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# Pseudo-Solid-State Suzuki-Miyaura Reaction and the Role of Water Formed by Dehydration of Arylboronic Acids

Evgeniy O. Pentsak,[a] and Valentine P. Ananikov*[a]

**Abstract:** Solvent-free reactions belong to a very attractive area of organic chemistry. The solvent-free Suzuki-Miyaura coupling is of special importance due to the problem of catalyst leaching in the presence of a solvent. This study investigates the course of reaction of solid aryl halides with arylboronic acids in the absence of a solvent and without any liquid additives. For the first time, a number of important conditions for performing a solid-state Suzuki-Miyaura reaction were analyzed in details. The results indicate a prominent role of water, which is formed as a by-product in the side reaction of arylboronic acid trimerization. Electron microscopy study revealed surprising changes occurring within the reaction mixture during the reaction and indicated the formation of spherical nano-sized particles containing the reaction product. Catalyst recycling was easily performed in the developed system and the product was isolated by sublimation, thus providing a possibility to completely avoid the use of solvents at all stages.

## Introduction

Global transition to green chemistry is associated with increasing interest in solvent-free reactions.[1,2] Solvents used in chemical processes represent a major source of waste. Degree of environmental impact for a chemical process is determined predominantly by the amount of solvents. Solid-phase organic reactions are therefore very important as they represent an attractive alternative to the classical organic transformations in solution.[3] For this reason, many studies are focused on solvent-free cross-coupling reactions.[4] Another problem that arises when carrying out cross-coupling reactions in solution is leaching,[5] which results in contamination of the product with the metal traces and makes the catalyst less reusable. Thus, efficient solvent-free cross-couplings will help to protect the environment, as well as to reduce toxic metal contamination[6] of fine chemicals and decrease the rates of catalyst degradation.

The majority of solvent-free reactions are conducted in the presence of liquid reagents; otherwise, the reaction may take place in a melt. The real solid-phase solvent-free reactions are quite rare. A very limited number of studies describe Suzuki–Miyaura reaction as a solid-phase synthesis (i.e. involving only solid reagents and no solvents).[7] Such reactions are typically carried out either in a ball mill[8,9] or under microwave irradiation[10-12], which requires specific equipment and sometimes is difficult to scale.[13] A solid-phase Pd/C-catalyzed Suzuki-Miyaura coupling process has been reported.[14]

It should be noted that mechanistic understanding of solid-state catalytic reaction is a challenge. The known mechanisms for Suzuki-Miyaura coupling emphasize the crucial role of nucleophile at the stage of transmetallation leading to production of active boronate and/or formation of active palladium intermediate through the ligand exchange reaction with a base.[15]

Alkali metal carbonates are commonly used as a source of nucleophilic species in the solvent-free Suzuki–Miyaura reactions. The way it works under solid state conditions is yet unknown; conventionally, carbonates of alkali metals form nucleophilic/base species only as a result of hydrolysis, which is hardly possible in the absence of water. Besides, the solid-phase reaction is apparently impeded by the mass transfer limitation factor.

The important role of water in Suzuki–Miyaura reaction has been emphasized in many studies. Earlier, it has been reported that water promotes Suzuki–Miyaura coupling involving carbonates by formation of hydroxide anion.[16,17] Carrying out the reaction in neat water reveals many interesting aspects related to the role of water in Suzuki-Miyaura reaction, as well as a number of mechanistic problems typical for the aqueous media. For example, exact location of the catalytic process in multiphase systems is an open question, along with the ways the substrates overcome diffusion limitations and the restricted mobility over water/organic phase boundaries. In addition, there are many unknown aspects of the behavior of hydrophobic substrates and the influence of the hydrophobic nature of carbon materials (used as catalyst supports) on the course of Suzuki–Miyaura reaction in aqueous media. Interestingly, Köhler and co-workers have noted that hydrophobic surfaces of catalyst support can create advantages for Suzuki–Miyaura reaction as compared to hydrophilic oxide supports.[18] This is due to the high affinity of lipophilic substances to the surface of carbon support, while adhesion of water to the surface of hydrophilic supports may impede access of reagents to catalytic sites.

Practically important is the fact that water can have an effect on reactions in which the presence of water was not intended. For example, the idea was expressed earlier that water can play an important role in mechanism of Suzuki–Miyaura reaction involving pre-formed boronates in an anhydrous medium (dry toluene).[20] As has been noted earlier,[19] water can emerge by dehydration of arylboronic acids that are found in equilibrium with the initial boronates and this amount of water can dissolve the hydrophilic components of the reaction.

In this study we investigate a solvent-free Suzuki–Miyaura reaction under conventional heating without using special equipment (a microwave oven or a ball mill) to identify factors responsible for the observed reactivity of solid substances. We demonstrate that a prominent role in their reactivity is played by side reaction of boronic acid trimerization. This side reaction

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proceeds with release of water, which promotes the interaction of solid reagents. The study elucidates the possibility of carrying out cross-coupling reactions in solid phase without the use of solvents and liquid reagents, which remains an important fundamental issue.

## Results and Discussion

**Reaction of solid aryl halides with phenylboronic acid in the absence of any liquid substrates.** The range of conditions for the solid-phase Suzuki–Miyaura reaction has limitations on the heating temperature of the reaction mixture. Boronic acids are solid in a wide range of temperatures, but aryl halides often have low melting points. For this reason, 1-iodo-4-nitrobenzene and 1-bromo-4-nitrobenzene with high melting points of 171-173 °C and 124-126 °C, respectively, have been chosen here as aryl halides for the model reaction to allow its heating to relatively high temperatures. Importantly, for the thorough confinement of the reaction to belong to the solid state, melting points of the products should also exceed the reaction temperature thereby excluding the possibility of reaction in the molten product. Suzuki–Miyaura coupling of the chosen aryl halides with phenylboronic acid results in formation of 4-nitrobiphenyl with a melting point of 111-115 °C. The reaction can therefore be carried out at temperatures up to 100 °C without the risk of switching to a semi-liquid state. The melting point of the mixture of the reagents with base was measured, in order to exclude the effect of decreased melting point for the mixture. No significant decreases in melting points were observed in both cases, as the mixture with 1-iodo-4-nitrobenzene melted at 170 °C, whereas the mixture with 1-bromo-4-nitrobenzene melted at 120 °C, i.e. melting points of the mixtures decrease by about 5 °C. The reaction was catalyzed by a composite of palladium nanoparticles supported on multi-walled carbon nanotubes (PdNPs/MWCNT) with $K_2CO_3$ as a base. The complete reaction mixture was grinded to homogeneous powder in a ceramic mortar; no spontaneous formation of the product was observed during this procedure. The reaction mixture was a black loose powder (Figure 1a).

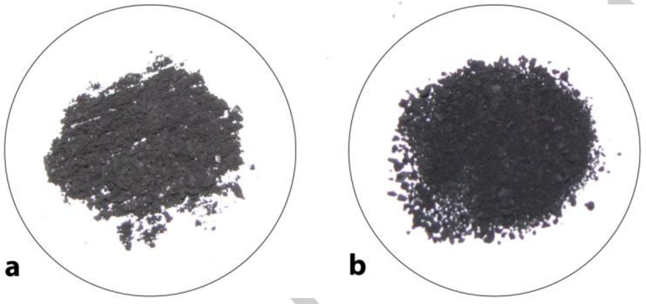

**Figure 1.** Initial appearance of reaction mixture after grinding in a mortar (a) and reaction mixture after the reaction (b).

The powder was heated to 95 °C for 6 h in a closed vessel under argon atmosphere without mixing. During the reaction, the observable weak sintering of the mixture was accompanied by formation of a small amount of white deposit (a mixture of the product with the starting halide) in the upper part of the reaction vessel. At the end, the reaction mixture was a sintered, but easily crumbling mass without visually detectable traces of the liquid phase (Figure 1b). Thus, we could propose that the reaction takes place in the solid phase. The yields reached 97 % for 1-bromo-4-nitrobenzene and 95 % for 1-iodo-4-nitrobenzene.

In order to exclude the possibility of reaction in solution during preparation of the samples for NMR spectroscopy, control analyzes of the reaction mixture were carried out before the heating. Only traces of the product were observed after 3 h incubation of the mixture in chloroform (Figure S6). This result indicates that the product forms as a result of heating of the dry solid reagents with the solid catalyst and the solid base.

**Optimization of the reaction conditions.** Optimization of the reaction conditions was accomplished by varying the temperature, the loading of catalyst and the substrates (see Table S1). In the first series of experiments, the reaction of phenylboronic acid with 1-bromo-4-nitrobenzene was carried out at different temperatures ranging from 50 °C to 100 °C. Although a decrease in temperature led to a decrease in conversion, at 70 °C the conversion was still good (73% in 6 h). A significant decrease in conversion occurred when the reaction was carried out at 50 °C (traces of product in 6 h).

Different bases were studied in the reaction (Table S2). The highest conversion was observed in the presence of potassium and cesium carbonates, as well as potassium hydroxide: the conversion reached 99%, 96% and 97%, respectively (95°C, 6 h). By contrast, in the presence of sodium acetate and potassium fluoride, the reaction almost did not proceed.

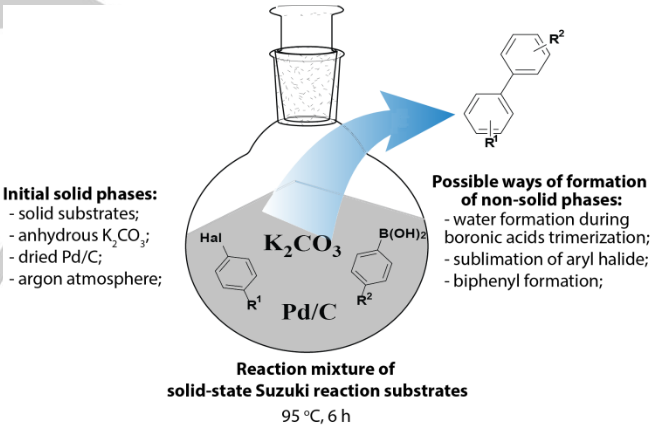

**Figure 2.** Characteristic features of the solid-phase Suzuki-Miyaura reaction.

In another series of experiments, the same reaction was carried out at 95 °C for 6 h with different loadings of the catalyst. With a low catalyst loading of 0.01 mol%, the conversion was still very good (77%). At the same time, unexpectedly, high catalyst loadings led to a slight decrease in conversion (Table S1; Entry 1) probably due to the “dilution” of the solid reagents by the supported catalyst, which is critical in the absence of a solvent and under the impeded mass transfer conditions. No product was formed in the absence of the catalyst. A comparison of the two catalysts Pd/MWCNT and PdNPs supported on graphite (Pd/graphite) was carried out. Pd/graphite was less effective (85% conversion) as compared to Pd/MWCNT (98% conversion) at the same conditions.

A decrease in conversion was observed with upscaling the reaction and increasing the reagent loading. This may be due to

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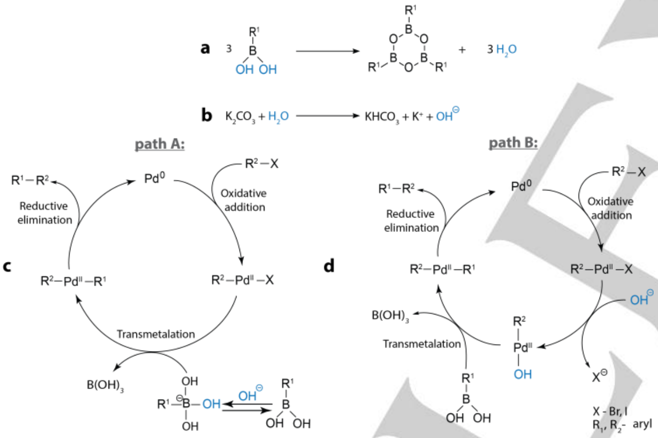
difficulties in mass transfer of reagents in the absence of a solvent (Table S3). The drop in conversion was observed at various catalyst loadings (0.1 mol% and 1 mol%). Based on the obtained data, the optimal ratio of reactants and catalyst was selected: 0.25 mmol of aryl halide, 0.3 mmol each of boronic acid and base, and 1 mol% of the catalyst.

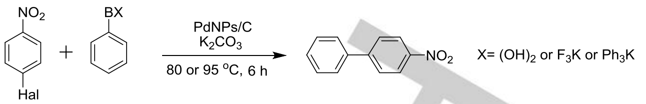
**Mechanistic concept of the reaction and the role of water.** Despite the use of solid reagents and prevention of the contact with water, the solid-phase nature of the transformation itself is questionable. A key role in the reaction between solid reagents may be played by side processes (Figure 2), the main of which are as follows: 1) sublimation of the starting halide or the reaction product; 2) formation of biphenyl by homocoupling of arylboronic acid; 3) formation of boroxine with the release of water[19] (Scheme 1a).

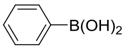
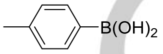
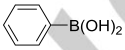
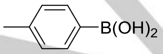
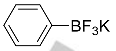
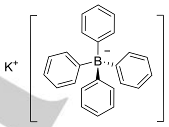
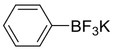
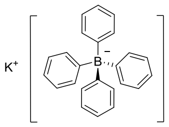
The starting aryl halides, as well as the reaction product, have high vapor pressure over solid, which contributes to their sublimation. A thin deposit of the product and the starting aryl halide, which is observed on the walls of the reaction vessel at the end of the reaction, indicates the presence of aryl halide in the vapor during the reaction. Its presence clearly enhances the mass transfer within the system and thereby may influence the mechanism of product formation. In addititon, sublimation of a product can be used for solvent-free separation.[21] Homocoupling of boronic acids to biphenyl under argon atmosphere is inefficient, since it is an oxygen-dependent process.[22]



**Scheme 1.** A plausible mechanism of the solid-phase Suzuki–Miyaura process: a) trimerization of boronic acid with formation of boroxine and release of water; b) hydrolysis of base leading to nucleophile formation; c) Pd catalytic cycle with pathway A: the hydroxyl group formed at the previous stages acts as a nucleophile species in the formation of the active reagents for transmetallation; d) Pd catalytic cycle with pathway B: the hydroxyl group formed at the previous stages interacts with palladium complex, replaces halide ligand, and the formed palladium complex reacts with arylboronic acid at the transmetalation stage.

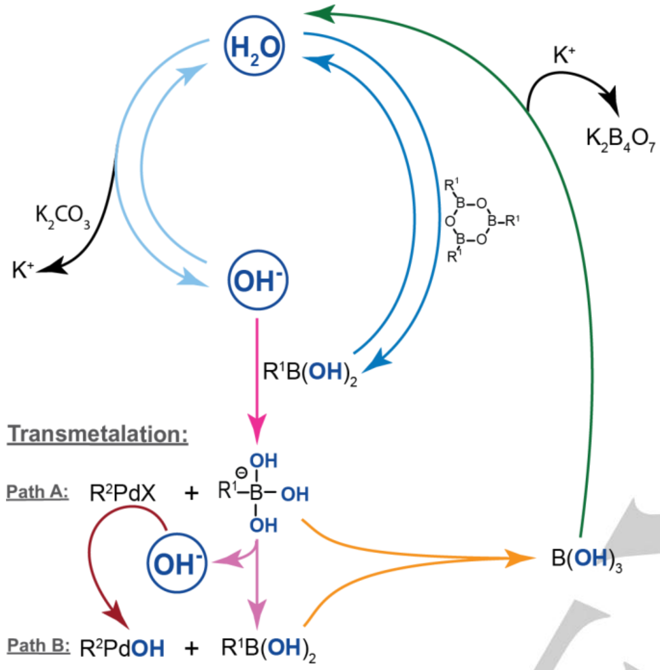
**Table 1.** The influence of water on the solid-phase Suzuki-Miyaura reaction.



| Entry | Boron reagent | Conditions[a] | Conversion, %[b] |
|---|---|---|---|
| 1 | <br>Phenylboronic acid | 80 °C | 91 |
| 2 | <br>Tolylboronic acid | 80 °C | 95 |
| 3 | <br>Phenylboronic acid | preheating of boronic acid, 80 °C | 19 |
| 4 | <br>Tolylboronic acid | preheating of boronic acid, 80 °C | 2 |
| 5 | <br>Potassium phenyltrifluoroborate | 95 °C | 0 |
| 6 | <br>Potassium tetraphenylborate | 95 °C | 0 |
| 7 | <br>Potassium phenyltrifluoroborate | addition of water[c], 95 °C | 95 |
| 8 | <br>Potassium tetraphenylborate | addition of water[c], 95 °C | 31 |

[a] Reaction conditions: 0.25 mmol 1-bromo-4-nitrobenzene, 0.3 mmol aryl borate or aryl boronic acid, 0.5 mol% of PdNPs/C catalyst, 0.3 mmol of $K_2CO_3$ at 80 or 95 °C for 6 h. [b] Determined by $^1$H NMR and GC-MS of $CDCl_3$ extract of the mixture. [c] 25 µl of water per 150-250 mg of the mixture.

Most importantly, the molecular water, which forms as a by-product of arylboronic acid trimerization, may play an essential role in the reactivity of the solids, enhancing the mass transfer and promoting formation of the nucleophile species (Scheme 1). High conversion was observed under developed conditions with phenylboronic and tolylboronic acids (Table 1; Entries 1 and 2). However, the solid-phase Suzuki–Miyaura reaction was suppressed upon usage of phenylboronic and tolylboronic acids calcinated at 150 °C for elimination of water (Table 1; Entries 3 and 4). To further evaluate the importance of this water for the efficiency of the solid-phase solvent-free Suzuki–Miyaura process we carried out the same synthesis with non-trimerizable borate salts instead of the boronic acid (Table 1; Entries 5 and 6). We used potassium salts, tetraphenylborate or phenyltrifluoroborate, incapable of trimerization with the release of water, which ensured the absence of water in the solid-phase reaction. It turned out that under such conditions the reaction does not proceed, but it can be induced by adding a small amount of water (no more than 25 µl per 150-250 mg of the mixture) to the dry reaction mixture (Table 1; Entries 7 and 8). The experiments with tetraphenylborate and phenyltrifluoroborate also indicate that the vapors of halide over the solid only insignificantly contribute to the overall reactivity. In overall, this series of experiments (Table 1) confirmed the principal role of water in the studied process.



**Scheme 2.** Schematic representation of water and hydroxide anion transformations: blue arrows – water molecule formation during trimerization arylboronic acid with formation boroxine; light blue arrows – hydrolysis of potassium carbonate with formation of hydroxide anion; magenta arrow – the interaction of the arylboronic acid with hydroxide anion with formation of trihydroxyboronate anion; pink arrows - trihydroxyboronate anion can converse back to arylboronic acid with the release of anion hydroxide; brown arrow – halide organopalladium complex $R^2PdX$ interact with hydroxide anion with formation complex $R^2PdOH$; orange arrow – formation of boric acid as result of transmetalation stage in pathway A or pathway B; green arrow - in basic media boric acid can converse to tetraborate with formation of water molecules. It is important to note that although the scheme considers both paths, it is probably that only one of them makes major contribution under certain conditions (either path A or path B).

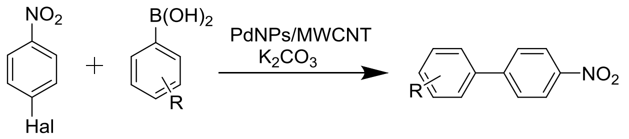
We assume that the water formed during trimerization of aryl boronic acid (Scheme 2, blue arrow) can play several important roles in the course of the reaction under the described conditions. This water is of key importance as a medium providing diffusion, mass transfer and mobility of the interacting hydrophilic species. In particular, the base, salts, phenyl boronate and ionic Pd species tend to concentrate in the aqueous phase.[23]

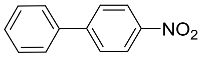
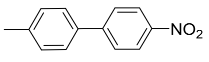
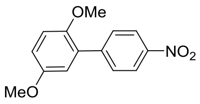
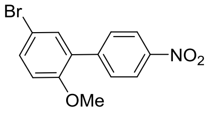
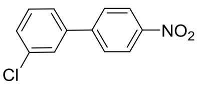
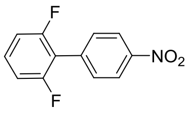
Water can also be considered as a source of basic nucleophilic species: hydroxide anions generated by interaction of water with carbonate base (Scheme 2, light blue arrow) can participate in a variety of complex dynamic transformations (Scheme 2). Several studies have emphasized the important role of the anionic base, especially at the stage of transmetalation.[17,24,25,26] The stage of transmetalation can proceed by two possible paths.[15,17,27] In the case of path A, the palladium halide complex interacts with the negatively charged nucleophilic aryltrihydroxyboronate. This trihydroxyboronate is the product of interaction of initial arylboronic acid with the hydroxy anion (Scheme 1c, Scheme 2, magenta arrow). In the case of path B, the initial arylboronic acid reacts with palladium complex, where base replaces the halide ligand in the coordination sphere of the metal (Scheme 1d, Scheme 2, brown arrow). The resulting palladium complex reacts with arylboronic acid at the transmetalation stage. Previously, it has been shown that direct interaction of halide palladium complex with arylboronic acid may not occur.[16,17,28] Thus, in order to carry out the transmetalation stage, it may be necessary to have a hydroxide anion or another nucleophilic species in the system. In our case, such a nucleophilic species can be represented by a hydroxide anion, formed by the interaction of water with potassium carbonate. Regardless of the path, the organopalladium product and boric acid are produced as a result of transmetallation stage (Scheme 2, orange arrow). Boric acid in basic media can be converted to tetraborate with formation of water (Scheme 2, green arrow).[29] Thus, the water molecules leave the cycle of transformations unchanged, and no water consumption occurs. It has also been previously reported that hydroxide anion catalyzes the reductive elimination stage.[16] On this basis, it can be proposed that a small amount of water is necessary for the reaction to proceed.

**Scope of the reaction.** The solid-phase Suzuki–Miyaura coupling protocol was applied to a range of arylboronic acids substituted with various electron donating and electron withdrawing groups (Table 2). 1-Bromo-4-nitrobenzene, contrary to expectations, was more active than the corresponding aryl iodide, for example, in affording 5-bromo-2-methoxy-4'-nitro-1,1'-biphenyl and 3-chloro-4'-nitro-1,1'-biphenyl. Although some cases of cross-coupling, in which aryl bromides give higher yields than aryl iodides, have been described previously,[30] this phenomenon is not trivial. It is usually assumed that the reactivity at the oxidative addition step depends on the energy of the R-X bond and aryl iodides should be more reactive. Nevertheless, it is possible that other parameters, such as crystal lattice energies of the solid aryl halide, can be more important in the case of solid substances.

The distribution of activity among arylboronic acids corresponded to common expectations: electron donating substituents increased the yields, whereas an opposite influence of electron withdrawing substituents was observed. As an illustration, the reaction of 1-bromo-4-nitrobenzene with 2,6-difluorophenylboronic acid yielded very small amounts of the product, and the reaction of 1-iodo-4-nitrobenzene with 2,6-difluorophenylboronic acid did not give a product (Table 2). The best conversions were achieved for arylboronic acids with methyl and methoxy substituents, e.g. for 4-tolylboronic and 2,5-dimethoxyphenylboronic acids (Table 2). The side reaction of arylboronic acid homocoupling was also observable, with the yields corresponding to 1–4% of the target product.

**Table 2.** Solid-phase Suzuki–Miyaura reaction with different reagents.[a]



|  | |  | |  | |
|---|---|---|---|---|---|
| Hal = I | Hal = Br | Hal = I | Hal = Br | Hal = I | Hal = Br |
| 95%[b] | 97%[b] | 99%[b] | 100%[b] | 100%[b] | 100%[b] |
|  | |  | |  | |
| Hal = I | Hal = Br | Hal = I | Hal = Br | Hal = I | Hal = Br |
| 53%[b] | 94%[b] | 48%[b] | 68%[b] | 0[b] | 4%[b] |

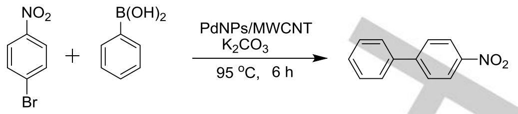
[a] Reaction conditions: 0.25 mmol of aryl halide, 0.3 mmol of aryl boronic acid, 0.5 mol% of PdNPs/MWCNT catalyst, 0.3 mmol of $K_2CO_3$ at 95 °C for 6 h. [b] Conversion was determined by GC-MS and NMR of $CDCl_3$ extract of the mixture.

Alternatively, the solvent-free Suzuki–Miyaura coupling under the same conditions was attempted with aryl halides having melting points below the reaction temperature (Table S5). Although the reaction proceeded in the melt, the less active 4-bromoacetophenone and 4-bromoanisole showed lower conversions compared to high melting point aryl halides (1-bromo-4-nitrobenzene and 1-iodo-4-nitrobenzene). Increasing the reaction time from 6 h to 8 h resulted in slightly better conversions, which were still lower than the conversions of the high melting point aryl halides (1-bromo-4-nitrobenzene and 1-iodo-4-nitrobenzene). The products of side reactions (biaryls, the products of deboration and arylboronic acid trimerization) were observed in various quantities (1–13%) depending on the nature of the arylboronic acid.

As we have mentioned above, there are a number of limitations in order to perform solid-state reactions. Thus, a strict selection of substrates was employed (Table 2). The products scope evaluated here confirms practical potential of the developed methodology and is in agreement with the mechanistic findings.

**Investigation of catalyst recycling.** Recycling of the Pd-NPs/MWCNT catalyst in the solid-phase Suzuki–Miyaura coupling of phenylboronic acid with 1-bromo-4-nitrobenzene was evaluated by sequential monitoring of the reaction in two parallel series of experiments with different loadings of the catalyst (0.1 mol% and 0.5 mol%, Table 3). All reactions were carried out under the same conditions; after completion of each cycle in the series, the catalyst was straightforwardly recovered from the mixture by centrifugation.

**Table 3.** Reuse of the PdNPs/MWCNT catalyst in the solid-phase Suzuki-Miyaura process.[a]



| Cycle | Conversion, %[b] | |
|---|---|---|
| | 0.1 mol% of the catalyst | 0.5 mol% of the catalyst |
| 1 | 95 | 79 |
| 2 | 75 | 80 |
| 3 | 94 | 88 |
| 4 | 84 | 86 |
| 5 | 100 | 96 |
| 6 | 98 | 97 |
| 7 | 100 | 93 |

[a] Reaction conditions: 1 mmol of aryl halide, 1.2 mmol of phenylboronic acid, 1.2 mmol of $K_2CO_3$, 95 °C for 6 h. [b] Determined by GC-MS of $CDCl_3$ extract of the mixture.

All obtained conversion values were in the range from 75% to 100% for the experiment with catalyst loading of 0.1 mol% and from 79% to 97% for the experiment with catalyst loading of 0.5 mol%. The high conversion was observed throughout the series with a standard deviation of 9% and 8% for catalyst loadings of 0.1 mol% and 0.5 mol%, respectively (Table 3). Observed variation in conversion values may be explained by the impeded mass transfer in a solvent-free system and may be also related to mechanical mixing of solid powders. A slight tendency towards increase in the catalyst activity upon reuse may be explained by activation of the surface of palladium nanoparticles during the reaction. However, microscopic examination did not reveal noticeable changes in the morphology of the catalyst (Figures S10-S15). The results indicate that the PdNPs/MWCNT catalyst is stable during the solid-phase Suzuki–Miyaura reaction and can be multiply reused without any loss of activity.

**Isolation of product by sublimation without using solvents.** The use of solvents at the of product isolation stage makes the main impact to an increase in amounts of waste and, as a result, an increase in E-factor.[31] For this reason, solvent-free reactions are of much importance from environmental point of view if it is possible to isolate a pure product without the use of solvents. Isolation of a product by its sublimation from a solid reaction mixture may be one of the possible approaches to solve this problem. Another important aspect of this product isolation method is elimination of the loss of palladium catalyst due to leaching (since leaching is facilitated in the presence of solvents).

To examine this possibility, after completion of the reaction of 1-bromo-4-nitrobenzene with phenylboronic acid, the reaction mixture was heated at 90 °C on a rotary evaporator under low pressure (5 mbar). The sublimated product formed yellow crystals that were collected in a trap. The product in an amount of 30 mg out of a possible 82 mg was accumulated within 6 h. To increase the efficiency of product isolation, the remaining reaction mixture was heated to a temperature of 150 °C in an oil bath at a pressure of 0.7 mbar, and the product was collected in a vacuum trap (Figures S54, S55). The remaining substance was collected in this manner for 6 h. NMR spectroscopy showed that the crystallized product contained 10% of boroxine impurity. Boroxine was removed by washing the resulting material with a large amount of water or a solution of potassium carbonate. Finally, the pure product was obtained in 98% yield.

An NMR analysis of the residual reaction mixture showed only trace amounts of the product remaining after sublimation. The activity of the catalyst remaining in the reaction mixture after removal of the product by sublimation was investigated. Substrates and base were added to this reaction mixture, from which the product was removed by sublimation; the reaction was carried out under similar conditions after grinding the mixture in a mortar. Full conversion was detected after 6 h. The product was also isolated by sublimation in an oil bath at similar conditions (150 °C, 0.7 mbar). The amount of product corresponding to the yield of 79% was collected in 4 h. To isolate the remaining product, the reaction mixture was kept for 10 h under the same conditions. As a result, the total yield of the isolated product was 92% and NMR spectroscopy showed the absence of impurities in the isolated product. Thus, not only the possibility of product isolation without the use of solvents was demonstrated by sublimation, but also the possibility of catalyst recycling by adding reagents directly to the reaction mixture immediately after sublimation of the product.

After product isolation with sublimation, the catalyst was examined by TEM. No significant morphological changes were found with the size of palladium nanoparticles slightly increased to 2-4 nm (Figures S14-S15).

**Microscopic study of the solid reaction mixture.** The course of the reaction in the solid mixture should largely depend on the uniformity of the mixing of the solid reactants in the mortar and the homogeneity of the final mixture. To address this issue, scanning electron microscopy (SEM) studies were carried out. The images showed that a powder of 1-100 µm microparticles is formed after grinding of reagents in a mortar (Figures S16, S17). The results of Energy-dispersive X-ray spectroscopy (EDS) studies indicate uniform distribution of the microparticles of reagents in the reaction mixture (Figure S18). EDS mapping by potassium signal revealed individual particles of potassium carbonate. Since Kα signal of boron is of low intensity and it is partially overlapped by Kα signal of carbon, it is difficult to unambiguously determine the localization of phenylboronic particles. Similarly, due to the overlapping of the most intense Lα signal of bromine and Kα signal of aluminum (contained in the microscopy sample stubs), it is difficult to identify the distribution of bromonitrobenzene. Nevertheless, the particles of organic substances in the secondary electron mode look darker than the particles of $K_2CO_3$ due to the specific interaction with the electron beam of the microscope (Figures S19, S25). Carbon nanotubes have a characteristic morphology, so their distribution can be easily determined in SEM images. Good surface coverage and penetration into the organic particles volume was typical for the Pd/MWCNT catalyst (Figures S20, S21).

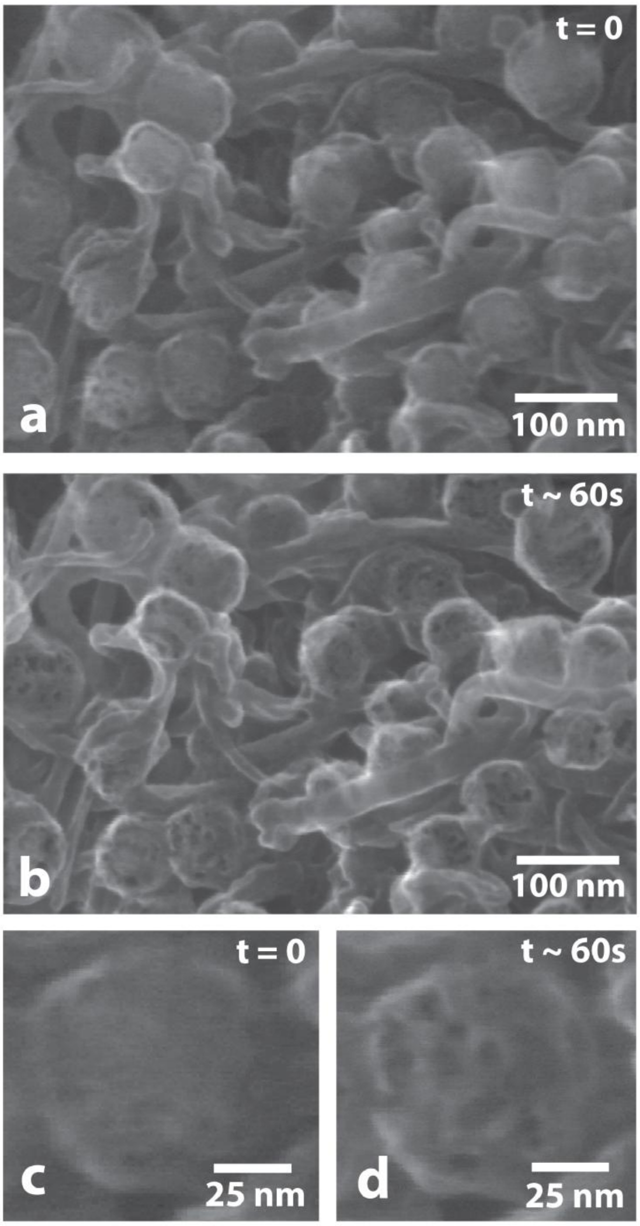


**Figure 3.** SEM images of the spherical nanoparticles formed in the reaction mixture (a), appearance of pores and the process of sublimation under the influence of electron beam for 1 min (b), and an individual nanoparticle under higher magnification showing the sublimation process directly in the microscope chamber (c and d),

The sample obtained after completion of the reaction was also examined by SEM. It consisted of microparticles with the size close to the particles size of the initial reaction mixture (1-100 µm), but their morphology was substantially different from the initial one (Figures S26-S28, S30, S33). The particles of the reaction mixture consisted of a bulk penetrated by carbon nanotubes; in addition, there were inclusions of spherical particles about 100 nm in size inside the bulk (Figures S34-S36). In some cases, spherical particles were not included in the bulk of larger particles and located in piles on the surface of other particles (Figures S37-S40). Nano-sized pores in spherical particles appeared during long-term positioning of the electron beam (Figure 3, Figures S37-S39).

Next, a sample of the reaction mixture after sublimation of the product was also studied. It was found that the spherical particles were porous after sublimation, or porous areas were observed in the places where the spherical particles were supposedly located (Figures S51-S53).

It can be assumed that accumulation of the product occurs inside the detected spherical particles. Electron microscopy provide excellent opportunity to visualize the sublimation process from these spherical particles due to the heating of the substance under an electron beam in a high vacuum (Figure 3). Amazingly, the formation of pores was observed in the studied sample directly inside the electron microscope chamber (Figure 3). In the sublimation process the evaporated product trapped and isolated from the reaction mixture.

## Conclusions

The study shows that solid arylboronic acids and aryl halides can react in the absence of added liquids (solvents or melts). Under optimized conditions the quantitative yields can be achieved by conventional heating of the solid-phase reaction mixture, and no additional mixing is required during the reaction.

We demonstrate that molecular water, which forms as a result of arylboronic acid dehydration, is essential for the efficient solid-phase Suzuki-Miyaura coupling. This conclusion is based on the following findings:

1) The reaction efficiently proceeds under conditions that favor formation of boroxine from phenylboronic acid with the release of water, which is an expected process.

2) Pre-calcination of the initial arylboronic acid leads to a significant reduction in the observed conversion.

3) Under studied conditions the reaction does not proceed with potassium tetraphenylborate and potassium trifluoroborate, while the addition of minimal amounts of water initiated the reaction with these reagents.

4) The formation of nucleophilic species from potassium carbonate is facilitated by the presence of water.

In the absence of side processes leading to formation of water (and consequently to the appearance of activated nucleophilic species) the reaction between the solid reagents is blocked.

The presence of a small amount of water in the reaction mixture does not diminish the advantages of the solid-phase reaction, but it might be a key factor for initiating and maintaining the reaction. The formation of liquid promoters during the reaction may also be an important factor in the mechanisms of other solid-phase reactions and we may anticipate more studies in this fascinating area in the nearest future.

In the studied Suzuki–Miyaura reaction between solid substances, the PdNPs/MWCNT catalyst can be reused multiple times without loss of efficiency. The absence of a liquid phase (reagents of solvents) is an important factor to avoid metal leaching.

Electron microscopy study suggested that product formation/accumulation occurs in spherical nanoparticles with a diameter of about 100 nm, which are capable to undergo sublimation. Indeed, the possibility of product isolation from the reaction mixture by sublimation was successfully demonstrated. Avoiding solvents in cross-coupling reactions is an important advantage to improve Green metrics and to prevent the loss of palladium due to leaching.

## Experimental Section

**General Remarks.** The reagents (aryl halides, boron reagents, anhydrous bases) were obtained from commercial sources and used after spectroscopic check ($^1$H and $^{13}$C NMR, GC-MS). The PdNPs/C catalysts were prepared as described previously.[32]

Catalysts and bases dried in advance at 150 °C for 8 h *in vacuo* were used in all reactions. The reaction products were purified by extraction and column chromatography; mixtures of petroleum ether with benzene or ethyl acetate were used as eluents. After the extraction and chromatography, the solvent was evaporated and the product was dried in a rotary evaporator at 40 °C.

Melting points were measured by a 1101D MEL-TEMP digital melt point apparatus.

**NMR spectroscopy.** The $^1$H NMR spectra were recorded on Bruker DRX500, Bruker AVANCE III 400 WB and Bruker Fourier 300 HD spectrometers. The conversions for solid-phase reactions were determined by extraction with deuterochloroform (99.8% atom D, stabilized with silver foil). Processing of the spectra was accomplished with Bruker Topspin 2.1 and MestReNova (version: 6.0.2-5475) software packages. Chemical shifts are reported in ppm relative to the solvent resonance signal as an internal standard – $CDCl_3$ (7.26 and 77.16 ppm for $^1$H and $^{13}$C, respectively).

**Sample preparation for NMR.** An aliquot of the solid reaction mixture was suspended in 2 ml of $CDCl_3$. The suspension was centrifuged, and the solution was analyzed NMR spectroscopy.

Control experiment was performed to rule out the possibility of cross-coupling reaction during the sample preparation. Solid reaction mixture (4 mg 1-Bromo-4-nitrobenzene, 4 mg phenylboronic acid, 4 mg potassium carbonate and 2 mg PdNPs/MWCNT) was placed in 1 mL $CDCl_3$. Only traces of the product were observed after 3 h keeping of the mixture in $CDCl_3$.

**GC-MS analysis.** GC-MS data were recorded on Agilent 7890B system with an Agilent 5977A quadrupole mass analyzer using an Agilent HP-5MS (19091s-433) column (5%-Phenyl Methyl Siloxane, 0-325 °C, 30 m×250 µm×0.25 µm) and helium grade 7.0 as a carrier gas. Calibration was performed automatically by PFTBA on the day of analysis. Acquisition mode: ionization energy 70 eV, m/z scan range of 50-600 Da with a step of 0.1, 6.7 scans/sec, transfer capillary temperature 280 °C, source temperature 230 °C, analyzer temperature 150 °C. Chromatography mode: evaporator temperature 280 °C, injection volume 1 µl, split ratio 1:100, isocratic mode, flow 1 ml/min; 70 °C for 2 min, 10 °C/min to 240 °C, 35 °C/min to 310 °C, 310 °C for 5 min. For the analysis, 30 µl of the sample was diluted to 1.5 ml with $CH_2Cl_2$ (Sigma-Aldrich, HPLC, 50-150 ppm amylene).

**TEM analysis.** Before measurements the samples were mounted on a 3 mm copper grid with lacey carbon film and fixed in a grid holder. Samples morphology was studied using Hitachi transmission electron microscope (TEM). Images were acquired in bright-field TEM mode at 100 kV accelerating voltage.

**SEM and EDX studies.** Before the measurements the samples were mounted on a 25 mm aluminum specimen stub and fixed by conductive graphite adhesive tape. Sample morphology was studied under native conditions to exclude the possible metal coating surface effects.[33] The observations were carried out using Hitachi SU8000 field-emission scanning electron microscope (FE-SEM). Images were acquired in secondary electron mode at 10-30 kV accelerating voltage and at working distance 8-10 mm. EDX studies were carried out using Oxford Instruments X-max EDX system.

**Control for the lack of reactivity during the grinding.** 1-Bromo-4-nitrobenzene (0.25 mmol), phenylboronic acid (0.3 mmol), a base (0.3 mmol) and PdNPs/MWCNT (1 mol%) were grinded thoroughly in a ceramic mortar. An aliquot of the mixture was suspended in 2 ml of $CDCl_3$ and sonicated. The suspension was centrifuged or filtered after 30 min and 3 h of keeping under solvent. The solution was analyzed by GC-MS and NMR spectroscopy.

**Control experiments in absence of the catalyst.** Aryl halide (1-bromo-4-nitrobenzene and 1-iodo-4-nitrobenzene in two separate experiments; 0.25 mmol each), phenylboronic acid (0.3 mmol), $K_2CO_3$ (0.3 mmol) were mixed thoroughly in a ceramic mortar and transferred to a screw-capped test tube. The reactions were heated at 90 °C for 6 h. After completion of the reactions, the samples were analyzed by NMR spectroscopy.

**Varying the reaction temperature.** 1-Bromo-4-nitrobenzene (0.25 mmol), phenylboronic acid (0.3 mmol), $K_2CO_3$ (0.3 mmol) and PdNPs/C (1 mol%) were mixed thoroughly in a ceramic mortar and transferred to a screw-capped test tube. The reaction was heated at 50 °C, 70 °C, 80 °C, 90 °C or 100 °C for 6 h. After completion of the reaction, the sample was analyzed by NMR spectroscopy.

**Varying the base for the reaction.**1-Bromo-4-nitrobenzene (0.25 mmol), phenylboronic acid (0.3 mmol), a base (0.3 mmol) and PdNPs/MWCNT (1 mol%) were mixed thoroughly in a ceramic mortar and transferred to a screw-capped test tube. The reaction was heated at 95 °C for 6 h. After completion of the reaction sample was analyzed by NMR spectroscopy.

**Varying the amount and type of catalyst.** 1-Bromo-4-nitrobenzene (0.25 mmol), phenylboronic acid (0.3 mmol), $K_2CO_3$ (0.3 mmol) and PdNPs/MWCNT (2, 1, 0.5, 0.1 or 0.01 mol%) or PdNPs/graphite (0.5 mol%) were mixed thoroughly in a ceramic mortar and transferred to a screw-capped test tube. The reaction was heated at 100 °C for 6 h. After completion of the reaction, the sample was analyzed by NMR spectroscopy.

**Experimental scaling up of the reaction volume.** 1-Bromo-4-nitrobenzene (0.25 mmol for a standard reaction or 1 mmol for a bigger scale reaction), phenylboronic acid (0.3 mmol for a standard reaction or 1.2 mmol for a bigger scale reaction), $K_2CO_3$ (0.3 mmol for a standard reaction or 1.2 mmol for a bigger scale reaction) and PdNPs/C (0.1 mol% or 1 mol% independently of the scale) were mixed thoroughly in a ceramic mortar and transferred to a screw-capped test tube. The reactions were heated at 100 °C for 6 h. After completion of the reaction, the sample was analyzed by NMR spectroscopy.

**Assessment of the influence of added water on the solid-phase Suzuki–Miyaura reaction.** 1-Bromo-4-nitrobenzene (0.25 mmol), aryl borate (0.3 mmol), $K_2CO_3$ (0.3 mmol) and PdNPs/C (1 mol%) were mixed thoroughly in a ceramic mortar and transferred to a screw-capped test tube. In a control series of reactions, the mixtures were supplemented with 25 µl of distilled water. The reaction was heated at 95 °C for 6 h; after completion of the reaction, the sample was analyzed by GC-MS and NMR spectroscopy.

**Experiments with pre-treatment of boronic acids.** A 37 mg aliquot of phenylboronic acid or 4-tolylboronic acid was heated on air at 150 °C for 2 h. The treated substance was grinded in a ceramic mortar with 1-bromo-4-nitrobenzene (0.25 mmol), PdNPs/C (1 mol%) and $K_2CO_3$ (0.3 mmol) and transferred to a screw-capped test tube. The reaction was heated at 80 °C for 6 h. After completion of the reaction, the sample was analyzed by NMR spectroscopy.

**Varying aryl halides and boronic acids for the reaction.** Aryl halide (0.25 mmol), arylboronic acid (0.3 mmol), $K_2CO_3$ (0.3 mmol) and PdNPs/MWCNT (0.5 mol%) were mixed thoroughly in a ceramic mortar and transferred to a screw-capped test tube. The reactions were heated at 95 °C for 6 h. After that, an aliquot of the reaction mixture was suspended in 2 ml of chloroform. The suspension was filtered, and the solution was analyzed by GC-MS and NMR. The known products were identified according to the published data.[34]

**Catalyst recycling study.** 1-Bromo-4-nitrobenzene (1 mmol), phenylboronic acid (1.2 mmol), $K_2CO_3$ (1.2 mmol) and PdNPs/MWCNT (0.1 mol% or 0.5 mol%) were mixed thoroughly in a ceramic mortar and transferred to a screw-capped test tube. The reactions were heated at 100 °C for 6 h. After that, an aliquot of the reaction mixture was suspended in 2 ml of chloroform. The suspension was filtered, and the solution was analyzed by GC-MS. The solid residue was washed 5 times with acetone and 2 times with water; the catalyst was dried *in vacuo* at 120 °C for 30 min and reused under the same conditions.

**Isolation of product by sublimation.** The solid reaction mixture after completion of the reaction was placed in a round bottom flask. The flask was placed in an oil bath so that it was completely immersed in silicone oil, and equipped with a glass trap. Then the flask with the mixture was heated at 150 °C and a pressure of 0.7 mbar for 6-14 h. The sublimated product was collected at the bottom of the trap in the form of yellow crystals and characterized by GC-MS and NMR.

**Keywords:** Suzuki-Miyaura coupling • solvent-free reaction • solid-state reaction • water • boronic acids • supported catalysts • Pd/C catalyst • mechanistic study

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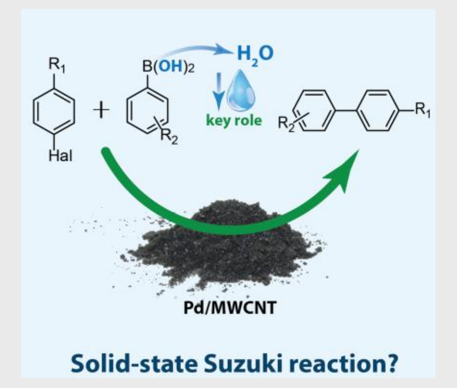
# Entry for the Table of Contents

## FULL PAPER

Conditions for a Suzuki-Miyaura solid-state reaction were analyzed in details. The results show key role of water, which is formed as a by-product in the side reaction of arylboronic acid trimerization.



**Key Topic: Solid-State Coupling**

*Evgeniy O. Pentsak, Valentine P. Ananikov **

***Page No. – Page No.***

**Pseudo-Solid-State Suzuki-Miyaura Reaction and the Role of Water Forming by Dehydration of Arylboronic Acids**