to deprotonate the alkyne for the reaction with Pd(II) complex $R^1Pd(L)_2X$; therefore, complexation of the alkyne to the complex is supposed to proceed first with displacement of one ligand to give intermediate complex η^2-alkyne palladium.**[136a]** The ligated alkyne would be more easily deprotonated by the amine (or other base), forming the new complex, which gives the coupling product by reductive elimination.

However, these hypothesized/acceptable mechanisms present vary complication. At example, the terminal alkynes involved in the coupling reactions can also play an important role in the Pd-cycle. Thus, the carbon-carbon triple bond is able to coordinate the palladium(0) active complex prior to the oxidative addition step, therefore producing a decelerating effect by formation of unreactive or low-reacting $(RC\equiv CH)Pd(0)L_2$ complexes.**[321]**

A further mechanistic complication has been found in copper-free Sonogashira reactions. In these processes, the role of the base is crucial, and specific amines (usually added in excess or as solvent) are required, with secondary amines such as piperidine, morpholine, or diisopropylamine proving to be efficient. It has been discovered that these amines can react with trans-$R^1PdX(L)_2$ complexes by substitution of one ligand to generate $R^1PdX(L)$-(amine) complexes in a reversible reaction whose equilibrium constant depends on R^1, X, the basicity and the steric hindrance of the amine.**[322]** Therefore, competition between the amine and the alkyne for the substitution of one ligand group (generally phosphane) in $R^1PdX(L)_2$ complexes may also occur.

2.4.1 State of art of Sonogasira reaction with aryl and alkenyl halides in batch mode

As mentioned in general for all cross-coupling in paragraph 1.1, classic and/or more modern Pd complexes with phosphane ligands,**[317, 326]** palladium nitrogen complexes,**[324]** Pd-NHC complexes**[325]** and palladacycles,**[326]** are intensively employed as homogeneous catalysts in Cu co-catalyzed, but also in more interesting copper-free, Sonogashira reaction of vinyl/aryl iodides and bromides.**[6a, 6g]**

The systems most commonly used are precisely species Pd(0) and/or Pd(II) triphenylphosphane-related complexes (since 1975 in classical procedure and since 1986 in Cu-free Sonogashira).

Despite their success (high catalytic activity and selectivity), such systems may lead to problems related to the difficult availability of the catalyst, to the precarious stability, to the difficult handling and ultimately high cost of the system itself. As already mentioned in the paragraph 1.1, all these difficulties with the inability to recycle the catalyst in a simple way, as well as the frequent contamination of the product of synthesis or the use of catalytic systems efficient but very expensive, have resulted in a continuous increase, as regards the reaction of Sonogashira copper-free, and the study of the use of supported catalytic systems, at low release of palladium and easily recyclable.**[6a, 6g, 9c-d]**

The supported catalyst most studied and used in the reaction of Sonogashira is the Pd/C because its availability, easy handling, and reusability;**[327]** it can further be used in classical and copper and/or ligand-free coupling of various aryl halides different from iodide compounds, such as bromides, and very low reactive chlorides. The first example of Pd/C-catalyzed Sonogashira-Hagihara reaction was reported by Guzman and co-workers in 1990.**[327a]** Subsequently, Pd/C is used with or without additional copper and/or phosphine ligands, and often the application of aqueous solvents or absence of solvent is advantageous.**[328]**

In general, the Pd/C-catalyzed Sonogashira-Hagihara reaction using a palladium load between 3.0 at 5.0 mol % with or without additional phospine ligands and CuI, in the presence of more than stoichiometric quantities of amines (Et_3N, diisopropylamine, pyrrolidine, piperidine) and also inorganic bases (Na_2CO_3, K_2CO_3, NaOH, K_3PO_4); in organic solvents (alcohols, DME, NMP, DMF, DMA) dry or aqueous under inert atmosphere and at temperatures up to 100 °C, obtaining excellent results even with deactivated aryl bromides.**[327b-d]**

Recently new protocols Cu-free and ligand-free have been developed to use low amount of Pd/C (0.125-1.0 mol% of Pd) in environmental-friendly conditions to use aqueous solvents mixtures and absence of the solvent directly at air**[328a-b]** However, these environmentally-friendly conditions are limited at use of opportune form of Pd/C, to present highly palladium dispersion and highly contents of water (> 50 %).**[328a, 327b]**

Many interesting, result the work of Rothenberg and co-work that reported a convenient method for Cu-free Pd/C-catalyzed Sonogashira coupling of aryl chlorides and bromides;**[6o]** method is based on an in situ halogen exchange by a iodide source such as an alkali iodide, termed as HALEX-Sonogashira reaction.

Despite the large amount of examples reported in the literature on the use of Pd/C, the information regarding its effective leaching and the tendency to recycled it is most limited and approximate. While, interesting information regard the effect of addition or not of Cu salts are reported, and appears that the addition of CuI did not result in higher reactivities or selectivities. Larger amounts of copper even decreased activity and selectivity.**[328a]**

In addition to the Pd/C, in Sonogashira-Hagihara reaction have been employed other supported catalysts consisting of palladium supported on metal oxides; **[6g, 9d, 328b]** such as Pd/γ-Fe_2O_3**[103, 269g]** Pd/TiO_2,**[329]** and Pd- supported on nano-crystal oxides (in particular NAP-MgO)**[330]**; as well as systems of Pd on modified silica,**[331]** Pd on zeolites,**[332]** Pd/Cu-containing perovskites**[143]** and LDH (Layered Double Hydroxyde) **[211]** are the only examples in this field reported in the literature. Each of these catalysts, of course, has the characteristics and activities different, but in general, all require a dose range between 1.0 and 7.0 mol%, although there are cases in which they have been used a larger amount; normally they are employed in the presence of CuI using amines ad bases in solvents such as DMF or THF dry or aqueous solutions under mild temperatures (50-80 ° C).**[6g, 9d]** These systems formed by Pd simply deposited and/or adsorbed directly on oxides and/or zeolites, are more reactive than Pd/C but less reactive than homogeneous Pd catalysis in the reaction of Sonogashira, but regarding they're effective leaching and the tendency to recycled it is most limited. In fact, in some cases palladium leaching during catalysis was evidenced. Although no noble metal leaching was observed using vary mixed oxides. While recycling and reuse of the catalyst was possible but with a considerable loss of activity in the firstly reuse.**[27e, 146d, 147a, 269l]**

The layered double hydroxide supported palladium nanoparticles (LDH-Pd(0)) allowed Sonogashira coupling of chloroarenes to be carried out under Cu-free conditions (THF/water,

NEt_3) and provided high activity.**[211]** The catalyst (1 mol %) was used in five cycles and showed consistent activity in the coupling of phenylacetylene and chlorobenzene.

The Pd/Cu-containing perovskite catalyst was recycled five times under copper and ligand free conditions with apparent loss of activity after the three reuse.**[143]** While the systems supported on zeolites and/or functionalized oxides show low leaching; however, the recyclability of the catalyst is possible, but with considerable loss of activity after the first reuse.**[332a-b]**

More recently, were to be published an increased number of articles that used in Sonogashira coupling, palladium catalysts supported onto organic polymers: metal anchored on the polymer matrix, or incapsulated into the matrix.**[46m, 146a,g,l, 149, 177, 333]**

These systems are both commercial systems, such as FibreCat**[171]** and PdEnCat^{TM} (Pd is encapsulated in a tioureic resin)**[146a,g, 149]**, that non-commercial polystyrene systems, with coordinating groups to the metal**[334]** and other polymer systems such as polymethyl methacrylate (PMMA) microspheres, **[335]** Merrifield resin,**[336]** PVC,**[337]** and many others that already have the coordinating groups.

For these species are described good and efficient reactions with both aryl iodides that with aryl bromides, under copper co-catalyzed or not conditions. In a few cases, these systems were are used in reaction with vinyl halides obtaining good yields with highly stereo-specificity (as better mentioned in paragraph 2.4.2.3).

Finally, have been described some, for now limited, examples of nano-particles of palladium prepared in various ways and supported on cellulose,**[338]** polyvinylpyrrolidone (PVP),**[6i]** and other organic polymers**[6l, 339].**

Usually they are very efficient in Sonogashira copper-free reactions even in aqueous environments and are efficiently recyclable with low levels of leaching.

2.4.2 Development of batch conditions for Sonogashira type reactions

As outline in paragraph 1.4, our studies focused on three principal different cross-coupling among which the Sonogashira coupling, and seven different catalysts: three prepared “via” MVS with the collaboration of Dr Claudio Evangelisti (previously see above in paragraph 2.1.4) and four commercially available (previously see above in paragraph 2.1.3).

For regard the Sonogashira coupling reaction, taking into account our research objectives and working plan (previously mentioned in paragraph 1.4) we decided to investigate principally

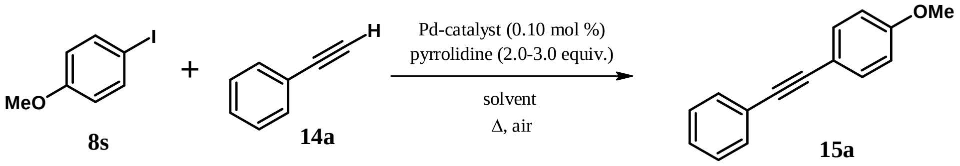
Sonogashira "Cu-free" reactions, because more sustainable and selective of the reaction co-catalyzed; and for this in accordance with our principles.

In this work we tested only six different catalysts: all four commercially available catalysts previously selected in paragraph 2.1.3 and one mono-metal (Pd/MCM-41) and one bi-metal (Pd-Cu/PVPy) MVS-prepared catalysts previously prepared in paragraph 2.1.4.

In fact, previously studies performed in our laboratory showed that the Pd/PVPy catalyst was not suitable to promote efficient Sonogashira-type reactions on substrates other than iodobenzene (substrate model in these studies) even after several attempts to optimize conditions.**[218]** Therefore it was not taken into account in our study.

In our study we determine the most efficient and feasible reaction conditions in which these catalysts are able to promote the Sonogashira CuI-free reaction, taking into account their applicability in flow.

The reaction conditions were optimised by screening of solvents, temperature and reaction atmosphere for the model reaction of 2-iodoanisole (**8s**) as halide electron-rich (we select an iodide electron-rich because much less reactive), with phenylacetylene (**14a**) as alkyne (**Scheme 2.4.2.1**); evaluating, from point of view of efficiency (conversion, yield and reaction time), generality and possibility in flow.



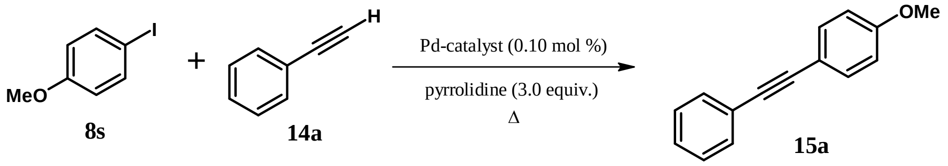
Scheme 2.4.2.1: Model reaction used for optimization of Sonogashira cross-coupling reaction

Taking into account our experience in the use of Pd/PVPy and PdEnCats in Sonogashira copper-free;**[218, 146g, 333a]** the catalytic trials were run in three different conditions using low doses of catalysts (0.10 mol% of Pd): a) Solventless condition using an appropriate excess of pyrrolidine as base (in this case the base is also the solvent), because very practical, economical, compatible with the principles of green chemistry and in line with the objectives of this thesis work (the reaction mixture are completely homogeneous both as cold and hot but many viscose); b) Water condition using the only water as solvent thank to the addition of an additive (TBAB), because very practical, economical and compatible with the principles of green chemistry, despite this condition appears not applicable in flow, because completely not homogeneous at cold and at hot; and c) DMF/H_2O condition, because despite its less economical and green of the other two, this condition was most used in Sonogashira coupling copper-free and appears many applicable in flow (completely homogeneous at cold and at hot with acceptable viscosity).

Initially, we examined the effect of the temperature, and aerobic atmosphere in the presence of 0.10 mol % of Pd-catalysts under solventless condition (**Table 2.4.2.1**).

In these conditions the catalysts result able to promote the reaction with interesting yields (> 50 %) in low reaction time (< 5 h) both were used in aerobic or not atmosphere. Unfortunately, in many cases the cross-coupling product was obtained in conjunction with vary secondary product that vary from case to case.

Table 2.4.2.1: Effect of temperature and aerobic atmosphere on the Cu-free Sonogashira coupling reaction under solventless condition.[a]



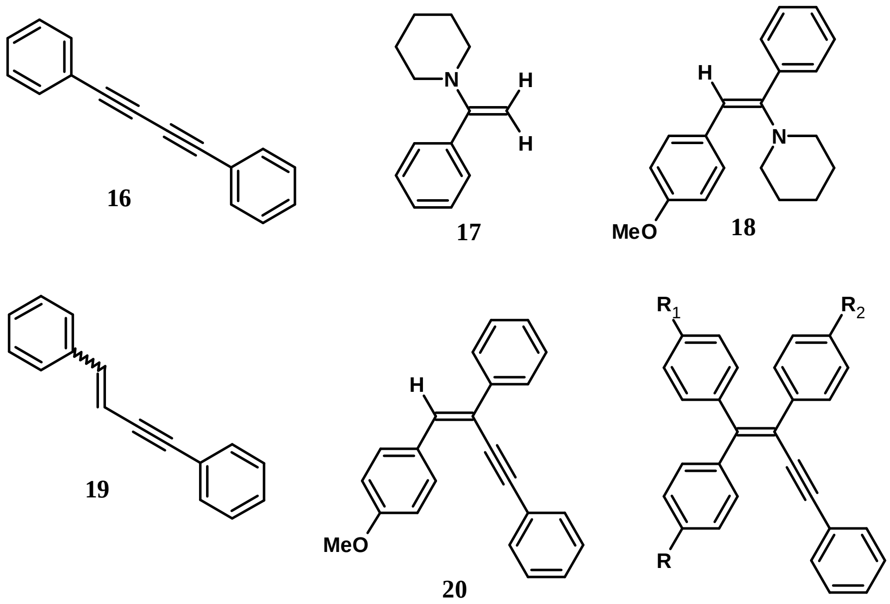
Entry	*Catalyst*	*Temperature (°C)*	*Atmosphere*	*Reaction time (h)*	*Conversion of **8s**[b] (%)*	*Selectivity[b] **15a** / by-products*	*Yield of **15a**[c] (%)*
1	Pd-Cu/PVPy	95	air	3	88	85 : 15	51
2		85	air	6	60	90 : 10	-
3		95	Ar	3	85	90 : 10	61
4	Pd/MCM-41	95	air	4	94	81 : 19	52
5		85	air	5	89	83 : 17	47
6		95	Ar	4	95	90 : 10	53
7	PdEnCat-40	95	air	3	80	94 : 6	62
8		85	air	3	99	78 : 25	65
9		95	Ar	4	85	90 : 10	65
10	PdCl$_2$(PPh$_3$)$_2$-PS	95	air	3	95	98 : 2	82
11		85	air	3	93	91 : 9	80
12		95	Ar	4	95	98 : 2	81
13	Fibrecat 1007	95	air	5	99	90 : 10	61
14		85	air	5	65	92 : 8	40
15		95	Ar	5	99	95 : 5	78
16	Pd(PPh$_3$)$_4$-PS	95	air	5	95	95 : 5	55
17		85	air	3	80	91 : 9	65
18		95	Ar	4	95	93 : 7	60

a) Reaction conditions: 1.0 equivalent of aryl halide (**8s**), 1.30 equivalent of phanylacetilene (**14a**), 3.00 equivalent of pyrrolidine, 0.10 mol % of Pd as catalyst; b) Evaluated by GC analyses; c) Isolated Yield by MPLC

For regard the bi-metallic MVS-prepared catalyst (Pd-Cu/PVPy), good conversion of 4-iodoanisole (**8s**) was achieved in 3.0 h at 95 °C both used in aerobic or not atmosphere. Unfortunately, in these conditions this catalyst produce many secondary products, especial the product of homocoupling of the alkyne (**16**) (Glaser reaction)**[242]** correlated with the presence of Cu; using a loss temperature (85 °C) the catalytic system result not able to promote efficiently the coupling (**Table 2.4.2.1**, entry 1-3).

The mono-metallic MVS-prepared catalyst (Pd/MCM-41) and the all commercial catalysts showed almost complete conversion of **8s** in short time (3-5 h) at 95 °C both used in aerobic or not atmosphere. The performance of these mono-metallic catalysts were appear similarly, however the Pd/MCM-41 showed highly leaching data (above 6.0 %) and the more active in this condition appear the $PdCl_2(PPh_3)_2$-PS () that showed excellent yields (80-82 %) at any temperature tested. However, the reduction of the temperature at 85 °C in general not showed a drastic loss of the activity (that remain unchanged), and with PdEnCat-40 and $Pd(PPh_3)_4$-PS were obtained yields increased of 10 %. The secondary products, using mono-metallic catalysts were limited, but always present (< 10 %), and constitute essentially from the addition of the pyrrolidine into the alkyne to form the corresponding enamine (**17**).

In general all the secondary product given in our tests were formed to consume alkyne (**14**), by homocoupling (Glaser reaction), addition of pyrrolidine (to form the enamine) and addition of alkynil palladium complex (an intermediate of the catalytic cycle *Cu-free*) into the desiderated product or other alkyne (**Scheme 2.4.2.2**). Furthermore, these secondary product were the principal cause of the not complete conversion (the alkynes finish before the halides despite its was in excess) and the not excellent yields (the desiderated product could be consumed).



21a $R=R_1=OMe$; $R_2=H$

21b $R=R_2=OMe$; $R_1=H$

21c $R_2=R_1=OMe$; $R=H$

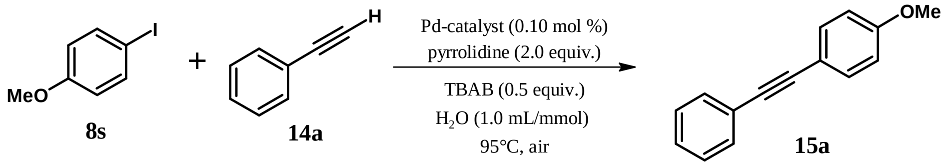
Scheme 2.4.2.2: Principal secondary products given in our tests

These by-products were identified and establishing its regio- and stereochemistry by means of GC-MS comparison with authentic and previously characterized samples (compare retention time, molecular weight and ms-fragmentation with samples standard obtained in previously works)**[146g, 333a]**

In conclusion this soventless condition result able to promote efficiently the Sonogashira CuI-free reaction both with bi-metallic catalysts that mono-metallic systems, but unfortunately, these conditions (most green respect to other) appears not perfectly applicable in flow, because the salts, product and/or high molecular weight by-product that to form during the reaction result not completely solubilized at hot.

At the light of these results, and taking into account the literature dates we decided to examine the supported catalysts under aerobic atmosphere in only H_2O as solvent at 95 °C, despite this condition can not be employed in flow because completely not homogeneous. However, this condition may be useful in Pd-catalyzed Sonogashira coupling reactions, to test the versatility of all catalysts, object of our study (**Table 2.4.2.2**).

Table 2.4.2.2: Effect of the only water as solvent on the Sonogashira Cu-free coupling reaction catalyzed by our supportd Pd systems.^{a}



Entry	*Catalyst*	*Atmosphere*	*Reaction time (h)*	*Conversion of* ***8s***^{b} *(%)*	*Selectivity*^{b} ***15a****/ by-products*	*Yield of* ***15a***^{c} *(%)*	*Leaching*^{d} *(%)*
1	*Pd-Cu/PVPy*	*air*	*3*	*98*	*95 : 5*	*66*	*< 0.1 of Pd* *< 3.5 of Cu*
2^{d}		*Ar*	*3*	*99*	*95 : 5*	*60*	*-*
3	*Pd/MCM-41*	*air*	*4*	*98*	*72 : 28*	*58*	*2.1*
4^{d}		*Ar*	*4*	*92*	*74 : 26*	*48*	*-*
5	*PdEnCat-40*	*air*	*3*	*99*	*85 : 15*	*50*	*2.1*
6	*PdCl$_2$(PPh$_3$)$_2$-PS*	*air*	*1*	*99*	*90 : 10*	*58*	*2.2*
7	*Fibrecat 1007*	*air*	*3*	*99*	*86 : 14*	*50*	*1.8*
8	*Pd(PPh$_3$)$_4$-PS*	*air*	*1*	*99*	*85 : 15*	*50*	*2.7*

a) Reaction conditions: 1.0 equivalent of aryl halide (**8s**), 1.2 equivalent of phanylacetilene (**14a**), 2.0 equivalent of pyrrolidine, 0.10 mol % of Pd as catalyst, 95 °C, air atmosphere; b) Evaluated by GC analyses; c) Isolated Yield by MPLC; d) in Ar atmosphere

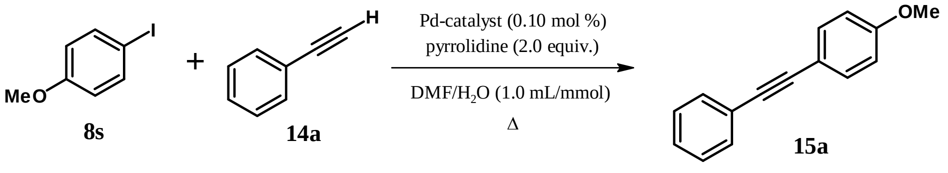
Under these conditions the our studied catalysts result able to promote the Sonogashira CuI-free in short time (1-4 h) with good yields (> 50 %). Unfortunately in these conditions the majority of the supported catalyst object of our study showed an important amount of by-products (> 15 %) except for regard the bi-metallic system Pd-Cu/PVPy, that showed substantially higher selectivity of the desired product **15a**, and this catalysts showed the better isolated yield (66 %) in short time (3 h). While the Pd/MCM-41 result the catalyst with worse selectivity producing about 30 % of by-product. However, with pure water condition, all commercial catalysts have a loss catalytic activity compared with solventless condition. Most interesting result the leaching of the catalysts in water, in fact all catalysts showed a similar leaching date (about 2.0 %), except the bi-metallic Pd-Cu/PVPy that showed a loss leaching date of Pd (< 0.1 %) and 3.5 % of Cu leaching. Cu leaching date that whereas the copper content into the catalyst (see paragraph 2.1), corresponds to a presence of copper in the raw products equal to several ppm.

Finally, at the light of the results previously obtained in pure water and specially in solventless condition; taking into account the our necessity of most generally and efficient conditions easily translated in flow mode; we examined the supported catalysts in DMF/H_2O (4:1) condition at 95 °C. In fact, this reaction condition, most used in Sonogashira coupling copper-free, could be easily applicable in flow resulting completely homogeneous at cold with optimum viscosity of the mixture before and after the coupling.

In detail we tested the effect of the temperature, and aerobic atmosphere in the presence of 0.10 mol % of Pd-catalysts in DMF/H_2O condition (**Table 2.4.2.3**).

In these conditions the catalysts result able to promote the reaction with interesting yields (> 60 %) in low reaction time (< 5 h) both were used in aerobic or not atmosphere, with very low leaching data (< 1.0 %). Obviously, also in these cases the cross-coupling product was obtained in conjunction with vary secondary product that vary from case to case.

Table 2.4.2.3: Effect of the DMF/H_2O as solvent on the Sonogashira Cu-free coupling reaction catalyzed by our supportd Pd systems.[a]



Entry	Catalyst	Additive (equiv.)	Atmosphere	Reaction time (h)	Conversion of **8s**[b] (%)	**15a**/by-products[b]	Yield of 15**a**[c] (%)	Leaching[d] (%)
1	Pd-Cu/PVPy		air	4	99	70 : 30	65	< 0.2 of Pd < 6.0 of Cu
3			Ar	8	99	70 : 30	60	-
4	Pd/MCM-41		air	4	97	80 : 10	63	0.73
5			Ar	3	99	91 : 9	73	-
6		TBAB (0.5)	air	4	69	89 : 11	-	-

7	*PdEnCat-40*		*air*	*3*	*99*	*85 : 15*	*61*	*3.00*
8			*Ar*	*3*	*99*	*68 : 32*	*60*	-
9		*TBAB (0.5)*	*air*	*3*		*85 : 15*	*60*	-
10	$PdCl_2(PPh_3)_2$*-PS*		*air*	*3*	*99*	*90 : 10*	*66*	*0.73*
11			*Ar*	*1*	*99*	*85 : 15*	*69*	-
12		*TBAB (0.5)*	*air*	*3*	*98*	*88 : 12*	*60*	-
13	*Fibrecat 1007*		*air*	*3*	*99*	*90 : 10*	*65*	*0.53*
14			*Ar*	*3*	*99*	*88 : 12*	*85*	-
15		*TBAB (0.5)*	*air*	*3*	*98*	*87 : 13*	*65*	-
16	$Pd(PPh_3)_4$*-PS*		*air*	*3*	*99*	*87 : 13*	*69*	*0.76*
17			*Ar*	*3*	*99*	*71 : 29*	*55*	-
18		*TBAB (0.5)*	*air*	*3*	*98*	*92 : 8*	*65*	-

a) Reaction conditions: 1.0 equivalent of aryl halide (**8s**), 1.2 equivalent of phanylacetilene (**14a**), 2.0 equivalent of pyrrolidine, 0.10 mol % of Pd as catalyst, 95 °C; b) Evaluated by GC analyses; c) Isolated Yield by MPLC; d) Evaluated by ICP-OES after microfiltration (0.45 mm) and reported as Pd leached wt.% of the total available metal

Under these conditions the majority of our studied catalysts result most efficient to promote the Sonogashira CuI-free in short time (1-4 h) showed the better yields of the all conditions examined (> 60 %).

Generally, the use of anaerobic conditions has not evident effects on the efficiency of the various systems in terms of reaction time and conversion. In fact, in other cases the use of Ar atmosphere showed a loss of activity (increasing the reaction time for obtain the complete conversion) obtaining loss or similar yields at the same reaction in aerobic atmosphere. Only in the use of Pd/MCM-41 and $PdCl_2(PPh_3)_2$-PS the use of Ar atmosphere showed evident positive effects on the efficiency, increasing the yields and reducing the reaction times.

More interesting appear the behaviour of the bi-metallic catalyst Pd-Cu/PVPy. This catalyst in DMF/H_2O showed the worst selectivity (only 70 % of the desiderated product **15a**), but with good yield (65 %). Yield which is similar to that obtained in only water, where it has the better selectivity (95 % of **15a**). This phenomena is correlated to the promotion of the Glaser reaction in the different conditions; in fact, the by-product in DMF/H_2O is principally the homocoupling of terminal alkyne, while in water as solvent this by-product were almost completely absent.

In conclusion, at the light of the previously mentioned study results, we observed that all our supported catalysts result able to promote efficiently the Sonogashira CuI-free coupling in three interesting, practical, economical and more or less environmentally friendly conditions. However, taking into account the our necessity of most generally and efficient conditions easily translated in flow mode, we observed that the majority of the our supported catalysts showed the better activity (higher yields, selectivity and lower metal leaching) using the pyrrolidine as base in DMF/H_2O.

Therefore, the conditions that we use subsequently to evaluate the performance and limitation of the catalysts in this cross-coupling are 1.0 equivalent of aryl halide, 1.2 equivalent of terminal alkyne, 2.0 equivalent of pyrrolidine as base, 1.00 mL/mmol of DMF/H_2O (4:1) as solvent, at 95°C using 0.10 mol% of the palladium under aerobic atmosphere.

For regard the new MVS-prepared catalysts mono- and bi-metallic systems, we decided to evaluate the performance also in only water; given that Pd-Cu/PVPy catalyst in this condition has showed the better performance in the model reaction with the lower palladium and copper leaching, while the Pd/MCM-41 showed the worse selectivity, but with acceptable yield and leaching data.

2.4.2.1 Performance of the catalysts in Sonogashira coupling reaction with aryl iodides in batch

To explore the scope and generality of the catalysts, the better aerobic protocol was applied for reactions of a variety of differently substituted aryl iodides and terminal alkynes. Therefore, a study was set up by selecting aryl iodides bearing electron withdrawing and donating groups and a few examples of terminal alkynes. The outcomes are summarized in **Table 2.4.2.4**.

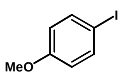
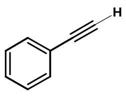
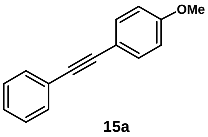
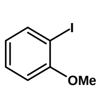
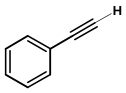
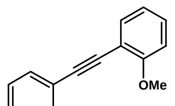
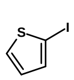
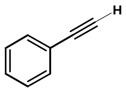
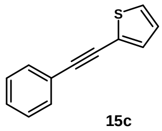
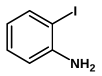
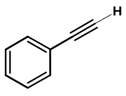
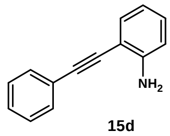
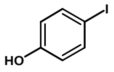
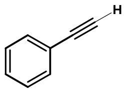
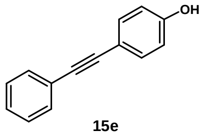
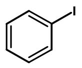
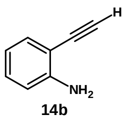
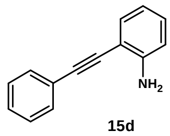
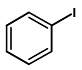
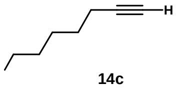
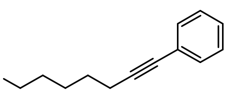
Generally, deactivated and/or sterically hindered aryl iodides were completely converted into the corresponding products in 40–92% yields within 1 h–6 h (**Table 2.4.2.4**). The reactions showed good diversity in the presence of both electron withdrawing and donating groups. For the deactivated aryl iodides sterically hindered, satisfactory yields could be obtained in short time with the majority of the catalysts;

It was interesting to note that both protic free groups (-OH and -NH_2) were not perfectly tolerated in the reaction conditions with all catalysts (**Table 2.4.2.4**, entries 19-28) presenting the main formation of the dahalogenation products (phenol and aniline).

Regarding the terminal alkynes, the coupling reaction of electron-rich, but sterically hindered such as 2-ethynylaniline (**14b**) led to the corresponding product in excellent yields (68-90 %) although with very high data leaching (3-15 %) (**Table 2.4.2.4**, entry 29-32). While the coupling reaction of aliphatic terminal alkyne such as 1-octyne (**14c**) led to the corresponding product in very scarce yields (17-22 %) (**Table 2.4.2.4**, entry 33-36).

Table 2.4.2.4: Scope and generality of our supported catalysts in Sonogashira coupling reaction with aryl iodides in DMF/H_2O.[a]

$$\underset{\mathbf{8}}{\text{(Het)Ar-I}} + \underset{\mathbf{14}}{\text{Ar'-C}\equiv\text{C-H}} \xrightarrow[\substack{\text{DMF/H}_2\text{O (4:1) 1.0 mL/mmol} \\ 95\ ^\circ\text{C, air}}]{\substack{0.10 \text{ mol \% di Pd} \\ \text{pyrrolidine (2.0 equiv)}}} \underset{\mathbf{15}}{\text{(Het)Ar-C}\equiv\text{C-Ar'}}$$

Entry	*(Het)Ar-I* ***(8)***	*Ar'-C≡C-H* ***(14)***	*Catalyst*	*Time (h)*	*Product* ***(15)***	*Yield of* ***15***[b] *(%)*	*Leaching*[c] *(%)*
1	 **8s**	 **14a**	***PdEnCat-40***	***3.0***	 **15a**	***61***	***3.00***
2			***Fibrecat 1007***	***3.0***		***65***	***0.53***
3			***PdCl2(PPh3)2-PS***	***3.0***		***66***	***0.73***
4			***Pd(PPh3)4-PS***	***3.0***		***69***	***0.76***
5			***Pd/MCM-41***	***4.0***		***63***	***0.73***
6			***Pd-Cu/PVPy***	***4.0***		***65***	***<0.20 of Pd*** ***<6.00 of Cu***
7	 **8t**	 **14a**	***PdEnCat-40***	***3.0***	 **15b**	***67***	***0.15***
8			***Fibrecat 1007***	***3.0***		***44***	***0.09***
9			***PdCl2(PPh3)2-PS***	***3.0***		***40***	***0.10***
10			***Pd(PPh3)4-PS***	***3.0***		***60***	***4.80***
11			***Pd/MCM-41***	***2.0***		***75***	***0.55***
12			***Pd-Cu/PVPy***	***3.0***		***60***	***-***
13	 **8u**	 **14a**	***PdEnCat-40***	***3.0***	 **15c**	***92***	***0.50***
14			***Fibrecat 1007***	***3.0***		***87***	***0.35***
15			***PdCl2(PPh3)2-PS***	***3.0***		***85***	***0.73***
16			***Pd(PPh3)4-PS***	***3.0***		***90***	***< 0.01***
17			***Pd/MCM-41***	***2.0***		***88***	***-***
18			***Pd-Cu/PVPy***	***2.5***		***80***	***-***
19	 **8v**	 **14a**	***PdEnCat-40***	***3.0***	 **15d**	***33***	***0.03***
20			***Fibrecat 1007***	***3.0***		***40***	***0.72***
21			***PdCl2(PPh3)2-PS***	***3.0***		***75***	***0.15***
22			***Pd(PPh3)4-PS***	***3.0***		***60***	***0.14***
23			***Pd-Cu/PVPy***	***3.0***		***68***	***-***
24	 **8w**	 **14a**	***PdEnCat-40***	***5.0***	 **15e**	***trace***	
25			***Fibrecat 1007***	***5.0***		***trace***	
26			***PdCl2(PPh3)2-PS***	***5.0***		***trace***	
27			***Pd(PPh3)4-PS***	***5.0***		***trace***	
28			***Pd-Cu/PVPy***	***8.0***		***16***	***-***
29	 **8x**	 **14b**	***PdEnCat-40***	***3.0***	 **15d**	***68***	***12.00***
30			***Fibrecat 1007***	***3.0***		***90***	***15.00***
31			***PdCl2(PPh3)2-PS***	***3.0***		***85***	***3.00***
32			***Pd(PPh3)4-PS***	***3.0***		***70***	***14.00***
33	 **8x**	 **14c**	***PdEnCat-40***	***24***	 **15f**	***22***	
34			***Fibrecat 1007***	***24***		***20***	
35			***PdCl2(PPh3)2-PS***	***24***		***17***	
36			***Pd(PPh3)4-PS***	***24***		***20***	

a) Reaction conditions: 1.0 equivalent of aryl iodide (**8**), 1.20 equivalent of terminal alkyne (**14**), 2.0 equivalent of pyrrolidine, 0.10 mol % of Pd as catalyst, DMF/H_2O 4:1 (1.00 mL/mmol), air atmosphere

b) Isolated Yield by MPLC; c) Evaluated by ICP-OES after microfiltration (0.45 mm) and reported as Pd leached wt.% of the total available metal

In detail, the results obtained with the commercial catalysts, to consisting in a Pd(0) and Pd(II) complex deposited on polymeric supports, are very interesting. More in particular, from a long series of tests, carried out on various compounds (aromatic and aliphatic terminal alkynes and 2-iodo or 4-iodoarenes electron-rich and electron-neutral as halides), allowed to establish that all catalysts studied showed a fairly good efficiency in short times (1-5 h), with some specific features of each catalyst.

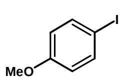
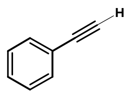
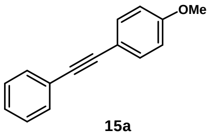
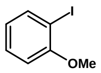
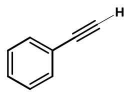
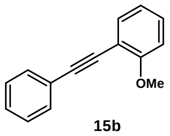
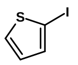
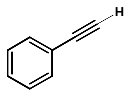
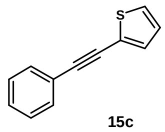
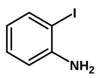
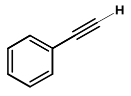
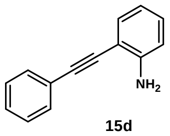
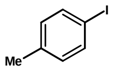
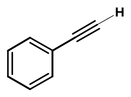
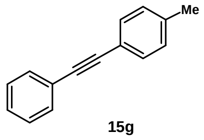
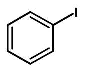
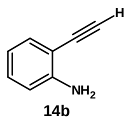
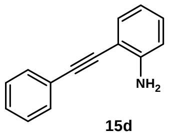
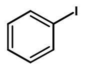
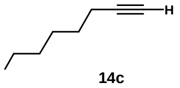
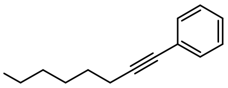
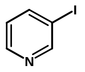
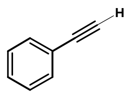
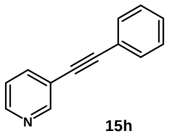
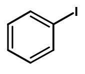
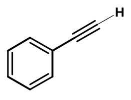
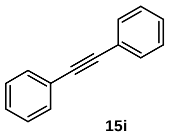
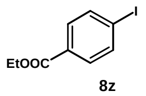
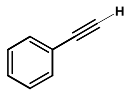
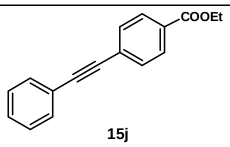
These systems affording good to excellent yields in short times with an (hetero)aryl iodide such as 2-iodothiophene (85-92 %) with low palladium leaching (< 0.73 %). In these conditions the four commercial catalysts showed a very low Pd leaching (< 1.0 %) with majority of the substrates, at exception of the reaction between iodobenzene (**8x**) and 2-alkynyaniline (**14b**) where only the $PdCl_2(PPh_3)_2$-PS (**3**) showed a leaching date lower of 10 %. The Fibrecat-1007 (**2**) and $PdCl_2(PPh_3)_2$-PS (**3**) seem to suffer the steric hindrance of the iodides, though in the reaction between 2-iodoaniline (**8v**) and phenylacetylene (**14a**), $PdCl_2(PPh_3)_2$-PS (**3**) showed the better yield (75 %) with very low leaching data (0.15 %). Unfortunately, in these conditions none of the catalysts tested was able to significantly promote the reaction with 4-iodophenol (**8w**) both in aerobic and Ar atmosphere.

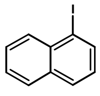
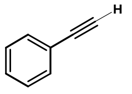
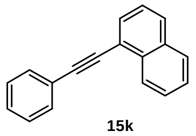
As regard the MVS-prepared catalysts, these affording good to excellent yields in short times with sterically hindered aryl iodides (60-65 %) and (hetero)aryl iodides (80-88 %) with acceptable leaching for Pd/MCM-41 (**6**), while the Pd-Cu/PVPy (**7**) showed low Pd leaching, but not indifferent copper leaching (above 6 %). However, the Pd-Cu/PVPy result the only catalyst able to promote the coupling with 4-iodophenol (**8w**) even if with very low yield (< 20%).

For regard the new MVS-prepared catalysts mono- and bi-metallic systems, we decided to evaluate the performance also in only water; given that Pd-Cu/PVPy catalyst in this condition has showed the better performance in the model reaction with the lower palladium and copper leaching, while the Pd/MCM-41 showed the worse selectivity, but with acceptable yield and leaching data. The outcomes are summarized in **Table 2.4.2.5**.

Table 2.4.2.5: Scope and generality of our MVS-prepared supported catalysts in Sonogashira coupling reaction with aryl iodides in H_2O.[a]

$$\underset{\mathbf{8}}{\text{(Het)Ar-I}} + \underset{\mathbf{14}}{\text{Ar'-C}{\equiv}\text{C-H}} \xrightarrow[\substack{\text{TBAB (0.5 equiv.)} \\ \text{H}_2\text{O 1.0 mL/mmol} \\ \text{95 °C, air}}]{\substack{\text{0.10 mol \% di Pd} \\ \text{pyrrolidine (2.0 equiv.)}}} \underset{\mathbf{15}}{\text{(Het)Ar-C}{\equiv}\text{C-Ar'}}$$

Entry	*(Het)Ar-I* ***(8)***	*Ar'-C≡C-H* ***(14)***	*Catalyst*	*Time (h)*	*Product* ***(15)***	*Yield of* ***15***[b] *(%)*	*Leaching*[c] *(%)*
1	 **8s**	 **14a**	***Pd-Cu/PVPy***	***3.0***	 **15a**	***66***	***<0.1 of Pd*** ***<3.5 of Cu***
2			***Pd/MCM-41***	***4.0***		***58***	***2.10***
3	 **8t**	 **14a**	***Pd-Cu/PVPy***	***2.5***	 **15b**	***63***	
4			***Pd/MCM-41***	***2.5***		***63***	
5	 **8u**	 **14a**	***Pd-Cu/PVPy***	***2.5***	 **15c**	***87***	
6			***Pd/MCM-41***	***3.0***		***74***	
7	 **8v**	 **14a**	***Pd-Cu/PVPy***	***2.0***	 **15d**	***75***	***0.03***
8	 **8c**	 **14a**	***Pd-Cu/PVPy***	***5.5***	 **15g**	***65***	***0.10 of Pd*** ***3.50 of Cu***
9	 **8x**	 **14b**	***Pd-Cu/PVPy***	***2.0***	 **15d**	***91***	
10	 **8x**	 **14c**	***Pd-Cu/PVPy***	***5.0***	 **15f**	***47***	
11	 **8y**	 **14a**	***Pd-Cu/PVPy***	***2.0***	 **15h**	***96***	
12	 **8x**	 **14a**	***Pd-Cu/PVPy***	***2.5***	 **15i**	***87***	***0.10 of Pd*** ***1.40 of Cu***
13			***Pd EnCat-40***	***2.5***		***94***	***0.50***
14	 **8z**	 **14a**	***Pd-Cu/PVPy***	***2.0***	 **15j**	***65***	

15	 **8aa**	 **14a**	*Pd-Cu/PVPy*	*2.0*	 **15k**	*89*

a) Reaction conditions: 1.0 equivalent of aryl iodide (**8**), 1.20 equivalent of terminal alkyne (**14**), 2.0 equivalent of pyrrolidine, 0.10 mol % of Pd as catalyst, H_2O (1.00 mL/mmol), air atmosphere
b) Isolated Yield by MPLC; c) Evaluated by ICP-OES after microfiltration (0.45 mm) and reported as Pd leached wt.% of the total available metal

Generally, deactivated and/or sterically hindered aryl iodides were completely converted into the corresponding products in 40–92% yields within 1 h–6 h (**Table 2.4.2.4**). The reactions showed good diversity in the presence of both electron withdrawing and donating groups. For the deactivated aryl iodides sterically hindered, satisfactory yields could be obtained in short time with the majority of the catalysts;

It was interesting to note that both protic free groups (-OH and -NH_2) were not perfectly tolerated in the reaction conditions with all catalysts (**Table 2.4.2.4**, entries 19-28) presenting the main formation of the dahalogenation products (phenol and aniline).

Regarding the terminal alkynes, the coupling reaction of electron-rich, but sterically hindered such as 2-ethynylaniline (**14b**) led to the corresponding product in excellent yields (68-90 %) although with very high data leaching (3-15 %) (**Table 2.4.2.4**, entry 29-32). While the coupling reaction of aliphatic terminal alkyne such as 1-octyne (**14c**) led to the corresponding product in very scarse yields (17-22 %) (**Table 2.4.2.4**, entry 33-36).

2.4.2.2 Performance of the catalysts in Sonogashira coupling reaction with aryl bromides in batch

Generally aryl bromides, especially nonactivated aryl bromides, are notoriously less reactive than that of aryl iodides in Sonogashira-Hagihara reaction; due to the stability of the C–Br bond (relative reactivities of Ar–X are correlated to their respective bond dissociation energies: Ph–Cl, 96 kcal/mol; Ph–Br, 81 kcal/mol; Ph–I, 65 kcal/mol). In fact, generally only two possible approaches can be used to expand this reaction to aryl bromides: elevating the temperature or adding the ligands.

Running the coupling at higher temperature is the general and easy method. However, at elevated temperatures, the by-products of the homocoupling and dehalogenation tend to be produced through the Sonogashira reaction.**[341]**

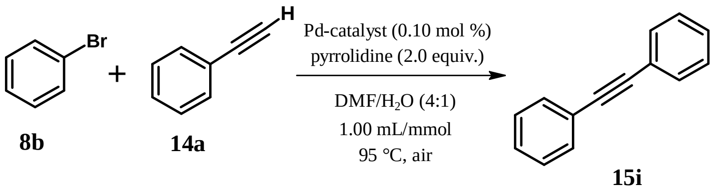
For regard the addition of ligands, these can be increased the catalytic activity of the catalysts, but frequently these ligands are difficult available and very expensive. Furthermore, the addition of ligands can present potentially complication in the product isolation, to increasing the purification (similar to the presence of metal contamination).

For these reasons in literature have been described only examples of efficiently supported palladium catalyzed reactions with only the few activated bromoarenes.**[146g, 342]**

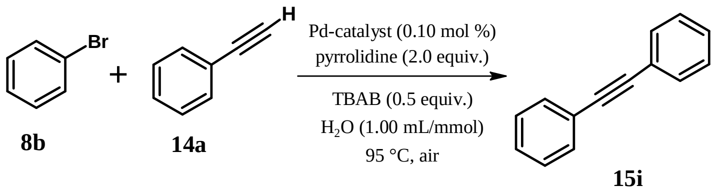
At the light of the results obtained in the Sonogashira Cu-free reactions with deactivated and/or sterically hindered aryl iodides we decided to evaluate the performance of our catalysts with aryl bromides.

Initially, we have also evaluated the coupling ability of aryl bromides (generally lower reactive than that of aryl iodides) using the previously mentioned conditions. Unfortunately, under the above choice better conditions (0.10 mol % of metal loads with an excess of pyrrolidine as base, under aerobic atmosphere in DMF/H_2O (4:1) as solvent (for the majority of the catalysts) or only H_2O (for the MVS-prepared catalysts), none of the studied catalysts result able to significantly promote the reaction between aryl bromides and terminal alkynes.

In detail, we examined the catalysts in the reaction of bromobenzene (**8b**) with phenylacetylene (**16a**) evaluating the conversions and yields (**Scheme 2.4.2.3**).



Catalyst	conversion	time
PdEnCat-40	32 %	24h
Fibrecat 1007	33 %	24h
$PdCl_2(PPh_3)_2$-PS	30 %	24h
$Pd(PPh_3)_4$-PS	29 %	24h
Pd/MCM-41	4 %	24h
Pd-Cu/PVPy	10 %	24h



Catalyst	conversion	time
Pd/MCM-41	20 %	24h
Pd-Cu/PVPy	10 %	24h

Scheme 2.4.2.3: Efficiency of previously optimized condition with aryl bromides in Sonogashira Cu-free reaction

The four commercial catalysts under DMF/H_2O condition showed very low efficiency after long reaction times; while the two “home-made” catalysts appear completely inactive under this condition and in only water.

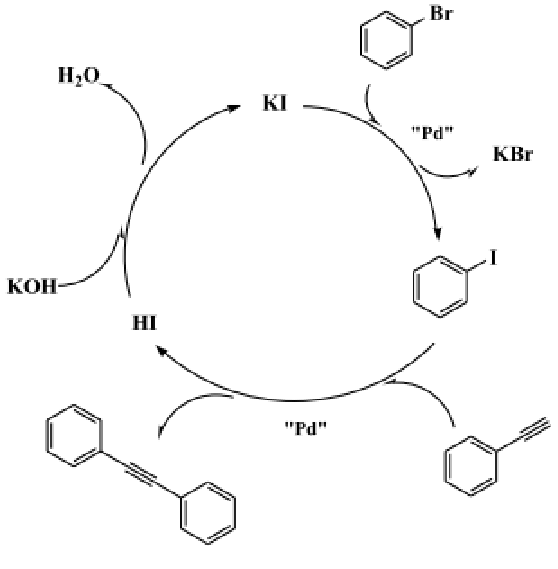
Given the presence (even if very low) of the catalytic activity in the coupling of bromobenzene with commercial catalysts, we decided to determine the most efficient and feasible reaction conditions in which any our catalysts are able to promote the Sonogashira Cu-free reaction between aryl bromides and terminal alkynes, taking into account (if possible) their versatility, environmentally friendly and applicability in flow.

Taking into account the literature dates in the supported Pd-catalyzed reaction with aryl bromides (above mentioned) and at the light of previously studies with aryl iodides, we decided to examine the supported catalysts using an interesting practical procedure; to provided the addition of catalytic amount of iodine salts.**[6o]** In fact, the increasing of the reaction temperature (the more general and easy method reported in literature), at the light of the results obtained with aryl iodides, could aim at increasing the formation (already important at 95°C in any cases) of by-products.

For regard the addition of ligands, these can be increased the catalytic activity of the catalysts (if the systems acts in homogeneous catalysis), but principally can present potentially complication in the easily and environmentally friendly of the process and in the product isolation, to increasing the costs of the processes.

While the addition of a of sample iodine salt result most interesting because respected the our principle of easily, generality and environmentally friendly of the reaction conditions.

In general, this process is based on an “in situ” halogen exchange of the aryl bromides by a iodide source such as an alkali iodide, and subsequently Sonogashira reaction with “in-situ” formed aryl iodide as reported in **Scheme 2.4.2.4**.

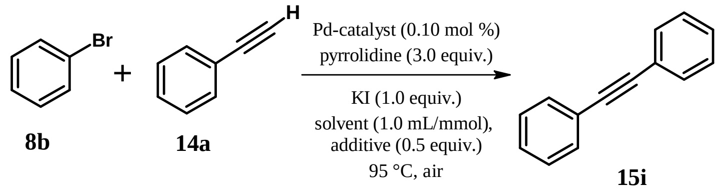


Scheme 2.4.2.3: Schematic Halex-Sonogashira process

During this process were obtained the desiderated Sonogashira product plus the HI. This acid could be neutralized by excess of base (KOH in the work of Rothenberg) releasing I^- back to the system and closing the cycle. Therefore, if the KI would be to use in catalytic amounts, the I$^-$ releasing after the neutralization can continue the cycle until the aryl bromide is consumed. Unfortunately, this catalytic effect were not obtained by Rothenberg and co-works; although in theory the acid-base reaction step looks simple. The authors attributed this failed at the low solubility of KOH and/or reactants in the used solvent (DMF/H_2O 3:1).

Therefore, we decided to examine the efficiency of this “one-pot” Halex-Sonogashira reaction with our supported catalysts in the better conditions previously individuated on aryl iodides. For these explorative tests we increased the excess of pyrrolidine at 3.0 equivalents with the addition of KI (1.0 equivalent) in the same model reaction between bromobenzene (**1**) and phenylacetylene (**6a**) evaluating the conversions and yields (**Table 2.4.2.6**)

Table 2.4.2.6: Effect of the “one-pot” HALEX-Sonogashira coupling reaction with aryl bromides.[a]



Entry	*Solvent*	*Additive*	*Catalyst*	*Reaction time (h)*	*Conversion of **8**[b] (%)*	*Yield of **15i**[c] (%)*
1	***DMF/H_2O (4:1)***	***-***	***PdEnCat-40***	***24***	***55***	***40***
2			***Fibrecat 1007***	***24***	***75***	***65***
3			***Pd(PPh3)4-PS***	***24***	***45***	***33***
4			***PdCl2(PPh3)2-PS***	***24***	***35***	***23***
5			***Pd-Cu/PVPy***	***24***	***98***	***27***
6	***H_2O***	***TBAB***	***Pd-Cu/PVPy***	***14***	***68***	***46***

a) Reaction conditions: 1.00 equivalent of aryl halide (**8**), 1.20 equivalent of phenylacetylene (**14a**), 3.0 equivalent of pyrrolidine, 0.10 mol % of Pd as catalyst, solvent (1.00 mL/mmol), air atmosphere; b) Evaluated by GC analyses; c) gas-chromatography Yield evaluated using an internal standard (naphthalene).

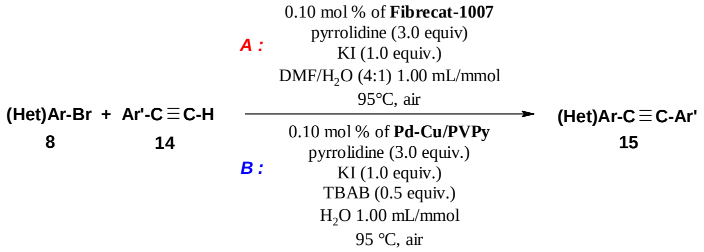
At the light of these preliminary results carried out a first series of pilot trials on the possibility to use these catalysts, in Sonogashira Cu-free reaction of bromoarenes. It has thus been established, that only the Fibrecat 1007 and Pd-Cu/PVPy are able to efficiently promote the reactions of aryl bromides electron-neutral (bromobenzene), thanks to the use of a potassium iodide, respectively in DMF/H_2O with Fibrecat 1007 and in only water with Pd-Cu/PVPy.

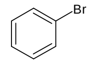
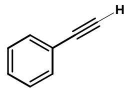
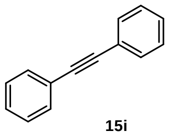
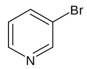
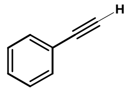
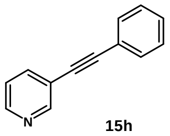
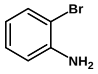
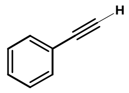
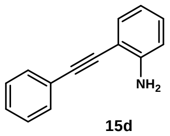
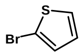
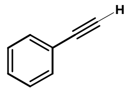
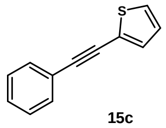
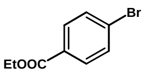
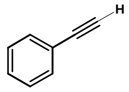
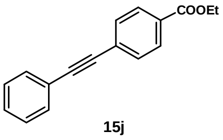
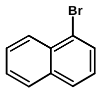
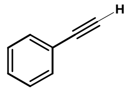
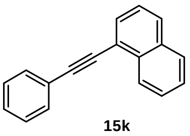
The MVS-prepared catalyst under Halex-Sonogashira process showed evident increasing of the efficiency compared with the classic procedures, but in the DMF/H_2O condition the principal product obtained was the Glaser product (only 27 % of the desiderated product were obtained). While in water, the catalyst given the desiderated product in low time (14 h) with good yield (46 %).

Identified two catalysts that are able to promote the reactions with aryl bromides, even if under Halex reaction conditions, but however, even these conditions require low metals loads and are not affected by the presence of air. For Fibrecat 1007 is necessary use the addition of KI (1.0 equiv.) in DMF/H_2O (4:1) at 95°C directly in aerobic atmosphere; while for Pd-Cu/PVPy is necessary the addition of the iodine salt in only water as solvent at 95°C directly.

We proceeded to explore the scope and generality of these catalysts, applied the above mentioned aerobic protocol for reactions of a variety of differently substituted aryl bromides. The outcomes are summarized in **Table 2.4.2.7**.

Table 2.4.2.7: Scope and generality of our supported catalysts in Sonogashira Cu-free coupling reaction with aryl bromides.[a]



Entry	*(Het)Ar-Br* ***(8)***	*Ar'-CC-H* ***(14)***	*Catalyst*	*condition*	*Time* *(h)*	*Product* ***(15)***	*Yield of 15*[b] *(%)*
1	 **8b**	 **14a**	***Fibrecat 1007***	***A***	***24***	 **15i**	***65***
2			***Pd-Cu/PVPy***	***B***	***14***		***46***
3	 **8m**	 **14a**	***Fibrecat 1007***	***A***	***3.0***	 **15h**	***80***
4			***Pd-Cu/PVPy***	***B***	***2.0***		***71***
5	 **8ab**	 **14a**	***Pd-Cu/PVPy***	***B***	***2.5***	 **15d**	***35***
7	 **8g**	 **14a**	***Pd-Cu/PVPy***	***B***	***2***	 **15c**	***74***
8	 **8i**	 **14a**	***Fibrecat 1007***	***A***	***5.0***	 **15j**	***58***
9			***Pd-Cu/PVPy***	***B***	***2.0***		***60***
10	 **8ac**	 **14a**	***Pd-Cu/PVPy***	***B***	***2.5***	 **15k**	***68***

a) Reaction conditions: ***A*** = 1.00 equivalent of aryl halide (**8**), 1.20 equivalent of alkyne (**14**), 3.00 equivalent of pyrrolidine, 1.00 equivalent of KI, 0.10 mol % of Pd as catalyst, DMF/H_2O 4:1 (1.00 mL/mmol), 95°C, air atmosphere; ***B*** **=** 1.00 equivalent of aryl halide (**8**), 1.20 equivalent of alkyne (**14**), 3.00 equivalent of pyrrolidine, 1.00 equivalent of KI, 0.50 equivalent of TBAB, 0.10 mol % of Pd as catalyst, H_2O (1.00 mL/mmol), 95°C, air atmosphere; b) Isolated Yield by MPLC.

Under the “one-pot” Halex-Sonogashira conditions these catalysts are able to promote the reaction with vary bromoarenes (both electron-rich and electron-poor) to obtain good yields (35-80 %). In particular, the catalysts are very efficient to promote the reactions with (hetero)arylbromides such as 3-bromopyridine and 2-bromothiophene, obtaining yield superior at 70 %.

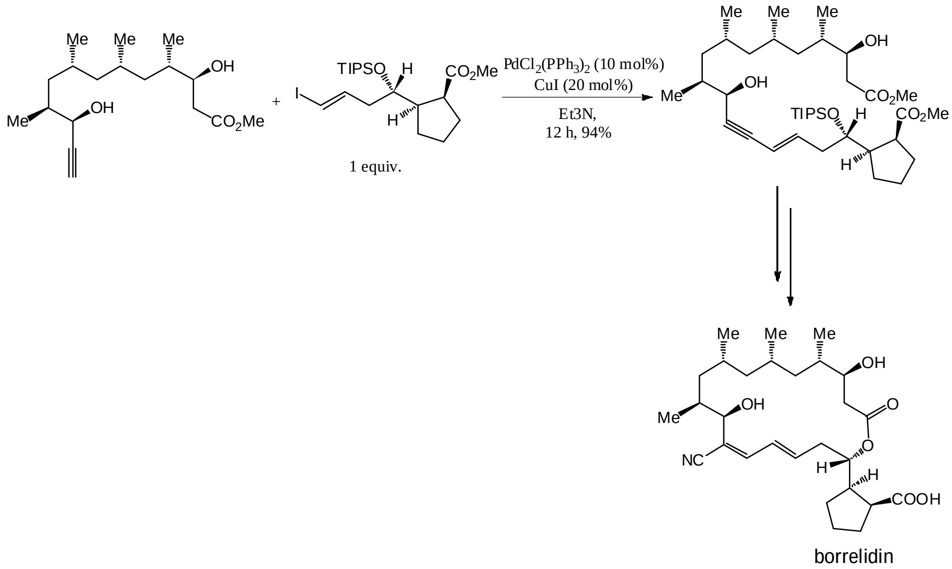
2.4.2.3 Performance of the catalysts in Sonogashira Cu-free coupling reaction with vinyl halides in batch

The enynes represent important building blocks in organic synthesis of biological, pharmacological and/or agrarian compounds**[343]**

Therefore, given the excellent results obtained with aryl iodides and the good result obtained with aryl bromides, it was considered appropriate to test our catalysts and conditions previously optimized/studied, on vinyl halides; since in the literature there are few data on the real-reactivity of these systems in supported catalysis, moreover the vinyl halides were intensively applied (used even more of aryl halides) to the synthesis of compounds of biological, pharmacological and/or agrarian interest, also to industrial level, in homogeneous catalysis.**[344]**

Here under we report any examples to show off the great importance of the vinyl halides in industrial and synthetic sphere.

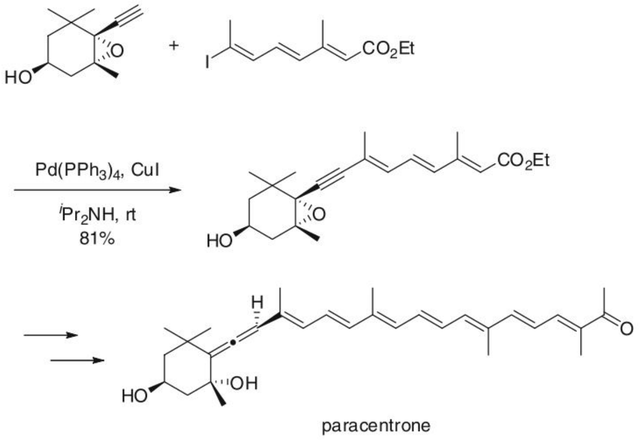
An interesting example is represented to the synthesis of borrelidin (an macrolide antibiotic investigated as potential anticancer drug) by Duffey and co-works (**Scheme 2.4.2.4**).**[345]**



Scheme 2.4.2.4 : A synthetic route to borrelidin

The key step to the process is represented to the Sonogashira Cu co-catalyzed using high palladium and copper load. The reaction result very efficient (94 % of yield) and the presence of vary functional groups (even the –OH) not interfered.

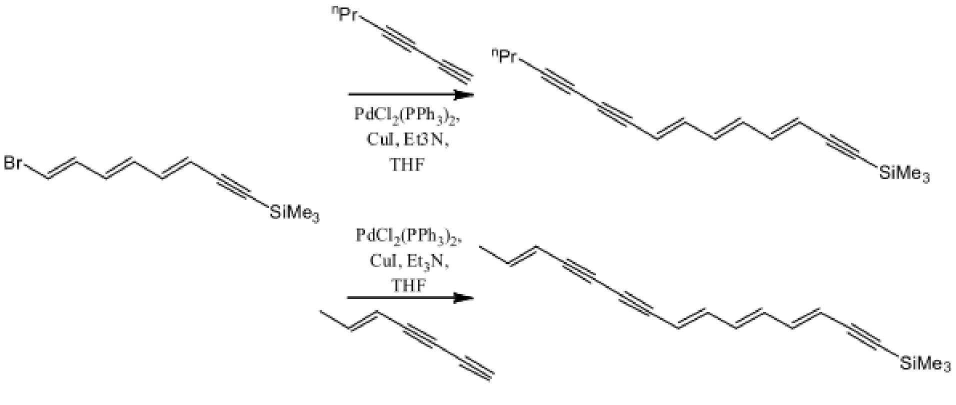
Other interesting example is represented to the total synthesis of paracentrone, a natural C_{31}-*apo*-carotenoid isolated from the sea urchin *Paracentrous lividus***[346]** shown in **Scheme 2.4.2.5.[347]**



Scheme 2.4.2.4 : A synthetic route to paracentrone

This is a representative example showing that Sonogashira–Hagihara coupling (the key step to the process) can be applied to a substrate bearing a reactive epoxide moiety which remains intact during the reaction.

An interesting example is the synthesis of xerulin and dehydroxerulin reported in **Scheme 2.4.2.5**.**[348]**



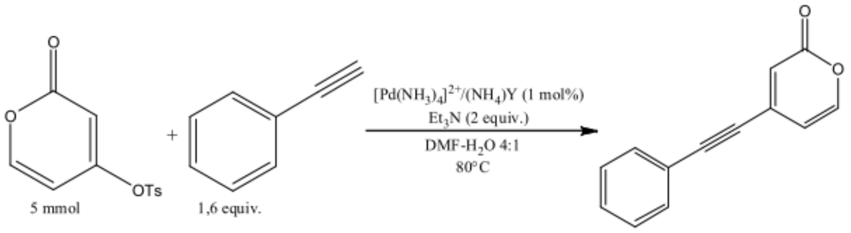
Scheme 2.4.2.5 : A synthetic route to xerulin and dehydroxerulin intermediate

In this case, the Sonogashira-Hagihara reaction were obtained both with vinyl bromides, in the synthesis of primary substructure, that with an iodo acrylate, in the final Sonogashira-cyclization tandem step.

Additionally, the following are examples of total syntheses utilizing Sonogashira–Hagihara coupling reported after 2000: callipeltoside A**[349**], mucocin**[350]**, tetrodotoxin**[351]**, 34-hydroxyasimicin**[352]**, oximidine II**[353]**, (-)-disorazole C_1**[354]**, (-)-siphonodiol, (-)-tetrahydrosiphonodiol**[355]**, peroxyacarnoates A and D**[356]**, macbecin I**[357]**, furopyrans **[358]**, leiodolide B**[359]**, iso- and bongkrekic acids**[360]**, cis- and trans- bupleurynol**[361]**, and penarolide sulfate A_1**[362]**.

In literature, the studies and applications that analyze the reactivity of olefin halides in Sonogashira-Hagihara reactions co-catalyzed or not, promoted by supported catalysts have a fairly small number. In fact in the majority of cases the Pd-supported catalysts are used with aryl halides, always more easily available, more stable and not affected from stereo-selectivity problems (theoretically one vinyl halides could be form the two stereo-isomers E and Z of the coupling product). Moreover, the aryl halides are considered less reactive compared to corresponding olefin (the general reactivity order of the sp^2 species is vinyl iodide ≥ vinyl triflate > vinyl bromide > vinyl chloride > aryl iodide > aryl triflate ≥ aryl bromide >> aryl chloride)**[282]**, but this is generally true in homogeneous catalysis, where the vinyl halides were intensively studied and applied since the firstly works of Sonogshira.**[6e,6g,13b]**

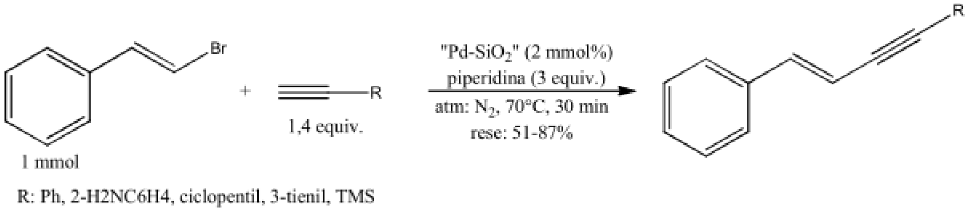
The first work that describes the use of a supported catalyst in the Sonogashira reaction with vinyl halides was reported by Djakovitch and co-workers in 2004 (**Scheme 2.4.2.5**).**[332b]** In this work the authors studied a zeolites-supported catalyst $[Pd(NH_3)_4]^{2+}/(NH_4)Y$ in the reaction between vary aryl halides (after optimization using bromobenzene as halide) and one formal alkenyl tosylate under Cu-free condition at 80°C in DMF/H_2O (4:1). In this work the authors obtained excellent yield (95 %) with vinyl halide. In the same work the authors evaluated the leaching of the catalyst (< 10 ppm), but only in the reaction between one aryl halide (4-iodoanisole) and phenylacetylene.



Scheme 2.4.2.5: Heterogeneous Sonogashira Cu-free reaction of vinyl halides catalyzed by $[Pd(NH_3)_4]^{2+}/(NH_4)Y$

In 2009 Tyrrel et co-workers describe the copper-free synthesis of indolic rings by opportune Sonogashira and hetero-cyclization steps.**[363]** In this work the author reported the use of palladium supported on modified silica in the Sonogashira Cu-free coupling under solventless conditions.

In these conditions the authors examined the coupling between vary terminal alkynes and vary aryl halides obtained excellent/good yields, and the commercial cis/trans mixture of β-bromostyrene (the β-bromostyrene is commercialized in E/Z ratio 87:13) obtaining good yields (51-87 %) in short time (**Scheme 2.4.2.6**).



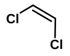
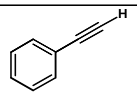
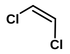
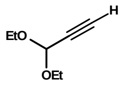
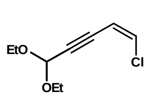
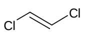
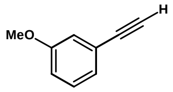
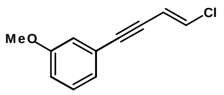
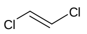
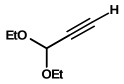
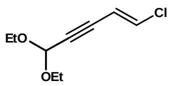
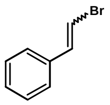
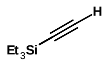
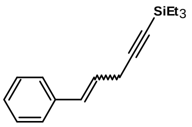
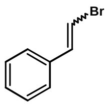
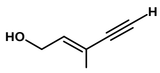
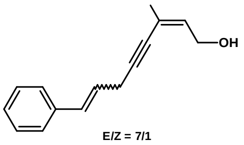
Scheme 2.4.2.6: Heterogeneous Sonogashira Cu-free reaction of β-bromostyrene catalyzed by "Pd/SiO_2"

In the same work the authors evaluated the recycle of the catalyst, showed the possibility of recycled the catalyst for 4 run (using 4 mol% of the Pd load); but were not understand that halides used.

Finally, same in 2009 Ley and co-works have reported an efficient Sonogashira copper-free catalyzed by commercial supported catalyst PdEnCat-TPP30 under microwave heating.**[149a]**

In this work the authors reported efficient coupling between vary aryl halides and terminal alkynes (55-99 % of the yields) using DBU as base in acetonitrile as solvent.

Under the same conditions, the authors reported the coupling of vary vinyl halides such as cis/trans mixture of β-bromostyrene, (E)-1,2-dichloroethene and (Z)-1,2-dichloroethene (**Scheme 2.4.2.7**).

Vinyl halide (equiv.)	*Alkyne (equiv.)*	*CuI/mol%*	*Pd/mol%*	*Solvent (c [M])*	*Temp. [°C]*	*Time [min]*	*Product*	*Isolated Yield [%]*
 (1.0)	 (3.0)	-	10	MeCN (0.2)	75	180	incomplete reaction, complex mixture	-
 (1.0)	 (0.5)	6	4	PhMe (0.33)	100	10		89
 (1.0)	 (0.5)	6	4	PhMe (0.33)	100	10		67
 (1.0)	 (0.5)	6	4	PhMe (0.33)	100	10		67
 E/Z = 7/1 (0.3)	 (0.36)	-	3.5	2.0	100	40	 E/Z = 7/1	60
 E/Z = 7/1 (0.3)	 (0.36)	-	3.5	2.5	100	20	 E/Z = 7/1	66

Scheme 2.4.2.7: Heterogeneous Sonogashira Cu-free reaction of vinyl halides catalyzed by PdEnCat-TPP30

Using a cis/trans-mixture of β-bromostyrene as a vinyl bromide type substrate, the corresponding enynes were isolated as mixtures of their geometric isomers in good yields (60-66 %). When using both cis- and trans-1,2-dichloroethylene as halogen partners were effective in Sonogashira couplings, unfortunately, only traces of the desired enynes were observed when employing the standard conditions. Working in dry toluene as solvent under inert atmosphere with addition of catalytic amount of copper(I) iodide the desired enynes could be generated in reasonable yields.

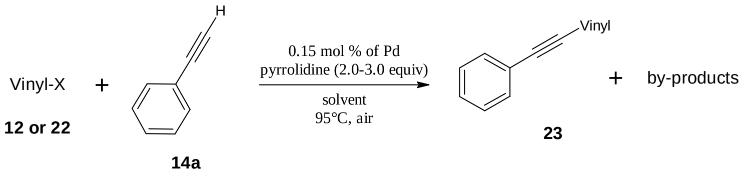
At the light of these limited literature data, and to consider the synthetic importance of this reaction; we decided to investigate the coupling ability of our supported catalysts with vinyl halides (generally considered more reactive of the corresponding aryl halides, but not completely confirm from the literature data above mentioned).

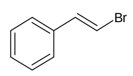
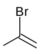
Initially, taking account the performance study with aryl iodides (see paragraph 2.4.2.1) and the presume more reactivity of alkenyl systems regards at aryl halides; we decided to examine the our supported catalysts in the better condition previously individuated on aryl iodides like pyrrolidine as base in DMF/H_2O as solvent using low doses of catalyst (0.15 mol % of Pd) in aerobic atmosphere at the same temperature used with aryl halides.

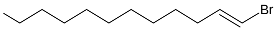
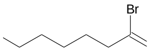
Obviously in these tests we not use the only water as solvent (better condition with Pd-Cu/PVPy catalyst) resulting completely unhomogeneous with all type of reagents and at any temperature and not usable for our scope (possible application in flow). While, given the presume high reactivity of the vinyl halides respect to aryl halide could be interesting tested the efficiency also in the solventless conditions (to compared the reactivity between vinyl and aryl halides).

In detail we examined the coupling ability of our commercial supported catalysts with vinyl halides, and consequently evaluate the true more reactivity of these halides, by screening the previously mentioned conditions for the reaction of vary alkenyl halides such as the commercials (E)-β-bromostyrene (**12a**), 2-bromo-1-propene (**12g**) and the synthetized, but disponible in our laboratory, 2-bromo-1-octene (**12c**) and 1-bromo-1-dodecene (**12h**) with phenylacetylene (**14a**); evaluating from point of view of the yield, reaction time and leaching data (**Table 2.4.2.8**).

Table 2.4.2.8: Efficiency of Sonogasira reaction with vinyl halides



Entry	*Alkenyl halide*	*Solvent*	*Catalyst*	*time (h)*	*Conversion of **12**[b] (%)*	***23**/by-product[c]*	*Yield of **23**[d] (%)*	*Leaching[e] (%)*
1	 **12a**	*DMF/H2O (4:1)*	*PdEnCat-40*	*4.0*	96	*90 : 10*	*48*	-
2			*Fibrecat 1007*	*4.0*	93	*90 : 10*	*51*	0.05
3			*$Pd(PPh_3)_4$-PS*	*4.0*	92	*90 : 10*	*46*	-
4			*$PdCl_2(PPh_3)_2$-PS*	*4.0*	98	*90 : 10*	*49*	-
6		-	*PdEnCat-40*	*4.0*	90	*90 : 10*	*45*	-
7			*Fibrecat 1007*	*4.0*	92	*92 : 8*	*55*	0.08
8			*$Pd(PPh_3)_4$-PS*	*4.5*	93	*88 : 12*	*47*	-
9			*PdCl2$(PPh_3)_2$-PS*	*4.0*	91	*90 : 10*	*45*	-
16	 **12g**	*DMF/H2O (4:1)*	*PdEnCat-40*	5.5	83	*89 : 11*	*50*	*0.32*
17			*Fibrecat 1007*	7.0	99	*89 : 11*	*49*	*0.23*
18			*$Pd(PPh_3)_4$-PS*	6.0	96	*90 :10*	*52*	-
19			*$PdCl_2(PPh_3)_2$-PS*	3.5	90	*99 : 1*	*39*	*0.50*
21		-	*PdEnCat-40*	2.0	93	*77 : 23*	*64 (60)[f]*	*0.27*
22			*Fibrecat 1007*	3.5	98	*75 : 25*	*40*	*0.23*
23			*$Pd(PPh_3)_4$-PS*	3.0	94	*73 :27*	*60*	-
24			*$PdCl_2(PPh_3)_2$-PS*	2.0	93	*65 : 35*	*44*	*4.11*

25	 **12h**	DMF/H2O (4:1)	*PdEnCat-40*	22	n.r	-	-	-
26			*Fibrecat 1007*	22	n.r	-	-	-
27			*Pd(PPh$_3$)$_4$-PS*	22	n.r	-	-	-
28			*PdCl$_2$(PPh$_3$)$_2$-PS*	22	46	*61 : 39*	-	-
29		-	*PdEnCat-40*	24	47	*47 : 53*	-	-
30			*Fibrecat 1007*	24	40	*37 : 63*	-	-
31			*Pd(PPh$_3$)$_4$-PS*	24	n.r.	-	-	-
32			*PdCl$_2$(PPh$_3$)$_2$-PS*	24	72	*50 : 50*	*20*	*0.39*
33	 **12c**	DMF/H2O (4:1)	*PdEnCat-40*	5.0	94	*96 : 4*	*56*	*2.51*
34			*Fibrecat 1007*	10	90	*94 : 6*	*58*	*< 0.02*
35			*Pd(PPh$_3$)$_4$-PS*	8.0	92	*93 : 7*	*61*	*14.83*
36			*PdCl$_2$(PPh$_3$)$_2$-PS*	5.5	94	*97 : 3*	*67*	*0.47*
37		-	*PdEnCat-40*	3.0	98	*93 : 7*	*83 (77)*^{f}	*0.61*
38			*Fibrecat 1007*	5.5	97	*96 : 4*	*80*	*0.10*
39			*Pd(PPh$_3$)$_4$-PS*	3.5	98	*96 : 4*	*82*	*3.59*
40			*PdCl$_2$(PPh$_3$)$_2$-PS*	5.5	98	*96 : 4*	*80*	*2.51*

a) Reaction conditions: 1.0 equivalent of vinyl halide (**12** or **16**), 1.25 equivalent of terminal alkyne (**14a**), 2.00-3.00 equivalent of pyrrolidine, 0.15 mol % of Pd as catalyst, solvent (1.00 mL/mmol), air atmosphere; b) Evaluated by GC analyses and reported as areas of product + by-product on area of start material **12** or **16**; c) Evaluated by GC analyses and reported as areas ratio; d) Gas-chromatography Yield evaluated by internal standard (naphthalene); e) Evaluated by ICP-OES after microfiltration (0.45 mm) and reported as Pd leached wt.% of the total available metal; f) Isolated Yield.

Obviously even these tests showed the formation of by-products in variable amount, but principally formed to enamines. These preliminary tests showed interesting but discordant result.

Using 1-bromo-1-dodecene (**12h**) none of the catalysts tested are efficiently able to promote the reaction both in DMF/H$_2$O that in absence of solvent (conversion of the vinyl halide < 70 %); and the principal product of the reaction is the pyrrolidine addition to the terminal alkyne forming the corresponding enamine to finishing the alkyne. When the 1-bromo-1-alkenes is the (E)-β-bromostyrene (**12a**), the reaction was promoted in short time (4-6 h) with complete conversion, but unfortunately the yields of the desiderated product were moderate if compared with those obtained using aryl iodides in the same conditions. While using the 2-bromo-1-octene (**12c**) the reaction was efficiently promoted with complete conversion and low amount of by-products, to showing in DMF/H$_2$O good yield (56-67 %), but the better performance were obtained in absence of solvent, with excellent yields (80-83 %) in short time (3.0-5.5 h).

For regard the efficiency of the single catalysts, the PdEnCat-40 (**1**) was able to promote the coupling in shorter times with similar yields of the other catalysts in both conditions; while the Fibrecat-1007 (**2**) promote the reaction in long times, but similar yields, showed the smaller leaching date.

Really at regard the leaching data, generally the leaching in DMF/H_2O and in absence of solvent are similar and low (< 1.00 %), independently from the vinyl halide used. However in detail, the supported $PdCl_2(PPh_3)_2$-PS (**3**) and $Pd(PPh_3)_4$-PS (**4**) showed the worse leaching date especially in the reaction with **12c** (> 2.00 %); while the Fibrecat-1007 (**2**) showed the better leaching date independently from the vinyl halide used (< 0.23 %).

At the light of these results, we examined other bases such as 1,4-diazabicycle[2.2.2]octane (DABCO) and N-methyl-pyrrolidine to reducing the formation of enamine by-product (very highly in the reaction between **12h** and **12a**); and one condition successfully used in the Sonogashira Cu-free catalyzed by supported Pd catalyst with aryl halides such as K_2CO_3 as base in EtOH as solvent**[6i, 364]**. In fact with this bases the formation of enamine could be reduced thanks to them hindrance and/or nature. Unfortunately using these conditions none of the catalysts tested were efficiently able to promote the reaction both in DMF/H_2O that in absence of solvent; not showing improvement.

Finally, at the light of these results (above mentioned and resumed in **Table 2.4.2.8**) we proceeded to explore the scope and generality of our supported catalysts, applied the better aerobic protocol (previously reported and used in preliminary tests resumed in **Table 2.4.2.8**) to provide the absence of the solvent. Obviously, to explore the scope and generality of the catalysts we needed of vary vinyl halides, generally not much commercially available and/or at low cost. The vinyl bromides **12** and iodide **22** were synthesized by opportune and selective literature procedure of *one-pot* hydroallumination-bromuration and/or hydroboration-ioduration of terminal alkynes, previously optimized and best mentioned in paragraph 2.6.

The results obtained in this not completely exhaustive study are very interesting and particular.

These confirms the strange low reactivity of 1-bromo-1-alkenes **12**, et in particular, the systems not conjugates like 1-bromo-1-dodecene (**12h**), 1-bromo-1-propene (**12i**), and [[(3E)-4-bromo-3-buten-1-yl]oxy]tris(1-methylethyl)-silane (**12j**) showed completely no reactivity; while bromides with conjugation like 1-[(E)-2-bromoethenyl]cyclohex-1-ene (**12k**) showed very low reactivity with not complete conversion over 5 h and complete consumption of the terminal alkyne in several by-product.

Very low yield were given also with 1-iodo-1-octene (**22**); in fact with this substrate we obtained complete conversion in very short times with vary alkynes, but unfortunately this not represented in term of yields; at exception of the reaction with phenylacetylene (**14a**) and 1-ethynylcyclohexene (**14d**) as terminal alkynes.

At the same mode, these results confirms the major efficiency of the coupling with 2-bromo-1-alkenes with vary terminal alkynes. In fact, the 2-bromo-1-propene (**12g**) showed good yields when coupled with phenylacetylene (**14a**) or 1-ethynylcyclohexene (**14d**), while with aliphatic alkynes showed only mediocre yields (16-21 %).

Regarding the terminal alkynes, the coupling reaction of conjugates alkynes, such as phenylacetylene (**14a**) and 1-ethynylcyclohexene (**14d**) proceeded quite efficiently with vary vinyl halides. While the reaction with aliphatic alkynes appears very difficult.

Particular was the effect of alcoholic group, in fact in the reaction with **12g** the presence of the alcoholic group into the terminal alkyne showed unexpected results. The reaction with 3-butyn-1-ol (**14e**) showed good yield (45 %) in very short time (2.5 h), but using an alkyne theoretically more acid as 2-methyl-3-butyn-2-ol (**14f**) or the same (**14e**) with alcoholic group protect as triisopropylsilyl ether (1-triisopropylsilyloxy-3-butyne, **14g**) the reaction resulted more slow obtaining complete conversion in 5-6 h showing only very mediocre yields (16-21 %).

The same mediocre results were obtained in the reaction between 1-iodo-1-octene (**22**) with 1-triisopropylsilyloxy-3-butyne (**14g**).

2.4.2.4 Conclusions

In conclusion we have individuated and optimized simple, Cu-free, general and environmentally friendly conditions that use pyrrolidine as base in DMF/H_2O as solvent, or "*solventless*" conditions and that allow efficient Sonogashira-type reactions promoted by all our four commercially available supported catalysts. It is worth noting that these studies on Sonogashira-type reactions confirmed and completed our previous work on the use of Pd EnCats in this reactions,**[162i]** but are new as regards the use of commercial $PdCl_2(PPh_3)_2$-PS (**3**), $Pd(PPh_3)_4$-PS (**4**) and Fibrecat 1007 (**2**).

Moreover, we have developed two new supported catalysts MVS-prepared that appear very efficient in the same above mentioned conditions. One of these is the bimetallic Pd-Cu/PVPy (**7**), for which it has been ascertained an interesting and strong dependence of the catalytic activity on the peculiar bimetallic nature (it is essentially an alloy).

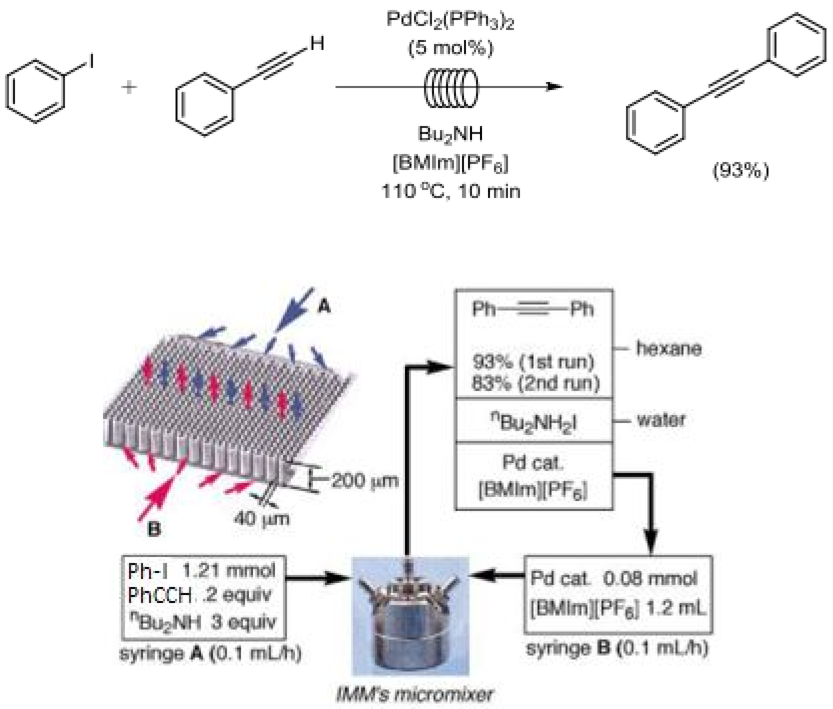
Generally the studied catalysts gave high catalytic activities in Sonogashira-type cross-coupling reaction performed in batch mode with both aryl and vinyl halides, but the specific results depend from the type of halide and terminal alkyne used.

As aryl bromides alkynylation, it was necessary to find different conditions; in particular, it has been developed original "one- pot" domino processes Halex-Sonogashira-type, thanks to the addition of KI in the reaction mixture (carried out under suitable conditions, carefully developed); this expedient allowed to perform efficient alkynilations of bromoarenes promoted by **7** and **2**. However, even these conditions require low metals loads and are not affected by the presence of air. Under these new conditions the alkynylation of bromobenzene with phenylacetylene gave a moderate yield, but with different bromoarenes much better results were obtained.

It was also found that the alkynilation of vinyl bromides and iodides is more problematic than appears from the limited informations reported in literature. In fact these systems react in conditions and times similar to that of aryl iodides, but the yields of the corresponding product are much lower, particularly in the reaction with vinyl iodides.
Probably vinyl halides (and in particular the iodides) result more sensible and less stable in these reaction conditions, but unfortunately our supported catalysts, but in general all supported catalyst, require more drastic conditions (respect to homogeneous catalysts) to promote the cross-coupling.

2.4.3 Sonogashira copper-free reaction in flow

Sonogashira couplings have become a routine transformation in synthetic chemistry and as such there has been much interest in translating their use into continuous flow processing. A demonstration of the efficiency of flow *vs* batch for Sonogashira copper-free couplings was undertaken by Fukuyama and co-workers.**[365]** They reported Sonogashira coupling of iodobenzene and phenyl acetylene was performed in an ionic liquid ([BMIm][PF_6]) in the absence of a copper salt by using an IMM micromixer reactor, comprising 2×15 interdigital channels (dimensions = 40 µm (wide) × 200 µm (deep)) (**Scheme 2.4.3.1**).

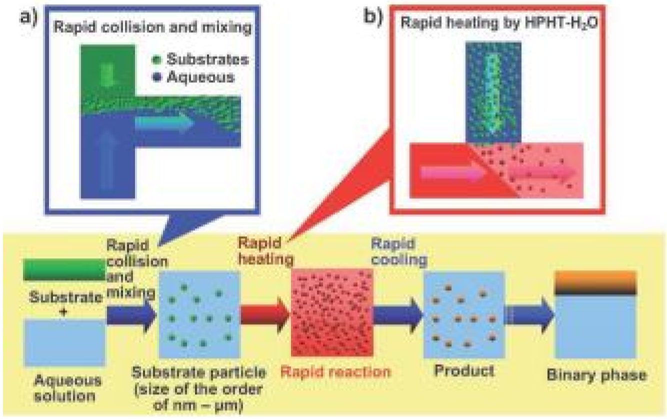


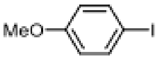
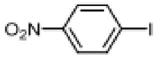
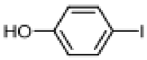
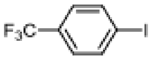
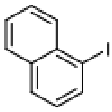
Scheme 2.4.3.1: Comparison of batch *vs* flow Sonogashira copper-free coupling

With $PdCl_2(PPh_3)_2$ (5 mol%) as the catalyst and $^nBu_2NH$ as the base at 110 °C, the authors obtained diphenylacetylene in excellent yield (93 %) yield in a 10 min residence time, which compared favorably with the results obtained in batch. Moreover, after extraction of the product and ammonium salts with hexane/water, the $[BMIm][PF_6]/PdCl_2(PPh_3)_2$ solution was reused up to 3 times, with yields gradually decreasing to 63% for the final run.

An efficient continuous flow methodology for copper-free Sonogashira couplings was reported by Kawanami and Ikushima taking advantage of a high pressure and temperature water (HPHT-H2O) reaction medium to promote rapid reaction times (residence time = 0.1–4.0 s) in a homogeneous microfluidic system (with fluid channels typically in the submillimeter range). **[225]**

Employing a $PdCl_2$ (2 mol%) catalyst coupling of aryl iodides with phenylacetylene was achieved in excellent yields in residence times of less than 1 s, at 250 °C and a 160 bar by using an efficient tubular reactor where they met at a T-mixer, generating a fine dispersion of phenyl acetylene (nm to µm) in the aqueous phase (**Scheme 2.4.3.2**).

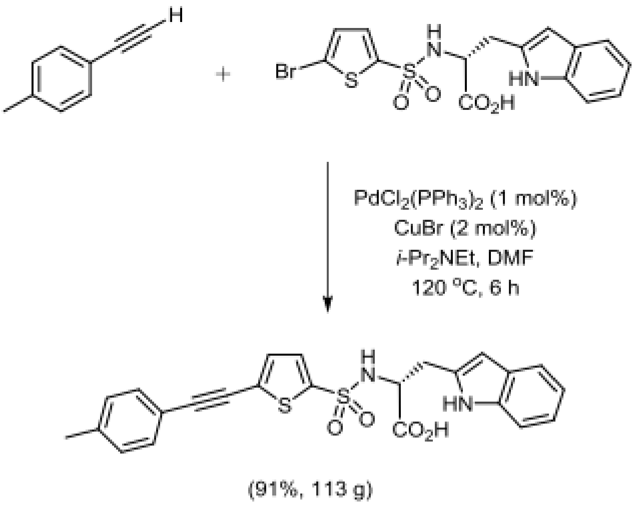


Entry[a]	Ar-I	Time (s)	Yield (%)
1		4	99
2		0.1	90
3		0.1	91
4		0.1	92
5		0.1	88
6		0.1	99
7		0.1	98
8		1.0	81

Scheme 2.4.3.2 : Schematic illustration of a reaction under the conditions of step-by-step rapid mixing and heating in high-pressure, high-temperature water .

HPHT-H_2O provides excellent mixing and completely dissolves all of the reagents under this high pressure/temperature condition, negating the need for organic solvents. It was also postulated that hydrogen bonding occurs between the terminal acetylinic hydrogen and H_2O, thus lowering the activation energy, speeding up the reaction and negating the need for a Cu co-catalyst.

More recently, Fukujama and co-workers reported the scale-up of a Sonogashira coupling in flow, for the production of a matrix metalloproteinase inhibitor (**Scheme 2.4.3.3**).**[367]**



Scheme 2.4.3.3 : 100 g scale production of a metalloproteinase inhibitor in flow

The authors synthesised the desired product on a 100 g scale with a residence time of 20 min, in the presence of $PdCl_2(PPh_3)_2$ (1 mol%), CuBr (2 mol%) and i-Pr_2NEt at 120 °C in DMF. The system was run continuously for 6 h and gave an overall yield of 113 g (91%).

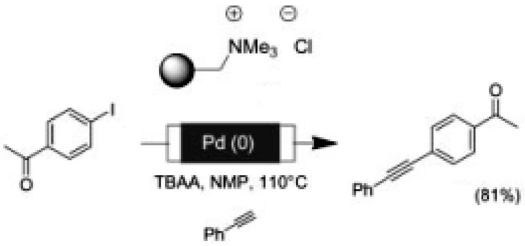
2.4.3.1 State of art of Sonogashira reaction with aryl and alkenyl halides in flow mode

As previously mentioned in paragraph 1.3.1; in general for all cross-coupling there are a wide variety of different catalytic technologies available for conducting cross-couplings in continuous flow. Traditionally heterogeneous systems were favoured due to their ease of separation, recycling and high surface areas making for more efficient processing. **[124, 190b]**.

For regard the Sonogashira cross-coupling reaction, despite a broad range of solid supported catalysts were developed and applied in batch conditions (as previously mentioned in paragraph 2.4.1); currently, it is still very limited their application in continuous-flow chemistry.

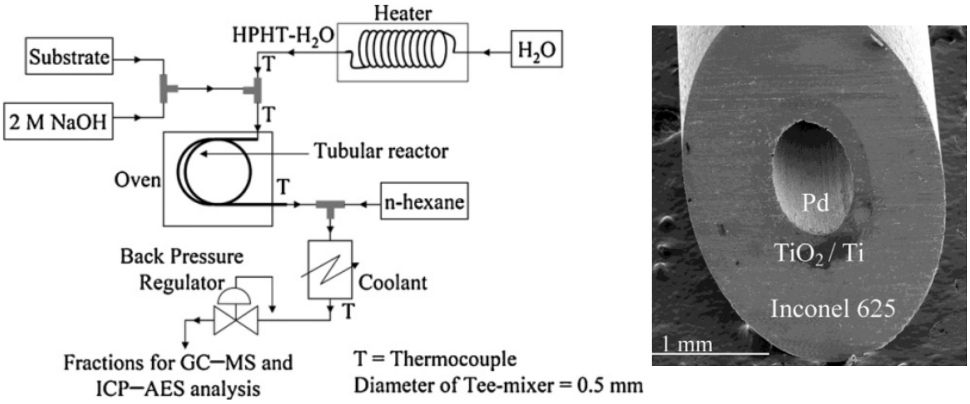
In 2004 Kirschning and co-workers reported the first use of a continuous-flow reactors with a monolithic glass/polymer composite interior are loaded with palladium particles by ion exchange followed by reduction (PASSFlow reactor).**[37]**.

Using the palladium(0) particles, the Sonogashira reaction of phenylacetylene and 4-iodoacetophenone led to complete consumption of the starting material and formation of alkyne product with only negligible traces (< 9%) of homo-coupling product (**Scheme 2.4.3.4**).



Scheme 2.4.3.4 : Ligand-free palladium-catalysed Sonogashira reactions in the PASSflow reactor

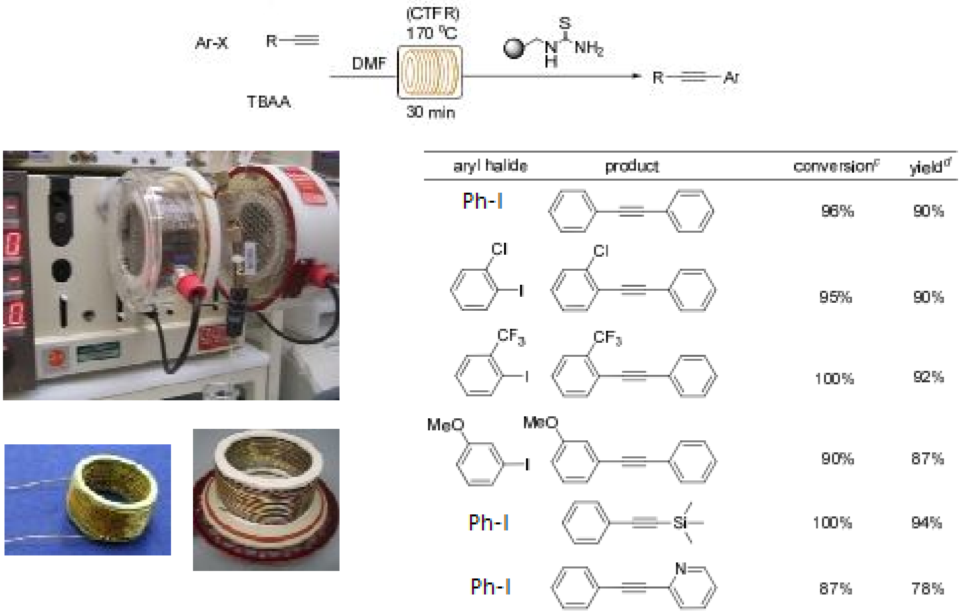
Only over the 2011 the use of continuous flow packing with supported catalysts were increased. In 2011 Kawanami et collaborators developed a Pd-Cu alloy on the inner surface of the tubular reactor and investigated Sonogashira C-C coupling under elevated temperature and pressure (**Scheme 2.4.3.5**).**[368]**



Scheme 2.4.3.5 : Diagram of high pressure and high temperature water flow reactor system and cross-sectional SEM image of the triple layered catalytic tubular reactor.

Under the optimized reaction conditions of 250 °C and 16 MPa of pressure, diphenylethyne was obtained with good yield and 100% selectivity within a very short residence time of ~1.6 s. The reaction proceeds without any additional promoters, additives or organic solvents. Leaching of catalytic metal from the reactor tube was not found under the studied reaction conditions. Alloying of Pd with Cu remarkably improved the efficiency of the reaction due to co-catalytic effect that is related to the easy electron transfer between two metals.

In the same period, Zhang and co-workers reported a convenient and efficient flow method for Sonogashira couplings, using a commercially available copper tube flow reactor (CTFR), obtaining high yields in 30 minutes at 170 °C (**Scheme 2.4.3.6**).



Scheme 2.4.3.6 : CTFR reactors and Sonogashira in CTFR reactor

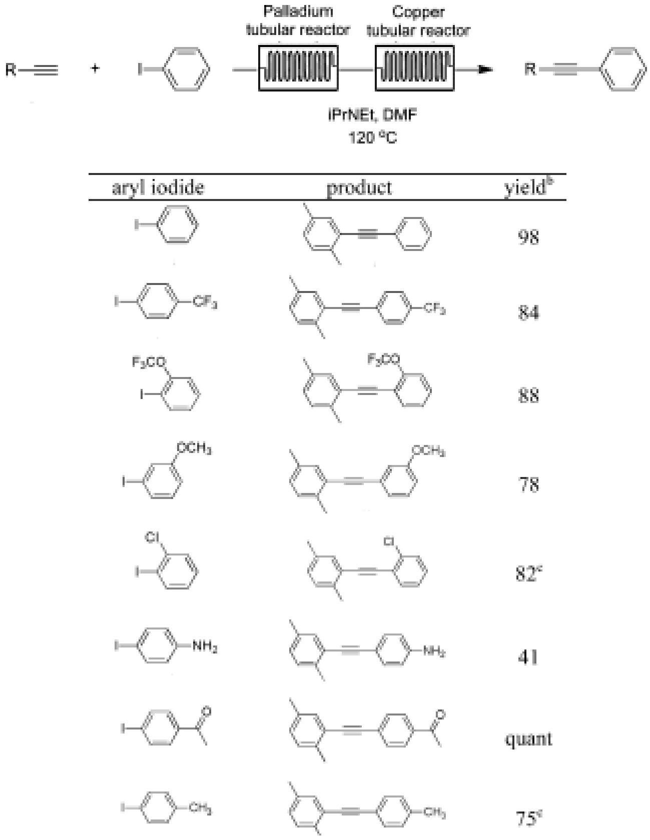
Under this condition no added of Pd was necessary, and notably Hay-Glaser coupling by-products (symmetrical 1,3-diynes) were not observed in any case, possibly attributable to the flow reaction format (rate of alkyne addition and short residence time).**[369]**

Only more recently, the use of continuous flow packing with supported catalysts were reported in literature.

In 2012, Dormán et collaborators reported a rapid catalyst evaluation for Sonogashira coupling in continuous flow, applied a continuous flow device for rapid catalyst screening of 4 commercial heterogeneous catalysts (Fibrecat 1001, Fibrecat 1007, Pd/C and $PdCl_2(PPh_3)_2$-PS) over many Sonogashira coupling reactions together with longevity estimation.**[171]**

The authors reported 24 reactions (6 reactions x 4 catalyts) of 10 minutes with flow-rate of 0.1 mL/min at 100 °C and 70-100 bar of pressure, obtaining good yield and highly selectivity with good yields.

Finally, it is interesting to mention the most recently systems to use heterogeneous palladium-copper dual reactor, reported in literature after the starting of this PhD work. In 2013 Lee and co-workers reported the development of a heterogeneous palladium catalyst coated tubular reactor was placed in line with copper tubing, This system was using as continuous flow platform in a Sonogashira C-C coupling reaction, to evaluate the performance (**Scheme 2.4.3.7**).**[370]**



Scheme 2.4.3.7 : Palladium-Copper Dual Reactor in Sonogashira reaction

The reaction with the Pd-Cu flow reactor afforded the desired product in quantitative conversions (Scheme 2.4.3.7) maintained the performance even after a continuous run of 10 cycles. Notably, the Pd collected from the Pd-Cu dual reactor was much lower (51.7 ppb) than the single Pd reactor (3785 ppb), probably due to the re-deposition of Pd particles on the Cu reactor.**[32b]**

However, the backend of the continuous flow was fitted with a chromatographic column, packed with metal scavenging resin (QuadraPure TU), and trace amounts of Pd and Cu were effectively trapped with less than 20 ppb of these metals detected using ICP-OES.

While, in 2014 Srogl and Voltrova reported a Sonogashira cross-coupling under non-basic conditions in flow regime comparing the result obtained using two in-line reactors (one for Pd/Al_2O_3 and the other for Cu/Al_2O_3) with the result obtained using a single reactor packing with Escat ™ 1241 (5% Pd on alumina powder) : (0.1% Cu2O on alumina powder)=17:1 at 80 °C in dried THF–DMA 9:1.**[371]**

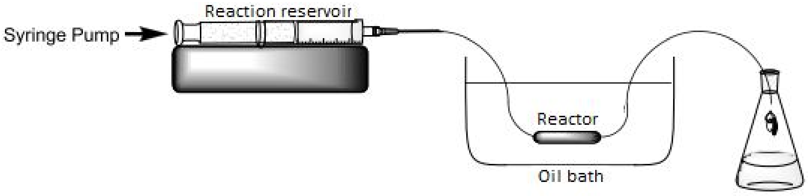
2.4.4 Study and application of packed-bed reactors in Sonogashira Cu-free reactions under continuous-flow

As outline in paragraph 1.4, our studies focused also on applicability of supported catalysts under most efficient and feasible reaction condition in continuous-flow process. In fact, for regards the C-C and C-Heteroatoms cross-coupling reactions, and in particular for Sonogashira-Hagihara coupling; it is possible to affirm on the basis of literature data, that the application of the supported catalysis, in continuous-flow reactors is most limited, and to present problems and difficulties not yet actually overcome such as: difficult availability, need for high catalytic loads, inadequate performance, inadequate productivity and elevated leaching; that more them not really useful from applicative and industrial point of view (see above paragraph 2.4.3.1).

Given the good results obtained in batch mode (paragraph 2.4.2), we have been started the planned study and development of original packed-bed mini-reactors of design and construction extremely simple and cheap (see paragraph 2.2).

As the light of the results obtained in paragraph 2.4.2 and taking account the necessity of the reaction conditions most homogeneous possible for optimal application in flow.

For regard the application of the mini-reactors in Sonogashira Cu-free coupling, we test the model reaction between 4-iodoanisole (**8u**) with phenylacetylene (**14a**) (**Scheme 2.4.2.1**, paragraph 2.3.2) applied the more efficient, previously described in paragraph 2.4.2, reaction condition in batch mode like 1.3 equivalents of terminal alkyne, 2.0 equivalents of pyrrolidine as base, 1,33 mL/mmol of DMF/H_2O 4:1 as solvent, at 95 °C; using, in the tests, reactors packed with the four commercial catalysts pure or mixed at glass beads in different volume ratio (as subsequently better describe case to case) connected directly to one reservoir (**Scheme 2.4.4.1**).

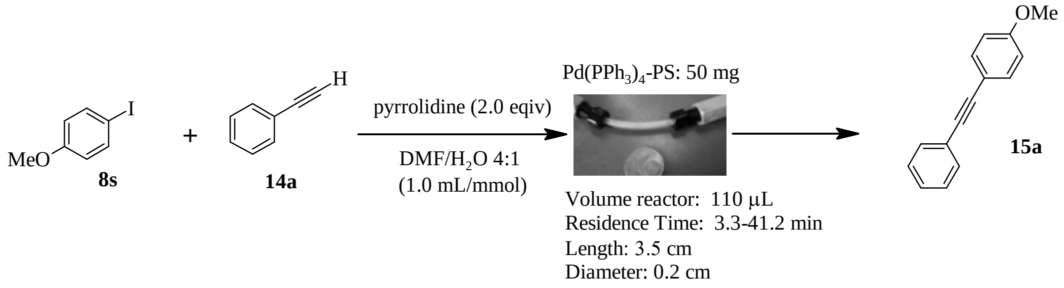


Scheme 2.4.4.1 : Generel experimental set-up of the flow systems used in our Sonogashira Cu-free tests

Initially, we examined the reactors packing with 50 mg of the pure commercial catalysts (length of 3.0-4.5 cm). The reaction mixture prepared directly at air was eluted in the reactor with a residence time equal at the reaction time in bath mode (0.5 h) corresponding at 0.16 mL/h of flow-rate.

In the explorative test (with reactor packing with 50 mg of $Pd(PPh_3)_4$-PS) the reaction mixture were eluted at 0.16 mL/h corresponding at residence time of 41 min, and we observed complete conversion. Therefore we increasing the flow-rate at research the maximum flow-rate that permitted to obtain complete conversion in the reaction. After these explorative tests we observed complete conversion until at flow-rate of 0.75 mL/h (corresponding at residence time of 9 min) (**Table 2.4.4.1**).

Table 2.4.4.1: Variation of flow-rate



mmol of **8s**	Flow-rate (mL/h)	Residence time (min)	Conversion of **8s** (%)
0.52	0.16	41.2	99
0.52	0.32	20.6	99
0.52	0.75	8.8	99
0.52	1.00	6.6	70
0.52	2.00	3.3	40

Individuated the optimum parameters of flow-rate we examined the effect of different packing typology on all commercial catalysts. For this we tested reactors packing with commercial catalysts pure and mixed with glass beads in 1:1 or 1:10 volume ratio.

We select the glass beads to dilute the catalysts because these are inert not functionalized materials with similar size (150-200 μm) of the commercial catalysts object of this work.

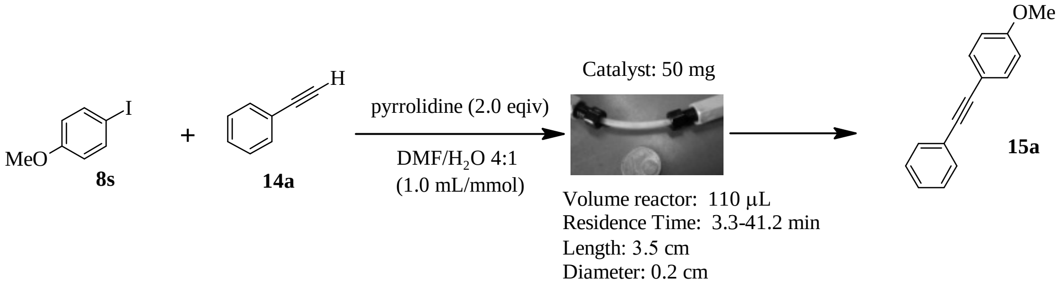
Initially we tested the other Pd catalysts (Fibrecat 1007, PdEnCat-40 and $PdCl_2(PPh_3)_2$-PS) pure, under previously optimized conditions.

The reactors were prepared introducing the catalyst into the reactors as slurry or dry. Then the catalyst is compressed (2-4 bar) and conditioned with about 5 mL of the DMF/H_2O (4:1); their length varies from case to case, but usually is between 3.0 and 4.5 cm.

The reaction mixture, aryl halide, terminal alkyne and pyrrolidine in DMF/H_2O 4:1 (1.00 mL/mmol of **8s**); was eluted in the system at the same flow-rate of 0.75 mL/h with a general residence time usually range to 7.5-11.3 min.

Under these reaction conditions the catalysts showed highly conversion (> 98 %) except the PdEnCat-40 (**Table 2.4.4.3**) that showed the polymer matrix to collapse, melt and eventually block the tube (phenomena already given in the its use in Suzuki coupling, see paragraph 2.3.4, and reported in literature by Ley for its use under MW heating**[146f]**).

Table 2.4.4.3: Sonogashira Cu-free coupling using reactors packing with pure catalysts[a]



Fraction	Catalyst (mmol of Pd)	Vol. Fractions (mL)	**8s** eluted (mmol)	Conversion of **8s**[b] (%)	Pd release[c] (%)
1	$Pd(PPh_3)_4$-PS (0.035)	1.00	0.75	99	
2		1.00	0.75	80	
3		1.00	0.75	60	
4		1.00	0.75	46	
5		1.00	0.75	42	
Total		**5.00**	**3.75**	**65**	**0.10**
1	Pd EnCat-40 (0.055)	1.28	0.60	0	
2		1.28	0.60	0	
Total		**2.56**	**1.20**	**0**	**-**
1	Fibrecat 1007 (0.036)	3.00	2.25	99	
2		3.00	2.25	99	
3		1.60	1.20	60	
4		1.40	1.05	40	
Total		**9.00**	**6.75**	**83**	**0.98**
1	$PdCl_2(PPh_3)_2$-PS (0.051)	5.00	3.75	99	
2		3.00	2.25	99	
3		5.50	4.13	99	
4		1.00	0.75	84	
5		1.90	1.42	80	
6		1.00	0.75	70	
7		1.00	0.75	60	
Total		**18.40**	**14.25**	**90**	**0.97**

a) Reaction conditions: 1.0 equivalent of aryl halide (**8s**), 1.2 equivalent of phanylacetilene (**14a**), 2.0 equivalent of pyrrolidine, 95 °C; b) Evaluated by GC analyses; c) Evaluated by ICP-OES

The result obtained using these reactors (packing with pure catalysts) were interesting, but not yet comparable, in term of efficiency**[309]**, with the result obtained in the same reaction conditions in batch reactors.

In detail, the reactor packing with $PdCl_2(PPh_3)_2$-PS showed the better efficiency obtained using the reactor packing with pure catalyst (90 % of medium conversion) eluted 14.25 mmol of **8s** with global efficiency of 279 (corresponding at 0.36 mol% of Pd load in batch), but the productivity and efficiency are not yet comparable with that obtained in batch mode (efficiency of 1000 corresponding at 0.10 mol% of Pd load with complete conversion).

The PdEnCat-40 result the only system that showed problem of blocking the reactor, resulting none able to promote the coupling in flow under these conditions, in fact this system not showed initial conversion.

The reactors packing with the Fibrecat-1007 (**2**) and $Pd(PPh_3)_4$-PS (**4**) showed good conversions, with efficiency of 133 and 103 respectively. Result were most inferior at the data obtained with the same catalysts in batch mode.

Most interesting result the Pd release of the reactors (analysed directly the contents of the palladium in the solution out from the reactors without microfiltration); in fact, despite the activity of the catalysts drops after many eluted **8s** (varied from case to case), the data of Pd released were very low (< 1.0 % of the Pd packing into the reactors).

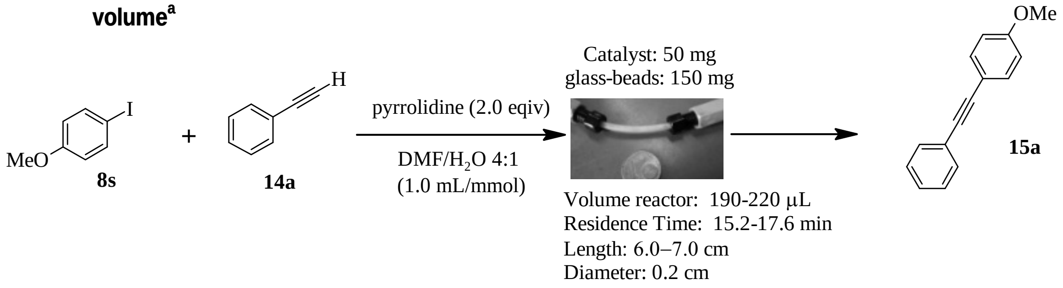
These results were deduce that the loss of activity were must at passivation of the palladium or structural modification of the supported catalysts.

At the light of these positive results, to better the performances in the Sonogashira Cu-free coupling with these catalysts, we decided to prepare the reactors “diluted” introducing as dry the commercial catalysts (50 mg) mixed with an approximately 1:1 volume ratio of the above mentioned glass beads (150 mg). The obtained reactors had lengths varies from case to case, but usually is between 6.0 and 7.0 cm corresponding at internal volume of 190-220 μL.

These reactors were examined in the same model reaction maintaining unchanged the parameters (concentration, flow-rate, etc.) of the above mentioned tests that use the pure catalysts.

Under these conditions the systems showed similar medium conversions (> 60 %) respect at the data obtained with reactors packing with pure catalysts, within 15-18 minutes of the residence times and keep them for long time (20-50 hours), showed, for the best catalytic systems, an efficiency of 400 and a limited leaching of Pd (**Table 2.4.4.4**).

Table 2.4.4.4: Sonogashira Cu-free coupling using reactors packing with catalysts mixed glass beads in 1:1 volume[a]



Fraction	Catalyst (mmol of Pd)	Vol. fractions (mL)	**8s** eluted (mmol)	Conversion of **8s**[b] (%)	Pd release[c] (%)
1	Pd(PPh$_3$)$_4$-PS (0.035)	4.25	2.00	99	
2		2.15	1.00	70	
3		4.25	2.00	60	
4		4.25	2.00	40	
Total		**14.90**	**7.00**	**67**	**0.68**
1	Pd EnCat-40 (0.055)	4.25	2.00	10	
2		2.15	1.00	0	
Total		**6.40**	**3.00**	**7.0**	**-**
1	Fibrecat 1007 (0.036)	6.40	3.00	99	
2		6.40	3.00	68	
3		4.25	2.00	30	
Total		**17.05**	**8.00**	**70**	**1.00**
1	PdCl$_2$(PPh$_3$)$_2$-PS (0.051)	6.40	3.00	99	
2		6.40	3.00	99	
3		4.25	2.00	99	
4		4.25	2.00	99	
5		4.25	2.00	99	
6		4.25	2.00	90	
7		4.25	2.00	85	
8		4.25	2.00	80	
9		4.25	2.00	43	
Total		**38.55**	**20.00**	**89**	**0.96**

a) Reaction conditions: 1.0 equivalent of aryl halide (**8s**), 1.2 equivalent of phanylacetilene (**14a**), 2.0 equivalent of pyrrolidine, 95 °C; b) Evaluated by GC analyses; c) Evaluated by ICP-OES

The reactor packing with the catalysts mixed at glass beads showed a higher efficiency respect to using the reactor with pure catalyst.

The Pd(PPh$_3$)$_4$-PS mixed at glass beads showed similar conversion at the test of pure catalyst (70 % of medium conversion), but eluted 7.00 mmol of **8s** with global efficiency of 200 (corresponding at 0.5 mol% of Pd load in batch).

The PdEnCat-40 result the only system none able to promote the coupling in flow under these conditions, in fact this system showed a very low initial conversion (10 % in the first 2.00 mmol of eluted **8s**). However, this result was most better at the result obtained using the reactor packing with pure catalyst, and the phenomena of blocking the reactor were not observed.

The better performances in this reaction were achieved again by packing the reactors with the $PdCl_2(PPh_3)_2$-PS mixed with glass beads, that showed a high conversions within 17 minutes and keep them for long time (51 hours), with a efficiency of 400, respect at 1000 of the batch mode.

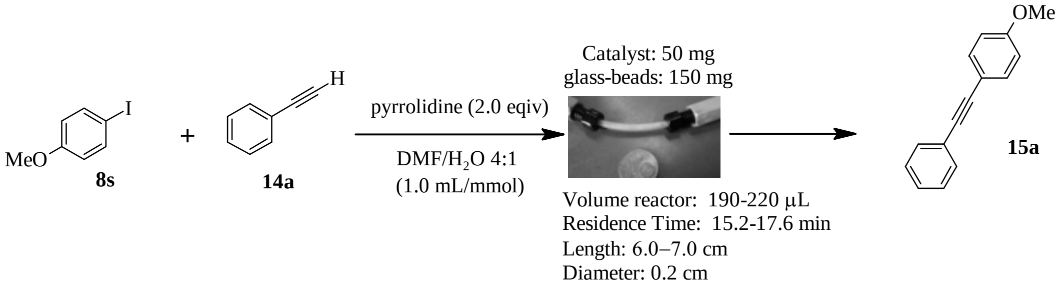
For regard the Pd release of the reactors, the data were similar at result obtained with pure catalysts.

At the light of these positive improvement of the results, and taking to account the result obtained in the continuous-flow Suzuki coupling; we decided to prepare the reactors most diluted introducing as dry the commercial catalysts (5.0 mg) mixed with an approximately 1:10 volume ratio of the above mentioned glass beads (150 mg). The obtained reactors had lengths varies from case to case, but usually is between 4.0 and 5.0 cm corresponding at internal volume of 126-160 μL.

These reactors were examined in the same model reaction maintaining unchanged the parameters (concentration, flow-rate, etc.) of the above mentioned tests that use the pure and 1:1 mixed catalysts.

Unfortunately, under these conditions the systems showed very low conversion at exception of the only $PdCl_2(PPh_3)_2$-PS that showed a similar conversion respect at the date obtained with reactors 1:1 mixed (**Table 2.4.4.5**).

Table 2.4.4.5: Sonogashira Cu-free coupling using reactors packing with catalysts mixed glass beads in 1:10 volume[a]

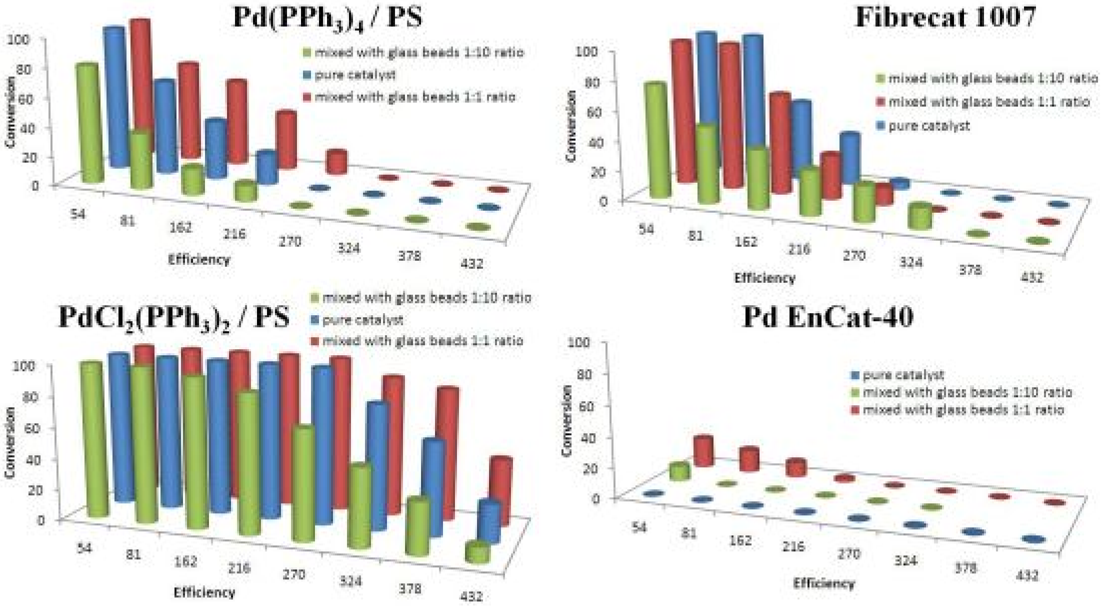


Fraction	Catalyst (mmol of Pd)	Vol. fractions (mL)	**8s** eluted (mmol)	Conversion of **8s**[b] (%)	Pd release[c] (%)
1	$Pd(PPh_3)_4$-PS (0.0039)	0.10	0.075	99	
2		0.10	0.075	86	
3		0.10	0.075	57	
4		0.10	0.075	38	
5		0.10	0.075	26	
Total		**0.50**	**0.375**	**61.0**	
1	Pd EnCat-40 (0.0055)	1.20	0.90	2	
2		0.10	0.075	0	
Total		**0.84**	**0.40**	**23.3**	**-**

1	Fibrecat 1007 (0.0051)	0.10	0.075	93
2		0.10	0.075	76
3		0.10	0.075	62
4		0.10	0.075	52
5		0.15	0.1125	47
6		0.10	0.075	43
7		0.15	0.1125	40
Total		**0.80**	**0.60**	**57**
1	$PdCl_2(PPh_3)_2$-PS (0.0055)	0.10	0.075	99
2		0.10	0.075	99
3		0.10	0.075	99
4		0.10	0.075	99
5		0.10	0.075	96
6		0.10	0.075	96
7		0.10	0.075	96
8		0.10	0.075	96
9		0.10	0.075	88
10		0.10	0.075	88
11		0.10	0.075	70
12		0.10	0.075	70
13		0.10	0.075	50
14		0.10	0.075	50
Total		**1.40**	**1.05**	**85**

a) Reaction conditions: 1.0 equivalent of aryl halide (**8s**), 1.2 equivalent of phanylacetilene (**14a**), 2.0 equivalent of pyrrolidine, 95 °C; b) Evaluated by GC analyses; c) Evaluated by ICP-OES

The results obtained are very interesting. In fact, the reactors packing with commercial catalysts mixed at glass beads in 1:10 ratio showed very lower efficiency respect at 1:1 ratio and at use of pure catalysts as reported in **Scheme 2.4.4.2**.



Scheme 2.4.4.2: Efficiency comparison between reactors packing with catalysts pure and mixed with glass beads in 1:1 and 1:10 ratio

In detail, for all catalysts, these tests showed a similar efficiency between the different filling type, but not yet comparable that to obtained in batch mode (corresponding at efficiency of 1000). Anyway the better performances in these reactions were achieved packing the reactors with the commercial catalysts mixed with an approximately equal volume of the glass bead. In fact, these reactors allowed high conversions within 15-17 minutes of residence time, with contained leaching.

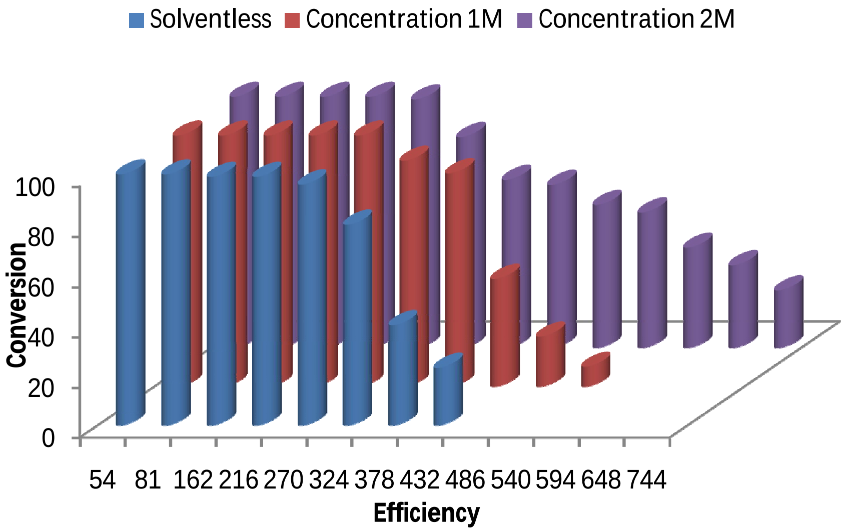
However, The best performances in this reaction were achieved by packing the reactors with the $PdCl_2(PPh_3)_2$-PS, that showed a high conversions within 16 minutes and an fairly good efficiency about 400, but the productivity and efficiency are not yet comparable with that obtained in batch mode.

More particular appear the use of catalysts mixed at glass beads in ratio 1:10, that showed the worst efficiency. Probably this effect was due at the reduced amount of Pd present in the reactors, that quickly reduce its catalytic activity. In fact to confirm this, in the first eluted fraction of 0.075 mmol in the majority of the catalysts we observed complete, or almost, conversion; which then falls quickly. Moreover, to exclude that this effect could result from excessive flow-rate (the same used in the other systems), we examined the effect of the flow-rate in the reactor packing with $Pd(PPh_3)_4$-PS mixed with glass beads in 1:10 ratio.

Unfortunately we have observed the same result even though we reduced the flow-rate to 0.50 and to 0.35 mL/h.

Given these results we decide to increase the efficiency of the better reactor fill. To do this we examined the possibility of increasing the efficiency of the reactor packed with palladium dichlorobistriphenylphosphyne mixed at glass beads (1:1 volume ratio), performing (normalized the flow-rate) the study at different concentrations.

In these study we have compared the efficiency of the reactor using different reaction mixture concentrations such as 1 Molar (the normal concentration used in all precedent tests), 2 Molar, and solvent-free; showing a drastic reduction in the efficiency when using the solvent-free condition, and an increase of the efficiency concentrating at half volume (**Scheme 2.4.4.3**).



Scheme 2.4.4.3: Efficiency comparison of the $PdCl_2(PPh_3)_2$-PS mixed at glass beads reactors at different reaction mixture concentration

In these tests we achieved a comparable batch efficiency (0.13 mol% total catalytic load of the reactor, respect at 0.10 mol% used in batch mode) in the case of 2 Molar concentration, that can be already classified among the best so far reported in the literature, but not yet satisfactory in term of productivity showing a conversion medium of the 70 %.

Finally, taking into account the literature data; we decide to compare our obtained results with two interesting reaction conditions used with supported catalyst in flow such as MeOH or EtOH/H_2O as solvent.

These tests were performed at concentration of 1 mmol/mL, using a flow-rate of 0.30 mL/h at 95 °C.

The results obtained showed good efficiency (450-238 respectively) and conversion (63-66 respectively); but generally inferior at result obtained under our condition.

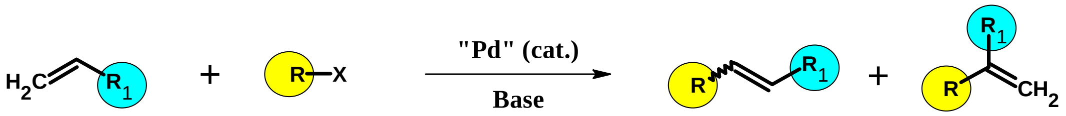
2.4.4.1 Conclusions

In conclusion, at the light of these results (resumed in **Table 2.4.4.4-2.4.4.6**) we could affirm that with our packed-bed reactors (at least if packed with $PdCl_2(PPh_3)_2$-PS, **3**), it was possible to reach performances equivalent to that those obtained in batch with the same catalyst (used in similar conditions).

In addition, the performances achieved with these catalysts and our reactors (and then in a simple, practical and cheap way) appear almost comparable to the best obtained in the literature works mentioned in paragraph 2.4.3.1 (which usually employ apparatuses/catalysts/procedures complex, expensive and/or not readily available). In fact, the great majority of described packed bed reactors, used in Sonogashira Cu-free reactions, works “de facto” with catalytic loads in the range from 1.0 to even more than 20 mol%, while the our reactors reach the 0.2 mol% in the better cases.

2.5 Mizoroki-Heck reaction and classical catalyst used

The Mizoroki-Heck reaction**[5]** is the vinylation characterised by a metal catalyzed (principally palladium) cross-coupling of two sub-units, an olefine (most frequently monosubstituted, given their higher reactivity and the best regiochemical control) and an organohalide or triflate (aryl and alkenyl halides) to give variously substituted olefinic compounds, in the presence of a base (**Scheme 2.5.1**).**[5b, 11b, 31b, 372]**



R = **1-alkenyl, (hetero)aryl**

R_1 = **1-alkenyl, (hetero)aryl, ester**

X = **I, Br, Cl, OTf**

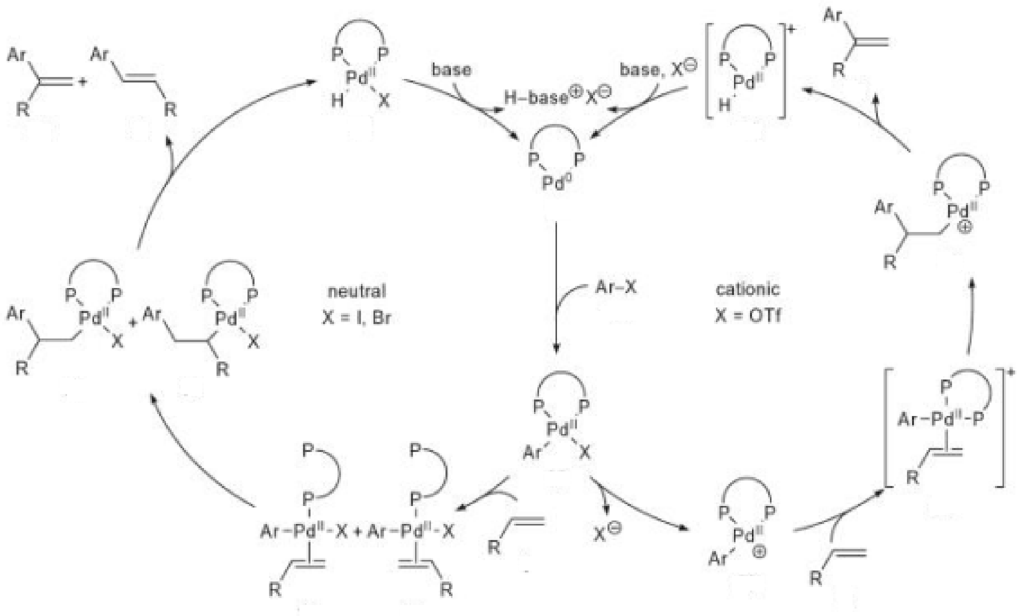
Scheme 2.5.1. Generic scheme of Mizoroki-Heck cross-coupling reaction

This reaction is one of the most important reactions for the formation of C–C bonds in organic synthesis, from both the research and industrial points of view since its discovery in 1972 **[11b, 27, 372]**. In fact, this reaction constitutes a powerful and versatile method for the synthesis of polyfunctional compounds, e.g., dienes, cinnamic esters, and other variously substituted olefinic compounds, which are primarily applied as dyes, UV absorbers, and intermediates for pharmaceuticals, agrochemicals, and fragrances **[210a]**. The reaction is also useful in polymerization chemistry, giving access to conjugated polymers applicable, e.g., as new materials for optoelectronic devices **[5b]**.

The popularity of Mizoroki-Heck reaction is due to its versatility, and efficiency in the synthesis of C(sp^2)-C(sp^2) bond and most important of all, high regio- and stereo selectivity in the synthesis of C(sp^2)-C(sp^2) bonds.**[184a]**

A variety of substrates and functional groups can be used under the reaction conditions, which is ideal to synthesize many intermediates in constructing the complex drug molecules.

Besides that, the non-toxicity and simplicity related to the preparation of organoboron compounds (e.g. aryl, vinyl, alkyl);**[254h, 257]** their relative stability to air and water, combined with the relatively mild conditions for the reaction as well as the formation of nontoxic by-products, makes Suzuki-Miyaura reaction an important method for enlarging carbon skeleton. Unfortunately, the organoboron compounds have a low nucleophilicity date from the small electronegativity difference between the boron and the carbon atom. To reduce this problem requires the addition of negatively charged species that complexing the boron atom, make the organoboron compound more nucleophilic.



Scheme 2.5.1: General catalytic cycle of Mizoroki-Heck

The general mechanism of the Mizoroki-Heck reaction can be seen on **Scheme 2.5.1**. The first step of the catalytic cycle is attachment of palladium (Pd) catalyst to the halides by oxidative addition, which increases the oxidation state of Pd catalyst from 0 to 2. This step is much less sensitive to the substituents in the unsaturated system but much more sensitive to the nature of nucleophile and the strength of C-X and M-X bonds**[5b]**.

The oxidative addition of the aryl halide (or equivalent reagent) is followed by an alkene coordination and insertion of the aryl into the alkene to form an alkyl intermediate. If the halide in the aryl moiety instead is replaced by a weakly coordinating anion, such as OTf, a cationic catalytic cycle will occur (**Scheme 2.5.1** at right). In the opposite case, an anionic catalytic cycle can take place if an excess of anions, such as Br^-, is present and replaces the ligand.**[373]** The insertion step of the Heck reaction occurs through a planar or nearly planar complex, where the metal, alkene and aryl/vinyl form a coplanar assembly.**[5c]** This feature ensures that the insertion process occurs in a *syn* manner, and is stereospecific, something that was observed experimentally by Heck already in the end of 1960s.**[5g]** For substituted olefins, the selectivity between the α- and β-insertion is dependent on many different factors. The preferred reaction pathway (neutral or cationic), substitution pattern on the olefin, steric and electronic preferences of the Pd-ligands, and the solvent are some factors capable of influencing the product distribution. In general it can be postulated that the electronic properties of the olefin are important for the regioselective outcome. Olefins can be divided into three different groups: electron-rich, neutral, and electron-poor. Electron-poor olefins almost exclusively lead to terminal arylation, which is favored by both electronic and steric effects. The neutral olefins, for example styrenes and aliphatic alkenes, which are governed by steric properties, give rise to predominantly linear products, but can be forced to give branched products by clever selection of reaction conditions.**[5c, 374]** For the electron-rich olefins, the important factors, steric and electronic effects, favors different products. The steric hindrance promotes the linear product, but the more electron-rich β-carbon is more prone to bind to the electron-poor Pd(II) moiety resulting in the branched product. This contradiction results in product mixtures. One way to circumvent this problem was the development of the cationic reaction pathway, where the electronic properties are more important and therefore can promote a selective reaction giving the branched product.**[5c, 374]**

Finally, a β-hydride elimination forms the product alkene and a palladium hydride. Through a base-assisted reductive elimination the catalyst is reformed and the catalytic cycle is closed. This step, of the β-hydride elimination, is also stereospecific since it, like the insertion, occurs through a *syn* complex.**[5g]** It also worth mentioning that since the elimination requires a vacant *cis* coordination site, complexes that are coordinatively saturated give stable metal-alkyl species, and will not easily perform a β-hydride elimination.**[12]**

A base is required in Heck reactions to neutralize the acid (HX) that is produced when the hydridopalladium(II) species is reduced to regenerate the active Pd(0) catalyst. A stoichiometric amount of base is needed, but in practice, 3-5 molar equivalents are often used. A variety of inorganic bases have been used in Heck reactions, K_2CO_3 and $CaCO_3$ were the most reported frequently. Tertiary amine bases such as Et_3N, $i\text{-}Pr_2NEt$, a Proton Sponge and

1,2,2,6,6-pentamethylpiperidine (PMP) are also commonly employed. Among these, the extremely hindered base PMP has become a favorite choice for asymmetric Heck cyclizations. The reaction in the presence of inorganic bases such as NaOAc gave the mixture of internal and terminal olefins with a ratio equal to the ratio of the number of protons at the respective sites, which has been interpreted as a result of conventional base-independent syn-elimination. The reaction in the presence of amine base yielded almost exclusively the internal product. Indeed, the stronger base can switch the process to base-catalyzed elimination, giving a more stable internal olefin. In conclusion, as if base-catalyzed elimination can indeed occur, a base would have a strong influence both on the reactivity and stereochemistry of Heck reaction.**[5b]**

2.5.1 State of art of Mizoroki-Heck reaction with aryl and alkenyl halides in batch mode

As mentioned in general for all cross-coupling in paragraph 1.1, classic and/or modern Pd complexes with phosphine ligands and not only are intensively employed as homogeneous catalysts in reactions of Mizoroki-Heck.**[9d, 375]**

The Heck reaction is generally catalyzed in solution by palladium species generated from either Pd(0) compounds, such as $Pd(PPh_3)_4$ and $Pd_2(dba)_3$, or Pd(II) salts, such as the acetate and the chloride;**[31]** and recent studies reported the use of vary palladacycles,**[21, 235, 376]** Pd-NHC complex,**[377]**

Despite their success (high catalytic activity and regioselectivity), such systems may lead to problems associated with the need and handling of sensitive ligands, and the difficult availability of the catalyst, to the precarious stability, to the difficult handling and ultimately high cost of the system itself. As already mentioned in the paragraph 1.1, all these difficulties with the inability to recycle the catalyst in a simple way, as well as the frequent contamination of the product of synthesis or the use of catalytic systems efficient but very expensive, have resulted in a continuous increase, as regards the reaction of Mizoroki-Heck, and the study of the use of supported catalytic systems, at low release of palladium and easily recyclable.

The recovery and recycling of the expensive Pd have led to the development of immobilized homogeneous catalyst systems. Successful methods include supporting Pd complexes on polymers, the anchoring of Pd complexes to various solids such as modified silicas or layered double hydroxide, and ion-exchange of Pd^{2+} into suitable solid materials. Furthermore, there has been a search for suitable supported heterogeneous Pd catalysts. In fact, heterogeneous Pd catalyst systems were found to be highly effective. In addition, to stabilized colloidal palladium and palladium nanoparticles numerous reports have shown the utility of various supported palladium catalysts.**[9c-d]**

Pd/C was applied to this reaction in the pioneering work of Julia et al. as early as in 1973**[138a]** and has been the most important heterogeneous catalyst since then, because it is efficient and commercially available. In fact this system is applied in the coupling of 1-bromo-4-methoxybenzene with octyl acrylate for the industrial production of octyl 4-methoxycinnamate, a common UV absorber utilized in the manufacture of sunscreen lotion.
In the Julia work early report, styrene was reacted with aromatic chlorides and iodides in pure methanol at 120 °C (the reaction was carried out in an autoclave under pressure). The stilbene was afforded in 62% yield (82% conversion of styrene), without any added phosphine. In this connection the authors showed that under these conditions added triphenylphosphine was an inhibitor rather than a promoter.

Subsequently, Pd/C was also employed by Köhler et al. to provided a very detailed investigation about the application of Pd/C in the Heck reaction of aryl bromides with olefins.**[10a, 63]**
A variety of Pd/C catalysts differing in Pd dispersion, Pd distribution, Pd oxidation state, and water content were tested. The experimental results indicated a (quasi-)homogeneous reaction mechanism, that is, the Pd complex or colloidal particles in solution act as the catalytically active species. Under these optimized reaction conditions, turnover numbers (TON) up to 36000 and turnover frequencies (TOF) up to 18000 h^{-1} were achieved using a Pd concentration as low as 0.0025 mol %. Complete conversion was achieved for activated (electron-withdrawing substituents) and nonactivated, as well as deactivated, bromoarenes (electron-donating substituents) within a few hours. The extraordinarily high activity seems to be connected with dissolution-reprecipitation processes, where dissolved Pd species formed at this temperature are the active species.

In general, the Pd/C-catalyzed Heck reaction using a palladium load between 1.0 at 5.0 mol % with or without additional phospine ligands**[378]** in the presence of stoichiometric quantities of inorganic (Na2CO3, AcONa) or amines bases; in organic solvents (alcohols, Dioxane, NMP, Toluene, Ethylene glycol) under inert atmosphere and at temperatures up to 100 ° C, obtaining excellent results even with deactivated aryl bromides.**[378]**

Recently new protocols have been developed to use Pd/C in ionic liquid alone as a solvent,**[32c, 379]** and/or the application of microwave irradiation.**[380]**

Pd/C was also employed by Beller and Külhein as the catalyst for the reported first HETHR involving 4-methoxyphenyldiazonium (p-anisidyldiazonium) tetrafluoborate.**[381]** According to them, this could be the alternative route to classical condensation for the synthesis of substituted cinnamic esters, which are industrially important UV absorbers.

Despite the large amount of examples reported in the literature on the use of Pd/C, the information regarding its effective leaching and the tendency to recycled it is most limited.**[9d]** However, evidence for dissolved Pd species formed by leaching from Pd/C being the active moieties in Heck reactions was also found by Arai and co-workers**[32a-b]** in case of aryl iodides in NMP in the present of triethylamine or Na_2CO_3 as base. However, almost all dissolved Pd species re-deposited onto the surface of the support after the reaction had been completed. Thus, the catalysts were recyclable without loss of activity. Low activities and dehalogenation were observed for aryl bromides and aryl chlorides.

In addition to the Pd/C, in Suzuki-Miyaura reaction have been employed other supported catalysts consisting of palladium supported on metal oxides;**[9d, 31, 382]** such as Pd/MgO,**[138]** Pd/Al2O3 e Pd/SiO2,**[10a, 54b, 63, 383]** Pd/TiO2,**[384]** and Pd-doped mixed oxides Mg-LaO**[382]**; as well as systems of Pd on modified silica**[385]** and microporous-mesoporous supports (MCM-41 and zeolites)**[33b-c, 33e, 36, 51, 210b, 386]** are the only few examples in this field reported in the literature. Each of these catalysts, of course, has the characteristics and activities different, but in general, all require a dose range between 0.5 and 1.0 mol%, although there are cases in which they have been used a very small amount (0.001 mol%); normally they are employed in the presence of bases such as carbonates or amines using solvents polar aprotic such as NMP or DMF under mild temperatures (50-100 °C), principally under inert atmosphere in presence or not of phosphine ligand or additives.**[9b, 31b]** These systems formed by Pd simply deposited and/or adsorbed directly on oxides and/or zeolites, are very catalytically active in the reaction of Mizoroki-Heck, but, at least for MOx systems, this highly activity is correlated to about one-third of the palladium was leached from the surface of the support, generating in situ highly active palladium species stabilized against agglomeration by re-precipitation on the surface at fine of the reaction.**[34c, 384, 387]**

However, the majority of the catalysts result recyclable for several run without loss of activity. The Pd-Mg/LaO catalyst could be reused without additional activation four times without a significant loss of activity and could be stored under air without problems,**[382]** the Pd-MCM-41 are stable under the reaction conditions and retain high activity and selectivity for at least 20 successive runs without the need to exclude air or moisture.**[61]** While the systems supported on zeolites showed no substantial leaching in most cases. But evidence for dissolved molecular Pd species being responsible for the catalysis was found.**[38]** The catalysts could be easily separated from the reaction mixture and reused up to five times without a considerable loss in activity.**[33e]**

In last decades, were to be published an increased number of articles that used a palladium catalysts supported onto organic polymers: metal anchored on the polymer matrix, or incapsulated in to the matrix.**[31, 388]**
These systems are both commercial systems, such as FibreCat**[167]** and PdEnCat^{TM} (Pd is encapsulated in a thioureic resin)**[146e-f, 163, 164, 333]**, that non-commercial polystyrene systems, with coordinating groups to the metal**[389]** and other polymer systems such as polyvinylpyrrolidone (PVP),**[390]** modified cross-linked polyacrylamide**[391]**, polytriallylamine (MPTAT-1)**[392]** that already have the coordinating groups.
For these species are described good and efficient reactions with both aryl iodides that with aryl bromides, under biphasic and/or three-phase conditions. In any cases, these systems were are used in reaction with alkenyl halides obtaining good/excellent yields with highly stereo-specificity.

Finally, have been described some, for now limited, examples of nano-particles of palladium prepared in various ways and supported on polyvinylpyridine,**[30c]** polyvinylpyrrolidone (PVP),**[249, 393]** and PEG,**[394]** as well as other organic polymers of various types**[395]** and functionalized grapheme derivates or carbon nanotubes.**[238c, 396]** Usually they are very efficient in Heck reactions even in aqueous environments and are efficiently recyclable with low levels of leaching.

2.5.2 Development of batch conditions for Mizoroki-Heck reactions

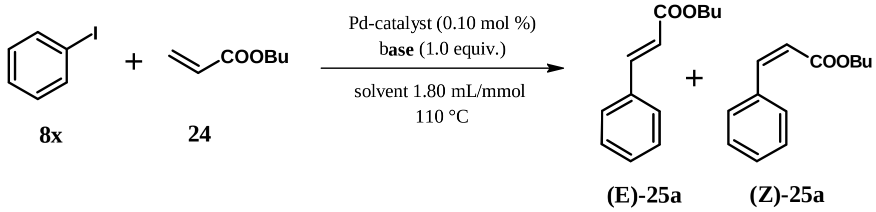
As outline in paragraph 1.5, our studies focused on three different cross-coupling between Mizoroki-Heck coupling and seven different catalysts: three prepared "via" MVS with the collaboration of Dr Claudio Evangelisti (previously see above in paragraph 2.1.4) and four commercially available (previously see above in paragraph 2.1.3).

In Mizoroki-Heck reaction we investigated only six different catalysts: all four commercially available catalysts previously selected in paragraph 2.1.3 and the two mono-metal MVS-prepared catalysts previously prepared in paragraph 2.1.4.

In this study we determine the most efficient and feasible reaction conditions in which these catalysts are able to promote the Mizoroki-Heck reaction, taking into account their applicability in flow.

We next focused on applying the Heck reaction protocol to continuous-flow conditions; To be applicable, two key points would be addressed. First, the reaction time should be significantly decreased to minimize the required reactor volume. Second, the use of insoluble bases and the formation of precipitates had to be minimized to prevent clogging of the microchannels.

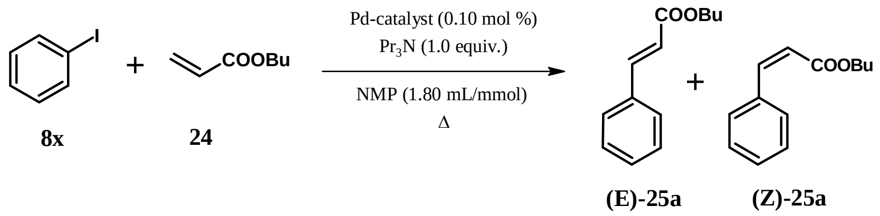
The reaction conditions were evaluated using iodobenzene (**8x**) and butyl acrylate (**24**) as a substrate (model reaction, **Scheme 2.5.2.1**), from point of view of the yield and reaction time; taking account of efficiency, generality and possibility in flow reactors.



Scheme 2.5.2.1: Mizoroki-Heck optimization model reaction

Initially, the catalytic trials were run using tripropylamine as base in NMP as solvent at 110°C, according to our previous studies on Pd-catalyzed Heck reactions using Pd/PVP**[249]** and Pd/PVPy**[30c]** as catalyst (**Table 2.5.2.1**).

Table 2.5.2.1: Catalytic activity of our supported catalyst on the Heck coupling reaction with iodobenzene.[a]



Entry	Catalyst	Temperature (°C)	Atmosphere	Reaction time (h)	Conversion of **8**[b] (%)	Selectivity[b] **E/Z**	Yield of **25**[c] (%)	Leaching[d] (%)
1	Pd/PVPy (**5**)	120	Ar	2.0	99	99.9 / 0.1	90 (88)[e]	-
2		110	Ar	2.0	99	99.9 / 0.1	92	0.10
3		100	Ar	4.0	35	99.9 / 0.1	-	-
4[f]		100	Ar	3.0	99	99.9 / 0.1	57	0.70
5		120	air	2.5	99	99.9 / 0.1	88	-
6	Pd/MCM-41 (**6**)	120	Ar	1.0	99	99.9 / 0.1	88 (80)[e]	-
7		110	Ar	2.0	99	99.9 / 0.1	92	0.12
8		100	Ar	4.0	35	99.9 / 0.1	-	-
9	Pd EnCat-40 (**1**)	110	Ar	1.0	98	99.9 / 0.1	97 (89)[e]	2.60
10		80	Ar	4.0	96	99.9 / 0.1	75	0.29
11		60	Ar	4.0	-	-	-	-
12		110	air	1.0	99	99.9 / 0.1	98	7.00
13	Fibrecat 1007 (**2**)	110	Ar	1.0	99	99.9 / 0.1	97	0.45
14		80	Ar	3.0	78	99.9 / 0.1	72	0.36
15		60	Ar	4.0	-	-	-	-
16		110	air	1.0	99	99.9 / 0.1	99	15.00
17	$Pd(PPh_3)_4$-PS (**4**)	110	Ar	2.0	96	99.9 / 0.1	95	1.10
18		80	Ar	3.0	99	99.9 / 0.1	98	0.38
19		60	Ar	4.0	-	-	-	-
20		110	air	1.0	99	99.9 / 0.1	88	9.00
21	$PdCl_2(PPh_3)_2$-PS (**3**)	110	Ar	3.0	97	99.9 / 0.1	81 (76)[e]	0.19
22		80	Ar	3.0	98	99.9 / 0.1	78	0.45
23		60	Ar	4.0	-	-	-	-
24		110	air	1.0	99	99.9 / 0.1	99	9.00

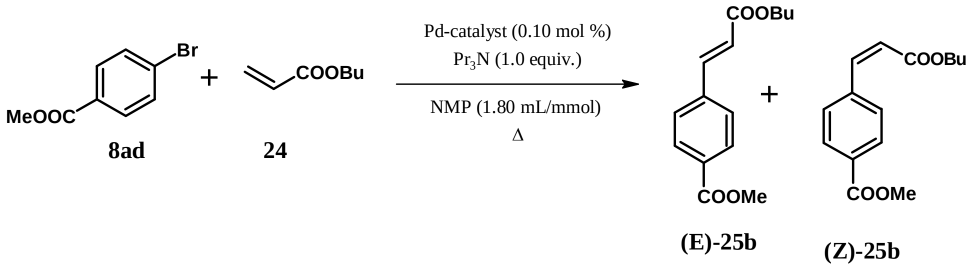
a) Reaction conditions: 1.0 equivalent of aryl halide (**8**), 1.00 equivalent of Pr_3N, 2.00 equivalent of butyl acrylate (**24**), 0.10 mol % of Pd as catalyst, NMP (1.80 mL/mmol); b) Evaluated by GC analyses; c) gascromatography Yield evaluated by internal standard (naphthalene); d) Evaluated by ICP-OES after microfiltration (0.45 mm) and reported as Pd leached wt.% of the total available metal; e) Isolated Yield by MPLC; f) Added 0.5 equivalent of tetrabutylammonium bromide and/or LiCl.

Under these conditions all catalysts showed substantially higher selectivity of the desired product **(Z)-25a**, with very very good yields in short time (1-4 h) at 110 °C under Ar atmosphere. While, when the catalysts were used directly in aerobic conditions, the performance remain unchanged (in terms of conversion and yield), but in the majority of the catalysts the leaching date greatly increases.

More interesting appears the influence of the temperature in the Heck reaction catalyzed by our supported catalysts. The MVS-prepared catalysts, Pd/PVPy and Pd/MCM-41, appear more sensible at the temperature, in fact reducing the temperature to 100°C we showed an extension of the reaction time and lowered of the conversion. While the commercial catalysts result completely inactive only under the 80°C, and at this temperature the catalysts showed the better date of leaching (< 0.50 %).

On the light of these excellent results, and taking into account the our experience in this reaction, we decided to examine the catalytic activity of the our supported catalysts in a Pd-catalyzed reaction of aryl bromide under the previously used reaction conditions for aryl iodide, to evaluated the reaction heating, time and efficiency of this catalyst in Heck coupling. More precisely we study the Heck reaction using 4-bromo-methylbenzoate (**8ad**) with butyl acrylate (**24**) as a coupling partner (**Table 2.5.2.2**).

Table 2.5.2.2: Catalytic activity of our supported catalyst on the Heck coupling reaction with 4-bromo-methylbenzoate.[a]



Entry	*Catalyst*	*Temperature (°C)*	*Atmosphere*	*Reaction time (h)*	*Conversion of **8**[b] (%)*	*Selectivity[b] **E/Z***	*Yield of **25**[c] (%)*
1	*Pd/PVPy*	*120*	*Ar*	*4.0*	*trace*	-	-
2	*(**5**)*	*150*	*Ar*	*4.0*	*99*	*99.9 / 0.1*	*67*
6	*Pd/MCM-41*	*120*	*Ar*	*5.0*	*trace*	-	-
7	*(**6**)*	*150*	*Ar*	*5.0*	*94*	*99.9 / 0.1*	*66*
9	*Pd EnCat-40*	*110*	*Ar*	*6.0*	*trace*	-	-
10	*(**1**)*	*150*	*Ar*	*6.0*	*64*	*99.9 / 0.1*	*36*
13	*Fibrecat 1007*	*110*	*Ar*	*6.0*	*trace*	-	-
14	*(**2**)*	*150*	*Ar*	*6.0*	*73*	*99.9 / 0.1*	*36*
17	*$Pd(PPh_3)_4$-PS*	*110*	*Ar*	*5.0*	*trace*	-	-
18	*(**4**)*	*150*	*Ar*	*5.0*	*99*	*99.9 / 0.1*	*50*
21	*$PdCl_2(PPh_3)_2$-PS*	*110*	*Ar*	*3.0*	*trace*	-	-
22	*(**5**)*	*150*	*Ar*	*3.0*	*60*	*99.9 / 0.1*	*50*

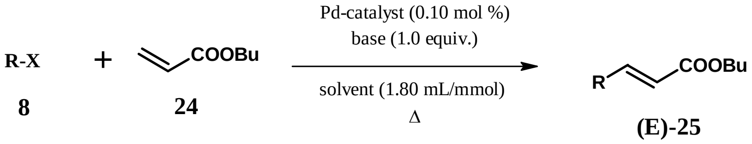
a) Reaction conditions: 1.0 equivalent of aryl halide (**8**), 1.00 equivalent of Pr_3N, 2.00 equivalent of butyl acrylate (**24**), 0.10 mol % of Pd as catalyst, NMP (1.80 mL/mmol); b) Evaluated by GC analyses; c) Isolated Yield by MPLC

Unfortunately, under this reaction conditions the four commercial catalysts and the two "*home-made*" catalysts showed very low efficiency at 120 °C. Mediocre results were obtained increasing the reaction temperature at 150 °C, in fact at this temperature the catalytic systems showed an catalytic activity, but at this temperature the organic substrates (principally butyl acrylate) suffer secondary reaction of polymerization, obtaining not complete conversion in any cases.

Moreover, taking into account the possible application in flow, under this condition (150 °C of heating) vary supports showed structural modification (melting or softening of the supports) that could be blocking the flow reactors (as reported for Pd EnCat in literature and in our application in Suzuki and Sonigashira flow coupling).

At the light of these results we were decide to examine other reaction conditions. Taking into account the literature date we examined the possible addition of additive as tetraalkyl ammonium halide or lithium chloride salts (*Jeffery-type conditions*)**[28a, 397]** and different bases and solvents, both with iodobenzene and 4-bromo-methylbenzoate (**Table 2.5.2.3**).

Table 2.5.2.3: Effect of additive and other bases on the Heck coupling reaction.[a]



Entry	Catalyst	R-X	Temperature (°C)	Base / Solvent	Additive	Reaction time (h)	Conversion of **8**[b] (%)	Yield of **25**[c] (%)	Leaching[d] (%)
1	Pd/PVPy (**5**)	**8x**	90	Pr_3N / NMP	TBAB	5.0	80	57	-
2			90	Pr_3N / NMP	LiCl	5.0	91	55	-
3			90	Pr_3N / NMP	TBAB + LiCl	3.0	99	57	5.00
4[f]			90	AcOK / NMP:H_2O	-	4.0	97	75	< 0.20
5		**8ad**	120	AcOK / NMP:H_2O	-	-	-	-	-
6			130	Pr_3N / NMP	TBAB + LiCl	3.0	99	53	0.50
7			130	Pr_3N / NMP	TBAB	3.0	76	50	0.40
9	Pd EnCat-40 (**1**)	**8ad**	150	Pr_3N / NMP	TBAB	3.0	85	70	0.90
10			110	Pr_3N / NMP	TBAB	6.0	64	36	-
13	Fibrecat 1007 (**2**)	**8ad**	150	Pr_3N / NMP	TBAB	3.0	88	85	0.70
14			110	Pr_3N / NMP	TBAB	6.0	73	36	-
17	$Pd(PPh_3)_4$-PS (**4**)	**8ad**	150	Pr_3N / NMP	TBAB	3.0	99	70	1.09
18			110	Pr_3N / NMP	TBAB	5.0	99	50	-
21	$PdCl_2(PPh_3)_2$-PS (**3**)	**8ad**	150	Pr_3N / NMP	TBAB	1.0	99	87	1.26
22			110	Pr_3N / NMP	TBAB	3.0	60	50	-

a) Reaction conditions: 1.0 equivalent of aryl halide (**8**), 1.00 equivalent of base, 2.00 equivalent of butyl acrylate (**24**), 0.10 mol % of Pd as catalyst, solvent (1.80 mL/mmol); b) Evaluated by GC analyses; c) Isolated Yield by MPLC; d) Evaluated by ICP-OES after microfiltration (0.45 mm) and reported as Pd leached wt.% of the total available metal;

When additive we tested principally the TBAB and LiCl obtaining interesting results. The addition of additive as TBAB increase the catalytic activity of the systems, showing complete conversion in the reaction with 4-bromo-methylbenzoate at 150 °C with commercial catalysts. Unfortunately the addition of this additive not permit the reduction of the reaction temperature, obtaining not complete conversion at 120 °C. For regard the Pd/PVPy (the principal catalyst that showed structural modification at 150 °C), the addition of the additive such as TBAB or LiCl showed good increasing of the efficiency with iodobenzene, but this effect appear more limited with the aryl bromide. However the contemporary addition of TBAB and LiCl showed complete conversion in 3 h at 130 °C with 4-bromo-methylbenzoate with acceptable leaching data (0.50 %).

More several additive were tested in these reaction, such as TBAI, LiBr and TBAC, but the results not changed.

For regard the test of other bases and solvents, taking into account the necessity to have homogeneous reaction conditions, and considering the date reported in literature on the Mizoroki-Heck catalyzed by supported catalysts; more interesting we appears the use of AcOK as base in NMP/H_2O.

This condition in our tests showed complete conversion with iodobenzene at 90 °C, to obtain a good yield (75 %) in short time (4 h) with very low leaching data (< 0.20 %), but unfortunately the same result were not obtained with 4-bromo-methylbenzoate.

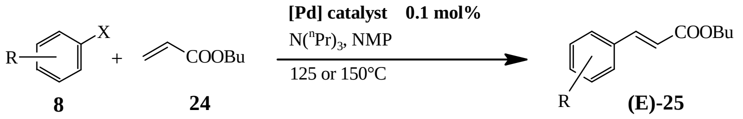
At the light of all these optimized study results, we found that aryl iodides and bromides were efficiently coupled with butyl acrylate to give the corresponding 1,2-substituted alkenes in good to excellent yields involved 2.0 equivalents of butyl acrylate, 1.0 equivalents of Pr_3N as a base and Pd-catalysts amounts as low as 0.1 mol% in NMP (1.8 mL/mmol) at 80-110°C for aryl iodide or 150°C for aryl bromide, under inert atmosphere with side reactions (dehalogenation) and Pd black formation can be excluded.

2.5.2.1 Performance of the catalysts in Mizoroki-Heck coupling reaction with aryl iodides and bromides in batch

To explore the scope and generality of the catalysts, the optimized protocol was applied for reactions of a variety of differently substituted aryl halides **8** with butyl acrylate (**24**). Therefore, a study was set up by selecting aryl iodides bearing electron withdrawing and donating groups and a any examples of aryl bromides. The catalysts were compared with Pd/C and the outcomes are summarized in **Table 2.5.2.4**.

Generally, deactivated aryl iodides and both activated aryl bromides were completely converted into the corresponding products in 35–96% yields within very short time 1 h–6 h (**Table 2.5.2.4**). The reactions with aryl bromides showed several diversity between the vary catalysts. The MVS-prepared catalysts showed satisfactory yield obtained in short time directly at 150°C without the addition of additive, while the commercial catalysts require the addition of TBAB at 150°C to obtaining satisfactory yields (**Table 2.5.2.4**, entries 17-20). It was interesting to note that both nitro groups on the aryl bromide (4-bromo-1-nitrobenzene, **8d**), all catalysts were able to promote the coupling directly at 150°C without addition of additive (**Table 2.5.2.4**, entries 22-25).

Table 2.5.2.4: Scope and generality of our supported catalysts in Heck coupling reaction with aryl halides.[a]



Run	Substrate (**8**)	Catalyst	Reaction Time (h)	Conversion[b] (%)	Yield in **25**[c] (%)	Specific Activity[d] (h^{-1})	Metal Leaching[e] (%)
1	R = H X = I (**8x**)	*Pd/MCM-41*	1.0	99	80	800	0.12 (0.8 ppm)[f]
2		*Pd/PVPy*	2.0	99	88	440	0.22
3		*Fibrecat 1007*	1.0	98	89	890	0.45
4		*$PdCl_2(PPh_3)_2$/PS*	3.0	97	76	253	0.19
5		*$Pd(PPh_3)_4$/PS*	3.0	96	88	293	1.10
6		*Pd EnCat-40*	1.0	99	89	890	2.60
7		*Pd/C*	1.0	98	78	760	1.60
8	R = 4-Me X = I (**8c**)	*Pd/MCM-41*	1.0	96	76	760	0.20
9		*Pd/PVPy*	2.0	95	65	325	-
10		*Pd/C*	1.0	95	83	830	2.00
11	R = 4-COOMe X = I (**8ad**)	*Pd/MCM-41*	0.5	99	96	1920	1.50
12		*Pd/PVPy*	1.0	99	83	830	0.51
13		*Pd/C*	0.5	99	92	1840	2.50
14		*Pd EnCat-40*	0.5	99	90	1800	4.00
15	R = 4-COOMe X = Br (**8ae**)	*Pd/MCM-41*	5.0	94	66	132	1.90 (11 ppm)[f]
16		*Pd/PVPy*	4.0	99	67	168	1.30
17[g]		*Fibrecat 1007*	6.0	95	43	72	0.70
18[g]		*$PdCl_2(PPh_3)_2$/PS*	3.0	98	50	167	1.30
19[g]		*$Pd(PPh_3)_4$/PS*	5.0	98	60	120	1.10
20[g]		*Pd/C*	5.0	96	68	136	4.00
21[g]		*Pd EnCat-40*	6.0	85	35	58	0.90
22	R = 4-NO_2 X = Br (**8d**)	*Pd/MCM-41*	2.0	98	80	400	1.55
23		*Pd/PVPy*	4.0	99	87	218	-
24		*Pd/C*	1.5	99	89	593	5.00
25		*Pd EnCat-40*	2.0	99	90	445	4.00

a) Reaction conditions: 1.0 equivalent of aryl halide (**8**), 2.0 equivalent of *n*-butyl acrylate (**24**), 1.0 equivalent of Pr_3N, NMP (1.8 mL/mmol), 125 °C for X = I or 150 °C for X = Br, Ar atmosphere; b) Evaluated by GC analyses; c) Isolated Yield; d) Calculated as moles of aryl halide converted/moles of metal per hour; e) Evaluated by ICP-OES after microfiltration (0.45 mm) and reported as Pd leached wt.% of the total available metal; f) amount of Pd on the amount of crude product obtained in the process; g) Added 0.5 equivalent of tetrabutylammonium bromide or LiCl.

In detail, the results obtained with the two "*home-made*" catalysts, consist in a Pd nanoparticles deposited on two different supports, are very interesting. More in particular, from the series of tests, carried out on various compounds, allowed to establish that the Pd/MCM-41 (**6**) is the most efficient to promoting the reaction under the previously optimized conditions. In fact, the Pd/PVPy (**5**) showed good/excellent yields with aryl iodides in 1-2 h under rather simple and convenient conditions with low leaching date. While in the reaction with aryl bromides this system showed good yields at 150°C in 4 h.

The Pd/MCM-41 (**6**) showed a good oven excellent yields with aryl iodides (both electron-rich and electron-poor) with very very low leaching (0.12-1.50 % of the total Pd load)in short time (0.5-1 h). Good result were obtained in the reaction with aryl bromides electron-poor in short times (2-5 h) with acceptable leaching date (1.55-1.90 % of the total Pd load).

As regard the four chosen commercial catalysts investigated in the Mizoroki-Heck cross-coupling of aryl iodides, under above mentioned conditions (Pr_3N as base, NMP as solvent, at 110 °C in inert atmosphere), low doses (0.10 mol% Pd) of all the catalysts studied showed a good and similar efficiency in short times (1-3 h); however some specific features of each catalyst that have been identified, thanks to a suitable series of reactions carried out with a limited, but significant, variety of aryl bromides (electron-poor).

These systems affording acceptable yields in short times with 4-bromo-methylbenzoate (**8ae**) only over the addition of TBAB or LiCl, with acceptable leaching (< 1.50 % of the total Pd load).

2.5.2.2 Conclusions

In summary, we have demonstrated that Mizoroki–Heck reactions of both iodo- and bromoarenes with an acrylate building block can be successfully performed under batch conditions by using the chosen ligandless supported Pd catalysts, tripropylamine as base and NMP as solvent.

Using 0.1 mol % of palladium, full conversions combined with high regio- and steroselectivities were obtained under batch conditions for aryl iodides and bromides.

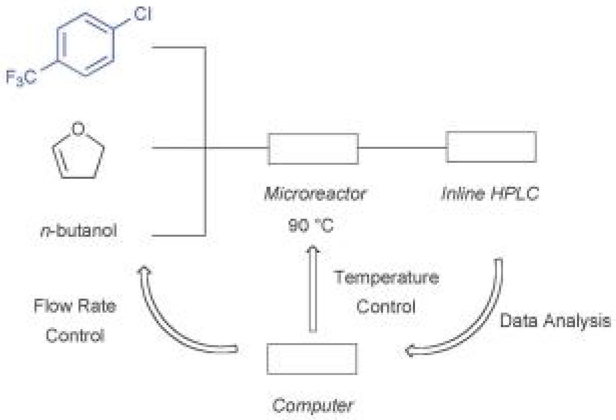
Our Pd/PVPy and Pd/MCM-41 “home-made” systems, resulted efficient and stable catalysts for the C–C Heck-type coupling reaction of iodo- and bromoarenes with alkyl acrylates. The corresponding trans-cinnamates were obtained with yields in the range 66–96% at 110–150°C depending on the aryl halide. The catalysts are particularly stable and the leaching of palladium into the solution is very low.

As regard the commercial catalysts, it is worth of nothing that those chosen are little or not used in this reaction, as best described in paragraph 2.1.1.2. However, are efficient catalysts for this reaction, but only with aryl iodides as acceptors. In fact, unfortunately we have ascertained that they are not very active with bromoarenes, and require the addition of additives, that increase the catalytic activity (suitable ammonium salts).

2.5.3 Mizoroki-Heck coupling reaction in flow

Mizoroki-Heck couplings have become a routine transformation in synthetic chemistry and as such there has been much interest in translating their use into continuous flow processing. A demonstration of this, the Mizoroki-Heck couplings have been developed for use in flow with a variety of different Pd catalyst systems and coupling reagents.**[190]**

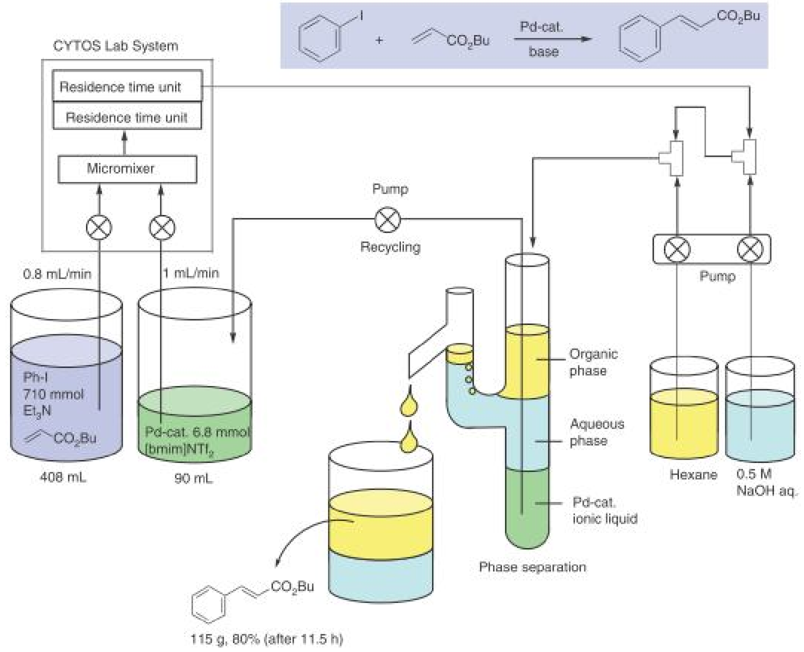
Jensen, Buchwald and co-workers have developed an 'intelligent' and completely automated microfluidic system, which is capable of maximizing the yield of a Mizoroki–Heck reaction by adjusting several reaction parameters (**Scheme 2.5.3.1**).**[398]** At certain time intervals, the yield and selectivity (monoarylated/diarylated) of the reaction were analyzed by inline HPLC. This data was analyzed by using DoE software and immediate feed back regarding concentration and residence time resulted in an adjustment of the pump flow rates.



Scheme 2.5.3.1 : Schematic microreactor setup for continuous-flow Pd-catalyzed Mizoroki-Heck cross-coupling

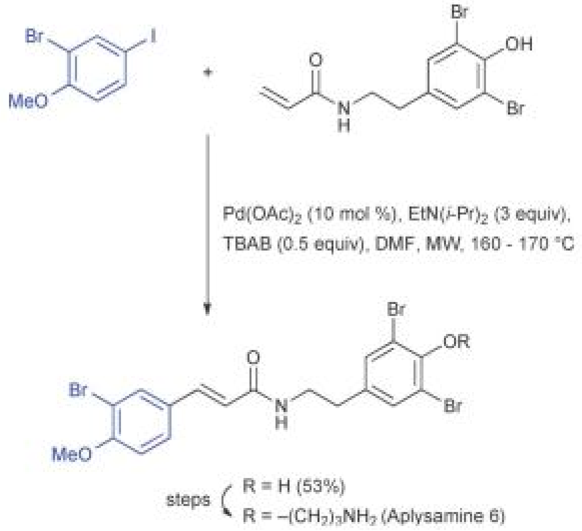
As a result, the reaction of 4-chlorobenzotrifluoride with 2,3-dihydrofuran could be optimized after 19 automated experiments, and the test required a residence time of 6 min and 5 equivalents of dihydrofuran leading to a 83% yield of the desired compound.

Flow processing also offers advantages to combining vary technologies. For example, Ryu and co-workers immobilized a palladium catalyst in a low viscosity ionic liquid,**[399]** which allowed for a continuous catalyst recycling in flow (**Scheme 2.5.3.2**).**[399]** The reagents were introduced into a CYTOS lab system (17 min residence time, 1.0 ml/min flow rate), a commercially available microreactor system. Next, the Mizoroki–Heck coupled product was removed from the ionic liquid in a hexane wash. After removal of the ammonium salt in a H_2O wash, the catalyst could be recycled. The system was run for 11.5 h producing 115.3 g of trans-butyl cinnamate (80% yield, 10 g/h) in which the catalyst system was recycled a total of five times.



Scheme 2.5.3.2 : Schematic setup for continuous-flow Pd-catalyzed Mizoroki-Heck cross-coupling in ILs

Besides, Organ and co-workers employed a microwave-assisted capillary flow system for the continuous-flow synthesis of an intermediate of Aplysamine 6, which is an alkaloid inhibitor of ICMT (isoprenylcysteine carboxyl methyltransferase) (**Scheme 2.5.3.3**).**[400]**



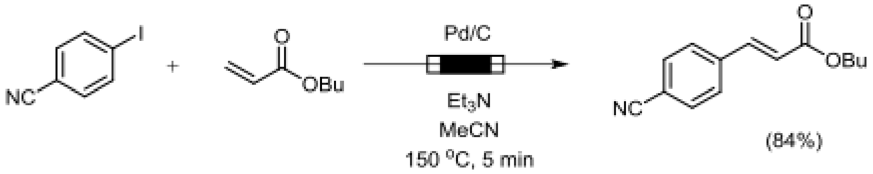
Scheme 2.5.3.3 : Schematic setup for continuous-flow Pd-catalyzed Mizoroki-Heck cross-coupling with MW

The use of a microwave-assisted continuous-flow synthesis provided an excellent method to scale-up the synthesis without the need for process re-optimization.

2.5.3.1 State of art of Mizoroki-Heck reaction with aryl and alkenyl halides in flow mode

As previously mentioned in paragraph 1.3.1; in general for all cross-coupling there are a wide variety of different catalytic technologies available for conducting cross-couplings in continuous flow. Traditionally heterogeneous systems were favoured due to their ease of separation, recycling and high surface areas making for more efficient processing.**[124, 190b]** However, with issues surrounding leaching of Pd into solution and subsequent loss of activity making their use problematic over extended periods of time.

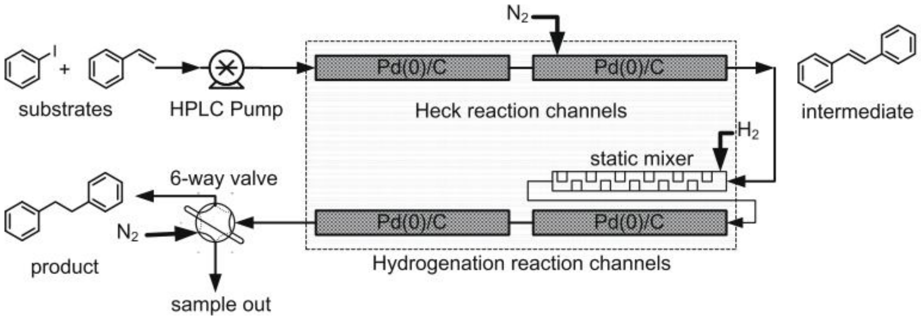
For regard the Mizoroki-Heck cross-coupling reaction a broad range of solid supports were developed and applied in continuous-flow chemistry, such as, charcoal,**[63, 140, 401]** silica,**[173, 303]** monolithic supports,**[37, 130d, 289a-b, 298, 299, 402]** magnetic nanoparticles,**[153, 300]** and functionalized polymers **[130c, 403]**.
However, strong evidence indicates that these solid supports function as "palladium reservoir" and gradually leach the catalytically active Pd species into solution.**[135]**
Kappe and co-workers investigated the use of a Pd/C precatalyst in the Heck coupling of aryl iodide with butyl acrylate in flow (**Scheme 2.5.3.4**).**[140]** The reactions were carried out using pre-packed stainless steel cartridges of the catalyst (60 x 4 mm i.d., ca. 310 mg Pd/C).



Scheme 2.5.3.4 : Continuous-flow Pd-catalyzed Mizoroki-Heck cross-coupling using Pd/C

Complete conversion was achieved at 150°C, with a residence time of approximately 5 min in the presence of Et_3N. Under flow conditions it was found that product was accompanied by a significant amount of homocoupling (9%) and dehalogenated (7%) by-products, in comparison to microwave-batch which gave only trace amounts. The significant amount of dehalogenation was thought to be due to the high catalyst loading employed under continuous flow conditions, which was also observed with high catalyst loadings in batch. This, however, did not account for the homocoupling which was attributed to a chromatographic separation effect exhibited by the packed column. ICP-MS analysis of the used cartridge indicated that 89% of the palladium had leached into the solution after conducting twelve consecutive reactions utilising the same solid support. It was thought that the reaction mechanism involved a quasi-homogeneous Pd species, where the Pd/C was acting as a reservoir for soluble, active Pd species which were constantly undergoing absorption/dissolution.**[63]**

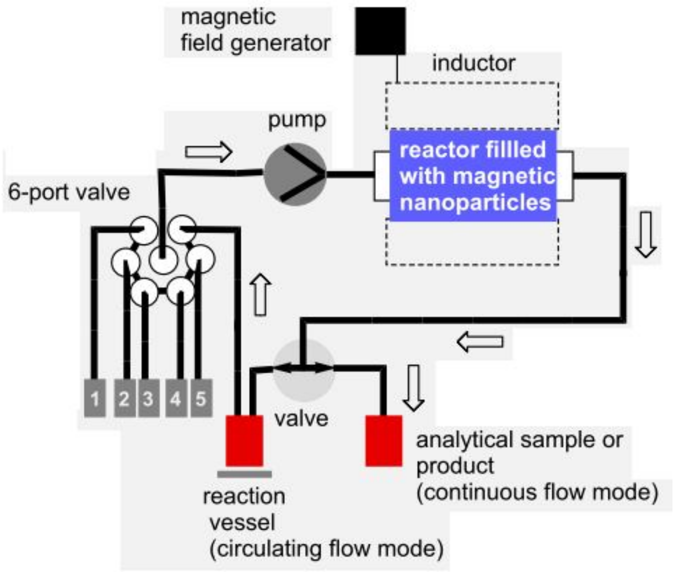
Plucinski et al. have also demonstrated the use of Pd/C in flow to promote a sequential Heck coupling, hydrogenation protocol in a custom made multichannel flow reactor.**[506]** The production of 1,2-diphenylethane was reported via Heck coupling of styrene and iodobenzene, followed by hydrogenation of the resulting alkene (**Scheme 2.5.3.5**), using 5 wt% Pd/C for both steps. Excellent conversions of 84% and 99% were achieved for both Heck coupling and hydrogenation respectively with a total residence time of 6 min (c.a. 3 min for each step) and an H_2 flow rate of 8 mL/min, at 95 °C.



Scheme 2.5.3.5 : Schematic continuous-flow Pd-catalyzed Mizoroki-Heck cross-coupling using Pd/C

However, a significant amount of Pd leaching was observed from the column used for Heck coupling and conversion dropped by c.a. 60% for subsequent runs. Interestingly though it was found that the hydrogenation column could act as a scavenger for palladium leached from the previous column used for cross coupling. The authors devised an alternating forward/reverse reaction strategy, where the order of the columns was swapped after each run so that the leached Pd was consistently re-deposited and both channels remained active. This concept was proven to be effective at maintaining activity and consecutive forward and reverse runs achieved consistently high conversions.

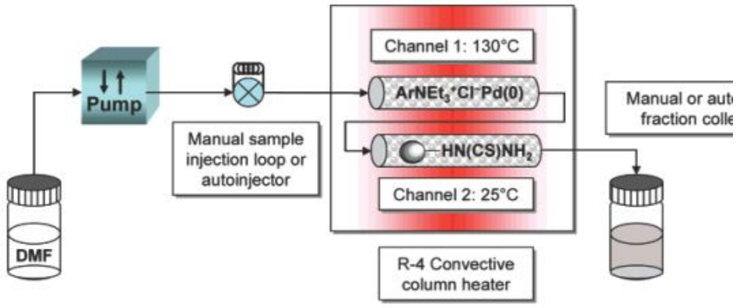
Kirschning and collaborators prepared Pd functionalised, silica coated Fe_3O_4/Fe_2O_3 nanoparticles (10-40 nm), which were used for Suzuki and Heck couplings under flow conditions.**[153, 300]** An added advantage of these particles is their superparamagnetic behaviour, which allows them to be heated via magnetic induction when subjected to an electromagnetic field (**Scheme 2.5.3.6**). This was exploited as a way of heating the flow reactor remotely and allowing heat to be generated directly at the reaction site inside the reactor.



Scheme 2.5.3.6 : Schematic continuous-flow Pd-catalyzed Mizoroki-Heck cross-coupling using Pd/magnetic NPs

The Heck coupling between p-iodoacetophenone and styrene in the presence of Bu3N in DMF afforded a 76% isolated yield, again with a residence time of 1 h, at 120 °C. ICP-MS analysis revealed not indifferent level of palladium leaching was occurring at 100 ppm for the Heck; however, the catalyst could be reused for more than three runs with no loss of activity.

Ley and co-workers prepared palladium supported monoliths to catalyse the Heck reaction.**[402]** Their monolithic support was constructed using vinylbenzyl chloride (35%), cross-linked with divinylbenzene (20%) and with 1-dodecanol (45%) being employed as the porogen, within Omnifit glass columns**[296]** (70 mm, 6.6 mm i.d.). A variety of aryl iodides and alkenes were examined utilising DMF as the reaction solvent in the presence of triethylamine at 130 °C (**Scheme 2.5.3.7**).



ırough reactor setup.

Scheme 2.5.3.7 : Schematic continuous-flow Pd-catalyzed Heck cross-coupling using Pd derivatised monolith

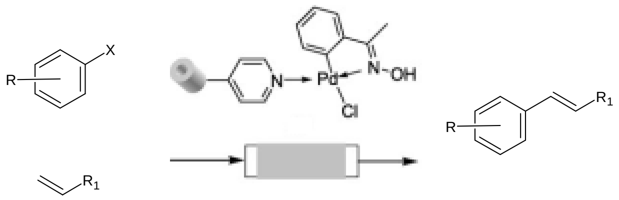
At 0.05 mL/min each reaction carried out afforded 100% conversion with isolated yields ranging from 82 to 87%. Unfortunately, aryl chlorides were unreactive under these conditions.

Due to the toxicity and difficult removal of DMF an alternative solvent was sought that could also carry out the reaction at 130 °C. It was found that superheating EtOH at elevated pressure, by using an in-line 100 psi back pressure regulator, afforded similar results to those obtained using DMF. ICP-MS analysis on the isolated solid products indicated a very high level of Pd contaminate (270 ppm). This was resolved by inserting an on line, thiourea based metal scavenger resin (Quadrapure TM TU)**[404]** prior to compound collection.

In 2006, also Luis and co-works has been demonstrated that the combination of Pd IL like moieties polymer monolithic reactors with superheating conditions, results in a high percentage yield of the desired reaction products for Mizoroki–Heck reactions under flow conditions.**[405]**

In the same year Organ et co-works reported the combination of Pd coated capillaries reactor with microwave heating conditions, results in good yield of the desired reaction products for the Heck coupling.

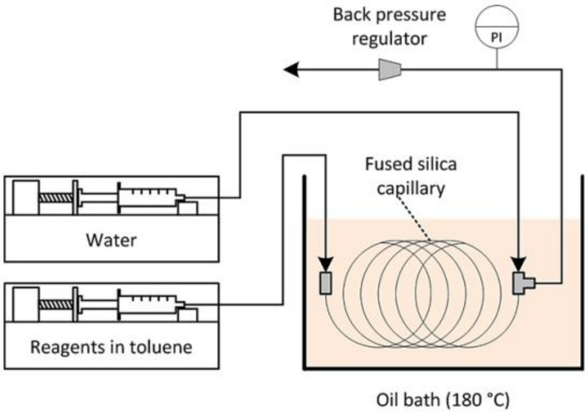
Kirschning et al. in 2008 prepared palladacycle to poly(vinylpyridine)/glass composite material placed within the PASSFlow™ microreactor, which were used for Heck and Suzuki couplings under flow conditions (**Scheme 2.5.3.8**).**[153, 300]** An added advantage of these particles is their superparamagnetic behaviour, which allows them to be heated via magnetic induction when subjected to an electromagnetic field. This was exploited as a way of heating the flow reactor remotely and allowing heat to be generated directly at the reaction site inside the reactor. The silica coating on the surface of the magnetic nanoparticles prevents oxidation of the highly reactive metallic surface in air and also allows for easy functionalisation and transition metal loading.



Scheme 2.5.3.8: Palladium supported on poly(vinylpyridine)/glass composite material inside microreactors in Heck coupling

The catalyst (50 mol% loading) was utilised in both the Suzuki and Heck coupling reactions. The Heck coupling of iodoarenes, in the presence of Et_3N in DMF afforded a 64-99% isolated yield of the desired product with a residence time of 2-24 h at 120 °C.

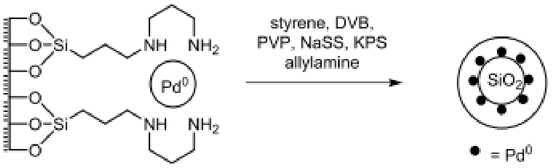
Most recently, but after the starting of this PhD work, Hassel and co-works at the start of 2013 reported our investigation in the reaction of iodobenzene and butyl acrylate using a silica-coated capillary palladium supported catalyst in continuous flow.**[406]** A solution of the reagents in toluene was combined with a water solution via a T-piece to dissolve the ammonium salt, preventing clogging due to crystallization of the salt at room temperature. The mixture was then passed through a microreactor containing the supported catalyst at 12 bar (**Scheme 2.5.3.9**) and the system gave only 21% yield in 2.9 minutes.



Scheme 2.5.3.9: General experimental set-up of the flow system

In the same period Styring and co-works report the MIzoroki-Heck coupling reaction between 4-methoxybenzene and methyl acrylate in CO_2sc under flow using Pd on silica, (250 mg) thoroughly mixed with the packing material (Chromosorb 750; 100–120 mesh; 750 mg) were packed into standard HPLC columns (length 300 cm, internal diameter 1 mm).**[403b]** The substrate was converted into coupled products in good yields after only 4 hours flow and this conversion was maintained while flow continued.

Frost and co-work described in 2014 the preparation and use of a novel silica-supported polymer-encapsulated Pd catalyst for both Heck and Suzuki couplings in flow.**[303]** Pd was supported onto surface functionalized amorphous silica, before being subjected to a polymerisation of styrene, divinylbenzene (DVB) and allyl amine to form spherical particles with a porous copolymer coating (**Scheme 2.3.3.9**).



Scheme 2.3.3.9: Preparation of silica-supported polymer-encapsulated Pd catalyst

The reagent solutions were pumped over an Omnifit column, packed with a mixture of the supported Pd catalyst and sand (100 x 6 mm, ca. 200 mg catalyst, 1.5 g sand). Heck coupling of the same aryl iodides with styrene was also demonstrated. These were conducted at 140 °C with residence times of 80-100 min and gave slightly lower conversions. The need for relatively long residence times was attributed to the need for the reagents to diffuse across the porous polymer coating before coupling could occur. However, this was offset by low levels of Pd leaching (0.05% Pd per run, measured by ICP-MS). The same batch of catalyst was reused for over 50 runs with no appreciable change in the structure or decrease in activity of the catalyst.

In 2015 Kappe and Cantillo reported interesting studies of efficiency, durability and metal leaching of commercial supported catalyst (EnCat TPP-30, FibreCat 1001, polymer-bound Pd tetrakis and SiliaCat DPP-Pd) in Heck and Suzuki coupling under continuous flow conditions.**[173]**

The data presented herein enable a direct comparison of these catalysts and provide further insights into the leaching phenomena of these palladium catalysts.

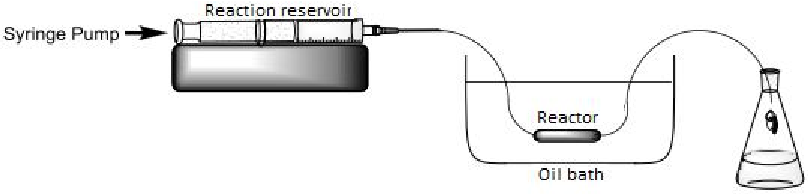
2.5.4 Study and application of packed-bed reactors in Mizoroki-Heck reactions under continuous-flow

As outline in paragraph 1.4, our studies focused also on applicability of supported catalysts under most efficient and feasible reaction condition in continuous-flow process. In fact, for regards the C-C and C-Heteroatoms cross-coupling reactions, and in particular for Mizoroki-Heck coupling; it is possible to affirm on the basis of literature data, that the application of the supported catalysis, in continuous-flow reactors present problems and difficulties not yet actually overcome such as: difficult availability, need for high catalytic loads, inadequate performance, inadequate productivity and elevated leaching; that more them not really useful from applicative and industrial point of view (see above paragraph 2.5.3.1).

Given the good results obtained in batch mode (paragraph 2.5.2), we have been started the planned study and development of original packed-bed mini-reactors of design and construction extremely simple and cheap (see paragraph 2.2) for the application in Mizoroki-Heck coupling.

As the light of the results obtained in paragraph 2.5.2 and taking account the necessity of the reaction conditions most homogeneous possible for optimal application in flow.

For regard the application of the mini-reactors in Heck coupling, we test the model reaction between iodobenzene (**8ac**) with butyl acrylate (**24**) (**Scheme 2.5.2.1**, paragraph 2.5.2) applied the more efficient, previously described in paragraph 2.5.2, reaction condition in batch mode like 2.0 equivalents of acrylate, 1.0 equivalents of Pr_3N as base, 1.80 mL/mmol of NMP as solvent, at 110 °C; using, in the tests, reactors packed with the two MVS-prepared catalysts and four commercial catalysts pure or mixed at glass beads (as subsequently better describe case to case) connected directly to one reservoir (**Scheme 2.5.4.1**).



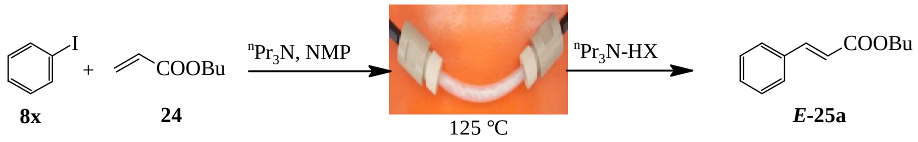
Scheme 2.5.4.1 : Generel experimental set-up of the flow systems used in our tests

Initially, we examined the our reactors packing with pure supported catalysts, 20-50 mg of the pure catalysts (length of 2.0-3.5 cm). The reaction mixture prepared directly at air was eluted in the reactor with a flow-rate of 0.12 mL/h corresponding at residence time of 31-55 min.

Unfortunately, in this test we observed several problems of reactor blocking for the majority of the reactors. In fact, only the Pd/MCM-41 (**6**) not shows this problem, probably because it's the only catalyst supported on inorganic matrix.

In detail, in the explorative tests with reactors packed with pure catalysts (about 50 mg of the commercial catalysts, and 20 mg of MVS-prepared catalysts), eluting the reaction mixture at 0.12 mL/h, we observed generally complete conversion in the collected fraction; but at the same time for the polymer-supported palladium catalysts (commercial and MVS prepared) we observed a slowdown of the collection (**8ac**/time) with increasing of the system's pressure, and consequent blocking of the reactors in the case of Pd EnCat-40 (**1**) and Pd/PVPy (**5**) (**Table 2.5.4.1**).

Table 2.5.4.1 : Reactors packed with pure catalysts in the model reaction[a]



Volume reactor: 62.8-110.2 mm^3
Flow-rate: 0.12 mL/h
Diameter: 2.0 mm
Lenght: 20-35 mm

Fraction	Catalyst (µmol Pd)	Volume reactor (mm^3)	Residence time (min)	Volume (mL)	**8x** eluted (mmol)	Conversion of **8x**^{b} (%)	Collection **8x**/time^c (mmol/h)
1	Pd/PVPy (**5**) (1.98)	62.8	31.4	0.8	0.33	97	0.050
2				2.0	0.83	96	0.050
3				4.0	1.66	97	0.050
4				1.0	0.42	95	0.036
5				1.8	0.75	98	0.005
TOT.				9.6	3.99	97	
1	Pd EnCat-40 (**1**) (12.60)	75.3	37.6	0.2	0.08	97	0.050
2				0.2	0.08	98	0.005
TOT				0.4	0.16		
1	Fibrecat 1007 (**2**) (21.10)	74.2	37.1	1.0	0.42	99	0.050
2				3.8	1.60	99	0.050
3				8.5	3.57	98	0.045
4				5.5	2.31	96	0.045
5				6.8	2.86	99	0.025
6				6.4	2.69	99	0.020
TOT				32.0	13.45	98	
1	$PdCl_2(PPh_3)_2$-PS (**4**) (26.50)	76.2	38.1	1.0	0.42	98	0.050
2				2.8	1.60	99	0.050
3				6.5	3.57	98	0.045
4				4.5	2.31	97	0.045
5				6.6	2.86	98	0.025
6				5.4	2.69	99	0.020
TOT				26.8	11.26	98	
1	$Pd(PPh_3)_4$-PS (**3**) (27.60)	78.1	39.0	5.0	2.10	99	0.050
2				4.0	1.68	98	0.050
3				4.0	1.68	99	0.043
4				4.0	1.68	98	0.030
5				3.9	1.64	98	0.025
6				2.0	0.84	98	0.020
				22.9	9.62	98	
1	Pd/MCM-41 (**6**) (1.98)	110.2	55.1	3.0	1.26	98	0.050
2				5.6	2.36	96	0.050
3				5.0	2.10	97	0.050
4				4.7	1.98	50	0.050
5				5.0	2.10	46	0.050
				23.3	9.80	76	

a) Reaction conditions: 1.0 equivalent aryl iodide (**8x**), 2.0 equivalent of *n*-butyl acrylate (**24**), 1.0 equivalent of tripropylamine, NMP (1.8 mL/mmol), 125 °C; b) Evaluated by GC analysis; c) Determined as ratio between the mmol of the halide **8ac** to the time necessary to collect it.

In detail, using the Fibrecat 1007 (**2**), $PdCl_2(PPh_3)_2$-PS (**3**) and $Pd(PPh_3)_4$-PS (**4**) we observed a soft, but continuous, loss of the collection ratio after the first fractions. While the Pd EnCat-40

(**1**) and Pd/PVPy (**5**) showed a drastic loss of the ratio collection after the first fractions, with consequent blocking of the reactors.

The Pd/MCM-41 (**6**) showed in all collect fractions the same collection, observing the only loss of the conversion (loss of the catalytic activity of the catalyst) after 5.72 mmol of **8x** eluted; to obtain a medium conversion of 76 % eluting 9.80 mmol of **8x** at 0.12 mL/h.

At the light of these results we decided to continue the studi with **6** using the reactor packing with pure catalyst, and if possible could solve the observed problem for the other catalytic systems.

At regard the study of Pd/MCM-41 (**6**) in continuous flow, after this optimum result obtained at 0.12 mL/h, initially we have decided to research the maximum usable flow-rate.

Therefore, we increased the flow-rate passing from 0.12 mL/h at 0.30 mL/h, corresponding at residence time of 22 minutes, obtaining similar performance in term of medium conversion (75 %) and mmol of **8x** eluted (9.90 mmol), but with an about double output (**Figure 2.5.4.1**).

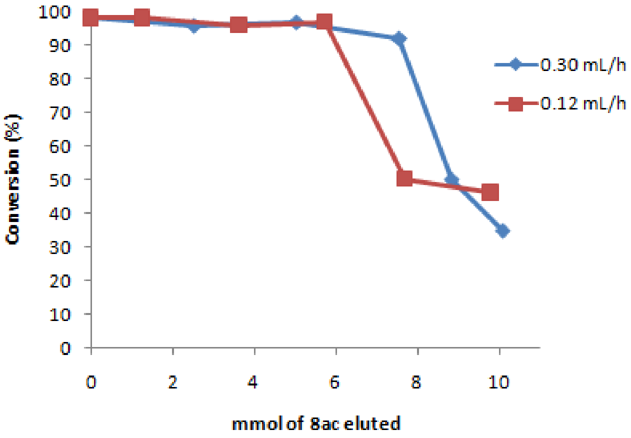
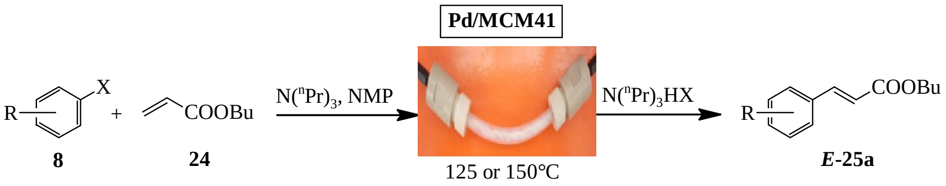


Figure 2.5.4.1: Comparison of continuous process at different flow-rate

Individuated the optimum flow-rate for the use of Pd/MCM-41 (**6**) packed reactor in MIzoroki-Heck reaction between an aryl iodide electron-neutral (**8x**) and butyl acrylate (**24**), we evaluated in term of yield, productivity and leaching, the effective potentiality of this system in the reaction with several aryl iodides and any bromides (**Table 2.5.4.2**). Moreover, the catalytic behaviour of Pd/MCM-41 catalyst will be compared with the commercial heterogeneous palladium catalyst Pd/C in terms of catalytic activity, productivity and palladium leaching in the reaction mixture at the same reaction conditions (**Table 2.5.4.2**).

Table 2.5.4.2: Potentiality of Pd/MCM-41 reactor in Mizoroki-Heck reaction[a]



Volume reactor: 110 mm^3
Flow-rate: 0.30 mL/h
Diameter: 2.0 mm
Lenght: 35 mm

Run	Substrate	Column	Pd Load (µmol)	Residence Time (min)	Mmols of **8** Eluited	Conversion[b] (%)	Yield of *E*-**19a**[c] (%)	Output (mg/h)	Space Time Yield[d] (Kg/[Lxh])	Productivity [*E*-**25a**/Pd][e]	Metal Leaching[f] (%)
1	R = H X = I (**8x**)	***6*** *(21 mg)*	1.98	22.0	9.8	75	70	17.9	0.162	3465	0.04 (0.06 ppm)[g]
2		*Pd/C* *(25 mg)*	5.90	19.0	2.5	87	80	13.6	0.217	339	0.70
9	R = 4-Me X = I (**8c**)	***6*** *(21 mg)*	1.98	22.0	11.5	72	45	12.3	0.112	2588	0.05
10	R = 4-COOMe X = I (**8ad**)	***6*** *(21 mg)*	1.98	22.0	3.5	80	77	25.3	0.229	1361	-
11	R = 4-NO$_2$ X = Br (**8d**)	***6*** *(21 mg)*	1.98	22.0	2.6	75	60	18.2	0.165	780	0.76 (4.11 ppm)[g]
10	R = 4-COOMe X = Br (**8ae**)	***6*** *(21 mg)*	1.98	22.0	2.2	45	-	25.3	-	-	-

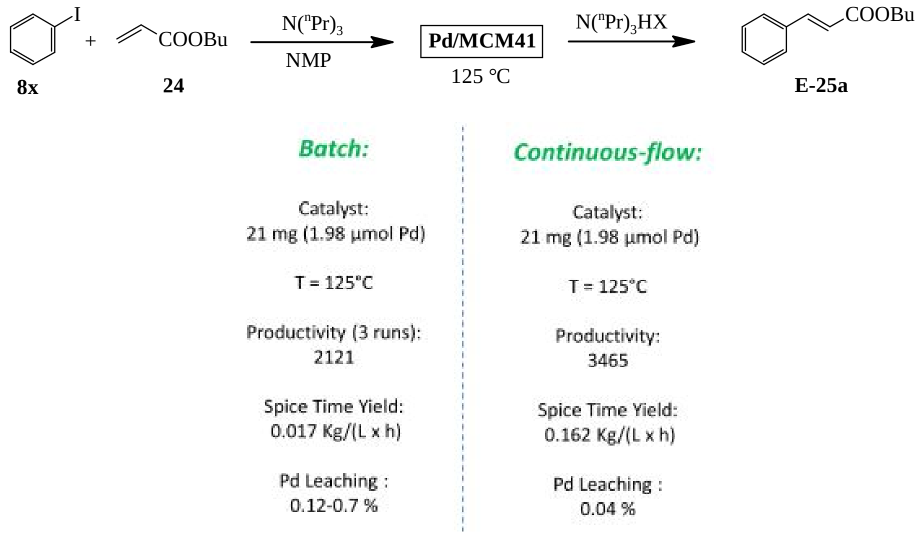
a) Reaction conditions: 1.0 equivalent aryl iodide (**8**), 2.0 equivalent of *n*-butyl acrylate (**24**), 1.0 equivalent of tripropylamine, NMP (1.8 mL/mmol), 125 °C for X = I or 150°C for X = Br; b) Evaluated by GC analysis to the complete deactivation of catalytic system; c) Isolated Yield; d) Determined as ratio between the mass of the product ***E*-25a** compared to the reactor volume and the time taken to acquire; e) Determined as ratio between mmol product with mmol Pd available; f) Evaluated by ICP-OES to output reaction mix and reported as Pd leached wt.% of the total available metal; g) Calculated as mg of Pd leached/Kg of crude ***E*-25a**.

In these tests we observed that the Pd/MCM-41 (**6**) system appear an efficient and stable catalyst for the C-C Mizoroki-Heck coupling reaction of several haloarenes with butyl acrylate (**24**) in continuous flow conditions. In fact, this catalyst showed very good activity and efficiency both with aryl iodide electron-poor (Run 3, **Table 2.5.4.2**) that electron-rich (Run 4, **Table 2.5.4.2**), but also with aryl bromides electron-poor; obtaining the corresponding trans-cynnamates with conversions in the range 72-80 % at 125°C for iodoerenes and 150°C for bromoarenes, with loss of Pd from the reactor very low (0.04-0.75%, corresponding to 0.06-4.11 ppm of Pd in the crude products) in almost all case. Most particular appear the result obtained in the reaction with 4-bromo-methylbenzoate (**8ad**); in fact in this case, the reaction showed complete conversion in the first millilitres collected, immediately after dropping drastically to 30 %, obtaining only a medium conversion of 45 % in the elution of only 2.20 mmol of **8ad**. It is worth noting that a comparison of Run 1-2 of this table shows how, under flow conditions, the commercial Pd/C catalyst can afford a higher yield, but in spite of a dramatically lower productivity and a much greater loss of Pd.

Moreover, it is interesting to mention that the reactions mix have been prepared under air, indicating that these processes do not require the use of inert atmosphere.

At the light of these results, compared with those obtained in conventional conditions (**Scheme 2.5.4.2**), taking into account several parameters such as: space time yield, productivity and leaching, we can affirmed that the our continuous-flow system appears a similar, if not the better, alternative to traditional process in this C-C reaction for an academic and/or industrial application.

Scheme 2.5.4.2: Batch process vs. Continuous-flow process in the Heck reaction catalyzed by Pd/MCM-41



Batch:	Continuous-flow:
Catalyst: 21 mg (1.98 µmol Pd)	Catalyst: 21 mg (1.98 µmol Pd)
T = 125°C	T = 125°C
Productivity (3 runs): 2121	Productivity: 3465
Spice Time Yield: 0.017 Kg/(L x h)	Spice Time Yield: 0.162 Kg/(L x h)
Pd Leaching : 0.12-0.7 %	Pd Leaching : 0.04 %

As above mentioned, if possible we could solve the observed stoppage problem for the other our five catalytic systems.

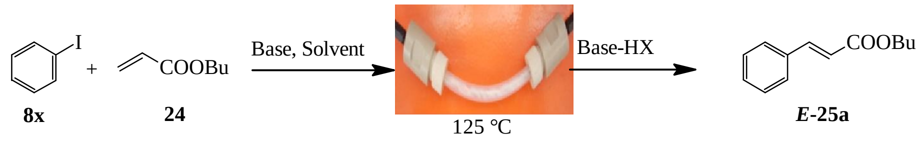
To resolve the problem we could opted to: ***a)*** applied conditions at low temperature and/or ***b)*** diluting the catalysts with glass beads.

Initially we tested the application of low temperature conditions. Taking into account the results obtained in batch study (see paragraph 2.5.2), the use of low temperature conditions generally increase slightly the reaction time, but at regard the commercial catalysts **1-4** showed most low leaching data. For regard the Pd/PVPy, the low reaction temperature were applicable only by add of additive or using the AcOK as base, with low increasing the reaction time, but showed high leaching data.

Therefore, we decided to examine the five reactors packed with pure catalysts at 0.12 mL/h under these low temperature (90-95 °C) reaction conditions (**Table 2.5.4.2**).

Effectively these conditions have solved the problem, but unfortunately, despite these condition were appeared interesting in batch mode, in continuous flow process we observed starting low conversion, with rapid reduction of the activity and efficiency of the reactors, obtaining rapidly very low medium conversions.

Table 2.5.4.2 : Continuous flow process at low temperature conditions (90 °C)[a]



Volume reactor: 62.8-78.1 mm^3
Flow-rate: 0.12 mL/h
Diameter: 2.0 mm
Lenght: 20-35 mm

Fraction	Catalyst (μmol Pd)	Volume reactor (mm^3)	Condition base/additive/solvent	Volume (mL)	**8x** eluted (mmol)	Conversion of **8x** (%)[b]	Collection **8x**/time (mmol/h)[c]
1	Pd/PVPy (1.98)	62.8	Pr_3N/TBAB+LiCl/NMP	0.5	0.20	99	0.048
2				2.5	1.00	30	0.048
TOT				**3.0**	**1.20**	**42**	
1	Pd/PVPy (1.98)	62.8	AcOK/-/DMF:H_2O	0.5	0.23	78	0.054
2				3.8	1.71	77	0.054
3				9.1	4.10	68	0.054
4				2.4	1.08	56	0.054
TOT				**15.8**	**7.12**	**69**	
1	Pd EnCat-40 (12.60)	75.3	Pr_3N/-/NMP	0.4	0.16	65	0.050
2				3.0	1.26	65	0.050
3				4.0	1.68	50	0.050
4				4.0	1.68	35	0.050
TOT				**11.4**	**4.79**	**49**	
1	Fibrecat 1007 (21.10)	74.2	Pr_3N/-/NMP	1.0	0.42	96	0.050
2				4.0	1.68	94	0.050
3				8.5	3.57	70	0.050
4				5.5	2.31	64	0.050
5				6.0	2.52	50	0.050
6				6.5	2.73	37	0.050
TOT				**31.5**	**13.23**	**62**	
1	$PdCl_2(PPh_3)_2$-PS (26.50)	76.2	Pr_3N/-/NMP	1.0	0.42	95	0.050
2				3.0	1.26	93	0.050
3				6.5	2.73	65	0.050
4				4.5	1.89	50	0.050
5				6.5	2.73	43	0.050
6				5.5	2.31	38	0.050
TOT				**27.0**	**11.34**	**56**	
1	$Pd(PPh_3)_4$-PS (27.60)	78.1	Pr_3N/-/NMP	7.0	2.94	99	0.050
2				7.0	2.94	98	0.050
3				6.0	2.52	95	0.050
4				5.0	2.10	90	0.050
5				6.0	2.52	66	0.050
6				6.0	2.52	56	0.050
7				4.3	1.81	37	0.050
TOT				**41.3**	**17.35**	**78**	

a) Reaction conditions: 1.0 equivalent aryl iodide (**8x**), 2.0 equivalent of *n*-butyl acrylate (**24**), 1.0 equivalent of base, 0.5 equivalent of additive, solvent (1.8 mL/mmol), 125 °C; b) Evaluated by GC analysis; c) Determined as ratio between the mmol of the halide **8x** to the time necessary to collect it

The Pd/PVPy (**5**) using the addition of additive (TBAB + LiCl), showed complete conversion in the first 0.20 mmol of **8x** eluted; but unfortunately immediately after it dropped drastically to 30 %, obtaining only a medium conversion of 42 % in the elution of only 1.20 mmol of **8x**. More interesting was the use of AcOK in DMF/H_2O (4:1); in fact the Pd/PVPy showed a generally conversion of 69 % in the elution of 7.12 mmol of **8x**, in agreement with the result obtained in batch process.

FibreCat 1007 (**2**) and $PdCl_2(PPh_3)_2$-PS (**3**) showed in the first fractions high conversions (96-93 %), but immediately after it has been observed an immediate and continuous lowering of the values, joints well below 50 % after the passage of a few millilitres of mixture reaction. Therefore these systems are turned off quickly, revealing unable to operate efficiently and lasting at 90 °C.

The Pd EnCat-40 (**1**) in this case showed already in the first fractions, very low conversion (65 %) that immediately lowering of the value, joint well below 35 % after the passage of few millilitres. The only advantage it was the not blocking of the reactor.

More interesting appear the use of $Pd(PPh_3)_4$-PS (**4**) at low temperature condition. In fact, the catalyst showed high conversions (99-90 %) for several fractions (corresponding at the passage of 22 millilitres), and only next these, the conversion lowering the value, obtaining in total a conversion of 78 % in the elution of 17 mmol of **8x**.

At the light of these discordant results, and taking into account the results obtained in the other C-C cross-coupling, object of this work, in continuous-flow process using diluted catalysts (see paragraph 2.3.5 and 2.4.5); we tested the application of reactors packed with the catalysts diluted by glass beads.

For a better comparison between the systems we examined reactors at equal reactor volume (141 mm^3) and flow-rate (0.15 mL/h), preparing reactors packed with catalyst and glass beads in volume ratio about 1:1 and 1:10.

Initially we examined the 1:1 volume ratio systems, introducing as dry the commercial catalysts (30 mg) or **5** (21 mg) mixed with an approximately 1:1 volume ratio of the above mentioned glass beads (about 130 mg). The obtained reactors had similar lengths (usually 4.5 cm) corresponding at internal volume of 141 μL. These reactors were examined in the same model reaction maintaining unchanged the parameters (concentration, temperature, etc.) of the above mentioned tests that use the pure catalysts. Under these conditions the majority of the systems not showed blocking problems, obtaining good medium conversions (79-89 %)

eluting several mmol of **8x**, within 56 minutes of the residence times and keep them for long time (140-530 hours) (**Table 2.5.4.3**).

Table 2.5.4.3: Heck coupling using reactors packing with catalysts mixed glass beads in 1:1 volume ratio[a]

Volume reactor: 141 mm^3
Flow-rate: 0.15 mL/h
Residence time: 56.4 min
Diameter: 2.0 mm
Lenght: 45 mm

Run	Catalyst	Pd Load (µmol)	Volume Eluted	**8x** eluted (mmol)	Conversion[b] (%)	Yield of ***E*-25a**[c] (%)	Output (mg/h)	Space Time Yield[d] (Kg/[Lxh])	Efficiency [**8x**/Pd][e]	Productivity [***E*-25a**/Pd][f]	Metal Leaching[g] (%)
1	***1*** *(30 mg)*	12.60	1.83	0.8	97	90	12.0	0.195	64	57	0.37
2	***2*** *(25 mg)*	21.70	78.80	33.1	86	70	9.0	0.064	1525	1100	0.22
3	***3*** *(21 mg)*	26.50	68.10	28.6	80	54	6.9	0.049	1079	583	10.30
4	***4*** *(21 mg)*	19.30	59.52	25.0	79	60	7.7	0.055	1295	777	0.47
5	***5*** *(21 mg)*	1.98	20.20	8.5	86	77	9.9	0.070	4293	3306	0.02

a) Reaction conditions: 1.0 equivalent aryl iodide (**8x**), 2.0 equivalent of *n*-butyl acrylate (**24**), 1.0 equivalent of tripropylamine, NMP (1.8 mL/mmol), 125 °C for X = I; b) Evaluated by GC analysis to the complete deactivation of catalytic system; c) Isolated Yield; d) Determined as ratio between the mass of the product ***E*-25a** compared to the reactor volume and the time taken to acquire; e) Determined as ratio between mmol **8x** eluted with mmol Pd available; f) Determined as ratio between mmol product with mmol Pd available; g) Evaluated by ICP-OES to output reaction mix and reported as Pd leached wt.% of the total available metal.

In detail, the results obtained are very interesting. The reactors packing with Pd(PPh$_3$)$_4$-PS (**4**) mixed at glass beads showed a similar result at that obtained using the reactor with pure catalyst (79 % of medium conversion) eluted 25.00 mmol of **8x** with global productivity of 777 and an efficiency of 1295 (corresponding at 0.08 mol% of Pd load in batch).

The PdEnCat-40 (**1**) result the only system that showed again the problem of blocking the reactors, eluting only 0.80 mmol of **8x** in the reactor with conversion of 97 %, obtaining an yield of 90% but with very low productivity (only 57) and efficiency (only 64).

The PdCl$_2$(PPh$_3$)$_2$-PS (**3**) mixed at glass beads showed good result comparable with the result obtained in batch process in terms of efficiency, but not in term of yield and productivity. In fact in continuous flow this catalyst showed a good total conversion (80 %) eluting 28.60 mmol of **8x** with an efficiency of 1079 (corresponding at 0.09 mol% of Pd load in batch process), but with very low total yield in ***E*-25a** (only 54 %) and global productivity of 583 (in batch process this catalyst showed 76 % of yield with productivity of 1520). Moreover, this catalyst showed a very high loss of palladium in solution, corresponding at 10 % of the Pd load in the reactor.

The better performances in this reaction were achieved packing the reactors with the Fibrecat-1007 (**2**) and Pd/PVPy (**5**) mixed with glass beads, that showed similar high total conversions (86 %) within 56 minutes and keep them for long time (133-500 hours). The Fibrecat 1007 (**2**) showed an efficiency of 1525, corresponding at 0.07 mol% of Pd load in batch process, with a global productivity of 1100 and a low palladium loss (0.22 % of the Pd load in the reactor).

While the Pd/PVPy (**5**) showed results similar at the performance obtained using the reactor packing with Pd/MCM-41 pure; with a productivity of 3306 and an efficiency of 4293 corresponding at 0.02 mol% of Pd load in batch process.

Most interesting result the Pd release of the reactors (analysed directly the contents of the palladium in the solution out from the reactors without microfiltration); in fact, despite the activity of the catalysts drops after many eluted **8x** (varied from case to case), the data of Pd released were very low for the majority of the catalyst (< 0.50 % of the Pd packing into the reactors), with case very interesting such Pd/PVPy (**5**) that showed a very very low release of Pd (0.02%) and the $PdCl_2(PPh_3)_2$-PS (**3**) that showed a very high Pd release (> 10%).

At the light of these positive results, in particular at regard of the Pd/PVPy (**5**), to better the performances in the Heck coupling with the commercial catalysts, we decided to prepare the reactors most diluted introducing as dry the commercial catalysts (about 5.0 mg) mixed with an approximately 1:10 volume ratio of the above mentioned glass beads (150 mg); in order to obtain reactors had lengths similar at the above prepared and usually is 4.5 cm corresponding at internal volume of 141 μL.

These reactors were examined in the same model reaction maintaining unchanged the parameters (concentration, flow-rate, etc.) of the above mentioned tests that use the 1:1 mixed catalysts.

Under these conditions the systems showed similar medium conversions (77-89 %) respect at the data obtained with reactors 1:1 mixed, showed better catalytic performance and limited Pd release (**Table 2.5.4.4**).

Table 2.5.4.4: Heck coupling using reactors packing with catalysts mixed glass beads in 1:1 volume ratio[a]

Volume reactor: 141 mm^3
Flow-rate: 0.15 mL/h
Residence time: 56.4 min
Diameter: 2.0 mm
Lenght: 45 mm

Run	Catalyst	Pd Load (μmol)	Volume Eluted	**8x** eluted (mmol)	Conversion[b] (%)	Yield of ***E*-25a**[c] (%)	Output (mg/h)	Space Time Yield[d] (Kg/[Lxh])	Efficiency [**8x**/Pd][e]	Productivity [***E*-25a**/Pd][f]	Metal Leaching[g] (%)
1	***1*** *(6.0 mg)*	2.50	16.86	7.08	89	62(60)	8.0	0.057	2778	1756	0.37
2	***2*** *(3.3 mg)*	2.40	10.41	4.37	85	50(46)	6.5	0.046	1852	910	0.37
3	***3*** *(3.0 mg)*	3.00	22.43	9.42	79	64	8.3	0.058	3226	2010	0.31
4	***4*** *(3.1 mg)*	2.20	9.93	4.17	77	49(43)	6.4	0.045	1923	929	0.43

a) Reaction conditions: 1.0 equivalent aryl iodide (**8**), 2.0 equivalent of *n*-butyl acrylate (**24**), 1.0 equivalent of tripropylamine, NMP (1.8 mL/mmol), 125 °C for X = I; b) Evaluated by GC analysis to the complete deactivation of catalytic system; c) Isolated Yield; d) Determined as ratio between the mass of the product ***E*-25a** compared to the reactor volume and the time taken to acquire; e) Determined as ratio between mmol **8x** eluted with mmol Pd available; f) Determined as ratio between mmol product with mmol Pd available; g) Evaluated by ICP-OES to output reaction mix and reported as Pd leached wt.% of the total available metal.

The results obtained are very interesting. In fact, the reactors packing with commercial catalysts mixed at glass beads in about 1:10 ratio showed bigger efficiency respect at 1:1 ratio. In detail, Pd(PPh$_3$)$_4$-PS (**4**) and Fibrecat-1007 (**2**) mixed at glass beads showed a similar result obtained using the reactor with 1:1 mixed ratio (77-85 % of medium conversion) eluted about 4.50 mmol of **8x** with global efficiency of 2000 about (corresponding at 0.05 mol% of Pd load in batch) with low Pd release (< 0.45 %).

The PdEnCat-40 (**1**) in this case not showed the blocking problem, obtaining good medium conversions (89 %) eluting 7.08 mmol of **8x**, within 56 minutes of the residence times and keep them for long time (113 hours).

The better performances in this test were achieved packing the reactors with the PdCl$_2$(PPh$_3$)$_2$-PS (**3**) mixed with glass beads; that in this case showed a low Pd release (0.31 %).

This catalyst showed a total conversions of 79 %, with an efficiency of 3226, corresponding to use 0.03 mol% of the Pd load in batch mode, with a good productivity of 2010.

Given these optimum results we decide to examine under this flow system also the low temperature condition, in prospect of being able to apply all at aryl bromides. In this case the catalysts (about 3.0 mg) mixed at glass beads (150 mg) were introduced in the reactors, and were examined in the same model reaction maintaining unchanged the parameters (concentration, flow-rate, etc.) of the above mentioned test that use the 1:10 mixed catalysts at 125 °C (**Table 2.5.4.5**).

Unfortunately, under these conditions the majority of the catalysts result less able to promote the reaction, showing low total conversion, yield and efficiency; except the Pd(PPh3)4-PS that showed the better result in term of efficiency.

Table 2.5.4.5 : Continuous flow process at low temperature conditions (90 °C) with diluted reactors[a]

Volume reactor: 141 mm^3
Flow-rate: 0.15 mL/h
Residence time: 56.4 min
Diameter: 2.0 mm
Lenght: 45 mm

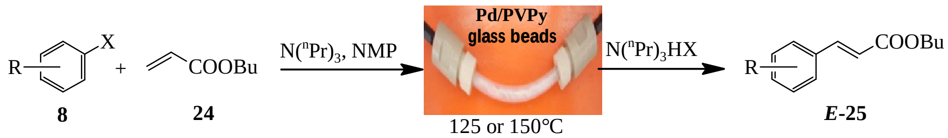
Run	Catalyst	Pd Load (μmol)	Volume Eluted	**8x** eluted (mmol)	Conversion[b] (%)	Yield of ***E*-25a**[c] (%)	Output (mg/h)	Space Time Yield[d] (Kg/[Lxh])	Efficiency [**8x**/Pd][e]	Productivity [***E*-25a**/Pd][f]	Metal Leaching[g] (%)
1	***1*** *(5.9 mg)*	2.30	6.20	2.60	67	34	4.4	0.031	1130	384	-
2	***2*** *(3.2 mg)*	2.50	7.15	3.00	57	-	-	-	1200	-	-
3	***3*** *(3.1 mg)*	3.10	5.00	2.10	75	42	5.4	0.038	677	285	3.50
4	***4*** *(4.0 mg)*	2.80	23.80	10.00	80	78	10.0	0.071	3571	2786	1.20

a) Reaction conditions: 1.0 equivalent aryl iodide (**8x**), 2.0 equivalent of *n*-butyl acrylate (**24**), 1.0 equivalent of tripropylamine, NMP (1.8 mL/mmol), 125 °C for X = I; b) Evaluated by GC analysis to the complete deactivation of catalytic system; c) Isolated Yield; d) Determined as ratio between the mass of the product ***E*-25a** compared to the reactor volume and the time taken to acquire; e) Determined as ratio between mmol **8x** eluted with mmol Pd available; f) Determined as ratio between mmol product with mmol Pd available; g) Evaluated by ICP-OES to output reaction mix and reported as Pd leached wt.% of the total available metal.

In detail, the only catalyst that showed good result is the Pd(PPh$_3$)$_4$-PS, as already seen in the tests on reactors packed with pure catalysts, obtaining good total conversion (80 %) eluting about 10 mmol of **8x**, with an efficiency very similar to that obtained with Pd/PVPy diluted 1:1 at 125° C and Pd/MCM-41 pure at 125 °C such 3571, corresponding at 0.03 mol% of Pd load in batch.

At the light of these results we decided to evaluate in term of yield, productivity and leaching, the effective potentiality of the best catalytic system (Pd/PVPy) in the reaction with several aryl iodides and any bromides (**Table 2.5.4.6**).

Table 2.5.4.6: Potentiality of Pd/PVPy reactor in Mizoroki-Heck reaction[a]



Volume reactor: 125.5 mm^3
Flow-rate: 0.15 mL/h
Diameter: 2.0 mm
Lenght: 40 mm

Run	Substrate	Pd Load (μmol)	Flow-rate (mL/h)	Residence Time (min)	Mmols of **8** Eluited	Conversion[b] (%)	Yield of ***E*-25**[c] (%)	Output (mg/h)	Space Time Yield[d] (Kg/[Lxh])	Productivity [***E*-25**/Pd][e]	Metal Leaching[f] (%)
1	R = H X = I (**8x**)	1.98	0.15	50.0	8.3	91	80	10.2	0.081	3353	0.02
2	R = 4-Me X = I (**8c**)	1.98	0.12	63.0	4.6	85	55	5.6	0.048	1278	-
3	R = 4-COOMe X = I (**8ad**)	1.98	0.18	28.0	5.4	85	70	10.7	0.110	1910	0.22
4	R = 4-COOMe X = Br (**8ae**)	1.98	0.08	96.0	4.5	trace	-	-	-	-	-

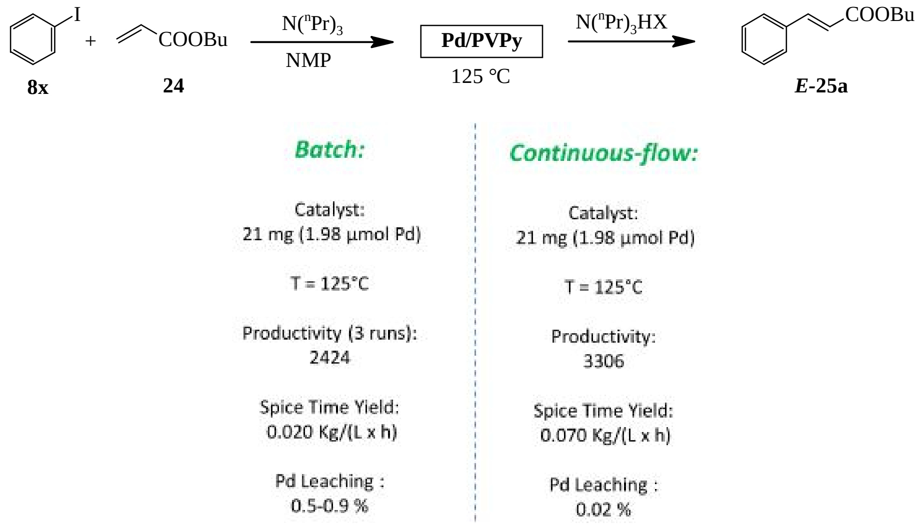
a) Reaction conditions: 1.0 equivalent aryl iodide (**8**), 2.0 equivalent of *n*-butyl acrylate (**24**), 1.0 equivalent of tripropylamine, NMP (1.8 mL/mmol), 125 °C for X = I or 150°C for X = Br; b) Evaluated by GC analysis to the complete deactivation of catalytic system; c) Isolated Yield; d) Determined as ratio between the mass of the product ***E*-25** compared to the reactor volume and the time taken to acquire; e) Determined as ratio between mmol product with mmol Pd available; f) Evaluated by ICP-OES to output reaction mix and reported as Pd leached wt.% of the total available metal.

In these tests we observed that the Pd/PVPy (**5**) appear an efficient and stable catalyst for the C-C Mizoroki-Heck coupling reaction of several haloarenes with butyl acrylate (**24**) in continuous flow conditions. In fact, this catalyst showed moderate to good activity and efficiency both with aryl iodide electron-poor (Run 2, **Table 2.5.4.6**) that electron-rich (Run 3, **Table 2.5.4.6**), after appropriate optimization of the opportune flow-rate, corresponding to longer residence times of 63 minutes for the iodotoluene (**8c**) and much shorter residence times of 28 minutes for 4-iodo-methylbenzoate (**8ad**). Unfortunately, with aryl bromides the system was not efficient despite much longer residence times of 96 min.

Moreover, it is interesting to mention that the reactions mix have been prepared under air, indicating that these processes do not require the use of inert atmosphere.

At the light of these results, compared with those obtained in conventional conditions (**Scheme 2.5.4.3**), taking into account several parameters such as: space time yield, productivity and leaching, we can affirmed that the our continuous-flow system appears a similar, if not the better, alternative to traditional process in this C-C reaction for an academic and/or industrial application.

Scheme 2.5.4.2: Batch process vs. Continuous-flow process in the Heck reaction catalyzed by Pd/PVPy



Batch:	Continuous-flow:
Catalyst: 21 mg (1.98 μmol Pd)	Catalyst: 21 mg (1.98 μmol Pd)
T = 125°C	T = 125°C
Productivity (3 runs): 2424	Productivity: 3306
Spice Time Yield: 0.020 Kg/(L x h)	Spice Time Yield: 0.070 Kg/(L x h)
Pd Leaching : 0.5-0.9 %	Pd Leaching : 0.02 %

Finally we investigate the effect of the reactor dimension (diameter and length) on the efficiency and stability of the catalytic process. For this study we used as catalyst the Pd/PVPy (**5**), that we introduced (mixed at glass beads) in reactor of diameter 2.0 mm and 4.0 mm (**Table 2.5.4.7**).

The reactor of diameter 2.0 mm (the same PTFE tube used in all previously tests) were packing with 40 mg of the catalyst and 260 mg of glass beads, obtaining a reactors of 100 mm length, corresponding at internal volume of 314 μL (about double of the previously used reactor). This reactor was examined in the same model reaction unchanged the output date, increasing proportionally at the reactor volume the flow-rate of the above mentioned tests that use a reactor of volume 141 μL. Unfortunately, the system not allows to operate at this flow-rate (0.25 mL/h), and next opportune optimization we observed that the optimum flow-rate for this reactor was 0.18 mL/h (slightly higher than that applied to the reactors long about half).

However, this system showed similar conversion and yield with the short reactor, but with a sharp deterioration in terms of efficiency and productivity, eluting only 7.3 mmol of **8x** using the double amount of the catalyst.

While, the reactor of diameter 4.0 mm were packing with 21 mg of the catalyst and 150 mg of glass beads, obtaining a reactor of 20 mm length, corresponding at internal volume of 141 μL (equal at the initial used reactor), and with 84 mg of the catalyst and 520 mg of the glass beads, obtaining a reactor of 80 mm length, corresponding at internal volume of 502 μL.

Unfortunately the reactor of 141 μL showed several problem of packaging, and we continue the study only on the reactor of 502 μL.

This reactor was examined in the same model reaction unchanged, if possible, the output date, increasing proportionally at the reactor volume the flow-rate of the above mentioned tests that use a reactor of volume 141 μL. Unfortunately, the system not allows to operate at this flow-rate (0.60 mL/h), and next opportune optimization we observed that the optimum flow-rate for this reactor was 0.30 mL/h (decidedly low considering a volume quadrupled respect at classic reactor used in our study).

However, this system showed good similar total conversion with the small reactor, eluting 57.4 mL of reaction mixture, corresponding at 23.9 mmol of **8x** (corresponding at efficiency of 3018), but with a very low yield (only 56 %) and consequently productivity (1690) and space time yield (0.028 Kg L^{-1} h^{-1}); that make this system worse than the batch process, resumed in **Scheme 2.5.4.3**

Scheme 2.5.4.3: Batch process vs. Continuous-flow process in the Heck reaction using semi-microreactor.

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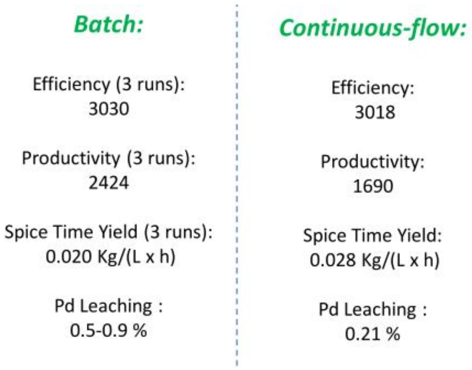


Batch:	Continuous-flow:
Efficiency (3 runs): 3030	Efficiency: 3018
Productivity (3 runs): 2424	Productivity: 1690
Spice Time Yield (3 runs): 0.020 Kg/(L x h)	Spice Time Yield: 0.028 Kg/(L x h)
Pd Leaching : 0.5-0.9 %	Pd Leaching : 0.21 %

2.5.4.1 Conclusions

In conclusion, at the light of these results (resumed in Table 2.5.4.1-2.5.4.6) we could affirm that with our packed-bed reactors (at leasts if filled with Pd/PVPy and Pd/MCM-41), it was possible to achieve performances even better than those obtained in batch mode with the same catalysts (used in similar conditions).

Aniway, our “home-made” catalysts appared to be superior, and the results achieved with these catalysts, are quite better then the best obtained in the literature works mentioned in paragraph 2.5.3.1.

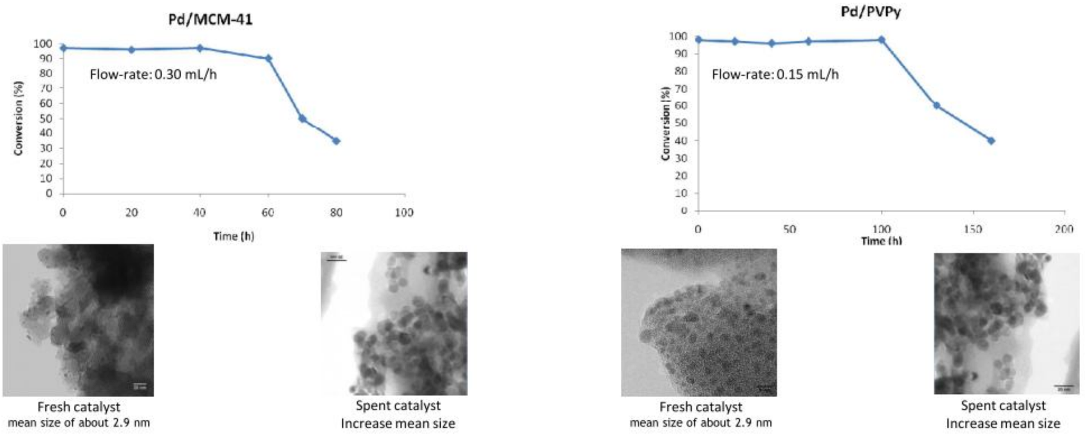
In fact, the great majority of described packed bed reactors used in Mizoroki-Heck reactions, require an actual catalytic load in the range from 1.0 to even more than 20 mol%; only in a few examples are reported ratio Pd into the reactor/halide up to the 0.2 mol%. But, in several cases our reactors work with a Pd loading lower than the 0.1 mol%.

Moreover, with Pd/MCM-41 (**6**) it was possible to obtain good performance with electro-poor aryl bromides without use of additive.

Therefore, Pd/PVPy (**5**) and Pd/MCM-41 (**6**) catalysts have been conveniently used in Mizoroki-Heck reaction of phenyl iodides with alkyl acrylates in continuous flow packed-bed reactors showing higher efficiency, productivity and lower Pd leaching than those observed in batch reaction conditions.

Moreover TEM studies of the spent Pd/PVPy (**5**) and Pd/MCM-41 (**6**) catalysts showed only an increase in mean particle size with respect to that observed in a fresh samples; this phenomenon can be attributed to the Ostwald ripening process which can occur under the reaction conditions (**Figure 2.5.4.2**).

Figure 2.5.4.2: TEM of catalyst fresh and spent next continuous flow process



Fresh catalyst
mean size of about 2.9 nm

Spent catalyst
Increase mean size

Fresh catalyst
mean size of about 2.9 nm

Spent catalyst
Increase mean size

2.6 Preparation of the required alkenyl halides and boronic acids as starting materials

As mentioned in paragraph 2.3.2.3 and 2.4.2.3, to explore the scope and generality of our chosen supported catalysts in the Suzuki and Sonogashira reaction, under the optimized conditions, we necessity of several alkenyl halides not much commercially available and/or at high cost.

In addition as we stated in section 1.4, part of our plan was to synthesize bioactive natural compounds as the hydroxystilbenes, and for this we have to need for suitable precursors (β-bromostyrenes and boronic acids) for the possible application of our systems in the synthesis of these natural compounds, as better reported in paragraph 2.7.2.

In particular, we necessity of several differently substituted alkenyl bromides generally not much commercially available and/or at high cost, such as (E)-β-bromostyrenes **12d-f** (in the case of the Suzuki reaction, see paragraph 2.3.2.3, and as starting materials for the synthetic process of the hydroxystilbenes, see paragraph 2.7.2) and 1-bromo- (**12h**, **12j** and **12k**) or 1-iodo-alkene **22** (in the case of the Sonogashira reaction, see paragraph 2.4.2.3).

In addition, for regard the Suzuki reaction and the synthetic process to obtain the natural hydroxystilbenes, we necessity of some boronic acids.

The vinyl bromides and iodides were synthesized by opportune and selective literature procedures of *one-pot* hydroallumination-bromuration and/or hydroboration-ioduration of terminal alkynes about opportune optimization.

The (E)-β-Bromostyrenes were synthetized by opportune and selective procedure of catalytic halo-decarboxylation, about opportune optimization taking account its application in a possible continuous-flow sequential process.

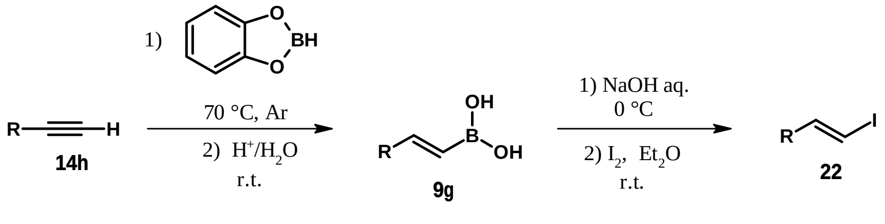
Finally, the boronic acids were synthesized by opportune literature procedures of hydroboration-hydrolysis (to obtain vinyl boronic acids) and electrophilic borylation of aryl Grignard reagents (to obtain aryl boronic acids).

2.6.1 Synthesis of (E)-1-iodo-1-dodecene (22) and (E)-1-bromo-1-alkenes 12h, 12j and 12k

As about mentioned vinyl bromides and iodides were synthesized by selective literature procedures of one-pot hydroallumination-bromuration and/or hydroboration-ioduration of terminal alkynes.

In detail, the (E)-1-iodo-1-dodecene (**22**), generally not easily and cheap commercially available, was synthesized by a classical hydroboration of the opportune terminal alkyne **14h** with catecholborane, to obtain the vinyl-boronic acid **9g** after the hydrolysis of the corresponding catecholboronic ester **26**, and next stereospecific iodo-deboronation conducted under suitable conditions (**Scheme 2.6.1**).

Scheme 2.6.1: Synthesis of (E)-1-iodo-1-dodecene



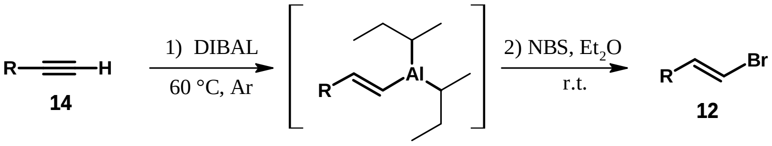
$R = C_{10}H_{21}$

The hydroboration's step was conducted using a simple procedure of Brown,**[407]** suitably modified in the hydrolysis of the catecholboronic ester intermediate. In fact, in the work of Brown the hydrolysis was performed in only water stirring overnight, but in our case GC and GC-MS analysis showed incomplete conversion next this time. While performing the hydrolysis in 1 % HCl aqueous solution for overnight, we observed the complete formation of the desired boronic acid **9g**.

The stereospecific iodo-deboronation's step was conducted using another simple procedure of Brown,**[408]** that was performed introducing respectively the NaOH aqueous solution at 0°C and subsequently the ether solution of iodine to obtain the desiderated (E) isomer of the vinyl iodide **22**.

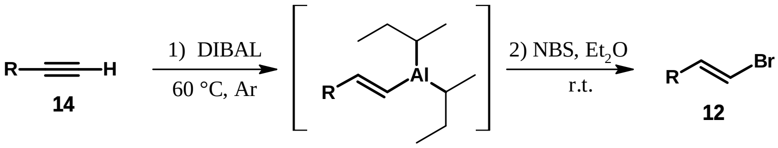
For regard the (E)-1-bromo-1-alkenes (**12h**, **12j** and **12k**), generally not easily and cheap commercially available, were synthesized by hydroalumination of the opportune terminal alkyne **14** with diisobutylaluminium hydride (DIBAL), and next one-pot bromuration by use the N-bromosuccinimide (NBS) (**Scheme 2.6.2**).

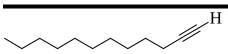
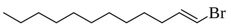
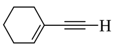
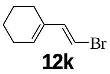
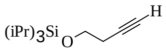
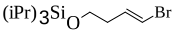
Scheme 2.6.2: Synthesis of (E)-1-bromo-1-alkenes by *one-pot* hydroallumination-bromuration



This process steps were conducted using a simple procedure of Alexakis,**[409]** to obtain the desiderated (E) isomer of the desired vinyl bromide **12** in good yields (**Table 2.6.1**).

Table 2.6.1: Synthesis of (E)-vinyl bromides



Alkyne (14)	Viny halide (12)	Yield in 12 (%)
 **14h**	 **12h**	83
 **14d**	 **12k**	67
 **14g**	 **12j**	20

2.6.2 Synthesis of (E)-β-bromostyrenes

For regard the (E)-β-bromostyrenes, in literature it was prepared by several stereoselective procedures such halodeboronation,**[408, 410]**, chemoselective reduction of 1,1-dibromoalkenes**[411]** and decarboxylative bromination of cinnamic acids**[412]** for cite the principals.

At the light of the works reported in literature on the preparation of the (E)-β-bromostyrenes, and taking into account the our work plan, the decarboxylative bromination of cinnamic acids could appear very interesting for our scopes.

In fact, this reaction appear a simple and favorable protocol, that could be easily performed in continuous flow mode, after opportune optimization of the reaction conditions, and require simple cinnamic acids as start materials. Cinnamic acids **27** could be prepared by the our optimized Mizoroki-Heck reaction conditions between aryl halide **8** and butyl acrylate (**24**) in batch and/or flow mode (see paragraph 2.5), followed from a saponification step by NaOH (2M) solution.

Moreover, as better reported in paragraph 2.7.2, in the synthesis of interesting bioactive natural hydroxystilbenes, we have been decided to focus our synthetic approach on the key step of the Suzuki-Miyaura reaction on the 4-hydroxy-(E)-β-bromostyrene (**12e**) and/or the corresponding silylated 4-t-butyldimethylsilyloxy-(E)-β-bromostyrene (**12f**), already easily prepared in literature through catalytic decarboxylative bromination of the p-cumaric acid (**27b**)**[413]**.

The literature procedure reported to obtain the desiderated 4-hydroxy-(E)-β-bromostyrene (**12e**), showed good yield, by decarboxylative bromination of the p-cumaric acid (**27b)**, using N-bromo succinimide (NBS) under micellar media, in the presence of cetyl trimethyl ammonium bromide (CTAB) as catalyst.

This reaction condition respect our parameters of novelty, simplicity and environmental friendly. In fact, this reaction of halo-decarboxylation of the carboxylic acids (Hunsdiecker reaction), classically to provide the use of toxic and hazards molecular bromine and stechiometric salts of Hg (II), Tl (I), Pb (IV) and Ag (I), that involve organic radical intermediates.**[414]** While this reaction protocol, together at others, provide the use of less toxic NBS, and catalytic amount of ammonium salt pool.

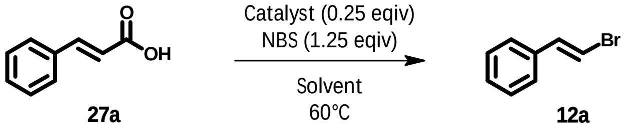
Unfortunately, this reaction condition showed several problems of homogeneity the reaction mixture, to make difficult the work-up procedures, and result inapplicable in flow.

On the light of these results, we examined several catalytic Hunsdiecker processes reported in literature on cinnamic acids,**[425]** in order to identify reaction conditions in which all reagents were solubilized and the reaction mixture are completely homogeneous even at room temperature (crucial issue for an easy application of reactions in continuous flow, see paragraph 1.2). In particular, the use of insoluble catalysts and the formation of precipitates had to be minimized, and the solvent must be able to dissolve completely at room temperature the cinnamic acid **27**, the NBS (used as donor Br) and the catalyst; all without having increase strongly the dilutions and decrease the efficiency of the reaction.

After these preliminary studies of solubility and homogeneity of the reaction mixture, we have chosen a set of possible homogeneous reaction conditions, that provide the use of LiOAc, or CTAB, or Et_3N as catalyst and CH_3CN/H_2O (7:1), or DMF/H_2O (7:1), or CH_3CN, or DCE as solvent.

Subsequently, these reaction conditions were applied in the preparation of (E)-β-bromostyrene (**12a**) to evaluated the efficiency and goodness of the same (**Table 2.6.2**)

Table 2.6.2: Identification of the better catalytic Hunsdiecker reaction condition[a]



Entry	Solvent	Dilution (mL/mmol)	Catalyst	Time (min)	Conversion[b] (%)	Yield[c] (%)	E/Z Ratio[d]
1	CH_3CN/H_2O (7:1)	1.25	LiOAc	30	> 99	45	95/5
2	CH_3CN/H_2O (7:1)	2.50	TBAB	30	> 99	38	95/5
3	CH_3CN/H_2O (7:1)	1.25	Et_3N	30	80	41	99/1
4	CH_3CN	1.25	Et_3N	120	< 10	-	-
5	DCE	6.00	Et_3N	120	< 10	-	-
6	DMF/H_2O (7:1)	1.25	LiOAc	30	90	20	95/5

a) Reaction conditions: 4.0 mmol of cinnamic acid (**27a**), 1.25 equivalent of NBS, 0.25 equivalent of catalyst, solvent, 60°C; b) Evaluated by GC analyses and reported as areas of product + by-product on area of start material; c) Isolated Yield; d) Evaluated by GC analyses and reported as areas ratio

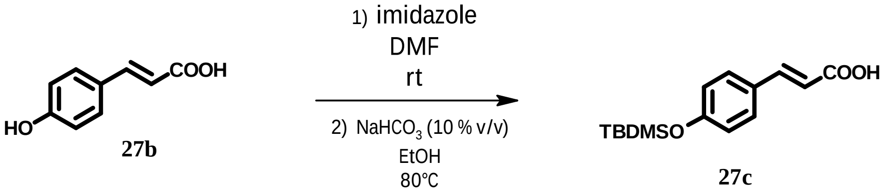
Taking into account several parameters such as yield, reaction time, total dilution and isomeric ratio, the better reaction condition result be use of LiOAc as catalyst in CH_3CN/H_2O (7:1) as solvent. In fact, under this conditions we have homogeneous reaction mixture using only 1.25 mL/mmol of the solvent, and obtaining the desired product **12a** in 45 % yield after 30 minutes at 60°C, with an E/Z ratio of 95/5.

Identified the reaction condition most easily, homogeneous and efficient, we proceeded to synthesize several differently substituted (E)-β-bromostyrenes **12e-m,** , starting from the corresponding cinnamic acids **27** in batch mode.

Therefore, the study was set up by selecting a few examples of cinnamic acids, and in particular the p-cumaric acid (**27b**) and its *t*-butyldimethylsilylated derivative (**27c**); start materials of the our possible synthetic approach to prepare the natural pterostilbene (**13k**) and two new natural derivatives **13l** and **13m**.

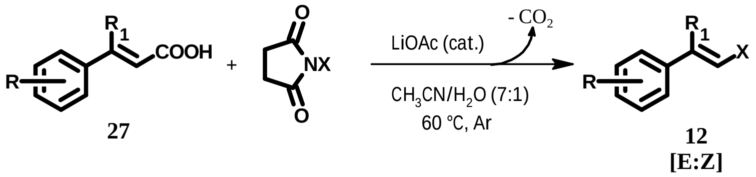
(E)-3-(4-(*tert*-butyldimethylsilyloxy)phenyl)acrylic acid (**27c**) was prepared by **27b** using a modified literature procedure of silylation (**Scheme 2.6.3**), that to provide the silylation with t-butyldimethylsilyl chloride in presence of imidazole in DMF at room temperature, and subsequently treatment with $NaHCO_3$ at 80°C, to obtain the saponification of the possible silylester by-product that we have obtained in the process.

Scheme 2.6.3: Silylation of p-cumaric acid



Several commercial and/or prepared cinnamic acids **27** were used in the synthesis of **12a** and **12e-m** using the about mentioned reaction condition to obtain the desired products in acceptable yields and good selectivity (**Table 2.6.3)**.

Table 2.6.3: Batch synthesis of (E)-β-bromostyrenes 12e-m by catalytic Hunsdiecker reaction condition[a]



R = H, 4-Me, 2-OMe, 4-NO_2, 4-Cl, 4-OH, 4-TBDMSO
R_1 = H, Me
X = I, Br

Run	Cinnamic acid (27)	NXS	Time (h)	Conversion[b] (%)	Yield in 12[c] (%)	Selectivity[b] [E:Z]	Space Time Yield[d] (Kg/[L x h])
1	*R = H* *R_1 = H*	*X = Br*	0.5	99	45	95.0: 5.0	0.03
2	*R = H* *R_1 = H*	*X = I*	30	70	23	99.0 : 1.0	0.02
3	*R = 4-Me* *R_1 = H*	*X = Br*	0.5	99	63	99.9 : 0.1	0.05
4	*R = 2-OMe* *R_1 = H*	*X = Br*	1.0	99	78	99.9 : 0.1	0.05
5	*R = 4-NO_2* *R_1 = H*	*X = Br*	2.0	99	20	96.0 : 4.0	0.02
6	*R = 4-Cl* *R_1 = H*	*X = Br*	0.5	99	65	99.0 : 1.0	0.05
7	*R = 4-OH* *R_1 = H*	*X = Br*	1.0	40	10	96.0 : 4.0	0.01
8	*R = 4-TBDMSO* *R_1 = H*	*X = Br*	1.0	99	58	98.0 : 2.0	0.06
9	*R = H* *R1 = Me*	*X = Br*	2.0	30	10	94.0 : 6.0	0.01

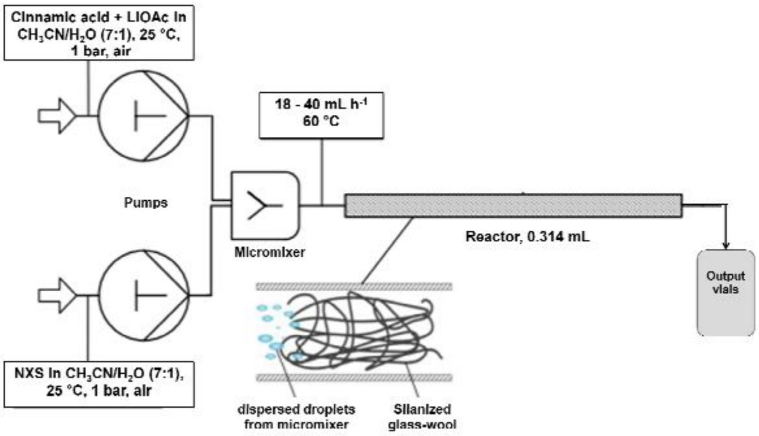
a) Reaction conditions: 1.0 equiv of cinnamic acids (**27**), 1.25 equiv of n-halosuccinimide, 0.25 equiv of LiOAc, CH_3CN/H_2O (7:1) (3.0 mL/mmol), 60°C, Ar atmosphere; b) Evaluated by GC analyses; c) Isolated Yield; d) Determined as ratio between the mass of the product **12** compared to the reactor volume and the time taken to acquire.

Given the good result obtained in the synthesis of the (E)-β-bromostyrenes **12e-m**, and in particular of the **12e** and **12f**, in batch mode, and taking into account the simplicity and homogeneity of the reaction conditions, we have been decided to perform this catalytic Hunsdiecker reaction in flow mode, with a several concern related at the evolution of CO_2 during the reaction.

The flow reactions were performed under the above-described condition developed in batch reactors, optimizing the residence time and the concentration for a possible application in continuous flow reactors.

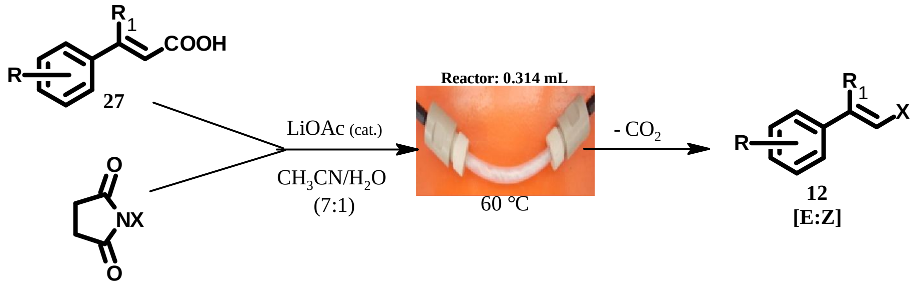
The reactors (columns) were prepared using PTFE tubes of 2-4 mm i.d. and 100 mm long, filled with dry silanized glass wool locked with a PEEK fitting. For a major reaction control the reaction mixture were divided in two reactant reservoirs (one witch contains the cinnamic acid **27** and the catalyst, and one for the halogenation agent, NBS) were connected to reactor by an opportune arrowhead mixer, commercially available (Cheminert mixing tee in PEEK). The elution of the reactant mixtures through these systems was carried out by means of suitable syringe pumps as reported in **Scheme 2.6.4**.

Scheme 2.6.4: Flow-reactor scheme for catalytic Hunsdiecker reaction



Under these continuous-flow processes we obtain the desired product **12a** and **12e-m** in the same yields achieved in batch, but with better performance, and very controlled CO_2 emission. The outcomes are summarized in **Table 2.6.4**.

Table 2.6.4: Continuous flow synthesis of (E)-b-bromostyrenes by catalytic Hunsdiecker reaction condition[a]



R = H, 4-Me, 2-OMe, 4-NO_2, 4-Cl, 4-OH, 4-TBDMSO
R_1 = H, Me
X = I, Br

Run	Cinnamic acid (27)	NXS	Flow-rate (mL/h)	Residence Time (min)	Conversion[b] (%)	Yield in 12[c] (%)	Selectivity[b] [E:Z]	Output[d] (g/h)	Space Time Yield[e] (Kg/[L x h])
1	*R = H* *R_1 = H*	*X = Br*	36.0	0.5	99	46	95.0: 5.0	1.20	3.88
2	*R = H* *R_1 = H*	*X = I*	0.8	40	98	25	99.0 : 1.0	0.02	0.07
3	*R = 4-Me* *R_1 = H*	*X = Br*	50.0	0.4	99	62	99.0 : 1.0	0.76	2.46
4	*R = 2-OMe* *R_1 = H*	*X = Br*	40.0	0.5	99.9	78	99.9 : 0.1	0.83	2.68
5	*R = 4-NO_2* *R_1 = H*	*X = Br*	10.0	2.0	99	25	96.0 : 4.0	0.06	0.15
6	*R = 4-Cl* *R_1 = H*	*X = Br*	40.0	0.5	99.9	69	99.9 : 0.1	0.40	1.29
7	*R = 4-TBDMSO* *R_1 = H*	*X = Br*	20.0	1.0	99	58	98.0 : 2.0	0.45	1.46
8	*R = 4-OMe* *R1 = H*	*X = Br*	50.0	0.4	99	64	95.0 : 5.0	0.85	2.75

a) Reaction conditions: 1.0 equiv of cinnamic acids (**27**), 1.25 equiv of n-halosuccinimide, 0.25 equiv of LiOAc, CH_3CN/H_2O (7:1) (3.0-10.0 mL/mmol), 60°C; b) Evaluated by GC analysis; c) Isolated Yield; d) Determined as mass of product **12** obtained per hour; e) Determined as ratio between the mass of the product **12** compared to the reactor volume and the time taken to acquire.

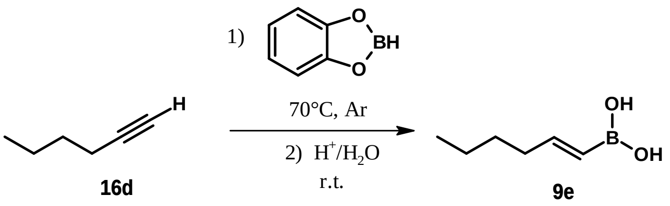
2.6.3 Synthesis of boronic acids

Finally, we prepared the boronic acids to use in the Suzuki-Miyaura study, and in particular in the synthetic process to obtain the hydroxystilbenes (see paragraph 2.7.)

Generally, these boronic acids were synthesized by opportune literature procedures of hydroboration-hydrolysis (to obtain vinyl boronic acids) and electrophilic borylation of aryl Grignard reagents (to obtain aryl boronic acids).

In particular, the first boronic acid that we have synthesized was the (E)-1-hexenyl-boronic acid (**9e**), prepared by hydroboration of the 1-hexyne (**16d**) with catecholborane and following hydrolysis of the catecholboronic ester, providing **9e** with a yield of 56% (**Scheme 2.6.4**).**[416]**

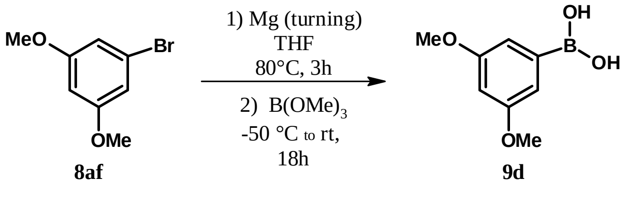
Scheme 2.6.5: preparation of (E)-1-hexenyl-boronic acid



The second boronic acid, essential for the synthesis of pterostilbene (**13k**) and derivatives **13l** and **13m** was the 3,5-dimethoxyphenyl-boronic acid (**9d**). It was prepared by electrophilic borylation of the corresponding aryl Grignard reagents.

In detail, the preparation of **9d** started from the 1-bromo-3,5-dimethoxybenzene (**8af**) that was converted in the Grignard reagent, and subsequently, the Grignard reagent was processed with $B(OMe)_3$ to obtain the desired boronic acid after acid hydrolysis (**Scheme 2.6.6**).**[417]**

Scheme 2.6.6: Preparation of 3,5-dimethoxyphenyl-boronic acid



Under this procedure we synthesized the 3,5-dimethoxyphenylboronic acid (**9d**) with a yield of 80% and purity of 95 %.

2.7 Synthesis of interesting natural and/or bioactive compounds

Finally, as mentioned in paragraph 1.3.2.3, next the study of the scope and generality of our supported catalysts in the Suzuki, Sonogashira-type and Heck reactions, under the optimized conditions, in batch and flow mode; we have been started the planned application to the synthesis of interesting natural and/or bioactive compounds of our chosen catalysts.

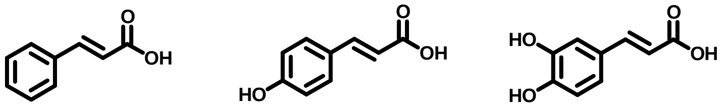
On the light of the results obtained in the tests with model substrates in batch and flow processes, and reported in the previously mentioned paragraphs 2.3-2.5, we decided to applied our systems (both in batch that in flow process) in the synthesis of interesting natural and/or bioactive compounds.

2.7.1 Cinnamic acids and derivatives

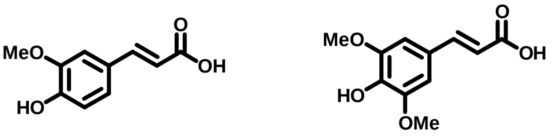
An interesting class of the bioactive compound are the cinnamic acids and derivatives, such as cinnamides, because more used and studied as antimicrobical agents, and/or it is considered an interesting scaffold for the development of novel antimicrobials, however little is known about its antimicrobial mechanism of action.**[418]** In the last ten years, the interest of researchers on the cinnamic acid moiety has notably increased. The number of published reports having the word “cinnamic” in the title, has almost doubled, from 341 in the years 1993–2003 to 633 in the period 2004–2014 according to the Scopus database (until mid-November 2014). If both “cinnamic” and “antimicrobial” keywords are used, the number of published articles increased from 1 in the period 1993–2003, to 7 in the period 2004–2014. There is no doubt that the cinnamic acids currently attracts the attention of chemists from different perspectives.

Infectious diseases caused by bacteria, fungi and viruses are still a prominent global health problem, particularly in developing, low-income countries.**[419]** Every year in the whole planet, around 4 million persons die from acute respiratory infections, around 3 million individuals die from enteric infections, around 1.8 persons die from human immunodeficiency virus (HIV), around 1.3 million die from tuberculosis (TB), and 0.7 million die from malaria **[420]**. Other thousand people deeply suffer the consequences of being infected by neglected tropical pathogens *Schistosoma mansoni*, *Onchocerca volvulus*, *Trypanosoma spp.*, *Leishmania spp.*, *Mycobacterium ulcerans*, *Mycobacterium leprae*, *Wucheria spp.*, and others. Although some of these diseases are caused by parasites, many are caused by bacteria and fungi. Antibacterial and anti-fungal drugs, which are broadly known as antimicrobials, started to be used in chemotherapy since the 1940 decade.**[421]** New antimicrobial classes were discovered in the 1940–1970 period, and were successfully introduced to clinical practice. However as soon as the new drugs were employed, the first drug-resistant strains started to appear.**[422]** The cinnamic skeleton is considered an interesting scaffold for the development of novel antimicrobials, however little is known about its antimicrobial mechanism of action. A recent report proposed that cinnamic acids caused fungal growth inhibition by interacting with benzoate 4-hydroxylase, an enzyme responsible for aromatic detoxification.**[423]** However this enzyme occurs in fungi but not in prokaryotes, and because the cinnamic acids have proven anti-bacterial effects,**[424]** other targets may be implicated in their biological effects.

The natural cinnamic acid (**27a**, Figure 2.7.1) showed a weak antibacterial effect against most of Gram-negative and Gram-positive species of bacteria, with MIC values higher than 5.0 mM.**[424d, 425]** The same level of potency was observed against the fish pathogens *Aeromonas hydrophila*, *Aeromonas salmonicida* and *Edwardiella tarda* with MIC values between 5.6 and 7.7 mM.**[426]** However cinnamic acid was found to be much more active against the tuberculosis-causing bacteria, *Mycobacterium tuberculosis* H37Rv, with an MIC values of 270–675 μM using the SPOTi and the radiometric Bactec assays.**[427]** The free carboxylic acid and the presence of the α,β-unsaturation were both required for the anti-TB activity.**[427a]** The specific anti-TB effect of cinnamic acid may explain the traditional use of storax (Liquidambar orientalis) and cinnamon for treating TB in the 19th century.**[428]** Cinnamic acid also demonstrated anti-fungal activity with MIC values of 1.7 mM against *Aspergillus terreus* and *Aspergillus flavus*, being more active against *Aspergillus niger* with an MIC value of 844 μM.**[429]** Against *Candida albicans,* an MIC value of 405 μM has been found,**[430]** which is comparable to the potency against *M. tuberculosis*. The widely distributed natural phenol 4-hydroxycinnamic acid (**27b**, Figure 2.7.1), also known as 4-coumaric acid, has been found to be comparatively more potent bacterial growth inhibitor compared to cinnamic acid. The other abundant cinnamic acids in nature are caffeic acid (**27c**), ferulic acid (**27d**) and sinapic acid (**27e**) (Figure 2.7.1), which have been studied for their antimicrobial activities,**[425a, 431]** observed a similar pattern for these three natural cinnamic acids, showing a weak growth inhibition against Gram-negative bacteria compared to Gram-positive bacteria and fungi. The caffeic acid showed significant growth inhibition of planktonic *C. albicans* with MIC between 694 and 710 μM;**[432]** bur other species of bacteria and fungi were less susceptible to caffeic acid (**27c**). The ferulic acid (**27d**) demonstrated significant antibacterial activity against *Streptococcus aureus* 209 and *Streptococcus pyogenes* 10535 with MIC values of 644 μM.**[432a]**



cinnamic acid (27a) cumaric acid (27b) caffeic acid (27c)

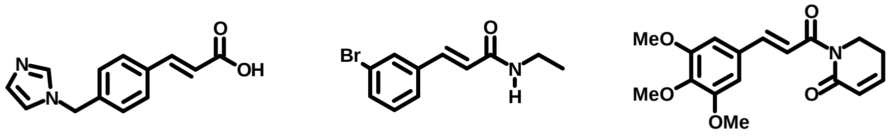


ferulic acid (27d) sinapic acid (27e)

Figure 2.7.1: Some natural important cinnamic acid:

Some cinnamic acids and derivatives with a particular substitution pattern on the aryl ring, and the cinnamic skeleton in interesting scaffolds have been developed, prepared and examined for their antimicrobial activity.

The Ozagrel (**27f**, Figure 2.7.2), a thromboxane A2 synthase inhibitor, is in fact an imidazole para-substituted cinnamic acid that is employed therapeutically for treating acute ischemic stroke.**[433]** Cinromide (**28a**, Figure 2.7.2) is an antiepileptic experimental drug studied in clinical trials during the 80 decade with a favorable profile to suppress generalized convulsions, but however displayed considerable toxicity.**[434]** The Piplartine (**28b**, Figure 2.7.2) is another cinnamic-related molecule showing an attractive biological horizon.**[435]** This cinnamic amide was first-time isolated from the roots of Piper tuberculatum,**[436]** and later proved to be a promising anti-cancer scaffold.**[437]** Several reviews and studies have appeared in the literature focusing on a particular medicinal application of cinnamic-related molecules, for example on anticancer,**[438]** antituberculosis,**[439]** antimalarial,**[440]** antifungal,**[441]** antimicrobial,**[442]** antiatherogenic**[443]** and antioxidant**[442]** activities. In addition a number of reviews directed towards the synthetic methods used to prepare cinnamic acids and related molecules have appeared in the literature.**[40a, 444]** Cinnamic acids and derivatives have also been used by medicinal chemists to alter the potency, permeability, solubility or other parameters of a selected drug or pharmacophore.



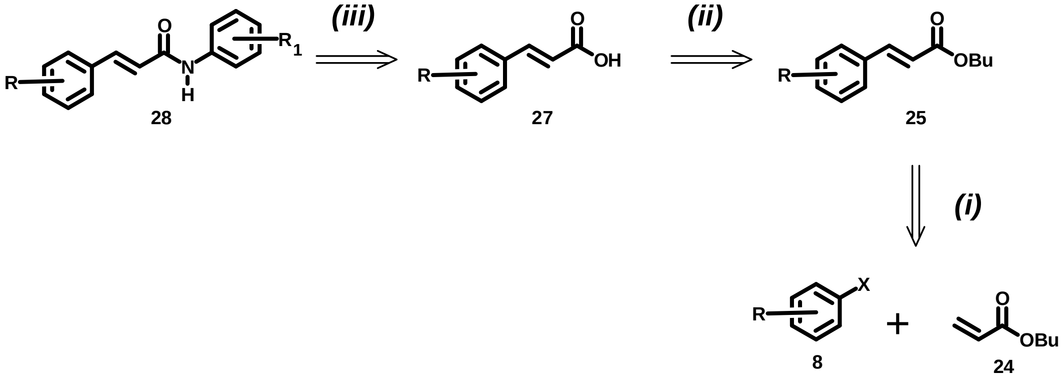
Ozagrel (27f) Cinromide (28a) Piplartine (28b)

Figure 2.7.2: Chemical structures of some therapeutically important cinnamic acid-containing molecules: ozagrel, cinromide and piplartine.

2.7.1.1 Synthesis of interesting natural and/or bioactive cinnamic acids and cinnamides

At the light of these interesting biological activity of the some natural and not cinnamic acids and cinnamic amides (cinnamides), and taking into account the notably increased of the interest of researchers in the last ten years on these cinnamic compounds; we decided to investigated and applied the our systems in the synthesis of some cinnamic acids and derivatives, in particular cinnamides.

Generally in our retrosynthetic approach, we envisioned forming the cinnamic acids **27** and derivatives from butyl cinnamates **25** obtained by Mizoroki-Heck coupling from commercially available precursors. So our strategy focused on cinnamic acids and cinamides formation involving i) an Mizoroki-Heck coupling to form the C-C bond, ii) an ester hydrolysis reaction to form the cinnamic acids **27** and iii) an classic amidation to form the corresponding cinamides **28** (**Scheme 2.7.1**)



Scheme 2.7.1: Our retrosynthetic approach

Once we found that it was possible to achieve the Mizoroki-Heck reaction in batch and flow processes (reported in paragraph 2.5), we dedicated part of our efforts in the synthesis of four cinnamic acids and derivatives, in particular cinnamides, with particular substitution pattern on the aryl ring, that showed interesting antimicrobial and allelochemicals activity.

An interesting compound is 4-methoxycinnamic acid (**27g**, **Figure 2.7.3**) that was isolated from the argentinian medicinal plant *Baccharis grisebachii* and its antimicrobial activity was evaluated**[445]**. This acid showed a potent antibacterial and antifungal effect with MIC values ranging between 50.4 and 449 μM (Table 2.7.1) **[424b, 445]**.

Table 2.7.1: antibacterial and antifungal activity of 4-methoxycinnamic acid (**27g**)

Compound	Microbial Strain	MIC
4-methoxycinnamic acid (**27g**)	*Aspergillus niger*	50.4 μM
	Bacillus subtilis	203 μM
	Candida albicans	50.4 μM
	Escherichia coli	164-281 μM
	Micrococcus luteus	449 μM
	Salmonella enteriditis	337 μM
	Staphylococcus aureus	2.03-337 μM

Interestingly, the acid **27g** showed higher growth inhibition against fungal species compared to bacteria, and Gram-negative and Gram-positive bacteria were equally inhibited by the compound. This acid also shows good insulin releasing activity when Glibenclamide was used as a positive control in the experiment,**[446]** and Adisakwattana and co-workers reported that **22g** showed antihyperglycemic effect**[447]**.

Another interesting compound with antimicrobical activity is 4-chlorocinnamic acid (**27h, Figure 2.7.3**). In fact, this acid showed MIC values of 708 μM against both *Escherichia coli* and *Bacillus subtilis* **[448]**. Interestingly, the acid derivatives, methyl-4-chlorocinnamate (**29**) and isopropyl-4-chlorocinnamide (**30**) showed higher growth inhibition against fungal species**[444b]**.

The 4-nitrocinnamic acid (**27i**, **Figure 2.7.3**) generally showed very low antimicrobical activity, in fact found that none of the positional isomers of nitrocinnamic acid inhibited *S. aureus* or *E. coli* at the highest dilution tested**[449]**. However, this acid is more active than corresponding 2- and 3-nitro compound, in fact the effect of the position of the nitro group is very important on the activity. This acid **27i** showed highly germinative inhibition activity, with an activity similar at commercial herbicide metribuzin as reported from Vishnoi and co-workers**[450]**.

Other at the cinnamic acids we dedicated part of our efforts in the synthesis of one very interesting cinnamides, such as (E)-N-(2-bromophenyl)cinnamamide (**28c, Figure 2.7.3**), an new potential active antitumor agent.**[451]** This cinnamide **28c** was evaluated for antiproliferative activity against the human cancer cell line MCF-7 and EGFR-inhibitory activity; showed a modest EGFR kinase inhibitory effect with IC_{50} value of 15.7 μM, and an potent antiproliferative activity against the cancer cell line MCF-7, with IC_{50} value of 4.0 μM.**[451]**

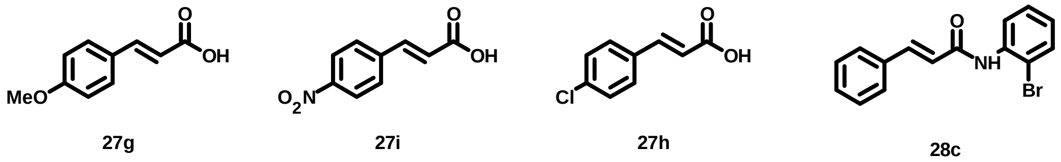


Figure 2.7.3: Chemical structures of the our synthesized cinnamic acid and cinnamide compounds.

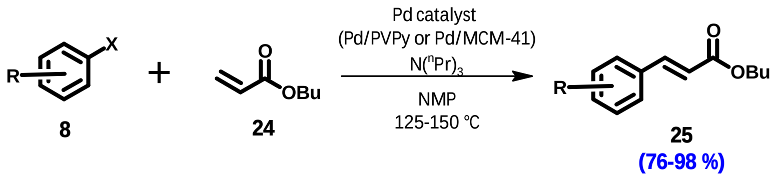
As previously mentioned, the key step in the synthesis of these four cinnamic acid derivatives compounds (reported in **Figure 2.7.3**) is the Mizoroki-Heck coupling.

Taking into account the date obtained during the study of our chosen supported catalysts in the Heck reaction under batch and flow processes (reported in paragraph 2.5), we have decided to apply only the Pd/PVPy and Pd/MCM-41 as catalysts, in the synthesis of previously mentioned compounds, under the better reaction conditions in batch and flow mode.

2.7.1.1.1 Synthesis of cinnamic acids and cinnamides in batch process

In the batch processes, we obtained the desired intermediates butyl cinnamates **25** with good yield in short time using the two “home-made” catalysts indifferently; starting from commercially available aryl halides **8** and the butyl acrylate (**24**) using NMP as solvent and tripropylamine as base at 125°C for aryl iodides and 150°C for aryl bromides (**Table 2.7.1**).

Table 2.7.1: Mizoroki-Heck key step of the cinnamic derivates synthesis[a]



Substrate		Catalyst	Time (h)	25	Yield (%)
R= 4-MeO X = I	(8u)	Pd/PVPy	3.0	(25e)	86
		Pd/MCM-41	2.5		98
R = H X = I	(8ac)	Pd/PVPy	2.0	(25a)	88
		Pd/MCM-41	1.0		80
R = 4-Cl X = Br	(8am)	Pd/PVPy	4.0	(25f)	87
		Pd/MCM-41	2.5		98
R = 4-NO$_2$ X = Br	(8al)	Pd/PVPy	4.0	(25d)	87
		Pd/MCM-41	2.0		80

a) Reaction conditions: 1.0 equivalent of aryl halide (**8**), 1.00 equivalent of Pr_3N, 2.00 equivalent of butyl acrylate (**24**), 0.10 mol % of Pd as catalyst, NMP (1.80 mL/mmol)

In detail, using the two “home-made” catalysts, consist in a Pd nanoparticles deposited on two different supports, in the reaction between 4-methoxy-1-iodobenzene (**8u**) and butyl acrilate (**24**), we obtained the desiderated butyl cinnamate ***E*-25e** in good oven excellent yields.

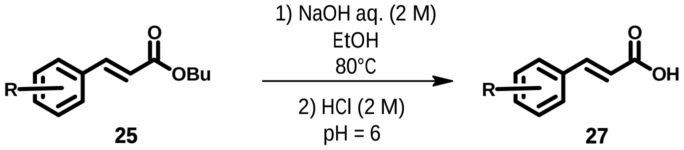
In fact, the Pd/PVPy showed a good yield (86 %) in 3.0 h under rather simple and convenient conditions, while the Pd/MCM-41 showed a good/excellent yield (98 %) in 2.5 h under the same reaction conditions.

In the reaction between iodobenzene (**8ac**) and butyl acrilate (**24**), we obtained the desiderated butyl cinnamate ***E*-25a** in good similar yields, corresponding at 88 % using the Pd/PVPy catalyst, and 80 % with the Pd/MCM-41 catalyst with very low Pd leaching, as already stated in **Table 2.5.2.4** of the paragraph 2.5.

The other two butyl acrylates **25f** and **25d** were obtained using the commercial aryl bromides 4-chloro-1-bromobenzene (**8am**) and 4-nitro-1-bromobenzene (**8al**) as start materials, obtaining good and excellent yields in short times 2.0-4.0 h at 150°C (**Table 2.7.1**).

In detail with **8am**, the Pd/PVPy showed a good yield (87 %) in 4.0 h under rather simple and convenient conditions, and the Pd/MCM-41 showed a excellent yield (98 %) in 2.5 h under the same reaction conditions. While in the reaction between 4-nitro-1-bromobenzene (**8al**) and butyl acrilate (**24)**, we obtained the desiderated butyl cinnamate **25d** in good similar yields, corresponding at 87 % using the Pd/PVPy catalyst, and 80 % with the Pd/MCM-41 catalyst as already stated in **Table 2.5.2.4** of the paragraph 2.5.

Subsequently, the obtained butyl cinnamates **25**, were hydrolyzed in ethanol using a aqueous solution of NaOH (2M) at 80°C for 2-3 h,**[452]** producing after acidification at pH=6, the corresponding cinnamic acids **22** in 90-98 % yields (**Scheme 2.7.3**)



25

27

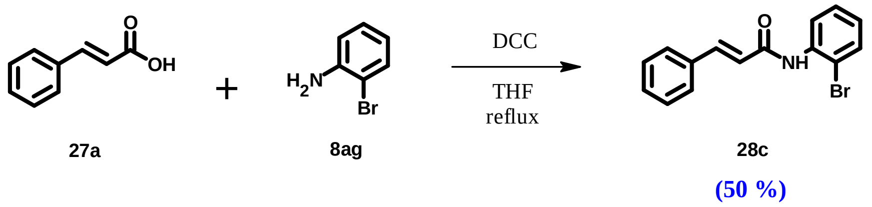
(90-98 %)

R = H, 4-MeO, 4-Cl, 4-NO$_2$

Scheme 2.7.3: Ester hydrolysis step of the cinnamic derivates synthesis

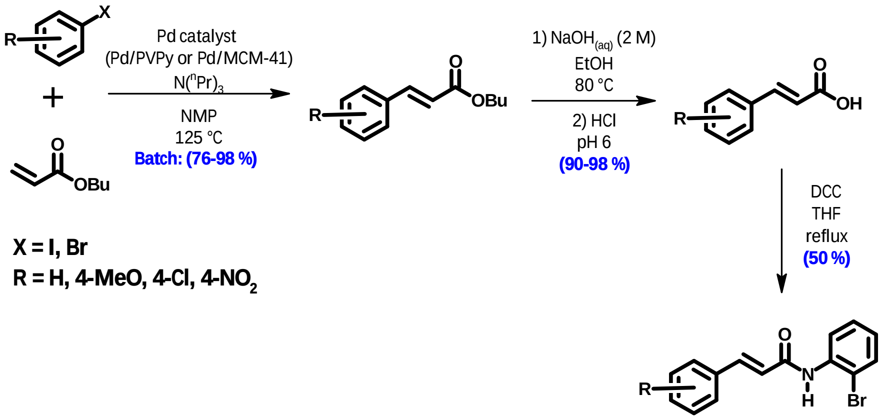
With this step we obtained three of the four compounds that we have decide to synthesize, and reported in **Figure 2.7.3**; and the intermediate acid **27a** for the synthesis of cinnamide **28c** by a literature procedure of amidation**[453].**

The amidation procedure, between the previously obtained cinnamic acid **27a** and the commercial 2-bromo-1-aniline (**8ag**), producing the last compound (the cinnamide **28c**) in 50 % yield, using the DCC in THF at reflux for 7 h (**Scheme 2.7.4**).



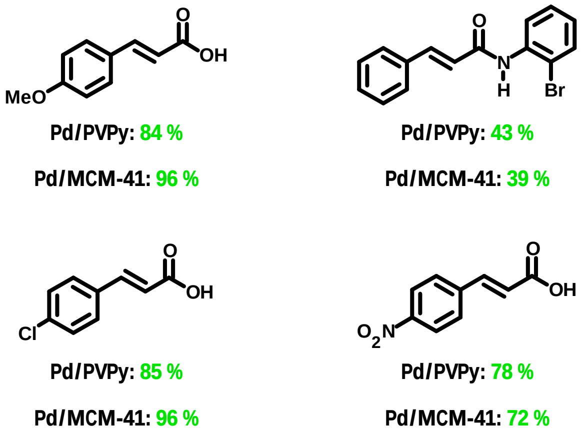
Scheme 2.7.4: Amidation step of the cinnamic derivates synthesis

In total we synthesized three interesting cinnamic acid **27g**, **27h**, **27i** in two step, and one cinnamide derivative **28c** in three step, in batch process using in the first key step (Mizoroki-Heck coupling) simple and cheap supported catalysts (**Scheme 2.7.5**).



Scheme 2.7.5: Total our synthetic process to made the three cinnamic acid 27g-i and the cinnamide 28c

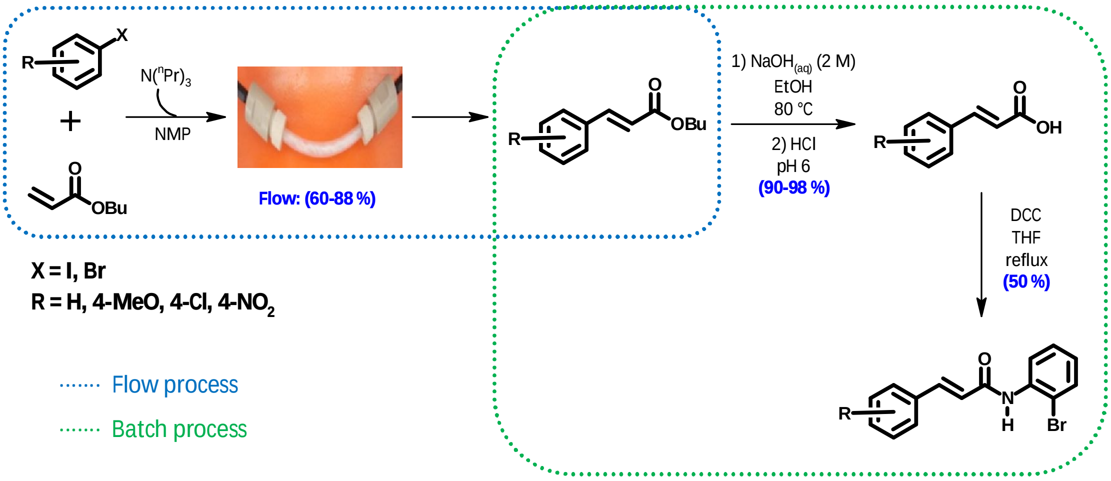
Obtained the desired compounds under batch process, with good total yields (**Scheme 2.7.6**)



Scheme 2.7.6: Total yields of the our synthetic process to made the desired compounds

2.7.1.1.2 Synthesis of cinnamic acids and cinnamides in flow process

For regard the synthesis of the three cinnamic acids **27g-i** and the cinnamide **28c** in flow, we shifted the key step of Heck coupling in flow, using original packed-bed mini-reactors of design and construction extremely simple and cheap previously developed (see paragraph 2.2) and studied in this reaction (see paragraph 2.5.4); and we preserved the other steps in batch (**Scheme 2.7.7**).



Scheme 2.7.7: Flow synthetic process

We performed the Mizoroki-Heck reaction key step in continuous flow using reactors packaged with Pd/MCM-41 pure and Pd/PVPy mixed at glass beads in 1:1 volume ratio (because these types of filler were results the best in the previously study carried out on the reaction model reported in paragraph 2.5.4), under the same reaction conditions of the batch process.

In the use of reactor packaged with Pd/PVPy (21 mg; 1.98 µmol of Pd) mixed at glass beads, the reaction mixtures were eluted at 0.10-0.20 mL/h (corresponding at residence time of 26-63 minutes) depending to aryl halides. Under these flow-rate we observed high conversions for long times (50-100 h) to obtain the desired butyl cinnamates **25** with good yields (76-82 %), high productivity (990-3306) and space time yield (0.070-0.160).

While, in the use of reactor packaged with pure Pd/MCM-41 (21 mg, 1.98 µmol of Pd), the reaction mixtures were eluted at 0.30 mL/h (corresponding at residence time of 22 minutes) indifferently to aryl halides used. Under this flow-rate we observed high conversions for long times (30-70 h) to obtain the desired butyl cinnamates **25** with good yields (60-88 %), high productivity (780-3465) and space time yield (0.140-0.210).

In detail, the reaction between 4-methoxy-1-iodobenzene (**8u**) and butyl acrilate (**24**), to produce the desiderated butyl cinnamate **25e** is performed at flow-rate of 0.15 mL/h using

Pd/PVPy (**5**) as catalyst, and 0.30 mL/h with Pd/MCM-41 (**6**), obtaining good yields (78 and 88 %) eluting 5-10 mmol of **8u**.

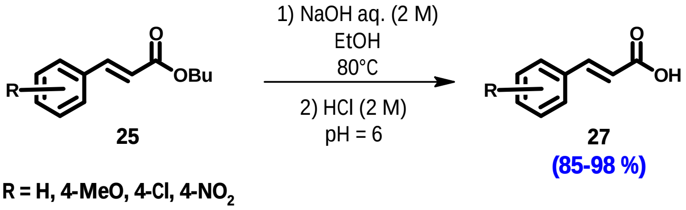
In the reaction between iodobenzene (**8ac**) and butyl acrilate (**24)**, we obtained the desiderated butyl cinnamate **25a** in good yields, corresponding at 80 % using the Pd/PVPy (**5**) catalyst, and 70 % with the Pd/MCM-41 (**6**) catalyst with very low Pd leaching, as already stated in **Table 2.5.4.2** and **Table 2.5.4.6** of the paragraph 2.5.4.

The other two butyl cinnamates **25f** and **25d** were obtained from the commercial aryl bromides 4-chloro-1-bromobenzene (**8am**) and 4-nitro-1-bromobenzene (**8al**) as start materials, using the reactor packing with Pd/MCM-41 (**6**), obtaining good and excellent yields at 150°C, eluting 2.6-4.3 mmol of the corresponding bromides **8al** and **8am**.

While in the case of the use of the reactor packing with Pd/PVPy (**5**) mixed at glass beads, we prepared only the butyl cinnamate **25f**, starting from the commercial aryl iodide 4-chloro-1-iodobenzene (**8an**), because as previously observed and reported in paragraph 2.5.4, this system were not able to promote the reaction with aryl bromides electron-poor, even at low flow-rate (see **Table 2.5.4.6** of paragraph 2.5.4); and the catalyst Pd/PVPy (**5**) showed several problem of structure stability at 150-160°C causing the possible blocking of the reactor. In this case, we obtained the desired product **25f** in excellent yield (98 %) eluting 7.0 mmol of **8an** at 0.15 mL/h (corresponding at 44 min of residence time).

The subsequently ester hydrolysis step, to obtain the cinnamic acids **27**, were performed directly on previous butyl cinnamates **25** both purified that not purified, added ethanol and aqueous solution of NaOH (2M) and heating at 80°C for 2-3 h.

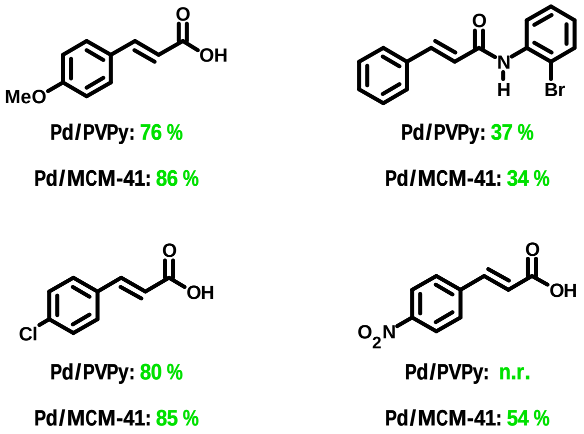
Starting with **25** purified we obtained, after acidification at pH=6.0, the desired cinnamic acids **27** in 90-98 % yields with gas-cromatography purity 97-98 %. While in the case when we use **25** not purified, the desired cinnamic acids **27** obtained after acidification showed major impurity (GC purity 80-86 %), and require subsequently re-crystallization in EtOH/H_2O (1:1), obtaining at the end **27** in 85-95 % yields and purity of 96-98 % (**Scheme 2.7.8**).



Scheme 2.7.8: Ester hydrolysis step of the cinnamic derivates synthesis on 19 obtained in flow

Finally, the amidation step, between the previously obtained cinnamic acid **27a** and the commercial 2-bromo-1-aniline (**8ag**), were performed in the same mode previously reported for the synthesis in batch, producing the cinnamide **28c** in 50 % yield, using the DCC in THF at reflux for 7 h (**Scheme 2.7.4**).

In total, under these synthetic process (**Scheme 2.7.7**), that showed a flow process in the first key step (Mizoroki-Heck coupling), using simple and cheap flow reactors and supported catalysts; we synthesized three interesting cinnamic acid **27g**, **27h**, **27i** and one cinnamide derivative **28c** with acceptable good total yields (**Scheme 2.7.9**)



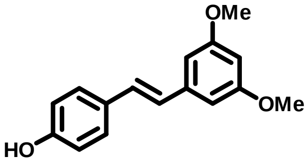
Scheme 2.7.9: Total yields of the our flow synthetic process

2.7.2 Pterostilbene and natural derivatives

Another class of interesting natural and bioactive compounds are the hydroxystilbene derivatives, because to have been found to antiinflammatory, antineoplastic, and antioxidant actions.**[454]** In particular we have been dedicate major attention at the natural pterostilbene (**13n**) and two new isolated natural isopropenylated derivatives **13o** and **13p**, that showed anti-germinative activity**[455]**.

The pterostilbene or 4-[(E)-2-(3,5-dimethoxyphenyl)ethenyl]phenol (**13n**), is a natural stilbenoid, which biochemically belongs to the family of phenylpropanoids.**[456]** It is structurally and chemically related to resveratrol and together at several molecules of the stilbenoid family is a phytoalexin, which are antimicrobial and antifungine compounds produced by plants in response to pathogen infection, as well as to excessive ultraviolet exposure.**[457]**

Together with resveratrol, it has been isolated from several natural plant sources, notably blueberries; it has been identified also in *Vitis Vinifera* leaves, in infected as well as healthy and immature grape berries (Chardonnay, Gamay, Pinot Noir);**[458]** but unlike resveratrol, which is found in red wine, pterostilbene is not present in wine because it is not stable in light and air.**[459]** Another the pterostilbene was found to be one of the active constituents in extracts of the heartwood of *Pterocarpus marsupium*.**[460]**

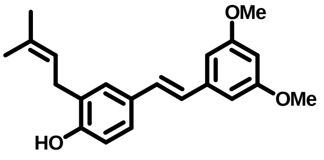


pterostilbene (13n)

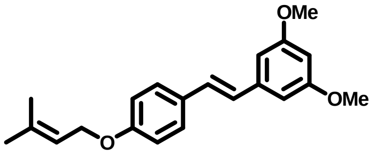
Substantial evidence suggests that pterostilbene may have numerous preventive and therapeutic properties in a vast range of human diseases that include cancer,**[461]** dyslipidemia,**[458]** diabetes,**[462]** cardiovascular and cognitive function degeneration,**[463]** and antioxidant actions via modulations of gene expression and enzyme activity.**[464]** Further benefits of pterostilbene have been reported in preclinical trials, in which pterostilbene was shown to be a potent anticancer agent in several malignancies**[465]**. Pterostilbene is structurally similar to resveratrol that has comparable antioxidant, anti-inflammatory, and anticarcinogenic properties; however, pterostilbene exhibits increased bioavailability due to the presence of two methoxy groups which cause it to exhibit increased lipophilic and oral absorption**[466]**. In animal studies, pterostilbene was shown to have 80% bioavailability compared to 20% for resveratrol making it potentially advantageous as a therapeutic agent**[466a]**. The multiple benefits of pterostilbene in the treatment and prevention of human disease have been attributed to its antioxidant, anti-inflammatory, and anticarcinogenic properties leading to improved function of normal cells and inhibition of malignant cells **[458, 467]**

The two natural isopropenylated derivatives, 3,5-dimethoxy-4′-hidroxy-3′-prenyl-trans-stilbene (**13o**) and 3,5-dimethoxy-4′-prenyloxy-trans-stilbene (**13p**) are new natural stilbenoid products isolated and identified from the leaves of “timbó vermelho” (*Deguelia rufescens* var. *urucu*)**[455]**; although **15p** has been previously cited as synthesis product**[454a]**.

Generally these two compounds showed a potential allelopathic activity over seed germination and plant growth of *Mimosa pudica* weed. The effects over seed germination, did not vary significantly ($p < 0.05$) when the substances were considered separately, the intensity of inhibitions on seed germination did not exceed 20%. **13p** presented over radicle development inhibitory activity below 10%, while **13o** presented the highest inhibitor activity, around 30%, significantly higher ($p < 0.05$) than **13p**. When tested in pairs, these showed antagonism for seed germination and synergism for radicle and hypocotyl development.**[455]**



13o



13p

2.7.2.1 Synthesis of Pterostilbene (13n) and two new isolated natural isopropenylated derivatives 13o and 13p

On the light of the results obtained in the tests with (E)-β-bromostyrenes substrates in batch and flow processes (reported in the paragraphs 2.3.2.3 and 2.3.4), and taking into account the literature procedures to produce the pterostilbene (**13n**) and also **13o** with relatively drawbacks; we decided to applied our systems (both in batch that in flow process) in the synthesis of these three interesting natural bioactive hydroxystilbenes.

It is should be noted that several synthesis methods to prepare the pterostilbene (**13n**) have been already described. The more performing procedures reported in literature are based on the Wittig, Witting-Horner reaction,**[468]** Julia olefination,**[469]** Perkin reaction**[470]** and transition metal catalyzed Heck coupling**[471]**.

Generally, these procedures allow to obtain **13n** in good yields (50-95 %), but however, these procedures showed several application problems.

In the classic Wittig olefination approach,**[468a-b]** employing triphenylphosphine-derived semi-stabilized ylides suffers from notoriously poor (E):(Z) stereocontrol and the problematic removal of triphenylphosphine oxide. Recently these problems have been solved partially through the use of aqueous Wittig methods employing ylides derived from short chain trialkylphosphines, obtained **13n** in E:Z ratio 95:5.**[468]**

In the Julia olefination**[469]**, and Perkin reaction**[470a]**, **15n** is obtained in 69 and 64 % yields respectively with excellent geometrical selectivity, but the reaction conditions were extremely complex in the case of Julia reaction, or required the use of MW in Perkin reaction.

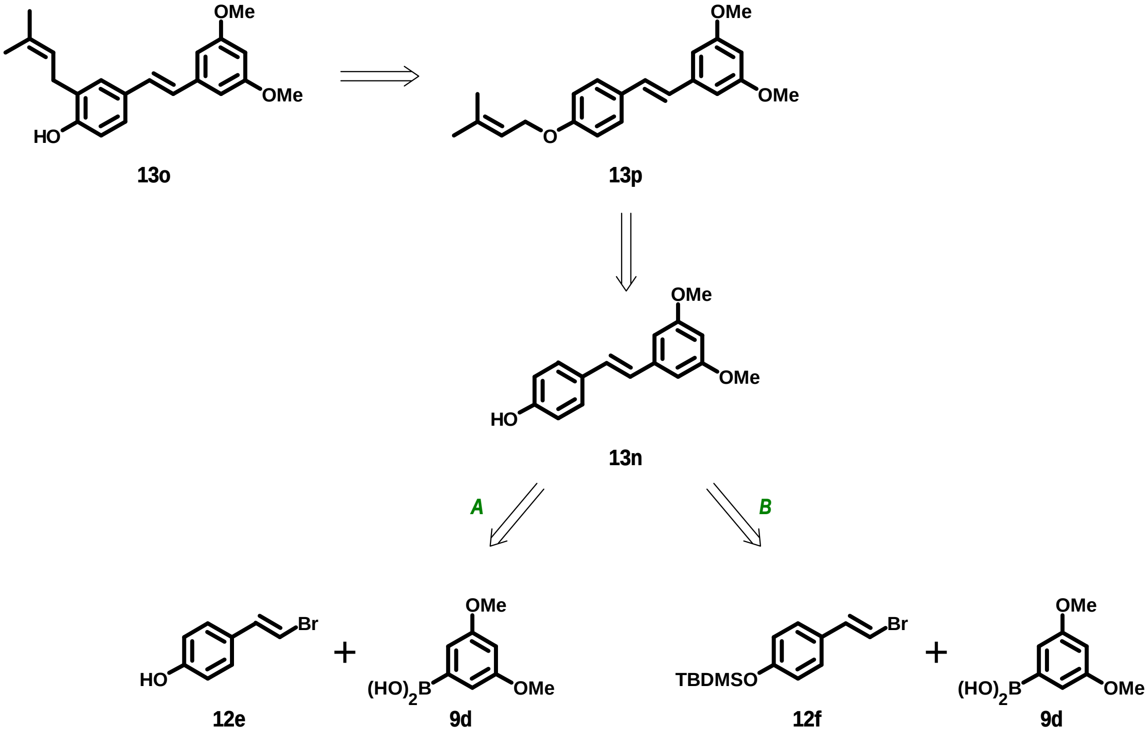
For regard the transition metal catalyzed Heck coupling**[471a-b]**, the principal procedure problems are the geometrical selectivity and the use of high palladium loading (2-5 mol %). However, one of the coupling partners, that is, styrene, is inevitably prone to polymerization, difficult to synthesize, and tricky to purify. Recently to counteract this problem correlated with one of the coupling partners, Shina and co-workers reported a palladium-catalyzed tandem Heck/decarboxylation/Heck (HDH) cross-coupling**[471c]** obtaining **13n** in 54% overall yield (scalable up to 1 gm).

However, it is interesting to note that the transition metal catalyzed Heck coupling procedures reported in literature provide the exclusive use of homogeneous palladium catalysts, with all the problems that ensue.

While for regard the compound 3,5-dimethoxy-4′-hidroxy-3′-prenyl-trans-stilbene (**13o**), in literature is reported a synthetic procedure to provide three step such as: the Wittig-Horner reaction to form the trans-stilbene structure, followed from removal of benzyl group and subsequent treatment with NaH and isopropenyl bromide, to obtain **15o** in 17.7 % yield**[5454a]** showed several problems.

Given the literature synthetic procedures to obtain **13n**, and **13o**, taking into account the several problems that arise, the good results obtained in our precedent study in the Suzuki reaction with (E)-β-bromostyrenes (see paragraph 2.3.4) and the good result obtained in the synthesis of (E)-β-bromostyrenes starting from corresponding cinnamic acids (see paragraph 2.6); we decided to focus our synthetic approach on the key step of the Suzuki-Miyaura reaction between the (E)-β-bromostyrenes and corresponding arylboronic acid opportunely prepared.

Generally in our possible retrosynthetic approach, we envisioned forming **13o** and **13p** from the pterostilbene **13n** using opportune literature procedures. Therefore the formation of **13n** represent the key step of the synthesis of the three compounds, and can provide two possible synthetic ways (**Scheme 2.7.10**).



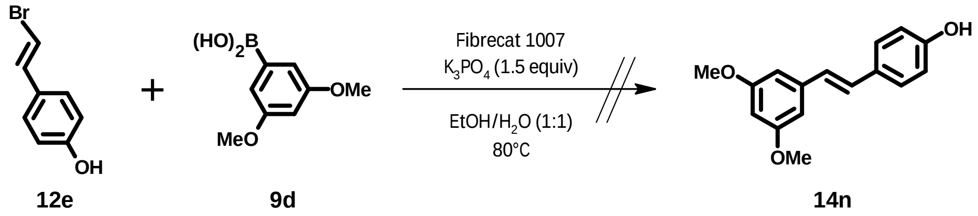
Scheme 2.7.10: Our retrosynthetic approach

The disconnection type ***A***, provide the direct formation of **13n** by simple Suzuki reaction between 4-hydroxy-(E)-β-bromostyrene (**12e**, obtained from p-cumaric acid by halo-decarboxylation, see paragraph 2.6) and 3,5-dimethoxyphenylboronic acid (**9d**, opportunely prepared from 3,5-dimethoxy-1-bromobenzene, see paragraph 2.6). While the disconnection type ***B***, provide the use of protection group TBDMS on hydroxyl, increasing the steps to obtain the desired **13n**.

Taking into account the results obtained in the Suzuki study on (E)-β-bromostyrenes, and in particular on 4-hydroxy-(E)-β-bromostyrene (**12e**) and the corresponding silylated **12f**, in these synthesis, we decided to use the Fibrecat 1007 as catalyst.

2.7.2.1.1 Synthesis of pterostilbene and natural derivatives in batch process

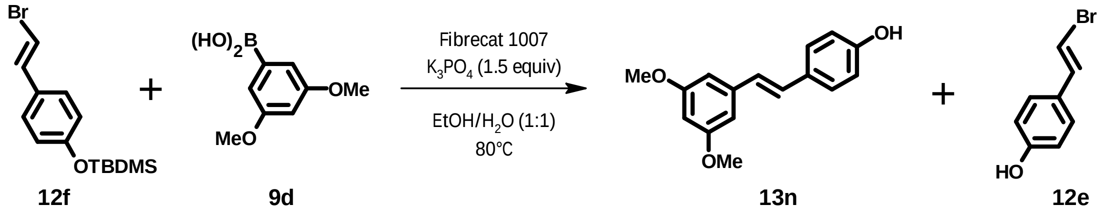
In our first approach (type ***A***) we should be obtain **13n** by the direct Suzuki reaction starting from 4-hydroxy-(E)-β-bromostyrene (**12e**) and 3,5-dimethoxyphenylboronic acid (**9d**) using 0.15 mol % of the Fibrecat 1007 as catalyst in EtOH/H_2O (1:1) as solvent and K_3PO_4 as base at 80°C (**Scheme 2.7.11**).



Scheme 2.7.11: Synthesis of pterostilbene via synthetic approach type *A*

Unfortunately, this approach result completely inappropriate to prepared the desired pterostilbene **13n**. In fact, under this reaction condition the catalyst showed very low reactivity (10 % of conversion in 24 h). Oltre al fatto, that the preparation of **12e** starting from the cumaric acid (**27b**) by Hunsdiecker process (for major information see paragraph 2.6) result extremely difficult and not acceptable of the point of view of the yield (generally obtained 10 % yield of **12e**).

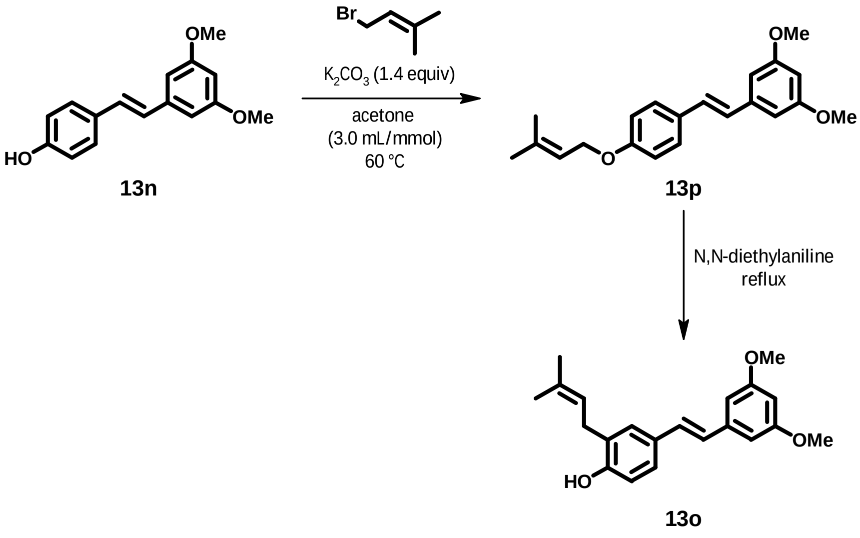
Given this, we applied the second approach (type ***B***), that provide the preparation of **13n** by one-pot Suzuki coupling-desilylation step, starting from 4-t-butyldimethylsilyloxy-(E)-β-bromostyrene (**12f**) and 3,5-dimethoxyphenylboronic acid (**9d**) using 0.15 mol % of the Fibrecat 1007 as catalyst in EtOH/H_2O (1:1) as solvent and K_3PO_4 as base at 80°C (**Scheme 2.7.12**).



Scheme 2.7.12: Synthesis of pterostilbene via synthetic approach type *B*

In this synthetic approach, the catalyst result able to promote the reaction, and under this reaction condition (K_3PO_4 in EtOH/H_2O at 80°C), the protecting group (TBDMS) is eliminate obtaining directly **13n** at the end of the reaction. Unfortunately, this concomitance of the coupling and the protect group elimination (desilylation process) cause a moderate yield of the desiderate pterostilbene (50 %) with formation of many amount of the 4-hydroxy--bromostyrene **12e**.

Obtained the pterostilbene **13n**, we applied the subsequently literature procedures (described and carried out on cinnamic esters)**[472]** to obtain the desired 3,5-dimethoxy-4′-prenyloxy-trans-stilbene (**13p**) and 3,5-dimethoxy-4′-hidroxy-3′-prenyl-trans-stilbene (**13o**) respectively (**Scheme 2.7.13**).

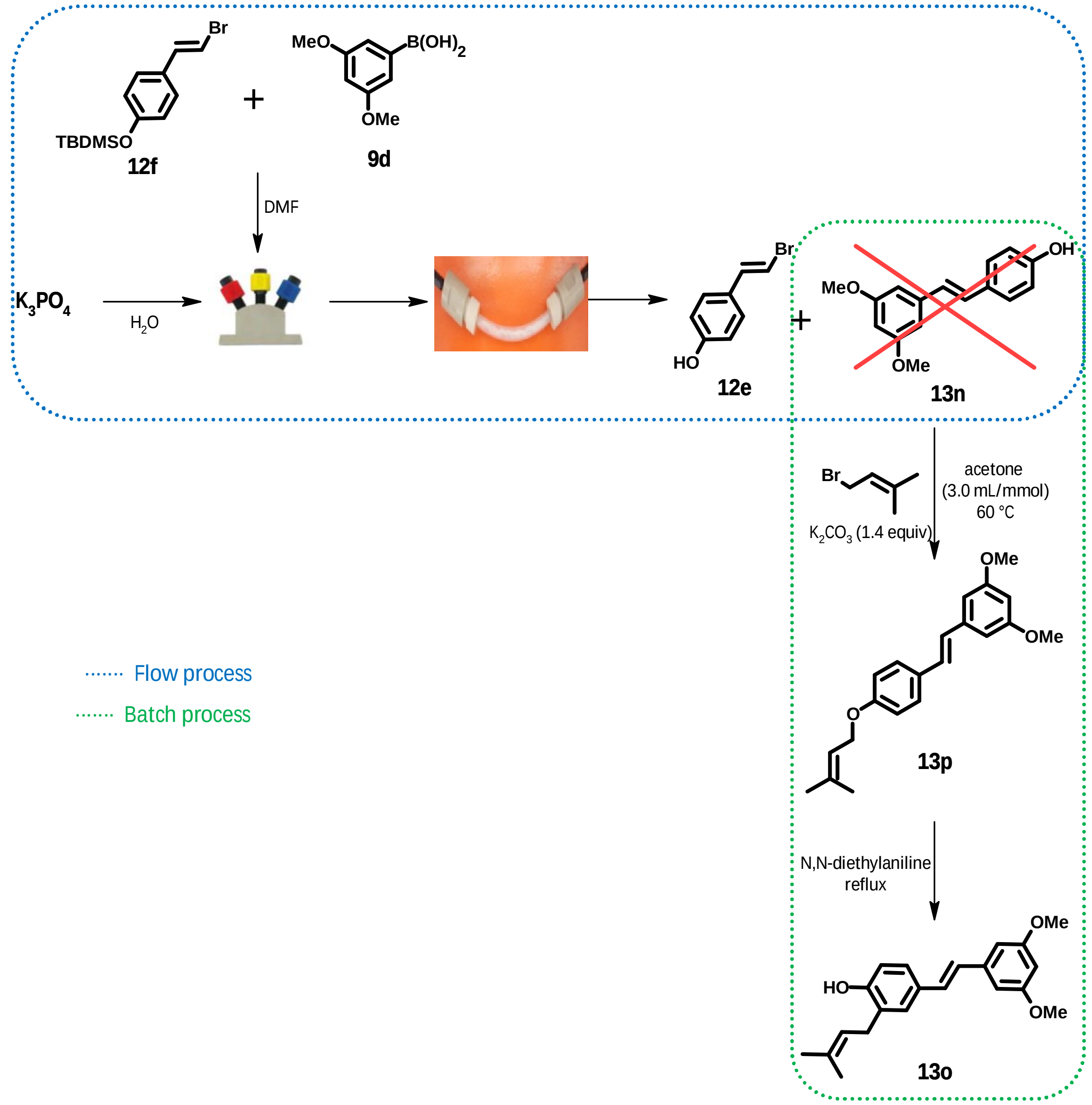


Scheme 2.7.13: Synthesis of two new natural pterostilbene derivates 15p and 15o

In detail, the previously obtained pterostilbene (**13n)**, were etherified in acetone using K_2CO_3 and 1-bromo-3-methyl-2-butene at 60°C for 3 h,**[472a]** producing the desired 3,5-dimethoxy-4′-prenyloxy-trans-stilbene (**13p**) in 80 % yield (**Scheme 2.7.13**). Next the compound **13p** was dissolved in N,N-diethylaniline and heated to reflux for 6 h, obtaining, after acidification at pH 4 by the addition of HCl (2 M) the desired 3,5-dimethoxy-4′-hidroxy-3′-prenyl-trans-stilbene (**13o**) in 48 % yield (**Scheme 2.7.13**).

2.7.2.1.2 Synthesis of pterostilbene and natural derivatives in flow process

For regard the synthesis of the three natural hydroxystilbenes **13n-p** in flow, we shifted the key step of Suzuki coupling in flow, using original packed-bed mini-reactors of design and construction extremely simple and cheap previously developed (see paragraph 2.2) and studied in this reaction (see paragraph 2.3.4); and we preserved the other steps in batch (**Scheme 2.7.14**).



Scheme 2.7.14: Flow synthetic process

We performed the Suzuki-Miyaura reaction key step in continuous flow using reactors packaged with Pd Fibrecat 1007 mixed at glass beads in 1:10 volume ratio (because these types of filler were results the best in the previously study carried out on the reaction model reported in paragraph 2.3.4), under the better applicable flow reaction conditions (DMF:H_2O as solvent and K_3PO_4 as base) previously individuated and studied (see paragraph 2.3.4).

Unfortunately, under these flow process we have not obtain the same good results reported in the synthesis in batch process. In fact in the flow process we observed the complete desililation of the start material **12f** with consequent not reactivity in the Suzuki reaction step.

2.7.3 Conclusions

In conclusion, we have established that the our chosen supported systems are really suitable in new, efficient and straightforward formal total synthesis of bioactive and/or natural compounds in batch and flow process.

In particular, we have conveniently prepared cinnamic acids **27g-i** and cinnamide **28**, employing the corresponding butyl cinnamates intermediate **25**, using a Mizoroki-Heck coupling catalyzed by two supported catalysts under batch and flow conditions, obtaining good and comparable results.

Moreover, at least in batch process, we have established a new, efficient and simple total synthesis of pterostilbene (**13n**), and the first synthesis of two new natural bioactive stilbenoid **13o** and **13p**, using Suzuki-Miyaura reaction catalyzed by supported catalysts.

3. Final conclusions

In conclusion the main purpose of this thesis work has been essentially achieved. It has been demonstrated that, in general, low doses of simple, cheap and easily available, commercial or laboratory prepared, supported catalysts (such as those chosen, **1-7**) can be able to promote C-C cross-coupling reactions with satisfactory efficiency both in batch and flow processes, enough to be really considered of applied and industrial interest; it is therefore not necessary to employ, for these reactions, complex, very elaborate and poorly available catalytic systems/reactors, ,(like most of the more recently reported in the literature), and/or use high loadings of palladium or expensive and difficult to remove ligands.

As planned, for this demonstration we have applied the chosen catalysts in three important C-C cross-coupling reactions (Suzuki-Miyaura, see section 2.3, Sonogashira-type, see section 2.4, and Mizoroki-Heck, see section 2.5), using rather green and industrially acceptable optimized conditions.

During these studies we have identified and optimized simple, efficient and environmentally friendly conditions that can allow the efficient use of the chosen catalysts in the above mentioned cross-coupling:

i) For the Suzuki-Miyaura reaction we have found conditions based on K_3PO_4 as base and DMF/H_2O, or EtOH/H_2O, or only water as solvent, under aerobic atmosphere.

ii) For the Sonogashira-type reactions we have found conditions based on pyrrolidine as base and DMF/H_2O, or only water, as solvent (but also solventless), under aerobic atmosphere.

iii) For the Mizoroki-Heck reaction we have found conditions based on tripropylamine as base and NMP as solvent.

Under these optimized conditions we have extended the knowledge on the four chosen commercial catalysts (**1-4**) and the Pd/PVPy (**5**, MVS-prepared), which previously had been tested, for the most part, insufficiently and only in some of the cross-couplings examined (see section 2.1.1.2). The same reaction conditions allowed the successful use in the examined reactions of the new Pd/MCM-41 (**6**) and Pd-Cu/PVPy (**7**).

The main novelties and the most important results of these studies are summarized and discussed in the partial conclusions reported at the end of the single sections (2.3.2, 2.3.3, 2.4.2, 2.4.3, 2.5.2 and 2.5.3)

However, in more detail as regard the batch mode, all the studied catalysts were able to give high catalytic activity in the studied cross-coupling reactions, both with aryl and vinyl halides, but the results depend strongly from the specific halide and reaction partner used; furthermore some specifities of each catalyst have been identified.

For example, as regards the Suzuki-Miyaura reaction, in the above mentioned conditions all the tested catalysts were able to promote the coupling with both deactivated aryl iodides and activated and/or deactivated (hetero)aryl bromides, also stericaly hindered, as well as with electron-poor and electron-rich (E)-β-bromostyrenes, giving satisfactory yields and tolerating the presence of free amino and ester groups (as in **8f and 8i,** respectively); but only the new Pd/MCM-41 was able to promote the reaction with 3-bromothiophene (**8j,** 73 % of yield in 22 h). On the other hand, only this catalyst and the Fibrecat 1007, even if under different conditions, were able to promote efficient Suzuky cross-couplings on aryl chlorides. It should be pointed that, on the basis of the available literature, so far Suzuki reactions carried out with supported catalysts on bromostyrenes have been poorly studied, and that the Fibrecat 1007 had never been used in Suzuky reactions on chloroarenes.

Also as regards Sonogashira-type reactions, under the above mentioned conditions the essayed catalysts were able to promote alkynylations of several aryl iodides and alkenyl halides, giving good yields in short time with aryl iodides, and acceptable yields with alkenyl halides. The main limitations included the presence of free hydroxyl groups on aryl iodides and the low stability of vinyl halides (and of enynes obtained from them), as well as the low reactivity of aliphatic alkynes and, above all, of aryl bromides. However, at least this last problem was successfully solved with a simple change of reaction conditions. In fact, tanks to the addition of 1.0 equivalent of KI in the reaction mixture (carried out under suitable conditions, carefully developed), we realized an original and general “one-pot” domino Halex-Sonogashira process; this process, which proceeds efficiently only in the presence of Fibrecat 1007 and Pd-Cu/PVPy, allowed the alkynylations of several aryl bromides, providing very good results with a low metal loading.

As regards, finally, the Mizoroki-Heck reaction, it is noteworthy that, even if in the literature are reported good results with some of the commercial catalysts tested, the more efficient catalysts have been our “home-made” Pd/PVPy and Pd/MCM-41.

Moreover, with this Thesis work, It has been also demonstrated that, in general, simple, versatile and low-cost packed-bed mini-reactors (prepared as described in section 2.2) can be able to promote C-C cross-coupling reactions with a satisfactory efficiency, at least comparable to that obtained in batch reactions carried out with the same catalyst (see section 2.3.3.1, 2.4.3.1, and 2.5.3.1).

In fact, in Suzuki-Miyaura and Sonogashira-type reactions we obtained performances equivalent to those reached in batch mode (at least in the case of the reactors filled with **3**), and that are among the best results so far reported in the literature for these reactions carried out in flow mode.

For regard the Mizoroki-Heck reaction, we have obtained performances even better than those reached in batch mode (at least using the reactors filled with **4** and **5**) and that so far can be classified as the best results reported in the literature on Heck alkenylations carried out with packed-bed flow reactors.

Finally, with this Thesis work, It has been demonstrated that, in general, simple, cheap and easily available, commercial or laboratory prepared, supported catalysts, and simple, versatile and low-cost packed-bed mini-reactors can be conveniently used in the synthesis of interesting natural and/or bioactive compounds of potential applied and industrial interest.

In more detail, we have established that the chosen supported systems are really suitable to be used in new, efficient and straightforward formal total synthesis of bioactive and/or natural compounds, both in batch and flow mode (see section 2.7 with partial conclusion).

In particular, we have conveniently prepared the cinnamic acids **27** and the cinnamides **28**, employing the same intermediate **25**, using a Mizoroki-Heck reaction catalyzed by two supported catalysts (**5** or **6**) under batch and flow conditions, obtaining good and comparable results.

Moreover, at least in batch mode, we have accomplished a new, efficient and simple total synthesis of pterostilbene (**13n**), and outlined the first synthesis of two new natural bioactive stilbenoids, **13o** and **13p**, by using Suzuki-Miyaura reactions catalyzed by the supported catalyst Fibrecat 1007 (**2**).

4. Experimental Section

4.1 Materials and apparatus

All operations involving the preparation of MVS products were performed under a argon atmosphere. The co-condensation of palladium and the appropriate solvent was carried out in a static reactor described previously. The solvated Pd atom solutions were worked up under argon atmosphere with the use of the standard Schlenk techniques. The amound of palladium in the above solutions was evaluated by inductively coupled plasma-optical emission spectrometers (ICP-OES) with a Spectro-Genesis instrument, using a software Smart Analyzer Vision. The limit of detection (lod) calculated for palladium was 2 ppb. Solvents were purified by conventional methods, distilled and store under argon. PVPy was supplied from Aldrich. Amines, aryl halides, terminal alkynes, boronic acids and butyl acrylate were purchased from Aldrich and used as received.

The GLC analyses were performed on a Dani GC1000 gas chromatograph, equipped with a flame ionisation detector (FID), using a SiO_2 capillary column FSOT Alltech (AT-5, 30 m x 0,25 mm i.d.) and FSOT Alltech (AT-20, 30 m x 0.25 mm i.d.) used nitrogen as carrier gas.

The GLC-MS analyses were performed on a Agilent 6890 Network GC System, equipped with a mass electron impact detector (Agilent 5973 Network Mass Selective Detector), using a SiO_2 capillary column Agilent (HP-5MS, 30 m x 0,25 mm i.d.) and helium as carrier gas.

The purification were performed on a MPLC Büchi Sepacore® Easy Purification System (equipped with a pump module C-601/C-605 and glass columns) equipped with a Refractory Index detector (Jasco Detector), using silica gel (Merck 60-40) as stationary phase.

The melting point of the isolated products were performed on

The ^{1}H-NMR of the isolated products were performed on a Varian INOVA 600 MHz. spectrometer in $CDCl_3$.

The ICP-OES analysis of the mineralized catalysts samples and crude reaction mixtures, were performer on an ICP-OES Spectro Genesis iCAP 6200 Duo upgrade, Thermofisher (Spectro Analitical Instrument).

4.2 Preparation of MVS-supported catalysts 5, 6 and 7

Pd–PVPy and Pd/MCM-41 samples with 1 mol% Pd contents were prepared via Metal Vapour Synthesis, and Pd incorporation, according to the modified synthesis method reported by Evangelisti et al

4.2.1 Preparation of the solvated Pd atoms

In a typical experiment, Pd vapour, generated at 10^{-4} bar by resistive heating of the metal (500 mg) in an alumina-coated tungsten crucible, was co-condensed at liquid nitrogen temperature with a 1:1 mixture of mesitylene (30 ml) and 1-hexene (30 ml) in a glass reactor described elsewhere.

The reactor chamber was heated to the melting point of the solid matrix (-40°C), and the resulting red-brown solution was siphoned and handled at low temperature (-30/-40°C) with the Schlenk tube technique.

For ICP-OES analysis, the metal-containing mesitylene/1-hexene solution (1 ml) was heated over a heating plate in a porcelain crucible, in the presence of *aqua regia* (2 ml), four times and the solid residue was dissolved in 0.5 M aqueous HCl. The palladium content of the solvated metal solution was 2.8 mg/ml.

4.2.2 Preparation of palladium on polyvinylpyridine, Pd/PVPy (5, 1 wt % Pd)

The mesitylene/1-hexene Pd atoms solution (36 ml, 100.8 mg Pd) was added to a suspension of PVPy (10 g) in mesitylene (30 ml). The mixture was stirred for 24 h at room temperature. The colour-less solution was removed and the light-brown solid was washed with pentane (3 x 40 ml) and dried under reduced pressure.

4.2.3 Preparation of palladium on silica mesoporous, Pd/MCM-41 (6, 1 wt % Pd)

The mesitylene/1-hexene Pd atoms solution (36 ml, 100.8 mg Pd) was added to a suspension of MCM-41 (10 g) in mesitylene (30 ml). The mixture was stirred for 24 h at room temperature. The colour-less solution was removed and the light-brown solid was washed with pentane (3 x 40 ml) and dried under reduced pressure.

4.2.4 Preparation of Pd-Cu/PVPy systems, (7)

The co-condensation of palladium and copper metals together with mesitylene and 1-hexene solvents was carried out in a static MVS reactor, similar to those previously described, equipped with two alumina-coated tungsten crucibles heated by Joule effect with two generators, respectively, with a maximum power of 2 kW which allowed to evaporate independently two metals. 150 mg of Pd (shot, ca. 6 mm, 99.9 %) and 60 mg of Cu (shot, 2-8 mm, 99.999 %), respectively, were co-condensed with a mixture of 1-hexene (30 mL) and mesitylene (30 mL) on the cooled wall (-196°C) of a glass MVS reactor chamber for 1 hour. The reactor chamber was warmed to the melting point of the solid matrix, and the resulting brown solvated metal atoms (SMA), was siphoned at low temperature into a Schlenk tube under argon atmosphere and kept in a refrigerator at - 40 °C. The palladium and copper content, obtained by Inductively Coupled Plasma-Optical Emission Spectrometers (ICP-OES) analysis (iCAP 6200 Duo upgrade, Thermofisher), was 1.35 mg/mL of Pd and 0.40 mg/mL of Cu, corresponding to a Pd/Cu molar ratio = 2. 30 mL of the Pd-Cu/(mesitylene-1-hexene) SMA (0.38 mmols, 40.5 mg of Pd and 0.19 mmols, 12 mg of Cu) was added to a suspension of the support (4.0 g) (PVPy, Adrich product, poly-4-vinylpyridine 2% cross-linked with divinylbenzene in mesitylene (20 mL). The mixture was stirred at room (25°C) temperature for 12 h. Pd-Cu bimetallic nanoparticles were quantitatively deposited on the supports, the colourless solution was removed and the solid was washed with n-pentane (two portions, 20 mL) and dried under reduced pressure. As previously observed for monometallic Pd SMA, the high thermal stability of the Pd-Cu/(mesitylene;1-hexene) SMA allowed a more controlled deposition of the metal particles on the PVPy resin.

4.2.5 Determination of the palladium and content

The Pd content of the Pd/PVPy, Pd/MCM-41 and Pd-Cu/PVPy samples was determined by inductively coupled plasma atomic emission spectroscopy, using a sequential all-argon Spectro-Genesis type spectrometer. For each sample, three parallel determinations were performed at the 229.7 nm and 324.3 nm emission wavelengths. Standard solutions for calibration were prepared from a commercial Pd stock solution through dilution by deionized water. The preparation of the catalyst samples (10 mg) for measurement was done by digestion in 4 x 10 mL of aqua regia solutions.

4.2.4 Preparation of Pd-Cu/PVPy systems, (7)

The co-condensation of palladium and copper metals together with mesitylene and 1-hexene solvents was carried out in a static MVS reactor, similar to those previously described, equipped with two alumina-coated tungsten crucibles heated by Joule effect with two generators, respectively, with a maximum power of 2 kW which allowed to evaporate independently two metals. 150 mg of Pd (shot, ca. 6 mm, 99.9 %) and 60 mg of Cu (shot, 2-8 mm, 99.999 %), respectively, were co-condensed with a mixture of 1-hexene (30 mL) and mesitylene (30 mL) on the cooled wall (-196°C) of a glass MVS reactor chamber for 1 hour. The reactor chamber was warmed to the melting point of the solid matrix, and the resulting brown solvated metal atoms (SMA), was siphoned at low temperature into a Schlenk tube under argon atmosphere and kept in a refrigerator at - 40 °C. The palladium and copper content, obtained by Inductively Coupled Plasma-Optical Emission Spectrometers (ICP-OES) analysis (iCAP 6200 Duo upgrade, Thermofisher), was 1.35 mg/mL of Pd and 0.40 mg/mL of Cu, corresponding to a Pd/Cu molar ratio = 2. 30 mL of the Pd-Cu/(mesitylene-1-hexene) SMA (0.38 mmols, 40.5 mg of Pd and 0.19 mmols, 12 mg of Cu) was added to a suspension of the support (4.0 g) (PVPy, Adrich product, poly-4-vinylpyridine 2% cross-linked with divinylbenzene in mesitylene (20 mL). The mixture was stirred at room (25°C) temperature for 12 h. Pd-Cu bimetallic nanoparticles were quantitatively deposited on the supports, the colourless solution was removed and the solid was washed with n-pentane (two portions, 20 mL) and dried under reduced pressure. As previously observed for monometallic Pd SMA, the high thermal stability of the Pd-Cu/(mesitylene;1-hexene) SMA allowed a more controlled deposition of the metal particles on the PVPy resin.

4.3 Typical procedure for the Suzuki reaction in batch

Tipically, directly at air the catalyst (3.00×10^{-3} mmol of Pd, or equivalent amounts of the other catalysts indicated in the **Table 2.3.2.1-2.3.2.11**), an aryl halide **8** or vinyl halide **12** (2.00 mmol), base (3.00 mmol,) and boronic acid **9** (2.50 mmol), were sequentially mixed in 2.66 mL of solvent as indicated in **Table 2.3.2.1-2.3.2.11**, and the resulting mixture was stirred at 80°C-125°C for the time indicated in **Table 2.3.2.1-2.3.2.11**. After this time the reaction mixture was cooled at room temperature, poured into water (20 mL) and extracted with diethyl ether (4×10 mL), then the collected organic extracts were washed with water (2×5 mL) and dried over Na_2SO_4. The extracts were added of a known amount of naphthalene as an internal standard, and the GLC yield was evaluated by using calibration curves obtained with naphthalene and an authentic sample of the expected product.

In cases where the isolated yield was determined, the crude product resulting after filtration and evaporation of dried organic extracts was purified by MPLC on silica gel.

In cases where the amounts of leached palladium at the end of reactions were assessed, ICP-OES analyses of the reactions mixtures cooled, filtered on Teflon filter (0.45 µm) and mineralized (aqua regia, 3 mL for 4 times) were performed.

4.3.1 2-methoxy-1,1’-biphenyl (10a)

Following the general procedure, 2-bromoanisole (**8a**, 2.0 mmol) and phenylboronic acid (**9a**, 1.2 equiv) provided the coupling product after purification by MPLC chromatography (eluent: Exane/AcOEt 98:2) of the crude product (**Table 2.3.2.6**, entry 1-6).

White solid; mp 28-31 °C (lit. 30-33 °C) **[473]**

1H NMR (600 MHz, CDCl 3): δ = 3.81 (s, 3H), 6.99–6.98 (m, 1H) 7.04–7.01 (m, 1H), 7.33–7.31 (m, 3H), 7.42–7.39 (t, J = 7.8 Hz, 2H), 7.53–7.52 (q, J = 7.2 Hz, 2H); MS, m/z (%): 185 (15), 184 (100), 183 (21), 169 (53), 168 (15), 152 (9), 141 (33), 139 (15), 115 (30). Spectral properties were in accordance with the literature.**[473]**

4.3.2 4-methyl-1,1’-biphenyl (10c)

Following the general procedure, 4-bromotoluene (**8c**, 2.0 mmol) and phenylboronic acid (**9a**, 1.2 equiv) or similarly, chlorobenzene (**8m**, 2.0 mmol) and toluilboronic acid (**9b**, 1.2 equv) provided the coupling product after purification by MPLC chromatography (eluent: Exane pure) of the crude product (**Table 2.3.2.6**, entry 7-12 and **Table 2.3.2.8**, entry 1-2).

White solid; mp 43-46 °C (lit. 44-46 °C)**[474]**

1H-NMR (600 MHz, $CDCl_3$): δ = 2.38 (s, 3H), 7.29 (d, *J*= 8.1Hz, 2H), 7.33-7.39 (m, 1H), 7.36-7.39 (m, 2H), 7.45 (d, *J*= 7.2 Hz, 2H), 7.59 (d, *J*= 8.1 Hz, 2H); MS, m/z (%): 169 (14), 168 (100), 167 (69), 166 (8), 165 (28), 153 (16), 152 (22), 115 (6), 83 (6).Spectral properties were in accordance with the literature **[474]**

4.3.3 4,4’-dimethyl-1,1’-biphenyl (10d)

Following the general procedure, 4-clorotoluene (**8n**, 2.0 mmol) and toluilboronic acid (**9b**, 1.2 equiv) provided the coupling product after purification by MPLC chromatography (eluent: Exane) of the crude product (**Table 2.3.2.8**, entry 7).

White solid; mp 118-120 °C (lit. 117-121 °C)**[475]**

MS, m/z (%): 182 (15), 182 (100), 181 (29), 178 (29), 178 (5), 168 (7), 167 (47), 166 (14), 165 (36), 153 (4), 152 (11), 128 (4), 115 (6), 91 (6), 90 (7), 89 (8), 76 (4). Spectral properties were in accordance with the literature**[475]**

4.3.4 biphenyl (10e)

Following the general procedure, clorobenzene (**8m**, 2.0 mmol) and phenylboronic acid (**9a**, 1.2 equiv) provided the coupling product after purification by MPLC chromatography (eluent: Exane) of the crude product (**Table 2.3.2.8**, entry 3-4).

White solid; mp 69-70 °C (lit. 68-70 °C)**[476]**

1H NMR (500 MHz, CDCl3): δ = 7.62–7.61 (d, J = 7.5 Hz, 4H), 7.47–7.44 (t, J = 7.5 Hz, 4H), 7.38–7.35 (t, J = 7.5 Hz, 2H); MS, m/z (%): 155 (13), 154 (100), 153 (40), 152 (28), 151 (8), 128 (5), 115 (4), 77 (4), 76(9). Spectral properties were in accordance with the literature**[476]**

4.3.5 4-nitro-1,1'-biphenyl (10f)

Following the general procedure, 4-nitrobromobenzene (**8d**, 2.0 mmol) and phenylboronic acid (**9a**, 1.2 equiv), or similarly, 4-nitrochlorobenzene (**8q**, 2.0 mmol) and phenylboronic acid (**9a**, 1.2 equiv) provided the coupling product after purification by MPLC chromatography (eluent: Exane/AcOEt 95:5) of the crude product (**Table 2.3.2.6**, entry 19-24 and **Table 2.3.2.8**, entry 11).

Pale yellow solid; mp 110–113 °C (lit. 112-114 °C)**[477]**

1H NMR (600 MHz, CDCl3): δ = 8.32–8.30 (m, 2H), 7.76–7.74 (m, 2H), 7.65–7.63 (m, 2H), 7.53–7.50 (m, 2H), 7.48–7.45 (m, 1H); MS, m/z (%): 200 (14), 199 (100), 169 (29), 153 (26), 152 (89), 151 (26), 141 (25), 115 (11), 76 (8). Spectral properties were in accordance with the literature**[477]**

4.3.6 2-methoxy-2'-methyl-1,1'-biphenyl (10g)

Following the general procedure, 2-bromotoluene (**8e**, 2.0 mmol) and phenylboronic acid (**9a**, 1.2 equiv), provided the coupling product after purification by MPLC chromatography (eluent: Exane/CH_2Cl_2 90:10) of the crude product (**Table 2.3.2.6**, entry 25-30.

With solid; mp 41-43 °C (lit. 42-44 °C)**[478]**

MS, m/z (%): 199 (16), 198 (100), 197 (12), 183 (35), 168 (29), 167 (36), 165 (42), 153 (15), 152 (18). Spectral properties were in accordance with the literature**[478]**

4.3.7 4-amino-1,1'-biphenyl (10h)

Following the general procedure, 4-bromoaniline (**8f**, 2.0 mmol) and phenylboronic acid (**9a**, 1.2 equiv) provided the coupling product after purification by MPLC chromatography (eluent:) of the crude product (**Table 2.3.2.6**, entry 31-36).

Pale yellow solid; mp 51-55 °C (litt. mp 52-54 °C)**[479]**

MS, m/z (%): 170 (13), 170 (100), 169 (10), 141 (21), 139 (6), 115 (15), 85 (4), 77 (2). Spectral properties were in accordance with the literature**[479]**

4.3.8 2-phenylthiophene (10i)

Following the general procedure, 2-bromothiophene (**8g**, 2.0 mmol) and phenylboronic acid (**9a**, 1.2 equiv) provided the coupling product after purification by MPLC chromatography (eluent: Exane pure) of the crude product (**Table 2.3.2.6**, entry 37-42).

White solid; mp 33-37 °C (lit. 34-35 °C)**[480]**

1H NMR (600 MHz, CDCl3): δ = 7.68–7.65 (m, 2H), 7.51–7.48 (t, J = 7.8 Hz, 1H), 7.44–7.39 (m, 2H), 7.37–7.36 (q, J = 7.8 Hz, 1H), 7.34–7.31 (m, 1H), 7.13–7.12 (m, 1H); MS, m/z (%): 161 (12), 160 (100), 159 (7), 134 (4), 128 (10), 116 (8), 115 (28), 102 (4), 89 (5). Spectral properties were in accordance with the literature**[480]**

4.3.9 2,6-dimethyl-2'-methoxy-1,1'-biphenyl (10j)

Following the general procedure, 2,6-dimethyl-1-bromobenzene (**8h**, 2.0 mmol) and 2-methoxyphenylboronic acid (**9c**, 1.2 equiv) provided the coupling product after purification by MPLC chromatography (eluent: Exane/CH_2Cl_2 90:10) of the crude product (**Table 2.3.2.6**, entry 43-48).

Colorless liquid;

1H NMR (600 MHz, CDCl3) δ 7.37-7.28 (m, 1H), 7.20-7.05 (m, 3H), S11 7.05-6.93 (m, 3H), 3.71 (s, 3H), 2.01 (s, 6H); MS, m/z (%): 213 (16), 212 (100), 197 (40), 183 (7), 182 (24), 181 (51), 179 (15), 178 (11), 169 (12), 153 (12), 152 (16), 115 (6), 105 (6), 91 (4), 89 (4). Spectral properties were in accordance with the literature**[481]**

4.3.10 ethyl 4-phenylbenzoate (10k)

Following the general procedure, ethyl 4-bromobenzoate (**8i**, 2.0 mmol) and phenylboronic acid (**9a**, 1.2 equiv) provided the coupling product after purification by MPLC chromatography (eluent: Exane/AcOEt 95:5) of the crude product (**Table 2.3.2.6**, entry 49-50).

Yellow solid; mp 46-49 °C (lit. 47-50 °C)**[482]**

MS, m/z (%): 227 (10), 226 (61), 198 (31), 182 (18), 181 (100), 153 (26), 152 (50), 151 (13), 76 (6). Spectral properties were in accordance with the literature**[482]**

4.3.11 3-phenylthiophene (10l)

Following the general procedure, 3-bromothiophene (**8j**, 2.0 mmol) and phenylboronic acid (**9a**, 1.2 equiv) provided the coupling product after purification by MPLC chromatography (eluent: Exane pure) of the crude product (**Table 2.3.2.6**, entry 51-55).

Yellow solid; mp 85-91 °C (litt. mp 89-93 °C)**[483]**

MS, m/z (%): 162(6), 161 (13), 160 (100), 159 (8), 134 (4), 128 (9), 116 (10), 115 (34), 102 (4), 89 (6). Spectral properties were in accordance with the literature**[483]**

4.3.12 3-phenylpyridine (10m)

Following the general procedure, 3-bromopyridine (**8k**, 2.0 mmol) and phenylboronic acid (**9a**, 1.2 equiv) provided the coupling product after purification by MPLC chromatography (eluent:) of the crude product (**Table 2.3.2.6**, entry 56-60).

Pale yellow liquid;

MS, m/z (%): 156 (12), 155 (100), 154 (52), 128 (10), 127 (13), 102 (10), 77 (5), 76 (5). Spectral properties were in accordance with the literature**[484]**

4.3.13 4-trifluoromethyl-1,1'-biphenyl (10n)

Following the general procedure, 4-trifluoromethyl-chlorobenzene (**8i**, 2.0 mmol) and phenylboronic acid (**9a**, 1.2 equiv) provided the coupling product after purification by MPLC chromatography (eluent: Exane pure) of the crude product (**Table 2.3.2.8**, entry 5-6).

White solid; mp 63-65 °C (litt. mp 64-66 °C)**[485]**

MS , m/z (%) : 223 (15), 222 (100), 203 (10), 201 (12), 153 (16), 152 (23), 151 (7), 86 (4), 76 (3). Spectral properties were in accordance with the literature**[485]**

4.3.14 4-acetyl-1,1'-biphenyl (10o)

Following the general procedure, 4-chlorocetophenone (**8o**, 2.0 mmol) and phenylboronic acid (**9a**, 1.2 equiv) provided the coupling product after purification by MPLC chromatography (eluent: Exane/AcOEt 90:10) of the crude product (**Table 2.3.2.8**, entry 8-9).

White solid; mp 117-119 °C (lit. 118-120 °C)**[486]**

1H NMR (600 MHz, CDCl3): δ = 8.04–8.05 (m, 2H), 7.69–7.71 (m, 2H), 7.64–7.65 (q, J = 5.4 Hz, 2H), 7.47–7.50 (t, J = 7.2 Hz, 2H), 7.40–7.43 (m, 1H), 2.65 (s, 3H); MS, m/z (%): 197 (8), 196 (53), 182 (14), 181 (100), 153 (32), 152 (52), 151 (14), 126 (4), 76 (11). Spectral properties were in accordance with the literature**[486]**

4.3.15 4-fluoro-1,1'-biphenyl (10p)

Following the general procedure, 4-fluoro-1-chlorobenzene (**8p**, 2.0 mmol) and phenylboronic acid (**9a**, 1.2 equiv) provided the coupling product after purification by MPLC chromatography (eluent: Exane pure) of the crude product (**Table 2.3.2.8**, entry 10).

White solid; mp 74-78 °C (lit. 73-76 °C)**[487]**

MS, m/z (%): 173 (13), 172 (100), 171 (38), 170 (27), 154 (34), 153 (15), 152 (13), 85 (8), 76 (9). Spectral properties were in accordance with the literature**[487]**

4.3.16 2-phenylpyridine (10q)

Following the general procedure, 2-chloropyridine (**8r**, 2.0 mmol) and phenylboronic acid (**9a**, 1.2 equiv) provided the coupling product after purification by MPLC chromatography (eluent:) of the crude product (**Table 2.3.2.8**, entry 12).

Pale yellow liquid; MS, m/z (%): 155 (100), 154 (81), 127 (14), 156 (12), 77 (12), 128 (10), 51 (10), 77 (6). Spectral properties were in accordance with the literature**[488]**

4.3.17 stilbene (13a)

Following the general procedure, β-bromostyrene (**12a**, 2.0 mmol) and phenylboronic acid (**9a**, 1.2 equiv) provided the coupling product after purification by MPLC chromatography (eluent: Exane pure) of the crude product (Table 2.3.2.11, entry 5-7).

White solid; mp 124-126 °C (lit. 126-127 °C)**[489]**

MS, m/z (%): 180 (100), 179 (86), 178 (57), 177 (8), 176 (8), 166 (13), 165 (37), 153 (4), 152 (9), 139 (1), 115 (1), 102 (2), 89 (4), 77 (2), 76 (5), 63 (2), 51 (2). Spectral properties were in accordance with the literature**[489]**

4.3.18 1,1-diphenylethene (13b)

Following the general procedure, α-bromostyrene (**12b**, 2.0 mmol) and phenylboronic acid (**9a**, 1.2 equiv) provided the coupling product after purification by MPLC chromatography (eluent: Exane pure) of the crude product (Table 2.3.2.11, entry 1-4).

Colorless liquid; MS, m/z (%): 180 (100), 165 (81), 152 (12), 102 (7), 89 (16), 77 (10), 51 (7). Spectral properties were in accordance with the literature[**490**]

4.3.19 2-phenyl-1-octene (13c)

Following the general procedure, 2-bromo-1-octene (**12c**, 2.0 mmol) and phenylboronic acid (**9a**, 1.2 equiv) provided the coupling product after purification by MPLC chromatography (eluent: Exane pure) of the crude product (Table 2.3.2.10, entry 21-22).

Pale yellow liquid; MS, m/z (%): 188 (11), 131 (18), 118 (100), 103 (16), 91 (22), 77 (11), 65 (3). Spectral properties were in accordance with the literature**[491]**

4.3.20 1-methoxy-2-(1-phenylethenyl)-benzene (13d)

Following the general procedure, α-bromostyrene (**12b**, 2.0 mmol) and 2-methoxyphenylboronic acid (**9c**, 1.2 equiv) provided the coupling product after purification by MPLC chromatography (eluent: Exane pure) of the crude product (Table 2.3.2.11, entry 9-10).

Pale yellow solid; mp 35-38 °C

1H NMR (600 MHz CDCl3) δ: 3.65 (s, 3H), 5.34 (d, J = 1 Hz, 1H), 5.75 (d, J = 1 Hz, 1H), 6.91–6.94 (m, 1H) 6.98–7.02 (m, 1H), 7.25–7.36 (m, 3H). Spectral properties were in accordance with the literature**[492]**

4.3.21 1,3-dimethoxy-5-(1-phenylethenyl)-benzene (13e)

Following the general procedure, α-bromostyrene (**12b**, 2.0 mmol) and 3,5-dimethoxyphenylboronic acid (**9d**, 1.2 equiv) provided the coupling product after purification by MPLC chromatography (eluent: Exane pure) of the crude product (Table 2.3.2.11, entry 11-13).

Yellow solid; mp 40-45 °C;

1H NMR (600 MHz, CDCl3) δ: 3.79 (s, 6H), 5.49 (s, 2H), 6.48 (t, J = 2.44 Hz, 1H), 6.53 (d, J = 1.95 Hz, 2H), 7.31-7.40 (m, 5H). Spectral properties were in accordance with the literature**[493]**

4.3.22 (E)-(1-methylene-2-heptenyl)-benzene (13f)

Following the general procedure, α-bromostyrene (**12b**, 2.0 mmol) and (E)-1-hexenyl-boronic acid (**9e**, 1.2 equiv) provided the coupling product after purification by MPLC chromatography (eluent: Exane) of the crude product (Table 2.3.2.11, entry 14-16).

Colorless liquid; 1H NMR (600 MHz CDCl3) δ: 0.91 (t, 3 H), 1.2-1.5 (m, 4 H), 1.95-2.25 (m. 2 H), 5.02 (d, 1 H, J = 2 Hz), 5.13 (d, 1 H, J = 2 Hz), 5.59 (dt, 1 H, J = 7 16 Hz), 6.27 (d, 1 H, J = 16 Hz), 7.24 (s, 5 H). Spectral properties were in accordance with the literature**[494]**

4.3.23 (E,E)-octadienyl-benzene (13g)

Following the general procedure, β-bromostyrene (**12a**, 2.0 mmol) and (E)-1-hexenyl-boronic acid (**9e**, 1.2 equiv) provided the coupling product after purification by MPLC chromatography (eluent: Exane) of the crude product (Table 2.3.2.11, entry 17-19).

Colorless liquid; 1H NMR (600 MHz, CDCl3) δ: 7.27 (m, 5 H), 6.73 (dd, J = 15.6, 10.3 Hz, 1 H), 6.41 (d, J= 15.6 Hz, 1 H), 6.18 (dd, J = 15.1,10.3 Hz, 1 H), 5.80 (dt, J = 15.1, 7.5 Hz, 1 H), 2.12 (m, 2 H), 1.34 (m, 4 H), 0.88 (t, J = 6.9 Hz, 3 H). Spectral properties were in accordance with the literature**[495]**

4.3.24 4-hydroxy-stilbene (13i)

Following the general procedure, 4-hydroxy-β-bromostyrene (**12e**, 2.0 mmol) or (E)-4-t-butyldimethylsilyloxy-(E)-β-bromostyrene (**12f**, 2.0 mmol) and phenylboronic acid (**9a**, 1.2 equiv) provided the coupling product after purification by MPLC chromatography (eluent: Exane/AcOEt 90:10) of the crude product (Table 2.3.2.11, entry 23-29).

Light brown solid; mp 180-183 °C (lit 183-185 °C)**[495]**

1H NMR (600 MHz, CDCl3) δ: 7.49 (d, J = 7.0 Hz, 2H), 7.42 (d, J = 8.5 Hz, 2H), 7.35 (t, J = 7.5 Hz, 2H), 7.24 (t, J = 7.5 Hz, 1H), 7.06 (d, J = 16.5 Hz, 1H), 6.97 (d, J = 16.5 Hz, 1H), 6.84 (d, J = 9.0 Hz, 2H), 4.97 (s, 1H). Spectral properties were in accordance with the literature**[495]**

4.3.25 4-hydroxy-2'-methyl-stilbene (13j)

Following the general procedure, (E)-4-t-butyldimethylsilyloxy-(E)-β-bromostyrene (**12f**, 2.0 mmol) and 2-toluilboronic acid (**9f**, 1.2 equiv) provided the coupling product after purification by MPLC chromatography (eluent: Exane/AcOEt 90:10) of the crude product (Table 2.3.2.11, entry 30-33).

Colorless oil;

MS, m/z (%): 210 (100), 209 (12), 195 (33), 194 (17), 178 (13), 177 (17), 167 (13), 165 (21), 152 (8), 116 (19), 115 (18), 104 (7), 91 (6); Anal. calcd for C15H14O: C 85.68; H 6.71. Found: C, 87.70; H, 6.69.

4.4 Typical procedure for the Sonogashira reaction in batch

Tipically, directly at air the catalyst (2.00x10^{-3} mmol of Pd , or equivalent amounts of the other catalysts indicated in the **Table 2.4.2.1-2.4.2.9**), an aryl halide **8** or vinyl bromide **12** or vinyl iodide **22** (2.00 mmol), base (2.00-3.00 mmol, as indicated in Table) and terminal alkyne **14** (2.60-3.00 mmol, as indicated in Table), were sequentially mixed in 1.0 mL of solvent (if used) as indicated in **Table 2.4.2.1-2.4.2.9**, and the resulting mixture was stirred at 95°C for the time indicated in **Table 2.4.2.1-2.4.2.9**. After this time the reaction mixture was cooled at room temperature, poured into water (20 mL) and extracted with diethyl ether (4×10 mL), then the collected organic extracts were washed with water (2×5 mL) and dried over Na2SO4. The extracts were added of a known amount of naphthalene as an internal standard, and the GLC yield was evaluated by using calibration curves obtained with naphthalene and an authentic sample of the expected product.

In cases where the isolated yield was determined, the crude product resulting after filtration and evaporation of dried organic extracts was purified by MPLC on silica gel.

In cases where the amounts of leached palladium and copper at the end of reactions were assessed, ICP-OES analyses of the reactions mixtures cooled, filtered on Teflon filter (0.45 μm) and mineralized (aqua regia, 3 mL for 4 times) were performed.

4.4.1 1-methoxy-4-(phenylethynil)-benzene (15a)

Following the general procedure, 4-iodoanisole (**8s**, 2.0 mmol) and phenylacetylene (**14a**, 1.2 or 1.5 equiv) provided the coupling product after purification by MPLC chromatography (eluent: Exane/Toluene 80:20) of the crude product (Table 2.4.2.4, entry 1-6 and Table 2.4.2.5 entry 1-2).

With solid; mp 78-80 °C (lit. 79-81 °C)**[496]**

MS, m/z (%): 208 (100), 193 (50), 165 (40), 164 (13), 163 (10), 139 (9), 115 (4), 104 (4), 88 (3). Spectral properties were in accordance with the literature**[496]**

4.4.2 1-methoxy-2-(phenylethynil)-benzene (15b)

Following the general procedure, 2-iodoanisole (**8t**, 2.0 mmol) and phenylacetylene (**14a**, 1.2 or 1.5 equiv) provided the coupling product after purification by MPLC chromatography (eluent: CH_2Cl_2/Exane 60:40) of the crude product (Table 2.4.2.4, entry 7-12 and Table 2.4.2.5 entry 2-3).

Yellow solid; mp 137–139 °C (lit. 138–140 °C)**[497]**

MS, m/z (%): 208 (100), 207 (77), 189 (7), 179 (11), 178 (22), 165 (37), 164 (14), 163 (13), 131 (24). Spectral properties were in accordance with the literature**[497]**

4.4.3 2-(phenylethyl)-thiophene (15c)

Following the general procedure, 2-iodothiophene (**8u**, 2.0 mmol) and phenylacetylene (**14a**, 1.2 or 1.5 equiv) provided the coupling product after purification by MPLC chromatography (eluent: Exane/Toluene 92:8) of the crude product (Table 2.4.2.4, entry 13-18; Table 2.4.2.5 entry 5-6 and Table 2.4.2.7 entry 7).

White solid; mp 50-51 °C (lit 50-51 °C)**[498]**

MS, m/z (%): 185(14) ,184 (100), 152 (12), 139 (18), 126 (5), 92 (4), 86 (2), 74 (2), 69 (2), 45 (1). Spectral properties were in accordance with the literature**[498]**

4.4.4 2-(phenylethyl)-aniline (15d)

Following the general procedure, 2-iodoaniline (**8v**, 2.0 mmol) and phenylacetylene (**14a**, 1.2 or 1.5 equiv), or similarly, iodobenzene (8x, 2.0 mmol) and (14b, 1.2 or 1.5 equiv) provided the coupling product after purification by MPLC chromatography (eluent: CH_2Cl_2/Exane 70:30) of the crude product (Table 2.4.2.4, entry 19-23, 29-32; Table 2.4.2.5 entry 7 and Table 2.4.2.7 entry 5).

Yellow solid; mp 88-89 °C (lit. 88-90 °C)**[499]**

MS, m/z (%): 193 (100), 192 (16), 191 (8), 165 (39), 139 (5), 96 (7), 90 (12), 89 (12), 83 (4). Spectral properties were in accordance with the literature**[499]**

4.4.5 1-phenyl-1-octyne (15f)

Following the general procedure, iodobenzene (**8x**, 2.0 mmol) and octyne (**14c**, 1.2 equiv) provided the coupling product after purification by MPLC chromatography (eluent: Exane) of the crude product (Table 2.4.2.4, entry 33-36 and Table 2.4.2.5 entry 10).

Pale yellow liquid;

MS, m/z (%): 186 (41), 157 (24), 144 (33), 143 (82), 130 (31), 129 (73), 128 (45), 117 (86), 115 (100), 102 (27), 91 (35). Spectral properties were in accordance with the literature**[500]**

4.4.6 1-methyl-4-(phenylethynil)-benzene (15g)

Following the general procedure, iodotoluene (**8c**, 2.0 mmol) and phenylacetylene (**14a**, 1.2 or 1.5 equiv) provided the coupling product after purification by MPLC chromatography (eluent: Exane) of the crude product (Table 2.4.2.5, entry 12-13 and Table 2.4.2.7 entry 1-2).

White solid; mp 71-73 °C (lit. 72-73 °C)**[501]**

MS, m/z (%): 192 (100), 191 (47), 190 (12), 189 (23), 165 (12), 163 (4), 115 (5), 96 (4), 82 (5). Spectral properties were in accordance with the literature**[501]**

4.4.7 3-(phenylethyl)-pyridine (15h)

Following the general procedure, 3-iodopyridine (**8y**, 2.0 mmol) and phenylacetylene (**14a**, 1.2 or 1.5 equiv), or similarly, 3-bromopyridine (**8m**, 2.0 mmol) and phenylacetylene (**14a**, 1.2 or 1.5 equiv) provided the coupling product after purification by MPLC chromatography (eluent: Exane/AcOEt 60:40) of the crude product (Table 2.4.2.5, entry 11 and Table 2.4.2.7 entry 3-4).

White solid; mp 50-51 °C (lit. 50-51 °C)**[496]**

MS, m/z (%): 179 (100), 178 (22), 177 (4), 152 (9), 151 (12), 126 (14), 98 (3), 76 (7), 63 (5). Spectral properties were in accordance with the literature**[496]**

4.4.8 1,2-diphenylacetylene (15i)

Following the general procedure, iodobenzene (**8x**, 2.0 mmol) and phenylacetylene (**14a**, 1.2 or 1.5 equiv), or similarly, bromobenzene (**8b**, 2.0 mmol) and phenylacetylene (**14a**, 1.2 or 1.5 equiv) provided the coupling product after purification by MPLC chromatography (eluent: Exane) of the crude product (Table 2.4.2.5, entry 12-13 and Table 2.4.2.7 entry 1-2).

White solid; mp 63-66 °C (lit. 63-65 °C)**[502]**

MS, m/z (%): 179 (15), 178 (100), 177 (11), 176 (21), 152 (11), 151 (8), 150 (6), 126 (4), 76 (5). Spectral properties were in accordance with the literature**[502]**

4.4.9 ethyl 4-(phenylethyl)-benzoate (15j)

Following the general procedure, ethyl 4-iodobenzoate (**8z**, 2.0 mmol) and phenylacetylene (**14a**, 1.2 or 1.5 equiv), or similarly, ethyl 4-bromobenzoate (**8i**, 2.0 mmol) and phenylacetylene (**14a**, 1.2 or 1.5 equiv) provided the coupling product after purification by MPLC chromatography (eluent: Exane/AcOEt 60:40) of the crude product (Table 2.4.2.5, entry 14 and Table 2.4.2.7 entry 8-9).

Pale yellow solid; mp 72-74 °C (lit. 72-73 °C)**[503]**

MS, m/z (%): 250 (99), 222 (29), 205 (100), 177 (18), 176 (50), 151 (18), 150 (11), 88 (14), 75 (3). Spectral properties were in accordance with the literature**[503]**

4.4.10 1-(phenylethyl)-naphtalene (15k)

Following the general procedure, 1-iodonaphtalene (**8aa**, 2.0 mmol) and phenylacetylene (**14a**, 1.2 or 1.5 equiv), or similarly, 1-bromonaphtalene (**8ac**, 2.0 mmol) and phenylacetylene (**14a**, 1.2 or 1.5 equiv) provided the coupling product after purification by MPLC chromatography (eluent: Exane/Toluene 90:10) of the crude product (Table 2.4.2.5, entry 15 and Table 2.4.2.7 entry 10).

White solid; mp 51-53 °C (lit. 52-54 °C)**[504]**

MS, m/z (%): 228 (100), 227 (18), 226 (40), 224 (8), 202 (6), 200 (5), 187 (2), 114 (6), 113 (7). Spectral properties were in accordance with the literature**[504]**

4.4.11 (E)-1,4-diphenyl-3-buten-1-yne (23a)

Following the general procedure, β-bromostyrene (**12a**, 2.0 mmol) and phenylacetylene (**14a**, 1.2-1.5 equiv) provided the coupling product after purification by MPLC chromatography (eluent:Exane pure) of the crude product (Table 2.4.2.8, entry 1-9).

White solid;

MS, m/z (%): 205 (16), 204 (100), 203 (89), 201 (12), 200 (11), 189 (5), 101 (16), 76 (6). Spectral properties were in accordance with the literature**[505]**

4.4.12 2-(2-phenyl-1-ethynil)-1-propene (23b)

Following the general procedure, 2-bromo-1-propene (**12g**, 2.0 mmol) and phenylacetylene (**14a**, 1.2-1.5 equiv) provided the coupling product after purification by MPLC chromatography (eluent: Exane pure) of the crude product (Table 2.4.2.8 entry 16-24).

Colorless oil;

MS, m/z (%): 143 (11), 142 (100), 141 (100), 139 (7), 127 (26), 126 (10), 115 (37), 77 (9), 63 (7). Spectral properties were in accordance with the literature**[506]**

4.4.13 (E)-1-phenyl-3-tetradecen-1-yne (23c)

Following the general procedure, (E)-1-bromo-1-dodecene (**12h**, 2.0 mmol) and phenylacetylene (**14a**, 1.2-1.5 equiv) provided the coupling product after purification by MPLC chromatography (eluent: Exane pure) of the crude product as colorless oil (108 mg, 20 % yield).

MS, m/z (%): 269 (13), 268 (58), 155 (26), 142 (17), 141 (64), 129 (20), 128 (100), 115 (41), 91 (11); Anal. calcd for C20H28: C 89.49; H 10.51. Found: C 89.47; H 10.53.

4.4.14 2-(2-phenyl-1-ethynil)-1-octene (23d)

Following the general procedure, 2-bromo-1-octene (**12c**, 2.0 mmol) and phenylacetylene (**14a**, 1.2-1.5 equiv) provided the coupling product after purification by MPLC chromatography (eluent:Exane pure) of the crude product (Table 2.4.2.8 entry 33-40).

Colorless oil;

1H NMR (600 MHz, CDCl3): 7.47-7.37 (m, 2H) 7.34-7.27 (m 3H) 5.40 (s, 1H) 5.28 (s, 1H) 2.23 (t, J = 7.6 Hz, 2H) 1.62-1.55 (m, 2H) 1.30 (s, 6H) 0.89 (t, J = 6.9, 3H); MS, m/z (%): 155 (14), 143 (14), 142 (100), 141 (49), 129 (8), 128 (9), 127 (11), 115 (19), 77 (7). Spectral properties were in accordance with the literature**[507]**

4.4.15 5-methyl-5-hexen-3-yn-1-ol (23e)

Following the general procedure, 2-bromo-1-propene (**12g**, 2.0 mmol) and 3-butyn-1-ol (**14e**, 1.2 equiv) provided the coupling product after purification by MPLC chromatography (eluent: Exane pure) of the crude product, obtaining a colorless oil (99 mg, 45 % yield).

MS, m/z (%): 110 (71), 91 (15), 80 (43), 79 (100), 77 (64), 65 (15), 53 (14), 51 (15), 39 (14); Anal. calcd for C7H10O: C 76.33; H 9.15. Found: C 76.42; H 9.11.

4.4.16 4-methyl-4-penten-2-yn-1-ol (23f)

Following the general procedure, 2-bromo-1-propene (**12g**, 2.0 mmol) and 2-methyl-3-butyn-2-ol (**14f**, 1.2-1.5 equiv) provided the coupling product after purification by MPLC chromatography (eluent:Exane pure) of the crude product, obtaining a colorless oil (20 mg, 10% yield).

MS, m/z (%): 96 (100), 95 (79), 81 (91), 77 (49), 67 (86), 53 (71), 51 (35), 41 (48), 39 (47); Anal. calcd for C6H8O: C 74.97; H 8.39. Found: C 75.02; H 8.28.

4.4.17 2-(4-triisopropylsilyloxy-1-butynil)-1-propene (23g)

Following the general procedure, 2-bromo-1-propene (**12g**, 2.0 mmol) and (1-triisopropylsilyloxy-3-butyne (**14g**, 1.2-1.5 equiv) provided the coupling product after purification by MPLC chromatography (eluent: Exane pure) of the crude product, obtaining a colorless oil (90 mg, 20 % yield).

MS, m/z (%): 224 (21), 223 (100), 181 (76), 153 (49), 151 (24), 123 (17), 77 (14), 75 (22), 59 (16); Anal. calcd for C16H30O: C 72.11; H 11.35. Found: C 72.14; H 11.47.

4.4.18 (E)-1-phenyl-3-decen-1-yne (23h)

Following the general procedure, 1-iodo-1-octene (**22**, 2.0 mmol) and phenylacetylene (**14a**, 1.2-1.5 equiv) provided the coupling product after purification by MPLC chromatography (eluent:Exane pure) of the crude product as colorless oil (284 mg, 67 % yield);

MS, m/z (%): 213 (10), 212 (58), 155 (26), 153 (9), 142 (15), 141 (71), 128 (100), 115 (52), 91 (11). Spectral properties were in accordance with the literature**[505]**

4.4.19 [(3*E*)-4-(1-cyclohexen-1-yl)-3-buten-1-yn-1-yl]-benzene (23i)

Following the general procedure, 1-[(E)-2-bromoethenyl]cyclohex-1-ene (**12k**, 2.0 mmol) and phenylacetylene (**14a**, 1.2-1.5 equiv) provided the coupling product after purification by MPLC chromatography (eluent:Exane pure) of the crude product obtaining a colorless oil (284 mg, 25 % yield);

MS, m/z (%): 208 (100), 180 (91), 179 (72), 178 (68), 167 (66), 166 (23), 165 (94), 152 (32), 115 (27). Spectral properties were in accordance with the literature**[505]**

4.5 Typical procedure for the Heck reaction in batch

Tipically, under N_2 atmosphere the catalyst (2.00×10^{-3} mmol of Pd, or equivalent amounts of the other catalysts indicated in the **Table 2.5.2.1-2.5.2.4**), an aryl halide **8** (2.00 mmol), base (2.00 mmol,) and butyl acrylate (**24**, 4.00 mmol, 575 µL), were sequentially mixed in 3.6 mL of solvent as indicated in **Table 2.5.2.1-2.5.2.4**, and the resulting mixture was stirred at 80°C-150°C for the time indicated in **Table 2.5.2.1-2.5.2.4**. After this time the reaction mixture was cooled at room temperature, poured into water (20 mL) and extracted with diethyl ether (4×10 mL), then the collected organic extracts were washed with water (2×5 mL) and dried over Na2SO4. The extracts were added of a known amount of naphthalene as an internal standard, and the GLC yield was evaluated by using calibration curves obtained with naphthalene and an authentic sample of the expected product.

In cases where the isolated yield was determined, the crude product resulting after filtration and evaporation of dried organic extracts was purified by MPLC on silica gel.

In cases where the amounts of leached palladium at the end of reactions were assessed, ICP-OES analyses of the reactions mixtures cooled, filtered on Teflon filter (0.45 μm) and mineralized (aqua regia, 3 mL for 4 times) were performed.

4.5.1 (E)-cinnamic acid n-butyl ester (E-25a)

Following the general procedure, iodobenzene (**8x**, 2.0 mmol) and butyl acrylate (**24**, 4.0 mmol) provided the coupling product after purification by MPLC chromatography (eluent: Exane/AcOEt 95:5) of the crude product (Table 2.5.2.4, entry 1-7).

Colorless liquid; 1H NMR (600 MHz, CDCl3) δ 7,66 (d, J=16,0 Hz, 1H), 7,50 (dd, J1= 6,3 Hz J2=2,8 Hz, 2H), 7,40-7,30 (m, 3H), 6,42 (d, J=16,1 Hz, 1H), 4,19 (t, J= 6,7 Hz, 2H), 1,73-1,60 (m, 2H), 1,67 (dd, J1= 14,7 Hz J2= 7,0 Hz, 2H), 1,47-1,33 (m, 2H), 0,95 (t, J= 7,4 Hz, 3H); MS, m/z (%): 205 (3), 204 (20), 149 (12), 148 (72), 147 (63), 133 (11), 132 (100), 104 (10), 103 (48), 102 (13), 77 (31). Spectral properties were in accordance with the literature**[508]**

4.5.2 4-[(1*E*)-3-butoxy-3-oxo-1-propen-1-yl]-benzoic acid methyl ester (E-25b)

Following the general procedure, methyl 4-iodobenzoate (**8ad**, 2.0 mmol) and butyl acrylate (**24**, 4.0 mmol), or similarly, methyl 4-bromobenzoate (**8ae**, 2.0 mmol) and butyl acrylate (**24**, 4.0 mmol) provided the coupling product after purification by MPLC chromatography (eluent: Exane/AcOEt 85:15) of the crude product (Table 2.5.2.4, entry 11-21).

White solid; mp 56–58 °C (lit. 55–56 °C)**[385e]**

1H NMR (600 MHz, CDCl3) δ 8,02 (d, J=8,3 Hz, 12H), 7,66 (d, J= 16,1 Hz, 6H), 7,55 (d, J= 8,3 Hz, 14H), 6,49 (d, J= 16,1 Hz, 6H), 4,20 (t, J=6,7 Hz, 14H), 3,90 (s, 21H), 1,74-1,57 (m, 15H), 1,42 (dt, J1=14,9 Hz J2=7,4 Hz, 13H), 0,94 (t, J=7,4 Hz, 19 Hz); MS, m/z (%): 277 (7), 276 (40), 231 (40), 221 (23), 220 (86), 203 (56), 192 (81), 176 (20), 175 (100), 147 (29), 131 (58). Spectral properties were in accordance with the literature**[385e]**

4.5.3 (E)-4-methylcinnamic acid n-butyl ester (E-25c)

Following the general procedure, 4-iodotoluene (**8c**, 2.0 mmol) and butyl acrylate (**24**, 4.0 mmol) provided the coupling product after purification by MPLC chromatography (eluent:

Exane/AcOEt 85:15) of the crude product (Table 2.5.2.4, entry 8-10 and Table 2.5.4.2, entry 3 and Table 2.5.4.6, entry 2).

White solid; mp 197-199 °C (lit. 199-200 °C)**[509]**

1H NMR (600 MHz, CDCl3) δ 7,64 (d, J= 16,0 Hz, 1H), 7,40 (d, J=8,0 Hz, 2H), 7,17 (d, J=7,9 Hz, 2H), 6,37 (d, J= 16,0 Hz, 1H), 4,18 (t, J= 6,7 Hz, 2H), 1,69-1,63 (m, 2H), 1,41 (dt, J1= 14,8 Hz J2= 7,5 Hz, 2H), 0,94 (t, J= 7,4, 3H); MS, m/z (%): 218 (91), 162 (100), 145 (99), 115 (75), 91 (73). Spectral properties were in accordance with the literature**[509]**

4.5.4 (E)-4-nitrocinnamic acid n-butyl ester (E-25d)

Following the general procedure, 4-nitro-bromobenzene (**8d**, 2.0 mmol) and butyl acrylate (**24**, 2.0 equiv) provided the coupling product after purification by MPLC chromatography (eluent: Exane/AcOEt) of the crude product (Table 2.5.2.4, entry 22-25 and Table 2.5.4.2, entry 5).

Yellow solid; mp 62-65 °C (lit. 63-65 °C);**[510]**

1H NMR (600 MHz, $CDCl_3$) δ 8.27 (d, J = 8.9 Hz, 2H), 7.72 (d, J = 16.0 Hz, 1H), 7.69 (d, J = 8.8 Hz, 2H), 6.58 (d, J = 16.1 Hz, 1H), 4.26 (t, J = 6.7 Hz, 2H), 1.77-1.67 (m, 2H), 1.50-1.40 (m, 2H), 0.99 (t, J = 7.4 Hz, 3H). Spectral properties were in accordance with the literature**[510]**

4.6 Preparation of Pd-supported packed-bed mini-reactors

Packed bed flow reactors were mad with simple PTFE tubes (an inexpensive, versatile, chemically resistant, easily available and manipulable material). In general, the reactors (columns) were prepared with 2.0 mm internal diameter (outside diameter 3.0 mm) PTFE tubing; their length varies from case to case, but usually is between 20 and 40 mm. The catalyst, pure, is introduced into the reactors as dry; this is held in place by silanized glass wool stopped (portion of 5 mm length) at the reactor exit. In a typical experiment, supports-immobilised palladium catalyst pure or mixed at glass beads was weighed into a PTFE tube reactors (bed size = 2 mm i. d. x 20 mm l.) and connected by 1/4”-28 PEEK fitting to the fluidic system, at the reactor entrance and exit. At entrance the syringe container the reaction mixture, was connected to the fixed bed reactor (bed size = 20-40 mm x 2 mm), using 1.0 mm internal diameter PTFE tubing. In exit the collecting vessel was more connected with 1.0 mm i.d. PTFE tubing. Then the catalyst is compressed (2-10 bar) and conditioned with about 5 mL of the reaction solvent.

4.7 Typical procedure for the Suzuki reaction in flow

In this study, the reactions of 2-bromoanisole (**8a**), or α-bromostyrene (**12b**), or β-bromostyrene (**12a**) and phenylboronic acid (**9a**) in DMF/H_2O or EtOH/H_2O were carried out in a flow reactor constructed from catalyst packed in PTFE tube, and connected by 1/4”-28 PEEK fitting to the arroweld mixer connected turn to two syringes container the organic phase (halides and boronic acid in DMF or EtOH) and aqueous phase (K_3PO_4 in H_2O), in entrance, and the collecting vessel in exit (see paragraph 2.3.4). The reactors were heated by immersing it in a oil bath at 125 °C. Reactants from a syringe at room temperature were then pumped through 1.0 mm internal diameter PTFE tubing at 125 °C and then through the palladium catalyst in the flow reactor at known flow rates (see **Table 2.3.4.1-2.3.4.5**). The crude reaction mixture in exit was portioned (as reported in Tables), and valuated the conversion. The reaction run was finished when the medium conversion was inferior at 75%.

In cases where the amounts of leached palladium at the end of reactions were assessed, ICP-OES analyses of the reactions mixtures cooled, and mineralized (aqua regia, 3 mL for 4 times) were performed.

4.8 Typical procedure for the Sonogashira reaction in flow

In this study, the reactions of 4-iodoanisole (**8s**) and phenylacetylene (**14a**) in DMF/H_2O (4:1) were carried out in a flow reactor constructed from catalyst packed in PTFE tube, and connected by 1/4”-28 PEEK fitting to the syringe container the reaction mixture, in entrance, and the collecting vessel in exit (see paragraph 2.4.4). The reactors were heated by immersing it in a oil bath at 95 °C. Reactants from a syringe at room temperature were then pumped through 1.0 mm internal diameter PTFE tubing at 95 °C and then through the palladium catalyst in the flow reactor at known flow rates (see **Table 2.4.4.1-2.4.4.5**). The crude reaction mixture in exit was portioned (as reported in Tables), and valuated the conversion. The reaction run was finished when the medium conversion was inferior at 75%.

In cases where the amounts of leached palladium and copper at the end of reactions were assessed, ICP-OES analyses of the reactions mixtures cooled, and mineralized (aqua regia, 3 mL for 4 times) were performed.

4.9 Typical procedure for the Heck reaction in flow

In this study, the reactions of aryl halides **8** and butyl acrylate (**24**) in NMP were carried out in a flow reactor constructed from catalyst packed in PTFE tube, and connected by 1/4”-28 PEEK fitting to the syringe container the reaction mixture, in entrance, and the collecting vessel in exit (see paragraph 2.5.4). The reactors were heated by immersing it in a oil bath at 80-150 °C. Reactants from a syringe at room temperature were then pumped through 1.0 mm internal diameter PTFE tubing at 80-150 °C and then through the palladium catalyst in the flow reactor at known flow rates (see **Table 2.5.4.1-2.5.4.5**). The crude reaction mixture in exit was portioned (portions of 2 mL of reaction mixture), and valuated the conversion. The reaction run was finished when the medium conversion was inferior at 75%.

In cases where the amounts of leached palladium at the end of reactions were assessed, ICP-OES analyses of the reactions mixtures cooled, and mineralized (aqua regia, 3 mL for 4 times) were performed.

4.10 Preparation of 1-bromo-alkenes12h, 12j and 12k

A flame-dried reaction flask was purged with argon and charged with terminal alkyne (14, 1 equiv). DIBAL-H (1.1-1.5 equiv, 1.0 M solution in hexane) was added slowly via syringe. The reaction was heated at 60 °C for 5 h, then cooled 0 °C followed by sequential addition of Et_2O (0.5 mL/mmol) and NBS (1.2-1.6 equiv). The cooling bath was removed and the reaction was stirred for nother 16 h at rt. The reaction mixture was then poured into a mixture of aqueous 10% hydrochloric acid (2.0 mL/mmol) and crushed ice and extracted with pentane (3 x 5 mL/mmol). The combined organic extracts were washed with aqueous 10% sodium hydroxide (2.0 mL/mmol) and an aqueous solution of sodium sulfite (10%, 1.5 mL/mmol), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The resulting brown viscous oil was purified by flash chromatography to afford 1-bromo-alkene desidered.

4.10.1 (E)-1-bromo-1-dodecene (12h)

Following the general procedure, dodecyne (**14h**, 2.0 mmol) provided the product after purification (eluent: Exane pure) of the crude product (Table 2.6.1, entry 1).

Colorless liquid (83 %); 1H NMR (600 MHz, CDCl 3): δ = 6.19-6.11 (m, 1H) 5.98 (d, J = 13.5 Hz, 1H) 2.01 (qd, J = 7.4 Hz, 1.2 Hz, 3H) 1.34 (s, 16H) 0.86 (t, J = 7.0 Hz, 3H); Anal. calcd for C12H23Br: C, 58.30; H, 9.38. Found: C, 58.34; H, 9.37.

4.10.2 [[(3E)-4-bromo-3-buten-1-yl]oxy]tris(1-methylethyl)-silane (12j)

Following the general procedure, 1-triisopropylsilyloxy-3-butyne (**14g**, 2.0 mmol) provided the product after purification (eluent: Exane pure) of the crude product (Table 2.6.1, entry 1).

Colorless liquid (106 mg, 20 %); MS, m/z (%): 265 (100), 263 (98), 195 (50), 193 (96), 191 (50), 183 (51), 181 (75), 179 (56), 165 (69). Spectral properties were in accordance with the literature**[511]**

4.10.3 1-[(E)-2-bromoethenyl]cyclohex-1-ene (12k)

Following the general procedure, 1-ethynylcyclohexene (**14d**, 2.0 mmol) provided the product after purification (eluent: Exane pure) of the crude product (Table 2.6.1, entry 2).

Dark oil (67 %); 1H NMR (600 MHz, CDCl3): δ = 6.67 (d, J = 13.8 Hz, 1H) 6.10 (d, J = 13.8 Hz, 1H) 5.72 (s, 1H) 1.64 (dd, J = 11.3; 5.7 Hz, 4H) 1.57 (dd, J = 11.2; 5.8 Hz, 4H); MS, m/z (%): 188 (34), 186 (35), 107 (84), 105 (13), 91 (40), 79 (100), 77 (31), 65 (15), 51 (14). Spectral properties were in accordance with the literature**[512]**

4.11 Preparation of 1-iodoalkene 22

1-dodecyne (**14h**, 40 mmol) and catecholborane (44 mmol) were carried under Ar in a reaction flask. The mixture was stirred for 2 h at 70 °C to form the catechol ester of 1-dodecylboronic acid (**26**). The mixture was cooled to room temperature and stirred with 1 % hydrochloric acid solution (50 ml) for 2-3 h at 25 °C, to effect the hydrolysis of the ester. The resulting mixture was cooled to 0°C and the white solid, trans- 1-dodecylboronic acid, was collected by filtration and washed free of the catechol using ice-cold water.

The boronic acid **9g** was then dissolved in 40 ml of Et_2O and cooled to 0 °C. Aqueous sodium hydroxide (22 ml, 3 M) was then added dropwise, followed by 42 mmol of elemental iodine in about 70 ml of Et_2O, while stirring at 0 °C. The mixture was stirred for 30 min. The excess iodine was then destroyed with aqueous sodium thiosulfate solution, and extracted with Et_2O (2 x 30 mL). The combined organic layers were washed with brine and dried over anhydrous $MgSO_4$. After removing the solvent, the pure (E)-1-iodo-dodecene was obtained in 2.7 g (52 % yield) by flash chromatography (eluent: Exane pure).

Orange-red liquid; 1H NMR (600 MHz, CDCl3): 6.49 (dt, J = 14.3; 7.2 Hz, 1H) 5.95 (dt, J = 14.3; 1.4 Hz, 1H) 2.02 (qd, J = 7.3; 1.4 Hz, 2H) 1.36 (s, 2H) 1.26 (s, 6H) 0.70 (t, J = 7.0 Hz, 3H); MS, m/z (%): 238 (59), 167 (29), 154 (29), 69 (100), 56 (13), 55 (48), 43 (37), 41 (39), 39 (23). Spectral properties were in accordance with the literature**[513]**

4.12 Preparation of boronic acids 9d and 9e

4.12.1 3,5-dimethoxyphenylboronic acid (9d)

To a mixture of freshly ground magnesium (2.7 g, 110 mmol) in 100 ml of dry THF was added few drops 1,2-dibromoethane and refluxed at 80°C. Next, 3,5-dimethoxybromobenzene (**8af**, 15.0 g, 69 mmol) in 80 ml of dry THF is added dropwise via addition funnel over a period of 1 h. The reaction was refluxed for 2 h at 80 °C. The freshly prepared Grignard reagent was siphoned into a funnel, and added dropwise to a solution of trimethylborate (13.2 g, 127 mmol) in 100 mL of dry THF at -50 °C for 1 h and allowed to warm slowly to room temperature for 18 h. The mixture was acidified with HCl (10%) to pH 2.0 and extracted twice with ethyl acetate (3 x 100 mL). The organic layers were dried over $MgSO_4$ and concentrated under reduced pressure (orange liquid). The crude boronic acid was precipitated with hexane to yield 9.6 g of boronic acid (80 % yield) with a GC purity of 95 % .

^{1}H NMR (d6-DMSO, 600 MHz,): 3.73 (s, 6H), 6.50 (t, 1H, J = 2.4 Hz), 6.95 (d, 2H, J = 2.4 Hz), 7.95 (s, 2H). All chemycal-physical property and spectral characteristics are in accord with literature values.**[417]**

4.12.2 (E)-1-hexenyl-boronic acid (9e)

1-hexyne (10 mmol) was hydroborated with catecholborane (10 mmol) at 70°C for 6 h. The product boronic ester was then hydrolyzed overnight with a large excess of water. The solid boronic acid was filtered and recrystallized from an acetone/petroleum ether mixture, to give a white crystalline **9e** in 56 % yield, and 95 % of GC purity.

P.f. : 67-69 °C (lett. P.f. 68-70 °C) **[514]**

1H NMR (DMSO-d6, 600 MHz) δ: 0.87 (t, J= 7.2, 3H), 1.24-1.38 (m, 4H), 2.07 (q, J = 6.4, 2H), 5.30 (d, J = 17.9, 1H), 6.42 (dt, J = 17.9, 6.4, 1H), 7.48 (s, 2H). All chemycal-physical property and spectral characteristics are in accord with literature values.**[514]**

4.13 Silylation of p-cumaric acid

p-cumaric acid (**27b**) (5.0 g, 30.46 mmols) and imidazole (5.2 g, 76.15 mmols) were dissolved in 25 mL of dry DMF and the solution was cooled to 0 °C. To the chilled solution, t-butyldimethylsilylchloride (11.5 g, 76.15 mmols) was added and the reaction was stirred at room temperature for 4 h. The resulting reaction mixture was poured into 50 mL of water and extracted with CH_2Cl_2 (3 x 20 mL) and the combined organic layers were washed with brine and dried with sodium sulfate. The organic layer was evaporated to dryness and the residue was dissolved with EtOH (3 mL) and a saturated solution of $NaHCO_3$ (40 mL) was added and the reaction mixture was stirred at 60°C for 1 h. After this time, a solution of 2M chloridric acid was added until pH of 2. When the The resulting reaction mixture was extracted with AcOEt (3 x 20 mL) and filtered and washed with water (20 mL) and the combined organic layers were washed with brine and dried with sodium sulfate. The organic layer was evaporated obtained the desired product (6.2 g, 75 %)

1H NMR (300 MHz, CDCl 3) d: 0.22 (s, 6H), 0.99 (s, 9H), 6.29 (d, J Z 15.8 Hz, 1H), 6.86 (d, J Z 8.4 Hz, 2H), 7.45 (d, J Z 8.4 Hz, 2H), 7.74 (d, J Z 15.8 Hz, 1H). All chemycal-physical property and spectral characteristics are in accord with literature values.**[515]**

4.14 Preparation of (E)-β-bromostyrenes 12a and 12e-l

4.14.1 General procedure to prepare (E)-β-bromostyrenes in batch mode

Typically, under Ar atmosphere, cinnamic acid **27** (4.0 mmol) and LiOAc (1.0 mmol) were added into the flask and dissolved to CH_3CN/H_2O (5 mL, 7:1 v/v). Successivaly, NBS (5.0 mmol) was added at reaction mixture, then the mixture was stirred at 60 °C. The progress of the reaction was monitored by GC.

After completion of the reaction, when the mixture was cool to rt, water (10 mL) was added to the solution, and extracted with Et_2O, or Pentane, or CH_2Cl_2 (3 x 5 mL). The organic layer was washed with brine (10 mL), dried over $MgSO_4$ and the solvent evaporated in vacuo. The crude product was purified by MPLC or flash chromatography on silica gel (eluent: Pentane) to give the products desidered.

4.14.2 General procedure to prepare (E)-β-bromostyrenes in flow mode

Typically, In this study, the reactions of cinnamic aid **27** and NBS (1.2 equiv) catalyzed by LiOAc (0.25 equiv) in CH_3CN/H_2O (1.25-6 mL/mmol, 7:1 v/v) were carried out in a flow reactor constructed from silanized glass wool packed in PTFE tube, and connected by 1/4”-28 PEEK fitting to the arrowed mixer connected turn to two syringes container the Solution 1 (cinnamic acid 27 and LiOAc in CH_3CN/H_2O) and Solution 2 (NBS in CH_3CN/H_2O), in entrance, and the collecting vessel in exit (see paragraph 2.6.2). The reactors were heated by immersing it in an oil bath at 60-70 °C. Reactants from a syringe at room temperature were then pumped through 1.0 mm internal diameter PTFE tubing at 60-70 °C and then through the glass wool in the flow reactor at known flow rates (see **Table 2.6.4**). In the crude reaction mixture in exit was evaluated the conversion by GC analysis. After completion of the syringes, in the mixture was added water (10 mL/mmol), and extracted with Et_2O, or Pentane, or CH_2Cl_2 (3 x 5 mL/mmol). The organic layer was washed with brine (10 mL/mmol), dried over $MgSO_4$ and the solvent evaporated in vacuum. The crude product was purified by MPLC or flash chromatography on silica gel (eluent: Pentane) to give the products desiderate.

4.14.3 (E)-β-bromostyrene (12a)

Following the general procedure in batch and flow, cinnamic acid (**27a**, 1.0 equivl) provided the coupling product after purification by MPLC chromatography (eluent: Exane) of the crude product (Table 2.6.3, entry 1 and Table 2.6.4, entry 1).

Colorless liquid; 1H NMR (600 MHz, CDCl3) δ 7.16 (s, 2H), 7.28-7.34 (m, 2H), 7.37-7.46 (m, 4H), 7.53-7.62 (m, 4H); MS, m/z (%): 180 [M+](100), 179 (86), 178 (57), 177 (8), 176 (8), 166 (13), 165 (37), 153 (4), 152 (9), 139 (1), 115 (1), 102 (2), 89 (4), 77 (2), 76 (5), 63 (2), 51 (2). Spectral properties were in accordance with the literature**[410b]**

4.14.4 (E)-4-(2bromoetenil)fenolo (12e)

Following the general procedure in batch, p-cumaric acid (**27b**, 1.0 equivl) provided the coupling product after purification by MPLC chromatography (eluent: Exane) of the crude product (Table 2.6.3, entry 7).

Colorless liquid; 1H NMR (600 MHz, CDCl 3) δ: 6.62 (d, 1H, J = 14.0 Hz), 6.81 (d, 1H, J = 8.6 Hz), 7.05 (d, 1H, J = 14.0 Hz), 7.20 (d, 1H, J = 8.6 Hz). Spectral properties were in accordance with the literature**[516]**

4.14.5 (E)-4-[(1,1-dimetiletil)dimetilsililossi]-1-(2-bromoetenil)benzene (12f)

Following the general procedure in batch and flow, (E)-3-(4-(tert-butyldimethylsilyloxy)phenyl)acrylic acid (**27c**, 1.0 equivl) provided the coupling product after purification by MPLC chromatography (eluent: Exane) of the crude product (Table 2.6.3, entry 8 and Table 2.6.4, entry 7).

Colorless liquid; 1H NMR (600 Mhz, CDCl3) δ: 0.22 (s, 6H), 0.98 (s, 9H), 6.59 (d, J = 16.0 Hz, 1H), 6.76 (d, J = 8.7 Hz, 2H), 7.00 (d, J = 16.0 Hz, 1H), 7.15 (d, J = 8.7 Hz, 2H). Spectral properties were in accordance with the literature**[411b]**

4.14.6 (E)-β-iodostyrene (12g)

Following the general procedure in batch and flow, cinnamic acid (**27a**, 1.0 equivl) provided the coupling product after purification by MPLC chromatography (eluent: Exane) of the crude product (Table 2.6.3, entry 2 and Table 2.6.4, entry 2).

Pale yellow liquid; 1H NMR (600 MHz; CDCl3) δ 7.44 (d, J = 14.9 Hz, 1H), 7.38-7.27 (m, 5H), 6.84 (dd, J = 14.9, 1.8 Hz, 1H). Spectral properties were in accordance with the literature**[517]**

4.14.7 (E)-4-(2bromoetenil)toluene (12h)

Following the general procedure in batch and flow, p-chlorocinnamic acid (**27**, 1.0 equivl) provided the coupling product after purification by MPLC chromatography (eluent: Pentane) of the crude product (Table 2.6.3, entry 3 and Table 2.6.4, entry 3).

Colorless liquid; 1H NMR (600 Mhz, CDCl3): δ 2.32 (s, 3H), 6.58 (d, 1H, J = 14.0 Hz), 6.75 (d, 1H, J = 14.0 Hz), 7.09–7.19 (m, 4H). Spectral properties were in accordance with the literature**[410b]**

4.14.8 (E)-2-(2bromoetenil)anisolo (12i)

Following the general procedure in batch and flow, 2-methoxycinnamic acid (**27**, 1.0 equivl) provided the coupling product after purification by MPLC chromatography (eluent: Pentane) of the crude product (Table 2.6.3, entry 4 and Table 2.6.4, entry 4).

Colorless liquid

1H NMR (600 MHz, CDCl3): d 3.86 (s, 3H), 6.88 (dd, 1H, J = 8, 1 Hz), 6.91 (d, 1H, J = 14 Hz), 6.93 (dd, 1H, J = 8, 1 Hz), 7.24–7.29 (m, 2H), 7.31 (d, 1H, J = 14 Hz). Spectral properties were in accordance with the literature**[518]**

4.14.9 (E)-β-bromo-4-nitrostyrene (12j)

Following the general procedure in batch and flow, p-nitrocinnamic acid (**27**, 1.0 equivl) provided the coupling product after purification by MPLC chromatography (eluent: Pentane) of the crude product (Table 2.6.3, entry 5 and Table 2.6.4, entry 5).

Pale yellow solid; mp 156-158 °C (lit. 155-157 °C)**[519]**

1H NMR (600 Mhz, CDCl 3) δ: 6.69 (d, 1H), 7.03 (d, 1H), 7.80 (dd, 4H). Spectral properties were in accordance with the literature**[519]**

4.14.10 (E)-β-bromo-4-chlorostyrene (12k)

Following the general procedure in batch and flow, p-chlorocinnamic acid (**27**, 1.0 equivl) provided the coupling product after purification by MPLC chromatography (eluent: Pentane) of the crude product (Table 2.6.3, entry 6 and Table 2.6.4, entry 6).

White solid; mp 47-49 °C (lit. 46-48 °C)**[410b]**

H NMR (CDCl3): δ 6.75 (d, 1H, J = 14 Hz), 7.05(d, 1H, J = 14.0 Hz), 7.19(d, 2H, J = 8.4Hz), 7.28(d, 2H, J = 8.4 Hz) Spectral properties were in accordance with the literature**[410b]**

4.14.11 (E)-1-Bromo-2-phenylpropene (12l)

Following the general procedure in batch and flow, p-chlorocinnamic acid (**27**, 1.0 equivl) provided the coupling product after purification by MPLC chromatography (eluent: Pentane) of the crude product (Table 2.6.3, entry 6 and Table 2.6.4, entry 6).

Colorless liquid; 1H NMR (600 MHz, CDCl3): δ 2.22 (s, 3H,), 6.50 (s, 1H,), 7.19 (d, 2H, J = 8.4Hz), 7.28-7.36 (m, 3H, J = 8.4 Hz); MS, m/z (%): 198 (70), 196 (65), 117 (60), 115 (100). Spectral properties were in accordance with the literature**[520]**

4.15 Synthesis of cinnamic acids 27g, 27h, 27i and cinnamide 28

4.15.1 Preparation of (E)-cinnamic acid butyl esters (25a, 25d, 25e and 25f)

Typically, we applied the general procedure (in batch and flow) for the Mizoroki-Heck reaction (4.5 and 4.9) using Pd/PVPy (**5**) and Pd/MCM-41 (**6**) as catalysts.

4.15.1.1 n-butyl 4-methoxycinnamate *(25e)*

Prepared from 4-methoxyiodobenzene (**8u**) and butyl acrylate (**24**) using the general procedure in batch and flow processes, obtaining the desired product isolated as Colorless liquid (yield 86 and 98 % in batch; 78-88 in flow); 1H NMR (600 MHz, CDCl3) 0.93 (t, J = 7.3 Hz, 3H), 1.40 (sext, J = 7.3 Hz, 2H), 1.65 (quint, J = 6.4 Hz, 2H), 4.16 (t, J = 6.4 Hz, 2H), 6.28 (d, J = 16.0 Hz, 1H), 6.84-6.86 (m, 3H), 7.42-7.44 (m, 2H), 7.60 (d, J = 16.0 Hz, 1H). Spectral properties were in accordance with the literature**[521]**

4.15.1.2 n-butyl 4-chlorocinnamate *(25f)*

Prepared from 4-chloro-1-bromobenzene (**8am**) and butyl acrylate (**24**) using the general procedure in batch and flow processes, obtaining the desired product isolated as Colorless liquid (yield 86 and 98 % in batch; 78-88 in flow); 1H NMR (600 MHz, CDCl3) 0.97 (t, 3H, J = 7.3 Hz), 1.30 – 1.48 (m, 2H), 1.56 – 1.73 (m, 2H), 4.21 (t, 2H, J = 6.6 Hz), 6.41 (d, 1H, J = 16.1 Hz), 7.35 (d, 2H, J = 8.4 Hz), 7.45 (d, 2H, J = 8.4 Hz), 7.62 (d, 1H, J = 16.1 Hz). Spectral properties were in accordance with the literature**[522]**

4.15.2 Preparation of cinnamic acid 27g, 27h, 27i

The reaction flask was charged with 2M aqueous NaOH (1.1 mL/mmol), ethanol (0.12 mL/mmol) and (E)-cinnamic acid butyl esters **25** produced in 4.2.1. The reaction mixture was heated to 80° C and kept at this reaction temperature for about 2 hours. Conversion of the starting material **25** was checked by GC. At conversion complete the reaction mixture was cooled to room temperature. A this point, a solution of 2M chloridric acid (1.3 mL/mmol) was added and observed the precipitation of the desired cinnamic acid **27** at pH of 2. The solid was filtered and washed with water (20 mL) and then dried on the filter and in essicator.

4.15.2.1 4-methoxycinnamic acid (27g)

Prepared from n-butyl 4-methoxycinnamate (**25e**) using general procedure and isolated as light brown solid (yield %); mp 172-175 °C (lit. 174 °C)**[450]**
1H NMR (600 MHz, CDCl3): δ (ppm) 6.28 (d, J = 16 Hz, 1H), 7.57 (d, J = 16 Hz, 1H), 3.81 (s, 3H), 7.48 (d, J = 13 Hz, 2H), 6.90 (d, J = 14.5, 2H). Spectral properties were in accordance with the literature**[450]**

4.15.2.2 4-chlorocinnamic acid (27h)

Prepared from n-butyl 4-chlorocinnamate (**25f**) using general procedure and isolated as white solid (yield %); mp 245-248 °C (lit. 247-249 °C)**[523]**
1H NMR (600MHz, DMSO-d6) δ 7.71 (d, 2H, J = 8.5 Hz), 7.56 (d, 1H, J = 16.1 Hz), 7.45 (d, 2H, J = 8.5 Hz), 6.54 (d, 1H, J = 16.0 Hz). Spectral properties were in accordance with the literature**[523]**

4.15.2.3 4-nitrocinnamic acid (27i)

Prepared from n-butyl 4-nitrocinnamate (**25d**) using general procedure and isolated as pale yellow solid (yield %); mp 278-280 °C (lit. 280 °C)**[450]**
1H NMR (600 MHz, DMSO-d6) δ = 8.16 (d, 2H, J=6.9 Hz), δ = 7.86 (d, 2H, J=5.4 Hz), δ = 7.59 (d, 1H, J= 9.9 Hz), δ = 6.64 (d, 1H, J=9.9 Hz). Spectral properties were in accordance with the literature**[395c]**

4.15.2.4 cinnamic acid (27a)

Prepared from n-butyl cinnamate (**25a**) using general procedure and isolated as white solid (yield %); mp 190-193 °C (lit. mp 191 °C)**[450]**
1H NMR (600 MHz, CDCl3): δ (ppm) 6.43 (d, J = 16 Hz, 1H), 7.64 (d, J = 16 Hz, 1H), 7.94 (s, 1H), 7.35 (m,4H). Spectral properties were in accordance with the literature**[450]**

4.15.3 Preparation of cinnamide 28

2-Bromoaniline (**8ag**, 4.00 mmol) and N,N′-dicyclohexylcarbodiimide (1.1 equiv) were added to a solution of cinnamic acid (**27a**, 1.0 equiv) in THF (25 mL), and the resulting mixture was stirred at reflux for 7 h. After cooling to room temperature, the solid residue was filtered off and the remaining solution was evaporated. The residue was purified by flash silica chromatography (elution gradient: 20–50% EtOAc in n-hexane) to afford (E)-N-(2-bromophenyl)cinnamamide in (604 mg, 50 %) as a white solid; mp 146-149 °C (lit. 148–149 °C) 1H NMR (600MHz, CDCl3): δ (ppm) 6.60 (d, J 15.6, 1H); 7.01 (t, J = 8.0, 1H); 7.37 (t, J = 8.0, 1H); 7.41–7.45 (m, 3H); 7.56–7.61 (m, 3H); 7.79 (d, J = 15.6, 1H); 7.81 (br. s, 1H); 8.53 (br. s, 1H). Spectral properties were in accordance with the literature**[451]**

4.12 Synthesis of natural pterostilbene 13n and derivatives 13o and 13p

The **13o** and **13p** compounds were syunthesized by pterostilbene (**13n)** using opportune literature procedures. The pterostilbene (**13n)** were synthesized using the Suzuki-Miyaura reaction.

4.12.1 (E)-4-(3,5-dimethoxystyril)phenol (13n)

Directly at air the Fibrecat 1007 ($3.00x10^{-3}$ mmol of Pd), 4-*t*-butyldimethylsilyloxy-(E)-β-bromostyrene (**12f**, 2.00 mmol), K_3PO_4 (3.00 mmol,) and 3,5-dimethoxyphenylboronic acid (**9d**, 2.50 mmol), were sequentially mixed in 6.0 mL of EtOH/H_2O (1:1), and the resulting mixture was stirred at 80°C for 6h. After this time the reaction mixture was cooled at room temperature, poured into water (20 mL) and extracted with diethyl ether (4×10 mL), then the collected organic extracts were washed with brine (5 mL) and dried over Na_2SO_4. The extracts were filtrated and concentrated. The crude product resulting after filtration and evaporation of dried organic extracts was purified by MPLC on silica gel (eluent: Exane/AcOEt 90:10) obtaining 13n as white solid (236.3 mg, yield 50 %); mp 84-85 °C (lit. 85-86 °C)**[524]**
H NMR: (600 MHz, DMSO-d6) δ: 7.40 (d, J = 8.4 Hz, 2H), 7.15 (d, J = 16.4 Hz, 1H), 6.93 (d, J = 16.4 Hz, 1H), 6.76 (d, J = 8.8 Hz, 2H), 6.74 (d, J = 2.4 Hz, 2H), 6.36 (t, J = 2.4 Hz, 1H), 3.75 (s, 6H). Spectral properties were in accordance with the literature**[524]**

4.12.2 3,5-dimethoxy-4′-prenyloxy-trans-stilbene (13p)

Compound **13n** (236 mg, 1.00 mmol) was dissolved in 3.0 mL of acetone, 216.2 mg (1.56 mmol) K_2CO_3 and 0.20 mL (2.34 mmol) 1-bromo-3-methyl-2-butene were added, and the solution was heated to reflux. After reaction completion (3 h) the solvent was evaporated in vacuo. The residue was extracted three times with AcOEt and the combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, and evaporated in vacuo. The residue was purified by MPLC on silica gel (eluent: Exane/AcOEt 90:10) obtaining **13p** as white solid (244.3 mg, yield 80 %)

1H NMR: (600 MHz, DMSO-d6) δ 7.25 – 7.08 (m, 4H), 6.95 (dd, *J* = 8.8, 3.5 Hz, 2H), 6.76 (d, *J* = 1.9 Hz, 2H), 6.50 (s, 1H), 6.18 (t, *J* = 1.9 Hz, 1H), 3.75 (s, 6H), 1.62 – 1.57 (m, 6H).

4.12.3 3,5-dimethoxy-4′-hidroxy-3′-prenyl-trans-stilbene (13o)

Compound **13p** (152.5 mg, 0.50 mmol) was dissolved in 6.0 mL of N,N-diethylaniline, and the solution was heated to reflux. After reaction completion (6 h) the mixture was brought to pH 4 by the addition of 2 M HCl and extracted three times with Et_2O and the combined organic layer was washed with brine and dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure. The residue was purified by MPLC on silica gel (eluent: Exane/AcOEt 90:10) obtaining **13p** as pale yellow oil (72.2 mg, yield 48 %).

1H NMR: (600 MHz, DMSO-d6) δ 7.30-7.25 (m, 2H) 7.01-6.88 (d, J = 15.8 Hz, 2H) 6.80 (d, J = 8 Hz, 1H), 6.65 (s, 2H), 6.39 (s, 1H), 5.35 (t, *J* = 7.2 Hz, 1H), 5.28 (s, 1H), 3.80 (s, 6H), 3.43 (d, J = 7.5 Hz, 2H), 1.82 (m, 6H). Spectral properties were in accordance with the literature**[454a]**

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