

DOI: 10.1002/cplu.201200015

Detection of Trace Palladium in Flasks and Metal Reagents Using a Fluorogenic Tsuji–Trost Reaction

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It has been debated in several instances whether trace palladium in flasks or other metal reagents in reaction mixtures catalyzed the observed chemical reactions. For example, a palladium-free Suzuki–Miyaura coupling reaction^[1] was later found to be catalyzed by residual palladium present in Na₂CO₃.^[2] An iron-catalyzed Suzuki–Miyaura coupling reaction might be catalyzed by trace palladium present in reagents, glassware, or stir bars.^[3] A copper-catalyzed Sonogashira coupling reaction might be significantly impacted by residual palladium.^[4] A gold(I)-catalyzed Sonogashira coupling reaction was shown to require trace palladium.^[5] An apparently CuI-catalyzed domino reaction was facilitated by ppb levels of palladium.^[6] A trace amount of palladium was extensively investigated in LiOtBu-mediated cross-coupling reactions of pyrrole and iodobenzene compounds.^[7] To improve the reproducibility of these and other related reactions, it was proposed that the reagents be analyzed by ICP-MS.^[8] However, the detection of trace palladium in metal reagents by ICP-MS is not trivial because it is detrimental to introduce a large amount of other metals into the ICP-MS instrument (memory effect).^[9] Moreover, ICP-MS analyses of reagents and reaction vessels cannot be routinely employed in synthetic organic chemistry laboratories owing to the high cost and limited availability of ICP-MS spectrometers.

Colorimetric and fluorometric methods may be more convenient for detecting palladium^[10] in chemicals and reaction vessels on a routine basis. Our research group developed a method to visualize the presence of palladium by green fluorescence.^[10b,d,f,i,t] Our most recently published method is highly sensitive and capable of detecting 0.1 ppb palladium in aqueous solutions regardless of the initial structures of the palladium species.^[10] In this method, various palladium species are converted into tri(2-furyl)phosphine (TFP)-bound palladium(0) upon treatment with NaBH₄ and TFP in a concentrated pH 7 phosphate buffer (Figure 1). This palladium species catalyzes the conversion of the nearly nonfluorescent allyl ether **1** to the green fluorescent phenoxide **2**.^[10] We showed that the presence of ten equivalents of other metals did not interfere with palladium detection. However, neither our method nor the methods of others^[10] were shown to be robust enough to detect palladium in the presence of > 1 000 000 equivalents of other metals. In other words, at the outset of this study, it was not clear whether trace palladium could be detected in non-palladium metal reagents. Herein, we demonstrate the utility of this method for detecting palladium in metal reagents and glassware. Considering the ease of use, this method can be

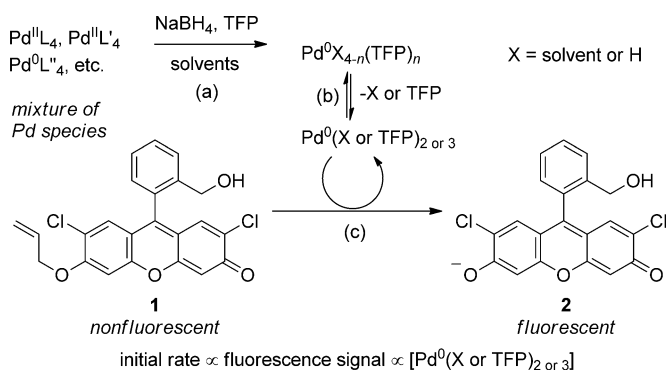


Figure 1. a) Various palladium species are converted to Pd⁰ bound to TFP. b) Ligand(s) are dissociated to form catalytically active palladium species. c) Palladium catalyzes the conversion of allyl ether **1** into phenoxide **2**.

employed in a high-throughput manner and may offer a practical solution to those engaged in the development of palladium-free chemical reactions or in the quality control of reactors to ensure complete removal of the palladium.

We chose chemicals relevant to reagent preparations, metal-catalyzed reactions, or workup procedures. These chemicals included FeCl₃, CoCl₂, Na₂CO₃, K₂CO₃, Cs₂CO₃, NaHCO₃, KHCO₃, CuCl, Cu₂O, CuI (3 batches), CuBr₂, Cu(NO₃)₂, Cu(OAc)₂, Cu(OTf)₂, InCl₃, AuCl, AuCl₃, NaCl, NaBr, NaI, ZnCl₂ (4 batches), Zn(OAc)₂, and Zn(OTf)₂ (4 batches). Each of these reagents was added to a mixture of allyl ether **1**, NaBH₄, and TFP in dimethyl sulfoxide (DMSO)/1.23 M phosphate buffer (pH 7; 1:9 v/v) at a 0.5 mg mL⁻¹ concentration. The resulting solutions were incubated at 45 °C for 80 minutes. The fluorescence intensities were measured and compared to a standard curve generated by the conversion of allyl ether **1** into phenoxide **2** under the same reaction conditions in the presence of palladium at 0, 0.1, 0.2, and 0.4 ppb (Figure 2). All of the data points for both the standard curves and sample analyses were generated in duplicate or triplicate. Because the standard curve for this study was generated by a limited number of data points, we do not claim that the following data are precise. Rather, the purpose of this study is to showcase the utility of our fluorescence-based method for detecting and crudely measuring trace palladium in laboratory chemicals and flasks on a routine basis. The standard curve was generated every time the method was employed throughout this study and showed sufficient linearity between the concentration of palladium and fluorescence intensity (510–570 nm) as shown previously.^[10]

Among these reagents, one of the two batches of Cs₂CO₃, one of the four batches of ZnCl₂ (two of them are shown in Figure 2), one of the three batches of CuI (two of them are

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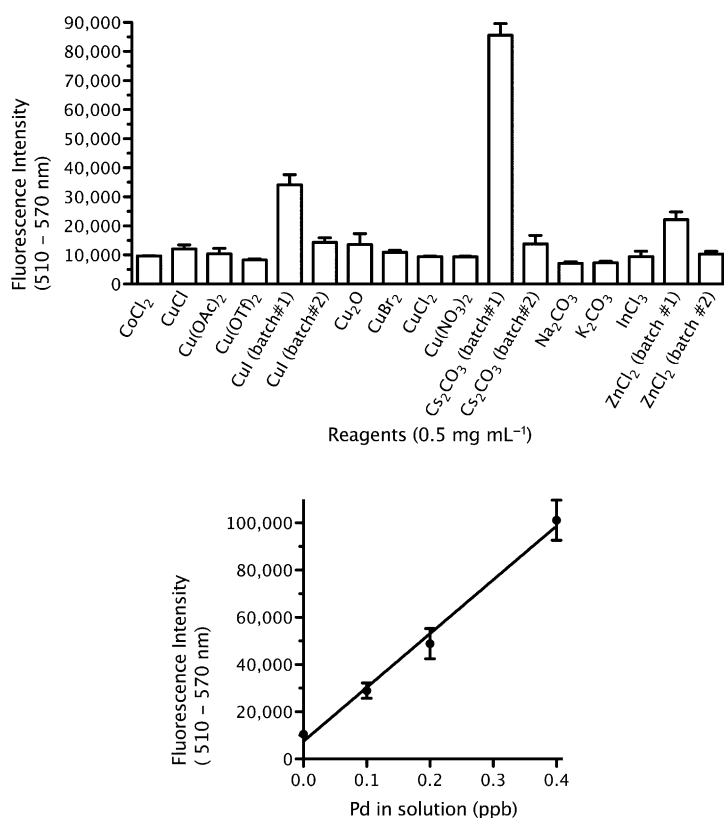


Figure 2. Fluorescence data for some of the reagents ($n=2$ or 3) and standard curve ($y=228,009x+7493$, $r^2=0.9748$, $n=3$). AuCl is not shown because the reaction conditions were different (0.67 mg mL^{-1}).

shown in Figure 2), and AuCl (data not shown) showed increased fluorescence signals by catalyzing the conversion of allyl ether **1** into phenoxide **2**. These data indicate that palladium may be present at 0.69, 0.13, 0.24, and 0.21 ppm in Cs₂CO₃, ZnCl₂, CuI, and AuCl, respectively (Table 1). Because the conver-

Reagent	Pd [ppm]	Reagent	Pd [ppm]
AuCl	0.21	CuI (batch#1)	0.24
ZnCl ₂ (batch#1)	0.13	Cs ₂ CO ₃ (batch#1)	0.69

sion of allyl ether **1** into phenoxide **2** can be catalyzed by rhodium species, albeit less effectively,^[10] we cannot exclude the possibility that the impurity is rhodium. The ICP-MS analyses of the palladium-contaminated ZnCl₂ sample indicated that palladium was below the detection limit ($<0.2\text{ ppm}$). Therefore, these experiments can imply, but not confirm, that trace amounts of palladium are present in these reagents.

The palladium-contaminated Cs₂CO₃ batch#1 (5 equiv) was used for the coupling between PhI and PhB(OH)₂ in the presence of Ph₃P and water. However, this experiment did not produce a detectable amount of biphenyl, unlike the positive control experiment in which Pd(OAc)₂ (5 mol%) was added. There-

fore, the trace palladium species in this batch of Cs₂CO₃ may not be synthetically relevant in some instances.

It is impractical to analyze reaction vessels and stir bars for palladium by ICP-MS on a routine basis in synthetic organic laboratories, especially at academic institutions. Therefore, it would be beneficial to develop a method analogous to the litmus test to determine whether these materials are contaminated with palladium before performing "palladium-free" reactions. Our research group has performed palladium-catalyzed reactions in the past for several distinct projects. Therefore, we wondered whether flasks in our laboratory were contaminated with palladium even after washing with diluted nitric acid (not always), detergents, and acetone. Fifteen round-bottom and pear-shaped flasks were randomly chosen from personnel not involved in this project, and a pre-mixed solution (5 mL) of allyl ether **1** (3 μM), NaBH₄ (1 mM), and TFP (120 μM) in DMSO/1.23 M phosphate buffer (pH 7; 1:19 v/v) was added to each of these flasks. After heating the flasks at 42 °C for 2 hours in a water bath, these flasks were placed above a UV lamp (325 or 365 nm). A negative control reaction was performed by using an unused glass vial as a reaction vessel. As Figure 3 shows, one flask (Flask 6) showed a strong green fluorescence, thus indicating palladium contamination. Two other flasks (Flasks 4 and 8) showed moderate fluorescence signals, and one flask (Flask 2) showed a weak fluorescence signal. The other eleven flasks (four of them shown) exhibited equally negligible fluorescence signals as the negative control. This experiment shows that our method is capable of identifying flasks contaminated with palladium. For the purpose of clear photography, the reactions were performed for 2 hours, but distinct fluorescence was visible after 1 hour.

ICP-MS is a powerful method for quantifying metals but is not readily available to most synthetic organic chemists. The fluorescence-based method presented here was capable of detecting and semi-quantifying trace palladium in metal reagents

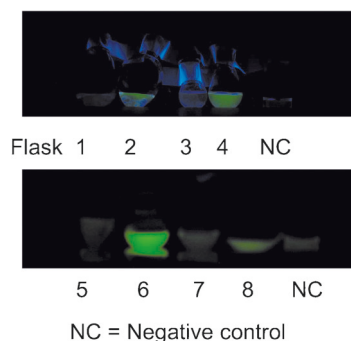


Figure 3. Photo images of flasks containing a solution of allyl ether **1**, NaBH₄, and TFP in DMSO/1.23 M phosphate buffer (pH 7; 1:9 v/v). The flasks were placed above a UV lamp (325 nm), and the photographs were taken in a dark room.

at sub-ppm levels. This method also enabled visual inspection of glassware for trace palladium. Because this method is based on a Tsuji–Trost reaction, the palladium species responsible for the enhanced fluorescence signals are catalytically active under the reaction conditions. Thus, this protocol may be used as a litmus-like test for palladium to identify materials that need to be analyzed more rigorously.

Experimental Section

Analysis of chemicals (Figure 2 and Table 1)

FeCl₃, CoCl₂, Cs₂CO₃ (2 batches), Na₂CO₃, K₂CO₃, Cs₂CO₃, NaHCO₃, KHCO₃, CuCl, Cu₂O, CuI (3 batches), CuBr₂, Cu(NO₃)₂, Cu(OAc)₂, Cu(OTf)₂, InCl₃, AuCl, AuCl₃, NaCl, NaBr, NaI, ZnCl₂ (4 batches), Zn(OAc)₂, and Zn(OTf)₂ (4 batches; 25 mg) were each placed in a vial (2 dram). Each of these reagents was treated with 0.5% ultra-pure HNO₃ (1.0 mL) to prepare a 50× stock solution. When a reagent was insoluble, the solid was added directly to the following reaction solution.

A 1.23 M phosphate buffer (pH 7; 1.27 mL) and a solution of 1.8 mM TFP in DMSO (100 µL) were transferred to a glass vial (2 dram) or an Eppendorf tube. The resulting solution was treated with a palladium solution (0, 5, 10, or 20 ppb in 0.5% HNO₃; 30 µL) or the solution of a chemical described above (30 µL) at 25 °C. Subsequently, the solution was treated with a 30 mM solution of NaBH₄ in 0.12 N NaOH (50 µL) and a 375 µM solution of allyl ether 1 in DMSO (50 µL) in sequence at 25 °C. The resulting solution was heated at 45 °C for 80 min. After cooling the reaction vessel on ice, the solution (200 µL) was transferred to a black 96-well plate before fluorescence measurement using a Modulus II Microplate Multimode Reader (Turner BioSystem; excitation: 490 nm, emission: 510–570 nm). The data were produced in duplicate or triplicate and analyzed by using GraphPad Prism 5.

A representative example is as follows: The standard curve for palladium was $y = 228000x + 7493$ (y = fluorescence intensity in arbitrary unit, x = palladium concentration in ppb) with the $r^2 = 0.9748$. The fluorescence intensities with CuI were 11,044, 13,692, 14,256, 10,966, and 11,522. The highest and the lowest values were eliminated, and the average and the standard deviation of the remaining three values were calculated. The average palladium concentration in the solutions was 0.12 ppb. Therefore, the palladium content in CuI was 0.24 ppm.

Analysis of used flasks (Figure 3)

A 1.23 M phosphate buffer (pH 7; 95 mL) and DMSO (4.9 mL) were added to a glass vial that was rinsed with 2% HNO₃ and deionized water prior to use. To this solution were added a 3 mM solution of allyl ether 1 in DMSO (100 µL) and TFP (2.8 mg) at 25 °C. After sonicating the mixture for approximately 5 min to dissolve TFP, NaBH₄ (3.8 mg) was added to the solution (the resulting solution was: [1] = 3 µM, [NaBH₄] = 1 mM, and [TFP] = 120 µM in DMSO/buffer (1:19 v/v)). This solution, within 5 min after preparation, was transferred to fifteen flasks at 25 °C (5 mL for each flask). All of these flasks were sealed with polypropylene caps and heated at 42 °C in a water bath for 2 h. A negative control experiment was performed using an unused glass vial. The flasks were then cooled to 25 °C and placed above a UV lamp (325 nm) in order to take photo-

graphs in a dark room. It should be noted that a UV lamp with a wavelength of 365 nm could also be used to visualize green fluorescence.

Acknowledgements

We thank Dr. Tiebang Wang (Merck and Co.) for the ICP-MS analysis of ZnCl₂. D.L. was partly supported by the China Scholarship Council Postgraduate Scholarship Program. L.D.C. and B.A.A. were part of the First Experiences in Research Program at the University of Pittsburgh for first-year undergraduate students. This research was supported by the US National Science Foundation (CHE-0911092).

Keywords: allylic compounds • cleavage reactions • fluorescence spectroscopy • sensors • Tsuji–Trost reactions

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Received: January 21, 2012

Published online on February 16, 2012