

Article

# Development of Titanium Dioxide-Supported Pd Catalysts for Ligand-Free Suzuki–Miyaura Coupling of Aryl Chlorides

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**Abstract:** The catalyst activities of various heterogeneous palladium catalysts supported by anatase-, rutile- and brookite-type titanium oxide for ligand-free Suzuki–Miyaura cross-coupling reactions of aryl chlorides were evaluated. Palladium acetate [Pd(OAc)<sub>2</sub>], supported on anatase-type titanium oxide (TiO<sub>2</sub>) via acetonitrile solution impregnation process without reduction [Pd/TiO<sub>2</sub> (anatase-type)], demonstrated the highest catalyst activity in comparison to those of other titanium oxide (rutile- or brookite-type) supported Pd(OAc)<sub>2</sub> without reduction and reduced Pd/TiO<sub>2</sub> (anatase-type) [Pd(red)/TiO<sub>2</sub> (anatase-type)]. Various aryl chloride and bromide derivatives were smoothly coupled with arylboronic acids including heteroarylboronic acids in the presence of 5–10 mol% Pd/TiO<sub>2</sub> (anatase-type) without the addition of any ligands. Although the fresh Pd/TiO<sub>2</sub> (anatase-type) catalyst was surprisingly comprised of ca. 1:2 mixture of palladium(II) and palladium(0) species according to X-ray photoelectron spectroscopy (XPS), in spite of no reduction process, significant further increment of palladium(0) species was observed during the Suzuki–Miyaura coupling reaction, and Pd/TiO<sub>2</sub> (anatase-type) was converted into a catalyst, which contained palladium(0) species as the main component [ca. 1:5 mixture of palladium(II) and palladium(0) species]. Therefore, the reduction via the electron donation process to the palladium(II) species may have occurred during the reaction on anatase-type titanium oxide.

**Keywords:** Suzuki–Miyaura reaction; palladium; heterogeneous catalyst; titanium oxide; anatase titania; aromatic chloride

## 1. Introduction

Palladium (Pd)-catalyzed Suzuki–Miyaura coupling reaction [1–12] of aryl halides and arylboronic acid derivatives is one of the most reliable and useful synthetic methods for constructing biaryl derivatives as fundamental skeletons of various biologically active compounds [2,4,6], pharmaceuticals [2,4] and functional materials [5,6]. Various heterogeneous catalysts, including heterogeneous Pd catalysts, have been developed from the perspective of sustainability and process chemistry based on their advantages, such as recoverability, reusability and low residual metal

property [7–60]. Heterogeneous Pd-catalyzed ligand-free Suzuki–Miyaura coupling reactions have attracted attention as environmentally friendly, metal-contamination-free (or low) and cost-effective methods over the past couple of decades [7–12,17–19]. Particularly, aryl chlorides, which are easily available and less expensive organic compounds in comparison with aryl iodides and bromides, are preferred substrates for the Suzuki–Miyaura coupling reaction, although special ingenuity is necessary for the effective activation of the low-reactive carbon-chloride bond. Therefore, various heterogeneous catalysts have been developed to achieve the heterogeneously catalyzed Suzuki–Miyaura coupling reaction using aryl chlorides [21–40].

Incidentally, the supports for the heterogeneous Pd catalysts are roughly categorized into two. One is ligand-like nitrogen- [21–24,39,40] or phosphine- [25–30] substituted polystyrene-polymers for the purpose of stabilizing the Pd-arene complexes, and/or the enhancement of the catalyst activity based on the coordination effect of the substituent. Furthermore, we developed heterogeneous Pd catalysts immobilized on a ligand-like tertiary amine polystyrene-divinylbenzene-based polymer for the ligand-free Suzuki–Miyaura coupling reaction of aryl chlorides [39,40]. The other category is polymers [34] or inorganics [31–33,35–50] without additional and coordinable functionalities, such as activated carbon [31–33], polystyrene [34], metal-organic frameworks [35], polyoxometalate [36] and titanium dioxide (TiO<sub>2</sub>) [42–50].

Some TiO<sub>2</sub>-supported Pd catalysts have been applied to various organic and inorganic reactions such as the Suzuki–Miyaura reaction [42–50], hydrogenation [51–58] and Heck reaction [59]. However, the effect on the catalyst activity, depending on the difference of the TiO<sub>2</sub> crystal forms of TiO<sub>2</sub>-supported Pd catalysts toward cross-coupling reactions, has never been systematically evaluated, except for a report related to the oxidative homo coupling reaction of 4-methylpyridines in the presence of Pd oxide-loaded TiO<sub>2</sub> (PdO/TiO<sub>2</sub>) as a catalyst [60].

In this study, we prepared and investigated the physical properties of the anatase-, rutile- and brookite-type TiO<sub>2</sub>-supported Pd catalysts by using X-ray photoelectron spectroscopy (XPS) and transmission electron microscopy (TEM), and comprehensively investigated the effect on the catalyst activities depending on the crystal form of TiO<sub>2</sub> to the TiO<sub>2</sub>-supported Pd-catalyzed ligand-free Suzuki–Miyaura coupling reaction. Consequently, the anatase-type TiO<sub>2</sub>-supported Pd catalyst was found to have quite an efficient catalyst activity toward the Suzuki–Miyaura coupling reaction, including the coupling of aromatic chlorides due to the quite highly distributed small Pd nanoparticles (1–2 nm) on the anatase-type TiO<sub>2</sub>.

## 2. Results and Discussion

Initially, nine kinds of heterogeneous TiO<sub>2</sub>-supported Pd catalysts (Table 1, Categories Cat. A–I) were prepared in a manner analogous to the previously established preparation method in our laboratory for a chelate resin-supported heterogeneous Pd catalyst (7% Pd/WA30) [39–41]. Pd(OAc)<sub>2</sub>, which was 5 wt% of Pd metal equivalent of the usage of TiO<sub>2</sub>, was embedded on the colorless anatase-, rutile- or brookite-type TiO<sub>2</sub> powder by gentle stirring in acetonitrile (MeCN) or ethyl acetate (EtOAc) at 25 °C for 4 days under argon atmosphere. Colorless TiO<sub>2</sub> powders gradually turned to light yellow due to the interaction between Pd(OAc)<sub>2</sub> and TiO<sub>2</sub>; subsequently, the resulting insoluble powder was filtered, washed with EtOAc and H<sub>2</sub>O and dried in vacuo to afford a light yellowish powder (Entries 4–9, Pd/TiO<sub>2</sub>, Cat. D–I). The Pd content in Pd/TiO<sub>2</sub> (Cat. A–D and F–I) and Pd/TiO<sub>2</sub> (Cat. E) were determined to be approximately 5 wt% and 4 wt% by the atomic absorption analysis of the residual Pd species in the collected organic and aqueous filtrates, respectively.

The filtered Pd/TiO<sub>2</sub> prepared in MeCN suspension (Entry 4, Cat. D, anatase-type) was stirred at 25 °C for 24 h in H<sub>2</sub>O accompanied by hydrazine monohydrate or sodium borohydride, or in EtOAc under hydrogen atmosphere. The filtered resulting powder was sequentially washed with EtOAc and H<sub>2</sub>O, and dried under reduced pressure to afford grayish white Pd(red)/TiO<sub>2</sub> catalysts (Entries 1–3, Cat. A–C, anatase-type).

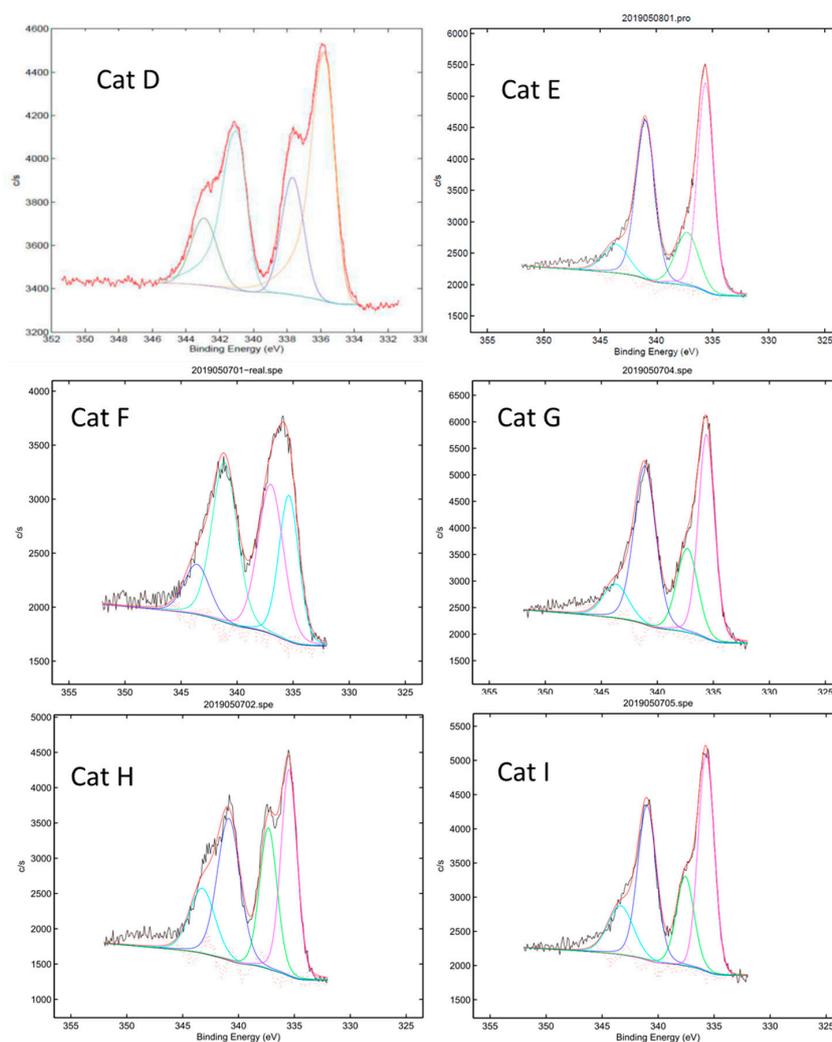
**Table 1.** Preparation of Pd/TiO<sub>2</sub> and Pd(red)/TiO<sub>2</sub>.

Entry	Solvent	Reductant of Pd Catalyst	Pd Catalyst	Color
1	MeCN	NH <sub>2</sub> NH <sub>2</sub> •H <sub>2</sub> O <sup>a</sup>	5% Pd(red)/TiO <sub>2</sub> (Cat. A, anatase-type)	Grayish white
2	MeCN	NaBH <sub>4</sub> <sup>a</sup>	5% Pd(red)/TiO <sub>2</sub> (Cat. B, anatase-type)	Grayish white
3	MeCN	H <sub>2</sub> <sup>b</sup>	5% Pd(red)/TiO <sub>2</sub> (Cat. C, anatase-type)	Grayish white
4	MeCN	–	5% Pd/TiO <sub>2</sub> (Cat. D, anatase-type)	Light yellow
5	EtOAc	–	4% Pd/TiO <sub>2</sub> (Cat. E, anatase-type)	Light yellow
6	MeCN	–	5% Pd/TiO <sub>2</sub> (Cat. F, rutile-type)	Light yellow
7	EtOAc	–	5% Pd/TiO <sub>2</sub> (Cat. G, rutile-type)	Light yellow
8	MeCN	–	5% Pd/TiO <sub>2</sub> (Cat. H, brookite-type)	Light yellow
9	EtOAc	–	5% Pd/TiO <sub>2</sub> (Cat. I, brookite-type)	Light yellow

<sup>a</sup> The reduction of Pd/TiO<sub>2</sub> (Cat. D, anatase-type) was carried out in H<sub>2</sub>O. <sup>b</sup> The reduction of Pd/TiO<sub>2</sub> (Cat. D, anatase-type) was carried out in EtOAc.

The XPS analysis of the Pd/TiO<sub>2</sub> catalysts (Cat. E–I) prepared without reduction processes surprisingly indicated an approximately 2:1 mixture of Pd(0) species and Pd(II) ions (Figure 1). The characteristic peaks of Pd3d<sub>3/2</sub> and Pd3d<sub>5/2</sub> and the area % of Pd(0) species and Pd(II) ions are shown in the Supporting Information (Figure S1).

The catalyst activities of various TiO<sub>2</sub>-supported Pd catalysts (Cat. A–I) for the Suzuki–Miyaura coupling reaction using 4'-chloroacetophenone (**1a**) and phenylboronic acid (**2a**) as substrates were evaluated. A portion of each of the catalysts (5 mol%) was added to the mixture of **1a** (0.25 mmol), **2a** (1.5 equiv) and cesium carbonate (Cs<sub>2</sub>CO<sub>3</sub>; 2.0 equiv) in dimethylacetamide (DMA; 1 mL) and stirred at 600 rpm for 24 h at 80 °C under argon atmosphere (Table 2, Entries 1–10). While the reduced TiO<sub>2</sub>-supported Pd catalysts [Pd(red)/TiO<sub>2</sub>, (Cat. A–C, anatase-type)] using hydrazine monohydrate, sodium borohydride or hydrogen gas indicated less catalyst efficiencies for the Suzuki–Miyaura coupling reaction (Entries 1–3), the use of Pd/TiO<sub>2</sub> (Cat. D and E, anatase-type), without the reduction process, afforded biaryls (**3a**) in relatively good conversion ratios (Entries 4 and 5). The catalyst activities of other Pd/TiO<sub>2</sub> catalysts without reduction process (Cat. F and G, rutile-type, and Cat. I, brookite-type) indicated low to moderate conversion ratios (Entries 6–8), except for Cat. H (brookite-type), which had a good conversion ratio (65%, Entry 9). **1a** was completely converted to the corresponding 4-acetylbiphenyl (**3a**) in the presence of 5% Pd/TiO<sub>2</sub> (Cat. D, anatase-type, 5 mol%) by enhancing the stirring speed to 1000 rpm from 600 rpm (Entry 10), while the coupling reaction was never completed using 5% Pd/TiO<sub>2</sub> (Cat. I, brookite-type, 5 mol%) at 1000 rpm (Entry 11). Based on these results, the catalytic activity depends in part on the difference of TiO<sub>2</sub> crystal forms based on the different interaction properties between Pd species and TiO<sub>2</sub> crystal forms, and the catalytic activities are approximately catalysts D and E (anatase type) > catalysts F and G (rutile type) > catalysts H and I (brookite type) in this order [61–63]. Therefore, 5% Pd/TiO<sub>2</sub> (Cat. D, anatase-type) indicated quite a high catalyst activity toward the ligand-free Suzuki–Miyaura coupling reaction of aryl chlorides.



**Figure 1.** X-ray photoelectron spectroscopy (XPS) spectra of 5% Pd/TiO<sub>2</sub> (Cat. D and F–I) and 4% Pd/TiO<sub>2</sub> (Cat. E).

**Table 2.** Catalyst activity of TiO<sub>2</sub>-supported Pd catalysts for the Suzuki–Miyaura coupling reaction of 4'-chloroacetophenone (**1a**) with phenylboronic acid (**2a**).<sup>a</sup>

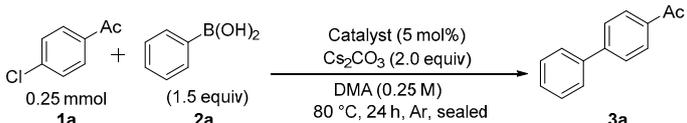
Reaction conditions: Catalyst (5 mol%), Cs<sub>2</sub>CO<sub>3</sub> (2.0 equiv), DMA (0.25 M), 80 °C, 24 h, 600 rpm, Ar, sealed.

Entry	Catalyst	Ratio of <b>1a</b> and <b>3a</b> <sup>b</sup>
1	5% Pd(red)/TiO <sub>2</sub> (Cat. A, anatase-type)	70:30
2	5% Pd(red)/TiO <sub>2</sub> (Cat. B, anatase-type)	96:4
3	5% Pd(red)/TiO <sub>2</sub> (Cat. C, anatase-type)	89:11
4	5% Pd/TiO <sub>2</sub> (Cat. D, anatase-type)	35:65
5	4% Pd/TiO <sub>2</sub> (Cat. E, anatase-type)	38:62
6	5% Pd/TiO <sub>2</sub> (Cat. F, rutile-type)	63:37
7	5% Pd/TiO <sub>2</sub> (Cat. G, rutile-type)	56:44
8	5% Pd/TiO <sub>2</sub> (Cat. H, brookite-type)	49:51
9	5% Pd/TiO <sub>2</sub> (Cat. I, brookite-type)	35:65
10	5% Pd/TiO <sub>2</sub> (Cat. D, anatase-type)	0:100 (99) <sup>c,d</sup>
11	5% Pd/TiO <sub>2</sub> (Cat. I, brookite-type)	32:68 <sup>c</sup>

<sup>a</sup> Reactions were carried out on a 0.25 mmol scale in 1 mL of dimethylacetamide (DMA). <sup>b</sup> Ratios were determined by GC/MS (JEOL JMS Q1000GC Mk II Quad GC/MS). <sup>c</sup> The reaction mixture was stirred at 1000 rpm. <sup>d</sup> The isolated yield was indicated in parenthesis.

The catalyst activity of the 5% Pd/TiO<sub>2</sub> (Cat. **D**, anatase-type) was compared with other heterogeneous and homogeneous Pd catalysts (Table 3). The quantitative conversion of **1a** could be achieved by using 5 mol% of 7% Pd/WA30 developed in our research group [39–41], although high speed and vigorous stirring (1600 rpm) conditions were required (Entry 2). On the other hand, 10% Pd on carbon (Pd/C) (5 mol%) indicated ineffective catalyst activity (Entry 3). Furthermore, some homogeneous Pd catalysts are known to have high catalyst activity in Suzuki–Miyaura coupling reaction [64,65], however, the use of 5 mol% of Pd(OAc)<sub>2</sub> as a homogeneous catalyst gave only moderate conversion (Entry 4). Therefore, 5% Pd/TiO<sub>2</sub> (Cat. **D**) is suitable as an active catalyst for the Suzuki–Miyaura coupling reaction for aryl chlorides.

**Table 3.** Comparison of the catalyst activity. <sup>a</sup>

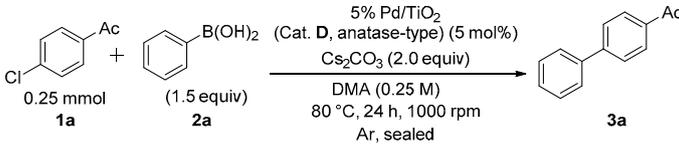


Entry	Catalyst	Ratio of 1a and 3a
1	5% Pd/TiO <sub>2</sub> (Cat. <b>D</b> , anatase-type)	0:100 (99) <sup>b,c,d</sup>
2	7% Pd/WA30	0:100 <sup>e</sup> [35]
3	10% Pd/C	97:3 <sup>e</sup> [35]
4	Pd(OAc) <sub>2</sub>	57:43 <sup>a,b,c</sup>

<sup>a</sup> Reactions were carried out on a 0.25 mmol scale in 1 mL of DMA. <sup>b</sup> Ratio was determined by GC/MS (JEOL JMS Q1000GC Mk II Quad GC/MS). <sup>c</sup> The reaction mixture was stirred at 1000 rpm. <sup>d</sup> The isolated yield was indicated in parenthesis. <sup>e</sup> The reaction mixture was stirred at 1600 rpm under Ar and the product ratio was determined by <sup>1</sup>H NMR using 1,4-dioxane added as an internal standard.

Next, we investigated the effects of the reaction temperature and atmospheric conditions in a test tube as a reaction vessel on 5% Pd/TiO<sub>2</sub> (Cat. **D**, anatase-type)-catalyzed Suzuki–Miyaura coupling reaction (Table 4). The reaction did not proceed at 25 °C (Entry 2). While the reaction quantitatively proceeded in a test tube sealed with a septum under argon atmosphere at 80 °C for 24 h in Entry 1, the reaction efficiency was drastically decreased under atmospheric exposure (Entry 3). Therefore, the elimination of oxygen from the reaction vessel is strongly required for the Pd/TiO<sub>2</sub> (Cat. **D**, anatase-type)-catalyzed ligand-free Suzuki–Miyaura coupling reaction of aryl chloride. Further detailed optimization of the base, solvent and reaction time are indicated in the Supporting Information (Tables S1–S3).

**Table 4.** Effect of various reaction conditions.

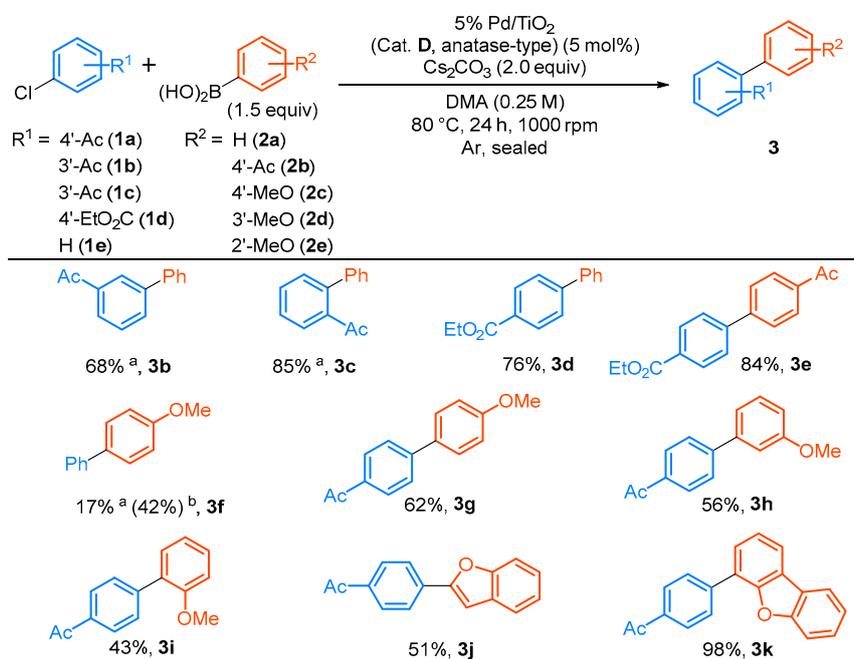


Entry	Gas/Reaction Vessel	Ratio of 1a and 3a <sup>a</sup>
1	Ar/sealed vessel	0:100 (99) <sup>b</sup>
2	Ar/sealed vessel	100:0 <sup>c</sup>
3	Air/sealed vessel	90:10

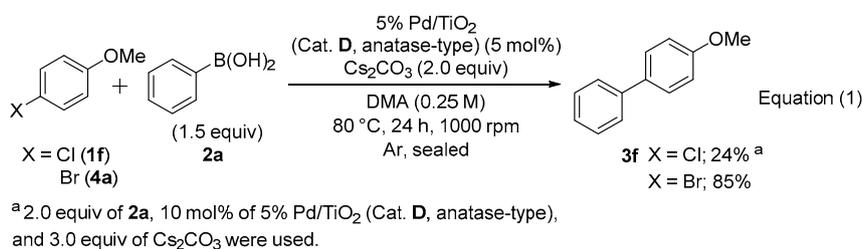
<sup>a</sup> The reaction was carried out in a test tube (the internal volume of 18 mL) tightly sealed with a septum under each atmospheric conditions (Ar and Air) and the ratio was determined by <sup>1</sup>H NMR using 1,4-dioxane added as an internal standard. <sup>b</sup> The isolated yield was indicated in parenthesis. <sup>c</sup> The reaction was performed at 25 °C.

The substrate applicability was investigated using 5 mol% of 5% Pd/TiO<sub>2</sub> (Cat. **D**, anatase-type) and Cs<sub>2</sub>CO<sub>3</sub> (2 equiv) in DMA at 80 °C for 24 h at 1000 rpm (Scheme 1). Aryl chlorides bearing an electron withdrawing group such as Ac and EtO<sub>2</sub>C on the aromatic ring (**1a–1d**) efficiently reacted

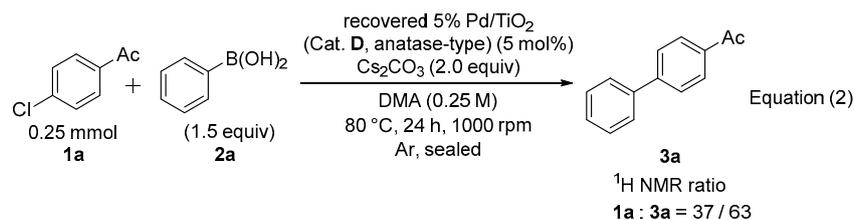
with **2a** or 4-acetylphenylboronic acid (**2b**) regardless of their substitution pattern (**3b–3e**). Although the coupling of chlorobenzene (**1e**) with 4-methoxyphenylboronic acid (**2c**) was inefficient and only a 17% yield of **3f** was obtained, the reaction efficiency was significantly improved using 2.0 equiv of KO<sup>t</sup>Bu instead of Cs<sub>2</sub>CO<sub>3</sub>. Furthermore, **1a** was reacted with 4′-, 3′- or 2′-methoxyphenylboronic acid (**2c**, **2d**, or **2e**) in moderate to good yields (**3g**, **3h**, or **3i**). The direct formation of heterobiaryl skeletons is important for the construction of partial scaffolds of biologically active compounds [66–72] and functional materials [73,74]. The coupling of 4′-chloroacetophenone (**1a**) with heteroarylboronic acid derivatives afforded the corresponding heterobiaryl derivatives (**3j** and **3k**) in moderate to excellent yields. Although **3f** was obtained in a relatively low yield (24%) using 4-chloroanisole (**1f**) possessing an electron donating methoxy group on the aromatic ring even by the increased usage of 5% Pd/TiO<sub>2</sub> (10 mol%, Cat. **D**, anatase-type), phenylboronic acid (**2a**, 2.0 equiv) and Cs<sub>2</sub>CO<sub>3</sub> (3.0 equiv), the use of 4′-methoxyphenylbromide (**4a**) as an aryl bromide afforded a high yield (85%) of **3e** under the original reaction conditions [5% Pd/TiO<sub>2</sub> (Cat. **D**, anatase-type, 5 mol%), **2a** (1.5 equiv) and Cs<sub>2</sub>CO<sub>3</sub> (2.0 equiv), Equation (1)].



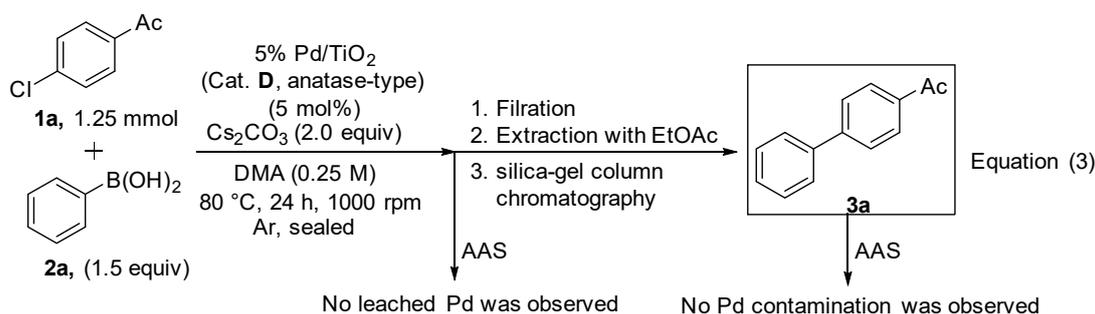
**Scheme 1.** Scope and limitations of the Suzuki–Miyaura coupling reactions. <sup>a</sup> 2.0 equiv of an arylboronic acid, 10 mol% of 5% Pd/TiO<sub>2</sub> (Cat. **D** anatase-type) and 3.0 equiv of Cs<sub>2</sub>CO<sub>3</sub> were used. <sup>b</sup> 2.0 equiv of KO<sup>t</sup>Bu was used instead of Cs<sub>2</sub>CO<sub>3</sub>.



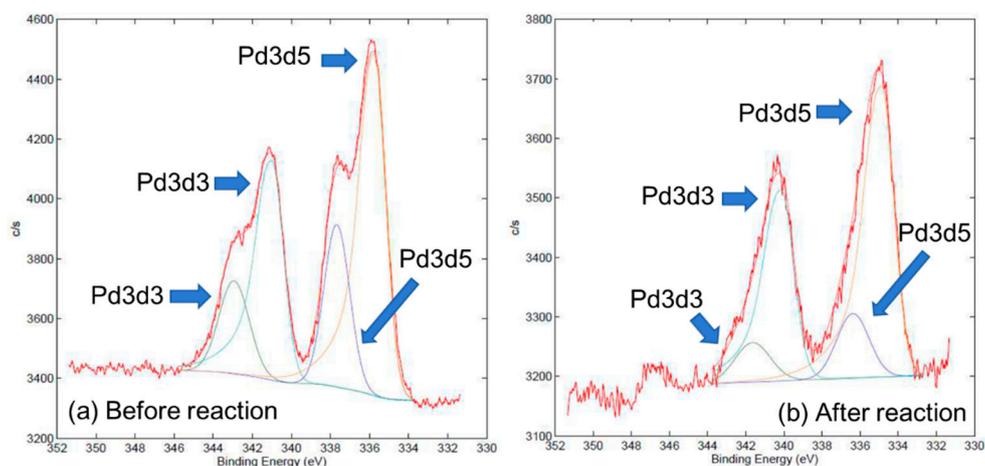
Although one of the advantages of the heterogeneous catalyst is reusability, the catalyst efficiency of 5% Pd/TiO<sub>2</sub> (Cat. **D**, anatase-type) recovered after the first Suzuki–Miyaura coupling reaction using **1a** and **2a** significantly decreased, and the coupling reaction was never completed at 80 °C even after 24 h [Equation (2)].



The Pd leaching behavior into the Suzuki–Miyaura coupling reaction medium and the trace Pd contamination in the coupling product after the purification process were examined using atomic absorption spectrometry [AAS, Equation (3)]. As a result, Pd species were never observed in both the reaction media after reaction and the coupling product **3a** after purification including filtration, extraction with EtOAc and silica-gel column chromatography.

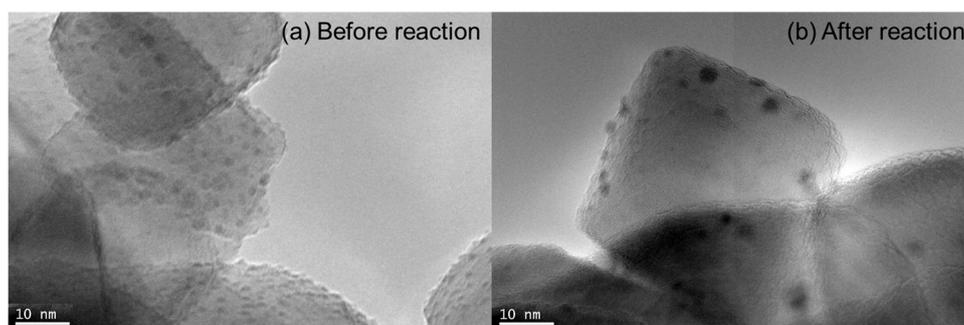


Although the fresh 5% Pd/TiO<sub>2</sub> (Cat. **D**, anatase-type) without any reduction processes during the preparation amazingly consisted of ca. 1:2 mixture of Pd(II) ion (characteristic peaks at ca. 342.9 and 337.7 eV for Pd3d<sub>3/2</sub> and Pd3d<sub>5/2</sub>) and Pd(0) species (characteristic peaks at ca. 341.0 and 335.7 eV for Pd3d<sub>3/2</sub> and Pd3d<sub>5/2</sub>) according to XPS (Figure 2a), a significant increment in Pd(0) species (characteristic peaks at ca. 340.1 and 334.9 eV for Pd3d<sub>3/2</sub> and Pd3d<sub>5/2</sub>) was observed and the recovered 5% Pd/TiO<sub>2</sub> (Cat. **D**, anatase-type) was composed of ca. 1:5 mixture of Pd(II) ion (characteristic peaks at ca. 341.6 and 336.4 eV for Pd3d<sub>3/2</sub> and Pd3d<sub>5/2</sub>) and Pd(0) species after the coupling reaction [Figure 2b]. From these results, Pd(II) species might be reduced by the significant electron donation during the Suzuki–Miyaura coupling reaction, probably due to the interaction between Pd species and a mass of TiO<sub>2</sub> via metal-support interaction [strong metal support interaction (SMSI) or weak metal support interaction (WMSI) reported in the literature] [61–63]. Therefore, 5% Pd/TiO<sub>2</sub> (Cat. **D**, anatase-type) indicated efficient catalyst activity toward the Suzuki–Miyaura coupling reaction, while TiO<sub>2</sub> possessed only a small specific surface area (from 110 m<sup>2</sup>g<sup>−1</sup> of the fresh catalyst to 22 m<sup>2</sup>g<sup>−1</sup>).



**Figure 2.** XPS spectra of 5% Pd/TiO<sub>2</sub> (Cat. **D**, anatase-type) before (a) and after (b) the Suzuki–Miyaura coupling reaction.

The average palladium particle sizes on 5% Pd/TiO<sub>2</sub> (Cat. D, anatase-type) before and after the Suzuki–Miyaura coupling reaction (Figure 3a and 3b) were each roughly estimated to be 1 to 2 and 3 to 4 nm based on TEM images. These results strongly suggested that the high catalyst activity of fresh 5% Pd/TiO<sub>2</sub> (Cat. D, anatase-type) might be induced by the extensively distributed small Pd nanoparticles (Figure 3a) while the gradual increase of the Pd particle size during the Suzuki–Miyaura coupling reaction probably caused the decreasing of catalytic activity [Figure 3b and Equation (2)].



**Figure 3.** Transmission electron microscopy (TEM) images of 5% Pd/TiO<sub>2</sub> (Cat. D, anatase-type) before (a) and after (b) the Suzuki–Miyaura coupling reaction.

Furthermore, the chemisorption behavior of carbon monoxide on 5% Pd/TiO<sub>2</sub> (Cat. D, anatase-type) indicated the significant degradation of the specific surface area from 110 m<sup>2</sup>g<sup>−1</sup> of the fresh catalyst to 22 m<sup>2</sup>g<sup>−1</sup> after the Suzuki–Miyaura coupling reaction due to the remarkable Pd sintering. Based on these experimental and analytical investigations, the decreasing of catalytic activity of the recovered 5% Pd/TiO<sub>2</sub> (Cat. D, anatase-type) should be caused by the deterioration of the specific surface area due to the Pd sintering. Therefore, 5% Pd/TiO<sub>2</sub> (Cat. D, anatase-type) was unfortunately hard to reuse, while the fresh catalyst was suitable for the ligand-free Suzuki–Miyaura coupling reaction of aryl chlorides.

### 3. Materials and Methods

#### 3.1. General

All reagents and solvents were obtained from commercial sources and used without further purification. Pd(OAc)<sub>2</sub> was obtained from N.E. Chemcat Co. (Tokyo, Japan). The <sup>1</sup>H NMR and <sup>13</sup>C NMR spectra were recorded on a JEOL ECZ-400 (400 MHz for <sup>1</sup>H NMR and 100 MHz for <sup>13</sup>C NMR) spectrometer. CDCl<sub>3</sub> was used as the solvent for NMR measurement. Chemical shifts (δ) are expressed in part per million and internally referenced (0.00 ppm for tetramethylsilane or 7.26 ppm for CHCl<sub>3</sub> for <sup>1</sup>H NMR for CDCl<sub>3</sub> and 77.0 ppm for CDCl<sub>3</sub> for <sup>13</sup>C NMR). SHIMADZU AA-7000 was used for the atomic absorption spectrometry (AAS). All of <sup>1</sup>H and <sup>13</sup>C NMR spectra of known products were identical with those in the literature.

#### 3.2. Experimentals

##### 3.2.1. Preparation of 5% Pd/TiO<sub>2</sub> (Cat. D, anatase-type)

A suspension of anatase-type TiO<sub>2</sub> (3.00 g, colorless powder) in MeCN solution (30 mL) of Pd(OAc)<sub>2</sub> [316 mg, 1.41 mmol (150 mg, palladium quantity)] was stirred under argon atmosphere at 25 °C for 4 days. The resulting light yellow solid was collected by filtration (1 μm filter paper), washed with H<sub>2</sub>O (5 mL × 5) and EtOAc (5 mL × 5) and dried in vacuo for 24 h to afford the Pd/TiO<sub>2</sub> (3.15 g, Cat. D, anatase-type). The filtrate was concentrated in vacuo, and then transferred to a 100 mL volumetric flask with H<sub>2</sub>O and 15.58 ppm (1.56 mg) of palladium species were observed in the diluted filtrate by atomic absorption spectrometry (SHIMADZU AA-7000, Kyoto, Japan). Since the total

palladium species which was not absorbed on anatase-type TiO<sub>2</sub> was 1.56 mg, the palladium content of the anatase-type Pd/TiO<sub>2</sub> (Cat. D) was approximately 5% (4.7%) [(150 – 1.56)/3150 × 100].

### 3.2.2. Preparation of 5% Pd(red)/TiO<sub>2</sub> (Cat. A, Anatase-Type)

The collected anatase-type 5% Pd/TiO<sub>2</sub> (Cat. D, 500.0 mg) was stirred with NH<sub>2</sub>NH<sub>2</sub>·H<sub>2</sub>O (29.2 μL, 0.6 mmol) in H<sub>2</sub>O (40 mL) under argon atmosphere at 25 °C for 24 h. The grayish white solid was collected by filtration (1 μm filter paper), washed with H<sub>2</sub>O (10 mL × 5) and EtOAc (10 mL × 5) and dried in vacuo for 12 h to give 5% Pd(red)/TiO<sub>2</sub> (343 mg, Cat. A, anatase-type).

### 3.2.3. Typical Procedure for the Coupling Reaction between Aryl Chlorides and Arylboronic Acids

A mixture of 5% Pd/TiO<sub>2</sub> (30.0 mg, 12.5 μmol), an aryl chloride (250 μmol), an arylboronic acid (375 μmol) and Cs<sub>2</sub>CO<sub>3</sub> (163 mg, 500 μmol) in DMA (1 mL) was stirred at 80 °C in a test tube tightly sealed under argon atmosphere. After 24 h, the mixture was cooled to 25 °C, diluted with EtOAc (10 mL) and H<sub>2</sub>O (10 mL), and filtered through a membrane filter (pore size: 0.2 μm). The catalyst on the filter was washed with EtOAc (10 mL) and H<sub>2</sub>O (10 mL), and combined filtrates were separated to two layers. The aqueous layer was extracted with EtOAc (15 mL × 3), and combined EtOAc layers were washed with H<sub>2</sub>O (20 mL × 3) and brine (20 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated in vacuo. The residue was purified by silica-gel column chromatography using hexane/EtOAc (10:1) as eluents to afford the corresponding biaryl derivative.

### 3.2.4. Procedure for Reuse Test of Recovered 5% Pd/TiO<sub>2</sub> (Cat. D, anatase-type) (Equation (2))

Three exactly the same reaction mixtures containing 5% Pd/TiO<sub>2</sub> (Cat. D, anatase-type) (30.0 mg, 12.5 μmol), 4'-chloroacetophenone (**1a**, 38.6 mg, 250 μmol), a phenylboronic acid (**2a**, 45.7 mg, 375 μmol), Cs<sub>2</sub>CO<sub>3</sub> (163 mg, 500 μmol) in DMA (1 mL) were stirred at 80 °C in each separate sealed test tube under argon atmosphere. After 24 h, the combined reaction mixture was filtered using a funnel (1 μm filter paper). The catalyst on the filter was washed with EtOAc (3 mL × 5), and the recovered catalyst was dried at room temperature under reduced pressure overnight, then weighed (90.0 mg, 100 %). The reaction of the second run was carried out in the same manner as the first run except for using the recovered 5% Pd/TiO<sub>2</sub> (30.0 mg, 12.5 μmol) and only one reaction mixture in a test tube. The <sup>1</sup>H NMR ratio of **1a** and **3a** indicated 37:63.

### 3.2.5. Procedure for the Confirmation Experiment of Pd Leaching in the Reaction Medium and Pd Contamination of the Coupling Product after Purification Processes (Equation (3))

A mixture of 5% Pd/TiO<sub>2</sub> (Cat. D, anatase-type) (150.0 mg, 62.5 μmol), 4'-Chloroacetophenone (**1a**, 193.0 mg, 1.25 mmol), a phenylboronic acid (**2a**, 229.1 mg, 1.88 mmol) and Cs<sub>2</sub>CO<sub>3</sub> (815 mg, 2.5 mmol) in DMA (5 mL) was stirred at 80 °C in a test tube sealed under argon. After 24 h, the mixture was filtered using a funnel (1 μm filter paper). The catalyst on the filter paper was washed with EtOAc (15 mL × 5). The filtrate was concentrated in vacuo and transferred to a 100 mL volumetric flask with EtOAc. No palladium species were observed [0.0 ppm (0.0 mg)] in the diluted filtrate by measurement of atomic absorption spectrometry (SHIMADZU AA-7000). The organic layer was washed with H<sub>2</sub>O (20 mL × 3) and brine (20 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated in vacuo. The residue was purified by silica-gel column chromatography using hexane/EtOAc (10:1) as eluents to afford the corresponding analytically pure 4-acetylbiphenyl (**3a**). The obtained **3a** was transferred to a 100 mL volumetric flask with EtOAc, and no palladium species were observed [0.0 ppm (0.0 mg)] in the diluted filtrate by measurement of atomic absorption spectrometry.

## 4. Conclusions

We have prepared TiO<sub>2</sub>-supported catalysts possessing different crystalline structure of TiO<sub>2</sub>-and evaluated the significant effect based on the crystalline types on the ligand-free Suzuki–Miyaura cross coupling reaction mainly of aryl chlorides for the first time. The anatase-type TiO<sub>2</sub> supported Pd

catalyst [Pd/TiO<sub>2</sub> (Cat. D, anatase-type)] demonstrated efficient catalyst activity toward the ligand-free Suzuki–Miyaura cross coupling reaction of aryl chlorides. The quite high catalyst activity would be due to the extensively distributed small Pd nanoparticles on the anatase-type TiO<sub>2</sub> and the appropriate interaction between the Pd species and anatase-type TiO<sub>2</sub> based on the reduction of the Pd(II) to Pd(0) species, although details of the actual electron donating process have not been clarified. Various aryl chlorides possessing electron withdrawing substituents, such as acetyl and ester functionalities, on the aromatic ring were smoothly coupled with aryl and heteroarylboronic acids in moderate to excellent yields. For aryl halides possessing an electron donating substrate on the aromatic ring, the coupling reaction could be performed using the corresponding aryl bromide.

**Supplementary Materials:** The following are available online at <http://www.mdpi.com/2073-4344/9/5/461/s1>, Figure S1. XPS image and curve-fitting of Pd peaks (Cat. D–I). Figure S2. XPS image and curve-fitting of the Pd peaks of 5% Pd/TiO<sub>2</sub> (Cat. D, anatase-type) before and after use. Table S1. Base efficiency. Table S2. Solvent efficiency. Table S3. Time course study.

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