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Studies Toward an Ideal Fluorescence Method to Measure Palladium in Functionalized Organic Molecules: Effects of Sodium Borohydride, Temperature, Phosphine Ligand, and Phosphate Ions on Kinetics

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Abstract: Residual metals in fine chemicals are currently detected by using inductively coupled plasma mass spectrometry, which requires expensive instrumentation and does not have high-throughput capabilities. Although fluorescent probes can be amenable to high-throughput analyses of metals, the utility of such analyses is limited due to the lack of generality. Herein, we report a significant improvement (≈19-fold) to our previously reported catalysis-based fluorescent probe for palladium. Specifically, we found that slightly elevated temperature dramatically improved the generality of the method and that the deallylation reaction of the nonfluorescent compound **1** was accelerated by phosphate ions in aqueous media. This method was capable of detecting 0.2 ppb palladium. We demonstrated reasonably accurate palladium detection in various active pharmaceutical ingredients and highly functionalized organic compounds.

Keywords: chemodosimeter · fluorescence · palladium · phosphate ions · Tsuji–Trost reaction

Introduction

Detection[1] and removal[2] of toxic metals are crucial steps in the preparation of organic compounds. These steps, involving active pharmaceutical ingredients (APIs) and bioactive compounds, are particularly important for safe pharmaceutical practice and reproducible biological studies.[1,3] However, detection of metals in synthetic organic compounds cannot always be achieved by currently used techniques, such as inductively coupled plasma mass spectroscopy (ICP-MS).[4] False negative data for toxic metals in APIs are of particular concern because such data could expose the general public to tainted pharmaceuticals. In order to ensure public safety, an alternative approach for the quality control of synthetic compounds is warranted. Palladium is frequently found in synthetic compounds because the metal is used in numerous types of organic reactions,[5,6] but cannot be removed by typical purification protocols.[6,7] Because ICP-MS is not likely to be a unified solution to the detection of palladium in all synthetic compounds, it is important to develop alternative methods that are sensitive, specific, rapid, and inexpensive. Such methods must be able to detect residual palladium in the presence of APIs in a 5–10 ppm range that is suitable for government regulations. Fluorescence assays provide an opportunity to perform analyses in a high-throughput fashion. As such, many research groups have been actively engaged in the development of colorimetric and fluorometric detection methods for palladium. For example, the Tang group used salicylaldehyde furfuralhydrazone as an indicator for palladium.[8] Additionally, the Anslyn group reported a reactivity-based chemodosimeter,[9] which exploited the thiophilicity of palladium.[10] The Qian group further exploited the affinity of palladium toward sulfides and alkynes for palladium detection.[11] The Peng group disclosed an indicator based on the reactivity of an N-diallyl system with palladium.[12] Most recently, the Holdt group developed a fluorescent sensor that is specific for $PdCl_2$,[13] the goal of which is similar to that of our previously reported study.[14]

In 2007, we reported a fluorescence method ("2007 method") to detect palladium on the basis of the Tsuji–Trost reaction of the nonfluorescent compound **1** to form the fluorescent compound **2** (Scheme 1).[15] In this reaction, Ph_3P was used both as the reducing agent and as a palladium ligand. The method was found to be sensitive because palladium, and platinum to a lesser extent, generated the fluorescent compound **2** in a catalytic manner. By fine-tuning the reaction conditions, we improved the specificity toward palladium over platinum for environmental and geological study.[16] Furthermore, platinum could be detected in serum

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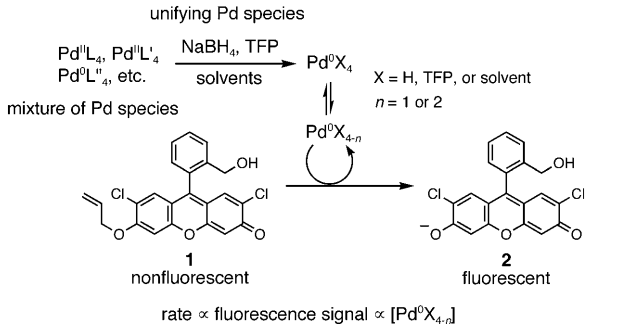
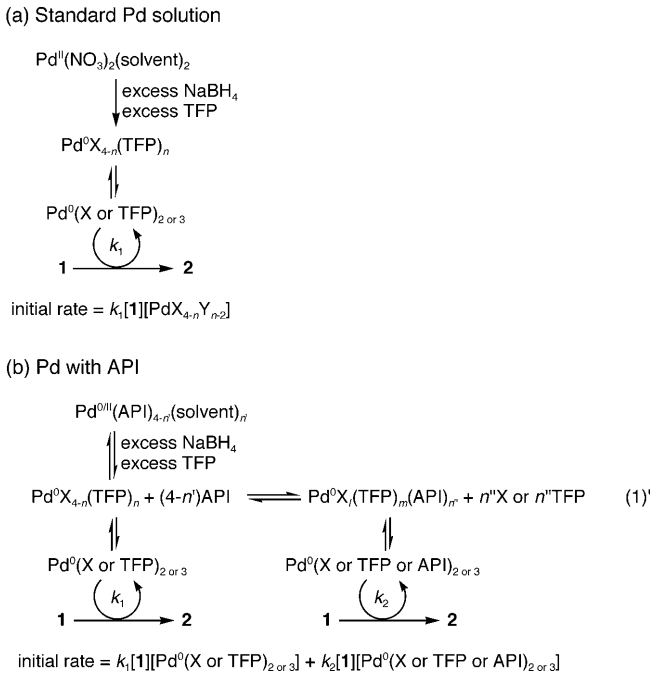


Scheme 1. Various palladium species are converted to Pd^0X_4 that is in equilibrium with Pd^0X_{4-n}, forming the coordinatively unsaturated and catalytically active palladium species. This active species catalyzes the conversion of the nonfluorescent compound **1** to the fluorescent compound **2**. Because the reaction rate is linearly correlated to the concentration of palladium, the measurement of fluorescence signal allows for palladium quantification (TFP = tris(2-furyl)phosphine).

and samples in working environments, indicating potential applications for synthetic chemists, pharmacists, and patients who are subjected to platinum-based drugs.[17] We continued studying the Tsuji–Trost deallylation method to substantially improve the rate, sensitivity, and functional group compatibility over the 2007 method.[18] In this more recent method ("2009 method"), tris(2-furyl)phosphine (TFP) was used as a palladium ligand and $NaBH_4$ as the reagent to reduce palladium(II) to palladium(0). The reaction rate (i.e., the sensitivity of the method) was approximately eight times greater in the 2009 method than in the 2007 method. It was assumed that any palladium species would be converted to Pd^0X_4 (X = H, TFP, or solvent) in the presence of more than 10^4 equivalents of $NaBH_4$, TFP, and solvent molecules relative to palladium. However, more recently, we found that this assumption was incorrect (see below). Herein, we present solutions to these problems, which led us to the development of more general and sensitive methods. Additionally, interesting rate acceleration by phosphate ions was discovered, which might be applied to other Tsuji–Trost reactions in the future.

Results and Discussion

API concentration: In our previous study, it was demonstrated that the palladium spiked into various API-like compounds[19] was nearly as catalytically active as API-free palladium for the conversion of **1** to **2**.[18] In that study, we arbitrarily chose $[API] = 1.25\ mg\,mL^{-1}$ for the palladium detection reactions. Considering the complex dynamics of palladium species, we deemed it critical to determine the range of API concentrations in which the fluorescence method for palladium quantification would be reasonably accurate. The rate of the deallylation of **1** under the reaction conditions was found to be in the first order with respect to the concentration of palladium.[18] At lower API concentrations, the equilibrium between $Pd^0X_{4-n}(TFP)_n$ and $Pd^0X_l(TFP)_m(API)_{n''}$ (Scheme 2b) presumably shifts toward the left, generating the API-free palladium species $Pd^0X_{4-n}(TFP)_n$. This method compares the rates ($\propto$ fluorescence signal) of the reactions catalyzed by palladium in standard solutions (Scheme 2a) to those of the reactions catalyzed by palladium in solutions containing APIs. A 100% signal recovery is achieved when $[Pd^0X_{4-n}(TFP)_n]$ is the same in the palladium-spiked API solution and the API-free palladium standard solution, provided that API-bound palladium species are catalytically inactive (i.e., $k_2 = 0$). As such, we hypothesized that reducing the concentration of an API should enable one to achieve the equilibrium shift toward the left in Equation (1) based on the principle of Le Chatelier, thereby enabling us to achieve near 100% signal recovery.



Scheme 2. Comparison of palladium detection by using a standard palladium solution and API samples containing palladium. X = solvent, H, etc. a) $Pd(NO_3)_2$ in a palladium standard solution is subjected to $NaBH_4$ (excess) and TFP (excess) to form the TFP-bound palladium(0) species. One or two ligands are dissociated from this species to form the catalytically active palladium(0) species. This catalyst converts the nonfluorescent compound **1** to the fluorescent compound **2**. b) API-bound palladium species are subjected to the same conditions.

In order to test this hypothesis, we employed the 2009 method with various concentrations of amines with palladium (API/palladium = 100000:1 w/w). Specifically, imidazole (imid), pyridine (pyr), and dimethylaminopyridine (DMAP) were dissolved so that the final concentrations were 0.5, 1, 2, 4, and $8\ mg\,mL^{-1}$ and the palladium concentrations were 5, 10, 20, 40, 80, and $160\ ng\,ml^{-1}$, respectively. The results were compared to the standard curve (Figure 1).[18] The deviation from the standard curve became increasingly noticeable for $[amine] > 2\ mg\,mL^{-1}$, supporting our hypothesis.

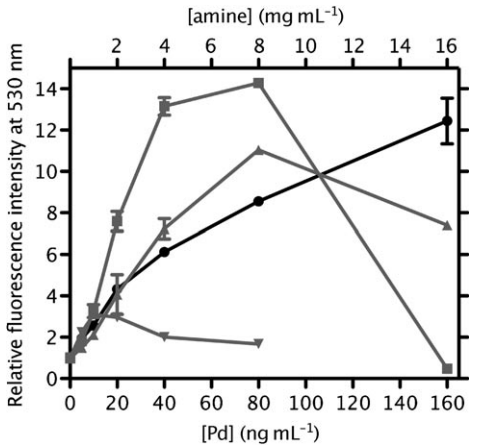


Figure 1. Dependence of the palladium detection on the concentration of the amine. For palladium, 1 ppb (ng ml^{-1}) = 9.4 nM. When an excess of palladium-tainted amines are used, the accuracy is poor (● = Pd standard, ▲ = imid + Pd, ■ = pyr + Pd, and ▼ = DMAP + Pd).

Therefore, the optimal range for this palladium detection assay was in the range of 0.5–1 mg API per mL. At this point, the origin of the signals higher than the standard curve, particularly with pyridine, in the presence of reducing agents (TFP, $NaBH_4$), is not clear.[20] Signals lower than the standard curve might be due to fluorescence quenching at high amine concentrations[21] or due to the equilibrium shift toward catalytically inactive amine-bound palladium species. When synthetic materials contain much higher concentrations of palladium, this method should be used with a smaller amount of the palladium-contaminated material. For example, we successfully employed our method with a synthetic sample containing ≈2000 ppm palladium at a concentration of 0.01 mg mL^{-1}.[18] An additional merit of using this technique at low API concentrations is that under such conditions, fluorescence signals from **2** are less likely to be quenched by the photoinduced electron transfer process or collisions.[21]

Identification of major problems: In our previous studies, the preparation of palladium-containing API samples and the deallylation of **1** were performed on the same day.[18] For example (Figure 2a), when solutions of imidazole were spiked with palladium 30 min before the deallylation of **1**, the method generated excellent signal recovery (≈100%). However, our continued efforts toward developing a better palladium detection method revealed that the 2009 method was not compatible with older palladium-contaminated samples. For example, 72 hours old palladium-spiked imidazole samples showed very poor signal recovery (Figure 2a). Most of the functionalized organic compounds that we tested exhibited the same trend (data not shown). These failures raised a major concern because an ideal palladium assay should not depend on the age of the sample. We speculated that the failures might be due to the formation of less reactive palladium species, such as more stable palladium–API

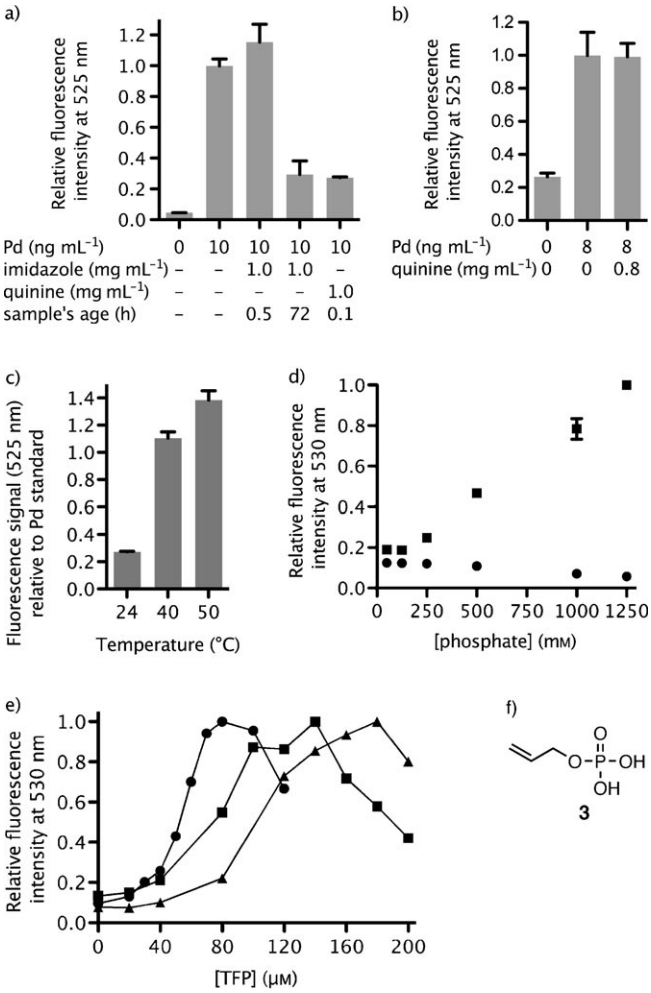


Figure 2. a) Comparison of palladium standard and a palladium–quinine mixture. The experiment was performed in duplicate. [**1**] = 12.5 μM, [TFP] = 80 μM, [$NaBH_4$] = 1.0 mM, 10% DMSO in phosphate buffer (1.04 M, pH 7). b) Quinine does not interfere with the fluorescence method when palladium-contaminated quinine samples are treated with HNO_3. The experiment was performed in triplicate and repeated twice. c) Temperature effect: the fluorescence intensity of a solution of palladium (1 ng ml^{-1}) and quinine (0.1 mg mL^{-1}) was compared to that of a solution of palladium (1 ng ml^{-1}) at 24, 40, and 50 °C. [**1**] = 12.5 μM, [TFP] = 160 μM (24 °C), 200 μM (40 °C), 320 μM (50 °C), [$NaBH_4$] = 1.0 mM, 10% DMSO in phosphate buffer (50 mM, pH 7). The experiment was performed in triplicate. Each data set was standardized by comparing to the fluorescence data under the same reaction conditions in the absence of quinine. d) The conversion of **1** to **2** was linearly accelerated by phosphate ions. Conditions: [**1**] = 12.5 μM, [Pd] = 0 (■) or 1 ppb (●), [TFP] = 120 μM, [$NaBH_4$] = 1.0 mM, 45 °C, 1 h, 1:9 v/v DMSO/phosphate buffer (pH 7). The experiment was performed in triplicate. e) Dependence on [TFP] at 25 (●), 43 (■), and 50 °C (▲). Each data set is normalized so that the maximum fluorescence intensity at 530 nm is 1. [Pd] = 8 ng ml^{-1} (ppb) at 25 °C, [Pd] = 1 ng ml^{-1} (ppb) at 43 and 50 °C. f) Structure of allyl phosphate **3**.

complexes,[22,23] high-order palladium nanoparticles,[24] colloidal species,[25] insoluble $Pd(OH)_2$,[26] or palladium black.[27] Therefore, it became clear that a better method was needed to convert these less reactive or unreactive palladium species to reactive palladium species in situ.

Pretreatment of samples with HNO_3: Among many highly functionalized organic compounds we tested (see Figure 4b for their structures), quinine (**22**) was the most challenging because it significantly retarded the deallylation reaction under the previously reported conditions (2009 method). Specifically, even when palladium was spiked 5 min before the deallylation reaction, the signal recovery was only 24% (Figure 2a). This may be attributed to the recently reported palladium–quinine complex formation.[22] Thus, we set out to develop a more general and reproducible protocol with the palladium-containing quinine (palladium/quinine = 1:100000 w/w, 10 ppm palladium in quinine) for ≈100% signal recovery. Therefore, the palladium–quinine mixture was treated with aqua regia. However, this pretreatment gave results that depended on the freshness of the aqua regia, which does not suit our goal. Thus, we turned our attention to concentrated, virtually palladium-free (<10 ppt) HNO_3. A solution of the palladium–quinine mixture was first treated with concentrated HNO_3 to presumably convert high-order palladium species and palladium–quinine complexes into $Pd(NO_3)_2$. The sample was then neutralized with concentrated phosphate buffer (1.25 M, pH 7). The resulting solution was then treated with $NaBH_4$ to reduce palladium(II) to palladium(0), with TFP to form catalytically active $Pd(TFP)_n$ species, and finally with compound **1**, all at ambient temperature. This sample was compared to an identically treated palladium-standard solution containing the same amount of palladium. Both the quinine-free control reactions and the quinine-containing reactions were performed in triplicate, and the fluorescence signals of these reaction solutions were measured after 1 h. It was found that the signal recovery was 99% on average (Figure 2b), indicating that the pretreatment of samples with HNO_3 might solve the problems associated with aged and functionalized API samples contaminated with palladium. For well-trained chemists, this protocol could be recommended; however, we wished to develop an alternative method that would not call for the use of concentrated HNO_3.

Temperature: During this study, it was serendipitously found that when the laboratory was warmer (≈28 °C) or colder (≈19 °C) than usual (25 °C), the deallylation rates were noticeably different. Enlightened by this, we hypothesized that higher temperatures might also facilitate the formation of reactive monomeric palladium species due to the larger contributions of entropy at higher temperatures. With the palladium-contaminated quinine sample, we screened temperatures and found, as shown in Figure 2c, that higher percentage of signal recoveries could be achieved when the deallylation reaction was performed at $T \geq 40$ °C without acid treatment prior to the addition of $NaBH_4$, TFP, and **1**.

From these results, it appears that palladium is stably bound to quinine under the reaction conditions ([**1**] = 12.5 μM, [TFP] = 250–500 μM, [$NaBH_4$] = 1.0 mM, 1:9 v/v DMSO/phosphate buffer (50 mM, pH 7) at room temperature. We speculate that at $T \geq 40$ °C, the palladium–quinine complex and an uncharacterized catalytically more active palladium complex (presumably palladium bound to TFP) interconvert rapidly. Moreover, even if the catalytically more active palladium species is scarce, the activation energy for the deallylation of **1** should be lower with this active species than with the palladium–quinine complex. Thus, according to the Curtin–Hammett principle,[28] the rate is determined by ΔG_{TS} and the temperature, which are presumably independent of the equilibrium constant for the dynamics of palladium species. Further studies are warranted to understand the origin of the temperature effect.

Phosphate ions: In order to determine whether phosphate ions in the buffer play any role other than maintaining the pH of the media, we measured the rate of the deallylation of **1** at various concentrations of phosphate. Interestingly, the rate was linearly correlated to the concentration of phosphate ions (Figure 2d). This could be explained by either the ionic strength or the involvement of a phosphate ion in the rate-determining step. The reaction rate was not influenced by Na_2SO_4 or $LiClO_4$ concentrations in the range of 0.05–50 mM, or by a Tris buffer (pH 7) in the range of 0.1–1 M salt concentration, excluding the possibility for ionic strength-accelerated kinetics (data not shown). Because the phosphate buffer (1.25 M, pH 7) is commercially available, the remaining experiments were performed by using this buffer. If higher sensitivity is desired, a higher concentration of buffer (pH 7) may be used.

We continued to investigate the role of phosphate ions in the system. In organic solvents, the rate-determining step of the Tsuji–Trost reaction is the nucleophilic attack of a π-allylpalladium complex.[29] However, it is unclear whether the rate-determining step is the same in aqueous media. Nonetheless, if this is the case and phosphate ions are the nucleophiles that attack the π-allylpalladium complex, allyl phosphate **3**[30] (Figure 2f) should be formed in the reaction mixture. However, a mass spectrometric analysis of the reaction mixture indicated no presence of this compound (data not shown). It was also confirmed that under the reaction conditions, allyl phosphate **3** was not hydrolyzed into an inorganic phosphate ion and allyl alcohol. Therefore, we tentatively exclude the possibility that phosphate ions act as nucleophiles. We also considered an ion pairing between the π-allylpalladium complex and a phosphate ion. However, this is more reasonable in less polar solvents such as THF.[31] In a polar solvent, cationic π-allylpalladium complexes (i.e., no ion pairs) are afforded,[31] implying that the ion pairing is not likely. One remaining possibility is that a phosphate ion acts as a ligand for palladium(0). Related crystal structures of palladium(II)–diphosphate complexes are known,[32] but to the best of our knowledge, palladium(0)–phosphate complexes have not yet been characterized. We are currently continuing to study the origin of the phosphate-accelerated deallylation reaction.

Tris(2-furyl)phosphine: By virtue of the study described above, the concentration of phosphate salts is significantly different (1.25 M) from that used in the 2009 method

(50 mM). This significant difference prompted us to revisit the concentration effects of TFP and found that optimal TFP concentrations are in the range of 70–100, 100–140, and 160–180 μM at 25, 43, and 50 °C, respectively (Figure 2e). The requirement for lower concentrations of TFP compared to our previously described method may be a reflection of the higher ion strength, facilitating the formation of a hydrophobic complex between palladium and TFP. The apparent second-order kinetics with respect to the concentration of TFP at lower concentrations suggests that two TFP molecules are involved in the rate-determining step. It should be noted that these optimal TFP concentrations are not typical reaction conditions in synthetic organic chemistry. In most palladium-catalyzed organic reactions, the stoichiometry of the phosphine ligands is less than ten equivalents relative to palladium. In this aqueous Tsuji–Trost-type reaction the optimal TFP stoichiometry is in the range of 13000–19000 equivalents, presumably because at such low palladium concentrations, excessive TFP is necessary to shift the binding equilibrium toward the palladium–TFP complex.

Sodium borohydride: Next, we studied the rate of deallylation of chemodosimeter **1** with respect to the concentration of $NaBH_4$. Figure 3a shows the first-order dependence at low concentrations of $NaBH_4$ and the zero-order dependence for $[NaBH_4] \geq 30$ μM. Thus, the reaction exhibits saturation kinetics,[33] in which the rate-determining step is the reduction of palladium(II) to palladium(0) at low concentrations of $NaBH_4$. At higher concentrations of $NaBH_4$, the rate-determining step is presumably the nucleophilic attack of a π-allylpalladium complex as discussed above. It should be noted that even in the absence of $NaBH_4$ the reaction proceeds, presumably because TFP can, albeit slowly, reduce palladium(II) to palladium(0).

Compound 1: The next question was whether compound **1** was involved in the rate-determining step. To address this question, the molecularity of the deallylation was measured and was found to be first-order for **1** (Figure 3b), indicating that this compound is involved in the transition state of the rate-determining step. From this and aforementioned studies, it is highly likely that the rate-determining step is the nucleophilic attack of the π-allyl palladium complex. This was not obvious from current literature because many factors (e.g., solvent, phosphine ligand, nucleophile, and reducing agent) are different from typical Tsuji–Trost reactions in organic solvents.

Metal specificity: Because significant changes were made to the reaction conditions, we found it necessary to study the metal specificity of the current procedure. Under the new conditions ($[TFP] = 120$ μM, $[NaBH_4] = 1$ mM, $[\mathbf{1}] = 12.5$ μM, 45 °C, 30 min, 1:9 v/v DMSO/phosphate buffer (1.25 M pH 7)), the metals shown in Figure 3c were tested at a concentration of 100 nM with the exception of palladium, which was tested at a concentration of 10 nM. As expected, the assay was most responsive to palladium despite the lower

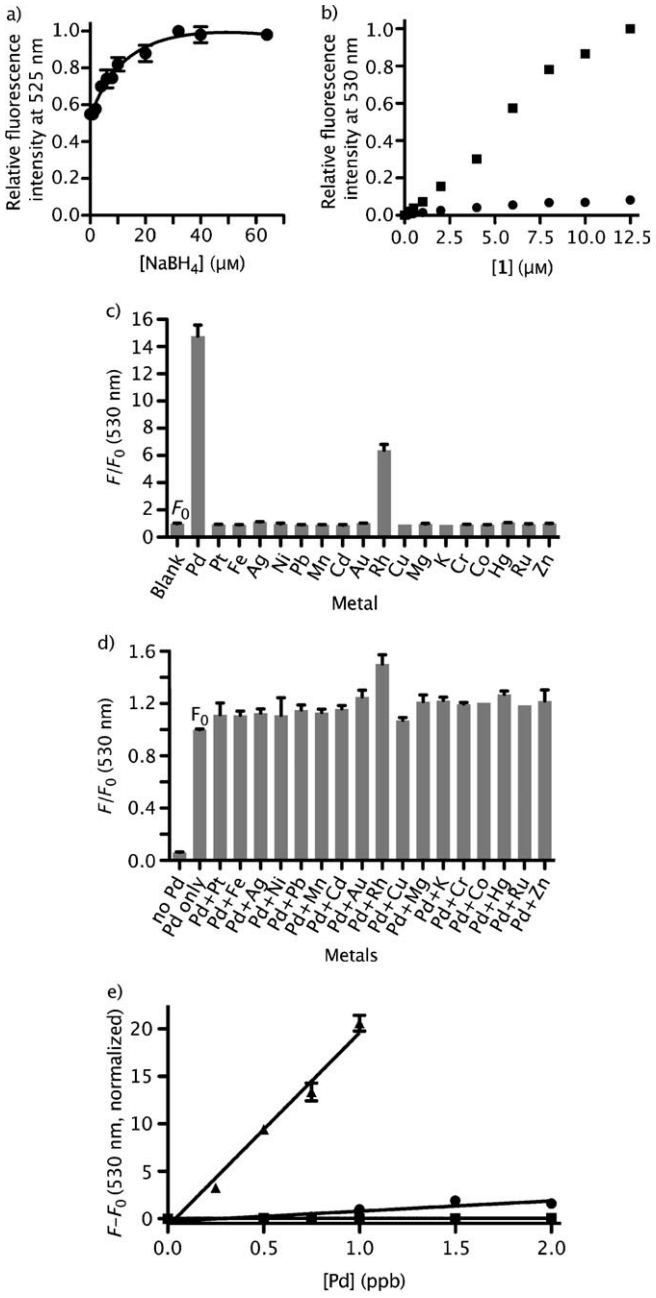


Figure 3. a) Relative fluorescence intensity versus the concentration of $NaBH_4$. The data show saturation kinetics. Conditions: $[\mathbf{1}] = 12.5$ μM, $[TFP] = 120$ μM, $[Pd] = 1$ ppb, 45 °C, 1 h, 1:9 v/v DMSO/phosphate buffer (1.25 M, pH 7). b) Relative fluorescence intensity versus the concentration of **1**. Conditions: $[Pd] = 1$ ppb (■), $[TFP] = 120$ μM, $[NaBH_4] = 1.0$ mM, 45 °C, 1 h, 1:9 v/v DMSO/phosphate buffer (1.25 M, pH 7) (● = no Pd). c) Metal specificity: Each metal was tested separately. Conditions: $[\mathbf{1}] = 12.5$ μM, $[Pd] = 10$ nM = 1.06 ppb, [other metal] = 100 nM, $[TFP] = 120$ μM, $[NaBH_4] = 1.0$ mM, 45 °C, 1 h, 1:9 v/v DMSO/phosphate buffer (1.25 M, pH 7). d) Interference by other metals. Conditions: $[\mathbf{1}] = 12.5$ μM, $[Pd] = 10$ nM = 1.06 ppb, [other metal] = 100 nM, $[TFP] = 120$ μM, $[NaBH_4] = 1.0$ mM, 45 °C, 1 h, 1:9 v/v DMSO/phosphate buffer (1.25 M, pH 7). e) Correlation of the fluorescence intensity and the concentration of palladium, and comparison of this method to the previous methods (▲ = 2010, ● = 2009, and ■ = 2007). Conditions: $[\mathbf{1}] = 12.5$ μM, $[TFP] = 120$ μM, $[NaBH_4] = 1.0$ mM, 45 °C, 1 h, 1:9 v/v DMSO/phosphate buffer (1.25 M, pH 7). All of the experiments shown here were performed in triplicate.

concentration. Interestingly, unlike the previous method that showed a moderate response with platinum,[15,17] this method did so with rhodium (note that the concentration of rhodium was ten times higher than that of palladium). This shortcoming should not be of great concern, as a compound synthesized by palladium-catalyzed reactions will not be contaminated with rhodium unless rhodium is used in an earlier step in the synthesis. To further examine the generality of the method, palladium and each of these metals were mixed in a 1:10 ratio and used for the deallylation reaction (Figure 3d). Except for the mixture of palladium and rhodium, which showed a significantly higher signal, the combination of metals did not produce false negative data, indicating that metal contaminations in palladium samples do not interfere with our method.

The rhodium-catalyzed deallylation of **1** deserves additional comments. Oxidative insertions of rhodium(I) catalysts into allylic C–O bonds are known in the literature. For example, allylic acetates can be converted to allylic silanes by $[RhCl(PPh_3)_3]$.[34] In this work, the reactions were much faster with palladium catalysts than with rhodium catalysts, corroborating our data. The same rhodium catalyst was used in an aqueous–organic, two phase system that cleaves an allylic C–O bond and reorganizes the carbon framework.[35] Presumably by a similar mechanism, allyl acetate was transformed into propene in the presence of $[RhH(PPh_3)_4]$.[36] Very recently, the combination of allyl acetate and $[Rh(cod)Cl]_2$ (cod = cyclooctadiene) was found to allylate conjugated aldehydes.[37] Interestingly, in all of these cases the reaction mixtures were heated to $T \geq 75\,^{\circ}C$, which may be the reason why we did not observe the rhodium-catalyzed fluorescence enhancement in our previous study at room temperature.[15] The results presented here also indicate that TFP might be a superior phosphine ligand for rhodium-catalyzed Tsuji–Trost type reactions because the allylic ether bond of **1** was cleaved only at $T = 45\,^{\circ}C$. Although the detection of rhodium is not the subject of this paper, the facile monitoring of the conversion of **1** to **2** by fluorescence signal increase should provide a high-throughput platform to screen for ligand optimization.

Sensitivity and comparison with previous methods: Next, we compared the kinetics of this new method to those of previous versions. The 2010 version was approximately 19 times faster than the 2009 version (Figure 3e). The rate enhancement can be explained by the increased phosphate concentration, elevated temperature, and optimized TFP concentration. According to the linear relationship with respect to the phosphate concentration, it should be possible to further improve the rate of the reaction (i.e., sensitivity). However, we believe that the sensitivity is already sufficient and that it would be more convenient to use a commercially available buffer solution than to manually prepare a more concentrated buffer solution.

Scope of the fluorescence methods with various APIs: Finally, we proceeded to demonstrate the utility of the new assay with functionalized organic compounds (Figure 4b) spiked with palladium (palladium/organic compound = 1:100000 w/w). These palladium-spiked compounds were at least three days old before being subjected to the new fluorescence method. As Figure 4a shows, the average signal recovery

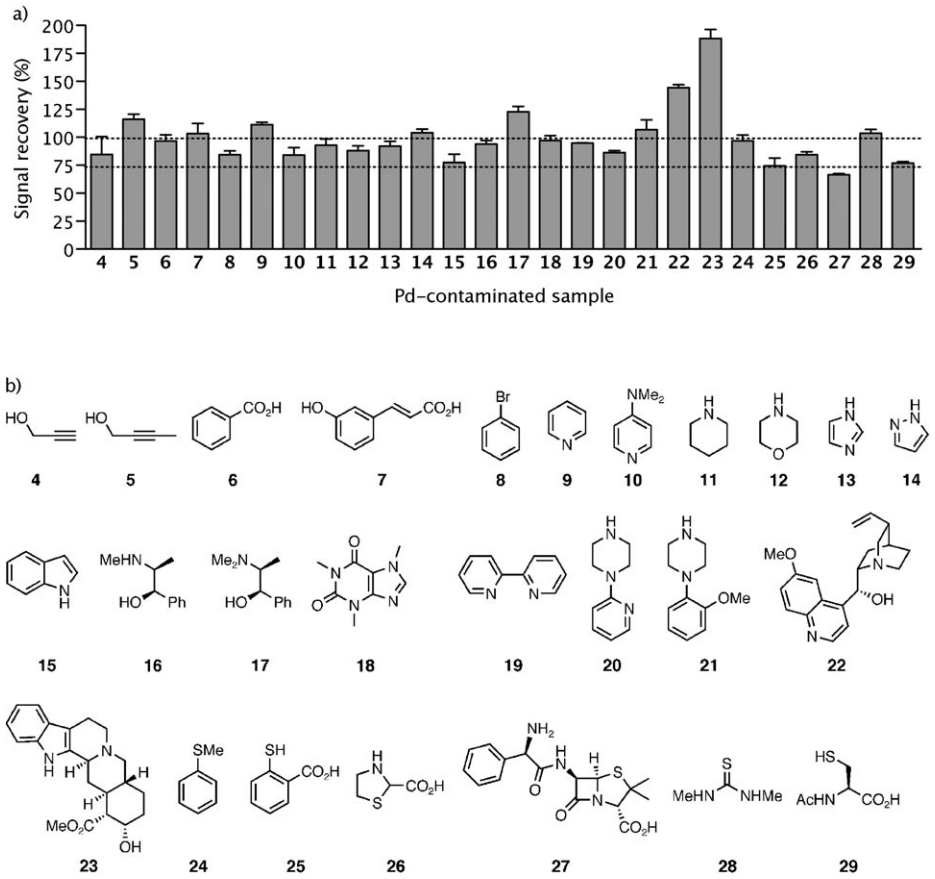


Figure 4. Applicability of the 2010 method with different functionalized organic compounds. a) Average signal recovery. Conditions: [**1**] = 12.5 μM, [TFP] = 120 μM, [$NaBH_4$] = 1.0 mM, (compound shown in Figure 4b) = 100 μg mL^{-1}, [Pd] = 1 ng ml^{-1}, 1:9 v/v DMSO/phosphate buffer (1.25 M, pH 7), 45 °C, 1 h. For compounds **23** and **29**: [**1**] = 12.5 μM, [TFP] = 160 μM, [$NaBH_4$] = 1.0 mM, [**23**] = [**29**] = 50 μg mL^{-1}, [Pd] = 0.5 ng ml^{-1}, DMSO/phosphate buffer (1.25 M, pH 7), 45 °C, 1 h. The experiments were performed in triplicate. The mean values and standard deviations are shown. b) Structures of the organic compounds that were used in Figure 4a.

was 99±25%. The result with yohimbine (**23**) significantly skewed the statistical analysis, and without this example the average signal recovery was 95±17%, a reasonable percentage recovery and an acceptable standard deviation considering the challenging reaction conditions. In our previous report, these values were 106±61% in pH 7 buffer and 89± 47% in pH 10 buffer, indicating that the sensitivity and generality of the fluorescence assay were significantly improved. Minor adjustments were needed for compounds **23** and **29**. Under the standard conditions ([**23**]=100 μg mL^{-1}, [Pd]= 1 ng ml^{-1}), the fluorescence signal recovery of the yohimbine sample was even higher than that shown in Figure 4a, implying that yohimbine (**23**) might accelerate the deallylation reaction by reacting with heterogeneous Pd/C-like species.[38] Compound **29** somewhat retarded the deallylation under the standard conditions ([**29**]=100 μg mL^{-1}, [Pd]=1 ng ml^{-1}), which prompted us to use more diluted conditions ([**29**]= 50 μg mL^{-1}, [Pd]=0.5 ng ml^{-1}) to discourage the **29**–palladium complex formation. Out of 26 compounds that were arbitrarily chosen based on drug-like functional groups, only two compounds posed minor problems, which were solved by dilution.

The data presented in Figure 4 revealed several noteworthy features: 1) This method was compatible with potential fluorescence quenchers by the photoinduced electron transfer mechanism (e.g., **9**, **10**, **15**, **20**–**23**). 2) Even strong chelators such as **19**, **28**, and **29** did not interfere with the method. 3 Both acidic and basic functional groups were compatible with the method in the phosphate buffer (pH 7) unlike the 2009 version.[18]

Conclusion

In conclusion, we developed a more sensitive and general method for the quantification of palladium contamination in functionalized organic molecules. Fluorescence signals may be measured by using a bench-top fluorometer, a microplate reader, or a hand-held fluorometer. Under the reaction conditions used in Figure 4, API concentrations were 50–100 μg mL^{-1} to achieve higher accuracy. In general, it appears that better signal recovery can be obtained with a lower concentration of a palladium-contaminated compound. Mechanistically, it was found that two molecules of TFP were involved in the rate-determining step of the reaction and that phosphate ions linearly accelerated the palladium-catalyzed deallylation of compound **1**. We discovered that by switching phosphine ligands from Ph_3P to TFP, platinum became inert and rhodium became the second most reactive metal for the deallylation of **1**. The data shown in Figure 4 with aged palladium-contaminated samples imply that this method can be used to measure palladium in various forms (colloid, particles, etc.). However, more direct studies with well-characterized palladium colloid and particles are needed to verify this claim. Further mechanistic studies on the phosphate-accelerated Tsuji–Trost reaction are also warranted.

Experimental Section

General techniques: All reactions were carried out with commercial-grade solvents without distillation, unless otherwise noted. Yields refer to chromatographically and spectroscopically (^{1}H NMR spectroscopy) homogeneous materials, unless otherwise stated.

Reagents: Compound **1** was prepared in our laboratory. A palladium standard solution was purchased from VWR and used as received. $NaBH_4$ was purchased from VWR and used as received. Tri(2-furyl)phosphine (TFP) was purchased from TCI and used after recrystallization from EtOH. Quinine was purchased from VWR and used as received. Ultra pure HNO_3 was purchased from EMD and used as received. Ultra pure HCl was purchased from VWR and used as received. Ultra pure water was purchased from VWR and used as received. DMSO was purchased from J. T. Baker and used as received. Na_2SO_4 was purchased from EMD and used as received. $LiClO_4$ was purchased from VWR and used as received. A buffer solution (pH 7) was purchased from J. T. Baker ([phosphate]=0.050 M, [K^+]=0.025 M, catalog number 5608-01) and used as received. A concentrated buffer (pH 7) was purchased from Fisher ([phosphate]=1.25 M, catalog number SB109-1) and either used as received or used after dilution.

A solution of TFP in DMSO was freshly prepared before each experiment. A solution of $NaBH_4$ (2.5 M in 10 N NaOH) was stored at ambient temperature, and a solution of $NaBH_4$ (30 mM) was freshly prepared before each experiment by diluting the 2.5 M solution with water.

Fluorescence spectroscopy: Fluorescence spectra were recorded in a 1× 1 cm disposable cuvette (VWR, catalog number 58017-880) on a Jobin Yvon FluoroMax-3 spectrometer under the control of a Windows-based PC running FluorEssence software. The samples were excited at λ= 497 nm and the emission intensities were collected at λ=525 nm. All spectra were corrected for emission intensity by using the manufacturer supplied photomultiplier curves.

Deviation from the standard curve depends on the concentration of the API: **(Figure 1)**: In this experiment, all operations were conducted at room temperature with a palladium/API mimic ratio of 1:100000 w/w (i.e., 10 ppm palladium in API mimic). For this experiment, a 250 ppm palladium solution was prepared by a four-fold dilution of a commercial palladium standard solution (1000 ppm) with ddH_2O (doubly distilled water). A 16 mM TFP solution was prepared by dissolving TFP (37.1 mg, 0.16 mmol) in a mixture of DMSO and ddH_2O (7:3 v/v, 10.0 mL). A 2.5 M $NaBH_4$ solution was prepared by dissolving $NaBH_4$ (943 mg, 25.0 mmol) in NaOH (10 M, 10.0 mL) and stored in a polypropylene bottle for > 2 months. A fraction of this solution (100 μL) was diluted with ddH_2O (6.15 mL) to give a 40 mM $NaBH_4$ solution in 0.16 M NaOH prior to this experiment. A 172 mM phosphate buffer (pH 7) was prepared by diluting concentrated phosphate buffer (1.25 M, pH 7, 30 mL) with ddH_2O (188 mL).

Imidazole, pyridine, or DMAP (1.60 g) was placed in a 10 mL volumetric cylinder. A mixture of DMSO and ddH_2O (3:1 v/v) was added to the cylinder until the total volume became 10 mL. The resulting solution was 160 mg mL^{-1} for each amine.

These solutions were treated with a palladium standard solution (250 μg mL^{-1}, 64 μL). The resulting solution had an API concentration of 160 mg mL^{-1} and a palladium concentration of 1600 ng ml^{-1}. Next, 2 mL of this solution were diluted with 2 mL of a mixture of DMSO and ddH_2O (3:1 v/v). The resulting solution had an API concentration of 80 mg mL^{-1} and a palladium concentration of 800 ng ml^{-1}. This two-fold dilution was repeated to prepare a solutions with an API concentration of 40 mg mL^{-1} and a palladium concentration of 400 ng ml^{-1} palladium, an API concentration of 20 mg mL^{-1} and a palladium concentration of 200 ng ml^{-1} palladium, an API concentration of 10 mg mL^{-1} and a palladium concentration of 100 ng ml^{-1}, and an API concentration of 5 mg mL^{-1} and a palladium concentration of 50 ng ml^{-1} palladium. These solutions were used as stock solutions (10×).

Either a mixture of DMSO/ddH_2O (3:1 v/v, 400 μL) or one of the above-described palladium-spiked API solutions was transferred to three empty vials. Each of these solutions was then treated with aqueous HCl (6 N,

40 μL). After 15 min, each of the resulting acidic solutions was treated with the phosphate buffer (172 mM, pH 7, 3.26 mL). The TFP solution (16 mM, 100 μL) was then added to each of these solutions. After 5 min, the $NaBH_4$ solution (40 mM, 100 μL) was added to each of these solutions. Soon thereafter, a solution of **1** in DMSO (500 μM, 100 μL) was added to each of these solutions with a two-minute interval. The final reaction conditions were: [**1**] = 12.5 μM, [$NaBH_4$] = 1 mM, [TFP] = 400 μM, [phosphate] = 140 mM in DMSO/dd H_2O (1:9 v/v).

Fluorescence was measured 60 min after compound **1** was added. The data were normalized in Microsoft Excel, and the graph was drawn by using Prism 5.0. The average and standard deviation of the triplicate samples are shown in Figure 1.

Comparison of a palladium standard and palladium–imidazole and palladium–quinine mixtures (Figure 2a): A palladium standard solution (15 μL, 800 ppb in 1% HNO_3), a palladium–imidazole mixture, or a palladium–quinine mixture (15 μL, palladium 2 ppm = 2 μg mL^{-1}, imidazole or quinine 200 mg mL^{-1} in DMSO/water 1:1 v/v) was added to a 2-dram vial. A solution of hydrochloric acid (70 μL, 37%) was added. After being shaken and mixed by a vortex mixer for 1 s, the resulting mixture was incubated at 24 °C for 5 s. A phosphate buffer (pH 7, 2.52 mL, [phosphate] = 0.050 M) was added. TFP (200 μL, 1.2 mM in DMSO), $NaBH_4$ (100 μL, 30 mM in 0.12 N NaOH), and compound **1** (100 μL, 375 μM in DMSO) were added to these solutions in sequence (total volume: 3.0 mL). The resulting samples were shaken for 3 s and incubated for 1 h at 24 °C before fluorescence measurement. The experiments were performed in duplicate.

Pre-treatment with HNO_3 (Figure 2b): A solution of nitric acid (195 μL, 69%), prepared from ultra-pure nitric acid and ultra-pure water, was mixed with a palladium standard solution (30 μL, 800 ppb = 800 ng mL^{-1} in 1% HNO_3) or a palladium–quinine mixture (30 μL, palladium 800 ppb = 800 ng mL^{-1}, quinine 80 mg mL^{-1} in DMSO/water 1:1 v/v) in a 2-dram vial. A concentrated phosphate buffer (pH 7, 2.075 mL, [phosphate] = 1.25 M) and a solution of NaOH (300 μL, 10.0 N) were added. TFP (200 μL, 1.2 mM in DMSO), $NaBH_4$ (100 μL, 30 mM in 0.12 N NaOH), and compound **1** (100 μL, 375 μM in DMSO) were added in sequence (total volume: 3.0 mL). The resulting samples were shaken for 3 s and incubated for 1 h at 24 °C before fluorescence measurement. The experiment was performed in triplicate.

Temperature effect (Figure 2c): A solution of TFP in DMSO (200 μL, 2.4 mM for the experiment at T = 24 °C, 3.0 mM for T = 40 °C and 4.8 mM for T = 50 °C) was mixed with a palladium–quinine mixture (30 μL, palladium 100 ppb, quinine 1 mg mL^{-1} in DMSO/water 1:1 v/v) in a 2-dram vial. A phosphate buffer (pH 7, 2.57 mL, [phosphate] = 0.050 M) was added. The resulting mixture was incubated at 24 °C, 40 °C, or 50 °C for 30 min, then treated with $NaBH_4$ (100 μL, 30 mM in 0.12 N NaOH), and compound **1** (100 μL, 375 μM in DMSO). The resulting samples were incubated for 1 h at 24 °C, 40 °C, or 50 °C while shaken at 200 RPM before fluorescence measurement. As positive controls, the same reaction conditions were employed without quinine. The experiments were performed in triplicate.

Phosphate concentrations (Figure 2d): A solution of TFP ((200 μL, 1.8 mM in DMSO) was mixed with a palladium standard solution (30 μL, 100 ppb in 1% HNO_3) in a 2-dram vial. Different phosphate buffers (pH 7, 2.57 mL, [phosphate] = 0–1250 mM) were added. The resulting mixtures were incubated at 45 °C for 30 min. $NaBH_4$ (100 μL, 30 mM in 0.12 N NaOH) and compound **1** (100 μL, 375 μM in DMSO) were added in sequence. The resulting samples were incubated for 1 h at 45 °C while shaken at 200 RPM before fluorescence measurement. The experiments were performed in triplicate.

TFP concentrations at 25, 43, and 50 °C (Figure 2e): Solutions of TFP with different concentrations (200 μL, 0–3.0 mM in DMSO) were mixed with a palladium standard solution (30 μL, 800 ppb or 100 ppb in 1% HNO_3) in a 2-dram vial. A concentrated phosphate buffer (pH 7, 2.57 mL, [phosphate] = 1.25 M) was added. The resulting mixtures were incubated at 25 °C, 43 °C, or 50 °C, respectively for 30 min. $NaBH_4$ (100 μL, 30 mM in 0.12 N NaOH), and compound **1** (100 μL, 375 μM in DMSO) were added in sequence. The resulting samples were incubated for 1 h at 25 °C, 43 °C, or 50 °C while shaken at 200 RPM before fluorescence measurement. The experiments were performed in triplicate.

Testing ionic strength effect (Data not shown): A solution of TFP (200 μL, 3.0 mM in DMSO) was mixed with a palladium standard solution (30 μL, 100 ppb in 1% HNO_3) in a 2-dram vial. A solution of Na_2SO_4 or $LiClO_4$ (500 μL, 0.3 mM, 3.0 mM, 30 mM or 300 mM in water) and a phosphate buffer (pH 7, 2.57 mL, [phosphate] = 0.050 M) were added. The resulting mixtures were incubated at 45 °C for 30 min. $NaBH_4$ (100 μL, 30 mM in 0.12 N NaOH) and compound **1** (100 μL, 375 μM in DMSO) were added in sequence. The resulting samples were incubated for 1 h at 45 °C while shaken at 200 RPM before fluorescence measurement. The experiments were performed in triplicate.

$NaBH_4$ concentrations (Figure 3a). A solution of TFP (200 μL, 1.8 mM in DMSO) was mixed with a palladium standard solution (30 μL, 100 ppb in 1% HNO_3) in a 2-dram vial. A concentrated phosphate buffer (pH 7, 2.57 mL, [phosphate] = 1.25 M) was added. The resulting mixture was incubated at 45 °C for 30 min. $NaBH_4$ (100 μL, 0–1.92 mM in pH 9 buffer), and compound **1** (100 μL, 375 μM in DMSO) were added in sequence. The resulting samples were incubated for 1 h at 45 °C while shaken at 200 RPM before fluorescence measurement. The experiments were performed in triplicate.

Concentrations of 1 (Figure 3b): A solution of TFP (200 μL, 1.8 mM in DMSO) was mixed with a palladium standard solution (30 μL, 100 ppb in 1% HNO_3) in a 2-dram vial. A concentrated phosphate buffer (pH 7, 2.57 mL, [phosphate] = 1.25 M) was added. The resulting mixture was incubated at 45 °C for 30 min. $NaBH_4$ (100 μL, 30 mM in pH 9 buffer) and compound **1** (100 μL, 0–375 μM) were added in sequence. The resulting samples were incubated for 1 h at 45 °C while shaken at 200 RPM before fluorescence measurement. The experiments were performed in triplicate.

Metal selectivity (Figure 3c): A solution of TFP (200 μL, 1.8 mM in DMSO) was mixed with a palladium standard solution (30 μL, 1.0 μM in 1% HNO_3) or other metal solutions (30 μL, 10 μM in water) in a 2-dram vial. A concentrated phosphate buffer (pH 7, 2.57 mL, [phosphate] = 1.25 M) was added. The resulting mixture was incubated at 45 °C for 30 min. $NaBH_4$ (100 μL, 30 mM in 0.12 N NaOH) and compound **1** (100 μL, 375 μM in DMSO) were added in sequence. The resulting samples were incubated for 1 h at 45 °C while shaken at 200 RPM before fluorescence measurement. The experiments were performed in triplicate.

Co-existing metal selectivity (Figure 3d): A solution of TFP (200 μL, 1.8 mM in DMSO) was mixed with a palladium standard solution (15 μL, 2.0 μM in 1% HNO_3) and a solution of another metal (15 μL, 20 μM in water) in a 2-dram vial. A concentrated phosphate buffer (pH 7, 2.57 mL, [phosphate] = 1.25 M) was added. The resulting mixture was incubated at 45 °C for 30 min. $NaBH_4$ (100 μL, 30 mM in 0.12 N NaOH) and compound **1** (100 μL, 375 μM in DMSO) were added in sequence. The resulting samples were incubated for 1 h at 45 °C while shaken at 200 RPM before fluorescence measurement. The experiments were performed in triplicate.

Standard curve (Figure 3e): A solution of TFP (200 μL, 1.8 mM in DMSO) was mixed with a palladium standard solution (30 μL, 0–400 ppb in 1% HNO_3). A concentrated phosphate buffer (pH 7, 2.57 mL, [phosphate] = 1.25 M) was added. The resulting mixture was incubated at 45 °C for 30 min. $NaBH_4$ (100 μL, 30 mM in 0.12 N NaOH) and compound **1** (100 μL, 375 μM in DMSO) were added in sequence. The resulting samples were incubated for 1 h at 45 °C while shaken at 200 RPM before fluorescence measurement. The experiments were performed in triplicate.

Determination of fluorescence recovery with various API-like compounds (Figure 4a): A solution of TFP (200 μL, 1.8 mM) was mixed with a combined solution of an API-like compound with a palladium standard (30 μL, API 10 mg mL^{-1} in DMSO, palladium 100 ppb in 1% HNO_3). A concentrated phosphate buffer (pH 7, 2.57 mL, [phosphate] = 1.25 M) was added. The resulting mixtures were incubated at 45 °C for 30 min. $NaBH_4$ (100 μL, 30 mM in 0.12 N NaOH) and compound **1** (100 μL, 375 μM in DMSO) were added in sequence. The resulting samples were incubated for 1 h at 45 °C while shaken at 200 RPM before fluorescence measure-

ment. The data were generated in triplicate. The signal recovery was calculated as previously described.[18]

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