

# Heterogeneous Pd/C-Catalyzed Ligand-Free, Room-Temperature Suzuki–Miyaura Coupling Reactions in Aqueous Media\*\*

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**Abstract:** A mild and efficient ligand-free Suzuki–Miyaura coupling reaction catalyzed by heterogeneous Pd/C was developed. Aryl bromides and triflates undergo the cross-coupling with aryl boronic acids in excellent yields without the presence of any additives in aqueous media at room temperature. Aryl vinyl boronic acids are also applicable to this coupling reaction and provide the *trans*-stilbene derivatives in

high yields. The application of wet-type Pd/C to the coupling reaction was achieved without any loss of activity under aerobic conditions, and the reuse of Pd/C is feasible for a fifth run without significant loss of activity. Inductively

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coupled plasma (ICP) mass-spectrometric analysis of the filtrate from the reaction mixture of 4-bromonitrobenzene with phenylboronic acid demonstrated that the palladium metal hardly leached into the solution within the limits of the detector (<1 ppm), thus suggesting that the present Suzuki–Miyaura reaction proceeded by heterogeneous catalysis.

## Introduction

The palladium-catalyzed Suzuki–Miyaura coupling reaction, which involves the cross-coupling reaction of aryl halides with aryl boronic acids, is one of the most powerful and convenient synthetic methods for the preparation of biaryl and alkene derivatives that are structural components of natural products, agrochemicals, pharmaceuticals, and polymers, such as organic electroluminescence (EL) materials.<sup>[1]</sup> The

Suzuki–Miyaura coupling reaction has many advantages: tolerance of a wide range of functional groups, low toxicity, and easy handling of reagents and by-products. Traditional Suzuki–Miyaura coupling reactions generally employ homogeneous palladium catalysts in the presence of phosphine ligands.<sup>[2]</sup> Current developments into expansion of the coupling reaction have been carried out chiefly by Buchwald et al.<sup>[3]</sup> and Fu et al.,<sup>[4]</sup> so that now it is easy to perform the coupling of various compounds such as aryl chlorides, hindered substrates, heteroaromatic compounds, alkenyl derivatives, and so forth at room temperature and under low-catalyst-loading conditions. However, the principal drawbacks are the availability, stability, and cost of the palladium complexes and phosphine ligands. Furthermore, homogeneous palladium catalysts are usually not reusable and the products are frequently contaminated by residual palladium and ligands, which can be difficult to separate from the end product.<sup>[2d]</sup> To overcome these difficulties, the application of a reusable heterogeneous palladium-catalyzed Suzuki–Miyaura cross-coupling reaction has been developed.<sup>[2d,5]</sup> Pd/C is one of the most common heterogeneous catalysts<sup>[6]</sup> because of its availability, easy handling, and reusability, and many applications of Pd/C to Suzuki–Miyaura coupling reactions have been reported.<sup>[7–10]</sup> However, some additives, such as phosphine ligands and quaternary ammonium salts (tetrabutylammonium bromide (TBAB) or hexadecyltri-

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[\*\*] Although the present method was developed independently by us, one of the temporary researchers in our laboratory from the College of Pharmaceutical Sciences, Zhejiang University (Guolin Zhang, P.R. China) reported part of the results without our authorization. We therefore submit this article to attest to the reliability of the results and to uphold our right to the originality of our research. See erratum: *Synthesis* **2005**, 852 and *J. Chem. Res.* **2005**, 344.

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methylammonium bromide (CTAB)), and/or the application of heat, microwave irradiation, and pressure are required for effective reaction progress.<sup>[8]</sup> There are several reports of additive-free Pd/C-catalyzed Suzuki–Miyaura coupling reactions with heating,<sup>[9]</sup> but only a few examples at room temperature without any additives have reported, and then only for limited substrates, such as halophenols and iodocycloenones.<sup>[10]</sup> Herein, we report a mild and efficient ligand-free Pd/C-catalyzed Suzuki–Miyaura coupling reaction at room temperature in aqueous media and the successful application of this method to a wide variety of substrates, such as aryl bromides, aryl triflates, and aryl vinyl boronic acids in good-to-high yields.

## Results and Discussion

Initially, we examined the effect of bases using 4-bromonitrobenzene and phenylboronic acid as substrates in the presence of 10% Pd/C<sup>[11]</sup> in 50% ethanol at room temperature. The use of inorganic bases, such as Na<sub>2</sub>CO<sub>3</sub>, NaHCO<sub>3</sub>, or Na<sub>3</sub>PO<sub>4</sub>·12H<sub>2</sub>O, gave the cross-coupling product in high yield (Table 1, entries 3, 4, and 8). It was surprising that the cross-coupling reaction also proceeded with NaHCO<sub>3</sub>, a fairly weak base relative to Na<sub>2</sub>CO<sub>3</sub> or Na<sub>3</sub>PO<sub>4</sub>, which is commonly used for the Suzuki–Miyaura coupling reaction.<sup>[12]</sup> On the other hand, organic bases, such as Et<sub>3</sub>N and 1,4-diazabicyclo[2.2.2]octane (DABCO), gave disappointing results (Table 1, entries 1 and 2). Consequently, Na<sub>2</sub>CO<sub>3</sub>, NaHCO<sub>3</sub>, and Na<sub>3</sub>PO<sub>4</sub>·12H<sub>2</sub>O were chosen as bases for further optimization.

The choice of solvent was also important for the present method. Alcoholic and alcoholic/aqueous solvents, especially MeOH, MeOH/H<sub>2</sub>O (1:1), EtOH, EtOH/H<sub>2</sub>O (1:1), and *i*PrOH/H<sub>2</sub>O (1:1) gave satisfactory results (Table 2, entries 2–7), whereas the use of pure H<sub>2</sub>O gave quite poor results for each base (Table 2, entry 1). On the other hand, aprotic polar solvents, such as *N,N*-dimethylformamide (DMF), dimethylacetamide (DMA), dioxane, and 1,2-dimethoxyethane (DME), which are commonly used in Pd-catalyzed coupling reactions, were not effective in the present coupling reaction.

Next, we examined the supplier-dependent catalyst activity of Pd/C, as we already found significant supplier-dependent disparity in the catalyst activity of commercial Pd/C in the hydrogenolysis of triethylsilyl ether.<sup>[13]</sup> Among them, 10% Pd/C (K type) manufactured by N.E. Chemcat was the

Table 1. Effect of bases on the Suzuki–Miyaura coupling reaction.

| Entry | Base                                                | Yield [%] <sup>[a]</sup> |
|-------|-----------------------------------------------------|--------------------------|
| 1     | Et <sub>3</sub> N                                   | 45                       |
| 2     | DABCO                                               | nr <sup>[b]</sup>        |
| 3     | Na <sub>2</sub> CO <sub>3</sub>                     | 98                       |
| 4     | NaHCO <sub>3</sub>                                  | 92                       |
| 5     | NaOH                                                | 5                        |
| 6     | NaOAc                                               | 59                       |
| 7     | Na <sub>2</sub> HPO <sub>4</sub>                    | 34                       |
| 8     | Na <sub>3</sub> PO <sub>4</sub> ·12H <sub>2</sub> O | 92                       |

[a] Yields were determined by GC. [b] No reaction.

Table 2. Effect of solvents on the Suzuki–Miyaura coupling reaction.

| Entry | Solvent                              | Yield [%] <sup>[a]</sup> |                                 |                                                     |
|-------|--------------------------------------|--------------------------|---------------------------------|-----------------------------------------------------|
|       |                                      | NaHCO <sub>3</sub>       | Na <sub>2</sub> CO <sub>3</sub> | Na <sub>3</sub> PO <sub>4</sub> ·12H <sub>2</sub> O |
| 1     | H <sub>2</sub> O                     | 4                        | 16                              | 4                                                   |
| 2     | MeOH                                 | 100 (4 h) <sup>[b]</sup> | 88 (6 h) <sup>[b]</sup>         | 90 (4 h) <sup>[b]</sup>                             |
| 3     | MeOH/H <sub>2</sub> O (1:1)          | 94 (12 h) <sup>[b]</sup> | 89 (6 h) <sup>[b]</sup>         | 94 (3 h) <sup>[b]</sup>                             |
| 4     | EtOH                                 | 87                       | 97 (12 h) <sup>[b]</sup>        | 89 (6 h) <sup>[b]</sup>                             |
| 5     | EtOH/H <sub>2</sub> O (1:1)          | 92 (12 h) <sup>[b]</sup> | 98 (2 h) <sup>[b]</sup>         | 92 (3 h) <sup>[b]</sup>                             |
| 6     | <i>i</i> PrOH                        | 87                       | 82                              | 88                                                  |
| 7     | <i>i</i> PrOH/H <sub>2</sub> O (1:1) | 89 (12 h) <sup>[b]</sup> | 93 (6 h) <sup>[b]</sup>         | 100 (1 h) <sup>[b]</sup>                            |
| 8     | DMF                                  | 24                       | 20                              | 4                                                   |
| 9     | DMA                                  | 25                       | 40                              | 79                                                  |
| 10    | dioxane                              | 21                       | 16                              | 31                                                  |
| 11    | MeCN                                 | 13                       | 8                               | 21                                                  |
| 12    | acetone                              | 27                       | 56                              | 50                                                  |
| 13    | DME                                  | 45                       | 41                              | 49                                                  |
| 14    | THF                                  | 7                        | 27                              | 24                                                  |
| 15    | toluene                              | 4                        | 10                              | 2                                                   |

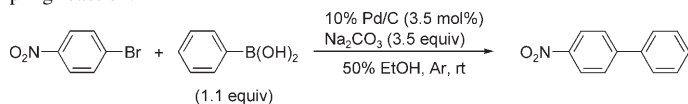
[a] Yields were determined by GC. [b] The completion time of the coupling reaction is given in parentheses.

most efficient catalyst for the present Suzuki–Miyaura coupling reactions (completed within 2 h at room temperature: Table 3, entry 1), whereas the use of Pd/C from other suppliers gave the corresponding coupling product in high yield with longer reaction times (4–8 h; Table 3).

Although the reason for the difference in the catalyst activity is not clear, it might be caused by the presence of acid and residual nonreduced Pd<sup>II</sup> species in the Pd/C or the quality of the activated carbon.<sup>[13]</sup> In this system, the addition of a small amount of concentrated HCl or the use of Pd<sup>II</sup>/C instead of Pd<sup>0</sup>/C impeded the coupling reaction.

**Optimization of dosages of Pd/C and base:** Further optimization of the reaction conditions, especially the optimal amounts of Pd/C and base with a view to application in industry, was investigated (Table 4). In the case of the NaHCO<sub>3</sub>/MeOH system, the amount of Pd/C could be decreased to 1.5 mol% without significant loss of reactivity (compare Table 4, entry 1 with Table 2, entry 2), whereas further decrease of either Pd/C or NaHCO<sub>3</sub> caused an ex-

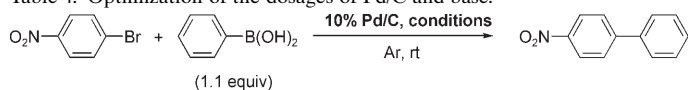
Table 3. Catalyst activity of 10% Pd/C toward the Suzuki–Miyaura coupling reaction.



| Entry | Supplier of 10% Pd/C <sup>[a]</sup> | Time [h] | Yield [%] <sup>[b]</sup> |
|-------|-------------------------------------|----------|--------------------------|
| 1     | N.E. Chemcat (K type)               | 2        | 98                       |
| 2     | Aldrich (205699–50G)                | 7        | 93                       |
| 3     | Merck (8.07104.0010)                | 6        | 88                       |
| 4     | Acros (19503–0100)                  | 4        | 90                       |
| 5     | Wako (163–15272)                    | 6.5      | 94                       |
| 6     | Kishida (400–59095)                 | 4        | 94                       |
| 7     | Nacalai (25928–84)                  | 8        | 99                       |

[a] Supplier's product number is given in parentheses. [b] The yields were determined by GC.

Table 4. Optimization of the dosages of Pd/C and base.

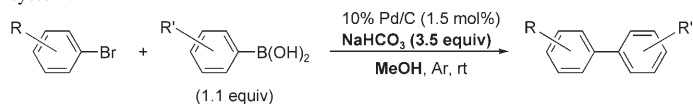


| Entry | Conditions                                         | 10% Pd/C [mol %] | Base [equiv] | Time [h] | Yield [%] <sup>[a]</sup> |
|-------|----------------------------------------------------|------------------|--------------|----------|--------------------------|
| 1     | NaHCO <sub>3</sub> /MeOH                           | 1.5              | 3.5          | 4        | 96                       |
| 2     | NaHCO <sub>3</sub> /MeOH                           | 1.5              | 2.5          | 6        | 93                       |
| 3     | NaHCO <sub>3</sub> /MeOH                           | 1.0              | 2.5          | 9        | 87                       |
| 4     | Na <sub>2</sub> CO <sub>3</sub> /50% EtOH          | 1.5              | 1.5          | 3        | 97                       |
| 5     | Na <sub>2</sub> CO <sub>3</sub> /50% EtOH          | 1.5              | 1.0          | 6        | 96                       |
| 6     | Na <sub>2</sub> CO <sub>3</sub> /50% EtOH          | 1.0              | 1.5          | 5        | 96                       |
| 7     | Na <sub>3</sub> PO <sub>4</sub> /50% <i>i</i> PrOH | 0.5              | 3.5          | 3.5      | 93                       |
| 8     | Na <sub>3</sub> PO <sub>4</sub> /50% <i>i</i> PrOH | 0.5              | 2.5          | 7        | 83                       |
| 9     | Na <sub>3</sub> PO <sub>4</sub> /50% <i>i</i> PrOH | 0.2              | 3.5          | 24       | 82                       |

[a] Yields were determined by GC.

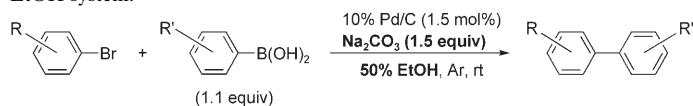
tension of the reaction time (Table 4, entries 2 and 3). Under the Na<sub>2</sub>CO<sub>3</sub>/50% EtOH conditions, the amounts of both Pd/C and Na<sub>2</sub>CO<sub>3</sub> could be successfully decreased to 1.5 mol% (compare Table 4, entry 4 with Table 2, entry 5). Further decrease in the amount of either Pd/C or Na<sub>2</sub>CO<sub>3</sub> still produced the biphenyl compound quantitatively, although the reaction time was extended (Table 4, entries 5 and 6). When the Na<sub>3</sub>PO<sub>4</sub>/50% *i*PrOH system was employed for the coupling reaction, the amount of Pd/C could be decreased to 0.5 mol% (compare Table 4, entry 7 with Table 2, entry 7). However, further decrease of the amount of either Na<sub>3</sub>PO<sub>4</sub> or Pd/C lowered the yield of 4-nitrobiphenyl and extended the reaction time (Table 4, entries 8 and 9).

We next explored the scope and limitations of substrates for the Suzuki–Miyaura coupling reaction under the optimized conditions using 10% Pd/C in alcoholic solvents at room temperature (Table 5, entries 6 and 7). Under each reaction condition (NaHCO<sub>3</sub>/MeOH (Table 5), Na<sub>2</sub>CO<sub>3</sub>/50% EtOH (Table 6), Na<sub>3</sub>PO<sub>4</sub>/50% *i*PrOH (Table 7)), various aryl bromides bearing electron-withdrawing groups, such as nitro, aldehyde, ester, and carboxylic acid moieties, and electron-donating groups, such as methyl, hydroxy, and methoxy moieties, coupled with phenylboronic acid in high yields accompanied with a trace amount of the homocoupling prod-

Table 5. Suzuki–Miyaura coupling reaction using the NaHCO<sub>3</sub>/MeOH system.

| Entry | R                    | R'     | Time [h] | Yield [%] <sup>[a]</sup> |
|-------|----------------------|--------|----------|--------------------------|
| 1     | 4-NO <sub>2</sub>    | H      | 4        | 96                       |
| 2     | 4-CHO                | H      | 5.5      | 94                       |
| 3     | 4-CO <sub>2</sub> Et | H      | 24       | 92                       |
| 4     | 2-Me                 | H      | 4.5      | 92                       |
| 5     | 2,6-Me <sub>2</sub>  | H      | 48       | nr                       |
| 6     | 1-nap                | H      | 48       | 70 <sup>[b]</sup>        |
| 7     | 4-OH                 | H      | 25       | 93                       |
| 8     | 4-CO <sub>2</sub> H  | H      | 25       | 91                       |
| 9     | 4-OMe                | H      | 48       | 98                       |
| 10    | 4-OMe                | 2-OMe  | 8        | 100                      |
| 11    | 4-OMe                | 3-OMe  | 24       | 90                       |
| 12    | 4-OMe                | 4-OMe  | 24       | 94                       |
| 13    | 4-OMe                | 4-COMe | 48       | 45 <sup>[b]</sup>        |

[a] Yield of the isolated product. [b] The reaction did not go to completion. 1-nap = 1-naphthalene.

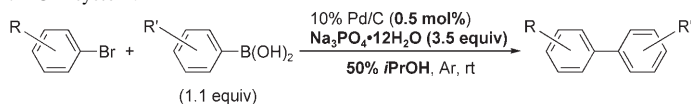
Table 6. Suzuki–Miyaura coupling reaction using the Na<sub>2</sub>CO<sub>3</sub>/50% EtOH system.

| Entry | R                    | R'     | Time [h] | Yield [%] <sup>[a]</sup> |
|-------|----------------------|--------|----------|--------------------------|
| 1     | 4-NO <sub>2</sub>    | H      | 3        | 97                       |
| 2     | 4-CHO                | H      | 3        | 98                       |
| 3     | 4-CO <sub>2</sub> Et | H      | 12       | 99                       |
| 4     | 2-Me                 | H      | 3.5      | 90                       |
| 5     | 2,6-Me <sub>2</sub>  | H      | 48       | nr                       |
| 6     | 1-nap                | H      | 24       | 78                       |
| 7     | 4-OH                 | H      | 11       | 90                       |
| 8     | 4-CO <sub>2</sub> H  | H      | 8        | 94                       |
| 9     | 4-OMe                | H      | 24       | 91                       |
| 10    | 4-OMe                | 2-OMe  | 9        | 93                       |
| 11    | 4-OMe                | 3-OMe  | 12       | 91                       |
| 12    | 4-OMe                | 4-OMe  | 11       | 96                       |
| 13    | 4-OMe                | 4-COMe | 48       | 77 <sup>[b]</sup>        |

[a] Yield of the isolated product. [b] The reaction did not go to completion.

ucts of aryl boronic acids as side products, whereas completion of the reaction took a longer time when NaHCO<sub>3</sub>, a weaker base, was used (compare Tables 5–7).<sup>[2d,14]</sup> Steric hindrance based on the *ortho* substituents on the aryl bromide affected the reaction progress. The coupling reaction of 2,6-dimethylbromobenzene did not proceed with each base (Table 5–7, entry 5). The reaction of 1-bromonaphthalene with phenylboronic acid using NaHCO<sub>3</sub> or Na<sub>2</sub>CO<sub>3</sub> took longer than other cases (Tables 5 and 6, entry 5), although the reaction concluded within 5.5 h in the case of Na<sub>3</sub>PO<sub>4</sub> (Table 7, entry 6). Furthermore, aryl bromides with a hydroxy or carboxylic acid group underwent the coupling reaction in high yields without any protection (Table 5–7, entries 7 and 8). Regarding aryl boronic acids, the coupling re-

Table 7. Suzuki–Miyaura coupling reaction using the  $\text{Na}_3\text{PO}_4$ /50% *i*PrOH system.



| Entry | R                    | R'     | Time [h] | Yield [%] <sup>[a]</sup> |
|-------|----------------------|--------|----------|--------------------------|
| 1     | 4-NO <sub>2</sub>    | H      | 3.5      | 93                       |
| 2     | 4-CHO                | H      | 3        | 91                       |
| 3     | 4-CO <sub>2</sub> Et | H      | 6        | 99                       |
| 4     | 2-Me                 | H      | 4        | 90                       |
| 5     | 2,6-Me <sub>2</sub>  | H      | 48       | nr                       |
| 6     | 1-nap                | H      | 5.5      | 94                       |
| 7     | 4-OH                 | H      | 3.5      | 91                       |
| 8     | 4-CO <sub>2</sub> H  | H      | 3.5      | 100                      |
| 9     | 4-OMe                | H      | 24       | 93                       |
| 10    | 4-OMe                | 2-OMe  | 6        | 90                       |
| 11    | 4-OMe                | 3-OMe  | 10       | 96                       |
| 12    | 4-OMe                | 4-OMe  | 5        | 95                       |
| 13    | 4-OMe                | 4-COMe | 48       | 100                      |

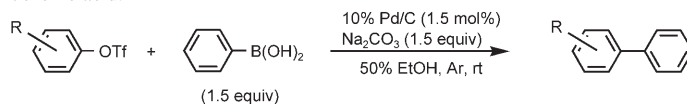
[a] Yield of the isolated product.

action of electron-rich aryl boronic acid, such as 2-, 3-, or 4-methoxyphenylboronic acids, proceeded quite efficiently relative to nonsubstituted phenylboronic acids. On the other hand, a phenylboronic acid with an electron-withdrawing group (COMe) showed lower reactivity, and the reaction with 4-bromoanisole could not go to completion in the case of  $\text{NaHCO}_3$  and  $\text{Na}_2\text{CO}_3$ , even after 48 h (Tables 5 and 6, entries 13), whereas the use of  $\text{Na}_3\text{PO}_4$  as a base gave a gratifying result (Table 7, entry 13). Hence, the combination of  $\text{Na}_3\text{PO}_4$  and 50% *i*PrOH indicates higher reactivity for the Pd/C-catalyzed Suzuki–Miyaura coupling reaction, which may be attributed to the difference in basicity.<sup>[2d,15]</sup>

**Suzuki–Miyaura coupling reactions using aryl triflates:** We further explored the application of the present method to the coupling of aryl triflates. Aryl triflates are important starting materials for metal-catalyzed coupling reactions because they are readily prepared from phenol derivatives,<sup>[16]</sup> although they are known to be less reactive than the corresponding iodides and bromides in the Suzuki–Miyaura coupling reactions.<sup>[17]</sup> Buchecker and co-workers reported a Pd/C-catalyzed cross-coupling reaction of aryl triflates and phenylboronic acids in the presence of  $\text{Na}_2\text{CO}_3$  with LiCl as an additive in DMF at 80°C.<sup>[8j]</sup> However, only two applicable examples of aryl triflates were indicated, and both the additive and heat were required for the reaction to proceed.

It was surprising that diverse aryl triflates with either an electron-withdrawing or -donating substituent on the aromatic ring smoothly underwent the coupling reaction in high yields under our reaction conditions (at room temperature) without significant hydrolysis of the aryl triflate even under alcoholic and/or aqueous basic reaction conditions, whereas extension of the reaction times relative to those needed for the aryl bromides was necessary for completion (Table 8, entries 3–8). Recently, Linden and co-workers used the Suzuki–Miyaura reaction between aryl boronic acids and 5-bromo-1-indanone as a key reaction to synthesize 6-aryl-8*H*-

Table 8. Pd/C-catalyzed cross-coupling between aryl triflates and phenylboronic acid.



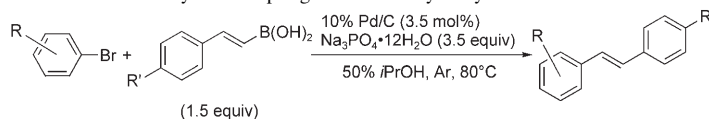
| Entry | R                    | Time [h] | Yield [%] <sup>[a]</sup> |
|-------|----------------------|----------|--------------------------|
| 1     | H                    | 24       | 97                       |
| 2     | 4-OMe                | 48       | 90                       |
| 3     | 4-CO <sub>2</sub> Me | 24       | 91                       |
| 4     | 4-NO <sub>2</sub>    | 24       | 95                       |
| 5     | 4-CHO                | 24       | 95                       |
| 6     | 4-CN                 | 24       | 98                       |
| 7     | 4-F                  | 24       | 92                       |
| 8     | 4-Cl                 | 24       | 93                       |
| 9     | 4-NHAc               | 48       | 90                       |
| 10    |                      | 48       | 78                       |
| 11    |                      | 48       | 93                       |

[a] Yield of the isolated product.

indeno[1,2-*d*]thiazol-2-ylamines for the screening of A1 adenosine receptor agonists.<sup>[18]</sup> Our procedure using 5-trifluoromethanesulfonyloxy-1-indanone (Table 8, entry 11) would be an alternative for the synthesis of such analogues. To our best of our knowledge, this is the first heterogeneous Pd/C-catalyzed Suzuki–Miyaura reaction using aryl triflates that requires neither heating nor the addition of ligands.

**Application to aryl vinyl boronic acids:** We further attempted to expand this method to the coupling of aryl vinyl boronic acid with aryl bromides. Although aryl vinyl boronic acids usually show lower reactivity in the coupling reaction relative to aryl boronic acids, various aryl vinyl boronic acids were applicable to the reaction conditions ( $\text{Na}_3\text{PO}_4$  in 50% *i*PrOH at 80°C). The substituents on the aromatic ring of aryl vinyl boronic acids (*R'* in Table 9) did not affect the reaction progress (Table 9, entries 1 and 3–6), although the reaction took longer to go to completion with the use of electron-rich 4-bromoanisole (*R*=OMe) as a substrate (Table 9, entry 2). It should be noted that no isomerization

Table 9. Suzuki–Miyaura coupling of various aryl vinyl boronic acids.



| Entry | R                 | R' | Time [h] | Yield [%] <sup>[a]</sup> |
|-------|-------------------|----|----------|--------------------------|
| 1     | 4-NO <sub>2</sub> | H  | 24       | 89                       |
| 2     | 4-OMe             | H  | 48       | 80                       |
| 3     | 2-Me              | H  | 24       | 85                       |
| 4     | 4-NO <sub>2</sub> | Me | 24       | 91                       |
| 5     | 4-NO <sub>2</sub> | Cl | 24       | 82                       |
| 6     | 4-NO <sub>2</sub> | Ph | 24       | 87                       |

[a] Yield of the isolated product.

of the corresponding *trans*-olefin was observed and the obtained coupling products were only *E* isomers, whereas significant isomerization of the generated alkenes by a homogeneous Pd complex and ligand-catalyzed Suzuki–Miyaura coupling reaction using aryl vinyl boronic acids at elevated temperatures (60–100 °C) were reported by Buchwald and co-workers.<sup>[3]</sup> This example is the first to be reported of a heterogeneous Pd/C-catalyzed coupling reaction of aryl vinyl boronic acids with aryl bromides.

**The use of wet Pd/C under aerobic conditions:** The use of dry-type Pd/C is quite common at the laboratory level because of its easy handling for weight and allowance for compact storage. However, it is problematic in a large-scale reaction, such as industrial production because of its pyrophoric and static properties. Furthermore, complete replacement of air with an inert gas is absolutely vital to avoid ignition, but this process is tedious and painstaking. Therefore, the use of wet-type Pd/C under aerobic conditions is preferred to establish a safety-conscious reaction process. Considering the facile use of the present method with a high safety level, we attempted to apply wet-type Pd/C to the reaction. Consequently, wet-type Pd/C (containing 50 weight % of water) catalyzed the Suzuki–Miyaura coupling reaction under aerobic conditions to give approximately equivalent results the use of dry-type Pd/C under an argon atmosphere without the loss of activity and production of by-products (compare Table 10 with Table 6, entries 1, 4, and 9).<sup>[19]</sup>

Table 10. Application of wet-type Pd/C to the Suzuki–Miyaura coupling reaction under aerobic conditions.

| $\text{R}-\text{C}_6\text{H}_4-\text{Br} + \text{C}_6\text{H}_5-\text{B}(\text{OH})_2 \xrightarrow[\text{50\% EtOH, Air, rt}]{\text{wet 10\% Pd/C (1.5 mol\%)}, \text{Na}_2\text{CO}_3 (1.5 \text{ equiv})} \text{R}-\text{C}_6\text{H}_4-\text{C}_6\text{H}_5$ <p style="text-align: center;">(1.1 equiv)</p> |                   |          |                          |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------|----------|--------------------------|
| Entry                                                                                                                                                                                                                                                                                                          | R                 | Time [h] | Yield [%] <sup>[a]</sup> |
| 1                                                                                                                                                                                                                                                                                                              | 4-NO <sub>2</sub> | 3        | 97                       |
| 2                                                                                                                                                                                                                                                                                                              | 2-Me              | 3.5      | 81                       |
| 3                                                                                                                                                                                                                                                                                                              | 4-OMe             | 24       | 93                       |

[a] Yield of the isolated product.

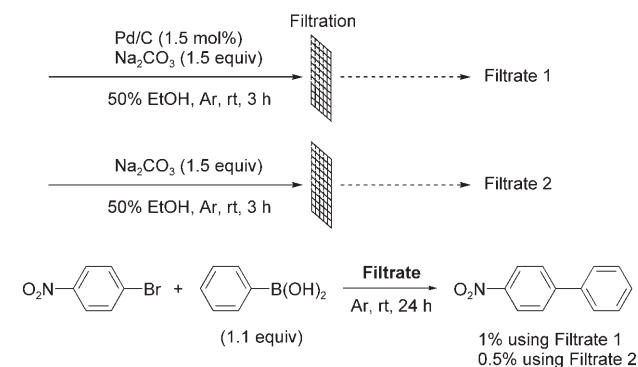
**Reuse of Pd/C:** The reusability of Pd/C is a great advantage in the cost reduction of process chemistry. We examined the reuse of Pd/C in the coupling reaction using 4-bromonitrobenzene and phenylboronic acids as substrates in the presence of Na<sub>2</sub>CO<sub>3</sub> in 50 % EtOH at room temperature. Pd/C could be reused successfully until the fifth run without either significant loss of yield or extension of the reaction time (Table 11). There are some examples of investigations into the reuse of Pd/C in the Suzuki–Miyaura coupling reaction in which the gradual decrease in yields with reuse was reported in most cases.<sup>[8a,g,10]</sup> In our heterogeneous Pd/C-catalyzed coupling reaction, the dissolved (leached) palladium metal in the solvent might work as the catalytically active species.<sup>[20]</sup>

Table 11. Investigation in the reuse of Pd/C.

| $\text{O}_2\text{N}-\text{C}_6\text{H}_4-\text{Br} + \text{C}_6\text{H}_5-\text{B}(\text{OH})_2 \xrightarrow[\text{50\% EtOH, Ar, rt}]{\text{10\% Pd/C (1.5 mol\%)}, \text{Na}_2\text{CO}_3 (1.5 \text{ equiv})} \text{O}_2\text{N}-\text{C}_6\text{H}_4-\text{C}_6\text{H}_5$ <p style="text-align: center;">(1.1 equiv)</p> |     |          |                          |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----|----------|--------------------------|
| Entry                                                                                                                                                                                                                                                                                                                         | Run | Time [h] | Yield [%] <sup>[a]</sup> |
| 1                                                                                                                                                                                                                                                                                                                             | 1   | 4        | 98                       |
| 2                                                                                                                                                                                                                                                                                                                             | 2   | 4        | 99                       |
| 3                                                                                                                                                                                                                                                                                                                             | 3   | 4        | 98                       |
| 4                                                                                                                                                                                                                                                                                                                             | 4   | 5        | 97                       |
| 5                                                                                                                                                                                                                                                                                                                             | 5   | 5        | 98                       |

[a] Yield of the isolated product; an average of two independent reuse tests.

To confirm the real active catalyst in our reaction, 10 % Pd/C was pretreated with Na<sub>2</sub>CO<sub>3</sub> in 50 % EtOH under argon for 3 hours and passed through a 0.45-μm membrane filter, and the filtrate (Scheme 1, filtrate 1) was employed



Scheme 1. The effect of leached palladium species on the present Suzuki–Miyaura coupling reaction

for the cross-coupling reaction between 4-bromonitrobenzene and phenylboronic acid. However, only 1 % of coupled product was detected by <sup>1</sup>H NMR spectroscopic analysis. When the filtrate prepared without Pd/C (filtrate 2) was used for the same reaction, the formation of the “cross-coupled” product was also observed in 0.5 % yield, thus indicating that aromatic nucleophilic substitution took place to a small extent. Furthermore, the leached palladium in either the filtrate of the reaction mixture of the Pd/C-catalyzed Suzuki–Miyaura reaction of 4-bromonitrobenzene with phenylboronic acid using Na<sub>2</sub>CO<sub>3</sub> in 50 % EtOH or filtrate 1 in Scheme 1 was not detected within the limits of the assay (< 1 ppm) by analysis with inductively coupled plasma atomic emission spectrometry (ICP-AES).<sup>[21]</sup> These results strongly suggest that the Pd/C-catalyzed Suzuki–Miyaura reaction virtually proceeds in heterogeneous media, although the process of the “release and capture” of the Pd metal catalyst on the activated carbon might take place.<sup>[20]</sup>



## Conclusion

In conclusion, we have developed a ligand-free and heterogeneous Pd/C-catalyzed Suzuki–Miyaura coupling reaction under mild reaction conditions. Aryl bromides underwent the coupling reaction with various aryl boronic acids in good-to-high yields at room temperature. Less reactive aryl triflates were also applicable in this method and resulted in high yields without hydrolysis. Furthermore, the reaction of aryl vinyl boronic acids with aryl bromides afforded the *trans*-stilbene derivatives as only a single stereoisomer. The use of wet-type Pd/C in an air atmosphere and the reusability of Pd/C will lead to industrial application. It is noteworthy that the palladium metal was hardly leached into the solution. This methodology will provide a facile, efficient, and environmentally friendly process for the Suzuki–Miyaura coupling reaction because of its wide applicability to various substrates, the use of less toxic reagents, and mild reaction conditions.

## Experimental Section

**General methods:** Unless otherwise stated, all the reactions were carried out under argon and commercially obtained materials were used without further purification. Aryl bromides and boronic acids were purchased from Aldrich Chemical Co., Alfa Aesar, or Tokyo Chemical Industry Co. Aryl triflates were prepared according to a known procedure.<sup>[22]</sup> Pd/C was purchased from Acros Organics, Aldrich Chemical Co., Kishida Chemical Co., Merck, Nacalai Tesque, and Wako Pure Chemical Industries or received as a gift from N. E. Chemcat Co. The bases and solvents were purchased from Hayashi Pure Chemical Industries, Kanto Chemical Co., Nacalai Tesque, Tokyo Chemical Industry Co., or Wako Pure Chemical Industries.

**General procedure for the Suzuki–Miyaura cross-coupling reaction using the NaHCO<sub>3</sub>/MeOH system:** Aryl bromide (500 μmol), aryl boronic acid (550 μmol), NaHCO<sub>3</sub> (147 mg, 1.75 mmol), 10% Pd/C (8.0 mg, 7.50 μmol), and MeOH (2 mL) were added to a test tube with a stirring bar, and the system was sealed with a septum. The air inside was replaced with argon (balloon) by three vacuum/argon cycles, and the reaction mixture was stirred at room temperature. After a certain period, the reaction mixture was diluted with H<sub>2</sub>O (10 mL) and Et<sub>2</sub>O (10 mL) and passed through a membrane filter (Millipore, Millex-LH, 0.45 μm). The filtrate was separated into two layers and the aqueous layer was extracted with Et<sub>2</sub>O (2 × 10 mL). The combined organic layers were washed with brine (10 mL), dried over MgSO<sub>4</sub>, and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (*n*-hexane/EtOAc, 50:1) to give the corresponding biaryl compound.

**General procedure for the Suzuki–Miyaura cross-coupling reaction using the Na<sub>2</sub>CO<sub>3</sub>/50% EtOH system:** Pd/C (10%; 8.0 mg, 7.50 μmol), Na<sub>2</sub>CO<sub>3</sub> (79.5 mg, 750 μmol), and H<sub>2</sub>O/EtOH (2 mL, 1:1) were used instead of NaHCO<sub>3</sub> (1.75 mmol) and MeOH (2 mL) in the above procedure.

**General procedure for the Suzuki–Miyaura cross-coupling reaction using the Na<sub>3</sub>PO<sub>4</sub>/50% iPrOH system:** Pd/C (10%; 2.7 mg, 2.50 μmol), Na<sub>3</sub>PO<sub>4</sub>·12H<sub>2</sub>O (665 mg, 1.75 mmol), and H<sub>2</sub>O/iPrOH (2 mL, 1:1) were used instead of 10% Pd/C (8.0 mg, 7.50 μmol), NaHCO<sub>3</sub> (1.75 mmol), and MeOH (2 mL) in the above procedure.

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