

Carbon–Carbon Coupling Reactions Catalyzed by Heterogeneous Palladium Catalysts

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1. Introduction

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

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structure of the catalytic species is often known, and structure–activity relations could be established. Recent developments of ligand-free Pd catalysts have provided interesting and practically important alternatives to ligand-assisted methodologies. On the other hand, homogeneous catalysis has a number of drawbacks, in particular, the lack of reuse of the catalyst or at least the problem of recycling of the catalyst. This leads to a loss of expensive metal and ligands and to impurities in the products and the need to remove residual metals.^{1,2} These problems have to be overcome in the application of the homogeneous Pd-catalyzed coupling reactions in industry and are still a challenge.^{3–9}

In order to address these problems, heterogeneous Pd catalysis is a promising option. Here, Pd is fixed to a solid support,^{7,10} such as activated carbon (charcoal, for a recent review of application in C–C coupling reactions, see Seki, ref 11a),^{11–13} zeolites and molecular sieves,^{10,14–18} metal oxides^{10,19–21} (mainly silica or alumina but also MgO, ZnO, TiO₂, ZrO₂), clays,^{22,23} alkali and alkaline earth salts (CaCO₃, BaSO₄, BaCO₃, SrCO₃), porous glass,²⁴ organic polymers,¹⁰ or polymers embedded in porous glass.²⁵ On the other hand, Pd can also be fixed to a solid support as a complex; that is, the ligands are covalently bound to the support. Both techniques allow one to separate the heterogeneous catalyst after the reaction or to reuse it as long as it is not too deactivated or both. For a review about product separation techniques in Heck reactions, see Arai et al.⁹ Alternatively such catalysts can also be used in continuous-flow systems²⁵ or in flow injection microreactors.²⁶ Normally, supported Pd catalysts require more drastic reaction conditions than homogeneous catalysts, but this does not cause problems as far as the stability of the catalysts is concerned, because they often are relatively stable. In this way, the somewhat lower activities can be compensated to some extent by using higher temperatures and catalyst loadings. See Djakovitch et al. for a comparative study of homogeneous versus heterogeneous Pd catalysis in Heck reactions.²⁷ There are also cases reported, where Pd immobilized at zeolites showed higher activity than free Pd(OAc)₂ or [Pd(C₃H₅)Cl]₂, probably because of the stabilization of the active Pd species by the zeolite framework.¹⁶ The comparatively high stability of Pd on solid supports sometimes allows running the reaction even under normal ambient conditions, that is, without the exclusion of air.²⁸ There were cases reported where solid-supported Pd catalysts show higher activities than homogeneous catalysts, probably because of their higher stability.²⁹ The application of supported Pd was introduced into Pd-catalyzed coupling reactions relatively late (early 1970s) but has been increasingly used up to now. Some industrial applications have already been developed.^{30,31}

It is the aim of this review to give insight into the state of art in the field of the application of heterogeneous catalysts in coupling reactions to synthetic chemists. Scope, limitations, and problems associated with the application of heterogeneous catalysts in coupling reactions will be covered. There are also cases included where Pd is fixed to an inorganic solid support (e.g., silica or iron oxide) by the help of organic ligands, that is, as a complex. Such ligands can be part of a polymer, for example, in glass/polymer composites.³² Pd catalysts supported by entirely organic polymers are not included.^{10,33,34} Mechanistic aspects of the catalysis are briefly addressed, but an extensive survey about this field is beyond the scope of this review. This limitation is also attributed to the fact that the mechanisms are not yet fully understood and findings in this field are sometimes contradictory. To an extreme, in many cases it is not even clear whether the genuine catalysis is heterogeneous or homogeneous.^{19,35} An up-to-date critical review about mechanistic aspects of homogeneous and heterogeneous catalysis and the nature of active species in Mizoroki–Heck and Suzuki–Miyaura couplings was recently published by Jones et al.³⁶

In the present review, catalysts are covered that are used as solids and are not soluble in the reaction mixture, regardless of whether the acting catalytic palladium species is homogeneous or heterogeneous. Other recent developments in Pd catalysis in cross-coupling reactions such as the

application of colloidal Pd,^{37,38} Pd clusters,³⁹ Pd black,⁴⁰ and Pd nanoparticles^{41–45} are not considered in this review but will be occasionally mentioned when the heterogeneous catalyst serves as a source for such Pd species.

1.1. Catalysts

Solid-supported catalysts are complex assemblies. Their preparation is a challenging task. Minor changes of their preparation conditions can significantly influence the delicate balance of conflicting demands: high activity, high selectivity, and long lifetime. Palladium can be deposited on a solid support in different ways.¹⁴ The preferred mode of deposition depends also on the type of support. With oxides and carbon supports, wet or dry impregnation, deposition–precipitation, deposition–reduction, and ion-exchange methods can be applied using most often an aqueous solution of a suitable Pd(II) precursor, such as PdCl₂, Pd(NH₃)₄Cl₂, Pd(NO₃)₂, H₂-PdCl₄, or [Pd(NH₃)₄](NO₃)₂. On the other hand, organic solutions of Pd(0) complexes, such as Pd(acac)₂ (acac = acetylacetonate) or Pd(C₃H₅)₂ are also sometimes used.¹⁴ Metal oxide surfaces are hydroxylated as such or become hydroxylated in the presence of aqueous Pd(II) solutions. Pretreatment of carbon in an oxidizing environment is used to introduce oxygen-containing surface groups, thus enhancing the interaction with the metal. The catalyst obtained by the different methods can later on be calcined. This thermal treatment often overrides the prior application of the Pd precursor to the solid support as far as the ultimate metal dispersion is concerned. On the other hand, the surface of the support can be covalently functionalized by ligands, such as phosphines, pyridines, or mercaptanes, which form complexes with dissolved Pd salts. This methodology is widely used in polymer-⁴⁶ and silica-supported⁴⁷ palladium catalysts. Grafting of Pd complexes to the solid support by starting with a Pd complex bearing linker groups in the ligands is another method to prepare solid-supported Pd catalysts.⁴⁸

Sol–gel processes can also be used for the preparation of solid-supported Pd catalysts, mainly for silica- and alumina-supported Pd catalysts. The support is generated from a monomer, such as tetraethoxysilane or aluminum isopropoxide in the presence of a soluble Pd compound, such as PdCl₂, Pd(NH₃)₄Cl₂, or Pd(acac)₂ (coprecipitation) and eventually a linker. In this way, usually amorphous materials are obtained, where a part of the Pd is encapsulated. Again these systems can be calcined later on.

Although the active species in Pd-catalyzed cross-coupling reactions is Pd(0), the metal can generally be used as Pd(0) or Pd(II)²⁸ on the solid support. In the latter case, *in situ* reduction to Pd(0) occurs during the application in cross-coupling reactions without the addition of extra reducing reagents, that is, an amine, a phosphine used as ligand, or a reactant reduces the Pd(II) species. In the case of carbon-supported Pd, part of the Pd(II) is already reduced to Pd(0) during the preparation of the catalyst. On the other side, transformation of Pd(II) into Pd(0) can be implemented by an extra reduction step, for example, by hydrazine, formaldehyde, or hydrogen, or occurs already in its preparation, when the deposition–reduction methodology is used. Gas-phase reduction leads to smaller Pd particles than liquid-phase reduction.¹⁴ Generation of the Pd(0) from Pd(II) at the solid support can often be advantageous because species are generated, which exhibit a higher catalytic activity.

A loading with 5 wt % Pd is used for most of the Pd catalysts; however, for special purposes higher loadings are

used. On the other hand, cases were reported where the catalyst loading went through an optimum, that is, higher Pd loadings decreased the activity.⁴⁹ Important parameters of the active metal are the surface area, the dispersion (typically only 10–60% of the metal atoms are exposed), the size of the crystallites (typically in a range of 2 to >20 nm), the location in the pores of the support, the oxidation state, the counter ions if Pd(II) is used, the water content, and the conditions of its preparation.^{7,50}

The support usually has an impact on the activity of the catalytic system. Particle size, surface area, pore structure, and acid–base properties are important parameters of the support.⁷ The support can affect the catalyst activity either by creating reactive spots at the Pd metal crystallites^{51–53} or by improved release of Pd(0) into the solution by leaching.^{11,13,54} In the latter case, the genuine catalytic system is homogeneous (*vide infra*). Basic supports such as basic zeolites, layered double hydroxides, or sepiolites can play a similar supporting role as phosphines in homogeneous catalysis^{49,55,56} or can act as bases,⁵⁷ that is, no external bases are necessary in these cases.

Due to their controlled pore size, microporous and mesoporous materials, such as zeolites, can be advantageous over simple metal oxides. Pd(0) clusters can be encapsulated in these pores. The pore size and structure of such supports can have an important impact on the reactivity and selectivity of those catalysts.⁵⁸ Thus, cases were reported where a larger pore size of mesoporous silica allowed reaction of larger substrates as compared with microporous supports.⁵⁸

Pd on solid supports can be used as such or in combination with additional soluble ligands, such as phosphines, carbenes, and amines. It is assumed that such ligands support leaching of Pd into the solution acting as homogeneous catalyst there.⁵⁹ In other cases, the addition of ligands, such as phosphines, inhibits the reaction rather than accelerates.^{7,60} As in homogeneous cases, heterogeneously catalyzed Heck reactions can be promoted by ammonium salts.⁶¹

A number of solid-supported Pd catalysts are commercially available. However, they often differ in structure (support and Pd), composition, and activity depending on the supplier. Laboratory chemical suppliers normally do not specify the catalyst manufacturer and the exact catalyst type. For optimization of a catalytic system for larger scale production, it is necessary to have contact with the supplier to get always the same quality of supported Pd or to buy a stock of material in order to guarantee the reproducibility of results. When synthetic chemists want to apply methods reported in the literature for heterogeneous catalysis, they should be sure to get the same or similar catalyst as reported in the procedure. Differences from the originally used system can cause unwanted effects.

The characterization of a heterogeneous Pd catalyst on a molecular level is still a problem, although TEM, X-ray diffractometry, and IR spectroscopy allow important insights into the structure. Often, heterogeneous catalysts are still chosen on an empirical basis without understanding why a given catalyst is superior to another one.

Reusage of a heterogeneous catalyst is often possible but is sometimes limited due to leaching of the Pd without redeposition (leaching up to 14% Pd from Pd/C was observed in Heck reactions⁶²), changing of crystallite structure of the Pd on the support surface,^{28,50} chemical change of Pd ligands (e.g., oxidation of phosphines leading to high leaching of Pd) grafted to the solid support, or congesting the catalyst

surface, for example, by salts formed as byproducts in the coupling reaction.⁵⁸ There were cases reported where the catalytic activity dropped considerably in the second run, while marginal losses of catalytic activity were observed in the following runs.⁵⁸ Reuse of catalytic Pd can also be achieved, when colloidal Pd is formed by leaching from the support and these colloidal particles are separated and submitted to another run.³⁸ Interestingly, there are a few cases reported where the recycled catalyst exhibited higher activity than the original one.⁵²

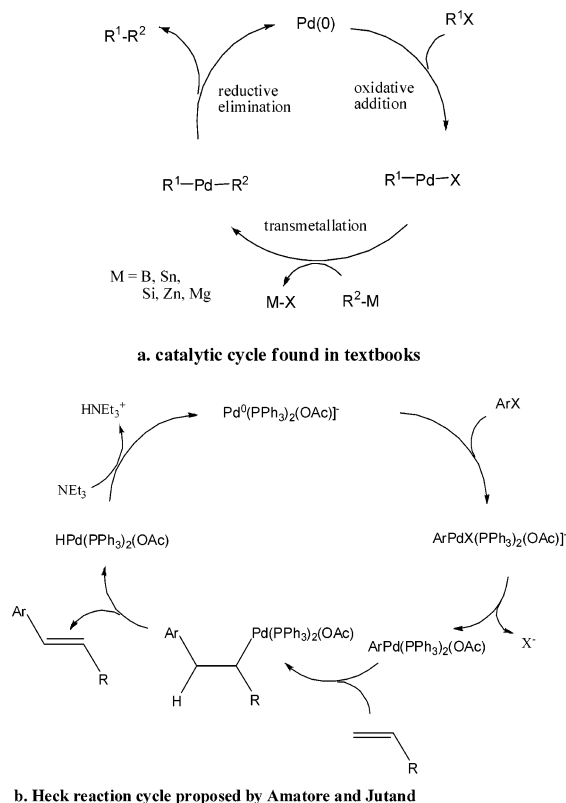
Palladium metal without a solid support has rarely been used in cross-coupling reactions.^{40,63,64} Palladium on charcoal (also called activated carbon) (Pd/C) is by far the most often used catalyst in heterogeneous Pd-catalyzed coupling reactions. It can be purchased from various laboratory suppliers, such as Acros, Aldrich, Lancaster, or Alfa Aesar, or from the manufacturers Degussa or Johnson Matthey in various qualities with a Pd content ranging from 1% to 20%. The materials can contain water up to 50%. Pd/C is used with or without additional ligands. Procedures for the preparation of Pd/C were reported.^{14,65}

Cross-couplings catalyzed by solid-supported Pd can be carried out in organic solvents. Organic solvent/water mixtures were also used, and a few cases were reported using ionic liquids^{12,66–69} or working under solvent-free conditions.

1.2. Mechanistic Aspects

In general, carbon–carbon coupling reactions catalyzed by solid-supported Pd follow the usual reaction mechanism, as shown for coupling of organometallics with organohalides or -triflates in Scheme 1.^{70–72}

Scheme 1. Major Steps of Pd-Catalyzed Coupling Reactions



Recent results from Amatore and Jutand gave evidence for an anionic version of the catalytic cycle in Heck and other Pd-catalyzed coupling reactions under homogeneous condi-

tions (Scheme 1b).⁷² Probably this mechanism is more abundant than the textbook cycle shown in Scheme 1a unless aryl triflates or arenes with non-halide leaving groups are used.³⁶ Involvement of Pd(IV) species as intermediates was taken into consideration⁷³ but seems to be unlikely in light of later results.^{36,74,75} Each of the steps of the catalytic cycles can be rate-determining, depending on the type of substrate and catalyst.

As far as the interaction of the Pd catalyst with the substrate and intermediates is concerned, several mechanisms have to be taken into consideration.³⁶ Thus the reaction can take place at the surface of solid Pd^{51,76} as a truly heterogeneous reaction. On the other side, a quasi-homogeneous mechanism can occur, where Pd gets dissolved as colloids^{42,74,77} or as complexes that have been leached from the supported Pd, for example, by oxidative addition to the substrate.^{10,11,13,19,21,28,38,48,50,74,78,79} Despite earlier reports giving some evidence (hot filtration test, Hg(0) poisoning, ...) for, but not proving,⁸⁰ a heterogeneous mechanism, it has become more and more accepted that leached soluble Pd species are the genuine catalytically active species in Heck and also in most other coupling reactions implemented by solid-supported Pd.^{36,74} The phenomenon that homeopathic doses of dissolved Pd can catalyze cross-coupling reactions makes it difficult to find out the true nature of the acting catalytic species.^{74,81} There were cases reported where the dissolved Pd formed by leaching catalyzes the Heck reaction, whereas solid Pd particles give rise to side reactions such as dehalogenation reductive coupling of haloarenes.^{27,82} In general, leaching is supported by polar solvents, such as DMF or *N,N*-dimethylacetamide.^{49,83,84} The oxidation state of the Pd on the solid support can also have an effect on the extent of leaching (Pd(II) is prone to leaching).^{61,84} In the case of a heterogeneous mechanism, the support can affect the structure of the Pd creating reactive spots (edges, corners, adatoms) of high catalytic activity in the crystallite structure or can provide reaction cavities, for example, in case of Pd supported by zeolites. On the other hand, activation of the Pd surface by the support can also provide better desorption leading to faster formation of colloids or complexes in solution, the heterogeneous Pd thus serving as a reservoir for dissolved species. As found in Heck reactions catalyzed by Pd/C, Pd/alumina, Pd on zeolites, or Pd on silicoaluminophosphates, Pd can dissolve in the beginning of the reaction, while reactants probably act as ligands for the formation of complexes.^{11,19,28,35,38,82,84–86} The concentration of Pd in solution was found to be highest at the beginning of the reaction (20% of the total content of Pd) and gradually dropped with the progress of the reaction. As the reaction comes to an end, most of the Pd reprecipitated at the carbon due to the lack of “reactant ligands”. Properly established reaction conditions (increased reaction temperature, addition of reducing agents, and working under inert conditions) allowed then the minimization of the final Pd concentration in solution.^{28,38,87} Sometimes the final concentration could be reduced to less than 1 ppm.²⁸

Changes of the crystallite structure of the starting Pd/C as compared with the final Pd/C were observed in such cases.²⁸ Effective retrapping of the regenerated Pd(0) species formed in the reductive elimination by the solid support (e.g., charcoal) is a precondition for reusable catalysts.^{11,38,88} Sometimes re-deposition of leached Pd can be so fast and comprehensive that it can mask the leaching phenomenon. The deposition of dissolved Pd species can occur not only

to the original support (re-deposition) but also to other supports added to the mixture, or the dissolved species can precipitate as free Pd particles.³⁸ Naturally the re-deposited Pd exhibits different properties due to crystallite growth as compared with the starting Pd system, and thus normally the catalytic activity drops after each run when the material is used several times.^{28,50} As another effect, re-deposited Pd can catalyze unwanted side reactions, while only the dissolved Pd supports the envisaged cross-coupling.^{11,28}

2. Suzuki Reactions

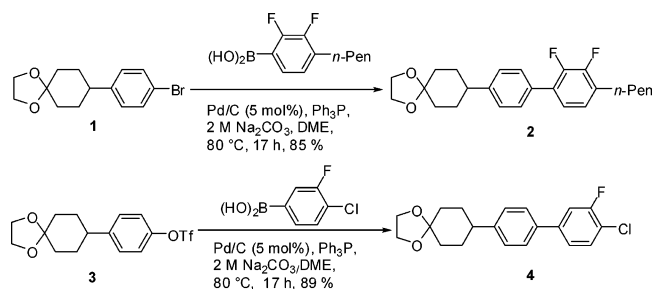
2.1. Pd on Carbon (Pd/C)

The Suzuki–Miyaura reaction has become a mainstay of modern synthetic organic chemistry for the preparation of biaryl compounds.^{89–91} In the past decade, the Pd/C-catalyzed arylation by Suzuki–Miyaura reaction has been applied widely in organic synthesis of biaryl compounds, which can also be heterocyclic. It can further be used in coupling of various organic moieties different from aryl compounds, such as alkenes, alkynes, or alkanes. The first example of Pd/C-catalyzed Suzuki reaction was reported by Marck and co-workers in 1994.⁹² In general, Pd/C is used with or without additional phosphine ligands, and often the application of aqueous solvents is advantageous.

2.1.1. In the Presence of Phosphine Ligands

In the first examples of the application of Pd/C in Suzuki–Miyaura couplings (Scheme 2), triphenylphosphine was used as a ligand adopting the methodology from homogeneous catalysis.³ The bromoarene **1** and the triflate **3** were transformed into the corresponding diaryl products **2** and **4** in high yields.⁹²

Scheme 2. Pd/C-Catalyzed Suzuki Coupling in the Presence of PPh₃



Nishida and co-workers⁵⁹ found that a phosphine ligand was indispensable for the Pd/C-catalyzed Suzuki reactions of halopyridines and haloquinolines in most cases (Table 1). The reactions of bromopyridines **5a–c**, 2-chloropyridine (**5g**), 2-chloropyridines with an electron-withdrawing group **5d–f**, **5h**, and **5i**, and haloquinoline **7a** and **7b** proceeded smoothly and gave the products in good yields (Table 1, entries 1–9, 14, 15, and 17). However, the reactions of 2-chloropyridines with an electron-donating group, **5j** and **5k**, gave unsatisfactory results (Table 1, entries 10 and 11). The reactivity of the substrate showed the same tendency as was seen in the reaction with a homogeneous catalyst; that is, chloropyridines with an electron-withdrawing group were more reactive than those with an electron-donating group.

In order to improve the yields of less-reactive substrates such as 3-chloropyridine (**5l**), 4-chloropyridine (**5m**), and 6-chloroquinoline (**7c**), ligand effects were studied by using

Table 1. Pd/C-Catalyzed Suzuki Coupling of N-Heterocycles **5**, **7**, or **8** with PPh₃

entry	haloheterocycle	ligand	yield ^a (%)
1	5a : R = H, X = 2-Br	PPh ₃	85
2	5b : R = H, X = 3-Br	PPh ₃	90
3	5c : R = H, X = 4-Br ^b	PPh ₃	60
4	5d : R = 3-NO ₂ , X = 2-Cl	PPh ₃	94
5	5e : R = 5-CN, X = 2-Cl	PPh ₃	90
6	5f : R = 5-NO ₂ , X = 2-Cl	PPh ₃	85
7	5g : R = H, X = 2-Cl	none	0
		PPh ₃	82
8	5h : R = 3-CN, X = 2-Cl	none	16
		PPh ₃	100
9	5i : R = 5-CF ₃ , X = 2-Cl	none	30
		PPh ₃	85
10	5j : R = 6-OMe, X = 2-Cl	PPh ₃	25
11	5k : R = 3-NH ₂ , X = 2-Cl	PPh ₃	19
12	5l : R = H, X = 3-Cl	PPh ₃	2
13	5m : R = H, X = 4-Cl ^b	PPh ₃	9
14	7a : X = 2-Cl	none	0
		PPh ₃	91
15	7b : X = 3-Br	none	0
		PPh ₃	91
16	7c : X = 6-Cl	PPh ₃	0
17	8	none	36
		PPh ₃	72

^a Isolated yield. ^b Pyridinium hydrochloride was used.

3-chloropyridine (**5l**) and Pd/C. The sterically hindered 2-(dicyclohexylphosphino)biphenyl **12** (9 mol %) was found to improve the yield dramatically (Table 2, compare entries 1 and 3).^{59,93} It has been reported that bulky and electron-rich ligands increase the yields of homogeneous Suzuki–Miyaura and other coupling reactions.⁹¹ These ligands facilitate oxidative addition, and the spatial bulk around the metal promotes reductive elimination. Thus, during the Pd/C-catalyzed reaction, **12** would interact with the leaching Pd and show the same effects. The combination of Pd/C and **12** was also effective for the reactions of 4-chloropyridine **5m** and 6-chloroquinoline **7c** (Table 2, entries 4 and 5).⁵⁹ Remarkably, this combination was not effective in the reaction of 4-methoxychlorobenzene **11**, but Pd(II)/C and **12** provided high yields of the product. (Table 2, entry 6).

Table 2. Pd/C-Catalyzed Suzuki Coupling of N-Heterocycles **5**, **7c**, or 4-Methoxychlorobenzene, **11**, with Different Ligands

entry	haloheterocycle	ligand	yield ^a (%)
1	5l : R = H, X = 3-Cl	dppp	0
2	5l : R = H, X = 3-Cl	dppb	0
3	5l : R = H, X = 3-Cl	12	88
4	5m : R = H, X = 4-Cl	12	92
5	7c : X = 6-Cl	12	77
6	11	12	80 ^b

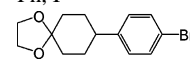
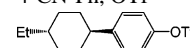
^a Isolated yield. ^b Pd(II)/C was used.

2.1.2. In the Absence of Phosphine Ligands

Already in the early investigations of the application of Pd/C in Suzuki–Miyaura couplings, it was found that ligand-free methodology can be advantageous.⁹² Good to excellent yields of coupling products were obtained when bromide, iodide, or triflate acted as leaving group (Table 3). Chloro substituents in the arylboronic acid were tolerated; that is, they do not react in the Suzuki coupling. The results gave evidence that the Pd/C-assisted coupling reactions might occur by heterogeneous catalysis under these conditions.

Table 3. Ligand-Free Pd/C-Catalyzed Suzuki Coupling

$$\text{Ar-X} + \text{Ar}'\text{-B(OH)}_2 \xrightarrow[\text{EtOH, 80 }^\circ\text{C}]{\text{Pd/C (4 mol\%)}} \text{Ar-Ar}' \quad \mathbf{14}$$

Ar, X	Ar'	base	<i>t</i> (h)	yield ^a (%)
4-CHO-Ph, Br	4-F-Ph	Et ₃ N	5	84
4-CN-Ph, Br	4-Cl-3-F-Ph	Na ₂ CO ₃	1	94
3,5-(CF ₃) ₂ -Ph, Br	4- <i>n</i> -Pr-Ph	Na ₂ CO ₃	0.5	90
4- <i>n</i> -Pr-Ph, Br	3,5-di-F-Ph	2 M Na ₂ CO ₃	19	88
3-F-4-OH-Ph, Br	4- <i>n</i> -Pen-Ph	Na ₂ CO ₃	19	80 ^b
4-Me ₂ N-Ph, Br	4-Cl-3-F-Ph	Na ₂ CO ₃	19	95
Ph, I	4-Cl-3-F-Ph	Na ₂ CO ₃	19	91
	4-Cl-3-F-Ph	Na ₂ CO ₃	19	94
4-Et-Ph, Br	4-Cl-3-F-Ph	2 M Na ₂ CO ₃	19	87 ^b
4-CN-Ph, OTf	Ph	Na ₂ CO ₃	19	50
	Ph	Na ₂ CO ₃	18	84 ^c

^a Isolated yields. ^b DME as solvent. ^c DMF as solvent.

In 2001, LeBlond and co-workers⁷⁶ found an efficient methodology to couple weakly reactive aryl chlorides, which had been a problem in homogeneous Suzuki coupling for a long time. Pd/C in DMA/water was appropriate. The optimal volumetric ratio of DMA/water was found to be 20:1, enabling the cross-coupling to go to completion within 1.5 h without the formation of homocoupling products from the aryl chlorides. These conditions are generally applicable toward aryl chlorides with electron-withdrawing groups and gave 79–95% yields (Table 4). Moderate yields were obtained with neutral or electron-rich aryl chlorides, which could be improved by using greater amounts of catalyst (see entry 7).

Table 4. Pd/C-Catalyzed Suzuki Coupling of Aryl Chlorides

$$\text{Ar-Cl} + \text{Ar}'\text{-B(OH)}_2 \xrightarrow[\text{DMA/H}_2\text{O (20:1), 80 }^\circ\text{C, 24 h}]{\text{Pd/C (5 mol\%), K}_2\text{CO}_3 \text{ (2 equiv)}} \text{Ar-Ar}' \quad \mathbf{15}$$

entry	R	R'	yield ^a (%)	conv (%)
1	NO ₂	H	93	100
2	CF ₃	H	95	100
3	CN	H	83	100
4	Ac	H	79	100
5	H	OMe	45	61
6	OMe	H	32	37
7	Me	H	36, ^b 54 ^c	65, ^b 76 ^c

^a Isolated yield. ^b 48 h. ^c 15 mol % of Pd/C.

Detailed investigations by Köhler's group on Suzuki reactions of aryl bromides and chlorides with phenylboronic acid gave important insights in the effect of the concentration of the Pd/C catalyst and other reaction conditions on the catalytic activity, the yield, and the selectivity.⁸¹ Under optimized conditions, coupling products of bromoarenes and

phenylboronic acid were obtained in excellent yields after short reaction times by using extremely low Pd concentrations of only 0.005–0.01 mol % (Table 5, entries 1–4). High TON, up to 20 000, were achieved. Also deactivated bromoarenes like *p*-bromoanisole could be converted up to 83% without dehalogenation within 60 min (Table 5, entry 5). The highest TOF was 16 600 h⁻¹, and 100% selectivity for the Suzuki coupling product (cross-coupling) was found nearly without exceptions. *p*-Chloroacetophenone could be converted quantitatively at Pd concentrations of 0.25 mol % within 4 h. Conversions up to 90% were achieved after 2 h using 0.005–0.10 mol % Pd.

Table 5. Pd/C-Catalyzed Suzuki Coupling of Aryl Halides with Phenylboronic Acid

$$\text{R-Ar-X} + \text{(HO)}_2\text{B-Ph} \xrightarrow[\text{NMP/H}_2\text{O, 120 }^\circ\text{C}]{\text{Pd/C, base}} \text{R-Ar-Ph} \quad \mathbf{16}$$

X = Br, Cl

entry	X	R	Pd/C (mol %)	NMP/H ₂ O	base	<i>t</i> (h)	conv (%)	yield (%)	TON	TOF
1	Br	CN	0.01	10:4	Na ₂ CO ₃	1.5	100	100	10000	6666
2	Br	H	0.005	10:4	Na ₂ CO ₃	2	100	100	20000	10000
3	Br	OH	0.01	10:4	Na ₂ CO ₃	2	100	100	10000	5000
4	Br	OMe	0.005	10:4	Na ₂ CO ₃	2	100	100	20000	10000
5	Br	OMe	0.005	10:4	Na ₂ CO ₃	1	83	83	16600	16600
6	Cl	Ac	0.25	10:3	NaOH	4	100	98	400	100
7	Cl	Ac	0.10	10:3	NaOH	2	90	88	900	450
8	Cl	Ac	0.05	10:3	NaOH	2	80	78	1600	800

The addition of water to the organic solvent increased the activity. A crucial influence was found for the base. Na₂CO₃ gave the best results for couplings of aryl bromides, whereas NaOH promoted the deborylation and dehalogenation resulting in a decreased selectivity. In contrast, NaOH is found to be the best choice for activated aryl chlorides under the conditions applied (120 °C, NMP/water). Again it has to be mentioned that the optimum reaction temperature (120 °C) is higher than in a typical homogeneously catalyzed Suzuki reaction (about 80 °C).

On the other hand, room temperature was appropriate in Pd/C-catalyzed coupling of iodophenols **17** with arylboronic acids in water in the presence of K₂CO₃ (Table 6).⁸⁸ In the case of bromophenol, higher temperature was advantageous (entries 8 and 9).

Table 6. Pd/C-Catalyzed Coupling of Halophenols with Arylboronic Acid in Aqueous Media

$$\text{Ar-X-OH} + \text{Ar}'\text{-B(OH)}_2 \xrightarrow[\text{H}_2\text{O, RT, 12 h}]{\text{Pd/C (0.3 mol\%), K}_2\text{CO}_3} \text{Ar-Ar}'\text{-OH} \quad \mathbf{18}$$

entry	halophenol	arylboronic acid	<i>T</i> (°C)	yield (%)
1	2-iodophenol	PhB(OH) ₂	RT	70
2	3-iodophenol	PhB(OH) ₂	RT	97
3	4-iodophenol	PhB(OH) ₂	RT	>99
4	4-iodophenol	4-FC ₆ H ₄ B(OH) ₂	RT	>99
5	4-iodophenol	4-MeOC ₆ H ₄ B(OH) ₂	RT	>99
6	4-iodophenol	4-MeC ₆ H ₄ B(OH) ₂	RT	>99
7	4-iodophenol	2-MeOC ₆ H ₄ B(OH) ₂	RT	98
8	4-bromophenol	PhB(OH) ₂	RT	35
9	4-bromophenol	PhB(OH) ₂	50	76

It is noteworthy that the recovered Pd/C possesses enough catalytic activity for further coupling reactions. Application of recovered Pd/C to the coupling of 4-iodophenol and phenylboronic acid revealed that the catalytic activity gradu-

ally diminished, but the yield was still 89% after the fifth reuse (Table 7).

Table 7. Reaction of 4-Iodophenol with Phenylboronic Acid Using Recovered Pd/C as Catalyst

entry	Pd/C catalyst	yield (%)
1	fresh	>99
2	first reuse	95
3	second reuse	94
4	third reuse	90
5	fourth reuse	89
6	fifth reuse	89

Recently, Sajiki et al. reported an efficient protocol⁹⁴ for the phosphine-free Suzuki reaction catalyzed by Pd/C at room temperature. Unlike in the procedure used by Köhler et al.⁸¹ (*vide supra*), a commercial catalyst was used, and the reaction could be carried out at room temperature omitting the need for sealed tubes but needing much higher quantities of catalyst (10 mol %). Bromoarenes with either electron-withdrawing substituents, such as NO₂, CHO, COCH₃, or CO₂C₂H₅, or electron-donating substituents, such as OCH₃, coupled readily with arylboronic acids in excellent yields (Table 8) using commercially available 10% Pd/C (3.5 mol %) in ethanol–H₂O (1:1) and Na₂CO₃. Aryl bromides containing electron-withdrawing substituents reacted faster than those with electron-donating substituents (for example, entry 1 vs entries 2–4).

Table 8. Pd/C-Catalyzed Suzuki Coupling of Aryl Bromides and Arylboronic Acids at RT

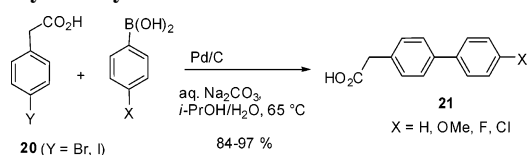
entry	R	R'	t (h)	yield ^a (%)
1	OMe	H	6	95
2	Ac	H	5	99
3	NO ₂	H	2	>99
4	CHO	H	5	>99
5	Ac	4-OMe	2	97
6	CHO	4-OMe	2	96
7	NO ₂	4-OMe	1	98
8	OMe	4-OMe	5	>99
9	Ac	3-OMe	3	>99
10	OMe	2-OMe	5	94
11	NO ₂	2-OMe	4	>99
12	CHO	2-OMe	5	98
13	Ac	2-OMe	4	>99
14	NO ₂	4-Ac	19	>99
15	CO ₂ Et	H	3	99

^a Isolated yield.

The catalyst could be recovered using a simple filtration and washing sequence. Reuse was possible without significant decrease in coupling yield even in the fourth run.

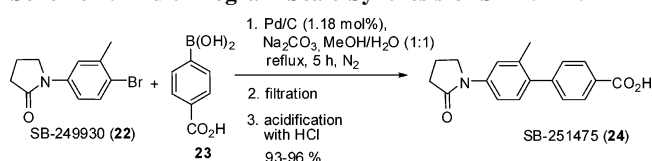
Ligand-free Pd/C-catalyzed Suzuki–Miyaura coupling also tolerates acid groups in the haloarene and in the arylboronic acid. It was used in the synthesis of biarylacetic acids **21** (Scheme 3).⁹⁵

Scheme 3. Synthesis of Biarylacetic Acids by Pd/C-Catalyzed Arylation



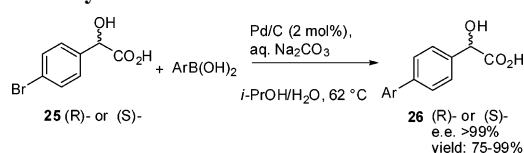
The Pd/C-mediated synthesis of the diarylcarboxylic acid **24** was implemented on a large scale (2 × 6.3 kg batches) in a pilot plant (Scheme 4).³¹ Similarly, a phenyldiboronate was coupled twice with 3-iodophthalate under ligand-free conditions in the presence of Cs₂CO₃.⁹⁶

Scheme 4. Multikilogram-Scale Synthesis of SB-251475



The integrity of the configuration was maintained in the Pd/C-catalyzed Suzuki coupling of optically active 4-bromomandelic acids in the presence of Na₂CO₃ providing enantiopure 4-arylmandelic acids **26** (Scheme 5).⁹⁷ Both, electron-donating and electron-withdrawing groups were tolerated in the arylboronic acid.

Scheme 5. Coupling of Optically Active 4-Bromomandelic Acid with Arylboronic Acids



Recently, it was shown that tetraarylborates can be used in ligand-free Pd/C-catalyzed Suzuki reaction of bromoarenes.⁹⁸ Various biaryl carboxylic acids and phenols were prepared in high yields (Table 9). Again, the catalyst could be reused several times. For example, coupling of 4-bromobenzoic acid with sodium tetraphenylborate catalyzed by recovered Pd/C provided 88%, 84%, 81%, and 76% yield in the first to the fourth reuse, respectively.

Bromo- and iodoheteroarenes can also be used in ligand-free Pd/C-catalyzed Suzuki coupling. Thus the quinoline **30** was obtained with a very low level of residual Pd. Leached Pd was found in the reaction mixture, which diminished to less than 4 ppm after completion of the reaction; that is, the reaction runs by homogeneous catalysis (Scheme 6).⁸⁷

The Pd/C-catalyzed synthesis of pyrazolylphenylsulfonamides **32** was implemented in 100-mg scale using a Quest model 210 synthesizer (Scheme 7).⁹⁹

5-Aryl-2-furfurals **34** were synthesized by Pd/C catalyzed, ligand-free Suzuki coupling starting from the corresponding diethyl acetal **33** (Table 10).¹⁰⁰

A strong effect of the halide was found in Pd/C-catalyzed ligand-free Suzuki cross-coupling of 2-halocycloalkenones with arylboronic acids.¹⁰¹ While 2-iodocycloalkenones **35** reacted under mild conditions at 25 °C under air in aqueous DME (Table 11), the corresponding 2-bromo-2-cyclohexen-1-one completely failed to undergo Suzuki coupling under the same conditions. Only extensive decomposition of starting materials was observed.¹⁰¹

The coupling of 2-iodo-2-cyclohexen-1-one with phenylboronic acid was also examined using recovered catalyst. It was found that the Pd/C catalyst could be reused at least five runs without affecting the yield (79–85%). The progressive decrease in the activity could be efficiently balanced by increasing the temperature of the reaction from 25 to 50 °C.¹⁰¹

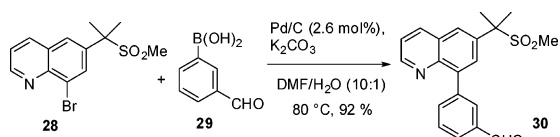
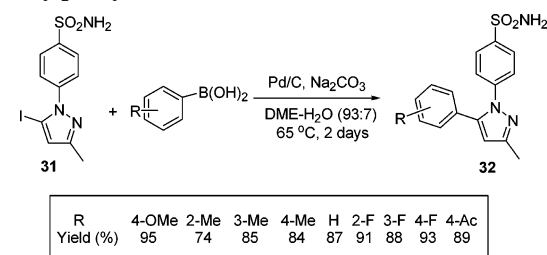
Table 9. Pd/C-Catalyzed Suzuki Reactions of Aryl Bromides with Sodium Tetraphenylborate

Tetraphenylborate

$$\text{Ar-Br} + \text{Ph}_4\text{BNa} \xrightarrow[\text{Na}_2\text{CO}_3, \text{H}_2\text{O}]{5\% \text{ Pd/C}} \text{Ar-Ph} \quad \mathbf{27}$$

Product 27 ^a	Pd/C (mol %)	Yield ^b (%)	TON
	0.0025	94	37,600
	0.01	95	9500
	0.05	97	1940
	0.05	>99	>1980
	0.05	>99	>1980
	0.05	94	1880
	0.01	99	9900
	0.005	>99	>19,800
	0.1	74	740 ^c
	0.05	98	1960
	0.05	99	1980

^a Reaction conditions: 0.27 equiv (based on bromide) Ph₄BNa, 2.00 equiv Na₂CO₃, reflux under air for 1 h. ^b Yields determined by HPLC analysis. ^c Reaction time was 24 h.

Scheme 6. Pd/C-Catalyzed Synthesis of Arylquinoline 30**Scheme 7. Pd/C-Catalyzed Synthesis of Pyrazolyphenylsulfonamides 32**

2.1.3. Ligand-Free Suzuki Coupling in Aqueous Surfactants

Although many Pd/C-catalyzed Suzuki reactions provided good results in water or water/organic solvent mixtures, it can be useful to use water in the presence of surfactants,

Table 10. Pd/C-Catalyzed One-Pot Synthesis of 5-Aryl-2-furfurals

$$\mathbf{33} + \text{Ar-I} \xrightarrow[\text{36 h}]{\text{1) 10\% Pd/C (10 wt\%), Et}_3\text{N, EtOH, 60}^\circ\text{C, 2-}} \mathbf{34}$$

2) H₂O, CF₃CO₂H

Ar	t (h)	yield ^a (%)
4-NO ₂ -Ph	2	81
3-NO ₂ -Ph	2	91
2-NO ₂ -Ph	16	84
4-MeO ₂ C-Ph	18	78
4-CF ₃ -Ph	6	91
2-thienyl	36	79 ^b

^a Isolated yield. ^b Additional Pd/C (10 wt %) was required.

such as tetrabutylammonium bromide. The methodology can provide the following advantages in comparison with more conventional procedures: no organic solvent is needed; ultralow surface tension allows fast and easy mixing of reagents; the systems are formed spontaneously and vigorous mechanical or ultrasonic agitation is not needed to obtain and maintain these systems.

Arcadi et al. reported a mild and versatile method for Pd/C-catalyzed Suzuki coupling of aryl halides in water and surfactants.¹⁰² The concentration of the surfactants in water played a pivotal role for the outcome of the reaction. A series of biaryls were obtained in good to excellent yields from aryl iodides, bromides, and chlorides (Table 12, exception of 4-chloroanisole in entry 12).

The experimental procedure is very simple. Liquid–liquid extraction with a common organic solvent, such as diethyl ether, allows the quantitative recovery of the product from the water–surfactant Pd/C system. The activity of the recovered water–surfactant Pd/C system was monitored using the reaction of 4-bromoanisole with PhB(OH)₂. Although the catalytic activity gradually diminished (yield of 4-methoxybiphenyl for first reuse 95%, second reuse 88%, third reuse 85%, and fourth reuse 80%), the yield was still 80% even after the fourth reuse.

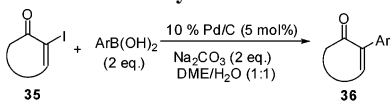
A marked effect of tetrabutylammonium bromide (TBAB) on the yield of products **39** was found in the Pd/C-catalyzed Suzuki reaction of chloro- and bromopyridines **38** with phenylboronic acid in water.⁵⁹ The yields increased from 21–55% to 67–95% when TBAB was used (Table 13).

In 2005, Köhler's group developed ligandless Pd/C-catalyzed Suzuki cross-coupling reactions of various aryl chlorides in aqueous surfactant (TBAB). This procedure is a very attractive way of accessing multifunctional biaryls because sensitive functional groups like ester and nitrile groups are tolerated (Table 14).¹⁰³

2.1.4. Ligand-Free Suzuki Coupling under Microwave or Ultrasound Conditions

Microwave (MW) heating and high-intensity ultrasound (US) have emerged as powerful techniques by which reactions can be brought to completion in shorter reaction times in a number of cases. Such conditions can also be advantageous in Pd/C-catalyzed Suzuki cross-coupling reactions.

Leadbeater et al. reported the Pd/C-catalyzed Suzuki coupling of aryl chlorides with phenylboronic acid in water using microwave heating with simultaneous cooling (Table 15).¹⁰⁴

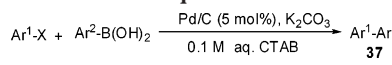
Table 11. Pd/C-Catalyzed Suzuki Coupling of 2-Iodocycloalkenones with Arylboronic Acids¹⁰¹


2-iodocyclo- alkenone	Ar-B(OH) ₂	T (°C), t (h)	Yield (%)
		25, 12	86
		25, 12	90
		25, 12	80
		25, 12	98
		25, 12	81
		25, 12	78
		25, 12	81
		25, 12	71
		25, 12	85
		50, 12	81
		25, 12	95
		25, 12	96
		80, 6	91

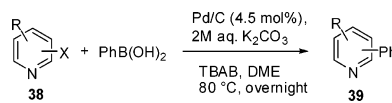
^a Isolated yields.

Pd/C-catalyzed coupling of iodoarenes with methoxyphenylboronic acids in methanol/water using KF as the base gave high yields of the diaryl **42** under ultrasound irradiation (Scheme 8).⁷⁰

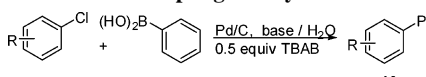
In the bromo- and iodoarene series, the simultaneous use of high-intensity ultrasound and microwave irradiation

Table 12. Pd/C-Catalyzed Suzuki Coupling of Aryl Halides with Arylboronic Acids in 0.1 M aq CTAB


entry	Ar ¹	X	Ar ²	T (°C)	t (h)	yield (%)
1	4-MeO-Ph	I	Ph	RT	24	95
2	4-MeO-Ph	Br	Ph	RT	24	94
3	4-MeO-Ph	Br	4-Me-Ph	RT	24	96
4	4-MeO-Ph	Br	4-F	RT	24	89
5	4-MeO-Ph	Br	3-OMe	RT	24	65
6	5-pyrimidyl	Br	Ph	RT	24	65
7	4-CHO-Ph	Br	Ph	RT	24	74
8	2-NO ₂ -Ph	Br	Ph	60	24	95
9	2-Ac-Ph	Br	Ph	60	4	89
10	4-Ac-Ph	Cl	Ph	100	24	85
11	2-NH ₂ -4-CF ₃ -Ph	Cl	Ph	100	24	96
12	4-MeO-Ph	Cl	Ph	100	24	6

Table 13. Pd/C-Catalyzed Suzuki Coupling of Pyridyl Halides in Aqueous TBAB


pyridyl halide	TBAB (equiv)	yield ^a (%)
R = H, X = 2-Br	0	21
	0.1	67
R = H, X = 3-Br	0	54
	0.1	85
R = H, X = 4-Br ^b	0	55
	0.3	67
	1.5	95
R = 3-NO ₂ , X = 2-Cl	0	49
	0.1	67
R = 5-CN, X = 2-Cl	0.3	87
	0	34
	1.5	69

^a Isolated yields. ^b Pyridinium hydrochloride was used.**Table 14. Suzuki Cross-Coupling of Aryl Chlorides in aq TBAB**


R	Pd (%)	base, equiv	PhB(OH) ₂ (equiv)	T (°C), t (h)	yield ^a (%)
4-Ac	0.2	NaOH, 2.5	1.1	100, 2	99
4-CN	0.5	KF, 2.5	1.1	100, 3	98
2-CN	0.5	KF, 2.5	1.1	140, 3	89
4-CO ₂ Me	0.5	KF, 2.5	1.1	140, 3	87
H	0.5	KF, 2.5	1.1	140, 6	73 ^b
4-Me	2	NaOH, 5	1.5	140, 6	81
2-Me	2	NaOH, 5	1.5	140, 6	74
4-OMe	2	NaOH, 5	1.5	140, 6	83
4-NH ₂	2	NaOH, 5	1.5	140, 6	66 ^c

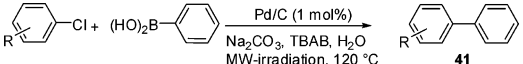
^a Isolated yield; reaction conditions, 4 mmol of ArCl in 6 mL of water. ^b 4-Tolylboronic acid was used. ^c Determined by ¹H NMR.

sometimes gave better results in ligand-free Pd/C-catalyzed Suzuki cross-coupling reactions than just using one of these effects (Table 16).¹⁰⁵

2.2. Palladium on Metal Oxides

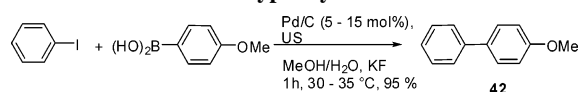
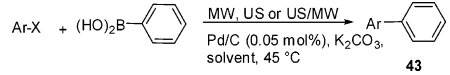
2.2.1. Palladium-Doped KF/Al₂O₃

Palladium-doped KF/Al₂O₃ was used in solvent-free Suzuki couplings. A series of bases, organohalides **44**, and boronic acids **45** were investigated.¹⁰⁶ KF turned out to be

Table 15. Coupling of Aryl Chlorides with Phenylboronic Acid under Microwave Irradiation^a


aryl chloride (R)	reaction time (min)	simultaneous cooling	yield (%)
4-Ac	10	no	89
4-NO ₂	10	yes	90
		no	96
4-CN	10	yes	94
		no	79
4-Me	10	yes	80
		no	40
2-Me	10	yes	75
		no	25
H	10	yes	64
		no	59
4-OMe	10	yes	65
		no	36
2-NH ₂	30	yes	65
		no	21
		yes	56

^a Reactions were run in a sealed tube using 1 mmol of aryl chloride, 1.3 mmol of phenylboronic acid, 1 mol % Pd/C, 3.7 mmol of Na₂CO₃, 1 mmol of TBAB, and 2 mL of H₂O. An initial microwave irradiation of 300 W was used, the temperature being ramped from room temperature to 120 °C.

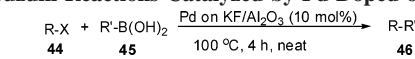
Scheme 8. Ultrasound-Promoted Suzuki Coupling of Iodobenzene and 4-Methoxyphenylboronic Acid**Table 16. Suzuki Coupling of Aryl Halides with Phenylboronic Acid^a**







aryl halide	US ^b yield (%)	MW ^c yield (%)	US/MW ^d yield (%)
4-iodoaniline	90	86	
4-bromoaniline	97	90	
4-iodoanisole	72	78	
3-bromoanisole	54	64	88
2-bromoanisole	79	70	
2-iodothiophene	40	37	59
1-iodonaphthalene	32	63	
4-bromobenzonitrile	78	74	

^a Under argon atmosphere, 1 mmol of phenylboronic was reacted with 1 mmol of aryl halide and 2 mmol of K₂CO₃, using 0.05 mmol of Pd/C as catalyst. ^b Ultrasound irradiation (20.5 kHz, 90 min), THF/water or DME/water, 1:1, as solvent at 45 °C. ^c MW irradiation (700 W, 20 min), DME as solvent. ^d DME/water, 2:1, as solvent, 1 h irradiation (US 20.5 kHz, MW 700 W).

the most effective base. As usual, aryl iodides gave better results than the bromides and chlorides (Table 17). Arylboronic acids are more reactive than alkenylboronic acids and alkylboronic acids. Relatively high quantities of Pd were used.

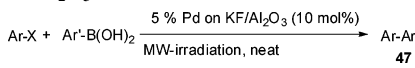
Solvent-free Suzuki reactions catalyzed by Pd-doped KF/Al₂O₃ were also investigated under microwave irradiation.^{107,108} Reduction of reaction times from hours to a few minutes could be achieved in this way (Table 18). Again, relatively high amounts of Pd were necessary. The catalyst could be recovered by a simple filtration and washing

Table 17. Suzuki Reactions Catalyzed by Pd Doped on KF/Al₂O₃


R-X	R'-B(OH) ₂	Yield (%) ^a
Ph-I	Ph-B(OH) ₂	99
Ph-Br	Ph-B(OH) ₂	60
Ph-Cl	Ph-B(OH) ₂	5
	Ph-B(OH) ₂	39
	Ph-B(OH) ₂	66
	Ph-B(OH) ₂	0
Ph-I	4-Me-Ph-B(OH) ₂	98
Ph-I		79
Ph-I		29

^a Isolated yields.

sequence and could be reused. Suzuki–Miyaura coupling of iodobenzene with tolylboronic acid under solvent-free conditions applying thermal and microwave enhancement revealed that the recovered catalyst exhibited the same activity through at least six cycles.¹⁰⁷

Table 18. MW-Enhanced Solvent-Free Suzuki Reactions on Pd-Doped KF/Al₂O₃


Ar-X	Ar'	conditions	yield (%)	ref
Ph-I	4-Me-Ph	15 min, 30 W	98	108
Ph-I	4-MeO-Ph	2 min, 90 W	95	108
4-Me-Ph-I	Ph	2 min, 90 W	82	108
Ph-I	3-Cl-Ph	2 min, 60 W	58	108
2-Py-Br	Ph	5 min, 60 W	66	108
2-Py-Br	Ph	5 min, 60 W	40	108
Ph-I	4-Me-Ph	2 min, 100 W	82	107
Ph-Br	4-Me-Ph	2 min, 100 W	52	107
Ph-Cl	4-Me-Ph	2 min, 100 W	4	107
Ph-I	4-Cl-Ph	2 min, 100 W	87	107

2.2.2. Iron Oxide Nanoparticle-Supported Pd–N-Heterocyclic Carbene Complexes

A kind of Pd–N-heterocyclic carbene complex (Pd–NHC complex) fixed to iron oxide via a polymer was prepared by Gao's group as shown in Scheme 9. The catalyst was stable and demonstrated high catalytic activity in promoting Suzuki reactions.¹⁰⁹ High yields were achieved with various aryl iodides or bromides and arylboronic acids using only 0.015 mol % catalyst (Table 19).

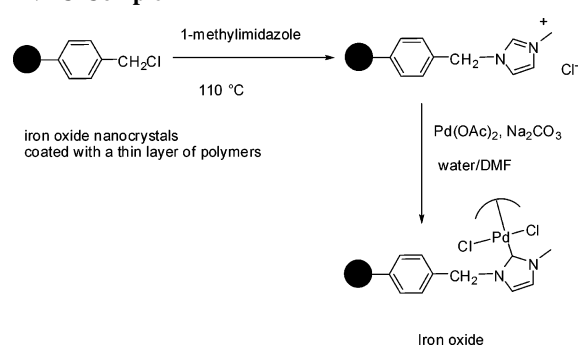

Scheme 9. Preparation of Fe₂O₃ Nanoparticle-Supported Pd–NHC Complex

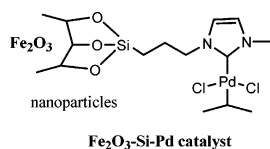
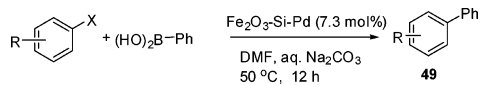
Table 19. Suzuki Couplings of Aryl Halides and Arylboronic Acids Catalyzed by Fe₂O₃-Nanoparticle-Supported Pd–NHC Complex


R ¹	X	R ²	yield ^a (%)
H	I	2-Me	86
H	I	3-Me	88
H	I	2-OMe	84
H	I	3-Ac	89
H	I	1-Naph	82
H	I	4-CN	82
2-Me	I	H	87
4-Me	I	H	88
2-OMe	I	H	74
4-OMe	I	H	83
4-Ac	I	H	80
3-Me	Br	H	74
2-OMe	Br	H	70
3-OMe	Br	H	72
4-OMe	Br	H	78

^a Isolated yields; average of at least two runs.

As a special feature, the recovery of this paramagnetic catalyst was facilely achieved by using a permanent magnet. Isolated catalysts were used for subsequent new rounds of reactions without significant loss of catalytic activity.

Later, Gao's group prepared another kind of magnetic maghemite (γ -Fe₂O₃)–silica nanoparticles where Pd was complexed via a tethered nitrogen heterocyclic carbene (Fe₂O₃–Si–Pd catalyst) (Figure 1). Application of this catalyst in Suzuki coupling reactions of aryl iodides or aryl bromides gave good results (Table 20).¹¹⁰

**Figure 1.** Structure of maghemite–silica nanoparticle-supported NHC Pd complex.**Table 20. Maghemite–Silica-Nanoparticle-Supported Pd-Catalyzed Suzuki Reactions**


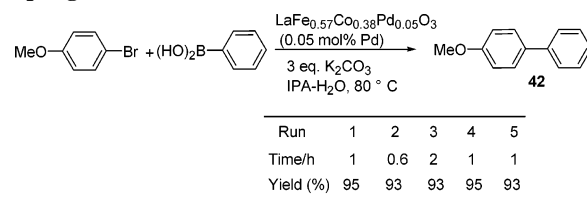
R	X	GC yield (%)	isolated yield (%)
2-Me	I	95 ^a	87
2-Me	Br	93	84
2-OMe	I	99	91
4-Ac	I	99	93

^a First run; the second to fifth round yield gave 94%, 95%, 93%, and 93% yield, respectively.

2.2.3. Palladium-Containing Perovskites

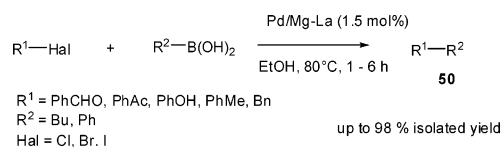
It was demonstrated that Pd-containing perovskites are a general class of heterogeneous catalysts possessing utility in cross-coupling reactions.¹¹¹ The mechanism involves the generation of soluble, catalytically active palladium species that have been desorbed from the bulk inorganic phase and will probably be re-deposited on a modified solid phase after the reaction is complete. Palladium-containing perovskites

also turned out to be effective catalysts in Suzuki coupling reactions of aryl iodides and aryl bromides.¹¹² The catalyst could easily be recovered and reused.¹¹³ In the case of coupling of 4-bromoanisole and phenylboronic acid, the catalyst could be used for five runs without any detectable loss of catalytic activity (Scheme 10).

Scheme 10. Recovered Pd-Perovskites-Catalyzed Suzuki Coupling

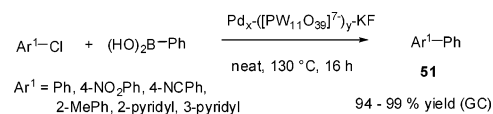
2.2.4. Miscellaneous Metal Oxides

Recently, Hell et al. used a Pd/MgLa mixed oxide catalyst in Suzuki–Miyaura cross-coupling reactions of boronic acids with aryl halides, as well as with benzyl bromide, in ethanol using potassium carbonate or triethylamine as bases (Scheme 11).¹¹⁴ The catalyst could be reused several times and provided high yields also if aryl chlorides were used.

Scheme 11

Pd catalysts using sepiolites as solid support allowed the Suzuki reaction of iodobenzene with phenylboronic acid to be carried out without using an additional base.⁵⁷ Reusage of such catalysts was possible, however, under considerable loss of activity. The catalyst could be reactivated to a certain extent when alkali exchanged sepiolites were used.

The application of a Pd_x–([PW₁₁O₃₉]^{7–})_y–KF catalyst obtained by fixing Pd_x–([PW₁₁O₃₉]^{7–})_y–nanoparticles on KF allowed the synthesis of biaryls **51** from aryl or heteroaryl chlorides and phenylboronic acid under solvent-free conditions in excellent yields (Scheme 12).⁴⁵

Scheme 12

2.3. Pd on Porous Aluminosilicates

Zeolites as well-defined porous materials can be used as supports for Pd as such or in a modified manner. Pd(II) on basic zeolites was reported in the Suzuki–Miyaura coupling of bromobenzene with phenylboronic acid in toluene.¹¹⁵ No leaching was observed, and the solid catalyst could be reused after washing with water. Only a minor decrease in the catalytic activity was observed.

Pd(II)–NaY zeolite or Pd(0)–NaY zeolite performed very well in Suzuki reactions of aryl bromides without the addition of a ligand.^{116,117} The catalysts exhibited excellent activity with K₂CO₃ or Na₂CO₃ as base at room temperature allowing high yields to be achieved after short reaction times. However they were less useful for aryl chlorides. It was found out that the coupling reactions occurred on the external surface

of the zeolites. The solid catalyst could be reused after regeneration (Table 21).

Table 21. Pd(II)–NaY- and Pd(0)–NaY-Catalyzed Suzuki Reactions

Ar-X + Ar'-B(OH) ₂		Pd-catalyst (2.5 mol%) Na ₂ CO ₃ , DMF/H ₂ O RT, 1 h	
Ar-X	Ar'	Pd(II)–NaY yield ^a (%)	Pd(0)–NaY yield ^a (%)
4-MeOC ₆ H ₄ I	C ₆ H ₅	>99	
4-MeOC ₆ H ₄ Br	C ₆ H ₅	93 (92)	95
3-MeOC ₆ H ₄ Br	C ₆ H ₅		97
2-MeOC ₆ H ₄ Br	C ₆ H ₅		85
C ₆ H ₅ Br	4-MeC ₆ H ₄	(94)	98
4-CNC ₆ H ₄ Br	C ₆ H ₅	90 (78)	100
4-NO ₂ C ₆ H ₄ Br	C ₆ H ₅	54 (44)	51
4-AcC ₆ H ₄ Br	C ₆ H ₅	>99 (88)	71
4-AcC ₆ H ₄ Cl	C ₆ H ₅		26 ^b
4-CF ₃ C ₆ H ₄ Cl	C ₆ H ₅	52 ^b	

^a GC yield, isolated yields in parenthesis. ^b At 100 °C.

As a further way to solid-supported Pd catalysts, the complexes PdCl₂[Ph₂P(CH₂)₄SO₃Na] or K were directly loaded to alkylsulfonated mesoporous supports. The resulting heterogeneous catalyst was applied to the coupling of 4-iodoanisole with phenylboronic acid.^{118,119} It could be recycled and reused. Remarkably, the recycled catalysts showed an enhanced activity.

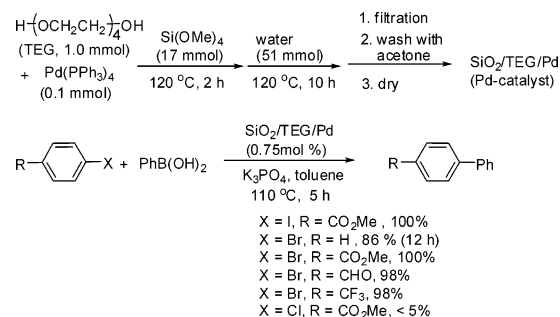
2.4. Pd on Modified Silica

Silica-supported Pd catalysts useful for Suzuki and also other cross-coupling reactions can be prepared in various ways providing different structures. Thus, Pd can directly be deposited onto silica, or it can be anchored as a complex by ligands, which are covalently linked to the silica. In the latter case, postmodification of mesoporous silica or silica spheres is possible, for example, by grafting a ligand (such as SH) separated by a spacer. Pd(II) finally forms a complex with this solid-supported ligand. As an alternative, it is also possible to use a Pd complex with a reactive linker substituent, which can covalently bind to the mesoporous silica. As a further method of catalyst preparation, a sol-gel method can be applied using tetraalkoxysilane and a Pd ligand (e.g., OH or stable carbene) bearing a spacer-separated functional group, which is able to react with the tetraalkoxysilane. An amorphous material is formed, which is treated with Pd(OAc)₂ to provide a catalyst on amorphous silica. In these cases, Pd is mainly encapsulated in the silica matrix.

A highly active Pd catalyst on amorphous silica (SiO₂/TEG/Pd) for Suzuki couplings was prepared via Pd nanoparticles obtained from Pd(PPh₃)₄ in tetra(ethylene glycol) and tetramethoxysilane, which become encapsulated in a silica matrix.¹²⁰ It was efficient in coupling of aryl iodides and aryl bromides but not active enough toward aryl chlorides. The reusability was tested in the coupling of phenyl boronic acid and methyl 4-bromobenzoate. The catalyst could be reused three times without losing activity (Scheme 13).

Pd(II) on silica fixed by mercaptopropyl ligands using mercaptopropylsiloxane was prepared on mesoporous silica (Pd–SH–FSM) and on amorphous silica (Pd–SH–SiO₂). The activity of the different recycled catalysts were in the order Pd–SH–FSM > Pd–SH–SiO₂ > Pd deposited on nonfunctionalized mesoporous silica. Obviously the SH ligands prevent formation of less active Pd aggregates. In

Scheme 13. Preparation of SiO₂/TEG/Pd and Its Use as Catalyst in Suzuki Reactions



particular, Pd–SH–FSM had been shown to act as an active, stable, and recyclable heterogeneous catalysts for the Suzuki reaction of 4-bromoanisole and phenylboronic acid.⁴⁷

Suzuki coupling of less reactive aryl chlorides and bromides could be achieved with a Pd catalyst on another mercaptopropyl-modified mesoporous silica (SBA-15–SH–Pd, Table 22).¹²¹ It could be reused four times without any loss of catalytic activity. Several heterogeneity tests (hot filtration experiments, three-phase tests) indicated that the majority of the catalysis (>95%) occurred on the supported Pd, but leaching was also found to a low extent.

Table 22. SBA-15–SH–Pd-Catalyzed Suzuki Reactions

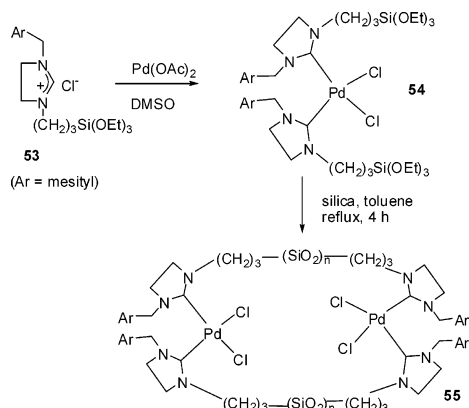
Ar-X + PhB(OH) ₂		SBA-15-SH-Pd (1 mol %) K ₂ CO ₃ , solvent		Ar-Ph	
entry	Ar-X	solvent	T (°C)	t (h)	yield ^a (%)
1	chlorobenzene	DMF	100	24	67
2	4-chloroacetophenone	H ₂ O	100	24	96
3	4-bromoacetophenone	DMF/H ₂ O ^b	80	8	98 ^c
4	4-bromoacetophenone	H ₂ O	80	5	98 ^d
5	3-bromopyridine	DMF/H ₂ O ^b	90	15	98
6	4-bromotoluene	DMF/H ₂ O ^b	90	15	82
7	4-bromoanisole	H ₂ O	90	15	96
8	4-bromobenzaldehyde	H ₂ O	90	15	97

^a Isolated yield. ^b DMF/H₂O (20:1). ^c Recycles of 1, 2, 3, and 4 gave yields of 97%, 97%, 95%, and 95%. ^d Recycles of 1, 2, 3, and 4 gave yields of 99%, 97%, 96%, and 92%.

Similar to mercaptopropyl ligands, aminopropyl ligands were grafted to amorphous silica by reaction with the corresponding aminopropyltriethoxysilane. These modified silica were loaded with Pd nanoparticles by treating with Pd(OAc)₂. These catalysts worked well in Suzuki reaction of aryl bromides with arylboronic acids (K₃PO₄, toluene, 100 °C) when chelating diamines and triamines were used as organic modifiers.¹²² An optimal catalyst could be reused four times without a significant loss of activity, but the activity decreased in further runs.

Electron-rich imidazolidine carbene Pd(II) complexes **54** could be grafted onto mesoporous silica via a propyltriethoxysilane linker (Scheme 14).^{122,123} The resulting catalyst **55** exhibited excellent activity in Suzuki coupling of non-activated chloroarenes (Table 23).¹²³ The catalyst was stable and could be reused.

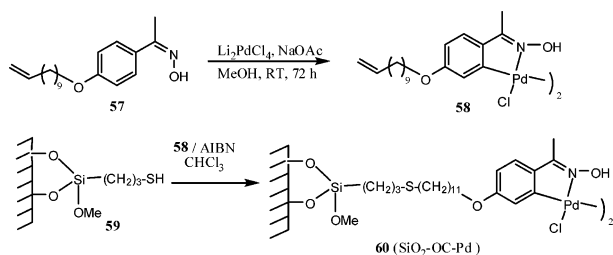
Another very effective catalyst **60** (SiO₂–OC–Pd) was obtained by Corma, García et al. by grafting a preformed oxime-carbapalladacycle Pd(II) complex **58** onto silica using a mercaptopropyl linker (Scheme 15).¹²⁴ The catalyst provided a quantitative yield in the Suzuki reaction of *p*-chloroacetophenone and phenylboronic acid in water; leach-

Scheme 14. Synthesis of Carbene–Pd Complexes Fixed to Modified SiO₂**Table 23. Suzuki Reactions of Chloroarenes with Phenylboronic Acid^a**

R	catalyst	yield ^b (%)
Ac	Pd(OAc) ₂ /53	90
	Pd complex 55	86 ^c
OCH ₃	Pd(OAc) ₂ /53	93
	Pd complex 55	88 ^c
CH ₃	Pd(OAc) ₂ /53	91
	Pd complex 55	85 ^c
CHO	Pd(OAc) ₂ /53	97
	Pd complex 55	90 ^c

^a Reaction conditions: 1.0 mmol of chloride, 1.5 mmol of PhB(OH)₂, 3 mL of dioxane. ^b Isolated yield. ^c Fourth run.

ing was not found, and the same catalyst sample was reused eight times without decreased activity (Table 24).¹²⁴

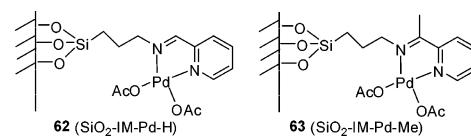
Scheme 15. Preparation of SiO₂–OC–Pd Catalyst 60**Table 24. SiO₂–OC–Pd-Catalyzed Suzuki Reactions in Aqueous Media**

conditions	X	t (h)	conv (%)
water/TBAB	Br	1	62
water	Br	<0.1	>99
water	Cl	0.25	91
water ^a	Cl	2	99
water/dioxane (3:2)	Cl	0.25	55 ^b

^a Catalyst was reused eight times. ^b Biphenyl was detected as byproduct.

Silica-supported imidazole-palladacycles SiO₂–IM–Pd–H **62** and SiO₂–IM–Pd–Me **63** (Figure 2) exhibited excellent catalytic activity, recyclability, and stability in Suzuki–Miyaura coupling of aryl bromides and phenylboronic acid

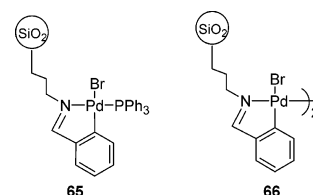
(Table 25).^{125,126} The catalysts had very low loading of palladium and were considered to be completely heterogeneous under the reaction conditions.

**Figure 2. SiO₂–IM–Pd–H, **62**, and SiO₂–IM–Pd–Me, **63**.****Table 25. Suzuki Reactions Catalyzed by Modified SiO₂-Supported Pd Complexes**

R	catalyst	t (min)	yield ^a (%)
H	62 (1.2 mol %)	180	95
CN	62 (1.2 mol %)	120	92
Cl	62 (1.2 mol %)	180	88
OMe	62 (1.2 mol %)	360	79
CH ₂ Br	62 (1.2 mol %)	360	60
H	63 (0.4 mol %)	90	100
OMe	63 (0.4 mol %)	120	92
CN	63 (0.4 mol %)	60	97
PhCO	63 (0.4 mol %)	90	95
OH	63 (0.4 mol %)	90	85

^a GC yield.

The imine-based palladacyclic silico-supported catalysts **65** and **66** (Figure 3) were found to be less active in Suzuki reactions of aryl bromides with phenylboronic acid than their homogeneous counterparts. These catalysts also exhibited poor recyclability probably because of the instability of the complex liberating zero-valent Pd species in the solution by reductive elimination.¹²⁷

**Figure 3. Imine-based palladacyclic catalysts **65** and **66**.****2.5. Pd on Clays and Other Inorganic Materials**

Sepiolite clay supported Pd (Pd(II)–sepiolite) could easily be obtained by treating the clay with aqueous [Pd(NH₃)₄]Cl₂ and drying under vacuum. It effectively catalyzed the Suzuki coupling of phenylboronic acid with aryl halides in DMF including less reactive electron-rich aryl bromides (Table 26).¹²⁸ The catalyst exhibited a remarkably high TON, and thus low amounts of catalyst were necessary (0.02 mol %).

The unusually high reactivity of electron-rich bromoarenes in comparison with the commonly much more reactive electron-poor bromoarenes (entries 3–5 versus entries 6–7) suggests that the oxidative addition of aryl halide to the Pd-catalyst cannot be the rate-determining step in these cases.

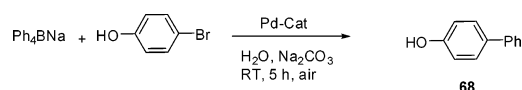
Shimizu et al. also applied Pd(II)–sepiolite to the Suzuki coupling of 4-bromophenol with phenylboronic acid or sodium tetraphenylborate in water at room temperature in air.¹²⁹ It provided higher yields than unsupported Pd(II) salts and some other supported-Pd catalysts (Scheme 16).

Table 26. Pd(II)–Sepiolite-Catalyzed Suzuki Coupling of Aryl Halides with Phenylboronic Acid

$$\text{Ar-X} + \text{PhB(OH)}_2 \xrightarrow[\text{DMF, K}_2\text{CO}_3]{\text{Pd}^{2+}\text{-sepiolite}} \text{Ar-Ph} \quad \mathbf{67}$$

entry	cat. (mol %)	aryl halide	T (°C)	GC yield (%)	TON
1	0.02	C ₆ H ₅ I	100	80	4000
2	0.02	C ₆ H ₅ Br	100	81	4050
3	0.02	4-NH ₂ -C ₆ H ₄ Br	100	77	3850
4	0.02	4-MeO-C ₆ H ₄ Br	100	85 (84) ^a	4250
5	0.02	3-Cl-C ₆ H ₄ Br	100	91	4550
6	0.02	4-Ac-C ₆ H ₄ Br	100	83	4150
7	0.02	4-NO ₂ -C ₆ H ₄ Br	100	91	4550
8	0.1	4-Ac-C ₆ H ₄ Cl	100	23	230
9	0.001	C ₆ H ₅ Br	130	65	65000
10	0.001	4-MeO-C ₆ H ₄ Br	130	56	56000
11	0.001	4-Ac-C ₆ H ₄ Br	130	94	94000

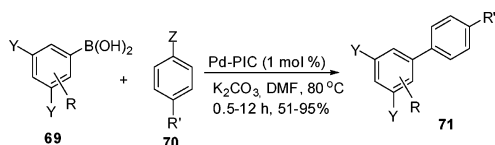
^a Yield of cycle 2.

Scheme 16. Comparison of Various Catalysts in Suzuki Reaction of 4-Bromophenol with Ph₄BNa

Catalyst (wt %)	GC yield (%)
Pd ²⁺ -sepiolite (0.5)	99
Pd ²⁺ -NaY (0.7)	83
Pd ²⁺ -mica (0.7)	73
Pd/C (2)	23
Pd-SiO ₂ (0.5)	57
PdCl ₂ (0.1 mol%)	47
Pd(OAc) ₂ (0.1 mol%)	36
Pd(OAc) ₂ (1 mol%)	43

Pd (1.8%) on unmodified silica could be used in a flow injection microreactor in the Suzuki reaction of 4-bromobenzonitrile with phenylboronic acid without the addition of an extrinsic base. The catalyst showed a low leach rate and provided yields of about 67%.²⁶

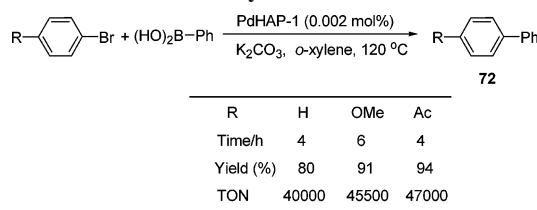
Clay-supported Pd catalysts (Pd–PIC) can be obtained by intercalation using clay and PdCl₂/Ph₄P⁺Br[−]. It provided good yields in Suzuki–Miyaura reactions of aryl iodides or aryl bromides with arylboronic acids (Scheme 17).¹³⁰

Scheme 17. Pd–PIC-Catalyzed Suzuki–Miyaura Reactions

R = H, 2-Ph, 4-Ph, 4-SMe and 4-*tert*-Bu;
Y = H, F
R' = H, CHO; Z = I, Br

Treatment of Ca-deficient hydroxyapatite Ca₉(HPO₄)(PO₄)₅(OH) (Ca/P = 1.50, HAP-1) with an acetone solution of PdCl₂(PhCN)₂ yielded a hydroxyapatite-supported Pd catalyst (PdHAP-1), which was highly efficient in Suzuki coupling of various aryl bromides with phenylboronic acid (Scheme 18).¹³¹ No Pd leaching was observed, and the catalyst could be recycled.

Mg–Al-layered double hydroxide (LDH) could also successfully be used as solid support for Pd as shown by

Scheme 18. PdHAP-1-Catalyzed Suzuki Reactions

Choudary et al.⁶⁶ The ligand-free LDH–Pd(0) catalysts were prepared by an exchange of PdCl₄^{2−} followed by reduction and exhibited high activity in Suzuki reactions of chloroarenes (Table 27), as well as in Heck, Sonogashira, and Stille couplings. The catalyst showed almost consistent activity and selectivity in coupling reactions of chlorobenzene and phenylboronic acid after reusing it in five cycles. It could also be applied under nonaqueous ionic liquid conditions.

Table 27. LDH–Pd(0)-Catalyzed Suzuki Coupling of Chloroarenes with Arylboronic Acids

$$\text{R-C}_6\text{H}_4\text{-Cl} + \text{Ar-B(OH)}_2 \xrightarrow[\text{KF, dioxane/water (5:1), 100 }^\circ\text{C, 10 h}]{\text{LDH-Pd(0) (1 mol\%)}} \text{R-C}_6\text{H}_4\text{-Ar} \quad \mathbf{73}$$

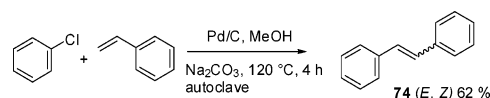
R	Ar	yield (%)
H	Ph	93 (92) ^a
H	3-NO ₂ -Ph	90
H	4-Me-Ph	60
H	2-Naph	80
H	4-F-Ph	70
4-OMe	Ph	90
4-Ac	4-Me-Ph	88

^a Under NAIL (nonaqueous ionic liquid) conditions, 8 h.

3. Heck Reactions

3.1. Pd on Carbon (Pd/C)

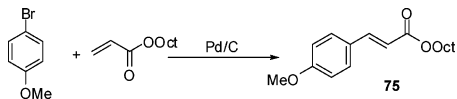
The Heck reaction is the most powerful and widely used method to couple alkenes with organic moieties bearing a suitable leaving group such as a halide, a triflate, or a diazonium. Pd/C was applied to this reaction in the pioneering work of Julia et al. as early as in 1973^{60,132} and has been the most important heterogeneous catalyst since then, because it is efficient and commercially available. In this early report, styrene was reacted with aromatic chlorides and iodides. About 50% yield was achieved in the most favorable cases. It reached 62% yield (82% conversion of styrene) in pure methanol at 120 °C and in an autoclave under pressure. Remarkably, it was found that the addition of triphenylphosphine, which is a common ligand in homogeneous Heck reaction, inhibits the reaction rather than promoting it (Scheme 19). Therefore it is not surprising that later on Pd/C was used in Heck reactions without additional ligands.

Scheme 19. Pd/C-Catalyzed Heck Reaction of Chlorobenzene with Styrene

Pd/C-catalyzed heterogeneous Heck reaction has become so matured that it is applied in the coupling of 1-bromo-4-methoxybenzene with octyl acrylate^{6,30} for the industrial production of octyl 4-methoxycinnamate **75**, a common UV

absorber utilized in the manufacture of sunscreen lotion (Scheme 20).

Scheme 20. Heck Reaction of 1-Bromo-4-methoxybenzene with Octyl Acrylate



Köhler et al. provided a very detailed investigation about the application of Pd/C in the Heck reaction of aryl bromides with olefins.^{28,50} A variety of Pd/C catalysts differing in Pd dispersion, Pd distribution, Pd oxidation state, and water content were tested. The experimental results indicated a (quasi-)homogeneous reaction mechanism, that is, the Pd complex or colloidal particles in solution act as the catalytically active species. E 105 CA/W 5% Pd from Degussa AG turned out to be the best Pd/C catalyst. It has a high Pd dispersion (36%), a low reduction degree [mainly Pd(II)], and a high water content (~55%). Its high catalytic activity in *N*-methylpyrrolidone/sodium acetate at 140 °C allowed working with extremely low catalyst concentrations (Table 28). An argon atmosphere helps to decrease the Pd leaching while maintaining the high activity. Under these optimized reaction conditions, turnover numbers (TON) up to 36 000 and turnover frequencies (TOF) up to 18 000 h⁻¹ (for bromobenzene) were achieved using a Pd concentration as low as 0.0025 mol % (Table 28, entry 3). Complete conversion was achieved for activated (electron-withdrawing substituents) and nonactivated, as well as deactivated, bromoarenes (electron-donating substituents) within a few hours. The extraordinarily high activity seems to be connected with dissolution–reprecipitation processes, where dissolved Pd species formed at this temperature are the active species. Much lower catalytic activity (TON and TOF reduced by magnitudes) in Heck coupling was found with pre-reduced Pd/C catalysts (Table 28, entries 4 and 5) in accordance with previous findings.¹¹

Table 28. Effect of Reaction Conditions on the Heck Reaction of Aryl Bromides with Styrene⁸¹

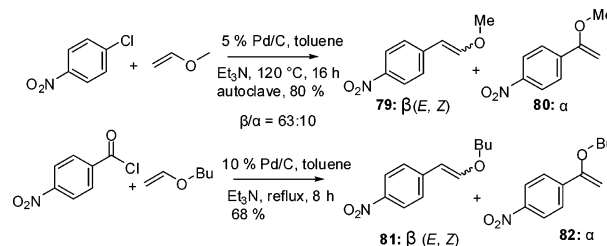
entry	R	catalyst (mol %)	T (h)	conv (%)	yield ^d (%)			TON	TOF
					76	77	78		
1	Ac	0.005	4	96	90	0	5	19200	4800
2	H	0.005	1	90	83	1	6	18000	18000
3	H	0.0025	2	90	83	1	6	36000	18000
4 ^b	H	1.0	20	58	52	0	5	58	3
5 ^c	H	1.0	20	12	10	0	1	12	<1
6	Cl	0.05	6	100	92	1	7	2000	333
7	OMe	0.05	2	92	80	1	9	1840	920
8	OMe	0.01	2	63	63	0	7	7200	3600

^a Yields from GLC analysis. ^b Reduced under H₂ atmosphere at 300 °C for 1 h. ^c Treated under N₂ atmosphere at 500 °C for 1 h.

Evidence for dissolved Pd species formed by leaching from Pd/C being the active moieties in Heck reactions was also found by Arai and co-workers¹¹ in case of aryl iodides in *N*-methylpyrrolidone in the presence of triethylamine or Na₂CO₃ as base. However, almost all dissolved Pd species re-deposited onto the surface of the support after the reaction had been completed. Thus, the catalysts were recyclable

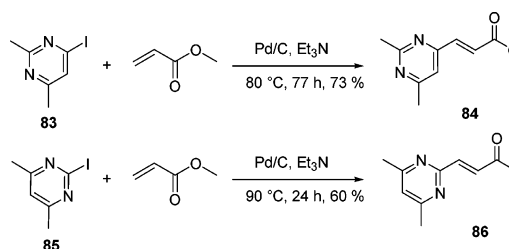
without loss of activity. Low activities and dehalogenation were observed for aryl bromides and aryl chlorides. On the other hand, 4-nitrochlorobenzene and vinyl alkyl ether as more reactive reactants could be coupled in toluene/triethylamine under pressure, but with low regioselectivity (Scheme 21).^{133–135} These conditions were also successful in the coupling of aryl chlorides with butyl vinyl ether (Scheme 21).^{133–135} In these cases, also other heterogeneous Pd catalysts were investigated, showing that the type of solid support affects the regioselectivity of the coupling.^{51,136} However, the heterogeneous catalysts were less regioselective than the homogeneous system based on Pd(OAc)₂.

Scheme 21. Pd/C-Catalyzed Heck Reactions of Vinyl Alkyl Ethers



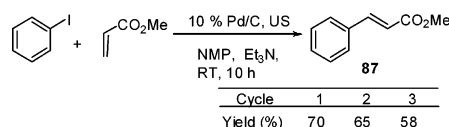
Advantage over homogeneous catalysis was found with Pd/C in the Heck reaction of 4- and 2-iodopyrimidines **83** and **85** with methyl acrylate.¹³⁷ High yields were obtained and homocoupling was not observed (Scheme 22).

Scheme 22. Pd/C-Catalyzed Heck Reactions of Iodopyrimidines with Methyl Acrylate



The application of ultrasound in Pd/C-catalyzed Heck reactions can be advantageous as demonstrated for the reaction of iodobenzene with methyl acrylate in NMP.¹³⁸ The rate of the reaction increased and the catalyst showed high activity under ambient conditions (air and moisture). It could be conveniently separated from the reaction mixture and reused (Scheme 23).

Scheme 23. Heck Reaction of Iodobenzene with Methyl Acrylate under Ultrasound



As shown by Beller and Kühlein, heterogeneous Pd/C catalysis can also be applied to the Heck reaction of aryldiazonium salts **88**.¹³⁹ Excellent yields were obtained with acrylate as reactant without using a base or phosphine ligand (Table 29). Interestingly, no difference in reactivity in relation to the electronic nature of the diazonium compound was observed. This effect makes it very likely that for this type of Heck reaction, contrary to the reaction of aryl halides,

Table 29. Pd/C-Catalyzed Heck Reactions of Diazonium Salts with Acrylates

$$\text{Ar-N}_2\text{BF}_4 + \text{CH}_2=\text{CHCO}_2\text{R} \xrightarrow[\text{EtOH, 60}^\circ\text{C, 12 h}]{5\% \text{ Pd/C (1 mol\%)} } \text{Ar-CH}=\text{CHCO}_2\text{R}$$

Ar-N ₂ BF ₄	R	Product	Yield (%) ^a
	C ₂ H ₅		98 ^b
	C ₂ H ₅		89
	C ₂ H ₅		92
	C ₈ H ₁₇		84

^a Isolated yield.

the insertion of the palladium catalyst is not the rate-determining step.

Ionic liquids have attracted growing interest as environmentally benign reusable solvents.^{140,141} Because of their highly polar nature, they are promising activating and stabilizing solvents for Pd/C-catalyzed Heck reactions (Table 30).¹² The reaction was carried out simply by heating a solution of an aryl substrate, an olefin, and a base in an ionic liquid ([bmim]PF₆) with 3 mol % of 10% Pd/C. Pd/C dispersed well in [bmim]PF₆. After the reaction, the product was extracted simply by stirring with *n*-hexane or diethyl ether several times followed by decantation of the upper organic layer. No aqueous workup was required. The Pd/C was kept and suspended completely in the ionic liquid layer after the extraction.

Table 30. Pd/C-Catalyzed Heck Reactions of Aryl Halides with Ethyl Acrylate in Ionic Liquids

$$\text{Ar-X} + \text{CH}_2=\text{CHCO}_2\text{Et} \xrightarrow[\text{[bmim]PF}_6, 60^\circ\text{C, 12 h}]{\text{Pd/C (3 mol\%), Et}_3\text{N}} \text{Ar-CH}=\text{CHCO}_2\text{Et}$$

Ar, X	T (°C)	t (h)	yield (%)
Ph, I	100	1	92
4-Me-Ph, I	100	12	53
4-MeO-Ph, I	100	12	69
4-Ac-Ph, I	100	24	65
Ph, Br	140	12	40
4-NO ₂ -Ph, Br	140	12	85
3-Cl-Ph, Br	140	12	52
4-MeO-Ph, Br	140	12	25

Aryl iodides gave higher yields than bromides. Aryl triflates resisted the reaction and were recovered completely even at 140 °C with or without a phosphine ligand.¹² Since Pd/C remained only in ionic liquid, the ionic liquid containing Pd/C can be reused as catalyst system itself (Table 31). Although a certain decrease in yields was observed after the second reuse, probably due to accumulation of triethylammonium iodide (Table 31, entries 3–5), washing the ionic liquid layer with water recovered the catalytic activity to the same level as in the fresh system (entry 6).

It was found by inductively coupled plasma (ICP) emission spectroscopy that after filtration of the Pd/C the concentration of Pd before and after the Heck reaction was negligible. The authors concluded that the Heck reaction was catalyzed by the Pd at the surface of Pd/C.

Table 31. Pd/C-Catalyzed Heck Reactions of Iodobenzene with Ethyl Acrylate in Ionic Liquid by a Recyclable Catalytic System

entry	recycles	T (°C)	t (h)	yield (%)
1	0	100	12	95
2	1	100	12	93
3	2	100	12	84
4	3	100	12	81
5	4	100	12	80
6 ^a	5	100	12	95

^a Catalytic system was washed with water before use.

Pd/C-catalyzed Heck arylation of 2-methylprop-2-en-1-ol with 1-*tert*-butyl-4-iodo-benzene in an ionic liquid results in the formation of the fragrance β-Lilial **91**.⁶⁹ Higher activity was observed in ionic liquid media, and the catalyst could be reused with only marginal decrease in yield and selectivity (Table 32).

Table 32. Pd/C-Catalyzed Heck Reaction of 1-(*tert*-Butyl)-4-iodobenzene with 2-Methylprop-2-en-1-ol in Ionic Liquids

$$\text{1-(tert-butyl)-4-iodobenzene} + \text{2-methylprop-2-en-1-ol} \xrightarrow[\text{NEt}_3, [\text{bmim}][\text{PF}_6], [\text{NTf}_2], 100^\circ\text{C}]{10\% \text{ Pd/C (5 mol\%)}} \text{β-Lilial (91)}$$

run	conv (%)	select. (%)
1	96	96
2	94	95
3	95	93
4	91	93
5	93	92

In Heck reactions catalyzed with Pd/C, ionic liquid methodology can be combined with microwave heating.⁶⁸ The reaction was conducted in an open system with 5% Pd/C as catalyst. Modest to good yields of coupling products were obtained in shorter times (Table 33). The reactivity of the halobenzenes followed the usual sequence, that is, electron-withdrawing substituents increase the reactivity and electron-donating substituents decrease it. Iodoarenes react faster than bromoarenes, while chloroarenes only react if substituted by strong electron-withdrawing groups (entries 9–11). All of the reactions went smoothly and the (*E*)-butyl cinnamates **92** were the only products. Reaction times are very short, and the catalyst system could be reused.

Table 33. Pd/C-Catalyzed Heck Reactions in Ionic Liquid by Microwave Irradiation

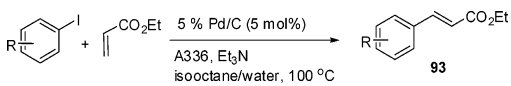
$$\text{Ar-X} + \text{CH}_2=\text{CHCO}_2\text{OBu} \xrightarrow[\text{[OMIM]BF}_4, \text{ about 1 min}]{\text{Pd/C (3 mol\%), } n\text{-Bu}_3\text{N, MWI (225 W)}} \text{Ar-CH}=\text{CHCO}_2\text{OBu}$$

entry	Ar	X	t (min)	yield ^a (%)
1	Ph	I	1.5	86
2	2-MeO ₂ C-Ph	I	1.5	35
3	Ph	Br	1.5	80
4	4-NO ₂ -Ph	Br	1.5	89
5	4-Ac-Ph	Br	1.5	61
6	4-OMe	Br	1.5	30 (56) ^b
7	4-Me	Br	1.5	33
8	2-Naph	Br	1.5	79
9	Ph	Cl	2.0	0 ^b
10	4-NO ₂ -Ph	Cl	2.0	27 (42) ^b
11	4-CHO-Ph	Cl	2.0	0

^a Isolated yield. ^b Under 375 W of microwave irradiation.

As another technique worth mentioning, the Pd/C catalyst is kept in a separate liquid triphase system. In isooctane/water/Aliquat 336 (methyltrioctylammonium chloride),¹⁴² it was found that the rate of Heck coupling of aryl iodides with olefins was accelerated 10-fold in the presence of Aliquat 336. Both when conducted in A336 as solvent and when conducted in an isooctane/A336/water triphasic mixture, the Heck reaction of aryl iodides with electron-deficient olefins proceeded with high yields and selectivities (Table 34).

Table 34. Triphase Heck Coupling of Aryl Iodides with Ethyl Acrylate^a



entry	R	A336	T (h)	yield (% GC)
1	H	no	1.5	5
			20	17
2	H	yes	1.5	30
			20	94
3	4-NO ₂	no ^b	6.0	10
4	4-NO ₂	yes ^b	3.0	78
5	4-Ac	yes	20	80
6	4-Cl	yes	20	78
7	4-OMe	yes	20	68
8	4-NH ₂	yes ^b	20	68
9	3-CN	yes	20	81

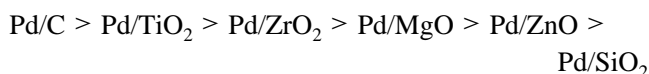
^a Reaction conditions: aryl iodide (1.0 mmol), ethyl acrylate (1.5 mmol), Et₃N (1.5 mmol), Pd/C (0.05 mmol), 10 mL of isooctane, 5 mL of water, A336 (0.30 mmol). ^b Since the substrate is insoluble in isooctane, toluene was used.

Pd on graphite was prepared by reduction of PdCl₂ by C₈K and could be used (7 mol % catalyst) in Heck reactions of acrylates, fumarates, and styrene with aryl or vinyl iodides in the presence of tributylamine.¹⁴³

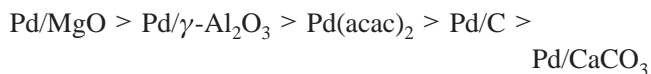
3.2. Pd on Metal Oxides

The first report about a heterogeneous Heck reaction using Pd supported on metal oxide was published by Kaneda et al. in 1990.¹⁴⁴ Chlorobenzene was coupled with styrene in methanol at 150 °C using Pd/MgO as catalyst and Na₂CO₃ as base. Later on several metal oxides (MgO, Al₂O₃, SiO₂, TiO₂, ZrO₂, ZnO, mixed MgLaO, etc.) have been used as supports for Pd catalysts in Heck reactions. Ar–X with X = I, Br, Cl, OTf, COCl, SO₂Cl, or N₂BF₄ were coupled with acrylates,^{12,19,38,55,67,145–147} acrylonitrile,^{52,53,55} styrene,^{20,21,55,146,147} vinyl alkyl ether,^{51,55,136} terminal alkenes,⁵⁵ and cycloalkenes.²⁷ Biffis and co-workers reviewed palladium metal catalysts in Heck reactions in 2001.¹⁰

Most applications were performed under ligand-free conditions. Detailed studies of Köhler and co-workers on catalyst efficiency and on optimization of Heck reaction of bromobenzene with styrene catalyzed by solid-supported Pd (5% Pd (w/w) in DMF/NaOAc, 140 °C, 20 h) revealed the following order of effectiveness:^{20,21}



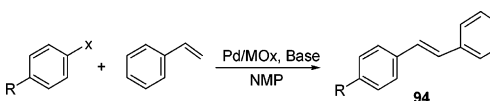
A different order was found in Heck coupling of iodobenzene with acrylonitrile in the presence of PPh₃ (5% Pd, Et₃N as base, CH₃CN, 140 °C, 14 h) by Wali and co-workers:⁵²



Köhler and co-workers reported for the first time that specifically prepared heterogeneous Pd/MO_x catalysts (M = metal center) converted even nonactivated aryl chlorides into stilbenes in Heck reactions with styrene. Short reaction times and remarkably low amounts of catalysts were sufficient.^{85,148} The highly active palladium species were generated *in situ* by dissolution in the support and stabilized against agglomeration by reprecipitation on the surface. These processes could be controlled by a specific choice of catalyst and tuning the reaction conditions. Evidence was found that the solid catalyst functions as a reservoir for molecular palladium species in solution. Their concentration in solution correlates with the progress of the reactions. Kinetic investigation of the Heck reaction of bromobenzene with styrene showed that only a little palladium leached to the solution in the starting period. After the reaction temperature reached 140 °C,²¹ about one-third of the palladium was leached from the surface of the support. Simultaneously, the majority of the aryl halide was converted. After the reaction was finished, the palladium was re-deposited onto the support to a great extent.

Analogous investigations were performed with different aryl chlorides under modified conditions affording comparable results (Table 35).¹⁴⁸

Table 35. Heck Coupling of Aryl Bromides and Chlorides with Styrene

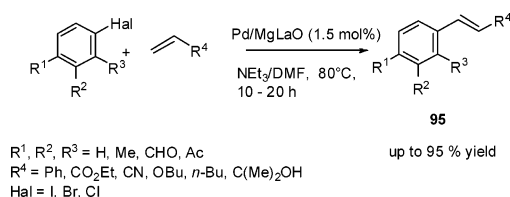


entry	R, X	catalyst	cat. conc. [mol %]	base	T (°C), t (h)	conv (%)	yield (%)
1	H, Br	Pd/TiO ₂ ^a	0.0011	NaOAc	140, 4	95	86
2	H, Br	Pd/Al ₂ O ₃ ^a	0.0009	NaOAc	140, 4	96	87
3 ^b	Ac, Cl	Pd/Al ₂ O ₃ ^a	0.01	Ca(OH) ₂	160, 2	98	90
4 ^b	Ac, Cl	Pd/Al ₂ O ₃ ^c	0.01	Ca(OH) ₂	160, 2	87	83
5	Ac, Cl	Pd/NaY	0.005	Ca(OH) ₂	160, 2	99	95
6 ^b	H, Cl	Pd/NaY	0.05	Ca(OH) ₂	160, 6	49	45
7 ^b	H, Cl	Pd/NaY	0.05	Ca(OH) ₂	160, 6	85	83 ^d
8 ^b	Me, Cl	Pd/NaY	0.05	Ca(OH) ₂	160, 6	40	36 ^d

^a Precipitation of Pd(OH)₂ on MO_x. ^b Addition of TBAB. ^c Prepared by coprecipitation. ^d Under O₂ atmosphere.

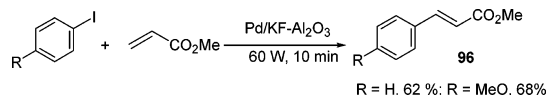
A recently developed Pd catalyst on Mg–La mixed oxide turned out to be superior for Heck coupling of activated and inactivated aryl iodides, bromides, and chlorides even at low temperatures (80 °C) under ambient atmosphere (Scheme 24).⁵⁵ High *E/Z* ratios of products **95** were observed in most cases, depending on the nature of alkene. The solvent had a determinant effect on the yield. The catalyst could be reused without additional activation four times without a significant loss of activity and could be stored under air without problems.

Scheme 24



Microwave irradiation can be applied to Heck reaction catalyzed by Pd on several metal oxides as shown in the coupling of iodobenzene with 1-decene.⁵² Slightly higher yields were achieved in the microwave-mediated solventless Heck reaction of aryl iodides with methyl acrylate in the presence of palladium on KF/alumina (Scheme 25).

Scheme 25. Palladium on KF/Al₂O₃ Catalyzed Heck Reactions under Microwave Irradiation



The application of nonaqueous ionic liquids can be advantageous in heterogeneous Heck reactions. Silica-supported palladium complexes (Pd(II)/SiO₂) exhibited higher catalytic activity in Heck reactions of aryl iodides with acrylates in an ionic liquid ([bmim]PF₆) than in DMF (Table 36).⁶⁷

Table 36. Pd(II)/SiO₂-Catalyzed Heck Reactions of Aryl Iodides with Acrylates Using Ionic Liquids

R	R'	solvent	t (h)	conv (%)
H	Me	[bmim]PF ₆	1	98
H	Me	DMF	1	88
H	Bu	[bmim]PF ₆	1	70
H	Bu	DMF	1	67
4-Me	Et	[bmim]PF ₆	2	99
4-Me	Et	DMF	2	78
4-OMe	Et	[bmim]PF ₆	6	79
4-OMe	Et	DMF	6	85
4-Ac	Et	[bmim]PF ₆	6	33
4-Ac	Et	DMF	6	99

Pd complexes can also be supported by iron oxide–silica nanoparticles. Thus a Pd catalyst consisting of magnetic maghemite (γ -Fe₂O₃), silica, and a tethered heterocyclic carbene (imidazole) ligand (Fe₂O₃–Si–Pd) gave good results in Heck reactions of aryl iodides or aryl bromides with *n*-butyl acrylate (Table 37, see also Figure 1).¹¹⁰

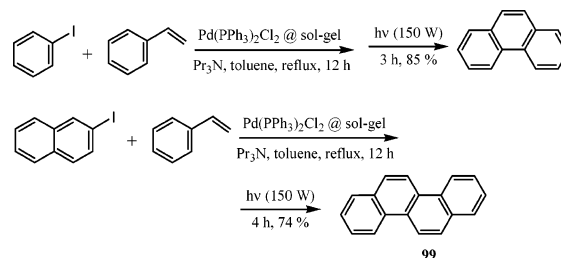
Table 37. Maghemite–Silica Nanoparticle-Supported Pd-Catalyzed Heck Reactions

R	X	isolated yield (%)
2-Me	I	90 ^a
2-Me	Br	88
3-OMe	I	89
3-OMe	Br	90
4-Ac	I	88

^a GC-analysis revealed 97% yield in the first run and 97%, 95%, 94%, and 92% in the second to fifth rounds, respectively.

Silica sol–gel encaged Pd(PPh₃)₂Cl₂ could be used as a recyclable catalyst without loss of catalytic activity in Heck reaction of aryl iodides with styrene.¹⁴⁹ It was possible to combine the Heck reaction with subsequent photocyclization in a one-pot process affording phenanthrene and chrysene **99** (Scheme 26).¹⁴⁹

Scheme 26. One-Pot Synthesis of Phenanthrene and Chrysene by Heck Coupling and Photocyclization



3.3. Pd on Microporous and Mesoporous Supports

Pd on molecular sieves as catalysts in heterogeneous Heck reactions was first investigated by Mehnert and Ying.^{15,145} Palladium catalysts supported on a niobium-modified mesoporous silicalite (Nb-MCM-41) were prepared by vapor grafting. These mesoporous materials showed remarkable activity in Heck reactions of bromoarenes with electron-withdrawing substituents in *p*-position.

Papp and co-workers prepared a heterogeneous ligand-free Pd-MCM-41 system, which could be used as an efficient and recyclable catalyst in Heck reactions. Palladium loadings of 1.39%, 3.0%, and 5.85% showed high activity and selectivity in the Heck coupling of iodobenzene with styrene (conversions of 76–84%, selectivities of 84–87%) and methyl acrylate (89–100% conversions and 100% selectivities).¹⁴⁶ Moreover, these catalysts performed well in Heck reactions of activated bromoarenes (4-bromonitrobenzene and 4-bromoacetophenone). In all reactions, complete (*E*)-selectivity was observed. α -Coupling was observed as a side reaction in the case of styrene. It was found that the catalyst activities depend on palladium loading and metal dispersion. In most cases, catalytic performance of 3.0% Pd-MCM-41 with lower Pd dispersion showed lower activity. A series of other bromoarenes were investigated in the Heck coupling of styrene and methyl acrylate using 1.39% Pd-MCM-41 catalyst (Table 38). Importantly, the catalysts are stable under the reaction conditions and retain high activity and selectivity for at least 20 successive runs without the need to exclude air or moisture.¹⁴⁶

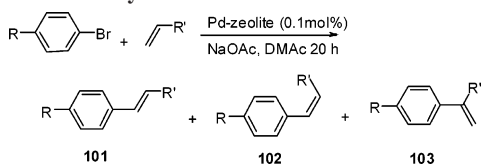
Table 38. Heck Reaction of Bromoarenes over 1.39% Pd–MCM-41 Catalyst^a

Ar	R	t (h)	conv (%)	select. (%)
Ph	CO ₂ Me	3	86	96
Ph	Ph	6	93	93
4-CN-Ph	CO ₂ Me	3	97	93
Ph	Ph	6	90	95
4-MeO-Ph ^b	CO ₂ Me	3	82	94
4-MeO-Ph ^b	Ph	6	91	89
4-Br-Ph ^c	CO ₂ Me	3	100	93
4-Br-Ph ^c	Ph	6	85	92
4-Cl-Ph	CO ₂ Me	3	64	100
4-Cl-Ph	Ph	6	54	91
1-Naph	CO ₂ Me	3	100	100
1-Naph	Ph	6	100	92
pyrid-3-yl	CO ₂ Me	22	94	100
pyrid-3-yl	Ph	22	57	93

^a Conditions: 1 equiv of ArBr, 1.2 equiv of alkene and Na₂CO₃, 0.2 equiv of Bu₄NCl, and 0.3 mol % Pd. ^b Without Bu₄NCl. ^c Without Bu₄NCl, with NaOAc as the base.

Djakovitch and Köhler studied a series of palladium catalysts obtained by ion exchange at Na- or H-zeolites (mordenite, Y) with Pd(NH₃)₄Cl₂. Pd-modified zeolites exhibited a high activity comparable to homogeneous catalysis toward the Heck reaction of aryl bromides with styrene for small Pd concentrations.^{10,16–18,21,27} The zeolite obviously controlled the selectivity of the reaction.¹⁶ Reaction temperature plays an important role. No substantial leaching was observed in most cases. But evidence for dissolved molecular Pd species being responsible for the catalysis was found.²⁷ The catalysts could be easily separated from the reaction mixture and reused up to five times without a considerable loss in activity. Some of the results are summarized in Table 39.^{16,18} The catalyst could also be applied to Heck coupling of 4-chloroacetophenone but did not perform so well even at higher temperatures.¹⁸

Table 39. Heck Reaction of Various Aryl Bromides with Alkenes by Pd–Zeolite Catalysts

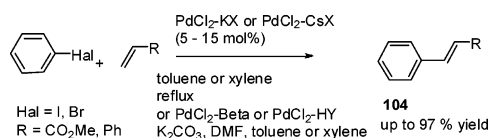


Pd–zeolite	R	R'	T (°C)	GLC yield ^a (%)		
				101	102	103
[Pd(0)]–NaY	F	Ph	140	89.4 (86.0)	0.9	8.2
			100	85.1 (80.1)	1.0	7.9
[Pd(NH ₃) ₄] ²⁺ –NaY	F	Ph	140	93.0 (80.9)	1.0	8.8
			100	94.5 (89.5)	0.7	6.7
[Pd(OAc) ₂] [–] –NaY	F	Ph	140	79.2 (81.2)	0.9	7.2
			100	57.6 (39.9)	0.4	3.9
[Pd(NH ₃) ₄] ²⁺ –NaY	OMe	Ph	140	81.2 (75.8)	9.5	9.5
[Pd(NH ₃) ₄] ²⁺ –NaY	NO ₂	Ph	140	94.8 (89.8)	1.1	4.1
[Pd(NH ₃) ₄] ²⁺ –NaY	H	Ph	140	84.9 (75.8)	0.7	6.5
[Pd(NH ₃) ₄] ²⁺ –NaY	H	BuO	140	25.7	20.4	12.4
[Pd(NH ₃) ₄] ²⁺ –NaY	H	CO ₂ Me	140	91.0 (69.4)	0.5	0.4

^a Isolated yields in parenthesis.

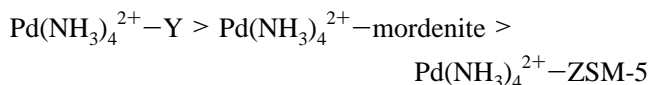
K⁺- and Cs⁺-exchanged X-zeolites containing PdCl₂ (bifunctional catalysts) developed by Garcia and co-workers allowed implementation of the Heck reaction of iodo- and bromobenzene with styrene in the absence of an extrinsic base.⁴⁹ Obviously, sites of the support act as base in these cases. No leaching was observed. The activity of the used catalyst could be regained to a large extent by reactivation by washing with water. As an alternative to styrenes **104**, the formation of 1,1-diphenylethene regioisomer can be favored by high Pd loadings (Scheme 27). The authors also investigated the effect of pore size and Pd loading of different zeolites on the catalytic activity. When DMF was used as solvent, the catalytic activity was mainly attributed to leached Pd.

Scheme 27



In contrast to the conclusions of Djakovitch and Köhler to the nature of catalysis of Pd on zeolites (molecular Pd species in solution, *vide supra*), Dams and co-workers.^{61,150} and Okumura⁸⁴ et al. assumed that the heterogeneous nature

of the catalysis with Pd-zeolites in Heck reactions largely depended on the pretreatment of the catalyst, the oxidation state of Pd, the solvent, and the base. For a critical review about this subject favoring homogeneous catalysis as the general mode of action see Jones et al.³⁶ The excellent performance of Pd(0)/HY was attributed to the formation of stable Pd₁₃ clusters kept inside the supercage of HY.⁸⁴ This catalyst had to be generated by calcination in O₂ and reduction by H₂ before it could be reused. With tributylamine as the base in toluene, the Heck olefination with Pd-(NH₃)₄²⁺–zeolites (0.4 wt % Pd; mordenite, Y, ZSM-5) and Pd(0)–mordenite (0.4 and 4 wt % Pd) were concluded as truly heterogeneous.^{61,150} Pd leaching from the zeolites was evaluated in a very strict filtrate activity test. It was clearly related to the presence of oxidized Pd(II) in an all-oxygen environment, that is, ionic Pd(II) or PdO. The heterogeneous reactions with the zeolite-supported catalyst can be accelerated by the addition of a quaternary ammonium salt promoter. The catalytic activity of Pd–zeolites in Heck reaction followed the order



Pd on porous glass served as a useful, reusable catalyst for Heck reaction of iodobenzene and 4-bromoacetophenone with styrene and allylic alcohol allowing the reaction to be carried out in the presence of air.²⁴

3.4. Pd on Modified Silica (Organic–Inorganic Hybrid Support)

Organochemically modified silica can also serve as solid support for Pd catalysts. Silica was modified by various chlorohydrosilanes (trichloro-, dichloromethyl-, chlorodimethyl-, dichlorophenyl-, and chlorodiphenylsilane). The resulting materials, which were modified at the surface by methyl or aryl groups, were treated with saturated solutions of PdCl₂ in methanol to form different Pd-on-silica catalysts with various Pd loadings (Pd/SiO₂Me, Pd/SiO₂Me₂, Pd/SiO₂-Ph, Pd/SiO₂Ph₂).

Pd/SiO₂Ph exhibited high catalytic activity in the Heck reaction of aryl iodides and bromides with styrene or methyl acrylate (Table 40).^{151,152} The catalyst could be recovered and reused.

Table 40. Catalytic Performance of 0.3% Pd–Silica Catalysts in Heck Coupling

Pd cat.	R ¹ , X	R ²	t (h)	conv (%)	select. (%)
Pd/SiO ₂ Me	H, I	CO ₂ Me	2	84	99
Pd/SiO ₂ Me ₂	H, I	CO ₂ Me	2	54	99
Pd/SiO ₂ Ph	H, I	CO ₂ Me	2	97	99
Pd/SiO ₂ Ph ₂	H, I	CO ₂ Me	2	51	99
Pd/SiO ₂ Me	NO ₂ , Br	CO ₂ Me	2	100	99
Pd/SiO ₂ Me ₂	NO ₂ , Br	CO ₂ Me	2	68	99
Pd/SiO ₂ Ph	NO ₂ , Br	CO ₂ Me	2	100	99
Pd/SiO ₂ Ph ₂	NO ₂ , Br	CO ₂ Me	2	66	99
Pd/SiO ₂ Me	Ac, Br	CO ₂ Me	2	67	99
Pd/SiO ₂ Ph	Ac, Br	CO ₂ Me	2	75	99
Pd/SiO ₂ Me	H, I	Ph	5	58	86
Pd/SiO ₂ Ph	H, I	Ph	5	80	83

As an alternative to mercaptopropyl modification, also arsanopropyl or methylselenoundecyl groups were introduced

into silica and allowed to act as solid support for Pd as shown by Cai et al. (Figure 4). In all these cases, the Pd is

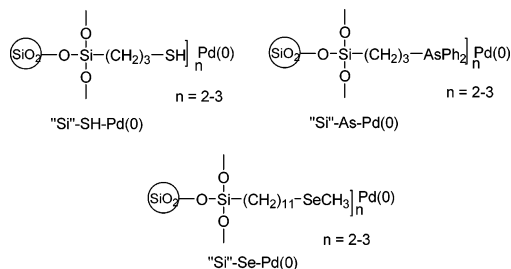


Figure 4. Three kinds of modified silica supported palladium catalysts.

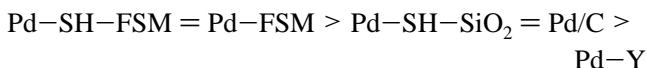
complexed by the donor atoms of the organic modification of the silica (S, As, Se). These catalysts exhibited high activity and selectivity in the Heck coupling of aryl iodides and bromides (Table 41) and could easily be separated and reused.^{153–156}

Table 41. Heck Reaction Catalyzed by “Si”-X-Pd(0) Complex^a

entry	cat. X (concn, mol %)	R, X	R'	T (°C)	t (h)	yield ^b (%)	ref
1	SH (0.4)	H, I	Ph	100	6	92	153
2	SH (0.4)	OMe, I	Ph	100	6	90	153
3	SH (0.4)	H, I	CO ₂ H	100	6	95	153
4	SH (0.4)	OMe, I	CO ₂ H	100	6	92	153
5	As (0.6)	H, I	Ph	100	6	92	154
6	As (0.6)	NO ₂ , Br	Ph	140	12	75	154
7	As (0.6)	H, I	CO ₂ H	100	6	94	154
8	As (0.6)	NO ₂ , Br	CO ₂ H	140	12	79	154
9	As (0.6)	H, I	CO ₂ Bu	100	6	90	155
10	As (0.6)	NO ₂ , Br	CO ₂ Bu	140	12	78	155
11	As (0.6)	H, I	CO ₂ NH ₂	100	6	90	155
12	As (0.6)	NO ₂ , Br	CO ₂ NH ₂	140	12	76	155
13	Se (0.4)	H, I	CO ₂ Bu	100	6	90	156
14	Se (0.4)	NO ₂ , Br	CO ₂ Bu	140	12	78	156
15	Se (0.4)	H, I	CO ₂ NH ₂	100	6	89	156
16	Se (0.4)	NO ₂ , Br	CO ₂ NH ₂	140	12	83	156

^a Reaction conditions: aryl halide (5 mmol), olefin (5.5 mmol), and Bu₃N (6 mmol) in 1.0 mL of *p*-xylene or DMF were used. When aryl bromide was used, PPh₃ (0.05 mmol) was added. ^b Isolated yield.

Mesoporous silica was modified by mercaptopropylsilane and transformed into Pd(II) complexes (Pd–SH–FSM and Pd–SH–SiO₂). Such solid-supported Pd complexes can act as active, stable, and recyclable heterogeneous catalysts in the Heck reactions of 4-bromoacetophenone and ethyl acrylate.⁴⁷ The kinetic results obtained with the fresh Pd catalysts exhibited the following order of catalytic activity:



For the fresh Pd–SH–FSM catalyst, TON and TOF were obtained as 73 000 and 36 000 h^{−1}, respectively. The “hot filtration test” demonstrated that Pd–SH–FSM was a true heterogeneous catalyst. Pd–SH–FSM and Pd–SH–SiO₂ showed excellent recyclability in the Heck reaction of 4-bromoacetophenone with ethyl acrylate (Table 42).⁴⁶ The catalysts could be reused at least five times with no indication of deactivation.

Table 42. Heck Reaction Using Recovered Catalysts

cycle	yield ^a (%) (Pd–SH–FSM)	yield ^a (%) (Pd–SH–SiO ₂)
fresh	92	84
first reuse	95	93
fifth reuse	97	95

^a Determined by GC.

Mercaptopropyl-modified mesoporous silica Pd complex, SBA-15–SH–Pd,¹²¹ and aminopropyl-modified mesoporous silica Pd complexes, SBA-15–NH₂–Pd¹²¹ or Y–NH₂–Pd,¹⁵⁷ were also efficient reusable catalysts in Heck reactions of nonactivated aryl bromides or iodobenzene (Table 43).

Table 43. SBA-15-Modified Pd Catalysts for the Heck Reactions^{121 a}

entry	R, Y	catalyst (loading)	yield (%)
1	H, Br	SBA-15-SH–Pd (1%)	95
2	COMe, Br	SBA-15-SH–Pd (0.5%)	96
3	COMe, Br	reused from entry 2	93
4	H, I	SBA-15-NH ₂ –Pd (1%)	96
5	H, Br	SBA-15-NH ₂ –Pd (1.5%)	97

^a Reaction conditions: 1 mmol of halide, 1.5 mmol of olefin, 2 mmol of NaOAc.

Silica was also modified by tethered imine palladacycles^{158,159} or SCS–N-pincer complexes⁴⁸ (Figure 5) to provide solid supports for Pd in Heck coupling reactions. These catalysts exhibited high catalytic activity in Heck reactions of aryl iodides and activated aryl bromides and could be reused without significant loss of activity and selectivity (Table 44).

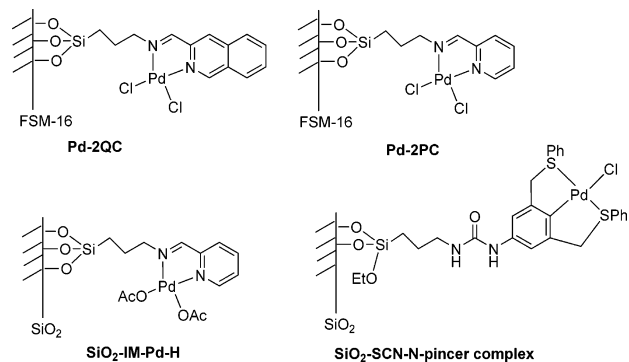
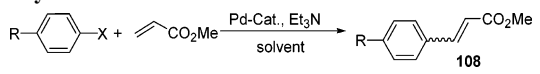


Figure 5. Four kinds of modified silica tethered imine palladacycles.

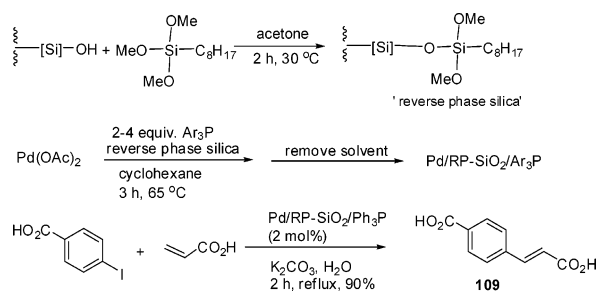
As another possibility, reverse phase silica obtained by treatment with alkyltrimethoxysilanes can be used as solid support for Pd. Triaryl phosphines served as external ligands in these cases. High yields were achieved with aryl iodide or bromides (Scheme 28).¹⁶⁰

Pd nanoparticles encapsulated in silica matrices could be generated from Pd(PPh₃)₄ in a mixture of tetra(ethylene glycol) (TEG) and tetramethoxysilane and final treatment with water.¹²⁰ During this process, PPh₃ was oxidized to the triphenylphosphine oxide, which was recovered from the final filtrate of the catalyst preparation in more than 90%

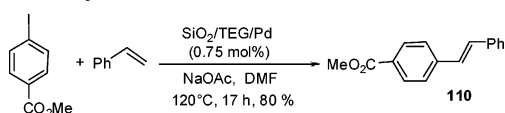
Table 44. Heck Reactions by Modified Silica Supported Imine Palladacycles^a


entry	R, X	catalyst	solvent	T (°C), t (h)	conv (%)
1	H, I	SiO ₂ –IM–Pd–H (0.2 mol %)	MeCN	82, 24	82
2	H, I	SCS–N–pincer	DMF	120, 2	93
3	OMe, I	Pd–2QC (0.01 mol %)	NMP	130, 3	98
4	OMe, I	Pd–2PC (0.01 mol %)	NMP	130, 3	99
5	Me, I	Pd–2QC (0.1 mol %)	NMP	130, 1	100
6	Me, I	Pd–2PC (0.1 mol %)	NMP	130, 1	100
7	NO ₂ , Br	Pd–2QC (0.1 mol %)	NMP	130, 1	95
8	NO ₂ , Br	Pd–2PC (0.1 mol %)	NMP	130, 1	90
9	Ac, Br	Pd–2QC (0.1 mol %)	NMP	130, 1	51
10	Ac, Br	Pd–2PC (0.2 mol %)	NMP	130, 1	46
11	H, Br	Pd–2QC (0.2 mol %)	NMP	130, 24	32
12	H, Br	Pd–2PC (0.1 mol %)	NMP	130, 24	30

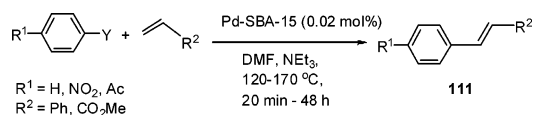
^a Entry 1 is from ref 158; entry 2 from ref 48; others are from ref 159.

Scheme 28. Preparation of Reverse Phase Silica Supported Palladium Catalysts and Their Application to Heck Reactions

yield. This heterogeneous catalyst (SiO₂/TEG/Pd) showed high activity in the Heck coupling reactions of aryl iodides with styrene (Scheme 29).¹²⁰

Scheme 29. SiO₂/TEG/Pd-Catalyzed Heck Reaction of Aryl Iodide with Styrene

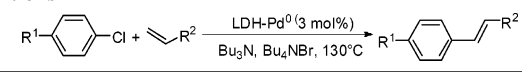
As another way of fixing Pd to mesoporous silica SBA-15, SiH groups were introduced by reaction with trimethoxysilane, which reduce Pd(OAc)₂. As shown by Shi et al., this procedure results in the deposition of metal colloid layers on the pore walls, creating one of the most active heterogeneous catalysts for Heck reactions.^{147,161} Excellent yields were achieved in the coupling of iodo- and bromoarenes with styrene or methyl acrylate, even when low amounts of catalyst were used and the coupling was carried out in air (Scheme 30). The catalyst could easily be separated by filtration and reused at least five times without a significant

Scheme 30

loss of activity. Indications for heterogeneity were found, although small amounts of leached Pd could be detected in the reaction mixture of the first run.

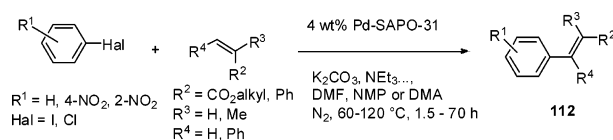
3.5. Pd on Clay and Other Inorganic Materials

Mg–Al-Layered double hydroxide supported palladium nanoparticles (LDH–Pd(0)), developed by Choudary et al., served as versatile catalysts in ligand-free Heck couplings of various substituted chloroarenes and olefins under non-aqueous ionic liquid (NAIL) conditions (Table 45).⁶⁶ The reactivity of these chloroarenes is correlated to the electron density of the aromatic ring. The catalyst was reused for five cycles in the Heck olefination of 4-chloroanisole with styrene under microwave and thermal conditions. The higher efficacy, as displayed in the nonaqueous ionic liquid under microwave conditions, is ascribed to the ionic conductance.

Table 45. LDH–Pd(0)-Catalyzed Heck Olefination of Chloroarenes under Nonaqueous Ionic Liquid (NAIL) Conditions


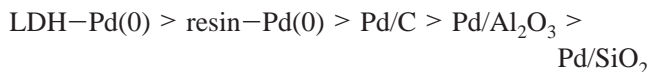
R ¹	R ²	MW (400 W)		thermal heating	
		t (h)	yield (%)	t (h)	yield (%)
H	Ph	0.5	95	30	98
NO ₂	Ph	0.5	96	10	95
Ac	Ph	0.5	93	15	97
CHO	Ph	0.5	95	15	98
Bz	Ph	0.5	91	15	93
OMe	CO ₂ Bu	1	85	40	86
OMe	Ph	1	80	40	76
Me	Ph	0.5	92	30	96
CH ₂ OH	Ph	0.5	90	30	92

A palladium-containing silicoaluminophosphate-31 (Pd–SAPO-31) was developed by Srinivas, Ratnasamy, et al. as a highly active catalyst for the Heck reactions of aryl iodides and chlorides (Scheme 31).⁸⁶ The catalyst was found to be more effective than other solid-supported Pd catalysts (Pd on carbon, MgO, Al₂O₃, or graphite). It worked well at relatively low temperatures (60–120 °C) and allowed completion of the reactions in short times (about 1.5 h). Pd leached during the reaction but re-deposited to the solid support when the reaction had finished. The catalyst could be recovered by simple filtration and reused without a significant loss of activity or selectivity for a minimum of three cycles.

Scheme 31. Heck Reaction Catalyzed by Pd-Containing Silicoaluminophosphate-31

In an effort to compare the reactivity of LDH–Pd(0) with those of other heterogeneous catalysts, namely, Pd/C, Pd/SiO₂, resin–Pd(0), and Pd/Al₂O₃, in the Heck olefination, corresponding experiments were conducted under identical

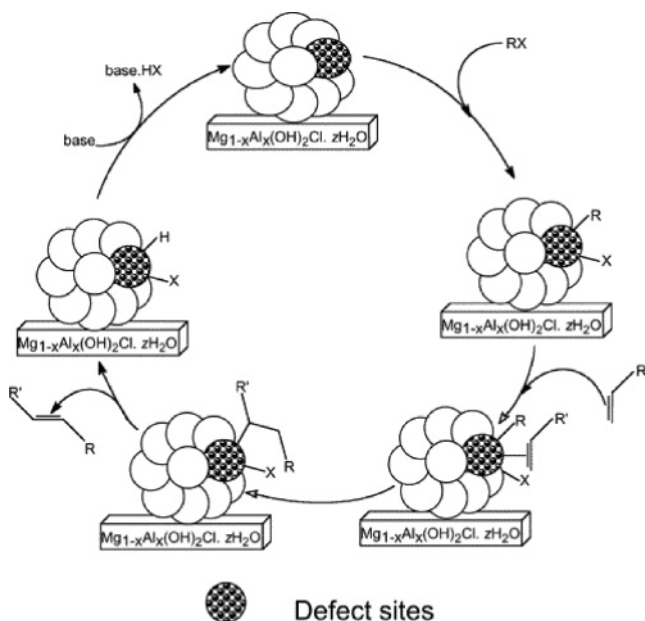
conditions with the same reactants. The activity in the Heck olefination of 4-chloroanisole was found in the order⁶⁶



These results indicated that the basic support (LDH) facilitated the oxidative addition of Pd(0) with 4-chloroanisole and eventually the Heck olefination reaction.

All results of mechanistic experiments reinforced that the Heck olefination of 4-chloroanisole occurs exclusively and with iodobenzene predominantly on the surface of the palladium nanoparticle presumably at defect sites. The plausible mechanism proceeds similarly to that in the homogeneous phase involving the Pd(0)/Pd(II) cycle (Scheme 32). The nanopalladium undergoes oxidative addition with haloarenes to afford ArPdX, as is evident from XPS and TGA-MS studies. The C 1s XPS spectra of the used catalysts show extra lines accounting for the other possible intermediates.

Scheme 32. Plausible Mechanism for the LDH-Pd(0)-Catalyzed Heck Olefination of Chloroarenes⁶⁶

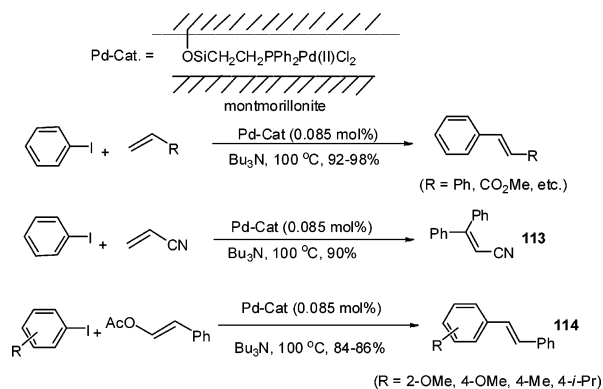


Thus, palladium stabilized on the basic support LDH enables even deactivated chloroarenes to undergo Heck reactions. The basic LDH surface increases the electron density of the Pd center to promote the oxidative addition of chlorobenzene to the Pd(0), resulting in a higher activity.

A montmorillonite-supported Pd complex (montmorillonite-ethylsilyldiphenyl-phosphine-palladium) served as a highly active catalyst in Heck coupling of aryl iodides with olefins.^{162,163} Using this catalyst, iodobenzene coupled with styrene and various acrylates in quantitative yield and 95% (*E*) selectivity. When acrylonitrile was subjected to arylation, a double arylated product **113** was obtained as an exceptional case. It was also found that coupling of substituted iodobenzenes with phenylvinylacetate afforded various unsymmetrical (*E*)-stilbenes **114** in high yields (Scheme 33).¹⁶³ The catalyst could be reused without any noticeable deactivation.

Hydroxyapatite-supported palladium (PdHAP-1) was demonstrated as an outstanding catalyst for the Heck reaction of aryl bromides with styrene or *n*-butyl acrylate (Table 46).¹³¹ The recycled PdHAP-I had the original monomeric Pd(II)

Scheme 33. Heck Reactions Catalyzed by Montmorillonite-Pd Complex



structure and was recyclable with retention of its high catalytic activity. Pd leaching in the filtrate could not be detected. Therefore, it is likely that the Heck reaction proceeds on the PdHAP-1 surface, that is, not with dissolved palladium species. It was suggested that the Heck reaction does not proceed via a traditional Pd(0)/Pd(II) cycle but via the Pd(II)/Pd(IV) mechanism.^{73,164,165} But this became questionable in the light of later results.^{36,74,75}

Table 46. PdHAP-1-Catalyzed Heck Reactions of Aryl Bromides and Olefins

R	R'	<i>t</i> (h)	yield ^a (%)	TON
H	Ph	24	94	47000
OMe	Ph	24	90	45000
Ac	Ph	20	96	48000
H	CO ₂ Bu	20	91	45500
OMe	CO ₂ Bu	24	94	47000
Ac	CO ₂ Bu	20	98	49000

^a GC yields.

As further solid-supported Pd catalysts useful for Heck reactions, Pd/CaCO₃,^{139,166} Pd/BaSO₄,¹³⁹ Pd on GaAs (001),¹⁶⁷ Pd on graphite,^{143,168} Pd on single-walled carbon nanotubes (SWNT),¹⁶⁹ and Pd on hydrocalcite¹⁷⁰ have to be mentioned. The latter was not useful for aryl chlorides but could be recycled. Interestingly, the reaction was faster with the recycled catalyst than with the fresh one, which was explained by an increase in surface area of the catalyst.

PdCl₂ on sepiolites allowed Heck coupling of bromobenzene and iodobenzene with styrene to be run in the absence of an additional base.⁵⁷ Reusage of the catalyst was possible, however, with a considerable loss of activity. It is supposed that the basic sites of the support get blocked by the hydrohalides formed as byproducts in the Heck reaction. Reactivation by steaming of the catalyst before reuse was advantageous. Evidence for heterogeneous catalysis was found by the hot filtration test.

4. Sonogashira Reactions


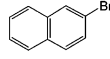
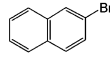
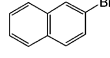
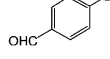
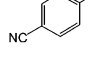
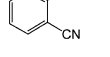
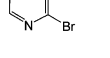
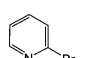
4.1. Pd on Carbon (Pd/C)

4.1.1. In Anhydrous Media

Early investigations of Pd/C-catalyzed Sonogashira coupling by Guzman and co-workers¹⁷¹ revealed that aryl bromides coupled with trimethylsilylacetylene, phenyl acety-

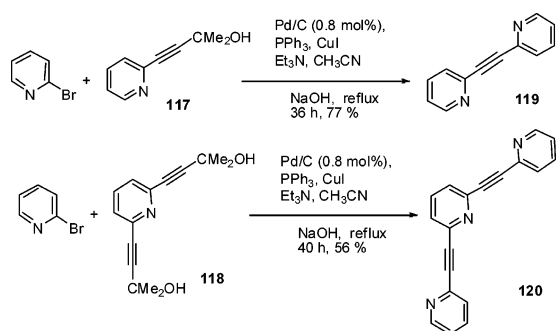
lene, and butyne in the presence of PPh₃ and CuI in an anhydrous mixture of triethylamine and acetonitrile (Table 47). Remarkably, the yields of products are higher than those reported under some homogeneous Pd(0) catalysis. Thus Pd/C–PPh₃–CuI has been developed as an efficient catalytic system for Sonogashira coupling reactions. This system can also be applied in the synthesis of some ethynylpyridines (Table 47, entries 8, 9). Interestingly, 2-bromopyridine¹⁷² could be coupled with 2-(3-hydroxy-3-methyl-but-1-ynyl)-substituted pyridines **117** and **118** to form dipyriddyethynes **119** and **120**. The 2-hydroxy-2-propyl groups are split off by Grob fragmentation under the basic conditions (reflux in NaOH/Et₃N/MeCN) (Scheme 34).

Table 47. Pd/C-Catalyzed Sonogashira Coupling of Aryl Bromides with Acetylenes

Ar-Br + \equiv R		Pd/C (4 mol%), PPh ₃ , CuI Et ₃ N-MeCN, 80 °C		Ar- \equiv R
Entry	Ar-Br	R	Yield (%) ^a	116
1		Ph	53	
2		Ph	58	
3		SiMe ₃	88	
4		Et	72	
5		Ph	64	
6		Ph	59	
7		SiMe ₃	80	
8		Ph	67	
9		SiMe ₃	75	

^a Isolated yield.

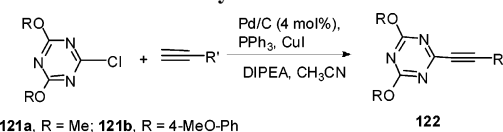
Scheme 34. Pd/C-Catalyzed One-Pot Synthesis of Dipyriddyethynes **119 and **120****



Pd/C catalysis is useful for the Sonogashira coupling of *s*-triazines **121**¹⁷³ and in the pyran-2-one series¹⁷⁴ where chloride or bromide, respectively, served as leaving groups (Tables 48 and 49).

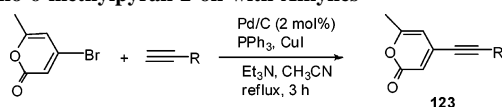
A heterogeneous protocol for the ligand-free Sonogashira reaction that employed Pd/C as a catalyst and a resin-bound

Table 48. Pd/C-Catalyzed Sonogashira Coupling of Chlorotriazines **121 with Alkynes¹⁷³**



halide	R'	T (°C)	t (h)	yield (%)
121a	Ph	65	70	65
121a	cyclohexyl	65	86	75
121a	<i>n</i> -Bu	65	70	40
121a	CMeEtOH	65	144	25
121a	<i>s</i> -Bu	110	90	20
121a	CMe ₂ OH	82	40	66
121a	1-OH-cyclohexyl	82	26	92
121a	CH ₂ CHMeOH	82	26	50
121b	CMe ₂ OH	82	48	62
121b	1-OH-cyclohexyl	82	48	90

Table 49. Pd/C-Catalyzed Sonogashira Coupling of 4-Bromo-6-methylpyran-2-one with Alkynes¹⁷⁴



entry	R	yield (%)	entry	R	yield (%)
1	<i>n</i> -Pr	72	9	4-AcNH-Ph	95
2	<i>n</i> -Bu	77	10	4-NO ₂ -Ph	95
3	<i>n</i> -Pen	79	11	4-Ac-Ph	35
4	<i>n</i> -hexyl	81	12	CH ₂ OAc	0
5	TMS	82	13	1-OH-cyclopentyl	61
6	Ph	74	14	1-OH-cyclohexyl	84
7	CH ₂ OH	5	15	9-OH-9-fluorenyl	90
8	CH ₂ OTHP	81	16	estradiol-17 α -yl	85

tertiary amine as base was particularly useful for the facile isolation of polar nucleoside coupling products obtained from iodionucleosides with protected propargyl amines (Table 50).¹⁷⁵

A selective coupling with various alkynes was achieved in the 4-position of 5-bromo-4-chloropyrimidines **125** (Scheme 35).¹⁷⁶ The remaining bromo substituent could be exchanged by a second alkyne within a subsequent Sonogashira coupling. Position 5 was attacked first by Sonogashira reaction of corresponding 4-chloro-5-iodopyrimidines.¹⁷⁶

4.1.2. In Organic Solvent/Water Mixtures

Organic solvent/water mixtures provide a generally useful, robust, and efficient medium for Pd/C-catalyzed Sonogashira couplings. K₂CO₃ is usually used in these cases. Thus DME–water was used to couple aryl iodides and bromides bearing either electron-donating or electron-withdrawing substituents (Table 51).^{177,178}

This methodology could also be applied to heteroaromatic halides and triflates^{178,179} providing excellent yields of coupling products **127** (Table 52).

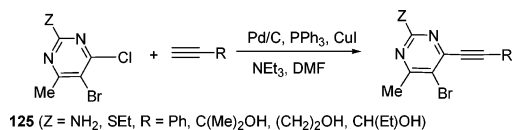
It was further used as the key step to synthesize the enantiomerically pure (*S*)-5-ethynyl-3-(1-methyl-2-pyrrolidinyl)-pyridine **130** (SIB-1508Y) as a novel enantiopure nicotinic acetylcholine receptor agonist (Scheme 36).^{178–179,180}

The coupling of *N*-propargyl amino acids **131** with aryl or heteroaryl bromides provides an easy access to unnatural α -amino acids **132**, which could be further hydrogenated to **133** (Scheme 37).¹⁸¹ It should be mentioned that none of the typical conditions of homogeneous sources of Pd(0) [Pd-(PPh₃)₂Cl₂, Pd(PPh₃)₄, Pd₂(dba)₃] were successful to synthesize the pyridine cross-coupling product **132** (Ar = 3-pyridyl).

Table 50. Sonogashira Coupling of Deoxynucleoside Derivatives^a

Ar-I	Alkyne	Products 124	t (h)	Yield (%) ^b
			16	72
			10	71
			16	69
			25	94
			14	78
			18	73

^a Standard conditions: 10% Pd/C (5 mol %), alkyne (2 equiv), CuI (20 mol %), Amberlite IRA-67 (5 equiv), DMF (0.1 M), 50 °C.
^b Isolated yield.

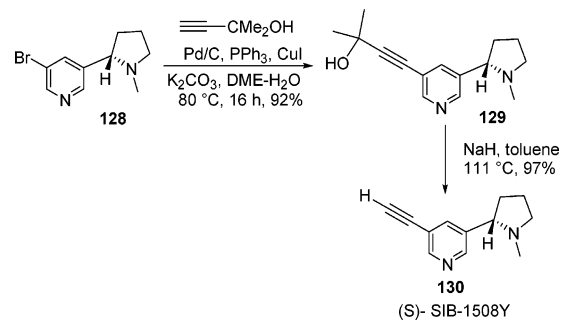
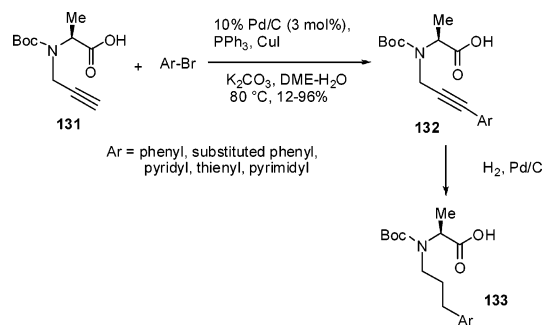
Scheme 35. Pd/C-Catalyzed Sonogashira Coupling of 4-Chloropyrimidines**Table 51. Pd/C-Catalyzed Sonogashira Coupling of Aryl Halides with Substituted Alkynes**

X	R	R'	yield (%)
Br	3-CHO	CMe ₂ OH	98
Br	4-NO ₂	CMe ₂ OH	92
I	3-NH ₂	CMe ₂ OH	78
Br	2-CN	CMe ₂ OH	89
Br	2-CN	CH ₂ NMe ₂	92
I	4-OH	1-cyclohexenyl	50
I	4-CO ₂ H	1-cyclohexenyl	80

Recently, we applied the methodology of Pd/C-catalyzed Sonogashira coupling in aqueous media for the synthesis of

Table 52. Sonogashira Coupling of Heteroaromatic Halides with Substituted Alkynes

Het-X	R	Yield (%)
	CH ₂ OH	90
	CMe ₂ OH	95
	CH ₂ NMe ₂	50
	CH(OH)Ph	95
	CH ₂ CH ₂ OH	85

Scheme 36. Pd/C-Catalyzed Synthesis of SIB-1508Y**Scheme 37. Pd/C-Catalyzed Synthesis of Compounds 133**

ω -functionalized alkynylpyrazolo[1,5-*a*]pyrimidines **135** starting from 3-iodopyrazolo[1,5-*a*]pyrimidines **134** as potential calcineurin inhibitors (Table 53).¹⁸² It turned out that Pd/C was advantageous over other commonly used homogeneous Pd(II) or Pd(0) catalysts [Pd(PPh₃)₂Cl₂, Pd(PPh₃)₄, and Pd(OAc)₂] in a number of cases.

In the case of application of 4-tosyloxybutyne (entry 11), the coupling product was obtained in only 18% yield together with its elimination product 3-(3-buten-1-ynyl)pyrazolo[1,5-*a*]pyrimidine **136** in 36% yield (Scheme 38).¹⁸²

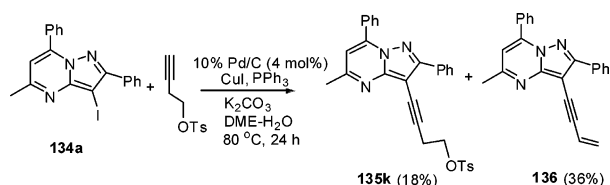
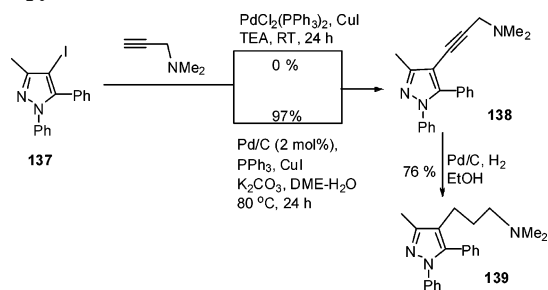
As an efficient way to introduce a dimethylaminopropyl chain into a pyrazole ring, Pd/C-catalyzed Sonogashira coupling of 3-iodopyrazole **137** with *N,N*-dimethylpropargylamine was used, followed by catalytic hydrogenation.¹⁸³ Pd/C was applied in both steps. Remarkably, catalysis with Pd-(PPh₃)₂Cl₂ and CuI completely failed, while Pd/C, PPh₃, and CuI provided quantitative Sonogashira coupling (Scheme 39).

Similar phenomena were observed by Fairlamb et al. in Sonogashira reactions of 4-bromo-6-methyl-2-pyrone.¹⁸⁴

Table 53. Pd/C-Catalyzed Sonogashira Coupling of 3-Iodopyrazolo[1,5a]pyrimidines

entry	R ¹	R ²	R ³	R	yield ^a (%)
1	Ph	Me	Ph	CH ₂ NMe ₂	70
2	H	Ph	Ph	CH ₂ NMe ₂	91
3	Me	Ph	Ph	CH ₂ NMe ₂	76
4	<i>p</i> -Cl-Ph	Me	Ph	CH ₂ NMe ₂	69
5	Ph	Me	<i>p</i> -Cl-Ph	CH ₂ NMe ₂	54
6	H	Ph	Ph	CH ₂ OH	78
7	Ph	Me	Ph	CH ₂ OH	72
8	Ph	Me	Ph	CH ₂ CH ₂ OH	71
9	H	Ph	Ph	CH ₂ CH ₂ OH	75
10	Me	Ph	Ph	CH ₂ CH ₂ OH	70
11	Ph	Me	Ph	CH ₂ CH ₂ OTs	18 ^b

^a Isolated yield. ^b Enyne **136** (36%) was isolated.

Scheme 38. Pd/C-Catalyzed Coupling of 134a with 4-Tosyloxybutyne**Scheme 39. Pd/C-Catalyzed Sonogashira Coupling of 3-Iodopyrazole 137**

Coupling of haloarenes with 3-butyne-1-ol in the presence of Pd/C, PPh₃, and CuI provided the expected Sonogashira coupling product, while homogeneous catalysis by PdCl₂(PPh₃)₂/NEt₃ gave 1-aryl-4-hydroxy-1-butanones and derivatives, obviously by additional hydration.¹⁸⁵

As an alternative to K₂CO₃, diisopropylamine can be used as base in Sonogashira coupling in DMA–water as reported by Kotschy and co-workers (Table 54),⁷⁹ but the yields were not very high. The Pd/C catalyst could be recovered and reused. After the reaction, just minor amounts of palladium had leached from the support.

As a further solvent system, water and 2-aminoethanol proved to be useful.¹⁸⁶ A variety of terminal alkynes were coupled with aryl iodides and bromides possessing functional groups to give the coupling products **141** in good to excellent yields (Table 55).

4.1.3. Copper-Free and Ligand-Free Sonogashira Coupling

In most cases of Pd/C-catalyzed Sonogashira coupling, CuI and phosphine ligands (PPh₃) were applied. But there were cases reported where a Pd/C-catalyzed Sonogashira reaction

Table 54. Pd/C-Catalyzed Sonogashira Coupling of Aryl Halides with Alkynes in DMA–Water/Diisopropylamine

Ar	X	alkyne (R)	yield (%)
2-pyridyl	Br	CH ₂ CH ₂ OH	58
2-pyridyl	Br	<i>n</i> -Bu	62
2-pyridyl	Br	CMe ₂ OH	65
3-pyridyl	Br	CH ₂ CH ₂ OH	77
3-pyridyl	Br	<i>n</i> -Bu	81
3-pyridyl	Br	CMe ₂ OH	69
3-tolyl	Br	CH ₂ CH ₂ OH	44
3-tolyl	Br	<i>n</i> -Bu	26
3-tolyl	Br	CMe ₂ OH	48
4-tolyl	Br	CH ₂ CH ₂ OH	46
4-tolyl	Br	<i>n</i> -Bu	31
4-tolyl	Br	CMe ₂ OH	51
2-pyridyl	Cl	<i>n</i> -Bu	54
2-pyridyl	Cl	CMe ₂ OH	51
4-CN-Ph	Cl	<i>n</i> -Bu	0

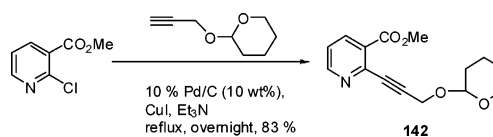
Table 55. Pd/C-Catalyzed Sonogashira Reactions in Water and 2-Aminoethanol

R ¹	X	R ²	<i>t</i> (h)	yield ^a (%)
H	I	CMe ₂ OH	9	78
2-CH ₂ CO ₂ Et	I	Ph	15	93
4-SMe	Br	CMe ₂ OH	8	77
4-Me	Br	CMe ₂ OH	9	84
4-Me	Br	CH ₂ OH	6	77
4-CHO	Br	CHMeOH	10	85
4-CHO	Br	CHPhOH	9	59
4-Ac	Br	CMe ₂ OH	9	69
4-Ac	Br	CH ₂ CH ₂ OH	5.5	85
4-Ac	Br	Ph	5	72
	Br	CMe ₂ OH	15	80 ^b
	Br	CH ₂ OH	15	82 ^b

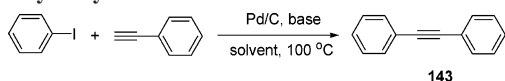
^a Isolated yield; all reactions were carried out in water and 2-aminoethanol (3 equiv). ^b Acetonitrile–H₂O (1/1) was used as solvent.

was successful in the absence of phosphine ligands or even in the absence of both phosphine ligands and CuI.

In the synthesis of (±)-tashiromine, Bates and co-workers reported a Pd/C-catalyzed Sonogashira coupling without phosphine ligand.¹⁸⁷ Methyl 2-chloronicotinate was coupled with 2-prop-2-ynyloxytetrahydropyran to give the pyridyl alkyne **142** in 83% yield (Scheme 40).

Scheme 40. Pd/C-Catalyzed Sonogashira Coupling of Methyl 2-Chloronicotinate

Köhler and co-workers reported the Pd/C-catalyzed Sonogashira coupling of iodobenzene with phenylacetylene without the addition of CuI or PPh₃ (Table 56).⁸¹ Good yields were achieved. Conversions up to 74% were found after 30 min using Pd concentrations of only 0.125 mol % (Table 56, entry 6; TON = 592, TOF = 1184). The addition of

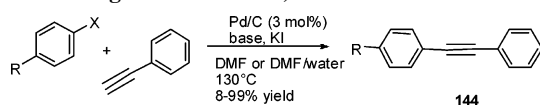
Table 56. Pd/C-Catalyzed Sonogashira Coupling of Iodobenzene with Phenylacetylene

entry	catalyst (mol %)	solvent	base	<i>t</i> (h)	conv (%)	yield ^a (%)
1	0.50	piperidine	piperidine	6	77	61
2	0.50	pyrrolidine	pyrrolidine	6	88	80
3	0.125	DMA	pyrrolidine	6	100	77
4	0.125	NMP	pyrrolidine	6	96	80
5	0.125	DMA	pyrrolidine	1	79	54
6	0.125	DMA	pyrrolidine	0.5	74	53

^a Determined by NMR.

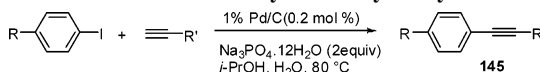
CuI was tested as well. However, this did not result in higher reactivities or selectivities. Larger amounts of copper even decreased activity and selectivity.

A convenient method for CuI-free Pd/C-catalyzed Sonogashira coupling of aryl chlorides and bromides is based on an *in situ* halogen exchange by a iodide source such as an alkali iodide, termed as HALEX-Sonogashira reaction by Rothenberg et al.¹⁸⁸ Pd/C worked best as compared with Pd on other solid supports (Al₂O₃, BaSO₄) or homogeneous Pd(0). The Pd/C catalyst could be reused at least five times without significant decrease of yields (Scheme 41).

Scheme 41. Pd/C-Catalyzed CuI-Free Sonogashira Coupling of Aryl Chlorides and Bromides in the Presence of KI (HALEX-Sonogashira Reaction)

X = Br, Cl, R = H, Me, CF₃, CHO, Ac, CN
base = KF, TBAF, KOH...

Further facilitation of Pd/C-catalyzed Sonogashira coupling is possible by circumventing ligands, CuI, and amine and by working under a noninert atmosphere. Under these conditions, a range of aromatic iodides could be coupled with aliphatic and aromatic alkynes using commercially available 1% Pd/C (0.2 mol %) as catalyst, *i*-PrOH–H₂O (1:1), and Na₃PO₄·12H₂O as base at 80 °C (Table 57).¹⁸⁹ Aryl iodides

Table 57. Amine- and Copper-Free Sonogashira Coupling of Aryl Iodides with Terminal Alkynes Catalyzed by Pd/C

entry	R	R'	<i>t</i> (h)	product	yield ^a (%)
1	NO ₂	CH ₂ CH ₂ OH	2	145a	79
2	Ac	CH ₂ CH ₂ OH	5	145b	80
3	OMe	CH ₂ CH ₂ OH	5	145c	37
4	H	CH ₂ CH ₂ OH	5	145d	45
5	NO ₂	Ph	3	145e	98
6	Ac	Ph	2	145f	98
7	OMe	Ph	6	145g	60
8	H	Ph	6	145h	67
9	NO ₂	2-CF ₃ -Ph	2	145i	96
10	Ac	2-CF ₃ -Ph	2	145j	94
11	OMe	2-CF ₃ -Ph	5	145k	88
12	H	2-CF ₃ -Ph	5	145l	96
13	NO ₂	4-MeO-Ph	5	145m	98
14	Ac	4-MeO-Ph	3	145n	94
15	OMe	4-MeO-Ph	6	145o	60
16	H	4-MeO-Ph	6	145p	72

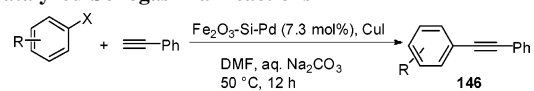
^a Isolated yields.

bearing electron-withdrawing substituents (NO₂, Ac) gave almost quantitative yields (entries 5, 6, 9, 10, 13, 14), while somewhat lower yields were obtained in the other cases.

The potential advantages of the Pd/C catalyst system, that is, the ease of separation and facile recycling of the metal and the low level of metal contamination in the product, suggest that a copper-, ligand-, and amine-free Sonogashira coupling protocol based on the use of a Pd/C catalyst system would be of major interest for both industrial and academic applications.

4.2. Pd on Metal Oxides

A magnetic maghemite (γ-Fe₂O₃)–silica nanoparticle-supported Pd–nitrogen–heterocyclic carbene complex (Fe₂O₃–Si–Pd catalyst, see also Figure 1) was applied in Sonogashira reactions of aryl iodides or bromides with phenylacetylene providing high yields of coupling products **146** (Table 58).¹¹⁰

Table 58. Maghemite–Silica–Nanoparticle-Supported Pd-Catalyzed Sonogashira Reactions

R	X	GC yield (%)	isolated yield (%)
2-Me	I	94 ^a	89
2-Me	Br	94	91
3-OMe	I	96	88
3-OMe	Br	95	93
4-Ac	I	96	91

^a The first round yield; the second to fifth round yields were 91%, 90%, 91%, and 89%, respectively.

4.3. Pd on Microporous and Mesoporous Supports

In 2004, Djakovitch and Rollet reported effective heterogeneous Sonogashira reactions using palladium zeolites [Pd(NH₃)₄]²⁺/NH₄Y under copper-free and ligand-free conditions (Table 59).^{190,191} Omission of copper is advantageous to suppress Glaser-type coupling of the alkynes as side reaction. Later on, microporous [Pd(NH₃)₄]²⁺/NaY (prepared by impregnation and calcination of zeolite) and mesoporous [Pd]-SBA-15 (prepared by grafting a phosphine ligand to silica) were prepared and used as highly reactive and selective catalysts in copper-free Sonogashira couplings (Table 59).⁵⁸ Both catalysts showed excellent stability toward leaching. The latter was found to be more reactive. It could also be applied in transforming large substrates (2-bromonaphthalene, 10-bromoanthracene) because of its larger pore size. Remarkably, these catalysts were more reactive than Pd/C but less reactive than homogeneous Pd catalysis (Table 59, footnote c). Recycling and reuse of the catalyst was possible but with a considerable loss of activity in the first reuse. Since no change in the structure of the support could be detected, the loss of reactivity is probably attributed to changes of the complexed phosphine ligand. Aryl iodides and activated aryl bromides gave almost quantitative yields (Table 59). The catalyst was stable and recyclable. Amorphous silica could also serve as solid support but was less much less effective.⁵⁸

Pd on porous glass tubing provided high yields in Cu-free Sonogashira reactions of iodo- and bromoarenes or 2-bromopyridine with alkynes.²⁴

Table 59. $[\text{Pd}(\text{NH}_3)_4]^{2+}/\text{NH}_4\text{Y}$ -Catalyzed Copper-Free Sonogashira Reactions

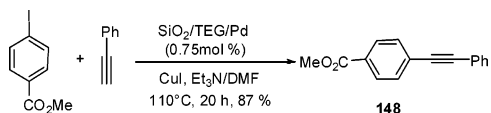
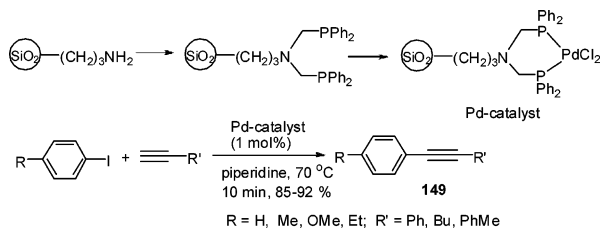
$$\text{Ar-X} + \text{R-C}\equiv\text{C-H} \xrightarrow[\text{Et}_3\text{N, DMF/H}_2\text{O (4:1), 80}^\circ\text{C}]{\begin{array}{l} [\text{Pd}(\text{NH}_3)_4]^{2+}/\text{NH}_4\text{Y (1 mol\%)} \\ \text{or } [\text{Pd}(\text{NH}_3)_4]^{2+}/\text{NaY (1 mol\%)} \\ \text{or } [\text{Pd}]/\text{SBA-15 (1 mol\%)} \end{array}} \text{Ar-C}\equiv\text{C-R} \quad \mathbf{147}$$

ArX	R	$[\text{Pd}(\text{NH}_3)_4]^{2+}/\text{NH}_4\text{Y}$ yield ^a (%)	$[\text{Pd}(\text{NH}_3)_4]^{2+}/\text{NaY}$ yield ^b (%)	$[\text{Pd}]/\text{SBA-15}$ yield ^b (%)
Ph-I	Ph	100		
4-MePh-I	Ph	100 (82)		
4-AcPh-I	Ph	100 (85)		
2-NO ₂ Ph-I	Ph	100 (89)		
2-MePh-I	Ph	82 (67)		
Ph-I	C≡C-CH ₂ O-TMS			80 (57)
Ph-Br	Ph	45 ^c		73
4-MePh-Br	Ph	30		
4-AcPh-Br	Ph	100		
2-Naphthyl-Br	Ph		0	100 (99)
10-Anthryl-Br	Ph		0	100 (76)
2 <i>H</i> -pyran-2-one-4-yl-tosylate	Ph		100 (95)	100

^a GC yields; isolated yields in parentheses. ^b Conversion; isolated yields in parentheses. ^c Yield 85% (GC) with $[\text{Pd}(\text{PPh}_3)_2]\text{Cl}_2$, 73% (GC) with $[\text{Pd}]/\text{SBA-15}$, 20% (GC) with $[\text{Pd}(\text{II})]/\text{NaY}$, and 3% (GC) with $\text{Pd}(0)/\text{C}$.

4.4. Pd on Modified Silica

The catalyst obtained by encapsulation of palladium nanoparticles in a silica matrix ($\text{SiO}_2/\text{TEG}/\text{Pd}$) showed high catalytic activity in the Sonogashira coupling of methyl 4-iodobenzoate with phenylacetylene (Scheme 42).¹²⁰ Phosphines as ligands were not necessary. Another type of Pd catalyst on silica was obtained when 3-aminopropyl-modified silica gel was functionalized with phosphine ligands and transformed into a stable immobilized palladium complex (Scheme 36). This catalyst was successfully applied in a series of fast, copper-free Sonogashira coupling reactions (Scheme 43).¹⁹²

Scheme 42. $\text{SiO}_2/\text{TEG}/\text{Pd}$ -Catalyzed Sonogashira Reaction**Scheme 43.** Modified Silica Supported Palladium Catalyzed Copper-Free Sonogashira Coupling

4.5. Pd on Clay and Other Inorganic Materials

Layered double hydroxide supported palladium nanoparticles ($\text{LDH-Pd}(0)$) allowed Sonogashira coupling of chloroarenes to be carried out under Cu-free conditions (THF/water , NEt_3) and provided high activity (Table 60).⁶⁶ Even electron-rich chloroarenes could be coupled in this way (Table 60, entry 2). The catalyst (1 mol %) was used in five

cycles and showed consistent activity in the coupling of phenylacetylene and chlorobenzene. Nonaqueous ionic liquids (NAIL) could also be used for this catalytic system (Table 60, entry 1).

Table 60. $\text{LDH-Pd}(0)$ -Catalyzed Sonogashira Reaction of Chloroarenes with Phenylacetylene

$$\text{Ar-Cl} + \text{Ph-C}\equiv\text{C-H} \xrightarrow[\text{THF/water or NAIL conditions}]{\text{LDH-Pd}^0 (1 \text{ mol\%}), \text{NEt}_3, 80^\circ\text{C}} \text{Ar-C}\equiv\text{C-Ph} \quad \mathbf{150}$$

Entry	Chloroarene	Product 150	t (h)	Yield (%)
1			30 27	95 95 ^a
2			48	60
3			40	82

^a Under NAIL conditions.

5. Stille, Fukuyama, and Negishi Reactions

5.1. Stille Reactions

5.1.1. Pd on Carbon (Pd/C)

Liebekind and co-workers^{193,194} reported Pd/C -catalyzed Stille cross-coupling reactions. The protocol was optimized by the addition of CuI as cocatalyst and the ligand AsPh_3 [Pd/C (0.5 mol %), CuI (10 mol %), AsPh_3 (20 mol %)] to allow the reaction to occur at a reasonable rate with a variety of substrates. Besides the advantage of using a stable form of $\text{Pd}(0)$, the yields of the products under these conditions were better than those obtained using $\text{Pd}_2(\text{dba})_3$ as the source of $\text{Pd}(0)$ (Table 61). The use of vinyl halides and triflates as well as aryl halides was well tolerated. However, aryl fluorosulfonates and aryl triflates performed poorly under these conditions (20–30% conversion) due to competing triflate hydrolysis.

As an alternative to halides or sulfonates, hypervalent iodonium salts were used in Pd/C -catalyzed Stille couplings as reported by Kang and co-workers. The reaction can conveniently be carried out at room temperature in aqueous acetonitrile (Table 62).¹⁹⁵

5.1.2. Palladium on $\text{KF}/\text{Al}_2\text{O}_3$

Solventless Stille reactions on palladium-doped $\text{KF}/\text{Al}_2\text{O}_3$ were investigated under microwave irradiation (Scheme 44).¹⁰⁸

5.1.3. Pd on Modified Silica ($\text{SiO}_2/\text{TEG}/\text{Pd}$)

The catalyst $\text{SiO}_2/\text{TEG}/\text{Pd}$ consisting of palladium nanoparticles encapsulated in a silica matrix showed high catalytic activity in the Stille coupling of aryl iodides with allyltributylstannane (Scheme 45).¹²⁰

5.2. Fukuyama Reactions

5.2.1. Pd on Carbon (Pd/C)

Coupling of organozinc reagents with thiol esters to ketones can be catalyzed by Pd/C . This methodology was applied to the aliphatic organozinc compound **159** by Seki and co-workers¹⁹⁶ representing the first example of coupling of sp^3 -hybridized organometallics in the presence of hetero-

Table 61. Pd/C-Catalyzed Stille Cross-Coupling¹⁹³

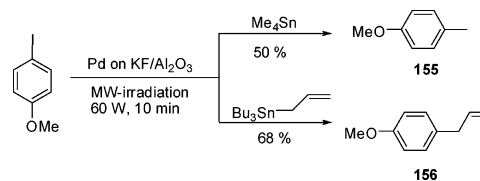
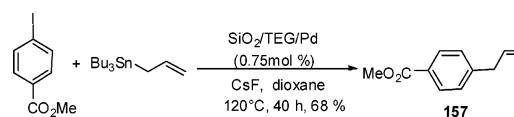
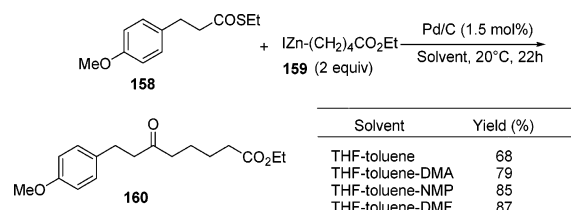
R-X	Product 152	t (h)	Yield (%) ^a
		24	85 ^b
		16	77
		16	79
		16	82
		12	86
		16	80
		24	67
		48	88
		24	80 ^c

^a Isolated yield of pure product. ^b 5 mol % Pd was used. ^c Reference 194, 95 °C.

Table 62. Pd/C-Catalyzed Coupling of Organostannanes with Hypervalent Iodonium Salts

R-SnBu ₃	Iodonium Salts 153	Product 154	t (h)	Isolated yields (%)
PhSnBu ₃	Ph ₂ I ⁺ BF ₄ ⁻	Ph-Ph	2	95
	Ph ₂ I ⁺ BF ₄ ⁻		1.5	96
PhSnBu ₃	Ph-CH=CH-I ⁺ PhBF ₄ ⁻	Ph-CH=CH-Ph	2	82
	Ph ₂ I ⁺ BF ₄ ⁻		4	93
	Ph-CH=CH-I ⁺ PhBF ₄ ⁻		2	54

geneous Pd/C (Scheme 46). It is worth mentioning that no poisoning of the catalyst occurred by the released thiol. The

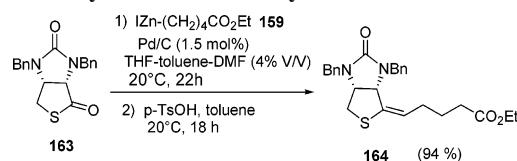
Scheme 44. Solventless Stille Reactions by Palladium-Doped KF/Al₂O₃**Scheme 45. SiO₂/TEG/Pd-Catalyzed Stille Reaction****Scheme 46. Pd/C-Catalyzed Fukuyama Reactions in Various Solvents**

addition of a polar aprotic solvent such as DMA, NMP, or DMF (4% v/v) improved the yield considerably, probably because of deaggregation of the organozinc compound. These optimized conditions were applied to the Fukuyama reaction of a series of other thiol esters **161** (Table 63).

Table 63. Pd/C-Catalyzed Fukuyama Coupling Reactions

R	yield (%)
CH ₃ (CH ₂) ₆	91
3-thienyl	67
3-Cl-Ph	90
EtO ₂ C(CH ₂) ₆	76
4-EtO ₂ C-Ph	70
PhCO(CH ₂) ₂	74

The Pd/C-catalyzed Fukuyama reaction could also be efficiently used in the synthesis of the dehydrobiotin derivative **164** (Scheme 47). Pd/C turned out to be advantageous over homogeneous Pd catalysts.¹⁹⁶

Scheme 47. Synthesis of the Dehydrobiotin Derivative **164**

5.2.2. Pd(OH)₂ on Carbon (Perlmans Catalyst)

As also found in Sonogashira and Suzuki couplings, Pd(OH)₂/C catalyst (Perlmans catalyst) was found to be superior to Pd/C in Fukuyama coupling of thiol esters with the organozinc reagent **159** (Table 64) affording much higher yields.^{197–199} The better performance of Pd(OH)₂/C was explained by better leaching of Pd(0) formed by reduction by the organozinc compound.

5.3. Pd/C-Catalyzed Negishi Reactions

Rossi and co-workers reported the Pd/C-catalyzed cross-coupling of aryl zinc chlorides with β -haloacrylates and

Table 64. Fukuyama Coupling Reaction in the Presence of Pd(OH)₂/C

RCOSET + IZn-(CH ₂) ₄ -CO ₂ Et		Pd(OH) ₂ /C or Pd/C		RCO-(CH ₂) ₄ -CO ₂ Et	
159 (2 equiv)		THF-toluene-DMF		165	
		RT		yield ^a (%)	
R	Pd catalyst (mol %)	T (h)	Pd(OH) ₂ /C	Pd/C	
4-MeOPh(CH ₂) ₂	0.15	50	84	30	
CH ₃ (CH ₂) ₆	0.6	24	93	52	
cyclohexyl	0.6	72	79	41	
EtO ₂ C(CH ₂) ₆	0.9	17	78	67	
PhCO(CH ₂) ₂	0.9	23	70	50	
Ph	0.9	71	72	39	
3-Cl-Ph	0.6	25	73	25	
3-thienyl	0.9	68	61	19	

^a Isolated yield.

cinnamates **167**.²⁰⁰ AsPh₃ was superior to PPh₃ as ligand (Table 65), and the β-halide was attacked selectively.

Table 65. Pd/C-Catalyzed Negishi Reactions

Ar-ZnCl + Alkenyl-X		Pd/C (5 mol%)		Ar-Alkenyl	
166		AsPh ₃ or PPh ₃		168	
Entry	Aryl	167	t(h)/T(°C)	168	Yield ^a (%)
1	Ph		140/20		45
2	Ph		23/20		89
3	2,4,5-tri-Me-Ph		2.5/20		96
4	4-MeO-Ph		31/20		69
5	4-MeO-Ph		7/20		58

^a Isolated yield. In entry 1, PPh₃ was used; in entries 2–5, AsPh₃ was used.

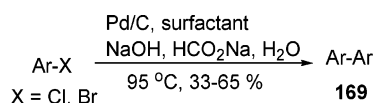
6. Ullmann-Type Coupling Reactions

The Ullmann-type reaction, that is, homocoupling of aryl or vinyl halides is conventionally mediated by copper at high temperatures. In recent years, Pd/C-catalyzed Ullmann-type coupling in the presence of reducing reagents, such as sodium formate, hydrogen, zinc, indium, or triethylamine has attracted increasing attention.

6.1. Pd/C-Catalyzed Aryl–Aryl Coupling

As found by Bamfield and co-workers²⁰¹ in 1978, biaryls **169** can be obtained in modest yields from chloro- or bromoarenes in the presence of Pd/C and a surfactant in aqueous alkaline sodium formate as a reducing agent (Scheme 48).

Kinetics and mechanism of the reaction was investigated by Sasson et al. suggesting a single electron transfer (SET) process from Pd(0) to the chloroarene forming chloroarene radical anions.²⁰² Working in a two-phase system under phase-transfer catalysis conditions helped to increase the yield (Scheme 49).²⁰³ The Pd/C catalyst was recycled without

Scheme 48. Pd/C-Catalyzed Aryl–Aryl Coupling in the Presence of a Surfactant and HCO₂Na

losing its catalytic activity simply by filtration and washing with methanol.

Scheme 49. Pd/C-Catalyzed Homocoupling of Chlorobenzene

Excellent yields of biaryls **169** were achieved in an oil-in-water microemulsion.^{203,204} These results demonstrate that many industrially important substituted biaryls may be amenable to synthesis in very high yields by simply modifying the solvent assemblage (Table 66).²⁰⁴

Table 66. Ullmann-Type Coupling of Haloarenes in Microemulsion^a

entry	microemulsion water/oil	haloarene	t (h)	conv (%)	select. (%) Ar–Ar	select. (%) Ar–H
1	O/W	PhCl	3.5	100	92	8
2	O/W	PhBr	3.5	100	94	6
3	O/W	PhI	3.5	100	98	2
4	O/W	4-Me-Ph-Cl	6	83	89	11
5	O/W	4-CHO-Ph-Cl	5	92	92	8
6 ^b	O/W	PhCl	22	92	53	47
7	W/O	PhCl	5.5	100	31	69
8	none ^c	PhCl	4	100	54	46

^a Reaction conditions: haloaryl (0.013 mol); 5% Pd/C (1 g); TBAB (1 g); sodium formate (1.5 g); NaOH (1.5 g); 75 °C. ^b No TBAB was used. ^c Water was used as solvent.





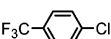

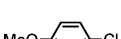
Hydrogen was used as reducing reagent in Pd/C-catalyzed Ullmann-type coupling of various chlorobenzenes and bromobenzene to biaryls **169** in the presence of aqueous sodium hydroxide and a small amount of PEG-400 (Table 67).²⁰⁵ Arenes **171** formed by simple reduction of the halobenzenes were observed as byproducts to various extents. The Pd/C catalyst could be recycled simply by filtration and washing with water and methanol. After seven runs, the catalyst retained >99% of its activity.

Zinc could also be used as reducing reagent in Pd/C-catalyzed aryl–aryl coupling of haloarenes in aqueous sodium hydroxide in the presence of PEG-400,²⁰⁶ in aqueous acetone without an additional base under mild convenient conditions (air, RT),²⁰⁷ or in water in the presence of crown ethers.²⁰⁸ Although high yields were achieved, only iodo- and bromoarenes could be used in the latter method (Table 68).²⁰⁷

In contrast, Pd/C-catalyzed zinc-mediated Ullmann-type coupling could be implemented with a variety of halides including chlorobenzenes when the reaction was carried out under carbon dioxide (Table 69).^{209,210}

Indium as reducing agent in Pd/C-catalyzed aryl–aryl coupling of aryl and pyridyl iodides provided high yields. Short reaction times were sufficient with DMF as solvent and LiCl as additive (Table 70).²¹¹ Aldehyde, keto, and thioether groups were tolerated in the aryl iodide components.

Table 67. Pd/C-Catalyzed Aryl–Aryl Coupling in the Presence of Hydrogen

Entry	Substrate	Conv. (%)	Pd/C (0.5 mol%) PEG-400 (7 mol%) NaOH, H ₂ O 110 °C, 150 min	
			Ar–Ar 169	Ar–H 171
			Yield (%) ^{a, b}	Yield (%) ^a
1		100	79 (73)	20
2		100	76 (71)	24
3		100	56 (51)	43
4		73	33	40
5		100	77 (69)	22
6		76	39	36
7		82	36	46

^a Yields based on GC. ^b Isolated yields in parenthesis.

Triethylamine was also used as reducing reagent in Pd/C-catalyzed Ullmann-type coupling. Excellent yields were achieved with *N,N*-bis(4-fluorophenethyl)-5-iodoisophthalamide (Scheme 50).²¹² The methodology was applied to the combinatorial synthesis of biaryl libraries.

6.2. Pd/C-Catalyzed Homocoupling of Vinyl Halides

For Pd/C-catalyzed homocouplings of vinyl halides, indium was used as reducing reagent.²¹¹ Excellent regioselectivities and high yields of the bivinyl products **178** were obtained in DMF in the presence of LiCl (Table 71). *p*-Bromo- α -bromostyrene selectively afforded 2,3-di(*p*-bromophenyl)-1,3-butadiene in 88% yield (entry 9) implying that a vinyl bromide moiety is more reactive than aryl bromide in this coupling reaction. (*E*)-Bromostyrene produced (*E,E*)-1,4-diphenyl-1,3-butadiene in 91% yield accordingly (entry 11).

6.3. Pd/C-Catalyzed Intramolecular Coupling of Aryl and Vinyl Halides


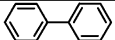

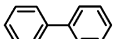





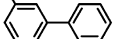





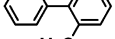





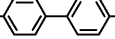

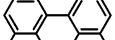
Indium is also useful as a reducing reagent in intramolecular Pd/C-catalyzed Ullmann-type coupling reactions affording carbocycles and heterocycles.²¹¹ The two reactive moieties can be aryl–aryl, aryl–vinyl, and vinyl–vinyl (Table 72).

7. Homocoupling of Arylboronic Acids, Pyridines, and Alkynes

7.1. Pd/C-Catalyzed Homocoupling of Arylboronic Acids (Suzuki-Type Homocoupling)

In 1996, a mechanistic study about Pd-catalyzed Suzuki-type homocoupling of arylboronic acids revealed²¹³ that low to moderate yields of symmetrical biaryls were formed from arylboronic acids when Pd(PPh₃)₄ or Pd(OAc)₂ was used as catalyst. An efficient high yielding approach to the homo-

Table 68. Zn-Mediated Ullmann-Type Coupling of Aryl Halides Catalyzed by Pd/C

Ar–X	Product (169)	Yield (%) ^a
		94
		92
		84
		89
		92
		73
		79
		82
		70
		94
		96
		64

^a Determined by GC/MS analysis.

coupling of arylboronic acid was found later on by Koza and Carita based on the addition of copper nitrate to enhance the coupling rate.²¹⁴

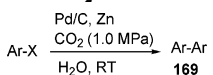
In 2005, Cravotto et al. reported a heterogeneous Pd/C-catalyzed Suzuki-type homocoupling of arylboronic acid. High-intensity ultrasound (US) or microwave (MW), alone or combined, promoted this reaction.^{105,215} These ligand-free couplings were carried out in aqueous media and afforded the corresponding biaryls **185** in acceptable to good yields (Table 73).¹⁰⁵

7.2. Pd/C-Catalyzed Homocoupling of Pyridines

4,4'-Dialkyl-2,2'-bipyridines **187** and 2,2':6',2''-terpyridines **188** are widely used as chelating agents. Transition metal complexes of these compounds are very important due to their chemical reactivity and photochemical properties.^{216,217}

There are several methods to prepare compounds **187** and **188**, among them, a one-step synthesis via Pd/C-catalyzed

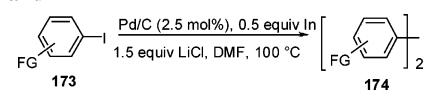
Table 69. Pd/C-Catalyzed Ullmann-Type Coupling of Aryl Halides in the Presence of CO₂²¹⁰



entry	Ar-X	<i>t</i> ^a (h)	yield ^b (%)
1 ^c	Ph-I	15	27
2 ^d	Ph-I	15	41
3	Ph-I	8	> 99
4 ^e	Ph-I	8	65
5	4-Me-Ph-I	15	95
6	2-Me-Ph-I	24	87
7	4-MeO-Ph-I	15	97
8	4-CF ₃ -Ph-I	48	95
9	1-Naph-I	24	100
10	Ph-Br	15	91
11	4-MeO-Ph-Br	24	95
12	4-Me ₂ N-Ph-Br	48	85
13	2,6-di-MeO-Ph-Br	72	78
14 ^f	2-OH-1-Naph-Br	48	81
15	Ph-Cl	36	56
16 ^g	Ph-Cl	36	96
17 ^g	3,5-di-MeO-Ph-Cl	48	81
18 ^g	1-Naph-Cl	36	95
19 ^g	3-EtO ₂ C-Ph-Cl	96	93

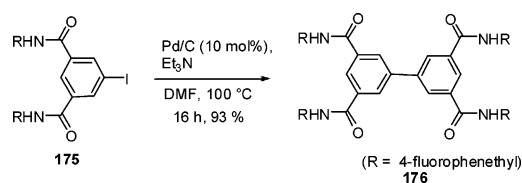
^a Reaction conditions: ArX (2 mmol); 5% w/w Pd/C (300 mg); Zn (170 mg); H₂O (5 mL); CO₂ (1.0 MPa). ^b Isolated yields. ^c In the absence of CO₂. ^d CO₂, 1 atm, bubbling. ^e CO₂, 6.0 MPa. ^f 2-Naphthol was obtained in 17% yield. ^g 5% Pd/C (400 mg).

Table 70. Ullmann-Type Coupling Reactions of Aryl Halides with Pd/C and In



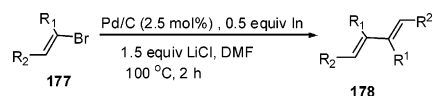
biaryl product 174	<i>t</i> (h)	yield ^a (%)
(1-Naph) ₂	2.5	87
(4- <i>n</i> -Bu-Ph) ₂	2.5	85
(4-MeO-Ph) ₂	2.5	91
(3-MeO-Ph) ₂	2.5	86
(4-HO-Ph) ₂	2.5	87
(4-EtO ₂ C-Ph) ₂	2	88
(3-EtO ₂ C-Ph) ₂	2.5	86
(4-F ₃ C-Ph) ₂	2	92
(2-F ₃ C-Ph) ₂	2.5	85
(4-CHO-Ph) ₂	3	87
(4-Ac-Ph) ₂	2.5	88
(4-Cl-Ph) ₂	2	91
(2-thienyl) ₂	1.5	92
(2-Py) ₂	1.5	86
(3-Py) ₂	3	89

^a Isolated yield.

Scheme 50. Pd/C-Catalyzed Homocoupling of Aryl Iodide 175 in the Presence of Et₃N

dehydrogenative homocoupling of pyridines. This is the simplest and most efficient method. In the early 1960s, Pd/C was extensively applied as a catalyst to synthesize bipyridine by oxidative coupling of pyridine in the absence of base or additives.^{218–220} In 1971, a series of 2,2'-bipyridines **187** and 2,2':6',2''-terpyridines **188** were prepared by refluxing alkylpyridines **186** in the presence of 5% Pd/C catalyst (Table 74).²²¹

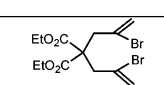
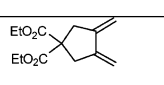
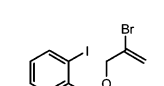
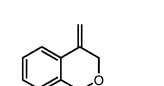
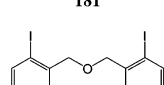
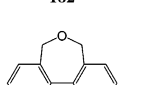
Table 71. Synthesis of Butadienes by Pd/C-Catalyzed Coupling of Vinyl Halides



entry	R ¹	R ²	yield ^a (%)
1	<i>n</i> -Hex	H	92
2	Ph	H	93
3	Ph	H	89
4	4-MeO-Ph	H	87
5	3-NH ₂ -Ph	H	79
6	3-HO-Ph	H	72
7	2-Cl-Ph	H	89
8	4-F ₃ C-Ph	H	88
9	4-Br-Ph	H	88
10	4-Py	H	89
11	H	Ph	91

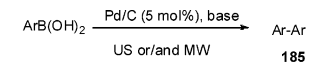
^a Isolated yield.

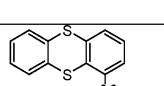
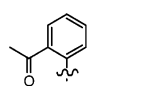
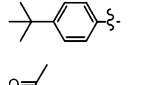
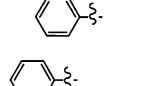
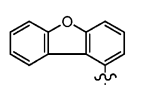
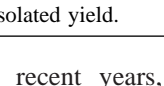
Table 72. Intramolecular Vinyl and Aryl Coupling Reactions^a

Halide	Product	<i>t</i> (h)	Yield (%) ^b
		2	69
		2	91
		3	77 ^c

^a Reaction performed in the presence of 2.5 mol % of Pd/C, 50 mol % In and 1.5 equiv of LiCl in DMF (0.5 M) at 100 °C. ^b Isolated yield. ^c 0.05 M LiCl in DMF was used.

Table 73. Pd/C-Catalyzed Suzuki-Type Homocoupling of Arylboronic Acids



Ar	US	MW	Combined US + MW
	Yield (%) ^a	Yield (%) ^a	Yield (%) ^a
	48	55	69
	80	88	-
	68	74	86
	71	70	-
	86	90	-
	72	66	-

^a Isolated yield.

In recent years, the Pd/C-catalyzed dehydrogenative coupling of pyridines was widely applied to the synthesis

Table 74. Pd/C-Catalyzed Synthesis of 4,4'-Dialkyl-2,2'-bipyridines **187 and 4,4''-Trialkyl-2,2':6',2''-terpyridines **188**^a**

pyridine (R)	bipyridine 187 yield ^b (%)	terpyridine 188 yield ^b (%)
Me	10–15 (15–25)	1–2 (1.5–3)
Et	17–25 (20–25)	3–5 (2–3)
<i>i</i> -Pr	40–50 (20–30)	12–15 (5–8)
<i>n</i> -Pen	13–20 (15–20)	3–5 (2–3)

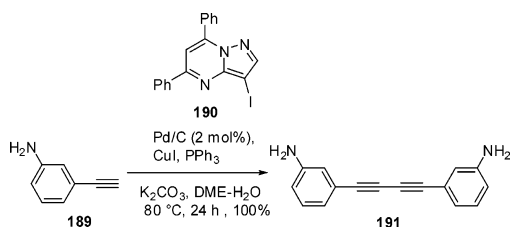
^a Reaction conditions: 5% Pd/C (1 g); 4-alkylpyridine (25 mL).
^b Isolated yields achieved by undegassed catalyst; in parenthesis yields with degassed catalyst

of 4,4'-dimethyl-2,2'-bipyridines,^{222–224} 4,4'-di-(3-pentyl-2,2'-bipyridines),²²⁵ 4,4'-di-(5-nonyl-2,2'-bipyridines),²²⁶ 4,4',5,5'-tetramethyl-2,2'-bipyridines,²²⁷ and diethyl 2,2'-bipyridine-5,5-dicarboxylate.²²⁸ When 4-ethylpyridine was refluxed with 10% Pd/C for 9 days, 4,4',4''-triethyl-2,2':6',2''-terpyridine (Et₃tPy) was isolated in 20% yield.²²⁹ These bipyridines and terpyridines were further used in preparation of transition metal complexes and other functionalized compounds.

7.3. Pd/C-Catalyzed Homocoupling of Alkynes (Glaser-Type Coupling)

The oxidative coupling of terminal acetylenes has been extensively investigated and reviewed.^{230–232} The Glaser coupling reaction, i.e., the copper-mediated oxidative homocoupling,^{233–236} is the classic method. This method is still widely used in modern organic synthesis.^{237–239}

However, there are some reports about the Pd-catalyzed homocoupling of alkynes (Glaser-type coupling) under homogeneous catalytic conditions using I₂,²⁴⁰ chloroacetone,^{241,242} or ethyl bromoacetate²⁴³ as oxidant. Fairlamb reported the homocoupling of alkynes catalyzed by Pd-(PPh₃)₂Cl₂/CuI without the addition of an oxidant.²⁴⁴ Heterogeneous Pd/C-catalyzed homocoupling of (3-aminophenyl)ethyne was first reported by us (Scheme 51). We attempted the Sonogashira coupling of 3-iodo-5,7-diphenylpyrazolo-[1,5-*a*]pyrimidine **190** with (3-aminophenyl)ethyne **189** under Pd/C–CuI–PPh₃ catalysis. No Sonogashira coupling product was found, but the homocoupling product **191** was isolated in quantitative yield.^{182,245} Running the reaction without **190** gave the product **191** only in 74% yield.²⁴⁵

Scheme 51. Pd/C-Catalyzed Homocoupling of (3-Aminophenyl)ethyne **189**

Strauss et al. demonstrated that Pd on porous glass in the presence of air can be used for a Glaser-type coupling of phenylethyne.²⁴

8. Other Coupling Reactions

8.1. Cyanation of Aryl Bromides

The utilization of homogeneous Pd catalysts in the cyanation of aryl halides has aroused considerable attention in recent years.²⁴⁶ In order to make this reaction more attractive to industrial application, heterogeneous Pd/C-catalyzed cyanation was approached. Hatsuda et al. reported a practical high-yielding synthesis of aryl nitriles **192** by Pd/C-catalyzed cyanation of aryl bromide with Zn(CN)₂ in the presence of PPh₃ and ZnBr₂.^{247,248} Functional groups such as acetyl, hydroxy, amino, and sulfide were all compatible with the reaction conditions (Table 75).

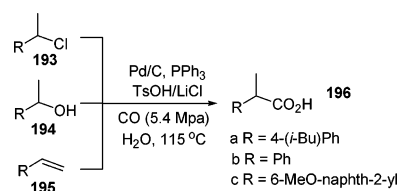
Table 75. Pd/C-Catalyzed Cyanation of Aryl Bromides

Ar-Br	Temp. (°C)	t (h)	Yield ^a (%)
	80	3	97
	80	5	82
	115	8	89
	115	8	93
	115	2	92
	125	4	65 ^b
	125	4	60 ^b
	80	5	75
	115	8	89

^a Determined by HPLC; Pd/C (4 mol %), PPh₃ (0.16 equiv), Zn dust (0.4 equiv), Br₂ (0.2 equiv), and Zn(CN)₂ (0.6 equiv) were used. ^b Pd/C (8 mol %), PPh₃ (0.32 equiv), Zn dust (1.2 equiv), Br₂ (0.4 equiv), and Zn(CN)₂ (0.5 equiv) were used.

8.2. Carbonylations

Carbon monoxide is another option to introduce a C-1 unit into a substrate by solid-supported Pd-catalysis. Pd/C was used in the presence of PPh₃/TsOH/LiCl to synthesize 2-arylpropionic acids **196** by carbonylation of 1-aryl-1-chloroethanes **193** (Scheme 52).²⁴⁹ The catalyst system was also applicable to the carbonylation of various 1-arylethanol **194** and their corresponding olefins **195** (Scheme 52), as

Scheme 52. Pd/C-Catalyzed Synthesis of 2-Arylpropionic Acids **196**

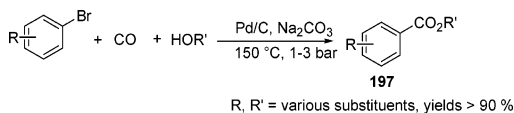
demonstrated in Table 76. In all cases, high conversions, selectivities, and TOF were achieved.

Table 76. Synthesis of 2-Arylpropionic Acids **196 by Pd/C-Catalyzed Carbonylations**

substrate	<i>t</i> (h)	conv. (%)	select. (%)	TOF (h ⁻¹)
193a	4.2	96	99.2	3375
194a	4	92	99.1	3400
195a	4	90	99.3	3300
193b	13	90	98	1010
194b	4.6	92	98	2900
193c	24	90	99	552

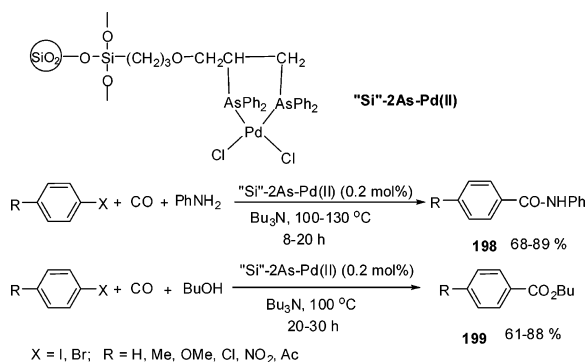
Esters **197** were obtained, when the Pd/C-catalyzed carbonylation⁶² was carried out in the presence of alcohols (Scheme 53).

Scheme 53. Pd/C-Catalyzed Alkoxy-carbonylation



As an alternative, esters and also anilides could be synthesized by Pd-catalyzed carbonylation of aryl iodides or activated aryl bromides in the presence of butanol or aniline, respectively, using a silica-supported bidentate arsine palladium complex “Si”–2As–Pd(II) under atmospheric conditions (Scheme 54).²⁵⁰ The catalyst showed high activity and could be recovered and reused.

Scheme 54. Carbonylations by Silica-Supported Bidentate Arsine Palladium Complex



8.3. α -Arylations of Diethyl Malonate

The homogeneous palladium-catalyzed arylation of carbonyl compounds using aryl halides has become a useful and general synthetic method.^{251–254} The reaction could also be catalyzed in heterogeneous fashion with diethyl malonate as the carbonyl compound.²⁵⁵ For aryl bromides **200**, Pd-exchanged NaY zeolites ([Pd(0)], [Pd(II)], and entrapped [Pd(NH₃)₄]) exhibited good activity at low Pd concentrations (2 mol %) (Table 77). The catalysts could easily be separated and reused without a real loss in activity (entries 1–4).

8.4. Arylations of Aromatic Compounds

Pd-catalyzed arylation reactions of arenes by haloarenes to biaryl products were successfully applied in intermolecular fashion to a variety of heterocyclic arenes^{256–258} and arenes possessing a directing group.^{259–261} In an intramolecular fashion, five- and six-membered rings were formed.^{262–265} In these couplings, hydrogen halide is eliminated. Palladium hydroxide on carbon (Pearlman's catalyst) effectively cata-

Table 77. Pd/Zeolite-Catalyzed α -Arylations of Diethyl Malonate^a

entry	catalyst	R	GLC yield (%)	isolated yield (%)
1	Pd(0)–NaY	Me	31 (33) ^b	21
2	Pd(II)–NaY	Me	41 (38) ^b	32
3	Pd(OAc) ₂ –NaY	Me	41 (39) ^b	29
4	Pd(NH ₃) ₄ –NaY	Me	51 (49) ^b	38
5	Pd(NH ₃) ₄ –NaY	OMe	57	45
6	Pd(NH ₃) ₄ –NaY	H	47	41
7	Pd(NH ₃) ₄ –NaY	F	64	50
8	Pd(NH ₃) ₄ –NaY	Ac	70	60
9	Pd(NH ₃) ₄ –NaY	NO ₂	98	84

^a Reaction conditions: 15 mmol of aryl bromide, 10 mmol of diethyl malonate, 20 mmol of base, 2 mol % Pd-catalyst, 6 mL solvent, 110 °C, 20 h. ^b Yield of second run in parentheses.

lyzes arylation reactions of aryl iodides and bromides, providing excellent arylation-to-hydrodehalogenation ratios (>30:1) with a broad scope for both intra- (Table 78) and intermolecular arylation processes (Table 79).^{29,266} The studies indicated that an active homogeneous palladium species is produced under the reaction conditions.

Table 78. Scope of Intramolecular Direct Arylation Reactions^a

Substrate 202	Product 203	Yield ^b
		95
		92
		69 ^c
		98
		86
		80
		92
		84
		84

^a Conditions: substrate, KOAc (2 equiv), and Pd(OH)₂/C (10 mol %) added to a screw cap vial followed by DMA (0.2 M) and heating to 140 °C for 12–24 h. ^b Isolated yield. ^c 20% of hydrodebrominated product was also obtained.

Table 79. Intermolecular Arylations^a

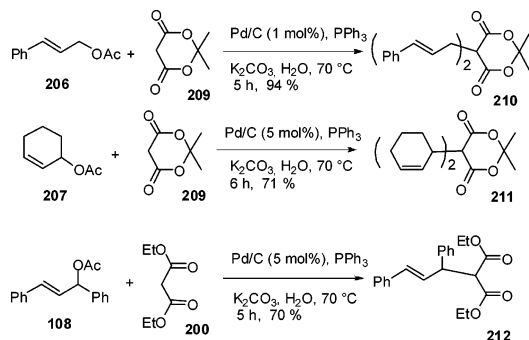
Heterarene (204)	Aryl halide	Product (205)	Yield ^b
			75
			76
			81
			82
			73
			75 ^c
			36 ^d

^a Conditions: substrate, KOAc (2 equiv), and Pd(OH)₂/C (10 mol %) added to a screw cap vial followed by DMA (0.2 M) and heating to 140 °C for 12–24 h. ^b Isolated yield. ^c Isolated as a 12:1 mixture of the 2,5/2,3 isomers. ^d Mesoporous [Pd]/SBA-15 was used; NMP, NaOAc, 140 °C, 12 d.²⁹

8.5. Allylations

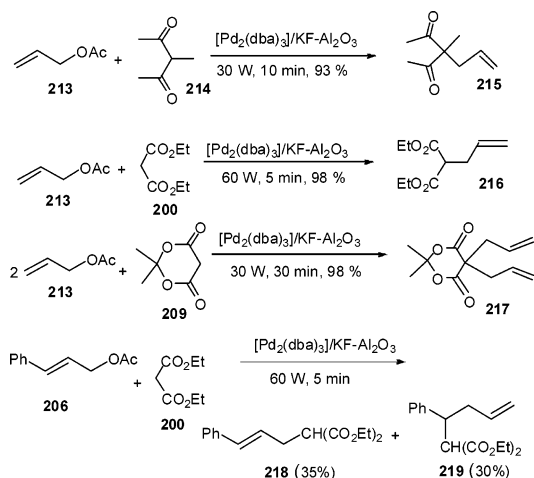
Several solid supports can be used in Pd-catalyzed allylic substitutions. Already in 1983, Bergbreiter and Chen reported the first Pd/C-catalyzed allylic substitution of allyl acetate by diethyl amine in the presence of triphenylphosphine.²⁶⁷ The catalyst used in the reaction was readily recyclable at least 10 times.

Using triphenylphosphine as the ligand, Felpin and Landais reported a practical Pd/C-mediated allylic substitution in water (for some examples, see Scheme 55).²⁶⁸ Allyl acetates **206**, **207**, and **208** coupled with 2,2-dimethyl-[1,3]-dioxane-4,6-dione **209** affording biallyl-substituted products **210** and **211**. Under the same conditions, **208** coupled with malonic acid diethyl ester **200** to provide monoallyl-substituted product **212**.

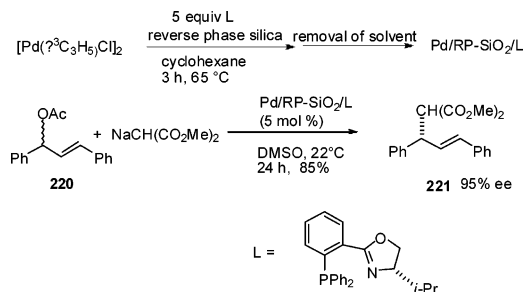
Scheme 55. Pd/C-Catalyzed Allylations of Malonates

Palladium on or in KF–Al₂O₃ was used as an effective catalyst in ligandless and solvent-free allylic substitutions

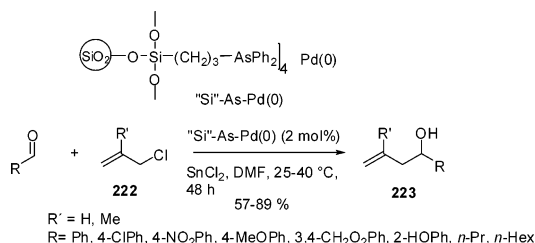
under microwave irradiation (Scheme 56).¹⁰⁸ The catalyst system was prepared by grinding [Pd₂(dba)₃] together with KF–Al₂O₃. Several acidic carbonyl compounds were used as nucleophile. Monoallylation products **215** and **216** or diallylation product **217** could be achieved. Mixtures of regioisomeric products **218** and **219** were observed with the substituted allyl acetate **206**.

Scheme 56. Pd/KF–Al₂O₃-Catalyzed Allylations under MW Irradiation

Allylation of malonate could be achieved in highly enantioselective fashion and high yield when [Pd(η³-C₃H₅)-Cl]₂ supported by reverse phase silica was modified by the chiral phosphine–oxazoline ligand L (Scheme 57).¹⁶⁰

Scheme 57. Enantioselective Allylation of Malonate

Allylations of the less acidic acetaldehyde or acetone with allylic chlorides could be implemented using a modified silica-supported palladium complex “Si”–As–Pd(0), where an arsine acts as ligand. Since SnCl₂ was used as an additional reducing agent, homoallylic alcohols were obtained as products (Scheme 58).²⁶⁹ The catalyst could be recovered and reused.

Scheme 58. Carbonyl Allylations under Reductive Conditions Catalyzed by “Si”–As–Pd(0)

8.6. Intermolecular Heck-Type Coupling

Lautens and co-workers reported a Pd/C-catalyzed ligand-free intermolecular Heck-type coupling of aryl iodides with

allyl acetates. Unlike in a genuine Heck reaction where hydride is eliminated after the oxidative addition, acetate serves as leaving group in this case (Table 80).²⁷⁰ Substrates bearing electron-donating groups required longer reaction times (entry 5). However, substrates with strongly electron-withdrawing substituents led to rapid isomerization of the alkenes to the thermodynamically more stable styryl system (entries 6 and 8). Both chloro and bromo substituents (entries 2 and 3) were tolerated under the reaction conditions.²⁷⁰

Table 80. Heck-Type Coupling of Allyl Acetate with Various Aryl Iodides

Entry	Aryl iodide	Product 224	t (h)	Yield (%) ^a
1			3	80
2			3	79
3			3	54
4			3	71
5			8	58
6			3	67
7			1	58 ^b
8			3	85

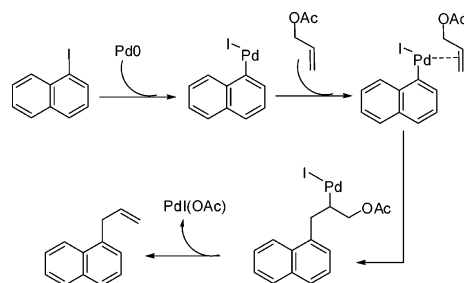
^a Isolated yields. ^b 5% Pd/C was used; 18% of internal olefin was observed.

A possible mechanism (Scheme 59) for this reaction involves initial oxidative addition to Pd(0) followed by carbopalladation of the olefin. Subsequent β -acetoxy elimination gives the final allyl product. Reduction of the resulting Pd(II) to Pd(0) is most likely achieved by coordination of an amine base followed by β -hydride transfer and reductive elimination of hydrogen iodide.

9. Pd on Solid Support in Tandem Reactions

Solid-supported Pd-catalyzed coupling reactions by C–C bond formation, such as Sonogashira or Heck reaction, can

Scheme 59. Proposed Mechanism for the Heck-Type Coupling

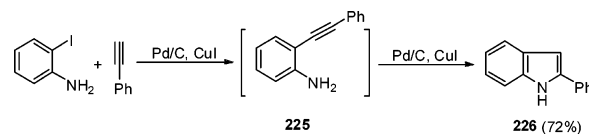


be followed by further addition reactions. In this way, heterocycles can be formed under cyclization.

9.1. Sonogashira Coupling in Tandem Reactions

When *o*-aminoaryl iodides are submitted to Sonogashira reactions, intramolecular addition of the amino group to the C–C triple bond can lead to the formation of indoles. As one possibility, Pd/C–CuI could be used as catalyst (Scheme 60).²⁷¹ The intermediate compound **225** resulting from the Sonogashira C–C coupling reaction between 2-iodoaniline and phenylacetylene was never observed in these experiments. This indicates that the heteroannulation is rapid under the reaction conditions.

Scheme 60. Pd/C-Catalyzed Synthesis of 2-Phenylindole^a



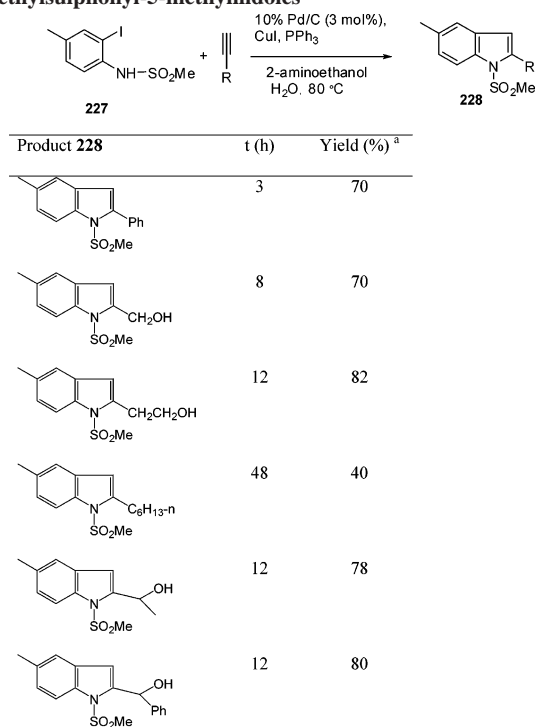
^a Reaction conditions: 5 mmol of 2-iodoaniline, 5 mmol of phenylacetylene, 15 mmol of Et₃N, 1 mol % Pd/C, 1 mol % CuI, 15 mL of DMF/H₂O (1:1), 120 °C, 6 h.

Pal and co-workers reported a general one-pot synthesis of 2-alkyl/aryl-substituted indoles **228** via Pd/C-mediated coupling/5-endo-dig cyclization of terminal alkynes with *o*-iodo-*N*-mesylanilines **227** in water.²⁷² The reaction was carried out using PPh₃ and CuI as cocatalyst and 2-aminoethanol as a base (3 equiv). The reaction appeared to tolerate a variety of functional groups present in the alkynes and did not require the use of any organic cosolvent (Table 81).

A greater variety of *N*-substituents at the 2-iodoanilines was possible when Pd–NaY was used as catalyst (Table 82).²⁷³ Cu catalysis was not necessary. It was found that the product formation largely depended on the solvent, base, and reaction temperature. The recycled catalyst showed good reusability in this heteroannulation reaction.

[Pd(NH₃)₄]²⁺/(NH₄)Y as catalysts allowed implementation of the synthesis of 2-phenylindole starting from *o*-iodoaniline and phenylacetylene under Cu-free conditions in 72% yield (Table 83).¹⁹¹ Similarly, microporous [Pd(NH₃)₄]²⁺/NaY or mesoporous [Pd]/SBA-15 silica could be used for the syntheses of a series of 2-substituted indoles.²⁹

When *o*-iodophenols were submitted to Sonogashira coupling with alkynes the subsequent intramolecular cyclization led to benzo[*b*]furans. Because of its relevance to natural products and to pharmacy many 2-substituted benzo[*b*]furan derivatives were prepared in this way during the last years using a homogeneous palladium catalyst and copper iodide as cocatalyst under mild conditions.^{274–277} As a heterogeneous alternative, Pd/C was applied in the presence

Table 81. Pd/C-Catalyzed Synthesis of 2-Substituted *N*-Methylsulphonyl-5-methylindoles^a Isolated yields.**Table 82. Synthesis of Indoles Catalyzed by Pd–NaY^a**

Aryl halide 229	Alkyne	Product 230	Yield (%) ^b
	\equiv -Ph		82
	\equiv -Cyclohexyl		78
	\equiv -2-pyridyl		51
	\equiv -(CH ₂) ₄ CH ₃		72
	HC≡CH (balloon)		40
	\equiv -Ph		68
	\equiv -Cyclohexyl		42

^a Reaction conditions: 0.5 mmol of aryl halide, 1.0 mmol of alkyne, 5 mol % Pd-cat., 0.5 mmol of LiCl, 1.0 mmol of Cs₂CO₃, 10 mL of DMF, at 140 °C for 6 h. ^b Isolated yield.

of CuI, PPh₃, and prolinol.²⁷⁸ This method tolerated a variety of functional groups in the alkynes, as well as a base labile nitro group in the *o*-iodophenols (Table 84). The protocol does not require the use of phase transfer catalyst or water-soluble phosphine ligands and is free from the use of any organic cosolvent.

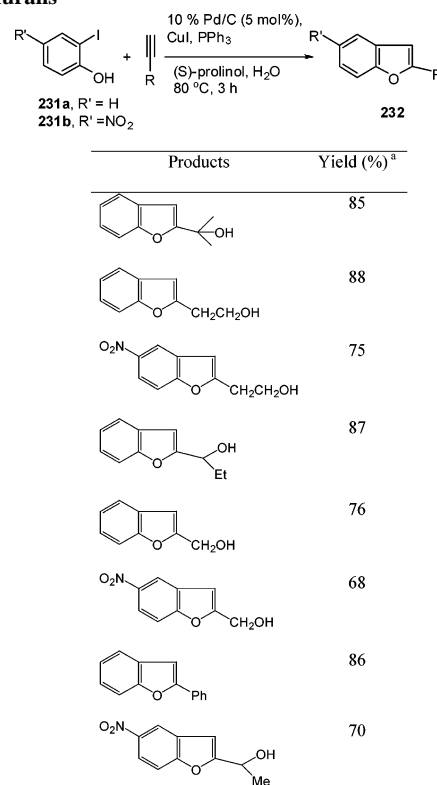
Pd(NH₃)₄²⁺/(NH₃)Y as a zeolite-supported version allowed implementation of a copper-free coupling of *o*-iodophenol or 2-iodo-4-nitrophenol with phenylacetylene (Scheme 61).¹⁹¹

Isocoumarins **235** could be synthesized by Sonogashira tandem reactions when *o*-iodobenzoic acids **234** were

Table 83. Cu-Free Synthesis of Indoles Catalyzed by Mesoporous [Pd(NH₃)₄]²⁺/NaY or Mesoporous [Pd]/SBA-15 Silica^a

Aryl halide 229	Alkyne	Product 230	[Pd(NH ₃) ₄] ²⁺ /NaY Yield (%) ^b	Pd/SBA-15 Yield (%) ^b
	\equiv -Ph		91	95 (72) ^c
	\equiv -Ph		91 (76)	89 (65)
	\equiv - <i>n</i> -Bu		89 (70)	93 (62)
	\equiv -C(CH ₃) ₂ OH		94 (64)	93
	C≡C(CH ₂) ₃ CO ₂ Me		91	90 (61)

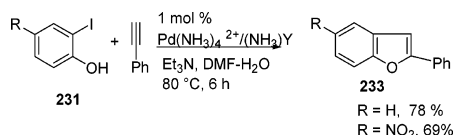
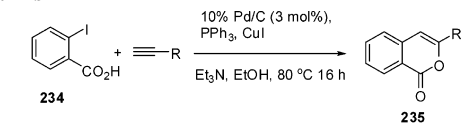
^a Reaction conditions: 5 mmol of aryl halide, 7 mmol of alkyne, 1 mol % Pd catalyst, 8 mmol of NEt₃, 0.5 mmol of LiCl, 1.0 mmol of Cs₂CO₃, 10 mL of DMF, at 140 °C for 6 h. ^b GC yield; isolated yield in parenthesis. ^c 75% GC yield with Pd(OAc)₂.

Table 84. Pd/C-Catalyzed Synthesis of 2-Substituted Benzo[*b*]furans^a Isolated yield.

coupled with terminal alkynes. Ten years after the homogeneous version,²⁷⁹ Pal et al. found a Pd/C-mediated synthesis of isocoumarins in 2005 (Table 85).²⁸⁰ The catalyst was used in the presence of Et₃N, PPh₃, and CuI.

9.2. Heck Coupling in Tandem Reactions

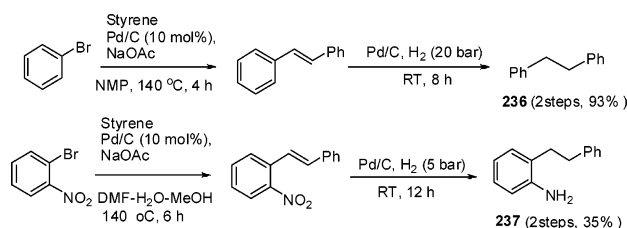
Pd/C-catalyzed Heck coupling reactions could be combined with hydrogenation using the same catalytic system.

Scheme 61. Pd(NH₃)₄²⁺/(NH₃)₂Y-Catalyzed Synthesis of 2-Phenylbenzo[*b*]furans**Table 85. Pd/C-Catalyzed Synthesis of 3-Substituted Isocoumarins^a**

Alkyne (R)	Product 235	Yield (%) ^b
CMe ₂ OH		75
CHMeOH		66
CH ₂ CH ₂ OH		63
CH ₂ (CH ₂) ₂ OH		70
CH ₂ (CH ₂) ₂ CH ₃		60
CH ₂ (CH ₂) ₃ CH ₃		70
CH ₂ (CH ₂) ₄ CH ₃		75
Ph		40

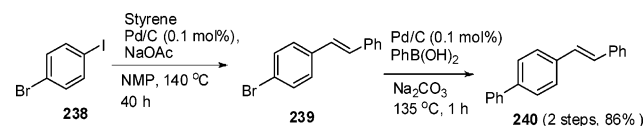
^a All reactions were carried out using iodide (1.0 equiv), alkyne (2.0 equiv), Et₃N (5.0 equiv), and a 1/4/2 ratio of 10% Pd/C (3 mol %), PPh₃, and CuI, in EtOH for 16 h. ^b Isolated yields.

In this way, 1,2-diphenylethanes **236** and **237** were obtained from styrene and bromobenzene or *o*-bromonitrobenzene, respectively (Scheme 62).²⁷¹

Scheme 62. One-Pot Synthesis of 1,2-Diphenylethanes 236 and 237

Pd/C-catalyzed Heck coupling was further combined with subsequent Suzuki coupling in order to synthesize 4-styryl-biphenyl **240**, a substructure of pharmaceutically active

compounds.²⁷¹ Because Heck coupling is more selective for different leaving groups than Suzuki coupling, the Heck coupling was applied as the first reaction step and Suzuki coupling as the second (Scheme 63).

Scheme 63. Pd/C-Catalyzed One-Pot Synthesis of 4-Styrylbiphenyl 240**10. Conclusions and Perspectives**

Nowadays, Pd-catalyzed homogeneous coupling reactions belong in the toolbox of each synthetic organic chemist and have been used in many fields of organic synthesis leading to products of various interests. However, industrial applications of these reactions are still challenging because the catalysts are expensive, cannot be recycled, and are difficult to remove from the product. The latter fact is a drawback in particular for pharmaceutical industries.

Although Pd fixed on inorganic and organic supports have been known for a long time and applied to C–C coupling reactions in single cases more than 30 years ago, their versatility has only recently been shown in almost all types of C–C couplings during the last decades. This methodology has not been appreciated by many organic chemists so far. In most cases, their first choice is homogeneous Pd catalysts.

The heterogeneous methodology offers a number of advantages such as high stability of the catalyst, easy removal of the catalyst from the reaction mixture by filtration, reusability of the catalyst for several times with often minimal loss of activity, and, remarkably, a better performance than homogeneous Pd catalysts in a considerable number of cases. On the other hand, catalysis by Pd on solid supports can require higher reaction temperatures and have limitations in stereoselective reactions. Pd catalysts supported by inorganic and organic materials can also offer the possibility of circumventing ligands such as phosphines or arsines in certain cases and often do not need water- and oxygen-free conditions.

The majority of catalysts applied so far are Pd/C catalysts, which are commercially available in most cases and can directly be used. Other supported Pd catalysts have to be prepared by the user. They can provide advantages over Pd/C, and they can allow tuning of the properties of the catalyst. Many activities can be expected in this field in future.

The mechanism of most of the coupling reactions catalyzed by solid-supported Pd is still unclear. Future research in this field will help the understanding of the sometimes contradictory results in this field. It has been increasingly accepted that most heterogeneous Pd catalysts catalyze in a homogeneous way by leached Pd species, which can re-deposit when the reaction comes to an end. However, general conclusions are difficult to attain because in most cases the mechanism of a certain reaction is affected by the conditions very much.

Although there are also other modern trends in Pd catalysis, such as polymer-supported Pd, Pd nanoparticles, or Pd clusters, it can be expected that the application of Pd supported by inorganic materials will gain increasing importance and application in future.

11. Abbreviations

Ac	acetyl
Aliquat 336 (A336)	methyltriocylammonium chloride
aq	aqueous
[bmim]PF ₆	1-butyl-3-methylimidazolium hexafluorophosphate
Bn	benzyl
BOC	<i>tert</i> -butoxycarbonyl
Bu (<i>n</i> -Bu)	<i>n</i> -butyl
<i>t</i> -Bu	<i>tert</i> -butyl
cat.	catalyst
concn	concentration
conv	conversion
CTAB	cetyltrimethyl ammonium bromide
DIPEA	diisopropyl ethyl amine
DMA (DMAc)	<i>N,N</i> -dimethylacetamide
DME	1,2-dimethoxyethane
DMF	<i>N,N</i> -dimethylformamide
Dppb	1,4-bis(diphenylphosphino)butane
Dppp	1,3-bis(diphenylphosphino)propane
equiv	equivalent
Et	ethyl
FSM	one kind of modified silica
GC	gas chromatography
GLC	gas-liquid chromatography
HAP	hydroxyapatite
Hex	hexyl
HPLC	high-pressure liquid chromatography
IPA	isopropyl alcohol
LDH	layered double hydroxide
MCM-41	one kind of mesoporous silica
Me	methyl
min	minute
MW	microwave
MOM	methoxymethyl
NAIL	nonaqueous ionic liquid
Naph	naphthyl
NHC	nitrogen-containing heterocyclic carbene
NMAc	<i>N</i> -methylacetamide
NMP	<i>N</i> -methylpyrrolidone
[OMIM]BF ₄	1-octanyl-3-methylimidazolium tetrafluoroborate
Pen	pentyl
Ph	phenyl
Pr	propyl
Py	pyridine
RT	room temperature
select.	selectivity
SBA	kind of structured mesoporous silica
<i>t</i>	time
<i>T</i>	temperature
TBAB	tetrabutylammonium bromide
TEA	triethylamine
TEG	tetra(ethylene glycol)
THF	tetrahydrofuran
Ts	tosyl
US	ultrasound
Y	type of faujasite with specific structural, physical, and chemical properties
ZSM-5	type of synthetic zeolite with specific structural properties

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