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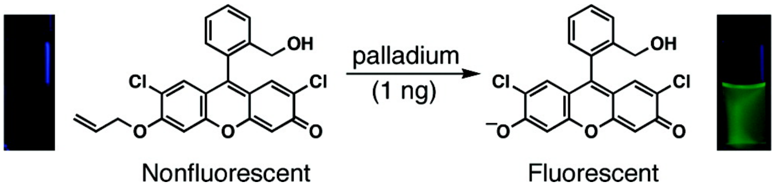

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A Highly Sensitive Fluorescent Sensor for Palladium Based on the Allylic Oxidative Insertion Mechanism

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Palladium is a rare transition metal that plays a pivotal role in materials and chemistry. Palladium (Pd)-catalyzed reactions such as the Buchwald−Hartwig, Heck, Sonogashira, and Suzuki−Miyaura reactions are becoming increasingly important because of the power of making difficult covalent bonds.[1] However, even after purification, residual palladium is often found in the final product, which may be a health hazard.[2] While the proposed dietary intake is $<$1.5 to 15 μg/day per person[3] (10 ppm of Pd in active pharmaceutical ingredients as a threshold),[4] Pd-catalyzed reactions often produce materials contaminated with Pd at a much higher level requiring extensive purifications and analyses.[3,5] Although typical analytical methods for Pd detection require the use of expensive spectrometers (atomic absorption spectroscopy, X-ray fluorescence, plasma emission spectroscopy), a more desirable approach would rely on detection with the naked eye in a high-throughput fashion. Here we report that we have developed a fluorescein-based Pd sensor that relies on fluorescence emission. We found that with a standard fluorometer, less than 1 ppm of Pd can be quantified from a 1-mg sample.

Pd(0) is capable of catalyzing the allylic oxidative insertion to cleave the allylic C−O bond of allylic ethers **A** to form Pd complexes **B** (Figure 1).[6] These complexes then react with various nucleophiles to form compounds **C** and byproducts **D**, which is known as the Tsuji−Trost reaction.[7] Therefore, if **A** is nonfluorescent and **D** is fluorescent, such a system could be used to specifically detect the presence of Pd(0). Moreover, since Pd(II) can be readily reduced to Pd(0), Pd(II) could also be detected by the same principle.

Fluorescein compounds are nonfluorescent when the phenolic hydroxy group is alkylated (**E**) while strongly green fluorescent ($\Phi \approx 0.9$) when the hydroxy group is deprotonated (**F**).[8] This principle has been used for various purposes, primarily in biology for fluorescent imaging.[9] We hypothesized that this same chemical principle could be used for Pd sensing in a scenario where compounds **A** and **D** correspond to **E** and **F**, respectively.

As shown in Scheme 1, allyl ether **2** (corresponding to **A** and **E**) was prepared in two steps from commercially available 2′,7′-dichlorofluorescein (DCF) in multiple gram quantities via the known compound **1**.[10] Compound **2** was converted to compound **3** (corresponding to **D** and **F**) using 0.5 mol % of $Pd(PPh_3)_4$ in quantitative yield. The same efficient conversion was achieved when $Pd(OAc)_2$ and PPh_3 were used in lieu of $Pd(PPh_3)_4$. Compound **3** was 442 times more fluorescent than compound **2** at $\lambda_{em} =$ 526 nm (pH 10 borate buffer) and was as fluorescent as fluorescein. Because both of the Pd oxidation states (0 and II) could be present in fine chemicals and pharmaceutical ingredients after Pd-catalyzed cross-couplings, these successful transformations of **2** to **3** and the distinct fluorescent signals were quite encouraging and would allow for fluorescent detection of Pd species. Compound **3** is soluble in both water and organic solvents and might prove to be useful for fluorescein-based sensor development.[11]

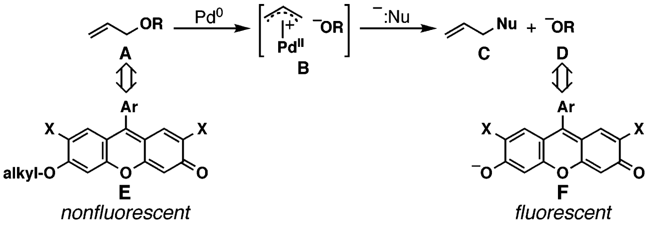
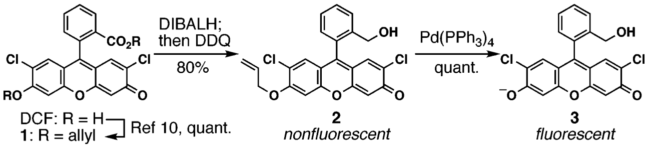


Figure 1. Correlation between palladium-catalyzed allyl ether cleavage and this work: X = H, F, Cl, etc.; Y = CO_2H, etc.

Scheme 1. Preparation of Pd Sensor **2** and Pd-Catalyzed Transformation of **2** to **3**



In the next stage, we studied the metal-specificity of this fluorescent sensing system (Figure 2). We found that the conversion of **2** to **3** in pH 10 borate buffer using PPh_3 as a reducing agent and a ligand was particularly efficient with Pd and to a lesser extent with Pt. It is noteworthy that other π-philic metals such as Ag, Ni, Au, Rh, Co, Hg, and Ru did not catalyze the deallylation reaction (**2** to **3**).

We then proceeded to develop a quantitative method to sense Pd. In the pharmaceutical industry, 5 mg samples are routinely used for Pd analyses. Thus, we set out to develop a fluorescent method that allows for the detection of $\leq$50 ng of Pd ($\leq$10 ppm for a 5 mg sample). The final solutions in each pH 10 borate buffer solution contained $Pd(PPh_3)_4$ in various quantities and Pd sensor **2** at 10 μM. After 1 h incubation at 24 °C, the fluorescent signal of each sample was measured. As Figure 3a shows, fluorescent signals were linearly correlated ($R^2 = 0.993$) to the Pd concentrations from 3 to 300 nM (0.95 to 95 ng). To verify that this system can detect Pd(II) with the same sensitivity, we compared a $Pd(PPh_3)_4$ solution with a $PdCl_2-PPh_3$ solution. As Figure 3b indicates, both samples exhibited nearly the same fluorescence intensity, and $PdCl_2$ without PPh_3 did not convert **2** to **3** efficiently (almost negligible; data not shown). These results support the generality of the Pd sensor system for both Pd(0) and Pd(II) under reducing conditions.

To determine whether this fluorescent sensor could be applied to Pd analyses in pharmaceutical products, we prepared a sample that contained a commercially available aspirin tablet and $PdCl_2$ at the 10 ppm level. A solution of this sample containing 1 mg of the drug and 10 ng of $PdCl_2$ was added to the pH 10 borate buffer solution of Pd sensor **2** and PPh_3. The fluorescent intensity of the resulting solution was then measured (Figure 3c) and compared to a positive control (aspirin-free Pd solution) and a negative control (Pd-free aspirin solution). The signals from the Pd-contaminated aspirin solutions were nearly the same as the positive controls,

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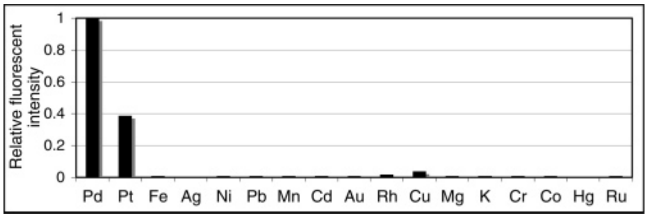

Figure 2. Metal specificity: “Pd” = $PdCl_2$, “Pt” = $PtCl_2$, “Fe” = $FeCl_3$, “Ag” = $AgNO_3$, “Ni” = $NiCl_2$, “Pb” = $Pb(NO_3)_2$, “Mn” = $MnCl_2$, “Cd” = $CdCl_2$, “Au” = $AuCl_3$, “Rh” = $RhCl(PPh_3)_3$, “Cu” = $CuCl_2$, “Mg” = $MgSO_4$, “K” = KCl, “Cr” = $CrCl_3$, “Co” = $CoCl_2$, “Hg” = $HgCl_2$, “Ru” = $RuCl_3$.

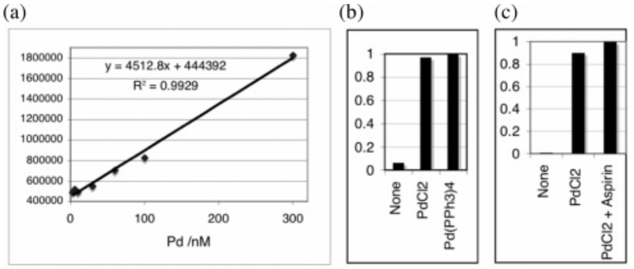

Figure 3. Quantitative fluorescent analysis of Pd: *y*-axis = relative fluorescent intensity. (a) The linear correlation between Pd quantity and fluorescence. (b) Pd(0) and Pd(II) show nearly the same signals: (left) no Pd reagent; (center) $[PdCl_2] = 2.0\ \mu M$; (right) $[Pd(PPh_3)_4] = 2.0\ \mu M$. (c) Proof of concept for Pd detection in drugs: (left) no Pd; (center) $PdCl_2$ (10 ng); (right) $PdCl_2$ (10 ng) + aspirin (1 mg).

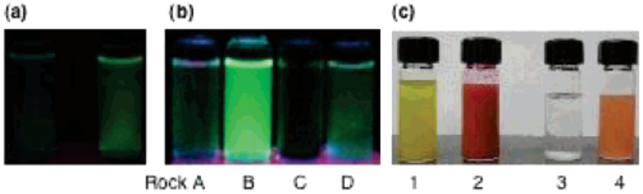

Figure 4. Further applications of **2**. (a) Detection of Pd on the surface of glassware: (left) The solution in a vial not exposed to Pd reagents; (right) the solution in a vial exposed to $Pd_2(dba)_3$ (10 mg) in THF and washed extensively. The photo was taken above a hand-held UV lamp (365 nm). (b) Photo of Pd/Pt detection in rocks: rock A, no metals; rock B, 120 ppm Pd/Pt; rock C, only Au/Ag; rock D, 35 ppm Pd/Pt (Pd/Pt = 3.4:1). The photo was taken above a hand-held UV lamp (365 nm). (c) Naked eye detection of Pd: (vial 1) $PdCl_2$ (1.6 mM), dimethylglyoxime (1% w/v in ethanol) in 0.25 N HCl; (vial 2) $PdCl_2$ (1.6 mM), **2**, $NaBH_4$ in THF; (vial 3) $PdCl_2$ (10 μM), dimethylglyoxime (1% w/v in ethanol) in 0.25 N HCl; (vial 4) $PdCl_2$ (10 μM), **2**, $NaBH_4$ in THF.

supporting the robustness of the Pd sensing method under such heterogeneous conditions.

An additional concern with Pd contamination is the reactors used for Pd-catalyzed reactions. To test whether our method can detect residual Pd in a reactor, a THF solution of $Pd_2(dba)_3$ was stirred in a flask for 1 h at 24 °C. After standard laboratory washing procedure (brushing with detergent, washing with water and acetone), the Pd sensor solution was added to this flask and stirred for 1 h at 24 °C. Presumably because of residual Pd on the glass surface, the solution became more green fluorescent (Figure 4a, right) than a negative control (Figure 4a, left), showing that this Pd sensing method can be used for the quality control of reactors.

Current methods of discovering Pd/Pt-containing rocks (Pd and Pt coexist in most rocks) involve atomic absorption analysis, which miners cannot employ at the mining site. We wanted to determine whether we can detect Pd in rock samples for Pd/Pt detection at mining sites. Rock samples from mining were obtained from Stillwater Mining. Rock stock solutions (50 μL each) were prepared and mixed with Pd sensor solution for 1 h at 24 °C and the fluorescent intensity of the resulting solutions was measured (see Supporting Information). Rock B contains Pd/Pt (3.4:1, 120 ppm), an economically viable quantity. Rock D contains 30% of Pd/Pt compared to rock B. Rock A contains no transition metals and rock C contains Au/Ag but no Pd/Pt. Only rocks B and D converted **2** to **3** and the fluorescent intensity was relative to the amount of Pd/Pt in the sample. Rock samples A and C exhibited negligible fluorescence demonstrating the viability of our sensor in Pd/Pt detection at mining sites via a simple hand-held UV lamp (Figure 4b).

To demonstrate that Pd can be detected even without a UV lamp, we prepared four $PdCl_2$ solutions (Figure 4c). The Pd sensor was added to vials 2 and 4, and dimethylglyoxime was added to vials 1 and 3. At a lower Pd concentration (vials 3 and 4; $[PdCl_2] = 10\ \mu M$), only the solution containing our sensor (vial 4) exhibited a color change detectable with the naked eye showing the usefulness of our sensor.

In conclusion, we have developed a highly sensitive and robust fluorescent method to detect small quantities of Pd regardless of its oxidation state. Sensor **2** was readily synthesized and may find other applications such as monitoring the presence of Pd(0) during Pd-catalyzed reactions. Although each sample was incubated for 1 h in this study, Pd quantities can be determined after 5−10 min incubation using a fluorescent plate reader. This user-friendly sensor technology should greatly aid in the detection of Pd in both the pharmaceutical and mining industries by enabling colorimetric analysis of Pd that can be performed even by untrained scientists.

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Supporting Information Available: Experimental procedures for Scheme 1, Figures 2, 3, and 4. This material is available free of charge via the Internet at http://pubs.acs.org.

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