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# Pd/C: An Old Catalyst for New Applications – Its Use for the Suzuki–Miyaura Reaction

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**Keywords:** C–C coupling / Green chemistry / Heterogeneous catalysis / Palladium / Supported catalysts

In this review we focus on the widely used Suzuki–Miyaura reaction and show that Pd/C is an efficient catalyst for carbon–carbon bond formation. The advantages and limitations of Pd/C are presented through selected examples. Mechanistic as well as practical aspects are also discussed.

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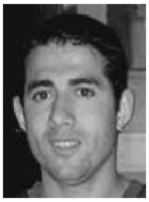

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**MICROREVIEWS:** This feature introduces the readers to the authors' research through a concise overview of the selected topic. Reference to important work from others in the field is included.

## 1. Introduction

Palladium-catalysed reactions have become a "classic" for chemical synthesis. Amongst them, the Suzuki–Miyaura reaction has proved over the years to be extraordinarily useful for carbon–carbon bond formation.[1] This reaction involves the palladium-catalysed cross-coupling of electrophiles with boron compounds in the presence of a base. Since its discovery by Suzuki and Miyaura in 1979,[2] this process has become very popular in both academic and industrial laboratories for several reasons: (1) a wide range of functional groups are tolerated due to mild conditions; (2) boron compounds (and specially boronic acids) are readily available, stable and weakly toxic; (3) dry solvents are generally not required; (4) the reaction is possible with a wide range of substrates.

Despite the remarkable utility of the Suzuki–Miyaura reaction, most of the procedures described require the use of a homogeneous palladium catalyst. This is a significant drawback due to contamination of the products by palladium residues even after the purification step, which poses an acute problem for large-scale synthesis of biologically active compounds where close monitoring of the metal contamination of products is required, especially in the pharmaceutical industry.

The advantage of using heterogeneous catalysts is that they can be removed by filtration at the end of the reaction. The product is uncontaminated with a transition metal or any other ligands and allows the catalyst to be recycled for another reaction. Amongst them, Pd/C has been found to act as an efficient and inexpensive alternative to usual homogeneous conditions. Pd/C is known to have been widely used for hydrogenation, hydrogenolysis and hydrodechlorination. However, its use as a catalyst for carbon–carbon bond formation is quite recent.[3] For instance, the first Pd/C-catalysed Suzuki–Miyaura reaction appeared in 1994,[4] two and a half decades after the seminal work of Suzuki and Miyaura.

This review aims to get a total picture, from the discovery to the latest developments of Pd/C as a catalyst for the Suzuki–Miyaura reactions, highlighting its power and weaknesses. After a preliminary introduction about the catalyst characteristics, the mechanism of the reaction will be discussed. Although Pd/C is also known to be efficient for other cross-coupling reactions, such as Heck or Sonogashira reactions, we have voluntary restricted our discussion to the Suzuki–Miyaura reaction for several reasons: (a) Contrary to other cross-couplings, such as Heck or Sonogashira reactions, the Suzuki–Miyaura reaction can be conducted at relatively low temperature (25–80 °C) with a variety of substrates; (b) Pd/C is most of the time recyclable for the Suzuki–Miyaura reaction, whereas this is rarely possible for Heck couplings; (c) the Suzuki–Miyaura reaction is widely used in both academic and industrial laboratories due to the innocuousness and stability of the boron derivatives.

## 2. Catalyst

The abbreviation "Pd/C" denotes palladium metal supported on charcoal. The concentration of the metal is usually indicated in the description of the catalyst. For instance, 5 wt.-% of palladium metal on charcoal is designated as 5% Pd/C. Most of the catalysts are in the range of 5 to 20 wt.-%. Two types of catalyst have been used for the Suzuki–Miyaura cross-coupling reactions which differ with regard to the oxidation state of palladium. Indeed, Pd/C with a low reduction degree, mainly $Pd^{II}$, and Pd/C with a high reduction degree, mainly $Pd^0$, are both commercially available. Limited studies have been performed in order to determine the activity of catalysts for Suzuki–Miyaura reactions. Most of the time no evident differences in catalytic activity were observed, since both $Pd^0/C$ and $Pd^{II}/C$ were able to catalyze the Suzuki–Miyaura reactions. However, notable formation of dimerized by-products were detected with $Pd^{II}/C$ due to its reduction to $Pd^0/C$ by the boronic acid, which must consequently be used in excess.[4]

It is probably a restrictive view of the problem to consider only the oxidation state of the palladium. Indeed, numerous Pd/C catalysts are commercially available with regard to several characteristics:

*Palladium distribution*: Three types of palladium distribution can be found on charcoal, which is characterised by their impregnation depth: *egg shell*, *thick shell* and *uniform* (Figure 1). In the *egg shell* catalyst, palladium is distributed close to the surface (within 50–150 nm), in the *thick shell* the palladium is distributed 200–500 nm from the surface, while in the *uniform* catalyst the palladium is dispersed homogeneously.

*Palladium dispersion*: Typically only 10–60% of the metal atoms are exposed.

*Average of crystallite size*: Typically in the range 2 to >20 nm.

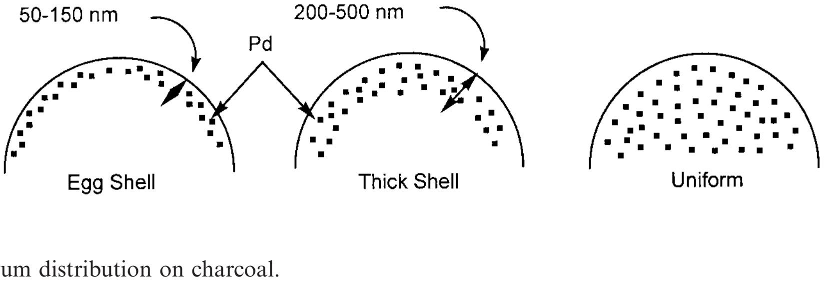


Figure 1. Types of palladium distribution on charcoal.

*Water content*: Charcoal can absorb a large amount of water. For safety reasons, Pd/C with 50% water content is convenient on a large-scale synthesis.

*Oxidation state*: $Pd^0$ or $Pd^{II}$

Moreover, charcoal generally bears oxygen groups on its surface, which are responsible for many of its chemical properties. These groups are introduced before the metal impregnation by thermal or chemical pre-treatment.

Recently, Köhler and co-workers[5] studied the influence of these parameters for the Pd/C-catalysed Heck reaction and noted the superiority of Pd/C with low reduction degree (mainly $Pd^{II}$) and an *egg shell* distribution. Unfortunately, it is difficult at this time to extend these results to the Suzuki–Miyaura reaction because the mechanisms involved in these two reactions differ significantly. More mechanistic investigations are needed for the development of a highly active catalyst for the Suzuki–Miyaura reaction. In addition, some authors fail to note the characteristic properties and the provenance of the Pd/C used, which makes it difficult to rationalize the role of Pd/C.[6] The $Pd^0$/C usually used for hydrogenation is probably the most common catalyst employed for the Suzuki–Miyaura reaction. It should be noted that $Pd(OH)_2/C$[7] and $PdCl_2/C$[8] have also been deployed as effective catalysts for biaryl formation, with a similar activity to $Pd^0$/C.

Pd/C can usually be used under ligandless conditions and without additives for most aryl iodides or bromides. Moreover, Pd/C catalysts are not air or moisture sensitive, thus rendering their use extremely practicable for large-scale preparations. However, in the case of aryl chloride, phosphane ligands[9] or additives such as tetrabutylammonium bromide (TBAB)[10] have been successfully used to enhance the reaction rate (vide infra). Catalyst loadings as low as 0.0025 mol-% of Pd/C have been described,[5,11] although 1 to 5 mol-% is more generally observed.

An added advantage of Pd/C is the possibility of reusing it in a subsequent run after filtration from the reaction mixture. The recycling depends dramatically on the stability of Pd particles on the charcoal. It is well established that the deactivation of Pd catalyst occurs by aggregation of Pd nanoclusters during the course of the reaction to form larger Pd clusters.[12,13] This aggregation causes an increase of Pd crystallite size and destroys the uniform Pd distribution of the fresh catalyst. Recently, Shimizu and co-workers[14] found that for ligandless Pd sources like Pd/C, most of the $Pd^0$ nanoclusters become aggregated during the course of the reaction to form Pd clusters, which causes partial catalyst deactivation. However, several successful examples of catalyst reuse have been described for the Suzuki–Miyaura reaction, in contrast to the Heck reaction. Indeed, Köhler and co-workers[5] have shown that crystallite size dramatically increases during the Heck reaction, thereby rendering the recycling process of Pd/C inefficient. It is possible to assume that less important structural changes of Pd/C occur during the Suzuki–Miyaura reaction than the Heck reaction. The better stability of Pd/C for Suzuki–Miyaura reactions could be explained by the different mechanism involved (Suzuki–Miyaura vs. Heck) and the lower temperatures used.

## 3. Solvents and Bases

A wide variety of solvents have been used for Pd/C-catalysed Suzuki–Miyaura reactions. For instance, DME, DMA, DMF, NMP, THF, MeOH, EtOH, *i*PrOH and *n*BuOH, most of the time in combination with water, have been described as good solvent systems. For environmental concerns, the selection of solvents with low toxicity is of primary interest. To this end, water alone or in association with EtOH, *i*PrOH or *n*BuOH represents the most economical and safety-conscious solvent combination.

Although one report has described[15] the use of $NEt_3$, inorganic bases such as $Na_2CO_3$, $K_2CO_3$, $Cs_2CO_3$ or $Na_3PO_4$ are the most efficient for Suzuki–Miyaura cross-coupling reactions. For sensitive substrates bearing hydrolysable ester functions, the use of KF could be of particular interest.[16]

## 4. Heterogeneous or Homogeneous Mechanism?

The central question concerning the mechanism is whether the cross-coupling occurs through a heterogeneous or homogeneous catalytic pathway. In a heterogeneous catalysis, the reaction takes place predominantly on the palladium surface and not in the solution phase, therefore the reaction would occur inside the pores of the charcoal. This mechanism would lead to a complete recovery of palladium because leaching into the solution phase would not occur. In homogeneous catalysis with a heterogeneous catalyst, the reaction takes place in the solution phase with palladium species that are leached from the support.

In order to determine whether the palladium is acting in a heterogeneous or homogeneous form, Buchecker and co-workers[4] performed an interesting experiment. They stopped a cross-coupling reaction after the formation of approximately 50% of the product. Then after filtration of the heterogeneous materials, they allowed the reaction to continue under the same reaction conditions. The authors later found that the reaction was completely stopped. This observation led them to conclude that the reaction takes place via a heterogeneous pathway because no active catalytic palladium species were present in solution.

To explain the remarkable activity of Pd/C for the coupling of aryl chlorides under ligandless conditions, Sowa and co-workers[17] have also invoked a heterogeneous mechanism. The authors postulated that the observed activity could be the result of both synergistic anchimeric and electronic effects that favour the anchoring of the aryl chloride to a palladium site on the surface. These effects might favour the chemical interaction of the C–Cl bond with a separate but nearby palladium site. The modified electronic properties of the surface could result in a net electron flow from the substrate to the palladium surface, which, in turn, acts as an electron-withdrawing group to activate the C–Cl bond. However, no experimental evidence was provided to support these suggestions. In contrast, two years later the same group[16] published a report with strong experimental evidence for a homogeneous pathway. They studied the mechanism of the Pd/C-catalysed Suzuki–Miyaura reaction in detail. ICP-MS analysis showed substantial leaching of palladium into the solvent, which reached a maximum at abour 90% conversion. After completion of the reaction, the concentration of soluble palladium falls to less than 4 ppm. This extremely important observation led them to postulate that the oxidative addition step gives a Ar–Pd$^{II}$–X species, which desorbs from the charcoal. After the transmetallation step, the soluble palladium precipitates onto the support and the system cools down. This interesting observation has been described as the "boomerang effect".[18,19] The authors remarked that palladium leaching with KF is more than two times greater than with $K_2CO_3$, thus indicating a strong effect of the base. However, the reaction rate is slower with KF, which suggests that the oxidative-addition step is not the rate-determining step.

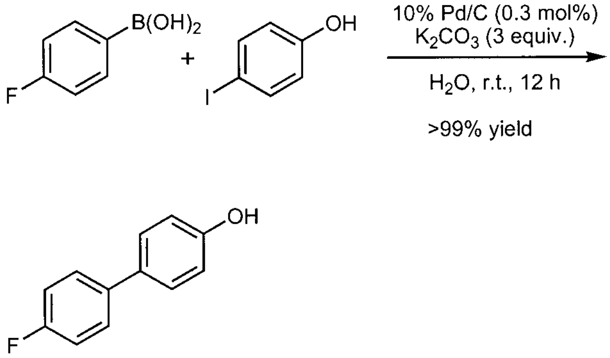
Köhler and co-workers have realized a similar study for the Heck reaction.[5] While similar observations and conclusions to those of Conlon and co-workers were made, they also found an important effect of the catalyst properties on the leaching and reaction rate. Additionally, Arai and co-workers[20] have found that the "boomerang effect" is strongly dependant on the solvent used for the Heck reaction: while a substantial amount of soluble palladium is detected in NMP, almost no leaching occurs in water, which, on the other hand, favours the formation of colloidal palladium particles. These results could suggest two distinct mechanisms depending on the solvent. However, it is not possible at this time to extend these results to a plausible mechanistic explanation of the Suzuki–Miyaura reaction. Clearly, we require more studies for a better understanding of the mechanism. Therefore, it is probably premature to definitively rule on the debate.

## 5. Formation of Biaryls or Heterobiaryls

The formation of a biaryl linkage has attracted considerable interest due to its broad spectrum of applications, ranging from materials science to drug synthesis. Numerous natural products[21] or drug candidates that are under development[22] contain biaryl groups that have been assembled in a Suzuki–Miyaura reaction.

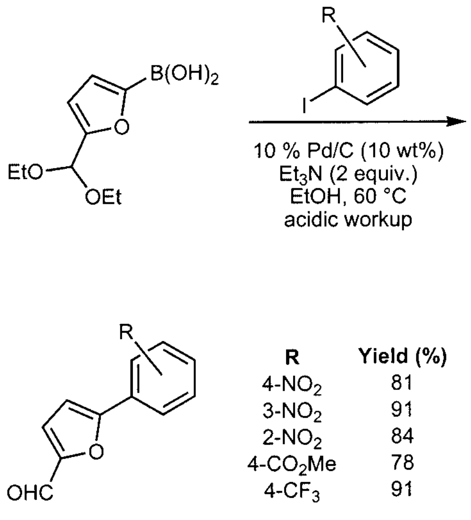
### 5.1. Aryl Iodides

Although aryl iodides are the most reactive amongst the aryl halides, they did not initially attract much interest since they are more expensive than their bromide or chloride congeners. However, Hirao and co-workers[23] have reported an interesting study where they described the cross-coupling of unprotected iodophenols with a variety of boronic acids, as depicted in Scheme 1. This method merits attention because the reactions were carried out in water at room temperature with low catalyst loading (0.3 mol-% of 10% Pd/C, Wako Pure Chemical Industries). Yields greater than 98% were generally obtained, and were quite independent of the nature of the boronic acid. It should be noted that the corresponding bromophenol showed low reactivity at room temperature, although a slight elevation of the temperature to 50 °C gave the expected hydroxybiphenyl with good yield (76%). Interestingly, these workers not only showed that Pd/C could be easily recovered by simple filtration but it can also be re-used five times with excellent yields.



Scheme 1. Cross-coupling of iodophenol.

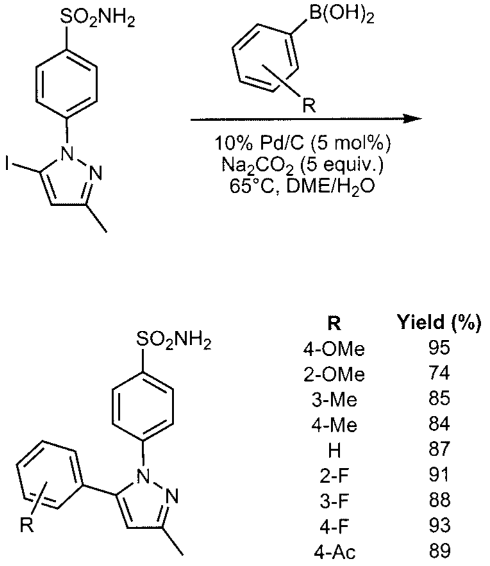
Roschangar and co-workers[14] from the GlaxoSmithKline group have reported the use of iodoaryls for coupling with furylboronic acid derivatives (Scheme 2). Initially they used [$PdCl_2$(dppf)] as the homogeneous catalyst, but contamination of the cross-coupled products by Pd residue (520–850 ppm) after purification rendered the protocol inapplicable for large-scale synthesis of biologically active compounds. Using 10% Pd/C (Degussa type E101 NE/W) as a catalyst, however, they were able to develop an efficient coupling method with a level of palladium contamination twenty times lower after purification. Surprisingly, they used $NEt_3$, which has proved to be generally less efficient for the Suzuki–Miyaura reaction catalysed by Pd/C, as a base. The method applied to bromoaryls was found to be unsuccessful when catalysed by Pd/C.



| R | Yield (%) |
|---|---|
| 4-$NO_2$ | 81 |
| 3-$NO_2$ | 91 |
| 2-$NO_2$ | 84 |
| 4-$CO_2Me$ | 78 |
| 4-$CF_3$ | 91 |

Scheme 2. Synthesis of 5-aryl-2-furaldehydes.

During their studies toward a COX II inhibitor library, Organ and Mayer[24] elaborated a Pd/C catalysed Suzuki–Miyaura reaction as the key step (Scheme 3). An iodopyrazole derivative was efficiently coupled with various boronic acids in aqueous DME. Excellent purities were obtained after simple filtration, thus making the method very convenient for parallel synthesis.



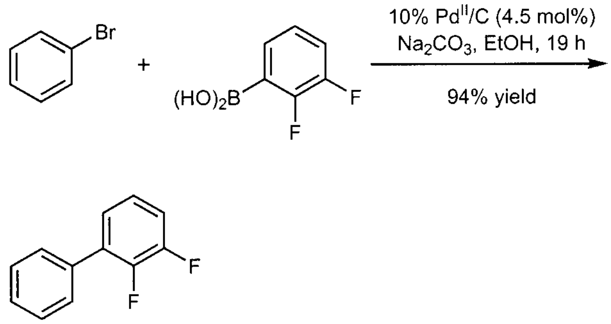
| R | Yield (%) |
|---|---|
| 4-OMe | 95 |
| 2-OMe | 74 |
| 3-Me | 85 |
| 4-Me | 84 |
| H | 87 |
| 2-F | 91 |
| 3-F | 88 |
| 4-F | 93 |
| 4-Ac | 89 |

Scheme 3. Cross-coupling of iodopyrazole.

## 5.2. Aryl Bromides

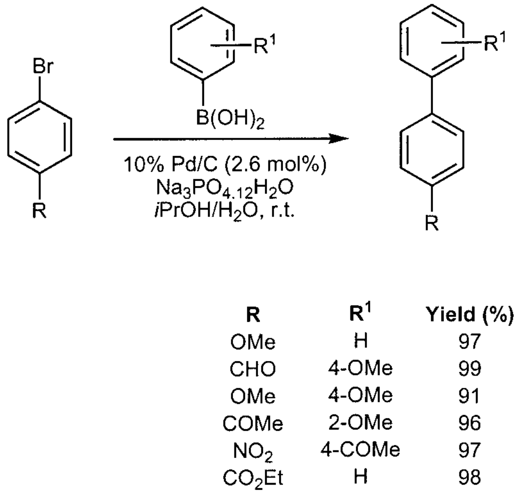
Aryl bromides represent a good compromise between cost and reactivity compared to the more expensive aryl iodides and less reactive aryl chlorides. Consequently, the vast majority of Pd/C-catalysed Suzuki–Miyaura reactions have been carried out with aryl bromide, affording generally excellent results.

The first report of a Pd/C catalysed Suzuki–Miyaura reaction appeared in 1994 from the Hoffmann-La Roche group (Scheme 4).[4] These workers noted the beneficial effect of ethanol as solvent when associated with $Na_2CO_3$ as base at 80 °C in order to obtain good yields of the required biphenyls. They experimented with both 5% $Pd^0/C$ (Degussa type E101 R/D) and 10% $Pd^{II}/C$ (Degussa type E101 N/D) to catalyze the Suzuki–Miyaura reaction, and found that there was no significant difference in catalytic activity. However, when 10% $Pd^{II}/C$ was used, notable formation of dimerized by-products were detected. The formation of these undesired by-products was attributed to the reduction of $Pd^{II}/C$ to $Pd^0/C$ by the boronic acid.



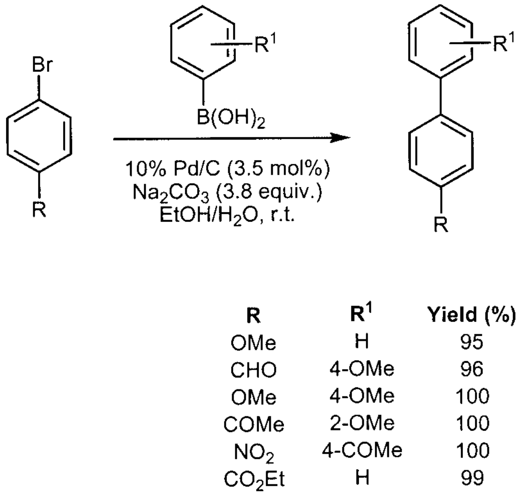
Scheme 4. The first Pd/C catalysed Suzuki–Miyaura reaction.

In order to carry out the coupling reaction at room temperature, Zhang and co-workers[25] have demonstrated that the addition of water to alcoholic solvents dramatically enhances the catalytic activity of Pd/C (Schemes 5 and 6). For instance, a mixture of $i$PrOH/$H_2O$ associated with $Na_3PO_4$ or EtOH/$H_2O$ with $Na_2CO_3$ forms a very active catalytic system with 10% Pd/C (2.6–3.5 mol-%, Aldrich company). The authors pointed out that the alcohol/$H_2O$ volumetric ratio is critical for the success of the cross-coupling reactions, with a low water concentration having a deleterious effect and only resulting in a partial conversion. A wide variety of bromoaryls and boronic acids were also screened, although the use of boronic acids deactivated at the *ortho* or *meta* positions was not reported.



| R | $R^1$ | Yield (%) |
|---|---|---|
| OMe | H | 97 |
| CHO | 4-OMe | 99 |
| OMe | 4-OMe | 91 |
| COMe | 2-OMe | 96 |
| $NO_2$ | 4-COMe | 97 |
| $CO_2Et$ | H | 98 |

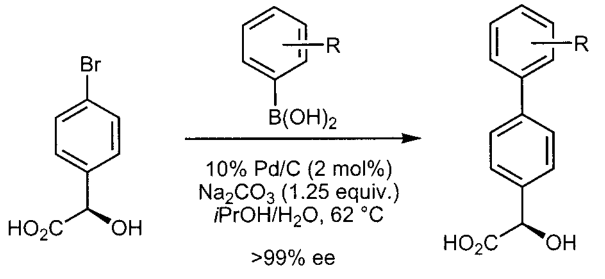
Scheme 5. Selected examples of the Suzuki–Miyaura reaction using $i$PrOH/$H_2O$ and $Na_3PO_4$ as catalytic system.



| R | $R^1$ | Yield (%) |
|---|---|---|
| OMe | H | 95 |
| CHO | 4-OMe | 96 |
| OMe | 4-OMe | 100 |
| COMe | 2-OMe | 100 |
| $NO_2$ | 4-COMe | 100 |
| $CO_2Et$ | H | 99 |

Scheme 6. Selected examples of the Suzuki–Miyaura reaction using EtOH/$H_2O$ and $Na_2CO_3$ as catalytic system.

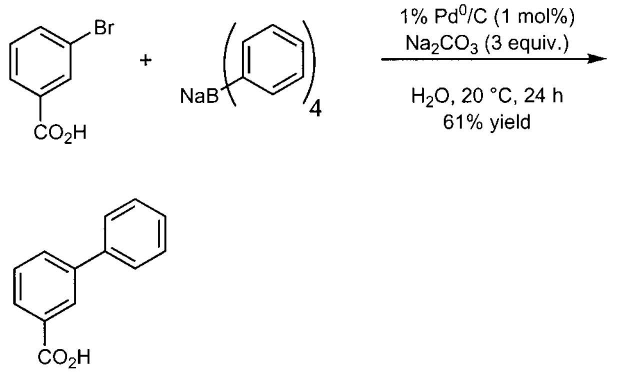
Unprotected carboxylic acids, phenols and alcohols have been reported to be compatible with Pd/C-mediated Suzuki–Miyaura reactions (Scheme 7). For instance, Tiffin and co-workers[26] have reported the preparation of enantiopure 4-arylmandelic acids from the corresponding 4-bromomandelic acid in aqueous *i*PrOH catalysed by 10% Pd/C (2 mol-%). After completion of the reaction, a simple filtration of the catalyst followed by precipitation of the required 4-arylmandelic acid made the protocol described extremely convenient to prepare a small library of compounds.



| R | Yield (%) |
|---|---|
| 4-H | 75 |
| 4-Me | 90 |
| 4-$CF_3$ | 88 |
| 4-F | 85 |
| 3-Me | 89 |
| 3-Cl | 92 |
| 3-OMe | 96 |
| 2-Me | 99 |

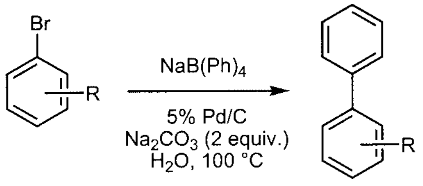
Scheme 7. Preparation of enantiopure 4-arylmandelic acids.

Bumagin and Bykov[8] have disclosed the cross-coupling of 3-bromobenzoic acid with sodium tetraphenylborate ($NaBPh_4$), which is a very stable and inexpensive reagent used as a substitute for phenylboronic acid (Scheme 8). The authors noted that all four phenyl groups in $NaBPh_4$ were involved in the reaction.



Scheme 8. Use of sodium tetraphenylborate as a substitute for phenylboronic acid.

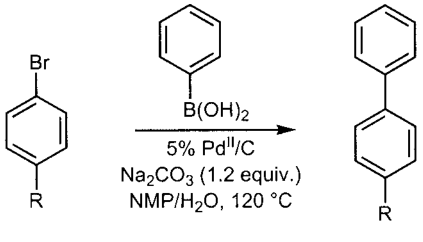
Very recently, Xu and co-workers[11] studied the conditions described by Bumagin and Bykov in exhaustive detail. They showed that a variety of bromobenzoic acids or bromonaphthoic acids are suitable for reactions with $NaBPh_4$ or $NaB(tol)_4$ in refluxing water in air for only 1 h with $Na_2CO_3$ as base (Scheme 9). The authors were able to use extremely low catalyst loadings (0.1–0.0025 mol-%) with turnover numbers (TON) of up to 37600, which are remarkably high for heterogeneously catalysed Suzuki–Miyaura reactions. However, the authors noticed that sterically hindered *ortho*-bromoaryls, such as 2-bromobenzoic acid, gave only modest results even after prolonged reaction times. The recycling test of Pd/C showed the possibility of recycling it five times with good retention of the catalytic activity, although this gradually diminished with repeated use.



| Pd/C (mol%) | R | Yield (%) |
|---|---|---|
| 0.01 | 4-COOH | 95 |
| 0.05 | 3-COOH | 97 |
| 0.005 | 4-$CH_2$COOH | >99 |
| 0.1 | 2-$CH_2$COOH | 74 |
| 0.05 | 4-$COC_2H_4$COOH | 98 |
| 0.05 | 4-OH | 99 |

Scheme 9. Selected examples of Suzuki–Miyaura reactions with $NaBPh_4$.

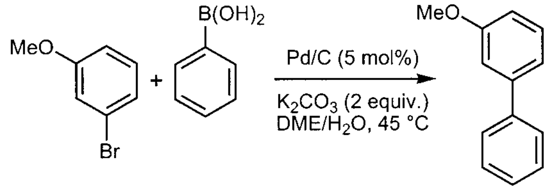
A low catalyst loading (0.01–0.005 mol-%) has also been described by Köhler and co-workers[27] using a Pd/C (Degussa type E105 CA/W) catalyst initially developed for Heck reactions (Scheme 10). This Pd/C is characterised by high Pd dispersion (36%), low reduction degree (mainly $Pd^{II}$) and high water content (approx. 55%). The described protocol uses a mixture of NMP in water with $Na_2CO_3$ as a base at 120 °C to enable the coupling of phenylboronic acid with electron-poor or electron-rich bromoaryls. Remarkable TONs of around 20000 were obtained, with turnover frequencies (TOF) of up to 16600.



| Pd/C (mol%) | R | Yield (%) |
|---|---|---|
| 0.005 | H | 100 |
| 0.01 | CN | 100 |
| 0.01 | OH | 100 |
| 0.005 | OMe | 100 |

Scheme 10. Low catalyst loading for Suzuki–Miyaura reactions.

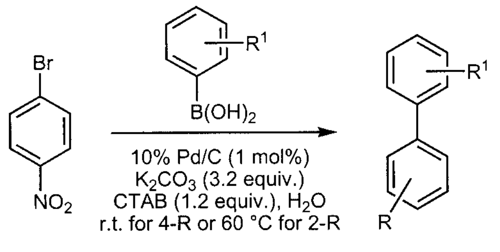
Ultrasound has also been employed to promote the cross-coupling of *ortho*-, *meta*- and *para*-bromoanisole with phenylboronic acid in aqueous DME (Scheme 11).[28,29] However, the results obtained remain modest and inferior to conventional thermal activation. The combination of ultrasound and microwaves seems to give better results, although only one such example has been reported.[28]



| Activation | Yield (%) |
|---|---|
| US | 54 |
| MW | 64 |
| US/MW | 88 |

Scheme 11. Ultrasound (US) and microwave (MW) activation.

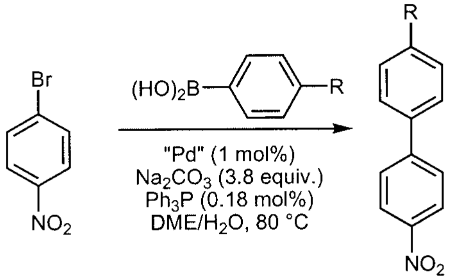
In order to design an active catalytic system with Pd/C, several research groups have also studied the use of additives. In this context, surfactants such as cetyltrimethylammonium bromide (CTAB) have been found to be an effective additive when combined with $K_2CO_3$ in water under air for Suzuki–Miyaura cross-coupling catalysed by just 0.25 mol-% of 10% Pd/C (Scheme 12).[30] A variety of bromoaryls, including both activated and deactivated derivatives, have been found to react with aryl boronic acids at room temperature. *ortho*-Substituted bromoaryls also react but at higher temperature (60 °C). The water-surfactant Pd/C system gave good catalytic activity after several recycling experiments, thus rendering the method environmentally friendly. The activation role of CTAB is thought to be twofold. Firstly, the presence of positive $R_4N^+$ ions could favour the transmetallation step by forming a highly reactive boronate complex $[ArB(OH)_3]^-[R_4N]^+$. Secondly, the ammonium salt could facilitate the solvation of organic molecules in aqueous media. In contrast to the work with aryl chlorides,[10] these workers found that TBAB was ineffective with aryl bromides.



| R | $R^1$ | Yield (%) |
|---|---|---|
| 4-OMe | H | 94 |
| 4-OMe | 4-Me | 96 |
| 4-OMe | 4-F | 89 |
| 4-OMe | 3-OMe | 65 |
| 4-CHO | H | 74 |
| 2-$NO_2$ | H | 95 |
| 2-COMe | H | 89 |

Scheme 12. CTAB activation for Suzuki–Miyaura cross-coupling.

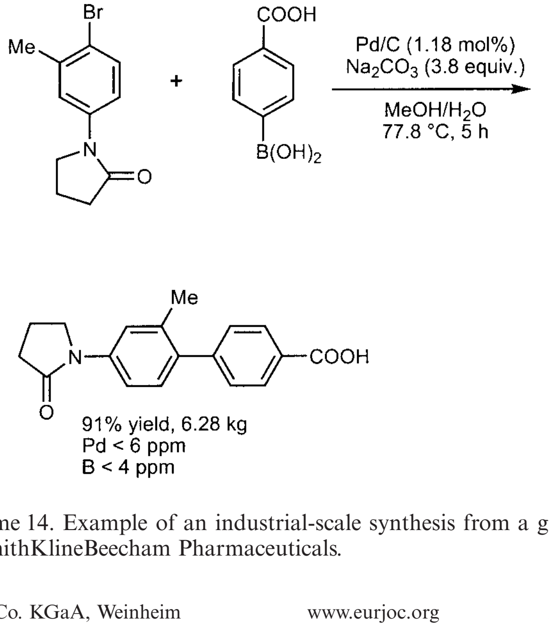
Triphenylphosphane has also been used as an additive with $Pd(OH)_2/C$ (Pearlman's catalyst) or Pd/C for the coupling of 4-nitrobromobenzene with phenyl- or 4-methoxyphenylboronic acids in aqueous DME (Scheme 13).[7] Excellent yields (≥92%) were obtained but with long reaction times (43 h) and relatively high temperature (80 °C). The authors disclosed only two examples.



| "Pd" | R | Yield (%) |
|---|---|---|
| Pd/C | H | 90 |
| Pd/C | 4-OMe | 92 |
| $Pd(OH)_2/C$ | H | 91 |
| $Pd(OH)_2/C$ | 4-OMe | 91 |

Scheme 13. Phosphane activation for Suzuki–Miyaura cross-coupling.

The recognition of the power of a method comes only when industrial applications on a large-scale synthesis are feasible. Ennis and co-workers[31] from SmithKlineBeecham Pharmaceuticals and Gala and co-workers[32] from Schering–Plough have both reported a multikilogram-scale synthesis of biphenyl derivatives (Scheme 14). The authors have judiciously noticed several advantages of Pd/C for the large-scale synthesis of biologically important compounds over usual homogeneous conditions: (1) Pd/C is inexpensive and readily available, (2) the catalyst can be recovered by simple filtration, (3) extremely low contamination of the product by residual Pd, and (4) the degassing of the solvent was not necessary.

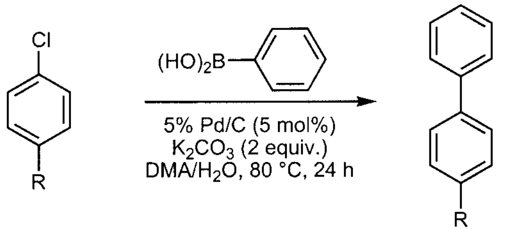


Scheme 14. Example of an industrial-scale synthesis from a group at SmithKlineBeecham Pharmaceuticals.

### 5.3. Aryl Chlorides

Until recently, the major limitation of the Suzuki–Miyaura reaction was the poor reactivity of aryl chlorides compared to aryl bromides and iodides. However, aryl chlorides are notably the most attractive aryl halides due to their low cost and ready availability. Recently, several research groups have intensively studied the cross-coupling of aryl chlorides with boronic acids under homogeneous conditions. The protocols developed are remarkably efficient, sometimes even at room temperature, but require expensive and sensitive ligands such as sterically hindered and electron-rich phosphanes,[33] N-heterocyclic carbenes[34] or palladacycles.[35] Ligand-less conditions using Pd/C were therefore particularly attractive to overcome handling problems but were met with lack of reactivity of the aryl chlorides. Worthy of note are the scattered studies reporting efficient cross-coupling reaction of aryl chlorides with boronic acids under homogeneous palladium-catalysed ligandless conditions.[36]

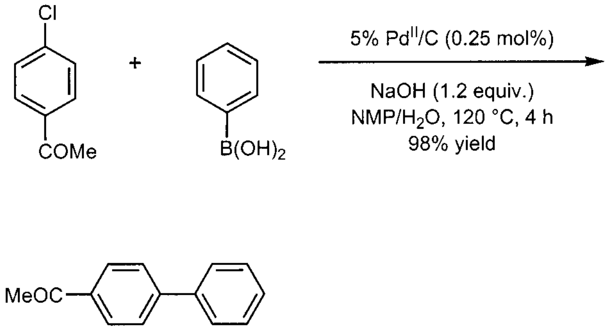
A breakthrough was reached in 2001 when Sun, Sowa and co-workers[17] reported the high yielding cross-coupling reaction of electron-poor aryl chlorides with phenylboronic acid catalysed by 5% Pd/C (5 mol-%) using $K_2CO_3$ as base, as depicted in Scheme 15. The authors noted the crucial importance of the solvent system. While Pd/C with the common EtOH/water solvent mixture produced mainly homo-coupled products, the use of the very polar solvent dimethylacetamide (DMA) with a small amount of water ($DMA/H_2O$: 20:1) afforded excellent results. Electron-rich aryl chlorides also react, albeit with much lower yields. The authors invoked synergistic anchimeric and electronic effects in order to explain the observed reactivity.



| R | Yield (%) |
|---|---|
| $NO_2$ | 93 |
| $CF_3$ | 95 |
| CN | 83 |
| COMe | 79 |
| OMe | 32 |
| Me | 36 |

Scheme 15. Efficient cross-coupling of electron-deficient aryl chlorides.

A similar activation in an aqueous highly polar solvent has also been reported by Köhler and co-workers (Scheme 16).[27] For instance, chloroacetophenone could be coupled with phenylboronic acid using a low catalyst loading of $Pd^{II}/C$ (0.25 mol-%, Degussa type E105 CA/W) in a mixture of NMP and $H_2O$ (10:3) with NaOH as base at 120 °C. The authors noted the importance of high temperature, which could favour a dissolution and re-precipitation of Pd species on the support. The activity observed could be attributed to the Pd species dissolved in the solvent.

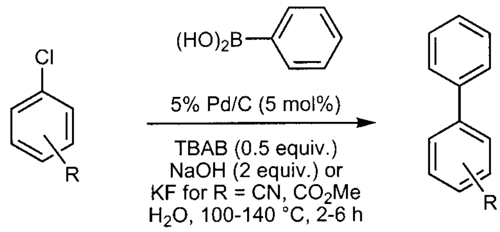


Scheme 16. Efficient cross-coupling of electron-deficient aryl chlorides.

While activated (electron deficient) aryl chlorides were seen to be coupled with high yield, non-activated (electron rich) aryl chlorides remained mostly unreactive. Clearly, additives to enhance the catalytic activity of Pd/C would address this issue.

While CTAB seems only to be efficient for aryl bromides or electron-rich aryl chlorides,[30] TBAB has shown very promising results. For instance, in 2005 Lysén and Köhler[10] reported an exceptional catalytic activity enhancement of 5% $Pd^{II}/C$ (0.2 mol-%, Degussa type E105 CA/W) by TBAB when water and NaOH (or KF for substrates sensitive to hydrolysis) were used as catalytic system (Scheme 17). Quite interestingly, the use of co-solvents proved to have deleterious effects on the yields. With this catalytic system in hand, the authors were not only able to couple electron-poor aryl chlorides but also neutral and electron-rich aryl chlorides. Although a relatively high temperature is required (100–140 °C), the protocol describing the use of water under air with only inexpensive reagents renders the method very competitive and probably the most effective one described so far for the coupling of aryl chlorides catalysed by Pd/C. The authors did not discuss the mechanism involved. However, as we have already mentioned in Section 4, water favours the precipitation of palladium to produce colloidal nanoparticles. Moreover, Reetz et al.[37] have reported the role of additives such as $R_4N^+X^-$ in the stabilisation of palladium colloids, which are catalytically active. Hence, such a mechanism under the conditions described by Lysén and Köhler[10] cannot be ruled out.

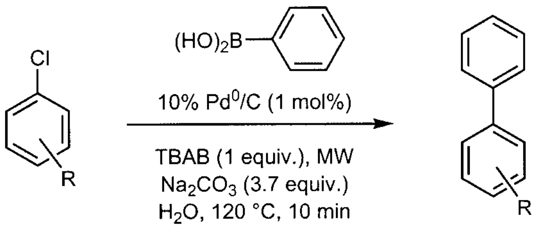
Another interesting way to enhance the catalytic activity of ligandless Pd/C has been reported recently by Arvela and Leadbeater (Scheme 18).[38] Their method combines activation with TBAB and microwaves in water using 10% $Pd^0$/C (1 mol-%, Aldrich company) and $Na_2CO_3$. The originality of the method resides in the simultaneous cooling while the microwaves are producing heat. Indeed, the authors clearly showed that without the strict control of the temperature, aryl chlorides decomposed in only 10 minutes. The lifetime of the substrate can be substantially prolonged, however, with simultaneous cooling by passing a stream of compressed air over the reaction vessel. Very fast reaction



| R | Yield (%) |
|---|---|
| 4-COMe | 99 |
| 4-CN | 98 |
| 2-CN | 89 |
| 4-$CO_2Me$ | 87 |
| 2-$CO_2Me$ | 63 |
| H | 73 |
| 4-Me | 81 |
| 2-Me | 74 |
| 4-OMe | 83 |
| 4-$NH_2$ | 66 |

Scheme 17. Efficient cross-coupling of aryl chlorides with TBAB as activator.

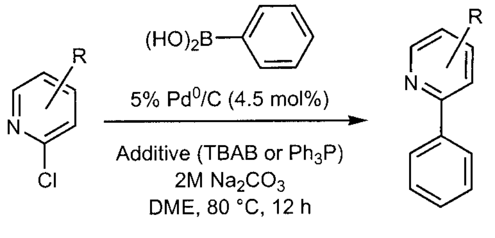
rates were observed with microwaves since full conversion was reached after only 10 minutes. Although the method was efficient for aryl chlorides bearing electron-withdrawing groups, it showed inferior results than the aforementioned work from Köhler and co-workers.



| R | Yield (%) |
|---|---|
| 4-COMe | 90 |
| 4-$NO_2$ | 94 |
| 4-CN | 80 |
| 4-Me | 75 |
| 2-Me | 64 |
| H | 65 |
| 4-OMe | 65 |
| 2-OMe | 48 |
| 4-$NH_2$ | 56 |

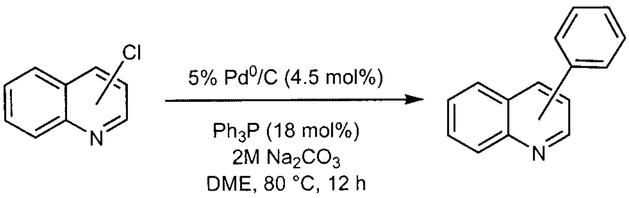
Scheme 18. Fast cross-coupling of aryl chlorides with TBAB and MW as activators.

Activation of Pd/C using TBAB or $PPh_3$ has been compared in a recent report from the Koei chemical company[9] for the cross-coupling of phenylboronic acid with chloropyridine derivatives. The authors unambiguously showed that TBAB (1.5 equiv.) or $PPh_3$ (18 mol-%) dramatically increase the catalytic activity of 5% $Pd^0/C$ (4.5 mol-%) in aqueous DME for the cross-coupling of chloro (or bromo) pyridines bearing electron-withdrawing substituents or chloroquinoline with $PhB(OH)_2$ (Scheme 19). The absence of additives almost completely inhibited the reaction. Unfortunately, unsubstituted 3- and 4-chloropyridines and 6-chloroquinoline remained unreactive even with additives (Scheme 20). The authors studied the combination of 5% $Pd^{II}/C$ (4.5 mol-%) and $PPh_3$ (18 mol-%) but observed reactivity similar to that of 5% $Pd^0/C$. In order to improve the yields of the cross-coupling of less reactive unsubstituted chloropyridines and 6-chloroquinoline, ligand effects were studied with 5% $Pd^0/C$. While $PPh_3$ (18 mol-%), dppb



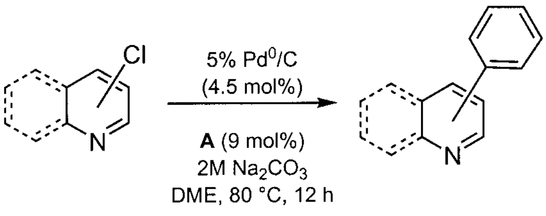
| R | TBAB<br>Yield (%) | $Ph_3P$<br>Yield (%) |
|---|---|---|
| 3-$NO_2$ | 87 | 94 |
| 5-$NO_2$ | 79 | 85 |
| 5-CN | 69 | 90 |

Scheme 19. Cross-coupling of chloropyridines with TBAB or $PPh_3$ as activator.



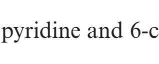
| Cl | Yield (%) |
|---|---|
| 2-Cl | 91 |
| 6-Cl | 0 |

Scheme 20. Coupling of chloroquinolines with $PPh_3$ as activator.



| Substrate | Yield (%) |
|---|---|
| 3-Cl-pyridine | 88 |
| 4-Cl-pyridine | 92 |
| 6-Cl-quinoline | 77 |

**A**



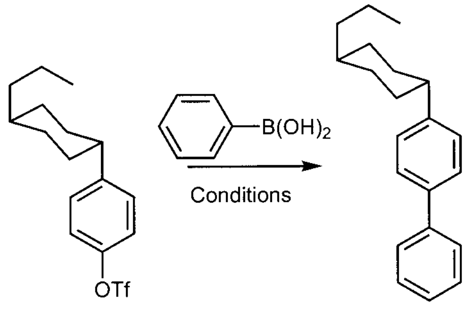
Scheme 21. Coupling of 3- and 4-chloropyridine and 6-chloroquinoline with **A** as ligand.

(9 mol-%) and dppp (9 mol-%) gave poor results, the electron-rich and sterically hindered 2-(dicyclohexylphosphanyl)biphenyl **A** (9 mol-%) dramatically improved the yield to 80–90%, depending on the substrate (Scheme 21). Interestingly, the combination of 5% Pd$^0$/C and 2-(dicyclohexylphosphanyl)biphenyl was ineffective in promoting the cross-coupling of 4-methoxyphenylchloride, whereas the use of 5% Pd$^{II}$/C gave an 80% yield of the biphenyl. The authors also postulated that Pd leaches into solution and interacts with the phosphane ligands to produce a reactive Pd$^0$–PPh$_3$ species.

### 5.4. Other Aryl Electrophiles

For practical reasons the aryl electrophile partner in the Pd/C-catalysed Suzuki–Miyaura reactions has almost always been limited to the conventional use of aryl halide (Cl, Br, I). However, aryl triflates or arenediazonium salts are excellent nucleofuges and can be easily prepared from the readily available phenols and amines, respectively. Moreover, arenediazonium salts are of special interest for sensitive substrates because they do not require the use of a base.

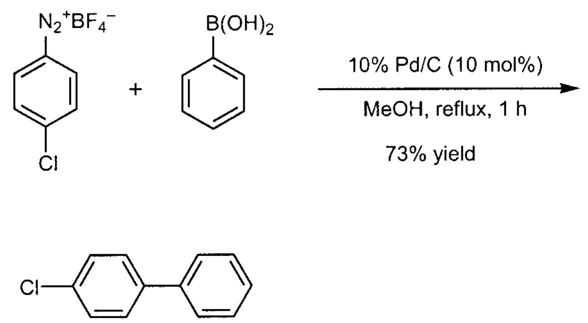
Buchecker and co-workers[4] have studied the cross-coupling of aryl triflates with boronic acids (Scheme 22). They noted that conventional systems developed for aryl bromides (2 M $Na_2CO_3$/DME or $Na_2CO_3$/EtOH) were inappropriate for aryl triflate. Indeed, under these conditions even activated aryl triflates were not reactive because they were quickly hydrolysed. Fortunately, better results were obtained with solid $Na_2CO_3$ in dry DMF. Moreover, 5% Pd$^0$/C (Degussa type E101 R/D) proved to be superior to 10% Pd$^{II}$/C (Degussa type E101 N/D) in order to avoid homocoupling side-reactions, and addition of LiCl to the above mixture was found to have beneficial effects on the reaction rate.



| Conditions | Yield (%) |
|---|---|
| Pd$^{II}$/C, 2M $Na_2CO_3$, DME | 0 |
| Pd$^{II}$/C, $NaHCO_3$, EtOH | 50 |
| Pd$^{II}$/C, $Na_2CO_3$, DMF | 62 |
| Pd$^0$/C, $Na_2CO_3$, DMF | 68 |
| Pd$^0$/C, $Na_2CO_3$, LiCl, DMF | 84 |

Scheme 22. Coupling of aryl triflates.

Unfortunately, Sengupta and Bhattacharyya (Scheme 23) have reported only one example of a Pd/C-catalysed cross-coupling reaction of an arenediazonium salt with phenylboronic acid.[39] They pointed out that the absence of bases and the use of alcoholic solvents such as MeOH was of crucial importance for the success of the cross-coupling. It should be noted that in the case of arenediazonium salts, ligandless conditions using Pd/C or Pd(OAc)$_2$ seemed especially appropriate for the cross-coupling. Indeed, initial screening of different conditions revealed that the usual protocol {aqueous $Na_2CO_3$, DME, [Pd(PPh$_3$)$_4$]} caused extensive decomposition of the diazonium salt.

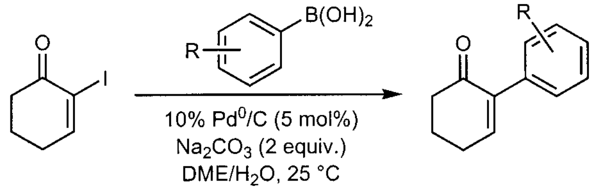


Scheme 23. Coupling of an arenediazonium salt.

## 6. Other Couplings

### 6.1. Cross-Coupling of Iodoenones with Boronic Acids

Almost all studies using Pd/C as catalyst have so far been realized for the preparation of biaryl compounds. However, Felpin[40] has very recently demonstrated that 10% Pd$^0$/C (Aldrich company) in aqueous DME with $Na_2CO_3$ as base serves as an effective cross-coupling catalyst for 2-iodocyclohexenone with a wide variety of boronic acids (Scheme 24). These couplings proceed in excellent yields at room temperature with both activated and deactivated boronic acids.

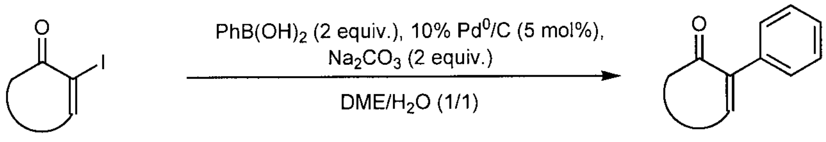


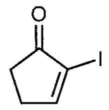
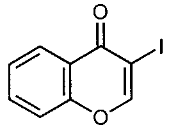
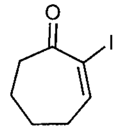
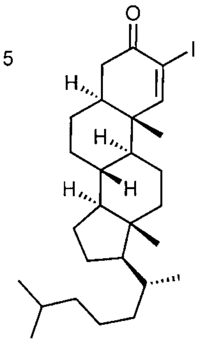
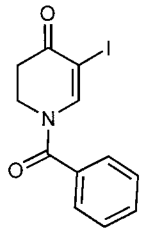
| R | Yield (%) |
|---|---|
| H | 86 |
| 4-OMe | 87 |
| 2-F | 80 |
| 3-NO$_2$ | 80 |
| 4-COMe | 98 |

Scheme 24. Selected examples of the cross-coupling of 2-iodocyclohexenone with boronic acids.

To expand the scope of these Pd/C-catalysed couplings, Felpin has surveyed a variety of 2-iodocycloenones (Table 1). He found that the method tolerates a reasonable range of structures. Non-hindered 2-iodocycloenones can be cross-coupled at room temperature, whereas hindered ones require a higher temperature. The limitation of the

Table 1. Selected examples of the cross-coupling of 2-iodocycloenone with phenylboronic acids.



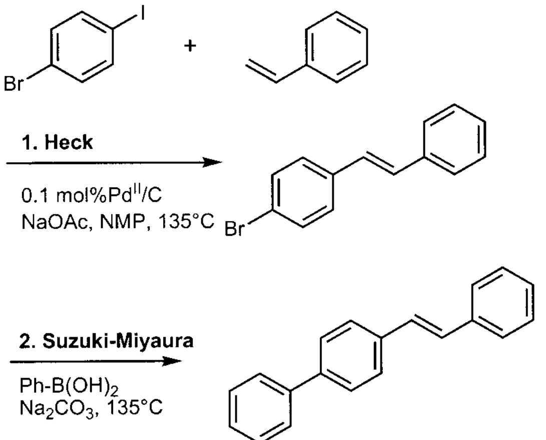
| Entry | Iodoenone | $T$ (°C) | Yield (%) | Entry | Iodoenone | $T$ (°C) | Yield (%) |
|---|---|---|---|---|---|---|---|
| 1 |  | 25 | 81 | 4 |  | 25 | 96 |
| 2 |  | 25 | 71 | 5 |  | 80 | 91 |
| 3 |  | 25 | 95 | | | | |

cross-coupling noted by the author can be found in the inherent instability of some of the 2-iodocycloenones.

In order to render the protocol highly valuable for environmental concerns, Felpin has also studied the possibility of recycling the catalyst. Although the catalytic activity was found to gradually diminish, a progressive increase of temperature still maintained high yields of the cross-coupled product (≥80%), even after five reuses.

### 6.2. Tandem Reactions: One-Pot Tandem Heck/Suzuki–Miyaura Reaction

The possibility of using Pd/C as a single catalyst for several successive transformations makes its utility even higher. Toward this end, Gruber and co-workers[41] have described a one-pot Heck/Suzuki–Miyaura reaction, which is a good example of a single heterogeneous Pd/C catalysis (Scheme 25).



Scheme 25. One-pot Heck/Suzuki–Miyaura reaction sequence.

The highest selectivity was obtained with 4-bromoiodobenzene as starting material. Only 0.1 mol-% of $Pd^{II}$/C (Degussa type E105 CA/W) was necessary to catalyze the Heck reaction, which occurs exclusively at the iodine position and leads to the expected 4-bromostilbene. The latter then reacts with phenylboronic acid to cleanly afford the 4-styrylbiphenyl (86% yield).

## 7. Summary and Outlook

The Pd/C-catalysed Suzuki–Miyaura reaction represents a valuable heterogeneous alternative to homogeneous conditions. Pd/C has many salient advantages: (1) it is an inexpensive source of palladium, (2) it is easily separated from the reaction mixture by simple filtration, (3) it can sometimes be recycled and good yields can be maintained with a progressive increase of temperature, (4) it can be used without ligands, (5) although catalytically less active than the last generation of homogeneous catalysts, it is compatible with a large variety of substrates, including aryl chlorides. During the last 10 years, much progress has been made in this field since its first use, although many exciting challenges remain unexplored. A deeper understanding of the mechanistic course will be necessary to allow chemists to design more active catalysts. Pd/C-catalysed Suzuki–Miyaura reactions now meet the growing interest in environmentally benign transformations, and will probably be used widely in both academia and industry. For the reasons mentioned above, along with the recent discoveries exemplifying the versatility of the catalyst, it will not be surprising to find Pd/C catalysed Suzuki–Miyaura reactions as one of the most preferred coupling methods in the near future.

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