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Palladium and Gold Perfluoro-Tagged Phosphine-Free Nanoparticles and Bio-Palladium Nanoparticles: New Catalysts for Organic Synthesis

CHIM-06

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To my family.

Preface

Solid-supported palladium-catalyzed reactions have become valuable tools for facilitating the recovery and reutilization of palladium and reducing the palladium contamination of the isolated products, a significant problem for the pharmaceutical industry. Activated carbon is the most commonly used insoluble support for palladium. Silica has also been used as an inert surface to adsorb palladium. A different approach to supported palladium catalysts involves the coordination of palladium to a ligand covalently bound to a polymer backbone. More recently, micro encapsulation of palladium in polymeric coating has been shown to be an efficient and cost effective technique to legate and retain palladium species and, in the same direction, aerogels, a new class of porous solids obtained via sol-gel processes coupled with supercritical drying of wet gels, have also been shown to exhibit a great potential for the preparation of heterogeneous catalysts.

In this thesis, was investigated the synthesis, growth and immobilization of phosphine-free perfluoro-tagged palladium and gold nanoparticles on fluorous silica gel (FSG). In order to establish a "tool box" for the synthesis of these supported catalysts, the study of several parameters such as the property of the support and the choice and the stability of the catalyst are necessary. To establish this set of rules, a limited number of catalytic transformations, were studied. These catalytic reactions are the Heck-Mizoroki, Suzuki-Miyaura and alkynylation Sonogashira-Heck-Cassar coupling and Oxidation reactions. These transformations became fundamental for the synthesis of drugs and materials. In the last part of this thesis was shown the green catalytic properties of an homogeneous bioinorganic catalyst. It was formed by palladium nanoparticles stabilizer by *DPS-Te* protein. This catalyst was tested on Suzuki cross-coupling reaction in water and in the one-pot synthesis of chiral biaryl alcohols through Suzuki- Miyaura cross-coupling and subsequent enzymatic reduction.

Contents

1 Introduction.

The application of catalysis, homogeneous and heterogeneous, for the production of bulk chemicals is well established.[1] Processes are known based on oxidation, hydroformylation, carbonylation, hydrocyanation, and metathesis. In fine chemical production, however, the use of the catalysis is still fairly limited, although the number of transformations applied in production is somewhat higher.[2,3] In addition to the above reaction types, processes are known based on aromatic substitutions, such as Heck, Suzuki, Sonogashira, Kumada and Negishi couplings (*see Fig.. chapter 2*), isomerisations, racemisations and enantioselective catalysis such as hydrogenation and cyclopropanation. The fine chemical industry is highly diverse, comprising pharmaceuticals, agrochemicals, polymer additives, dyestuffs, food additives, flavours and fragrances, chemical intermediates, and many more. Particularly in the lower range of production size, there is a long tradition of simply scaling up from known stoichiometric laboratory procedures as this reduces the time necessary for development and usually leads to robust and reliable processes. The downside of this approach is that it generates rather large amounts of waste. Especially in high-value-added products, such as pharmaceuticals that are often produced by lengthy multi-step syntheses, this approach can lead to quite excessive waste/product ratios of ca. 25-100.[4] There are many advantages to the catalysis using in fine chemical production, which may be summarised as follows:

- Reduction of waste.
- High selectivity.
- Production of a desired single enantiomer through asymmetric catalysis.
- Shortcuts in lengthy total syntheses.
- C-C bond formation under mild conditions obviating the use of protective group.

In view of all these advantages, it seems surprising that the percentage of fine chemical production processes making use of catalysis is still below 10%. There are a number of reasons for this. Economics is often a decisive factor when there is a choice of production methods.[5] Obviously, many transition-metals are very expensive and the same holds true for ligands that have to be prepared by lengthy total syntheses. A key success factor, therefore, is the reaction rate, usually expressed as its turnover frequency

(TOF = moles of product/moles of catalyst × hour). Of same importance is the stability of the catalyst, expressed as its turnover number (TON = moles of product/moles of catalyst). A second factor is the scalability and robustness of the process. Many transition metal-catalysed reactions may work well on a laboratory scale, but, on scaling up, substrate and product inhibition may be an issue and sensitivity to impurities may become apparent. It is very important to keep the number of components of a reaction to a minimum, as extraction, crystallization, and distillation are the only economically viable means of purification. The presence of ligands can be a nuisance in this respect, particularly if they are used in amounts over 5 mol %. Reproducibility is also necessary, but by far the most important limiting factors are the reaction time and the reuse of the catalyst. In order to optimize this aspect, it is interesting to consider the nanoscience point of view. This discipline, in fact, have recently evolved as a major research direction of our modern society resulting from an ongoing effort to miniaturize at the nanoscale processes that currently use Microsystems. Towards this end, it is well admitted that bottom-up approach should now replace the classic top-down one, a strategic move that is common to several areas of nanoscience including optoelectronics, sensing, medicine and *catalysis*. In a recent "Focus" Article in Chemical Communication, Samorjai emphasized that catalysis is the central-field of nanoscience and nanotechnology. [6] In this context, the control of the size, composition, surface structure, the anchorage and the support of the nanoparticles is required for the development of successful nano-catalyst on laboratory and industrial-scale. He claimed, also, as ultimate goal the role of recoverable nano-catalysts in *Green chemistry*.[7]

Green catalysis aspects, in fact, require that environmentally friendly (for instance phosphine-free) catalysts be designed for easy removal from the reaction media and recycling many times with very high efficiency. These conditions bring a new research impetus for catalyst development at the interface between homogeneous and heterogeneous catalysis, gathering the sophisticated fulfilment of all the constraints that were far from being fully taken into account by the pioneers and even the specialists in each catalytic discipline in the former decades. Yet the considerable knowledge gained from the past research in homogeneous, heterogeneous, supported and biphasic catalysis, including also studies in non-classical conditions (solvent-free, aqueous, use of ionic liquids, fluorine chemistry, micro-emulsions, micelles, surfactants, aereogels) should now help establish the desired optimized catalytic systems.

Transition metal NPs are clusters containing from a few tens to several thousand metal atoms, stabilized by ligands, surfactants, polymers or dendrimers protecting their surfaces. Their sizes vary between the order of one nanometer to several tens or hundreds of nanometres, but the most active in catalysis are only one or a few nanometers in diameter, they contain a few tens to a few hundred atoms only. The nanoscale size of catalyst systems is shown schematically in Figure 1. Enzyme catalyst active sites, which are inorganic nanoclusters containing iron, carry out important oxidation and reduction chemistry.

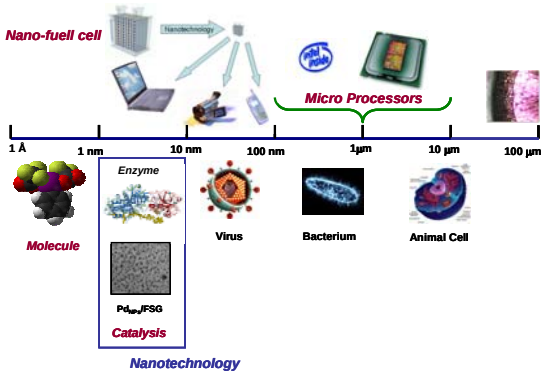


Figure 1. Nanoscale size of catalyst systems.

In view of the catalyst recycling, NPs catalysts are often immobilized or grafted onto inorganic or organic support. Using solid-supported systems for nano-palladium-catalyzed reactions, for example, have become valuable tools to improve recovery and reutilization of palladium and reducing the palladium contamination of isolated products (a significant problem for the pharmaceutical industry). Activated carbon is the most commonly used insoluble support for palladium. Silica has also been used as an inert surface to adsorb palladium. A different approach to supported palladium nanoparticle catalysts involves the coordination of palladium to a ligand covalently bound to a polymer backbone (for example polyvinyl pirrolidone).[7] More recently, micro encapsulation of palladium in polymeric coating has been shown to be an efficient and cost effective technique to legate and retain palladium species.[8] In the same direction, aereogels, a new class of porous solids, obtained via sol-gel processes coupled with supercritical drying of wet gels, have also been shown to exhibit a great potential for the preparation of heterogeneous catalysts.[9]

1.1 The Transition-Metal Nanoparticle History.

The use of NPs in catalysis apperared in the 19th century with photography (AgNPs) and the decomposition of hydrogen peroxide (PtNPs).[10] The real breakthrough came with *Haruta*'s seminal studies on oxide-supported Au_{np}-catalyzed CO oxidation by O_2 at low temperatures.[11] In the 1970s, *Bond* and *Sermon* [12] and *Hirai* et al.[13] disclosed Au_{np}-catalyzed olefin hydrogenation. In 1986 *Lewis* demonstrated the colloidal mechanism for the catalysis of olefin hydrosilylation by silanes using organometallic complexes of Co, Ni, Pd, or Pt including the Speier catalyst (alcoholic H_2PtCl_6).[14] These catalysts were formerly believed to follow the classic monometallic organometallic mechanism (oxidative addition of the Si-H bond of the silane onto the transition-metal center and subsequent alkene insertion and reductive elimination). In the mid-1990s, pioneering studies of Pd_{np} catalysis were reported by *Reetz* for Heck C-C coupling, such as the reaction between butyl acrylate and iodobenzene or aryl bromides and styrene.[15] In the first year of the 21st century have seem an growth in the number of publications in the Nano-catalysis field. Many scientists have contribute to improve the nano-catalyst activity and selectivity and to understand the catalytic mechanisms.[16] The modes of preparation of catalytically active NPs have been diversified and currently include impregnation,[17a] co-precipitation,[17b] deposition/precipitation,[17c] sol–gel,[17d] gas-phase organometallic deposition,[17e] sonochemical,[17f] micro-emulsion,[17g] laser ablation,[18a] electrochemical,[18b] and cross-linking. [18c]

1.2 Stabilizers and Support agents of Transition-Metal Nanoparticles.

The stabilizers for transition-metal NPs can be divided into three categories: (i) those that provide electrostatic stabilization, such as cationic and anionic surfactants; (ii) those that provide steric stabilization, including compounds possessing a functional group endowed with a high affinity for metals such thiols, sulfides, amines, and phosphine; and (iii) those that simply entrap nanoparticles, such as polymer, cyclodextrines, and dendrimers. In all cases, protecting agents ought to interact in an attractive manner with the surface of the metal. [19]

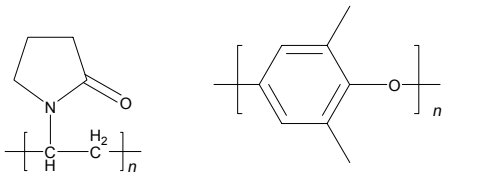


Figure 2. Two major polymer families used as metal NP supports and stabilizer.

Moreno-Mañas et al. have reported that some heavily fluorinated compounds and materials can stabilize transition-metal nanoparticles.[20] Thus, polymers such as Nafion and PTFE, as well as dendrimers fluorinated in the surface[21] have been reported as being stabilizing agents, probably by the inclusion of nanoparticulated metal into the interstices of the polymer or the no fluorinated core of the dendrimers.[22] Other heavily fluorinated stabilizing agents are considered to act by classical stabilizing mechanisms. Thus, thiols C_nF_{2n+1}-CH_2CH_2-SH (n = 6, 8) and anions C_nF_{2n+1}-COO^- (n = 11-17)[23] owe their stabilizing ability to the SH group and to the carboxylate rather than to the R_f moiety. On the other hand, nanoparticles in the water core of a water-in-CO_2 emulsion have been stabilized by perfluorinated surfactants; however, stabilization seems to be caused by the hydrophilic polar part, whereas the perfluorinated moiety imparts solubility in CO_2.[24] With the aim of understanding the interaction mechanism between Pd nanoparticles and stabilizers, they performed calculation for Pd interacting with alkanes (CH_4 and CF_3-CH_2CF_3), alkenes (CH_2=CH_2 and (E)-CF_3CH=$CHCF_3$) and aromatics (benzene and p-$(CF_3)_2C_6H_4$) at the B3LYP level of theory.[25]

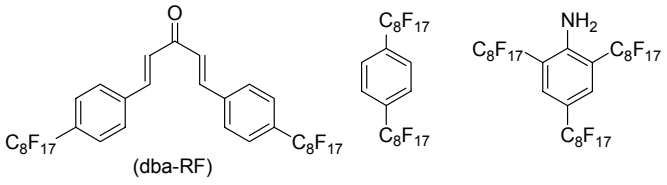


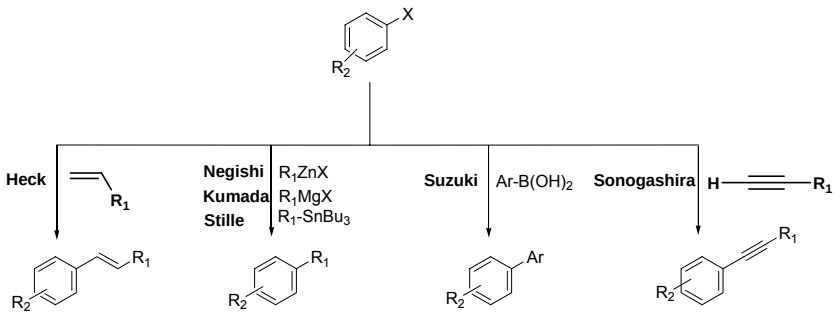
Figure 3. Heavily fluorinated compounds used in the preparation of Metal NPs.

This calculations suggested that the interaction between Pd and these organic molecules takes a place through the C-H bond in alkanes, or through the C=C bond of alkenes and aromatics. The order of Pd-molecule interaction is alkenes > aromatics > alkanes. These values correlate very well with the Pd-C distance: the larger the distances, the smaller the interaction energies. It is important to note that there is a charge transfer from Pd to

the organic molecule that increase when CF_3 groups are present because of their electron-withdrawing character.

1.3 Application of Transition-Metal Nanoparticles in Organic Chemistry.

The finding of catalytic formation of C-C and C-N bonds by Pd catalyst has been a considerable breakthrough in synthetic organic chemistry.



Scheme 1. Pd_{nps} catalysed aromatic substitution reactions (X = halides or other suitable leaving group).

Examples of Pd-catalyzed C-C coupling reactions include the Heck, Tsuji-Trost, Sonogashira, Suzuki, Stille, Negishi, Corriu-Kumada, and Ullmann reactions (see *Scheme 1*). The Heck reaction and the Suzuki cross-coupling are among the most used processes in C-C bond forming processes. The Heck reaction does not involve organometallic reagents and boronic acids used in the Suzuki cross-coupling are essentially non-toxic, contrary to the organometallics used in other cross-coupling protocols.

The Heck reaction has been widely studied using Pd_{np} catalysis whereas a few examples of the other C-C coupling reactions catalyzed by Pd_{np} have been described. The Heck reaction using Pd_{nps}, for instance, is a key reaction for the production of fine chemicals on a multi-ton scale per year such as the herbicide Prosulfuron™, the anti-inflammatory Naproxen™ or the anti-asthma Singulair™. On the other hand, in terms of *Green Chemistry*, it is likely that procedures involving chemicals such as ionic liquids, micelles, surfactants and other additives in homogeneous solution will retain less attention than those interested in atom economy problems and applicable organic synthesis.

Rh and Ru nanoparticles are mostly used as catalyst in hydrogenation reaction, particularly in olefin and alkyne hydrogenation. Moreover, soluble transition metal nanoparticles are considered as a reference in monocyclic arene catalytic hydrogenation under mild conditions and several stabilized system have been describe.[26]

Homogeneous and heterogeneous gold nanoparticles show interesting activity for a large number of reactions involving alkynes,[27a] alkenes,[27b] selective hydrogenations[27c] and oxidations[27d] among others.[27e] Selective oxidation of alcohols to carbonylic compounds is one of the most important transformations in organic chemistry. It is the final goal for solid catalysts to be able to perform this reaction with air at atmospheric pressure and low temperature, as well as to replace current stoichiometric alcohol oxidation by a general catalyst that is selective for any hydroxyl group. In response to this goal, various gold,[27f] palladium,[28] and gold/palladium[29] catalysts have given good results. Among these noble metals, gold, though less active than Pd or Au/Pd for some alcohols, is of more general use and exhibits higher selectivity than either Pd or Au/Pd. Owing to the interesting catalytic properties of Au for selective oxidation, A. Corma et al have carried out a detailed mechanistic study that addresses the influence of the gold nanoparticle size, nature of the support and influence of catalyst preparation procedure, to establish a detailed reaction mechanism that can help to design a new generation of more active gold catalysts for the aerobic oxidation of alcohols.

The problem of catalyst recovery and pollution by phosphine is a serious drawback with soluble Pd-catalysts. On the other hand, these aspects are crucial for the pharmaceutical industry, the inclusion of metal and phosphine contaminants in drugs being unacceptable. NP-supported catalysis provide a solution to catalyst removal from the reaction mixture by simple filtration or centrifugation. The amount of metal left in solution using this methodology is usually of the order of ppm. Moreover, as far as Pd_{nps}-catalyzed reactions are concerned, they are frequently carried out under phosphine-free conditions.

1.4 A Brief Review of Cross-Coupling Reactions Using Phosphine-Free Palladium Nanoparticles: Mechanicistic Aspects.

A general catalytic cycle for the cross-coupling reaction of organometallics, which involves *oxidative addition-transmetalation-reductive elimination* sequences, is depicted in Figure 5.

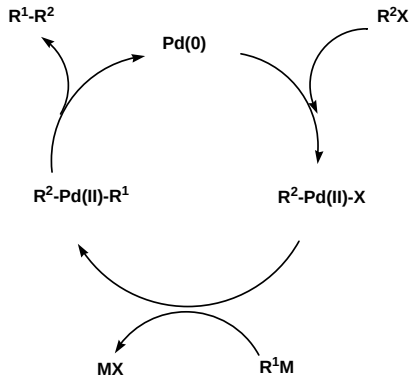


Figure 5. Traditional mechanism of the cross-coupling reaction

Although each step involves further knotty processes including ligand exchanges, there is no doubt about the presence of those intermediates (**R^2-Pd(II)-X** and **R^2-Pd(II)-R^1**) which have been characterized by isolation or spectroscopic analyses.[30a] It is significant that the great majority of cross-coupling reactions catalyzed by Ni(O), Pd(O), and Fe(1) are rationalized in terms of this common catalytic cycle. Oxidative addition of 1- alkenyl, 1-alkynyl, allyl, benzyl, and aryl halides to a palladium(0) complex affords a stable trans-a-palladium(II) complex **(R^2-Pd(II)-X).** The reaction proceeds with complete retention of configuration for alkenyl halides and with inversion for allylic and benzylic halides. Alkyl halides having β-hydrogen are rarely useful because the oxidative addition step is very slow and may compete with β-hydride elimination from the σ-organo-palladium-(II) species. However, it has been recently shown that iodo alkenes undergo the cross-coupling reaction with organoboron compounds.[31] Oxidative addition is often the rate-determining step in a catalytic cycle. The relative reactivity decreases in the order of **I** > **OTf** > **Br** >> **Cl**. Aryl and 1-alkenyl halides activated by the proximity of electron-withdrawing groups are more reactive to the oxidative addition than those with donating groups, thus allowing the use of chlorides such as 3-chloroenone for the cross-coupling reaction.

A very wide range of palladium(0) catalysts or precursors can be used for cross-coupling reaction. $Pd(PPh_3)$ is most commonly used, but $PdCl_2(PPh_3)_2$ and $Pd(OAc)_2$ plus PPh_3 or other phosphine ligands are also efficient since they are stable to air and readily reduced to the active Pd(0) complexes with organometallics or phosphines used for the cross-coupling. Palladium complexes that contain fewer than four phosphine ligands or bulky phosphines such as tris(2,4,6-tri-methoxypheny) phosphine are, in general, highly reactive for the oxidative addition because of the ready formation of coordinate unsaturated palladium species.[30b,c] Reductive elimination of organic partners from $\mathbf{R^2\text{-}Pd(II)\text{-}R^1}$ reproduces the palladium(0) complex . The reaction takes place directly from ***cis***- $\mathbf{R^2\text{-}Pd(II)\text{-}R^1}$**,** and the ***trans***- $\mathbf{R^2\text{-}Pd(II)\text{-}R^1}$ reacts after its isomerization to the corresponding *cis*-complex. The order of reactivity is diaryl-> (alky1)aryl > dipropyl > diethyl > dimethylpalladium(II), suggesting participation by the n-orbital of aryl group during the bond formation. Although the step of 1-alkenyl- or l-alkynylpalladium(II) complexes is not studied, the similar effect is observed in the reductive elimination of related platinum(II) complexes.

De Vries and co-workers have proposed a mechanism for the Heck reaction using palladium nanoparticles stabilized by tetraalkylammonium ions (see figure 6.).[30l,m] Soluble palladium clusters can be considerate as font of atomic Pd(0). This species can be inert in the traditional mechanism of Heck reaction. At the end of the cycle, Pd(0) can re-cluster in Pd black species (low reactivity) or in other soluble palladium clusters. The last species can be recycled many times without loss of activity.

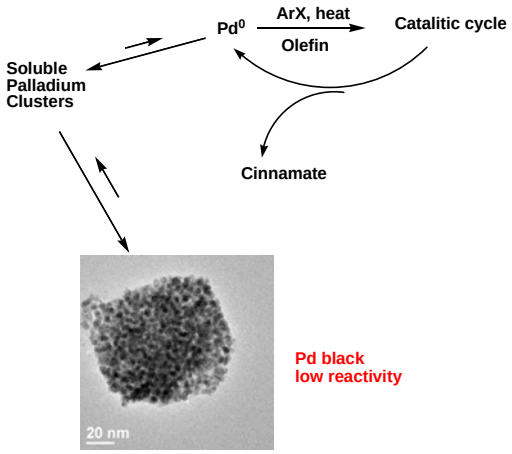


Figure 6. Hypothesis of the mechanism for the palladium nanoparticles in Heck reaction.

Compared to the large body of work concerning the Heck reaction, few reports deal with the use of the Pd-colloids in the Suzuki coupling. Reetz and co-workers reported the use of Pd and bimetallic Pd/Ni clusrers stabilized by tetrabutylammonium salts for the coupling of aryl bromide and chlorides with phenylboronic acid.[30j]

On the other hand El-Sayed has studied the influence of stabilizers in the Suzuki reaction in aqueous media, the authors concluded that this kind of reaction occurred at the metallic surface. Catalyst deactivation and Pd black precipitation were observed, suggesting that Pd aggregation occurred during the reaction. Subsequent contributions compared various stabilisers: PVP, PANAM-OH and dendrimers of different generation (G2-OH to G4-OH). Nanometric palladium clusters can exhibit catalytic activities comparable to those of traditional Pd complexes also in Sonogashira reaction. Recently G. Rothenberg et al. proposed a possible mechanism for the Pd cluster-catalyzed Sonogashira cross-coupling.[31]

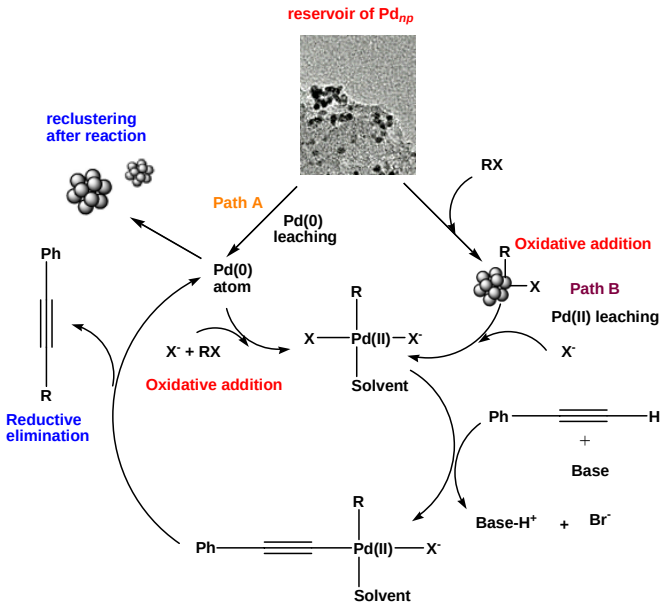


Figure 7. Hypothesis of the mechanism for the palladium Nanoparticles in Sonogashira C-C cross-coupling reaction.

This mechanism includes two pathways (Figure 7): Path **A** involves the leaching of Pd(0) from defect sites on the cluster, that is then stabilized by the coordinating anions and the solvent, forming a homogeneous Pd(0) complex. Subsequent oxidative addition of the aryl halide gives a Pd(II) complex that enters the conventional catalytic cycle. Alternatively, in path **B**, aryl halide first attacks a defect site on the Pd cluster, releasing a Pd(II) complex into solution, that then enters the catalytic cycle. The nucleophilic

attack of alkyne on the Aryl-Pd(II)-Br(solvent)X complex takes place concomitant with the deprotonation of alkyne. Finally, the dissolved Pd species can re-cluster, to form new (smaller) particles after the reductive elimination step. This mechanism is consistent with the results obtained from TEM analysis and kinetic studies, as well as with the one proposed by Hu and Liu for the analogous Suzuki cross-coupling.[32]

In summary, G. Rothenberg et al. showed that the cluster-catalyzed alkynylation of alkynes probably proceeds via a soluble Pd species, and that the counter anions present in solution influence the leaching of the Pd ions/atoms.

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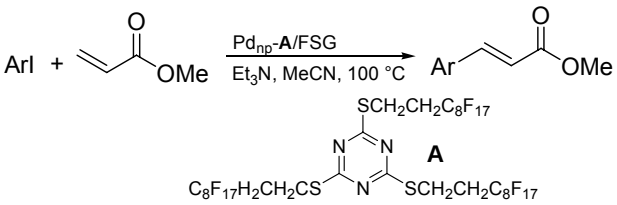
2 Perfluoro-tagged palladium nanoparticles supported on Fluorous Silica Gel. Application to C-C cross coupling reactions.



2.1 Introduction.

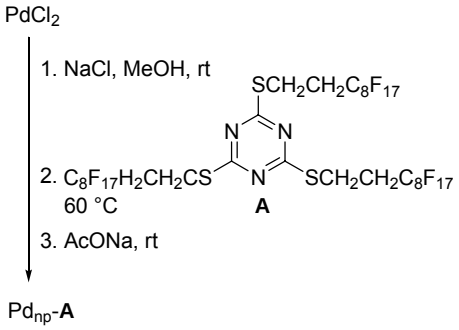
Solid-supported palladium-catalyzed reactions have become a valuable tool for facilitating the separation, recovery, and reuse of expensive palladium catalysts and for reducing palladium contamination of the isolated products. Both of these problems are in fact of primary importance for the pharmaceutical industry which has to transfer laboratory scale methods to large-scale cost-effective processes and limit the presence of heavy metal impurities in active substances.

A large number of materials have been used to support palladium, including activated carbon, silica gel, polymers containing covalently bound ligands, metal oxides, porous aluminosilicates, clays and other inorganic materials, and microporous and mesoporous supports.[1] Palladium has also been microencapsulated in polymeric coating,[2] and aerogels[3] have been used to prepare heterogeneous palladium catalysts. Recently, some of us found that palladium nanoparticles can be stabilized by entrapment in perfluoro-tagged phosphine-free compounds,[4] although heavily fluorinated compounds are not expected to be the best constituents of protecting shields for nanoparticles (perfluorinated chains are indeed known to exhibit very small attractive interactions toward other materials and among themselves[5]). Thus, we were intrigued by the idea of immobilizing phosphine-free perfluoro-tagged palladium nanoparticles on fluorous silica gel[6] (FSG) and evaluating the utilization of the immobilized catalyst in the C-C cross-coupling reactions (Heck, Suzuki and alkynylation reaction). In particularly, we were interested to the application of this kind of the catalyst to the environmentally friendly conditions (homeopathic palladium loading of the precatalyst, phosphine-free, copper-free and using water as solvent).

Herein we report the results of our study:

A previous attractive example of immobilization of palladium on FSG is due to Bannwarth et al.[7] who prepared several catalysts via adsorption of palladium(II) complexes containing perfluoro-tagged phosphine ligands and showed the advantages of their utilization (separation and recovery of perfluoro-tagged catalysts) compared with fluorous biphasic catalysis approaches using expensive and environmentally persistent perfluorinated solvents.[8] Phosphine-free perfluoro-tagged palladium nanoparticles Pd_{np}-**A** (diameter 2.3 (0.7 nm; 13.4% palladium) were prepared as described previously for similar systems[4e] by reduction of PdCl2 with methanol at 60 °C in the presence of sodium chloride and compound **A**, a stabilizing agent featuring long perfluorinated chains, followed by the addition of AcONa (Scheme 1 and Figure 1a). The electron diffraction patterns of this sample were obtained, and the diffraction rings can be ascribed to the (111), (200), (220), and (311) crystallographic planes of the fcc-Pd (Figure 1d).

Scheme 1.



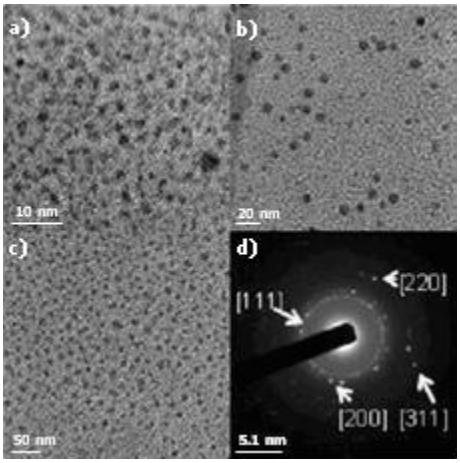
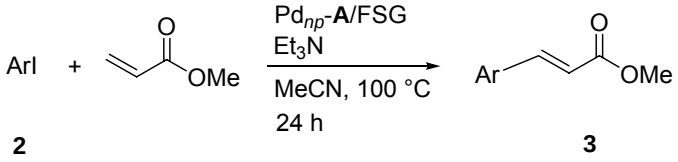


Figure 1. a) TEM image of Pd_{np}-**A**. b) TEM image of Pd_{np}-**A**/FSG. c) TEM image of recovered Pd_{np}-**A**/FSG after 15 runs. d) electron diffraction of Pd_{np}-**A.**

To prepare the immobilized precatalyst, nanoparticles Pd_{np}-**A** were dissolved in perfluoro-octane, commercially available FSG (C8; 35-70 μm) was added to the solution, and the solvent was evaporated. The immobilized precatalyst (Pd_{np}-**A** /FSG) was obtained as an air-stable powder. Transmission electron microscopy (TEM) of Pd_{np}-**A** /FSG was carried out. It showed well-defined spherical particles dispersed in the silica matrix (Figure 1b). The mean diameter of the nanoparticles was about 1.5 ± 0.7 nm.

2.2 Heck Reaction.

A silica gel containing 100 mg of Pd_{np}-**A** per g of FSG and a 0.6 mol % palladium loading was initially evaluated in the Heck reaction of methyl acrylate with iodobenzene in DMF at 80 °C for 24 h. The reaction could be carried out in the presence of air, and methyl cinnamate was obtained in almost quantitative yield in the first run as well in the second one. However, a loss of activity was observed in the third run (85% yield) which became even more substantial in the fourth run (75% yield). Assuming that these results might be due to the leaching of palladium in DMF, we switched to using MeCN. After some experimentation we found that complete conversion could be obtained in MeCN at 100 °C after 24 h using 20 mg of Pd_{np}-**A** per g of FSG and a catalyst loading down to 0.1 mol %. Recycling studies were then performed which showed that the supported catalyst system can be reused several times without significant loss of activity (Table 1). The recovery of the supported palladium involves centrifugation and decanting the solution in the presence of air, without any particular precaution. The resistance of Pd_{np}-**A** /FSG to leaching was assessed for the same reaction (iodobenzene and methyl acrylate).



2 **3**

Sector field inductively coupled plasma mass spectrometry (SF-ICP-MS) analysis indicated the level of palladium in the crude mixtures to be in the 2-7 ppm range. Agglomeration of nanoparticles was not observed upon recycling. The recovered material after the 15th run was examined by TEM showing nanoparticles of about 1.9 ± 0.3 nm (Figure 1c). Control experiments were also carried out to assess whether leaching of nanoparticle support may take place under reaction conditions. ^{19}F NMR analysis of the crude mixture derived from the reaction of methyl acrylate with *m*-

(trifluoromethyl)iodobenzene after filtration revealed the presence of small amounts of **A**, corresponding to an original nanoparticle support loss of about 5%. No evidence of fluorine was attained in the isolated vinylic substitution product. The crucial role of fluorous-fluorous interactions was assessed by immobilizing Pd_{np}-**A** on standard reversed-phase silica gel and using the resultant precatalyst in our model reaction (methyl acrylate and iodobenzene). Methyl cinnamate was obtained in 93% yield in the first run. However, a remarkable loss of activity was observed in the second run, the Heck product being isolated only in 59% yield. We then evaluated the efficiency of Pd_{np}-**A** /FSG with other aryl iodides (Scheme 2). Our preparative results are summarized in Table 2.

Table 2. Reaction of aryl iodides with methyl acrylate catalyzed by Pd_{np}-**A** /FSG (0.1 mol%).[a]

Entry	Aryl iodide **3**		Yield % of **3**[b,c]
1	PhI	**a**	98
2	*p*-MeCO-C_6H_4-I	**b**	89 (90)
3	*p*-MeO-C_6H_4-I	**c**	90 (70)
4	*p*-Me-C_6H_4-I	**d**	90
5	*p*-NO_2-C_6H_4-I	**e**	74 (65)
6	*m*-CF_3-C_6H_4-I	**f**	93 (90)
7	*p*-EtOCO-C_6H_4-I	**g**	98
8	*m*-Me,*p*-NO_2-C_6H_4-I	**h**	96
9	*o*-NH_2-C_6H_4-I	**i**	84
10	*o*-MeOCO-C_6H_4-I	**j**	89

Recycling studies were also performed with different amount of palladium. using 0.2 mg of Pd_{np}-**A** per g of FSG and a palladium loading down to 0.001mol% (Table 3). The cumulated turn-over number (TON) over three runs is 265000.

Table 3. Heck-Mizoroki, Suzuki-Miyaura and Alkynylation reactions with different amounts of Pd_{np}-**A /FSG.**

Entry	Catalyst loading of FSG [mg g^{-1}]	Catalyst loading [mol%]	t [min.]	T [°C]	Yield %	TON
Heck-Mizoroki						
1	20	0.1	1440	100	90 (96, 96, 93, 87, 89, 97, 96, 95, 98, 97, 90,90, 84, 80)	13780
2	2	0.01	1440	120	100 (96, 81, 97,85)	45900
3	0.2	0.001	1440	140	100 (82, 83)	265000
Suzuki-Miyaura						
1	20	0.1	300	100	99 (86, 84, 88, 91, 90, 86, 92, 87, 90, 90, 85, 84, 91, 93)	13360
2	2	0.01	300	100	98 (95, 99, 92, 99, 70)	55300
3	0.2	0.001	300	100	89 (85, 87, 72)	333000
Alkynylation						
1	300	1.5	120	100	85 (92,91,95,55)	279
2	200	1	45	100	97 (92,90,80,60)	419
3	100	0.5	45	100	95 (96,93,83,15)	764
4	20	0.1	40	100	95(92,50)	2370

We have not investigated in detail whether the nanoparticles on the solid surface are the actual catalyst or just a source that leaches active catalyst species.[9] Nevertheless, when methyl acrylate, *p*-iodoanisole, and Et_3N were added to the crude mixture derived from the reaction of methyl acrylate with iodobenzene (after separation of the solid material), the corresponding vinylic substitution derivative was isolated in 40% yield after 23 h at 100 °C, showing that palladium species leached from the solid surface are, at least in part, responsible for the catalytic activity.

2.3 Suzuki-Miyaura Cross-Coupling in Water.

Transition-metal-catalyzed cross-coupling reactions are extremely useful synthetic tools for carbon–carbon bond formation.[10] The Suzuki reaction,[11] palladium-catalyzed cross-coupling of aryl boronic acids and aryl halides, has become an attractive standard process for the synthesis of biaryls, which have a diverse spectrum of applications, ranging from pharmaceuticals to materials science.[12] Consequently, much attention has been directed toward improving the Suzuki reaction by designing various new ligands and palladium-precursors, such as bulky electron-rich phosphine ligands,[13] N heterocyclic carbenes,[14] and palladacycles,[15] to accomplish efficient coupling of inexpensive and unreactive aryl bromides and chlorides. However, most of these ligands and palladium precursors are expensive, which significantly limits their industrial applications. Therefore, the development of efficient catalytic systems consisting of economical catalysts, bases, and solvents remains a highly desirable goal. In addition,

intensive efforts have been directed to reduce or eliminate the use of flammable, hazardous, and nonrenewable organic solvents in the Green chemistry focus area.[16] While a variety of environmentally benign media, such as ionic liquids, fluorous solvents, supercritical fluids, and PEGs, have been promoted as replacements to volatile organic compounds (VOCs),[17] water represents one of the most economically and environmentally viable options.[18] The use of water as the reaction solvent has several benefits, including low cost, improved safety, and abundance. Furthermore, phase separation is easier because most organic compounds are lipophilic and can be easily separated from the aqueous phase. To date, aqueous Suzuki coupling reactions have been largely limited to couplings of aryl iodides and activated aryl bromides.[19]

We were particularly interested in the application of the ligand-free homeopathic palladium loading procedure in Suzuki reaction in water.

Preliminary experiments coupling 4-iodide benzoic acid with o-tolylboronic acid using Pd_{np}-**A** /FSG (0.1 mol %) and K_3PO_4 in water revealed that this phosphine-free approach is promising, but with these unoptimised conditions 80% of yield was achieved. An screening of several different bases and bases combinations showed that K_2CO_3/KF (1:1), are especially suitable bases for the studied coupling (Scheme 3, Table 4). After some experimentation we found that complete conversion could be obtained in water at 100 °C after 5 h using 20 mg of Pd_{np}-**A** per g of FSG and precatalyst loading down to 0.1 mol%.

Scheme 3.

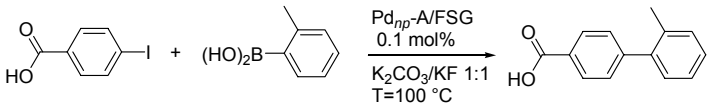


Table 4. Effect of base on the Suzuki reaction of 4-iodide benzoic acid and o-tolylboronic acid.

Entry	Base	Yield %
1	K_3PO_4	80
2	K_2CO_3	87
3	KF	64
4	K_2CO_3/KF	99

Initially, between 0.1 mol% and 0.001 mol% of Pd_{np}-**A** /FSG was tested as precatalyst for the Suzuki coupling of 4-iodide benzoic acid and o-tolylboronic acid in water (*see scheme 3 and Table 3*). The product was separated by decantation after centrifugation, and the supported catalyst was reused many times. For the higher catalyst loading (*Entries 1, Table 3*), complete yield was observed in the first run. Up to the fifteen run, the yield decreased only to 93%.

With the homeopathic catalyst loading (0.01 and 0.001 mol% *Entries 2 and 3, Table 3*), the yield was high in the first run but decreased in the sixth and fourth respectively. The cumulated turn-over number (TON) over four runs, using 0.001 mol% catalyst loading, is 333000 and the cumulated turn-over frequency is 16650 mole of product per mole of catalyst per hour. To assess the catalyst leaching, the coupling of 4-iodide benzoic acid and o-tolylboronic acid was carried out with 0.1 mol% of Pd_{np}-**A** /FSG. After each run, the mixture was cooled at room temperature, centrifuged and the solution was pipetted. Then, the supported catalyst was washed with methanol and the resulting suspension was centrifuged and the solvent was decanted each time. The Pd-content was determined by SF-ICP-MS analysis on different runs.

Table 5. Leaching test.

Run	Leaching in water [ppm]	Leaching in raw product [ppm]
1	0.0024	0.0227
2	0.0016	0.0222
3	0.0018	0.0060
5	0.001	0.0043
10	0.001	0.0035

This analysis indicates the content of palladium species in water to be in the range of 2.4-1 ppb as well as the high lipophilicity of the support. We investigated also the palladium leaching in the raw product, this is in the range of 23-3 ppb. Figure 2a shows a representative TEM image of the Pd_{np}-**A** /FSG before the first run of Suzuki reaction, and its Gaussian fits of the size distributions of the nanoparticles. It can be seen that the nanoparticles of Pd_{np}-**A** /FSG are monodispersed in the FSG matrix with an average size (center of distribution) of 1.5 ± 0.6 nm. Figure 2b shows a representative TEM image of the nanoparticles after the 15^{th} cycle of the Suzuki reaction, and its Gaussian fits of the size distributions of the nanoparticles.

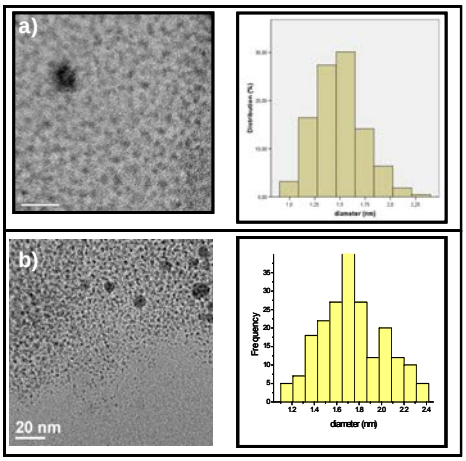


Figure 2. (a)TEM image of Pd_{np}-**A** /FSG before first run and and particle size distribution histogram, diameter: 1.5 ± 0.6 nm, (b) TEM image of Pd_{np}-**A** /FSG after 15th run and particle size distribution histogram, diameter: 1.7 ± 0.3 nm.

By comparing the Gaussian fits before and after the 15th cycle (Figure 2a; Figure 2b), we could see that both the widths and the centers of the size distributions of the nanoparticles increase after the runs and that the size distribution shifts toward larger size. In addition, the width of the size distribution after the 15th run is very broad (bimodal distribution). The observation of the increase in the size of the nanoparticles might be explained by the Ostwald ripening processes during the refluxing of the reaction mixture containing the nanoparticles. The Ostwald ripening process is a mechanism for cluster growth. In this growth process, there is detachment of atoms from the smaller clusters and then reattachment on the more stable surface of the larger clusters.

Next, we performed a screening study of different arylboronic acids using 4-iodobenzoic acid as the coupling partner, phosphine-free conditions, and homeopathic palladium loading. As shown in Table 6, several functional groups are tolerated in the organoboron reagent.

Scheme 4.

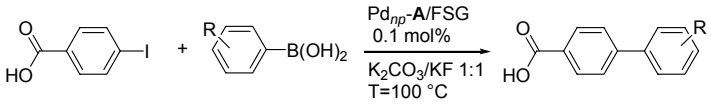


Table 6. Screening on different Boronic acid.

Entry	R	Yield %
1	*p*-OCH_3	95
2	*p*-CF_3	94
3	*o*-CH_3	99
4	H	83

To survey the generality of this Suzuki reaction, the reaction was investigated using a variety of aryl iodides and bromides, and a wide range of aryl boronic acids as substrates under the optimized conditions. Our results are summarized in in Table 7. Neutral, electron-rich and electron-poor aryl iodides and a variety of aryl boronic acids afford the corresponding cross-coupling products in excellent yield under standard conditions (Entries 1-2, 7-13, Table 7). 4-Bromobenzoic acid was reacted with different aryl-boronic acids to provide the corresponding coupling products in good yields (Entries 3-6, Table 7).

Scheme 5.

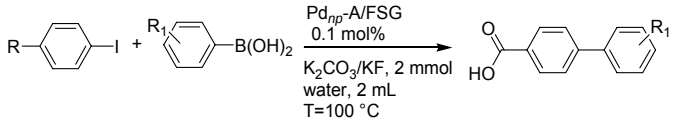


Table 7. Reaction of Aryl iodide and aryl bromide with different boronic acids with 0.1 mol% catalyst loading [a].

Entry	R	R_1	t(h)	Isolate yield% [a]
1	*p*-CH_3O-C_6H_4-I	*o*-CH_3-$C_6H_4BOH_2$	24	92
2	*p*-HOOC-C_6H_4-I	*p*-F,*m*-CH_3-$C_6H_4BOH_2$	5	72
3	*p*-HOOC-C_6H_4-Br	*p*-F,*m*-CH_3-$C_6H_4BOH_2$	44	80
4		*p*-$CF_3C_6H_4$-BOH_2	7	71
5		$C_6H_5BOH_2$	8	72
6		*p*-CH_3O-$C_6H_4BOH_2$	6	91(90)
7	*p*-HOOC-C_6H_4 -I	*p*-CH_3O-$C_6H_4BOH_2$	5	95(99)
8		*p*-CF_3-$C_6H_4BOH_2$	2	94(99, 84)
9		*o*-CH_3-$C_6H_4BOH_2$	6	99
10		$C_6H_5BOH_2$	5	83
11	*p*-CH_3O-C_6H_4-I	*p*-$CF_3C_6H_4$-BOH_2	24	80
12	C_6H_5I	*p*-$CF_3C_6H_4$-BOH_2	24	50
13	*p*-CH_3CO-C_6H_4-I	*p*-$CF_3C_6H_4$-BOH_2	8	91

[a] The yields in parentheses are for the other runs with the same catalyst. Compounds were purified on columns, packed with SiO_2 25-40 μm (Macherey Nagel), and eluting with *n*-hexane/AcOEt/ mixtures.

2.4 Copper- and Phosphine-Free Alkynylation of Aryl Halides in water.

The aim of our study was to develop the a procedure for coupling terminal alkynes with aryl halides using Pd_{np}-**A** /FSG as the catalyst system in the absence of phosphine and copper. When we searched for a cross-coupling protocol of *m*-trifluoromethyl iodobenzene and phenylacetylene, we observed that *m*- trifluoromethyl iodobenzene could react with phenylacetylene in the presence of 0.1 mol% of Pd_{np}-**A** /FSG and 2 equiv of K_2CO_3 in methanol under phosphine and copper free conditions at 100 °C for 5h to afford the desired cross-coupling product as the sole product in 45% yield (no homo-coupling product was formed). Encouraged by this result, we continued to improve the yield by using different bases. As shown in Table 8, with N-ethylendiamine and triethylamine a 66 and 70% yield were achieved.

Table 8. Different bases in MeOH.

Entry	Base	Yield %
1	K_2CO_3	45
2	Et_2NH	66
3	Et_3N	70

[a] Reactions were carried out using 1 mmol of aryl iodide, 1 mmol of terminal alkynes,2 mmol of bases at 100 °C in the presence of 0.1 mol% of Pd_{np}-**A**/FSG in 2 mL of methanol.[b] Yields are given for isolated products.

The influence of solvents on the alkynylation of aryl iodides was also explored (Table 9) as well as that of bases (Table 10).

Table 9. Different solvents.

Entry	Solvent	Yield %
1	MeOH	70
2	MeCN	87
3	Water	90

[a] Reactions were carried out using 1 mmol of aryl iodide, 1 mmol of terminal alkynes,2 mmol of triethylamine at 100 °C in the presence of 0.1 mol % of Pd_{np}-**A** /FSG in 2 mL of solvents.[b] Yields are given for isolated products.

Table 10. Different bases in water as solvent.

Entry	Base	Yield %
1	K_2CO_3	5
2	KOAc	5
3	Pyrrolidine	99
4	Piperidine	95
5	Et_2NH	89
6	Et_3N	92

[a] Reactions were carried out using 1 mmol of aryl iodide, 1 mmol of terminal alkynes,2 mmol of bases at 100 °C in the presence of 0.1 mol % of Pd_{np}-**A** /FSG in 2 mL of water.[b] Yields are given for isolated products.

Reactions conducted in MeCN and water were the most effective (Entries 2 and 3, Table 9). We decided to use the environmentally friendly water.[73] As to the bases, best results were obtained using pyrrolidine and piperidine (*Entries 3-4, Table 10*). Other bases such as K_2CO_3, and KOAc gave lower yields. As to the catalyst loading, 1.5, 1, 0.5, and 0.1 mol% of Pd_{np}-**A**/FSG were tested. Using 1.5 mol% was found to be the best choice for the recycling studies. With this catalyst loading only decreases in reaction yields were observed after five cycles (*Entry 1, Table 3*). The cumulated turn-over number over three run with 0.1 mol% catalyst loading is 2370. The resistance of Pd_{np}-**A**/FSG to leaching was assessed for the benchmark (1-iodo-3-(trifluoromethyl)benzene and phenylacetylene). Sector field inductively coupled plasma mass spectrometry (SF-ICP-MS) analysis indicated the level of palladium in water to be in the range of 0.05-0.08 ppm. The leaching test was also performed on the raw product, in this case the content of palladium is in the range of 39-240 ppm. To examine the scope for this coupling reaction, a variety of terminal alkynes were coupled with different aryl iodides (*Scheme 2*). The experimental results are summarized in Table 11.

Scheme 6.

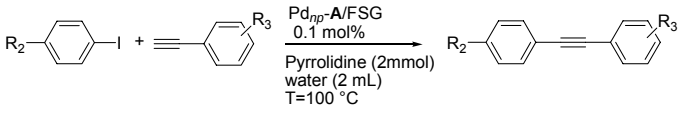
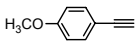
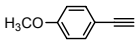
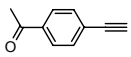
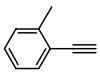
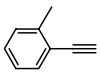
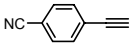
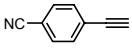
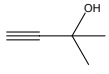


Table 11. Reaction of Aryl iodide and Aryl bromide with different terminal alkynes with 0.1 mol% catalyst loading.

Entry	Ar-X	R	t(h)	Yield % [a]
1	*p*-EtO_2C-C_6H_4-I		5	95
2	*m*-CF_3-C_6H_4-I		3	95
3	*p*-NO_2-C_6H_4-I		5	93 (93, 40)
4	*p*-Ac-C_6H_4-I		5	93
5	*p*-MeO-C_6H_4-I		44	70
6	*p*-CN-C_6H_4-I		6	86
7	*p*-CN-C_6H_4-Br		24	99
8	*p*-NO_2-C_6H_4-Br		24	92
9	*p*-Ac-C_6H_4-Br		44	50
10	*p*-CN-C_6H_4-I		5	85
11	*o*-CH_3-C_6H_4-I		29	80
12	*p*-CN-C_6H_4-I		4	90
13	*p*-CN-C_6H_4-I		4	84
14	*p*-OCH_3-C_6H_4-I		5	85
15	p-OCH_3-C_6H_4-I		3	85
16	m-CF_3-C_6H_4-I		2	89
17	p-OCH_3-C_6H_4-I		48	83

[a] Reactions were carried out using 1 mmol of aryl iodide, 1 mmol of terminal alkynes, 2 mmol of Pyrrolidine at 100 °C in the presence of 0.1 mol % of Pd_{np}-**A** /FSG in 2 mL of water. [b] Yields are given for isolated products.

As shown in Table 11, the Sonogashira coupling reactions of aryl iodides with a variety of terminal alkynes proceeded smoothly at 100 °C in water under aerobic conditions giving the corresponding coupling products in high yields. The optimized catalyst system is quite general and tolerant of a range of functionalities. For the electron-deficient phenyl iodides, the coupling reactions were completed within c.a. 6 h, , and the others required slightly longer reaction times. In all reactions only 0.1 mol% of Pd_{np}-**A** /FSG based on the aryl iodides was used, the molar turnover numbers are larger than those in the corresponding coupling reaction catalyzed by other heterogeneous catalysts reported.[74] This cross-coupling was also tolerant of ortho substitution in aryl iodide and led to the good yield (*Entry 13, Table 11*).The coupling reaction of activated and deactivated aryl iodide with a hydrophilic terminal alkynes were very slow under the same conditions, but good yield of coupling product was obtained after 24-48 h of reaction time respectively (*Entries 19-20, Table 11*). Activated aryl bromides was coupled with phenylacetylene and good yields were achieved (*Entries 9-11, Table 11*).

2.5. Conclusions.

In conclusion, we have demonstrated that phosphine-free perfluoro-tagged palladium nanoparticles can be immobilized on fluorous silica gel to give a precatalyst which can be successfully used in the Heck, Suzuki and Sonogashira cross-coupling reactions. The utilization of Pd_{np}-**A** /FSG does not require an inert atmosphere. Reactions and recovery of the catalyst system can be carried out in the presence of air without any particular precaution. The catalyst system can be easily recovered and reused several times without any appreciable loss of activity in many cases. It is also conceivable that the characteristics of this type of precatalyst can be adjusted by using different heavily fluorinated compounds. In general, the immobilized palladium nanoparticles described herein holds promise as the first example of a new class of solid-supported precatalysts. Further studies on this immobilization strategy are currently underway.

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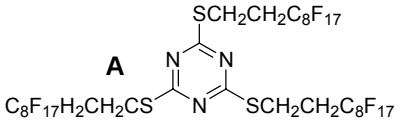
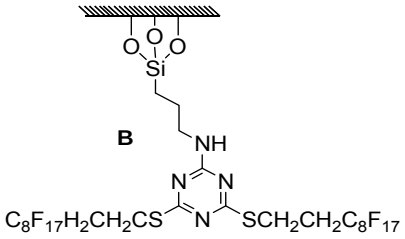
3. Palladium Nanoparticles Supported on Perfluorinated Hybrid Organic-Inorganic Material.

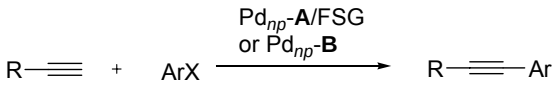
In collaboration with the group of A. Vallribera, we have previously reported that heavily fluorinated compounds can favor the formation of Pd_{nps} and that a number of these nanoparticles are catalytically active in C-C bond-forming processes. More recently, we have reported the synthesis of a 3-fold symmetric fluorinated compound **A** (Figure 1) and showed that the palladium nanoparticles degrade somewhat. Analysis of the supernatant liquid obtained after a catalytic run confirmed the leaching of both palladium and small amounts of the fluorous stabilizer. When nanoparticles stabilized by **A** were tested under microwave irradiation, the loss of catalytic activity became evident, with the material decomposing rapidly through complete loss of stabilizer and the formation of bulk palladium.





In an effort to create a catalyst compatible with the use of microwave heating and to improve the recycling studies for the alkynylation of aryl halides, Vallribera et al. envisioned the synthesis of a more robust hybrid material with the stabilizer linked covalently to the silica gel matrix. Specifically, she proposed the synthesis of fluorinated stabilizer **B** based on a substituted triazine (Figure 1).[1] We tested palladium nanoparticles stabilized by **B,** Pd-**B,** as a precatalyst system in the C-C cross coupling reaction and compared Pd-**B** with Pd_{np}-**A**/FSG.

4. Copper- and Phosphine-Free Alkynylation of Aryl Halides in Water with Perfluoro-Tagged Palladium Nanoparticles Immobilized on Silica Gel.



4.1 Introduction.

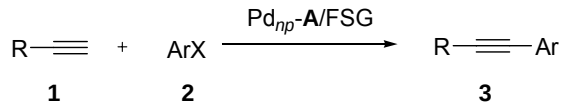
The palladium-catalyzed cross-coupling of terminal alkynes with aryl and vinyl halides or triflates is one of the most powerful tools for the formation of C-C bonds. The reaction, developed independently by Sonogashira, Heck,[2] and Cassar[3] in 1975 has found a large number of applications ranging from the preparation of fine chemicals to the synthesis of biologically active substances. Under Sonogashira conditions (copper salts are used as cocatalysts) the reaction can be carried out under milder conditions than those typical of Heck and Cassar protocols and this can explain the enormous success of the Pd/Cu cocatalyzed cross-coupling chemistry.[4] Nevertheless, since its discovery a great deal of work has been done to modify the original protocol so as to include an even wider range of reactants as well as to limit some of the major drawbacks of the process: the presence of copper salts and phosphines. Indeed, copper salts can induce Glaser-type homocoupling[5] of terminal alkynes when copper acetylide intermediates are exposed to oxidative agents or air. In addition, the utilization of two metals hinders the recovery and reutilization of the expensive palladium catalysts (its recovery would be the best way to overcome cost related problems). Phosphines, which are frequently used in this reaction, are often air-sensitive. As to this point, interesting results have been achieved by enhancing the catalyst efficacy employing more efficient phosphines.[6] However, these phosphines are not readily available and some limits to their use in large scale applications still remain. To avoid these drawbacks, and consequently to provide access to alkynylation reactions under aerobic conditions, copper- and phosphine-free procedures have been developed. This approach is exceedingly convenient in industrial applications and when the reactions are carried out in multiple vessels for library generation. A subject that appears to be particularly

attractive is combining the use of copper- and phosphine-free conditions with solid supported palladium catalysts.[7] This approach can provide two additional advantages: it can facilitate the recovery and reutilization of palladium and can also reduce the palladium contamination of the isolated product, a significant problem for the pharmaceutical industry.[8]

4.2 Results and Discussion.

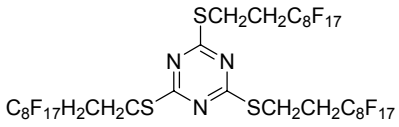
In this context, on the basis of the positive results we obtained with air stable perfluoro-tagged palladium nanoparticles supported on fluorous silica gel (Pd_{np}-**A**/FSG) in the Heck reaction in terms both of yields and recovery and reutilization of the catalyst system,[9] we became interested in investigating their use in the reaction of terminal alkynes with aryl halides under aerobic, copper-, and phosphine-free conditions (Scheme 1).

Scheme 1.



The air stable immobilized precatalyst was prepared as described previously adsorbing palladium nanoparticles stabilized by compound **A** (Pd_{np}-**A**) on commercially available fluorous silica gel (FSG).

Figure 1.



A

Using the reaction of 3-(trifluoromethyl)iodobenzene with phenylacetylene as a probe for evaluating the reaction conditions, we observed that the corresponding coupling product could be isolated in 45% yield after 5 h at 100 °C in MeOH under aerobic conditions with 0.1 mol% of Pd_{np}-**A**/FSG and 2 equiv of K_2CO_3. No homocoupling derivative formation was observed. Encouraged by this result, we explored the role of bases and solvents on the reaction outcome. Some results of our optimization studies are summarized in Table 1. Et_3N was found to be superior to K_2CO_3 and Et_2NH in MeOH

(Table 1, compare entry 3 with entries 1 and 2). Using Et_3N as the base, the influence of other solvents were investigated and, although MeCN gave **3a** in high yield, we were pleased to find that water was the best reaction medium (Table 1, entry 6). The use of water as the reaction medium is very attractive in organic synthesis due to safety, economical, and environmental reasons.[10] In addition, water has a high dielectric constant and density so that reactions involving water insoluble substrates when carried out in water often benefit from the hydrophobic effect.[11]

There are only a few reports of alkynylation reactions of aryl halides in the presence of immobilized palladium catalysts under copper- and phosphine-free conditions in water[12, 13] or using water as cosolvent.[14] None of them, however, involve palladium nanoparticles. We then came back and investigated the use of other bases in water and found that an almost quantitative yield could be obtained with pyrrolidine (Table 1, entry 10).

Table 1. The influence of solvents and bases on the cross-coupling of phenylacetylene with 3-(trifluoromethyl)iodobenzene catalyzed by Pd_{np}-**A**/FSG .

entry	solvent	base	yield% of **3a**
1	MeOH	K_2CO_3	45
2	MeOH	Et_2NH	66
3	MeOH	Et_3N	70
4	MeCN	Et_3N	87
5	H_2O	Et_3N	91
6	H_2O	K_2CO_3	5
7	H_2O	KOAc	5
8	H_2O	Et_2NH	89
9	H_2O	piperidine	95
10	H_2O	pyrrolidine	99

[a] Reactions were carried out using 1 mmol of 3-(trifluormethyl)iodobenzene, 1 mmol of phenylacetylene, 2 mmol of base at 100 °C for 5 h in the presence of 0.1 mol % of Pd-**A**/FSG in 2 mL of solvent. [b] Yields are given for isolated products.

A variety of terminal alkynes and aryl halides were then subjected to the following "optimal" conditions: H_2O, pyrrolidine, Pd_{np}-**A**/FSG, 100 °C. Our preparative results are summarized in Table 2 (entries 1, 4, 5, 7, 9, 11, 13, 15, 18, 21).

Although coupling products were usually isolated in high to excellent yields, recycling studies performed with our model reaction revealed a limited tendency of Pd_{np}-**A**/FSG to be reused. Indeed, a significant loss of activity was observed in the third run (Table 1, entry 1). Using 0.5 mol% of Pd_{np}-**A**/FSG resulted only in a slight increase of the number of runs that could be performed (Table 2, entry 2). Although sector field inductively coupled plasma mass spectrometry (SF-ICP-MS) analysis indicated the level of palladium to be in the range of only 0.05-0.08 ppm in water, a high level of palladium (39-240 ppm) was found in the crude product. Most probably, the main cause of this result is the relative weakness of fluorous-fluorous interactions, responsible for binding Pd_{np}-**A** to FSG, in the alkynylation reaction (no such effect was observed in the Heck reaction). Accordingly, ^{19}F NMR analysis of the crude mixture derived from the reaction of phenylacetylene with *m*-(trifluoromethyl)iodobenzene after filtration revealed the presence of significant amounts of **A**, corresponding to an original nanoparticle support loss of about 50% per run.

Consequently, we decided to investigate the use of palladium nanoparticles stabilized by a perfluorinated compound covalently bound to silica gel. This precatalyst system (Pd_{np}-**B**), containing 3.47 % of palladium in the form of nanoparticles with an average particle size of 3.9 ± 0.9 nm, was prepared by the sol-gel process described previously.[15]

Table 2. The reaction of terminal alkynes with aryl iodides and bromides in the presence of Pd_{np}-**A**/FSG and Pd_{np}-**B**.[a]

entry	terminal alkyne **1** R	ArX **2**	proc	t (h)	yield% of **3**[b,c]	
1	Ph	3-CF_3-C_6H_4-I	A	3	**3a**	95(92, 50)
2		3-CF_3-C_6H_4-I	A	3	**3a**	95(96, 93,83)[d]
3		3-CF_3-C_6H_4-I	B	1	**3a**	95
4		4-EtO_2C-C_6H_4-I	A	5	**3b**	95
5		4-NO_2-C_6H_4-I	A	5	**3c**	93 (93)
6		4-MeO-C_6H_4-I	B	12	**3d**	90
7	4-MeO-C_6H_4	4-CN-C_6H_4-I	A	5	**3e**	85
8		4-CN-C_6H_4-I	B	7	**3e**	95
9		2-Me-C_6H_4-I	A	29	**3f**	80

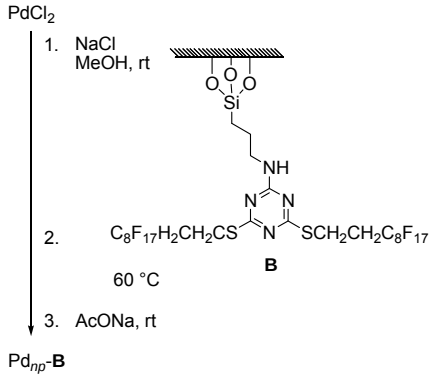
10		2-Me-C_6H_4-I	B	9	**3f**	90
11	4-CN-C_6H_4	3-CF_3-C_6H_4-I	A	2	**3g**	89
12		3-CF_3-C_6H_4-I	B	2	**3g**	99
13	4-MeCO-C_6H_4	4-CN-C_6H_4-I	A	4	**3h**	90
14		4-CN-C_6H_4-I	B	2	**3h**	99
15	4-CN-C_6H_4	4-MeO-C_6H_4-I	A	3	**3i**	85
16		4-MeO-C_6H_4-I	B	24	**3i**	87
17	$HOCH_2$	4-CN-C_6H_4-I	B	24	**3j**	89
18	$HO(Me)_2C$	4-MeO-C_6H_4-I	A	48	**3k**	83
19	HOMe(Ph)C	4-MeO-C_6H_4-I	B	24	**3l**	90
20	OH-C_6H_{12}	4-MeCO-C_6H_4-I	B	14	**3m**	92
21		4-MeCO-C_6H_4-Br	A	44	**3n**	50
22	Ph	3-CF_3-C_6H_4-Br	B	9	**3o**	91
23		4-MeO-C_6H_4-Br	B	48	**3p**	65

[a] Reactions were carried out under aerobic conditions using 1 mmol of aryl halide, 1 mmol of terminal alkyne,2 mmol of pyrrolidine at 100 °C in 2 mL of H_2O with 0.1 mol % of Pd_{np}-**A**/FSG (procedure A) or 0.5 mol% of Pd_{np}-**B** (procedure B). [b] Yields are given for isolated products. [c] Figures in parentheses refer to recycles. [d] In the presence of 0.5 mol% of Pd-**A**/FSG.

Activated aryl bromides reacted with phenylacetylene to generate the corresponding products in good yields (entries 1-3, Table 5) whereas deactivated aryl bromides afforded relatively lower yields (entry 4, Table 5).

The catalytic activity and stability of Pd_{np}-**B** was tested using our model system in water with a variety of bases (K_2CO_3, KOAc, pyrrolidine, piperidine, Et_2NH, and Et_3N). After some experimentations we found that **3a** could be isolated in 95% yield using 0.5 mol% of Pd_{np}-**B** and 2 equiv of pyrrolidine at 100 °C for 1 h. Recycling studies were then performed which showed that this supported catalyst system allowed for a number of cycles largely higher than with Pd_{np}-**A**/FSG (Table 3). The recovery of the supported palladium involves centrifugation and decanting the solution in the presence of air, without any particular precaution. Ostwald ripening process[16] was not observed upon recycling. The recovered material after 11 runs was examined by TEM showing nanoparticles of about 3.6 nm of diameter (Figure 2).

Scheme 2.



The resistance of Pd$_{np}$-**B** to leaching was assessed for the same reaction [3-(trifluoromethyl)iodobenzene with phenylacetylene]. SF-ICP-MS analysis indicated the level of palladium in water to be 1 ppb. Control experiments were also carried out to investigate the palladium leaching in the crude product. The level of palladium was found to be in the range of 0.48-4.8 ppm. On the basis of this positive results, Pd$_{np}$-**B** was then used in the alkynylation of a variety of aryl iodides and bromides. As shown by the results listed in Table 2 (entries 3, 6, 8, 10, 12, 14, 16, 17, 19, 20, 22), coupling products were isolated in yields similar to or higher than those obtained with Pd$_{np}$-**A**/FSG, at least with the substrates that we have investigated.

Table 3. Recycling studies for the reaction of 3-(trifluoromethyl)iodobenzene with phenylacetylene catalyzed by Pd$_{np}$-**B**.[a]

Entry	Pd$_{np}$-B mol%	t(min.)	T(°C)	Yield %[a]	TON
1	0.1	60	100	99(86,93,60)	3380
2	0.5	45	100	95(90, 91, 86, 95, 92, 95, 90, 88, 86, 65)	1946

[a] Reactions were carried out using 1 mmol of 3-(trifluoromethyl)iodobenzene, 1 mmol of phenylacetylene, 2 mmol of pyrrolidine at 100 °C for 1 h in the presence of 0.5 mol % of Pd$_{np}$-**B** in 2 mL of H_2O.

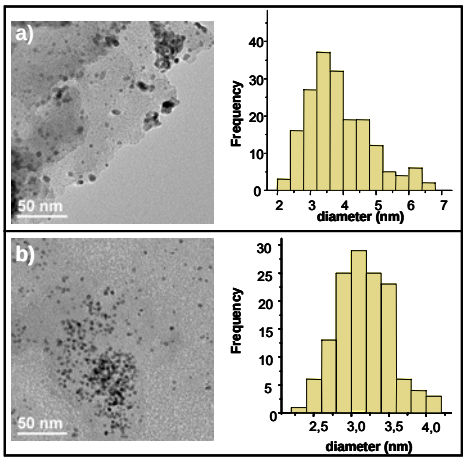


Figure 2. (a) TEM image and particle size distribution histogram of Pd_{np}-**B** (particle size 3.9 ± 0.9 nm) (b) TEM image and particle size distribution histogram of Pd_{np}-**B** after 11th runs (particle size 3.2 ± 0.4 nm).

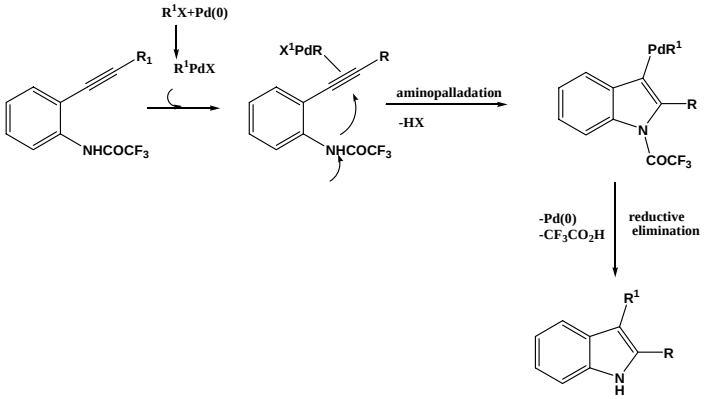
In conclusion, we have demonstrated that perfluoro-tagged palladium nanoparticles immobilized on fluorous silica gel by fluorous-fluorous interactions (Pd_{np}-**A**/FSG) and linked to silica gel by covalent bonds (Pd_{np}-**B**) can be used under aerobic conditions in the alkynylation of aryl halides under copper- and phosphine-free conditions in water. Both the catalyst systems allow for the isolation of coupling products in high to excellent yields. However, the use of Pd_{np}-**B** gives the best results in term of recovery (which can be carried out in the presence of air without any particular precaution) and reutilization.

4.3 Synthesis of the Indole Nucleus Using Pd_{np}-B.

The substituted indole nucleus (indole is the acronym from **ind**igo - the natural dye- and **ole**um – used for the isolation) is a structural component of a vast number of biologically active natural and unnatural compounds. Synthetic methods for the synthesis and functionalization of indoles have been developed through many classical methods such as the Fischer indole synthesis, the Batcho-Limgruber synthesis from o-nitrotoluenes and dimethylformamide acetals, The Gassman synthesis from N-haloanilines, the reductive cyclization of o-nitrobenzyl ketones, and the Medelung cyclization of N-acyl-o-toluidines.[16] More recently, transition metal-based widely employed providing increased functional group tolerance and improved yields as outlined by the number of studies developed in this area. A considerable part of the

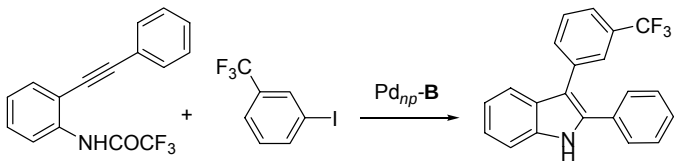
studies dedicated to the development of new sequences in the bond-making process leading to the construction of the pyrrole ring is based on the utilization, as precursors, of compounds containing nitrogen nucleophiles and carbon-carbon triple bonds. Nitrogen nucleophiles and alkyne moieties can be part of the same molecule or belong to two different molecules. In our laboratory was deeply investigated the cyclization of o-alkynylanilides via aminopalladation-reductive elimination for the synthesis of the indole nucleus, see scheme 3. In this way, we investigated the catalytic activity and stability of the Pd_{np}-**B** in the synthesis of the indole nucleus (Scheme 3).

Scheme 3.



The reaction of 2-(phenylethynyl)trifluoroacetanilide with 1-iodo-3-trifluoromethylbenzene in K_2CO_3 and acetonitrile with 0.1mol % precatalyst loading, at 100 °C gave the desired indole in 91% isolated yield.

Scheme 4.



Recycling studies were also performed. Using 0.1 mol% precatalyst loading, a significant loss of activity was observed at the third run (Table 6, entry 1). Switching to

Table 6. Recycling studies with Pd_{np}-**B**.

Entry	Pd-1/FSG mol% Loading	Yield %	TON
1	0.1	91(90,45)	2260
2	0.5	91(90, 86, 87)	708

0.5 mol% of precatalyst loading four runs were carried out without any appreciable loss of activity. The cumulated turnover number is 708. We then evaluated the efficiency of Pd_{np}-**B** with other aryl iodides. Our preparative results are summarized in **Table 7.**

Scheme 5.

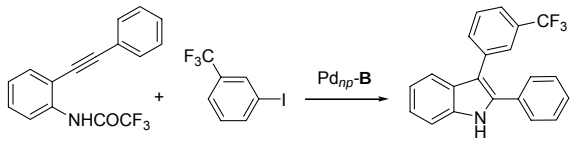


Table 7. Reaction of aryl iodides with 2,2,2-trifluoro-N-2(phenylethynyl)phenyl)acetamide catalyzed by Pd_{np}-**B** (0.1 mol%) [a].

Entry	Ar-I	t(h)	Yield % of ..[b,c]
1	*m*-CF_3-C_6H_4-I	2	91
2	*p*-CN-C_6H_4-I	4	84(92,90,86)
3	*p*-Ac-C_6H_4-I	2	89(91,87)
4	*m*-CH_3-C_6H_4-I	40	77
5	*p*-MeO-C_6H_4-I	48	70
6	*p-Cl*- C_6H_4-I	5	96(92,83)
7	C_6H_5-I	9	82
8	*p*-NO_2-C_6H_4-I	4	90

[a] Reactions were carried out using 1 mmol of aryl iodide,1 mmol of 2,2,2-trifluoro-N-2(phenylethynyl)phenyl)acetamide,2 mmol of K_2CO_3 at 110 °C in the presence of 0.5 mol % of Pd_{np}-**B** in 2 mL of CH_3CN. [b] Yields are given for isolated products. [c] Yields in parentheses are for the other runs carried out with the recovered catalyst.

Neutral, electron-rich, and electron-poor aryl iodides were tested. The corresponding 2,3 di-substituted indoles were isolated in good yields (entries 1-6, Table 7).

4.4 Suzuki-Myiaura Cross-Coupling in Water Using Pd_{np}-B.

In catalytic chemistry, there is an increasing requirement to optimize reactions in terms of environmental and process safety as well as in terms of economic viability. Important aspects are the reduction of waste, straightforward isolation of products, recycling of catalysts, and the use of environmentally benign reaction media.[18] Water is in these regards a suitable solvent, since it is cheap, non flammable and nontoxic. However, it is

important to remove products and catalyst efficiently to allow for easy disposal of H_2O. Solid-supported catalysts have become valuable tools for simplified product isolation and catalyst recycling. For immobilization, catalysts can be linked covalently to different supports, such as polymer resins or inorganic solids. Polar catalysts can be adsorbed on silica gel, [19] or immobilized in a thin layer of H_2O, [20] ethylene glycol, [21] or ionic liquids [22, 23] on a silica support. The reaction is carried out in an apolar organic solvent. These applications usually require suitable derivatization of the catalyst with polar functionalities. In this chapter we reported the use of Perfluoro-tagged phosphine free palladium nanoparticles supported on perfluorinated hybrid organo-inorganic material, Pd_{np}-**B** . These supported Pd_{np}-**B** was applied to Suzuki cross-coupling reaction in water and comparison with the results previously obtained using Pd_{np}-**A**/FSG in the same conditions (see chapter 2.3).

The Pd_{np}-**B** and Pd_{np}-**A**/FSG were prepared by our reported procedures. [24] [25]

Initially, between 0.01 mol-% and 0.1 mol-% of Pd_{np}-**B** was tested as precatalyst for the Suzuki coupling of *o*-tolylboronic acid and *p*-iodobenzoic acid in water (see Scheme 6 and Table 7).

Scheme 6.

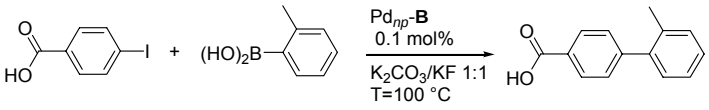


Table 7. Recycling studies of Suzuki-Miyaura cross-coupling catalyzed by Pd_{np}-**B**.

Entry	Catalyst loading mol%	T [°C]	Run	TON	TOF [h^{-1}]
1	0.1	100	99 (99, 91, 99, 97, 99, 97, 100, 95, 90, 92, 95, 90, 85, 85)	14130	14130
2	0.01	100	97 (95, 90, 87)	37000	37000

The product was separated by decantation after centrifugation, and the supported catalyst was reused up several times. For the higher catalyst loadings, nearly quantitative yield was observed in the first run. Up to the 15th run, the yield decreased only to 85%. The yield remained on a fairly high level with 0.01 mol% of catalyst during four runs still leading to cumulated turn-over numbers (TON) of more than 37000. This value is lower than that obtained with Pd_{np}-**A**/FSG (TON 55300) under the

same conditions. However, the reactions are faster with Pd_{np}-**B** than with Pd_{np}-**A**/FSG as can be seen on the basis of TOF values (respectively 14130 h^{-1} vs 2672 h^{-1}).

To assess the catalyst leaching, coupling of *o*-tolylboronic acid and *p*-iodobenzoic acid was carried out with 0.1 mol-% of Pd_{np}-**B**. The Pd content in the crude product and in water was determined by sector field inductively coupled plasma mass spectrometry technique (SF-ICP-MS): the amount of Pd in the crude product was in the range of 0.0046-0.45ppm and in the aqueous solution was 0.001 ppm. Pd in the crude product was in the range of 0.0046-0.45ppm, in aqueous solution is 0.001 ppm.

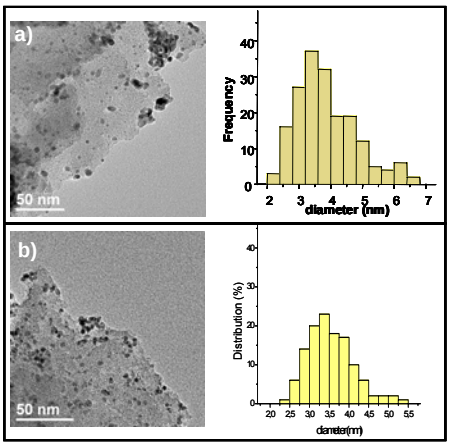


Figure 3. (a)TEM image of Pd_{np}-**B** after 15th run at high resolution, (b) Particle size distribution histogram of Pd_{np}-**B** (Diameter: 3.6 ± 0.6 nm).

Figure 3a shows a representative TEM image of the Pd_{np}-**B** before the first run of Suzuki reaction, and the Gaussian fits of the size distributions of the nanoparticles. It can be seen that the Pd_{np}-**B** nanoparticles are monodispersed with an average size (center of distribution) of 3.7± 0.3 nm. Figure 3b shows a representative TEM image of the nanoparticles after the 15th cycle of the Suzuki reaction, and shows the Gaussian fits of the size distributions of the nanoparticles. By comparing the Gaussian fits before and after the 15th cycle we could see that both the widths and the centers of the size distributions of the nanoparticles are the same. Contrary to Pd_{np}-**A**/FSG, in this case no Ostwald ripening process was observed.

Table 8. Reaction of Aryl iodide and aryl bromide with different boronic acids with Pd_{np}-**B** 0.1 mol% catalyst loading [a].

Entry	R^1	R^2	t(h)	Isolate yield% [a]
1	*p*-HOOC-C_6H_4-Br	*p*-$CF_3C_6H_4$-BOH_2	8	90(92)
2		*p*-CH_3O-$C_6H_4BOH_2$	8	87
3		$C_6H_5BOH_2$	8	91
4		*o*-CH_3-$C_6H_4BOH_2$	5	90
5		*p*-CH_3-$C_6H_4BOH_2$	5	87
6		*o*-Br-$C_6H_4BOH_2$	48	63
7	C_6H_5I	*p*-$CF_3C_6H_4BOH_2$	48	50
8		*o*-CH_3-$C_6H_4BOH_2$	9	99
9	*p*-CH_3O-C_6H_4-Br	*p*-$CF_3C_6H_4$-BOH_2	24	88(85)
10		*o*-CH_3-$C_6H_4BOH_2$	48	80
11	*p*-CH_3CO-C_6H_4-Br	*p*-$CF_3C_6H_4$-BOH_2	8	92(93)
12		*p*-OCH_3-$C_6H_4BOH_2$	24	84
13		$C_4H_5BO_2S$	5	90
14	*p*-CH_3O-C_6H_4-Br	$C_4H_5BO_2S$	16	89

[a] The yields in parentheses are for the other runs with the same catalyst. Compounds were purified on columns, packed with SiO_2 25-40 μm (Macherey Nagel), and eluting with *n*-hexane/AcOEt/ mixtures.

Furthermore, Pd_{np}-**B** was evaluated in the Suzuki coupling of different substrates (see Scheme 3 and Table 2). The reaction proceeded well with a range of water-soluble and insoluble substrates, and the catalyst could be recycled. Only in the case of iodobenzene, the yield was low and recycling of the catalyst was not successful (Table 8, Entry 4). In the boronic acid, small *o*-substituents were well tolerated, as the comparison of p-tolylboronic acid (Table 8, Entry 5) and o-tolylboronic acid (Table 8, Entry 5), but coupling *o*-iodo-toluene and *o*-tolylboronic acid no product was obtained. Soluble and insoluble aryl bromide with activated and deactivated functional groups were tested in Suzuki reaction with good yield.

4.5 Conclusions.

We have demonstrated that palladium nanoparticles phosphine-free, supported on perfluorinated hybrid organo-inorganic material can be utilized in the Sonogashira reaction using environmentally friendly protocol (copper-free, using water as solvent) and for the synthesis of the indole nucleus. The utilization of Pd_{np}-**B** does not require an inert atmosphere. Reactions and recovery of the catalyst system can be carried out in the presence of air without any particular precaution. The catalyst system can be easily recovered and reused several times without any appreciable loss of activity in many cases.

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5. Gold Nanoparticles: a Good Opportunity for Sustainable and Green Chemistry.

There is a general concern in developing new chemistry that can be sustainable and benign for the environment.[1] Most of the current chemical industry is based on the use of oil and natural gas as feedstock and this situation has to change substantially in the near future. Also, sustainability has to be accompanied by the development of new processes that do not produce, or minimize up to an acceptable extent, any negative impact on the environment. For these reasons, a new scenario in chemistry has been set in which not only inefficient processes, but even the efficient ones, have to be replaced if they do not comply with certain principles that constitute the base of what has been called *Green Chemistry.*

In Green Chemistry , two parameters, the *E-factor* (*E*) and the *Atom Efficiency* (*AE*), have been established to quantify the greenness of a transformation. The E-factor indicates the Kg of waste per Kg of products and AE-factor measures the percentage of the starting material that ends up in products.[2a-d] Both parameters are obviously interrelated. Considering a brief overview of organic reactions , it can be stated that there are some reaction types that have a low E-factor and high AE. One example of this green general organic reaction type will be hydrogenations and also C-C couplings catalyzed by transition metals such as Suzuki, Heck, Sonogashira, Buchwald, etc. the vast majority of organic oxidations at the laboratory scale level or in the fine chemical industry also produce a large amount of wastes. Perusal of the current organic chemistry textbooks shows that all of the classical oxidation reactions, even though they give high product yields, are far from complying with the green chemistry principles, using hazardous or toxic chemicals, requiring volatile organic solvents and producing large amounts of toxic waste. Most of the current methods, in fact, for the oxidation in organic chemistry are not catalytic, but stoichiometric. It is mean that equivalent amounts of an oxidizing reagent, such as transition metal oxides or halo-oxo acids, are needed to effect the oxidation, leading to the stoichiometric formation of waste corresponding to the reduced form of the oxidizing reagent. Other non-metallic oxidants that have been used as oxidizing reagents are halogens, peroxy and hydro-peroxy compounds or even sulfoxides. The latter noxious reagents are transformed into equivalent amounts of sulphide in the selective Swern alcohol oxidation.[3a-c]

Table 1. List of some oxidizing reagents.

Oxidizing reagent	Waste	O_2 %
$KMnO_4$	Mn^{2+}/MnO_2	-
K_2CrO_4	Cr^{3+}	-
CH_3COOH	CH_3CO_2H	26
t-BuOOH	*t*-BuOH	27
ClO^-	Cl^-	30
H_2O_2	H_2O	46
O_2	H_2O	50

Table 1 shows some typical oxidizing reagents, indicating the resulting by-product and the percentage of oxygen content.

One of the principles of green chemistry is to substitute stoichiometric processes by catalytic processes. Application of these principles is particularly necessary in oxidations reactions, for which the ratio between kg of by-products per kg of product formed is notably high. By transforming a stoichiometric into catalytic process, is meant the use of unconventional, environmentally-friendly oxidizing reagents that do not readily react in a selective way with organic substrates unless suitable catalysts for the process are developed. One example of a catalytic oxidation is the *Meerwein-Ponndorf-Verley* that is carried out using Lewis acid catalysts.

Following the rapid growth of gold nanotechnologies during the last decades the application of this metal in catalysis has become an important research area. However, only in recent years gold has been evaluated in fundamental reaction for organic synthesis such as oxidation and hydrogenation,[4] and the use of gold catalysts for industrial application in fine chemical intermediates has been explored by academic and industrial researchers.[5] Compared to other metals, one of the outstanding properties of gold in catalysis is represented by the high selectivity which allows discrimination within chemical group and geometrical positions, favoring high yield of the desired product. Considering other concomitant properties, such as *biocompatibility*, availability and easy recovery, gold appears as a promising green catalyst for sustainable processes using clean reagents, particularly O_2 and H_2, often in aqueous solution under mild conditions or in the absence of the solvent. In the book by Bond, Louis and Thompson there are five introductory chapters covering all aspects related to physical properties and characterization of gold nanoparticles as well as preparation of supported gold catalysts. The reader is referred to this reference book for a coverage of these important

aspects in gold catalysis. Another key precedent is the review from Hashmi and Hutchings on gold catalysis covering both homogeneous catalysis using gold salts and heterogeneous catalysis using supported gold nanoparticles.[6-8]

Hutchings's Au/TiO_2 or Au/zeolite catalysts yielded at low conversion with benzyl alcohol a $TOF_{t=0.5\ h}$ of 200–500 h^{-1} at 100 °C and 2 atm O_2 under solvent-less conditions. Baiker's catalyst (Au on Cu–Mg–Al mixed oxides) gave at 90 °C and 1 atm O_2 in mesitylene a $TOF_{t=0.5\ h}$ of 316 h^{-1} with benzyl alcohol and a $TOF_{t=3\ h}$ of 11 h^{-1} with 1-octanol; much better results were obtained with 1-phenylethanol ($TOF_{t=1\ h}$ of 1294 h^{-1}).[9] Oxidation of 1-phenylethanol with Kobayashi's Au on polystyrene gave a $TOF_{t=1\ h}$ of 32 h^{-1} at room temperature and 1 atm O_2 in benzotrifluoride/water 1:1.[10] Oxidation of 4-hydroxybenzyl alcohol using Tsukuba's PVP-stabilized Au nanoclusters in water gave an actual $TOF_{t=1\ h}$ at 23 °C and 1 atm O_2 of 15 h^{-1} and an estimated $TOF_{t=1\ h}$ at 60 °C and 1.5 atm O_2 of 33 h^{-1}.[11] Finally, Corma's Au on nanocrystalline CeO_2 with benzylic alcohols exhibited a $TOF_{t=2\ h}$ of about 80 h^{-1} at 50 °C and 1 atm O_2 in water,[12] although in this case alcohol oxidation actually was carried out by the cerium(IV) centers in the support, with the Au metal merely acting to regenerate these centers with concomitant O_2 reduction.

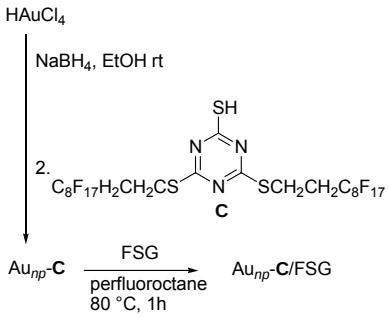
5.1. Oxidation of Alcohols with Molecular Oxygen Using Perfluoro-Tagged Gold Nanoparticles Supported on Fluorous Silica Gel.

In the fine chemical industry, as well as in traditional organic chemistry, many oxidations are being carried out using high valent inorganic oxidants. The application of these types of reagents often containing chromium or manganese inevitably leads to the generation of huge amounts of metal waste. In recent years several new procedures have been developed wherein a catalyst is used to facilitate oxidation of alcohols employing molecular oxygen as the stoichiometric oxidant.[13-19] In this emerging field of *green oxidation chemistry*, catalysts comprising gold nanoparticles have attained a very prominent role,[20] since they are often surprisingly active and on some occasions exhibit different chemoselectivity than platinum metal based catalysts. Thus, from a fundamental point of view, as well as from a technical one, gold catalysis is a topic of intense scientific interest; drawing attention from a very diverse group of researchers. So far, literature reports on selective oxidations using gold catalysts have focused primarily on oxidation of alcohols to aldehydes,[14] carboxylic acids [15] or esters,[21, 22]

oxidation of aldehydes to esters,[23] epoxidations of olefins,[24–27] and activation of C–H bonds in alkanes.

Herein we report the results of our study:

Perfluoro-tagged gold nanoparticles Au_{np}-**C** (diameter 2.7 ± 0.6 nm; 17.3% gold) were prepared as described previously for similar systems [28] by reduction of $HAuCl_4$ in ethanol at room temperature in the presence of $NaBH_4$ and compound **C**, a stabilizing agent featuring long perfluorinated chains.



Scheme 1. Preparation of Au_{np} and Au_{np}-**C**/FSG.

To prepare the immobilized precatalyst, nanoparticles Au_{np}-**C** were dissolved in perfluorooctane, commercially available FSG (C8; 35-70 mm) was added to the solution, and the solvent was evaporated. The immobilized precatalyst (Au_{np}-**C**/FSG) was obtained as an air-stable powder. Transmission electron microscopy (TEM) of Au_{np}-**C** /FSG was carried out. It showed well-defined spherical particles dispersed in the silica matrix (see Figure 1b).

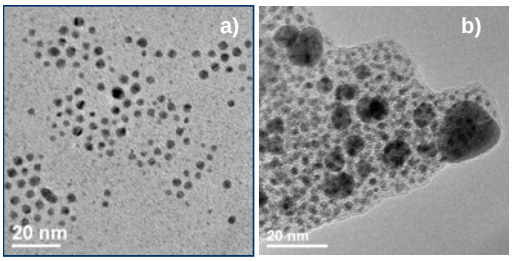
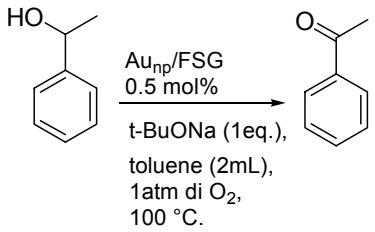


Figure 1. a)TEM image of Au_{np}-**C** (particle size 2.7 ± 0.6 nm).
b)TEM image of Au_{np}-**C**/FSG (particle size 1.9 ± 0.3 nm).

The catalytic activity of Au_{np}-**C**/FSG in the aerobic oxidation of alcohols was assessed using (±)-1-phenylethanol as a model substrate. Best results were obtained using 0.5 mol% catalyst loading, t-BuONa as base with molecular oxygen in toluene at 100 °C for 48h (see scheme 2 and Table 1). Increasing the catalyst loading under the same

conditions to 1 and 1.5 mol% led to they isolation of the oxidation product in 85 (23 h) and 88,% (20 h) yield respectively.

Scheme 2.



Optimized conditions of atmospheric-pressure oxidation of (±)-1-phenylethanol by molecular oxygen in the presence of the Au$_{np}$-**C**/FSG catalyst.

Table 1. The influence of solvents and bases on the oxidation reaction of 1-phenylethanol catalyzed by Au$_{np}$-**C**/FSG.[a]

Entry	Base	Solvent	Time [h]	Yield %[b]
1	NaOH	MeOH	48	trace
2	NaOH	Water	48	trace
3	K_2CO_3	MeOH	48	trace
4	Cs_2CO_3	MeOH	48	trace
5	Cs_2CO_3	DMF	48	trace
6	t-BuONa	Toluene	48	89

Reactions were carried out using 1 mmol of (±)-1-phenylethanol, 1 mmol of base at 100 °C for 48 h in the presence of 0.5mol % of Au$_{np}$-**C**/FSG in 2 mL of solvent.[b] Yield was determined by HPLC analysis using biphenyl as internal standard.

Recycling studies were then performed which showed that the supported catalyst system can be reused eight times with a low loss of activity (Table 2). The recovery of the supported palladium involves centrifugation and decanting the solution in the presence of air, without any particular precaution.

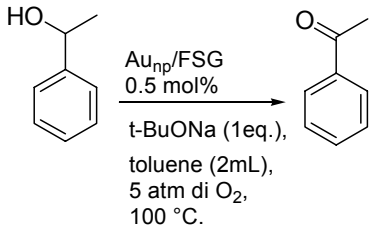
Table 2. Recycling studies for the oxidation reaction of (±)-1-phenylethanol catalyzed by Au$_{np}$-**C**/FSG.[a]

Entry	Catalyst loading (mol%)	T(h)	Yield %[b]	TON
1	0.1	48	87 (80, 78, 80, 51)	3760
2	0.5	48	91(99, 65, 95, 70, 81, 80, 66)	1294

[a] Reactions were carried out using 1 mmol of (±)-1-phenylethanol, 1mmol of base at 100 °C in the presence of different loading of Au$_{np}$-**C**/FSG in 2 mL of toluene.[b] Yield was determined by HPLC analysis using biphenyl as internal standard.

The oxidation of (±)-1-phenylethanol, catalyzed by 0.5 mol% of Au$_{np}$-**C**/FSG, was also carried out in the presence of high pressure of O_2 (5 atm) with t-BuONa as base and in toluene at 100 °C. As shown in Figure 2, acetophenone was isolated in 90% yield after14h.

Scheme 3.



High-pressure oxidation of (±)-1-phenylethanol by molecular oxygen in the presence of the Au$_{np}$-**C**/FSG catalyst.

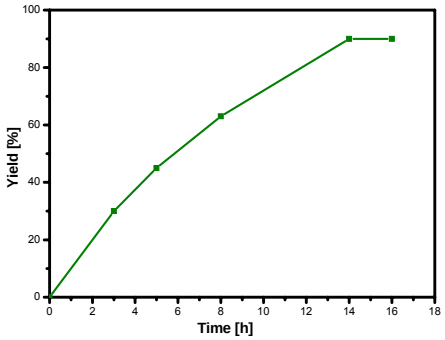


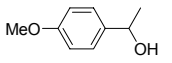
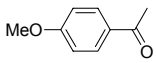
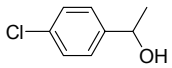
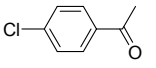
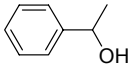
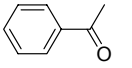
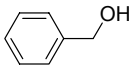
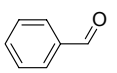
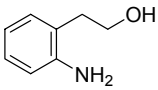
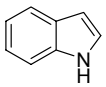
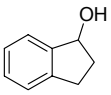
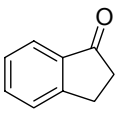
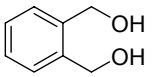
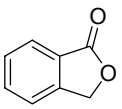
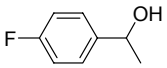
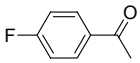
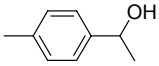
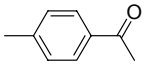
Figure 2. kinetic of the oxidation reaction of (±)-1-phenylethanol catalyzed by Au$_{np}$-**C**/FSG.

The utilization of Au$_{np}$-**C**/FSG under solvent-free conditions was also investigated. (±)-1-Phenylethanol, frequently employed in this type of reaction,[29] was used as model substarte. Control experiments using O_2 in the absence of gold revealed that less than 46% of the (±)-1-phenylethanol can be converted to acetophenone after 48 h at 100 °C. This result supports the notion that Au$_{np}$ play a pivotal role in the alcohol oxidation.

A way to rank the activity of catalysts that exhibit almost quantitative conversion and selectivity is to consider the turnover frequency (TOF), that is calculated by dividing the initial reaction rate to the number of catalytic sites. Initial reaction rate can be obtained from the slope of the time-conversion plot at zero time.[30]. The results showed that the Au$_{np}$-**C**/FSG catalyst exhibited a specific rate of 2140 h^{-1} under similar reaction conditions. Several secondary alcohols were then oxidized in the presence of 0.1 mol% of Au$_{np}$-**C**/FSG (Table 3). Aromatic alcohols were oxidized smoothly to afford the corresponding ketones in quantitative yields (Table 3, entries 1-5). 2-Aminophenethyl

alcohol was also found to undergo oxidative *N*-heterocyclization under optimized conditions to give indole in 99% yield (entry 5, Table 3).

Table 3. Oxidation of various alcohols catalyzed by Au_{np}-**C**/FSG.

Entry	Substrate	Product	T (°C)	time (h)	yield% [a]
1			100	2	**84**
2			100	31	**71**
3			100	48	**89**
4			100	48	**94**
5			120	21	**99**
6			100	19	**90**
7			100	24	**70**
8			100	24	**75**
9			100	48	**40**

Reactions were carried out using 1 mmol of aromatic alcohol with 2 mmol of *t*-ButONa in the presence of 0.5 mol% of Au_{np}-**C**/FSG in 2 mL of toluene.
[a] Yield was determined by HPLC analysis using biphenyl as internal standard.

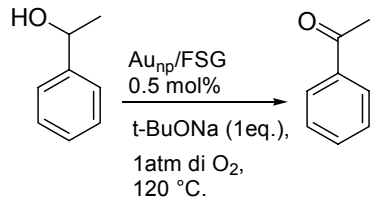
Then we investigated Au_{np}-**C**/FSG oxidative *N*-heterocyclization of 2-aminophenethyl alcohol under optimized conditions. Indole was formed in a yield of 99% when the reaction was performed at 120 °C for 21 h with use of 0.5 mol% of Au_{np}-**C**/FSG (entry 5, Table 3).

5.2 Solvent-Free Conditions.

Aerobic oxidation of 1-phenylethanol was performed at atmospheric pressure by bubbling oxygen through 1-phenylethanol and the catalyst in the absence of solvent. This experimental procedure has the additional advantage of avoiding the use of any solvent, thus meet the eight principle of Green-Chemistry. [31] Complete conversion

with high selectivity toward acetophenone was obtained when the reaction was conducted at 120 °C.

Scheme 4.

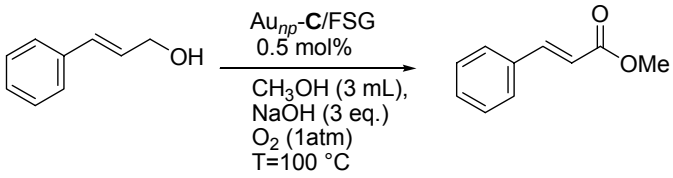


Solvent-free, atmospheric-pressure oxidation of (±)-1-phenylethanol by molecular oxygen in the presence of the Au$_{np}$-**C**/FSG catalyst. Reaction conditions: (±)-1-phenylethanol (5 mmol), Au$_{np}$-**C**/FSG (0.5 mol.%), t-BuONa (5 mmol) at 120 °C.

5.3 Oxidative Transformation of Alcohols into Esters.

Esterification is one of the most important reactions in organic synthesis.[32] Although a number of methods have been developed, the search for new, facile and environmentally friendly procedures that avoid the large excess of reagents and expensive activators has attracted substantial interests.[33] An attractive alternative is the direct catalytic transformation of alcohols or aldehydes to esters, without the use of the corresponding acid or acid derivative.[34] In particular, the direct oxidative conversion of alcohols under mild condition is an attractive goal. As opposed to the traditional esterification method in which a two-step synthetic procedure first involving the synthesis of carboxylic acids or activated carboxylic acid derivatives (such as acid anhydrides or chlorides) is required,[35] the single-step nature of the oxidative esterification procedure has economic and environmental benefits in the synthesis of esters. Heterogeneous gold nanoparticles have attracted tremendous recent attention owing to their unique catalytic properties for a broad spectrum of organic transformations,[36] especially for aerobic oxidation of alcohols under mild conditions.[37] In this context, on the basis of the positive results we obtained with air-stable perfluoro-tagged gold nanoparticles supported on fluorous silica gel (Au$_{np}$-**C**/FSG) in the oxidation reaction in terms both of yields and recovery and reutilization of the catalyst system, we became interested in investigating their use in the reaction of transformation of alcohols into esters (scheme 5).

Scheme 5.



Optimized conditions of atmospheric-pressure oxidation of cinnamyl alcohol by molecular oxygen in the presence of the Au$_{np}$-**C**/FSG catalyst.

Using the esterification reaction of cinnamyl alcohol as a probe for evaluating the reaction conditions, we observed that the corresponding product could be isolated in 64% yield after 48 h at 100 °C in MeOH under aerobic conditions. Encouraged by this result, we explored the amount of bases on the outcome of the reaction. After some experimentation we find that using 2 eq. of NaOH the desired product could be isolated in 86% yield. Recycling studies were then performed which showed that this supported catalyst system allowed for a number of cycles largely higher than other heterogeneous gold nanoparticles catalytic system (Table 4).[38]

Table 4. Recycling studies for the reaction of cinnamyl alcohol catalyzed by Au$_{np}$-**C**/FSG.

Run	Yield %[a]
1	89
2	85
3	87
4	67

Reactions were carried out using 1 mmol of cinnamyl alcohol with 2 mmol of NaOH in the presence of 0.5 mol% of Au$_{np}$-**C**/FSG in 3 mL of Methanol and atmospheric pressure of oxygen.
[a] Yield was determined by HPLC analysis using biphenyl as internal standard.

The recovery of the supported palladium involves centrifugation and decanting the solution in the presence of air, without any particular precaution. The cumulated turn-over number (TON) over four runs was 656.

5.4 Conclusion.

In conclusion, we have demonstrated that perfluoro-tagged gold nanoparticles can be immobilized on fluorous silica gel to give a precatalyst which can be successfully used in the oxidation of alcohols with molecular oxygen and esterification reaction.

Reactions and recovery of the catalyst system can be carried out without any particular precaution. The catalyst system can be easily recovered and reused several times without any appreciable loss of activity in many cases. It is also conceivable that the characteristics of this type of precatalyst can be adjusted by using different heavily fluorinated compounds. In general, the immobilized gold nanoparticles described herein holds promise as the first example of a new class of solid supported precatalysts. Further studies on this immobilization strategy are currently underway.

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6. Bio-Inorganic Catalysts.

There has been much interest lately in chemical transformations in single capsules of supramolecular assemblies.[1–4] Well-designed capsule structures could provide increased concentration of substrates in the cavities with high selectivity to allow transformation of the substrates. Proteins are very attractive building components for the construction of self-assembled cage structures.[1,5–12] For example, Mann and coworkers have reported in their pioneering works the preparation of size-restricted metal oxides and sulfides by using the biosupramolecular cage of ferritin.[5–7] In addition, protein assemblies of viruses and the chaperonin protein GroEL were also utilized for the encapsulation of metal nanoclusters.[10–12] However, difficulties still remain in controlling reactions catalyzed by metal clusters with the protein cages.

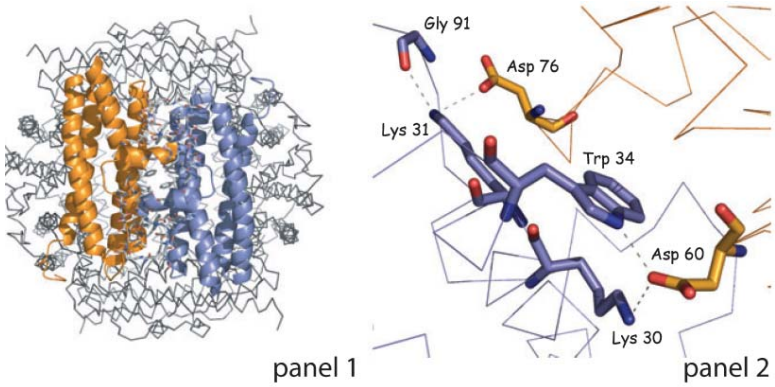


Figure 1. Interfaces of T. elongatus Dps. Panel 1, view along the interfaces; panel 2, blow-up indicating relevant interactions. Pictures were generated using PYMOL.

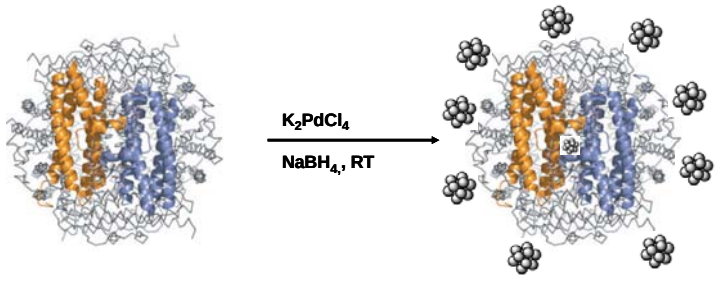
Dps-Te is known as an iron-storage protein and comprises twelve monomers assemble to form a hollow protein cage with 23-tetrahedral symmetry. Iron atoms are stored as a cluster of ferric oxyhydroxide within a cavity of diameter 4.5 nm formed by the protein subunits. The threefold symmetry-related subunits make two types of interaction. One defines the so-called 'ferritin-like' interface because the interactions resemble those of ferritin subunits along the threefold symmetry axes,[13] the other defines the interface specific to this protein family named 'Dps-like' (Figure 1). Herein we describe the catalytic properties of a new kind of biocatalyst in the Suzuki cross-coupling reaction in water and in the one pot two step asymmetric biotrasformation.

6.1 One-Pot Suzuki-Myiaura Cross-Coupling and Asymmetric Biotrasformation in Water.

Palladium-catalyzed C-C coupling by Suzuki-Myiaura reactions is a versatile and well established methodology in modern organic synthesis.[14] The coupling products provide a variety of valuable intermediates in the preparation of materials, natural products, and bioactive compounds. The use of water as a solvent for palladium-catalyzed C-C coupling reactions has merited increasing attention, to decrease the use of volatile organic solvents and to simplify catalyst recovery.[15] Water, being cheap, readily available, nontoxic, and non flammable, has clear advantages as a solvent for use in chemistry.[16] The C-C coupling reactions that can proceed in aqueous media have certainly been required to solve the problems of solubility of substrates, which have to some extent been surmounted by the use of water-soluble palladium catalysts, amphiphilic polymer-supported palladium catalysts, and phase transfer catalysts or the design of novel heterogeneous catalysts.[17] However, the activity of these systems remains too low to be industrially viable.[18] The majority of these studies on Suzuki-Miyaura,[19] coupling reaction in aqueous media have been carried out with water-soluble palladium catalysts containing water-soluble supporting ligands (e.g. TPPTS) meta-trisulfonated triphenylphosphine). There are few report dealing with soluble palladium nanoparticles catalysts.[20]

The Pd cluster is synthesized by in situ reduction of Pd (II) species in the presence of *Dps-Te* (Scheme 1.)

Scheme 1. Preparation of Pd_{np}-*Dps-Te*.



K_2PdCl_4 (100mM) was used as the silver ion source, while $NaBH_4$ (30mM) was used as the reducing agent. A *Dps-Te* solution (0.15 M NaCl) was brought to pH 8.5 using 30 mM NaOH (TITRINO, Metrohm AG) and 90 eq. of palladium ions per *Dps-Te*

molecule were added to the protein solution (1 mg/ml) under stirring at room temperature. After 30 min, $NaBH_4$ (2 eq. per Pd) was added to reduce the silver ions and the resulting solution was stirred for over 15 min. According to the reduction, the solution spectrum has been changed significantly; there is a broad intense absorption at a longer wavelength (Figure 2a). A similar spectroscopic change was observed for the reduction of Pd (II) ions in dendrimers.[21] Under the same conditions, black precipitates were observed in a protein-free control experiment, whereas the solution containing *Dps-Te* remained a clear brown solution. These results suggest the formation of Pd clusters inside and outside the protein cavities.

Finally, the Pd$_{np}$-*Dps-Te* composite was isolated by size-exclusion chromatography (Supherose 6 gel-filtration column, GE Healthcare). The product elution was monitored either at 280 nm (protein) or at 400 nm (zero-valent Pd cluster),and the co-elution of the protein and metallic components through the column is the clear indication of the composite nature of the material (Figure 2c).

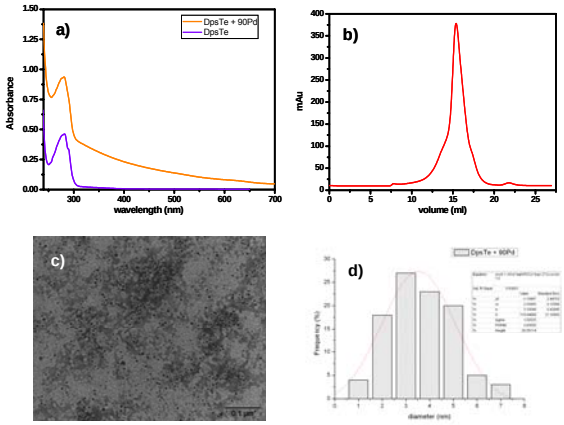


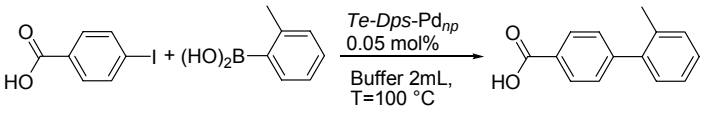
Figure 2. a) UV-Vis spectra of *Te-Dps* and *Te-Dps*-Pd$_{np}$,
b) Gel-filtration chromatogram c) TEM image of Te-Dps-Pd$_{np}$,
d) Particle size distribution histogram of *Te-Dps*-Pd$_{np}$
(Diameter: 3.5 ± 0.5 nm).

The composite materials in aqueous solution were examined by transmission electron microscopy (TEM). The TEM images clearly show that the metal clusters are almost monodispersed particles, and their shape is roughly spherical (Figure 2d). The diameter of the metal particles of Pd$_{np}$-*Dps-Te* is 3.5± 0.6 nm.

The catalytic properties of water-soluble palladium nanoparticles *Te-DPS*-Pd$_{np}$ with a palladium loading of 0.05 mol% was initially evaluated in the Suzuki-Miyaura cross-coupling reaction of *p*-idodo-benzoic acid and o-tolyl boronic acid using

$NaHCO_3$/NaOH buffer at pH = 10 at 80 °C for 18h. Under these conditions, the coupling product was isolated in 50% yield.

Scheme 1.



Encouraged by this result, we explored the role of various buffers on the reaction outcome. Some results of our optimization studies are summarized in Table 1, Tris (pH=8.9, 100mM) and CAPS (pH=10.5, 100 mM) were found to be superior to $NaHCO_3$/NaOH (pH=10) and CAPS (pH=11, 100 mM) (Table 1, compare entries 1 and 3 with entries 2 and 4).

Table 1. The influence of buffers on Suzuki-Miyaura cross-coupling reaction catalyzed by *Te-Dps*-Pd_{np}.

Entry	Buffer	pH	T [°C]	t[h]	Yield% [a]
1	Tris	8.9	100	24	88
2	$NaHCO_3$/NaOH	10	100	24	50
3	CAPS	10.5	100	24	78
4	CAPS	11	100	24	47

[a] Reactions were carried out using 0.25 mmol of 4-iodo benzoic acid, 0.25 mmol of o-tolyl boronic acid, 2 mL of buffer at 100 °C in the presence of 0.05 mol % of *Te-Dps*-Pd_{np}. [b] Yields are given for isolated products.

The reaction was also performed using a palladium loading down to 0.001 mol% for 48 h at 100 °C. The turn-over number (TON) was 22250. The synthetic scope of the reaction was investigated using a variety of aryl iodides and bromides, and a wide range of aryl boronic acids under the optimized conditions (Table 2). Electron-rich and electron-poor aryl iodides gave the corresponding cross-coupling products in excellent yields (Entries 1-6 and 9-10, Table 2). Aryl bromides containing electron-withdrawing substituents afforded good results with deactivated aryl-boronic acids (Entry 7, Table 2) whereas disappointing results were obtained with neutral aryl-boronic acids.

Scheme 2.

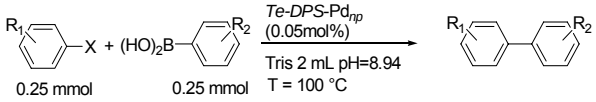


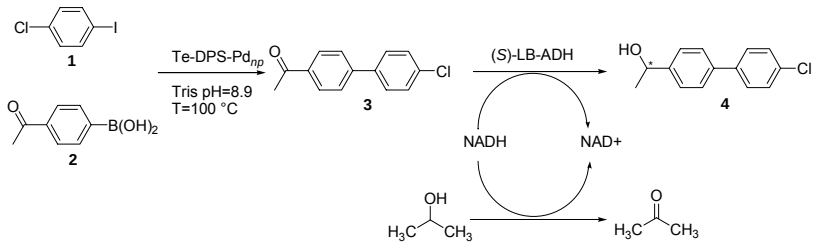
Table 2. Reaction of Aryl halides with different boronic acids with 0.05 mol% catalyst loading of *Te-Dps*-Pd_{np}.

Entry	R_1	X	R_2	t(h)	Yield%[a, b]
1	*p*-OCH_3	I	*p*-CF_3	48	87 (**80**)
2	*p*-CN	I	*o*-CH_3	24	77
3	*m*-CF_3	I	*p*-CH_3	24	80
4	*p*-COOH	I	*o*-Br	24	70
5	*p*-COOH	I	*p*-OCH_3	24	92
6	*p*-COOH	I	*p*-Cl	24	83
7	*p*-COOH	Br	*p*-OCH_3	48	71
8	*p*-Cl	I	*p*-$COCH_3$	24	89
9	*p*-OCH_3	I	*o*-CH_3	24	65

[a] Reactions were carried out using 0.25 mmol of aryl halides, 0.25 mmol of boronic acid, 2 mL of Tris (pH=8.9, 100 mM) at 100 °C in the presence of 0.05 mol % of *Te-Dps*-Pd_{np}. [b] Yields are given for isolated products.

Then focused our attention on the development of a one-pot process. One-pot processes are an attractive synthetic concept for the improvement of overall process efficiency through a decrease in the required number of workup and purification steps. By avoiding such time-, effort-, and solvent- intensive steps, multisteps one-pot syntheses contribute to a significantly improved process economy as well as to more sustainable synthetic routes.[22] Herein, we report an example of a one-pot process in which a palladium-catalyzed cross-coupling is followed by an asymmetric enzymatic reduction.[23]

Scheme 3.



The prerequisites for an enzyme-compatible Suzuki cross-coupling reaction are:

a) no phosphane additive has to be used;

b) no excess of the boronic acid has to be used;

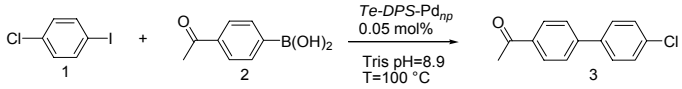
c) conversion must be quantitative with complete consumption of the boronic acid;

d) water must be used as the reaction medium.

We developed such a Suzuki cross-coupling for the synthesis of compound **3**. In the presence of *Te-Dps*-Pd_{np} with a loading down to 0.1 mol% and one equivalent of **2,**

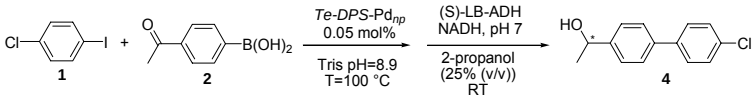
using Tris (pH=8.9, 100 mM) as base, the reaction proceeded successfully in water to give **3** with a conversion greater than 90% (Scheme 4.)

Scheme 4.



We were pleased to find that the resulting reaction mixture was compatible with a subsequent reduction catalyzed by (*S*)-LB-ADH, an alcohol dehydrogenase from Lactobacillus brevis.

Scheme 5.



When this Suzuki cross-coupling was followed by an enzymatic reduction (after adjustment of the pH value to pH 7) with substrate-coupled cofactor regeneration with 2-propanol, the desired biaryl-substituted alcohol (*S*)-4 was formed in 50 % yield.
Further studies for the optimization of the process are currently underway.

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7 Materials and Method.

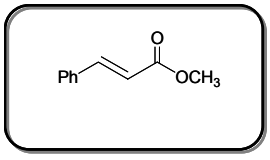
General Information.

Melting points were determined with a Büchi B-545 apparatus and are uncorrected. All of the reagents and solvents are commercially available and were used as purchased, without further purification. Compounds were purified on axially compressed columns, packed with SiO_2 25-40 μm (Macherey Nagel), connected to a Gilson solvent delivery system and to a Gilson refractive index detector, and eluting with *n*-hexane/AcOEt mixtures. ^{1}H NMR (400.13 MHz) and ^{13}C NMR (100.6 MHz) spectra were recorded with a Bruker Avance 400 spectrometer. Infrared (IR) spectra were recorded on a JASCO FT/IR-430 spectrophotometer. Mass spectra were determined with a QP2010 Gas Chromatograph Mass spectrometer (EI ion source). Determination of Pd at mass 105 was performed by means of a sector field inductively coupled plasma mass spectrometry technique (SF-ICP-MS, Thermo-Fischer, Bremen, Germany) in medium resolution ($m/\Delta m$=3000) to avoid that interferent signals coming from molecular species, *i.e.*, $^{40}Ar^{65}Cu$, could overlap the signal of Pd at the chosen mass and overestimate the actual Pd value. Quantification of Pd was carried out through the external calibration curve. Rhodium (Rh), selected at mass 103, was used as internal standard to keep under control the instrumental drift. Single element calibrant and internal standard were prepared from 1000 mg/mL stock solutions of Pd in 10% HNO_3 and Rh in 10% HCl (High-Purity Standards, Charleston, USA) by dilution with high purity deionized water. Trasmission electron microscopy (TEM) analyses were performed in the "Servei de Microscòpia" of the Universitat Autònoma de Barcelona, in a JEOL JEM-2010 model at 200 kV. The TEM measurements were made by sonication of the nanoparticulate material in perfluorooctyl bromide for several minutes; then, one drop of the finely divided suspension was placed on a specially produced structure less carbon support film having a thickness of 4-6 nm and dried before observation.

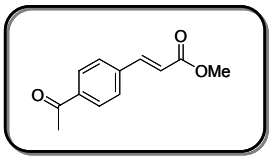
Preparation of phosphine-free perfluoro-tagged palladium nanoparticles Pd_{np}-**A**: A mixture of $PdCl_2$ (0.060 g, 0.34 mmol), NaCl (0.022 g, 0.38 mmol) and 2 mL of MeOH was stirred at room temperature for 24 h. The mixture was filtered through a glass wool plug. Additional MeOH (28 mL) was added to the filtrate. The solution was heated at 60 ºC under stirring and 2,4,6-tris(1H,1H,2H,2H-perfluorodecylthio)-1,3,5-triazine (0.250 g, 0.16 mmol) was added. Then, the mixture was heated under stirring during 24 h. AcONa (0.190 g, 2.32 mmol) was added and stirring was maintained at room temperature for 1 h. The formed black solid was filtered, washed with MeOH, H_2O and Me_2CO; it was then dried to afford 0.270 g of Pd_{np}-**A** as a black solid. The size of the nanoparticles was 2.3 ± 0.7 nm, as determined by transmission electron microscopy. Pd analysis (ICP): 13.4 %.

Preparation of Pd_{np}-**A** /**FSG**: 0.020 g of Pd- **A** were added to 10 mL of perfluorooctane and the mixture was heated at 100 °C for 14 h. Then, 1 g of FSG (C8; 35-70 μm) was added and the mixture was stirred at the same temperature for 1 h. After this time , the solvent was evaporated under vacuum to obtain the desired catalyst system.

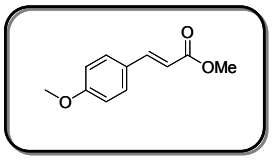
Typical procedure for the preparation of methylcinnamate esters using 0.1 mol% of Pd_{np}-**A** /FSG: *p*-acetil iodobenzene (246.05 mg, 1 mmol), Pd_{np}-**A** /FSG (40 mg), Et_3N (303 mg, 3 mmol) and methyl acrylate (172 mg, 2 mmol.) in MeCN (2 mL) were orbitally stirred for 24 h at 100 °C with a Heidolph Synthesis System for 5 h. Then, after cooling, the reaction mixture was centrifuged. The liquid phase was decanted, diluted with AcOEt, washed with deionized water and dried over Na_2SO_4. The solvent was removed under vacuum and the residue was purified by chromatography (SiO_2, 35 g, *n*-Hexane/AcOEt 96/4 v/v) to give 182 mg (89% yield) of:



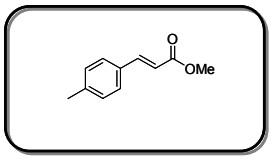
m.p.: 105-106 °C; IR (KBr) 2919, 1710, 1681, 1639 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.99-7.97 (d, *J* = 3.18 Hz, 2 H), 7.74-7.70 (d, *J* = 16 Hz, 1 H), 7.63-7.61 (d, *J* = 8.2 Hz, 2 H), 6.56-6.52 (d, *J* =16 Hz, 1 H), 3.84 (s, 3 H), 2.63 (s, 2 H); ^{13}C NMR ($CDCl_3$) δ 197.2, 166.8, 143.2, 138.6, 138.0, 128.8, 128.1, 120.3, 51.8, 26.6; MS *m/z* (relative intensity) 204 (M+, 34), 189 (100), 161 (15), 102 (12); Anal calcd for $C_{12}H_{12}O_4$ C, 65.45; H, 5.49; found C, 65.39; H, 5.43. (Known compound, see: C. Rocaboy, J. A Gladysz, *Org. Lett.* **2002**, *4*, 1993).



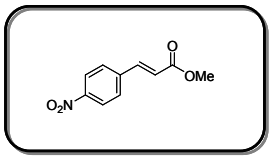
mp: 36.1-37.1 °C; IR (KBr) 2361, 1718, 1637 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.73-7.69 (d, *J* = 15.9 Hz, 1 H), 7.53-7.38 (m, 4 H), 6.47-6.43 (d, *J* = 15.9 Hz, 1 H), 3.81 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 167.4, 144.8, 134.4, 130.3, 128.9, 128.1, 117.8, 51.6, MS m/z (relative intensity) 162 (M+, 47), 131 (100), 103 (83), 77 (68). Anal Calcd for $C_{10}H_{10}O_2$ C, 74.06; H, 6.21; found C, 74.12; H, 6.27. (Known compound, see: S. Crosignani, P. D. White, B. Linclau, *Org. Lett.* **2002**, *4*, 1035).



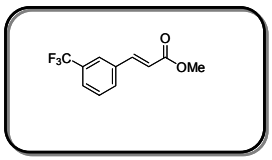
mp: 90-91°C; IR (KBr) 2947, 2843, 1717, 1637, 1603, 1256 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.67- 7.63 (d, *J* =15.9 Hz, 1 H); 7.49-7.46 (d, *J* =8.7 Hz, 2 H), 6.91-6.89 (d, *J* =8.7 Hz, 2 H), 6.3-6.2 (d, *J* = 15.9 Hz, 1 H), 3.84 (s, 3H), 3.7 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 167.8, 161.4, 144.5, 129.7, 127.2, 115.3, 114.4, 55.43, 51.64; MS m/z (relative intensity) 192 (M+, 65), 161 (100), 133 (41), 89 (30); Anal calcd for $C_{11}H_{12}O_3$ C, 68.74; H, 6.29; found C, 68.68; H, 6.22. (Known compound, see: M. B. Andrus, C. Song, J. Zhang, *Org. Lett.* **2002**, *4*, 2079).



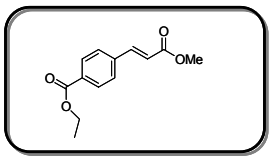
mp: 56.5-57.4 °C; IR (KBr) 2922, 1709, 1631, 1168 cm^{-1}; ^{1}H NMR ($CDCl_3$); 7.7-7.6 (d, *J* = 16Hz, 1 H), 7.45-7.43 (d, *J* =8.1 Hz, 2 H), 7.22-7.20 (d, *J* = 7.9 Hz, 2 H), 6.4-6.3 (d, *J* = 16 Hz, 1 H), 3.8 (s, 3 H), 2.3 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 167.5, 144.8, 140.6, 131.6, 129.5, 128.0, 116.6, 51.57, 21.40; MS m/z (relative intensity) 176 (M+, 51), 145 (100), 115 (62), 91 (32); Anal calcd for $C_{11}H_{12}O_2$ C, 74.98; H, 6.86; found C, 74.89; H, 6.80. (Known compound, see: M. B. Andrus, C. Song, J. Zhang, *Org. Lett.* **2002**, *4*, 2079).



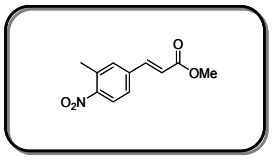
mp: 132-3 °C; IR (KBr) 3039, 2958, 1721, 1637, 1512 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.26-8.24 (d, *J*= 8.8 Hz, 2 H), 7.7-7.7 (d, , *J* = 16.3 Hz, 1 H), 7.69-7.66 (m, 2H), 6.6-6.5 (d, *J* = 16.2 Hz, 1 H), 3.8 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 166.4, 148.5, 141.9, 140.5, 128.6, 124.2, 122.1, 52.1; MS m/z (relative intensity) 207 (M+, 46), 176 (100), 130 (51), 102 (72); Anal calcd for $C_{10}H_9NO_4$ C, 57.97;H, 4.38; N, 6.76; found C, 57.89; H, 4.30; N, 6.71. (Known compound, see: M. B. Andrus, C. Song, J. Zhang, *Org. Lett.* **2002**, *4*, 2079).



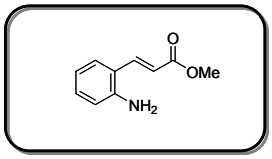
mp: 49.2-50.2 °C; IR (KBr) 3075, 3035, 1726, 1528 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.75 (m, 3 H), 7.63 (d, *J* =7.7 Hz, 1 H) 7.52-7.48 (t, 1 H), 6.52 (d, *J* =15.9 Hz, 1 H), 3.82 (s, 3 H); ^{13}C NMR (CDCl3) δ 166.84, 142.9, 135.2, 131.6, 131.3, 131.0, 129.4, 126.6, 124.6, 124.5, 119.8, 51.8; MS m/z (relative intensity) 230 (M+, 41), 199 (100), 171 (40), 151 (69); Anal calcd for $C_{11}H_9F_3O_2$ C, 57.40; H, 3.94; found C, 57.31; H, 3.90. (Known compound, see: Z. Xiong, N. Wang, M Dai, A. Li, J. Chen, Z. Yang, *Org. Lett.* **2004**, *6*, 3337).



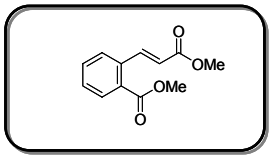
mp: 59.3-60.4 °C; IR (KBr) 2988, 1718, 1637, 1437, 1279 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.06-9.04 (d, *J* = 8.32 Hz, 2 H), 7.72-7.68 (d, *J* = 16 Hz, 1 H), 7.58-7.56 (d, *J* = 8.3 Hz, 2 H), 6.53-6.49 (d, *J* =16 Hz, 1 H), 4.41-4.36(q, 2 H), 3.81 (s, 3 H), 1.40 (t, 3 H); ^{13}C NMR ($CDCl_3$) δ 166.9, 165.9, 143.5, 138.4, 131.7, 130.1, 127.8, 120.1, 61.2, 51.8, 14.3; MS m/z (relative intensity) 234 (M+, 49), 189 (100), 131 (34), 102 (19); Anal calcd for $C_{13}H_{14}O_4$ C, 66.66; H, 6.02; found C, 66.58; H, 5.95.



mp: 108.3-109.4 °C; IR (KBr) 2958, 1716, 1643, 1337 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.11-8.10 (s, 1 H), 7.68-7.64 (m, 2 H), 7.38-7.36 (d, *J* = 7.9 Hz, 1 H), 6.51-6.47 (d, *J* = 16 Hz, 1 H), 3.82 (s, 3 H), 2.62 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 166.7, 149.5, 141.9, 135.3, 133.7, 133.4, 131.7, 123.8, 119.9, 51.97, 20.46; MS m/z (relative intensity) 221 (M+, 30), 204 (67), 144 (34), 115 (100); Anal calcd for $C_{11}H_{11}NO_4$ C, 59.73; H, 5.01; N, 6.33; found C, 59.65; H, 4.97; N, 6.30.



mp: 67.5-68.6 °C; IR (KBr) 3414, 3353, 2953, 1700, 1622 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.86-7.82 (d, *J* = 15.8 Hz, 1 H), 7.39-7.37 (d, *J* = 9.1 Hz, 2 H), 7.19-7.15 (m, 1 H), 6.78-6.69 (m, 2 H), 6.38-6.34 (d, *J* = 15.8 Hz, 1 H), 4.01 (s, 2 H), 3.8 (s, 3 H); ^{13}C NMR (CDCl3) δ 167.7, 145.6, 140.3,S4 131.3, 128.1, 119.8, 118.9, 117.6, 116.7, 51.68; MS m/z (relative intensity) 177 (M+, 43), 146 (99), 118 (100), 90 (50); Anal calcd for $C_{10}H_{11}NO_2$ C, 67.78; H, 6.26; N, 7.9; O, 18.06; found C, 67.79; H, 6.27; N, 7.9; O, 18.08. (Known compound, see: D. C. Dibakar, P. Maunita, *J. Chem. Res.* **2006**, *2*, 102).

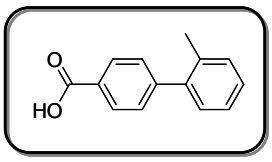


mp: 91.2-92.2 °C; IR (KBr) 2988, 1718, 1637, 1437cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.39-8.35 (d, *J* = 15.9 Hz, 1 H), 7.86-7.84 (d, *J* = 7.8 Hz, 1 H), 7.5-7-3 (m, 3 H), 6.23-6.19 (d, *J* = 15.9 Hz, 1 H), 3.82 (s, 3 H), 3.71 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 166.9, 166.8, 143.7, 136.2, 132.3, 130.7, 129.6, 129.3,127.8, 120.5, 52.26, 51.64; MS m/z (relative intensity) 220 (M+, 46), 189 (100), 131 (34), 102 (19); Anal calcd for $C_{12}H_{12}O_4$ C, 65.45; H, 5.49; O, 29.06; found C, 65.46; H, 5.50; O, 29.08. (Known compound, see: S. Karthikeyan, V. Ramamurthy, *J. Org. Chem.*. **2007**, *72*, 452).

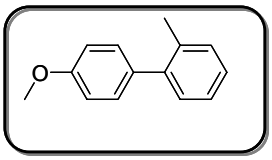
Typical procedure for the preparation of Suzuki cross-coupling product using 0.1 mol% of Pd_{np}-**A** /FSG **or** Pd_{np}-**B**.

4-iodobenzoic acid (248 mg, 1 mmol), Pd_{np}-**A** /FSG (40 mg) or Pd_{np}-**B** (3 mg), K_2CO_3 (276 mg, 2 mmol) and KF (116.2, 2mmol) and o-tolylboronic acid (136 mg, 1 mmol.)

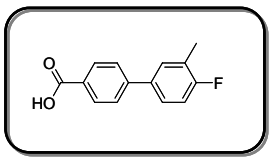
in water (2 mL) were orbitally stirred for 5 h (for Pd_{np}-**A** /FSG) or 1h (for Pd_{np}-**B**) at 100 °C with a Heidolph Synthesis System for 5 h. Then, after cooling, the reaction mixture was centrifuged. The liquid phase was decanted, diluted with AcOEt, washed with deionized water and dried over Na_2SO_4. The solvent was removed under vacuum and the residue was purified by chromatography (SiO_2, 35 g, *n*-Hexane/AcOEt 96/4 v/v) to give 210 mg (99% yield) of:



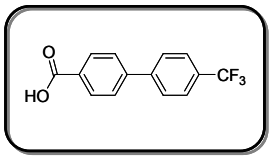
mp: 187.5-188.8 °C; IR (KBr) 2949, 2905, 1673, 1608, 1427, 1321, 1291 cm^{-1}; ^1H NMR (DMSO) δ 8.02–7.99 (d, *J* = 8.6Hz, 2H), (H), 7.44-7.43(d, *J* = 8Hz, 2 H), 7.33-7.21(m, 4 H), 2.24(s, 3H); ^{13}CNMR(DMSO) δ 167.7, 146.24, 140.84, 135.17, 130.99, 129.86, 129.75, 129.73, 128.35, 126.56, 20.58. Anal Calcd for $C_{14}H_{12}O_{22}$ C, 79.22; H,5.70; found C, 79.20; H,5.68.



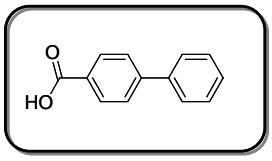
mp: 97.8-98.6 °C; IR (KBr) 2923, 2853, 1607, 1586, 1500, 1287, 1245, 806 cm^{-1}; ^1H NMR($CDCl_3$) δ = 7.25-7.21 (m, 6H), 6.95 (d, *J* = 8.8 Hz, 2H), 3.85 (s, 3H), 2.27 (s, 3H); ^{13}C NMR (DMSO) δ = 158.5, 141.5, 135.5, 134.4, 130.3, 130.2, 129.9, 126.9, 125.7, 113.5, 55.3, 20.5 ,. Anal Calcd for; found. $C_{14}H_{14}O$ C, 84.81; H, 7.12; found C, 84.75; H, 7.07.



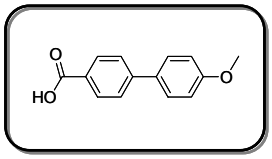
mp: 235.0-235.4 °C; IR (KBr) 2925, 1685, 1605, 1560, 1356, 1322, 1262 cm^{-1}; ^1H NMR (DMSO) δ 12.9 (s, 1H), 8.0-7.9 (d, *J* = 8 Hz, 2H), 7.77-7.75 (d, *J* = 8 Hz, 2H),7.68-7.66 (d, *J* = 8 Hz, 2H), 7.57 (s, 1H), 7.25 (t, 1H); ^{13}C NMR (DMSO) δ 167.62, 143.90, 135.65, 130.83, 130.42, 130.01, 127.17, 126.73, 125.34, 116.12, 115.90, 14.74,. Anal Calcd for $C_{14}H_{11}FO_2$ C, 73.03, H, 4.82; found C, 73.05, H, 4.83.



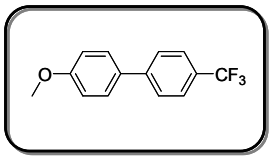
mp: 120.0-121.1 °C; IR (KBr) 2846, 2673, 2551, 1689, 1609, 1500, 1428, 1398, 1125 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 8.07–8.05 (d, J =8 Hz, 2H), 7.93-7.91 (d, J = 8Hz, 2H), 7.84-7.80 (m, 4 H); ^{13}C NMR (DMSO-d_6)δ 167.5, 143.5, 143.1, 131.1, 130.5, 128.3, 127.7, 126.4, 126.4. Anal Calcd for $C_{14}H_9F_3O_2$ C, 63.16; H, 3.41; found C, 63.17; H, 3.42.



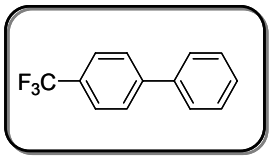
mp: 218.0-219.4 °C; IR (KBr) 2949, 2668, 2548, 1680, 1607, 1422, 1318, 1288 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 12.9 (s, 1H), 8.04-8.02 (d, J = 8 Hz, 2H), 7.81-7.79 (d, J = 8 Hz, 2H), 7.74-7.72 (d, J = 8 Hz, 2H), 7.75-7.48 (t, 2 H), 7.44-7.42 (d, J = 8 Hz, 2H); ^{13}C NMR (DMSO-d_6) δ 167.5, 144.7, 139.5, 130.4, 130.0, 129.5, 128.7, 127.4, 127.2,. Anal Calcd for $C_{13}H_{10}O_2$ C, 78.77; H, 5.09 found C, 78.78; H, 5.10.



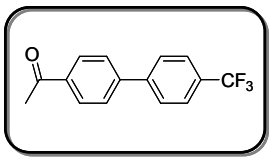
mp: 250.0-251.7 °C; IR (KBr) 2953, 2834, 2547, 1678, 1601, 1430, 1313, 1289 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 8.00–7.98 (d, J = 7.73 Hz, 2H), 7.76-7.68 (m, 4H), 7.07-7.05 (d, J = 6.4 Hz, 2H), 3.81 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 167.7, 160.07, 144.46, 131.76, 130.46, 129.37, 128.64, 126.62, 115.02, 55.73. Anal Calcd for $C_{14}H_{12}O_3$ C, 73.67; H,5.30; found C, 73.65; H,5.28.



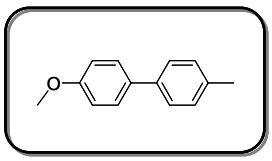
mp: 73.5-73.6 °C; IR (KBr) 2923, 2853, 1607, 1586, 1500, 1287, 1245, 806 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.68 (s, 4H), 7.58-7.56 (d, J = 8 Hz, 2 H), 7.04-7.01 (d, J = 8 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 159.9, 144.35, 132.2, 128.4, 126.9, 125.77, 125.73, 125.7, 125.6, 123.1, 114.5, 55.4. Anal Calcd for $C_{14}H_{11}F_3O$ C, 66.6; H, 4.4; found C, 66.7; H, 4.5.



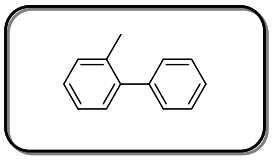
mp: 65.5-66.8 °C; IR (KBr) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.72 (s, 4 H), 7.64-7.62 (d, *J* = 8 Hz, 2H), 7.52-7.48 (t, J_1= 8 Hz, J_2= 4 Hz, 2 H); 7.45-7.43 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 129.0, 128.2, 127.4, 127.3, 125.7. Anal Calcd for $C_{13}H_9F_3$ C, 70.27; H, 4.08 found C, 70.28; H, 4.09.



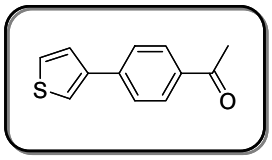
mp: 120.6-121.4 °C; IR (KBr) 1685, 1605, 1396, 1356, 1322, 823 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.09-8.07 (d, *J* = 8 Hz 2 H), 7.75-7.70 (m, 6H), 2.67 (s, 3H); ^{13}C NMR ($CDCl_3$) δ197.6, 144.2, 143.4, 136.6, 129.1, 127.6, 127.5, 125.9, 26.73. Anal Calcd for $C_{15}H_{11}F_3O$ C, 68.19; H, 4.20 found. C, 68.20; H, 4.21.



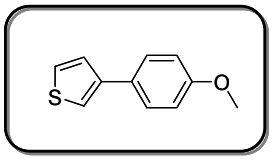
Oil; IR (KBr) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.57–7.55 (d, *J* = 8 Hz, 2 H), 7.51-7.49 (d, *J* = 8 Hz, 2 H), 7.28-7.26 (d, *J* = 8 Hz, 2 H), 7.02-7.00 (d, *J* = 8 Hz, 2 H), 3.88 (s, 3 H), 2.43 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 159.0, 138.0, 136.4, 133.83, 129.5, 128.0, 126.6, 114.2, 55.4, 21.1. MS *m/z* (relative intensity) ; Anal Calcd for $C_{14}H_{14}O$ C, 84.8; H, 7.12; found C, 84.9; H, 7.13.



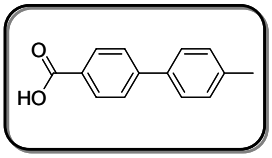
Oil; IR (neat) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.51–7.48 (m, 2 H), 7.44-7.40 (m, 3 H), 7.35-7.32 (m, 4 H), 2.36 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 142.1, 135.4, 130.4, 129.9,129.3, 128.2, 127.3, 126.9, 125.9, 29.8, 20.6; Anal Calcd for $C_{13}H_{12}$ C, 92.81; H, 7.19; found C, 92.87; H, 7.23.



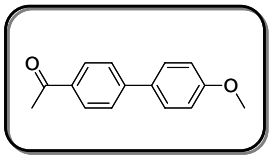
mp: 151.7-152.2 °C; IR (KBr) 3099, 1674, 1600, 1273, 785 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.01–7.99 (d, *J* = 8 Hz, 2 H), 7.71-7.69 (d, *J* = 8 Hz, 2 H), 7.60-7.59 (m, 1 H), 7.46-7.43 (m, 2 H), 2.60 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 197.6, 141.1, 140.2, 135.7, 129.1, 126.8, 126.4, 126.2, 122.1, 26.6; Anal Calcd for $C_{12}H_{10}OS$ C, 71.25; H, 4.98; found C, 71.20; H, 4.92.



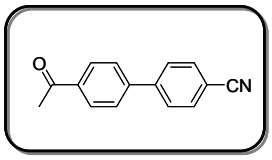
mp: 126.2-127.4 °C; IR (KBr) 3097, 1606, 1535, 1502, 1245, 781 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.58–7.56 (d, *J* = 8 Hz, 2 H), 7.41-7.39 (m, 3 H), 6.98-6.96 (d, , *J* = 8 Hz, 2 H), 3.87 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 158.9, 142.1, 128.8, 127.6, 126.3, 126.1, 118.9, 114.3, 55.39; Anal Calcd for $C_{11}H_{10}OS$ C, 69.44; H, 5.30; found C, 69.50; H, 5.35.



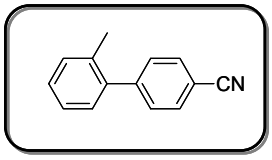
Oil; IR (neat) 2949, 2668, 2548, 1680; ^1H NMR (DMSO-d_6) δ 8.00–7.98 (d, *J* = 7.73 Hz, 2H), 7.76-7.68 (m, 4H), 7.07-7.05 (d, *J* = 6.4 Hz, 2H), 2.36 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 167.7, 160.07, 144.46, 131.76, 130.46, 129.37, 128.64, 126.62, 115.02, 20.58; Anal Calcd for $C_{14}H_{12}O_2$ C, 79.22; H, 5.70; found C, 79.17; H, 5.66.



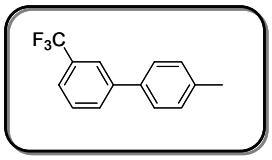
mp: 153.3-154.5 °C; IR (KBr) 1673, 1600, 1294, 1818 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.03–8.01 (d, *J* = 8 Hz, 2 H), 7.67-7.65 (d, *J* = 8 Hz, 2 H), 7.61-7.58 (d, , *J* = 8 Hz, 2 H), 7.03-7.01 (d, *J* = 8 Hz 2H), 3.88 (s, 3H), 2.64 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 197.7, 159.9,145.4, 135.4, 132.3, 129.0, 128.4, 126.6, 114.4, 55.4, 26.6 ; Anal Calcd for $C_{11}H_{10}OS$ C, 69.44; H, 5.30; found C, 69.50; H, 5.35.



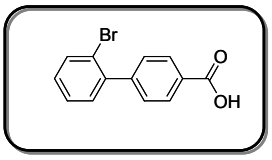
mp: 117.2-118.4 °C; IR (KBr) 2227, 1685, 1604, 1523, 1268 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.10–8.08 (d, *J* = 8 Hz, 2 H), 7.80-7.70 (m, 6 H), 2.67 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 197.5, 144.3,143.5, 136.9, 132.8, 129.2, 127.9, 127.5, 118.6, 111.9, 26.7 ; Anal Calcd for $C_{15}H_{11}NO$ C, 81.43; H, 5.01; found C, 81.49; H, 5.07.



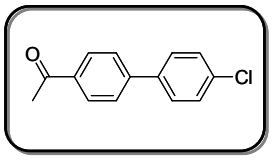
Oil; IR (neat) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.74–7.72 (d, *J* = 8 Hz, 2 H), 7.47-7.45 (d, *J* = 8 Hz, 2 H), 7.34-7.28 (m, 3H), 2.28 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 140.7, 137.2, 133.6, 132.7, 129.5, 128.6, 127.8, 127.6, 126.3, 115.7, 111.5, 21.7, Anal Calcd for $C_{14}H_{11}N$ C, 87.01; H, 5.74; found C, 86.96; H, 5.01.



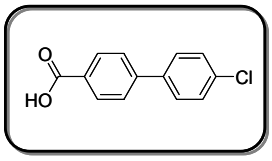
Oil; IR (neat) 3030, 2925, 1901, 1611, 1484, 1438, 1330, 1258 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.83 (s, 1H), 7.79-7.74 (m, 1 H), 7.62-7.48 (m, 4H), 7.29 (d, *J* = 7.9 Hz, 2 H), 2.42 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 141.9, 137.9, 131.1 (d, *J* = 32.1 Hz), 130.2, 129.7, 129.2, 127.0, 124.2 (d, *J* = 272.0 Hz), 123.6 (q, *J* = 4.1 Hz), 21.1; Anal Calcd for $C_{14}H_{11}F_3$ C, 71.18; H, 4.69; found C, 71.12; H, 4.63.



Oil; IR (neat) 3349, 3054, 2360, 1683, 1265 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.05–8.03 (d, *J* = 8 Hz, 2 H), 7.71-7.69 (d, *J* = 8 Hz, 1 H),7.54-7.52 (d, *J* = 8 Hz, 2 H), 7.42-7.38 (m, 1 H), 7.34-7.32 (m, 1 H), 7.28-7.24 (m, 1 H) 2.67 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 197.7, 145.8, 141.5, 136.2, 133.3, 131.1, 129.8, 129.4, 128.1, 127.6, 122.3, 26.7 ; Ana l Calcd for $C_{14}H_{11}BrO$ C, 61.11; H, 4.03; found C, 61.05; H, 3.98.



mp: 97.9-98.4 °C; IR (KBr) 2923, 2360, 2341, 1673, 815 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.06–8.04 (d, *J* = 8 Hz, 2 H), 7.68-7.66 (d, *J* = 8 Hz, 2 H), 7.59-7.57 (d, *J* = 8 Hz, 2 H), 7.47-7.45 (d, *J* = 8 Hz, 2 H) 2.66 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 197.8, 141.2, 136.6, 135.1, 134.2, 129.4, 127.6, 29.3. Anal Calcd for $C_{14}H_{11}ClO$ C, 72.89; H, 4.81; found C, 72.85; H, 4.78.



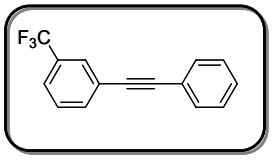
mp: 250.6-251.8 °C; IR (KBr) 2949, 2668, 2548, 1680 cm^{-1}; ^1H NMR (DMSO-d_6) δ 8.03–8.01 (d, *J* = 8 Hz, 2 H), 7.81-7.75 (m, 4 H), 7.56-7.54 (d, *J* = 8 Hz, 2 H); ^{13}C NMR (DMSO-d_6) δ 169.3, 141.6, 133.7, 132.8, 130.8, 129.4, 128.8, 127.2. Anal. Calcd. for $C_{13}H_9ClO_2$ C, 67.11; H, 3.90; found C, 67.06; H, 3.084.

Preparation of Pd_{np}-B: A 5 mL round-bottom flask was charged with $PdCl_2$ (17.0 mg, 96 μmol) and NaCl (6.6 mg, 113 μmol). MeOH (1 mL) was added and the mixture was left stirring at room temperature for 24 h; the mixture was then filtered through a plug of glass wool and the filtrate diluted with additional 9 mL of MeOH. Material **B** (199.9 mg) was added to the flask, and the resulting mixture was heated to 60 °C for 24 h. At the end of this period, NaOAc (56.0 mg, 0.68 mmol) was added, the mixture was removed from the oil bath and was allowed to cool for 90 min. The precipitate was separated by centrifugation, and was washed successively with MeOH, water and acetone, giving the product as a black solid. Yield: 226.3 mg. Palladium content: 3.47 %. Average particle diameter: 3.2 ± 0.4 nm (based on TEM; measurement of 260 particles).

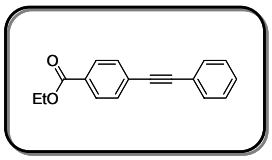
Typical procedure for alkynylation of aryl halides using 0.1 mol% of Pd_{np}**-A /**FSG or **Pd_{np}-B:**

3-(trifluoromethyl)iodobenzene (272 mg, 1 mmol), Pd_{np}-**A /**FSG (40 mg) or Pd_{np}-**B** (3mg), pyrrolidine (142 mg, 2 mmol) and phenyl acetylene (102 mg, 1 mmol.) in Water (2 mL) were orbitally stirred for 3 h at 100 °C with a Heidolph Synthesis System. Then, after cooling, the reaction mixture was centrifuged. The liquid phase was decanted,

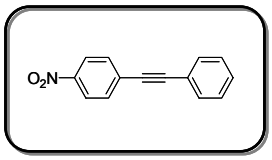
diluted with AcOEt, washed with deionized water and dried over Na_2SO_4. The solvent was removed under vacuum and the residue was purified by chromatography (SiO_2, 35 g, *n*-hexane/AcOEt 96/4 v/v) to give 233.7 mg (95% yield) of :



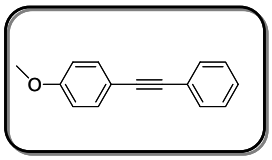
m.p.: 40.1-41.4 °C; IR (KBr) 2925, 1606, 1340, 1168, 1132, 1070 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.84 (s, 1 H), 7.74–7.72 (d, *J* =8 Hz, 1 H), 7.62-7.59 (t, 3 H), 7.52-7.50 (t, 1 H), 7.41,7.40 (t, 3 H); $^{13}CNMR$ ($CDCl_3$) δ 134.7, 131.8, 131.2, 130.9, 128.9, 128.8, 128.5, 128.4, 128.4, 125.2,124.8, 124.8, 124.3, 122.7, 122.5, 90.9, 87.8, 1.1, MS m/z (relative intensity) 246 (M^+,100), 225 (8), 196 (6), 176 (10), 150 (5). Anal Calcd for $C_{15}H_9F_3$ C, 73.17; H, 3.68; found C, 73.11; H, 3.62. (Know compound, see: W.-B. Yi, et al., *Eur. J. Org. Chem*. **2007**, 3445).



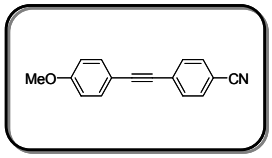
mp: 72.0-73.1 °C; IR (KBr) 1714, 1604, 1263, 1097, 756 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.06–8.04 (d, *J* = 8 Hz, 2 H), 7.62-7.56 (m, 3 H), 7.37-7.28 (m, 3 H), 4.43-4.37 (q, 2 H), 1.44-1.38 (t, 3 H); ^{13}C NMR ($CDCl_3$) δ 166.1, 131.8, 131.5, 129.9, 129.5, 128.8, 128.5, 127.9, 122.8, 92.3, 88.8, 61.2, 14.4, MS m/z (relative intensity) 250 (M^+, 96), 222 (6), 204 (100), 176 (24), 151 (31), 88 (30). Anal Calcd for $C_{17}H_{14}O_2$, C, 81.58; H, 5.64; found C, 81.52; H; 5.58. (Known compound, see: R. Soler, et al., *Synthesis*, **2007**, *19*, 3068).



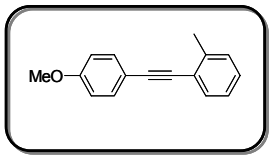
mp: 118.1-119.2 °C; IR (KBr) 2215, 1590, 1509, 1346, 858 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.24–8.22 (d, *J* = 8 Hz, 2 H), 7.69-7.67 (d, *J* = 8Hz, 2 H), 7.60-7.57 (m, 2 H), 7.42-7.39 (m,3 H); $^{13}CNMR(CDCl_3)$ δ 147.0, 132.3, 131.9, 130.3, 129.3, 128.6, 123.7, 12.2, 94.7, 87.6, MS m/z (relative intensity) 223 (M^+,100), 192 (49), 176(85), 165 (59), 151 (43). Anal Calcd for $C_{14}H_9NO_2$, C, 75.33; H, 4.06; found C, 75.27; H, 4.00. (Known compound, see: S. Lee, et al., *Org. Lett.*, **2008**, *10*, 945).



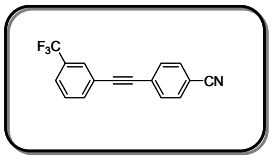
mp: 57-59 °C; IR (KBr) 2215, 1592, 1508, 1245cm^{-1}; ^{1}H NMR ($CDCl_3$) δ7.55–7.49 (m, 4 H), 7.39-7.28 (m, 2 H), 6.91-6.89 (d, *J* = 8Hz, 2 H) , 3.85 (s, 3 H); ^{13}CNMR ($CDCl_3$) δ 159.7, 133.1, 131.5, 128.4, 127.9, 123.6, 114.1, 89.4, 88.1, 55.4, MS m/z (relative intensity) 208 (M^+,100), 192 (52), 165 (52), 139 (15), 87 (14). Anal Calcd. for $C_{15}H_{12}O$ C, 86.51; H, 5.81; found C, 86.46; H, 5.75. (Known compound, see: R. Soler, et al., *Synthesis,* **2007**, *19*, 3068).



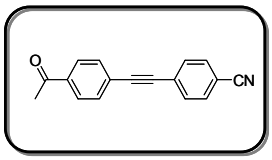
mp: 121.7-122.5 °C; IR (KBr) 2224, 2210, 1595, 1563, 1509, 1291, 1251 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.62–7.56 (q, J_1 = 8 Hz, J_2 = 8 Hz, 4 H), 7.50-7.48 (d, *J* = 8 Hz, 2 H), 6.92-6.90 (d, *J* = 8 Hz, 2 H), 3.84 (s, 3 H); ^{13}C NMR($CDCl_3$)δ 160.4, 133.4, 132.1, 131.9, 128.7, 118.7, 114.3, 114.2, 111.0, 94.2, 86.8, 55.4. MS m/z (relative intensity) 233 (M^+, 100), 218 (47), 190 (49), 163 (15). Anal Calcd. for $C_{16}H_{11}NO$ C, 82.38; H, 4.75; found C, 82.32; H, 4.69. (Known compound, see: A. Mori, et al., *J. Org. Chem.,* **2000**, *65*, 1780).



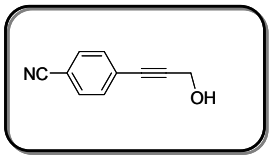
mp: 77.6-78.5 °C; IR (KBr) 2931, 1594, 1508, 1245, 1029 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.54-7.52 (d, *J* = 8 Hz, 2 H), 7.28-7.19 (m, 3 H), 6.94-6.91(d, *J* = 8 Hz, 2 H), 3.86 (s, 3 H), 2.56 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 159.7, 140.0, 133.0, 131.7, 129.5, 128.0, 125.6, 123.4, 115.8, 114.1, 93.4, 87.1, 55.4, 20.8; MS m/z (relative intensity) 222 (M^+,100), 207 (45), 179 (69), 152 (35), 89 (22). Anal Calcd for $C_{16}H_{14}O$ C, 86.45; H, 6.35; found C, 86.39; H 6.29. (Known compound, see: H. Meier, et al., *Tetrahedron Lett.,* **1976**, *3*, 171).



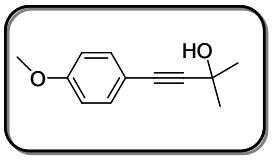
mp: 129.5-130.4 °C; IR (KBr) 2360, 2230, 1605, 1503, 1431, 1339, 1115 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.82 (s, 1H), 7.74–7.72 (d, J = 8 Hz, 1 H), 7.68-7.62 (dd, J_1 = 8 Hz, J_2 = 8 Hz 5 H), 7.54-7.50 (t, 1 H); ^{13}C NMR ($CDCl_3$) δ 134.8, 132.2, 132.1, 131.8-130.7 (q, J_1 = 15 Hz, J_2 = 15 Hz), 129.1, 128.7-128.5 (q, J_1 = 20 Hz, J_2 = 20 Hz), 127.7-119.6 (q, J_1 = 270 Hz, J_2 = 270 Hz), 127.5, 125.7- 125.6 (q, J_1 = 10 Hz, J_2 = 10 Hz), 123.3, 118.4, 112.1 MS m/z (relative intensity) 271 (M^+, 100), 250 (7), 231(3), 69 (76), 50 (33). Anal Calcd. for $C_{16}H_8F_3N$ C, 70.85; H, 2.97; found C, 70.79; H, 2.91.



mp: 88.1-89.0 °C; IR (KBr) 2361, 2224, 1686, 1602, 1402, 1356, 1263 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.96-7.94 (d, J = 8 Hz, 2 H), 7.65-7.60 (m, 6 H); ^{13}C NMR ($CDCl_3$) δ 197, 136.9, 132.3, 132.2, 131.9, 128.4, 127.6, 126.9, 118.4, 112.1, 92.7, 90.6, 26.67 MS m/z (relative intensity) 245 (M^+, 45), 229 (100), 201 (33), 175 (29), 151 (17). Anal Calcd. for $C_{17}H_{11}NO$ C, 83.25; H, 4.52; found C, 83.19; H, 4.46. (Known compound, see: A. Mori, et al., *J. Org. Chem.,* **2000**, *65*, 1780).

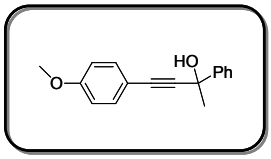


mp: 80.3-81.4 °C; IR (KBr) 3455, 2923, 2235, 1604, 1504, 1033cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.63–7.61 (d, J =8 Hz, 2 H), 7.54-7.52 (d, J =8 Hz, 2 H), 4.54 (s, 2 H), 1.82 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 132.2, 132.1, 127.5, 118.4, 111.9, 91.7, 84.1, 51.5. Anal Calcd. for $C_{10}H_7NO$ C, 76.42; H, 4.49; found C, 76.36; H, 4.43. (Known compound, see: M. Santelli, et al., *Tetrahedron Lett.,* **2004**, *45*, 1603).

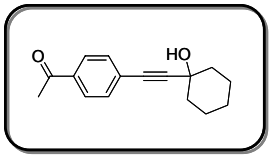


Oil; IR (neat) 3390, 2979, 1606, 1509, 1250, 1169 cm^{-1} ;^1H NMR ($CDCl_3$) δ 7.37–7.35 (d, J = 8 Hz, 2 H), 6.85-6.83 (d, J = 8 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 159.6, 133.1, 114.8, 113.9, 92.5, 82.0, 65. 7, 55.3, 31.6, MS m/z (relative intensity)

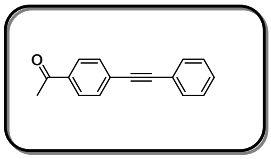
190 (M^+, 4), 172 (32), 157 (66), 128 (18), 51 (100). Anal Calcd for $C_{12}H_{14}O_2$ C, 75.76; H, 7.42; found C, 75.70; H, 7.36. (Known compound, see: A. Capretta, et al., *J. Org. Chem.,* **2004**, *69*, 5082).



Oil; IR (neat) 3425, 2981, 2931, 1606, 1509, 1247 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.78-7.765 (d, *J* = 8 Hz, 2 H), 7.48-7.40 (m, 4 H), 7.36-7.32 (m, 1 H), 6.89-6.87 (d, *J* = 8 Hz, 2 H), 3.84 (s, 3 H), 2.62 (s, 1 H), 1.89 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 159.7, 145.9, 133.2, 128.4, 127.7, 125.1, 114.7, 114.0, 91.2, 84.9, 70.5, 55.4, 33.5 MS m/z (relative intensity) 252 (M^+, 3), 234 (18), 219 (30), 191 (38), 159 (20), 78 (100). Anal Calcd for $C_{17}H_{16}O_2$ C, 80.93; H, 6.39; found C, 80.87; H, 6.33. (Known compound, see: jr, R. E Maleczka. et al., *J. Org. Chem.,* **2003**, *68*, 6775).



mp: 82.2-83.1 °C; IR (KBr) 3379, 2941, 2854, 1664, 1600 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.86-7.84 (d, *J* = 8 Hz, 2 H), 7.47-7.45 (d, *J* = 8 Hz, 2 H), 2.84 (s, 1 H), 2.57 (s, 3 H), 2.02-2.00 (d, *J* = 8Hz, 2 H), 1.75-1.54 (m, 7 H); ^{13}C NMR ($CDCl_3$) δ 197.5, 136.1, 131.8, 128.2, 127.9, 96.6, 83.5, 69.0, 39.9, 26.6, 25.3, 23.4, MS m/z (relative intensity) 242 (M^+,), 131 (100), 103 (83), 77 (68). Anal Calcd for $C_{16}H_{18}O_2$ C, 79.31; H, 7.49; found C, 79.25; H, 7.43. (Known compound, see: K. V. Srinivasan, et al., *J. Org. Chem.,* **2005**, *70*, 4869).



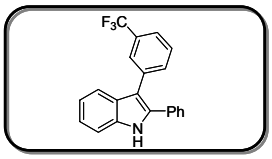
mp: 94.7-95.6 °C; IR (KBr) 1679, 1602, 1403, 1359, 1263 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.96–7.94 (d, *J* =8 Hz, 2 H) , 7.63–7.61 (d, *J* =8Hz, 2 H), 7.58-7.56 (m, 2 H), 7.39-7.37 (m, 3 H); ^{13}CNMR ($CDCl_3$)δ 197.3, 136.3, 131.8, 131.7, 128.8, 128.5, 128.3, 28.2, 122.7, 92.8, 88.7, 26.6, MS m/z (relative intensity) 220 (M^+, 6), 205 (10), 176 (74), 150 (40), 126 (20). Anal Calcd for $C_{16}H_{12}O$ C, 87.25; H, 5.49; found C, 87.19; H, 5.43. (Known compound, see: R. Soler, et al., *Synthesis,* **2007**, *19*, 3068).

Typical procedure for the synthesis of o-(Phenylethynyl)trifluoroacetanilide

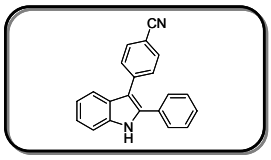
A 250 mL round-bottom flask, equipped with a magnetic stirring bar, was charged with o-phenylethynylaniline (7.66 g, 39.69 mmol) in THF (70 mL) and cooled at O °C. Trifluoroacetic anhydride (11.2 mL, 79.38 mmol) was added drop wise with stirring in 0.5 h. Then the reaction mixture was stirred at = °C until the disappearance of o-phenylethynylaniline (1.5 h monitored by TLC). The mixture was poured into EtOAc (300 mL) and with brine (3×15 mL). The organic layer was separated, dried (Na2SO4) and concentrated under vacuum. The residue was connected to a vacumm line (1mm/Hg for 2 h) to yield as a grey powder (9.90 g, 86%), which was used without further purification; mp: 94-96 °C; IR (KBr) 3344, 3058, 2217, 1711 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.92 (s, 1 H), 8.40 (d, J = 8.3 Hz, 1 H), 7.61-7.54 (m, 3 H), 7.45-7.40 (m, 4 H), 7.25 (dt, J_1 = 7.6 Hz, J_2 = 1.1 Hz 1 H) ; ^{13}C NMR ($CDCl_3$) δ 154.8 (q, J = 37.4 Hz), 136.5, 132.1, 131.9, 130.3, 129.7, 129.1, 126.2, 122.1, 120.0, 116.2 (q, J = 289.0 Hz); Anal Calcd for $C_{21}H_{14}F_3N$ C, 74.77; H, 4.18; found C, 74.70; H, 4.14.

Typical procedure for the synthesis of 3-Substituted 2-Phenylindoles using 0.1 mol% of Pd_{np}-B:

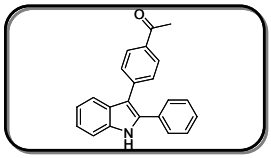
2,2,2-trifluoro-N-(2-(phenylethynyl)phenyl)acetamide (289 mg, 1 mmol), Pd_{np}-**B** (3mg), K_2CO_3 (276 mg, 2 mmol) and 1-iodo-3-(trifluoromethyl)benzene (272 mg, 1 mmol.) in CH_3CN (2 mL) were orbitally stirred for 3 h at 100 °C with a Heidolph Synthesis System. Then, after cooling, the reaction mixture was centrifuged. The liquid phase was decanted, diluted with AcOEt, washed with deionized water and dried over Na_2SO_4. The solvent was removed under vacuum and the residue was purified by chromatography (SiO_2, 35 g, *n*-hexane/AcOEt 96/4 v/v) to give 307 mg (91% yield) of :



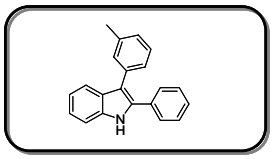
mp: 70 °C; IR (KBr) 3383, 1456, 1324 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.28 (s, 1 H), 7.82 (s, 1 H), 7.75-7.73 (d, J = 8 Hz, 1 H), 7.64, 7.60 (t, J = 8 Hz, 2 H), 7.53-7.32 (m, 8 H), 7.28-7.25 (t, J = 8 Hz, 1 H) ; ^{13}C NMR ($CDCl_3$) δ 136.1, 135.9, 134.9, 133.5 (q, J = 1.2 Hz) , 132.2, 131.2, 130.8, 129.0, 128.9, 128.4, 128.2, 126.8, 126.7, 124.3 (q, J = 272.5 Hz), 123.1, 122.9 (q, J = 3.9 Hz), 120.9, 119.3, 113.5111.2 ; Anal Calcd for $C_{21}H_{14}F_3N$ C, 74.77; H, 4.18; found C, 74.70; H, 4.14. (Known compound, see: S. Cacchi, et al., *Synthesis,* **2003**, *5*, 728).



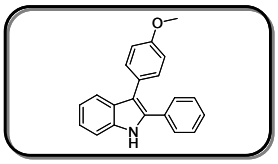
mp: 211-212 °C; IR (KBr) 3325, 2227 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 11.81 (s, 1 H), 7.80 (d, *J* = 8.2 Hz, 2 H), 7.67-7.28 (m, 9 H), 7.22 (t, *J* = 6.4 Hz, 1 H), 7.10 (t, *J* = 6.4 Hz, 1 H); ^{13}C NMR (DMSO-d_6) δ 140.7, 136.2, 135.7, 13.5, 131.9, 130.3, 128.8, 128.6, 128.1, 127.1, 122.4, 120.3, 119.1, 118.3, 111.8, 111.5, 108.1; Anal Calcd for $C_{21}H_{14}N_2$ C, 85.69; H, 4.79; found C, 85.61; H, 4.77. (Known compound, see: S. Cacchi, et al., *Synthesis,* **2003**, *5*, 728)



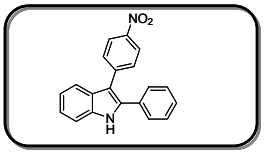
mp: 203-204 °C; IR (KBr) 3264, 2923, 1658, 1599 cm^{-1}; ^{1}H NMR (CDCl3) δ 11.77 (s, 1 H), 7.99 (d, *J* = 8.3 Hz, 2 H), 7.00-7.68 (m, 11 H), 2.61 (s, 3 H); ^{13}C NMR (CDCl3) 197.4, 140.6, 136.3, 135.3, 134.3, 132.2, 129.6, 128.7, 128.6, 128.5, 128.0, 127.4, 122.3 120.2, 118.5, 112.1, 111.7, 26.6; Anal Calcd for $C_{22}H_{17}NO$ C, 86.86; H, 5.50; found C, 84.61; H, 5.50. (Known compound, see: S. Cacchi, et al., *Synthesis,* **2003**, *5*, 728)



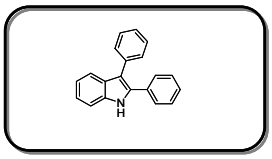
Oil; IR (KBr) 3401, 1455, 1328 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.22 (s, 1 H), 7.76-7.74 (d, , *J* = 8 Hz 1 H), 7.49-7.45 (m, 3 H), 7.40-7.17 (m, 9 H), 2.42 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 138.9, 136.4, 136.2, 135.5, 134.2, 133.0, 129.3, 129.0, 128.8, 128.3, 127.5, 124.4, 122.2, 120.1, 118.7, 111.4, 25.7; Anal Calcd for $C_{21}H_{17}N$ C, 89.01; H, 6.05; found C, 88.94; H, 6.01. (Known compound, see: S. Cacchi, et al., *Synthesis,* **2003**, *5*, 728).



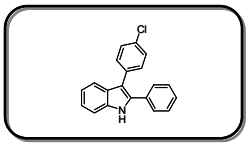
mp: 184-185 °C; IR (KBr) 3418, 1602, 1510 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8. 22 (s, 1 H), 7.71-7.69 (d, *J* = 8 Hz 1 H), 7.51-7.15 (m, 11 H), 6.99-6.97 (d, *J* = 8 Hz 1 H), 3.86 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 159.8, 143.4, 143.0, 139.4, 135.6, 132.3, 128.9, 128.7, 127.9, 127.4, 126.5, 126.2, 125.7, 114.2, 55.8; Anal Calcd for $C_{22}H_{18}NO$ C, 85.56; H, 6.08; found C, 85.50; H, 6.02. (Known compound, see: S. Cacchi, et al., *Synthesis,* **2003**, *5*, 728).



mp: 227-228 °C; IR (KBr) 3374, 1591, 1500, 1336 cm^{-1}; ^1H NMR (DMSO-d_6) δ 11.88 (s, 1 H), 8.22 (d, *J* = 8.8 Hz 2 H), 7.68-7.35 (m, 9H), 7.23 (dt, J_1 = 7.5 Hz, J_2 = 1.2 Hz 1 H), 7.11(dt, J_1 = 7.5 Hz, J_2 = 1.1 Hz 1 H); ^{13}C NMR ($CDCl_3$) δ 145.0, 143.0, 136.3, 136.1, 131.7, 130.2, 128.8, 128.7, 128.3, 127.0, 123.9, 122.5, 120.5, 118.3, 111.9 111.1; Anal Calcd for $C_{20}H_{14}N_2O_2$ C, 76.42; H, 4.49; found C, 76.35; H, 4.48. (Known compound, see: S. Cacchi, et al., *Synthesis,* **2003**, *5*, 728).



mp: 120-121 °C; IR (KBr) 3387, 1454 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.25 (s, 1 H), 7.78-7.62 (m, 1 H), 7.11-7.58 (m, 13 H); ^{13}C NMR ($CDCl_3$) δ 136.0, 135.2, 134.2, 132.8, 130.3, 128.9, 128.7, 128.6, 128.3, 127.8, 126.3, 122.8, 120.5, 119.8, 115.1, 111.0; Anal Calcd for $C_{20}H_{15}N$ C, 89.19; H, 5.61; found C, 89.10; H, 5.59.(Known compound, see: S. Cacchi, et al., *Synthesis,* **2003**, *5*, 728).

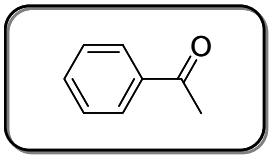


Oil; IR (KBr) 3374, 1591, 1500 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.23 (s, 1 H), 7.72-7.70 (d, *J* = 8 Hz, 1 H), 7.46-7.22 (m, 12 H); ^{13}C NMR ($CDCl_3$) δ 135.9, 134.5, 133.7, 132.4,

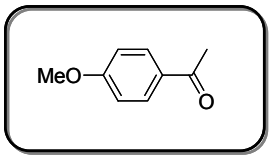
132.1, 131.5,128.9, 128.8, 128.5, 128.3, 128.1, 122.9, 120.7, 119.5, 113.1, 111.1; Anal Calcd for $C_{20}H_{14}ClN$ C, 79.07; H, 4.65; found C, 79.00; H, 4.59.

Typical procedure for green oxidation using 0.1 mol% of Au_{np}**-C/**FSG:

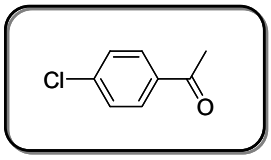
1-phenylethanol (122 mg, 1 mmol), Au_{np}**-C/**FSG (15 mg), t-BuONa (96.10 mg, 1 mmol) in toluene (2 mL) were orbitally stirred for 48 h at 100 °C with a Heidolph Synthesis System. Then, after cooling, the reaction mixture was centrifuged. The liquid phase was decanted, diluted with AcOEt, washed with deionized water and dried over Na_2SO_4. The solvent was removed under vacuum and the residue was purified by chromatography (SiO_2, 35 g, *n*-hexane/AcOEt 96/4 v/v) to give 307 mg (89% yield) of :



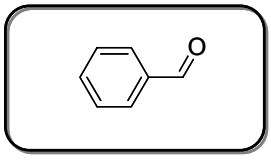
Commercially available.



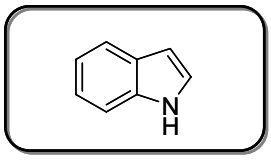
mp: 117 °C; IR (KBr) 2964, 2842, 1672, 1602, 1259, 1172 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.95–7.93 (d, *J* = 8 Hz, 2 H), 6.95-6.93 (d, *J* = 8 Hz, 2 H), 3.87 (s, 3 H), 2.56 (s, 3 H) ; ^{13}C NMR ($CDCl_3$) δ 196.8, 163.5, 130.6, 130.4, 113.7, 55.5, 26.4 ; Anal Calcd for $C_9H_{10}O_2$ C, 71.98; H, 6.71; found C, 71.92; H, 6.64.



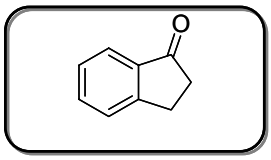
IR (KBr) 2925, 1685, 1589, 1261, 1093 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.91–7.89 (d, *J* = 8 Hz, 2 H), 7.45-7.43 (d, *J* = 8 Hz, 2 H), 2.60 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 196.8, 139.6, 135.5, 129.7, 128.9, 29.7, 26.6 ; Anal Calcd for C_8H_7ClO C, 62.15; H, 4.56; found C, 62.10; H, 4.50.



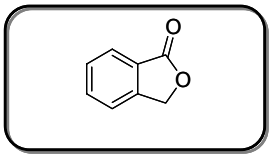
Commercially available, Sigma-Aldrich CAS Number 100-52-7.



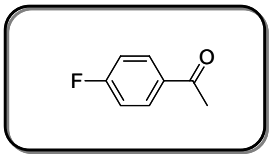
mp: 55-56 °C. Commercially available, Sigma-Aldrich CAS Number 120-72-9.



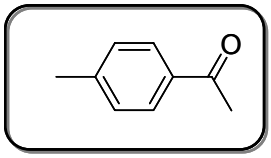
mp: 117 °C; IR (KBr) 2925, 1712, 1610, 1278, 758 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.78–7.76 (d, *J* = 8 Hz, 1 H), 7.60 (t, *J* = 8 Hz, 1 H), 7.50-7.48 (d, *J* = 8 Hz, 1 H), 7.40-7.36 (d, *J* = 8 Hz, 1 H), 3.1 (s, 2 H), 2.7 (s, 2 H) ; ^{13}C NMR ($CDCl_3$) δ 207.1, 155.2, 137.1, 134.6, 127.3, 126.7, 123.7, 36.3, 25.8; Anal Calcd for C_9H_8O C, 81.79; H, 6.10; found C, 81.74; H, 6.05.



Oil; IR (KBr) 2923, 2854, 1749, 1465, 1439 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.93–7.91 (d, *J* = 8 Hz, 1 H), 7.71-7.67 (dt, J_1 = 4 Hz, J_2 = 8 Hz, 1 H), 7.56-7.50 (m, 2 H), 5.33 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 170.1, 146.6, 134.1, 129.1, 125.7, 122.2, 69.7 ;
Anal Calcd for $C_8H_6O_2$ C, 71.64; H, 4.51; found C, 71.59; H, 4.47.



Oil; IR (neat) 2227, 1685, 1604, 1523, 1268 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.01–7.91 (m, 2 H), 7.15-7.11 (t, 2 H), 2.59 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 196.5, 167.1, 164.5; 133.6, 133.6, 131.0, 130.9, 115.8, 115.6, 26.5; Anal Calcd for C_8H_7FO C, 69.56; H, 5.11; found C, 69.50; H, 5.03.



Oil; IR (neat) 2923, 1681, 1606, 1267 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.87–7.85 (d, *J* = 8 Hz, 2 H), 7.26-7.24 (d, *J* = 8 Hz, 2 H), 2.57 (s, 3 H), 2.41 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 197.8, 144.0, 134.1, 129.2, 128.5, 26.6, 21.6 ; Anal Calcd for $C_9H_{10}O$ C, 80.56; H, 7.51; found C, 80.50; H, 7.44.

Typical procedure for oxidative transformation of alcohols into esters using 0.1 mol% of Au_{np}**-C/**FSG:

Cinnamyl alcohol (134 mg, 1 mmol), Au_{np}**-C/**FSG (15 mg), NaOH (80 mg, 2 mmol) in methanol (3 mL) were orbitally stirred for 48 h at 100 °C with a Heidolph Synthesis System. Then, after cooling, the reaction mixture was centrifuged. The liquid phase was decanted, diluted with AcOEt, washed with deionized water and dried over Na_2SO_4. The solvent was removed under vacuum and the residue was purified by chromatography (SiO_2, 35 g, *n*-hexane/AcOEt 96/4 v/v) to give 144 mg (89% yield) of methyl cinnamate:

Recycling procedure: The mixture was cooled at room temperature, centrifuged (3000 rpm × 20 min.) and the solution was pipetted. Then, the solid supported palladium was washed with methanol (4 × 3 mL), the resulting suspension was centrifuged and the solvent was decanted each time. The recovered solid material was dried under high vacuum at 60 °C for 2 h and reused.

Pd nanoparticles synthesis in ***Te-Dps*****.**

K_2PdCl_4 (100mM) was used as the silver ion source, while $NaBH_4$ (30mM) was used as the reducing agent. A Dps solution (0.15 M NaCl) was brought to pH 8.5 using 30 mM NaOH (TITRINO, Metrohm AG) and 90 eq of palladium ions per Dps molecule were added to the protein solution (1 mg/ml) under stirring at room temperature. After 30 min, $NaBH_4$ (2 eq per Pd) was added to reduce the silver ions and the resulting solution was stirred for over 15 min. Any aggregates of Dps and/or palladium particles produced during NPs formation were removed by centrifugation at 12,000 rpm for 10 min followed by filtration through 0.22 μm filters. The solution was dialyzed against deionized water and concentrated for the following analysis. The samples containing NPs was checked using Supherose 6 gel-filtration column (GE Healthcare), equilibrated with 0.15 M NaCl. UV-Vis absorption spectra were recorded between 240-700 nm at rt with a spectrophotometer Varian Cary 50 and using a quartz cuvette with 0.1 cm path length. The samples (10 μl) were applied to carbon coated copper grids (200-mesh) and after 30 s on the grid the samples were dried and negatively stained with (10 μl) phosphotungstic acid (PTA) 2% w/v solution buffered at pH = 7.3 and observed by a Philips 208 transmission electron microscope (FEI Company).