

Article

# Preparation of Metal Oxides Containing ppm Levels of Pd as Catalysts for the Reduction of Nitroarene and Evaluation of Their Catalytic Activity by the Fluorescence-Based High-Throughput Screening Method

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**Abstract:** Herein, an easily accessible and efficient green method for the reduction of nitroarene compounds was developed using metal oxide catalysts. Heterogeneous metal oxides with or without Pd were prepared by a simple and scalable co-precipitation method and used for the reduction of nitroarenes. A fluorescence-based high-throughput screening (HTS) method was also developed for the rapid analysis of the reaction conditions. The catalytic activity of the metal oxides and reaction conditions were rapidly screened by the fluorescence-based HTS method, and Pd/CuO showed the highest catalytic activity under mild reaction conditions. After identifying the optimal reaction conditions, various nitroarenes were reduced to the corresponding aniline derivatives by Pd/CuO (0.005 mol% of Pd) under these conditions. Furthermore, the Pd/CuO catalyst was used for the one-pot Suzuki–Miyaura cross-coupling/reduction reaction. A gram-scale reaction (20 mmol) was successfully performed using the present method, and Pd/CuO showed high reusability without a loss of catalytic activity for five cycles.

**Keywords:** high-throughput screening; chemosensor; metal oxide; palladium; nitroarenes reduction

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## 1. Introduction

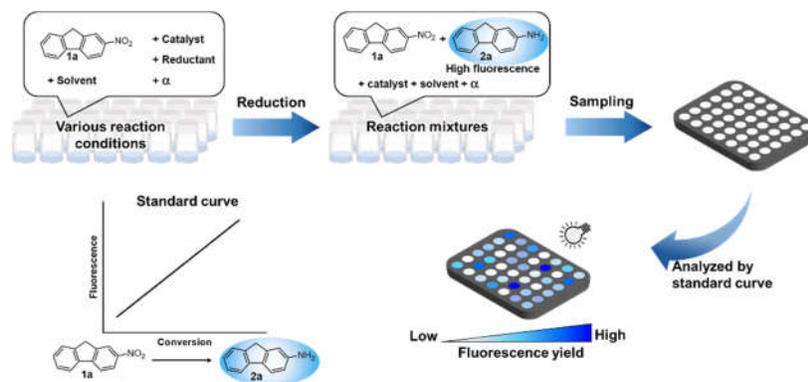
The synthesis of highly functionalized aniline derivatives is an important chemical reaction, because these derivatives are key intermediates in the production of valuable chemicals including pharmaceuticals, agrochemicals, dyes, and polymers [1]. Among several methods available for the synthesis of aniline, the catalytic transformation of a nitro group to the corresponding amine group is a widely used method based on noble metals such as Pd, Pt, Rh, and Au, or non-noble metals such as Fe, Zn, and Ni [2–5]. However, these methods have some drawbacks, such as the use of toxic organic solvents, expensive hydrides, flammable hydrogen gas, high-pressure equipment, and a large amount of expensive metal catalysts. The latter could result in high levels of residual metals in the product, which is a serious problem in pharmaceutical chemistry [6]. In addition, some methods require harsh reaction conditions, such as acidic pHs and high temperatures. These conditions hinder the application of the method to nitro compounds containing sensitive functional groups. To solve these problems, several methods using Pd nanoparticles (NPs)-based catalysts, such as Pd NPs in nanomicelle [7,8] and polymer-supported Pd NPs [9], have recently been developed. These

approaches could efficiently achieve the reduction of nitro to amine groups under mild conditions. However, reactive reagents, surfactants, polymers, and electrochemical methods were used to prepare the catalysts, which could limit their accessibility. Thus, the development of an easily accessible green methodology for the reduction of nitro groups remains a challenge.

Supported noble metal catalysts are widely used in the synthetic field because of their high activity and/or selectivity for specific chemical reactions, including coupling [10–12], oxidation [13–15], and reduction [16–19]. In general, the supporting material is one of the most important parts of a catalyst because it affects many of its properties, such as stability, distribution, and size. Thus, the interaction between the noble metal and supporting material plays a crucial role in their catalytic activity. Various materials have been used as support, such as carbon-based materials as well as non-metal and metal oxides. Among these systems, metal oxides are attracting increasing attention as promising supporting materials due to their large surface area, easy preparation, low cost, and controllable morphology. Owing to these advantages, several researchers have recently explored the combination of metal oxides and noble metals to develop active catalysts [20,21]. These studies showed that the activity of the catalyst was controlled by the type of metal oxide. We thought that this strategy could be applied to the development of a green methodology for the reduction of nitroarene.

In order to develop a new synthetic method, numerous reaction parameters, including catalysts, temperature, reagents, and solvent, should be screened to optimize the reaction conditions. This screening consumes significant human and material resources and slows down the development of a new method. To overcome this issue, several high-throughput screening (HTS) methods have been designed to enhance the efficiency of the development process, facilitating the analysis required to develop an efficient approach. In general, automated analysis instruments such as high-performance liquid chromatography (HPLC) [22,23], gas chromatography (GC) [24–26], mass spectrometry (MS) [27–29], and nuclear magnetic resonance (NMR) [30,31] have been used in HTS methods. Although these approaches provide accurate results, they require long analysis times per sample; another issue is represented by the cost of the automated instruments. To address these problems, colorimetric [32–35] or fluorescent [36–42] HTS methods have been developed; these approaches require short analysis times and relatively inexpensive instruments. Based on these advantages, our group previously developed several HTS methods for chemical reactions, using an optical chemosensor system to evaluate the efficiency of reaction parameters including catalysts, additives, solvents, and substrates [43–50]. The efficiency of the reaction conditions was rapidly analyzed based on optical changes in the chemosensor. We thought that this strategy could be applied to accelerate the development of new methods for the reduction of nitroarene compounds.

Herein, we developed a fluorescence-based HTS method and a green approach for the nitroarene reduction. The fluorescence-based HTS method using a chemosensor was designed to rapidly evaluate the efficiency of the reaction conditions. Metal oxides containing Pd were prepared by a simple and scalable co-precipitation method and used for the reduction of nitroarene. In order to determine the optimal conditions, the catalytic activity of the metal oxides and the reaction conditions were screened using the fluorescence-based HTS method (Scheme 1). Using the optimal reaction conditions, we investigated the substrate scope and evaluated the synthetic application of the prepared catalysts.



**Scheme 1.** Schematic representation of fluorescence-based high-throughput screening method for the reduction of nitroarene.

## 2. Results and Discussion

### 2.1. Development of Fluorescence-Based HTS Method for the Reduction of Nitroarene

The present fluorescence-based HTS method was developed to evaluate the catalytic activity of metal oxides for the reduction of nitroarenes. The transformation of a nitro group to the corresponding amine has been widely used in the development of chemosensors for targets or enzyme assay because the reaction induces a dramatic change in the chemosensor signal [51–53]. We also used this strategy to develop a fluorescence-based HTS method for the reduction of nitroarenes. To achieve an efficient and accessible HTS method, we considered two important properties of a chemosensor: sensitivity and accessibility. Therefore, 2-nitro-9H-fluorene (**1a**) was selected as a chemosensor for the following reasons. First, fluorene, which is the signal portion of **1a**, consists only of carbon and hydrogen and thus exhibits a high chemical stability in various reaction conditions [54]. Second, the quantum yield of **1a** showed a dramatic increase when **1a** was reduced to 9H-fluoren-2-amine (**2a**) [55]. Third, **1a** is a commercially available chemosensor and no synthetic preparation step of **1a** is required. Based on these advantages, a sensitive and accessible fluorescence-based HTS method was developed using the chemosensor **1a**. As shown in Figure S1, the fluorescence intensity at 358 nm increased with the ratio of **2a**. The linear standard curve for **2a** was obtained from these results and then used to calculate the yield of **2a**. After the reduction of **1a** under various reaction conditions, the fluorescence of **2a** in the reaction mixture was analyzed by a fluorescence spectrophotometer. The fluorescence of the reaction mixture was converted to yield using the standard curve, and the obtained yield was denoted as the fluorescence yield. The present HTS method enables a rapid analysis of the efficiency of metal oxides and reaction conditions.

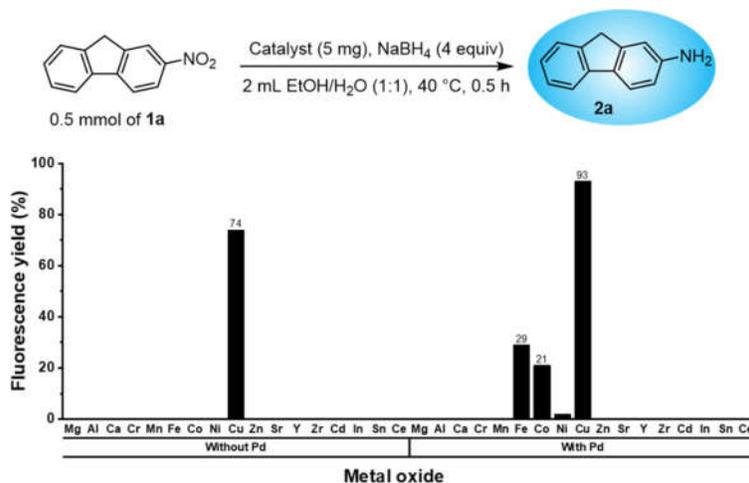
### 2.2. Preparation of Metal Oxides

Metal oxides with or without Pd were prepared by co-precipitation following a previously reported procedure, with some modifications [13,56]. In this method, we used 50 mmol of metal ions and only 50  $\mu\text{mol}$  (0.1 mol%) of Pd. A mixed EtOH/H<sub>2</sub>O solvent was used because lowering the dielectric constant of the solvent influences the solubility and particle size of the precursor [57–59]. After the calcination at 600 °C, a quantitative amount of metal oxides was obtained. The metal oxides containing Pd were denoted as Pd/M<sub>x</sub>O<sub>y</sub>. Most of the metal oxides were successfully prepared by following general procedures, but in some cases the pH was adjusted because high pH values increased the solubility of the hydroxide form of zinc and alumina. The metal hydroxides were calcinated at 600 °C. Finally, gram-scale metal oxides were obtained via simple procedures. The metal oxides were analyzed by X-ray diffraction (XRD); the results are summarized in Table S1. In all cases, no XRD peaks of palladium species were present, and the XRD patterns of the metal oxides with or without Pd were identical. These results indicate that the metal oxides contained a small amount of

Pd, which did not change their structure. After the preparation of the metal oxides, their catalytic activity for the reduction of nitroarene was evaluated by the fluorescence-based HTS method.

### 2.3. HTS of Metal Oxides Catalysts

The first screening was performed using 5 mg of metal oxides (34 kinds of metal oxides with or without Pd) and 0.5 mmol of **1a**. To test the reaction conditions, we used 2 mL of mixed EtOH/H<sub>2</sub>O (1:1) solvent. NaBH<sub>4</sub> (4 equiv) was selected as a reducing reagent because of its non-toxic by-products, easy accessibility, and cost-effectiveness [9,60,61]. After 0.5 h, H<sub>2</sub>O and toluene were added to the reaction mixture. An aliquot of the toluene layer was collected and diluted using toluene. The diluted sample was analyzed by a fluorescence spectrophotometer within 1 min. The fluorescence value of the samples was converted to fluorescence yield using a standard curve. As shown in Figure 1, few metal oxides showed catalytic activity. Pd/Fe<sub>2</sub>O<sub>3</sub> and Pd/Co<sub>3</sub>O<sub>4</sub> showed a low fluorescence yield of less than 30%. In the case of CuO, unexpectedly, the fluorescence yield was observed (74%). To confirm the Pd content in CuO, the CuO was analyzed by inductively coupled plasma-mass spectroscopy (ICP-MS), and 1 ppm of Pd was observed in CuO. By adding a small amount of Pd to the CuO (Pd:Cu = 1:1000), the Pd/CuO showed a very high yield (93%). Considering the high yield and application to the palladium-catalyzed sequential reaction, Pd/CuO was selected as a hit catalyst. In general, the mechanism of the support effect has been described in terms of metal cluster stabilization [62], charge transfer [63,64], size of metal [65,66], and support–substrate interaction [67]. However, the reason of the present result could not be explained in this case, because it is difficult to monitor trace amounts of Pd in metal oxides (1366 ppm of Pd in Pd/CuO, as estimated by inductively coupled plasma optical emission spectrometry (ICP-OES)). After the first screening of the metal oxides, the Pd/CuO was further analyzed by X-ray photoelectron spectroscopy (XPS), scanning electron microscopy (SEM), and transmission electron microscopy (TEM); the obtained data can be found in the supporting information (Figures S7–S10).



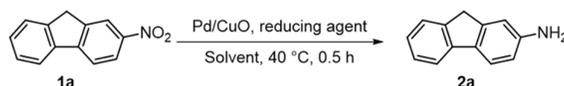
**Figure 1.** Results of the first screening of the catalytic activity of metal oxides.

### 2.4. Optimization of Reaction Conditions

To optimize the reaction conditions, various types and amounts of solvents and reducing agents were screened by the fluorescence-based HTS method. Initially, a reduced amount of Pd/CuO was employed. As shown in Table 1, a low yield was obtained with 1 mg of Pd/CuO, whereas 2 mg resulted in a similar yield with 5 mg (Table 1, entries 1 and 2). Thus, 2 mg of Pd/CuO was selected as an appropriate amount of catalyst. This result highlighted the high catalytic activity of Pd/CuO: 2 mg of Pd/CuO per 0.5 mmol of substrate corresponded to only 0.005 mol% of Pd. This low Pd content is one of the most important features of these catalysts. The amount of NaBH<sub>4</sub> was also initially reduced, resulting in a decreased yield of **2a**. However, 3 equiv of NaBH<sub>4</sub> produced a similar yield as that

obtained with 4 equiv (Table 1, entries 3–5). The reduction of **1a** was performed without Pd/CuO. For 12 h, **1a** was not reduced and ~99% of **1a** was recovered. Several reducing agents and solvents were also studied.  $\text{NH}_3\text{BH}_3$  (4 equiv) showed a good yield, although lower than that of 3 equiv of  $\text{NaBH}_4$  (Table 1, entry 6). Other reducing agents could not reduce **1a** (Table 1, entries 7–9). The protic solvent, EtOH, showed a high yield (Table 1, entry 10). When  $\text{H}_2\text{O}$  was used as a solvent, **1a** was not reduced because of the low solubility of **1a** in  $\text{H}_2\text{O}$ . In addition, **1a** was not reduced when aprotic or non-polar solvents were used (Table 1, entries 12–15). According to recent studies, protic solvents play an important role in nitro group reduction using  $\text{NaBH}_4$ , and our results were similar to the reported studies [68,69].

**Table 1.** Optimization of the nitroarene reduction <sup>a</sup>.



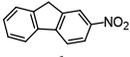
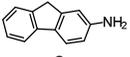
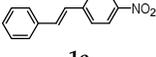
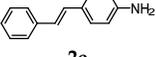
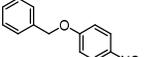
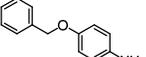
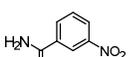
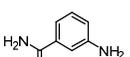
Entry	Catalyst	Reducing Agent	Solvent	Yield <sup>c</sup>
1	Pd/CuO 2 mg	$\text{NaBH}_4$ 4 equiv	EtOH/ $\text{H}_2\text{O}$ (1:1)	90
2	Pd/CuO 1 mg	$\text{NaBH}_4$ 4 equiv	EtOH/ $\text{H}_2\text{O}$ (1:1)	75
3	Pd/CuO 2 mg	$\text{NaBH}_4$ 3 equiv	EtOH/ $\text{H}_2\text{O}$ (1:1)	89
4	Pd/CuO 2 mg	$\text{NaBH}_4$ 2 equiv	EtOH/ $\text{H}_2\text{O}$ (1:1)	86
5	Pd/CuO 2 mg	$\text{NaBH}_4$ 1 equiv	EtOH/ $\text{H}_2\text{O}$ (1:1)	46
6	Pd/CuO 2 mg	$\text{NH}_3\text{BH}_3$ 4 equiv	EtOH/ $\text{H}_2\text{O}$ (1:1)	74
7	Pd/CuO 2 mg	$\text{NaBH}_3\text{CN}$ 4 equiv	EtOH/ $\text{H}_2\text{O}$ (1:1)	0
8 <sup>b</sup>	Pd/CuO 2 mg	$\text{H}_2$ (1 atm)	EtOH/ $\text{H}_2\text{O}$ (1:1)	0
9	Pd/CuO 2 mg	$\text{NH}_2\text{NH}_2$ 4 equiv	EtOH/ $\text{H}_2\text{O}$ (1:1)	0
10	Pd/CuO 2 mg	$\text{NaBH}_4$ 3 equiv	EtOH	>99
11	Pd/CuO 2 mg	$\text{NaBH}_4$ 3 equiv	$\text{H}_2\text{O}$	0
12	Pd/CuO 2 mg	$\text{NaBH}_4$ 3 equiv	Acetonitrile	9
13	Pd/CuO 2 mg	$\text{NaBH}_4$ 3 equiv	DMF	0
14	Pd/CuO 2 mg	$\text{NaBH}_4$ 3 equiv	Toluene	0
15	Pd/CuO 2 mg	$\text{NaBH}_4$ 3 equiv	Dioxane	0

<sup>a</sup> Reaction conditions: 0.5 mmol of **1a**, 2 mg of Pd/CuO (0.005 mol% Pd, 5 mol% Cu), reducing agent, solvent (2 mL) at 40 °C for 0.5 h. <sup>b</sup> Room temperature. <sup>c</sup> Fluorescence yield calculated by the standard curve.

### 2.5. Substrate Scope

To evaluate the scope of the methodology, several nitroarenes (Table 2) were reduced under the optimized reaction conditions determined by HTS. 1-Nitronaphthalene (**1b**) and 2-nitro-1,1'-biphenyl (**1c**) were successfully reduced (Table 2, entries 2 and 3). Two nitroarenes with alkene substituents, **1d** and **1e**, were also investigated. The stilbene derivative **1e**, which contains an internal alkene group, was reduced with a high selectivity (Table 2, entry 5). However, in the case of **1d**, bearing a terminal alkene, both the alkene and nitro groups were reduced under the optimized reaction conditions, resulting in ethylaniline (Table 2, entry 4). Several nitroarenes substituted with halides such as fluorine, chlorine, and bromine were reduced to the corresponding anilines within 2 h, and dichloronitrobenzene was successfully reduced without protodehalogenation (Table 2, entries 6–9). Anilines bearing nitrile (**2j**), benzyloxy (**2k**), and amide (**2l**) groups were obtained with a high selectivity for the nitro group (Table 2, entries 10–12). The sterically hindered triphenyl substrate **1m** was reduced efficiently but required long reaction times compared to the other substrates.

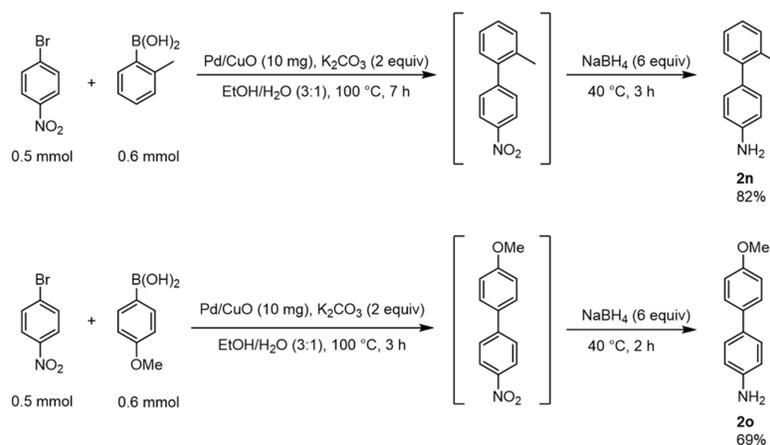
**Table 2.** Evaluation of the scope of the nitroarene reduction <sup>a</sup>.

Entry	Substrate	Product	Time	Yield (%) <sup>b</sup>
1	 <b>1a</b>	 <b>2a</b>	0.5 h	94
2	 <b>1b</b>	 <b>2b</b>	4 h	93
3	 <b>1c</b>	 <b>2c</b>	17.5 h	73
4 <sup>c</sup>	 <b>1d</b>	 <b>2d</b>	3 h	62
5	 <b>1e</b>	 <b>2e</b>	12 h	86
6 <sup>c</sup>	 <b>1f</b>	 <b>2f</b>	1 h	68
7	 <b>1g</b>	 <b>2g</b>	2 h	71
8	 <b>1h</b>	 <b>2h</b>	1.5 h	61
9	 <b>1i</b>	 <b>2i</b>	11 h	80
10	 <b>1j</b>	 <b>2j</b>	6 h	53
11	 <b>1k</b>	 <b>2k</b>	1.5 h	98
12 <sup>c</sup>	 <b>1l</b>	 <b>2l</b>	3 h	88
13 <sup>c,d</sup>	 <b>1m</b>	 <b>2m</b>	40 h	80

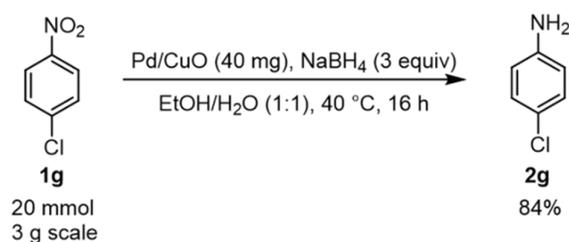
<sup>a</sup> Reaction conditions: 0.5 mmol of nitro substrate, 2 mg of Pd/CuO (0.005 mol% Pd, 5 mol% Cu), 1.5 mmol of NaBH<sub>4</sub>, 2 mL of EtOH/H<sub>2</sub>O (1:1) at 40 °C. <sup>b</sup> Isolated yield. <sup>c</sup> Obtained as HCl salt form. <sup>d</sup> EtOH (2 mL) was used in the reaction.

## 2.6. Synthetic Applications

After studying the substrate scope, we investigated the synthetic application of the present method. First, we assessed the potential of the Pd/CuO catalyst for one-pot reactions. The Suzuki–Miyaura cross-coupling/reduction reaction was selected as a representative one-pot reaction. 4-Bromonitrobenzene was selected as a halide-containing nitroarene and reacted with phenylboronic acid derivatives (Figure 2). After the cross-coupling, the temperature of the reaction mixture was reduced to 40 °C. Then, NaBH<sub>4</sub> was directly added to the reaction mixture. We initially used 3 equiv of NaBH<sub>4</sub>, but this amount could not completely reduce the intermediates; hence, the amount of NaBH<sub>4</sub> was increased to 6 equiv. After the one-pot reaction, the biaryl compounds **2n** and **2o** were obtained in 82% and 69% yields, respectively. These results showed that Pd/CuO catalyzed the cross-coupling reaction and could then be used for sequential one-pot reactions. After the one-pot reaction, we investigated a gram-scale reaction (Figure 3). 1-Chloro-4-nitrobenzene (**1g**, 20 mmol, 3.15 g) was used and reduced under the optimized reaction conditions. Although the gram-scale reaction required more time to completely reduce **1g**, the isolated yield of this reaction was higher than that of the 0.5 mmol-scale reaction (Table 2, entry 7). This result shows that the present methodology is suitable for performing gram-scale reactions.

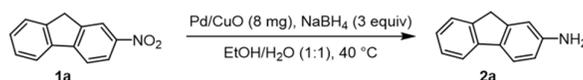


**Figure 2.** One-pot Suzuki–Miyaura cross-coupling and nitro group reduction catalyzed by Pd/CuO.



**Figure 3.** Gram-scale reaction.

As reusability is another important feature of a catalyst, we investigated the recyclability of Pd/CuO. The **1a** compound was used as a substrate and reduced under the optimized reaction conditions. Once the reduction was completed, the reaction medium except for Pd/CuO was carefully separated from the reaction vial. The product in the reaction medium was purified following general reduction procedures. The residual Pd/CuO in the reaction vial was washed and dried in an oven, and the recovered Pd/CuO was reused to reduce **1a**. The yields of five runs are summarized in Table 3. Pd/CuO could successfully reduce **1a** with a high yield for five runs, but the reused catalysts needed slightly more time to completely reduce **1a**. The longer reaction time may be due to the loss of a small amount of catalyst during the separation of the reaction medium. Thus, these results demonstrated the high reusability of Pd/CuO.

**Table 3.** Reusability of Pd/CuO <sup>a</sup>.

Cycle	Time	Yield (%) <sup>b</sup>
1 <sup>st</sup>	1.0 h	96
2 <sup>nd</sup>	1.5 h	95
3 <sup>rd</sup>	1.5 h	98
4 <sup>th</sup>	5.0 h	96
5 <sup>th</sup>	5.5 h	95

<sup>a</sup> Reaction conditions: 2.0 mmol of **1a**, 8 mg of Pd/CuO (0.005 mol% Pd, 5 mol% Cu), 6.0 mmol of NaBH<sub>4</sub>, 8 mL of EtOH/H<sub>2</sub>O (1:1) at 40 °C. <sup>b</sup> Isolated yield.

### 3. Materials and Methods

#### 3.1. Materials and Instruments

All the chemical reagents were purchased from commercial sources (Sigma-Aldrich (St. Louis, MO, USA), Tokyo Chemical Industry Co., Ltd. (Tokyo, Japan), and Alfa Aesar (Ward Hill, MA, USA)) and used as received without further purification. The NMR spectra were recorded using a JEOL (400 MHz) NMR spectrometer (JEOL Ltd., Tokyo, Japan). The fluorescence spectra were recorded on an Agilent Cary Eclipse fluorescence spectrophotometer (Agilent, Santa Clara, CA, USA). The XRD measurement was conducted on a D8 Advance (Bruker, Billerica, MA, USA). The XPS studies were carried out with a Thermo Scientific K-Alpha (Thermo Fisher Scientific, Waltham, MA, USA). The SEM images were obtained on a Hitachi SU-70. The TEM images were collected on a FEI Tecnai F20 UT. The Pd loadings in the catalyst sample were determined by an ICP-OES (Avio 500, Perkin Elmer, Waltham, MA, USA) and ICP-MS (Nexion 300X, PerkinElmer, Waltham, MA, USA).

#### 3.2. General Procedure for the Preparation of Pd/M<sub>x</sub>O<sub>y</sub>

In general, 50 mmol of metal salts were dissolved in 500 mL of mixed EtOH/H<sub>2</sub>O (2:3) solvent. To this solution, K<sub>2</sub>PdCl<sub>4</sub> (0.0163 g, 50 μmol) was added. The solution was stirred vigorously at room temperature. An aqueous NaOH solution (20 g of NaOH in 100 mL of H<sub>2</sub>O) was added to the solution. In this step, the clear solution turned to a turbid suspension very quickly (generation of metal hydroxide). After 4 h, the suspension was filtered. The filtered solid was washed with mixed EtOH/H<sub>2</sub>O (1:1) solvent until the pH of the filtrate become neutral and dried in an oven. The dried solid was calcinated at 600 °C for 6 h. Finally, a gram-scale of Pd/M<sub>x</sub>O<sub>y</sub> was obtained. In the case of M<sub>x</sub>O<sub>y</sub>, the M<sub>x</sub>O<sub>y</sub> was prepared by same procedure, except for the addition of K<sub>2</sub>PdCl<sub>4</sub>.

#### 3.3. General Procedure for High-Throughput Screening Method for the Reduction of Nitroarene

The metal oxide catalyst (5 mg) was added to a reaction vial containing a PTFE-coated magnetic stirring bar. To the reaction vial, 2 mL of mixed solvent EtOH/H<sub>2</sub>O (1:1) was added and sonicated for about 20 s to disperse the catalyst. Pre-fluorescent chemosensor 2-nitro-9H-fluorene (**1a**) (0.1056 g, 0.5 mmol) was added to the suspension. The reaction mixture was stirred vigorously at 40 °C in a heating block. NaBH<sub>4</sub> (0.0757 g, 2.0 mmol) was added to the reaction mixture directly. After 0.5 h, the stirring bar was stopped and 0.5 mL of H<sub>2</sub>O and 2 mL of toluene were added to the mixtures. The reaction mixture was shaken gently by hand for about 10 s. The reaction mixture was separated into two layers. An aliquot of the toluene layer was collected and diluted with toluene. The solution was further diluted by toluene (5 μM based on **1a**). The solution was analyzed by a fluorescence spectrophotometer. The fluorescence value of the solution was converted to the fluorescence yield using a standard curve.

### 3.4. General Procedure for the Reduction of Nitroarene

Pd/CuO (2 mg) was added to a reaction vial containing a PTFE-coated magnetic stirring bar. To the reaction vial, 2 mL of mixed EtOH/H<sub>2</sub>O (1:1) solvent was added and sonicated about 20 s to disperse a Pd/CuO. The nitroarene (0.5 mmol) was added to the suspension. The reaction mixture was stirred vigorously at 40 °C in a heating block. NaBH<sub>4</sub> (0.0568 g, 1.5 mmol) was added to the reaction mixture directly. The reaction was monitored by thin layer chromatography (TLC). After the starting material was consumed, the reaction mixture was diluted with H<sub>2</sub>O and ethyl acetate. The organic layer was collected and washed with brine. The organic layer was dried with Na<sub>2</sub>SO<sub>4</sub>, filtered, and evaporated under reduced pressure. The residue was purified by silica gel column chromatography. In some cases, the column-purified product was dissolved in organic solvent and bubbled by HCl (g) to give a HCl salt form of product.

### 3.5. One-Pot Procedure for Suzuki-Miyaura Cross Coupling and Nitro Reduction

Pd/CuO (10 mg) was added to a reaction vial containing a PTFE-coated magnetic stirring bar. To the reaction vial, 4 mL of mixed EtOH/H<sub>2</sub>O (3:1) solvent was added and sonicated for about 20 s to disperse the Pd/CuO. 1-Bromo-4-nitrobenzene (0.1010 g, 0.5 mmol), phenylboronic acid derivatives (0.6 mmol), and K<sub>2</sub>CO<sub>3</sub> (0.1382 g, 1.0 mmol) were added to the suspension. The reaction mixture was stirred vigorously at 100 °C in a heating block. The reaction was monitored by TLC. After the consumption of aryl halide, the temperature was cooled to 40 °C. Without any purification of the reaction mixture, NaBH<sub>4</sub> (0.1135 g, 3.0 mmol) was added to the reaction mixture directly. After the reduction was finished, the reaction mixture was diluted with H<sub>2</sub>O and ethyl acetate. The organic layer was collected and washed with brine. The organic layer was dried with Na<sub>2</sub>SO<sub>4</sub>, filtered, and evaporated under a reduced pressure. The residue was purified by silica gel column chromatography.

### 3.6. Gram-Scale Reaction of Reduction of Nitroarene

Pd/CuO (40 mg) was added to a round bottom flask containing a PTFE-coated magnetic stirring bar. To the flask, 40 mL of mixed EtOH/H<sub>2</sub>O (1:1) solvent was added and sonicated for about 20 s to disperse the Pd/CuO. 1-Chloro-4-nitrobenzene (3.15 g, 20 mmol) was added to the suspension. The reaction mixture was stirred vigorously at 40 °C in an oil bath. NaBH<sub>4</sub> (2.27 g, 60 mmol) was added to the reaction mixture. The reaction was monitored by TLC. After the starting material was consumed, the reaction mixture was diluted with H<sub>2</sub>O and ethyl acetate. The organic layer was collected and washed with brine. The organic layer was dried with Na<sub>2</sub>SO<sub>4</sub>, filtered, and evaporated under a reduced pressure. The residue was purified by silica gel column chromatography.

### 3.7. Procedure for the Reuse of Catalyst

Pd/CuO (8 mg) was added to a reaction vial containing a PTFE-coated magnetic stirring bar. To the reaction vial, 8 mL of mixed EtOH/H<sub>2</sub>O (1:1) solvent was added and sonicated for about 20 s to disperse the Pd/CuO. **1a** (0.4224 g, 2.0 mmol) was added to the suspension. The reaction mixture was stirred vigorously at 40 °C in a heating block. NaBH<sub>4</sub> (0.2270 g, 6.0 mmol) was added to the reaction mixture directly. The reaction was monitored by TLC. After the starting material was consumed, the reaction media were carefully separated from the reaction vial using a syringe (be careful of the loss of catalyst). The separated reaction media were purified following the general procedure for the reduction of nitroarene to obtain **2a**. The remaining Pd/CuO in the vial was washed with H<sub>2</sub>O and EtOH carefully and dried in an oven. The recovered Pd/CuO was reused for the reduction of **1a**.

## 4. Conclusions

In this work, we developed an easily accessible green methodology for the reduction of nitroarenes. To achieve this goal, metal oxides with or without Pd were prepared by a simple and scalable co-precipitation method and used as catalysts for the reduction of nitroarene compounds. A fluorescence-based HTS method for the rapid analysis of the reaction conditions was developed using

chemosensor **1a**. Using this HTS method, the catalytic activity of the prepared metal oxides and various reaction conditions were rapidly screened. Among the present metal oxides, Pd/CuO showed an outstanding catalytic activity in the reduction of nitroarene compounds. After optimization, various nitroarenes were successfully reduced to the corresponding aniline derivatives by the Pd/CuO catalyst (0.005 mol% of Pd) under mild reaction conditions. These low Pd contents and mild reaction conditions are important features of the method developed in this study.

Furthermore, we investigated the synthetic application of the present method. Using Pd/CuO, biaryl compounds containing amine groups were synthesized by a one-pot Suzuki–Miyaura cross-coupling/reduction reaction. Furthermore, gram-scale amounts of aniline derivatives were prepared by a large-scale reaction. We also examined the reusability, one of the most important features of the catalysts; Pd/CuO maintained a high activity over five runs. These results demonstrated the excellent performance of the present easily accessible green methodology in synthetic applications.

**Supplementary Materials:** The following are available online at [www.mdpi.com/2073-4344/10/5/542/s1](http://www.mdpi.com/2073-4344/10/5/542/s1): Figure S1: standard curve; Figures S2–S6: XRD analysis; Figures S7–S9: TEM and SEM analysis; Figures S10 and S11: XPS analysis; Table S1: summary of XRD results and  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra copies.

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