



A highly sensitive fluorescence method reveals the presence of palladium in a cross-coupling reaction mixture not treated with transition metals

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ABSTRACT

We previously reported a Suzuki–Miyaura coupling in dimethyl carbonate without adding additional transition metals. Here, we show an analysis of the reaction mixture that revealed the presence of palladium using a fluorogenic Tsuji–Trost reaction.

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Palladium-catalyzed cross-coupling reactions are widely used in synthetic organic chemistry.¹ Because it is difficult to remove palladium from the products after palladium-catalyzed reactions,² minimizing the stoichiometry of palladium is an important goal in synthetic organic chemistry.³ A viable alternative approach is to discover a metal-free system or a different metal that catalyzes the same cross-couplings.⁴ Nonetheless, even though palladium reagents were not used, palladium was present in the reactions that were typically catalyzed by this transition metal.^{4a,5} These examples called for more rigorous analyses of trace metals in the reaction mixtures.⁶ Inductively coupled plasma mass spectroscopy (ICP-MS) has become a standard technique in this regard; however, unlike other routine spectroscopic techniques such as NMR, IR, UV, and LC-MS, ICP-MS analyses are performed mostly off site.

The Inamoto–Doi group recently reported that the cross-coupling between aryl iodides and organoboron reagents could be accomplished in dimethyl carbonate without adding a transition metal catalyst.^{5f} Trace palladium, which is typically needed for such cross-couplings,⁷ was present at a 0.42 ppb level in the mixture of the reaction shown in Scheme 1a.^{5f} We hypothesized that a fluorescence-based method for palladium detection developed by the Koide group⁸ could also be used to quantify palladium in the reaction mixture. This method has been shown to be more effective than ICP-MS for detecting palladium in organic and inorganic

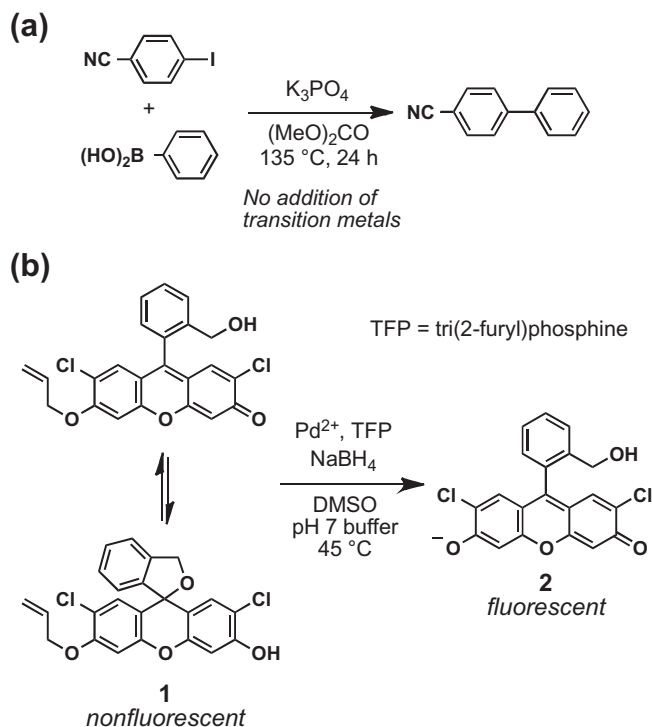
compounds.^{8c,d,9} A synthetic sample prepared by a palladium-catalyzed cross-coupling reaction was purified and analyzed by this method, and the result matched those generated by ICP-MS and inductively coupled plasma atomic emission spectrometry (ICP-AES) methods in a double-blind format.^{8c} It should be noted that rhodium can also give rise to fluorescence signals when tri(2-furyl)phosphine is used, although the signals are far smaller than those from palladium.^{8c,d}

The sample was prepared according to the published protocol^{5f}: a mixture of 4-iodobenzonitrile (60.0 mg, 0.262 mmol), phenylboronic acid (38.3 mg, 0.314 mmol), and K₃PO₄ (66.7 mg, 0.314 mmol) was heated at 135 °C for 24 h in dimethyl carbonate (2.6 mL). After the completion of the reaction, the dimethyl carbonate was evaporated in vacuo. The resulting residue was treated with 10% HNO₃ (1.0 mL) for 20 min at 50 °C. After this mixture was cooled to 25 °C, ethanol (1 mL) and DMSO (0.50 mL) were added to this mixture (sample A).

We prepared a premixed solution for palladium detection similarly to our previous studies:⁹ A 1.23 M phosphate pH 7 buffer (95 mL) and DMSO (4.58 mL) were added to an amber glass reagent bottle that was rinsed with 5–10% HNO₃ and deionized water prior to use. To this solution were added a 3 mM solution of allyl ether **1** in DMSO (0.417 mL) and tri(2-furyl)phosphine (2.8 mg) at 25 °C. After sonicating the mixture for 5 min to dissolve tri(2-furyl)phosphine, NaBH₄ (38 mg) was added to the solution. The resulting solution contained allyl ether **1** at 12.5 μM, NaBH₄ at 10 mM, and tri(2-furyl)phosphine at 120 μM in DMSO/buffer (1:19 v/v).

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Scheme 1. (a) Cross-coupling reaction without adding transition metals. The reaction mixture was dried under a vacuum, and the resulting crude mixture was treated with 10% HNO₃ before palladium analysis. (b) Palladium(0) generated in situ catalyzes the conversion of the nonfluorescent allyl ether **1** to the green fluorescent phenoxide **2**. The fluorescence signals were measured using a Modulus II Microplate Multimode Reader (excitation: 490 nm, emission: 510–570 nm).

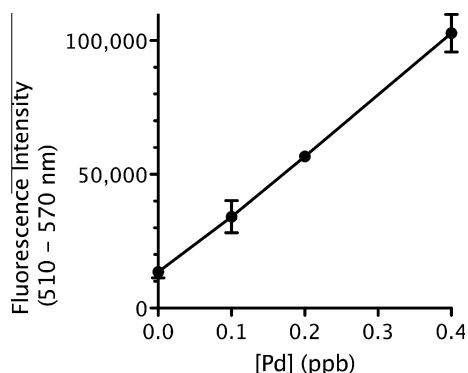


Figure 1. Standard curve based on the method in Scheme 1b.

The above pre-mixed stock solution was immediately transferred to eppendorf tubes at 25 °C (1.47 mL in each container). This experiment was performed in duplicate, and the standard curve was generated in triplicate. Each of these solutions was treated with a palladium solution (0, 5, 10, or 20 ppb in 5% HNO₃; 30 μ L; 50-fold dilution) or sample A (30 μ L; 50-fold dilution) at 25 °C. All of these eppendorf tubes were sealed and heated at 45 °C in an incubator for 1 h. After cooling the reaction mixtures, the solutions (200 μ L from each reaction) were transferred to a black 96-well plate for fluorescence measurement.

As Figure 1 shows, the standard curve for palladium was $y = 224,200[\text{Pd}] + 12,560$ (y = fluorescence intensity in arbitrary unit, $[\text{Pd}]$ = palladium concentration in ppb) with the $r^2 = 0.9855$. The fluorescence intensities with sample A were 15702 and 16665 (average = 16184). The average palladium concentration, according to the equation, was determined to be 16.2 ppt in the

reaction solution for the conversion of allyl ether **1** to phenoxide **2**. The fluorescence method was performed three times (duplicate or triplicate each time), all of which resulted in similar conclusions. Because sample A was diluted 50-fold to perform this deallylation reaction, the average palladium concentration in sample A (2.5 mL) was determined to be 0.81 ppb (7.6 nM). Therefore, in the original reaction mixture (2.6 mL) Scheme 1a, palladium was present at 0.78 ppb (7.3 nM). The reaction mixture (Scheme 1a) used in this study was different from that in our previous study; therefore, we consider this palladium level to be within a reasonable range compared to the previous ICP-MS analysis for the same transformation.^{5f} Because the conversion of allyl ether **1** to phenoxide **2** can be catalyzed by rhodium, although to a lesser extent,^{8d} we are not able to exclude the presence of rhodium in sample A. However, since the Suzuki–Miyaura coupling reactions are typically catalyzed by palladium, we believe that the presence of palladium is more relevant to the previously reported reactions.^{5f} If the trace palladium is indeed the catalyst, then the turnover number would be over ten million under the previously reported reaction conditions in which the limiting agent (4-iodobenzonitrile) was at a 100 mM concentration.^{5f}

In summary, we demonstrated the utility of the fluorescence method to analyze a reaction mixture to detect palladium although no palladium reagents were added to the mixture. Trace palladium impurities have caused confusion in the literature.^{4c} This case study exemplifies potential applications of this user friendly¹⁰ fluorescence method in other synthetic laboratories to detect palladium on site.

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- For example, first-year undergraduate students without research experience were able to use this method after 2–3 h of training in our laboratory.